Synthesis and application of stereogenic nitrogen-containing ammonium salts as phase-transfer catalysts

By

Mark Jason Dutton

UNIVERSITY OF BIRMINGHAM

A thesis submitted to

The University of Birmingham

For a degree of

DOCTOR OF PHILOSOPHY

School of Chemistry

College of Engineering and Physical Sciences

University of Birmingham

August 2014

UNIVERSITY OF BIRMINGHAM

University of Birmingham Research Archive

e-theses repository

Abstract

The chirality of nitrogen was at the forefront of chemistry over 110 years ago. Since then it has been widely under-acknowledged as a potential chirality source in organic synthesis. This thesis demonstrates the diastereoselective formation of stereogenic nitrogen-containing ammonium salts. Over 150 compounds were synthesised and employed as phase-transfer catalysts in order to assess the chiral-at-nitrogen influence on the outcome of two common phase-transfer-catalysed reactions. Several X-ray crystal structures of single diastereoisomer chiral-at-nitrogen ammonium salts were isolated as well as the synthesis of a library of secondary and tertiary amines.

This thesis is dedicated to Tiernan Kerr

Probably the bravest boy I know

Abbreviations

R/*S*	Rectus/sinister
1st gen	First-generation compounds
2nd gen	Second-generation compounds
3D	Three dimensional
3rd gen	Third-generation compounds
Acac	Acetylacetone
AIBN	Azobisisobutyronitrile
app	apparent
Ar	Aryl
Aux	Auxiliary
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Bu / ^{t}Bu	Butyl/tert-butyl
C_2	180° plane of symmetry around the z axis
ca.	circa
Cbz	carboxybenzyl
CD	Circular dichroism
cf.	Confer
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DAS	Diastereomeric ammonium salt
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DiPAMP	1,2-Bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DMAP	4-Dimethylamino pyridine
DMC	Dimethyl carbonate

DME	Dimethyl ether
DMF	Dimethylformamide
DNA	Deoxyribonucleic acid
e.g.	For example
e.r.	Enantiomeric ratio
ee	Enantiomeric excess
Et al.	Et alia (and others)
HBTU	N, N, N ,N-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
IR	Infra red
Me	Methyl
MeCN	Acetonitrile
MS	Mass spectrometry
MTPACl	α-Methoxytrifluoromethylphenylacetyl chloride
NBS	N-bromo succinimide
NIR	Nitrogen inversion barrier
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
^{n}Pr	Propyl
Ph	Phenyl
phen	phenanthroline
Pr	Propyl
PTC	Phase-transfer catalyst
rac	Racemic
S_N2	Bi-molecular nucleophilic substitution
TBAB	Tetra butyl ammonium bromide
TBAF	Tetra butyl ammonium fluoride

TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TS	Transition state
VT	Variable temperature
w/w	Weight/weight

Contents

1 Introduction

1.1 Stereogenic nitrogen

1.1.1 Introduction to heteroatom-centred chirality

In 1902 Pope addressed an audience of his peers, his first sentence was:

"*The subject on which I want to say a few words this evening must, I venture to think, ever be regarded as one of the most remarkable developments recorded in the history of science of modern chemistry.*"[1]

Of course this was the description of the asymmetric carbon atom. With the newly established technique of polarimetry, it had become far simpler to identify optically active compounds. In paying homage to such distinguished luminaries of the chemistry world, such as Pasteur and Van't Hoff, the discussion began considering the properties of light.

In essence, a short tutorial on the working of polarimetry and then how this tool provided insight into enantiomorphism and proof for the resolution of saccharides and other asymmetric carbon atom-containing molecules. Pope concluded efforts towards resolving tetravalent sulfur and tin compounds, before encroaching onto the quinquilevance of nitrogen, namely ammonium iodides (**Figure 1**).[2]
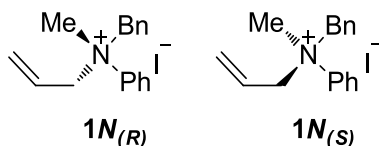

Figure 1 Pope successfully resolved stereogenic-at-nitrogen ammonium salts in 1899

What was Pope's area of expertise, having been the first to achieve resolution of a quaternary nitrogen stereogenic centre (where the only asymmetric component in the molecule was nitrogen) by fractional recrystallisation with silver (I) camphorsulfonate which gave enantiomers **1N$_{(R)}$** and

N(S). This breakthrough in organic chemistry of resolution of chiral-at-nitrogen[I] ammonium salt enantiomers has received less attention than warranted and revisits to the dissymmetric nitrogen atom in its ammonium salt form in intervening years have, as yet, failed to compete with methodology surrounding the formation of asymmetric carbon-carbon bond-forming reactions. This disparity in the literature can be accounted for by some considerations:

1) Due to nitrogen's proclivity to undergo inversion when existing as a pyramidal amine, leading to apparently uncontrollable rapid racemisation of amines[II].
2) Decomposition due to the deliquescent nature of ammonium salts formed.
3) Their reactivity and susceptibility to rearrangement reactions.
4) The overall difficulty in isolation of enantiomerically pure stereogenic nitrogen compounds.

Asymmetric carbon-carbon bond formation has been at the forefront of organic chemistry for many years and continues to provide an extensive output for today's research chemist.[5] However the consideration of nitrogen's chirality, specifically that in the form of ammonium salts, has not yet been fully exploited since the initial work by Pope in 1899.[2]

[I] Pertaining to a stereogenic tetrahedral nitrogen atom in a molecule which may or may not contain another stereogenic centre

[II] The barrier to inversion for ammonia which contains an sp^3 hybridised nitrogen has a pyramidal geometry is 24 kcal mol^{-1} (*cf.* phosphine 132 kcal mol^{-1}) which means it inverts approximately 5 x 10^{5} s^{-1} at room temperature.

[3] C. Kölmel, C. Ochsenfeld and R. Ahlrichs, *Theoret. Chim. Acta*, 1992, **82**, 271-284
[4] M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, 1963, **85**, 1882-1882.
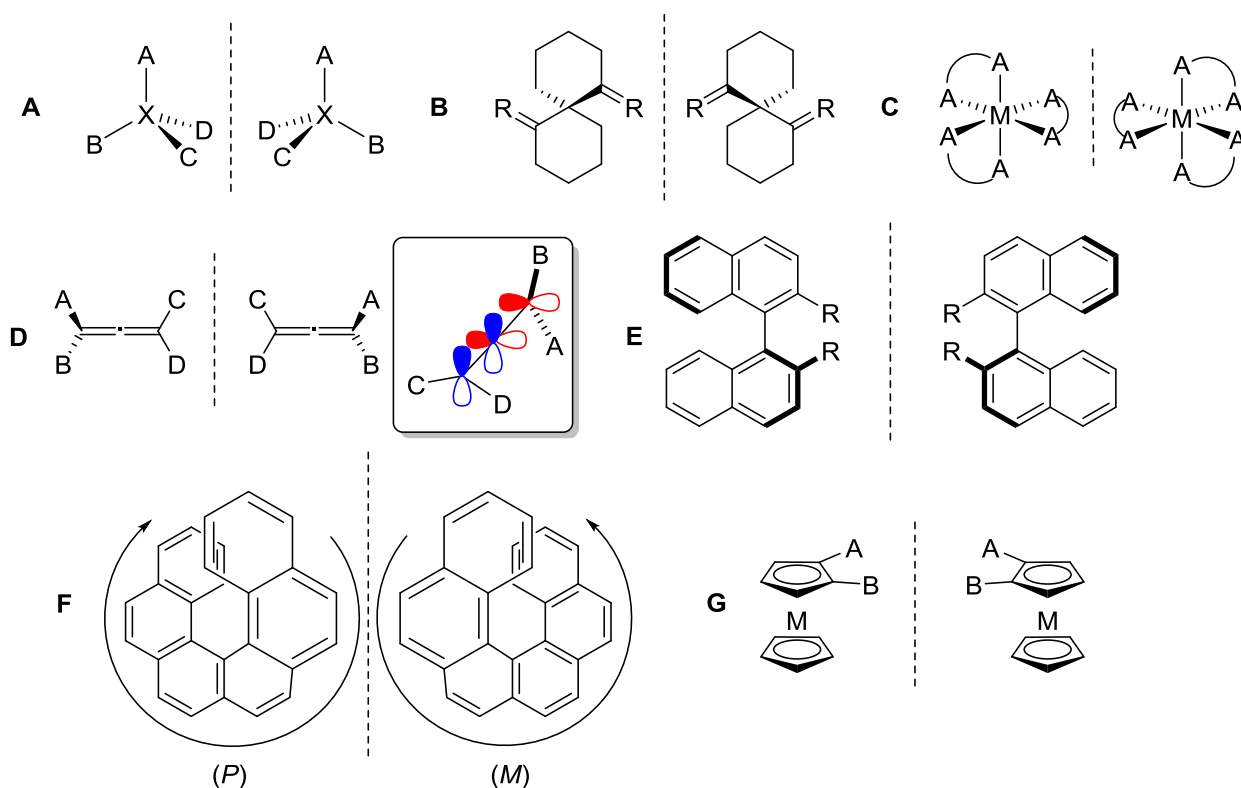
Figure 2 Different forms of chirality: A) Central chirality, B) Spirocyclic chirality, C) Octahedral complexes, D) Axial chirality in allenes, E) Atropisomers, F) Helical chirality, G) Planar chirality in metallocenes.

Chirality is present in many forms (**Figure 2**). Perhaps the most well recognised is the central chirality of a tetrahedral carbon atom **A** (X = sp^3 carbon, *P, N, S*).[6] Here, an atom (carbon or heteroatom) is appended with four different groups. Spirocyclic compounds, such as **B**, may contain a stereogenic centre which is chiral through rotational dissymmetry. Compound **B** is an example of a molecule which displays central chirality. Octahedral metal centres can be chiral and display Λ / Δ propeller chirality by arrangement of bidentate ligands **C**. Sandwich complexes **G**, such as ferrocene derivatives, can display planar chirality where dissymmetric di-substitution on one arene ring leads to systems with non-superimposable mirror-images. Allenes **D**, exhibit axial chirality when there are different groups attached (e.g. A≠B≠C≠D).[7] The dissymmetry arises due to the non-conjugated nature of the π-system as the adjacent π-molecular orbitals are orthogonal to each other. Atropisomers **E** have restricted bond rotation resulting in configurationally stable enantiomeric forms. For example, BINOL (R = OH) is stable to

5

racemisation up to 100 $^{\circ}$C in refluxing dioxane and water although racemises at that temperature when strong base or acid is added.[8, 9] Helicenes **F** display helical chirality which can be assigned in a similar fashion to other axially chiral molecules.

Various forms of heteroatom centred chirality are also known and shown in phosphines **2** and amines **7** with three different groups attached (**Figure 3**). Chiral phosphines are far more configurationally stable (see next section) and readily separable.[3] *P*-Chiral[III] phosphines have found extensive use in asymmetric synthesis and catalysis and have been heavily utilised as chiral ligands such as DiPAMP **10**.[10] *P*-Oxides **3**, *N*-oxides **8** and *S*-oxides **5** have been used extensively as the field of organocatalysis has grown over the last 30 years.[11-13] Ellman's auxiliary **11** could even be considered as a modern-day classic and is one of the most widely used chiral auxiliaries in science today.[14] Onium salts **4**, **6** and **9** have widespread use as asymmetric catalysts most notably in asymmetric phase-transfer catalysis.[15-19] Amines, *N*-oxides and ammonium salts shall be discussed in more depth in the following sections.

The first asymmetric phosphine ligand **12** was reported by Knowles in 1968.[20] Although compound **12** was isolated in a modest *ee* of 17% it proved to catalyse a body of work in phosphine chemistry with applications in the asymmetric catalysis arena that resulted in his award of the Nobel Prize in Chemistry along with Noyori and Sharpless in 2001.[21-23] That work helped shape and define the direction of research into heteroatom chirality as a meaningful asymmetric tool for organic synthesis.[24-26]

[III]Pertaining to a stereogenic tetrahedral phosphorus atom in a molecule which may or may not contain another stereogenic centre.
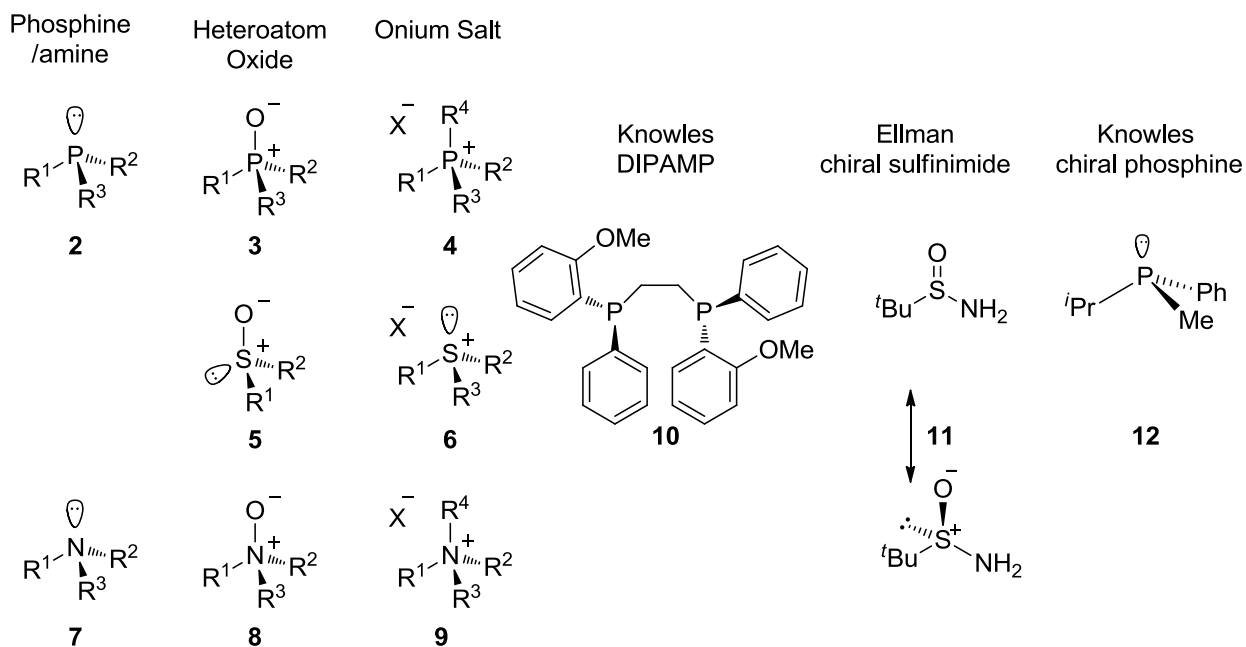
Figure 3 classification of chiral heteroatom containing molecules and some widely used chiral heteroatom containing molecules

This Chapter continues with discussion into ventures employing stereogenic nitrogen containing molecules. Although investigations into nitrogen chirality have been ongoing for over 120 years, it is still in its infancy in terms of a developed understanding and general utility of application. Central to this discussion is the importance, or otherwise, of nitrogen-centred chirality.

1.1.2 Pyramidal nitrogen containing molecules

The barrier to inversion for ammonia which contains an sp^3 hybridised nitrogen and has a pyramidal geometry is 24 kcal mol^{-1} (*cf.* phosphine 132 kcal mol^{-1}) which means it inverts approximately 5 x 10^5 s^{-1} at room temperature.[3, 4] Tertiary amines (when $R^1 \neq R^2 \neq R^3$) are chiral, however, due to this rapid rate of inversion chiral information is generally lost on any reasonable synthetic or analytical timescale (**Figure 4**). At room temperature the sp^3 nitrogen (regular tetrahedron with bond angles of approximately 109°) can undergo inversion and passes through an intermediary planar (bond angle of 120°) geometry before returning again to a sp^3 geometry. This facile inversion is one reason for the relative sparsity of reports in the nitrogen chirality arena compared with the larger number of reports into *P*-chiral phosphines. Compared with

phosphines, amines are environmentally benign, easier to handle and store and as such, often cheaper.
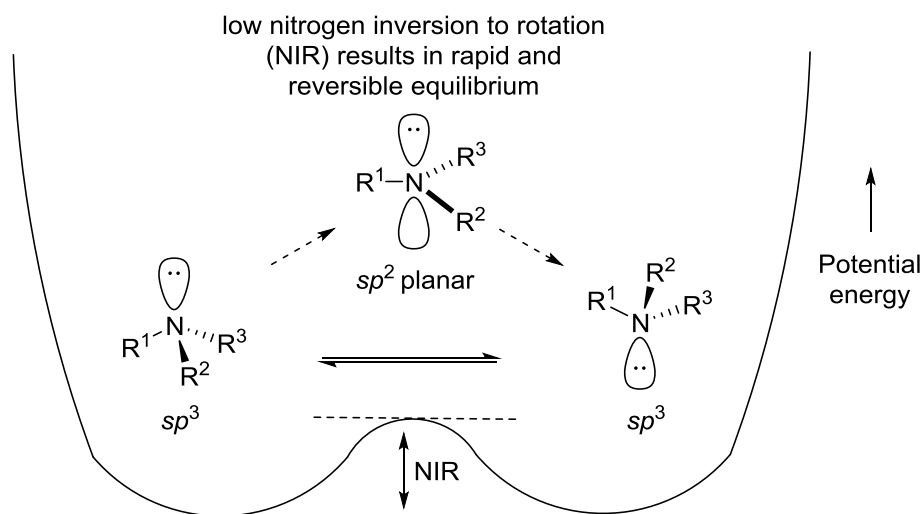

low nitrogen inversion to rotation
(NIR) results in rapid and
reversible equilibrium

sp^2 planar

R^1-N,,,R^3

R^2

Potential
energy

R^1,,,R^3
R^2

sp^3

R^2
R^1,,,R^3
N

sp^3

NIR

Figure 4 nitrogen inversion is rapid and reversible

Configurationally stable chiral-at-nitrogen tertiary amines (**8**) will be discussed in the next sections and can be distinguished by the following categories.

i)   Mutual stabilisation of rings

ii)   Chiral at bridgeheads

iii) π-Stabilisation

1.1.2.1 Mutual Stabilisation in rings

Nitrogen's inversion rotation (NIR) barrier can be increased when the nitrogen atom is incorporated in a ring and arises from the increased strain induced in the sp^2 state (**Figure 5**). Trimethylamine **13** with a relatively low NIR of 8.2 kcal mol^{-1} readily inverts at room temperature.[3] The higher NIR barrier of *N*-Methylpyrrolidine **14** however shows that in a simple five-membered ring the inversion process requires more energy.[27] When nitrogen is placed at the bridgehead position in a cyclic molecule **15**, its inversion is totally arrested, due to the geometric constraints imposed by the skeletal carbon framework.
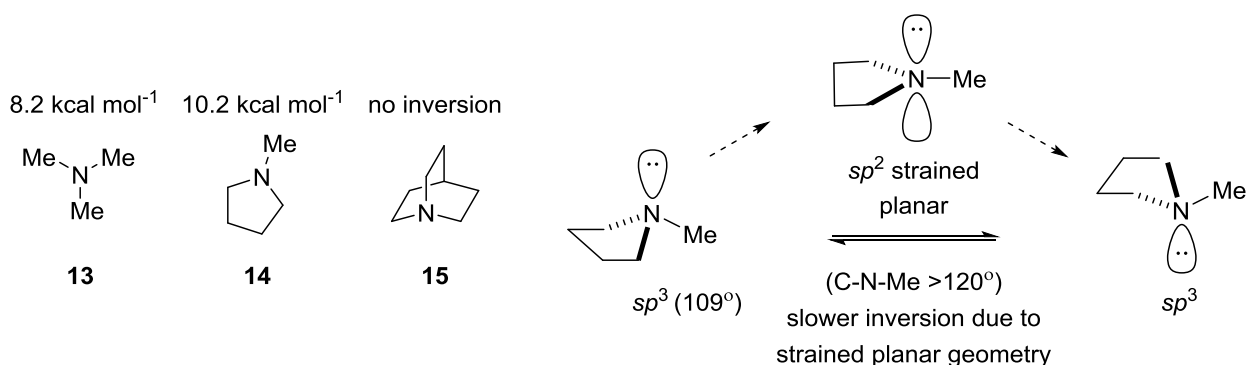
Figure 5 NIR of acyclic **13**, cyclic **14** and bicyclic **15** amines and proposed process of inversion for compound **14**

Adjacent nitrogen atoms in a ring have an even higher barrier to double inversion due to lone pair-lone pair repulsion and steric interactions. The larger the nitrogen substituent the more the transition state is destabilised. The lone pairs would also have to pass each other during an inversion process which would be extremely unfavourable.
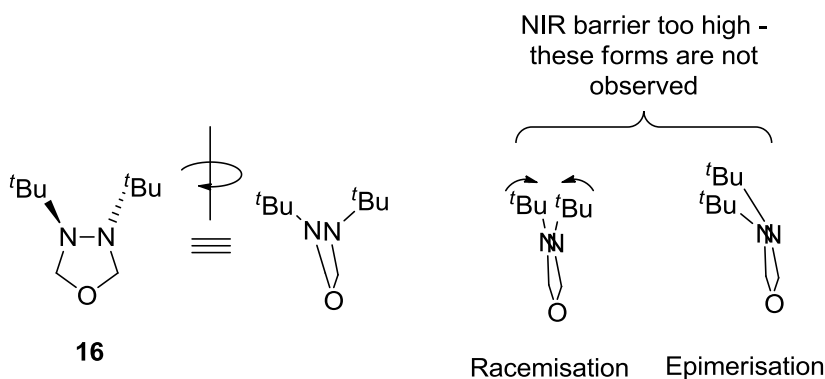

Figure 6 Lone pair-lone pair repulsion coupled with steric avoidance prevents inversion

Experimental work proved difficult to confirm this inversion process as conducting NMR spectroscopy experiments on **16**, no change was observed in attempting to calculate the barrier to nitrogen inversion by coalescence of the CH_2 signals adjacent to the nitrogens. The NMR study did lead to the estimation of the double nitrogen inversion at >22.7 and >23.8 kcal mol^{-1} at 130 °C.[28] Work by Katritzky, Kostyanovsky and others explored this possibility of imparting configurational stability through sterically encumbered groups on nitrogen in rings through synthesis of C_2-symmetric chiral diamines (e.g. **16**, **Figure 6**).[28-33] Lone pair-lone pair repulsion coupled with sterically demanding groups appended to the nitrogen prevent inversion under

standard conditions (room temperature and atmospheric pressure). In order for racemisation to occur the two bulky groups would have to pass by each other whilst for epimerisation both lone pairs would need to be on one face of the ring and the two bulky groups would occupy the opposite face; however that is extremely unlikely due to the highly unfavourable steric interaction. Both of these possibilities are strongly disfavoured. Kostyanovsky devoted a great deal of work to this area and confirmed that a number of heteroatoms could be used to replace one of the nitrogen atoms and prohibit inversion primarily on electronic grounds (**Scheme 1**). In the case of acyclic dialkoxyamine **17,** resolution of each of the compounds was carried out separately by diastereomeric salt formation of the hydrolysed acids with the opposite configurations of α-methylbenzylamine followed by crystallisation with hexafluorobenzene to give stable forms **17** $N_{(R)}$**-(+)** and **17** $N_{(S)}$**-(-)** of the *N,N*-dialkoxyamines.[34] The barrier to inversion was found to be 24 kcal mol^{-1} and racemisation rate increased above 20 ^{o}C.
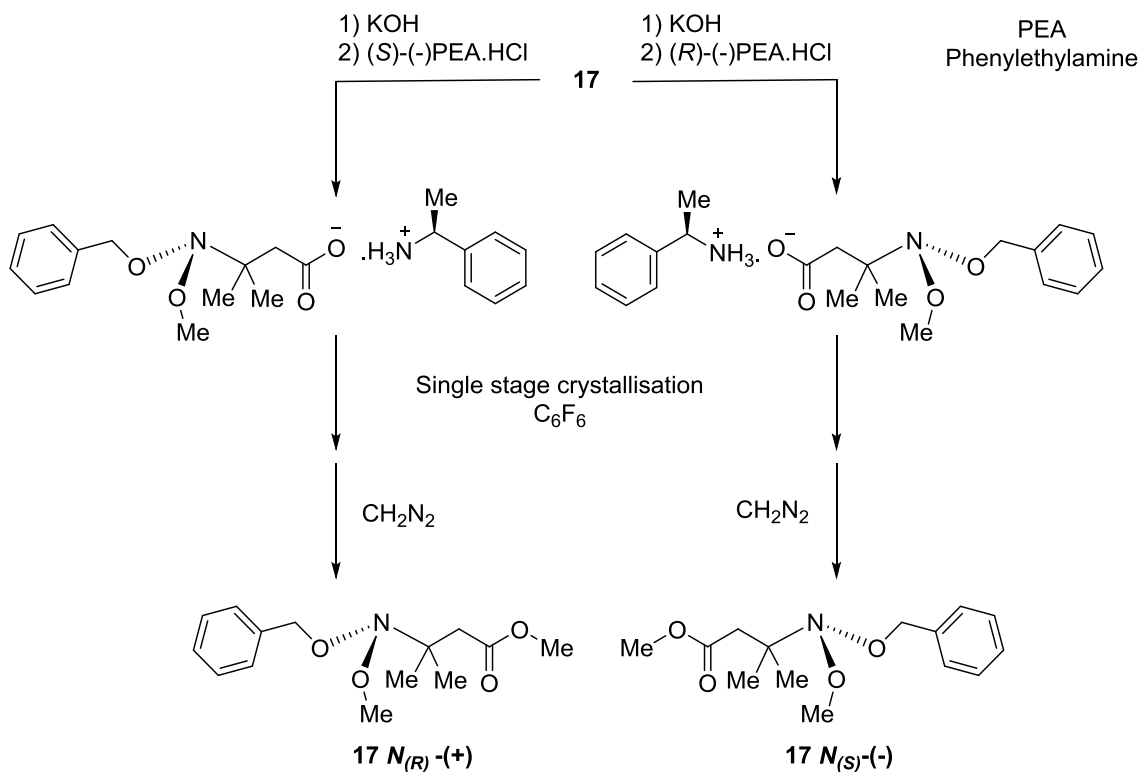
Scheme 1 Configurationally stable *N,N*-dialkoxyamine enantiomers resolved through hydrolysis and crystallisation of diastereomeric ammonium carboxylates

10

1.1.2.2 Chiral at bridgeheads

The cinchona alkaloids **18** and **19** (**Figure 7**), have been described as "privileged organic chirality inducers" and as such are among the most important stereogenic-nitrogen containing molecules.[35,36, 37] This class of compounds have long intrigued chemists, not only for their antibacterial properties but also for their use in asymmetric synthesis.[5, 38, 39] They have found extensive use as chiral resolving agents and as asymmetric catalysts used (with modification) for a host of transformations.[39] Most notably Sharpless was awarded the Nobel Prize in 2001 (half shared along with Knowles and Noyori) for his work on asymmetric dihydroxylation reactions in which cinchona alkaloids are used as chiral ligands.[40,5, 22, 41-43] The quinuclidine portion of the molecule containing the stereogenic nitrogen atom is unable to invert due to its bicyclic bridgehead position which results in a fixed nitrogen orientation and has been utilised in many works.[39, 44-46]
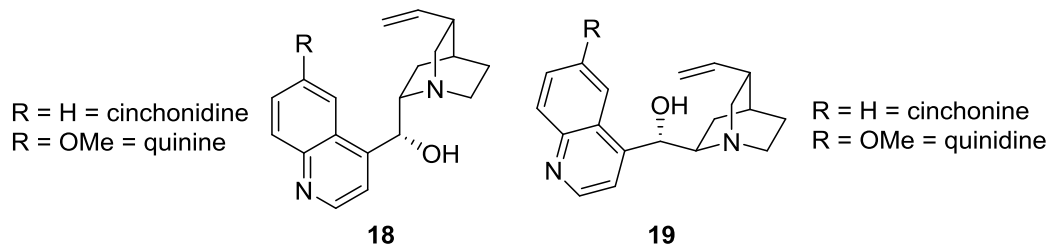

Figure 7 Naturally occurring cinchona alkaloids

The cinchona alkaloids also benefit from the chiral carbon scaffold with four carbon stereogenic centres which can contribute to any subsequent chiral information transfer during their application in catalysis.[36, 39, 44, 45, 47] For the benefit of this discussion, the main focus will revolve around the less reported cases of nitrogen chirality (**Figure 8**) in the absence of other stereogenic centres such as is found in Tröger's base **21**.[48] There are many similarities (and differences) between Tröger's base **21** and sparteine **20**. They both have asymmetric bridgehead nitrogen environments and both can be separated into their diastereomerically pure forms. Sparteine is naturally occurring and contains four stereogenic carbon atoms; Tröger's base is synthetic and its

only centres of chirality are at nitrogen. The 3D perspective (**Figure 8**) really highlights the difference in structure between these molecules which governs their application. Sparteine is well disposed to act as a bidentate ligand with nitrogen lone pairs in proximity on the concave face of the large bicyclic central rings. There are several examples where sparteine has been used as an asymmetric ligand.[49] The lone pairs in Tröger's base are pointed away from each other on the convex face of the bicyclic central rings, so it has not been exploited in asymmetric synthesis.
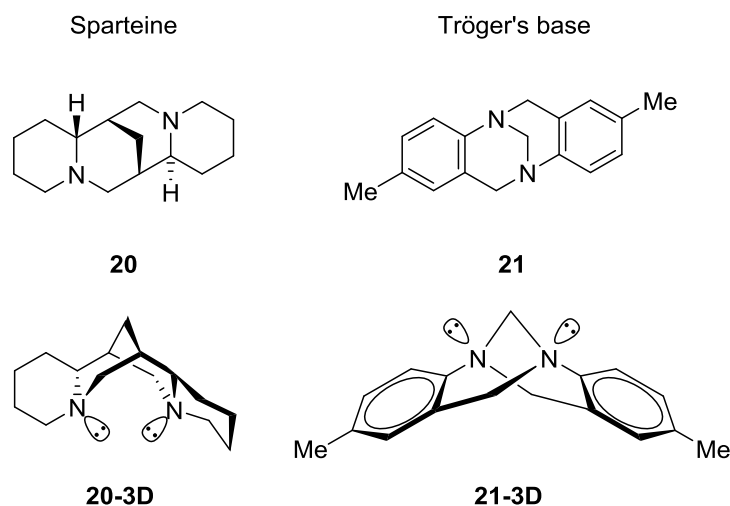

**Figure 8** Bicyclic stereogenic nitrogen molecules sparteine and Tröger's base

Tröger's base **21** was synthesised as a racemate in 1887 although the structure was not determined until 1935.[50] The compound contains two stereogenic nitrogen centres linked *via* a methylene bridge and it is resolvable into its enantiomeric forms.[48, 50, 51] Prelog and Wieland's resolution of Tröger's base is thought to be the first example of a resolution of a tertiary amine using cellulose modified silica.[51]

Cvengroš and co-workers accessed related functionalised methylene bridgehead structures **24**, through a double aza-Michael addition (**Scheme 2**). These were accessed through simple addition of propiolic acid **23** to tetrahydrodiazocine (R=methyl) **22** to give Tröger's base derivatives which contained a pendant ester group **24**.[52]
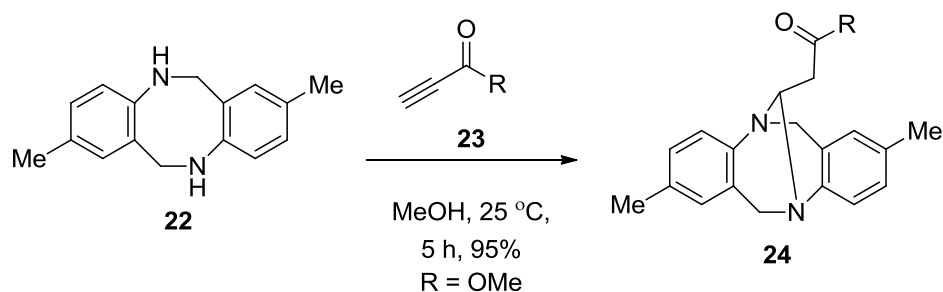
Scheme 2 Double aza-Michael addition to functionalised bridgehead Tröger's base derivatives

Chiral auxiliaries with alkyne groups were employed to build on the use of methyl propiolate **23** to effect diastereoselective transformations to give molecules such as **25** which could in-turn undergo diastereoselective methanolysis to give **24** $N_{(S)}N_{(S)}$ (**Scheme 3**).
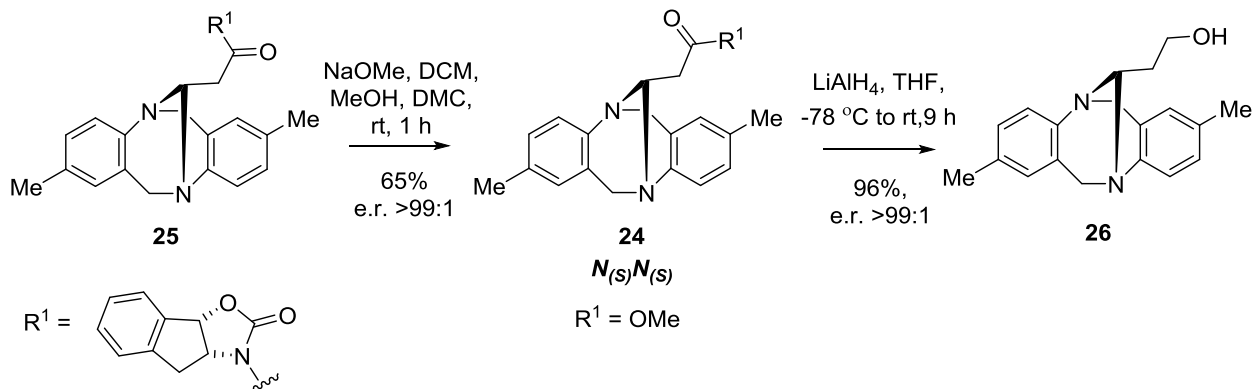
Scheme 3 Enantiomeric purity unaffected by removal of chiral auxiliary and reduction to the alcohol

Initial diastereoselectivity varied when screening for solvents, with perhaps the most notable being the reversal of selectivity observed when using isopropanol (2:3) and hexafluoroisopropanol (7:3), thought to be incurred due to the increased acidity of the fluorinated solvent. This is quite an unusual choice of solvent and it is not known if it is possible to use this solvent when approaching the synthesis of other tertiary amines/ammonium salts with stereogenic nitrogen to establish if similar trends can be observed. Through optimisation, suitable conditions were found to furnish Tröger's base derivatives in good yield and e.r. (**Scheme 3**). Removal of the auxiliary to the ester **24** and reduction to the alcohol **26** was carried out without diminishing the high (>99:1) enantiomeric ratio obtained.

Cvengroš and co-workers also conducted the kinetic resolution of Tröger's base analogues **27** (**Scheme 4**) using the lipase from *Candida antarctica* with excellent results.[53] Not only were both isomers isolated with good yield (42 and 49% - max yield is 50% for each isomer) but with excellent enantioselectivity, **27** (N_S, N_S) 94% *ee* and **28** (N_R, N_R) 84% *ee*. One of the most impressive aspects of this benzylic 1° alcohol kinetic resolution approach was its ability to be scaled up without any detrimental features. Resolution of 0.5-1.0 gram quantities means that significant amounts of material could be prepared with the additional benefit of the product possessing added functionality allowing further transformations to occur.
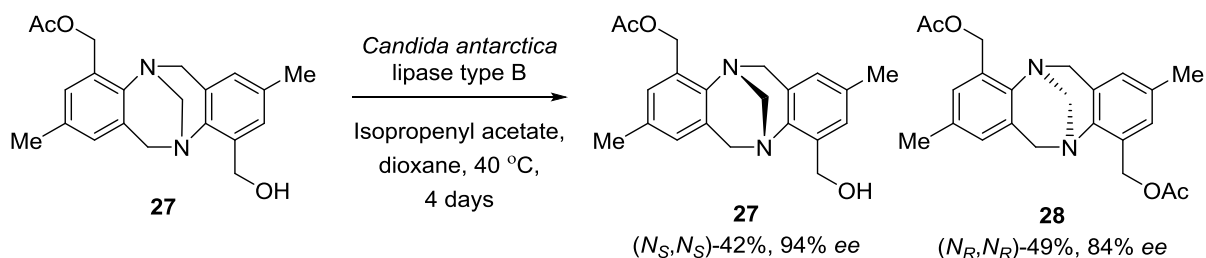
Scheme 4 Kinetic resolution of racemic Tröger's base derivative using *Candida antarctica* lipase

This enzymatic resolution was exploited by preparing non-racemic samples which could undergo further transformation to furnish heavily functionalised (compared with other literature examples) Tröger's base derivatives with no loss of enantiopurity. Several reactions were performed including Dess-Martin oxidation, Appel reaction, Buchwald-Hartwig-type amidation (palladium catalysed) and although not detailed, the authors mentioned that Stille couplings could also be performed. The methodology developed by Cvengroš and co-workers has really catapulted the ability to produce functionalised molecules where the only asymmetric component is nitrogen and its configurational purity is not compromised by their synthetic approach. Further examples show that resolution of racemic Tröger's base derivatives with chiral disulfoxides can also be achieved.[54]

Tröger's base can, unfortunately, when alkylated to provide **29,** alleviate strain by formation of an iminium ion **30** by severing the bridgehead methylene unit (**Figure 9**). This is extremely similar to the racemisation pathway proposed by Prelog, who suggested under acidic conditions the formation of the corresponding iminium intermediate.[55, 56]
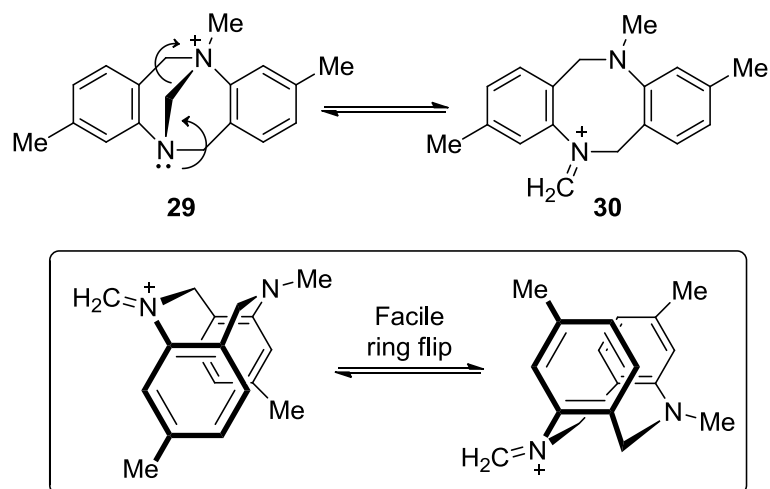

Figure 9 Racemisation of alkylated Tröger's base

Kostyanovsky and co-workers reported that alkylated homologues of Tröger's bases **32** were configurationally stable at nitrogen, when an ethylene **31** rather than a methylene **21** nitrogen bridging group was used.[57] This extended bridge allowed the structure of configurationally stable chiral at nitrogen ammonium salts to be determined (Flack parameter of 0.01(2)) by X-ray crystallography (**Figure 10-1**). Tröger's base derivatives have been employed as molecular tweezers exploiting π-stacking interactions and taking advantage of their rigid structure.[58] However, a distinct lack of functionality prevents obvious further uses by synthetic chemists. Cvengroš and co-workers demonstrated that their enzymatic resolution approach allows a great many more synthetic opportunities without loss of stereochemical integrity.
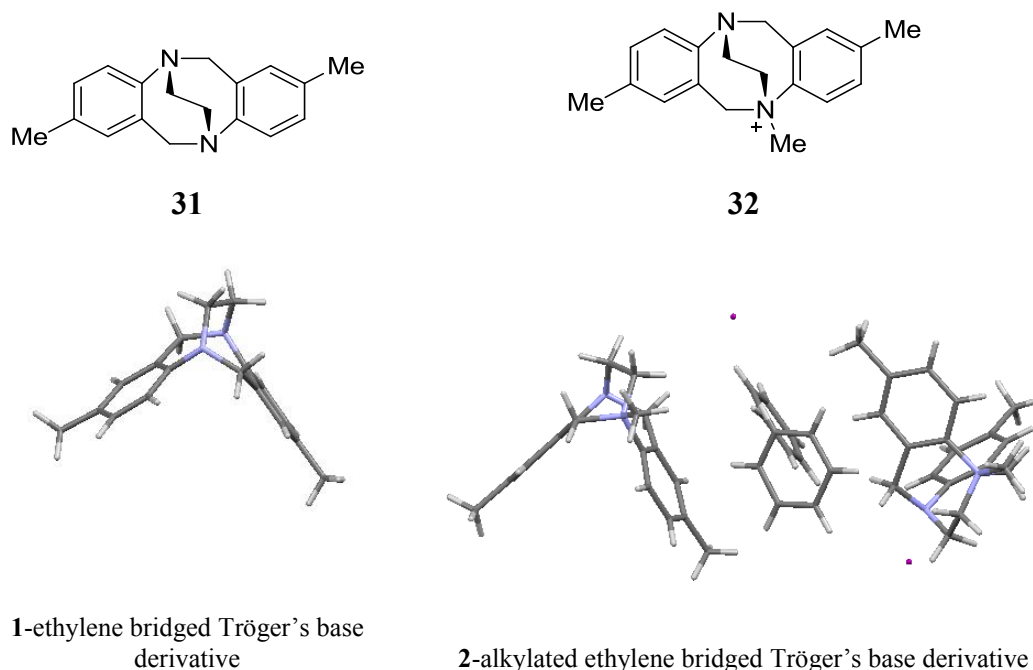
31

32

1-ethylene bridged Tröger's base derivative

2-alkylated ethylene bridged Tröger's base derivative

Figure 10 X-ray crystal structure of Tröger's base and alkylated ethylene bridged derivative[59]

One example of Tröger's base being used as a ligand is by Pierard and co-workers who modified the base to include phenanthroline to form an octahedral complex **33** (**Figure 11**) with ruthenium.[60] Initial approaches used racemic ruthenium complex and racemic Tröger's base derivative which gave rise to a 1:1 mixture of diastereoisomers.[61] The development of this work used resolved ruthenium centres (Λ or Δ) with racemic Tröger's base derivative. It was not reported how the use of the non-racemic ruthenium complex affected the d.r. of the reaction but diastereomerically enriched samples were obtained by repeated crystallisations. The (Δ, N_S, N_S) diastereoisomer (**Figure 11**) was found to have a higher affinity constant than *rac*-[Ru(phen)$_3$]$^{2+}$ for DNA binding (previous studies showed no preference for either racemic mixture synthesised) showing the inherent chirality of the complex is important.[60]
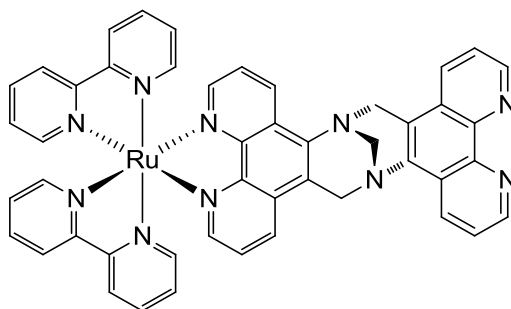
33

A new class of chiral-at-nitrogen, cage like structures (**Scheme 5**) were fortuitously discovered by Tomkinson and co-workers.[62] One major attraction of these molecules is that, unlike other synthetic approaches to chiral-at-nitrogen molecules, these chiral-at-nitrogen cages do not require resolution and are easy to access. In efforts to make substituted imidazolidinone, the ytterbium(III) trifluoromethanesulfonate (Lewis acid)-catalysed reaction of various amino acids **34** with paraformaldehyde gave the diastereomeric cage structures **35** and **36**. These cages contain stereogenic nitrogen atoms which, after further experiments (stable to base and re-exposure to the catalyst in formation conditions) were found not to epimerise. The two amide groups give the potential for further transformations, enhancing the versatility of these compounds. Furthermore, great diversity can be achieved through use of different α-amino acids **34** and combinations thereof.
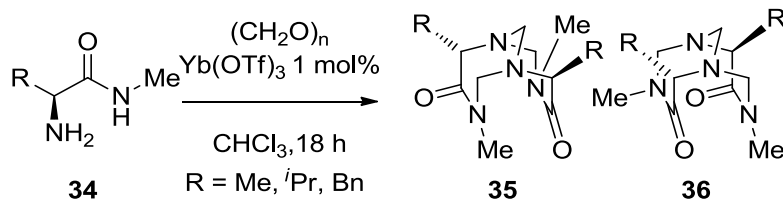
Scheme 5 Synthesis of chiral-at-nitrogen cage structures

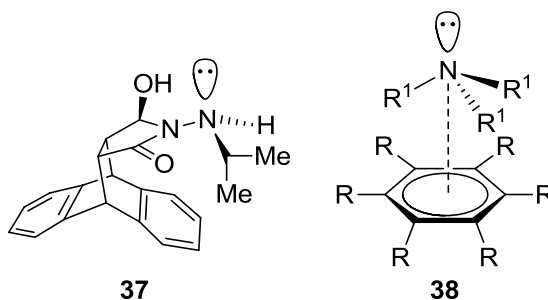## 1.1.2.3 π-stabilisation

37   **38**

Figure 12 Experimental evidence for π-lone pair repulsion in tetracyclic system and theoretical proof of π-lone pair co-ordination

Verma and co-workers designed a system to investigate whether nitrogen inversion can be restricted by intramolecular stabilisation by a π-system.[63, 64] The secondary amine **37** is possibly the first example of a secondary amine displaying restricted inversion (**Figure 12**), with the barrier to inversion estimated at 22 kcal mol^{-1} (160 ^{o}C). Good experimental evidence in both the solid (X-ray crystallography structure) and solution states (^{1}H NMR and VT NMR spectroscopy experiments) indicates the secondary amine nitrogen lone pair is *anti* to the cyclic system. Whilst this study shows that it is possible to control nitrogen's configuration, it is severely hindered in possible applications due to the complexity of the required scaffold needed to observe this phenomenon. Furthermore it is not impossible to disregard this finding as being a consequence of hydrogen bonding between the lone pair and hydroxyl proton.[63]

Theoretical work carried out by Fossey and co-workers related to this area suggest similar observations to the experimental findings by Verma.[65] It is well known that the lone pair-π-interaction is attractive but new studies show that as relativistic effects are taken into account with improved computational methods, the more stable conformation is the lone pair pointing away from the π-surface (although this is dependent on solvent and the electronic nature of the R group), **38** (**Figure 12**).[66] The theoretical findings confirm experimental observations recorded by Verma and co-workers. Much more evidence is required from both experimental and theoretical

study to identify major trends in the nitrogen lone-pair π-surface interactions and how it affects the nitrogen conformational and configurational stability.

1.1.3 Tetrahedral nitrogen

Nitrogen can have stable central chirality when bound by four different groups, much like a carbon atom. Theoretically it should be possible to exploit the same asymmetric methodology for C-C bond-forming reactions to N-C bonds going from tertiary amines to ammonium salts. The obvious stumbling block is the inversion of the tertiary amine which readily and rapidly inverts resulting in loss of chiral information. There are limited examples of chemistry arresting inversion through bond formation, where there are three differently appended groups with N-C bonds. These fall into the following categories:

i)   Complexes, with metal or metalloid (co-ordination of lone pair)

ii)   Formation of a nitrogen heteroatom bond, *N*-oxides

iii)   Four different N-C bonds, ammonium salts
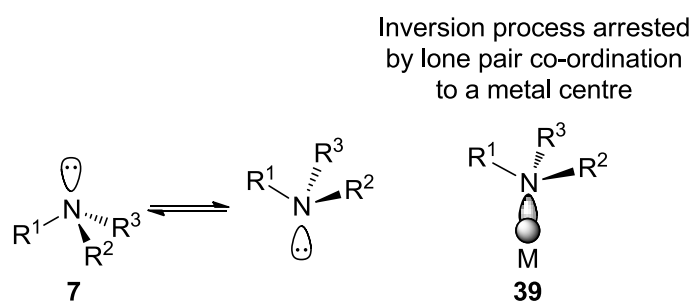
1.1.3.1 Co-ordination to metal

Figure 13 Inversion can be disturbed by lone-pair co-ordination (arbitrary metal orbital shown)

One way to arrest nitrogen inversion is co-ordination of the lone pair to a metal centre **39** (**Figure 13**). Gagné and co-workers used (*R*)-Na$_2$BINOL **41** to separate the diastereomeric salts of racemic amines **40** to set the nitrogen chirality resulting in the diamine **42** matching the stereochemistry of the chiral (*R*)-BINOL scaffold attached (**Scheme 6**).[67, 68] The Diels-Alder

reaction of an α,β-unsaturated carbonyl compound **43** and cyclopentadiene **44** catalysed by chiral

complex **46** gave the *endo* bicyclic product **45** in 25% *ee*. No racemisation of the metal complex

was observed and after a series of control reactions, Gagné described the non-zero

enantioselectivity was due to the "persistent chirality of nitrogen".[67]
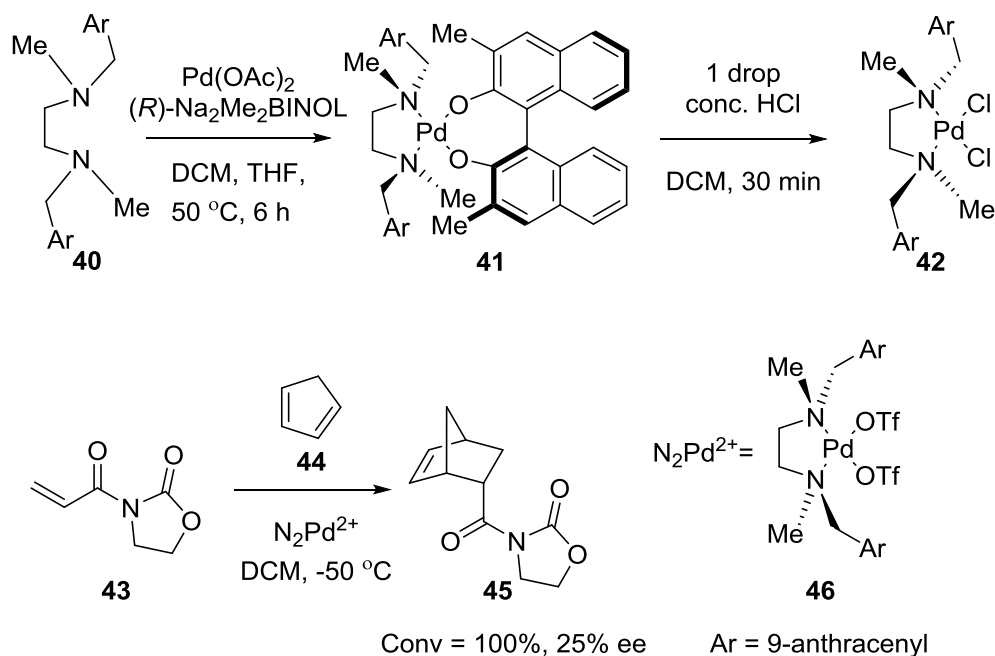
Scheme 6 Application of chiral-at-nitrogen palladium diamine catalyst in Diels-Alder reaction
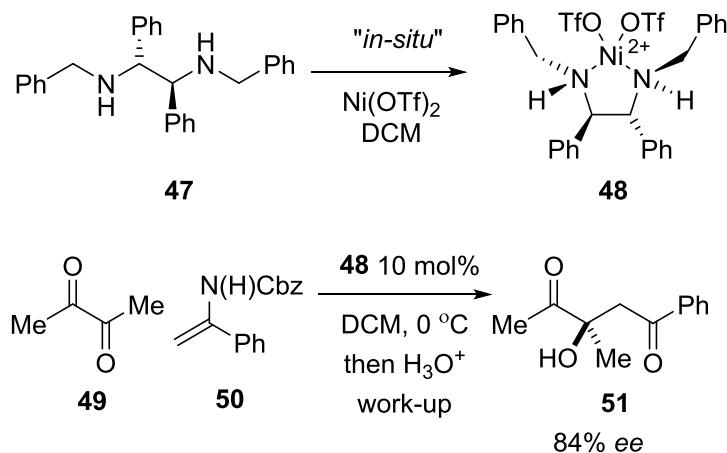
Scheme 7 Aldol type enecarbamate addition to dione using a chiral-at-nitrogen nickel complex

Another similar example by Kobayashi and co-workers involved the use of a chiral diamine **47** to

relay chiral information from stereogenic carbon atoms to the metal-coordinating nitrogen atoms

48 (**Scheme 7**). The Lewis acid **48** catalysed the aldol type addition of an enecarbamate **50** to dione **49**, which, following aqueous work-up, gave **51** with 84% ee.[69]

1.1.3.2 *Chiral-at-nitrogen N-oxides*

After the earlier success of Pope, who successfully resolved enantiomers of stereogenic nitrogen molecules by diastereomeric salt formation with camphorsulfonic acid (**Figure 1** and in more detail in **1.1.3.3.1**),[2] Meisenheimer applied a similar tactic to the resolution of *N*-oxides.[70] In 1908 he used 3-bromocamphor-8-sulfonic acid to resolve the *N*-oxide **52** (**Figure 14**). The optical rotation of **53** was recorded, $[\alpha]_D=+67^o$, but only one of the diastereoisomers is reported (configuration unknown). The HCl salt of the resolved compound **53** was reported as having an optical rotation value of $[\alpha]_D=+17^o$. The chiral resolving agents' optical rotation (3-bromocamphor-8-sulfonic acid) was found to be $[\alpha]_D=+50^o$, however it is difficult to infer any conclusions due to a lack of further experimentation.
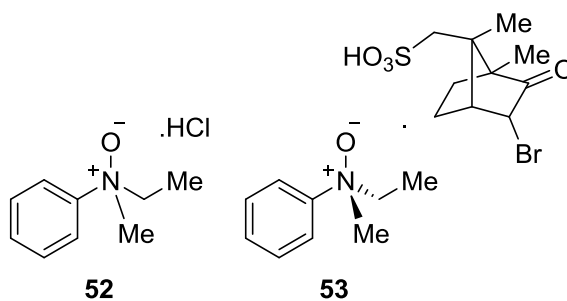

Figure 14 Resolution of stereogenic nitrogen *N*-oxide

The subject of resolving *N*-oxides was not revisited until much later when Drabowicz who conducted a number of NMR experiments using a chiral thiophosphoric acid (**Scheme 8**).[71] *t*Butylphenylphosphinothioic acid **55** in both enantiopure forms (*R* and *S*) was used as a chiral solvating agent in ^{1}H NMR spectroscopy studies to separate racemic **54** into its enantiomeric forms by formation of diastereomeric complexes.
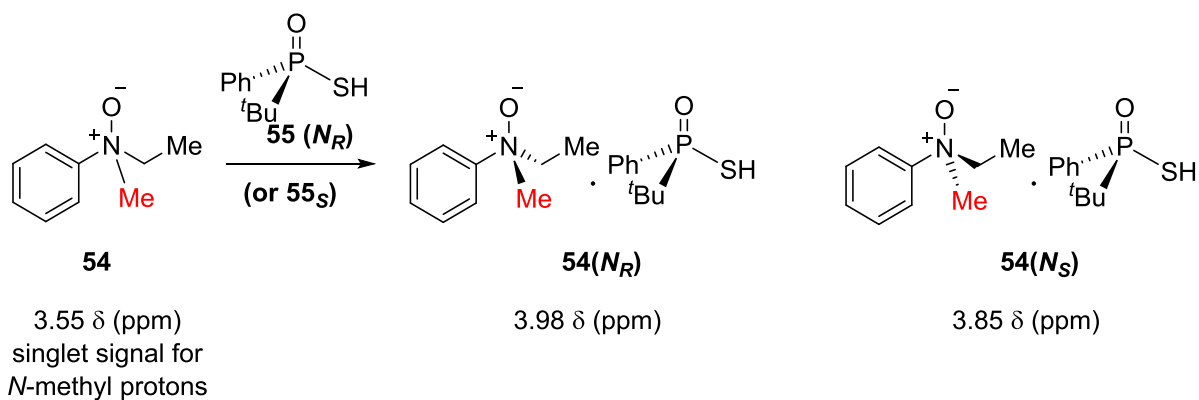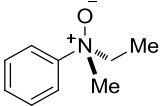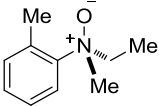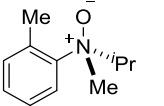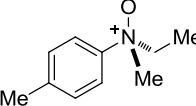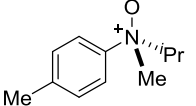
Scheme 8 ^{1}H NMR resolution of *N*-oxide enantiomers **54** through use of chiral shift reagents **55**

Differences in δ (ppm) shift for the *N*-methyl protons in the diastereomeric complexes were recorded, **54 (N_S)**=3.85 δ (ppm) and **54 (N_R)**=3.98 δ (ppm). Whilst these were not unexpected results (protons in different environments due to nitrogen's stereogenicity) it showed a measureable method to distinguish between enantiomers although it can only be carried out on an analytical scale.

Toda and co-workers opted for fractional crystallisation as their preferred method for resolution of *N*-oxides using BINOL (**Table 1**).[72] One of the compounds reported was the same *N*-oxide **56** studied by the Drabowicz and Meisenheimer groups, **entry 1**. The optical rotation was reported by Meisenheimer is (+16.4), however Toda's reported optical rotation arises from a 1:1 complex with (*R*)-(-)-BINOL and not the isolated *N*-oxide. Toda and co-workers managed to exploit the use of both enantiomers **57** and described the isolation of both *N*-oxide enantiomers. The methodology was extended to investigate substituted aryl units, *ortho*-methyl, **entries 2** and **3** and *para*-methyl **entries 4** and **5**. *N-iso*-propyl units were resolved in the cases of **entries 3** and **5**. The experiments were carried out on such a scale however that X-ray crystal structures were obtained for both configurations of *N*-oxide **57**. No information was provided regarding the stereogenicity of nitrogen in the other *N*-oxide complexes though and the 1:1 complexes were just described with regard to their H-bonding network. However the reported X-ray structure

reported shows the *N*-oxide **57** has a $N_{(R)}$ configuration so by extension it is possible that **entries 2-5, Table 1** could all have the same configuration.

Table 1 Resolution of several *N*-oxides with BINOL

Entry	1	2	3	4	5
N-oxide[a]					
	56	**57**	**58**	**59**	**60**
Yield (%)	21	48	39	30	68
$[\alpha]_D$ (*R*)-(+)- BINOL	+16.4	+11.9	+24.6	+13.0	+29.5
$[\alpha]_D$ (*S*)-(-)- BINOL	N/R	-11.9[b]	N/R	N/R	N/R

[a]**Configuration of nitrogen unreported although the (*R*)-(+)-BINOL was used for the first step in the fractional crystallisation process. [b]Only case where the fraction crystallisation was repeated with the opposite enantiomer of (*S*)-(-)-BINOL and data reported showing equal and opposite specific rotation for the *N*-oxide.**

Whilst the efforts of Meisenheimer, Toda and Drabowicz show that *N*-oxides can be resolved and subsequently analysed, more experiments must be conducted to study both possible nitrogen configurations of *N*-oxides which could be facilitated using recent advances in chromatographic techniques.

Hoveyda and co-workers reported the use of a single diastereoisomer of a chiral-at-nitrogen *N*-oxide **62,** derived from proline, for the reactions of allyltrichlorosilane **63** and aldehydes **61** to give a variety of alcohols **64** in good *ee* (**Scheme 9**).[73]
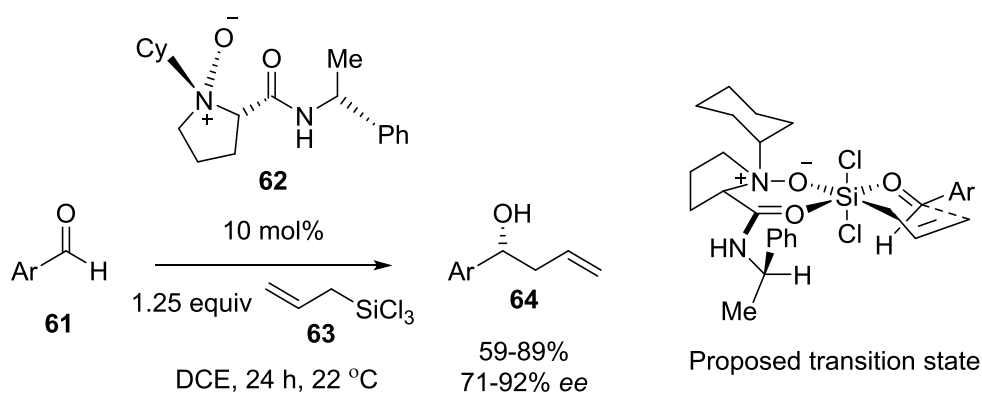
Scheme 9 Proline-derived *N*-oxide-catalysed allylation of aldehydes

The *syn* relationship, between the *N*-oxide and amide, is essential for selectivity in their proposed transition state where the two oxygen atoms of **62** form a six-membered ring with the silicon. The N-oxide *trans* to the allyl group on silicon helps to co-ordinate the reactants in the complicated silyl complex transition state. The allyl group *trans* to the *N*-oxide experiences enhanced nucleophilicity and the aldehyde *trans* to the electron-withdrawing amide has increased electrophilicity (proposed transition state, **Scheme 9**).[73] This epimer of the *N*-oxide **62** is essential for the success of the reaction as it places the cyclohexane ring in an axial position that is necessary to obtain high ee's. Feng developed the catalyst concept further to build a *C*$_2$-symmetric bis *NN'*-dioxide catalyst **65** (**Figure 15**) similar to Hoveyda's which was used in a Michael/hemiacetalisation to synthesise chiral dihydropyrans with high yields and enantioselectivities.[74]
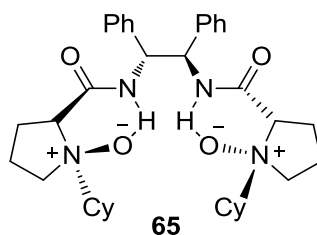

Figure 15 *C*$_2$ Proline derived *N*-oxide catalyst by Feng

This section has shown that the low-barrier to inversion means it is challenging to synthesise chiral-at-nitrogen compounds. However it has been demonstrated by the literature reported here

that there are examples that allow chiral-at-nitrogen molecules to be synthesised in synthetically useful amounts as well as showing that enantiomers of chiral-at-nitrogen compounds are distinguishable.

1.1.3.3 Chiral-at-nitrogen Ammonium salts

In the absence of any chiral influence, quaternisation of a chiral, racemic tertiary amine will afford a racemic ammonium salt. One method to resolve the enantiomeric ammonium salts is to use a chiral resolving agent, such as that so elegantly used by Pope & Peachey (**Scheme 10**), who exchanged the anion to form a pair of separable diastereomeric salts.[2] In more recent times, chiral HPLC has been used to separate enantiomers and as methods improve, the possibility of using supercritical CO_2 as a mobile phase in HPLC has been probed to separate compounds (see section 1.2).[55]

1.1.3.3.1 Acyclic stereogenic at nitrogen ammonium salts

Seminal work carried out by Pope and Peachey in the late stages of the 19th century demonstrated the first resolution of a *N*-chiral ammonium salt.[2]
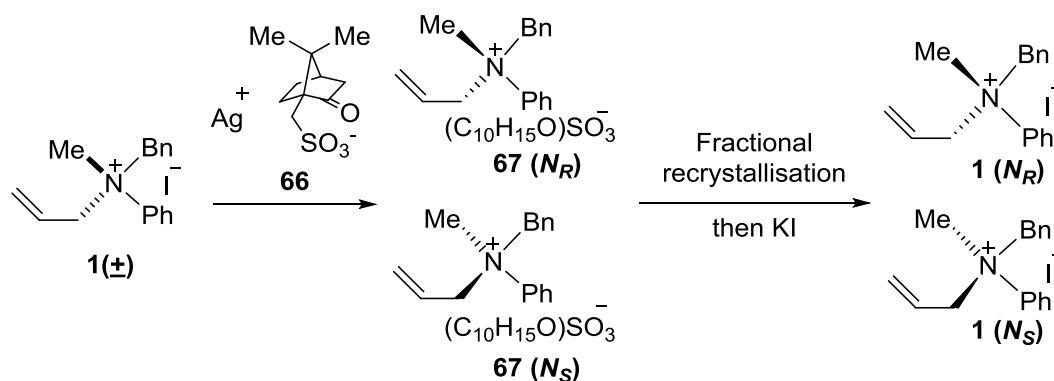

**Scheme 10** The first example of enantiomeric resolution by Pope and Peachey in 1899

Several conditions for recrystallisation of **1** were attempted before finding suitable conditions, with care to avoid alcohols and use a minimum of water as to avoid decomposition. Anion exchange with the silver camphorsulfonic acid salt **66** by boiling in acetone and ethyl acetate with

a few drops of water resulted in obtaining a mixture of diastereomeric camphorsulfonic ammonium salts **67**. Boiling in acetone resulted in collecting the dextrorotary (d)-salt ((+) rotates polarised light clockwise) and evaporation of the acetone mother liquor followed by recrystallisation from ethyl acetate gave the levorotatory (l)-salt ((-) rotates polarised light anti-clockwise). Treatment of each with potassium iodide returned the enantiomerically pure ammonium iodide salts. Through several recrystallisations essentially equal and opposite optical rotation values of (*d*) $[\alpha]_D = +68.6$ and (*l*) $[\alpha]_D = -67.3$ were achieved.

Many of the problems encountered on the way to this landmark achievement of stereogenic nitrogen resolution are still relevant today. The hygroscopic nature of ammonium salts leads to decomposition and difficulty in analysis and selective fractional recrystallisation is difficult.
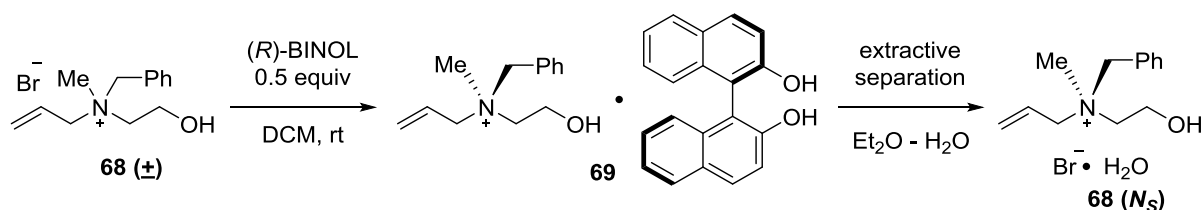
Scheme 11 Use of (*R*)-BINOL forms a 1:1 complex and allows resolution of enantiomers

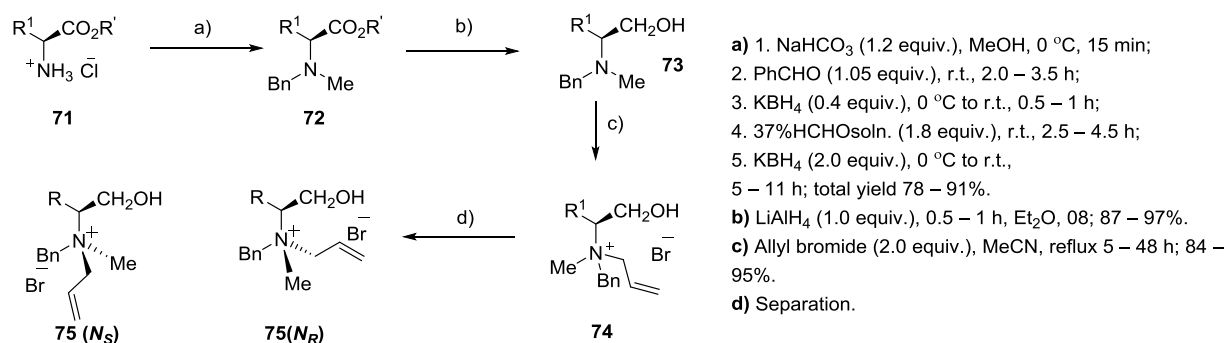Ar=2-Me-Ph, 2-MeO-Ph, 2-CF₃-Ph
R=Me or ᵗBu
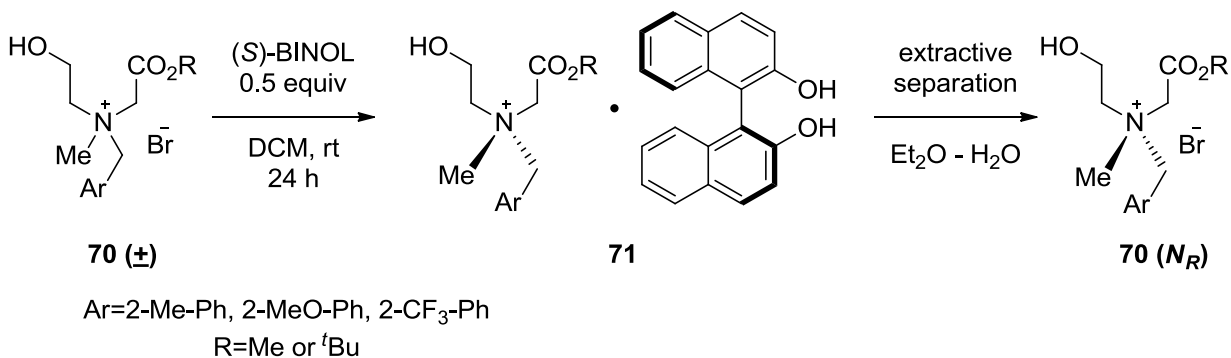
Scheme 12 Tayama achieved resolution of ammonium salts with no *N*-allyl groups

Tayama resolved ammonium salt mixtures **68** and **70** through complexation with BINOL as a stoichiometric resolving agent to give diastereomeric complexes **69** and **71**, which accessed single enantiomer forms of **68(*N_S*)** and **70(*N_R*)** (**Scheme 11** and **12**).[77, 78] Both enantiomers were

accessible through judicious choice of the appropriate BINOL enantiomer. This work reported several examples of chiral-at-nitrogen ammonium salts and an X-ray crystal structure of the (*R*)-BINOL ammonium complex **71** which allowed unambiguous determination of the absolute configuration at nitrogen **68(*N_S*)**. Upon first inspection, comparison of Pope & Peachey's, Tayama & Tanaka's and Kostyanovsky's works, the resolved structures **1(*N_R*)**, **1(*N_S*)** and **68(*N_S*)** all contain *N*-allyl groups.[79] However any thoughts that this substituent was a prerequisite for resolution were abated when Tayama & Tanaka resolved a further series of ammonium salts **70(*N_R*)** using the same resolution procedure with BINOL (both enantiomers).[77, 78]

Wu *et al.* applied the same BINOL (both enantiomers) resolution protocol to epimeric mixtures of ammonium salt diastereoisomers derived from natural amino acids (**Scheme 13**).[80] A one-pot approach involving sequential reductive aminations followed by alkylation of the tertiary amine gave a high-yielding route to diastereomeric mixtures of ammonium salts **75**. Several groups were included in each of the final six pairs of diastereoisomers and the R^1 groups included a mixture of alkyl and aryl groups, however, no great influence was observed on the diastereomer ratios obtained of 1:1.5 for ammonium salts **75**. With the different diastereomeric mixtures in hand, Tayama's fractional recrystallisation procedure with BINOL allowed separation of the diastereoisomers.

a) 1. NaHCO$_3$ (1.2 equiv.), MeOH, 0 °C, 15 min;
2. PhCHO (1.05 equiv.), r.t., 2.0 – 3.5 h;
3. KBH$_4$ (0.4 equiv.), 0 °C to r.t., 0.5 – 1 h;
4. 37%HCHOsoln. (1.8 equiv.), r.t., 2.5 – 4.5 h;
5. KBH$_4$ (2.0 equiv.), 0 °C to r.t.,
5 – 11 h; total yield 78 – 91%.
b) LiAlH$_4$ (1.0 equiv.), 0.5 – 1 h, Et$_2$O, 08; 87 – 97%.
c) Allyl bromide (2.0 equiv.), MeCN, reflux 5 – 48 h; 84 – 95%.
d) Separation.

R = a) Me, b) Bu, c) Ph, d) Bn, e) PhCH$_2$CH$_2$, f) 4-OH-Bn

Scheme 13 Application of Tayama's resolution method to amino acid derived ammonium salts

Wu and co-workers found it possible to exploit the difference in physical properties of the BINOL diastereomeric salt complexes to separate the mixtures of **75b**, **d** and **e** by precipitation. Using column chromatography enabled the separation of the BINOL salt of **75c**. Tayama and Tanaka's recrystallisation method was applied to **75a** and direct recrystallisation enabled the separation of **75f**.[77, 78] Whilst it would have been good to compare the initial reaction mixture to see the d.r. achieved and then the separated compounds to compare the ^{1}H NMR spectra, some ^{1}H NMR data were reported studying the difference in ppm shift of the diastereotopic benzylic protons. The ^{1}H NMR data showed a trend that N_S diastereoisomers displayed a greater shift in ppm of 0.34–0.80 compared with N_R = 0.00–0.50 ppm.[80]

Resolution through fractional crystallisation is probably the most straightforward route to obtain enantiomerically pure nitrogen compounds however it is not a guaranteed method to resolution of enantiomeric mixtures. Kostyanovsky's continued work yielded a new example of isomorphism in an ammonium salt **76** however the enantiomeric forms of the ammonium salt could distinguished from one another (**Figure 16**).
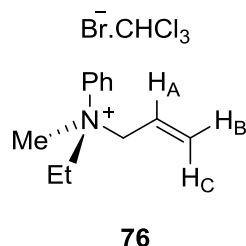

76

Figure 16 X-ray crystallography could not distinguish between enantiomeric forms of this ammonium salt

1.1.3.3.2 Cyclic chiral-at-nitrogen ammonium salts

One of the earliest examples of a cyclic chiral-at-nitrogen ammonium salt **77** (**Figure 17**) was reported by Wedekind, who dedicated most of his research career to the study of ammonium salts and provided some of the first examples of cyclic ammonium salts where nitrogen was included in the ring. He also reported some more elaborate examples like the C_2 symmetric bis-ammonium

salt **79** as well as the mono **78**. It is difficult (original paper in German) to confirm the accuracy of these structures and indeed if the nitrogen centres were resolved.[81-83]
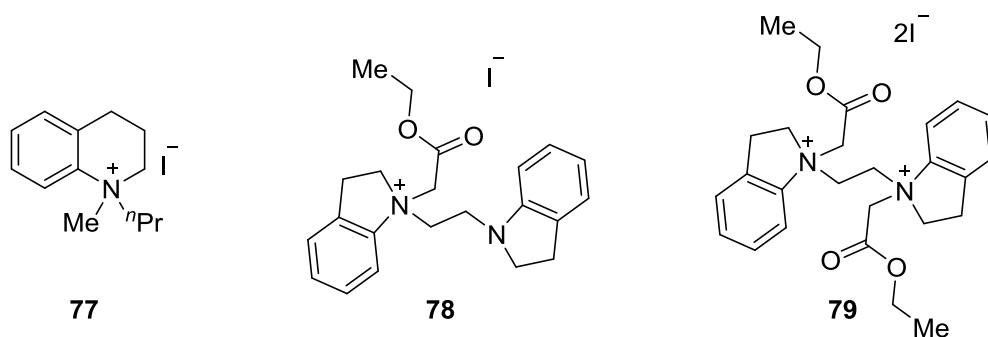

77   78   79

Figure 17 Wedekind started to make cyclic ammonium salts in the 1900s

It is difficult to establish whether any compounds were fully resolved and believe it may be the case that the reference to asymmetry in the article's title is simply reference to knowledge that two enantiomers are formed.[81] Pope noted several attempts by Wedekind to resolve mixtures of compounds using sugars.[2]

Aziridinium species **80** are the most reactive cyclic, nitrogen-containing species (**Figure 18**). They are susceptible to nucleophilic attack in order to alleviate the strain associated with a three-membered ring. Along with azetidinium salts **81,** these are viewed as reactive intermediates and chiral building blocks. It has been found that the regioselectivity of ring-opening is dependent on substitution and as such, is often predictable. Pyrrolidinium **82** salts are relatively stable to ring opening conditions *cf.* its lower homologues but can undergo rearrangement reactions which shall be discussed later.
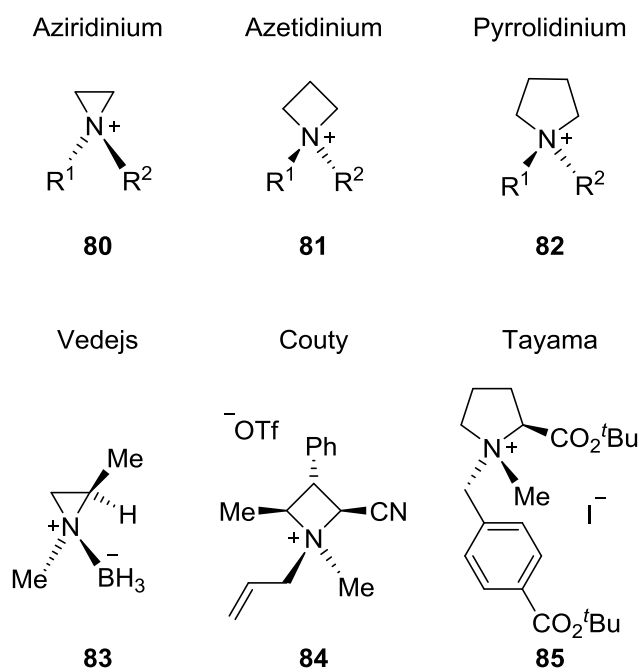
Vedejs   Couty   Tayama

Figure 18 Classes and examples of common cyclic ammonium salts

Vedejs has selectively synthesised aziridinium amino-borane complexes **83** and Couty has developed a stereoselective synthesis of azetidines **84**.[84, 85] Tayama demonstrated good use of proline to make diastereomeric ammonium salts **85** selectively for application in rearrangement chemistry.[86]

1.1.3.3.3 Asymmetric alkylation

If the quaternisation of tertiary amines could be carried out asymmetrically then it would remove the need for complex enantiomeric separation or diastereomer resolution. Kobayashi and co-workers approached this by alkylation of a tertiary amine **87** with a chiral sulfur *O*-methyl compound **86** (**Scheme 14**).[87] Only the optical rotation is reported of the methylating agent $[\alpha]_D$=+17 and the ammonium salt **88** product $[\alpha]_D$=+4. There appears to be poor transfer of chiral information from the sulfoxide to the tertiary amine and the enantiopurity of **88** was based on a comparison of another compound (phenyl *p*-tolyl sulfoxide) synthesised by a different research group led by Mislow.[88]
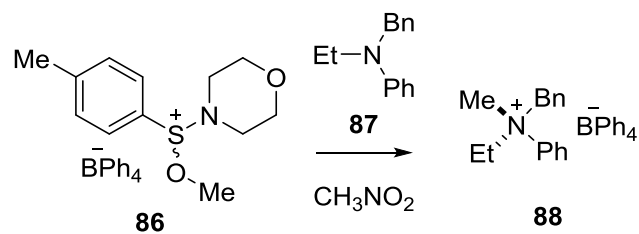
Scheme 14 Asymmetric alkylation of a tertiary amine with a chiral sulfoxide salt

1.1.4 Applications of nitrogen chirality

Due to the need to arrest inversion of nitrogen in order to synthesise single-enantiomer *N*-chiral ammonium salts, chiral-at-nitrogen ammonium salts have yet to find many applications outside of rearrangement reactions. There are many other applications of ammonium salts such as in ionic liquids, chiral extractions, natural product synthesis, biological activity and in materials chemistry but as yet, the potential for exploiting nitrogen chirality in ammonium salts has been restricted due to the small number of examples reported in the literature.[89-94] Ammonium rearrangements have been used for a plethora of transformations including accessing natural products. Isopavines **89** (**Figure 19**), known for their central nervous system activity and activity against Parkinson's disease, Alzhiemer's disease and Down's syndrome, can be accessed through alkylated azocines.[95] Similar in structure to morphine **90**, the full range of their biological application potential has yet to be probed.
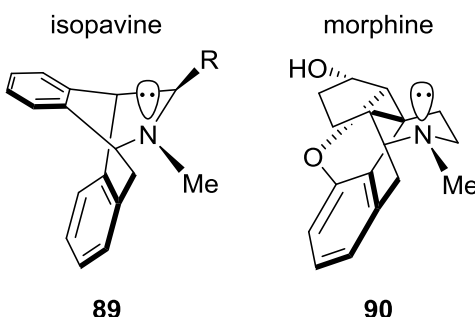

Figure 19 Complex isopavine series has varied biological activity and is structurally similar to morphine

Other applications of chiral-at-nitrogen ammonium salts **91** N_S (**Figure 20**) as directing agents in the synthesis of aluminosilicates have been investigated.[89, 90] The inclusion of the stereogenic

nitrogen ammonium[IV] salt displays a new example of co-operative structure directing from cations somewhat like a template-mediated synthesis.
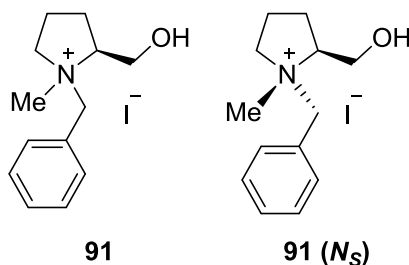

Figure 20 Diastereomeric mixture and then resolved ammonium salts used in cation directed synthesis of zeolites

Initial studies focused on using the epimeric mixture of salts **91** along with theoretical modelling to identify the (*S*,*S*) diastereoisomer **91** N_S to be more effective at creating a larger cage size within the membranes of the zeolites formed (**Figure 21**). Whilst the full mechanism of formation is unknown it is proposed the (*S*,*S*) epimer offers an optimal π-interaction with the zeolite surface. Investigations on the applicability of the zeolite materials as asymmetric catalysts are ongoing.

[IV] Describing an ammonium salt where the nitrogen is a stereogenic tetrahedral centre but the molecule may contain another stereogenic centre.
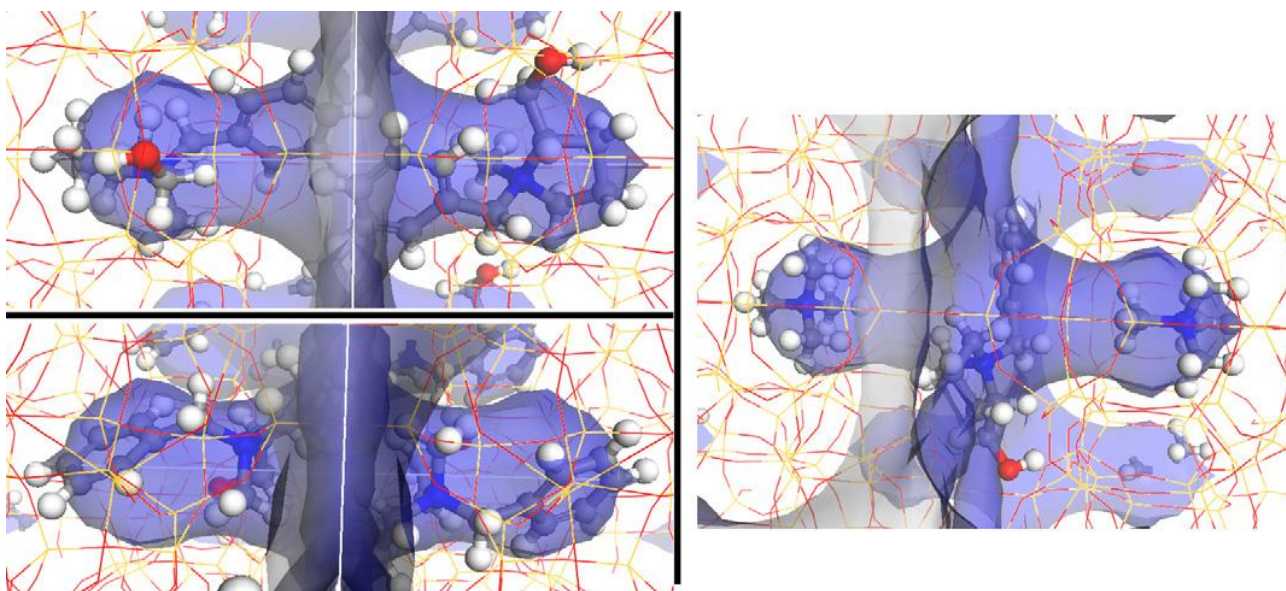
Figure 21 Modelled image of ammonium salts in the supercages of zeolites (image taken with permission from, Tetrahedron: Asymmetry, 18, **2007**, 23, 2828.)

There are many reactions of ammonium salts but few with asymmetric variants. The Stevens rearrangement, the Sommelet-Hauser rearrangement and other [1, 2] and [2, 3] sigmatropic rearrangements are such examples where the asymmetric nitrogen plays a vital role in the transfer of chiral information. These are base-induced rearrangements and often proceed via competing reactivity pathways.

1.1.4.1 Rearrangement reactions

The Stevens rearrangement (**Scheme 15**), first reported in 1928 involves a [1,2] *N*-alkyl shift to give an α-tertiary amine **94** product.[96] Alkylation of amine **92** with benzyl bromide forms the ammonium salt **93**, which rearranges when exposed to base. Whilst the full details of the mechanism have yet to be elucidated, the most widely accepted hypothesis is that deprotonation of the α-proton in **93** and ylide formation results in homolytic cleavage of a benzyl radical species, which is held by a solvent cage (allowing retention of stereochemistry in asymmetric variants) followed by recombination of the benzyl radical and the carbanion to give the α-substituted tertiary amine **94**.
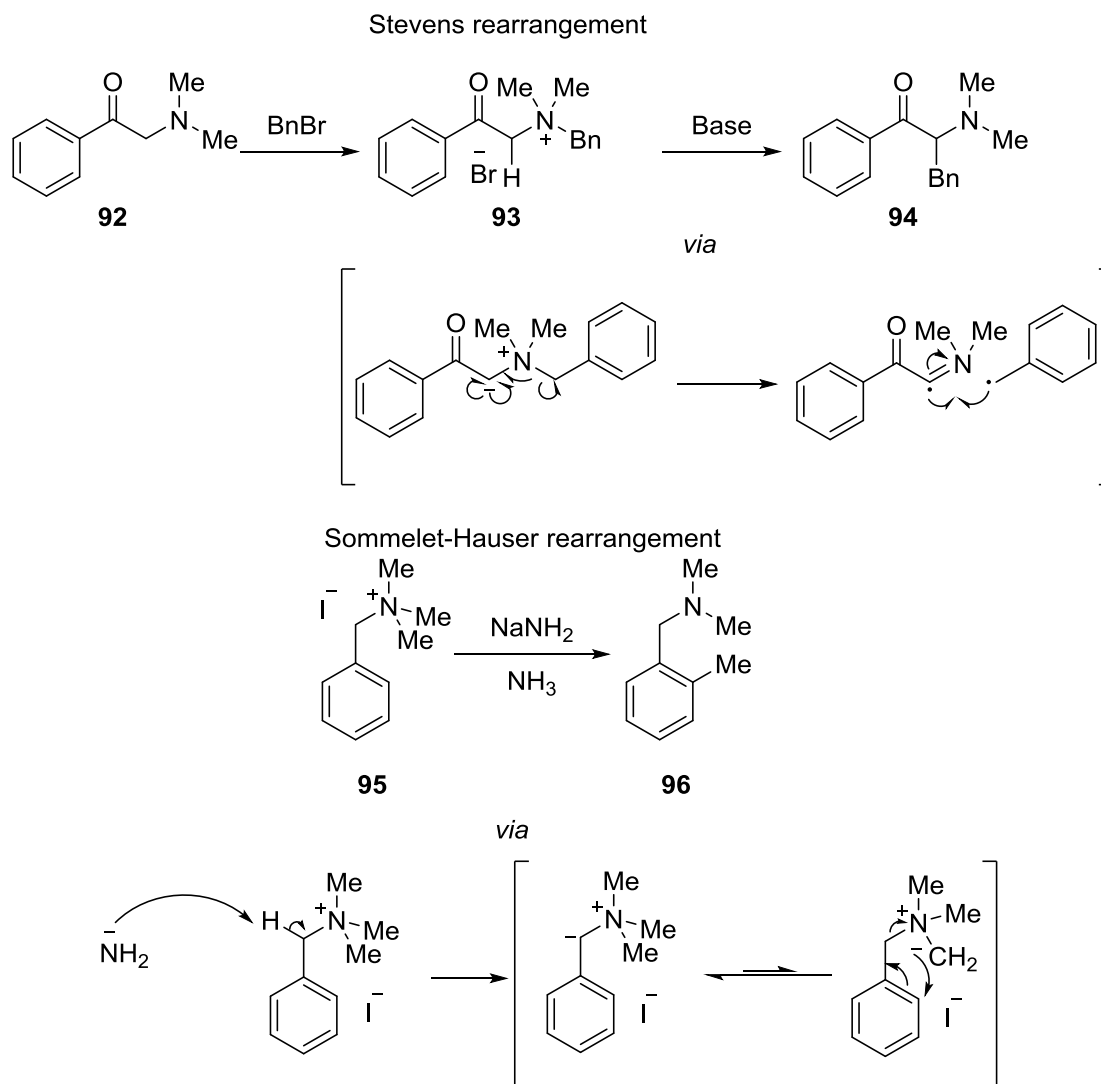
Scheme 15 The two classical ammonium rearrangement reactions, Stevens and Sommelet-Hauser

The Sommelet-Hauser (**Scheme 15**) rearrangement requires an *N*-benzyl ammonium salt **95**. Addition of base enables deprotonation of a benzylic proton to form an ylide. A second ylide form is in equilibrium and undergoes a [2,3]-rearrangement to give an *ortho*-substituted *N*-benzyl tertiary amine **96**. The two rearrangement reactions have competing pathways so it is possible to obtain different products from one starting material.[97, 98]

Interest in the Stevens rearrangement has continued to develop asymmetric variants where a transmission of *N* to *C* chirality can be utilised as a useful and dependable tool for asymmetric

synthesis. This is dependent on starting from a resolved compound containing a stereogenic nitrogen centre and also controlling the reactivity (Stevens *vs* Sommelet-Hauser).
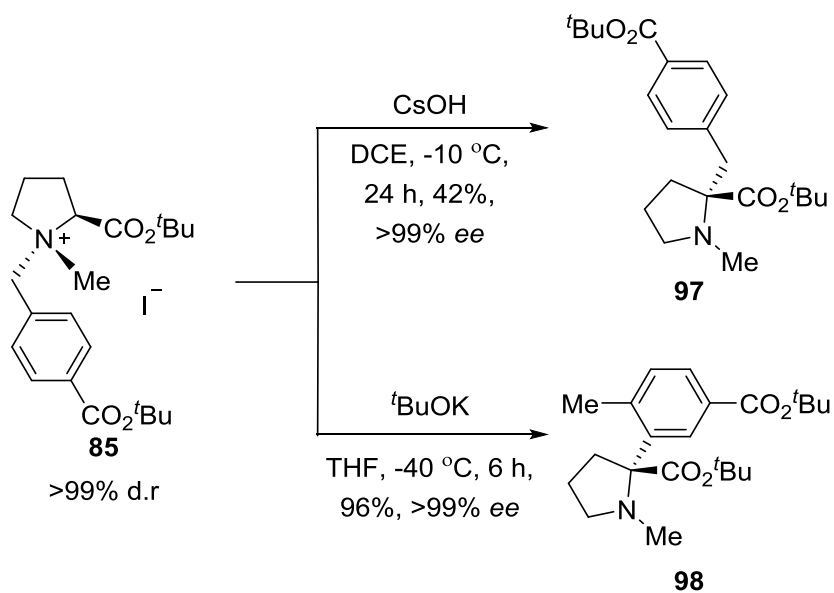
Scheme 16 Ammonium salt **85** can react to give the Stevens product (top) or the Sommelet-Hauser product (bottom).

Ammonium salt **85** is able to deliver both the Stevens [1,2] product **97** along with the Sommelet-Hauser [2.3] product **98** (**Scheme 16**).[86] The Stevens product proceeds with use of cesium hydroxide in dichloroethane, which has a high di-electric constant, so can encapsulate the radical pair preventing diffusion in a solvent cage. Excellent stereoselectivity was observed, >99% *ee* with full (*N* to *C* transmission) retention of stereochemistry. When carrying out the reaction at a slightly lower temperature (-40 ^{o}C *versus* -10 ^{o}C), using potassium ^{t}butoxide as the base the Sommelet-Hauser product is delivered with near quantitative yield, 96% and excellent transmission of *N* to *C* chirality, >99% *ee*. This provides great synthetic utility and again shows that rearrangements are sensitive to subtle changes in reaction conditions.

1.1.4.2 Aziridinium and azetidinium stereogenic at nitrogen

Aziridines **99** and azetidines **100** are three- and four-membered rings containing a nitrogen atom and because of their small ring size are very strained. Aziridines are planar molecules and azetidines exist in a conformational equilibrium of puckered forms.
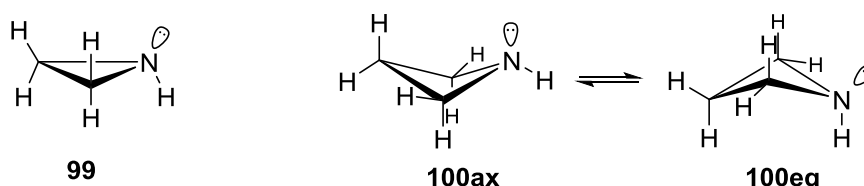

**Figure 22** Conformation of aziridine and azetidine molecules

The energy released upon ring-opening of aziridines or azetidines acts as a powerful driving force in synthesis. They can be utilised as nitrogen-containing building blocks in synthetic strategies as they can be prepared with high degrees of stereogenic nitrogen control.

Vedejs & Kendall carried out a detailed study into the formation of amino-borane complexes (**Scheme 17**) and lithiation of the resulting aziridine complexes.[84] The study was intended to evaluate the stability of the amino-borane complexes so both diastereoisomers were formed. Treatment of the *N*-methyl aziridine **101** with borane in THF gave the *trans* [1,2]-dimethyl aziridinium salt **83**$_{RR}$ in 66% yield. The selectivity observed, 10:1 is understandable due to fixed chirality of the α-methyl group which forces the N-methyl group to adopt this *trans* conformation to minimise further steric interactions allowing the co-ordination of the borane to occur *syn* in relation to the α-methyl group. Alternately, methylation of the amino-borane aziridine sodium salt **102** with iodomethane proceeds with a reversal of selectivity to give the *cis*-[1,2]-dimethyl aziridine **83**$_{SR}$ in 55% yield. The [1,2]-dimethyl aziridinium salts **83** were found to be configurationally stable.
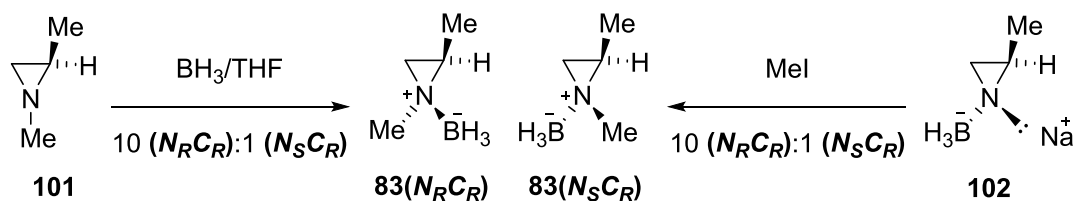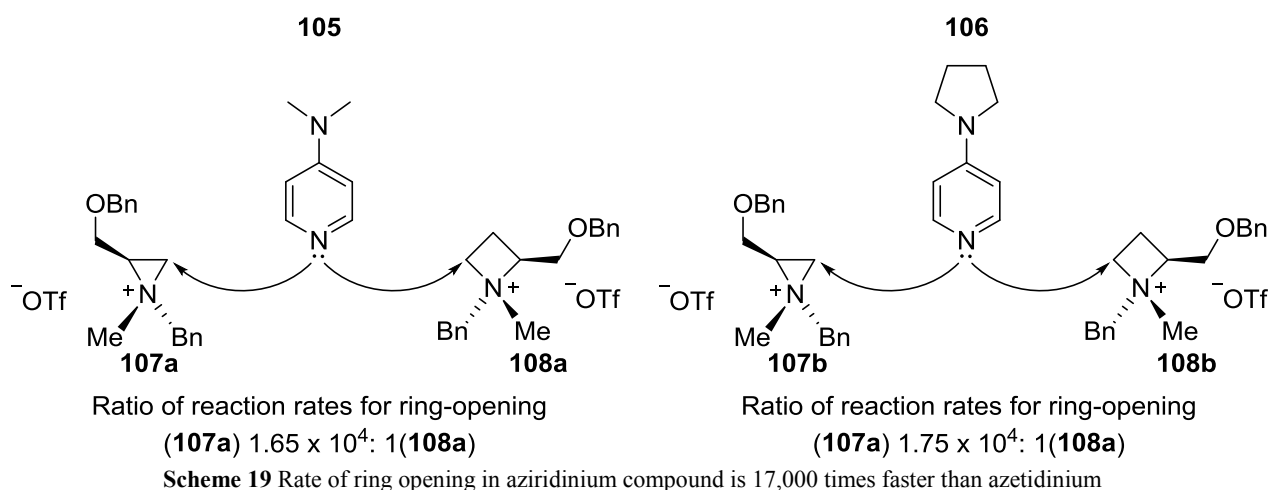
Scheme 17 Complementary reaction sequence to synthesise aziridinium epimers selectively

Couty and co-workers developed a stereoselective azetidinium synthesis combined with theoretical investigations which has allowed predictable regioselectivity (**Scheme 18**).[85] High selectivity can be observed when treating an azetidinium trifluoromethanesulfonate salt with sodium azide (**Scheme 18**). Nucleophilic attack of the azide at the unsubstituted C-4 position of azetidinium salt **103** led to the ring-opened product **104**$_{(RR)}$ in preference to reaction at the C-2 carbon, which led to the minor product **104**$_{(RS)}$ to give a distribution of 93:7 of the open chain α-substituted glycine derivative.
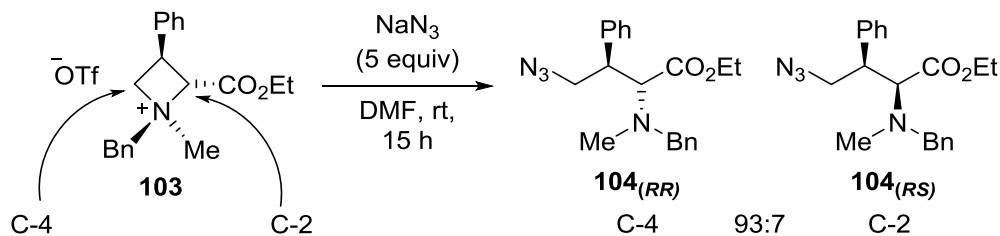

Scheme 18 Regioselective ring opening of azetidinium molecules

A study from Couty *et al.* (**Scheme 19**), compared the rate of reaction for the ring-opening of aziridinium species **107** and its higher homolog **108** with 4-dimethylaminopyridine (DMAP) **105** and was the first direct study to establish the relative electrophilicity as the only difference is the ring size.[99] Conducting kinetics studies, Couty *et al.* established the second order rate constants for each reaction showing a much faster rate for the ring opening of the aziridinium species with ratios of 1.65×10^4 for DMAP **105** and 1.75×10^4 for 4-pyrrolidinopyridine **106**.

105   **106**

Ratio of reaction rates for ring-opening
(**107a**) 1.65 x 10^4: 1(**108a**)

Ratio of reaction rates for ring-opening
(**107a**) 1.75 x 10^4: 1(**108a**)

Scheme 19 Rate of ring opening in aziridinium compound is 17,000 times faster than azetidinium

1.1.4.3 Stereogenic nitrogen phase-transfer catalysis

Ammonium salts are widely used as PTCs.[15] A great deal of work has been done to investigate asymmetric variants over the last 30 years. O'Donnell and co-workers (**Scheme 20**) were the first to synthesise α-amino acid derivatives **110** from alkylation of **109** using phase-transfer catalysis and to demonstrate its viability as a powerful synthetic approach towards enantioselective bond-forming reactions.[100]

Scheme 20 Alkylation of a Schiff base offers a route to α-substituted amino acid derivatives.
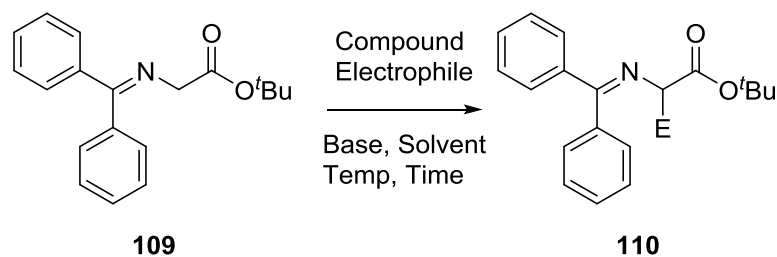
Wang *et al.* utilised Nature's chiral pool and synthesised a series of ammonium salts **111** and **112** derived from amino acids (**Figure 23**).[101] Starting with the natural amino acids, a modified one-pot procedure consisting of two reductive aminations followed by quaternisation of the resulting tertiary amine with allyl or benzyl bromide gave ammonium salts **111 a-d** and **112 a-d** in very high overall yield.
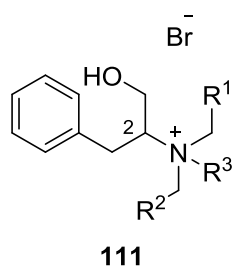
a: R^1 = Ph, R^2 = H, R^3 = Bn (2*S*)
b: R^1 = R^2 = CH=CH$_2$, R^3 = Bn (2*S*)
c: R^1 = R^2 = CH=CH$_2$, R^3 = Bn (2*R*)
d: R^1 = R^2 = CH=CH$_2$, R^3 = CH$_2$CH=CH$_2$ (2*S*)
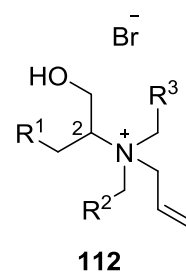
a: R^1 = R^2 = Ph, R^3 = H (2*S*, *N*$_S$)
b: R^1 = R^2 = Ph, R^3 = H (2*S*, *N*$_R$)
c: R^1 = H, R^2 = Ph, R^3 = H (2*S*, *N*$_S$)
d: R^1 = H, R^2 = Ph, R^3 = H (2*S*, *N*$_R$)

Figure 23 Amino acid-derived ammonium salts with stereogenic carbon, **111** and with adjacent stereogenic nitrogen, **112**

Wang *et al.* attempted to investigate any effect on the diastereoselectivity observed from inclusion of an adjacent stereogenic nitrogen atom, compounds **111a-d**. There were no details of any resolution of the diastereoisomers formed in compounds **112a-d** or reports of the diastereoisomer ratio. When the catalysts were screened in the alkylation of a Schiff base **109** (**Table 2**), the reaction proceeded in good yield. However the chiral induction observed was quite low, 13-16% *ee* with a preference for the (*S*)-alkylated product. If the reported stereochemistry of the nitrogen is correct then evaluation of the data would imply that the stereogenicity of the nitrogen has no influence over the reaction outcome. The chiral carbon (2*S* or 2*R*) in the ammonium salts **111** and **112** from the starting amino acid material seems to dominate the stereochemistry observed in the product (**Table 2**). The hypothesis of using a chiral-at-nitrogen ammonium salt in phase-transfer catalysis was good but the report is disappointing due to the ambiguity of the nitrogen chirality surrounding their claims.

Table 2 PTC carried out using ammonium salt catalysts **111 a-d** and **112 a-d**
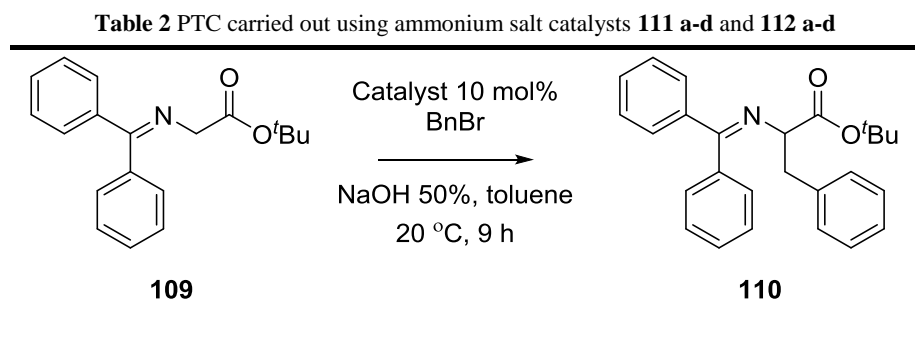
Entry	Catalyst	Yield (%)	*ee* (%)
1	**111a**	86	*16 (S)*
2	**111b**	84	*15 (S)*
3	**111c**	84	*15 (R)*
4	**111d**	83	*14 (S)*
5	**112a**	85	*16 (S)*
6	**112b**	84	*16 (S)*
7	**112c**	81	*13 (S)*
8	**112d**	83	*13 (S)*

Dehmlow *et al.* synthesised a number of novel chiral-at-nitrogen prolinol derived PTCs (**Figure 24**) and evaluated their performance in a number of common PTC reactions.[102] Both (N_S and N_R) configurations of ammonium salts were prepared to investigate if the nitrogen chirality directly affected the stereochemical outcome involved with each reaction.

a Bn   **a** 2-naphthyl-CH$_2$
b 2-naphthyl-CH$_2$ **b** 2-quinolyl-CH$_2$
c 2-quinolyl-CH$_2$
d 4-quinolyl-CH$_2$
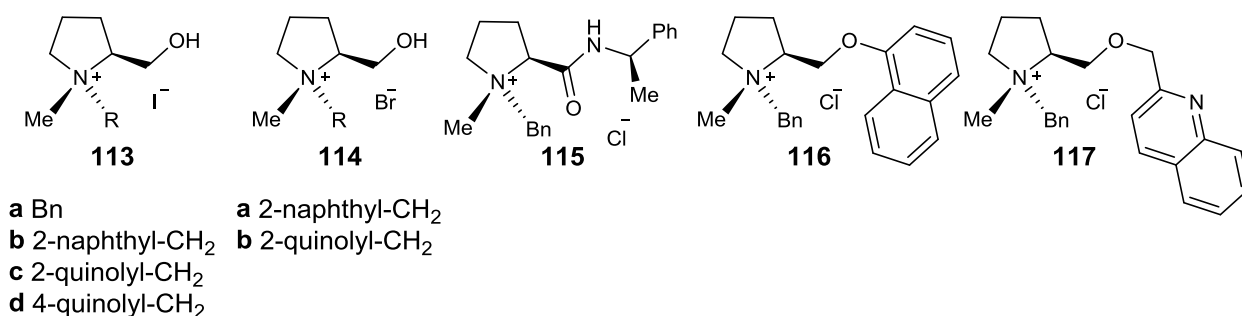
Figure 24 Stereogenic nitrogen-containing ammonium salts made by Dehmlov

Dehmlow *et al.* found alkylation of *N*-methyl prolinol with a variety of electrophiles gave difficult to separate mixtures with low d.r. up to 1:1.5. Nevertheless, repeated crystallisation afforded the diastereomerically pure ammonium salts **114**. The scope was expanded by synthesis of various tertiary amines and alkylating them with iodomethane to give another series of salts **113**. The reversal of addition allowed a much higher selectivity to be observed which led to easier

isolation of the chiral ammonium salt. A number of *N,N*-benzyl methyl ammonium salts were modified to include an amide **115** and ether linkages also, **116** and **117**.

The catalysts were then evaluated in several common PTC reactions. The catalysts (**Scheme 21**) were tested alongside a number of other commonly used PTCs to compare reported literature performances. Michael additions of both 2-methoxycarbonyl-1-indanone and 2-ethoxycarbonylcyclohexanone with methyl vinyl ketone were found to be difficult reactions to attempt due to the background reaction of the substrates meaning the window of opportunity for the catalyst to affect the reaction outcome was extremely small.
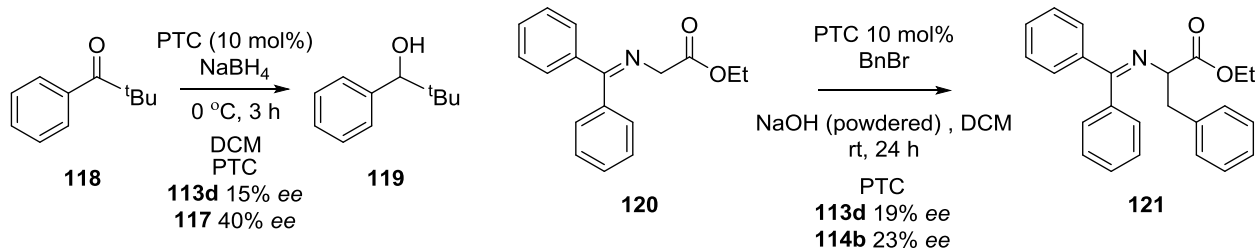
Scheme 21 PTC reduction of ketone **169** using Dehmlow catalysts **156** and **158**

The reduction of pivalophenone **118** (**Scheme 21**) with sodium borohydride had been examined several times by Dehmlow *et al.* who found that using PTC **113d** gave a modest 15% *ee*. A previously reported effort of the pivalphenone reduction was carried out with ammonium salt **117**. The PTC **117** was used without the absolute configuration of the nitrogen being known and the reaction was reported to produce the alcohol in 40% *ee*.[103] Resynthesis of the ammonium salt **117** and retrospective comparison of results showed it was a 90 (N_S):10 (N_R) mixture of diastereoisomers favouring the N_S configuration although there was no report of the diastereomerically pure salt being used again and its performance with the minor diastereomeric component removed. Another reaction attempted was the alkylation of Schiff base. To prevent saponification of the ester, powdered NaOH was used as opposed to a normal 50% w/w solution. After catalyst screening it was found that **113d** could deliver the alkylated product **121** in 19% *ee*

while catalyst **114b** performed slightly better at 23% *ee*. The major alkylated product of the reaction was the (*S*) enantiomer, which leads to difficulty in determining the major stereocontrolling element in PTC reactions.

Although the barrier to inversion for nitrogen (*cf.* ammonia 24 kcal mol^{-1}) is low and occurs rapidly at room temperature, several examples of chiral-at-nitrogen compounds have been reported and discussed including acyclic and cyclic (ring sizes of three, four and five), secondary and tertiary amines. Ammonium salts and *N*-oxides which include chiral-at-nitrogen stereogenic centres demonstrate how, in the limited examples discussed in this chapter , use of a chiral shift reagent allowed *N*-oxide enantiomers to be distinguishable in ^{1}H NMR and how fractional recrystallisation provided a way to separate ammonium salts into their enantiomers. Applications of chiral-at-nitrogen ammonium salts include use as PTCs or in rearrangement reaction reactions.

1.2 Previous work

Fossey and Chen developed a synthesis to build racemic mixtures of ammonium salts where the only asymmetric component was nitrogen. Reductive amination using 2-(methylamino)-ethanol **122** and 2-quinolinecarboxaldehyde **121** (**Scheme 22**) and then alkylation with benzyl bromide gave the required ammonium salt **124** which could be crystallised and characterised by X-ray crystallography.
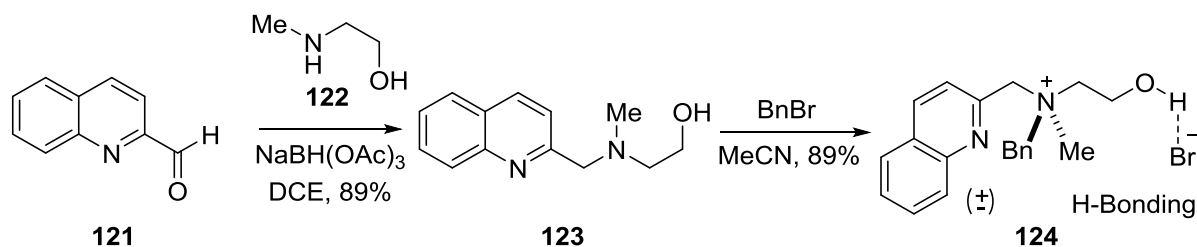
Scheme 22 Procedure for the racemic synthesis of ammonium salt **124**

Experiments were conducted using the series of salts **124** methodically with different solvents and different chiral resolving agents. L-Tartaric acid **125**, *R*-BINOL **127**, (+)-dibenzyl-L-tartrate

126, trisphat **128**, chiral phosphoric acid **129,** (*R*)-mandelic acid **130** and camphorsulfonic acid **66** were all used in an effort to mimic the results from Pope and Peachey in resolution of the enantiomers through diastereomeric chiral anion exchange (**Figure 25**).[2] Efforts to resolve the enantiomeric pairs were not unsuccessful and in some cases, their measured optical rotations were zero suggesting that a racemic mixture was probably isolated.
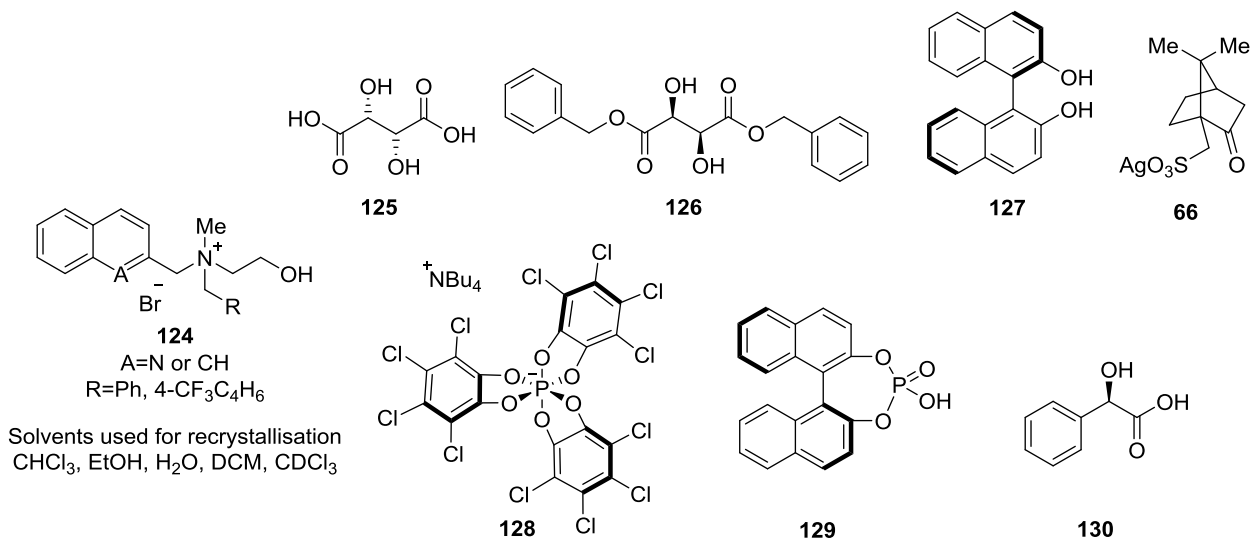

Figure 25 Summary of ammonium salts made, solvents used for recrystallisation and chiral resolving agents used to attempt enantiomeric resolution

There was one partial success with *N*-benzyl-*N*-ethyl-*N*-methyl-*N*-phenyl ammonium bromide which precipitated as a 1:1 mixture of diastereoisomers using camphorsulfonic acid (**Scheme 23**).

Scheme 23 Diastereomeric ammonium salt formation
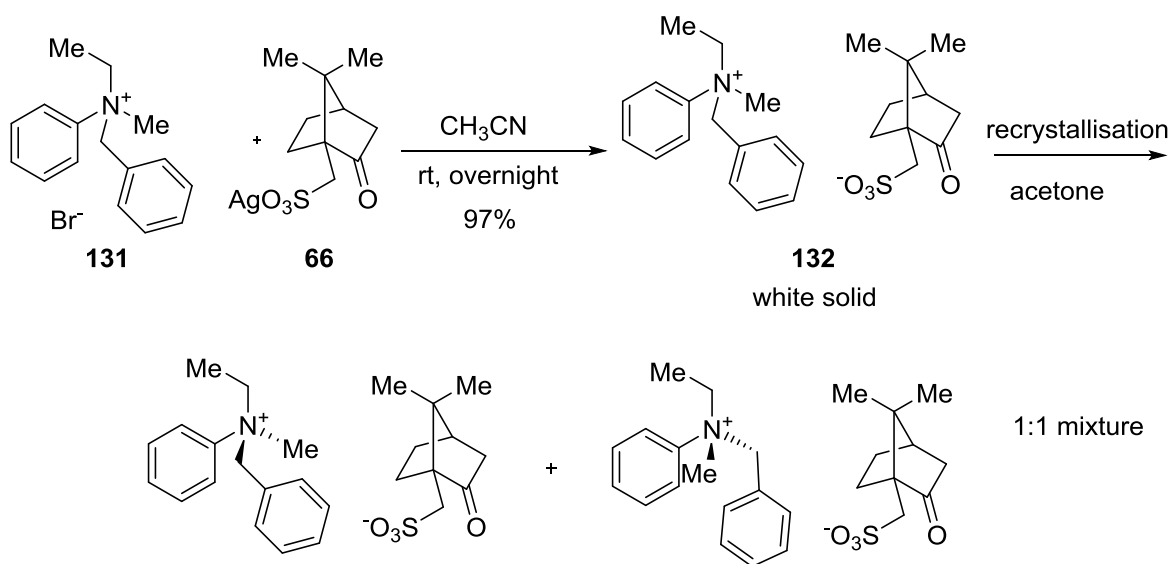
Treatment of the bromide salt **131** with silver CSA **66** salt led to insoluble silver bromide being formed and the chiral CSA then acting as the chiral anion for the salt **132**. The salt **132** could not be resolved into its enantiomers despite several efforts.

Having been unable to resolve the salt **132**, a breakthrough came when, in collaboration with Lotus Separations (Princeton University) an analytical separation of the bromide **131** was found using SFC (**Figure 26**). Despite repetition of these conditions by Lotus Separations, the separation could not be reproduced. All chiral HPLC possibilities were exhausted by this point and subsequently research had stopped.
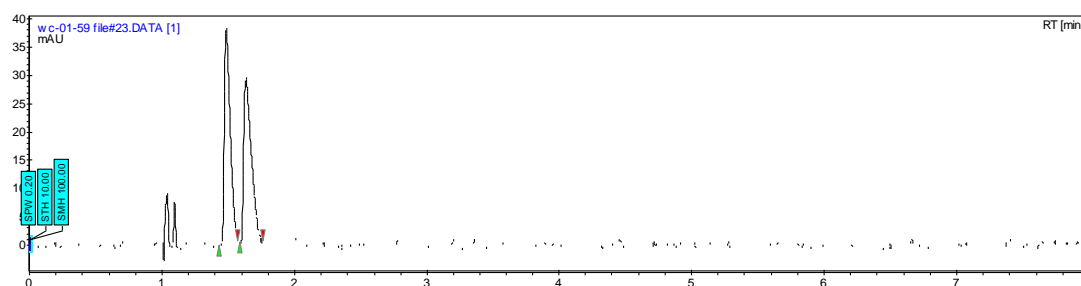
Figure 26 SFC of compound **131** Chiralpak AD-H (25 x 0.46 cm), 40% methanol (0.1% DEA)/CO$_2$, 100 bar,3 mL/min, 220 nm

Having exhausted possibilities of using fractional recrystallisation and chromatography to resolve enantiomeric mixtures of ammonium salts, the future direction of research was thought to be;

1) Use of an enzyme to resolve the chiral-at-nitrogen ammonium salts.

2) To modify the synthetic approach to synthesise a diastereomeric mixture of ammonium salts and exploit any possible diastereoselectivity arising from the quaternisation of tertiary amines.

2 Aims

The main aim of this project is to synthesise chiral-at-nitrogen ammonium salts to uncover potential synthetic utility for application in asymmetric synthesis. There are two possible synthetic routes envisaged: a racemic synthesis followed by resolution, and formation of diastereomeric mixture of ammonium salts. It is proposed that the first approach could be achieved through use of enzymes to attempt kinetic resolution of racemic ammonium salts (**Scheme 24**).
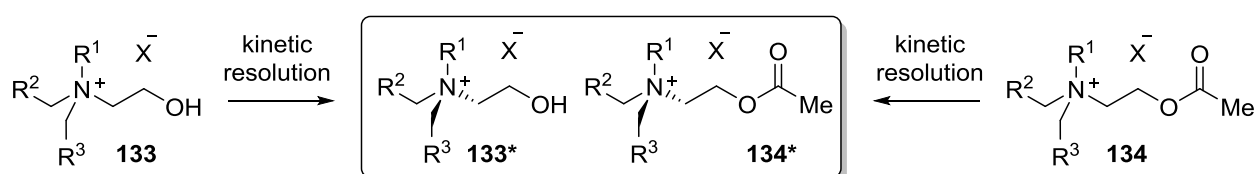
Scheme 24 Proposed route to resolve enantiomers of chiral-at-nitrogen ammonium salts

The alternative route would involve the quaternisation of a tertiary amine, which includes a fixed carbon stereogenic centre. The possibility of uncovering diastereoselectivity during the quaternisation will be investigated (**Scheme 25**).
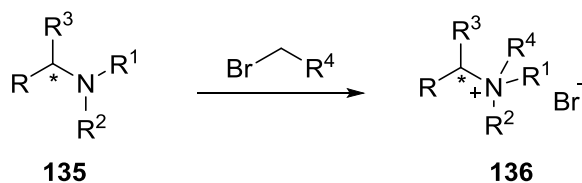
Scheme 25 Quaternisation of tertiary amine will result in the formation of a diastereoisomeric ammonium salt mixture

Use of the chiral-at-nitrogen ammonium salts will enable their application as catalysts in literature phase-transfer catalysed reactions. This allows the investigation of stereogenic nitrogen and whether it has any asymmetric influence on the outcome of a PTC reaction when acting as a catalyst.

3 Results and Discussion

3.1 Enzymatic resolution

It was decided that an alternative strategy of enzymatic resolution would be investigated as opposed to fractional recrystallisation or chromatography. By including some functionality in the ammonium salt, e.g. an ester group, use of an appropriate esterase enzyme, would theoretically allow the enantiomers to be resolved. An enzymatic approach to resolution of chiral-at-nitrogen compounds (ammonium salts) had not been investigated. A diverse range of molecules (**Figure 27**) were planned based on the route established by Chen and Fossey.
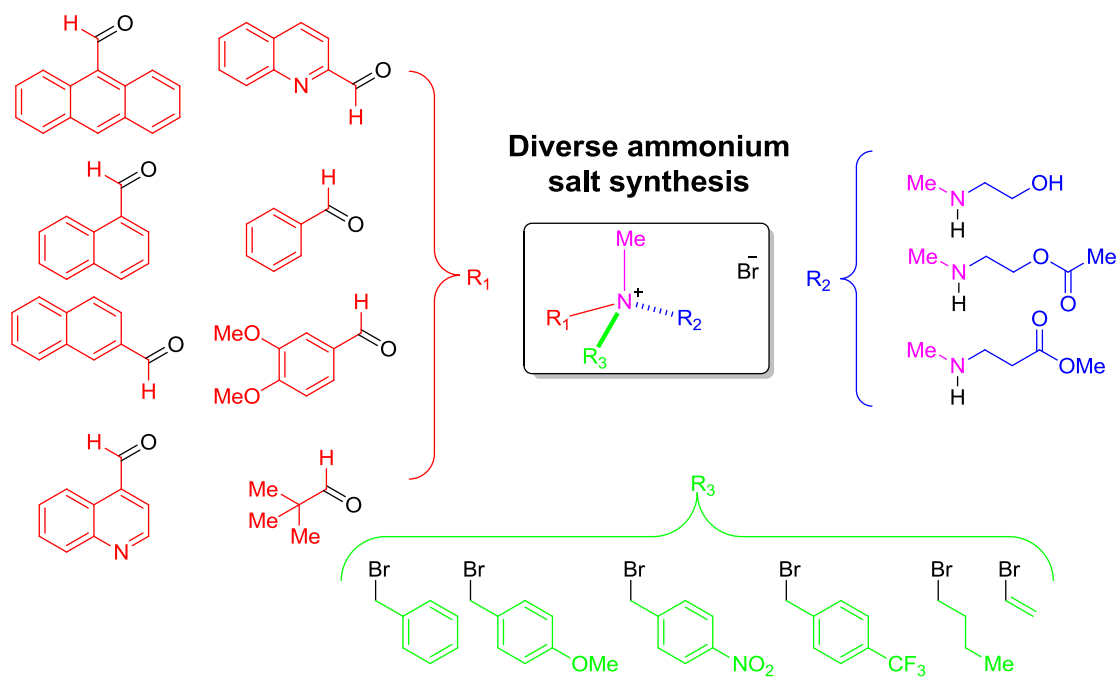
Figure 27 Synthetic plans to form ammonium salts

Synthesis of several dozen molecules ensured a wide range of ammonium salts could be tested in enzymatic studies. From the literature, it was decided that selective acylation and de-acylation enabling enzymes could be suitable as we had previously demonstrated in our laboratory that alcohol groups in ammonium salts could be easily converted to esters. The enzymes, pig's liver esterase (PLE) (de-acylation) and *Candida antarctica* lipase (acylation) were identified as suitable choices (**Scheme 26**).[104]
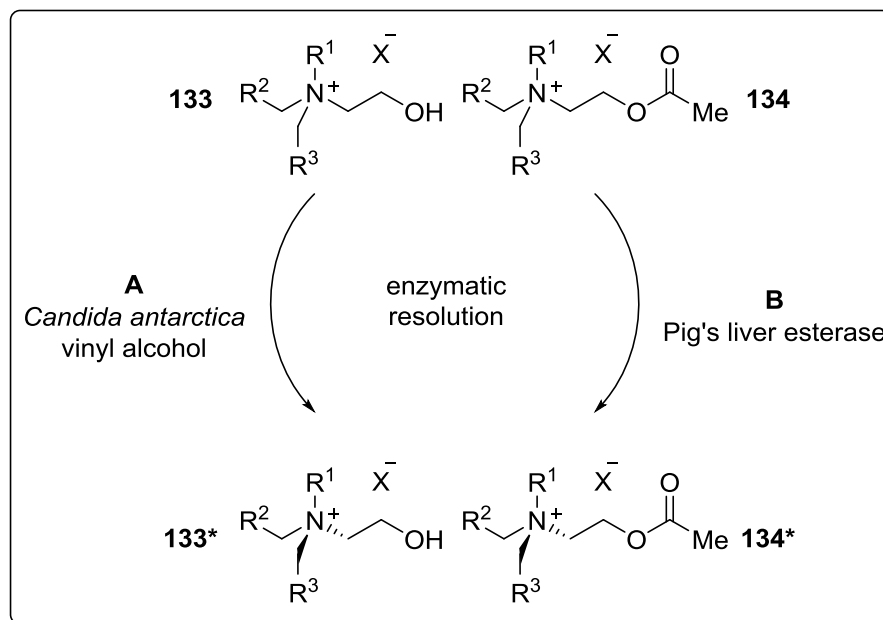
Scheme 26 Attempted routes to resolve enantiomeric ammonium salts

In order to establish a baseline of experimental operation two test molecules were formed to conduct optimisation experiments (**Figure 28**).
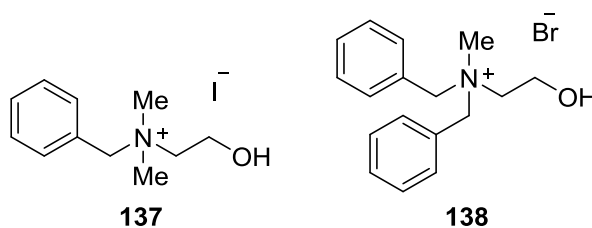

**Figure 28** Test molecules with achiral nitrogen centres and X-ray structures

It was difficult to find a suitable balance between solubility and shutting down the reaction of the enzymes used when choosing an appropriate solvent. When the experiments were conducted using PLE, following literature reported organic solvents like MeCN and DCM, the reaction did not proceed. THF and mixtures with water were then also tried but with no success. That directed investigations into use of a variety of neutral buffered solutions (**Scheme 27**). The intention was to be able to separate usable amounts of material from this method so consistency in mass recovery as well as good reaction yield was desired.
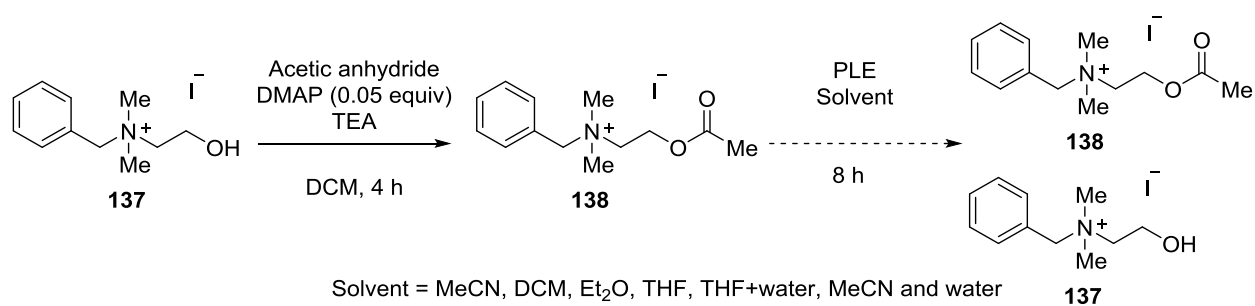
Scheme 27 Attempted enzymatic resolution test reaction

Whenever any resolution experiments were conducted using ammonium salts, it was extremely difficult to recover any materials from the reaction mixture, which in turn affected accurate analysis as removal of the solvent was very challenging. *Candida antarctica* lipase (**Scheme 28**) was used to selectively acylate and deacylate ammonium salts but again issues with reactivity of the substrate, solubility (use of >50 mL for 0.1 g scale reaction) and reaction work-up led to erratic results. Although many failed reactions were carried out it was decided to reach an end-point with this direction of research by carrying out some control reactions. It was decided to carry out literature acylation and a deacylation procedures and confirm the enzyme's reactivity and then repeat the experiments in the presence of one equivalent of TBAB to evaluate the effect of having an ammonium salt present in the reaction mixture (**Scheme 28**).

Following the literature procedure, first phenylethanol **139** was selectively acylated with *Candida antarctica* lipase in the presence of vinyl acetate to give the resolved alcohol **139** and ester **140** in good yield and in accordance with the literature in terms of enantioselectivity. When repeated with an ammonium salt present, the reaction did not proceed and no alcohol or ester could be recovered. The literature procedure chosen also had examples of deacylation and when this reaction was attempted the same result was obtained. As the literature only reported organic solvents, it was difficult to get a direct comparison when using ammonium salts as only small organic molecules like phenylethanol **139** were reported, obviously the solubility issues of ammonium salts in diethyl ether presented reactivity issues but efforts at using buffered solutions or even THF/water mixtures did not yield any significant results.

49
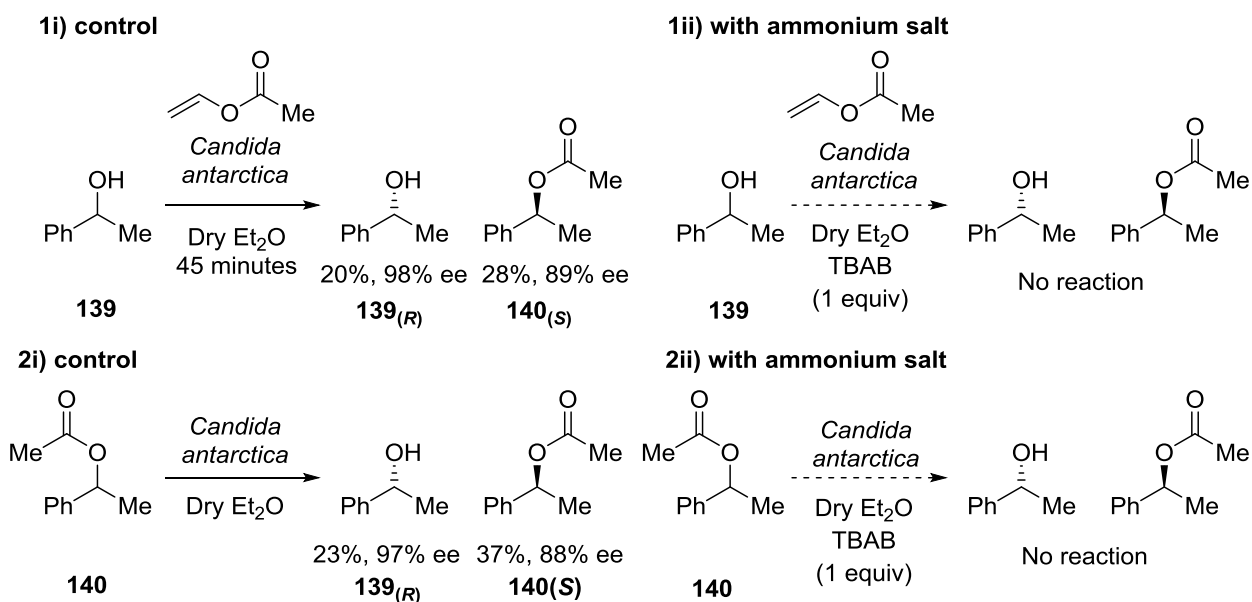
Scheme 28 Control reactions showing incompatibility of enzymatic resolution with ammonium salts

The control reactions (**Scheme 28**) show that when an ammonium salt is added to the reaction mixture, the outcome of the reaction totally changes and mass recovery of any alcohol or ester was not possible. It was hypothesised that use of enzymes would not be compatible with ammonium salts and research in this area stopped.

3.2 First-generation ammonium salts

It was planned to create some simple DAS in order to optimise reaction conditions and establish the limits of modification obtainable from the reductive amination reaction. Reductive amination (**Scheme 29**) was used to alkylate the nitrogen in the amine **141** in high yield to give the tertiary amines **142**.[105-107] Use of formaldehyde or acetaldehyde allowed installation of *N*-methyl **142a** or *N*-ethyl **142b** branches in high yield. Despite several attempts, only small alkyl branches could be added to the amine **141**, aromatic aldehydes were too large to be added and no reaction occurred with starting materials recovered during reactions tried.

Iodomethane/iodoethane was used (**Scheme 30**), to attempt to alkylate tertiary amine **142**. However there was no evidence for the formation of an ammonium salt by TLC or proton NMR.

The reaction was repeated at higher temperatures (50 °C and reflux) with little or no conversion (<5% consumption by TLC) and the intended product **186** could not be isolated or formed.
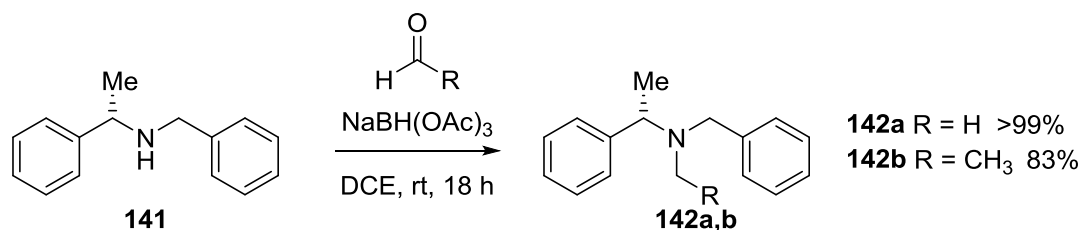
**Scheme 29** Tertiary amine synthesis

Increasing the excess of the electrophile or prolonging the reaction time still resulted in no conversion to the expected product **143**. Due to the volatility of iodomethane and iodoethane (bp 42 °C and 72 °C respectively) when refluxing, two Liebig condensers were used in conjunction to avoid accidental evaporation. To try and overcome the lack of reactivity, the reaction conditions were repeated with both electrophiles conducting separate reactions using a microwave reactor. All efforts resulted in either decomposition or recovery of starting material (>95%).

144a R = H at rt = 55% at reflux = 40%
144b R = Me at rt = 55%
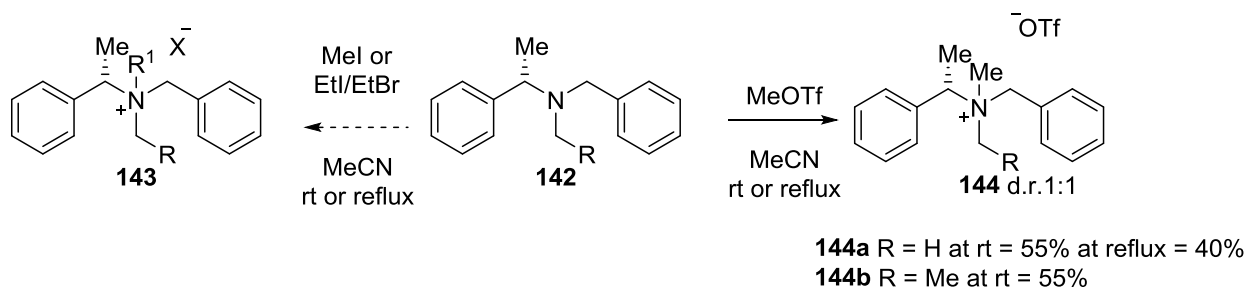
Scheme 30 DAS formation with methyl triflate

A large part of our strategy was to include an anthracenyl group, which, due to its large π-surface, was thought would offer a greater chance for imparting diastereoselectivity in the quaternisation reaction. [108, 109] Using chiral amine **145** and 9-anthraldehyde **146** in a reductive amination reaction gave secondary amine **147** in 90% yield (**Scheme 31**). Subjection to N-methylation with formic acid and formaldehyde in refluxing ethanol formed the tertiary amine **148** in 80% yield. Many different strategies were investigated in the alkylation of the tertiary amine **148** including

different solvents, alkylating agents, microwave reactor, sealed-tube reactions, addition of halide scavengers (silver (I) salts) and also variable reaction pathways (use of 9-bromomethylanthracene to quaternise tertiary amine **149**, (**Figure 29**)), however, after exhausting all possibilities, no salts were formed. It is hypothesised that this inability to form the target quaternary ammonium salts is due to the steric bulk of the anthracenyl moiety.
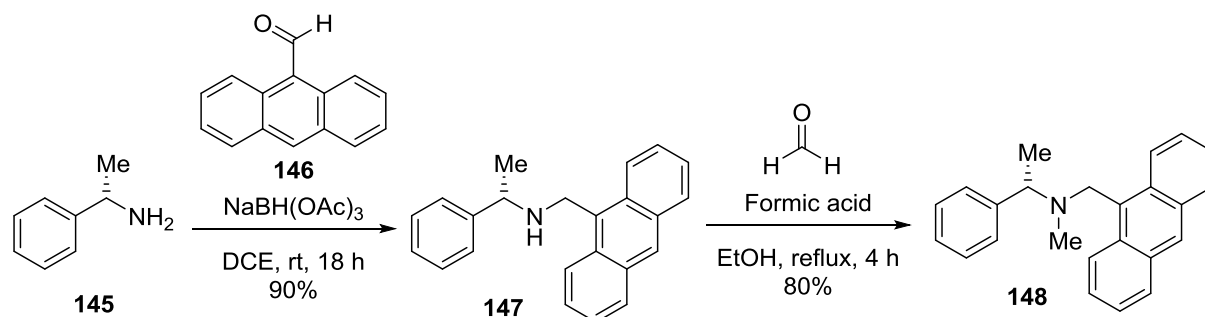
Scheme 31 Inclusion of anthracenyl unit in tertiary amines

In order to probe the reaction limits further it was decided to investigate the order of addition in forming the tertiary amines for the second *N*-benzyl unit, using two common intermediates (**Figure 29**), which act as points of variance in the synthesis of a small library of DASs:

i)   Synthesise (*S*)-*N*-ethyl-*N*-methyl-α-methylbenzylamine **149** in order to allow quaternisation using more reactive substituted benzyl bromide derivatives

ii)   Vary the starting aldehyde followed by *N*-ethylation, **150** and then DAS formation with treatment of methyl triflate
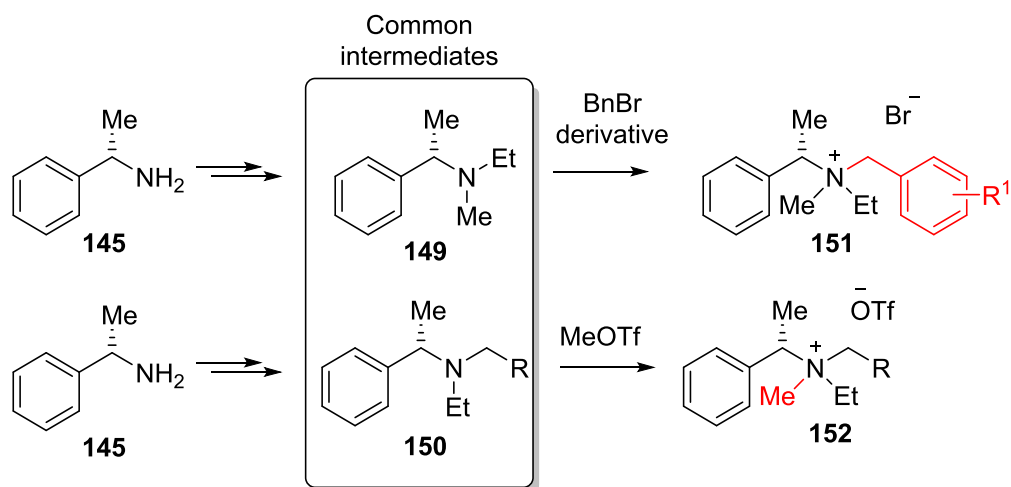
Figure 29 Common intermediates for points of diversity

Using the reductive amination strategy to construct tertiary amine **149** from the chiral amine **145** was straightforward with acetaldehyde giving the *N*-ethylated amine **153** quantitatively. The *N*-methylation of **153** with aqueous formaldehyde (35% w/w solution), under the same reaction conditions, occurred with a similarly high yield to give the tertiary amine **149**. Treatment of key tertiary amine **149** with a slight excess of benzyl bromide (1.2 equiv) (**Scheme 32**) afforded the DAS **151a** in excellent yield.
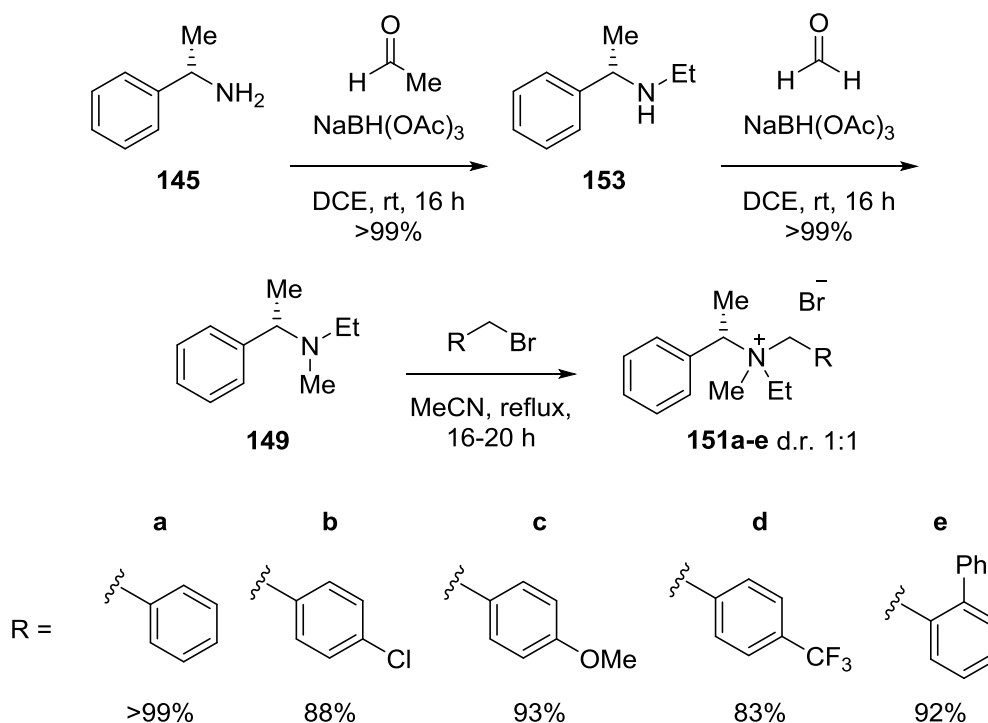
Scheme 32 Synthesis of 1st Gen DAS using benzyl bromide derivatives in the final quaternisation step

Having previously established purification conditions by column chromatography for DAS **144** it was found the same conditions were suitable for **151a** also. The conditions (20:1 DCM:MeOH) were found to be suitable for all benzyl ammonium salts **151a-e**. Compounds **151b** and **d**, with *para*-substituted electron-withdrawing groups suffered slightly reduced yields isolating 88% and 83% respectively. Ammonium salt **151c**, containing an electron rich *N*-benzyl branch was formed in good yield 93% as well as the more sterically demanding *ortho*-phenyl *N*-benzyl ammonium salt **151e** 92%.

Introducing the *N*-benzyl group early, compromised further alkylation as the *N*-centre was now possibly too crowded. Reversing the order of addition was crucial to be able to take advantage of more reactive benzyl halides in the final quaternisation, which proceeded in all cases with essentially no diastereoselectivity. In order to access the other proposed tertiary amine intermediate **150**, different aldehydes would be reacted with chiral amine **145**. A number of substrates were compatible with this method including heteroaromatic, substituted aromatic,

branched alkyl, cyclic alkyl (**Table 3**, **entry 1-5**) aldehydes, which all provided the corresponding secondary amines **155a-e** with excellent yields.

Table 3 Route to DAS using array of starting aldehydes

Entry	R	Step 1	Step 2	Step 3	d.r.[d]
1 (a)	2-thiophene	97	>99	93	1:1
2 (b)	(OMe, OMe phenyl)	>99	84	79	3:2
3 (c)	${}^tBu$	94	89	67	2:1[e]
4 (d)	cyclohexyl	97	95	44[a,b]	1:1
5 (e)	4-pyridine	>99	>99	0[c]	-

[a] Dimethyl sulfate was used as alkylating agent (56%, 1:1 d.r.). [b] Reaction carried out at -40 °C with methyl triflate and dimethyl sulfate and no change in d.r. recorded. [c] Evidence supports pyridine nitrogen was alkylated. [d] d.r. calculated on ratio of benzylic protons AB system. [e] d.r. calculated on ratio of ^{t}butyl signal.

Subsequent *N*-ethylation provided **150a-e** in quantitative yield for 4-py and 2-thiophene derivatives (**Table 3**, Step 2 **entry 1** and **5**) whilst 3,4-methoxyphenol 84%, ^{t}butyl 89% and Cy 95% were made in good yield (**Table 3**, Step 2 **entry 2-4**). As the tertiary amines **150a-e** contained structurally variant groups there was a chance to observe some selectivity in the quaternisation reaction with methyl triflate. Ammonium salts **152a-d** were formed in wide-ranging yields, from 44% for **152d** (**Table 3**, Step 3 **entry 4**) to 93% for compound **152a** (**Table**

3, Step 3 **entry 1**) with both found in a 1:1 d.r. However with the formation of compounds **152b** and **152c** d.rs of 3:2 and 2:1 were obtained (**Table 3**, Step 3 **entry 2-3**).

Unfortunately, several attempts to alkylate **150e** did not yield the desired product. The inclusion of the additional nitrogen in the pyridine ring proved problematic and no evidence for formation of the expected corresponding ammonium salt **152e** was found (**Scheme 33**). The expected product **152e** was not detected when the reaction of the tertiary amine **150e** and methyl triflate took place. This result shows that although the central nitrogen (pK_a~10) is more nucleophilic than the pyridine nitrogen (pK_a~5.25), preferential pyridine alkylation occurs to give the kinetic product **156**. When trying to react further to form the bis-ammonium salt **157**, decomposition led to no recovered starting material or expected product.
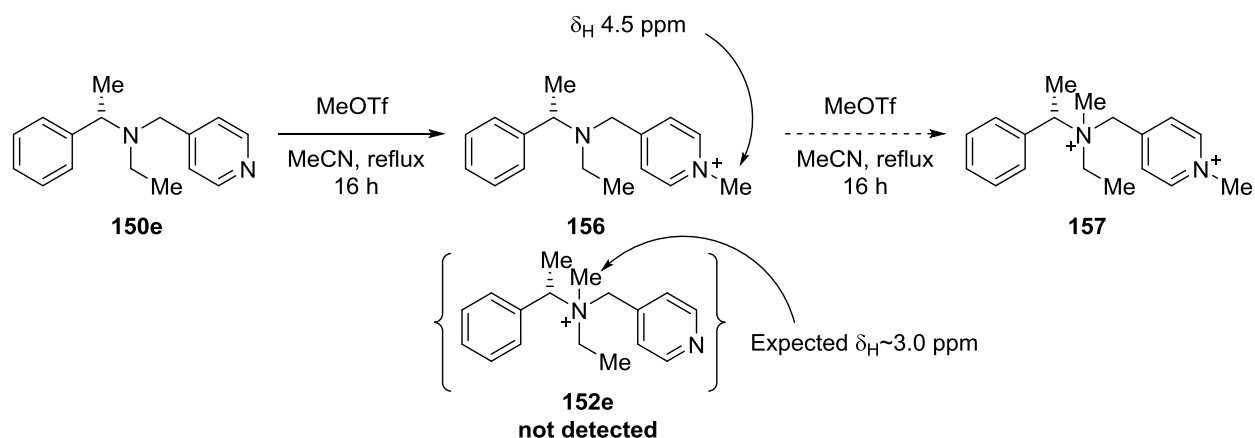
Scheme 33 attempted alkylation of tertiary amine when a pyridine was incorporated into the structure

Evaluation of similar ammonium salt derivatives (**Figure 30**) shows that it is difficult to explain the origin of diastereoselectivity in the quaternisation step.
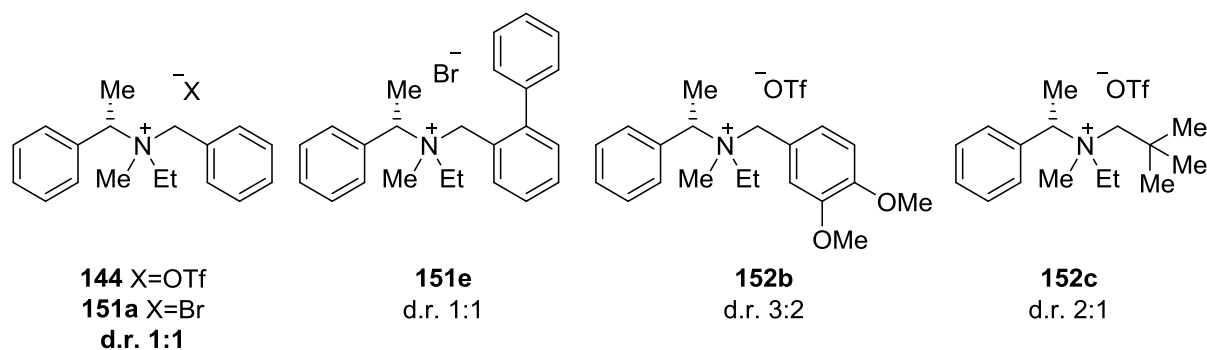
Figure 30 Similar structures but only find non 1:1 ratio in **152b** and **c**

It was decided that with a number of DASs (**144a** and **b**, **151a-e** and **152a-d**), efforts would be best directed towards establishing a method for separating the diastereoisomers.

3.2.1 Separation of 1ˢᵗ Gen DAS

As previously alluded to, fractional recrystallisation, enzymatic resolution and supercritical fluid chromatography (SFC) have been used to resolve/separate enantiomers (**Section 1.2**). It was therefore decided to concentrate on chromatographic techniques to separate the DAS described in the previous section.

Purification of the DAS (**144a** and **b**, **151a-e** and **152a-d**) used column chromatography (20:1 DCM:MeOH) initially, to remove the excess electrophile but was found not to be suitable for separation of the diastereoisomers. As a complementary alternative, preparative TLC was undertaken (20x20 cm, 50-100 mg per plate) to try and find conditions to separate the diastereomeric mixtures. Again the same exhaustive approach was taken to identify possible conditions for separation as well as trying to mimic C18 reverse-phase column conditions. Use of water: acetonitrile in varying ratios with TFA (0.05 mol%) as an additive still uncovered no separation of the diastereoisomers **144a** and **b**, **151a-e** and **152a-d**. It was thought that anion exchange could possibly aid the separation of the diastereoisomers, with a more diffuse counter-ion as oppose to the harder bromide.

A mixture of DAS **151e** and potassium hexafluorophosphate in acetone followed by aqueous work-up and extraction with DCM gave the desired product **158** in 85% yield (**Scheme 34**). ^{31}P and ^{19}F NMR spectroscopy confirmed the successful anion exchange. Repetition of the TLC, column chromatography and prep-TLC again gave no indication of separation or change in d.r.
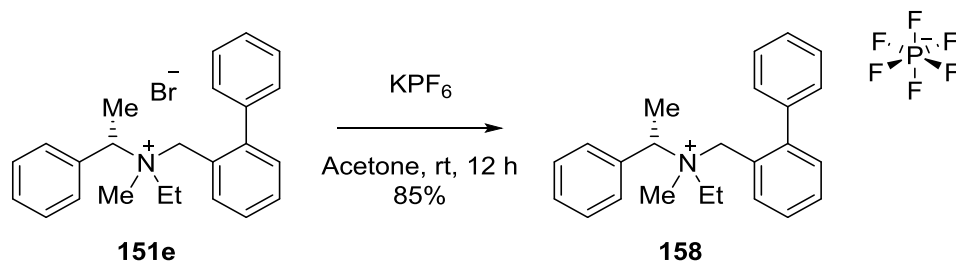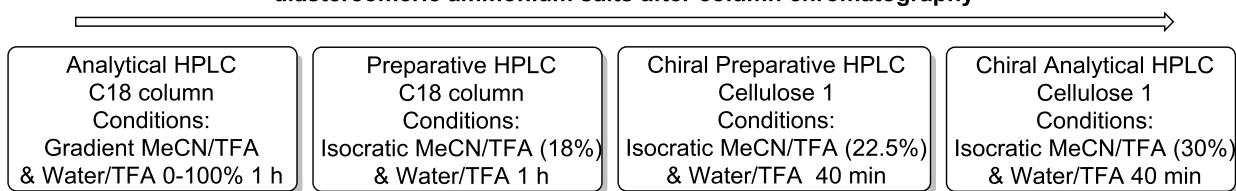

Scheme 34 Anion exchange of DAS **151e**

Efforts were directed to attempting recrystallisations, however no successful results were obtained after a thorough study of single solvent, co-solvent and diffusion conditions. The most promising conditions of dissolving in a minimum of hot acetonitrile followed by dropwise addition of diethyl ether gave rise to the formation of precipitate. However assessment of the precipitate showed that the ammonium salts were still in a 1:1 d.r. Efforts at trying to increase the observed non 1:1 d.r. result from the formation of **151b** and **151c** after a similarly rigorous study of solvents, temperatures and recrystallisation techniques also failed.

Having exhausted all options of resolution by laboratory methods, we explored HPLC as an alternative. In order to establish general conditions, compound **151a** was used as it was proposed that the introduction of any other functionality or increased steric bulk would enhance or at least affect the separation.

Analytical HPLC C18 column Conditions: Gradient MeCN/TFA & Water/TFA 0-100% 1 h	Preparative HPLC C18 column Conditions: Isocratic MeCN/TFA (18%) & Water/TFA 1 h	Chiral Preparative HPLC Cellulose 1 Conditions: Isocratic MeCN/TFA (22.5%) & Water/TFA 40 min	Chiral Analytical HPLC Cellulose 1 Conditions: Isocratic MeCN/TFA (30%) & Water/TFA 40 min

Baseline separation of the diastereoisomers of **151a** was achieved using an analytical chiral column (cellulose 1) confirmed by further analysis (^{1}H NMR spectroscopy and mass spectrometry). Evaluation of isolated DAS by ^{1}H NMR spectroscopy showed that single diastereoisomers were observed (some spectra are shown in appendix 7.1).

Due to the extensive HPLC work involved with resolution of the DAS, it was decided that efforts would be best spent in trying to synthesise more functionalised DAS with the expectation that increased diastereoselectivity could be incurred through inclusion of chemically diverse groups.

3.3 Second generation ammonium salts

- steric bulk
- π-surface
- Chiral amino-alcohol
- electron-poor benzyl group
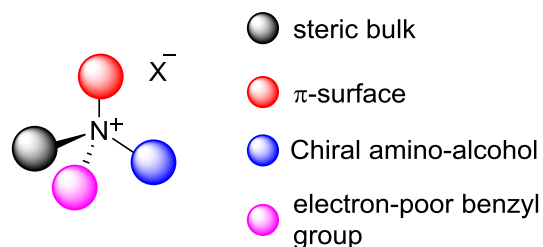
Figure 31 Ideal system components for 2nd gen DAS

Review of the literature allowed identification of various features common to PTCs (**Figure 31**). Desirable features were an electron poor *N*-benzyl group as this was thought to affect and hopefully improve enantioselectivity during PTC reactions.[110, 111] Many different π-surfaces have been used (Maruoka uses binaphthyl and cinchona alkaloids have quinoline units). Another common feature of many PTCs is an oxygen atom, in hydroxyl or ether functionality, two

carbons away from the nitrogen.[109-113] The synthesis of 2nd gen ammonium salts would be designed to explore incorporation of units such as these features.

Chiral amino alcohols **159a-c** were used in the formation of the 2nd gen DAS (**Scheme 35**). The reductive amination of the chiral amino alcohol **159** and aromatic aldehydes, for the most part, took place with good reproducible yields. Yields were affected when the α-methyl amino alcohol **159a** was reacted with 1-naphthaldehyde which afforded the corresponding secondary amine in 60% **160c** and in the case of the reaction with 4-quinolinecarboxaldehyde gave the product in 54% **160d**.
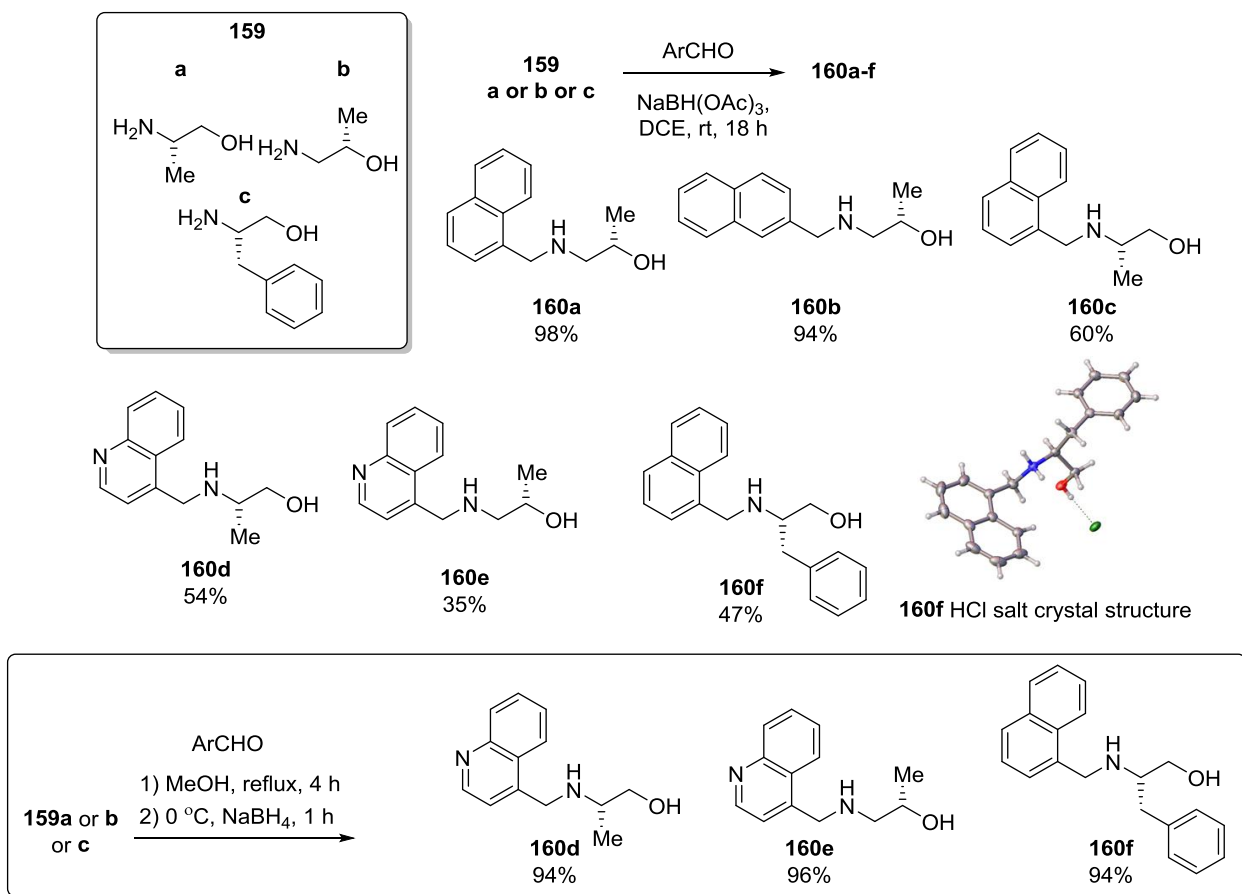
Scheme 35 Formation of 2nd gen secondary amines and crystal structure of the HCl salt of **160f** (appendix 7.2.1)

The lower yield in these cases of amines **160c, d** and **e** was due to the formation of a side product of type **161**. The tertiary amine **161** arises from a second reductive amination reaction involving

60

the intended secondary amine product **160c** (**Scheme 35**). An alternate strategy of secondary amine synthesis related to methodology widely used in the Fossey laboratory was used (**Scheme 35**).[114] Refluxing the aldehyde and the primary amine in an alcohol (MeOH or EtOH) provides the corresponding imine, which can then be reduced with sodium borohydride. This method was used to prepare **160d** in a higher yield, 94%. Use of (*S*)-phenylalaninol **159c**, led to a lower yield and the secondary amine **160f** was only formed in 47%, using the reductive amination with sodium triacetoxyborohydride, however when forming the imine and reducing it with sodium borohydride a much higher yield of 94% was obtained.
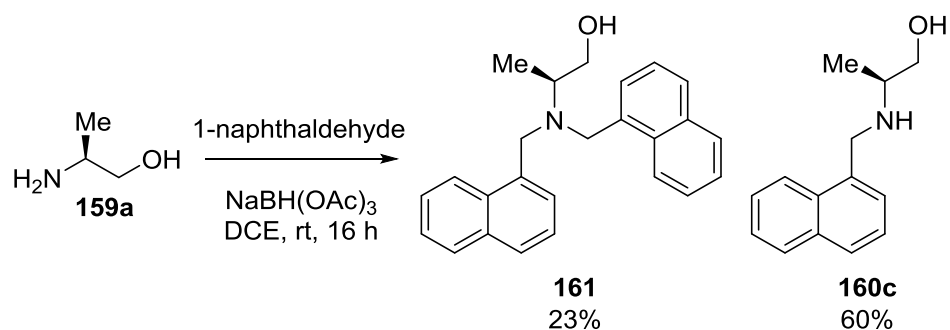
Scheme 36 Unexpected tertiary amine formation

Installation of an *N*-methyl group, using reductive amination of acetaldehyde, to give tertiary amines, proceeded in high yield for **162c** 82%**, 162d** 93% and **162g** 95% (**Scheme 36**) demonstrating that different amino alcohols could be tolerated under the reaction conditions. Yields were slightly lower for **162e** and **f** as the purification was far more challenging to remove the side products arising from the extra nitrogen in the amine starting material. Addition of butyraldehyde to **160a** and exposure to the reductive amination conditions with sodium triacetoxyborohydride gave the tertiary amine **162a** in a good yield of 80%, likewise the formation of the 2-naphthalene derivative **162b** from **160b** occurred in 82% yield.

acetaldehyde
or
butyraldehyde

160a-f $\longrightarrow$ **162a-g**

$NaBH(OAc)_3$,
DCE, rt, 18 h

162a
80%

162c
82%

162b
82%

162d
93%

162e
67%

162f
41%

162g
95%
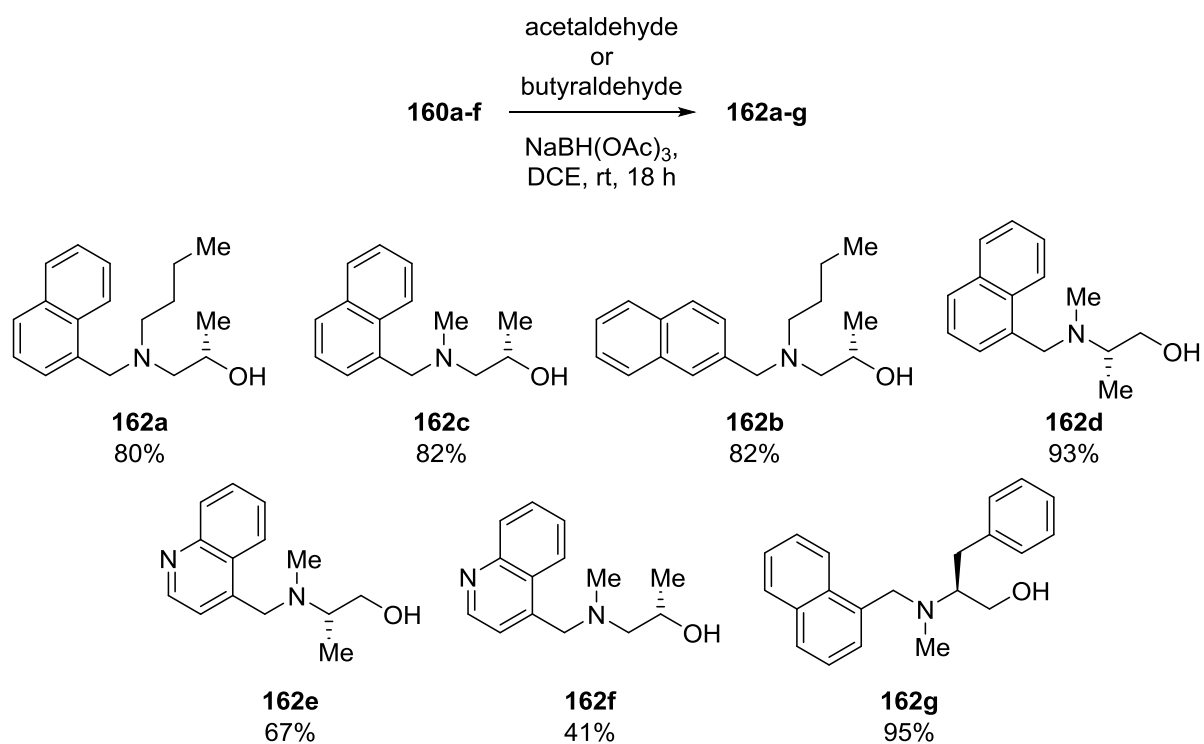
Scheme 37 Formation of 2nd gen tertiary amines

With the tertiary amines in hand, attempts at *N*-alkylation with a α-substituent proved difficult (**162d, e** and **g**). Although experimental evidence suggests the formation of DAS (TLC and ^{1}H NMR), the mass recovery was so poor that these were not studied further. Focus was spent on trying to synthesise DAS in a reproducible manner in meaningful amounts to attempt separation strategies. It was hypothesised that the *N*-alkylation of β-methyl amino alcohols would proceed with greater ease due to a less hindered *N*-centre, however lower diastereoselectivity was envisaged as the stereogenic centre was not in as close proximity to the nitrogen. Using standard quaternisation conditions (1.2 equiv of electrophile) the tertiary amines **162** (1 equiv) were subjected to a selected set of benzyl bromide derivatives in refluxing acetonitrile. Reactions proceeded in good yield with the exception of **162f** which could have been affected by the electronically deficient quinolyl unit

62

Systematic study of electronically neutral benzyl **163a** and **d**, electron-rich **163b** and **e** and electron-poor **163c** and **f** was undertaken (**Scheme 38**) to discern how the electronics of the benzyl derivatives affected levels of diastereoselectivity in the quaternisation step. Interpretation of ^{1}H NMR spectra obtained for second generation ammonium salts **163a-f** was extremely challenging. TLC analysis showed good conversions from starting materials, and upon isolation of the DAS mixture, salts from column chromatography were obtained (which would visibly transform into sticky oils rapidly upon removal of solvent under pressure) in variable yield. Establishing a distinct signal to compare the ratio of diastereoisomers was very challenging and very difficult to do consistently with both series of ammonium salts, **163a-c** and **d-f**.
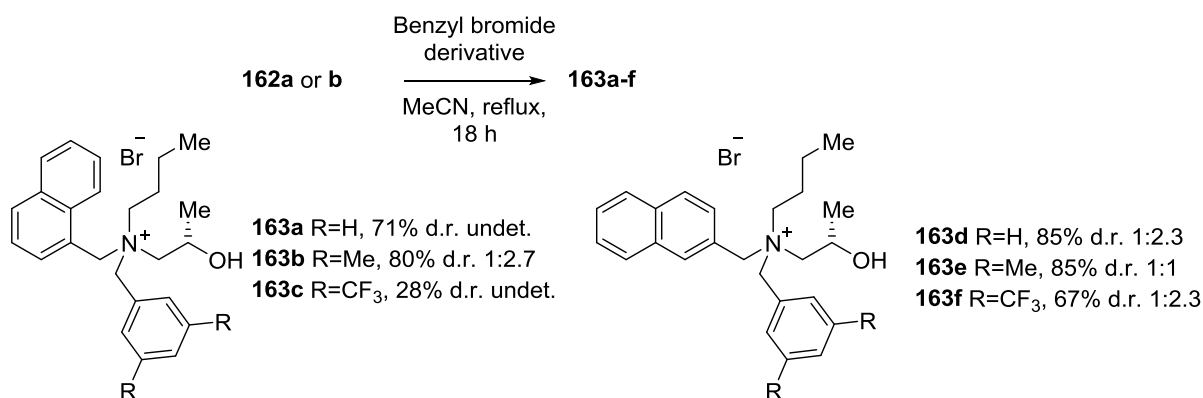
Scheme 38 2nd gen DAS formation

Having synthesised the 2nd-gen salts, with more diverse functionality, similar levels of separation in HPLC could be observed. It would have still required preparative-HPLC to separate the 2nd-gen diastereoisomers. The diastereoselectivity levels observed to this point were low, it was envisaged that increasing the d.r. would assist efforts at separation, so attention turned to the use of a cyclic amine (Section 3.4).

3.3.1 Work towards chiral-only-at-nitrogen ammonium salts

DAS formation offers a potential route to truly understand if chiral-at-nitrogen compounds have synthetic potential in enantioselective/asymmetric synthesis. This could be accomplished by

separation of DAS, followed by removal of the carbon stereogenic centre, which if an appropriate molecule and reactant were used would yield chiral only at nitrogen salts (**Scheme 39**). As previously mentioned ammonium salts are relatively unreactive and often require addition of a base (ylide formation) to induce rearrangements.[115, 116]
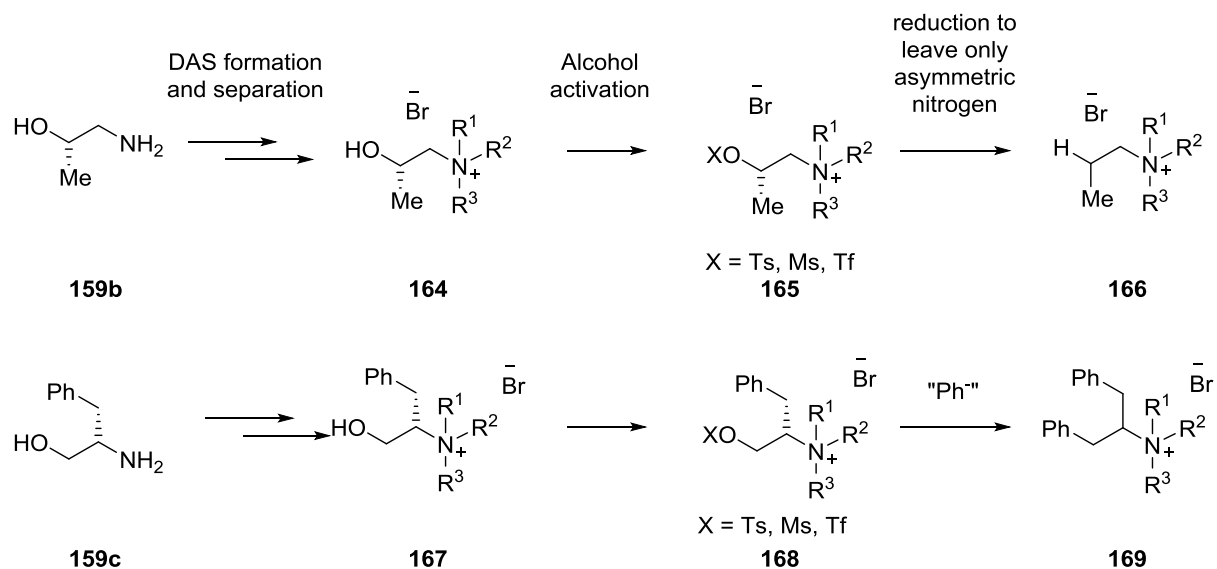
Scheme 39 Possible route to chiral only at nitrogen ammonium salts

The separation of 1st gen DAS, was a long and arduous task so the chemistry would have to be high yielding so as not to waste what would be precious material. The amino alcohols **159b** and **c** were selected as potential candidates that could be capable of transformation to chiral-only-at-nitrogen salts (**Scheme 39**). Following the same stepwise construction of the DAS, **164** and **167** attempts at separation of the DAS were theoretically possible. Then the isolated diastereoisomers of **164** or **167** could be used in further reactions. The hydroxyl group could be converted to a better leaving group **165** and **168** and then displaced with an appropriate nucleophile. It was thought that a hydride source could result in an *N*-propyl group **166**, whilst substitution with phenyl magnesium bromide would give **169**.
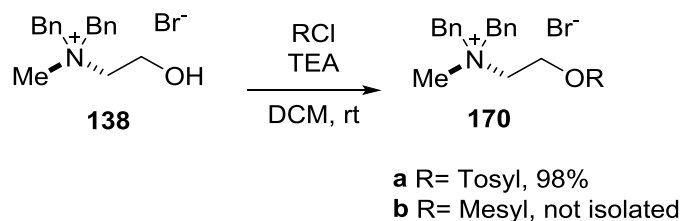
Scheme 40 Activation of the ammonium salt hydroxyl group

To test this hypothesis a control molecule **138** (**Scheme 40**) was synthesised and used to conduct preliminary experiments. Standard conditions to make sulfonate esters were used and converting the ammonium salt **138** to the tosylate 98% **170a** occurred with high yield. When attempting conversion to a mesyl group however, it was difficult to isolate any identifiable material and the starting material was recovered.

In trying to displace the tosylate **170a** (**Scheme 41**), sodium borohydride, lithium aluminium hydride and methyl Grignard were used but in all cases no desired product was formed according to TLC, ^{1}H or ^{13}C NMR spectroscopy and mass spectrometry. Use of water during the work-up led to substantial material loss as the salt was found to be quite soluble in water.

i) NaBH$_4$, MeOH, 0 $^{\circ}$C to rt,12 h (R=H)
ii) LiAlH$_4$, dry THF, 0 $^{\circ}$C to rt, 6 h, N$_2$ atmosphere (R=H)
iii) MeMgBr, dry toluene, 0 $^{\circ}$C to rt, 12 h, N$_2$ atmosphere (R=Me)
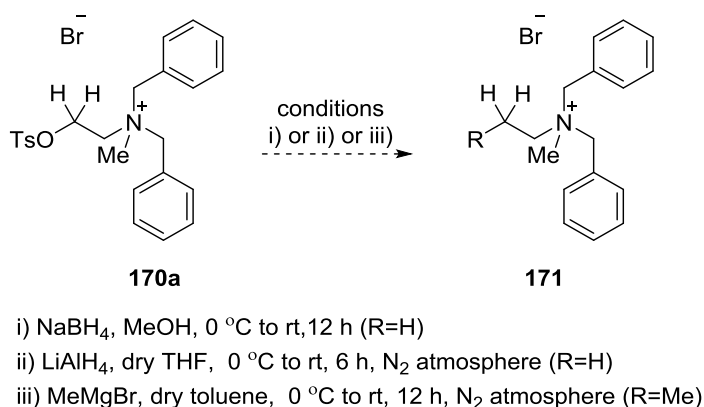
Scheme 41 Attempted displacement of activated alcohol

Revisiting the literature for deoxygenation reactions that could be compatible with ammonium salts offered the prospect of a direct deoxygenation (**Scheme 42**) using a silane and Lewis acid catalyst system.[117]
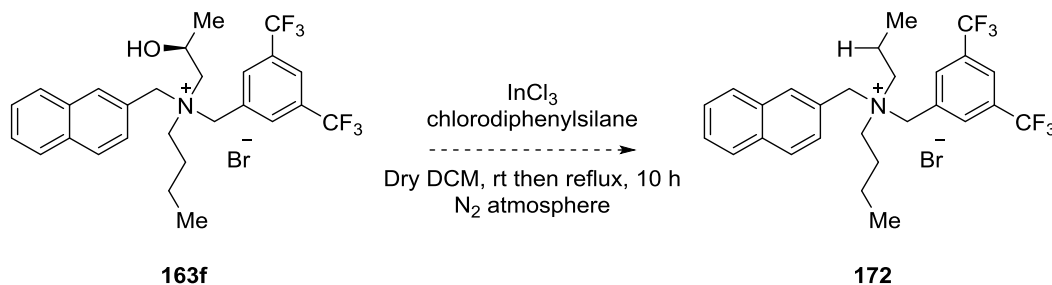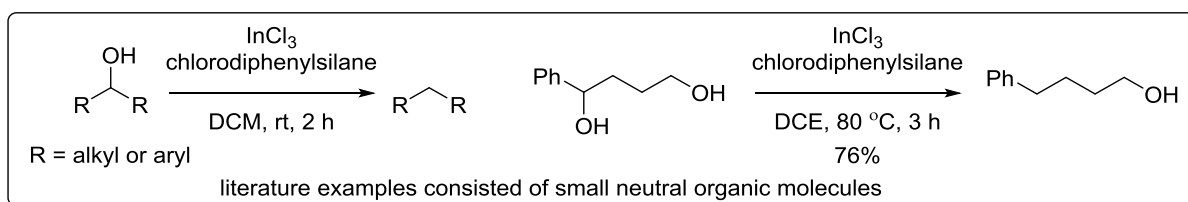
Scheme 42 Attempted Lewis acid-mediated deoxygenation

Baba and co-workers reported the selective deoxygenation of secondary alcohols with a chlorodiphenylsilane and catalytic indium trichloride system (**Scheme 42**).[117] Whilst their substrates were small simple organics, it was deemed worthwhile to attempt the procedure with ammonium salts. Following the reaction progress by TLC was again difficult as a complex mixture of products was obtained with similar R_f values to the starting material. The isolation of any single compound from work-up of the reaction mixture and column chromatography was difficult and mass recovery was again an issue (<30%). The literature procedure involved the addition of tetrabutylammonium fluoride (TBAF) to recover unreacted alcohol followed by pouring into diethyl ether and washing with water. Due to the potential hindrance of introducing another ammonium salt, the reaction was tried twice, once with and once without the addition of TBAF during the work-up procedure. However, TLC, MS, ^{19}F and ^{1}H NMR spectroscopy did not identify any of the target compound or starting material. Another reaction was tried circumventing the work-up procedure and trying to directly column the reaction mixture but unfortunately after the same analysis no identifiable products were isolated. It was thought the highly ionic nature of the ammonium salt substrate could interfere with Lewis acid co-ordination of the alcohol which instigates the reaction. Whilst these points were taken into account before

attempting the reactions, the actual outcome was unknown so whilst the substrate was far more complex than studied substrates, the chance of possible success validated efforts.
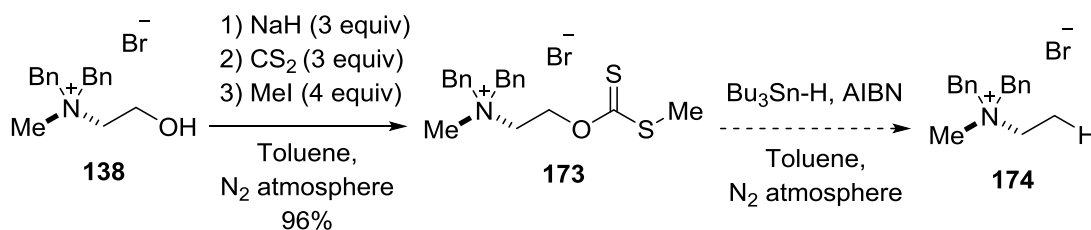
Scheme 43 Classical deoxygenation by Barton-McCombie reaction

Application of the Barton-McCombie deoxygenation could provide an alternative route to carry out the conversion of the hydroxyl group in the ammonium salt.[118] Xanthate formation of the hydroxyl group required the stepwise addition of sodium hydride (3 equiv), carbon disulfide (5 equiv) and methyl iodide (8 equiv). The xanthate functionality was successfully installed albeit with low yield 43% **173**. Simple modification (**Scheme 43**) of the amount of reagents added allowed it to be prepared in a very high yield, 96%. Removal of the xanthate group using tributyltin hydride and AIBN was attempted and although again the reaction mixture was difficult to analyse due to low mass recovery, mass spectrometry evidence was obtained for the formation of **224**. A peak of m/z 240.2 which correlates to the deoxygenated product was found giving credence to this approach. Much more work is required however to combine the separation of DAS along with this potential route to obtain chiral-only-at-nitrogen compounds.

3.4 Third generation ammonium salts
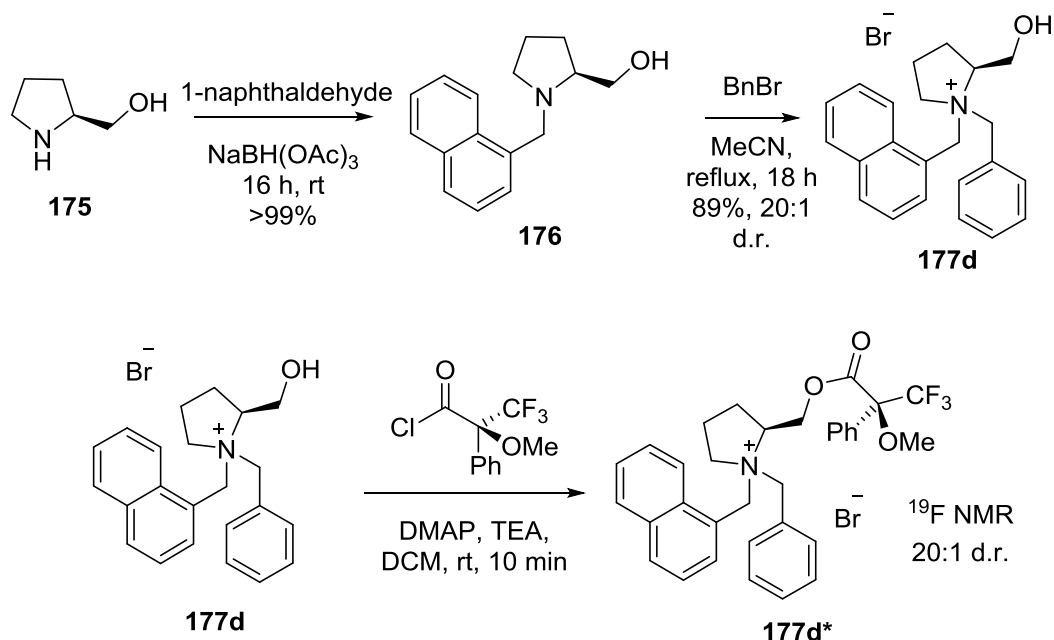
Scheme 44 Diastereoselective formation of ammonium salt **177d** and confirmation of ratio by Mosher's ester formation **178**

A lack of diastereoselectivity in the synthesis of acyclic DAS predominantly led to mixtures which were extremely difficult to separate. Improving the diastereoselectivity would hopefully offer a better chance of separation. As already mentioned, cyclic nitrogen-containing compounds have a lower inversion rate due to the ring strain involved. A readily available chiral cyclic amine is (S)-proline. Described as having a privileged structure it is easily modified for use as an asymmetric ligand.[119] Using (S)-(+)-2-pyrrolidinemethanol **175** in a reductive amination with 1-naphthaldehyde gave the cyclic tertiary amine **176** in excellent yield (**Scheme 44**). Quaternisation of amine **176** with benzyl bromide after refluxing overnight in acetonitrile gave the ammonium salt **177d** in 89% yield and d.r. of 20:1 measure by ^{1}H NMR spectroscopy. Confirmation of the d.r. by ^{19}F NMR spectroscopy of the ester **177d*** was also obtained.[120]
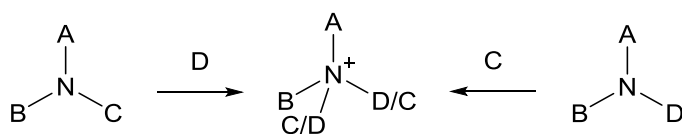
Scheme 45 Change order of addition to get reversal of selectivity

This diastereoselective formation of **177d** proved an excellent beginning to the study of cyclic amines. Buoyed by the result, the addition sequence (**Scheme 45**) was investigated to see if a reversal of diastereoselectivity could be obtained. Simple alteration of the addition sequence could be carried out to find if the diastereoselectivity could be reversed by changing the order in which "C" and "D" are introduced. This selectivity in formation of DAS was initially probed by Zhang and co-workers however no d.r. reported reached above 1:1.5 (**Figure 32**).[80]
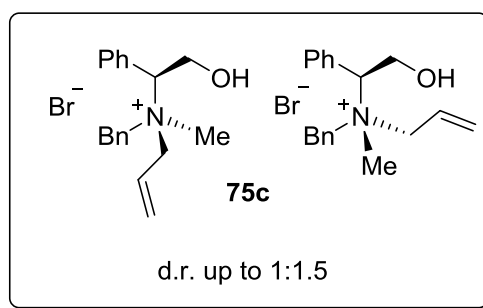
Figure 32 Zhang and workers diastereomeric ammonium salts

When the sequence of addition to form **177d** was altered, the opposite selectivity was observed suggesting that the tertiary amine configuration was the major contributory factor in diastereoselectivity observed in the quaternisation step (**Table 4 entry 4** and **8**). A similar result was observed when an *N*-alkyl substituent was introduced (**entry 1** and **5**) with no selectivity during the quaternisation using benzyl bromide to the tertiary amine. However, when 2-naphthaldehyde was added to the amine **175** and quaternised with benzyl bromide, it proceeded with 1:4 d.r. When this sequence was reversed, and alkylation of *N*-benzyl pyrrolidine with 2-bromonaphthalene was tried, the same levels of selectivity were observed for the opposite

diastereoisomer of 4:1 d.r. (**entry 2** and **6**). A similar result was obtained when using the

bistrifluoromethylphenyl substituent (**entry 3** and **7**) with selectivity of 4:1 and 1:3 d.r.

Table 4 Effect of addition order on d.r. in DAS formation

Entry	R	R^1	Compound	d.r.
1	Ph	C_3H_7	**178d**	1:4
2	Ph	2-naphth	**179d**	1:4
3	Ph	$3,5\text{-}(CF_3)_2C_6H_3$	**180d**	1:4
4	Ph	1-naphth	**177d**	1:1
5	C_3H_7	Ph	**178d**	1:1
6	2-naphth	Ph	**179d**	4:1
7	$3,5\text{-}(CF_3)_2C_6H_3$	Ph	**180d**	3:1
8	1-naphth	Ph	**177d**	20:1

These results showing a reversal of d.r. is possible were promising (**Table 4**) so a temperature

study was carried out to evaluate if lower temperatures can increase the diastereoselectivity.

Interrogation of any temperature effect on diastereoselectivity was probed by methylation of **176**

at -40 $^{\circ}$C (**Scheme 46**) and then allowing the reaction mixture to warm to room temperature

overnight; to form **182** and analysis of the crude mixture showed a d.r. of 10:1. Purification of the

crude reaction mixture gave the major diastereoisomer in 71% yield and 11:1 d.r. and also the

minor diastereoisomer was isolated in 14% yield with 1:10 d.r. Carrying out the reaction at room

temperature and at reflux, the DAS **182** was formed in 87% and 94% yield respectively with both

giving diastereoselectivity of 10:1.

Scheme 46 Temperature effect on formation of ammonium salt **235**
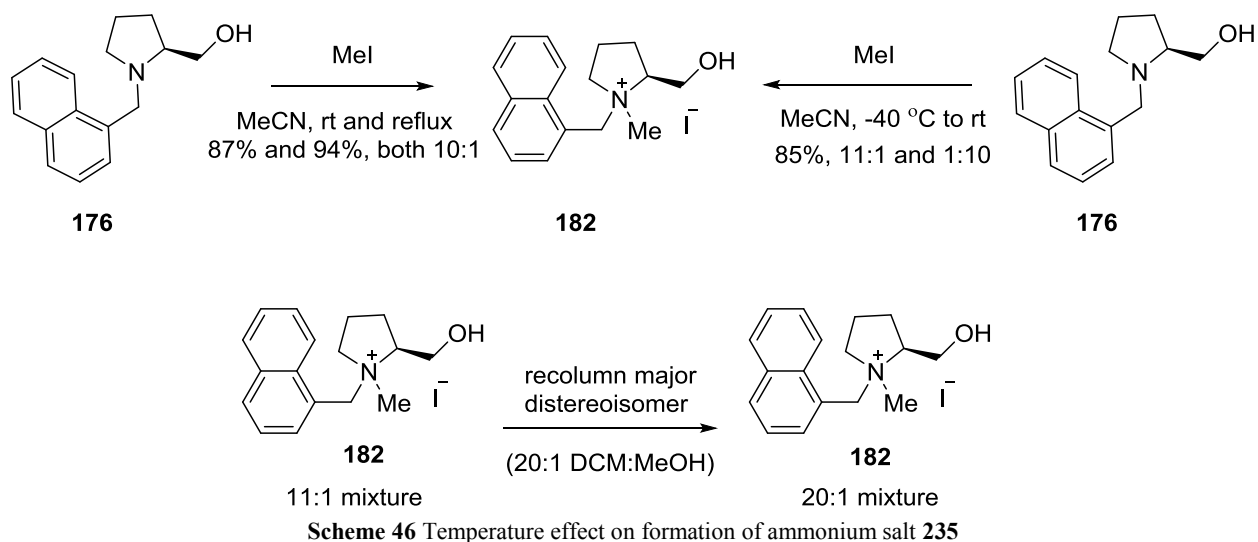
In going from **176** to **182** (**Scheme 46**) it was one of the few times when column chromatography achieved a reportable measure of success in the separation of diastereoisomers. Due to the larger ratio obtained, re-columning the major product increased the d.r. to 20:1. It was still not possible to determine the chirality-at-nitrogen so this sample was recrystallised from acetonitrile giving a single diastereoisomer which was analysed by x-ray crystallography and NMR experiments (**Figure 33**). Comparison of ^{1}H NMR spectra of the isolated diastereoisomer and the crude reaction mixture, show clearly that it was the major diastereoisomer isolated. The crystal structure shows the tetrahedral nitrogen environment where the *N*-methyl occupies the same face as the hydroxymethyl group and the naphthyl unit is pointing down giving a (*S*,*S*) stereochemical relationship for **182** (*N*$_S$). The *N*-methyl protons have an nOe interaction with the hydroxymethyl protons and 4-spin aromatic system interacts with the pseudo axial proton adjacent to the nitrogen. The hydroxymethyl group means the corresponding axial proton on the same carbon can see the 3-spin aromatic system. These results indicate that the tertiary amine's preference would be to have the *N*-naphthalen-1-ylmethyl down, *anti* to the hydroxymethyl group. So the origin of diastereoselectivity arises from the most stable conformer of the tertiary amine.

nOe Interactions observed in ¹H NMR spectroscopy

182 (*N*ₛ)
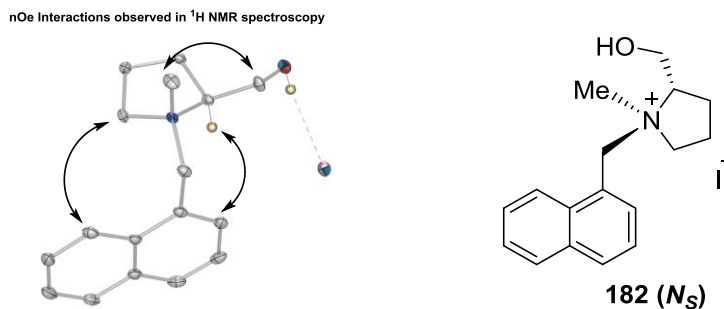
Figure 33 Crystal structure of **235** with ellipsoids drawn at the 50 % probability level, nOe interactions (appendix 7.2.2)

Having gained some insight into the selectivity involved with the prolinol system, it was decided to synthesise a library of DAS to explore the varying diastereoselectivity that arises from electronically and sterically diverse groups.

Construction of a series of tertiary amines (**Scheme 47**) and reaction with a series of different alkylating agents (**Figure 34**) by medium-throughput synthesis would lead to a large amount of compounds (**Table 6-18** with the results summarised in **Table 5**) which could be compared in terms of yield and d.r. obtained and then tested as PTCs to assess the effect of the stereogenic nitrogen. Due to the difficulty in separating the epimeric mixtures, it was decided to compile a library and carry out a hit-to-lead type search for catalytic activity. It was envisaged one (or more) of the compounds would stand-out when used as a PTC and efforts would be concentrated on separation of that specific example(s). The tertiary amines were all made by our established reductive amination procedure on a 15 mmol scale with good yield except for **194**. The pentafluoro substitution may inhibit hydride delivery to the iminium intermediate generated due to the highly polarised C-F bonds resulting in electrostatic repulsion, which may account for the lower yield. The tertiary amines were selected as several trends could be studied through the series. Compounds with benzyl, phenethyl and phenylpropyl substituents were selected to investigate the effect of changing the linker length from the phenyl ring to the nitrogen.
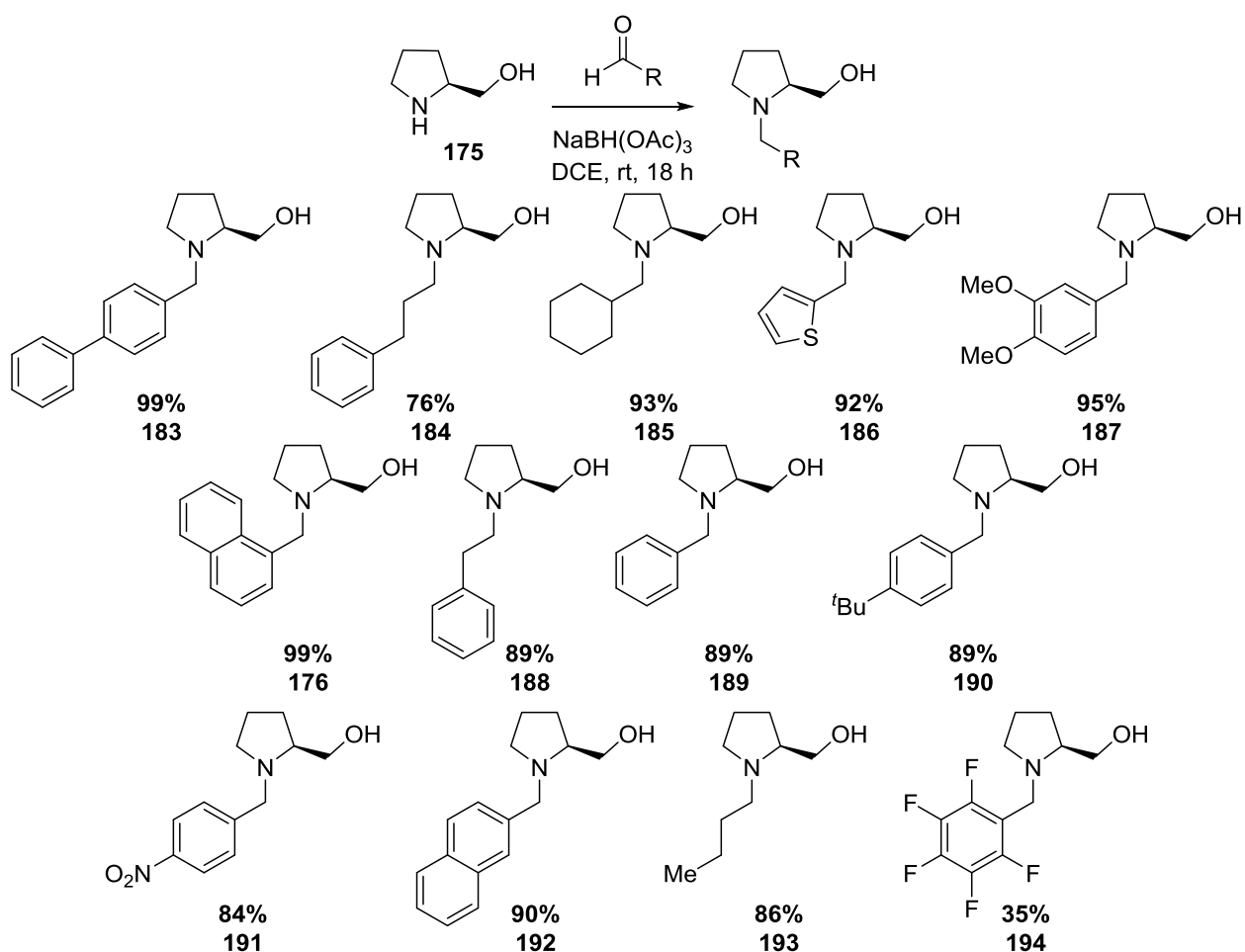
Scheme 47 Series of prolinol-derived tertiary amines

To investigate non-aromatic substituents, cyclic (*N*-cyclohexymethyl) and acyclic (*N*-butyl) variants were made to study any significant effects from subsequent quaternisation. A variety of para-substituted benzyl derivatives were investigated so that phenyl *vs* tert-butyl *vs* nitro *vs* hydrogen could be evaluated, as well as comparison of larger aromatic groups, 1-naphthyl and 2-naphthyl. Due to trouble of alkylating tertiary amines with quinoline units it was decided that they would not be used as regioselectivity would become an issue. Electron-rich (methoxy groups) and electron-poor (pentafluoro substituted) aromatics as well as heteroaromatics would also be investigated.

A similar approach was taken with the choice of alkylating agents. Based on previous experience of failed quaternisation of tertiary amines with neopentyl bromide, iodoethane, 1-bromohexane

and very long reaction time with 1-bromobutane these alkyl halides were not considered for use. Although iodomethane could successfully undergo the quaternisation with tertiary amine **176** (**Scheme 46**) with good selectivity (11:1 d.r.), due to a lack of reported asymmetric PTCs containing *N*-methyl groups it was decided they would not be included either. Survey of the literature also showed that there are no examples of asymmetric PTCs with *N*-methyl groups. Discussions (Professor Guy Lloyd Jones and Professor Mike Willis) also highlighted that ammonium salts could potentially be used as methylating agents, although the literature did not support these claims it was decided to avoid the use of such a small group due to lack of evidence in its application. The addition of benzyl bromide to tertiary amine **176** in excellent yield and selectivity to make **177d** (**Scheme 44**) encouraged screening a series of benzyl bromide derivatives in the quaternisation reaction.
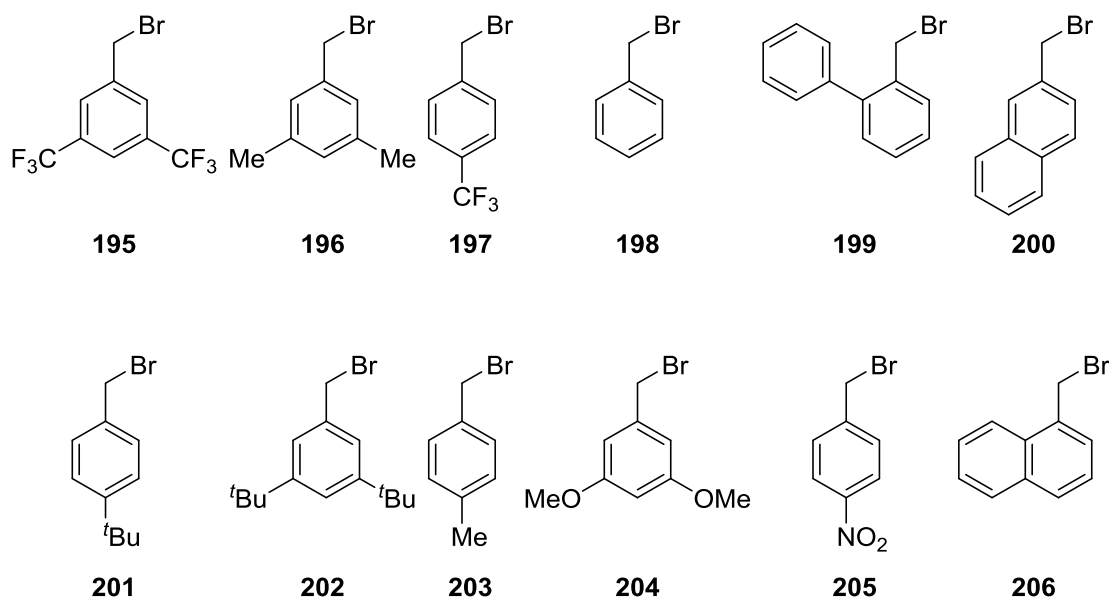
Figure 34 Range of benzyl bromide derivatives used to quaternise tertiary amines

A range of 3,5-disubstituted benzyl derivatives were used to directly compare both steric and electronic effects, H *vs* Me *vs* tert-butyl and OMe *vs* H *vs* CF$_3$. Similar compounds were selected to gauge para-substituted effects with H *vs* Me *vs* tert-butyl and also the electron withdrawing

groups CF_3 and NO_2. Again larger aromatics were used and 2-phenyl benzyl *vs* 1-naphthyl *vs* 2-naphthyl to see if the increase in size and possibility for π-stacking could have any influence on the diastereoselectivity of the quaternisation step.

In order to simplify the results obtained from generation of a large amount of ammonium salts the average d.r. recorded for each tertiary amine series and then each alkylating agent is shown (**Table 5**). It is indicative of the observed trends highlighting that the **194** perfluorinated amine (1:26 d.r.) gave better results as did benzyl bromide **198** (1:14 d.r.) and *'*butylbenzyl bromide **201** (1:6 d.r.). The lowest d.r. obtained were for salts derived from amine **184** which has a propyl linker between the phenyl and nitrogen (ave=1:2). What was surprising is that the *N*-butyl derived DAS (ave=1:3) **193** did not have the lowest set of d.r. as it is conformationally unrestricted. The electrophile that gave the poorest selectivity was 2-phenylbenzyl bromide **199** (ave=1:3) closely followed by 1-bromomethylnaphthalene **206** (ave=1:3).

Table 5 Average and range of d.r. obtained for prolinol-derived ammonium salts

Reaction scheme: pyrrolidine-2-ylmethanol (N–R, 2-(hydroxymethyl)) + Br–CH₂–R¹ → quaternary ammonium salt (R–N^+, R^1), Br^-; MeCN, reflux, 18 h

Entry	1	2	3	4	5	6	7	8	9	10	11	12	13
Ave d.r.	4	2	2	3	4	3	2	3	5	3	5	3	26
d.r. range	2-6	1-2	1-4	2-4	2-6	2-3	1-4	1-5	2-10	1-4	2-7	1-8	2->99
R	biphenyl-CH₂	Ph(CH₂)₃	Cy-CH₂	thiophen-2-yl-CH₂	3,4-(MeO)₂C₆H₃CH₂	naphthalen-1-yl-CH₂	Ph(CH₂)₂	Bn	4-ᵗBu-C₆H₄CH₂	4-O₂N-C₆H₄CH₂	naphthalen-2-yl-CH₂	C₄H₉	2,3,4,5,6-pentafluorobenzyl-pyrrolidinylmethanol

Entry	14	15	16	17	18	19	20	21	22	23	24	25
Ave d.r.	4	4	4	14	3	3	5	6	4	5	3	3
d.r. range	1-8	1-6	1-5	1->99	1-4	1-5	1-10	1-17	1-8	2-11	1-5	1-6
R¹	3,5-(CF₃)₂C₆H₃CH₂	3,5-Me₂C₆H₃CH₂	4-CF₃-C₆H₄CH₂	Bn	biphenyl-2-yl-CH₂	naphthalen-2-yl-CH₂	4-ᵗBu-C₆H₄CH₂	3,5-ᵗBu₂C₆H₃CH₂	4-Me-C₆H₄CH₂	3,5-(OMe)₂C₆H₃CH₂	4-O₂N-C₆H₄CH₂	naphthalen-1-yl-CH₂

Purple indicates highest diastereoselectivity and is universally applied to all following tables in this Chapter

All d.r. reported are in a ratio to 1

Table 6 Ammonium salts derived from parent amine **183**

Entry	1	2	3	4	5	6
R	F$_3$C / F$_3$C substituted benzyl	Me / Me substituted benzyl	4-CF$_3$ benzyl	phenyl	2-Ph benzyl	naphthalene
	a	**b**	**c**	**d**	**e**	**f**
Yield (%)	87	83	86	99	87	99
d.r.	1:6	1:5	1:5	1:4	1:2	1:3
Entry	7	8	9	10	11	12
R	4-^{t}Bu benzyl	^{t}Bu / ^{t}Bu substituted benzyl	4-Me benzyl	MeO / MeO substituted benzyl	4-NO$_2$ benzyl	naphthalene
	g	**h**	**i**	**j**	**k**	**l**
Yield (%)	81	99	99	85	61	69
d.r.	1:5	1:6	1:5	1:4	1:2	1:2

Alkylation of amine **183** with bromides **195-206** occurred with yields ranging from 61-99% (**Table 6**). A significant drop was observed for alkylation with *p*-nitrobenzyl bromide and 1-bromomethylnaphthalene giving salts **207k** and **l** in 61% and 69% respectively, they, along with DAS **207e** had the lowest d.r. of 1:2. Higher selectivity was observed for the salts arising from quaternisation with bis-3,5-trifluoromethylbenzyl bromide **207a** and bis-3,5-^{t}butylbenzyl bromide **207h** with d.r. 1:6. The bulky aromatics did not fare as well as 3,5-disubstituted or 4-substituted compounds so the overriding factor affecting the diastereoselectivity appeared to be the substitution pattern of the electrophile in the quaternisation step as oppose to any electronic effects.

Table 7 Ammonium salts derived from parent amine **184**

Entry	1	2	3	4	5	6
R	F$_3$C, F$_3$C (3,5-bis(trifluoromethyl)phenyl)	Me, Me (3,5-dimethylphenyl)	4-CF$_3$-phenyl	phenyl	Ph (2-phenylphenyl)	2-naphthyl
	a	**b**	**c**	**d**	**e**	**f**
Yield (%)	99	99	78	99	99	99
d.r.	-	-	1:1	1:1	1:1	1:2

Entry	7	8	9	10	11	12
R	4-^{t}Bu-phenyl	^{t}Bu, ^{t}Bu (3,5-di-tert-butylphenyl)	4-Me-phenyl	MeO, MeO (3,5-dimethoxyphenyl)	4-NO$_2$-phenyl	1-naphthyl
	g	**h**	**i**	**j**	**k**	**l**
Yield (%)	85	99	99	99	99	94
d.r.	1:1	1:2	1:2	1:2	1:1	1:2

X-ray crystal structure obtained for highlighted entry (**Figure 35**)

Compounds **208a-l** were all formed with excellent yields (94-99%) with only two being formed moderately, **207c** and **g** 78% and 85% respectively (**Table 7**). This series experienced the lowest d.r. in the quaternisation and only compounds **208f**, **h**, **i**, **j** and **l** (1:2 d.r.) were obtained in a non 1:1 ratio.

Diastereomeric ammonium salt **208f** was recrystallised from chloroform and two drops of methanol with slow evaporation to give a single compound **208f** (*N$_R$*) (**Figure 35**). Many of the DAS formed from tertiary amine **184** were low melting point solids and attempts to recrystallise these related compounds were unsuccessful. Although formed in lower d.r. **208f** again shows that the tertiary amine adopts a conformation where the phenylpropyl linker is *trans* relative to the hydroxyl methyl group, with the electrophile adding *cis* to the hydroxymethyl group.
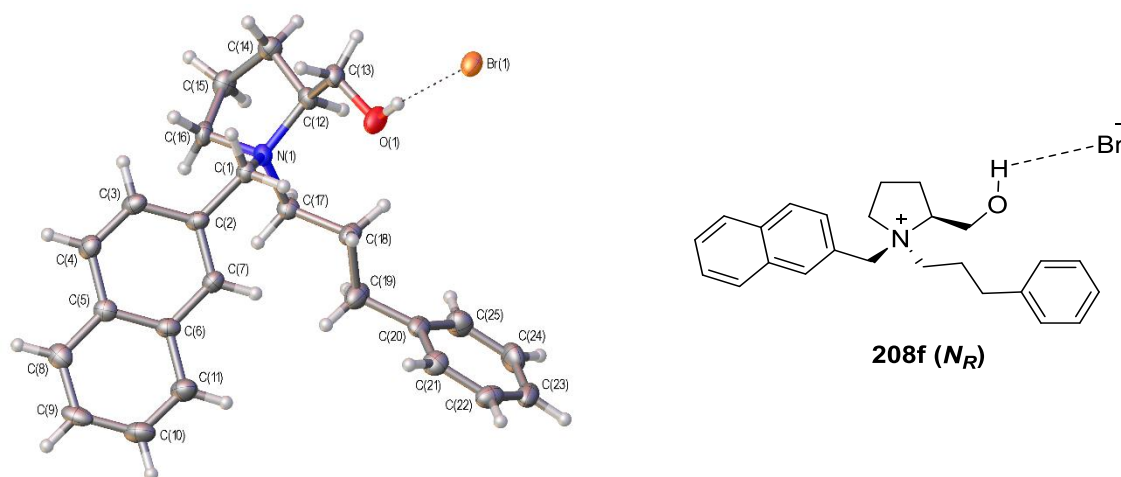
Figure 35 X-ray crystal structure of **208f** with ellipsoids drawn at the 50 % probability level. (appendix 7.2.3).

The tertiary amine **185** showed a consistently lower set of yields illustrating a decreased level of nucleophilicity during quaternisations to form compounds **209a-l** (**Table 8**). Alkylation of amine **185** with 2-bromomethylnaphthalene gave the highest yield, 94% to form **209f** however this was only accomplished with 1:2 d.r. Comparison with the electrophile 1-bromomethylnaphthalene whilst added in a lower yield had a slightly higher selectivity of 1:3 d.r. **209l**. The highest ratio (1:4 d.r.) obtained was in the reaction with 2-phenylbenzyl bromide which provided DAS **209e** in 76% yield.

No diastereoselectivity was observed for alkylations with bis-trifluoromethylbenzyl bromide and *p*-nitrobenzyl bromide, yields of the salts were 60% **209a** and 74% **209k**. 3,5-Disubstituted benzyl halides regardless of electronic factors were used to alkylate the amine **185** with 1:2 d.r. observed and the salts forming in similar yields of 82% **209b**, 74% **209h** and 71% **209j**. Similar effects were observed with the remaining *p*-substituted electrophiles where 1:2 d.r. and moderate yields 69% **209c**, 74% **209g** and 72% **209i** were achieved during DAS formation.

Table 8 Ammonium salts derived from parent amine **185**

Entry	1	2	3	4	5	6
R						
	a	b	c	d	e	f
Yield (%)	60	82	69	89	76	94
d.r.	1:1	1:2	1:2	1:2	1:4	1:2

Entry	7	8	9	10	11	12
R						
	g	h	i	j	k	l
Yield (%)	74	74	72	71	74	68
d.r.	1:2	1:2	1:2	1:2	1:1	1:3

When amine **186** was treated to the same alkylation conditions, the reintroduction of an aromatic substituent in the tertiary amine saw an increase in yield where all reactions proceeded in 94-99% (**Table 9**). Only the salts derived from reaction with bis-trifluoromethylbenzyl bromide **210a,** 84%, *p*-nitrobenzyl bromide **210k,** 74% and 1-bromomethylnaphthalene **210l**, 71% did not reach that level of efficiency. The DAS **210a**, **b**, **h** and **j** all display a 1:4 ratio which all have the 3,5-disubstituted benzyl derivative. The sizes of the 3,5-disubstituted groups are very different and as the substituent is increased from a proton **210d** (1:3 d.r.), then regardless of electronic nature, methyl **210b**, methoxy **j**, trifluoromethyl **a** and tert-butyl **h** all give d.r. of 1:4. The salt formed from addition of *p*-methylbenzyl bromide **210i**, was slightly lower in 1:3 ratio and when bulkier aromatics were used in the reaction, 2-phenylbenzyl bromide **210e** and 2-bromomethylnaphthalene **210f** a moderate 1:2 ratio was observed.

Table 9 Ammonium salts derived from parent amine **186**

Reaction: **186** + R-CH₂-Br (**195-206**), MeCN, reflux 18 h → **210a-l**

Entry	1	2	3	4	5	6
R	F_3C / F_3C benzyl	Me / Me benzyl	benzyl-CF_3	phenyl	Ph (ortho)	naphthyl
	a	**b**	**c**	**d**	**e**	**f**
Yield (%)	84	99	94	99	99	99
d.r.	1:4	1:4	1:3	1:3	1:2	1:2

Entry	7	8	9	10	11	12
R	^tBu / ^tBu benzyl	^tBu / ^tBu benzyl	Me benzyl	MeO / MeO benzyl	NO_2 benzyl	naphthyl
	g	**h**	**i**	**j**	**k**	**l**
Yield (%)	99	96	99	99	74	71
d.r.	1:4	1:4	1:3	1:4	1:2	1:2

In the case of amine **187** (**Table 10**), the best diastereoselectivity was observed with larger electrophiles such as the reaction with 1-bromomethylnaphthalene giving the DAS **211l** with a d.r. of 1:6. Addition of the other regioisomer, 2-bromomethylnaphthalene took place with much better yield, 96% but selectivity suffered, reducing to 1:3 **211f**. Benzyl bromide was reacted with amine **187** to give the corresponding DAS **211d** in good yield and with selectivity of 1:4. The more sterically demanding 2-phenylbenzyl bromide was reacted with the amine **187** in higher yield 96% and selectivity of 1:3 to give salt **211e**. The results for reactions with *p*-substituted alkylating agents display similar selectivity with **211c** and **g** in 1:5 d.r. and also good yields of 99 and 92% respectively. When using *p*-tolylbenzyl bromide in the reaction to form **211i**, high yield 99% and 1:4 d.r. was found but when compared with the nitro group **211k**, the yield drops off dramatically to 54% and selectivity drops to 1:2 d.r. The salt **211a**, with a 3,5-bistrifluoromethyl benzyl group, was formed with the lowest selectivity of 1:2 and lowest yield of these derivatives 73%. When **187** was alkylated with the

dimethyl **211b** (99%,1:4 d.r.), di-*tert*-butyl **211h** (99%, 1:5 d.r.) and dimethoxy **211h** (99%, 1:4 d.r.) yields and ratios were found to be higher.

Table 10 Ammonium salts derived from parent amine **240**

Entry	1	2	3	4	5	6
R						
	a	b	c	d	e	f
Yield (%)	73	99	99	83	96	96
d.r.	1:2	1:4	1:5	1:4	1:3	1:3
Entry	7	8	9	10	11	12
R						
	g	h	i	j	k	l
Yield (%)	92	99	99	99	54	47
d.r.	1:5	1:5	1:4	1:4	1:2	1:6

Consistent but moderate selectivity was observed in quaternisations of **176** with only addition of bistrifluoromethyl and p-nitro benzyl derivatives (both 1:2 d.r.) to give salts **177a** and **k** not occurring in 1:3 ratio (**Table 11**). It can be deduced that the effects of the electrophiles had no overbearing influence over the transition states involved with quaternisation of amine **176** and the controlling effect must come from the tertiary amine. Yields were affected with the reactions of electron-poor benzyl derivatives that led to salts being formed in lower yields notably **177a** 46%, **177c** 68% and **177k** 65%. The control compound **177l** was formed and x-ray crystal structure obtained, it would be used in PTC reactions to compare with chiral-at-nitrogen compounds with regard to the effective asymmetric performance of these 3rd-gen ammonium salts.

Table 11 Ammonium salts derived from parent amine **176**

Entry	1	2	3	4*	5	6
R	a	b	c	d	e	f
Yield (%)	46	93	68	99	72	84
d.r.	1:2	1:3	1:3	1:3	1:3	1:3
Entry	7	8	9	10	11	12
R	g	h	i	j	k	l
Yield (%)	99	87	99	98	65	65
d.r.	1:3	1:3	1:3	1:3	1:2	-

*When previously synthesised on a 1 mmol scale (0.2 M) 20:1 d.r. was obtained but when repeating the reaction with this series it was carried out under similar conditions (0.1 M) and a reduced d.r. was found so for consistency it is used here and both ^{1}H NMR spectra were reported for the differing d.r. obtained.
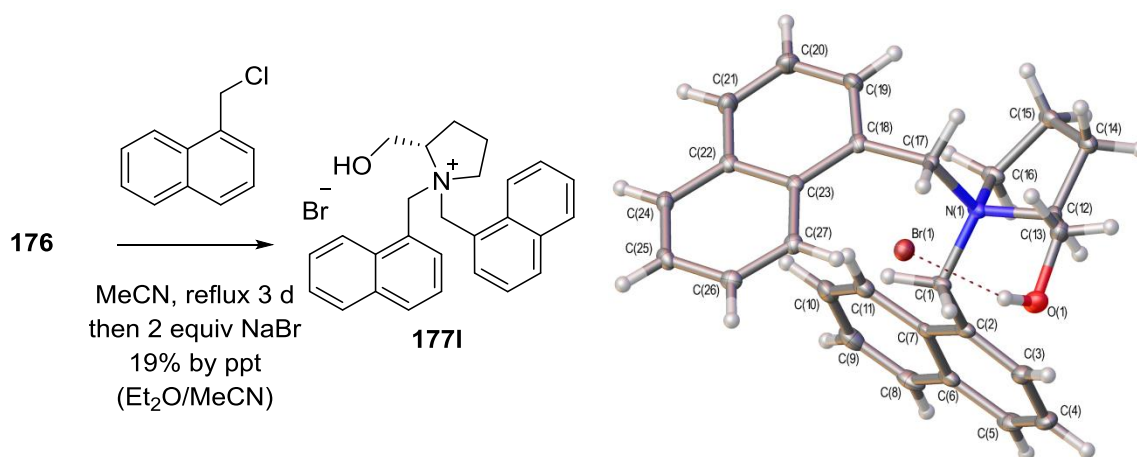
Figure 36 Crystal structure of **177l** with ellipsoids drawn at the 50 % probability level and atomic labelling given. Hydrogen bonding is shown using a dashed line (appendix 7.2.4).

Table 12 Ammonium salts derived from parent amine **188**

Entry	1	2	3	4	5	6
R	F$_3$C / F$_3$C benzyl	Me / Me benzyl	4-CF$_3$ benzyl	benzyl	Ph benzyl (ortho)	naphthyl
	a	b	c	d	e	f
Yield (%)	83	85	87	97	89	95
d.r.	1:1	1:2	1:1	1:2	1:1	1:2

Entry	7	8	9	10	11	12
R	4-^{t}Bu benzyl	^{t}Bu / ^{t}Bu benzyl	4-Me benzyl	MeO / MeO benzyl	4-NO$_2$ benzyl	naphthyl
	g	h	i	j	k	l
Yield (%)	99	98	82	20	87	55
d.r.	1:2	1:2	1:1	1:4	1:3	1:3

Low diastereoselectivity was recorded in the formation of DASs **212a-l** derived from *N*-phenethylprolinol **188** (**Table 12**). **212j** was formed in the greatest d.r. of 1:4 however in only 20% yield. During the formation of **212l** (55%, 1:3 d.r.) slightly higher selectivity was observed compared with **212f** (95%, 1:2 d.r.) although the reaction proceeded in much lower yield. No diastereoselectivity was observed for compounds **212a**, **c** and **i** with yields of 83, 87 and 82% respectively. **212g** (99%, 1:2 d.r.) which has a 4-*tert*-butyl group on the benzyl substituent and a slightly higher d.r. was found forming the salt **212k**, 87% and 1:3. Other 3,5-benzyl derivatives **212b** and **h** were formed with good yield 85% and 98% but selectivity for both is 1:2 which was eclipsed by compound **212j** with a d.r. of 1:4.

Although formed in a 1:1 ratio, **212e** was successfully recrystallised (**Figure 37**) and the X-ray crystals were recovered and comparison of the ^{1}H NMR spectra of **212e(N_S)** with the crude reaction mixture **212e** shows a well-defined spectra (**Figure 38**).
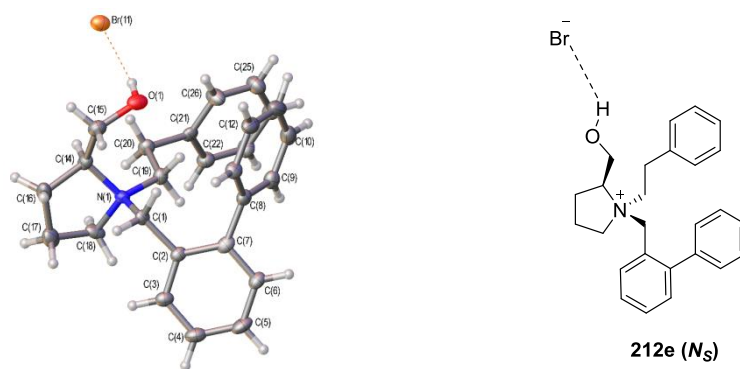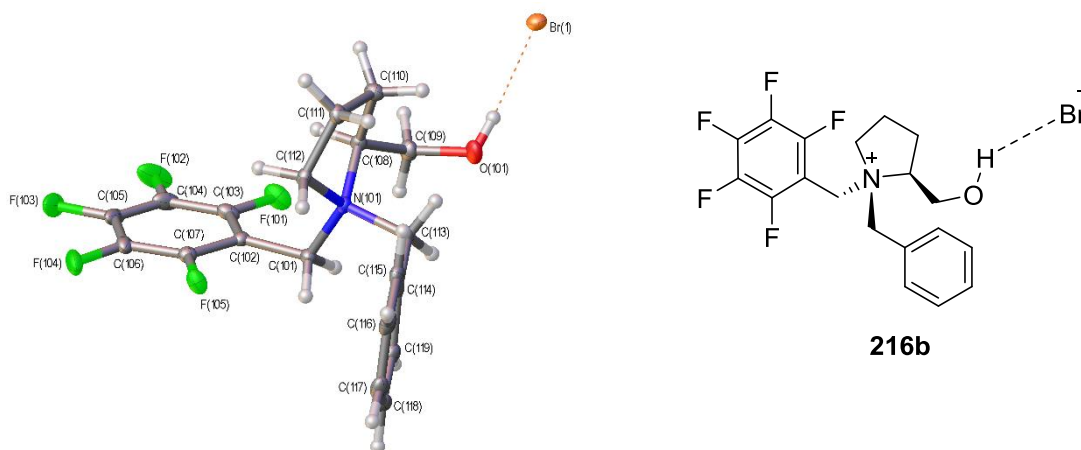
Figure 37 Crystal structure of **212e(N_S)** with ellipsoids drawn at the 50 % probability level. Hydrogen bonding is shown using dashed lines.
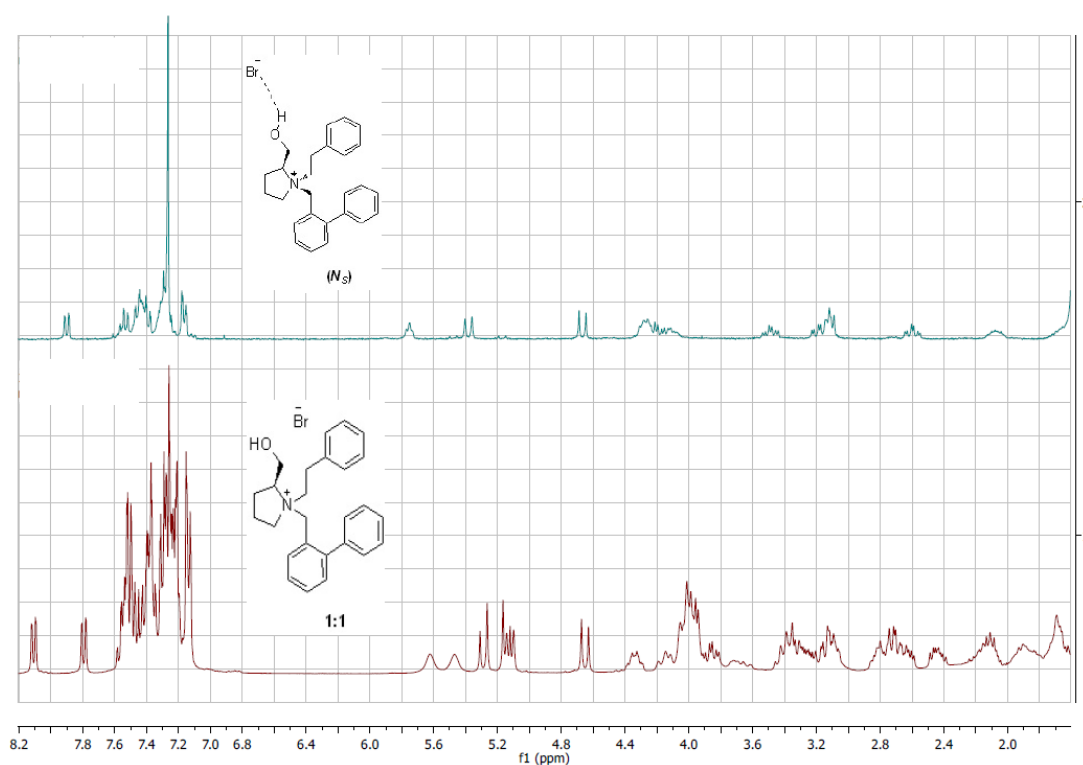
Figure 38 ^{1}H NMR spectra comparison of single crystal of **212e(N_S)** with original 1:1 mixture of diastereoisomers

The reaction of the bulky 1-bromomethylnaphthalene with amine **189** led to a 1:1 d.r. with reasonable yield 71% **177d** (the reversal of addition of the *N*-branches resulted in a 1:20 ratio-**Table 4**). Addition of benzyl bromide to the amine **189** in high yield 97%, leads to forming *NN*-dibenzyl prolinium bromide **213c** (**Table 13**).

Table 13 Ammonium salts derived from parent amine **189**

HO‑[pyrrolidine N-benzyl] **189** + R–CH₂Br **195-206** → (MeCN, reflux, 18 h) → **213a-i, 177d, 179d, 180d**

Entry	1	2	3	4	5	6
R	3,5-(CF₃)₂-benzyl	3,5-Me₂-benzyl	4-CF₃-benzyl	benzyl	2-Ph-benzyl	naphthyl
	180d	a	b	c	d	**179d**
Yield (%)	85	87	73	97	81	82
d.r.	1:2	1:4	1:4	-	1:2	1:2

Entry	7	8	9	10	11	12
R	4-^{t}Bu-benzyl	3,5-^{t}Bu₂-benzyl	4-Me-benzyl	3,5-(MeO)₂-benzyl	4-NO₂-benzyl	naphthyl
	e	f	g	h	i	**177d**
Yield (%)	92	99	99	90	74	71
d.r.	1:3	1:3	1:3	1:5	1:2	1:1

This is a test molecule required to evaluate effects arising from only containing a single stereogenic atom (carbon) in the molecule during PTC reactions. The largest selectivity for the quaternisation of amine **189** was observed during the reaction of 3,5-dimethoxybenzyl bromide to form **213a**, 1:5 d.r. and 90%. The other 3,5-disubstituted derivatives were reacted to form DAS in similar yields but with reduced ratios, **180d** 1:2 and 85% and **213f** 1:3 and 99%. Compounds **213d** (1:2 and 81%) and **179d** (1:2 and 82%) were formed in modest yields and selectivity. Comparisons of the para-substituted effects show that the when the electron withdrawing CF₃ benzyl derivative was used to quaternise the amine it gave rise to a d.r. of 1:4 and slightly lower 73% yield **213b**. The salt **213e** was formed in increased yield (92%) but with lower selectivity of d.r. 1:3 which was very similar to **213g** (1:3 d.r. and 99%) showing the size of group in that position doesn't affect the selectivity observed.

Table 14 Ammonium salts derived from parent amine **190**

Entry	1	2	3	4	5	6
R						
	a	**b**	**c**	**d**	**e**	**f**
Yield (%)	68	90	75	80	74	87
d.r.	1:2	1:3	1:5	1:7	1:2	1:5
Entry	7	8	9	10	11	12
R						
	g	**h**	**i**	**j**	**k**	**l**
Yield (%)	99	81	86	79	68	90
d.r.	-	1:10	1:6	1:5	1:4	1:5

Some good diastereoselectivity was observed when alkylating amine **190** (**Table 14**), notably when **214h** was formed with a d.r. of 1:10 and yield of 81%. A decrease in selectivity is observed during the quaternisation to form DAS with the other 3,5-disubstituted bromides, **214j** (1:5 d.r. and 79%), **214a** (1:2 d.r. and 68%) and **214b** (1:3 d.r. and 90%). Ammonium salt **214f** (1:5 d.r. and 87%) was formed in good yield and d.r. and selectivity was similar in forming DAS **214d** (1:7 d.r. and 80%) but a large drop in selectivity is seen in the result with **214e** (1:2 d.r. and 74%). DAS **214c** was formed with good selectivity (1:5 d.r. and 75%) as were other DAS **214j** (1:6 d.r. and 86%) and **214k** (1:4 d.r. and 68%).

Table 15 Ammonium salts derived from parent amine **191**

Entry	1	2	3	4	5	6
R	F₃C / F₃C substituted phenyl **a**	Me / Me substituted phenyl **b**	CF₃ phenyl **c**	phenyl **d**	Ph phenyl **e**	naphthyl **f**
Yield (%)	56	71	59	99	58	48
d.r.	1:1	1:3	1:3	1:3	1:2	1:2
Entry	7	8	9	10	11	12
R	ᵗBu phenyl **g**	ᵗBu / ᵗBu phenyl **h**	Me phenyl **i**	MeO / MeO phenyl **j**	NO₂ phenyl **k**	naphthyl **l**
Yield (%)	71	70	86	80	54	57
d.r.	1:3	1:2	1:3	1:4	-	1.2

Yields were significantly lower overall during additions to amine **191** although the increased ionic nature of the products did not have any untoward effects on purification or analysis (**Table 15**). Although all alkylations proceeded with non 1:1 d.r. they were consistently quite low. Compounds **215b** (1:3 d.r. and 71%), **215h** (1:2 d.r. and 70%) and **215j** (1:4 d.r. and 80%) formed in fair yield with the 3,5-dimethoxy benzyl derivative DAS giving the highest d.r. in the series. Compounds **215c** (1:3 d.r. and 59%), **215g** (1:3 d.r. and 71%) and **215i** (1:3 d.r. and 86%) were made with reasonable selectivity. The 1-bromo and 2-bromomethylnaphthalene electrophiles were reacted with amine **191** to give DAS **215l** (1:2 d.r. and 57%), **215f** (1:2 d.r. and 48%). Addition of benzyl bromide to the amine **191** gave the corresponding salt **215d** (1:3 d.r. and 99%) which occurred with good yield and slightly increased selectivity.

Table 16 Ammonium salts derived from parent amine **192**

Entry	1	2	3	4	5	6
R	F$_3$C / F$_3$C substituted phenyl	Me / Me substituted phenyl	CF$_3$ substituted phenyl	phenyl	Ph substituted phenyl	naphthyl
	a	**b**	**c**	**d**	**e**	**f**
Yield (%)	58	92	79	90	77	78
d.r.	1:4	1:3	1:5	1:4	1:3	-
Entry	7	8	9	10	11	12
R	^{t}Bu substituted phenyl	^{t}Bu / ^{t}Bu substituted phenyl	Me substituted phenyl	MeO / MeO substituted phenyl	NO$_2$ substituted phenyl	naphthyl
	g	**h**	**i**	**j**	**k**	**l**
Yield (%)	88	89	96	91	89	68
d.r.	1:7	1:5	1:6	1:5	1:4	1:2

Addition of 4-substituted benzyl bromide groups to amine **192** occurs with the highest d.r. in this series with **179g** (1:7 d.r. and 88%) followed by **179i** (1:6 d.r. and 96%) (**Table 16**). Electron-withdrawing groups in this position slightly decrease the d.r. but still proceed in good yield **170c** (1:5 d.r. and 79%) and **179k** (1:4 d.r. and 89%). 3,5-Disubstituted benzyl derivatives reacted with the amine **192** and good selectivity was observed, comparison of the groups would indicate that the size of group in the 3,5- positions is not important, comparison of *tert*-butyl **179h** (1:5 d.r. and 89%) and methoxy **179i** (1:5 d.r. and 91%) gives the same d.r. The 3,5-bistrifluoromethyl benzyl derivative reacted with the amine in reduced yield **179a** (1:4 d.r. and 58%) and the 3,5-dimethyl benzyl derivative reacting to give the corresponding salt **179b** (1:3 d.r. and 92%). Reaction of benzyl bromide with the amine proceeded with good yield 90% and 1:4 d.r. to give **179d**. Formation of **179e** (1:3 d.r. and 77%) and **179l** (1:2 d.r. and 68%) again occurred with lower than average yield and with moderate d.r.

Alkylations of the amine **193** (**Table 17**) with bromides containing electron-withdrawing groups, for the most part, offered the highest levels of selectivity, with the formation of **178a** (1:8 d.r. and 76%) and **178k** (1:5 d.r. and 95%). However the salt **178c** formed from quaternisation proceeded with no selectivity (1:1 d.r. 94%) as do the reactions to give DAS **178b** (32%) and **178h** (99%). The naphthalene bromide derivatives were reacted with the amine **193** and no selectivity was observed in the products, **178f** (1:1 d.r. and 83%) or **178l** (1:1 d.r. and 84%).

Table 17 Ammonium salts derived from parent amine **193**

Entry	1	2	3	4	5	6
R	a	b	c	d	e	f
Yield (%)	76	32	94	95	96	83
d.r.	1:8	1:1	1:1	1:3	1:1	1:1
Entry	7	8	9	10	11	12
R	g	h	i	j	k	l
Yield (%)	99	99	99	95	95	84
d.r.	1:2	1:1	1:2	1:5	1:5	1:1

Tertiary amine **194** with its perfluorinated phenyl ring possesses a greater electron-withdrawing effect compared with other amines discussed in this chapter due to the polarised C-F bonds (**Table 18**). The reduced nucleophilicity of the amine completely shuts down reactivity in some cases and no product was formed when the reaction of the amine **194** and benzyl bromide derivatives that contained fluorine were carried out. Product formation was observed when the amine was reacted with *p*-nitrobenzyl bromide **216h**, in what appears to be

a single diastereoisomer albeit in very poor yield (13%). The lowest observed d.r. 1:8 was observed in the quaternisation to form the DAS, **216a** (52%) and **216f** (76%). High selectivity was observed in the formation of **216d** (55%) and **216g** (28%) showing that substitution around the benzyl bromide derivative did not drastically affect the selectivity outcome of the reaction just the overall yield.

Table 18 Ammonium salts derived from parent amine **194**

Entry	2	4	5	7
R	a	b	c	d
Yield (%)	52	56	33	55
d.r.	1:6	1:>99	1:3	1:10
Entry	8	9	10	11
R	e	f	g	h
Yield (%)	51	76	28	13
d.r.	1:17	1:8	1:11	1:2

The reaction with di-*tert*-butylbenzyl bromide with amine **194** to give DAS **216e** occurred with high selectivity d.r. 1:17 (51%). The reaction of benzyl bromide with amine **194** to form DAS **216b** proceeded with complete diastereoselectivity and the salt precipitated out of solution and was easily filtered in fair yield 55%. As the reaction was carried out on 0.2 mmol scale, it was repeated on 1 mmol scale to see if the result was reproducible. Again the product had precipitated and could be filtered. Three more precipitations carried out by adding diethyl ether to the acetonitrile eventually led to 49% yield for the combined precipitates. The product

was easily recrystallised from boiling acetonitrile to obtain suitable crystals for x-ray crystallography. The structure was solved and nitrogen configuration unambiguously determined to be (*R*) (**Figure 39**).

Figure 39 Crystal structure of **216b** with ellipsoids drawn at the 50 % probability level. Hydrogen bonding is shown using a dashed line (appendix 7.2.6).

Overall, the low d.r. observed in the formation of 1st and 2nd-gen ammonium salts was addressed by synthesis of the 3rd-gen DAS where higher levels of selectivity were observed. In many cases, low levels were still observed but in the cases of alkylation of tertiary amines, **183**, **190** and **194**, higher levels of d.r. were found including the synthesis of a diastereomerically pure **216b**. Higher levels of d.r. were observed when using benzyl bromide **198** as well as the derivatives inclusive of a *tert*-butyl group, **201** and **202** (**Table 5**). This demonstrates that it is easier to incur higher levels of d.r. using a cyclic amine (where the nitrogen is an atom of the ring) like prolinol as the inversion process of nitrogen occurs at a lower rate allowing more selectivity in the quaternisation of the tertiary amine.

3.5 Application of stereogenic nitrogen in PTC

Phase-transfer catalysis is now a widely established methodology, regularly used in industry as well as a continued research avenue for many prominent chemists today.[15] Whilst PTC has been used for a host of transformations, useful asymmetric variants have only been described since 1976.[45, 109, 112, 121-127] A significant breakthrough came when O'Donnell synthesised α-

92

amino acid derivatives in 1989 using *N*-alkylated cinchona-based alkaloids **217** (**Figure 40**) carving out a significant niche for asymmetric PTC.[100]

217
Chiral at *N*
-electronically governed?

218
Achiral at *N*
-sterically governed?
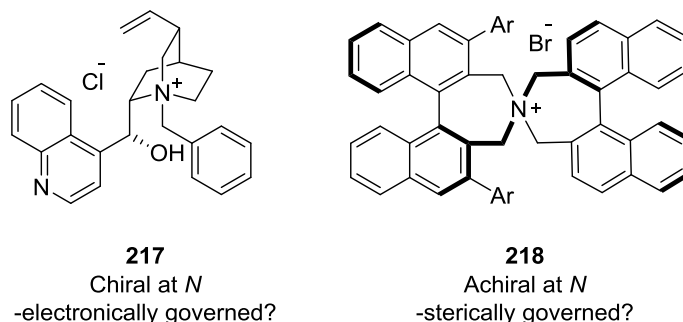
Figure 40 Different nitrogen environments in common PTC motifs

Since then many people have contributed to elevating this to a substantial area of organocatalysis including Corey, Lygo, Maruoka, Denmark and several other world leading research groups[45, 128, 129] carrying out some very elegant and exciting chemistry.[15, 45, 108-111] The reaction that O'Donnell reported has become the widely accepted method by which all asymmetric PTC's can be measured (**Scheme 48**).

The exact mechanism of PTC has yet to be elucidated, with many working off an initial proposition from Starks and Makzosa in the 1960s.[130, 131] Two very successful types of asymmetric PTC that exist today are the cinchona alkaloid-derived structures **217** and Maruoka inspired C_2-symmetric binaphthyl structures **218** (**Figure 40**).[15, 45] The cinchona alkaloids contain a fixed stereogenic nitrogen and the Maruoka structures do not, and as yet it is not fully understood if steric or electronic influence is key to the success of asymmetric PTC reactions. As theoretical chemistry has developed, modelling of PTC reactions has been attempted in an effort to understand the origin of enantioselective induction in reactions.[110, 111, 132-135] Looking at the most common PTC reaction established by O'Donnell, alkylation of a *t*butyl glycine benzophenone imine, an interfacial mechanism is widely accepted (**Scheme 48**).[136, 137] Deprotonation of the *t*butyl glycine benzophenone imine **109** occurs first, generating an enolate **109a** at the interface between phases as a metal/enolate ion pair. Due to

its polar nature this ion pair remains at the interface of the organic and aqueous phase. The exchange of the metal and the ammonium salt **109b** occurs at a rate faster than the alkylation. The ion pair formed between the ammonium salt and enolate only leaves one face open to alkylation which gives rise to the selectivity observed in the reactions. The rate of alkylation is enhanced with the ammonium salt ion pair as it has higher organic solubility.[15, 138, 139] Once alkylation occurs with the ion pair the catalyst is regenerated giving the product **110**.
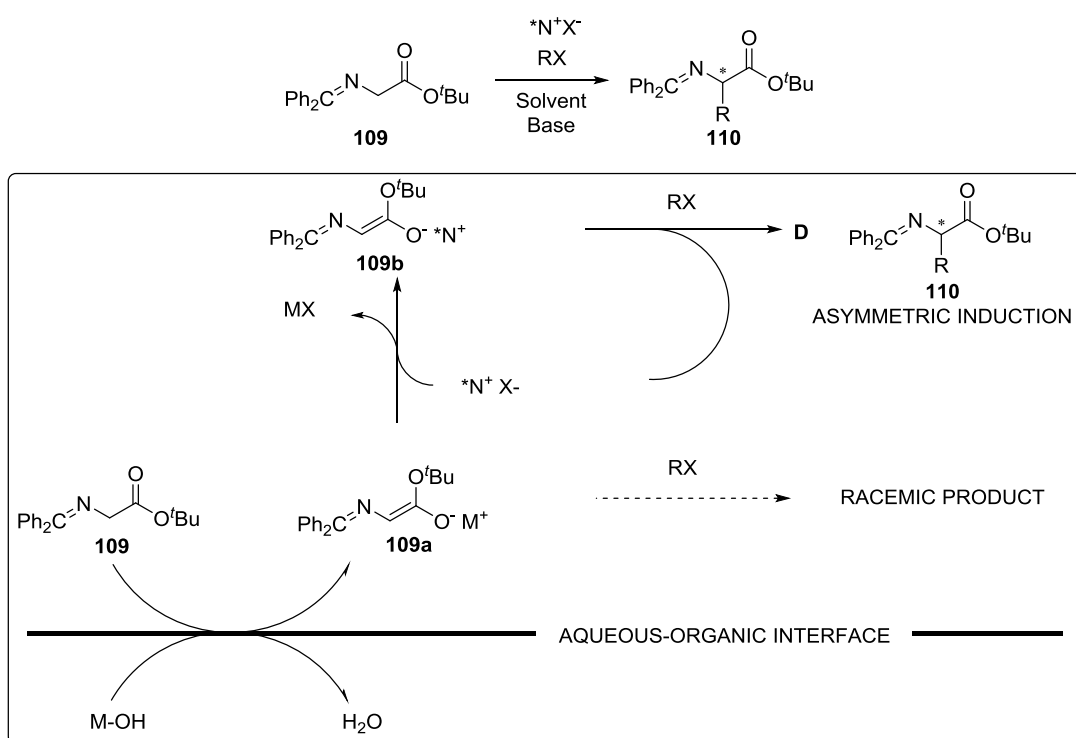
Scheme 48 Proposed interfacial mechanism of asymmetric PTC reaction applied to tert-butyl glycine benzophenone imine alkylation

In order to gain as much information about the stereogenic nitrogen contribution two phase-transfer reactions were selected for study. Whilst the mechanism described in **Scheme 48** applies to the alkylation of a glycine-derived Schiff base, the epoxidation of an α,β-unsaturated carbonyl system proceeds via a modified extractive mechanism (**Scheme 49**).[131]
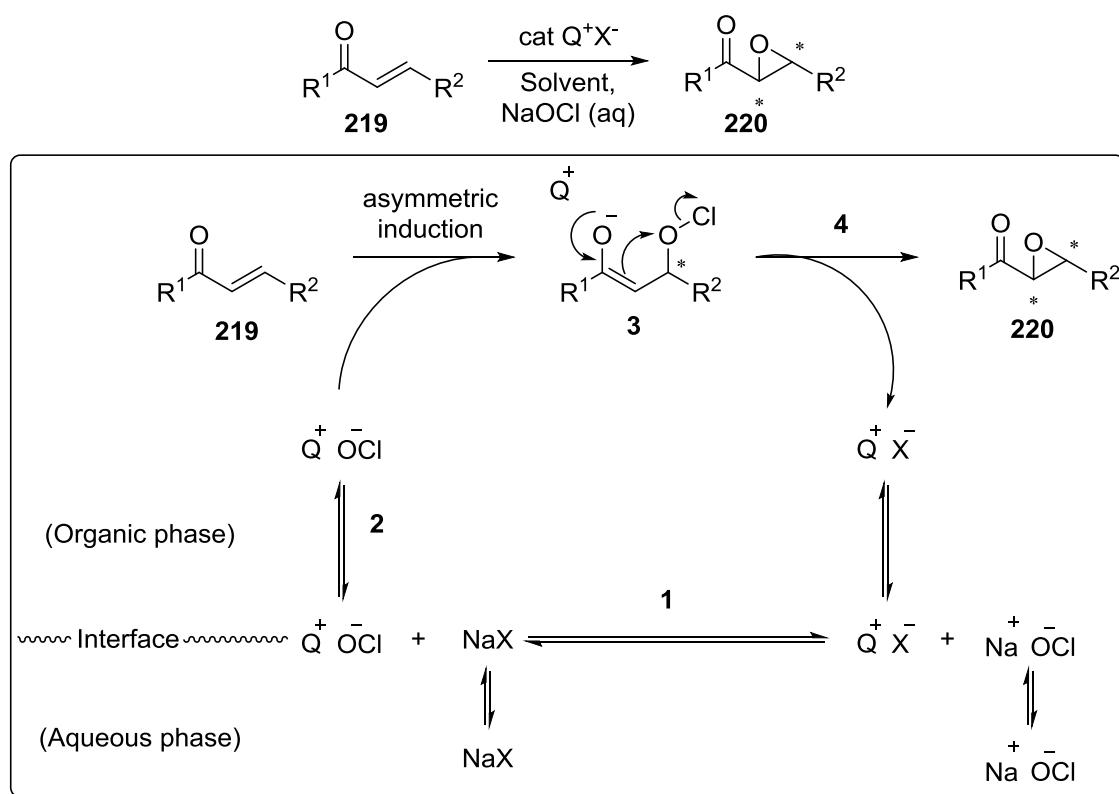
Scheme 49 Proposed extractive mechanism for epoxidation of an α,β-unsaturated carbonyl compound

The Brändström-Montanari modification is a better representation of the epoxidation reaction.[140] The catalyst (ammonium cation) forms an equilibrium with the oxidant (in this case sodium hypochlorite but can also be hydrogen peroxide) **1** to form an onium salt. This salt is then extracted into the organic phase **2** and can react with the α-β-unsaturated system. The asymmetric induction arises from ion-pair formation of the ketone and onium salt which then allows the hypochlorite to distinguish between the enantiotopic faces and attack the enone **3**. Regeneration of the ketone and epoxide formation along with expulsion of the onium salt allows the cycle to continue **4**.[139, 140]

As these two reactions, alkylation (**Scheme 48**) and epoxidation (**Scheme 49**) operate by slightly different mechanisms, they were chosen to investigate stereogenic nitrogen effects.

One important question which is not considered by any mechanism but worth consideration is,

"Does the chirality of nitrogen play a role in asymmetric PTC?"

As the nitrogen accommodates the formal positive charge and forms a contact ion pair with the deprotonated enone, which is prochiral (epoxidation reaction) then the chirality of nitrogen should play a pivotal role in the transfer of chiral information. The unique chiral chemical environment created by the nitrogen would be relevant to influencing the substrate orientation in the ion-pair formation and consequently the outcome of the reaction.

The inverse of this argument must also be taken into account is that a chiral carbon scaffold inclusive of a tetravalent nitrogen dominates interactions with substrates.

Whilst the latter is supported by evidence of asymmetric induction from extensive study.[15] A lack of evidence for chiral nitrogen effects does not prove that the nitrogen chirality is not important. Although reports involving stereogenic nitrogen compounds are extremely modest,[101, 102] whenever chemists venture to new fields of study preliminary results often have much room for improvement. The first chiral phosphine by Knowles[20] (17% *ee*), the first asymmetric PTC by Wynberg *et al.*[126] (25% *ee*) are just two examples where the respective fields have exploded within 30 years of the initial report.

Whilst the ideal situation would have been to investigate chiral only at nitrogen molecules as catalysts, the application of stereogenic nitrogen-containing molecules acting as PTCs would allow a measurable method of evaluating their asymmetric induction in common reactions. This study is not intended to uncover new catalysed reactions or compete with existing catalysts but it is the goal to assess if the stereogenic nitrogen has a meaningful effect during a catalysis event. With the appropriate control molecules (achiral at nitrogen environments) used as catalysts in a PTC reaction, measurement of the *ee* will allow comparison with stereogenic nitrogen containing compounds. The earlier described 3rd generation DAS (Chapter 3.4) will be evaluated as PTCs in the alkylation (**Scheme 48**) and epoxidation reactions (**Scheme 49**) to ascertain if stereogenic nitrogen plays a role in the chiral induction process.

Due to the deliquescent nature[V] of the 2nd generation DAS, their handling was difficult to accurately utilise them as PTC with two exceptions, compound **163f** and **163d** which were used in the epoxidation reaction. In order to achieve the highest levels of reproducibility from the PTC reactions, the crystalline 3rd generation DAS would be evaluated as PTCs.

3.5.1 Alkylation of glycine Schiff base

Many of the 3rd generation DAS were tested in the alkylation PTC reaction and those that successfully catalysed the reaction are displayed below (**Table 19**).

Evaluation of the enantiomeric ratio data shows that the products are essentially racemic. There were three 3rd-gen DAS (compounds **215e**, **179e** and **179j Table 19**) which did perform better than the others, all produced, a 59:41 e.r. in the alkylation PTC reaction. Also shown are the results of the three achiral at nitrogen control molecules (compounds **177l**, **179f** and **213c Table 19**) and their respective e.r. of 55:45 and 50:50. Whilst the stereogenic nitrogen-containing ammonium salts, with differing diastereomeric ratios, catalyse the reaction, there is, in general terms, no overwhelming effect from the stereogenic nitrogen centre in either diastereoisomer. Consideration of the mechanism proposed earlier would suggest that during the asymmetric induction (step **109b**–ion pair formation, **Scheme 48**), the 3rd generation DAS (no matter the d.r.) do not efficiently differentiate between the two faces of the enolate and therefore do not give rise to high levels of asymmetry.

[V] The salts were difficult to weigh out due to the varying water content; therefore it was challenging to accurately account for the catalyst loading when using the salts so they were not utilised in the PTC reactions.

Table 19 3rd gen DAS employed as PTCs in alkylation reaction

Ph—N=C(Ph)—CH₂—C(=O)—O^{t}Bu **109** → PTC (10 mol%), BnBr (1.2 equiv), Toluene (1 mL), KOH (50%, 0.5 mL), 24 h → Ph—N=C(Ph)—C*(Bn)H—C(=O)—O^{t}Bu **110**

Entry	PTC	Yield (%)	e.r. (R:S)	Entry	PTC	Yield (%)	e.r. (R:S)	Entry	PTC	Yield (%)	e.r. (R:S)
1	207c	13	56:44	28	211j	26	50:50	55	214c	21	51:49
2	207e	38	56:44	29	211k	11	48:52	56	214d	45	51:49
3	207f	32	55:45	30	211l	16	52:48	57	215b	29	55:45
4	207g	45	52:48	31	177c	29	51:49	58	215d	26	54:46
5	207h	10	50:50	32	177d	40	51:49	59	215e	13	**59:41**
6	207i	36	50:50	33	177g	32	54:46	60	215f	24	55:45
7	207k	9	51:49	34	177h	34	50:50	61	215g	13	50:50
8	208a	42	50:50	35	177j	34	47:53	62	215h	34	55:45
9	208b	68	52:48	36	177k	13	50:50	63	215i	34	55:45
10	208c	61	49:51	37*	177l	34	50:50	64	215j	26	54:46
11	208d	58	51:49	38	212b	16	50:50	65	179a	16	56:44
12	208e	79	53:47	39	212c	29	52:48	66	179b	21	49:51
13	208g	58	53:47	40	212d	32	52:48	67	179c	26	57:43
14	208h	55	51:49	41	212e	16	51:49	68	179d	34	56:44
15	208i	66	52:48	42	212f	34	50:50	69	179e	34	**59:41**
16	208j	66	52:48	43	212g	37	51:49	70*	179f	40	55:45
17	208k	21	56:44	44	212i	11	49:51	71	179g	34	49:51
18	208l	39	51:49	45	213a	24	55:45	72	179h	29	51:49
19	209b	47	51:49	46	213b	24	52:48	73	179j	29	**59:41**
20	209c	18	49:51	47*	213c	37	55:45	74	179k	34	53:47
21	209g	18	53:47	48	213d	26	47:53	75	179l	13	51:49
22	209h	71	52:48	49	179d	18	55:45	76	178f	26	51:49
23	209j	32	51:49	50	213e	34	55:45	77	178g	32	51:49
24	211d	5	54:46	51	213h	34	54:46	78	178h	34	48:52
25	211g	32	56:44	52	177d	26	52:48	79	178j	11	51:49
26	211h	26	51:49	53	214a	40	50:50	80	178l	63	52:48
27	211i	8	54:46	54	214b	40	53:47				

Entry 32 PTC **177d** 1:3 d.r. and **entry 52** PTC **177d** 1:20 d.r. *are control compounds. The highlighted entries indicate the highest observed e.r.

By comparison of the control molecules synthesised, a base level of performance can be obtained to assess the resulting effect from the carbon stereogenic centre. Both the benzyl **213c** and the 2-naphthalene **179f** derivatives have an e.r. of 55:45. So this is the common type

98

of result expected from this series (**Table 19**, **entries 65-75**) and indeed the average e.r. for this series was 54:46.
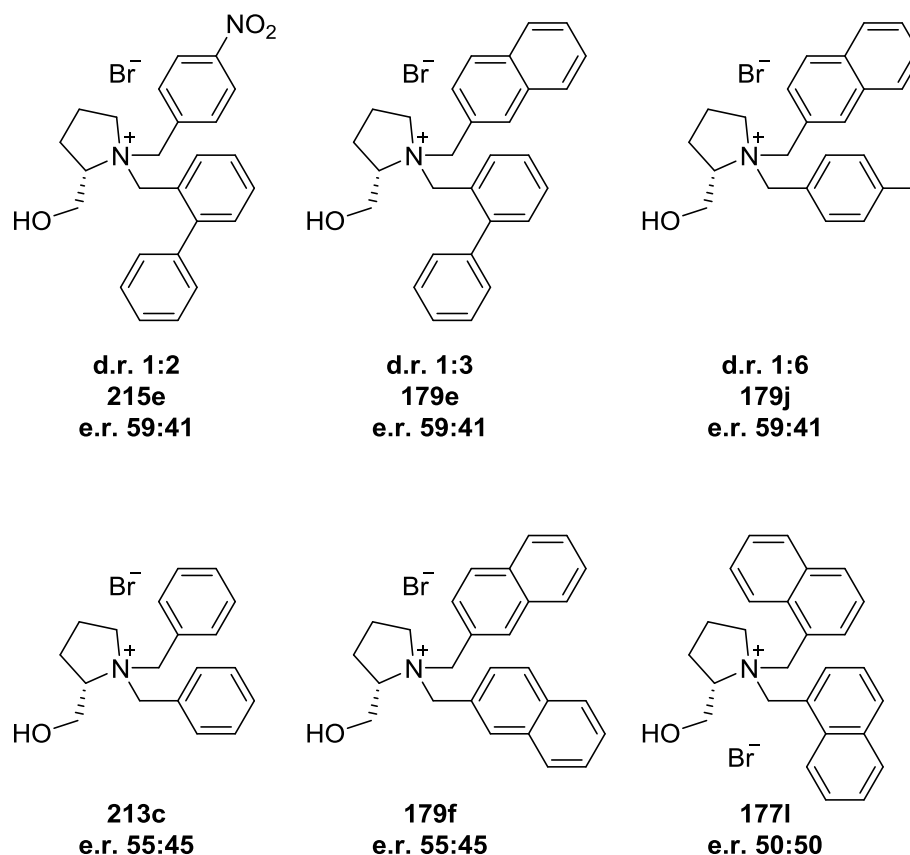
Figure 41 Control molecules and 3rd-gen DAS which give 59:41 e.r. during the alkylation PTC reaction (**Table 19**)

Understanding the outcome of the catalysis reaction becomes more complex as considerations must be taken to appreciate the different nitrogen configurations which lead to the e.r observed in the product (**Figure 42**). The d.r. of the ammonium salt **215e** was tentatively assigned as 1:2 and it is impossible to infer the major diastereoisomer from ^{1}H NMR spectroscopy. By analogous determination (comparison with nOe studied molecule **182**), the (C_S, N_S) was assigned as the major diastereoisomer. When the nitrogen configuration is (*S*) the *N-para*-nitrobenzyl group is down (**figure 42 A**) and offers the opportunity for π-stacking to arise with the diphenylimine unit of the substrate, the facial selectivity occurs from the orientation of the bulky ester group which can point toward (**C**) or away (**A**) from the *N*-2-phenylbenzyl group. The opposite configuration of nitrogen (*R*) then would result in the cases

for ion-pair formation occurring with the diphenyl imine sandwiched between the two nitrogen appended aromatic units (**B**) or with the bulky ester in this position (**D**). Possible π-stacking interactions could help stabilise the ion-pair (**B**). As the ratio is in favour of the (*R*) it is likely that (**A** and **B**) are more favourable propositions.
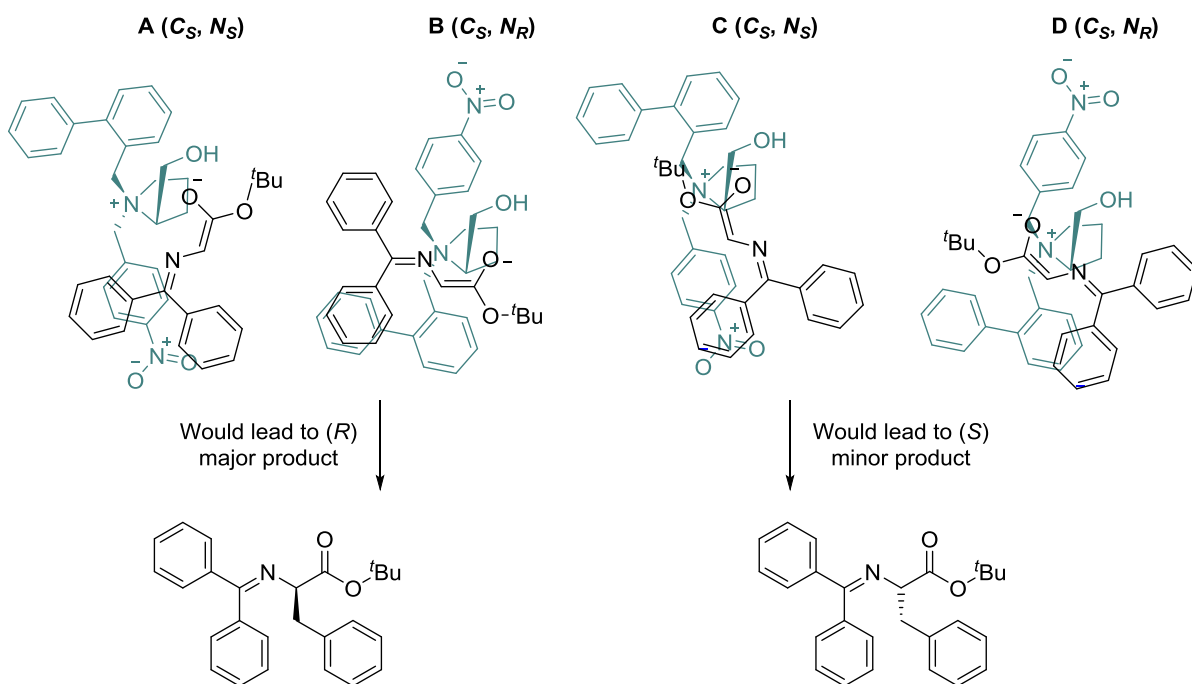
Figure 42 Plausible ion-pair arrangements of alkylation PTC reaction with compound **215e** leading to major (*R*) and minor (*S*) products

3.5.2 Epoxidation of chalcone

The second choice of PTC reaction was the epoxidation of chalcone (**Scheme 49, Table 20**). It provided the opportunity to assess if the chirality of nitrogen has more of an effect when the mechanism is different. In this situation the oxidant is delivered as a nucleophile to a prochiral substrate.

By use of a control molecule (TBAB) and literature conditions of lithium hydroxide, di-*n*-butyl ether and hydrogen peroxide, the enone was epoxidised (**entry 1**). Use of a control molecule (**entry 2**) allowed the influence of the sterogenic carbon to be assessed with an e.r. of 55:45. Regardless of the d.r. in the ammonium salts, no exceptional differences in e.r. were recorded. In the cases of higher d.r. the salts (**entry 3** and **4**) still imparted a minimum e.r.

56:44 (20:1 d.r.) and 49:51 (10:1 d.r.) respectively. The comparison of the same molecules in differing d.r. highlighted that the stereogenic nitrogen did play a role in the enantioselectivity of the reaction. Whilst one case shows that when different ratios were used there was no effect (**entry 7** and **9**) with 4:1 and 1:1 ratios both giving an e.r. of 50:50. However, a bulkier catalyst (**entry 5** and **6**) showed e.r. of 59:41 and 48:51 using PTCs with d.r. of 1:1 and 6:1. What was surprising was that the 1:1 d.r. gave the higher e.r. this would lead to the assumption that the opposite nitrogen configuration (*S*) had a greater effect on the reaction. Further efforts to separate the diastereoisomers or synthesise the opposite configuration of the ammonium salt **177b** could not increase the d.r. from 1:1.

Only two of the 2nd generation DAS were tested (**entries 10** and **13**). Whilst they both had tentatively assigned d.r. of 2:1 they directly compared the electronic effect of the *N*-benzylic group. There did not appear to be any overriding effect and the reaction proceeded with an e.r. of 51:49. When the *N*-3,5-bistrifluoromethyl benzyl group was in the DAS a more significant e.r. of 42:58 was obtained.

Perhaps the most disappointing results were testing three single diastereomerically pure compounds (**entries 13**, **14** and **15**). No isolated yields of the reactions were calculated but analysis of the crude reaction product showed an e.r. of 50:50 for each compound. These two results underline that there appears to be no significant discrimination of the enone faces in the epoxidation PTC reaction. Therefore it would appear that the chirality of nitrogen has no outcome on the effect of the reaction.

Table 20 Epoxidation of chalcone using diastereomeric mixtures of ammonium salts
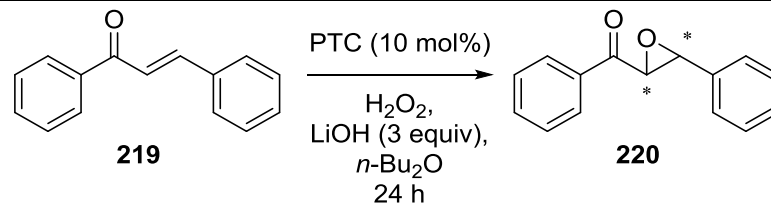
Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
PTC	TBAB	213c	177d	182	177b		178d		177a	163f	179d	163d	216b	216e	212e
PTC d.r.	-	-	20:1	10:1	1:1	6:1	1:1	4:1	3:1	2:1	4:1	2:1	>99:1	17:1	>99:1
Yield (%)	62	78	60	32	65	18	60	62	17	17	25	25	75	80	64
e.r.	50-50	55:45	56:44	49:51	59:41	52:48	50:50	50:50	53:47	42:58	50:50	51:49	50:50	50:50	50:50

The highlighted entry shows the highest e.r. observed

4 Conclusions

4.1 Summary

This thesis describes the synthesis of diastereomeric ammonium salts containing a stereogenic nitrogen centre and fixed carbon stereogenic centre. 10 1st generation ammonium salts were synthesised. The combination of analytical HPLC, preparative HPLC, analytical chiral HPLC and preparative chiral HPLC resulted in conditions found to separate the diastereoisomers.

A series of 2nd generation diastereomeric ammonium salts were synthesised with a wider range of reagents to increase the functionality in the molecules. Several chiral amines were used as well as more sterically demanding and electronically divergent groups. When the 2nd generation ammonium salts were subjected to the same conditions for chromatographic separation, initial tests suggested that the separation conditions established could be generally applied with good effect.

Work towards the synthesis of chiral-only-at-nitrogen compounds was attempted. Several strategies were employed with little success. Some experimental evidence suggests that the Barton-McCombie deoxygenation radical chemistry could overcome the difficulty of ammonium salt reactivity and provide a route to chiral-only-at-nitrogen compounds.

In order to circumvent a difficult separation of diastereoisomers, a library of over 150 3rd-generation prolinol-derived ammonium salts were synthesised and characterised as diastereomeric mixtures. A wide range of diastereoselectivities were obtained from 1:1 to 99:1 and several X-ray crystal structures were obtained. These 3rd generation DAS were all applied as phase-transfer catalysts in the alkylation of a glycine Schiff base and a range of them used in the epoxidation of chalcone. The contribution from the stereogenic nitrogen was found to be

negligible in most cases. Compounds **179e**, **179j** and **215e** catalysed the alkylation reaction with 59:41 e.r. Compound **177b** catalysed the epoxidation reaction with 18% ee also. Evaluation of the catalysts suggests the higher ee observed for the alkylation reaction may be due to the catalyst structure rather than the stereogenic nitrogen influence.

4.2 Conclusions

Several strategies based upon the reductive amination reaction were used in order to construct a diverse array of diastereomeric ammonium salts. This powerful reaction allowed sequential construction of tertiary amines without compromising the chiral integrity of the starting materials. Its general application was able to tolerate aromatic, heteroaromatic, cyclic, acyclic, electron rich and electron poor substrates in high yield with excellent regioselectivity. Favourable trends of diastereoselectivity were observed (3rd generation DAS) upon treatment of the tertiary amines with an appropriate electrophile. Many limits of reactivity (alkyl halides were poor electrophiles for quaternisation, anthracenyl moiety could not be added to any synthesised tertiary amine nor could any tertiary amine be alkylated which included an anthracenyl group) were observed enabling alternative routes to be investigated. Benzyl bromide derivatives were found to be excellent electrophiles and were commonly employed due to the versatility of substituents that it could incorporate. Methyl and ethyl triflate as well as dimethyl sulfate were found to be far more effective at alkylation of tertiary amines than alkyl halides. In cases of tertiary amines with reduced nucleophilicity attempts at using the microwave reactor or a sealed tube did not result in any alkylation.

HPLC was the primary route to separate diastereoisomers. Extensive method development through trial, error and consultation was used to enable separation of the 1st generation ammonium salts on an analytical scale. This developed method was applied to several crude mixtures of 2nd and 3rd generation DAS with promising initial results.

An automated column chromatography machine was used which incorporated several new technologies as a means to investigate diastereomeric resolution. Use of functionalised silica, C18, chiral silica, diethylaminopropyl silica and high grade silica (gold column) always showed promising results warranting further exploration. Unfortunately no solutions were found following up the interesting leads *en-route* to separation of diastereoisomers of stereogenic nitrogen ammonium salts.

One compound **216b** was formed in a single diastereoisomer and several in very high diastereoselectivity (all 3rd gen DAS). There was no correlation between structure and the d.r. of the compounds with regards to the ease of recrystallisation. Although several X-ray crystal structures of stereogenic nitrogen ammonium salts were obtained, no general method was developed as a route to diastereomerically pure ammonium salts.

Investigation found temperature dependence of the d.r. to be inconclusive with some compounds more susceptible than others. A higher temperature ensured alkylation occurred consistently with a high yield and diastereoselectivity.

Test reactions to ascertain if ammonium salts were compatible with chemistry as a possible route to access chiral only at nitrogen compounds by removal of a fixed chiral carbon stereogenic centre were carried out. Functionalisation of the hydroxyl group in an ammonium salt to a better leaving group (tosylate) allowed tests to evaluate removal of this functionality. Use of hydride agents and Grignards did not lead to the expected product and the reactions proved very troublesome. Further tests to directly remove a hydroxyl group using indium chemistry were also unsuccessful. Investigations into the use of radical chemistry (Barton McCombie reaction) showed it was possible to install xanthate functionality into ammonium salts. The deoxygenation, although no product was isolated, provided some experimental evidence for working.

The application of DAS as PTCs was carried out to evaluate whether stereogenic nitrogen has any effect in transferring chiral information to substrates. Having tested dozens of stereogenic nitrogen ammonium salts, it was shown that the contribution from the nitrogen stereogenic centre, regardless of the diastereomer ratio was minimal. Four compounds (**179e**, **179j**, **215e**, **216b**) managed to catalyse a phase-transfer reaction in 18% *ee*. Common structural features would suggest that the *N*-benzyl substituents were more influential for the higher observed *ee* in the product than the nitrogen stereogenic centre. Three diastereomerically pure compounds were used as catalysts but in every case provided a racemic product.

As organocatalysis has developed in recent years, there has not been the emergence of a general catalyst capable of mediating a wide array of transformations.[5, 142, 143] Successful catalysts are extremely specific to their substrates. It is possible that the design of these ammonium salts was just not suitable for the transformation. More likely though is that stereogenic nitrogen diastereomeric ammonium salts do not have any effect on the outcome of phase-transfer reactions. The chirality of nitrogen is and will remain to be important as well as challenging to control, but it would appear that it is not in phase-transfer catalysis.

5 Future Work

Evidence for the synthesis of chiral-only-at-nitrogen compounds whilst minimal, still offers hope that given more investigation the Barton-McCombie reaction can be used as a route to access these compounds (**Scheme 50**).[118] Although only a control reaction with an achiral substrate was attempted, this could be applied to chiral-at-nitrogen compounds. The 2nd generation DAS designed can be prepared on scale and early efforts at chiral HPLC of these compounds suggest separation could be possible and so would provide ample opportunity to fully investigate this potential route to chiral-at-nitrogen compounds.
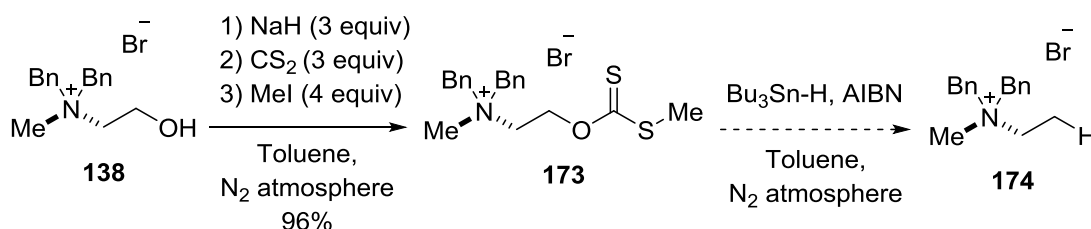
Scheme 50 Classical deoxygenation by Barton-McCombie reaction

Whilst the direction of this research suggests that asymmetric nitrogen atoms in ammonium salts do not influence the stereochemical outcome of PTC reactions, it would still be interesting to carry out a PTC reaction with a chiral-only-at-nitrogen ammonium salt as well as expand the scope of a well-documented reaction.

6 Experimental

6.1 General

^{1}H (300 MHz), ^{19}F (282 MHz), ^{31}P (121 MHz) NMR spectra were recorded on a Bruker AVIII300 NMR spectrometer. All ^{13}C NMR experiments (HMBC, HSQC, NOSY, COSY and pendant) were recorded at 101 MHz on an AV400 NMR spectrometer. nOe experiments were recorded at 500 MHz on a DRX500 spectrometer. All spectra were recorded at 22 °C. All spectra were processed with MestReNova (version 6.0.2-5475). Chemical shifts of resonances in ^{1}H NMR spectra are reported in ppm relative to either chloroform (δ 7.26) or TMS (δ 0.00). All spectroscopy work carried out used deuterated chloroform unless otherwise stated. When methanol-d4 was used, chemical shifts relative to methanol (δ 3.34) were reported. Not all *NH* and *OH* protons were visible so are not reported if they were not observed. Chemical shifts of resonances in ^{13}C NMR spectra are reported in ppm relative to chloroform (δ 77.36) or methanol (δ 49.86).[144] All coupling constants are expressed as *J* and measured in Hertz (Hz). All reported spectra are single compounds or mixtures of diastereoisomers, with traces of residual solvents. All carbon assignments are based on ^{13}C DEPT spectra. There are no ^{13}C NMR spectra for diastereoisomers as the spectra were too complex to accurately assign.

Mass spectrometry analysis was carried out using a Synapt G2-HDMS mass spectrometer in both positive and negative mode. In positive mode, samples were dissolved in a 2:1 (chloroform:methanol) mixture and introduced into a 50:50 (acetonitrile:water) stream doped with 0.01% formic acid and directed towards the ESI source. Negative ESI experiments involved a stream with no formic acid. All molecules with chlorine reported were measured as the ^{35}Cl isotope. The accuracy of HRMS values reported, was under 5.0 ppm. Melting points were carried out in triplicate and reported as the average and in cases, as a range using a Melting Point SMP10 apparatus.

The melting points of diastereomeric mixtures were not recorded[VI]. All IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with Universal ATR Sampling Accessory as an average (10 scans) with the background (10 scans) subtracted. Optical rotations (all optical rotations reported have the units $deg \cdot mL \cdot g^{-1} \cdot dm^{-1}$) were recorded on a polar 2001 Automatic Polarimeter. Measurements of each sample were recorded three times and used as an average to calculate the value. HPLC was carried out on a Shimadzu LC2010 instrument and chiral HPLC Shimadzu LC2010 and Dionex p580 instruments. All PTC-catalysed reactions were analysed by HPLC-MS using Shimadzu LC2010 coupled with Advion CMS.

Purification of compounds was carried out using a Combiflash *Rf* 200i (Teledyne ISCO) and ELSD and UV measurements (210-280 nm) were recorded. Silica cartridges were purchased from Teledyne ISCO, 4, 12, 25, 40, 150 g columns packed with 25-50 nm silica were used and Gold cartridges 12, 25, 40, 120 g packed with 20 nm silica. Column chromatography was carried out using 35-70 nm silica as purchased from suppliers. TLC visualisation was conducted with UV, $KMnO_4$ and ninhydrin on F_{254} plates. Where deactivated (neutralised silica) chromatography analysis was carried out (HPLC, column chromatography or Prep TLC or TLC) the same eluent that was intended to be used was ran on the plates or through the column with added 0.5% TEA added. The silica was then left to dry and reused. In the case of column chromatography, the column was loaded using the added base and once a sample was added reverted back to the original mixture with no base. Solvents and reagents were purchased from Sigma Aldrich and Alfa Aesar and used directly unless otherwise stated. Where dry solvents are mentioned, these were obtained from a solvent purification system calibrated by Karl-Fisher titration equipment

---

[VI] Having tried to determine the melting points of several diastereomeric mixtures, no reproducibility could be achieved. As the $1^{st}/2^{nd}/3^{rd}$-gen ammonium salts are a mixture of two compounds with different physical properties, it did not seem logical to try and record the melting points after the initial failures.

and contain less than 5 ppm water. If no colour has been assigned to the reported compounds then they were colourless in nature. All Grignard reagents used had their concentration determined according to the Love and Jones method.[145]

The following compounds were prepared according to the general experimental procedures reported in the next section and experimental analysis found was consistent with that reported: **206**,[146] **200**,[147] 9-(Bromomethyl)anthracene,[148] **153**,[149] **155a**,[150] **155c**,[151] **141**,[152] **142a**,[153, 154] **142b**,[155] **147**,[156] **138**,[157] **160c**,[158] **185**,[159] **186**,[160] **176**,[161] **189**,[162] **192**,[161] **109**,[163] **110**.[163]

6.2 General Experimental procedures

General method 1 Reductive amination
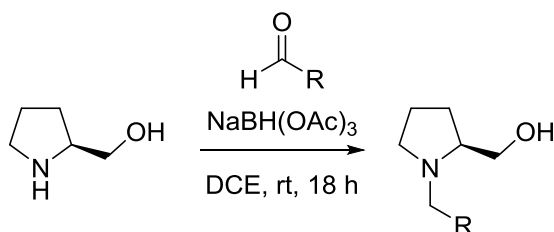
A round bottomed flask was charged with (*S*)-prolinol (or primary or secondary amine) (1.517 g, 1 equiv, 15 mmol,), 1,2-dichloroethane (50 mL), and an aldehyde (1.05 equiv, 15.75 mmol). The solution was allowed to stir for 5 minutes before portion-wise addition of sodium triacetoxyborohydride (4.769 g, 1.5 equiv, 22.5 mmol,). The solution was allowed to stir overnight (~18 hours) and reaction progress monitored by TLC (10:1 CH_2Cl_2:methanol). Once the reaction was complete, the solvent was removed under reduced pressure and HCl solution (1 M, 25-40 mL) was added to the crude reaction mixture. Once fully dissolved the acidic solution was extracted with diethyl ether (3 x 20-40 mL). The acidic layer was then neutralised and basified with potassium hydroxide solution (2 M) until a reading of pH 14 was obtained from indicator paper. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers dried (magnesium sulfate) and solvent removed under reduced pressure. All crude

mixtures were purified using an 80 g silica cartridge using the combiflash automated column machine. The compounds were isolated by a gradient 15 minute column going from 1-13 minutes 0-10% methanol in CH_2Cl_2 with ELSD and UV_{254} to afford tertiary amines.

General method 2 Ammonium salt formation
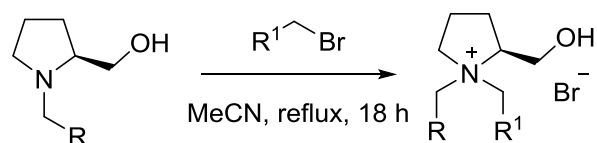
Tertiary amine (0.2 mmol) was added to round bottomed flask followed by a benzyl bromide derivative (or methyl triflate) (0.25 mmol) followed by MeCN (2 mL). The vessel was then heated with stirring to reflux overnight (~18 h) and the reaction progress was monitored by TLC (10:1 methanol: CH_2Cl_2). Once the reaction was complete, silica (35-70 nm, ~0.5-1.0 g) was added and the solvent was removed under reduced pressure and then the reaction mixture loaded on silica was purified by column chromatography. A silica cartridge (4 g) was used with a 9 minute gradient run of 1-8 minutes 0-20% methanol in CH_2Cl_2. The ELSD and UV_{254} was used to monitor the separation to isolate a diastereomeric mixture of ammonium salts.

6.3 Determination of d.r. for ammonium salts

^{1}H NMR spectroscopy was used to determine the d.r. of the ammonium salts (1st, 2nd and 3[rd]gen) made by comparison of certain diagnostic signals from the molecules There were a large number of compounds made so the following details the method by which the d.r. was calculated. Where possible, efforts were made to display the maximum amount of resonances which characterise the diastereoisomer ratio.

Interpretation 1   Benzylic protons (δ 3.8-6.2) e.g **209i**
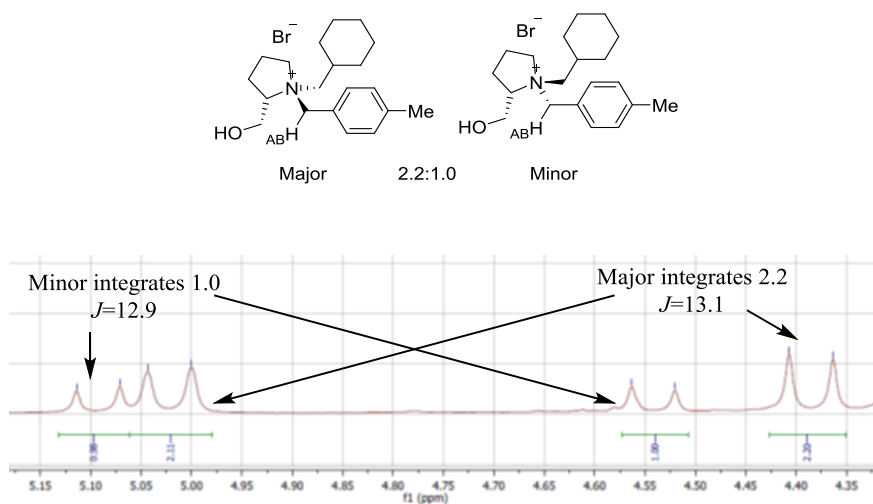
Figure 43 diastereotopic benzylic resonances to determine d.r.

Interpretation 2   3,5-dimethyl benzyl protons (δ 2.3-2.8) e.g. **212b**
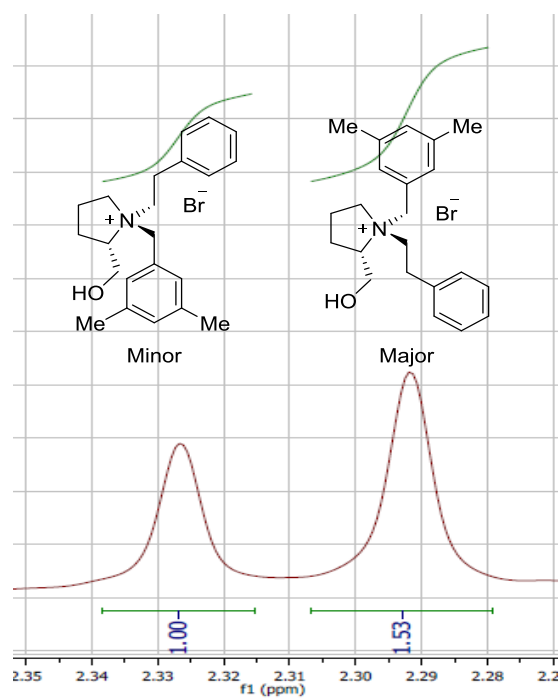
Figure 44 3,5-dimethyl substituted benzyl resonances to determine d.r.

Interpretation 3   4-*t*butyl group (δ ~1.3) e.g. **214d**
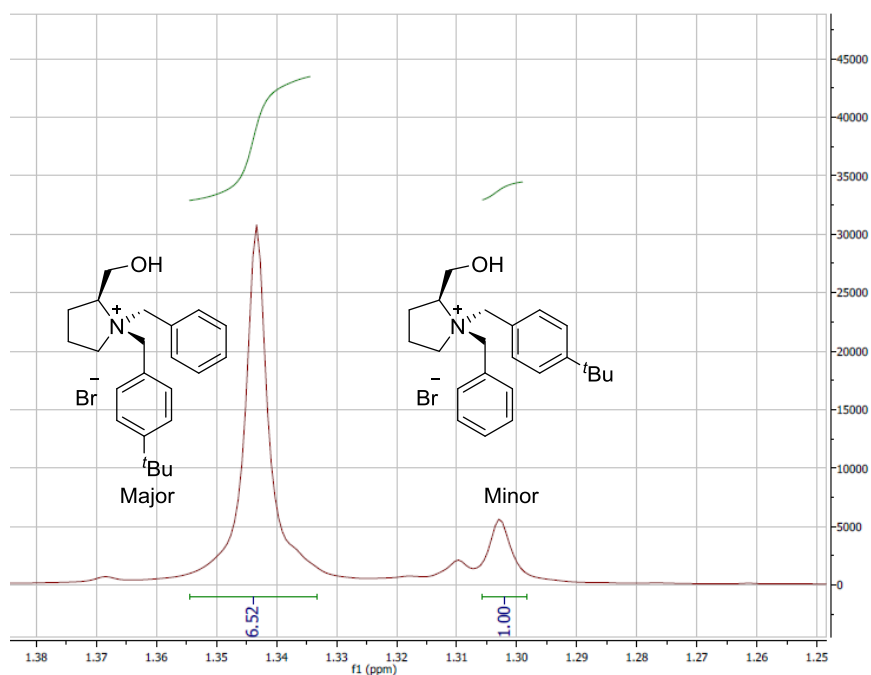
Figure 45 4-*t*-Bu substituted benzyl resonances to determine d.r.

Interpretation 4   3,5-di-*t*butyl benzyl (δ ~1.3) e.g. **207h**
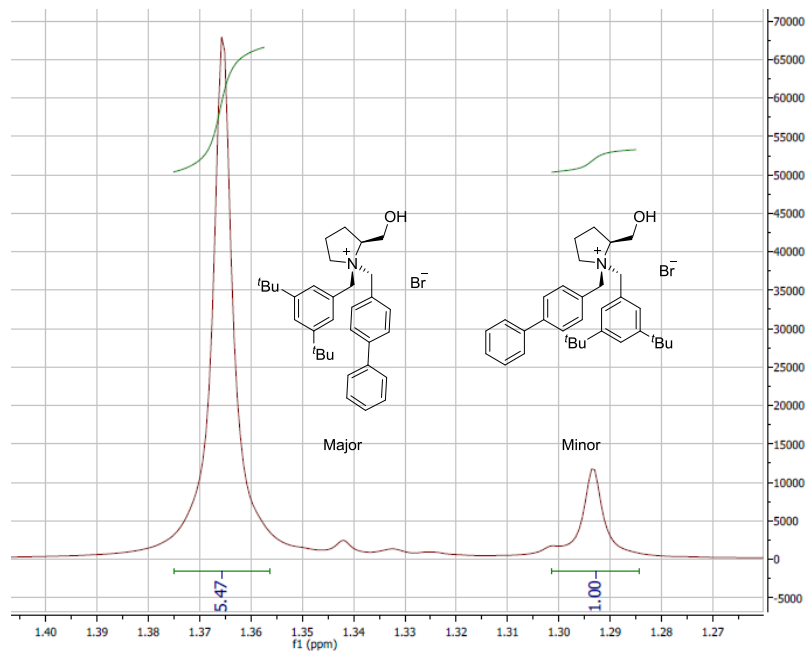
Figure 46 3,5- *t*-Bu di-substituted benzyl benzylic resonances to determine d.r.

Interpretation 5   4-methyl benzyl (δ ~2.4) e.g. **207i**
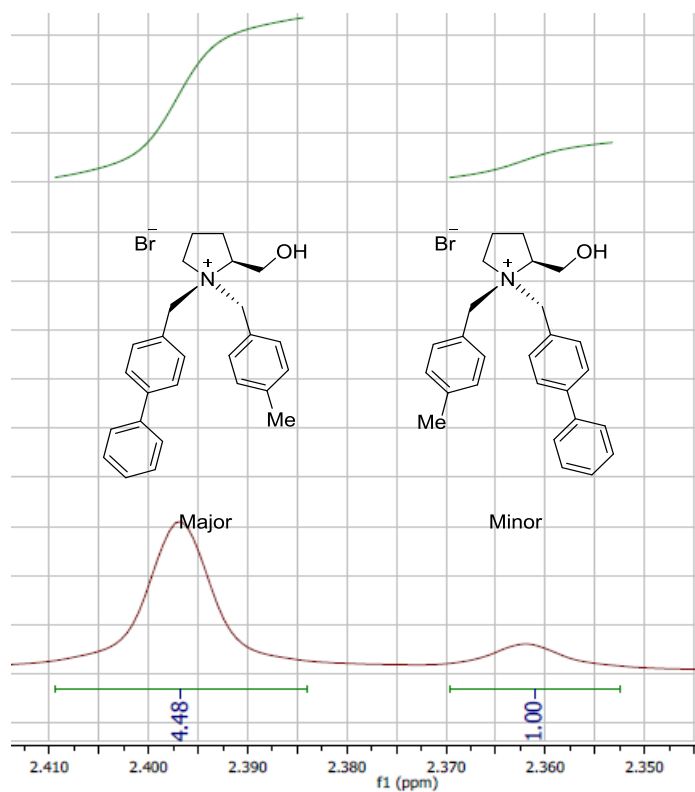
Figure 47 4-Me benzyl substituted resonance to determine d.r.

Interpretation 6   4-ArH in 3,5-disubstituted benzyl (δ 6.9-6.6) e.g. **207j**
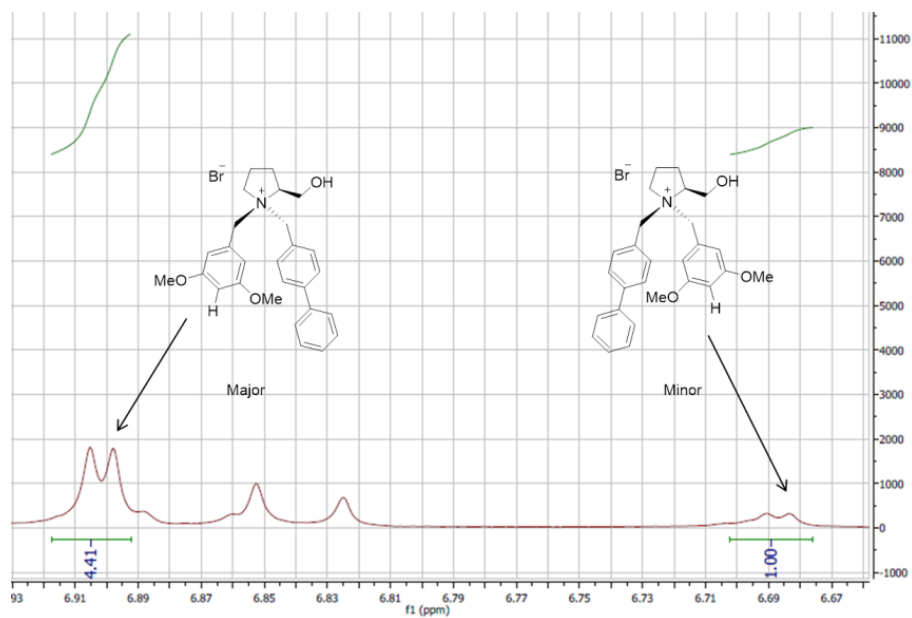
Figure 48 Aromatic proton resonance used to determine d.r.

Interpretation 7 and 8   2,6-ArH and 3,5-ArH in 4-substituted benzyl (δ 7.8-8.3) e.g. **208c**
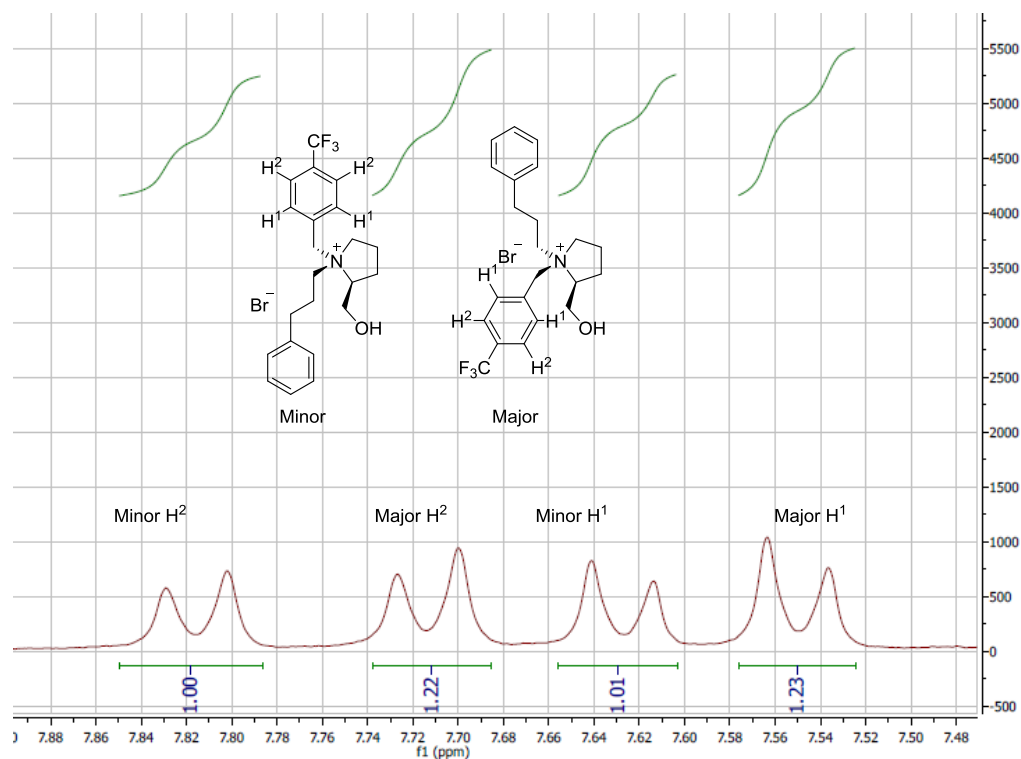
Figure 49 Aromatic proton resonance used to determine d.r.

Interpretation 9   ArH (δ ~8.1) e.g. **208f**
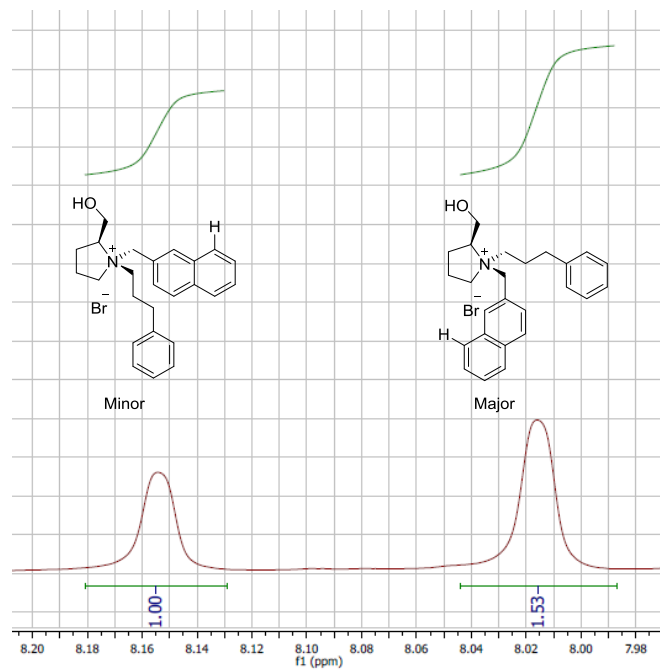
Figure 50 Aromatic proton resonance used to determine d.r.

Interpretation 10   OH (δ 5-6) e.g. **212e**
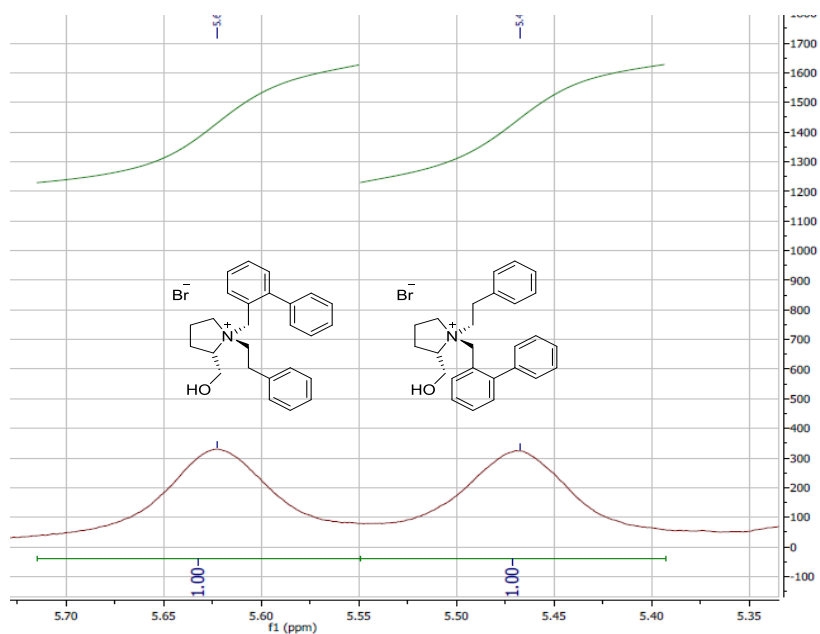
Figure 51 Hydroxyl proton used to determine d.r.

Interpretation 11   2x OMe (δ ~3.8) e.g. **207j**
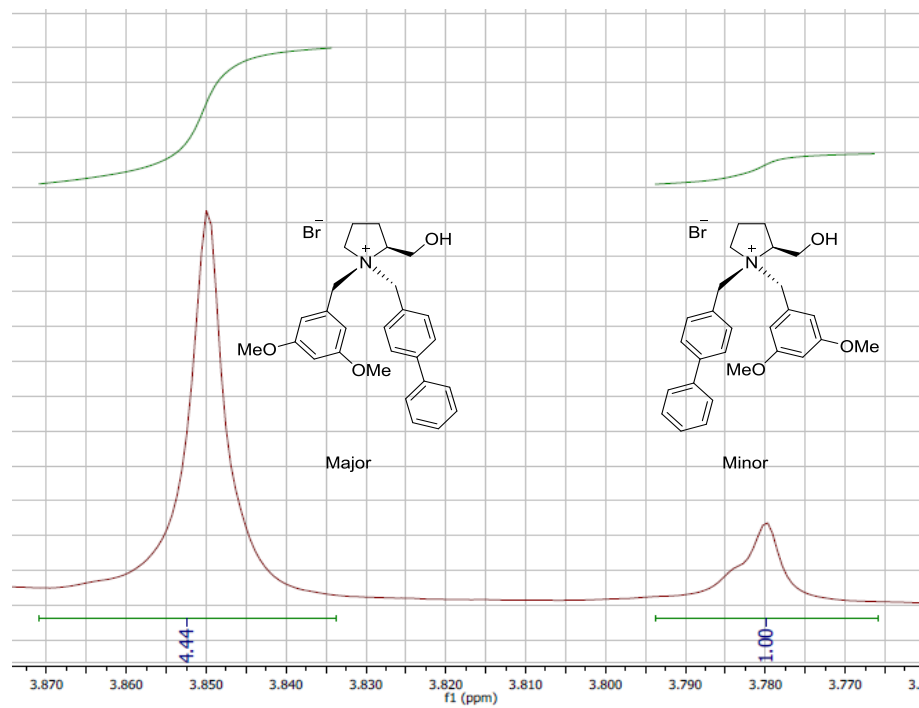
Figure 52 3,5-dimethoxy di-substituted benzyl resonance to determine d.r.

Interpretation 12   Me from *N*-butyl (δ ~0.9) e.g. **178l**
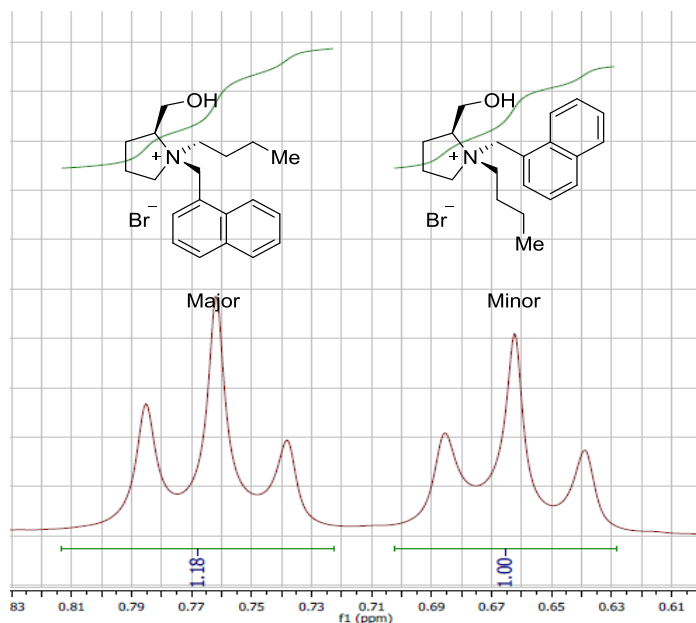
Figure 53 Pendant methyl resonance to determine d.r.

Interpretation 13   4-CF$_3$ (δ ~-63) e.g. **208c**
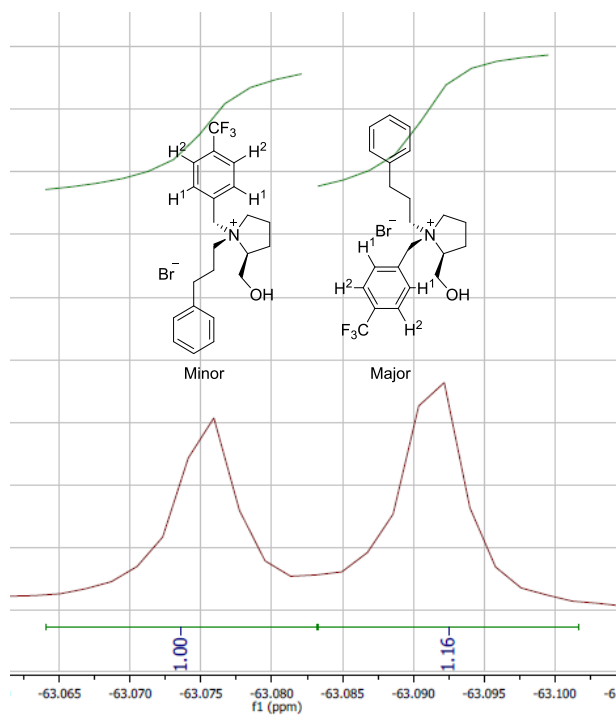
Figure 54 CF$_3$ resonance in ^{19}F NMR to determine the d.r.

Interpretation 14   3,5-bis-CF$_3$ (δ -63) e.g. **207a**
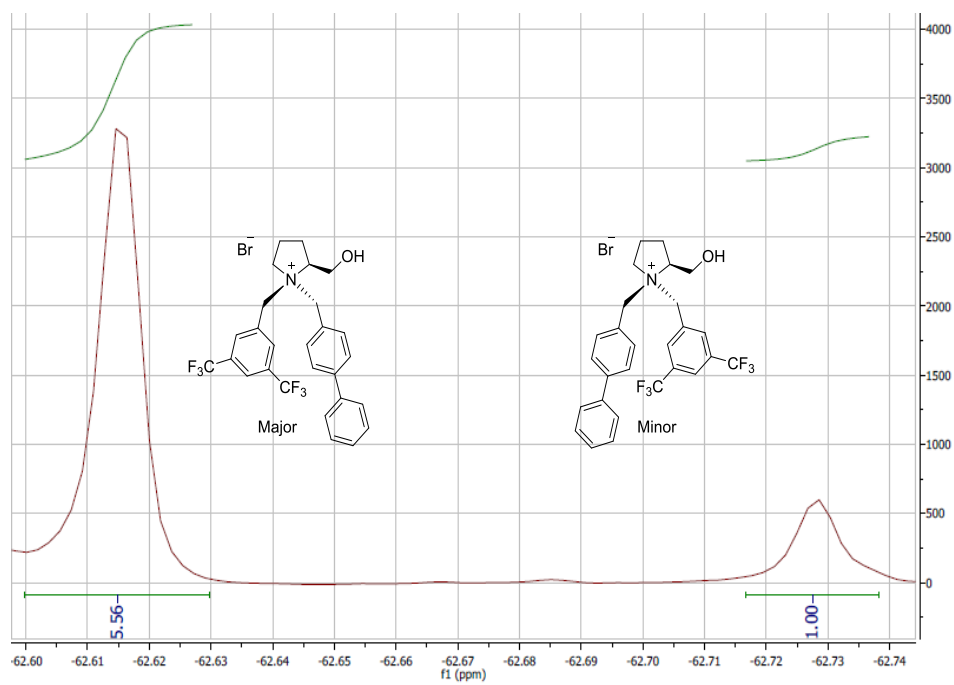
Figure 55 bis-**CF$_3$** resonance in ^{19}F NMR to determine the d.r.

Interpretation 15   CH$_3$ from *N*-ethyl (δ ~1.5) **151b**
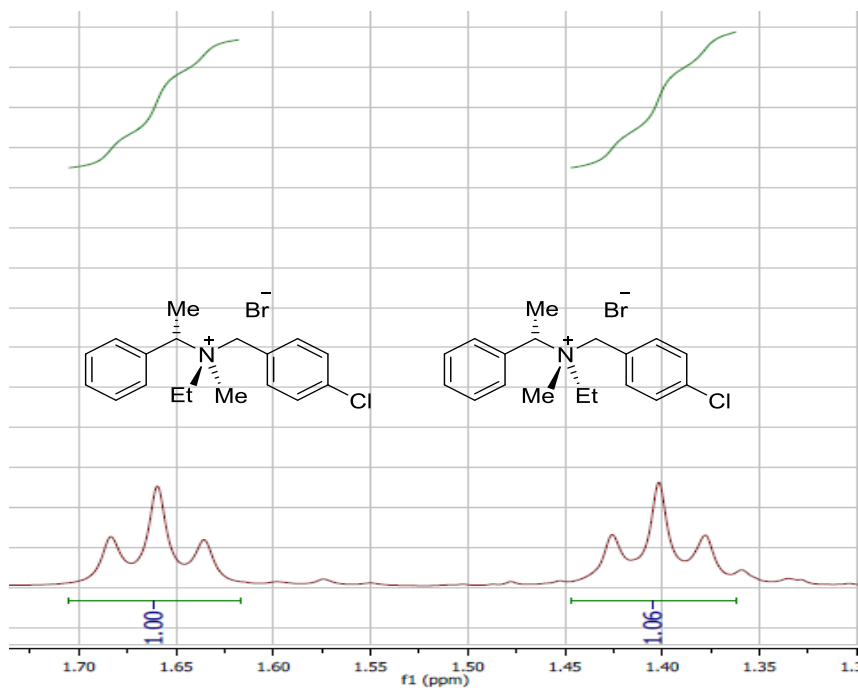
Figure 56 CH$_3$ resonance from *N*-ethyl group used to determine d.r.

Interpretation 16   CH$_3$ from α-methyl (δ ~2.0) **151a**
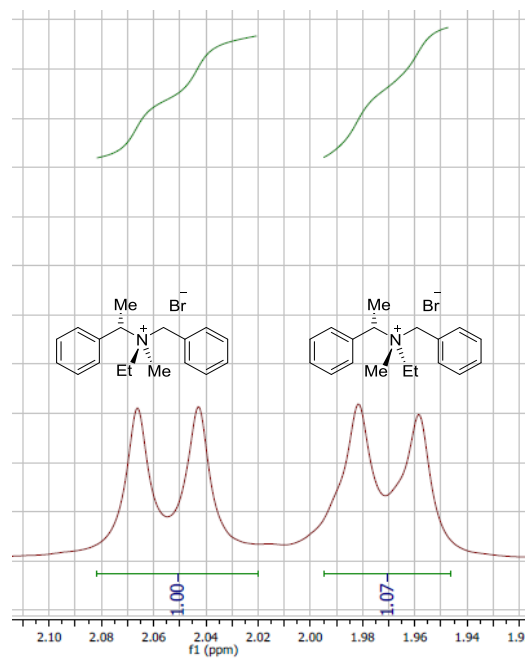
Figure 57 α-methyl resonance to determine d.r.

Interpretation 17   *N*-methyl (δ ~3.0) **151e**
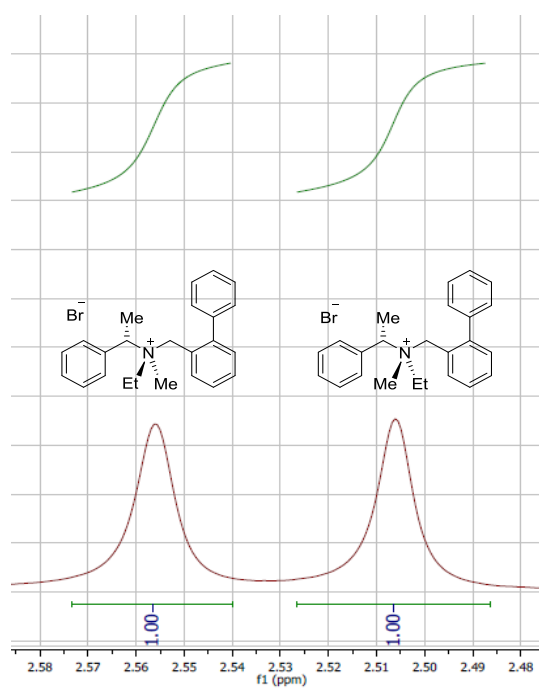
Figure 58 *N*-methyl resonance to determine the d.r.

6.4   1st generation experimental

(S)-N-ethyl-N-methyl-1-phenylethanamine 149

General procedure 1 (15 mmol scale) used to prepare the tertiary amine which was isolated as a yellow oil, 2.45 g in >99% yield. R_f = 0.65 in 10:1 CH$_2$Cl$_2$:MeOH. *m/z* ([M]+H) 164.1. HRMS ([M]+H) calcd for C$_{11}$H$_{18}$N: 164.1439; found 164.1445. $[\alpha]_D^{23}$= −26 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 7.49 − 7.18 (m, 5H, ArH), 3.56 (q, *J* = 6.7 Hz, 1H, 7), 2.67 − 2.28 (m, 2H, 10), 2.21 (s, 3H, 11), 1.38 (d, *J* = 6.7 Hz, 3H, 9), 1.05 (t, *J* = 7.1 Hz, 3H, 12). ^{13}C NMR δ 145.12 (5), 128.76 (4 and 6), 128.43 (1 and 3), 127.12 (2), 74.50 (7), 51.72 (10), 43.33 (11), 19.49 (9), 13.21 (12).IR 3375, 3024, 2983, 1608, 1491, 760, 694 cm^{-1}.
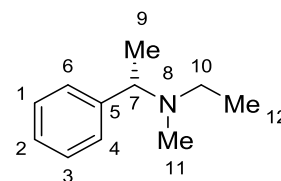
(S)-N-ethyl-N-(thiophen-2-ylmethyl)-1-phenyl-ethanamine 150a

General procedure 1 (5 mmol scale) used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.27 g in >99% yield. R_f = 0.20 in 10:1 CH$_2$Cl$_2$:MeOH. *m/z* ([M]+H) 246.1. HRMS ([M]+H) calcd for C$_{15}$H$_{20}$NS: 246.1316; found 246.1318. $[\alpha]_D^{23}$= −47 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 7.49 − 7.47 (m, 2H, 15 and 2), 7.35 (app t, *J* = 7.4 Hz, 2H, 6 and 4), 7.20 − 7.26 (m, 2H, 1 and 3), 6.90 − 6.96 (m, 2H, 13 and 14), 3.95 (q, *J* = 6.7 Hz, 1H, 7), 3.79 (ABq, J_{AB} = 14.7 Hz, 2H, 10), 2.73 − 2.45 (m, 2H, 11), 1.41 (d, *J* = 6.7 Hz, 3H, 9), 1.07 (t, *J* = 7.1 Hz, 3H, 17). ^{13}C NMR δ 145.41 (5), 144.39 (12), 128.48 (6 and 4), 127.06 (1 and 3), 126.63 (2), 126.58 (13), 124.65 (14), 124.37 (15), 57.22 (7), 49.11 (10), 46.12 (11), 24.44 (9), 13.84 (17). IR 3021, 2970, 1601, 1487, 1451, 1369, 762, 695 cm^{-1}.
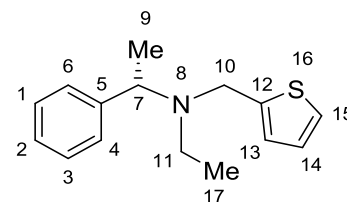
(S)-N-(3,4-dimethoxybenzyl)-1-phenylethanamine 155b
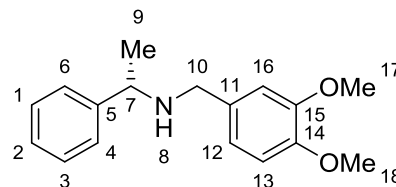
General Procedure 3 (5 mmol scale) was used to prepare the secondary amine which was isolated as a clear oil, 1.36 g in >99% yield. R_f = 0.17 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 272.2. HRMS ([M]+H) calcd for $C_{17}H_{22}NO_2$: 272.1651; found 272.1660. $[\alpha]_D^{23}$= −38 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.58 – 7.24 (m, 5H, ArH), 6.99 (d, J = 1.8 Hz, 1H, 16), 6.78 (m, 2H, 12 and 13), 3.97 (q, J = 6.7 Hz, 1H, 7), 3.84 (s, 3H, 17 or 18), 3.82 (s, 3H, 18 or 17), 3.70 (d, J_{AB} = 13.1 Hz, 1H, 10), 3.56 (d, J_{AB} = 13.1 Hz, 1H, 10), 1.54 (d, J = 6.8 Hz, 3H, 9). ^{13}C NMR δ 148.97 (15), 148.16 (14), 144.52 (5), 132.07 (11), 128.57 (6 and 4), 127.20 (1 and 3), 126.88 (2), 120.56 (12), 111.81 (13), 111.11 (16), 57.38 (2), 55.86 (10), 51.10 (17 and 18), 24.05 (9). IR 3324, 3081, 2958, 2833, 1591, 1513, 1462, 1450, 1233 cm^{-1}.

(S)-N-(3,4-dimethoxybenzyl)-N-ethyl-1- phenylethanamine 150b

General procedure 1 (5 mmol scale) was used to prepare the tertiary amine which was isolated as a clear oil, 1.26 g in 84% yield. R_f = 0.49 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 300.2. HRMS ([M]+H) calcd for $C_{19}H_{26}NO_2$: 300.1964; found 300.1967. $[\alpha]_D^{23}$= −50 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.53 – 7.20 (m, 5H, ArH), 7.01 – 6.78 (m, 3H, 13, 14 and 17), 4.01 – 3.79 (m, 1H, 10), 3.57 – 3.44 (m, 7H, 10, 19 and 18), 2.76 – 2.40 (m, 2H, 11), 1.41 (d, J = 6.8 Hz, 3H, 9), 1.05 (t, J = 7.1 Hz, 3H, 20). ^{13}C NMR δ 148.68 (18), 147.05 (17), 143.97 (5), 132.66 (12), 128.20 (6 and 4), 127.74 (1 and 3), 126.82 (2), 120.80 (13), 111.85 (14), 111.05 (17), 62.67 (7), 55.83 (19 or 18), 55.81 (18 or 19), 49.04 (10), 38.26 (11), 18.05 (9), 13.58 (20). IR 3061, 2940, 2838, 1587, 1507, 1461, 1450, 1221, 763, 700 cm^{-1}.
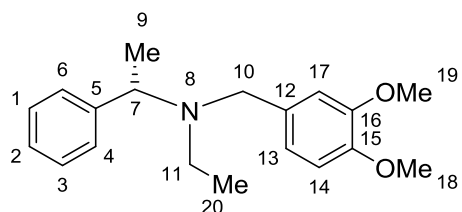
(*S*)-*N*-ethyl-2,2-dimethyl-*N*-(1-phenylethyl)propan-1-amine 150c
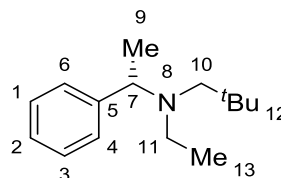
General procedure 1 (5 mmol scale) was used to prepare the tertiary amine which was isolated as a pale yellow oil, 0.98 g in 89% yield. R_f = 0.78 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 220.2. HRMS ([M]+H) calcd for $C_{15}H_{26}N$: 220.2065; found 220.2067. $[\alpha]_D^{23}$= −25 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 7.51 – 7.20 (m, 5H, ArH), 3.82 – 3.66 (q, *J* = 6.9 Hz, 1H, 7), 2.34 – 2.10 (m, 4H, 10 and 11), 1.37 (d, *J* = 6.9 Hz, 3H, 9), 1.09 (t, *J* = 7.1 Hz, 3H, 13) 0.91 (s, 9H, 12). ^{13}C NMR δ 145.18 (5), 128.83 (4 and 6), 128.37 (1 and 3), 127.21 (2), 73.11 (7), 64.22 (10), 50.03 (11), 31.65 (q12), 27.53 (12), 19.88 (9), 13.62 (13). IR 3022, 2985, 1607, 1488, 762, 691 cm^{-1}.

## (*S*)-*N*-(cyclohexylmethyl)-1-phenylethanamine 155d
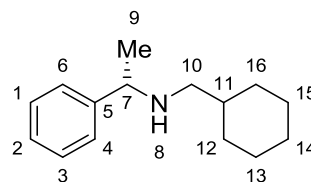
General procedure 1 (15 mmol) was used to prepare the secondary amine which was isolated as a dark yellow oil, 3.16 g in 97% yield. R_f = 0.70 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 218.2. HRMS ([M]+H) calcd for $C_{15}H_{24}N$: 218.1909; found 218.1912. $[\alpha]_D^{23}$= −26 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 7.39 – 7.22 (m, 5H, ArH), 3.75 (q, *J* = 6.6 Hz, 1H, 7), 2.37 (dd, *J* = 11.5, 6.2 Hz, 1H, 10), 2.26 (dd, *J* = 11.5, 7.1 Hz, 1H, 10), 1.84 – 1.59 (m, 5H), 1.52 – 1.35 (m, 5H), 1.30 – 1.08 (m, 3H), 0.99 – 0.77 (m, 1H). ^{13}C NMR δ 144.14 (5), 128.56 (4 and 6), 127.93 (1 and 3), 127.02 (2), 62.31 (7), 50.47 (10), 38.75 (11), 30.80 (12 and 16), 26.11 (14), 25.41 (13 and 15), 21.94 (9).

(*S*)-*N*-(cyclohexylmethyl)-*N*-ethyl-1-phenylethanamine 150d
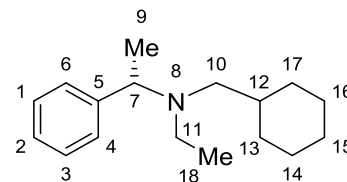
General procedure 1 (5 mmol scale) was used to prepare the tertiary amine which was isolated as a dark brown oil, 1.17 g in 95% yield.

R_f = 0.43 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 246.2. HRMS ([M]+H) calcd for $C_{17}H_{28}N$: 246.2222; found 246.2220. $[\alpha]_D^{23}$= −33 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 7.47 – 7.18 (m, 5H, ArH),

3.85 (q, J = 6.7 Hz, 1H, 7), 2.62 – 2.34 (m, 2H, 10 and 11), 2.20 (app dd, J = 12.8, 7.1 Hz, 2H, 10 and 11), 1.89 – 1.60 (m, 6H), 1.46 – 1.14 (m, 6H), 0.99 (t, J = 7.0 Hz, 3H, 18), 0.90 – 0.63 (m, 2H). ^{13}C NMR δ 144.14 (5), 128.56 (4 and 6), 127.93 (1 and 3), 127.02 (2), 62.31 (7), 50.47 (10), 38.75 (11), 30.80 (12 and 16), 26.11 (14), 25.41 (13 and 15), 21.94 (9).

(*S*)-*N*-(pyridin-4-ylmethyl)-1-phenylethanamine 155e

General Procedure 1 (15 mmol) was used to prepare the secondary amine which was isolated as a dark brown oil, 3.18 g in >99% yield.
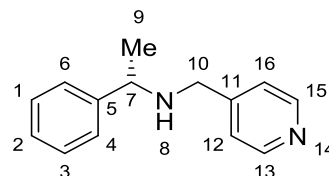
R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 213.1. HRMS ([M]+H) calcd for $C_{14}H_{17}N_2$: 213.1392; found 213.1393. $[\alpha]_D^{23}$= −41 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 8.54 (app dd, J = 4.5, 1.6 Hz, 2H, 13 and 15), 7.45 – 7.19 (m, 12 and 16, 7H, ArH), 3.81 (q, J = 6.6 Hz, 1H, 7), 3.69 (d, J_{AB} = 14.5 Hz, 1H, 10), 3.63 (d, J_{AB} = 14.5 Hz, 1H, 10), 2.36 (s, 1H, 8), 1.41 (d, J = 6.6 Hz, 3H, 9). ^{13}C NMR δ 150.32 (13 or 15), 149.69 (15 or 13), 144.90 (5), 128.58 (1 and 3), 127.18 (6 and 4), 126.62 (2), 123.02 (12 and 16), 57.66 (7), 50.47 (10), 24.38 (9). IR 3411, 3027, 2966, 1600, 1559, 1492, 1450, 1413, 761, 699 cm^{-1}.

(*S*)-*N*-ethyl-*N*-(pyridin-4-ylmethyl)-1-phenylethanamine 150e

General procedure 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark brown oil, 1.20 g in >99% yield. R_f = 0.58 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 241.2. HRMS ([M]+H) calcd for $C_{16}H_{21}N_2$: 241.1705; found 241.1708. $[\alpha]_D^{23}$= −47 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 8.52 (d, J = 5.9 Hz, 2H, 14 and 16), 7.50 – 7.20 (m, 7H, 13, 17 and ArH), 3.94 (q, J = 6.8 Hz, 1H, 7), 3.61 (d, J_{AB} = 15.1 Hz, 1H, 10), 3.52 (d, J_{AB} = 15.1 Hz, 1H, 10), 2.67 (dq, J = 14.0, 7.1 Hz, 1H, 11), 2.46 (dq, J = 14.1, 7.1 Hz, 1H, 11), 1.41 (d, J = 6.8 Hz, 3H, 9), 1.04 (t, J = 7.1 Hz, 3H, 18). ^{13}C NMR δ 150.30 (14
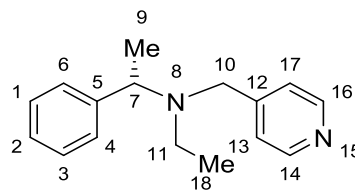
and 16), 149.65 (12), 144.90 (5), 128.58 (4 and 6), 127.18 (1 and 3), 126.64 (2), 122.97 (13 and 17), 57.64 (7), 50.43 (10), 49.06 (11), 24.38 (9), 13.84 (18).

(S)-N-(anthracen-9-ylmethyl)-N-methyl-1-phenylethanamine 148

General Procedure 1 (5 mmol scale) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.30 g in 80% yield. R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 312.3. [α] $_D^{23}$= −64 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 8.57 – 8.43 (m, 3H, 14, 17 and 24), 8.07 (d, J = 7.8 Hz, 2H, 20 and 21), 7.65 – 7.38 (m, 9H, ArH), 4.62 – 4.49 (m, 2H, 10), 3.98 (q, J = 6.6 Hz, 1H, 2), 2.17 (s, 3H, 25), 1.72 (d, J = 6.6 Hz, 3H, 4). ^{13}C NMR δ 143.88 (1), 134.06 (11), 131.55 (12 or 16), 130.95 (16 or 12), 129.10, 128.28 (13 or 15), 128.15 (15 or 13), 127.43, 127.13, 125.54, 125.23, 124.87, 64.12 (2), 50.61 (10), 37.54 (25), 17.03 (4). IR 3052, 2986, 2959, 1623, 1601, 1445, 1338, 1317, 761, 700 cm^{-1}.
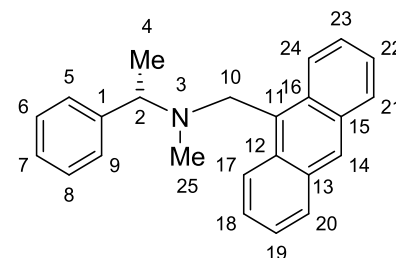
(S)-N-benzyl-N,N-dimethyl-1-phenylethanaminium trifluoromethanesulfonate 144a

General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as an amorphous oily solid, 0.21 g in 55% yield. R_f = 0.46 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 240.2. HRMS ([M]) calcd for $C_{17}H_{22}N$: 240.1747; found 240.1739. [α] $_D^{23}$= −12 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.68 – 7.34 (m, 10H, ArH), 5.11 (q, J = 6.9 Hz, 1H, 2), 4.62 (d, J_{AB} = 12.6 Hz, 1H, 10), 4.44 (d, J_{AB} = 12.6 Hz, 1H, 10), 2.95 (s, 3H, 18 or 17), 2.79 (s, 3H, 17 or 18), 1.94 (d, J = 6.9 Hz, 3H, 4). ^{13}C NMR δ 133.25 (1), 132.65 (11), 130.79 (5, 9, 12 and 16), 129.39 (6 and 8), 129.27 (13 and 15), 127.06 (7 and 14), 74.57 (2), 65.91 (10), 46.83 (17 or 18), 45.56 (18 or 17), 15.22 (4). ^{19}F NMR δ -78.29 (s). IR 3028, 2983, 1600, 1463, 1374, 760, 702 cm^{-1}.
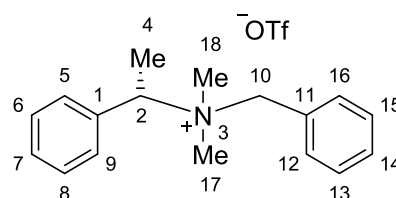
(S)-N-ethyl-N-methyl-N-(4-(trifluoromethyl)benzyl)-1-phenylethanaminium bromide 151d

General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.33 g in 83% yield and d.r. 1:1 (Interpretation 13, 15 and 16 used). R_f = 0.25 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 322.2. HRMS ([M]) calcd for $C_{19}H_{23}F_3N$: 322.1777; found 322.1780. ^{1}H NMR δ 2.07 (d, *J* = 7.0 Hz, 3H, 1), 1.97 (d, *J* = 7.0 Hz, 3H, 1), 1.65 (t, *J* = 7.0 Hz, 3H, 2), 1.40 (t, *J* = 7.0 Hz, 3H, 2). ^{19}F NMR δ -63.08 (s, 3F, 3), -63.03 (s, 3F, 3). IR 3021, 2987, 1594, 1462, 1370, 761, 701 cm^{-1}.
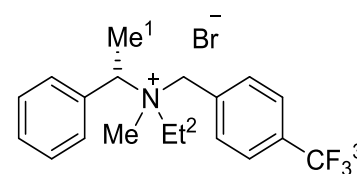
(S)-N-benzyl-N-ethyl-N-methyl-1-phenylethanaminium bromide 151a
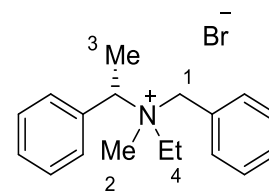
General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.33 g in 99% yield and d.r. 1:1 (Interpretation 1, 15, 16 and 17 used). R_f = 0.30 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 254.2. HRMS ([M]) calcd for $C_{18}H_{24}N$: 254.1903; found 254.1907. ^{1}H NMR δ 4.43 (d, J_{AB} = 12.7 Hz, 1H, 1), 4.26 (d, J_{AB} = 13.1 Hz, 1H, 1), 2.98 (s, 3H, 2), 2.96 (s, 3H, 2), 2.05 (d, *J* = 6.9 Hz, 3H, 3), 1.97 (d, *J* = 6.9 Hz, 3H, 3), 1.66 (t, *J* = 7.2 Hz, 3H, 4), 1.41 (t, *J* = 7.2 Hz, 3H, 4). IR 3030, 2972, 1586, 1461, 1374, 763, 700 cm^{-1}.

(S)-N-ethyl-N-methyl-N-(thiophen-2-ylmethyl)-1-phenylethanaminium trifluoromethanesulfonate 152a
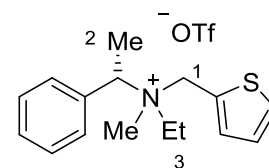
General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.38 g in 93% yield and d.r. 1:1 (Interpretation 1, 15 and 16 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 260.1. HRMS ([M]) calcd for $C_{16}H_{22}NS$: 260.1467; found 260.1470. ^{1}H NMR δ 4.67 (d, J_{AB} = 13.8 Hz, 1H, 1), 4.55 (d, J_{AB} = 14.3 Hz, 1H, 1), 4.20 (d, J_{AB} = 14.3 Hz,

1H, 1), 1.89 (d, J = 7.1 Hz, 3H, 2), 1.81 (d, J = 7.0 Hz, 3H, 2), 1.51 (t, J = 7.2 Hz, 3H, 3), 1.36 (t, J = 7.2 Hz, 3H, 3). ^{19}F NMR δ -78.44 (s). IR 3035, 2984, 1590, 1464, 761, 702 cm^{-1}.

(*S*)-*N*-(4-chlorobenzyl)-*N*-ethyl-*N*-methyl-1-phenylethanaminium bromide 151b

General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.32 g in 88% yield and d.r. 1:1 (Interpretation 1, 15, 16 and 17 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 288.2. HRMS ([M]) calcd for $C_{18}H_{23}ClN$: 288.1514; found 288.1520. ^{1}H NMR δ 4.52 (d, J_{AB} = 12.7 Hz, 1H, 1), 4.43 (d, J_{AB} = 13.1 Hz, 1H, 1), 2.98 (s, 3H, 2), 2.97 (s, 3H, 2), 2.08 (d, J = 7.0 Hz, 3H, 3), 1.99 (d, J = 6.9 Hz, 3H, 3), 1.66 (t, J = 7.2 Hz, 3H, 4), 1.40 (t, J = 7.2 Hz, 3H, 4). IR 3015, 2964, 1600, 1462, 762, 701 cm^{-1}.
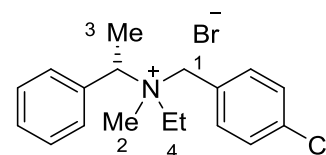
(*S*)-*N*-ethyl-*N*-(4-methoxybenzyl)-*N*-methyl-1-phenylethanaminium bromide 151c

General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.34 g in 93% yield and d.r. 1:1 (Interpretation 1, 15, 16 and 17 used). R_f = 0.26 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 284.2. HRMS ([M]) calcd for $C_{19}H_{26}NO$: 284.2009; found 284.2008. ^{1}H NMR δ 4.51 (d, J_{AB} = 12.8 Hz, 1H, 1), 4.33 (d, J_{AB} = 13.2 Hz, 1H, 1), 2.98 (s, 3H, 2), 2.94 (s, 3H, 2), 2.06 (d, J = 7.0 Hz, 3H, 3), 1.98 (d, J = 7.2 Hz, 3H, 3), 1.65 (t, J = 7.2 Hz, 3H, 4), 1.39 (t, J = 7.2 Hz, 3H, 4). IR 3028, 2969, 1600, 1480, 760, 699 cm^{-1}.
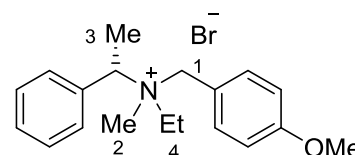
(*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-ethyl-*N*-methyl-1-phenylethanaminium bromide 151e

General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.38 g in 92% yield and d.r. 1:1 (Interpretation 15, 16 and 17 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 330.2. HRMS ([M]) calcd for $C_{24}H_{28}N$: 330.2216; found 330.2212. ^{1}H NMR δ 2.56 (s, 3H, 1), 2.51 (s, 3H, 1), 1.82 (d, *J* = 7.1 Hz, 3H, 2), 1.78 (d, *J* = 6.9 Hz, 3H, 2), 1.53 (t, *J* = 7.2 Hz, 3H, 3), 1.30 (t, *J* = 7.3 Hz, 3H, 3). IR 3030, 2962, 1590, 1470, 761, 701 cm^{-1}.
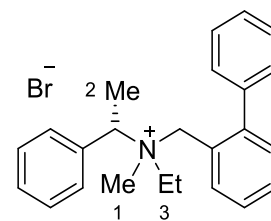
(*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-ethyl-*N*-methyl-1-phenylethanaminium trifluoromethanesulfonate 152b
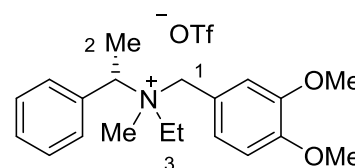
General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.37 g in 79% yield and d.r. 3:2 although unable to confirm the major diastereoisomer (Interpretation 1, 15 and 16 used). R_f = 0.24 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 314.2. HRMS ([M]) calcd for $C_{20}H_{28}NO_2$: 314.2115; found 314.2112. ^{1}H NMR δ 4.70 (d, J_{AB} = 12.9 Hz, 1H, 1), 4.57 (d, J_{AB} = 13.2 Hz, 1.6H, 1), 4.23 (d, J_{AB} = 12.9 Hz, 1H, 1), 4.14 (d, J_{AB} = 13.2 Hz, 1.6H, 1), 1.95 (d, *J* = 6.5 Hz, 3H, 2), 1.89 (d, *J* = 6.9 Hz, 4.8H, 2), 1.55 (t, *J* = 7.1 Hz, 4.8H, 3), 1.37 (t, *J* = 7.1 Hz, 3H, 3). ^{19}F NMR δ -78.20 (s). IR 3020, 2988, 1594, 1487, 760, 704 cm^{-1}.

(*S*)-*N*-(cyclohexylmethyl)-*N*-ethyl-*N*-methyl-1-phenylethanaminium trifluoromethanesulfonate 152d
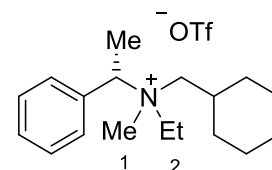
General method 2 (1 mmol scale) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.18 g in 44% yield

127

and d.r. 1:1 (Interpretation 15 and 17 used). R_f = 0.24 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 260.2. HRMS ([M]) calcd for $C_{18}H_{30}N$: 260.2373; found 260.2375. ^{1}H NMR δ 2.96 (s, 3H, 1), 2.94 (s, 3H, 1), 1.47 (t, *J* = 7.2 Hz, 3H, 2), 1.40 (t, *J* = 7.0 Hz, 3H, 2). ^{19}F NMR δ -78.23 (s). IR 3032, 2988, 1594, 1487, 760, 704 cm^{-1}.

N-ethyl-*N*-2,2-trimethyl-*N*-((*S*)-1-phenylethyl)propan-1-aminium trifluoromethanesulfonate 152c
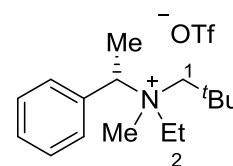
General method 2 (1 mmol scale) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.26 g in 67% yield

and d.r. 2:1 although unable to determine the major diastereoisomer (Interpretation 1 and 15

used). R_f = 0.24 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]) 234.2. HRMS ([M]) calcd for $C_{16}H_{28}N$:

234.2216; found 234.2217. ^{1}H NMR δ 4.70 (d, J_{AB} = 12.8 Hz, 1H, 1), 4.56 (d, J_{AB} = 13.2 Hz, 2H,

1), 4.26 (d, J_{AB} = 12.8 Hz, 1H, 1), 4.18 (d, J_{AB} = 13.2 Hz, 2H, 1), 1.56 (t, *J* = 7.2 Hz, 6H, 2), 1.38

(t, *J* = 7.2 Hz, 3H, 2). ^{19}F NMR δ -78.31 (s). IR 3018, 2967, 1590, 1486, 761, 703 cm^{-1}.

(*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-ethyl-*N*-methyl-1-phenylethanaminium hexafluorophosphate(V) 158
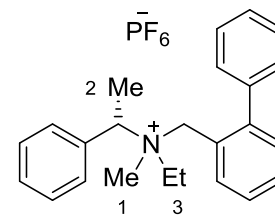
To a round bottom flask was added ammonium salt **151e** (1 equiv, 1

mmol, 0.41 g) followed by acetone (10 mL) and the mixture was stirred

until completely dissolved. Then potassium hexafluorophosphate (2 equiv, 2 mmol, 0.37 g) was

added and the mixture was stirred for 12 hours. To the reaction mixture was added water (20 mL)

and the phases were added to a separating funnel and the mixture was extracted with CH_2Cl_2 (3 x

20 mL). The combined organic phases were dried with magnesium sulfate and the solvent

removed under reduced pressure to afford the anion-exchanged product as a white crystalline salt,

0.40 g in 85% yield and d.r. 1:1 (Interpretation 15, 16 and 17 used). R_f = 0.40 in 10:1

CH₂Cl₂:MeOH. *m/z* ([M]) 330.2. HRMS ([M]) calcd for $C_{24}H_{28}N$: 330.2216; found 330.2212.

MP 132 °C. ^{1}H NMR δ 2.56 (s, 3H, 1), 2.51 (s, 3H, 1), 1.82 (d, *J* = 7.1 Hz, 3H, 2), 1.78 (d, *J* = 6.9 Hz, 3H, 2), 1.53 (t, *J* = 7.2 Hz, 3H, 3), 1.30 (t, *J* = 7.3 Hz, 3H, 3). ^{19}F NMR δ -71.21 (d, *J* = 713.5 Hz). ^{31}P NMR δ -144.12 (hept, *J* = 713.5 Hz). IR 3030, 2962, 1590, 1470, 761, 701 cm⁻¹.

6.5 2nd Generation experimental

(*S*)-*N*-((naphthalen-1-ylmethyl)amino)propan-2-ol 160a

General method 1 (15 mmol) was used to prepare the secondary amine which was isolated as a yellow solid, 3.16 g in 98% yield. R_f = 0.41 in 10:1 CH₂Cl₂:MeOH. *m/z* ([M]+H) 216.1. HRMS ([M]+H) calcd for $C_{14}H_{18}NO$: 216.1388; found 216.1390. $[\alpha]_D^{23}$ = −15 (*c* 1.0, CH₂Cl₂). Mp = 96-98 °C. ^{1}H NMR δ 8.13 (d, *J* = 8.2 Hz, 1H, ArH), 7.96 − 7.73 (m, 2H, ArH), 7.62 − 7.39 (m, 4H, ArH), 4.27 (ABq, *J* = 13.2 Hz, 2H, NHC*H₂*C), 3.84 (dqd, *J* = 9.3, 6.2, 3.0 Hz, 1H, C*H*Me), 2.86 (dd, *J* = 12.0, 3.0 Hz, 1H, NHC*H*H), 2.55 (dd, *J* = 12.0, 9.5 Hz, 1H, NHCH*H*), 2.49 − 2.09 (s br, 2H, N*H* and O*H*), 1.18 (d, *J* = 6.2 Hz, 3H, Me). ^{13}C NMR δ 135.62 (1), 133.92 (5), 131.73 (10), 128.80 (2), 128.00 (6), 126.23 (3), 126.17 (4), 125.74 (8), 125.37 (7), 123.58 (9), 65.71 (14), 57.00 (13), 51.44 (11), 20.40 (16).
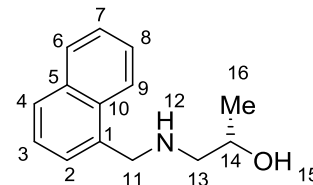
(*S*)-*N*-((naphthalen-2-ylmethyl)amino)propan-2-ol 160b
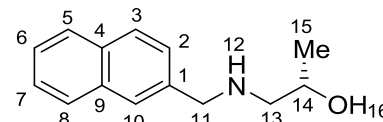
General method 1 (15 mmol) was used to prepare the secondary amine which was isolated as a yellow oil, 3.03 g in 94% yield. R_f = 0.40 in 10:1 CH₂Cl₂:MeOH. *m/z* ([M]+H) 216.1. HRMS ([M]+H) calcd for $C_{14}H_{18}NO$: 216.1388; found 216.1383. $[\alpha]_D^{23}$ = −15 (*c* 1.0, CH₂Cl₂). ^{1}H NMR δ 7.92 − 7.67 (m, 4H, ArH), 7.59 − 7.38 (m, 3H, ArH), 3.97 (ABq, *J* = 12.0 Hz, 2H, 11), 3.82 (dqd, *J* = 9.4, 6.2, 3.0 Hz, 1H, 14), 2.78 (dd, *J* = 12.0, 3.0 Hz, 1H, 13), 2.47 (dd, *J* = 12.0, 9.4 Hz, 1H, 13), 2.22 (s br, 2H, 12 and 16), 1.15 (d, *J* = 6.2 Hz, 3H, 15). [13]C

NMR δ 137.60 (1), 133.41 (9), 132.70 (4), 128.22 (2), 127.69 (5), 126.47 (8), 126.43 (3), 126.11 (10), 125.67 (7 and 6), 65.74 (143), 56.29 (13), 53.78 (11), 20.44 (15).

(S)-N-((quinolin-4-ylmethyl)amino)propan-1-ol 160d

General method 1 (15 mmol) was used to prepare the secondary amine which was isolated as a dark yellow oil, 3.05 g in 94% yield. R_f = 0.52 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 217.2. HRMS ([M]+H) calcd for $C_{13}H_{17}N_2O$: 217.1341; found 217.1344. $[\alpha]_D^{23}$= -16.1 (c 1.0, $CHCl_3$). ^1H NMR δ 8.85 (d, J = 4.4 Hz, 1H, 2), 8.11 (m, 2H, 7 and 10), 7.73 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, 9), 7.59 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, 8), 7.46 (d, J = 4.4 Hz, 1H, 3), 4.39 (d, J_{AB} = 13.8 Hz, 1H, 11), 4.23 (d, J_{AB} = 13.8 Hz, 1H, 11), 3.70 (dd, J = 10.7, 4.0 Hz, 1H, 14), 3.39 (dd, J = 10.7, 6.5 Hz, 1H, 13), 2.99 (dqd, J = 13.0, 6.5, 4.0 Hz, 1H, 14), 1.89 (s br, 2H, 12 and 15), 1.19 (d, J = 6.5 Hz, 3H, 16). ^{13}C NMR δ 150.40 (2), 148.30 (6), 145.81 (4), 130.29 (7 or 10), 129.37 (10 or 7), 127.07 (5), 126.64 (8), 123.28 (9), 120.06 (3), 65.95 (13), 54.74 (14), 51.16 (11), 17.31 (16).
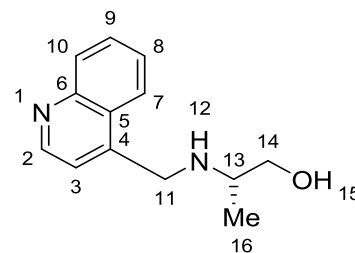
(S)-N-((quinolin-4-ylmethyl)amino)propan-2-ol 160e

General method 1 (15 mmol) was used to prepare the secondary amine which was isolated as a dark yellow oil, 3.11 g in 96% yield. R_f = 0.27 in 20:1 CH_2Cl_2:MeOH. m/z ([M]+H) 217.2. HRMS ([M]+H) calcd for $C_{13}H_{17}N_2O$: 217.1341; found 217.1343. $[\alpha]_D^{23}$= -18 (c 1.0, $CHCl_3$). ^1H NMR δ 8.85 (d, J = 4.4 Hz, 1H, 2), 8.15 – 8.05 (m, 2H, 7 and 10), 7.72 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, 9), 7.58 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, 8), 7.42 (d, J = 4.4 Hz, 1H, 3), 4.39 – 4.20 (m, 2H, 11), 3.89 (dqd, J = 9.2, 6.2, 3.0 Hz, 1H, 14), 2.85 (dd, J = 12.0, 3.0 Hz, 1H, 13), 2.58 (dd, J = 12.0, 9.2 Hz, 1H, 13), 1.19 (d, J = 6.2 Hz, 3H, 16). ^{13}C NMR δ 150.27 (2), 148.20 (6), 145.40 (4), 130.18 (7 or 10), 129.25
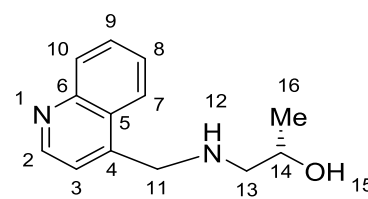
(10 or 7), 126.92 (5), 126.70 (8), 123.14 (9), 119.83 (3), 65.98 (14), 56.88 (13), 49.65 (11), 20.58 (16).

(S)-N-((naphthalen-1-ylmethyl)amino)-3-phenylpropan-1-ol 160f

General method 1 (15 mmol) was used to prepare the secondary amine which was isolated as a pale yellow solid, 4.11 g in 94% yield. R_f = 0.32 in 20:1 CH_2Cl_2:MeOH. m/z ([M]+H) 292.2. HRMS ([M]+H) calcd for $C_{20}H_{22}NO$: 292.1701; found 292.1702. MP = 85-88 °C. $[\alpha]_D^{23}$= -24 (c 1.0, $CHCl_3$). ^{1}H NMR δ 8.14 – 7.66 (m, 3H, ArH), 7.40 (m, 9H, ArH), 4.39 – 4.08 (m, 2H, 7), 3.75 (dd, J = 10.7, 3.9 Hz, 1H, 10), 3.41 (dd, J = 10.7, 5.4 Hz, 1H, 10), 3.19 – 3.03 (m, 1H, 9), 2.95 – 2.76 (m, 2H, 12), 1.64 (s br, 2H, 8 and 11). ^{13}C NMR δ 138.39 (13), 135.48 (5), 133.88 (3), 131.66 (4), 129.16, 128.75, 128.61, 128.03, 126.49, 126.26, 125.68, 125.34, 123.39, 62.76 (10), 60.31 (9), 49.26 (7), 38.24 (12).
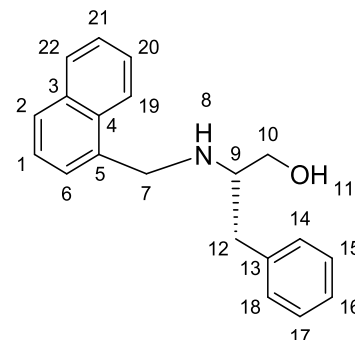
An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.1.

(S)-N-(butyl(naphthalen-1-ylmethyl)amino)propan-2-ol 162a

General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.08 g in 80% yield. R_f = 0.59 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 272.2. HRMS ([M]+H) calcd for $C_{18}H_{26}NO$: 272.2014; found 272.2012. $[\alpha]_D^{23}$= -90 (c 1.0, $CHCl_3$). ^{1}H NMR δ 8.20 (d, J = 8.5 Hz, 1H, 7), 7.90 – 7.73 (m, 2H, 1 and 10), 7.57 – 7.35 (m, 4H, ArH), 4.29 (d, J_{AB} = 13.2 Hz, 1H, 11), 3.80 (d, J_{AB} = 13.2 Hz, 1H, 11), 3.76 – 3.65 (m, 1H, 14), 3.22 (s br, 1H, 15), 2.73 – 2.56 (m, 1H, 13), 2.56 – 2.29 (m, 3H, 13 and 17), 1.71 – 1.43 (m, 2H, 18), 1.41 – 1.11 (m, 2H, 19), 1.02 (d, J = 6.1 Hz, 3H, 16), 0.86 (t, J = 7.3 Hz, 3H, 20). ^{13}C NMR δ 134.59 (4), 133.93 (6), 132.29
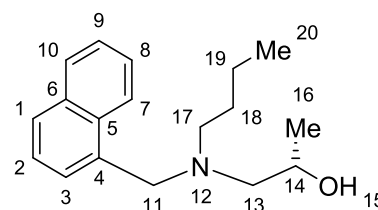
(5), 128.75, 128.19, 127.60, 126.04, 125.69, 125.12, 123.87, 63.33 (14), 62.08 (13), 57.72 (11), 54.57 (17), 28.78 (18), 20.66 (19), 19.76 (16), 14.00 (20).

(S)-N-(methyl(naphthalen-1-ylmethyl)amino)propan-2-ol 162c

General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 0.94 g in 82% yield. R_f = 0.59 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 230.2. HRMS ([M]+H) calcd for $C_{15}H_{20}NO$: 230.1545; found 230.1549. $[\alpha]_D^{23}$= -89 (c 1.0, $CHCl_3$). ^{1}H NMR δ 8.22 (d, J = 8.6 Hz, 1H, 7), 8.02 – 7.70 (m, 2H, 1 and 10), 7.68 – 7.30 (m, 4H, ArH), 4.07 (d, J_{AB} = 12.8 Hz, 1H, 11), 4.01 – 3.79 (d and m overlapping, J_{AB} = 12.8 Hz, 2H, 11 and 14), 3.33 (s br, 1H, 15), 2.51 – 2.40 (m, 2H, 13), 2.29 (s, 3H, 17), 1.13 (d, J = 6.1 Hz, 3H, 16). ^{13}C NMR δ 134.18 (4), 133.96 (6), 132.34 (5), 128.67, 128.33, 127.73, 126.10, 125.72, 125.05, 124.17, 65.33 (14), 63.10 (13), 61.27 (11), 42.00 (17), 19.88 (16).
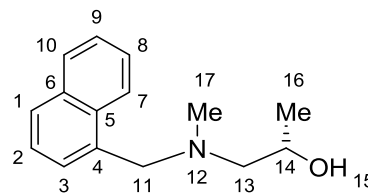
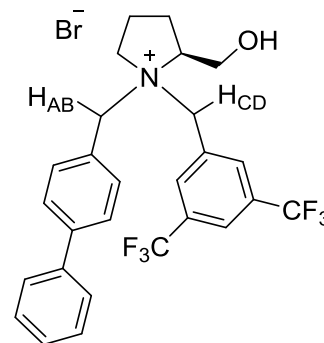### (S)-N-(butyl(naphthalen-2-ylmethyl)amino)propan-2-ol 162b

General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.11 g in 82% yield. R_f = 0.57 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 272.2. HRMS ([M]+H) calcd for $C_{18}H_{26}NO$: 272.2014; found 272.2010. $[\alpha]_D^{23}$= -9 (c 1.0, $CHCl_3$). ^{1}H NMR δ 7.88 – 7.76 (m, 3H, ArH), 7.68 (s, 1H, ArH), 7.52 – 7.39 (m, 3H, ArH), 3.98 (d, J_{AB} = 13.5 Hz, 1H, 7), 3.88 – 3.75 (m, 1H, 10), 3.55 (s br and d overlapping, J_{AB} = 13.5 Hz, 2H, 7 and 11), 2.66 – 2.54 (m, 1H, 9), 2.48 – 2.31 (m, 3H, 17 and 9), 1.58 – 1.41 (m, 2H, 18), 1.31 – 1.24 (m, 2H, 19), 1.09 (d, J = 6.1 Hz, 3H, 12), 0.86 (t, J = 7.3 Hz, 3H, 20). ^{13}C NMR δ 136.62 (4), 133.32 (2), 132.77 (1), 128.14, 127.71, 127.66, 127.50, 127.06, 126.03,
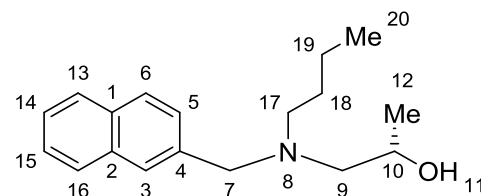
125.64, 63.11 (10), 61.97 (9), 59.03 (7), 53.79 (17), 29.17 (18), 20.51 (19), 19.85 (12), 14.02 (20).

(S)-N-(methyl(naphthalen-1-ylmethyl)amino)propan-1-ol 162d

General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.07 g in 93% yield. R_f = 0.57 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 272.2. HRMS ([M]+H) calcd for $C_{18}H_{20}NO$: 230.1545; found 230.1548.
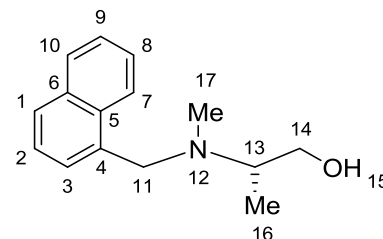
$[\alpha]_D^{23}$= -101 (c 1.0, CHCl₃). ^{1}H NMR δ 8.18 (d, J = 8.6 Hz, 1H, 7), 8.00 – 7.72 (m, 2H, 10 and 1), 7.68 – 7.31 (m, 4H, ArH), 4.10 (d, J_{AB} = 12.9 Hz, 1H, 11), 4.03 (d, J_{AB} = 12.9 Hz, 1H, 11), 3.39 (d, J = 7.8 Hz, 2H, 14), 3.19 – 2.99 (m, 1H, 13), 2.18 (s, 3H, 17), 1.02 (d, J = 6.6 Hz, 3H, 16). ^{13}C NMR δ 134.43 (4), 134.00 (6), 132.35 (4), 128.71, 128.26, 127.50 (5), 126.14, 125.72, 125.05, 124.04, 62.97 (13), 58.06 (14), 57.22 (11), 34.13 (17), 8.01 (16).

(S)-N-(methyl(quinolin-4-ylmethyl)amino)propan-1-ol 162e

General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 0.77 g in 67% yield. R_f = 0.33 in 20:1 CH_2Cl_2:MeOH. m/z ([M]+H) 231.1.
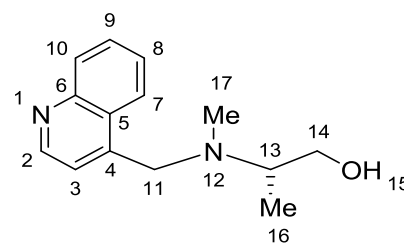
HRMS ([M]+H) calcd for $C_{14}H_{19}N_2O$: 231.1497; found 231.1494. $[\alpha]_D^{23}$= +29.5 (c 1.0, CHCl₃). ^{1}H NMR δ 8.89 (d, J = 4.3 Hz, 1H, 2), 8.16 (app d, J = 8.5 Hz, 2H, 7 and 10), 7.74 (ddd, J = 8.5, 7.0, 1.3 Hz, 1H, 9), 7.60 (ddd, J = 8.5, 7.0, 1.3 Hz, 1H, 8), 7.41 (d, J = 4.3 Hz, 1H, 3), 4.12 (d, J_{AB} = 13.8 Hz, 1H, 11), 4.03 (d, J_{AB} = 13.8 Hz, 1H, 11), 3.54 – 3.36 (m, 2H, 13 and 14), 3.09 (m, 1H, 14), 2.23 (s, 3H, 17), 1.68 (s br, 1H, 15), 1.05 (d, J = 6.6 Hz, 3H, 16). ^{13}C NMR δ 150.10 (2), 148.52 (6), 144.23 (4), 130.27 (9 or 10), 129.23 (10 or 9), 127.52 (5), 126.65, 123.55, 121.37, 63.10 (13), 59.14 (14), 55.49 (11), 34.94 (17), 8.04 (16).

(*S*)-*N*-(methyl(quinolin-4-ylmethyl)amino)propan-2-ol 162f
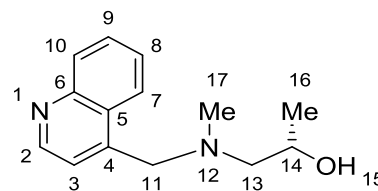
General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 0.47 g in 41% yield. R_f = 0.70 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 231.1. HRMS ([M]+H) calcd for $C_{14}H_{19}N_2O$: 231.1497; found 231.1494. [α] $_D^{23}$= +22.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 8.89 (d, *J* = 4.4 Hz, 1H, 2), 8.17 (2 x d, *J* = 8.5 Hz, 2H, 10 and 7), 7.74 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H, 9), 7.60 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H, 8), 7.40 (d, *J* = 4.4 Hz, 1H, 3), 4.09 (d, J_{AB} = 13.7 Hz, 1H, 11), 4.04 – 3.79 (d and m overlapping, J_{AB} = 13.7 Hz, 2H, 11 and 14), 3.18 (s, 1H, 15), 2.61 – 2.38 (m, 2H, 13), 2.32 (s, 3H, 17), 1.15 (d, *J* = 6.1 Hz, 3H, 16). ^{13}C NMR δ 150.10 (2), 148.51 (6), 143.85 (4), 130.23 (10 or 9), 129.25 (9 or 10), 127.47 (5), 126.64 (8), 123.68 (7), 121.57 (3), 65.66 (14), 63.26 (13), 59.72 (11), 42.31 (17), 19.91 (16).

(*S*)-*N*-(methyl(naphthalen-1-ylmethyl)amino)-3-phenylpropan-1-ol 162g
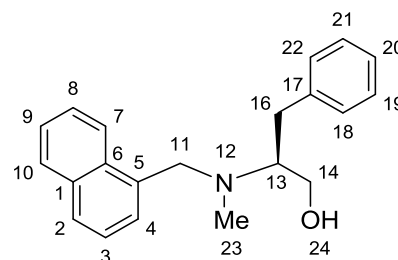
General method 1 (5 mmol) was used to prepare the tertiary amine which was isolated as a dark yellow oil, 1.45 g in 95% yield. R_f = 0.62 in 20:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 306.2. HRMS ([M]+H) calcd for $C_{21}H_{24}NO$: 306.1858; found 216.1857. [α] $_D^{23}$= -87 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 8.15 (d, *J* = 8.3 Hz, 1H, 7), 8.03 – 7.72 (m, 2H, 10 and 2), 7.61 – 7.15 (m, 9H, ArH), 4.29 – 4.04 (ABq, J_{AB} = 13.2 Hz, 2H, 11), 3.56 – 3.29 (m, 2H, 16), 3.25 – 3.11 (m, 2H, 13 and 14), 2.60 – 2.39 (m, 1H, 14), 2.35 (s, 3H, 23), 1.62 (s, 1H, 24). ^{13}C NMR δ 139.25 (17), 134.20 (5), 134.04 (1), 132.30 (6), 129.04 (4 or 10), 128.77 (10 or 4), 128.58, 128.41, 127.61, 126.24, 126.22, 125.78, 125.03, 123.95 (7), 64.83 (13), 60.63 (14), 57.63 (11), 34.73 (23), 31.06 (16).

N-benzyl-N-((S)-2-hydroxypropyl)-N-(naphthalen-1-ylmethyl)butan-1-aminium bromide 164a

General method 2 (1 mmol) was used to prepare the ammonium salt and was isolated as a diastereomeric mixture as an amorphous oily solid, 0.31 g in 71% yield in d.r. 1.0:3.3 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.53 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 362.2. HRMS ([M]+H) calcd for $C_{25}H_{32}NO$: 362.2490; found 362.2484. ^{1}H NMR δ 5.46 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.24 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 3.3H), 5.07 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 3.3H), 5.00 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 3.3H), 4.90 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 3.3H), 4.72 (d, $J_{AB\ or\ CD}$ = 11.2 Hz, 1H), 4.62 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.53 (d, $J_{AB\ or\ CD}$ = 11.2 Hz, 1H). IR 3440, 3038, 2961, 1587, 1464, 1378, 761, 703 cm^{-1}.
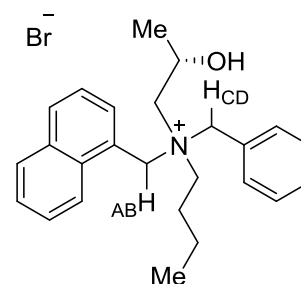
N-benzyl-N-((S)-2-hydroxypropyl)-N-(naphthalen-2-ylmethyl)butan-1-aminium bromide 164d

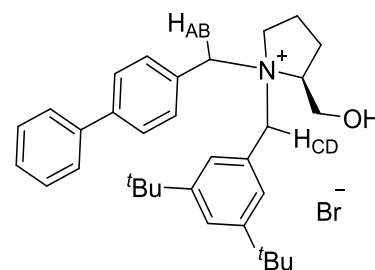General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.38 g in 85% yield in d.r. 1.0:2.7 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.56 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 362.2. HRMS ([M]+H) calcd for $C_{25}H_{32}NO$: 362.2484; found 362.2490. ^{1}H NMR δ 5.81 (d, $J_{AB\ or\ CD}$ = 8.4 Hz, 2.7H), 5.77 (d, $J_{AB\ or\ CD}$ = 8.5 Hz, 2.7H), 5.73 (d, $J_{CD\ or\ AB}$ = 8.4 Hz, 1H), 5.50 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.7H), 5.01 (2 x d, $J_{CD\ or\ AB}$ = 14.1 Hz, 1H, $J_{AB\ or\ CD}$ = 13.2 Hz, 2.7H), 4.94 (d, $J_{CD\ or\ AB}$ = 10.0 Hz, 1H), 4.86 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 2.7H). IR 3447, 3047, 2958, 1585, 1460, 1374, 761, 703 cm^{-1}.
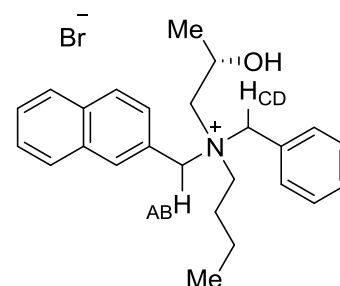
**N-(3,5-dimethylbenzyl)-N-((S)-2-hydroxypropyl)-N-(naphthalen-1-ylmethyl)butan-1-aminium bromide 164b**

General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.38 g in 80% yield in d.r. 1.0:3.1 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.50 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 390.3. HRMS ([M]+H) calcd for $C_{27}H_{36}NO$: 390.2791; found 390.2794. ^{1}H NMR δ 4.98 (2 xd, $J_{AB\ or\ CD}$= 12.6 Hz, 1H), 4.86(d, $J_{CD\ or\ AB}$= 13.2 Hz, 3.1H), 4.71 (d, $J_{CD\ or\ AB}$= 13.1 Hz, 3.1H), 4.58 (d, $J_{AB\ or\ CD}$= 12.8 Hz, 1H). IR 3441, 3043, 2965, 1594, 1453, 1370, 769, 710 cm^{-1}.
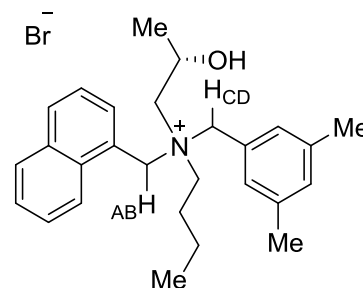
N-(3,5-dimethylbenzyl)-N-((S)-2-hydroxypropyl)-N-(naphthalen-2-ylmethyl)butan-1-aminium bromide 164e

General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.40 g in 85% yield in d.r. 1.0:3.5 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.55 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 390.3. HRMS ([M]+H) calcd for $C_{27}H_{36}NO$: 390.2791; found 390.2792. ^{1}H NMR δ 5.36 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 3.5H), 4.94 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 3.5H), 4.82 (2 x d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3.5H, $J_{CD\ or\ AB}$ = 13.2 Hz, 1H), 4.74 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 3.5H), 4.67 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 1H). IR 3427, 3038, 2964, 1593, 1460, 1369, 771, 731 cm^{-1}.
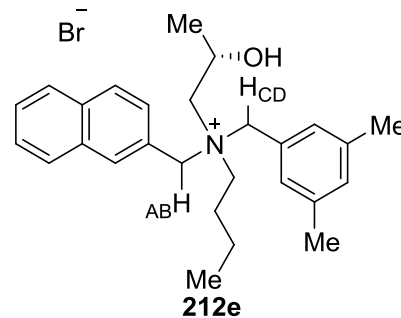
**N-(3,5-bis(trifluoromethyl)benzyl)-N-((S)-2-hydroxypropyl)-N-(naphthalen-1-ylmethyl)butan-1-aminium bromide 164c**
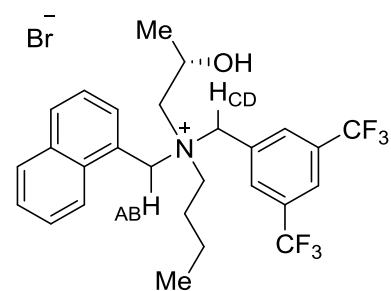
General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.16 g in 28% yield in d.r. 1.0:2.8 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.50 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 498.2. HRMS ([M]+H) calcd for $C_{27}H_{30}F_6NO$: 498.2232; found 498.2234. ^{1}H NMR δ 4.98 (2 x d, $J_{AB\ or\ CD}$ = 12.6 Hz, 1H and $J_{CD\ or\ AB}$ = 13.2 Hz, 2.8H), 4.71 (d, $J_{CD\ or\ AB}$ = 13.1 Hz, 2.8H), 4.58 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H). IR 3442, 3045, 2961, 1597, 1461, 1376, 770, 732 cm^{-1}.

N-(3,5-bis(trifluoromethyl)benzyl)-N-((S)-2-hydroxypropyl)-N-(naphthalen-2-ylmethyl)butan-1-aminium bromide 164f
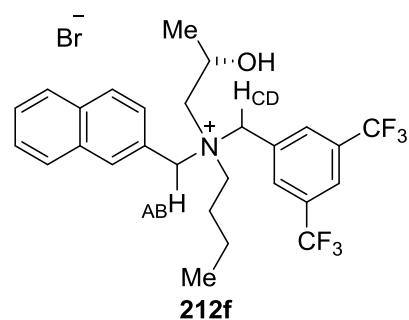
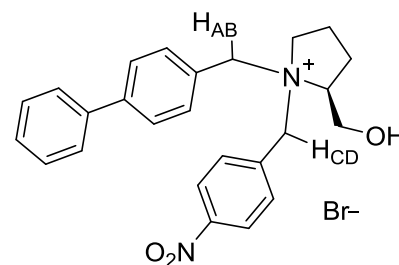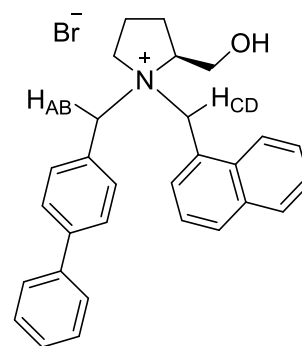General method 2 (1 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an amorphous oily solid, 0.39 g in 67% yield in d.r. 1:2 although unable to determine the major diastereoisomer (Interpretation 1 used). R_f = 0.47 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 498.2. HRMS ([M]+H) calcd for $C_{27}H_{30}F_6NO$: 498.2232; found 498.2234. ^{1}H NMR δ 5.89 (d, $J_{AB\ or\ CD}$ = 12.6 Hz, 1H), 5.71 (d, $J_{AB\ or\ CD}$ = 11.7 Hz, 1H), 5.62 (d, $J_{CD\ or\ AB}$ = 13.2 Hz, 2H), 5.45 (2 x d, $J_{AB\ or\ CD}$ = 13.2 and $J_{AB\ or\ CD}$ = 12.9 Hz, 2H), 5.05 (d, $J_{CD\ or\ AB}$ = 13.5 Hz, 2H). R_f = 0.54 in 10:1 CH_2Cl_2:MeOH. IR 3447, 3047, 2958, 1597, 1458, 1374, 774, 733 cm^{-1}.

N,N-dibenzyl-*N*-methyl-2-(((methylthio)carbonothioyl)oxy)ethanaminium bromide 173

Ammonium salt **138** (1 equiv, 2 mmol, 0.672 g) was added to a round bottom flask and MeCN (35 mL) was added. The mixture was heated until the salt fully dissolved, use of an external heating source was required. Once the solution had cooled and remained fully dissolved it was placed in an ice bath and sodium hydride (3 equiv, 6 mmol, 0.144 g) was added to the solution. After stirring for 10 minutes, carbon disulfide (3 equiv, 6 mmol, 0.456 g) was added. The clear solution turned from opaque to a bright yellow colour. After 20 minutes, iodomethane (4 equiv, 8 mmol, 1.135 g) was added dropwise (over 5 minutes) and the ice bath removed. Stirring continued for 30 minutes and the reaction was quenched with dropwise addition of ice cold methanol (10 mL). The pungent mixture was concentrated under reduced pressure and purified by machine chromatography. R_f = 0.50 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 346.1. HRMS ([M]+H) calcd for $C_{19}H_{24}NOS_2^+$: 346.1284; found 346.1289. MP 87-89 °C. ^1H NMR δ 7.80 − 7.64 (m, 4H, ArH), 7.59 − 7.46 (m, 6H, ArH), 5.25 (d, J_{AB} = 12.6 Hz, 2H), 5.20 − 5.13 (m, 2H, 6), 5.07 (d, J_{AB} = 12.6 Hz, 2H), 4.27 − 4.17 (m, 2H, 5), 3.14 (s, 3H, 3), 2.63 (s, 3H, 23). ^{13}C NMR δ 186.2 (20), 133.47 (8 and 14), 131.20 (9, 15, 13 and 19), 129.56 (10, 12, 16 and 18), 126.45 (17 and 11), 65.97 (1 and 4), 65.37 (5), 57.96 (6), 47.01 (3), 19.78 (23).
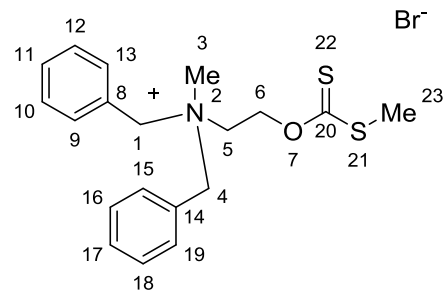
6.6 3rd Generation experimental

(S)-(N-([1,1'-biphenyl]-4-ylmethyl)pyrrolidin-2-yl)methanol 183

General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a brown oil, 3.97 g in 99% yield. R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 268.2. HRMS ([M]+H) calcd for $C_{18}H_{22}NO$: 268.1701; found 268.1710. $[\alpha]^{23}_D$ = -30 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.70 – 7.51 (m, 4H, ArH), 7.51 – 7.30 (m, 5H, ArH), 4.05 (d, J_{AB} = 13.1 Hz, 1H, 8), 3.72 (dd, J = 11.0, 3.4 Hz, 1H, 6), 3.47 – 3.51 (m, 2H, 6 and 8), 3.07 (app qn, J = 4.5 Hz, 1H, 2), 2.93 – 2.74 (m, 1H, 5), 2.38 – 2.36 (m, 1H, 5), 2.06 – 1.68 (m, 4H, 3 and 4). ^{13}C NMR δ 140.81 (15), 140.25 (12 and 9), all ArC 129.34, 128.76, 127.26, 127.15, 127.06, 64.69 (2), 61.71 (6), 58.27 (8), 54.43 (5), 27.66 (3), 23.51 (4). IR 3361, 3028, 2955, 2872, 2801, 1601, 1448, 1039, 759, 696 cm^{-1}.
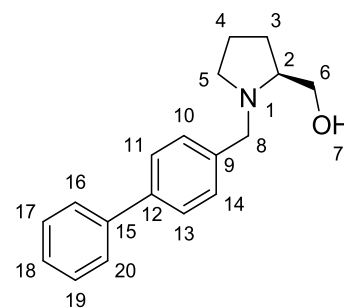
(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(3,5-bis(trifluoromethyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 207a

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.100 g in 87% yield in d.r. 1.0:5.6 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 14 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 494.2. HRMS ([M]+H) calcd for $C_{27}H_{26}F_6NO$: 494.1920; found 494.1922. ^{1}H NMR δ 6.17 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 5.6H), 5.70 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 5.6H), 5.60 (d, $J_{CD\ or\ AB}$ = 12.8 Hz, 1H), 5.04 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 5.6H), 4.83 (d, $J_{CD\ or\ AB}$ = 12.7 Hz, 1H). ^{19}F NMR δ -62.62 (s, 33.6F), -62.73 (s, 6F). IR 3247, 3031, 2969, 1613, 1369, 1277, 1129, 765, 739, 698 cm^{-1}.
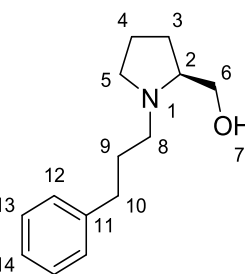
(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(3,5-dimethylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 207b
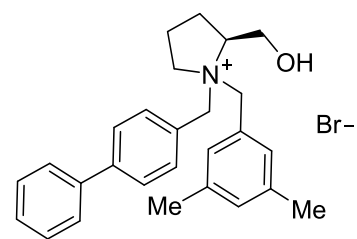
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.077 g in 83% yield in d.r. 1.0:5.4 $N_{(S)}$ is major diastereoisomer (Interpretation 2 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 386.2. HRMS ([M]+H) calcd for $C_{27}H_{32}NO$: 386.2484; found 386.2491. ^{1}H NMR δ 2.37 (s, 32.4H, 2x Me), 2.31 (s, 6H, 2x Me). IR 3238, 2917, 1606, 1450, 1374, 1065, 766, 737, 698 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 207c
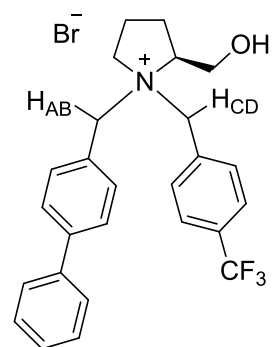
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.087 g in 86% yield in d.r. 1.0:5.4 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 13 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 426.2. HRMS ([M]+H) calcd for $C_{26}H_{27}F_3NO$: 426.2045; found 426.2052. ^{1}H NMR δ 5.87 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5.4H), 5.78 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H), 5.69 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1H), 5.61 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 5.4H), 4.91 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5.4H), 4.75 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H). ^{19}F NMR δ -62.98 (s, 5.4F), -63.01 (s, 3F). IR 3250, 2965, 1618, 768, 697 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-benzyl-2-(hydroxymethyl)pyrrolidinium bromide 207d
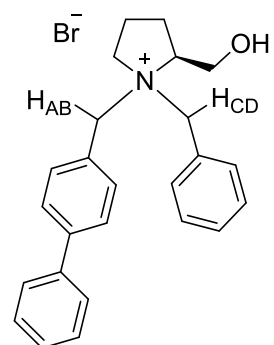
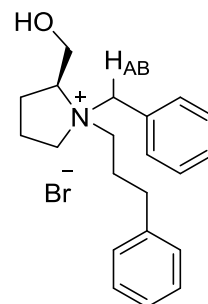General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline

salt, 0.086 g in 99% yield in d.r. 1:4 $N_{(S)}$ is major diastereoisomer (interpretation 1 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 358.2. HRMS ([M]+H) calcd for $C_{25}H_{28}NO$: 358.2171; found 358.2182. ^{1}H NMR δ 5-61 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4H), 5-59 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H). IR 3232, 3030, 2961, 1610, 1487, 1453, 1373, 1215, 762, 699 cm^{-1}.

**(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-([1,1'-biphenyl]-4-ylmethyl)-2-(hydroxymethyl)pyrrolidinium bromide 207e**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark yellow crystalline salt, 0.087 g in 85% yield in d.r. 1.0:1.8 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 434.2. HRMS ([M]+H) calcd for $C_{31}H_{32}NO$: 434.2484; found 434.2477. ^{1}H NMR δ 5.53 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H), 5.48 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.8H), 4.94 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H), 4.77 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.8H). IR 3244, 3029, 2967, 1610, 1482, 1450, 1375, 763, 722, 699 cm^{-1}.
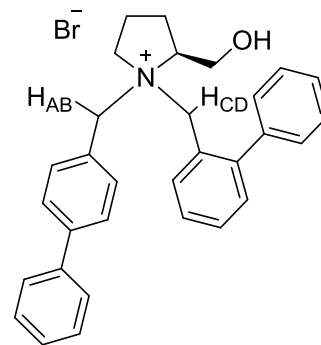
(2*S*)-*N*-([1,1'-biphenyl]-4-ylmethyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 207f
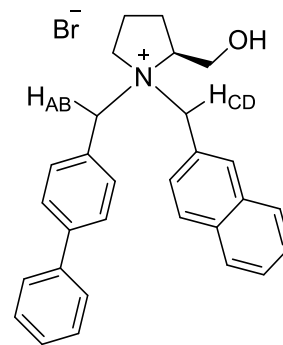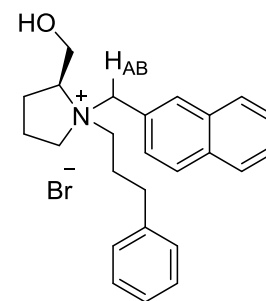
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark yellow crystalline salt, 0.096 g in 99% yield in d.r. 1.0:2.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 408.2. HRMS ([M]+H) calcd for $C_{29}H_{30}NO$: 408.2327; found 408.2321. ^{1}H NMR δ 5.85 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 2.5H), 5.73 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 5.63 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 2.5H), 4.82 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 2.5H), 4.38 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H). IR 3247, 3028, 2961, 1600, 1487, 1450, 1369, 765, 696 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 207g
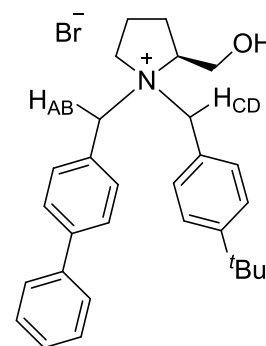
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark yellow crystalline salt, 0.080 g in 81% yield in d.r. 1.0:4.6 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 3). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 414.3. HRMS ([M]+H) calcd for $C_{29}H_{36}NO$: 414.2797; found 414.2790. ^{1}H NMR δ 5.72 (d, $J_{AB \text{ or } CD}$ = 13.4 Hz, 1H), 5.63 (d, $J_{AB \text{ or } CD}$ = 12.9 Hz, 4.6H), 5.56 (d, $J_{AB \text{ or } CD}$ = 12.9 Hz, 4.6H), 5.49 (d, $J_{AB \text{ or } CD}$ = 13.0 Hz, 1H), 4.64 (d, $J_{AB \text{ or } CD}$ = 13.4 Hz, 1H), 4.46 (d, $J_{AB \text{ or } CD}$ = 12.9 Hz, 4.6H), 4.27 (d, $J_{AB \text{ or } CD}$ = 12.9 Hz, 4.6H), 1.34 (s, 41.4H, *t*Bu), 1.30 (s, 9H, *t*Bu). IR 3238, 2961, 1612, 1513, 1487, 1460, 1413, 1063, 765, 697 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(3,5-di-tert-butylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 207h

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark yellow crystalline salt, 0.109 g in 99% yield in d.r. 1.0:5.5 $N_{(S)}$ is major diastereoisomer (interpretation 1 and 4 used). R_f = 0.45 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 470.3. HRMS ([M]+H) calcd for $C_{33}H_{44}NO$: 470.3423; found 470.3416. ^{1}H NMR δ 5.47 (d, $J_{AB \text{ or } CD}$ = 12.8 Hz, 1H), 4.69 (d, $J_{AB \text{ or } CD}$ = 13.0 Hz, 1H), 4.46 (d, $J_{AB \text{ or } CD}$ = 12.8 Hz, 1H), 1.37 (s, 99H, 2x *t*Bu), 1.29 (s, 18H, 2x *t*Bu). IR 3231, 2959, 1600, 1460, 1393, 1066, 765, 737, 697 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-4-ylmethyl)-*N*-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 207i
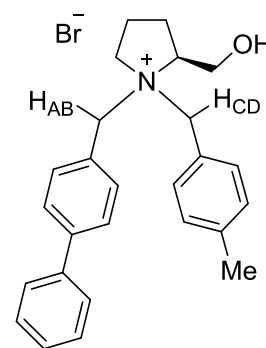
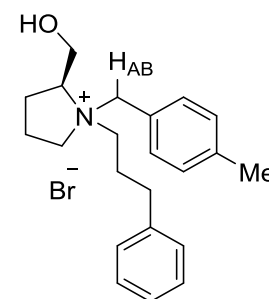General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark yellow crystalline salt, 0.090 g in 99% yield in d.r. 1.0:4.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 5 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 372.2. HRMS ([M]+H) calcd for $C_{26}H_{30}NO$: 372.2327; found 372.2335. ^{1}H NMR δ 5.73 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.64 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 4.5H), 5.55 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4.5H), 2.40 (s, 13.5H, Me), 2.36 (s, 3H, Me). IR 3235, 2968, 1612, 1515, 1487, 1450, 1412, 1373, 1064, 769, 698 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-4-ylmethyl)-*N*-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 207j
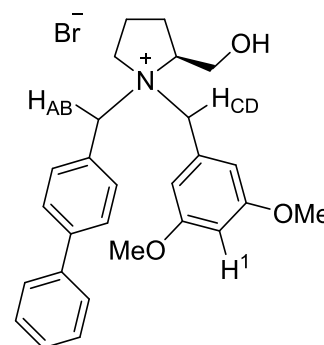
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.085 g in 85% yield in d.r. 1.0:4.4 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 6 and 11 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 418.2. HRMS ([M]+H) calcd for $C_{27}H_{32}NO_3$: 418.2382; found 418.2398. ^{1}H NMR δ 6.93 (t, *J* = 2.2 Hz, 4.4H, H^1), 6.70 (t, *J* = 2.2 Hz, 1H, H^1), 5.76 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.69 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4.4H), 5.60 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 4.4H), 5.48 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.45 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4.4H), 4.28 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 4.4H), 3.85 (s, 26.4H, 2x OMe), 3.78 (s, 6H, 2x OMe). IR 3235, 2966, 2838, 1595, 1457, 1432, 1413, 1204, 1058, 837, 766, 698 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 207k
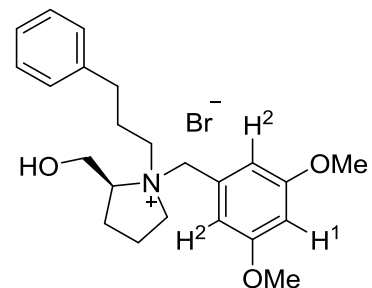
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an orange crystalline salt, 0.059 g in 61% yield in d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 403.2. HRMS ([M]+H) calcd for $C_{25}H_{27}N_2O_3$: 403.2022; found 403.2027. ^{1}H NMR δ 5.66 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 2H), 5.59 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.09 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.94 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 2H). IR 3247, 2966, 1606, 1520, 1451, 1412, 1379, 1345, 1064, 854, 765, 699 cm^{-1}.

**(2S)-N-([1,1'-biphenyl]-4-ylmethyl)-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 207l**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.067 g in 69% yield in d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 408.2. HRMS ([M]+H) calcd for $C_{29}H_{30}NO$: 408.2327; found 408.2336. ^{1}H NMR δ 5.23 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 2H), 5.00 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 2H), 4.91 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1H). IR 3230, 2969, 1598, 1487, 1450, 1064, 766, 697 cm^{-1}.

(S)-(N-(3-phenylpropyl)pyrrolidin-2-yl)methanol 184

General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a yellow oil, 2.50 g in 76% yield. R_f = 0.28 in 10:1 CH_2Cl_2:MeOH (visualised with ninhydrin). m/z ([M]+H) 220.2. HRMS ([M]+H) calcd for $C_{14}H_{22}NO$: 220.1701; found 220.1706. $[\alpha]_D^{23}$ = −31 (c 1.0, CH_2Cl_2). ^{1}H NMR

δ 7.39 – 7.12 (m, 5H, 12-14), 3.60 (dd, J = 10.6, 3.6 Hz, 1H, 6), 3.37 (dd, J = 10.6, 2.0 Hz, 1H, 6), 3.23-3.15 (m, 1H, 2), 2.91 – 2.47 (m, 5H, 10, 8 and 5), 2.38 – 2.16 (m, 2H, 5 and 3), 1.97 – 1.66 (m, 5H, 3, 9 and 4). ^{13}C NMR δ 142.16 (11), 128.35 (12, 13), 125.79 (14), 64.76 (2), 61.81 (6), 54.11 (5), 53.91 (8), 33.62 (10), 30.67 (9), 27.72 (3), 23.65 (4). IR 3381, 3026, 2941, 2867, 1603, 1496, 1453, 1387, 1034, 744, 698 cm^{-1}.

(2*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208a
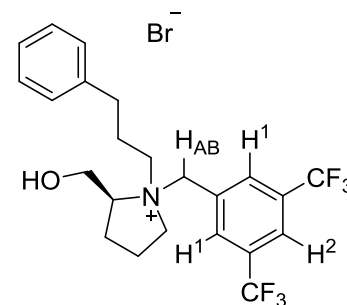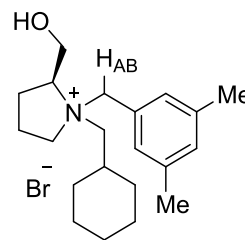

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.104 g in >99% yield in d.r. 1.0:1.1 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 6 and 7 used). R$_f$ = 0.30 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 446.2. HRMS ([M]+H) calcd for C$_{23}$H$_{26}$F$_6$NO: 446.1919; found 446.1917. ^{1}H NMR δ 8.30 (s, 2H, H^1), 8.19 (s, 2.2H, H^1), 7.99 (s, 1H, H^2), 7.95 (s, 1.1H, H^2), 5.66 (d, J_{AB} = 12.9 Hz, 1.1H), 5.51 (d, J_{AB} = 12.9 Hz, 1H), 5.04 (d, J_{AB} = 9.6 Hz, 1.1H), 5.00 (d, J_{AB} = 9.6 Hz, 1H). IR 3242, 2969, 1606, 1523, 1455, 1350, 1057, 752, 702 cm^{-1}.

(2*S*)-*N*-(3,5-dimethylbenzyl)-*N*-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208b
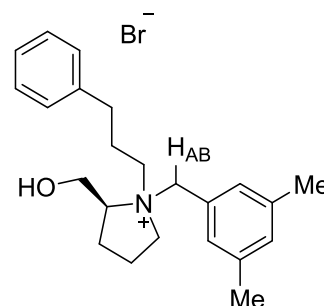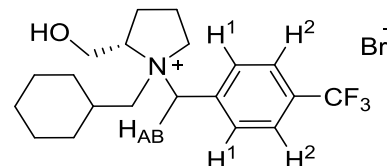

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.083 g in >99% yield and d.r. 1.0:1.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R$_f$ = 0.40 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 338.2. HRMS ([M]+H) calcd for C$_{23}$H$_{32}$NO: 338.2484; found 338.2497. ^{1}H NMR δ 4.79 (d, J_{AB} = 13.0 Hz, 1H), 4.75 (d, J_{AB} = 12.6 Hz, 1.3H), 4.60 (d, J_{AB} = 13.0 Hz, 1H). IR 3295, 2971, 2921, 1605, 1495, 1454, 1046, 857, 751, 701 cm^{-1}.

(2*S*)-*N*-(3-phenylpropyl)-*N*-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208c
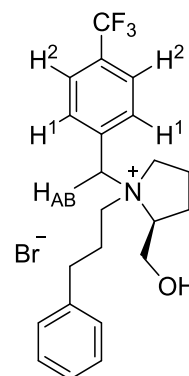
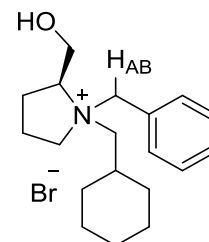General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.071 g in 78% yield in d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 7, 8 and 13 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 378.2. HRMS ([M]+H) calcd for $C_{22}H_{27}F_3NO$: 378.2045; found 378.2055. ^{1}H NMR δ 7.82 (d, *J* = 8.1 Hz, 2H, H^2), 7.71 (d, *J* = 8.0 Hz, 2.4H, H^2), 7.63 (d, *J* = 8.1 Hz, 2H, H^1), 7.55 (d, *J* = 8.0 Hz, 2.4H, H^1), 5.68 (t, *J* = 5.3 Hz, 1.2H), 5.52 (t, *J* = 5.2 Hz, 1H), 5.33 (d, J_{AB} = 12.9 Hz, 1.2H), 5.21 (d, J_{AB} = 13.0 Hz, 1H), 4.92 (d, J_{AB} = 13.0 Hz, 1H), 4.83 (d, J_{AB} = 12.9 Hz, 1.2H). ^{19}F NMR δ -63.08 (s, 3F), -63.09 (s, 3.6F). IR 3279, 2970, 1621, 1496, 1454, 1068, 753, 702 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.077 g in >99% yield and d.r. 1.0:1.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 310.2. HRMS ([M]+H) calcd for $C_{21}H_{28}NO$: 310.2171; found 310.2167. ^{1}H NMR δ 5.22 (d, J_{AB} = 13.0 Hz, 1.3H), 5.06 (d, J_{AB} = 13.0 Hz, 1H), 4.63 (d, J_{AB} = 13.0 Hz, 1H), 4.41 (d, J_{AB} = 13.0 Hz, 1.3H). IR 3229, 3021, 2968, 2909, 1497, 1454, 1064, 770, 702 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-2-ylmethyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208e
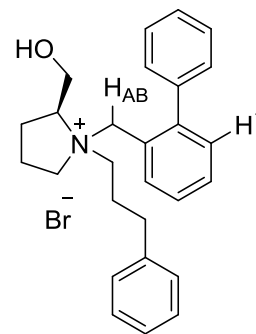
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.092 g in >99% yield and d.r. 1.0:1.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 9). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 386.2. HRMS ([M]+H) calcd for $C_{27}H_{32}NO$: 386.2484; found 386.2489. ^1H NMR δ 8.04 (d, J = 7.5 Hz, 1H, H^1), 7.93 (d, J = 7.7 Hz, 1.3H, H^1), 5.77 (t, J = 5.7 Hz, 1H), 5.61 (t, J = 5.9 Hz, 1.3H), 5.27 (2 x d overlapping, J_{AB} = 13.5, 1H, J_{AB} = 13.0 Hz, 1.3H), 4.99 (d, J_{AB} = 13.5 Hz, 1H), 4.68 (d, J_{AB} = 13.0 Hz, 1.3H). IR 3245, 3024, 2969, 1601, 1479, 1383, 1059, 781, 749, 702 cm^{-1}.

(2S)-N-(naphthalen-2-ylmethyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208f
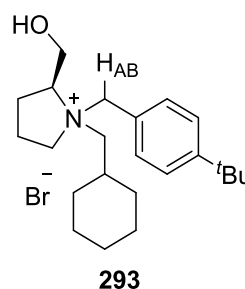
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.087 g in >99% yield and d.r. 1.0:1.5 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 360.2. HRMS ([M]+H) calcd for $C_{25}H_{30}NO$: 360.2327; found 360.2340. ^1H NMR δ 8.15 (s, 1H, ArH), 8.02 (s, 1.5H, ArH), 5.09 (2 x d overlapping, J_{AB} = 13.0, 1H, J_{AB} = 13.0 Hz, 1.5H), 4.91 (d, J_{AB} = 13.0 Hz, 1H), 4.70 (d, J_{AB} = 13.0 Hz, 1.5H). IR 3248, 3060, 3024, 2972, 2892, 1600, 1495, 1463, 1453, 1063, 752, 699 cm^{-1}.

An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.3.
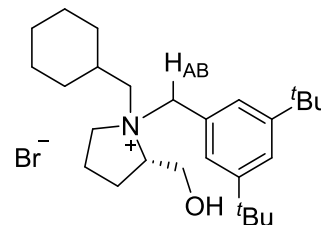
(2S)-N-(4-(tert-butyl)benzyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208g
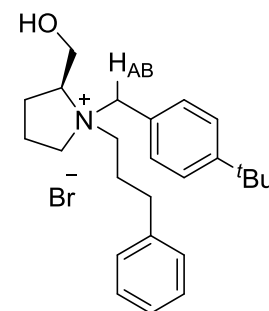
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.076 g in 85% yield and d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 366.3. HRMS ([M]+H) calcd for $C_{25}H_{36}NO$: 366.2797; found 366.2801. ^{1}H NMR δ 5.11 (d, J_{AB} = 12.9 Hz, 1.2H), 4.95 (d, J_{AB} = 13.1 Hz, 1H), 4.59 (d, J_{AB} = 13.1 Hz, 1H), 4.33 (d, J_{AB} = 12.9 Hz, 1.2H). IR 3273, 2963, 2903, 1613, 1513, 1495, 1454, 1393, 1064, 751, 701 cm^{-1}.

(2S)-N-(3,5-di-tert-butylbenzyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208h
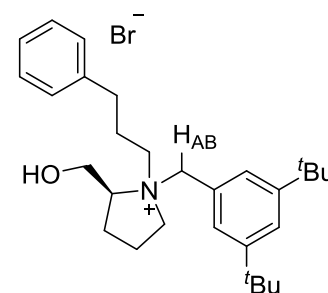
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.100 g in >99% yield and d.r. 1.0:1.5 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 422.3. HRMS ([M]+H) calcd for $C_{29}H_{44}NO$: 422.3423; found 422.3432. ^{1}H NMR δ 4.95 (2 x d overlapping, J_{AB} = 13.1, 1H, J_{AB} = 12.9 Hz, 1.5H), 4.66 (d, J_{AB} = 13.1 Hz, 1H), 4.33 (d, J_{AB} = 12.9 Hz, 1.5H). IR 3252, 2957, 2904, 2867, 1600, 1496, 1455, 1363, 1064, 749, 699 cm^{-1}.

(2S)-N-(4-methylbenzyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208i

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.080 g in

283

>99% yield and d.r. 1.0:1.5 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). $R_f = 0.40$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 324.2. HRMS ([M]+H) calcd for $C_{22}H_{30}NO$: 324.2327; found 324.2329. ^{1}H NMR δ 5.11 (d, $J_{AB} = 13.0$ Hz, 1.5H), 4.97 (d, $J_{AB} = 13.1$ Hz, 1H), 4.57 (d, $J_{AB} = 13.1$ Hz, 1H), 4.37 (d, $J_{AB} = 13.0$ Hz, 1.5H). IR 3238, 2958, 1614, 1515, 1494, 1476, 1381, 1058, 747, 704 cm^{-1}.

### (2*S*)-*N*-(3,5-dimethoxybenzyl)-*N*-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208j

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.089 g in >99% yield and d.r. 1.0:1.5 $N_{(R)}$ is major diastereoisomer (Interpretation 6 used). $R_f = 0.34$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 370.2. HRMS ([M]+H) calcd for $C_{23}H_{32}NO_3$: 370.2382; found 370.2384. ^{1}H NMR δ 6.79 (d, $J = 2.2$ Hz, 2H, H^2), 6.72 (d, $J = 2.2$ Hz, 3H, H^2), 6.52 (t, $J = 2.2$ Hz, 1H, H^1), 6.49 (t, $J = 2.2$ Hz, 1.5H, H^1), 5.14 (d, $J_{AB} = 12.5$ Hz, 1.5H), 4.96 (d, $J_{AB} = 13.0$ Hz, 1H), 4.67 (d, $J_{AB} = 13.0$ Hz, 1H). IR 3241, 2972, 2893, 1600, 1515, 1455, 1409, 1383, 1303, 1087, 1045, 879, 747, 703 cm^{-1}.

(2*S*)-*N*-(4-nitrobenzyl)-*N*-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208k
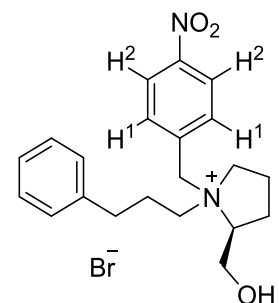
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.086 g in >99% yield and d.r. 1.0:1.1 $N_{(R)}$ is major diastereoisomer (Interpretation 7 and 8 used). $R_f = 0.35$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 355.2. HRMS ([M]+H) calcd for $C_{21}H_{27}N_2O_3$: 355.2022; found 355.2012. ^{1}H NMR δ 8.22 (d, $J = 8.7$ Hz, 1H, H^2), 8.12 (d, $J = 8.8$ Hz, 1H, H^2), 7.94 (d, $J =$

8.7 Hz, 1.1H, H[1]), 7.82 (d, J = 8.8 Hz, 1.1H, H[1]). IR 3237, 2951, 1606, 1522, 1350, 1057, 814, 751, 703 cm^{-1}.

(2S)-N-(naphthalen-1-ylmethyl)-N-(3-phenylpropyl)-2-(hydroxymethyl)-pyrrolidinium bromide 208l
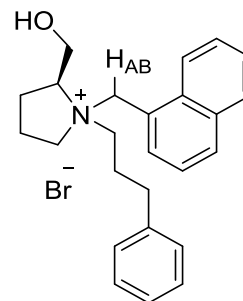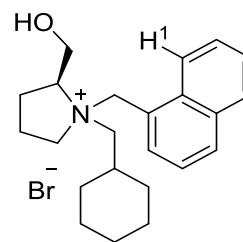
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an oily solid, 0.060 g in 68% yield and d.r. 1.0:1.8 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 360.2. HRMS ([M]+H) calcd for $C_{25}H_{30}NO$: 360.2327; found 360.2340. ^{1}H NMR δ 5.64 (d, J_{AB} = 13.5 Hz, 1.8H), 5.46 (d, J_{AB} = 13.5 Hz, 1H), 5.34 (d, J_{AB} = 13.5 Hz, 1.8H), 4.91 (d, J_{AB} = 13.5 Hz, 1H). IR 3248, 3060, 3024, 2972, 2892, 1600, 1495, 1463, 1453, 1063, 752, 699 cm^{-1}.

(2S)-N-(3,5-bis(trifluoromethyl)benzyl)-N-(cyclohexylmethyl)-2-(hydroxymethyl)pyrrolidinium bromide 209a
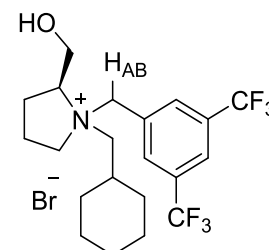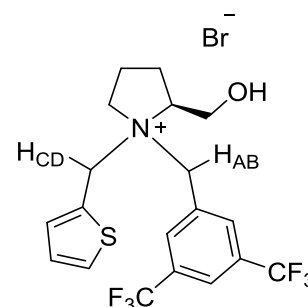
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.061 g in 60% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 14 used). R_f = 0.31 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 424.2. HRMS ([M]+H) calcd for $C_{21}H_{28}F_6NO$: 424.2075; found 424.2082. ^{1}H NMR δ 5.47 (d, J_{AB} = 13.3 Hz, 1.3H), 5.30 (d, J_{AB} = 12.9 Hz, 1H), 5.17 (d, J_{AB} = 12.9 Hz, 1H), 5.01 (d, J_{AB} = 13.3 Hz, 1.3H). ^{19}F NMR δ -62.58 (s, 6F), -62.74 (s, 7.8F). IR 3337, 2973, 2930, 1451, 1373, 1047, 880 cm^{-1}.

(2*S*)-*N*-(cyclohexylmethyl)-*N*-(3,5-dimethylbenzyl)-2-

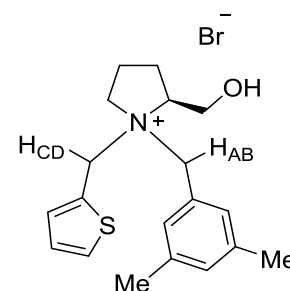**(hydroxymethyl)pyrrolidinium bromide 209b**

General method 2 (0.2 mmol) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.065 g in 82% yield

and d.r. 1.0:1.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1

CH_2Cl_2:MeOH. *m/z* ([M]+H) 316.3. HRMS ([M]+H) calcd for $C_{21}H_{34}NO$: 316.2640; found

316.2645. ^{1}H NMR δ 4.99 (d, J_{AB} = 12.8 Hz, 1H), 4.84 (d, J_{AB} = 13.0 Hz, 1.7H), 4.52 (d, J_{AB} =

12.8 Hz, 1H). IR 3318, 2973, 2927, 1451, 1379, 1330, 1045, 879 cm^{-1}.

(2*S*)-*N*-(cyclohexylmethyl)-*N*-(4-(trifluoromethyl)benzyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 209c

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a

diastereomeric mixture as a yellow crystalline salt, 0.060 g in 69% yield and d.r. 1.0:1.3 $N_{(S)}$ is

major diastereoisomer (Interpretation 1, 7 and 13 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. *m/z*

([M]+H) 356.2. HRMS ([M]+H) calcd for $C_{20}H_{29}F_3NO$: 356.2201; found 356.2196. ^{1}H NMR δ

8.08 (d, J = 8.1 Hz, 2H, H^1), 7.87 (d, J = 8.1 Hz, 2.6H, H^1), 5.26 (d, J_{AB} = 13.0 Hz, 1.3H), 5.19

(d, J_{AB} = 12.8 Hz, 1H), 4.89 (d, J_{AB} = 12.8 Hz, 1H), 4.75 (d, J_{AB} = 13.0 Hz, 1.3H). ^{19}F NMR δ -

62.97 (s, 1F), -62.99 (s, 1.3F). IR 3323, 2973, 2928, 1451, 1380, 1045, 879 cm^{-1}.

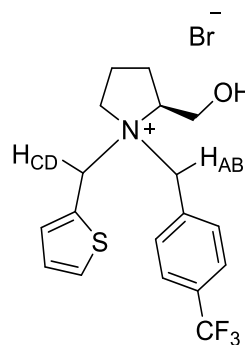**(2*S*)-*N*-benzyl-*N*-(cyclohexylmethyl)-2-(hydroxymethyl)pyrrolidinium**

bromide 209d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which

was isolated as a diastereomeric mixture as a white crystalline salt, 0.066 g in

89% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1

CH_2Cl_2:MeOH. *m/z* ([M]+H) 288.2. HRMS ([M]+H) calcd for $C_{19}H_{30}NO$: 288.2327; found

288.2333. ^{1}H NMR δ 4.59 (d, J_{AB} = 12.9 Hz, 1H), 4.45 (d, J_{AB} = 13.1 Hz, 2H). IR 3307, 2973, 2927, 1452, 1379, 1325, 1045, 879, 708 cm^{-1}

(2S)-N-([1,1'-biphenyl]-2-ylmethyl)-N-(cyclohexylmethyl)-2-(hydroxymethyl)pyrrolidinium bromide 209e
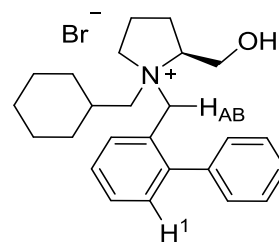
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.068 g in 76% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.37 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 364.3. HRMS ([M]+H) calcd for C$_{25}$H$_{34}$NO: 364.2640; found 364.2639. ^{1}H NMR δ 8.18 (d, J = 8.9 Hz, 1H, H[1]), 7.96 (d, J = 8.8 Hz, 1.3H, H[1]), 5.38 (d, J_{AB} = 13.4 Hz, 1H), 5.28 (d, J_{AB} = 13.2 Hz, 1.3H), 4.87 (d, J_{AB} = 13.4 Hz, 1H), 4.66 (d, J_{AB} = 13.2 Hz, 1.3H). IR 3310, 2972, 2927, 1450, 1380, 1045, 879, 753, 708 cm^{-1}.

### (2S)-N-(cyclohexylmethyl)-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 209f
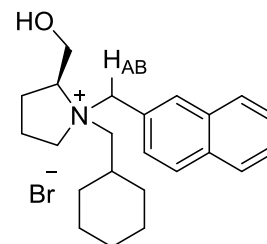
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.079 g in 94% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.37 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 338.3. HRMS ([M]+H) calcd for C$_{23}$H$_{32}$NO: 338.2484; found 338.2501. ^{1}H NMR δ 8.29 (s, 1H, ArH), 8.09 (s, 2H, ArH), 5.95 (t, J = 5.4 Hz, 1H), 5.66 (t, J = 4.7 Hz, 2H), 4.69 (d, J_{AB} = 12.9 Hz, 1H), 4.60 (d, J_{AB} = 13.0 Hz, 2H). IR 3299, 2927, 2853, 1509, 1450, 1047, 879, 828, 758 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(cyclohexylmethyl)-2-(hydroxymethyl)pyrrolidinium bromide 209g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.063 g in 74% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). $R_f = 0.36$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 344.3. HRMS ([M]+H) calcd for $C_{23}H_{38}NO$: 344.2953; found 344.2957. ^{1}H NMR δ 5.18 (2 x d, $J_{AB} = 13.1$, 1H, $J_{AB} = 13.1$ Hz, 1.7H), 4.46 (d, $J_{AB} = 13.1$ Hz, 1H). IR 3325, 2971, 2928, 1513, 1451, 1087, 1045, 879 cm^{-1}.

293

(2S)-N-(cyclohexylmethyl)-N-(3,5-di-tert-butylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 209h

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.071 g in 74% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). $R_f = 0.40$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 400.4. HRMS ([M]+H) calcd for $C_{27}H_{46}NO$: 400.3579; found 400.3584. ^{1}H NMR δ 5.11 (d, $J_{AB} = 13.0$ Hz, 1H), 5.04 (d, $J_{AB} = 12.9$ Hz, 2H), 4.51 (d, $J_{AB \text{ or } CD} = 13.0$ Hz, 1H). IR 3256, 2952, 2927, 1599, 1450, 1393, 1363, 1249, 1204, 1067, 884, 714 cm^{-1}.

(2S)-N-(cyclohexylmethyl)-N-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 209i
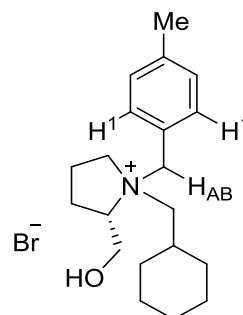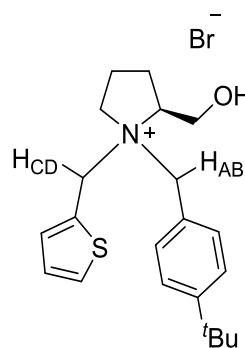
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.055 g in 72% yield and d.r. 1.0:2.2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 7 used). $R_f = 0.37$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 302.2. HRMS ([M]+H) calcd for $C_{20}H_{32}NO$: 302.2484; found

302.2495. ^{1}H NMR δ 7.59 (d, J = 8.0 Hz, 2H, H^1), 7.44 (d, J = 8.0 Hz, 4.4H, H^1), 5.09 (d, J_{AB} = 12.9 Hz, 1H), 5.02 (d, J_{AB} = 13.1 Hz, 2.2H), 4.54 (d, J_{AB} = 12.9 Hz, 1H), 4.39 (d, J_{AB} = 13.1 Hz, 2.2H). IR 3308, 2973, 2927, 1451, 1087, 1045, 879 cm^{-1}.

(2*S*)-*N*-(cyclohexylmethyl)-*N*-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 209j
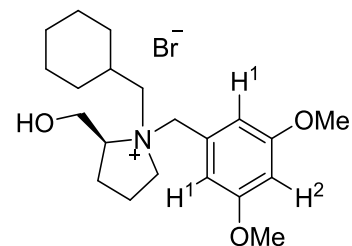
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.061 g in 71% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer (Interpretation 6 and 7 used). R$_f$ = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 348.3. HRMS ([M]+H) calcd for C$_{21}$H$_{34}$NO$_3$: 348.2539; found 348.2550. ^{1}H NMR δ 6.84 (d, J = 2.2 Hz, 2H, H^1), 6.76 (d, J = 2.2 Hz, 4H, H^1), 6.54 (t, J = 2.2 Hz, 1H, H^2), 6.51 (t, J = 2.2 Hz, 2H, H^2). IR 3327, 2973, 1599, 1454, 1326, 1274, 1087, 1045, 879 cm^{-1}.

(2*S*)-*N*-(cyclohexylmethyl)-*N*-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 209k
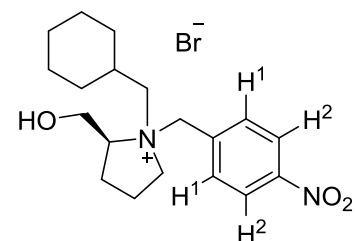
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.061 g in 74% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 7 and 8). R$_f$ = 0.33 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 333.2. HRMS ([M]+H) calcd for C$_{19}$H$_{29}$N$_2$O$_3$: 333.2178; found 333.2180. ^{1}H NMR δ 8.30 (d, J = 8.8 Hz, 2H, H^1), 8.25 (d, J = 8.7 Hz, 2.6H, H^1), 8.08 (d, J = 8.8 Hz, 2H, H^2), 7.96 (d, J = 8.7 Hz, 2.6H, H^2). IR 3236, 2958, 1602, 1521, 1349, 1051, 816, 754, 701 cm^{-1}.

(2*S*)-*N*-(cyclohexylmethyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 209l

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.057 g in 68% yield and d.r. 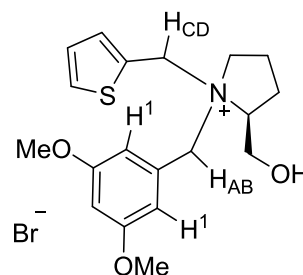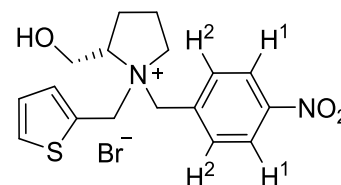1.0:3.7 $N_{(S)}$ is major diastereoisomer (Interpretation 9 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 338.3. HRMS ([M]+H) calcd for $C_{23}H_{32}NO$: 338.2484; found 338.2500. ^1H NMR δ 8.32 (d, *J* = 8.6 Hz, 1H, H^1), 8.19 (d, *J* = 7.9 Hz, 3.7H, H^1). IR 3324, 2973, 2927, 1450, 1379, 1087, 1045, 879, 782 cm^{-1}.

(2*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210a

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an orange crystalline salt, 0.085 g in 84% yield and d.r. 1.0:3.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 14 used). R_f = 0.28 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 424.1. HRMS ([M]+H) calcd for $C_{19}H_{20}F_6NOS$: 424.1170; found 424.1161. ^1H NMR δ 6.14 (d, $J_{AB\,or\,CD}$ = 13.0 Hz, 3.7H), 5.97 (d, $J_{AB\,or\,CD}$ = 12.5 Hz, 1H), 5.89 (d, $J_{AB\,or\,CD}$ = 13.8 Hz, 3.7H), 4.98 (d, $J_{AB\,or\,CD}$ = 13.0 Hz, 3.7H). ^{19}F NMR δ -62.62 (s, 22.2F), -62.74 (s, 6F). IR 3257, 2953, 1464, 1369, 1277, 1170, 1126, 706, 682 cm^{-1}.

(2*S*)-*N*-(3,5-dimethylbenzyl)-*N*-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210b
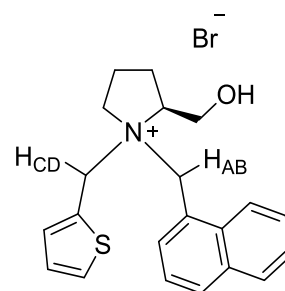
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.078 g in 99% yield and d.r. 1.0:3.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 2

used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 316.2. HRMS ([M]+H) calcd for $C_{19}H_{26}NOS$: 316.1735; found 316.1724. ^{1}H NMR δ 5.72 (d, $J_{AB\ or\ CD}$ = 14.0 Hz, 3.7H), 5.51 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 3.7H), 5.39 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H), 4.77 (d, $J_{AB\ or\ CD}$ = 14.1 Hz, 1H), 2.36 (s, 22.2H, Me), 2.32 (s, 6H, Me). IR 3237, 2949, 2917, 1606, 1448, 1063, 855, 720 cm^{-1}

(2S)-N-(thiophen-2-ylmethyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210c

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.082 g in 94% yield and d.r. 1.0:2.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 356.1. HRMS ([M]+H) calcd for $C_{18}H_{21}F_3NOS$: 356.1296; found 356.1290. ^{1}H NMR δ 5.96 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.7H), 5.74 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 1H), 5.67 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.26 (d, $J_{AB\ or\ CD}$ = 13.9 Hz, 2.7H). IR 3302, 2973, 2891, 1452, 1424, 1379, 1325, 1045 cm^{-1}.

## (2S)-N-benzyl-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210d
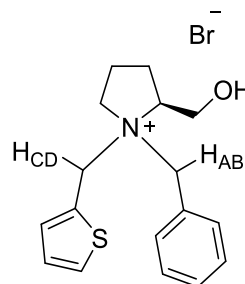
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.073 g in 99% yield and d.r. 1.0:3.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 288.1. HRMS ([M]+H) calcd for $C_{17}H_{22}NOS$: 288.1422; found 288.1423. ^{1}H NMR δ 4.76 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 1H), 4.36 (d, $J_{AB\ or\ CD}$ = 14.0 Hz, 3.3H). IR 3302, 2973, 2885, 1455, 1379, 1045, 705 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-(thiophen-2-ylmethyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 210e
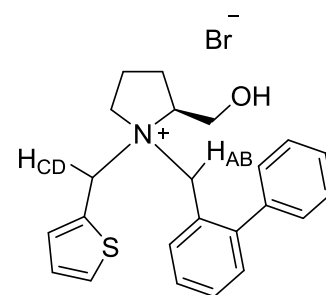
General method 2 (0.2 mmol) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as a yellow crystalline

salt, 0.088 g in 99% yield and d.r. 1.0:1.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f

= 0.38 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 364.2. HRMS ([M]+H) calcd for $C_{23}H_{26}NOS$:

364.1735; found 364.1723. ^{1}H NMR δ 5.59 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1H), 5.47 (d, $J_{AB\ or\ CD}$ = 13.3

Hz, 1.7H), 5.23 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1H), 5.07 (d, $J_{AB\ or\ CD}$ = 13.3 Hz, 1.7H), 4.83 (d, $J_{AB\ or\ CD}$ =

13.0 Hz, 1H), 4.76 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1.7H). IR 3234, 3053, 2958, 1479, 1450, 1374, 1061,

853, 752, 706 cm^{-1}.

(2*S*)-*N*-(naphthalen-2-ylmethyl)-*N*-(thiophen-2-ylmethyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 210f
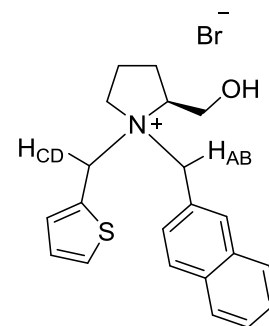
General method 2 (0.2 mmol) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as a yellow crystalline salt,

0.083 g in 99% yield and d.r. 1.0:2.4 $N_{(R)}$ is major diastereoisomer

(Interpretation 1 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 338.2. HRMS ([M]+H)

calcd for $C_{21}H_{24}NOS$: 338.1579; found 338.1573. ^{1}H NMR δ 5.69 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H),

4.38 (d, $J_{AB\ or\ CD}$ = 14.0 Hz, 2.4H). IR 3236, 3054, 2955, 1599, 1508, 1450, 1427, 1364, 1062,

857, 825, 716 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.084 g in 99% yield and d.r. 1:4 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 3 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 344.2. HRMS ([M]+H) calcd for $C_{21}H_{30}NOS$: 344.2048; found 344.2044. ^{1}H NMR δ 5.79 (d, $J_{AB\ or\ CD}$ = 14.0 Hz, 4H), 5.72 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 4H), 5.44 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.71 (d, $J_{AB\ or\ CD}$ = 14.1 Hz, 1H), 1.34 (s, 36H, [t]Bu), 1.31 (s, 9H, [t]Bu). IR 3237, 2959, 1612, 1513, 1460, 1426, 1364, 1063, 841, 786, 718 cm^{-1}.

**(2S)-N-(3,5-di-tert-butylbenzyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210h**
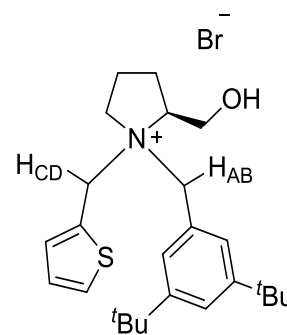
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.092 g in 96% yield and d.r. 1:4 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 4 used). R_f = 0.41 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 400.3. HRMS ([M]+H) calcd for $C_{25}H_{38}NOS$: 400.2674; found 400.2680. ^{1}H NMR δ 5.79 (d, $J_{AB\ or\ CD}$ = 14.0 Hz, 4H), 5.61 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4H), 5.41 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 4.75 (d, $J_{AB\ or\ CD}$ = 14.1 Hz, 1H), 1.36 (s, 72H, 2x [t]Bu), 1.31 (s, 18H, 2x [t]Bu). IR 3248, 2955, 2902, 1599, 1476, 1461, 1363, 1064, 881, 714 cm^{-1}.

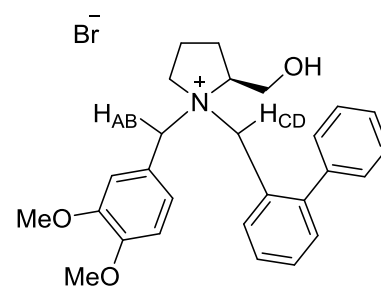**(2S)-N-(4-methylbenzyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210i**
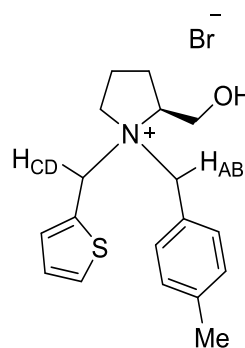
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.076 g in 99% yield and d.r. 1.0:3.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 5 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 302.2. HRMS ([M]+H) calcd for $C_{18}H_{24}NOS$: 302.1579; found 302.1589. ^1H NMR δ 5.77 (d, $J_{AB\ or\ CD}$ = 14.1 Hz, 3.2H), 5.67 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 3.2H), 5.45 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.71 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 1H), 2.40 (s, 9.6H, Me), 2.37 (s, 3H, Me). IR 3235, 2956, 1613, 1515, 1450, 1427, 1062, 808, 724 cm^{-1}.

(2S)-N-(3,5-dimethoxybenzyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210j
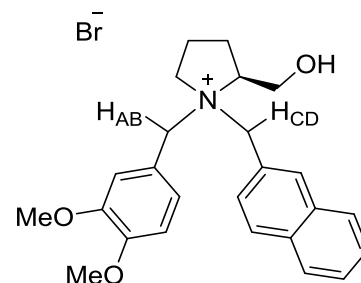
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.085 g in 99% yield and d.r. 1.0:3.6 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 7 and 11 used). R_f = 0.33 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 348.2. HRMS ([M]+H) calcd for $C_{19}H_{26}NO_3S$: 348.1633; found 348.1640. ^1H NMR δ 6.92 (d, J = 2.2 Hz, 7.2H, H^1), 6.70 (d, J = 2.2 Hz, 2H, H^1), 5.80 (d, $J_{AB\ or\ CD}$ = 14.1 Hz, 3.6H), 5.65 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 3.6H), 5.40 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.75 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 1H), 3.84 (s, 21.6H, 2x OMe), 3.80 (s, 6H, 2x OMe). IR 3248, 2965, 1594, 1457, 1430, 1347, 1153, 1056, 846, 717 cm^{-1}.
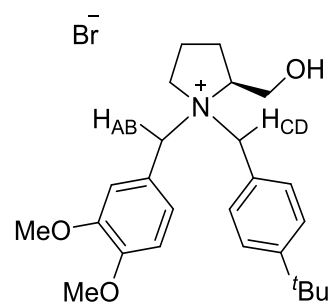
(2S)-N-(4-nitrobenzyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210k

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.059 g in 71%

yield and d.r. 1.0:1.7 $N_{(R)}$ is major diastereoisomer (Interpretation 7 and 8 used). R_f = 0.28 in 10:1

CH_2Cl_2:MeOH. m/z ([M]+H) 333.1. HRMS ([M]+H) calcd for $C_{17}H_{21}N_2O_3S$: 333.1273; found

333.1274. ^{1}H NMR δ 8.31 (d, J = 8.7 Hz, 1H, H^1), 8.25 (d, J = 8.7 Hz, 1.7H, H^1), 8.03 (d, J = 8.7

Hz, 1H, H^2), 7.94 (d, J = 8.7 Hz, 1.7H, H^2). IR 3312, 2973, 1607, 1453, 1523, 1349, 1047, 857,

710 cm^{-1}.

(2S)-N-(naphthalen-1-ylmethyl)-N-(thiophen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 210l

General method 2 (0.2 mmol) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as a yellow crystalline

salt, 0.062 g in 74% yield and d.r. 1.0:2.4 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f

= 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 338.2. HRMS ([M]+H) calcd for $C_{21}H_{24}NOS$:

338.1579; found 338.1573. ^{1}H NMR δ 5.69 (d, $J_{AB \ or \ CD}$ = 12.8 Hz, 1H), 4.38 (d, $J_{AB \ or \ CD}$ = 14.0

Hz, 2.4H). IR 3320, 2973, 1453, 1380, 1087, 1045, 879 cm^{-1}.

(S)-(N-(3,4-dimethoxybenzyl)pyrrolidin-2-yl)methanol 187

General method 1 (15 mmol) was used to prepare the tertiary amine

which was isolated as a brown oil, 3.58 g in 95% yield. R_f = 0.40 in

10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 252.1. HRMS ([M]+H) calcd for
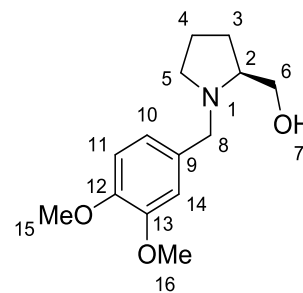
$C_{14}H_{22}NO_3$: 252.1600; found 252.1597. $[\alpha]_D^{23}$ = −23 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.03 − 6.71 (m,

3H, ArH), 3.86 − 3.90 (m, 7H, 8, 15 and 16), 3.65 (app dt, J = 7.7, 4.4 Hz, 1H, 6), 3.42 (dd, J =

10.7, 2.1 Hz, 1H, 6), 3.31 (d, J_{AB} = 12.8 Hz, 1H, 8), 3.05 – 2.92 (m, 1H, 2), 2.72 (ddd, J = 9.2,

5.8, 2.8 Hz, 1H, 5), 2.37 – 2.23 (m, 1H, 5), 2.03 – 1.77 (m, 2H, 3), 1.76 – 1.62 (m, 2H, 4). [13]C

NMR δ 148.89 (13), 148.11 (12), 131.89 (9), 120.79 (10), 111.82 (11), 110.87 (14), 64.26 (2),

61.79 (6), 58.41 (8), 55.89 (5), 54.50 (15 and 16), 27.86 (3), 23.44 (4). IR 3391, 2952, 2873,

2834, 1606, 1591, 1513, 1463, 1233, 1138, 1026, 763, 731, 700 cm^{-1}.

(2*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(3,4-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211a
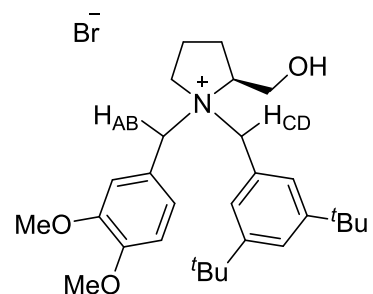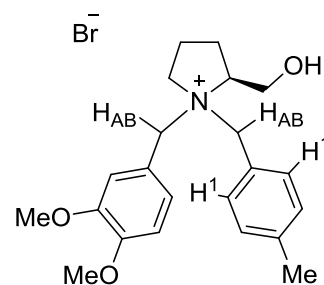
General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as a peach-

coloured crystalline salt, 0.082 g in 73% yield and d.r. 1.0:2.1 $N_{(S)}$

is major diastereoisomer (Interpretation 1 used). R_f = 0.27 in 10:1
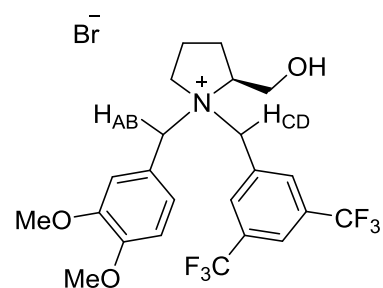
CH$_2$Cl$_2$:MeOH. *m/z* ([M]+H) 478.0. HRMS ([M]+H) calcd for C$_{23}$H$_{26}$F$_6$NO$_3$: 478.1817; found

478.1831. ^{1}H NMR δ 6.06 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 2.1H), 5.83 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 1H), 5.67 (d,

$J_{AB\ or\ CD}$ = 13.4 Hz, 1H), 5.55 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 2.1H), 5.43 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 1H), 4.99

(d, $J_{AB\ or\ CD}$ = 13.1 Hz, 2.1H), 4.74 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 1H). IR 3257, 2939, 2839, 1606, 1465,

1425, 1518, 1277, 1021, 893, 769, 707 cm^{-1}.

(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(3,5-dimethylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211b

General method 2 (0.2 mmol) was used to prepare the ammonium

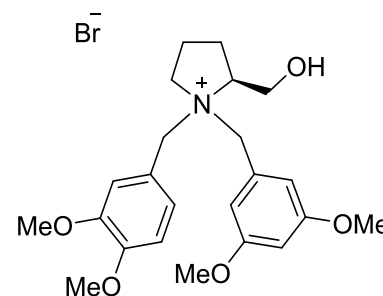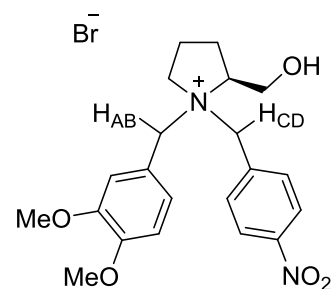salt which was isolated as a diastereomeric mixture as a peach-

coloured crystalline salt, 0.089 g in 99% yield and d.r. 1.0:3.7 $N_{(S)}$
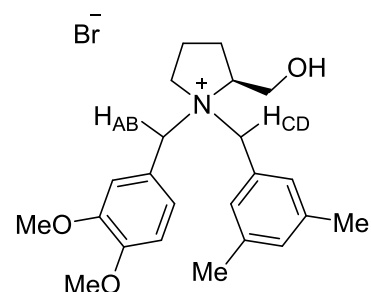
is major diastereoisomer (Interpretation 1 and 2 used). R_f = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. *m/z*

([M]+H) 370.2. HRMS ([M]+H) calcd for C$_{23}$H$_{32}$NO$_3$: 370.2382; found 370.2385. ^{1}H NMR δ

5.66 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 4.31 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3.7H), 2.37 (s, 22.2H, 2x Me), 2.30 (s, 6H, 2x Me). IR 3238, 2917, 2836, 1605, 1517, 1461, 1264, 1245, 1065, 1020, 857, 769, 719 cm^{-1}.

(2S)-N-(3,4-dimethoxybenzyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 211c
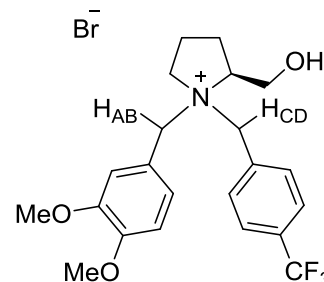
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.097 g in 99% yield and d.r. 1.0:5.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 13 used). R_f = 0.32 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 410.1. HRMS ([M]+H) calcd for C$_{22}$H$_{27}$F$_3$NO$_3$: 410.1943; found 410.1957. ^{1}H NMR δ 5.48 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5.3H), 4.83 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5.3H), 4.65 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.23 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H). ^{19}F NMR δ -62.97 (s, 15.9F), -63.02 (s, 3F). IR 3282, 2968, 1606, 1518, 1464, 1377, 1323, 1066, 861, 769, 692 cm^{-1}.

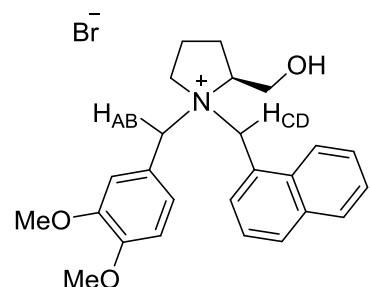**(2S)-N-benzyl-N-(3,4-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211d**
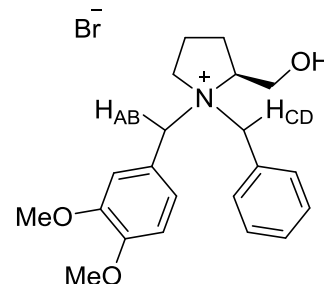
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an orange coloured crystalline salt, 0.070 g in 83% yield and d.r. 1.0:2.8 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 342.2. HRMS ([M]+H) calcd for C$_{21}$H$_{28}$NO$_3$: 342.2069; found 342.2073. ^{1}H NMR δ 5.55 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.48 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.8H), 4.43 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.8H). IR 3241, 2960, 2836, 1604, 1517, 1454, 1424, 1374, 1266, 1244, 1019, 818, 762, 704 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-(3,4-dimethoxybenzyl)-
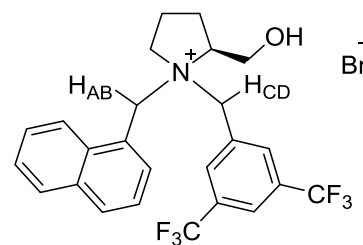
2-(hydroxymethyl)pyrrolidinium bromide 211e

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as a yellow

coloured crystalline salt, 0.099 g in 99% yield and d.r. 1:3 $N_{(S)}$ is major diastereoisomer

(Interpretation 1 used). R_f = 0.32 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 418.2. HRMS ([M]+H)

calcd for $C_{27}H_{32}NO_3$: 418.2382; found 418.2371. ^{1}H NMR δ 5.77 (d, $J_{AB \, or \, CD}$ = 13.1 Hz, 3H),

5.50 (d, $J_{AB \, or \, CD}$ = 13.4 Hz, 1H), 5.35 (d, $J_{AB \, or \, CD}$ = 12.9 Hz, 3H), 4.89 (d, $J_{AB \, or \, CD}$ = 13.4 Hz,

1H), 4.74 (d, $J_{AB \, or \, CD}$ = 13.1 Hz, 3H). IR 3237, 2959, 2835, 1591, 1517, 1451, 1424, 1262, 1245,

1020, 753, 707 cm^{-1}.

(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(naphthalen-2-ylmethyl)-2-
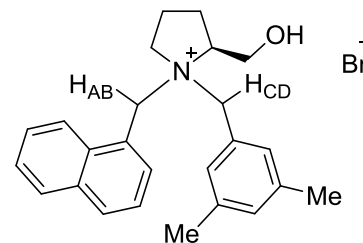
(hydroxymethyl)-pyrrolidinium bromide 211f

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as an orange

coloured crystalline salt, 0.091 g in 96% yield and d.r. 1.0:2.8 $N_{(S)}$ is major diastereoisomer

(Interpretation 1 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 392.2. HRMS ([M]+H)

calcd for $C_{25}H_{30}NO_3$: 392.2226; found 392.2220. ^{1}H NMR δ 5.80 (d, $J_{AB \, or \, CD}$ = 12.8 Hz, 2.8H),

5.69 (d, $J_{AB \, or \, CD}$ = 13.0 Hz, 1H), 5.51 (d, $J_{AB \, or \, CD}$ = 13.0 Hz, 2.8H), 4.71 (d, $J_{AB \, or \, CD}$ = 13.0 Hz,

2.8H), 4.33 (d, $J_{AB \, or \, CD}$ = 13.0 Hz, 1H). IR 3241, 2959, 1590, 1517, 1461, 1423, 1369, 1269,

1245, 1019, 865, 820, 768, 698 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(3,4-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211g
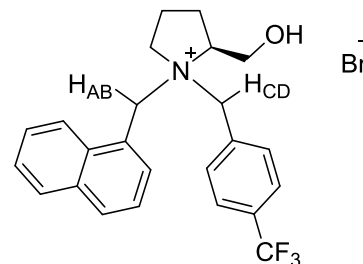
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a peach coloured crystalline salt, 0.088 g in 92% yield and d.r. 1.0:4.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 3 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 398.3. HRMS ([M]+H) calcd for $C_{25}H_{36}NO_3$: 398.2695; found 398.2690. ^{1}H NMR δ 5.68 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 4.7H), 5.46 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 4.7H), 4.39 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.30 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 4.7H), 1.35 (s, 42.3H, ^tBu), 1.31 (s, 9H, ^tBu). IR 3255, 2960, 2836, 1606, 1517, 1461, 1366, 1266, 1246, 1020, 861, 818, 769, 694 cm^{-1}.

**(2S)-N-(3,5-di-tert-butylbenzyl)-N-(3,4-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211h**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a peach coloured crystalline salt, 0.106 g in 99% yield and d.r. 1:5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 4 used). R_f = 0.36 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 454.3. HRMS ([M]+H) calcd for $C_{29}H_{44}NO_3$: 454.3321; found 454.3312. ^{1}H NMR δ 5.72 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 1H), 5.63 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5H), 5.56 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5H), 4.64 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 1H), 4.27 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 5H), 1.34 (s, 90H, 2x ^tBu), 1.30 (s, 18H, 2x ^tBu). IR 3261, 2957, 1599, 1519, 1464, 1424, 1363, 1269, 1247, 1023, 879, 821, 770, 718 cm^{-1}.

**(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 211i**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a peach coloured crystalline salt, 0.086 g in 99% yield and d.r. 1:4 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 5 and 7 used). R_f = 0.32 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 356.2. HRMS ([M]+H) calcd for $C_{22}H_{30}NO_3$: 356.2226; found 356.2219. ^{1}H NMR δ 7.57 (d, *J* = 8.1 Hz, 8H, H[1]), 7.41 (d, *J* = 8.0 Hz, 2H, H[1]), 5.73 (d, $J_{AB\,or\,CD}$ = 12.6 Hz, 1H), 5.65 (d, $J_{AB\,or\,CD}$ = 13.0 Hz, 4H), 5.45 (d, $J_{AB\,or\,CD}$ = 13.0 Hz, 4H), 2.41 (s, 12H, Me), 2.36 (s, 3H, Me). IR 3240, 2959, 2835, 1590, 1516, 1452, 1424, 1373, 1265, 1245, 1019, 857, 769, 691 cm^{-1}.

(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 211j

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow coloured crystalline salt, 0.095 g in 99% yield and d.r. 1.0:4.1 $N_{(S)}$ is major diastereoisomer (Interpretation 11 used). R_f = 0.27 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 402.2. HRMS ([M]+H) calcd for $C_{23}H_{32}NO_5$: 402.2280; found 402.2285. ^{1}H NMR δ 3.94 (d, *J* = 5.7 Hz, 6H, 2x OMe), 3.89 (d, *J* = 2.3 Hz, 24.6H, 2x OMe), 3.85 (s, 24.6H, 2x OMe), 3.78 (s, 6H, 2x OMe). IR 3238, 2938, 1594, 1517, 1458, 1432, 1374, 1346, 1265, 1245, 1149, 1020, 846, 769, 716 cm^{-1}.

(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(4-nitrobenzyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 211k

General method 2 (0.2 mmol) was used to prepare the ammonium salt

which was isolated as a diastereomeric mixture as a dark orange

coloured crystalline salt, 0.050 g in 54% yield and d.r. 1:2 $N_{(S)}$ is major diastereoisomer

(Interpretation 1 used). R_f = 0.24 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 387.2. HRMS ([M]+H)

calcd for $C_{21}H_{27}N_2O_5$: 387.1920; found 387.1914. ^{1}H NMR δ 6.25 (d, $J_{AB\ or\ CD\text{-}(R)}$ = 13.6 Hz, 1H),

6.12 (d, $J_{AB\ or\ CD}$ = 12.3 Hz, 2H), 5.67 (d, $J_{AB\ or\ CD}$ = 11.9 Hz, 1H), 5.58 (d, $J_{AB\ or\ CD}$ = 13.1 Hz,

2H), 5.45 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 4.98 (d, $J_{AB\ or\ CD}$ = 11.9 Hz, 1H), 4.78 (d, $J_{AB\ or\ CD}$ = 13.1

Hz, 2H). IR 3318, 2942, 1607, 1521, 1464, 1349, 1349, 1022, 857,

707 cm^{-1}.

(2*S*)-*N*-(3,4-dimethoxybenzyl)-*N*-(naphthalen-1-ylmethyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 211l

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as an orange coloured crystalline salt, 0.044 g

in 47% yield and d.r. 1.0:2.8 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.30

in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 392.2. HRMS ([M]+H) calcd for $C_{25}H_{30}NO_3$: 392.2226;

found 392.2233. ^{1}H NMR δ 8.20 (s, 2.8H, ArH), 8.06 (s, 1H, ArH), 5.69 (d, $J_{AB\ or\ CD}$ = 13.0 Hz,

1H), 5.51 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 2.8H), 4.71 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 2.8H). IR 3309, 2960, 1593,

1518, 1463, 1023, 807 cm^{-1}.

(2*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177a

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.050 g in 46% yield and d.r. 1.0:2.5 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 14 used). R_f = 0.28 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 468.2. HRMS ([M]+H) calcd for $C_{25}H_{24}F_6NO$: 468.1762; found 468.1778. ^{1}H NMR δ 6.59 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 2.5H), 6.43 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.85 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 2.5H), 5.17 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H). ^{19}F NMR δ -62.53 − -62.63 (m, 15F), -62.70 − -62.82 (m, 6F). IR 3265, 2969, 1624, 1597, 1462, 1369, 1277, 1171, 1127, 1065, 780, 682 cm^{-1}.

(2*S*)-*N*-(3,5-dimethylbenzyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177b
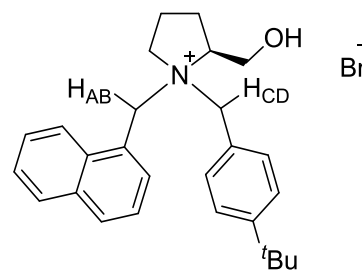
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.082 g in 93% yield and d.r. 1:2 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 360.2. HRMS ([M]+H) calcd for $C_{25}H_{30}NO$: 360.2327; found 360.2334. ^{1}H NMR δ 5.85 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 2H), 5.72 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 2H), 5.58 (d, $J_{AB\ or\ CD}$ = 12.6 Hz, 1H), 5.41 (d, $J_{AB\ or\ CD}$ = 12.6 Hz, 1H). IR 3220, 2968, 2915, 1605, 1512, 1459, 1376, 1064, 857, 782, 739 cm^{-1}.

(2S)-N-(naphthalen-1-ylmethyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177c
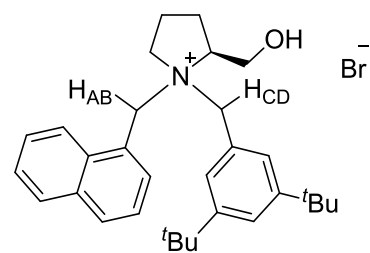
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.065 g in 68% yield and d.r. 1:3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 13 used). R_f = 0.33 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 400.2. HRMS ([M]+H) calcd for $C_{24}H_{25}F_3NO$: 400.1888; found 400.1895. ^{1}H NMR δ 5.91 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 3H), 5.74 (d, $J_{AB\ or\ CD}$ = 8.8 Hz, 1H), 5.08 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 3H), 4.85 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3H). ^{19}F NMR δ -62.94 (s, 9F), -63.03 (s, 3F). IR 3266, 2970, 1620, 1598, 1322, 1066, 780, 692 cm^{-1}.

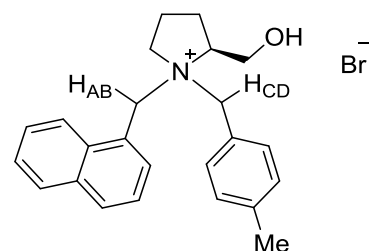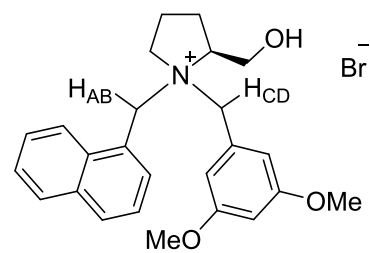**(2S)-N-benzyl-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide177d**
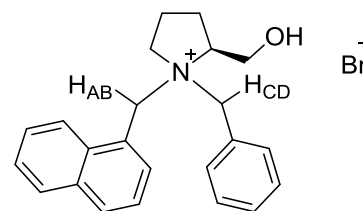
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.081 g in 99% yield and d.r. 1:3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 332.2. HRMS ([M]+H) calcd for $C_{23}H_{26}NO$: 332.2014; found 332.2025. ^{1}H NMR δ 5.87 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 3H), 5.76 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 5.57 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 5.21 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 3H). IR 3238, 2972, 1454, 1058, 783, 759, 704 cm^{-1}. d.r. 1:20 $N_{(R)}$ is major diastereoisomer. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.81 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 20H), 5.67 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 20H), 5.50 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H), 5.20 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 20H), 5.14 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 4.74 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 20H).

^{13}C NMR δ 135.39 (10), 134.36 (13), 133.84 (12), 133.76 (ArH), 133.29 (ArH), 131.71 (ArH), 130.79 (11), 129.57 (ArH), 129.11
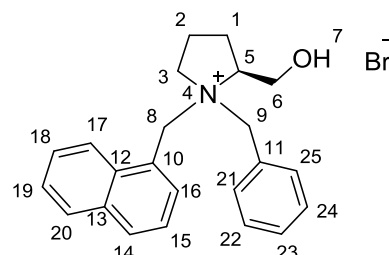
(ArH), 127.86 (ArH), 127.74 (ArH), 126.18 (ArH), 125.61 (ArH), 122.83 (ArH), 121.61 (ArH), 71.11 (5), 58.39 (3), 57.69 (6), 56.58 (9), 55.84 (8), 22.76 (1), 19.09 (2).

(2S)-N-benzyl-N-(naphthalen-1-ylmethyl)-2-(((3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)methyl)pyrrolidin-1-ium bromide 177d*
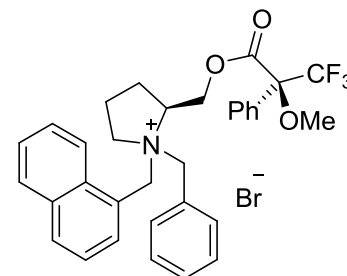
Under inert conditions a round bottomed flask was charged with ammonium salt **177d** (1 equiv 0.017 mmol, 7 mg), DMAP (0.1 equiv, 0.0017 mmol, 0.2 mg) and CH_2Cl_2 (0.5 mL). To the mixture was then added TEA (1.2 equiv, 0.0204 mmol 2.62 µL) followed by (R)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.2 equiv, 0.0204 mmol, 4 µL). The mixture was stirred at room temperature for 10 minutes and then the solvent removed under reduced pressure. The reaction mixture was dissolved in $CDCl_3$ and analysed by ^{19}F NMR spectroscopy. d.r. 1:20 $N_{(R)}$ is major diastereoisomer. ^{19}F NMR δ -70.51 excess of Mosher's ester, -71.16 (s, 3F), -71.77 (s, 60F).

(2S)-N-([1,1'-biphenyl]-2-ylmethyl)-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177e
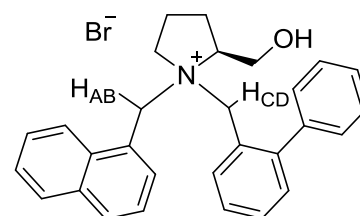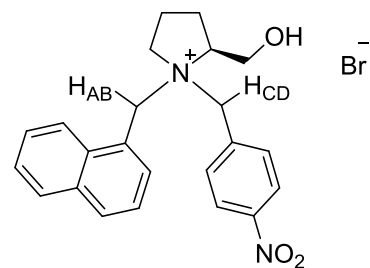
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.070 g in 72% yield and d.r. 1.0:2.9 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 408.2. HRMS ([M]+H) calcd for $C_{29}H_{30}NO$: 408.2327; found 408.2320. ^{1}H NMR δ 5.90 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 2.9H), 5.66 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 2.9H), 5.51 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H), 5.20 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 2.9H), 4.96 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H). IR 3267, 2970, 1596, 1455, 1324, 1065, 780, 751, 706 cm^{-1}.
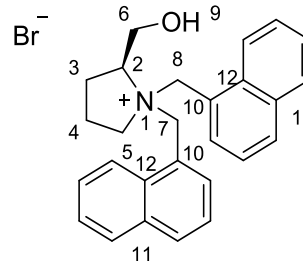
(2*S*)-*N*-(naphthalen-1-ylmethyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177f
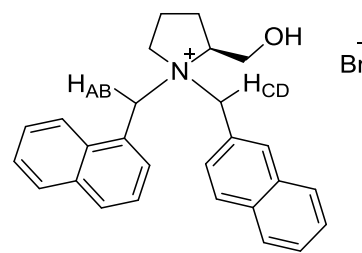
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.078 g in 84% yield and d.r. 1:3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 382.2. HRMS ([M]+H) calcd for $C_{27}H_{28}NO$: 382.2171; found 382.2160. ^{1}H NMR δ 6.02 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3H), 5.92 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3H), 5.80 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1H), 5.27 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3H). IR 3246, 2971, 1598, 1510, 1460, 1371, 1065, 864, 781, 757cm^{-1}.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.093 g in 99% yield and d.r. 1:3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 3 used). R_f = 0.41 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 388.3. HRMS ([M]+H) calcd for $C_{27}H_{34}NO$: 388.2640; found 388.2647. ^{1}H NMR δ 5.87 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 3H), 5.79 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 3H), 5.65 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.46 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.26 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 3H), 1.41 (s, 27H, *t*Bu), 1.34 (s, 9H, *t*Bu). IR 3244, 2962, 1612, 1512, 1460, 1364, 1064, 782 cm^{-1}.

(2*S*)-*N*-(3,5-di-tert-butylbenzyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177h

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.091 g in 87% yield and d.r. 1.0:2.9 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 4 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 444.3. HRMS ([M]+H) calcd for $C_{31}H_{42}NO$: 444.3266; found 444.3256. ^1H NMR δ 5.93 (d, $J_{AB \, or \, CD}$ = 13.8 Hz, 3H), 5.68 (d, $J_{AB \, or \, CD}$ = 12.9 Hz, 2.9H), 5.46 (d, $J_{AB \, or \, CD}$ = 12.8 Hz, 1H), 5.32 (d, $J_{AB \, or \, CD}$ = 13.8 Hz, 2.9H), 1.40 (s, 52.2H, 2x ^tBu), 1.37 (s, 18H, 2x ^tBu). IR 3245, 2958, 1599, 1460, 1363, 1065, 781, 737 cm^{-1}.

(2*S*)-*N*-(4-methylbenzyl)-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177i

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.084 g in 99% yield and d.r. 1.0:2.9 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 5 and 9 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 346.2. HRMS ([M]+H) calcd for $C_{24}H_{28}NO$: 346.2171; found 346.2164. ^1H NMR δ 8.28 (d, *J* = 7.1 Hz, 2.9H, ArH), 8.15 (d, *J* = 8.3 Hz, 1H, ArH), 5.65 (d, $J_{AB \, or \, CD}$ = 12.3 Hz, 1H), 5.46 (d, $J_{AB \, or \, CD}$ = 13.0 Hz, 1H), 5.21 (d, $J_{AB \, or \, CD}$ = 13.6 Hz, 2.9H), 4.45 (d, $J_{AB \, or \, CD}$ = 13.0 Hz, 2.9H), 2.48 (s, 8.7H, Me), 2.40 (s, 3H, Me). IR 3238, 2971, 1613, 1513, 1451, 1063, 781 cm^{-1}.

(2*S*)-*N*-(3,5-dimethoxybenzyl)-*N*-(naphthalen-1-ylmethyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 177j

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.093 g in 98%

yield and d.r. 1.0:2.5 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.34 in 10:1

CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 392.2. HRMS ([M]+H) calcd for C$_{25}$H$_{30}$NO$_3$: 392.2226; found

392.2223. ^{1}H NMR δ 5.84 (d, $J_{AB \, or \, CD}$ = 13.6 Hz, 2.5H), 5.77 (d, $J_{AB \, or \, CD}$ = 12.7 Hz, 2.5H), 5.63

(d, $J_{AB \, or \, CD}$ = 12.6 Hz, 1H), 5.45 (d, $J_{AB \, or \, CD}$ = 12.6 Hz, 1H), 5.27 (d, $J_{AB \, or \, CD}$ = 13.6 Hz, 2.5H).

IR 3238, 2971, 1594, 1457, 1321, 1204, 1153, 1057, 846, 807, 781

cm^{-1}.

(2*S*)-*N*-(naphthalen-1-ylmethyl)-*N*-(4-nitrobenzyl)-2-

(hydroxymethyl)-pyrrolidinium bromide 177k

General method 2 (0.2 mmol) was used to prepare the ammonium

salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.059 g in 65%

yield and d.r. 1.0:2.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.32 in 10:1

CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 377.2. HRMS ([M]+H) calcd for C$_{23}$H$_{25}$N$_2$O$_3$: 377.1865; found

377.1870. ^{1}H NMR δ 6.23 (d, $J_{AB \, or \, CD}$ = 13.3 Hz, 2.3H), 5.81 (d, $J_{AB \, or \, CD}$ = 12.6 Hz, 1H), 5.74 (d,

$J_{AB \, or \, CD}$ = 12.6 Hz, 1H), 5.24 (d, $J_{AB \, or \, CD}$ = 12.6 Hz, 1H), 4.98 (d, $J_{AB \, or \, CD}$ = 13.3 Hz, 2.3H). IR

3266, 2969, 1606, 1521, 1461, 1346, 1059, 780, 706 cm^{-1}.

(S)-N,N-bis(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidin-1-ium bromide 177l

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a white crystalline solid, 0.060 g in 65% yield. R_f = 0.22 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 382.2. HRMS ([M]+H) calcd for $C_{27}H_{28}NO$: 382.2165; found 382.2170. $[\alpha]_D^{23}$ = −18 (*c* 1.0, CH_2Cl_2). MP = 166-168 °C. ^1H NMR δ 8.61 (d, *J* = 8.5 Hz, 1H, ArH), 8.27 (d ArH, *J* = 7.0 Hz, 1H, ArH), 8.06 (d, *J* = 8.4 Hz, 1H, ArH), 7.97 − 7.79 (m, 4H, ArH), 7.69 − 7.67 (m, 1H, ArH), 7.63 − 7.51 (m, 3H, ArH), 7.41 − 7.34 (m, 1H, ArH), 7.20 − 7.12 (m, 1H, ArH), 6.60 (d, *J* = 8.5 Hz, 1H, ArH), 6.45 (app t, *J* = 4.8 Hz, 1H, 9), 6.15 (d, J_{AB} = 13.6 Hz, 1H, 7 or 8), 5.88 (d, J_{AB} = 13.5 Hz, 1H, 7 or 8), 4.98 − 4.71 (m, 3H, 2, 7 or 8), 4.57 − 4.39 (m, 2H, 7 or 8), 3.58 − 3.56 (m, 1H, 5), 2.65 − 2.52 (m, 1H, 5), 2.42 (m, 1H, 3 or 4), 2.31 − 2.06 (m, 2H, 3 or 4), 1.98 − 1.77 (m, 1H, 3 or 4). ^{13}C NMR δ 135.38 and 134.20 (10), 133.84 and 133.73 (11), 133.61 and 133.20 (12), 132.04 (ArH), 131.73 (ArH), 129.55 (ArH), 129.26 (ArH), 128.57 (ArH), 127.79 (ArH), 126.78 (ArH), 126.11 (ArH), 125.76 (ArH), 125.18 (ArH), 124.12 (ArH), 123.80 (ArH), 123.04 (ArH), 121.69 (ArH), 71.34 (2), 59.06 (5), 58.42 (6), 55.98 (8 or 7), 54.46 (7 or 8), 23.40 (3), 19.68 (4).

An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.4.

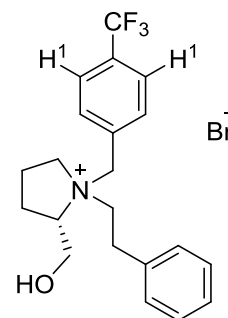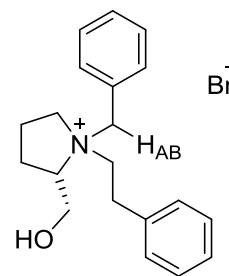**(1S,2S)-N-methyl-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidin-1-ium iodide 182**
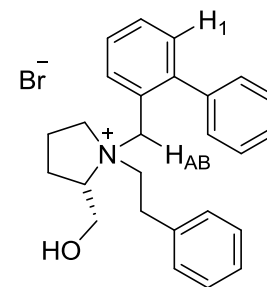
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.072 g in 94% yield and d.r. 1:10 $N_{(S)}$ is major diastereoisomer Rf value 0.48 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 257.2. HRMS ([M])
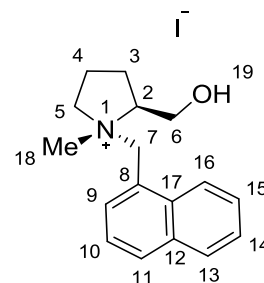
calcd for $C_{17}H_{22}NO$: 256.1696; found 256.1670. MP 112-113 °C. ^{1}H NMR δ 8.37 (d, J = 8.6 Hz, 1H, 16), 7.94 (d, J = 7.0 Hz, 1H, 9), 7.91 (d, J = 8.2 Hz, 1H, 11), 7.84 (d, J = 8.1 Hz, 1H, 13), 7.64 (app t, J = 7.7 Hz, 1H, 15), 7.49 (m, 2H, 14 and 10), 5.86 (d, J_{AB} = 13.7 Hz, 1H, 7), 5.38 (d, J_{AB} = 13.7 Hz, 1H, 7), 4.82 (app t, J = 5.0 Hz, 1H, 19), 4.75 (app qd, J = 9.6, 3.2 Hz, 1H, 2), 4.36 (d, J = 13.8 Hz, 1H, 6), 4.28 – 4.07 (m, 2H, 6 and 5), 3.39 – 3.29 (m, 1H, 5), 3.00 (s, 3H, 18), 2.51 – 2.38 (m, 1H, 3), 2.29 – 2.18 (m, 1H, 4), 2.07 – 1.95 (m, 4H, 4), 1.92 – 1.81 (m, 1H, 3). ^{13}C NMR δ 133.88 (8), 133.22 (9), 132.94 (17), 131.68 (11), 129.11 (13), 128.21 (15), 126.49 (14), 125.12 (10), 124.33 (12), 123.77 (16), 74.44 (2), 64.66 (5), 64.17 (7), 59.34 (6), 43.00 (18), 23.83 (3), 19.67 (4).

An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.2.

(*S*)-(*N*-phenethylpyrrolidin-2-yl)methanol 188

General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a yellow oil, 2.74 g in 89% yield. R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 206.2. HRMS ([M]+H) calcd for $C_{13}H_{20}NO$: 206.1545; found 206.1552. $[\alpha]_D^{23}$ = -42 (*c* 1.0, CH_2Cl_2). ^{1}H NMR δ 7.53 – 7.03 (m, 5H, 11, 12 and 13), 3.55 (dd, J = 10.7, 3.6 Hz, 1H, 6), 3.45 – 3.15 (m, 2H, 6 and 8), 3.10 – 2.88 (m, 1H, 8), 2.90 – 2.68 (m, 2H, 2), 2.68 – 2.42 (m, 4H, 5, 7 and 9), 2.42 – 2.24 (m, 1H, 5), 2.01 – 1.63 (m, 4H, 3 and 4). ^{13}C NMR δ 140.36 (10), 128.58 (11), 128.40 (12), 126.11 (13), 64.59 (2), 61.78 (6), 56.01 (8), 54.10 (5), 35.61 (9), 27.61 (3), 23.67 (4). IR 3410, 3027, 2946, 1603, 1496, 1453, 1381, 1034, 733, 698 cm^{-1}.
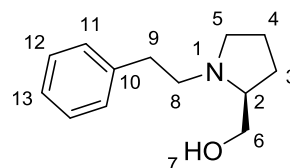
### (2*S*)-*N*-(3,5-bis(trifluoromethyl)benzyl)-*N*-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212a
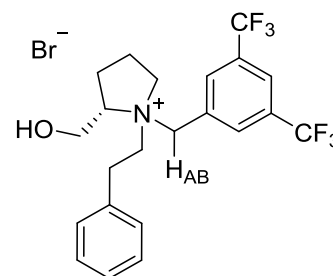
174

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.085 g in 83% yield and d.r. 1:1 was obtained (Interpretation 1 used). R_f = 0.27 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 432.2. HRMS ([M]+H) calcd for $C_{22}H_{24}F_6NO$: 432.1762; found 432.1769. ^{1}H NMR δ 5.56 (2x d, J_{AB} = 13.2, J_{AB} = 13.2 Hz, 2H), 5.29 (d, J_{AB} = 13.2 Hz, 1H), 5.17 (d, J_{AB} = 13.2 Hz, 1H). IR 3325, 3021, 2929, 1498, 1368, 1277, 1065, 758, 708 cm^{-1}.

(2S)-N-(3,5-dimethylbenzyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212b
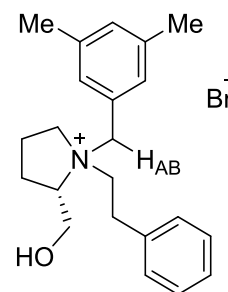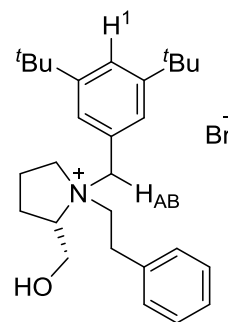
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.069 g in 85% yield and d.r. 1.0:1.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 2 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 324.2. HRMS ([M]+H) calcd for $C_{22}H_{30}NO$: 324.2327; found 324.2329. ^{1}H NMR δ 4.78 (d, J_{AB} = 13.0 Hz, 1H), 4.40 (d, J_{AB} = 13.0 Hz, 1.5H), 2.33 (s, 6H, 2x Me), 2.29 (s, 9H, 2x Me). IR 3305, 2973, 1606, 1455, 1372, 1279, 1046, 702 cm^{-1}.

(2S)-N-phenethyl-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 212c
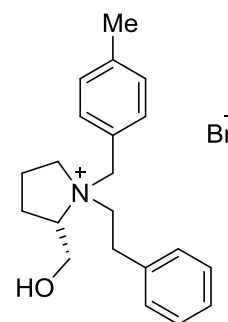
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.077 g in 87% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 8 used). R_f = 0.32 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 364.2. HRMS ([M]+H) calcd for $C_{21}H_{25}F_3NO$: 364.1888; found 364.1889. ^{1}H NMR δ 8.00 (d, J = 8.0 Hz, 2H, H^1), 7.78 (d, J = 8.1 Hz, 2.6H, H^1). IR 3291, 2973, 1603, 1497, 1324, 1068, 754, 703 cm^{-1}.

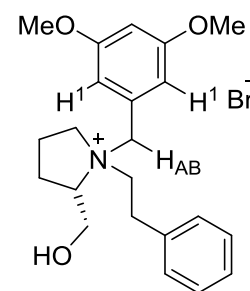**(2S)-N-benzyl-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212d**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.073 g in 97% yield and d.r. 1.0:2.2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 296.2. HRMS ([M]+H) calcd for $C_{20}H_{26}NO$: 296.2014; found 296.2021. ^{1}H NMR δ 5.02 (d, J_{AB} = 13.0 Hz, 2.2H), 4.92 (d, J_{AB} = 12.9 Hz, 1H). IR 3266, 2987, 1603, 1497, 1455, 1383, 1064, 756, 704 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-2-ylmethyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212e

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.081 g in 89% yield and d.r. 1:1 obtained (Interpretation 1, 9 and 10 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 372.2. HRMS ([M]+H) calcd for $C_{26}H_{30}NO$: 372.2327; found 372.2332. ^{1}H NMR δ 8.11 (dd, J = 7.5, 1.2 Hz, 1H, H[1]), 7.79 (dd, J = 7.6, 0.7 Hz, 1H, H[1]), 5.62 (s, 1H, br OH), 5.47 (s, 1H, br OH), 5.29 (d, J_{AB} = 13.4 Hz, 1H), 5.14 (d, J_{AB} = 13.4 Hz, 1H), 5.12 (d, J_{AB} = 13.0 Hz, 1H), 4.65 (d, J_{AB} = 13.0 Hz, 1H). IR 3252, 2981, 1601, 1493, 1455, 1383, 1064, 757, 703 cm^{-1}.

An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.5.

(2*S*)-*N*-(naphthalen-2-ylmethyl)-*N*-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212f
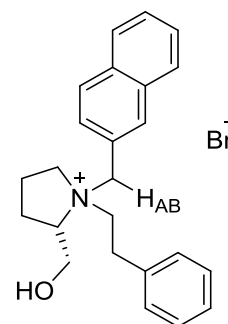
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.081 g in 95% yield and d.r. 1.0:1.5 $N_{(S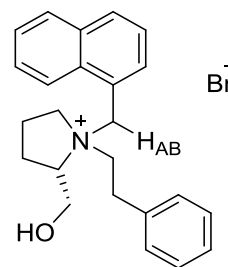)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 346.2. HRMS ([M]+H) calcd for $C_{24}H_{28}NO$: 346.2171; found 346.2158. ^{1}H NMR δ 8.26 (s, 1H, ArH), 8.03 (s, 1.5H, ArH), 5.06 (d, J_{AB} = 12.9 Hz, 1H), 4.68 (d, J_{AB} = 13.0 Hz, 1.5H). IR 3323, 3018, 2932, 1496, 1364, 1273, 755, 709 cm^{-1}.

(2S)-*N*-(3-(tert-butyl)benzyl)-*N*-phenethyl-2-(hydroxymethyl)-pyrrolidinium 212g
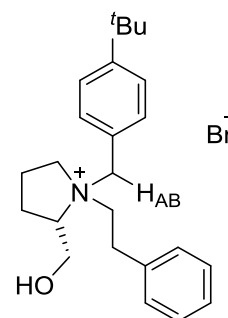
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.086 g in 99% yield and d.r. 1.0:1.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 3 used). R_f = 0.43 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 352.3. HRMS ([M]+H) calcd for $C_{24}H_{34}NO$: 352.2635; found 352.2638. ^{1}H NMR δ 4.83 (d, J_{AB} = 13.0 Hz, 1H), 4.44 (d, J_{AB} = 13.0 Hz, 1.5H), 1.30 (s, 9H, ^{t}Bu), 1.29 (s, 13.5H, ^{t}Bu). IR 3240, 2989, 1605, 1459, 1365, 1066, 857, 781, 734 cm^{-1}.

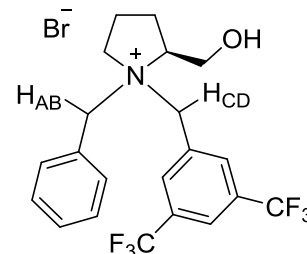**(2S)-N-(3,5-di-tert-butylbenzyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212h**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.096 g in 98% yield and d.r. 1.0:1.8 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 4 and 6 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 408.3. HRMS ([M]+H) calcd for $C_{28}H_{42}NO$: 408.3266; found 408.3269. ^{1}H NMR δ 7.52 (t, J = 1.7 Hz, 1H, H^1), 7.51 (t, J = 1.7 Hz, 1.8H, H^1), 5.83 (t, J = 6.0 Hz, 1.8H), 5.69 (t, J = 5.1 Hz, 1H), 4.81 (d, J_{AB} = 13.2 Hz, 1.8H), 4.37 (d, J_{AB} = 12.9 Hz, 1H), 1.32 (s, 18H, 2x ^{t}Bu), 1.28 (s, 32.4H, 2x ^{t}Bu). IR 3252, 2953, 1599, 1455, 1362, 1066, 755, 699 cm^{-1}.

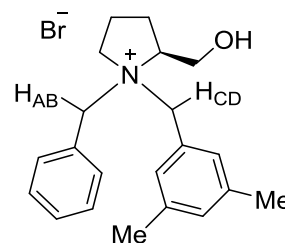**(2S)-N-(4-methylbenzyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212i**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.064 g in 82% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 5 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 310.2. HRMS ([M]+H) calcd for $C_{21}H_{28}NO$: 310.2171; found 310.2167. ^{1}H NMR δ 2.34 (s, 3H, Me), 2.33 (s, 3.9H, Me). IR 3329, 3016, 2933, 1495, 1365, 1267, 1062 cm^{-1}.

(2S)-N-(3,5-dimethoxybenzyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212j

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.017 g in 20% yield and d.r. 4:1 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 7 and 11

used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 356.2. HRMS ([M]+H) calcd for $C_{22}H_{30}NO_3$: 356.2226; found 356.2238. ^{1}H NMR δ 6.88 (d, J = 2.2 Hz, 2H, H^1), 6.72 (d, J = 2.2 Hz, 8H, H^1), 5.06 (d, J_{AB} = 13.0 Hz, 4H), 4.89 (d, J_{AB} = 12.9 Hz, 1H), 3.79 (s, 6H, 2x OMe), 3.75 (s, 24H, 2x OMe). IR 3324, 3017, 2926, 1495, 1365, 1279, 1064, 757, 707 cm^{-1}.

**(2S)-N-(4-nitrobenzyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212k**
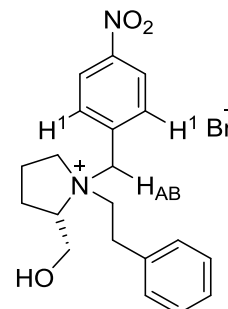
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.073 g in 87% yield and d.r. 1:3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 7 used). R_f = 0.29 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 341.2. HRMS ([M]+H) calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found 341.1870. ^{1}H NMR δ 8.09 (d, J = 8.8 Hz, 2H, H^1), 7.91 (d, J = 8.8 Hz, 6H, H^1), 5.57 (d, J_{AB} = 12.9 Hz, 3H), 5.45 (d, J_{AB} = 13.0 Hz, 1H), 5.21 (d, J_{AB} = 13.1 Hz, 1H), 4.94 (d, J_{AB} = 13.0 Hz, 3H). IR 3330, 3021, 2940, 1514, 1490, 1342, 1259, 1060 cm^{-1}.

(2S)-N-(naphthalen-1-ylmethyl)-N-phenethyl-2-(hydroxymethyl)-pyrrolidinium bromide 212l
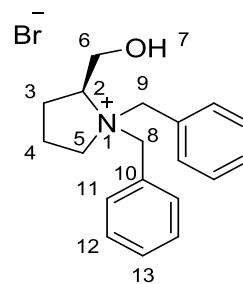
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as an off-white crystalline salt, 0.047 g in 55% yield and d.r. 2.8:1.0 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 346.2. HRMS ([M]+H) calcd for $C_{24}H_{28}NO$: 346.2171; found 346.2164. ^{1}H NMR δ 5.59 (d, J_{AB} = 13.5 Hz, 1H), 5.41 (d, J_{AB} = 13.7 Hz, 2.8H), 4.94 (d, J_{AB} = 13.5 Hz, 1H). IR 3323, 3017, 2932, 1496, 1364, 1273, 755, 710 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(3,5-bis(trifluoromethyl)benzyl)-2-

(hydroxymethyl)pyrrolidinium bromide 180d

General method 2 (0.2 mmol) was used to prepare the ammonium salt
which was isolated as a diastereomeric mixture as a white crystalline
salt, 0.085 g in 85% yield and d.r. 1.0:2.6 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 14
used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 418.2. HRMS ([M]+H) calcd for
$C_{21}H_{22}F_6NO$: 418.1606; found 418.1621. ^{1}H NMR δ 5.75 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 1H), 5.64 (d, J_{AB}
$_{or\ CD}$ = 12.7 Hz, 2.6H), 5.53 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 1H), 5.02 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 2.6H). [19]F
NMR δ -62.62 (s, 15.6F), -62.75 (s, 6F). IR 3247, 2972, 1371, 1277,
1133, 763, 706 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(3,5-dimethylbenzyl)-2-

(hydroxymethyl)pyrrolidinium bromide 213a

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a
diastereomeric mixture as a yellow crystalline salt, 0.068 g in 87% yield and d.r. 1:3 $N_{(S)}$ is major
diastereoisomer (Interpretation 1 and 2 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H)
310.2. HRMS ([M]+H) calcd for $C_{21}H_{28}NO$: 310.2171; found 310.2167. ^{1}H NMR δ 5.70 (d, $J_{AB\ or}$
$_{CD}$ = 12.2 Hz, 1H), 4.33 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3H), 2.36 (s, 18H, 2x Me), 2.30 (s, 6H, 2x Me). IR
3256, 2968, 1605, 1453, 1064, 760, 705 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-

pyrrolidinium bromide 213b

General method 2 (0.2 mmol) was used to prepare the ammonium salt
which was isolated as a diastereomeric mixture as a yellow crystalline salt,
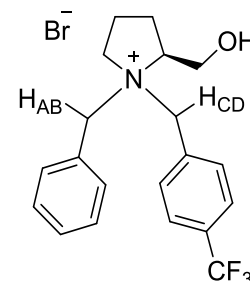
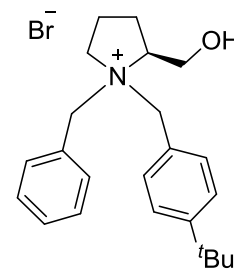0.063 g in 73% yield and d.r. 1:3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 13 used). R_f = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. *m/z* ([M]+H) 350.2. HRMS ([M]+H) calcd for C$_{20}$H$_{23}$F$_3$NO: 350.1732; found 350.1739. ^{1}H NMR δ 5.82 (d, $J_{AB\ or\ CD}$ = 12.4 Hz, 1H), 5.70 (d, $J_{AB\ or\ CD}$ = 12.4 Hz, 1H), 5.61 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3H), 4.74 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3H). ^{19}F NMR δ -63.01 (s, 9F), -63.03 (s, 3F). IR 3265, 2969, 1455, 1322, 1066, 753, 704 cm^{-1}.

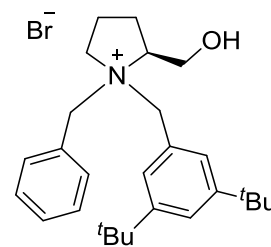### (*S*)-*N*,*N*-dibenzyl-2-(hydroxymethyl)pyrrolidinium bromide 213c

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.070 g in 97% yield. R_f = 0.38 in 10:1 CH$_2$Cl$_2$:MeOH. *m/z* ([M]+H) 282.2. HRMS ([M]+H) calcd for C$_{19}$H$_{24}$NO: 282.1858; found 282.1867. MP 195-197 °C. $[\alpha]\,^{23}_D$ = −2 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 7.86 – 7.69 (m, 2H, 13), 7.65 – 7.33 (m, 8H, 11 and 12), 6.03 (t, *J* = 5.6 Hz, 1H, 7), 5.77 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H, 8 or 9), 5.58 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H, 8 or 9), 4.61 – 4.48 (m, 1H, 2), 4.45 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H, 8 or 9), 4.19 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 2H, 5, 8 or 9), 3.95 (ddd, *J* = 19.4, 9.6, 2.8 Hz, 1H, 6), 3.37 (dd, *J* = 12.0, 9.6 Hz, 1H, 6), 3.13 – 2.89 (m, 1H, 5), 2.52 – 2.24 (m, 1H, 3 or 4), 2.22 – 1.89 (m, 3H, 3 or 4). ^{13}C NMR δ 134.40 (11), 133.62 (11), 130.66 (13), 130.56 (13), 129.43 (12), 129.15 (12), 127.63 (10), 126.79 (10), 70.46 (2), 61.58 (6), 58.17 (8 or 9), 57.87 (8 or 9), 55.08 (5), 23.05 (3), 18.78 (4). IR 3253, 3057, 2969, 1452, 1063, 1045, 751, 704 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-benzyl-2-(hydroxymethyl)pyrrolidinium bromide 213d
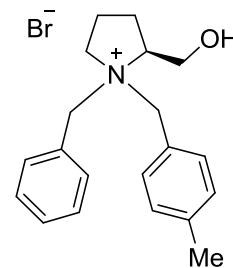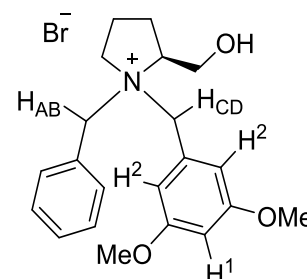
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.071 g in 81% yield and d.r. 1.0:1.9 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.39 in 10:1
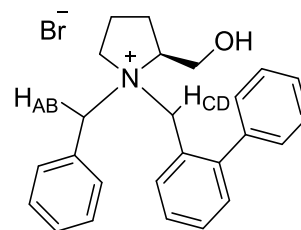
CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 358.2. HRMS ([M]+H) calcd for C$_{25}$H$_{28}$NO: 358.2171; found 358.2174. ^{1}H NMR δ 5.82 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1.9H), 5.75 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H), 5.49 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H), 5.43 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1.9H), 4.91 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H), 4.76 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1.9H), 3.98 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 1H). IR 3266, 2969, 1452, 1062, 1048, 750, 704 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179d
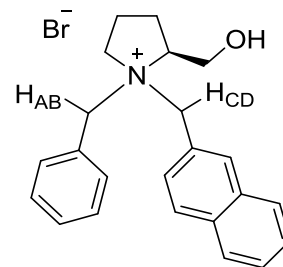
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.068 g in 82% yield and d.r. 1.0:2.2 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R$_f$ = 0.39 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 332.2. HRMS ([M]+H) calcd for C$_{23}$H$_{26}$NO: 332.2014; found 332.2019. ^{1}H NMR δ 5.96 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.2H), 5.87 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.76 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.65 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.2H). IR 3242, 2969, 1454, 1064, 756, 703 cm^{-1}.
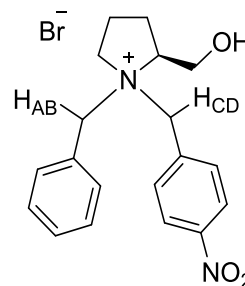
(2*S*)-*N*-benzyl-*N*-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 213e

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.077 g in 92% yield and d.r. 1:3 $N_{(S)}$ is major diastereoisomer (Interpretation 3 used). R$_f$ = 0.41 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 338.2. HRMS ([M]+H) calcd for C$_{23}$H$_{32}$NO: 338.2484; found 338.2487. ^{1}H NMR δ 1.35 (s, 27H, ^{t}Bu), 1.30 (s, 9H, ^{t}Bu). IR 3241, 2961, 1456, 1064, 761, 705 cm^{-1}.

(2S)-N-benzyl-N-(3,5-di-tert-butylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 213f

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.094 g in 99% yield and d.r. 1.0:3.4 $N_{(S)}$ is major diastereoisomer (Interpretation 4 used). R_f = 0.40 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 394.3. HRMS ([M]+H) calcd for $C_{27}H_{40}NO$: 394.3110; found 394.3117. ^1H NMR δ 1.36 (s, 61.2H, 2x ^tBu), 1.29 (s, 18H, 2x ^tBu). IR 3241, 2957, 1599, 1455, 1363, 1065, 760, 705 cm^{-1}.
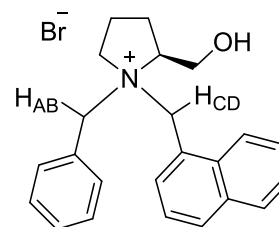
(2S)-N-benzyl-N-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 213g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.075 g in 99% yield and d.r. 1.0:2.8 $N_{(S)}$ is major diastereoisomer (Interpretation 5 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 296.2. HRMS ([M]+H) calcd for $C_{20}H_{26}NO$: 296.2014; found 296.2006. ^1H NMR δ 2.40 (s, 8.4H, Me), 2.36 (s, 3H, Me). IR 3241, 2971, 1612, 1453, 1211, 1064, 750, 704 cm^{-1}.

(2S)-N-benzyl-N-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 213h
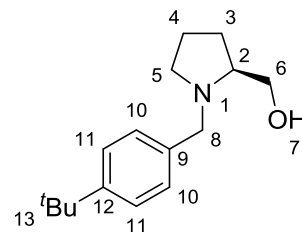
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline

salt, 0.076 g in 90% yield and d.r. 1.0:4.9 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 6, 7 and 11 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 342.2. HRMS ([M]+H) calcd for $C_{21}H_{28}NO_3$: 342.2069; found 342.2068. ^{1}H NMR δ 6.92 (d, J = 2.2 Hz, 9.8H, H^2), 6.68 (d, J = 2.2 Hz, 2H, H^2), 6.54 (t, J = 2.2 Hz, 4.9H, H^1), 6.51 (t, J = 2.2 Hz, 1H, H^1), 5.58 (d, $J_{AB\,or\,CD}$ = 13.0 Hz, 4.9H), 5.47 (d, $J_{AB\,or\,CD}$ = 12.9 Hz, 1H), 3.85 (s, 29.4H, 2x OMe), 3.78 (s, 6H, 2x OMe). IR 3241, 2970, 1594, 1454, 1204, 1152, 1057, 763, 704 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 213i

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.060 g in 74% yield and d.r. 1.0:4.9 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.31 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 327.2. HRMS ([M]+H) calcd for $C_{19}H_{23}N_2O_3$: 327.1709; found 327.1712. ^{1}H NMR δ 6.05 (d, $J_{AB\,or\,CD}$ = 12.6 Hz, 4.9H), 5.74 (d, $J_{AB\,or\,CD}$ = 12.8 Hz, 1H), 5.61 (d, $J_{AB\,or\,CD}$ = 12.6 Hz, 4.9H), 4.97 (d, $J_{AB\,or\,CD}$ = 12.6 Hz, 4.9H), 4.68 (d, $J_{AB\,or\,CD}$ = 12.8 Hz, 1H). IR 3264, 2968, 1606, 1520, 1346, 1062, 750, 704 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 177d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.059 g in 71% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 332.2. HRMS ([M]+H) calcd for $C_{23}H_{26}NO$: 332.2014; found 332.2029. ^{1}H NMR δ 8.49 (d, J = 8.7 Hz, 1.3H, ArH), 8.27 (d, J = 6.9 Hz, 1H, ArH), 5.98 (d, $J_{AB\,or\,CD}$ = 13.6 Hz, 1.3H), 5.55 (d, $J_{AB\,or\,CD}$ = 13.6 Hz, 1.3H), 5.20 (d, $J_{AB\,or\,CD}$ = 12.8 Hz, 1H), 4.93

(d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1.3H), 4.50 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 3.90 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1.3H).

IR 3241, 2969, 1454, 1057, 761, 704 cm^{-1}.

### (S)-(N-(4-(tert-butyl)benzyl)pyrrolidin-2-yl)methanol 190

General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a pale yellow oil, 3.30 g in 89% yield. R_f = 0.41 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 248.2. HRMS ([M]+H) calcd for $C_{16}H_{26}NO$: 248.2014; found 248.2015. $[\alpha]_D^{23}$ = −35 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 7.40 − 7.29 (d, J = 8.4 Hz, 2H, 11), 7.24 (d, J = 8.4 Hz, 2H, 10), 3.93 (d, J_{AB} = 13.0 Hz, 1H, 8), 3.67 (dd, J = 10.7, 3.4 Hz, 1H, 6), 3.42 (dd, J = 10.7, 1.8 Hz, 1H, 6), 3.32 (d, J_{AB} = 13.0 Hz, 1H, 8), 3.04 − 2.94 (m, 1H, 2), 2.74 − 2.72 (m, 1H, 5), 2.30 − 2.28 (m, 1H, 5), 2.00 − 1.76 (m, 2H, 4), 1.75 − 1.63 (m, 2H, 3), 1.31 (s, 9H, 13). ^{13}C NMR δ 149.94 (12), 136.25 (9), 128.39 (10), 125.22 (11), 64.20 (2), 61.73 (6), 58.07 (8), 54.47 (5), 31.40 (q13), 27.79 (13), 27.78 (3), 23.48 (4). IR 3399, 3055, 2960, 1514, 1460, 1411, 1362, 1019, 852, 734, 677 cm^{-1}.

(2S)-N-(3,5-bis(trifluoromethyl)benzyl)-N-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214a
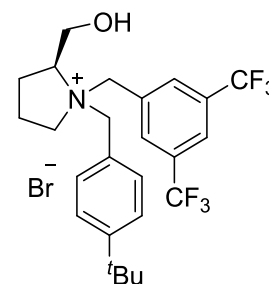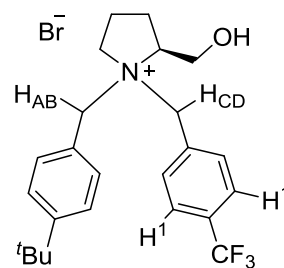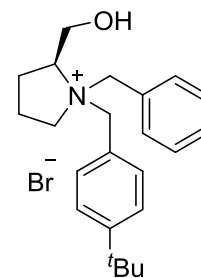
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.075 g in 68% yield and d.r. 2.2:1.0 $N_{(S)}$ is major diastereoisomer (Interpretation 3 used). R_f = 0.30 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 474.2. HRMS ([M]+H) calcd for $C_{25}H_{30}F_6NO$: 474.2232; found 474.2239. ^{1}H NMR δ 1.34 (s, 9H, ^tBu), 1.31 (s, 19.8H, ^tBu). IR 3398, 2959, 1514, 1364, 1277, 1132, 1019, 841 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(3,5-dimethylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214b
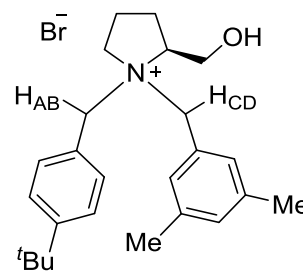
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.080 g in 90% yield and d.r. 3: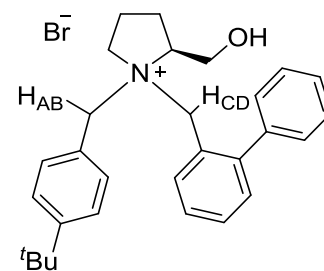1 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 4 used). $R_f = 0.39$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 366.3. HRMS ([M]+H) calcd for $C_{25}H_{36}NO$: 366.2797; found 366.2800. ^1H NMR δ 5.65 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.51 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3H), 5.42 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3H), 2.36 (s, 18H, 2x Me), 2.31 (s, 6H, 2x Me). IR 3236, 2960, 1607, 1461, 1367, 1066, 856, 782, 736 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 214c
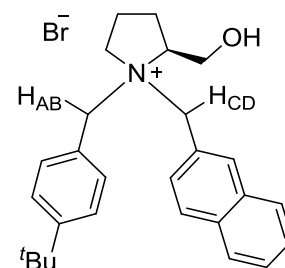
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.073 g in 75% yield and d.r. 1.0:5.1 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 3 and 9 used). $R_f = 0.34$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 406.2. HRMS ([M]+H) calcd for $C_{24}H_{31}F_3NO$: 406.2358; found 406.2372. ^1H NMR δ 8.00 (d, J = 8.1 Hz, 2H, H^1), 7.95 (d, J = 8.0 Hz, 10.2H, H^1), 5.48 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 5.1H), 5.05 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.89 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 5.1H), 4.28 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.03 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 5.1H), 1.34 (s, 9H, ^tBu), 1.30 (s, 45.5H, ^tBu). IR 3237, 2963, 1618, 1514, 1322, 1165, 1119, 1067, 839 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.067 g in 80% yield and d.r. 1.0:6.5 $N_{(S)}$ is major diastereoisomer (Interpretation 3 used). R_f = 0.39 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 338.2. HRMS ([M]+H) calcd for $C_{23}H_{32}NO$: 338.2484; found 338.2490. ^{1}H NMR δ 1.35 (s, 9H, *t*Bu), 1.30 (s, 58.5H, *t*Bu). IR 3237, 2959, 1612, 1455, 1062, 760, 707 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214e

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.073 g in 74% yield and d.r. 1.0:1.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. *m*/z ([M]+H) 414.3. HRMS ([M]+H) calcd for $C_{29}H_{36}NO$: 414.2797; found 414.2801. ^{1}H NMR δ 5.73 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.7H), 5.60 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1H), 5.46 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1H), 5.29 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.7H), 4.97 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1H), 4.76 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.7H). IR 3242, 2959, 1612, 1452, 1063, 751, 706 cm^{-1}.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 214f

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.082 g in 87% yield and d.r. 1:5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f =

0.41 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 388.3. HRMS ([M]+H) calcd for C$_{27}$H$_{34}$NO: 388.2640; found 388.2645. ^{1}H NMR δ 5.83 (d, *J$_{AB\ or\ CD}$* = 12.9 Hz, 5H), 5.53 (d, *J$_{AB\ or\ CD}$* = 12.9 Hz, 5H), 5.44 (d, *J$_{AB\ or\ CD}$* = 12.7 Hz, 1H), 4.78 (d, *J$_{AB\ or\ CD}$* = 12.7 Hz, 1H), 4.71 (d, *J$_{AB\ or\ CD}$* = 12.9 Hz, 5H). IR 3237, 2958, 1612, 1460, 1365, 1064, 824, 757 cm^{-1}.

(*S*)-*N*,*N*-bis(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214g
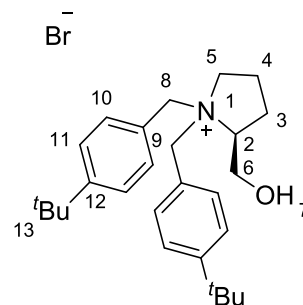
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a dark yellow crystalline salt, 0.094 g in 99% yield. R$_f$ = 0.38 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 394.3. HRMS ([M]+H) calcd for C$_{27}$H$_{40}$NO: 394.3110; found 394.3112. MP = 136-137 °C. [α] $_D^{23}$ = −20 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 7.61 (d, *J* = 8.4 Hz, 2H, ArH), 7.55 – 7.37 (m, 6H, ArH), 6.00 (app t, *J* = 5.5 Hz, 1H, 7), 5.66 (d, *J$_{AB\ or\ CD}$* = 13.2 Hz, 1H, 8), 5.46 (d, *J$_{AB\ or\ CD}$* = 12.9 Hz, 1H, 8), 4.60 – 4.39 (m, 1H, 2), 4.34 (d, *J$_{AB\ or\ CD}$* = 13.2 Hz, 1H, 8), 4.19 (d, *J$_{AB\ or\ CD}$* = 12.9 Hz, 1H, 8), 3.93 (dd, *J* = 17.4, 8.1 Hz, 1H, 6), 3.37 (dd, *J* = 12.1, 8.1 Hz, 1H, 6), 3.02 (dd, *J* = 17.4, 12.1 Hz, 1H, 5), 2.46 – 2.21 (m, 1H, 3 or 4), 2.32 – 2.30 (m, 1H, 5),2.21 – 1.93 (m, 3H, 3 or 4), 1.33 (d, *J* = 13.0 Hz, 18H, 13). IR 3238, 2959, 1612, 1460, 1364, 1065, 840, 700 cm^{-1}.
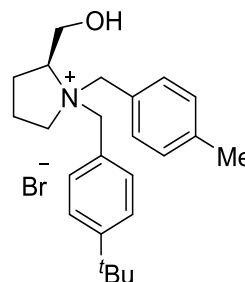
(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(3,5-di-tert-butylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214h
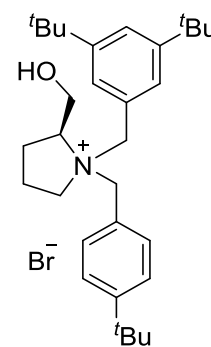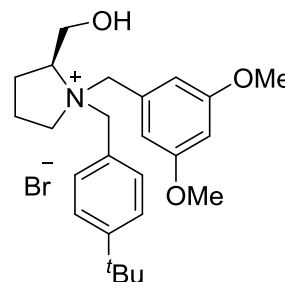

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.086 g in 81% yield and d.r. 10:1 *N*$_{(S)}$ is major diastereoisomer (Interpretation 3 used). R$_f$

= 0.42 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 450.4. HRMS ([M]+H) calcd for C$_{31}$H$_{48}$NO: 450.3736; found 450.3730. ^{1}H NMR δ 1.37 (s, 18H, 2x ^{t}Bu), 1.36 (s, 180H, 2x ^{t}Bu). IR 3239, 2956, 1600, 1461, 1363, 1249, 882, 780, 712 cm^{-1}.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 214i

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.074 g in 86% yield and d.r. 6.2:1.0 N$_{(S)}$ is major diastereoisomer (Interpretation 3 and 5 used). R$_f$ = 0.40 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 352.3. HRMS ([M]+H) calcd for C$_{24}$H$_{34}$NO: 352.2640; found 352.2650. ^{1}H NMR δ 2.41 (s, 18.6H, Me), 2.36 (s, 3H, Me), 1.35 (s, 9H, ^{t}Bu), 1.30 (s, 55.8H, ^{t}Bu). IR 3241, 2958, 1612, 1459, 1064, 821, 760, 723 cm$^-$

^{1}.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 214j

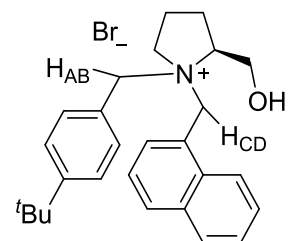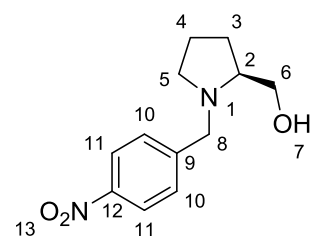General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.076 g in 79% yield and d.r. 1.0:4.3 N$_{(S)}$ is major diastereoisomer (Interpretation 3 and 11 used). R$_f$ = 0.33 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 398.3. HRMS ([M]+H) calcd for C$_{25}$H$_{36}$NO$_3$: 398.2695; found 398.2707. ^{1}H NMR δ 3.83 (s, 25.8H, 2x OMe), 3.79 (s, 6H, 2x OMe), 1.34 (s, 9H, ^{t}Bu), 1.31 (s, 38.7H, ^{t}Bu). IR 3238, 2960, 1596, 1458, 1153, 1059, 840, 782 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 214k
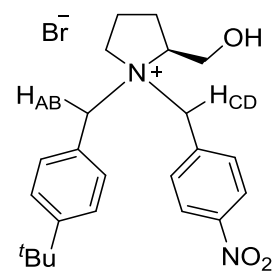
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.063 g in 68% yield and d.r. 1.0:3.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 3 used). R_f = 0.30 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 383.2. HRMS ([M]+H) calcd for $C_{23}H_{31}N_2O_3$: 383.2335; found 383.2332. ^{1}H NMR δ 5.53 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 3.5H), 5.40 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.95 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 3.5H), 1.32 (s, 9H, [t]Bu), 1.30 (s, 31.5H, [t]Bu). IR 3261, 2961, 1607, 1522, 1346, 855, 712 cm^{-1}.

(2S)-N-(4-(tert-butyl)benzyl)-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 214l

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.084 g in 90% yield and d.r. 1.0:4.8 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.37 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 388.3. HRMS ([M]+H) calcd for $C_{27}H_{34}NO$: 388.2640; found 388.2645. ^{1}H NMR δ 5.86 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 4.8H), 5.65 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H), 5.44 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 4.8H), 5.21 (d, $J_{AB\ or\ CD}$ = 13.8 Hz, 1H), 4.99 (d, $J_{AB\ or\ CD}$ = 13.5 Hz, 4.8H). IR 3225, 2959, 1612, 1512, 1459, 1364, 1068, 804, 779 cm^{-1}.

(S)-(N-(4-nitrobenzyl)pyrrolidin-2-yl)methanol 191

General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a brown oil, 2.98 g in 84% yield. R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 237.1. HRMS ([M]+H) calcd for $C_{12}H_{17}N_2O_3$: 237.1239; found 237.1247. $[\alpha]_D^{23}$ = −41 (c 1.0, CH_2Cl_2). ^{1}H NMR δ 8.34 − 8.09 (m, 2H, 11), 7.49 (d, J =

8.7 Hz, 2H, 10), 4.09 (d, J_{AB} = 13.9 Hz, 1H, 8), 3.68 (dd, J = 10.9, 3.5 Hz, 1H, 6), 3.60 – 3.35 (m, 2H, 8 and 6), 2.96 (ddd, J = 9.3, 6.0, 3.5 Hz, 1H, 2), 2.79 (ddd, J = 12.2, 6.1, 3.1 Hz, 1H, 5), 2.51 (s br, 1H, 7), 2.28 (td, J = 9.3, 7.4 Hz, 1H, 5), 2.13 – 1.60 (m, 4H, 3 and 4). ^{13}C NMR δ 147.31 (12), 147.10 (9), 129.28 (11), 123.66 (10), 64.78 (2), 62.12 (6), 58.11 (8), 54.66 (5), 27.59 (3), 23.54 (4). IR 3391, 2948, 1600, 1514, 1342, 855, 737 cm^{-1}.

(2S)-N-(3,5-bis(trifluoromethyl)benzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215a
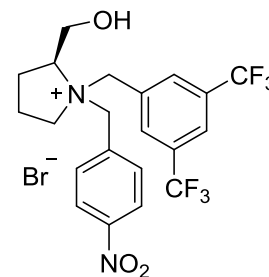
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.061 g in 56% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 14 used). R_f = 0.28 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 463.2. HRMS ([M]+H) calcd for $C_{21}H_{21}F_6N_2O_3$: 463.1497; found 463.1502. ^{19}F NMR δ -62.64 (d, J = 3.1 Hz, 7.8F), -62.78 (d, J = 2.8 Hz, 6F). IR 3282, 2987, 1607, 1523, 1371, 1349, 1277, 1128, 1064, 856, 705 cm^{-1}.
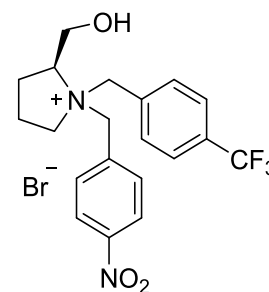
(2S)-N-(3,5-dimethylbenzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidin-1-ium bromide 215b
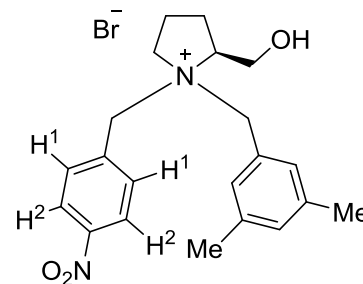
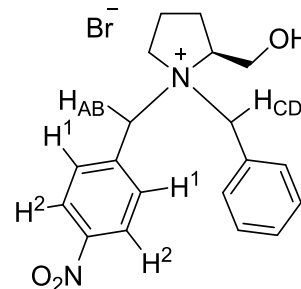General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.062 g in 71% yield and d.r. 1.0:2.8 $N_{(S)}$ is major diastereoisomer (Interpretation 7 and 8 used). R_f = 0.33 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 355.2. HRMS ([M]+H) calcd for $C_{21}H_{27}N_2O_3$: 355.2022; found 355.2026. ^{1}H NMR δ 8.26 (d, J = 8.7 Hz, 5.6H, H[2]), 8.17 (d, J = 8.8 Hz, 2H, H[2]), 8.06 (d, J = 8.8 Hz, 2H, H[1]), 7.88 (d, J = 8.7 Hz, 5.6H, H[1]). IR 3264, 2970, 1606, 1521, 1346, 1066, 1040, 855, 753, 704 cm^{-1}.

(2S)-N-(4-nitrobenzyl)-N-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215c
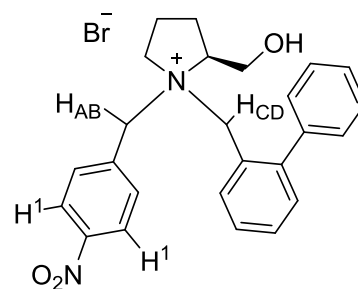
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.056 g in 59% yield and d.r. 1.0:1.7 $N_{(S)}$ is major diastereoisomer (Interpretation 13 used). R_f = 0.29 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 395.2. HRMS ([M]+H) calcd for $C_{20}H_{22}F_3N_2O_3$: 395.1583; found 395.1582. ^{19}F NMR δ -63.07 (s, 3F), -63.09 (s, 5.1F). IR 3266, 2971, 1608, 1523, 1348, 1322, 1117, 1066, 856, 704 cm^{-1}.

(2S)-N-benzyl-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.081 g in 99% yield and d.r. 1.0:3.4 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 7 and 8 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 327.2. HRMS ([M]+H) calcd for $C_{19}H_{23}N_2O_3$: 327.1709; found 327.1712. ^1H NMR δ 8.24 (d, J = 8.8 Hz, 6.8H, H^2), 8.14 (d, J = 8.8 Hz, 2H, H^2), 8.05 (d, J = 8.8 Hz, 2H, H^1), 7.85 (d, J = 8.8 Hz, 6.8H, H^1), 6.06 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 5.13 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.28 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 3.4H). IR 3266, 2969, 1606, 1520, 1346, 1061, 856, 750, 703 cm^{-1}.

(2S)-N-([1,1'-biphenyl]-2-ylmethyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215e

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.056 g in 58% yield and d.r. 1.0:1.8 $N_{(S)}$ is major diastereoisomer
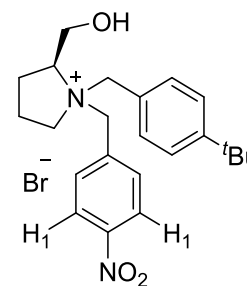
(Interpretation 1 and 8 used). R_f = 0.32 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 403.2. HRMS ([M]+H) calcd for $C_{25}H_{27}N_2O_3$: 403.2022; found 403.2011. ^{1}H NMR δ 7.84 (d, J = 8.8 Hz, 2H, H^1), 7.72 (d, J = 8.7 Hz, 3.6H, H^1), 5.87 (d, $J_{AB\ or\ CD}$ = 11.6 Hz, 1H), 5.67 (d, $J_{AB\ or\ CD}$ = 11.6 Hz, 1H), 5.57 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1.8H), 5.21 (d, $J_{AB\ or\ CD}$ = 11.6 Hz, 1H), 4.66 (d, $J_{AB\ or\ CD}$ = 13.1 Hz, 1.8H), 4.21 (d, $J_{AB\ or\ CD}$ = 11.6 Hz, 1H). IR 3267, 2969, 1606, 1520, 1346, 1063, 858, 750, 706 cm^{-1}.

(2*S*)-*N*-(naphthalen-2-ylmethyl)-*N*-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215f
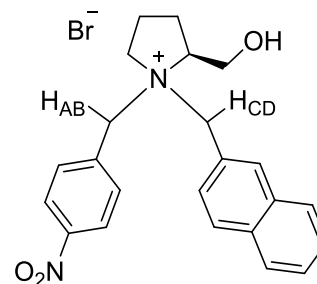
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.043 g in 48% yield and d.r. 1.0:1.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 377.2. HRMS ([M]+H) calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found 377.1873. ^{1}H NMR δ 5.02 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.89 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1.7H), 4.40 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.32 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1.7H). IR 3246, 2969, 1603, 1520, 1346, 1065, 856, 751, 703 cm^{-1}.
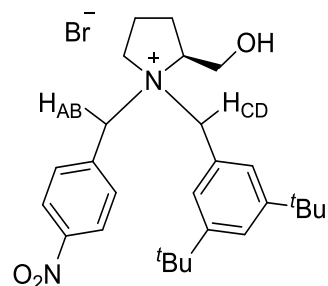
(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.066 g in 71% yield and d.r. 1.0:3.1 $N_{(S)}$ is major diastereoisomer (Interpretation 3 and 8 used). R_f = 0.35 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 383.2. HRMS ([M]+H) calcd for $C_{23}H_{31}N_2O_3$: 383.2335; found 383.2332. ^{1}H NMR δ 8.10 (d, J = 8.8 Hz, 2H, H^1), 7.88 (d, J = 8.7

Hz, 6.2H, H^1), 1.35 (s, 27.9H, ^tBu), 1.30 (s, 9H, ^tBu). IR 3267, 2970, 1607, 1520, 1346, 1065, 855, 749, 704 cm^{-1}.

(2S)-N-(3,5-di-tert-butylbenzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215h

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.073 g in 70% yield and d.r. 1.0:1.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.36 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 383.2. HRMS ([M]+H) calcd for C$_{23}$H$_{31}$N$_2$O$_3$: 383.2335; found 383.2332. ^{1}H NMR δ 6.13 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1H), 5.83 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.5H), 5.75 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.5H), 5.44 (d, $J_{AB\ or\ CD}$ = 12.2 Hz, 1H), 4.90 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H). IR 3268, 2961, 1605, 1522, 1346, 1065, 856, 751, 707 cm^{-1}.

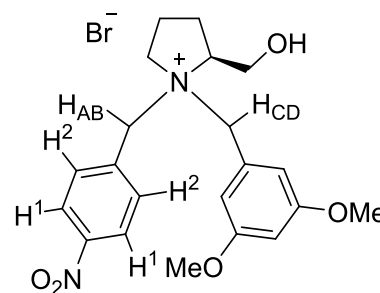**(2S)-N-(4-methylbenzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215i**
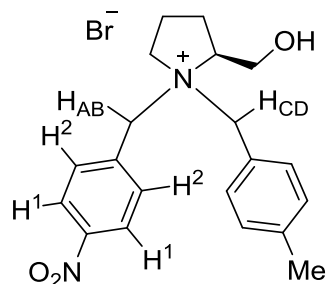
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.072 g in 86% yield and d.r. 1.0:2.9 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 5 and 8). R_f = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 341.2. HRMS ([M]+H) calcd for C$_{20}$H$_{25}$N$_2$O$_3$: 341.1865; found 341.1871. ^{1}H NMR δ 8.24 (d, J = 8.8 Hz, 5.8H, H^1), 8.15 (d, J = 8.8 Hz, 2H, H^1), 8.05 (d, J = 8.8 Hz, 2H, H^2), 7.85 (d, J = 8.8 Hz, 5.8H, H^2), 6.02 (d, $J_{AB\ or\ CD}$ = 12.0 Hz, 1H), 5.07 (d, $J_{AB\ or\ CD}$ = 12.0 Hz, 1H), 4.27 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.9H), 2.40 (s, 8.7H, Me), 2.36 (s, 3H, Me). IR 3268, 2971, 1607, 1520, 1346, 1065, 855, 749, 705 cm^{-1}.

(2S)-N-(3,5-dimethoxybenzyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215j
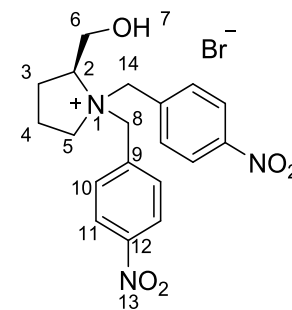
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.075 g in 80% yield and d.r. 1.0:4.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 7, 8 and 11 used). $R_f = 0.25$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 387.2. HRMS ([M]+H) calcd for $C_{21}H_{27}N_2O_5$: 387.1920; found 387.1922. ^{1}H NMR δ 8.25 (d, $J = 8.8$ Hz, 8.6H, H^1), 8.14 (d, $J = 8.7$ Hz, 2H, H^1), 8.02 (d, $J = 8.7$ Hz, 2H, H^2), 7.87 (d, $J = 8.8$ Hz, 8.6H, H^2), 6.01 (d, $J_{AB\ or\ CD} = 12.5$ Hz, 1H), 5.57 (d, $J_{AB\ or\ CD} = 12.8$ Hz, 1H), 5.16 (d, $J_{AB\ or\ CD} = 12.5$ Hz, 1H), 4.42 (d, $J_{AB\ or\ CD} = 12.8$ Hz, 1H), 4.32 (d, $J_{AB\ or\ CD} = 13.1$ Hz, 4.3H), 3.83 (s, 25.8H, 2x OMe), 3.77 (s, 6H, 2x OMe). IR 3271, 2971, 1606, 1520, 1346, 1064, 855, 750, 704 cm^{-1}.
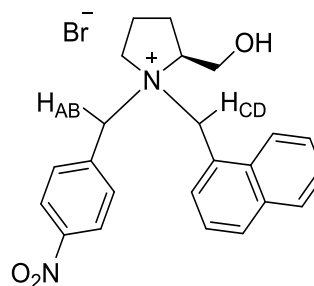
(2S)-N,N-bis(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215k

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a dark orange crystalline salt, 0.049 g in 54% yield. $R_f = 0.28$ in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 372.2. HRMS ([M]+H) calcd for $C_{19}H_{22}N_3O_5$: 372.1559; found 372.1567. $[\alpha]_D^{23} = +19.0$ (c 1.0, CH_2Cl_2). MP = 151-152 °C. ^{1}H NMR δ 8.31 – 8.27 (m, 4H, 11), 8.08 (d, $J = 8.8$ Hz, 2H, 10), 7.87 (d, $J = 8.8$ Hz, 2H, 10), 6.37 (d, $J_{AB} = 12.8$ Hz, 1H, 8 or 14), 6.21 – 6.07 (m, 1H, 7), 5.95 (d, $J_{AB} = 13.0$ Hz, 1H, 8 or 14), 4.78 – 4.58 (m, 1H, 8 or 14), 4.14 (d, $J_{AB} = 12.8$ Hz, 1H, 8 or 14), 3.90 – 3.88 (m, 1H, 2), 3.39 – 3.37 (m, 1H, 5), 3.11 – 2.88 (m, 2H, 5 and 3 or 4), 2.55 – 2.41 (m, 1H, 3 or 4), 2.35 – 2.00 (m, 2H, 3 or 4,). ^{13}C NMR (methanol-d4) δ 135.55 (12), 134.66 (9), 134.38 (9), 134.10 (10), 123.88 (11), 123.40 (11), 70.83 (2), 60.90 (6),

58.61(8 or 14), 56.97 (8 or 14), 56.32 (5), 22.42 (3), 18.47 (4). IR 3267, 2971, 1607, 1520, 1346, 1064, 855, 749, 704 cm^{-1}

(2S)-N-(naphthalen-1-ylmethyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 215l

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.052 g in 57% yield and d.r. 1.0:1.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 377.2. HRMS ([M]+H) calcd for C$_{23}$H$_{25}$N$_2$O$_3$: 377.1865; found 377.1871. ^{1}H NMR δ 5.78 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 5.66 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1.7H), 5.09 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 4.95 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1.7H). IR 3249, 2970, 1606, 1519, 1346, 1064, 780, 702 cm^{-1}.
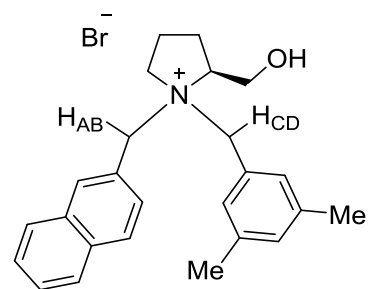
(2S)-N-(3,5-bis(trifluoromethyl)benzyl)-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179a
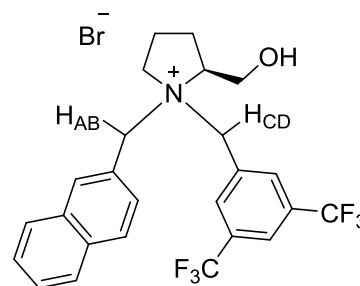
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.064 g in 58% yield and d.r. 1.0:3.5 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 14 used). R_f = 0.35 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 468.2. HRMS ([M]+H) calcd for C$_{25}$H$_{24}$F$_6$NO: 468.1762; found 468.1768. ^{1}H NMR δ 5.02 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 3.5H), 4.88 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.39 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.17 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 3.5H). ^{19}F NMR δ -62.60 (s, 21F), -62.79 (s, 6F). IR 3266, 2968, 1602, 1277, 1174, 1065, 899, 754, 682 cm^{-1}.

(2*S*)-*N*-(3,5-dimethylbenzyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179b

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.081 g in 92% yield and d.r. 1.0:3.1 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 2 used). R_f = 0.41 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 360.2. HRMS ([M]+H) calcd for $C_{25}H_{30}NO$: 360.2327; found 360.2336. ^{1}H NMR δ 5.54 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1H), 4.41 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 3.1H), 2.38 (s, 18.3H, 2x Me), 2.28 (s, 6H, 2x Me). IR 3233, 2961, 1602, 1368, 1041, 826, 753 cm^{-1}.

(2*S*)-*N*-(naphthalen-2-ylmethyl)-*N*-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179c
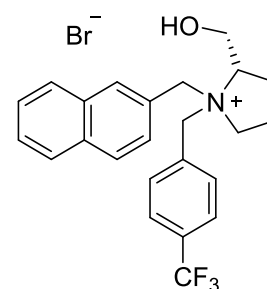
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.076 g in 79% yield and d.r. 1.0:3.1 $N_{(S)}$ is major diastereoisomer (Interpretation 9 and 13 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 400.2. HRMS ([M]+H) calcd for $C_{24}H_{25}F_3NO$: 400.1888; found 400.1895. ^{1}H NMR δ 8.32 (s, 1H, ArH), 8.06 (s, 3.1H, ArH). ^{19}F NMR δ -62.98 (s, 9.3F), -63.04 (s, 3F). IR 3241, 2968, 1600, 1323, 1066, 827, 758 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179d
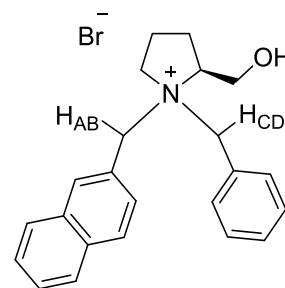
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.074 g in 90% yield and d.r. 1:4 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.39 in 10:1

CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 332.2. HRMS ([M]+H) calcd for C$_{23}$H$_{26}$NO: 332.2014; found 332.2017. ^{1}H NMR δ 8.26 (s, 1H, ArH), 8.10 (s, 4H, ArH), 5.88 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 5.62 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.76 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.36 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 4H). IR 3241, 2967, 1455, 1368, 1062, 757, 705 cm^{-1}.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179e
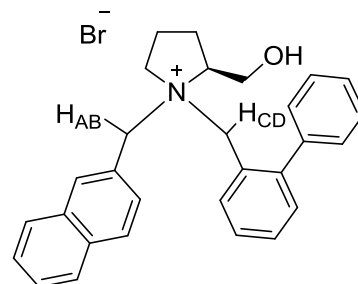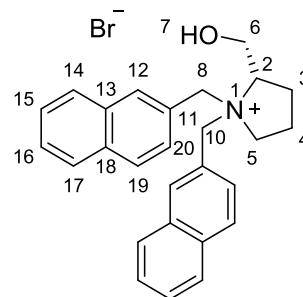
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.075 g in 77% yield and d.r. 1.0:2.6 N$_{(S)}$ is major diastereoisomer (Interpretation 1 used). R$_f$ = 0.40 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 408.2. HRMS ([M]+H) calcd for C$_{29}$H$_{30}$NO: 408.2327; found 408.2329. ^{1}H NMR δ 5.83 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.6H), 4.93 (d, $J_{AB\ or\ CD}$ = 13.2 Hz, 1H), 4.80 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 2.6H). IR 3241, 3052, 1598, 1450, 1369, 1063, 751, 706 cm^{-1}.

(*S*)-*N*,*N*-bis(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179f

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a dark orange crystalline salt, 0.072 g in 78% yield. R$_f$ = 0.39 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 382.2. HRMS ([M]+H) calcd for C$_{27}$H$_{28}$NO: 382.2171; found 382.2160. [α] $_D^{23}$= −32.0 (*c* 1.0, CH$_2$Cl$_2$). MP = 141-142 °C. ^{1}H NMR δ 8.26 (d, *J* = 8.3 Hz, 1H, 14), 8.05 (d, *J* = 8.3 Hz, 1H, 17), 7.98 – 7.71 (m, 7H, ArH), 7.65 – 7.47 (m, 5H, ArH), 6.20 (app t, *J* = 5.6 Hz, 1H, 7), 5.96 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H, 8 or 10), 5.80 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H, 8 or 10), 4.88 – 4.57 (m, 1H, 8 or 10), 4.41 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 1H, 8 or 10), 4.29 – 4.27 (m, 1H, 2), 4.07 (dd, *J* = 12.0, 7.5 Hz, 1H, 6), 3.48 (dd, *J* = 12.0, 7.5

Hz, 1H, 6), 3.08 – 3.06 (m, 1H, 5), 2.64 – 2.41 (m, 1H, 5), 2.37 – 2.15 (m, 2H, 3 or 4), 2.12 – 1.92 (m, 2H, 3 or 4). ^{13}C NMR δ 135.08, 134.18, 133.69 (11), 132.87 (18), 132.80 (18), 130.16, 129.43, 129.08, 128.86, 128.51, 128.45, 128.13, 127.85, 127.70, 127.67, 127.06, 126.94, 126.77, 124.87 (13), 124.07 (13), 70.65 (2), 61.79 (6), 58.29 (8 or 10), 57.99 (8 or 10), 55.28, 23.12, 18.87. IR 3241, 2960, 1599, 1459, 1365, 1063, 825, 756 cm^{-1}.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179g
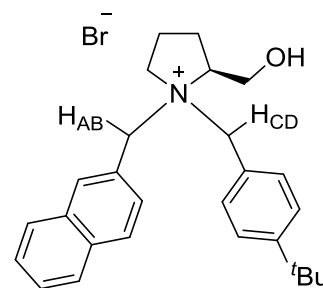
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.082 g in 88% yield and d.r. 1.0:7.1 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.41 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 388.3. HRMS ([M]+H) calcd for C$_{27}$H$_{34}$NO: 388.2640; found 388.2645. ^{1}H NMR δ 5.87 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 1H), 5.71 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 7.1H), 5.56 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 1H), 4.67 (d, $J_{AB\ or\ CD}$ = 12.5 Hz, 1H), 4.41 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 7.1H). IR 3234, 2958, 1599, 1460, 1363, 1066, 752, 720 cm^{-1}.

(2*S*)-*N*-(3,5-di-tert-butylbenzyl)-*N*-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179h
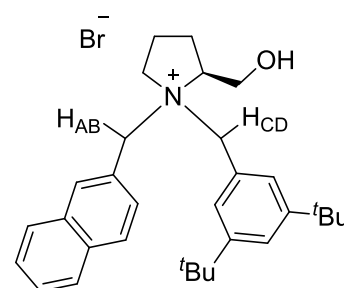
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.093 g in 89% yield and d.r. 1.0:4.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 and 4 used). R_f = 0.42 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 444.3. HRMS ([M]+H) calcd for C$_{31}$H$_{42}$NO: 444.3266; found 444.3249. ^{1}H NMR δ 6.03 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 5.76 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 4.7H), 5.68 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 4.7H), 5.56 (d, $J_{AB\ or\ CD}$ = 13.6 Hz, 1H), 4.41 (d,

$J_{AB \ or \ CD}$ = 12.8 Hz, 4.7H), 1.38 (s, 42.3H, 2x ^{t}Bu), 1.27 (s, 9H, 2x ^{t}Bu). IR 3241, 2961, 1612, 1460, 1365, 1064, 826, 754, 696 cm^{-1}.

(2S)-N-(4-methylbenzyl)-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidin-1-ium bromide 179i

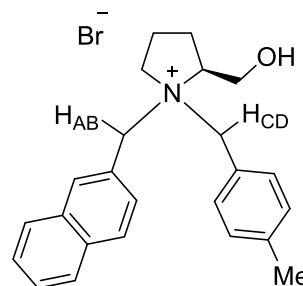General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.082 g in 96% yield and d.r. 1.0:4.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.38 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 346.2. HRMS ([M]+H) calcd for C$_{24}$H$_{28}$NO: 346.2171; found 346.2184. ^{1}H NMR δ 5.84 (d, $J_{AB \ or \ CD}$ = 13.4 Hz, 1H), 5.69 (d, $J_{AB \ or \ CD}$ = 12.9 Hz, 4.7H), 5.55 (d, $J_{AB \ or \ CD}$ = 13.4 Hz, 1H), 4.71 (d, $J_{AB \ or \ CD}$ = 13.4 Hz, 1H), 4.36 (d, $J_{AB \ or \ CD}$ = 12.9 Hz, 4.7H). IR 3233, 2970, 1613, 1511, 1368, 1064, 826, 759, 716 cm^{-1}.

(2S)-N-(3,5-dimethoxybenzyl)-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179j
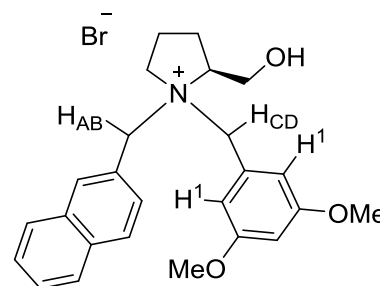

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.086 g in 91% yield and d.r. 1.0:4.7 $N_{(S)}$ is major diastereoisomer (Interpretation 1, 8 and 11 used). R_f = 0.36 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 392.2. HRMS ([M]+H) calcd for C$_{25}$H$_{30}$NO$_3$: 392.2226; found 392.2223. ^{1}H NMR δ 6.94 (d, J = 2.2 Hz, 9.4H, H[1]), 6.65 (d, J = 2.2 Hz, 2H, H[1]), 5.87 (d, $J_{AB \ or \ CD}$ = 12.7 Hz, 1H), 5.53 (d, $J_{AB \ or \ CD}$ = 12.7 Hz, 1H), 4.72 (d, $J_{AB \ or \ CD}$ = 12.7 Hz, 1H), 3.85 (s, 28.2H, 2x OMe), 3.75 (s, 6H, 2x OMe). IR 3229, 2968, 1594, 1457, 1321, 1204, 1153, 1058, 828, 755 cm^{-1}.

(2S)-N-(naphthalen-2-ylmethyl)-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179k
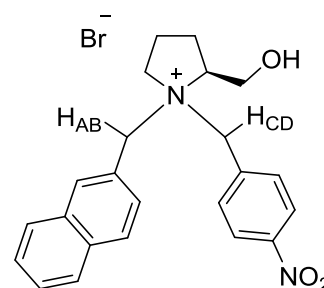
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.081 g in 89% yield and d.r. 1.0:3.1 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.34 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 377.2. HRMS ([M]+H) calcd for $C_{23}H_{25}N_2O_3$: 377.1865; found 377.1856. ^{1}H NMR δ 5.75 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 3.1H), 5.15 (d, $J_{AB\ or\ CD}$ = 12.7 Hz, 1H), 5.06 (d, $J_{AB\ or\ CD}$ = 12.8 Hz, 3.1H). IR 3250, 2970, 1605, 1520, 1346, 1064, 855, 752, 705 cm^{-1}.

(2S)-N-(naphthalen-1-ylmethyl)-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 179l
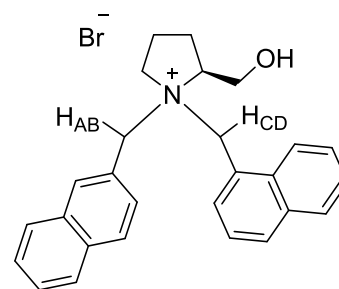
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a dark orange crystalline salt, 0.063 g in 68% yield and d.r. 1.0:1.3 $N_{(S)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 382.2. HRMS ([M]+H) calcd for $C_{27}H_{28}NO$: 382.2171; found 382.2175. ^{1}H NMR δ 6.05 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1.3H), 5.94 (d, $J_{AB\ or\ CD}$ = 13.8 Hz, 1H), 5.74 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1.3H), 4.91 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1.3H), 4.08 (d, $J_{AB\ or\ CD}$ = 12.9 Hz, 1.3H). IR 3266, 2969, 1599, 1460, 1350, 1065, 779, 755 cm^{-1}.

(S)-(N-butylpyrrolidin-2-yl)methanol 193
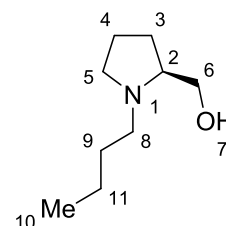
General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as a light yellow oil, 2.02 g in 86% yield. R_f = 0.43 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 158.2. HRMS ([M]+H) calcd for $C_9H_{20}NO$: 158.1545; found 158.1550. $[\alpha]\ _D^{23}$= −55 (c

1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 3.62 (dd, J = 10.6, 3.7 Hz, 1H, 6), 3.38 (dd, J = 10.6, 2.0 Hz, 1H, 6), 3.21 – 3.13 (m, 1H, 8), 3.00 (s br, 1H, 7), 2.71 (app dt, J = 11.9, 8.0 Hz, 1H, 8), 2.59 – 2.49 (m, 1H, 2), 2.29 – 2.16 (m, 2H, 5), 1.97 – 1.65 (m, 4H, 3 and 4), 1.56 – 1.22 (m, 4H, 11 and 9), 0.92 (t, J = 7.2 Hz, 3H, 10). ^{13}C NMR δ 64.71 (2), 61.82 (6), 54.24 (5), 54.14 (8), 31.28 (9), 27.79 (3), 23.53 (4), 20.63 (11), 14.05 (10). IR 3402, 2956, 1460, 1043 cm^{-1}.

(2S)-N-(3,5-bis(trifluoromethyl)benzyl)-N-butyl-2-(hydroxymethyl)pyrrolidinium bromide 178a

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white tacky oil, 0.071 g in 76% yield and d.r. 1.0:7.5 $N_{(R)}$ is the major diastereoisomer (Interpretation 14 used). R$_f$ = 0.34 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 384.2. HRMS ([M]+H) calcd for C$_{18}$H$_{24}$F$_6$NO: 384.1762; found 384.1777. ^{19}F NMR δ -62.72 (s, 6F), -62.80 (s, 45F). IR 3256, 2963, 1467, 1371, 1275, 1126, 844, 778, 709 cm^{-1}.

(2S)-N-butyl-N-(3,5-dimethylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 178b

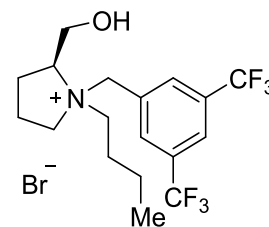General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline solid, 0.022 g in 32% yield and d.r. 1.0:1.3 $N_{(R)}$ is major diastereoisomer (Interpretation 12 used). R$_f$ = 0.39 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 276.2. HRMS ([M]+H) calcd for C$_{18}$H$_{30}$NO: 276.2327; found 276.2331. ^{1}H NMR δ 0.98 (t, J = 7.3 Hz, 3H, Me), 0.92 (t, J = 7.3 Hz, 3.9H, Me). IR 3228, 2960, 2918, 1605, 1464, 1061, 797, 736, 722 cm^{-1}.

(2*S*)-*N*-butyl-*N*-(4-(trifluoromethyl)benzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 178c
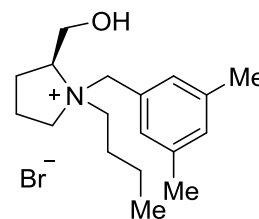
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white tacky oil, 0.075 g in 94% yield and d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 8 and 13 used). R_f = 0.36 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 316.2. HRMS ([M]+H) calcd for C$_{17}$H$_{25}$F$_3$NO: 316.1888; found 316.1879. ^{1}H NMR δ 7.98 (d, *J* = 8.0 Hz, 2H, H^1), 7.87 (d, *J* = 8.1 Hz, 2.4H, H^1), 5.60 (s, 1H), 5.44 (s, 1.2H), 5.26 (d, J_{AB} = 12.9 Hz, 1.2H), 5.13 (d, J_{AB} = 12.8 Hz, 1H), 4.98 (d, J_{AB} = 12.8 Hz, 1H), 4.86 (d, J_{AB} = 12.9 Hz, 1.2H). ^{19}F NMR δ -63.01 (s, 3F), -63.02 (s, 3.6F). IR 3231, 2967, 1455, 1382, 1059, 756, 700 cm^{-1}.

(2*S*)-*N*-benzyl-*N*-butyl-2-(hydroxymethyl)pyrrolidinium bromide 178d

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white tacky oil, 0.062 g in 95% yield and d.r. 1.0:1.3 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.39 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 248.2. HRMS ([M]+H) calcd for C$_{16}$H$_{26}$NO: 248.2014; found 248.2010. ^{1}H NMR δ 4.77 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1H), 4.56 (d, $J_{AB\ or\ CD}$ = 13.0 Hz, 1.3H). IR 3231, 2959, 1455, 1059, 756, 701 cm^{-1}.

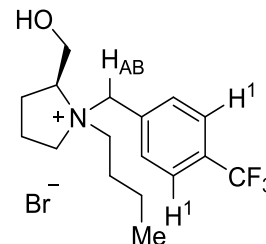**(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-butyl-2-(hydroxymethyl)pyrrolidinium bromide 178e**

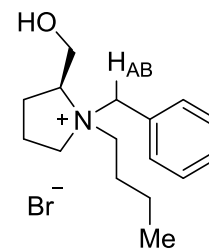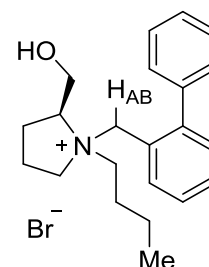General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.078 g in 96% yield and d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 9 used). R_f = 0.41 in 10:1 CH$_2$Cl$_2$:MeOH. *m*/z ([M]+H) 324.2. HRMS ([M]+H) calcd for C$_{22}$H$_{30}$NO: 324.2327; found

324.2329. ^{1}H NMR δ 8.04 (dd, J = 7.5, 1.4 Hz, 1H, ArH), 7.91 (dd, J = 7.6, 1.2 Hz, 1.2H, ArH), 5.00 (d, J_{AB} = 13.4 Hz, 1H), 4.70 (d, J_{AB} = 13.2 Hz, 1.2H). IR 3268, 2962, 1452, 1065, 782, 753, 708 cm^{-1}.

(2S)-N-butyl-N-(naphthalen-2-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 178f

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.063 g in 83% yield and d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 1, 9 and 10 used). R_f = 0.40 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 298.2. HRMS ([M]+H) calcd for C$_{20}$H$_{28}$NO: 298.2171; found 298.2178. ^{1}H NMR δ 8.24 (s, 1H, ArH), 8.10 (s, 1.2H, ArH), 5.63 (s br, 1H, OH), 5.50 (s br, 1.2H, OH), 5.17 (d, J_{AB} = 13.0 Hz, 1.2H), 5.11 (d, J_{AB} = 12.9 Hz, 1H), 4.90 (d, J_{AB} = 12.9 Hz, 1H), 4.73 (d, J_{AB} = 13.0 Hz, 1.2H). IR 3276, 2961, 1600, 1466, 1064, 760 cm^{-1}.

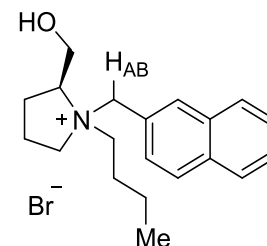### (2S)-N-butyl-N-(4-(tert-butyl)benzyl)-2-(hydroxymethyl)pyrrolidinium bromide 178g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.076 g in 99% yield and d.r. 1.0:1.6 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.41 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 304.3. HRMS ([M]+H) calcd for C$_{20}$H$_{34}$NO: 304.2640; found 304.2643. ^{1}H NMR δ 4.97 (d, J_{AB} = 13.0 Hz, 1.6H), 4.90 (d, J_{AB} = 13.0 Hz, 1H), 4.68 (d, J_{AB} = 13.0 Hz, 1H), 4.49 (d, J_{AB} = 13.0 Hz, 1.6H). IR 3244, 2962, 1614, 1460, 1059, 839, 791 cm^{-1}.

(2S)-N-butyl-N-(3,5-di-tert-butylbenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 178h

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.087 g in 99% yield and d.r. 1.0:1.6 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.42 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 360.3. HRMS ([M]+H) calcd for $C_{24}H_{42}NO$: 360.3266; found 360.3271. ^1H NMR δ 5.01 (d, J_{AB} = 12.9 Hz, 1.6H), 4.88 (d, J_{AB} = 13.0 Hz, 1H), 4.68 (d, J_{AB} = 13.0 Hz, 1H). IR 3266, 2959, 1600, 1465, 1058, 733, 715 cm^{-1}.
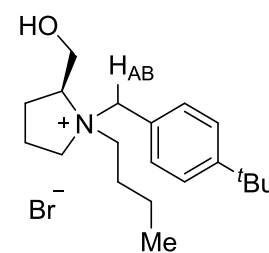
(2S)-N-butyl-N-(4-methylbenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 178i

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.068 g in 99% yield and d.r. 1.0:1.6 $N_{(R)}$ is major diastereoisomer (Interpretation 1 and 7 used). R_f = 0.38 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 262.2. HRMS ([M]+H) calcd for $C_{17}H_{28}NO$: 262.2171; found 262.2170. ^1H NMR δ 7.54 (d, J = 8.0 Hz, 2H, H^1), 7.45 (d, J = 8.1 Hz, 3.2H, H^1), 4.69 (d, J_{AB} = 13.0 Hz, 1H), 4.48 (d, J_{AB} = 13.0 Hz, 1.6H). IR 3266, 2962, 1614, 1463, 1065, 814, 738 cm^{-1}
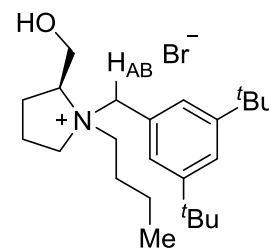
(2S)-N-butyl-N-(3,5-dimethoxybenzyl)-2-(hydroxymethyl)pyrrolidinium bromide 178j

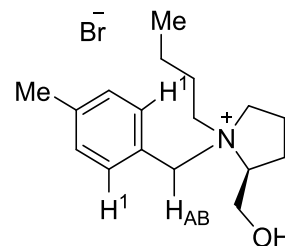General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.074 g in 95% yield and d.r. 1.0:4.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.33 in 10:1 CH_2Cl_2:MeOH. m/z ([M]+H) 308.2. HRMS ([M]+H) calcd for $C_{18}H_{30}NO_3$:

308.2226; found 308.2227. ^{1}H NMR δ 5.08 (d, J_{AB} = 12.8 Hz, 4.7H), 4.93 (d, J_{AB} = 12.9 Hz, 1H), 4.67 (d, J_{AB} = 12.9 Hz, 1H), 4.43 (d, J_{AB} = 12.8 Hz, 4.7H). IR 3246, 2955, 1597, 1204, 1153, 1065, 854, 795, 707 cm^{-1}.

(2S)-N-butyl-N-(4-nitrobenzyl)-2-(hydroxymethyl)-pyrrolidinium bromide 178k
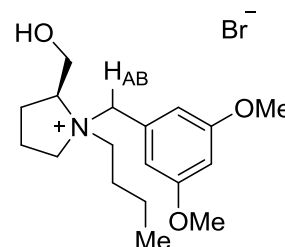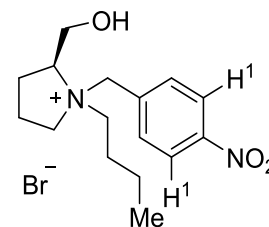

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a yellow crystalline salt, 0.071 g in 95% yield and d.r. 1.0:4.5 $N_{(R)}$ is major diastereoisomer (Interpretation 9 used). R_f = 0.30 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 293.2. HRMS ([M]+H) calcd for C$_{16}$H$_{25}$N$_2$O$_3$: 293.1865; found 293.1872. ^{1}H NMR δ 8.04 (d, J = 8.8 Hz, 2H, H^1), 7.98 (d, J = 8.8 Hz, 9H, H^1). IR 3284, 2963, 1607, 1522, 1347, 1062, 857, 752, 712 cm^{-1}.

(2S)-N-butyl-N-(naphthalen-1-ylmethyl)-2-(hydroxymethyl)-pyrrolidinium bromide 178l
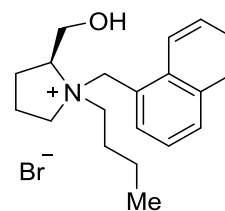
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.064 g in 84% yield and d.r. 1.0:1.2 $N_{(R)}$ is major diastereoisomer (Interpretation 9 and 12 used). R_f = 0.41 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 298.2. HRMS ([M]+H) calcd for C$_{20}$H$_{28}$NO: 298.2171; found 298.2175. ^{1}H NMR δ 8.32 (d, J = 8.6 Hz, 1H, ArH), 8.14 (d, J = 8.5 Hz, 1.2H, ArH), 0.76 (t, J = 7.0 Hz, 3.6H, Me), 0.66 (t, J = 7.0 Hz, 3H, Me). IR 3262, 2961, 1513, 1466, 1059, 807, 783, 744 cm^{-1}.

(S)-(N-((perfluorophenyl)methyl)pyrrolidin-2-yl)methanol 194
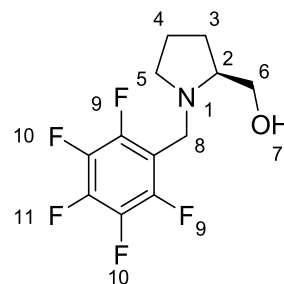
General method 1 (15 mmol) was used to prepare the tertiary amine which was isolated as an amorphous yellow oil, 1.48 g in 35% yield. R_f = 0.16 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 282.1. HRMS ([M]+H) calcd for C$_{12}$H$_{13}$F$_5$NO: 282.0917; found 282.0923. $[\alpha]_D^{23}$= −11 (c 1.0, CH$_2$Cl$_2$). ^{1}H NMR δ 4.00 (app dt, J = 13.1, 2.2 Hz, 1H, 8), 3.76 (dd, J = 11.1, 3.3 Hz, 1H, 6), 3.66 (d, J = 13.1 Hz, 1H, 8), 3.46 (dd, J = 11.1, 2.2 Hz, 1H, 6), 3.01 – 2.89 (m, 1H, 2), 2.73 (m, 1H, 5), 2.46 – 2.33 (m, 1H, 5), 2.00 – 1.61 (m, 4H, 3 and 4). ^{13}C NMR[VII] δ 63.52 (2), 61.87 (6), 54.03 (8), 43.86 (5), 27.55 (3), 23.45 (4). ^{19}F NMR δ -142.73 – -142.65 (m, 2F, 9), -155.07 (t, J = 20.9 Hz, 1F, 11), -161.80 – -162.08 (m, 2F, 10). IR 3314, 2951, 2811, 1655, 1497, 1095, 1045, 925, 755 cm^{-1}.

**(2S)-N-(3,5-dimethylbenzyl)-N-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidin-1-ium bromide 216a**

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.050 g in 52% yield and d.r. 1.0:5.7 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.18 in 10:1 CH$_2$Cl$_2$:MeOH. m/z ([M]+H) 400.2. HRMS ([M]+H) calcd for C$_{21}$H$_{23}$F$_5$NO: 400.1700; found 400.1701. ^{1}H NMR δ 5.69 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 5.7H), 5.55 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 1H), 5.47 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 5.7H), 4.90 (d, $J_{AB\ or\ CD}$ = 13.7 Hz, 1H), 4.67 (d, $J_{AB\ or\ CD}$ = 14.2 Hz, 5.7H), 4.44 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 5.7H). IR 3266, 2971, 1507, 1065, 791 cm^{-1}.

[VII] No resonances for the C$_6$F$_5$ are reported for compound **194** and **216b** as no discernible signals could be observed in the spectra due to extensive coupling between ^{19}F and ^{13}C nuclei.

(1*R*,2*S*)-*N*-benzyl-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidin-1-ium bromide 216b

General method 2 (0.2 mmol) was used to prepare the ammonium salt and was isolated as a single diastereoisomer, white crystalline salt, 0.051 g in 56% yield. R_f = 0.19 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 372.1. HRMS ([M]+H) calcd for $C_{19}H_{19}F_5NO$: 372.1387; found 372.1389. $[\alpha]_D^{23}$= −8 (*c* 1.0, MeOH). MP = 144-147 °C. ^{1}H NMR (methanol-d4) δ 7.90 − 7.35 (m, 5H, 18, 19 and 20), 5.29 (d, J_{AB} = 14.2 Hz, 1H, 8), 4.87 − 4.57 (m, 3H, 8 and 16), 4.37 (dd, *J* = 13.6, 3.6 Hz, 1H, 6), 4.18 (dd, *J* = 13.6, 6.2 Hz, 1H, 6), 3.84 − 3.80 (m, 1H, 2 or 5), 3.52 (dd, *J* = 11.7, 6.2 Hz, 1H, 5 or 2), 3.04 (dd, *J* = 19.1, 9.3 Hz, 1H, 5 or 2), 2.59 − 2.07 (m, 4H, 3 and 4). ^{13}C NMR (methanol-d4) δ 133.02 (19), 130.80 (20), 129.31 (18), 127.34 (17), 72.69 (2), 58.80 (6), 57.00 (8), 56.65 (16) 55.74 (5), 21.79 (3), 18.70 (4). ^{19}F NMR (methanol-d4) δ -138.62 (qd, *J* = 11.4, 6.2 Hz, 2F, 13), -150.77 − -152.20 (tt, *J* = 20.2, 4.4 Hz, 1F, 15), -162.11 − -163.54 (m, 2F, 14). IR 3450, 3167, 2996, 1662, 1509, 1059, 974, 767, 714 cm⁻¹. An X-ray crystal structure of this compound was obtained also and is reported in appendix 7.2.6.

(2*S*)-*N*-([1,1'-biphenyl]-2-ylmethyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216c
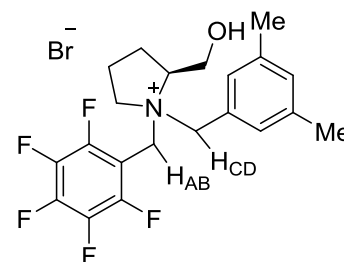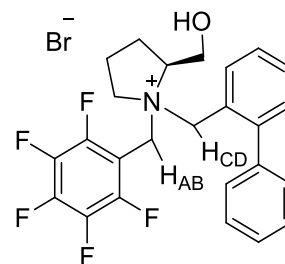
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.035 g in 33% yield and d.r. 1.0:2.9 $N_{(R)}$ is major diastereoisomer (Interpretation 1 used). R_f = 0.20 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 448.2. HRMS ([M]+H) calcd for $C_{25}H_{23}F_5NO$: 448.1700; found 448.1702. ^{1}H NMR δ 4.60 (d, $J_{AB \, or \, CD}$ = 14.2 Hz, 2.9H), 4.39 (d, $J_{AB \, or \, CD}$ = 15.0 Hz, 1H). IR 3268, 2959, 1660, 1599, 1508, 1055, 881 cm⁻¹.

(2*S*)-*N*-(4-(tert-butyl)benzyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216d
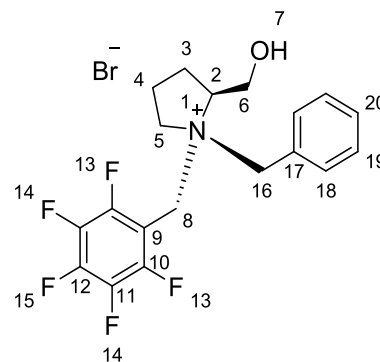
General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.056 g in 55% yield and d.r. 1:10 $N_{(R)}$ is major diastereoisomer (Interpretation 3 used). R_f = 0.22 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 428.2. HRMS ([M]+H) calcd for $C_{23}H_{27}F_5NO$: 428.2013; found 428.2020. ^1H NMR δ 1.34 (s, 90H, ^tBu), 1.32 (s, 9H, ^tBu). IR 3281, 2966, 1660, 1507, 1065, 862 cm^{-1}.

(2*S*)-*N*-(3,5-di-tert-butylbenzyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216e

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.058 g in 51% yield and d.r. 1.0:16.6 $N_{(R)}$ is major diastereoisomer (Interpretation 4, 6 and 8 used). R_f = 0.22 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 484.3. HRMS ([M]+H) calcd for $C_{27}H_{35}F_5NO$: 484.2639; found 484.2627. ^1H NMR δ 7.57 (t, *J* = 1.6 Hz, 16.6H, H^1), 7.56 – 7.53 (t, *J* = 1.6 Hz, 1H, H^1), 7.46 (d, *J* = 1.6 Hz, 33.2H, H^2), 7.38 (d, *J* = 1.6 Hz, 2H, H^2), 1.35 (s, 298.8H, 2x ^tBu), 1.32 (s, 18H, 2x ^tBu). IR 3249, 2970, 1660, 1506, 1065, 970, 752 cm^{-1}.

(2*S*)-*N*-(4-methylbenzyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216f

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.071 g in 76% yield and d.r. 1.0:7.6 $N_{(R)}$ is major diastereoisomer (Interpretation

1 used). R_f = 0.19 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 386.2. HRMS ([M]+H) calcd for $C_{20}H_{21}F_5NO$: 386.1543; found 386.1560. ^{1}H NMR δ 5.73 (d, $J_{AB\ or\ CD}$= 14.3 Hz, 7.6H), 5.45 (d, $J_{AB\ or\ CD}$ = 13.4 Hz, 7.6H), 4.90 (d, $J_{AB\ or\ CD}$ = 14.4 Hz, 1H), 4.12 (d, $J_{AB\ or\ CD}$ = 12.3 Hz, 1H). IR 3266, 2970, 1613, 1507, 1134, 1065, 761 cm^{-1}.

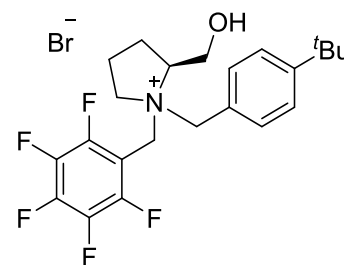## (2*S*)-*N*-(3,5-dimethoxybenzyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216g

General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.029 g in 28% yield and d.r. 1.0:11.4 $N_{(R)}$ is major diastereoisomer (Interpretation 11 used). R_f = 0.16 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 432.2. HRMS ([M]+H) calcd for $C_{21}H_{23}F_5NO_3$: 432.1598; found 432.1601. ^{1}H NMR δ 3.83 (s, 68.4H, 2x OMe), 3.79 (s, 6H, 2x OMe). IR 3308, 2952, 1659, 1594, 1507, 1067, 841 cm^{-1}.
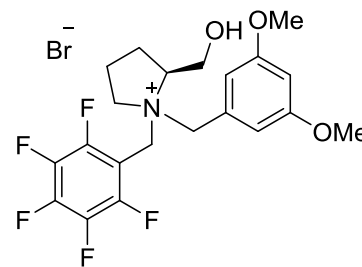
(2*S*)-*N*-(4-nitrobenzyl)-*N*-((perfluorophenyl)methyl)-2-(hydroxymethyl)-pyrrolidinium bromide 216h

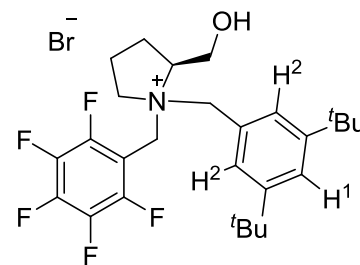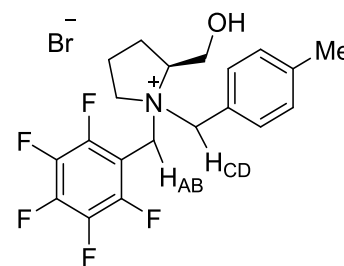General method 2 (0.2 mmol) was used to prepare the ammonium salt which was isolated as a diastereomeric mixture as a white crystalline salt, 0.013 g in 13% yield and d.r. 1.0:2.4 $N_{(R)}$ is major diastereoisomer. R_f = 0.15 in 10:1 CH_2Cl_2:MeOH. *m/z* ([M]+H) 417.1. HRMS ([M]+H) calcd for $C_{19}H_{18}F_5N_2O_3$: 417.1238; found 417.1245. ^{1}H NMR δ 4.25 (dd, *J* = 14.9, 5.9 Hz, 2.4H, H[1]), 3.85 (dd, *J* = 13.3, 3.6 Hz, 1H, H[1]). IR 3308, 2970, 1660, 1509, 1349, 1065 cm^{-1}.
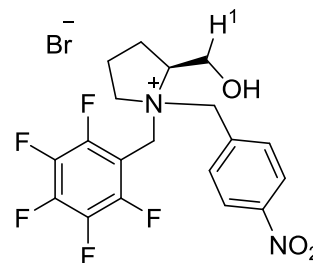
Tert-Butyl 2-((diphenylmethylene)amino)-3-phenylpropanoate 110
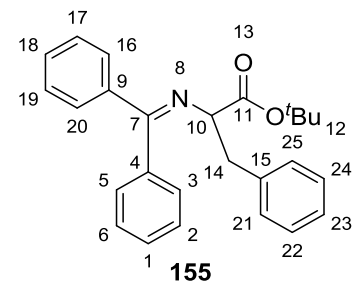
A reaction tube was charged with *tert*-butyl glycine benzophenone imine (0.1 mmol), PTC (10 mol%) along with a stirrer bar. This was placed into a Radley's carousel attached with cooling apparatus and cooled at 0 °C. To this cooled mixture was added toluene (1.0 mL) and the mixture allowed to stand for 2 minutes. Benzyl bromide (14.3 μL, 1.2 equiv, 0.12 mmol) was added and the mixture allowed to stir at 1400 rpm for 30 minutes before addition of potassium hydroxide solution (50 % w/w, 0.5 mL) dropwise so as not to increase the temperature above 5 °C. The reaction mixture was stirred at 1400 rpm. TLC analysis in hexane:diethyl ether (10:1) was used to monitor the reaction progress before quenching with ammonium chloride solution (3 mL) after 24 hours. The biphasic solution was then extracted with diethyl ether (2 x 5 mL) and the combined organic solution was washed with brine (3 mL). This mixture was then dried over magnesium sulfate and concentrated under reduced pressure onto silica (0.5 g). Purification by chromatography took place using combiflash, and a 4 gram silica column run on a gradient (0-1 minute 100% hexanes, 1-13 minutes 0-10% diethyl ether in hexanes, flow rate of 18 mL per minute) where the product eluted at 8-9 minutes and identified by UV_{254} and ELSD. The eluted fractions were concentrated under reduced pressure, dried for 12 hours and analysed by mass spectrometry and chiral HPLC (hexane:IPA,100:1, OD, 0.5 mL minute); t_r (*R*)-enantiomer: (*R*) 15.2 min and t_r (*S*)-enantiomer: (*S*) 22.2 min. HPLC conditions based on racemic reaction product using TBAB as PTC. $R_f = 0.24$ in 10:1 hexane:diethyl ether. *m/z* ([M]+H) 386.3. ^{13}C NMR δ 196.73 (11), 168.47 (7), 139.18 (4 and 9), 137.60 (15), 132.45 (1 and 18), 130.05 (2, 6, 17 and 19), 128.91 (3, 5, 16 and 20), 128.29 (22 and 24), 127.72 (21 and 25), 127.05 (23), 83.26 (qC 12), 72.72 (10), 42.14 (14), 28.10 (12). IR 3100, 2977, 1735, 1656, 1275, 763, 695 cm^{-1}.

7 Appendices

7.1 Representative ^{1}H NMR of 1st gen ammonium salts
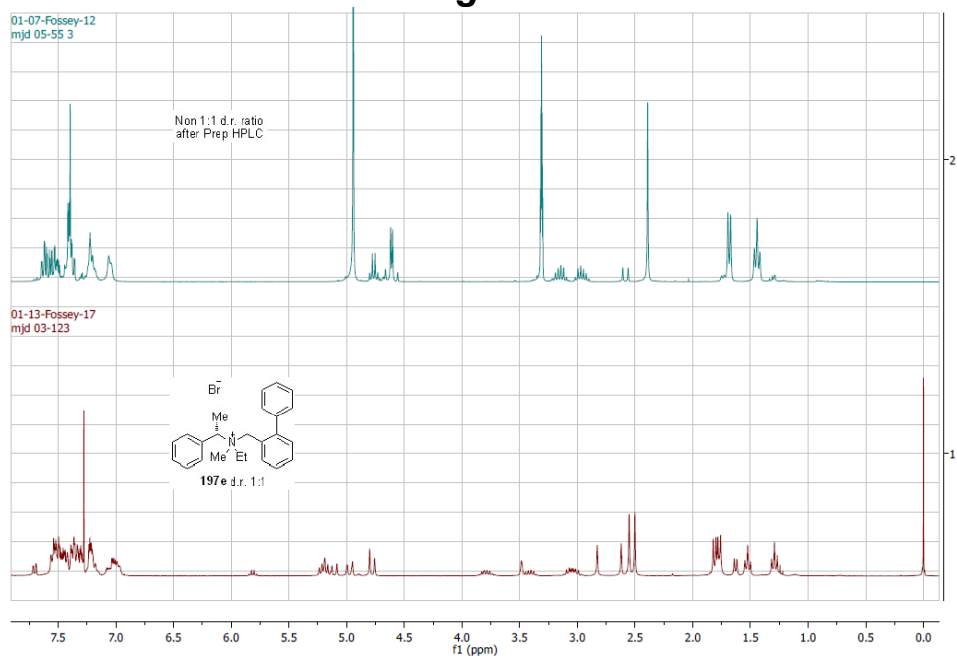
Figure 59 Compound **151e** as a 1:1 mixture after column chromatography compared with a sample after C18 preparative HPLC and chiral HPLC
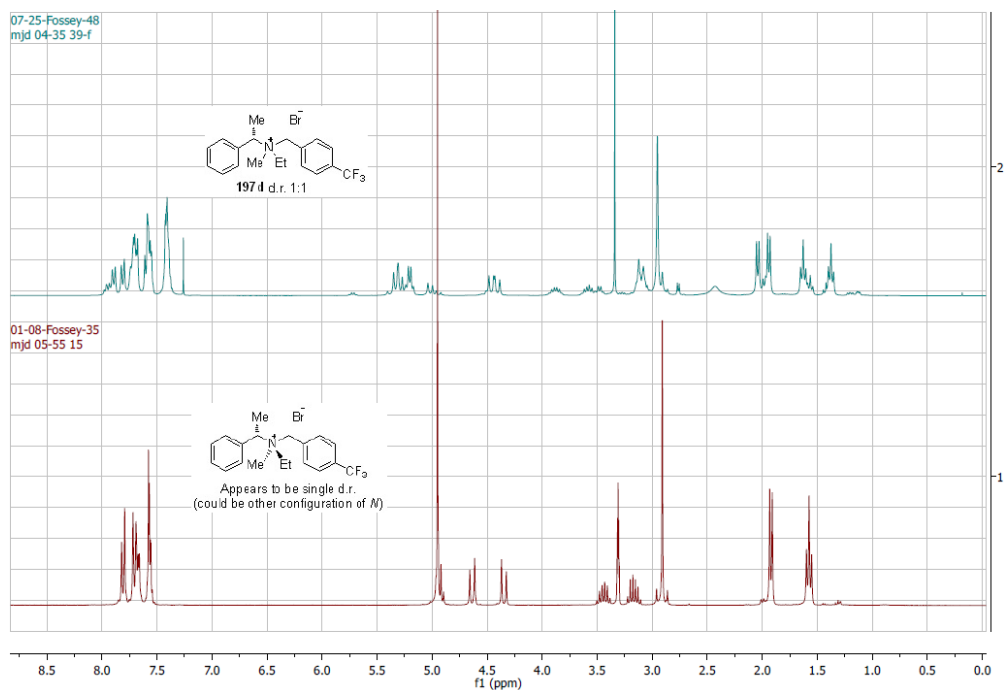
Figure 60 Compound **151d** as a 1:1 mixture after column chromatography compared with a sample after C18 preparative HPLC and chiral HPLC
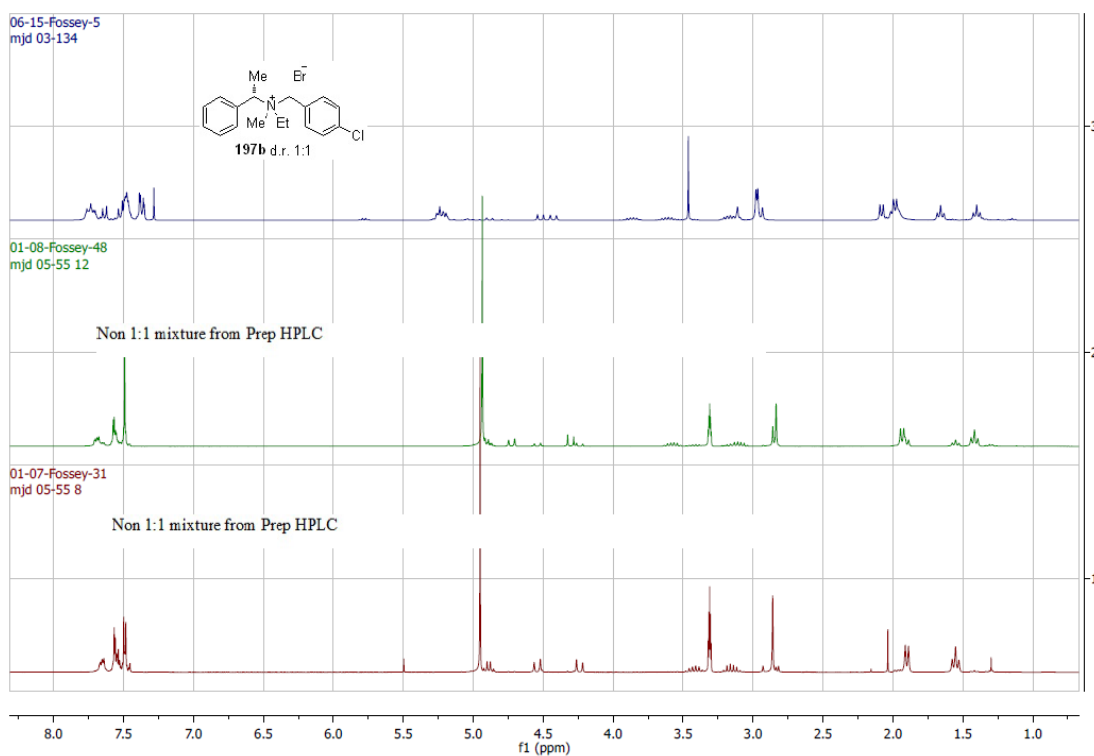
Figure 61 Compound **151b** as a 1:1 mixture after column chromatography compared with a sample after C18 preparative HPLC and chiral HPLC
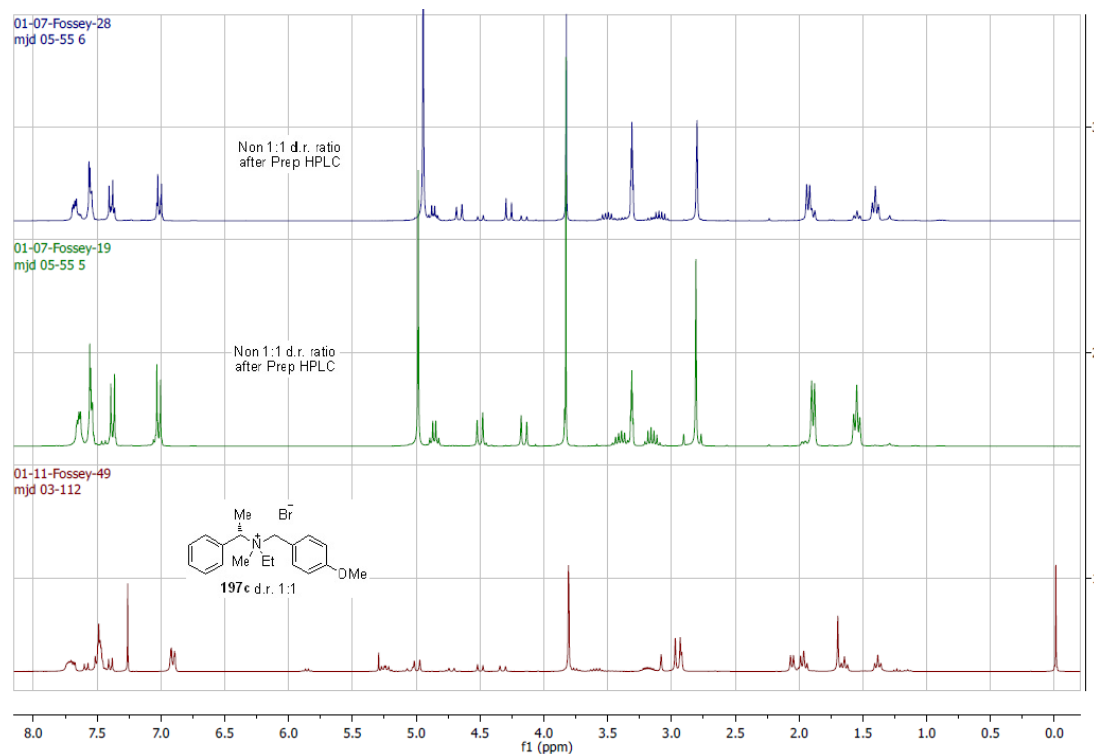
Figure 62 Compound **151c** as a 1:1 mixture after column chromatography compared with a sample after C18 preparative HPLC and chiral HPLC
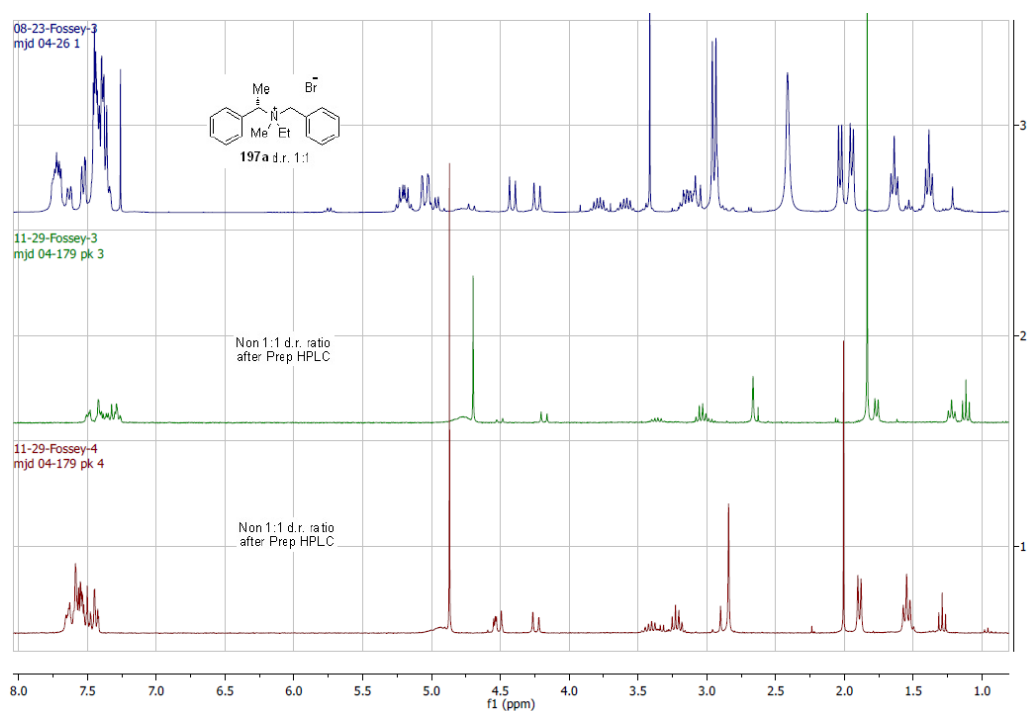
Figure 63 Compound **151a** as a 1:1 mixture after column chromatography compared with a sample after C18 preparative HPLC and chiral HPLC

7.2 X-ray crystal structure data tables

7.2.1 Compound 160f
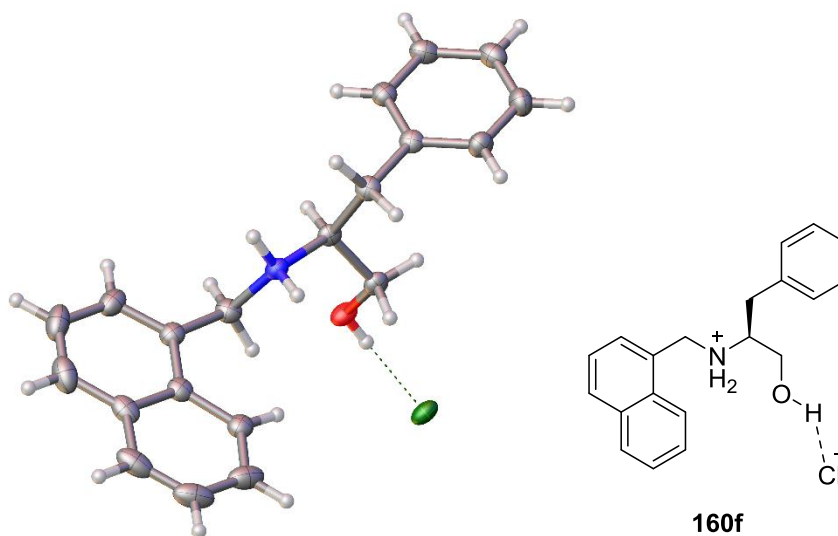
Figure 64 Crystal structure of the HCl salt of **160f** with ellipsoids drawn at the 50 % probability level.

Table 1. Crystal data and structure refinement for Mjd04_88.

Identification code	Mjd04_88
Empirical formula	$C_{20}H_{22}NO$, Cl
Formula weight	327.84
Temperature	100.01(10) K
Wavelength	1.5418 Å
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	a = 4.85502(8) Å $\quad \square= 90°$.
	b = 13.4847(3) Å $\quad \square= 90°$.
	c = 26.4394(5) Å $\quad \square = 90°$.
Volume	1730.95(6) Å3
Z	4
Density (calculated)	1.258 Mg/m3
Absorption coefficient	1.971 mm-1
F(000)	696

Crystal size   0.21 x 0.09 x 0.03 mm^3

Theta range for data collection   6.57 to 74.31°.

Index ranges   -6<=h<=6, -16<=k<=14, -33<=l<=32

Reflections collected   16322

Independent reflections   3469 [R(int) = 0.0488]

Completeness to theta = 74.31°   99.3 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission   1.0000 and 0.6870

Refinement method   Full-matrix least-squares on F2

Data / restraints / parameters 3469 / 0 / 211

Goodness-of-fit on F2 1.082

Final R indices [I>2sigma(I)] R1 = 0.0470, wR2 = 0.1114

R indices (all data)   R1 = 0.0489, wR2 = 0.1123

Absolute structure parameter 0.016(19)

Largest diff. peak and hole   0.692 and -0.267 e.Å-3

Notes:

The hydrogen atom belonging to the hydroxyl group O(1) was located in the electron density and the position refined, while the remaining hydrogen atoms were fixed as riding models. The isotropic displacement parameters of all hydrogen atoms are based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

7.2.2 Compound 182 (*N*_S)
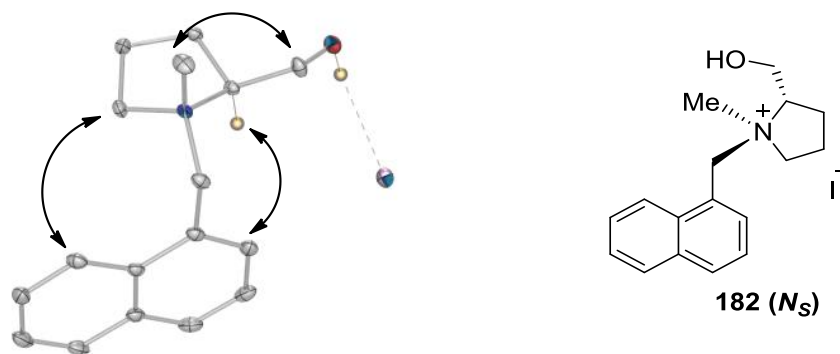
Figure 65 Crystal structure of **182** with ellipsoids drawn at the 50 % probability level, nOe interactions

Table 1. Crystal data and structure refinement for Mjd_05_108.

Identification code	Mjd_05_108
Empirical formula	$C_{17}H_{22}NO$, I
Formula weight	383.26
Temperature	100.00(10) K
Wavelength	1.5418 Å
Crystal system	Monoclinic
Space group	$P\,2_1$
Unit cell dimensions	a = 7.69003(9) Å $\quad$ $\square$= 90°.
	b = 6.23458(5) Å $\quad$ $\square$= 99.1505(10)°.
	c = 16.57461(14) Å $\quad$ $\square$ = 90°.
Volume	784.542(13) Å3
Z	2
Density (calculated)	1.622 Mg/m3
Absorption coefficient	15.989 mm-1
F(000)	384

Crystal size   0.14 x 0.11 x 0.08 mm^3

Theta range for data collection   6.81 to 74.53°.

Index ranges   -8<=h<=9, -7<=k<=7, -20<=l<=20

Reflections collected   15011

Independent reflections   3127 [R(int) = 0.0258]

Completeness to theta = 74.53°   98.0 %

Absorption correction Analytical

Max. and min. transmission   0.645 and 0.492

Refinement method   Full-matrix least-squares on F2

Data / restraints / parameters 3127 / 1 / 185

Goodness-of-fit on F2 1.070

Final R indices [I>2sigma(I)] R1 = 0.0135, wR2 = 0.0327

R indices (all data)   R1 = 0.0137, wR2 = 0.0329

Absolute structure parameter -0.017(3)

Largest diff. peak and hole   0.304 and -0.300 e.Å-3

Notes:

The hydrogen atom belonging to the hydroxyl group O(1) was located in the electron density and the position refined, while the remaining hydrogen atoms were fixed as riding models. The isotropic displacement parameters of all hydrogen atoms are based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

7.2.3 Compound 208f (N_R)
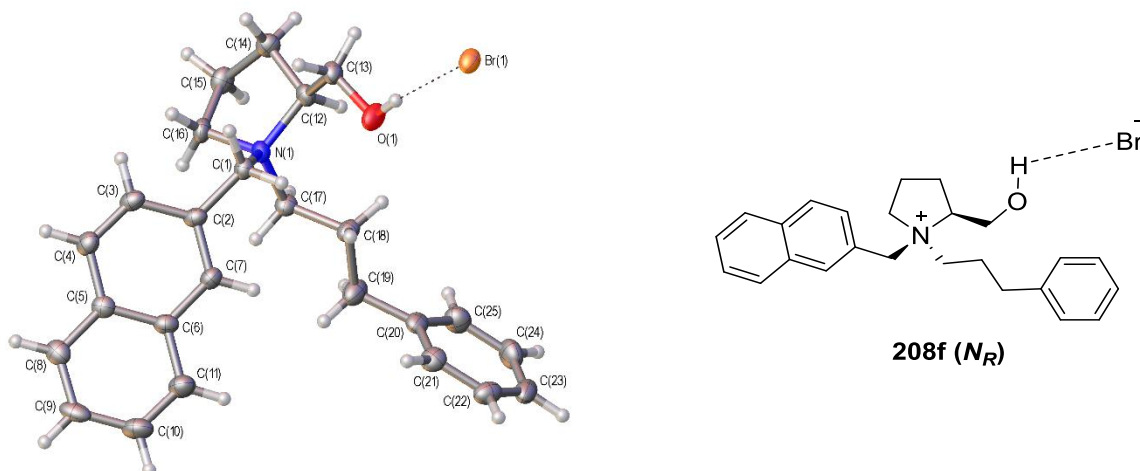
Figure 66 Crystal structure of **208f** with ellipsoids drawn at the 50 % probability level. Hydrogen bonding is shown using a dashed line.

Table 1. Crystal data and structure refinement for Mjd_07-25.

Identification code	Mjd_07-25
Empirical formula	$C_{25}H_{30}NO$, Br
Formula weight	440.41
Temperature	100.00(10) K
Wavelength	1.5418 Å
Crystal system	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$
Unit cell dimensions	a = 6.9432(2) Å $\square$= 90°.
	b = 12.0796(2) Å $\square$= 90°.
	c = 25.0965(5) Å $\square$ = 90°.
Volume	2104.87(8) Å3
Z	4
Density (calculated)	1.390 Mg/m3
Absorption coefficient	2.764 mm-1
F(000)	920
Crystal size	0.253 x 0.122 x 0.041 mm3

Theta range for data collection 3.522 to 74.519°.

Index ranges -7<=h<=8, -15<=k<=15, -30<=l<=31

Reflections collected 20126

Independent reflections 4240 [R(int) = 0.0351]

Completeness to theta = 67.684° 100.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.81166

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 4240 / 36 / 350

Goodness-of-fit on F2 1.037

Final R indices [I>2sigma(I)] R1 = 0.0222, wR2 = 0.0501

R indices (all data) R1 = 0.0234, wR2 = 0.0509

Absolute structure parameter -0.066(8)

Extinction coefficient n/a

Largest diff. peak and hole 0.433 and -0.404 e.Å-3

Notes:

The absolute structure has been determined from the diffraction data. The chirality of N(1) is *R* and that of C(12) is *S*.

The naphthalene group is disordered over two positions with the refined occupancy ratio (C1-C11 : C1'-C11') being 0.800(5) : 0.200(5).

The hydroxyl hydrogen atom, H(1) was located in the electron density and the position refined. The remaining hydrogen atoms were fixed as riding models. For all hydrogen atoms the isotropic displacement parameters were based on the equivalent isotropic displacement parameter (Ueq) of the parent atom. Hydrogen bonding is detailed in Table 7, page 14.

7.2.4 Compound 177I

Figure 67 Crystal structure of **177l** with ellipsoids drawn at the 50 % probability level and atomic labelling given. Hydrogen

bonding is shown using a dashed line.

Table 1. Crystal data and structure refinement for MJD_05_114.

Identification code	Mjd 05-114
Empirical formula	$C_{27}H_{28}NO$, Br
Formula weight	462.41
Temperature	100.01(10) K
Wavelength	1.5418 Å
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	a = 8.85255(10) Å □= 90°.
	b = 9.79850(9) Å □= 90°.
	c = 26.0845(2) Å □ = 90°.
Volume	2262.63(4) Å3
Z	4
Density (calculated)	1.357 Mg/m3
Absorption coefficient	2.603 mm-1
F(000)	960
Crystal size	0.21 x 0.045 x 0.03 mm3

Theta range for data collection   3.39 to 74.41°.

Index ranges   -10<=h<=9, -12<=k<=12, -32<=l<=32

Reflections collected 21634

Independent reflections   4536 [R(int) = 0.0308]

Completeness to theta = 74.41°   99.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission   1.00000 and 0.82255

Refinement method   Full-matrix least-squares on F2

Data / restraints / parameters 4536 / 0 / 274

Goodness-of-fit on F2 1.049

Final R indices [I>2sigma(I)] R1 = 0.0191, wR2 = 0.0436

R indices (all data)   R1 = 0.0214, wR2 = 0.0444

Absolute structure parameter -0.022(10)

Largest diff. peak and hole   0.249 and -0.200 e.Å-3

Notes:

The hydrogen atom belonging to the hydroxyl group O(1) was located in the electron density and the position refined, while the remaining hydrogen atoms were fixed as riding models. The isotropic displacement parameters of all hydrogen atoms are based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

7.2.5 Compound 212e (N_S)
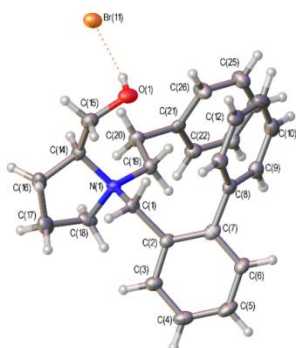
1) X-ray structure of **212e** (N_S)
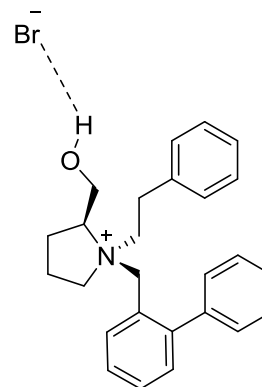
212e (N_S)
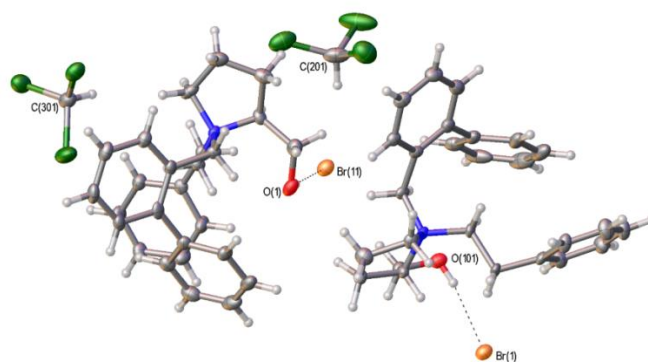
2) Shows chloroform molecules involved in the packing structure of **212e**

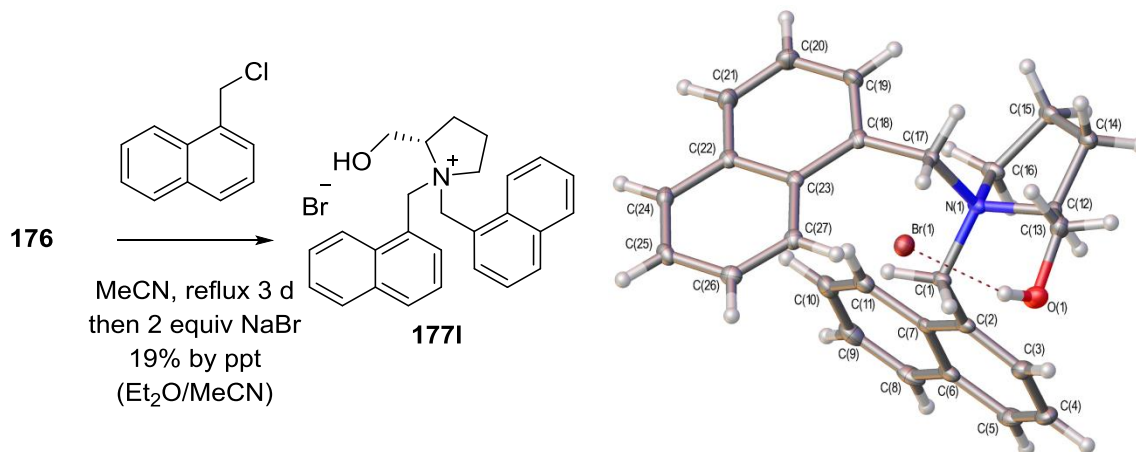**Figure 68 1)** Crystal structure of **212e** with ellipsoids drawn at the 50 % probability level. Hydrogen bonding is shown using dashed lines. **2)** Crystal structure of one of the two crystallographically-independent molecules of **212e** with ellipsoids drawn at the 50 % probability level. One of the bromide anions and both chloroform molecules have been omitted for clarity. Hydrogen bonding is shown using a dashed line.

Table 1. Crystal data and structure refinement for Mjd_07-138.

Identification code	Mjd_07-138	
Empirical formula	$C_{26}H_{30}NO$, Br, $CHCl_3$	
Formula weight	571.79	
Temperature	100.00(10) K	
Wavelength	1.5418 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 10.0666(4) Å	$\square$ = 79.592(2)°.
	b = 10.3790(2) Å	$\square$ = 87.607(3)°.
	c = 12.9065(4) Å	$\square$ = 89.577(2)°.
Volume	1325.14(7) Å3	

Z	2
Density (calculated)	1.433 Mg/m3
Absorption coefficient	5.048 mm-1
F(000)	588
Crystal size	0.210 x 0.100 x 0.050 mm3
Theta range for data collection	6.606 to 66.581°.

Index ranges   -11<=h<=11, -12<=k<=12, -15<=l<=15

Reflections collected   16947

Independent reflections   16947 [R(int) = ?]

Completeness to theta = 67.684°   97.2 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission   1.00000 and 0.66489

Refinement method   Full-matrix least-squares on F2

Data / restraints / parameters 16947 / 3 / 598

Goodness-of-fit on F2 1.059

Final R indices [I>2sigma(I)] R1 = 0.0605, wR2 = 0.1631

R indices (all data)   R1 = 0.0635, wR2 = 0.1681

Absolute structure parameter -0.028(14)

Extinction coefficient n/a

Largest diff. peak and hole   1.291 and -0.954 e.Å-3

Notes: The crystal was a non-merohedral twin with the domains related by 180° about the direct axis [0 1 0] and the refined percentage domain ratio being 63:37.

The structure contains two crystallographically-independent ammonium salts and bromide ions, with one molecule of chloroform per ion pair. Hydrogen atoms were treated as riding models with hydrogen bonding shown in Table 7.Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2x 103)

7.2.6 Compound 216b (*N_R*)
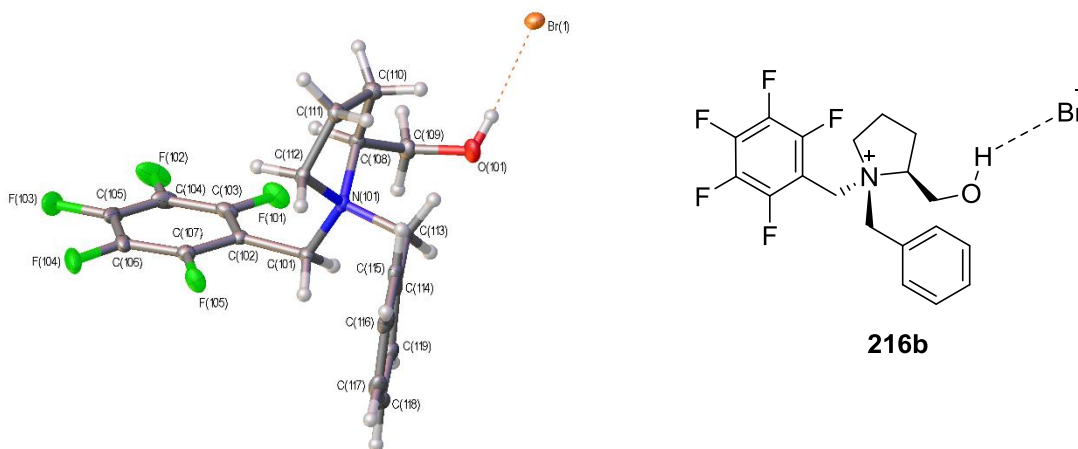
Figure 69 Crystal structure of one of the two crystallographically-independent molecules of **216b** with ellipsoids drawn at the 50 % probability level. One of the bromine anions and both acetonitrile molecules have been omitted for clarity. Hydrogen bonding is shown using a dashed line.

Table 1. Crystal data and structure refinement for Mjd_07-186.

Identification code	Mjd_07-186
Empirical formula	$C_{19}H_{19}F_5NO$, Br, C_2H_3N
Formula weight	493.31
Temperature	100.00(10) K
Wavelength	1.5418 Å
Crystal system	Triclinic
Space group	P 1
Unit cell dimensions	a = 7.72670(10) Å $\square$= 98.810(2)°.
	b = 10.3793(2) Å $\square$= 105.581(2)°.
	c = 14.3396(3) Å $\square$ = 103.014(2)°.
Volume	1050.95(4) Å3
Z	2
Density (calculated)	1.559 Mg/m3
Absorption coefficient	3.205 mm-1
F(000)	500
Crystal size	0.3685 x 0.2352 x 0.2053 mm3

Theta range for data collection 3.286 to 74.544°.

Index ranges -9<=h<=9, -12<=k<=12, -17<=l<=17

Reflections collected 19373

Independent reflections 7450 [R(int) = 0.0154]

Completeness to theta = 67.680° 98.5 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.81045

Refinement method Full-matrix least-squares on F2

Data / restraints / parameters 7450 / 3 / 549

Goodness-of-fit on F2 1.063

Final R indices [I>2sigma(I)] R1 = 0.0149, wR2 = 0.0384

R indices (all data) R1 = 0.0150, wR2 = 0.0385

Absolute structure parameter -0.019(3)

Extinction coefficient n/a

Largest diff. peak and hole 0.232 and -0.224 e.Å-3

Notes:

The structure contains two crystallographically-independent molecules, with one bromine anion and one molecule of acetonitrile per molecule.

The absolute structure has been determined from the diffraction data. The chirality of N(1) and N(101) is *R* and that of C(8) and C(108) is *S*.

The hydroxyl hydrogen atoms, H(1) and H(101) were located in the electron density and the positions refined. The remaining hydrogen atoms were fixed as riding models. For all hydrogen atoms the isotropic displacement parameters were based on the equivalent isotropic displacement parameter (Ueq) of the parent atom. Hydrogen bonding is detailed in Table 7, page 17.

8 References

1. W. J. Pope, *Birmingham University Chemistry Society. UB/SOC1/D/1/9. Cadbury Research Library: Special Collections. University of Birmingham*, 1902.
2. W. J. Pope and S. J. Peachey, *J. Chem. Soc.*, 1899.
3. C. Kölmel, C. Ochsenfeld and R. Ahlrichs, *Theoret. Chim. Acta*, 1992, **82**, 271-284.
4. M. Saunders and F. Yamada, *J. Am. Chem. Soc.*, 1963, **85**, 1882-1882.
5. P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138-5175.
6. K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319-3328.
7. T. Hashimoto, K. Sakata, F. Tamakuni, M. J. Dutton and K. Maruoka, *Nat Chem*, 2013, **5**, 240-244.
8. L. Meca, D. Řeha and Z. Havlas, *J. Org. Chem.*, 2003, **68**, 5677-5680.
9. E. P. Kyba, G. W. Gokel, F. De Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah and D. J. Cram, *J. Org. Chem.*, 1977, **42**, 4173-4184.
10. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946-5952.
11. A. V. Malkov and P. Kočovský, *Eur. J. Org. Chem.*, 2007, **2007**, 29-36.
12. G. Chelucci, G. Murineddu and G. A. Pinna, *Tetrahedron: Asymmetr.*, 2004, **15**, 1373-1389.
13. F. A. Davis and B.-C. Chen, *Chem. Soc. Rev.*, 1998, **27**, 13-18.
14. J. A. Ellman, *Abstr. Pap. Am. Chem. Soc.*, 2013, **245**.
15. S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312-4348.
16. M. Terada, *Synthesis-Stuttgart*, 2010, 1929-1982.
17. K. Maruoka, *Chem. Rec.*, 2010, **10**, 254-259.
18. T. Werner, *Adv. Synth. Catal.*, 2009, **351**, 1469-1481.
19. K. Maruoka, *Synlett*, 2009, 652-652.
20. W. S. Knowles and M. J. Sabacky, *Chem. Commun.*, 1968, 1445-1446.
21. W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998-2007.
22. K. B. Sharpless, *Nobel Lecture: The Search for New Chemical Reactivity Nobelprize.org. Nobel Media AB*, Web. 12 Apr 2014.
23. R. Noyori, *Adv. Synth. Catal.*, 2003, **345**, 15-32.
24. R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40-73.
25. R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97-102.
26. W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029-3070.
27. J. B. Lambert, W. L. Oliver and B. S. Packard, *J. Am. Chem. Soc.*, 1971, **93**, 933-937.
28. R. G. Kostyanovsky, G. K. Kadorkina, V. N. Voznesensky, I. I. Chervin, M. Y. Antipin, K. A. Lyssenko, E. V. Vorontzov, V. I. Bakhmutov and P. Rademacher, *Mendeleev Commun.*, 1996, **6**, 69-71.
29. R. G. Kostyanovsky, V. Schurig, K. A. Lyssenko, O. Trapp, G. K. Kadorkina, V. R. Kostyanovsky and B. Averkievc, *Mendeleev Commun.*, 2004.
30. O. Trapp, V. Schurig and R. G. Kostyanovsky, *Chem.-Eur. J.*, 2004, **10**.
31. R. G. Kostyanovsky, G. K. Kadorkina, V. R. Kostyanovsky, V. Schurig and O. Trapp, *Angew. Chem., Int. Ed.*, 2000, **39**.
32. V. J. Baker, A. R. Katritzky, J.-P. Majoral, S. F. Nelsen and P. J. Hintz, *J. Chem. Soc., Chem. Commun.*, 1974, 823-824.
33. R. G. Kostyanovsky, P. Rademacher, Y. I. El'natanov, G. K. Kadorkina, G. A. Nikiforov, I. I. Chervin, S. V. Usachev and V. R. Kostyanovsky, *Russ. Chem. Bull.*, 1997, **46**, 1291-1299.

34. R. G. Kostyanovsky, V. F. Rudchenko, V. G. Shtamburg, I. I. Chervin and S. S. Nasibov, *Tetrahedron*, 1981, **37**, 4245-4254.
35. Cinchona alkaloids included in 149 reviews for applications in asymmetric synthesis and cited 19,086 times as of 19/5/2014 - information taken from Web of Science.
36. C. E. Song, in *Cinchona Alkaloids in Synthesis and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2009, pp. 1-10.
37. T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691-1693.
38. J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719-724.
39. E. M. O. Yeboah, S. O. Yeboah and G. S. Singh, *Tetrahedron*, 2011, **67**, 1725-1762.
40. Nobel lecture can be found at http://www.nobelprize.org/mediaplayer/index.php?id=488
41. S. G. Hentges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263-4265.
42. H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483-2547.
43. M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520-1543.
44. T. Marcelli and H. Hiemstra, *Synthesis-Stuttgart*, 2010, 1229-1279.
45. S.-S. Jew and H.-G. Park, *Chem. Commun.*, 2009, 7090-7103.
46. H. M. R. Hoffmann and J. Frackenpohl, in *Cinchona Alkaloids in Synthesis and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2009, pp. 359-418.
47. H. M. R. Hoffmann, J. Frackenpohl and C. E. Song, *Organic Chemistry of Cinchona Alkaloids*, 2009.
48. R. Tröger, *J. Prakt. Chem.*, 1887, **36**.
49. D. Hoppe and T. Hense, *Angew. Chem., Int. Ed.*, 1997, **36**, 2282-2316.
50. M. A. Spielman, *J. Am. Chem. Soc.*, 1935, **57**, 583-585.
51. V. Prelog and P. Wieland, *Helv. Chim. Acta*, 1944, **27**, 1127-1134.
52. A. Lauber, B. Zelenay and J. Cvengros, *Chem. Commun.*, 2014, **50**, 1195-1197.
53. T. Kamiyama, M. S. Özer, E. Otth, J. Deska and J. Cvengroš, *ChemPlusChem*, 2013, **78**, 1510-1516.
54. J. Cvengros, P. Ondrisek and R. Schwenk, *Chem. Commun.*, 2014.
55. W. Chen and J. S. Fossey, *Unpublished Work*.
56. Ö. V. Rúnarsson, J. Artacho and K. Wärnmark, *Eur. J. Org. Chem.*, 2012, **2012**, 7015-7041.
57. D. A. Lenev, D. G. Golovanov, K. A. Lyssenko and R. G. Kostyanovsky, *Tetrahedron: Asymmetr.*, 2006, **17**, 2191-2194.
58. C. Pardo, E. Sesmilo, E. Gutiérrez-Puebla, A. Monge, J. Elguero and A. Fruchier, *J. Org. Chem.*, 2001, **66**, 1607-1611.
59. Images reproduced from CCDC cif files with permission
60. N. Claessens, F. Pierard, C. Bresson, C. Moucheron and A. Kirsch-De Mesmaeker, *J. Inorg. Biochem.*, 2007, **101**, 987-996.
61. C. Bresson, M. Luhmer, M. Demeunynck, A. Kirsch-De Mesmaeker and F. Pierard, *Tetrahedron Lett.*, 2004, **45**, 2863-2866.
62. J. H. Rowley, S. C. Yau, B. M. Kariuki, A. R. Kennedy and N. C. O. Tomkinson, *Org. Biomol. Chem.*, 2013, **11**, 2198-2205.
63. A. Srivastava, V. Srivastava, S. M. Verma and E. Subramanian, *J. Org. Chem.*, 1994, **59**, 3560-3563.
64. V. S. A. Srivatava, S. M. Verma, , *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1997, **36**.
65. T. Yang, J.-J. An, X. Wang, D.-Y. Wu, W. Chen and J. S. Fossey, *Phys. Chem. Chem. Phys.*, 2012, **14**, 10747-10753.
66. M. Egli and S. Sarkhel, *Acc. Chem. Res.*, 2006, **40**, 197-205.

67.	K. A. Pelz and M. R. Gagné, *Abstr. Pap. Am. Chem. Soc.*, 2003, **226**.
68.	K. A. Pelz, P. S. White and M. R. Gagné, *Organometallics*, 2004, **23**.
69.	J. S. Fossey, R. Matsubara, P. Vital and S. Kobayashi, *Org. Biomol. Chem.*, 2005, **3**.
70.	J. Meisenheimer, *Ber. Dtsch. Chem. Ges.*, 1908, **41**, 3966-3976.
71.	J. Drabowicz, B. Dudziński, M. Mikołajczyk, S. Colonna and N. Gaggero, *Tetrahedron: Asymmetr.*, 1997, **8**, 2267-2270.
72.	F. Toda, K. Mori, Z. Stein and I. Goldberg, *Tetrahedron Lett.*, 1989, **30**, 1841-1844.
73.	J. F. Traverse, Y. Zhao, A. H. Hoveyda and M. L. Snapper, *Org. Lett.*, 2005, **7**, 3151-3154.
74.	J. Feng, X. Fu, Z. Chen, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2013, **15**, 2640-2643.
75.	G. B. Kauffman, *Isis*, 1973, **64**.
76.	G. B. Kauffman and I. Bernal, *Pure Appl. Chem.*, 1988, **60**, 1379-1384.
77.	E. Tayama and H. Tanaka, *Tetrahedron Lett.*, 2007, **48**, 4183-4185.
78.	E. Tayama, S. Otoyama and H. Tanaka, *Tetrahedron: Asymmetr.*, 2009, **20**, 2600-2608.
79.	R. G. Kostyanovsky, K. A. Lyssenko, O. N. Krutius and V. R. Kostyanovsky, *Mendeleev Commun.*, 2009, **19**, 19-20.
80.	H. F. Wu, W. B. Lin, L. Z. Xia, Y. G. Luo, X. Z. Chen, C. Y. Li, G. L. Zhang and X. F. Pan, *Helv. Chim. Acta*, 2009, **92**, 677-688.
81.	E. Wedekind, *Ber. Dtsch. Chem. Ges.*, 1902, **35**, 178-185.
82.	E. Wedekind and R. Oechslen, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 1158-1163.
83.	E. Wedekind, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 1163-1169.
84.	E. Vedejs and J. T. Kendall, *J. Am. Chem. Soc.*, 1997, **119**, 6941-6942.
85.	B. Drouillat and F. Couty, *Synlett*, 2009, **5**, 767-770.
86.	E. Tayama and H. Kimura, *Angew. Chem., Int. Ed.*, 2007, **46**, 8869-8871.
87.	K. Okuma, H. Minato and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 435-437.
88.	K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, *J. Am. Chem. Soc.*, 1965, **87**, 1958-1976.
89.	R. García, L. Gómez-Hortigüela, F. Sánchez and J. Pérez-Pariente, *Microporous Mesoporous Mater.*, 2011, **146**, 57-68.
90.	R. García, L. Gómez-Hortigüela and J. Pérez-Pariente, *Catal. Today*, 2012, **179**, 16-26.
91.	M. Thomas, L. Rothman, J. Hatcher, P. Agarkar, R. Ramkirath, S. Lall-Ramnarine and R. Engel, *Synthesis*, 2009, **2009**, 1437-1444.
92.	S. J. A. Grove, J. Kaur, A. W. Muir, E. Pow, G. J. Tarver and M.-Q. Zhang, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 193-196.
93.	J. K. Clark, P. Cowley, A. W. Muir, R. Palin, E. Pow, A. B. Prosser, R. Taylor and M.-Q. Zhang, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2565-2568.
94.	T. Kano, T. Kumano, R. Sakamoto and K. Maruoka, *Chem. Sci.*, 2010, **1**, 499-501.
95.	S. Hanessian, C. Talbot and P. Saravanan, *Synthesis*, 2006, **2006**, 723-734.
96.	T. S. Stevens, E. M. Creighton, A. B. Gordon and M. MacNicol, *J. Chem. Soc.*, 1928, 3193-3197.
97.	M. Sommelet, *C. R. Chim.*, 1937, **56**.
98.	S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, 1951, **73**, 4122-4131.
99.	N. De Rycke, O. David and F. Couty, *Org. Lett.*, 2011, **13**, 1836-1839.
100.	M. J. O'Donnell, W. D. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353-2355.
101.	J. Lu, X.-L. Liao, X.-Z. Chen and C. Wang, *Chin. J. Org. Chem.*, 2011, **31**, 341-345.
102.	E. V. Dehmlow, R. Klauck, S. Düttmann, B. Neumann and H.-G. Stammler, *Tetrahedron: Asymmetr.*, 1998, **9**, 2235-2244.
103.	E. V. Dehmlow and S. Schrader, *Pol. J. Chem*, 1994, **68**, 2199–2208.

104. T. Ohtani, H. Nakatsukasa, M. Kamezawa, H. Tachibana and Y. Naoshima, *J. Mol. Catal. B: Enzym.*, 1998, **4**, 53-60.
105. H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 1933, **55**, 4571-4587.
106. W. Eschweiler, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 880-882.
107. C. Martelli, M. Coronnello, S. Dei, D. Manetti, F. Orlandi, S. Scapecchi, M. Novella Romanelli, M. Salerno, E. Mini and E. Teodori, *J. Med. Chem.*, 2010, **53**, 1755-1762.
108. B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1997, **38**, 8595-8598.
109. E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **119**, 12414-12415.
110. S. E. Denmark, N. D. Gould and L. M. Wolf, *J. Org. Chem.*, 2011, **76**, 4260-4336.
111. S. E. Denmark, N. D. Gould and L. M. Wolf, *J. Org. Chem.*, 2011, **76**, 4337-4357.
112. B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1997, **38**, 8595-8598.
113. T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519-6520.
114. A. Feula, L. Male and J. S. Fossey, *Org. Lett.*, 2010, **12**, 5044-5047.
115. A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341-2372.
116. J. B. Sweeney, *Chem. Soc. Rev.*, 2009, **38**, 1027-1038.
117. M. Yasuda, Y. Onishi, M. Ueba, T. Miyai and A. Baba, *J. Org. Chem.*, 2001, **66**, 7741-7744.
118. D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574-1585.
119. B. List, *Tetrahedron*, 2002, **58**, 5573-5590.
120. M. J. Rieser, Y. H. Hui, J. K. Rupprecht, J. F. Kozlowski, K. V. Wood, J. L. McLaughlin, P. R. Hanson, Z. Zhuang and T. R. Hoye, *J. Am. Chem. Soc.*, 1992, **114**, 10203-10213.
121. A. Nelson, *Angew. Chem., Int. Ed.*, 1999, **38**, 1583-1585.
122. K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013-3028.
123. M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506-517.
124. B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518-525.
125. T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656-5682.
126. R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering and H. Wynberg, *Tetrahedron Lett.*, 1976, **17**, 1831-1834.
127. U. H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446-447.
128. T. Shibuguchi, H. Mihara, A. Kuramochi, S. Sakuraba, T. Ohshima and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2006, **45**, 4635-4637.
129. M. Q. Hua, H. F. Cui, L. Wang, J. Nie and J. A. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 2772-2776.
130. M. Mąkosza and M. Wawrzyniewicz, *Tetrahedron Lett.*, 1969, **10**, 4659-4662.
131. C. M. Starks, *J. Am. Chem. Soc.*, 1971, **93**.
132. T. C. Cook, M. B. Andrus and D. H. Ess, *Org. Lett.*, 2012, **14**, 5836-5839.
133. E. de Freitas Martins and J. R. Pliego, *ACS Catalysis*, 2013, **3**, 613-616.
134. E. Gomez-Bengoa, A. Linden, R. López, I. Múgica-Mendiola, M. Oiarbide and C. Palomo, *J. Am. Chem. Soc.*, 2008, **130**, 7955-7966.
135. M. Jezierska-Zięba, J. E. Rode, M. Fedoryński, J. Cybulski and J. C. Dobrowolski, *J. Mol. Struct. Theochem*, 2010, **947**, 101-106.
136. M. Mąkosza, *Pure Appl. Chem.*, 1975, **43**, 439.
137. H. M. Yang and H. S. Wu, *Catal. Rev. - Sci. Eng.*, 2003, **45**, 463.
138. T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222-4266.
139. T. Hashimoto and K. Maruoka, in *Asymmetric Phase Transfer Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2008, pp. 1-8.
140. A. Brändström, in *Adv. Phys. Org. Chem.*, eds. V. Gold and D. Bethel, Academic Press, 1978, vol. Volume 15, pp. 267-330.

141.   M. Kitamra, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549-1551.
142.   P. I. Dalko, *Chimia*, 2007, **61**, 213-218.
143.   S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178-2189.
144.   G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw and K. I. Goldberg, *Organometallics*, 2010, **29**, 2176-2179.
145.   B. E. Love and E. G. Jones, *J. Org. Chem.*, 1999, **64**, 3755-3756.
146.   S. Lin, C.-X. Song, G.-X. Cai, W.-H. Wang and Z.-J. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 12901-12903.
147.   D. Suarez, G. Laval, S.-M. Tu, D. Jiang, C. L. Robinson, R. Scott and B. T. Golding, *Synthesis*, 2009, **2009**, 1807-1810.
148.   D. M. Singh and A. Ningombam, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49B**.
149.   D. A. Spivak, R. Simon and J. Campbell, *Anal Chim Acta*, 2004, **504**, 23-30.
150.   W. J. Kerr, M. Middleditch and A. J. B. Watson, *Synlett*, 2011, **2011**, 177-180.
151.   D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, 1952, **74**, 5851-5859.
152.   X. Ge, C. Qian, Y. Chen and X. Chen, *Tetrahedron: Asymmetr.*, 2014, **25**, 596-601.
153.   N. Vriamont, B. Govaerts, P. Grenouillet, C. de Bellefon and O. Riant, *Chem.-Eur. J.*, 2009, **15**, 6267-6278.
154.   A. Baeza and A. Pfaltz, *Chem.-Eur. J.*, 2009, **15**, 2266-2269.
155.   N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 5568-5569.
156.   G. Huelgas, S. Bernès, M. Sánchez, L. Quintero, E. Juaristi, C. Anaya de Parrodi and P. J. Walsh, *Tetrahedron*, 2007, **63**, 12655-12664.
157.   J. F. Kerwin, G. C. Hall, E. Macko, R. A. McLean, E. J. Fellows and G. E. Ullyot, *J. Am. Chem. Soc.*, 1951, **73**, 5681-5686.
158.   B. Duthion, T.-X. Métro, D. Gomez Pardo and J. Cossy, *Tetrahedron*, 2009, **65**, 6696-6706.
159.   T. Mashiko, S. Terashima and S. Yamada, *Yakugaku Zasshi*, 1980, **100**, 319-327.
160.   W. Yan, P. Li, J. Feng, D. Wang, S. Zhu, X. Jiang and R. Wang, *Tetrahedron: Asymmetr.*, 2010, **21**, 2037-2042.
161.   R. Almansa, D. Guijarro and M. Yus, *Tetrahedron: Asymmetr.*, 2007, **18**, 2828-2840.
162.   L. Zhu, L. Cheng, Y. Zhang, R. Xie and J. You, *J. Org. Chem.*, 2007, **72**, 2737-2743.
163.   T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519-6520.