Flexible Access to an Array of Enantiomerically-enriched Oxabispidines and Their Use as Chiral Ligands in Asymmetric Synthesis

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

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Abstract

A broad series of optically-enriched oxabispidine scaffolds incorporating a range aryl, heteroaryl, and alkyl side arms has been successfully prepared, utilising an optically-pure common oxazine intermediate and commercially available aldehydes. In efforts towards establishing efficient access to such molecules, a fully optimised route, which is amenable to the preparation of the optically-pure oxazine on a multigram scale, has been developed. In addition to the development of a general trifluoromethanesulfonic acid-activated intramolecular Mannich-type cyclisation protocol, which is accommodating to a wide range of aldehyde substrates, alternative conditions have also been developed for more challenging substrates. More forcing conditions utilising *p*-toluenesulfonic acid at elevated temperatures have been utilised for highly electron-rich aldehyde substrates, whereas the employment of a benzotriazole additive was required for enolisable alkyl aldehyde substrates. In addition to the broad range of bicyclic oxabispidines prepared under the conditions described, a more synthetically challenging and structurally complex tricyclic derivative has also been successfully prepared.

Further to the investigations into the scope of the developed approach to the construction of such scaffolds, efforts to confirm the proposed Mannich-type cyclisation mechanism, both experimentally and computationally, are disclosed. Additionally, a number of NMR studies have been performed to confirm the stereochemistry of the family of oxabispidine derivatives.

With a library of enantiomerically-enriched oxabispidines in hand, manipulation of the nitrogen functionalities was undertaken to allow the preparation of further oxabispidine derivatives, which could have potential applications as ligands in asymmetric synthesis, as well as derivatives of interest to pharmaceutical industry partners.

Following this work, a programme of research centred on the utilisation of oxabispidine scaffolds within the arena of magnesium-mediated asymmetric deprotonation processes was undertaken. Initial investigations focused on the use of the phenyl-substituted bis-secondary oxabispidine, with studies into the formation of both the corresponding magnesium bisamide and lithium amide species. Such endeavours indicated that the chiral amine species must be introduced as the bis-HCl salt. Investigations into the use of such amide base species in the

deprotonation of 4-*tert*-butylcyclohexanone to generate the corresponding enantioenriched enol phosphate product were undertaken. Whilst under lithium-mediated conditions, promising levels of enantioselectivity could be achieved (73:27 er at -78°C), only poor to moderate yields of the desired product were attained. Similarly poor reactivity was observed with the corresponding magnesium-amide base counterpart, with no improvement in the selectivity of the deprotonation process. Altering the substituent of the oxabispidine scaffold to incorporate a more electron-donating group, and therefore a potentially more reactive magnesium amide, did not lead to the desired increase in yield. Furthermore, with a view to increasing the reactivity of the oxabispidine magnesium amide system, the employment of *N*-methylated oxabispidine derivatives, bearing both phenyl and methyl side arms, was studied to allow the generation of chelating alkyl magnesium amides. As with previous oxabispidine-derived magnesium amides, these base systems were screened in the deprotonation of 4-*tert*-butylcyclohexanone, but again only poor yields of the enol phosphate product were recovered (≤ 25% yield at room temperature) with no significant enantioselectivity being observed, despite significant experimental efforts.

Acknowledgements

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Abbreviations

3D	Three-dimensional
18-c-6	18-Crown-6
Ac	Acetyl
AcOH	Acetic acid
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl group
BtH	Benzotriazole
t-Bu	*tert*-Butyl
Cbz	Carbobenzyloxy group
CEDD	Centre of Excellence for Drug Discovery
d	Days
DCM	Dichloromethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DOS	Diversity-orientated synthesis
dr	Diastereomeric ratio
ee	Enantiomeric excess
EQ	External quench
er	Enantiomeric ratio
Et	Ethyl
EXSY	Exchange spectroscopy
FBDD	Fragment-based drug discovery
g	Grams
GCMS	Gas chromatography mass spectrometry
GSK	GlaxoSmithKline
h	Hours
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography

HTS	High-throughput screening
Hz	Hertz
IMS	Industrial methylated spirits
IQ	Internal quench
IR	Infrared
LOS	Lead-orientated synthesis
M	Molar
μM	Micromolar
Me	Methyl
Mes	Mesityl
mg	Milligrams
MHz	Megahertz
Min	Minutes
mmol	millimoles
M.pt.	Melting point
Ms	Methanesulfonyl
MWI	Microwave irradiation
nbd	Norbornadiene
NCE	New chemical entity
NMR	Nuclear magnetic resonance spectra; s – singlet d – doublet t – triplet q - quartet dd – doublet of doublets dt – doublet of triplets dq – doublet of quartets m - multiplet
nOe	Nuclear Overhauser effect

NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
Phth	Phthalimide
PMI	Principal moment of inertia
i-Pr	*iso*-Propyl
Quant.	Quantitative
R&D	Research and development
RT	Room temperature
SM	Starting material
(-)-sp	(-)-Sparteine
Temp.	Temperature
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	*p*-Toluenesulfonyl
TsOH	*p*-Toluenesulfonic acid

Contents

It should be noted that each Chapter is self-contained possessing individually associated experimental procedures and reference section.

Chapter 1

Development of a Flexible Route Towards the Synthesis of Optically-enriched Oxabispidines

Contents

1. Introduction

In 2014, the average life expectancy is approximately 80 years,[1] compared to around 45 years at the beginning of the twentieth century.[2] This dramatic increase is, in part, due to the discovery and development of medicines within the pharmaceutical industry. Having said this, the industry has faced unparalleled challenges, both financially and politically, particularly over the past two decades. Amongst these are the industry's diminished revenue growth, decreasing numbers of new chemical entity (NCE) approvals, and fewer drug candidates making it to late stage research and development (R&D) phases.[2] As a result, and particularly in relation to the progression of drug candidates through the R&D pipeline, over recent years a shift in the way lead compounds are generated, and indeed the types of compounds being targeted, has taken place.

1.1 Early Drug Discovery

Historically within drug discovery, natural products such as (-)-sparteine and the others depicted in **Figure 1.1** have, perhaps unsurprisingly due to their origins in nature, proven to be highly biologically-active species. Although (-)-sparteine itself has not been approved for human use, in many cases the high potency, selectivity, and ability to cross biological membranes displayed by natural products and their derivatives has meant they have been an important source of therapeutic agents for decades.[3]

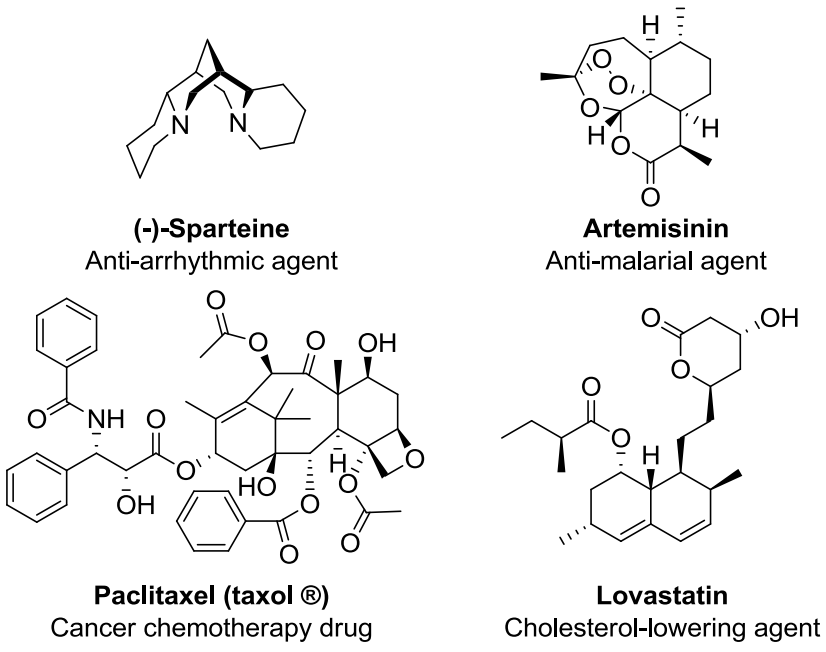


Figure 1.1: Biologically-active natural product species.

By the end of the 1980s, approximately 80% of pharmaceuticals were either natural products or derivatives thereof.[4] In general, it is believed that the high molecular complexity and the significant number of stereogenic centres within such species are the key attributes to their success as bioactive compounds.[5,6] Indeed, Artemisinin, Lovastatin, and Taxol (shown in **Figure 1.1**) represent a small proportion of natural compounds which display activity across a vast range of therapeutic areas. Having stated this, over the years, natural product research within the pharmaceutical industry has witnessed a decline, in part due to an emphasis on the use of relatively more time-efficient, often less labour intensive techniques, such as high-throughput screening (HTS) of synthetic libraries.

1.1.1 High-throughput Screening

High-throughput screening (HTS) has been the most dominant method of lead finding in drug discovery since the early 1990's.[7] This approach entails screening a vast collection of compounds (potentially >1000000) against a biological target of interest. The compounds that produce promising results undergo subsequent optimisation to deliver chemical leads. Success with this approach is thus closely linked to the type of molecules within the screening library. In relation to assessing the suitability of compounds within such libraries and the 'drug-like' characteristics of a collection of compounds, Lipinski *et al.* published a set of guidelines to assess the bioavailability of a candidate.[8] After studying the physicochemical properties of more than 2,000 drugs and candidate drugs in clinical trials, the criteria described take into account the molecular weight, the lipophilicity (logP), and consider the hydrogen-bonding donating and accepting ability of a compound. As the medicinal chemistry community became more focused on these physical properties of candidates, the screening of collections became more refined and HTS campaigns have led to the discovery of a number of important drugs (e.g. Imatinib).[7] Having stated this, although HTS is an effective way to source a large number of initial hit compounds, only a relatively small number of drugs actually reach the market, with hit rates as low as <0.001% for HTS of synthetic compound collections.[4]

1.1.2 Fragment-based Drug Discovery

More recently, fragment-based drug discovery (FBDD) has emerged as a complementary technique to high-throughput screening. FBDD utilises X-ray crystal structures of protein targets of interest to identify low molecular weight ligands (~150 Da) that bind effectively.[9,10]

Examples of typical fragments are depicted in **Figure 1.2**. This approach requires fewer molecules to be screened (relative to HTS) and, despite lower initial potency of screening hits due to their size, the fragments generally form high-quality interactions with the target. These hit fragments can then be elaborated using a structure-led optimisation process into potent lead compounds. As depicted in **Figure 1.2**, this optimisation process can often involve the linking of various fragments that are observed to interact with binding sites in close proximity to one another.[9]

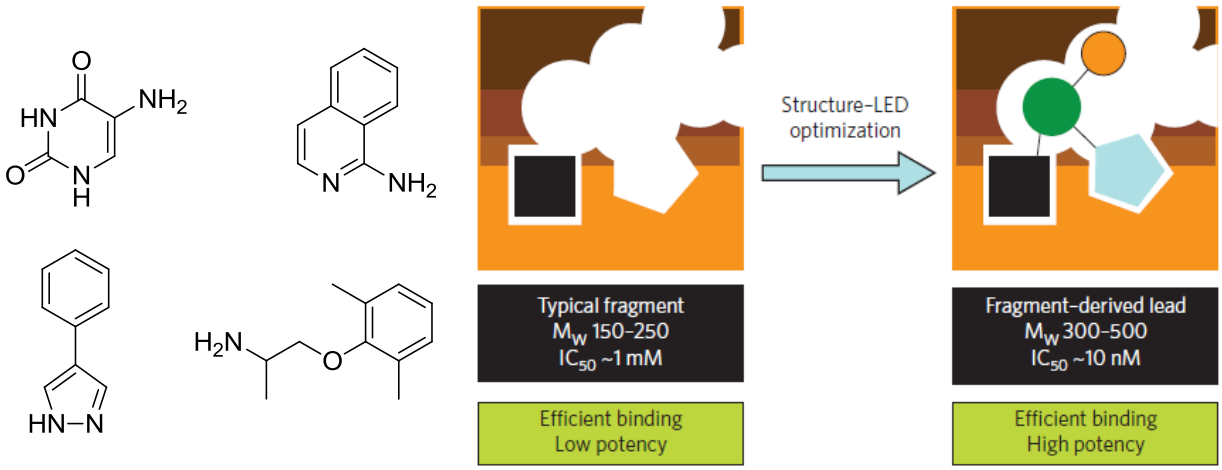


Figure 1.2: Typical molecular fragments and the general approach to fragment-based drug discovery (FBDD)[9]

1.2 3D Molecules Within Drug Discovery

The success of both fragment-based drug discovery and high-throughput screening is intimately linked to the collection of molecules screened. The sheer number of compounds required for HTS and the fragment-linking optimisation approach adopted in FBDD (**Figure 1.2**) has, in general, led to libraries containing aromatic/heteroaromatic-rich compounds. This is most likely a result of the desire of medicinal chemists to utilise robust, well-established methodologies, such as amide bond-forming reactions and metal-mediated coupling reactions which result in compound collections of predominantly sp^2-rich aromatic character.[10] Indeed, in 2010, MacDonald *et al*. reported a study carried out within the Respiratory CEDD at GSK, which focused on the classes of reactions carried out by medicinal chemists.[11] Of 577 reactions within the study period, 87% fell into just three classes: alkylations, condensations (amides and sulfonamides), and palladium-catalysed couplings. In particular, it was noted that reactions which generated new stereocentres were

distinct by their absence. Whilst a very specific example, there is a similar trend within the drug discovery industry in general, and Churcher *et al.* suggest that the reliance on such established and predictable reactions has inadvertently prejudiced pharmaceutical research to producing molecules with poorer drug-like properties.[12] In a similar vein, Nelson and MacLellan highlight the fact that "around half of all known compounds are based on just 0.25% of the known molecular scaffolds," and, as such, if R&D are using such easily accessible scaffolds (often of predominantly aromatic character) to guide the synthesis of new lead compounds, they may be biasing their view of which structures are biologically-relevant.[13]

In an effort to demonstrate the ubiquity of planar aromatic compounds within fragment libraries and assess the biological relevance of such compounds, an analysis of the molecular shape of selected fragment libraries was carried out by the 3D-Fragment Consortium.[14] Using principal moments of inertia (PMI) calculations[15] molecules were separated into those with 'rod-like', 'disc-like' and 'sphere-like' characteristics, and depicted as a triangular graphical output, as shown in **Figure 1.3**. Graph (a) represents commercially available fragment libraries, where the majority of the compounds lie towards the rod and disc like structures, i.e. generally planar, aromatic, and sp^2-rich. On the other hand, graph (b) represents compounds that have been screened in humans. It can be seen that these molecules populate more of the centre of the graph, moving towards the sphere-like structures, meaning that "fragments contained within clinically evaluated compounds appear to have greater 3D conformations than do those in fragment libraries".[14]

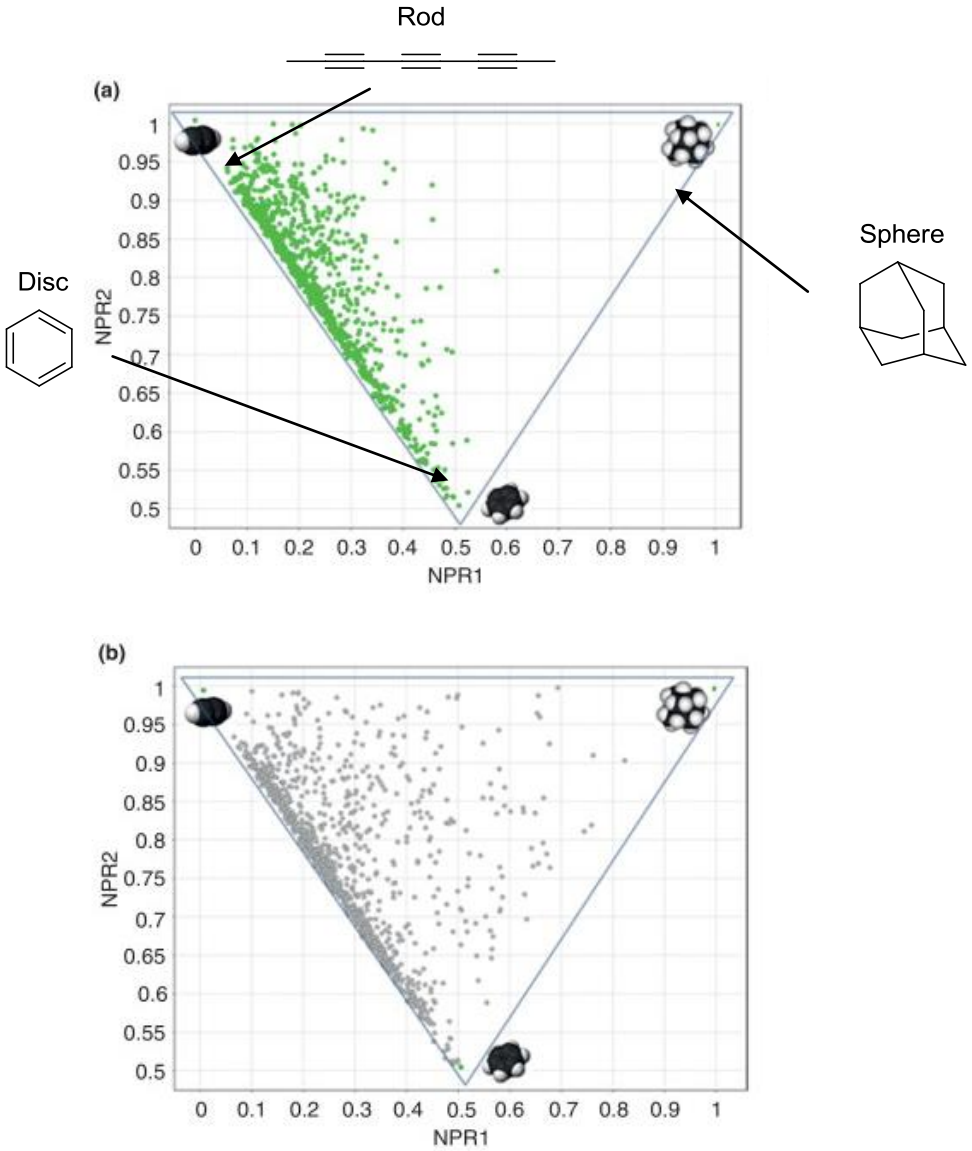


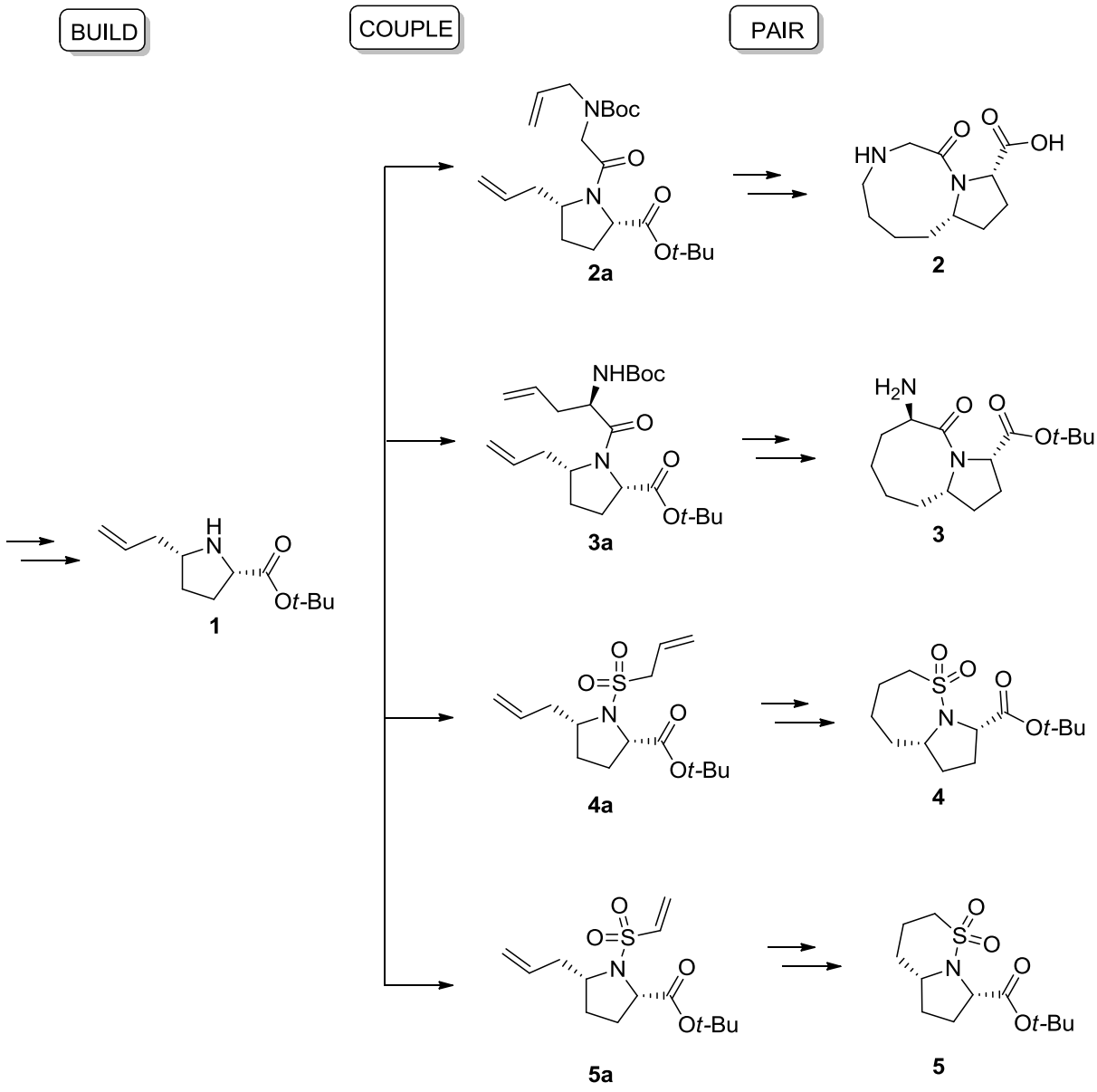
Figure 1.3: (a) PMI graph of selected fragment libraries; (b) PMI graph of clinically evaluated compounds[14]

Limiting compound libraries to sp^2-rich planar molecules intrinsically restricts the biological targets available for exploration. By extending the scope of screening libraries to incorporate more sp^3-rich, 3D-like molecules, a more diverse area of chemical space would be covered, which, in turn, might prove beneficial to the investigation of more challenging biological targets.[10] Increasing the molecular shape and complexity of the fragments for screening gives the molecules more natural product-like character, and, as mentioned previously, it is believed that the structural complexity and stereogenic centres embedded within natural products are important to their biological activity and thus their suitability as drugs.[5,6] In 2009, Lovering *et al.* evaluated a collection of compounds ranging from the discovery stage to marketed drugs based on the extent of the saturation of the molecule (measured by Fsp^3,

which is equal to the number of sp^3 carbons / total number of carbons) and the number of stereogenic centres present.[6] It was found that upon clinical progression, the average Fsp^3 increased by 31% from the discovery stage to market, showing that molecules with increased saturation are more likely to progress through the development phases of drug discovery. A similar trend was observed with regards to the number of stereogenic centres, with 46% of discovery phase compounds possessing one or more chiral centres compared to 61% within drugs.[6] The 3D nature that saturation imparts on a molecule may also result in increased selectivity at the target, resulting in fewer undesirable effects during biological screening, namely toxicity issues, which play a key role in the high attrition rates observed in the pharmaceutical industry. Indeed, a further study by Lovering involving the screening of a set of Pfizer discovery compounds within off-target activity assays, provides evidence for this argument.[16] This investigation illustrated that as both the saturation and number of stereogenic centres within the compounds increased, so did the selectivity or, more specifically, the promiscuity decreased (where promiscuity is defined as the number of targets inhibited at greater than 50% at 10μM divided by the number of targets tested).

1.2.1 Diversity-orientated Synthesis

With the potential advantages posed by more sp^3-rich, 3D-like molecules described above, a movement has developed over the past decade, often referred to as diversity-orientated synthesis (DOS).[10] DOS aims to quickly and efficiently generate libraries of molecules with diverse molecular shape and stereochemical properties. The DOS ethos was employed by Young *et al.* in their generation of a library of varied proline-derived bicyclic scaffolds using a build-couple-pair approach.[10] As depicted in **Scheme 1.1**, from enantiomerically pure proline derivative **1**, a variety of olefin-containing side-chains were introduced *via* an amide coupling process. It should be noted that it is at these early 'build' and 'couple' stages that the stereochemistry of the final fragment was embedded. From compounds **2a**-**5a**, metathesis and reduction reactions were undertaken to generate a selection of skeletally diverse chiral fragments. Fragments **2-5**, shown below, are only a small proportion of the molecules prepared; a further two proline-based starting materials were also used, generating an even greater number of bicyclic and spirocyclic molecules.[10]

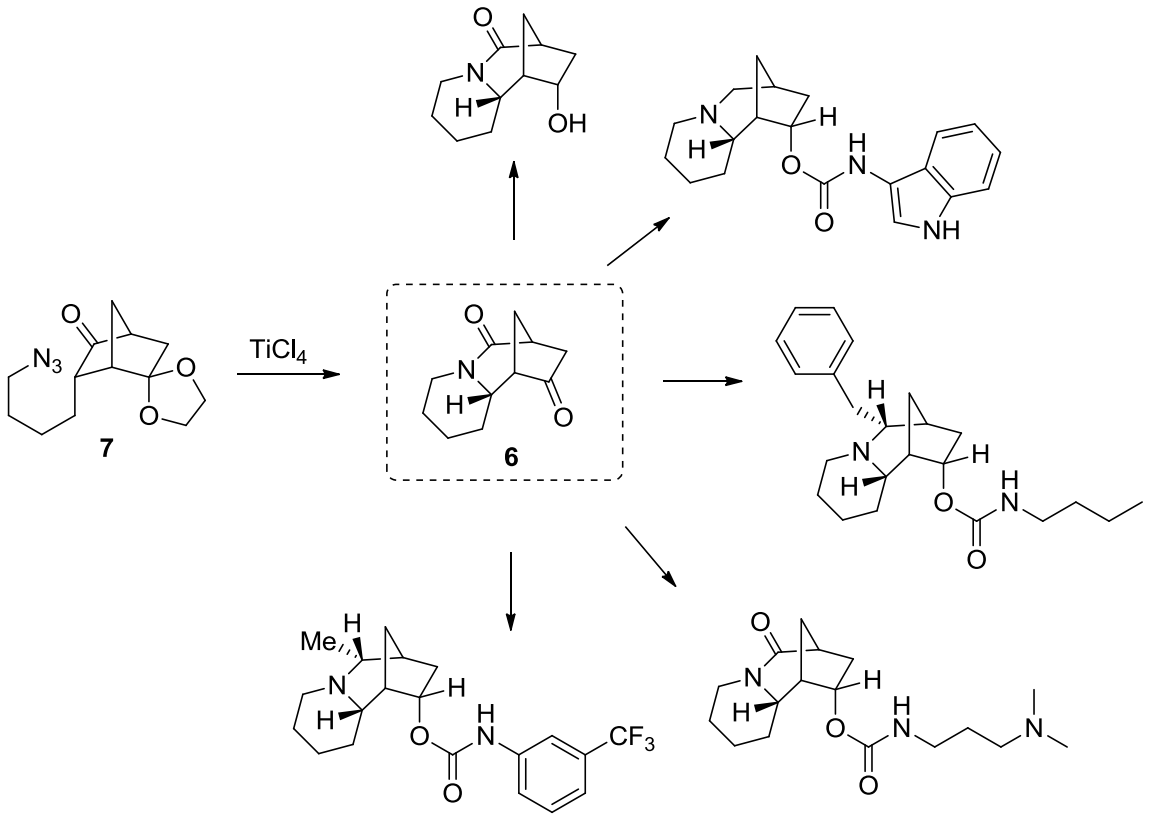


Scheme 1.1

The great advantage of such methodology is that from a single starting material, a diverse collection of enantiomerically-enriched, skeletally diverse, and sp^3-rich fragments has been prepared, with the potential for the library to be expanded further by simply utilising the opposite enantiomer of the starting material.

More recently, Aubé and co-workers designed a library of 3D-like fragments based on alkaloid natural products.[3] In addition to generating scaffolds based on the structurally diverse Stemonaceae, Cylindricine, and Amaryllidaceae families, they also synthesised a range of molecules based on the lupin alkaloid family, a member of which is the natural

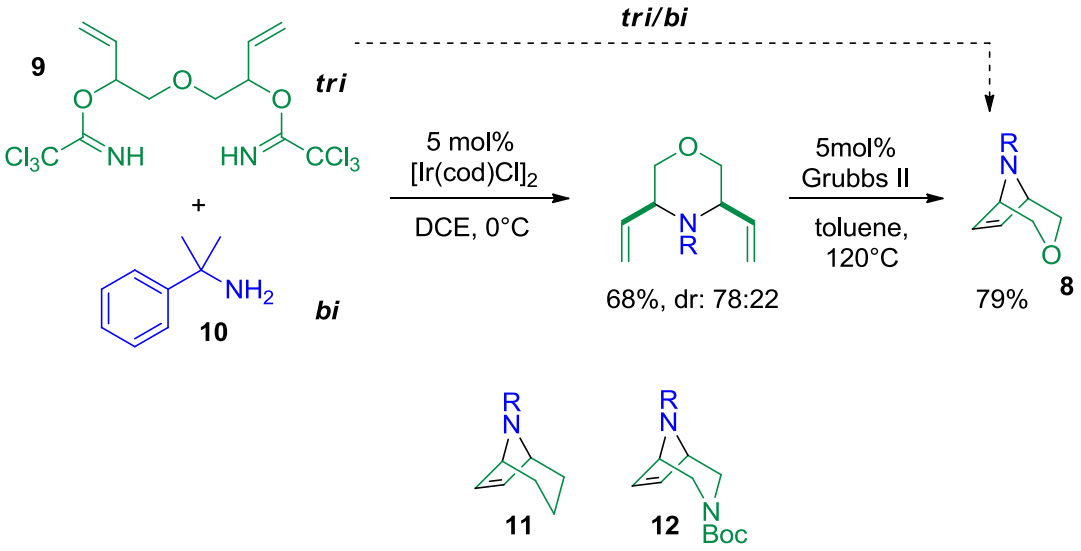
product (-)-sparteine. Common intermediate **6** was generated through an intramolecular Schmidt reaction from azide **7**, and from **6**, a range of more complex fragments were generated *via* one or two step processes (**Scheme 1.2**).



Scheme 1.2

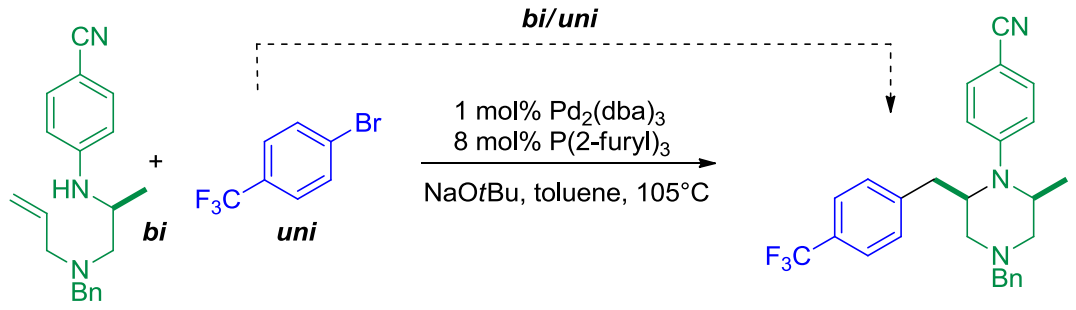
As the concept of DOS becomes increasingly prevalent, and novel reaction sequences to generate diverse 3D scaffolds are developed, a method to compare the relative effectiveness of unrelated synthetic approaches will be useful. In relation to this, Nelson and MacLellan have developed a hierarchical framework in which the number of new bonds formed to each starting material is considered.[13] The framework is a measure of the ability of each approach to increase molecular complexity (from starting materials to product) with the most powerful approaches being those where more bonds are formed to individual starting materials, or when a greater number of starting materials are employed, thus allowing more variation in the scaffolds generated. An illustrative example is shown in **Scheme 1.3**, in which the bridged morpholine compound **8** is prepared from the Ir-catalysed reaction of bis-allylic trichloroacetimate **9** and amine **10**, a transformation classified as a tri/bi process.[13,17] The combination of tri-connective building blocks similar to **9** with bi-connective amines allowed

the preparation of bridged bicyclic products (**11** and **12**), structures of greater complexity than the corresponding starting materials.

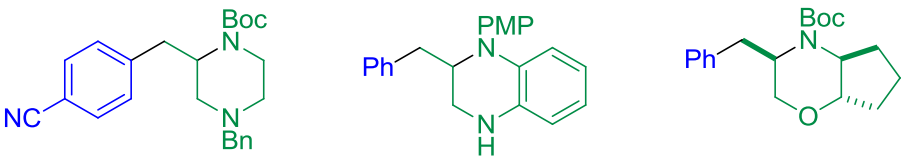


Scheme 1.3

If we compare the above tactic to a bi/uni approach, such as the example depicted in **Scheme 1.4**, we can see that although diversity can be introduced by making slight adjustments to the building blocks, the increase in structural complexity from starting materials to product is significantly less, and thus within Nelson's framework, this is deemed a less powerful approach towards diverse scaffolds.[13,18]

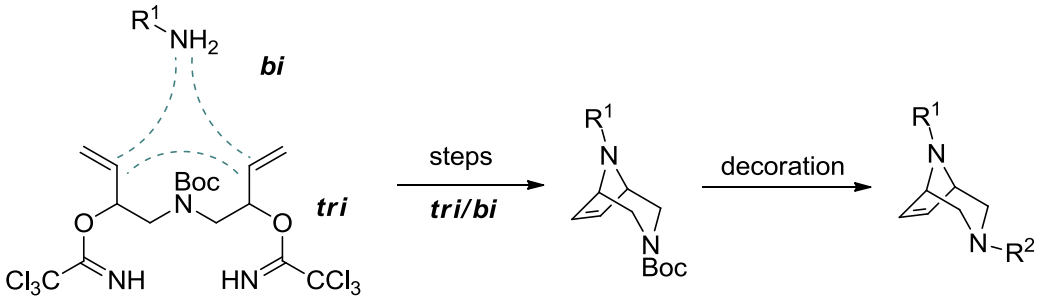


Examples of alternative scaffolds bulid through this approach:



Scheme 1.4

Whilst DOS addresses the issue of increased diversity and complexity in the molecular scaffolds generated, often these fragments lie well outside the physiochemical parameters for successful lead compounds. For this reason, one of the most recent concepts to evolve within drug discovery is that of lead-orientated synthesis.[12] Taking inspiration from DOS, diversity within the structures generated is still at the core of lead-orientated synthesis, however the molecular properties of the final compounds are also of key importance. Thus, the synthetic methods adopted, should allow access to scaffolds, which have, for example, the logP values, the molecular size and shape, and the polar group tolerance observed in lead-like molecules.[12,19] The bridged bicyclic structures discussed in **Scheme 1.3** were highlighted by Nelson and Marsden as a useful illustration of the LOS concept.[19] The initial tri/bi process can facilitate the generation of various scaffolds (**Scheme 1.5**), but it is *via* the "decoration" step that we can generate structures possessing physiochemical properties within the parameters (e.g. Lipinski's rules) required for more lead-like molecules, and thus establish a potentially more promising starting point for the development of novel therapeutic agents.



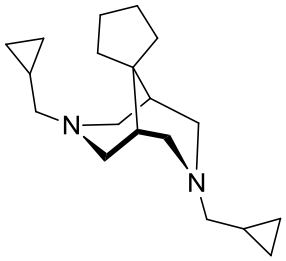
Scheme 1.5

1.3. Bispidines and Oxabispidines

The previous sections have described the recent focus within drug discovery towards more sp^3-rich, structurally complex fragment collections, particularly within the DOS movement. The examples shown in **Scheme 1.2** draw particular attention to the attractive structural features that bispidine-type cores possess, namely the inherent 3D structure and the potential for the incorporation of stereogenic centres. The bispidine moiety has a rigid cage-like structure, with the 3,7-diazabicyclo[3.3.1]nonane skeleton sitting preferentially in a chair-chair conformation (**Figure 1.4**).[20]

Figure 1.4: Bispidine structure.

In addition to being identified in the natural product (-)-sparteine and related chiral ligands (*vide infra*), the bispidine framework has also been highlighted as an attractive feature in many pharmaceutical targets, for example in αa4β2 nicotinic acetylcholine receptor ligands as potential neuroprotective agents.[21] Furthermore, the bispidine moiety is at the core of Tedisamil, a Phase III clinical trial compound in development by Solvay Pharmaceuticals for the treatment of cardiac arrhythmia (**Figure 1.5**). [22]



Tedisamil

Figure 1.5: Example of bispidine-based drug molecule.

Closely related to the bispidine scaffold, is that of oxabispidines. These molecules have the same rigid chair-chair conformation as bispidines, except in their case the methylene bridge is replaced with an oxygen atom (**Figure 1.6**). With this additional heteroatom in place it is believed that, in comparison to their bispidine counterparts, a greater number of synthetic avenues could be explored, and thus potentially more convenient access to oxabispidine scaffolds of greater structural diversity could be achieved.

Figure 1.6: Oxabispidine structure.

Akin to bispidines, over the past decade oxabispidine motifs have been embedded in a number of pharmaceutical targets, and have been reported to exhibit useful biological effects. AstraZeneca have utilised such motifs as atrial repolarisation-delaying agents in the treatment of cardiac arrhythmia, for example as embedded within the development compound depicted

in **Figure 1.7**.[23] Furthermore, such structures have had reported uses as mTOR and PI3 kinase inhibitors (Wyeth),[24] and Factor Xa inhibitors (GlaxoSmithKline).[25]

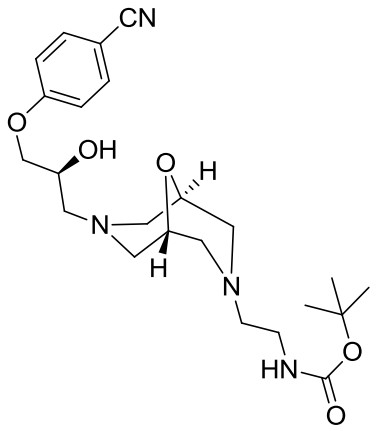
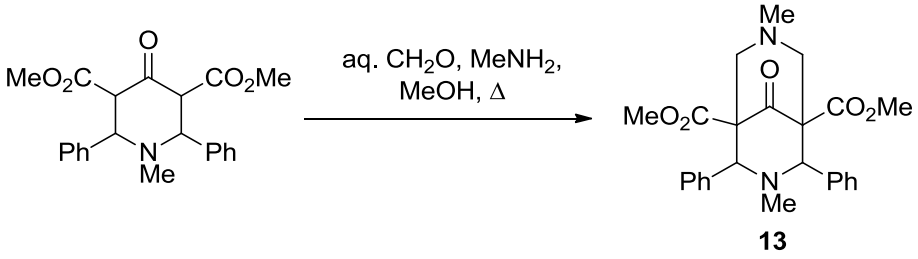


Figure 1.7: Example of oxabispidine-based drug candidate.

With the emerging potential that such sp^3-rich scaffolds hold within the field of drug discovery, in addition to the advantages lead compounds containing chiral centres possess, efficient and flexible access to a wide range of optically-enriched oxabispidine derivatives would be highly beneficial.

1.3.1 Synthesis of Bispidines

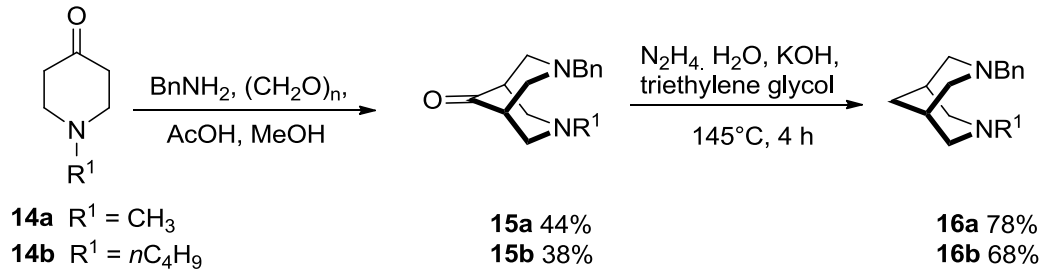
The earliest report of the preparation of a bispidine-type compound was in 1930, when Mannich and Mohs discovered that reacting 4-piperidone-3,5-diester with aqueous formaldehyde and methylamine in hot methanol led to the bicylic diamine **13** (**Scheme 1.6**).[26]



Scheme 1.6

For the synthesis of a simple bispidine core, the most common approach is still based on Mannich and Mohs initial discovery and utilises a double Mannich reaction and subsequent Wolff-Kishner type reduction. As shown in **Scheme 1.7**, condensation of a 4-piperidone derivative (**14a** and **14b**) with a primary amine and paraformaldehyde provides the

corresponding 9-bispidinone intermediates (**15a** and **15b**), albeit in fairly low yield. Upon subjection to hydrazine and KOH reduction, the desired bispidine products **16a** and **16b** were recovered in good yields.[27]



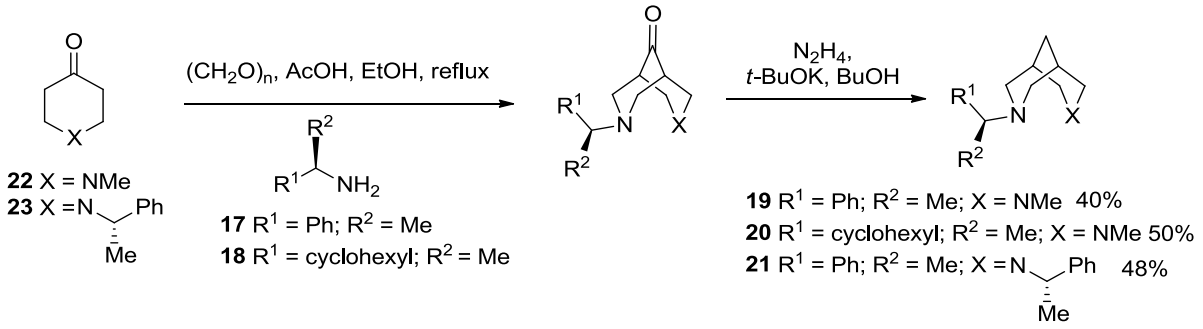
14a $R^1 = CH_3$
14b $R^1 = nC_4H_9$

15a 44%
15b 38%

16a 78%
16b 68%

Scheme 1.7

If there was a requirement for more complex bispidine structures or, indeed, if the incorporation of stereogenic centres was desired, the simplest way of doing so would be to introduce the chiral information *via* the substituents on the nitrogen atoms. Beak *et al.* synthesised a number of bispidine ligands bearing an α-stereogenic *N*-alkyl sidechain with a view to utilising these within asymmetric synthesis (*vide infra*).[28] Using the same double Mannich/Wolff-Kishner protocol described previously, this time employing chiral primary amines **17** and **18**, chiral bispidine ligands **19-21** were prepared from piperidone starting materials **22** and **23** in yields of 40-50% (**Scheme 1.8**).[28]

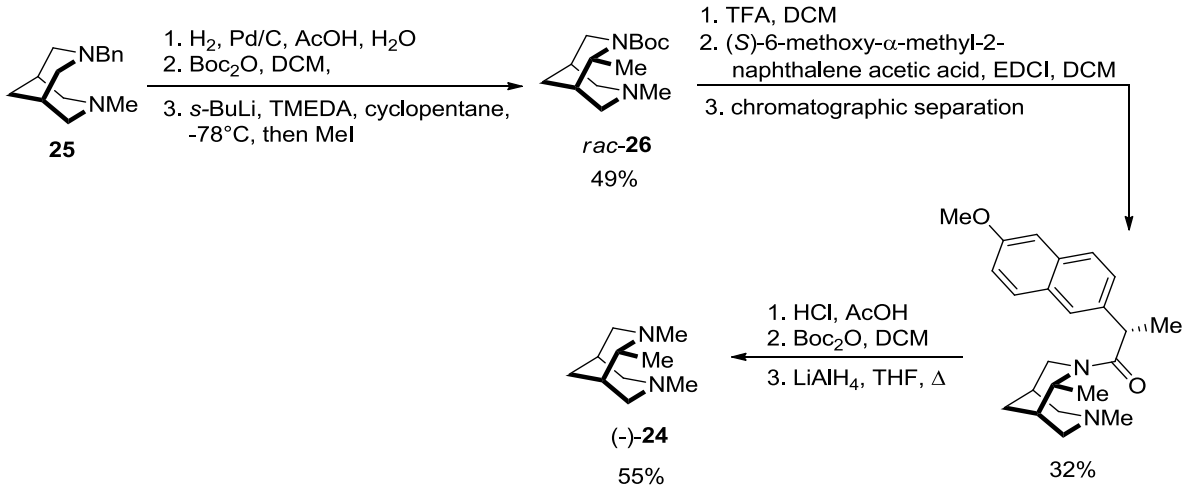


Scheme 1.8

Whilst a wide variety of bispidine compounds could be prepared in this manner, the above method is not particularly efficient. With regards to building up a collection of such molecules, e.g. for a pharmaceutical fragment library, points of late stage diversity are limited. Additionally, the elaboration of simple bispidine cores in the manner illustrated by this approach is the least synthetically demanding strategy. A much more challenging

endeavour is the synthesis of bispidines with substitutents embedded in the [3.3.1]nonane skeleton.

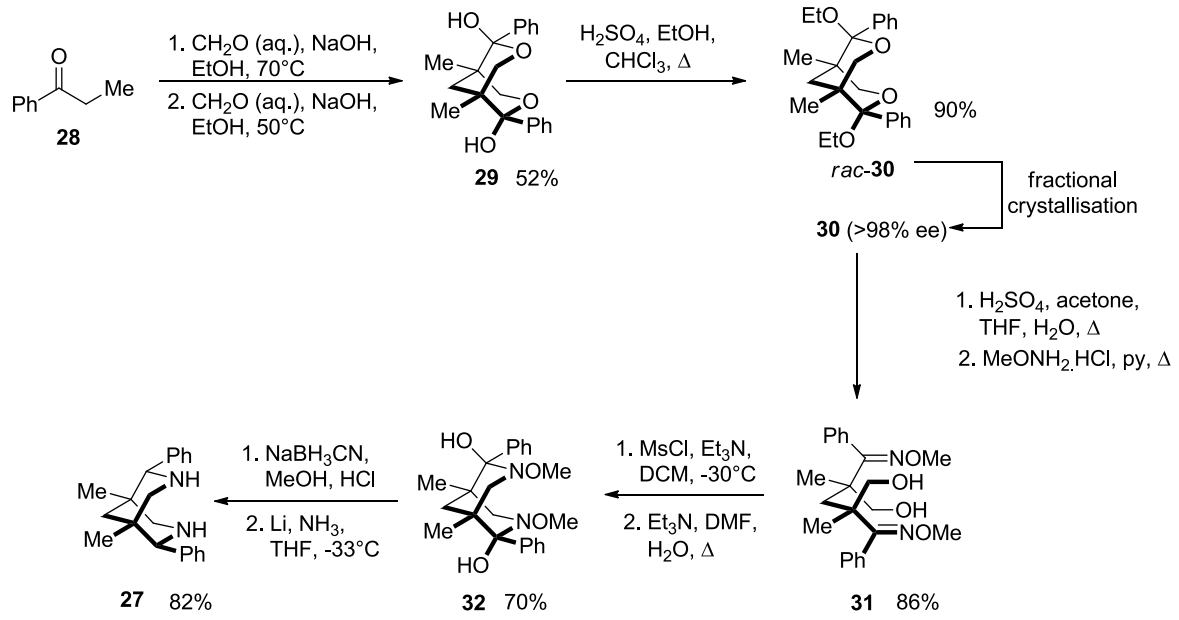
In 2004, Kozlowski *et al.* described the stereoselective preparation of *N*,*N*',2-*endo*-trimethylbispidine **24** from an achiral bispidine starting material (**Scheme 1.9**).[29] Debenzylation and *N*-Boc protection of **25** followed by α-lithiation and trapping with methyl iodide provided *rac*-**26** in 49% yield. Replacement of the Boc group with a bulky chiral protecting group allowed facile separation of the resulting diastereomers which, after cleavage of the amide and subsequent methylation, afforded the desired enantiopure bispidine **24** in moderate yield. Whilst this route does indeed give access to an enantio-enriched bispidine product, eleven steps, including the preparation of starting bispidine **25**, are required to give an overall yield of 4 % of the target molecule, meaning the process is not preparatively efficient.



Scheme 1.9

A theoretically different tactic to bicyclic bispidines containing a chiral core was described by Corey and Chau.[30] As depicted in **Scheme 1.10**, 2,6-di*endo*-diphenylbispidine, **27**, bearing methyl groups at the bridgehead positions was prepared from the simple starting material, propiophenone **28**. Treatment of **28** with formaldehyde under basic conditions led to hemiketal intermediate **29**, which, after conversion to *rac*-bisketal **30**, was made enantiomerically pure by fractional crystallisation to give **30** with an ee of >98%. Hydrolysis followed by treatment with *O*-methyl hydroxylamine gave open-chain intermediate **31**, which, upon mesylation, was cyclised to give bispidine **32**. Reduction of the hemiaminal

moieties and removal of the methoxy *N*-substituents provided the target bispidine product **27** in 11% overall yield.



Scheme 1.10

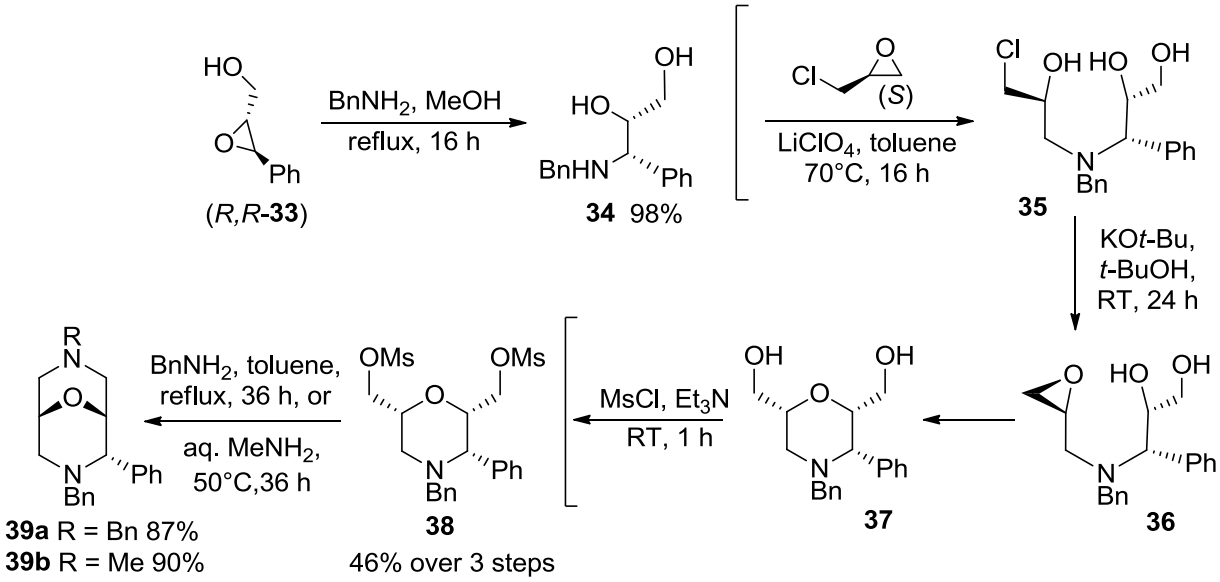
Again, in this case, a fairly extensive number of steps are required to prepare this desired chiral bispidine product and, in addition, this route also suffers from lack of opportunity for late stage diversity. For alternative substituents on the bispidine backbone the ketone starting material would have to be changed.

1.3.2 Synthesis of Oxabispidines

As shown in the previous section, the main limitations to the synthesis of a varied array of bispidine scaffolds are the lengthy developed synthetic sequences, and the limited points of diversity within the established routes. In the case of oxabispidines with the additional heteroatom in place, it is believed that a greater variety of possibilities are available for more convenient synthetic access to an array of scaffolds.

The majority of published research into synthetic routes towards oxabispidines has been reported by Breuning *et al*. During their studies into mono- and disubstituted morpholines as potential pharmaceutical targets,[31] a route to 2,6-dihydroxymethyl-substituted morpholines was developed, which they found could be extended to the formation of 2-substituted 9-oxabispidines.[32] As depicted in **Scheme 1.11** the synthetic sequence started with commercially available chiral epoxide **33**. Regioselective ring opening of this epoxide with

benzylamine delivered hydroxyl amine intermediate **34**. At this stage, a three step one-pot procedure was employed: $LiClO_4$-mediated addition to (*S*)-epichlorohydrin provided intermediate **35**, which after base-induced cyclisation produced epoxide **36** followed by subsequent intramolecular attack, to deliver morpholine **37**. Activation *via* the dimesylate species **38**, followed by attack with a primary amine, afforded the enanatiomerically-pure 2-substituted oxabispidine products **39a** and **39b** in moderate overall yields of 39% and 41% from **34**, respectively.



Scheme 1.11

Further modification of these derivatives could be achieved *via* debenzylation under hydrogenation conditions to give the free diamine **40** and the monomethylated amine **41** in excellent yields of 90% and 94%, respectively.[32]

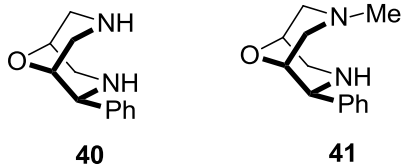
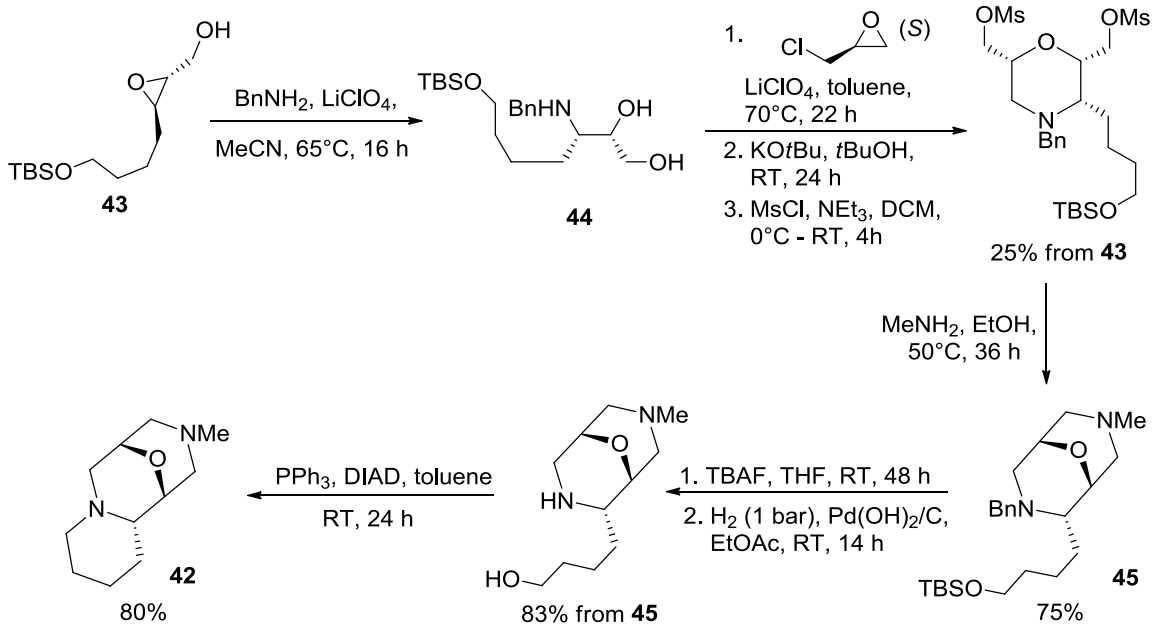


Figure 1.8

Whilst this establishes an expedient synthesis with a relatively short number of synthetic steps to the desired enantiopure oxabispidine products, a key limitation with this route is the lack of flexibility with regard to the substituent on the oxabispidine core. To alter this group,

a new chiral epoxide starting material would have to be sourced, or indeed synthesised, adding to the expense and complexity of the overall synthetic sequence.

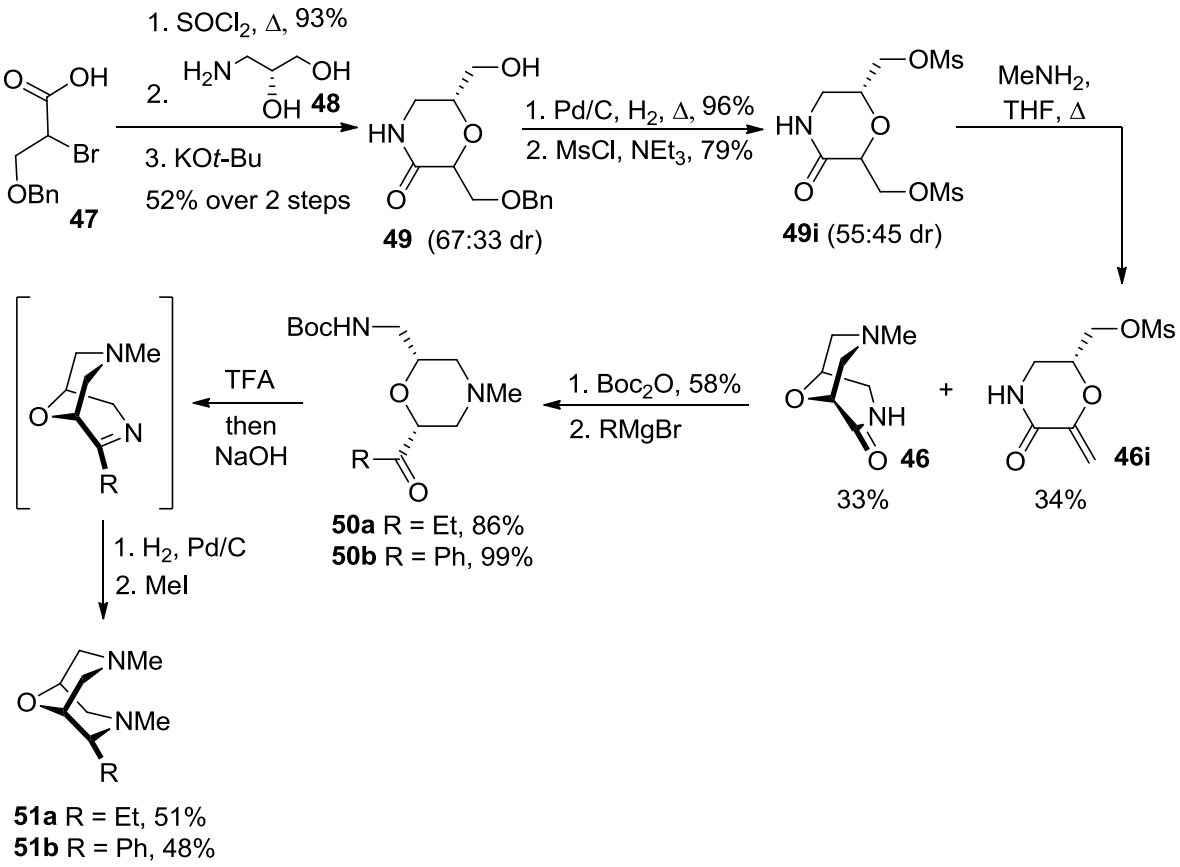
Breuning also utilised the above route for the preparation of a tricyclic oxabispidine derivative **42**, which possesses greater complexity and sp^3-character (**Scheme 1.12**).[33] Starting from known epoxy-alcohol **43**, ring opening with benzylamine gives intermediate **44**. Employing the same three step, one-pot procedure, described previously, yielded oxabispidine **45**, with an alkyl chain bearing a protected alcohol. Deprotection of the alcohol and amine moieties, followed by subjection to Mitsunobu conditions provided the desired tricyclic product **42** in 12% overall yield with ≥98% enantiopurity.



Scheme 1.12

In 2009, Breuning and co-workers addressed the issue of late stage variation at the 2-position of the oxabispidine core with the development of a conceptually different route, utilising oxabispidin-2-one **46** as a common late stage intermediate (**Scheme 1.13**).[34] This approach starts from known acid **47**,[35] which after activation and coupling with **48**, is cyclised under basic conditions to give morpholine intermediate **49** as a mixture of diastereomers. Deprotection of **49** followed by mesylation, and subsequent reaction with methylamine provided common intermediate **46** in 33% yield from the *cis*-mesylate intermediate, along with α,β-unsaturated morpholin-2-one by-product **46i** in similar yield derived from the *trans*-mesylate isomer. Intermediate **46** could then be Boc-protected and treated with a variety of

Grignard reagents (ethylmagnesium bromide and phenylmagnesium bromide in the example below) to give ketone substituted morpholines of the type **50**, which after Boc deprotection, cyclisation, reduction, and methylation provided the desired chiral 2-substituted oxabispidines **51** in good yields.

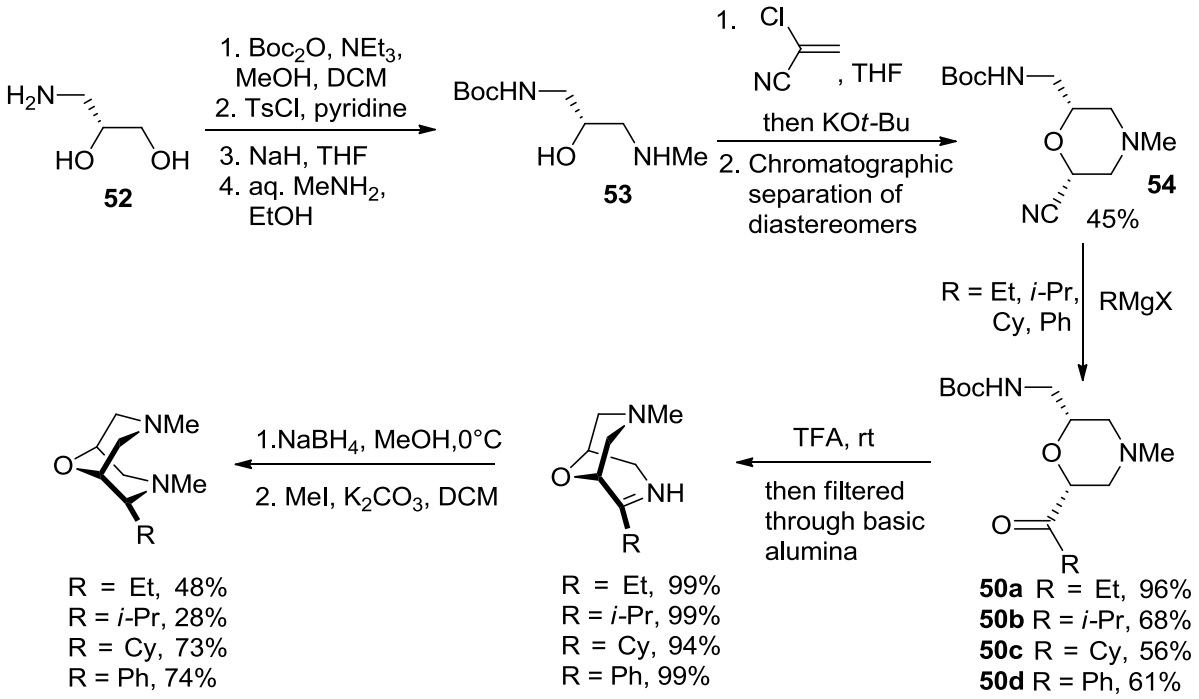


Scheme 1.13

Whilst this route addresses, to some extent, the issue of late stage diversification, another potential limitation is present in the form of accessibility of the required Grignard reagents. For simple Grignard reagents such as EtMgBr and PhMgBr this does not pose a problem, however, to gain access to more elaborately substituted oxabispidines the required reagents may not be commercially available and would have to be prepared. Additionally, the cyclisation step to generate the common intermediate **46** is relatively low yielding as a result of only the *cis* isomer of **49i** undergoing cyclisation. This along with the recovery of unwanted by-product **46i** also proved detrimental to the efficiency of the process.

The most recent route to 2-substituted oxabispidines developed by Breuning *et al*. also utilises a key chiral intermediate from which a range of derivatives can be synthesised.[36] Starting from commercially available chiral aminodiol **52**, a few simple synthetic

transformations provides aminoalcohol intermediate **53** (**Scheme 1.14**). Conjugate addition of **53** to chloroacrylonitrile, followed by base-induced cyclisation, provided morpholine intermediate **54** as a separable mixture of diastereomers (58:42 dr). The major isomer *cis*-**54** was then treated with a variety of Grignard reagents to afford amino ketones **50**, which, after the previously described deprotection, cyclisation, reduction, and methylation protocols delivered the desired oxabispidine products in good yields. As with the previous approach to optically-enriched oxabispidines, the opportunity for late stage diversity is an attractive feature of this route, however the lack of significant diastereoselectivity in the generation of intermediate **54** from **53** does impact the overall efficiency of this route.



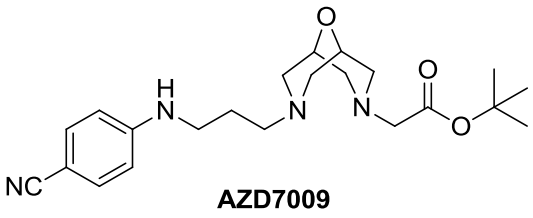
Scheme 1.14

Whilst a number of successful routes that allow access to bispidine and oxabispidine scaffolds have been described in the literature, in many cases the extensive number of steps required within the synthetic sequence or the lack of opportunity for late stage diversity could be considered disadvantages. Considering the sp^3-rich nature and associated molecular shape of such motifs, and, as such, the great potential they have within the recent diversity-orientated synthesis movement within the drug discovery process, the development of efficient and flexible routes towards such molecules would be highly advantageous.

2. Previous and Proposed Work

2.1 Previous Work

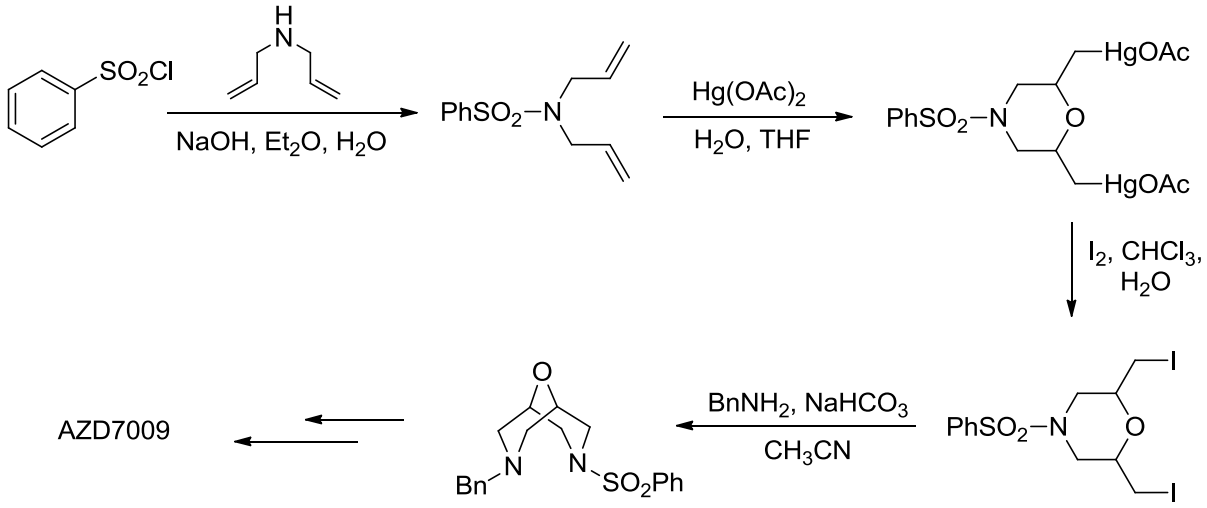
As discussed previously, oxabispidines have been reported as key fragments of more complex molecules with potential pharmaceutical properties. A more specific example published by AstraZeneca in a 2003 patent is the compound AZD7009 shown in **Figure 1.9**. AZD7009 was a compound in early clinical trials en route to the development of a drug for the treatment of cardiac arrhythmia.[37]



AZD7009

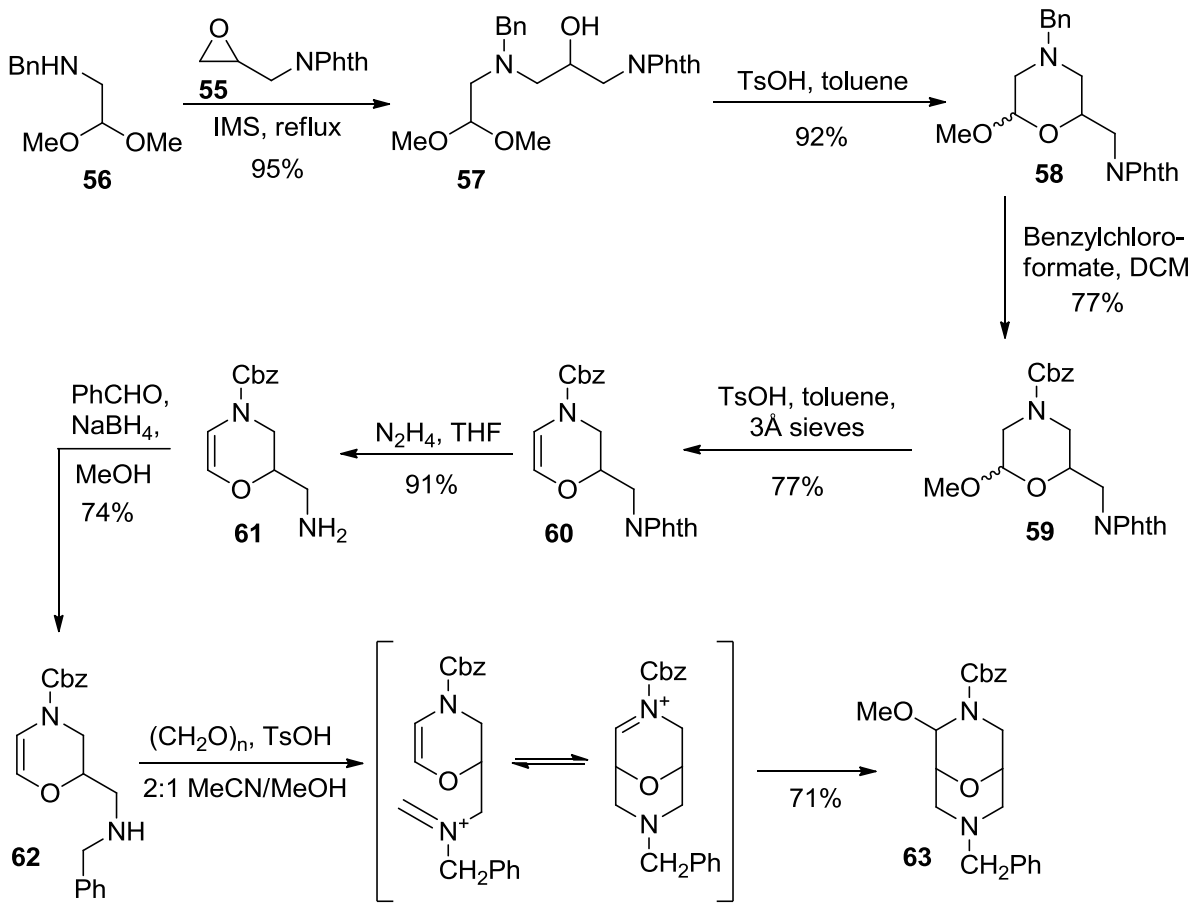
Figure 1.9: AstraZeneca development compound.

The initial development route towards the preparation of this compound, starting from benzenesulfonyl chloride, is depicted in **Scheme 1.15**.[38] Although a relatively simple synthetic sequence, a significant drawback is evident in the utilisation of stoichiometric mercury acetate. The extremely toxic nature of mercury limited the use of this sequence in future development studies, and investigations into alternative routes to such oxabispidine scaffolds were initiated.



Scheme 1.15

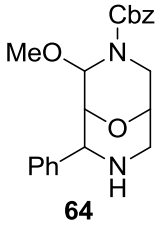
As part of this search for an expedient route to oxabispidine motifs, a novel intramolecular Mannich cyclisation was developed.[39] The synthetic sequence in which this cyclisation step is involved is similar to, although predates, Breuning's approach to oxabispidines.[32,33] More specifically, this route begins with the regioselective opening of an epoxide with an amine. As shown, the commercially available 2,3-epoxypropylphthalimide **55** was opened with benzyl-protected amine **56** (**Scheme 1.16**). The acid-catalysed cyclisation of intermediate **57** to form morpholine species **58** was achieved with *p*-tolunesulfonic acid in refluxing toluene and a subsequent protecting group switch from *N*-benzyl to *N*-carbamate was required to allow the following elimination step to proceed. Removal of the phthalimide moiety using hydrazine furnished oxazine **61**, and reductive amination was then performed to produce benzylamine **62**, which upon treatment with formaldehyde and *p*-toluenesulfonic acid, underwent the previously mentioned Mannich process to yield oxabispidine **63**.



Novel intramolecular Mannich cyclisation

Scheme 1.16

Whilst the desired oxabispidine product **63** was indeed synthesised, upon the preparation of benzyl-protected amine **62** an unexpected side product was also isolated in 5% yield. As depicted in **Figure 1.10**, the side product in question was oxabispidine **64**, bearing a phenyl substituent in the 2-position.



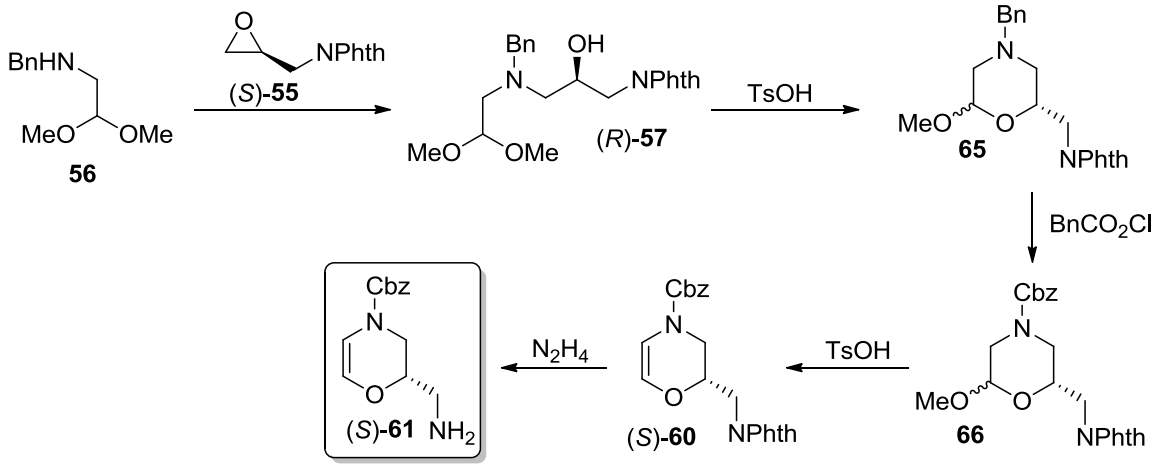
64

Figure 1.10: Side product isolated from AstraZeneca development route.

This structure was recognised as a potentially synthetically useful molecule. Based on this, collaborative interactions between AZ and our laboratory recognised the potential to efficiently synthesis a range of oxabispidine scaffolds incorporating a variety of substituents on the bicyclic skeleton. The potential to embed a diverse range of substituents, in combination with the sp^3-rich 3D-like nature of such oxabispidine molecules, would make them ideal candidates for inclusion in 3D fragment libraries, such as those being generated through diversity-orientated and lead-orientated synthesis (*vide supra*). Furthermore, if such structures could be generated in an asymmetric fashion, they may prove even more attractive to pharmaceutical partners. It was also noted that such enantiomerically-enriched oxabispidines would construct a chiral environment similar to that induced by (-)-sparteine and related ligands, and thus could find additional utility within asymmetric synthesis (*vide infra*).

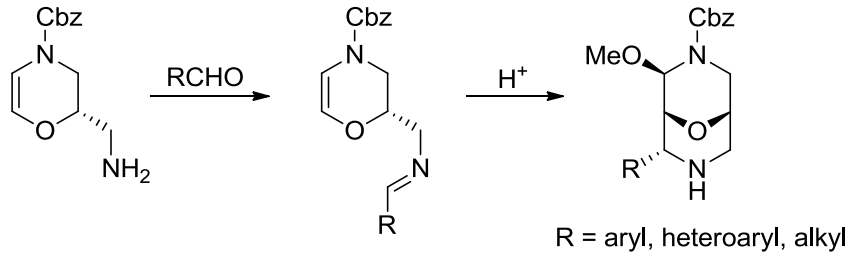
2.2 Proposed Work

With a route to oxazine **61** already in place, the programme of work described here was initiated to develop an efficient route towards enantio-enriched **61** and, in turn, a collection of enantiomerically-enriched oxabispidines. Of key importance to the synthesis of a broad range of oxabispidine scaffolds is the requirement for access to multigram quantities of chiral amine **61** in an expedient manner, thus the route developed must be amenable to scale-up. With this in mind, initial work will focus on conditions to efficiently access **61**, from the optically pure epoxide, (*S*)-2,3-epoxypropylphthalimide (*S*)-**55** *via* the route proposed in **Scheme 1.17**.



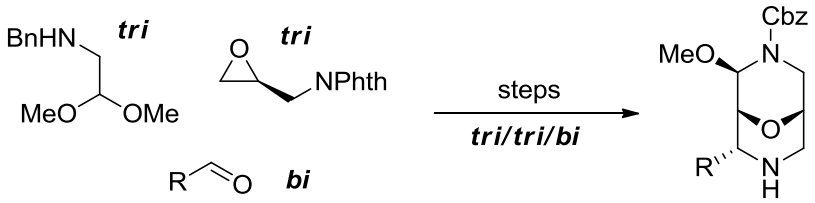
Scheme 1.17

With oxazine (*S*)-**61** in hand, development and optimisation of an approach for the selective synthesis of **64** will be undertaken; the proposed pathway is illustrated in **Scheme 1.18**. With optimised conditions in hand, attention will then be focused on the preparation of a collection of enantiomerically-enriched oxabispidines. Generation of imines of the type shown in **Scheme 1.18** will allow access to oxabispidines with a range of substituents in the α-position possessing a variety of steric and electronic properties (**Scheme 1.18**).



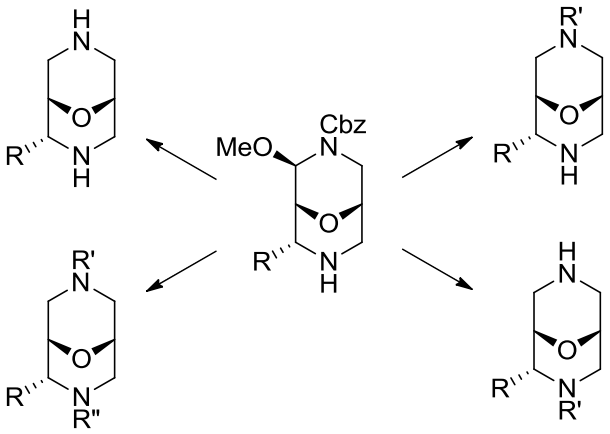
Scheme 1.18

It is pertinent to note that, within Nelson's framework discussed earlier (*section 1.2.1*), this synthetic methodology would be classified as a tri/tri/bi process (**Scheme 1.19**) and thus could be considered to be an extremely powerful approach towards potentially lead-like scaffolds.[13]



Scheme 1.19

With a view to utilising these compounds as fragments within drug discovery, the carbamate protecting group and methoxy unit will be removed, and investigation into the manipulation of the nitrogen functionality will be undertaken (**Scheme 1.20**).

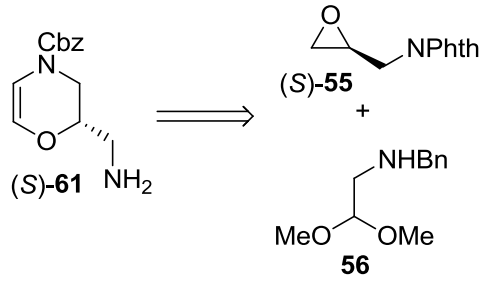


Scheme 1.20

3. Results and Discussion

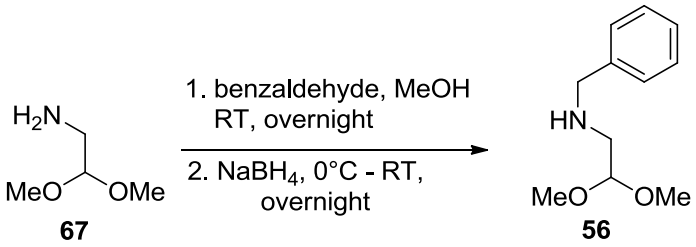
3.1 Towards Optically-enriched Common Oxazine Intermediate (*S*)-61

To allow the preparation of the enantiomerically-enriched oxazine intermediate (*S*)-**61**, from which a library of different oxabispidine motifs could be synthesised, the requisite starting materials, namely enantioenriched epoxide (*S*)-2,3-epoxypropylphthalimide, (*S*)-**55**, and benzyl-protected amine **56** had to be prepared.



Scheme 1.21

Initial work focused on the synthesis of amine **56**. In relation to this, commercially available aminoacetaldehyde dimethyl acetal **67** was treated with benzaldehyde at room temperature overnight leading to the formation of the corresponding imine, which upon reduction with sodium borohydride yielded the desired benzyl-protected secondary amine without incident (**Scheme 1.22, Table 1.1**).

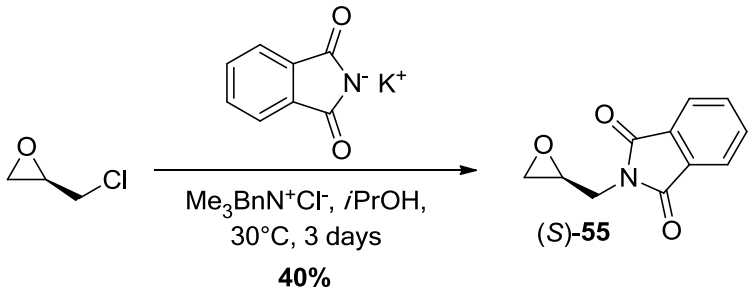


Scheme 1.22

Entry	Reaction Scale	Yield
1	190 mmol	Quant.
2	380 mmol	96%

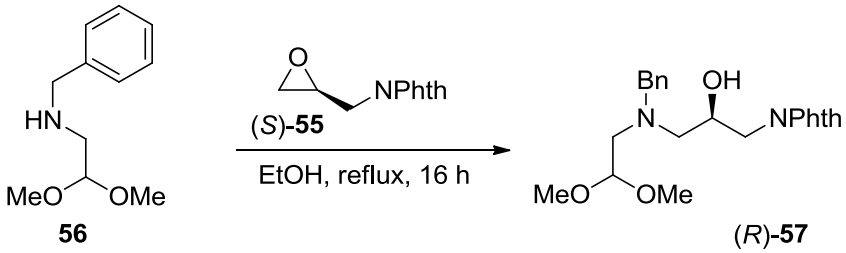
Table 1.1

With regards to the enantiomerically pure epoxide starting material (*S*)-**55**, a significant (1 kg) donation of (*S*)-epoxypropylphthalimide was received from collaborators at AstraZeneca. Having stated this, the required chiral epoxide can also be prepared by a simple substitution reaction utilising readily available (*R*)-epichlorohydrin and potassium phthalimide in the presence of trimethylbenzyl ammonium chloride. After a reaction time of 3 days, the desired optically pure (*S*)-**55** was recovered in a moderate 40% yield (**Scheme 1.23**).



Scheme 1.23

With significant quantities of each of the required starting materials in hand, the ring-opening of (*S*)-2,3-epoxypropylphthalimide with amine **56** was probed. Pleasingly, this reaction proceeded smoothly and, after refluxing in ethanol overnight, the desired chiral alcohol intermediate (*R*)-**57** was obtained in consistently outstanding yields with no need for chromatographic purification even upon significant scale-up (**Scheme 1.24, Table 1.2**).

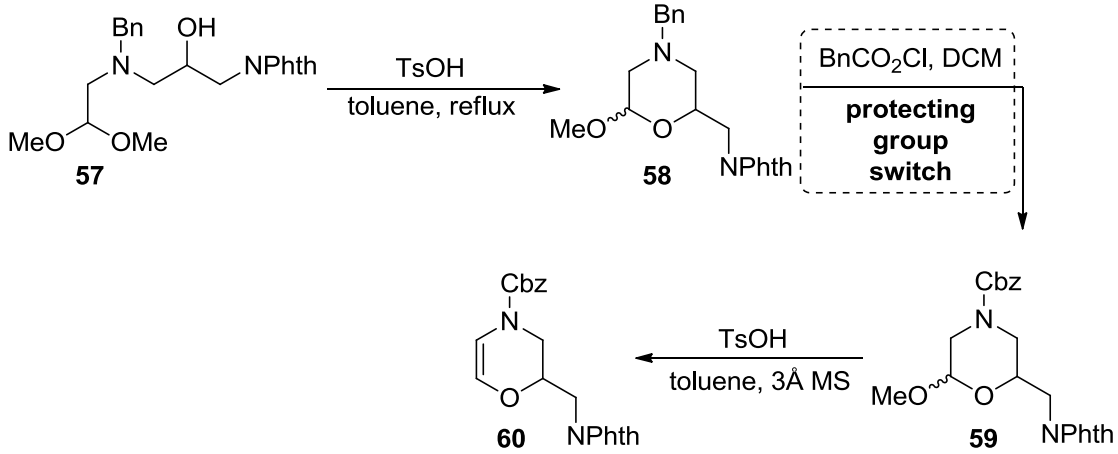


Scheme 1.24

Entry	Reaction Scale	Yield
1	4.9 mmol	96%
2	49 mmol	Quant.
3	363 mmol	99%

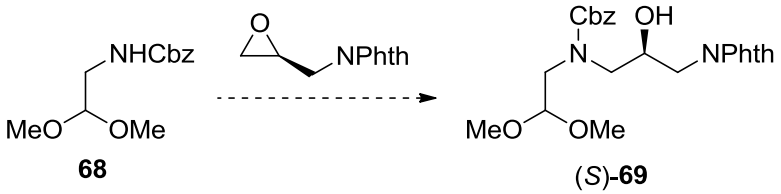
Table 1.2

At this stage, prior to extensive optimisation of the subsequent steps, we questioned whether we could prepare oxazine (*S*)-**61** in a more elegant and efficient manner. Previous work found that a switch from the benzyl protecting group to a carbamate protecting group is required later in the synthetic pathway to allow installation of the oxazine double bond to occur *via* elimination (**Scheme 1.25**).[38]



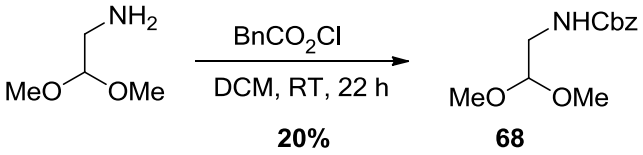
Scheme 1.25

With this in mind, it was envisaged that the protecting group switch could be avoided, by preparing the Cbz-protected amine **68**, and using this compound to open the chiral epoxide starting material (**Scheme 1.26**).



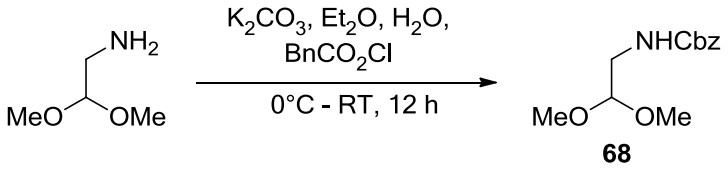
Scheme 1.26

Thus, we sought conditions to prepare carbamate-protected amine **68**. Utilising the same protocol employed for the previously reported protecting group interchange, namely stirring aminoacetaldehyde dimethyl acetal with benzyl chloroformate in DCM at room temperature, the desired product was obtained in 20% yield.



Scheme 1.27

It was assumed that the modest yield achieved in this reaction was due to the presence of the acid-sensitive acetal moiety in the substrate, which may be incompatible with the reaction conditions, and, more specifically, the generation of HCl as the reaction proceeds. To overcome this issue, potassium carbonate was added to the reaction mixture. In our initial attempt employing these alternative conditions, none of the desired product was recovered after column chromatography (**Scheme 1.28**, **Table 1.3, Entry 1**). However, as initial tlc analysis of the crude mixture showed two spots, and after column chromatography multiple spots were observed, it was believed the product was not compatible with silica gel for extended periods of time. In a subsequent attempt, we were pleased to find that quickly flushing through a small silica plug, to remove any residual benzylchloroformate, furnished the desired product in high yield (**Scheme 1.28, Table 1.3, Entry 2**). Even more pleasing was the ability to avoid chromatography entirely by simply performing a 5% citric acid wash during work-up, providing **68** in 100% yield (**Scheme 1.28**, **Table 1.3**, **Entry 3**).



68

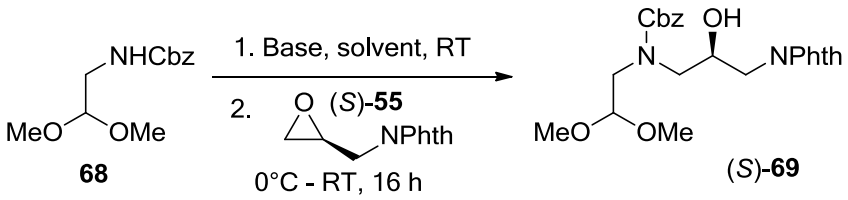
Scheme 1.28

Entry	Reaction Scale	Yield
1	9.5 mmol	-
2[a]	9.5 mmol	89%
3[b]	30 mmol	100%

[a] silica plug purification [b] citric acid wash

Table 1.3

With appreciable quantities of **68** in hand, attention was turned to the ring-opening of epoxide (*S*)-**55**. Adding **68** to a solution of NaH in THF, followed by the dropwise addition of the epoxide, disappointingly led to none of the desired product, with only a mixture of starting materials being recovered (**Scheme 1.29**, **Table 1.4**, **Entry 1**). Switching to DMF as the reaction solvent, based on literature precedent of the use of a Cbz-protected amine with NaH, albeit with a different electrophile,[40] yielded a similar outcome (**Scheme 1.29**, **Table 1.4**, **Entry 2**). Frustratingly, employing KHMDS as an alternative base, again only led to the recovery of a mixture of starting materials (**Scheme 1.29**, **Table 1.4**, **Entry 3**).



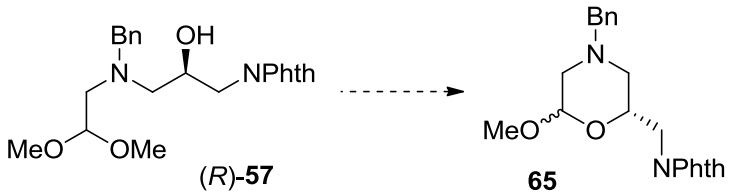
Scheme 1.29

Entry	Reaction Scale	Conditions	Yield
1	1.4 mmol	NaH, THF	-
2	0.6 mmol	NaH, DMF	-
3	0.6 mmol	KHMDS, THF	-

Table 1.4

With these preliminary reactions yielding no trace of the desired product (*S*)-**69**, and the precedented protecting group switch step itself being not particularly laborious, the decision was taken to abandon this line of research at this time, and focus on moving forward on the synthetic pathway.

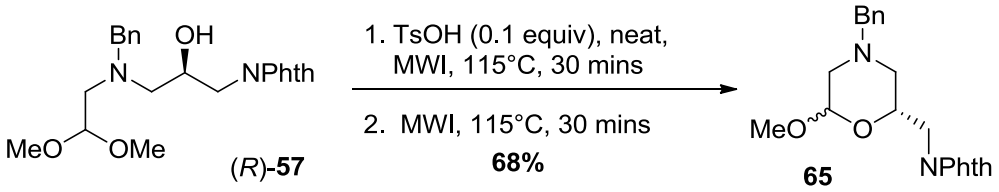
With large quantities of intermediate (*R*)-**57** readily available, the ring-closing procedure to access morpholine **65** was investigated (**Scheme 1.30**).



Scheme 1.30

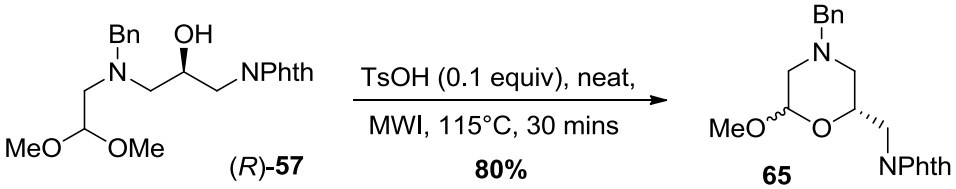
Previously, the synthesis of the racemic version of **65** was achieved by refluxing in toluene overnight.[39] Bearing in mind the shorter reaction times, and often higher yields, achieved utilising microwave irradiation over conventional heating,[41] it was proposed that such conditions could be employed for the cyclisation of (*R*)-**57**. As toluene is commonly known to be a 'microwave transparent' solvent,[41] it was suggested that removing it from the reaction mixture and performing the reaction neat would not have a detrimental effect. Thus, a mixture of neat intermediate (*R*)-**57** and a catalytic amount of TsOH were heated to 115°C

under microwave irradiation for 30 minutes (**Scheme 1.31**). After this time, it was found that the reaction had not gone to completion, however, after an additional 30 mins, tlc analysis showed only a trace amount of starting material still remaining. The decision was taken to purify the mixture at this stage, and after column chromatography a 68% yield of the desired morpholine product was obtained as a 70:30 mixture of diastereomers.



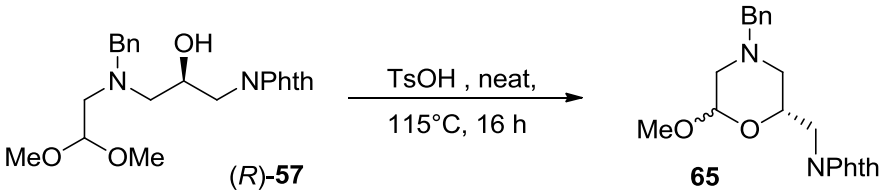
Scheme 1.31

With this promising yield being obtained in a relatively short reaction time, the reaction was repeated using freshly recrystallised TsOH (**Scheme 1.32**). Pleasingly, the reaction went to completion in 30 minutes, and an excellent 80% yield of morpholine **65** was recovered, with no need for chromatographic purification.



Scheme 1.32

At this stage, although the developed microwave conditions were efficient, it became apparent that the scale this reaction could be carried out on was limited by the size of the microwave vessels available. As such, it was deemed necessary to return to thermal conditions on scale; however the original issue of the use of large volumes of toluene being a practically undesirable requirement was still pertinent. In order to avoid the use of such a solvent, thermal conditions were proposed in which a neat mixture of intermediate (*R*)-**57**, and TsOH were reacted. On a moderate scale, a round-bottomed flask containing a stirrer bar, (*R*)-**57** and TsOH was sealed with a suba-seal and then lowered into a preheated oil bath set at 115°C. Following the reaction by tlc, it was observed that the reaction required 16 hours to reach completion, but satisfyingly the yield of the reaction was an impressive 90%, a result which was reproducible upon scaling-up the reaction further (**Scheme 1.33**, **Table 1.5**).

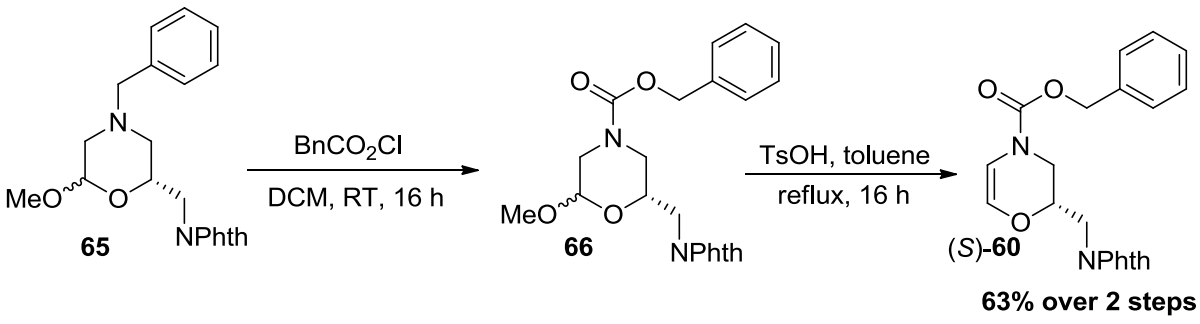


Scheme 1.33

Entry	Reaction Scale	Yield	d.r.
1	10 mmol	90%	70:30
2	110 mmol	94%	70:30

Table 1.5

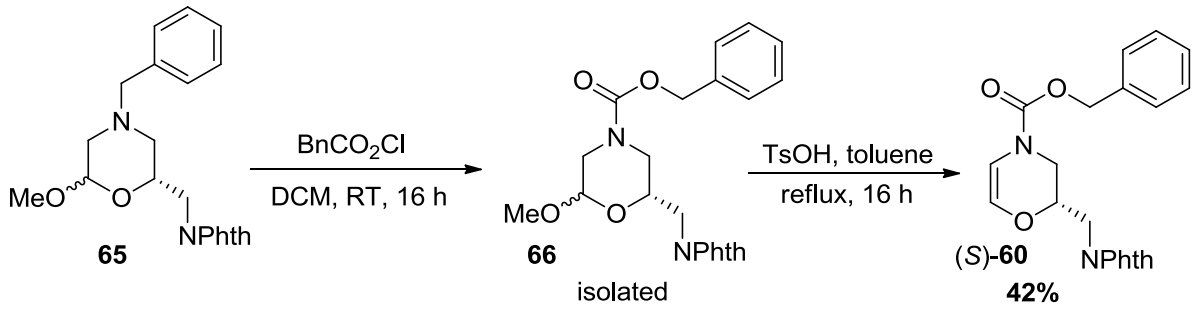
With the synthesis of morpholine **65** successfully optimised, attention was turned to the next steps in the synthetic pathway, namely the protecting group switch and elimination reactions. Stirring the benzyl-protected morpholine with benzyl chloroformate in DCM at room temperature overnight, led to complete consumption of the starting material, as observed by tlc (**Scheme 1.34**). After removal of the DCM *in vacuo*, the resulting residue was dissolved in toluene, and TsOH added. Under previous conditions, the elimination process was driven by the inclusion of molecular sieves to the reaction mixture, however crushing of the sieves was observed, making recovery of the desired product more difficult.[38] To avoid such product recovery issues, Dean-Stark conditions were employed to drive the methanol from the reaction mixture. Refluxing under Dean-Stark conditions overnight led to the desired protected-oxazine product (*S*)-**60** being delivered in 63% yield over 2 steps (**Scheme 1.34**).



Scheme 1.34

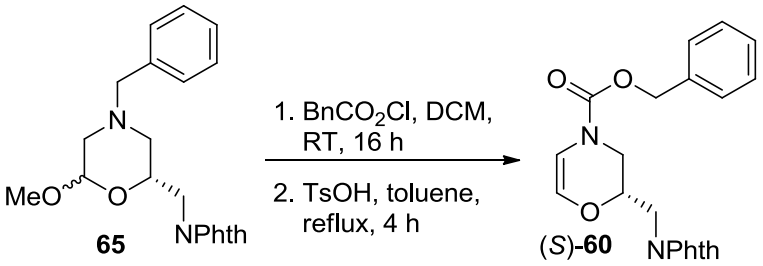
To determine if the excess benzyl chloroformate remaining after step 1 of this one-pot procedure was having a detrimental effect on the overall yield of the process, the Cbz-

protected morpholine **66** was isolated by column chromatography, then subjected to the elimination conditions. This, however, did not lead to an improvement in overall yield and the original telescoped procedure was retained subsequently.



Scheme 1.35

Close monitoring of the reaction by tlc analysis indicated that the elimination reaction was in fact complete after 4 hours, circumventing the need for extensive heating times (**Scheme 1.36**, **Table 1.6**, **Entry 1**). Upon increasing the reaction scale, this protecting group switch/elimination sequence proved highly reproducible, allowing access to significant quantities of intermediate (*S*)-**60**.



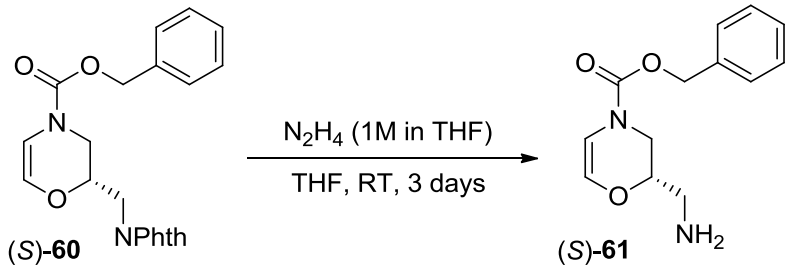
Scheme 1.36

Entry	Reaction Scale	Yield
1	38 mmol	63%
2	241 mmol	62%

Table 1.6

Attention was then focused on the development of an efficient procedure for the cleavage of the phthalimide protecting group. With regards to the racemic route, a 1M hydrazine in THF has been used for this purpose with mixed success.[39] In an initial attempt, employing this

reagent in the deprotection of (*S*)-**60** led to the recovery of 37% of the starting material only (**Scheme 1.37**, **Table 1.7**, **Entry 1**). Upon repetition of the reaction, the desired oxazine product (*S*)-**61** was isolated, albeit in a low yield of 30% after column chromatography (**Entry 2**). Increasing the scale of this process provided the deprotected product in a similarly poor yield (**Entry 3**).

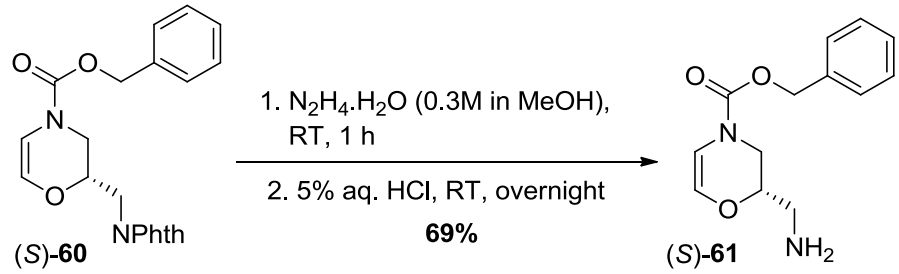


Scheme 1.37

Entry	Reaction Scale	Outcome
1	1.9 mmol	37% SM recovery
2	1.1 mmol	30% yield
3	16 mmol	39% yield

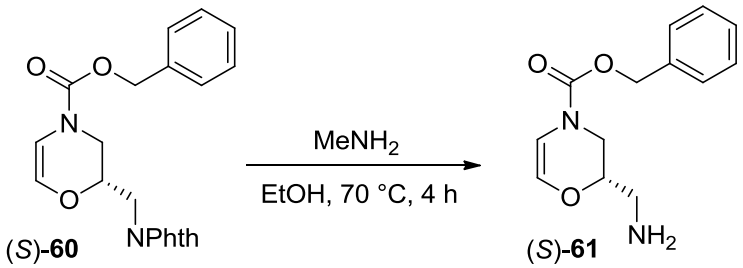
Table 1.7

As well as the low yields obtained, an additional drawback to the above protocol was the lengthy reaction time of 3 days. With these issues in mind, alternative procedures were surveyed in order to improve the efficiency of this deprotection step. In this regard, a phthalimide cleavage protocol reported by Sen and Roach utilising hydrazine hydrate, was employed (**Scheme 1.38**).[42] Treatment of protected oxazine (*S*)-**60** with 0.3M $N_2H_4.H_2O$ in methanol for 1 hour followed by stirring with 5% HCl overnight afforded the desired deprotected oxazine (*S*)-**61** in a significantly improved 69% yield, with no need for chromatographic purification.



Scheme 1.38

An additional, practically more convenient, procedure which utilised the less toxic methylamine was also screened.[42] Satisfyingly, heating a mixture of (*S*)-**60** and methylamine in ethanol at 70°C for 4 hours led to the deprotected product (*S*)-**61** in an excellent 76% yield, again with no need for additional chromatographic purification (**Scheme 1.39**, **Table 1.8**, **Entry 1**). The improved yield and shorter reaction time, coupled with the avoidance of the environmentally undesirable hydrazine, led to the adoption of this methylamine protocol in subsequent phthalimide cleavage reactions, with high yields being maintained on more elevated scale (**Table 1.8**, **Entries 2** & **3**).



Scheme 1.39

Entry	Reaction Scale	Yield
1	3.2 mmol	76%
2	31 mmol	83%
3	228 mmol	89%

Table 1.8

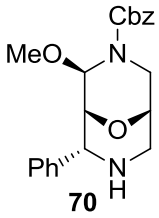
With the optimisation of this final deprotection step complete, we were pleased to have gained access to key chiral intermediate (*S*)-**61** in only six high yielding steps. The fact that

only one step in the sequence required column chromatography, makes the process highly amenable to scale-up and adds to the overall efficiency of this developed route.

3.2 Synthesis of a Family of Optically-enriched Oxabispidines

3.2.1 Synthesis of Phenyl-substituted Oxabispidine 70

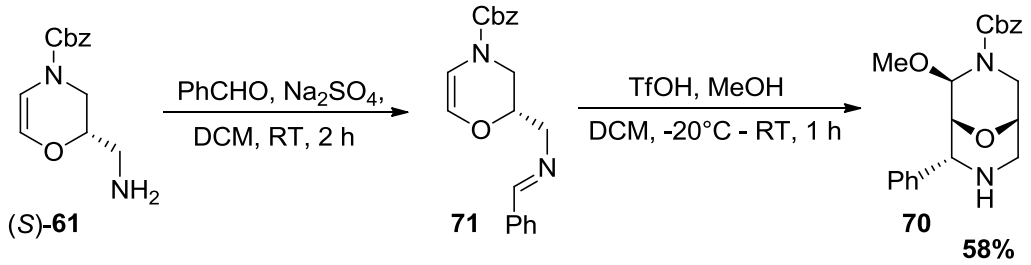
Having prepared multigram quantities of oxazine (*S*)-**61**, attention was then focused on utilising this common intermediate in the synthesis of a number of enantiomerically-enriched substituted oxabispidines, starting with the phenyl-substituted derivative **70**, illustrated in **Figure 1.11**, in initial optimisation studies.



70

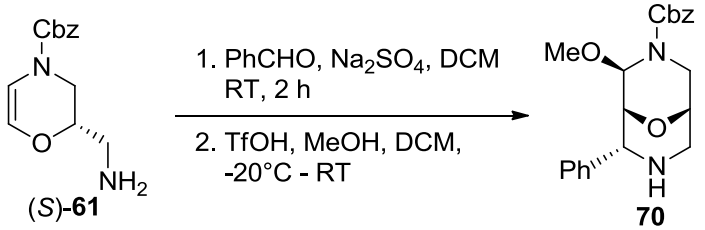
Figure 1.11

Based on the preliminary pathway adopted previously within AstraZeneca (**Scheme 1.16**) and the recovery of by-product **64** (**Figure 1.10**),[38] we wished to amend the route and develop conditions to selectively access compound **70**. Accordingly, the reaction of oxazine (*S*)-**61** with benzaldehyde in the presence of excess Na_2SO_4 led to successful formation of *E*-imine **71** (*vide infra*), which was confirmed by crude NMR of the reaction mixture. After removal of the Na_2SO_4, the solution of imine in DCM was cooled to -20°C and treated with methanol followed by triflic acid. After removing the cooling bath and stirring for 1 hour the reaction was quenched with a saturated solution of sodium bicarbonate. Satisfyingly, the desired oxabispidine product was recovered in a promising 58% yield (**Scheme 1.40**).



Scheme 1.40

At this stage we were pleased to have accessed the first oxabispidine structure in synthetically useful quantities as part of these studies. With the aim of improving this yield a number of experiments were carried out in order to ascertain the optimal reaction conditions for the intramolecular cyclisation of imine **71** (**Table 1.9**, **Entries 1-4**). Keeping the reaction vessel in the cooling bath after the addition of triflic acid, and allowing the reaction mixture to slowly warm to room temperature over a longer time period had no significant effect on the yield of desired product obtained (**Entry 1**). On the other hand, removing the cooling bath after the addition of triflic acid at -20°C, and allowing the reaction mixture to warm to room temperature before stirring at room temperature for 1 hour (**Entry 2**) provided an improved yield of 71%. Extending the stirring time at room temperature to 2 hours surprisingly had a slight detrimental effect on the yield (**Entry 3**). This outcome suggests that the oxabispidine product **70** is not stable to the acidic reaction medium for an extended period of time. To evaluate whether a shorter length of time at room temperature would be advantageous to the yield, the reaction was stirred for 30 minutes at room temperature, after the low temperature addition of the acid; however, this did not lead to an increase in the yield obtained (**Entry 4**). Following this short series of optimisation studies, the conditions detailed in **Table 1.9**, **Entry 2** were selected as the optimal conditions for the Mannich-type cyclisation process.



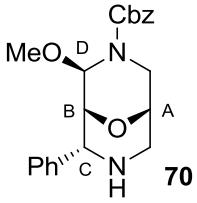
Scheme 1.41

Entry	Reaction Conditions	Yield
1	-20°C for 10 min and allowed to slowly warm to RT over 3 h	50%
2	Allowed to warm to RT then stirred at RT for 1 h	71%
3	Allowed to warm to RT then stirred at RT for 2 h	60%
4	Allowed to warm to RT then stirred at RT for 30 min	58%

Table 1.9

3.2.1.1 Determination of Stereochemistry

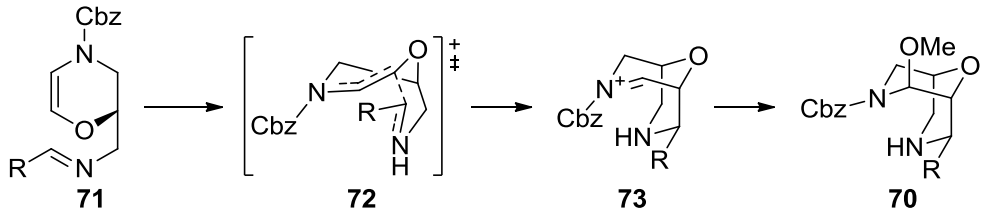
Having successfully prepared oxabispidine **70** in good yield, and with the ultimate goal being the incorporation of these bicyclic molecules into lead-like compounds within drug discovery processes, it was essential to confirm the stereochemistry of the product compound **70**. It was proposed that the stereochemistry contained within the initial epoxide (stereocentre **A**; **Figure 1.12**) is retained throughout the synthesis and that this stereocentre determines the stereoselectivity observed in the subsequent steps.



70

Figure 1.12

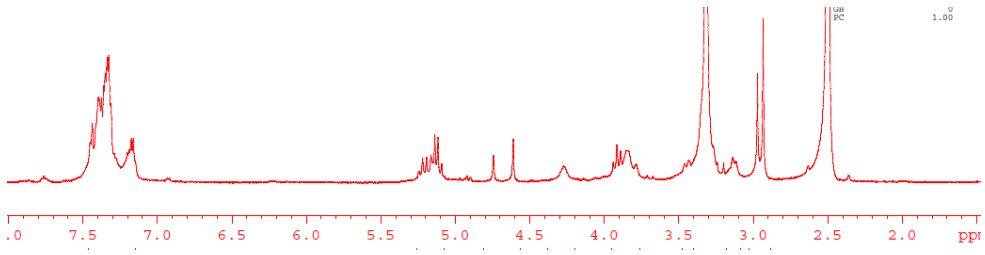
The chirality at the second bridgehead position (**B**) and at the stereogenic centre α to the nitrogen (**C**) are believed to be determined in the imine formation and at the intramolecular cyclisation stage (**Scheme 1.42**). It was assumed that the oxabispidines sit in a chair-chair conformation similar to the conformation determined for the bispidine skeleton.[20] Based on this, a chair-like transition state for the cyclisation of *E*-imine **71** to oxabispidine **70** was proposed. Through transition state **72**, iminium ion **73** is formed and stereocentres **B** and **C** are set. Finally, axial attack of methanol onto iminium ion **73** generates the last chiral centre **D** and provides the final oxabispidine product.



Scheme 1.42

Our initial attempts to probe our mechanistic proposal, and thus confirm the proposed stereochemistry, involved NMR experiments. Prior to discussion of this study, it should first be noted that upon initial inspection of the ^{1}H NMR spectrum of oxabispidine **70** in $CDCl_3$ it appears to be a mixture of isomers. Variable temperature studies (**Figure 1.13**) showed that this is, in fact, due to restricted rotation of the carbamate protecting group (a feature also observed with oxazines (*S*)-**60** and (*S*)-**61**). As depicted in **Figure 1.13**, upon heating a sample of **70** in DMSO from 27°C to 80°C the signals coalesce, which is an observation made when rotamers are present. This is particularly apparent for the singlets between 4.6 and 4.8 ppm (corresponding to the proton at stereocentre D in **Figure 1.12**), which coalesce to one broad singlet at 80°C.

(a) ^{1}H NMR of **70** in DMSO at 27°C



(b) ^{1}H NMR of **70** in DMSO at 80°C

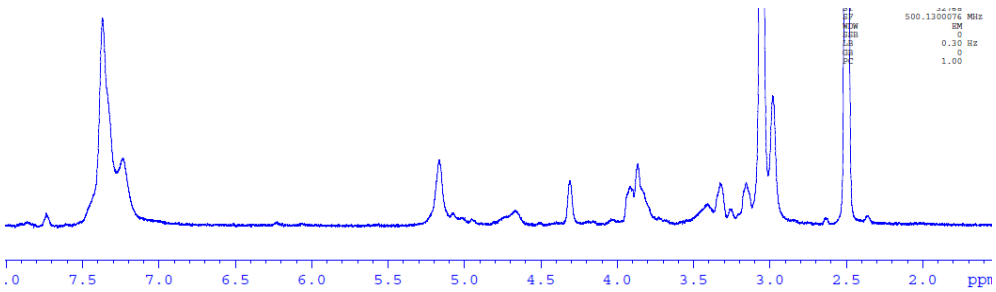


Figure 1.13: Variable temperature ^{1}H NMR spectra of imine **71**.

Having rationalised the additional complexity observed in the NMR spectra of **70** (and associated compounds), attention initially turned to the use of more detailed NMR experiments to divulge the stereochemistry of imine **71**. These revealed that imine **71** forms with exclusively *E*-geometry (**Figure 1.14**); more specifically, NOESY experiments showed that imine proton H7 is close in space to protons H1, which can only be achieved if they have a *cis* relationship, i.e. the imine double bond has *E*-geometry.

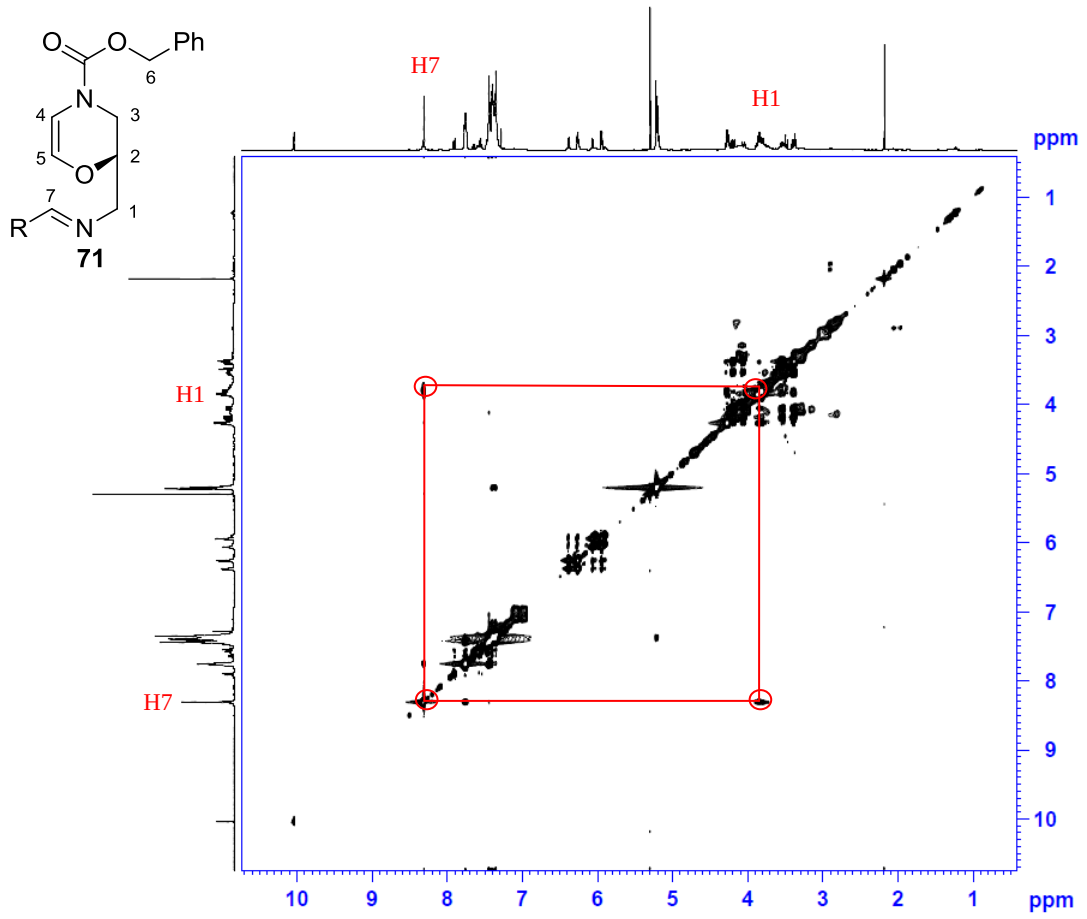


Figure 1.14: NOESY spectrum of crude imine **71**.

Bearing this in mind, and considering our proposed chair-like transition state, it can be seen that retention of the imine geometry would result in the Ph substituent sitting down and equatorial in **70**, and the geometry at the bridgehead position would be locked. This proposed stereochemistry was, again, confirmed by through-space NMR studies (*vide infra*).

Having previously assigned the complex ^{1}H and ^{13}C NMR spectra with the aid of various 2D techniques (HSQC, HMBC, COSY), we employed NOESY experiments with oxabispidine derivative **70** to establish that the cyclisation occurs with retention of configuration and that

the phenyl group sits in an equatorial position *trans* to the bridgehead. As shown in **Figure 1.15** there is an nOe effect between proton H4 on the carbon bearing the phenyl substituent and axial proton $H3_{ax}$, thus placing the phenyl group in an equatorial position. The lack of nOe between H4 and H6 on the carbon bearing the methoxy group corroborates this observation.

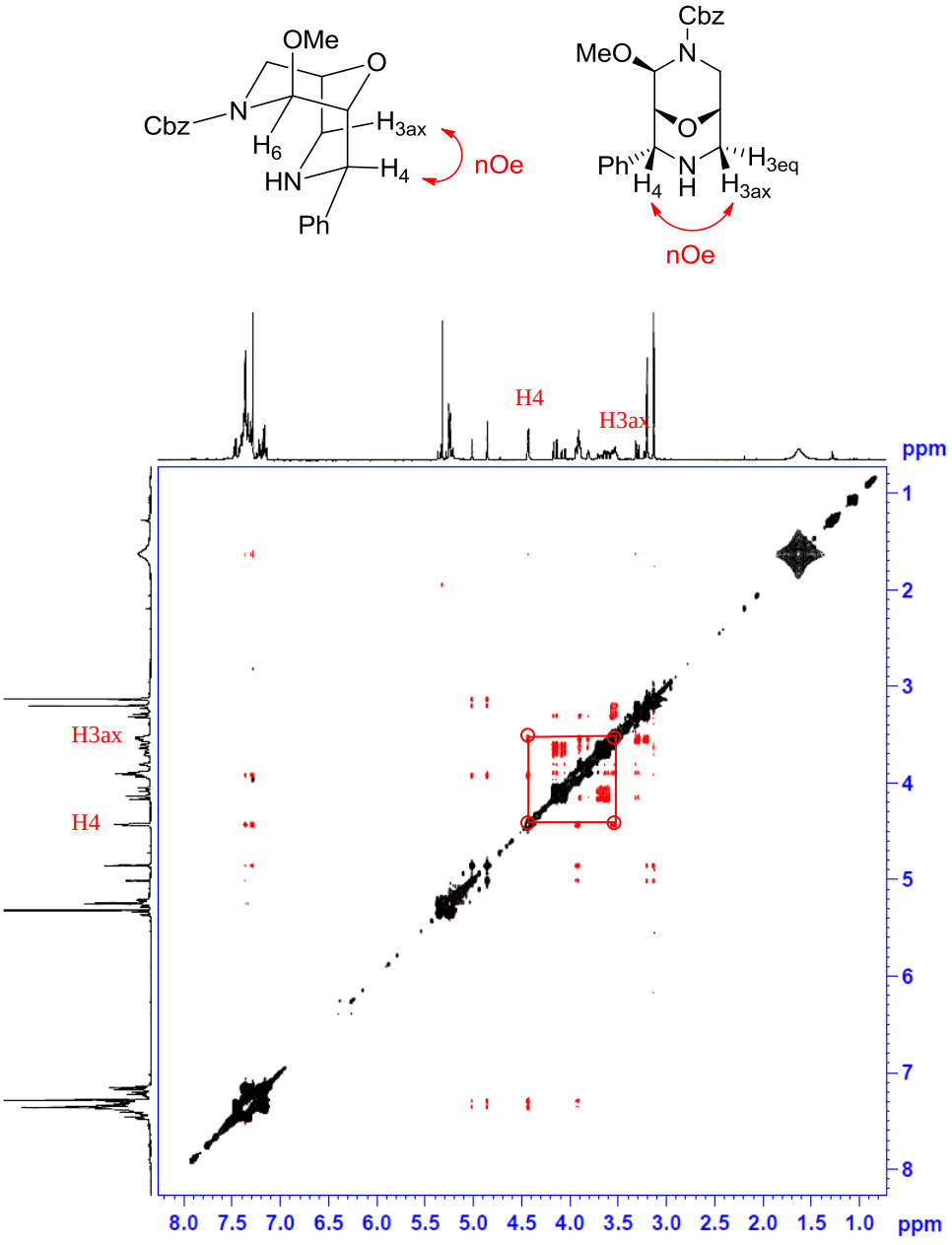


Figure 1.15: NOESY spectrum of oxabispidine **70**.

In addition, it was noted that nOe signals were observed from the bridgehead protons H2 and H5 to all other protons in the bicyclic system, supporting the initial assumption of a chair-chair conformation (**Figure 1.16**).

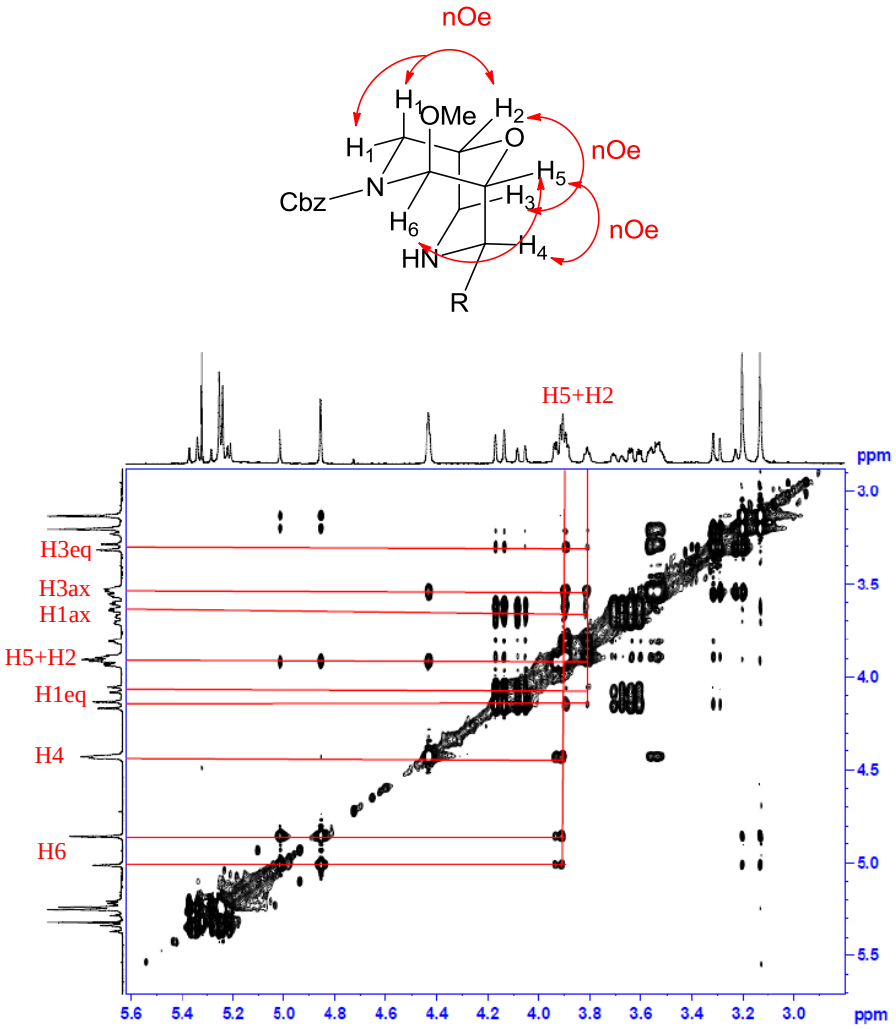


Figure 1.16: NOESY spectrum of **70** showing bridgehead protons nOes.

Indeed, such observations could not be expected for the pseudoaxial protons if a boat conformation were to be adopted (**Figure 1.17**).

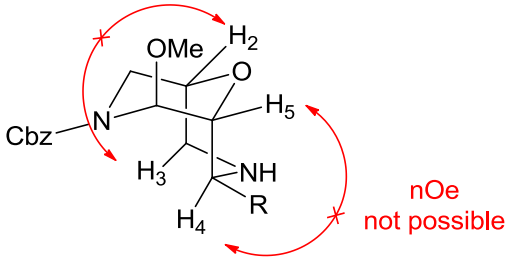


Figure 1.17: Chair/boat conformation of **70**.

The final stereocentre of the oxabispidine (**D**; **Figure 1.12**) is determined by the attack of methanol onto the iminium ion **73** that is proposed to form during the cyclisation of imine **71**. Bearing in mind the rotameric effects described earlier, two distinct methoxy peaks are observed in the ^{1}H NMR spectrum of **70**. In the NOESY spectrum of **70** both methoxy peaks display an nOe with axial proton $H1_{ax}$, as depicted in **Figure 1.18**, indicating that oxabispidine **70** was in fact a single diastereomer, with the methoxy substituent having positioned itself axially.

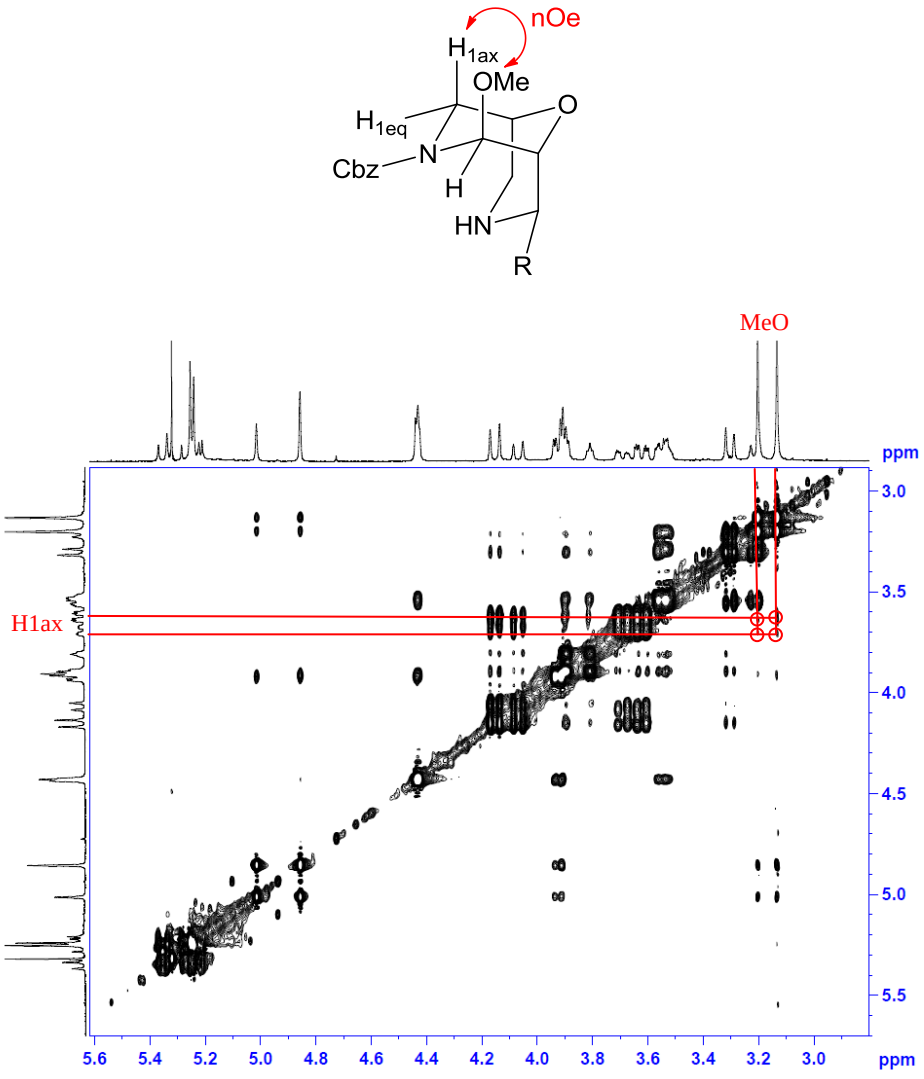
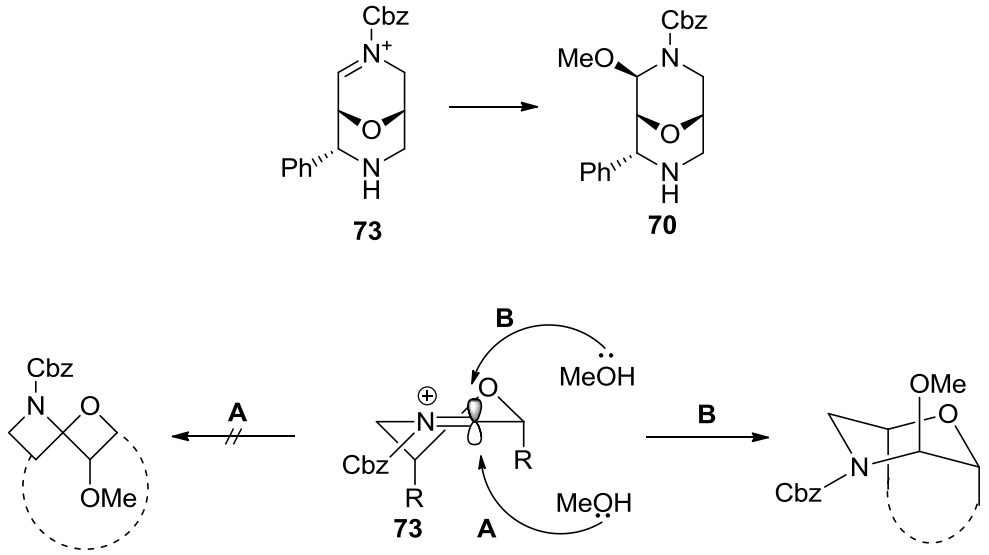


Figure 1.18; NOESY showing MeO nOe

As stated previously, the stereochemistry at this final stereocentre must be defined by the preferential attack by methanol onto a single face of the intermediate iminium ion **73**, formed upon intramolecular cyclisation of imine **71**. The rationale for this stereochemical outcome is depicted in **Scheme 1.43**, in which iminium ion **73** sits in the half-chair conformation, with

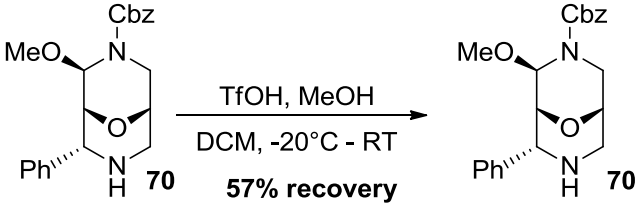
the anti-bonding orbital of the iminium carbon sitting axially. If the methanol attacked from below the plane of the double bond, a twist-boat conformation would result (Pathway A). This is thermodynamically unstable and therefore does not form. Thus, the methanol must attack from the top face (Pathway B), producing the thermodynamically favourable chair conformation.



Scheme 1.43

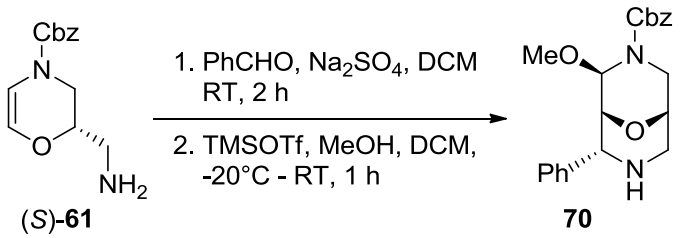
3.2.1.2 Lewis Acid Activation

During the optimisation process of the formation of phenyl-oxabispidine **70**, an additional reaction was carried out in which **70** was re-subjected to the reaction conditions (**Scheme 1.44**) in order to determine if this species was stable in the acidic reaction media. After stirring for 1 hour at room temperature only 57% recovery of material was obtained, suggesting that **70** degrades when exposed to the strongly acidic media for extended periods of time.



Scheme 1.44

To circumvent this, it was proposed that a Lewis acid may be able to replace triflic acid in the above transformation, thus providing milder reaction conditions, and potentially higher yields of the desired oxabispidine product. With this in mind, a stoichiometric quantity of TMSOTf was utilised in place of triflic acid under the conditions described previously in **Table 1.9, Entry 2**. As shown in **Scheme 1.45**, **Table 1.10**, **Entry 1**, a 73% yield of oxabispidine **70** was delivered, which is comparable to the result obtained with the original triflic acid conditions. Having said this, the chemical yield increased to an excellent 86% upon scale-up, the highest yield of **70** achieved to this stage in the programme.

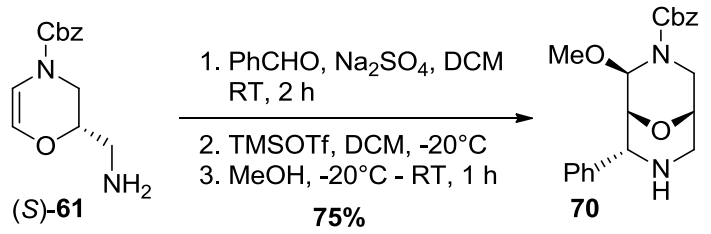


Scheme 1.45

Entry	Scale	Yield
1	1 mmol	73%
2	13 mmol	86%

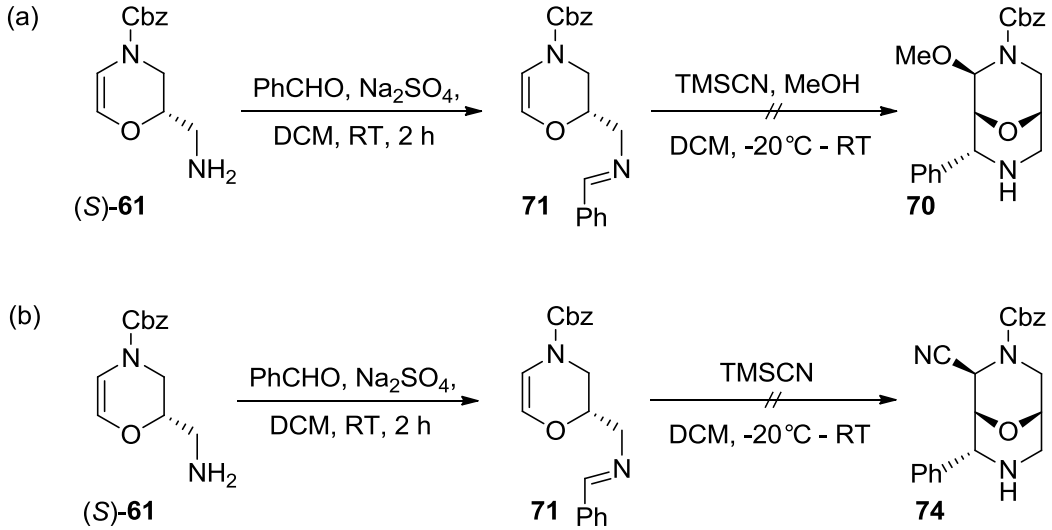
Table 1.10

At this stage, we questioned whether TMSOTf was indeed acting as a Lewis acid or whether it was simply trace amounts of triflic acid that were activating the cyclisation process. It was proposed that triflic acid was potentially being generated *in situ* by the reaction of TMSOTf with the protic solvent methanol. To investigate this, the initial and most simple experiment was to alter the order of addition of the reagents, and add the TMSOTf prior to the inclusion of methanol. After cooling a solution of imine **71** to -20°C, TMSOTf was added and, with no methanol present, the usual colour change from pale to bright yellow, assumed to be the formation of an iminium ion, was observed. Subsequent quenching with methanol, followed by stirring at RT for 1 hour, as in previous reactions, led to the recovery of oxabispidine **70** in 75% yield. This suggests that triflic acid is not being generated *in situ* from TMSOTf and MeOH, however it does not rule out the fact that traces of triflic acid may always be present in commercially available TMSOTf.



Scheme 1.46

To probe this issue further, an alternative Lewis acid was considered, namely TMSCN. If TMSOTf is in fact acting as a Lewis acid, then TMSCN should activate the intramolecular cyclisation in a similar manner, with the added advantage that it could also potentially provide a nucleophile ($^{-}$CN) to quench the final step in the overall process. With this in mind, two reactions were performed (reactions (a) and (b), **Scheme 1.47**). The first utilised identical conditions to the reaction described previously (**Scheme 1.45**), except that TMSOTf was replaced with TMSCN. In the second reaction, TMSCN was the only reagent added to the cooled solution of imine, with the hope that it would both activate the cyclisation step and deliver CN as the final nucleophilic quench.



Scheme 1.47

Unfortunately, neither of the reactions depicted above resulted in the desired oxabispidine product, and instead only a mixture of starting amine (*S*)-**61** and the CN addition product **75** (**Figure 1.19**) was recovered in each instance. It was presumed that TMSCN was acting as a

Lewis acid, however it was simply delivering CN to the initially-formed iminium ion rather than activating the intramolecular cyclisation.

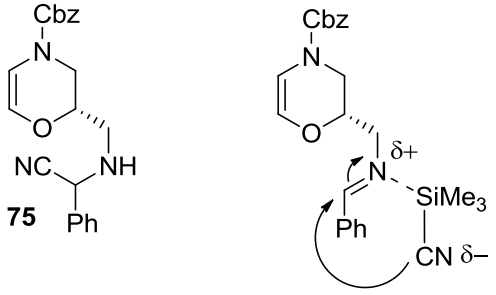
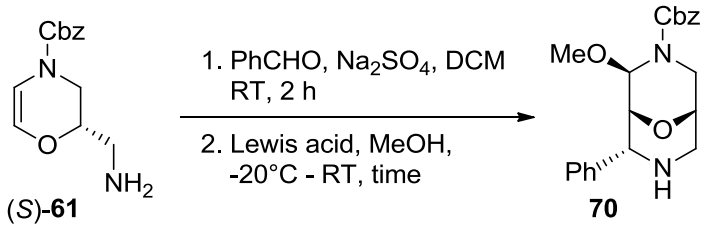


Figure 1.19

It was noted in the above reactions (**Scheme 1.47**) that the addition of TMSCN was not accompanied by the usual colour change of pale to bright yellow observed when TfOH and TMSOTf are used (presumed to be the formation of an iminium ion), suggesting that TMSOTf is more than likely acting as a source of slowly released TfOH rather than a Lewis acid as proposed for TMSCN. With the observation that TMSCN was activating the initial imine intermediate, but simply quenching this species before it underwent cyclisation, we screened a selection of other common Lewis acids, where such an occurrence was not possible. As shown in **Scheme 1.48**, **Table 1.11**, four Lewis acids of varying strength were examined. The use of weak Lewis acids such as silica (**Entry 1**) and lithium perchlorate (**Entry 2**) was unsuccessful with only the imine intermediate being observed, even after extending the reaction time to 48 h. Moving to a stronger Lewis acid, namely zinc chloride, the result was more promising with a yield of 5% of **70** being obtained after 24 h (**Entry 3**). The strongest of the Lewis acids screened was $AlCl_3$ (**Entry 4**). After 1 hour stirring at room temperature, only imine **71** was observed by crude ^1H NMR, however, as the reaction proceeded a gradual colour change from pale to bright yellow was noted. After 24 h the reaction was stopped and the desired oxabispidine product was recovered in 27% yield.



Scheme 1.48

Entry	Lewis acid	Time	Yield
1	SiO_2	48 h	-
2	$LiClO_4$	48 h	-
3	$ZnCl_2$	24 h	5%
4	$AlCl_3$	24 h	27%

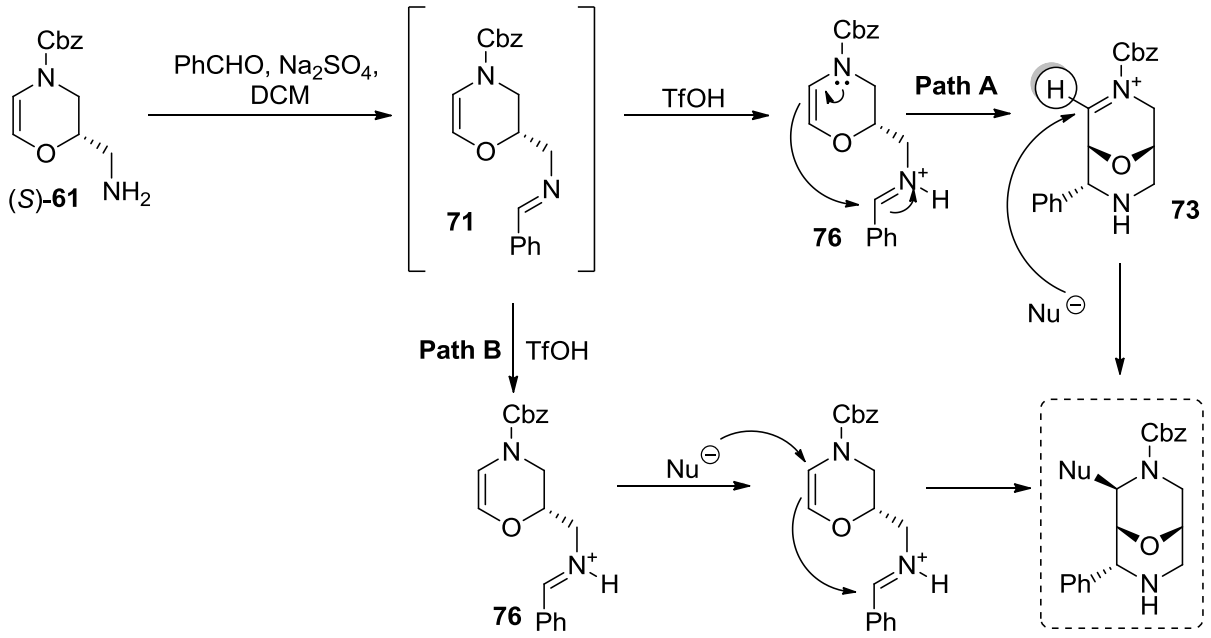
Table 1.11

With this final result we had shown that it was indeed possible to initiate the intramolecular Mannich-type reaction using Lewis acid activation, however, as a much longer reaction time was required to achieve a significantly more modest yield, our focus would remain on the use of triflic acid promotion.

3.2.2 Mechanism of Oxabispidine Formation

The brief investigation into Lewis acid activation detailed above led us to consider the cyclisation mechanism in a more general sense, as the Mannich-type mechanism proposed previously (see *3.2.1.1 Determination of Stereochemistry*) has yet to be proven experimentally. The proposed mechanism (**Path A**, **Scheme 1.49**) involves activation of the relevant imine (prepared from oxazine (*S*)-**61** and the chosen aldehyde) by triflic acid to form iminium ion **76**. Subsequent intramolecular cyclisation *via* attack on iminium **76** by the enamine moiety forms a second iminium ion **73**, which is then quenched with a nucleophile; methanol up to this stage. Whilst this is the most likely mechanism, and provides a rationale for the stereochemical outcome of the process, the fact that the nitrogen responsible for the intramolecular attack bears a highly electron-withdrawing protecting group (Cbz) does pose a

question over the availability of its lone pair. An alternative pathway could also be suggested in which external attack of methanol onto the double bond of the six-membered ring occurs with concomitant cyclisation (**Path B**, **Scheme 1.49**).

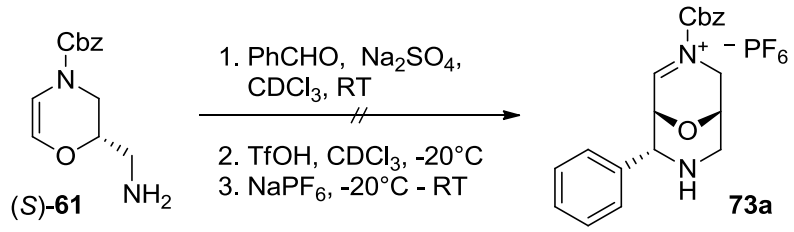


Scheme 1.49

3.2.2.1 Iminium Intermediate Isolation Attempts

^{1}H NMR experiments were carried out in an attempt to ascertain the iminium species present after addition of triflic acid in the absence of methanol (the formation of which is indicated by the colour change from pale to bright yellow as mentioned previously). It was envisaged that the presence of a signal corresponding to the highlighted hydrogen of iminium **73** (**Scheme 1.49**) in a ^{1}H NMR spectrum would be observed, thus indicating that Path A was in operation and methanol was not required for cyclisation. Unfortunately, the spectra obtained on several occasions did not yield any valuable structural information. Believing that the intermediate iminium species was simply too unstable to be observed for any extended period of time, we turned our attention towards the formation of a species that could be observed more easily. In this regard, the initial idea proposed was to employ a non-nucleophilic and more robust counterion to isolate the iminium species as a more stable salt. On interrogation of relevant published material specific literature was identified in which iminium species were isolated as their hexafluorophosphate salts.[43] With this in mind, and again using the substrates required to prepare oxabispidine **70**, the imine (**71**) was formed in the usual

manner, except in this case the reaction was performed in deuterated chloroform. After addition of triflic acid, accompanied by the usual colour change from pale to bright yellow, $NaPF_6$ was added. Unfortunately, $NaPF_6$ was completely insoluble in the reaction medium and thus no reaction was observed (**Scheme 1.50**, **Table 1.12**, **Entry 1**). Finding that $NaPF_6$ was sparingly soluble in acetonitrile, in the following experiment the salt was added to the reaction as a solution in CD_3CN. After 5 minutes, a sample of the reaction mixture was analysed by ^1H NMR spectroscopy. Unfortunately, as before, the spectrum did not elucidate any information regarding structure. The reaction was held at -20°C for 2 hours before warming to room temperature. After this time, a solid had precipitated out of solution, however, disappointingly, after collection of the solid it was found to be merely unreacted $NaPF_6$.



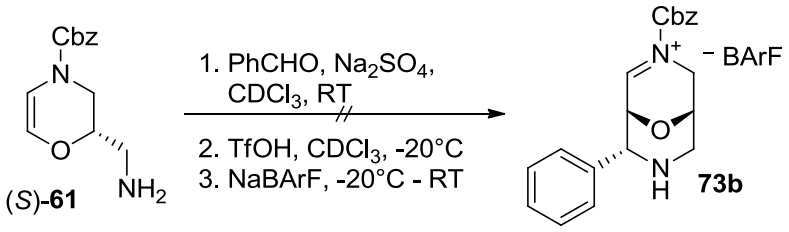
Scheme 1.50

Entry	Reaction Scale	Yield
1	0.8 mmol	0%
2[a]	0.8 mmol	0%

[a]$NaPF_6$ solubilised in CD_3CN

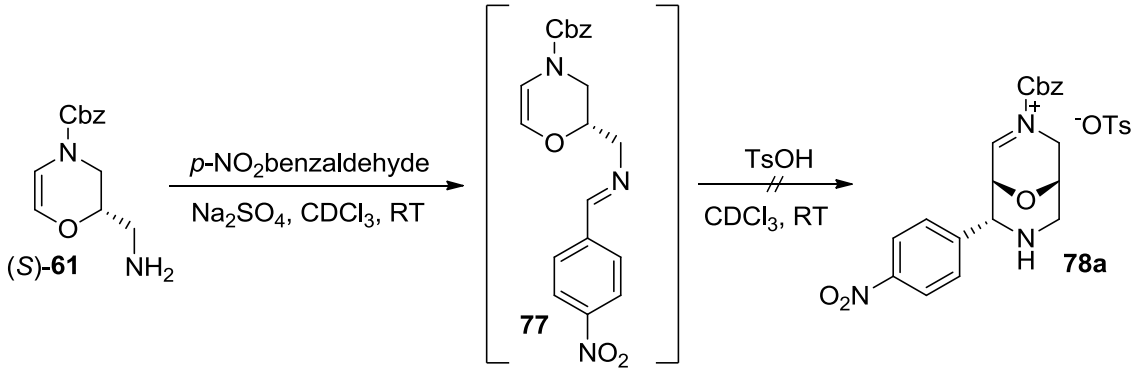
Table 1.12

Undeterred by the above results, we turned to a counterion which is more compatible with organic solvents, namely tetrakis(3,5-trifluoromethyl)phenylborate (BArF). As in the previous case, NaBArF was added after the addition of triflic acid at -20°C. After 30 minutes, a sample of the reaction mixture was taken, however, no structural information could be obtained from the ^1H NMR spectrum.



Scheme 1.51

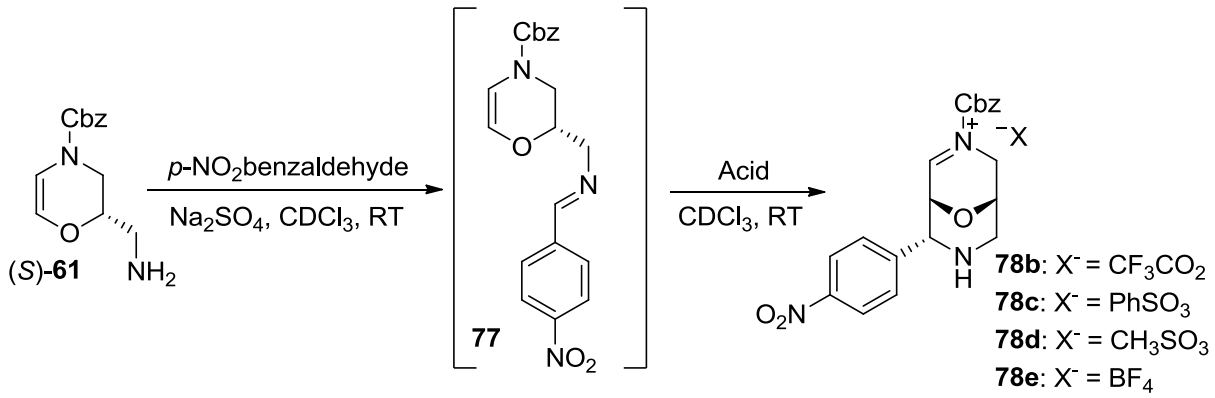
With these initial disappointing results in mind, an alternative approach was explored. It was proposed that if the reactivity of the aldehyde and acid were tuned appropriately, it would allow for the imine to react at ambient temperature rather than -20°C, hopefully affording an isolable cyclized iminium ion intermediate. By using a weaker acid than triflic acid the requirement for the reaction to be carried out at -20°C would be unnecessary, however, in order for a weaker acid to be effective a more reactive imine and, as such, a more reactive aldehyde was required. In this instance a strongly electron-withdrawing aldehyde, such as *p*-nitrobenzaldehyde, in combination with TsOH was deemed suitable. Reaction of oxazine (*S*)-**61** with *p*-nitrobenzaldehyde to form the corresponding imine **77** occurred without incident (**Scheme 1.52**). Treating this with TsOH, a colour change from pale to bright yellow was observed. As the reaction had been performed in $CDCl_3$ an aliquot of the reaction mixture was taken after 5 min and analysed by ^1H NMR spectroscopy. Unfortunately, the ^1H NMR spectrum showed that hydrolysis of the initial imine had in fact taken place to return mainly starting amine and aldehyde.



Scheme 1.52

To ensure that moisture was excluded to as great an extent as possible (in order to minimise hydrolysis of the imine), the decision was taken to move away from the use of TsOH (obtained as the commercially available hydrate), and instead screen a range of anhydrous

acids of varying strengths (**Scheme 1.53**, **Table 1.13**). The first acid to be screened was the weakest of the set, namely trifluoroacetic acid (**Scheme 1.53**, **Table 1.13**, **Entry 1**). After preparation of the requisite imine in $CDCl_3$, the acid was added at room temperature. After 5 minutes, a sample of the reaction mixture was taken for ^1H NMR analysis, which showed, in addition to the acid reagent, only the unreacted imine **77**. Leaving the reaction to stir at room temperature overnight resulted in no significant changes to the ^1H NMR spectrum. Disappointingly, moving to the stronger benzenesulfonic acid led to a similar outcome (**Scheme 1.53**, **Table 1.13**, **Entry 2**). Undeterred, methanesulfonic acid was the next acid screened, in a similar manner to that described above (**Scheme 1.53**, **Table 1.13**, **Entry 3**). After 5 minutes reaction time, ^1H NMR analysis revealed a more complex spectrum than those obtained in the previous entries. Promisingly, after leaving the reaction for 3 hours, a small amount of a pale orange solid had precipitated out of solution. This solid was collected by filtration and dried *in vacuo* for several hours. ^1H NMR analysis of the solid showed a species with no olefinic signals (indicating that the enamine moiety was no longer present), a peak ~9 ppm, the region in which the iminium proton would potentially appear, and a singlet corresponding to the mesyl CH_3, all of which are encouraging indications for the formation of mesylate iminium salt **78d**. Having stated this, complete elucidation of the structure was not possible. With this promising result in hand, it was proposed that by utilising an alternative acid with a non-nucleophilic counterion as the conjugate base, more specifically $HBF_4.Et_2O$, successful, clean isolation of a stable iminum salt could be achieved (**Scheme 1.53**, **Table 1.13**, **Entry 4**). Unfortunately this was not the case, with none of the desired product **78e** being observed.

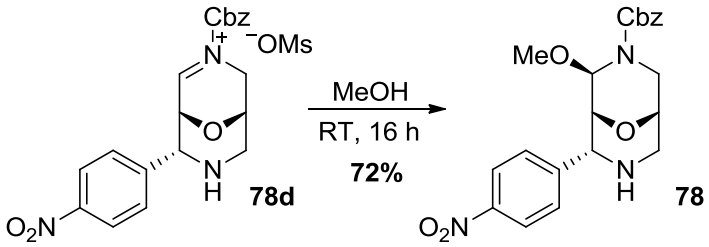


Scheme 1.53

Entry	Acid	X^-	Outcome
1	Trifluoroacetic acid	CF_3CO_2	Only imine **77** observed
2	Benzenesulfonic acid	$PhSO_3$	Only imine **77** observed
3	Methanesulfonic acid	CH_3SO_3	Pale orange precipitate
4	$HBF_4.Et_2O$	BF_4	Solid precipitated

Table 1.13

Returning to the most promising result up to this point, that being the solid recovered from the reaction with methanesulfonic acid, we wished to ascertain whether this was indeed the desired iminium salt **78d**. As the spectroscopic data for the material recovered was rather complex, we initially took a sample of the material and simply stirred it in methanol at room temperature overnight. Pleasingly, after this time oxabispidine **78** was observed by ^{1}H NMR analysis, and after filtration through a plug of silica, a 72% yield of **78** was obtained. This provided good supporting evidence that the precipitate recovered was indeed iminium salt **78d**.



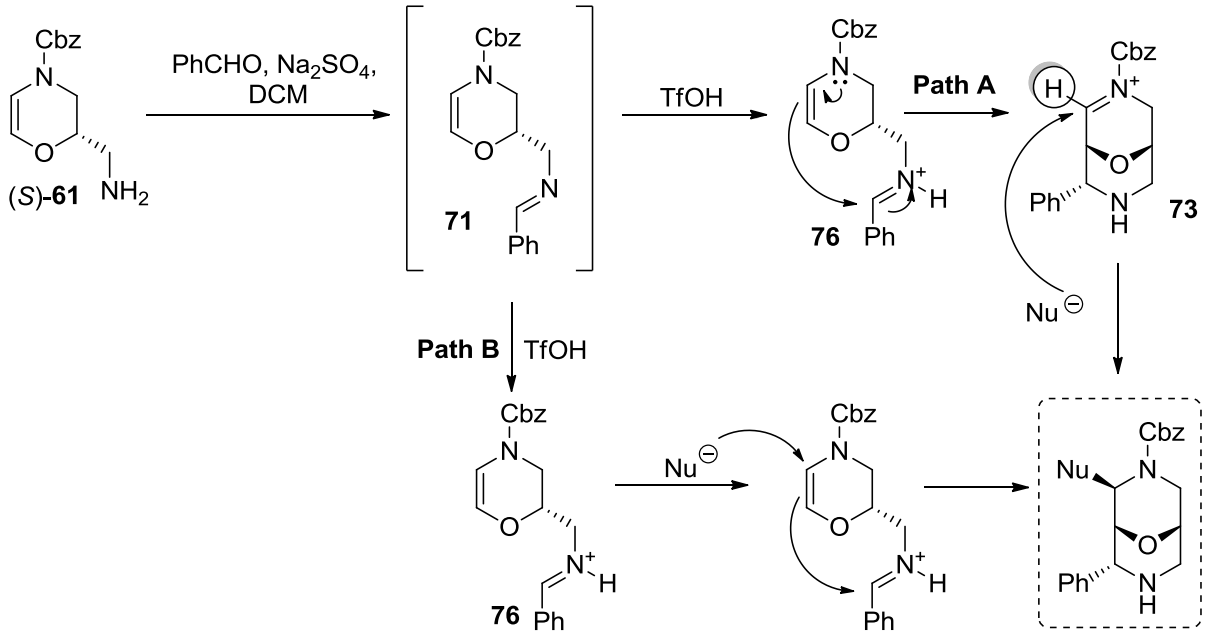
Scheme 1.54

To gain definitive proof that the isolated solid was **78d**, several recrystallization attempts were made in order to allow X-ray crystallography to be carried out. Bearing in mind that the use of alcoholic solvents may lead to quenching of the iminium species, the solvents used in these crystallisation attempts were limited. Despite several attempts, crystals of sufficient quality were never obtained. Although disappointed that we were unable to gain an X-ray crystal structure, we were pleased to discover that the mass ion observed for the iminium cation and anion in high resolution mass spectrometry was in agreement with our proposed structure. Having gained strong experimental evidence that we had in fact isolated iminium salt **78d**, and thus evidence that the oxabispidine forming step occurs *via* path A in **Scheme**

1.49, as opposed to the concerted MeOH addition/cyclisation process described in path B, we wished to model the reaction computationally in order to assess if the outcomes match these experimental findings, as well as the stereochemical outcomes discussed previously (*Section 3.2.1.1*).

3.2.2.2 Computational Study of Oxabispidine Formation

Initially, we proposed to investigate both Pathways A and B, shown in **Scheme 1.55**, computationally. However, based on the strong experimental evidence gained from isolating the mesylate salt **78d**, and in an effort to maximise both time and cost efficiency with regards to the computational experiments, ultimately only pathway A (towards the formation of iminium **73**) was modelled to confirm that this mechanism was indeed energetically favourable.[44] Additionally, such theoretical calculations would allow us to corroborate the stereochemistry of oxabispidine **70** that was identified through our NMR studies.



Scheme 1.55

The graph below summarises the cyclisation mechanism, starting from the protonated iminium **76**. It should be noted that the Cbz group has been truncated to the simple methyl carbamate in order to alleviate computational cost. Having established through NMR experiments that the imine intermediate **71**, and thus iminium **76**, were of *E*-geometry, we

chose to model the two conformations of the starting *E*-iminium intermediate necessary to deliver the two possible diastereomers of the product. The two lines on the graph represent these conformers (**76**-*conformer 1* and **76**-*conformer 2*), and, pleasingly it was found that the lower energy path is that which leads to the product **70** with the stereochemistry proposed from our NMR studies.

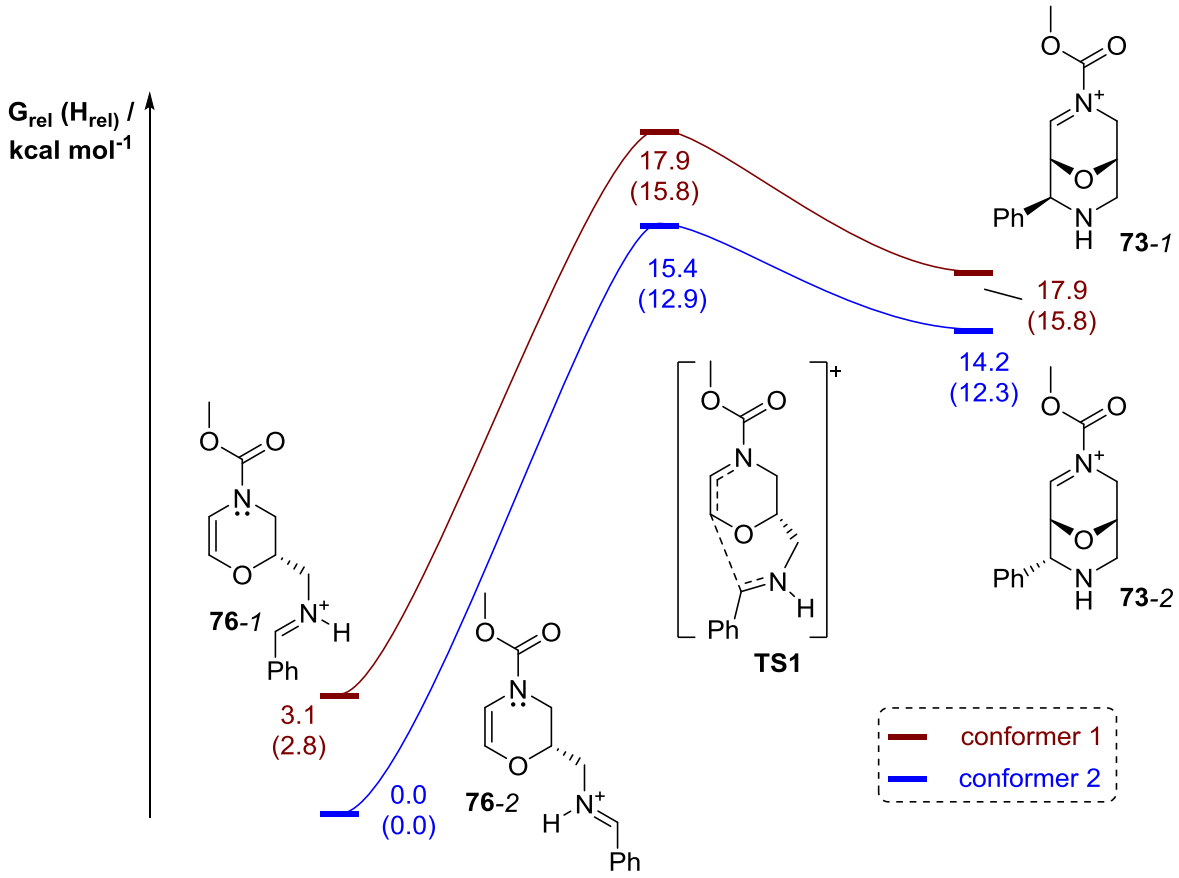


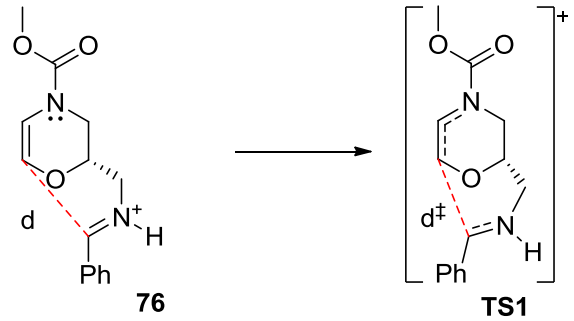
Figure 1.20

Table 1.14 below summarises the absolute values of transition state energies of both pathways, and shows that the overall free energy change for the cyclisation is in fact similar for both reactions. However, the enthalpy change (ΔH) is far more discriminatory. The pathway leading to the observed product is significantly lower in energy (**Entry 2**, **Table 1.14**), with **76**-*conformer 2* also being most stable as well as the most reactive.

Entry	Conformer	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$
1	**1**	14.8	17.0
2	**2**	15.4	12.9

Table 1.14

From the above results, it appears that $\Delta G^{\ddagger}$ is slightly more favourable for the unobserved reaction, i.e. that which gives rise to oxabispidine with the phenyl group possessing the opposite stereochemistry to **70** (**Entry 1**, **Table 1.14**), whilst $\Delta H^{\ddagger}$ favours the reaction which gives rise to the observed **70** (**Entry 2**). This is down to entropy, with the entropy change on reaching the transition state being slightly more favourable for the unobserved pathway due to the reacting centres have to move less to reach the activated complex in *conformer 1* vs. *2*. This is summarised in the table below. The enthalpy change, on the other hand, favours the reaction which forms **70** with the observed stereochemistry.



Scheme 1.56

Entry	Conformer	d (Å)	$d^{\ddagger}$ (Å)	$d - d^{\ddagger}$ (Å)
1	**1**	3.11	1.95	1.16
2	**2**	3.16	1.90	1.26

Table 1.15

Whilst we were able to successfully model the formation of iminium ion **73**, and show that the pathway which generated **73** with the experimentally observed stereochemistry was the most thermodynamically favourable pathway (*via* **76**-*conformer 2*), we were unable to model the final methanol addition step. This outcome was not a significant issue, as we were confident of the orientation of the methanol attack from our previous NMR work.

Furthermore, upon modelling the final oxabispidine, we found that the diastereomer with our previously proposed stereochemistry, was indeed the most stable (**70**-*diastereoisomer 2*, **Figure 1.21**).[44]

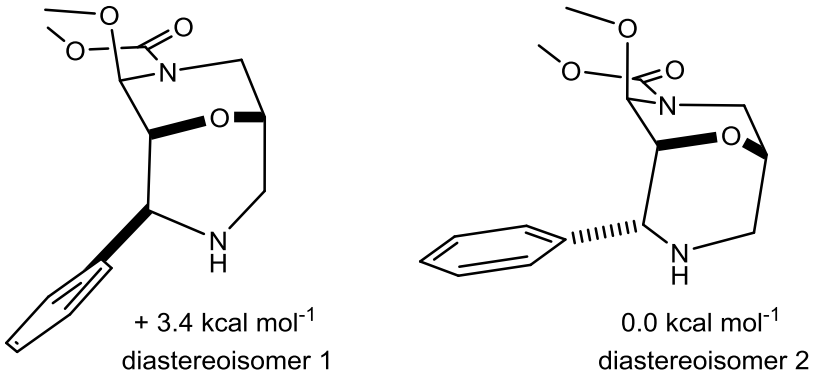


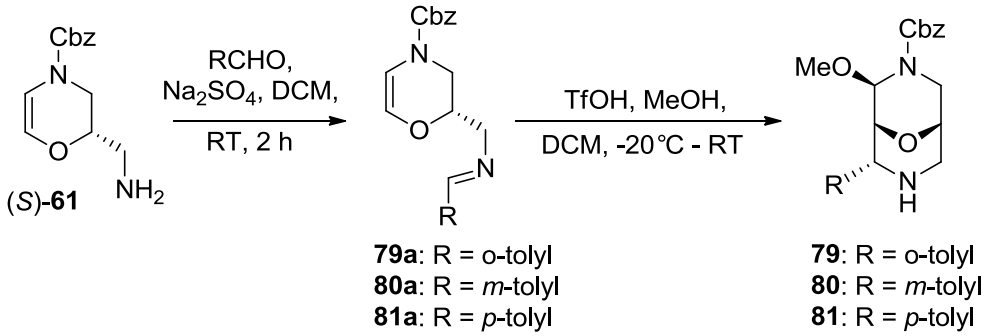
Figure 1.21: ΔH values for **70**-*conformer 1* and *2*

3.2.3 Preparation of a Range of Oxabispidine Derivatives

Although we were unable to acquire definitive proof that we had isolated the proposed iminium intermediate through X-ray crystallography, the mass spectrometry result provided strong evidence in our favour and valuable mechanistic insight was gained from our computational studies. With our successfully developed protocol (amenable to both TfOH and TMSOTf activation) in hand, we wished to explore the generality of the procedure and apply it in the reaction of oxazine (*S*)-**61** with a broad scope of aldehydes, encompassing those with a variety of steric and electronic properties. If successful, this would allow a wide array of oxabispidine scaffolds to be prepared, which, in turn, would allow the generation of a library of compounds of potential biological interest in a robust and efficient way.

3.2.3.1 Preparation of Aryl/Heteroaryl-substituted Oxabispidines

At the outset, we wished to evaluate the effect that steric parameters would have on our developed cyclisation process. Initially, three tolualdehyde derivatives were chosen, with the expectation that these reactions would proceed smoothly due to the merely subtle change in structure from benzaldehyde. This was indeed the case, with each of the corresponding imines being successfully formed in 2 hours, and the subsequent TfOH-promoted cyclisations providing the desired oxabispidine structures in good yields (**Scheme 1.57**, **Table 1.16**).



79a: R = o-tolyl
80a: R = *m*-tolyl
81a: R = *p*-tolyl

79: R = o-tolyl
80: R = *m*-tolyl
81: R = *p*-tolyl

Scheme 1.57

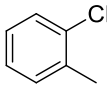
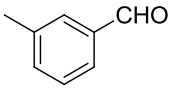
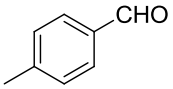
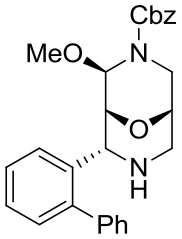
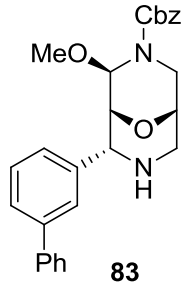
Entry	Aldehyde	Yield
1		62%
2		64%
3		48%

Table 1.16

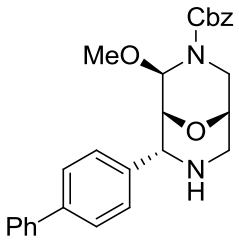
Having successfully constructed the three tolyl-substituted oxabispidine structures, attention was next focused on the synthesis of the more sterically hindered biphenyl derivatives (**Figure 1.22**).



82



83

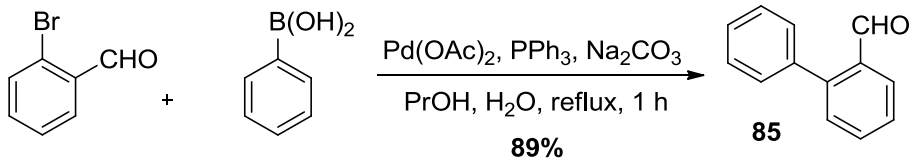


84

Figure 1.22

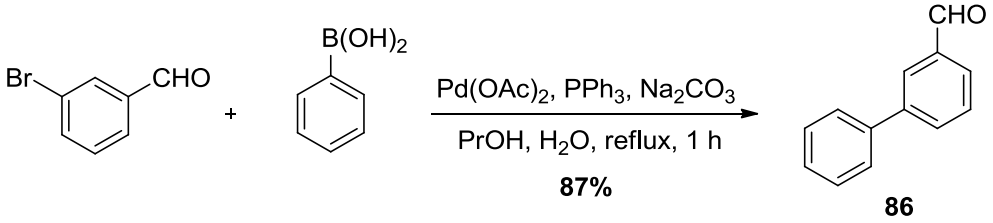
In the first instance, two of the requisite aldehydes (for the preparation of oxabispdines **82** and **83**) had to be synthesised. For this, a simple Suzuki cross-coupling reaction was proposed. In the initial attempt to couple 2-bromobenzaldehyde with phenylboronic acid, the

aryl halide and boronic acid were treated with palladium acetate, triphenylphosphine, and sodium carbonate in propanol heating at reflux (**Scheme 1.58**).[45] Gratifyingly, the reaction was complete after only 1 hour, affording the desired biphenyl product **85** in excellent yield with no need for chromatographic purification.



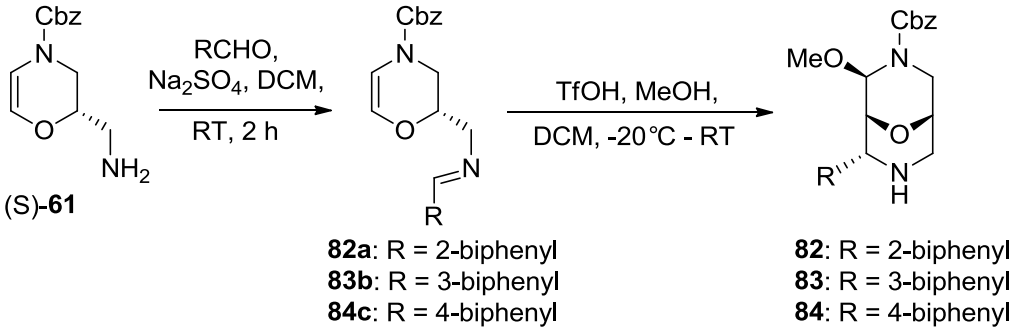
Scheme 1.58

Applying the above conditions in the preparation of *m*-biphenyl aldehyde **86**, the desired product was obtained in a similarly high yield of 87%.



Scheme 1.59

With aldehydes **85** and **86**, alongside the commercially available 4-biphenyl derivative, in hand, the synthesis of oxabispidines **82**, **83**, and **84** was attempted. Reaction of amine (*S*)-**61** with each of the biphenyl aldehydes proceeded efficiently, with full conversion to the corresponding imines **82a-84a** achieved in 2 hours. Treatment of each of these imines with methanol and triflic acid resulted in the desired oxabispidines being obtained in high yields for derivatives **83** and **84**, and a moderate yield for **82** (**Scheme 1.60**, **Table 1.17**). This is perhaps unsurprising due to the increased steric hindrance imposed by the *ortho*-substituent within derivative **82**, leading to a decrease in overall reactivity.



82a: R = 2-biphenyl
83b: R = 3-biphenyl
84c: R = 4-biphenyl

82: R = 2-biphenyl
83: R = 3-biphenyl
84: R = 4-biphenyl

Scheme 1.60

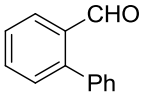
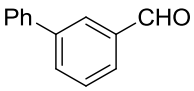
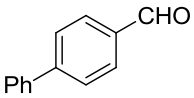
Entry	Aldehyde	Yield
1		51%
2		82%
3		75%

Table 1.17

With the construction of a library of optically-enriched oxabispidines underway, attention turned to the preparation of oxabispidines with a bulky naphthyl-substituent α to the nitrogen (**Figure 1.23**).

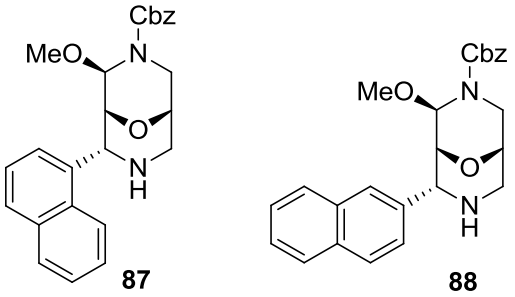
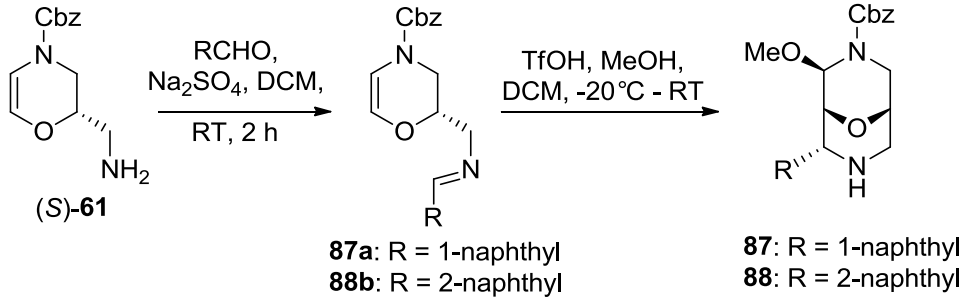


Figure 1.23

Subjecting the commercially available 1- and 2-naphthaldehydes to the TfOH-promoted reaction conditions, led to the desired oxabispidines **87** and **88** in significant yields.



Scheme 1.61

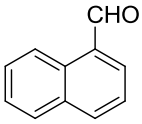
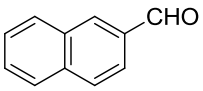
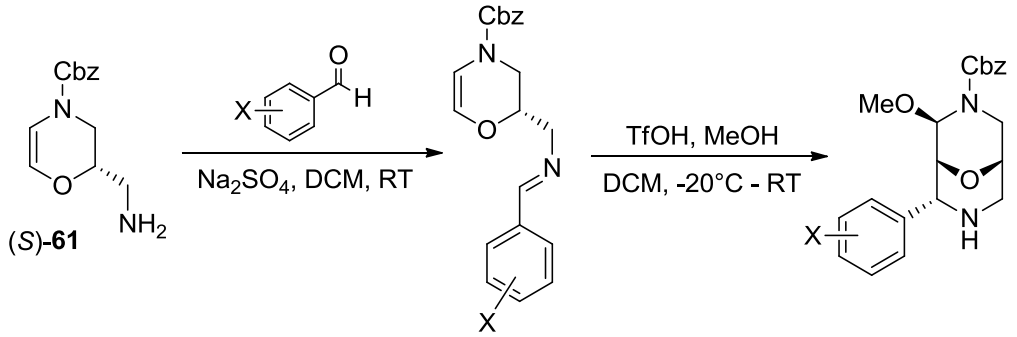
Entry	Aldehyde	Yield
1		73%
2		70%

Table 1.18

It should be noted at this point that all of the oxabispidines described above were also prepared using TMSOTf activation with comparable yields being achieved in all cases;[46] however, for convenience, the decision was taken to utilise triflic acid for the most part in future reactions. The successful results illustrated above, particularly with regards to *o*-biphenyl derivative **82** and 1-naphthyl derivative **87**, indicated that steric bulk does not seem to present a significant issue for the developed Mannich-type cyclisation process.

We next wished to turn our attention to a range of benzaldehydes bearing various electron-withdrawing and electron-donating substituents, to observe the influence of electronics on the reaction (**Scheme 1.62**, **Table 1.19**).

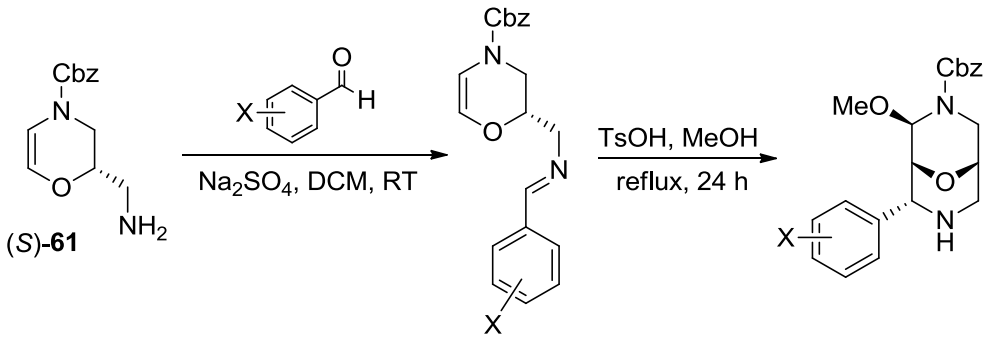


Scheme 1.62

Entry	X	Imine	Product	Yield
1	*o*-CF_3	**89a**	**89**	76%
2	*o*-Br	**90a**	**90**	89%
3	*p*-NO_2	**77**	**78**	73%
4	*p*-CN	**91a**	**91**	48%
5	*o*-OH	**92a**	**92**	0%
6	*p*-OCH_3	**93a**	**93**	0%

Table 1.19

As demonstrated above in **Table 1.19**, **Entries 1-4**, aryl aldehydes bearing electron-withdrawing groups reacted smoothly to give the corresponding oxabispidine products in good to excellent yields under the previously developed optimal conditions. Unfortunately, moving to electron-rich aldehyde substrates, such as salicylaldehyde and anisaldehyde, was less successful under standard conditions. Despite successful formation of the corresponding imines, no desired oxabispidine product was recovered in either case (**Table 1.19**, **Entries 5 and 6**). Based on these results, it became apparent that more forcing conditions would be required for electron-rich substrates. Believing that elevated temperatures would be needed to push the cyclisation reaction in the case of these substrates, *p*-toluenesulfonic acid was chosen as a more compatible acid with higher reaction temperatures. After formation of the requisite imine, TsOH was added and the reaction was stirred in refluxing methanol for 24 h. Pleasingly, as shown in **Scheme 1.63**, **Table 1.20**, these more forcing conditions did indeed deliver the desired oxabispidine products **92** and **93** in moderate yields.

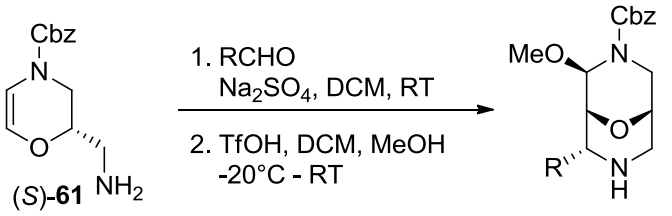


Scheme 1.63

Entry	X	Product	Yield
1	*o*-OH	**92**	40%
2	*p*-OCH_3	**93**	53%

Table 1.20

Having found suitable conditions to afford access to oxabispidines from both electron-rich and electron-poor aryl aldehydes, attention was turned to assessing whether these conditions were compatible with heteroaromatic aldehydes. Heterocycles are ubiquitous within pharmaceutical research and, as such, incorporation of such moieties within our oxabispidine scaffolds would be highly attractive. With regards to their prospective use as chiral ligands, oxabispidines with an additional heteroatom in the sidearm of the molecule have the potential of a further chelating effect, and therefore presented an interesting avenue to explore. In this regard 2- and 4-pyridylcarboxaldehyde, as well as 2-thiophenecarboxaldehyde, were submitted to the original triflic acid conditions (**Scheme 1.64**, **Table 1.21**).



Scheme 1.64

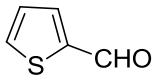
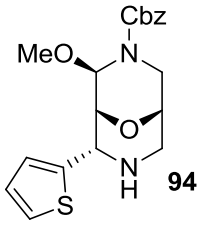
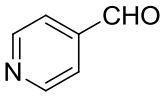
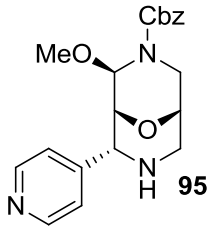
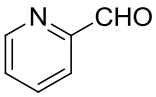
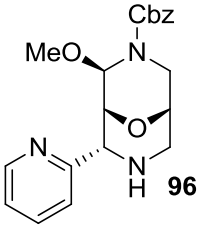
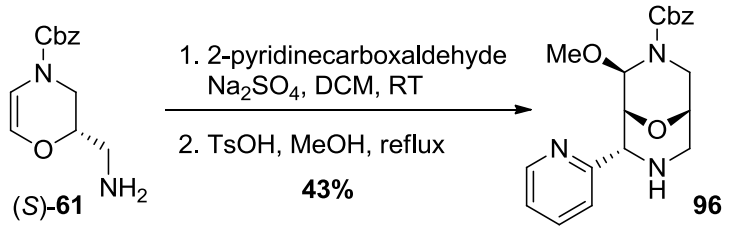
Entry	Aldehyde	Product	Yield
1		 **94**	20%
2		 **95**	43%
3		 **96**	10%

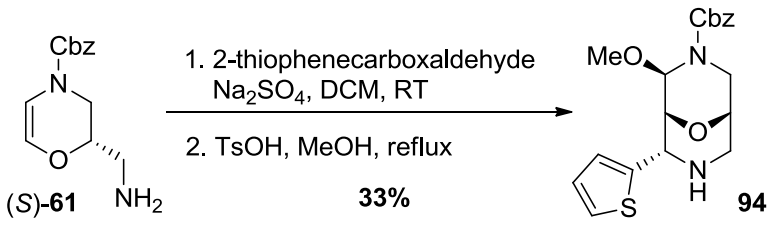
Table 1.21

Pleasingly, under these conditions the 2-thiophene and 4-pyridyl compounds **94** and **95** were easily accessed, albeit in more modest yields compared to the majority of the aryl derivatives synthesised previously. Unfortunately, the reaction employing 2-pyridinecarboxaldehyde was more capricious, and the desired oxabispidine **96** was not recovered in any significant quantity under the original triflic acid conditions. Having said this, switching to the more forcing conditions described above led to the desired product **96** being obtained in a more respectable 43% yield (**Scheme 1.65**).



Scheme 1.65

In an attempt to improve the yield for the thiophene analogue, the same *p*-toluenesulfonic acid conditions were screened. Whilst a slight improvement was observed, the yield remained relatively modest, with only 33% of **94** being recovered (**Scheme 1.66**). Nonetheless and overall, we were pleased to have gained access to oxabispidine motifs bearing heterocyclic sidearms.



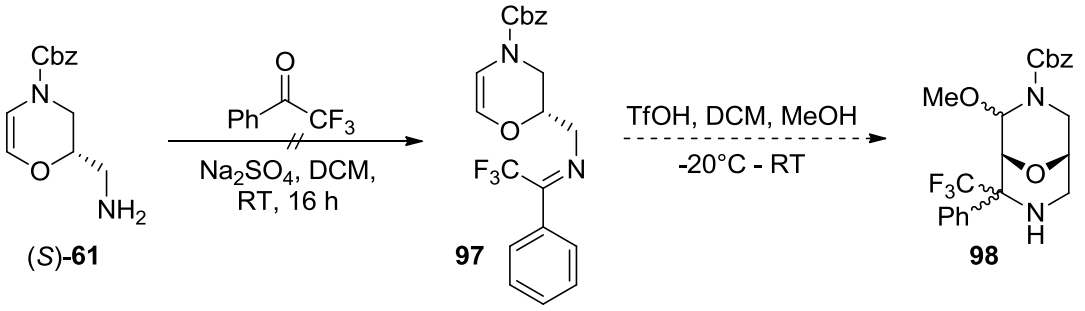
Scheme 1.66

3.2.3.2 Attempts to Access More Heavily Functionalised Analogues

Having successfully broadened the scope of aryl-oxabispidines, and having demonstrated that the procedure can be extended to heteroaromatic aldehydes, we wished to examine if the developed cyclisation procedure was amenable to aryl ketone substrates. This class of substrate would allow efficient access to oxabispidine scaffolds with increased complexity, a desirable attribute aligned to the drug discovery trends discussed earlier. The successful application of ketone substrates would allow the installation of a tetra-substituted stereogenic centre within the oxabispidine structure, a significant challenge in general within synthetic chemistry.

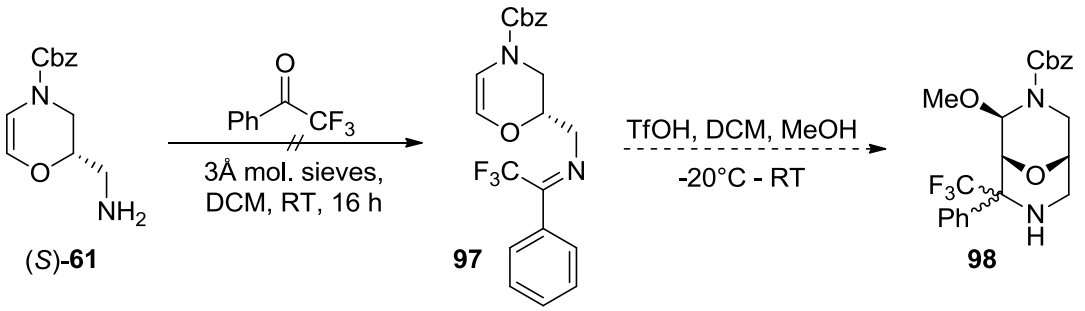
Careful consideration of the initial substrate led us to choose 2,2,2-trifluoroacetophenone for our preliminary investigations. Through the use of this substrate it was believed that the potential for side reactions would be reduced due to its inability to enolise, and we envisaged

that the electron-poor nature of the ketone would favour the cyclisation reaction. Unfortunately, under our original imine-forming conditions, we observed none of the desired imine **97**, even after extending the reaction time to 16 hours (**Scheme 1.67**).



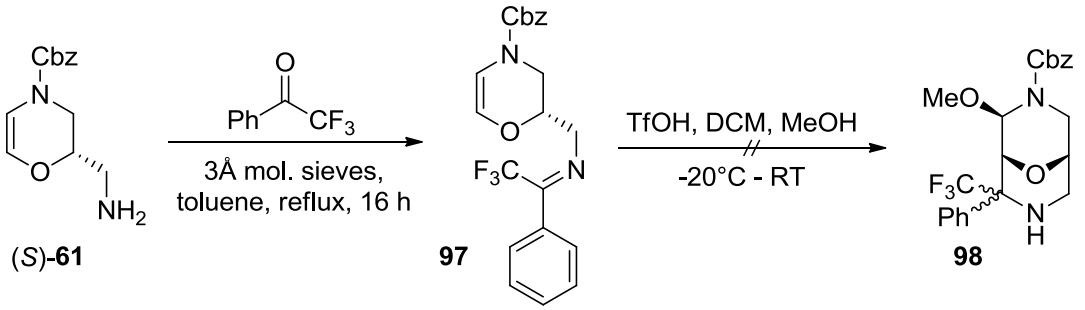
Scheme 1.67

It was proposed that the use of molecular sieves may be more effective in sequestering the water generated upon imine formation and, in turn, drive the reaction forward. However, at room temperature the process summarised in **Scheme 1.68** was unsuccessful.



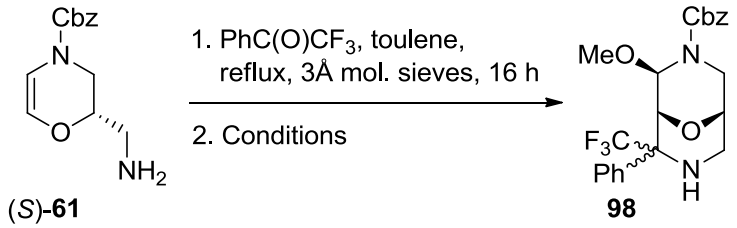
Scheme 1.68

Considering the reactivity difference between an aldehyde and ketone, we believed that significantly more forcing conditions would be required to enable imine formation. Pleasingly, performing the reaction in toluene at reflux led to conversion to the desired imine, with crude ^{1}H and ^{19}F NMR analysis showing full conversion after 16 hours. However, treatment of the imine with triflic acid and methanol, followed by stirring at room temperature overnight, led to a complex reaction profile, with none of the desired product **98** being obtained (**Scheme 1.69**).



Scheme 1.69

Based on the success we observed previously when employing more damanding electron-rich aldehyde substrates, we moved to the use of elevated temperatures in combination with tosic acid. Employing tosic acid heating in methanol at reflux overnight, unfortunately only led to the recovery of imine and starting oxazine (*S*)-**61** (**Scheme 1.70**, **Table 1.22**, **Entry 1**). Futhermore, moving to acetonitrile to increase the temperature of the reaction led to a similar outcome (**Entry 2**). Considering the forcing conditions required for the imine formation, we chose to maintain the use of refluxing toluene in the oxabispidine formation step. In this case, the tlc profile of the reaction was significantly more complex after 16 h; however, upon chromatography only the imine intermediate was recovered (**Scheme 1.70**, **Table 1.22**, **Entry 3**).



Scheme 1.70

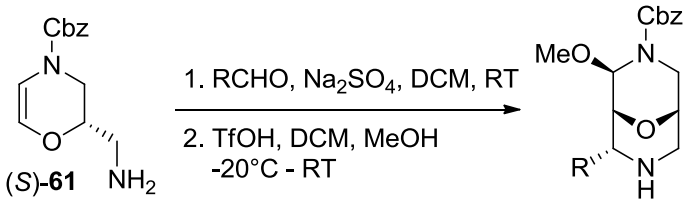
Entry	Conditions	Outcome
1	TsOH, MeOH, reflux, 16 h	Imine and SM recovered
2	TsOH, MeOH, MeCN, reflux, 16 h	Imine and SM recovered
3	TsOH, MeOH, toluene, reflux, 16 h	Imine recovered

Table 1.22

Based on the described outcomes, it became clear that the use of aryl ketones in our developed Mannich-type cyclisation was perhaps not going to be viable. With no trace of the oxabispidine product **98** being observed in any of the above reactions, and with an extensive range of aldehyde substrates still to explore, the decision was taken to abandon the screening of ketone substrates at this time. As such, we focused our efforts on potentially more productive lines of enquiry.

3.2.3.3 Preparation of Alkyl-substituted Oxabispidines

Undeterred by the disappointing results obtained during our attempts to extend the scope of the reaction to include ketone substrates, we next turned our attention to the installation of alkyl substituents in the α-position of the oxabispidine skeleton. To avoid any possible problems which may arise from aldehydes with α-protons undergoing aldol-type side reactions, the decision was taken to initially screen aldehydes for which no such issue would occur, namely pivaldehyde and trifluoroacetaldehyde (**Scheme 1.71**, **Table 1.23**, **Entries 1 & 2**). Under our standard conditions using triflic acid, the corresponding oxabispidine formation occurred without incident and afforded products **99** and **100** in good yields. It was noted that en route to oxabispidine **100**, rather than the imine being isolated as with previous examples, the corresponding aminal intermediate **100a** was observed instead. Additionally, we chose to screen the use of ethyl glyoxylate in the developed protocol. It was envisaged that the ester moiety present in this substrate would provide a potential functional handle and an additional point of diversity within our oxabispidine core. Indeed, as shown in **Table 1.23**, **Entry 3**, we were able to successfully access **101**, albeit in a lower yield that the previous examples.



Scheme 1.71

Entry	R	Product	Yield
1	*t*-Bu	**99**	67%
2	CF_3	**100**	66%
3	EtO_2C	**101**	40%

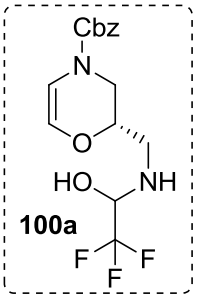
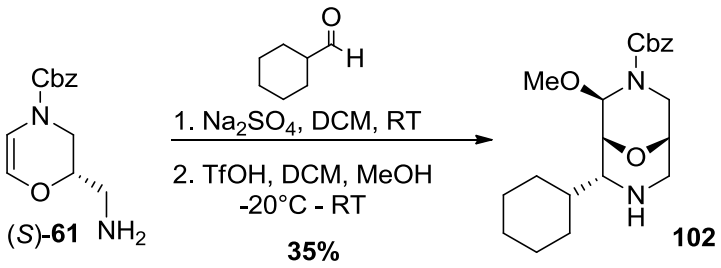


Table 1.23

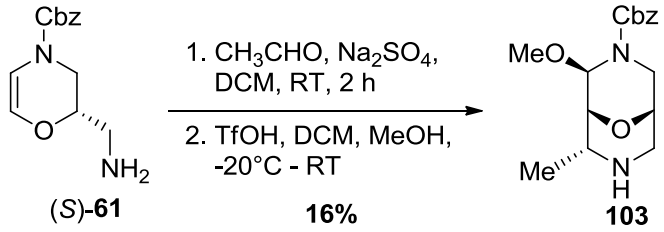
We were pleased to have developed an efficient and robust protocol, with the good yields obtained for oxabispidine **100** being particularly illustrative of this, owing to the fact that trifluoroacetaldehyde is purchased and used as the hydrate. This successful outcome demonstrates that rigorously anhydrous conditions were not required for such a transformation.

With the above results in hand, we turned our attention to the perhaps more challenging enolisable aldehyde substrates to fully explore the generality of our developed protocol. The first substrate chosen to test was cyclohexylcarboxaldehyde. Although the corresponding oxabispidine **102** was indeed formed, the yield was significantly lower than the reactions involving alkyl aldehydes **99** and **100** (**Scheme 1.72**).



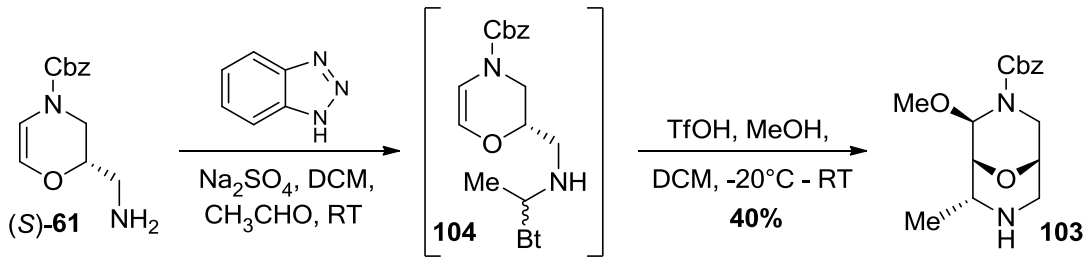
Scheme 1.72

Indeed a similar outcome was observed when the simplest aldehyde, acetaldehyde, was screened, with a very poor 16% yield of the desired methyl-substituted oxabispidine **103** being obtained (**Scheme 1.73**).



Scheme 1.73

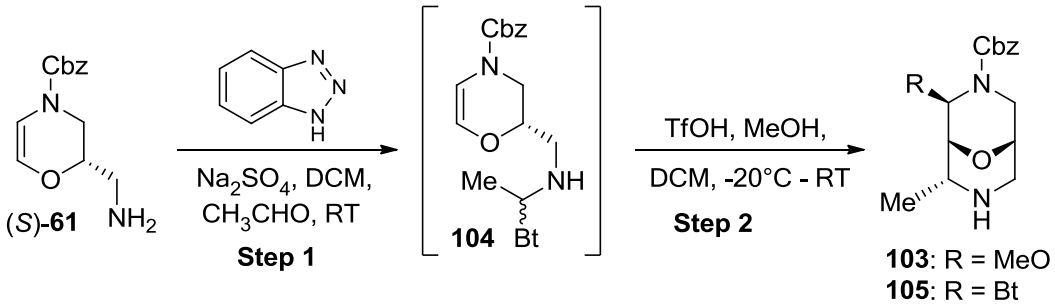
These less efficient outcomes with alkyl aldehydes led us to explore the use of Katritzky's technique of stabilising highly reactive aldehydes as the benzotriazole adduct.[47] The decision was taken to use acetaldehyde as the substrate to optimise the reaction conditions for this new protocol. With the inclusion of 1 equivalent of benzotriazole in the reaction mixture in order to generate benzotriazole adduct **104**, access to the desired oxabispidine **103** was achieved in an improved 40% yield.



Scheme 1.74

In attempts to maximise the yield of **103**, a brief optimisation study was carried out (**Scheme 1.75**, **Table 1.24**). Initially, the conditions described above were repeated to ensure the result was reproducible. Unfortunately, upon repetition, the desired product was only recovered in a poor 8% yield along with a small amount of the benzotriazole-substituted product **105** (**Entry 1**). Increasing the reaction time of step 1 to allow sufficient time to generate intermediate **104** improved the yield slightly (**Entry 2**), but again quantities of **105** were also recovered. Believing that the order of addition was also a significant factor in this first step, the next experiment performed was one in which the acetaldehyde and benzotriazole were stirred together for 15 minutes prior to the addition of oxazine (*S*)-**61** (**Entry 3**) which

resulted in a yield of 25% being achieved. As in the previous reactions, it was noted that, in addition to the desired product **103**, the benzotriazole-substituted product **105** was also recovered.



Scheme 1.75

Entry	Conditions for step 1	Yield of 103	Yield of 105
1	RT, 1 h	8%	5%
2	RT, 16 h	25%	10%
3	BtH + CH_3CHO, RT, 15 min, then (*S*)-**61**, RT, 30 min.	25%	12%

Table 1.24

Considering the above reactions, the presence of **105** in each case indicated that the liberated benzotriazole was itself a competent nucleophile capable of quenching the final iminium ion (**Figure 1.24**).

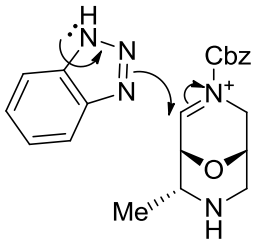
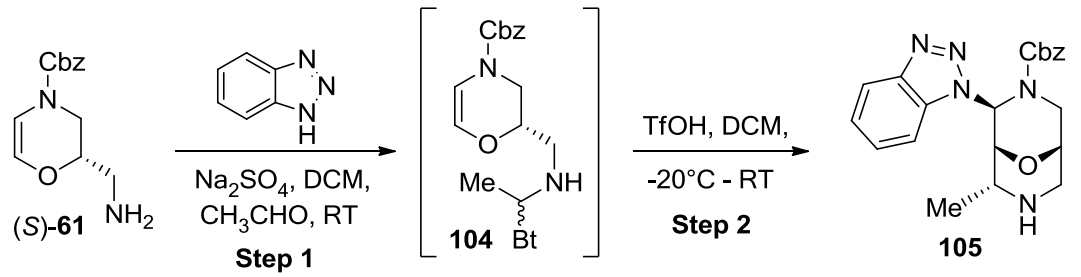


Figure 1.24

With this in mind, the decision was taken to omit methanol from the reaction mixture, and focus on optimising the yield of benzotriazole adduct **105**.

To this end, the original conditions depicted in **Scheme 1.74** were revisited, this time without the addition of methanol. After activation with triflic acid and stirring at room temperature for 1 h the desired product **105** was produced in a promising 39% yield (**Scheme 1.76**, **Table 1.25**, **Entry 1**). In an attempt to increase the yield further, our next iterative development focused on the order of addition of reagents in order to allow the benzotriazole sufficient time to stabilise the acetaldehyde prior to addition of oxazine (*S*)-**61**, a process believed to be fairly rapid. As shown in **Scheme 1.76, Table 1.25, Entry 2**, stirring benzotriazole and acetaldehyde for 15 min, prior to the addition of (*S*)-**61** and stirring for a further 30 min, then carrying out the second step, as described previously, led to the desired product in a slightly improved yield. Maintaining the step 1 sequence as described in **Entry 2**, attention was next turned to optimising the second step of the reaction, i.e. the triflic acid activation. It was postulated that perhaps the collapse of intermediate **104** (**Scheme 1.74**) would be slow, thus the reaction time of this step may need to be extended beyond the 1 hour at room temperature required for the previous aryl-derived substrates. With this in mind, an experiment was performed where, following the addition of triflic acid, the reaction mixture was allowed to warm to room temperature and stirred overnight (**Scheme 1.76**, **Table 1.25**, **Entry 3**). Unfortunately, this extended reaction time did not lead to an improvement in yield. This result was somewhat unsurprising as previous attempts to resubject phenyl-substituted oxabispidine **70** to the strongly acidic reaction media resulted in degradation. With this in mind, the reaction time was shortened to 3 hours, and pleasingly the desired product **105** was recovered in 58% yield, the best result up to this point (**Scheme 1.76**, **Table 1.25**, **Entry 4**). Gratifyingly, repetition of these conditions to ensure reproducibility again furnished **105** in a comparable yield (**Scheme 1.76**, **Table 1.25**, **Entry 5**).

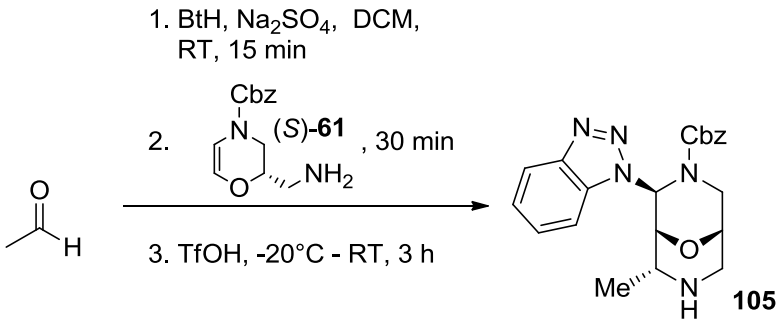


Scheme 1.76

Entry	Step 1 conditions	Step 2 conditions	Yield of 105
1	BtH, CH_3CHO, (*S*)-**61**, 1 h.	RT, 1 h	39%
2	BtH, CH_3CHO, 15 min, then (*S*)-**61**, 30 min	RT, 1 h	42%
3	BtH, CH_3CHO, 15 min, then (*S*)-**61**, 30 min	RT, 16 h	31%
4	BtH, CH_3CHO, 15 min, then (*S*)-**61**, 30 min	RT, 3 h	58%
5	BtH, CH_3CHO, 15 min, then (*S*)-**61**, 30 min	RT, 3 h	52%

Table 1.25

Pleased with the establishment of a synthetic protocol which allowed access to synthetically useful yields of methyl-oxabispidine **105**, attention was turned to performing this reaction on a larger scale. As shown in **Scheme 1.77**, **Table 1.26**, and perhaps indicated by the inconsistency observed during optimisation, the reaction proved to be rather capricious, with yields ranging from 12-64%. This variability was attributed to the volatile nature of acetaldehyde, and with a reasonable amount of oxabispidine **105** in hand, no further optimisation was undertaken at this time.

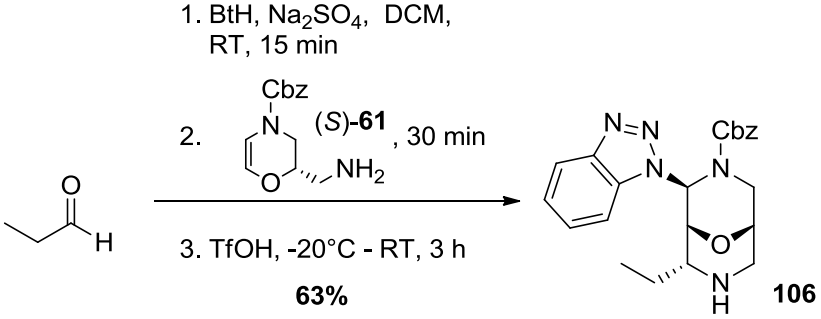


Scheme 1.77

Entry	Reaction Scale	Yield
1	8.1 mmol	12%
2	12.1 mmol	39%
3	12.1 mmol	64%

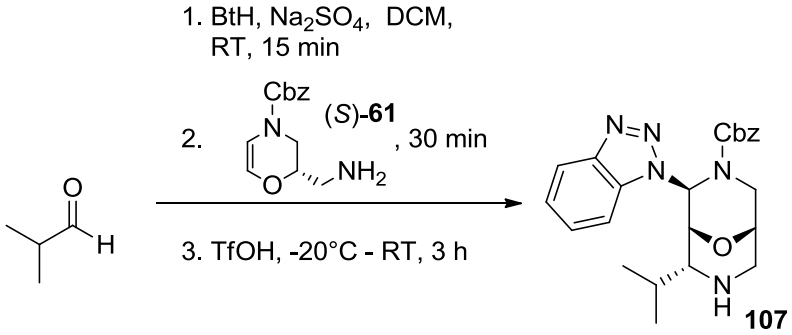
Table 1.26

With an effective procedure utilising benzotriazole now developed, the scope of the reaction was broadened to include propionaldehyde and *i*-butyraldehyde as starting materials to deliver the ethyl- and *i*-Pr substituted oxabispidines **106** and **107**, respectively. Employing propionaldehyde the reaction proceeded smoothly, providing **106** in good yield (**Scheme 1.78**). This outcome was reproducible,[48] and suggests that the volatility of acetaldehyde was a significant factor in the capricious nature of the previously described reaction. Indeed, with the carbon chain extended by one in propionaldehyde, volatility is less of an issue, and in turn the yields of the corresponding oxabispidines are noticeably higher and more consistent.



Scheme 1.78

Somewhat disappointingly, moving to the more sterically bulky *i*-butyraldehyde under the same reaction conditions, yields of no higher than 32% were achieved (**Scheme 1.79**, **Table 1.27**).

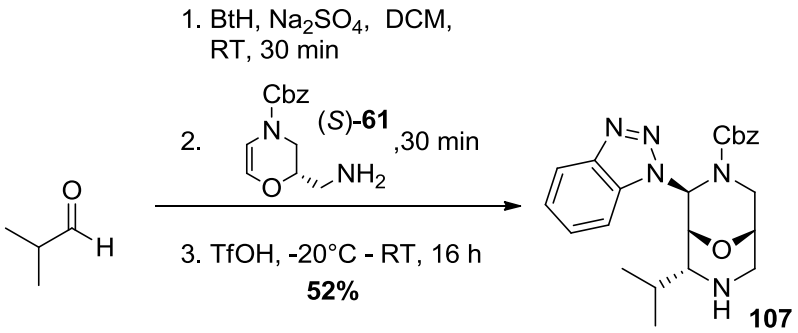


Scheme 1.79

Entry	Reaction Scale	Yield
1	0.8 mmol	32%
2	0.8 mmol	12%

Table 1.27

With increased steric bulk as compared to propionaldehyde, the low yields observed in the above reaction could not be attributed to a volatility issue. Having said this, it was believed that perhaps the increased steric bulk of this aldehyde were in fact making it less reactive, and thus a longer reaction time was investigated to increase the chemical yield of the desired oxabispidine **107**. Pleasingly, prolonging the reaction time of the triflic acid-mediated cyclisation led to an additional increase in yield; overnight stirring at room temperature provided the desired product in a respectable 52% yield (**Scheme 1.80**).



Scheme 1.80

At this stage, it is pertinent to discuss the NMR spectra of the above benzotriazole substituted oxabispidine derivatives **105**-**107**. The ^{1}H NMR spectra of these species display increased complexity as compared to the corresponding aryl oxabispidines with a methoxy substituent. This was originally attributed to *additional* rotameric effects from the benzotriazole moiety leading to a mixture of 4 rotamers. However, variable temperature ^{1}H NMR experiments disproved this initial assumption. Using the methyl-derivative **105** as an example, it can be seen that the 1D ^{1}H NMR data as a function of temperature indicate that whilst some of the resonances go through coalescence on sample heating, others, such as many of those in the 6-8 ppm region, remain unchanged (**Figure 1.25**).

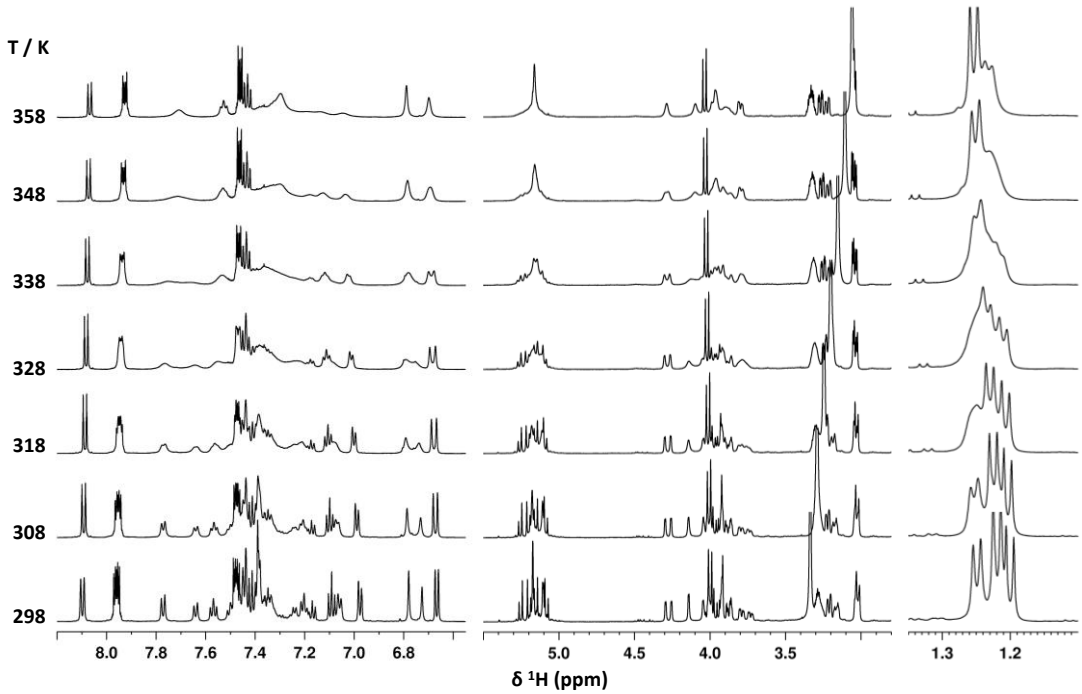


Figure 1.25: 1D ^{1}H NMR spectra of **105** acquired as a function of temperature.

Initially, we questioned whether the persistent doubling of the signals at elevated temperatures could still be due to rotameric effects, and that the energy barrier to overcome the restricted rotation was simply too high for the temperatures at which the spectra were run. To rule out such a situation, 2D [^{1}H, ^{1}H] EXSY NMR experiments at both 298 K and 358 K (**Figure 1.26**) that focused on the aromatic region were used.[49] EXSY experiments offer a simple way to obtain information about dynamic processes (for instance, conformational or chemical exchange) in a molecule. Thus, with regards to oxabispidine **105**, if the additional peaks still present at higher temperatures are indeed due to a further set of rotamers, off diagonal signals between these sets of peaks would be observed.

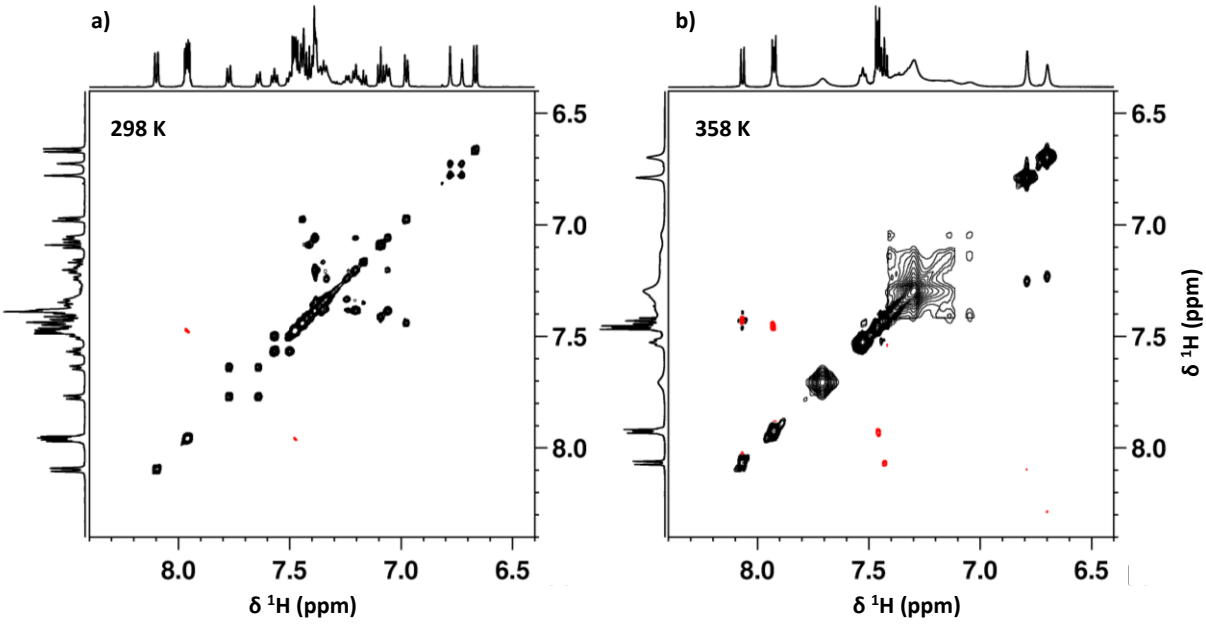


Figure 1.26: 2D [^{1}H, ^{1}H] EXSY NMR data for the sample at a) 298 K and b) 358 K.

Referring back to the spectra shown in **Figure 1.25**, in particular focusing on the resonances between δ^1H = 6.70 ppm and 6.80 ppm, it can be seen that whilst coalescence is observed to an extent, at 358 K (the highest temperature screened) two distinct resonances are still observed. Considering these same resonances at δ^1H = 6.70 and 6.78 ppm in **Figure 1.26b**, presumed to be from two different species in solution, it was noted that they did not appear to share mutual exchange (no intervening cross-peak). To be more specific, if these two signals observed at elevated temperature were a result of rotamers, Figure 1.26b would display an off-diagonal signal for δ^1H = 6.70 ppm corresponding to δ^1H = 6.78 ppm and vice versa; however this is not the case. A more detailed examination of this condition was carried out

by means of 1D selective EXSY (**Figure 1.27**). If the two species observed were in fact rotamers, then when the signal at δ^1H = 6.78 ppm is selectively irradiated as shown in (b) **Figure 1.27**, an enhancement of the signal at δ^1H = 6.70 ppm would be observed. The absence of any response in b) at δ^1H = 6.70 ppm again indicated lack of chemical exchange between the species giving rise to the signals at δ^1H = 6.78 and 6.70 ppm.

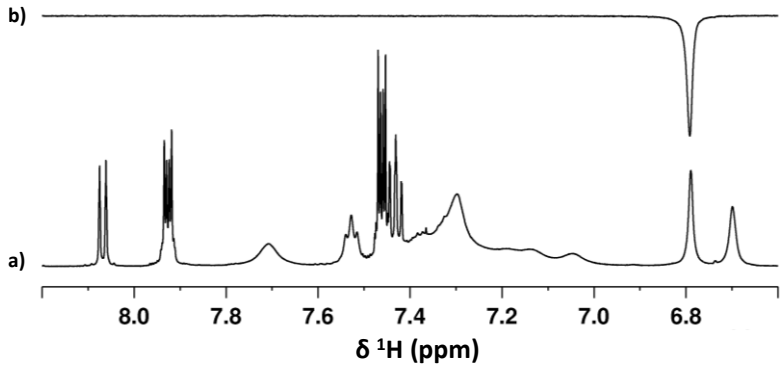


Figure 1.27: a) 1D ^{1}H NMR spectrum at 358 K; b) 1D ^{1}H selective EXSY NMR spectrum showing selective inversion at δ^1H = 6.78 ppm.

These data suggested the presence of two similar species in solution which did not interconvert with one another but which individually underwent dynamic exchange with a second conformational partner, i.e. the carbamate rotamers observed previously.

Careful consideration of the structure of **105** led us to propose that the additional species observed could be as a result of the presence of diastereomers or benzotriazole positional isomers, for which there is literature precedent (**Figure 1.28**).[47,50]

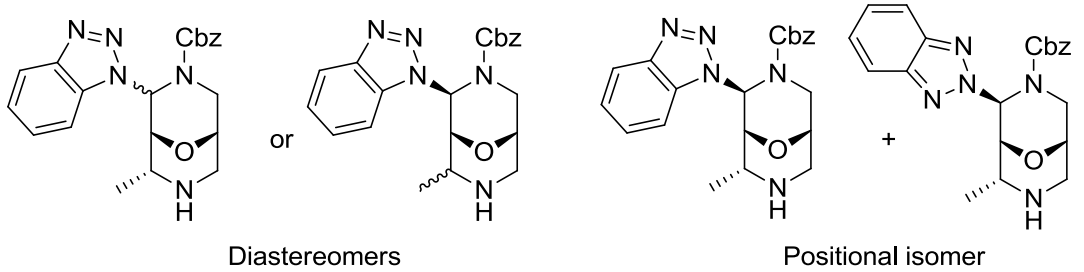


Figure 1.28

Extensive 2D NMR experiments were carried out in order to ascertain the correct structure of the species present in solution.[49] Full details of the experiments ran, in addition to full spectral assignment of each structure, can be found in the Appendix, however, key points

which led to the conclusion that the additional spectral complexity in **105** (and associated compounds) was due to the presence of benzotriazole positional isomers are highlighted in **Figure 1.29**. The presence of diastereomers was ruled out with the observation of nOe signals between the methyl group and proton H_a (**Figure 1.29**), indicating that these were on the same side of the molecule in both species present. On the other hand, nOe signals between both H_a and H_b on the oxabispidine core and H_c on the benzotriazole substituent were only observed in isomer **105i**, as highlighted in **Figure 1.29**. Such nOe signals would only be possible if the *N*-1 benzotriale adduct had formed. With regards to isomer **105ii**, no such nOe signals with the benzotriazole protons were noted, indicating that the *N*-2 benzotriazole adduct had also formed, as the aryl protons in this case are too far away to observe any through-space effects.

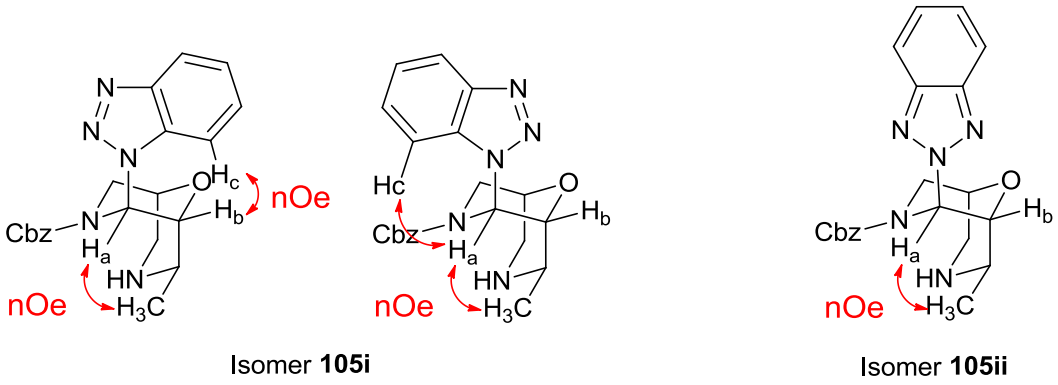


Figure 1.29

Having established the additional complexity in our benzotriazole series was due to the presence of both *N*-1 and *N*-2 isomer and, in the process, confirming that the stereochemical integrity of our oxabispidine collection remained intact upon switching nucleophiles, we turned our attention back to expanding the scope of our optically-enriched oxabispidine library.

*3.2.3.4 Preparation of Tricyclic Oxabispidine **108***

Having successfully broadened the library of oxabispidines to include alkyl-substitutents, the next area of interest was to establish access to the more challenging tricyclic compound **108** (**Figure 1.30**). This compound, compared to previous oxabispidine examples, has a more

similar structure to (-)-sparteine (**109**), which, in addition to being an extensively utilised chiral ligand, has been shown to have uterotonic and anti-arrhythmic properties.[51]

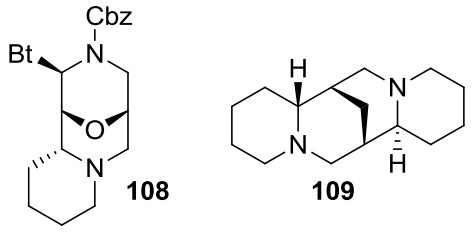
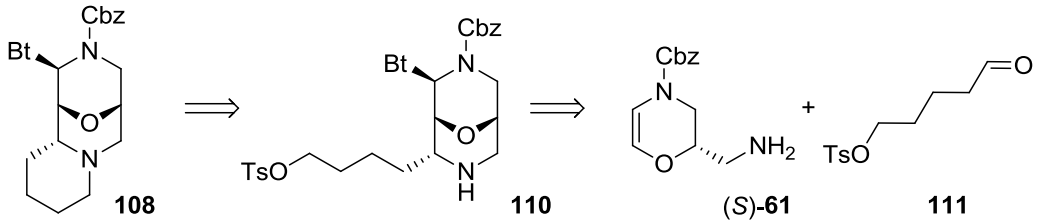


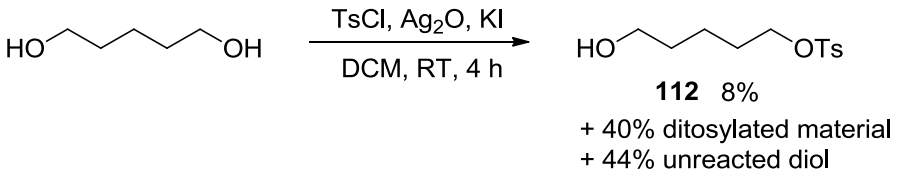
Figure 1.30

As depicted in **Scheme 1.81** it was envisioned that **108** could be easily accessed *via* an intramolecular nucleophilic attack of the free nitrogen of oxabispidine **110** onto the extended alkyl chain bearing a leaving group on the terminal carbon. Oxabispidine **110** itself would be prepared in the same manner as previous oxabispidines described: from oxazine (*S*)-**61** in combination with aldehyde **111**, which can ultimately be prepared from the cheap commercially available 1,5-pentanediol.



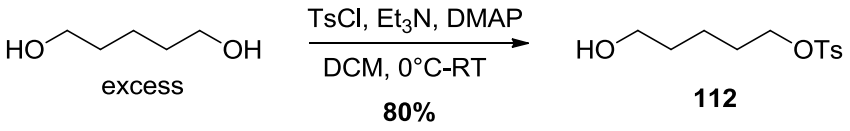
Scheme 1.81

The first step in the synthesis was the monotosylation of 1,5-pentanediol (**Scheme 1.82**). Following a recent literature procedure,[52] which utilised tosyl chloride in combination with silver (I) oxide and potassium iodide and avoided the need for low temperatures or slow addition, unfortunately led to a poor 8% yield of the desired monotosylated product **112**, with the majority of material recovered being the ditosylated species and unreacted diol.



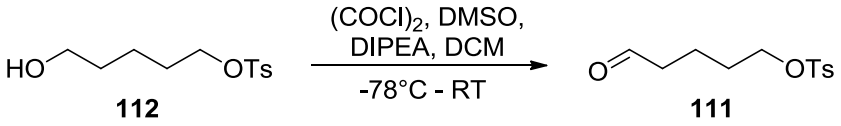
Scheme 1.82

Following this result, employment of a more traditional method of syringe pump addition of tosyl chloride over several hours to an excess of the diol starting material led to the desired monotosylated product in a much improved 80% yield (**Scheme 1.83**).[53]



Scheme 1.83

With significant quantities of alcohol **112** in hand, oxidation to the corresponding aldehyde **111** was carried out under standard Swern conditions. On a small scale, an initially disappointing yield of 37% was achieved, however, upon increasing the scale of the reaction, an excellent yield of 90% was obtained (**Scheme 1.84**).



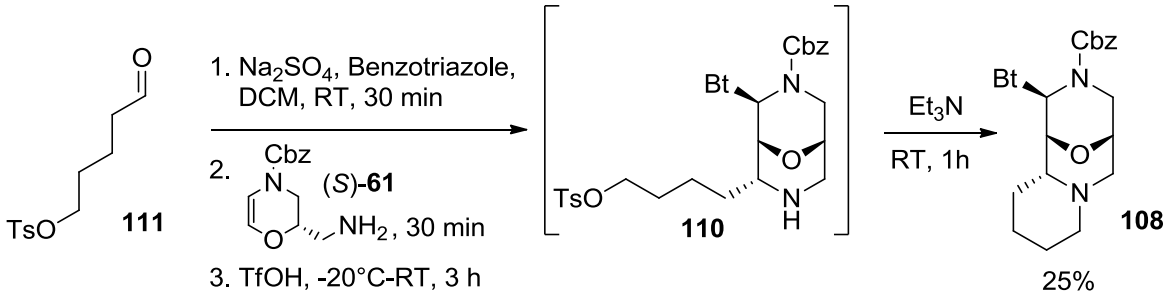
Scheme 1.84

Entry	Reaction Scale	Yield
1	1.6 mmol	37%
2	7.7 mmol	90%

Table 1.26

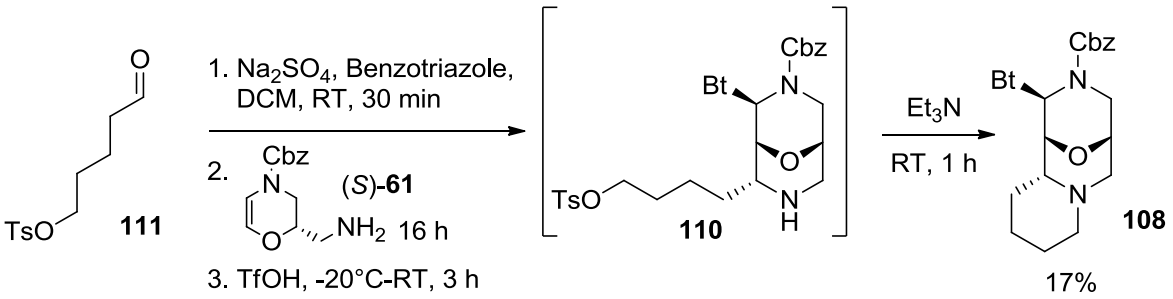
Having prepared the requisite aldehyde, attention turned to utilising **111** in the oxabispidine forming reaction (**Scheme 1.85**). Employing a similar protocol to the reactions of alkyl aldehydes described previously, the aldehyde was treated with benzotriazole prior to the addition of oxazine (*S*)-**61**. After stirring for 30 min at room temperature the reaction was cooled to -20°C and triflic acid was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. After this time, tlc analysis of the reaction mixture showed several compounds to be present. Believing that any residual acid present may be preventing the displacement of the tosylate leaving group of intermediate **110**, in the process required to form the third ring of **108**, 1.1 equivalents of triethylamine were added. It was hoped that after addition of a base, tlc analysis would show disappearance of a spot on the tlc

plate, indicating conversion from **110** to **108**. Unfortunately, such an occurrence was not observed. The reaction was quenched and, after purification, the desired product was obtained in 25% yield. Despite this modest yield, we were pleased to have prepared the first tricyclic derivative within our oxabispidine series.



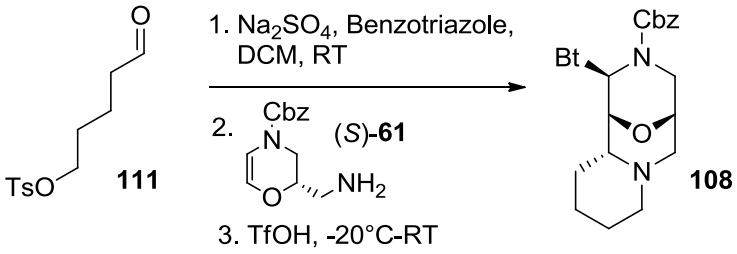
Scheme 1.85

Having noted that in the previous reaction a significant amount of unreacted aldehyde **111** was returned, it was proposed that prolonging the stirring time after addition of oxazine (*S*)-**61** may improve the chemical yield. Unfortunately, extending the reaction time to 16 h before addition of the triflic acid did not afford the desired outcome, with the yield falling slightly to 17% (**Scheme 1.86**).



Scheme 1.86

In an attempt to gain a better understanding of the reaction sequence, and, in turn, determine the most appropriate reaction times for each step, the reaction was monitored by GCMS (**Scheme 1.87**).



Scheme 1.87

As described above, aldehyde **111** was first treated with benzotriazole, and the GC trace after 3 hours showed the presence of both reagents, in addition to the presence of the resulting benzotriazole adduct **113** (**Figure 1.31**). Having said this, a similar trace was observed after only 15 minutes, therefore the extended reaction time for this step appears unnecessary.

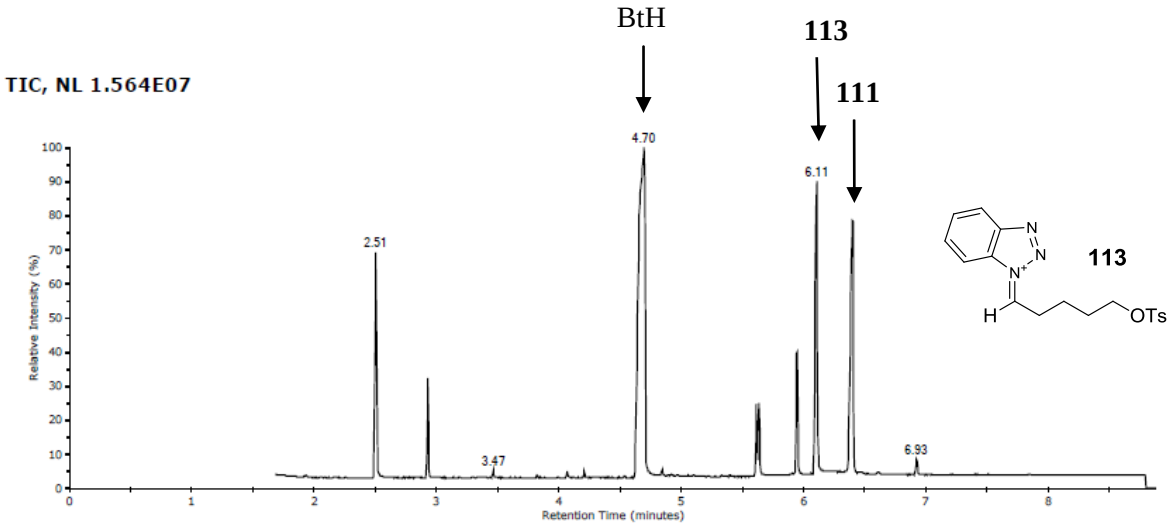


Figure 1.31: GCMS trace of reaction of BtH and aldehyde **111** after 3 h.

Oxazine (*S*)-**61** was then added, and the reaction mixture stirred for 3 hours, with GCMS monitoring over this period showing no significant changes to the profile, apart from the appearance of a peak corresponding to (*S*)-**61**. After filtration to remove the sodium sulfate, cooling to -20°C, and the addition of triflic acid, the reaction was again warmed to room temperature. After 1 hour stirring, GCMS analysis of the reaction mixture showed mainly benzotriazole and a small amount of oxazine (*S*)-**61**, in addition to a set of small complex peaks (retention time: 6.6 – 6.7 min) which the spectrometry analysis indicated could potentially be reaction intermediates **114** and **110** (**Figure 1.32**).

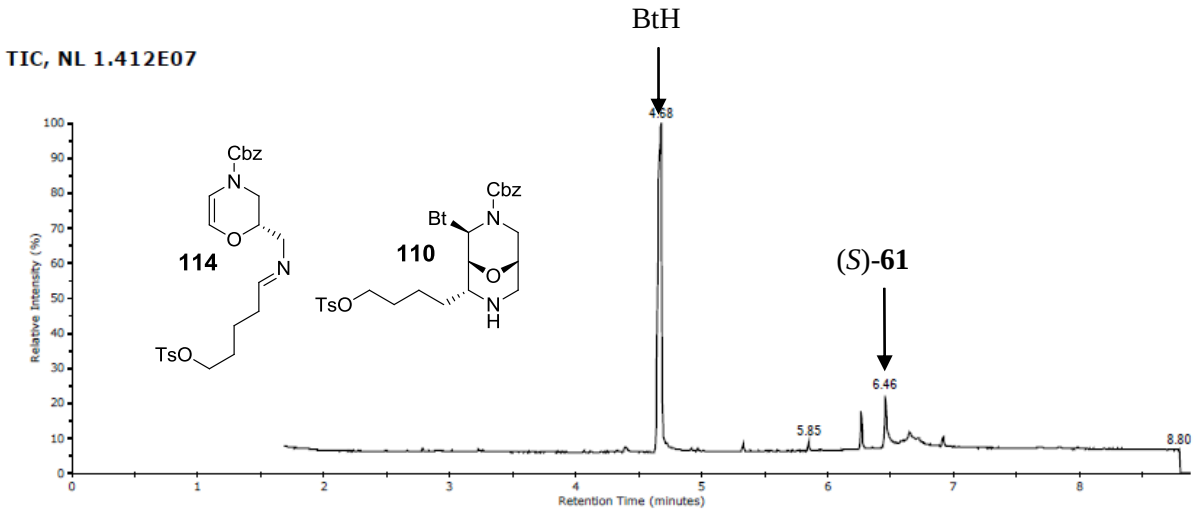


Figure 1.32: GCMS trace 1 hour after addition of triflic acid.

After a further 3 hours, the same peaks were still present (largely BtH at a retention time of 4.68 min) in addition to a new peak with a retention time of 6.27 min (**Figure 1.33**).

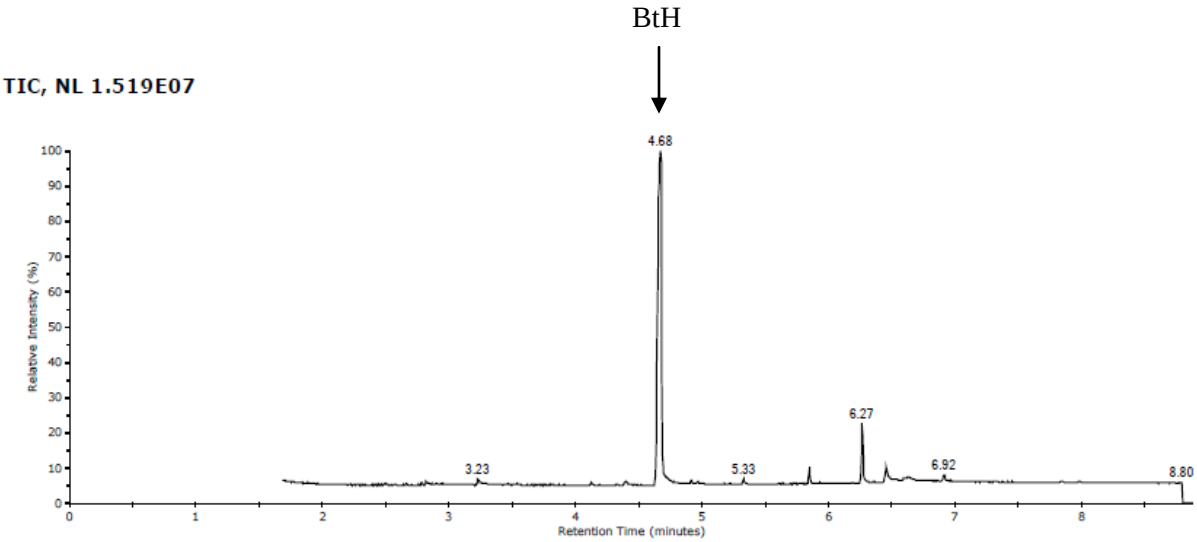


Figure 1.33: GCMS trace 4 hours after addition of triflic acid.

Promisingly, extending the reaction time overnight led to a GCMS trace which indicated that oxazine (*S*)-**61** had been completely consumed and that the new peak with a retention time of 6.27 min had increased in intensity (**Figure 1.34**).

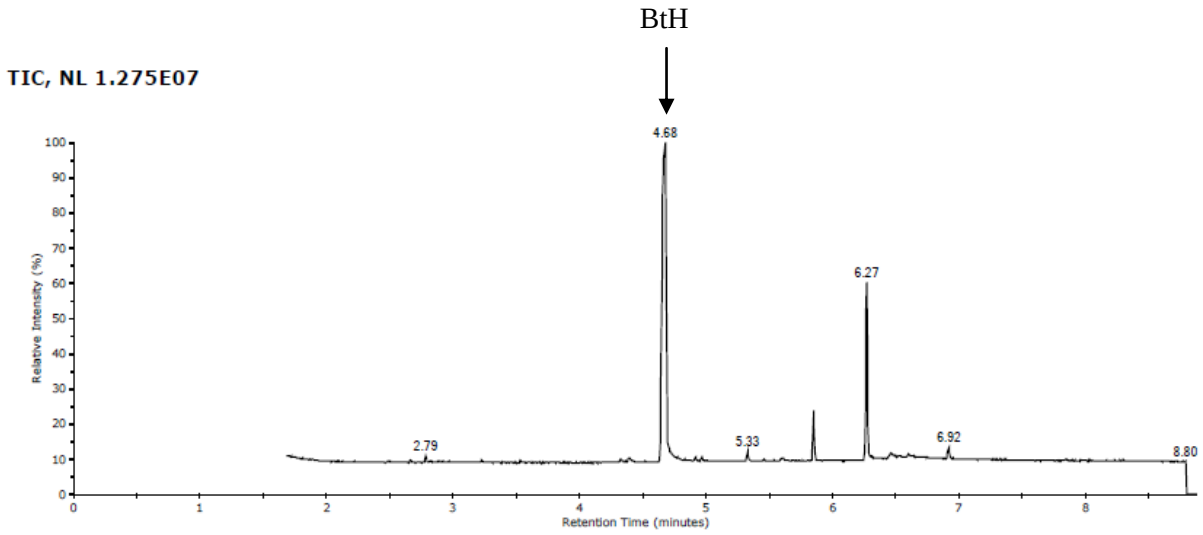
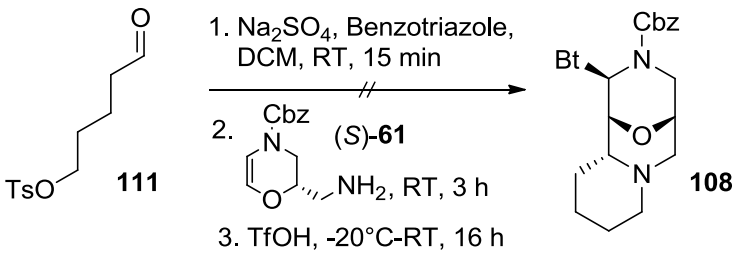


Figure 1.34: GCMS trace 20 hours after addition of triflic acid.

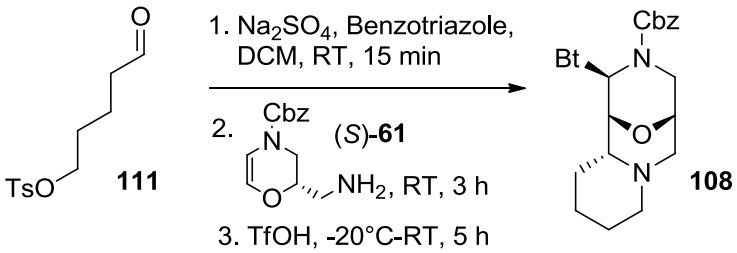
Despite the above encouraging results, extending the reaction time further appeared to lead to decomposition of the compound, as the GCMS trace had become significantly more complex, with the only recognisable peak being that corresponding to benzotriazole. The reaction was worked up and subjected to column chromatography at this stage, however, no starting materials or products were recovered. Although the presumed product peak observed could not be assigned by its mass spectrum as our desired product, the above GCMS data provides a better grasp on the required reaction times for each step in the formation of oxabispidine **108**.

With this knowledge in hand, the reaction was attempted again, first stirring the benzotriazole and aldehyde **111** for 15 min before addition of oxazine (*S*)-**61**. After stirring for 3 hours and removal of the Na_2SO_4, the triflic acid was added and the reaction mixture was stirred overnight, based on our GCMS data. Unfortunately this led to a complex reaction profile, with none of the desired product being cleanly isolated (**Scheme 1.88**).



Scheme 1.88

Undeterred by this initial disappointing outcome, we proposed that overnight stirring in such acidic reaction media, as discussed previously, could potentially be causing problems. As such, the reaction time for the cyclisation step was reduced to 5 hours, with the hope that this would be sufficient time for the reaction to progress from species such as **114** and **110** (present after 1 hour stirring with TfOH) shown in **Figure 1.33**, but not too long such that the desired product would degrade. As shown in **Scheme 1.89**, **Table 1.29**, **Entry 1**, the desired tricyclic oxabispidine **108** was recovered in a promising 33% yield. Indeed, employing a fresh batch of aldehyde **111**, led to a pleasing increase in yield to 45% (**Scheme 1.89**, **Table 1.29**, **Entry 2**).



Scheme 1.89

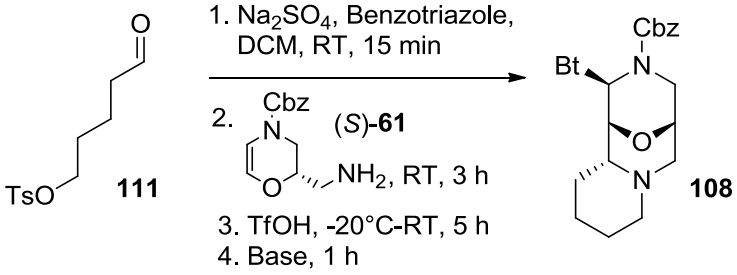
Entry	Reaction Scale	Yield
1	0.8 mmol	33%
2	0.8 mmol	45%[a]

[a] Fresh aldehyde

Table 1.29

In order to ensure any trace quantities of bicyclic compound **110** present were converted to tricyclic **108**, we wished to revisit the idea of utilising a base to quench any excess acid and help facilitate the closure of the final ring. With this in mind we repeated the reaction described above (**Scheme 1.89**, **Table 1.29**, **Entry 2**), however, following stirring with triflic acid for 5 hours, triethylamine was added and the reaction stirred for a further hour. This led to the recovery of desired tricyclic oxabispidine **108** in slightly improved 48% yield (**Scheme 1.90**, **Table 1.30**, **Entry 1**). In concurrent work, during which we developed conditions for the alkylation of the nitrogen of alternative oxabispidines derivatives (*vide infra*), we found K_2CO_3 to be effective; as such, we repeated the reaction using this base. Pleasingly this led to the recovery of **108** in an improved yield of 55% (**Scheme 1.90**, **Table 1.30**, **Entry 2**).

Although a subsequent attempt to increase this yield further by extending the reaction time was unsuccessful, we were satisfied to have developed conditions to allow access to **108** in a synthetically useful yield



Scheme 1.90

Entry	Base	Reaction Scale	Yield
1	Et_3N	1 mmol	48%
2	K_2CO_3	1 mmol	55%
3	K_2CO_3	1 mmol	52%[a]

[a] stirred for 16 h after base addition.

Table 1.30

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3.2.4 Manipulation of Nitrogen Functionalities

With an extensive collection of enantiomerically-enriched oxabispidines in hand, further functional manipulation was required to show the inherent adaptability of the synthesised molecules. For these molecules to have applications as fragments within drug discovery and potentially within asymmetric synthesis, manipulation of the nitrogen functionalities should be simple and flexible.

In the first instance, this study was focused on the manipulation of phenyl substituted oxabispidine **70** to generate simple amine moieties (**Figure 1.35**). It was believed we could efficiently gain access to derivative **115** containing a bis-secondary amine moiety and oxabispidines **116** and **117** with both combinations of secondary/tertiary amines. Additionally, it was proposed access to the bis-tertiary amine species **118** could also be easily achieved.

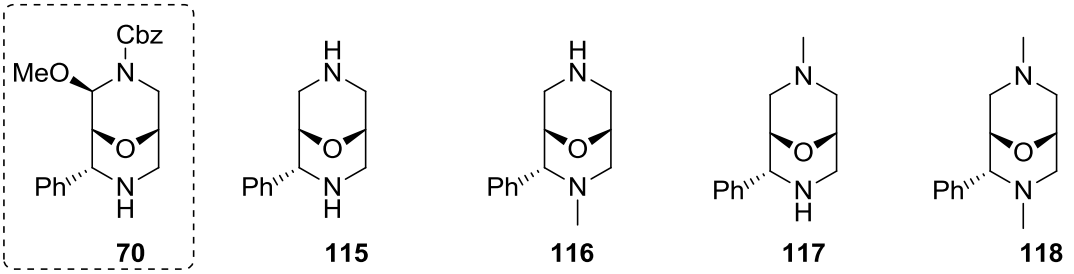
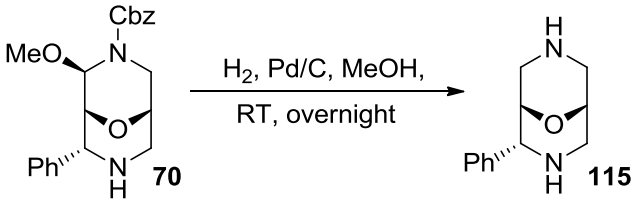


Figure 1.35

Initially, attention was focused on the preparation of the bis-secondary amine derivative **115**, with hydrogenation being the most facile method for the cleavage of the carbamate protecting group and methoxy substituent. Stirring oxabispidine **70** with palladium on charcoal overnight under an atmosphere of H_2 led to complete conversion to the product. After filtering through celite and concentrating *in vacuo*, the desired product was recovered in a good 75% yield (**Scheme 1.91, Table 1.31, Entry 1**). We were pleased to find that this procedure could be scaled up without incident (**Entry 2**).

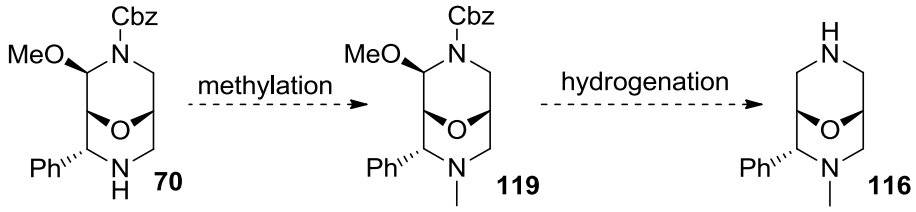


Scheme 1.91

Entry	Reaction Scale	Yield
1	0.54 mmol	75%
2	27 mmol	89%

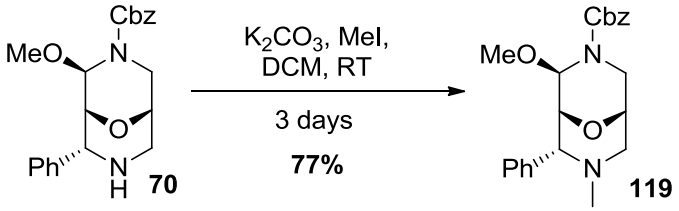
Table 1.31

With a successful hydrogenation protocol in place, application of this technique in the preparation of mono-methylated oxabispidine **116** was investigated. It was proposed that a methylation/hydrogenation sequence (**Scheme 1.92**) would allow efficient access to this derivative.



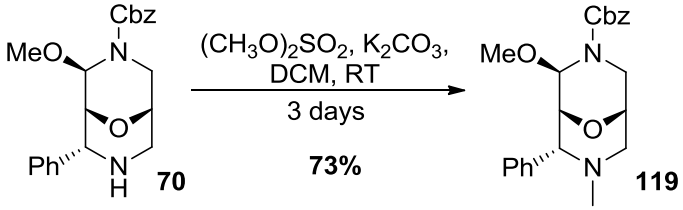
Scheme 1.92

The preparation of methylated intermediate **119** was achieved by treatment of oxabispidine **70** with potassium carbonate and methyl iodide (**Scheme 1.93**). Stirring at room temperature for 3 days led to the desired product **119** being obtained in good yield.



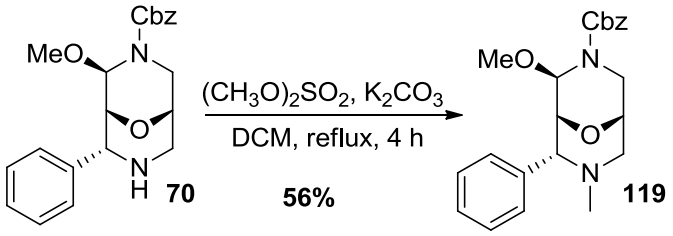
Scheme 1.93

To establish whether an alternative methylating reagent could lead to an improvement in reaction rate or yield, dimethyl sulfate was also screened (**Scheme 1.94**). Following the reaction by tlc, it was observed that a reaction time of 3 days was still required and no improvement in yield was noted.



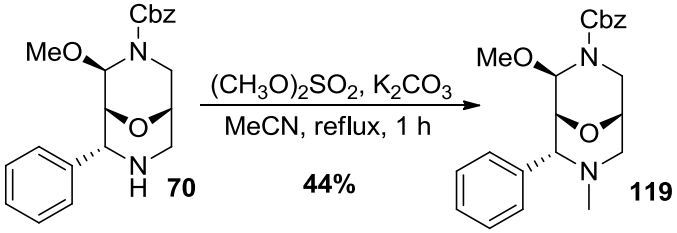
Scheme 1.94

Whilst the yield for this methylation was satisfactory, the extended reaction time was undesirable. As such, alternative conditions screened in order to ascertain if the methylation time could be reduced, and perhaps an accompanying increase in yield observed. Again, utilising the less volatile methylating agent dimethyl sulfate, the reaction was heated to reflux in DCM. Pleasingly, the tlc analysis of the reaction mixture indicated the starting oxabispidine **70** had been completely consumed after 4 hours, however only a 56% yield of **119** was obtained (**Scheme 1.95**).



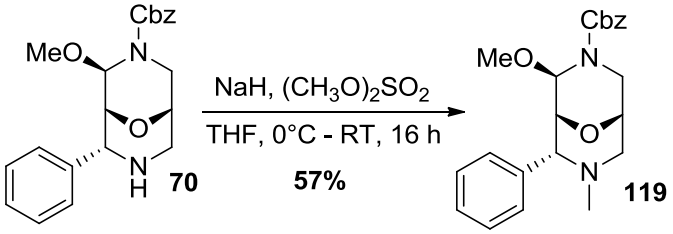
Scheme 1.95

Moving to a solvent with a higher boiling point, namely acetonitrile, shortened the reaction time even further to 1 hour, but again this had a detrimental effect on the yield, with only 44% of **119** being obtained.



Scheme 1.96

To avoid higher temperatures, which appear to have a negative impact on the reaction yield, a stronger base was screened (**Scheme 1.97**). Utilising sodium hydride at room temperature did indeed lead to a faster reaction, with the starting material being consumed after 16 h, and yield of 57% of **119** being obtained.

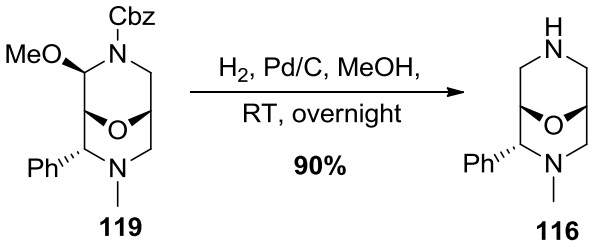


Scheme 1.97

Whilst the alternative conditions screened did in fact shorten the reaction time of this methylation reaction, the associated drop in yield in all cases led us to continue with the use of the original 3 day methylation protocol in future reactions.

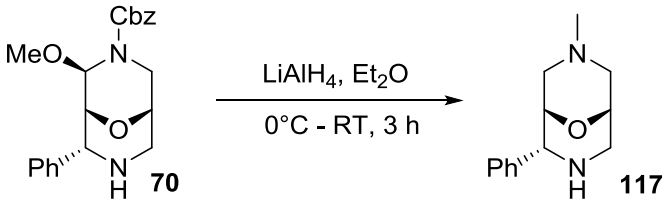
With significant quantities of methylated intermediate **119** in hand, hydrogenation of this species to deliver the desired oxabispidine **116** had to be performed. Employing the same

conditions developed for the preparation of bis-secondary amine **115**, the desired oxabispidine **116** was obtained in excellent yield (**Scheme 1.98**).



Scheme 1.98

The next compound targeted was $3^y/2^y$ oxabispidine **117**. The reduction of the MeO- and the carbamate group to afford the *N*-methyl moiety present in **117** was achieved using lithium aluminium hydride. Addition of phenyl-substituted oxabispidine **70** to a suspension of $LiAlH_4$ in diethyl ether resulted in complete consumption of the starting material in 3 hours. After work-up and column chromatography, a moderate yield of 43% was obtained (**Scheme 1.99**, **Table 1.32**, **Entry 1**). Upon repeating the reaction it was found that if excess sodium bicarbonate was added at the end of the work-up procedure, filtration of the reaction mixture was more facile and an improved yield of 61% was achieved (**Entry 2**). This outcome was maintained on scale-up.

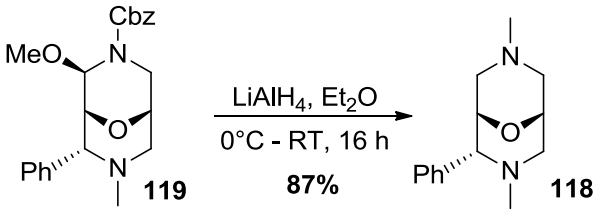


Scheme 1.99

Entry	Reaction Scale	Yield
1	0.54 mmol	43%
2	0.54 mmol	61%
3	6.8 mmol	62%

Table 1.32

To demonstrate that the full spectrum of nitrogen substitution patterns could be accessed, we also wished to prepare bis-tertiary amine **118**. Subjecting the previously prepared oxabispidine **119** to the $LiAlH_4$ conditions described earlier, albeit extending the reaction time to 16 hours, led to the desired product **118** in excellent yield (**Scheme 1.100**).



Scheme 1.100

The reduction techniques described above clearly demonstrate that the oxabispidine cores we have prepared can be elaborated in a flexible and relatively facile manner; an attractive feature when considering methodology for use within drug discovery programmes.

3.2.4.1 Preparation of Analogues for Use in Current AstraZeneca Drug Discovery Projects

As discussed previously, oxabispidines have already proven to be effective in several therapeutic areas and are of increasing interest to pharmaceutical partners.[23-25] To further demonstrate the flexibility of our synthesised oxabispidine scaffolds, and as part of on-going collaborations between AstraZeneca and our laboratory, several oxabispidines were suggested as key units to be embedded in pharmaceutical targets of particular interest to high priority lead optimisation projects within the Oncology Innovative Medicine unit at AstraZeneca, Alderley Park. In particular, the three derivatives based on the methyl-oxabispidine analogue shown in **Figure 1.36** were requested.

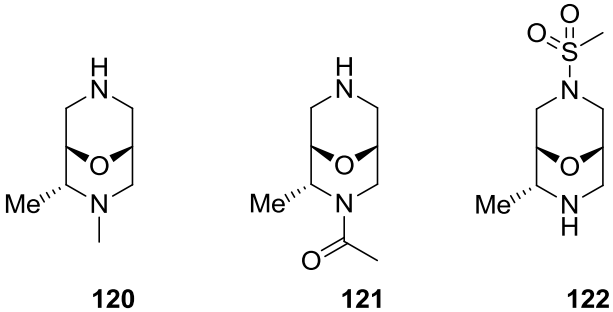
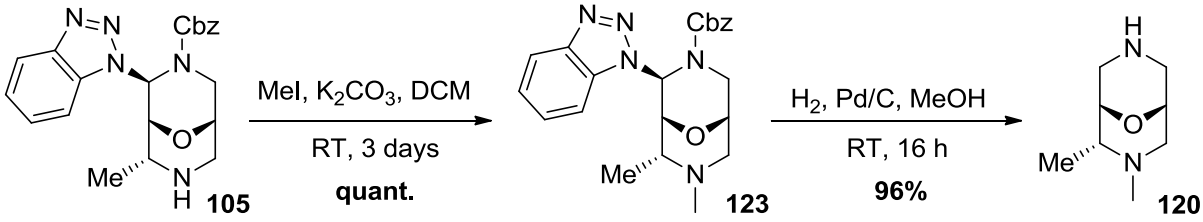


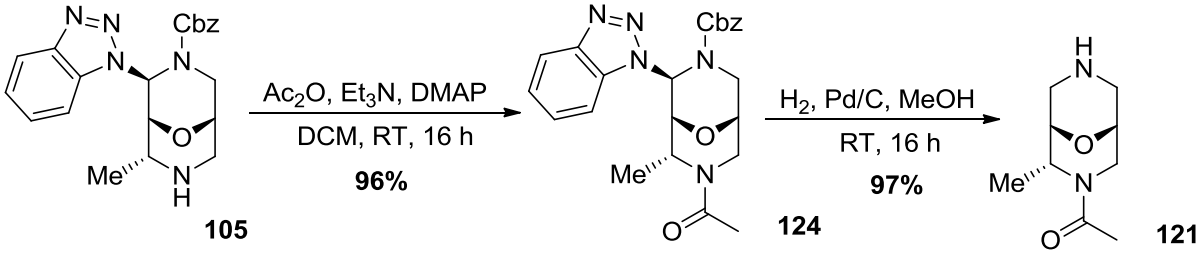
Figure 1.36

Starting with derivative **120**, the simplest method for its preparation was *via* the methylation of the previously prepared intermediate **105**, followed by cleavage of the carbamate protecting group and benzotriazole substituent *via* hydrogenation (**Scheme 1.101**). As such, reaction of methyl oxabispidine **105** with methyl iodide and K_2CO_3 led to the desired product in excellent yield, with subsequent hydrogenation providing the desired product in 96% yield.



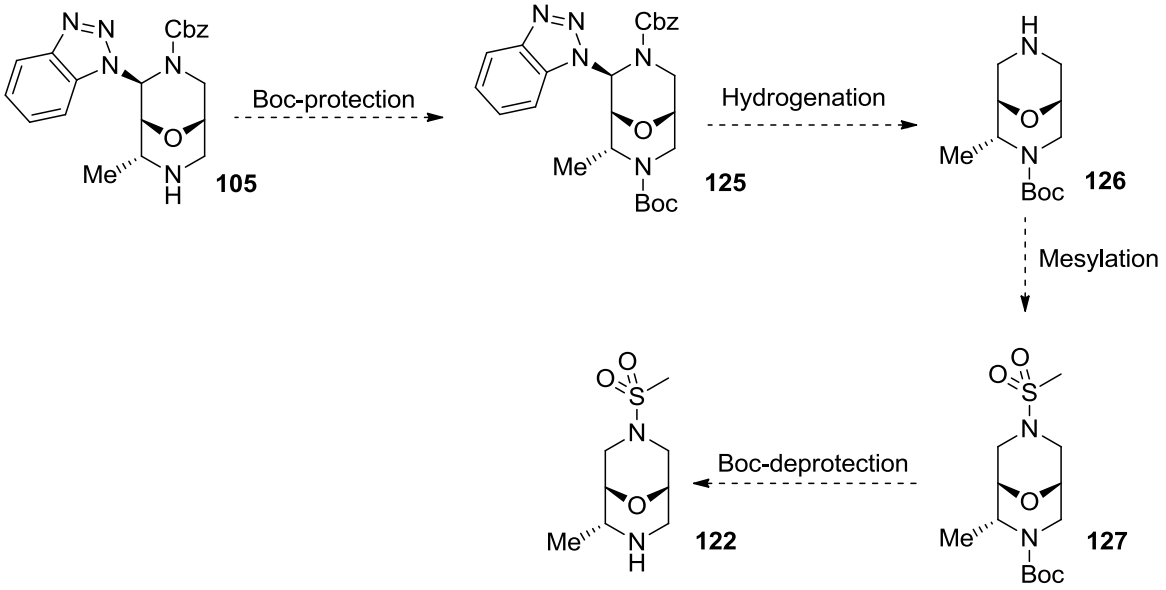
Scheme 1.101

Turning attention to the preparation of oxabispidine **121**, a similar approach was adopted; firstly the secondary amine present in **105** was acylated, and this was followed by hydrogenation to cleave the benzotriazole and Cbz-groups (**Scheme 1.102**). Treating methyl oxabispidine **105** with acetic anhydride in the presence of triethylamine and catalytic DMAP, the reaction occurred without incident, furnishing the desired acylated product **124** in high yield. Subjecting acylated oxabispidine **124** to hydrogenation conditions led to the desired product **121** being obtained in an excellent yield of 97% (**Scheme 1.102**).



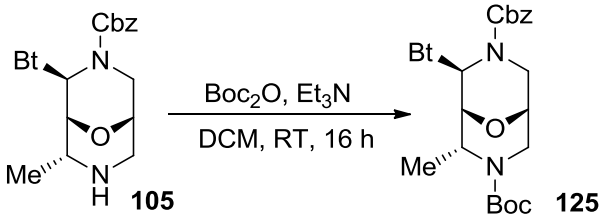
Scheme 1.102

Turning attention to the final mesylated analogue **122**, the envisaged approach, depicted in **Scheme 1.103**, consisted of Boc-protection of the secondary amine moiety in **105** followed by hydrogenation. Subsequent mesylation and a final Boc-deprotection would deliver the desired product.



Scheme 1.103

Initial Boc protection of the secondary amine with Boc-anhydride proceeded smoothly providing the desired product **125** in excellent yields.

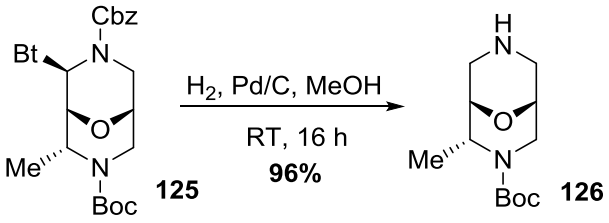


Scheme 1.104

Entry	Reaction Scale	Yield
1	2.5 mmol	100%
2	4.6 mmol	89%

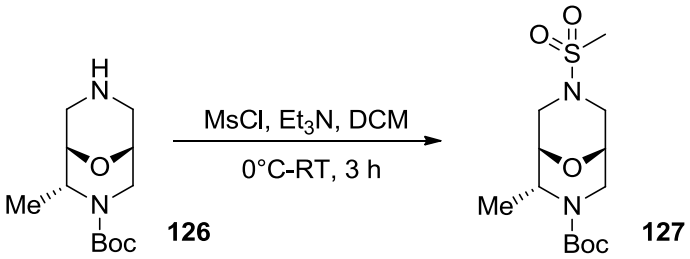
Table 1.33

Subsequent hydrogenation to cleave the benzotriazole and carbamate groups, proceeded in high yield (**Scheme 1.105**).



Scheme 1.105

With **126** in hand, treatment with triethylamine followed by methanesulfonyl chloride to furnish the desired product **127** proceeded initially in excellent yield. However, as shown in **Table 1.34**, **Entries 2 and 3**, the yields inexplicably fell upon increasing the scale of the reaction.



Scheme 1.106

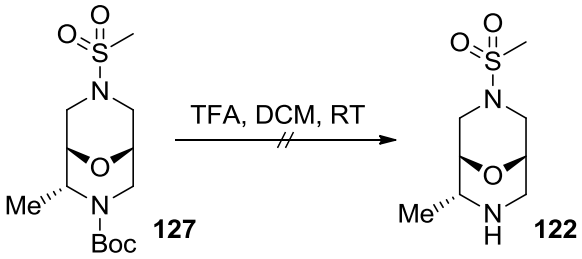
Entry	Reaction Scale	Yield
1	0.87 mmol	100%
2	2.9 mmol	50%
3	3.1 mmol	32%

Table 1.34

Nonetheless, a synthetically useful quantity of **127** had been prepared to move on to the final Boc-deprotection step. Stirring oxabispidine **127** in a 1:1 mixture of TFA and DCM for 2 hours unfortunately led to none of the desired product **122** or any unreacted starting material being recovered from the reaction (**Scheme 1.107**).

Scheme 1.107

Postulating that perhaps the excess TFA conditions in the above reaction were too harsh, the reaction was repeated this time using only 2 equivalents of TFA. Tlc analysis after 3 hours showed only starting material present, therefore, an additional 2 equivalents of TFA were added, however, after a further 2 hours, no change was observed by tlc. After addition of a further 2 equivalents of TFA and stirring at room temperature overnight, no starting material was observed upon tlc analysis. Unfortunately, after work-up a crude yield of only 27% was obtained (**Scheme 1.108**, **Table 1.35**, **Entry 1**). Repeating the reaction, but adding the total 6 equivalents of TFA at the start of the reaction, no starting material was remaining after 6 hours, but again a disappointing, albeit improved, crude yield of only 37% prior to purification was achieved (**Scheme 1.108**, **Table 1.35**, **Entry 2**). To ensure the product was not being lost to the aqueous washings, additional sodium bicarbonate was added to the aqueous and several washes with ethyl acetate were carried out, however no additional quantities of the crude product were recovered.

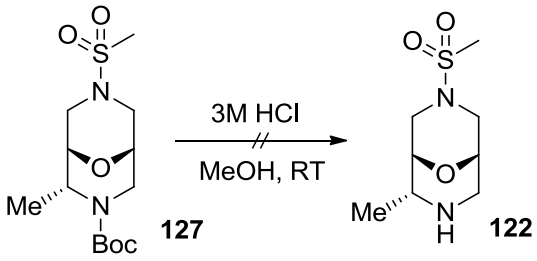


Scheme 1.108

Entry	Reaction Scale	Crude Yield
1	0.47 mmol	27%
2	1.10 mmol	37%

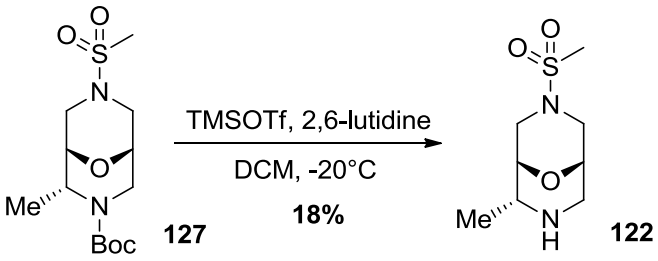
Table 1.35

Moving away from protocols utilising TFA, attention turned to the use of alternative acidic conditions, namely HCl-mediated Boc-deprotection (**Scheme 1.109**). After stirring overnight with 3M HCl in MeOH and subsequent work-up, ensuring all aqueous extracts were basified and washed several times, we were disappointed to find that neither the desired product nor starting material was recovered.



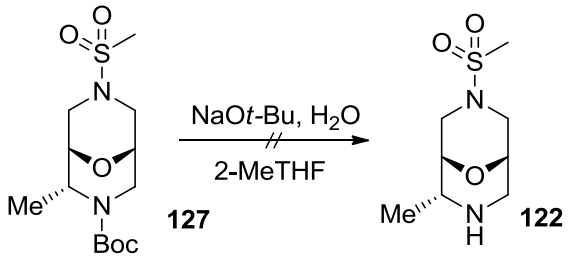
Scheme 1.109

As an alternative to the strongly acidic conditions already screened, the combination of TMS-triflate and 2,6-lutidine, which has proven effective for Boc-deprotections previously in the literature, was employed.[54] However, following the literature procedure, only an 18% yield of **122** was recovered along with 20% of unreacted starting material.



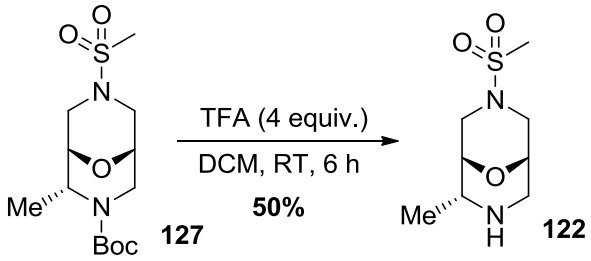
Scheme 1.110

With a view to avoiding acidic conditions completely, a basic Boc-deprotection protocol was screened.[55] Unfortunately, employing a combination of sodium *tert*-butoxide in water and 2-MeTHF led to none of the desired product **122** being recovered.



Scheme 1.111

With the final Boc-deprotection step of this sequence proving surprisingly difficult, we returned to our best conditions to date, namely the use of TFA. Considering the conditions screened previously (**Scheme 1.108**, **Table 1.35**), in addition to the acid sensitivity observed with previous oxabispidine structures (*vide supra*), we chose to reduce the amount of TFA added to the reaction to 4 equivalents from 6. This afforded a moderate yield of 50% of the desired oxabispidine **122**.

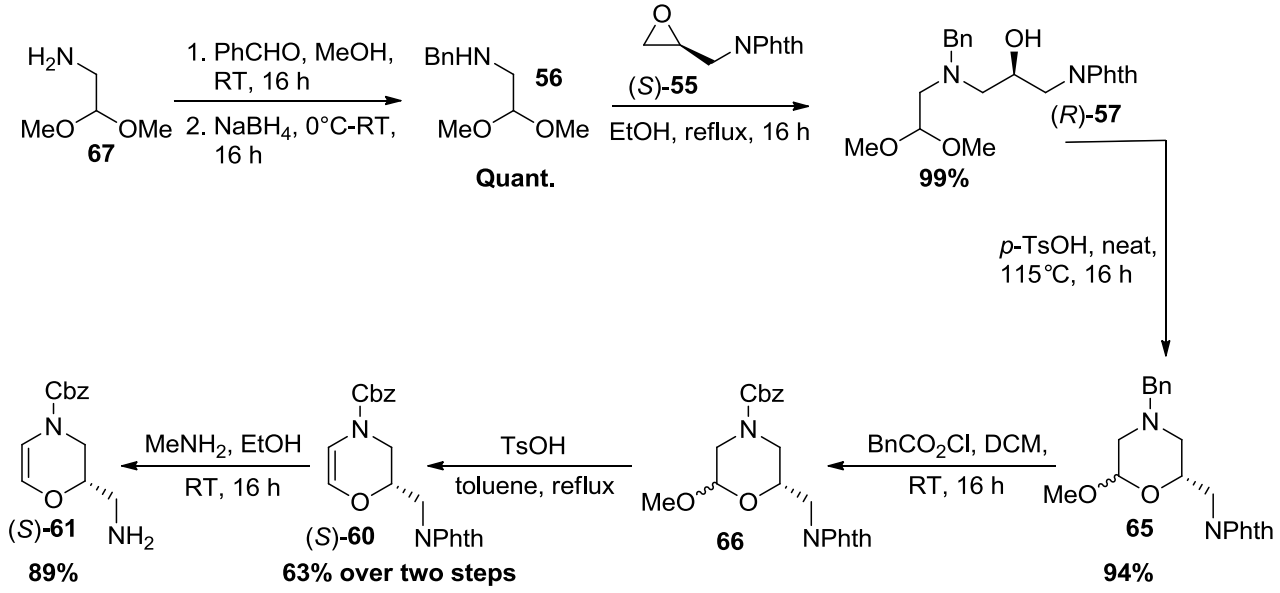


Scheme 1.112

With sufficient quantities of **122** having been generated to pass on to our AstraZeneca colleagues for further investigations (along with **120** and **121**), and considering the obvious sensitivity of **122** to the acidic deprotection conditions, the decision was taken to perform no further optimisation on the transformation of **127** to **122** at this time.

4. Conclusions

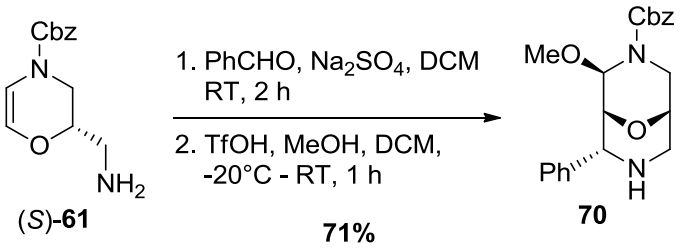
Inspired by recent interest in oxabispidine scaffolds within the pharmaceutical industry, more specifically by work carried out by AstraZeneca collaborators, we set out to develop an efficient and flexible route towards a variety of enantiomerically-enriched oxabispidine derivatives. At the outset of the project, investigations into the development of a synthetic sequence towards the common enantiomerically-pure oxazine intermediate (*S*)-**61**, that was amenable to scale up, were undertaken (**Scheme 1.113**). Although our initial attempt to simplify the route, by circumventing the requirement for a switch in protecting groups (**65** to **66**) was unsuccessful, the development of improved thermal cyclisation conditions for the preparation of morpholine **65** allowed efficient scale-up of this transformation. In addition, the screening of alternative phthalimide deprotection conditions allowed the utilisation of methylamine in place of hydrazine as a less toxic reagent in a practically more convenient procedure. From commercially available amine **67**, 7 steps are required to generate common oxazine (*S*)-**61** in 52% yield overall, with only a single step requiring column chromatography purification.



Scheme 1.113

With significant quantities of common intermediate (*S*)-**61** available, studies into a novel intramolecular Mannich-type cyclisation to generate oxabispidine compounds took place. Initially we focused on the synthesis of oxabispidine **70** in order to acquire optimum

conditions with which to generate our library of oxabispidines. After imine formation, from (*S*)-**61** and benzaldehyde, treatment of this with triflic acid and methanol led to the desired product **70** being obtained in good yield (**Scheme 1.114**). Pleasingly, the developed conditions allowed access to compound **70** in significant quantities for the first time.



Scheme 1.114

In addition to the development of the above conditions, the proposed stereochemistry of **70**, was successfully confirmed by extensive 1 and 2D NMR studies, including NOESY and variable temperature NMR experiments. With regards to the proposed mechanism of the oxabispidine-forming reaction, although initial NMR experiments and the employment of non-nucleophilic counterions to stabilise iminium intermediates proved unsuccessful, we were pleased to find that tuning the reactivity of the imine and acid used allowed us to isolate iminium mesylate salt **78d** (**Figure 1.37**).

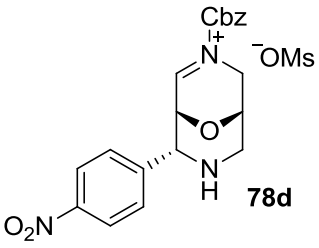


Figure 1.37

This result suggested that the reaction was indeed proceeding *via* intramolecular attack facilitated by the enamine moiety, followed by quenching with a nucleophile, as opposed to external attack of methanol onto the double bond of oxazine (*S*)-**61**. In addition to these experimental results, we gained valuable mechanistic and stereochemical insight *via* computational studies.

With a greater understanding of the mechanism of the Mannich-type reaction, and with optimised triflic acid-promoted conditions in hand, the scope of the oxabispidine-forming

process was then evaluated. Using oxazine (*S*)-**61** as the common starting material, a broad selection of aryl-substituted oxabispidines of varying electronic and steric properties were prepared (**Figure 1.38**). Additionally, heterocyclic-derivatives, and selected alkyl-substituted oxabispidines were prepared in moderate to excellent yields.

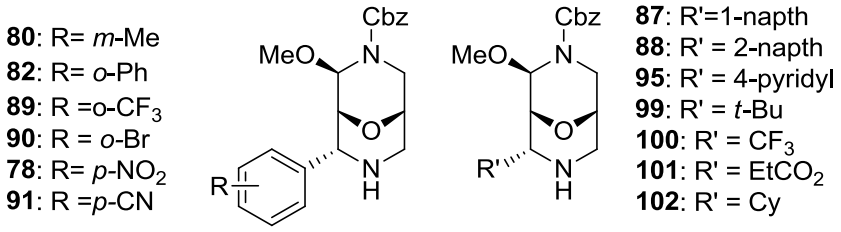


Figure 1.38

Unfortunately, aryl-rings bearing strongly electron-donating groups (e.g. **92** & **93** in **Figure 1.39**) and pyridine derivative **94** were incompatible with the developed triflic acid-mediated conditions. Having stated this, it was found that utilising more forcing conditions, namely refluxing in methanol overnight in the presence of *p*-toluenesulfonic acid, allowed access to these targets, albeit in more modest yields.

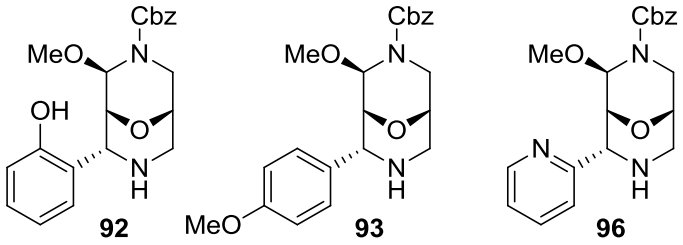
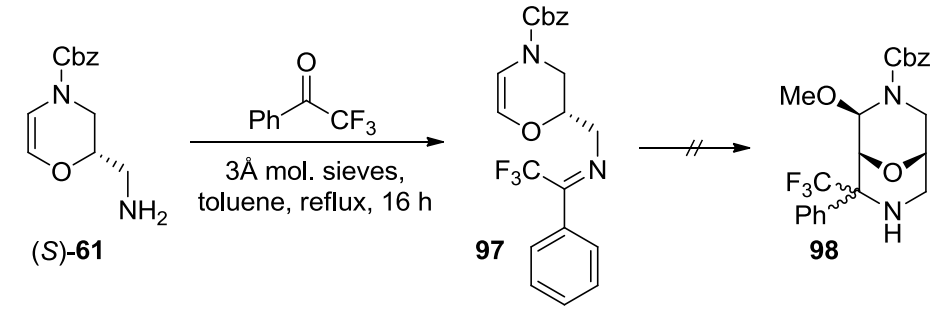


Figure 1.39

In an effort to extend the scope of the developed reaction even further, preliminary investigations into utilising ketone substrates, as opposed to aldehydes, were undertaken to allow access to more heavily substituted oxabispidines containing quaternary centres. Although access to imine **97** was successfully achieved, the final acid-promoted cyclisation step to generate the corresponding oxabispidine proved significantly more challenging, and ultimately we were unable to gain access to a ketone-derived oxabispidine unit, despite screening a variety of more forcing conditions.



Scheme 1.115

To broaden the scope of our oxabispidine library even further, we wished to deliver additional oxabispidines bearing alkyl-sidearms. Having stated this, enolisable alkyl units such as Me, Et, and *i*-Pr, were not so readily applicable due to the propensity for such species to undergo side reactions. To overcome this issue, we successfully employed Katritzky's technique of stabilising such reactive aldehydes as the benzotriazole adduct. As a result, several alkyl-substituted oxabispidines (**105** – **107**) were accessed in good yields, including the more synthetically challenging target **108**.

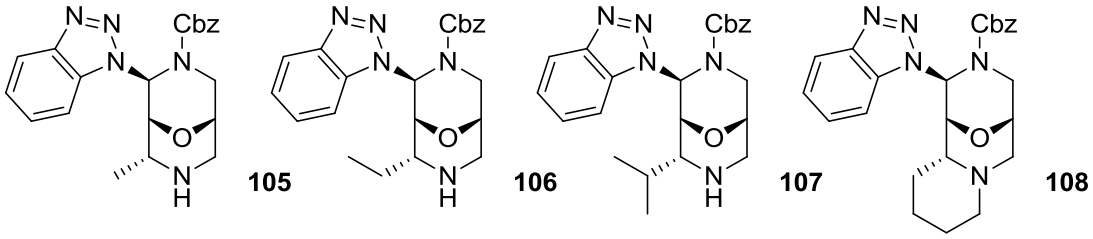


Figure 1.40

Finally, in order to display the inherent flexibility of the oxabispidine scaffolds prepared, the phenyl and methyl derivatives were selected as vehicles to show how the nitrogen functionalities could be manipulated. Utilising various reduction strategies, we were able to gain access to a range of substitution patterns, and found that the oxabispidine cores generated through our Mannich-type cyclisation were, in general, tolerant to the various reaction conditions required to incorporate functional groups of relevance to pharmaceutical collaborators.

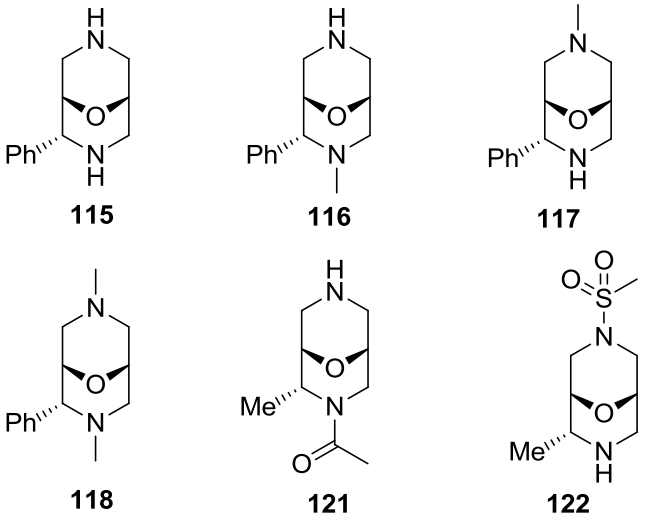


Figure 1.41

As a whole, this newly developed approach towards enantiomerically-enriched oxabispidines molecules fits well into the diversity-orientated synthesis movement which has witnessed a surge in interest over the past decade within drug discovery. From a common oxazine intermediate, a broad range of electronically and sterically diverse oxabispidines scaffolds have been prepared, with the opportunity for these derivatives to be diversified even further *via* manipulation of the nitrogen substituents. The highly sp^3-rich character of the oxabispidine core, and the inherent 3D nature of such molecules, would serve to enhance fragment libraries within the pharmaceutical industry, particularly at a time when the drive for molecular and structural diversity in such screening collections is at its highest. Indeed, as mentioned earlier, the developed methodology towards these optically-enriched oxabispidine molecules would be classified as a tri/tri/bi process within Nelson's framework discussed earlier (*Section 1.2.1*).[13] This indicates that a large increase in molecular complexity has occurred on going from starting materials to product and, thus, within this context, the developed reaction is an extremely powerful approach towards potentially lead-like scaffolds.

5. Future Work

With the developed intramolecular Mannich-type cyclisation proving to be a relatively general process, one of the most obvious areas of future work is to evaluate the limit to the complexity of the oxabispidine scaffolds that can be prepared. In particular, bearing in mind the successful access to tricyclic derivative **108**, by selection of the requisite aldehyde starting material an even wider range of polycyclic oxabispidines could become available as single diastereomers, such as tetracyclic compounds **128** and **129** shown in **Figure 1.42**.

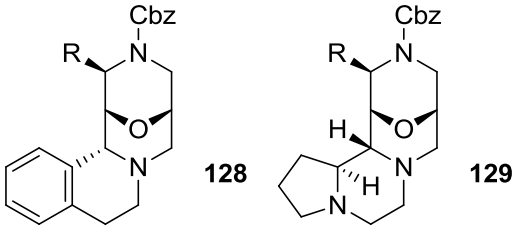


Figure 1.42

With regards to structural diversity in the oxabispidine series, to date only methanol and benzotriazole have been utilised as the final nucleophile required within the Mannich cyclisation process. Replacing the methoxy and benzotriazole substituents of the oxabispidine products with alternative functionalities (**Figure 1.43**) would allow access to a wider range of oxabispidine-based fragments; this would constitute an attractive feature if such a compound collection were to be used in a drug discovery programme.

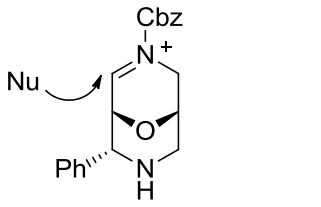
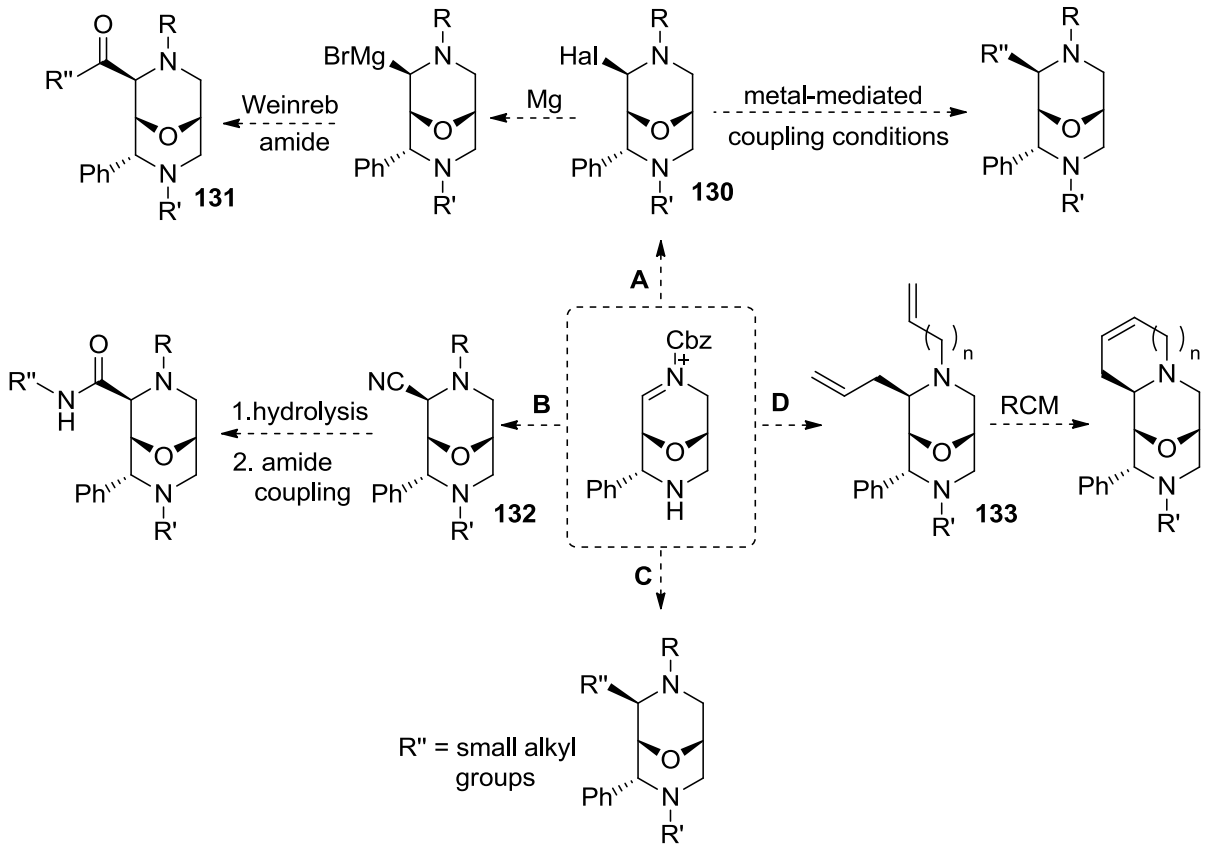


Figure 1.43

Indeed, introduction of halides, to generate derivatives such as **130** (**Scheme 1.116, pathway A**), could potentially allow for cross-coupling reactions to take place, or allow the formation of Grignard reagents, which could, in turn, be reacted with other fragments, such as Weinreb amides to prepare derivatives such as **131** (**Scheme 1.116**). If the introduction of a nitrile

group was possible, to yield compounds such as **132** (**pathway B**), hydrolysis to the acid, followed by a condensation reaction could be carried out to elaborate the oxabispidine core further. By utilising carbon-centred nucleophiles the introduction of additional small alkyl groups could be achieved, thereby increasing the sp^3-rich nature of such oxabispidine scaffolds even further (**pathway C**). Indeed, in a similar vein, the introduction of an allyl group to this position, in combination with an appropriate substituent on the adjacent nitrogen atom (e.g. **133**), may allow for a variety of rings to be constructed *via* ring-closing metathesis methodology.



Scheme 1.116

With the ultimate goal of this project being the adoption of the developed methodology within the pharmaceutical industry, and the oxabispidine scaffolds generated to be incorporated into fragment screening libraries, the ability to provide further points of functionalisation, in addition to the already diverse range of compounds accessed, would be a highly attractive feature.

6. Experimental

6.1 General

- All reagents were obtained from commercial suppliers and were used without further purification unless stated otherwise. Purification was carried out according to standard laboratory methods.[56]

- Tetrahydrofuran was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, and then distilled under nitrogen.

- Dichloromethane was dried by heating to reflux over calcium hydride and then distilled under nitrogen.

- Petroleum ether refers to light petroleum ether, b.p. range 40 – 60°C.

Reactions performed under microwave irradiation were carried out in a CEM Discover instrument using sealed glass tubes.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. Plates were analysed using a Mineralight UVGL-25 lamp and developed using vanillin solution.

Flash chromatography was carried out using ZEOCHEM® silica gel (ZEOprep60 HYD 40-60 μm).

FTIR spectra were obtained on a Shimadzu IRAffinity-1 FT-IR Spectrophotometer.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer at 400 and 100 MHz, respectively, unless otherwise stated. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise stated.

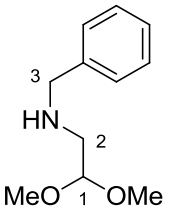
High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, Swansea University, Swansea.

Elemental analysis was obtained using a Carlo Ebra 1106 CHN analyser.

Optical rotations were obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm. Concentration is expressed in g/100 cm^3.

6.2 Experimental Procedures

Preparation of N-benzyl-2,2-dimethoxyethanamine ***56***[57]



$C_{11}H_{17}NO_2$
Molecular Weight: 195.26

General Procedure

To a solution of 2,2-dimethoxyethylamine in methanol was added benzaldehyde, and the resulting mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was cooled to 0°C and sodium borohydride added slowly, in a portionwise manner, ensuring the temperature of the mixture did not exceed 10°C. After complete addition of sodium borohydride, the reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. The pH of the mixture was then adjusted to pH 9-10 using 2M hydrochloric acid. The methanol was removed under reduced pressure, an equivalent volume of water added, and the pH again corrected to pH 9-10. The product was extracted into an approx. equivalent volume to that of the reaction solvent (x 2). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired product as a pale yellow liquid which required no further purification.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of 2,2-dimethoxyethylamine; (b) volume of MeOH; (c) quantity of benzaldehyde; (d) quantity of $NaBH_4$; and (e) yield.

Table 1.1, Entry 1

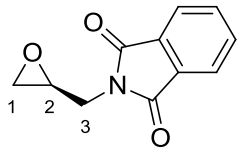
(a) 21 ml, 190 mmol; (b) 400 ml; (c) 20.3 ml, 200 mmol; (d) 10.8 g, 285 mmol; and (e) 40.9 g, quant.

Table 1.1, Entry 2

(a) 40 g, 380 mmol; (b) 800 ml; (c) 40 ml, 399 mmol; (d) 21.6 g, 570 mmol; and (e) 71 g, 96%.

IR ($CDCl_3$): 2834, 2938, 3030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.17 (br. s, 1H, NH), 2.74 (d, 2H, *J* = 5.6 Hz, H2), 3.35 (s, 6H, 2 x OCH_3), 3.79 (s, 2H, H3), 4.48 (t, *J* = 5.6 Hz, 1H, H1), 7.23-7.31 ppm (m, 5H, H_{Ar}).; ^{13}C NMR (100 Hz, $CDCl_3$): δ 50.4, 53.8, 53.9, 103.8, 127.0, 128.2, 128.4, 139.9 ppm; HRMS *m/z* Calc. for $C_{11}H_{18}NO_2$ (M^++H): 196.1332. Found: 196.1327.

*Preparation of (S)-2-(oxiran-2-ylmethyl)isoindoline-1,3-dione (S)-**55***[58]



$C_{11}H_9NO_3$
Molecular Weight: 203.19

Procedure

Scheme 1.23

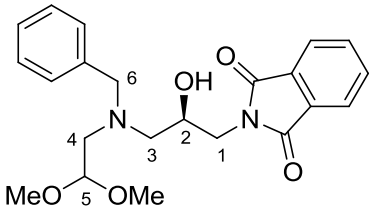
To a stirred solution of potassium phthalimide (10 g, 54 mmol) and trimethylbenzylammonium chloride (1 g, 5.4 mmol) in *i*-PrOH (110 ml) was added (*R*)–epichlorohydrin (4.25 ml, 54 mmol). The mixture was stirred at 30°C for 72 h, before the solvent was removed under reduced pressure to give a pale yellow residue. This residue was diluted with ethyl acetate (100 ml) and washed with water (100 ml). The aqueous layer was washed with additional ethyl acetate (100 ml) and the organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a yellow solid. The crude product was purified by column chromatography (eluent: 4:1 petroleum ether:diethyl ether) to provide the desired clean product as a white solid (4.7 g, 40%).

Melting point: 100-102°C. Lit. value: 102-103°C.[58]

IR (neat): 1357, 1615, 1687, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.71 (dd, *J* = 4.8, 2.5 Hz, 1H, H1); 2.83 (t, *J* = 4.8 Hz, 1H, H1); 3.25-3.27 (m, 1H, H2); 3.83 (dd, ^2J = 14.4, *J* = 5.0 Hz, 1H, H3); 3.99 (dd, ^2J = 14.4, *J* = 5.0 Hz, 1H, H3); 7.75-7.77 (m, 2H, H_{Ar}); 7.89-7.91 ppm (m, 2H, H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$): δ 39.7, 46.1, 49.1, 123.5, 132.0, 134.1, 168.0 ppm.

$[\alpha]_D^{27}$ -9.9 (*c* 1.0, $CHCl_3$). Lit value: $[\alpha]_D^{25}$ -9.7 (*c* 1.0, $CHCl_3$).[58]

*Preparation of (R)-2-(3-(benzyl(2,2-dimethoxyethyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (R)-**57***



$C_{22}H_{26}N_2O_5$
Molecular Weight: 398.45

General Procedure

To a solution of amine **56** in ethanol was added (*S*)-glycidyl phthalimide, (*S*)-**55**. The mixture was heated to reflux and stirred for 16 h. The reaction mixture was then concentrated *in vacuo* to provide the desired product as a yellow oil with no need for further purification.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of amine **56**; (b) volume of ethanol; (c) quantity of (*S*)-glycidyl phthalimide; and (d) yield.

Table 1.2, Entry 1

(a) 1 g, 5.2 mmol; (b) 30 ml; (c) 1 g, 4.9 mmol; and (d) 1.99 g, 96%.

Table 1.2, Entry 2

(a) 10 g, 52 mmol; (b) 300 ml; (c) 9.9 g, 49 mmol; and (d) 19.3 g, quant.

Table 1.2, Entry 3

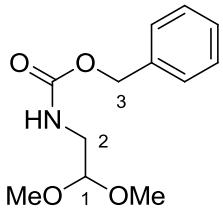
(a) 71 g, 363 mmol; (b) 1000 ml; (c) 77 g, 384 mmol; and (d) 143 g, 99%.

IR ($CDCl_3$): 1394, 1714, 1772, 2832, 2937, 3465 (br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.58-2.78 (m, 4H, H3 & H4), 3.28 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.65-3.83, (m, 4H, H1 & H6), 3.94-4.00 (m, 1H, H2), 4.30 (dd, *J* = 6.1, 4.8 Hz, 1H, H5), 7.21-7.38 (m, 5H, H_{Ar}) 7.72 (dd, *J* = 5.6, 3.1 Hz, 2H, H_{Ar} (phth)), 7.84 ppm (dd, *J* = 5.4, 3.1 Hz, 2H, H_{Ar} (phth));^{13}C NMR (100 Hz, $CDCl_3$): δ 41.2, 53.0, 53.4, 55.6, 60.3, 66.5, 102.8, 122.8, 127.8, 127.9, 128.6,

131.6, 133.4, 138.0, 168.0 ppm; HRMS *m/z* Calc. for $C_{22}H_{27}N_2O_5$ (M^++H): 399.1914. Found: 399.1909.

$[\alpha]_D^{20}$ +18.2 (*c* 1.0, $CHCl_3$).

Preparation of benzyl (2,2-dimethoxyethyl)carbamate ***68***[59]



$C_{12}H_{17}NO_4$
Molecular Weight: 239.27

Procedure A

Scheme 1.27

To a stirred solution of 2,2-dimethoxyethylamine (0.96 ml, 9.5 mmol) in DCM (100 ml) was added benzylchloroformate (1.4 ml, 10 mmol). The reaction mixture was stirred at ambient temperature for 22 h, before being poured into water. The organic layer was washed with saturated aqueous sodium bicarbonate solution followed by brine, then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude residue was purified *via* column chromatography (eluent: 1:1, petroleum ether:diethyl ether) to yield the desired product as a colourless oil (0.42 g, 20%).

Procedure B

Table 1.3, Entry 1

To a stirred solution of 2,2-dimethoxyethylamine (0.96 ml, 9.5 mmol) in Et_2O (16 ml) was added water (16 ml) and K_2CO_3 (3.9 g, 28.5 mmol). The reaction mixture was cooled to 0°C and benzyl chloroformate (1.62 ml, 9.5 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 12 h. After this time, the phases were separated and the aqueous layer was extracted with Et_2O (2 x 15 ml). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*.

Attempted purification of the crude residue by column chromatography (eluent: 1:1, petroleum ether:diethyl ether) led to none of the desired product being recovered.

Procedure C

Table 1.3, Entry 2

To a stirred solution of 2,2-dimethoxyethylamine (0.96 ml, 9.5 mmol) in Et_2O (16 ml), was added water (16 ml) and K_2CO_3 (3.9 g, 28.5 mmol). The reaction mixture was cooled to 0°C and benzyl chloroformate (1.62 ml, 9.5 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 12 h. After this time, the phases were separated and the aqueous layer was extracted with Et_2O (2 x 15 ml). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was loaded onto a small plug of silica and washed with petroleum ether, before being flushed with Et_2O. After removal of the solvent under reduced pressure, the desired product was recovered as a colourless oil (2.0 g, 89%).

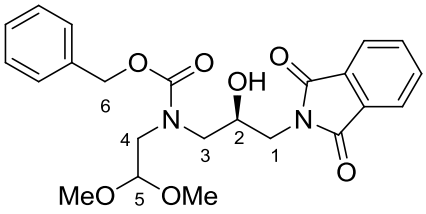
Procedure D

Table 1.3, Entry 3

To a stirred solution of 2,2-dimethoxyethylamine (3.3 ml, 30 mmol) in Et_2O (50 ml), was added water (50 ml) and K_2CO_3 (12.4 g, 90 mmol). The reaction mixture was cooled to 0°C and benzyl chloroformate (4.3 ml, 30 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 12 h. After this time, the phases were separated and the aqueous layer was extracted with Et_2O (2 x 100 ml). The combined organics were washed with 5% citric acid solution (3 x 75 ml) followed by brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired product as a colourless oil (7.2 g, 100%).

IR (neat): 1220, 1305, 1730, 3350, 3465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.36 (t, J = 5.7 Hz, 2H, H2), 3.40 (s, 6H, 2 × OCH_3), 4.40 (t, J = 5.7 Hz, 1H, H1), 4.99 (br. s, 1H, NH), 5.13 (s, 2H, H3), 7.28-7.39 ppm (m, 5H, H_{Ar}) ^{13}C NMR (100 Hz, $CDCl_3$): δ 41.9, 53.4, 69.1, 102.2, 127.5, 127.9, 128.5, 136.4, 156.1 ppm.

*Attempted Preparation of (S)-benzyl (2,2-dimethoxyethyl)(3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)carbamate (S)-**69***



$C_{23}H_{26}N_2O_7$
Molecular Weight: 442.46

General Procedure A

To a vigorously stirring solution of NaH in the specified dry solvent (volume 1) was added a solution of **68** in the specified solvent (volume 2) in a dropwise manner at room temperature. The resulting mixture was stirred at room temperature for 5 min before being cooled to 0°C. A solution of (*S*)-epoxypropylphthalimide (volume 3) was added in a dropwise fashion and the resulting mixture was allowed to warm to room temperature and stirred overnight. After this time, water was added, the phases separated, and the aqueous layer extracted with Et_2O (x 3). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Attempted purification of the crude residue by column chromatography led to none of the desired product being recovered, and only an inseparable mixture of starting materials.

Following ***General Procedure A***, results are presented as follows:

(a) quantity of NaH; (b) solvent; (c) volume 1 of solvent; (d) quantity of **68**; (e) volume 2 of solvent; (f) quantity of (*S*)-epoxypropylphthalimide; and (g) volume 3 of solvent.

Table 1.4, Entry 1

(a) 0.04 g, 1.4 mmol; (b) THF; (c) 10 ml (d) 0.34 g, 1.4 mmol; (e) 5 ml; (f) 0.29 g, 1.4 mmol; and (g) 5 ml.

Table 1.4, Entry 2

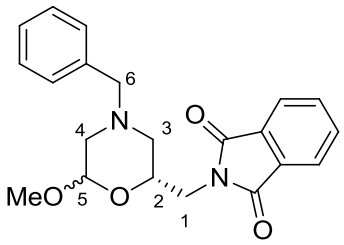
(a) 0.02 g, 0.6 mmol; (b) DMF; (c) 5 ml (d) 0.15 g, 0.6 mmol; (e) 2 ml; (f) 0.13 g, 0.6 mmol; and (g) 2 ml.

Procedure B

Table 1.4, Entry 3

To a solution of **68** (0.02 g, 0.6 mmol) in THF (3 ml) was added KHMDS (1.26 ml, 0.5M solution in THF) in a dropwise manner at room temperature. The resulting mixture was stirred at room temperature for 5 min before being cooled to 0°C. A solution of (*S*)-epoxypropylphthalimide (0.13 g, 0.6 mmol) in THF (2 ml) was added in a dropwise fashion and the resulting mixture was allowed to warm to room temperature and stirred overnight. After this time, water was added, the phases separated, and the aqueous layer extracted with Et_2O (x 3). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo*. Attempted purification of the crude residue by column chromatography led to none of the desired product being recovered, and only an inseparable mixture of starting materials.

Preparation of 2-(((2R)-4-benzyl-6-methoxymorpholin-2-yl)methyl)isoindoline-1,3-dione ***65***



$C_{21}H_{22}N_2O_4$
Molecular Weight: 366.41

Procedure A

Scheme 1.31

To a microwave vial containing a magnetic stirrer was added (*R*)-**57** (3.1 g, 7.7 mmol) and *p*-toluenesulfonic acid (0.15g, 0.77 mmol). The reaction mixture was heated to 115°C under microwave irradiation for 30 mins. After this time, the reaction mixture had turned from yellow to dark brown. Tlc analysis showed that starting material still remained after this time, so the reaction was subjected to the same microwave conditions for a further 30 mins. The reaction mixture was then dissolved in DCM (100 ml) and washed with water (100 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a brown residue. The crude product was purified by column chromatography

(eluent: 1:1 Et_2O:petroleum ether) to yield the desired product as a mixture of diastereomers (1.97 g, 68%).

Procedure B

Scheme 1.32

To a microwave vial containing a magnetic stirrer was added (*R*)-**57** (15 g, 38 mmol) and freshly recrystallised *p*-toluenesulfonic acid (0.72 g, 3.8 mmol). The reaction mixture was heated to 115°C under microwave irradiation for 30 min. After this time the reaction mixture had turned from yellow to dark brown. The reaction mixture was dissolved in DCM (400 ml) and washed with water (400 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired product as a mixture of diastereomers (11.1 g, 80%).

General Procedure C

To a flask containing (*R*)-**57** was added a magnetic stirrer bar and freshly recrystallised *p*-toluenesulfonic acid. The flask was sealed with a suba seal and lowered into an oil bath which had been pre-heated to 115°C. The reaction mixture was stirred at this temperature for 16 h before being allowed to cool to room temperature. The resulting brown resiude was dissolved in DCM and washed with a saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to provide the desired product, which was used in subsequent reactions without further purification, as a mixture of diastereomers.

Following ***General Procedure C***, results are presented as follows:

(a) quantity of (*R*)-**57**; (b) quantity of TsOH; and (c) yield.

Table 1.5, Entry 1

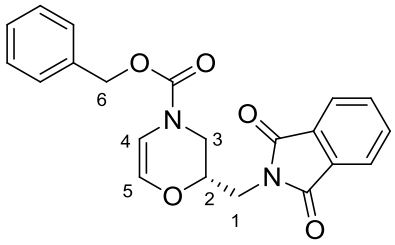
(a) 4.0 g, 10 mmol; (b) 0.29 g, 1.5 mmol; and (c) 3.3 g, 90%.

Table 1.5, **Entry 2**

(a) 44 g, 110 mmol; (b) 3.2 g, 16.6 mmol; and (c) 38.1 g, 94%.

IR ($CDCl_3$): 1396, 1715, 1774, 2853, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.91 (dd, ^2J = 11.5, J = 8.5 Hz, 0.7H, H4); 2.02 (dd, ^2J = 11.0, J = 10.2 Hz, 0.7H, H3); 2.13 (dd, ^2J = 11.0, J = 9.7 Hz, 0.3H, H3); 2.30 (dd, ^2J = 11.5, J = 2.7 Hz, 0.3H, H4); 2.73-2.84 (m, 2H, H3+H4); 3.27 (s, 0.9H, OCH_3); 3.41(s, 2.1H, OCH_3); 3.44-3.61 (m, 2H, H6); 3.65 (dd, ^2J = 13.5, J = 4.9 Hz, 0.3H, H1); 3.79 (dd, ^2J = 13.5, J = 6.1 Hz, 0.7H, H1); 3.89-4.02 (m, 1.7H, H1+H2); 4.30-4.37 (m, 0.3H, H2); 4.46 (dd, J = 8.5, 2.4 Hz, 0.7H, H5); 4.72 (t, J = 2.3 Hz, 0.3H, H5): 7.25-7.34 (m, 5H, H_{Ar} partially obscured by solvent peak); 7.72-7.74 (m, 2H, H_{Ar} (phth)); 7.87-7.90 ppm (m, 2H, (m, 2H, H_{Ar} (phth)); ^{13}C NMR (100 Hz, $CDCl_3$): δ 39.5, 39.6, 54.5, 54.8, 55.0, 55.1, 55.6, 62.1, 62.6, 66.1, 70.9, 96.5, 99.7, 122.9, 122.8, 126.8, 127.7, 127.8, 128.6, 128.8, 131.4, 131.5, 133.4, 133.5, 133.6, 167.6, 167.7 ppm; HRMS *m/z* Calc. for $C_{21}H_{23}N_2O_4$ (M^++H): 367.1652. Found: 367.1647.

*Preparation of (S)-benzyl 2-((1,3-dioxoisoindolin-2-yl)methyl)-2H-1,4-oxazine-4(3H)-carboxylate (S)-**60***



$C_{21}H_{18}N_2O_5$
Molecular Weight: 378.38

Procedure A

Scheme 1.34

To a stirred solution of **65** (1.0 g, 2.7 mmol) in DCM (15 ml) was added benzylchloroformate (0.55 ml, 3.8 mmol). The reaction mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resulting brown liquid was diluted with toluene (30 ml) and *p*-toluenesulfonic acid (0.14 g, 0.27 mmol) was added. The resulting mixture was heated at reflux, under Dean-Stark conditions, for 16 h. After this time the reaction mixture was allowed to cool to room temperature before being washed with water (50 ml) followed by brine (50 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting brown residue was purified by column chromatography

(eluent: 0-50% Et_2O in petroleum ether) to yield the desired product as a yellow oil (0.65 g, 63%).

Procedure B

Scheme 1.35

To a stirred solution of **65** (1 g, 2.7 mmol) in DCM (15 ml) was added benzylchloroformate (0.55 ml, 3.8 mmol). The reaction mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resulting brown liquid was purified by column chromatography (eluent: 0-50% Et_2O in petroleum ether) to yield a colourless oil (1.04 g). This oil, indentified as intermediate **66** by NMR, was dissolved in toluene (30 ml) and recrystallised *p*-toluenesulfonic acid (0.13 g, 0.66 mmol) was added. The resulting mixture was heated at reflux, under Dean-Stark conditions, for 16 h. After this time the reaction mixture was allowed to cool to room temperature before being washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting brown residue was purified by column chromatography (eluent: 0-50% Et_2O in petroleum ether) to yield the desired product as a yellow oil (0.43 g, 42%).

General Procedure C

To a stirred solution of **65** in DCM was added benzylchloroformate. The reaction mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resulting brown liquid was diluted with toluene and *p*-toluenesulfonic acid was added. The resulting mixture was heated at reflux for 4 hours under Dean-Stark conditions. After this time, the reaction mixture was allowed to cool to room temperature before being washed with a volume of water roughly equal to the reaction solvent, followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The excess benzylchloroformate was distilled off (distilled at 103°C, 26 mbar) and then the resulting brown residue was purified by column chromatography (eluent: 50% diethyl ether in petroleum ether) to yield the desired product as a yellow oil.

Following the ***General Procedure C***, results are presented as follows:

(a) quantity of **65**; (b) volume of DCM; (c) quantity of benzylchloroformate; (d) volume of toluene; (e) quantity of TsOH; and (f) yield over 2 steps.

Table 1.6, Entry 1

(a) 14.0 g, 38 mmol; (b) 200 ml; (c) 7.6 ml, 53.5 mmol; (d) 475 ml; (e) 1.96 g, 10.3 mmol; and (f) 9.05 g, 63%.

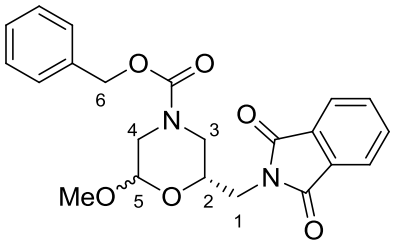
Table 1.6, Entry 2

(a) 88.8 g, 241 mmol; (b) 800 ml; (c) 48 ml, 337 mmol; (d) 800 ml; (e) 13.7 g, 72.3 mmol; and (f) 57 g, 62%.

IR ($CDCl_3$): 1614, 1714, 1722, 1774, 2942, 3033, 3063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (dd, ^2J = 13.3, J = 7.3 Hz, 0.6H, H3); 3.47-3.51 (m, 0.4H, H3); 3.77-3.83 (m, 1H, H1); 3.92-4.06 (m, 2H, H1+H3); 4.33-4.38 (m, 1H, H2); 5.21 (s, 2H, H6); 5.87 (d, J = 4.9 Hz, 0.6H, H4); 5.99 (d, J = 4.9 Hz, 0.4H, H4); 6.26 (d, J = 4.9 Hz, 0.6H, H5); 6.39 (d, J = 4.9 Hz, 0.4H, H5); 7.34-7.40 (m, 5H, H_{Ar}); 7.74-7.77 (m, 2H, H_{Ar} (phth)); 7.87-7.90 ppm (m, 2H, H_{Ar} (phth)); ^{13}C NMR (100 Hz, $CDCl_3$): δ 38.2, 42.8, 67.3, 69.9, 70.3, 105.0, 122.9, 127.4, 127.6, 127.7, 127.8, 128.1, 128.2, 128.4, 133.6, 135.5, 167.5 ppm; HRMS *m/z* Calc. for $C_{21}H_{19}N_2O_5$ (M^++H): 379.1288. Found: 379.1282.

$[\alpha]_D^{21}$ -7.9 (*c* 1.0, $CHCl_3$).

Experimental Data for *benzyl 2-((1,3-dioxoisoindolin-2-yl)methyl)-6-methoxymorpholine-4-carboxylate* **66**:

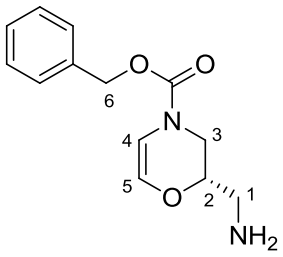


$C_{22}H_{22}N_2O_6$
Molecular Weight: 410.42

IR (neat): 1710, 1774, 2936 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.69-2.75 (m, 1H, H3), 3.13 (dd, ^2J = 13.5, J = 2.7 Hz, 1H, H4), 3.24 (s, 1.6H, OCH_3), 3.41 (s, 1.4H, OCH_3), 3.64-4.11

(m, 4.4H, H1+H3+H4+H2), 4.16-4.29 (m, 0.6H, H2), 4.37 (dd, *J* = 8.6, 2.6 Hz, 0.6H, H5), 4.64 (s, 0.4H, H5), 5.12 (d, *J* = 4.8 Hz, 2H, H6), 7.15-7.43 (m, 5H, H_{Ar}), 7.66-7.90 ppm (m, 4H, H_{Ar} (phth)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6, 42.2, 46.1, 46.3, 54.6, 56.1, 64.9, 67.4, 71.1, 95.6, 99.1, 123.5, 128.0, 128.4, 128.5, 128.6, 128.7, 131.9, 134.1, 137.5, 168.0, 168.1 ppm; HRMS *m/z* Calculated for $C_{22}H_{23}N_2O_6$ (M^++H): 411.1551. Found: 411.1552.

*Preparation of (S)-benzyl 2-(aminomethyl)-2H-1,4-oxazine-4(3H)-carboxylate (S)-**61***



$C_{13}H_{16}N_2O_3$
Molecular Weight: 248.28

General Procedure A

To a solution of (*S*)-**60** in THF was added a solution of hydrazine (1M in THF). The solution was stirred for 3 d at ambient temperature. The resulting mixture was treated with water until the precipitate dissolved and then extracted with DCM (x 2). The combined organic extracts were washed with water (x 2) and brine and then acidified with 1M hydrochloric acid. The aqueous layer was neutralised with $NaHCO_3$ and extracted with DCM (x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0- 5% MeOH in DCM) to yield the desired product as a pale yellow waxy solid.

Following ***General Procedure A***, results are presented as follows:

(a) quantity of (*S*)-**60**; (b) volume of THF; (c) quantity of hydrazine; and (d) yield.

Table 1.7, Entry 1

(a) 0.75 g, 1.9 mmol; (b) 10 ml; (c) 7.96 ml; and (d) 37% of starting material recovered.

Table 1.7, Entry 2

(a) 0.42 g, 1.1 mmol; (b) 6 ml; (c) 4.44 ml; and (d) 0.08 g, 30%.

Table 1.7, Entry 3

(a) 6 g, 16 mmol; (b) 84 ml; (c) 63 ml; and (d) 1.54 g, 39%.

Procedure B

Scheme 1.38

Phthalimide (*S*)-**60** (1.2 g, 3.17 mmol) was dissolved in a solution of hydrazine hydrate (0.3 M in MeOH, 35 ml) and the mixture was stirred at room temperature for 1 hour. After this time 5% aqueous HCl (14 ml) was added and the mixture was stirred at room temperature for a further 16 h. The reaction mixture was filtered to remove the white suspension which had formed and the filtrate was diluted with an equal amount of water, acidified using aqueous HCl (pH <2), and washed with diethyl ether. The organic layer was discarded and the aqueous layer was basified with solid KOH (pH >10) then extracted with diethyl ether (50 ml x 2). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the desired product as a pale yellow waxy solid (0.54 g, 2.17 mmol, 69%) with no further purification required.

General Procedure C

To a solution of (*S*)-**60** in ethanol was added $MeNH_2$ (33% in EtOH). The mixture was heated at 70°C for 4 h. After this time, tlc analysis showed no starting material remaining. The reaction mixture was diluted with an equal amount of water, acidified with 2M HCl (pH 2), and washed with diethyl ether. The organic layer was discarded and the aqueous layer was basified with solid KOH (pH >10) then extracted with diethyl ether (x 2). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired product as a pale yellow waxy solid with no further purification required.

Following the ***General Procedure C***, results are presented as follows:

(a) quantity of (*S*)-**60**; (b) volume of ethanol; (c) quantity of methylamine; and (d) yield.

Table 1.8, Entry 1

(a) 1.2 g, 3.2 mmol; (b) 30 ml; (c) 1.18 ml, 9.5 mmol; and (d) 0.6 g, 76%.

Table 1.8, Entry 2

(a) 11.7 g, 31 mmol; (b) 300 ml; (c) 11.6 ml, 93 mmol; and (d) 6.4 g, 83%.

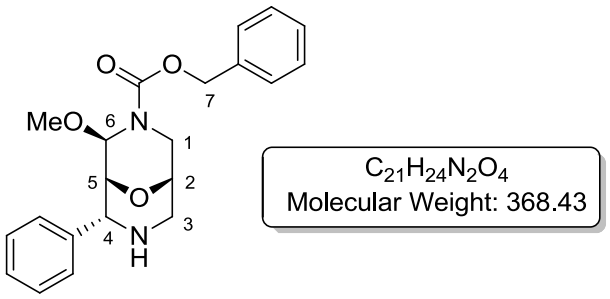
Table 1.8, Entry 3

(a) 86 g, 228 mmol; (b) 1000 ml; (c) 85 ml, 684 mmol; and (d) 51 g, 89%.

IR ($CDCl_3$): 1663, 1704, 2934, 3033, 3064, 3275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (br. s, 2H, NH_2); 2.88 (m, 2H, H1); 3.23 (dd, ^2J = 12.8, J = 8.3 Hz, 0.6H, H3); 3.30 (dd, ^2J = 12.8, J = 8.3 Hz, 0.4H, H3); 3.85-3.90 (m, 1H, H2); 3.96 (d, ^2J = 12.8 Hz, 0.4H, H3); 4.05 (d, ^2J = 12.8 Hz, 0.6H, H3); 5.21 (s, 2H, H6) 5.93 (d, J = 4.8 Hz, 0.6H, H4); 6.06 (d, J = 4.8 Hz, 0.4H, H4); 6.23 (d, J = 4.8 Hz, 0.6H, H5); 6.35 (d, J = 4.8 Hz, 0.4H, H5); 7.31-7.39 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$): δ 43.4, 43.6, 44.1, 67.7, 74.8, 75.3, 105.3, 105.9, 128.1, 128.2, 128.3, 128.5, 128.6, 129.5, 136.1, 152.0, 152.3 ppm; HRMS *m/z* Calc. for $C_{13}H_{17}N_2O_3$ (M^++H): 249.1234. Found: 249.1236.

$[\alpha]_D^{21}$ +6.2 (*c* 1.0, $CHCl_3$).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***70***



Procedure A

Scheme 1.40

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.4 g, 10 mmol) followed by a solution of oxazine (*S*)-**61** (0.25 g, 1 mmol) in DCM (5 ml). To this was added

benzaldehyde (0.1 ml, 1 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine, as confirmed by ^1H NMR analysis. This was then cooled to -20 °C and distilled methanol (0.04 ml, 1 mmol) was added. To the reaction mixture was added triflic acid (0.09 ml, 1 mmol) in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale to bright yellow. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was stirred for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil (0.21 g, 58%).

Procedure B

Table 1.9, Entry 1

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.4 g, 1 mmol) followed by a solution of oxazine (*S*)-**61** (0.25 g, 1 mmol) in DCM (5 ml). To this was added benzaldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol (0.04 ml, 1 mmol) was added. To the reaction mixture was added triflic acid (0.09 ml, 1 mmol) in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale to bright yellow. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C, and then remaining in the cooling bath was allowed to slowly warm to RT over 3 hours before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil (0.18 g, 50%).

General Procedure C

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added benzaldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol was added. To the reaction mixture was added triflic acid in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale yellow to an intense bright yellow. After complete addition of the triflic acid, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for the specified amount of time before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil.

Following ***General Procedure C***, results are presented as follows:

(a) quantity of (*S*)-**61**; (b) volume of DCM; (c) quantity of Na_2SO_4; (d) quantity of benzaldehyde; (e) quantity of methanol; (f) quantity of triflic acid; (g) time; and (h) yield.

Table 1.9, Entry 2

(a) 0.25 g, 1 mmol; (b) 5 ml; (c) 1.4 g, 10 mmol; (d) 0.1 ml, 1 mmol; (e) 0.04 ml, 1 mmol; (f) 0.09 ml, 1 mmol; (g) 1 h; and (h) 0.26 g, 71%.

Table 1.9, Entry 3

(a) 0.25 g, 1 mmol; (b) 5 ml; (c) 1.4 g, 10 mmol; (d) 0.1 ml, 1 mmol; (e) 0.04 ml, 1 mmol; (f) 0.09 ml, 1 mmol; (g) 2 h; and (h) 0.22 g, 60%.

Table 1.9, Entry 4

(a) 0.25 g, 1 mmol; (b) 5 ml; (c) 1.4 g, 10 mmol; (d) 0.1 ml, 1 mmol; (e) 0.04 ml, 1 mmol; (f) 0.09 ml, 1 mmol; (g) 30 min; and (h) 0.21 g, 58%.

Procedure D

Scheme 1.44

To a flame-dried flask containing a stirrer bar was added a solution of oxabispidine **70** (0.1 g, 0.27 mmol) in DCM (3 ml). This was then cooled to -20 °C and distilled methanol (0.01 ml, 0.27 mmol) was added followed by triflic acid (0.02 ml, 1 mmol) in a dropwise fashion over 10 min. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction was stirred at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude mixture was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield oxabispidine **70** as a yellow oil (0.057 g, 57%).

General Procedure E

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added benzaldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol was added. To the reaction mixture was added TMS triflate in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale to bright yellow. After complete addition of the TMS triflate the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil.

Following ***General Procedure E***, results are presented as follows:

(a) quantity of (*S*)-**61**; (b) volume of DCM; (c) quantity of Na_2SO_4; (d) quantity of benzaldehyde; (e) quantity of methanol; (f) quantity of TMSOTf; and (g) yield.

Table 1.10, Entry 1

(a) 0.25 g, 1 mmol; (b) 5 ml; (c) 1.4 g, 10 mmol; (d) 0.1 ml, 1 mmol; (e) 0.04 ml, 1 mmol; (f) 0.18 ml, 1 mmol; and (g) 0.68 g, 73%.

Table 1.10, Entry 2

(a) 3.4 g, 13 mmol; (b) 70 ml; (c) 19.5 g, 130 mmol; (d) 1.4 ml, 13 mmol; (e) 0.55 ml, 13 mmol; (f) 2.5 ml, 13 mmol; (g) 1 h; and (h) 4.1 g, 86 %.

Procedure F

Scheme 1.46

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.4 g, 10 mmol) followed by a solution of oxazine (*S*)-**61** (0.25 g, 1 mmol) in DCM (5 ml). To this was added the benzaldehyde (0.1 ml, 1 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **71**. This was then cooled to -20 °C and TMS triflate (0.18 ml, 1 mmol) was added in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale to bright yellow. After complete addition of the TMS triflate the reaction mixture was stirred at -20 °C for 10 min then distilled methanol (0.04 ml, 1 mmol) was added and the mixture stirred for a further 10 min at -20°C before the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil (0.7 g, 75%).

Procedure G

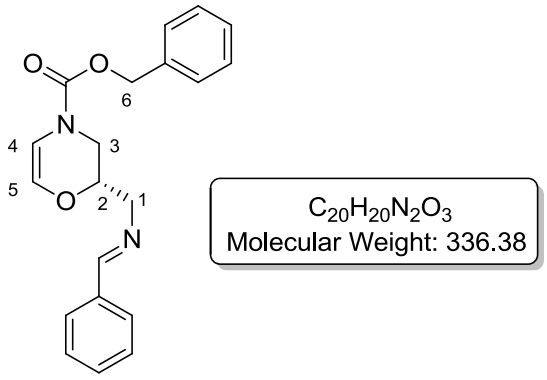
Scheme 1.47, Reaction (a)

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.57 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.15 g, 0.4 mmol) in DCM (3 ml). To this was added benzaldehyde (0.04 ml, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **71**. This was then cooled to -20 °C and distilled methanol (0.02 ml, 0.4 mmol) was added followed by TMSCN (0.05 ml, 0.4 mmol) in a dropwise fashion over 10 min. After complete addition of the TMSCN, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude residue was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to yield not the desired product, but addition product **75** as a yellow oil (0.04 g, 28%). *For experimental data for **75**, please refer to data on page 130.*

IR ($CDCl_3$): 1705, 2789, 2930, 3027, 3295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (br.s. 1H, NH), 3.13 (s, 2H, OCH_3), 3.20 (s, 1H, OCH_3, overlapping with signal corresponding to 0.4H, H3), 3.30 (d, ^2J = 11.8 Hz, 0.6H, H3); 3.53-3.57 (m, 1H, H3), 3.59-3.65 (m, 0.6H, H1), 3.67-3.70 (m, 0.4H, H1), 3.79-3.81 (m, 0.4H, H2), 3.88-3.93 (m, 1.6 H, H2+H5), 4.07 (d, ^2J =13.4 Hz, 0.4H, H1), 4.14 (d, ^2J = 13.4 Hz, 0.6H, H1), 4.42-4.44 (m, 1H, H4), 4.86 (s, 0.6H, H6), 5.01 (s, 0.4H, H6), 5.21-5.37 (m, 2H, H7), 7.14-7.47 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$): δ 42.0, 42.5, 49.9, 52.9, 53.8, 54.1, 61.1, 61.7, 65.5, 65.8, 66.8, 67.0, 74.3, 74.7, 78.3, 126.1, 126.5, 127.0, 127.2, 127.4, 127.6, 127.7, 128.9, 128.1, 135.6, 138.7, 138.9, 154.6 ppm; HRMS *m/z* Calc. for $C_{21}H_{25}N_2O_4$ (M^++H): 369.1809. Found: 369.1815.

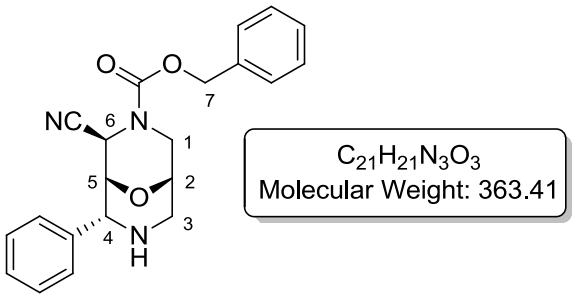
$[\alpha]_D^{20}$ -104.3 (*c* 1.0, $CHCl_3$).

NMR analysis of *(S,E)-benzyl 2-((benzylideneamino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* **71**:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (dd, ^{2}J = 13.0, J = 8.2, Hz, 0.6H, H3), 3.54 (dd, ^{2}J = 13.0, J = 7.7, Hz, 0.4H, H3), 3.78-3.90 (m, 2H, H1), 4.06 (d, ^{2}J = 13.0 Hz, 0.4H, H3), 4.19 (d, ^{2}J = 13.0 Hz, 0.6H, H3), 4.25-4.30 (m, 1H, H2), 5.19 (s, 1H, H6), 5.22 (s, 1H, H6), 5.92 (d, J = 4.9 Hz, 0.6 H, H4), 6.05 (d, J = 4.9 Hz, 0.4H, H4), 6.25 (d, J = 4.9 Hz, 0.6H, H5), 6.37 (d, J = 4.9 Hz, 0.4H, H5), 7.18-7.44 (m, 10H, H_{Ar}), 8.31 ppm (s, 1H, N=C*H*Ph).

Attempted preparation of (1R,2R,5S,8R)-benzyl 2-cyano-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***74***

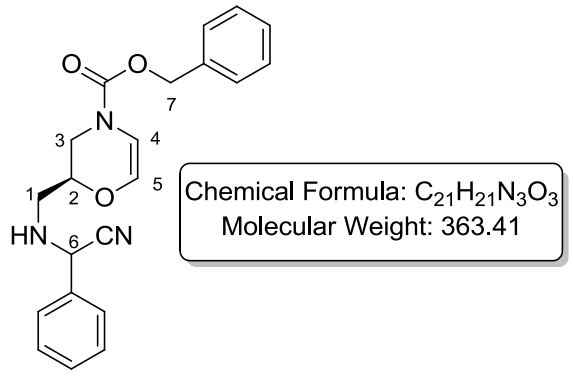


Scheme 1.47, Reaction (b)

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.57 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.1 g, 0.4 mmol) in DCM (3 ml). To this was added benzaldehyde (0.04 ml, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **71**. This was then cooled to -20 °C and TMSCN (0.05 ml, 0.4 mmol) was added in a dropwise fashion over 10 min. After complete addition of the TMSCN, the

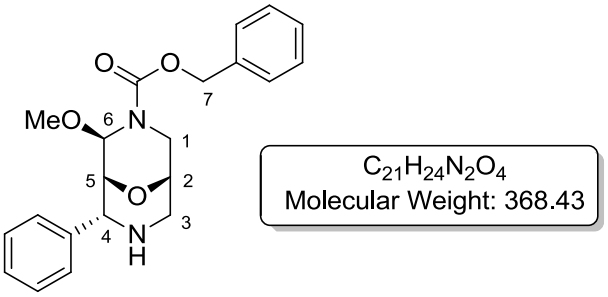
reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude residue was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to yield not the desired product, but addition product **75** as a yellow oil (0.035 g, 24%).

*Experimental data for (2S)-benzyl 2-(((cyano(phenyl)methyl)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate **75***



IR ($CDCl_3$): 1670, 2249, 2928, 3064, 3324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 1H, H6); 3.28-3.42 (m, 1.6H, H1); 3.48-3.52 (m, 0.4H, H1); 3.94-3.96 (m, 0.4H, H3); 4.04-4.06 (m, 1.6H, H3); 4.82-4.92 (m, 1H, H2); 5.18-5.20 (m, 2H, H7); 5.90 (d, *J* = 4.7 Hz, 0.6H, H5); 6.03-6.04 (m, 0.4H, H5); 6.23 (t, *J* = 4.3 Hz, 0.6H, H4); 6.36 (d, *J* = 4.6 Hz, 0.4H, H4); 7.31-7.39 (m, 8H, H_{Ar}); 7.41-7.43 ppm (m, 2H, H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$): δ 43.0, 43.1, 47.2, 47.3, 47.5, 53.8, 53.9, 67.3, 71.9, 72.1, 72.4, 72.6, 105.1, 105.6, 118.0, 126.7, 126.8, 127.6, 127.7, 127.8, 128.1, 128.5, 128.7, 133.8, 133.9, 135.5, 151.7 ppm

Lewis Acid Screening in the Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***70***



General Procedure

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added benzaldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol was added. To the reaction mixture was added the specified Lewis acid and the reaction was stirred at -20 °C for 10 min before the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for the specified period of time before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then 5% MeOH in DCM) to yield the desired product as a yellow oil.

Following ***General Procedure***, results are presented as follows:

(a) quantity of (*S*)-**61**; (b) volume of DCM; (c) quantity of Na_2SO_4; (d) quantity of benzaldehyde; (e) quantity of methanol; (f) Lewis acid; (g) quantity of Lewis acid; (h) time; and (i) yield.

Table 1.11, Entry 1

(a) 0.2 g, 0.8 mmol; (b) 5 ml; (c) 1.14 g, 8 mmol; (d) 0.08 ml, 0.8 mmol; (e) 0.03 ml, 0.8 mmol; (f) SiO_2; (g) 0.05 g, 0.8 mmol; (h) 48 h; and (i) -.

Table 1.11, Entry 2

(a) 0.2 g, 0.8 mmol; (b) 5 ml; (c) 1.14 g, 8 mmol; (d) 0.08 ml, 0.8 mmol; (e) 0.03 ml, 0.8 mmol; (f) $LiClO_4$; (g) 0.09 g, 0.8 mmol; (h) 48 h; and (i) -.

Table 1.11, Entry 3

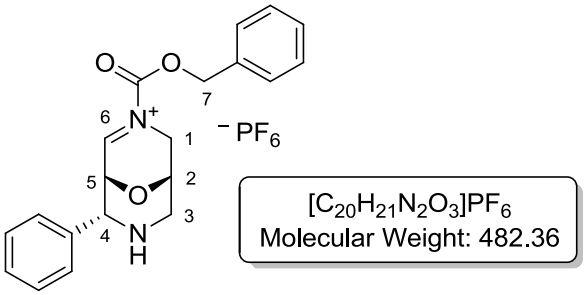
(a) 0.2 g, 0.8 mmol; (b) 5 ml; (c) 1.14 g, 8 mmol; (d) 0.08 ml, 0.8 mmol; (e) 0.03 ml, 0.8 mmol; (f) $ZnCl_2$; (g) 0.11 g, 0.8 mmol; (h) 24 h; and (i) 0.015 g, 0.08 g, 5%.

Table 1.11, Entry 4

(a) 0.2 g, 0.8 mmol; (b) 5 ml; (c) 1.14 g, 8 mmol; (d) 0.08 ml, 0.8 mmol; (e) 0.03 ml, 0.8 mmol; (f) $AlCl_3$; (g) 0.11 g, 0.8 mmol; (h) 24 h; and (i) 27%.

*For experimental data for oxabispidine **70**, please refer to data on page 129.*

*Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium hexafluorophosphate **73a***



Procedure A

Table 1.12, Entry 1

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in $CDCl_3$ (5 ml). To this was added benzaldehyde (0.08 ml, 0.81 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.8 mmol) was added accompanied by a colour change from pale to bright yellow. After stirring for 2 min, $NaPF_6$ (0.14 g, 0.8 mmol) was added to the reaction, however this was insoluble in the reaction solvent and no reaction to give the desired product was observed.

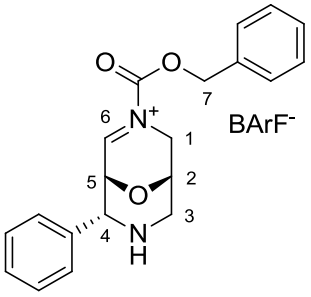
Procedure B

Table 1.12, Entry 2

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in $CDCl_3$ (5 ml). To this was added benzaldehyde (0.08 ml, 0.81 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.8 mmol) was added accompanied by a colour change from pale to bright yellow. After stirring for 2 min, $NaPF_6$ (0.14 g, 0.8 mmol) in CD_3CN (0.75 ml) was added to the reaction, accompanied by a slight exotherm. The reaction was held at -20°C for 2 h, after which time a solid was observed. The reaction was warmed to room temperature, and the solid was

collected by filtration. ^{1}H NMR analysis of the solid and of a sample of the reaction solution revealed none of the desired product had been formed.

Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ***73b***



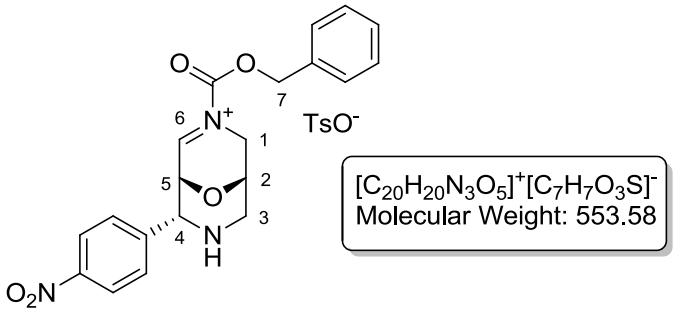
$[C_{20}H_{21}N_2O_3]^+[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
Molecular Weight: 1200.60

Procedure

Scheme 1.51

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.6 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.1 g, 0.4 mmol) in $CDCl_3$ (3 ml). To this was added benzaldehyde (0.04 ml, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and trifluoromethanesulfonic acid (0.035 ml, 0.4 mmol) was added accompanied by a colour change from pale to bright yellow. After stirring for 2 min, NaBArF (0.35g, 0.4 mmol) was added and the reaction was stirred at -20°C for 30 min. After this time, a sample of the reaction mixture was taken, and ^{1}H NMR analysis displayed a complex spectrum from which no structural information could be taken. As such, the experiment was terminated.

Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium 4-methylbenzenesulfonate ***78a***

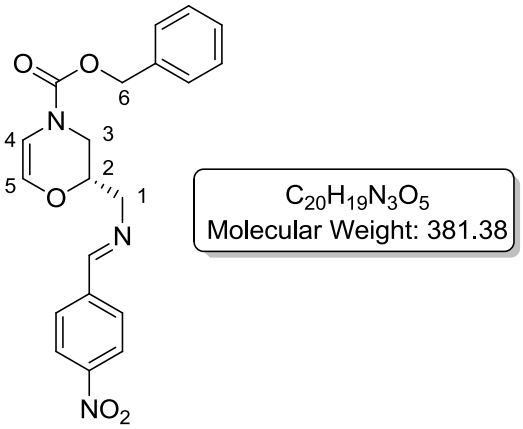


Procedure

Scheme 1.52

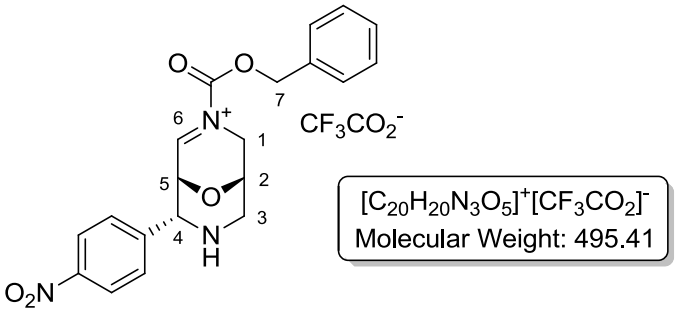
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in $CDCl_3$ (5 ml). To this was added *p*-nitrobenzaldehyde (0.12 g, 0.8 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **77**, the formation of which was confirmed by crude ^{1}H NMR. To this imine solution was added *p*-toluenesulfonic acid which had prior to use, been heated at 50°C under vacuum for 4 hours (0.15 g, 0.8 mmol). After stirring for 5 min, a sample of the reaction mixture was taken and ^{1}H NMR analysis revealed that the reaction mixture consisted mainly of the starting amine and aldehyde.

^{1}H NMR analysis of *(S,E)-benzyl 2-(((4-nitrobenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***77***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (dd, ^2J = 13.0, J = 8.0 Hz, 0.6H, H3), 3.47 (dd, ^2J = 13.0, J = 7.5 Hz, 0.4H, H3), 3.77-3.81 (m, 2H, H1), 3.96 (dd, ^2J = 13.0, J = 1.9 Hz, 0.6H, H3), 4.07 (dd, ^2J = 13.0, J = 1.9 Hz, 0.4H, H3), 4.21 (m, 1H, H2), 5.11 (s, 0.8H, H6), 5.12 (s, 1.2H, H6), 5.84 (d, J = 4.9 Hz, 0.6H, H4), 5.96 (d, J = 4.9 Hz, 0.4H, H4), 6.18 (d, J = 4.9 Hz, 0.6H, H5), 6.29 (d, J = 4.9 Hz, 0.4H, H5), 7.27-7.31 (m, 5H, H_{Ar}), 7.79-7.84 (m, 2H, H_{Ar}), 8.16-8.20 (m, 2H, H_{Ar}), 8.29 ppm (s, 1H, N=C*H*Ph).

Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium 2,2,2-trifluoroacetate ***78b***



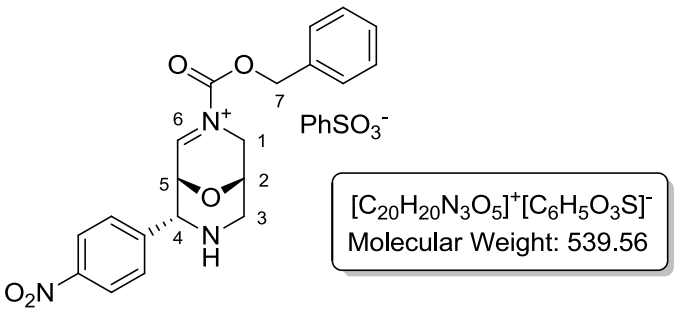
Procedure

Table 1.13, Entry 1

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.6 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.1 g, 0.4 mmol) in $CDCl_3$ (3 ml). To this was added *p*-nitrobenzaldehyde (0.06 g, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **77**, the formation of which was confirmed by crude ^{1}H NMR spectroscopy. To this imine solution was added trifluoroacetic acid (0.03 ml, 0.4 mmol). After stirring for 5 min, a sample of the reaction mixture was taken and ^{1}H NMR analysis of the sample revealed that only the imine was present. The reaction was left stirring at room temperature overnight, however, after this time, no significant change in the ^{1}H NMR spectrum of the reaction mixture was observed.

*For ^{1}H NMR analysis of imine **77**, please refer to data on page 136.*

Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium benzenesulfonate ***78c***



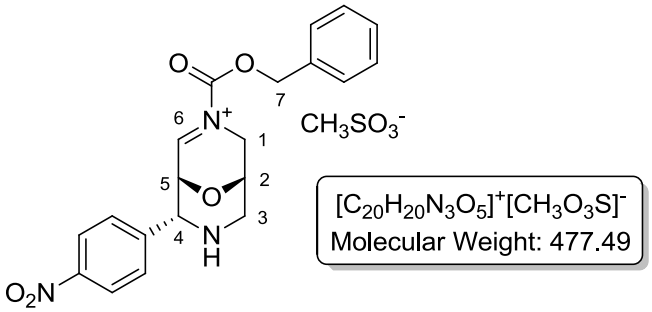
Procedure

Table 1.13, Entry 2

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.6 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.1 g, 0.4 mmol) in $CDCl_3$ (3 ml). To this was added *p*-nitrobenzaldehyde (0.06 g, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **77**, the formation of which was confirmed by crude ^{1}H NMR spectroscopy. To this imine solution was added benzenesulfonic acid (0.06 g, 0.4 mmol). After stirring for 5 min a sample of the reaction mixture was taken, and NMR of the sample revealed that, in addition to the acid, only the imine was present. The reaction was left stirring at room temperature overnight, however after this time no significant change in the NMR spectrum of the reaction mixture was observed.

*For ^{1}H NMR analysis of imine **77**, please refer to data on page 136.*

Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium methanesulfonate ***78d***



Procedure

Table 1.13, Entry 3

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.6 g, 4 mmol) followed by a solution of oxazine (*S*)-**61** (0.1 g, 0.4 mmol) in $CDCl_3$ (3 ml). To this was added *p*-nitrobenzaldehyde (0.06 g, 0.4 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **77**, the formation of which was confirmed by crude ^{1}H NMR. To this imine solution was added methanesulfonic acid (0.03 ml, 0.4 mmol). After stirring for 3 hours at room temperature a pale orange solid had precipitated out of solution. The solid in question was collected by filtration and placed in a vacuum oven for 4 hours. NMR of this solid revealed that along with small quantities of the starting aldehyde a new unknown species had been isolated (0.04 g).

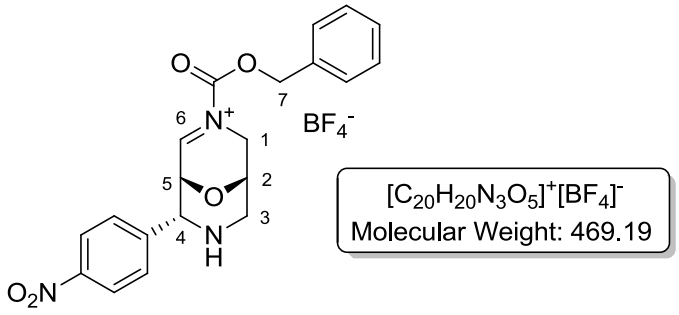
Melting Point: 146-148°C

IR (neat): 1519, 1709, 2792, 3018, 3433 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H), 3.55-3.73 (m, 4H, H1+H3), 4.17-4.30 (m, 3H, H2, H4+H5), 7.31-7.46 (m, 5H, H_{Ar}), 7.81 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 8.38 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 9.23 ppm (br. s, 1H C*H*=N); ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.6, 46.3, 57.3, 63.4, 67.5, 70.8, 72.4, 124.4, 124.5, 124.8, 128.1, 128.5, 128.6, 128.8, 128.9, 131.0, 136.5, 140.6, 147.9, 155.6 ppm; HRMS *m/z* Calc. for cation $C_{20}H_{20}N_3O_5$ (M^+): 382.1397. Found: 382.1400. LRMS *m/z* Calc. for anion CH_3SO_3 (M): 95.0. Found: 95.1.

$[\alpha]_D^{28}$ -49.6 (*c* 0.25, DMSO).

*For ^{1}H NMR analysis of imine **77**, please refer to data on page 136.*

*Attempted Preparation of (1S,5R,6R)-3-((benzyloxy)carbonyl)-6-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-en-3-ium tetrafluoroborate **78e***



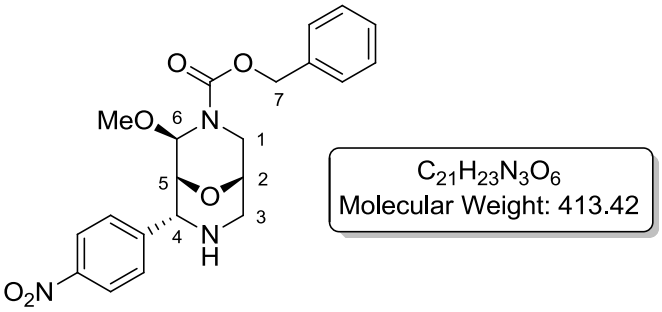
Procedure

Table 1.13, Entry 4

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in $CDCl_3$ (5 ml). To this was added *p*-nitrobenzaldehyde (0.12 g, 0.8 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine **77**, the formation of which was confirmed by crude ^{1}H NMR spectroscopy. To this imine solution was added $HBF_4.Et_2O$ (0.11 ml, 0.8 mmol). After stirring for 15 min at room temperature a solid had precipitated out of solution. The solid in question was collected by filtration and placed in a vacuum oven for 2 hours. ^{1}H NMR analysis of this solid revealed that the desired product had not been formed.

*For ^{1}H NMR analysis of imine **77**, please refer to data on page 136.*

*Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **78***



Procedure

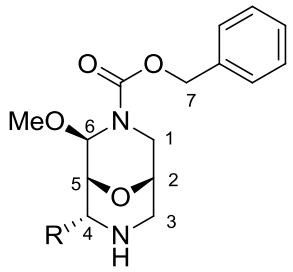
Scheme 1.54

To a flame-dried flask containing a stirrer bar was added the unidentified solid presumed to be **78d** (0.03 g, 0.06 mmol) prepared in **Scheme 1.53**, **Table 1.13**, **Entry 3**. To this was added methanol (1 ml) and the resulting mixture was stirred at room temperature overnight. After this time, crude ^{1}H NMR analysis indicated the presence of the desired oxabispidine product. The solution was concentrated *in vacuo* and the resulting residue dissolved in DCM and filtered through a plug of silica. The filtrate was concentrated *in vacuo* to yield a yellow solid (0.018 g, 72%) which was confirmed to be **78** by ^{1}H NMR analysis.

IR (neat): 1344, 1519, 1697, 2331, 2380, 2941 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (br. s, 1H, NH), 3.14 (s, 2H, OCH_3), 3.18 (s, 1H, OCH_3), 3.21 (d, ^{2}J = 12.1 Hz, 0.4H, H3), 3.30 (d, ^{2}J = 11.8 Hz, 0.6H, H3), 3.51-3.55 (m, 1H, H3), 3.59-3.70 (m, 1H, H1), 3.82 (t, J = 3.4 Hz, 0.4H, H5), 3.89-3.95 (m, 1.6H, H2+H5), 4.07 (d, ^{2}J = 13.6 Hz, 0.4H, H1), 4.16 (d, ^{2}J = 13.4 Hz, 0.6H, H1), 4.50 (d, J = 3.7 Hz, 1H, H4), 4.67 (s, 0.6H, H6), 4.84 (s, 0.4H, H6), 5.07-5.37 (m, 2H, H7), 7.32-7.49 (m, 7H, H_{Ar}), 7.84 (d, J = 8.7 Hz, 1.2H, H_{Ar}), 7.86 ppm (d, J = 8.7 Hz, 0.8H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 42.9, 49.9, 54.3, 54.5, 61.1, 61.6, 65.9, 66.2, 67.4, 67.8, 74.4, 74.9, 78.5, 123.7, 123.8, 127.5, 127.9, 128.0, 128.2, 128.4, 128.7, 128.8, 135.7, 146.5, 146.7, 154.8 ppm; HRMS *m/z* Calc. for $C_{21}H_{23}N_3O_6Na$ (M^++Na) 436.1476. Found 436.1479.

$[\alpha]_D^{21}$ -74.8 (*c* 1.0 in $CHCl_3$).

Preparation of Oxabispidines



General Procedure A

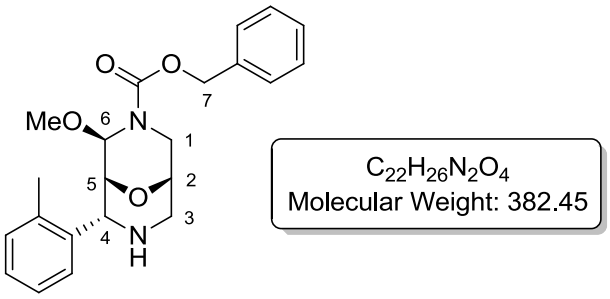
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added the relevant aldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This solution was then cooled to -20 °C and distilled methanol was added. To the reaction mixture was added trifluoromethanesulfonic acid in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min before the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a crude oil. The crude product was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to yield the desired product.

General Procedure B

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added the relevant aldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. The DCM was removed *in vacuo* and the resulting imine residue was dissolved in methanol. To this solution was added *p*-toluenesulfonic acid and the reaction mixture was then heated at reflux for 24 h. The methanol was removed under reduced pressure and the crude residue dissolved in DCM before being washed with a saturated aqueous sodium bicarbonate solution. The aqueous

layer was washed with an additional portion of DCM and the combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to yield the desired product.

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(o-tolyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***79***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.16, Entry 1

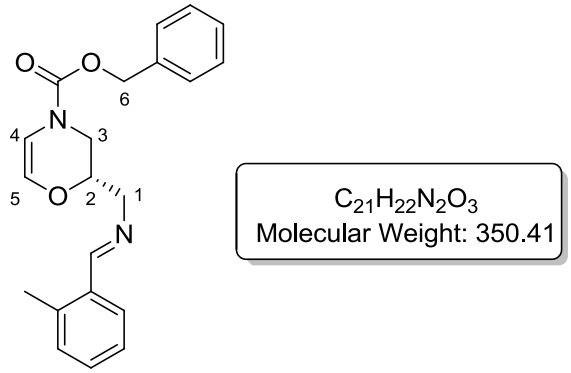
(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) *o*-tolualdehyde; (e) 0.12 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.24 g, 62% as a yellow oil.

IR (neat): 756, 1704, 2825, 2938, 3318 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (br.s, 1H, NH), 2.38 (s, 1.8H, CH_3), 2.40 (s, 1.2H, CH_3), 3.14 (s, 1.8H, OCH_3), 3.21 (s, 1.2H, OCH_3), 3.23 (d, *J* = 11.7 Hz, 0.4H, H3), 3.32 (d, *J* = 11.7 Hz, 0.6H, H3), 3.56-3.59 (m, 1H, H3), 3.60-3.65 (m, 0.6H, H1), 3.70 (d, ^2J = 13.4 Hz, 0.4H, H1), 3.81 (m, 0.4H, H2), 3.88-3.91 (m, 1.6H, H5+H2), 4.09 (d, ^2J = 13.4 Hz, 0.4H, H1), 4.18 (d, ^2J = 13.4 Hz, 0.6H, H1), 4.57 (d, *J* = 3.1 Hz, 1H, H4), 4.93 (s, 0.6H, H6), 5.06 (s, 0.4H, H6), 5.23-5.39 (m, 2H, H7), 6.80 (t, *J* = 7.8 Hz, 0.6H, H_{Ar}), 7.09-7.49 ppm (m, 8.4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 18.8, 42.1, 42.6, 50.3, 53.8, 54.1, 58.4, 58.6, 65.5, 65.8, 66.8, 67.1, 71.7, 72.2, 78.4, 78.5,

125.6, 126.0, 126.1, 126.7, 126.8, 127.0, 127.3, 127.6, 127.7, 127.9, 128.0, 129.8, 130.0, 134.6, 134.8, 135.7, 136.4, 136.6, 136.9, 154.6 ppm; HRMS: m/z Calc. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1956. Found: 383.1966

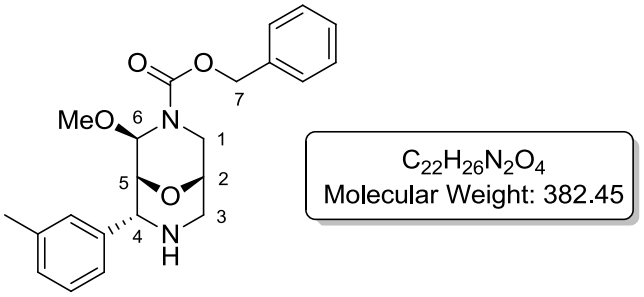
$[\alpha]_D^{20}$ -101.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((2-methylbenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***79a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 1.6H, CH_3), 2.52 (s, 1.4H, CH_3), 3.41 (dd, ^2J = 12.6, J = 8.0, Hz, 0.6H, H3), 3.53 (dd, ^2J = 12.6, J = 8.0, Hz, 0.4H, H3), 3.76-3.90 (m, 2H, H1), 4.08 (d, ^2J = 12.6 Hz, 0.4H, H3), 4.19 (d, ^2J = 12.6 Hz, 0.6H, H3), 4.25-4.28 (m, 1H, H2), 5.19 (s, 1H, H6), 5.21 (s, 1H, H6), 5.94 (d, J = 4.9 Hz, 0.6 H, H4), 6.07 (d, J = 4.9 Hz, 0.4H, H4), 6.26 (d, J = 4.9 Hz, 0.6H, H5), 6.38 (d, J = 4.9 Hz, 0.4H, H5), 7.19-7.49 (m, 9H, H_{Ar}), 8.61 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(m-tolyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***80***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.16, Entry 2

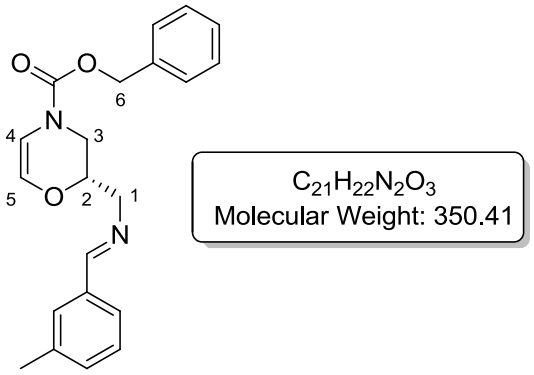
(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) distilled *m*-tolualdehyde; (e) 0.12 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.25 g, 64% as a yellow oil.

IR (neat): 763, 1704, 2825, 2941, 3320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (br.s, 1H, NH), 2.25 (s, 1.9H, CH_3), 2.35 (s, 1.1H, CH_3), 3.13 (s, 1.9 H, OCH_3), 3.21 (s, 1.1H, OCH_3), 3.30 (d, ^2J = 11.8 Hz, 0.6H, H3), 3.53-3.60 (m, 1H, H3), 3.61-3.68 (m, 0.6H, H1), 3.70-3.80 (m, 0.4H, H1), 3.88-3.89 (m, 0.4H, H3), 3.91-3.92 (m, 2H, H2+H5), 4.07 (d, ^2J = 13.2 Hz, 0.4H, H1), 4.14 (d, ^2J = 13.1 Hz, 0.6H, H1), 4.38-4.41 (m, 1H, H4), 4.88 (s, 0.6H, H6), 5.01 (s, 0.4H, H6), 5.16-5.23 (m, 1H, H7), 5.32-5.39 (m, 1H, H7); 7.04-7.14 (m, 4H, H_{Ar}), 7.23-7.48 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ20.9, 42.0, 42.5, 49.9, 50.0, 53.0, 53.8, 54.1, 61.0, 61.6, 64.6, 65.5, 65.7, 66.7, 67.0, 74.3, 74.8, 78.2, 78.3, 123.1, 123.5, 126.4, 126.8, 126.9, 127.0, 127.03, 127.11,127.14, 127.17, 127.20, 127.22, 127.25, 127.28, 127.31, 127.34, 127.37, 127.40, 127.42, 127.46, 127.48, 127.55, 127.59, 127.79, 127.93, 127.97,

128.04, 128.07, 128.09, 128.12, 128.15, 128.39, 135.69, 136.48, 137.62, 138.67, 138.96, 154.62, 154.67 ppm; HRMS: m/z Calc. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965. Found: 383.1962

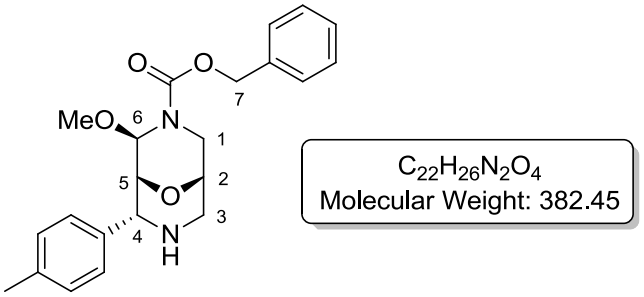
$[\alpha]_D^{20}$ -96.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((3-methylbenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***80a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 3.35-3.40 (m, 0.6H, H3), 3.47-3.55 (m, 0.4H, H3), 3.76-3.89 (m, 2H, H1), 4.06 (d, ^2J = 13.8 Hz, 0.4H, H3), 4.20 (d, ^2J = 13.8 Hz, 0.6H, H3), 4.26-4.29 (m, 1H, H2), 5.19 (s, 1H, H6), 5.22 (s, 1H, H6), 5.94 (d, *J* = 4.9 Hz, 0.6 H, H4), 6.06 (d, *J* = 4.9 Hz, 0.4H, H4), 6.26 (d, *J* = 4.9 Hz, 0.6H, H5), 6.38 (d, *J* = 4.9 Hz, 0.4H, H5), 7.30-7.41 (m, 9H, H_{Ar}), 8.28 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(p-tolyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***81***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

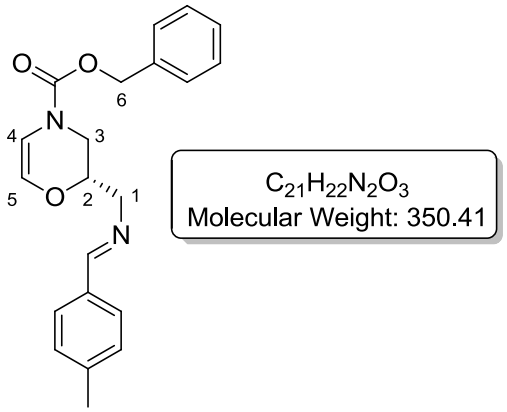
Table 1.16, Entry 3

(a) 1.4 g, 10 mmol ;(b) 0.25 g, 1 mmol; (c) 5 ml; (d) *p*-tolualdehyde; (e) 0.12 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.18 g, 48% as a yellow oil.

IR (neat): 750, 764, 1704, 2825, 2940, 3320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (br.s, 1H, NH), 2.30 (s, 2H, CH_3), 2.36 (s, 1H, CH_3), 3.14 (s, 2H, OCH_3), 3.20 (s, 1H, OCH_3, overlapping with signal corresponding to 0.4H, H3), 3.28 (d, J = 11.9 Hz, 0.6H, H3), 3.52-3.54 (m, 1H, H3), 3.59-3.64 (m, 0.6H, H1), 3.66-3.70 (m 0.4H, H1), 3.78-3.79 (m, 0.4H, H2), 3.88-3.91 (m, 1.6H, H5+H2), 4.06 (d, ^2J = 13.4 Hz, 0.4H, H1), 4.14 (d, ^2J = 13.3 Hz, 0.6H, H1), 4.39-4.40 (m, 1H, H4), 4.85 (s, 0.6H, H6), 5.01 (s, 0.4H, H6), 5.21-5.37 (m, 2H, H7), 6.94-6.96 (m, 1H, H_{Ar}), 7.16-7.24 (m, 3H, H_{Ar}), 7.28-7.48 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 20.6, 42.0, 42.5, 49.9, 50.0, 53.8, 54.1, 60.7, 61.3, 65.5, 65.7, 66.7, 67.0, 74.4, 74.8, 78.2, 78.3, 125.9, 126.4, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.6, 128.7, 135.6, 135.7, 135.9, 136.4, 136.5, 136.8, 154.6, 154.7 ppm; HRMS: m/z Calc. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965 Found: 383.1968

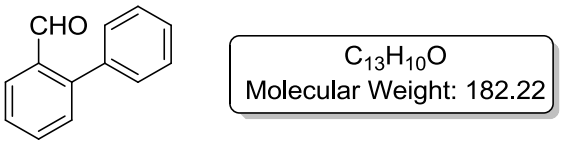
$[\alpha]_D^{20}$ -110.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((4-methylbenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***81a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3 H, CH_3), 3.34-3.39 (m, 0.6H, H3), 3.49-4.57 (m, 0.4H, H3), 3.73-3.87 (m, 2H, H1), 4.05 (d, ^2J = 13.2 Hz, 0.4H, H3), 4.18 (d, ^2J = 13.2 Hz, 0.6H, H3), 4.23-4.31(m, 1H, H2), 5.19 (s, 1H, H6), 5.21 (s, 1H, H6), 5.94 (d, *J* = 4.8 Hz, 0.6 H, H4), 6.06 (d, *J* = 4.8 Hz, 0.4H, H4), 6.26 (d, *J* = 4.8 Hz, 0.6H, H5), 6.37 (d, *J* = 4.8 Hz, 0.4H, H5), 7.22-7.40 (m, 7H, H_{Ar}), 7.62-7.64 (m, 2H, H_{Ar}), 8.27 ppm (s, 1H, N=C*H*Ph).

Preparation of [1,1'-biphenyl]-2-carbaldehyde ***85***[60]



Procedure

Scheme 1.58

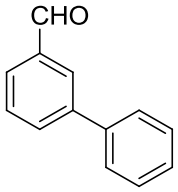
2-Bromobenzaldehyde was distilled from CaH_2 at 89°C, 5 mbar.

To a 3-necked flask fitted with a condenser was added 2-bromobenzaldehyde (1 g, 5.4 mmol), phenylboronic acid (0.7 g, 5.7 mmol) and propanol (10 ml). The resulting mixture was stirred under N_2 at room temperature for 30 min. After this time, the mixture was treated with $Pd(OAc)_2$ (0.004 g, 0.016 mmol), PPh_3 (0.012 g, 0.05 mmol), 2M Na_2CO_3 aqueous solution (3.2 ml) and deionised water (1.9 ml), then heated at reflux for 1 hour. As the reaction progressed a colour change from yellow to orange to brown was noted. Crude ^{1}H

NMR analysis of the reaction mixture indicated complete conversion to the desired product had occurred, so the reaction was removed from the heat source and water was added to the mixture. The reaction was allowed to cool whilst stirring open to the atmosphere for 2 hours. After this time the mixture was diluted with ethyl acetate and the two phases were separated. The aqueous layer was washed with two additional portions of ethyl acetate and then the combined organics were washed with 5% aqueous sodium bicarbonate solution followed by brine. After filtration through a plug of celite followed by rinsing with addition ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired product as a colourless oil (0.86 g, 89%) with no further purification required.

IR ($CHCl_3$): 1699, 2835, 3027, 3356 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.54 (m, 7H, H_{Ar}), 7.67 (td, *J* = 7.5, 1.5 Hz, 1H), 8.06 (dd, *J* = 7.7, 1.1 Hz, 1H), 10.02 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3, 127.6, 128.1, 129.4, 130.0, 130.5, 133.6, 135.0, 140.1, 147.0, 192.3 ppm.

Preparation of [1,1'-biphenyl]-3-carbaldehyde ***86***[61]



$C_{13}H_{10}O$
Molecular Weight: 182.22

Procedure

Scheme 1.59

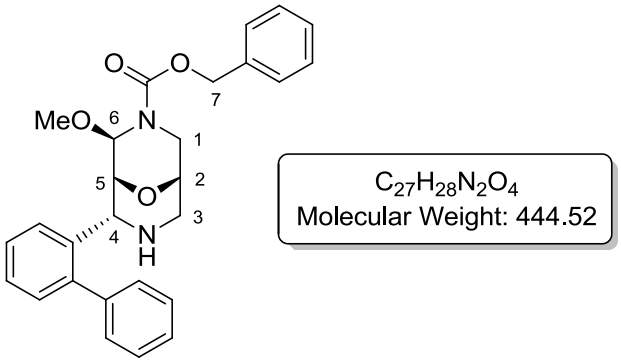
3-Bromobenzaldehyde was distilled from CaH_2 at 89°C, 5 mbar.

To a 3-necked flask fitted with a condenser was added 3-bromobenzaldehyde (3 g, 16 mmol), phenylboronic acid (2.1 g, 16.8 mmol) and propanol (30 ml). The resulting mixture was stirred under N_2 at room temperature for 30 min. After this time, the mixture was treated with

$Pd(OAc)_2$ (0.012 g, 0.05 mmol), PPh_3 (0.036 g, 0.14 mmol), 2M Na_2CO_3 aqueous solution (9.6 ml) and deionised water (5.7 ml), then heated at reflux for 1 hour. As the reaction progressed a colour change from yellow to orange to brown was noted. Crude ^1H NMR analysis of the reaction mixture indicated complete conversion to the desired product had occurred, so the reaction was removed from the heat source and water was added to the mixture. The reaction was allowed to cool whilst stirring open to the atmosphere for 2 hours. After this time the mixture was diluted with ethyl acetate and the two phases were separated. The aqueous layer was washed with two additional portions of ethyl acetate and then the combined organics were washed with 5% aqueous sodium bicarbonate solution followed by brine. After filtration through a plug of celite, followed by rinsing with addition ethyl acetate, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired product as a pale yellow oil (2.55 g, 87%) with no further purification required.

IR ($CHCl_3$): 1701, 3019, 3372 $cm^{-}1$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.45 (m, 1H, H_{Ar}), 7.49-7.53 (m, 2H, H_{Ar}), 7.62-7.67 (m, 3H, H_{Ar}), 7.89 (dd, J = 7.5, 1.5 Hz, 2H, H_{Ar}), 8.14 (s, 1H, H_{Ar}), 10.12 ppm (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3, 128.6, 128.7, 129.0, 129.6, 130.5, 133.6, 137.4, 140.4, 143.0, 192.1 ppm.

Preparation of (1R,2R,5S,8R)-benzyl 8-([1,1'-biphenyl]-2-yl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***82***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.17, Entry 1

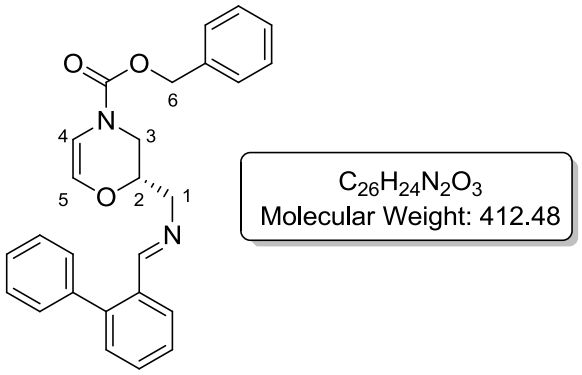
(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) 2-biphenylcarboxaldehyde; (e) 0.18 g, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.091 g, 51% as a white solid.

Melting point: 56-57°C

IR (neat): 757, 1704, 2830, 2939, 3029, 3060, 3318 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (br.s, 1H, NH), 3.15 (s, 1.8H, OCH_3), 3.22 (s, 1.2H, OCH_3), 3.23 (d, ^2J =11.8 Hz, 0.4H, H3), 3.32 (d, ^2J =11.8 Hz, 0.6H, H3), 3.40-3.44 (m, 1H, H3), 3.52-3.65 (m, 2.4H, H1, H2, H5), 3.75-3.76 (m, 0.6H, H5), 4.01 (d, ^2J = 13.1 Hz, 0.4H, H1), 4.08 (d, ^2J = 13.4 Hz, 0.6H, H1), 4.48-4.50 (m, 1H, H4), 4.95 (s, 0.6H, H6), 5.12 (s, 0.4H, H6), 5.24-5.39 (m, 2H, H7), 6.91-6.95 (t, *J* = 7.4 Hz, 0.6H, H_{Ar}), 7.16-7.62 ppm (m, 13.4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.3, 43.0, 50.4, 54.4, 54.7, 58.4, 58.6, 65.6, 65.9, 67.3, 67.6, 72.5, 73.0, 78.8, 79.0, 126.9, 127.1, 127.2, 127.3, 127.4, 127.6, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 130.1, 130.3, 136.2, 136.4, 136.7, 136.9, 140.8, 141.0, 141.8, 155.2, 155.3 ppm; HRMS: *m/z* Calc. for $C_{27}H_{29}N_2O_4$ $[M+H]^+$: 445.2122. Found: 445.2115.

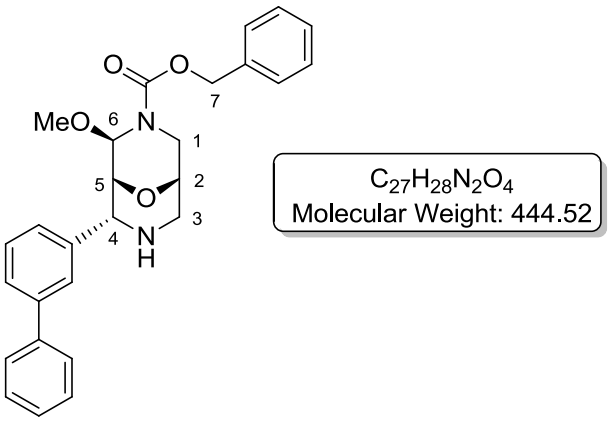
$[\alpha]_D^{20}$ -82.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-((([1,1'-biphenyl]-2-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***82a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (dd, ^2J = 12.9, J = 8.0, Hz, 0.6H, H3), 3.53 (dd, ^2J = 12.6, J = 8.0, Hz, 0.4H, H3), 3.67-3.77 (m, 2H, H1), 4.06 (d, ^2J = 12.9 Hz, 0.4H, H3), 4.17 (d, ^2J = 12.9 Hz, 0.6H, H3), 4.23-4.26 (m, 1H, H2), 5.20 (s, 1H, H6), 5.22 (s, 1H, H6), 5.93 (d, J = 4.7 Hz, 0.6 H, H4), 6.05 (d, J = 4.7 Hz, 0.4H, H4), 6.25 (d, J = 4.7 Hz, 0.6H, H5), 6.37 (d, J = 4.7 Hz, 0.4H, H5), 7.37-7.52 (m, 14H, H_{Ar}), 8.29 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 8-([1,1'-biphenyl]-3-yl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***83***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**1**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.17, Entry 2

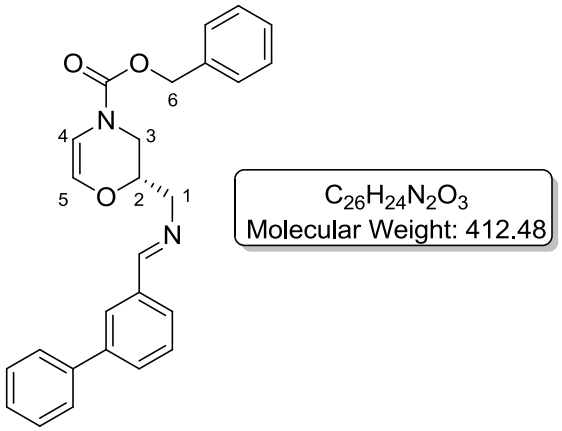
(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) 3-biphenylcarboxaldehyde; (e) 0.18 g, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.15 g, 82% as a white solid.

Melting Point: 51-53°C

IR (neat): 763, 1704, 2247, 2941, 3032, 3061, 3319 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (br.s, 1H, NH), 3.08 (s, 2H, OCH_3), 3.24 (s, 1H, OCH_3) overlapping with signal corresponding to 0.4H, H3), 3.33 (d, ^{2}J = 11.8 Hz, 0.6H, H3), 3.54-3.64 (m, 1.6H, H3+H1), 3.70-3.73 (m, 0.4H, H1), 3.82-3.83 (m, 0.4H, H2), 3.91 (m, 0.6H, H2), 3.96 (d, *J* = 3.4 Hz, 0.6H, H4), 3.99 (d, *J* = 3.4 Hz, 0.4H, H4), 4.10 (d, ^{2}J = 13.4 Hz, 0.4H, H1), 4.16 (d, ^{2}J = 13.2 Hz, 0.6H, H1), 4.50 m, 1H, H5), 4.90 (s, 0.6H, H6), 5.13 (s, 0.4H, H6), 5.20-5.42 (m, 2H, H7), 7.13-7.23 (m, 1 H, H_{Ar}), 7.25-7.72 ppm (m, 13H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.9, 42.5, 49.9, 50.0, 53.7, 54.1, 61.1, 61.8, 65.6, 65.8, 66.8, 66.9, 74.4, 74.9, 78.3, 125.0, 125.4, 125.6, 125.9, 126.0, 126.6, 126.7, 126.8, 127.0, 127.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.2, 128.3, 128.4, 135.6, 136.4, 139.3, 139.6, 140.3, 140.5, 140.9, 141.0, 154.6, 154.8 ppm; HRMS: *m/z* Calc. for $C_{27}H_{29}N_2O_4$ $[M+H]^+$: 445.2122. Found: 445.2119.

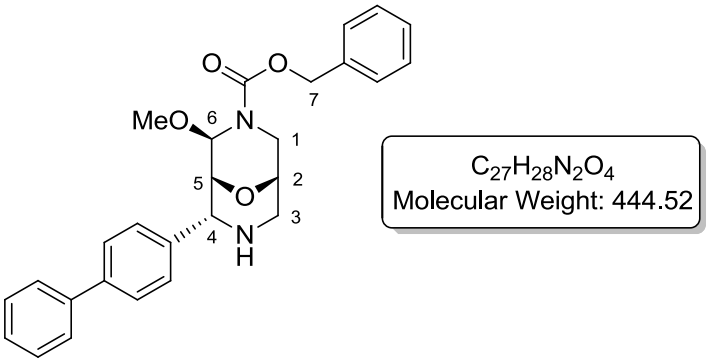
$[\alpha]_D^{20}$ -90.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-((([1,1'-biphenyl]-3-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***83a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (dd, ^{2}J = 13.3, J = 7.6, Hz, 0.6H, H3), 3.54 (dd, ^{2}J = 13.3, J = 7.6, Hz, 0.4H, H3), 3.79-3.92 (m, 2H, H1), 4.06 (d, ^{2}J = 13.2 Hz, 0.4H, H3), 4.20 (d, ^{2}J = 13.2 Hz, 0.6H, H3), 4.26-4.30 (m, 1H, H2), 5.19 (s, 1H, H6), 5.22 (s, 1H, H6), 5.95 (d, J = 4.8 Hz, 0.6 H, H4), 6.07 (d, J = 4.8 Hz, 0.4H, H4), 6.27 (d, J = 4.8 Hz, 0.6H, H5), 6.38 (d, J = 4.8 Hz, 0.4H, H5), 7.31-7.65 (m, 14H, H_{Ar}), 8.38 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 8-([1,1'-biphenyl]-4-yl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***84***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.17, Entry 3

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) 4-biphenylcarboxaldehyde (recrystallised from hexane); (e) 0.18 g, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.14 g, 75% as a white solid.

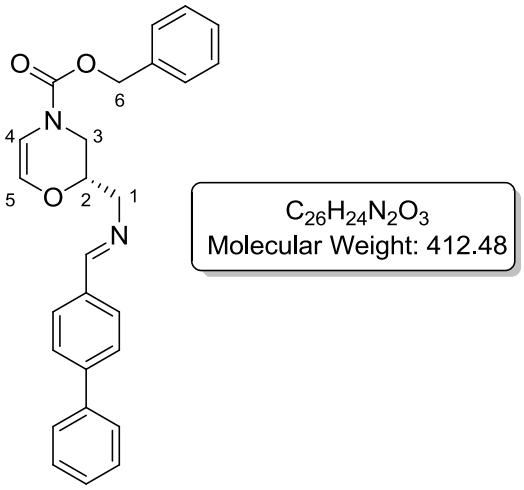
Melting Point: 54-57°C

IR (neat): 764, 1704, 2248, 2825, 2942, 3030, 3061, 3319 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (br.s, 1H, NH), 3.17 (s, 2H, OCH_3), 3.22 (s, 1H, OCH_3 overlapping with signal corresponding to 0.4H, H3), 3.32 (d, ^2J = 11.9 Hz, 0.6H, H3), 3.56-3.60 (m, 1H, H3), 3.63-3.66 (m, 0.6H, H1), 3.71-3.72 (m, 0.4H, H1), 3.82-3.97 (m, 2H, H2+H5), 4.09 (d, ^2J = 13.2 Hz, 0.4H, H1), 4.18 (d, ^2J = 13.2 Hz, 0.6H, H1), 4.47-4.48 (m, 1H, H4), 4.91 (s, 0.6H, H6), 5.09 (s, 0.4H, H6), 5.20-5.39 (m, 2H, H7), 7.32-7.52 (m, 13H, H_{Ar}), 7.61-7.64 ppm (m, 1H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0, 42.6, 49.8, 49.9, 53.8, 54.1, 60.8, 61.6, 65.5, 65.8, 66.8, 67.1, 74.4, 74.8, 78.2, 78.3, 126.4, 126.5, 126.6, 126.7, 126.8, 127.7, 127.4, 127.6,

127.7, 127.8, 127.9, 128.1, 128.2, 135.6, 136.4, 137.8, 137.9, 139.9, 140.0, 154.6, 154.7 ppm; HRMS: *m/z* Calc. for $C_{27}H_{29}N_2O_4$ $[M+H]^+$: 445.2122. Found: 445.2120.

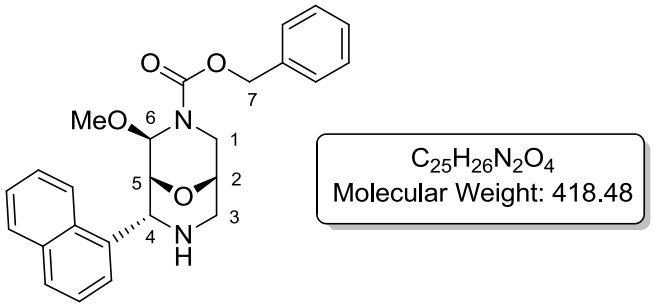
$[\alpha]_D^{20}$ -132.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-((([1,1'-biphenyl]-4-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***84a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37-3.43 (m, 0.6H, H3), 3.51-3.58 (m, 0.4H, H3), 3.78-3.91 (m, 2H, H1), 4.07 (d, ^2J = 13.4 Hz, 0.4H, H3), 4.21 (d, ^2J = 13.4 Hz, 0.6H, H3), 4.28-4.30 (m, 1H, H2), 5.20 (s, 1H, H6), 5.23 (s, 1H, H6), 5.95 (d, *J* = 4.9 Hz, 0.6 H, H4), 6.08 (d, *J* = 4.9 Hz, 0.4H, H4), 6.27 (d, *J* = 4.9 Hz, 0.6H, H5), 6.39 (d, *J* = 4.9 Hz, 0.4H, H5), 7.33-7.53 (m, 8H, H_{Ar}), 7.63-7.68 (m, 4H, H_{Ar}), 7.78-7.84 (m, 2H, H_{Ar}), 8.35 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(naphthalen-1-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***87***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.18, Entry 1

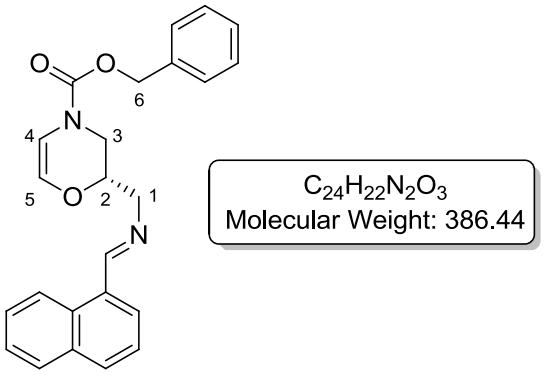
(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) 1-naphthaldehyde; (e) 0.14 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.31 g, 73% as a white solid.

Melting point: 66-67°C

IR (neat): 1699, 2826, 2942, 3062, 3319 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.05 (s, 1.9H, OCH_3), 3.12 (s, 1.1H, OCH_3), 3.32 (d, ^2J = 11.6 Hz, 0.4H, H3), 3.42 (d, ^2J = 11.6 Hz, 0.6H, H3), 3.64-3.74 (m, 2H, H3+H1), 3.89-3.90 (br.m, 0.4H, H2), 3.98-3.99 (m, 0.6H, H2), 4.13 (d, ^2J = 13.5 Hz, 0.4H, H1), 4.20-4.24 (m, 1.6H, H1+H5), 4.84 (s, 0.6H, H6), 4.98 (s, 0.4H, H6), 5.19 (m, 1H H4), 5.24-5.42 (m, 2H, H7), 7.02 ppm (t, *J* = 7.8 Hz, 0.6H, H_{Ar}), 7.34-8.13 (m, 9H, H_{Ar}), 7.81 (d, *J* = 7.7 Hz, 0.4H, H_{Ar}), 7.88-7.91 (m, 1H, H_{Ar}), 8.12 ppm (d, *J* = 8.4 Hz, 1H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0, 42.6, 50.5, 53.7, 54.0, 57.7, 57.9, 65.8, 66.1, 66.8, 67.0, 72.8, 73.2, 78.8, 121.8, 121.9, 123.8, 124.6, 124.9, 125.0, 125.2, 125.4, 125.8, 126.0, 127.4, 127.6, 127.7, 128.0, 128.1, 128.5, 128.6, 130.0, 133.2, 134.4, 135.7, 154.7 ppm; HRMS: *m/z* Calc. for $C_{25}H_{27}N_2O_4$ $[M+H]^+$: 419.1965. Found: 419.1965.

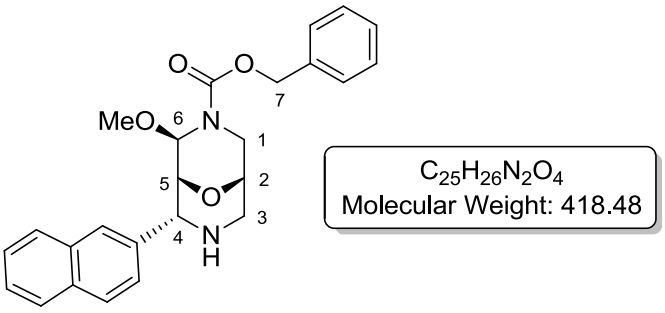
$[\alpha]_D^{20}$ -136.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((naphthalen-1-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***87a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47-3.52 (m, 0.6H, H3), 3.59-3.64 (m, 0.4H, H3), 3.92-4.01 (m, 2H, H1), 4.14 (d, ^2J = 12.4 Hz, 0.4H, H3), 4.26 (d, ^2J = 12.4 Hz, 0.6H, H3), 4.35-4.40 (m, 1H, H2), 5.18-5.24 (m, 2H, H6), 5.97 (d, *J* = 4.7 Hz, 0.6 H, H4), 6.10 (d, *J* = 4.7 Hz, 0.4H, H4), 6.29 (d, *J* = 4.7 Hz, 0.6H, H5), 6.41 (d, *J* = 4.7 Hz, 0.4H, H5), 7.31-7.72 (m, 9H, H_{Ar}), 7.89-7.96 (m, 3H, H_{Ar}), 8.95 ppm (s, 1H, N=C*H*naph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(naphthalen-2-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***88***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

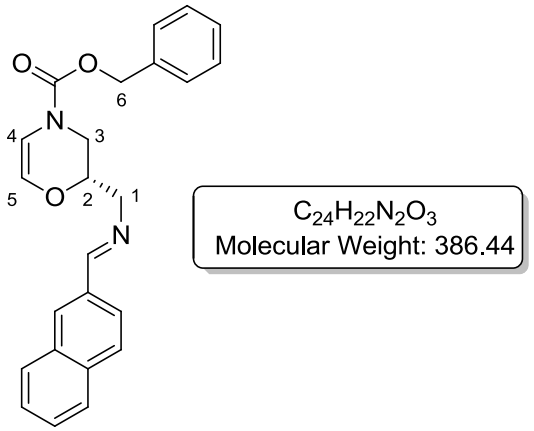
Table 1.18, Entry 2

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 5 ml; (d) 2-naphthaldehyde; (e) 0.14 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.29 g, 70% as a pale yellow oil.

IR (neat): 1709, 2824, 2987, 3057, 3319 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (br. s, 1H, NH), 3.07 (s, 2H, OCH_3), 3.17 (s, 1H, OCH_3), 3.26 (d, ^{2}J = 11.9 Hz, 0.4H, H3), 3.36 (d, ^{2}J = 11.9 Hz, 0.6H, H3), 3.58-3.66 (m, 1.6 H, H3+H1), 3.71-3.74 (m, 0.4H, H1), 3.83-3.84 (m, 0.4H, H2), 3.93-3.94 (m, 0.6H, H2), 4.03 (d, *J* = 3.3 Hz, 0.4H, H5), 4.05 (d, *J* = 3.4 Hz, 0.6H, H5), 4.12 (d, ^{2}J = 13.3 Hz, 0.6H, H1), 4.18 (d, ^{2}J = 13.4 Hz, 0.4H, H1), 4.58 (d, *J* = 3.3 Hz, 0.6H, H4), 4.61 (d, *J* = 3.4 Hz, 0.4H, H4), 4.86 (s, 0.6H, H6), 5.04 (s, 0.4H, H6), 5.18-5.44 (m, 2H, H7), 7.18-7.30 (m, 4H, H_{Ar}), 7.35-7.52 (m, 5H, H_{Ar}), 7.62-7.68 (m, 1H, H_{Ar}), 7.80-7.86 ppm (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0, 42.6, 49.8, 49.9, 53.8, 54.1, 60.9, 61.7, 65.6, 65.8, 66.8, 67.1, 74.3, 74.7, 78.4, 124.2, 124.6, 124.8, 125.4, 125.7, 125.8, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 132.4, 132.5, 132.8, 132.9, 135.6, 136.1, 136.5, 154.6, 154.7 ppm; HRMS: *m/z* Calc. for $C_{25}H_{26}N_2O_4$ $[M+H]^+$: 419.1965. Found: 419.1965.

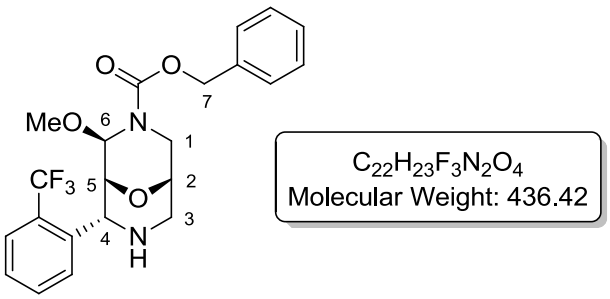
$[\alpha]_D^{20}$ -102.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((naphthalen-2-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***88a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.43 (dd, ^2J = 12.7, J = 7.9, Hz, 0.6H, H3), 3.58 (dd, ^2J = 12.7, J = 7.9, Hz, 0.4H, H3), 3.81-3.94 (m, 2H, H1), 4.09 (d, ^2J = 12.7 Hz, 0.4H, H3), 4.23 (d, ^2J = 12.7 Hz, 0.6H, H3), 4.31-4.32 (m, 1H, H2), 5.20 (s, 1H, H6), 5.23 (s, 1H, H6), 5.96 (d, J = 4.7 Hz, 0.6 H, H4), 6.09 (d, J = 4.7 Hz, 0.4H, H4), 6.28 (d, J = 4.7 Hz, 0.6H, H5), 6.40 (d, J = 4.7 Hz, 0.4H, H5), 7.31-7.55 (m, 7H, H_{Ar}), 7.87-8.06 (m, 5H, H_{Ar}), 8.46 ppm (s, 1H, N=C*H*naph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(2-(trifluoromethyl)phenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***89***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

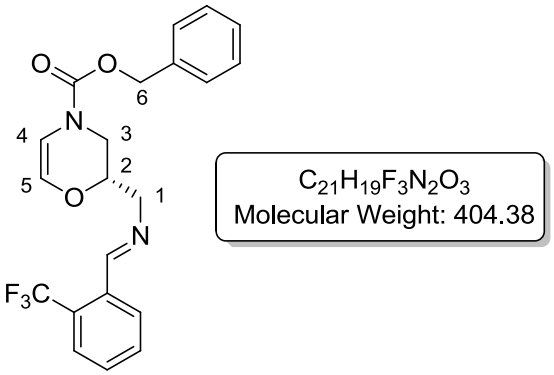
Table 1.19, Entry 1

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) 2-trifluoromethyl benzaldehyde; (e) 0.17 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.33 g, 76% as a yellow oil.

IR (neat): 1311, 1701, 2948, 3071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (br. s, 1H, NH), 3.15 (s, 1.8H, OCH_3), 3.18 (s, 1.2H, OCH_3 overlapping with signal corresponding to 0.4H, H3), 3.22 (d, ^{2}J = 11.8 Hz, 0.6H, H3), 3.52 (m, 1H, H3), 3.59-3.72 (m, 1H, H1), 3.79 (m, 0.4H, H2), 3.88-3.89 (m, 0.6H, H2), 3.92 (d, *J* = 2.9 Hz, 0.6H, H5), 3.96 (d, *J* = 2.9 Hz, 0.4H, H5), 4.06 (d, ^{2}J = 13.5 Hz, 0.6H, H1), 4.16 (d, ^{2}J = 13.5 Hz, 0.4H, H1), 4.72 (m, 1H, H4), 5.00 (s, 0.6H, H6), 5.15 (s, 0.4H, H6), 5.19-5.39 (m, 2H, H7), 6.86 (t, *J* = 7.6 Hz, 0.6H, H_{Ar}), 7.22-7.38 (m, 5.4H, H_{Ar}), 7.44-7.46 (m, 1H, H_{Ar}), 7.55-7.65 (m, 1H, H_{Ar}), 7.74 (d, *J* = 7.8 Hz, 0.6H, H_{Ar}), 7.89 ppm (d, *J* = 7.8 Hz, 0.4H, H_{Ar});^{13}C NMR (100 MHz, $CDCl_3$) δ 42.6, 43.0, 50.6, 50.7, 54.4, 54.7, 58.5, 58.7, 65.8, 66.1, 67.4, 67.7, 73.3, 73.7, 78.5, 78.6, 126.0, 126.1, 126.2, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.5, 130.2, 131.8, 132.4, 136.1, 136.8, 137.9, 138.1, 155.0, 155.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.4, -58.5 ppm; HRMS *m/z* Calc. for $C_{22}H_{24}F_3N_2O_4$ (M^++H) 437.1683. Found 437.1680.

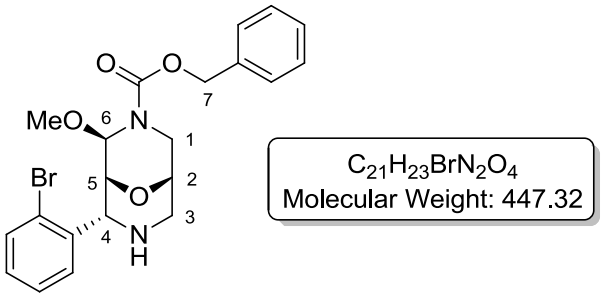
$[\alpha]_D^{20}$ -80.7 (*c* 1.0 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((2-(trifluoromethyl)benzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***89a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (dd, ^2J = 12.9, J = 8.0, Hz, 0.6H, H3), 3.49-3.53 (m, 0.4H, H3), 3.81-3.92 (m, 2H, H1), 4.05-4.08 (m, 0.4H, H3), 4.19 (dd, ^2J = 13.2, J = 1.8 Hz, 0.6H, H3), 4.27-4.32 (m, 1H, H2), 5.20-5.22 (m, 2H, H6), 5.94 (d, J = 4.9 Hz, 0.6H, H4), 6.07 (d, J = 4.9 Hz, 0.4H, H4), 6.27 (d, J = 4.9 Hz, 0.6H, H5), 6.39 (d, J = 4.9 Hz, 0.4H, H5), 7.36-7.41 (m, 5H, H_{Ar}), 7.55-7.61 (m, 2H, H_{Ar}), 7.70-7.76 (m, 1H, H_{Ar}), 8.15-8.20 (m, 0.4H, H_{Ar}), 8.25 (d, J =7.5 Hz, 0.6H, H_{Ar}), 8.68 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 8-(2-bromophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***90***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

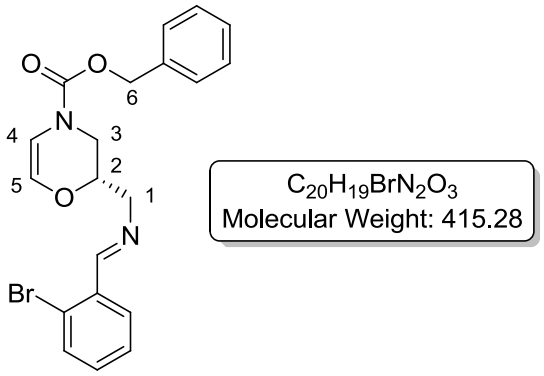
Table 1.19, Entry 2

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) 2-bromobenzaldehyde; (e) 0.12 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.4 g, 89% as a yellow oil.

IR (neat): 1114, 1419, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 1.8H, OCH_3), 3.16 (s, 1.2H, OCH_3), 3.17 (d, ^{2}J = 11.5 Hz, 0.4H, H3), 3.26 (d, ^{2}J = 11.5 Hz, 0.6H, H3), 3.50-3.55 (m, 1H, H3), 3.62 (ddd, ^{2}J = 13.4, J = 4.2, ^{4}J = 2.0 Hz, 0.6H, H1), 3.67 (ddd, ^{2}J = 13.5, J = 4.2, ^{4}J = 2.0 Hz, 0.4H, H1), 3.78 (t, J = 3.8 Hz, 0.4H, H5), 3.87 (t, J = 3.9 Hz, 0.6H, H5), 4.04 (d, ^{2}J = 13.4 Hz, 0.4H, H1), 4.12 (d, ^{2}J = 13.2 Hz, 0.6H, H1), 4.13-4.15 (m, 1H, H2), 4.67 (d, J = 3.7 Hz, 0.6H, H4), 4.69 (d, J = 3.7 Hz, 0.4H, H4), 4.77 (s, 0.6H, H6), 4.90 (s, 0.4H, H6), 5.08-5.38 (m, 2H, H7), 6.74 (t, J = 7.6 Hz, 0.6H, H_{Ar}), 7.01 (t, J = 7.6 Hz, 0.4H, H_{Ar}), 7.12-7.60 ppm (m, 8H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.5, 43.0, 50.4, 53.4, 54.3, 54.6, 61.0, 61.2, 65.8, 66.1, 67.4, 67.6, 71.3, 71.8, 78.9, 79.0, 123.3, 126.6, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 128.9, 129.1, 129.4, 129.5, 130.7, 132.8, 133.0, 136.1, 155.1, 155.3 ppm; HRMS *m/z* Calc. for $C_{21}H_{24}{}^{79}BrN_2O_4$ (M^++H) 447.0914. Found 447.0913.

$[\alpha]_D^{21}$ -54.7 (*c* 1.0 in $CHCl_3$).

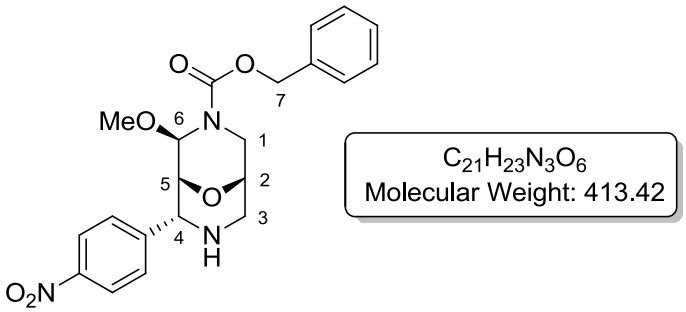
^{1}H NMR analysis of *(S,E)-benzyl 2-(((2-bromobenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***90a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37 (dd, ^{2}J = 13.0, J = 8.2 Hz, 0.6H, H3), 3.51 (dd, ^{2}J = 13.0, J = 7.7 Hz, 0.4H, H3), 3.75-3.85 (m, 2H, H1), 4.02 (d, ^{2}J = 11.7 Hz, 0.4H, H3), 4.17 (d, ^{2}J =

11.7 Hz, 0.6H, H3), 4.24-4.26 (m, 1H, H2), 5.17 (s, 0.8H, H6), 5.19 (s, 1.2H, H6), 5.92 (d, *J* = 5.0 Hz, 0.6H, H4), 6.04 (d, *J* = 5.0 Hz, 0.4H, H4), 6.24 (d, *J* = 5.0 Hz, 0.6H, H5), 6.36 (d, *J* = 5.0 Hz, 0.4H, H5), 7.25-7.45 (m, 6H, H_{Ar}), 7.55 (d, *J* = 7.8 Hz, 1H, H_{Ar}), 7.63-7.65 (m, 0.6H, H_{Ar}), 7.90-7.92 (m, 0.4H, H_{Ar}), 7.98 (d, *J* = 8.0 Hz, 0.4H, H_{Ar}), 8.03 (d, *J* = 8.0 Hz, 0.6H, H_{Ar}), 8.66 ppm (s, 1H, N=C*H*Ph).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(4-nitrophenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***78***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

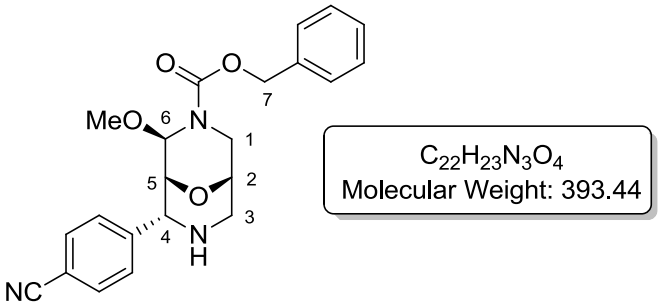
Table 1.19, Entry 3

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 4-nitrobenzaldehyde; (e) 0.15 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.24 g, 73% as a yellow solid.

For analysis of oxabispidine ***78****, please refer to data on page 141.*

For ^{1}*H NMR analysis of imine* ***77****, please refer to data on page 136.*

Preparation of (1R,2R,5S,8R)-benzyl 8-(4-cyanophenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***91***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

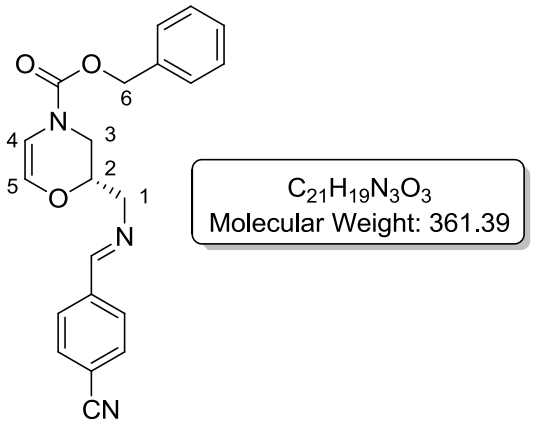
Table 1.19, Entry 4

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) 4-formylbenzonitrile; (e) 0.13 g, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.19 g, 48% as colourless oil.

IR (neat): 1697, 2227, 2331, 2358, 2825, 2941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84 (br. s, 1H, NH), 3.12 (s, 2H, OCH_3), 3.13 (s, 1H, OCH_3 overlapping with signal corresponding to 0.4H, H3), 3.18 (d, ^2J = 12.7 Hz, 0.6H, H3), 3.48-3.51 (m, 1H, H3), 3.57 (d, ^2J = 13.5 Hz, 0.4H, H1), 3.59 (d, ^2J = 13.5 Hz, 0.6 H, H1), 3.78-3.79 (m, 0.4H, H2), 3.87-3.89 (m, 1.6H, H2+H5), 4.05 (d, ^2J = 13.7 Hz, 0.4H, H1), 4.12 (d, ^2J = 13.5 Hz, 0.6H, H1), 4.42 (s, 1H, H4), 4.65 (s, 0.6H, H6), 4.82 (s, 0.4 H, H6), 5.07-5.33 (m, 2H, H7), 7.23 (d, J = 7.2 Hz, 1H, H_{Ar}), 7.29-7.61 (m, 7H, H_{Ar}), 7.61 ppm (d, J = 7.8 Hz, 1H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.3, 42.9, 49.9, 54.3, 54.5, 61.1, 61.6, 65.9, 66.2, 67.4, 67.8, 74.4, 74.9, 78.5, 123.7, 123.8, 127.5, 127.9, 128.0, 128.2, 128.4, 128.7, 128.8, 135.7, 146.5, 146.7, 154.8 ppm; HRMS *m/z* Calc. for $C_{22}H_{23}N_3O_4Na$ (M^++Na) 416.1581. Found 416.1580.

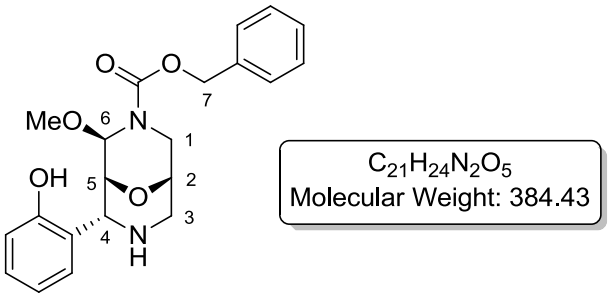
$[\alpha]_D^{20}$ -92.7 (*c* 0.8 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((4-nitrobenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***91a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (dd, ^2J = 13.1, J = 7.8 Hz, 0.6H, H3), 3.53 (dd, ^2J = 13.1, J = 7.8 Hz, 0.4H, H3), 3.83-3.88 (m, 2H, H1), 4.03 (d, ^2J = 13.0 Hz, 0.4H, H3), 4.15 (d, ^2J = 13.0 Hz, 0.6H, H3), 4.24-4.30 (m, 1H, H2), 5.19 (s, 1.2H, H6), 5.20 (s, 0.8H, H6), 5.91 (d, J = 4.9 Hz, 0.6H, H4), 6.03 (d, J = 4.9 Hz, 0.4H, H4), 6.23 (d, J = 4.9 Hz, 0.6H, H5), 6.37 (d, J = 4.9 Hz, 0.4H, H5), 7.33-7.39 (m, 7H, H_{Ar}), 7.69-7.71 (m, 2H, H_{Ar}), 8.31 ppm (s, 1H, N=C*H*Ph).

Attempted Preparation of (1R,2R,5S,8R)-benzyl 8-(2-hydroxyphenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***92***



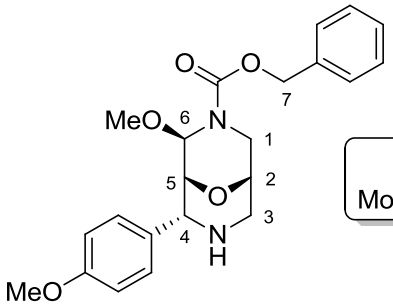
Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.19, Entry 5

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) salicylaldehyde; (e) 0.09 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0%.

Attempted Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(4-methoxyphenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***93***



$C_{22}H_{26}N_2O_5$
Molecular Weight: 398.45

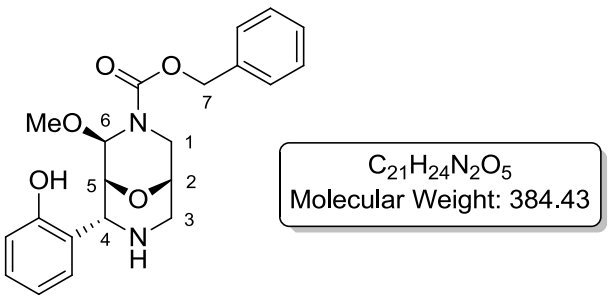
Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.19, Entry 6

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) *p*-anisaldehyde; (e) 0.12 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0%.

Preparation of (1R,2R,5S,8R)-benzyl 8-(2-hydroxyphenyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***92***



Following *Preparation of Oxabispidines* ***General Procedure B***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) volume of MeOH; (g) quantity of *p*-toluenesulfonic acid; and (h) yield.

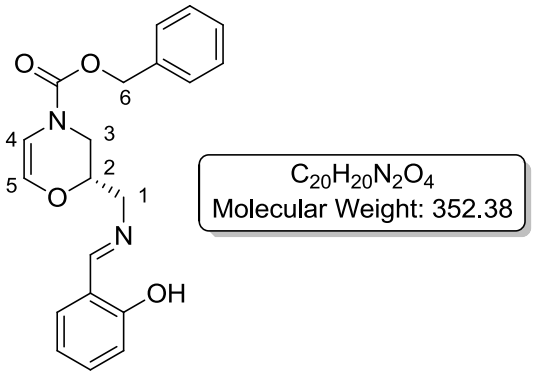
Table 1.20, Entry 1

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) salicylaldehyde; (e) 0.09 ml, 0.8 mmol; (f) 5 ml; (g) 0.07 ml, 0.8 mmol; and (h) 0.12 g, 40%.

IR (neat): 1705, 2357, 2870, 2937, 3010, 3282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.15 (s, 2H, OCH_3), 3.23 (d, ^2J = 11.7 Hz, 1H, H3), 3.29 (s, 1H, OCH_3), 3.46 (ddd, ^2J = 12.2, J = 4.1, ^4J = 1.6 Hz, 1H, H3), 3.64 (ddd, ^2J = 13.2, J = 4.6, ^4J = 1.6 Hz, 1H, H1), 3.88-3.92 (m, 0.4H, H2), 3.96 (d, J = 4.3 Hz, 0.6H, H2), 4.01 (t, J = 4.3 Hz, 1H, H5), 4.05-4.06 (m, 1H, H1), 4.54 (d, J = 4.4 Hz, 1H, H4), 5.01 (s, 1H, H6), 5.14-5.27 (m, 2H, H7), 6.73 (d, J = 8.3 Hz, 1H, H_{Ar}), 6.78-6.82 (m, 1H, H_{Ar}), 6.96-7.00 (m, 1H, H_{Ar}), 7.14-7.19 (m, 1H, H_{Ar}), 7.32-7.41 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.5, 48.1, 54.8, 60.5, 65.2, 67.3, 73.4, 78.4, 116.9, 117.1, 118.8, 118.9, 120.3, 127.4, 127.53, 127.58, 127.6, 127.7, 127.8, 127.9, 128.1, 128.9, 135.6, 154.9, 157.3 ppm; HRMS *m/z* Calc. for $C_{21}H_{25}N_2O_5$ (M^++H) 385.1758. Found 385.1761.

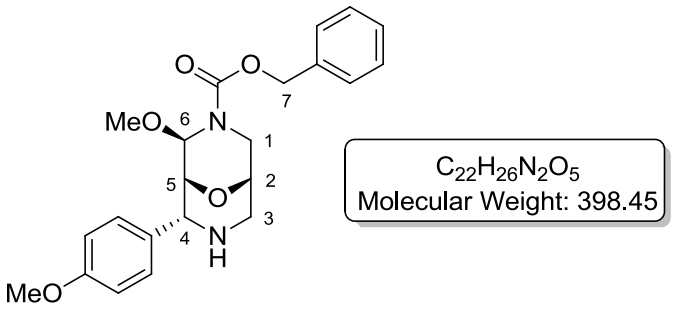
$[\alpha]_D^{20}$ -53.0 (*c* 1.0 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((2-hydroxybenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***92a***:



^{1}H NMR (500 MHz, $CDCl_3$): δ 3.38 (dd, ^2J = 13.3, J = 8.3 Hz, 0.6H, H3), 3.50 (dd, ^2J = 13.1, J = 7.8 Hz, 0.4H, H3), 3.80-3.84 (m, 2H, H1), 3.99-4.14 (m, 1H, H3), 4.23-4.28 (m, 1H, H2), 5.19-5.21 (m, 2H, H6), 5.92 (d, J = 5.1 Hz, 0.6H, H4), 6.04 (1H, d, J = 5.1 Hz, 0.4H, H4), 6.26 (d, J = 4.9 Hz, 0.6H, H5), 6.38 (d, J = 4.9 Hz, 0.4H, H5), 6.91 (t, J = 7.4 Hz, 1H, H_{Ar}), 7.26-7.40 (m, 8H, H_{Ar}), 8.37 ppm (s, 1H, ArC*H*=N).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(4-methoxyphenyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***93***



Following *Preparation of Oxabispidines* ***General Procedure B***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) volume of MeOH; (g) quantity of *p*-toluenesulfonic acid; and (h) yield.

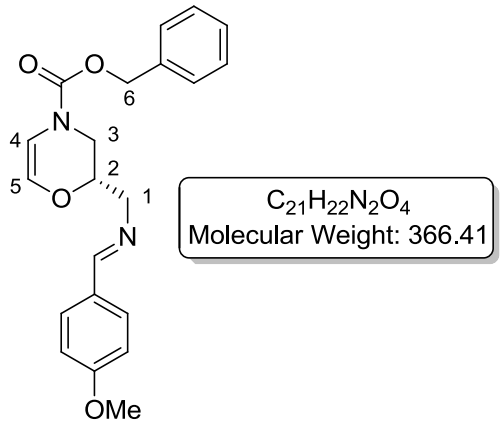
Table 1.20, Entry 2

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) *p*-anisaldehyde; (e) 0.09 ml, 0.8 mmol; (f) 5 ml; (g) 0.07 ml, 0.8 mmol; and (h) 0.17 g, 53% as a pale yellow oil.

IR (neat): 1075, 1231, 1247, 1420, 1512, 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13 (s, 1.8H, OCH_3), 3.15 (d, ^{2}J = 12.0 Hz, 0.4H, H3), 3.18 (s, 1.2H, OCH_3), 3.24 (d, ^{2}J = 11.9 Hz, 0.6H, H3), 3.48-3.50 (m, 1H, H3), 3.59 (ddd, ^{2}J = 13.4, J = 3.9, ^{4}J = 1.7 Hz, 0.6H, H1), 3.66 (ddd, ^{2}J = 13.5, J = 3.7, ^{4}J = 1.7 Hz, 0.4H, H1), 3.70 (s, 1.8H, CH_3O-Ar), 3.79 (s, 1.2H, CH_3O-Ar), 3.80 (t, J = 3.6 Hz, 0.4H, H5), 3.81 (d, J = 3.5 Hz, 0.6H, H5), 3.85 (m, 1H, H2), 4.04 (d, ^{2}J = 13.4 Hz, 0.4H, H1), 4.12 (d, ^{2}J = 13.4 Hz, 0.6H, H1), 4.32 (d, J = 3.5 Hz, 1H, H4), 4.86 (s, 0.6H, H6), 5.02 (s, 0.4H, H6), 5.16-5.34 (m, 2H, CH_2Ph), 6.61 (d, J = 8.7 Hz, 1.2H, H_{Ar}), 6.88 (d, J = 8.7 Hz, 0.8H, H_{Ar}), 7.17 (d, J = 8.5 Hz, 1.2H, H_{Ar}), 7.25 (d, J = 8.5 Hz, 0.8H, H_{Ar}), 7.25-7.45 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100MHz, $CDCl_3$) δ: 42.5, 43.0, 50.4, 50.5, 54.3, 54.6, 55.2, 55.6, 61.1, 61.6, 65.9, 66.2, 67.2, 67.5, 74.9, 75.3, 78.6, 78.7, 113.8, 114.3, 127.7, 127.8, 128.1, 128.2, 128.4, 128.5, 131.3, 131.4, 136.1, 136.8, 155.1, 155.2, 158.9, 159.0 ppm; HRMS *m/z* Calc. for $C_{22}H_{27}N_2O_5$ (M^++H) 399.1914. Found 399.1914.

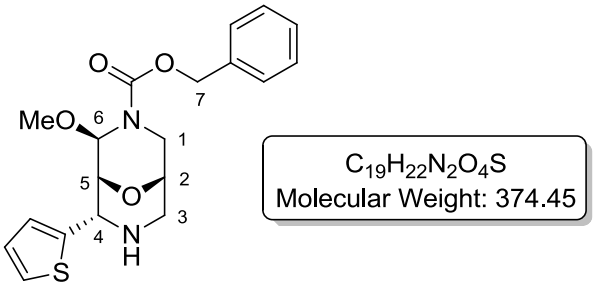
$[\alpha]_D^{21}$ -91.7 (*c* 0.53 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((4-methoxybenzylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***93a***:



^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.33 (dd, ^{2}J = 13.0, J = 8.3 Hz, 0.6H, H3), 3.49 (dd, ^{2}J = 13.0, J = 7.7 Hz, 0.4H, H3), 3.74-3.81 (m, 2H, H1), 3.84 (s, 1.2H, CH_3O-Ar), 3.89 (s, 1.8H, CH_3O-Ar), 4.02 (d, ^{2}J = 13.2 Hz, 0.4H, H3), 4.16 (d, ^{2}J = 13.2 Hz, 0.6H, H3), 4.20-4.24 (m, 1H, H2), 5.16 (s, 0.8H, H6), 5.19 (s, 1.2H, H6), 5.92 (d, J = 5.0 Hz, 0.6H, H4), 6.04 (1H, d, J = 5.0 Hz, 0.4H, H4), 6.23 (d, J = 4.9 Hz, 0.6H, H5), 6.34 (d, J = 4.9 Hz, 0.4H, H5), 6.92 (d, J = 8.7 Hz, 1.2H, H_{Ar}), 7.01 (d, J = 8.7 Hz, 0.8H, H_{Ar}), 7.26-7.38 (m, 5H, H_{Ar}), 7.67 (d, J = 8.5 Hz, 1.2H, H_{Ar}), 7.85 (d, J = 8.8 Hz, 0.8H, H_{Ar}); 8.21 ppm (s, 1H, ArC*H*=N).

Preparation of (1R,2R,5S,8S)-benzyl 2-methoxy-8-(thiophen-2-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***94***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

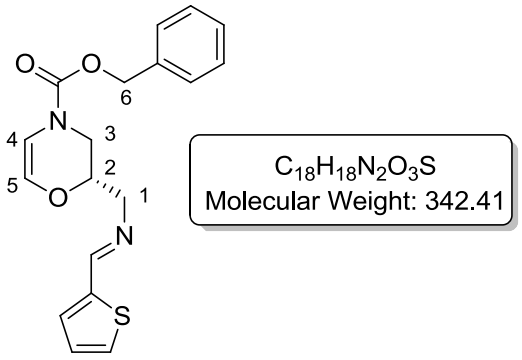
Table 1.21, Entry 1

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) 2-thiophenecarboxaldehyde; (e) 0.09 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.073 g, 20%.

IR (neat): 1701, 2335, 2358, 2939 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (br. s, 1H, NH), 3.19 (s, 1.8H, OCH_3), 3.27 (s, 1.2H, OCH_3 overlapping with signal corresponding to 1H, H3), 3.51-3.54 (m, 1H, H3), 3.60-3.64 (m, 0.6H, H1), 3.67-3.72 (m, 0.4H, H1), 3.80 (t, *J* = 3.8 Hz, 0.4H, H2), 3.87 (t, *J* = 3.8 Hz, 0.6H, H2), 3.95 (d, *J* = 3.9 Hz, 0.6H, H5), 3.99 (d, *J* = 3.9 Hz, 0.4H, H5), 4.03 (d, ^2J = 13.1 Hz, 0.4H, H1), 4.12 (d, ^2J = 13.1 Hz, 0.6H, H1), 4.67 (d, *J* = 3.5 Hz, 1H, H4), 5.04 (s, 0.6H, H6), 5.21-5.24 (m, 2.4H, H6+H7), 6.87-7.07 (m, 1.6H, H_{Ar}), 7.14 (d, *J* = 5.0 Hz, 0.4H, H_{Ar}), 7.25-7.28 ppm (m, 6H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 42.5, 49.6, 54.0, 54.5, 56.9, 65.6, 66.9, 67.1, 74.0, 78.6, 123.3, 123.7, 123.9, 126.5, 126.7, 127.3, 127.6, 127.9, 128.0, 135.6, 154.6 ppm; HRMS *m/z* Calc. for $C_{19}H_{23}N_2O_4S_1$ (M^++H) 375.1373. Found 375.1376.

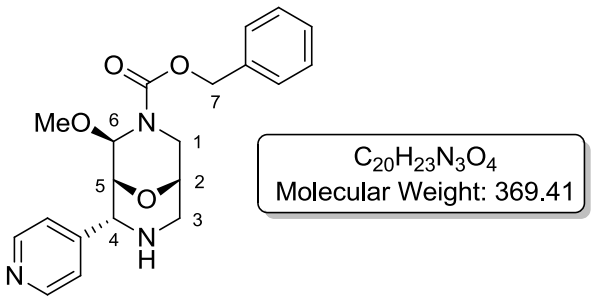
$[\alpha]_D^{20}$ -60.9 (*c* 0.11 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((thiophen-2-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***94a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (dd, ^2J = 12.8, J = 8.0 Hz, 0.6H, H3), 3.49 (dd, ^2J = 12.8, J = 7.8 Hz, 0.4H, H3), 3.70- 3.82 (m, 2H, H1), 4.00 (d, ^2J = 13.3 Hz, 0.4H, H3), 4.13 (d, ^2J = 12.8 Hz, 0.6H, H3), 4.21-4.27 (m, 1H, H2), 5.17-5.20 (m, 2H, H6), 5.91 (d, J = 4.9 Hz, 0.6H, H4), 6.03 (1H, d, J = 4.9 Hz, 0.4H, H4), 6.23 (d, J = 4.9 Hz, 0.6H, H5), 6.35 (d, J = 4.9 Hz, 0.4H, H5), 7.07-7.09 (m, 0.6H, H_{Ar}), 7.23 (dd, J = 4.8, 3.8 Hz, 0.4H, H_{Ar}), 7.34-7.43 (m, 6H, H_{Ar}), 7.49 (dd, J = 5.7, 3.3 Hz, 0.4H, H_{Ar}), 7.77-7.80 (m, 0.6H, H_{Ar}), 8.34 ppm (s, 1H, ArC*H*=N).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-(pyridin-4-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***95***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

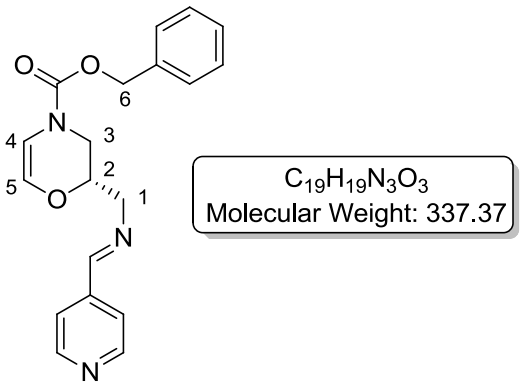
Table 1.21, Entry 2

(a) 1.4 g, 10 mmol; (b) 0.25 g, 1 mmol; (c) 6 ml; (d) 4-pyridinecarboxaldehyde; (e) 0.09 ml, 1 mmol; (f) 0.04 ml, 1 mmol; (g) 0.09 ml, 1 mmol; and (h) 0.16 g, 43%.

IR (neat): 1697, 2331, 2360, 2821, 2939 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.14 (s, 2H, OCH_3), 3.20 (s, 1H, OCH_3 overlapping with signal corresponding to 0.4H, H3), 3.30 (d, ^{2}J = 12.0 Hz, 0.6H, H3), 3.51-3.54 (m, 1H, H3), 3.59-3.71 (m, 1H, H1), 3.80-3.94 (m, 2H, H2+H4), 4.08 (d, ^{2}J = 13.6 Hz, 0.4H, H1), 4.16 (d, ^{2}J = 13.6 Hz, 0.6H, H1), 4.40 (s, 1H, H5), 4.72 (s, 0.6H, H6), 4.90 (s, 0.4H, H6), 5.14-5.37 (m, 2H, H7), 7.16 (d, *J* = 4.6 Hz, 1.2H, H_{Ar}), 7.26 (d, *J* = 4.6 Hz, 0.8H, H_{Ar}), 7.32-7.48 (m, 5H, H_{Ar}) 8.33 (d, *J* = 4.6 Hz, 1.2H, H_{Ar}), 8.60 ppm (d, *J* = 4.6 Hz, 0.8H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.4, 42.9, 49.7, 54.3, 54.6, 60.5, 61.0, 65.9, 66.2, 67.5, 67.7, 74.1, 74.5, 78.5, 78.6, 119.8, 120.0, 121.7, 122.1, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 135.9, 136.7, 147.9, 148.1, 149.9, 150.0, 150.6, 154.9, 155.2 ppm; HRMS *m/z* Calc. for $C_{20}H_{24}N_3O_4$ (M^{+}+H) 370.1761. Found 370.1762.

$[\alpha]_D^{20}$ -82.1 (*c* 0.52 in $CHCl_3$).

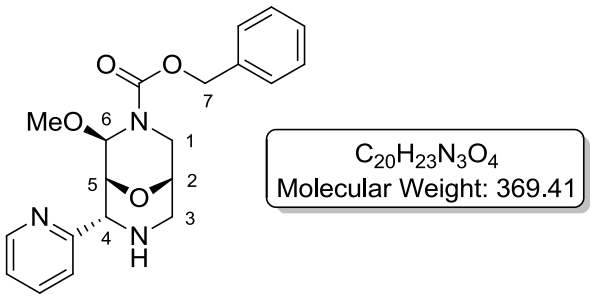
^{1}H NMR analysis of *(S,E)-benzyl 2-(((pyridin-4-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***95a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (dd, ^{2}J = 13.0, *J* = 8.1 Hz, 0.6H, H3), 3.54 (dd, ^{2}J = 12.8, *J* = 8.1 Hz, 0.4H, H3), 3.86-3.88 (m, 2H, H1), 4.03 (d, ^{2}J = 13.0 Hz, 0.4H, H3), 4.15 (d, ^{2}J = 13.1 Hz, 0.6H, H3), 4.26-4.31 (m, 1H, H2), 5.19 (s, 1.2H, H6), 5.21 (s, 0.8H, H6), 5.92 (d, *J*

= 4.9 Hz, 0.6H, H4), 6.04 (d, *J* = 4.9 Hz, 0.4H, H4), 6.26 (d, *J* = 4.9 Hz, 0.6H, H5), 6.38 (d, *J* = 4.9 Hz, 0.4H, H5), 7.35-7.40 (m, 5H, H_{Ar}), 7.59 (d, *J* = 5.6 Hz, 0.8H, H_{Ar}), 7.61 (d, *J* = 5.6 Hz, 1.2H, H_{Ar}), 8.28 (s, 1H, ArC*H*=N), 8.70 ppm (d, *J* = 5.0 Hz, 2H, H_{Ar}).

Preparation of ((1R,2R,5S,8R)-benzyl 2-methoxy-8-(pyridin-2-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***96***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

Table 1.21, Entry 3

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 2-pyridinecarboxaldehyde; (e) 0.08 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.032 g, 10%.

Following *Preparation of Oxabispidines* ***General Procedure B***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) volume of MeOH; (g) quantity of *p*-toluenesulfonic acid; and (h) yield.

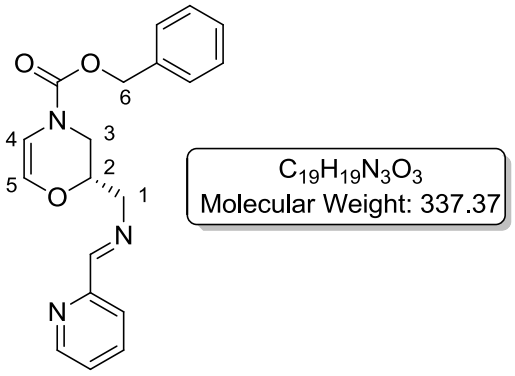
Scheme 1.65

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 2-pyridinecarboxaldehyde; (e) 0.08 ml, 0.8 mmol; (f) 5 ml; (g) 0.07 ml, 0.8 mmol; and (h) 0.16 g, 43%.

IR (neat): 1699, 2330, 2360, 2935 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (br. s, 1H, NH), 3.14 (s, 2H, OCH_3), 3.19 (s, 1H, OCH_3), 3.20 (d, ^{2}J = 12.9 Hz, 0.4H, H3), 3.28 (d, ^{2}J = 12.9 Hz, 0.6H, H3), 3.54-3.58 (m, 1H, H3), 3.60-3.71 (m, 1H, H1), 3.76-3.77 (m, 0.4H, H2), 3.83-3.85 (m, 0.6H, H2), 4.00 (d, ^{2}J = 13.2 Hz, 0.4H, H1), 4.09 (d, ^{2}J = 13.2 Hz, 0.6H, H1), 4.17 (d, *J* = 3.9 Hz, 0.6H, H4), 4.24 (1H, d, *J* = 3.9 Hz, 0.4H, H4), 4.54 (1H, d, *J* = 4.0 Hz, 1H, H5), 4.69 (s, 0.6H, H6), 4.77 (s, 0.4H, H6), 5.12-5.25 (m, 2H, H7), 7.08 (dd, *J* = 6.9, 5.0 Hz, 0.6 H, H_{Ar}), 7.19-7.44 (m, 7H, H_{Ar}), 7.68 (td, *J* = 7.1, ^{4}J = 1.5 Hz, 0.4H, H_{Ar}), 8.40 ppm (d, *J* = 4.2 Hz, 0.6H, H_{Ar}), 8.57 ppm (d, *J* = 4.3 Hz, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.5, 43.1, 49.3, 49.5, 54.5, 54.9, 61.0, 61.6, 65.5, 65.7, 67.4, 67.5, 72.8, 73.4, 79.1, 79.4, 121.0, 121.1, 122.3, 122.6, 127.8, 127.9, 128.1, 128.2, 128.5, 136.1, 136.5, 136.8, 149.3, 155.1, 158.1 ppm; HRMS *m/z* Calc. for $C_{20}H_{24}N_3O_4$ (M^{+}+H) 370.1761. Found 370.1763.

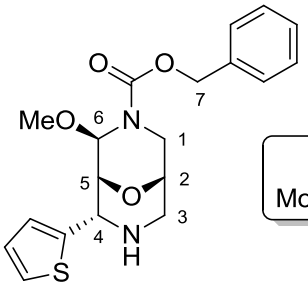
$[\alpha]_D^{21}$ -96.6 (*c* 0.39 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((pyridin-2-ylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***96a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (dd, ^{2}J = 13.0, *J* = 7.8 Hz, 0.6H, H3), 3.52 (dd, ^{2}J = 13.0, *J* = 7.8 Hz, 0.4H, H3), 3.84-3.92 (m, 2H, H1), 4.05 (dd, ^{2}J = 13.2, *J* = 2.0 Hz, 0.4H, H3), 4.19 (dd, ^{2}J = 13.1, *J* = 1.7 Hz, 0.6H, H3), 4.26-4.32 (m, 1H, H2), 5.19 (s, 1.2H, H6), 5.21 (s, 0.8H, H6), 5.93 (d, *J* = 4.8 Hz, 0.6H, H4), 6.06 (d, *J* = 4.8 Hz, 0.4H, H4), 6.25 (d, *J* = 4.8 Hz, 0.6H, H5), 6.37 (d, *J* = 4.8 Hz, 0.4H, H5), 7.26-7.38 (m, 7H, H_{Ar}), 7.75 (t, *J* = 7.7 Hz, 1H, H_{Ar}), 8.41 (s, 1H, ArC*H*=N), 8.66 ppm (d, *J* = 4.3 Hz, 1H, H_{Ar}).

*Preparation of (1R,2R,5S,8S)-benzyl 2-methoxy-8-(thiophen-2-yl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **94***



$C_{19}H_{22}N_2O_4S$
Molecular Weight: 374.45

Following *Preparation of Oxabispidines* ***General Procedure B***, results are presented as follows:

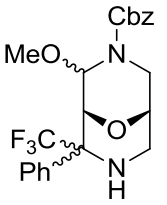
(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) volume of MeOH; (g) quantity of *p*-toluenesulfonic acid; and (h) yield.

Scheme 1.66

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d)) 2-thiophenecarboxaldehyde; (e) 0.09 ml, 1 mmol; (f) 5 ml; (g) 0.07 ml, 0.8 mmol; and (h) 0.1 g, 33%.

*For analysis of oxabispidine **94**, please refer to data on page 172.*

*Attempted Preparation of (1R,5S)-benzyl 2-methoxy-8-phenyl-8-(trifluoromethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **98***



$C_{22}H_{23}F_3N_2O_4$
Molecular Weight: 436.42

Procedure A

Scheme 1.67

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.14 g, 0.8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in DCM (5 ml). To this

was added 2,2,2-trifluoroacetophenone (0.11 ml, 0.8 mmol) and the resulting reaction mixture was stirred at room temperature for 16 hours. After this time, crude ^{1}H NMR analysis showed the desired imine intermediate **97** had not been formed, and as such, the reaction was abandoned.

Procedure B

Scheme 1.68

To a flame-dried flask containing a stirrer bar was added oven-dried 3Å powdered molecular sieves (0.5 g) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in DCM (5 ml). To this was added 2,2,2-trifluoroacetophenone (0.11 ml, 0.8 mmol) and the resulting reaction mixture was stirred at room temperature for 16 hours. After this time, crude ^{1}H NMR analysis showed the desired imine intermediate **97** had not been formed, and as such, the reaction was abandoned.

Procedure C

Scheme 1.69

To a flame-dried flask containing a stirrer bar was added oven-dried 3Å powdered molecular sieves (0.5 g) followed by oxazine (*S*)-**61** (0.2 g, 0.8 mmol) and toluene (6 ml). To this mixture was added 2,2,2-trifluoroacetophenone (0.11 ml, 0.8 mmol) and the reaction mixture was heated to reflux and stirred for 16 hours. After this time, crude ^{1}H and ^{19}F NMR analysis showed that full conversion to the desired imine intermediate **97** had occurred. The molecular sieves were removed by filtration and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in DCM, methanol was added, and the mixture was cooled to -20°C. Trifluoromethanesulfonic acid was added dropwise over 5 min and stirred at -20°C for 10 min before warming to room temperature. The reaction was stirred at RT for 1 hour, after which crude ^{1}H NMR analysis showed mainly imine present. The reaction was stirred for a further 3 hours, however after this time no significant change was observed in the ^{1}H NMR spectrum. Following this, the reaction mixture was allowed to stir at RT overnight, after which time it was quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate,

filtered, and concentrated *in vacuo* to give a crude oil. ^{1}H NMR analysis showed neither the desired product nor imine **97** was present. Therefore, the reaction was abandoned.

General Procedure D

To a flame-dried flask containing a stirrer bar was added oven-dried 3Å powdered molecular sieves followed by oxazine (*S*)-**61** and toluene. To this mixture was added 2,2,2-trifluoroacetophenone and the reaction mixture was heated to reflux and stirred for 16 hours. After this time, crude ^{1}H and ^{19}F NMR analysis showed that full conversion to the desired imine intermediate **97** had occurred. The molecular sieves were removed by filtration and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in the specified solvent, *p*-toluenesulfonic acid and methanol were added and the mixture was heated to reflux. The reaction was stirred at reflux for 16 hours. After this time, the reaction was quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a crude oil. The crude residue was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to return imine **97** and oxazine (*S*)-**61**.

Following ***General Procedure D***, results are presented as follows:

(a) quantity of molecular sieves; (b) quantity of (*S*)-**61**; (c) volume of toluene; (d) quantity of 2,2,2-trifluoroacetophenone; (e) solvent; (f) quantity of solvent; (g) quantity of MeOH; (h) quantity of TsOH; (i) quantity of recovered imine **97**; and (j) quantity of recovered oxazine (*S*)-**61**.

Table 1.22, Entry 1

(a) 0.5 g; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 0.11 ml, 0.8 mmol; (e) methanol; (f) 5 ml; (g) -; (h) 0.07 ml, 0.8 mmol; (i) 0.08g, 25%; and (j) 0.09 g, 45%.

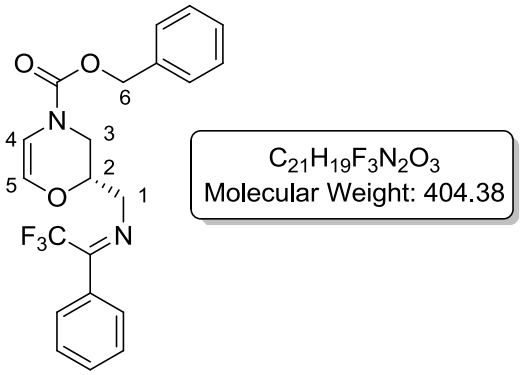
Table 1.22, Entry 2

(a) 0.5 g; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 0.11 ml, 0.8 mmol; (e) acetonitrile; (f) 5 ml; (g) 0.06 ml, 0.16 mmol; (h) 0.07 ml, 0.8 mmol; (i) 0.05 g, 15%; and (j) 0.07 g, 34%.

Table 1.22, Entry 3

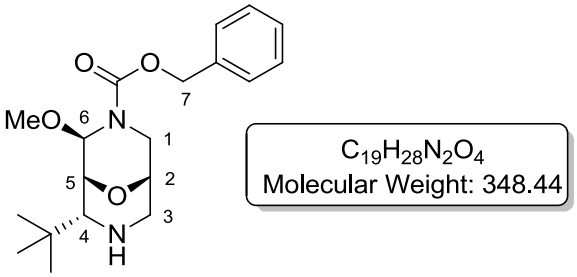
(a) 0.5 g; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 0.11 ml, 0.8 mmol; (e) toluene; (f) 5 ml; (g) 0.06 ml, 0.16 mmol; (h) 0.07 ml, 0.8 mmol; (i) 0.022 g, 7%; and (j) -.

NMR analysis of *(S,Z)-benzyl 2-(((2,2,2-trifluoro-1-phenylethylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***97***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25-3.32 (m, 0.6H, H3), 3.45-3.63 (m, 2.4H, H1 & H3), 4.01 (d, ^{2}J = 13.5 Hz, 0.4H, H3), 4.12 (d, ^{2}J = 13.5 Hz, 0.6H, H3), 4.25-4.28 (m, 1H, H2), 5.21 (s, 2H, H6), 5.89 (d, J = 5.0 Hz, 0.6H, H4), 6.00 (1H, d, J = 5.0 Hz, 0.4H, H4), 6.22 (d, J = 5.0 Hz, 0.6H, H5), 6.34 (d, J = 5.0 Hz, 0.4H, H5), 7.36-7.40 (m, 8H, H_{Ar}), 7.49-7.50 ppm (m, 2H, H_{Ar}); ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.1 ppm.

*Preparation of (1R,2R,5S,8R)-benzyl 8-(tert-butyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **99***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

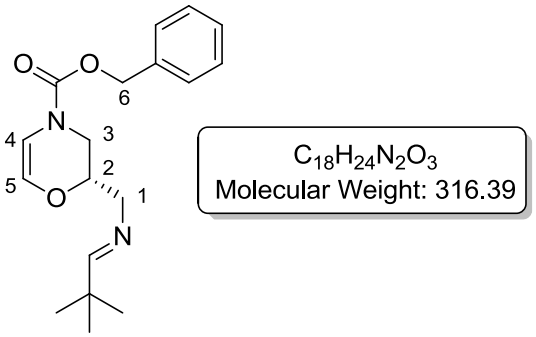
Table 1.23, Entry 1

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) pivalaldehyde; (e) 0.09 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.19 g, 67%.

IR (neat): 1061, 1415, 1700, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 5.4H, $C(CH_3)$), 0.94 (s, 3.6H, $C(CH_3)$), 2.93 (dd, J = 10.3, ^4J = 3.3 Hz, 1H, H4), 3.04 (d, ^2J = 13.1 Hz, 0.4H, H3), 3.10 (d, ^2J = 13.1 Hz, 0.6H, H3), 3.27 (s, 1.8H, OCH_3), 3.31 (ddd, ^2J = 13.1, J = 4.0, ^4J = 2.3 Hz, 1H, H3), 3.34 (s, 1.2H, OCH_3), 3.53-3.71 (m, 3H, H1 & H2 & H5), 3.84 (d, ^2J = 13.3 Hz, 0.6H, H1), 3.91 (d, ^2J = 13.3 Hz, 0.4H, H1), 5.06-5.27 (m, 2.4H, H6 & H7), 5.41 (s, 0.6H, H6), 7.33-7.41 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 32.4, 32.5, 42.8, 43.2, 51.0, 54.9, 55.4, 65.2, 65.6, 65.9, 66.1, 67.5, 67.9, 70.8, 71.1, 80.4, 80.8, 127.8, 128.2, 128.4, 128.5, 135.7, 136.3, 155.2 ppm; HRMS *m/z* Calc. for $C_{19}H_{29}N_2O_4$ (M^++H) 349.2122. Found 349.2122.

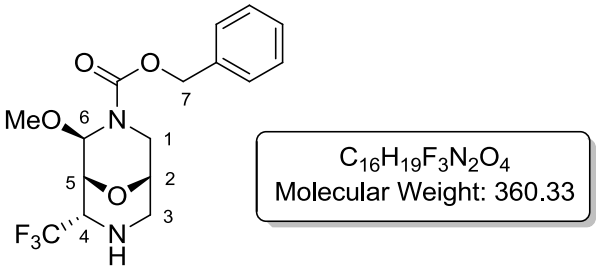
$[\alpha]_D^{20}$ +2.1 (*c* 1.0 in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((2,2-dimethylpropylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***99a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 5.4H, C(CH_3)), 1.06 (s, 3.6H, C(CH_3)), 3.25 (dd, ^2J = 13.1, J = 8.0 Hz, 0.6H, H3), 3.49 (dd, ^2J = 12.6, J = 7.5 Hz, 0.4H, H3), 3.45-3.67 (m, 2H, H1), 3.92-4.07 (m, 1H, H3), 4.05-4.17 (m, 1H, H2), 5.17 (s, 0.8H, H6), 5.19 (s, 1.2H, H6), 5.89 (d, J = 5.0 Hz, 0.6H, H4), 6.01 (d, J = 4.9 Hz, 0.4H, H4), 6.21 (d, J = 5.0 Hz, 0.6H, H5), 6.32 (d, J = 5.0 Hz, 0.4H, H5), 7.26-7.38 (m, 5H, H_{Ar}), 7.53 ppm (s, 1H, ArC*H*=N).

Preparation of (1R,2R,5S,8S)-benzyl 2-methoxy-8-(trifluoromethyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***100***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

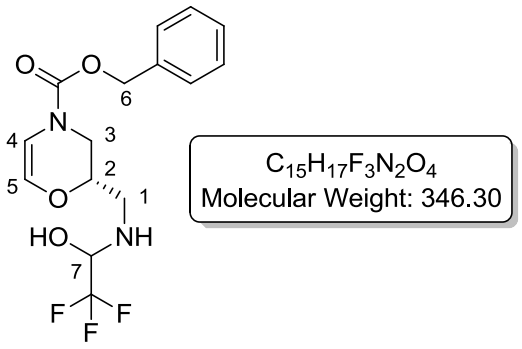
Table 1.23, Entry 2

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) Trifluoroacetaldehyde monohydrate (75%); (e) 0.09 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.19 g, 66%.

IR (neat): 1415, 1701, 2357, 2939 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (br. s, 1H, NH), 3.11 (d, ^{2}J = 13.3 Hz, 0.3H, H3), 3.19 (d, ^{2}J = 13.3 Hz, 0.7H, H3), 3.29 (s, 2H, OCH_3), 3.36 (m, 0.7H, H3), 3.41 (s, 1H, OCH_3 overlapping with signal corresponding to 0.3H, H3), 3.64 (ddd, ^{2}J = 13.5, J = 4.2, ^{4}J = 2.1 Hz, 0.7H, H1), 3.73 (m, 0.6H, H1+H2), 3.81 (t, J = 4.0 Hz, 0.7H, H2), 3.83-3.94 (m, 1.3H, H1+H4), 3.96 (d, J = 3.3 Hz, 0.7H, H4), 4.01-4.04 (m, 1H, H5), 5.13-5.27 (m, 2H, H7), 5.30 (s, 0.7H, H6), 5.43 (s, 0.3H, H6), 7.37-7.39 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100MHz, $CDCl_3$): δ 42.1, 42.8, 49.0, 55.0, 55.6, 58.5 (q, $^{2}J_{CF}$ = 23 Hz), 65.3, 65.8, 67.5, 67.8, 68.0, 79.7, 80.0, 128.0, 128.2, 128.4, 128.6, 155.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.2, -73.3 ppm; HRMS *m/z* Calc. for $C_{16}H_{19}F_3N_2O_4Na$ (M^++Na) 383.1189. Found 383.1191.

$[\alpha]_D^{20}$ -3.7 (*c* 0.22 in $CHCl_3$).

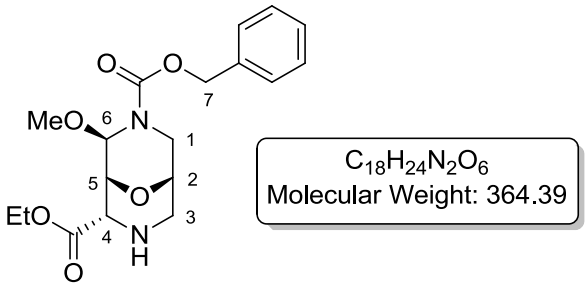
^{1}H NMR analysis of *(2S)-benzyl 2-(((2,2,2-trifluoro-1-hydroxyethyl)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***100a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88-3.45 (m, 3H, H1+H3), 3.71 (d, J = 6.1Hz, 0.4H, H3), 3.85-4.02 (m, 1.6H, H2+H3), 4.13-4.19 (m, 0.4H, H7), 4.51-4.52 (m, 0.6H, H7), 5.10-5.12

(m, 2H, H6), 5.81-5.84 (m, 0.6H, H4), 5.93-5.96 (m, 0.4H, H4), 6.15-6.18 (m, 0.6H, H5), 6.28-6.30 (m, 0.4H, H5), 7.26-7.33 (m, 5H, H_{Ar}) ppm.

Preparation of (1R,2S,5S,8R)-7-benzyl 2-ethyl 8-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-2,7-dicarboxylate ***101***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

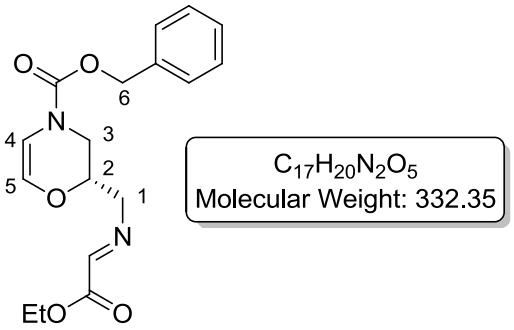
Table 1.23, Entry 3

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) ethyl glyoxylate (50% wt in toluene); (e) 0.16 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.12 g, 40%.

IR (neat): 1705, 1738, 2938, 2980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.1 Hz, 1.6H, C*H*$_3$CH$_2$), 1.30 (t, *J* = 7.1 Hz, 1.4H, C*H*$_3$CH$_2$), 3.04 (d, ^2J = 13.2 Hz, 0.4H, H3), 3.15 (d, ^2J = 13.2 Hz, 0.6H, H3), 3.25 (s, 1.6H, OCH_3), 3.35 (s, 1.4H, OCH_3), 3.58 (ddd, ^2J = 13.3, *J* = 3.9, ^4J = 2.0 Hz, 1H, H3), 3.64-3.73 (m, 2H, H1 & H4), 3.88-4.30 (m, 5H, H1+H2+H5+CH$_3$C*H*$_2$)), 5.00 (s, 0.4H, H6), 5.08-5.25 (m, 2.6H, H6+H7), 7.31-7.38 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100MHz, $CDCl_3$): δ 13.5, 13.6, 41.7, 42.3, 48.1, 54.3, 54.8, 57.7, 57.8, 60.7, 61.0, 64.8, 65.2, 67.1, 67.3, 69.3, 69.7, 79.7, 80.1, 127.4, 127.5, 127.7, 127.9, 128.1, 128.4, 135.5, 154.6, 154.8, 169.0, 169.2 ppm; HRMS *m/z* Calc. for $C_{18}H_{25}N_2O_6$ (M^++H) 365.1707. Found 365.1708.

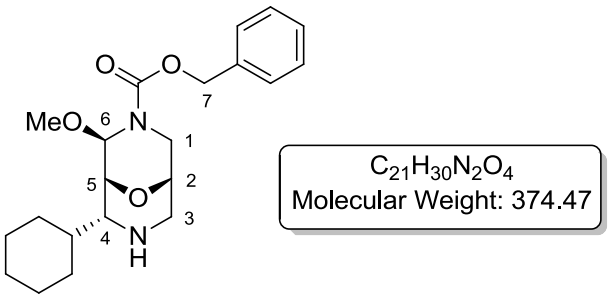
$[\alpha]_D^{21}$ -31.3 (*c* 0.53, in $CHCl_3$).

^{1}H NMR analysis of *(S,E)-benzyl 2-(((2-ethoxy-2-oxoethylidene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***101a***:



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.41 (m, 3H, C*H*$_3$CH$_2$), 3.25 (dd, ^2J = 13.5, J = 7.9 Hz, 1H, H3), 3.44-3.48 (m, 1H, H3), 3.81-3.86 (m, 2H, H1), 4.00-4.12 (m, 1H, H2), 4.29-4.41 (m, 2H, CH$_3$C*H*$_2$), 5.20 (s, 1H, H6), 5.22 (s, 1H, H6), 5.89 (d, J = 4.9 Hz, 0.6H, H4), 6.02 (1H, d, J = 4.9 Hz, 0.4H, H4), 6.25 (d, J = 4.9 Hz, 0.6H, H5), 6.37 (d, J = 4.9 Hz,0.4H, H5), 7.37-7.40 (m, 5H, H$_{Ar}$), 7.73 ppm (s, 1H, EtCO$_2$C*H*=N).

Preparation of (1R,2R,5S,8R)-benzyl 8-cyclohexyl-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***102***



Following *Preparation of Oxabispidines* ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) aldehyde; (e) quantity of aldehyde; (f) quantity of MeOH; (g) quantity of trifluoromethanesulfonic acid; and (h) yield.

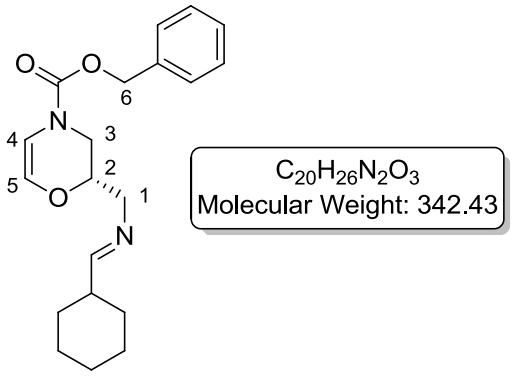
Scheme 1.72

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) cyclohexanecarboxaldehyde; (e) 0.1 ml, 0.8 mmol; (f) 0.03 ml, 0.8 mmol; (g) 0.07 ml, 0.8 mmol; and (h) 0.1 g, 35%.

IR (neat): 1420, 1700, 2852, 2925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84-1.28 (m, 6H, *c*HexCH_2), 1.65- 1.72 (m, 4H, *c*HexCH_2), 1.80-1.88 (m, 1H, *c*HexCH), 2.79 (dd, *J* = 9.7, 3.5 Hz, 1H, H4), 2.95 (d, ^2J = 12.8 Hz, 0.4H, H3), 3.07 (d, ^2J = 12.7 Hz, 0.6H, H3), 3.25 (s, 1.8H, OCH_3), 3.29 (ddd, ^2J = 12.8, *J* = 3.8, ^4J = 2.3 Hz, 1H, H3), 3.34 (s, 1.2H, OCH_3), 3.55 (ddd, ^2J = 13.4, *J* = 4.2, ^4J = 2.2 Hz, 0.4H, H1), 3.59 (t, *J* = 3.8 Hz, 0.4H, H2), 3.61 (ddd, ^2J = 13.4, *J* = 4.2, ^4J = 2.2 Hz, 0.6H, H1), 3.67 (t, *J* = 3.8 Hz, 0.6H, H2), 3.75 (d, *J* = 3.5 Hz, 0.6H, H5), 3.81 (d, *J* = 3.5 Hz, 0.4H, H5), 3.88 (d, ^2J = 13.3 Hz, 0.6H, H1), 3.99 (d, ^2J = 13.3 Hz, 0.4H, H1), 5.09-5.31 (m, 3H, H6 & H7), 7.29-7.37 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100MHz, $CDCl_3$): δ 25.7, 25.8, 25.9, 26.0, 26.4, 26.5, 28.8, 28.9, 30.3, 30.4, 39.3, 39.5, 42.6, 43.3, 50.2, 50.3, 54.8, 55.2, 61.1, 61.3, 65.7, 66.2, 67.6, 67.8, 71.1, 71.3, 79.8, 80.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8, 136.4, 136.7, 155.2, 155.6 ppm; HRMS *m/z* Calc. for $C_{21}H_{31}N_2O_4$ (M^++H) 375.2278. Found 375.2280.

$[\alpha]_D^{20}$ -27.5 (*c* 1.0 in $CHCl_3$).

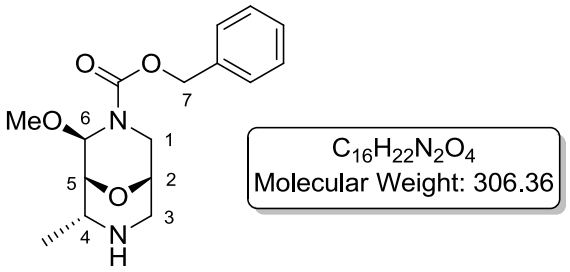
^1H NMR analysis of *(S,E)-benzyl 2-(((cyclohexylmethylene)amino)methyl)-2H-1,4-oxazine-4(3H)-carboxylate* ***102a***:



^1H NMR (400 MHz, $CDCl_3$): δ 1.08-1.40 (m, 5H, *c*HexCH_2), 1.59-1.94 (m, 5H, *c*HexCH_2), 2.10-2.28 (m, 1H, *c*HexCH), 3.24 (dd, ^2J = 13.1, *J* = 8.2 Hz, 0.6H, H3), 3.34 (dd, ^2J = 12.9, *J*

= 5.5 Hz, 0.4H, H3), 3.46 (dd, ^{2}J = 12.1, J = 5.5 Hz, 0.8H, H1), 3.50 (dd, ^{2}J = 12.4, J = 5.5 Hz, 1.2H, H1), 3.95 (dd, ^{2}J = 12.9, J = 1.9 Hz, 0.4H, H3), 4.03 (dd, ^{2}J = 13.1, J = 1.7 Hz, 0.6H, H3), 4.07-4.16 (m, 1H, H2), 5.16 (s, 0.8H, H6), 5.18 (s, 1.2H, H6), 5.92 (d, J = 5.0 Hz, 0.6H, H4), 6.04 (d, J = 4.9 Hz, 0.4H, H4), 6.24 (d, J = 5.0 Hz, 0.6H, H5), 6.36 (d, J = 5.0 Hz, 0.4H, H5), 7.28-7.42 (m, 5H, H_{Ar}), 7.52 ppm (s, 1H, ArC*H*=N).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***103***



Procedure A

Scheme 1.73

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.2 g, 8.1 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.81 mmol) in DCM (8 ml). To this was added acetaldehyde (0.05 ml, 0.81 mmol) and the reaction was stirred at room temperature for 2 hours. The Na_2SO_4 was removed by filtration and the resulting solution was cooled to -20 °C before distilled methanol (0.03 ml, 0.841 mmol) was added. To the reaction mixture was added triflic acid (0.07 ml, 0.81 mmol) in a dropwise fashion over 10 min. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C for 10 min before being allowed to warm to room temperature. The reaction mixture was then allowed to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude yellow oil. The crude product was purified by column chromatography (eluent: 0% to 3% MeOH in DCM) to afford the desired clean product as a colourless oil (0.04 g, 16%).

Procedure B

Scheme 1.74

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.2 g, 8.1 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.81 mmol) in DCM (8 ml). To this was added benzotriazole (0.1 g, 0.81 mmol) and the resulting mixture was stirred at room temperature for 10 min. After this time acetaldehyde (0.05 ml, 0.81 mmol) was added and the reaction was stirred at room temperature for a further 1 hour. The Na_2SO_4 was removed by filtration and the resulting solution was cooled to -20 °C before distilled methanol (0.03 ml, 0.841 mmol) was added. To the reaction mixture was added triflic acid (0.07 ml, 0.81 mmol) in a dropwise fashion over 10 min. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C for 10 min before being allowed to warm to room temperature. The reaction mixture was then allowed to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude colourless oil. The crude product was purified by column chromatography (eluent: 0% to 3% MeOH in DCM) to afford the desired clean product as a colourless oil (0.1 g, 40%).

General Procedure C

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**61** in DCM. To this was added benzotriazole followed by acetaldehyde and the reaction was stirred at room temperature for the specified time. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and distilled methanol was added. To the reaction mixture was added trifluoromethanesulfonic acid in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over

anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then 3% MeOH in DCM) to yield the desired product as a colourless oil along with side-product **105** on an increased eluent gradient (5% MeOH in DCM).
Following ***General Procedure C***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) quantity of (*S*)-**61**; (c) volume of DCM; (d) quantity of benzotriazole; (e) quantity of acetaldehyde; (f) stirring time; (g) quantity of MeOH; (h) quantity of trifluoromethanesulfonic acid; (i) yield; and (j) yield of side-product **105**

Table 1.24, Entry 1

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 0.1 g, 0.8 mmol; (e) 0.04 g, 0.8 mmol; (f) 1 h; (g) 0.03 ml, 0.8 mmol; (h) 0.07 ml, 0.8 mmol; (i) 0.019 g, 8%; and (j) 0.017 g, 5%.

Table 1.24, Entry 2

(a) 1.15 g, 8 mmol; (b) 0.2 g, 0.8 mmol; (c) 5 ml; (d) 0.1 g, 0.8 mmol; (e) 0.04 g, 0.8 mmol; (f) overnight; (g) 0.03 ml, 0.8 mmol; (h) 0.07 ml, 0.8 mmol; (i) 0.06 g, 25%; and (j) 0.032 g, 10%.

Procedure D

Table 1.24, Entry 3

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) DCM (5 ml), benzotriazole (0.1 g, 0.8 mmol) and acetaldehyde (0.04 g, 0.8 mmol). The reaction was stirred at room temperature for 15 min, before the addition of (*S*)-**61**. The reaction was then stirred for 30 min at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and distilled methanol (0.03 ml, 0.8 mmol) was added. To the reaction mixture was added trifluoromethanesulfonic acid (0.07 ml, 0.8 mmol) in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were

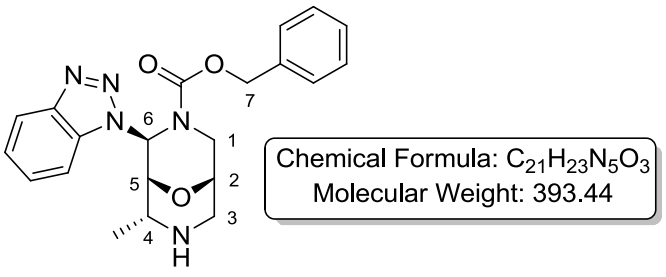
washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then 3% MeOH in DCM) to yield the desired product as a colourless oil (0.06 g, 25%) along with side-product **105** (0.038 g, 12%) on an increased eluent gradient (5% MeOH in DCM).

IR ($CHCl_2$): 1704, 2825, 2938, 3032, 3327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.9 Hz, 1.6H, CH_3), 0.99 (d, *J* = 6.9 Hz, 1.4H, CH_3), 2.95 (d, ^2J = 12.9 Hz, 0.4H, H3), 3.04 (d, ^2J = 12.9 Hz, 0.6H, H3), 3.29 (s, 1.6H, OCH_3), 3.38 (s, 1.4H, OCH_3), 3.30-3.39 (m, 2H, H3+H1), 3.56-3.70 (m, 3H, H4+H2+H5), 3.92 (d, ^2J = 13.3 Hz, 0.4H, H1), 4.01 (d, ^2J = 13.3 Hz, 0.6H, H1), 5.18-5.26 (m, 2.6H, H6+H7), 5.34 (s, 0.4H, H6), 7.33-7.38 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 17.9, 42.5, 43.1, 49.7, 49.8, 51.6, 51.7, 54.6, 54.9, 65.2, 65.7, 67.5, 67.8, 73.2, 73.6, 79.3, 79.5, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 136.1, 136.4, 155.0, 155.4 ppm; HRMS: *m/z* Calc. for $C_{16}H_{23}N_2O_4$ $[M+H]^+$: 307.1652. Found: 307.1656.

$[\alpha]_D^{20}$ -14.1 (*c* 0.25, $CHCl_3$).

*For analysis of **105**, please refer to data on page 193.*

*Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **105***



Procedure A

Table 1.25, Entry 1

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by a solution of oxazine (*S*)-**61** (0.2 g, 0.8 mmol) in DCM (5 ml). To this was

added benzotriazole (0.1 g, 0.8 mmol) followed by acetaldehyde (0.04 g, 0.8 mmol) and the reaction was stirred at room temperature for 1 hour. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.8 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a colourless gum (0.12 g, 39%).

General Procedure B

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by DCM and benzotriazole. Acetaldehyde was added and the reaction stirred at room temperature for 15 min. After this time (*S*)-**1** was added and the resulting mixture stirred for 30 min. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for the specified amount of time before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a colourless gum.

Following ***General Procedure B***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) volume of DCM; (c) quantity of benzotriazole; (d) quantity of acetaldehyde; (e) quantity of (*S*)-**61**; (f) quantity of trifluoromethanesulfonic acid; (g) stirring time; and (h) yield.

Table 1.25, Entry 2

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.04 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; (g) 1 h; and (h) 0.14 g, 42%.

Table 1.25, Entry 3

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.04 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; (g) 16 h; and (h) 0.1 g, 31%.

Table 1.25, Entry 4

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.04 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; (g) 3 h; and (h) 0.18 g, 58%.

Table 1.25, Entry 5

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.04 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; (g) 3 h; and (h) 0.16 g, 52%.

Table 1.26, Entry 1

(a) 11.5 g, 81 mmol; (b) 50 ml; (c) 1 g, 8.1 mmol; (d) 0.4 g, 8.1 mmol; (e) 2 g, 8.1 mmol; (f) 0.7 ml, 8.1 mmol; (g) 3 h; and (h) 0.38 g, 12%.

Table 1.26, Entry 2

(a) 17.2 g, 121 mmol; (b) 90 ml; (c) 1.44 g, 12.1 mmol; (d) 0.53 g, 12.1 mmol; (e) 3 g, 12.1 mmol; (f) 1.08 ml, 12.1 mmol; (g) 3 h; and (h) 1.8 g, 39%.

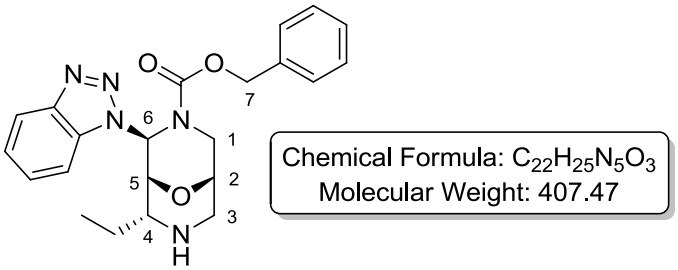
Table 1.26, Entry 3

(a) 17.2 g, 121 mmol; (b) 90 ml; (c) 1.44 g, 12.1 mmol; (d) 0.53 g, 12.1 mmol; (e) 3 g, 12.1 mmol; (f) 1.08 ml, 12.1 mmol; (g) 3 h; and (h) 3.05 g, 64%.

IR (neat): 1712, 2331, 2360, 2850, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.6 Hz, 0.6H, CH_3), 1.31 (d, *J* = 6.9 Hz, 0.9H, CH_3), 1.34 (d, *J* = 6.6 Hz, 0.9H, CH_3), 1.38 (d, *J* = 6.9 Hz, 0.6H, CH_3), 1.80 (br. s, 1H, NH), 3.08-3.21 (m, 1H, H3), 3.42-3.55 (m, 2H, H3+H4), 3.82-4.25 (m, 3.3H, H1+H2+H5), 4.31 (d, *J* = 3.2 Hz, 0.3H, H5), 4.41 (d, *J* = 3.4 Hz, 0.2H, H5), 4.53 (d, *J* = 3.2 Hz, 0.2H, H5), 5.12-5.34 (m, 2H, H7), 6.74 (s, 0.3H, H6), 6.78 (s, 0.2H, H6), 6.87 (s, 0.2H, H6), 6.92 (s, 0.3H, H6), 7.02-7.50 (m, 7.2H, H_{Ar}), 7.71 (d, *J* = 8.6 Hz, 0.3H, H_{Ar}), 7.86-7.90 (m, 1H, H_{Ar}), 8.10 ppm (d, *J* = 8.6 Hz, 0.5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 17.8, 43.5, 43.6, 43.9, 44.0, 49.5, 49.6, 51.8, 51.9, 52.5, 52.6, 61.8, 62.6, 64.5, 64.9, 65.3, 67.4, 67.8, 67.9, 68.9, 69.2, 72.3, 72.7, 73.0, 109.3, 109.6, 117.9, 119.5, 119.6, 123.5, 123.6, 125.8, 125.9, 127.0, 127.1, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 131.7, 132.1, 135.0, 135.2, 135.4, 135.5, 143.7, 143.8, 145.2, 153.9, 154.6, 154.9, 155.4 ppm; HRMS: *m/z* Calc. for $C_{21}H_{23}N_5O_3Na$ $[M+Na]^+$: 416.1693. Found: 416.1690.

$[\alpha]_D^{26}$ -53.6, (*c* 0.75, $CHCl_3$).

Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-ethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***106***



Procedure

Scheme 1.78

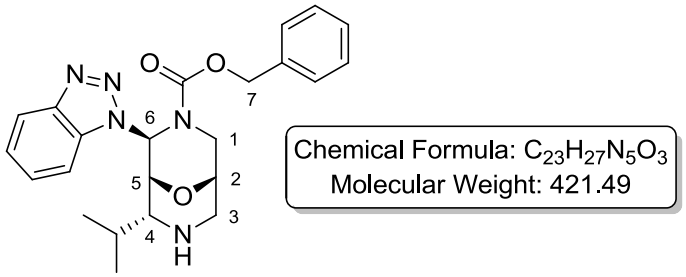
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by DCM (5 ml) and benzotriazole (0.1 g, 0.8 mmol). Propionaldehyde (0.06 ml, 0.8 mmol) was added and the reaction stirred at room temperature for 15 min. After this time (*S*)-**61** (0.2 g, 0.8 mmol) was added and the resulting mixture stirred for 30 min. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.8 mmol) was added in a dropwise fashion over 5

min. After complete addition of the trifluoromethanesulfonic acid, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 3 h before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a colourless gum (0.21 g, 63%).

IR (neat): 1707, 2358, 2939, 3055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00-1.07 (m, 1.7 H, CH_2CH_3), 1.12-1.18 (m, 1.3H, CH_2CH_3), 1.58-1.75 (m, 2H, CH_2CH_3), 3.10-3.15 (m, 2H, H3+H4), 3.41-3.50 (m, 1H, H3), 3.93-4.25 (m, 3.3H, H1+H2+H5), 4.37 (d, *J* = 3.1 Hz, 0.3H, H5), 4.46 (d, *J* = 3.4 Hz, 0.2H, H5), 4.59 (d, *J* = 3.2 Hz, 0.2H, H5), 5.14-5.32 (m, 2H, H7), 6.68 (s, 0.3H, H6), 6.73 (s, 0.2H, H6), 6.82 (s, 0.2H, H6), 6.87 (s, 0.3H, H6), 7.01-7.03 (m, 0.5H, H_{Ar}), 7.11 (t, *J* = 7.1 Hz, 0.5H, H_{Ar}), 7.28-7.48 (m, 6.2H, H_{Ar}), 7.72 (d, *J* = 8.4 Hz, 0.3H, H_{Ar}), 7.85-7.90 (m, 1H, H_{Ar}), 8.11 ppm (d, *J* = 8.7 Hz, 0.5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 10.2, 13.7, 20.6, 25.4, 29.2, 43.5, 43.6, 43.8, 44.0, 49.6, 49.7, 58.0, 58.8, 59.9, 62.1, 62.9, 65.0, 65.3, 65.7, 67.3, 67.6, 67.8, 69.0, 69.3, 71.4, 71.5, 71.8, 72.0, 109.4, 109.6, 117.8, 117.9, 119.5, 119.7, 123.5, 123.6, 125.8, 125.9, 127.0, 127.1, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 131.7, 132.1, 135.2, 135.4, 143.7, 145.2, 154.6, 154.8 ppm; HRMS: *m/z* Calc. for $C_{22}H_{26}N_5O_3$ $[M+H]^+$: 408.2030. Found: 408.2029.

$[\alpha]_D^{26}$ -65.9 (*c* 1.0, $CHCl_3$).

Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-isopropyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***107***



General Procedure A

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by DCM and benzotriazole. *iso*-Butyraldehyde was added and the reaction stirred at room temperature for 15 min. After this time, (*S*)-**61** was added and the resulting mixture stirred for 30 min. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 3 h before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a yellow oil.

Following ***General Procedure A***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) volume of DCM; (c) quantity of benzotriazole; (d) quantity of *iso*-butyraldehyde; (e) quantity of (*S*)-**61**; (f) quantity of trifluoromethanesulfonic acid; and (g) yield.

Table 1.27, Entry 1

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.07 ml, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; and (g) 0.11 g, 32%.

Table 1.27, Entry 2

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.07 ml, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; and (g) 0.04 g, 12%.

Procedure B

Scheme 1.80

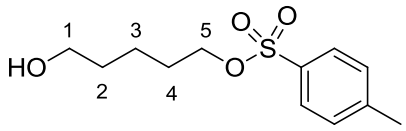
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15 g, 8 mmol) followed by DCM (5 ml) and benzotriazole (0.1 g, 0.8 mmol). *iso*-Butyraldehyde (0.07 ml, 0.8 mmol) was added and the reaction stirred at room temperature for 30 min. After this time (*S*)-**61** (0.2 g, 0.8 mmol) was added and the resulting mixture stirred for 30 min. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid was added in a dropwise fashion over 10 min. After complete addition of the trifluoromethanesulfonic acid, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 16 hours before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a yellow oil (0.18 g, 52%).

IR (neat): 1705, 2390, 2928, 3050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95-1.13 (m, 4H, CH*(CH$_3$)$_2$*), 1.19 (d, *J* = 6.4 Hz, 1H, CH*(CH$_3$)$_2$*), 1.21 (d, *J* = 6.8 Hz, 1H, CH*(CH$_3$)$_2$*), 1.65-1.83 (m, 1H, *CH*(CH_3)$_2$), 2.90 (td, *J* = 6.8, 3.4 Hz, 1H, H4), 3.10-3.20 (m, 1H, H3), 3.38-3.46 (m, 1H, H3), 3.81-3.93 (m, 1H, H2), 4.03 (d, ^2J = 13.1 Hz, 0.4H, H1), 4.07 (d, ^2J = 13.2 Hz, 0.6H, H1), 4.16-4.26 (m, 1H, H1), 4.46 (s, 0.2H, H5), 4.60 (d, *J* = 3.4 Hz, 0.5H, H5), 4.73 (d,

J = 3.2 Hz, 0.3H, H5), 5.11-5.33 (m, 2H, H7), 6.70 (s, 0.3H, H6), 6.77 (s, 0.2H, H6), 6.83 (s, 0.3H, H6), 6.89 (s, 0.2H, H6), 7.00-7.48 (m, 7.5H, H_{Ar}), 7.76 (d, *J* = 8.7 Hz, 0.2H, H_{Ar}), 7.86-7.90 (m, 1H, H_{Ar}), 8.11 ppm (d, *J* = 8.7 Hz, 0.3H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 18.5, 18.6, 19.7, 19.8, 19.9, 29.8, 30.0, 30.1, 43.6, 43.7, 43.9, 49.9, 62.2, 62.7, 62.8, 63.6, 64.7, 65.0, 65.1, 67.2, 67.6, 69.1, 69.4, 70.1, 70.9, 71.1, 109.6, 109.8, 117.9, 118.0, 119.5, 119.6, 123.5, 125.7, 125.8, 127.0, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 135.4, 135.6, 143.7, 143.8, 154.6, 155.3 ppm; HRMS: *m/z* Calc. for $C_{23}H_{28}N_5O_3$ $[M+H]^+$: 422.2187. Found: 422.2186.

$[\alpha]_D^{25}$ -85.1 (*c* 0.95, $CHCl_3$).

Preparation of 5-hydroxypentyl 4-methylbenzenesulfonate ***112***[51]



$C_{12}H_{18}O_4S$
Molecular Weight: 258.33

Procedure A

Scheme 1.82

To a stirred solution of 1,5-pentanediol (2 g, 19.2 mmol) in DCM (200 mL) were added fresh Ag_2O (6.6 g, 28.8 mmol), tosyl chloride (4 g, 21.1 mmol), and KI (0.63 g, 3.8 mmol). The reaction mixture was stirred at room temperature for 4 h and then filtered through a small pad of silica gel and washed with EtOAc. Evaporation of the solvent, followed by column chromatography (eluent: 33% hexane in EtOAc), yielded the desired monotosylate product as a colourless oil (0.4 g, 8%), in addition to the ditosylated by-product (3.1 g, 40%) and unreacted diol starting material (0.89 g, 44%).

Procedure B

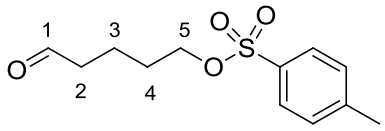
Scheme 1.83

A solution of tosyl chloride (2.3 g, 12 mmol) in DCM (48 ml) was added to a well-stirred mixture of 1,5-pentanediol (5 g, 48 mmol), triethylamine (6.7 ml, 48 mmol) and DMAP (0.29 g, 2.4 mmol) in DCM (190 ml) at 0°C over a 2 h period *via* syringe pump. When the addition

was complete, the reaction was warmed to room temperature and stirred for a further 2 h, before being washed with a saturated aqueous sodium bicarbonate solution followed by saturated aqueous citric acid solution. The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: 33% hexane in EtOAc) to yield the desired mono-tosylated product as a colourless oil (2.5 g, 80%).

IR (neat): 1170, 1185, 1350, 1590, 2930, 3330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 – 1.71 (m, 6H, H2+H3+H4), 2.45 (s, 3H, CH_3Ar), 3.61 (t, *J* = 6.0 Hz, 2H, H1), 4.04 (t, *J* = 6.0 Hz, 2H, H5), 7.35 (d, *J* = 6.0 Hz, 2H, H_{Ar}), 7.79 (d, *J* = 8.0 Hz, 2H, H_{Ar}) ppm; ^{13}C NMR (100 Hz, $CDCl_3$): δ 21.3, 21.6, 28.6, 32.2 62.8, 69.9, 128.3, 130.5, 140.3, 144.5 ppm.

Preparation of 5-oxopentyl 4-methylbenzenesulfonate ***111***[51]



$C_{12}H_{16}O_4S$
Molecular Weight: 256.32

General Procedure

In a flame-dried, three-necked flask, oxalyl chloride was dissolved in DCM (volume 1) and cooled to -78°C under a nitrogen atmosphere. To this cold solution was added a solution of DMSO in DCM (volume 2) over a 25 min period. Following this, a solution of **112** in DCM (volume 3) was added dropwise over a 10 min period and the mixture stirred at -78°C for 40 min. *N*,*N*-Diisopropylethylamine was added and the solution warmed to room temperature before being washed with water and saturated aqueous citric acid solution. The combined organics were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was purified by column chromatography (eluent: DCM) to yield the desired product as a colourless oil.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of oxalyl chloride; (b) DCM volume 1; (c) quantity of DMSO; (d) DCM volume 2; (e) quantity of **112**; (f) DCM volume 3; (g) quantity of *N*,*N*-diisopropylethylamine; and (h) yield.

Table 1.28, Entry 1

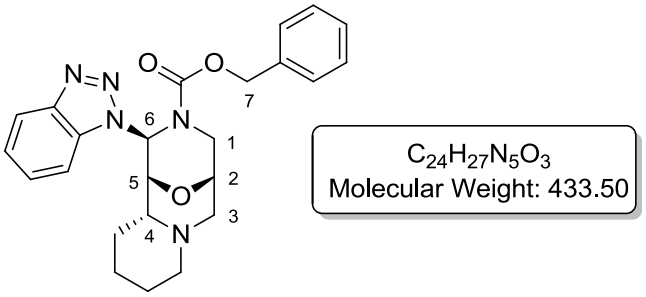
(a) 0.15 ml, 1.7 mmol; (b) 5 ml; (c) 0.24 ml, 3.4 mmol; (d) 2 ml; (e) 0.4 g, 1.6 mmol; (f) 3 ml; (g) 6.8 ml, 38.8 mmol; and (h) 0.15 g, 37%.

Table 1.28, Entry 2

(a) 0.73 ml, 8.5 mmol; (b) 23 ml; (c) 1.21 ml, 17 mmol; (d) 8 ml; (e) 2 g, 7.7 mmol; (f) 16 ml; (g) 1.35 ml, 7.8 mmol; and (h) 1.79 g, 90%.

IR (neat): 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57-1.70 (m, 4H, H3 & H4), 2.42 (t, *J* = 6.0 Hz, 2H, H2), 2.45 (s, 3H, CH_3Ar), 4.04 (t, *J* = 6.0 Hz, 2H, H5), 7.34 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 7.78 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 9.73 ppm (s, 1H, C*H*O); ^{13}C NMR (100 Hz, $CDCl_3$): δ 18.5, 22.0, 28.4, 43.9, 70.2, 128.5, 131.2, 133.2, 145.0, 200.9 ppm.

Preparation of (1R,5S,11aR)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)octahydro-1H-1,5-epoxypyrido[1,2-a][1,5]diazocine-3(2H)-carboxylate ***108***



Procedure A

Scheme 1.85

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.84 g, 5.9 mmol) DCM (5 ml) and benzotriazole (0.07 g, 0.59 mmol) followed by **111** (0.15 g, 0.59 mmol). The reaction was stirred at room temperature for 30 min, before the addition of (*S*)-**61** (0.15 g, 0.59 mmol). The reaction mixture was then stirred for a further 30 min at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid (0.05 ml, 0.59 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 3 hours. After this time, tlc analysis showed a complex reaction profile. Triethylamine (0.08 ml, 0.60 mmol) was added, and the reaction mixture was stirred for a further 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then 3% MeOH in DCM) to yield the desired product as a yellow oil (0.06 g, 25%).

Procedure B

Scheme 1.86

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15g, 8.1 mmol) DCM (6 ml) and benzotriazole (0.1 g, 0.81 mmol) followed by **111** (0.21 g, 0.81 mmol). The reaction was stirred at room temperature for 30 min, before the addition of (*S*)-**61** (0.2 g, 0.81 mmol). The reaction mixture was then stirred for a further 16 hours at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.81 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 3 hours. After this time, triethylamine (0.12 ml, 0.89 mmol) was added, and the reaction mixture was stirred for a further 1 hour before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then 3% MeOH in DCM) to yield the desired product as a yellow oil (0.06 g, 17%).

Procedure C *– GCMS monitoring process*

Scheme 1.87

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (0.84 g, 5.9 mmol) DCM (5 ml) and benzotriazole (0.07 g, 0.59 mmol) followed by **111** (0.15 g, 0.59 mmol). The reaction was stirred at room temperature for 15 min, before a sample was taken for GCMS analysis. The reaction was stirred for a further 2 hours 45 min before a second GCMS sample was taken, however no change was observed. Oxazine (*S*)-**61** (0.15 g, 0.59 mmol) was added and the reaction was stirred for 1 hour at room temperature. After this time, a further aliquot of the reaction mixture was taken for GCMS analysis. The reaction was stirred for a further 2 hours before another GCMS sample was taken. The reaction was then allowed to stir at room temperature overnight and, again, a GCMS sample was taken. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and

trifluoromethanesulfonic acid (0.05 ml, 0.59 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before an aliquot of the reaction was taken for GCMS analysis. The reaction was stirred for a further 3 hours and an additional GCMS sample was taken before the reaction was left to stir overnight. A GCMS sample was taken and the reaction left to stir overnight again before a final GCMS sample was taken. The reaction was then quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated, and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude residue was purified by column chromatography (eluent: DCM then 3% MeOH in DCM) however no starting materials or the desired product was recovered.

Procedure D

Scheme 1.88

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (1.15g, 8.1 mmol) DCM (6 ml) and benzotriazole (0.1 g, 0.81 mmol) followed by **111** (0.21 g, 0.81 mmol). The reaction was stirred at room temperature for 15 min, before the addition of (*S*)-**61** (0.2 g, 0.81 mmol). The reaction mixture was then stirred for a further 3 hours at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid (0.07 ml, 0.81 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 16 hours before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product

was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) however none of the desired product was recovered.

General Procedure E

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4, DCM, and benzotriazole followed by aldehyde **111**. The reaction was stirred at room temperature for 15 min, before the addition of (*S*)-**61**. The reaction mixture was then stirred for a further 3 hours at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 5 hours before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: 0% to 3% MeOH in DCM) to yield the desired product as a yellow oil.

Following ***General Procedure E***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) volume of DCM; (c) quantity of benzotriazole; (d) quantity of aldehyde **111**; (e) quantity of (*S*)-**61**; (f) quantity of trifluoromethanesulfonic acid; and (g) yield.

Table 1.29, Entry 1

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.21 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; and (g) 0.12 g, 33%.

Table 1.29, Entry 2

(a) 1.15 g, 8 mmol; (b) 5 ml; (c) 0.1 g, 0.8 mmol; (d) 0.21 g, 0.8 mmol; (e) 0.2 g, 0.8 mmol; (f) 0.07 ml, 0.8 mmol; and (g) 0.16 g, 45%.

General Procedure F

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4, DCM, and benzotriazole followed by **111**. The reaction was stirred at room temperature for 15 min, before the addition of (*S*)-**61**. The reaction mixture was then stirred for a further 3 hours at room temperature. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20 °C and trifluoromethanesulfonic acid was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was left to stir at room temperature for 5 hours. After this time, the specified base was added and stirred for the specified amount of time before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: 0% to 3% MeOH in DCM) to yield the desired product as a yellow oil.

Following ***General Procedure F***, results are presented as follows:

(a) quantity of Na_2SO_4; (b) volume of DCM; (c) quantity of benzotriazole; (d) quantity of aldehyde **111**; (e) quantity of (*S*)-**61**; (f) quantity of trifluoromethanesulfonic acid; (g) base; (h) quantity of base; (i) time; and (j) yield.

Table 1.30, Entry 1

(a) 1.43 g, 10 mmol; (b) 6 ml; (c) 0.12 g, 1 mmol; (d) 0.26 g, 1 mmol; (e) 0.25 g, 1 mmol; (f) 0.09 ml, 0.8 mmol; (g) triethylamine; (h) 0.28 ml, 2 mmol; (i) 1 h; (j) 0.21 g, 48%.

Table 1.30, Entry 2

(a) 1.43 g, 10 mmol; (b) 6 ml; (c) 0.12 g, 1 mmol; (d) 0.26 g, 1 mmol; (e) 0.25 g, 1 mmol; (f) 0.09 ml, 0.8 mmol; (g) K_2CO_3; (h) 0.28 ml, 2 mmol; (i) 1 h; (j) 0.23 g, 55%.

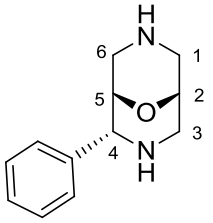
Table 1.30, Entry 3

(a) 1.43 g, 10 mmol; (b) 6 ml; (c) 0.12 g, 1 mmol; (d) 0.26 g, 1 mmol; (e) 0.25 g, 1 mmol; (f) 0.09 ml, 0.8 mmol; (g) K_2CO_3; (h) 0.28 ml, 2 mmol; (i) 16 h; (j) 0.22 g, 52%.

IR (neat): 1706, 2381, 2928, 3048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34-1.66 (m, 8H, *c*Hex *C*H_2), 2.45-2.93 (m, 3.2H, H1+H3+H4), 3.66-3.71 (m, 0.3H, H1), 3.93-3.94 (m, 0.3H, H2), 3.97 (t, *J* = 3.7 Hz, 0.2H, H2), 4.05-4.22 (m, 2H, H1+H2), 4.35 (d, *J* = 3.2 Hz, 0.2H, H5), 4.37 (d, *J* = 2.9 Hz, 0.3H, H5), 4.48 (d, *J* = 3.3 Hz, 0.2H, H5), 4.55 (d, *J* = 3.0 Hz, 0.3H, H5), 5.10-5.27 (m, 2H, H7), 6.83 (s, 0.3H, H6), 6.87 (s, 0.2H, H6), 6.99 (s, 0.3H, H6), 7.02 (s, 0.2H, H6), 7.13-7.22 (m, 1.5H, H_{Ar}), 7.34-7.51 (m, 5.7H, H_{Ar}), 7.74 (d, *J* = 8.3 Hz, 0.2H, H_{Ar}), 7.86-7.90 (m, 1.3H, H_{Ar}), 8.10-8.12 ppm (m, 0.3H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 24.0, 24.7, 17.4, 27.6, 43.3, 43.6, 43.7, 56.1, 56.2, 56.3, 58.1, 58.4, 58.5, 63.1, 63.2, 63.4, 63.5, 63.9, 66.6, 66.7, 66.9, 67.0, 67.1, 67.3, 67.7, 69.9, 70.0, 71.9, 73.2, 109.6, 109.9, 117.8, 117.9, 119.5, 119.6, 123.5, 123.6, 125.7, 125.8, 126.9, 127.1, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 135.6, 143.7, 143.8, 154.3, 155.1 ppm; HRMS: *m/z* Calc. for $C_{24}H_{28}N_5O_3$ $[M+H]^+$: 434.2187. Found: 434.2187.

$[\alpha]_D^{25}$ -72.3 (*c* 2.1, $CHCl_3$).

Preparation of (1S,2R,5R)-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***115***



$C_{12}H_{16}N_2O$
Molecular Weight: 204.27

General Procedure

A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium (10% on carbon) followed by a solution of **70** in methanol. The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was

left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 10% MeOH in DCM), to yield the desired product as a yellow oil.

Following ***General Procedure***, results are presented as follows:

(a) quantity of Pd/C; (b) quantity of **70**; (c) volume of MeOH; and (d) yield.

Table 1.31, Entry 1

(a) 0.06 g, 0.054 mmol; (b) 0.2 g, 0.54 mmol; (c) 10 ml; and (d) 0.08 g, 75%.

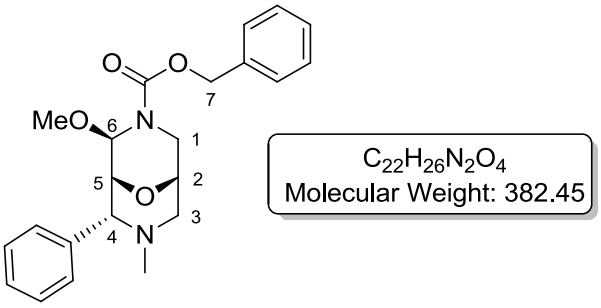
Table 1.31, Entry 2

(a) 2.8 g, 2.7 mmol; (b) 10 g, 27 mmol; (c) 500 ml; and (d) 5.7 g, 89%.

IR (neat): 2689, 2882, 3027, 3087, 3301 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (br. s, 2H, NH), 2.80 (d, ^{2}J = 13.8 Hz, 1H, H6), 2.99-3.02 (m, 1H, H6), 3.12 (d, ^{2}J = 13.3 Hz, 1H, H1), 3.32 (d, ^{2}J = 11.8 Hz, 1H, H3), 3.36-3.39 (m, 1H, H1), 3.57-3.66 (m, 3H, H2+H3+H5), 4.57 (s, 1H, H4), 7.26-7.39 ppm (m, 5H, H_{Ar}): ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 50.5, 51.1, 63.9, 67.0, 72.3, 126.5, 127.4, 128.7, 141.0 ppm; HRMS: *m/z* Calc. for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335. Found: 205.1335.

$[\alpha]_D^{26}$ -81.6 (*c* 0.18, MeOH).

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-7-methyl-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***119***



Procedure A

Scheme 1.93

To a solution of **70** (1 g, 2.7 mmol) in DCM (30 ml) was added methyl iodide (0.25 ml, 4.1 mmol) and potassium carbonate (0.56 g, 4.1 mmol). The reaction was stirred at room temperature and the progress followed by tlc. Complete consumption of the starting material was observed after 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0% to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (0.80 g, 77%).

Procedure B

Scheme 1.94

To a solution of **70** (0.8 g, 2.2 mmol) in DCM (20 ml) was added dimethyl sulfate (0.3 ml, 3.3 mmol), and potassium carbonate (0.45 g, 3.3 mmol). The reaction was stirred at room temperature and the progress followed by tlc. Complete consumption of the starting material was observed after 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0% to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (0.6 g, 73%).

Procedure C

Scheme 1.95

To a solution of **70** (0.4 g, 1.1 mmol) in DCM (10 ml) was added dimethyl sulfate (0.15 ml, 1.7 mmol), and potassium carbonate (0.27 g, 1.7 mmol). The reaction was heated to reflux and the progress followed by tlc. Complete consumption of the starting material was observed after 4 hours, after which time the reaction mixture was allowed to cool and poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0% to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (0.25 g, 56%).

Procedure D

Scheme 1.96

To a solution of **70** (0.4 g, 1.1 mmol) in acetonitrile (10 ml) was added dimethyl sulfate (0.15 ml, 1.7 mmol), and potassium carbonate (0.27 g, 1.7 mmol). The reaction was heated to reflux and the progress followed by tlc. Complete consumption of the starting material was observed after 1 hour, after which time the reaction mixture was allowed to cool and poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0% to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (0.2 g, 44%).

Procedure E

Scheme 1.97

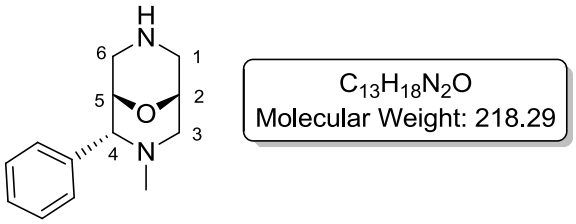
To a solution of **70** (0.4 g, 1.1 mmol) in THF (10 ml) was added dimethyl sulfate (0.15 ml, 1.7 mmol). The reaction was cooled to 0°C and NaH (0.04 g, 1.7 mmol) was added. The reaction was stirred at 0°C for 10 min before warming to RT and stirring for 16 h. After which time the reaction mixture was allowed to cool and poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined

organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0% to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (0.26 g, 57%).

IR (neat): 1706, 2889, 2930, 3030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 1.4H, NCH_3), 2.01(s, 1.6 H, NCH_3), 2.71-2.74 (m, 1H, H3), 2.99 (d, ^{2}J = 11.8 Hz, 0.4H, H3), 3.07 (d, ^{2}J = 11.8 Hz, 0.6H, H3), 3.12 (s, 1.6H, OCH_3), 3.20 (s, 1.4H, OCH_3), 3.44-3.47 (m, 1H, H1), 3.57-3.62 (m 0.6 H, H2), 3.64-3.69 (m, 0.4 H, H2), 3.78 (d, *J* = 3.7 Hz, 0.6H, H5), 3.83 (d, *J* = 3.6 Hz, 0.4 H, H5), 3.90-3.91 (m, 0.4H, H4), 4.00-4.03 (m, 0.6H, H4), 4.04 (d, ^{2}J = 13.6 Hz, 0.4 H, H1), 4.09 (d, ^{2}J = 13.3 Hz, 0.6H, H1), 4.94 (s, 0.6 H, H6), 5.13 (s, 0.4 H, H6), 5.16-5.47 (m, 2H, H7), 7.08-7.36 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.3, 42.8, 44.7, 54.5, 54.7, 59.3, 59.5, 67.0, 67.3, 67.5, 67.6, 70.8, 71.3, 75.1, 75.5, 78.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 136.1, 137.0, 137.5, 137.8, 155.0, 157.1 ppm; HRMS: m/z Calc. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965. Found: 383.1969.

$[\alpha]_D^{20}$ -62.6 (*c* 1.0, $CHCl_3$).

Preparation of (1S,2R,5R)-3-methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***116***



Procedure

Scheme 1.98

A 3-necked flask was flame-dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium (0.54 g, 10% on carbon) followed by a solution of **119** (1.96 g, 5.1 mmol) in methanol (100 ml). The vessel was then evacuated and back filled

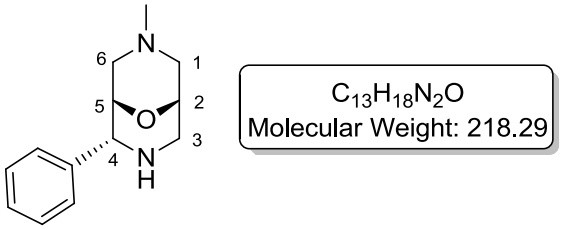
(x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 10% MeOH in DCM), to yield the desired product as a white solid (1 g, 90%).

Melting point: 69-71°C.

IR (neat): 2792, 2924, 3060, 3312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, NCH_3), 2.80 (ddd, ^2J = 11.8, J = 3.9, ^4J = 2.4 Hz, 1H, H6), 2.96 (m, 2H, H1), 3.15 (d, ^2J = 11.8 Hz, 1H, H6), 3.18 (d, ^2J = 13.7 Hz, 1H, H3), 3.39 (ddd, ^2J = 13.7, J = 3.6, ^4J = 2.5 Hz, 1H, H3), 3.57-3.58 (m, 1H, H2), 3.68 (d, J = 3.6 Hz, 1H, H4), 3.86 (t, J = 3.8 Hz, 1H, H5), 7.30-7.40 ppm (m, 5H, Ar): ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 45.0, 49.4, 59.8, 67.6, 72.0, 72.5, 127.6, 128.0, 128.8, 138.7 ppm; HRMS: *m/z* Calc. for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1492.

$[\alpha]_D^{23}$ -150.4 (*c* 1.0, $CHCl_3$).

Preparation of (1S,2R,5S)-7-methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***117***



Procedure A

Table 1.32, Entry 1

To a 3-necked flask, fitted with a low temperature thermometer, that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of N_2, was added $LiAlH_4$ powder (0.06 g, 1.6 mmol) followed by dry diethyl ether (5 ml). The resulting suspension was cooled to 0°C and then a solution of **70** (0.2 g, 0.54 mmol) in diethyl ether (4 ml) was added slowly. After complete addition of the substrate, the resulting mixture was stirred at

0°C for 10 minutes, then allowed to warm to room temperature and stirred for 3 hours. Tlc analysis after this time showed no starting material remained. The reaction was cooled to 0°C, and to the mixture was added water (0.06 ml; 1 ml per 1 g $LiAlH_4$) and the mixture was allowed to stir for 10 min. After this time 15% NaOH (0.06 ml; 1 ml per 1 g $LiAlH_4$) followed by water (0.18 ml; 3 ml per 1 g $LiAlH_4$) was added and the resulting white suspension was allowed to stir for 15 min. The suspension was filtered through a plug of celite, which was then washed with ether, and the filtrate concentrated *in vacuo*. Purification by column chromatography (eluent: 0% to 10% MeOH in DCM) resulted in the desired product being recovered as a yellow oil (0.06 g, 43%).

General Procedure B

To a 3-necked flask, fitted with a low temperature thermometer, that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of N_2, was added $LiAlH_4$ powder followed by dry diethyl ether. The resulting suspension was cooled to 0°C and then a solution of **70** in diethyl ether was added slowly. After complete addition of the substrate, the resulting mixture was stirred at 0°C for 10 minutes, then allowed to warm to room temperature and stirred for 3 hours. Tlc analysis after this time showed no starting material remained. The reaction was cooled to 0°C, and to the mixture was added water (1 ml per 1 g $LiAlH_4$) and the mixture was allowed to stir for 10 min. After this time, 15% NaOH (1 ml per $LiAlH_4$) followed by water (3 ml per 1 g $LiAlH_4$) was added and the resulting white granular suspension was allowed to stir for 15 min. An excess of solid sodium bicarbonate was then added and the mixture was stirred for a further 20 min. The suspension was filtered through a plug of Celite, which was then washed with diethyl ether, and the filtrate concentrated *in vacuo*. Purification by column chromatography (eluent: 0% to 10% MeOH in DCM) resulted in the desired product being recovered as a white solid.

Following ***General Procedure B***, results are presented as follows:

(a) quantity of $LiAlH_4$; (b) volume of Et_2O; (c) quantity of **70**; (d) volume of Et_2O; and (e) yield.

Table 1.32, Entry 2

(a) 0.06 g, 1.6 mmol; (b) 5 ml; (c) 0.2 g, 0.54 mmol; (d) 4 ml; and (e) 0.07 g, 61%.

Table 1.32, **Entry 3**

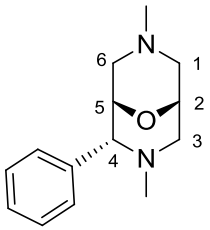
(a) 0.77 g, 20.4 mmol; (b) 68 ml; (c) 2.5 g, 6.8 mmol; (d) 50 ml; and (e) 2.7 g, 62%.

Melting point: 71-73°C.

IR ($CHCl_2$): 2789, 2934, 3057, 3060, 3294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3H, NCH_3), 2.25 (ddd, ^2J = 11.7, J = 3.7, ^4J = 1.5 Hz, 1H, H6), 2.58 (ddd, ^2J = 11.3, J = 2.9, ^4J = 2.9 Hz, 1H, H1), 2.66 (d, ^2J = 11.7 Hz, 1H, H6), 2.95 (d, ^2J = 11.3 Hz, 1H, H1), 3.25 (d, ^2J = 13.8 Hz, 1H, H3), 3.48 (dt, ^2J = 13.8, J = 2.9 Hz, 1H, H3), 3.73 (t, J = 3.7 Hz, 1H, H2), 3.86 (t, J = 3.4 Hz, 1H, H5), 4.44 (d, J = 2.8 Hz, 1H, H4), 7.26-7.37 ppm (m, 5H, H_{Ar}): ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7, 50.8, 54.5, 59.5, 62.4, 67.0, 72.1, 126.9, 126.1, 128.5, 140.4 ppm; HRMS: *m/z* Calc. for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1492.

$[\alpha]_D^{20}$ +54.5 (*c* 1.0, MeOH).

Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***118***



$C_{14}H_{20}N_2O$
Molecular Weight: 232.32

Procedure

Scheme 1.100

To a 3-necked flask, fitted with a low temperature thermometer, that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of N_2, was added $LiAlH_4$ powder (0.21 g, 6.3 mmol) followed by dry diethyl ether (22 ml). The resulting suspension was cooled to 0°C and then a solution of **119** (0.79 g, 2.1 mmol) in diethyl ether (16 ml) was added slowly. After complete addition of the substrate, the resulting mixture was stirred at 0°C for 10 minutes, then allowed to warm to room temperature and stirred for 16 h. Tlc analysis after this time showed that no starting material remained. To the reaction mixture was added water (0.21 ml; 1 ml per 1 g $LiAlH_4$) and the mixture was allowed to stir for 10 min. After this time 15% NaOH (0.21 ml; 1 ml per 1 g $LiAlH_4$) followed by water (0.63 ml;

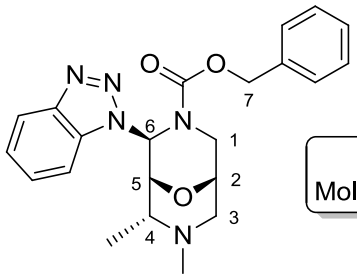
3 ml per 1 g $LiAlH_4$) was added and the resulting white suspension was allowed to stir for 15 min. An excess of solid sodium bicarbonate was then added and the mixture was stirred for a further 20 min. The suspension was filtered through a plug of celite, which was then washed with ether, and the filtrate concentrated *in vacuo*. Purification by column chromatography (eluent: 0% to 70% Et_2O in petroleum ether) resulted in the desired product being recovered as a white solid (0.08 g, 87%).

Melting point: 63-65°C.

IR (neat): 1088, 1265, 1450, 2785, 2936 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.04 (dd, ^2J = 11.9, J = 3.8 Hz, 1H, H6), 2.10 (s, 3H, NCH_3), 2.22 (s, 3H, NCH_3), 2.47 (ddd, ^2J = 11.5, J = 3.7, ^4J = 1.1 Hz, 1H, H1), 2.70-2.75 (m, 2H, H3+H6), 3.05 (d, ^2J = 11.5 Hz, 1H, H1), 3.15 (d, ^2J = 11.8 Hz, 1H, H3), 3.47 (d, J = 3.8 Hz, 1H, H4), 3.69 (t, J = 3.7 Hz, 1H, H2), 3.97 (t, J = 3.7 Hz, 1H, H5), 7.25-7.37 ppm (m, 5H, H_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$): 45.8, 47.3, 53.8, 58.4, 58.9, 68.8, 72.3, 73.1, 127.4, 128.5, 139.8 ppm; HRMS: *m/z* Calc. for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648. Found: 233.1649.

$[\alpha]_D^{20}$ -8.74 (*c* 1.0, $CHCl_3$).

Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-7,8-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***123***



$C_{22}H_{25}N_5O_3$
Molecular Weight: 407.47

Procedure

Scheme 1.101

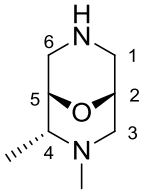
To a solution of **105** (0.8 g, 2 mmol) in DCM (20 ml) was added methyl iodide (0.19 ml, 3 mmol) and potassium carbonate (0.41 g, 3 mmol). The reaction was stirred at room temperature and the progress followed by tlc. Complete consumption of the starting material

was observed after 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a pale yellow oil (0.82 g, quant).

IR (neat): 1712, 2330, 2854, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.6 Hz, 0.6H, CH_3), 1.28 (d, *J* = 6.6 Hz, 1H, CH_3), 1.32 (d, *J* = 6.6 Hz, 0.7H, CH_3), 1.37 (d, *J* = 6.6 Hz, 0.7H, CH_3), 2.13 (s, 0.8H, NCH_3), 2.14 (s, 0.7H, NCH_3), 2.17 (s, 0.8H, NCH_3), 2.18 (s, 0.7H, NCH_3), 2.56-2.72 (m, 2H, H3), 2.83-2.95 (d, 1H, H4), 3.68-3.73 (m, 0.5H, H1), 3.94-4.17 (m, 2.3H, H1+H2), 4.21 (d, ^{2}J = 13.5 Hz, 0.2H, H1), 4.31-4.34 (m, 0.5H, H5), 4.45 (d, *J* = 3.3 Hz, 0.3H, H5), 4.50 (d, *J* = 3.3 Hz, 0.2H, H5), 5.12-5.24 (m, 2H, H7), 6.74 (s, 0.3H, H6), 6.77 (s, 0.2H, H6), 6.91 (s, 0.2H, H6), 6.92 (s, 0.3H, H6), 7.08-7.51 (m, 7.3H, H_{Ar}), 7.74 (d, *J* = 8.2 Hz, 0.2H, H_{Ar}), 7.86-7.92 (m, 1H, H_{Ar}), 8.09-8.11 ppm (m, 0.5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 15.8, 42.4, 42.5, 42.6, 42.7, 43.3, 43.6, 43.7, 53.0, 58.7, 58.8, 59.1, 59.2, 59.5, 59.6, 59.8, 59.9, 62.2, 63.0, 66.6, 66.7, 66.9, 67.0, 67.2, 67.3, 67.6, 69.0, 69.1, 72.9, 73.2, 74.4, 109.6, 109.9, 117.8, 117.9, 119.4, 119.6, 123.5, 123.6, 125.7, 125.8, 128.9, 127.0, 126.9, 127.0, 127.1, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 132.2, 135.6, 135.8, 135.9, 143.7, 143.8, 145.3, 153.9, 154.3, 154.9, 155.1 ppm; HRMS: *m/z* Calc. for $C_{22}H_{26}N_5O_3$ $[M+H]^+$: 408.2030. Found: 408.2029.

$[\alpha]_D^{27}$ -73.5 (*c* 0.35, $CHCl_3$).

Preparation of (1S,2R,5R)-2,3-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***120***



$C_8H_{16}N_2O$
Molecular Weight: 156.23

Procedure

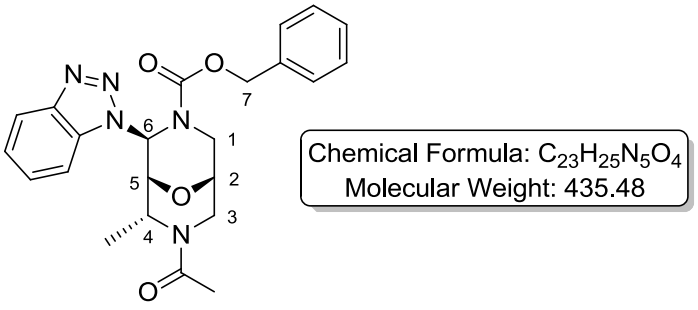
Scheme 1.101

A 3-necked flask was flame-dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium (0.22 g, 10% on carbon) followed by a solution of **123** (0.86 g, 2.1 mmol) in methanol (40 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 10% MeOH in EtOAc), to yield the desired product as a pale yellow solid (0.31 g, 96%).

IR (neat): 2358, 2787, 2908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J = 6.4 Hz, 3H, CH_3), 2.16 (s, 3H, NCH_3), 2.56-2.61 (m, 1H, H4), 2.70 (ddd, ^2J = 11.5, J = 3.7, ^4J = 2.5 Hz, 1H, H3), 2.86 (d, ^2J = 11.5 Hz, 1H, H3), 2.99 (d, ^2J = 13.8 Hz, 1H, H1), 3.12- 3.13 (m, 2H, H6), 3.28- 3.33 (m, 3H, NH+H1+H5), 3.67 ppm (t, J = 3.7 Hz, 1H, H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 43.5, 45.3, 50.1, 60.2, 61.6, 68.1, 72.1 ppm; HRMS: *m/z* Calc. for $C_8H_{17}N_2O_1$ $[M+H]^+$: 157.1335. Found: 157.1334.

$[\alpha]_D^{23}$ -41.2 (*c* 0.55 in $CHCl_3$).

Preparation of (1R,5S,8R)-benzyl 7-acetyl-2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***124***



Procedure

Scheme 1.102

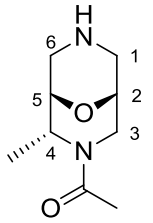
To a stirred solution of **105** (1.5 g, 3.8 mmol) in DCM (40 ml) was added triethylamine (1.06 ml, 7.6 mmol), DMAP (0.1 g, 0.1 mmol), and acetic anhydride (0.72 ml, 7.6 mmol). The reaction mixture was stirred at room temperature for 16 hours, before being partitioned between DCM and water. The organic layer was washed with a saturated aqueous sodium bicarbonate solution, water and brine then dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: DCM) to provide the desired product as a yellow oil (3.2 g, 96%).

IR (neat): 1708, 1643, 1708, 2331, 2341, 2360, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.6 Hz, 0.6H, CH_3), 1.63 (d, *J* = 6.6 Hz, 0.9H, CH_3), 1.66 (d, *J* = 6.4 Hz, 0.9H, CH_3), 1.72 (d, *J* = 6.4 Hz, 0.6H, CH_3), 2.10 (s, 0.6H, $CH_3C(O)N$), 2.11 (s, 0.9H, $CH_3C(O)N$), 2.13 (s, 0.6H, $CH_3C(O)N$), 2.16 (s, 0.9H, $CH_3C(O)N$), 3.41-3.51 (m, 0.8H, H3), 3.68 (d, ^2J = 13.2 Hz, 0.2H, H3), 3.84 (d, ^2J = 12.7 Hz, 0.2H, H3), 3.89 (d, ^2J = 13.2 Hz, 0.3H, H3), 3.93-4.28 (m, 4H, H1+H2+H3+H4), 4.46-4.64 (m, 1H, H2+H5), 4.78 (d, *J* = 7.0 Hz, 0.3H, H5), 4.95 (d, *J* = 7.9 Hz, 0.2H, H5), 5.10-5.33 (m, 2H, H7), 6.79 (s, 0.3H, H6), 6.85 (s, 0.2H, H6), 6.88 (s, 0.2H, H6), 6.93 (s, 0.3H, H6), 7.07-7.43 (m, 7H, H_{Ar}), 7.53 (t, *J* = 7.6 Hz, 0.3H, H_{Ar}), 7.75 (d, *J* = 8.4 Hz, 0.2H, H_{Ar}), 7.86-7.90 (m, 1H, H_{Ar}), 8.10 ppm (d, *J* = 8.4 Hz, 0.5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7, 14.9, 15.3, 15.8, 20.1, 21.7, 21.9, 22.1, 22.5, 42.9, 43.3, 43.7, 43.9. 50.7. 51.4. 51.8. 53.5. 61.5. 62.0. 64.0. 64.4. 64.6. 65.0. 67.8. 68.0. 68.1. 68.4. 69.3. 69.6. 71.3. 71.9, 109.0, 109.5, 117.8, 119.5, 119.6, 123.7, 126.0,

126.1, 127.1, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 131.6, 132.0, 134.6, 134.8, 135.0, 143.7, 144.9, 154.1, 154.8, 155.1, 170.5, 171.0 ppm; HRMS: *m/z* Calc. for $C_{23}H_{25}N_5O_4$ $[M+Na]^+$: 458.1799. Found: 458.1795.

$[\alpha]_D^{26}$ -78.9 (*c* 0.75 in $CHCl_3$).

Preparation of 1-((1S,2R,5R)-2-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)ethanone ***121***



$C_9H_{16}N_2O_2$
Molecular Weight: 184.24

Procedure

Scheme 1.102

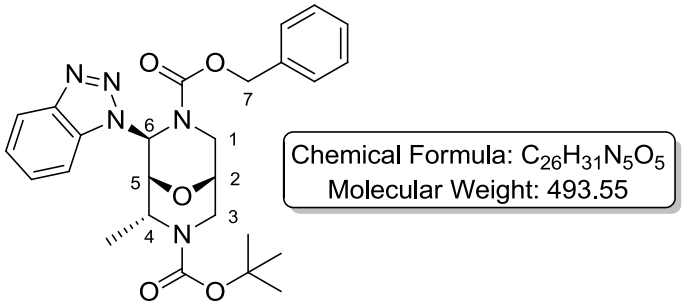
A 3-necked flask was flame-dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (0.15 g, 10% on carbon) followed by a solution of **124** (0.63 g, 1.4 mmol) in methanol (30 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 5% MeOH in EtOAc), to yield the desired product as a pale yellow oil (0.25 g, 97%).

IR (neat): 1649, 2333, 2360, 2929, 2968, 3388 cm^{-1}; ^1H NMR (400 MHz, DMSO): δ 0.92 (d, J = 6.6 Hz, 1.9H, CH_3), 0.98 (d, J = 6.7 Hz, 1.1H, CH_3), 1.95 (s, 1.9H, $CH_3C(O)N$), 1.97 (s, 1.1H, $CH_3C(O)N$), 2.77-2.88 (m, 1H, H6), 2.94 (ddd, ^2J = 13.5, J = 4.2, ^4J = 1.2 Hz, 0.4H, H3), 2.99 (m, 0.6H, H1), 3.06-3.12 (m, 2H, H1+H4), 3.35 (dd, ^2J = 13.5, 3.8 Hz, 0.6H, H3), 3.41-3.43 (m, 1H, H5), 3.47 (ddd, ^2J = 13.3, J = 4.2, ^4J = 2.1 Hz, 0.4H, H1), 3.62 (t, J = 4.0

Hz, 0.6H, H2), 3.67 (t, J = 4.0 Hz, 0.4H, H2), 3.75-3.80 (m, 1H, H3+H6), 4.21 (d, ^{2}J = 13.3 Hz, 0.4H, H3), 4.43 ppm (d, ^{2}J = 13.5 Hz, 0.6H, H6); ^{13}C NMR (100 MHz, DMSO): δ 22.7, 23.0, 26.0, 26.1, 26.2, 43.6, 43.8, 44.0, 44.2, 44.5, 44.7, 44.9, 48.4, 48.8, 53.7, 54.1, 54.4, 57.4, 57.8, 70.0, 70.1, 70.2, 74.6, 75.1, 75.2, 172.8, 172.9 ppm; HRMS: *m/z* Calc. for $C_9H_{17}N_2O_2$ $[M+H]^+$: 185.1285. Found: 185.1284.

$[\alpha]_D^{23}$ +2.1 (*c* 1.0 in $CHCl_3$).

Preparation of (1R,5S,8R)-3-benzyl 7-tert-butyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-dicarboxylate ***125***



General Procedure

To a stirred solution of **105** in DCM was added triethylamine and Boc-anhydride. The reaction mixture was stirred at room temperature overnight, before being partitioned between DCM and water. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and the aqueous layer was extracted with DCM (x 3). The combined organics were washed with brine then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: 0% to 50% EtOAc in petroleum ether) to provide the desired product as a white solid.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of **105**; (b) volume of DCM; (c) quantity of Et_3N; (d) quantity of Boc_2O; and (e) yield.

Table 1.33, Entry 1

(a) 1 g, 2.5 mmol; (b) 10 ml; (c) 0.4 ml, 2.8 mmol; (d) 0.64 ml, 2.8 mmol; (e) 1.26 g, 100%.

Table 1.33, Entry 2

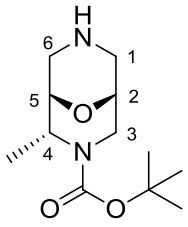
(a) 1.8 g, 4.6 mmol; (b) 20 ml; (c) 0.7 ml, 5 mmol; (d) 1.1 g, 5 mmol; (e) 2 g, 89%.

Melting point: 57-59°C.

IR (neat): 1703, 2331, 2360, 2935, 2976 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 2.5H, $C(CH_3)_3$), 1.48 (s, 2.0H, $C(CH_3)_3$), 1.51 (s, 4.5H, $C(CH_3)_3$), 1.73-1.77 (m, 3H, CH_3), 3.56-3.62 (m, 1H, H4), 3.97-4.28 (m, 5.2H, H1+H2+H3+H5), 4.27 (d, *J* = 4.0 Hz, 0.3H, H5), 4.50 (d, *J* = 4.5 Hz, 0.3H, H5), 4.60 (d, *J* = 4.5 Hz, 0.2H, H5), 5.00-5.33 (m, 2H, H7), 6.82 (s, 0.3H, H6), 6.84 (s, 0.2H, H6), 6.91 (s, 0.2H, H6), 6.95 (s, 0.3H, H6), 7.06-7.42 (m, 7H, H_{Ar}), 7.50 (t, *J* = 7.3 Hz, 0.3H, H_{Ar}), 7.75 (d, *J* = 8.4 Hz, 0.2H, H_{Ar}), 7.84-7.89 (m, 1H, H_{Ar}), 8.10 ppm (d, *J* = 8.4 Hz, 0.5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 17.1, 17.2, 17.6, 27.4, 28.3, 43.8, 44.2, 44.3, 47.9, 48.0, 48.7, 49.0, 54.3, 54.4, 54.6, 55.0, 61.9, 62.4, 65.6, 65.5, 65.8, 65.9, 67.8, 68.1, 68.3, 68.4, 69.3, 69.7, 73.4, 73.6, 73.8, 80.4, 80.5, 80.7, 85.1, 109.4, 109.8, 118.3, 120.0, 120.1, 120.3, 124.0, 124.2, 126.3, 126.4, 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 129.8, 132.0, 132.5, 135.1, 135.5, 135.8, 144.1, 144.2, 145.6, 146.7, 154.4, 154.8, 155.2, 155.3, 155.4, 156.0 ppm; HRMS: *m/z* Calc. for $C_{26}H_{31}N_5O_5Na$ $[M+Na]^+$: 516.2217. Found: 516.2209.

$[\alpha]_D^{26}$ -2.8 (*c* 0.75 in $CHCl_3$).

Preparation of (1S,2R,5R)-tert-butyl 2-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***126***



$C_{12}H_{22}N_2O_3$
Molecular Weight: 242.31

Procedure

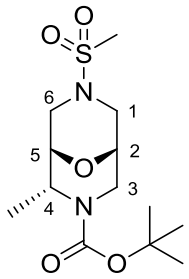
Scheme 1.105

A 3-necked flask was flame-dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (0.34 g, 10% on carbon) followed by a solution of **125** (1.6 g, 3.2 mmol) in methanol (60 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 5% MeOH in EtOAc), to yield the desired product as a pale yellow oil (0.76 g, 96%).

IR (neat): 1690, 2331, 2360, 2929, 2976 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, J = 6.8 Hz, 3H, CH_3), 1.45 (s, 9H, $C(CH_3)_2$), 2.17 (br. s, 1H, NH), 3.02 (d, ^2J = 13.3 Hz, 1H, H6), 3.16 (d, J = 6.8 Hz, 1H, H3), 3.27-3.35 (m, 3H, H1+H4+H6), 3.40 (s, 1H, H5), 3.61 (s, 1H, H2), 3.98 (s, 1H, H1), 4.12 ppm (d, ^2J = 12.4 Hz, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.1, 28.4, 28.5, 42.7, 46.6, 49.6, 52.8, 65.6, 70.4, 80.1, 154.4 ppm; HRMS: *m/z* Calc. for $C_{12}H_{23}N_2O_3$ $[M+H]^+$: 243.1703. Found: 243.1704.

$[\alpha]_D^{23}$ -4.5 (*c* 0.53 in $CHCl_3$).

*Preparation of (1S,2R,5S)-tert-butyl 2-methyl-7-(methylsulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **127***



$C_{13}H_{24}N_2O_5S$
Molecular Weight: 320.41

General Procedure

To a solution of methanesulfonyl chloride in DCM at 0°C was added **126** followed by dropwise addition of Et_3N. The reaction was allowed to warm to room temperature and stirred for 3 h. After this time, tlc analysis showed no starting material remained. The reaction mixture was partitioned between DCM and water and the organics washed with 0.5M HCl. The aqueous layer was washed with DCM (x 2) and the combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: DCM then 5% MeOH in DCM) to yield the desired product as a white solid.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of methanesulfonyl chloride; (b) volume of DCM; (c) quantity of **126**; (d) quantity of Et_3N; and (e) yield.

Table 1.34, Entry 1

(a) 0.07 ml, 0.91 mmol; (b) 8 ml; (c) 0.21 g, 0.87 mmol; (d) 0.13 ml, 0.91 mmol; and (e) 0.28 g, 100%.

Table 1.34, Entry 2

(a) 0.24 ml, 3.1 mmol; (b) 30 ml; (c) 0.7 g, 2.9 mmol; (d) 0.43 ml, 3.1 mmol; and (e) 0.47 g, 50%.

Table 1.34, Entry 3

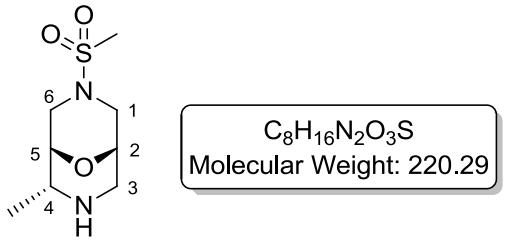
(a) 0.4 ml, 3.5 mmol; (b) 30 ml; (c) 0.76 g, 3.1 mmol; (d) 0.48 ml, 3.5 mmol; and (e) 0.32 g, 32%.

Melting point: 119-122°C

IR (neat): 1159, 1329, 1685, 2331, 2341, 2368, 2980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 12H, $C(CH_3)_3$+CH_3), 2.84 (s, 1.5H, SO_2CH_3), 2.87 (s, 1.5H, SO_2CH_3), 3.12 (d, ^{2}J = 13.5 Hz, 0.5H, H6), 3.22-3.30 (m, 2H, H1+H3+H6), 3.41 (d, ^{2}J = 13.7 Hz, 0.5H, H6), 3.56-3.60 (m, 2H, H4+H5), 3.74 (t, ^{2}J = 12.7 Hz, 1H, H1), 3.92-4.04 (m, 1.5H, H2+H6), 4.17 (d, ^{2}J = 14.3 Hz, 0.5H, H3), 4.24 (d, ^{2}J = 14.3 Hz, 0.5H, H3), 4.40 ppm (d, ^{2}J = 14.3 Hz, 0.5H, H3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 28.5, 36.4, 37.5, 41.2, 42.4, 45.4, 46.9, 49.6, 52.6, 55.1, 55.4, 66.7, 71.4, 71.8, 80.4, 154.0 ppm; HRMS: *m/z* Calc. for $C_{13}H_{28}N_3O_5S_1$ $[M+NH_4]^+$: 338.1744. Found: 338.1748.

$[\alpha]_D^{21}$ -42.1 (*c* 0.28 in $CHCl_3$).

Preparation of (1S,2R,5S)-tert-butyl 2-methyl-7-(methylsulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***122***



Procedure A

Scheme 1.107

To a mixture of DCM (2 ml) and TFA (2 ml) was added **127** (0.24 g, 0.75 mmol). The reaction mixture was stirred at room temperature for 2 h, after which time tlc analysis showed no starting material remained. The reaction mixture was concentrated *in vacuo*, then dissolved in EtOAc and poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (x 3) and the combined organics were dried over

anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Attempted purification by column chromatography led to no starting material or desired product being recovered.

Procedure B

Table 1.35, Entry 1

To a solution of **127** (0.15 g, 0.47 mmol) in DCM (5 ml) was added TFA (0.07 ml, 0.94 mmol). The reaction mixture was stirred at room temperature for 3 h, after which time tlc analysis showed starting material still remained. An additional 2 equiv. of TFA (0.07 ml, 0.94 mmol) were added and the reaction stirred for a further 2 h. After this time, no significant change was observed by tlc, therefore a further portion of TFA (0.07 ml, 0.94 mmol) was added and the reaction stirred at room temperature overnight. After this time, no starting material was observed by tlc. The reaction mixture was concentrated *in vacuo*, then dissolved in EtOAc and poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (x 3) and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired crude product (0.03 g, 27%).

Procedure C

Table 1.35, Entry 2

To a solution of **127** (0.35 g, 1.10 mmol) in DCM (6 ml) was added TFA (0.49 ml, 6.6 mmol). The reaction mixture was stirred at room temperature for 6 h, after which time tlc analysis showed no starting material remained. The reaction mixture was concentrated *in vacuo*, then dissolved in EtOAc and poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (x 3) and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield the desired crude product (0.09 g, 37%). This crude product was combined with the crude product from the reaction decribed in **Table 1.35**, **Entry 1**, and purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to provide 0.06 g of the desired clean product as a colourless oil.

Procedure D

Scheme 1.109

To a solution of **127** (0.22 g, 0.69 mmol) in MeOH (7 ml) was added 3M HCl (0.69 ml). The reaction mixture was stirred at room temperature overnight. After this time, the solution was concentrated *in vacuo*, then dissolved in EtOAc and poured into 2M KOH solution. The aqueous layer was extracted with EtOAc (x 3) and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Attempted purification by column chromatography led to no starting material or desired product being recovered.

Procedure E

Scheme 1.110

To a solution of **127** (0.15 g, 0.47 mmol) in DCM (25 ml) at -20°C was added trimethylsilyl trifluoromethanesulfonate (0.41 ml, 2.3 mmol). The reaction mixture was stirred at -20°C for 1 h. 2,6-Lutidine (0.44 ml, 3.8 mmol) was then added and the reaction mixture was stirred for an additional 20 min. The reaction was then quenched by the addition of a saturated aqueous sodium bicarbonate (10 ml). The basic aqueous phase was extracted with EtOAc (3 x 20 ml) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluent: 0% to 5% MeOH in DCM) to give the desired product (0.018 g, 18%) as well as unreacted starting material (0.03 g, 20%).

Procedure F

Scheme 1.111

Sodium *t*-butoxide (0.1 g, 0.9 mmol) was added to a solution of **127** (0.1 g, 0.3 mmol) in 2-methyltetrahydrofuran (2 ml). Water (0.005 ml, 0.3 mmol) was added and the reaction was heated at reflux for 6 h. The reaction was cooled to room temperature and quenched with 10% citric acid solution. The resulting solution was stirred at room temperature for 30 min and then the pH was adjusted to 10–12 with 6N NaOH solution. The layers were separated. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were dried and concentrated *in vacuo*. Crude ^{1}H NMR indicated that the desired product was not present, and, as such, the reaction was abandoned.

Procedure G

Scheme 1.112

To a solution of **127** (0.35 g, 1.10 mmol) in DCM (6 ml) was added TFA (0.33 ml, 4.4 mmol). The reaction mixture was stirred at room temperature for 6 h, after which time tlc analysis showed no starting material remained. The reaction mixture was concentrated *in vacuo*, then dissolved in EtOAc and poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (x 3) and the combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired crude product. The crude oil was purified by column chromatography (eluent: DCM to 5% MeOH in DCM) to provide the desired product as a colourless oil (0.12 g, 50%).

IR (neat): 1153, 1199, 1317, 2920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, *J* = 7.0 Hz, 1.8H, CH_3), 1.46 (d, *J* = 6.8 Hz, 1.2H, CH_3), 2.76 (s, 1.8H, SO_2CH_3), 2.84 (s, 1.2H, SO_2CH_3), 3.05-3.09 (m, 1H, H1), 3.13 (d, ^{2}J = 14.0 Hz, 0.6H, H6), 3.17-3.28 (m, 1.8H, H3+H6), 3.33-3.44 (m, 2H, H1+H4+H5), 3.54-3.56 (m, 0.4H, H4), 3.58 (t, *J* = 3.8 Hz, 0.6H, H5), 3.73 (d, ^{2}J = 11.4 Hz, 0.6H, H6), 3.76 (t, *J* = 3.8 Hz, 0.6H, H2), 3.81 (t, *J* = 3.8 Hz, 0.4H, H2), 3.86 (dd, ^{2}J = 11.9, *J* = 1.4 Hz, 0.4H, H3), 3.90 ppm (d, ^{2}J = 11.9 Hz, 0.6H, H3); ^{13}C NMR (100 MHz, DMSO): δ 17.7, 17.9, 32.1, 33.5, 44.3, 44.6, 48.7, 49.0, 49.2, 51.2, 52.4, 56.7, 65.3, 66.9, 69.8, 71.4 ppm; HRMS: *m/z* Calc. for $C_8H_{17}N_2O_3S_1$ $[M+H]^+$: 221.0954. Found: 221.0955.

$[\alpha]_D^{21}$ -37.0 (*c* 0.41 in $CHCl_3$).

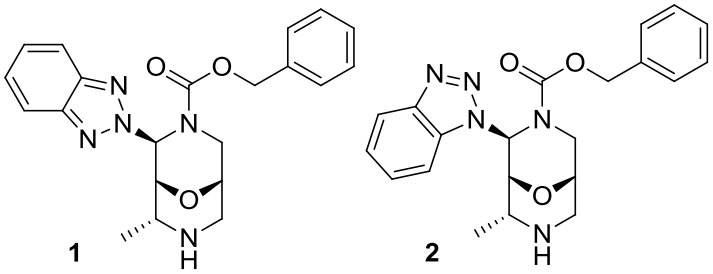
8. Appendix

8.1 Computational Data

For experimental details of the computational methods employed please refer to information on accompanying CD.

8.2 Full Spectral Data for Methyl Oxabispidine 105

Proposed structures for the methyl oxabispidine are shown as **1** and **2**.



Experimental

NMR data were acquired using a Bruker AVANCE III 14.1 T NMR spectrometer operating at 600.13 MHz for ^{1}H resonance using a triple resonance TBI-z ([^{1}H, ^{13}C, BB]-z) probehead and running under Topspin Version 2.1.

Typically, standard 1D ^{1}H NMR data at 298 K (and including variable temperature data at 308, 318, 328, 338, 348 and 358 K) were acquired over a frequency width equivalent to 11 ppm centred at 5 ppm with 32 transients acquired into 32K data points. 1D ^{1}H pure shift NMR data were acquired according to the method of Meyer and Zangger[i] using a 25 ms selective EBurp 90° pulse and a 4.5 ms selective Gaussian 180° pulse over a slice selective gradient of 0.5 G/cm. Data were acquired with 128 transients over a frequency width equivalent to 10 ppm into 8192 data points using a chunking time equivalent to $1/3J_{HH}$.

2D [^{1}H, ^{1}H] EXSY/NOESY data were acquired either using narrow ω_2 and ω_1 frequency windows (2 ppm) centred at 7.4 ppm or using full frequency widths of 5 kHz equivalent to 8.33 ppm centred at 5 ppm. Mixing times, τ_m, of 0.5 s or 1.0 s were used. Narrow frequency width data sets were acquired with a standard, non-gradient, phase-sensitive pulse sequence (noesyph) using 8 transients acquired into 512 data point for each of 128 States-TPPI t_1 increments. Wide frequency width data were acquired using a phase sensitive, gradient accelerated approach with zero-quantum suppression

according to the approach of Thrippleton and Keeler.[ii] Data were acquired with 8 transients into 2048 data points for each of 360 State-TPPI t_1 increments.

Phase sensitive 2D [^{1}H, ^{1}H] TOCSY NMR data were acquired using either a zero-quantum suppression approach[ii] or an instant pure shift approach according to the method of Meyer and Zangger.[i] Zero-quantum suppressed data were acquired with 4 transients into 2K data points for each of 360 TPPI t_1 increments. Pure shift data were acquired with 32 transients into 2K data points for each of 360 State-TPPI t_1 increments using a 25 ms EBurp2 slice selective soft 90° pulse and a 4.5 ms slice selective refocusing Gaussian pulse both over a 0.5 G/cm z-pulse field gradient. 1D TOCSY data were acquired with zero-quantum suppression using a frequency selective RSnob refocusing pulse. Data were acquired with 32 transients into 32K data points over a frequency width equivalent to 12 ppm centred at 5 ppm with frequency shifted pulse computed on the fly according to the relevant offset values for selected resonances. In all cases, the TOCSY spin-lock mixing time, τ_m, was set to 70 ms.

2D [^{1}H, ^{13}C] multiplicity edited HSQC NMR data were acquired using an Echo-Antiecho, sensitivity improved gradient selected approach using the pulse sequence hsqcedetgpsisp2.4. Data were acquired with 8 transients into 2048 data points over a ω_2 (^{1}H) frequency width equivalent to 12 ppm centred at 5 ppm for each of 256 t_1 increments over a ω_1 (^{13}C) frequency width equivalent to 180 ppm centred at 70 ppm.

2D [^{1}H, ^{13}C] multiplicity edited pure shift HSQC NMR data were acquired according to the method of Morris *et al.*[iii] using equivalent parameters to those described for the standard HSQC experiment.

2D [^{1}H, ^{13}C] multiplicity edited HSQC-TOCSY NMR data were acquired in a similar manner to that described for the 2D [^{1}H, ^{13}C] HSQC data with a spin-lock mixing time, τ_m, set to 70 ms.

2D [^{1}H, ^{13}C] HMBC NMR data were acquired without ^{13}C decoupling during data acquisition in a non-phase sensitive mode using the gradient selective pulse program hmbcetgpl3nd incorporating a 3 fold low-pass J-filter for suppression of $^1J_{CH}$ correlations according to the method of Cicero *et. al.*[iv] Data were acquired with 32 transients into 2048 data points over a ω_2 (^{1}H) frequency width equivalent to 16 ppm centred at 5 ppm for each of 128 echo-antiecho t_1 increments over a ω_1 (^{13}C) frequency width of 222 ppm centred at 100 ppm.

2D [^{1}H, ^{15}N] HMBC NMR data acquisition was attempted using a CIGAR-HMBC approach according to Hadden *et al.*[v] but proved to be unsuccessful.

All data were processed using TopSpin version 2.1 according to standard processing protocols.

Results

The result of acquiring 1D ^{1}H NMR data on the supplied sample as a function of temperature are shown in **Fig. 1**.

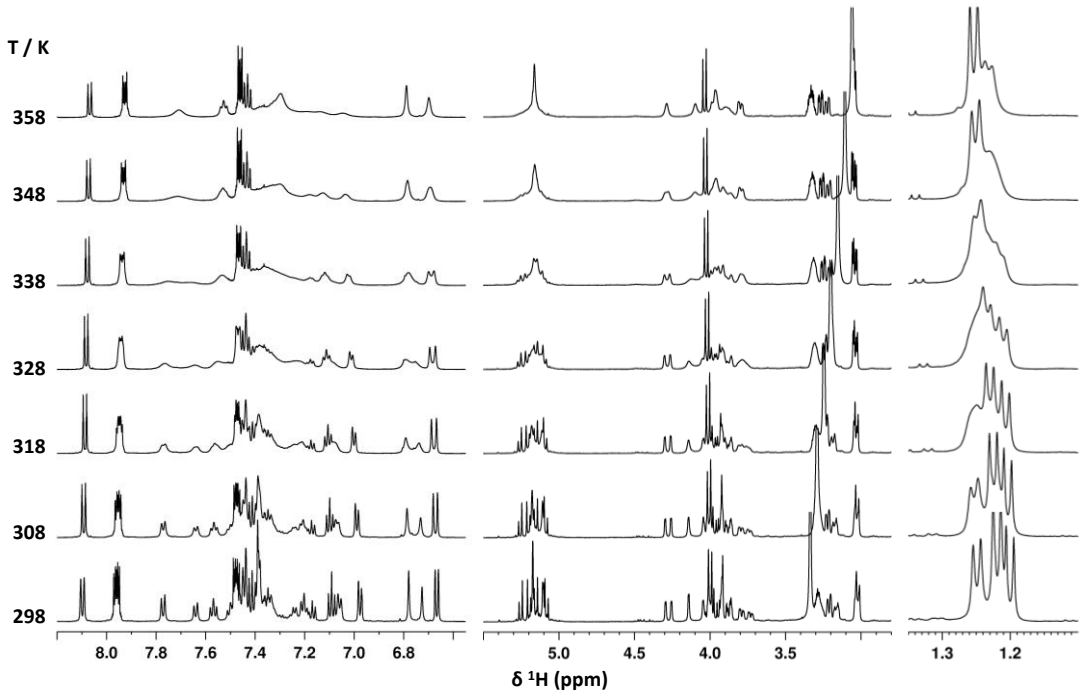


Fig. 1: 1D ^{1}H NMR spectra of sample acquired as a function of temperature.

The data indicated that whilst some of the resonances go through coalescence on sample heating, others, such as many of those in the aromatic region, remain in the intermediate exchange regime. In contrast, other resonances, including those at δ^{1}H = 8.098 and 7.960 ppm, appear simply to change shape.

Integration of the ^{1}H NMR spectrum (**Fig. 2**) showed that when the signal at δ^{1}H = 7.960 ppm was calibrated to 2 proton equivalents, the signal at δ^{1}H = 8.098 ppm integrated to 1 proton equivalent. The selection of a calibration of 2 proton equivalents for the signal at δ^{1}H = 7.960 ppm was based on its shape and appearance, with characteristics similar to those found in AA'BB' spin systems.

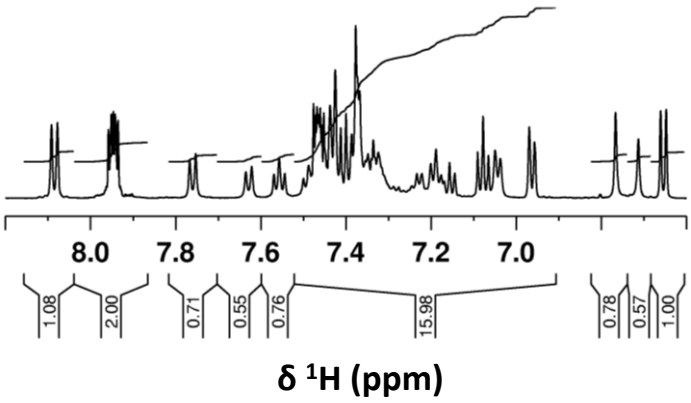


Fig. 2. Integration of the aromatic region of the 1D ^{1}H NMR spectrum of the sample.

2D [^{1}H, ^{1}H] EXSY NMR spectra (**Fig. 3**) that focussed on the same aromatic region and was used to acquired data at both 298 K and 358 K, showed the source of the substantial resonance broadening and sharpening observed in the 1D ^{1}H NMR data acquired as a function of temperature (as shown in **Fig. 1**).

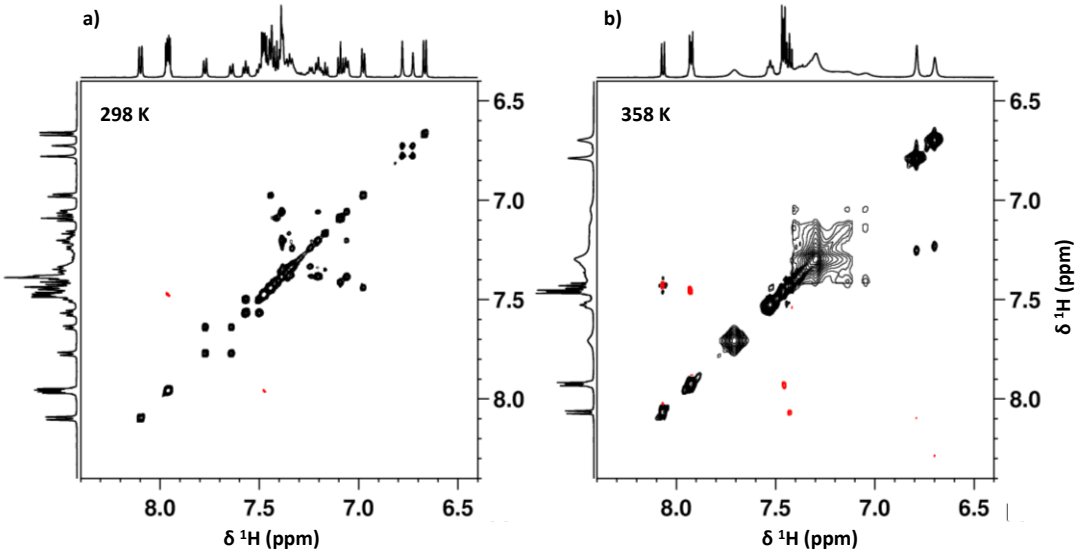


Fig. 3: 2D [^{1}H, ^{1}H] EXSY NMR data for the sample at a) 298 K and b) 358 K. Red contours arise through NOE or ZQC. In b) the off-diagonal peaks at δ^{1}H = 6.78 and 6.70 ppm are due to folded NOE cross-peaks between aromatic and aliphatic proton resonances arising from the narrow spectral width used.

Although resonances at δ^1H = 6.78 and 6.70 ppm from **Fig. 3b** did not appear to share mutual exchange (no intervening cross-peak) a more detailed examination of this condition was carried out by means of 1D selective EXSY (**Fig. 4**).

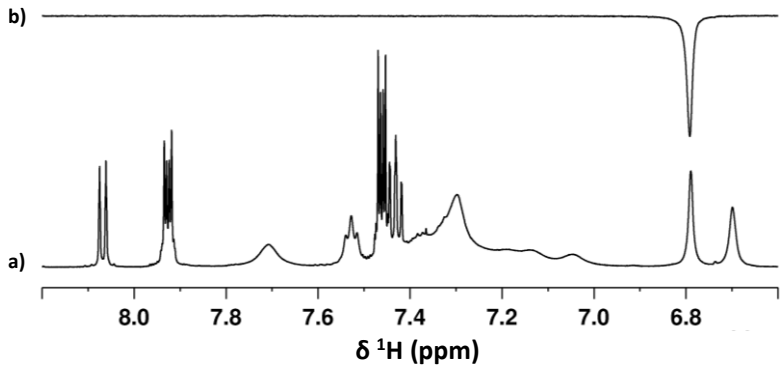


Fig. 4: ^{1}H NMR data showing a lack of chemical exchange. a) 1D ^{1}H NMR spectrum at 358 K; b) 1D ^{1}H selective EXSY NMR spectrum showing selective inversion at δ^1H = 6.78 ppm. The absence of any response in b) at δ^1H = 6.70 ppm indicated lack of chemical exchange between the species giving rise to the signals at δ^1H = 6.78 and 6.70 ppm.

These data suggested the presence of two similar species in solution which did not interconvert with one another but which individually underwent dynamic exchange with a second conformational partner, for which there is precedent from previous work.[vi]

In order to confirm this and the identity of the two species, a set of NMR data was acquired on the sample at 298 K to provide the richest information possible. 2D [^{1}H, ^{13}C] HSQC and 2D [^{1}H, ^{1}H] EXSY NMR data were initially used to establish the exchange-based relationship between resonances (**Fig. 5**).

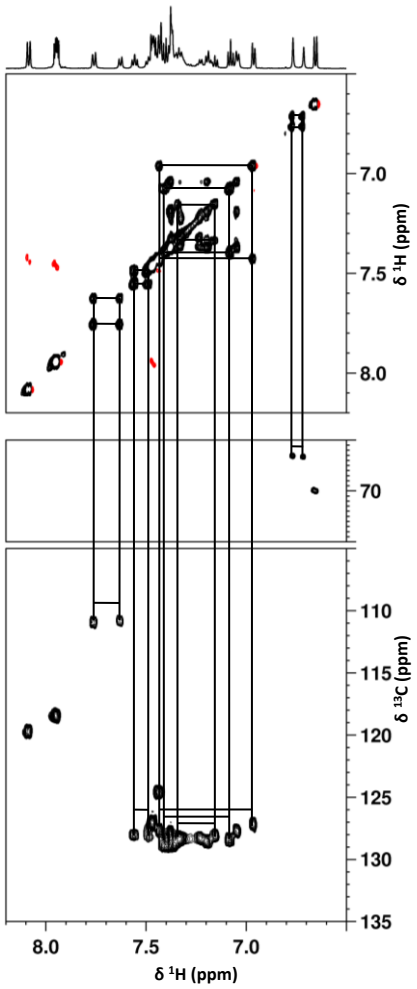


Fig. 5: Establishing the exchange-based relationship between [^{1}H, ^{13}C] correlations (bottom) *via* 2D [^{1}H, ^{1}H] EXSY (top).

Using these data and in combination with 1D and 2D TOCSY NMR spectra, it was possible to establish a labelling scheme as shown in the annotated 2D [^{1}H, ^{13}C] HSQC NMR spectra shown in **Fig. 6** for the ^{1}H chemical shift region 6.5-8.5 ppm. In an attempt to simplify these data and to reduce the overlap between cross-peaks that was observed even at a magnetic field strength of 14.1 T, pure shift HSQC NMR data were acquired according to the scheme proposed by Morrisiii (**Fig. 7**), which improved the resolution in a manner consistent with reports and provided cleaner looking data in the aromatic cross-peaks region to improve confidence in identifying relevant correlations.

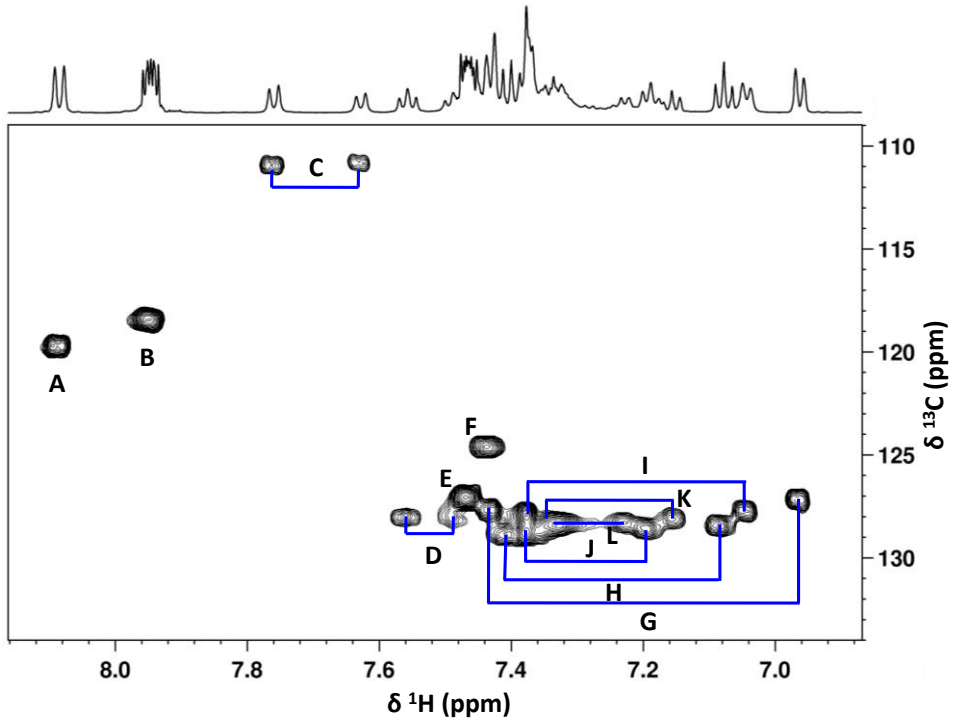


Fig. 6: Aromatic cross-peak region of the standard 2D [^{1}H, ^{13}C] HSQC NMR spectrum of the sample. Pairs of exchange-related cross-peaks are tied by means of blue lines and labelled with a single identifier.

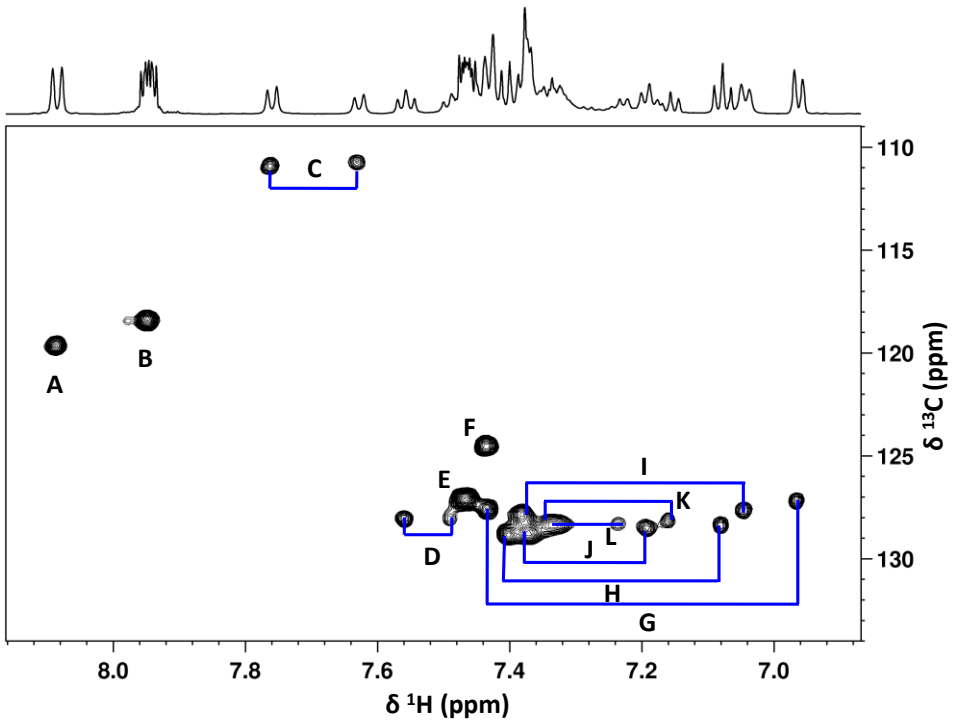


Fig 7: Aromatic cross-peak region of the pure-shift 2D [^{1}H, ^{13}C] HSQC NMR spectrum of the sample showing the expected improvement in resolution arising from homo-nuclear ^{1}H decoupling during the acquisition phase of the experiment.

Selective 1D ^{1}H-TOCSY experiments enabled related spin-systems to be clearly identified and allowed the 1D ^{1}H NMR spectrum to be appropriately edited (**Fig. 8**).

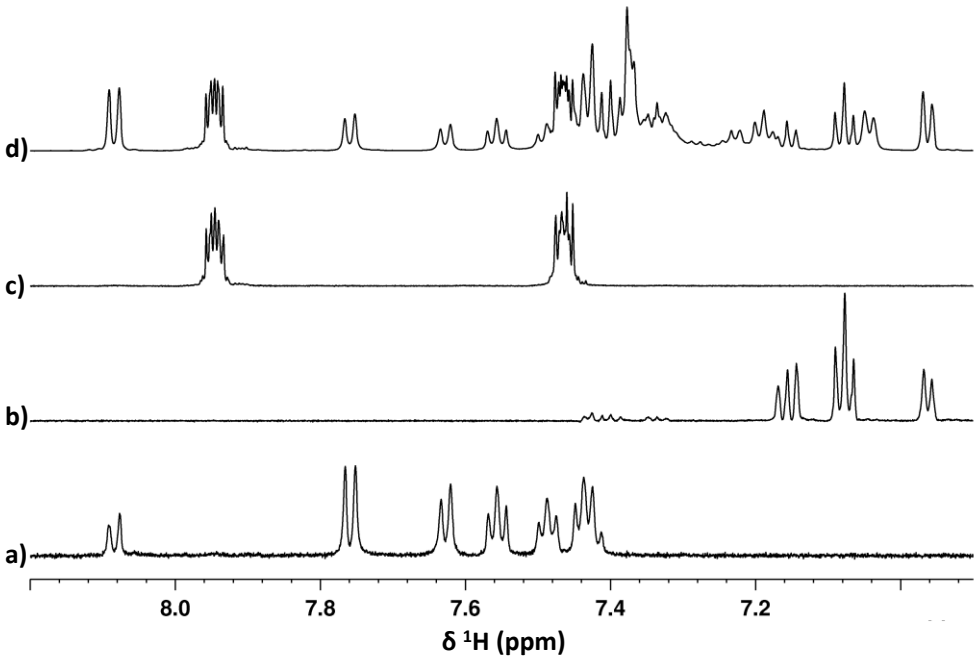


Fig 8: Selective 1D ^{1}H-TOCSY NMR data **(a)-(c)** compared with standard 1D ^{1}H NMR spectrum of the sample **(d)**. **(a)** Selective excitation at δ ^{1}H = 8.085 ppm; **(b)** Selective excitation at δ ^{1}H = 7.946 ppm; **(c)** Selective irradiation at δ ^{1}H = 6.962 ppm.

The remaining aliphatic proton-related correlations are identified by letter in **Fig. 9**.

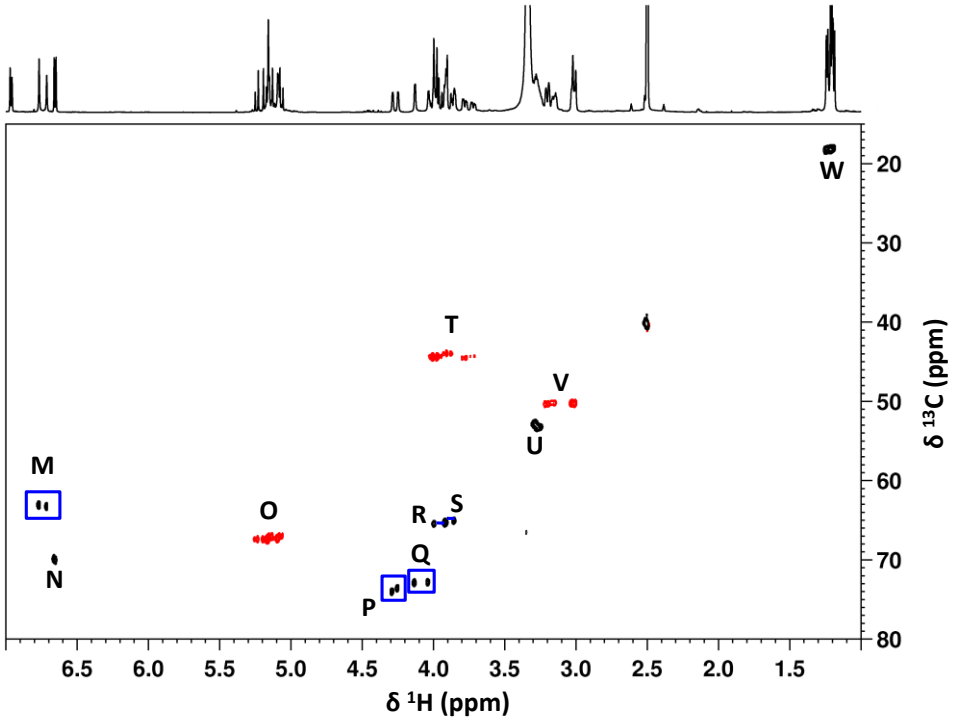
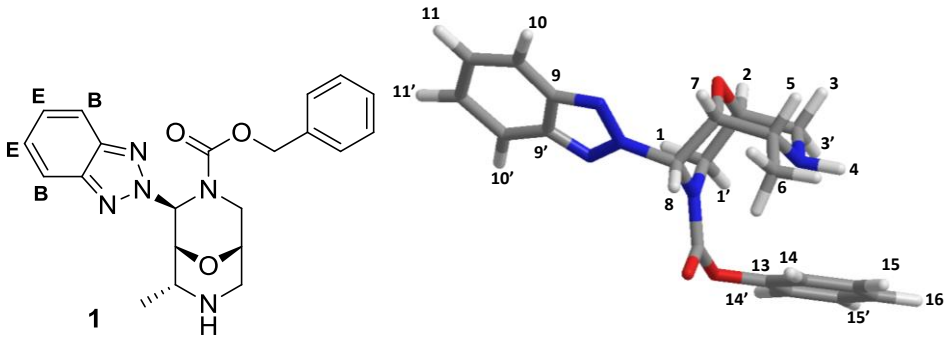


Fig 9: Aliphatic correlation region of the 2D [^{1}H, ^{13}C] HSQC NMR spectrum of the sample with signal identifiers

Assignment

Structure 1

Fig. 8c indicates the presence of two signals, **B** and **E**, with relative integrals for two proton equivalents each, which suggested a AA'BB' spin system within a symmetrical aromatic environment.



Thus protons/(carbons) **10** and **10'** in the structure shown were assigned to the signal at $\delta\,^{1}H$ = 7.946 ppm/($\delta\,^{13}C$ = 118.39 ppm) and protons labelled **11** and **11'** were assigned to the signal at $\delta\,^{1}H$ = 7.466 ppm/($\delta\,^{13}C$ = 126.94 ppm). 2D [^{1}H, ^{13}C] HMBC NMR data showed the presence of a quaternary carbon resonance at $\delta\,^{13}C$ = 143.96 ppm corresponding to carbons **9**/**9'**. Proton/(carbon) **8** in two conformations of **1** ($\delta\,^{1}H$/ $\delta\,^{13}C$ = 6.66/69.816 [**a**] ppm and 6.647/70.056 [**b**] ppm) were assigned by elimination due to the absence of any NOE with the aromatic protons **10/10'/11/11'** in the structure in contrast to the partner structure **2**. TOCSY correlation between proton **8** and proton **7** allowed the bridgehead proton/carbon to be assigned in two conformations as $\delta\,^{1}H$/ $\delta\,^{13}C$ = 4.290/73.89 ppm [**a**] and 4.250/73.54 ppm [**b**]. Further TOCSY correlation between proton **7**, proton **5** and methyl protons **6** enabled further proton/carbon assignments to be made in two conformations as $\delta\,^{1}H$/ $\delta\,^{13}C$ = 3.285/52.610 ppm [**a**] and 3.274/53.080 ppm [**b**] (proton/carbon **5**) and $\delta\,^{1}H$/ $\delta\,^{13}C$ = 1.209/18.113 ppm [**a**] and 1.190/18.113 ppm [**b**] (proton/carbon **6**). NOE between the resonances corresponding to protons **6** (the methyl group) and **8** confirmed that these two groups were on the same face of the molecule as one another. HMBC correlation was observed between the carbon associated with proton **5** ($\delta\,^{13}C$ = 52.610/53.080 ppm) and proton resonances at **V** (**Fig. 9**) associated with CH_2 groups. Proton **3'** was assigned for both conformations [**a**] and [**b**] to the signal at $\delta\,^{1}H$ = 3.020 ppm ($\delta\,^{13}C$ = 50.09 ppm) with partner protons **3** assigned to signals at $\delta\,^{1}H$ = 3.206 [**a**] and 3.161 [**b**] ppm. TOCSY correlation between signals arising for protons **3** and **3'** and signals at chemical shifts consistent with bridgehead protons enabled proton **2** to be assigned to signals at $\delta\,^{1}H$ = 3.854/($\delta\,^{13}C$ = 64.98), $\delta\,^{1}H$ = 3.916/($\delta\,^{13}C$ = 65.12) and $\delta\,^{1}H$ = 3.992/($\delta\,^{13}C$ = 65.40) ppm. Distinction between which signal corresponded to which conformer/compound was not made in this instance due to signal degeneracy for proton **3**. Protons **1** and **1'** (and the associated carbon, signals labelled **T** in **Fig. 9**) were also not specifically assigned due to signal degeneracy. However, it was possible to determine from HMBC NMR data that the carbon at position **3** coupled to proton **1** with a large coupling constant resulting in HMBC correlation that did not occur to proton **1'**. Hence it was possible to establish that proton **1** resonated in the region $\delta\,^{1}H$ = 3.85 – 4.00 ppm.

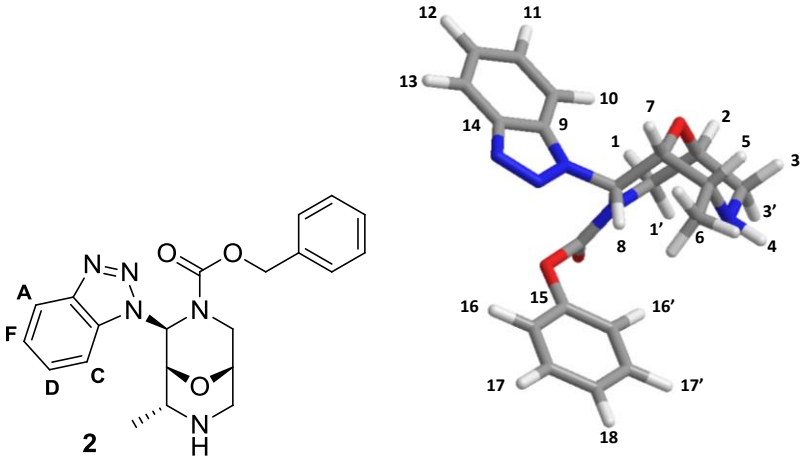
A summary of the assignment made as far as possible for **1** is provided in **Table 1**.

Table 1: ^{1}H and ^{13}C NMR data assignments associated with the methyloxabispidine component of structure **1**

Atom ID	δ ^{1}H/ppm	Multiplicity	δ ^{13}C/ppm
H1	Range 3.85-4.00	m	
H1’	Range 3.85-4.00	m	
C1			Range 44.45-43.71
H2	3.854; 3.916	narrow multiplet	
C2			64.98; 65.12
H3	3.206; 3.161	m	
H3’	3.020 (degenerate)	m	
C3			50.09 (degenerate)
H5	3.285; 3.274	m	
C5			52.610; 53.080
H6 (methyl)	1.209; 1.190	d	
C6			18.113 (degenerate)
H7	4.290; 4.250	narrow multiplet	
C7			73.89; 73.54
H8	6.660; 6.647	s	
C8			69.816; 70.056
C9/9’			143.96
H10/10’	7.946	AA’BB’ multiplet	
C10/10’			118.39
H11/11’	7.466	AA’BB’ multiplet	

C11/11’	126.94

Structure 2



The starting point for identification of resonances in **2** began with the occurrence of NOEs between resonances at $\delta\ ^{1}H$ = 6.713/6.766 ppm (**M** in **Fig. 9**, related by chemical exchange) and resonances at $\delta\ ^{1}H$ = 7.630/7.762 ppm (**C** in **Fig. 6 and 7**, also related by chemical exchange, $\delta\ ^{13}C$ = 110.89/110.70 ppm). Resonances at **M** were assigned to proton **8** through reference to the assignment of structure **1**. Signals at **C** were doublets in the ratio 56% to 44% which provided the relative ratio of conformers for **2**. NOE was expected between proton **8** and proton **10**. Hence resonances at **C** were assigned to proton **10** in two conformers. Proton **10** in two conformations also showed NOE to resonances **Q** (**Fig. 9**) with chemical shifts characteristic of bridgehead protons. Hence resonances **Q** were assigned to proton **7** in two interchanging conformations of structure **2** at $\delta\ ^{1}H$ = 4.130/4.036 ppm ($\delta\ ^{13}C$ = 72.72 ppm). Resonances **C** showed NOE correlation to triplet resonances **D** ($\delta\ ^{1}H$ = 7.557/7.488 ppm [$\delta\ ^{13}C$ = 127.98] related by chemical exchange to one another) which were assigned to proton **11** in structure **2**. HMBC data showed $^{3}J_{HC}$ correlation between resonances **C** and resonance **F** (**Fig. 6** and **Fig. 7**) which corresponded to two overlapping triplets that were assigned to proton **12** in two conformations of structure **2** ($\delta\ ^{1}H$ = 7.439/7.427 ppm, [$\delta\ ^{13}C$ = 124.48 ppm]). HMBC correlation occured between carbon **D** and the doublet proton resonance at **A** (integrating to two proton equivalents) which was therefore assigned to proton **13** in two conformations of structure **2**.

Having identified the bridgehead proton **7** resonances as **Q**, it was possible to further elaborate the assignment of the methyl oxabispidine unit as follows. Proton **5** resonated at $\delta\ ^{1}H$ = 3.255 ppm for both conformations ($\delta\ ^{13}C$ = 53.096 ppm) being TOCSY correlated with proton **7**. Methyl **6** was

correlated with proton **5** *via* TOCSY for two conformations (δ ^{1}H/ δ ^{13}C = 1.211/18.099 ppm). As for structure **1**, strong NOE correlation between the resonances associated with methyl protons **6** and protons **8** confirmed that these groups were on the same face of structure **2**. Further assignments for the remaining protons followed by comparison with structure **1**. Thus protons **3**/**3'** were assigned to signals at **V**, bridgehead protons/carbons **2** were assigned to signals **R** at δ ^{1}H/ δ ^{13}C = 3.994/65.322 ppm and 3.913/65.269 ppm for two conformations and protons **1**/**1'** were assigned to signals at **T** of **Fig. 9** but could not be distinguished due to signal degeneracy.

A summary of the assignment made as far as possible for **2** is provided in **Table 2**.

Table 2: ^{1}H and ^{13}C NMR data assignments for the methyl oxabispidine component of structure **2**

Atom ID	δ **^{1}H/ppm**	**Multiplicity**	δ **^{13}C/ppm**
H1	Range 3.85-4.00	m	
H1'	Range 3.85-4.00	m	
C1			Range 44.45-43.71
H2	3.994; 3.913	s	
C2			65.322; 65.269
H3	3.020 (degenerate)	m	
H3'	Range 3.14-3.22	m	
C3			50.09 (degenerate)
H5	3.255 (degenerate)	m	
C5			53.096
H6 (methyl)	1.211 (degenerate)	d	
C6			18.099 (degenerate)
H7	4.130; 4.036	Narrow d	
C7			72.72
H8	6.713; 6.766	s	

C8			63.21; 63.00
C9			132.04
H10	7.630; 7.762	d	
C10			110.89; 110.70
H11	7.557; 7.488	t	
C11			127.98
H12	7.439; 7.427	t	
C12			124.48
H13	8.084	d	
C13			119.58
C14			145.31

The remaining unassigned aromatic proton NMR signals were associated with the CBz phenyl ring in two different conformations for each of structures **1** and **2** (i.e. 4 sets of phenyl ring signals in total). A set of resonances for the CBz phenyl ring in one conformation occurred at δ ^{1}H = 6.964 ppm (2H, d, δ ^{13}C = 127.15 ppm) – **G** in **Fig. 6** and **7**, 7.079 ppm (2H, t, δ ^{13}C = 128.37 ppm) – **H** in **Fig. 6** and **Fig. 7** and 7.157 ppm (1H, t, δ ^{13}C = 128.13 ppm) – **K** in **Fig. 6** and **Fig. 7**, which were in chemical exchange with signals at δ ^{1}H = 7.433 ppm (2H, d, δ ^{13}C = 127.57 ppm) – **G** in **Fig. 6** and **Fig. 7**, 7.40 ppm (2H, t, δ ^{13}C = 128.79 ppm) – **H** in **Fig. 6** and **Fig. 7** and 7.337 ppm (1H, t, δ ^{13}C = 128.20 ppm) – **K** in **Fig. 6** and **Fig. 7**. Exchange-related proton(carbon) resonances **I** (2H, d, δ ^{1}H = 7.042/7.378 ppm (δ ^{13}C = 127.65/127.80 ppm), **J** (2H, t, δ ^{1}H = 7.188/7.365 ppm (δ ^{13}C = 128.47/128.59 ppm) and **L** (1H, t, δ ^{1}H = 7.231/7.326 (δ ^{13}C = 128.3 ppm in both cases) corresponded to a second set of resonances for two conformations associated with the phenyl ring of the CBz group. No NOE information existed which tied the CBz phenyl ring resonances to either structure **1** or structure **2**. Although integration might have enabled this distinction to be made, the similarity in the populations of structure **1** and structure **2** in solution meant that reliability could not be placed on this method for distinction. For these reasons it was not possible to relate the sets of CBz phenyl ring resonances to the relevant structures.

[i] N. H. Meyer and K. Zangger, *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 7143.

[ii] M. J. Thrippleton and J. Keeler, *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3938.

[iii] L. Paudel, R. W. Adams, P. Király, J. A. Aguilar, M. Foroozandeh, M. J. Cliff, M. Nilsson, P. Sándor, J. P. Waltho, and G. A. Morris, *Angew. Chem. Int. Ed*., **2013**, *52*, 11616.

[iv] D. O. Cicero, G. Barbato, and R. Bazzo, *J. Magn. Reson.* **2001**, *148*, 209.

[v] a) C. E. Hadden, G. E. Martin and V. V. Krishnamurthy, *Magn. Reson. Chem.* **2000**, *38*, 143-147; b) C. E. Hadden, G. E. Martin and V. V. Krishnamurthy, *J. Magn. Reson.* **1999**, *140*, 274-280.

[vi] R Bogacki, D. M. Gill, W. J. Kerr, S. Lamont, J. A. Parkinson, and L. C. Paterson, *Chem. Commun*. **2013**, *49*, 8931.

Chapter 2

Investigations into the use of Chiral Oxabispidines within Magnesium-mediated Asymmetric Deprotonations.

Contents

1. Introduction

The introduction of asymmetry into a molecule represents one of the most challenging areas of research in modern day organic chemistry. In this regard, much attention has been focused on the preparation of compounds in enantiomerically pure form, with varying methods being employed to embed chirality within a molecule in an efficient and expedient manner.[1] Firstly, the most simple and well-established approach starts with a naturally occurring chiral compound and involves modifying the functionality present utilising achiral reagents. Furthermore, chiral auxiliaries can be utilised, whereby the auxiliary forms a chiral adduct with the substrate and further manipulation takes place with achiral reagents. A more challenging and attractive approach in asymmetric synthesis is the use of achiral substrates with either stoichiometric or catalytic amounts of chiral reagents. This technique exhibits several advantages over those mentioned previously, namely less wastage and fewer synthetic steps, both key disadvantages in the use of chiral auxiliaries. An additional advantage is the potential that, in some cases, the chiral reagents employed may be recycled.

1.1 (-)-Sparteine and Related Compounds

1.1.1 (-)-Sparteine

(-)-Sparteine is an alkaloid derivative from the lupine family used extensively in asymmetric synthesis. It is easily isolated from Scotch broom (*Cytisus scorparius*)[2] and, until recent years, was commercially available; however, its availability is now reportedly extremely limited.[3] The bispidine core (*vide supra*) of (-)-sparteine, **1**, and its isomers (**Figure 2.1**) is a semi-rigid, cage-like structure and provides the natural product with a desirable metal-chelating conformation that has allowed its successful utilisation as a chiral bidentate ligand in a broad range of enantioselective transformations, in both stoichiometric and catalytic quantitites.[4] Whilst other isomers of **1** have been isolated and prepared, they have generally received less attention due, in part, to the lower natural abundance of these forms, and, in the case of the C_2-symmetric diastereomers α,- and β-isosparteine, their lowered effectiveness within asymmetric processes.[5]

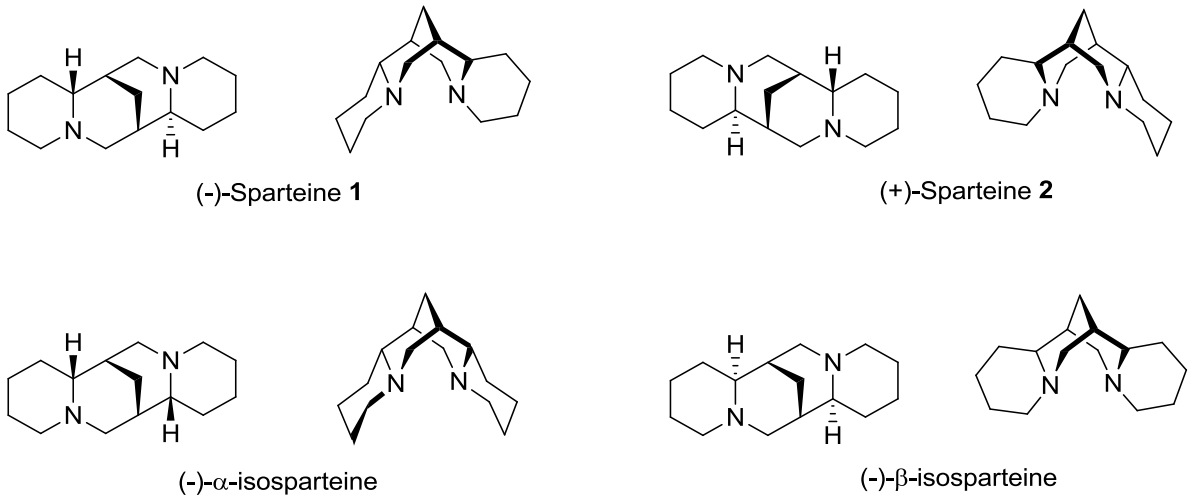


Figure 2.1

In relation to its utility within synthetic chemistry, (-)-sparteine has found most widespread application in the arena of organolithium chemistry. Having stated this, this species has also been successfully employed in combination with other metals such as palladium, copper, and magnesium. Whilst selected transformations will be highlighted herein, the use of (-)-sparteine as a chiral additive has received significant attention and has been reviewed thoroughly within the chemical literature.[4-7] As such, an extensive discussion will not be carried out within this report.

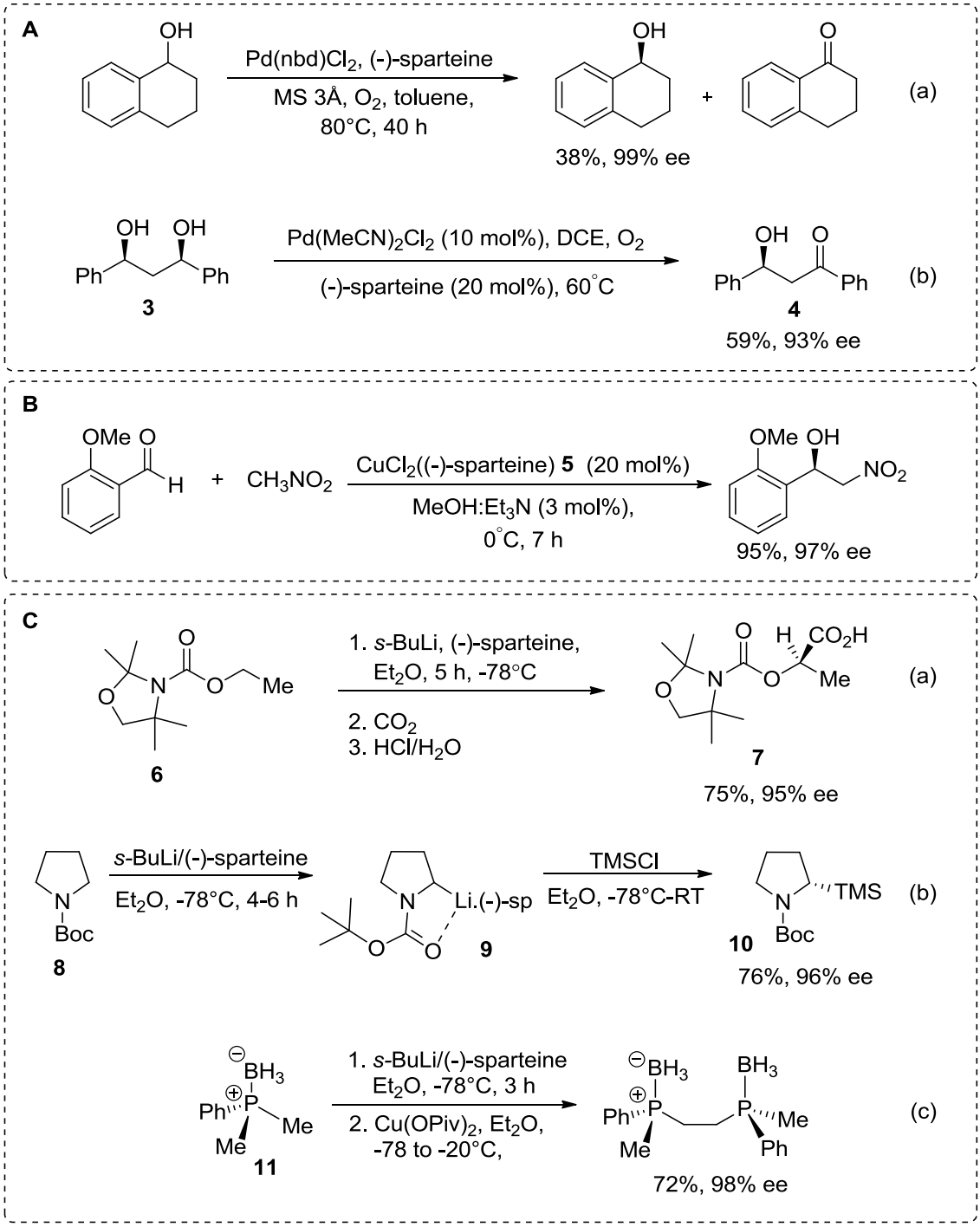
Shown in **Scheme 2.1** is a small selection of reactions in which (-)-sparteine has been shown to be highly effective. Illustrated in **A**, **Scheme 2.1** is the work of the research groups of Stoltz and Sigman who simultaneously, yet individually, investigated the Pd-catalysed oxidative kinetic resolutions of secondary alcohols. Both found that, of all the chiral ligands screened (including BINAP, cinchonidine, and bisoxazoline) (-)-sparteine, in catalytic quantities, was found to be the most efficient,[8,9] and obtained a range of benzylic and allylic alcohols in enantio-enriched form, with impressively high enantiomeric excesses. A specific example from Stoltz is shown in **A**, **Scheme 2.1**, **Reaction (a)**, where the desired enantiomerically-enriched alcohol was obtained in outstanding 99% ee, utilising a combination of $Pd(nbd)Cl_2$ and **1**.[8] An additional facet to Sigman's work was the oxidative desymmetrization of 1,3-*meso*-diols (**A**, **Scheme 2.1, Reaction (b)**). Treatment of 1,3-diol **3** with the previously mentioned Pd(II)/(-)-sparteine catalytic system resulted in enantioselective oxidation providing compound **4** in good yield and high enantioselectivity.[9]

(-)-Sparteine has also been employed in many copper-catalysed transformations. Great success has been achieved in the asymmetric Henry reaction with the use of copper (II) (-)-sparteine complexes (**B, Scheme 2.1**).[10] Maheswaran and co-workers found that treatment of nitromethane with a variety of aromatic and aliphatic aldehydes in the presence of Cu/(-)-sparteine complex **5** gave rise to the corresponding nitro aldol product in excellent yields and high enantiomeric excesses.[10]

The incredible impact of (-)-sparteine on asymmetric synthesis is best, and most commonly, exemplified in its use in lithium-mediated processes. Hoppe and co-workers were the first to employ the combination of an alkyllithium reagent and (-)-sparteine effectively in enantioselective deprotonations. The deprotonating system of *s*-BuLi complexed to (-)-sparteine was first applied to alkylcarbamates such as **6** (**C**, **Scheme 2.1**, **Reaction (a)**).[11] It was found that the chiral base system was able to effectively distinguish between the two protons of a methylene group, leading to a configurationally stable lithiated intermediate which can then be trapped with an electrophile with complete retention of stereochemistry.[12]

Following on from Hoppe's early work, Beak and co-workers went on to demonstrate that this asymmetric deprotonation/alkylation process could be applied to a variety of substrates.[13] It was discovered that nitrogen-containing substrates bearing a Boc protecting group could undergo α-deprotonation leading to configurationally stable organolithium species, with particular attention being paid to the enantioselective deprotonation of *N*-Boc pyrrolidine **8**.[14] Reaction of a 1:1 mixture of *s*-BuLi and (-)-sparteine at -78°C with *N*-Boc pyrrolidine generated chiral organolithium intermediate **9**, which was subsequently treated with a variety of electrophiles to give the desired 2-substituted pyrrolidines in good yield and high enantiopurity (**C**, **Scheme 2.1, Reaction (b)**).[14]

Another class of substrate for which the BuLi/(-)-sparteine asymmetric deprotonation protocol has proven highly effective is phosphine boranes, which are used towards the synthesis of chiral diphosphine ligands. In 1995, Evans *et al*. reported an expedient synthesis of C_2-symmetric P-chiral diphosphines which employs successive asymmetric deprotonation of aryldimethylphosphine-boranes such as **11** and subsequent oxidative coupling (**Reaction (c), Box C, Scheme 2.1).**[15]

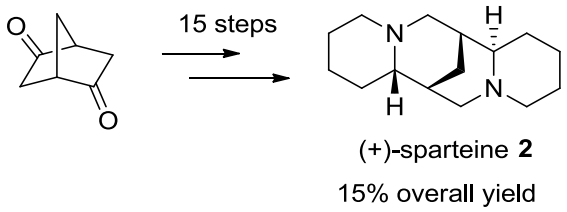


Scheme 2.1

1.1.2 (+)-Sparteine and (+)-Sparteine Surrogate

(+)-Sparteine, **2**, like (-)-sparteine, is a natural product, however significant quantities from its natural source are unavailable. Furthermore, attempts to develop an expedient synthetic

route towards (+)-sparteine have been limited in their success. Ebner and co-workers isolated lupanine from its natural source, which upon resolution could then be converted into (+)-sparteine.[16] Thereafter, Aubé *et al.* reported the first asymmetric total synthesis of (+)-sparteine from 2,5-norbornadione (**Scheme 2.2**).[17] Whilst an elegant synthesis, the 15 steps required is extensive, and would have to be simplified for this method to become a practical route to significant quantities of (+)-sparteine for use as a ligand in asymmetric synthesis.



Scheme 2.2

This lack of availability of (+)-sparteine is a major drawback in sparteine-mediated asymmetric processes, as processes using a chiral ligand would be more universally utilisable when the required ligand is readily available in both enantiomeric forms. In 1997, O'Brien and co-workers initiated a programme of work to address the obvious issue posed by the fact that only a single antipode of sparteine was readily available at the time.[18] Inspired by computational models reported by Beak,[19] O'Brien noted that the D-ring of sparteine is held away from the metal, with regards to the *s*-BuLi/(-)sparteine complex. It was therefore postulated that this ring could be detached without altering the chiral environment surrounding the lithium (**Figure 2.2**).

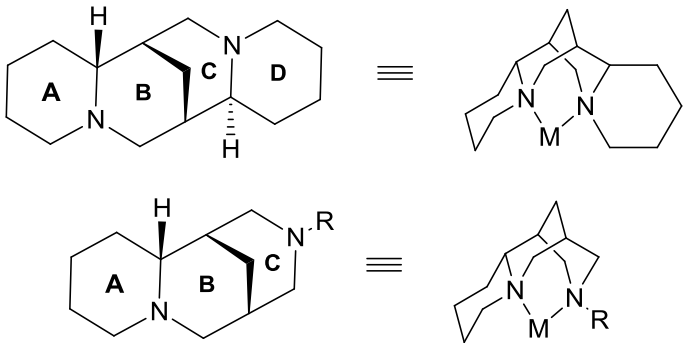
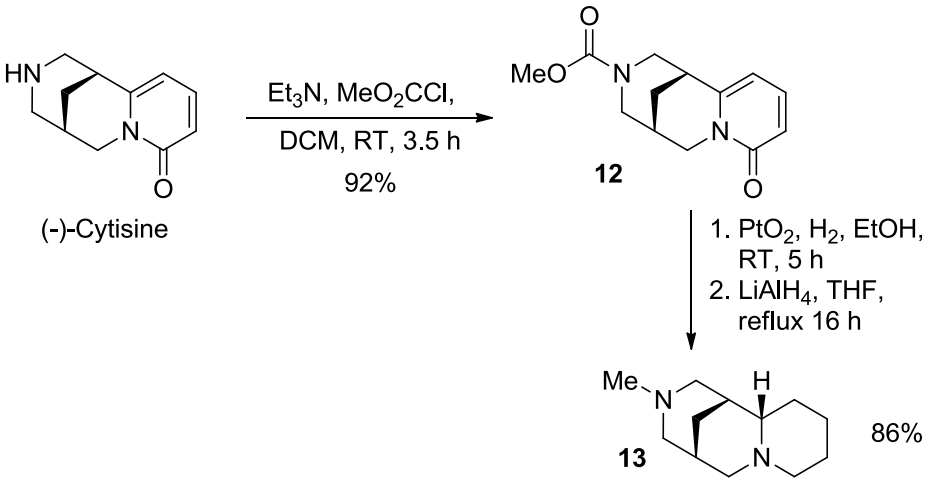


Figure 2.2

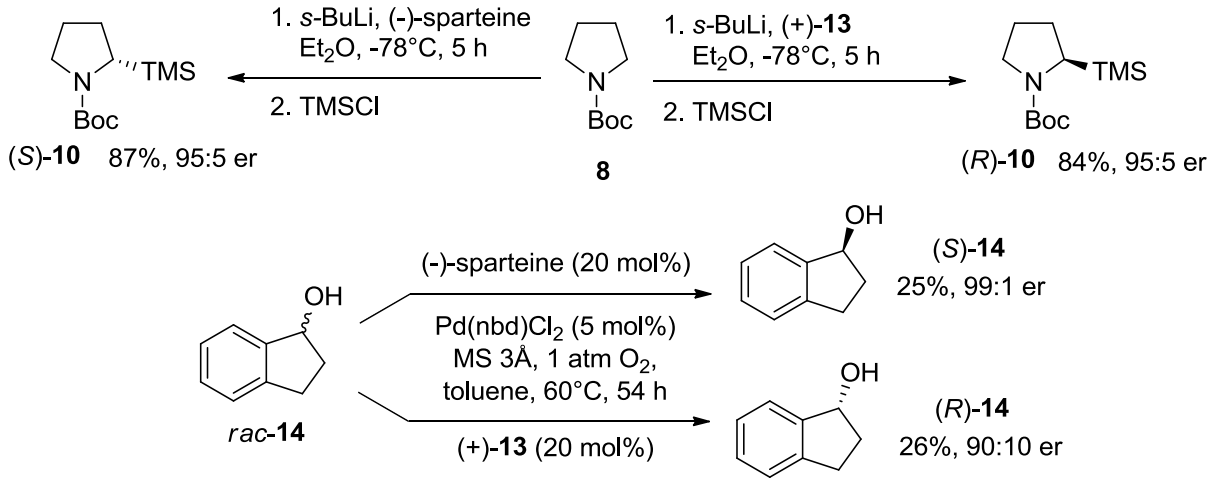
From this initial idea, O'Brien developed a route towards a (+)-sparteine surrogate with the D-ring removed.[19,20] In this regard, it was found that the ABC ring system could be efficiently prepared in three steps from (-)-cytisine (**Scheme 2.3**).



Scheme 2.3

(-)-Cytisine can be easily and reproducibly extracted from *Laburnum anagyroides* seeds on a large scale. Protection of the free nitrogen as the methyl carbamate gives pyridone **12**, which upon hydrogenation and subsequent $LiAlH_4$ reduction to remove the amide carbonyl unit and install the *N*-Me group gives the desired (+)-sparteine surrogate **13** in high yield.[20]

Having developed an efficient synthesis of a (+)-sparteine surrogate, O'Brien next investigated the use of **13** in well established (-)-sparteine chemistry to confirm the efficacy of the new ligand. A range of asymmetric transformations were selected, for which (-)-sparteine has proven to be highly effective, including Beak's deprotonation/electrophilic trapping of *N*-Boc pyrrolidine, and the Pd-catalysed oxidative kinetic resolution process described previously (**Scheme 2.4**). In all cases, the (+)-sparteine surrogate **13** gave almost equal but opposite levels of yield and enantioselectivity when compared with (-)-sparteine.[20]



Scheme 2.4

O'Brien had therefore shown that **13** was indeed a viable (+)-sparteine surrogate, and since these initial investigations this (+)-sparteine surrogate has become widespread in its use, with its effectiveness being clearly demonstrated in the fact that it is now a commercially available reagent.[21] Having stated this, with the recent decline in availability of (-)-sparteine mentioned earlier,[3] and the developed route towards the (+)-sparteine surrogate being unsuitable for the synthesis of the (-)-surrogate, the need for a sparteine mimic with both isomers being readily available is still an unmet challenge.

1.2 Bispidines and Oxabispidines as Chiral Ligands

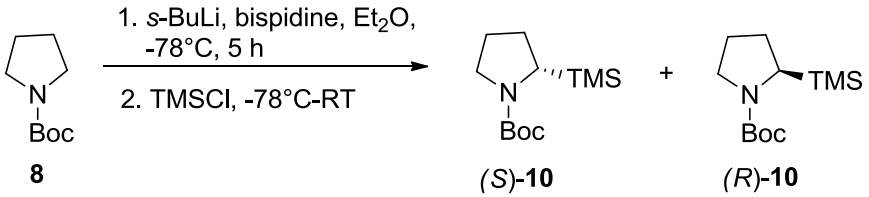
1.2.1 Application of Bispidines as Chiral Ligands

As touched upon in the previous chapter, the bispidine moiety, present in sparteine and associated scaffolds, has a rigid cage-like structure, with the 3,7-diazabicyclo[3.3.1]nonane skeleton sitting preferentially in a chair-chair conformation.[22]

Figure 2.3

In order to address the need for easily accessible sparteine alternatives of both antipodes for use as chiral ligands, extensive research and development of synthetic routes towards bispidine motifs has been carried out (*vide supra,* Chapter 1, *Section 1.3.1*). With a variety of

chiral bispidine derivatives having been accessed, their potential as chiral ligands was screened. In what is often thought of as the benchmark reaction for (-)-sparteine-mediated techniques, namely the asymmetric deprotonation of *N*-Boc pyrrolidine, it was found that, in general, for the bispidine derivatives investigated to date, their performance as chiral ligands was less effective than that of (-)-sparteine and O'Brien's (+)-sparteine surrogate. As shown in **Scheme 2.5**, **Table 2.1**, the bispidine ligands **15** and **16** with chiral *N*-substituents gave the 2-substituted pyrrolidine product with the same configuration as the (+)-sparteine surrogate **13** but with much lower enantiomeric excesses (**Entries 3** & **4**). In the case of bispidine **17** (**Entry 5**) with a chiral substituent on both nitrogens, no enantioselectivity was observed at all in the deprotonation process. The bispidine ligands with chirality embedded in the carbon framework did not fare much better (**Entries 6** & **7**). The 2-methyl substituted bispidine **18** provided the TMS substituted product with the same configuration as (-)-sparteine but with significantly lower ee (35% vs. 90%), and employment of the 2-phenyl substituted bispidine **19**, showed no reactivity at all.



Scheme 2.5

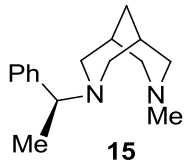
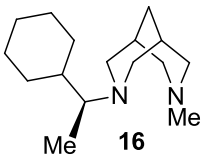
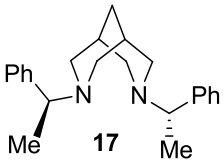
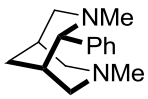
Entry	Bispidine	Yield	ee, Config.	Ref.
1	(-)-sparteine	87%	90%, (*S*)	[20]
2	(+)-sparteine surrogate	84%	90%, (*R*)	[20]
3	 **15**	5 %	75%, (*R*)	[18, 23]
4	 **16**	80%	34%, (*R*)	[18, 23]
5	 **17**	20%	0	[18, 23]
6	 **18**	45%	35%, (*S*)	[23, 24]
7	 **19**	0%	-	[23]

Table 2.1

The lower enantioselectivity observed when this collection of synthesised bispidines are utilised in asymmetric processes commonly mediated by (-)-sparteine appears to be a general trend. In addition to the deprotonation of *N*-Boc pyrrolidine, the deprotonation of *O*-alkyl

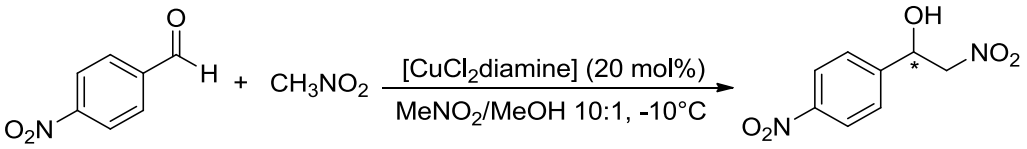
carbamates and phosphine boranes, as well as the oxidative kinetic resolution of secondary alcohols, in general, all show a decrease in the enantiomeric excess of the products when a bispidine other than (-)-sparteine or the (+)-sparteine surrogate is employed.[23]

1.2.2 Application of Oxabispdines as Chiral Ligands

More recently in the search for easily accessible and efficient alternatives to sparteine, the idea of using oxabispidines has been introduced. Oxabispidines have the same rigid chair-chair conformation as bispidines, except in their case the methylene bridge is replaced with an oxygen atom (**Figure 2.4**). With this additional heteroatom in place, it is believed that a greater variety of possibilities are available for more convenient synthetic access to an array of potential chiral ligands.

Figure 2.4

Although relatively limited in number, successful synthetic routes towards chiral oxabispidines have been reported (*vide supra*, Chapter 1, *Section 1.3.2*). Having said this, to date, only a limited number of examples of oxabispidines as ligands in asymmetric processes have been disclosed. Mixed success was achieved in the copper-catalysed enantioselective Henry reaction.[25] From the results shown in **Scheme 2.6, Table 2.2** it can be seen that utilising the 2-substituted 9-oxabispidines **20** and **21** as ligands in this process provided the desired products in similar yield and with the same configuration as (-)-sparteine, however the enantiomeric excesses achieved were significantly lower (**Entries 2** and **3**). With the tricyclic oxabispidine **22** the opposite enantioselectivity was observed in the product; this is unsurprising when it is considered that this compound possesses the same architecture as the (+)-sparteine surrogate. However, a little more surprising is that this derivative outperforms (-)-sparteine achieving an impressive ee of 95%.



Scheme 2.6

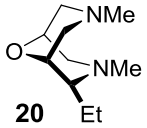
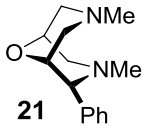
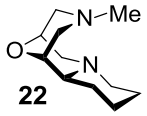
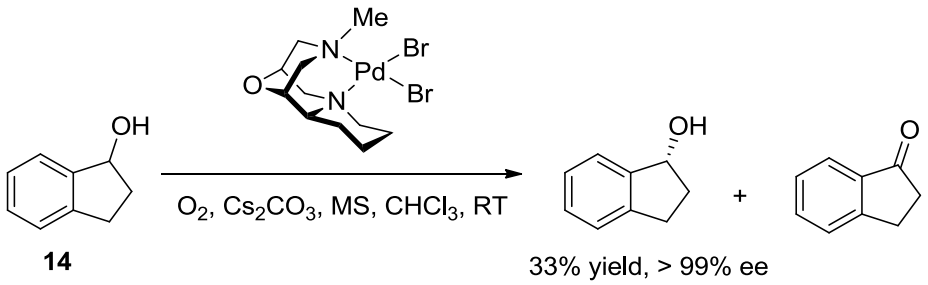
Entry	Diamine	Yield	ee, config	Ref.
1	(-)-sparteine	90%	86%, (*R*)	[10]
2	 **20**	96%	36%, (*R*)	[25]
3	 **21**	93%	56%, (*R*)	[25]
4	 **22**	95%	95%, (*S*)	[25]

Table 2.2

Tricyclic oxabispidine **22** has also proved to be extremely successful when employed as a chiral ligand in the palladium-catalysed oxidative kinetic resolution of secondary alcohols.[26] As shown in **Scheme 2.7**, the resolution of alcohol **14** provided the enantiomerically pure alcohol with the same configuration as the (+)-sparteine surrogate with an improved ee of 99% compared to 80% achieved with (+)-sparteine surrogate (*cf.* **Scheme 2.4**) and with comparable enantioselectivity to that achieved with (-)-sparteine (98% ee). Unfortunately bicyclic oxabispidines **20** and **21** performed poorly in comparison, with effectively no selectivity being observed when these derivatives where employed as the ligand.[26]



Scheme 2.7

Within the limited range of oxabispidines synthesised to date, the tricyclic derivative **22** has proven to be the most successful sparteine mimic. However, as of yet, the screening of all these diamines in a range of asymmetric processes has not been carried out. Having disclosed in Chapter 1, an efficient and flexible route towards a broad range of optically-enriched oxabispidine derivatives, it was proposed that such a collection may allow us to gain an insight into the relationship between structure and observed enantioinduction of this class of diamine ligand in asymmetric reactions. Indeed, with a programme of research in our laboratory centred around the use of chiral amine ligands within amide base chemistry, such lines of enquiry may prove highly beneficial.

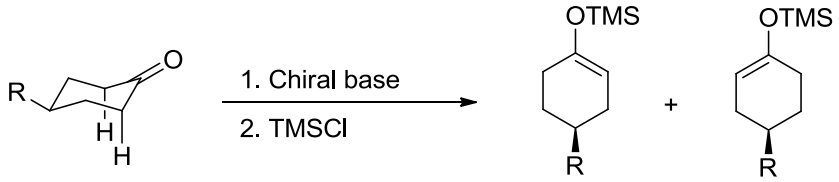
1.3 Chiral Lithium Amide Bases

In modern day organic chemistry the ongoing need for the preparation of enantiomerically-enriched compounds has led to considerable focus on the development of chiral base reagents for use in asymmetric transformations.[27] Within this area of research, lithium amide bases have become well established reagents. More specifically, these species have the ability to distinguish between two enantiotopic protons of prochiral substrates. The use of lithium amides in this regard is well known for the desymmetrisation of a range of substrates,[28] however, they are most closely associated with the asymmetric deprotonation of conformationally locked prochiral ketones.

Deprotonation of Prochiral Ketones

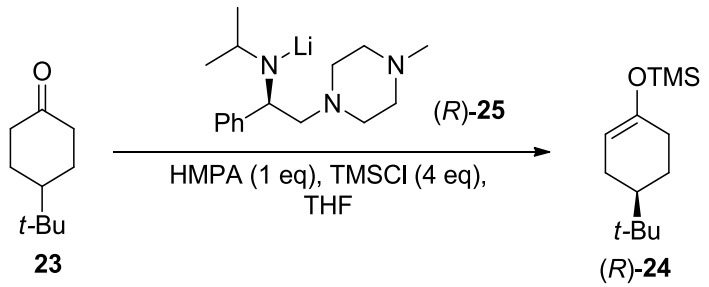
In the deprotonation of prochiral ketones, as shown in **Scheme 2.8**, it has been proposed that, due to the preference for the substituent in the 4-position to sit equatorially, the conformation of the ketone is locked, and there is a stereoelectronic preference for the removal of the α-axial protons, over the equatorial protons. When a chiral base is employed, selective removal

of one of the axial protons takes places, generating a single enantiomer of the enolate which can subsequently be trapped by an electrophile on carbon or oxygen to yield the enantioenriched product.



Scheme 2.8

The seminal work in this field of asymmetric synthesis was carried out by Koga and Simpkins (independently), with their initial findings being published in 1986.[29] Koga investigated lithium amides of the type shown in **Scheme 2.9**, which incorporate the potential to form a 5-membered chelate structure. It is thought enantioinduction occurs as result of the *i*-Pr substituent's preference to sit *trans* to the bulky group on the stereogenic centre fixing the orientation of the nitrogen lone pair. When these internally-ligating bases were employed in the deprotonation of 4-*tert*-butylcyclohexanone **23**, excellent enantioselectivities were achieved.[29a] As shown in **Scheme 2.9**, **Table 2.3** these early results identified that the best selectivity could be achieved with base (*R*)-**25** in a coordinating solvent, employing HMPA as an additive at low temperatures. The enantioenriched silyl enol ether was produced with an impressive enantiomeric excess of 97% at -105°C (**Entry 1**). Unfortunately, carrying out the same reaction at a more practically convenient temperature of -78°C led to a fall in the selectivity observed (**Entry 2**).



Scheme 2.9

Entry	Temperature	Yield	ee
1	-105 °C	51%	97%
2	-78°C	87%	84%

Table 2.3

With regards to Simpkins' initial findings,[29b] no additional chelating heteroatom was present in the chiral amine, thus these base systems represented simpler structures, as compared to those developed by Koga. A selection of these structures is displayed in **Figure 2.5**.

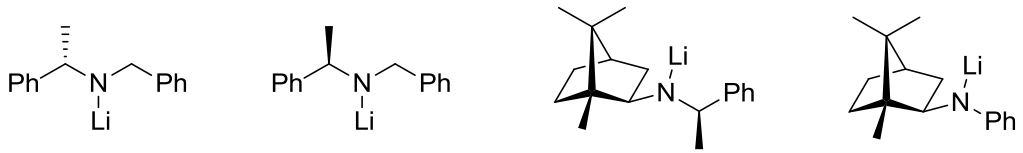
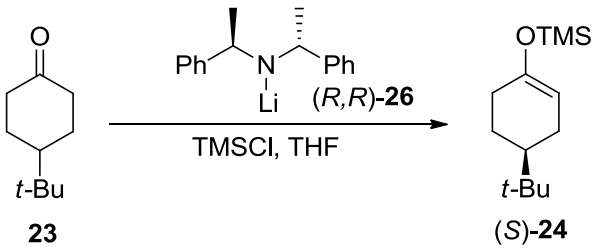


Figure 2.5

In the deprotonation of 4-*tert*-butylcyclohexanone **23** Simpkins found that lithium amide base (*R*,*R*)-**26** delivered the best results.[30] When employing this C_2-symmetric base in the presence of TMSCl at -90°C, a good yield of 66% and an enantioselectivity of 88% ee was achieved (**Scheme 2.10**, **Table 2.4**, **Entry 1**). However, again, as seen in Koga's results, increasing the temperature of the reaction led to a decrease in selectivity.



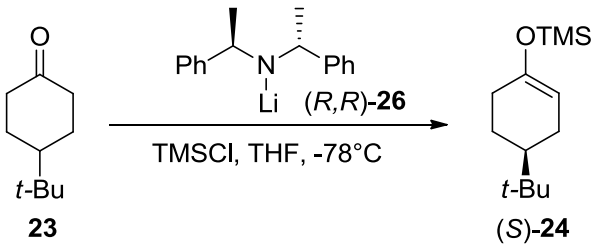
23 (*S*)-**24**

Scheme 2.10

Entry	Temperature	Yield	ee
1	-90 °C	66%	88%
2	-78°C	73%	69%

Table 2.4

Since this early work, the asymmetric deprotonation of this conformationally-locked pro-chiral ketone has emerged as the benchmark transformation in which the enantioselectivity of new base systems is determined. Embarking upon intensive optimisation studies of this asymmetric process both Koga and Simpkins investigated the role of additives, and found that salt additives could play a crucial role in achieving high selectivities. When performing the lithium amide-mediated deprotonations described in **Scheme 2.10**, Koga[29a] and Simpkins[30] adopted Corey's internal quench (IQ) protocol.[31] This procedure involves adding a solution of the ketone substrate to a pre-formed solution of the lithium amide base and electrophile. Higher enantioselectivities were achieved with this IQ protocol compared to the complementary external quench (EQ) procedure, in which the electrophile is added to a solution of lithium enolate (**Scheme 2.11**, **Table 2.5**). This enhanced selectivity when employing the IQ protocol has been attributed to the *in situ* generation of LiCl as the reaction proceeds, either *via* reaction of TMSCl with a lithium amide or electrophilic trapping of TMSCl by a lithium enolate. Simpkins confirmed the beneficial effect of LiCl by demonstrating that an improved selectivity of 83% could be achieved using the EQ protocol by addition of LiCl to the reaction mixture (**Table 2.5**, **Entry 3**) compared to EQ without LiCl (**Entry 2**).[32] Subsequent work by Koga went on to use NMR techniques to elucidate the structure of the lithium amide species present under each of the conditions described in **Scheme 2.11**, **Table 2.5**.[33]



Scheme 2.11

Entry	Protocol	Equivalents of LiCl	ee
1	IQ	-	69%
2	EQ	-	23%
3	EQ	0.5	83%

Table 2.5

Since the initial reports in 1986,[29] extensive optimisation studies have been carried out, not only into the reaction conditions, briefly touched upon above, but also on the structural development of the base systems. A wide structural range of chiral lithium amides have been prepared by a number of researchers[34] (**Figure 2.6**). Having stated this, the development of these species, along with the broadening of the substrate scope applicable to the asymmetric deprotonation process will not be discussed in this report. For further reading on this topic several articles are available.[35,36]

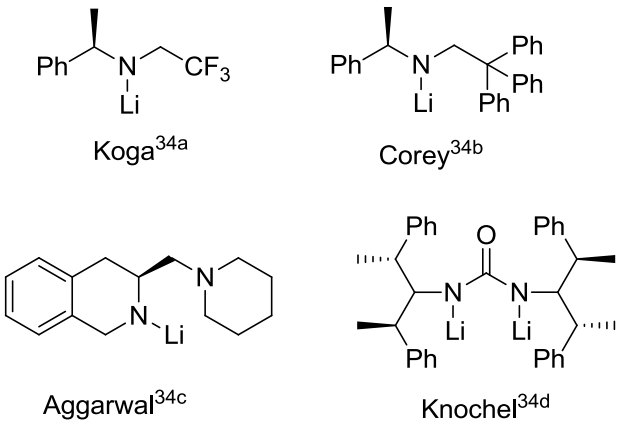


Figure 2.6

1.4 Chiral Magnesium Amide Bases

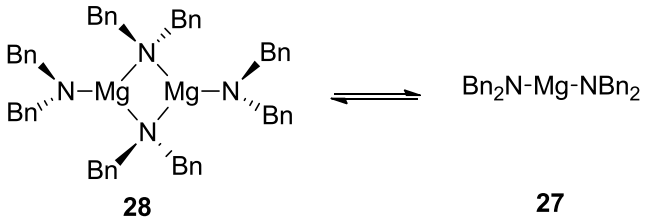
As highlighted in the previous section, the use of lithium amide reagents in asymmetric deprotonations has been widely demonstrated. However, there are several issues which have imposed limitations to their applicability. These issues include the need for reactions to be carried out at low temperatures (generally -78°C or lower), the complex structural behaviour of the lithium amide in solution, and the need for relatively complex amine structures to achieve high selectivity in asymmetric doprotonation processes. For these reasons, the potential of chiral magnesium bisamides has been explored, as it was believed that these reagents may possess several advantages over lithium amides.

Thermal Stability

As mentioned previously, lithium amides require reactions to be carried out at low temperatures, generally between -78°C and -100°C. This is due, not only to their poor thermal stability, but also as a consequence of their high reactivity. On the other hand, their magnesium counterparts are more stable and less reactive.[37] This decreased reactivity is a desirable property, as it could allow for high enantioselectivities to be achieved at temperatures higher than -78°C, which is highly practically and economically attractive.

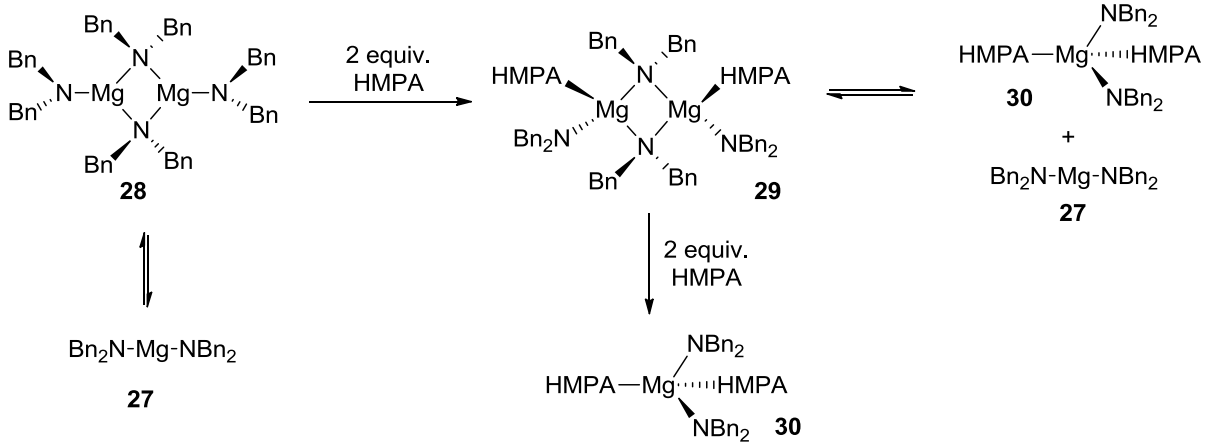
Solution Behaviour

Without the presence of coordinating solvents, lithium amides exist as a complex mixture of oligomeric species. When a coordinating solvent is introduced, however, these complexes can be broken down into much simpler monomers and dimers. Lewis basic additives, such as HMPA, perform a similar role, and are often necessary. It has been reported that, in order to obtain high enantioselectivity in any given asymmetric process, a specific aggregation state is essential.[33] However, it is often difficult to attain such species in a reproducible fashion with lithium amides. In contrast, magnesium amides' solution aggregation states have been shown to be mainly monomeric and dimeric.[38] For example in non-coordinating toluene, bis(dibenzylamido)magnesium equilibriates between the monomer **27** and dimer **28** exclusively (**Scheme 2.12**).



Scheme 2.12

This simple solution behaviour means that the aggregation state of magnesium amides can be controlled and, in turn, reproducible reaction conditions can be achieved. The introduction of HMPA to a solution of bis(dibenzylamido)magnesium illustrates this predictability (**Scheme 2.13**). The addition of two equivalents of HMPA to **28** produces the bis-solvated dimer, which is in equilibrium with the solvated (**30**) and non-solvated (**27**) monomers. A further two equivalents of the Lewis basic additive results in deaggreagation to produce **30** exclusively.[38]



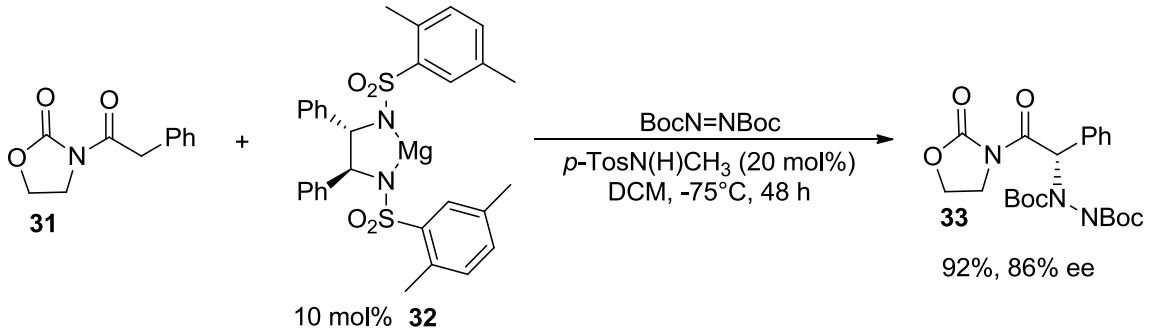
Scheme 2.13

Divalent Nature of Magnesium

With regard to magnesium's divalency, magnesium amides possess yet another advantage over their lithium equivalents, in that both homo- and heteroleptic complexes can be utilised. This allows the synthesis of reagents with both a reactive ligand and a spectator ligand. More specifically with regards to asymmetric deprotonations, this could constitute a chiral ligand to carry out the deprotonation to produce the enatioenriched Mg-enolate, and a spectator ligand which could serve to influence subsequent reactions.

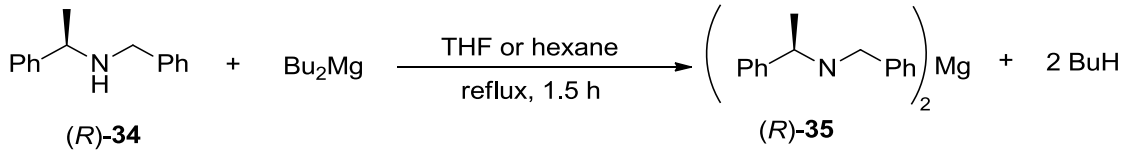
1.4.1 Magnesium Bisamides

The first report of the use of a chiral magnesium bisamide was in 1997 from Evans and Nelson.[39] A catalytic amount of chiral magnesium bis(sulfonamide) **32** was utilised in an asymmetric amination process of substrate **31** to provide the desired product in enantiomerically enriched form.



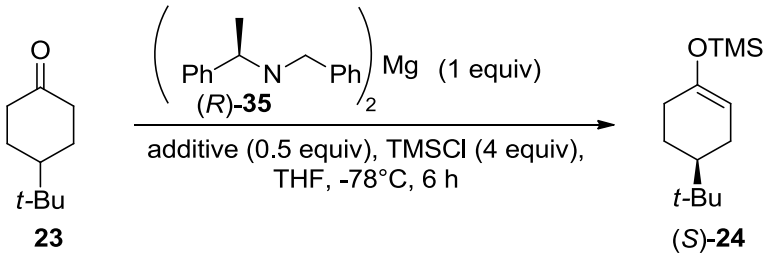
Scheme 2.14

After this initial publication, the research field of chiral magnesium bases remained relatively untouched until 2000, when Kerr and Henderson developed novel magnesium bisamide (*R*)-**35** (**Scheme 2.15**) for the asymmetric deprotonation of prochiral ketones.[40] The base in question is simply prepared by reacting two equivalents of commercially available chiral amine **34** with dibutylmagnesium in refluxing THF or hexane.



Scheme 2.15

Applying magnesium bisamide (*R*)-**35** to the benchmark asymmetric deprotonation of 4-*tert*-butylcyclohexanone, the corresponding enantioenriched silyl enol ether was obtained with high conversion and impressive selectivity (**Scheme 2.16, Table 2.6**), especially considering the simplicity of the amide base unit. During the optimisation of this reaction, it was found that the highly toxic Lewis basic additive HMPA (traditionally used in the corresponding lithium amide mediated process) could be replaced with DMPU without any detrimental effect to the enantioselectivity being observed.[40] These initial findings elegantly demonstrate that chiral magnesium bisamides are able to efficiently mediate asymmetric deprotonations.

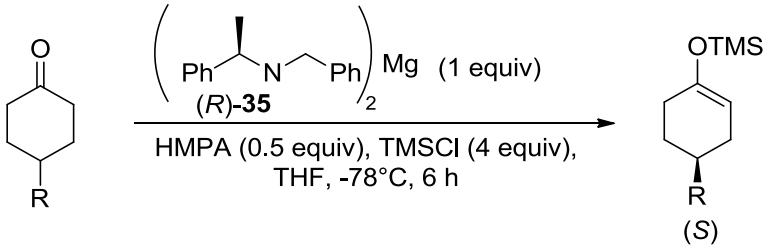


Scheme 2.16

Entry	Additive	Conversion	(*S*):(*R*)
1	HMPA	82%	91:9
2	DMPU	89%	90:10

Table 2.6

As outlined in **Table 2.7**, screening *(R)*-**35** in the deprotonation of a range of 4-substituted cyclohexanones illustrated the impressive selectivities that can be achieved with this relatively simple base system. In particular, the deprotonation of 4-*iso*-propylcyclohexanone provided the corresponding silyl enol ether with an exceptional er of 95:5 (**Entry 4**).



Scheme 2.17

Entry	R	Conversion	Yield	(*S*):(*R*)
1	*t*-Bu	82%	64%	91:9
2	Ph	79%	48%	87:13
3	Me	81%	68%	91:9
4	*i*-Pr	77%	39%	95:5

Table 2.7

With a robust asymmetric deprotonation protocol employing magnesium bisamide (*R*)-**35** in place, Kerr envisaged that if a library of alternative bisamides were prepared and screened in the benchmark deprotonation, it would be possible to establish any patterns in the relationship between the structure and efficiency of each base, and thus higher enantioselectivities could be achieved. Early investigations into the amide ligand structure focused on altering both the achiral sidearm and chiral sidearm in turn (**Figure 2.7**).[41] Whilst substituting the benzyl sidearm of (*R*)-**35** for various alkyl or aryl substituents did not provide any improvement over the original structure, elaboration of the chiral sidearm on the other hand, did show enhanced enantioselectivity in the benchmark deprotonation (specifically on moving from R' = Me to R' = Et). Having stated this, the original bisamide (*R*)-**35** was still considered the most efficient, with the correct balance of conversion and selectivity being achieved.[41]

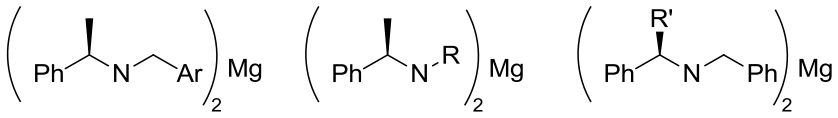
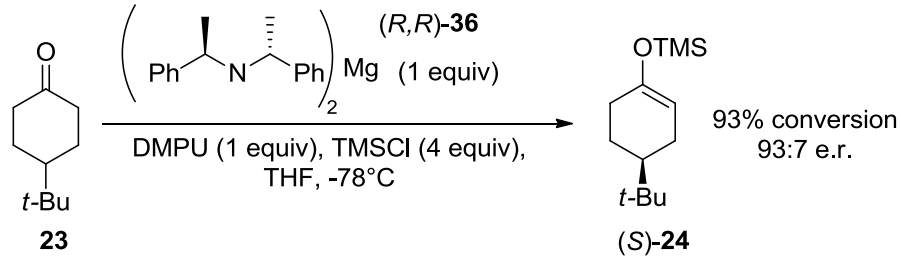


Figure 2.7

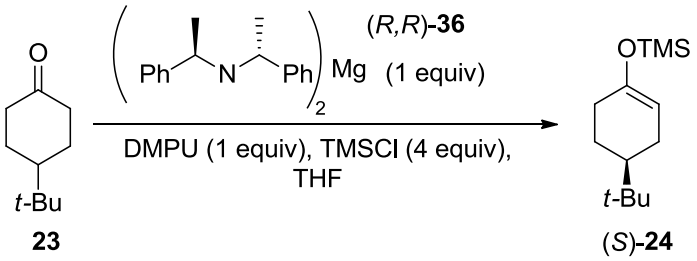
Further research into alternative magnesium bisamide structural motifs, led to the preparation of C_2-symmetric bisamide (*R,R*)-**36** (**Scheme 2.18**).[42] It was believed that, when employed in the desymmetrisation of 4-*tert*-butylcyclohexanone, excellent levels of enantioinduction would be achieved based on the relative success of its lithium counterpart.[30] This was indeed the case with both a high conversion of 93% and an outstanding enatiomeric ratio of 93:7 being observed.



Scheme 2.18

The greatest advantage of this novel bisamide is the high levels of selectivity and conversion possible at more elevated temperatures. As outlined in **Scheme 2.19**, **Table 2.8**, Kerr and co-

workers found that even at the comparatively high temperature of 0°C, a significant drop in selectivity was not observed. Perhaps most impressive is the fact that to achieve an er similar to the 86:14 obtained at 0°C with (*R*,*R*)-**36** would require a reaction temperature of -78°C if the corresponding lithium amide (*R*,*R*)-**26** was applied.[42,30]

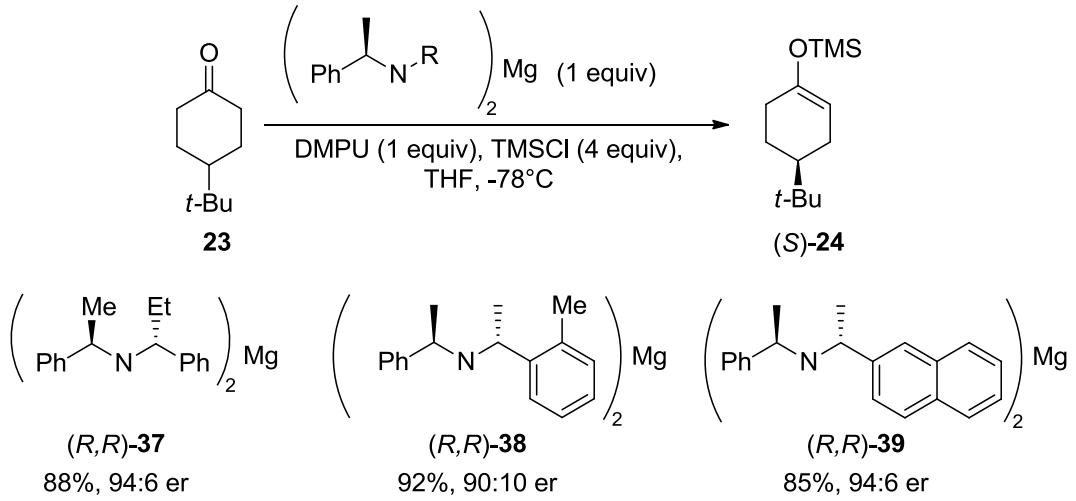


Scheme 2.19

Entry	Temperature	Conversion	Yield	(*S*):(*R*)
1	-78°C	96%	75%	91:9
2	-20°C	90%	55%	90:10
3	0°C	93%	66%	86:14
4	25°C	89%	66%	75:25

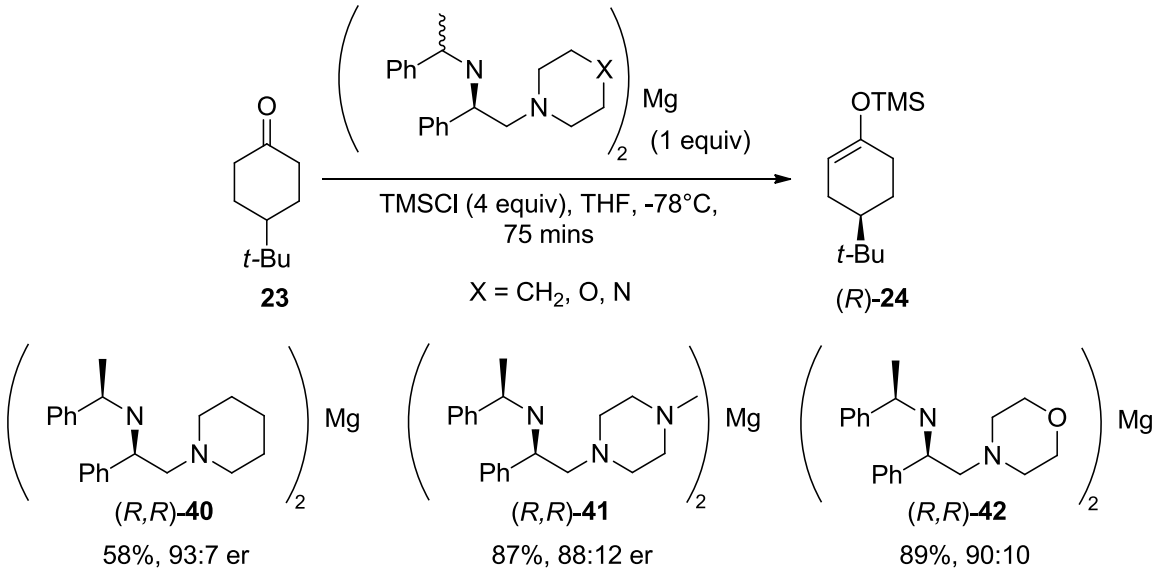
Table 2.8

Based on the success of the simple C_2-symmetric bisamide (*R*,*R*)-**36**, a collection of novel *pseudo*-C_2-symmetric magnesium bisamides were synthesised and evaluated as potential chiral bases in the benchmark desymmetrisation reaction (**Scheme 2.20**).[42a,42d] Overall, it was observed that remarkable selectivities and conversions were achieved, with selected examples being depicted below.



Scheme 2.20

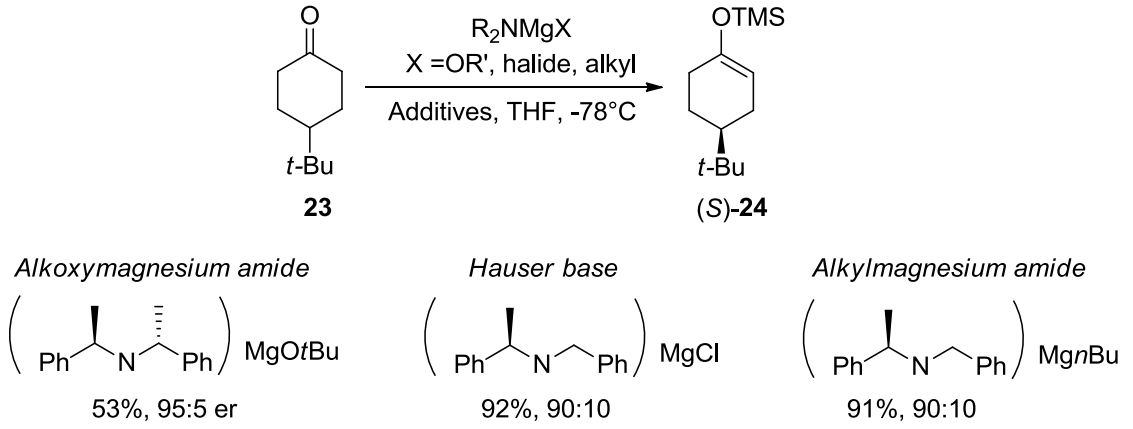
To broaden the range of magnesium bisamides further, more significant structural development was undertaken with the preparation of a selection of chelating diamines, similar to those developed by Koga within lithium amide processes.[29a] Such species, which are able to form a stable 5-membered chelate with magnesium were synthesised and applied in the deprotonation process.[43] For the benchmark deprotonation of 4-*tert*-butylcyclohexanone, whilst the conversions were variable, ranging from 58-89%, the enantioselectivities achieved were excellent with ers as high as 93:7 being obtained in the case of base (*R,R*)-**40**. A significant advantage these chelating derivatives have over the alternative bisamides described is that the high selectivities observed were achieved in the absence of a Lewis basic additive.[43]



Scheme 2.21

1.4.2 Heteroleptic Magnesium Amides

The magnesium bases discussed so far have all been homoleptic derivatives, bearing two identical amide ligands. However, as mentioned previously, a potential advantage of magnesium over lithium in these types of reagents, is the divalent nature of the former which can allow access to heteroleptic complexes. Indeed, the development of bases containing a reactive anion and a spectator anion would mean only half the quantity of chiral amine would be required. To this end, a variety of heteroleptic base systems were developed within the Kerr laboratory, incorporating a wide selection of spectator ligands, some of the most effective being depicted in **Scheme 2.22**. As shown, under individually optimised conditions, with the correct combination of additives, alkoxymagnesium amides,[42b] Hauser bases (which incorporate a halide spectator anion),[42b,44] and alkylmagnesium amides[42b,45] allowed the deprotonation of 4-*tert*-butylcyclohexanone to proceed with high levels of enantioselectivity.



Scheme 2.22

In addition to the relative simple heteroleptic bases describes above, slightly more elaborate systems such as aryloxymagnesium amides[45] and aminonaphthol-derived bases[46] have also proven to be effective in asymmetric deprotonation protocols.

Substrate Scope with Magnesium Amide Bases

Having established a wide repertoire of highly effective magnesium amide base systems utilising 4-*tert*-butylcycloxanone as the benchmark substrate, expansion of the substrate scope with these emerging base systems was also undertaken. In addition to a variety of groups in the 4-position of cyclohexanone,[40] a range of 2,6-disubstituted cyclohexanones,[47] bridged-bicyclic ketone substrates,[42d] and various substituted cyclobutanones[48] have all been successfully desymmetrised under magnesium amide-mediated conditions. As such, access to a wide variety of enantiomerically enriched silyl enol ether products has been successfully achieved.

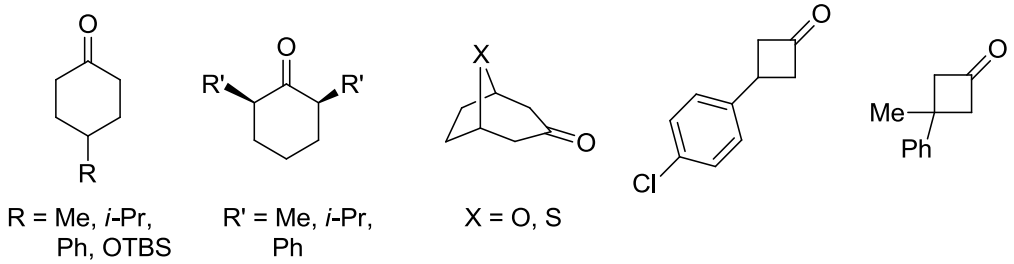
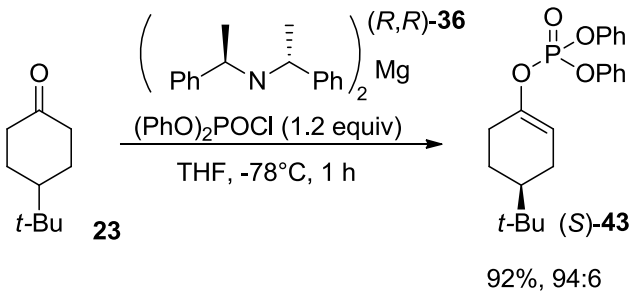


Figure 2.8

Alternative Electrophile – Preparation of Enol Phosphate Species

In addition to expanding the collection of magnesium amide bases available and broadening the scope of substrates to which these bases can be applied, more recent work within the Kerr group has focused on the investigation of alternative electrophiles. For the most part, efforts have centred on the generation of enantio-enriched silyl enol ethers to date, however, in recent years, the development of procedures to allow access to enol phosphate derivatives in an asymmetric fashion has been ongoing.[49] The ability of such products to participate in transition metal-catalysed cross-coupling reactions[50] means that access to enantiomerically-enriched enol phosphate species would be highly valuable. With this in mind and as depicted in **Scheme 2.23**, when utilising diphenylphosphoryl chloride as the electrophile in combination with C_2-symmetric base (*R*,*R*)-**36**, Kerr and co-workers showed that the enantio-enriched product **43** can be prepared with extremely high levels of efficiency and selectivity.[42d]



Scheme 2.23

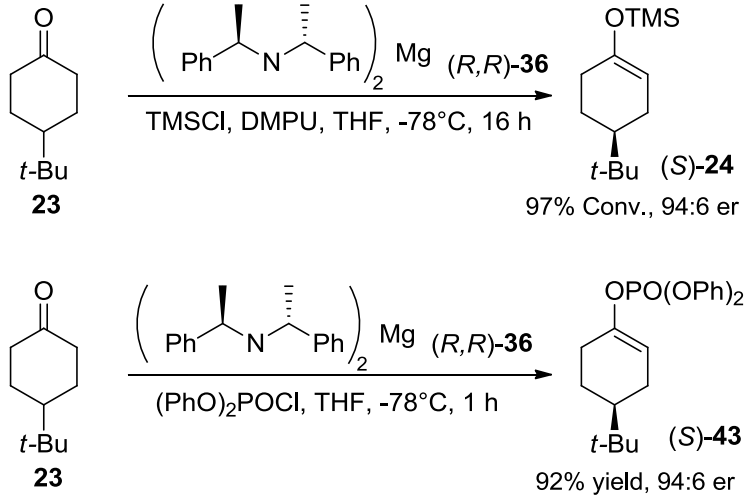
Research is currently on-going into extending the substrate scope of this process, in addition to the application of the enantiomerically enriched enol phosphate products in cross-coupling chemistry.[49]

As demonstrated within this introductory section, chiral amines, in general, are extremely important as ligands within asymmetric processes. Initially, this discussion highlighted the effectiveness of (-)-sparteine and associated bispidine, and oxabispidine derivatives as diamine ligands within metal-mediated asymmetric reactions. The latter portion of this introduction focused on the use of chiral amines in the preparation of important lithium and magnesium amide base species, which have displayed excellent reactivity in asymmetric deprotonation chemistry. Indeed, magnesium-derived bases have evolved as the most useful species for achieving high levels of enanatioselectivity in such processes at practically

convenient temperatures. As such, this thesis reports our most recent endeavours to combine these two streams of amine-centred chemistry.

2. Proposed Work

As delineated in the previous section, over the past decade studies within our laboratory have focused on the development and use of magnesium amide bases as realistic and more efficient alternatives to lithium amide bases for the asymmetric deprotonation of conformationally locked pro-chiral ketones. More specifically, it has been demonstrated that bases such as the C_2-symmetric derivative (*R,R*)-**36**, depicted in **Scheme 2.24**, can asymmetrically deprotonate 4-*tert*-butylcyclohexanone, and provide products with high enantioselectivity upon trapping the magnesium enolate with silicon- and phosphorus-based electrophiles.[42d, 49]



Scheme 2.24

As an extension of this area of research, we wish to evaluate the novel oxabispidine scaffolds, disclosed previously in Chapter 1, as potential chiral amines in this process as it is believed that oxabispidines possess key structural features that support their use as potentially very effective ligands within such Mg-centred reagents. We believe that bis-secondary amines of type **44** would allow the preparation of structurally rigid magnesium bisamides, and the use of either combination of secondary/tertiary oxabispidine dervatives (**45** and **46**) will lead to the generation of chelating amino Mg-amides such as **48** and **49** (**Figure 2.9**). Indeed, chelating base systems have proven to be highly effective within this area of research previously (*vide supra*).[43]

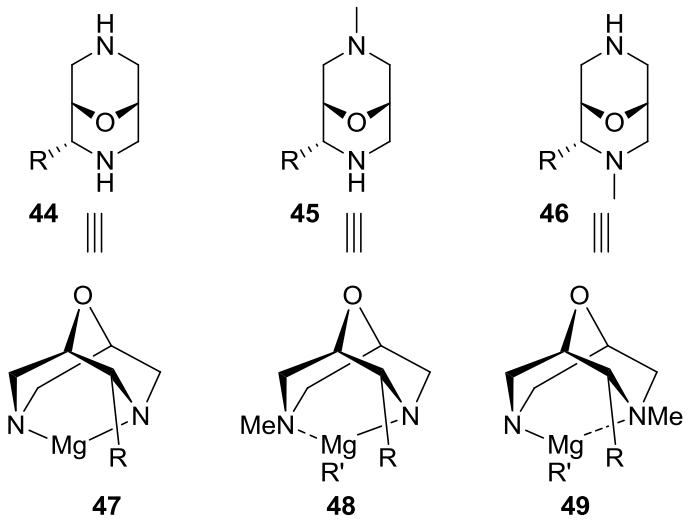
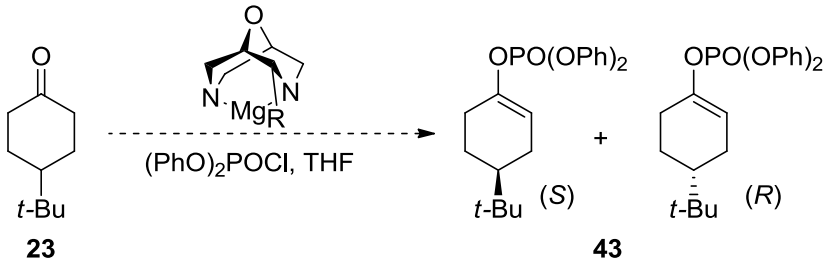


Figure 2.9

As mentioned earlier, a current focus within our laboratory in the arena of magnesium-mediated deprotonation reactions is the generation of enol phosphate derivatives. Not only are such species more stable than their silicon-based counterparts, which will allow for more facile evaluation of the effectiveness of the novel base systems studied, but they are also synthetically useful in their own right, with potential applications within cross-coupling methodology.[50] As such, the novel oxabispidine-derived magnesium amide bases will be screened in combination with diphenylphosphoryl chloride as the electrophile in the deprotonation of 4-*tert*-butylcyclohexanone to generate enol phosphate **43** (**Scheme 2.25**).

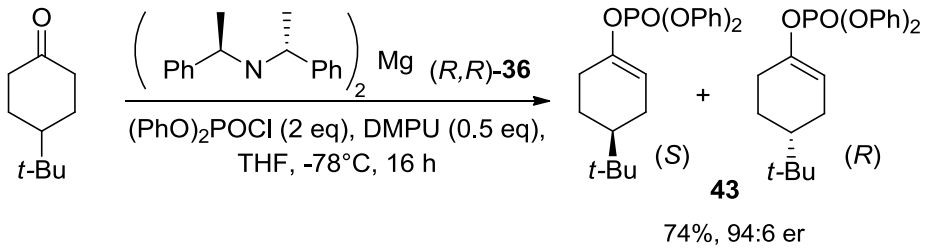


Scheme 2.25

3. Results and Discussion

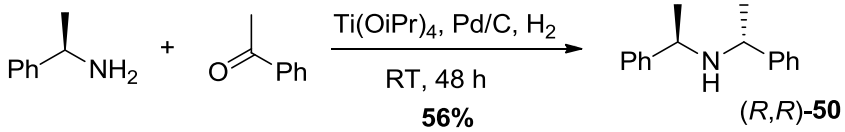
3.1 Benchmark Deprotonations using C_2-symmetric base (R,R)-36

Although the ultimate goal of this project is the utilisation of oxabispidines as ligands in magnesium-mediated asymmetric deprotonation reactions of conformationally-locked pro-chiral ketones, it was first necessary to perform benchmark reactions to ensure that the requisite practical techniques required for carrying out such air- and moisture-sensitive reactions had been mastered successfully. The benchmark reaction referred to was the deprotonation of 4-*tert*-butylcyclohexanone using the magnesium bisamide derived from C_2-symmetric amine **50**, with subsequent trapping by an electrophile, in this case diphenylphosphoryl chloride (**Scheme 2.26**).[42d] In this experiment, utilising the conditions depicted in **Scheme 2.26** a 74% yield of the desired compound has been achieved previously with an excellent 94:6 enantiomeric ratio.[42d]



Scheme 2.26

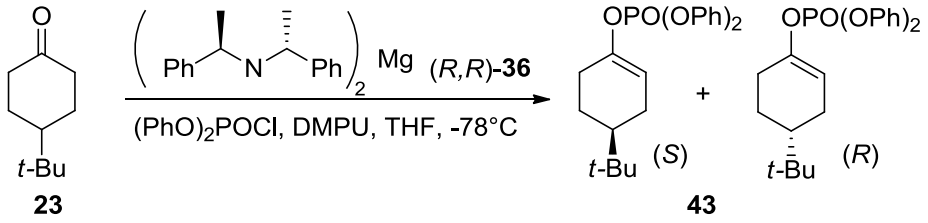
Before this benchmark reaction could be carried out, amine **50** had to be synthesised. Employing a reductive amination procedure developed by Alexakis,[51] the desired C_2-symmetric amine was prepared in a good 56% yield.



Scheme 2.27

With a significant quantity of the requisite amine prepared, the first attempt of the asymmetric deprotonation of the benchmark substrate was attempted (**Scheme 2.28**, **Table 2.9**, **Entry 1**). Carrying out the reaction in duplicate, and after initial base formation in refluxing THF, the reaction was cooled to -78°C and an internal quench procedure adopted.

After work-up, the desired product was obtained in good yields and impressive enantiomeric ratios. Performing this duplicate procedure a second time to ensure reproducibility yielded similarly excellent enantioselectivities and improved yields (**Scheme 2.28**, **Table 2.9**, **Entry 2**).



Scheme 2.28

Entry	Reaction Scale	Yield	e.r.
1	1 mmol	63%	95:5
	1 mmol	76%	92:8
2	1 mmol	80%	95:5
	1 mmol	85%	96:4

Table 2.9

3.2 Formation of Metal Amide Bases with Oxabispidine 51

Having ensured that the practicalities of the magnesium chemistry had been grasped, the next step was to employ our novel oxabispidine scaffolds in this process. For initial investigations into the use of such scaffolds, we chose to focus our attention on the preparation and use of phenyl-substituted oxabispidine **51** (**Figure 2.10**), as it contains the simple benzylic amine moiety present in successful base systems, such as (*R*)-**35** and (*R*,*R*)-**36**, used previously.[40-42]

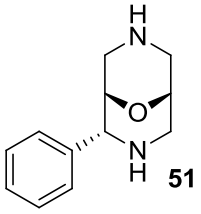
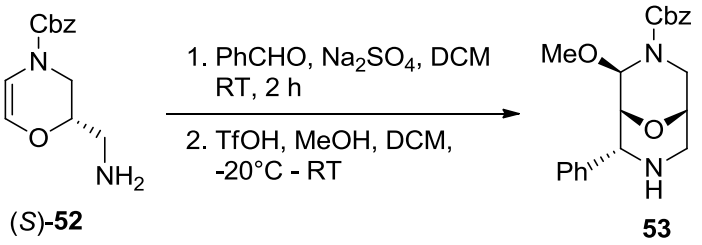


Figure 2.10

In this regard, oxabispidine **51** first had to be prepared. On a relatively large scale, under the triflic acid promoted conditions, oxazine (*S*)-**52** (the preparation of which was disclosed in Chapter 1) was converted to phenyl-oxabispidine **53** in good yield (**Scheme 2.29**).

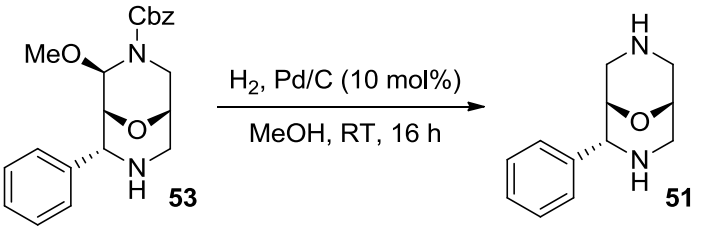


Scheme 2.29

Entry	Reaction Scale	Yield
1	44.3 mmol	54%
2	95.1 mmol	57%

Table 2.10

Subsequent cleavage of the Cbz-protecting group and the methoxy-substituent under the previously developed hydrogenation conditions led to the desired bis-secondary amine **51** in high yields (**Scheme 2.30**, **Table 2.11**).



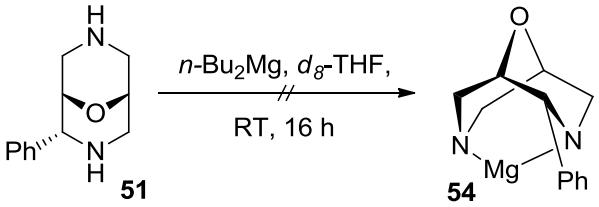
Scheme 2.30

Entry	Reaction Scale	Yield
1	5 mmol	73%
2	27 mmol	89%

Table 2.11

*3.2.1 Formation of a Magnesium Bisamide Derived from **51***

With reasonable quantities of **51** in hand, attention was turned to the formation of an oxabispidine-derived magnesium bisamide. Prior to the utilisation of such a species in the benchmark asymmetric deprotonation of 4-*tert*-butylcyclohexanone, it was first vital to confirm the formation of the desired magnesium bisamide, in order to be sure that the results of subsequent reactions were indicative of the performance of the base within the deprotonation process and not as a result of the incomplete base formation. With this in mind, the decision was taken to carry out the base formation step and to follow the reaction by ^{1}H NMR analysis to ensure the desired Mg-amide base was indeed forming before attempting the deprotonation step (**Scheme 2.31**). As such, and after removal of the heptanes from the 1M *n*-Bu_2Mg, a solution of **51** (which had previously been dried in a Kügelrhor oven at 120°C under full vacuum for 16 hours) in d_8-THF was added. Unexpectedly, a small amount of solid began to precipitate out of solution as the amine was dissolved. Postulating that perhaps there was a solubility issue with oxabispidine **51**, additional d_8-THF was added and the resulting suspension was added to the *n*-Bu_2Mg. After one hour stirring at room temperature, a sample was taken and the ^{1}H NMR spectrum showed that the broad singlet corresponding to the NH's still remained. Allowing a prolonged reaction time (16 h) resulted in no significant changes to the ^{1}H NMR spectrum; the NH peak still remained, despite no peaks corresponding to dibutylmagnesium species being observed.



Scheme 2.31

These observations suggested that the dibutylmagnesium was reacting with another species initially, meaning there was insufficient reagent to react with amine **51**. Bearing this in mind, the precipitate observed was investigated further. Taking another sample of the stock of bis-secondary oxabispidine **51** and precipitating more of the white solid observed in the above reaction, ^{1}H NMR analysis showed no NH signals were present, suggesting that, which was believed to be the free bis-secondary amine, was in fact a salt. Indeed, crystallisation of a sample of this white solid, allowed an X-ray structure to be obtained, which confirmed that it

was in fact a mixture of two independent HCl salts **55a** and **55b** (**Figure 2.11**; see Appendix for full details).

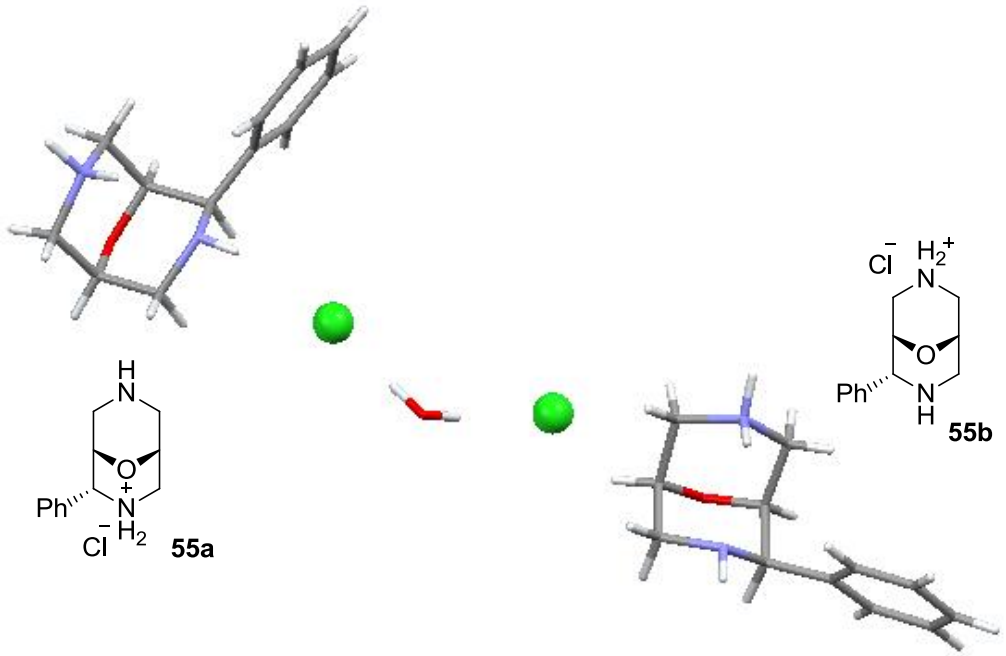
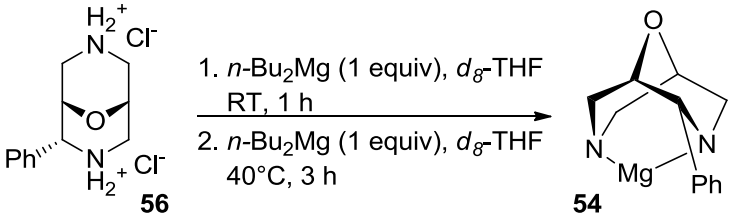


Figure 2.11: X-ray crystal structure of precipitate. Depicts a mixture of mono-HCl salts **55a** and **55b** in addition to a single water molecule.

This result explains why, when following the base formation by ^{1}H NMR analysis, complete consumption of *n*-Bu_2Mg was observed, along with an NH signal still being present. If a mixture of the bis-free amine **51** and the HCl salts **55a** and **55b** was present, with only 1 equivalent of *n*-Bu_2Mg present there was not sufficient magnesium reagent to form the free amine **51** and perform the subsequent deprotonation reaction to form the desired bisamide base **54**. Taking this into account, the remaining amine **51** was washed with 1M NaOH solution and again dried under vacuum. When repeating the attempted base formation, again a small amount of solid was observed in d_8-THF. With this result, it became apparent that the best way to ensure that the composition of the oxabispidine **51** being added to the reaction is known with confidence, the bis-HCl salt should be deliberately prepared. As such, 2 equivalents of *n*-Bu_2Mg would then be required for the formation of magnesium amide **54** in future reactions. In this regard, oxabispidine **51** was treated with concentrated hydrochloric acid to generate the bis-secondary HCl salt **56**. With this salt in hand, we again attempted to follow the base formation by ^{1}H NMR analysis. It was envisaged that upon addition of 1 equivalent of *n*-Bu_2Mg the ^{1}H NMR would show the appearance of an NH signal, indicating

the free amine had been generated, and then upon addition of a second equivalent of the organometallic reagent, this NH signal would disappear, which would be indicative of the magnesium bisamide's formation. Pleasingly, upon the addition of 1 equivalent of *n*Bu_2Mg an NH signal appeared in the ^{1}H NMR after 30 min. After a second equivalent was added, no NH signal was present in the ^{1}H NMR after 16 hours, and all the signals had shifted upfield slightly, indicating that the magnesium bisamide **54** had, indeed, been formed. Unfortunately, despite several attempts, the above result was not reproducible thus alternative evidence for the complete formation of magnesium bisamide **54** was sought.



Scheme 2.32

At this stage, and for further confirmation of the successful preparation of species **54**, it was decided that the best way to evaluate the optimal base formation conditions was to employ an electrophile to quench any of the bisamide that had formed. Methyl iodide was selected as the most appropriate electrophile, as the resulting products would allow comparison with previously prepared compounds within this overall programme of work, namely oxabispidines **57**-**59** (**Figure 2.12**). If the bisamide was fully forming, quenching out with MeI would provide **57** only. On the other hand, if full conversion to the bisamide was not occurring under our selected conditions, **58** and **59** may also be recovered.

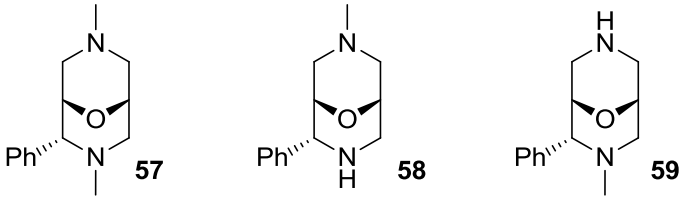
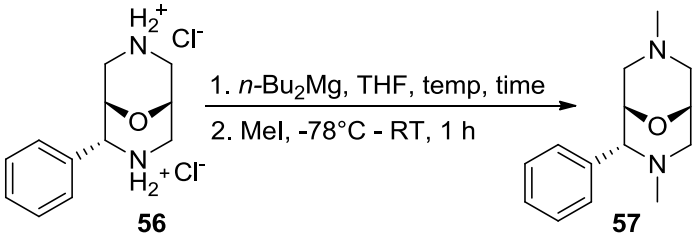


Figure 2.12

In this regard, oxabispidine salt **56** was treated with 2 equivalents of *n*Bu_2Mg at a range of reaction temperatures for varying amounts of time, after which the reaction mixture was cooled to -78°C and methyl iodide was added before warming to room temperature and stirring for 1 hour (**Scheme 2.33**, **Table 2.12**). Utilising the base forming conditions

employed as standard for our research team, namely refluxing in THF for 1.5 hours resulted in sole recovery of the dimethylated product **57** in good yield. This yield was improved upon with the employment of distilled MeI (**Entry 2**). Following these initial results a lower temperature protocol was considered. In fact, previous work centred on the use of chelating-type amines has shown that in some instances, bases can form at much lower temperatures. Indeed, with regards to the oxabispidine scaffold, it can be easily envisaged that the deprotonation of the second NH would be much more facile, given that it would be an intramolecular process, and thus milder reaction condition would be required. With this in mind, we also screened base forming conditions at 40°C and room temperature (**Entries 3**-**5**). Extending the reaction times to 3 hours and 16 hours, respectively (**Entry 3** and **Entry 4**, **Table 2.12**), led to the isolation of **57** in similar yields to **Entry 1**. At these lower temperatures, the extended reaction times were found to be necessary, as exemplified by **Entry 5**, in which room temperature base formation for only 3 hours led to poor recovery of **57**, indicating that base **54** had not fully formed under these conditions. Based on the results from **Table 2.12** the decision was taken to retain the original refluxing conditions due the more practically convenient 1.5 hour reaction time. A final point to note with regards to the use of this MeI quench protocol is that a control reaction was carried out in which only 1 equivalent of *n*-Bu_2Mg was added (**Entry 5**, **Table 2.12**). The poor 3% yield of **57** recovered indicates that the amine **51** is not reacting with the electrophile, and that in the previous reactions in **Table 2.12** it is the bisamide which is responsible for the formation of **57**.



56 **57**

Scheme 2.33

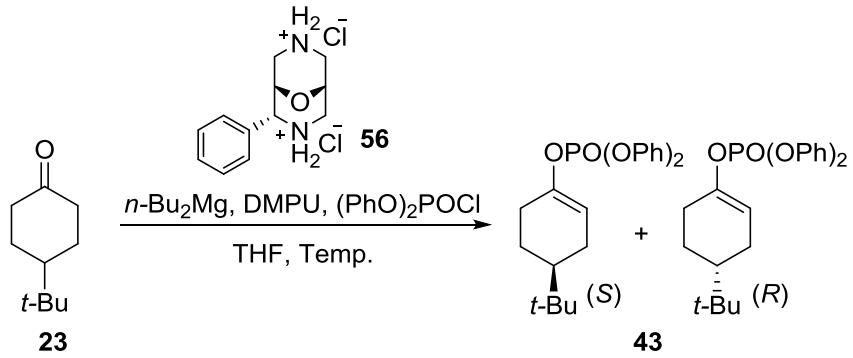
Entry	Temperature	Time	Yield
1	Reflux	1.5 h	66%
2	Reflux	1.5 h	75%[a]
3	40°C	3 h	68%
4	RT	16 h	64%
5	RT	3 h	30%
6	Reflux	1.5 h	3%[b]

[a]distilled MeI, [b]1 equiv of *n*Bu_2Mg employed

Table 2.12

*Application of Magnesium Bisamide **54** in Deprotonation 4-tert-Butylcyclohexanone*

With confidence that the desired bisamide **54** was indeed forming, we next turned our attention to its use in the benchmark deprotonation of 4-*tert*-butylcyclohexanone. Employing the same internal quench protocol used in the highly successful deprotonation with C_2-symmetric Mg amide (*R*,*R*)-**36**, and incorporating the Lewis basic additive DMPU, it was found that at both -78°C and room temperature none of the desired enol phosphate **43** was obtained (**Scheme 2.34**, **Table 2.13**).



Scheme 2.34

Entry	Temperature	Quench	Yield
1	-78°C	IQ	0%
2	RT	IQ	0%

Table 2.13

Instead, almost quantitative recovery of ketone starting material was isolated along with by-product **60**, obtained *via* reaction of the magnesium base species with the phosphoryl chloride electrophile (**Figure 2.13**).

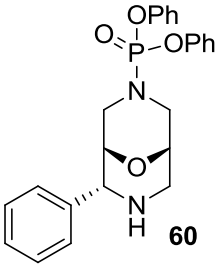
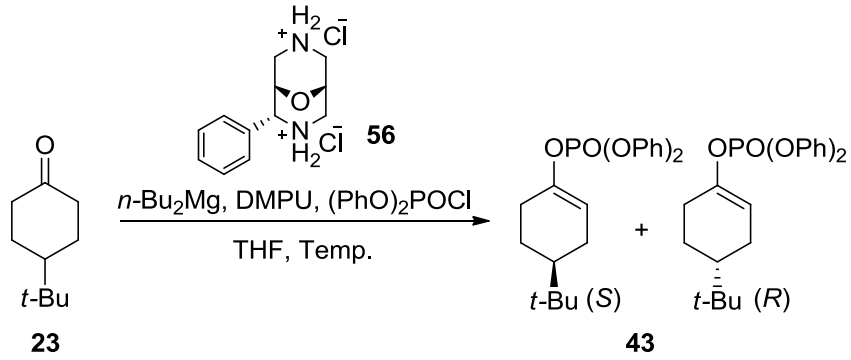


Figure 2.13

The outcome of the above reactions indicated that the internal quench procedure, found to be highly effective in previous asymmetric deprotonation studies, was unsuitable for use with our novel oxabispidine-derived base, which appeared to be reacting with the electrophile rapidly, thereby shutting down the requisite ketone deprotonation process. As such, we turned our attention to utilising an external quench procedure, where the ketone is added to a solution of the base to generate a magnesium enolate, prior to the addition of a solution of electrophile. As shown in **Scheme 2.35**, **Table 2.14**, at -78°C only trace enol phosphate was observed, however performing the deprotonation reaction at room temperature led to the

desired enol phosphate **43** product in 35% yield. Similar to the internal quench reactions carried out previously, the external quench reactions detailed in **Table 2.14** also resulted in quantities of the by-product **60** being recovered (*see experimental for details*).



Scheme 2.35

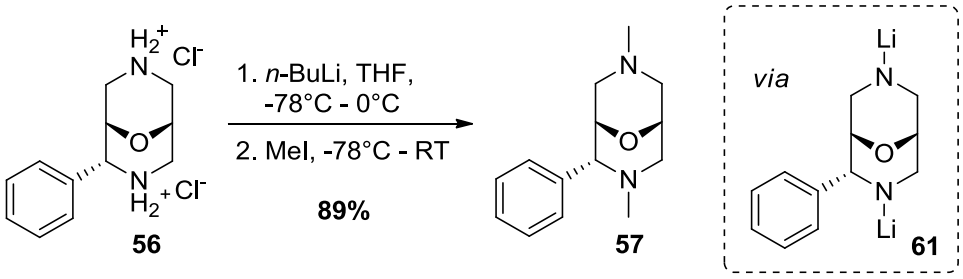
Entry	Temperature	Quench	Yield	er (*S*):(*R*)
1	-78°C	EQ	trace	-
2	RT	EQ	35%	45:55

Table 2.14

Whilst this outcome was positive, in that it was the first significant yield of **43** achieved using our new oxabispidine-derived base **54**, the low yield achieved at the relatively elevated temperature was concerning, and posed the question of the reactivity of the novel base system. In particular, the recovery of by-product **60** suggests the base **54** is not effectively deprotonating the ketone substrate before the electrophile is added. With regards to their reactivity, as mentioned earlier, magnesium bisamides are more thermally stable, less reactive alternatives to their more traditional lithium amide counterparts.[37] Whilst, in general, this is an attractive property in relation to higher enantioselectivities being achievable at higher temperatures, in this particular case perhaps the more stable magnesium-centred reagent in combination with the cage-like structure of the oxabispidine was hindering the reactivity.

3.2.2 Application of an Oxabispidine-derived Lithium Amide

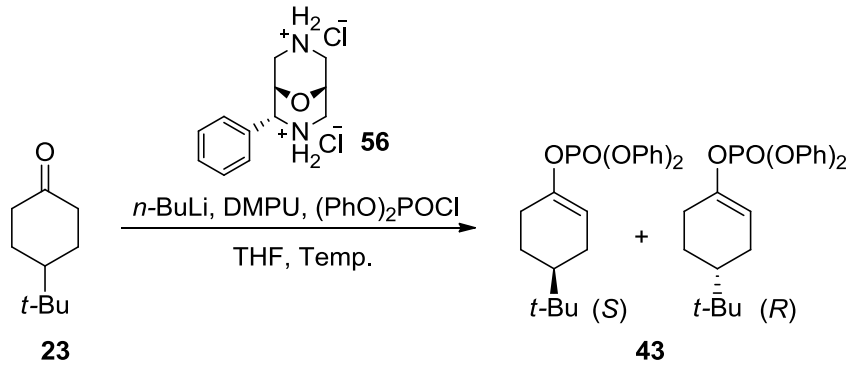
With this in mind, it was proposed that preparing the lithium amide counterpart may provide an oxabispidine-derived base of suitable reactivity to perform the desired asymmetric deprotonation. Although our laboratory's research focuses mainly on the application of magnesium-based reagents in asymmetric deprotonations, as the use of chiral oxabispidines as the amine within this line of research is completely novel, the investigation of oxabispidine-derived lithium amides is also considered to be of importance. In this regard, and similar to the earlier work with magnesium, we first wished to demonstrate that we could effectively form the lithium amide by performing the methyl iodide protocol used previously. As shown in **Scheme 2.36**, treating oxabispidine salt **56** with *n*-BuLi at -78°C, followed by warming to 0°C for 20 min and quenching with methyl iodide, led to the isolation of dimethylated product **57** in excellent yield, proving the desired lithium amide species had been successfully prepared.



Scheme 2.36

With conditions to effectively generate the required lithium amide in hand, we went on to screen this species in our benchmark deprotonation reaction, utilising the same external quench protocol employed with the magnesium derivative. At room temperature, we were pleased to find that the enol phosphate product was obtained in an improved 50% yield, albeit with a lack of enantioselectivity, as expected for a lithium amide at this temperature (**Scheme 2.37**, **Table 2.15**, **Entry 1**). This indicates that the lithium amide generated from **56** does in fact have a slightly increased reactivity over the magnesium variant. Having stated this, some of the by-product **60**, resulting from reaction of the base and the electrophile was still observed, indicating that the lithium amide was also unable to fully deprotonate the ketone. As the temperature of the reaction was lowered, an expected drop off in yield was also observed, with the reaction at 0°C providing the desired product **43** in 43% (**Entry 2**), and lowering further to -78°C resulted in **43** being recovered in poor 6% yield (**Entry 3**). With

regards to the enantioselectivity of the deprotonation, although moving from RT to 0°C provided a slight increase in selectivity, upon lowering the temperature to -78°C we were pleased to find a significant increase in selectivity, with an er of 27:73 being observed. It was noted that the bases derived from oxabispidine salt **56** provided the enol phosphate **43** with the opposite selectivity to more traditional bisamide (*R,R*)-**36**. Although an er of 27:73 is relatively modest, in this instance it is an extremely promising result, as this outcome is comparable to other lithium amide bases without salt additives reported at this temperature.[52] An additional part of this study involved carrying out the reaction in the absence of DMPU to ascertain whether the additive was in fact having a similar beneficial effect with this oxabispidine-derived base structure as it has with previous base systems (**Entry 4**). As shown, removing the DMPU from the reaction has a detrimental effect on both the yield and selectivity of the enol phosphate product.



Scheme 2.37

Entry	Temperature	Quench	Yield	er (*S*):(*R*)
1	RT	EQ	50%	50:50
2	0°C	EQ	43%	45:55
3	-78°C	EQ	6%	27:73
4	-78°C	EQ	3%	34:66*

*No DMPU

Table 2.15

LiCl Additive Study

The requirement for additives within lithium amide base methodology has been well documented.[32,33,53] In addition to the requirement of the use of Lewis basic additives such as HMPA or DMPU and solvents such as THF, the role of lithium halide salts has also shown to be of great importance on reactivity and enantioselectivity. As mentioned previously, both Simpkins and Koga have demonstrated the presence of LiCl is key to achieving high levels of enantioselectivity in many lithium amide systems, with Koga utilising NMR techniques to identify the specific species in solution responsible for high selectivity.[33] Employing ^{6}Li and ^{15}N NMR analysis, the solution structure of base (*S*,*S*)-**26** was elucidated, with four separate species being detected (**Figure 2.14**). With no LiCl additive present, (*S*,*S*)-**26** exists almost exclusively as homo dimer **62**, while in the presence of the salt two mixed aggregates were observed (**63** and **64**). Heterodimer **64** was found to be the principal species and, as such, it has been concluded that this is the reacting species responsible of the high enantioselectivity of the deprotonation process.[33]

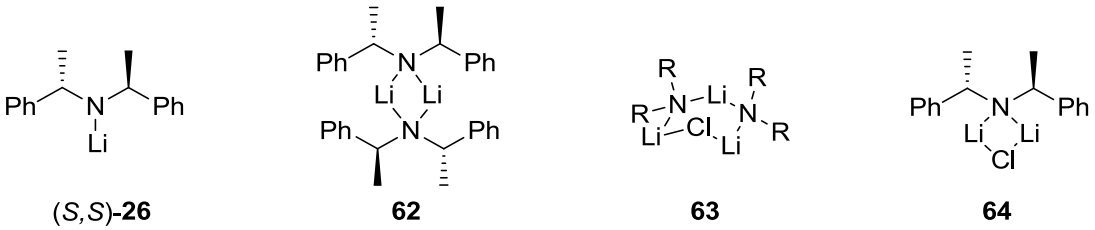
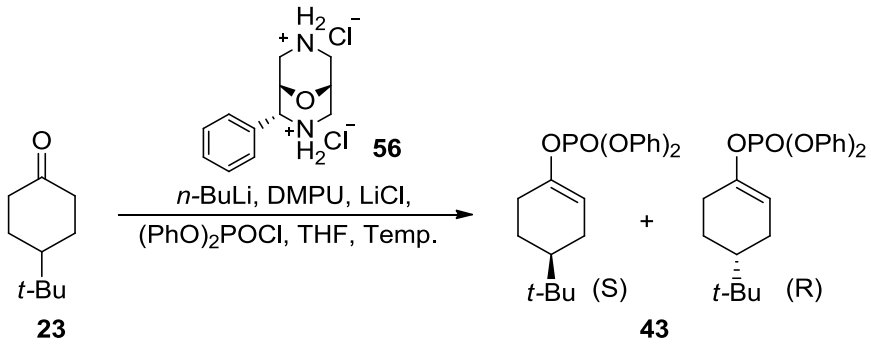


Figure 2.14

With this in mind, we wished to assess whether LiCl would have a similar beneficial effect on the reactivity/selectivity of our oxabispidine-derived lithium amide base system (**Scheme 2.38**, **Table 2.16**). Initially, the deprotonation reaction was performed at room temperature, with the belief that any effect on yield would be more obvious at this temperature. Pleasingly, it was found that the yield of enol phosphate **43** was a much improved 72% (**Entry 1**), compared to 50% without LiCl (**Table 2.15**, **Entry 1**). Lowering the temperature to 0°C (**Entry 2**) and -78°C (**Entry 3**) the yield decreased as expected, however the yields obtained were still higher than in the corresponding reactions without LiCl at the same temperatures. Importantly, the incorporation of 1 equivalent of LiCl had no effect on the enantioselectivities achieved at each temperature, with the promising 28:72 er still being obtained at -78°C. In order to ascertain whether a different quantity of LiCl would have a beneficial effect, lower and higher loadings of LiCl were screened (**Table 2.16**, **Entries 4** &

5). For these reactions the reaction temperature was kept at -78°C to allow an easier evaluation of the effect on enantioselectivity. Whilst incorporation of 0.5 equivalents of LiCl made no significant difference to either yield or selectivity, the use of 4 equivalents unfortunately led to decrease in the enantioselectivity achieved. Again, as in previous deprotonation reactions with magnesium amide **54**, all the reactions detailed in **Table 2.16**, resulted in varying quantities of by-product **60** being isolated.



Scheme 2.38

Entry	Temperature	LiCl (equiv)	Yield	er (*S*):(*R*)
1	RT	1	72%	50:50
2	0°C	1	57%	49:51
3	-78°C	1	9%	28:72
4	-78°C	0.5	6%	27:73
5	-78°C	4	10%	40:60

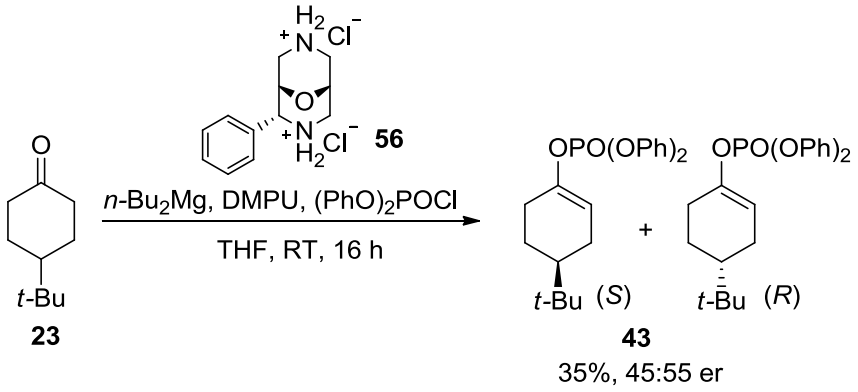
Table 2.16

Whilst the oxabispidine-derived lithium amide base in combination with 1 equivalent of LiCl provided the highest yield of enol phosphate **43** so far (72% at RT), the fact that this yield was only achievable at room temperature is a significant drawback with regards to achieving high levels of enantioselectivity. At the temperatures required to gain levels of selectivity approaching acceptable (e.g. -78°C is required to attain an er of 28:72), access to **43** is only allowed in very low yield. Although the recovery of by-product **60** in all cases suggests that there is an inherent reactivity issue with this base system in the deprotonation process, if we

were able to develop a system that could achieve improved levels of selectivity at higher temperatures, a balance between the reactivity and enantioselectivity might be achieved. To do this it was believed that turning our attention back to a magnesium-mediated protocol, which have historically proven to provide higher asymmetry at more elevated temperatures,[42] was required.

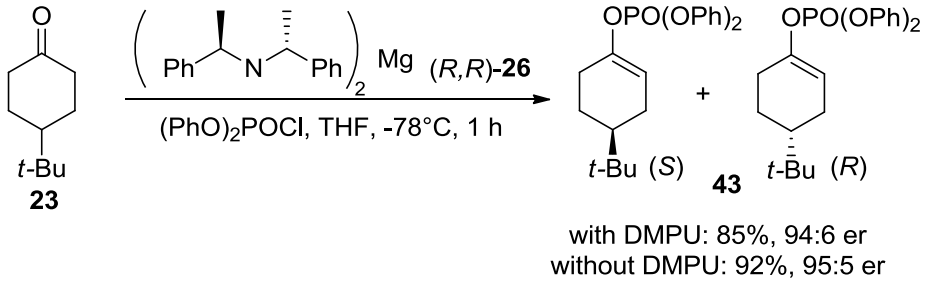
*3.2.3 Application of Oxabispidine-derived Magnesium Bisamide **54***

To this stage, the best yield achieved utilising bisamide **54**, derived from salt **56**, in the deprotonation of 4-*tert*-butylcyclohexanone is 35%, under the conditions shown in **Scheme 2.39**.



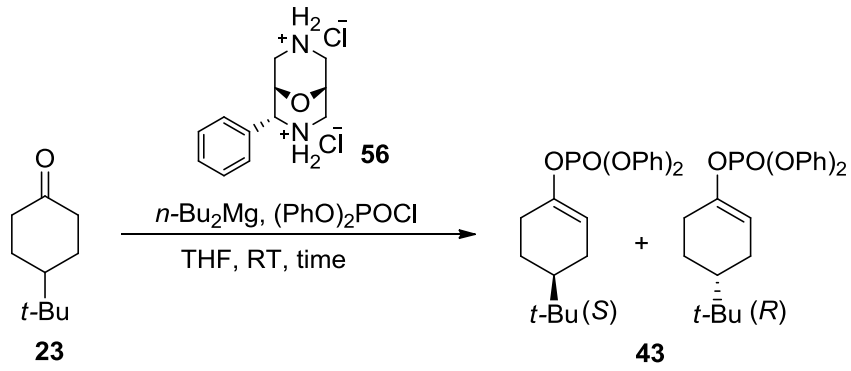
Scheme 2.39

Having observed the beneficial effect LiCl had on the yield of the lithium amide base protocol, we wished to assess whether it would have a similar effect in the magnesium-mediated process. Before embarking on this line of investigation however, we first wished to assess if the DMPU additive included in the above reaction (as a result of its necessity in previous Mg bisamide procedures),[40-47] was indeed required with our novel oxabispidine base. In utilising C_2-symmetric base (*R*,*R*)-**26**, work carried out alongside our current oxabispidine-based research has shown that slightly better yields of enol phosphate products can actually be obtained in the absence of DMPU (**Scheme 2.40**).[49]



Scheme 2.40

In this regard, we repeated the deprotonation reaction depicted in **Scheme 2.41**, however this time without the addition of DMPU. It was found that this led to an increase in yield from 35% to 46% (**Scheme 2.41**, **Table 2.17**, **Entry 1**). Whilst we were pleased to observe this increase, the relatively modest yield at room temperature was still an issue. Although it was believed that the 16 h reaction time should be sufficient for the deprotonation to take place, to ensure we were allowing enough time for the base **54** to react, the reaction time was extended to 24 h. Unfortunately, this led to a slight decrease in yield (**Scheme 2.41**, **Table 2.17**, **Entry 2**). At this stage, the limited yields being achieved at room temperature were highly concerning with regards to the reactivity of the simple oxabispidine-derived magnesium bisamide.

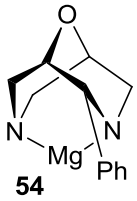


Scheme 2.41

Entry	Time	Yield	er (*S*):(*R*)
1	16 h	46%	47:53
2	24 h	37%	49:51

Table 2.17

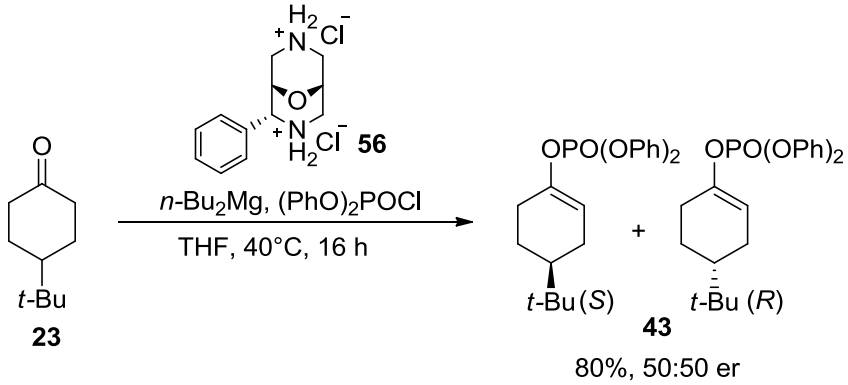
Although the solution structure of bisamide **54** is unknown, assuming even the simplest monomeric structure, it could be envisaged that the almost cage-like structure of the oxabispidine scaffold surrounding the magnesium centre could be imparting a significant amount of stability to the structure, and thus be limiting its reactivity (**Figure 2.15**).



54

Figure 2.15

To probe this inherent reactivity issue with the magnesium bisamide species further, the deprotonation reaction, in the absence of DMPU, was carried out at a slightly elevated temperature (**Scheme 2.42**). Heating the reaction to 40°C led to a significant increase in yield to 80%, indicating that the reactivity of the magnesium bisamide **54** is clearly restricted at room temperature. Of course, as expected, no enantioinduction was observed at this temperature.

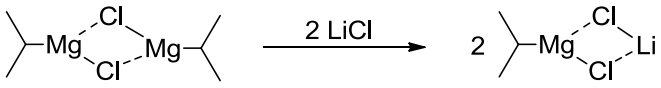


Scheme 2.42

LiCl Additive Study

Whilst the simple magnesium bisamide conditions detailed above did not seem viable to obtain a good balance of yield and enantioselectivity in our deprotonation reaction, we were still hopeful that the beneficial effect LiCl displayed in the lithium amide base protocols (*vide supra*), would be emulated in the magnesium-mediated reaction. Indeed, the use of LiCl in magnesium-centred chemistry has also been well documented over the last decade. Knochel and co-workers have developed a so-called "turbo Grignard" species in the form of

iPrMgCl.LiCl.[54] The inclusion of LiCl with a simple Grignard reagent allowed the reactivity of the resulting species to be modulated relative to the simple magnesium reagent. Two effects are proposed to be in operation. First, as in lithium chemistry, the LiCl is proposed to break up polymeric aggregates, which will produce a more reactive complex (**Scheme 2.43**).[54]



Scheme 2.43

Additionally, it has been proposed that the magnesiate character of such a species, with an increased electron density at the magnesium centre, also enhances the reactivity of the reagent (**Figure 2.16**).[54]

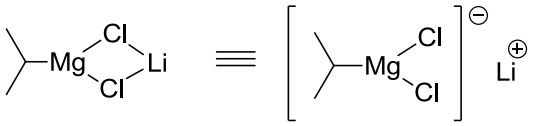
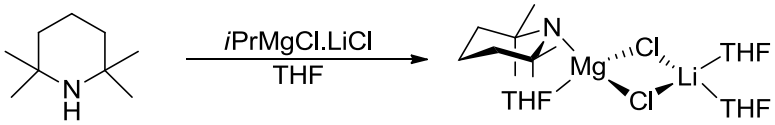


Figure 2.16

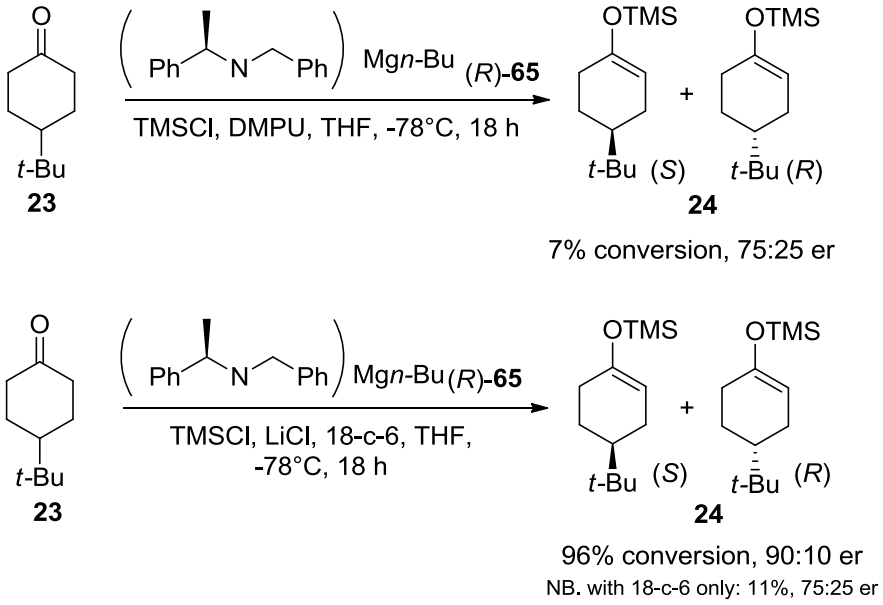
In a similar vein, a "turbo Hauser base" shown in **Scheme 2.44** has also been developed. Again it is the 'ate' structure that is believed to be responsible for the enhanced reactivity of this species over the simple Hauser base counterpart.[55]



Scheme 2.44

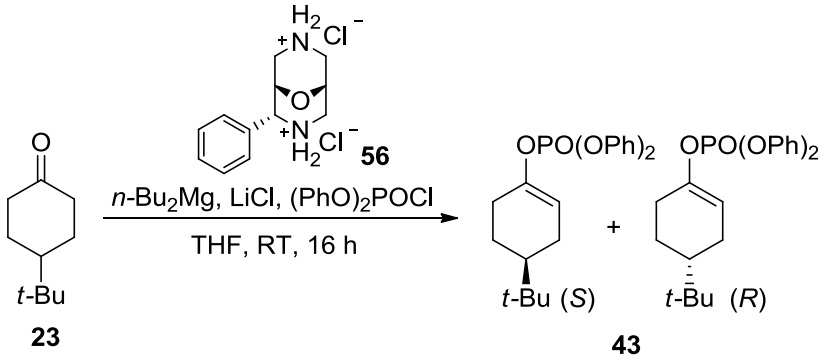
In addition to the well precedented effects of LiCl detailed above, work within our laboratories has also shown that LiCl can have a positive effect on both the yield and the enantioselectivity of a deprotonation reaction. For example, as shown in **Scheme 2.45**, when investigating the use of alkylmagnesium amide (*R*)-**65** within the benchmark deprotonation, it was found that when DMPU was used as the additive a poor yield and moderate er of the enantio-enriched product **24** was achieved. On the other hand, employing conditions that incorporated LiCl as an additive led to the desired product being recovered in excellent yield

and selectivity.[42b] Although 18-c-6 was also employed in this protocol, as highlighted in **Scheme 2.45**, the LiCl was crucial for high yields and selectivity.



Scheme 2.45

Bearing all of the above in mind, we wished to ascertain whether similar effects would be observed when LiCl was added to our novel oxabispidine-derived base system. As shown in **Scheme 2.46**, **Table 2.18**, the benchmark deprotonation was performed at room temperature with varying equivalents of LiCl. Whilst it was found that 1 equivalent of LiCl had no significant effect on the reaction outcome (**Entry 1**), 2 equivalents did allow the enol phosphate product to be obtained in significantly improved yield (**Entry 2**). Increasing the number of equivalents further had a detrimental effect.

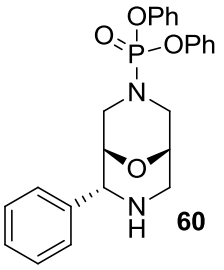


Scheme 2.46

Entry	Equiv. LiCl	Yield	er (*S*):(*R*)
1	1	49%	49:51
2	2	67%	49:51
3	4	55%	50:50

Table 2.18

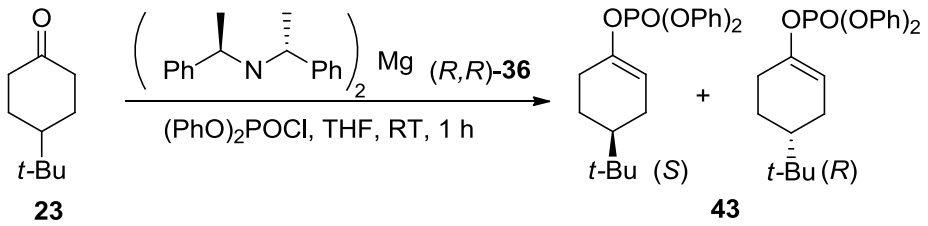
Whilst we were pleased that the yield of the deprotonation reaction had increased, we wished to probe this further. The main issue with the oxabispidine-derived base **54** is its low reactivity with ketone **23**, which is indicated by the isolation of by-product **60** (**Figure 2.17**) in addition to the desired product. This is the case for the reactions in **Table 2.18** and, indeed, all of the deprotonations carried out with base **54**.



60

Figure 2.17

Our attempts to increase the reactivity of the base by the inclusion of LiCl succeeded to an extent, however, to improve reaction yields further it was proposed that perhaps enhancing the reactivity of the ketone itself would also be beneficial. Previously within our laboratories, when standard internal quench protocols were proving unsuitable, but the alternative external quench protocol was providing only moderate yields (as with the current oxabispidine-derived system), an alternative co-addition protocol was developed.[49] This method involves premixing a solution of the ketone substrate with the electrophile and adding this mixture to the base solution. As shown in **Scheme 2.47**, **Table 2.19**, performing the deprotonation of **23** at room temperature with (*R*,*R*)-**36** under the external quench procedure led to a 64% yield of **43** with a 79:21 er, whereas the co-addition technique gave access to **43** in improved 81% yield, with no negative effect on er and no side reactions being observed.[49]

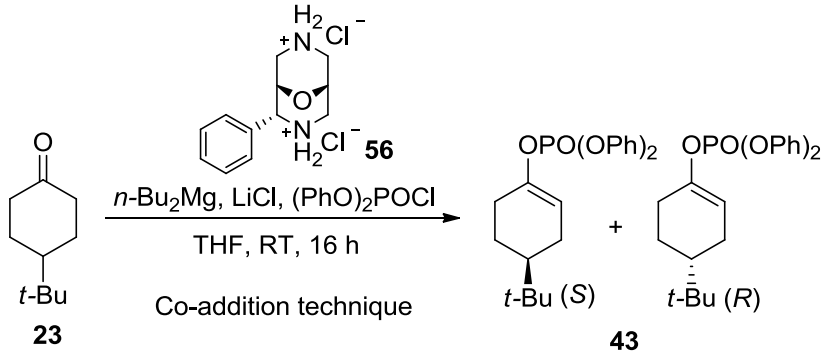


Scheme 2.47

Entry	Quench	Yield	er (*S*):(*R*)
1	EQ	64%	79:21
2	Co-addition	81%	80:20

Table 2.19

Hoping that we would observe a similar increase in reactivity in the oxabispidine base system we applied the above co-addition technique. Unfortunately, the utilisation of this quench method had a negative impact on the yield of the reaction (**Scheme 2.48**, **Table 2.20**, **Entry 1**). Whilst up to this stage an excess of the electrophile has been employed, it was proposed that reducing the quantity of diphenylphosphoryl chloride may minimise the undesired side reaction (resulting in the formation of **60**). However, utilising a 1:1 ratio of ketone:electrophile led to a 47% yield; a poorer yield than the 67% obtained with the best EQ conditions to this stage (**Table 2.20**, **Entry 2** *cf.* **Table 2.18, Entry 2**).



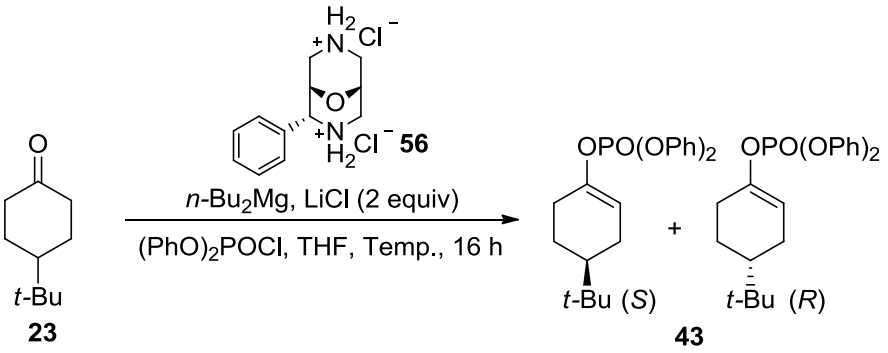
Scheme 2.48

Entry	*Equiv. E^+	Yield	er (*S*):(*R*)
1	2.5	35%	50:50
2	1	47%	47:53

*relative to ketone

Table 2.20

Again, as with all other previous reactions reported, significant quantities of the by-product **60** were recovered (78% and 67% in the case of **Entries 1** and **2** of **Table 2.20**), demonstrating that oxabispidine-derived base **54** is simply not active enough to react with ketone **23** within the temperature range required for achieving good levels of enantioselectivity. As such, it was deemed necessary to investigate the modification of the oxabispidine scaffold used within the magnesium amide base system. However before we embarked upon the structural alteration of our base system, we first wished to utilise the best conditions to date with base **54** at temperatures below room temperature, in order to gain information on the enantioselectivities that are achievable with it, and also to gauge the levels of reactivity at these temperatures. As depicted in **Scheme 2.49**, **Table 2.21**, utilising the best conditions developed to date, namely the addition of 2 equivalents of LiCl to oxabispidine base **54**, we performed the deprotonation reaction of 4-*tert*-butylcyclohexanone at various temperatures. As expected, upon lowering the temperature the yield of the deprotonation reaction decreased dramatically, with only trace enol phosphate product being observed at -78°C. Whilst the enantioselectivity began to look more promising as the reaction was cooled to 0°C (an er of 40:60 was observed), upon lowering the temperature even further, rather than the enantioselectivity increasing as we would expect, the selectivity in fact decreased, with no selectivity at all being observed at -40°C.



Scheme 2.49

Entry	Temperature	Yield	er (*S*):(*R*)
1	0°C	29%	40:60
2	-20°C	10%	43:57
3	-40°C	6%	49:51
4	-78°C	trace	-

Table 2.21

Although the modest level of enantioselectivity achieved at 0°C indicated that there may be some promise for oxabispidine scaffolds as ligands in such an asymmetric deprotonation process, the phenyl substituted derivative **50** clearly forms both a lithium amide and magnesium bisamide of limited reactivity, and, as such, alternative base structures were probed.

3.3 Alternative Oxabispidine Scaffolds

With regards to investigating alternative enantiomerically-enriched oxabispidines for use within the magnesium amide deprotonation chemistry, and bearing in mind the wide array of chiral oxabispidines at our disposal, two possible approaches were envisaged. The first involved altering the chiral sidearm of the oxabispidine scaffold (**A**, **Figure 2.18**). Modulating the sterics and electronics of this group we believed could tune the reactivity of the corresponding bisamide. The second approach involved utilising mono-methylated oxabispidine derivatives (**B**, **Figure 2.18**). This would allow the preparation of chelating

amino magnesium amides, which could provide a less rigid structure and thus an improved reactivity over their bisamide counterparts.

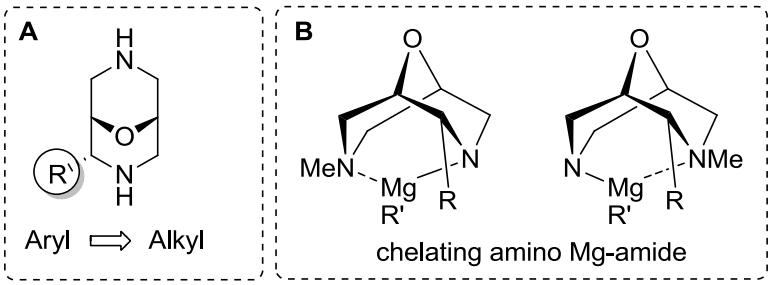


Figure 2.18

3.3.1 Alternative Chiral Sidearms

*t-Bu-substituted Oxabispidine **66***

In the first instance, we chose to focus on incorporating alternative substituents on the oxabispidine core, with the first derivative chosen for preparation being the *t*-Bu derivative (**Figure 2.19**). Initially the use of such a bulky group may seem counter-intuitive, given the poor reactivity observed with the phenyl derivative previously. However it was proposed that, in addition to a bulky group potentially providing higher levels of enantioselectivity in an asymmetric process, such as within the deprotonation of interest, the use of such a strongly electron-donating alkyl group may counteract the steric issue, and a balance of these factors may prove successful.

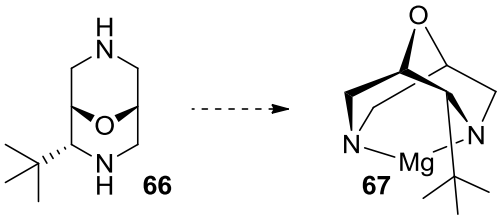
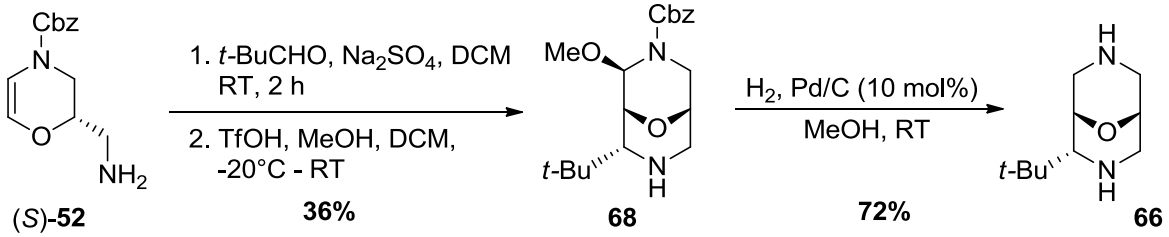


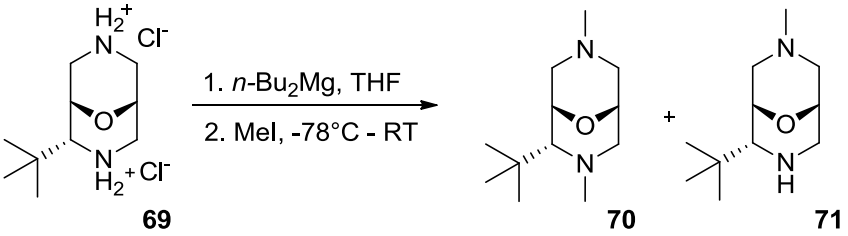
Figure 2.19

With this in mind, we synthesised a sufficient quantity of **66** to allow the investigation of the corresponding bisamide **67**. As shown in **Scheme 2.50**, synthesis of *t*-Bu-substituted oxabispidine **68** occurred in a relatively low 36% yield, however, sufficient material was recovered to allow hydrogenation, which provided the desired bis-secondary amine in good yield.



Scheme 2.50

With a sufficient amount of **66** in hand, this species was converted to the bis-HCl salt **69** in a similar fashion to the previous phenyl derivative, in order to determine if it would be a suitable scaffold for magnesium bisamide formation. To assess **69**'s ability to form a bisamide, the methyl iodide quench protocol employed with phenyl derivative was used. As shown in **Scheme 2.51**, **Table 2.22**, the standard base-forming conditions of refluxing in THF for 1.5 h were employed prior to addition of MeI. Such conditions resulted in only 66% of the mono-methylated product **71** being recovered (**Entry 1**). In order to assess whether the reaction simply required longer, the base formation was extended by an hour, however, this actually led to a decrease in yield (**Entry 2**).



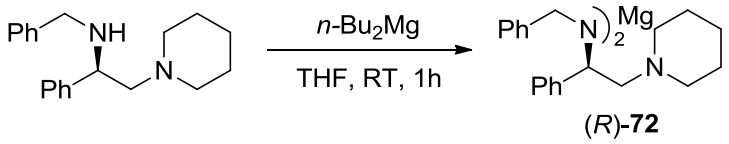
Scheme 2.51

Entry	Temperature	Time	Outcome
1	Reflux	1.5 h	66% **71**
2	Reflux	2.5 h	40% **71**

Table 2.22

That fact that only the mono-methyl derivative was being isolated suggested that the desired magnesium bisamide **67** was not forming. On the other hand, if only the single magnesium amide bond is being formed, we would expect the yield of **71** to potentially be slightly higher. Furthermore, the decrease in yield of **71** observed with an extended reaction time suggested that an additional process may be occurring. In was proposed that the relatively harsh reflux

conditions in combination with the bulky *t*-Bu group could be allowing *β*-hydride type eliminations to occur, leading to decomposition of the bisamide structure. Indeed, previous work within the our laboratory regarding chelating type amines, highlighted that bases such as **72** (depicted in **Scheme 2.51**) formed more effectively at room temperature.[56]



Scheme 2.52

In fact, it was believed that elevated temperatures actually led to degradation of the base (*R*)-**72** as a result of elimination at the methylene group α to the amide nitrogen, leading to aza-compounds such as **73**, as well as magnesium-hydride species such as **74**, and imine **75**. Additionally, these species may themselves degrade to compounds **76** and **77** (**Figure 2.20**).[56,57]

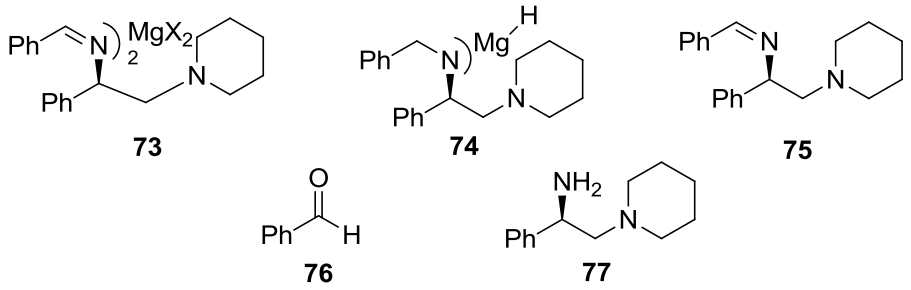
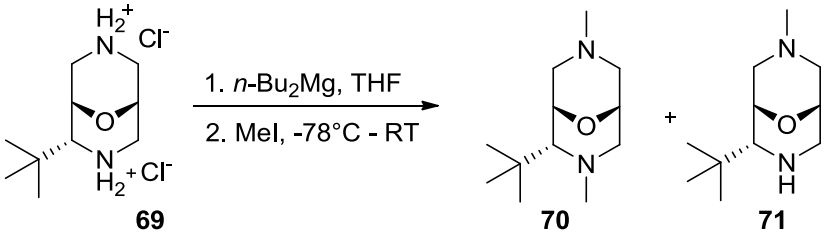


Figure 2.20

Bearing these findings in mind, we chose to employ less forcing conditions for the formation of our *t*-Bu-substituted magnesium bisamide (**Scheme 2.53**, **Table 2.23**). Performing the base formation step at 40°C overnight, led to the formation of the dimethylated product **70**, albeit in a poor 13% yield (**Entry 1**). Moving to even milder room temperature conditions provided **70** in slightly improved 25% yield (**Entry 2**). Strangely, in both cases, despite the low yield of **70**, none of the monomethylated species **71** was recovered.



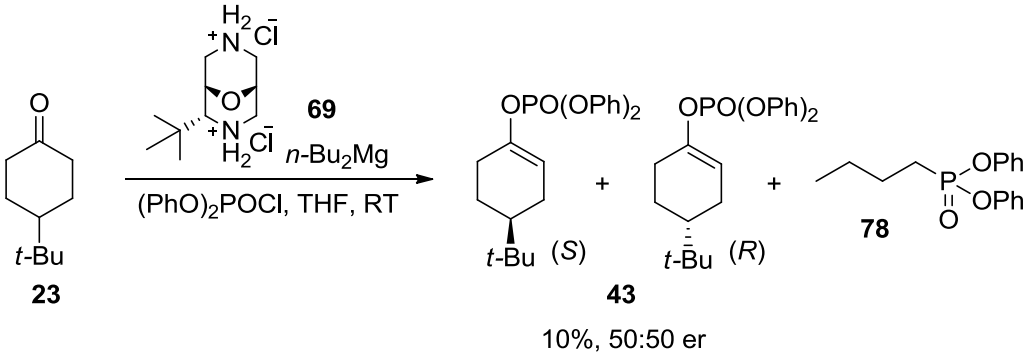
69 **70** **71**

Scheme 2.53

Entry	Temperature	Time	Outcome
1	40°C	16 h	13% **70**
2	RT	16 h	25% **70**

Table 2.23

Although it was evident that some of the bisamide was indeed forming in solution it appeared to be to only a little extent. Thus, the *t*-Bu-derivative was deemed too bulky to allow complete formation of the bisamide, and thus would be unsuitable for use in the deprotonation chemistry. Having stated this, it was thought appropriate to utilise the most successful conditions established above (**Table 2.23**, **Entry 2**) in a deprotonation reaction, to ensure that the poor yields above were indeed due to poor formation of the bisamide and not because of the sterics of the *t*-Bu group simply preventing the pick-up of the methyl electrophile. As expected, utilising salt **69** in the benchmark deprotonation of ketone **23** led to the enol phosphate product being obtained in poor yield with no enantioselectivity, along with the recovery of a significant quantity of by-product **78**, resulting from reaction of *n*Bu_2Mg with the electrophile. Bearing in mind an external quench procedure was in operation, the isolation of **78** indicates that the bisamide had not formed to any great extent, as *n*-Bu_2Mg was still present in solution after 16 h stirring with the ketone prior to addition of the electrophile.



Scheme 2.54

With this final confirmation that the *t*-Bu-derivative **66** (*via* salt **69**) was unsuitable for the formation of the corresponding magnesium bisamide, we turned our attention to the investigation of an alternative potential base system.

*Me-substituted Oxabispidine **79***

Bearing in mind the issues encountered with utilising relatively large groups in the position adjacent to the nitrogen, we chose to focus on incorporating a smaller group in this position. Indeed, we looked to the smallest of the alkyl groups, i.e. the methyl group, with the hope that by minimising the steric bulk in this position the reactivity of the oxabispidine-derived magnesium bisamide would be improved (**Figure 2.21**).

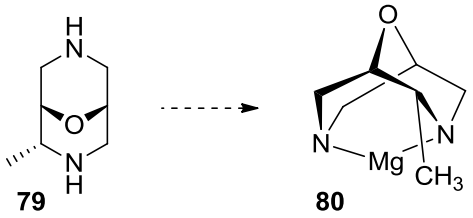
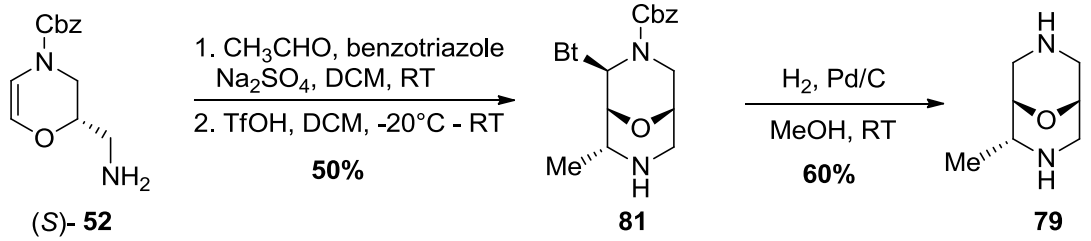


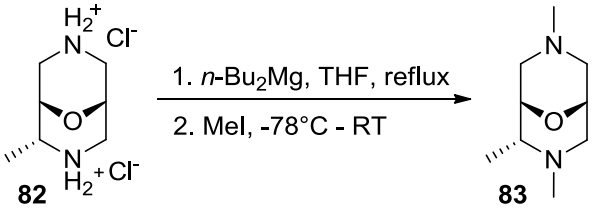
Figure 2.21

As such, we first prepared a fresh batch of methyl-substituted oxabispidine **81** from oxazine starting material (*S*)-**52**, in the manner described in Chapter 1. This occurred in a relatively good yield considering the capricious nature of this reaction (**Scheme 2.55**). With a sufficient quantity of **81** in hand, it was subjected to hydrogenation conditions to generate the desired bis-secondary oxabispidine unit in 60% yield.



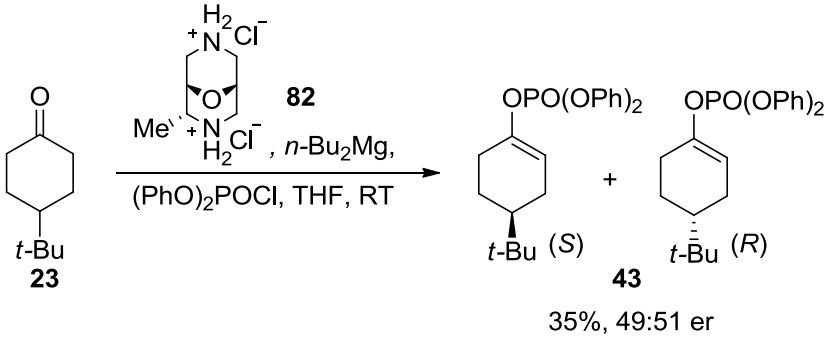
Scheme 2.55

As with previous derivatives, the methyl oxabispidine would be employed as its bis-HCl salt **82**, and its ability to successfully form the corresponding bisamide would be tested by utilising the methyl iodide quench protocol described previously (**Scheme 2.56**). Using the standard base-forming conditions of refluxing in THF, followed by quenching with methyl iodide, the desired dimethylated product **83** was observed by crude ^{1}H NMR analysis. However, attempting to isolate the species by column chromatography led to decomposition. Any further attempts to isolate **83** cleanly, unfortunately, led to its loss on the column.



Scheme 2.56

Whilst we were unable to isolate **83**, its diagnostic peaks in the crude NMR indicated it was the major component of the crude product, thus we were confident that the desired bisamide had successfully formed. As such, salt **82** was next screened in the benchmark deprotonation reaction, utilising simple bisamide conditions with no additives initially. As depicted in **Scheme 2.57**, under our external quench protocol at room temperature, enol phosphate product **43** was recovered in 35% yield with a 49:51 er, a similar outcome to that achieved with the phenyl-derivative under identical conditions.



Scheme 2.57

In a similar fashion to the phenyl-substituted bisamide **54**, the recovery of by-product **84** (**Figure 2.22**), resulting from the reaction of unreacted base with the diphenylphosphoryl chloride electrophile, was also observed. Again, this indicated that the reactivity of oxabispidine-derived bisamide is still limited in the deprotonation reaction, even with the sterics of the sidearm having been reduced appreciably.

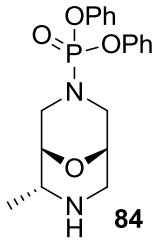
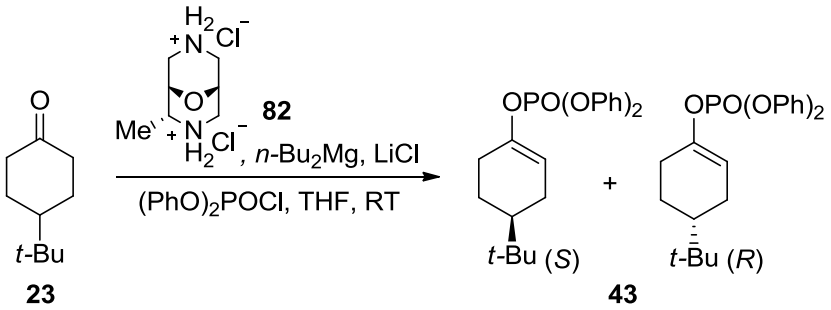


Figure 2.22

Bearing in mind the beneficial effect LiCl had previously in the phenyl-substituted oxabispidine base system, we also evaluated the use of this additive with our methyl-derivative. As shown in **Scheme 2.57**, **Table 2.24**, **Entry 1**, the addition of 1 equivalent of LiCl led to a slight increase in both yield and er, however, increasing this loading further to 2 equivalents unfortunately led to no further improvement (**Entry 2**). This differs from the experiments employing the phenyl-derivative, which saw an increase of ~20% in chemical yield upon going from no LiCl additive to 2 equivalents. This suggested that the different sidearm portion of the oxabispidine scaffold may potentially be affecting the active species/aggregate present in solution, and thus alternative additive conditions might be required.

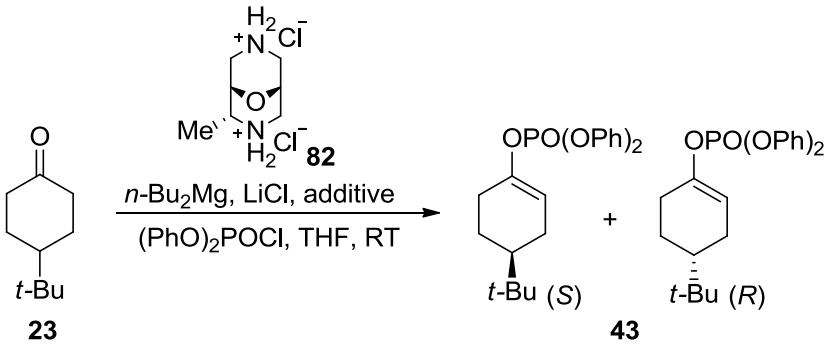


Scheme 2.58

Entry	Equiv. LiCl	Yield	er (*S*):(*R*)
1	1	40%	46:54
2	2	40%	50:50

Table 2.24

Previous work within our laboratory has demonstrated that the use of LiCl as an additive on its own can be only moderately effective, and that the incorporation of an additional Lewis basic additive or donor solvent can be highly advantageous.[42b] In this regard, a small selection of such species were utilised in combination with our Me-substituted bisamide **80** and 1 equivalent of LiCl (**Scheme 2.59**, **Table 2.25**). Whilst DMPU was not effective at all as an additive in the deprotonation reaction (**Table 2.25**, **Entry 1**), and actually led to a decrease in yield, we were pleased to find that alternative donor species in combination with LiCl, led to improvements in yield, with TMEDA and 18-c-6 delivering yields of 45% and 50%, respectively (**Entries 2** & **3**). The most effective additive screened was 1,4-dioxane, which was employed without the LiCl additive (due to the potential incompatibility with the salt additive) with a yield of 55% being achieved, and a small level of enantio-induction being observed, with an er of 44:56.



Scheme 2.59

Entry	Additive	Yield	er (*S*):(*R*)
1	DMPU	13%	50:50
2	TMEDA	45%	50:50
3	18-crown-6	50%	47:53
4	1,4-Dioxane	55%	44:56[a]

[a]No LiCl

Table 2.25

In addition to the Lewis basic properties that 1,4-dioxane presents, which can facilitate the breaking up of any higher order aggregates of magnesium amides in solution, 1,4-dioxane is also known to interact with MgX_2 salts to produce an insoluble polymeric chain, hence removing these species from solution (**Figure 2.23**).[58] Such an occurrence often leads to an improvement in reactivity of a magnesium amide base system.[42b]

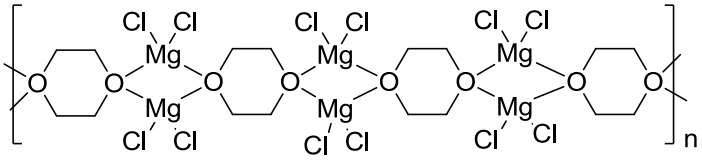
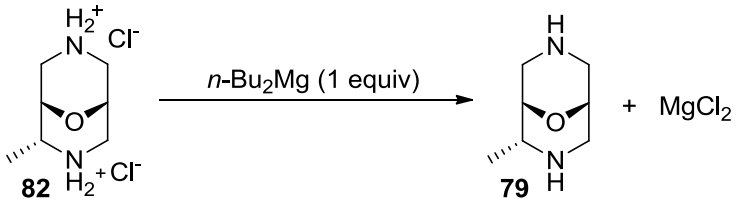


Figure 2.23

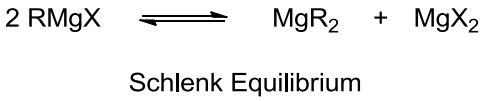
Considering our developing oxabispidine-based deprotonating system, due to practical issues, we were required to utilise our chiral amine species as the bis-HCl salt. This meant that double the amount of organometallic reagent was required to generate our desired magnesium

bisamide. Upon deprotonation of the salt to provide the free amine **79** we are therefore generating 1 equivalent of $MgCl_2$ (**Scheme 2.60**).



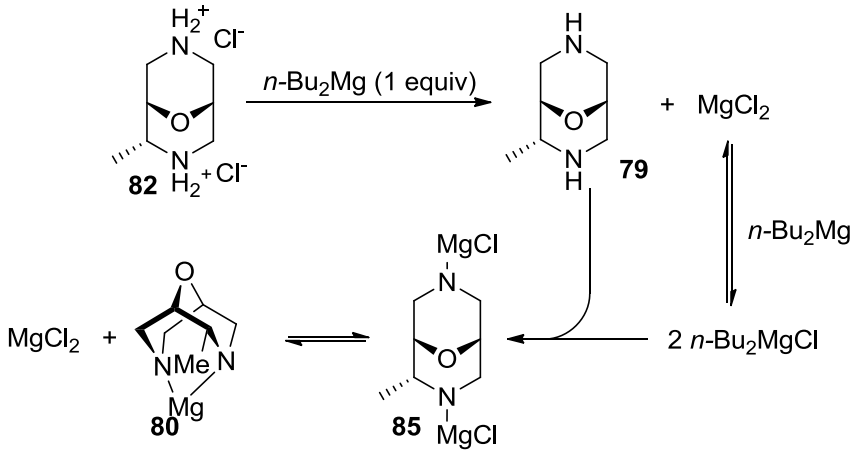
Scheme 2.60

Based on the Schlenk equilibrium, we know that a heteroleptic magnesium reagent (e.g. a Grignard or Hauser base) exists in equilibrium with its homoleptic components i.e. a dialkyl magnesium compound or bisamide compound, respectively, and $MgCl_2$.[59]



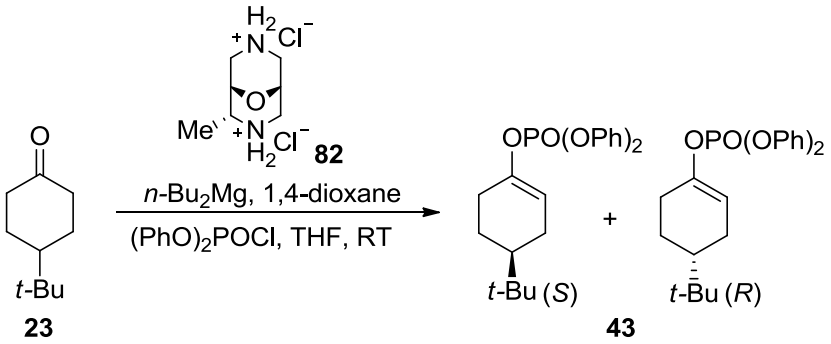
Scheme 2.61

If after the first deprotonation of our salt **82** we generate $MgCl_2$, this may react with the remaining equivalent of *n*Bu_2Mg, generating small quantities of the corresponding Grignard reagent, which, in turn, can react with the free amine **79** to generate some of the corresponding Hauser base **85** (**Scheme 2.62**). From previous work within our laboratories, it is known that without tuning the reaction conditions appropriately, the presence of a Hauser base within the asymmetric deprotonation reaction can be detrimental to the process.[42b,46a] Thus, the presence of small quantities of such a species in our new system may be limiting the effectiveness of our desired transformation. With the incorporation of 1,4-dioxane, and thus the removal of $MgCl_2$ from the system, we may be ensuring that solely the magnesium bisamide **80** is present and it is this species that is responsible for the increase in yield observed in **Table 2.25**, **Entry 4**.



Scheme 2.62

To explore this theory further, we wished to ascertain whether the 1,4-dioxane loading would have an effect on the reaction outcome (**Scheme 2.63**, **Table 2.26**). It was discovered that the original loading of 2 equivalents of dioxane (utilised in the initial additive screen) was optimal. Upon reducing the amount to 1 equivalent, the small level of enantioselectivity observed was retained, however, the yield decreased (**Table 2.26**, **Entry 1**), whereas increasing to 3 equivalents led to a decline in both yield and selectivity (**Table 2.26**, **Entry 3**).

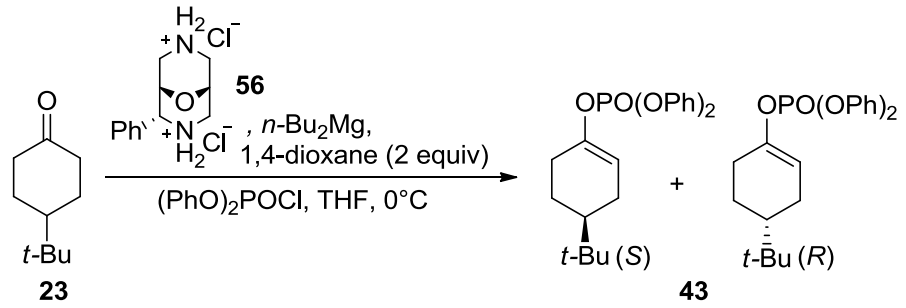


Scheme 2.63

Entry	1,4-dioxane Equiv.	Yield	er (*S*):(*R*)
1	1	35%	43:57
2	2	55%	44:56
3	3	40%	49:51

Table 2.26

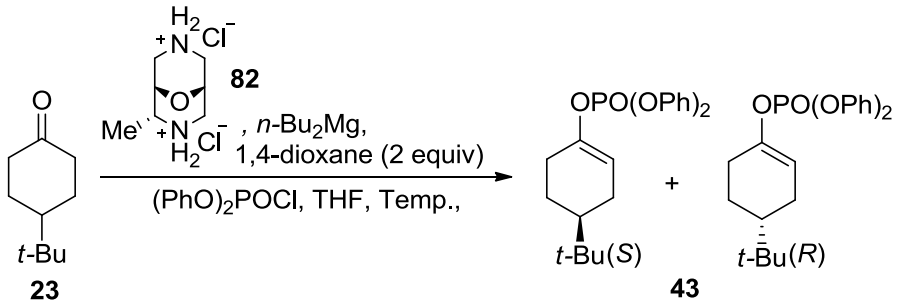
With these newly developed conditions in hand, we wished to assess if they would have a beneficial effect on the phenyl-substituted oxabispidine base system discussed previously. Wishing to obtain the maximum amount of information from a single reaction, we performed the reaction at 0°C to better evaluate the effect on both yield and enantioselectivity (**Scheme 2.64**). It was found that the dioxane additive conditions actually had a negative effect on this system, with only 14% of the enol phosphate **43** being recovered with a 48:52 er (compared to 29% yield and 40:60 er with the previous best conditions).



Scheme 2.64

This outcome again seems to support the observation made earlier when discussing the different degree to which LiCl benefited the deprotonation reaction in the presence of varying oxabispidine sidearms. More specifically, altering this sidearm portion of the oxabispidine scaffold may potentially be affecting the species/aggregate present in solution, and therefore different reaction conditions are required to generate the active species in solution, and thus achieve an optimal outcome from the deprotonation process.

Returning to the methyl-substituted oxabispidine base, we wished to assess the level of enantioselectivity that could be achieved with this system, and so a temperature study was undertaken (**Scheme 2.65**, **Table 2.27**). As anticipated, the yield steadily dropped upon lowering the temperature of the deprotonation. The slight level of enantioselectivity observed at room temperature, was maintained upon lowering to 0°C and -20°C, however, lowering the temperature even further led to no selectivity at all being observed.



Scheme 2.65

Entry	Temperature	Yield	er (*S*):(*R*)
1	0°C	26%	43:57
2	-20°C	23%	43:57
3	-40°C	12%	49:51
4	-78°C	1%	50:50

Table 2.27

In addition to the desired enol phosphate product **43**, by-product **84** was also recovered (**Figure 2.24**), not only in the reactions in **Table 2.27**, but in all of the previous reactions utilising bisamide **80**, at room temperature. This outcome demonstrates that, as with the phenyl-derivative, the methyl-substituted oxabispidine base **80**, is not reactive enough to effectively deprotonate the ketone substrate and instead reacts with the electrophile. It was apparent that bisamides derived from *bis*-secondary oxabispidines were unsuitable for use in the desired asymmetric deprotonation, with such bicyclic scaffolds clearly imparting an inherent stability/unreactivity to the magnesium bisamide reagent.

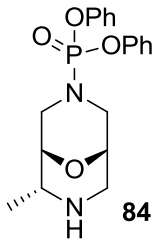


Figure 2.24

3.3.2 Nitrogen Substitution to Generate Chelating Magnesium Amide Bases

Having explored the area of secondary oxabispidines bearing differing chiral sidearms within magnesium bisamide chemistry as far as was thought necessary at this time, we wished to turn our attention to an alternative modification to the oxabispidine scaffolds. As described earlier, capping of one of the nitrogen atoms with a methyl group would allow the preparation of chelating amino magnesium amides, which could provide a less rigid structure and thus a potentially improved reactivity over their simple bisamide counterparts. As depicted in **Figure 2.25**, either nitrogen could be methylated, to generate either combination of secondary/tertiary amines, in order to assess which substitution pattern, if any, would provide optimal reactivity/selectivity.

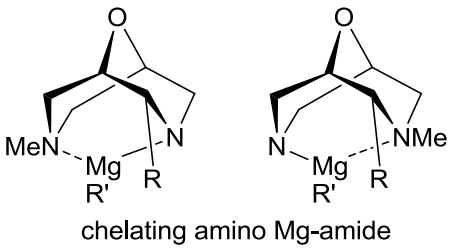


Figure 2.25

With regards to R' shown above, we envisage this could be another oxabispidine unit, to provide a homoleptic chelating base of the type **86**, shown below, in **Figure 2.26**, or could be an alkyl group to provide a heteroleptic reagent. Both of these types of magnesium bases, for example bisamide (*R,R*)-**40** and alkyl magnesium amide **87**, have proven to be highly effective in the asymmetric deprotonation of conformationally-locked prochiral ketones.[42b,43]

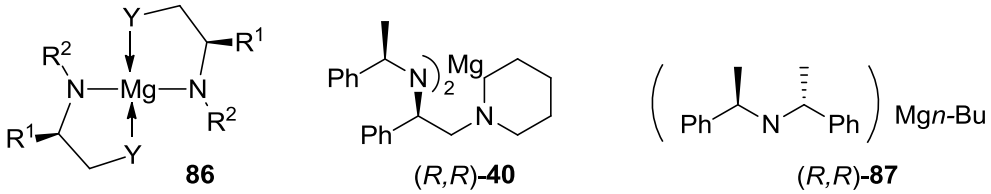
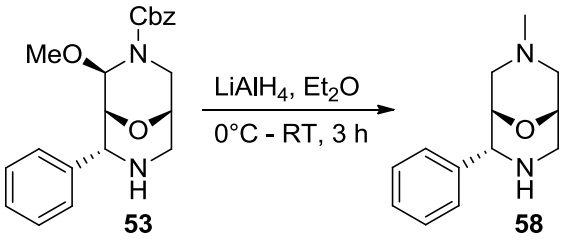


Figure 2.26

Initially, we wished to investigate the use of tertiary/secondary oxabispidine **58**. The phenyl derivative was selected because the highest selectivity achieved as part of this programme of work to date was with the bisamide **54** containing the phenyl substituent. It was proposed that forming the magnesium amide bond with nitrogen atom adjacent to the chiral sidearm

could potentially, but not necessarily, impart a higher selectivity over the alternative nitrogen substitution pattern. Thus, oxabispidine **58** was prepared from the parent oxabispidine **53** *via* the lithium aluminium hydride reduction conditions described in Chapter 1. As shown in **Scheme 2.66**, **Table 2.28**, the reaction proceeded in good yield.



Scheme 2.66

Entry	Scale	Yield
1	10 mmol	59%
2	16.3 mmol	60%

Table 2.28

With **58** in hand, we proposed to first prepare the chelating amino magnesium bisamide **88** (**Figure 2.27**), to compare its reactivity to **54** utilised previously. It was anticipated that the chelation present in the species would mean that it would be highly likely to exist as a monomer in solution. Previously utilised species such as **54**, had the potential to exist as a higher order aggregate.

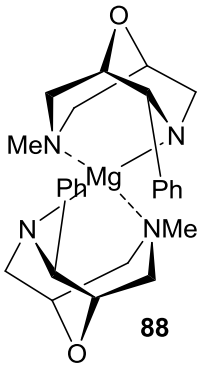
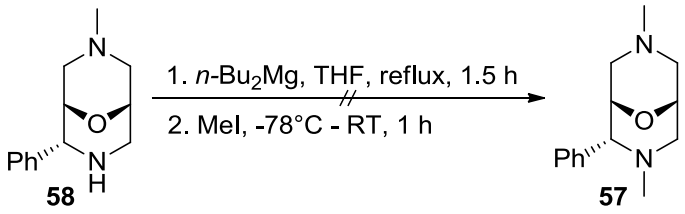


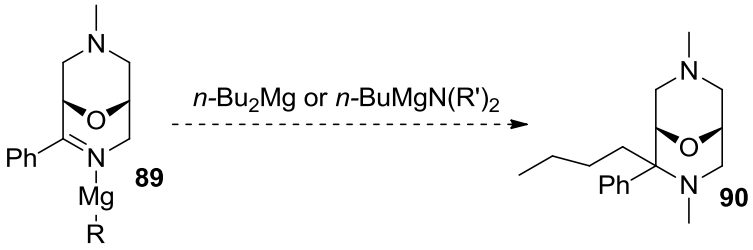
Figure 2.27

As oxabispidine **58** was an easy to handle white solid the decision was taken to utilise it as the free amine as opposed to the corresponding HCl salt, which had been used previously. First, to ensure the bisamide-forming conditions employed previously were suitable, **58** was screened in the methyl iodide quench protocol developed earlier (**Scheme 2.67**). Unfortunately, after refluxing in THF for 1.5 h, followed by the MeI quench, the desired dimethylated product was not isolated. Instead, an unknown product was isolated which by ^{1}H NMR analysis seemed to exhibit similarities to the expected dimethylated product, however contained an extra butyl moiety.



Scheme 2.67

This outcome was unexpected, considering the bisamide **54** derived from the bis-secondary oxabispidine formed without incident under identical conditions. Nonetheless, initially it was proposed that, in this case, perhaps an elimination process may be in operation, such as the type discussed earlier with regards to the *t*-Bu-derivative. This could generate a species such as **89**, to which a butyl group from *n*-Bu_2Mg may add (**Scheme 2.68**).



Scheme 2.68

Upon closer inspection of the NMR data, however, it was deduced that the isolated side product was in fact ammonium salt **91**, shown in **Figure 2.28**, which in addition to the desired methylation of the nitrogen atom also bore a pentyl chain. At this stage, the identity of the counterion to cation **91** was unknown, although it was proposed that I^- was likely.

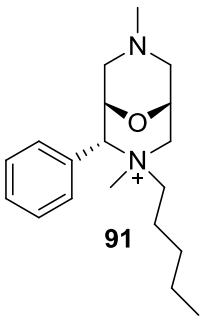
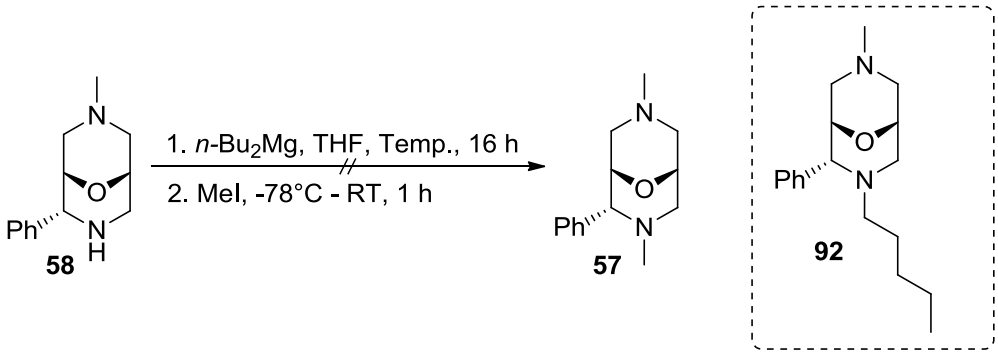


Figure 2.28

This reaction outcome was highly unexpected, with lack of clarity surrounding how such a product could form. In order to evaluate whether milder conditions would avoid this unwanted reaction, the base formation was performed at 40°C and RT (**Scheme 2.69**, **Table 2.29**). Whilst **91** described above was not obtained in either of these instances, the desired dimethylated product **57** was not recovered either. Instead, an alternative side product identified by NMR as compound **92** was isolated.

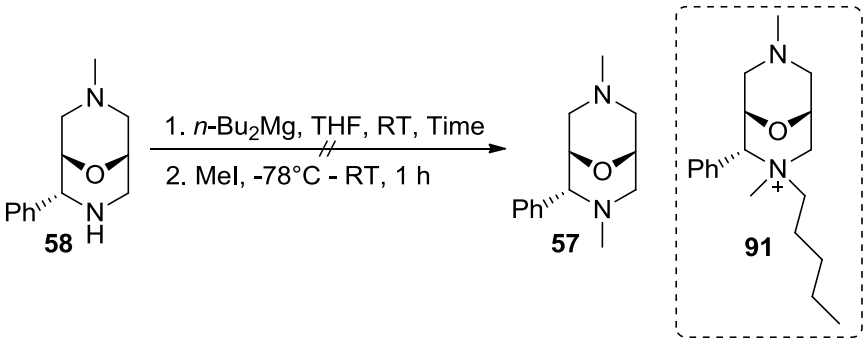


Scheme 2.69

Entry	Temperature	Outcome
1	40°C	49% **92**
2	RT	33% **92**

Table 2.29

In an attempt to curb the formation of such side products, it was proposed that a combination of a low temperature and shorter reaction time might be beneficial. Unfortunately, reducing the reaction time at room temperature to 2 hours or 30 minutes only resulted in the recovery of **91** again.



Scheme 2.70

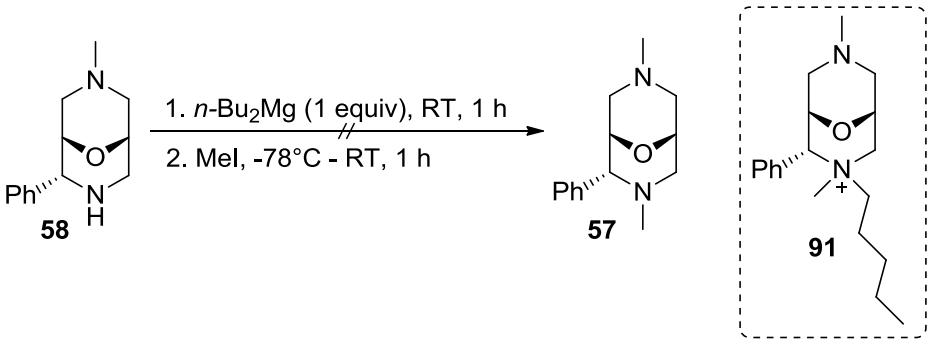
Entry	Time	Outcome
1	2 h	**91** isolated
2	30 min	**91** isolated

Table 2.30

Based on the results of this short study, it was proposed that a similar side reaction was occurring in all cases, however the distinct side products obtained suggests that different species were present in solution under the different reaction conditions. For example, the original refluxing base formation conditions (depicted in **Scheme 2.67** which give rise to side product **91**), may be generating portions of the chelating amino magnesium bisamide species. However, the preparation of this chelating amino magnesium bisamide may be disfavoured due the highly bulky nature of such a species and, as such, the desired bisamide may not be fully forming. Thus excess *n*-Bu_2Mg may still be present in solution upon methyl iodide addition. Such an occurrence would mean that any of the desired **57** that did form, may go on to reaction with the excess organometallic reagent and electrophile. With regards to the reactions performed at lower temperatures, we may only be generating the alkylmagnesium amide. If this were the case, the different outcomes observed at different reaction times, (recovery of **92** in **Scheme 2.69** vs. recovery of **91** in **Scheme 2.70**) could potentially be a result of the varying extents to which the alkylmagnesium amide had formed. In the case of the reactions carried out at lower temperature and shorter reaction times (**Scheme 2.70**, **Table 2.30**), if the proposed alkyl magnesium amide was not allowed sufficient time to form completely, both excess *n*-Bu_2Mg and MeI would be present increasing the chance of unwanted side reactions with these reagents. Whilst at this time, evidence to support firm

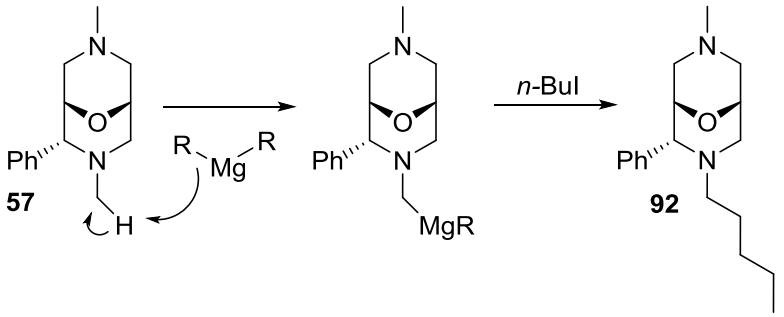
conclusions based on this discussion are not available, a point that does seem evident is that, regardless of the specific process occurring, for the generation of the alkyl chain on the nitrogen atom, it appears that a source of an electrophilic butyl group (most likely *n*-BuI) is required.

At this stage we wished to assess the outcome of the methylation reaction if the oxabispidine-derived alkylmagnesium amide was deliberately prepared, and compare this with our previous results. As such, we incorporated 1 equivalent of *n*-Bu_2Mg as opposed to the 0.5 equivalent used in the previous experiments (**Scheme 2.71**). Unfortunately, this only led to **91** being recovered in an increased quantity.



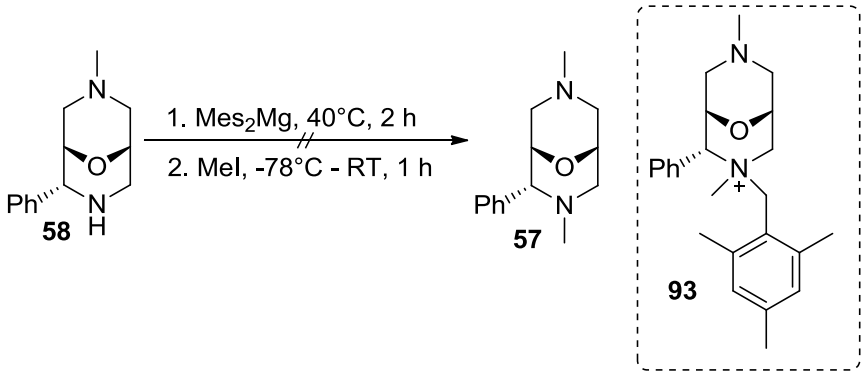
Scheme 2.71

With the isolation of either **91** or **92** occurring under all the previous reaction conditions attempted, a mechanism in which **57** is formed and subsequently deprotonated by an organo-magnesium species (e.g. either a magnesium amide or unreacted *n*Bu_2Mg) could be postulated. This deprotonated oxabispidine could then react with an electrophilic butyl group as mentioned previously to install the pentyl chain in **92** (**Scheme 2.72**), which could in turn react with MeI to generate **91**.



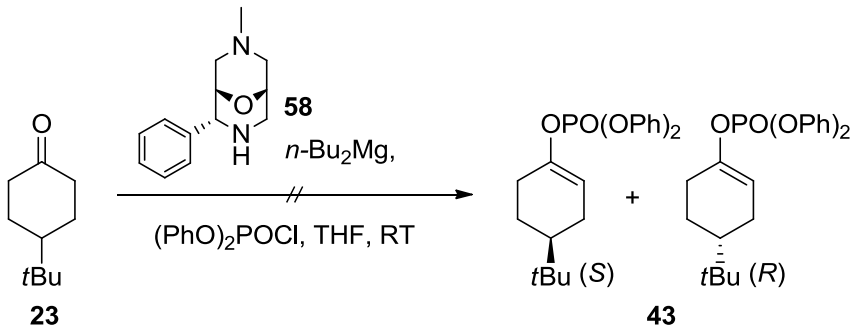
Scheme 2.72

With a view to probing this reaction further and assessing what effect altering the organometallic reagent would have on the reaction outcome, *bis*-mesitylmagnesium was employed and the formation of an oxabispidine-derived bisamide was attempted by heating to 40°C for 2 h. After the methyl iodide quench the only material recovered from the reaction was **93** (**Scheme 2.73**). Again, the identity of the counterion could not be identified at this time, although it was presumed to be iodide. The isolation of **93** was informative, as it ruled out the deprotonation mechanism suggested in **Scheme 2.72**, and suggested that a radical mechanism was likely in operation.



Scheme 2.73

It was becoming apparent that oxabispidine **58** was not a viable amine for use in our deprotonation chemistry. Having said this, to rule out the possibility that the unwanted side reactions were characteristic of the methylation reaction and not the oxabispidine itself, we screened **58** in the benchmark deprotonation protocol. Utilising the standard base formation conditions (reflux, 1.5 h), unfortunately, afforded a similar outcome to the methylation reactions, with only ketone starting material and **92** (42%) being recovered. This outcome was highly unexpected, as the presence of the 5 carbon chain on the nitrogen atom infers that, in this instance, the additional carbon, presumed to originate from the methyl iodide in previous reactions, was delivered from an alternative source, with the only available one carbon unit being from oxabispidine **58** itself.



Scheme 2.74

Whilst uncovering the source of the unusual reactivity of tertiary/secondary oxabispidine **58** would be of interest, due to time constraints within this line of research, efforts were focused on finding a successful oxabispidine-derived magnesium base system for the asymmetric deprotonation process. As such, we turned our attention to the preparation of the alternative chelating amino-magnesium bisamide **94** with the opposite substitution pattern (**Figure 2.29**), to discover if a similar unusual reactivity was observed in this case.

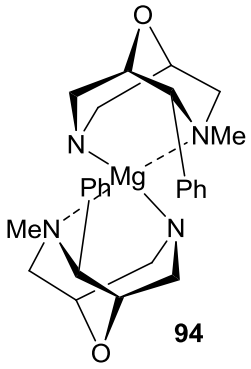
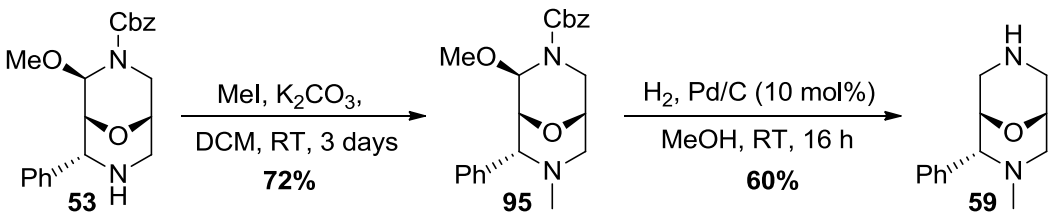


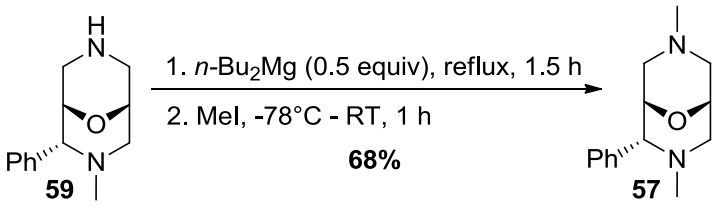
Figure 2.29

To prepare the required oxabispidine, the parent oxabispidine **53** was methylated under the condition depicted in **Scheme 2.75** in 72% yield. Following this, the Cbz- and MeO- groups were cleaved under hydrogenation conditions, to provide the desired oxabispidine product **59** in good yield.



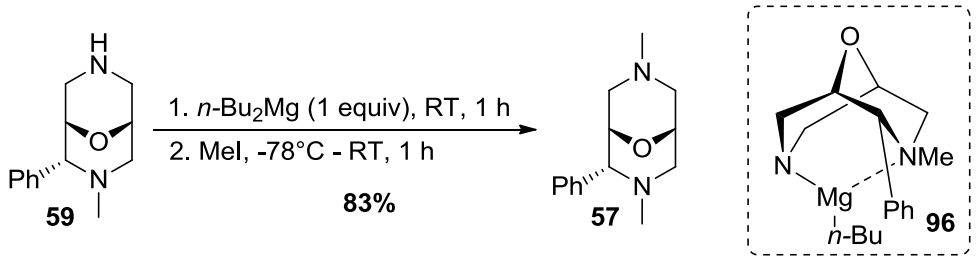
Scheme 2.75

With oxabispidine **59** in hand, we proceeded to carry out our standard methylation protocol to ensure the chelating bisamide **94** was forming (**Scheme 2.76**). Pleasingly, and unlike the previous example, the desired dimethylated product **57** was obtained in this instance. Although the yield of **57** was not high, it was not too dissimilar to previous examples, and we providing confidence that the desired base had indeed been formed.



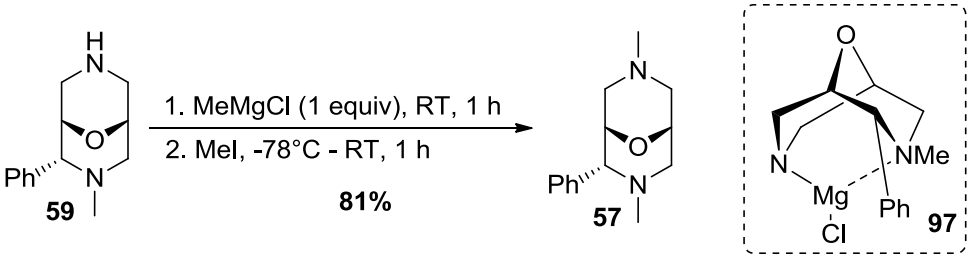
Scheme 2.76

At this stage it was also of interest to establish if heteroleptic magnesium bases could be prepared from oxabispidine **59** (**Scheme 2.77**), such as alkylmagnesium amide **96**. By employing 1 equivalent of *n*-Bu_2Mg, and utilising conditions to form alkylmagnesium amides developed previously within our laboratory[42b] (stirring at room temperature for 1 hour), led to the isolation of **57** in an improved yield over the chelating amino-magnesium bisamide described above.



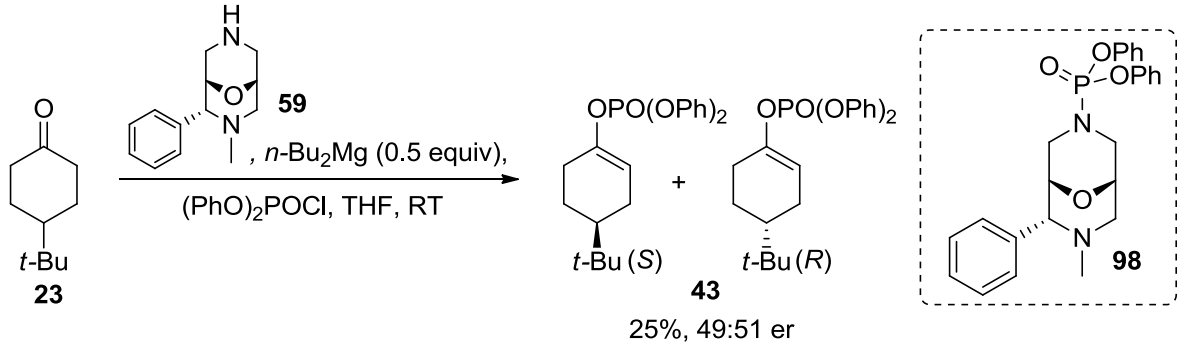
Scheme 2.77

In addition to the alkylmagnesium amide base above, we also attempted to synthesise the oxabispidine-derived Hauser base (**Scheme 2.78**). The successful preparation of such a species, would also be useful to gain experimental evidence for or against our earlier proposal, that the presencce of a Hauser base species may be detrimental to our deprotonation system (*Section 3.3.1*). Under the same room temperature conditions used above, but employing MeMgCl as the organometallic reagent, the desired dimethylated product was obtained in high yield, indicating the successful formation of the Hauser base **97**.



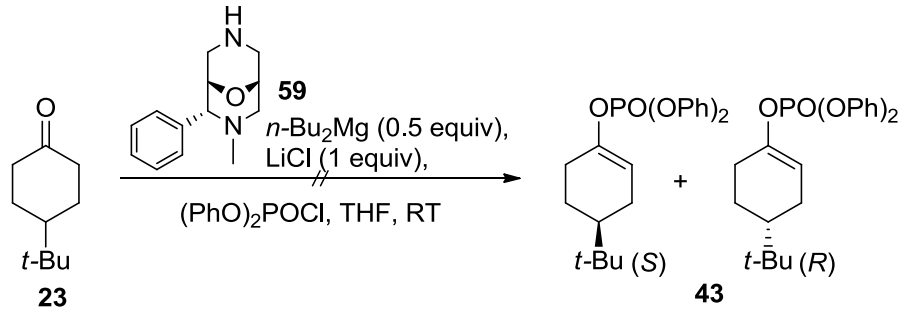
Scheme 2.78

Having demonstrated that we can successfully prepare both homoleptic and heteroleptic magnesium amide species from oxabispidine **59**, we looked to assess and compare their application in our asymmetric deprotonation process. First, we chose to utilise the chelating aminomagnesium bisamide in the deprotonation of 4-*tert*-butylcyclohexanone (**Scheme 2.79**). Performing the deprotonation reaction at room temperature to allow us to compare the reactivity to previous oxabispidine-derived bases, it was found that the enol phosphate product **43** was obtained in 25% yield, along with a similar phosphorylated by-product **98** to those observed previously. Disappointingly, the yield of **43** was lower than those achieved under the same conditions with alternative oxabispidine-derived amides.



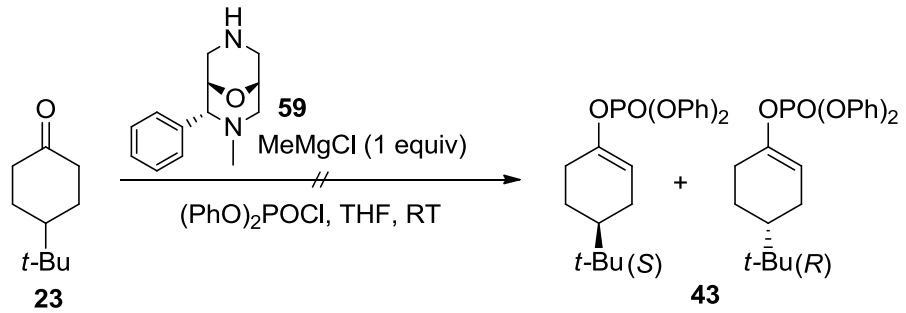
Scheme 2.79

With the hope of improving this result, the reaction was repeated with the inclusion of 1 equivalent of LiCl (**Scheme 2.80**). Unfortunately, this only led to quantitative recovery of ketone, with none of the desired enol phosphate product being observed.



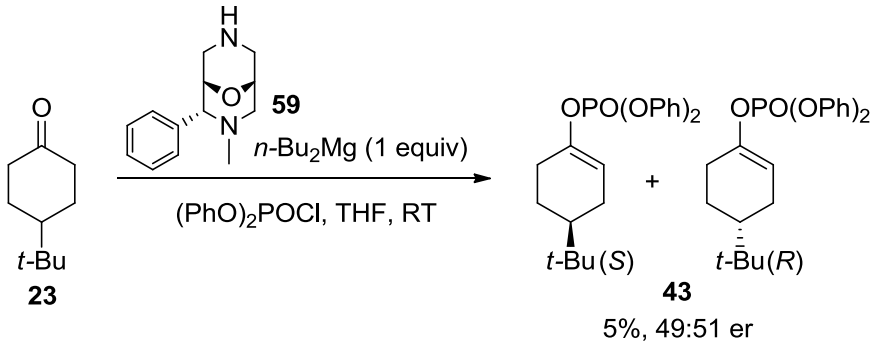
Scheme 2.80

With the chelating aminomagnesium bisamide **94** having much more limited success than previous oxabispidine-derived bases, and the LiCl additive having such a negative impact on the reaction, the decision was taken not to investigate other additive conditions further. Instead, we focused on screening the alternative heteroleptic base derivatives of **59**. Examining the Hauser base **97** initially, it was found that, whilst in the methylation reaction described previously the desired product had been accessed in high yield (indicating that the base had formed), in the deprotonation of **23** none of the desired enol phosphate was recovered. This outcome suggests that the Hauser base is not able to perform the desired deprotonation. Indeed, this corroborates the proposal made earlier when discussing the role of 1,4-dioxane in the methyl-substituted base **80** conditions, that the presence of a Hauser base was having a negative effect on the overall system (*Section 3.3.1*).



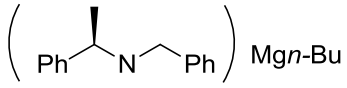
Scheme 2.81

Moving on to the final magnesium amide species derived from secondary/tertiary oxabispidine **59**, that being alkyl magnesium amide **96**, it was found that only a 5% yield of the desired enol phosphate **43** was obtained at room temperature.



Scheme 2.82

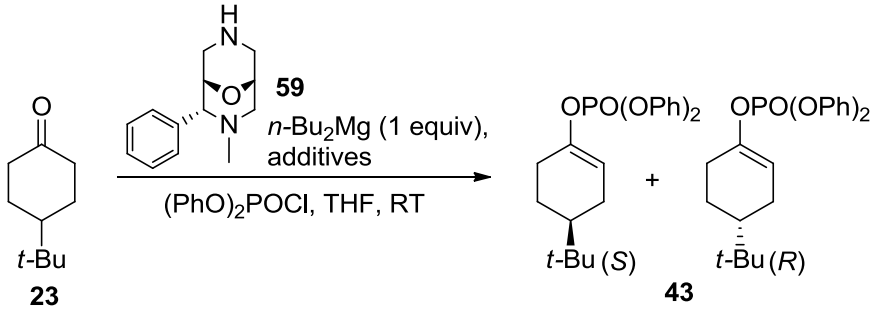
With a view to improving this yield, we turned to previous research within our laboratory which focused on the effect of additives within alkyl magnesium amide systems.[42b] This work found that in order to obtain high conversions and enantioselectivity with alkylmagnesium amide reagents such as **65**, shown in **Figure 2.30**, a combination of LiCl and a Lewis basic additive was crucial.



(*R,R*)-**65**

Figure 2.30

With this in mind, two sets of conditions were selected and screened with our novel oxabispidine-derived alkylmagnesium amide **96**. The first utilised the combination of LiCl and DMPU, and the second employed LiCl and 18-c-6. As shown in **Scheme 2.83, Table, 2.31**, whilst both sets of additive conditions resulted in a slight improvement in yield, the change was not as significant as desired.



Scheme 2.83

Entry	Additives	Yield	er (*S*):(*R*)
1	LiCl + DMPU	16%	49:51
2	LiCl + 18-c-6	13%	49:51

Table 2.31

Again, it appears that the reactivity of alkylmagnesium amide **96**, like the previous bisamide and Hauser base derivatives, is limited. To investigate if the combination of a smaller chiral sidearm and methyl-capped nitrogens would be more effective, the decision was taken to prepare oxabispidines **99** and **100** (**Figure 2.31**) in order to assess their use in the targeted deprotonation reaction.

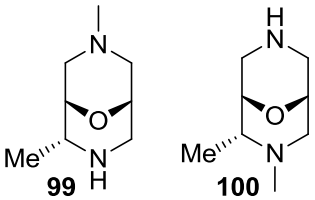
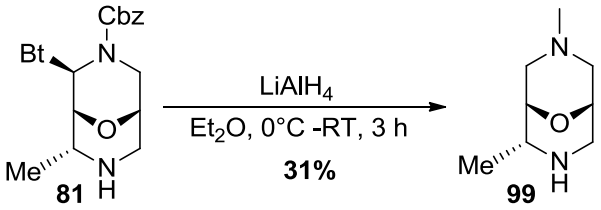


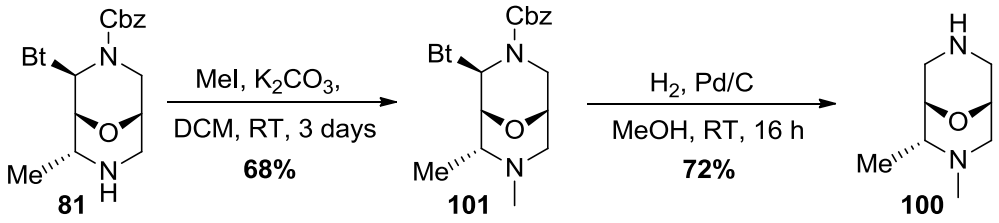
Figure 2.31

To prepare **99**, the parent oxabispidine was simply treated with $LiAlH_4$, to afford the desired oxabispidine in relatively poor yield (**Scheme 2.84**). However, sufficient material was obtained for our synthetic requirements.



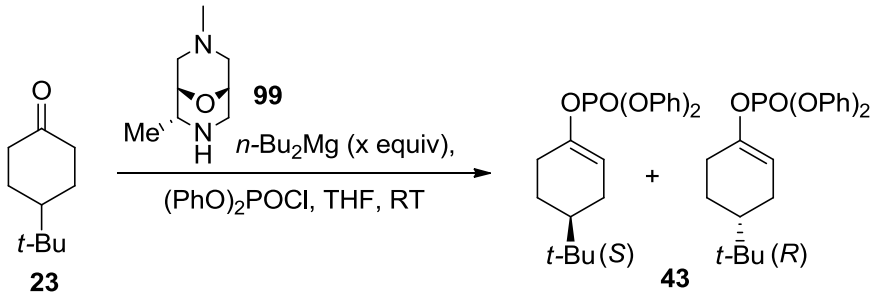
Scheme 2.84

With regards to the synthesis of **100**, oxabispidine **81** was first methylated in good yield to provide **101**, and subsequent hydrogenation delivered the desired product in 72% yield.



Scheme 2.85

In order to provide answers quickly as to whether **99** or **100** would give rise to more effective magnesium-centred bases, the decision was taken to screen both the chelating amino-magnesium bisamide and the alkylmagnesium amide in each case. Starting with **99**, it was found that utilising either type of base in the deprotonation of 4-*tert*-butylcyclohexanone led only to the recovery of ketone starting material. It was noted that no other material was recovered from either reaction, not even a by-product resulting from the reaction of the base with the phosphoryl chloride electrophile, which has been recovered in almost all reactions with our oxabispidine-derived bases previously. This suggested that the oxabispidine-derived amide species may have been degrading before it has a chance to react with either the ketone or the subsequent electrophile, perhaps through a similar elimination pathway to the corresponding phenyl-substituted oxabispidine **58**.



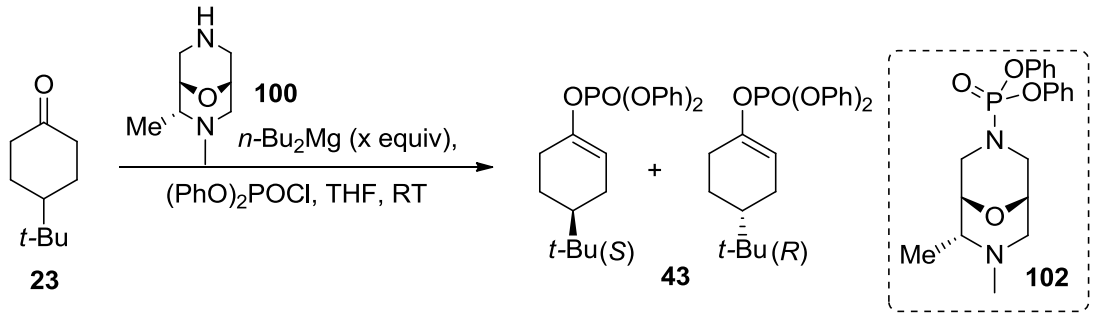
Scheme 2.86

Entry	Base	*n*Bu_2Mg	Yield
1	Chelating bisamide	0.5 equiv.	0%
2	Alkyl magnesium amide	1 equiv.	0%

Table 2.32

Next, we turned our attention to oxabispidine **100** with the alternative nitrogen substitution pattern (**Scheme 2.87**, **Table 2.33**). Although more successful than the above derivative **99**,

it was still found that both the chelating amino-magnesium bisamide and the alkyl magnesium amide derivatives were limited in their reactivity. The bisamide derived from **100**, gave only 5% of the enol phosphate product at room temperature (**Entry 1**), whilst the heteroleptic counterpart provided a 10% yield (**Entry 2**). Again, as with previous oxabispidine-derived magnesium base systems within this deprotonation process, the corresponding phosphorylated oxabispidine by-product **102** was isolated.



Scheme 2.87

Entry	Base	*n*-Bu_2Mg	Yield	er (*S*):(*R*)
1	Chelating bisamide	0.5 equiv.	5%	50:50
2	Alkylmagnesium amide	1 equiv.	10%	49:51

Table 2.33

Yet again, we had gained further evidence that our oxabispidine scaffolds, in general, appeared to be unsuitable for the proposed application in magnesium amide base chemistry. Having stated this, there was one final derivative we wished to screen before completely ruling out this class of amine, and that was tricyclic oxabispindine **103** (**Figure 2.32**). This compound, compared to previous oxabispidine examples, has a more similar structure to (-)-sparteine **1**, which, as discussed earlier, has been extensively utilised as a successful chiral ligand in asymmetric synthesis. It was hoped that, although the reactivity might not be greatly improved, the combination of a thermally stable magnesium reagent and a chiral environment more similar to sparteine, would allow a respectable level of selectivity to be achieved, even at room temperature.

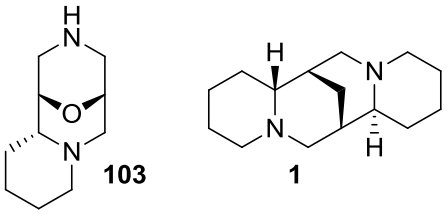
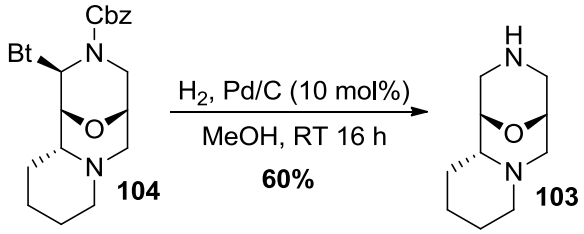


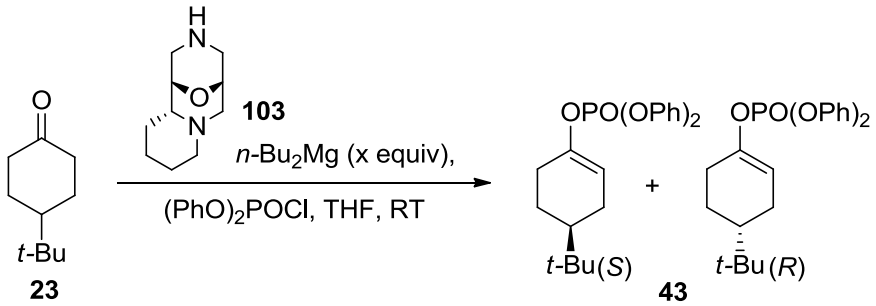
Figure 2.32

To prepare tricyclic **103**, the parent oxabispidine **104** was subjected to hydrogenation conditions for 16 hours, which provided access to the desired product in 60% yield.



Scheme 2.88

With tricyclic **103** in hand, we chose to prepare both the bisamide and the alkylmagnesium amide to assess if either of these species would be effective in the benchmark deprotonation reaction (**Scheme 2.89**, **Table 2.34**).



Scheme 2.89

Entry	Base	*n*Bu_2Mg	Yield	er (*S*):(*R*)
1	Bisamide	0.5 equiv.	0%	-
2	Alkylmagnesium amide	1 equiv.	7%	50:50

Table 2.34

As shown in **Table 2.34**, utilising the chelating amino-magnesium bisamide at room temperature did not lead to any of the desired enol phosphate product **43** being obtained

(**Entry 1**). Instead, 98% of the ketone starting material was recovered and a significant quantity of the by-product **105** (**Figure 2.33**) was obtained.

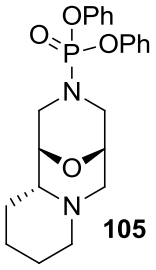


Figure 2.33

The use of the alkylmagnesium amide generated from oxabispidine **103**, did lead to a small amount of the desired product being recovered, but unfortunately HPLC ananlysis showed no level of enantioselectivity was achieved during the reaction (**Table 2.34**, **Entry 2**). Again, ketone substrate was returned, along with the by-product **105**.

At this stage experimental work was halted, as it had become clear that our oxabispidine scaffolds were unsuitable amine ligands for application within the arena of magnesium amide base-mediated asymmetric deprotonation processes. We therefore turned our attention to the potential reasons for the lack of reactivity of the novel oxabispidine-derived base systems investigated.

3.4 Reactivity of the Oxabispidine-derived Magnesium Amide Bases

Having studied a selection of oxabispidine compounds within the magnesium-mediated asymmetric deprotonation process, it has become obvious that there was an inherent issue with these scaffolds in terms of reactivity within such a manifold.

As proposed earlier, it could be envisaged that the chair-chair conformation of the oxabispidines forms a cage-like structure around the magnesium centre imparting a significant amount of stability to the structure. This, in addition to the further steric factor of a sidearm (e.g. Ph in **Figure 2.34**), may be limiting the reactivity of these species.

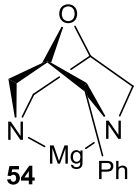


Figure 2.34

This would be the case even for the simplest scenario in solution i.e. a monomeric structure (**Figure 2.34**). However, there is also the possibility that more complicated aggregation states are present in solution, which could also lead to the oxabispidine-derived bases exhibiting poor reactivity. For example we could postulate that dimeric species **106** could be formed (**Figure 2.35**), or, despite magnesium amides generally existing as monomers and dimers, we could also propose an even more complex oligomeric structure such as **107**.

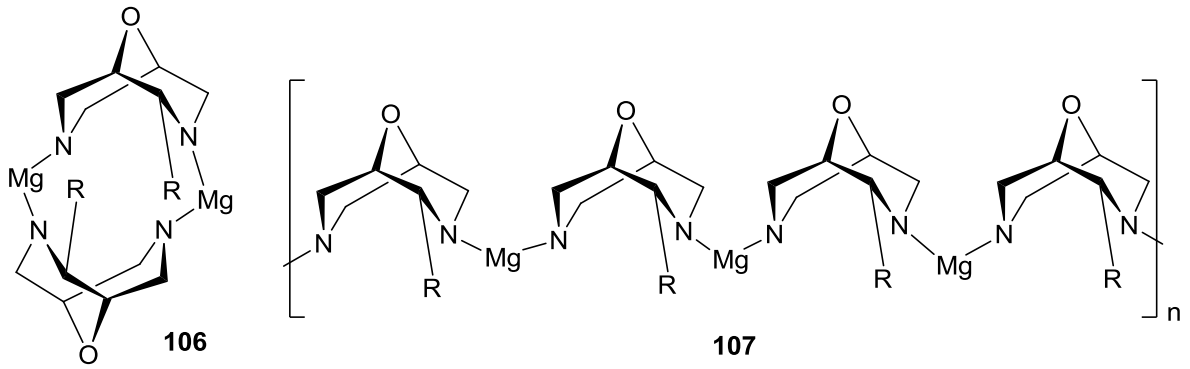


Figure 2.35

If scenarios such as those depicted above were the case, then the addition of LiCl could disrupt such aggregation states and generate mixed metal 'ate' species, which have proven to be more active species in previous amide base systems. Indeed, such an occurrence could explain the enhanced reactivity observed with the inclusion of LiCl in some of our oxabispidine-derived base potocols. Based on research in the area, such as the identification of structure **64** by Koga in lithium amide chemistry[33] or Knochel's work on turbo Grignards which proposes magnesiate structures such as **108**,[54] we could propose analogous structure such as **109** and **110** within our oxabispidine base chemistry (**Figure 2.36**).

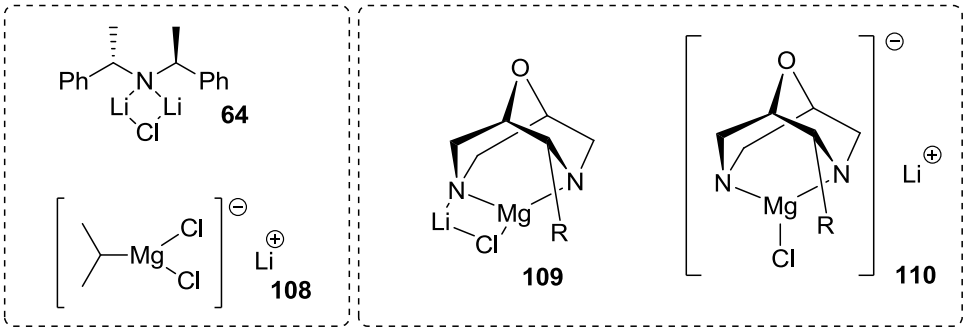


Figure 2.36

With the move to the use of methyl-capped derivatives of the type **48** and **49** (**Figure 2.37**), it was hoped that with only one amide bond formed to each oxabispidine unit, a less rigid magnesium amide would be prepared which might be less stable and thus may lead to increased reactivity.

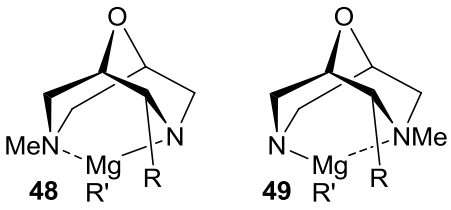
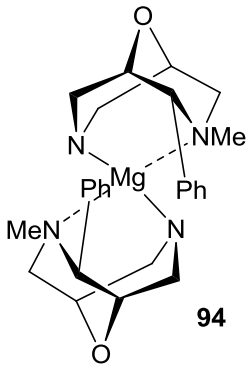


Figure 2.37

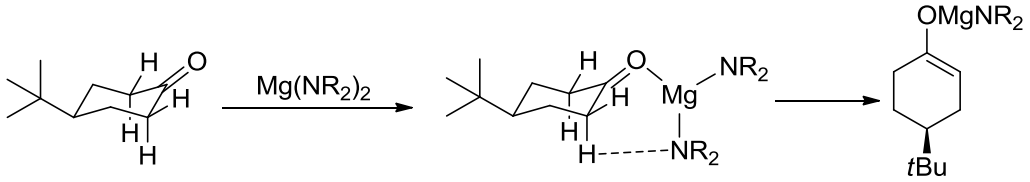
Unfortunately, this was not the case for the chelating amino-magnesium bisamide (where R' = second oxabispidine unit), the alkylmagnesium amide (where R' = *n*-butyl), or the Hauser base (where R' = Cl). One could argue that for the chelating aminomagnesium bisamide, the steric hindrance of two oxabispidine units around the magnesium may render such a species unreactive (**Figure 2.38**). Having stated this, if this were the case, we would then assume that the corresponding alkylmagnesium amide bearing only one oxabispidine unit and a small alkyl group would be more reactive, however this was not observed experimentally.



94

Figure 2.38

In almost all of the deprotonations carried out in this study, regardless of whether a homoleptic or heteroleptic oxabispidine-derived base was used, the base reacted with the diphenyl phosphoryl chloride electrophile, despite significant reaction time with the ketone substrate. Indeed, this indicated a lack of reactivity with the ketone specifically; the bases were able to effectively nucleophilically attack the phosphorus-based electrophile and effectively react with methyl iodide, however limited reactivity with the ketone was observed in all cases. If we consider the deprotonation process, it is assumed that the reaction between 4-*tert*-butylcyclohexanone and a magnesium bisamide occurs *via* complexation of the magnesium centre to the oxygen of the carbonyl substrate to form a base-ketone complex in the first instance, followed by intramolecular transfer of the enantiotopic proton from the α-carbon of the bound ketone to the nitrogen of the magnesium bisamide generating the magnesium enolate (**Scheme 2.90**). Thus, the initial complexation step is of fundamental importance.



Scheme 2.90

It may be the case that the chiral side arm of the oxabispidine, or indeed the oxabispidine framework itself, could be restricting the interaction of the magnesium centre with the carbonyl oxygen thus preventing the deprotonation reaction from proceeding to a significant extent (**A**, **Figure 2.39**). An alternative possibility is that the complexation could be taking place, but the rigid structure of the oxabispidine-derived bisamide, may be restricting the

conformation of the base in such a way that the amide nitrogens are not favourably aligned to abstract the α axial protons (**B**, **Figure 2.39**).

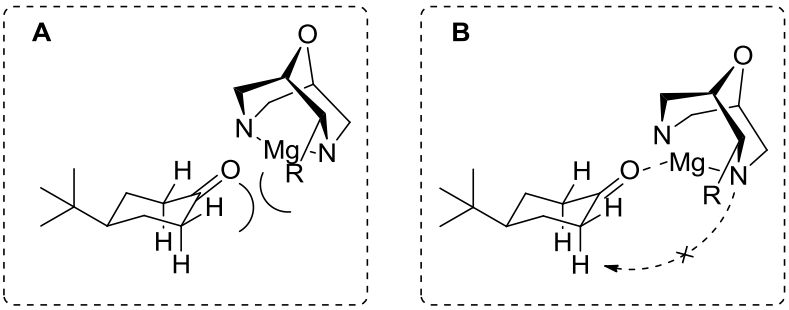


Figure 2.39

A further problem which may be associated with the oxabispidine scaffold, and thus affect the outcome of the deprotonation reaction, is the presence of an additional heteroatom. If we consider oxabispidine **59** as an example, whilst it could sit in the chair/chair conformation proposed earlier (**49i**, **Figure 2.40**), there is also the possibility it could adopt a chair/boat conformation in which the oxygen, as opposed to the N-Me, binds to the magnesium centre (**49ii, Figure 2.40**).

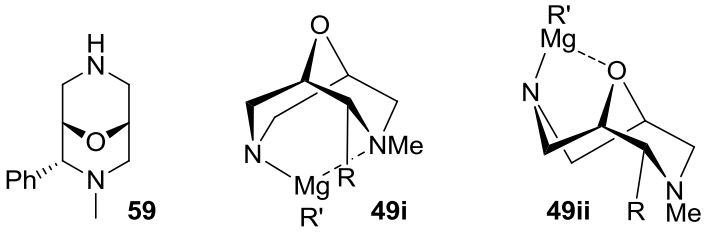
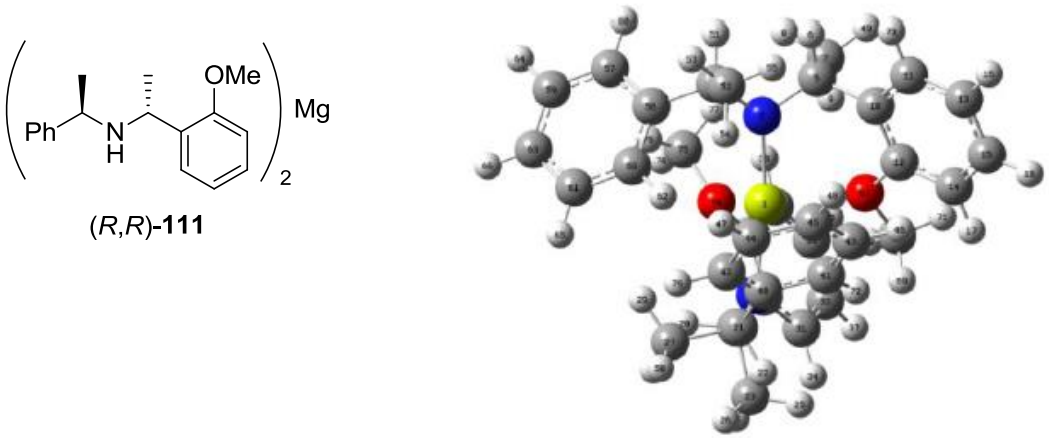


Figure 2.40

Indeed, during previous magnesium bisamide studies it was found that methoxy-substituted base (*R*,*R*)-**111** was completely non-selective in the deprotonation of 4-*tert*-butylcyclohexanone, which was postulated to be a result of direct interaction of the oxygen with the magnesium atom (**Figure 2.41**).[42d] Computational studies later found that of three optimised structures of bisamide (*R*,*R*)-**111**, the structure with the lowest energy was that where simultaneous interactions of both methoxy substituents were present. It was noted that such interactions meant that this structure was vastly different to the optimised structures calculated for various other highly successful magnesium bases.[42d] This result indicated that the presence of an additional heteroatom can have a significant influence on the effectiveness of a magnesium amide base system.



(*R*,*R*)-**111**

Figure 2.41: Optimised structure of (*R*,*R*)-**111** at M06/6-31+G(d) Level of Theory.

With this in mind, we turned to computational techniques in an attempt to gain further insight on the intrinsic issues associated with our novel oxabispidine-derived bases. More specifically, we wished to determine if the presence of the oxygen atom in our oxabispidine scaffolds was potentially having a detrimental effect to their application within magnesium amide base chemistry. As such, the decision was taken to model the previously discussed alkylmagnesium amide bases derived from oxabisbidines **58** and **59** (**Figure 2.42**), both in the chair/chair conformation and the chair/boat conformation in which the oxygen, as opposed to the *N*-Me, binds to the magnesium centre (discussed in **Figure 2.40**).

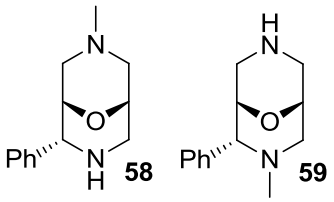


Figure 2.42

It was envisaged that by modelling the alkylmagnesium amides as opposed to the chelating amino bisamides, the calculations would be simplified somewhat, with only a single oxabispidine unit to consider. Depicted in **Figure 2.43** are the alkylmagnesium amide bases that were successfully optimised and the associated enthalpy differences between them.[60] In each case the amide nitrogen is coloured red. Structures A and B show the two possible conformations of the base derived from oxabispidine **58**, and as indicated by the enthalpy values, the chair/chair conformation (A) is significantly more stable than the alternatively

proposed chair/boat scenario (B) where the oxygen chelates to the magnesium. This outcome indicates that a chair/chair base structure seems likely to predominate for the case of oxabispidine **58**, and that the proposed interaction of oxygen is unlikely to be the source of the poor reactivity of oxabispidine-centred amide base system, based on this representative example.

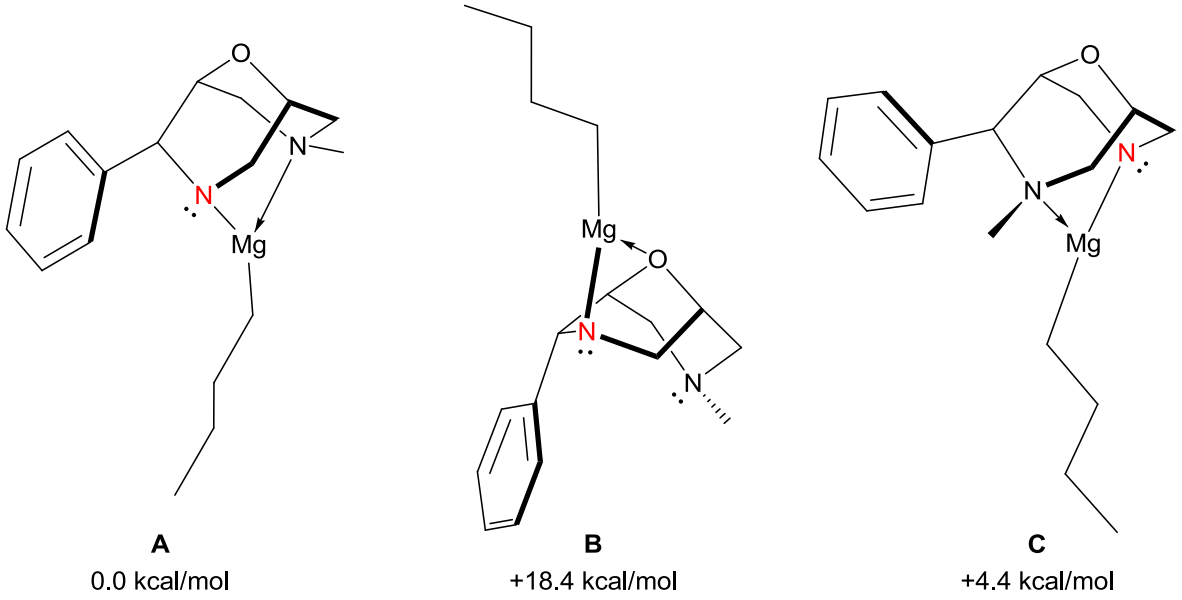


Figure 2.43: Computationally modelled alkyl magnesium amide base structures.

When attempting to model the alkylmagnesium amide base derived from oxabispidine **59**, only the chair/chair conformation C was successfully optimised (**Figure 2.43**). Work is on-going to rectify this issue in order to allow a more complete assessment of the possible base structures. Whilst this meant we were unable to directly compare the chair/boat conformation, it did allow us to compare the stability of alkylmagnesium amide bases derived from oxabispidine **58** and **59** (Structures A and C, **Figure 2.43**) and thereby assess the effect of the nitrogen substitution pattern of the oxabispidine on the base formed. It was found that the alkylmagnesium amide base derived from **59** was less stable that its counterpart derived from **58** (4.4 kcal/mol difference in enthalpy). This could potentially be due to steric interactions between the *N*-Me and phenyl groups in structure C.

We were pleased that these very preliminary theoretical calculations indicated that the oxygen bridge of the oxabispidine scaffold was unlikely to be having a major effect on the oxabispidine-derived magnesium base formed. Unfortunately, with this programme of work

coming to an end, the source of the obvious reactivity issues associated with oxabispidine-derived magnesium amide bases has yet to be identified.

4. Conclusions

To conclude, a programme of research centred on the application of enantiomerically-enriched oxabispidine scaffolds within the arena of magnesium-mediated asymmetric deprotonation processes was undertaken. Initial studies focused on the use of the phenyl-substituted bis-secondary oxabispidine **51** (**Figure 2.44**), and demonstrated that both the magnesium bisamide and lithium amide derivatives could be successfully prepared from the bis-HCl salt **56**.

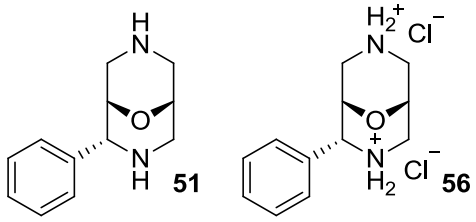
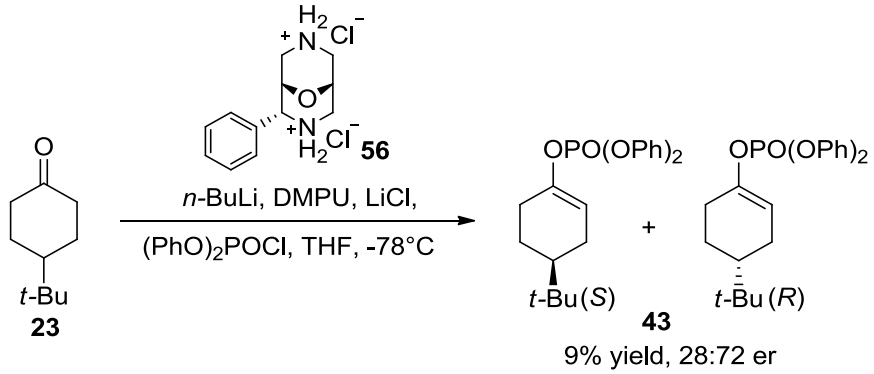


Figure 2.44

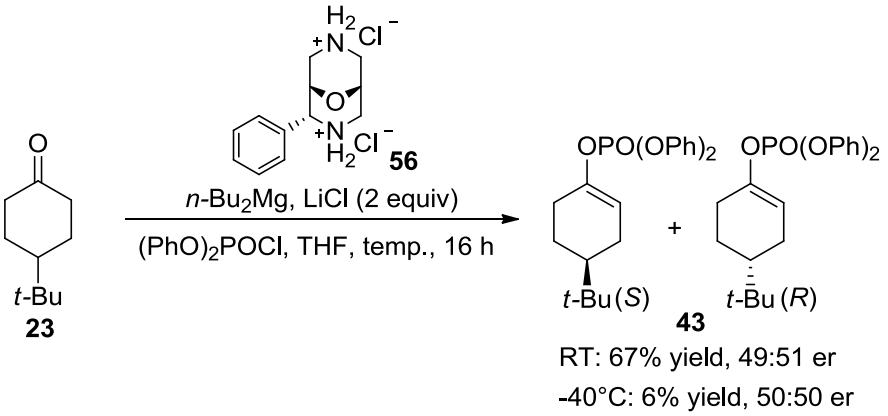
Investigations into the use of such amide base species in the deprotonation of 4-*tert*-butylcyclohexanone showed that under lithium-mediated conditions, whilst promising levels of enantioselectivity could be achieved (72:28 er at -78°C) only poor to moderate yields of the enol phosphate product were attained, even when LiCl and Lewis basic additives were incorporated (**Scheme 2.91**).



Scheme 2.91

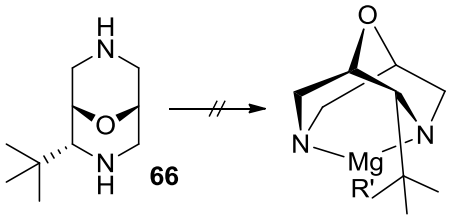
Similarly, poor reactivity was observed with the corresponding magnesium-amide base. Indeed, no improvement over the lithium amide counterpart was observed in either the yield or selectivity of the deprotonation process. Whilst the inclusion of 2 equivalents of LiCl to the magnesium base system did provide more promising yields at room temperature,

presumably through the generation of a 'magnesiate' species, at lower reaction temperatures which generally allow high levels of enantioselectivity in other systems, no selectivity was observed at all with the novel oxabispidine based system (**Scheme 2.92**).



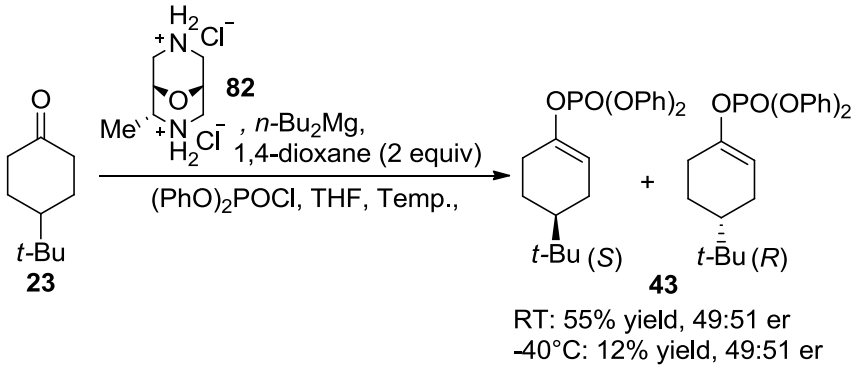
Scheme 2.92

Altering the sidearm of the oxabispidine scaffold to incorporate a more electron-donating substituent, and therefore a potentially more reactive magnesium amide, did not lead to the desired increase in yield. It was found that the *tert*-butyl derivative **66** was too bulky to allow the desired bisamide to form.



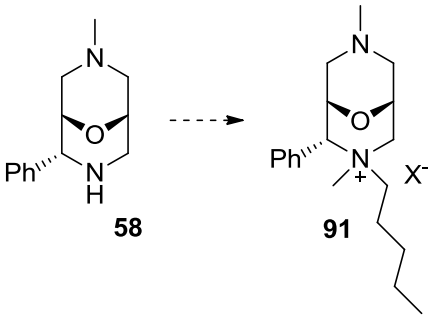
Scheme 2.93

Having stated this, moving to the smaller methyl derivative led to yields similar to those achieved with the original phenyl derivative **56**, albeit with newly optimised additive conditions. In this case, addition of 1,4-dioxane provided the optimal protocol (**Scheme 2.94**).



Scheme 2.94

An alternative route of investigation with a view to increasing the reactivity of the oxabispidine magnesium amide system was the capping of one of the nitrogen atoms with a methyl group, to allow the generation of chelating amino-magnesium bisamides. Unfortunately, and quite surprisingly, when utilising tertiary/secondary oxabispidine **58**, an unwanted side-reaction took place leading to the generation of compounds such as **91** (**Scheme 2.95**). Disappointingly, this rendered oxabispidine **58** unsuitable for use in our desired transformation.



Scheme 2.95

The secondary/tertiary derivative **59**, in addition to being used to prepare the chelating bisamide **94**, was also used to successfully prepare heteroleptic bases **96** and **97**, namely the Hauser base and alkylmagnesium amide, respectively (**Figure 2.45**). Upon screening in the deprotonation of 4-*tert*-butylcyclohexanone, again only poor yields of the enol phosphate product were recovered (≤ 25% yield at room temperature) with no significant enantioselectivity being observed for any of the species shown below.

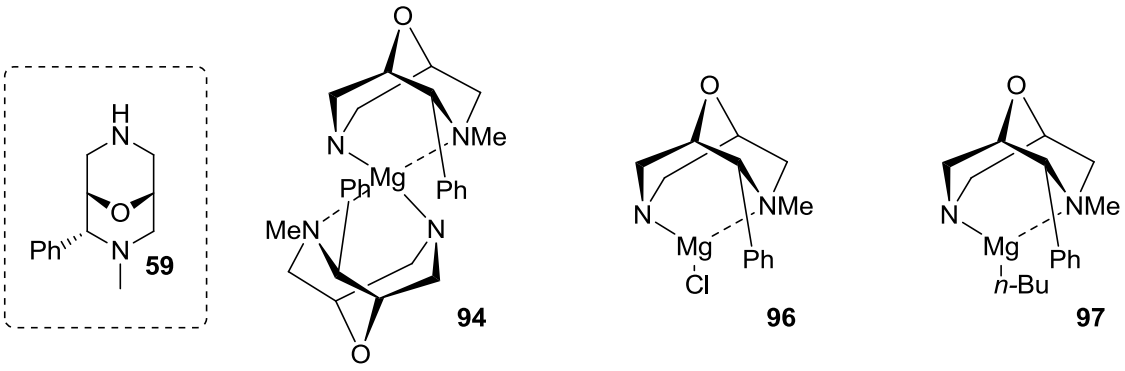
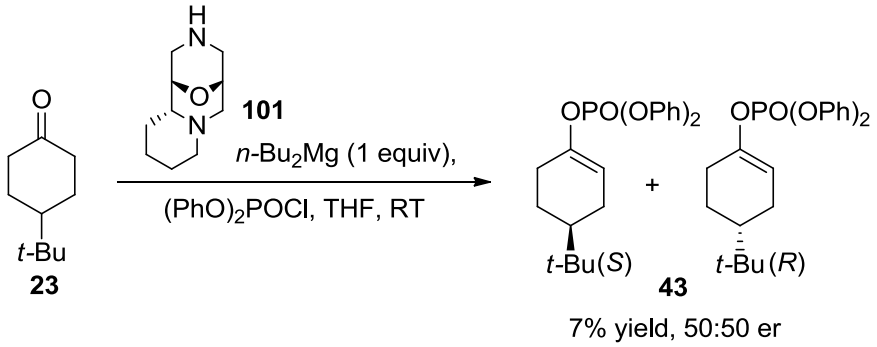


Figure 2.45

In a final attempt to discover an oxabispidine derivative suitable for application in our magnesium-mediated deprotonation protocol, we employed tricyclic derivative **101** (**Scheme 2.96**). With its more closely related structure to the commonly used chiral ligand (-)-sparteine, it was hoped that improved reactivity/enantioselectivity would be observed. However, as with previous oxabispidine-derived bases, neither the homoleptic or heteroleptic magnesium amide species generated from **101** were effective in the benchmark deprotonation reaction.



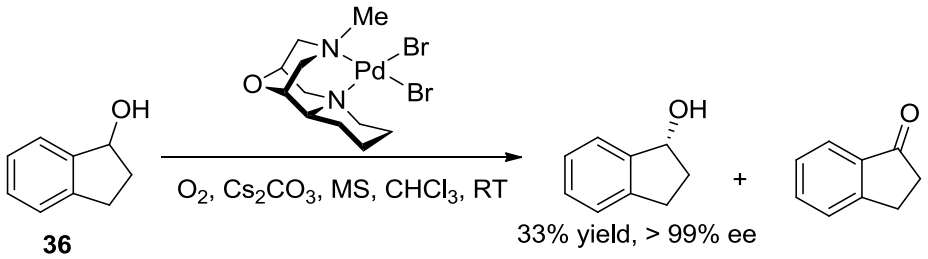
Scheme 2.96

Despite significant investigation, the poor yields and selectivities achieved in the asymmetric deprotonation study, indicated that there was an inherent reactivity issue associated with the newly developed oxabispidine amide base systems. Preliminary theoretical studies indicated that the presence of an additional heteroatom (in the form of the oxygen bridge) did not appear to have a significant effect on the structure of the amide base formed, and thus is unlikely to be the cause of the reactivity issues observed.

5. Future Work

To gain an understanding of why oxabispidine scaffolds are unsuitable for use in our laboratory's work on magnesium-mediated deprotonation reactions, further theoretical studies on the asymmetric deprotonation reaction mechanism and energetics may prove beneficial. Modelling the reaction with an oxabispidine-derived bisamide and comparing the results to previous computational modelling of a successful magnesium bisamide may provide useful insight.[42d] Furthermore, it may be useful to gain a better understanding of the aggregation states of the oxabispidine-derived magnesium bases, to evaluate if higher order solution structures are responsible for the lack of reactivity.

Whilst it has been demonstrated that optically-enriched oxabispidine scaffolds of the type discussed herein are unsuitable for use in magnesium-mediated asymmetric deprotonations of pro-chiral ketones, they still possess key structural features which give them the potential to be effective chiral ligands. As such, screening these species as potential (-)-sparteine mimics would be a useful avenue of research, especially given the current shortage of (-)sparteine being reported.[3] Although the use of oxabispidines in combination with *sec*-butyllithium may not be viable due to the potential for bridgehead lithiation,[61] their application within other metal-mediated processes could be explored. With our recent endeavours developing the largest collection of chiral oxabispidines reported to date, we have the opportunity to screen a wide variety of electronically and sterically different ligands within established chemistry, for example, in the palladium-catalysed oxidative chiral resolution of alcohols or the copper-catalysed Henry reaction.[26] In these cases, only a very limited number of oxabispidine ligands have been screened and, as of yet, only the tricyclic derivative shown in **Scheme 2.97** has been effective. With the ability to prepare and test a broader selection of oxabispidines, a more comprehensive understanding of the properties required in the oxabispidine ligand could be gained.



Scheme 2.97

Finally, with the wide range of oxabispidines now available, these could, in fact, be screened in completely novel metal-mediated chemistry where (-)-sparteine is not commonly used, but where the application of a diamine ligand may prove beneficial.

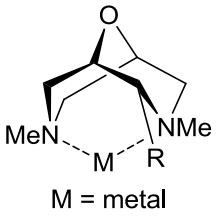


Figure 2.46

6. Experimental

6.1 General Experimental Considerations

All reagents were obtained from commercial suppliers and were used without further purification unless stated otherwise. Purification was carried out according to standard laboratory methods.[62]

- Tetrahydrofuran was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, and then distilled under nitrogen.
- Dichloromethane was dried by heating to reflux over calcium hydride and then distilled under nitrogen.
- Petroleum ether refers to light petroleum ether, b.p. range 40 – 60°C.
- DMPU was distilled from calcium hydride (0.03 mbar, 88°C) and was stored over 4 Å molecular sieves under argon.
- 18-crown-6 was dried by heating to 125°C under high vacuum (0.005 mbar) using Kügelrohr apparatus for two hours, then were stored under argon over 4 Å molecular sieves.
- *N*,*N*,*N'*,*N'*-Tetramethylethylenediamine (TMEDA) and was dried by distillation over sodium under reduced pressure, then purged with and stored under argon over 4 Å molecular sieves.
- 1,4-Dioxane was dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, and then distilled under nitrogen.
- LiCl was flame-dried under high vacuum, then purged with and stored under argon.
- Diphenylphosphoryl chloride was dried by heating to reflux over calcium hydride and distilled under reduced pressure, then purged with and stored under argon over 4 Å molecular sieves.

- *n*-Bu_2Mg obtained as 1M solution in heptane and *n*-BuLi, obtained as a 2.5M solution in hexane or THF were standardised using salicylaldehyde phenylhydrazone.[62]

- 4-*tert*-Butylcyclohexanone was purified by recrystallisation from hexane and dried by placing under vacuum (0.005 mbar) for 16 h, then purged with and stored under argon.

- Oxabispidine HCl salts were prepared by addition of concentrated HCl to the bis-secondary amine and purified by recrystallisation from IPA.

- Oxabispidine amines and HCl salts used in air- and moisture-sensitive reactions were dried by heating to 80°C under high vacuum for 16 hours then purged with and stored under argon prior to use.

Air-sensitive reactions were carried out using Schlenk apparatus, which was initially evacuated and flame-dried under vacuum (0.005 mbar), then allowed to cool under an atmosphere of argon.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. This was analysed using a Mineralight UVGL-25 lamp and developed using either vanillin or potassium permanganate solution.

Flash chromatography was carried out using ZEOCHEM® silica gel (ZEOprep60 HYD 40-60 μm).

FTIR spectra were obtained on a Nicolet Impact 400D machine.

^{1}H, ^{13}C and ^{31}P spectra were obtained on a Bruker DPX 400 spectrometer at 400, 100, and 162 MHz, respectively, unless otherwise stated. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions unless otherwise stated.

High-resolution mass spectra were obtained on a Finnigan MAT900XLT instrument at the EPSRC National Mass Spectrometry Services Centre, University of Swansea, Wales.

Elemental analysis was obtained using a Carlo Ebra 1106 CHN analyser.

Optical rotations were obtained on Perkin Elmer 341 polarimeter using a cell with a path length of 1 dm. Concentration is expressed in g/100 cm^3.

High performance liquid chromatography was carried out using a Chirasil OD-H column using a Waters 501 HPLC pump, a Waters 484 tuneable absorbance detector (set at 254 nm unless otherwise specified), and processed using a Waters 746 data module.

6.2 General Experimental Procedures

General Procedure A - *The preparation of magnesium bisamide reagents*

To a Schlenk flask which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon was added the required oxabispidine or oxabispidine salt. This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To a second Schlenk flask was added *n*-Bu_2Mg in heptane, and the heptane was removed *in vacuo* until a white solid was obtained. This white solid was dissolved in THF and the resulting solution was transferred to the Schlenk flask containing the oxabispidine *via* syringe. The reaction mixture was stirred at the specified temperature for the specified period of time under argon. After this time, quantitative formation of the chiral magnesium bisamide was assumed.

General Procedure B - *The preparation of magnesium bisamide reagents with the inclusion of LiCl*

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added LiCl. The Schlenk containing the LiCl was then flame-dried under vacuum again (taking care to ensure the LiCl did not melt) and allowed to cool under an atmosphere of argon. To this was added the required oxabispidine or oxabispidine salt. The solids were then placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To a second Schlenk flask was added *n*-Bu_2Mg in heptane. The heptane was removed *in vacuo* until a white solid was obtained. This white solid was dissolved in THF and the resulting solution was transferred to the Schlenk containing the oxabispidine and LiCl *via* syringe. The reaction mixture was stirred at reflux for 1.5 h under argon. After this time, quantitative formation of the chiral magnesium bisamide was assumed.

General Procedure C *- The preparation of lithium amide reagents*

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added the required oxabispidine or oxabispidine salt. This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To this was added THF to generate a suspension of the oxabispidine. The mixture was cooled to -78°C and *n*-BuLi was added dropwise. After complete addition of *n*-BuLi, the reaction was stirred at -78°C for 10 min, before warming to 0°C and stirring for 20 min at this temperature. After this time quantitative formation of the chiral lithium amide was assumed.

General Procedure D *- The preparation of lithium amide reagents with the inclusion of LiCl*

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added LiCl. The Schlenk containing the LiCl was then flame-dried under vacuum again (taking care to ensure the LiCl did not melt) and allowed to cool under an atmosphere of argon. To this was added the required oxabispidine or oxabispidine salt. The solids were then placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To the Schlenk containing the oxabispidine and LiCl was added THF to generate a suspension of the solids. The mixture was cooled to -78°C and *n*BuLi was added dropwise. After complete addition of *n*-BuLi, the reaction was stirred at -78°C for 10 min, before warming to 0°C and stirring for 20 min at this temperature. After this time, quantitative formation of the chiral lithium amide was assumed.

General Procedure E *- The preparation of alkyl magnesium amide reagents*

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added the required oxabispidine. This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To a second Schlenk flask was added *n*-Bu_2Mg in heptane. The heptane was removed *in vacuo* until a white solid was obtained. This white solid was dissolved in THF and the resulting solution was transferred to the Schlenk containing the oxabispidine *via* syringe. The reaction mixture was stirred at room temperature for 1 h under argon. After this time quantitative formation of the alkyl magnesium amide was assumed.

General Procedure F *- The preparation of alkyl magnesium amide reagents with the inclusion of LiCl*

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added LiCl. The Schlenk containing the LiCl was then flame-dried under vacuum again (taking care to ensure the LiCl did not melt) and allowed to cool under an atmosphere of argon. To this was added the required oxabispidine. The solids were then placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To a second Schlenk flask was added *n*-Bu_2Mg in heptane. The heptane was removed *in vacuo* until a white solid was obtained. This white solid was dissolved in THF and the resulting solution was transferred to the Schlenk containing the oxabispidine and LiCl *via* syringe. The reaction mixture was stirred at room temperature for the 1.5 h under argon. After this time, quantitative formation of the alkyl magnesium amide was assumed.

General Procedure G *- The methylation of oxabispidine-derived metal amide bases*

A solution of chiral amide base prepared *via* one of the **General Procedures A** to **F** was cooled to -78°C under argon. To the reaction mixture was added methyl iodide dropwise. The resulting solution was allowed to stir at -78°C for 30 min before warming to room temperature and stirring for 1 h. After this time, the reaction was quenched with a saturated solution of $NaHCO_3$ (10 ml), warmed to room temperature, and extracted with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (eluent: gradient from DCM to 10% MeOH in DCM) to give the desired clean product.

General Procedure H *- The asymmetric deprotonation of 4-tert-butylcyclohexanone by metal amide bases to form enol phosphate* ***43***

A solution of chiral amide base prepared *via* one of the **General Procedures A** to **F** was cooled to the appropriate temperature under argon. To the reaction mixture was added a solution of 4-*tert*-butylcyclohexanone in THF (1 ml) over a period of 1 h *via* syringe pump. The resulting solution was allowed to stir at the temperature stated for 16 h. After this time, a solution of diphenyl phosphoryl chloride in THF (1 ml) was added over a period of 1 h *via* syringe pump. After complete addition of the electrophile the reaction was stirred for 30 min

before quenching with a saturated solution of $NaHCO_3$ (10 ml), warming to room temperature, and extracting with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified *via* flash chromatography (eluent: gradient from petroleum ether to 12% diethyl ether in petroleum ether) to give the enol phosphate as a colourless oil.

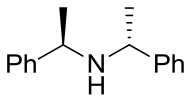
General Procedure I *- The asymmetric deprotonation of 4-tert-butylcyclohexanone by metal amide bases to form enol phosphate* ***43*** *with the inclusion of a Lewis basic additive*

A solution of chiral amide base prepared *via* one of the **General Procedures A** to **F** was cooled to the appropriate temperature under argon. The specified additive was added and the reaction stirred at the temperature stated for 15 min. To the reaction mixture was added a solution of 4-*tert*-butylcyclohexanone in THF (1 ml) over a period of 1 h *via* syringe pump. The resulting solution was allowed to stir at the temperature stated for 16 h. After this time, a solution of diphenyl phosphoryl chloride in THF (1 ml) was added over a period of 1 h *via* syringe pump. After complete addition of the electrophile, the reaction was stirred for 30 min before quenching with a saturated solution of $NaHCO_3$ (10 ml), warming to room temperature, and extracting with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified *via* flash chromatography (eluent: gradient from petroleum ether to 12% diethyl ether in petroleum ether) to give the enol phosphate as a colourless oil.

Full experimental data for enol phosphate 43 and by-products resulting from asymmetric deprotonation reactions can be found in Section 6.7

6.3 Benchmark Deprotonations using C_2-symmetric base *(R,R)-50*

*Preparation of (R)-bis((R)-1-phenylethyl)amine (R,R)-**50***[64]



$C_{16}H_{19}N$
Molecular Weight: 225.33

Procedure

Scheme 2.27

(*R*)-1-Phenylethylamine (20.0 g, 165 mmol), acetophenone (19.8 g, 165 mmol) and titanium tetra-*iso*-propoxide (141.0 g, 500 mmol) were stirred for 30 minutes before addition of palladium (720 mg, 16.5 mmol, 10% on carbon). The reaction mixture was then hydrogenated under H_2 (8 bar) with stirring for 48 h before being partitioned between H_2O (500 ml) and EtOAc (500 ml), and filtered through celite. The aqueous layer was extracted with EtOAc (3 x 300 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give an orange oil. The dr was determined as 67:33 by ^{1}H NMR analysis. The crude product was converted to its HCl salt by addition of concentrated HCl and purified by recrystallisation from IPA. The diastereomerically pure free amine was then generated by dissolving the salt in 2M NaOH (500 ml), extracting with EtOAc (3 x 300 ml), drying over Na_2SO_4, and concentrating *in vacuo* to give the desired product as a colourless oil (21.5 g, 56%). The amine was heated at 50°C over CaH_2 *in vacuo* (0.4 mbar) for 2 h before being distilled *in vacuo* (98°C, 0.4 mbar).

IR: ($CDCl_3$): 2880, 2962, 3010, 3050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.7 Hz, 6H, N(CHC*H*$_3$)$_2$), 3.53 (q, *J* = 6.7 Hz, 2H, N(CH)$_2$), 7.23-7.34 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 55.2, 126.7, 126.8, 128.5, 145.9 ppm.

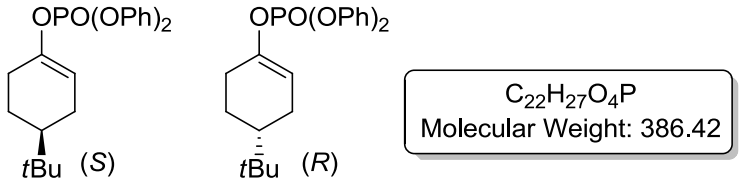
Peaks used to determine dr of crude amine from ^{1}H NMR (400 MHz, $CDCl_3$):

δ 3.53 ((*R*,*R*), q, 1H, CH).

δ 4.15 ((*R*,*S*), q, 1H, CH).

$[\alpha]_D^{20}$ +171.6 (*c* 6.71, $CHCl_3$). Lit: $[\alpha]_D^{20}$ -171.6 ((*S*,*S*), c = 6.71, $CHCl_3$).[55]

*Asymmetric Deprotonation of tert-Butylcyxlohexanone using Magnesium Bisamide (R,R)-**34***



General Procedure

nBu_2Mg in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon. The heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. THF (10 mL) was then added, followed by (*R,R*)-**50**, and the solution was heated at reflux for 1.5 h, assuming quantitative formation of the magnesium bisamide (*R,R*)-**36**. The solution of magnesium base was cooled under argon to -78°C. The Schlenk flask was then charged with DMPU followed by diphenylphosphoryl chloride, and the reaction mixture was stirred for 10 minutes at -78°C. *tert*-Butylcyclohexanone was then added as a solution in THF (2 ml) over 1 h using a syringe pump. The reaction mixture was stirred at -78°C overnight before being quenched with a saturated aqueous sodium bicarbonate solution and allowed to warm to room temperature. Extraction with Et_2O (2 x 25 ml) and removal of the solvent *in vacuo* gave the crude product, which was purified by column chromatography on silica gel using 10% Et_2O in petroleum ether to give the product as a colourless oil. The enantiomeric ratio of the product was determined by analysis using chiral HPLC.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of *n*Bu_2Mg; (b) quantity of (*R,R*)-**50**; (c) quantity of DMPU; (d) quantity of $(PhO)_2POCl$; (e) quantity of ketone; (f) yield of enol phosphate; and (g) (*S*):(*R*).

Table 2.9, Entry 1

Run 1

(a) 0.98 ml, 1 mmol; (b) 0.44 ml, 2 mmol; (c) 0.06 ml, 0.5 mmol; (d) 0.42 ml, 2 mmol; (e) 0.12 g, 0.8 mmol; (f) 0.20 g, 63%; and (g) 95:5.

Run 2

(a) 0.98 ml, 1 mmol; (b) 0.44 ml, 2 mmol; (c) 0.06 ml, 0.5 mmol; (d) 0.42 ml, 2 mmol; (e) 0.12 g, 0.8 mmol; (f) 0.24 g, 76%; and (g) 92:8.

Table 2.9, Entry 2

Run 1

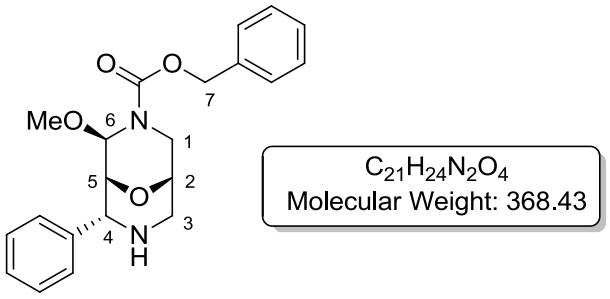
(a) 0.98 ml, 1 mmol; (b) 0.44 ml, 2 mmol; (c) 0.06 ml, 0.5 mmol; (d) 0.42 ml, 2 mmol; (e) 0.12 g, 0.8 mmol; (f) 0.25 g, 80%; and (g) 95:5.

Run 2

(a) 0.98 ml, 1 mmol; (b) 0.44 ml, 2 mmol; (c) 0.06 ml, 0.5 mmol; (d) 0.42 ml, 2 mmol; (e) 0.12 g, 0.8 mmol; (f) 0.26 g, 85%; and (g) 96:4.

6.4 Application of Metal Amide Bases derived from Oxabispidine 51

*Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **53***



General Procedure

To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 followed by a solution of oxazine (*S*)-**52** in DCM. To this was added benzaldehyde and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol was added. To the reaction mixture was added triflic acid in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale yellow to an intense bright yellow. After complete addition of the triflic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed

to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a yellow oil.

Following the ***General Procedure***, results are presented as follows:

(a) quantity of (*S*)-**52**; (b) volume of DCM; (c) quantity of Na_2SO_4; (d) quantity of benzaldehyde; (e) quantity of methanol; (f) quantity of triflic acid; and (g) yield.

Table 2.10, Entry 1

(a) 11 g, 44.3 mmol; (b) 450 ml; (c) 63 g, 443 mmol; (d) 4.5 ml, 44.3 mmol; (e) 1.8 ml, 44.3 mmol; (f) 3.9 ml, 44.3 mmol; and (g) 8.8 g, 54%.

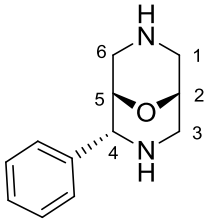
Table 2.10, Entry 2

(a) 23.6 g, 95.1 mmol; (b) 700 ml; (c) 135 g, 951 mmol; (d) 9.7 ml, 95.1 mmol; (e) 3.8 ml, 95.1 mmol; (f) 8.4 ml, 95.1 mmol; and (g) 20 g, 57%.

IR ($CDCl_3$): 1705, 2789, 2930, 3027, 3295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (br.s. 1H, NH), 3.13 (s, 2H, OCH_3), 3.20 (s, 1H, OCH_3, overlapping with signal corresponding to 0.4H, H3), 3.30 (d, ^2J = 11.8 Hz, 0.6H, H3); 3.53-3.57 (m, 1H, H3), 3.59-3.65 (m, 0.6H, H1), 3.67-3.70 (m, 0.4H, H1), 3.79-3.81 (m, 0.4H, H2), 3.88-3.93 (m, 1.6 H, H2+H5), 4.07 (d, ^2J =13.4 Hz, 0.4H, H1), 4.14 (d, ^2J = 13.4 Hz, 0.6H, H1), 4.42-4.44 (m, 1H, H4), 4.86 (s, 0.6H, H6), 5.01 (s, 0.4H, H6), 5.21-5.37 (m, 2H, H7), 7.14-7.47 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$): δ 42.0, 42.5, 49.9, 52.9, 53.8, 54.1, 61.1, 61.7, 65.5, 65.8, 66.8, 67.0, 74.3, 74.7, 78.3, 126.1, 126.5, 127.0, 127.2, 127.4, 127.6, 127.7, 128.9, 128.1, 135.6, 138.7, 138.9, 154.6 ppm; HRMS *m/z* Calc. for $C_{21}H_{25}N_2O_4$ (M^++H): 369.1809. Found: 369.1815.

$[\alpha]_D^{20}$ -104.3 (*c* 1.0, $CHCl_3$).

*Preparation of (1S,2R,5R)-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **51***



$C_{12}H_{16}N_2O$
Molecular Weight: 204.27

General Procedure

A three-necked flask was flame-dried under vacuum before cooling under an atmosphere of Ar. The flask was then charged with palladium (10% on carbon) followed by a solution of **53** in methanol. The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: 0% to 10% MeOH in DCM), to yield the desired product as a yellow oil.

Following the above ***General Procedure***, results are presented as follows:

(a) quantity of Pd/C; (b) quantity of **53**; (c) volume of MeOH; and (d) yield.

Table 2.11, Entry 1

(a) 0.52 g, 0.5 mmol; (b) 1.84 g, 5 mmol; (c) 100 ml; and (d) 0.75 g, 73%.

Table 2.11, Entry 2

(a) 2.8 g, 2.7 mmol; (b) 10 g, 27 mmol; (c) 500 ml; and (d) 5.7 g, 89%.

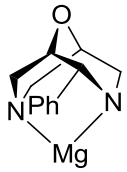
IR (neat): 2689, 2882, 3027, 3087, 3301 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.62 (br. s, 2H, NH), 2.80 (d, ^2J = 13.8 Hz, 1H, H6), 2.99-3.02 (m, 1H, H6), 3.12 (d, ^2J = 13.3 Hz, 1H, H1), 3.32 (d, ^2J = 11.8 Hz, 1H, H3), 3.36-3.39 (m, 1H, H1), 3.57-3.66 (m, 3H, H2+H3+H5), 4.57 (s, 1H, H4), 7.26-7.39 ppm (m, 5H, H_{Ar}): ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.2, 50.5, 51.1,

63.9, 67.0, 72.3, 126.5, 127.4, 128.7, 141.0 ppm; HRMS: *m/z* Calc. for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335. Found: 205.1335.

$[\alpha]_D^{26}$ -81.6 (*c* 0.18, MeOH).

6.4.1 Confirmation of formation of 54

Attempted Preparation of magnesium (1S,2R,5R)-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-diide ***54***



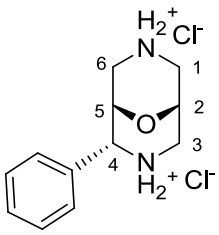
$C_{12}H_{14}MgN_2O$
Molecular Weight: 226.56

Procedure

Scheme 2.31

nBu_2Mg (0.82 ml, 0.98 mmol) in heptane was transferred to a Schlenk flask, which had been flame-dried under vacuum (0.005 mbar) and allowed to cool under an atmosphere of argon, and the heptane was removed *in vacuo* (0.005 mbar) until a white solid was obtained. Diamine **51**(0.2 g, 0.98 mmol), as a solution in d_8-THF (9.8 ml), was added to the Schlenk flask. A small quantity of white solid had precipitated out of the amine solution prior to transfer to the Schlenk flask, therefore an additional quantity of d_8-THF (0.5 ml) was added to the flask containing this unexpected solid, and the resulting suspension transferred to the reaction Schlenk. Addition of the amine solution was accompanied by an intensifying of colour of the solution from pale to bright yellow. The reaction mixture was stirred at room temperature for 1 h, before a sample was taken for analysis. Following ^{1}H NMR analysis, it was evident that the broad signal corresponding to the NHs was still present. Continued stirring of the reaction overnight led to no significant change in the ^{1}H NMR spectrum of the reaction mixture. The experiment was ended at this point.

Preparation of (1S,2R,5R)-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-diium chloride ***56***



$C_{12}H_{18}Cl_2N_2O$
Molecular Weight: 277.19

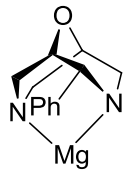
Procedure

A round-bottomed flask containing **51** (6 g, 29.4 mmol) as an oil was cooled in an ice bath and concentrated HCl (5 ml, 60.3 mmol) was added. The resulting solid was dried *in vacuo*. The HCl salt (4.9 g, 60%) was recrystallised from IPA and dried heating to 80°C under high vacuum for 16 hours, then purged with and stored under argon prior to use.

IR (neat): 1608, 2280, 3041 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 3.14 (dd, ^2J = 14.0, J = 2.0 Hz, 1H, H6), 3.42 (dd, ^2J = 14.0, J = 7.1 Hz, 1H, H6), 3.47-3.50 (m, 1H, H1), 3.58-3.62 (m, 1H, H1), 3.69-3.77 (m, 2H, H3), 4.54-4.55 (m, 1H, H2), 4.61-4.64 (m, 1H, H5), 4.93 (d, J = 3.4 Hz, 1H, H4), 7.40-7.52 ppm (m, 5H, H_{Ar}): ^{13}C NMR (100 MHz, D_2O): δ 38.5, 42.6, 45.6, 58.9, 61.2, 66.1, 125.3, 128.9, 129.1, 131.8 ppm; HRMS: *m/z* Calc. for cation $C_{12}H_{17}N_2O$ [M+]: 205.1335. Found: 205.1331. Cl^- isotope ions at m/z 35/37 are observed.

$[\alpha]_D^{25}$ -65.4 (*c* 0.35, MeOH).

Preparation of magnesium (1S,2R,5R)-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-diide ***54***



Procedure

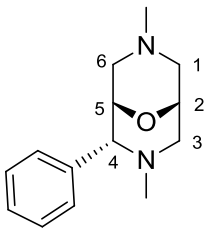
Scheme 2.32

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added bis-HCl salt **56** (0.08 g, 0.3 mmol). This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To a second Schlenk flask was added *n*-Bu_2Mg (0.6 ml, 0.6 mmol) and the heptane was removed *in vacuo* until a white solid was obtained. This white solid was dissolved in d_8-THF (4.8 ml). A portion of this solution (2.4 ml) was transferred to the Schlenk flask containing **56**. The reaction was stirred at room temperature for 1 h, before a sample was taken for ^{1}H NMR analysis. The NMR spectrum showed the appearance of a broad singlet corresponding to the newly generated free NH signals. To the reaction mixture was added the second portion of the *n*Bu_2Mg solution (2.4 ml), and the reaction was heated to 40°C and stirred at this temperature for 3 h, before a second sample of the reaction mixture was taken. ^{1}H NMR showed that no NH signal was present and all the signals had shifted slightly upfield, indicating the generation of the magnesium bisamide.

Diagnostic peaks of bisamide **54** from crude ^{1}H NMR spectrum:

^{1}H NMR (400 MHz, d_8-THF): δ 2.34-3.62 (m, 8H), 4.48 (s, 1H), 7.16-7.44 (m, 3H), 7.50 (d, J = 7.4 Hz, 2H) ppm.

*Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57** via methylation of **54**.*



$C_{14}H_{20}N_2O$
Molecular Weight: 232.32

Scheme 2.33, Table 2.12

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **54**, data are presented as follows: (a) quantity of MeI; and (b) yield of **57**.

Entry 1

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.51 ml, 0.6 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.046 g, 66%, as a white solid.

Entry 2

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.51 ml, 0.6 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.052 g, 75%, as a white solid.

Entry 3

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.51 ml, 0.6 mmol; (d) 5 ml; (e) 40°C; and (f) 3 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.047 g, 68%, as a white solid.

Entry 4

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.51 ml, 0.6 mmol; (d) 5 ml; (e) RT; and (f) 16 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.045 g, 64%, as a white solid.

Entry 5

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.51 ml, 0.6 mmol; (d) 5 ml; (e) RT; and (f) 3 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.021 g, 30%, as a white solid.

Entry 6

General procedure A: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 0.26 ml, 0.3 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.002 g, 3%, as a white solid.

Melting point: 63-65°C.

IR (neat): 1088, 1265, 1450, 2785, 2936 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.04 (dd, ^{2}J = 11.9, J = 3.8 Hz, 1H, H6), 2.10 (s, 3H, NCH_3), 2.22 (s, 3H, NCH_3), 2.47 (ddd, ^{2}J = 11.5, J = 3.7, ^{4}J = 1.1 Hz, 1H, H1), 2.70-2.75 (m, 2H, H3+H6), 3.05 (d, ^{2}J = 11.5 Hz, 1H, H1), 3.15 (d, ^{2}J = 11.8 Hz, 1H, H3), 3.47 (d, J = 3.8 Hz, 1H, H4), 3.69 (t, J = 3.7 Hz, 1H, H2), 3.97 (t, J = 3.7 Hz, 1H, H5), 7.25-7.37 ppm (m, 5H, H_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$): 45.8, 47.3, 53.8, 58.4, 58.9, 68.8, 72.3, 73.1, 127.4, 128.5, 139.8 ppm; HRMS: *m/z* Calc. for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648. Found: 233.1649.

$[\alpha]_D^{20}$ -8.74 (*c* 1.0, $CHCl_3$).

6.4.2 Application of Magnesium Bisamide 54 in Deprotonation of 4-tert-Butylcyclohexanone

Scheme 2.34, Table 2.13

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of $n$$Bu_2Mg$; (d) volume of THF; (e) temperature; and (f) time.

Entry 1

General procedure A: (a) **56**; (b) 0.28 g, 1 mmol; (c) 1.7 ml, 2 mmol; (d) 10 ml; (e) reflux; and (f) 1.5 h.

Asymmetric Deprotonation Procedure

A solution of magnesium base prepared following General Procedure A was cooled under argon to -78°C. The Schlenk flask was then charged with DMPU (0.06 ml, 0.5 mmol) followed by diphenylphosphoryl chloride (0.42 ml, 2 mmol), and the reaction mixture was stirred for 10 minutes at -78°C. 4-*tert*-Butylcyclohexanone (0.12 g, 0.8 mmol) was then added as a solution in THF (2 ml) over 1 h using a syringe pump. The reaction mixture was stirred at -78°C overnight before quenching with a saturated solution of $NaHCO_3$ (10 ml), warming to room temperature, and extracting with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (eluent: gradient from petroleum ether to 12% diethyl ether in petroleum ether followed by DCM) to give recovered starting material (0.12 g, 100%) and by-product **60** (0.25 g).

Entry 2

General procedure A: (a) **56**; (b) 0.28 g, 1 mmol; (c) 1.7 ml, 2 mmol; (d) 10 ml; (e) reflux; and (f) 1.5 h.

Asymmetric Deprotonation Procedure

A solution of magnesium base prepared following General Procedure A was stirred under argon at RT. The Schlenk flask was then charged with DMPU (0.06 ml, 0.5 mmol) followed by diphenylphosphoryl chloride (0.42 ml, 2 mmol), and the reaction mixture was stirred for 10 minutes at RT. 4-*tert*-Butylcyclohexanone (0.12 g, 0.8 mmol) was then added as a solution in THF (2 mL) over 1 h using a syringe pump. The reaction mixture was stirred at RT overnight before quenching with a saturated solution of $NaHCO_3$ (10 ml), and extracting with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (eluent: gradient from petroleum ether to 12% diethyl ether in petroleum ether followed by DCM) to give recovered starting material (0.11 g, 92%) and by-product **60** (0.35 g).

Scheme 2.35, Table 2.14

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of $n$$Bu_2Mg$; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **60**.

Entry 1

General procedure A: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 0.85 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) -78°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) trace; (g) -; (h) 0.05 g, 83%; and (i) 0.08 g.

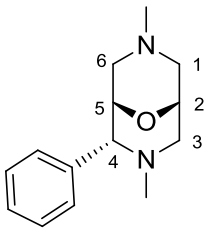
Entry 2

General procedure A: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 0.85 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) RT; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.054 g, 35%; (g) 45:55 (h) 0.033 g, 55%; and (i) 0.09 g.

*For analytical data for by-product **60** please refer to data on page 401.*

6.4.3 Application of Lithium Amide 61 in Deprotonation of 4-tert-Butylcyclohexanone

*Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57** via lithium amide **61***



$C_{14}H_{20}N_2O$
Molecular Weight: 232.32

Following General Procedure C for the preparation of base **61**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) volume of THF; and (d) quantity of *n*-BuLi.

Following General Procedure G for the methylation of **61**, data are presented as follows: (a) quantity of MeI; and (b) yield of **57**.

Scheme 2.36

General procedure C: (a) **56**; (b) 0.08 g, 0.3 mmol; (c) 5 ml; and (d) 0.55 ml, 1.16 mmol. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.062 g, 89%, as a white solid.

*For analytical data for **57** please refer to data on page 356.*

*Asymmetric Deprotonation of tert-butylcyxlohexanone using Lithium Amide **61***

Scheme 2.37, Table 2.15

Following General Procedure C for the preparation of base **61**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) volume of THF; and (d) quantity of *n*-BuLi.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **60**.

Entry 1

General procedure C: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 5 ml; and (d) 0.95 ml, 2 mmol. General procedure I: (a) RT; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.077 g, 50%; (g) 50:50; (h) 0.021 g, 36%; and (i) 0.11 g.

Entry 2

General procedure C: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 5 ml; and (d) 0.95 ml, 2 mmol. General procedure I: (a) 0°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.067 g, 43%; (g) 45:55; (h) 0.021 g, 42%; and (i) 0.09 g.

Entry 3

General procedure C: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 5 ml; and (d) 0.95 ml, 2 mmol. General procedure I: (a) -78°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.009 g, 6%; (g) 27:73; (h) 0.036 g, 60%; and (i) 0.095 g.

Scheme 2.37, Table 2.15, Entry 4

Following General Procedure C for the preparation of base **61**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) volume of THF; and (d) quantity of *n*-BuLi.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **60**.

General procedure C: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 5 ml; and (d) 0.95 ml, 2 mmol. General procedure H: (a) -78°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.005 g, 3%; (e) 34:66; (f) 0.05 g, 83%; and (g) 0.12 g.

Scheme 2.38, Table 2.16

Following General Procedure D for the preparation of base **61**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) volume of THF; and (e) quantity of *n*BuLi.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **60**.

Entry 1

General procedure D: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 5 ml; and (e) 0.95 ml, 2 mmol. General procedure I: (a) RT; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.113 g, 72%; (g) 50:50; (h) 0.015 g, 25%; and (i) 0.09 g.

Entry 2

General procedure D: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 5 ml; and (e) 0.95 ml, 2 mmol. General procedure I: (a) 0°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.088 g, 57%; (g) 49:51; (h) 0.025 g, 40%; and (i) 0.1 g.

Entry 3

General procedure D: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 5 ml; and (e) 0.95 ml, 2 mmol. General procedure I: (a) -78°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.014 g, 9%; (g) 28:72; (h) 0.042 g, 70%; and (i) 0.09 g.

Entry 4

General procedure D: (a) 0.01 g, 0.25 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 5 ml; and (e) 0.95 ml, 2 mmol. General procedure I: (a) -78°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.01 g, 6%; (g) 27:73; (h) 0.023 g, 38%; and (i) 0.13 g.

Entry 5

General procedure D: (a) 0.08 g, 2 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 5 ml; and (e) 0.95 ml, 2 mmol. General procedure I: (a) -78°C; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.016 g, 10%; (g) 40:60; (h) 0.03 g, 50%; and (i) 0.107 g.

*For analytical data for by-product **60** please refer to data on page 401.*

6.4.4 Returning to the Application of Magnesium Bisamide 54 in Deprotonation of 4-tert-butylcyclohexanone

Scheme 2.41, Table 2.17

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **60**.

Entry 1

General procedure A: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 0.85 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.071 g, 46%; (e) 47:53; (f) 0.007 g, 12%; and (g) 0.2 g.

Entry 2

General procedure A: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 0.85 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H*: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.057 g, 37%; (e) 49:51; (f) 0.03 g, 50%; and (g) 0.157 g.

*As an amendment to this procedure, prior to the addition of diphenylphosphoryl chloride, the reaction mixture was stirred for 24 h.

Scheme 2.42

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **60**.

General procedure A: (a) **56**; (b) 0.14 g, 0.5 mmol; (c) 0.85 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) 40°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.124 g, 80%; (e) 50:50; (f) 0.006 g, 10%; and (g) 0.189 g.

Scheme 2.46, Table 2.18

Following General Procedure B for the preparation of base **54**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; (e) volume of THF; (f) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl

phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **60**.

Entry 1

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.075 g, 49%; (e) 49:51; (f) 0.02 g, 33%; and (g) 0.175 g.

Entry 2

General procedure B: (a) 0.04 g, 1 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.104 g, 67%; (e) 49:51; (f) 0.008 g, 13%; and (g) 0.151 g.

Entry 3

General procedure B: (a) 0.08 g, 2 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.085 g, 55%; (e) 50:50; (f) 0.018 g, 30%; and (g) 0.192 g.

Scheme 2.48, Table 2.20

Following General Procedure B for the preparation of base **54**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; (e) volume of THF; (f) temperature; and (f) time.

Entry 1

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h.

Asymmetric Deprotonation using Co-addition Procedure

A solution of magnesium base prepared *via* General Procedure B was stirred under argon at RT. 4-*tert*-Butylcyclohexanone (0.06 g, 0.4 mmol) was dissolved in THF (2 ml) and to this was added diphenylphosphoryl chloride (0.21 ml, 1 mmol). The THF solution containing the mixture of ketone and electrophile was added over 2 h to the solution of base using a syringe pump. The resulting reaction mixture was stirred at RT overnight before being quenched with a saturated aqueous sodium bicarbonate solution. Extraction with Et_2O (2 x 25 ml) and removal of the solvent *in vacuo* gave the crude product, which was purified by column

chromatography on silica gel using 10% Et_2O in petroleum ether to give the product as a colourless oil (0.054 g, 35%, 50:50 er), along with 0.17 g of by-product **60**.

Entry 2

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h.

Asymmetric Deprotonation using Co-addition Procedure

A solution of magnesium base prepared *via* General Procedure B was stirred under argon at RT. 4-*tert*-butylcyclohexanone (0.06 g, 0.4 mmol) was dissolved in THF (2 ml) and to this was added diphenylphosphoryl chloride (0.08 ml, 0.4 mmol). The THF solution containing the mixture of ketone and electrophile was added over 2 h to the solution of base using a syringe pump. The resulting reaction mixture was stirred at RT overnight before being quenched with a saturated aqueous sodium bicarbonate solution.. Extraction with Et_2O (2 x 25 ml) and removal of the solvent *in vacuo* gave the crude product which was purified by column chromatography on silica gel using 10% Et_2O in petroleum ether to give the product as a colourless oil (0.073 g, 47%, 47:53 er), along with 0.15 g of by-product **60**.

Scheme 2.49, Table 2.21

Following General Procedure B for the preparation of base **54**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; (e) volume of THF; (f) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **60**.

Entry 1

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) 0°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.04 g, 29%; (e) 40:60; (f) 0.026 g, 43%; and (g) 0.155 g.

Entry 2

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) -20°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.016 g, 10%; (e) 43:57; (f) 0.02 g, 33%; and (g) 0.167 g.

Entry 3

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) -40°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.009 g, 6%; (e) 49:51; (f) 0.031 g, 52%; and (g) 0.175 g.

Entry 4

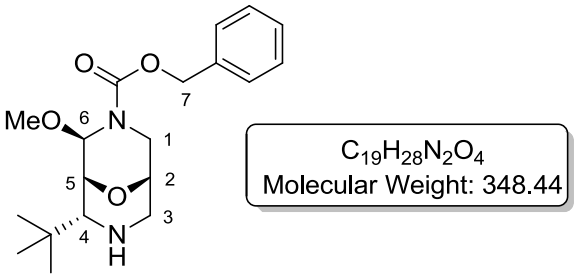
General procedure B: (a) 0.02 g, 0.5 mmol; (b) **56**; (c) 0.14 g, 0.5 mmol; (d) 0.85 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) -78°C; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) trace; (e) -; (f) 0.049 g, 82%; and (g) 0.188 g.

*For analytical data for by-product **60** please refer to data on page 401.*

6.5 Application of Metal Amide Bases derived from Oxabispidines with Alternative Sidearms

6.5.1 Application of tBu-substituted Oxabispidine Magnesium Amide Bases

*Preparation of (1R,2R,5S,8R)-benzyl 8-(tert-butyl)-2-methoxy-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **68***



Procedure

Scheme 2.50

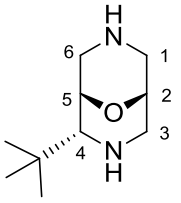
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (60 g, 423 mmol) followed by a solution of oxazine (*S*)-**52** (10.5 g, 42.3 mmol) in DCM (260 ml). To

this was added pivaldehyde (4.7 ml, 42.3 mmol) and the resulting reaction mixture was stirred at room temperature for 2 hours. Removal of Na_2SO_4 by filtration provided a solution of the corresponding imine. This was then cooled to -20 °C and distilled methanol (1.7 ml, 42.3 mmol) was added. To the reaction mixture was added triflic acid (3.7 ml, 42.3 mmol) in a dropwise fashion over 10 min. This addition was accompanied by a colour change from pale yellow to an intense bright yellow. After complete addition of the triflic acid, the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 1 hour before being quenched with saturated sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: DCM then DCM:MeOH:2M NH_3 in MeOH 94:5:1) to yield the desired product as a colourless oil (5.3 g, 36%).

IR (neat): 1061, 1415, 1700, 2953 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 5.4H, $C(CH_3)$), 0.94 (s, 3.6H, $C(CH_3)$), 2.93 (dd, J = 10.3, ^4J = 3.3 Hz, 1H, H4), 3.04 (d, ^2J = 13.1 Hz, 0.4H, H3), 3.10 (d, ^2J = 13.1 Hz, 0.6H, H3), 3.27 (s, 1.8H, OCH_3), 3.31 (ddd, ^2J = 13.1, J = 4.0, ^4J = 2.3 Hz, 1H, H3), 3.34 (s, 1.2H, OCH_3), 3.53-3.71 (m, 3H, H1 & H2 & H5), 3.84 (d, ^2J = 13.3 Hz, 0.6H, H1), 3.91 (d, ^2J = 13.3 Hz, 0.4H, H1), 5.06-5.27 (m, 2.4H, H6 & H7), 5.41 (s, 0.6H, H6), 7.33-7.41 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.5, 32.4, 32.5, 42.8, 43.2, 51.0, 54.9, 55.4, 65.2, 65.6, 65.9, 66.1, 67.5, 67.9, 70.8, 71.1, 80.4, 80.8, 127.8, 128.2, 128.4, 128.5, 135.7, 136.3, 155.2 ppm; HRMS *m/z* Calc. for $C_{19}H_{29}N_2O_4$ (M^++H) 349.2122. Found 349.2122.

$[\alpha]_D^{20}$ +2.1 (*c* 1.0 in $CHCl_3$).

Preparation of (1S,2R,5R)-2-(tert-butyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***66***



$C_{10}H_{20}N_2O$
Molecular Weight: 184.28

Procedure

Scheme 2.50

A three-necked flask was flame-dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (10% on carbon, 1.6 g, 1.5 mmol) followed by a solution of **68** (5.2 g, 15 mmol) in methanol (300 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: DCM then gradient up to 10% MeOH in DCM), to yield the desired product as a colourless oil (1.6 g, 72%). The product was treated with concentrated HCl (1.5 ml, 17.8 mmol) to generate the corresponding bis-HCl salt **69** (1.5 g, 68%).

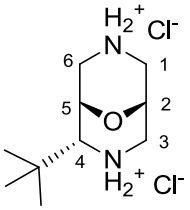
It should be noted that a mixture of both a chair/chair and a chair/boat conformation was observed in the ^{1}*H NMR of* ***66****, and these have been reported separately.*

IR (neat): 2689, 2793, 3087, 3301 cm^{-1}; ^{1}H NMR conformer A (400 MHz, $CDCl_3$): δ 0.95 (s, 9H, $C(CH_3)_3$), 2.52 (d, J = 4.5 Hz, 1H, H4), 2.53 (d, ^2J = 12.1 Hz, 1H, H6), 2.58 (d, ^2J = 12.1 Hz, 1H, H1), 2.82 (dd, ^2J = 13.0, J = 4.3 Hz, 1H, H3), 3.14 (dd, ^2J = 12.1, J = 3.2 Hz, 1H, H1), 3.19 (dd, ^2J = 12.1, J = 3.4 Hz, 1H, H6), 3.30 (dd, ^2J = 13.0, J = 9.0 Hz, 1H, H3), 3.62-3.64 (m, 1H, H5), 3.68-3.72 ppm (m, 1H, H2); ^{1}H NMR conformer B (400 MHz, $CDCl_3$): δ 1.01 (s, 9H, $C(CH_3)_3$), 2.52 (d, J = 4.5 Hz, 1H, H4), 3.06-3.10 (m, 1H, H1), 3.23 (d, ^2J = 12.4 Hz, 1H, H6), 3.33-3.34 (m, 2H, H3), 3.38 (ddd, ^2J = 12.6, J = 3.9, ^4J = 2.6 Hz, 1H, H1), 3.43 (ddd, ^2J = 12.4, J = 3.9, ^4J = 2.5 Hz, 1H, H6), 3.58 (q, J = 2.6 Hz, 1H, H2), 3.61-3.62 ppm (m, 1H, H5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 26.8, 32.2, 33.4, 44.3, 48.0, 48.9, 49.7,

50.1, 51.5, 62.9, 64.2, 66.4, 66.8, 67.9, 68.6 ppm; HRMS: *m/z* Calc. for $C_{10}H_{21}N_2O$ $[M+H]^+$: 185.1648. Found: 185.1646.

$[\alpha]_D^{24}$ +5.3 (*c* 0.52, MeOH).

Experimental data for (1S,2R,5R)-2-(tert-butyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-diium chloride ***69***



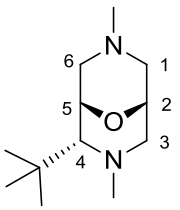
$C_{10}H_{22}Cl_2N_2O$
Molecular Weight: 257.20

Melting point: Decomposed >300°C.

IR (neat): 2281, 2789, 2855 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 1.10 (s, 9H, $C(CH_3)_3$), 3.23 (d, ^2J = 13.6 Hz, 1H, H6), 3.36 (d, ^2J = 13.6 Hz, 1H, H1), 3.46 (dd, ^2J = 13.6, J = 3.6 Hz, 1H, H1), 3.52 (dd, ^2J = 13.6, J = 4.1 Hz, 1H, H6), 3.63-3.67 (m, 2H, H3+H4), 3.77 (dd, ^2J = 13.9, J = 10.7 Hz, 1H, H3), 4.46 (t, J = 4.6 Hz, 1H, H5), 4.54-4.58 (m, 1H, H2) ppm; ^{13}C NMR (100 MHz, D_2O): δ 25.6, 31.4, 41.3, 43.2, 46.3, 61.4, 63.7, 65.3 ppm; HRMS: *m/z* Calc. for cation $C_{10}H_{21}N_2O$ [M+]: 185.1648. Found: 185.1644. Cl^- isotope ions at m/z 35/37 are observed.

$[\alpha]_D^{25}$ +8.2 (*c* 0.15, MeOH).

*Preparation of (1S,2R,5R)-2-(tert-butyl)-3,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **70** via methylation of magnesium bisamide **67**.*



$C_{12}H_{24}N_2O$
Molecular Weight: 212.33

Scheme 2.51, Table 2.22

Following General Procedure A for the preparation of base **67**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **67**, data are presented as follows: (a) quantity of MeI; and (b) yield of **70**.

Entry 1

General procedure A: (a) **69**; (b) 0.08 g, 0.3 mmol; (c) 0.6 ml, 0.6 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) -.

* 0.04 g, 66% of mono-methylated **71** was recovered.

Entry 2

General procedure A: (a) **69**; (b) 0.08 g, 0.3 mmol; (c) 0.6 ml, 0.6 mmol; (d) 5 ml; (e) reflux; and (f) 2.5 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) -.

* 0.025 g, 40% of mono-methylated **71** was recovered.

Scheme 2.53, Table 2.23

Following General Procedure A for the preparation of base **67**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **67**, data are presented as follows: (a) quantity of MeI; and (b) yield of **70**.

Entry 1

General procedure A: (a) **69**; (b) 0.08 g, 0.3 mmol; (c) 0.6 ml, 0.6 mmol; (d) 5 ml; (e) 40°C; and (f) 16 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.008 g, 13%.

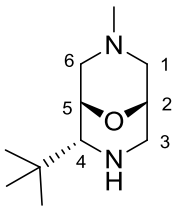
Entry 2

General procedure A: (a) **69**; (b) 0.08 g, 0.3 mmol; (c) 0.6 ml, 0.6 mmol; (d) 5 ml; (e) RT; and (f) 16 h. General procedure G: (a) 0.04 ml, 0.6 mmol; and (b) 0.016 g, 25%.

IR (neat): 1083, 1265, 1461, 2793, 2959 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 5H, $C(CH_3)_3$), 1.05 (s, 4H, $C(CH_3)_3$), 2.16 (s, 1.4H, NCH_3), 2.18 (s, 3H, NCH_3), 2.22 (s, 1.6H, NCH_3), 2.29 (dd, ^{2}J = 11.5, J = 3.4 Hz, 0.5H, H1), 2.33 (dd, ^{2}J = 11.5, J = 3.4 Hz, 0.5H, H1), 2.39-2.47 (m, 1H, H1), 2.54-2.57 (m, 1H, H4), 2.84 (dd, ^{2}J = 12.9, J = 4.3 Hz, 0.5H, H6), 2.89-2.92 (m, 0.5H, H6), 3.05 (dd, J = 3.2 Hz, ^{4}J = 1.8 Hz, 0.5H, H6), 3.07-3.10 (m, 0.5H, H6), 3.22-3.30 (m, 1H, H3), 3.34 (ddd, ^{2}J = 13.4, J = 3.7, ^{4}J = 2.4 Hz, 1H, H3), 3.71-3.80 ppm (m, 2H, H2+H5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 26.8, 30.3, 32.1, 33.2, 44.8, 46.0, 46.1, 50.7, 56.9, 58.4, 59.1, 59.2, 63.2, 64.3, 66.2, 66.9, 67.0, 68.4 ppm; HRMS: *m/z* Calc. for $C_{12}H_{25}N_2O$ $[M+H]^+$: 213.1961. Found: 213.1952.

$[\alpha]_D^{25}$ +2.1 (*c* 0.15, MeOH).

Experimental Data for (1S,2R,5S)-2-(tert-butyl)-7-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***71***



$C_{11}H_{22}N_2O$
Molecular Weight: 198.31

IR (neat): 1370, 1471, 2793, 2960 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 9H, $C(CH_3)_3$), 2.17 (s, 3H, NCH_3), 2.53-2.59 (m, 2H, H1), 2.90-2.93 (m, 1H, H6), 3.06-3.07 (m, 1H, H4), 3.08-3.11 (m, 1H, H6), 3.30-3.41 (m, 2H, H3), 3.76-3.77 ppm (m, 2H, H2+H5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 32.2, 46.1, 50.7, 57.0, 59.1, 66.2, 67.0, 68.4 ppm; HRMS: *m/z* Calc. for $C_{11}H_{23}N_2O$ $[M+H]^+$: 199.1805. Found: 199.1804.

$[\alpha]_D^{28}$ +12.0 (*c* 0.1, $CHCl_3$).

*Asymmetric Deprotonation of 4-tert-butylcyxlohexanone using Magnesium Bisamide **67***

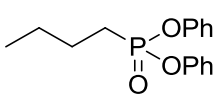
Scheme 2.54

Following General Procedure A for the preparation of base **67**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **78**.

General procedure A: (a) **69**; (b) 0.13 g, 0.5 mmol; (c) 1.03 ml, 1 mmol; (d) 5 ml; (e) RT; and (f) 16 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.015 g, 10%; (e) 50:50; (f) 0.057 g, 96%; and (g) 0.08 g.

*Experimental Data for **78***[65]

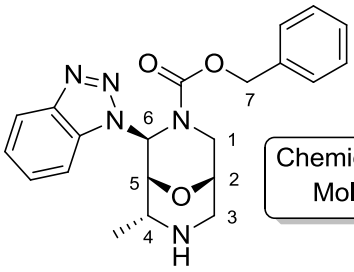


$C_{16}H_{19}O_3P$
Molecular Weight: 290.29

^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, *J* = 7.2 Hz, 3H, CH_3), 1.78-2.20 (m, 6H, -$CH_2CH_2CH_3$), 7.10-7.42 (m, 10H, H_{Ar}); ^{31}P NMR (162 MHz, $CDCl_3$): 25.0 ppm.

*6.5.2 Application of Methyl Oxabispidine **79** in the deprotonation of 4-tert-butylcyclohexanone*

*Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-8-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate **81***



Procedure

Scheme 2.55

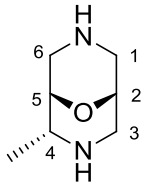
To a flame-dried flask containing a stirrer bar was added anhydrous Na_2SO_4 (57 g, 403 mmol) followed by DCM (310 ml) and benzotriazole (4.8 g, 40.3 mmol). Acetaldehyde (1.8 g, 40.3 mmol) was added and the reaction stirred at room temperature for 15 min. After this time (*S*)-**52** (10 g, 40.3 mmol) was added and the resulting mixture stirred for 30 min. After removal of Na_2SO_4 by filtration, the reaction mixture was cooled to -20°C and trifluoromethanesulfonic acid (3.5 ml, 40.3 mmol) was added in a dropwise fashion over 5 min. After complete addition of the trifluoromethanesulfonic acid the reaction mixture was stirred at -20 °C for 10 min then the cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction mixture was then left to stir at room temperature for 3 h before being quenched with a saturated aqueous sodium bicarbonate solution. The organic and aqueous layers were separated and the aqueous layer washed once more with DCM. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a crude oil. The crude product was purified by column chromatography (eluent: EtOAc then 3% MeOH in EtOAc) to yield the desired product as a colourless gum (8 g, 50%).

IR (neat): 1712, 2331, 2360, 2850, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.6 Hz, 0.6H, CH_3), 1.31 (d, *J* = 6.9 Hz, 0.9H, CH_3), 1.34 (d, *J* = 6.6 Hz, 0.9H, CH_3), 1.38 (d, *J* = 6.9 Hz, 0.6H, CH_3), 1.80 (br. s, 1H, NH), 3.08-3.21 (m, 1H, H3), 3.42-3.55 (m, 2H, H3+H4),

3.82-4.25 (m, 3.3H, H1+H2+H5), 4.31 (d, *J* = 3.2 Hz, 0.3H, H5), 4.41 (d, *J* = 3.4 Hz, 0.2H, H5), 4.53 (d, *J* = 3.2 Hz, 0.2H, H5), 5.12-5.34 (m, 2H, H7), 6.74 (s, 0.3H, H6), 6.78 (s, 0.2H, H6), 6.87 (s, 0.2H, H6), 6.92 (s, 0.3H, H6), 7.02-7.50 (m, 7.2H, H_{Ar}), 7.71 (d, *J* = 8.6 Hz, 0.3H, H_{Ar}), 7.86-7.90 (m, 1H, H_{Ar}), 8.10 ppm (d, *J* = 8.6 Hz, 0.5H, H_{Ar}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 17.8, 43.5, 43.6, 43.9, 44.0, 49.5, 49.6, 51.8, 51.9, 52.5, 52.6, 61.8, 62.6, 64.5, 64.9, 65.3, 67.4, 67.8, 67.9, 68.9, 69.2, 72.3, 72.7, 73.0, 109.3, 109.6, 117.9, 119.5, 119.6, 123.5, 123.6, 125.8, 125.9, 127.0, 127.1, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 131.7, 132.1, 135.0, 135.2, 135.4, 135.5, 143.7, 143.8, 145.2, 153.9, 154.6, 154.9, 155.4 ppm; HRMS: *m/z* Calc. for $C_{21}H_{23}N_5O_3Na$ $[M+Na]^+$: 416.1693. Found: 416.1690.

$[\alpha]_D^{26}$ -53.6, (*c* 0.75, $CHCl_3$).

Preparation of (1S,2R,5R)-2-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***79***



$C_7H_{14}N_2O$
Molecular Weight: 142.20

Procedure

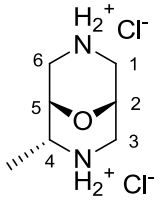
Scheme 2.55

A three-necked flask was flame-dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (10% on carbon, 2.2 g, 2.0 mmol) followed by a solution of **81** (8 g, 20.3 mmol) in methanol (400 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: DCM then gradient up to 10% MeOH in DCM), to yield the desired product as a colourless oil (1.7 g, 60%). The product was treated with concentrated HCl (2.05 ml, 24.6 mmol) to generate the corresponding bis-HCl salt **82** (1.8 g, 70%).

IR (neat): 2850, 2924, 3300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.7 Hz, 3H, CH_3), 1.82 (br. s., 2H, NH x2), 3.04 (d, ^{2}J = 12.5 Hz, 1H, H1), 3.10 (d, ^{2}J = 12.4 Hz, 1H, H6), 3.21-3.22 (m, 1H, H3), 3.23 (dd, *J* = 3.5, ^{4}J = 1.3 Hz, 1H, H3), 3.33 (t, *J* = 3.2 Hz, 1H, H5), 3.39 (ddd, ^{2}J = 12.5, *J* = 3.7, ^{4}J = 2.5 Hz, 1H, H1), 3.43-3.49 (m, 2H, H4+H6), 3.57-3.58 ppm (m, 1H, H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 45.6, 50.3, 50.5, 53.7, 66.5, 71.1 ppm; HRMS: *m/z* Calc. for $C_7H_{15}N_2O$ $[M+H]^+$: 143.1179. Found: 143.1176.

$[\alpha]_D^{28}$ -16.1 (*c* 0.4, $CHCl_3$).

Experimental data for (1S,2R,5R)-2-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3,7-diium chloride ***82***



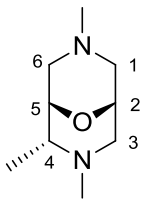
$C_7H_{16}Cl_2N_2O$
Molecular Weight: 215.12

Melting point: 239-241°C.

IR (neat): 1616, 2285, 2642, 2783, 2947, 2991 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 1.31 (d, *J* = 6.9 Hz, 3H, CH_3), 3.34 (d, ^{2}J = 13.7 Hz, 1H, H1), 3.44-3.49 (m, 2H, H3+H6), 3.56-3.68 (m, 2H, H3+H6), 3.72 (dd, ^{2}J = 13.7, *J* = 7.3 Hz, 1H, H1), 3.82-3.85 (m, 1H, H4), 4.36-4.38 (m, 1H, H5), 4.51-4.53 ppm (m, 1H, H2); ^{13}C NMR (100 MHz, D_2O): δ 12.8, 37.7, 41.6, 43.6, 50.7, 60.2, 64.5 ppm; HRMS: *m/z* Calc. for cation $C_7H_{15}N_2O$ [M+]: 144.1213. Found: 144.1207. Cl^- isotope ions at m/z 35/37 are observed.

$[\alpha]_D^{28}$ -6.9 (*c* 0.8, MeOH).

*Preparation of (1S,2R,5R)-2,3,7-trimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **83** via methylation of magnesium bisamide **80***



$C_9H_{18}N_2O$
Molecular Weight: 170.25

Scheme 2.56

Following General Procedure A for the preparation of base **80**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **80**, data are presented as follows: (a) quantity of MeI; and (b) yield of **83**.

General procedure A: (a) **82**; (b) 0.08 g, 0.37 mmol; (c) 0.77 ml, 0.74 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.05 ml, 0.74 mmol; and (b) -.

Diagonostic peaks for **83** in crude ^{1}H NMR spectrum:

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J = 6.8 Hz, 3H, CH_3), 2.26 (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3 overlapping with signal corresponding to 1H, H1), 2.43-2.50 (m, 2H, H3+H6), 2.61 (ddd, ^2J = 11.6, J = 4.1, ^4J = 1.5 Hz, 1H, H1), 2.97-3.03 (m, 3H, H3+H4+H6), 3.56 (t, J = 3.7 Hz, 1H, H5), 3.89 (t, J = 4.1 Hz, 1H, H2) ppm.

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium Bisamide **80***

Scheme 2.57

Following General Procedure A for the preparation of base **80**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **84**.

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.01 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.053 g, 35%; (e) 49:51; (f) 0.027 g, 45%; and (g) 0.11 g.

*For analytical data for by-product **84** please refer to data on page 402.*

Scheme 2.58, Table 2.24

Following General Procedure B for the preparation of base **80**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; (e) volume of THF; (f) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **84**.

Entry 1

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **82**; (c) 0.11 g, 0.5 mmol; (d) 1.01 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.062 g, 40%; (e) 46:54; (f) 0.012 g, 20%; and (g) 0.155 g.

Entry 2

General procedure B: (a) 0.04 g, 1 mmol; (b) **82**; (c) 0.11 g, 0.5 mmol; (d) 1.01 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.062 g, 40%; (e) 50:50; (f) 0.021 g, 35%; and (g) 0.12 g.

Scheme 2.59, Table 2.25

Following General Procedure B for the preparation of base **80**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of

oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; (e) volume of THF; (f) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **84**.

Entry 1

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **82**; (c) 0.11 g, 0.5 mmol; (d) 1.05 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure I: (a) RT; (b) DMPU; (c) 0.03 ml, 0.25 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.02 g, 13%; (g) 50:50; (h) 0.03 g, 50%; and (i) 0.1 g.

Entry 2

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **82**; (c) 0.11 g, 0.5 mmol; (d) 1.05 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure I: (a) RT; (b) TMEDA; (c) 0.07 ml, 0.5 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.07 g, 45%; (g) 50:50; (h) 0.018 g, 30%; and (i) 0.09 g.

Entry 3

General procedure B: (a) 0.02 g, 0.5 mmol; (b) **82**; (c) 0.11 g, 0.5 mmol; (d) 1.05 ml, 1 mmol; (e) 5 ml; (f) reflux; and (g) 1.5 h. General procedure I: (a) RT; (b) 18-c-6; (c) 0.13 ml, 0.5 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.078 g, 50%; (g) 47:53; (h) 0.016 g, 27%; and (i) 0.087 g.

Scheme 2.59, Table 2.25, Entry 4

Following General Procedure A for the preparation of base **80**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **84**.

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) RT; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.085 g, 55%; (g) 44:56; (h) 0.006 g, 4%; and (i) 0.098 g.

*For analytical data for by-product **84** please refer to data on page 402.*

Scheme 2.63, Table 2.26

Following General Procedure A for the preparation of base **80**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **84**.

Entry 1

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) RT; (b) 1,4-dioxane; (c) 0.04 ml, 0.5 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.055 g, 35%; (g) 43:57; (h) 0.013 g, 21%; and (i) 0.11 g.

Entry 2

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) RT; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.085 g, 55%; (g) 44:56; (h) 0.006 g, 4%; and (i) 0.098 g.

Entry 3

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) RT; (b) 1,4-dioxane; (c) 0.13 ml, 1.5 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.062 g, 40%; (g) 49:51; (h) 0.019 g, 32%; and (i) 0.121 g.

*For analytical data for by-product **84** please refer to data on page 402.*

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium Bisamide **54***

Scheme 2.64

Following General Procedure A for the preparation of base **54**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **60**.

General procedure A: (a) **56**; (b) 0.07 g, 0.25 mmol; (c) 0.53 ml, 0.5 mmol; (d) 3 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) 0°C; (b) 1,4-dioxane; (c) 0.04 ml, 0.5 mmol; (d) 0.03 g, 0.2 mmol; (e) 0.1 ml, 0.5 mmol; (f) 0.011 g, 14%; (g) 48:52; (h) 0.016 g, 53%; and (i) 0.061 g.

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium Bisamide **80***

Scheme 2.65, Table 2.27

Following General Procedure A for the preparation of base **80**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **84**.

Entry 1

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) 0°C; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.04 g, 26%; (g) 43:57; (h) 0.012 g, 20%; and (i) 0.1 g.

Entry 2

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) -20°C; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.035 g, 23%; (g) 43:57; (h) 0.018 g, 30%; and (i) 0.096 g.

Entry 3

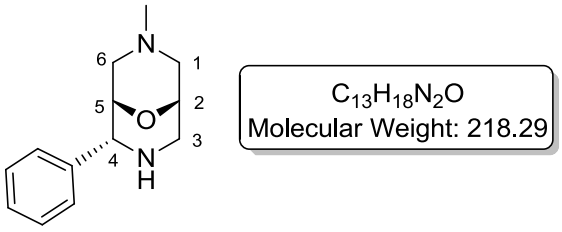
General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) -40°C; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.019 g, 12%; (g) 49:51; (h) 0.018 g, 12%; and (i) 0.099 g.

Entry 4

General procedure A: (a) **82**; (b) 0.11 g, 0.5 mmol; (c) 1.05 ml, 1 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure I: (a) -78°C; (b) 1,4-dioxane; (c) 0.08 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.002 g, 1%; (g) 50:50; (h) 0.029 g, 48%; and (i) 0.11 g.

6.6 Application of Chelating Magnesium Amide Bases in the Asymmetric Deprotonation of 4-*tert*-butylcyclohexanone

*Preparation of (1S,2R,5S)-7-methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **58***



General Procedure

Scheme 2.66, Table 2.28

To a 3-necked flask, fitted with a low temperature thermometer that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of N_2, was added $LiAlH_4$ powder followed by dry diethyl ether. The resulting suspension was cooled to 0°C and then a

solution of **53** in diethyl ether was added slowly. After complete addition of the substrate, the resulting mixture was stirred at 0°C for 10 minutes, then allowed to warm to room temperature and stirred for 3 hours. Tlc analysis after this time showed no starting material remained. To the reaction mixture was added water (1 ml per 1 g $LiAlH_4$) and the mixture was allowed to stir for 10 min. After this time 15% NaOH (1 ml per 1 g $LiAlH_4$) followed by water (3 ml per 1 g $LiAlH_4$) was added and the resulting white granular suspension was allowed to stir for 15 min. An excess of solid sodium bicarbonate was then added and the mixture was stirred for a further 20 min. The suspension was filtered through a plug of celite, which was then washed with ether, and the filtrate concentrated *in vacuo*. Purification by column chromatography (eluent: 0% to 10% MeOH in DCM) resulted in the desired product being recovered as a white solid.

Following the above ***General Procedure***, data are presented as follows:

(a) quantity of $LiAlH_4$; (b) volume of Et_2O; (c) quantity of **70**; (d) volume of Et_2O; and (e) yield.

Entry 1
(a) 1.1 g, 30 mmol; (b) 51 ml; (c) 3.7 g, 10 mmol; (d) 40 ml; and (e) 1.3 g, 59%.

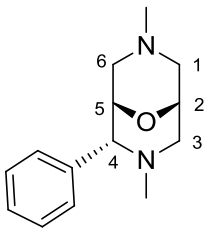
Entry 2
(a) 1.9 g, 48.9 mmol; (b) 83 ml; (c) 6 g, 16.3 mmol; (d) 67 ml; and (e) 2.1 g, 60%.

Melting point: 71-73°C.

IR ($CHCl_2$): 2789, 2934, 3057, 3060, 3294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3H, NCH_3), 2.25 (ddd, ^2J = 11.7, J = 3.7, ^4J = 1.5 Hz, 1H, H6), 2.58 (ddd, ^2J = 11.3, J = 2.9, ^4J = 2.9 Hz, 1H, H1), 2.66 (d, ^2J = 11.7 Hz, 1H, H6), 2.95 (d, ^2J = 11.3 Hz, 1H, H1), 3.25 (d, ^2J = 13.8 Hz, 1H, H3), 3.48 (dt, ^2J = 13.8, J = 2.9 Hz, 1H, H3), 3.73 (t, J = 3.7 Hz, 1H, H2), 3.86 (t, J = 3.4 Hz, 1H, H5), 4.44 (d, J = 2.8 Hz, 1H, H4), 7.26-7.37 ppm (m, 5H, H_{Ar}): ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7, 50.8, 54.5, 59.5, 62.4, 67.0, 72.1, 126.9, 126.1, 128.5, 140.4 ppm; HRMS: *m/z* Calc. for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1492.

$[\alpha]_D^{20}$ +54.5 (*c* 1.0, MeOH).

*Attempted preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57**via methylation of **88**.*



$C_{14}H_{20}N_2O$
Molecular Weight: 232.32

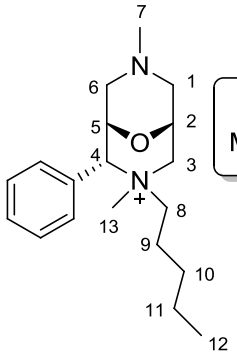
Scheme 2.67

Following General Procedure A for the preparation of base **88**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **88**, data are presented as follows: (a) quantity of MeI; (b) yield of **57**; and (c) quantity of by-product **91**.

General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.17 ml, 0.16 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.07 g.

*Experimental Data for (1S,2R,5R)-3,7-dimethyl-3-pentyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-ium **91***



$C_{19}H_{31}N_2O^+$
Molecular Weight: 303.46

IR (neat): 1095, 2810, 2858, 2954, 3003, 3431 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83-0.87, m, 3H, H12), 1.08-1.31 (m, 4H, H10+H11), 1.45-1.48 (m, 2H, H9), 2.00-2.07 (m, 1H, H8), 2.61 (dd, ^2J = 12.4, J = 2.8 Hz, 1H, H6), 2.69-2.76 (m, 1H, H8), 2.98 (d, ^2J = 12.4 Hz, 1H, H6), 3.35-3.52 (m, 3H, H1+H3), 3.69-3.73 (m, 7H, H4+H7+H13), 4.20-4.24 (m, 1H,

H2), 4.46-4.55 (m, 2H, H3+H5), 7.25-7.40 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 22.0, 25.2, 28.8, 53.3, 54.2, 55.2, 56.6, 57.7, 59.7, 63.2, 67.5, 67.9, 127.9, 128.5, 129.3, 135.2 ppm; HRMS: *m/z* Calc. for $C_{19}H_{32}N_2O^+$ $[M+H]^+$: 304.2465. Found: 304.2455.

Scheme 2.69, Table 2.29

Following General Procedure A for the preparation of base **88**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **88**, data are presented as follows: (a) quantity of MeI; (b) yield of **57**; and (c) quantity of by-product **92**.

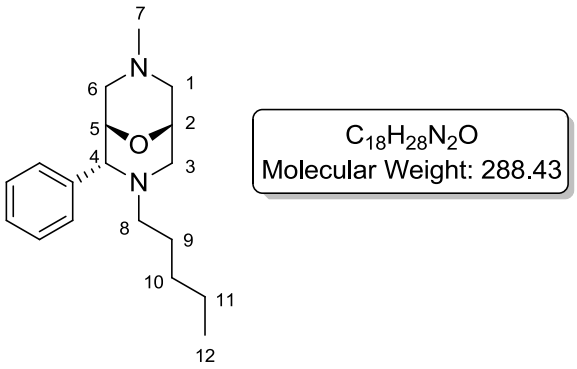
Entry 1

General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.17 ml, 0.16 mmol; (d) 5 ml; (e) 40°C; and (f) 16 h. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.045 g, 49%.

Entry 2

General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.17 ml, 0.16 mmol; (d) 5 ml; (e) RT; and (f) 16 h. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.03 g, 33%.

*Data for (1S,2R,5R)-7-methyl-3-pentyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **92***



IR (neat): 1089, 2702, 2860, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, *J* = 7.0 Hz, 3H, H12), 1.08-1.28 (m, 4H, H10+H11), 1.35-1.55 (m, 2H, H9), 1.90-2.02 (m, 2H, H6+H8), 2.17 (s, 3H, H7), 2.45 (dd, ^2J = 11.2, *J* = 3.0 Hz, 1H, H1), 2.50-2.58 (m, 1H, H8), 2.63 (d, ^2J = 11.9 Hz, 1H, H6), 2.71 (dd, ^2J = 11.1, *J* = 3.4 Hz, 1H, H3), 2.94 (d, ^2J = 11.2 Hz, 1H, H1), 3.16 (d, ^2J = 11.1 Hz, 1H, H3), 3.66-3.72 (m, 2H, H2+H5), 3.98 (t, *J* = 4.2 Hz, 1H, H4), 7.24-

7.36 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 22.1, 24.1, 29.1, 46.5, 53.5, 54.5, 56.2, 58.1, 68.6, 69.0, 72.8, 126.6, 127.7, 128.1, 140.2 ppm; HRMS: *m/z* Calc. for $C_{18}H_{29}N_2O^+$ $[M+H]^+$: 289.2274. Found: 289.2267.

Scheme 2.70, Table 2.30

Following General Procedure A for the preparation of base **88**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **88**, data are presented as follows: (a) quantity of MeI; (b) yield of **57**; and (c) quantity of by-product **91**.

Entry 1

General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.17 ml, 0.16 mmol; (d) 5 ml; (e) RT; and (f) 2 h. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.066 g.

Entry 2

General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.17 ml, 0.16 mmol; (d) 5 ml; (e) RT; and (f) 30 min. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.042 g.

*For analysis of **91** please refer to data on page 382.*

Scheme 2.71

Following General Procedure A for the preparation of alkyl magnesium amide base derived from **58**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **58**, data are presented as follows: (a) quantity of MeI; (b) yield of **57**; and (c) quantity of by-product **91**.

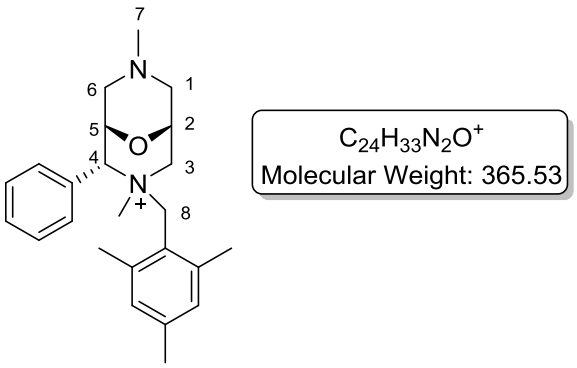
General procedure A: (a) **58**; (b) 0.07 g, 0.32 mmol; (c) 0.34 ml, 0.32 mmol; (d) 5 ml; (e) RT; and (f) 1 h. General procedure G: (a) 0.02 ml, 0.32 mmol; (b) -; and (c) 0.08 g.

*For analysis of **91** please refer to data on page 382.*

Scheme 2.73

To a Schlenk flask which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon was added oxabispidine **58** (0.07 g, 0.32 mmol). This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. THF (5 ml) was added to the Schlenk followed by bismesitylmagnesium (0.5M in THF, 0.32 ml, 0.16 mmol). The reaction mixture was stirred at 40°C for 2 h under argon. After this time, quantitative formation of the chiral magnesium bisamide was assumed. The reaction mixture was cooled to -78°C and methyl iodide (0.02 ml, 0.32 mmol) was added dropwise. The resulting solution was allowed to stir at -78°C for 30 min before warming to room temperature and stirring for 1 h. After this time the reaction was quenched with a saturated solution of $NaHCO_3$ (10 ml), warming to room temperature, and extracting with diethyl ether (3 x 10 ml). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified *via* flash chromatography (eluent: gradient from DCM to 10% MeOH in DCM) to give by-product **93** only (0.061 g).

Data for (1S,2R,5R)-3,7-dimethyl-2-phenyl-3-(2,4,6-trimethylbenzyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-ium ***93***



IR (neat): 1092, 2818, 2920, 2953, 3003, 3435 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H, $ArCH_3$), 2.41-2.43 (m, 7H, H1+$ArCH_3$ x 2), 2.56 (dd, ^2J = 12.5, J = 2.8 Hz, 1H, H1), 3.13 (dd, ^2J = 12.3, J = 4.7 Hz, 1H, H3), 3.21 (d, ^2J = 12.5 Hz, 1H, H8), 3.51-3.56 (m, 1H, H6), 3.69-3.72 (m, 4H, NCH_3+H6), 3.79-3.80 (m, 4H, NCH_3+H4), 3.99 (d, ^2J = 12.5 Hz, 1H, H8), 4.26-4.30 (m, 1H, H5), 4.39-4.42 (m, 1H, H2), 4.51-4.57 (m, 1H, H3), 6.8(s, 2H, H_{Ar}), 7.38-7.46 ppm (m, 5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 20.6, 51.6, 53.1, 54.4,

56.9, 58.0, 58.9, 63.1, 67.2, 71.6, 128.5, 128.6, 128.9, 129.2, 134.2, 136.9 ppm; HRMS: *m/z* Calc. for $C_{24}H_{33}N_2O^+$ $[M]^+$: 365.2579. Found: 365.2578.

*Attempted Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium Bisamide **88***

Scheme 2.74

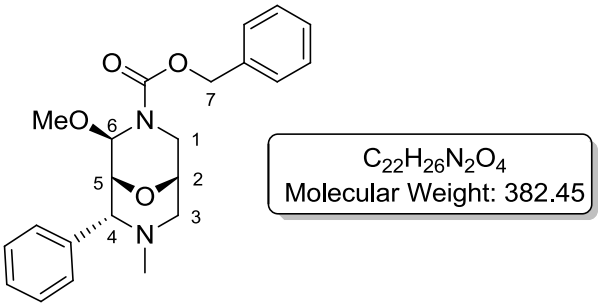
Following General Procedure A for the preparation of base **88**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **92**.

General procedure A: (a) **58**; (b) 0.11 g, 0.5 mmol; (c) 0.27 ml, 0.25 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) -; (e) -; (f) 0.058 g, 97%; and (g) 0.06 g, 42%.

*For analytical data for **92** please refer to data on page 383.*

Preparation of (1R,2R,5S,8R)-benzyl 2-methoxy-7-methyl-8-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***95***



Procedure

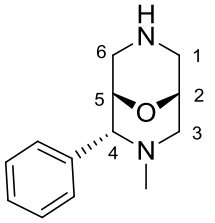
Scheme 2.75

To a solution of **53** (6 g, 16.3 mmol) in DCM (160 ml) was added methyl iodide (1.2 ml, 19.6 mmol) and potassium carbonate (2.5 g, 17.9 mmol). The reaction was stirred at room temperature and the progress followed by tlc. Complete consumption of the starting material was observed after 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: gradient to 70% diethyl ether in petroleum ether) to afford the desired product as a pale yellow oil (4.5 g, 72%).

IR (neat): 1706, 2889, 2930, 3030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 1.4H, NCH_3), 2.01(s, 1.6 H, NCH_3), 2.71-2.74 (m, 1H, H3), 2.99 (d, ^2J = 11.8 Hz, 0.4H, H3), 3.07 (d, ^2J = 11.8 Hz, 0.6H, H3), 3.12 (s, 1.6H, OCH_3), 3.20 (s, 1.4H, OCH_3), 3.44-3.47 (m, 1H, H1), 3.57-3.62 (m 0.6 H, H2), 3.64-3.69 (m, 0.4 H, H2), 3.78 (d, *J* = 3.6 Hz, 0.6H, H5), 3.83 (d, *J* = 3.6 Hz, 0.4 H, H5), 3.90-3.91 (m, 0.4H, H4), 4.00-4.03 (m, 0.6H, H4), 4.04 (d, ^2J = 13.6 Hz, 0.4 H, H1), 4.09 (d, ^2J = 13.3 Hz, 0.6H, H1), 4.94 (s, 0.6 H, H6), 5.13 (s, 0.4 H, H6), 5.16-5.47 (m, 2H, H7), 7.08-7.36 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.3, 42.8, 44.7, 54.5, 54.7, 59.3, 59.5, 67.0, 67.3, 67.5, 67.6, 70.8, 71.3, 75.1, 75.5, 78.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 136.1, 137.0, 137.5, 137.8, 155.0, 157.1 ppm; HRMS: m/z Calc. for $C_{22}H_{27}N_2O_4$ $[M+H]^+$: 383.1965. Found: 383.1969.

$[\alpha]_D^{20}$ -62.6 (*c* 1.0, $CHCl_3$).

Preparation of (1S,2R,5R)-3-methyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***59***



$C_{13}H_{18}N_2O$
Molecular Weight: 218.29

Procedure

Scheme 2.75

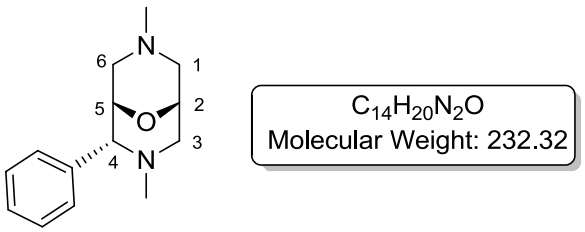
A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of N_2. The flask was then charged with palladium (10% on carbon, 1.2 g, 1.2 mmol) followed by a solution of **95** (4.5 g, 11.8 mmol) in methanol (240 ml). The vessel was then evacuated and back filled (x 3) with H_2 via a 3 way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: DCM then gradient up to 10% MeOH in DCM), to yield the desired product as a white solid (1.6 g, 60%).

Melting point: 69-71°C.

IR (neat): 2792, 2924, 3060, 3312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, NCH_3), 2.80 (ddd, ^2J = 11.8, J = 3.9, ^4J = 2.4 Hz, 1H, H6), 2.96 (m, 2H, H1), 3.15 (d, ^2J = 11.8 Hz, 1H, H6), 3.18 (d, ^2J = 13.7 Hz, 1H, H3), 3.39 (ddd, ^2J = 13.7, J = 3.6, ^4J = 2.5 Hz, 1H, H3), 3.57-3.58 (m, 1H, H2), 3.68 (d, J = 3.6 Hz, 1H, H4), 3.86 (t, J = 3.8 Hz, 1H, H5), 7.30-7.40 ppm (m, 5H, Ar): ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 45.0, 49.4, 59.8, 67.6, 72.0, 72.5, 127.6, 128.0, 128.8, 138.7 ppm; HRMS: *m/z* Calc. for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1492.

$[\alpha]_D^{23}$ -150.4 (*c* 1.0, $CHCl_3$).

*Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57** via methylation of bisamide **94**.*



Scheme 2.76

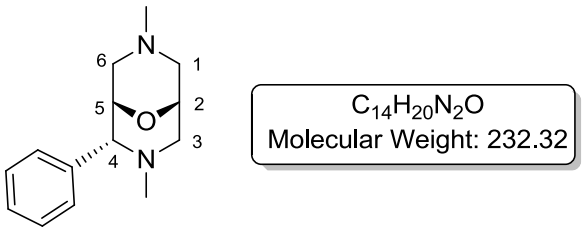
Following General Procedure A for the preparation of base **94**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of -*n*Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure G for the methylation of **94**, data are presented as follows: (a) quantity of MeI; and (b) yield of **57**.

General procedure A: (a) **59**; (b) 0.07 g, 0.32 mmol; (c) 0.16 ml, 0.16 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure G: (a) 0.02 ml, 0.32 mmol; and (b) 0.05 g, 68%.

*For analytical data for **57** please refer to data on page 356.*

*Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57** via methylation of alkyl magnemsium amide **96**.*



Scheme 2.77

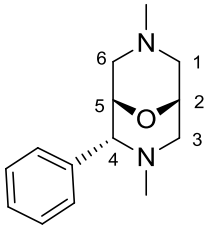
Following General Procedure E for the preparation of base **96**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; and (d) volume of THF.

Following General Procedure G for the methylation of **96**, data are presented as follows: (a) quantity of MeI; and (b) yield of **57**.

General procedure E: (a) **59**; (b) 0.07 g, 0.32 mmol; (c) 0.34 ml, 0.32 mmol; and (d) 5 ml. General procedure G: (a) 0.02 ml, 0.32 mmol; and (b) 0.061 g, 83%.

For analytical data for please refer to data on page 356.

*Preparation of (1S,2R,5R)-3,7-dimethyl-2-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **57** via methylation of Hauser base **97**.*



$C_{14}H_{20}N_2O$
Molecular Weight: 232.32

Scheme 2.78

Hauser Base Preparation Procedure

To a Schlenk flask, which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added oxabispidine **59** (0.06 g, 0.27 mmol). This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To the Schlenk flask was added THF (5 ml) followed by MeMgCl (3M in THF, 0.09 ml, 0.27 mmol). The reaction mixture was stirred at room temperature for 1 h under argon. After this time quantitative formation of the Hauser base was assumed.

Following General Procedure G for the methylation of **97**, data are presented as follows: (a) quantity of MeI; and (b) yield of **57**.

General procedure G: (a) 0.02 ml, 0.32 mmol; and (b) 0.06 g, 81%.

*For analytical data for **57** please refer to data on page 356.*

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium amide reagents derived from Oxabispidine **59***

Scheme 2.79

Following General Procedure A for the preparation of base **94**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of nBu$_2$Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **98**.

General procedure A: (a) **59**; (b) 0.11 g, 0.5 mmol; (c) 0.27 ml, 0.25 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.039 g, 25%; (e) 49:51; (f) 0.019 g, 32%; and (g) 0.097 g.

*For analytical data for by-product **98** please refer to data on page 402.*

Scheme 2.80

Following General Procedure B for the preparation of base **94**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of n-Bu$_2$Mg; (e) volume of THF; (f) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **98**.

General procedure B: (a) 0.03 g, 0.82 mmol; (b) **59**; (c) 0.09 g, 0.41 mmol; (d) 0.22 ml, 0.21 mmol; (e) 4 ml; (f) reflux; and (g) 1.5 h. General procedure H: (a) RT; (b) 0.051 g, 0.33 mmol; (c) 0.17 ml, 0.82 mmol; (d) -; (e) -; (f) 0.051 g, quant.; and (g) 0.1 g.

*For analytical data for by-product **98** please refer to data on page 402.*

Scheme 2.81

*Preparation of base **97***

To a Schlenk flask which had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon was added oxabispidine **59** (0.11 g, 0.5 mmol). This was placed under vacuum and heated to 80°C for 1 hour, before being purged with argon and allowed to cool to room temperature. To the Schlenk flask was added THF (5 ml) followed by MeMgCl (3M in THF, 0.17 ml, 0.5 mmol). The reaction mixture was stirred at room temperature for 1.5 h under argon. After this time quantitative formation of the Hauser base was assumed.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **98**.

General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 0.21 mmol; (d) -; (e) -; (f) 0.044 g, 73%; and (g) 0.2 g.

Scheme 2.82

Following General Procedure E for the preparation of base **96**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; and (d) volume of THF.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **98**.

General procedure E: (a) **59**; (b) 0.11 g, 0.5 mmol; (c) 0.53 ml, 0.5 mmol; and (d) 5 ml. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.007 g, 5%; (e) 49:51; (f) 0.048 g, 80%; and (g) 0.13 g.

Scheme 2.83, Table 2.31

Following General Procedure F for the preparation of base **94**, data are presented as follows: (a) quantity of LiCl; (b) oxabispidine/oxabispidine salt; (c) quantity of oxabispidine/oxabispidine salt; (d) quantity of *n*-Bu_2Mg; and (e) volume of THF.

Following General Procedure I for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) additive; (c) quantity of additive; (d) quantity of ketone; (e) quantity of diphenyl phosphoryl chloride; (f) yield of **43**; (g) (*S*):(*R*); (h) quantity of recovered ketone; and (i) quantity of by-product **98**.

Entry 1

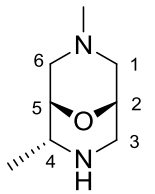
General procedure F: (a) 0.04 g, 1 mmol; (b) **59**; (c) 0.11 g, 0.5 mmol; (d) 0.53 ml, 0.5 mmol; and (e) 5 ml. General procedure I: (a) RT; (b) DMPU; (c) 0.12 ml, 1 mmol; (d) 0.06 g, 0.4 mmol; (e) 0.21 ml, 1 mmol; (f) 0.025 g, 16%; (g) 49:51; (h) 0.022 g, 37%; and (i) 0.098 g.

Entry 2

General procedure F: (a) 0.03 g, 0.82 mmol; (b) **59**; (c) 0.09 g, 0.41 mmol; (d) 0.44 ml, 0.41 mmol; and (e) 4 ml. General procedure I: (a) RT; (b) 18-c-6; (c) 0.09 ml, 0.41 mmol; (d) 0.051 g, 0.33 mmol; (e) 0.17 ml, 0.82 mmol; (f) 0.016 g, 13%; (g) 49:51; (h) 0.015 g, 29%; and (i) 0.094 g.

*For analytical data for by-product **98** please refer to data on page 402.*

*Preparation of (1S,2R,5S)-2,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane **99***



$C_8H_{16}N_2O$
Molecular Weight: 156.23

Procedure

Scheme 2.84

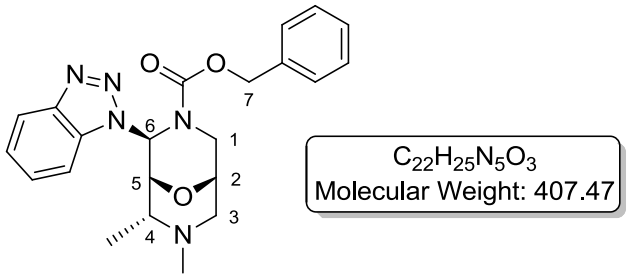
To a 3-necked flask, fitted with a low temperature thermometer that had been previously flame-dried under vacuum and allowed to cool under an atmosphere of argon, was added $LiAlH_4$ powder (1.4 g, 35.7 mmol) followed by dry diethyl ether (57 ml). The resulting

suspension was cooled to 0°C and then a solution of **81** in diethyl ether (45 ml) was added slowly. After complete addition of the substrate, the resulting mixture was stirred at 0°C for 10 minutes, then allowed to warm to room temperature and stirred for 3 hours. Tlc analysis after this time showed no starting material remained. To the reaction mixture was added water (1.4 ml; 1 ml per 1 g $LiAlH_4$) and the mixture was allowed to stir for 10 min. After this time, 15% NaOH (1.4 ml; 1 ml per 1 g $LiAlH_4$) followed by water (4.2 ml; 3 ml per 1 g $LiAlH_4$) was added and the resulting white granular suspension was allowed to stir for 15 min. An excess of solid sodium bicarbonate was then added and the mixture was stirred for a further 20 min. The suspension was filtered through a plug of celite, which was then washed with ether, and the filtrate concentrated *in vacuo*. Purification by column chromatography (eluent: 0% to 10% MeOH in DCM) resulted in the desired product being recovered as a pale yellow waxy solid (0.5 g, 31%).

IR (neat): 1452, 2791, 2935, 3385 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (d, J = 7.0 Hz, 3H, CH_3), 2.17 (s, 3H, N-CH_3), 2.44 (ddd, ^2J = 11.8, J = 3.5, ^4J = 1.4 Hz, 1H, H6), 2.55 (ddd, ^2J = 11.3, J = 3.6, ^4J = 2.7 Hz, 1H, H1), 2.88(d, ^2J = 11.3 Hz, 1H, H1), 2.99 (d, ^2J = 11.8 Hz, 1H, H6), 3.10 (d, ^2J = 13.5 Hz, 1H, H3), 3.34-3.39 (m, 2H, H3+H4), 3.52 (t, J = 3.5 Hz, 1H, H5), 3.71 (t, J = 3.7 Hz, 1H, H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 46.3, 49.4, 53.2, 54.3, 59.0, 66.1, 70.7 ppm; HRMS: *m/z* Calc. for $C_8H_{17}N_2O$ $[M+H]^+$: 157.1335. Found: 157.1333.

$[\alpha]_D^{25}$ -9.0 (*c* 0.2, $CHCl_3$).

Preparation of (1R,5S,8R)-benzyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)-7,8-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate ***101***



Procedure

Scheme 2.85

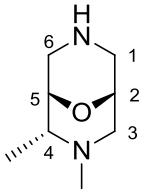
To a solution of **81** (3.1 g, 7.9 mmol) in DCM (80 ml) was added methyl iodide (0.59 ml, 9.5 mmol) and potassium carbonate (1.2 g, 8.7 mmol). The reaction was stirred at room temperature and the progress followed by tlc. Complete consumption of the starting material was observed after 3 days, after which time the reaction mixture was poured into water and the phases separated. The aqueous layer was extracted with another portion of DCM and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield a pale yellow oil (2.2 g, 68%).

IR (neat): 1712, 2330, 2854, 2924 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.6 Hz, 0.6H, CH_3), 1.28 (d, *J* = 6.6 Hz, 1H, CH_3), 1.32 (d, *J* = 6.6 Hz, 0.7H, CH_3), 1.37 (d, *J* = 6.6 Hz, 0.7H, CH_3), 2.13 (s, 0.8H, NCH_3), 2.14 (s, 0.7H, NCH_3), 2.17 (s, 0.8H, NCH_3), 2.18 (s, 0.7H, NCH_3), 2.56-2.72 (m, 2H, H3), 2.83-2.95 (m, 1H, H4), 3.68-3.73 (m, 0.5H, H1), 3.94-4.17 (m, 2.3H, H1+H2), 4.21 (d, ^{2}J = 13.5 Hz, 0.2H, H1), 4.31-4.34 (m, 0.5H, H5), 4.45 (d, *J* = 3.3 Hz, 0.3H, H5), 4.50 (d, *J* = 3.3 Hz, 0.2H, H5), 5.12-5.24 (m, 2H, H7), 6.74 (s, 0.3H, H6), 6.77 (s, 0.2H, H6), 6.91 (s, 0.2H, H6), 6.92 (s, 0.3H, H6), 7.08-7.51 (m, 7.3H, H_{Ar}), 7.74 (d, *J* = 8.2 Hz, 0.2H, H_{Ar}), 7.86-7.92 (m, 1H, H_{Ar}), 8.09-8.11 ppm (m, 0.5H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 15.8, 42.4, 42.5, 42.6, 42.7, 43.3, 43.6, 43.7, 53.0, 58.7, 58.8, 59.1, 59.2, 59.5, 59.6, 59.8, 59.9, 62.2, 63.0, 66.6, 66.7, 66.9, 67.0, 67.2, 67.3, 67.6, 69.0, 69.1, 72.9, 73.2, 74.4, 109.6, 109.9, 117.8, 117.9, 119.4, 119.6, 123.5, 123.6, 125.7, 125.8, 128.9, 127.0, 126.9, 127.0, 127.1, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1,

132.2, 135.6, 135.8, 135.9, 143.7, 143.8, 145.3, 153.9, 154.3, 154.9, 155.1 ppm; HRMS: *m/z* Calc. for $C_{22}H_{26}N_5O_3$ $[M+H]^+$: 408.2030. Found: 408.2029.

$[\alpha]_D^{27}$ -73.5 (*c* 0.35, $CHCl_3$).

Preparation of (1S,2R,5R)-2,3-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane ***100***



$C_8H_{16}N_2O$
Molecular Weight: 156.23

Procedure

Scheme 2.85

A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (10% on carbon, 0.57 g, 0.54 mmol) followed by a solution of **101** (2.2 g, 5.4 mmol) in methanol (110 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3-way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: EtOAc, followed by 10% MeOH in EtOAc then 10% MeOH in DCM), to yield the desired product as a pale yellow solid (0.61 g, 72%).

IR (neat): 2358, 2787, 2908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.4 Hz, 3H, CH_3), 2.16 (s, 3H, NCH_3), 2.56-2.61 (m, 1H, H4), 2.70 (ddd, ^2J = 11.5, *J* = 3.7, ^4J = 2.5 Hz, 1H, H3), 2.86 (d, ^2J = 11.5 Hz, 1H, H3), 2.99 (d, ^2J = 13.8 Hz, 1H, H1), 3.12- 3.13 (m, 2H, H6), 3.28- 3.33 (m, 3H, NH+H1+H5), 3.67 ppm (t, *J* = 3.7 Hz, 1H, H2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 43.5, 45.3, 50.1, 60.2, 61.6, 68.1, 72.1 ppm; HRMS: *m/z* Calc. for $C_8H_{17}N_2O_1$ $[M+H]^+$: 157.1335. Found: 157.1334.

$[\alpha]_D^{23}$ -41.2 (*c* 0.55 in $CHCl_3$).

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium amide reagents derived from Oxabispidine **99***

Scheme 2.86, Table 2.32, Entry 1

Following General Procedure A for the preparation of chelating bisamide base derived from **99**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product.

General procedure A: (a) **99**; (b) 0.07 g, 0.44 mmol; (c) 0.2 ml, 0.22 mmol; (d) 4 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.051 g, 0.35 mmol; (c) 0.18 ml, 0.88 mmol; (d) -; (e) -; (f) 0.013 g, 25%; and (g) -.

Scheme 2.86, Table 2.32, Entry 2

Following General Procedure E for the preparation of alkyl magnesium amide base derived from **99**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; and (d) volume of THF.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product.

General procedure E: (a) **99**; (b) 0.07 g, 0.44 mmol; (c) 0.4 ml, 0.44 mmol; and (d) 4 ml. General procedure H: (a) RT; (b) 0.051 g, 0.35 mmol; (c) 0.18 ml, 0.88 mmol; (d) -; (e) -; (f) 0.019 g, 37%; and (g) -.

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium amide reagents derived from Oxabispidine **99***

Scheme 2.87, Table 2.33, Entry 1

Following General Procedure A for the preparation of chelating bisamide base derived from **100**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **102**.

General procedure A: (a) **100**; (b) 0.08 g, 0.5 mmol; (c) 0.18 ml, 0.25 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.007 g, 5%; (e) 50:50; (f) 0.054 g, 90%; and (g) 0.12 g.

*For analytical data for by-product **102** please refer to data on page 403.*

Scheme 2.87, Table 2.33, Entry 2

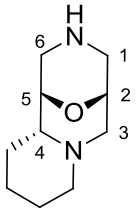
Following General Procedure E for the preparation of alkyl magnesium amide base derived from **100**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; and (d) volume of THF.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **102**.

General procedure E: (a) **100**; (b) 0.08 g, 0.5 mmol; (c) 0.36 ml, 0.5 mmol; and (d) 5 ml. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.015 g, 10%; (e) 49:51; (f) 0.044 g, 74%; and (g) 0.10 g.

*For analytical data for by-product **102** please refer to data on page 403.*

Preparation of (1S,5R,11aR)-decahydro-1H-1,5-epoxypyrido[1,2-a][1,5]diazocine ***103***



$C_{10}H_{18}N_2O$
Molecular Weight: 182.26

Procedure

Scheme 2.88

A 3-necked flask was flame dried under vacuum before cooling under an atmosphere of argon. The flask was then charged with palladium (10% on carbon, 0.73 g, 0.69 mmol) followed by a solution of **104** (3 g, 6.9 mmol) in methanol (140 ml). The vessel was then evacuated and back filled (x 3) with H_2 *via* a 3 way tap attached to a vacuum manifold and a hydrogen balloon. Upon the last refill, the mixture was left stirring at room temperature overnight. After filtration through a plug of celite, and washing with additional methanol followed by 1M ammonia in methanol, the resulting solution was concentrated *in vacuo*. The resulting crude product was purified by column chromatography (eluent: EtOAc, followed by 10% MeOH in EtOAc then 10% MeOH in DCM), to yield the desired product as a white solid (0.75 g, 60%).

Melting Point: 198-200°C.

IR (neat): 1440, 1535, 2804, 2929, 3393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31-1.51 (m, 3H, -C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N), 1.61-1.67 (m, 2H, -C*H*$_2$C*H*$_2$CH$_2$CH$_2$N), 1.79-1.87 (m, 2H, -CH$_2$CH$_2$C*H*$_2$C*H*$_2$N), 2.51-2.53 (m, 1H, H4), 2.73 (ddd, ^2J = 11.5, J = 3.6, ^4J = 2.5 Hz, 1H, H3), 2.81-2.86 (m, 2H, H3+C*H*$_2$N), 3.14 (d, ^2J = 13.6 Hz, 1H, H6), 3.21 (ddd, ^2J = 13.9, J = 3.6, ^4J = 1.3 Hz, 1H, H1), 3.30 (d, ^2J = 13.9 Hz, 1H, H1), 3.36 (ddd, ^2J = 13.6, J = 3.6, ^4J = 2.5 Hz, 1H, H6), 3.40-3.42 (m, 1H, H5), 3.78 (t, J = 3.5 Hz, 1H, H2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 25.0, 27.7, 45.3, 49.0, 56.2, 58.6, 64.5, 67.0, 70.0 ppm; HRMS: *m/z* Calc. for $C_{10}H_{19}N_2O$ $[M+H]^+$: 183.1492. Found: 183.1490.

$[\alpha]_D^{26}$ -10.4 (*c* 0.4 in $CHCl_3$).

*Asymmetric Deprotonation of 4-tert-Butylcyxlohexanone using Magnesium Amide Reagents derived from Oxabispidine **103***

Scheme 2.89, Table 2.34, Entry 1

Following General Procedure A for the preparation of chelating bisamide base derived from **103**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; (d) volume of THF; (e) temperature; and (f) time.

Following General Procedure H for the deprotonation of 4-*tert*-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **105**.

General procedure A: (a) **103**; (b) 0.09 g, 0.5 mmol; (c) 0.15 ml, 0.25 mmol; (d) 5 ml; (e) reflux; and (f) 1.5 h. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) -; (e) -; (f) 0.059 g, 98%; and (g) 0.13 g.

Scheme 2.89, Table 2.34, Entry 2

Following General Procedure E for the preparation of alkyl magnesium amide base derived from **103**, data are presented as follows: (a) oxabispidine/oxabispidine salt; (b) quantity of oxabispidine/oxabispidine salt; (c) quantity of *n*-Bu_2Mg; and (d) volume of THF.

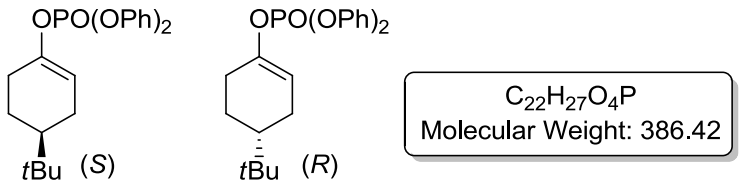
Following General Procedure H for the deprotonation of 4-tert-butylcyclohexanone, data are presented as follows: (a) temperature; (b) quantity of ketone; (c) quantity of diphenyl phosphoryl chloride; (d) yield of **43**; (e) (*S*):(*R*); (f) quantity of recovered ketone; and (g) quantity of by-product **105**.

*For analytical data for by-product **105** please refer to data on page 404.*

General procedure E: (a) **103**; (b) 0.09 g, 0.5 mmol; (c) 0.3 ml, 0.5 mmol; and (d) 5 ml. General procedure H: (a) RT; (b) 0.06 g, 0.4 mmol; (c) 0.21 ml, 1 mmol; (d) 0.011 g, 7%; (e) 50:50; (f) 0.03 g, 50%; and (g) 0.1 g.

6.7 Experimental Data for Enol Phosphate 43 and Phosphorylated Oxabispidine By-products

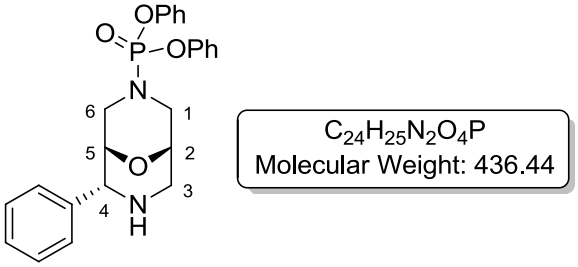
4-(tert-butyl)cyclohex-1-en-1-yl diphenyl phosphate ***43***[66]



IR (neat): 950, 1295, 1695, 2980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 9H, $C(CH_3)_3$), 1.28-1.35 (m, 2H, CH_2), 1.86-1.90 (m, 2H, CH_2), 2.09-2.15 (m, 1H,CHtBu), 2.26-2.30 (m, 2H, CH_2), 5.56-5.59 (m, 1H, C=C*H*), 7.20-7.28 (m, 6H, H_{Ar}), 7.35-7.39 ppm (m, 4H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.6, 24.6, 26.9, 28.3, 31.7, 42.8, 111.4, 119.7, 125.0, 147.4, 150.3 ppm; ^{31}P NMR (162 $CDCl_3$): -17.5 ppm.

Chiral HPLC analysis: Chiralcel OD-H column, 1% IPA in *n*-hexane, 1.0 ml/min, 254 nm detector, t_R (+) = 33.4 min, t_R (-) = 35.9 min.
For (*S*):(*R*) 96:4 er, $[\alpha]_D^{20}$ -34.7 (*c* 1.0 in $CHCl_3$). No literature data are available for comparison.

Diphenyl ((1S,5S,6R)-6-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)phosphonate ***60***

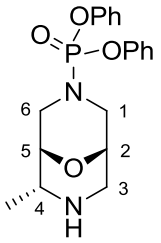


IR (neat): 922, 1259, 1487, 2989 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18-3.23 (m, 1H, H6), 3.25 (d, ^{2}J = 13.4 Hz, 1H, H1*)*, 3.50-3.59 (m, 3H, H1, H3+H6), 3.75-3.79 (m, 2H, H2+H3), 3.83 (q, *J* = 3.8 Hz, 1H, H5), 4.51 (d, *J* = 3.3 Hz, 1H, H4), 7.20-7.41 ppm (m, 15H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.0, 47.3, 49.2, 61.3, 64.6 (d, $^{2}J_{CP}$ = 8.0 Hz), 69.9 (d, $^{2}J_{CP}$ = 7.6 Hz), 119.4 (d, $^{3}J_{CP}$ = 4.9 Hz), 119.5 (d, $^{3}J_{CP}$ = 4.9 Hz), 124.7, 125.6, 127.0, 128.2, 129.2,

138.3, 150.1 ppm (d, $^{2}J_{CP}$ = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -2.6 ppm; HRMS: *m/z* Calc. for $C_{24}H_{26}N_2O_4P$ $[M+H]^+$: 437.1625. Found: 437.1617.

$[\alpha]_D^{26}$ –40.2 (*c* 0.95 in $CHCl_3$).

Diphenyl ((1S,5S,6R)-6-methyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)phosphonate ***84***

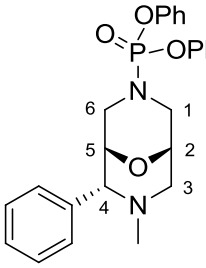


$C_{19}H_{23}N_2O_4P$
Molecular Weight: 374.37

IR (neat): 923, 1191, 2789, 2850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, *J* = 7.0 Hz, 3H, CH_3), 2.91 (d, ^{2}J = 14.1 Hz, 1H, H6), 3.31-3.37 (m, 3H, H3+H4+H6), 3.39-3.42 (m, 1H, H5), 3.46-3.50 (m, 1H, H1), 3.57-3.60 (m, 1H, H2), 3.64 (dd, ^{2}J = 12.6, *J* = 6.6 Hz, 1H, H1), 3.86 (dd, ^{2}J = 13.3, *J* = 6.9 Hz, 1H, H3), 7.19-7.32 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 42.8, 47.4, 48.7, 51.8, 64.3, 64.4, 119.4, 124.7, 125.0, 129.4 ppm; ^{31}P NMR (162 MHz, $CDCl_3$): -2.6 ppm; HRMS: *m/z* Calc. for $C_{19}H_{24}N_2O_4P$ $[M+H]^+$: 375.1468. Found: 375.1462.

$[\alpha]_D^{27}$ +0.43 (*c* 1.6 in $CHCl_3$).

Diphenyl ((1S,5S,6R)-7-methyl-6-phenyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)phosphonate ***98***



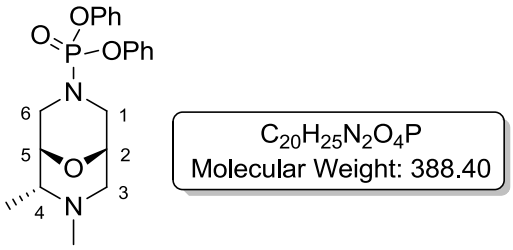
$C_{25}H_{27}N_2O_4P$
Molecular Weight: 450.47

IR (neat): 920, 1188, 1263, 2789, 2846, 2941 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H, CH_3), 2.74 (ddd, ^{2}J = 11.8, *J* = 4.2, ^{4}J = 1.7 Hz, 1H, H3), 2.98-3.03 (m, 2H, H1+H3), 3.45-3.49 (m, 1H, H6), 3.54 (d, *J* = 3.6 Hz, 1H, H1), 3.61-3.68 (m, 3H, H2+H4+H6), 3.96 (q,

J = 3.9 Hz, 1H, H5), 7.16-7.46 ppm (m, 15H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.3, 44.2, 46.4, 58.3, 68.0, 71.6, 71.7, 119.7, 124.2, 127.0, 128.1, 129.1, 129.2 138.0, 150.0 ppm (d, $^2J_{CP}$ = 5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -2.6 ppm; HRMS: *m/z* Calc. for $C_{25}H_{28}N_2O_4P$ $[M+H]^+$: 451.1781. Found: 451.1791.

$[\alpha]_D^{26}$ –35.8 (*c* 1.0 in $CHCl_3$).

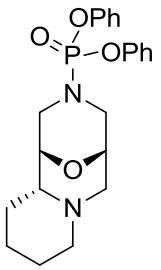
Diphenyl ((1S,5S,6R)-6,7-dimethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)phosphonate ***102***



IR (neat): 922, 1192, 1267, 1489, 2787, 2926, 2976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (d, *J* = 6.7 Hz, 3H, CH_3), 2.00 (s, 3H, NCH_3), 2.45-2.51 (m, 1H, H4), 2.59 (ddd, ^2J = 11.6, *J* = 4.2, ^4J = 1.8 Hz, 1H, H3), 2.77 (d, ^2J = 11.6 Hz, 1H, H3), 3.20-3.25 (m, 1H, H6), 3.39-3.44 (m, 1H, H1), 3.48 (q, *J* = 3.5 Hz, 1H, H5), 3.60 (dd, ^2J = 12.6, *J* = 7.4 Hz, 1H, H1), 3.78 (dd, ^2J = 13.1, *J* = 7.7 Hz, 1H, H6), 3.81-3.84 (m, 1H, H2), 7.15-7.18 (m, 2H, H_{Ar}), 7.32-7.38 ppm (m, 8H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 41.4, 42.6, 46.3, 58.4, 59.8, 67.0 (d, $^2J_{CP}$ = 7.1 Hz), 71.2 (d, $^2J_{CP}$ = 6.7 Hz), 119.6 (d, $^3J_{CP}$ = 5.5 Hz), 124.1, 129.1, 150.7 ppm ($^2J_{CP}$ = 6.4 Hz) ppm; ^{31}P NMR (162 MHz, $CDCl_3$): -2.8 ppm; HRMS: *m/z* Calc. for $C_{20}H_{26}N_2O_4P$ $[M+H]^+$: 389.1625. Found: 389.1623.

$[\alpha]_D^{26}$ –19.9 (*c* 0.35 in $CHCl_3$).

*Diphenyl ((1S,5S,11aR)-hexahydro-1H-1,5-epoxypyrido[1,2-a][1,5]diazocin-3(2H,4H,8H)-yl)phosphonate**105***



$C_{22}H_{27}N_2O_4P$
Molecular Weight: 414.43

IR (neat): 920, 1190, 1489, 1591, 2762, 2852, 2931 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.51 (m, 5H, -C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$N), 1.72-1.79 (m, 2H, CH$_2$N), 2.36 (dt, *J* = 10.8, *J* = 2.9 Hz, 1H, H4), 2.57-2.61 (m, 2H, NCH$_2$, H3), 2.72 (d, ^{2}J = 11.3 Hz, 1H, H3*)*, 3.24 (dt, ^{2}J = 13.0, *J* = 2.9 Hz, 1H, H6), 3.40-3.48 (m, 2H, H1+H5), 3.58 (dd, ^{2}J = 12.6, *J* = 7.4 Hz, 1H, H1), 3.80-3.85 (m, 2H, H2+H6), 7.14-7.39 ppm (m, 10H, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.5, 27.3, 42.4, 46.5, 56.2, 57.6, 63.6, 67.0 (d, $^{2}J_{CP}$ = 6.9 Hz), 70.3 (d, $^{2}J_{CP}$ = 6.7 Hz), 119.7 (d, $^{3}J_{CP}$ = 5.2 Hz), 124.2, 129.1, 150.7 (d, $^{2}J_{CP}$ = 7.6 Hz), ppm; ^{31}P NMR (162 MHz, $CDCl_3$): -2.5 ppm; HRMS: *m/z* Calc. for $C_{22}H_{28}N_2O_4P$ $[M+H]^+$: 415.1781. Found: 415.1775.

$[\alpha]_D^{26}$ –10.6 (*c* 0.75 in $CHCl_3$).

8. Appendix

8.1 X-ray Crystallography Data for 55a and 55b

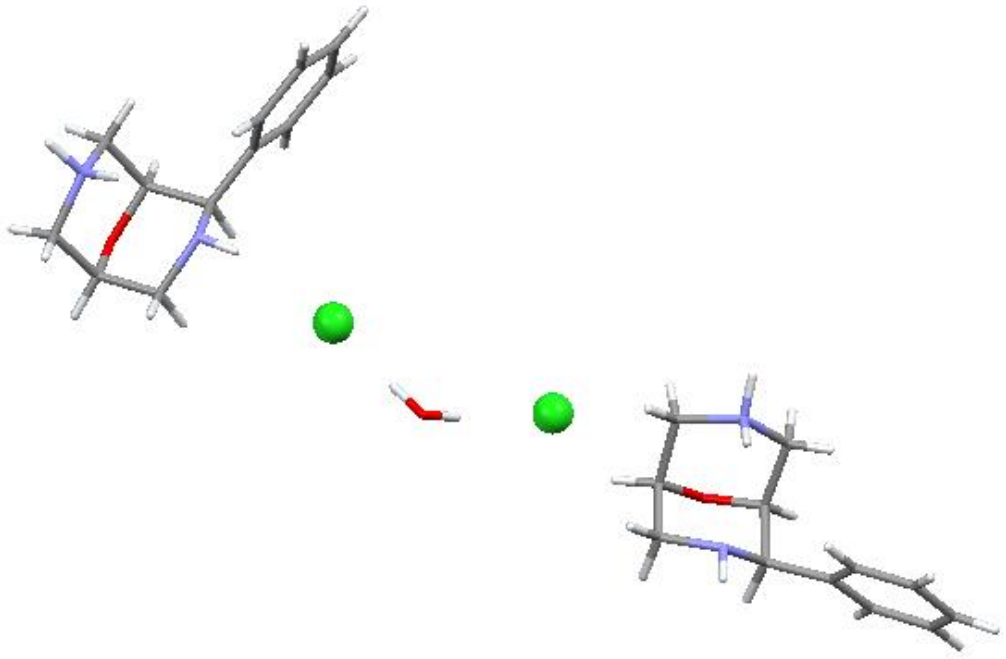


Figure 2.11: X-ray crystal structure of precipitate. Depicts a mixture of mono-HCl salts **55a** and **55b** in addition to a single water molecule.

Crystal data and structure refinement

Identification code	kerrmay2012lp	
Empirical formula	C12 H18 Cl N2 O1.50	
Formula weight	249.73	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.3808(2) Å	α= 90°.
	b = 13.9143(2) Å	β= 90°.
	c = 17.1550(3) Å	γ = 90°.
Volume	2477.90(7) $Å^3$	
Z	8	
Density (calculated)	1.339 Mg/m^3	
Absorption coefficient	0.295 mm^{-1}	

F(000)	1064
Crystal size	0.30 x 0.12 x 0.10 mm^3
Theta range for data collection	3.08 to 29.83°.
Index ranges	-14<=h<=14, -18<=k<=19, -22<=l<=23
Reflections collected	12376
Independent reflections	6266 [R(int) = 0.0244]
Completeness to theta = 27.00°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.98175
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6266 / 0 / 331
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0364, wR2 = 0.0711
R indices (all data)	R1 = 0.0432, wR2 = 0.0743
Absolute structure parameter	0.01(4)
Largest diff. peak and hole	0.278 and -0.220 e.$Å^{-3}$

For tables of additional X-ray crystallography data please refer accompanying CD.

8.2 Computational Data: Magnesium Amide Base Modelling

For experimental details of the computational methods employed please refer to information on accompanying CD.