Stereoselective cyclopropanations of allylic amines and derivatives

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by

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This thesis is concerned with the development and application of methods for the stereoselective cyclopropanation of allylic amines and derivatives.

Firstly, a highly chemo- and stereoselective cyclopropanation of *N*,*N*-dibenzyl-protected allylic amines was developed using the highly reactive Shi's carbenoid [$CF_3CO_2ZnCH_2I$]. Subsequent mechanistic studies revealed that the high diastereoselectivity of the reaction was likely to be due to coordination of the amine to the zinc carbenoid reagent. It is then shown that the reaction is general for a wide range of both cyclic and acyclic substrates giving the corresponding cyclopropanes in high yields and diastereoselectivities.

Secondly, a novel stereodivergent cyclopropanation of allylic carbamates and amides was developed. It was found that reaction of cyclic allylic carbamates with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] typically gives the *syn*-diastereoisomer in high yields and diastereoselectivities, whilst treatment of the same substrates with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gives the corresponding *anti*-diastereoisomers in high yields and diastereoselectivities. Mechanistic investigations suggested that reactions with the Wittig-Furukawa reagent proceed *via* a *N*-directed intramolecular cyclopropanation step whilst those with Shi's carbenoid proceed *via* a sterically directed intermolecular cyclopropanation step. Unsuccessful investigations into an asymmetric variant of the cyclopropanation reaction utilising chiral carbamate protecting groups are then described.

Finally, studies towards the total synthesis of the potential anti-obesity therapeutic *trans*-SCH-A and its epimer *cis*-SCH-A are described. A stereodivergent route towards the epimeric products was developed through the cyclopropanation of a common allylic carbamate intermediate with either the Wittig-Furukawa reagent or Shi's carbenoid to give the corresponding *trans*-2-amino-5-arylbicyclo[3.10]hexane or *cis*-2-amino-5-arylbicyclo [3.10]hexane intermediates respectively.

I would first and foremost like to thank my supervisor Prof. Steve Davies for allowing me the privilege of working in his research group over the past 4 years and for his generous funding throughout.

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Abbreviations

Relating to Nuclear Magnetic Resonance

NMR	nuclear magnetic resonance
δ	chemical shift
s	singlet
d	doublet
t	triplet
q	quartet
quin	quintet
m	multiplet
app	apparent
br	broad
obs	obscured
J	coupling constant (Hz)
ppm	parts per million
o	*ortho*
m	*meta*
p	*para*
i	*ipso*
nOe	nuclear Overhauser effect

Relating to Characterization

ν_{max}	infra-red absorption
m/z	mass/charge ratio
ESI	electrospray ionisation
CI	chemical ionisation
FI	field ionisation
GC Tof	gas chromatography time of flight
GC	gas chromatography
HPLC	high performance liquid chromatography
m.p.	melting point
t.l.c.	thin layer chromatography

Solvents

DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
TBME	*tert*-butylmethylether
THF	tetrahydrofuran

Functional Groups

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-butyl
Bus	*tert*-butylsulfonyl
Bz	benzoyl

Cbz	benzyloxycarbonyl
Cy	cyclohexyl
Et	ethyl
Me	methyl
Ms	methanesulfonyl
Ph	phenyl
Piv	pivaloyl
^{i}Pr	*iso*-propyl
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-methylsulfonyl

General Abbreviations

AAC	1-aminocyclopropanecarboxylic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
atm.	atmospheres
BTEAC	benzyl triethylammonium chloride
BuLi	*n*-butyl lithium
cat.	catalytic amount
Cp	cyclopentadienyl
*m*CPBA	*meta*-chloroperbenzoic acid
HOMO	highest occupied molecular orbital
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIBAL-H	di*iso*butylaluminium hydride
DIPEA	*N*,*N*-di*iso*propyl-*N*-ethyl amine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
d.r.	diastereomeric ratio
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
e.e.	enantiomeric excess
eq.	equivalents
e.r.	enantiomeric ratio
EWG	electron withdrawing group
gem	geminal
HOBt	1-hydroxybenzotriazole
HMDS	hexamethyldisilazane
hrs	hours
hν	photochemical irradiation
IBX	*O*-iodoxybenzoic acid
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
MCH	melanin-concentrating hormone
MCH-R1	melanin-concentrating hormone receptor-1
min	minutes
MIRC	Michael-initiated ring closure

MO	molecular orbital
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	molecular sieves
P	protecting group
PCC	pyridinium chlorochromate
PRSP	penicillin-resistant *Streptococcus pneumoniae*
quant.	quantitative yield
R	generic functional group
RT	room temperature
s	seconds
SAM	*S*-adenosylmethionine
TADDOL	trans-α,α'-(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
TPAP	tetra *n*-propylammonium perruthenate
p-TSA	*para*-toluenesulfonic acid
VRA	vancomycin-resistant *enterococci*

Contents

Chapter 1: Introduction

Within our research group we have become increasingly interested in chemo- and stereoselective functionalisations of unsaturated amines including epoxidation,[1] dihydroxylation,[2] aziridination[3] and ring-closing haloamination reactions.[4] This thesis delineates studies into the chemo- and stereoselective cyclopropanation of allylic amines and derivatives.[5]

This chapter introduces the concept of chemoselectivity with respect to the reaction of allylic amines and exemplifies this with the epoxidation reaction. The natural occurrence, use and stereoselective synthesis of cyclopropanes is then surveyed, culminating in the aims of this project.

1.1 Chemoselectivity in the reaction of allylic amines

Allylic amines possess two nucleophilic sites: the nitrogen lone pair, and the carbon-carbon double bond. As such, any reaction with an electrophile will be subject to the issue of chemoselectivity. Often the reaction of an allylic amine with an electrophile is found to proceed preferentially at nitrogen rather than at the olefin. This is generally seen as an undesirable reaction pathway, although it can sometimes be advantageous.[6]

The origin of the chemoselectivity of allylic amines is shown by the energies of the molecular orbitals involved. Quantum-chemical calculations (PM3 method) on allylamine **1** show that the nitrogen lone pair is the HOMO (–9.33 eV), with the carbon-carbon double bond being 1.10 eV (25 kcal/mol) lower in energy (Figure 1).[7]

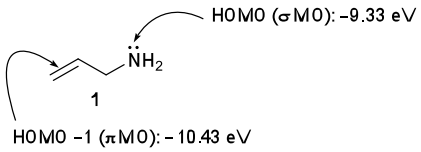
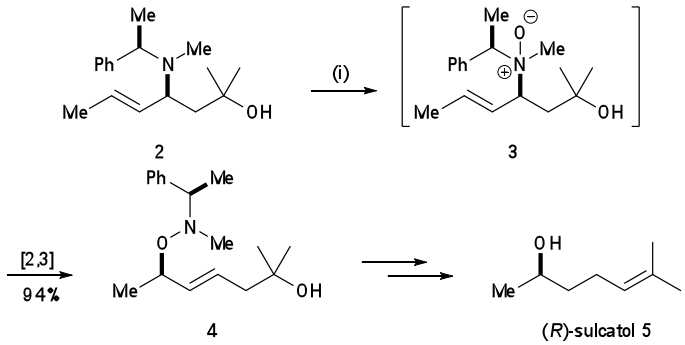


Figure 1: Calculated MO energy levels for allyl amine **1** (PM3 Method).

1.2 Epoxidation of allylic amines

Due to the importance of amino diols, both as naturally occurring motifs and as useful synthetic building blocks,[8,9] the epoxidation of allylic amines has been studied by several research groups and serves as a good case study for the chemoselective functionalisation of allylic amines.

It has been shown that under standard conditions for the epoxidation of olefins, allylic amines undergo *N*-oxidation rather than epoxidation. For example, Davies *et al.* have shown that reaction of allylic amine **2** with *m*CPBA results in formation of *N*-oxide **3** which then undergoes a rapid Meisenheimer [2,3] sigmatropic rearrangement to give **4** in 94% yield. This was then elaborated to the insect pheremone (*R*)-sulcatol **5** (Scheme 1).[10]



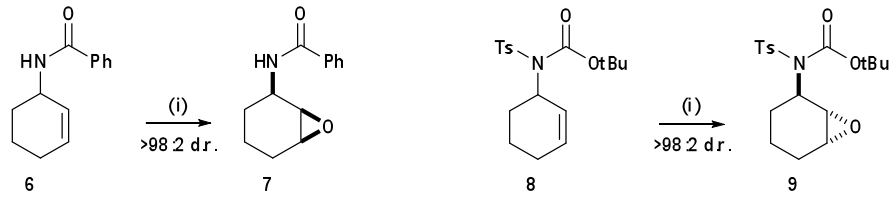
Scheme 1: *Reagents and conditions*; (i) *m*CPBA, $CHCl_3$.

There are two strategies which have been employed to overcome this undesired reaction pathway and facilitate olefin epoxidation: (i) the use of an electron-withdrawing protecting group, or (ii) temporary protection as a quaternary ammonium salt.

1.2.1 Electron-withdrawing *N*-protecting groups

A simple way to reverse the chemoselectivity is to make the nitrogen lone pair less nucleophilic than the olefin. This can be achieved through protection of the amine with an electron-withdrawing protecting group such as an amide, sulfonamide or carbamate, thereby lowering the energy of the lone pair through conjugation.

In a detailed study, O'Brien *et al*. have shown that mono-*N*-protected allylic amine **6** is chemo- and stereoselectively epoxidised by *m*CPBA to give the corresponding *syn*-epoxide **7**, whilst di-*N*-protected amine **8** gave the corresponding *anti*-epoxide **9** selectively. The rationale for the observed stereoselectivity is that for mono-*N*-protected allylic amines the epoxidation is hydrogen-bond directed in accordance with Henbest's model,[11] whilst di-*N*-protected allylic amines are incapable of hydrogen-bonding and are therefore epoxidised from the least hindered face (Scheme 2).[12,13]



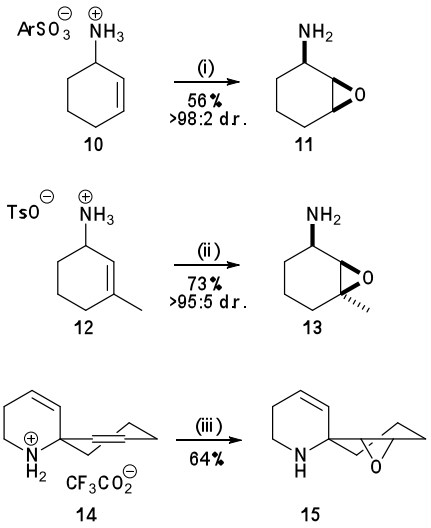
Scheme 2: *Reagents and conditions*; (i) 2 eq. *m*CPBA/$NaHCO_3$, CH_2Cl_2, RT, 19 hrs.

Whilst this protocol is very effective in allowing the chemo- and stereoselective epoxidation of allylic amines, the necessity for additional synthetic steps to introduce and remove the protecting group, often in the presence of other sensitive functionalities, is a significant drawback.

1.2.2 Temporary *N*-protection through protonation

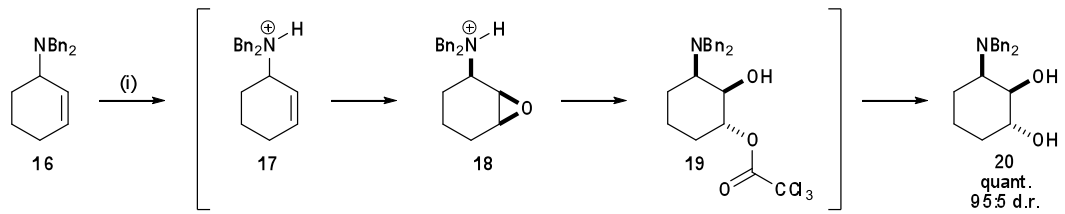
An alternative strategy for preventing *N*-oxidation during epoxidation involves the temporary protection of the nitrogen lone pair by formation of a quaternary ammonium salt. Asensio *et al*. have shown that **10** undergoes *syn*-directed epoxidation upon treatment with *m*CPBA.[14] Aggarwal *et al*. have also shown that

ammonium *p*-toluenesulfonate salt **12** is epoxidised by Oxone to give the *syn*-epoxide **13** in 73% yield.[15] Additionally, Harrity *et al*. have reported that **14** is epoxidised by *m*CPBA to give epoxide **15** in 64% yield as a single diastereoisomer (Scheme 3).[16]



Scheme 3: *Reagents and conditions*; (i) *m*CPBA, CH_2Cl_2, 0 °C, 2 hrs; (ii) 2 eq. Oxone, 10 eq. $NaHCO_3$, 0.5 eq. pyridine, MeCN/H_2O (95:5), –8 °C; (iii) 1.2 eq. *m*CPBA, CH_2Cl_2, 0 °C to RT, 18 hrs.

More recently, Davies *et al*. have reported a detailed study into the chemo- and diastereoselective epoxidation of allylic amine **16** through *in situ* protonation of the amine by trichloroacetic acid followed by ammonium-directed epoxidation with *m*CPBA. *In situ* epoxide ring-opening by the trichloroacetate counter-ion, followed by ester hydrolysis upon work up gives amino diol **20** in quantitative yield and 95:5 d.r. (Scheme 4).[17]



Scheme 4: *Reagents and conditions*; (i) 5 eq. Cl_3CCO_2H, 1.6 eq. *m*CPBA, CH_2Cl_2, RT, 21 hrs, then $NaHCO_3$ (0.1 M, aq.).

1.3 Cyclopropanes in nature

The cyclopropane motif is found in a wide range of natural products.[18] These range from very simple structures such 1-aminocyclopropanecarboxylic acid (AAC) **21**, a biosynthetic precursor of the plant hormone ethylene,[19] to polycyclopropanated structures such as the cholesteryl ester transfer protein inhibitor U-106305 **22**, isolated from the fermentation broth of *Streptomyces sp.* UC 11136 (Figure 2).[20]

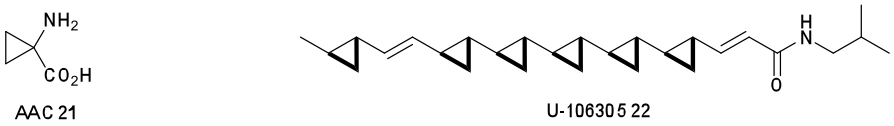


Figure 2: Representative natural products containing the cyclopropane motif.

In addition to being present in structures of wide-ranging complexity, the cyclopropane motif is also present in secondary metabolites from a variety of biosynthetic pathways. These include polyacetates (e.g. Dicytopterene B **23**), fatty acids (e.g. Lactobacillic acid **24**), amino acids (e.g. Coronamic acid **25**), polyether antibiotics (e.g. Ambruticin **26**), terpenoids (e.g. verrucosan-2β-ol **27**), steroids (e.g. Cycloartenol **28**) and alkaloids (e.g. Buxozine C **29**), (Figure 3).[21]

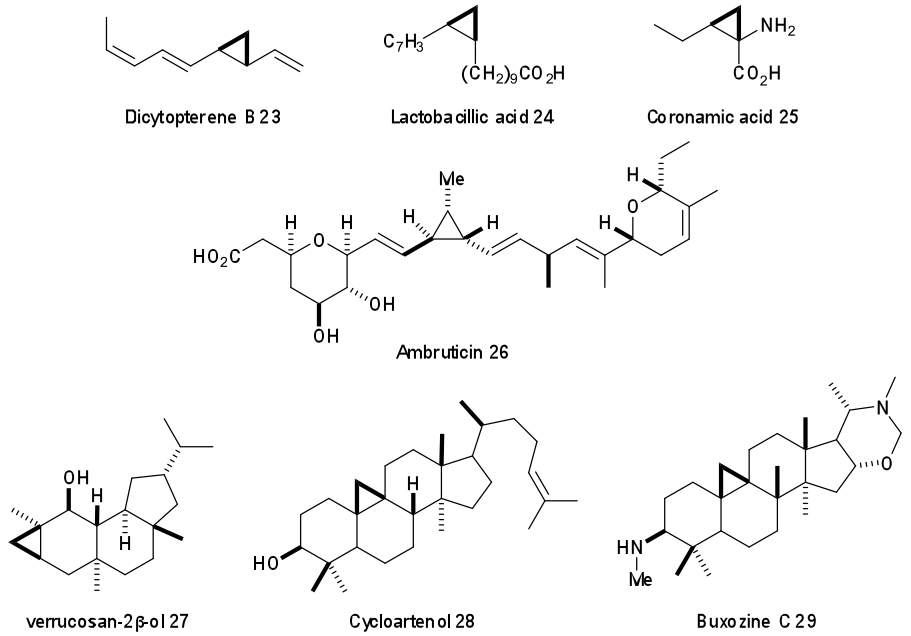


Figure 3: A selection of cyclopropane-containing natural products from differing biosynthetic pathways.

1.4 Biosynthesis of cyclopropanes

The most common mechanisms for cyclopropane formation in nature include cationic rearrangements of isoprenoids and *S*-adenosylmethionine (SAM) mediated cyclopropanation of unsaturated fatty acids but a wide range of alternative mechanisms such as photo-induced or transition-metal mediated radical cyclization, fragmentation of hydroperoxide intermediates and internal nucleophilic substitution (S_Ni) are also known.[21]

1.4.1 Cationic rearrangements

Cationic skeletal rearrangements have been implicated in the biosynthesis of a plethora of natural products and are the key step in one of the most important naturally occurring cyclopropanation reactions; the biosynthesis of presqualene pyrophosphate **31** from two molecules of farnesyl pyrophosphate **30**. This unusual head-to-head condensation of two isoprenoid fragments is the key step in the biosynthesis of squalene **32**, the common precursor of steroids and triterpenoids such as cholesterol **33** (Figure 4).[22]

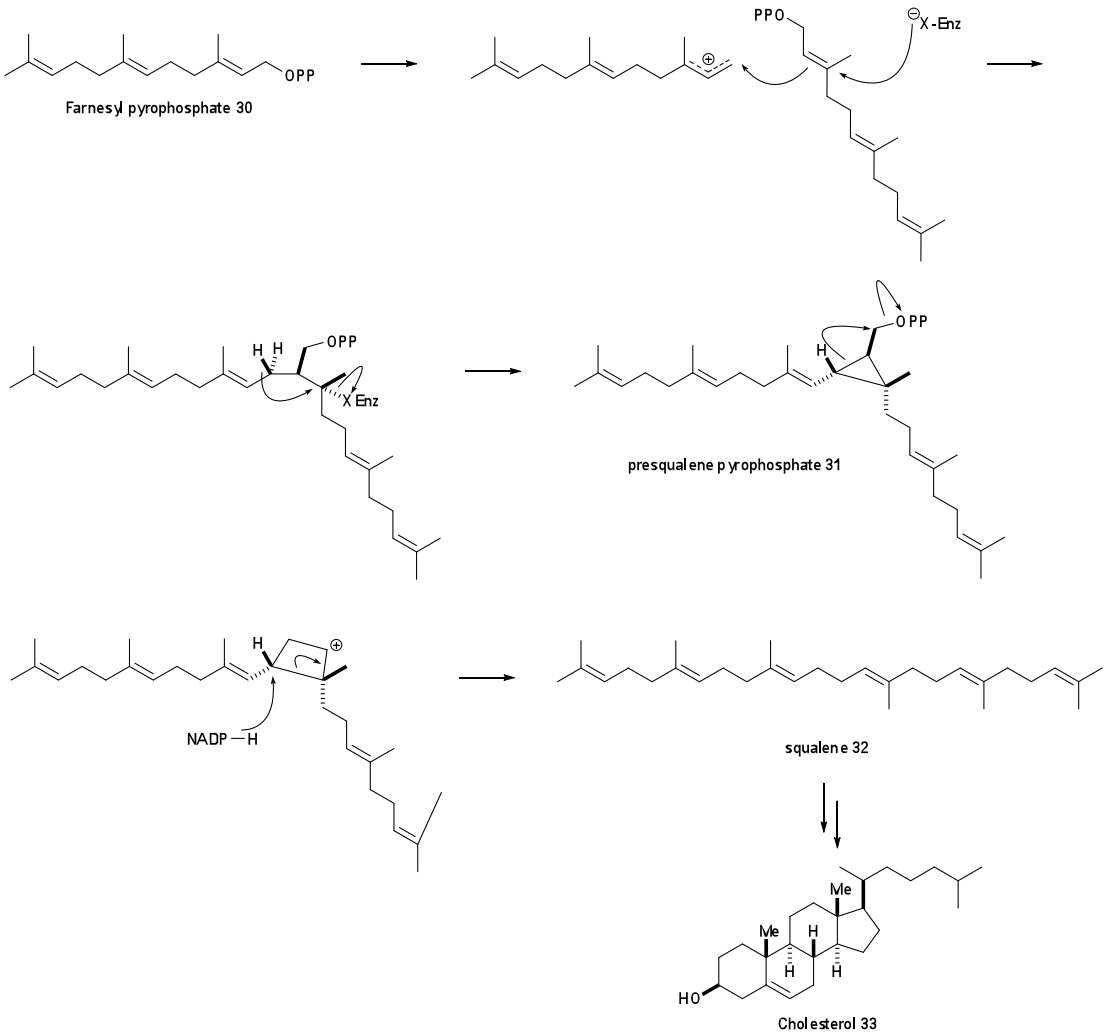


Figure 4: The biosynthesis of squalene **32** from farnesyl pyrophosphate **30** *via* presqualene pyrophosphate **31**.

1.4.2 Cyclopropanation mediated by *S*-adenosylmethionine (SAM) 34

S-Adenosylmethionine **34** is a co-enzyme involved in methyl group transfers and has been shown to be involved in a number of biosynthetic transformations including the cyclopropanation of olefins (Figure 5).

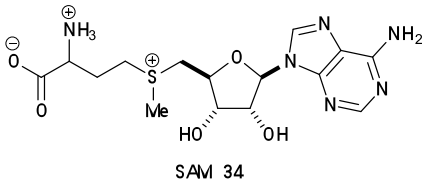


Figure 5: The structure of *S*-Adenosylmethionine **34**.

For example, the biosynthesis of gorgosterol **39** from brassicasterol **35** proceeds *via* initial attack of the C(22)-C(23) double bond by SAM **34** to give carbocation **36**.

Subsequent deprotonation affords dinosterol **37** which then undergoes a second methylation to generate carbocation **38**. Enzyme-mediated deproptonation and cyclopropane ring-closure gives gorgosterol **39** (Figure 6).[23]

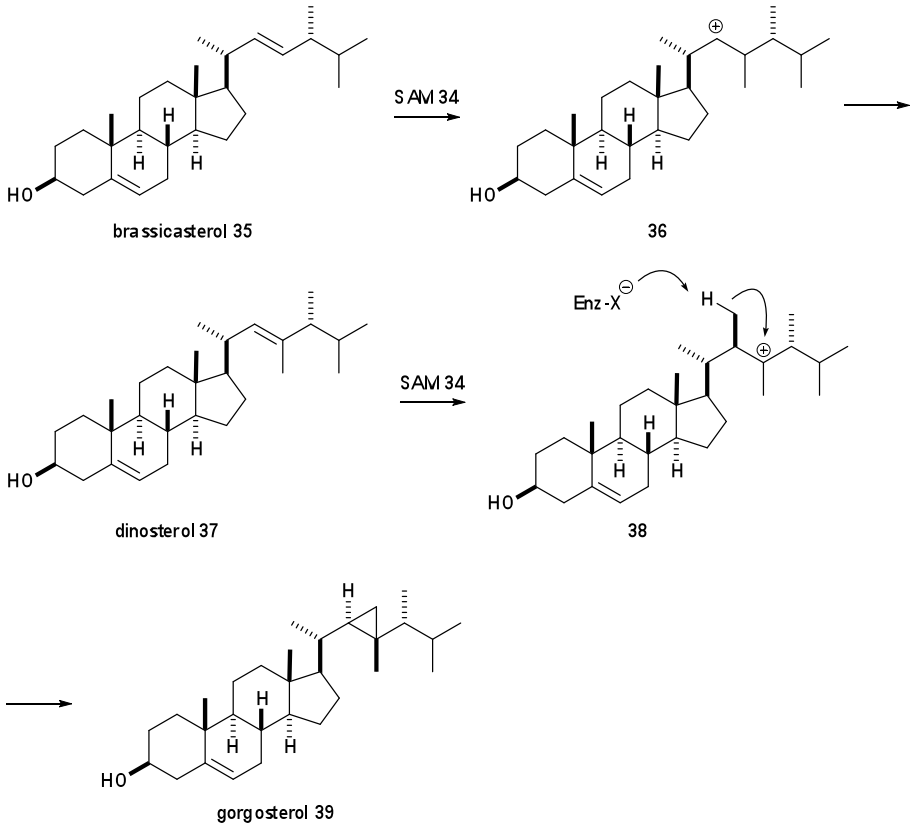


Figure 6: The SAM-mediated biosynthesis of gorgosterol **39** from brassicasterol **35**.

1.5 Stereoselective synthesis of cyclopropanes

Synthetic approaches to cyclopropanes differ markedly from the known biosynthetic pathways outlined above. The stereoselective synthesis of cyclopropanes has been dominated by three principal methods: (i) transition-metal catalysed decomposition of diazo compounds;[24] (ii) Michael-initiated ring closure (MIRC)[24] and; (iii) the cyclopropanation of olefins with halomethyl metal reagents.[25]

1.5.1 Cyclopropanes from the uncatalysed decomposition of diazo compounds

The cyclopropanation of olefins with diazo compounds can proceed *via* two distinct pathways: either decomposition of the diazo compound to form a carbene (or metal-

stabilised carbene complex) or alternatively *via* 1,3-dipolar cycloaddition to give an intermediate pyrazoline **40**, which then extrudes nitrogen to form the cyclopropane (Figure 7).

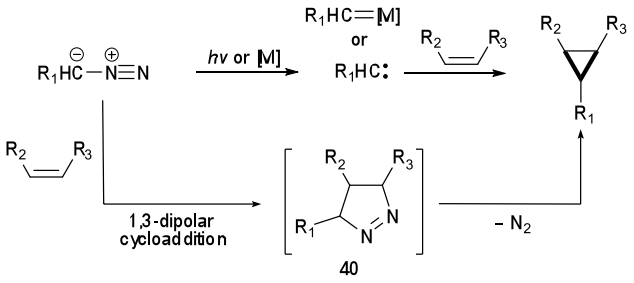
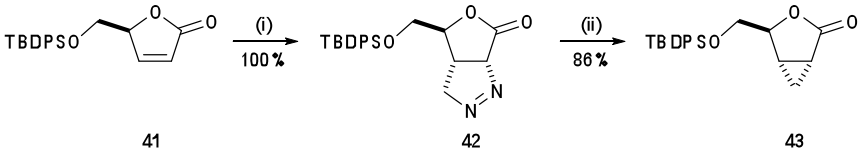


Figure 7: Pathways for the reaction of diazo compounds with alkenes.

Although the majority of research and development has focused on the former case, there are examples of high diastereoselectivity being observed *via* 1,3-dipolar cycloaddition. For example, Ortuño *et al*. have demonstrated that the 1,3-dipolar cycloaddition of diazomethane and lactone **41** proceeds *via* pyrazoline **42** to give cyclopropane **43** as a single diastereoisomer after photolytic extrusion of nitrogen (Scheme 5).[26]

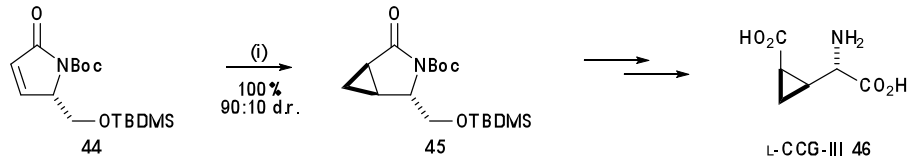


Scheme 5: *Reagents and conditions*; (i) CH_2N_2, Et_2O; (ii) *hv*, toluene, –40 °C.

1.5.2 Transition metal catalysed decomposition of diazo compounds

A wide range of transition metals have been shown to catalyse the decomposition of diazoalkanes to carbenes, and facilitate cyclopropane formation in the presence of an olefin. Copper and rhodium catalysts are the most commonly used for diazoacetates and diazoketones, however palladium catalysts are particularly effective for the decomposition of diazomethane. For example, Ofume *et al.* have shown that reaction of lactam **44** with diazomethane in the presence of palladium acetate gives cyclopropane **45** in quantitative yield and 90:10 d.r. (*anti*:*syn*). **45** was subsequently

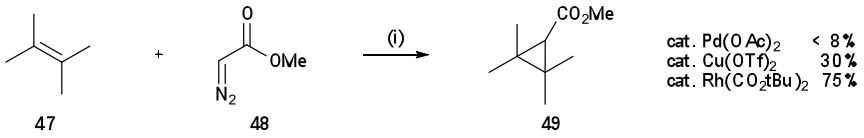
converted to L-CCG-III **46**, a conformationally restricted analogue of L-glutamic acid (Scheme 6).[27]



Scheme 6: *Reagents and conditions*; (i) CH_2N_2, 0.05 eq. $Pd(OAc)_2$, Et_2O, RT.

Although copper salts were first shown to catalyse the decomposition of diazoacetates,[28] in recent years rhodium complexes have become the catalysts of choice as they allow the cyclopropanation of olefins under relatively mild conditions, and the reactivity profile of the carbenoid can be easily altered by modifying the ligands.[29]

The use of rhodium catalysts was pioneered by Hubert *et al.* who, in 1976, reported the use of rhodium acetates as efficient catalysts for the cyclopropanation of olefins, and in particular for the cyclopropanation of more heavily substituted olefins which often give low yields with Cu or Pd catalysts. For example, the cyclopropanation of 2,3-dimethylbut-2-ene **47** with methyl diazoacetate **48** gave significantly higher yields of cyclopropane **49** when rhodium(II) *tert*-butylacetate was used as a catalyst compared to $Cu(OTf)_2$ or $Pd(OAc)_2$ (Scheme 7).[30]

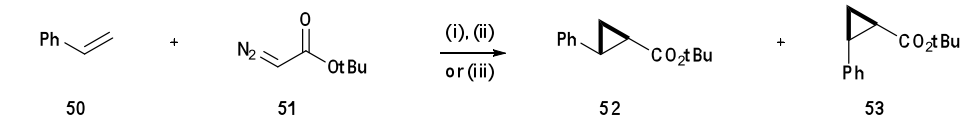


Scheme 7: *Reagents and conditions*; (i) 5.0 eq. **47**, 1.0 eq. **48**, *catalyst*, RT, 10 hrs.

1.5.3 Enantioselective cyclopropanation of olefins by diazo compounds

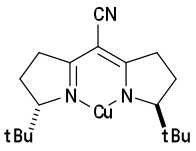
If chiral ligands are used in the reaction, very high enantioselectivities can be observed.[29b, 31] Copper catalysts are generally better for the synthesis of *trans*-cyclopropanes, though excellent results have been achieved with ruthenium catalysts. For example, the semicorrin type copper complex **54**, developed by Pfaltz *et al.*,[32] and

the bisoxazoline ruthenium complex **55**, developed by Nishiyama *et al*.[33,34] both give good diastereoselectivities and excellent enantioselectivities for the reaction of styrene **50** and *tert*-butyl diazoacetate **51** to give *trans*-**52** as the major product. An interesting variation is the use of cobalt catalyst **56**, developed by Katsuki *et al*.,[35] which gives excellent diastereoselectivities and enantioselectivities for the formation of the *cis*-cyclopropane. For example, reaction of styrene **50** and *tert*-butyl diazoacetate **51** with catalyst **56** gives *cis*-**53** in 89% yield and 98% e.e. (Scheme 8).



50 51 52 53

Catalyst	d.r.	e.e. (%) **52**	e.e. (%) **53**
54	84:16	93	92
55	97:3	94	87
56	2:98	-	98



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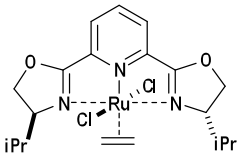
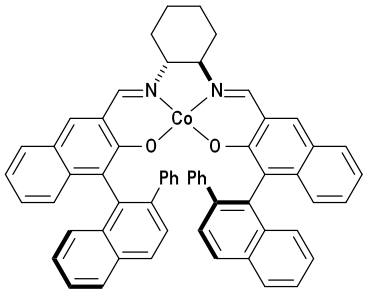


55



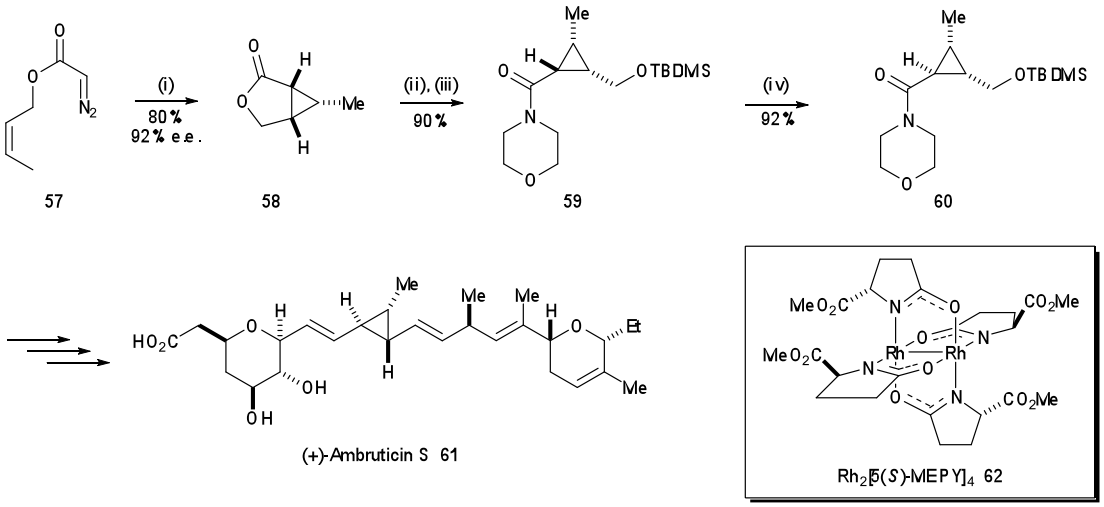
56

Scheme 8: *Reagents and conditions*; (i) 1 mol % **54**, $ClCH_2CH_2Cl$, RT (ii) 1.0 eq. **51**, 5.0 eq. **50**, 1 mol % **55**, CH_2Cl_2, RT, 12-16 hrs; (iii) 1.0 eq. **51**, 5.0 eq. **50**, 5 mol % **56**, 10 mol % *N*-methylimidazole, THF, RT, 24 hrs.

1.5.4 The total synthesis of (+)-Ambruticin S 61

Martin *et al*. have reported the use of an intramolecular asymmetric cyclopropanation as a key step in the total synthesis of (+)-ambruticin S **61**, a novel antifungal antibiotic isolated from fermentation extracts of *polyangium cellulosum var.* Synthesis of the cyclopropane fragment was achieved through the intramolecular cyclopropanation of allylic diazoacetate **57**, mediated by the chiral rhodium complex Rh_2[5(*S*)-MEPY]$_4$ **62**, to give cyclopropyl lactone **58** in 80% yield and 92% e.e. Ring-opening with morpholine and $AlMe_3$ followed by epimerisation α to the amide provided

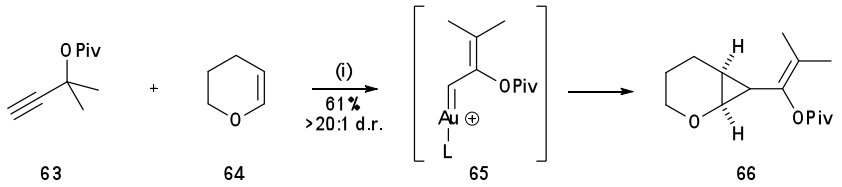
intermediate **60** which was subsequently transformed to (+)-ambruticin S **61** (Scheme 9).[36]



Scheme 9: *Reagents and conditions*; (i) 1 mol% $Rh_2[5(S)\text{-MEPY}]_4$ **62**, CH_2Cl_2; (ii) morpholine, $AlMe_3$, CH_2Cl_2; (iii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (iv) NaHMDS, THF, 0 °C.

1.6.1 Alternative carbenoid sources

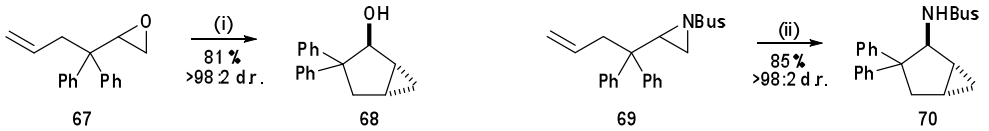
More recently, Toste *et al*. have pioneered the use of Au-carbene complexes in synthesis and these have been shown to be capable of affecting the efficient cyclopropanation of an olefin. For example, treatment of propargyl pivaloate **63** with PPh_3AuCl is thought to lead to formation of Au-carbene **65** which, in the presence of dihydro-pyran **64**, forms cyclopropane **66** in 61% yield and in >20:1 diastereoselectivity (Scheme 10).[37]



Scheme 10: *Reagents and conditions*; (i) 1.0 eq. **64**, 4.0 eq. **63**, 0.05 eq. PPh_3AuCl, 0.05 eq. $AgSbF_6$, $MeNO_2$, RT.

1.6.2 Cyclopropanation of α-lithiated terminal epoxides and aziridines

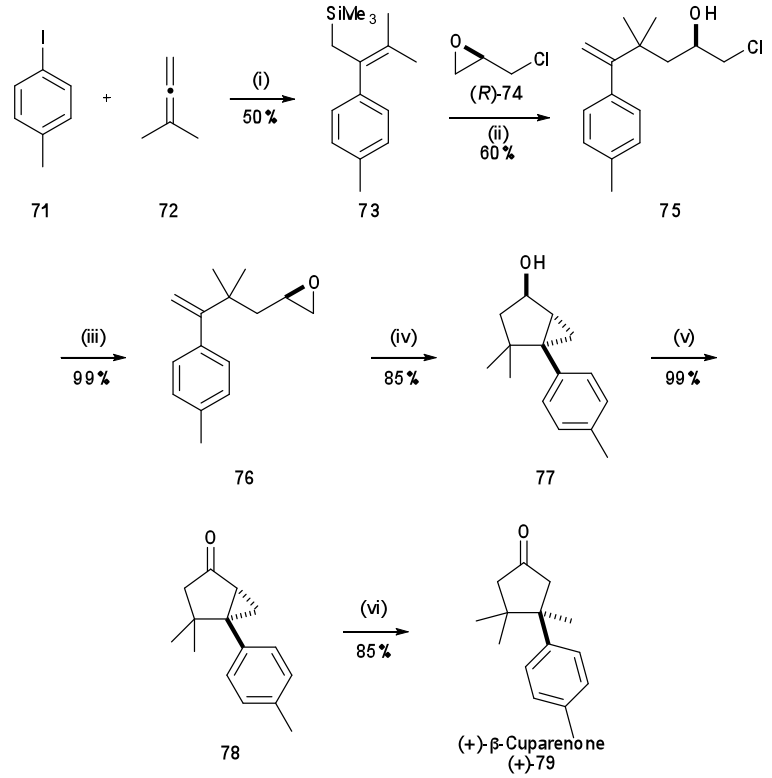
An alternative method for the synthesis of cyclopropanes has been developed by Hodgson *et al*. who have utilised α-lithiated terminal epoxides and aziridines as carbene equivalents.[38] For example, treatment of epoxide **67** with 2 equivalents of LTMP in ^{t}BuOMe at 0 °C results in formation of bicyclo[3.1.0]hexan-2-ol **68** in 81% yield after 16 hrs.[39] Similarly, treatment of *N*-Bus aziridine **69** with 3 equivalents of $LiNCy_2$ in ^{t}BuOMe at 0 °C results in formation of 2-amino bicyclo[3.1.0]hexane **70** in 85% yield after 2 hrs (Scheme 11).[40]



67 68 69 70

Scheme 11: *Reagents and conditions*; (i) 2 eq. LTMP, ^{t}BuOMe, 0 °C to RT, 16 hrs; (ii) 3 eq. $LiNCy_2$, ^{t}BuOMe, 0 °C, 2 hrs.

This methodology was applied to the total synthesis of (+)-β-Cuparenone (+)-**79** in 6 steps. The synthesis began with Pd catalysed 3-component coupling of 4-iodotoluene **71**, allene **72** and $Me_3SiSnBu_3$ to give allyl silane **73** in 50% yield. Regioselective alkylation of the allyl silane **73** with epichlorohydrin (*R*)-**74** gave chlorohydrin **75** in 60 % yield which then underwent epoxide ring closure in basic methanol to afford the desired epoxide **76** in 99% yield. Treatment of epoxide **76** with LTMP resulted in intramolecular cyclopropanation to give bicyclo[3.1.0]hexan-2-ol **77** in 85% yield. Subsequent oxidation with TPAP/NMO and reductive ring-opening of the cyclopropane with $Li/NH_3/^{t}$BuOH gave (+)-β-Cuparenone (+)-**79** in 84% yield over two steps (Scheme 12).[41]



Scheme 12: *Reagents and conditions*; (i) cat. $Pd(dba)_2$, $Me_3SiSnBu_3$, toluene, 80 °C, 7 hrs; (ii) (*R*)-**74**, $TiCl_4$, CH_2Cl_2, −78 °C, 30 min; (iii) NaOH, MeOH, 0 °C to RT, 1 hr; (iv) 0.5 eq. TMP, 2.0 eq, *n*-BuLi, ^{t}BuOMe, −2 °C, 4.5 hrs; (v) cat. TPAP, NMO, CH_2Cl_2, RT, 2 hrs; (vi) Li, NH_3, ^{t}BuOH, Et_2O, −78 °C, 15 min.

1.7 Michael-Initiated Ring Closure (MIRC)

A conceptually different strategy for the synthesis of cyclopropanes is through Michael-Initiated Ring Closure (MIRC). Mechanistically, this usually involves the Michael addition of a nucleophile which has a leaving group attached, such that the resultant enolate **81** can cyclise to give the desired cyclopropane **82** (Figure 8).

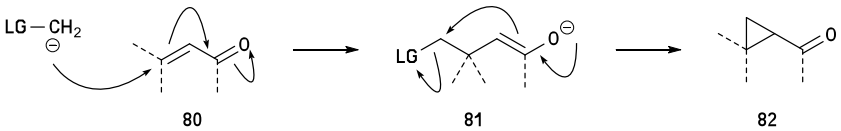
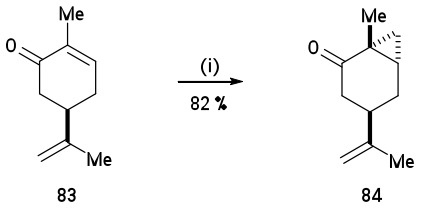


Figure 8: General mechanism for cyclopropanation through MIRC.

1.7.1 Corey-Chaykovsky reaction

This field of MIRC was largely pioneered by Corey *et al*. who developed the use of trimethyl sulfoxonium ylides for the generation of cyclopropanes. For example, the

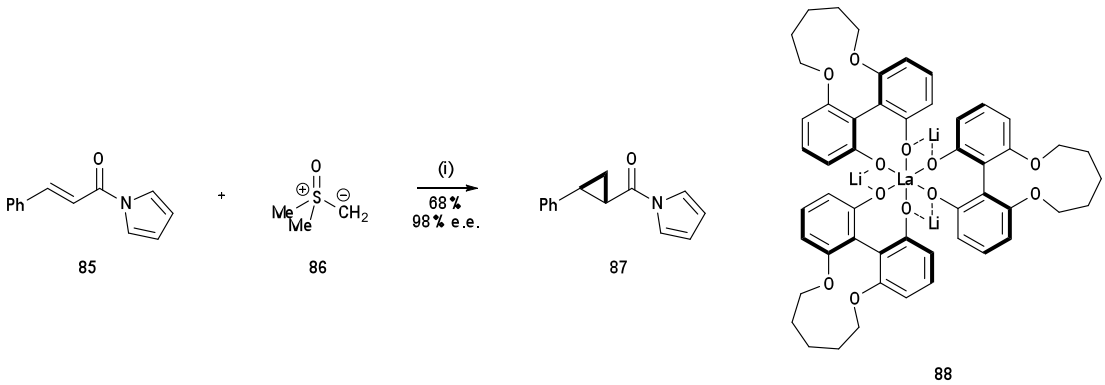
reaction of (*R*)-carvone (*R*)-**83** with trimethylsulfoxonium iodide and NaH in DMSO gives cyclopropane **84** in 82% yield as a single diastereoisomer (Scheme 13).[42]



83 84

Scheme 13: *Reagents and conditions*; (i) 1.05 eq. Me_3SOI, 1.05 eq. NaH, DMSO, RT to 50 °C.

Many asymmetric versions of this reaction have been developed through the use of removable chiral auxiliaries on either the substrate or reagent,[43] however a more elegant approach has recently been developed by Shibasaki *et al*. who showed that the addition of trimethylsulfoxonium ylide **86** to amide **85** in the presence of bifunctional catalyst **88** and NaI gives cyclopropane **87** in 98% e.e. and 68% yield (Scheme 14).[44]



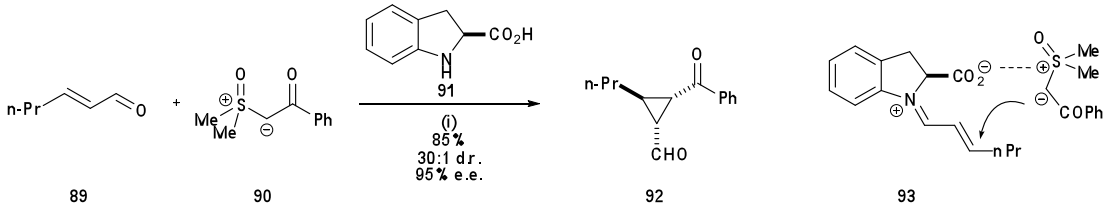
85 86 87 88

Scheme 14: *Reagents and conditions*; (i) 1.0 eq. **86**, 0.05 eq. **88**, 0.05 eq. NaI, THF/toluene (4/5), 4 Å MS, −55 °C, 18 hrs.

1.7.2 MacMillan cyclopropanation

An organocatalytic variant of the Corey-Chaykovsky reaction has also been developed by MacMillan *et al*. who showed that, for example, the addition of sulfoxonium ylide **90** to hexenal **89** in the presence of dihydroindole catalyst **91** proceeds to give cyclopropane **92** in 85% yield, 30:1 d.r. and 95% e.e. It is thought that addition of the ylide **90** to the intermediate iminium **93** is directed by electrostatic

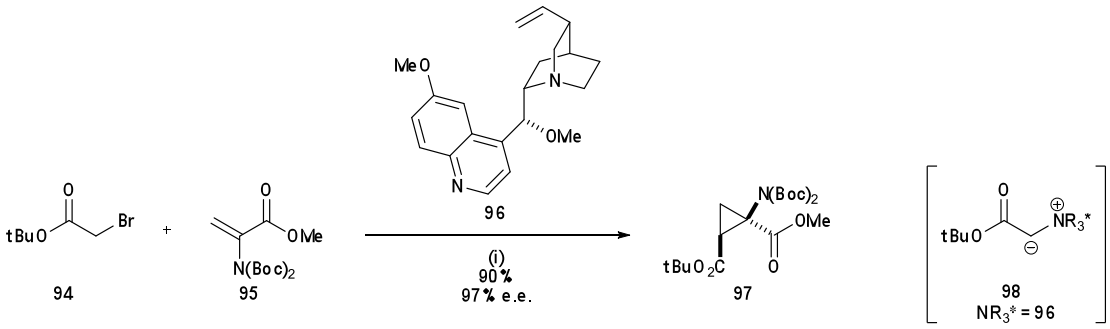
interactions between the carboxylate group of the catalyst and the thionium group of the ylide (Scheme 15).[45,46]



Scheme 15: *Reagents and conditions*; (i) 1.0 eq. **89**, 4.0 eq. **92**, 0.20 eq. **91**, $CHCl_3$, −10 °C, 24-48 hrs.

1.7.3 Gaunt Cyclopropanation

In addition to sulfoxonium ylides, it has been shown by Gaunt *et al*. that *in situ* generated ammonium ylides are effective reagents for enantioselective MIRC. For example, reaction of *tert*-butyl bromoacetate **94** with cinchona alkaloid catalyst **96** and a mild base generates a chiral ammonium ylide **98** which then undergoes MIRC with α,β-unsaturated ester **95** to give conformationally-restricted aspartic acid analogue **97** in 90% yield and 97% e.e. (Scheme 16).[47]

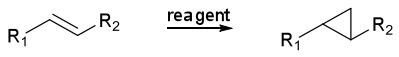


Scheme 16: *Reagents and conditions*; (i) 1.0 eq. **94**, 1.2 eq. **95**, 0.20 eq. **96**, 1.2 eq. Cs_2CO_3, MeCN, 80°C, 24 hrs.

1.8.1 Cyclopropanation by halomethyl metal reagents (Zn, Sm, Al, Cr)

Although Emschwiller was the first to show, in 1929, that the reaction of diiodomethane with zinc generates iodomethylzinc iodide ($IZnCH_2I$),[48] it wasn't until 1958 that Simmons and Smith first showed that this reagent was capable of the stereospecific cyclopropanation of olefins.[49]

In 1964, Wittig showed that the corresponding bis(iodomethyl)zinc reagent, $Zn(CH_2I)_2$,[50] could be prepared by treating zinc iodide with 2 equivalents of diazomethane, however a breakthrough in the synthetic utility of this reagent came in 1966 when Furukawa *et al*. showed that the same reactive species could be formed by the reaction of diethylzinc and diiodomethane.[51] In 1991, Denmark *et al*. showed that the corresponding bis(chloromethyl)zinc reagent, $Zn(CH_2Cl)$ could also be formed from diethylzinc and chloroiodomethane, and that this reagent is generally more reactive and often gives higher yields of the desired cyclopropane, particularly with less reactive olefins.[52] More recently, Charette *et al*. have shown that iodomethyl zinc aryloxides are very effective cyclopropanating reagents,[53] although the most reactive zinc carbenoids to date are the iodomethylzinc acetates developed by Shi *et al*., and in particular $CF_3CO_2ZnCH_2I$, which is easily formed from trifluoroacetic acid, diethylzinc and diiodomethane (Table 1).[54]



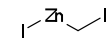
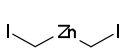
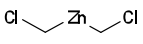
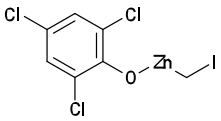
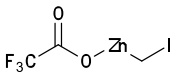
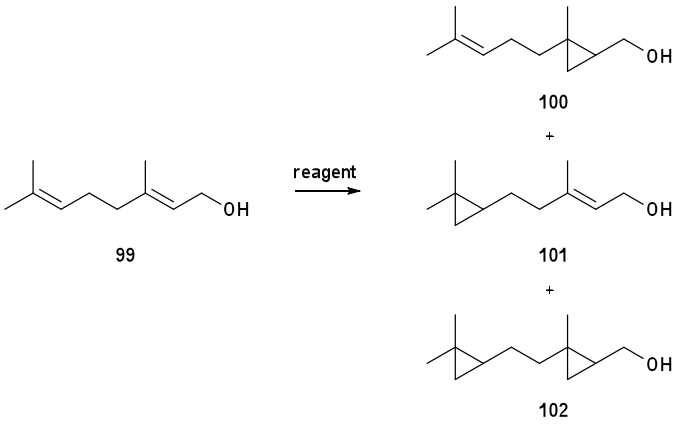
Reagent	Reactants	Authors
	Zn/Cu, CH_2I_2	Simmons, Smith[49]
	ZnI_2, CH_2N_2 $ZnEt_2$, CH_2I_2	Wittig[50] Furukawa[51]
	$ZnEt_2$, CH_2Cl_2	Denmark[52]
	2,4,6-$Cl_3C_6H_2OH$, $ZnEt_2$, CH_2I_2	Charette[53]
	CF_3CO_2H, $ZnEt_2$, CH_2I_2	Shi[54]

Table 1: A summary of halomethylzinc reagents.

In addition to these zinc carbenoids, similar reagents have been formed with samarium and aluminium. Molander *et al*. first showed that the reaction of activated Sm with diiodomethane generates iodomethylsamarium iodide,[55] whilst Yamamoto *et*

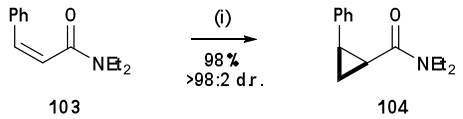
al. have developed the use of the aluminium carbenoid, iBu$_2$AlCH$_2$I, which is generated by reacting tri-isobutylaluminium with diiodomethane.[56] One main synthetic utility of the aluminium carbenoid iBu$_2$AlCH$_2$I comes from its antipodal chemoselectivity in the cyclopropanation of geraniol **99** when compared to the analogous reactions employing Zn and Sm carbenoids (Figure 9).



Reagents	**100** : **101** : **102**
Et_2Zn, CH_2I_2	74 : 2 : 3
Sm(Hg), ICH_2Cl	98 : 0 : 0
i-Bu_3Al, CH_2I_2	1 : 76 : 4

Figure 9: Chemoselectivity in the cyclopropanation of geraniol **99** by common halomethylmetal reagents.

More recently, Concellón *et al*. have reported the use of chloromethylchromium(III) chloride for the cyclopropanation of α,β-unsaturated amides. For example, reaction of cinnamide **103** with $CrCl_2$ and $ClCH_2I$ gives cyclopropylcarboxamide **104** in 98% yield as a single diastereoisomer (Scheme 17).[57]

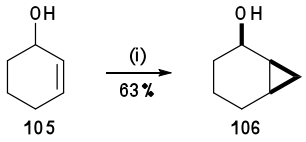


Scheme 17: *Reagents and conditions*; (i) 4.0 eq. $CrCl_2$, 3.75 eq. $ClCH_2I$, THF, reflux, 18 hrs.

1.8.2 Substrate directed cyclopropanation

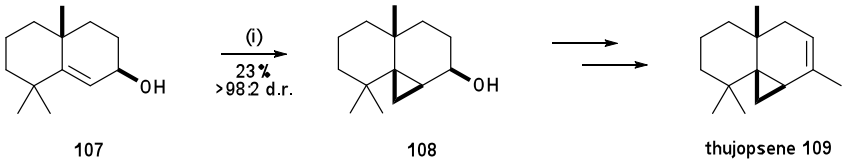
The synthetic utility of the Simmons-Smith cyclopropanation was greatly enhanced by Winstein *et al*.[58] and Dauben *et al*.[59] who independently observed that the cyclopropanation of cyclic allylic alcohols proceeds with excellent *syn*-selectivity. For example, Dauben *et al*. showed that cyclopropanation of 2-cyclohexen-1-ol **105** with

Zn/Cu couple and diiodomethane led to exclusive formation of *syn*-**106** in 63% yield (Scheme 18).



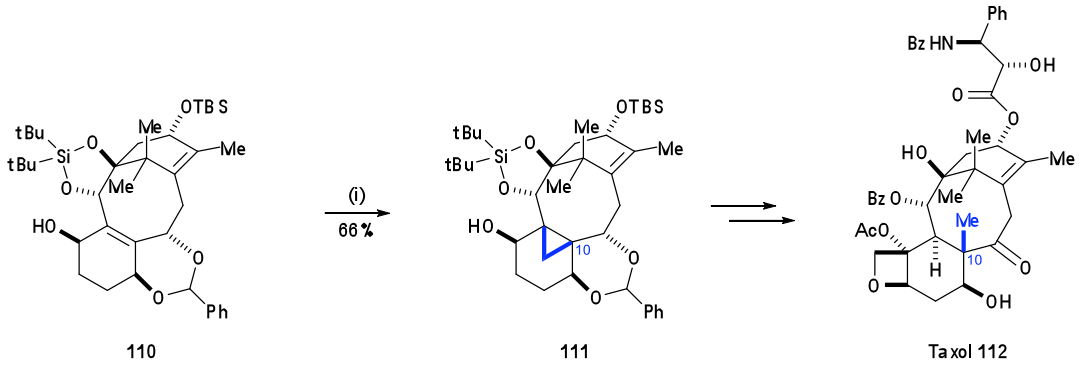
Scheme 18: *Reagents and conditions*; (i) 2.15 eq. CH_2I_2, 2.75 eq. Zn/Cu, Et_2O, reflux, 1 hr.

Morever, Dauben was quick to utilise this reaction in synthesis as exemplified by his synthesis of thujopsene **109**, which involves the cyclopropanation of allylic alcohol **107** to give *syn*-**108** in 23% yield as a single diastereoisomer as the key step (Scheme 19).[60]



Scheme 19: *Reagents and conditions*; (i) 2.4 eq. Zn/Cu, 2.2 eq. CH_2I_2, Et_2O/DME, reflux, 70 hrs.

The directed cyclopropanation of allylic alcohols has since been widely used in synthesis,[61,62] often as a means of installing quaternary stereocenters, as in the total synthesis of Taxol **112** by Kuwajima *et al*. Cyclopropanation of intermediate allylic alcohol **110** under Denmark's conditions[52] gives cyclopropane **111** in 66% yield as a single diastereoisomer. Ring-opening of the cyclopropane in a later step affords the C-10 quaternary stereocenter (Scheme 20).[63]



Scheme 20: *Reagents and conditions*; (i) 5.0 eq. $ZnEt_2$, 10.0 eq. $ClCH_2I$, toluene, 0 °C, 25 mins.

1.8.3 Mechanism of the alcohol-directed Simmons-Smith reaction

The mechanism of the Simmons-Smith reaction has been the subject of debate for a variety of reasons. The first point of contention has been whether the reaction proceeds *via* a methylene transfer or carbometallation pathway (Figure 10).

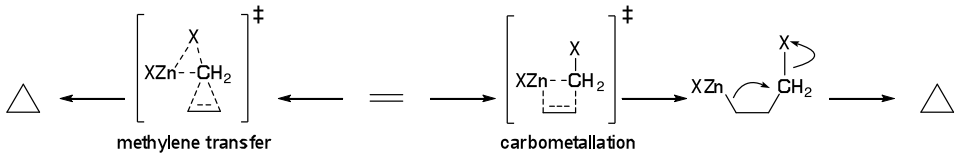


Figure 10: Methylene transfer *versus* carbometallation pathways in the Simmons-Smith reaction.

Although experimental evidence for a carbometallation pathway has been reported for the reaction of lithium carbenoids,[64] experimental evidence for the Simmons-Smith reaction has generally supported a methylene transfer mechanism.[50] In addition, a recent theoretical study by Nakamura *et al*. strongly supports a methylene transfer mechanism, with transition state **114** being 13.4 kcal mol^{-1} lower in energy than transition state **113** for the cyclopropanation of ethylene with (chloromethyl)zinc chloride (Figure 11).[65]

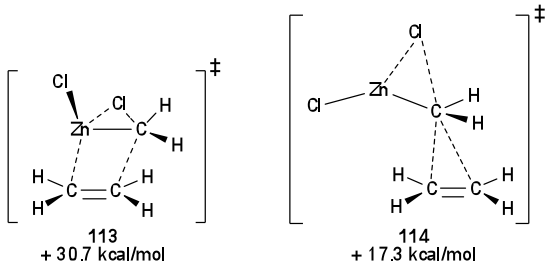


Figure 11: Calculated transitions state energies (relative to the starting materials) for the cyclopropanation of ethylene with (chloromethyl)zinc chloride (B3LYP/631A level).

The second point of contention concerns the formation of zinc alkoxide intermediates in the alcohol-directed Simmons-Smith reaction. In 1964, Simmons postulated that the reaction involves the formation of an intermediate zinc alkoxide species, since in the cyclopropanation of allylic alcohol **115**, approximately 1 molar equivalent of iodomethane was generated.[66] It was proposed that the intermediate zinc alkoxide **116**

could be formed by the deprotonation of alcohol **115** by bis(iodomethyl)zinc, generated *via* a Schlenk equilibrium from iodomethylzinc iodide. Intramolecular cyclopropanation would then afford the desired *syn*-cyclopropane **118** after hydrolysis (Figure 12).[67]

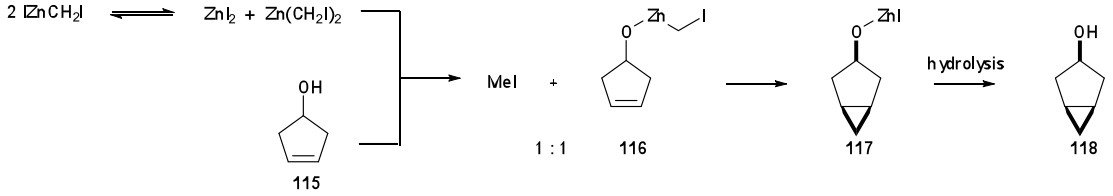
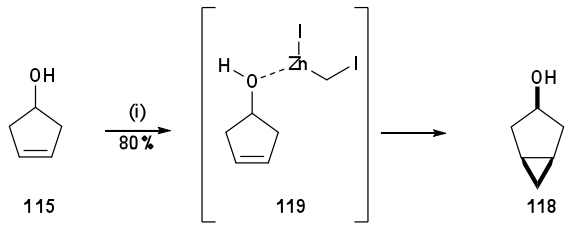


Figure 12: The formation of zinc alkoxide **116** as proposed by Simmons *et al*.

In contrast however, Dauben reported that the cyclopropanation of 2-cyclopenten-1-ol **115** with an equimolar amount of (iodomethyl)zinc iodide gave the desired product in 80% yield, suggesting that a zinc alkoxide intermediate was not formed. Instead, Dauben proposed that a dative complex **119** was formed rather than a covalent bond (Scheme 21).[68]



Scheme 21: *Reagents and conditions*; (i) 1.0 eq. $IZnCH_2I$, Et_2O, reflux, 1 hr.

The formation of a dative complex is certainly a possibility, and has been proposed to account for the observed *syn*-selectivity in the cyclopropanation of allylic ethers and esters.[69] However, more recent studies by Charette *et al.* appear to show that the formation of a zinc alkoxide intermediate depends upon the carbenoid used. An *in situ* NMR study showed that reaction of cinnamyl alcohol **120** with the Simmons-Smith reagent, $IZnCH_2I$ (1 eq., −20 °C, CD_2Cl_2), resulted in the formation of approximately 60% cyclopropane **121** and approximately 40% MeI. This suggests that for the Simmons-Smith reagent, which was used in the previous studies by Simmons *et al.*

and Dauben *et al.*, the cyclopropanation need not proceed *via* a zinc alkoxide intermediate but that the two pathways are competitive (Figure 13).

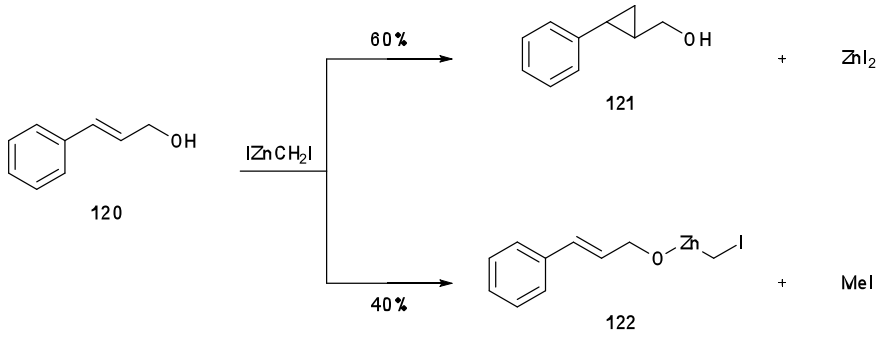


Figure 13: Competing pathways in the reaction of cinnamyl alcohol **120** with $IZnCH_2I$.

In contrast, Charette *et al*. showed that reaction of cinnamyl alcohol with the Wittig-Furukawa reagent, $Zn(CH_2I)_2$ (1 eq., −20 °C, CD_2Cl_2), resulted in quantitative formation of MeI and intermediate zinc alkoxide **122** (Figure 14).[70]

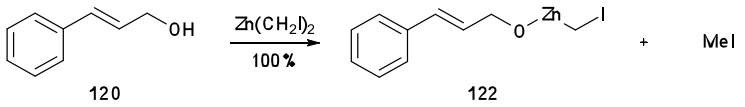


Figure 14: The reaction of $Zn(CH_2I)_2$ with cinnamyl alcohol to form zinc alkoxide **122**, as observed by ^1H NMR.

Interestingly, this study also found that the monomeric iodomethylzinc alkoxides do not readily undergo cyclopropanation at low temperature but that the addition of a Lewis acid greatly increases the rate of cyclopropanation. This has been corroborated by theoretical investigations by Nakamura *et al*. who have shown that the activation energy for cyclopropanation of ethylene is greatly reduced when complexed to $ZnCl_2$ (Figure 15).[65]

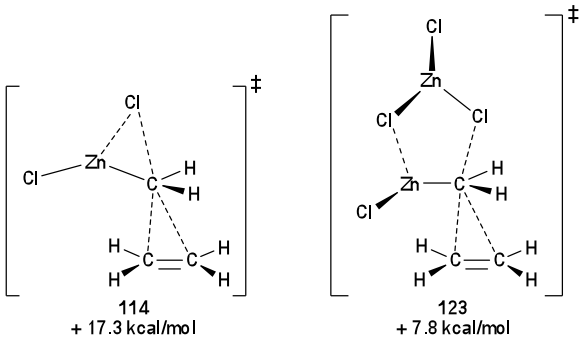
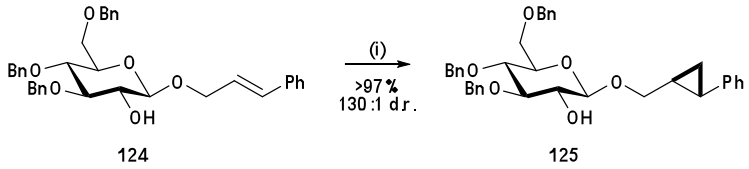


Figure 15: Calculated transition state energies (relative to the starting materials) for the cyclopropanation of ethylene with $ClZnCH_2Cl$ in the absence (**114**) and presence (**123**) of the Lewis acid $ZnCl_2$ (B3LYP/631A level).

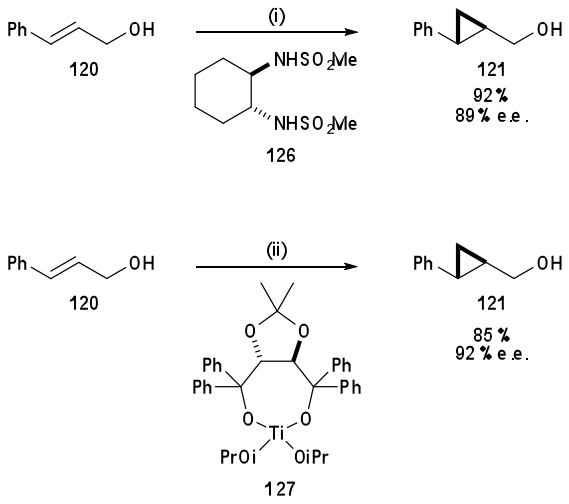
1.8.4 Enantioselective Simmons-Smith cyclopropanation

A wide range of enantioselective Simmons-Smith reactions have been reported based on the use of chiral auxiliaries, ligands, Lewis acids and stoichiometric additives.[24] For example, Charette *et al.* have shown that carbohydrate-derived chiral auxiliaries can impart excellent asymmetric induction on the cyclopropanation of allylic alcohols (Scheme 22).[71]



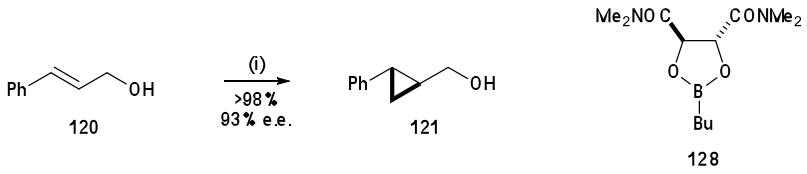
Scheme 22: *Reagents and conditions*; (i) 10 eq. $ZnEt_2$, 10 eq. CH_2I_2, toluene, –35 °C → 0 °C.

The development of catalytic asymmetric Simmons-Smith reactions has proven to be an extremely challenging area of research, primarily because it is difficult to ensure that the rate of the asymmetric reaction is significantly higher than the rate of the uncatalysed background reaction.[72] The best examples to date have been reported by Denmark *et al.* who showed that the chiral bismethanesulfonamide ligand **126** could be used in substoichiometric quantities for the cyclopropantion of allylic alcohols,[73] and by Charette *et al.* who reported the use of titanium TADDOL complex **127** for the same reaction (Scheme 23).[74]



Scheme 23: *Reagents and conditions*; (i) 1.1 eq. $ZnEt_2$, 0.1 eq. **126**, CH_2Cl_2, 0 °C; then 1.0 eq. $ZnEt_2$, 2.0 eq. I_2; then 1.0 eq. $Zn(CH_2I)_2$; (ii) 1.0 eq. $Zn(CH_2I)_2$, 0.25 eq. **127**, 4 Å MS, CH_2Cl_2, 0 °C, 1.5 hrs.

However, probably the most successful and widely used method for the asymmetric cyclopropanation of allylic alcohols is the chiral dioxaborolane-mediated asymmetric cyclopropanation developed by Charette *et al*. The authors showed that the chiral dioxaborolane ligand **128**, which is derived from tartaric acid, is extremely effective in mediating the enantioselective cyclopropanation of a wide range of allylic alcohols. For example, reaction of cinnamyl alcohol **120** with $Zn(CH_2I)_2$ in the presence of 1 equivalent of dioxaborolane ligand **128** gives cyclopropane **121** in >98% yield and 93% e.e. (Scheme 24).[75]

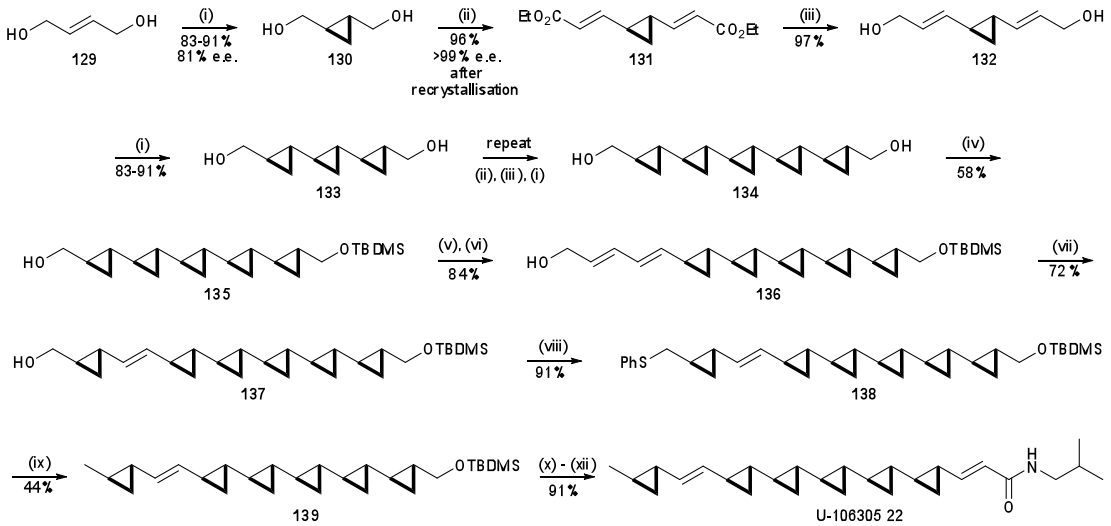


Scheme 24: *Reagents and conditions*; (i) 1.0 eq. **128**, 2.0 eq. $Zn(CH_2I)_2$, CH_2Cl_2, 0 °C to RT, 2 hrs.

1.8.5 The total synthesis of U-106305 22

Charette's dioxaborolane method was elegantly used in the first total synthesis of the cholesteryl ester transferase inhibitor U-106305 **22** by Barrett *et al*.[76] The synthesis began with cyclopropanation of (*E*)-2-butene-1,4-diol **129** in the presence of (*ent*)-**128** to give cyclopropane **130** in 83-91% yield and 81% e.e. The synthesis then proceeded

in a bi-directional fashion, with Dess-Martin oxidation followed by Wittig-olefination giving di-ester **131** in 96% yield as a single enantiomer after recrystallization. DIBAL-H reduction afforded bis(allylic alcohol) **132** in 96-97% yield which then underwent Charette cyclopropanation with (*ent*)-**128** to give tris-cyclopropane **133**. Iterative repetition of these three steps afforded pentacyclopropane **134** in excellent yield. Desymmetrisation by mono-TBDMS protection afforded **135** in 58% yield. Dess-Martin oxidation, Horner-Wadsworth-Emmons homologation and DIBAL-H reduction gave dienol **136** in 84% yield. Charette cyclopropanation of **136** at low temperature afforded hexacyclopropane **137** in 72% yield, with only minimal cyclopropanation of the bishomoallylic double bond. Deoxygenation of the free alcohol was achieved by conversion to phenylsulfide **138** followed by Raney nickel mediated desulfurization to give **139**. The total synthesis of U-106305 **22** was then completed in 91% by silyl-deprotection with TBAF, Dess-Martin oxidation and Wittig-olefination (Scheme 25).



Scheme 25: *Reagents and conditions*; (i) (*ent*)-**128**, $Zn(CH_2I)_2$·DME, CH_2Cl_2, −40 °C to −25 °C; (ii) Dess-Martin periodinane, pyridine, CH_2Cl_2 or DMSO, RT; then PPh_3, 10 °C, then $Ph_3P{=}CHCO_2Et$; (iii) DIBAL-H, CH_2Cl_2, hexane, −78 °C; (iv) TBDMSCl, imidazole, CH_2Cl_2, RT; (v) Dess-Martin periodinane, pyridine, DMSO, RT; then PPh_3, RT; then (*E*)-$(MeO)_2P(O)CH_2CH{=}CHCO_2Me$, NaH, DBU, RT; (vi) DIBAL-H, CH_2Cl_2, hexane, −78 °C; (vii) (*ent*)-**128**, $Zn(CH_2I)_2$·DME, CH_2Cl_2, −50 °C to −25 °C; (viii) *N*-(phenylsulfenyl)succinimide, PBu_3, C_6H_6, RT; (ix) Raney nickel, THF, RT; (x) $n$$Bu_4NF$, THF, RT; (xi) Dess-Martin periodinane, pyridine, DMSO, RT; (xii) $Cl^-Ph_3P^+{-}CH_2CONHCH_2$*i*Pr, DBU, RT.

The total synthesis of U-106305 **22** by Barrett *et al*. represents a *tour de force* in enantioselective cyclopropanation chemistry, with all six cyclopropane rings being installed using Charette dioxaborolane-mediated asymmetric cyclopropanation reactions**.**

1.9 Aims of the thesis

Given the enormous synthetic utility of zinc carbenoid reagents in the cyclopropanation of allylic alcohols, and the obvious parallels between allylic alcohols and allylic amines, this thesis focuses on the use of zinc carbenoids as reagents for the chemo- and stereoselective cyclopropanation of allylic amines and derivatives.

Chapter 2 describes the cyclopropanation of tertiary allylic amines with a range of zinc carbenoid reagents. Chapter 3 describes the development of a stereodivergent cyclopropanation of allylic carbamates and amides, and investigations into an asymmetric variant. Chapter 4 describes the application of this methodology towards the total synthesis of the potential anti-obesity therapeutic *trans*-SCH-A **140**.

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Chapter 2: Cyclopropanation of allylic amines

This chapter describes investigations into the chemo- and stereoselective cyclopropanation of allylic amines using zinc carbenoid reagents. The optimization, scope and mechanism of this process are discussed.

2.1 Introduction

Unlike the cyclopropanation of allylic alcohols, the cyclopropanation of allylic amines has received very little attention. It has been reported by Ciganek that the cyclopropanation of allyl amine **1** with Zn/Cu and diiodomethane affords cyclopropane **141** in 65% yield.[1] Additionally, Arnaud and Perraud reported in 1968 that 2-methyl-3-aminopropene **142** could be cyclopropanated to give 1-aminomethyl-1-methylcyclopropane **143** in 80% yield, however no experimental conditions are provided in either case (Figure 1).[2]

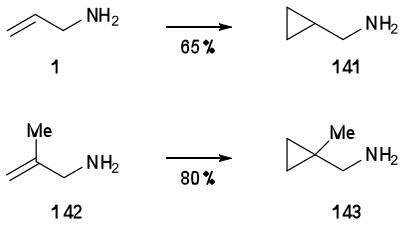
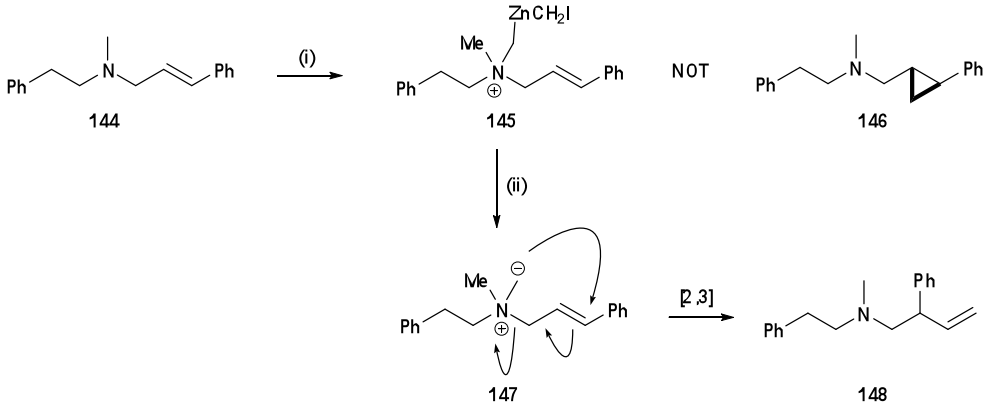


Figure 1: Early literature examples of the cyclopropanation of allylic amines.

Since these isolated reports, there has been a paucity of studies on the cyclopropanation of allylic amines and indeed the cyclopropanation of allyl amine **1** has never been formally reported, whilst the observations of Arnaud and Perraud had been cited only twice at the outset of this project.[3]

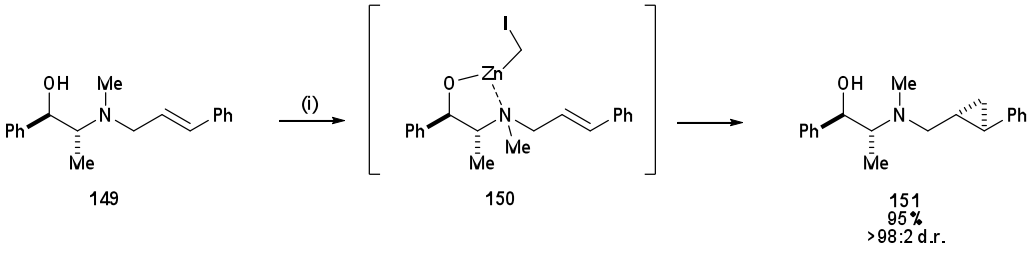
In a more recent study by Aggarwal *et al.* on the cyclopropanation of allylic amines, the authors proposed that the dearth of examples of cyclopropanation of allylic amines was principally due to the competing *N*-methylation pathway. Indeed, the authors showed that reaction of allylic amines such as **144** with the Wittig-Furukawa reagent

$[Zn(CH_2I)_2]$ did not result in the formation of cyclopropane **146**. Instead, *N*-methylation was the predominant pathway, generating ammonium species **145** that, upon treatment with *n*BuLi, forms an ammonium ylide **147** which can then undergo a [2,3]-sigmatropic shift to give homoallylic amine **148** in good yield (Scheme 1).[4]



Scheme 1: *Reagents and conditions*; (i) 1.1 eq. $Zn(CH_2I)_2$, Et_2O, 0 °C, 2 days; (ii) 3.9 eq. *n*BuLi, THF, –30 °C, 2 hrs.

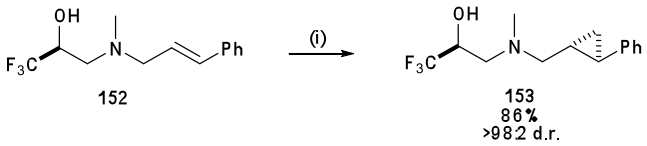
Aggarwal *et al*. were able to negate the *N*-methylation pathway by employing a pseudoephedrine moiety on the amine. For example, treatment of allylic amine **149** with 1.1 equivalents of $Zn(CH_2I)_2$ results in the formation of cyclopropane **151** in 95% yield as a single diastereoisomer after 2 days at 0 °C. The authors propose that co-ordination between the amine and the *in situ* generated zinc alkoxide provides a relatively stable complex **150** which does not readily undergo *N*-methylation but which can react with the olefin to form cyclopropane **151** (Scheme 2).[5]



Scheme 2: *Reagents and conditions*; (i) 1.1 eq $Zn(CH_2I)_2$, CH_2Cl_2, 0 °C, 2 days.

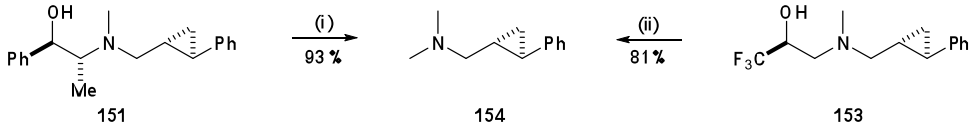
Katagiri *et al.* later showed that the reaction time can be significantly reduced by employing a trifluoromethylated amino alcohol auxiliary. For example, treatment of

152 with 2 eq. of $Zn(CH_2I)_2$ for just 1 hr at −5 °C leads to the formation of cyclopropane **153** in 86% yield as a single diastereoisomer (Scheme 3).[6]



Scheme 3: *Reagents and conditions*; (i) 2.0 eq. $Zn(CH_2I)_2$, CH_2Cl_2, −5 °C, 1 hr.

However, a drawback of both of these approaches is that removal of the auxiliary is difficult. In both cases the authors were able to produce the corresponding dimethylamine **154** by quaternisation with iodomethane, followed by treatment with base (Scheme 4).



Scheme 4: *Reagents and conditions*; (i) MeI (neat) then NaH, THF, reflux; (ii) MeI, EtOH, reflux, overnight, then 5.0 eq. *t*BuOK, 1.1 eq. 18-Crown-6, THF, RT, 24 hrs.

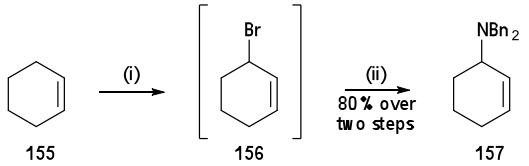
Clearly, this strategy is only applicable if a dimethylamine is the desired product, and if no other nucleophilic or base-sensitive functional groups are present in the molecule. As such, it was felt that the development of a more widely applicable strategy for the chemoselective cyclopropanation of allylic amines would be of value to the synthetic community.

2.2 Substrate synthesis

N,*N*-Dibenzylcyclohexylamine **157** was chosen as a model substrate for cyclopropanation, since previous work within the Davies group on the chemo- and stereoselective oxidation of allylic amines had utilized this substrate,[7] and due to the relative ease of removal of the *N*-benzyl groups.

The synthesis of **157** was achieved from cyclohexene **155** by Wohl-Ziegler allylic bromination with NBS and benzoyl peroxide to give intermediate bromide **156** which

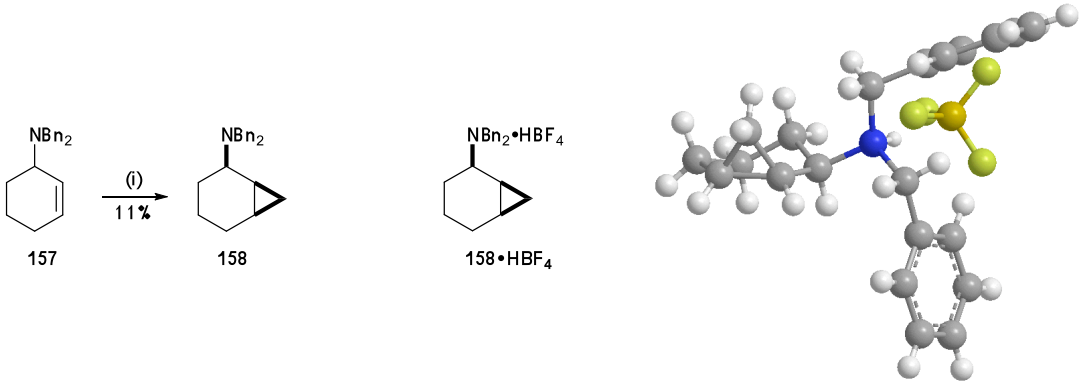
then underwent substitution with dibenzylamine to give the desired substrate in 80% yield (Scheme 5).



Scheme 5: *Reagents and conditions*; (i) 1.0eq. NBS, 0.01 eq. $(PhCOO)_2$, CCl_4, 90 °C, 4 hrs; (ii) 5.0 eq. $HNBn_2$, 0.10 eq. DMAP, CH_2Cl_2, 18 hrs.

2.3.1 Reaction with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$]

With substrate **157** in hand, its reactivity under standard cyclopropanation conditions with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] was next investigated. The carbenoid was preformed by reacting $ZnEt_2$ with CH_2I_2 in CH_2Cl_2 at 0 °C. Subsequent addition of substrate **157**, followed by stirring for 1 hr at room temperature gave, after chromatographic purification, cyclopropane **158** in 11% isolated yield as a single diastereoisomer. No other products were isolated from the reaction and it was noted that the crude mass recovery was low. The relative *syn*-configuration within cyclopropane product **158** was proven unambiguously by single-crystal X-ray crystallography of the corresponding HBF_4 salt **158•HBF$_4$** (Scheme 6).



Scheme 6: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, 0 °C → RT, 1 hr.

Since no other products were isolated from the organic extracts after aqueous work up, it was postulated that the side products of the reaction were likely to be *N*-

methylated ammonium salts such as **159** and **160**, by analogy to the products isolated in a separate example (*vide infra*) (Figure 2).

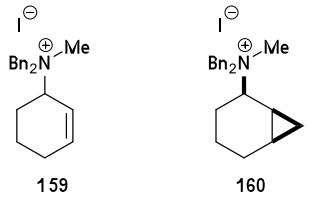
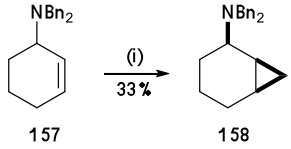


Figure 2: Proposed *N*-methylated side products **159** and **160**

Although reaction of substrate **157** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] had proceeded in excellent diastereoselectivity, it was clear that the chemoselectivity of the process was not synthetically useful and so alternative carbenoid reagents were next investigated.

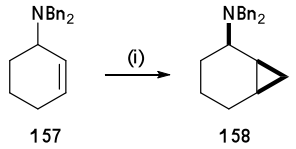
2.3.2 Reaction optimisation: choice of reagent

Reaction of substrate **157** with the more reactive Denmark reagent [$Zn(CH_2Cl)_2$][8] for 1 hr at room temperature, gave cyclopropane **158** in an improved 33% yield and as a single diastereoisomer (Scheme 7).



Scheme 7: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. $ClCH_2I$, CH_2Cl_2, 0 °C to RT, 1 hr.

Encouraged by the improved yield of the reaction with a more reactive carbenoid, we moved on to the highly reactive (iodomethyl)zinc acetate reagents pioneered by Shi *et al.*[9] It was found that the yield of the reaction broadly increased with the reactivity of the carbenoid, and that reaction with Shi's carbenoid [$CF_3CO_2ZnCH_2I$], prepared by addition of TFA to $Zn(CH_2I)_2$, gave cyclopropane **158** in an excellent 92% isolated yield and as a single diastereoisomer (Scheme 8).

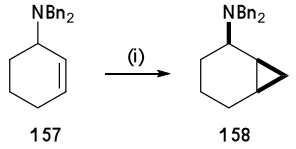


157 158

Additive	Yield (%)
AcOH	n.d. (~10% conversion)
$ClCH_2CO_2H$	62
Cl_2CHCO_2H	89
Cl_3CCO_2H	66
CF_3CO_2H	92

Scheme 8: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. additive, CH_2Cl, 0 °C to RT, 1 hr.

Given that *N*-methylation of the product may be an issue with prolonged reaction times, the reaction was repeated over 6 and 12 hours, giving **158** in isolated yields of 71% and 64% respectively (Scheme 9).



157 158

Time (hrs)	Yield (%)
1	92
6	71
12	64

Scheme 9: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, specified time.

Although this was not a dramatic decrease, the optimum reaction time was chosen as 1 hr, since gradual erosion of the isolated product yield occurred beyond this.

2.4.1 Mechanistic investigations

Although the diastereoselectivity observed in the cyclopropanation of **157** to give *syn*-**158** is consistent with a chelation-controlled model, a series of competition experiments were designed to probe this further.

4,4-Diphenylcyclohex-1-ene **161** and *N*,*N*-dibenzyl cyclohexylamine **162** were chosen as mimics for the olefin and amine functionalities of substrate **157** respectively.

4,4-Diphenylcyclohex-1-ene **161** was chosen in preference to cyclohexene **155** due to relatively low boiling point of cyclohexene (83 °C). Since it was proposed to assess reaction conversion by ^{1}H NMR analysis, any loss of cyclohexene **155** (or the corresponding cyclopropane) during concentration of the reaction mixtures *in vacuo* would invalidate the results. It was hoped that the *gem*-diphenyl group would significantly reduce the volatility of **161**, whilst being remote enough to have as little effect as possible upon the relative rate of cyclopropanation (Figure 3).

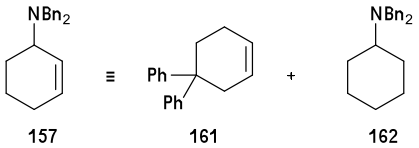
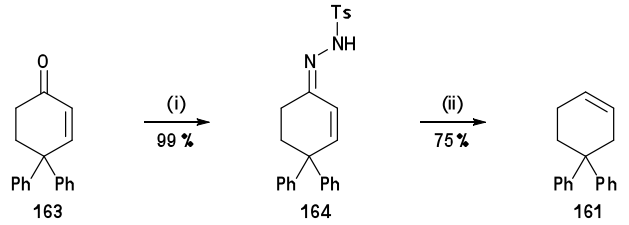


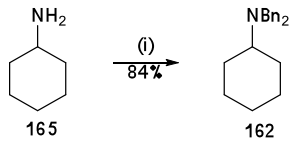
Figure 3: **161** and **162** as mimics for the olefin and amine functionalities of **157** respectively.

4,4-Diphenylcyclohex-1-ene **161** was synthesised in two steps from commercially available enone **163** in 74% overall yield (Scheme 10).



Scheme 10: *Reagents and conditions*; (i) 1.1 eq. $TsNHNH_2$, MeOH/toluene (2:1), RT, 16 hrs; (ii) 1.1 eq. catechol borane, $CHCl_3$, 0 °C to RT, 2 hrs then 3.0 eq. $NaOAc{\cdot}H_2O$, 60 °C, 1 hr.

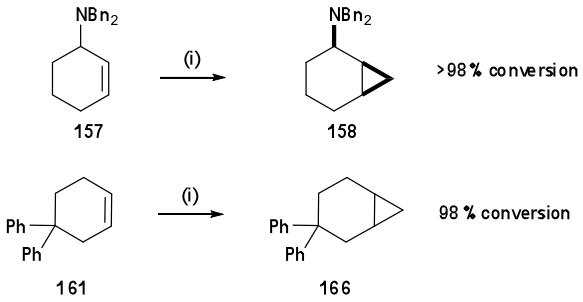
N,*N*-Dibenzyl cyclohexylamine **162** was next synthesised in 84% yield from cyclohexylamine **165** according to a literature procedure (Scheme 11).[10]



Scheme 11: *Reagents and conditions*; (i) 2.0 eq. BnBr, 2.2 eq. aq. NaOH (0.5M), 80 °C, 30 mins.

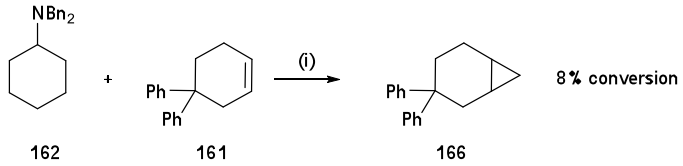
As control experiments, reaction of either **157** or **161** with 2 eq. of Shi's carbenoid for 30 minutes resulted in essentially complete conversion to cyclopropanes **158** or **166**

respectively and as such, 4,4-diphenylcyclohex-1-ene **161** was selected as a suitable mimic for the olefin functionality of **157** (Scheme 12).



Scheme 12: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

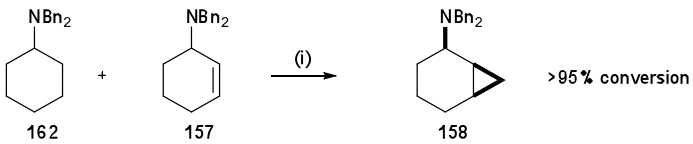
Next, the effect of addition of an external amine on the rate of cyclopropanation was investigated. Reaction of **161** with 2 equivalents of $CF_3CO_2ZnCH_2I$, in the presence of 1 equivalent of amine **162**, resulted in very low conversion to cyclopropane **166** (Scheme 13).



Scheme 13: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

The observation that the rate of intermolecular cyclopropanation is reduced by the presence of a tertiary amine is consistent with coordination of the amine to zinc, stabilizing the carbenoid, and reducing its reactivity.[11]

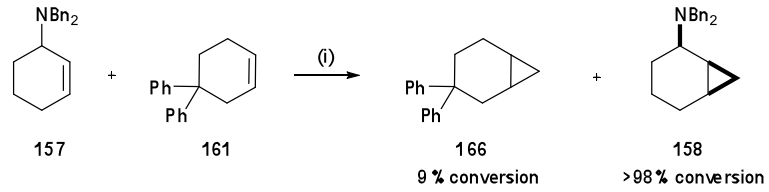
In contrast, the reaction of substrate **157** with 2 equivalents of $CF_3CO_2ZnCH_2I$, in the presence of 1 equivalent of amine **162**, still proceeded to >95% conversion (Scheme 14).



Scheme 14: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

Since the rate of reaction of **161** in the presence of amine **162** should represent the rate of intermolecular cyclopropanation in the presence of a tertiary amine, the observation that the rate of cyclopropanation of substrate **157** both in the presence and absence of an external amine is significantly greater strongly suggests that intramolecular cyclopropanation is taking place.

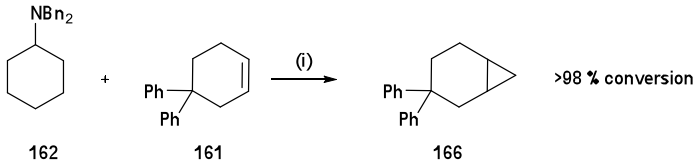
As a further experiment, it was shown that addition of substrate **157** to the reaction mixture also inhibited the rate of intermolecular cyclopropanation, suggesting that the amine may be binding to zinc, further supporting the proposed chelated cyclopropanation pathway (Scheme 15).



Scheme 15: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

2.4.2 Aggregation studies

One observation from the above results that has not been discussed is that, in the case of cyclopropanation of **161** in the presence of amine **162**, one equivalent of amine is able to inhibit two equivalents of carbenoid. This suggests that the carbenoid is likely to be present as a dimer. To test this, the reaction was repeated with 4 eq. of carbenoid and this resulted in >98% conversion to product **166** after 30 mins (Scheme 16).

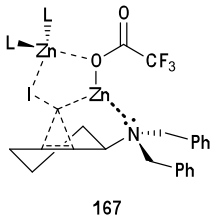


Scheme 16: *Reagents and conditions*; (i) 4 eq. $ZnEt_2$, 8 eq. CH_2I_2, 4 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

This result suggests that 2 equivalents of the carbenoid are sequestered by the amine, leaving the other 2 equivalents to effect cyclopropanation as normal.

2.4.3 Discussion

From the above mechanistic studies, a model is proposed in which cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] takes place in an intramolecular fashion *via* an *N*-Zn complex (Figure 4).[12]

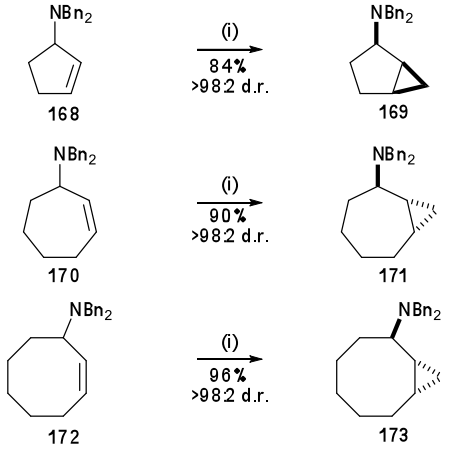


167

Figure 4: Proposed model for the cyclopropanation of allylic amines with $CF_3CO_2ZnCH_2I$.

2.5.1 Substrate scope

Having shown that Shi's carbenoid [$CF_3CO_2ZnCH_2I$] allows the cyclopropanation of cyclohexenyl allylic amine **157** in excellent yield and diastereoselectivity, the scope of the reaction with respect to the substrate structure was next investigated. The corresponding 5-, 7- and 8-membered ring substrates **168**, **170** and **172**[13] respectively were cyclopropanated under the standard reaction conditions to give 2-aminobicyclo[3.1.0]hexane **169** in 84% yield, 2-aminobicyclo[5.1.0]octane **171** in 90% yield and 2-aminobicyclo[6.1.0]nonane **173** in 96% yield (Scheme 17).



Scheme 17: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

The relative configurations within **171** and **173** were assigned unambiguously through single-crystal X-ray crystallography (Figure 5).

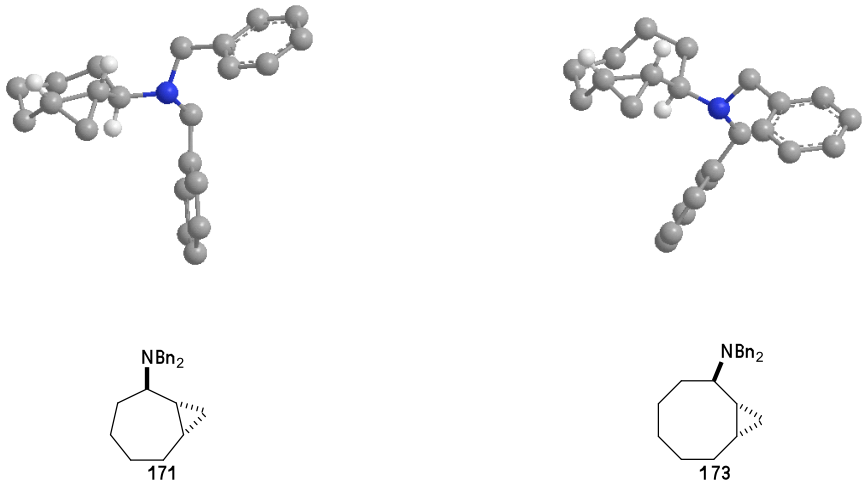
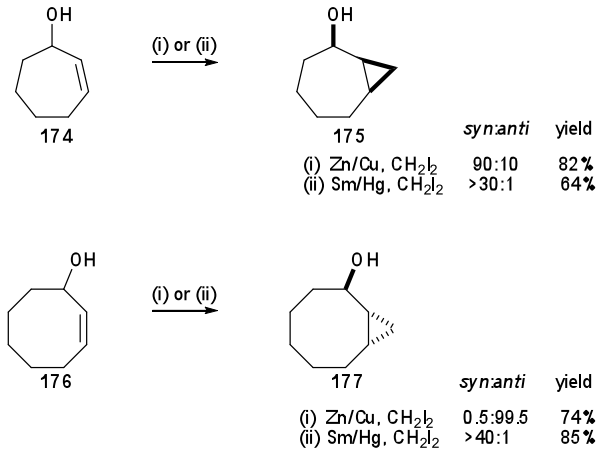


Figure 5: Chem 3D representations of the crystal stuructures of **171** and **173** (some H atoms have been omitted for clarity).

Whilst *anti*-selective cyclopropanation of cyclooctene substrate **172** was anticipated on the basis of literature precedent, the *anti*- selectivity observed in the cyclopropanation of cycloheptene substrate **170** is in contrast to the *syn*- selectivity observed in the cyclopropanation of the corresponding cycloheptenol **174** with either the Simmons-Smith (Zn-Cu, CH_2I_2) or Molander (Sm/Hg, CH_2I_2) reagents (Scheme 18).[14,15]



Scheme 18: *Reagents and conditions*; (i) Zn/Cu, CH_2I_2, Et_2O; (ii) Sm/Hg (xs), 4 eq. CH_2I_2, THF, −78 °C to RT, 2 hrs.

Examination of the X-ray crystal structures of both substrates **170** and **172**, obtained in a separate study within the Davies group, indicate that the amine may be capable of directing cyclopropanation *anti* through chelation.[16] In particular, viewing down the C=C bond in amino cycloheptene **170** shows that the nitrogen lone-pair projects towards the *anti*- face of the double bond (Figure 6).

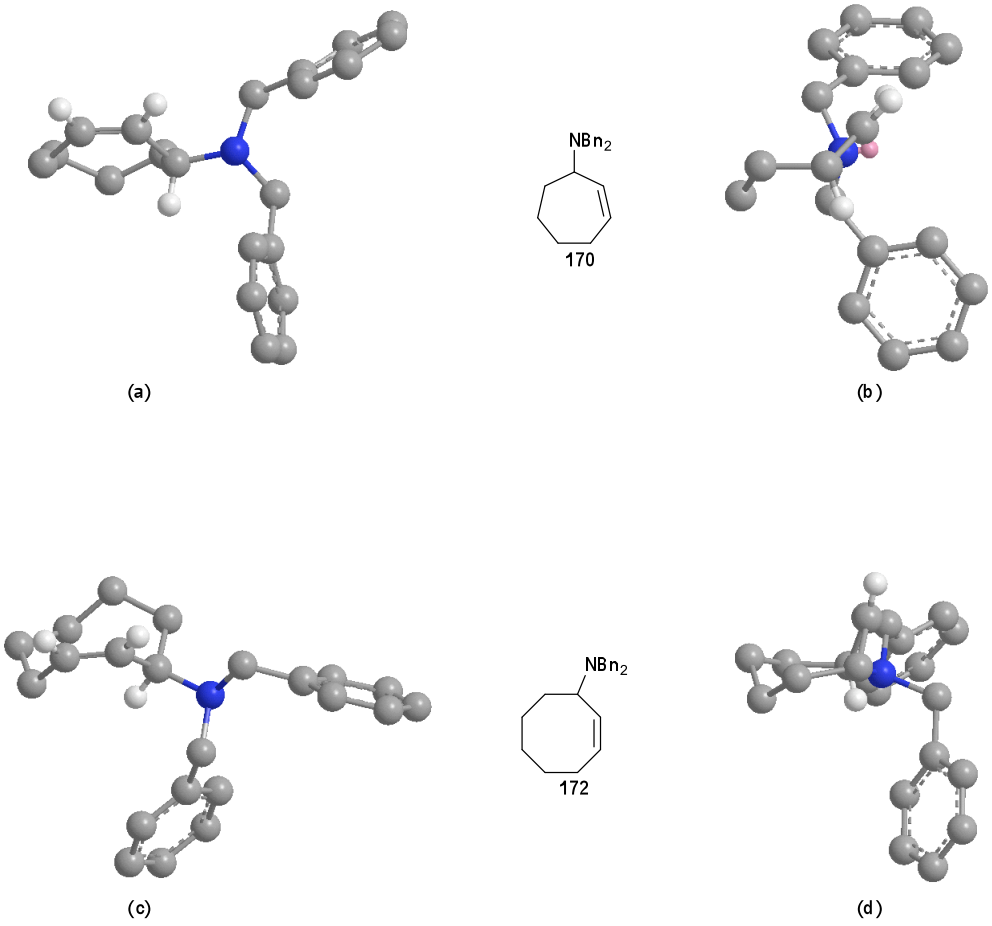


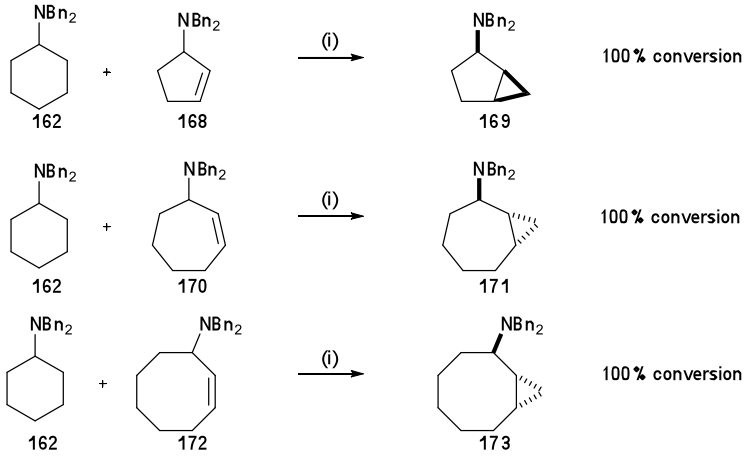
Figure 6: Chem 3D representation of the crystal structures of **170** and **172** (some H-atoms have been omitted for clarity); (a) normal view of **170**; (b) viewed down the C=C bond, indicating the orientation of the nitrogen lone pair (pink); (c) normal view of **172**; (d) viewed down the C=C bond.

2.5.2 Mechanistic investigations

Since, on the basis of previous results from competition experiments, it would appear that the rate of intermolecular cyclopropanation is inhibited by the addition of an external amine, whereas the rate of intramolecular cyclopropanation appears to be

unaffected, it was postulated that this could be used as a test for intra- versus intermolecular cyclopropanation.

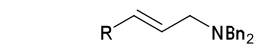
It was found that the cyclic substrates **168**, **170** and **172** all reacted with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] in the presence of amine **162** to give complete conversion to the desired products within 30 minutes, suggesting that the reaction may be chelation-controlled in each case (Scheme 19).



Scheme 19: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 30 mins.

2.6 Study into electronic effects

Having shown that the reaction is chemoselective for a range of cycloalkene substrates, electronic effects on the chemoselectivity of the reaction were next probed by examining the reactivity of the substituted cinnamyl substrates **170-180** and furyl-substituted substrate **181** (Figure 7).

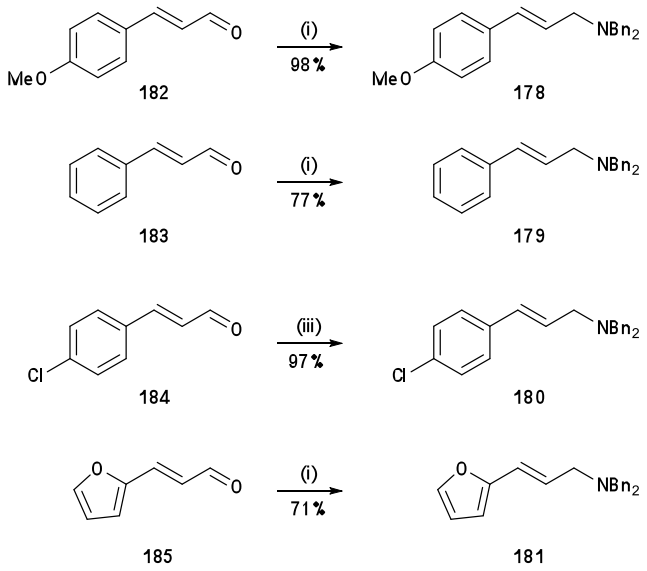


R = *p*-OMeC$_6$H$_4$ **178**
R = Ph **179**
R = *p*-ClC$_6$H$_4$ **180**
R = 2-Furyl **181**

Figure 7: Substituted cinnamyl substrates **170-180**, chosen to investigate electronic effects on the reaction.

2.6.1 Synthesis of 178-181

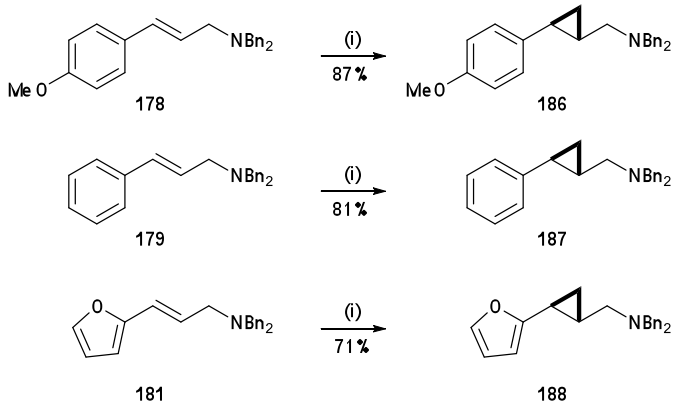
Substrates **178-181** were easily synthesised in 98, 77, 97 and 71% yields respectively from aldehydes **182-185**,[17] through reductive amination with dibenzylamine and sodium triacetoxyborohydride in CH_2Cl_2 (Scheme 20).



Scheme 20: *Reagents and conditions*; (i) 1.5 eq. $NaBH(OAc)_3$, 1.2 eq. $HNBn_2$, CH_2Cl_2, 0 °C to RT, 2 hrs.

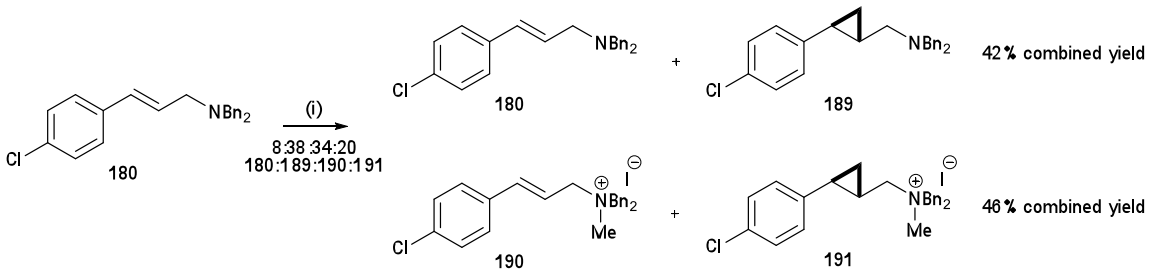
2.6.2 Cyclopropanation of 178-181

Cyclopropanation of *p*-OMe and *p*-H substrates **178** and **179**, and of furyl-substituted substrate **181** proceeded smoothly to give cyclopropanes **186**, **187** and **188**, respectively, in good yields within 1 hr (Scheme 21).



Scheme 21: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

Cyclopropanation of *p*-Cl substrate **180** was much slower in comparison and, after 16 hrs at RT, gave an 8:38:34:20 (**180:189:190:191**) mixture of starting material **180**, cyclopropane product **189** and *N*-methylated products **190** and **191**. Purification by flash column chromatography gave initially an inseparable 83:17 mixture of **189**:**180**, in a combined yield of 42%. Further elution of the column with CH_2Cl_2/MeOH (9:1) afforded an inseparable 57:43 mixture of ammonium salts **190**:**191** in a combined 46% yield (assuming that iodide is the counter-ion) (Scheme 22).

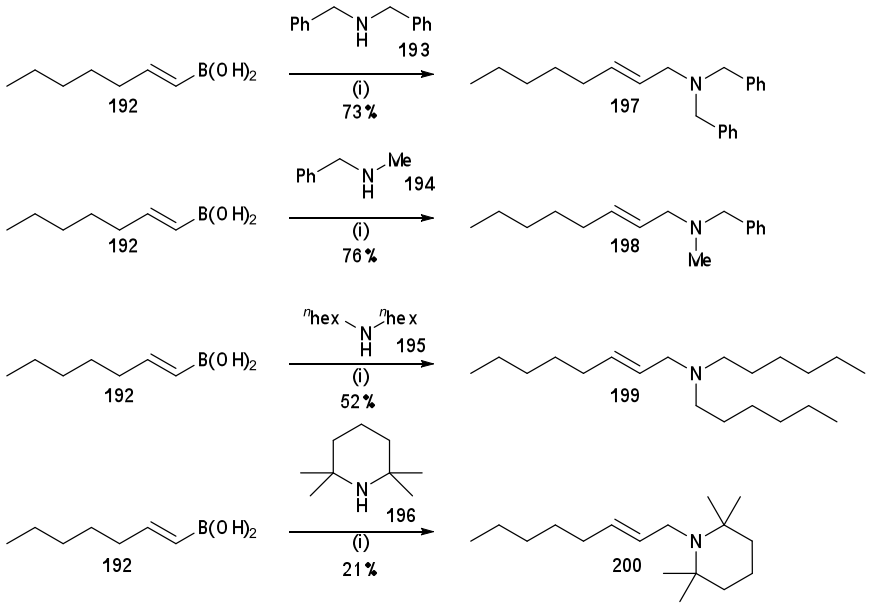


Scheme 22: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 16 hrs.

The isolation of the *N*-methylated side-products **190** and **191** in this case is presumably a result of their greater solubility in CH_2Cl_2, and their isolation lends support to the postulate that these *N*-methylated products are responsible for the low yields observed previously when using the Wittig-Furukawa reagent [$Zn(CH_2I_2)$] for the cyclopropanation of **157**. From these results, it is clear that the cyclopropanation reaction works best for electron-rich olefins, consistent with literature precedent for the reaction of zinc carbenoids.[18] Substrates which undergo relatively slow cyclopropanation are more likely to produce alternative products, such as those from *N*-methylation, as the rate of unwanted side-reactions becomes competitive, and correspondingly low yields of the desired cyclopropanation products are thus obtained.

2.7 Variation of the *N*-alkyl groups

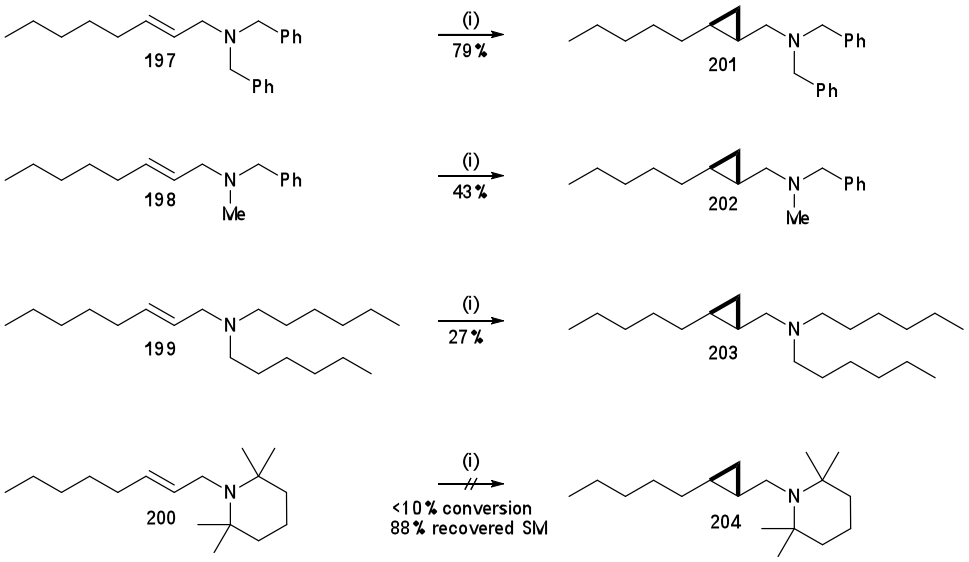
With conditions developed for the cyclopropanation of *N*,*N*-dibenzyl amine**s**, the role of the nitrogen substituents on the yield of the reaction was next investigated. Thus, allylic amines **197**-**200** were synthesised through the Petasis boronic acid-Mannich reaction of boronic acid **192**, paraformaldehyde and commercially available amines **193**-**196**, giving **197**-**200** in 21-76% yield (Scheme 23).



Scheme 23: *Reagents and conditions*; (i) 1.0 eq **192**, 1.0 eq amine **193**-**196**, 1.0 eq. paraformaldehyde, toluene, reflux, 2 hrs.

Cyclopropanation of these substrates with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] for 1 hr under the optimised conditions gave cyclopropanes **201**-**204** in varying yields. *N*,*N*-dibenzyl substrate **197** was found to be optimal, with cyclopropane **201** being isolated in 79% yield, perhaps indicating the importance of some steric protection for the nitrogen (c.f. *N*MeBn substrate **198**, 43% yield). In contrast however, tetramethylpiperidine substrate **200** failed to react to any significant degree within 1 hour, with starting material **200** being recovered in 88% yield. This is an interesting result, as it would be expected that should the nitrogen lone pair be too sterically hindered to bind to zinc, the carbenoid should still be able to cyclopropanate the

double bond *via* an intermolecular process. The observation that this is not the case suggests that the nitrogen lone pair can indeed bind to zinc, however it is then either too sterically hindered to undergo intramolecular cyclopropanation (or *N*-methylation) or it cannot adopt the required conformation. (Scheme 24).



Scheme 24: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

2.8 $A_{1,3}$ Strain directed cyclopropanation

Having shown that excellent diastereoselectivity is seen in the cyclopropanation of cyclic allylic amines, we next investigated the $A_{1,3}$ strain directed cyclopropanation of acyclic substrates **205** (Figure 8).[19]

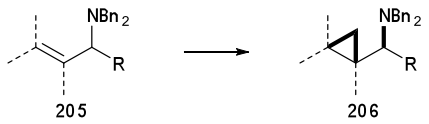
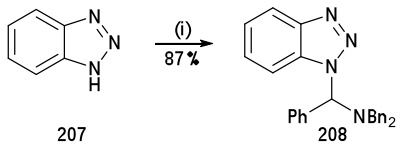


Figure 8: Proposed diastereoselective cyclopropanation of acyclic allylic amines.

2.8.1 Synthesis of acyclic substrates

An efficient synthesis of these substrates was achieved *via* the use of α-amino benzotriazoles as iminium surrogates.[20] α-Amino benzotriazole **208** was synthesised

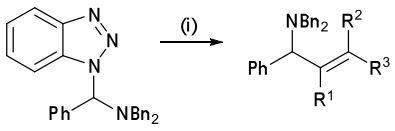
on a multigram scale (>20 g) in excellent yield through condensation of benzaldehyde with dibenzylamine and benzotriazole **207** (Scheme 25).



207 208

Scheme 25: *Reagents and conditions*; (i) 1.0 eq. PhCHO, 1.0 eq. $HNBn_2$, MeOH, Et_2O, 70 °C, 12 hrs.

Addition of a range of Grignard reagents to α-amino benzotriazole **208** gave substrates **209-215** in good to excellent yield. The Grignard reagents were all either commercially available (entries 1, 2, and 5) or prepared through standard means from the commercially available vinyl bromides (entries 4, 6, and 7) with the exception of entry 3. In this case, formation of the Grignard from (*E*)-1-bromo-1-propene resulted in significant isomerisation of the double bond geometry.[21] This was minimized by synthesis of the Grignard reagent by lithiation of the vinyl bromide with ^{t}BuLi followed by transmetallation to $MgBr_2$. In this case, the desired product **211** could be obtained in excellent diastereoselectivity, although in a modest 38% yield (Scheme 26).[22]



208 209-215

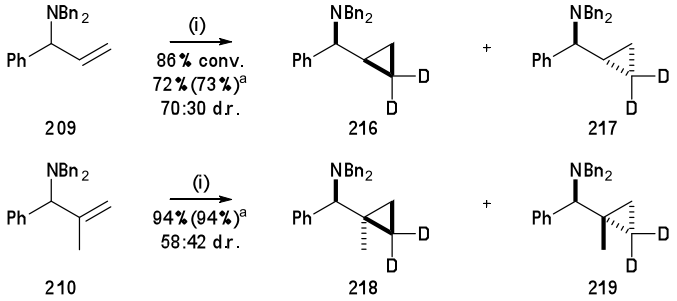
Entry	R^1	R^2	R^3	Yield (%)	d.r.	Product
1	H	H	H	92	-	**209**
2	Me	H	H	quant.	-	**210**
3	H	H	Me	38	>98:2	**211**
4	H	Me	H	75	91:9	**212**
5	H	Me	Me	93	-	**213**
6	Me	Me	H	87	96:4	**214**
7	Me	Me	Me	40	-	**215**

Scheme 26: *Reagents and conditions*; (i) 1.5 eq. Grignard reagent, toluene, 50 °C, 2 hrs.

2.8.2 Cyclopropanation of acyclic substrates

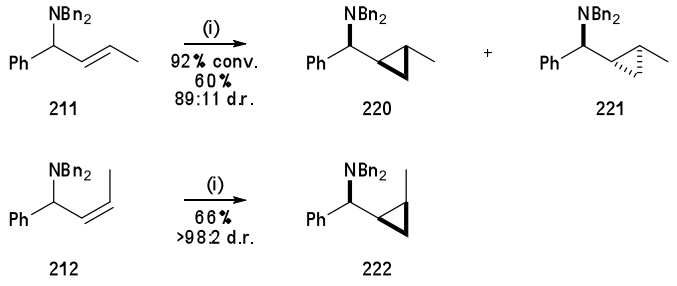
With these substrates in hand, their diastereoselective cyclopropanation was next investigated. As standard cyclopropanation of substrates **209** and **210** would give no

insight into the diastereoselectivity of the reaction, the reaction was performed using d_2-diiodomethane. In the case of **209** this gave a 70:30 mixture of deuterated cyclopropanes **216** and **217** in 72% yield, and in the case of **210**, cyclopropanation afforded a 58:42 mixture of deuterated cyclopropanes **218** and **219** 63% yield (Scheme 27).[1]



Scheme 27: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CD_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr. [a] The numbers in parentheses indicate the product yields obtained when CH_2I_2 was used.

The cyclopropanation of (*E*)- and (*Z*)- double bond isomers **211** and **212** were next investigated, anticipating that (*Z*)-**212** would show higher levels of diastereoselectivity upon cyclopropanation due to greater allylic 1,3 strain. This was indeed found to be the case with (*Z*)-**212** undergoing cyclopropanation with complete diastereoselectively,[23] whilst (*E*)-**211** reacted in a modest 89:11 d.r. (Scheme 28).[2]

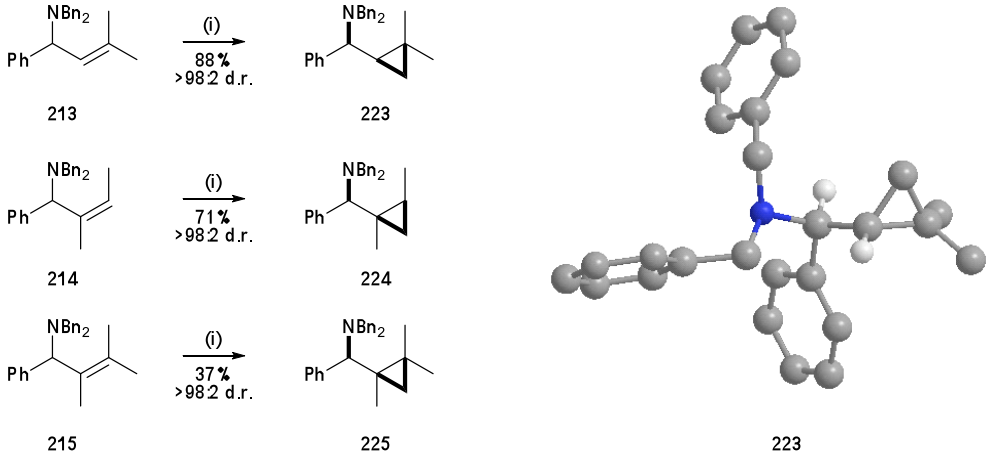


Scheme 28: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

On the basis of these results, it was anticipated that the remaining substrates **213**-**215** would all show excellent levels of diastereoselectivity upon cyclopropanation as they

[1] The major disatereoisomer has been assigned the *syn* relative configuration in each case on the basis of *N*-directed cyclopropanation *via* a conformation which minimizes allylic strain (*vide infra*).
[2] The major diastereoisomer in each case is assigned on the basis of *N*-directed cyclopropanation *via* a conformation with minimizes allylic strain (*vide infra*).

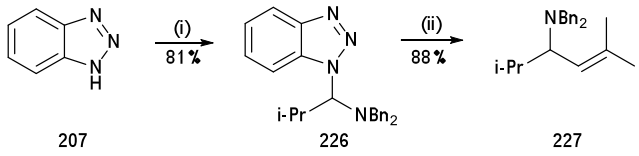
all contain the crucial *cis*-methyl group which greatly increases the allylic 1,3 strain. This was indeed found to be the case, with **213**, **214** and **215** all producing the desired cyclopropane products **223**-**225** in 37-88% yield and >98:2 d.r. The relative configuration within **223** was proven unambiguously by single-crystal X-ray crystallography, and that of **224** and **225** assigned by analogy (Scheme 29).



Scheme 29: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

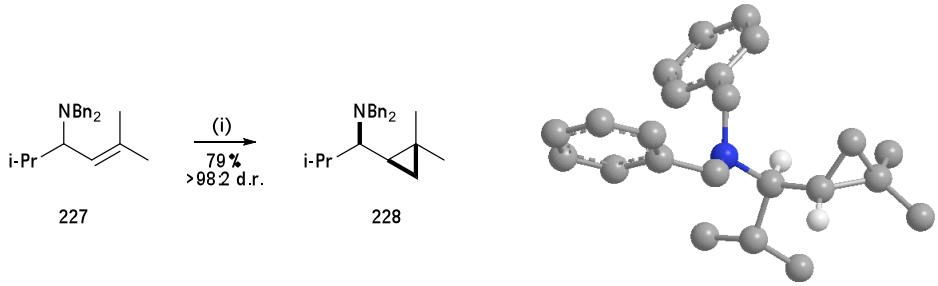
2.8.3 Variation of the α-substituent

The effect of varying the substituent in the α-position was next investigated, however this was limited by the stability of the α-amino benzotriazole precursors. Unfortunately, condensation of dibenzylamine and benzotriazole **207** with either acetaldehyde or pivaldehyde failed to give the desired α-amino benzotriazole. However, condensation with isobutyraldehyde was successful, giving α-amino benzotriazole **226** in 81% yield on >20 g scale. Reaction of **226** with 2-methyl-1-propenylmagnesium bromide gave allylic amine **227** in 88% yield (Scheme 30).



Scheme 30: *Reagents and conditions*; (i) 1.0 eq. *i*PrCHO, 1.0 eq. $HNBn_2$, MeOH, Et_2O, 70 °C, 12 hrs; (ii) 1.5 eq. 2-methyl-1-propenylmagnesium bromide, toluene, 50 °C, 2 hrs.

Cyclopropanation of substrate **227** afforded the desired cyclopropane **228** in 79% yield as a single diastereoisomer. The relative configuration within **228** was proven unambiguously by single crystal X-ray crystallography (Scheme 31).



Scheme 31: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, 0 °C to RT, 1 hr.

The observed stereoselectivity in the case of **213** and **227** is consistent with cyclopropanation being chelation controlled, with the 1,3 allylic strain being minimized in transition state **229** (Figure 9).

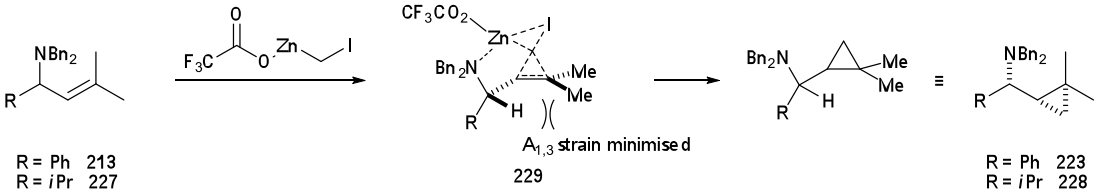
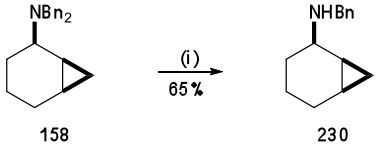


Figure 9: A simplified transition state model for allylic strain directed cyclopropanation.

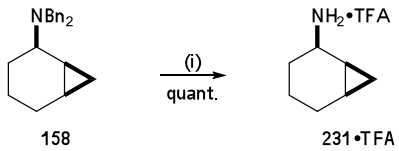
2.9 Deprotection

In order to prove the utility of the *N*,*N*-dibenzyl protecting group, we next investigated their deprotection by catalytic hydrogenation. It was found that under 1 atmosphere of hydrogen, in the presence of Pd/C, removal of the second benzyl group from substrate **158** was slow, thereby allowing selective mono-debenzylation to **230** in a reasonable 65% yield (Scheme 32).



Scheme 32: *Reagents and conditions*; (i) 1 atm.H_2, Pd/C (50 wt. %), MeOH/H_2O/AcOH (40:4:1) RT, 16 hrs.

At higher pressures (5 atm.) complete debenzylation of **158** could be achieved, giving the free amine which was isolated as the corresponding TFA salt **231·TFA**. Importantly, no hydrogenation of the cyclopropane ring was observed, even at high pressure (Scheme 33).



Scheme 33: *Reagents and conditions*; (i) 5 atm.H_2, Pd/C (50 wt. %), MeOH/H_2O/AcOH (40:4:1), RT, 16 hrs then TFA (xs).

2.10 Conclusion

It has been shown that the use of Shi's carbenoid [$CF_3CO_2ZnCH_2I$] has a pronounced effect on the chemoselectivity of the cyclopropanation of allylic amines. In both cyclic and acyclic $A_{1,3}$-strain-type systems, excellent levels of diastereoselectivity are observed for a wide range of substrates. Mechanistic investigations suggest that in all cases the reaction is directed by co-ordination of the amino group to the zinc carbenoid. This represents the first, generally applicable, strategy for the cyclopropanation of allylic amines.

2.11 References and notes

[1] Reported as a personal communication in Simmons, H. E., Cairns, T. L., Vladuchick, S. A., *Org. React*., **1973**, *20*, 1-131

[2] Pearraud, R., Arnaud, P., *Bull. Soc. Chim. Fr.*, **1968**, 1540-1542.

[3] In references 1 and 5.

[4] Aggarwal, V. K., Fang, G. Y., Charmant, J. P. H., Meek, G., *Org. Lett.*, **2003**, *5*, 1757-1760.

[5] Aggarwal, V.K., Fang, G. Y., Meek, G., *Org. Lett.*, **2003**, *5*, 4417-4420.

[6] Katagiri, T., Iguchi, N., Kawate, T., Takahashi, S., Uneyama, K., *Tetrahedron: Asymmetry*, **2006**, *17*, 1157-1160.

[7] Aciro, C., Claridge, T. D. W., Davies, S. G., Roberts, P. M., Russell, A. J., Thomson, J. E., *Org. Biomol. Chem.*, **2008**, *6*, 3751-3761.

[8] Denmark, S. E., Edwards, J. P., *J. Org. Chem.*, **1991**, *56*, 6974-6981.

[9] Lorenz, J. C., Long, J., Yang, Z., Xue, S., Xie, Y., Shi, Y., *J. Org. Chem.*, **2004**, *69*, 327-334.

[10] Ju, Y., Varma, R.S., *Green Chem.*, **2004**, *6*, 219-221.

[11] It is known that external ligands, such as DME, significantly reduce the rate of reaction of the Wittig-Furukawa reagent [$Zn(CH_2I)_2$]. See Denmark, S. E., Edwards, J. P., Wilson, S. R., *J. Am. Chem. Soc.*, **1992**, *114*, 2592-2602.

[12] Nakamura, M., Hirai, A., Nakamura, E., *J . Am. Chem. Soc.*, **2003**, *125*, 2341-2350

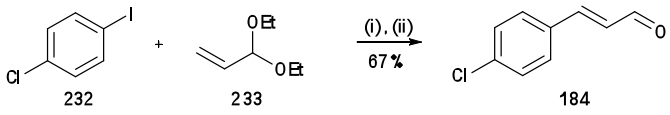
[13] Substrate **168** was kindly provided by Mr Marcus J. C. Long, and substrates **170** and **172** were kindly provided by Mr Alex C. Cresswell. For preparations of these compounds, see Cresswell, A. C., *Part II Thesis*, University of Oxford, **2008**.

[14] Poulter, C. D., Friedrich, E. C., Winstein, S., *J. Am. Chem. Soc.*, **1969**, *91*, 6892-6894.

[15] Molander, G. A., Harring, L. S., *J. Org. Chem.*, **1989**, *54*, 3525-3532.

[16] **170** and **172** were synthesized and crystallized by Mr Alex C. Cresswell. X-ray crystallography was performed by Dr. Jim. E. Thomson. The structures have been deposited with the Cambridge Crystallographic Data Centre; **170** CCDC733888, **172** CCDC733890.

[17] All of the aldehydes were commercially available with the exception of **184** which was synthesized in 67% yield according to the procedure of Battistuzi, G, Cacchi, S., Fabrizi, G, *Org. Lett.*, **2003**, *5*, 777-780;



232 233 184

Reagents and conditions; (i) 1.0 eq **232**, 3.0 eq. **233**, 0.03 eq. $Pd(OAc)_2$, 2.0 eq. KOAc, 1.5 eq. K_2CO_3, 1.0 eq. $n$$Bu_4NCl$, DMF, 90 °C, 1.5 hrs; (ii) 2 M aq. HCl, RT, 10 mins.

[18] (a) Simmons, H. E., Cairns, T. L., Vladuchick, S. A., Hoiness, C. M., *Org. React*., *20*, 1-131; (b) Charette, A. B., Beauchemin, A., *Org. React.*, *58*, 1-416; (c) Guerreiro, M. C, Schuchardt, U., *Synth. Comm.*, **1996**, *26*, 1793-1800.

[19] For the allylic strain directed cyclopropanation of allylic alcohols and ethers, see (a) Hoveyda, A. H., Evans, D. A., Fu, G.C., *Chem. Rev.*, **1993**, *93*, 1307-1370; (b) Lebel, H., Marcoux, J-F., Molinaro, C., Charette, A. B., *Chem Rev*, **1993**, *103*, 977-1050 and references contained therein.

[20] Katrizky, A. R., Nair, S. K., Qiu, Q., *Synthesis*, **2002**, 199-202.
[21] This was observed to a much lesser extent with (*Z*)-1-bromo-1-propene, giving the desired product **212** in 91:9 d.r.
[22] The yield of this process has since been optimised within our laboratory by Dr. Wataru Kurosawa. The principal difference in the procedure is the *in situ* formation of $MgBr_2$ under anhydrous conditions from Mg and 1,2-dibromoethane. This provides the desired product in up to 99% yield and >98:2 d.r.
[23] The 91:9 d.r. of the starting material was maintained in the product. Additionally, the observed minor diastereoisomer from the reaction of (*Z*)-**212** matched the major product from the reaction of (*E*)-**211** by ^{1}H NMR.

Chapter 3: Cyclopropanation of allylic imides, carbamates, amides and sulfonamides

This chapter describes the development of a novel stereodivergent protocol for the cyclopropanation of allylic imides, carbamates, amides and sulfonamides, and details investigations into an asymmetric variant of this reaction. The optimization, substrate scope and mechanisms of the stereodivergent cyclopropanation reactions are discussed.

3.1 Introduction

An obvious method for preventing the *N*-methylation pathway during the cyclopropanation of allylic amines is to convert the amine into a non-nucleophilic amide, carbamate or imide derivative.

The cyclopropanation of an allylic carbamate was first reported in 1972 by Tardella *et al*., who showed that reaction of ethyl carbamate **234** under Simmons-Smith conditions, gave *syn*-**235** as a single diastereoisomer in 75-95% yield (Figure 1).[1]

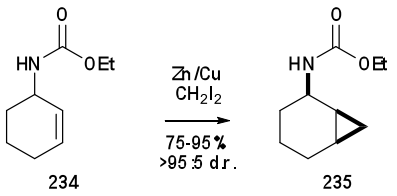
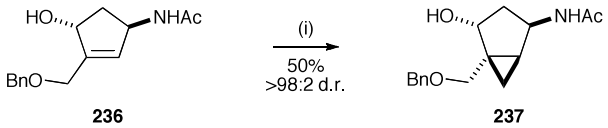


Figure 1: The cyclopropanation of ethyl carbamate **234** by Tardella *et al.*; No experimental details are reported.

The authors reported only this single example of the cyclopropanation of an allylic carbamate, and gave no experimental details for the procedure. As such the generality of this process with respect to the structure of the substrate is relatively unknown.

The cyclopropanation of an allylic amide was later reported by Marquez *et al*. in studies directed towards the synthesis of conformationally-restricted nucleosides. Interestingly, the authors showed that in the cyclopropanation of olefin **236**, which

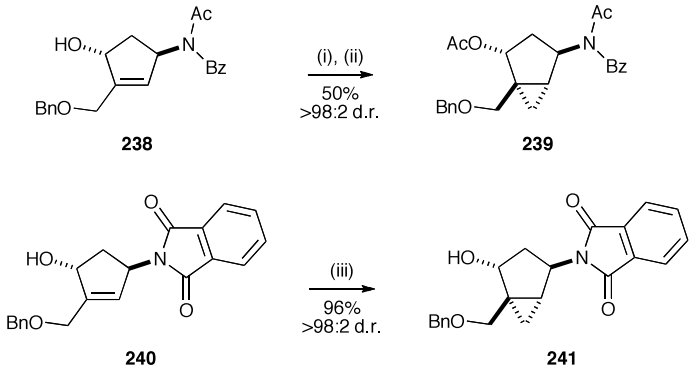
possesses both allylic OH and NHAc groups on opposite faces, the carbenoid is directed onto the same face as the amide group rather than the alcohol (Scheme 1).[2]



236 **237**

Scheme 1: *Reagents and conditions*; (i) 10 eq. $ZnEt_2$, 10 eq. CH_2I_2, CH_2Cl_2, 0 °C → RT, overnight.

In addition, the authors showed that the fully *N*-protected substrates **238** and **240** were cyclopropanated on the opposite face, giving **239** and **241** respectively. The *N*-phthalimido group is presumably only able to weakly co-ordinate the carbenoid and therefore acts as a steric blocking group; thus the reaction proceeds under the direction of the hydroxyl group (Scheme 2).[3]



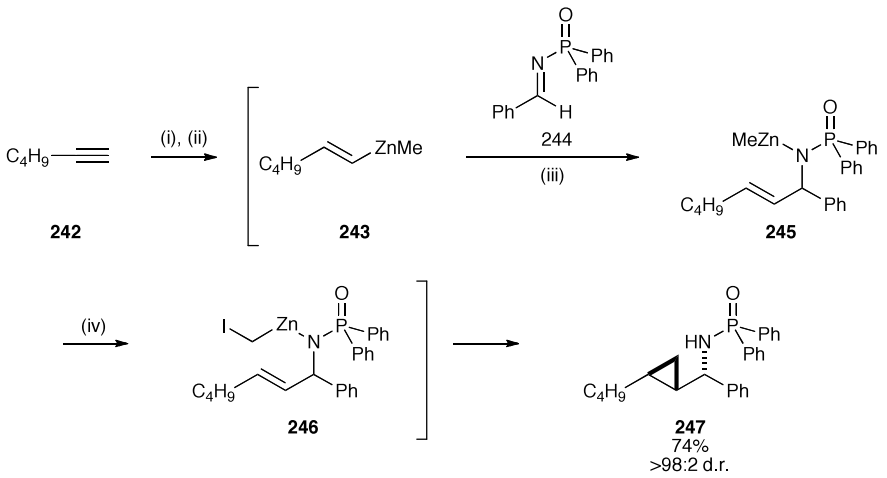
238 **239**

240 **241**

Scheme 2: *Reagents and conditions*; (i) 10 eq. $ZnEt_2$, 10 eq. CH_2I_2, CH_2Cl_2, 0 °C → RT, overnight; (ii) 2.25 eq. Ac_2O, NEt_3, cat. DMAP, THF, RT, 1 hr; (iii) 2.2 eq. $ZnEt_2$, 2.2 eq. CH_2I_2, CH_2Cl_2, 0 °C → RT, overnight.

Furthermore, Wipf *et al.* have developed an elegant cascade process for the synthesis of cyclopropylalkylamines from alkynes. The reaction sequence begins with hydrozirconation of alkyne **242** with the Schwartz reagent to afford a vinylzirconium intermediate which undergoes *in situ* transmetallation with $ZnMe_2$ to afford vinylzinc reagent **243**. Addition of an *N*-phosphinoylimine **244** results in formation of allylic zinc amide **245** which undergoes cyclopropanation to give *anti*-**247** as a single diastereosiomer upon addition of CH_2I_2. It is proposed that the unusual *anti* diastereoselectivity arises due to the minimization of 1,3-allylic strain between the

olefinic C-H bond and the bulky diphenylphosphinoyl group. This forces the olefin to adopt an orientation that would normally be disfavoured by 1,2-allylic strain. (Scheme 3).[4]



Scheme 3: *Reagents and conditions*; (i) Cp_2ZrHCl, CH_2Cl_2, RT, 5 mins; (ii) Me_2Zn, CH_2Cl_2, −78 °C → RT, 5 mins; (iii) **244**, CH_2Cl_2, reflux, 1 hr; (iv) CH_2I_2, CH_2Cl_2, reflux, 2 hrs.

3.2 Objectives of the methodology

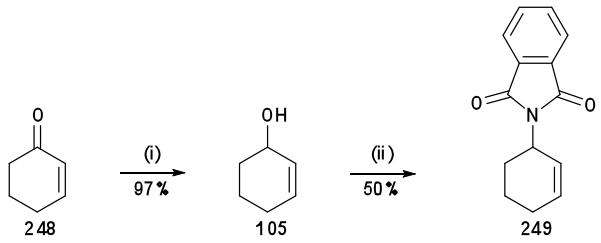
Having shown that allylic amines are capable of directing cyclopropanation *syn* to the amine, a more detailed study into the directing capabilities of allylic carbamates, amides, imides and sulfonamides was undertaken. In particular, it was hoped to develop a strategy that would allow access to the *anti* diastereoisomer.

3.3 *N*-Phthalimido protection

N-Phthalimido protection was selected for the initial studies since it was envisaged that conjugation of the nitrogen lone pair would nullify any chemoselectivity issues. Moreover, the steric bulk of the phthalimide group may direct cyclopropanation *anti* to the nitrogen and potentially this would provide complementary stereoselectivity to the cyclopropanation of allylic amines described in the previous chapter.

3.3.1 Substrate synthesis

The synthesis of *N*-phthalimido substrate **249** began with the preparation of 2-cyclohexen-1-ol **105**. This was achieved through Luche reduction of 2-cyclohexen-1-one **248** under standard conditions with $NaBH_4$ and $CeCl_3$, giving alcohol **105** in 97% yield, The synthesis of *N*-phthalimide substrate **249** was then achieved in 50% yield through Mitsunobu reaction of alcohol **105** and phthalimide in the presence of PPh_3 and DEAD (Scheme 4).

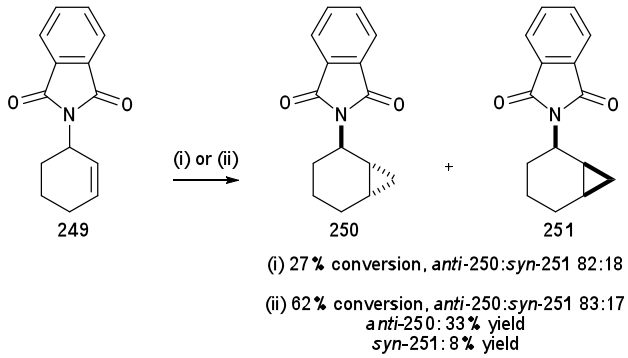


Scheme 4: *Reagents and conditions*; (i) 1.2 eq. $NaBH_4$, 1.0 eq. $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 30 mins; (ii) 2.0 eq. pthalimide, 2.0 eq. PPh_3, 2.0 eq. DEAD, THF, RT, 24 hrs.

3.3.2 Cyclopropanation of 249

With substrate **249** in hand, cyclopropanation with both the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] and Shi's carbenoid [$CF_3CO_2ZnCH_2I$] was investigated. Thus, treatment of **249** with 2 equivalents of $Zn(CH_2I)_2$ for 3 hrs led to 27% conversion to an 82:18 mixture of *anti*-**250**:*syn*-**251**, respectively, whereas reaction with $CF_3CO_2ZnCH_2I$ under the same conditions led to an improved 62% conversion to an 83:17 mixture of *anti*-**250**:*syn*-**251**, respectively. In the latter case, purification of the crude mixture by flash column chromatography enabled separation of the diastereoisomers to give *anti*-**250** and *syn*-**251** in 33%[i] and 8% yield[ii] respectively (Scheme 5).

[i] **250** was isolated as an inseparable 51:49 mixture of **250**:**249**. The yield is based on a 51:49 mole ratio of the isolated product.
[ii] **251** was isolated in 90:10 d.r.



Scheme 5: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, RT, 3 hrs; (ii) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, RT, 3 hrs.

The *syn*-relative configuration within the minor diastereoisomer *syn*-**251** was proven unambiguously through single-crystal X-ray crystallography (Figure 2).

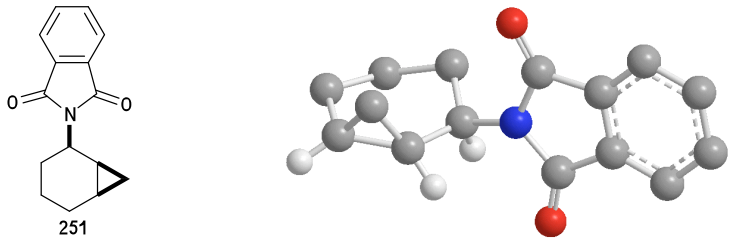
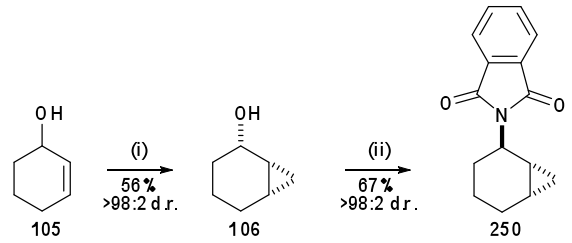


Figure 2: Chem 3D representation of the X-ray crystal structure of *syn*-**251** (some H-atoms omitted for clarity).

From this structure, it was postulated that the relatively low diastereoselectivity of the reaction is due to competition between sterically directed cyclopropanation (*anti*) *versus* cyclopropanation directed through chelation by the carbonyl group (*syn*).

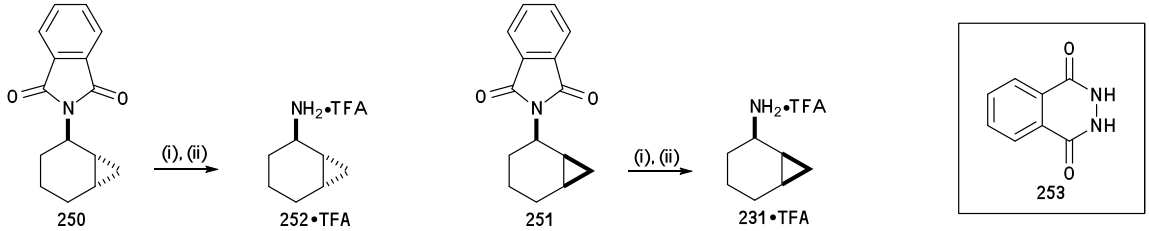
An authentic sample of the major diastereoisomer **250** was synthesised through cyclopropanation of allylic alcohol **105** with the Denmark reagent [$Zn(CH_2Cl)_2$] to give *syn*-**106** in 56% yield and >98:2 d.r., followed by Mitsunobu reaction of *syn*-**106** with phthalimide to effect inversion of the relative stereochemistry and provide *anti*-**250** in 67% yield and >98:2 d.r. (Scheme 6).



Scheme 6: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. $ClCH_2I$, CH_2Cl_2, 0 °C, 30 mins; (ii) 1.1 eq. phthalimide, 1.1 eq. PPh_3, 1.1 eq. DEAD, THF, RT, 24 hrs.

3.3.3 Deprotection

Removal of the *N*-phthalimido group from **250** and **251** could be achieved by hydrazinolysis giving the primary amine TFA salts **252·TFA** and **231·TFA,** respectively (Scheme 7).[iii]



Scheme 7: *Reagents and conditions*; (i) 1.1 eq. $N_2H_4{\cdot}H_2O$, EtOH, reflux, 16 hrs; (ii) TFA.

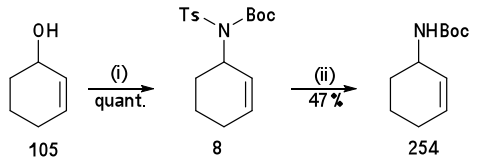
Although *N*-phthalimido protection had resulted in a switch in stereoselectivity, neither the diastereoselectivity nor the yield of the reaction were synthetically useful and so alternative *N*-carbamate protection was next investigated.

3.4.1 *N*-Boc protected substrate synthesis

N-Boc protected substrate **254** was prepared from alcohol **105** according to a literature procedure.[5] Thus, treatment of **105** with TsNHBoc **255**,[6] PPh_3 and DEAD afforded bis-protected allylic amine **8** in quantitative yield. Subsequent sulfonamide

[iii] Unfortunately the samples of **252·TFA** and **231·TFA** were found to contain significant impurities (such as **253**) from the phthalimido fragment. Due to the relatively high aqueous solubility of the free amine it was not possible to purify these mixtures further and, as such, isolated yields are not reported. However, the ^{1}H NMR spectra were sufficiently charachteristic to allow comparison with samples of **252·TFA** and **231·TFA** prepared *via* alternative routes (*vide infra*).

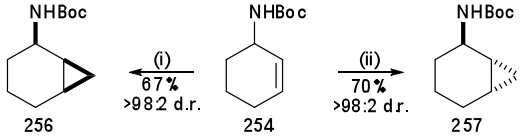
deprotection with sodium naphthalide gave *N*-Boc protected substrate **254** in 47% yield (Scheme 8).



Scheme 8: *Reagents and conditions*; (i) 1.5 eq. TsNHBoc **255**, 2.0 eq. PPh_3, 1.5 eq. DEAD, THF, RT, 24 hrs, (ii) 5 eq. Na, 5 eq. napthalene, THF, 0 °C to RT, 2 hrs.

3.4.2 Cyclopropanation of 254

Treatment of **254** with 2 eq. of the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] for 1 hr at room temperature gave cyclopropane **256** in 67% yield and >98:2 d.r., which was initially assigned the *syn* relative configuration by analogy to the observations of Tardella *et al*.[1] and Marquez *et al.* (*vide supra*).[2] In contrast, treatment of **254** with 2 eq. of Shi's carbenoid [$CF_3CO_2ZnCH_2I$] for 1 hr gave the diastereoisomeric product **257** in 70% yield and >98:2 d.r. which was assigned the *anti*- relative configuration (Scheme 9).



Scheme 9: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, RT, 1 hr.

3.4.3 Deprotection and proof of stereochemistry

In order to confirm the assigned relative stereochemistries of the two products **256** and **257**, both compounds were deprotected to their corresponding primary amine TFA salts, **231·TFA** and **252·TFA**, by treatment with TFA in CH_2Cl_2. Comparison of these samples with those prepared previously from *N*,*N*-dibenzylamine *syn*-**158** (see

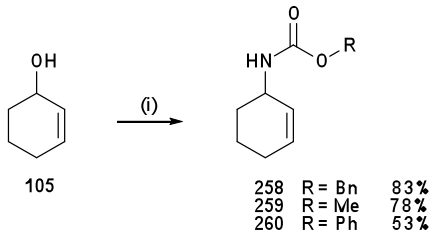
chapter 2) and *N*-phthalimido compound *anti*-**250**, enabled confirmation of this assignment (Scheme 10).

Scheme 10: *Reagents and conditions*; (i) 3.0 eq TFA, CH_2Cl_2, 0 °C, 3 hrs.

Having established that *N*-Boc protected substrate **254** can be efficiently cyclopropanated to give either the *syn* or *anti* 2-aminobicyclo[4.1.0]heptane products depending upon the carbenoid used, the scope and utility of these reactions were next investigated.

3.5.1 Substrate scope: variation of protecting group

In order to probe the generality of the observed stereodivergence, substrates **258-260** were prepared in 57-83% yield through the $Bi(OTf)_3$-catalysed substitution of allylic alcohol **105** with a range of carbamates according to the method developed by Shibasaki *et al.* (Scheme 11).[7]

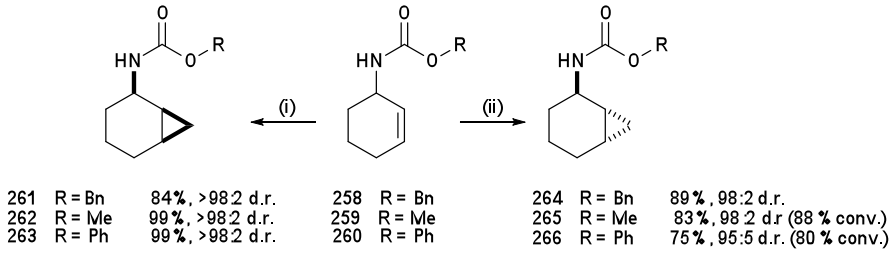


Scheme 11: (i) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. H_2NCO_2R, $MgSO_4$, THF (or 1,4-dioxane), RT, 16 hrs.

3.5.2 Cyclopropanation of 258-260

It was found that whilst reaction with 2 equivalents of $Zn(CH_2I)_2$ consistently gave complete conversion to the *syn* cyclopropanes **261-263** within 1 hr, the rate of reaction with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] was more variable. Although >95%

conversion of **258** to **264** was achieved using 2 equivalents of $CF_3CO_2ZnCH_2I$ for 4 hrs, treatment of **259** and **260** under these conditions gave only 34% and 51% conversion to **265** and **266** respectively. However, it was found that the use of 3 equivalents of carbenoid gave increased conversion to the cyclopropane (Scheme 12).



Scheme 12: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (i) 2.0-3.0 eq. $ZnEt_2$, 4.0-6.0 eq. CH_2I_2, 2.0-3.0 eq. TFA, CH_2Cl_2, RT, 4 hrs.

The relative configurations within **261** and **264** were confirmed by ^{1}H NMR nOe experiments. In particular, *anti*-**264** exhibited a strong nOe enhancement between C(2)*H* and the endo proton on the cyclopropane. This nOe enhancement was absent in *syn*-**261** which instead showed a strong enhancement between the N*H* proton and the endo proton on the cyclopropane (Figure 3).

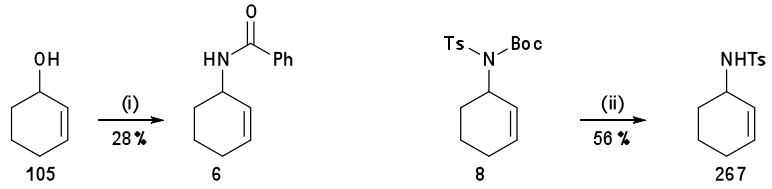
Figure 3: Important observed ^{1}H NMR nOe enhancements for **264** and **261**.

3.5.3 Cyclopropanation of amides and sulfonamides

Having shown that the stereodivergent cyclopropanation protocol works well for a range of carbamate protecting groups, it was decided to investigate the utilisation of amide and sulfonamide protecting groups in this reaction manifold.

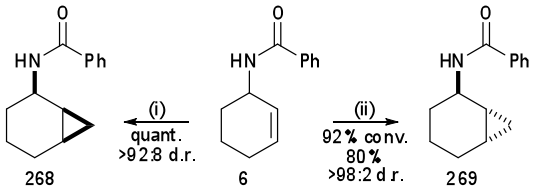
Thus, *N*-benzoyl protected substrate **6** was synthesised from 2-cyclohexen-1-ol **105** in 28% yield by an analogous procedure to that used previously. Additionally, *N*-tosyl

substrate **267** was synthesised from bis-protected **8** in 56% yield by treatment with TFA in CH_2Cl_2 (Scheme 13).



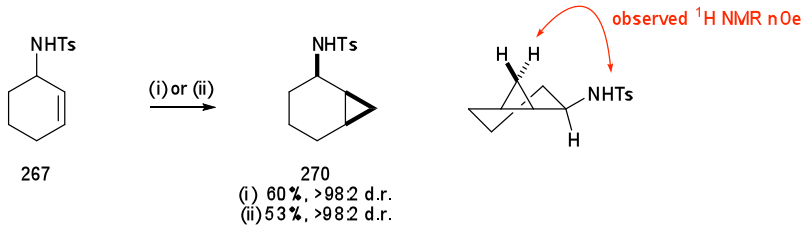
Scheme 13: *Reagents and conditions*; (i) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. H_2NCOPh, $MgSO_4$, THF, RT, 16 hrs; (ii) 3.0 eq. TFA, CH_2Cl_2, RT, 1 hr.

Cyclopropanation of **6** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] gave *syn*-**268** in quantitative yield and 92:8 d.r., whilst cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] afforded *anti*-**269** in 80% yield (92% conversion) as a single diastereoisomer. The relative configurations within **268** and **269** were assigned by analogy to the *N*-carbamate protected examples described above (Scheme 14).



Scheme 14: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, RT, 6 hrs.

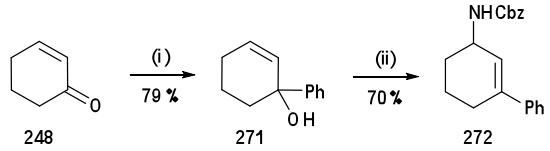
Surprisingly, cyclopropanation of *N*-tosyl protected substrate **267** with either the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] or Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gave the same product **270** in 60% and 53% yield respectively. The relative configuration within **270** was established by ^{1}H NMR nOe studies. As in the case of *N*-Cbz protected *syn*-**261**, a strong enhancement was observed between the sulfonamide N*H* proton and the endocyclic proton on the cyclopropane ring (Scheme 15).



Scheme 15: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, RT, 1 hr.

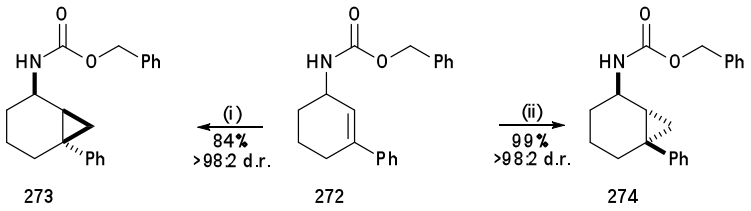
3.5.4 Synthesis and cyclopropanation of 3-phenyl substituted substrate 272

The incorporation of C(3)-substitution was next probed by the synthesis and cyclopropanation of 3-phenyl substituted substrate **272**. Substrate **272** was synthesized in two steps from 2-cyclohexene-1-one **105**: regioselective 1,2-addition of phenyllithium gave tertiary alcohol **271** in 79% yield and $Bi(OTf)_3$-mediated displacement with benzyl carbamate was found to occur at the less substituted end of the proposed allyl cation intermediate, giving the desired substrate **272** in 70% isolated yield (Scheme 16).



Scheme 16: *Reagents and conditions*; (i) 1.1 eq. PhLi, Et_2O, –78 °C → RT, 2 hrs; (ii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate, THF, $MgSO_4$, RT, 16 hrs.

Cyclopropanation of **272** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] gave **273** in 84% yield and >98:2 d.r., whilst reaction with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gave **274** in 99% yield and >98:2 d.r. (Scheme 17).



Scheme 17: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, 2 eq. TFA, CH_2Cl_2, RT, 12 hrs.

Having shown that the cyclopropanation reactions are applicable to a range of cyclohexenyl substrates, the mechanism and origin of the observed stereodivergence was next investigated.

3.6.1 Proposed mechanism

Based on literature precedent for cyclopropanation of the corresponding allylic alcohols, the following mechanisms were proposed to account for the observed stereodivergence.

It was though that, as with the cyclopropanation of allylic alcohols, the first step would be deprotonation of the relatively acidic amide proton, giving either iodomethylzinc amide **276** or trifluoroacetylzinc amide **277** depending upon the carbenoid used (Figure 4).

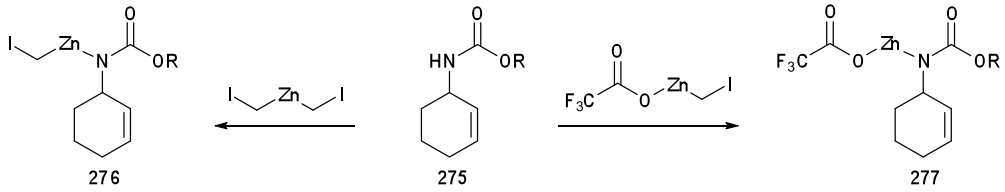


Figure 4: Proposed formation of zinc amides **276** and **277** by deprotonation of carbamate **275** by $Zn(CH_2I)_2$ or $CF_3CO_2ZnCH_2I$ respectively.

In the case of the Wittig-Furukawa reagent [$Zn(CH_2I)_2$], iodomethylzinc amide **276** can then undergo intramolecular cyclopropanation to give *syn*-**278**, by direct analogy to the *syn*-directed cyclopropanation of allylic alcohols (Figure 5).[8]

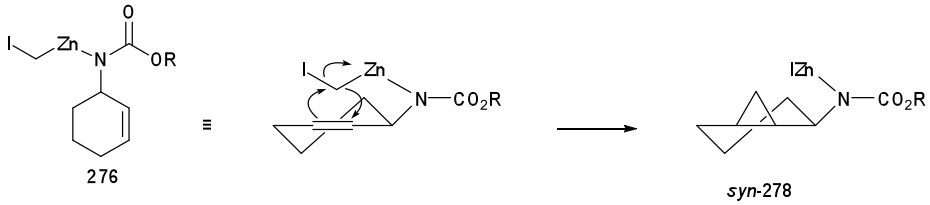


Figure 5: Proposed mechanism for cyclopropanation with $Zn(CH_2I)_2$.

However, in the case of Shi's carbenoid [$CF_3CO_2ZnCH_2I$], trifluoroacetylzinc amide **277** cannot undergo intramolecular cyclopropanation. Instead, it was proposed that a

second equivalent of carbenoid could intermolecularly cyclopropanate on the less sterically hindered *anti*-face of the double bond giving *anti*-**279** through an intermolecular cyclopropanation (Figure 6).

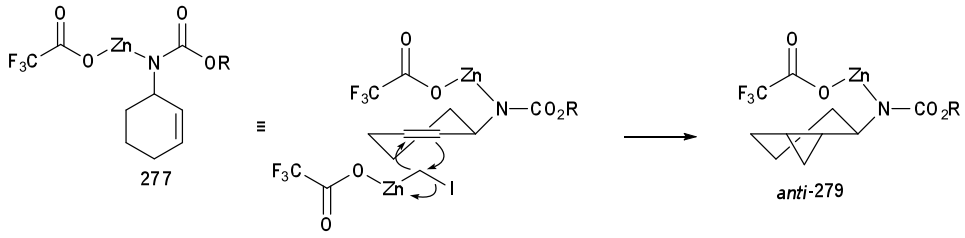


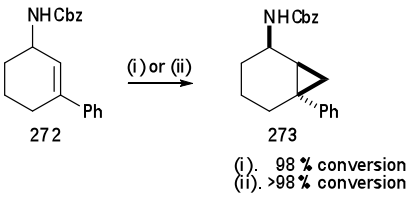
Figure 6: Proposed mechanism for cyclopropanation with $CF_3CO_2ZnCH_2I$.

3.6.2 Mechanistic investigations

Having proposed a mechanism to explain the observed stereodivergence, a series of experiments were next designed to test this hypothesis.

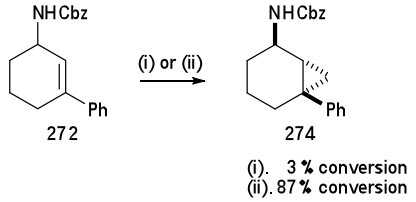
One distinct difference in the two mechanisms is that *syn*-cyclopropanation with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] should require only 1 equivalent of carbenoid, whereas *anti*-cyclopropanation should require 2 equivalents of Shi's carbenoid [$CF_3CO_2ZnCH_2I$] since one equivalent is consumed in the deprotonation step.

Using **272** as model system, treatment with 1 equivalent of the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] for 60 mins at room temperature resulted in 98% conversion to *syn*-**273**, whilst treatment with 2 equivalents of carbenoid resulted in 100% conversion to *syn*-**273** as expected (Scheme 18).



Scheme 18: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins.

Conversely, treatment of **272** with 1 equivalent of Shi's carbenoid [$CF_3CO_2ZnCH_2I$] resulted in only 3% conversion to *anti*-**274**, whilst treatment with 2 equivalents of carbenoid dramatically increased the extent of reaction, giving *anti*-**274** in 87% conversion after 60 mins (Scheme 19).



Scheme 19: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, 1.0 eq. TFA, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 60 mins.

3.6.3 Competition experiments

Having proposed that *syn*-cyclopropanation occurs *via* intramolecular cyclopropanation, whereas *anti*-cyclopropanation occurs *via* intermolecular cyclopropanation, a series of competition experiments were designed to verify this hypothesis.

As in the previous mechanistic investigations (see Chapter 2), the use of cyclohexene **155** as an external olefin was not practical due to its relatively low boiling point (83 °C). In contrast, commercially available 1-phenylcyclohexene **280** has a boiling point of 251-253°C and as such it was proposed that it should be suitable as a mimic for the olefin functionality within 3-phenyl substituted substrate **272**. In addition, it was proposed that **281** could be used as a mimic for the carbamate functionality within **272**, having similar steric and electronic properties (Figure 7).

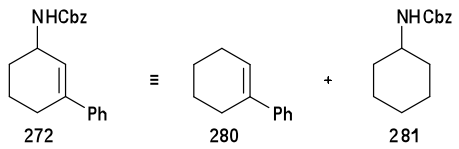
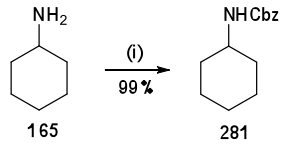


Figure 7: **280** and **281**, proposed mimics for the olefin and carbamate functionalities within **272** respectively.

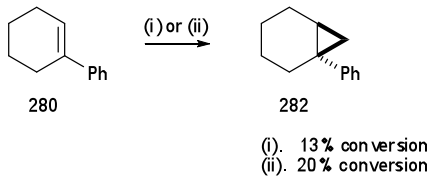
Carbamate **281** was easily synthesised from cyclohexylamine **165** in 99% yield by reaction with benzyl chloroformate (Scheme 20).



Scheme 20: *Reagents and conditions*; (i) 1.1 eq. CbzCl, 1.1 eq. NEt_3, THF, 0 °C → RT, 16 hrs.

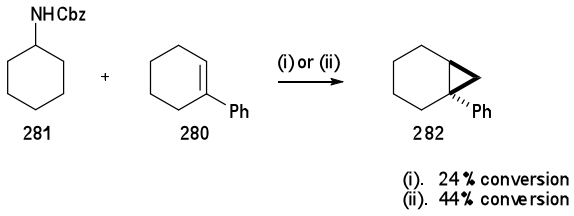
3.6.4 Competition experiments: Wittig-Furukawa reagent

Reaction of 1-phenylcyclohexene **280** with 1 equivalent of $Zn(CH_2I)_2$ for 60 mins resulted in 13% conversion to cyclopropane **282**, whilst reaction with 2 equivalents of $Zn(CH_2I)_2$ under identical conditions resulted in 20% conversion to **282** (Scheme 21).



Scheme 21: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins.

The effect of the carbamate functionality was next investigated. Reaction of **280** in the presence of 1 equivalent of carbamate **281** and 1 equivalent of $Zn(CH_2I)_2$ for 60 mins resulted in 24% conversion to **282** and reaction with 2 equivalents of $Zn(CH_2I)_2$ led to 44% conversion (Scheme 22).



Scheme 22: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins.

The increased reactivity of **280** in the presence of carbamate **281** can be rationalized by the formation of intermediate iodomethylzinc amide **283** which, due to the electron

withdrawing nature of the carbamate functionality, is postulated to be a more reactive carbenoid than $Zn(CH_2I)_2$, consistent with the observations of Shi *et al.* (Figure 8).[9]

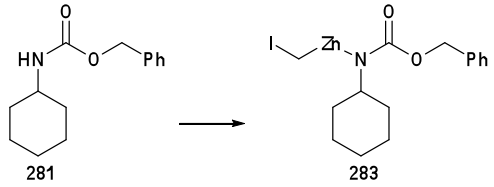
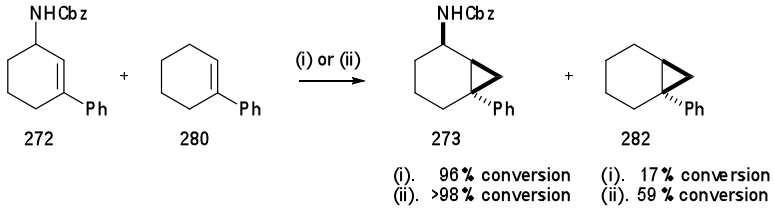


Figure 8: Proposed formation of intermediate **283** through reaction of **281** with $Zn(CH_2I)_2$

It should be noted however that the observed rate of intermolecular cyclopropanation mediated by iodomethylzinc amide **283** is still significantly slower than that observed for substrate **272**, consistent with intramolecular cyclopropanation in the later case.

To test this, cyclopropanation of 1-phenylcyclohexene **280** in the presence of 1 equivalent of substrate **272** was next investigated. Reaction with 1 equivalent of $Zn(CH_2I)_2$ resulted in 17% conversion of **280** to **282** and 96% conversion of **272** to **273**,[iv] whereas reaction with 2 equivalents of $Zn(CH_2I)_2$ resulted in 59% conversion of **280** to **282** and 100% conversion of **272** to **273** (Scheme 23).



Scheme 23: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 60 mins.

In order to probe these results further, the reactions of **272** and **280** with 2 equivalents of $Zn(CH_2I)_2$ was monitored more closely, with aliquots taken from the reaction every 5 minutes. It was found that cyclopropanation of substrate **272** was actually complete in 25 minutes, the conversion of **280** to **282** at this point being 27% (Figure 9).

[iv] The observation that the total conversion is greater than 100% may indicate that the deprotonation step does not proceed to 100% conversion. This would allow a proportion of the $Zn(CH_2I)_2$ to transfer more than one equivalent of carbene.

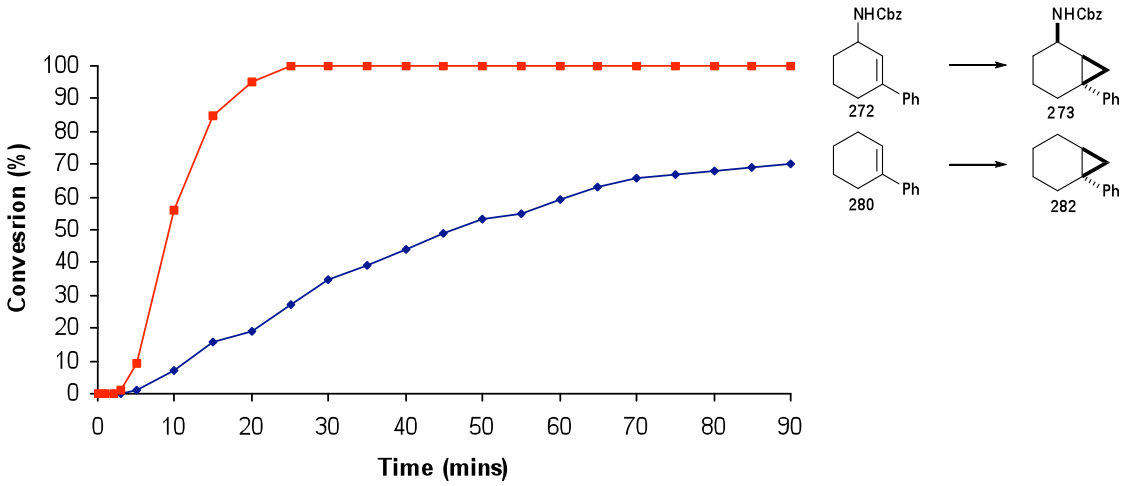


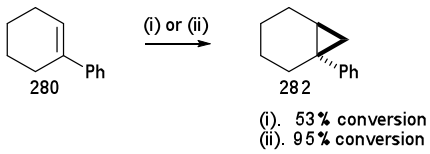
Figure 9: Time-study of reaction of **272** and **280** with 2 eq. $Zn(CH_2I)_2$.

These results strongly suggest that substrate **272** reacts *via* an intramolecular cyclopropanation step, since the reaction rate is significantly higher (ratio of **273**:**282** is 8:1 after 10 minutes) than that observed for intermolecular cyclopropanation in the presence of a carbamate.

3.6.5 Competition experiments: Shi's carbenoid

The same series of competition experiments were next performed with $CF_3CO_2ZnCH_2I$, in order to probe the proposed intermolecular nature of the *anti* selective cyclopropanation.

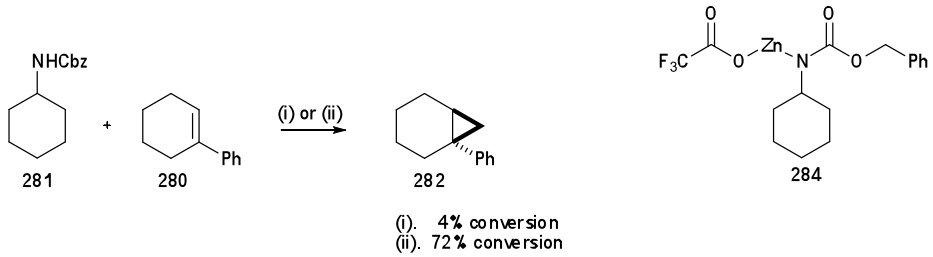
The control experiments found that reaction of 1-phenylcyclohexene **280** with 1 equivalent of $CF_3CO_2ZnCH_2I$ for 60 mins resulted in 53% conversion to **282**, whilst reaction with 2 equivalents of $CF_3CO_2ZnCH_2I$ led to 95% conversion (Scheme 24).



Scheme 24: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, 1.0 eq. TFA, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 60 mins.

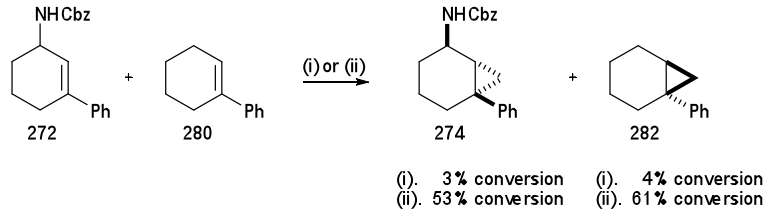
In the presence of carbamate **281**, reaction of **280** with 1 equivalent of $CF_3CO_2ZnCH_2I$ led to only 4% conversion to **282**, consistent with 1 equivalent of

$CF_3CO_2ZnCH_2I$ being consumed by deprotonation of carbamate **281** to form intermediate **284**. Reaction with 2 equivalents of $CF_3CO_2ZnCH_2I$ restores reasonably high reactivity, with 72% conversion to **282** being observed (Scheme 25).



Scheme 25: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, 1.0 eq. TFA, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 60 mins.

Again, as expected, reaction of 1-phenylcyclohexene **280** in the presence of substrate **272** and only 1 equivalent of $CF_3CO_2ZnCH_2I$ resulted in extremely low conversion to either **274** or **282**. Reaction of **272** and **280** with 2 equivalents of $CF_3CO_2ZnCH_2I$ resulted in 53% conversion of **272** to **274** and 61% conversion of **280** to **282**. Importantly, the carbenoid appears to show no strong preference for cyclopropanation of substrate **272** over 1-phenylcyclohexene **280**, consistent with intermolecular cyclopropanation rather than intramolecular (Scheme 26).



Scheme 26: *Reagents and conditions*; (i) 1.0 eq. $ZnEt_2$, 2.0 eq. CH_2I_2, 1.0 eq. TFA, CH_2Cl_2, RT, 60 mins; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 60 mins.

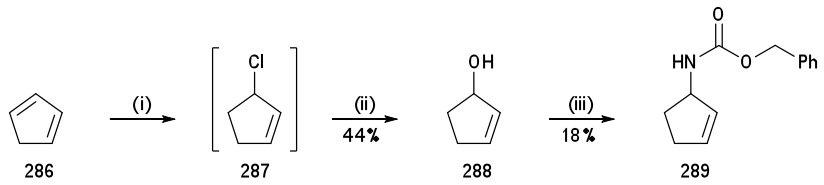
The above experiments support the proposed rationale that *syn*-cyclopropanation arises through *N*-directed intramolecular cyclopropanation whilst *anti*-cyclopropanation arises from sterically directed intermolecular cyclopropanation. Having established this, the scope of the reactions with respect to the structure of the substrate was next investigated.

3.7 Substrate Scope

Although a range of carbamate protecting groups have been shown to be effective in the reaction, it was decided to use *N*-Cbz protection as a standard, due partly to the lower cost of benzyl carbamate **285** in comparison to the alternative carbamates, and also because *N*-Cbz deprotection is known to be operationally simple and generally high yielding.

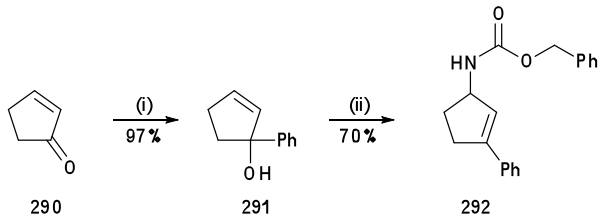
3.7.1 Synthesis of cyclopentyl substrates 289 and 292

Cyclopentyl substrate **289** was synthesised in 8% yield from cyclopentadiene **286** by chlorination, hydrolysis and $Bi(OTf)_3$-mediated displacement with benzyl carbamate **285** (Scheme 27).



Scheme 27: (i) HCl (g); (ii) sat. aq. $NaHCO_3$; (iii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate **285**, 1,4-dioxane, RT, 16 hrs.

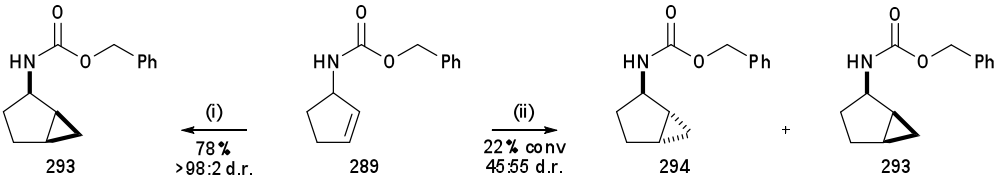
The corresponding 3-phenyl substituted derivative **292** was synthesized in two steps from 2-cyclopenten-1-one **290** by an analogous procedure to that used previously for the synthesis of **272**. Thus, addition of phenyllithium to **290**, followed by $Bi(OTf)_3$-mediated displacement of allylic alcohol **291** with benzyl carbamate **285** gave the desired substrate **292** in 68% yield over two steps (Scheme 28).



Scheme 28: *Reagents and conditions*; (i) 1.1 eq. PhLi, Et_2O, −78 °C → RT, 2 hrs; (ii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate **285**, THF, $MgSO_4$, RT, 1 hr.

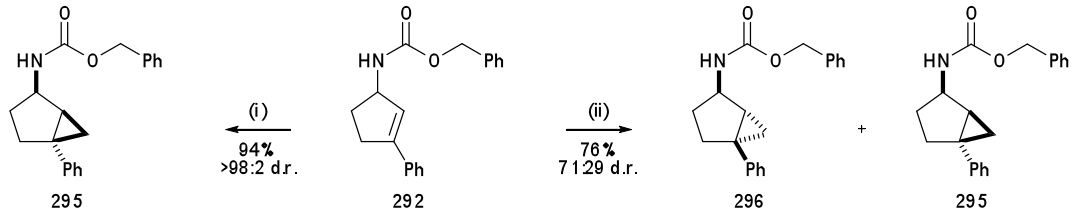
3.7.2 Cyclopropanation of cyclopentyl substrates 289 and 292

Cyclopropanation of **289** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] afforded *syn*-**293** in 78% yield as a single diastereoisomer;[v] however it was found that reaction of **289** with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] proceeded to only 22% conversion after 12 hours, giving a 45:55 mixture of *anti*-**294**:*syn*-**293** (Scheme 29).



Scheme 29: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 12 hrs.

Cyclopropanation of substrate **292** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] afforded **295** as a single diastereoisomer in 94% yield.[vi] Cyclopropanation of **292** with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gave an inseparable 71:29 mixture of **296**:**295** in 76% combined yield (Scheme 30).



Scheme 30: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 16 hrs.

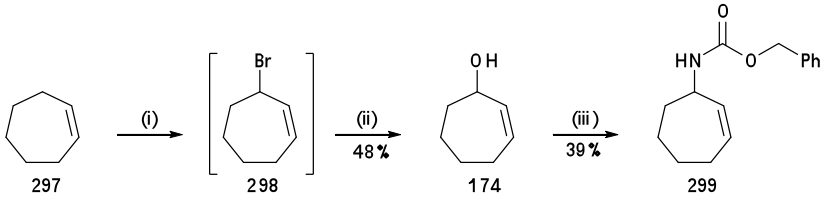
Although the observed diastereoselectivity in the cyclopropanation of **292** with Shi's carbenoid is not outstanding, it is a significant improvement over the cyclopropanation of the unsubstituted analogue **289**. The reasons for the decreased diastereoselectivity in the *anti*-cyclopropanation of cyclopentyl substrates **289** and **292** are not obvious. Since it is not known what the precise structure or

[v] The relative configuration within **293** was assigned on the basis of an *N*-directed reaction, by analogy with the previously studied examples.
[vi] The relative configuration within **295** was assigned on the basis of an *N*-directed reaction, by analogy with the previously studied examples.

conformational preference of the proposed intermediate zinc-amide is, it is difficult to rationalize the steric control that is imparted on either face of the olefin.

3.7.3 Synthesis of cycloheptyl substrate 299[10]

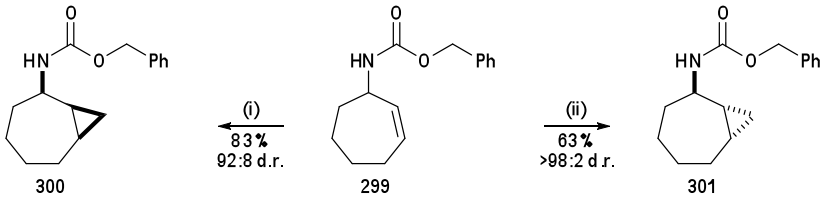
Cycloheptyl substrate **299** was synthesised in from cycloheptene by Wohl-Ziegler allylic bromination of cycloheptene **297**, hydrolysis of the allylic bromide **298** and $Bi(OTf)_3$-mediated displacement of allylic alcohol **174** with benzyl carbamate **285** to give **299** in 19% yield over 3 steps (Scheme 31).



Scheme 31: *Reagents and conditions*; (i) 1.0 eq NBS, 0.01 eq. AIBN, CCl_4, 90 °C, 3 hrs; (ii) 3.0 eq. $NaHCO_3$, THF/H_2O, RT, 16hrs; (iii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate **285**, 1,4-dioxane, RT, 16 hrs.

3.7.4 Cyclopropanation of 299 and proof of stereochemistry

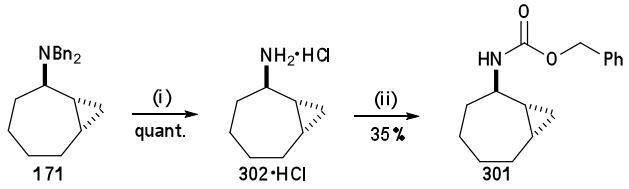
Reaction of **299** with either the Wittig-Furukawa reagent $[Zn(CH_2I)_2]$ or Shi's carbenoid $[CF_3CO_2ZnCH_2I]$ proceeded smoothly to give *syn*-**300** in 83% yield and 92:8 d.r., and *anti*-**301** as a single diasteroisomer in 63% yield, respectively (Scheme 32).



Scheme 32: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 12 hrs.

An authentic sample of *anti*-**301** was prepared from *N*,*N*-dibenzyl protected **171**[11] by hydrogenolysis and acidification to afford amine hydrochloride salt **302·HCl** in quantitative yield, followed by reaction with benzyl chloroformate to give **301** in 35%

yield, thus confirming the assigned relative configurations within *syn*-**300** and *anti*-**301** (Scheme 33).

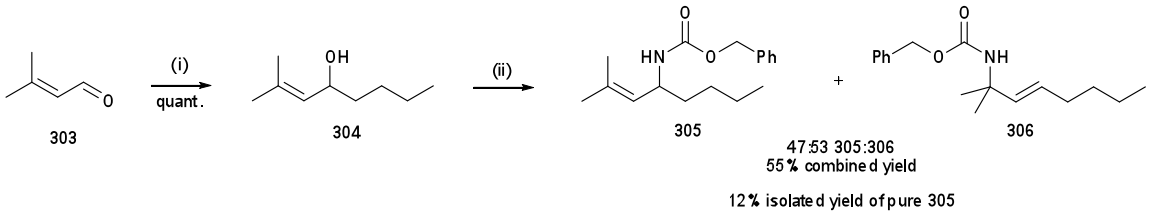


Scheme 33: *Reagents and conditions*; (i) 5 atm. H_2, 30 wt. % Pd/C, MeOH/H_2O/AcOH (40:4:1), RT, 18 hrs, then conc. HCl (ii) 1.2 eq. CbzCl, 2.4 eq. NEt_3, THF, 0 °C → RT, 16 hrs.

3.7.5 Cyclopropanation of acyclic allylic carbamates

Having shown that the cyclopropanation of cyclic allylic carbamates generally proceeds with excellent diastereoselectivity to access either the *syn*- or *anti*-diastereoisomer depending upon the carbenoid used, the cyclopropanation of an acyclic allylic carbamate was next investigated.

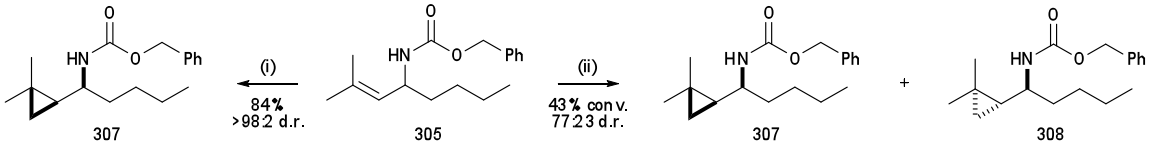
The synthesis of the target substrate **305** began with addition of BuLi to aldehyde **303** to give allylic alcohol **304** in quantitative yield. Subsequent treatment with benzyl carbamate and $Bi(OTf)_3$ resulted in formation of a 47:53 mixture of the desired product **305** and its regioisomer **306**. The regioisomers were partially separable by flash column chromatography, allowing the isolation of pure **305** in 12% yield, along with a 33:67 mixture of **305**:**306** in 43% yield (Scheme 34).[vii]



Scheme 34: *Reagents and conditions*; (i) 1.2 eq. BuLi, THF, −78 °C, 1 hr; (ii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate **285**, $MgSO_4$, THF, RT, 14 hrs.

[vii] For a discussion on the mechanism of the reaction, see ref. 7. The reaction has been shown to be reversible, and so the product distribution is presumably thermodynamically rather than kinetically controlled.

Cyclopropanation of **305** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] gave the desired cyclopropane **307** in 84% yield as a single diastereoisomer.[viii] However, reaction with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] for 6 hrs gave only 43% conversion to a 77:23 mixture of **307**:**308**, respectively (Scheme 35).



Scheme 35: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr; (ii) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, 2.0 eq. TFA, CH_2Cl_2, RT, 6 hrs.

In the case of the Wittig-Furukawa reagent [$Zn(CH_2I)_2$], reaction is proposed to take place in an intramolecular fashion from an intermediate zinc amide **309**. Minimisation of $A_{1,3}$-strain should result in cyclopropanation being directed as shown (Figure 10).

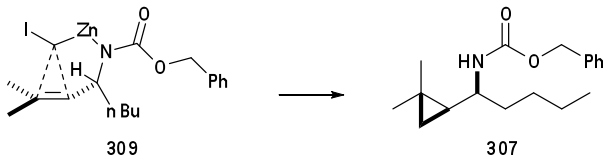


Figure 10: Intramolecular cyclopropantion of **305** by the Wittig-Furukawa reagent, $Zn(CH_2I)_2$.

In contrast, the cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] is proposed to be under steric control. In this case, the carbenoid has a choice of approaching **310** from the same face as the nitrogen (A), or the same face as the *n*-Bu group (B). Clearly the relatively low diastereoselectivity of the reaction indicates that the energies of the two alternative transition states resulting from these two approach paths are not significantly different (Figure 11).

[viii] The relative stereochemistry of **307** was assigned on the basis of *N*-directed cyclopropanation through a transition state which minimizes $A_{1,3}$-strain.

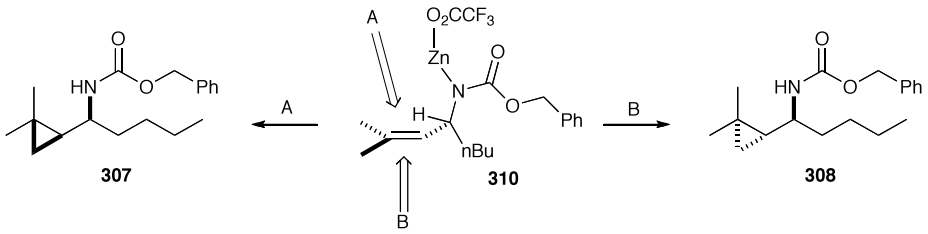
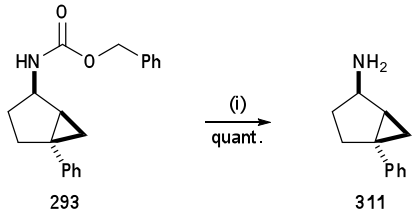


Figure 11: Approach paths for cyclopropanation of **305** with Shi's carbenoid, $CF_3CO_2ZnCH_2I$.

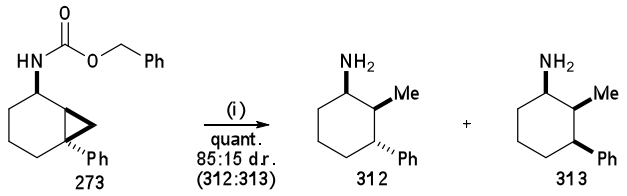
3.8.1 Deprotection of 293, 273 and 274

The deprotection of **293**, **273** and **274** to the corresponding primary amines was next investigated in order to probe the potential lability of the benzylic cyclopropane bonds to hydrogenolysis. It was found that hydrogenolysis of bicyclo[3.1.0]hexane **293** with Pd/C proceeded under 1 atm. of H_2 to give the corresponding primary amine **311** as the sole product in quantitative yield (Scheme 36).



Scheme 36: *Reagents and conditions*; (i) Pd/C (30 wt. %), 1 atm. H_2, MeOH/EtOAc, 3 hrs.

In contrast however, treatment of bicyclo[4.1.0]heptane **273** with Pd/C under 1 atmosphere of H_2 for 4 hrs resulted in exocyclic cleavage of the cyclopropane ring, giving an 85:15 mixture of **312**:**313** respectively in quantitative yield (Scheme 37).



Scheme 37: *Reagents and conditions*; (i) Pd/C (30 wt. %), 1 atm. H_2, MeOH/EtOAc, 4 hrs.

The relative configuration of the major product **312** was assigned on the basis of ^1H NMR nOe analysis. On the assumption that **312** and **313** adopt chair conformations, with the bulky phenyl ring in an equatorial position, the all-*syn* diastereoisomer **313**

would be expected to show a strong ^{1}H NMR nOe enhancement between the 1,3-diaxial C(1)*H* and C(3)*H* protons however this was not observed. Instead, strong ^{1}H NMR nOe enhancements were observed between the C(1)*H* and C(3)*H* protons and the equatorial C(2)*Me* protons, consistent with the 1,2-*syn*-2,3-*anti* configuration within **312** (Figure 12).

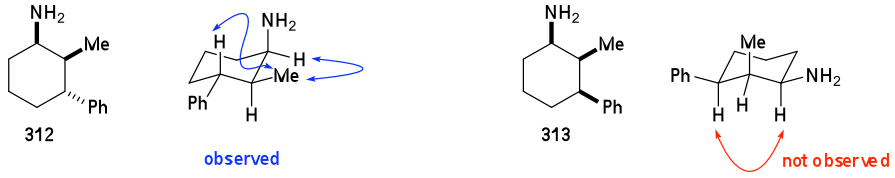
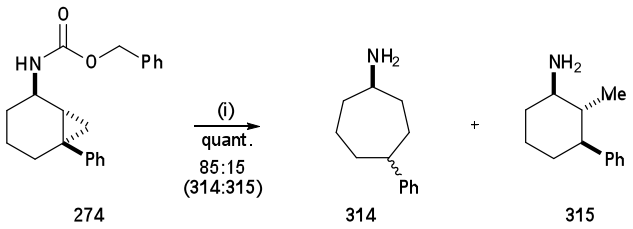


Figure 12: Observed ^{1}H NMR nOe enhancements (blue) for **312** and the expected nOe enhancements (red) for the alternative epimeric product **313**.

Surprisingly, hydrogenolysis of **274** under identical conditions resulted in almost complete endocyclic cleavage of the cyclopropyl ring, giving an inseparable 85:15 mixture of **314** and **315** in quantitative yield. Unfortunately, the relative configuration of cycloheptane **314** could not be determined; however it appears to have been formed in high diastereoselectivity.[ix] The relative configuration of minor product **315** was assigned by analogy with the major exocyclic-cleavage product observed during the hydrogenolysis of **274** (Scheme 38).

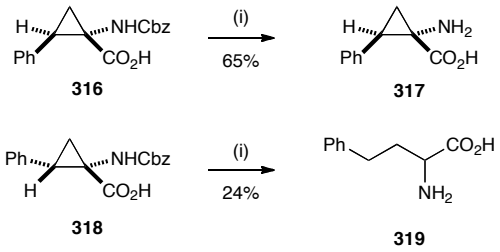


Scheme 38: *Reagents and conditions*; (i) Pd/C (30 wt. %), 1 atm. H_2, MeOH, 4 hrs.

[ix] Exhaustive attempts to obtain single-crystals of **314**, its *p*-nitrobenzoate derivative, or a variety of amine salts for X-ray crystallography were unsuccessful.

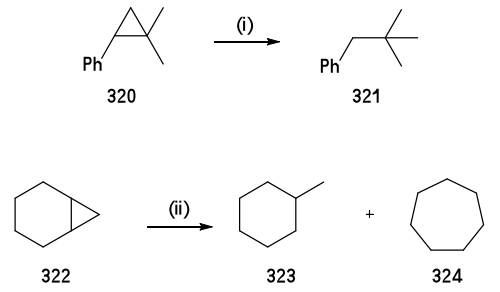
3.8.2 Discussion

It is not unexpected that the aryl-substituted cyclopropanes can be cleaved under hydrogenolysis conditions,[12] however the observation that both the relative rate and regioselectivity of the hydrogenolyses are highly dependent upon the structure of the substrate is interesting. In a related example, Stammer *et al.* have shown that the diastereoisomeric cyclopropanes **316** and **318** undergo hydrogenolysis to give **317** and **319** respectively under identical conditions, though no explanation is offered for this observation (Scheme 39).[13]



Scheme 39: *Reagents and conditions*; (i) 5% Pd/C, 1.0 eq. pyridine, EtOH, RT, 1.5 hrs.

It has also been shown by Schultz that hydrogenolysis of aryl substituted cyclopropanes such as **320** generally occurs between the aryl-substituted carbon and the less substituted of the other two carbons.[14] Additionally, Musso *et al.* have shown that the hydrogenolysis of bicyclo[4.1.0]hexanes such as **322** gives predominantly exocyclic cleavage (Scheme 40).[15]



Scheme 40: *Reagents and conditions*; (i) Pd/C, 1 atm. H_2, EtOH, RT; (ii) Pd/C, 150 atm. H_2, C_6H_{12}, 50 °C, 24 hrs.

On this basis, the exocyclic hydrogenolysis of **273** to **312** is not unexpected; however the high selectivity of **274** for endocyclic cleavage is unusual. One possible

explanation is that hydrogenolysis is directed by the amino group binding to the catalyst surface.[16] From this model, the relative stereochemistry of **314** would be predicted to be *anti*- as shown (Figure 13).

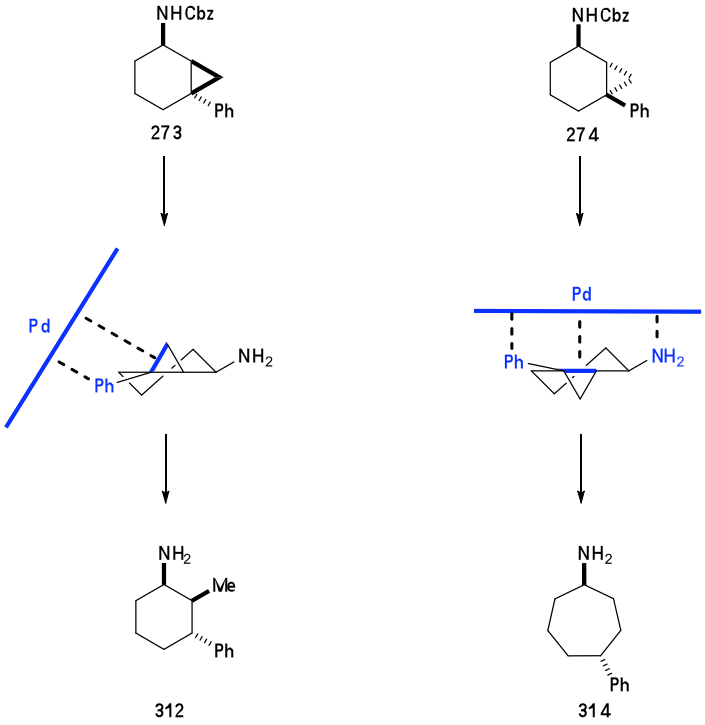
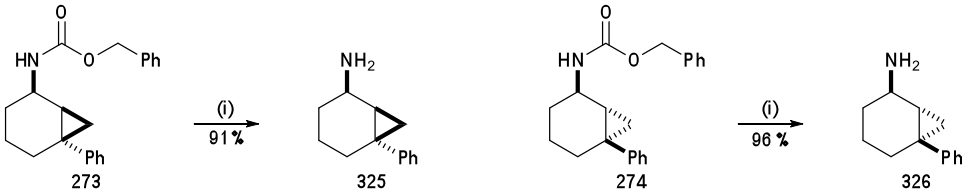


Figure 13: Proposed mechanism for the regioselective hydrogenolysis of **273** and **274**.

3.8.3 Alternative deprotection of 273 and 274

An alternative method for the *N*-Cbz deprotection of **273** and **274** was next sought in order to provide access to the desired 2-aminobicyclo[4.1.0]hexane products. It was found that deprotection of the *N*-Cbz groups within **273** and **274** could be achieved efficiently by treatment with TMSI in MeCN, giving **325** and **326** in 91 and 96% yield respectively (Scheme 41).

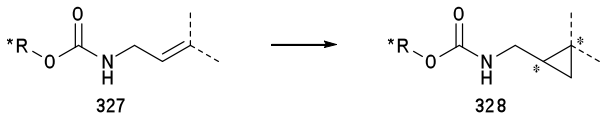


Scheme 41: *Reagents and conditions*; (i) 1.5 eq. TMSI, MeCN, RT, 30 mins.

This provides an alternative route for deprotection in cases where hydrogenolysis results in cleavage of the cyclopropane ring. Additionally, it has been shown that the cyclopropanation reactions work extremely well for a range of carbamate and amide protecting groups, and as such an alternative protecting group strategy can be readily employed if problems are encountered during hydrogenolysis.

3.9 Investigations towards the asymmetric cyclopropanation of allylic carbamates

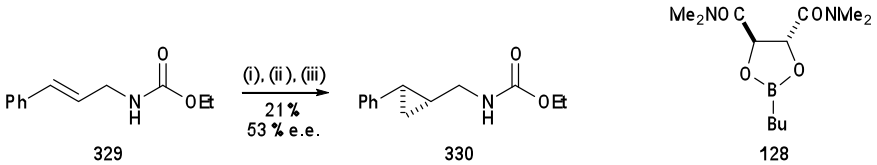
Having developed an effective protocol for the cyclopropanation of allylic carbamates, the possibility of using a chiral auxiliary in order to achieve asymmetric cyclopropanation was next investigated (Figure 14).



327 328

Figure 14: Asymmetric cyclopropanation using chiral carbamates.

The only previous example of the attempted asymmetric cyclopropanation of an allylic carbamate was reported by Charette *et al.* who showed that cyclopropanation of ethyl carbamate **329** in the presence of chiral dioxaborolane ligand **128** gives cyclopropane **330** in 21% yield and 53% e.e. (Scheme 42).[17]



329 330 128

Scheme 42: *Reagents and conditions*; (i) 1.1 eq $ZnEt_2$, CH_2Cl_2; (ii) 1.0 eq. **128**; (iii) 2.0 eq. $Zn(CH_2I)_2$, CH_2Cl_2.

3.9.1 Synthesis of substrates 331-334

It was decided to initially focus on carbamate protecting groups derived from the chiral pool. Thus, the substrates **331**, **332**, **333** and **334**, derived from (−)-menthol **335**, (*S*)-α-methylbenzyl alcohol **336**, (−)-myrtanol **337** and (−)-borneol **338** respectively, were selected for initial investigations (Figure 15).

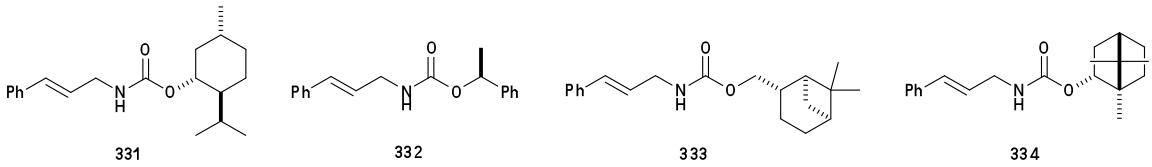
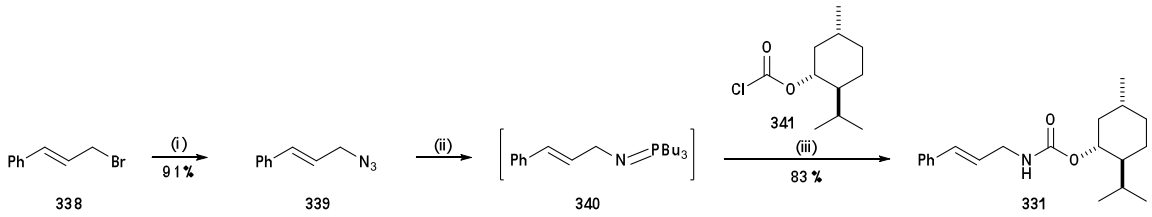


Figure 15: Substrates chosen to test the asymmetric cyclopropanation.

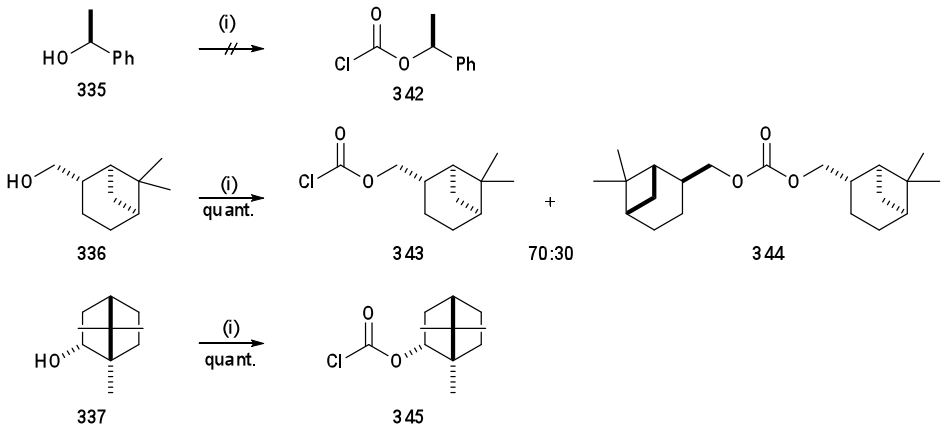
Menthyl-derived substrate **331** was synthesised from cinnamyl bromide **338** through formation of azide **339** in 91% yield, followed by Staudinger reaction to form iminophosphorane **340** and reaction with commercially available (−)-menthyl chloroformate **341** to give **331** in 83% yield (Scheme 43).



Scheme 43: *Reagents and conditions*; (i) 2.0 eq NaN_3, H_2O/acetone (1:3, v/v), RT, 16 hrs; (ii) 1.05 eq. *n*Bu_3P, RT, 2 hrs; (iii) 1.10 eq. (−)-menthyl chloroformate **341**, RT, 3 hrs.

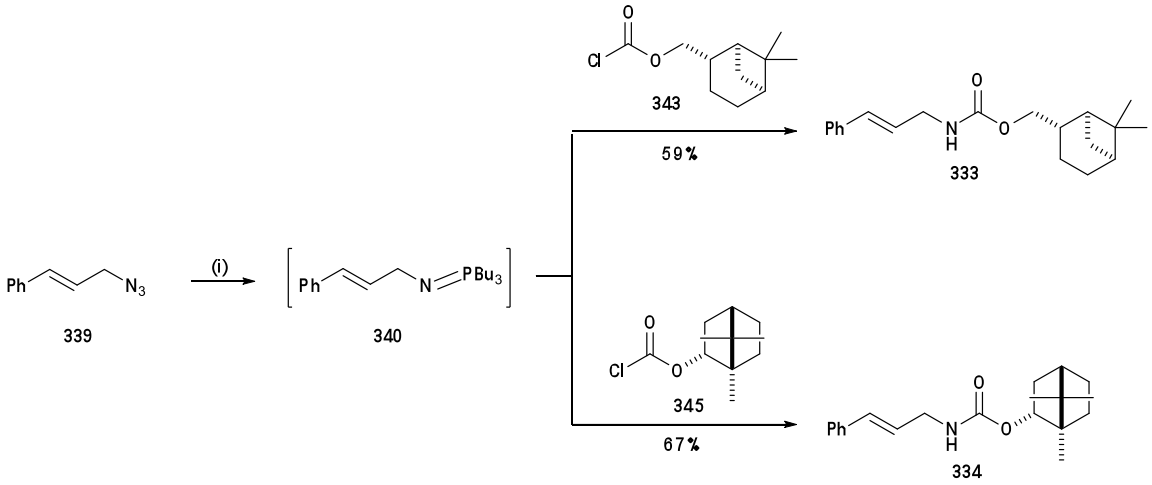
It was envisaged that a similar strategy may be used to synthesise the remaining substrates **332**, **333** and **334**. Unfortunately reaction of (*S*)-α-methylbenzyl alcohol **335** with triphosgene returned only starting material. Attempted synthesis of the requisite (−)-myrtanyl chloroformate **343** in fact gave a 70:30 mixture of the desired chloroformate **343** and the carbonate **344**, though it was found that this mixture could be successfully employed in the following reaction (*vide infra*). Synthesis of the

desired (–)-bornyl chloroformate **345** was successful, presumably as the alcohol is too hindered to undergo carbonate formation (Scheme 44).



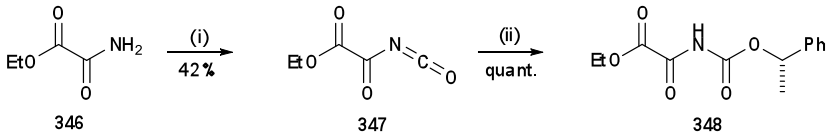
Scheme 44: *Reagents and conditions*; (i) 0.33 eq. triphosgene, 1.5 eq. pyridine, toluene, 60 °C, 6 hrs.

Reaction of iminophosphorane **340** with chloroformates **343** and **345** gave the desired products **333** and **334** in 59% and 67% yields respectively (Scheme 45).



Scheme 45: *Reagents and conditions*; (i) 1.05 eq. nBu$_3$P, RT, 2 hrs; (ii) 1.10 eq. **343** or **345**, RT, 3 hrs.

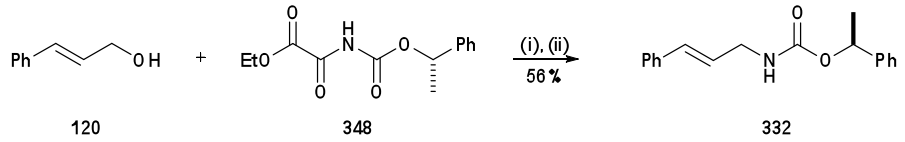
An alternative method for the synthesis of **332** was achieved by using the modified Mitsunobu reagent **348**. This was synthesized in 42% overall yield from ethyl oxamate **346** through formation of isocyanate **347** with oxalyl chloride followed by addition of (*S*)-α-methylbenzyl alcohol **335** (Scheme 46).



346 347 348

Scheme 46: *Reagents and conditions*; (i) $(COCl)_2$, CH_2Cl_2, reflux, 24 hrs; (ii) 1.0 eq. (*S*)-α-methylbenzyl alcohol **335**, toluene, 40 °C, 1 hr.

Mitsunobu reaction of cinnamyl alcohol **120** with **348**, followed by hydrolysis of the oxamate group gave substrate **332** in 56% yield (Scheme 47).



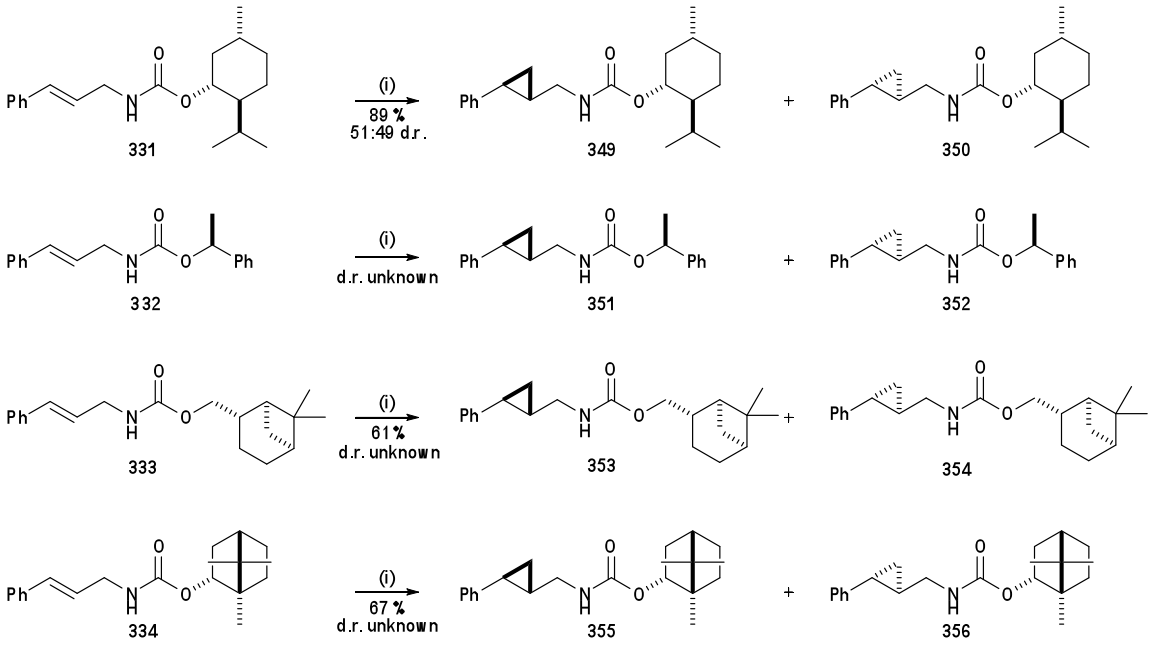
120 348 332

Scheme 47: *Reagents and conditions*; (i) 1.0 eq. **120**, 1.2 eq. **348**, 1.2 eq. PPh_3, 1.2 eq. DEAD, THF, RT, 24 hrs; (ii) 3.0 eq. $LiOH{\cdot}H_2O$, H_2O, RT, 3 hrs.

3.9.2 Cyclopropanation of 331-334

Cyclopropanation of substrates **331-334** was accomplished using the Wittig-Furukawa reagent [$Zn(CH_2I)_2$]. In all cases, the reaction appeared to give a single product by ^{1}H NMR analysis; however this was subsequently found to be uninformative since the two diastereoisomers had identical ^{1}H NMR spectra in all cases. Quantitative ^{13}C NMR analysis of the menthyl-derived diastereoisomers **349** and **350** allowed determination of the diastereoselectivity of the reaction by integration of the C(1′)*H* peaks. Unfortunately it was found that the diastereoselectivity was extremely low (51:49). In all other cases, the diastereomeric mixtures were found to have identical ^{13}C shifts (or sufficiently overlapping peaks such that integration was impossible) [x] (Scheme 48).

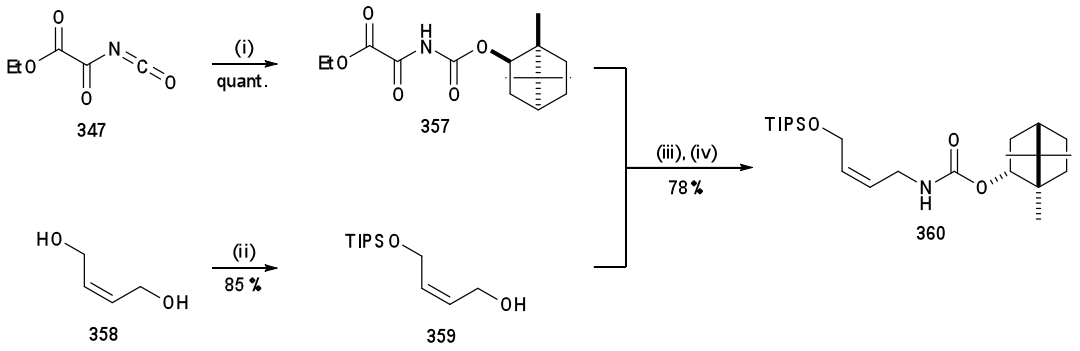
[x] On a qualitative level, the ^{13}C NMR spectrum of **351** and **352** indicated that the diastereoselectivity was low; however peak overlap prevented quantitative analysis.



Scheme 48: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT,1 hr.

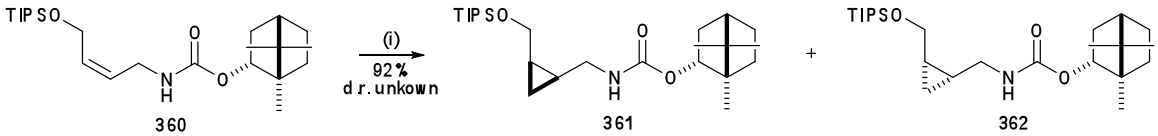
3.9.3 Synthesis and cyclopropanation of alternative substrate 360

In all of the above cases the normally characteristic cyclopropane proton shifts (typically δ_H is 0-1 ppm) were obscured by the carbocyclic proton shifts from the auxiliary, as a result of deshielding by the phenyl ring on the cyclopropane (δ_H increased to around 1-1.5 ppm). As such, it was hoped that synthesis of an alkyl-substituted substrate might result in more characteristic proton signals for the two diastereoisomers. Thus bornyl-derived substrate **360** was synthesized in 78% yield from alcohol **359** through Mitsunobu reaction with **357**, synthesized in quantitative yield by the reaction of (–)-borneol **337** with isocyanate **347** (Scheme 49).



Scheme 49: *Reagents and conditions*; (i) 1.0 eq. (–)-borneol **337**, toluene, 40 °C, 1 hr; (ii) 1.0 eq. TIPSCl, 10.0 eq. **358**, 1.12 eq. imidazole, THF, 0 °C → RT, 18 hrs; (iii) 1.0 eq. **359**, 1.2 eq. **357**, 1.2 eq. PPh_3, 1.2 eq. DEAD, THF, RT, 48 hrs; (iv) 3.0 eq. $LiOH{\cdot}H_2O$, H_2O, RT, 3 hrs.

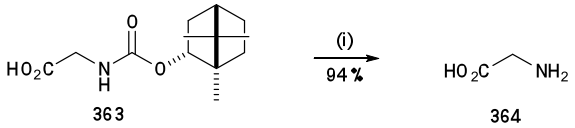
Cyclopropanation of **360** with $Zn(CH_2I)_2$ gave an 92% yield of an unknown mixture of diastereoisomers **361** and **362**. Although in this case the cyclopropane peaks were clearly visible in the ^1H NMR spectrum, it was again impossible to determine the diastereoselectivity of the reaction by NMR analysis (Scheme 50).



Scheme 50: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr.

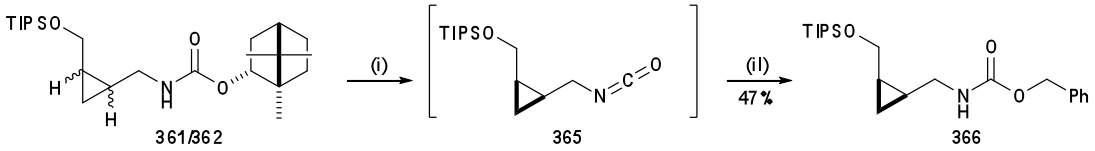
3.9.4 Deprotection of 361/362

It was hoped that deprotection of **361/362** to the primary amine or a derivative may allow determination of the enantioselectivity through chiral GC or HPLC analysis. Although there is a single literature example of the removal of a bornyl carbamate, the conditions (neat HF) were deemed to be entirely unsuitable for numerous practical, cost and safety reasons (Scheme 51).[18]



Scheme 51: *Reagents and conditions*; (i) anhydrous HF, anisole, –50 °C → 0 °C, 10 mins.

An alternative deprotection strategy was sought; however methods for the deprotection of secondary alcohol derived carbamates are limited. After some optimization it was found that the use of BCl_3 was effective in converting **361/362** to the corresponding isocyanate **365**, and that this could then be converted into the corresponding benzyl carbamate **366** by reaction with benzyl alcohol in the presence of CuCl, giving **366** in 47% yield. Unfortunately chiral HPLC analysis showed that the enantioselectivity was a disappointing 9% e.e. (Scheme 52).[19]



Scheme 52: *Reagents and conditions*; (i) 1.0 eq. BCl_3, 3.0 eq. NEt_3, toluene, 100 °C, 30 mins then 1 M aq. NaOH, RT, 15 mins; (ii) 1.2 eq. BnOH, 1.0 eq. CuCl, DMF, RT, 16 hrs.

3.9.5 Discussion

Although it was only possible to determine the level of asymmetric induction in a couple of examples, the observation that in all cases the ^{1}H and ^{13}C NMR signals of the two diastereoisomers are virtually identical suggests that there is very little interaction between the carbamate and the olefin. At this point, it was decided that the use of a chiral carbamate was unlikely to be a successful strategy for the asymmetric cyclopropanation of allylic amines.

3.10.1 A short application towards the synthesis of conformationally-restricted fluoroquinolone antibiotics

The need for novel antibiotic agents has grown dramatically as a result of the increasing occurrence of multidrug-resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant

S. pneumoniae (PRSP) and vancomycin-resistant enterococci (VRE).[20] The fluoroquinoline class of antibiotics have found extensive usage as broad-spectrum antibiotics, however their high potency is often accompanied by serious toxicity problems.[21]

In 2004, Inagaki *et al.* reported the development of the novel fluoroquinoline antibiotics **367** and **368**. These compounds both showed excellent antibacterial activity against a wide range of pathogens and additionally **367** showed greatly reduced genotoxicity in comparison to **368** and the analogous non-cyclopropanated compound **369**. The authors propose that the conformational constraints imposed by the cyclopropane increase enzyme specificity, thereby reducing toxicity (Figure 16).[22]

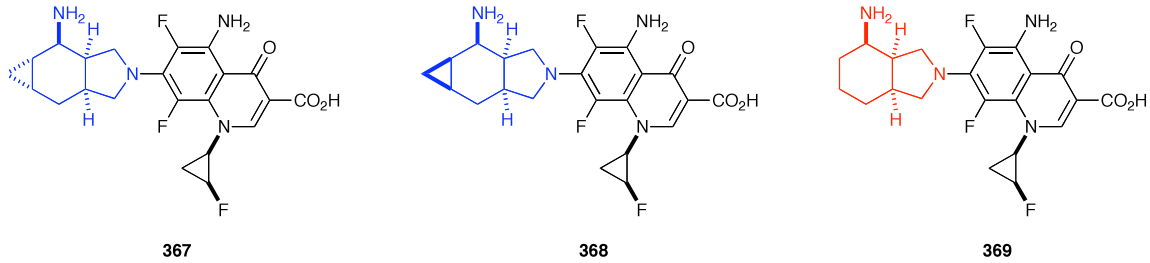
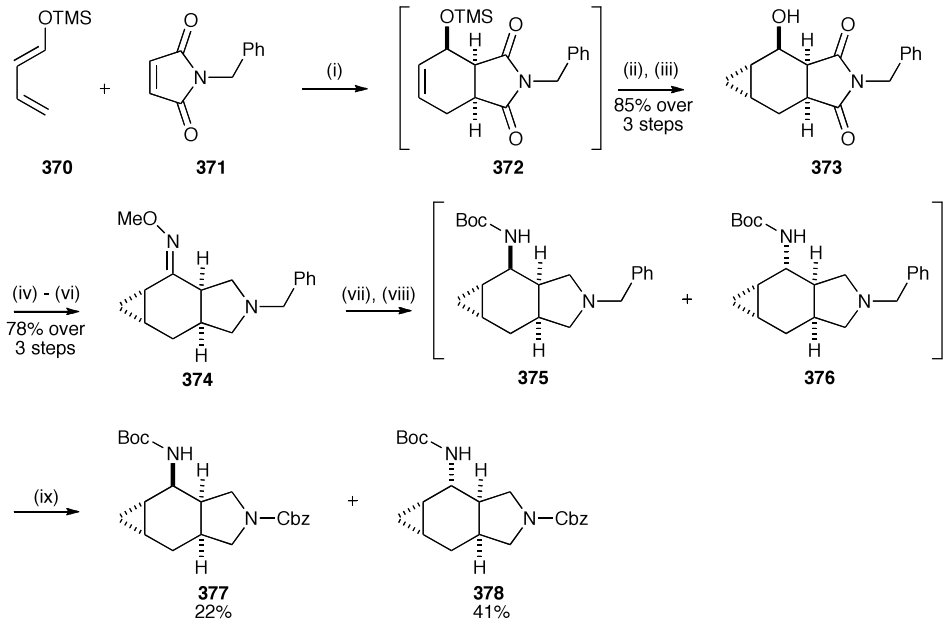


Figure 16: Fluoroquinoline antibiotics developed by Inagaki *et al.* showing the conformationally-restricted tricyclic motif (blue) of **367** and **368**, and the more conformationally flexible bicyclic motif (red) of **369**.

3.10.2 Synthesis of 367 by Inagaki *et al.*

The synthesis of the left-hand tricyclic portion of **367** by Inagaki *et al*. started with Diels-Alder reaction of diene **370** and *N*-benzyl maleimide **371** to give bicycle **372** in good yield. Subsequent cycopropanation of **372** using $Pd(OAc)_2$ and diazomethane gave **373** in 85% yield after silyl-deprotection. Amide reduction with lithium aluminium hydride followed by Swern oxidation and oxime formation gave **374** in 78% yield over 3 steps. Reduction of the oxime with borane resulted in formation of **375** and **376** as an inseparable mixture of diastereoisomers after *N*-Boc protection.[23] Manipulation of the protecting groups then gave diastereoisomers **377** and **378**, which

were separable by column chromatography, and isolated in 22% and 41% yield respectively (Scheme 53).

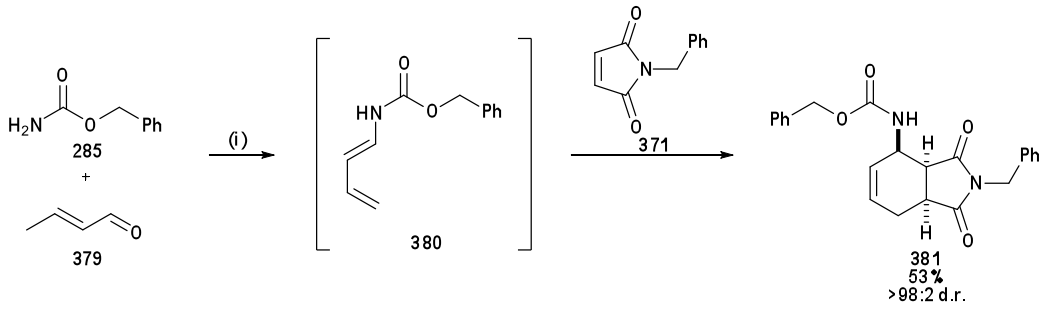


Scheme 53: *Reagents and conditions*; (i) toluene, heat; (ii) CH_2N_2, cat. $Pd(OAc)_2$, Et_2O; (iii) aq. HCl, MeOH; (iv) $LiAlH_4$, THF; (v) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (vi) $MeONH_2$·HCl, pyridine; (vii) BH_3·THF, THF; (viii) Boc_2O, $NaHCO_3$, THF, H_2O; (ix) Cbz-Cl, CH_2Cl_2.

It was envisaged that the synthesis of the tricyclic motif could be efficiently achieved using the cyclopropanation methodology developed in this chapter.

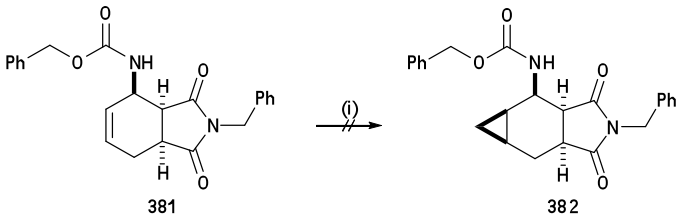
3.10.3 Synthesis of a core fragment of 367

A 3-component Diels-Alder strategy[24] was chosen to form the azabicylo[4.3.0]nonene core, with benzyl carbamate **285**, crotonaldehyde **379** and *N*-benzyl maleimide **371** reacting, *via* enamine **380**, to give the *endo* product **381** as a single diastereoisomer in 53% yield (Scheme 54).



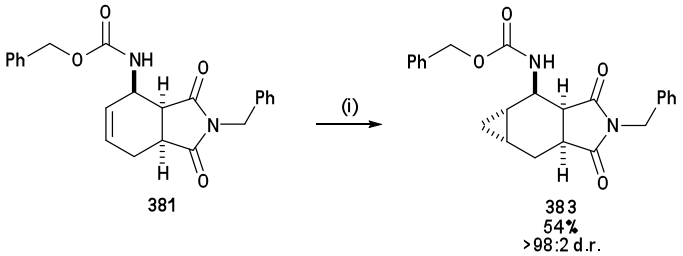
Scheme 54: *Reagents and conditions*; (i) 1.0 eq **285**, 1.0 eq **379**, 1.5 eq **371**, 0.02 eq *p*-TSA•H_2O, 1.0 eq Ac_2O, toluene, 120 °C (sealed tube), 24 hrs.

Attempted cyclopropanation of **381** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] failed to give any product. This was not surprising since it would require reaction on the already congested *endo* face (Scheme 55).



Scheme 55: *Reagents and conditions*; (i) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr.

However, cyclopropantion of **381** with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] proceeded to give the desired cyclopropane **383** in 54% yield as a single diastereoisomer, although it was found that a total of 6 equivalents of carbenoid were required in order to drive the reaction to completion (Scheme 56).



Scheme 56: *Reagents and conditions*; (i) 3.0 eq. $ZnEt_2$, 6.0 eq. CH_2I_2, 3 eq. TFA, CH_2Cl_2, RT, 5 hrs then 3.0 eq. $ZnEt_2$, 6.0 eq. CH_2I_2, 3 eq. TFA, CH_2Cl_2, RT, 5 hrs.

Although a formal or total synthesis of **367** was not pursued, the synthesis of the requisite tricyclic structural motif, in only two steps from readily available and

inexpensive starting materials, exemplifies the utility of the newly developed methodology.

3.11 Conclusion

A highly efficient and stereodivergent protocol for the cyclopropanation of allylic carbamates and amides has been developed, allowing access to either the *syn* or *anti* diastereoisomers of the corresponding cyclopropanes through a small change in the reaction conditions. The reaction has been shown to be applicable to a wide range of substrates, with excellent diastereoselectivities being observed in the majority of cases. Mechanistic studies suggest that *syn*-selective cyclopropanation with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] proceeds *via* an intramolecular pathway, whilst *anti*-selective cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] proceeds *via* an intermolecular pathway (Figure 17). Investigations into an asymmetric variant of the reaction utilizing chiral carbamate protecting groups unfortunately proved to be unsuccessful. However, the utility of the methodology has been exemplified by the synthesis of the core structural fragment of a fluoroquinolone antibiotic.

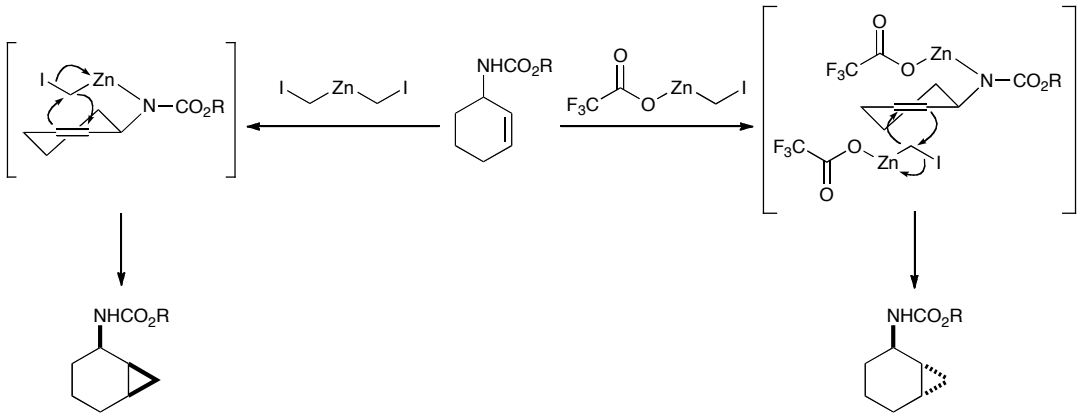


Figure 17: Mechanisms of the stereodivergent cyclopropanations of allylic carbamates.

3.12 References and notes

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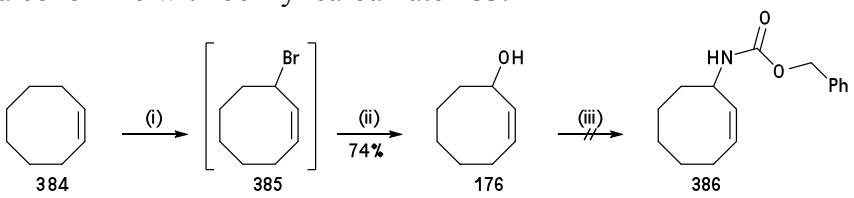
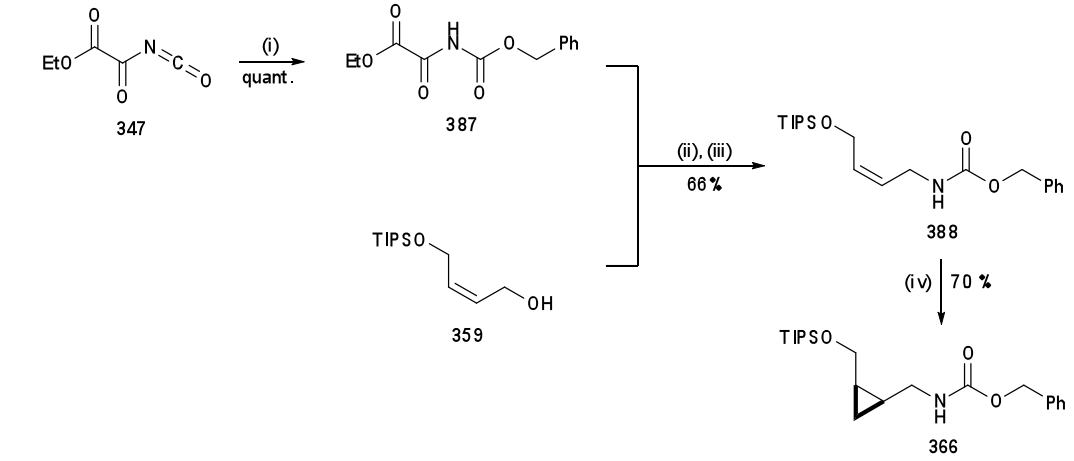
[6] TsNHBoc **255** was prepared by in 99% yield from *p*-toluenesulfonamide according to the procedure outlined in: Neustadt, B. R., *Tetrahedron Lett.*, **1994**, *35*, 379-380.
[7] Qin, H., Yamagiwa, N., Matsunaga, S., Shibasaki, M., *Angew. Chem. Int. Ed.*, **2007**, *46*, 409-413.
[8] Charette, A. B., Molinaro, C., Brochu, C., *J. Am. Chem. Soc.*, **2001**, *123*, 12160-12167.
[9] Lorenz, J. C., Long, J., Yang, Z., Xue, S., Xie, Y., Shi, Y., *J. Org. Chem.*, **2004**, *69*, 327-334.
[10] Unfortunately, attempted synthesis of the corresponding cyclooctyl substrate **386** *via* the same route gave a complex mixture of products during attempted displacement of allylic alcohol **176** with benzyl carbamate **285**:



Reagents and conditions; (i) 1.0 eq NBS, 0.01 eq. AIBN, CCl_4, 90 °C, 3 hrs; (ii) 3.0 eq. $NaHCO_3$, THF/H_2O, RT, 16hrs; (iii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq. benzyl carbamate **285**, 1,4-dioxane, RT, 16 hrs.

[11] The relative configuration within **171** has been proven unambiguously by single-crystal X-ray crystallography; see Chapter 2.
[12] For a review, see Augustine, R. L., *Heterogeneous catalysis for the synthetic chemist*, Marcel Dekker, Inc., New York, **1995.**
[13] Kimura, H., Stammer, C. H., *J. Org. Chem.*, **1983**, *48*, 2440-2441.
[14] Schultz, A. L., *J. Org. Chem.*, **1971**, *36*, 383-386.
[15] Stahl, K-J., Hertzsch, W., Musso, H., *Liebigs Ann. Chem.*, **1985**, 1474-1484.
[16] For an example of "amine-directed" hydrogenolysis, see Thomson, H.W., Wong, J. K., *J. Org.Chem.*, **1985**, *50*, 4270-4276.
[17] Charette, A. B., Juteau, H., Lebel, H., Molinaro, C. *J. Am. Chem. Soc.*, **1998**, *120*, 11943-11952.
[18] Fujino, M., Shinagawa, S., Nishimura, O., Fukuda, T., *Chem. Pharm. Bull.*, **1972**, *20*, 1017-1020.
[19] An authentic racemic sample of **366** was synthesised *via* the following procedure:



Reagents and conditions; (i) 1.0 eq. BnOH, toluene, 40 °C, 1 hr; (ii) 1.0 eq. **359**, 1.2 eq. **387**, 1.2 eq. PPh_3, 1.2 eq. DEAD, THF, 48 hrs; (iii) 3.0 eq. $LiOH•H_2O$, H_2O, RT, 3 hrs; (iv) 2.0 eq. $ZnEt_2$, 4.0 eq. CH_2I_2, CH_2Cl_2, RT, 1 hr.

[20] Endtz, H. P., van den Braak, N., Verbrugh, H. A., van Belkum, A., *Eur. J. Clin. Microbiol. Infect. Dis.*, **1999**, *18*, 683-690.
[21] De Sarro, A., De Sarro, G., *Curr. Med. Chem.*, **2001**, *8*, 371-384.
[22] Inagaki, H., Takahashi, H., Takemura, M., *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 5193-5198.
[23] Diastereoisomeric ratio not reported.
[24] Klaus, S., Hübner, S., Neumann, H., Strübing, D., Jacobi von Wangelin, A., Gördes, D., Beller, M., *Adv. Synth. Catal.*, **2004**, *346*, 970-978.

Chapter 4: Towards the total synthesis of *trans*-SCH-A 140

This chapter describes the development of routes towards the potential anti-obesity therapeutics *trans*-SCH-A **140** and *cis*-SCH-A **389**, using stereodivergent cyclopropanation reactions employing either the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] or Shi's carbenoid [$CF_3CO_2ZnCH_2I$] for the cyclopropanation of a common synthetic intermediate (Figure 1).

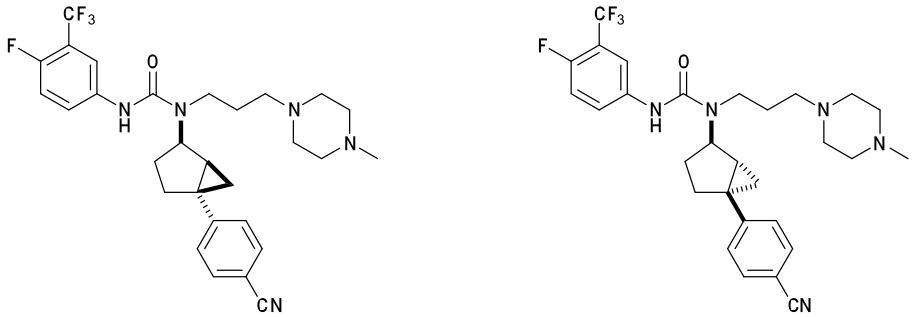


Figure 1: Potential anti-obesity therapeutics *trans*-SCH-A **140** and *cis*-SCH-A **389**.

4.1 *trans*-SCH-A 140

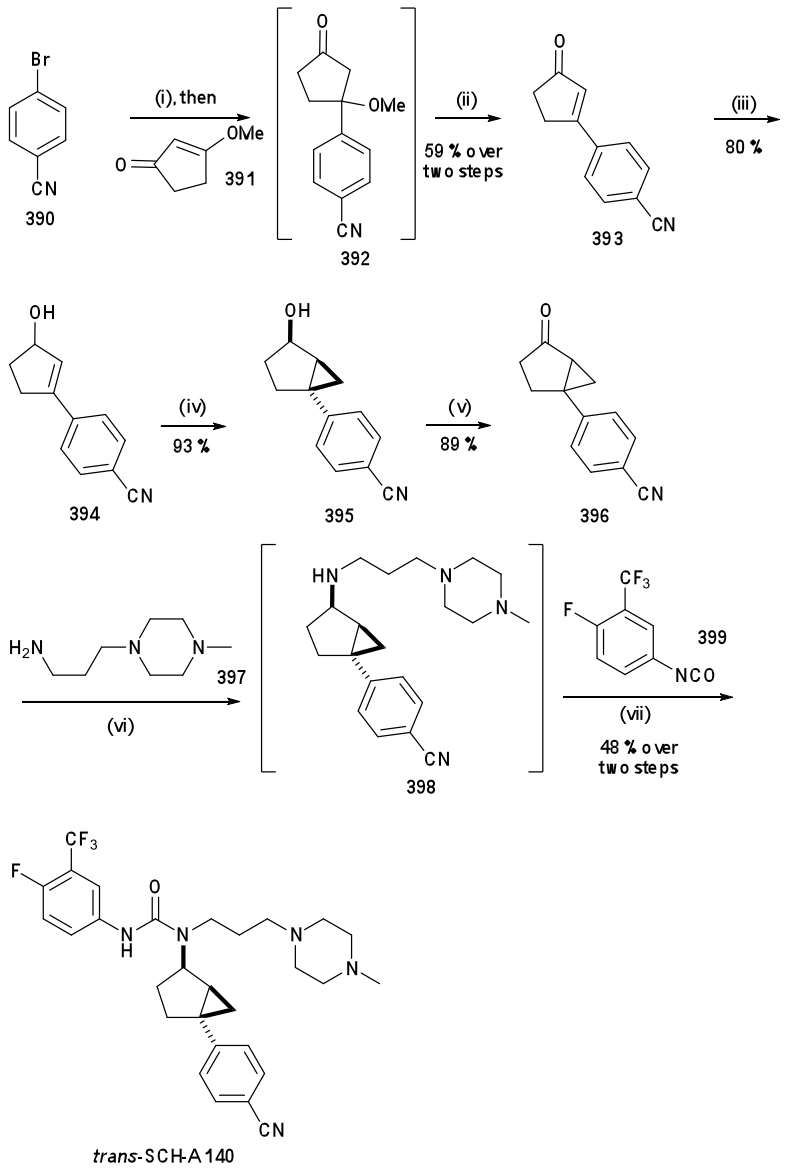
Melanin-concentrating hormone (MCH) is a cyclic 19-amino-acid polypeptide which has been implicated in the regulation of feeding and energy balance in several rodent models.[1] This has led to a great deal of interest in the use of MCH receptor-1 (MCH-R1) antagonists as potential therapeutics for the treatment of obesity, by acting as appetite suppressants.[2]

In 2005, medicinal chemists at Schering-Plough reported studies on the MCH-R1 antagonistic activity of *trans*-SCH-A **140**, which contains a core 2-aminobicyclo[3.1.0]hexane unit (see Figure 1 above).[3] *trans*-SCH-A **140** was the most biologically active of a range of bicyclic urea MCH-R1 antagonists, and testing showed that both chronic and acute admission of *trans*-SCH-A **140** in diet-induced obese mice led to an inhibition of food intake, decreased body weight and adiposity.

In addition, admission also prevented a compensatory reduction in energy expenditure, reinforcing the importance of MCH-R1 signaling in energy balance. Cessation of dosing resulted in the rapid regain of body weight. These findings suggest that administration of an MCH-R1 antagonist may be an effective means of reducing food intake and adiposity in obese humans.[4]

4.2 Synthesis of *trans*-SCH-A 140

The chemists at Schering-Plough synthesised *trans*-SCH-A **140** in 7 steps from commercially available 4-cyano-bromobenzene **390**. Addition of an *in situ* generated aryl lithium reagent to 3-methoxycyclopentenone **391**, followed by elimination of MeOH under acidic conditions and subsequent Luche reduction of the resulting enone **393** gave cyclopentenol **394** in 47% yield over 3 steps. Simmons-Smith cyclopropanation using the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] followed by oxidation fo the alcohol functionality using Dess-Martin periodinane gave ketone **396** in 83% yield over the 2 steps. The *trans* configuration within **140** was then introduced by stereoselective reductive amination of ketone **396** with amine **397**. Hydride attack on the *in situ* formed imine preferentially comes from the less-hindered convex face to give cyclopropane **398** as a single diastereoisomer. The synthesis was then completed by reaction of amine **398** with commercially available isocyanate **399** to give *trans*-SCH-A **140** in 19% overall yield from **390** in 7 steps (Scheme 1).



Scheme 1: *Reagents and conditions*; (i) BuLi, THF, −78 °C then **391**; (ii) 1 M HCl; (iii) $NaBH_4$, $CeCl_3$, MeOH, 0 °C to RT; (iv) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C to RT; (v) Dess-Martin periodinane, pyridine, CH_2Cl_2, 0 °C to RT; (vi) **397**, $Ti(O^iPr)_4$ then $NaBH_4$, 0 °C to RT; (vii) **399**, DIPEA, CH_2Cl_2, RT.

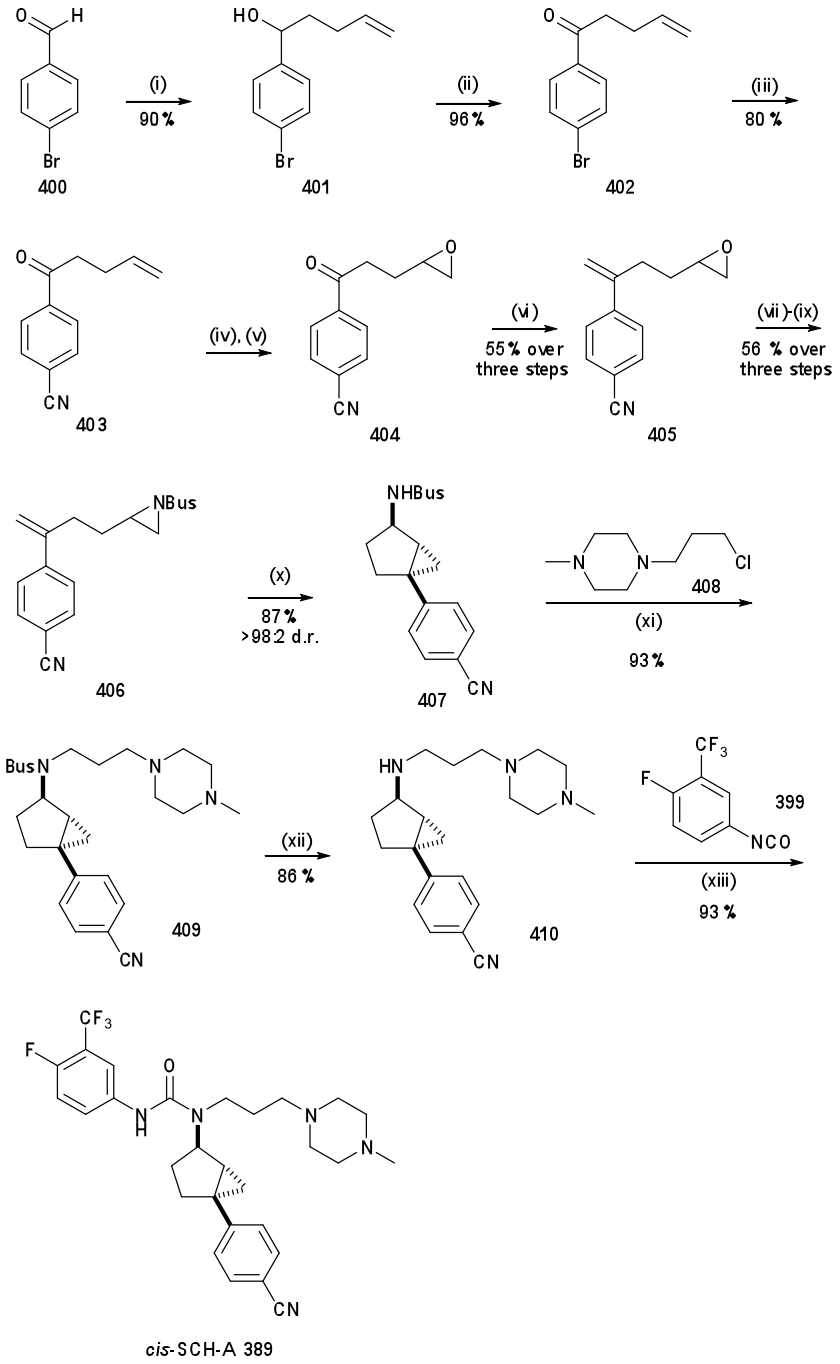
4.3 Synthesis of *cis*-SCH-A 389

Hodgson *et al.* have utilized the intramolecular cyclopropanation of an α-lithiated terminal aziridine as the key step in a recently reported synthesis of the epimeric compound *cis*-SCH-A **389**.[5]

In this synthesis ketone **402** was prepared in 86% yield through addition of but-3-enylmagnesium bromide to 4-bromobenzaldehyde **400**, followed by Swern oxidation

of the resultant alcohol **401**. A Rosenmund-von Braun reaction of bromide **402** then afforded nitrile **403** in 80% yield. Subsequent conversion of **403** to the corresponding bromohydrin with NBS in THF/water, followed by base-mediated ring closure, gave epoxide **404** which was converted *via* Wittig olefination to bishomoallylic epoxide **405** in 55% yield (over three steps). Conversion of **405** to the corresponding *N*-Bus protected aziridine **406** was achieved through a three step ring-opening, activation, and ring-closing procedure to give key aziridine intermediate **406** in 56% yield over three steps. Upon treatment of aziridine **406** with lithium dicyclohexylamide in TBME, intramolecular cyclopropanation of the α-lithiated aziridine intermediate proceeds to give cyclopropane **407** in 87% yield as a single diastereoisomer. The synthesis was then completed through *N*-alkylation with chloride **408**, *N*-Bus deprotection and urea formation to give *cis*-SCH-A **389** in 14% overall yield from **400** in 13 steps.[i] Due to the preferred transition-state adopted during the key intramolecular cyclopropanation reaction, this route only provides access to *cis*-SCH-A **389** (Scheme 2).

[i] The relative configuration within **389** was assigned by ^{1}H NMR nOe studies of amine precursor **410**. See ref. 5 for details.



Scheme 2: *Reagents and conditions*; (i) Mg, 4-bromo-1-butene, Et_2O, −78 °C to RT; (ii) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to RT; (iii) CuCN, DMF, 155 °C; (iv) NBS, THF, H_2O, 0 °C; (v) K_2CO_3, MeOH, RT; (vi) Ph_3PMeBr, BuLi, THF, −78 °C to RT; (vii) $BusNH_2$, K_2CO_3, BTEAC, dioxane, 90 °C; (viii) Ms_2O, pyridine, DMAP, CH_2Cl_2, RT; (ix) K_2CO_3, H_2O, THF, 85 °C; (x) 3 eq. $LiNCy_2$, TBME, 0 °C; (xi) **408**, NaH, DMF, 0 °C to 75 °C; (xii) TfOH, anisole, CH_2Cl_2, 0 °C; (xiii) **399**, DIPEA, CH_2Cl_2, RT.

In collaboration with GSK, the Hodgson group were subsequently able to evaluate the biological activity of *cis*-SCH-A **389**. Unfortunately, a MCH-R1 binding assay showed no inhibition of MCH-R1 activity. Whilst this was clearly a disappointing

result, it showed that the relative configuration of the amino and aryl groups is crucial for pharmacological efficacy.

4.4 Studies towards the synthesis of *trans*-SCH-A 140

Whilst the complimentary routes developed by Schering-Plough and the Hodgson group provide access to *trans*-SCH-A **140** and *cis*-SCH-A **389** respectively, in high diastereoselectivity, they are both limited in that they each only provide access to a single diastereosiomer. It was envisaged that the stereodivergent cyclopropanation strategy that had been developed in the present study (Chapter 3) could be applied to these two targets from a common synthetic intermediate.

In addition, whilst the chemists at Schering-Plough tested a wide range of 2-aminobicyclo[3.1.0]hexane and 3-aminobicyclo[4.1.0]heptane ureas **411** and **412**, the corresponding 2-aminobicyclo[4.1.0]heptane ureas **413** and **414** were not tested, and it was additionally envisaged that the sterodivergent cyclopropanation methodology could also be readily applied to the synthesis of a range of these analogues and other related structures (Figure 2).[3]

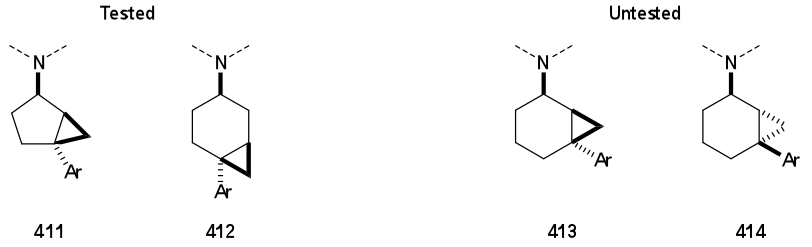


Figure 2: Structural motifs which have been tested by Schering-Plough (**411** and **412**) and related motifs which are currently untested (**413** and **414**).

4.4.1 1st Generation synthesis – late stage cyclopropanation

It was proposed that the most elegant, and efficient, syntheses of *trans*-SCH-A **140** and *cis*-SCH-A **389** would involve the stereodivergent cyclopropanation step as late in the synthesis as possible, and ideally as the final step. With this in mind, it was

initially envisaged that both *trans*-SCH-A **140** and *cis*-SCH-A **389** could be synthesised through reaction of allylic urea **415** with either the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] or Shi's carbenoid [$CF_3CO_2ZnCH_2I$] respectively. The urea itself could be derived from secondary amine **416**, which in turn could be synthesised from enone **417** through reductive amination. Aryl substituted enone **417** could be synthesised through the oxidative rearrangement of tertiary alcohol **418**, which could be derived from the addition of an aryllithium reagent **419** to 2-cyclopenten-1-one **290** (Figure 3).

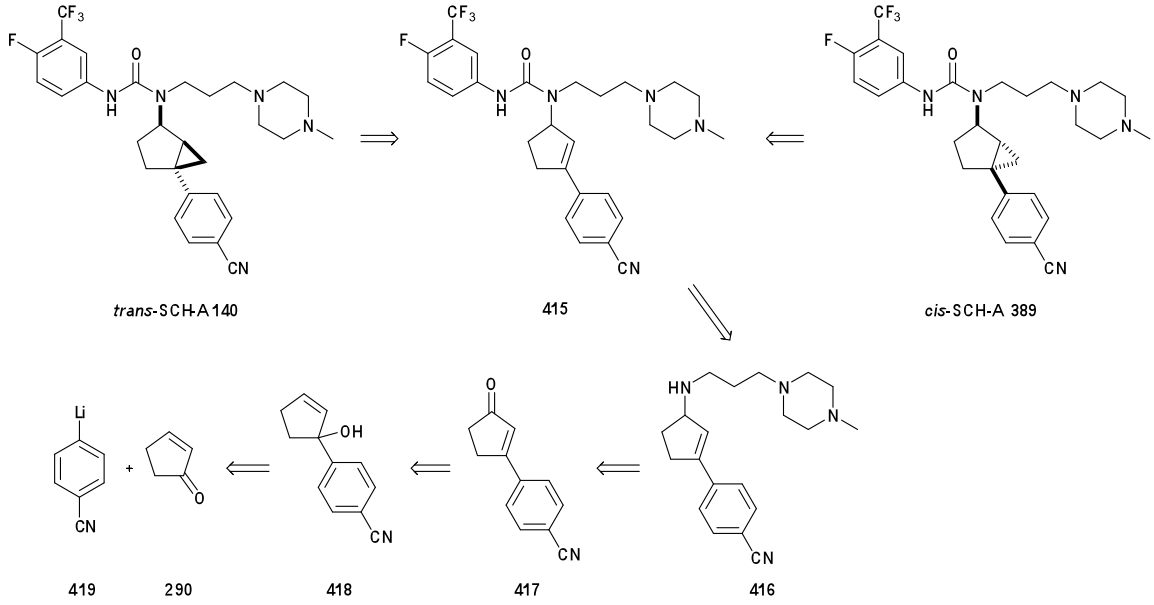
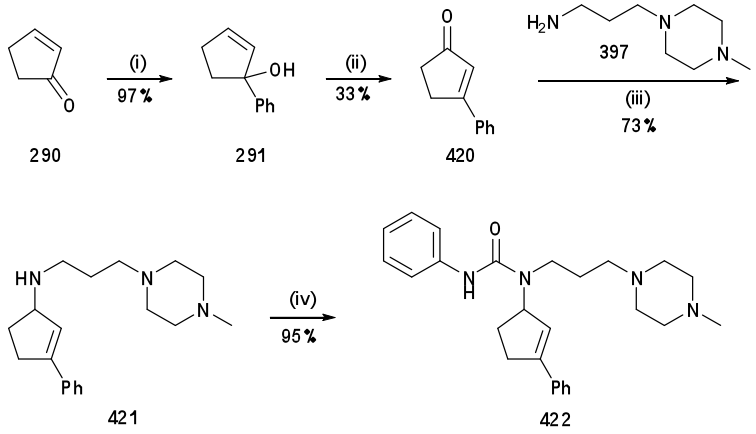


Figure 3: Retrosynthetic analysis of *trans*-SCH-A **140** and *cis*-SCH-A **389**

4.4.2 Model studies

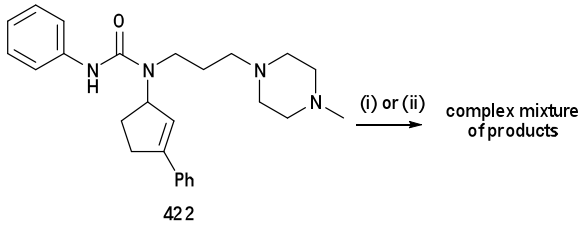
To test the viability of the proposed stereodivergent cyclopropanation reactions, it was decided to focus initially on the simpler substrate **422** as a model system. Thus **422** was prepared from 2-cyclopenten-1-one **290** in four steps. First, addition of phenyllithium (freshly prepared by transmetallation of bromobenzene and ^{t}BuLi) to 2-cyclopenten-1-one **290** at –78 °C gave tertiary alcohol **291** in 97%. Oxidative rearrangement of alcohol **291** with IBX in DMSO proceeded to give enone **420** in

33% yield.[6] Reductive amination of enone **420** with commercially available amine **397** was achieved in 73% yield through titanium isopropoxide mediated imine formation, followed by reduction with sodium borohydride in methanol.[7] The synthesis of model substrate **422** was then completed by the reaction of secondary amine **421** with phenyl isocyanate to give **422** in 95% yield (Scheme 3).



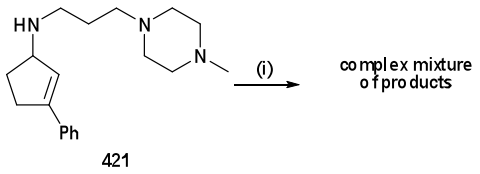
Scheme 3: *Reagents and conditions*; (i) 1.2 eq. bromobenzene, 2.4 eq. *t*BuLi, THF, −78 °C; (ii) 2.0 eq. IBX, DMSO, 55 °C, 1 hr; (iii) 3.0 eq. **397**, 1.3 eq. $Ti(O\textit{i}Pr)_4$, MeOH, RT, 16 hrs then 1.2 eq. $NaBH_4$, 0 °C to RT; (iv) 1.05 eq. PhNCO, 1.1 eq. DIPEA, CH_2Cl_2, RT, 16 hrs.

Unfortunately, attempted cyclopropanation of urea **422** with either the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] or Shi's carbenoid [$CF_3CO_2ZnCH_2I$] gave complex mixtures of products in each case (Scheme 4).



Scheme 4: *Reagents and conditions*; (i) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C to RT; (ii) $ZnEt_2$, CH_2I_2, TFA, CH_2Cl_2, 0 °C to RT.

As an alternative, cyclopropanation of secondary amine **421** with Shi's carbenoid [$CF_3CO_2ZnCH_2I$] was also attempted but, again, this led only to a complex mixture of products (Scheme 5).



Scheme 5: *Reagents and conditions*; (i) $ZnEt_2$, CH_2I_2, TFA, CH_2Cl_2, 0 °C to RT.

Although no single product could be isolated in any case, analysis of the crude ^1H NMR spectra showed that the piperazine *N*-Me protons had shifted up-field. This could indicate that *N*-methylation had occurred, resulting in formation of quaternary ammonium species.

Attempts to effect cyclopropanation by using an excess (10 equivalents) of carbenoid also failed, with the rapid formation of a complex mixture of products being observed. Given these results, it seemed likely that the *N*-methyl piperazine group was incompatible with the conditions for cyclopropanation and that an alternative strategy was required.

4.5 2nd Generation synthesis

As an alternative, it was decided to focus on the stereodivergent cyclopropanation of allylic carbamates (see Chapter 3). In order to investigate the conversion of a cyclopropanated allylic carbamate to the desired target molecule, it was again decided to focus on synthesis of the simplified analogue **423** from **295**, prepared as described in Chapter 3. Initially it was envisaged that a similar strategy to that employed by the Hodgson group in their synthesis of *cis*-SCH-A **389** (*vide ante*) could be utilized. Thus *N*- alkylation of **295** followed by *N*-carbamate deprotection and urea formation would give **423** in 3 steps (Figure 4).

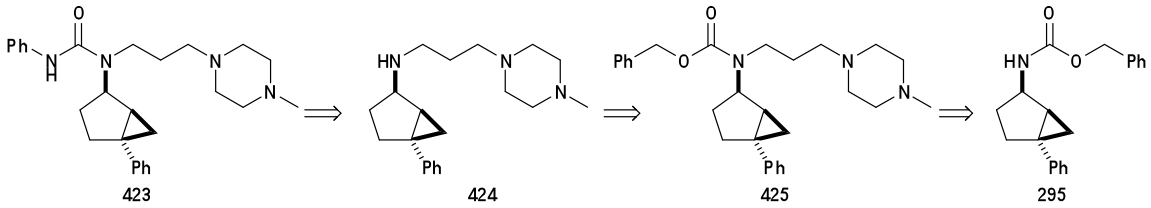
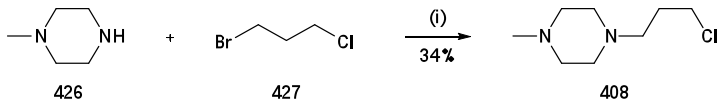


Figure 4: Proposed retrosynthesis of **423** from carbamate **295**.

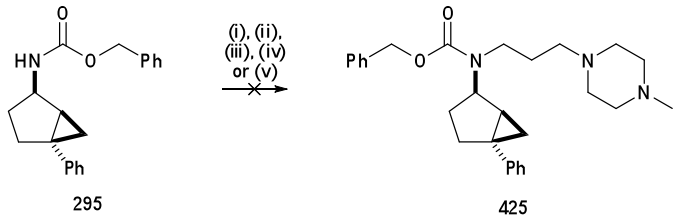
4.5.1 Attempted alkylation of 295

The synthesis of the required alkyl halide was achieved according to a literature procedure.[8] Thus treatment of 1-bromo-3-chloropropane **427** with *N*-methyl piperazine **426** in the presence of activated zinc powder gave piperazinyl chloride **408** in 34% yield (Scheme 6).



Scheme 6: *Reagents and conditions*: (i) activated Zn, THF, RT, 16 hrs.

Unfortunately, attempts to alkylate carbamate **295** with this electrophile under a variety of conditions[5,9] failed to give any conversion to the desired product **425**. Indeed, it was found that even attempted *N*-methylation of **295** with iodomethane failed (Scheme 7).



Scheme 7: *Reagent and conditions*; (i) 2 eq. NaH, 3 eq. **408**, DMF, 0 °C to 75°C, 18 hrs; (ii) 2 eq. NaH, 3 eq. **408**, 3 eq. Bu_4NI, DMF, 0 °C to 75°C, 18 hrs; (iii) 3 eq. Cs_2CO_3, 3 eq. Bu_4NI, 3 eq. **408**, DMF, RT, 18 hrs; (iv) 3 eq. Cs_2CO_3, 3 eq. Bu_4NI, 3 eq. **408**, DMF, 60 °C, 18 hrs; (v) 1.2 eq. NaH, 1.2 eq. Bu_4NI, 1.2 eq. **408**, THF/DMF, RT, 18 hrs.

One possible explanation for this lack of reactivity is that for *trans*-**295**, the reaction is required to take place on the same face as the cyclopropane (i.e. on the concave face of the bicycle). This is likely to be much more difficult than reaction on the convex

face of *cis*-**407**. Due to the difficulties faced in the alkylation of carbamate **295**, the elaboration of the deprotected amine **311** was next investigated.[ii]

4.6 One-pot alkylation-acyl transfer strategy

It was thought that direct alkylation of amine **311** would be problematic, due to the potential for over-alkylation. However, an elegant, one-pot, alkylation-acyl transfer reaction was proposed as a method for overcoming this. Thus, it was envisaged that after alkylation, secondary amine **429** would spontaneously undergo an *O*- to *N*-acyl transfer reaction to give urea **430**, thereby negating the possibility of over-alkylation (Figure 5).

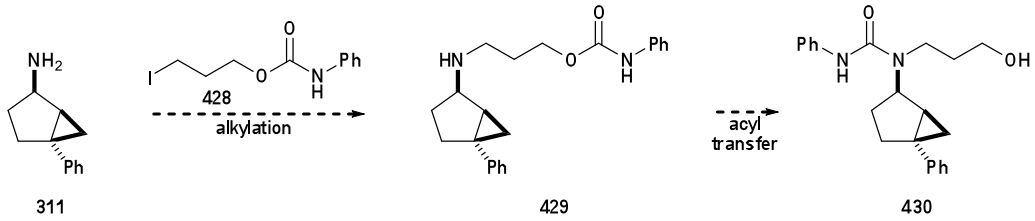
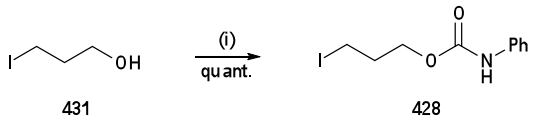


Figure 5: Proposed alkylation-acyl transfer strategy

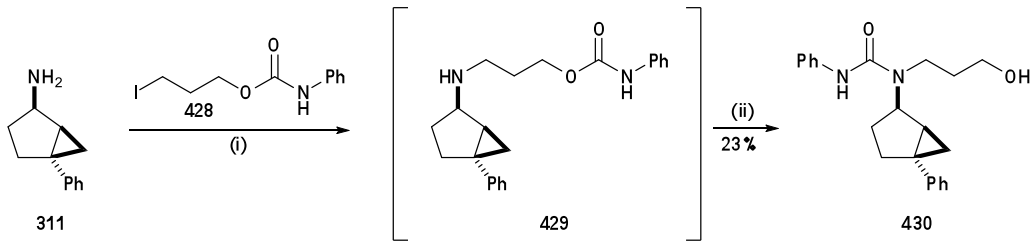
Iodo-carbamate **428** was easily synthesised in quantitative yield through the reaction of 3-iodopropan-1-ol **431** with phenyl isocyanate (Scheme 8).



Scheme 8: *Reagents and conditions*; (i) 1.05 eq. PhNCO, toluene, reflux, 3 hrs.

Unfortunately, it was found that intermediate **429** did not undergo spontaneous acyl transfer under the alkylation conditions. Treatment of the intermediate carbamate **429** with $AlMe_3$ did induce migration of the acyl fragment, however the desired product **430** could only be isolated in a maximum yield of 23% (Scheme 9).

[ii] Amine **311** was prepared as described in Chapter 3.

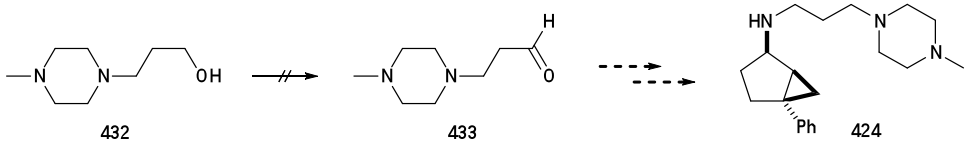


Scheme 9: *Reagents and conditions*; (i) 1.1 eq. **428**, 1.1 eq. NEt_3, DMF, 50 °C (microwave irradiation), 25 mins; (ii) 2.2 eq. $AlMe_3$, DMF, 80 °C, 2 hrs.

Given the low yield of this process, it was decided to abandon this route and explore other methods of attaching the piperazinyl side chain.

4.7 Reductive amination strategy

It was hoped that the formation of secondary amine **424** may be achieved through reductive amination of aldehyde **433** with amine **311**. Unfortunately, attempts to oxidize commercially available alcohol **432** to aldehyde **433** with a wide variety of oxidants failed to give any of the desired product (Scheme 10).



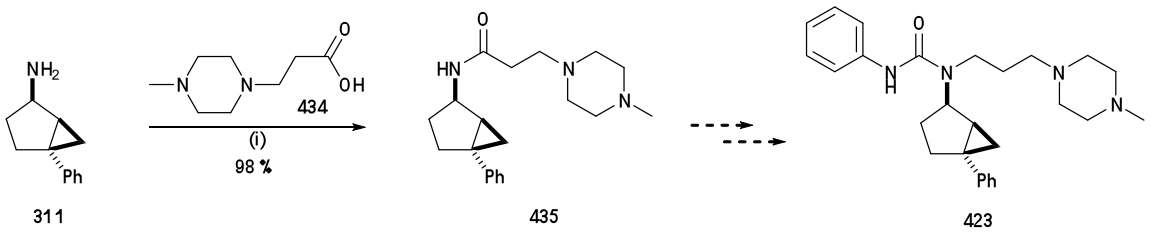
Entry	Conditions
1	0.05 eq. TPAP, 1.5 eq. NMO, CH_2Cl_2 or MeCN, 4Å molecular sieves, RT[10]
2	2 eq. $(COCl)_2$, 4 eq. DMSO, 6 eq. NEt_3, CH_2Cl_2, −78 °C to RT[11]
3	1.15 eq. Dess-Martin periodinane, CH_2Cl_2, RT[12]
4	1.5 eq. IBX, EtOAc, reflux[13]
5	1.5 eq. IBX, DMSO, RT[14]
6	1.5 eq. IBX, 2.2 eq. TFA, DMSO, RT
7	2.5 eq. SO_3·pyridine, 5 eq. NEt_3, CH_2Cl_2/DMSO (1:1), 0 °C[15]
8	1.5 eq. PCC, CH_2Cl_2, 0 °C to RT[16]
9	bis(trimethylsilyl)chromate supported on Montmorillonite K-10, CH_2Cl_2, RT[17]

Scheme 10: *Reagents and conditions are provided in the table above.*

4.8 Amide coupling strategy

It was next proposed that the piperazinyl side-chain could be attached through an amide coupling reaction. Thus, amine **311** was treated with carboxylic acid **434** in the

presence of EDCI, HOBt and NEt_3 to give amide **435** in 98% yield.[18] It was envisaged that subsequent reduction of the amide (e.g. $LiAlH_4$ or BH_3) followed by urea formation would be a suitable route to the desired products (Scheme 11).

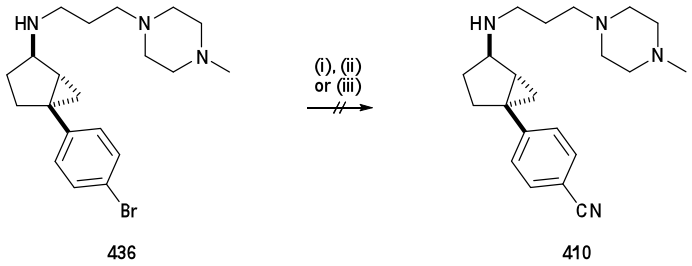


Scheme 11: *Reagents and conditions*; (i) 1.0 eq. **434**, 1.2 eq. EDCI, 1.2 eq. HOBt, 1.2 eq. NEt_3, $CHCl_3$, RT, 18 hrs; (ii) $LiAlH_4$, THF, reflux, 18 hrs; (iii) PhCNO, toluene, reflux, 30 mins.

With coupling of the piperazinyl side-chain successfully accomplished, the next stage was to apply this route this to the total synthesis of *trans*-SCH-A **140**.

4.9 Retrosynthetic analysis of *trans*-SCH-A 140

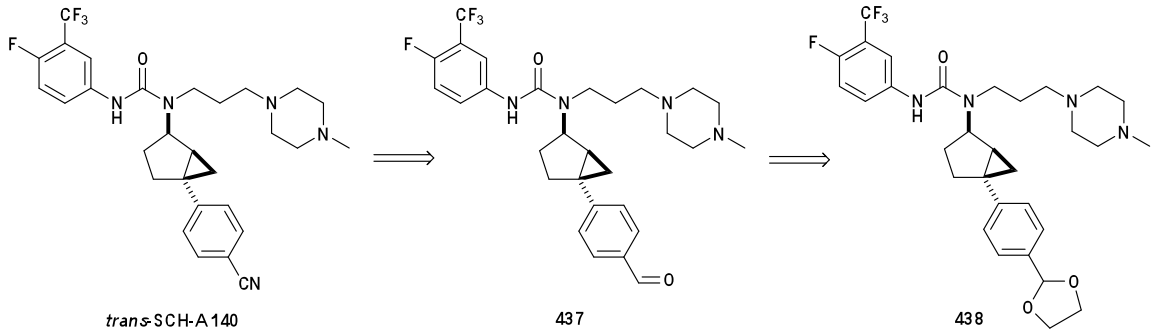
Although a route to the model system **423** had been developed, it was clear that the necessity for an amide reduction would be incompatible with the presence of the nitrile functionality required for the synthesis of *trans*-SCH-A **140**.[19] As such, it was necessary to investigate formation of the nitrile at a later stage in the synthesis. The possibility of affecting direct cyanation of an aryl bromide *via* a Rosenmund-von Braun reaction or variant was discounted since studies by Hodgson *et al*. on the conversion of aryl bromide **436** to aryl nitrile **410** under a range of cyanation conditions showed that decomposition occurred in all cases (Scheme 12).[5]



436 410

Scheme 12: *Reagents and conditions*; (i) CuCN, DMF, 165 °C, 12 hrs; (ii) CuI, KI, NaCN, *N′*,*N′′*-dimethylethane-1,2-diamine, toluene, 120 °C, 24 hrs; (iii) NaCN, CuI, $Pd(PPh_3)_4$, MeCN, reflux, 24 hrs.

As an alternative, it was hoped to effect cyanation *via* the oxidative amination of aldehyde **437**. It was anticipated that aldehyde **437** could be formed from acetal **438**, which should be stable to the reductive conditions required earlier in the synthesis (Figure 6).



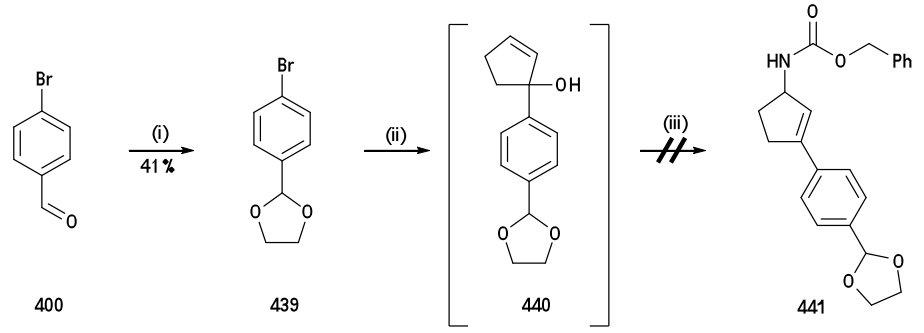
trans-SCH-A 140 437 438

Figure 6: Proposed retrosynthesis of nitrile **140** from acetal **438**

4.10 Attempted synthesis of 441

The synthesis of the required substrate began with reaction of 4-bromobenzaldehyde **400** with ethylene glycol, which gave ethylene ketal **439** in 41% yield according to a literature procedure.[20] Lithiation and addition to 2-cyclopenten-1-one **290** gave tertiary alcohol **440** which was reacted crude. Treatment of **440** with catalytic $Bi(OTf)_3$ and benzyl carbamate **285** under standard conditions unfortunately led to the formation of a complex mixture of unidentified products. One qualitative observation was the appearance of aldehyde peaks in the ^{1}H NMR spectrum, indicating that the

acetal functionality was likely to have been incompatible with the presence of the strong Lewis acid $Bi(OTf)_3$ required for the rearrangement step (Scheme 13).[21]



Scheme 13: *Reagents and conditions*; (i) 2 eq. ethylene glycol, 0.1 eq $TsOH{\cdot}H_2O$, toluene, reflux (Dean-Stark), 20 hrs; (ii) 1.0 eq. 2-cyclopenten-1-one **290**, 1.2 eq. **439**, 2.4 eq. ^{t}BuLi, THF, −78°C, 1 hr; (iii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq benzyl carbamate **285**, THF, $MgSO_4$, RT, 10 mins.

4.11 Synthesis of silyl protected alcohols 446 and 449

It was next decided to investigate the formation of aldehyde **437** by oxidation of the corresponding alcohol **442**, which could be introduced as a protected hydroxyl group from the start of the synthesis (Figure 7).

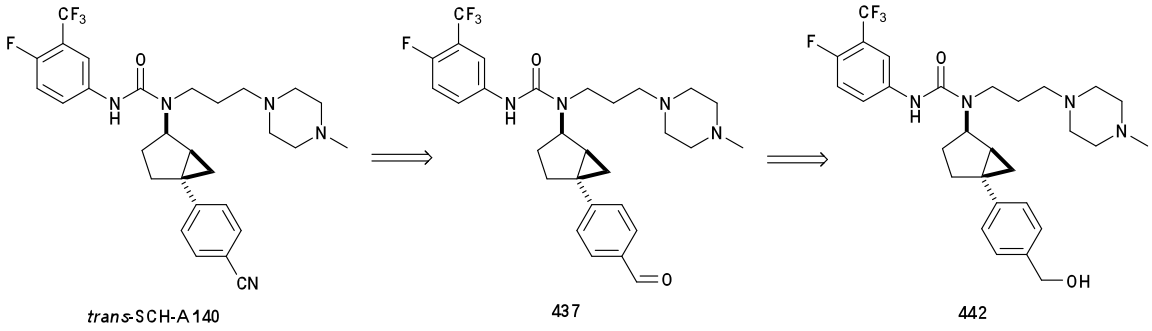
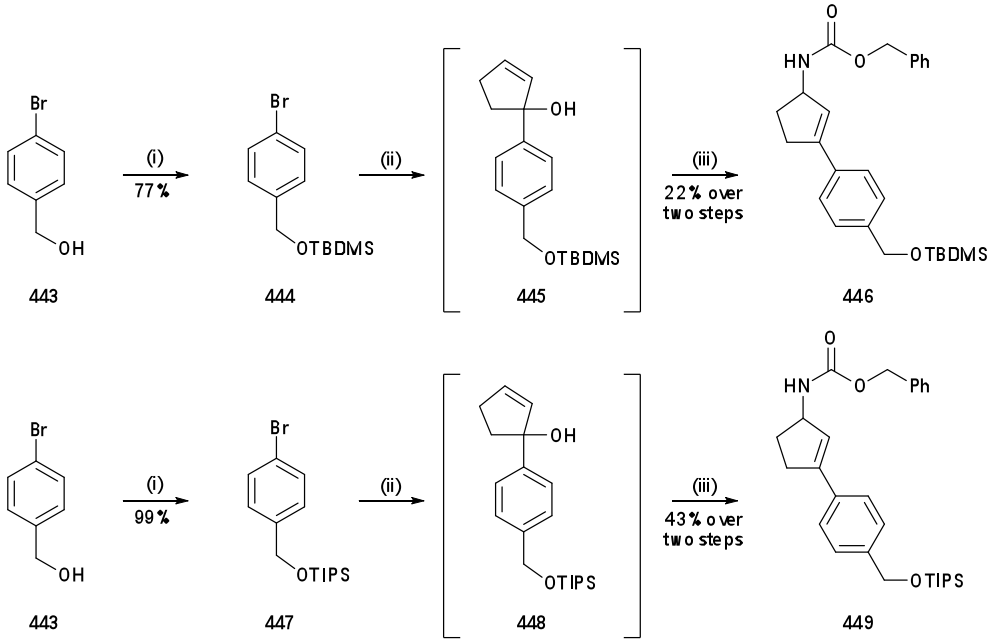


Figure 7: Proposed retrosynthesis of nitrile **140** from alcohol **442**

It was decided to investigate protection of the alcohol with both *tert*-butyldimethylsilyl and triisopropylsilyl groups first. The synthesis of the desired substrates **446** and **449** began with protection of 4-bromobenzyl alcohol **443** with either TBDMSCl or TIPSCl to give protected alcohols **444** and **447** in 77 and 99% yield repectively.[6] Lithiation of **444** and **447** followed by addition to 2-cyclopenten-1-one **290** gave tertiary alcohols **445** and **448** which were reacted immediately under

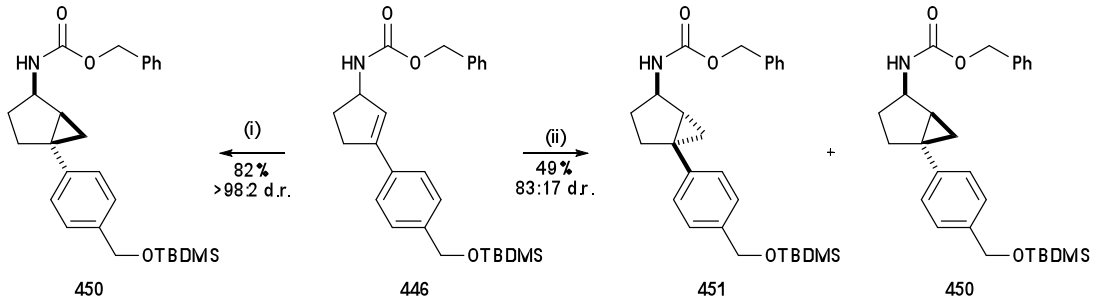
standard conditions for the $Bi(OTf)_3$ mediated amination to give the desired substrates **446** and **449** in 22 and 43% yield respectively over 2 steps (Scheme 14).



Scheme 14: *Reagents and conditions*; (i) 1.2 eq. TBDMSCl, 1.2 eq. imidazole, DMF, 0 °C to RT, 18 hrs; (ii) 1.0 eq. 2-cyclopenten-1-one **290**, 1.2 eq. **444** or **447**, 2.4 eq. ^{t}BuLi, THF, −78°C, 1 hr; (iii) 0.05 eq. $Bi(OTf)_3$, 0.05 eq. KPF_6, 1.5 eq benzyl carbamate, THF, $MgSO_4$, RT, 1 hr.

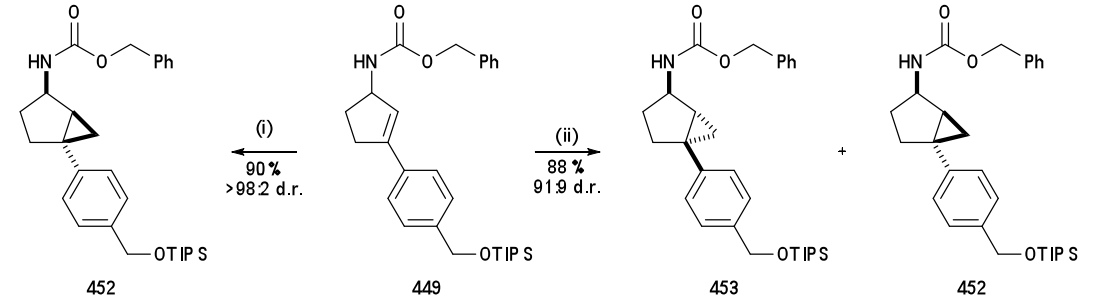
4.12 Cyclopropanation of substrates 446 and 449

Cyclopropanation of *O*-TBDMS protected substrate **446** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] gave *trans*-**450** as a single diastereoisomer in 82% yield. It was found that with 2 eq. of Shi's carbenoid [$CF_3CO_2ZnCH_2I$] the reaction conversion was only 62% after 4 hrs, however employing 3 equivalents of carbenoid gave complete conversion of **446** to an 83:17 mixture of *cis*-**451** and *trans*-**450** within 4 hrs. Purification afforded an inseparable 83:17 mixture of *cis*-**451** and *trans*-**450** in 49% combined yield (Scheme 15).



Scheme 15: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, 0 °C to RT, 1 hr; (ii) 3 eq. $ZnEt_2$, 6 eq. CH_2I_2, 3 eq. TFA, CH_2Cl_2, 0 °C to RT, 4 hrs.

Cyclopropanation of *O*-TIPS protected substrate **449** with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$] gave the desired *trans* isomer **452** in 90% yield as a single diastereoisomer, whereas reaction with 3 eq. of Shi's carbenoid gave a 91:9 mixture of *cis*-**453** and *trans*-**452** in 88% combined yield (Scheme 16).

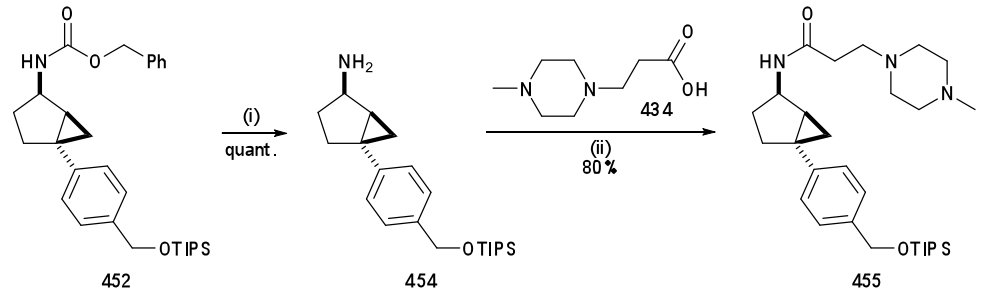


Scheme 16: *Reagents and conditions*; (i) 2 eq. $ZnEt_2$, 4 eq. CH_2I_2, CH_2Cl_2, 0 °C to RT, 1 hr; (ii) 3 eq. $ZnEt_2$, 6 eq. CH_2I_2, 3 eq. TFA, CH_2Cl_2, 0 °C to RT, 3 hrs.

The reason for the improved diastereoselectivity with *O*-TIPS protection is unclear, the silyl group being too remote from the reaction centre to have any direct steric influence. One possibility is that the alcohol is able to bind weakly to the zinc complex, perhaps creating a bulkier and therefore more selective carbenoid reagent for intermolecular cyclopropanation. Since *O*-TIPS protection results in higher yields and diasteroselectivities in the cyclopropanation reactions compared to *O*-TBDMS protection, the total synthesis of *trans*-SCH-A **140** from cyclopropane **452** was next investigated.

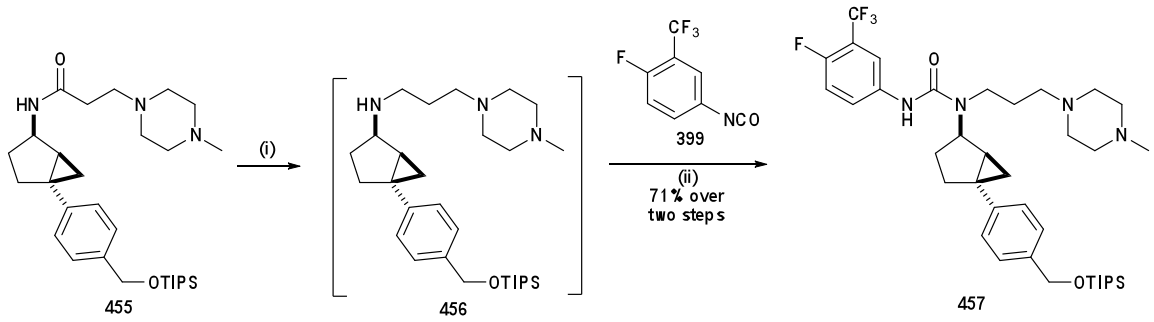
4.13 Towards the total synthesis of *trans*-SCH-A 140

With an effective, stereodivergent, cyclopropanation protocol developed, the elaboration of **452** to *trans*-SCH-A **140**, *via* the route previously demonstrated in the model system, was undertaken. *N*-Cbz deprotection of **452** again proved to be straightforward and coupling of the resultant amine **454** with carboxylic acid **434**, under the same EDCI/HOBt conditions used previously, gave amide **455** in 80% yield over the two steps (Scheme 17).



Scheme 17: *Reagents and conditions*; (i) H_2 (1 atm.), Pd/C (30 wt. %), MeOH/EtOAc (1:1), 3 hrs; (ii) 1.2 eq. **434**, 1.2 eq. EDCI, 1.2 eq. HOBt, 5.0 eq. NEt_3, $CHCl_3$, 18 hrs.

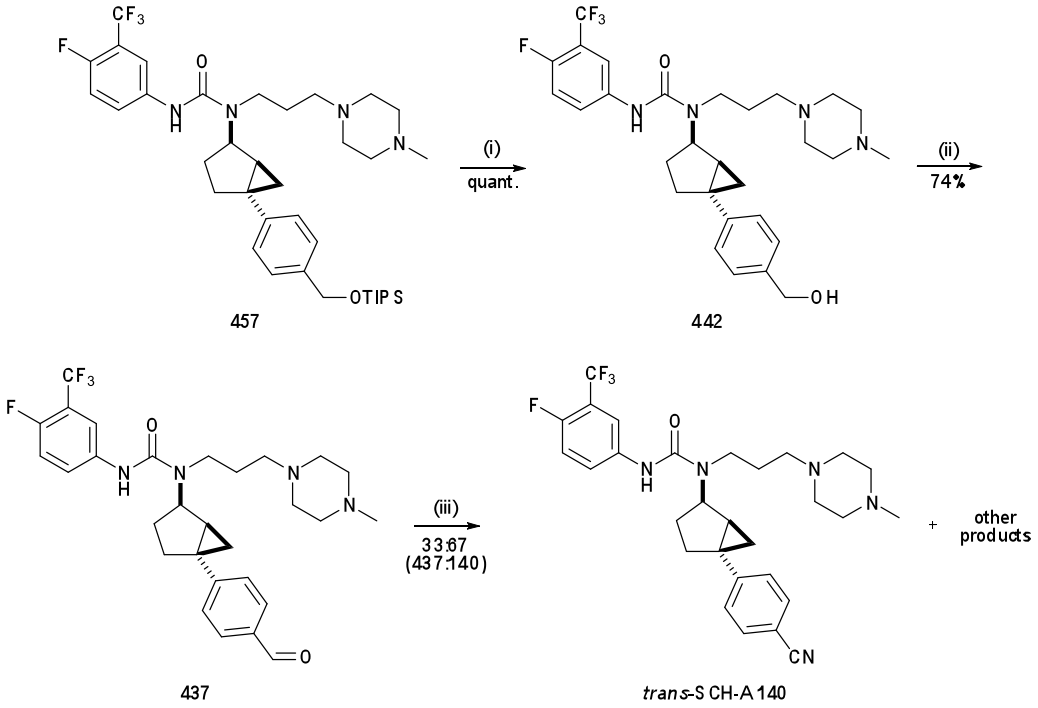
It was found that reduction of amide **455** could be accomplished with $LiAlH_4$ to give secondary amine **456** which was reacted immediately with isocyanate **399** to give urea **457** in 71% yield over two steps (Scheme 18).



Scheme 18: *Reagents and conditions*; (i) 2.5 eq. $LiAlH_4$, THF, reflux, 16 hrs; (ii) 1.2 eq. **399**, 1.2 eq. DIPEA, CH_2Cl_2, RT, 18 hrs.

O-Silyl deprotection was achieved under standard conditions using TBAF to give free alcohol **442** in quantitative yield. Alcohol **442** was then oxidized to aldehyde **437** in

74% yield using MnO_2 in CH_2Cl_2.[iii] Oxidative amination of aldehyde **437**, with IBX in NH_4OH,[22] gave a complex mixture of products containing a 33:67 mixture of aldehyde **437** and a compound tentatively assigned as *trans*-SCH-A **140**. Unfortunately due to limited material it was not possible to optimize this step further or isolate a pure sample of the desired product.[iv] Comparison of the ^1H NMR spectrum of nitrile **140** with that reported by Hodgson *et al.* showed that it did not match *cis*-SCH-A **389** [characteristic ^1H NMR signals, δ_H (500MHz, $CDCl_3$); **140**: 3.34-3.40 (1H, m), 3.48-3.54 (1H, m), 5.05-5.09 (1H, m); **389**: 3.29 (2H, t, *J* 6), 4.93 (1H, d, *J* 8)] (Scheme 19).



Scheme 19: *Reagents and conditions*; (i) 1.2 eq. TBAF, THF, 0 °C, 1 hr; (ii) 10 eq. MnO_2, CH_2Cl_2, RT, 3 hrs; (iii) 1.5 eq. IBX, NH_4OH/MeCN, RT, 12 hrs.

[iii] It was found that aldehyde **437** partially decomposed on silica gel, giving unidentified decomposition products which could not be separated.

[iv] The one-pot oxidative amination of an alcohol to a nitrile was briefly investigated however it was found that the IBX-mediated oxidation of an alcohol to the aldehyde did not occur in NH_4OH/MeCN.

4.14 Conclusion and future work

A route towards the total synthesis of *trans*-SCH-A **140** has been developed, though further studies are required in order to optimize the final oxidative amination step and provide the desired product in sufficiently high purity and yield. In addition, *cis*-**453** a precursor in the analogous synthesis of *cis*-SCH-A **389** has been synthesized in high diastereoselectivity (91:9; *cis*:*trans*).

Studies towards completing the total synthesis of *trans*-SCH-A **140** and *cis*-SCH-A **389** are ongoing within the Davies laboratory and the broad scope of this strategy has been exemplified by the synthesis of a range of cyclopropane intermediates **457**-**462** (Figure 8).[23]

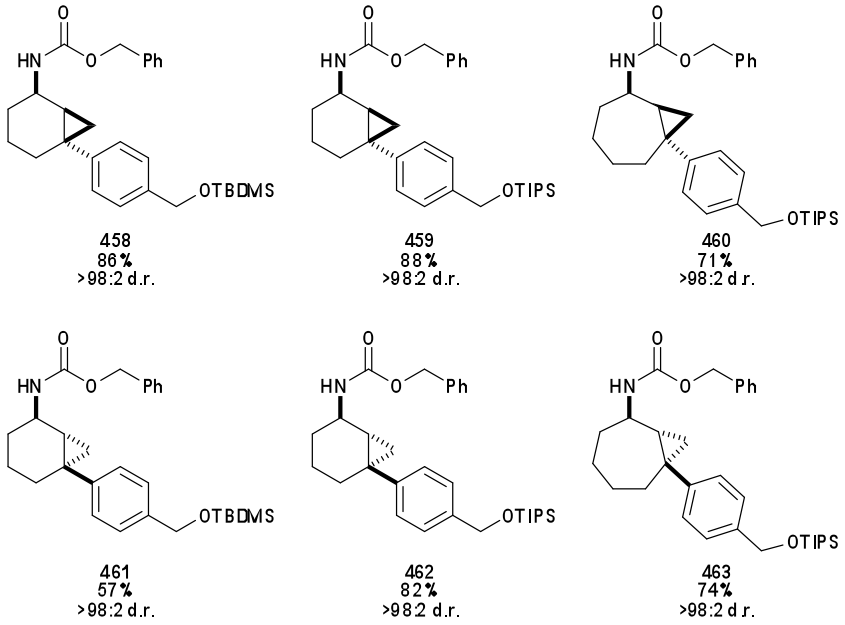


Figure 8: A range of cyclopropane intermediates.

4.15 References and notes

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Chapter 5: Experimental

5.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Reactions described as being performed at −78 °C were cooled by means of an acetone/dry ice bath and those at 0 °C by an ice bath.

5.1.1 Solvents

Solvents were dried by passing them through a column of activated basic alumina according to the procedure outlined by Grubbs and co-workers.[1] In the case of Et_2O, CH_2Cl_2 and toluene the resin used was Brockmann 1, standard grade, *ca*. 150 mesh alumina while for THF this was Alcoa Grade DD-2 alumina. Petrol is defined as petroleum ether 30-40 °C or 40-60 °C.

5.1.2 Reagents

All commercial reagents were used as supplied without further purification unless stated otherwise. Unless otherwise stated, all aqueous solutions were saturated and all organic layers were dried over $MgSO_4$.

5.1.3 Chromatography

Analytical chromatography (tlc) was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. Plates were visualised either by UV light (254 nm) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Flash column chromatography was performed manually on Kieselgel 60 silica gel or on an automated Biotage SP4 Platform using Biotage SNAP KP-Sil® cartridges using the solvent system stated.

5.1.4 Melting Points

Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected.

5.1.5 Polarimetry

Specific rotations were recorded using a Perkin-Elmer 241 polarimeter, using a path length of 10 cm, with concentrations (c) given in g/100 cm^3, solvent and temperature as recorded. Values are quoted in units of $10^{-1}degcm^2g^{-1}$.

5.1.6 NMR Spectroscopy

All chemical shifts (δ_X) are quoted in ppm and coupling constants (*J*) in Hz. ^1H NMR spectra were recorded on Bruker DPX-200 (200 MHz), DPX-250 (250 MHz), DPX-400 (400 MHz), AV-400 (400 MHz), AVII-500 (500 MHz) or DRX-500 (500 MHz) spectrometers. The spectra are referenced to the stated solvent peak. ^{13}C spectra were recorded on Bruker DPX-400 (100 MHz), AV-400 (100 MHz), DRX-500 (125 MHz) or AVII-500 (125 MHz) spectrometers. The spectra are referenced to the stated solvent peak. ^{19}F spectra were recorded on the Bruker AV-400 (376 MHz) spectrometer. The spectra are referenced externally to $CFCl_3$ in $CDCl_3$. Two-dimensional spectra were recorded on Bruker DPX-400, AV-400, AVII-500 or DRX-500 spectrometers. nOe spectra were obtained on the Bruker DRX-500 spectrometer.

Spectra recorded on the Bruker DPX-250 spectrometers were obtained by Dr. E. C. Goddard or Mr S. A. Bentley of the Chemistry Research Laboratory, University of Oxford. Spectra recorded on the Bruker DRX-500 or AVII-500 spectrometers were obtained by Dr. B. Odell of the Chemistry Research Laboratory, University of Oxford.

5.1.7 Mass Spectroscopy

Low resolution mass spectra (*m/z*) were recorded on either a VG Autospec instrument (CI^+, NH_3), a VG MassLab 20-250 (ESI) or a Micromass Platform I instrument (ESI). Those recorded on an Autospec instrument were obtained by Dr. J. Kirkpatrick, Dr. J. McCullagh, Dr. N. Oldham or Mr. R. Procter of the Chemistry Research Laboratory, University of Oxford. Major peaks are listed with intensities quoted as percentages of the principal peak. Accurate mass measurements were recorded by Dr. J. Kirkpatrick, Dr. J. McCullagh, Dr. N. Oldham or Mr. R. Procter of the Chemistry Research Laboratory. Accurate Mass ESI measurements were run on a Bruker MicroTof and were internally calibrated with polyalanine in positive and negative modes. Accurate Mass ESI measurements were also carried out a Micromass LCT instrument using a lock-spray source. Positive ion spectra were calibrated relative to PEG using tetraoctylammonium bromide as a lock mass. Negative ion spectra were calibrated relative to polyalanine with sodium dodecyl sulfate as a lock mass. GC Tof measurements (CI^+) were run on a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m x 0.25 mm), using amyl acetate as a lock mass.

5.1.8 Chiral HPLC

Chiral HPLC was performed on an Agilent 1200 Instrument, fitted with a DIACEL CHIRALPAK 1B column, by Mr David Daniels of the Chemistry Research Laboratory, University of Oxford.

5.1.9 X-ray Crystallography

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Ka radiation using standard procedures at the specified temperature. The structure was solved by direct methods (SIR92), all non-hydrogen

atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

5.2 General Experimental Procedures

General Procedure 1: Cyclopropanation with the Wittig-Furukawa reagent [$Zn(CH_2I)_2$]

To a stirred solution of $ZnEt_2$ (1.0 M in hexanes, 2.0 eq) in CH_2Cl_2 (0.5 M) at −78 °C was added CH_2I_2 (4.0 eq) dropwise. The mixture was vigorously stirred at 0 °C for 15 mins resulting in the formation of a white precipitate. To this was added the requisite substrate (1.0 eq) either neat or as a solution in the minimium amount of CH_2Cl_2. The resulting mixture was stirred at RT for the specified time and then quenched by the addition of sat. aq. Na_2EDTA (~1 mL/mmol substrate). The resulting mixture was vigorously stirred for 5 mins then diluted with CH_2Cl_2 (~10 mL/mmol substrate) and sat. aq. $NaHCO_3$ (~10 mL/mmol substrate). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product.

Safety note: The preparation of $Zn(CH_2I)_2$ on a large-scale (> 8 mmol) has been reported to be an explosion hazard.[3] Following the standard literature conditions (addition of CH_2I_2 to $ZnEt_2$ at 0 °C) this was indeed found to be the case. The modified procedure described above appears to significantly reduce the chance of explosion, and has been performed numerous times on large scale (> 20 mmol) without incident. The principal difference is the addition of CH_2I_2 to $ZnEt_2$ at -78 °C which allows the gradual formation of $Zn(CH_2I)_2$ (which is known to be exothermic). However, appropriate safety precautions should always be taken when handling these reagents.

General Procedure 2: Cyclopropanation with Denmark's reagent [$Zn(CH_2Cl)_2$]

To a stirred solution of $ZnEt_2$ (1.0 M in hexanes, 2.0 eq) in CH_2Cl_2 (0.5 M) at 0 °C was added $ClCH_2I$ (4.0 eq) dropwise. The mixture was allowed to stir at 0 °C for 15 mins resulting in the formation of a white precipitate. To this was added the requisite substrate (1.0 eq) either neat or as a solution in the minimium amount of CH_2Cl_2. The resulting mixture was stirred at RT for the specified time and then quenched by the addition of sat. aq. Na_2EDTA (~1 mL/mmol substrate). The resulting mixture was vigorously stirred for 5 mins then diluted with CH_2Cl_2 (~10 mL/mmol substrate) and sat. aq. $NaHCO_3$ (~10 mL/mmol substrate). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product.

General Procedure 3: Cyclopropanation with Shi's carbenoid [$CF_3CO_2ZnCH_2I$]

To a stirred solution of $ZnEt_2$ (1.0 M in hexanes, 2.0 – 3.0 eq) in CH_2Cl_2 (0.5 M) at −78 °C was added CH_2I_2 (4.0 – 6.0 eq) dropwise. The mixture was allowed to stir at 0 °C for 15 mins resulting in the formation of a white precipitate. TFA (2.0 – 3.0 eq) was added, resulting in the rapid formation of a homogeneous colourless solution, which was allowed to stir for 15 mins. To this was added the requisite substrate (1.0 eq) either neat or as a solution in the minimium amount of CH_2Cl_2. The resulting mixture was stirred at RT for the specified time and then quenched by the addition of sat. aq. Na_2EDTA (~1 mL/mmol substrate). The resulting mixture was vigorously stirred for 5 mins then diluted with CH_2Cl_2 (~10 mL/mmol substrate) and sat. aq. $NaHCO_3$ (~10 mL/mmol substrate). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product.

General Procedure 4: Synthesis of allylic amines *via* reductive amination with $NaBH(OAc)_3$

Dibenzylamine (1.2 eq) and the requisite aldehyde (1.0 eq) were allowed to stir neat for 30 mins, then diluted with CH_2Cl_2 (0.2 M) and cooled to 0 °C. $NaBH(OAc)_3$ (1.5 eq) was added portionwise over 5 mins and the resulting mixture stirred at RT for 2 hrs. The reaction was quenched by addition of H_2O (0.2 M) and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ and brine, dried, filtered and concentrated *in vacuo* to give a crude product.

General Procedure 5: Synthesis of allylic amines *via* the Petasis boronic acid-Mannich reaction

A solution of boronic acid (1.0 eq), amine (1.0 eq) and paraformaldehyde (1.0 eq) in toluene (0.2 M) was heated at 90 °C for the specified time then allowed to cool to RT and concentrated *in vacuo* to give a crude product.

General Procedure 6: Synthesis of allylic amines *via* addition of Grignard reagents to α-benzotriazoles

To a stirred solution of α-benzotriazole (1.0 eq) in toluene (0.4 M) at RT was added the requisite Grignard reagent *via* syringe and the resulting suspension stirred at 50 °C for 2 hrs. The suspension was allowed to cool to RT and sat. aq. NH_4Cl (0.4 M) was carefully added. The mixture was diluted with Et_2O, the organic layer separated and the aq. layer extracted with Et_2O (3 ×). The combined organic layers were washed sequentially with 1.0 M aq. NaOH and brine, dried, filtered and concentrated *in vacuo* to yield a crude product.

General Procedure 7: Synthesis of allylic amines *via* addition of non-commercially available Grignard reagents to α-benzotriazoles

To a stirred suspension of Mg turnings (1.5 eq) and cat. I_2 in THF (0.5 M) at RT was added the requisite bromide (1.5 eq) dropwise. The solution was gently heated with a heat gun to initiate Grignard formation, at which point the solution turned colourless. The resulting mixture was heated at reflux for 2 hrs or until all the Mg had been consumed. The Grignard reagent was then allowed to cool to RT and added to a stirred solution of α-benzotriazole (1.0 eq) in toluene (0.25 M) at RT *via* cannula. The resulting suspension was stirred at 50 °C for 2 hrs then allowed to cool to RT and sat. aq. NH_4Cl (0.4 M) was carefully added. The mixture was diluted with Et_2O, the organic layer separated and the aq. layer extracted with Et_2O (3 ×). The combined organic layers were washed sequentially with 1 M aq. NaOH and brine, dried, filtered and concentrated *in vacuo* to yield a crude product.

General Procedure 8: Hydrogenolysis of *N*,*N*-dibenzylamines

To a degassed solution of substrate in MeOH/H_2O/AcOH (40:4:1, v/v/v, ~2 mL/mmol substrate) was added Pd (10% wt. on carbon, 50% by mass of substrate). The vessel was charged with H_2 (5 atm) and the reaction mixture was stirred rapidly at RT for 16 hrs, after which time the solution was filtered through a pad of Celite® (eluent, MeOH) and either TFA (~1 mL/mmol substrate) or conc. HCl (~1 mL/mmol substrate) was added. The resulting mixture was concentrated *in vacuo* to give the crude product.

General Procedure 9: Synthesis of allylic carbamates and amides *via* the $Bi(OTf)_3$-mediated substitution of allylic alcohols

To a stirred mixture of $Bi(OTf)_3$ (0.05 eq), KPF_6 (0.05 eq), $MgSO_4$ (~150 mg/mmol substrate) and the requisite amide or carbamate (1.5 eq) in THF or 1,4-dioxane (0.1 – 0.2 M) at RT was added the requisite alcohol (1.0 eq) either neat or as a solution in the minimum amount of THF or 1,4-dioxane. The resulting solution was allowed to stir at RT for the specified time (monitored by tlc) then filtered through Celite® (eluent, Et_2O or EtOAc) and concentrated *in vacuo* to give a crude product.

General Procedure 10: 1,2-Addition of aryllithium reagents to enones

To a stirred solution of the requisite aryl halide (1.2 eq) in THF (0.2 M) at −78 °C was added ^{t}BuLi (1.7 M in pentanes, 2.4 eq) dropwise over 5 mins. The resulting solution was stirred at −78 °C for 30 mins and then the requisite enone (1.0 eq) was added dropwise *via* syringe. The resulting solution was stirred for 1 hr at −78 °C then carefully quenched by the addition of H_2O (0.2 M). The mixture was allowed to warm to RT, the organic layer separated and the aqueous layer extracted with Et_2O (3 ×). The combined organic layers were washed with brine, dried, filtered and concentrated *in vacuo* to give a crude product.

General Procedure 11: Hydrogenolysis of benzyl carbamates

To a degassed solution of substrate in MeOH/EtOAc (4:1, v/v, 0.1 - 0.2 M) was added Pd (10% wt. on carbon, 30% by mass of substrate) and the mixture stirred under 1 atm. of H_2 for the specified time (monitored by tlc). The reaction mixture was then filtered through Celite® (eluent, MeOH) and concentrated *in vacuo* to give the crude product.

General Procedure 12: Synthesis of carbamates *via* Staudinger-type reaction

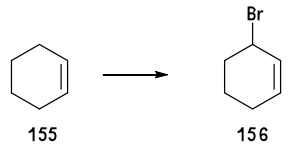
To a stirred solution of azide (1.0 eq) in THF (0.2 M) at RT was added *n*Bu_3P (1.05 eq) dropwise and the resulting solution stirred at RT for 1 hr. The requisite chloroformate (1.10 eq) was then added dropwise and the resulting mixture stirred at RT for 3 hrs. The reaction was quenched by addition of sat. aq. $NaHCO_3$, the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product.

General Procedure 13: Mitsunobu reaction with ethyl *N*-alkyloxycarbonyloxamates

To a stirred solution of the requisite alcohol (1.0 eq) in THF (0.1 M) at RT was added PPh_3 (1.2 eq), the requisite ethyl *N*-alkyloxycarbonyloxamate (1.2 eq) and DEAD (1.2 eq). The resulting solution was stirred at RT for 24-48 hrs and then $LiOH{\cdot}H_2O$ (3.0 eq) and H_2O (0.1 M) were added. The resulting mixture was stirred at RT for 3 hrs then diluted with brine and extracted with EtOAc (3 ×). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product.

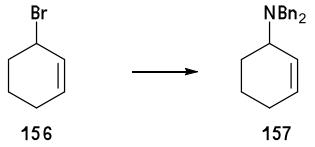
5.3 Experimental for Chapter 2

(*RS*)-3-Bromocyclohex-1-ene 156[4]



To a stirred solution of cyclohexene **155** (30.4 mL, 0.30 mol, 1.0 eq) in CCl_4 (500 mL) was added AIBN (493 mg, 3.0 mmol, 0.01 eq) and NBS (53.4 g, 0.30 mol, 1.0 eq). The resulting suspension was heated at reflux (~90 °C) for 3 hrs then cooled to 0 °C and filtered. The filtrate was concentrated *in vacuo* to give a crude product as a brown oil (48.3 g, quant.) which was used immediately without further purification; δ_H (400 MHz, $CDCl_3$) 1.68-1.75 (3H, m, 3 × C*H*$_2$), 1.91-2.25 (3H, m, 3 × C*H*$_2$), 4.85-4.90 (1H, m, C(1)*H*), 5.80-5.85 (1H, m, C(2)*H*), 5.87-5.93 (1H, m, C(3)*H*).

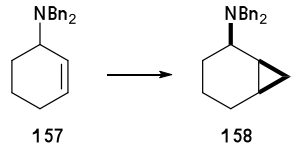
(*RS*)-3-(*N*, *N*- Dibenzylamino)cyclohexene 157[4]



To a stirred solution of **156** (5.00 g, 31.0 mmol, 1.0 eq) in THF (50 ml) was added dibenzylamine (30.4 g, 155 mmol, 5.0 eq) and DMAP (379 mg). The resulting mixture was stirred for 3 days at RT and then concentrated *in vacuo*. The mixture was dissolved in CH_2Cl_2 (500 mL), washed with 10% citric acid solution (500 mL) followed by sat. aq. $NaHCO_3$ (500 mL). The organic layer was dried, filtered and concentrated *in vacuo* to yield a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give **157** (6.20 g, 80%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 1.78-1.99 (2H, m, C(5)*H*$_2$), 2.19-2.49 (4H, m, C(4)*H*$_2$ and

C(6)H_2), 3.41 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 3.98-4.13 (1H, m, C(3)*H*), 5.65-5.85 (2H, m, C(1)*H* and C(2)*H*), 7.11-7.49 (10H, m, *Ph*).

(1*RS*,2*SR*,3*RS*)-*N*,*N*-Dibenzylbicyclo[4.1.0]heptan-2-amine 158



157 158

Method A:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (268 mg, 92%); ν_{max} (film) 2930 (C-H), 1494, 1453 (Ar); δ_H (400MHz, $CDCl_3$) 0.26-0.30 (1H, m, C(7)$H_A$$H_B$), 0.62-0.68 (1H, m, C(7)H$_A$$H_B$), 0.75-0.84 (1H, m, C(6)*H*), 0.97-1.08 (3H, m, C(1)*H*, C(4)$H_A$$H_B$, C(3)$H_A$$H_B$), 1.16-1.25 (1H, m, C(5)$H_A$$H_B$), 1.36-1.42 (1H, m, C(4)H$_A$$H_B$), 1.45-1.53 (1H, m, C(3)H$_A$$H_B$), 1.73-1.80 (1H, m, C(5)H$_A$$H_B$), 3.00-3.09 (1H, m, C(2)*H*), 3.64 (2H, d, *J* 14.1, N(C$H_A$$H_B$Ph)$_2$), 3.69 (2H, d, *J* 14.1, N(CH$_A$$H_B$Ph)$_2$), 7.09-7.13 (2H, m, *p-Ph*), 7.18-7.22 (4H, m, *m-Ph*), 7.31-7.33 (4H, m, *o-Ph*); δ_C (100MHz, $CDCl_3$) 8.7 (*C*(6)), 11.2 (C(7)), 12.7 (*C*(1)), 22.5 (*C*(3)), 23.8 (*C*(4), *C*(5)), 54.4 (*C*(2), N(*C*H$_2$Ph)$_2$), 126.6 (*p-Ph*), 128.2 (*m-Ph*), 128.6 (*o-Ph*), 141.4 (*i-Ph*); *m*/*z* (ESI^+) 292 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}N^+$ ($[M+H]^+$) requires 292.2065; found 292.2065.

Method B:

Following **General Procedure 1**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2

(2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (31 mg, 11%) with identical spectroscopic properties to **158** above.

Method C:

Following **General Procedure 2**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and $ClCH_2I$ (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (96 mg, 33%) with identical spectroscopic properties to **158** above.

Method D:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and acetic acid (0.11 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product. ^1H NMR analysis of the crude product showed that the reaction had reached <10% conversion to **158**. No further purification was attempted.

Method E:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and chloroacetic acid (189 mg, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (180 mg, 62%) with identical spectroscopic properties to **158** above.

Method F:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and dichloroacetic acid (0.16 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (260 mg, 89%) with identical spectroscopic properties to **158** above.

Method G:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and trichloroacetic acid (163 mg, 1.0 mmol, 1.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (169 mg, 58%) with identical spectroscopic properties to **158** above.

Method H:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), diethylzinc (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and diiodomethane (0.32 mL, 4.0 mmol, 4.0 eq) and trichloroacetic acid (327 mg, 2.0 mmol, 2.0 eq) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (191 mg, 66%) with identical spectroscopic properties to **158** above.

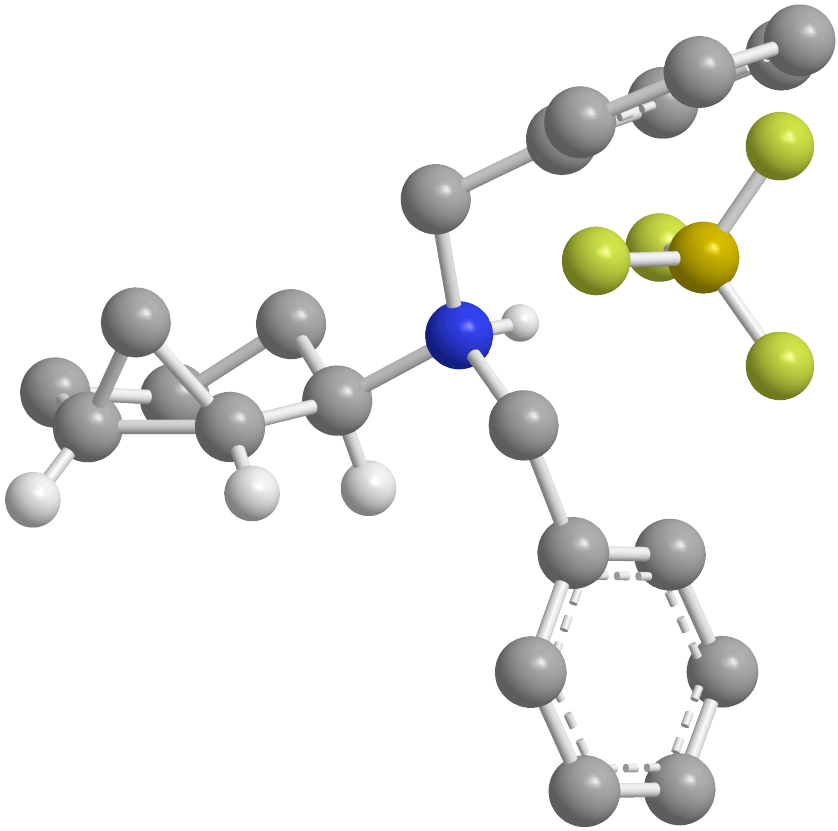
Method I:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 360 mins gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (207 mg, 71%) with identical spectroscopic properties to **158** above.

Method J:

Following **General Procedure 3**, **157** (277 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 720 mins gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **158** as a colourless oil (185 mg, 64%) with identical spectroscopic properties to **158** above.

X-Ray crystal structure data for (1*RS*,2*SR*,3*RS*)-158·HBF$_4$ (Some H atoms omitted for clarity)



X-ray crystal structure determination for 158·HBF$_4$

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **158·HBF$_4$** [$C_{21}H_{26}BF_4N$]: M = 379.25, monoclinic, space group *P 1 21/c 1*, a = 9.3534(2) Å, b = 15.3985(3) Å, c = 13.8619(4) Å, β = 100.7273(9)°, V = 1961.62(8) Å^3, Z = 4, μ = 0.100 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.1 mm^3. A total of 4489 unique reflections were measured for $5 < \theta < 27$ and 2693 reflections were used in the refinement. The final parameters were wR_2 = 0.146 and R_1 = 0.057 [I>3.0σ(I)]. X-ray crystal structure determination

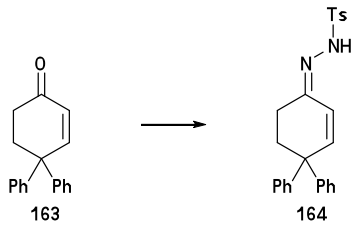
was performed by Dr J. E. Thomson and Mr K. B. Ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters ($Å^2$) (e.s.d. in parentheses)

Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
F(1)	0.4053(2)	0.58583(11)	0.10621(15)	0.0593
B(2)	0.4167(4)	0.6755(2)	0.1010(2)	0.0375
F(3)	0.5545(2)	0.69741(12)	0.08372(15)	0.0659
F(4)	0.4024(3)	0.71074(13)	0.18875(16)	0.0821
F(5)	0.3173(3)	0.70501(15)	0.02468(19)	0.0913
N(6)	0.4269(2)	0.42046(14)	0.20672(15)	0.0317
C(7)	0.4686(3)	0.41569(18)	0.31759(18)	0.0370
C(8)	0.3758(3)	0.47076(16)	0.37062(18)	0.0316
C(9)	0.3035(3)	0.43349(18)	0.43873(19)	0.0381
C(10)	0.2264(3)	0.4850(2)	0.4943(2)	0.0457
C(11)	0.2215(3)	0.5738(2)	0.4801(2)	0.0481
C(12)	0.2924(3)	0.6118(2)	0.4124(2)	0.0486
C(13)	0.3692(3)	0.56057(18)	0.3584(2)	0.0404
C(14)	0.2701(3)	0.38819(17)	0.17019(19)	0.0344
C(15)	0.2171(3)	0.41147(19)	0.0626(2)	0.0404
C(16)	0.0595(3)	0.38150(19)	0.0335(2)	0.0436
C(17)	0.0504(4)	0.2826(2)	0.0330(3)	0.0554
C(18)	0.1364(3)	0.2422(2)	0.1245(3)	0.0560
C(19)	0.2523(3)	0.29407(18)	0.1931(2)	0.0432
C(20)	0.2957(4)	0.2224(2)	0.1314(3)	0.0605
C(21)	0.5422(3)	0.37753(18)	0.15894(19)	0.0363
C(22)	0.6906(3)	0.41716(18)	0.19399(18)	0.0351
C(23)	0.7992(3)	0.3693(2)	0.2532(2)	0.0428
C(24)	0.9338(3)	0.4077(2)	0.2890(2)	0.0488
C(25)	0.9593(3)	0.4927(2)	0.2670(2)	0.0486
C(26)	0.8532(3)	0.5399(2)	0.2071(2)	0.0484
C(27)	0.7193(3)	0.50252(19)	0.1699(2)	0.0428
H(72)	0.5659(3)	0.43769(18)	0.33471(18)	0.0462
H(71)	0.4656(3)	0.35497(18)	0.33715(18)	0.0462
H(91)	0.3080(3)	0.37366(18)	0.44680(19)	0.0450
H(101)	0.1773(3)	0.4584(2)	0.5420(2)	0.0525
H(111)	0.1670(3)	0.6077(2)	0.5165(2)	0.0635
H(121)	0.2879(3)	0.6749(2)	0.4034(2)	0.0638
H(131)	0.4221(3)	0.58630(18)	0.3134(2)	0.0503
H(141)	0.2085(3)	0.42207(17)	0.20834(19)	0.0413
H(151)	0.2244(3)	0.47304(19)	0.0533(2)	0.0452
H(152)	0.2784(3)	0.38116(19)	0.0229(2)	0.0451
H(162)	0.0051(3)	0.40437(19)	0.0808(2)	0.0498

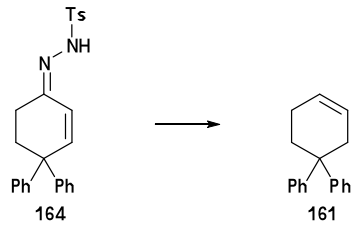
H(161)	0.0194(3)	0.40306(19)	-0.0321(2)	0.0501
H(171)	-0.0538(4)	0.2667(2)	0.0280(3)	0.0651
H(172)	0.0862(4)	0.2602(2)	-0.0235(3)	0.0653
H(181)	0.0800(3)	0.2016(2)	0.1599(3)	0.0676
H(191)	0.2641(3)	0.28000(18)	0.2639(2)	0.0532
H(202)	0.3435(4)	0.2375(2)	0.0768(3)	0.0813
H(201)	0.3372(4)	0.1676(2)	0.1642(3)	0.0816
H(211)	0.5153(3)	0.38529(18)	0.08805(19)	0.0453
H(212)	0.5457(3)	0.31535(18)	0.17598(19)	0.0452
H(231)	0.7810(3)	0.3092(2)	0.2686(2)	0.0558
H(241)	1.0100(3)	0.3763(2)	0.3283(2)	0.0652
H(251)	1.0490(3)	0.5184(2)	0.2934(2)	0.0600
H(261)	0.8721(3)	0.5979(2)	0.1918(2)	0.0613
H(271)	0.6443(3)	0.53489(19)	0.1282(2)	0.0524
H(61)	0.4315(2)	0.47678(14)	0.19229(15)	0.0480

4,4-Diphenyl-2-cyclohexenone tosylhydrazone 164[5]



To a stirred solution of 4,4-diphenyl-2-cyclohexen-1-one **163** (1.00 g, 4.03 mmol, 1.0 eq) in MeOH (10 mL) was added tosylhydrazide (825 mg, 4.43 mmol, 1.1 eq) in toluene (5 mL) and the mixture stirred at RT for 16 hrs. The mixture was then concentrated *in vacuo*, dissolved in EtOAc (25 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give **164** as a pale yellow solid (1.62 g, 96%) which was used without further purification; m.p. 165 °C (dec.) (lit. m.p.[5] 191-192 °C); δ_H (400MHz, $CDCl_3$) 2.23 (2H, t, *J* 6.3, C(5)H_2), 2.41-2.46 (2H, m, C(6)H_2) overlapping 2.44 (3H, s, CH_3), 6.37 (1H, d, *J* 10.2, C(2)*H*), 6.60 (1H, d, *J* 10.2, C(3)*H*), 7.15-7.38 (12H, m, *Ar*), 7.66 (1H, br s, N*H*), 7.85 (2H, d, *J* 8.3, *Ar*).

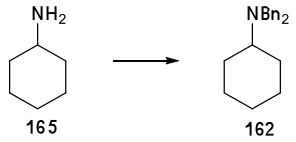
4,4-Diphenylcyclohex-1-ene 161[5]



To a stirred solution of **164** (833 mg, 2.0 mmol, 1.0 eq) in $CHCl_3$ (5 mL) at 0 °C was added catechol borane (0.23 mL, 2.2 mmol, 1.1 eq) and the mixture stirred at RT for 2 hrs. $NaOAc{\cdot}3H_2O$ (816 mg, 6.0 mmol, 3.0 eq) was added and the mixture heated at 60 °C for 1 hr. The mixture was allowed to cool to RT, H_2O (5 mL) was added and the

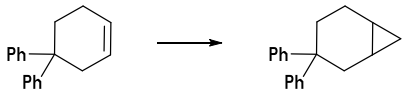
mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **161** as a white powder (351 mg, 75%); m.p. 59-60 °C (lit. m.p.[5] 62-63 °C); δ_H (400 MHz, $CDCl_3$) 1.77-1.83 (2H, m, C(5)H_2), 2.38 (2H, t, *J* 6.1, C(6)H_2), 2.61-2.64 (2H, m, C(3)H_2), 5.64-5.70 (1H, m, C(1)*H*), 5.85-5.90 (1H, m, C(2)*H*), 7.15-7.29 (10H, m, *Ph*).

(*RS*)-*N*,*N*-Dibenzylcyclohexanamine 162[6]



A mixture of cyclohexylamine **165** (0.44 mL, 4.0 mmol, 1.0 eq) and benzyl bromide (0.96 mL, 8.0 mmol, 2.0 eq) in 0.5 M aq. NaOH (17.6 mL, 8.8 mmol, 2.2 eq) was heated at 80 °C (microwave) for 30 mins. The mixture was then allowed to cool to RT and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, petrol → 20% EtOAc/petrol) to give **162** as a white powder (940 mg, 84 %); m.p. 61-62 °C (lit. m.p. 62°C); δ_H (400 MHz, $CDCl_3$) 1.13-1.44 (6H, m, 6 x CH_2), 1.81-1.89 (2H, m, 2 x CH_2), 1.95-2.01 (2H, m, 2 x CH_2), 2.56 (1H, tt, *J* 11.6, 3.4, C*H*NBn_2), 3.72 (4H, s, N(CH_2Ph)$_2$), 7.25-7.28 (2H, m, *p-Ph*), 7.34-7.49 (8H, m, *o/m-Ph*).

(*RS*)-3,3-Diphenylbicyclo[4.1.0]heptane 166



161 166

Prepared as outlined below; ν_{max} (film) 3055, 2995, 2935, 2860 (C-H), 1600, 1495, 1465 (Ar), 1110, 1020, 765, 740, 700; δ_H (400 MHz, $CDCl_3$) 0.12-0.16 (1H, m, C(7)H_AH_B), 0.66 (1H, app t, *J* 8.8, 4.5, C(7)H_AH_B), 0.82 (1H, app tt, *J* 9.3, 5.0, C(6)*H*), 1.19-1.23 (1H, m, C(1)*H*), 1.44 (1H, app tt, *J* 13.5, 5.3, C(5)H_AH_B), 1.65 (1H, app dd, *J* 15.0, 2.6, C(2)H_AH_B), 1.81-1.86 (1H, m, C(5)H_AH_B), 1.96 (1H, app td, *J* 13.2, 4.5, C(4)H_AH_B), 2.13 (1H, app ddt, *J* 13.1, 5.0, 2.6, C(4)H_AH_B), 2.95 (1H, app ddd, *J* 15.0, 9.2, 2.8, C(2)H_AH_B), 7.13-7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.4, 9.6 (*C*(1) and *C*(6)), 10.7 (*C*(7)), 19.8 (*C*(5)), 30.2 (*C*(4)), 38.1 (*C*(2)), 45.0 (*C*(3)), 125.4, 125.5, 126.6, 127.9, 128.0, 128.6 (*o/m/p-Ph*), 146.9, 152.0 (*i-Ph*); *m/z* (FI^+) 248 ($[M]^+$, 100%); HRMS (FI^+) $C_{19}H_{20}$ (M^+) requires 248.1572, found 248.1565.

Mechanistic studies:

A 0.45 M solution of $CF_3CO_2ZnCH_2I$ in CH_2Cl_2 was prepared according to **General Procedure 3**, from $ZnEt_2$ (10.0 mL, 10.0 mmol, 1.0 eq), CH_2I_2 (1.61 mL, 20.0 mmol, 2.0 eq) and TFA (0.74 mL, 10.0 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). The colourless solution was allowed to stir at 0 °C for 15 mins and then the appropriate amount was added *via* syringe to the reaction. The reactions were performed such that the final concentration of substrate was 0.1 M. In all cases the reaction conversion was assessed by integration of the appropriate peaks in the 400MHz ^1H NMR spectra of the crude products.

(i) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **157** (27.7 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was >98%.

(ii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **161** (23.4 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was 98%.

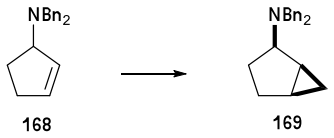
(iii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **161** (23.4 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was 8%.

(iv) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **157** (27.7 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was >95%.

(v) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **157** (27.7 mg, 0.10 mmol, 1.0 eq) and **161** (23.4 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the conversion of **157** to **158** was >98% and the conversion of **161** to **166** was 9%.

(vi) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.88 mL, 0.40 mmol, 4.0 eq) was added to **157** (27.7 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.12 mL). After 30 mins the reaction conversion was >98%.

(1*R*,2*S*,3*R*)-*N*,*N*-Dibenzylbicyclo[3.1.0]hexan-2-amine 169



168 169

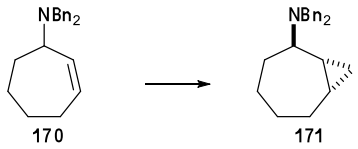
Method A:

Following **General Procedure 3**, **168** (263 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to yield pure **169** as a yellow oil (233 mg, 84%); ν_{max} (film) 3027, 2928, 2864, 2799 (C-H), 1493, 1453 (Ar); δ_H (400MHz, $CDCl_3$) 0.31-0.36 (1H, m, C(6)H_AH_B), 0.56 (1H, app q, *J* 4.0, C(6)H_AH_B), 1.18-1.24 (2H, m, C(5)*H*, C(3)H_AH_B), 1.28-1.32 (1H, m, C(1)*H*), 1.61-1.66 (1H, m, C(3)H_AH_B), 1.69-1.74 (2H, m, C(4)H_2), 3.41-3.46 (1H, m, C(2)*H*), 3.71-3.78 (4H, m, N(CH_2Ph)$_2$), 7.22-7.27 (2H, m, *p-Ph*), 7.33 (4H, app t, *J* 7.4, *m-Ph*), 7.42 (4H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 5.1 (*C*(6)), 15.1 (*C*(5)), 17.8 (*C*(1)), 23.0 (*C*(3)), 25.5 (*C*(4)), 55.9 (N(CH_2Ph)$_2$), 63.3 (*C*(2)), 126.5 (*p-Ph*), 128.0 (*m-Ph*), 128.8 (*o-Ph*), 140.7 (*i-Ph*); *m*/*z* (ESI^+) 278 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{24}N^+$ ($[M+H]^+$) requires 278.1903; found 278.1901.

Method B:

$CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **168** (26.3 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was >98%.

(1*RS*,2*RS*,7*SR*)-*N*,*N*-Dibenzylbicyclo[5.1.0]octan-2-amine 171



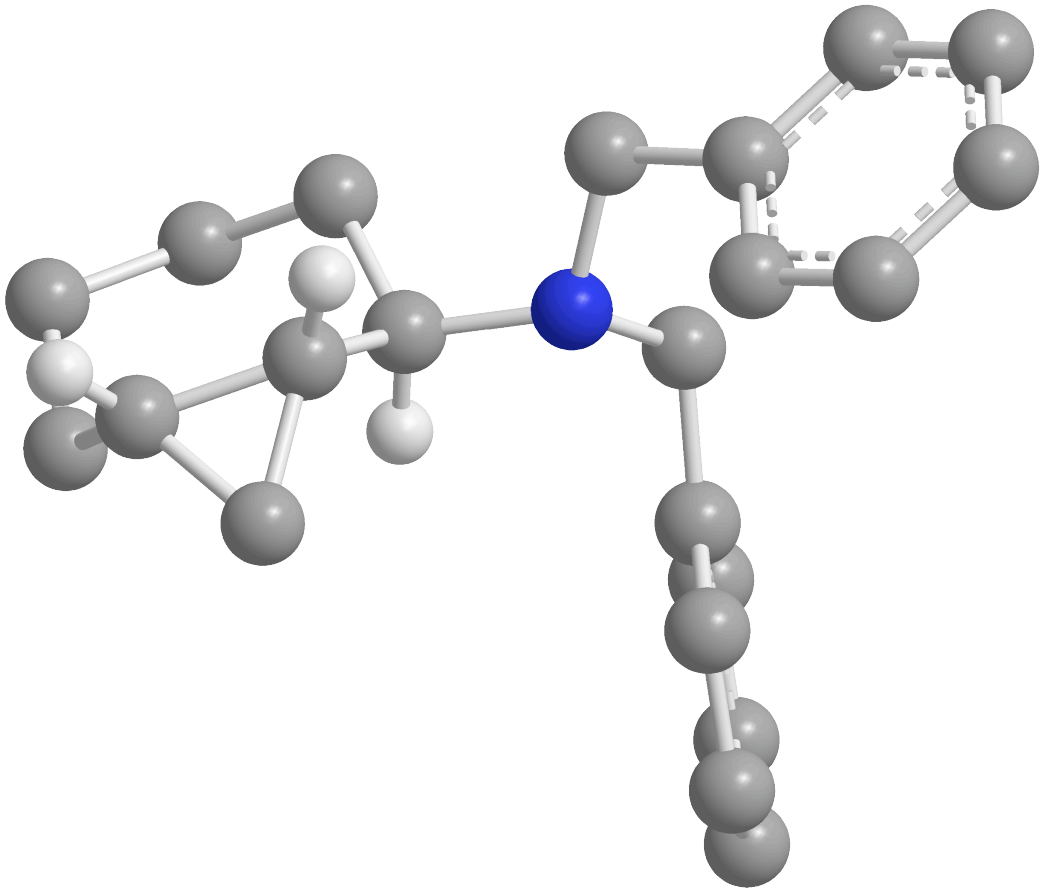
Method A:

Following **General Procedure 3**, **170** (1.00 g, 3.43 mmol, 1.0 eq), $ZnEt_2$ (6.86 mL, 1.0M in hexanes, 6.86 mmol, 2.0 eq), CH_2I_2 (1.10 mL, 13.7 mmol, 4.0 eq) and TFA (0.51 mL, 6.86 mmol, 2.0 eq) in CH_2Cl_2 (7 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 1% EtOAc/petrol) to give **171** as a white crystalline solid (940 mg, 90%); m.p. 43-45 °C; ν_{max} (KBr) 3025, 2920, 2850 (C-H), 1495, 1455 (Ar), 1125, 1030, 975, 740, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.08 (1H, q, *J* 4.7, C(8)H_AH_B), 0.48-0.57 (1H, m, C(6)H_AH_B), 0.72-0.78 (1H, m, C(7)*H*), 0.90 (1H, app td, *J* 8.0, 4.3, C(8)H_AH_B), 0.97-1.13 (2H, m, C(1)*H* and C(4)H_AH_B), 1.20-1.29 (1H, m, C(5)H_AH_B), 1.65-1.76 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 1.87-1.92 (1H, m, C(4)H_AH_B), 1.98-2.03 (1H, m, C(3)H_AH_B), 2.08-2.14 (1H, m, C(6)H_AH_B), 2.22 (1H, t, *J* 9.8, C(2)*H*), 3.75 (4H, s, N(CH_2Ph)$_2$), 7.21-7.25 (2H, m, *p-Ph*), 7.32 (4H, t, *J* 7.4, *m-Ph*), 7.45 (4H, d, *J* 7.4, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*(7)), 15.6, 15.6 (*C*(1), *C*(8)), 28.9 (*C*(5)), 30.1 (*C*(4)), 31.1 (*C*(6)), 35.5 (*C*(3)), 54.2 (N(*C*H_2Ph)$_2$), 61.4 (*C*(2)), 128.1, 128.5 (*o/m-Ph*), 128.5 (*p-Ph*), 141.1 (*i-Ph*); *m/z* (CI^+) 306 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{22}H_{28}N^+$ ($[M+H]^+$) requires 306.2222; found 306.2233.

Method B:

$CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **170** (29.1 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was >98%.

X-Ray crystal structure data for (1*RS*,2*RS*,7*SR*)-171 (Some H atoms omitted for clarity)



X-ray crystal structure determination for 171

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **171** [$C_{22}H_{27}N$]: M = 305.46, monoclinic, space group *C 1 21/c 1*, a = 25.5945(4) Å, b = 9.9031(2) Å, c = 14.6450(2) Å, β = 104.7501(8)°, V = 3589.67(10) Å^3, Z = 8, μ = 0.065 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.05 × 0.1 mm^3. A total of 4068 unique reflections were measured for $5 < \theta < 27$ and 4068 reflections were used in the refinement. The final parameters were wR_2 = 0.116 and R_1 = 0.070 [I>–3.0σ(I)]. X-ray crystal structure determination was

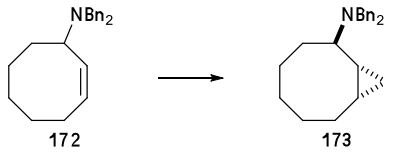
performed by Dr J. E. Thomson and Mr K. B. ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters ($Å^2$) (e.s.d. in parentheses)

Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
N(1)	0.60552(4)	0.99283(11)	0.39701(8)	0.0282
C(2)	0.57928(6)	0.87141(14)	0.42124(10)	0.0319
C(3)	0.60477(6)	0.74388(14)	0.39515(9)	0.0303
C(4)	0.66082(6)	0.72835(16)	0.42090(10)	0.0369
C(5)	0.68450(6)	0.60962(16)	0.40060(11)	0.0416
C(6)	0.65273(7)	0.50568(16)	0.35316(11)	0.0423
C(7)	0.59716(7)	0.52051(16)	0.32677(11)	0.0420
C(8)	0.57333(6)	0.63874(15)	0.34806(10)	0.0360
C(9)	0.58716(6)	1.02084(15)	0.29586(9)	0.0328
C(10)	0.62595(5)	1.10765(14)	0.25945(9)	0.0305
C(11)	0.60695(6)	1.20795(15)	0.19296(10)	0.0361
C(12)	0.64227(8)	1.28074(16)	0.15339(11)	0.0451
C(13)	0.69682(8)	1.25465(18)	0.18104(12)	0.0496
C(14)	0.71651(7)	1.15621(19)	0.24816(11)	0.0465
C(15)	0.68133(6)	1.08307(17)	0.28740(10)	0.0372
C(16)	0.60193(5)	1.11209(14)	0.45642(9)	0.0280
C(17)	0.64135(6)	1.09560(15)	0.55164(9)	0.0332
C(18)	0.69664(6)	1.15950(18)	0.57251(11)	0.0439
C(19)	0.65424(6)	1.21370(15)	0.61822(10)	0.0358
C(20)	0.62804(6)	1.34894(16)	0.59219(11)	0.0409
C(21)	0.56718(6)	1.34693(16)	0.58131(11)	0.0425
C(22)	0.53387(6)	1.28883(16)	0.48763(11)	0.0387
C(23)	0.54455(6)	1.14195(15)	0.46732(11)	0.0348
H(21)	0.58368(6)	0.87034(14)	0.49143(10)	0.0414
H(22)	0.53881(6)	0.87290(14)	0.38836(10)	0.0417
H(41)	0.68276(6)	0.80216(16)	0.45374(10)	0.0480
H(51)	0.72451(6)	0.59886(16)	0.41988(11)	0.0548
H(61)	0.66903(7)	0.42127(16)	0.33770(11)	0.0545
H(71)	0.57467(7)	0.44824(16)	0.29134(11)	0.0554
H(81)	0.53346(6)	0.64858(15)	0.33052(10)	0.0458
H(92)	0.54980(6)	1.06400(15)	0.28044(9)	0.0424
H(91)	0.58499(6)	0.93149(15)	0.26189(9)	0.0425
H(111)	0.56785(6)	1.22738(15)	0.17348(10)	0.0471
H(121)	0.62705(8)	1.35099(16)	0.10538(11)	0.0578
H(131)	0.72145(8)	1.30453(18)	0.15302(12)	0.0649
H(141)	0.75579(7)	1.13741(19)	0.26908(11)	0.0591
H(151)	0.69525(6)	1.01179(17)	0.33376(10)	0.0478
H(161)	0.61351(5)	1.19486(14)	0.42533(9)	0.0345
H(171)	0.64002(6)	1.00333(15)	0.58209(9)	0.0411

H(181)	0.72931(6)	1.10909(18)	0.61290(11)	0.0573
H(182)	0.70536(6)	1.21820(18)	0.52187(11)	0.0572
H(191)	0.66041(6)	1.18949(15)	0.68926(10)	0.0463
H(201)	0.64482(6)	1.41453(16)	0.64480(11)	0.0520
H(202)	0.63540(6)	1.37896(16)	0.52917(11)	0.0507
H(212)	0.55476(6)	1.44381(16)	0.58690(11)	0.0547
H(211)	0.55952(6)	1.28799(16)	0.63417(11)	0.0552
H(222)	0.54079(6)	1.34563(16)	0.43509(11)	0.0503
H(221)	0.49463(6)	1.29596(16)	0.48731(11)	0.0489
H(231)	0.53892(6)	1.08410(15)	0.52148(11)	0.0463
H(232)	0.51828(6)	1.11386(15)	0.40575(11)	0.0450

(1*RS*,2*RS*,8*SR*)-*N*,*N*-Dibenzylbicyclo[6.1.0]octan-2-amine 173



172 173

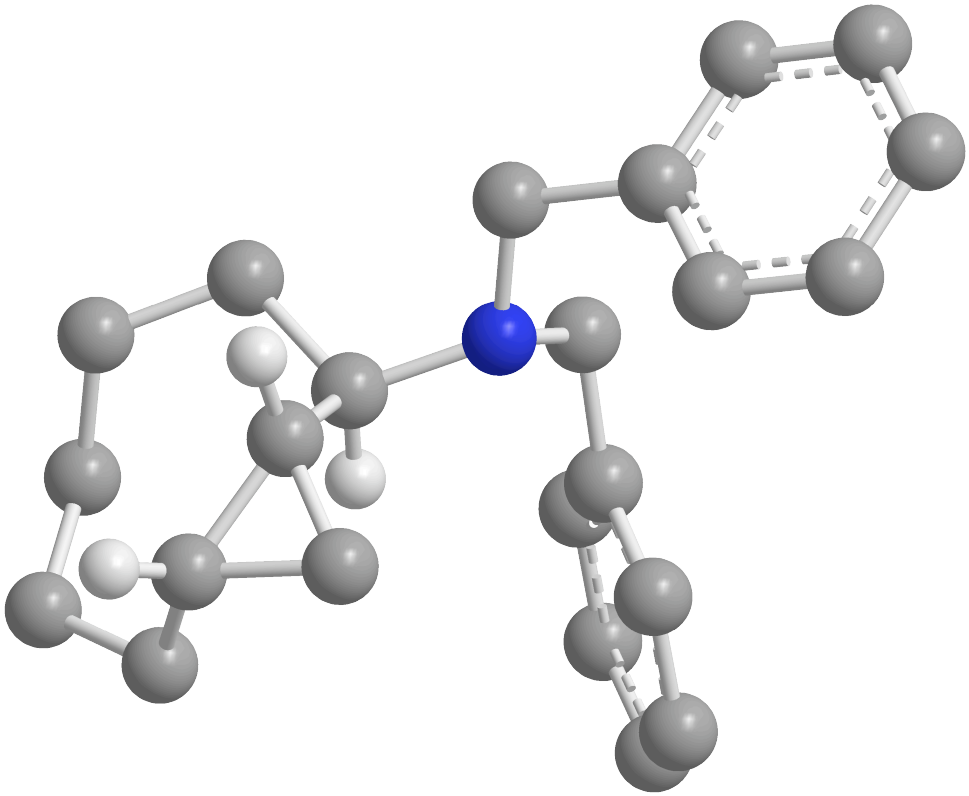
Method A:

Following **General Procedure 3**, **172** (916 mg, 3.0 mmol, 1.0 eq), $ZnEt_2$ (6.0 mL, 1.0M in hexanes, 6.0 mmol, 2.0 eq), CH_2I_2 (0.97 mL, 12.0 mmol, 4.0 eq) and TFA (0.45 mL, 6.0 mmol, 2.0 eq) in CH_2Cl_2 (6 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **173** as a white crystalline solid (920 mg, 96%); m.p. 80-82 °C; ν_{max} (KBr) 3060, 2925, 2850 (C-H), 1490, 1455 (Ar), 1125, 1025, 905, 745, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.03-0.06 (1H, m, C(9)H_AH_B), 0.36-0.46 (1H, m, C(7)H_AH_B), 0.69-0.84 (3H, m, C(1)*H*, C(8)*H* and C(9)H_AH_B), 0.97-1.05 (1H, m, C(5)H_AH_B), 1.23-1.33 (1H, m, C(6)H_AH_B), 1.42-1.69 (5H, m, C(3)H_AH_B, C(4)H_2, C(5)H_AH_B and C(6)H_AH_B), 1.77-1.82 (1H, m, C(3)H_AH_B), 1.87-1.95 (1H, m, C(7)H_AH_B), 2.24 (1H, app dt, *J* 10.4, 3.3, C(2)*H*), 3.63 (2H, d, *J* 13.8, N(CH_AH_BPh)$_2$), 3.84 (2H, d, *J* 13.8, N(CH_AH_BPh)$_2$), 7.22-7.25 (2H, m, *p-Ph*), 7.32 (4H, t, *J* 7.4, *m-Ph*), 7.44 (4H, d, *J* 7.4, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 9.9 (*C*(9)), 15.3, 17.5 (*C*(1) and *C*(8)), 25.4 (*C*(4)), 27.0 (*C*(5)), 28.6 (*C*(7)), 29.9 (*C*(6)), 30.7 (*C*(3)), 54.2 (N(*C*H_2Ph)$_2$), 55.8 (*C*(2)), 126.6 (*p-Ph*), 128.1, 128.7 (*o/m-Ph*), 141.3 (*i-Ph*); *m/z* (ESI^+) 320 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{23}H_{30}N^+$ ($[M+H]^+$) requires 320.2378; found 320.2375.

Method B:

$CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **172** (30.5 mg, 0.10 mmol, 1.0 eq) and **162** (27.9 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 30 mins the reaction conversion was >98%.

X-Ray crystal structure data for (1*RS*,2*RS*,8*SR*)-173 (Some H atoms omitted for clarity)



X-ray crystal structure determination for 173

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **173** [$C_{23}H_{29}N$]: M = 319.49, monoclinic, space group *P 1 21/c 1*, a = 12.1237(3) Å, b = 10.8303(2) Å, c = 14.6175(3) Å, β = 95.1731(11)°, V = 1911.51(7) Å^3, Z = 4, μ = 0.063 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.2 mm^3. A total of 4334 unique reflections were measured for $5 < \theta < 27$ and 3204 reflections were used in the refinement. The final parameters were wR_2 = 0.179 and R_1 = 0.079 [I>3.0σ(I)]. X-ray crystal structure determination was performed by Dr

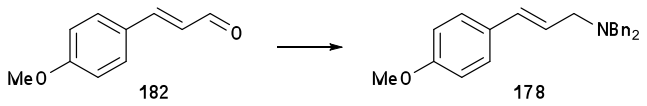
J. E. Thomson and Mr K. B. Ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters ($Å^2$) (e.s.d. in parentheses)

Atom	*x/a*	*y/b*	*z/c*	*U(iso)*
N(1)	0.71469(19)	0.7743(2)	0.59602(14)	0.0385
C(2)	0.6680(2)	0.7526(2)	0.50198(17)	0.0386
C(3)	0.7305(2)	0.6548(2)	0.45467(15)	0.0328
C(4)	0.8448(2)	0.6593(3)	0.45584(18)	0.0441
C(5)	0.9005(3)	0.5710(4)	0.4078(2)	0.0566
C(6)	0.8419(3)	0.4785(3)	0.3588(2)	0.0598
C(7)	0.7296(3)	0.4729(3)	0.3590(2)	0.0548
C(8)	0.6745(2)	0.5603(3)	0.40644(17)	0.0401
C(9)	0.7074(2)	0.6657(2)	0.65620(17)	0.0378
C(10)	0.5866(3)	0.6382(3)	0.6843(2)	0.0647
C(11)	0.5815(3)	0.5264(3)	0.7437(2)	0.0529
C(12)	0.6248(3)	0.4061(3)	0.7056(2)	0.0550
C(13)	0.7355(3)	0.3603(3)	0.7503(2)	0.0610
C(14)	0.8377(3)	0.4369(3)	0.7316(2)	0.0559
C(15)	0.8475(2)	0.5619(3)	0.7774(2)	0.0505
C(16)	0.7855(3)	0.6753(3)	0.7391(2)	0.0531
C(17)	0.9029(3)	0.6682(3)	0.7311(2)	0.0629
C(18)	0.6706(3)	0.8892(3)	0.6324(2)	0.0505
C(19)	0.7212(3)	1.0016(3)	0.59133(19)	0.0467
C(20)	0.6552(3)	1.0961(3)	0.5532(2)	0.0574
C(21)	0.7013(4)	1.1996(3)	0.5162(2)	0.0658
C(22)	0.8142(4)	1.2099(3)	0.5170(2)	0.0681
C(23)	0.8819(3)	1.1160(3)	0.5554(3)	0.0715
C(24)	0.8340(3)	1.0126(3)	0.5917(2)	0.0625
H(21)	0.6760(2)	0.8330(2)	0.46810(17)	0.0491
H(22)	0.5870(2)	0.7298(2)	0.50007(17)	0.0493
H(41)	0.8861(2)	0.7245(3)	0.48901(18)	0.0568
H(51)	0.9782(3)	0.5751(4)	0.4083(2)	0.0719
H(61)	0.8819(3)	0.4175(3)	0.3260(2)	0.0729
H(71)	0.6894(3)	0.4077(3)	0.3255(2)	0.0696
H(81)	0.5951(2)	0.5570(3)	0.40543(17)	0.0497
H(91)	0.7308(2)	0.5913(2)	0.62024(17)	0.0483
H(102)	0.5657(3)	0.7087(3)	0.7187(2)	0.0872
H(101)	0.5311(3)	0.6256(3)	0.6301(2)	0.0871
H(111)	0.6265(3)	0.5442(3)	0.8022(2)	0.0674
H(112)	0.5040(3)	0.5123(3)	0.7570(2)	0.0679
H(122)	0.5701(3)	0.3407(3)	0.7126(2)	0.0675
H(121)	0.6330(3)	0.4182(3)	0.6392(2)	0.0666
H(131)	0.7286(3)	0.3607(3)	0.8165(2)	0.0841

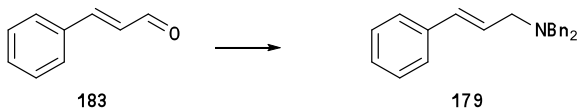
H(132)	0.7455(3)	0.2743(3)	0.7294(2)	0.0842
H(142)	0.9047(3)	0.3871(3)	0.7510(2)	0.0705
H(141)	0.8333(3)	0.4507(3)	0.6639(2)	0.0702
H(151)	0.8634(2)	0.5596(3)	0.8458(2)	0.0650
H(161)	0.7638(3)	0.7378(3)	0.7876(2)	0.0729
H(171)	0.9567(3)	0.7259(3)	0.7703(2)	0.0798
H(172)	0.9294(3)	0.6519(3)	0.6680(2)	0.0792
H(182)	0.6901(3)	0.8905(3)	0.6994(2)	0.0661
H(181)	0.5876(3)	0.8922(3)	0.6207(2)	0.0670
H(201)	0.5738(3)	1.0872(3)	0.5541(2)	0.0734
H(211)	0.6551(4)	1.2647(3)	0.4896(2)	0.0792
H(221)	0.8454(4)	1.2815(3)	0.4913(2)	0.0873
H(231)	0.9609(3)	1.1234(3)	0.5566(3)	0.0897
H(241)	0.8788(3)	0.9458(3)	0.6173(2)	0.0736

(2*E*)-*N*,*N*-Dibenzyl-3-(4'-methoxyphenyl)prop-2-en-1-amine 178



Following **General Procedure 4**, (*E*)-4-methoxycinnamaldehyde **182** (1.62 g, 10.0 mmol, 1.0 eq), dibenzylamine **193** (2.31 mL, 12.0 mmol, 1.2 eq) and $NaBH(OAc)_3$ (3.18g, 15.0 mmol, 1.5 eq) in CH_2Cl_2 (50 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 5% Et_2O/petrol) to give **178** as a pale yellow oil (3.35 g, 98%); ν_{max} (film) 3030, 2930, 2795 (C-H), 1610, 1510 (Ar), 1250, 1035, 965, 700, 665; δ_H (400 MHz, $CDCl_3$) 3.31 (2H, d, *J* 6.6, C(1)H_2), 3.72 (4H, s, N(CH_2Ph)$_2$), 3.86 (3H, s, O*Me*), 6.26 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.57 (1H, d, *J* 15.9, C(3)*H*), 6.94 (2H, d, *J* 8.8, C(3')*H* and C(5')*H*), 7.31-7.34 (2H, m, *p-Ph*), 7.38-7.43 (6H, m, *m-Ph*, C(2')*H* and C(6')*H*), 7.50 (4H, d, *J* 7.1, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 55.3 (O*Me*), 56.0 (*C*(1)), 58.0 (N(*C*H_2Ph)$_2$), 114.0 (*C*(3') and *C*(5')), 125.5 (*C*(2)), 126.9, 127.5, 128.3, 128.9 (*Ar*), 130.1 (*C*(1')), 132.1 (*C*(3)), 139.8 (*i-Ph*), 159.1 (*C*(4')); *m/z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{26}NO^+$ ($[M+H]^+$) requires 344.2009; found 344.2003.

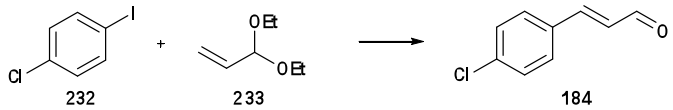
(2*E*)-*N*,*N*-Dibenzyl-3-phenylprop-2-en-1-amine 179[7]



Following **General Procedure 4**, (*E*)-cinnamaldehyde **183** (1.32 mL, 10.0 mmol, 1.0 eq), dibenzylamine **193** (2.31 mL, 12.0 mmol, 1.2 eq) and $NaBH(OAc)_3$ (3.18g, 15.0 mmol, 1.5 eq) in CH_2Cl_2 (50 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 5% Et_2O/petrol) to give **179** as a pale yellow oil (2.42 g, 77%); δ_H (400 MHz, $CDCl_3$) 3.24 (2H, d, *J* 6.5, C(1)H_2), 3.65 (4H,

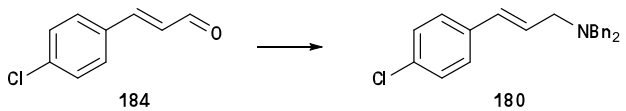
s, N(CH_2Ph)$_2$), 6.32 (1H, dt, *J* 15.7, 6.5, C(2)*H*), 6.55 (1H, d, *J* 15.7, C(3)*H*), 7.21-7.42 (15H, m, *Ph*); *m/z* (CI^+) 314 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{23}H_{24}N^+$ ($[M+H]^+$) requires 314.1920; found 314.1909.

(*E*)-4'-Chlorocinnamaldehyde 184[8]



To a stirred solution of 1-chloro-4-iodobenzene **232** (2.38 g, 10.0 mmol, 1.0 eq) in DMF (40 mL) was added acrolein diethyl acetal **233** (4.57 mL, 30.0 mmol, 3.0 eq), *n*Bu_4NCl (2.78 g, 10.0 mmol, 1.0 eq), K_2CO_3 (2.07 g, 15.0 mmol, 1.5 eq), KOAc (1.96 g, 20.0 mmol, 2.0 eq) and $Pd(OAc)_2$ (67 mg, 0.3 mmol, 0.03 eq). The mixture was stirred at 90 °C for 1.5 hrs then allowed to cool to RT. 2 M aq. HCl (20 mL) was slowly added and the reaction mixture was stirred at RT for a further 15 mins. The mixture was diluted with Et_2O (200 mL) and washed with water (2 × 100mL) and brine (1 × 100 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, petrol → 20% Et_2O/petrol) to give **184** as a white solid (1.11 g, 67%); m.p. 56-58 °C (lit. m.p.[8] 59-60 °C); δ_H (400 MHz, $CDCl_3$) 6.69 (1H, dd, *J* 15.5, 7.6, C(2)*H*), 7.39-7.51 (5H, m, C(3)*H*, C(2')*H*, C(3')*H*, C(5')*H* and C(6')*H*), 9.69 (1H, d, *J* 7.6, C*H*O).

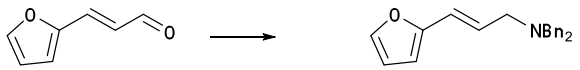
(2*E*)-*N*,*N*-Dibenzyl-3-(4'-chloroxyphenyl)prop-2-en-1-amine 180



Following **General Procedure 4**, (*E*)-4'-chlorocinnamaldehyde **184** (833 mg, 5.0 mmol, 1.0 eq), dibenzylamine **193** (1.15 mL, 6.0 mmol, 1.2 eq) and $NaBH(OAc)_3$

(1.60 g, 7.5 mmol, 1.5 eq) in CH_2Cl_2 (25 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 2% Et_2O/petrol) to give **180** as a pale yellow oil (1.63 g, 97%); ν_{max} (film) 3025, 2795 (C-H), 1490, 1455, 1365 (Ar), 1090, 700, 845, 735, 700; δ_H (400 MHz, $CDCl_3$) 3.28 (2H, d, *J* 6.4, C(1)H_2), 3.69 (4H, s, N(CH_2Ph)$_2$), 6.32 (1H, dt, *J* 15.9, 6.4, C(2)*H*), 6.54 (1H, d, *J* 15.9, C(3)*H*), 7.28-7.32 (6H, m, *Ar*), 7.39 (4H, t, *J* 7.4, *m-Ph*), 7.46 (4H, d, *J* 7.4, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 55.8 (*C*(1)), 58.1 (N(*C*H_2Ph)$_2$), 127.0, 127.5, 128.3, 128.7, 128.8 (*Ar*), 131.2 (*C*(3)), 132.9 (*C*(4')), 135.7 (*C*(1')), 139.5 (*i-Ph*); *m/z* (ESI^+) 348 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{23}NCl^+$ ($[M+H]^+$) requires 348.1514; found 348.1506.

(2*E*)-*N*,*N*-Dibenzyl-3-(2'-furyl)prop-2-en-1-amine 181

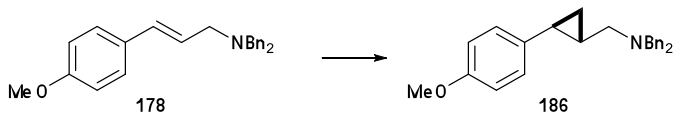


185 181

Following **General Procedure 4**, (*E*)-3-(2'-furyl)acrolein **185** (1.22 g, 10.0 mmol, 1.0 eq), dibenzylamine **193** (2.31 mL, 12.0 mmol, 1.2 eq) and $NaBH(OAc)_3$ (3.18 g, 15.0 mmol, 1.5 eq) in CH_2Cl_2 (50 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) gave **181** as a pale yellow oil (2.16g, 71%); ν_{max} (film) 3060, 3025, 2920, 2795 (C-H), 1495, 1455, 1365 (Ar), 1120, 1010, 960, 735, 700; δ_H (400 MHz, $CDCl_3$) 3.28 (2H, d, *J* 6.3, C(1)H_2), 3.70 (4H, s, N(CH_2Ph)$_2$), 6.26 (1H, d, *J* 3.3, C(3')*H*), 6.31-6.38 (1H, m, C(2)*H*), 6.43 (1H, dd, *J* 3.3, 1.8, C(4')*H*), 6.46 (1H, d, *J* 15.9, C(3)*H*), 7.29-7.33 (2H, m, *p-Ph*), 7.37-7.42 (5H, m, *m*-Ph and C(5')*H*), 7.44-7.50 (4H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 128.3, 128.8 (*o/m-Ph*), 55.3 (*C*(1)), 57.9 (N(*C*H_2Ph)$_2$), 107.1 (*C*(3')), 111.3 (*C*(4')), 120.9 (*C*(2)), 126.5 (*C*(3)), 126.9 (p-*Ph*), 139.6 (i-*Ph*), 141.7 (*C*(5')), 152.9 (*C*(2'));

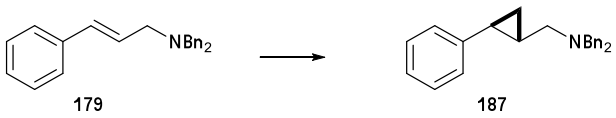
m/z (ESI^+) 304 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{21}H_{22}NO^+$ ($[M+H]^+$) requires 304.1701; found 304.1701.

(1'*E*)-*N*,*N*-Dibenzyl-1-[2'-(4''-methoxyphenyl)cyclopropyl]methanamine 186



Following **General Procedure 3**, **178** (343 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give **186** as a pale yellow oil (311 mg, 87%); ν_{max} (film) 3060, 3025, 2930, 2840, 2795 (C-H), 1515, 1455, 1245 (Ar), 1035, 825, 745, 600; δ_H (400MHz, $CDCl_3$) 0.84-0.89 (1H, m, cyclopropane CH_AH$_B$), 1.02-1.07 (1H, m, cyclopropane CH$_A$$H_B$), 1.39-1.42 (1H, m, C(1′)*H*), 1.75-1.78 (1H, m, C(2′)*H*), 2.62-2.67 (1H, m, C(1)H_AH$_B$), 2.73-2.77 (1H, m, C(1)H$_A$$H_B$), 3.87 (4H, m, N(C$H_2$Ph)$_2$), 3.92 (3H, s, O*Me*), 7.00 (2H, dd, *J* 8.6, 1.8, C(3′′)*H* and C(5′′)*H*), 7.18 (2H, dd, *J* 8,6, 1.8, C(2′′)*H* and C(6′′)*H*), 7.39-7.43 (2H, m, *p-Ph*), 7.48-7.51 (4H, m, *m-Ph*), 7.57-7.61 (4H, m, *o-Ph*); δ_C (100MHz, $CDCl_3$) 14.7 (cyclopropane *C*H$_2$), 20.5 (*C*(1′)), 22.2 (*C*(2′)), 55.4 (O*Me*), 57.8 (*C*(1)), 58.3 (N(*C*H$_2$Ph)$_2$), 114.0 (*C*(3′′) and *C*(5′′)), 127.0 (*p-Ph*, *C*(2′′) and *C*(6′′)), 128.4, 128.9 (*o/m-Ph*), 135.3 (*C*(1′′)), 140.2 (*i-Ph*), 157.8 (*C*(4′′)); *m/z* (ESI^+) 358 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}NO^+$ ($[M+H]^+$) requires 358.2165; found 358.2160.

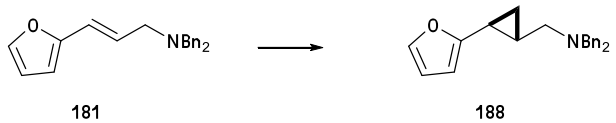
(1'*E*)-*N*,*N*-Dibenzyl-1-(2'-phenylcyclpropyl)methanamine 187



179 187

Following **General Procedure 3**, **179** (313 mg, 1.00 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.00 mL, 2.00 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 2% Et_2O/petrol) to give **187** as a pale yellow oil (265 mg, 81%); ν_{max} (film) 3060, 3025, 2925, 2795 (C-H), 1605, 1495, 1450, 1365 (Ar), 1030, 745, 700; δ_H (400 MHz, $CDCl_3$) 0.80 (1H, app dt, *J* 8.6, 5.2, cyclopropane C*H*$_A$H$_B$), 0.98 (1H, app dt, *J* 8.6, 5.0, cyclopropane CH$_A$*H*$_B$), 1.32-1.37 (1H, m, C(1′)*H*), 1.67 (1H, app dt, *J* 8.9, 4.6, C(2′)*H*), 2.57 (2H, app qd, *J* 12.7, 6.4, C(1)*H*$_2$), 3.73 (4H, s, N(C*H*$_2$Ph)$_2$), 7.10 (2H, dd, *J* 8.0, 1.0, *Ph*), 7.18-7.22 (1H, m, *Ph*), 7.26-7.48 (12H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (cyclopropane *C*H$_2$), 20.9 (*C*(1′)), 22.7 (*C*(2′)), 57.6 (*C*(1)), 58.2 (N(*C*H$_2$Ph)$_2$), 125.8, 126.1, 127.2, 128.6, 128.7, 129.1 (*Ph*), 140.4, 143.6 (*i-Ph*); *m/z* (CI^+) 328 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{24}H_{26}N^+$ ($[M+H]^+$) requires 328.2065; found 328.2071.

(1'*E*)-*N*,*N*-Dibenzyl-1-[2'-(2''-furyl)cyclopropyl]methanamine 188

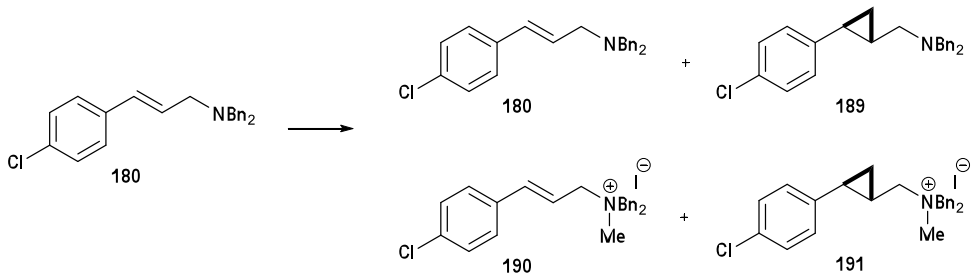


181 188

Following **General Procedure 3**, **181** (303 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (2.0 mL, 1.0M in hexanes, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 5% Et_2O/petrol) to

give **188** as a colourless oil (225 mg, 71%); ν_{max} (film) 3025, 2930, 2795 (C-H), 1600, 1495, 1450, 1370 (Ar), 1145, 1075, 1030, 1010, 730, 700; δ_H (400 MHz, $CDCl_3$) 0.66-0.72 (1H, m, cyclopropane CH_2), 1.01-1.07 (1H, m, cyclopropane CH_2), 1.38-1.44 (1H, m, C(2)*H*), 1.62-1.72 (1H, m, C(3)*H*), 2.43-2.49 (1H, m, C(1)H_AH_B), 2.54-2.59 (1H, m, C(1)H_AH_B), 3.73 (1H, m, N(CH_2Ph)$_2$), 5.97-5.99 (1H, m, C(3')*H*), 6.29-6.31 (3H, m, C(2')*H*), 7.25-7.29 (4H, m, *p*-Ph and C(5')*H*), 7.33-7.39 (4H, m, *m-Ph*), 7.43-7.49 (4H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (cyclopropane *C*H$_2$), 15.9 (*C*(3)), 18.2 (*C*(2)), 56.9 (*C*(1)), 58.1 (N(*C*H$_2$Ph)$_2$), 103.4 (*C*(3')), 110.3 (*C*(4')), 126.8 (*p-Ph*), 128.2, 128.8 (*o/m-Ph*), 139.9 (*i-Ph*), 140.5 (*C*(5')), 156.6 (*C*(2')); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{24}NO^+$ ([M+H]$^+$) requires 318.1852; found 318.1849.

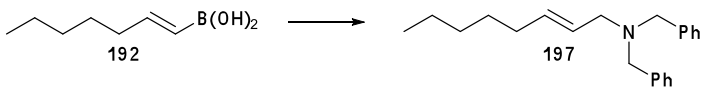
(2*E*)-*N*,*N*-Dibenzyl-3-(4'-chlorophenyl)prop-2-en-1-amine 180, (1'*E*)-*N*,*N*-dibenzyl-1-[2'-(4''-chlorophenyl)cyclopropyl]methanamine 189, (2*E*)-*N*,*N*-dibenzyl-3-(4'-chlorophenyl)-*N*-methylprop-2-en-1-aminium iodide 190 and (1'*E*)-*N*,*N*-dibenzyl-1-[2'-(4''-chlorophenyl)cyclopropyl]methanaminium iodide 191



Following **General Procedure 3**, **180** (174 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1 mL) for 16 hrs gave the crude product. 400 MHz ^{1}H NMR spectroscopic analysis indicated that a 8:38:34:20 mixture of **180**:**189**:**190**:**191** had

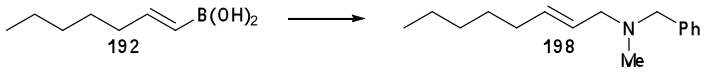
been formed. Purification by flash column chromatography (silica, 2% EtOAc/petrol) gave an inseparable 17:83 mixture of **180**:**189** as a colourless oil (76 mg, 42% combined yield based on a 17:83 molar ratio); further elution of the column with 10% CH_2Cl_2/MeOH eluted an inseparable 57:43 mixture of **190**:**191** as a yellow oil (115 mg, 46% combined yield based on a 57: 43 molar ratio); Data for **189**; ν_{max} (film) 3060, 3025, 2925, 2795 (C-H), 1600, 1495, 1455, 1365 (Ar), 1090, 1030, 1015, 820, 745, 700; δ_H (400 MHz, $CDCl_3$) 0.79 (1H, dd, *J* 8.7, 5.4, cyclopropane CH_AH$_B$), 0.90-0.96 (1H, m, cyclopropane CH$_A$$H_B$), 1.24-1.32 (1H, m, C(1')*H*), 1.61 (1H, dd, *J* 8.8, 4.7, C(2')*H*), 2.47-2.52 (1H, m, C(1)H_AH$_B$), 2.58-2.62 (1H, m, C(1)H_AH$_B$), 3.70 (4H, s, N(CH_2Ph)$_2$), 6.99 (2H, d, *J* 8.3, C(2")*H* and C(6")*H*), 7.23-7.46 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.3 (cyclopropane *C*H$_2$), 21.2 (*C*(1')), 22.2 (*C*(2')), 57.5 (*C*(1)), 58.2 (N(*C*H$_2$Ph)$_2$), 127.0, 128.3, 128.4, 128.7, 128.8 (*Ar*), 131.0 (*C*(4")), 139.9 (i-*Ph*), 141.8 (*C*(1")); *m/z* (ESI$^+$) 362 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{25}ClN$ (M+H$^+$) requires 362.1670, found 362.1669; Selected data for **190**: ν_{max} (film) 3450, 2955 (C-H), 1495, 1455 (Ar), 1215, 1090, 1010,975, 755, 720, 700; δ_H (400 MHz, $CDCl_3$) 3.02 (3H, s, N*Me*), 4.39 (2H, d, *J* 7.3, C(1)H_2), 4.83 (2H, d, *J* 12.6, N(CH_AH$_B$Ph)$_2$), 5.15 (2H, d, *J* 12.6, N(CH$_A$$H_B$Ph)$_2$), 6.46 (1H, dd, *J* 15.2, 7.4, C(2)*H*), 7.01-7.04 (1H, m, C(3)*H*); *m/z* (ESI$^+$) 362 ([M$^+$], 100%); HRMS (ESI$^+$) $C_{24}H_{25}ClN$ (M$^+$) requires 362.1670, found 362.1657; Selected data for **191**: δ_H (400 MHz, $CDCl_3$) 1.30 (1H, dt, *J* 8.2, 5.4, cyclopropane CH_AH$_B$), 1.38 (1H, dt, *J* 9.1, 5.4, cyclopropane CH$_A$CH_B), 1.5-1.60 (1H, m, C(1')*H*), 2.16-2.20 (1H, m, C(2')*H*), 3.06 (3H, s, N*Me*), 3.72-3.82 (2H, m, C(1)H_2), 4.75 (1H, d, *J* 12.6, NCH_ACH$_B$Ph), 4.84 (1H, obscured d, NCH_CCH$_D$Ph), 5.18 (1H, d, *J* 12.6, NCH$_A$CH_BPh), 5.31 (1H, d, *J* 13.6, NCH$_C$CH_DPh); *m/z* (ESI$^+$) 376 ([M$^+$], 100%); HRMS (ESI$^+$) $C_{25}H_{27}ClN$ (M$^+$) requires 376.1827, found 376.1814.

(2*E*)-*N*,*N*-Dibenzyloct-2-en-1-amine 197



Following **General Procedure 5**, (*E*)-hept-1-enylboronic acid **192** (280 mg, 2.0 mmol, 1.0 eq), paraformaldehyde (60 mg, 2.0 mmol, 1.0 eq) and dibenzylamine **193** (0.38 mL, 2.0 mmol, 1.0 eq) in toluene (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 3% EtOAc/petrol) to give **197** as a colourless oil (450 mg, 73%); ν_{max} (film) 3060, 3030, 2925, 2855, 2790 (C-H), 1495, 1455 (Ar), 970, 745, 670; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 6.8, C(8)H_3), 1.30-1.44 (4H, m, C(6)H_2 and C(7)H_2), 2.07 (2H, q, *J* 6.6, C(4)H_2), 3.05 (2H, d, *J* 6.3, C(1)H_2), 3.61 (4H, s, N(CH_2Ph)$_2$), 5.52-5.67 (2H, m, C(2)*H* and C(3)*H*), 7.24-7.29 (2H, m, *p-Ph*), 7.33-7.37 (4H, m, *m-Ph*), 7.41-7.44 (4H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 22.6 (*C*(6) or *C*(7)), 29.1 (*C*(5)), 31.4 (*C*(6) or *C*(7)), 32.5 (*C*(4)), 55.6 (*C*(1)), 57.6 (N(*C*H$_2$Ph)$_2$), 126.7 (*p-Ph*), 127.1 (*C*(3)), 128.2, 128.9 (*o/m-Ph*), 134.3 (*C*(2)), 139.9 (*i-Ph*); *m/z* (ESI$^+$) 308 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{22}H_{30}N^+$ ([M+H]$^+$) requires 308.2378; found 308.2373.

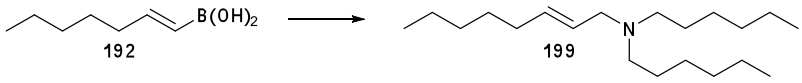
(2*E*)-*N*-Benzyl-*N*-methyloct-2-en-1-amine 198



Following **General Procedure 5**, (*E*)-hept-1-enylboronic acid **192** (280 mg, 2.0 mmol, 1.0 eq), paraformaldehyde (60 mg, 2.0 mmol, 1.0 eq) and *N*-methyl-*N*-benzylamine **194** (0.26 mL, 2.0 mmol, 1.0 eq) in toluene (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **198** as a colourless oil (350 mg, 76%); ν_{max} (film) 3000, 2950,

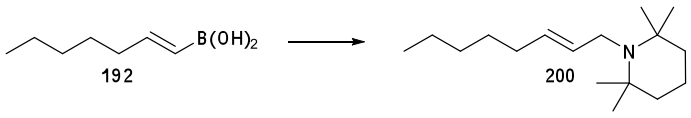
2925, 2855, 2780 (C-H), 1495, 1455, 1365 (Ar), 1020, 970, 735, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, C(8)H_3), 1.27-1.44 (6H, m, C(5)H_2, C(6)H_2 and C(7)H_2), 2.06 (2H, q, *J* 6.6, C(4)H_2), 2.20 (3H, s, N*Me*), 2.99 (2H, d, *J* 6.8, C(1)H_2), 3.50 (2H, s, NCH_2Ph), 5.51-5.66 (2H, m, C(2)*H* and C(3)*H*), 7.24-7.29 (1H, m, *p-Ph*), 7.31-7.34 (4H, m, *o/m-Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 22.5 (*C*(6) or *C*(7)), 29.0 (*C*(5)), 31.4 (*C*(6) or *C*(7)), 32.4 (*C*(4)), 42.0 (N*Me*), 59.8 (*C*(1)), 61.6 (N*C*H_2Ph), 126.9 (p-*Ph*), 127.0 (*C*(3)), 128.2, 129.1 (*o/m-Ph*), 134.4 (*C*(2)), 139.2 (*i-Ph*); *m/z* (CI^+) 232 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{16}H_{26}N^+$ ($[M+H]^+$) requires 232.2065; found 232.2074.

(2*E*)-*N*,*N*-Dihexyloct-2-en-1-amine 199



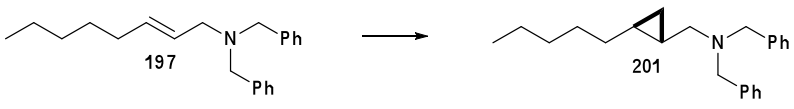
Following **General Procedure 5**, (*E*)-hept-1-enylboronic acid **192** (280 mg, 2.0 mmol, 1.0 eq), paraformaldehyde (60 mg, 2.0 mmol, 1.0 eq) and dihexylamine **195** (0.47 mL, 2.0 mmol, 1.0 eq) in toluene (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 1% EtOAc/petrol) to give **199** as a colourless oil (310 mg, 52%); ν_{max} (film) 2950, 2925, 2860 (C-H), 1465, 1380, 1100, 970, 725, 665; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, t, *J* 7.0, C(8)H_3 and 2 × C(6')H_3), 1.24-1.46 (22H, m, 11 × CH_2), 2.02 (2H, q, *J* 6.5, C(4)H_2), 2.37-2.40 (4H, m, 2 × C(1')H_2), 3.02 (2H, d, *J* 6.6, C(1)H_2), 5.42-5.58 (2H, m, C(2)*H* and C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (3 x *C*H_3), 22.7, 26.8, 27.4, 29.0, 31.4, 31.9, 32.4 (11 x *C*H_2), 53.7 (*C*(1')), 56.3 (*C*(1)), 127.1 (*C*(3)), 133.7 (*C*(2)); *m/z* (CI^+) 296 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{20}H_{42}N^+$ ($[M+H]^+$) requires 296.3317; found 296.3321.

2',2',6',6'-Tetramethyl-1'-[(2*E*)-oct-2-en-1-yl]piperidine 200



Following **General Procedure 5**, (*E*)-hept-1-enylboronic acid **192** (280 mg, 2.0 mmol, 1.0 eq), paraformaldehyde (60 mg, 2.0 mmol, 1.0 eq) and 2,2,6,6-tetramethylpiperidine **196** (0.34 mL, 2.0 mmol, 1.0 eq) in toluene (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **200** as a colourless oil (64 mg, 21%); ν_{max} (film) 2960, 2925, 2870 (C-H), 1465, 1380, 1260, 1130, 965, 665; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(8)H_3), 1.02 (12H, s, 4 × *Me*), 1.23-1.38 (6H, m, C(5)H_2, C(6)H_2 and C(7)H_2), 1.41-1.44 (4H, m, 2 × CMe_2CH_2), 1.51-1.57 (2H, m, $CMe_2CH_2CH_2$), 1.94-1.99 (2H, m, C(4)H_2), 3.06 (2H, br s, C(1)H_2), 5.41-5.44 (2H, m, C(2)*H* and C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(8)), 17.8 ($CMe_2CH_2CH_2$), 22.6 (*C*(5), *C*(6) or *C*(7)), 27.5 (4 × *Me*), 29.3, 31.4 (*C*(5), *C*(6) or *C*(7)), 32.4 (*C*(4)), 41.2 (2 × CMe_2CH_2), 46.1 (*C*(1)), 54.7 (CMe_2), 128.8 (*C*(3)), 134.6 (*C*(2)); *m/z* (CI^+) 252 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{17}H_{34}N^+$ ($[M+H]^+$) requires 252.2691; found 252.2684.

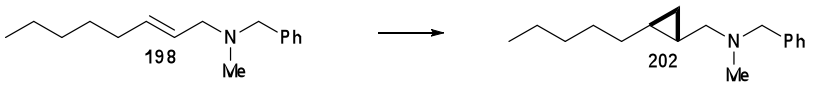
(1'*E*)-*N*,*N*-Dibenzyl-1-(2'-pentylcyclopropyl)methanamine 201



Following **General Procedure 3**, **197** (100 mg, 0.325 mmol, 1.0 eq), $ZnEt_2$ (0.65 mL, 1.0M in hexanes, 0.65 mmol, 2.0 eq), CH_2I_2 (105 μL, 1.30 mmol, 4.0 eq) and TFA (48 μL, 0.65 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 3% EtOAc/petrol) to give **201** as a colourless oil (82 mg, 79%); ν_{max} (film) 3060, 3025, 3000, 2950, 2925,

2850, 2790 (C-H), 1495, 1450, 1365 (Ar), 1030, 970, 745, 680; δ_H (400 MHz, $CDCl_3$) 0.21-0.31 (2H, m, cyclopropane CH_2), 0.45-0.52 (1H, m, C(2')*H*), 0.71-0.78 (1H, m, C(1')*H*), 0.95 (3H, t, *J* 6.8, C(7')H_3), 1.18-1.48 (8H, m, C(3')H_2, C(4')H_2, C(5')H_2, C(6')H_2), 2.31 (1H, dd, *J* 13.1, 7.1, C(1)H_AH$_B$), 2.47 (1H, dd, *J* 13.1, 5.8, C(1)H$_A$$H_B$), 3.70 (4H, AB_q, J_{AB} 13.6, N(CH_2Ph)$_2$), 7.26-7.30 (2H, m, *p-Ph*), 7.34-7.38 (4H, m, *m-Ph*), 7.42-7.48 (4H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 11.1 (cyclopropane *C*H$_2$), 14.2 (*C*(7')), 16.1 (*C*(1')), 18.5 (*C*(2')), 22.8, 29.3, 31.8, 34.1 (*C*(3'), *C*(4'), *C*(5') and *C*(6')), 58.1 (N(*C*H$_2$Ph)$_2$), 126.7 (*p-Ph*), 128.2, 128.8 (*o/m-Ph*), 140.1 (*i-Ph*); *m/z* (ESI^+) 322 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{23}H_{32}N^+$ ($[M+H]^+$) requires 322.2535; found 322.2529.

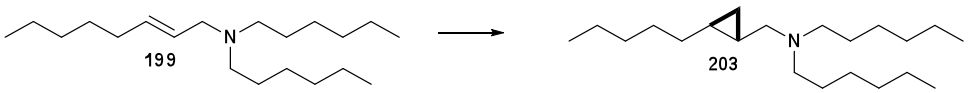
(1'*E*)-*N*-Benzyl-*N*-methyl-1-(2'-pentylcyclopropyl)methanamine 202



Following **General Procedure 3**, **198** (75 mg, 0.325 mmol, 1.0 eq), $ZnEt_2$ (0.65 mL, 1.0M in hexanes, 0.65 mmol, 2.0 eq), CH_2I_2 (105 µL, 1.30 mmol, 4.0 eq) and TFA (48 µL, 0.65 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **202** as a colourless oil (34 mg, 43%); ν_{max} (film) 3060, 2950, 2925, 2850, 2780 (C-H), 1450, 1365 (Ar), 1025, 735, 680; δ_H (400 MHz, $CDCl_3$) 0.23-0.31 (2H, m, cyclopropane CH_2), 0.46-0.54 (1H, m, C(2')*H*), 0.64-0.71 (1H, m, C(1')*H*), 0.89 (3H, t, *J* 7.1, C(7')H_3), 1.12-1.21 (1H, m, C(3')H_AH$_B$), 1.26-1.43 (7H, m, C(3')H$_A$$H_B$, C(4')$H_2$, C(5')$H_2$ and C(6')H_2), 2.22-2.27 (1H, m, C(1)H_AH$_B$) overlapping 2.27 (3H, s, N*Me*), 2.32-2.37 (1H, m, C(1)H$_A$$H_B$), 3.55 (2H, AB_q, J_{AB} 13.1, NCH_2Ph), 7.23-7.29 (1H, m, *p-Ph*), 7.30-7.35 (4H, m, *o/m-Ph*); δ_C (100 MHz, $CDCl_3$) 11.1 (cyclopropane *C*H$_2$), 14.1 (*C*(7')), 16.6 (*C*(1')), 18.3 (*C*(2')), 22.7, 29.2, 31.8 (*C*(4'), *C*(5') and *C*(6')),

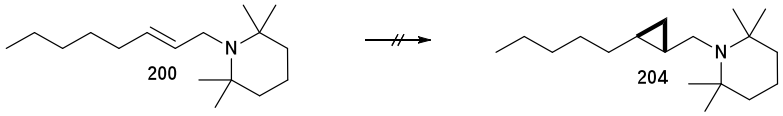
33.9 (*C*(3')), 42.3 (*Me*), 62.1 (*C*(1)), 62.1 (N*C*H_2Ph), 126.8 (*p-Ph*), 128.2, 129.1 (*o/m-Ph*), 139.2 (*i-Ph*); *m/z* (CI^+) 246 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{17}H_{28}N^+$ ($[M+H]^+$) requires 246.2222; found 246.2219.

(1'*E*)-*N*,*N*-Dihexyl-1-(2-pentylcyclopropyl)methanamine 203



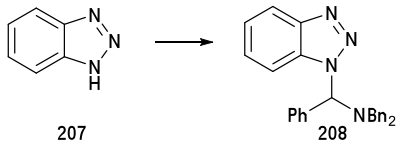
Following **General Procedure 3**, **199** (96 mg, 0.325 mmol, 1.0 eq), $ZnEt_2$ (0.65 mL, 1.0M in hexanes, 0.65 mmol, 2.0 eq), CH_2I_2 (105 µL, 1.30 mmol, 4.0 eq) and TFA (48 µL, 0.65 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **203** as a colourless oil (27 mg, 27%); ν_{max} (film) 2950, 2925, 2855 (C-H), 1465, 1380, 1090, 725, 665; δ_H (400 MHz, $CDCl_3$) 0.21-0.27 (2H, m, cyclopropane CH_2), 0.44-0.52 (1H, m, C(2')*H*), 0.55-0.62 (1H, m, C(1')*H*), 0.89 (9H, t, *J* 6.6, C(7')H_3 and 2 × C(6")H_3), 1.11-1.47 (24H, m, 12 × CH_2), 2.28-2.35 (1H, m, C(1)H_AH_B), 2.40-2.57 (5H, m, C(1)H_AH_B and 2 × C(1")H_2); δ_C (100 MHz, $CDCl_3$) 10.9 (cyclopropane *C*H_2), 14.1 (*C*(7') and 2 × *C*(6")), 15.9 (*C*(1')), 18.3 (*C*(2')), 22.7, 26.5, 27.4, 29.2, 31.8, 31.8, 34.0 (12 × *C*H_2), 53.7 (2 × *C*(1")), 58.1 (*C*(1)); *m/z* (ESI^+) 310 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{21}H_{44}N^+$ ($[M+H]^+$) requires 310.3474; found 310.3472

Attempted preparation of (1'*E*)-2,2,6,6-tetramethyl-1'-[(2'-pentylcyclopropyl)methyl]piperidine 204



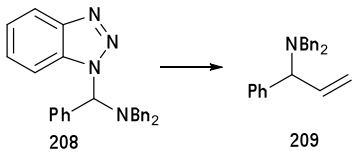
Following **General Procedure 3**, **200** (82 mg, 0.325 mmol, 1.0 eq), $ZnEt_2$ (0.65 mL, 1.0M in hexanes, 0.65 mmol, 2.0 eq), CH_2I_2 (105 μL, 1.30 mmol, 4.0 eq) and TFA (48 μL, 0.65 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave the crude product. 400 MHz ^{1}H NMR spectroscopic analysis of the crude product indicated that the reaction conversion was negligible (<10%). Purification of the crude reaction mixture by flash column chromatography (silica, petrol → 5% EtOAc/petrol) gave returned starting material **200** as a colourless oil (72 mg, 88%) with identical spectroscopic properties to above.

(*RS*)-1-[α-(Dibenzylamino)benzyl]benzotriazole 208



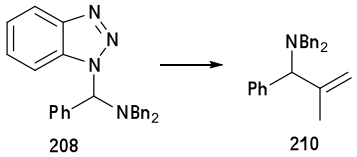
Benzaldehyde (10.1 mL, 100 mmol, 1.0 eq), dibenzylamine **193** (19.2 mL, 100 mmol, 1.0 eq) and benzotriazole **207** (11.9 g, 100 mmol, 1.0 eq) were stirred in MeOH:Et_2O (1:1, v/v, 100 mL) for 30 mins. The resultant homogeneous solution was stored at 0 °C overnight resulting in the precipitation of a white solid. Filtration (wash with cold Et_2O) gave pure **208** as a white crystalline solid (35.3 g, 87%) as a ~3:1 mixture of Bnt-1 and Bnt-2 isomers; data for major isomer **208**; m.p. 144-146 °C {lit.[9] m.p. 153 °C}; δ_H (400MHz, $CDCl_3$) 3.51 (2H, d, *J* 14.2, N(C*H*$_A$H$_B$Ph)$_2$), 4.26 (2H, d, *J* 14.2, N(CH$_A$*H*$_B$Ph)$_2$), 6.85 (1H, s, PhC*H*), 7.25-7.45 (18H, m, *Ar*), 8.19 (1H, d, *J* 8.2, *Ar*).

(*RS*)-*N*,*N*-Dibenzyl-1-phenyl-prop-2-en-1-amine 209



Following **General Procedure 6**, **208** (2.02 g, 5.0 mmol, 1.0 eq) and vinylmagnesium chloride (1.6 M in THF, 4.69 mL, 7.5 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **209** as a yellow oil (1.45 g, 92%); ν_{max} (film) 3027 (C-H), 1493, 1453 (Ar); δ_H (400MHz, $CDCl_3$) 3.56 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.70 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 4.30 (1H, d, *J* 8.6, C(1)*H*), 5.24 (1H, dd, *J* 17.2, 1.0, C(3)$H_A$$H_B$), 5.48 (1H, dd, *J* 10.1, 1.0, C(3)$H_A$$H_B$), 6.09-6.18 (1H, m, C(2)*H*), 7.23-7.29 (3H, m, *p*-*Ph*, *p*-*Ph*(Bn)), 7.32-7.39 (6H, m, *m*-*Ph*, *m*-*Ph*(Bn)), 7.44 (4H, d, *J* 7.3, *o*-*Ph*(Bn)), 7.53 (2H, d, *J* 7.6, *o*-*Ph*); δ_C (100MHz, $CDCl_3$) 53.7 (N(*C*H_2Ph)$_2$), 65.2 (*C*(1)), 119.4 (*C*(3)), 126.8 (*p*-*Ph*(Bn)), 127.0 (*p*-*Ph*), 128.1 (*o*-*Ph*), 128.2 (*m*-*Ph*), 128.3 (*o*-*Ph*(Bn)), 128.7 (*m*-*Ph*(Bn)), 135.3 (*C*(2)), 140.0 (*i*-*Ph*(Bn)), 141.4 (*i*-*Ph*); *m/z* (ESI^+) 314 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{24}N^+$ ($[M+H]^+$) requires 314.1903, found 314.1899.

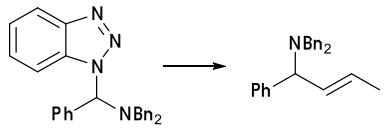
(*RS*)-*N*,*N*-Dibenzyl-2-methyl-1-phenylprop-2-en-1-amine 210



Following **General Procedure 6**, **208** (809 mg, 2.0 mmol, 1.0 eq) and *iso*-propenylmagnesium bromide (0.5 M in THF, 6.0 mL, 3.0 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography

(silica, 1% Et_2O/petrol) to give pure **210** as a yellow oil (655 mg, quant.); ν_{max} (film) 3027 (C-H), 1493 (Ar), 1453 (Ar); δ_H (400MHz, $CDCl_3$) 1.79 (3H, s, C(2)*Me*), 3.50 (2H, d, *J* 14.4, N(CH_AH_BPh)$_2$), 3.81 (2H, d, *J* 14.4, N(CH$_A$$H_B$Ph)$_2$), 4.30 (1H, s, C(1)*H*), 5.02 (1H, app br s, C(3)H_AH_B), 5.16 (1H, app br s, C(3)H$_A$$H_B$), 7.25-7.28 (2H, m, *Ar*), 7.33-7.41 (13H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 20.2 (C(2)*Me*), 53.4 (N(*C*H$_2$Ph)$_2$), 70.1 (*C*(1)), 114.3 (*C*(3)), 126.8 (*p-Ph*(Bn)), 127.0 (*p-Ph*), 128.0 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.8 (*m-Ph*(Bn)), 129.4 (*m-Ph*), 138.9 (*i-Ph*), 139.3 (*i-Ph*(Bn)), 145.6 (*C*(2)); *m/z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N^+$ ([M+H]$^+$) requires 328.2060, found 328.2061.

(1*RS*,2*E*)-*N*,*N*-Dibenzyl-1-phenylbut-2-ene-1-amine 211



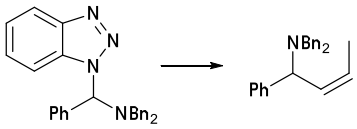
208 211

To a stirred solution of (*E*)-1-bromoprop-1-ene (0.64 mL, 7.5 mmol, 1.5 eq) in Et_2O (30 mL) at −78 °C was added *t*BuLi (1.7 M in pentane, 8.82 mL, 15.0 mmol, 3.0 eq) and the mixture stirred for 1 hr at −78 °C. Solid $MgBr_2{\cdot}OEt_2$ (1.55 g, 6.0 mmol, 1.2 eq) was the added and the mixture allowed to warm to 0 °C over 30 mins.

This mixture was then added to a solution of **208** (2.02 g, 5.0 mmol, 1.0 eq) in toluene (30 mL) at 0 °C *via* cannula. The resulting mixture was stirred at 0 °C for 2 hrs then quenched with sat. aq. NH_4Cl (20 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with 1 M aq. NaOH (30 mL) and brine (30 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give **211** as a white solid (621 mg, 38%);

m.p. 60-61 °C; ν_{max} (KBr) 3025 (C-H), 1495, 1450 (Ar), 1030, 975, 745, 700, 665; δ_H (400 MHz, $CDCl_3$) 1.97 (3H, d, *J* 7.1, C(3)*Me*), 3.65 (2H, d, *J* 13.7, N(CH_ACH_BPh)$_2$), 3.81 (2H, d, *J* 13.7, N(CH_ACH_BPh)$_2$), 4.37 (1H, d, *J* 8.6, C(1)*H*), 5.70-5.79 (1H, m, C(3)*H*), 5.84-5.90 (1H, m, C(2)*H*), 7.34 (3H, app q, *J* 7.0, 3 × *p-Ph*), 7.42-7.47 (6H, m, 6 × *m-Ph*), 7.55 (4H, d, *J* 7.1, 4 × *o-Ph*), 7.66 (2H, d, *J* 7.8, 2 × *o-Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(3)*Me*), 53.9 (N(*C*H_2Ph)$_2$), 64.7 (*C*(1)), 126.8, 126.9 (3 × *p-Ph*), 128.2, 128.2, 128.3, 128.8 (*Ar*), 129.0 (*C*(2)), 130.5 (*C*(3)), 140.4, 142.6 (3 × *i-Ph*); *m/z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N$ (M+H$^+$) requires 328.2060, found 328.2056.

(1*RS*,2*Z*)-*N*,*N*-Dibenzyl-1-phenylbut-2-ene-1-amine 212

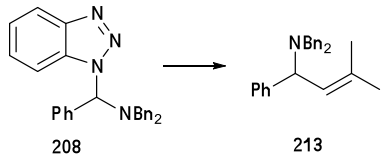


208 212

Following **General Procedure 7**, **208** (2.02 g, 5.0 mmol, 1.0 eq), (*Z*)-1-bromoprop-1-ene (0.64 mL, 7.5 mmol, 1.5 eq) and Mg (182 mg, 7.5 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **212** as a white solid (1.23 g, 75%) in 91:9 d.r.; mp 53-55 °C; ν_{max} (film) 3027 (C-H), 1493, 1453 (Ar); δ_H (400MHz, $CDCl_3$) 1.51 (3H, d, *J* 5.8, C(3)*Me*), 3.53 (2H, d, *J* 14.8, N(CH_AH$_B$Ph)$_2$), 3.78 (2H, d, *J* 14.8, N(CH$_A$$H_B$Ph)$_2$), 4.67 (1H, d, *J* 9.8, C(1)*H*), 5.84 (1H, app t, *J* 10.2, C(2)*H*), 5.99 (1H, m, C(3)*H*), 7.25-7.46 (13H, m, *Ar*), 7.61 (2H, d, *J* 7.6, *o-Ph*); δ_C (100MHz, $CDCl_3$) 13.5 (C(3)*Me*), 53.8 (N(*C*H_2Ph)$_2$), 58.4 (*C*(1)), 126.8 (*p-Ph*(Bn)), 126.8 (*C*(3)), 126.9 (*p-Ph*), 128.1 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.2 (*C*(2)), 128.7 (*m-Ph*(Bn)), 128.9 (*m-Ph*), 140.2 (*i-*

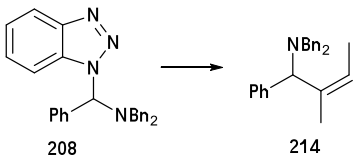
Ph(Bn)), 140.4 (*i-Ph*); *m/z* (ESI$^+$) 328 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{26}N^+$ ([M+H]$^+$) requires 328.2060, found 328.2059.

(*RS*)-*N*,*N*-Dibenzyl-3-methyl-1-phenylbut-2-en-1-amine 213



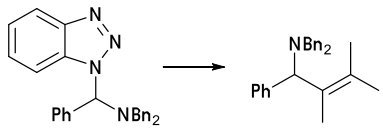
Following **General Procedure 6**, **208** (2.02 g, 5.0 mmol, 1.0 eq) and 2-methyl-1-propenyl magnesium bromide (0.5 M in THF, 15.0 mL, 7.5 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to yield pure **213** as a pale yellow semi-solid (1.59 g, 93%); ν_{max} (film) 3027 (C-H), 1493 (Ar), 1453 (Ar); δ_H (400MHz, $CDCl_3$) 1.54 (3H, s, C(3)*Me*$_A$Me$_B$), 1.94 (3H, s, C(3)Me$_A$*Me*$_B$), 3.57 (2H, d, *J* 13.8, N(C*H*$_A$H$_B$Ph)$_2$), 3.77 (2H, d, *J* 13.8, N(CH$_A$*H*$_B$Ph)$_2$), 4.58 (1H, d, *J* 9.8, C(1)*H*), 5.60 (1H, d, *J* 9.8, C(2)*H*), 7.25-7.28 (3H, m, *p-Ph*, *p-Ph*(Bn)), 7.34-7.41 (6H, m, *m-Ph*, *m-Ph*(Bn)), 7.47 (4H, d, *J* 7.6, *o-Ph*(Bn)), 7.61 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 18.5 (C(3)*Me*$_A$Me$_B$), 26.2 (C(3)Me$_A$*Me*$_B$), 53.9 (N(*C*H$_2$Ph)$_2$), 60.1 (*C*(1)), 121.5 (*C*(2)), 126.7 (*p-Ph*), 126.7 (*p-Ph*(Bn)), 128.1 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.7 (*m-Ph*), 128.7 (*m-Ph*(Bn)), 136.7 (*C*(2)), 140.4 (*i-Ph*(Bn)), 143.1 (*i-Ph*); *m/z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}N^+$ ([M+H]$^+$) requires 342.2216, found 342.2217.

(1*RS*,2*Z*)-*N*,*N*-Dibenzyl-2-methyl-1-phenylbut-2-en-1-amine 214



Following **General Procedure 7**, **208** (1.01 g, 2.5 mmol, 1.0 eq), (*Z*)-2-bromobut-2-ene (0.38 mL, 3.75 mmol, 1.5 eq) and Mg (91 mg, 3.75 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **214** as a colourless oil (740 mg, 87%) in 96:4 d.r.; ν_{max} (film) 3027, 2925 (C-H), 1493, 1453 (Ar); δ_H (400MHz, $CDCl_3$), 1.87 (3H, d, *J* 6.8, C(3)*Me*), 1.97 (3H, s, C(2)*Me*), 3.86 (2H, d, *J* 14.6, N(C$H_A$$H_B$Ph)$_2$), 4.03 (2H, d, *J* 14.6, N(CH$_A$$H_B$Ph)$_2$), 5.05 (1H, s, C(1)*H*), 5.61 (1H, q, *J* 6.8, C(3)*H*), 7.43-7.46 (3H, m, *Ar*), 7.51-7.60 (10H, m, *Ar*), 7.78 (2H, d, *J* 7.6, *m-Ph*); δ_C (100MHz, $CDCl_3$) 14.0 (C(3)*Me*), 19.6 (C(2)*Me*), 52.8 (N(*C*H$_2$Ph)$_2$), 63.9 (*C*(1)), 124.2 (*C*(3)), 126.9 (*p-Ph*(Bn)), 126.9 (*p-Ph*), 128.3 (*o-Ph*(Bn)), 128.3 (*o-Ph*), 128.5 (*m-Ph*), 129.5 (*m-Ph*(Bn)), 136.6 (*C*(2)), 138.8 (*i-Ph*(Bn)), 142.1 (*i-Ph*); *m/z* (ESI$^+$) 342 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{28}N^+$ ([M+H]$^+$) requires 342.2216, found 342.2217.

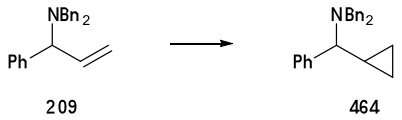
(*RS*)-*N*,*N*-Dibenzyl-2,3-dimethyl-1-phenylbut-2-en-1-amine 215



Following **General Procedure 7**, **208** (2.02 g, 5.0 mmol, 1.0 eq), 2-bromo-3-methylbut-2-ene (0.87 mL, 7.5 mmol, 1.5 eq) and Mg (182 mg, 7.5 mmol, 1.5 eq) were reacted to give a crude product which was purified by flash column chromatography (silica, petrol) to give pure **215** as a yellow oil (713 mg, 40%); ν_{max} (film) 3027, 2923 (C-H), 1493, 1453 (Ar); δ_H (400MHz, $CDCl_3$) 1.87 (3H, s, C(3)*Me*$_A$Me$_B$), 1.89 (3H, s, C(2)*Me*), 2.03 (3H, s, C(3)Me$_A$*Me*$_B$), 3.89 (2H, d, *J* 14.4, N(C$H_A$$H_B$Ph)$_2$), 4.00 (2H, d, *J* 14.4, N(CH$_A$$H_B$Ph)$_2$), 5.12 (1H, s, C(1)*H*), 7.45-7.49 (4H, m, *Ar*), 7.54-7.61 (9H, m, *Ar*), 7.81 (2H, d, *J* 7.6, *o-Ph*); δ_C (400MHz, $CDCl_3$) 14.0 (C(2)*Me*), 21.1 (C(3)Me$_A$*Me*$_B$), 21.7 (C(3)*Me*$_A$Me$_B$), 53.2 (N(*C*H$_2$Ph)$_2$), 66.1

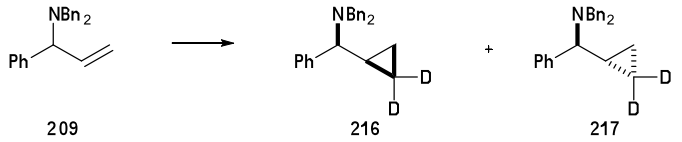
(*C*(1)), 126.7 (*p-Ph*), 126.9 (*p-Ph*(Bn)), 128.3 (*o-Ph*), 128.3 (*o-Ph*(Bn)), 128.4 (*m-Ph*), 128.8 (*C*(3)), 129.0 (*C*(2)), 129.5 (*m-Ph*(Bn)), 139.1 (*i-Ph*(Bn)), 143.0 (*i-Ph*); *m/z* (ESI^+) 356 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{30}N^+$ ($[M+H]^+$) requires 356.2373, found 256.2377.

(*RS*)-*N*,*N*-Dibenzyl-1-cyclopropyl-1-phenylmethanamine 464



Following **General Procedure 3**, **209** (157 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **464** as a pale yellow oil (119 mg, 73%); ν_{max} (film) 3026 (C-H), 1493 (Ar), 1453 (Ar); δ_H (400MHz, $CDCl_3$) 0.01-0.03 (1H, m, $CH_AH_BCH_CH_D$), 0.52-0.62 (2H, m, $CH_AH_BCH_CH_D$, $CH_AH_BCH_CH_D$), 0.81-0.88 (1H, m, $CH_AH_BCH_CH_D$), 1.30-1.39 (1H, m, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, $N(CH_AH_BPh)_2$), 3.93 (2H, d, *J* 13.8, $N(CH_AH_BPh)_2$), 7.27-7.34 (3H, m, *p-Ph*, *p-Ph*(Bn)), 7.38 (4H, app t, *J* 7.6, *m-Ph*(Bn)), 7.45 (2H, app t, *J* 7.6, *m-Ph*), 7.50 (4H, d, *J* 7.1, *o-Ph*(Bn)), 7.60 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 3.0 ($CH_AH_BCH_CH_D$), 6.7 ($CH_AH_BCH_CH_D$), 10.8 (*C*(1′)H), 54.1 ($N(CH_2Ph)_2$), 67.2 (*C*(1)H), 126.8 (*p-Ph*(Bn)), 128.0 (*p-Ph*), 128.2 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.7 (*m-Ph*(Bn)), 128.8 (*m-Ph*), 140.6 (*i-Ph*(Bn)), 142.4 (*i-Ph*); *m/z* (ESI^+) 328 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{26}N^+$ ($[M+H]^+$) requires 328.2060, found 328.2064.

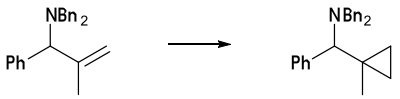
(1*SR*,1′*SR*)-*N*,*N*-Dibenzyl-1-(2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 216 and (1*SR*,1′*RS*)-*N*,*N*-Dibenzyl-1-(2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 217



Following **General Procedure 3**, **209** (157 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 mL, 1.0 mmol, 2.0 eq), CD_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 3 hrs gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give a 70:30 mixture of **216**:**217** as a pale yellow oil (118 mg, 72%); ν_{max} (film) 3060, 3025, 2805 (C-H), 1600, 1495, 1455 (Ar), 1120, 1070, 1030, 970, 910, 745, 700; Data for major isomer **216**; δ_H (400MHz, $CDCl_3$) −0.02 (1H, app t, *J* 4.9, CH_AH$_B$), 0.57 (1H, dd, *J* 8.3, 4.6, CH$_A$$H_B$), 1.30-1.39 (1H, ddd, *J* 9.7, 8.3, 5.0, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, N(CH_AH$_B$Ph)$_2$), 3.93 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ph)$_2$), 7.27-7.34 (3H, m, *p-Ph*, *p-Ph*(Bn)), 7.38 (4H, app t, *J* 7.6, *m-Ph*(Bn)), 7.45 (2H, app t, *J* 7.6, *m-Ph*), 7.50 (4H, d, *J* 7.1, *o-Ph*(Bn)), 7.60 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 3.0 (*C*H$_2$), 10.8 (*C*(1′)H), 54.1 (N(*C*H$_2$Ph)$_2$), 67.2 (*C*(1)H), 126.8 (*p-Ph*(Bn)), 128.0 (*p-Ph*), 128.2 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.7 (*m-Ph*(Bn)), 128.8 (*m-Ph*), 140.6 (*i-Ph*(Bn)), 142.4 (*i-Ph*), (*C*(2′) not observed); Data for minor isomer **217**; δ_H (400MHz, $CDCl_3$) 0.52-0.62 (1H, app t, *J* 4.6, CH_AH$_B$), 0.82 (1H, dd, *J* 7.7, 4.6, CH$_A$$H_B$), 1.30-1.39 (1H, m, C(1′)*H*), 3.01 (1H, d, *J* 9.8, C(1)*H*), 3.67 (2H, d, *J* 13.8, N(CH_AH$_B$Ph)$_2$), 3.93 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ph)$_2$), 7.27-7.34 (3H, m, *p-Ph*, *p-Ph*(Bn)), 7.38 (4H, app t, *J* 7.6, *m-Ph*(Bn)), 7.45 (2H, app t, *J* 7.6, *m-Ph*), 7.50 (4H, d, *J* 7.1, *o-Ph*(Bn)), 7.60 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 6.7 (*C*H$_2$), 10.8 (*C*(1′)H), 54.1 (N(*C*H$_2$Ph)$_2$), 67.2

(*C*(1)H), 126.8 (*p-Ph*(Bn)), 128.0 (*p-Ph*), 128.2 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.7 (*m-Ph*(Bn)), 128.8 (*m-Ph*), 140.6 (*i-Ph*(Bn)), 142.4 (*i-Ph*), (*C*(2′) not observed); *m/z* (ESI^+) 330 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{24}D_2N$ ($M+H^+$) requires 330.2185, found 330.2175.

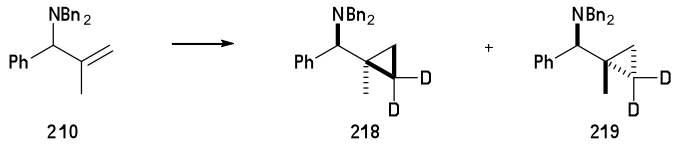
(*RS*)-*N*,*N*-Dibenzyl-1-(1′-methylcyclopropyl)-1-phenylmethanamine 465



210 465

Following **General Procedure 3**, **210** (164 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) gave a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **465** as a yellow oil (160 mg, 94%); ν_{max} (film) 3026, 2951 (C-H), 1493, 1452 (Ar); δ_H (400MHz, $CDCl_3$) 0.17-0.19 (1H, m, CH_AH$_B$CH$_C$H$_D$), 0.46-0.52 (3H, m, CH$_A$$H_BCH_CH_D$, CH$_AH_BCH_CH_D$, CH$_AH_BCH_C$$H_D$), 1.16 (3H, s, C*Me*), 3.08 (1H, s, PhC*H*), 3.72 (2H, d, *J* 14.5, N(CH_AH$_B$Ph)$_2$), 3.98 (2H, d, *J* 14.5, N(CH$_A$$H_B$Ph)$_2$), 7.26-7.30 (2H, m, *Ar*), 7.33-7.38 (8H, m, *Ar*), 7.40-7.45 (3H, m, *Ar*), 7.52 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 11.1 (*C*H$_A$H$_B$CH$_C$H$_D$), 16.5 (CH$_A$H$_B$*C*H$_C$H$_D$), 18.2 (*C*Me), 19.8 (C*Me*), 52.7 (N(*C*H$_2$Ph)$_2$), 71.0 (Ph*C*H), 126.7 (*p-Ph*(Bn)), 126.8 (*p-Ph*), 127.9 (*o-Ph*), 128.1 (*o-Ph*(Bn)), 129.2 (*m-Ph*), 129.2 (*m-Ph*(Bn)), 138.9 (*i-Ph*(Bn)), 141.5 (*i-Ph*); *m/z* (ESI^+) 342 ($[M+H^+]$, 100%); HRMS (ESI^+) $C_{25}H_{28}N^+$ ($[M+H]^+$) requires 342.2216, found 342.2209.

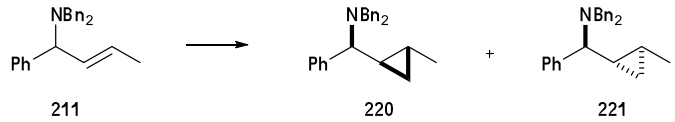
(1*SR*,2′*SR*)-*N*,*N*-Dibenzyl-1-(1′-methyl-2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 218 and (1*SR*,2′*RS*)-*N*,*N*-Dibenzyl-1-(1′-methyl-2′,2′-dideuteriocyclopropyl)-1-phenylmethanamine 219



Following **General Procedure 3**, **210** (164 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 mL, 1.0 mmol, 2.0 eq), CD_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 3 hrs gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give an 58:42 mixture of **218**:**219** as a pale yellow solid (108 mg, 63%); m.p. 57-59 °C; ν_{max} (KBr) 3060, 3025, 2960, 2810 (C-H), 1600, 1495, 1450 (Ar), 1120, 1070, 1030, 910, 775, 750, 700; Data for major isomer **218**; δ_H (400MHz, $CDCl_3$) 0.46-0.52 (2H, m, CH_2), 1.16 (3H, s, C*Me*), 3.08 (1H, s, PhC*H*), 3.72 (2H, d, *J* 14.5, N(C$H_A$$H_B$Ph)$_2$), 3.98 (2H, d, *J* 14.5, N(CH$_A$$H_B$Ph)$_2$), 7.26-7.30 (2H, m, *Ar*), 7.33-7.38 (8H, m, *Ar*), 7.40-7.45 (3H, m, *Ar*), 7.52 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 16.5 (*C*H$_2$), 18.2 (*C*Me), 19.8 (C*Me*), 52.7 (N(*C*H$_2$Ph)$_2$), 71.0 (Ph*C*H), 126.7 (*p-Ph*(Bn)), 126.8 (*p-Ph*), 127.9 (*o-Ph*), 128.1 (*o-Ph*(Bn)), 129.2 (*m-Ph*), 129.2 (*m-Ph*(Bn)), 138.9 (*i-Ph*(Bn)), 141.5 (*i-Ph*); Data for minor isomer **219**; δ_H (400MHz, $CDCl_3$) 0.17-0.19 (1H, m, C$H_A$$H_B$), 0.46-0.52 (1H, m, CH$_A$$H_B$), 1.16 (3H, s, C*Me*), 3.08 (1H, s, PhC*H*), 3.72 (2H, d, *J* 14.5, N(C$H_A$$H_B$Ph)$_2$), 3.98 (2H, d, *J* 14.5, N(CH$_A$$H_B$Ph)$_2$), 7.26-7.30 (2H, m, *Ar*), 7.33-7.38 (8H, m, *Ar*), 7.40-7.45 (3H, m, *Ar*), 7.52 (2H, d, *J* 7.3, *o-Ph*); δ_C (100MHz, $CDCl_3$) 11.1 (*C*H$_2$), 18.2 (*C*Me), 19.8 (C*Me*), 52.7 (N(*C*H$_2$Ph)$_2$), 71.0 (Ph*C*H), 126.7 (*p-Ph*(Bn)), 126.8 (*p-Ph*), 127.9 (*o-Ph*), 128.1 (*o-Ph*(Bn)), 129.2 (*m-Ph*), 129.2 (*m-*

Ph(Bn)), 138.9 (*i-Ph*(Bn)), 141.5 (*i-Ph*);*m/z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{26}D_2N$ ($M+H^+$) requires 344.2342, found 344.2335.

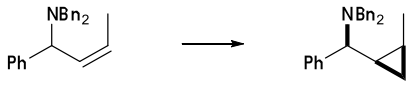
(1*SR*,1'*RS*,2'*RS*)-*N*,*N*-Dibenzyl-1-[2'-methylcyclopropyl]-1-phenylmethanamine 220 and (1*SR*,1'*SR*,2'*SR*)-*N*,*N*-dibenzyl-1-[2'-methylcyclopropyl]-1-phenylmethanamine 221



211 220 221

Following **General Procedure 3**, **211** (164 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0 mL, 1.0 mmol, 1.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give a 89:11 mixture of **220**:**221** as a pale yellow oil (102 mg, 60%); Data for major isomer **220**; ν_{max} (film) 3060, 3025, 2950 (C-H), 1495, 1450 (Ar), 1120, 1070, 1030, 745, 700; δ_H (400 MHz, $CDCl_3$) 0.33-0.40 (1H, m, C(2')*H*), 0.61-0.65 (1H, m, cyclopropane CH_AH_B), 0.70-0.74 (1H, m, cyclopropane CH_AH_B), 1.03-1.10 (1H, m, C(1')), 1.15 (3H, d, *J* 6.1, C(2')*Me*), 3.11 (1H, d, *J* 9.8, C(1)*H*), 3.68 (2H, d, *J* 13.6, N(CH_AH_BPh)$_2$), 3.88 (2H, d, *J* 13.6, N(CH_AH_BPh)$_2$), 7.26-7.51 (13H, m, *Ar*), 7.58 (2H, d, *J* 7.3, 2 x o-*Ph*); δ_C (100 MHz, $CDCl_3$) 10.4 (*C*(2')), 14.9 (cyclopropane *C*H_2), 18.6 (*C*(1')), 18.7 (*Me*), 54.0 (N(*C*H_2Ph)$_2$), 66.2 (*C*(1)), 126.7, 126.7 (*p-Ph*), 127.9, 128.2, 128.7, 128.7 (*o/m-Ph*), 140.6, 142.7 (*i-Ph*); *m/z* (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{28}N$ ($M+H^+$) requires 342.2216, found 342.2213; Characteristic peaks for minor diastereoisomer **221**; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.1, C(2')*Me*).

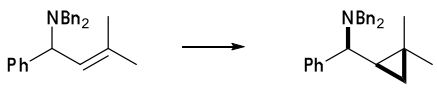
(1*SR*,1'*RS*,2'*SR*)-*N*,*N*-Dibenzyl-1-(2'-methylcyclopropyl)-1-phenylmethanamine 222



212 222

Following **General Procedure 3**, **212** (327 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol) to give **222** as a white solid (226 mg, 66%); m.p. 48-50 °C; ν_{max} (KBr) 3027, 2919, 2833, 2805 (C-H), 1493, 1453 (Ar); δ_H (400 MHz, $CDCl_3$) 0.35 (1H, app q, *J* 5.0, CH_AH_B), 0.77 (3H, d, *J* 6.3, *Me*), 0.96-1.02 (1H, m, C*H*Me), 1.09-1.17 (1H, m, CH_AH_B), 1.38-1.47 (1H, m, C*H*CH_2), 3.46 (1H, d, *J* 10.6, PhC*H*), 3.66 (2H, d, *J* 13.6, NCH_2Ph), 3.93 (2H, d, *J* 13.6, NCH_2Ph), 7.28-7.53 (13H, m, *Ar*), 7.63 (2H, d, *J* 7.3, *Ar*); δ_C (100MHz, $CDCl_3$) 8.3 (*C*HMe), 13.0 (*C*H_2), 13.5 (*Me*), 14.2 (*C*HCH_2), 54.0 (N(*C*H_2Ph)$_2$), 60.7 (Ph*C*H), 126.7, 126.8 (*p-Ar*), 127.9, 128.2, 128.8, 128.8 (*o/m-Ar*), 140.8, 142.7 (*i-Ar*); *m/z* (ESI^+) 342 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}N^+$ ($[M+H]^+$) requires 342.2216; found 342.2215.

(1*SR*,1'*RS*)-*N*,*N*-Dibenzyl-1-(2',2'-dimethylcyclopropyl)-1-phenylmethanamine 223

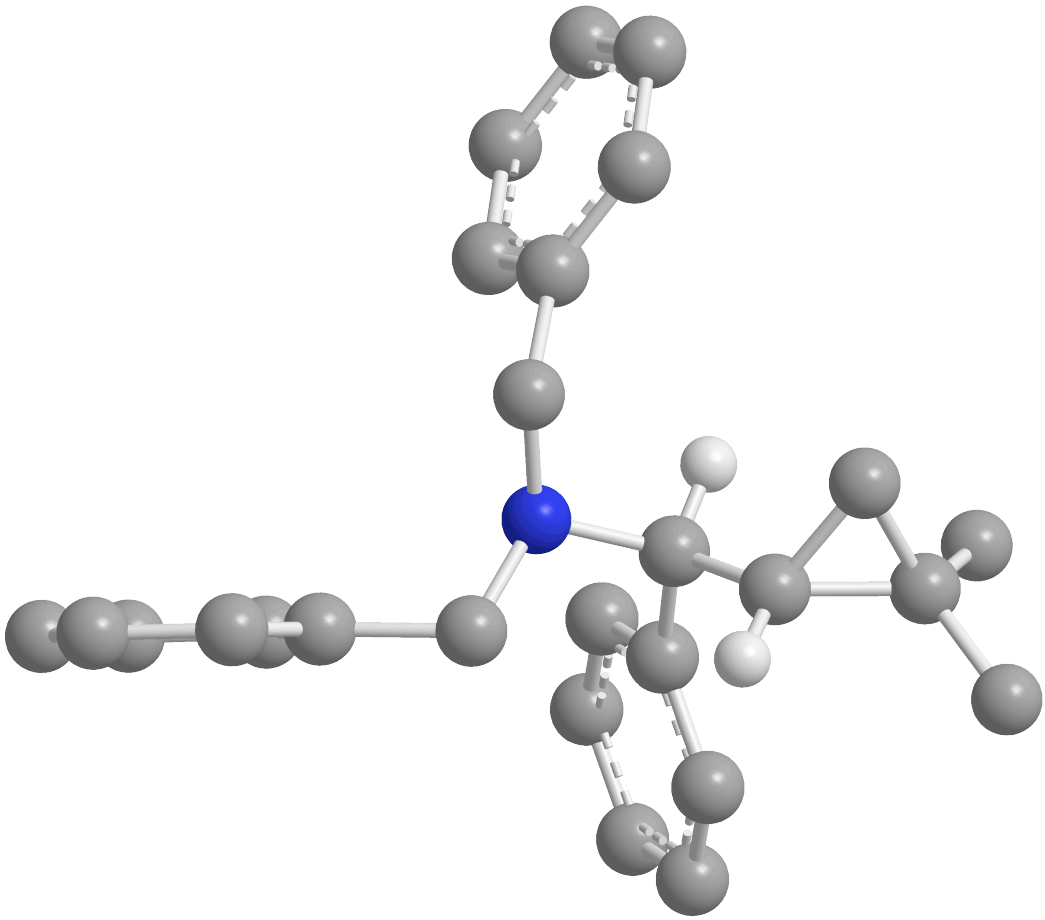


213 223

Following **General Procedure 3**, **213** (171 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA

(0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **223** as a white solid (156 mg, 88%); m.p. 60-62 °C; ν_{max} (film) 3027 (C-H), 1493 (Ar), 1453 (Ar); δ_H (400MHz, $CDCl_3$) 0.47 (1H, app t, *J* 4.9, CH_AH_B), 0.68 (3H, s, C(2′)*Me*$_A$Me$_B$), 0.85 (1H, dd, *J* 8.3, 4.3, CH$_A$*H*$_B$), 1.14-1.20 (1H, m, C(1′)*H*) overlapping 1.18 (3H, s, C(2′)Me$_A$*Me*$_B$), 3.42 (1H, d, *J* 10.6, C(1)*H*), 3.63 (2H, d, *J* 13.6, N(C*H*$_A$H$_B$Ph)$_2$), 3.82 (2H, d, *J* 13.6, N(CH$_A$*H*$_B$Ph)$_2$), 7.22-7.30 (3H, m, *p-Ph*, *p-Ph*(Bn)), 7.34 (4H, t, *J* 7.4, *m-Ph*(Bn)), 7.40 (2H, t, *J* 7.6, *m-Ph*), 7.45 (4H, d, *J* 7.4, *o-Ph*(Bn)), 7.52 (2H, d, *J* 7.6, *o-Ph*); δ_C (400MHz, $CDCl_3$) 13.6 (*C*(2′)Me$_2$), 20.0 (C(2′)*Me*$_A$Me$_B$), 20.4 (*C*H$_2$), 22.1 (C(2′)Me$_A$*Me*$_B$), 27.4 (*C*(1′)), 53.9 (N(*C*H$_2$Ph)$_2$), 61.6 (*C*(1)H, 126.6 (*p-Ph*), 126.7 (*p-Ph*(Bn)), 127.8 (*o-Ph*), 128.2 (*o-Ph*(Bn)), 128.6 (*m-Ph*), 128.7 (*m-Ph*(Bn)), 140.7 (*i-Ph*(Bn)), 143.0 (*i-Ph*); *m/z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}N^+$ ([M+H]$^+$) requires 356.2372, found 356.2372.

X-Ray crystal structure data for (1*SR*,1'*RS*)-223 (Some H atoms omitted for clarity)



X-ray crystal structure determination for 223

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **223** [$C_{26}H_{29}N$]: M = 353.51, orthorhombic, space group *F 2 d d*, a = 9.02980(10) Å, b = 19.3438(3) Å, c = 49.1328(3) Å, V = 8582.06(19) Å^3, Z = 16, μ = 0.063 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.05 × 0.3 mm^3. A total of 2589 unique reflections were measured for 5 < θ < 27 and

2029 reflections were used in the refinement. The final parameters were $wR_2 = 0.042$ and $R_1 = 0.034$ [$I>3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr K. B. Ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters ($Å^2$) (e.s.d. in parentheses)

Atom	x/a	y/b	z/c	U(iso)
C(1)	0.6643(2)	0.01794(10)	0.17797(4)	0.0501
C(2)	0.49828(19)	0.01207(9)	0.17432(4)	0.0419
N(3)	0.40808(19)	0.05775(7)	0.19196(3)	0.0441
C(4)	0.4133(3)	0.03852(10)	0.22082(4)	0.0530
C(5)	0.3353(3)	-0.02956(9)	0.22634(3)	0.0494
C(6)	0.3970(3)	-0.07871(11)	0.24336(4)	0.0627
C(7)	0.3191(4)	-0.13991(12)	0.24888(5)	0.0761
C(8)	0.1832(3)	-0.15190(12)	0.23740(5)	0.0718
C(9)	0.1214(3)	-0.10330(11)	0.22056(4)	0.0623
C(10)	0.1970(3)	-0.04255(10)	0.21516(4)	0.0529
C(11)	0.4395(2)	0.13172(9)	0.18837(4)	0.0505
C(12)	0.3028(2)	0.17501(9)	0.19344(4)	0.0485
C(13)	0.3030(3)	0.22938(10)	0.21175(4)	0.0617
C(14)	0.1772(4)	0.26987(11)	0.21532(4)	0.0728
C(15)	0.0526(3)	0.25721(13)	0.20071(5)	0.0705
C(16)	0.0500(3)	0.20306(13)	0.18220(5)	0.0704
C(17)	0.1745(3)	0.16238(11)	0.17880(4)	0.0606
C(18)	0.4486(2)	0.02311(8)	0.14487(4)	0.0404
C(19)	0.3074(2)	0.00158(9)	0.13774(4)	0.0449
C(20)	0.2543(2)	0.01038(11)	0.11146(4)	0.0539
C(21)	0.3433(3)	0.04089(11)	0.09199(4)	0.0592
C(22)	0.4837(3)	0.06293(11)	0.09883(4)	0.0591
C(23)	0.5368(2)	0.05370(10)	0.12521(4)	0.0517
C(24)	0.7677(2)	-0.03700(11)	0.16715(5)	0.0552
C(25)	0.7449(3)	-0.02993(13)	0.19735(5)	0.0641
C(26)	0.7054(3)	-0.10004(11)	0.15309(5)	0.0635
C(27)	0.9118(3)	-0.01264(15)	0.15513(7)	0.0782
H(11)	0.7034(2)	0.06615(10)	0.17786(4)	0.0657
H(21)	0.47149(19)	-0.03663(9)	0.18005(4)	0.0543
H(41)	0.5204(3)	0.03323(10)	0.22624(4)	0.0665
H(42)	0.3624(3)	0.07596(10)	0.23129(4)	0.0670
H(61)	0.4927(3)	-0.07014(11)	0.25100(4)	0.0819
H(71)	0.3606(4)	-0.17384(12)	0.26035(5)	0.0956
H(81)	0.1300(3)	-0.19484(12)	0.24147(5)	0.0914
H(91)	0.0246(3)	-0.11126(11)	0.21292(4)	0.0805
H(101)	0.1534(3)	-0.00791(10)	0.20308(4)	0.0680

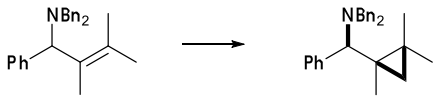
H(111)	0.5244(2)	0.14621(9)	0.19976(4)	0.0664
H(112)	0.4666(2)	0.13768(9)	0.16894(4)	0.0672
H(131)	0.3919(3)	0.23816(10)	0.22232(4)	0.0834
H(141)	0.1785(4)	0.30755(11)	0.22849(4)	0.0916
H(151)	-0.0338(3)	0.28494(13)	0.20320(5)	0.0961
H(161)	-0.0376(3)	0.19566(13)	0.17196(5)	0.0933
H(171)	0.1716(3)	0.12366(11)	0.16606(4)	0.0782
H(191)	0.2467(2)	-0.02030(9)	0.15120(4)	0.0578
H(201)	0.1549(2)	-0.00497(11)	0.10698(4)	0.0679
H(211)	0.3095(3)	0.04624(11)	0.07346(4)	0.0753
H(221)	0.5448(3)	0.08441(11)	0.08504(4)	0.0740
H(231)	0.6334(2)	0.06800(10)	0.13023(4)	0.0647
H(251)	0.8302(3)	-0.01373(13)	0.20820(5)	0.0828
H(252)	0.6884(3)	-0.06875(13)	0.20638(5)	0.0830
H(261)	0.7817(3)	-0.13651(11)	0.15334(5)	0.0987
H(262)	0.6152(3)	-0.11408(11)	0.16253(5)	0.0982
H(263)	0.6807(3)	-0.08714(11)	0.13413(5)	0.0982
H(271)	0.9858(3)	-0.05012(15)	0.15561(7)	0.1166
H(272)	0.9450(3)	0.02805(15)	0.16525(7)	0.1160
H(273)	0.8914(3)	0.00169(15)	0.13621(7)	0.1164

(1*SR*,1'*RS*,2'*SR*)-*N*,*N*-Dibenzyl-1-(1',2'-dimethylcyclopropyl)-1-phenylamine 224

214 224

Following **General Procedure 3**, **214** (171 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 1% Et_2O/petrol) to give pure **224** as a colourless oil (127 mg, 71%); ν_{max} (film) 3061, 3027, 2960 (C-H), 1493, 1452 (Ar); δ_H (400MHz, $CDCl_3$) 0.30-0.33 (1H, m, CH_AH_B), 0.60-0.65 (1H, m, C(2′)*H*), 0.77-0.80 (1H, m, CH_AH_B), 0.98-1.01 (3H, m, C(2′)*Me*), 1.33 (3H, s, C(1′)*Me*), 3.61 (1H, s, C(1)*H*), 3.88 (2H, d, *J* 14.2, N(CH_AH_BPh)$_2$), 4.08 (2H, d, *J* 14.2, N(CH_AH_BPh)$_2$), 7.30-7.52 (13H, m, *Ar*), 7.77 (2H, d, *J* 6.3, *m-Ph*); δ_C (100MHz, $CDCl_3$) 15.1 (C(2′)*Me*), 19.4 (*C*(2′)), 20.8 (*C*(1′)Me), 22.8 (*C*H_2), 23.3 (C(1′)*Me*), 53.8 (N(*C*H_2Ph)$_2$), 65.0 (*C*(1)H), 126.6 (*p-Ph*), 126.7 (*p-Ph*(Bn)), 128.0 (*m-Ph*), 128.2 (*m-Ph*(Bn)), 129.0 (*o-Ph*(Bn)), 129.5 (*o-Ph*), 139.9 (*i-Ph*(Bn)), 142.6 (*i-Ph*); *m/z* (ESI$^+$) 356 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}N^+$ ([M+H]$^+$) requires 356.2373, found 356.2375.

(1*RS*,1'*RS*)-*N*,*N*-Dibenzyl-1-phenyl-1-(1',2',2'-trimethylcyclopropyl)methanamine 225

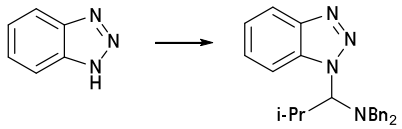


215 225

Following **General Procedure 3**, **215** (178 mg, 0.5 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA

(0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **225** as a yellow oil (68 mg, 37%); ν_{max} (film) 3027 (C-H), 1493 (Ar), 1453 (Ar); δ_H (400MHz, $CDCl_3$) 0.39 (1H, d, *J* 4.4, CH_AH$_B$), 0.44 (1H, d, *J* 4.4, CH$_A$$H_B$), 0.93 (3H, s, C(2′)*Me*$_A$Me$_B$), 1.08 (3H, s, C(2′)Me$_A$*Me*$_B$), 1.36 (3H, s, C(1′)*Me*), 3.68 (1H, s, C(1)*H*), 3.82 (2H, d, *J* 14.4, N(CH_AH$_B$Ph)$_2$), 4.00 (2H, d, *J* 14.4, N(CH$_A$$H_B$)$_2$), 7.23-7.46 (13H, m, *Ar*), 7.63 (2H, d, *J* 7.6, *m-Ph*); δ_C (100MHz, $CDCl_3$) 17.5 (C(1′)*Me*), 19.1 (*C*(2′)), 22.7 (C(2′)Me$_A$*Me*$_B$), 23.3 (C(2′)*Me*$_A$Me$_B$), 25.0 (*C*(1′)Me), 29.2 (*C*H$_2$), 53.9 (N(*C*H$_2$Ph)$_2$), 66.4 (*C*(1)), 126.5 (*p-Ph*), 126.6 (*p-Ph*(Bn)), 127.9 (*o-Ph*), 128.1 (*o-Ph*(Bn)), 128.8 (*m-Ph*(Bn)), 129.2 (*m-Ph*), 140.0 (*i-Ph*(Bn)), 142.8 (*i-Ph*); *m/z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N^+$ ([M+H]$^+$) requires 370.2529, found 370.25.28.

(*RS*)-*N*-(1-Benzotriazol-1-yl-2-methylpropyl)dibenzylamine 226

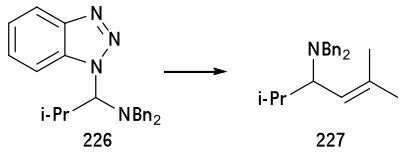


207 226

iso-Butyraldehyde (9.13 mL, 100 mmol, 1.0 eq), dibenzylamine **193** (19.2 mL, 100 mmol, 1.0 eq) and benzotriazole **207** (11.9 g, 100 mmol, 1.0 eq) were stirred in MeOH:Et_2O (1:1, v/v, 100 mL) for 30 mins. The resultant homogeneous solution was stored at 0 °C overnight resulting in the precipitation of a white solid. Filtration (wash with cold Et_2O) gave **226** as a white solid (29.8 g, 81%) as a ~2:1 mixture of Bnt-1 and Bnt-2 isomers; data for major isomer **226**; m.p. 96-98 °C {lit.[10] m.p. 83-85 °C}; δ_H (400MHz, $CDCl_3$) 0.48 (3H, d, *J* 6.5, CH*Me*$_A$Me$_B$), 1.39 (3H, d, *J* 6.5, CHMe$_A$*Me*$_B$), 3.01-3.14 (1H, m, C*H*Me$_2$), 3.21-3.30 (4H, m, N(CH_2Ph)$_2$), 5.09 (1H, d,

J 10.6, C*H*CHMe$_2$), 7.06-7.09 (1H, m, *Ar*), 7.27-7.50 (11H, m, *Ar*), 7.97-8.00 (1H, m, *Ar*), 8.11-8.13 (1H, m, *Ar*).

(*RS*)-*N*,*N*-Dibenzyl-2,5-dimethylhex-4-en-3-amine 227



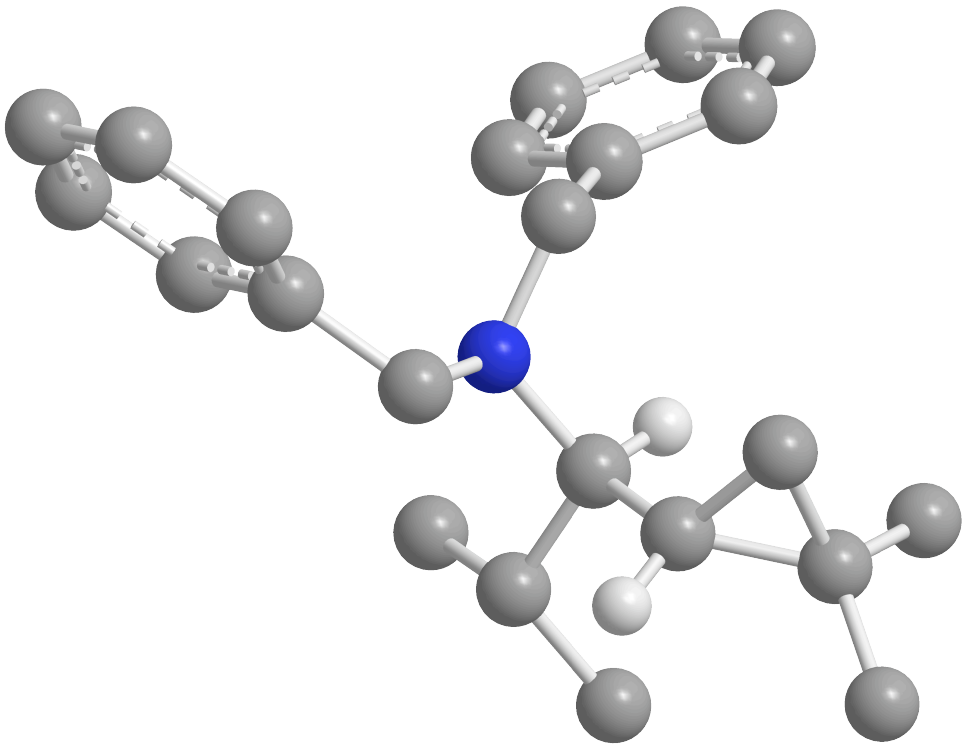
Following **General Procedure 6**, **226** (1.85 g, 5.0 mmol, 1.0 eq) and 2-methyl-1-propenylmagnesium bromide (15.0 mL, 0.5 M in THF, 7.5 mmol, 1.5 eq) in toluene (25 mL) gave a crude product which was purified by flash column chromatography (silica, petrol) to give **227** as a white crystalline solid (1.35 g, 88%); m.p. 42-44 °C; ν_{max} (KBr) 3025, 2955, 2920 (C-H), 1495, 1455 (Ar), 1100, 1070, 1030, 975, 740, 700; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.6, C(2)*Me*$_A$Me$_B$), 1.27 (3H, d, *J* 6.6, C(2)Me$_A$*Me*$_B$), 1.56 (3H, s, C(5)*Me*$_A$Me$_B$), 1.88-1.93 (1H, m, C(2)*H*), 1.96 (3H, s, C(5)Me$_A$*Me*$_B$), 2.93 (1H, app t, *J* 10.4, C(3)*H*), 3.42 (2H, d, *J* 14.2, N(C*H*$_A$H$_B$Ph)$_2$), 3.95 (2H, d, *J* 14.2, N(CH$_A$*H*$_B$Ph)$_2$), 5.29 (1H, d, *J* 10.6, C(4)*H*), 7.30-7.33 (2H, m, *p*-*Ph*), 7.41 (4H, t, *J* 7.5, *m*-*Ph*), 7.55 (4H, d, *J* 7.5, *o*-*Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(5)*Me*$_A$Me$_B$), 20.7 (C(2)*Me*$_2$), 26.2 (C(5)Me$_A$*Me*$_B$), 30.4 (*C*(2)), 53.9 (N(*C*H$_2$Ph)$_2$), 62.9 (*C*(3)), 122.4 (*C*(4)), 126.6 (*p*-*Ph*), 128.2 (*m*-*Ph*), 128.7 (*o*-*Ph*), 136.0 (*C*(5)), 141.1 (*i*-*Ph*); *m/z* (CI$^+$) 264 ([M-C$_3$H$_7$]$^+$, 100%), 308 ([M+H]$^+$, 10%); HRMS (CI$^+$) $C_{22}H_{30}N^+$ ([M+H]$^+$) requires 308.2378; found 328.2364.

(1*RS*,1'*RS*)-*N*,*N*-Dibenzyl-1-(2',2'-dimethylcyclopropyl)-2-methylpropan-1-amine 228

227 228

Following **General Procedure 3**, **227** (307 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (2.0 mL, 1.0M in hexanes, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol) to give **228** as a white crystalline solid (252 mg, 79%); m.p. 63-65 °C; ν_{max} (KBr) 3060, 3025, 2950 (C-H), 1495, 1455 (Ar), 745, 700; δ_H (400 MHz, $CDCl_3$) 0.63-0.67 (2H, m, CH_AH$_B$, C(1')*H*), 0.70-0.74 (1H, m, CH$_A$$H_B$), 0.92 (3H, s, C(2')*Me*$_A$Me$_B$), 0.95 (3H, d, *J* 6.7, C(2)*Me*$_A$Me$_B$), 1.08 (3H, d, *J* 6.7, C(2)Me$_A$*Me*$_B$), 1.15 (3H, s, C(2')Me$_A$*Me*$_B$), 1.86-1.94 (1H, m, C(2)*H*), 2.07-2.12 (1H, m, C(1)*H*), 3.81 (2H, d, *J* 13.5, N(CH_AH$_B$Ph)$_2$), 3.97 (2H, d, *J* 13.5, N(CH$_A$$H_B$Ph)$_2$), 7.28-7.32 (2H, m, *p-Ph*), 7.38 (4H, t, *J* 7.4, *m-Ph*), 7.47 (4H, d, *J* 7.4, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(2')), 18.3 (*C*H$_2$), 20.1, 21.5 (C(2)*Me*$_2$), 21.6 (C(2')*Me*$_A$Me$_B$), 26.4 (*C*(1')), 27.2 (C(2')Me$_A$*Me*$_B$), 32.0 (*C*(2)), 55.1 (N(*C*H$_2$Ph)$_2$), 61.9 (*C*(1)), 126.7 (*p-Ph*), 128.1, 129.2 (*o/m-Ph*), 141.1 (*i-Ph*); *m/z* (CI$^+$) 278 ([M-C$_3$H$_7$]$^+$, 100%), 322 ([M+H]$^+$, 10%); HRMS (CI$^+$) $C_{23}H_{32}N^+$ ([M+H]$^+$) requires 322.2535; found 322.2525.

X-Ray crystal structure data for (1*RS*,1'*RS*)-228 (Some H atoms omitted for clarity)



X-ray crystal structure determination for 228

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **228** [$C_{23}H_{31}N$]: M = 321.51, triclinic, space group $P-1$, a = 9.3589(2) Å, b = 10.0571(2) Å, c = 10.6726(3) Å, α = 102.2247(9)°, β = 95.2451(9)°, γ = 92.1221(9)°, V = 976.01(4) Å^3, Z = 2, μ = 0.062 mm^{-1}, colourless plate, crystal dimensions = 0.2 × 0.2 × 0.2 mm^3. A total of 4430 unique reflections were measured for $5 < \theta < 27$ and 3112 reflections were used in the refinement. The

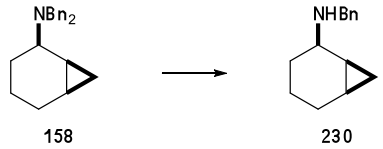
final parameters were $wR_2 = 0.043$ and $R_1 = 0.040$ [$I>3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr K. B. Ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters ($Å^2$) (e.s.d. in parentheses)

Atom	x/a	y/b	z/c	U(iso)
N(1)	0.77096(10)	0.48606(10)	0.70329(9)	0.0236
C(2)	0.80699(14)	0.60090(12)	0.64511(12)	0.0293
C(3)	0.79801(13)	0.73699(12)	0.73743(12)	0.0269
C(4)	0.86003(14)	0.75881(13)	0.86439(13)	0.0310
C(5)	0.85484(15)	0.88422(14)	0.94809(13)	0.0350
C(6)	0.78706(16)	0.98936(14)	0.90637(14)	0.0385
C(7)	0.72485(16)	0.96882(14)	0.78075(15)	0.0405
C(8)	0.73031(15)	0.84317(13)	0.69651(13)	0.0337
C(9)	0.61834(13)	0.48200(13)	0.72418(12)	0.0263
C(10)	0.58260(13)	0.39415(12)	0.81659(12)	0.0266
C(11)	0.46831(15)	0.29676(14)	0.78591(14)	0.0381
C(12)	0.43056(19)	0.22233(16)	0.87450(18)	0.0509
C(13)	0.50654(19)	0.24300(16)	0.99416(18)	0.0514
C(14)	0.62119(18)	0.33946(17)	1.02601(15)	0.0462
C(15)	0.65865(15)	0.41501(15)	0.93789(13)	0.0347
C(16)	0.82026(12)	0.35394(12)	0.63489(11)	0.0233
C(17)	0.79624(13)	0.32819(12)	0.48876(11)	0.0256
C(18)	0.73812(14)	0.19505(13)	0.39989(12)	0.0295
C(19)	0.65076(15)	0.31884(15)	0.41074(13)	0.0374
C(20)	0.80907(17)	0.14886(16)	0.27742(13)	0.0405
C(21)	0.68108(18)	0.07993(15)	0.45503(15)	0.0450
C(22)	0.98080(13)	0.34150(14)	0.67823(12)	0.0308
C(23)	1.03329(15)	0.20413(16)	0.61426(15)	0.0432
C(24)	1.00970(17)	0.36190(18)	0.82403(14)	0.0476
H(21)	0.91039(14)	0.59296(12)	0.62081(12)	0.0401
H(22)	0.73941(14)	0.59800(12)	0.56419(12)	0.0391
H(41)	0.90714(14)	0.68159(13)	0.89365(13)	0.0391
H(51)	0.89958(15)	0.89968(14)	1.03949(13)	0.0438
H(61)	0.78335(16)	1.07946(14)	0.96672(14)	0.0499
H(71)	0.67652(16)	1.04352(14)	0.75167(15)	0.0523
H(81)	0.68635(15)	0.82793(13)	0.60598(13)	0.0434
H(91)	0.59726(13)	0.57915(13)	0.76392(12)	0.0343
H(92)	0.55563(13)	0.45087(13)	0.63856(12)	0.0333
H(111)	0.41414(15)	0.28035(14)	0.69838(14)	0.0484
H(121)	0.34900(19)	0.15460(16)	0.85215(18)	0.0669
H(131)	0.48000(19)	0.18958(16)	1.05787(18)	0.0690
H(141)	0.67697(18)	0.35479(17)	1.11250(15)	0.0610

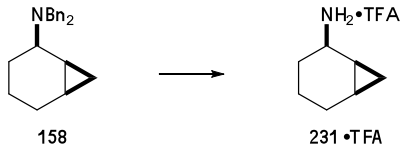
H(151)	0.73998(15)	0.48443(15)	0.95828(13)	0.0467
H(161)	0.76311(12)	0.27972(12)	0.66465(11)	0.0293
H(171)	0.87261(13)	0.37687(12)	0.45036(11)	0.0330
H(191)	0.64097(15)	0.36587(15)	0.33589(13)	0.0466
H(192)	0.56086(15)	0.32151(15)	0.45785(13)	0.0463
H(201)	0.73549(17)	0.09480(16)	0.20995(13)	0.0644
H(202)	0.89124(17)	0.09110(16)	0.29556(13)	0.0642
H(203)	0.84411(17)	0.23173(16)	0.24599(13)	0.0637
H(211)	0.61321(18)	0.02086(15)	0.38615(15)	0.0695
H(212)	0.76452(18)	0.02765(15)	0.48202(15)	0.0706
H(213)	0.62967(18)	0.11841(15)	0.53018(15)	0.0699
H(221)	1.03768(13)	0.41656(14)	0.64923(12)	0.0386
H(231)	1.13638(15)	0.20166(16)	0.64586(15)	0.0670
H(232)	0.97420(15)	0.12998(16)	0.63978(15)	0.0674
H(233)	1.02126(15)	0.19190(16)	0.51739(15)	0.0668
H(241)	1.11285(17)	0.35078(18)	0.84757(14)	0.0737
H(242)	0.98377(17)	0.45630(18)	0.86615(14)	0.0743
H(243)	0.95025(17)	0.29119(18)	0.85416(14)	0.0753

(1*RS*,2*SR*,3*RS*)- *N*-Benzylbicyclo[4.1.0]heptan-2-amine 230



To a degassed solution of **158** (58 mg, 0.20 mmol, 1.0 eq) in 40:4:1 MeOH:H_2O:AcOH (2 mL) was added Pd (10% wt. on C, 29 mg) and the suspension stirred under 1 atm. of H_2 for 16 hrs. The suspension was filtered through Celite® (eluent: MeOH) and the filtrate concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (3 × 10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give **230** as a pale yellow oil (28 mg, 65%); ν_{max} (film) 2930, 2857 (C-H), 1454 (Ar); δ_H (400MHz, $CDCl_3$) 0.19 (1H, app q, *J* 5.3, C(7)H_AH_B), 0.53-0.59 (1H, m, C(7)H_AH_B), 0.78-0.90 (1H, m, C(3)H_AH_B), 1.06-1.22 (3H, m, C(1)*H* and C(6)*H*, C(4)H_AH_B), 1.35-1.45 (2H, m, C(5)H_AH_B and C(4)H_AH_B), 1.52 (1H, br s, N*H*), 1.62-1.68 (1H, m, C(3)H_AH_B), 1.88-1.94 (1H, m, C(5)H_AH_B), 3.08-3.13 (1H, m, C(1)*H*), 3.88 (1H, d, *J* 12.9, NCH_AH_BPh), 3.96 (1H, d, *J* 12.9, NCH_AH_BPh), 7.24-7.27 (1H, m, *p-Ph*), 7.32-7.38 (4H, m, *o/m-Ph*); δ_C (100MHz, $CDCl_3$) 7.5 (*C*(7)), 11.6 (*C*(1)), 15.7 (*C*(6)), 21.6 (*C*(4)), 23.8 (*C*(5)), 27.9 (*C*(3)), 50.8 (N*C*H_2Ph), 51.8 (*C*(2)H), 126.8 (*p-Ph*), 128.2, 128.4 (*o/m-Ph)*, 141.0 (*i-Ph*); *m/z* (ESI^+) 202 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{20}N^+$ ($[M+H]^+$) requires 202.1590, found 202.1588.

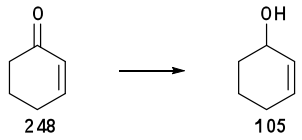
(1*RS*,2*SR*,3*RS*)-Bicyclo[4.1.0]heptan-2-amine trifluoroacetate 231·TFA



Following **General Procedure 8**, **158** (100 mg, 0.34 mmol, 1.0 eq), Pd (10% wt. on C, 50 mg) and TFA (1 mL) were reacted to give **231·TFA** as a pale yellow oil (77 mg, quant.); ν_{max} (film) 3425 (N-H), 2935 (C-H), 1680, 1205, 1140; δ_H (400MHz, $CDCl_3$) 0.38 (1H, app q, *J* 5.0, C(7)H_AH_B), 0.66-0.71 (1H, m, C(7)H_AH_B), 1.05-1.10 (1H, m, C(3)H_AH_B), 1.15-1.26 (3H, m, C(1)*H*, C(6)*H* and C(4)H_AH_B), 1.35-1.43 (1H, m, C(5)H_AH_B), 1.47-1.52 (1H, m, C(4)H_AH_B), 1.74-1.79 (1H, m, C(3)H_AH_B), 1.92-1.97 (1H, m, C(5)H_AH_B), 3.70-3.80 (1H, m, C(2)*H*), 7.62 (3H, br s, NH_3^+); δ_C (100MHz, $CDCl_3$) 8.1 (*C*(7)), 12.1 (*C*(1)), 13.0 (*C*(6)), 20.8 (*C*(4)), 22.1 (*C*(5)), 24.7 (*C*(3)), 49.0 (*C*(2)); trifluoroacetate peaks not observed. *m/z* (FI^+) 112 ($[M+H]^+$, 100%); HRMS (FI^+) $C_7H_{14}N$ ($M+H^+$) requires 112.1126, found 112.1124.

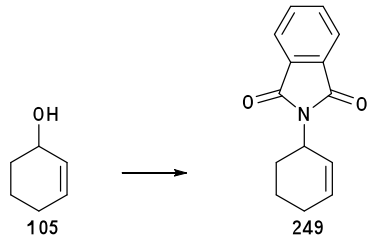
5.4 Experimental for Chapter 3

(*RS*)-Cyclohex-2-en-1-ol 105[11]



To a stirred solution of 2-cyclohexen-1-one **248** (5.04 mL, 52.0 mmol, 1.0 eq) in MeOH (50 mL) at 0 °C was added $CeCl_3 \cdot 7H_2O$ (19.4 g, 52.0 mmol, 1.0 eq) followed by $NaBH_4$ (2.36 g, 62.4 mmol, 1.2 eq) portionwise. The resulting mixture was stirred at 0 °C for 30 mins, then quenched with 0.2 M aq. HCl (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to give **105** as a colourless oil (4.92 g, 97%); δ_H (400MHz, $CDCl_3$) 1.53-1.77 (4H, m, 3 × C*H*$_2$, O*H*), 1.83-2.06 (3H, m, 3 × C*H*$_2$), 4.20 (1H, app s, C(1)*H*), 5.74-5.76 (1H, m, C(2)*H*), 5.83-5.86 (1H, m, C(3)*H*).

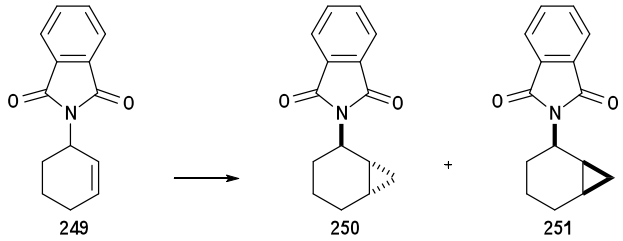
(*RS*)-*N*-(Cyclohex-2-enyl)phthalimide 249[12]



To a stirred solution of alcohol **105** (2.00 g, 20.4 mmol, 1.0 eq) in THF (150 mL) at RT was added phthalimide (6.00 g, 40.8 mmol, 2.0 eq), PPh_3 (10.7 g, 40.8 mmol, 2.0 eq) and DEAD (6.42 mL, 40.8 mmol, 2.0 eq). The resulting solution was stirred at RT for 24 hrs, silica was added and the solvent removed *in vacuo*. The residue was

purified by flash column chromatography (silica, 10% Et_2O/petrol) to give pure **249** as a white crystalline solid (2.32 g, 50%); m.p. 107-109 °C {lit. m.p.[12] 113-114 °C}; δ_H (400MHz, $CDCl_3$) 1.70-1.78 (2H, m, 2 × C*H*$_2$), 1.89-1.97 (2H, m, 2 × C*H*$_2$), 2.06-2.23 (2H, m, 2 × C*H*$_2$), 4.87-4.93 (1H, m, C(1)*H*), 5.56 (1H, app d, *J* 10.2, C(2)*H*), 5.93-5.96 (1H, m, C(3)*H*), 7.69-7.72 (2H, m, C(3′)*H* and C(4′)*H*), 7.82-7.84 (2H, m, C(2′)*H* and C(5′)*H*).

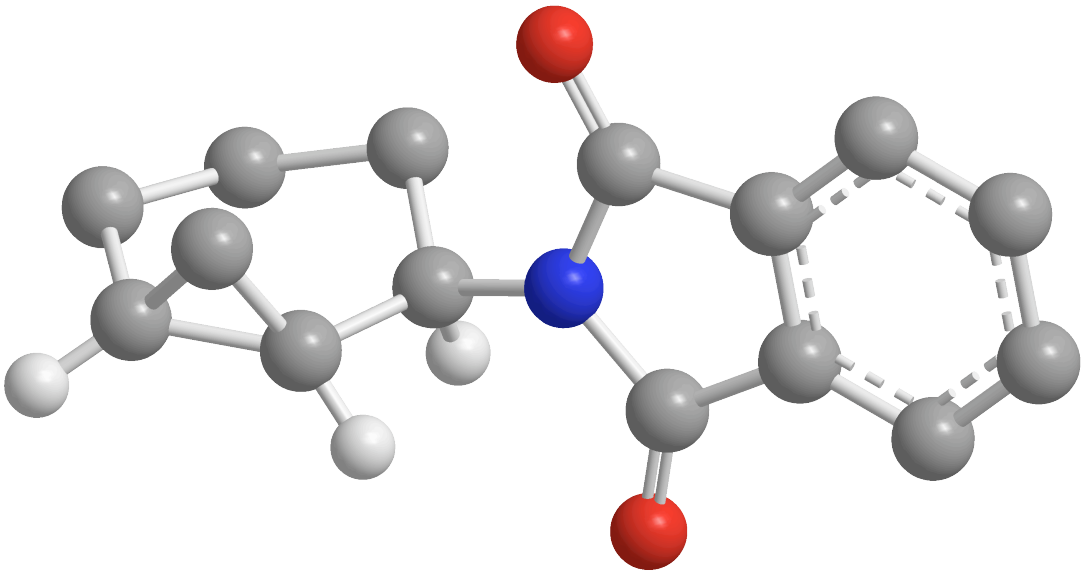
(*RS*)-(1*SR*,2*RS*,3*SR*)-*N*,*N*-Phthalimidobicyclo[4.1.0]heptan-2-amine 250 and (*RS*)-(1*RS*,2*RS*,3*SR*)-*N*,*N*-phthalimidobicyclo[4.1.0]heptan-2-amine 251



Following **General Procedure 3**, **249** (455 mg, 2.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 4.0 mL, 4.0 mmol, 2.0 eq), CH_2I_2 (0.64 mL, 8.0 mmol, 4.0 eq) and TFA (0.30 mL, 4.0 mmol, 2.0 eq) in CH_2Cl_2 (4.0 mL) for 3 hrs gave a crude product containing **250** and **251** in a ratio of 83:17 as well as 38% starting material. The crude product was purified by flash column chromatography (silica, 10% Et_2O/petrol) to give **251** as a white crystalline solid (38 mg, 8%, 90:10 d.r.) and an inseparable 51:49 mixture of **250** and starting material **249** (311 mg, 33% yield for **250** based on a mole ratio); data for **250**; ν_{max} (KBr) 2940 (C-H), 1709 (imide); δ_H (400MHz, $CDCl_3$) 0.18 (1H, app q, *J* 5.3, C(7)*H*$_A$H$_B$), 0.62-0.68 (1H, m, C(7)H$_A$*H*$_B$), 1.01-1.13 (2H, m, C(1)*H* and C(4)*H*$_A$H$_B$), 1.18-1.25 (1H, m, C(6)*H*), 1.51-1.58 (2H, m, C(4)H$_A$*H*$_B$ and C(3)*H*$_A$H$_B$), 1.75-1.91 (3H, m, C(3)H$_A$*H*$_B$ and C(5)*H*$_2$), 4.28 (1H, app dd, *J* 11.5, 5.7, C(2)*H*), 7.69-7.71 (2H, m, *Ar*), 7.82-7.84 (2H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 9.3

(*C*(7)), 11.3 (*C*(6)), 14.5 (*C*(1)), 18.1 (*C*(4)), 22.3 (*C*(5)), 27.0 (*C*(3)), 47.9 (*C*(2)), 123.1 (*C*(3′) and *C*(4′)), 132.1 (*C*(2′) and *C*(5′)), 133.8 (*C*(1′) and *C*(6′)), 168.2 (*C*=O); *m/z* (FI^+) 241 (M^+, 100%); HRMS (FI^+) $C_{15}H_{15}NO_2$ (M^+) requires 241.1103, found 241.1110; data for **251**; m.p. 140-142 °C; ν_{max} (KBr) 2947 (C-H), 1707 (imide); δ_H (400MHz, $CDCl_3$) 0.65-0.71 (1H, m, C(7)H_AH_B), 0.89 (1H, app q, *J* 5.2, C(7)H_AH_B), 1.03-1.12 (2H, m, C(1)*H* and C(6)*H*), 1.23-1.36 (1H, m, C(4)H_AH_B), 1.45-1.55 (2H, m, C(5)H_AH_B and C(3)H_AH_B), 1.63-1.72 (1H, m, C(4)H_AH_B), 1.97-2.02 (1H, m, C(5)H_AH_B), 2.09-2.19 (1H, m, C(3)H_AH_B), 4.72-4.77 (1H, m, C(2)*H*), 7.68-7.70 (2H, m, *Ar*), 7.81-7.83 (2H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 11.1 (*C*(6)), 11.2 (*C*(7)), 14.8 (*C*(1)), 23.0 (*C*(5)), 23.3 (*C*(3)), 23.9 (*C*(4)), 49.6 (*C*(2)), 123.0 (*C*(3′) and *C*(4′)), 132.2 (*C*(2′) and *C*(5′)), 133.7 (*C*(1′) and *C*(6′)), 168.9 (*C*=O); *m/z* (FI^+) 241 (M^+, 100%); HRMS (FI^+) $C_{15}H_{15}NO_2$ (M^+) requires 241.1103, found 241.1111.

X-Ray crystal structure data for (1*RS*,2*RS*,3*SR*)-251 (Some H atoms omitted for clarity)



X-ray crystal structure determination for 251

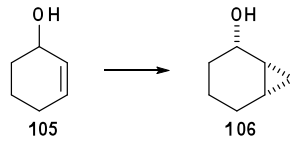
Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[2]

X-ray crystal structure data for **251** [$C_{15}H_{15}NO_2$]: M = 120.64, monoclinic, space group *P 21/m*, a = 8.5766(3) Å, b = 7.0349(3) Å, c = 10.694(5) Å, V = 604.40(4) Å^3, Z = 2, μ = 0.088 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.3 mm^3. A total of 1468 unique reflections were measured for $5 < \theta < 27$ and 1206 reflections were used in the refinement. The final parameters were wR_2 = 0.205 and R_1 = 0.104 [I>2.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr K. B. Ling, Chemistry Research Laboratory, University of Oxford, U.K.

Fractional atomic co-ordinates and equivalent isotropic displacement parameters (Å^2) (e.s.d. in parentheses)

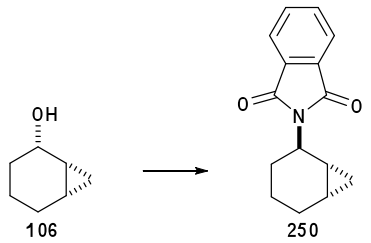
Atom	x/a	y/b	z/c	U(iso)	Occ
N(1)	0.1574(4)	0.2500	0.3577(3)	0.0544	1.0000
C(1)	0.2856(5)	0.2500	0.3046(4)	0.0461	1.0000
C(2)	0.4429(4)	0.2500	0.4211(4)	0.0373	1.0000
C(3)	0.6059(5)	0.2500	0.4278(5)	0.0516	1.0000
C(4)	0.7271(5)	0.2500	0.5535(5)	0.0569	1.0000
C(5)	0.6859(5)	0.2500	0.6676(5)	0.0562	1.0000
C(6)	0.5213(5)	0.2500	0.6609(4)	0.0572	1.0000
C(7)	0.4016(4)	0.2500	0.5356(4)	0.0420	1.0000
C(8)	0.2189(5)	0.2500	0.4960(4)	0.0576	1.0000
O(1)	0.2702(4)	0.2500	0.1882(3)	0.0701	1.0000
O(2)	0.1353(4)	0.2500	0.5676(3)	0.0883	1.0000
C(9)	-0.0236(6)	0.2063(10)	0.2855(5)	0.0467	0.5000
C(10)	-0.1019(8)	0.3973(13)	0.2540(9)	0.0651	0.5000
C(11)	-0.2549(19)	0.455(2)	0.1398(13)	0.0776	0.5000
C(12)	-0.3279(8)	0.2909(18)	0.0490(6)	0.0782	0.5000
C(13)	-0.2561(19)	0.088(2)	0.1022(12)	0.0830	0.5000
C(14)	-0.0635(10)	0.0691(16)	0.1780(10)	0.0769	0.5000
C(15)	-0.0996(12)	0.4943(19)	0.1367(11)	0.0957	0.5000
H(31)	0.6360	0.2500	0.3450	0.0640	1.0000
H(41)	0.8467	0.2500	0.5613	0.0676	1.0000
H(51)	0.7760	0.2500	0.7569	0.0637	1.0000
H(61)	0.4908	0.2500	0.7436	0.0675	1.0000
H(91)	-0.0714	0.1307	0.3432	0.0545	0.5000
H(101)	-0.0678	0.4130	0.3530	0.0738	0.5000
H(111)	-0.3574	0.5296	0.1316	0.0850	0.5000
H(121)	-0.4499	0.2887	0.0327	0.0851	0.5000
H(122)	-0.3086	0.3134	-0.0373	0.0851	0.5000
H(131)	-0.3129	0.0450	0.1650	0.0867	0.5000
H(132)	-0.2853	0.0013	0.0234	0.0867	0.5000
H(141)	-0.0355	-0.0622	0.2144	0.0831	0.5000
H(142)	-0.0010	0.0985	0.1163	0.0831	0.5000
H(151)	-0.0610	0.6296	0.1445	0.1068	0.5000
H(152)	-0.0595	0.4258	0.0715	0.1068	0.5000

(*RS*)-(1*SR*, 2*RS*,*6RS*)-Bicyclo[4.1.0]heptan-2-ol 106[13]



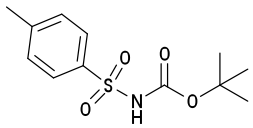
Following **General Procedure 2**, **105** (491 mg, 5.00 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 10.0 mL, 10.0 mmol, 2.0 eq) and $ClCH_2I$ (1.46 mL, 20.0 mmol, 4.0 eq) in CH_2Cl_2 (10.0 mL) gave a crude product which was purified by flash column chromatography (silica, 20% Et_2O/petrol) to give pure **106** as a colourless oil (313 mg, 56%); δ_H (400MHz, $CDCl_3$) 0.27-0.31 (1H, m, C(7)H_AH_B), 0.53-0.59 ((1H, m, C(7)H_AH_B), 0.92-1.01 (1H, m, 1 × CH_2), 1.11-1.28 (3H, m, 3 × CH_2), 1.39-1.41 (2H, m, 2 × CH_2), 1.50-1.64 (2H, m, 1 × CH_2 and O*H*), 1.80-1.87 (1H, m, 1 × CH_2), 4.16-4.21 (1H, m, C(2)*H*).

(*RS*)-(1*RS*,2*RS*,3*SR*)-*N*,*N*-Phthalimidobicyclo[4.1.0]heptan-2-amine 250



To a stirred solution of phthalimide (809 mg, 5.50 mmol, 1.1 eq) in THF (100 mL) was added PPh_3 (1.44 g, 5.5 mmol, 1.1 eq), **106** (561 mg, 5.00 mmol, 1.0 eq) and DEAD (0.87 mL, 5.50 mmol, 1.1 eq). The resulting mixture was stirred at RT for 24 hrs then silica was added, the solvent removed *in vacuo* and the residue purified by flash column chromatography (silica, 5% Et_2O/petrol) to give pure **250** as a white solid (600 mg, 50%) with identical spectroscopic properties to **250** above; m.p. 130-132 °C.

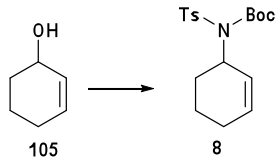
tert-Butyl tosylcarbamate 255[14]



255

To a stirred suspension of *p*-toluenesulfonamide (17.1 g, 100 mmol,1.0 eq) in CH_2Cl_2 (250 mL) was added DMAP (1.22 g, 10.0 mmol, 0.10 eq), NEt_3 (15.3 mL, 110 mmol, 1.10 eq) and di-*tert*-butyldicarbonate (25.1 g, 115 mmol, 1.15 eq). The resulting mixture was stirred at RT for 2 hrs then concentrated *in vacuo*. The residue was redissolved in EtOAc (500 mL) and washed with 1 M aq. HCl (250 mL), H_2O (250 mL) and brine (250 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give **255** as a white crystalline solid (26.8 g, 99%); m.p. 113-115 °C {lit. m.p.[14] 117-119 °C}; 1.39 (9H, s, C*Me*$_3$), 2.46 (3H, s, Ar*Me*), 7.16 (1H, br s, N*H*), 7.34 (2H, d, *J* 8.2, *m-Ar*), 7.90 (2H, d, *J* 8.2, *o-Ph*).

tert-Butyl (*RS*)-cyclohex-2-en-1-yl[(4′-methylphenyl)sulfonyl]carbamate 8[15]

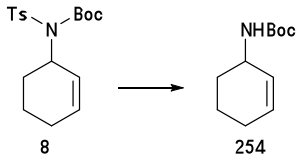


105 8

To a stirred solution of **255** (20.3 g, 75.0 mmol, 1.5 eq) in THF (100 mL) was added PPh_3 (26.2 g, 100 mmol, 2.0 eq), **105** (4.91 mL, 50.0 mmol, 1.0 eq) and DEAD (11.8 mL, 75.0 mmol, 1.5 eq). The resulting mixture was stirred at RT for 24 hrs then silica was added, the solvent removed *in vacuo* and the residue purified by flash column chromatography (silica, 10% Et_2O/petrol) to give pure **8** as a white solid (17.4 g, quant.); m.p. 84-86 °C; δ_H (400MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.71-1.78 (1H, m, 1 × C*H*$_2$), 1.88-1.93 (1H, m, 1 × C*H*$_2$), 2.00-2.08 (3H, m, 3 × C*H*$_2$), 2.17-2.27 (1H, m, 1

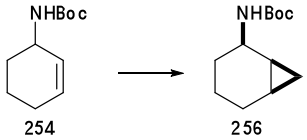
× CH_2), 2.45 (3H, s, C(4')*Me*), 5.10-5.12 (1H, m, C(1)*H*), 5.49-5.54 (1H, m,C(2)*H*), 5.73-5.76 (1H, m, C(3)*H*), 7.31 (2H, d, *J* 8.2, C(3′)*H* and C(5′)*H*), 7.82 (2H, d, *J* 8.2, C(2′)*H* and C(6′)*H*).

***tert*-Butyl (*RS*)-cyclohex-2-en-1-ylcarbamate 254**[15]



To a stirred solution of naphthalene (6.41 g, 50.0 mmol, 5.0 eq) in THF (50 mL) at 0°C was added sodium (1.15 g, 50.0 mmol, 5.0 eq) and the mixture stirred for 30 mins at RT. To this was added a solution of **8** (3.51 g, 10.0 mmol, 1.0 eq) in THF (50 mL) and the resulting solution stirred for 2 hrs at RT before the addition of H_2O (50 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 20% Et_2O/petrol) to give **254** as a white solid (1.65 g, 47 %); mp 32-34 °C; δ_H (400MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.49-1.55 (1H, m, 1 × CH_2), 1.62-1.63 (2H, m, 2 × CH_2), 1.85-1.93 (1H, m, 1 × CH_2), 1.97-1.99 (2H, m, 2 × CH_2), 4.15 (1H, br s, C(1)*H*), 4.53 (1H, br s, N*H*), 5.61 (1H, dd, *J* 9.9, 2.4, C(2)*H*), 5.80-5.83 (1H, m, C(3)*H*).

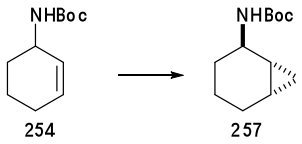
***tert*-Butyl (1*RS*,2*RS*,3*SR*)-Bicyclo[4.1.0]heptan-2-ylcarbamate 256**



Following **General Procedure 1**, **254** (197 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2

(2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to yield pure **256** as a white crystalline solid (141 mg, 67%, >98:2 d.r.); m.p. 41-43 °C; ν_{max} (film) 3343 (N-H), 2933 (C-H), 1701 (amide); δ_H (500MHz, $CDCl_3$) 0.04-0.06 (1H, m, C(7)H_AH_B), 0.48-0.52 (1H, m, C(7)H_AH_B), 0.77 (1H, app q, *J* 11.6, C(3)H_AH_B), 1.02-1.07 (1H, m, C(6)*H*), 1.11-1.20 (2H, m, C(1)*H* and C(4)H_AH_B), 1.28-1.36 (2H, m, C(5)H_AH_B and C(4)H_AH_B), 1.42 (9H, br s, CMe_3), 1.69 (1H, br s, C(3)H_AH_B), 1.84-1.87 (1H, m, C(5)H_AH_B), 3.98 (1H, br s, C(2)*H*), 4.53 (1H, br s, N*H*); δ_C (125MHz, $CDCl_3$) 7.8 (*C*(7)), 11.6 (*C*(6)), 15.5 (*C*(1)), 21.5 (*C*(4)), 23.0 (*C*(5)), 27.5 (*C*(3)), 28.4 (CMe_3), 46.5 (*C*(2)), 78.8 (*C*Me_3), 155.3 (*C*=O); *m/z* (ESI^+) 270 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{12}H_{21}NNaO_2$ ($[M+Na]^+$) requires 234.1465, found 234.1465.

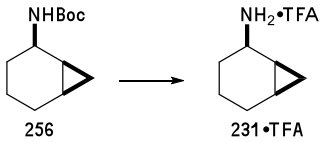
***tert*-Butyl (1*RS*,2*RS*,3*SR*)-Bicyclo[4.1.0]heptan-2-ylcarbamate 257**



Following **General Procedure 3**, **254** (197 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to give **257** as a white crystalline solid (148 mg, 70%, >98:2 d.r.); m.p. 40-42 °C; ν_{max} (film) 3333 (N-H), 2933 (C-H), 1703 (amide); δ_H (500MHz, $CDCl_3$) −0.03-(−)0.02 (1H, m, C(7)H_AH_B), 0.52-0.57 (1H, m, C(7)H_AH_B), 0.70-0.74 (1H, m, C(1)*H*), 0.83-0.88 (1H, m, C(6)*H*), 0.99-1.03 (1H, m, C(4)H_AH_B), 1.06-1.12 (1H, m, C(3)H_AH_B), 1.24-1.32 (1H, m, C(4)H_AH_B), 1.37 (9H, br s, CMe_3), 1.39-1.44 (1H, m, C(3)H_AH_B), 1.51-1.56 (1H, m, C(5)H_AH_B), 1.68-1.75 (1H, m, C(5)H_AH_B), 3.71 (1H, br s, C(2)*H*), 4.76 (1H, br s,

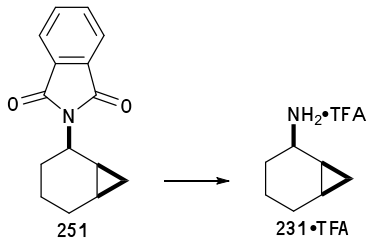
N*H*); δ_C (125MHz, $CDCl_3$) 9.2 (*C*(7)), 9.7 (*C*(6)), 16.3 (*C*(1)), 16.9 (*C*(4)), 24.8 (*C*(5)), 28.0 (*C*(3)), 28.4 (C*Me*$_3$), 46.4 (*C*(2)), 78.9 (*C*Me$_3$), 155.2 (*C*=O); *m/z* (ESI^+) 270 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{12}H_{21}NNaO_2$ ($[M+Na]^+$) requires 234.1465, found 234.1465.

(1*RS*,2*SR*,3*RS*)-Bicyclo[4.1.0]heptan-2-amine trifluoroacetate 231·TFA



Method A:

Toa stirred solution of **256** (30 mg, 0.14 mmol, 1.0 eq) in CH_2Cl_2 (1.0 mL) at 0 °C was added TFA (0.03 mL, 0.43 mmol, 3.0 eq) and the resulting solution allowed to stir at 0 °C for 3 hrs. The mixture was allowed to warm to RT and concentrated *in vacuo* to give **231·TFA** as a yellow oil (32 mg, quant.); identical spectroscopic properties to those described previously.

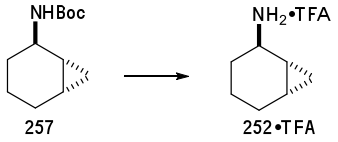


Method B:

To a stirred solution of **251** (34 mg, 0.15 mmol, 1.0 eq) in MeOH (2 mL) was added $N_2H_4.H_2O$ (8 μL, 0.16 mmol, 1.1 eq) and the resulting suspension stirred at reflux for 16 hrs. The reaction mixture was allowed to cool to RT, filtered, and the filtrate concentrated *in vacuo*. The residue was triturated with cold $CHCl_3$ (3 ×) and the organic extracts acidified with TFA (1 mL). The mixture was concentrated *in vacuo* to

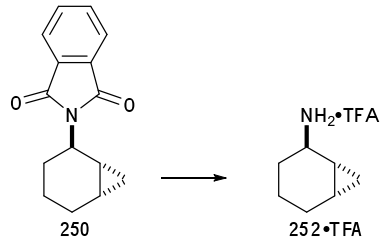
give crude **231·TFA** as a pale yellow oil. No further purification was attempted. ^{1}H NMR spectroscopic analysis of the crude product showed that the amine trifluroacetate formed had identical spectroscopic properties to **231·TFA** above, but contained impurities in the aromatic region.

(1*SR*,2*SR*,3*RS*)-Bicyclo[4.1.0]heptan-2-amine trifluoroacetate 252·TFA



Method A:

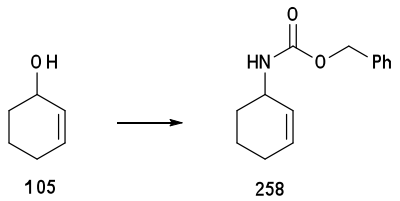
To a stirred solution of **257** (30 mg, 0.14 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at 0 °C was added TFA (0.03 mL, 0.43 mmol, 3.0 eq) and the resulting mixture stirred at 0 °C for 3 hrs. The mixture was then concentrated *in vacuo* to give **252·TFA** as a yellow oil (32 mg, quant.); ν_{max} (film) 3440 (N-H), 1680 (C=O), 1440, 1205, 1140; δ_H (400MHz, $CDCl_3$) 0.13 (1H, app d, *J* 4.6, C(7)H_AH_B), 0.72-0.77 (1H, m, C(7)H_AH_B), 0.87-0.91 (1H, m, C(1)*H*), 1.06-1.12 (2H, m, C(6)*H*, C(4)H_AH_B), 1.28-1.37 (1H, m, C(3)H_AH_B), 1.44-1.49 (1H, m, C(4)H_AH_B), 1.65-1.71 (2H, m, C(5)H_AH_B, C(3)H_AH_B), 1.80-1.88 (1H, m, C(5)H_AH_B), 3.44-3.48 (1H, m, C(2)*H*), 7.89 (3H, br s, NH_3^+); δ_C (100MHz, $CDCl_3$) 9.0 (*C*(7)), 10.1 (*C*(6)), 12.9 (*C*(1)), 15.7 (*C*(4)), 21.9 (*C*(5)), 26.3 (*C*(3)), 48.2 (*C*(2)). *m/z* (FI^+) 112 ($[M+H]^+$, 100%); HRMS (FI^+) $C_7H_{15}N$ ($M+H^+$) requires 111.1126, found 111.1124.



Method B:

To a stirred solution of **250** (50 mg, 0.21 mmol, 1.0 eq) in MeOH (2 mL) was added $N_2H_4.H_2O$ (11 μL, 0.23 mmol, 1.1 eq) and the resulting solution heated at reflux for 16 hrs. The reaction mixture was allowed to cool to RT, filtered, and the filtrate concentrated *in vacuo*. The residue was triturated with cold $CHCl_3$ (3 ×) and the organic extracts acidified with TFA (1 mL). The mixture was concentrated *in vacuo* to give crude **252·TFA** as a pale yellow oil. No further purification was attempted. ^{1}H NMR spectroscopic analysis of the crude product showed that the amine trifluroacetate formed had identical spectroscopic properties to **252·TFA** above, but contained impurities in the aromatic region.

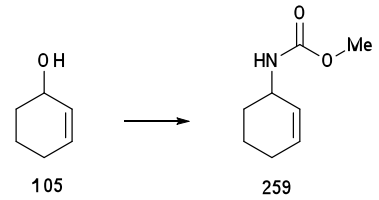
Benzyl (*RS*)-cyclohex-2-en-1-ylcarbamate 258[16]



Following **General Procedure 9**, **105** (0.98 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.5 mmol, 0.05 eq), KPF_6 (92 mg, 0.5 mmol, 0.05 eq), benzyl carbamate **285** (2.27 g, 15.0 mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **258** as a white solid (1.92 g, 83%); m.p. 65-67 °C; δ_H (400

MHz, $CDCl_3$) 1.01-1.93 (3H, m, 3 × C*H*$_2$), 1.45-1.64 (3H, m, 3 × C*H*$_2$), 4.22 (1H, br s, C(1)*H*), 5.02-5.09 (2H, m, OC*H*$_2$Ph), 5.39 (1H, br s, N*H*), 5.58 (1H, d, *J* 9.9, C(2)*H*), 5.74-5.79 (1H, m, C(3)*H*), 7.23-7.29 (5H, m, *Ph*).

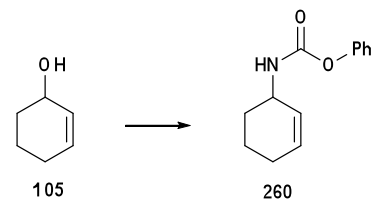
Methyl (*RS*)-cyclohex-2-en-1-ylcarbamate 259[16]



105 259

Following **General Procedure 9**, **105** (0.98 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.5 mmol, 0.05 eq), KPF_6 (92 mg, 0.5 mmol, 0.05 eq), methyl carbamate (1.13 g, 15.0 mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **259** as a white crystalline solid (1.21 g, 78%); m.p. 25-26 °C; ν_{max} (film) 3325 (N-H), 3025, 2940 (C-H), 1700 (C=O), 1530, 1450, 1310, 1240, 1070, 1010, 780, 725, 685; δ_H (400 MHz, $CDCl_3$) 1.47-1.55 (1H, m, C*H*$_2$), 1.56-1.66 (2H, m, C*H*$_2$), 1.84-1.92 (1H, m, C*H*$_2$), 1.94-2.00 (2H, m, C*H*$_2$), 3.64 (3H, s, O*Me*), 4.18 (1H, br s, C(1)*H*), 4.75 (1H, br s, N*H*), 5.58 (1H, dd, *J* 9.9, 2.0, C(2)*H*), 5.78-5.83 (1H, m, C(3)*H*).

Phenyl (*RS*)-cyclohex-2-en-1-ylcarbamate 260

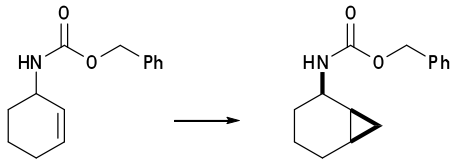


105 260

Following **General Procedure 9**, **105** (0.98 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.5 mmol, 0.05 eq), KPF_6 (92 mg, 0.5 mmol, 0.05 eq), phenyl carbamate (2.06 g, 15.0

mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **260** as a white solid (1.23 g, 57%); m.p. 108-110 °C; ν_{max} (KBr) 3330 (N-H), 3020, 2930, 2870 (C-H), 1735 (C=O), 1530, 1495 (Ar), 1340, 1210, 975, 725, 665; δ_H (400 MHz, $CDCl_3$) 1.61-1.70 (3H, m, C(5)H_2 and C(6)H_AH_B), 1.95-2.04 (3H, m, C(4)H_2 and C(6)H_AH_B), 4.29-4.50 (1H, m, C(1)*H*), 5.03 (1H, d, *J* 6.8, N*H*), 5.69-5.71 (1H, m, C(2)*H*), 5.88-5.93 (1H, m, C(3)*H*), 7.15 (2H, d, *J* 7.7, *o-Ph*), 7.20 (1H, t, *J* 7.5, *p-Ph*), 7.36 (2H, t, *J* 7.7, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (*C*(5)), 24.8 (*C*(6)), 29.6 (*C*(4)), 46.6 (*C*(1)), 121.6 (*o-Ph*), 125.2 (*p-Ph*), 127.4 (*C*(2)), 129.3 (*m-Ph*), 131.1 (*C*(3)), 151.0 (*i-Ph*), 153.8 (*C*=O); *m/z* (ESI^+) 276 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{13}H_{15}NNaO_2$ ($M+Na^+$) requires 240.0995, found 240.0997.

Benzyl (1*SR*,2*RS*,6*RS*)-bicyclo[4.1.0]hept-2-ylcarbamate 261

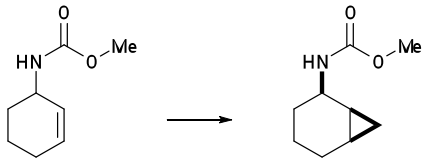


258 261

Following **General Procedure 1**, **258** (231 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 20% EtOAc/petrol) to give **261** as a white solid (206 mg, 84%, >98:2 d.r.); m.p. 48-50 °C; ν_{max} (KBr) 3330 (N-H), 2935, 2360 (C-H), 1695 (C=O), 1530, 1240, 1045, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.09 (1H, q, *J* 5.1, C(7)H_AH_B), 0.51-0.57 (1H, m, C(7)H_AH_B), 0.78-0.87 (1H, m, C(3)H_AH_B), 1.06-1.14 (1H, m, C(6)*H*), 1.14-1.25 (2H, m, C(1)*H* and C(4)H_AH_B), 1.28-1.42 (2H, m, C(5)H_AH_B and C(4)H_AH_B), 1.70-1.79 (1H, m, C(3)H_AH_B), 1.86-1.96 (1H, m,

C(5)H$_A$*H*$_B$), 4.06-4.15 (1H, m, C(2)*H*), 4.88 (1H, d, *J* 6.3, N*H*), 5.11 (2H, s, C*H*$_2$Ph), 7.30-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.9 (*C*(7)), 11.7 (*C*(6)), 15.4 (*C*(1)), 21.5 (*C*(4)), 22.9 (*C*(5)), 27.4 (*C*(3)), 47.2 (*C*(2)), 66.4 (O*C*H$_2$Ph), 128.0, 128.2, 128.5 (*Ph*), 136.7 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI$^+$) 268 ([M+Na]$^+$, 40%), 304.2 ([M+NH$_4$+MeCN]$^+$, 100%), 513 ([2M+Na]$^+$, 30%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_2$ (M+Na$^+$) requires 268.1308, found 268.1309.

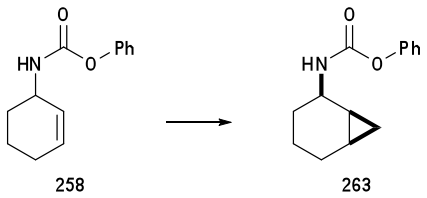
Methyl (1*SR*,2*RS*,6*RS*)-bicyclo[4.1.0]hept-2-ylcarbamate 262



258 262

Following **General Procedure 1**, **259** (155 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (2.0 mL, 1.0M in hexanes, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 20% EtOAc/petrol) to give **262** as a colourless oil (167 mg, 99%, >98:2 d.r.); ν_{max} (film) 3320 (N-H), 3015, 2930, 2855 (C-H), 1700 (C=O), 1540, 1460, 1250, 1045, 780, 645; δ_H (400 MHz, $CDCl_3$) 0.05 (1H, app q, *J* 5.2, C(7)*H*$_A$H$_B$), 0.49 (1H, td, *J* 8.8, 4.7, C(7)H$_A$*H*$_B$), 0.76 (1H, m, C(3)*H*$_A$H$_B$), 1.00-1.18 (3H, m, C(1)*H*, C(4)*H*$_A$H$_B$ and C(6)*H*), 1.24-1.38 (2H, m, C(4)H$_A$*H*$_B$ and C(5)*H*$_A$H$_B$), 1.64-1.72 (1H, m, C(3)H$_A$*H*$_B$), 1.82-1.89 (1H, m, C(5)H$_A$*H*$_B$), 3.60 (3H, s, O*Me*), 3.97-4.04 (1H, m, C(2)*H*), 4.78 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 7.8 (*C*(7)), 11.6 (*C*(1)), 15.4 (*C*(6)), 21.5 (*C*(4)), 22.9 (*C*(5)), 27.3 (*C*(3)), 47.0 (*C*(2)), 51.7 (O*Me*), 156.4 (*C*=O); *m/z* (ESI$^+$) 192 ([M+Na]$^+$, 80%), 361 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{15}NNaO_2$, (M+Na$^+$) requires 192.0995, found 192.0998.

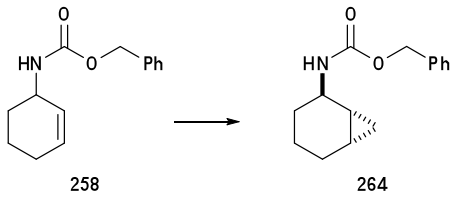
Phenyl (1*SR*,2*RS*,6*RS*)-bicyclo[4.1.0]hept-2-ylcarbamate 263



258 263

Following **General Procedure 1**, **260** (217 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **263** as a white solid (229 mg, 99%, >98:2 d.r.); m.p. 101-103 °C; ν_{max} (KBr) 3310 (N-H), 2930 (C-H), 1705 (C=O), 1535, 1495, 1215, 1020, 990, 795, 665; δ_H (400MHz, $CDCl_3$) 0.17 (1H, app t, *J* 5.1, C(7)H_AH_B), 0.61 (1H, app t, *J* 8.7, 4.7, C(7)H_AH_B), 0.86-0.95 (1H, m, C(3)H_AH_B), 1.11-1.29 (3H, m, C(1)*H*, C(4)H_AH_B and C(6)*H*), 1.33-1.45 (2H, m, C(4)H_AH_B and C(5)H_AH_B), 1.81-1.89 (1H, m, C(3)H_AH_B), 1.89-1.99 (1H, m, C(5)H_AH_B), 4.11-4.19 (1H, m, C(2)*H*), 5.07-5.08 (1H, m, N*H*), 7.11-7.21 (3H, m, *o/p-Ph*), 7.36 (2H, app t, *J* 7.8, *m-Ph*); δ_C (100MHz, $CDCl_3$) 7.9 (*C*(7)), 11.8 (*C*(6)), 15.3 (*C*(1)), 21.4 (*C*(4)), 22.9 (*C*(5)), 27.3 (*C*(3)), 47.5 (*C*(2)), 121.6 (*o-Ph*), 125.1 (*p-Ph*), 129.2 (*m-Ph*), 151.1 (*i-Ph*), 153.9 (*C*=O); *m/z* (ESI^+) 232 ($[M+H]^+$, 40%), 485 $(2M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_2$ ($M+Na^+$) requires 254.1151, found 254.1154.

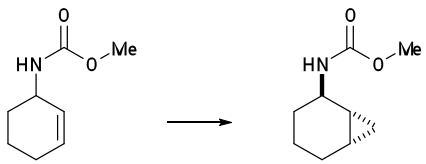
Benzyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 264



258 264

Following **General Procedure 3**, **258** (231 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 4 hrs gave a crude product which was purified by flash column chromatography (silica, 20% EtOAc/petrol) to give **264** as a white solid (218 mg, 89%, 98:2 d.r.); m.p. 44-45 °C; ν_{max} (KBr) 3330 (N-H), 2935 (C-H), 1700 (C=O), 1530, 1240, 1090, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.09 (1H, app d, *J* 5.0, C(7)H_AH_B), 0.63-0.68 (1H, m, C(7)H_AH_B), 0.80-0.85 (1H, m, C(1)*H*), 0.92-0.97 (1H, m, C(6)*H*), 1.06-1.13 (1H, m, C(4)H_AH_B), 1.20-1.26 (1H, m, C(3)H_AH_B), 1.37 (1H, dd, *J* 13.2, 6.9, C(4)H_AH_B), 1.50-1.54 (1H, m, C(3)H_AH_B), 1.60-1.66 (1H, m, C(5)H_AH_B), 1.79-1.84 (1H, m, C(5)H_AH_B), 3.89-3.93 (1H, m, C(2)*H*), 5.08-5.18 (3H, m, N*H* and OCH_2Ph), 7.29-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (*C*(7)), 9.7 (*C*(6)), 16.1 (*C*(1)), 16.8 (*C*(4)), 22.7 (*C*(5)), 27.9 (*C*(3)), 46.9 (*C*(2)), 66.5 (O*C*H_2Ph), 128.0, 128.1, 128.5 (*Ph*), 136.7 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI^+) 268 ($[M+Na]^+$, 60%), 304.2 ($[M+NH_4+MeCN]^+$, 100%), 513 ($[2M+Na]^+$, 80%); HRMS (ESI^+) $C_{15}H_{19}NNaO_2$ ($M+Na^+$) requires 268.1308, found 268.1308.

Methyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 265

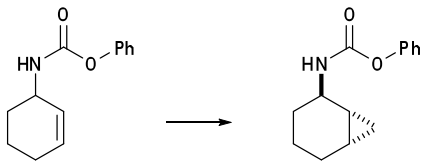


258 265

Following **General Procedure 3**, **259** (100 mg, 0.64 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.93 mL, 1.93 mmol, 3.0 eq), CH_2I_2 (0.31 mL, 3.87 mmol, 6.0 eq), TFA (0.15 mL, 1.93 mmol, 3.0 eq) in CH_2Cl_2 (2.0 mL) for 4 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **265** as a white crystalline solid (90 mg, 83%, 98:2 d.r.); m.p.

50-52 °C; ν_{max} (KBr) 3305 (N-H), 1690 (C=O), 1540, 1255, 1095, 665; δ_H (400MHz, $CDCl_3$) 0.01-0.05 (1H, m, C(7)H_AH_B), 0.59 (1H, td, *J* 9.2, 4.9, C(7)H_AH_B), 0.73-0.79 (1H, m, C(1)*H*), 0.87-0.95 (1H, m, C(6)*H*), 1.00-1.09 (1H, m, C(4)H_AH_B), 1.13-1.22 (1H, m, C(3)H_AH_B), 1.27-1.37 (1H, m, C(4)H_AH_B), 1.42-1.49 (1H, m, C(3)H_AH_B), 1.55-1.61 (1H, m, C(5)H_AH_B), 1.77 (1H, app dq, *J* 13.7, 6.9, C(5)H_AH_B), 3.62 (3H, s, O*Me*), 3.79-3.85 (1H, br m, C(2)*H*), 5.08 (1H, br s, N*H*); δ_C (100MHz, $CDCl_3$) 9.2 (*C*(7)), 9.7 (*C*(6)), 16.1 (*C*(1)), 16.7 (*C*(4)), 22.6 (*C*(5)), 27.9 (*C*(3)), 46.8 (*C*(2)), 51.7 (O*Me*), 156.3 (*C=O*); *m/z* (ESI^+) 170 ($[M+H]^+$, 25%), 192 ($[M+Na]^+$, 40%), 339 ($[2M+H]^+$, 30%), 361 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_9H_{15}NNaO_2$, ($M+Na^+$) requires 192.0995, found 192.0999.

Phenyl (1*RS*,2*RS*,6*SR*)-bicyclo[4.1.0]hept-2-ylcarbamate 266

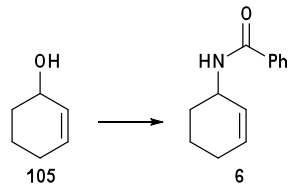


258 266

Following **General Procedure 3**, **260** (100 mg, 0.46 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.38 mL, 1.38 mmol, 3.0 eq), CH_2I_2 (0.22 mL, 2.76 mmol, 6.0 eq) and TFA (0.11 mL, 1.38 mL, 3.0 eq) in CH_2Cl_2 (1.5 mL) for 4 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **266** as a white solid (80 mg, 75%, 95:5 d.r.); m.p. 110-112 °C; ν_{max} (KBr) 3320 (N-H), 2930 (C-H), 1710 (C=O), 1540, 1490, 1215, 690, 665; δ_H (400MHz, $CDCl_3$) 0.12 (1H, app q, *J* 5.3, C(7)H_AH_B), 0.69 (1H, td, *J* 9.2, 5.0, C(7)H_AH_B), 0.87-0.93 (1H, m, C(1)*H*), 0.97-1.05 (1H, m, C(6)*H*), 1.11-1.20 (1H, m, C(4)H_AH_B), 1.25-1.37 (1H, m, C(3)H_AH_B), 1.37-1.46 (1H, m, C(4)H_AH_B), 1.54-1.73 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 1.87 (1H, app dq, *J* 13.7, 6.8, C(5)H_AH_B), 3.97 (1H, app q, *J* 6.3, C(2)*H*),

5.36 (1H, br d, *J* 6.9, N*H*), 7.14-7.21 (3H, m, *Ph*), 7.36 (2H, t, *J* 7.8, *Ph*); δ_C (100MHz, $CDCl_3$) 9.4 (*C*(7)), 9.7 (*C*(6)), 16.0 (*C*(1)), 16.8 (*C*(4)), 22.7 (*C*(5)), 27.7 (*C*(3)), 47.1 (*C*(2)), 121.6 (*o-Ph*), 125.2 (*p-Ph*), 129.2 (*m-Ph*), 151.1 (*i-Ph*), 153.8 (*C=O*); *m/z* (ESI^+) 232 ($[M+H]^+$, 30%), 290 ($[M+MeCN+NH_4]^+$, 60%), 485 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_2$ ($M+Na^+$) requires 254.1151, found 254.1163.

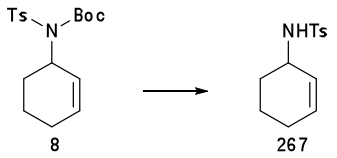
(*RS*)-*N*-(Cyclohex-2-en-1-yl)benzamide 6[16]



105 6

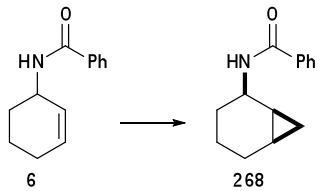
Following **General Procedure 9**, **105** (0.98 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.5 mmol, 0.05 eq), KPF_6 (92 mg, 0.5 mmol, 0.05 eq), benzamide (1.82 g, 15.0 mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **6** as a white solid (570 mg, 28%); m.p. 96-98 °C {lit. m.p.[17] 102-104 °C}; ν_{max} (KBr) 3300 (N-H), 2935 (C-H), 1635 (C=O), 1535, 1490, 1330, 1080, 695, 665; δ_H (400 MHz, $CDCl_3$) 1.57-1.72 (3H, m, 3 x C*H*$_2$), 1.93-2.02 (3H, m, 3 x C*H*$_2$), 4.64-4.70 (1H, m, C(1)*H*), 5.62-5.68 (1H, m, C(2)*H*), 5.85-5.90 (1H, m, C(3)*H*), 6.34 (1H, d, *J* 7.5, N*H*), 7.36-7.40 (2H, m, *m-Ph*), 7.44-7.48 (2H, m, *p-Ph*), 7.75-7.78 (2H, m, *o-Ph*).

(*RS*)-*N*-Cyclohex-2-en-1-yl-4′-methylbenzene sulfonamide 267[15]



To a stirred solution of **8** (3.51 g, 10.0 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) was added TFA (2.23 mL, 30.0 mmol, 3.0 eq) and the mixture stirred for 1 hr at RT. Volatiles were removed *in vacuo* and the crude product purified by flash column chromatography (silica, 30% Et_2O/petrol) to give pure **257** as a white crystalline solid (1.40 g, 56%); mp 82-84 °C {lit. m.p.[18] 97-98 °C}; δ_H (400MHz, $CDCl_3$) 1.52-1.64 (3H, m, 3 × C*H*$_2$), 1.75-1.80 (1H, m, 1 × C*H*$_2$), 1.91-1.95 (2H, m, 2 × C*H*$_2$), 2.44 (3H, s, C(4′)*Me*), 3.83 (1H, app s, C(1)*H*), 4.41 (1H, s, N*H*), 5.34-5.36 (1H, m, C(2)*H*), 5.76-5.79 (1H, m, C(3)*H*), 7.31 (2H, d, *J* 8.2, C(3′)*H* and C(5′)*H*), 7.78 (2H, d, *J* 8.2, C(2′)*H* and C(6′)*H*).

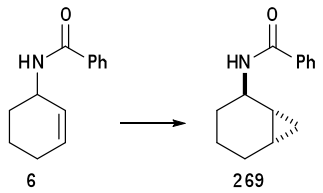
(1*SR*,2*RS*,6*RS*)-*N*-(Bicyclo[4.1.0]hept-2-yl]benzamide 268



Following **General Procedure 1**, **6** (201 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 30% EtOAc/petrol → 50% EtOAc/petrol) to give **268** as a white powder (215 mg, quant, 92:8 d.r.); m.p. 122-124 °C; ν_{max} (KBr) 3295 (N-H), 1625 (C=O), 1535, 665; δ_H (400 MHz, $CDCl_3$) 0.21 (1H, app q, *J* 5.2, C(7)*H*$_A$H$_B$), 0.62 (1H, td, *J* 8.7, 4.6, C(7)H$_A$*H*$_B$), 0.87-0.96 (1H, m, C(3)*H*$_A$H$_B$), 1.13-1.22 (1H, m,

C(6)*H*), 1.24-1.35 (2H, m, C(1)*H* and C(5)H_AH_B), 1.40-1.48 (2H, m, C(4)H_2), 1.85-1.92 (1H, m, C(5)H_AH_B), 4.51-4.58 (1H, m, C(2)*H*), 6.07 (1H, br s, N*H*), 7.42-7.52 (3H, m, *m/p-Ph*), 7.77-7.80 (2H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 8.0 (*C*(7)), 11.6 (*C*(6)), 15.4 (*C*(1)), 21.6 (*C*(4)), 23.0 (*C*(5)), 27.0 (*C*(3)), 46.0 (*C*(2)), 127.0, 128.4 (*o/m-Ph*), 131.1 (*p-Ph*), 135.0 (*i-Ph*), 166.9 (*C*=O); *m/z* (ESI^+) 216 ($[M+H]^+$, 40%), 238 ($[M+Na]^+$, 40%), 453 ($[2M+Na]^+$, 100%), 668 ($[3M+Na]^+$, 60%); HRMS (ESI^+) $C_{14}H_{17}NNaO$ ($M+Na^+$) requires 238.1202, found 238.1200.

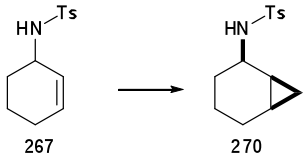
(1*RS*,2*RS*,6*SR*)-*N*-(Bicyclo[4.1.0]hept-2-yl]benzamide 269



Following **General Procedure 3**, **6** (201 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (2.0 mL, 1.0M in hexanes, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 6 hrs gave a crude product which was purified by flash column chromatography (silica, 30% EtOAc/petrol → 50% EtOAc/petrol) to give **269** as a white powder (173 mg, 80%, >98:2 d.r.); m.p. 128-130 °C; ν_{max} (KBr) 3310 (N-H), 3060, 2930 (C-H), 1630 (C=O), 1540, 1490 (Ar), 1320, 1270, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.10 (1H, app q, *J* 5.3, C(7)H_AH_B), 0.64 (1H, td, *J* 9.2, 4.9, C(7)H_AH_B), 0.81-0.87 (1H, m, C(1)*H*), 0.91-0.98 (1H, m, C(6)*H*), 1.06-1.14 (1H, m, C(4)H_AH_B), 1.26-1.43 (2H, m, C(3)H_AH_B and C(4)H_AH_B), 1.53-1.67 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 1.75-1.84 (1H, m, C(5)H_AH_B), 4.25-4.30 (1H, m, C(2)*H*), 6.74 (1H, d, *J* 7.6, N*H*), 7.34-7.38 (2H, m, *m-Ph*), 7.41-7.45 (1H, m, *p-Ph*), 7.78-7.80 (2H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 9.3 (*C*(7)), 9.9 (*C*(1)), 15.9 (*C*(6)), 17.1 (*C*(4)), 22.7 (*C*(5)), 27.8 (*C*(3)), 45.8 (*C*(2)), 127.0 (*o-Ph*), 128.4 (*m-Ph*), 131.2

(*p-Ph*), 135.0 (*i-Ph*), 166.7 (*C*=O); *m/z* (ESI$^+$) 274 ([M+NH$_4$+MeCN], 100%), 453 ([2M+Na]$^+$, 70%); HRMS (ESI$^+$) $C_{14}H_{17}NNaO$ (M+Na$^+$) requires 238.1202, found 238.1209.

_N_-((1_RS_,2_RS_,6_SR_)-Bicyclo[4.1.0]heptan-2-yl)-4′-methylbenzenesulfonamide 270



267 270

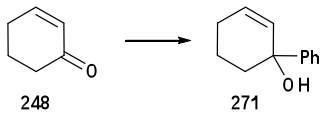
Method A:

Following **General Procedure 1**, **267** (251 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 25% Et_2O/petrol) to give **270** as a white solid (160 mg, 60%); m.p. 68-70 °C; ν_{max} (KBr) 3260 (N-H), 3065, 3005, 2935, 2860 (C-H), 1600, 1450, 1325 (SO_2N), 1160 (SO_2N), 1095, 1070, 930, 815, 670; δ_H (400MHz, $CDCl_3$) 0.09 (1H, app q, *J* 5.3, C(7)*H*$_A$H$_B$), 0.42 (1H, app td, *J* 8.8, 4.9, C(7)H$_A$*H*$_B$), 0.82-0.93 (2H, m, C(1)*H* and C(3)*H*$_A$H$_B$), 0.96-1.13 (2H, m, C(4)*H*$_A$H$_B$ and C(6)*H*), 1.20-1.36 (2H, m, C(4)H$_A$*H*$_B$ and C(5)*H*$_A$H$_B$), 1.56-1.62 (1H, m, C(3)H$_A$*H*$_B$), 1.77-1.84 (1H, m, C(5)H$_A$*H*$_B$), 2.41 (3H, s, C(4′)*Me*), 3.69 (1H, ddt, *J* 10.5, 7.8, 5.5, C(2)*H*), 4.90 (1H, d, *J* 7.7, N*H*), 7.28 (2H, d, *J* 8.4, C(3′)*H* and C(5′)*H*), 7.81 (2H, d, *J* 8.4, C(2′)*H* and C(6′)*H*); δ_C (100MHz, $CDCl_3$) 8.1 (*C*(7)), 12.4 (*C*(6)), 15.8 (*C*(1)), 21.5 (*C*(4)), 21.6 (C(4′)*Me*) 22.6 (*C*(5)), 28.3 (*C*(3)), 50.3 (*C*(2)), 127.0 (*C*(2′) and *C*(6′)), 129.6 (*C*(3′) and *C*(5′)), 138.7 (*C*(4′)), 143.0 (*C*(1′)); *m/z* (ESI$^-$) 264 ([M−H]$^-$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}NNaO_2S$ (M+Na$^+$) requires 288.1029, found 288.1032.

Method B:

Following **General Procedure 3**, **267** (126 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.0 mmol, 2.0 eq) in CH_2Cl_2 for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 25% Et_2O/petrol) to give **270** as a white solid (70 mg, 53%); m.p. 66-68 °C; identical spectroscopic properties to **270** above.

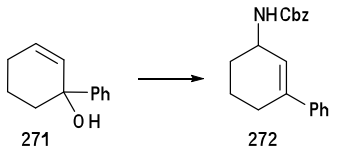
1-Phenyl-cyclohex-2-en-1-ol 271[19]



248 271

To a stirred solution of 2-cyclohexen-1-one **248** (4.84 mL, 50.0 mmol, 1.0 eq) in Et_2O (50 mL) at −78 °C was added PhLi (2.0 M in di-*n*-butylether, 27.5 mL, 55.0 mmol, 1.1 eq) dropwise. The resulting solution was stirred at −78 °C for 1 hr then quenched by the addition of H_2O (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL) then dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **271** as a colourless oil (6.85 g, 79%); δ_H (400MHz, $CDCl_3$) 1.53-1.63 (1H, m, 1 × C*H*$_2$), 1.73-1.99 (2H, m, 2 × C*H*$_2$), 1.99-2.20 (4H, m, 4 ×C*H*$_2$), 5.75 (1H, d, *J* 10.0, C(2)*H*), 6.01-6.08 (1H, m, C(3)*H*), 7.21-7.28 (1H, m, *p-Ph*), 7.31-7.36 2H, m, *m-Ph*), 7.42-7.49 (2H, m, *o-Ph*).

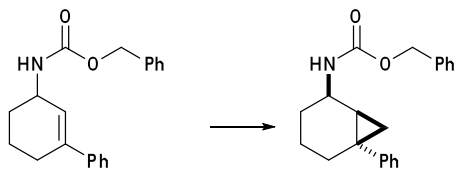
Benzyl (*RS*)-(3-phenylcyclohex-2-en-1-yl) carbamate 272



271 272

Following **General Procedure 9**, **271** (1.74 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.50 mmol, 0.05 eq), KPF_6 (92 mg, 0.50 mmol, 0.05 eq), benzyl carbamate (2.27 g, 15.0 mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 20% EtOAc/petrol) to give **272** as a white powder (2.14 g, 70%); m.p. 77-79 °C; ν_{max} (KBr) 3325 (N-H), 2935 (C-H), 1695 (C=O), 1525, 1235, 1070, 750, 695, 665; δ_H (400 MHz, $CDCl_3$) 1.57-1.65 (1H, m, C(6)H_AH_B), 1.78-1.89 (2H, m, C(5)H_2), 1.98-2.05 (1H, m, C(6)H_AH_B), 2.35-2.51 (2H, m, C(4)H_2), 4.47 (1H, br s, C(1)*H*), 4.95 (1H, d, *J* 8.6, N*H*), 5.15 (2H, s, OCH_2Ph), 6.03 (1H, s, C(2)*H*), 7.27-7.42 (10H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.2 (*C*(5)), 27.2 (*C*(4)), 29.4 (*C*(6)), 47.3 (*C*(1)), 66.7 (O*C*H_2Ph), 124.6 (*C*(2)), 125.3, 127.5, 128.1, 128.2, 128.4, 128.6 (*Ar*), 136.6 (*C*(3)), 140.2, 141.3 (*i-Ph*), 155.8 (*C*=O); *m/z* (ESI^+) 330 ($[M+Na]^+$, 20%), 366 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{20}H_{21}NNaO_2$ ($M+Na^+$) requires 330.1465, found 330.1461.

Benzyl [(1*SR*,2*RS*,6*SR*)-6-phenylbicyclo[4.1.0]hept-2-yl]carbamate 273

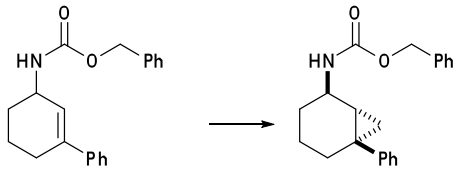


272 273

Following **General Procedure 1**, **272** (462 mg, 1.5 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 3.0 mL, 3.0 mmol, 2.0 eq), and CH_2I_2 (0.48 mL, 6.0 mmol, 4.0 eq) in CH_2Cl_2 (4 mL) for 1 hr gave a crude product which was purified by flash column

chromatography (silica, petrol → 20% EtOAc/petrol) to give **273** as a white powder (404 mg, 84%, >98:2 d.r.); m.p. 49-51 °C; ν_{max} (KBr) 3330 (N-H), 2935 (C-H), 1700 (C=O), 1495, 1435 (Ar), 1235, 1050, 760, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.71 (1H, app t, *J* 5.2, C(7)H_AH_B), 0.94 (1H, dd, *J* 9.2, 4.7, C(7)H_AH_B), 1.09-1.18 (1H, m, C(3)H_AH_B), 1.44-1.49 (2H, m, C(4)H_2), 1.59-1.64 (1H, m, C(1)*H*), 1.81-1.93 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 1.98-2.04 (1H, m, C(5)H_AH_B), 4.29-4.34 (1H, m, C(2)*H*), 4.87 (1H, d, *J* 6.8, N*H*), 7.18-7.40 (10H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.5 (*C*(7)), 20.7 (*C*(4)), 23.9 (*C*(1)), 27.4 (*C*(6)), 27.5 (*C*(3)), 31.4 (*C*(5)), 46.4 (*C*(2)), 66.6 (O*C*H_2Ph), 126.0, 127.5, 128.2, 128.2, 128.4, 128.6 (*Ar*), 136.6 (*i-Ph*), 148.0 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI^+) 380 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{21}H_{23}NNaO_2$ ($M+Na^+$) requires 344.1621, found 344.1622.

Benzyl [(1*RS*,2*RS*,6*RS*)-6-phenylbicyclo[4.1.0]hept-2-yl]carbamate 274



272 274

Method A:

Following **General Procedure 3**, **272** (77 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.5 mL, 0.5 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 1.0 mmol, 4.0 eq) and TFA (0.07 mL, 0.5 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 12 hrs gave a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol → 20% EtOAc/petrol) to give **274** as a colourless oil (80 mg, 99%, >98:2 d.r.); ν_{max} (KBr) 3330 (N-H), 2935 (C-H), 1695 (C=O), 1530, 1240, 1025, 760, 700, 665; δ_H (400 MHz, $CDCl_3$) 0.78 (1H, app t, *J* 5.2, C(7)H_AH_B), 1.10 (1H, dd, *J* 9.8, 5.1, C(7)H_AH_B), 1.25-1.33 (3H, m, C(1)*H*, C(3)H_AH_B and C(4)H_AH_B), 1.60-1.67 (1H, m,

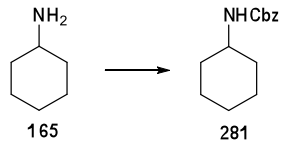
C(4)H_AH_B), 1.78-1.87 (1H, m, C(3)H_AH_B), 1.94-2.02 (1H, m, C(5)H_AH_B), 2.10-2.16 (1H, m, C(5)H_AH_B), 4.01-4.05 (1H, m, C(2)*H*), 5.18 (2H, s, OCH_2Ph), 5.27 (1H, d, *J* 8.3, N*H*), 7.20-7.24 (1H, m, *Ar*), 7.28-7.45 (9H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.9 (*C*(7)), 18.1 (*C*(4)), 25.5 (*C*(6)), 25.8 (*C*(1)), 28.8 (*C*(3)), 30.7 (*C*(5)), 47.8 (*C*(2)), 66.7 (O*C*H_2Ph), 125.9, 127.4, 128.2, 128.3, 128.4, 128.6 (*Ar*), 136.7, 148.0 (*i-Ph*), 155.8 (*C*=O); *m/z* (ESI^+) 344 ($[M+Na]^+$, 25%), 380 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{21}H_{23}NNaO_2$ ($M+Na^+$) requires 344.1621, found 344.1615.

Method B:

Following **General Procedure 3**, **272** (462 mg, 1.5 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 4.5 mL, 4.5 mmol, 3.0 eq), CH_2I_2 (0.72 mL, 9.0 mmol, 6.0 eq) and TFA (0.34 mL, 4.5 mmol, 3.0 eq) in CH_2Cl_2 (6.0 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 20% EtOAc/petrol) to give **274** as a colourless oil (382 mg, 78%) which crystallized on prolonged standing to a white solid; m.p. 64-66 °C.

Mechanistic studies:

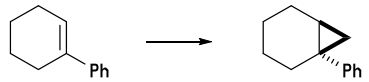
Benzyl (*RS*)-cyclohexylcarbamate 281[20]



To a stirred solution of cyclohexylamine **165** (1.14 mL, 10.0 mmol, 1.0 eq) in THF (100 mL) at 0 °C was added NEt_3 (1.53 mL, 11.0 mmol, 1.1 eq) followed by benzyl chloroformate (1.57 mL, 11.0 mmol, 1.1 eq). The resulting mixture was stirred for 16 hrs at RT then washed with brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers dried, filtered and concentrated

in vacuo to give **281** as a white solid (2.32 g, 99%) which was used without further purification; m.p. 82-84 °C {lit. m.p.[20] 79-80 °C}; δ_H (400MHz, $CDCl_3$) 1.08-1.22 (3H, m, 3 × C*H*$_2$), 1.31-1.40 (2H, m, 2 × C*H*$_2$), 1.56-1.64 (1H, m, 1 × C*H*$_2$), 1.66-1.74 (2H, m, 2 × C*H*$_2$), 1.93-1.96 (2H, m, 2 × C*H*$_2$), 3.51-3.53 (1H, m, C*H*N), 4.66 (1H, br s, N*H*), 5.09 (2H, br s, OC*H*$_2$Ph), 7.30-7.40 (5H, m, *Ph*).

1-Phenylbicyclo[4.1.0]heptane 282[21]



280 282

Prepared as outlined below; δ_H (400MHz, $CDCl_3$) 0.64 (1H, dd, *J* 5.6, 4.3, C(7)*H*$_A$H$_B$), 0.95 (1H, dd, *J* 9.4, 4.5, C(7)H$_A$*H*$_B$), 1.21-1.42 (4H, m, 3 × C*H*$_2$ and C(6)*H*), 1.45-1.52 (1H, m, 1 × C*H*$_2$), 1.92-1.99 (1H, m, 1 × C*H*$_2$), 2.03-2.12 (2H, m, 2 × C*H*$_2$), 7.14-7.18 (1H, m, *Ph*), 7.27-7.29 (4H, m, *Ph*).

(a) Wittig-Furukawa reagent, $Zn(CH_2I)_2$

Due to the heterogeneous nature of the reagent, it was found that performing the reactions on a small scale (0.10 mmol substrate) gave unreliable results. As such, all reactions were all performed on 0.50 mmol of substrate at a concentration of 0.1 M. The reactions were performed according to the procedure outlined in **General Procedure 1**. In cases where 2 substrates are involved, they were added as a pre-mixed solution in CH_2Cl_2. In all cases the reaction conversion was assessed by integration of the appropriate peaks in the 400MHz ^{1}H NMR spectra of the crude products.

(i) Following **General Procedure 1**, **272** (154 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (0.50 mL, 0.50 mmol, 1.0 eq) and CH_2I_2 (81 μL, 1.00 mmol, 2.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 98% conversion to **273**.

(ii) Following **General Procedure 1**, **272** (154 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.00 mL, 1.00 mmol, 2.0 eq) and CH_2I_2 (0.16 mL, 2.00 mmol, 4.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave >98% conversion to **273**.

(iii) Following **General Procedure 1**, **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (0.50 mL, 0.50 mmol, 1.0 eq) and CH_2I_2 (81 μL, 1.00 mmol, 2.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 13% conversion to **282**.

(iv) Following **General Procedure 1**, **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.00 mL, 1.00 mmol, 2.0 eq) and CH_2I_2 (0.16 mL, 2.00 mmol, 4.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 20% conversion to **282**.

(v) Following **General Procedure 1**, **281** (117 mg, 0.50 mmol, 1.0 eq), **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (0.50 mL, 0.50 mmol, 1.0 eq) and CH_2I_2 (81 μL, 1.00 mmol, 2.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 24% conversion to **282**.

(vi) Following **General Procedure 1**, **281** (117 mg, 0.50 mmol, 1.0 eq), **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.00 mL, 1.00 mmol, 2.0 eq) and CH_2I_2 (0.16 mL, 2.00 mmol, 4.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 44% conversion to **282**.

(vii) Following **General Procedure 1**, **272** (154 mg, 0.50 mmol, 1.0 eq), **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (0.50 mL, 0.50 mmol, 1.0 eq) and CH_2I_2 (81 μL, 1.00 mmol, 2.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave 96% conversion to **273** and 17% conversion to **282**.

(viii) Following **General Procedure 1**, **272** (154 mg, 0.50 mmol, 1.0 eq), **280** (79 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.00 mL, 1.00 mmol, 2.0 eq) and CH_2I_2 (0.16 mL, 2.00 mmol, 4.0 eq) in CH_2Cl_2 (5.0 mL) for 60 mins gave >98% conversion to **273** and 59% conversion to **282**.

(b) Shi's carbenoid, $CF_3CO_2ZnCH_2I$

A 0.45 M solution of $CF_3CO_2ZnCH_2I$ in CH_2Cl_2 was prepared according to **General Procedure 3**, from $ZnEt_2$ (10.0 mL, 10.0 mmol, 1.0 eq), CH_2I_2 (1.61 mL, 20.0 mmol, 2.0 eq) and TFA (0.74 mL, 10.0 mmol, 1.0 eq) in CH_2Cl_2 (10 mL). The colourless solution was allowed to stir at 0 °C for 15 mins and then the appropriate amount was added *via* syringe to the reaction. The reactions were performed such that the final concentration of substrate was 0.1 M. In all cases the reaction conversion was assessed by integration of the appropriate peaks in the 400MHz ^1H NMR spectra of the crude products.

(i) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.22 mL, 0.10 mmol, 1.0 eq) was added to **272** (30.7 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.78 mL). After 60 mins the reaction conversion was 3%.

(ii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **272** (30.7 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 60 mins the reaction conversion was 87%.

(iii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.22 mL, 0.10 mmol, 1.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.78 mL). After 60 mins the reaction conversion was 53%.

(iv) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 60 mins the reaction conversion was 95%.

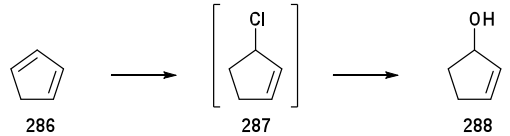
(v) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.22 mL, 0.10 mmol, 1.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) and **281** (23.3 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.78 mL). After 60 mins the reaction conversion was 4%.

(vi) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) and **281** (23.3 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 60 mins the reaction conversion was 72%.

(vii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.22 mL, 0.10 mmol, 1.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) and **272** (30.7 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.78 mL). After 60 mins the conversion of **280** to **282** was 4%, and of **272** to **274** was 3%.

(viii) $CF_3CO_2ZnCH_2I$ (0.45 M in CH_2Cl_2, 0.45 mL, 0.20 mmol, 2.0 eq) was added to **280** (15.8 mg, 0.10 mmol, 1.0 eq) and **272** (30.7 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.55 mL). After 60 mins the conversion of **280** to **282** was 61%, and of **272** to **274** was 53%.

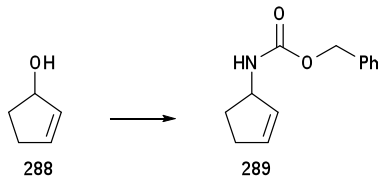
(*RS*)-2-Cyclopenten-1-ol 288[11]



HCl (g) was bubbled through a solution of cyclopentadiene **286** (6.6 mL, 100 mmol, 1.0 eq, prepared by bulb-to-bulb distillation of dicyclopentadiene at 170 °C) at 0 °C

for 1 hr and the crude mixture then slowly added to stirred sat. aq. $NaHCO_3$ (50 mL) at 0 °C. The mixture was stirred for a further 2 hrs at 0 °C then saturated with NaCl and the mixture extracted with Et_2O (5 × 20 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give crude **288** as a pale yellow oil (1.85 g, 44%) which was used without further purification; δ_H (400 MHz, $CDCl_3$) 1.64-1.73 (2H, m, 1 × C*H*$_2$ and O*H*), 2.20-2.31 (2H, m, 2 × C*H*$_2$), 2.46-2.54 (1H, m, 1 × C*H*$_2$), 4.84-4.89 (1H, m, C(1)*H*), 5.81-5.85 (1H, m, C(2)*H*), 5.96-6.00 (1H, m, C(3)*H*).

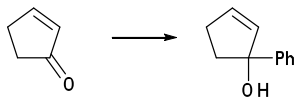
Benzyl (*RS*)-cyclopent-2-en-1-ylcarbamate 289



288 289

Following **General Procedure 9**, **288** (0.84 mL, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.50 mmol, 0.05 eq), KPF_6 (92 mg, 0.50 mmol, 0.05 eq) and benzyl carbamate (2.27 g, 15.0 mmol, 1.5 eq) in 1,4-dioxane (30 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to give **289** as a white powder (400 mg, 18%); m.p. 43-45 °C; ν_{max} (KBr) 3320 (N-H), 3060, 2950 (C-H), 1695 (C=O), 1530, 1240, 1050, 735, 695, 665; δ_H (400 MHz, $CDCl_3$) 1.55-1.61 (1H, m, C(5)*H*$_A$H$_B$), 2.25-2.45 (3H, s, C(4)*H*$_2$ and C(5)H$_A$*H*$_B$), 4.75-4.82 (1H, m, C(1)*H*), 4.99 (1H, d, *J* 7.6, N*H*), 5.09 (2H, s, OC*H*$_2$Ph), 5.68-5.72 (1H, m, C(2)*H*), 5.89-5.93 (1H, m, C(3)*H*), 7.30-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.1, 31.5 (*C*(4) and *C*(5)), 57.3 (*C*(1)), 66.5 (O*C*H$_2$Ph), 128.1, 128.1, 128.5 (*Ph*), 131.2 (*C*(2)), 134.4 (*C*(3)), 136.6 (*i-Ph*), 155.8 (*C*=O); *m/z* (ESI$^+$) 240 ([M+Na]$^+$, 20%), 276 ([M+MeCN+NH$_4$]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{15}NNaO_2$ (M+Na$^+$) requires 240.0995, found 240.0998.

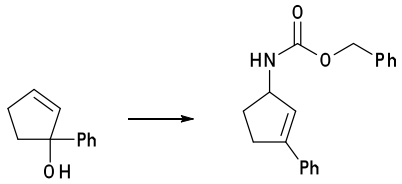
(*RS*)-1-Phenylcyclopent-2-en-1-ol 291[22]



290 291

Following **General Procedure 10**, 2-cyclopenten-1-one **291** (0.84 mL, 10.0 mmol, 1.0 eq), bromobenzene (1.58 mL, 15.0 mmol, 1.5 eq) and ^{t}BuLi (1.7 M in pentane, 17.6 mL, 30.0 mmol, 3.0 eq) in THF (50 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol) to give **291** as a colourless oil (1.55 g, 97%); δ_H (400 MHz, $CDCl_3$) 1.92 (1H, s, O*H*), 2.27 (2H, t, *J* 6.1, C(5)H_2), 2.44-2.52 (1H, m, C(4)H_AH_B), 2.61-2.70 (1H, m, C(4)H_AH_B), 5.89 (1H, dt, *J* 5.7, 2.4, C(3)*H*), 6.12 (1H, dt, *J* 5.7, 2.4, C(2)*H*), 7.24-7.27 (1H, m, *p-Ph*), 7.33-7.38 (2H, m, *m-Ph*), 7.44-7.46 (2H, m, *o-Ph*).

Benzyl (*RS*)-(3-phenylcyclopent-2-en-1-yl) carbamate 292

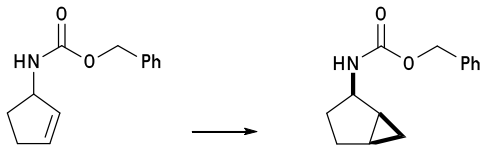


291 292

Following **General Procedure 9**, alcohol **291** (1.55 g, 9.7 mmol, 1.0 eq), $Bi(OTf)_3$ (318 mg, 0.49 mmol, 0.05 eq), KPF_6 (90 mg, 0.49 mmol, 0.05 eq) and benzyl carbamate **285** (2.20 g, 14.6 mmol, 1.5 eq) in THF (30 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol) to give **292** as a white solid (1.99 g, 70%); mp 101-103 °C; ν_{max} (film) 3340 (NH), 1680 (C=O) 1530 ; δ_H (400MHz, $CDCl_3$) 1.73-1.81 (1H, m, C(5)H_AH_B), 2.52-2.60 (1H, m, C(5)H_AH_B), 2.60-2.72 (1H, m, C(4)H_AH_B), 2.81-2.88 (1H, m, C(4)H_AH_B), 4.88 (1H, br s, N*H*), 4.97 (1H, br s, C(1)*H*), 5.14 (2H, s, OCH_2Ph), 6.11

(1H, s, C(2)*H*), 7.27-7.47 (10H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 31.5 (*C*(4)), 32.0 (*C*(5)), 57.7 (*C*(1)), 66.6 (O*C*H_2Ph), 125.5 (*C*(2)), 126.0, 128.0, 128.1, 128.2, 128.4, 128.6 (*Ar*), 135.5, 136.6 (2 × *i-Ph*), 145.5 (*C*(3)), 155.7 (*C*=O); *m/z* (ESI^+) 352 ($[M+NH_4+MeCN]^+$, 100%); HRMS (ESI^+) $C_{19}H_{19}NNaO_2$ ($[M+Na]^+$) requires 316.1308, found 316.1303.

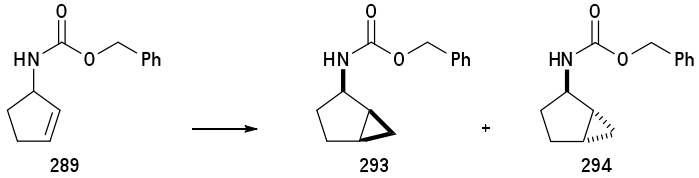
Benzyl (1*SR*,2*RS*,7*RS*)-bicyclo[3.1.0]hex-2-ylcarbamate 293



289 293

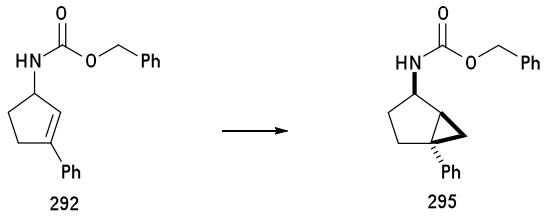
Following **General Procedure 1**, **289** (54 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.50 mL, 0.50 mmol, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) in CH_2Cl_2 (0.5 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% Et_2O/petrol) to give **293** as a white solid (45 mg, 78%, >98:2 d.r.); m.p. 53-55 °C; ν_{max} (KBr) 3325 (N-H), 3035, 2935, 2870 (C-H), 1700 (C=O), 1530, 1280, 1240, 1045, 700; δ_H (400 MHz, $CDCl_3$) 0.30-0.35 (2H, m, C(6)H_2), 0.84-0.95 (1H, m, C(3)H_AH_B), 1.31 (1H, br s, C(5)*H*), 1.49 (1H, br s, C(1)*H*), 1.74-1.82 (2H, m, C(4)H_2), 1.93-2.00 (1H, m, C(3)H_AH_B), 4.28-4.35 (1H, m, C(2)*H*), 4.83 (1H, br s, N*H*), 5.10 (2H, s, OCH_2Ph), 7.30-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.5 (*C*(6)), 16.0 (*C*(5)), 20.3 (*C*(1)), 25.8 (*C*(4)), 26.6 (*C*(3)), 53.3 (*C*(2)), 66.5 (O*C*H_2Ph), 128.1, 128.2, 128.5 (*Ph*), 136.6 (*i-Ph*), 156.1 (*C*=O); *m/z* (ESI^+) 254 ($[M+Na]^+$, 70%), 290 ($[M+MeCN+NH_4]^+$); HRMS (ESI^+) $C_{14}H_{17}NNaO_2$ $(M+Na)^+$ requires 254.1151, found 254.1152.

Benzyl (1*SR*,2*RS*,7*RS*)-bicyclo[3.1.0]hex-2-ylcarbamate 293 and benzyl (1*RS*,2*RS*,7*SR*)-bicyclo[3.1.0]hex-2-ylcarbamate 294



Following **General Procedure 3**, **289** (54 mg, 0.25 mmol, 1.0 eq) $ZnEt_2$ (1.0 M in hexanes, 0.50 mL, 0.50 mmol, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) and TFA (36 μL, 0.50 mmol, 2.0 eq) in CH_2Cl_2 (0.5 mL) for 12 hrs gave a crude product. ^{1}H NMR anaylsis showed that the crude product contained a 78:12:10 mixture of **289**:**293**:**294**; characteristic peaks for *anti*-**294**; δ_H (400 MHz, $CDCl_3$) 0.41-0.47 (1H, m, C(6)H_AH_B), 4.07-4.10 (1H, m, C(2)*H*).

Benzyl [(1*SR*,2*RS*,5*SR*)-5-phenylbicyclo[3.1.0]hex-2-yl]carbamate 295

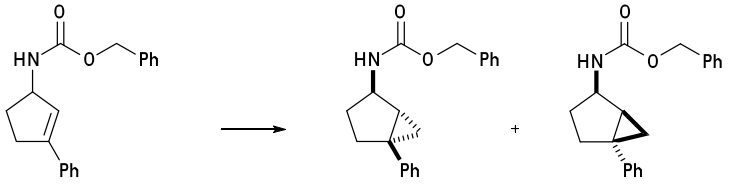


Following **General Procedure 1**, **292** (293 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0eq) and CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) in CH_2Cl_2 (2.0 mL) gave a crude product which was purified by trituration with petrol (20 mL) to give **295** as a white solid (245 mg, 80%); mp 116-118 °C; ν_{max} (film) 3330 (NH), 3060, 2930, 1700 (C=O), 1500, 1240; δ_H (400MHz, $CDCl_3$) 0.82 (1H, dd, *J* 7.6, 5.6, C(6)H_AH_B), 1.09 (1H, app t, *J* 4.6, C(6)H_AH_B), 1.13-1.20 (1H, m, C(1)*H*), 1.96-2.00 (1H, m, C(3)H_AH_B), 2.09-2.23 (3H, m, C(3)H_AH_B, C(4)H_2), 4.54 (1H, br s, C(2)*H*), 5.03 (1H, d, *J* 7.1, N*H*), 5.17 (2H, s, OCH_2Ph), 7.19-7.24 (4H, m, *Ar*), 7.31-7.43 (6H,

m, *Ar*); δ_C (100MHz, $CDCl_3$) 13.9 (*C*(6)), 28.0 (*C*(3)), 29.2 (*C*(1)), 30.8 (*C*(4)), 31.3 (*C*(5)), 53.0 (*C*(2)), 66.7 (O*C*H_2Ph), 125.8, 126.3, 128.2, 128.3, 128.4, 128.6 (*Ph*), 136.7, 144.2 (*i-Ph*), 156.1 (*C*=O); *m/z* (ESI^-) 306 ($[M-H]^-$, 100%); HRMS (ESI^-) $C_{20}H_{20}NO_2$ ($[M-H]^-$) requires 306.1500, found 306.1502.

The petrol extract was concentrated *in vacuo* and the off-white solid obtained was triturated with a further portion of petrol (10 mL). Filtration afforded **295** as a white solid (43 mg, 14%); mp 110-112 °C; identical spectroscopic properties as above.

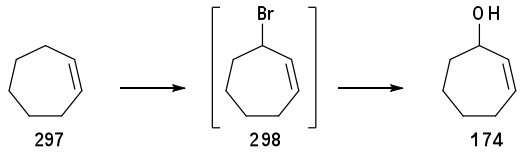
Benzyl [(1*RS*,2*RS*,5*RS*)-5-phenylbicyclo[3.1.0]hex-2-yl] carbamate 296 and benzyl [(1*SR*,2*RS*,5*SR*)-5-phenylbicyclo[3.1.0]hex-2-yl]carbamate 295



Following **General Procedure 3**, **292** (293 mg, 1.0 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 2.0 mL, 2.0 mmol, 2.0 eq), CH_2I_2 (0.32 mL, 4.0 mmol, 4.0 eq) and TFA (0.15 mL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (2.0 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, 20% EtOAc/petrol) to give an inseparable 71:29 mixture of **296**:**295** as a colourless oil (233 mg, 77%); data for **296**; δ_H (400MHz, $CDCl_3$) 0.92-0.98 (2H, m, C(6)H_2), 1.62-1.81 (3H, m, C(1)*H*, C(3)H_AH_B, C(4)H_AH_B), 2.10-2.22 (2H, m, C(3)H_AH_B, C(4)H_AH_B), 4.25 (1H, t, *J* 6.6, C(2)*H*), 5.04 (1H, d, *J* 6.8, N*H*), 5.13 (2H, s, OCH_2Ph), 7.19-7.23 (4H, m, *Ar*), 7.30-7.42 (6H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 17.4 (*C*(6)), 29.3, 29.5 (*C*(3), *C*(4)), 31.4 (*C*(1)), 32.1 (*C*(5)), 53.9 (*C*(2)), 60.4 (O*C*H_2Ph), 125.7, 126.0, 126.1, 128.0, 128.4, 128.5 (*Ar*), 136.6 (*i-Ph*(Cbz)), 144.1 (*i-Ph*), 155.5 (*C*=O); Data for mixture; ν_{max}

(film) 3330 (NH), 3030, 2950, 1705 (C=O), 1500, 1240; *m/z* (ESI^-) 306 ($[M-H]^-$, 100%); HRMS (ESI^-) $C_{20}H_{20}NO_2$ ($[M-H]^-$) requires 306.1500, found 306.1499.

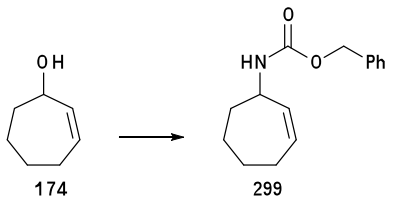
(*RS*)-2-Cyclohepten-1-ol 174[23]



To a stirred solution of cycloheptene **297** (11.7 mL, 100 mmol, 1.0 eq) in CCl_4 (100 mL) was added NBS (17.8 g, 100 mmol, 1.0 eq) and AIBN (164 mg, 1.00 mmol, 0.01 eq). The resulting suspension was heated at 90 °C for 3 hrs then cooled to 0 °C and filtered. The filtrate was concentrated *in vacuo* to give crude (*RS*)-3-bromocyclohept-1-ene **298** as a brown oil; δ_H (400 MHz, $CDCl_3$) 1.44-1.55 (1H, m, 1 × C*H*$_2$), 1.76-1.92 (2H, m, 2 × C*H*$_2$), 1.95-2.10 (2H, m, 2 × C*H*$_2$), 2.15-2.27 (3H, m, 3 × C*H*$_2$), 4.92-4.97 (1H, m, C(3)*H*), 5.82-5.89 (1H, m, C(1)*H*), 5.91-5.97 (1H, m, C(2)*H*).

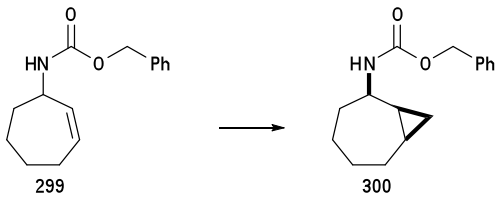
To a stirred suspension of $NaHCO_3$ (25.2 g, 300 mmol, 3.0 eq) in THF (70 mL) and H_2O (105 mL) was added crude 3-bromocyclohept-1-ene **298** (100 mmol, 1.0 eq) and the resulting mixture stirred at RT for 24 hrs. The mixture was then diluted with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol → 20% Et_2O/petrol) to give **174** as a colourless oil (5.40 g, 48% over 2 steps); δ_H (400 MHz, $CDCl_3$) 1.32-1.41 (1H, m, 1 × C*H*$_2$), 1.50-1.71 (4H, m, 3 × C*H*$_2$ and O*H*), 1.83-2.08 (3H, m, 3 × C*H*$_2$), 2.15-2.22 (1H, m, 1 × C*H*$_2$), 4.41 (1H, d, *J* 9.2, C(1)*H*), 5.74-5.80 (2H, m, C(2)*H* and C(3)*H*).

Benzyl (*RS*)-cyclohept-2-en-1-ylcarbamate 299



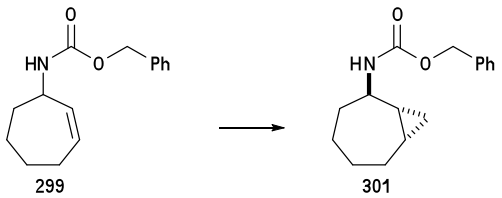
Following **General Procedure 9**, **174** (1.12 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.50 mmol, 0.05 eq), KPF_6 (92 mg, 0.50 mmol, 0.05 eq) and benzyl carbamate **285** (2.27 g, 15.0 mmol, 1.5 eq) in 1,4-dioxane (30 mL) for 16 hrs gave a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol → 20% Et_2O/petrol) to give **299** as a white powder (962 mg, 39%); m.p. 69-71 °C; ν_{max} (KBr) 3315 (N-H), 3030, 2915, 2850 (C-H), 1685 (C=O), 1540, 1315, 1255, 1040, 730, 695; δ_H (400 MHz, $CDCl_3$) 1.34-1.42 (1H, m, C(6)H_AH_B), 1.52-1.73 (3H, m, C(4)H_AH_B, C(5)H_AH_B and C(6)H_AH_B), 1.83-1.93 (2H, m, C(4)H_AH_B and C(5)H_AH_B), 2.08-2.21 (2H, m, C(7)H_2), 4.34-4.40 (1H, m, C(1)*H*), 4.97 (1H, br s, N*H*), 5.11 (2H, s, OCH_2Ph), 5.55-5.60 (1H, m, C(2)*H*), 5.77-5.84 (1H, m, C(3)*H*), 7.31-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6 (*C*(6)), 27.6 (*C*(5)), 28.5 (*C*(7)), 34.2 (*C*(4)), 52.2 (*C*(1)), 66.6 (O*C*H_2Ph), 128.1, 128.2, 128.5 (*Ph*), 132.1 (*C*(3)), 135.0 (*C*(2)), 136.6 (*i-Ph*), 155.6 (*C*=O); *m/z* (ESI^+) 304 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}NNaO_2$ $(M+Na)^+$ requires 268.1308, found 268.1306.

Benzyl (1*SR*,2*RS*,7*RS*)-bicyclo[5.1.0]oct-2-ylcarbamate 300



Following **General Procedure 1**, **299** (123 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.00 mL, 1.00 mmol, 2.0 eq) and CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% Et_2O/petrol) to give **300** as a white solid (107 mg, 83%); m.p. 74-76 °C; ν_{max} (KBr) 3325 (N-H), 2915 (C-H), 1685 (C=O), 1540, 1315, 1260, 1025, 755, 665; δ_H (400 MHz, $CDCl_3$) 0.30-0.35 (1H, m, C(8)H_AH_B), 0.41-0.46 (1H, app q, *J* 5.9, C(8)H_AH_B), 1.01-1.27 (5H, m, C(1)*H*, C(3)H_AH_B, C(4)H_2 and C(7)*H*), 1.54-1.62 (2H, m, C(6)H_2), 1.77-1.93 (3H, m, C(3)H_AH_B and C(5)H_2), 4.08-4.14 (1H, m, C(2)*H*), 4.91 (1H, d, *J* 6.8, N*H*), 5.10 (2H, s, OCH_2Ph), 7.30-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 1.4 (*C*(8)), 15.0 (*C*(7)), 21.2 (*C*(1)), 26.2 (*C*(4)), 26.7 (*C*(6)), 28.1 (*C*(5)), 33.4 (*C*(3)), 51.6 (*C*(2)), 66.4 (O*C*H_2Ph), 128.0, 128.2, 128.5 (*Ph*), 136.7 (*i-Ph*), 155.4 (*C*=O); *m/z* (ESI^+) 318 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{16}H_{21}NNaO_2$ $(M+Na)^+$ requires 282.1465, found 282.1467.

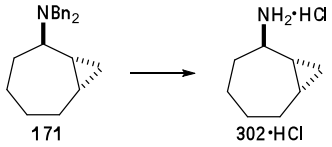
Benzyl (1*RS*,2*RS*,7*SR*)-bicyclo[5.1.0]oct-2-ylcarbamate 301



Method A:

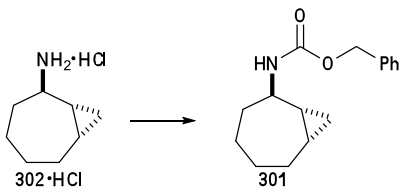
Following **General Procedure 3**, **299** (123 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.00 mL, 1.00 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (0.07 mL, 1.00 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 12 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% Et_2O/petrol) to give **301** as a white solid (82 mg, 63%); m.p. 86-88 °C; ν_{max} (KBr) 3325 (N-H), 2915 (C-H), 1685 (C=O), 1540, 1455, 1315, 1260, 1025, 755, 695; δ_H (400 MHz, $CDCl_3$) 0.34-0.39 (1H, m, C(8)H_AH_B), 0.72-0.93 (4H, m, C(1)*H*, C(5)H_AH_B, C(7)*H* and C(8)H_AH_B), 1.29-1.36 (2H, m, C(4)H_AH_B and C(6)H_AH_B), 1.58-1.90 (4H, m, C(3)H_2, C(4)H_AH_B and C(6)H_AH_B), 2.15-2.21 (1H, m, C(5)H_AH_B), 3.20-3.27 (1H, m, C(1)*H*), 5.00 (1H, br s, N*H*), 5.10 (2H, s, OCH_2Ph), 7.29-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(8)), 14.9 (*C*(1) and *C*(7)), 22.0 (*C*(4)), 28.6 (*C*(5)), 30.8 (*C*(6)), 37.7 (*C*(3)), 55.4 (*C*(2)), 66.5 (O*C*H_2Ph), 128.0, 128.1, 128.5 (*Ph*), 136.7 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI^+) 318 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{16}H_{21}NNaO_2$ $(M+Na)^+$ requires 282.1465, found 282.1466.

(1*RS*,2*RS*,7*SR*)-Bicyclo[5.1.0]octan-2-amine 302•HCl



Following **General Procedure 8**, **171** (153 mg, 0.50 mmol, 1.0 eq), Pd/C (10 wt. %, 75 mg) in MeOH/H_2O/AcOH (40:4:1, v/v/v) under 5 atm. H_2 for 16 hrs, followed by the addition of conc. HCl (1 mL) and concentration *in vacuo* gave **302•HCl** as a white solid (81 mg, quant.); m.p. 78-80 °C; ν_{max} (KBr) 3425 (N-H), 2590, 2060 (C-H), 1645, 1515, 1455; δ_H (400MHz, $CDCl_3$) 0.46 (1H, app q, *J* 4.6, C(8)H_AH_B), 0.81-0.90 (1H, m, C(6)H_AH_B), 0.94-1.08 (3H, m, C(1)*H*, C(7)*H* and C(8)H_AH_B), 1.29-1.45 (2H, m, C(4)H_AH_B and C(5)H_AH_B), 1.79-1.98 (4H, m, C(3)H_2, C(4)H_AH_B and C(5)H_AH_B), 2.26 (1H, app t, C(6)H_AH_B), 2.80-2.85 (1H, m, C(2)*H*); δ_C (100MHz, $CDCl_3$) 14.9 (*C*(8)), 15.3 (*C*(7)), 19.4 (*C*(1)), 28.4, 28.7 (*C*(4) and *C*(5)), 30.7 (*C*(6)), 35.1 (*C*(3)), 56.0 (*C*(2)); *m/z* (FI^+) 125 ($[M+H]^+$, 100%); HRMS (FI^+) $C_8H_{15}N$ ($M+H^+$) requires 125.1204, found 125.1208.

Benzyl (1*RS*,2*RS*,7*SR*)-bicyclo[5.1.0]oct-2-ylcarbamate 301

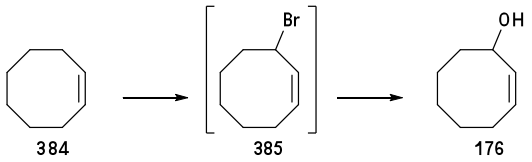


Method B:

To a stirred suspension of **302•HCl** (50 mg, 0.31 mmol, 1.0 eq) in THF (2 mL) at 0 °C was added NEt_3 (0.10 mL, 0.74 mmol, 2.4 eq) followed by benzyl chloroformate (53 μL, 0.37 mmol, 1.2 eq). The resulting mixture was allowed to warm to RT and

stirred for 16 hrs, then diluted with EtOAc (20 mL) and washed with brine (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **301** as a white crystalline solid (28 mg, 35%); m.p. 84-86 °C; identical spectroscopic properties as **301** above.

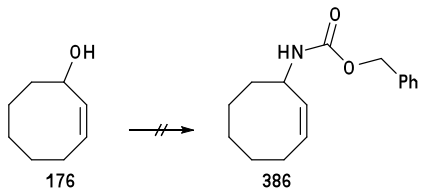
(1*RS*,2*Z*)-2-Cycloocten-1-ol 176[24]



To a stirred solution of (*Z*)-cyclooctene **384** (10.3 mL, 79.3 mmol, 1.0 eq) in CCl_4 (80 mL) was added NBS (14.1 g, 79.3 mmol, 1.0 eq) and AIBN (130 mg, 0.80 mmol, 0.01 eq). The resulting suspension was heated at 90 °C for 3 hrs then cooled to 0 °C and filtered. The filtrate was concentrated *in vacuo* to give crude (1*Z*,3*RS*)-3-bromocyclooct-1-ene **385** as a brown oil; δ_H (400 MHz, $CDCl_3$) 1.24-1.74 (6H, m, 6 × C*H*$_2$), 1.93-2.28 (4H, m, 4 × C*H*$_2$), 4.90-4.98 (1H, m, C(3)*H*), 5.55-5.64 (1H, m, C(1)*H*), 5.71-5.83 (1H, m, C(2)*H*).

To a stirred suspension of $NaHCO_3$ (20.0 g, 238 mmol, 3.0 eq) in THF (55 mL) and H_2O (83 mL) was added crude (1*Z*,3*RS*)-3-bromocyclooct-1-ene **385** (79.3 mmol, 1.0 eq) and the resulting mixture stirred at RT for 24 hrs. The mixture was then diluted with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% Et_2O/petrol → 20% Et_2O/petrol) to give **176** as a colourless oil (7.41 g, 74% over 2 steps).

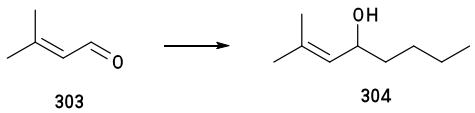
Attempted synthesis of benzyl (1*RS*,2*Z*)-cyclohept-2-en-1-ylcarbamate 386



176 386

Following **General Procedure 9**, **176** (1.26 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.50 mmol, 0.05 eq), KPF_6 (92 mg, 0.50 mmol, 0.05 eq) and benzyl carbamate (2.27 g, 150 mmol, 1.5 eq) in 1,4-dioxane (30 mL) for 16 hrs gave a crude product. ^{1}H NMR analysis showed that the crude product contained a complex mixture of unidentified products. No further purification was attempted.

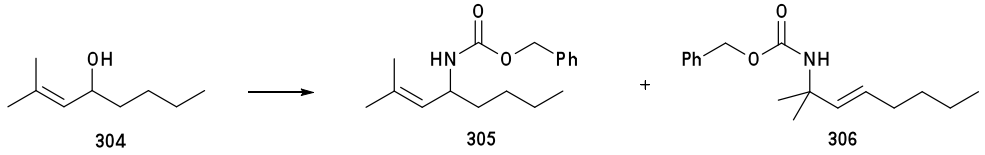
(*RS*)-2-Methyloct-2-en-4-ol 304



303 304

To a stirred solution of 3,3-dimethylbutenal **303** (0.96 mL, 10.0 mmol, 1.0 eq) in THF (50 mL) at −78 °C was added *n*BuLi (1.6M in hexane, 7.50 mL, 12.0 mmol, 1.2 eq) dropwise. The resulting solution was stirred at −78 °C for 1 hr then quenched with H_2O (50 mL) and allowed to warm to RT. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried, filtered and concentrated *in vacuo* to give **304** as a colourless oil (1.42 g, quant.) which was used without further purification; δ_H (400MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, C(8)*H*$_3$), 1.21-1.45 (5H, m, 5 × C*H*$_2$), 1.5-1.60 (2H, m, 1 × C*H*$_2$ and O*H*), 1.67 (3H, d, *J* 1.3, C(2)*Me*$_A$Me$_B$), 1.71 (3H, d, *J* 1.2, C(2)Me$_A$*Me*$_B$), 4.32 (1H, dt, *J* 8.7, 6.6, C(4)*H*), 5.15 (1H, m, C(3)*H*).

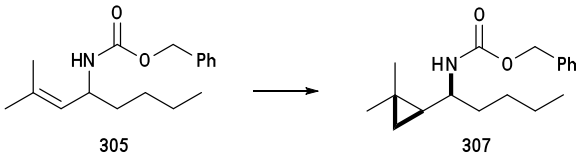
Benzyl (*RS*)-2-methyloct-2-en-4-ylcarbamate 305 and benzyl (*E*)-2-methyloct-3-en-2-ylcarbamate 306



Following **General Procedure 9**, **304** (1.42 g, 10.0 mmol, 1.0 eq), $Bi(OTf)_3$ (328 mg, 0.50 mmol, 0.05 eq), KPF_6 (92 mg, 0.50 mmol, 0.05 eq), benzyl carbamate (2.27 g, 15.0 mmol, 1.5 eq) and $MgSO_4$ (~1.5 g) in THF (50 mL) for 14 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give firstly a 33:67 mixture of **305**:**306** as a pale yellow oil (1.19 g, 43%) followed by pure **305** as a colourless oil (326 mg, 12%); data for **305**; ν_{max} (film) 3445 (N-H), 2935 (C-H), 1680 (C=O), 1535, 1455; δ_H (400MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, C(8)H_3), 1.25-1.40 (5H, m, 5 × CH_2), 1.53-1.58 (1H, m, 1 × CH_2), 1.71 (6H, s, C(2)Me_2), 4.28-4.34 (1H, m, C(4)*H*), 4.62 (1H, br s, N*H*), 4.96 (1H, d, *J* 9.0, C(3)*H*), 5.09 (2H, AB q, *J* 9.3, OCH_2Ph), 7.29-7.39 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.0 (*C*(8)), 18.3 (C(2)Me_AMe$_B$), 22.6 (*C*(7)), 25.7 (C(2)Me$_A$$Me_B$), 27.8 (*C*(6)), 36.0 (*C*(5)), 49.5 (*C*(4)), 66.5, (O*C*H$_2$Ph), 125.7 (*C*(3)), 128.0, 128.1, 128.5 (*Ph*), 136.7 (*i-Ph* and *C*(2)), 156.1 (*C*=O); *m/z* (ESI$^+$) 276 ([M+H]$^+$, 60%), 298 ([M+Na]$^+$, 45%), 551 ([2M+H]$^+$, 70%), 573 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{25}NNaO_2$ (M+Na$^+$) requires 298.1778, found 298.1777; selected data for **306**; δ_H (400MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(8)H_3), 1.24-1.45 (4H, m, C(6)H_2 and C(7)H_2) overlapping 1.41 (6H, s, C(2)Me_2), 2.00-2.05 (2H, m, C(5)H_2), 4.83 (1H, br s, N*H*), 5.06 (2H, s, OCH_2Ph), 5.49-5.62 (2H, m, C(3)*H* and C(4)*H*), 7.27-7.37 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.0 (*C*(8)), 22.2 (*C*(7)), 27.6, 27.8 (C(2)Me_2), 31.5 (*C*(6)), 31.9 (*C*(5)), 53.2 (*C*(2)), 66.1 (O*C*H$_2$Ph), 128.0, 128.1, 128.5 (*C*(4) and *Ph*), 135.7 (*C*(3)),

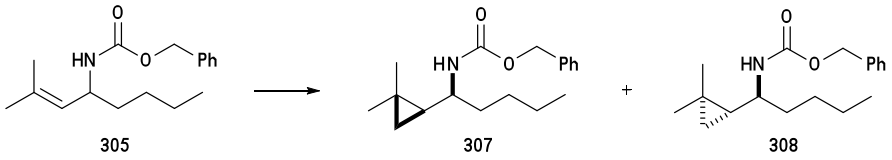
136.8 (*i-Ph*), 156.2 (*C*=O); *m/z* (ESI$^+$) 276 ([M+H]$^+$, 75%), 298 ([M+Na]$^+$, 70%), 551 ([2M+H]$^+$, 75%), 573 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{25}NNaO_2$ (M+Na$^+$) requires 298.1778, found 298.1773.

Benzyl (1*SR*,1′*SR*)-1-(2′,2′-dimethylcyclopropyl)pentylcarbamate 307



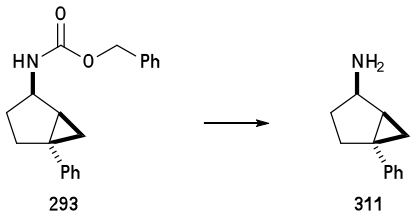
Following **General Procedure 1**, **305** (138 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.00 mL, 1.00 mmol, 2.0 eq), and CH_2I_2 (0.16 mL, 2.00 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **307** as a white solid (122 mg, 84%, >95:5 d.r.); m.p. 36-38 °C; ν_{max} (KBr) 3340 (N-H), 2930 (C-H), 1680 (C=O), 1535, 1455, 1375, 1265, 1025, 755, 695, 665; δ_H (400MHz, $CDCl_3$) 0.29-0.30 (1H, m, cyclopropane CH_AH$_B$), 0.40 (1H, dd, *J* 8.5, 4.4, cyclopropane CH$_A$$H_B$), 0.51 (1H, app td, *J* 9.2, 5.6, C(1′)*H*), 0.91 (3H, br t, *J* 6.6, C(5)H_3), 1.04 (3H, s, C(2′)*Me*$_A$Me$_B$), 1.12 (3H, s, C(2′)Me$_A$*Me*$_B$), 1.29-1.36 (4H, m, C(3)H_2 and C(4)H_2), 1.48-1.58 (2H, m, C(2)H_2), 3.22-3.26 (1H, m, C(1)*H*), 4.74 (1H, d, *J* 7.3, N*H*), 5.10 (2H, s, OCH_2Ph), 7.30-7.37 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.1 (*C*(5)), 17.0 (*C*(2′)), 18.1 (cyclopropane *C*H$_2$), 20.6 (C(2′)*Me*$_A$Me$_B$), 22.7 (*C*(4)), 27.2 (C(2′)Me$_A$*Me*$_B$), 27.8 (*C*(3)), 30.6 (*C*(1′)), 36.8 (*C*(2)), 52.6 (*C*(1)), 66.5 (O*C*H$_2$Ph), 128.0, 128.5 (*Ph*), 136.8 (*i-Ph*), 156.1 (*C*=O); *m/z* (ESI$^+$) 290 ([M+H]$^+$, 40%), 353 ([M+MeCN+Na]$^+$, 70%), 579 ([2M+H]$^+$, 80%), 601 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{28}NO_2$ (M+H$^+$) requires 290.2115, found 290.2120.

Benzyl (1*SR*,1′*SR*)-1-(2′,2′-dimethylcyclopropyl)pentylcarbamate 307 and benzyl (1*SR*,1′*RS*)-1-(2′,2′-dimethylcyclopropyl)pentylcarbamate 308



Following **General Procedure 3**, **305** (138 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.0 mL, 1.0 mmol, 2.0 eq), CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) and TFA (72 μL, 2.0 mmol, 2.0 eq) in CH_2Cl_2 (1.0 mL) for 6 hrs gave a crude product. ^{1}H NMR analysis showed that the reaction had reached 43% conversion, giving a 77:23 mixture of **307**:**308**. No further purification was attempted; data for major diastereoisomer **307** identical to above; characteristic peaks for minor diastereoisomer **308**; δ_H (400MHz, $CDCl_3$) 0.15-0.19 (1H, m, cyclopropane CH_2), 0.64-0.68 (1H, m, C(1′)*H*).

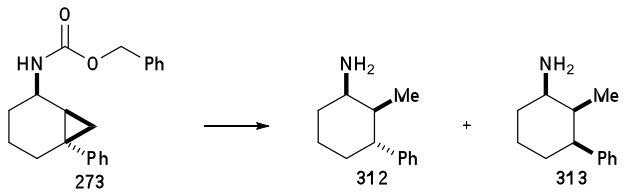
(1*SR*,2*RS*,5*SR*)-5-Phenylbicyclo[3.1.0]hexan-2-amine 311



Following **General Procedure 11**, **293** (200 mg, 0.65 mmol, 1.0 eq) and Pd/C (60 mg) in MeOH/EtOAc (4:1, v/v, 10 mL) gave amine **311** as a white solid (113 mg, quant.); m.p. 99-101 °C; ν_{max} (KBr) 3355 (N-H), 3060, 3010, 2935, 2865 (C-H), 1600, 1500, 1450, 1385 (Ar), 1100, 1030, 755, 700; δ_H (400 MHz, $CDCl_3$) 0.76 (1H, dd, *J* 8.0, 5.2, C(6)H_AH_B), 1.05-1.13 (2H, m, C(1)*H* and C(6)H_AH_B), 1.65 (2H, br s, NH_2), 1.79 (1H, dt, *J* 8.2, 4.2, C(3)H_AH_B), 1.94-2.03 (1H, m, C(3)H_AH_B), 2.05-2.17 (2H, m, C(4)H_2), 3.72-3.78 (1H, m, C(2)*H*), 7.15-7.19 (3H, m, *Ph*), 7.29-7.31 (2H, m, *o-Ph*);

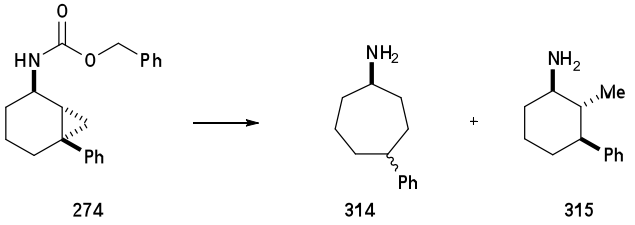
δ_C (100 MHz, $CDCl_3$) 13.6 (*C*(6)), 30.9, 31.1 (*C*(3) and *C*(4)), 31.7 (*C*(5)), 32.9 (*C*(1)), 53.5 (*C*(2)), 125.4 (*p-Ph*), 126.0, 128.2 (*Ph*), 145.0 (*i-Ph*); *m/z* (CI^+) 143 ([M-NH_2]$^+$, 100%); HRMS (CI^+) $C_{11}H_{11}$ ([M-NH_2]$^+$) requires 143.0861, found 143.0864.

(1*RS*,2*SR*,3*RS*)-2-Methyl-3-phenylcyclohexanamine 312 and (1*RS*,2*SR*,3*SR*)-2-methyl-3-phenylcyclohexanamine 313



Following **General Procedure 11**, **273** (161 mg, 0.50 mmol, 1.0 eq) and Pd (10% wt. on carbon, 50 mg) in MeOH (5 mL) under 1 atm. H_2 (g) for 4 hrs gave a 85:15 mixture of **312**:**313** as a pale yellow oil (95 mg, quant.); ν_{max} (film) 3360 (N-H), 3025, 2930 (C-H), 1495, 1450 (Ar), 1235, 1110, 1030, 755, 700; data for major diastereoisomer **312**; δ_H (400MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.9, C(2)*Me*), 1.42-1.52 (1H, m, C(4)H_AH_B), 1.57-1.63 (1H, m, C(5)H_AH_B), 1.67-1.97 (7H, m, C(2)*H*, C(4)H_AH_B, C(5)H_AH_B, C(6)H_2 and NH_2), 2.56 (1H, td, *J* 11.8, 3.4, C(3)*H*), 3.17 (1H, app d, *J* 2.7, C(1)*H*), 7.14-7.21 (3H, m, *Ph*), 7.26-7.31 (2H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 17.2 (C(2)*Me*), 20.1 (*C*(5)), 33.8 (*C*(6)), 35.4 (*C*(4)), 40.7 (*C*(2)), 44.4 (*C*(3)), 51.5 (*C*(1)), 125.9, 127.6, 128.4 (*Ph*), 146.1 (*i-Ph*); *m/z* (ESI^+) 190 ([M+H]$^+$, 100%), 231 (M+MeCN+H)$^+$, 70%); HRMS (ESI^+) $C_{13}H_{20}N$ (M+H$^+$) requires 190.1590, found 190.1589; selected data for minor diastereoisomer **313**; δ_H (400MHz, $CDCl_3$) 0.67 (1H, d, *J* 6.9, C(2)*Me*), 2.18-2.24 (1H, m, C(3)*H*); δ_C (100MHz, $CDCl_3$) 16.7 (C(2)*Me*), 46.2 (*C*(3)).

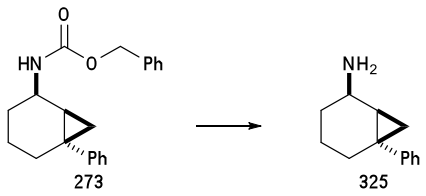
4-Phenylcycloheptanamine 314 and (1*RS*,2*RS*,3*SR*)-2-methyl-3-phenylcyclohexanamine 315



274 314 315

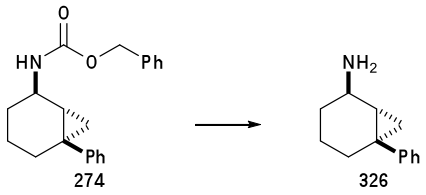
Following **General Procedure 11**, **274** (161 mg, 0.50 mmol, 1.0 eq) and Pd (10% wt. on carbon, 50 mg) in MeOH (5 mL) under 1 atm. H_2 (g) for 4 hrs gave a 85:15 misture of **314**:**315** as a white solid (95 mg, quant.); m.p. 77-79 °C; ν_{max} (KBr) 3425 (N-H), 2925 (C-H), 1625, 1575, 1450 (Ar), 1385, 1350, 755, 700; data for major product **314**; δ_H (400MHz, $CDCl_3$) 1.40-1.77 (6H, m, 6 × C*H*$_2$), 1.77-2.00 (6H, m, 4 × C*H*$_2$ and N*H*$_2$), 2.67-2.74 (1H, m, C(4)*H*), 3.05 (1H, ddt, *J* 10.8, 7.6, 3.7, C(1)*H*), 7.14-7.20 (3H, m, *Ph*), 7.25-7.30 (2H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 22.4, 33.2, 36.4, 37.4, 38.0 (*C*(2), *C*(3), *C*(5), *C*(6) and *C*(7)), 47.0 (*C*(4)), 52.7 (*C*(1)), 125.7, 126.7, 128.4 (*Ph*), 149.3 (*i-Ph*); *m/z* (ESI^+) 190 ($[M+H]^+$, 85%), 231 $(M+MeCN+H)^+$, 100%); HRMS (ESI^+) $C_{13}H_{20}N$ ($M+H^+$) requires 190.1590, found 190.1590; selected data for minor product **315**; δ_H (400MHz, $CDCl_3$) 0.76 (3H, d, *J* 6.4, C(2)*Me*), 2.16-2.22 (1H, m, C(3)*H*), 2.44 (1H, td, *J* 10.3, 4.1, C(1)*H*); δ_C (100MHz, $CDCl_3$) 16.4 (C(2)*Me*), 45.4 (*C*(2)), 50.9 (*C*(3)), 56.6 (*C*(1)).

(1*SR*,2*RS*,6*SR*)-6-Phenylbicyclo[4.1.0]heptan-2-amine 325



To a stirred solution of **273** (32 mg, 0.10 mmol, 1.0 eq) in MeCN (1.0 mL) was added TMSI (21 μL, 0.15 mmol, 1.5 eq) and the mixture stirred at RT for 30 mins. The reaction mixture was concentrated *in vacuo* and the crude product purified by trituration with Et_2O (2 × 5 mL) to give **325** as a white solid (17 mg, 91%); m.p. 174-176 °C; ν_{max} (KBr) 3425 (N-H), 2930 (C-H), 1630, 1560, 1450 (Ar), 1350, 755, 700; δ_H (400MHz, MeOD) 1.01 (1H, app t, *J* 5.6, C(7)H_AH_B), 1.12 (1H, dd, *J* 9.2, 5.2, C(7)H_AH_B), 1.32 (1H, dddd, *J* 13.3, 10.6, 8.3, 2.6, C(3)H_AH_B), 1.48-1.65 (3H, m, C(1)*H* and C(4)H_2), 1.85-2.03 (3H, m, C(3)H_AH_B and C(5)H_2), 3.99 (1H, app dt, *J* 8.5, 6.1, C(2)*H*), 4.65 (2H, br s, NH_2), 7.17-7.21 (1H, m, *p-Ph*), 7.27-7.33 (4H, m, *o/m-Ph*); δ_C (100MHz, MeOD) 14.3 (*C*(7)), 20.2 (*C*(4)), 21.6 (*C*(1)), 24.9 (*C*(3)), 28.1 (*C*(6)), 31.2 (*C*(5)), 47.7 (*C*(2)), 126.4 (*p-Ph*), 127.6, 128.6 (*o/m-Ph*), 147.6 (*i-Ph*); *m/z* (ESI^+) 171 ($[M-NH_2]^+$, 100%); HRMS (ESI^+) $C_{13}H_{18}N$ ($M+H^+$) requires 188.1434, found 188.1433.

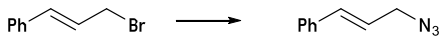
(1*RS*,2*RS*,6*RS*)-6-phenylbicyclo[4.1.0]heptan-2-amine 326



To a stirred solution of **274** (32 mg, 0.10 mmol, 1.0 eq) in MeCN (1.0 mL) was added TMSI (21 μL, 0.15 mmol, 1.5 eq) and the mixture stirred at RT for 30 mins. The

reaction mixture was concentrated *in vacuo* and the crude product purified by trituration with Et_2O (2 × 5 mL) to give **326** as a pale yellow solid (18 mg, 96%); m.p. 225 °C (dec.); ν_{max} (KBr) 3365 (N-H), 3025, 2925 (C-H), 1705, 1600, 1495, 1450 (Ar), 1375, 1235, 1110, 1030, 755, 700; δ_H (400MHz, MeOD) 0.89 (1H, app t, *J* 6.0, C(7)H_AH_B), 1.11-1.15 (1H, m, C(7)H_AH_B), 1.19-1.24 (1H, m, C(1)*H*), 1.29-1.42 (2H, m, C(3)H_AH_B and C(4)H_AH_B), 1.70-1.75 (1H, m, C(4)H_AH_B), 1.89-2.02 (2H, m, C(3)H_AH_B and C(5)H_AH_B), 2.16 (dt, *J* 13.7, 4.1, C(5)H_AH_B), 3.49-3.55 (1H, m, C(2)*H*), 4.64 (2H, br s, NH_2), 7.16-7.21 (1H, m, *p-Ph*), 7.27-7.32 (2H, m, *m-Ph*), 7.35-7.38 (2H, m, *o-Ph*); δ_C (100MHz, MeOD) 15.6 (*C*(7)), 17.6 (*C*(4)), 21.8 (*C*(1)), 26.6 (*C*(6)), 27.5 (*C*(3)), 30.6 (*C*(5)), 48.4 (*C*(2)), 126.4 (*p-Ph*), 127.8, 128.5 (*o/m-Ph*), 147.2 (*i-Ph*); *m/z* (ESI$^+$) 171 ([M-NH_2]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}N$ (M+H^+) requires 188.1434, found 188.1432.

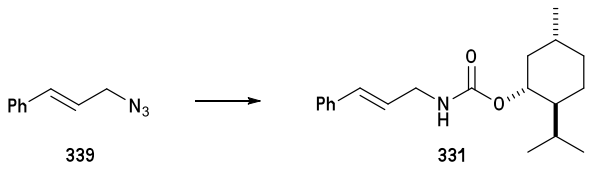
(*E*)-Cinnamyl azide 339[25]



338 339

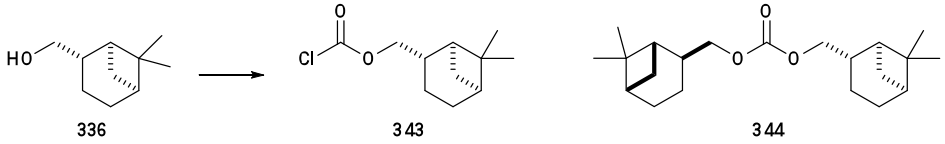
To a stirred solution of (*E*)-cinnamyl bromide **338** (9.85 g, 50.0 mmol, 1.0 eq) in H_2O (50 mL) and acetone (150 mL) was added NaN_3 (1.30 g, 100 mmol, 2.0 eq) and the resulting solution stirred at RT for 16 hrs. The mixture was diluted with CH_2Cl_2 (500 mL), the aqueous layer separated and the organic layer washed with H_2O (200 mL) and brine (200 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give **339** as a pale yellow oil (7.21 g, 91%); δ_H (400 MHz, $CDCl_3$) 3.96 (2H, d, *J* 6.6, C(1)H_2), 6.26 (1H, dt, *J* 15.8, 6.6, C(2)*H*), 6.66 (1H, d, *J* 15.8, C(3)*H*), 7.27-7.43 (5H, m, *Ph*).

(1′*R*,2′*S*,5′*R*)-Menthyl cinnamylcarbamate 331



Following **General Procedure 12**, cinnamyl azide **339** (636 mg, 4.0 mmol, 1.0 eq), *n*-Bu_{3P} (1.04 mL, 4.2 mmol, 1.05 eq) and (–)-menthyl chloroformate **341** (0.93 mL, 4.4 mmol, 1.10 eq) in THF (20 mL) for 24 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **331** as a pale yellow solid (1.05 g, 83%); m.p. 97-99 °C; $[\alpha]_D^{25}$ –40.5 (c = 1.0, $CHCl_3$); ν_{max} (KBr) 3340 (N-H), 2945 (C-H), 1680 (C=O), 1525; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 7.0, CH*Me*), 0.87-1.12 (9H, m, 2 × *Me* and 3 × C*H*$_2$), 1.27-1.38 (1H, m, C*H*i-Pr), 1.41-1.55 (1H, m, C*H*Me_2), 1.62-1.71 (2H, m, 2 × C*H*$_2$), 1.92-1.99 (2H, m, C*H*Me), 2.04-2.11 (1H, m, 1 × C*H*$_2$), 3.97 (2H, app br s, C(1)*H*$_2$), 4.59 (1H, td, *J* 10.7, 4.1, OC*H*), 4.82 (1H, br s, N*H*), 6.21 (1H, dt, *J* 15.7, 6.0, C(2)*H*), 6.51 (1H, d, *J* 15.7, C(3)*H*), 7.24-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5, 20.8, 22.1 (3 × *Me*), 23.5 (1 × CH_2), 26.3 (*C*HMe), 31.4 (*C*HMe_2), 34.3, 41.5 (2 × *C*H$_2$), 43.0 (*C*(1)), 47.4 (*C*Hi-Pr), 74.7 (O*C*H), 126.2, 126.4, 127.6, 128.6 (*o/m/p-Ph* and *C*(2)), 131.5 (*C*(3)), 136.6 (*i-Ph*), 156.4 (*C*=O); *m/z* (ESI^+) 338 ($[M+Na]^+$, 30%), 653 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{29}NNaO_2$ ($M+Na^+$) requires 338.2091, found 338.2089.

(1*S*,2*S*,5*S*)-Myrtanyl chloroformate 343 and bis-(1*S*,2*S*,5*S*)-myrtanyl carbonate 344

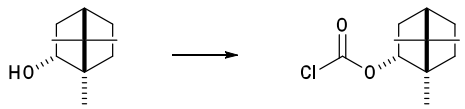


336 343 344

To a stirred solution of triphosgene (989 mg, 3.33 mmol, 0.33 eq) in toluene (25 mL) was added pyridine (1.21 mL, 15.0 mmol, 1.5 eq) dropwise and the resulting solution stirred for 10 mins at RT. A solution of (–)-myrtanol **336** (1.54 g, 10.0 mmol, 1.0 eq) in toluene (25 mL) was then added dropwise and the resulting solution stirred for 6 hrs at 60 °C. The reaction was allowed to cool to RT, H_2O (25 mL) was added, the organic layer separated and the aqueous layer extracted with toluene (2 × 25 mL). The combined organic layers were washed sequentially with H_2O (25 mL) and brine (25 mL), dried, filtered and concentrated *in vacuo* to give a 70:30 mixture of **343**:**344** as a pale yellow oil (2.53 g, quant.); Data for mixture; $[\alpha]_D^{25}$ –24.1 (c = 1.0, $CHCl_3$); ν_{max} (film) 2915, 1780 (OC(=O)Cl), 1745 (O_2C=O), 1260, 1155; Data for **343**; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, s, 1 × *Me*), 1.23 (3H, s, 1 × *Me*), 1.26-1.34 (2H, m, C(3)H_AH_B and C(7)H_AH_B), 1.61-1.71 (1H, m, C(3)H_AH_B), 1.75-1.93 (4H, m, C(1)*H*, C(4)H_2 and C(5)*H*), 2.04-2.13 (1H, m, C(7)H_AH_B), 2.32-2.45 (1H, m, C(2)*H*), 4.12 (1H, dd, *J* 7.2, 2.8, *C*H_2O); δ_C (100 MHz, $CDCl_3$) 17.9 (*C*(3)), 20.1 (1 × *Me*), 23.3, 23.9 (*C*(4) and *C*(7)), 26.6 (1 × *Me*), 34.2 (*C*(2)), 39.1 (*C*(6)), 40.8, 42.1 (*C*(1) and *C*(5)), 75.4 (*C*H_2O), 150.7 (*C*=O); *m/z* (FI^+) 216 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{17}O_2Cl$ (M^+) requires 216.0917, found 216.0927; data for **344**; δ_H (400 MHz, $CDCl_3$) 0.84 (6H, s, 2 × *Me*), 1.21 (6H, s, 2 × *Me*), 1.26-1.34 (4H, m, 2 × C(3)H_AH_B and 2 × C(7)H_AH_B), 1.61-1.71 (2H, m, 2 × C(3)H_AH_B), 1.75-1.93 (8H, m, 2 × C(1)*H*, 2 × C(4)H_2 and 2 × C(5)*H*), 2.04-2.13 (2H, m, 2 × C(7)H_AH_B), 2.32-2.45 (2H, m, 2 × C(2)*H*), 4.12 (4H,

dd, *J* 7.2, 2.8, 2 × C*H*$_2$O); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*(3)), 20.1 (1 × *Me*), 23.3, 23.8 (*C*(4) and *C*(7)), 26.5 (1 × *Me*), 34.1 (*C*(2)), 39.2 (*C*(6)), 40.6, 41.9 (*C*(1) and *C*(5)), 71.2 (*C*H$_2$O), 155.6 (*C*=O).

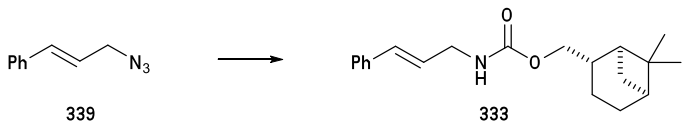
(1*S*,2*R*,4*S*)-Bornyl chloroformate 345



337 345

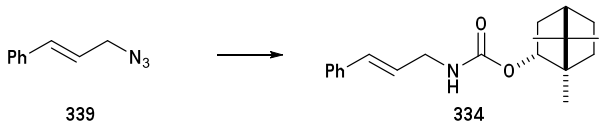
To a stirred solution of triphosgene (989 mg, 3.33 mmol, 0.33 eq) in toluene (25 mL) was added pyridine (1.21 mL, 15.0 mmol, 1.5 eq) dropwise and the resulting solution stirred for 10 mins at RT. A solution of (−)-borneol **337** (1.54 g, 10.0 mmol, 1.0 eq) in toluene (25 mL) was then added dropwise and the resulting solution stirred for 6 hrs at 60 °C. The reaction was allowed to cool to RT, H_2O (25 mL) was added, the organic layer separated and the aqueous layer extracted with toluene (2 × 25 mL). The combined organic layers were washed sequentially with H_2O (25 mL) and brine (25 mL), dried, filtered and concentrated *in vacuo* to give **345** as a colourless oil (2.16 g, quant.); $[\alpha]_D^{25}$ −35.5 (c = 1.0, $CHCl_3$); ν_{max} (film) 2950, 1775 (C=O), 1455, 1265, 1175, 1150; δ_H (400 MHz, $CDCl_3$) 0.87 (9H, m, 3 × *Me*), 1.15-1.39 (3H, m, C(3)H_AH_B and 2 × C*H*$_2$), 1.67-1.98 (3H, m, C(4)*H* and 2 × C*H*$_2$), 2.35-2.44 (1H, m, C(3)H_AH_B), 4.99 (1H, ddd, *J* 9.9, 3.2, 2.2, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 13.4, 18.8, 19.6 (3 × *Me*) 26.8, 27.8 (*C*(5) and *C*(6)), 36.1 (*C*(3)), 44.6 (*C*(4)), 48.1, 49.3 (*C*(1) and *C*(7)), 89.4 (*C*(2)), 150.7 (*C*=O); *m/z* (FI^+) 216 ([M^+], 100%); HRMS (FI^+) $C_{11}H_{17}O_2Cl$ (M^+) requires 216.0917, found 216.0924.

(1′*S*,2′*S*,5′*S*)-Myrtanyl cinnamylcarbamate 333



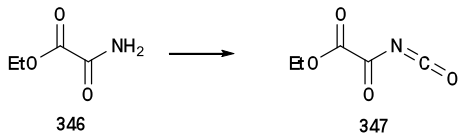
Following **General Procedure 12**, **339** (159 mg, 1.00 mmol, 1.0 eq), *n*-Bu_3P (0.26 mL, 1.05 mmol, 1.05 eq) and (1*S*,2*S*,3*S*)-myrtanyl chloroformate **343** (238 mg, 1.10 mmol, 1.1 eq) in THF (5 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **333** as a pale yellow oil (185 mg, 59%); $[\alpha]_D^{25}$ −15.8 (c = 1.0, $CHCl_3$); ν_{max} (film) 3335 (N-H), 2915, 1700 (C=O), 1515, 1255; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, 1 × *Me*), 1.22 (3H, s, 1 × *Me*), 1.26-1.36 (2H, m, C(3′)H_AH_B and C(7′)H_AH_B), 1.59-1.67 (1H, m, C(3′)H_AH_B), 1.72-1.91 (4H, m, C(1′)*H*, C(4′)H_2 and C(5′)*H*), 2.03-2.06 (1H, m, C(7′)H_AH_B), 2.30 (1H, app quintet, *J* 7.7, C(2′)*H*), 3.86-3.97 (4H, m, C(1)H_2 and CH_2O), 4.93 (1H, br s, N*H*), 6.20 (1H, dt, *J* 15.8, 6.2, C(2)*H*), 6.51 (1H, d, *J* 15.8, C(3)*H*), 7.22-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1 (*C*(3′)), 20.2 (1 × *Me*), 23.4 (*C*(7′)), 24.0 (*C*(4′)), 26.6 (1 × *Me*), 34.5 (*C*(2′)), 39.1 (*C*(6′)), 40.8, 42.3 (*C*(1′) and *C*(5′)), 43.1 (*C*(1)), 68.4 (*C*H_2O), 126.0, 126.4, 127.6, 128.5 (*C*(2) and *Ph*), 131.6 (*C*(3)), 136.6 (*i-Ph*), 156.8 (*C*=O); *m/z* (FI^+) 313 ($[M]^+$, 100%); HRMS (FI^+) requires 313.2042, found 313.2043.

(1′*S*,2′*R*,4′*S*)-Bornyl cinnamylcarbamate 334



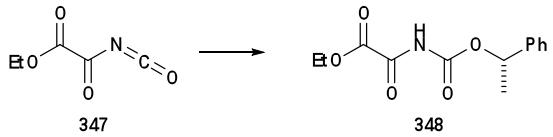
Following **General Procedure 12**, **339** (159 mg, 1.0 mmol, 1.0 eq), *n*-Bu_3P (0.26 mL, 1.05 mmol, 1.05 eq), and (1*S*,2*R*,4*S*)-bornyl chloroformate **345** (238 mg, 1.10 mmol, (1.10 eq) in THF (5 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **334** as a pale yellow oil (211 mg, 67%); $[\alpha]_D^{25}$ −25.1 (c = 1.0, $CHCl_3$); ν_{max} (film) 3335 (N-H), 2955, 2880, 1700 (C=O), 1515, 1455, 1255; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, 1 × *Me*), 0.87 (3H, s, 1 × *Me*), 0.91 (3H, s, 1 × *Me*), 1.05 (1H, dd, *J* 13.7, 3.4, C(3)H_AH_B), 1.20-1.32 (2H, m, 2 × CH_2), 1.61-1.77 (2H, m, C(4′)*H* and 1 × CH_2), 1.87-1.95 (1H, m, 1 × CH_2), 2.32-2.40 (1H, m, C(3′)H_AH_B), 3.95-4.00 (2H, m, C(1)H_2), 4.88 (1H, ddd, *J* 9.9, 3.4, 2.1, C(2′)*H*), 4.93 (1H, br s, N*H*), 6.21 (1H, dt, *J* 15.8, 6.2, C(2)*H*), 6.52 (1H, d, *J* 15.8, C(3)*H*), 7.22-7.27 (1H, m, *Ph*), 7.29-7.38 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4, 18.9, 19.8 (3 × *Me*), 25.9, 28.3 (*C*(5′) and *C*(6′)), 39.0 (*C*(3′)), 43.1 (*C*(1)), 44.8 (*C*(4′)), 48.8, 49.5 (*C*(1′) and *C*(7′)), 80.3 (*C*(2′)), 126.1, (*C*(2)), 126.4, 127.6, 128.6 (*Ph*), 131.7 (*C*(3)), 136.6 (*i-Ph*), 157.0 (*C*=O); *m/z* (ESI^+) 336 ($[M+Na]^+$, 90%), 649 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{27}NNaO_2$ ($M+Na^+$) requires 336.1934, found 336.1926.

Ethyloxalyl isocyanate 347[26]



To a stirred solution of ethyl oxamate **346** (11.7 g, 100 mmol, 1.0 eq) in CH_2Cl_2 (200 mL) at 0 °C was added oxalyl chloride (9.31 mL, 110 mmol, 1.1 eq) dropwise over 5 mins. The resulting mixture was stirred at reflux for 24 hrs then concentrated *in vacuo* to give a crude product which was purified by vacuum distillation to give **347** as a colourless oil (6.00 g, 42%); b.p. 58-63 °C (1 mm/Hg) {lit.[26] b.p. 78 °C (10 Torr)}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.2, OCH_2CH_3), 4.43 (2H, q, *J* 7.2, OCH_2CH_3).

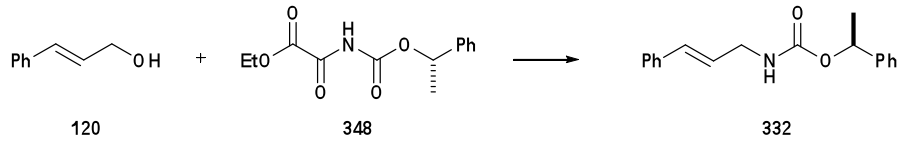
Ethyl *N*-(*S*)-1-phenylethyloxycarbonyloxamate 348



To a stirred solution of **347** (716 mg, 5.0 mmol, 1.0 eq) in toluene (5 mL) at 0 °C was added (*S*)-2-phenylethanol **335** (0.60 mL, 5.0 mmol, 1.0 eq) and the mixture stirred at 40 °C for 1 hr then concentrated *in vacuo* to give **348** as a colourless oil (1.33 g, quant.); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.2, OCH_2CH_3), 1.67 (3H, d, *J* 6.7, OCH*Me*), 4.36 (2H, q, *J* 7.2, OCH_2CH_3), 6.02 (1H, q, *J* 6.7, OC*H*Me), 7.27-7.40 (5H, m, *Ph*); which was found to hydrolyse on standing to give (*S*)-1-phenylethyl carbamate **466**; m.p. 54-56 °C; $[\alpha]_D^{25}$ –29.3 (c = 1.0, EtOH); ν_{max} (KBr) 3440 (N-H), 1705 (C=O), 1455, 1400 (Ar), 1310, 1210, 1060, 1030, 765, 700; δ_H (400 MHz, $CDCl_3$) 1.56 (1H, d, *J* 6.6, OCH*Me*), 4.97 (2H, br s, NH_2), 5.79 (1H, q, *J* 6.6, OC*H*Me), 7.27-7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.3 (*Me*), 73.2 (OC*H*Me),

126.0, 127.9, 128.4 (*o/m/p-Ph*), 141.8 (*i-Ph*), 156.8 (*C*=O); *m/z* (FI^+) 165 ($[M]^+$, 100%); HRMS (FI^+) $C_9H_{11}NO_2$ (M^+) requires 165.0790, found 165.0788.

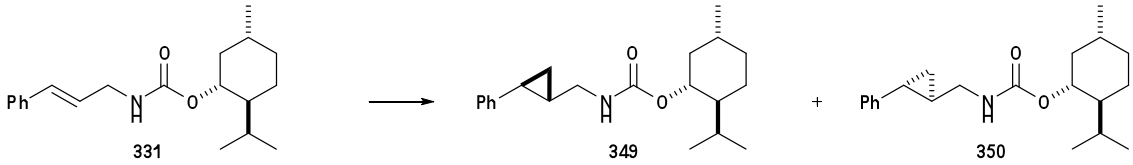
(*S*)-1′-Phenylethyl cinnamylcarbamate 332



120 348 332

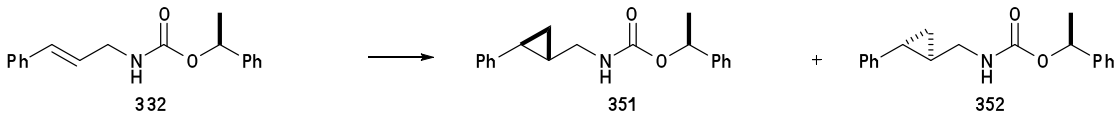
Following **General Procedure 13**, (*E*)-cinnamyl alcohol **120** (134 mg, 1.0 mmol, 1.0 eq), **348** (318 mg, 1.2 mmol, 1.2 eq), PPh_3 (315 mg, 1.2 mmol, 1.2 eq) and DEAD (0.19 mL, 1.2 mmol, 1.2 eq) in THF (10 mL) for 24 hrs, followed by $LiOH{\cdot}H_2O$ (128 mg, 3.0 mmol, 3.0 eq) and H_2O (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **332** as a white solid (158 mg, 56%); m.p. 51-53 °C; $[\alpha]_D^{25}$ +1.1 (c = 1.0, $CHCl_3$); ν_{max} (KBr) 3330 (N-H), 2980 (C-H), 1700 (C=O), 1520, 1450 (Ar), 1250, 1065, 965, 745, 700; δ_H (400 MHz, $CDCl_3$) 1.59 (3H, d, *J* 6.6, OCH*Me*), 3.95-3.99 (2H, m, C(1)H_2), 4.98 (1H, br s, N*H*), 5.88 (1H, q, *J* 6.6, OC*H*Me), 6.20 (1H, dt, *J* 15.9, 6.1, C(2)*H*), 6.52, (1H, d, *J* 15.9, C(3)*H*), 7.26-7.42 (10H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.5 (*Me*), 43.1 (*C*(1)), 72.9 (O*C*HMe), 125.9, 126.0, 126.4, 127.7, 127.8, 128.5, 128.6 (*C*(2) and 10 × *Ar*), 131.7 (*C*(3)), 136.6, 142.2 (2 × *i-Ph*), 155.9 (*C*=O); *m/z* (ESI^+) 304 ($[M+Na]^+$, 50%); 585 ($[2M+Na]^+$, 100%).

(1′′*R*,2′′*S*,5′′*R*)-Menthyl [(1′*S*,2′*S*)-2′-phenylcyclopropyl]methylcarbamate 349 and (1′′*R*,2′′*S*,5′′*R*)-menthyl [(1′*R*,2′*R*)-2′-phenylcyclopropyl]methylcarbamate 350



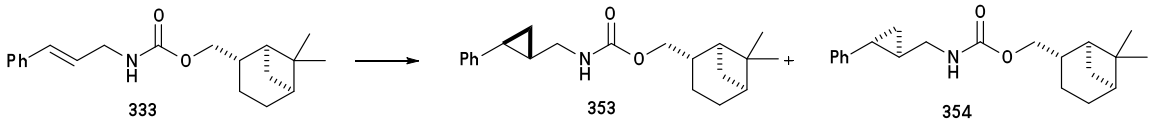
Following **General Procedure 1**, **331** (79 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.50 mL, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give a 51:49 mixture of **349** and **350** as a white solid (73 mg, 89%); m.p. 64-66 °C; $[\alpha]_D^{25}$ –47.6 (c = 1.0, $CHCl_3$); ν_{max} (KBr) 3400 (N-H), 2945, 2865 (C-H), 1690 (C=O), 1520, 1435, 1265, 1135; δ_H (400 MHz, $CDCl_3$) 0.80-1.09 (14H, m, 3 × C*H*$_3$, cyclopropane C*H*$_2$, 2 × C*H*$_2$ and C*H*Me$_2$), 1.29-1.33 (2H, m, C(1′)*H* and C*H*i-Pr), 1.49-1.51 (1H, m, C*H*Me), 1.62-1.71 (2H, m, 2 × C*H*$_2$), 1.78-1.86 (1H, m, 1 × C*H*$_2$), 1.89-2.01 (1H, m, C(2′)*H*), 2.02-2.11 (1H, m, 1 × C*H*$_2$), 3.13-3.35 (2H, m, C(1)*H*$_2$), 4.53-4.62 (1H, m, OC*H*), 4.75-4.86 (1H, m, N*H*), 7.04-7.08 (2H, m, *Ph*), 7.14-7.20 (1H, m, *Ph*), 7.22-7.29 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (cyclopropane *C*H$_2$), 16.4 (1 × *Me*), 20.8 (*C*HMe$_2$), 21.8, 22.1 (2 × *Me*), 23.0, 23.1 (C(1′)$_A$ and C(1′)$_B$), 23.5 (*C*H$_2$), 26.2 (*C*(2′)), 31.4 (*C*HMe), 34.3 (*C*H$_2$), 41.5 (*C*H$_2$), 45.0 (*C*(1)), 47.4 (*C*Hi-Pr), 74.4 (O*C*H), 125.6, 125.8, 128.3 (*Ph*), 142.4 (*i-Ph*), 156.5 (*C*=O); *m/z* (ESI$^+$) 352 ([M+Na]$^+$, 70%), 681 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{31}NNaO_2$ (M+Na$^+$) requires 352.2247, found 352.2246.

(*S*)-1′′-Phenylethyl [(1′*S*,2′*S*)-2′-phenylcyclopropyl]methylcarbamate 351 and (*S*)-1′′-phenylethyl [(1′*R*,2′*R*)-2′-phenylcyclopropyl]methylcarbamate 352



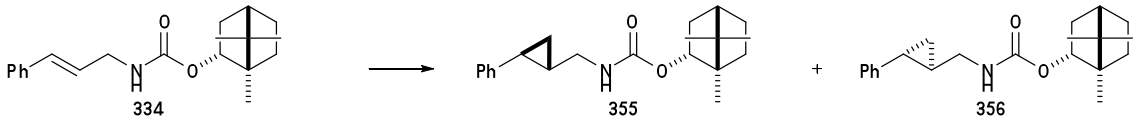
Following **General Procedure 1**, **332** (28 mg, 0.10 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.20 mL, 0.20 mmol, 2.0 eq) and CH_2I_2 (32 μL, 0.40 mmol, 4.0 eq) in CH_2Cl_2 (0.50 mL) for 1 hr gave a crude mixture of **351** and **352** containing CH_2I_2 as the only significant impurity. No further purification was attempted; $[\alpha]_D^{25}$ –6.1 (c = 1.0, $CHCl_3$); ν_{max} (film) 3335 (N-H), 3065, 3030, 2980, 2930 (C-H), 1700 (C=O), 1605, 1515, 1495, 1450 (Ar), 1250, 1065; δ_H (400 MHz, $CDCl_3$) 0.89-0.99 (2H, m, cyclopropane C*H*$_2$), 1.30-1.36 (1H, m, C(1′)*H*), 1.58 (3H, d, *J* 6.4, OCH*Me*), 1.79-1.86 (1H, m, C(2′)*H*), 3.14-3.33 (2H, m, C(1)*H*$_2$), 4.98 (1H, br s, N*H*), 5.83-5.87 (1H, m, OC*H*Me), 7.06 (2H, t, *J* 7.2, *Ar*), 7.17-7.21 (1H, m, *Ar*), 7.26-7.41 (7H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.4 (cyclopropane *C*H$_2$), 21.9 (*C*(2′)), 22.5 (*Me*), 22.9, 23.0 (*C*(1′)$_A$ and *C*(1′)$_B$), 45.2 (*C*(1)), 72.7 (O*C*HMe), 125.7, 125.8, 126.0, 127.8, 128.4, 128.5 (10 × *Ph*), 142.2, 142.4 (2 × *i-Ph*), 155.9 (*C*=O); *m/z* (ESI^+) 318 ($[M+Na]^+$, 70%), 613 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}NNaO_2$ ($M+Na^+$) requires 318.1465, found 318.1465.

(1′′*S*,2′′*S*,5′′*S*)-Myrtanyl [(1′*S*,2′*S*)-2′-phenylcyclopropyl]methylcarbamate 353 and (1′′*S*,2′′*S*,5′′*S*)-myrtanyl [(1′*R*,2′*R*)-2′-phenylcyclopropyl]methylcarbamate 354



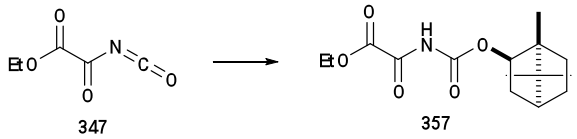
Following **General Procedure 1**, **333** (31 mg, 0.10 mmol, 1.0 eq), $ZnEt_2$ (0.20 mL, 0.20 mmol, 2.0 eq) and CH_2I_2 (32 μL, 0.40 mmol, 4.0 eq) in CH_2Cl_2 (0.50 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give an unknown mixture of **353** and **354** as a pale yellow oil (20 mg, 61%); $[\alpha]_D^{25}$ −11.9 (c = 1.0, $CHCl_3$); ν_{max} (film) 3335 (N-H), 2920 (C-H), 1700 (C=O), 1520, 1260, 700; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, 1 × *Me*), 0.89-0.97 (2H, m, cyclopropane C*H*$_2$), 1.22 (3H, s, 1 × *Me*), 1.24-1.37 (3H, m, C(1′)*H*, C(3′′)*H*$_A$H$_B$ and C(7′′)*H*$_A$H$_B$), 1.58-1.67 (1H, m, C(3′′)H$_A$*H*$_B$), 1.72-1.91 (5H, m, C(2′)*H*, C(1′′)*H*, C(4′′)*H*$_2$ and C(5′)*H*), 2.03-2.09 (1H, m, C(7′′)H$_A$*H*$_B$), 2.26-2.32 (1H, m, C(2′′)*H*), 3.14-3.20 (1H, m, C(1)*H*$_A$H$_B$), 3.25-3.31 (1H, m, C(1)H$_A$*H*$_B$), 3.84-3.92 (2H, m, C*H*$_2$O), 4.80 (1H, br s, N*H*), 7.04-7.06 (2H, m, *o-Ph*), 7.14-7.18 (1H, m, *p-Ph*), 7.24-7.28 (2H, m, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 14.4 (cyclopropane *C*H$_2$), 18.0 (*C*(3′′)), 20.2 (1 × *Me*), 21.9, 23.0 (*C*(1′) and *C*(2′)), 23.4, 24.0 (*C*(4′′) and *C*(7′′)), 26.6 (1 × *Me*), 34.5 (*C*(2′′)), 39.1 (*C*(6′′)), 40.8, 42.3 (*C*(1′′) and *C*(5′′)), 45.1 (*C*(1)), 68.3 (*C*H$_2$O), 125.6, 125.7, 128.3 (*o/m/p-Ph*), 136.8 (*i-Ph*), 156.8 (*C*=O); *m/z* (ESI$^+$) 350 ([M+Na]$^+$, 30%), 677 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_2$ (M+Na$^+$) requires 350.2091, found 350.2090.

(1′′*S*,2′′*R*,4′′*S*)-Bornyl [(1′*S*,2′*S*)-2′-phenylcyclopropyl]methylcarbamate 355 and (1′′*S*,2′′*R*,4′′*S*)-bornyl [(1′*R*,2′*R*)-2′-phenylcyclopropyl]methylcarbamate 356



Following **General Procedure 1**, **334** (157 mg, 0.50 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.0 mL, 2.0 eq) and CH_2I_2 (0.16 mL, 2.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give an unknown mixture of **355** and **356** as a colourless oil (110 mg, 67%); $[\alpha]_D^{25}$ −19.3 (c = 1.0, $CHCl_3$); ν_{max} (film) 3335 (N-H), 2955, 2880, 2360, 2340 (C-H), 1695 (C=O), 1515, 1455 (Ar), 1250; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, s, 1 × *Me*), 0.87 (3H, s, 1 × *Me*), 0.91-0.98 (2H, m, cyclopropane C*H*$_2$) overlapping 0.92 (3H, s, 1 × *Me*), 1.03 (1H, dd, *J* 13.6, 2.8, C(3′′)*H*$_A$H$_B$), 1.20-1.37 (3H, m, C(1′)*H* and 2 × C*H*$_2$), 1.67-1.92 (4H, m, C(2′)*H*, C(4′′)*H* and 2 × C*H*$_2$), 2.32-2.38 (1H, m, C(3′′)H$_A$*H*$_B$), 3.19-3.29 (2H, m, C(1)*H*$_2$), 4.84-4.87 (2H, m, C(2′′)*H* and N*H*), 7.07 (2H, d, *J* 7.3, *o-Ph*), 7.15-7.19 (1H, m, *p-Ph*), 7.25-7.29 (2H, m, *m-Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (1 × *Me*), 14.5 (cyclopropane *C*H$_2$), 18.9, 19.8 (2 × *Me*), 21.9 (*C*(2′)), 23.0 (*C*(1′)), 27.0, 28.1 (*C*(5′′) and *C*(6′′)), 36.8 (*C*(3′′)), 44.9 (*C*(1)), 45.2 (*C*(4′′)), 47.8, 48.7 (*C*(1′′) and *C*(7′′)), 80.1 (*C*(2′′)), 125.7, 125.8, 128.4 (*o/m/p-Ph*), 142.5 (*i-Ph*), 157.0 (*C*=O); *m/z* (ESI$^+$) 677 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_2$ (M+Na$^+$) requires 350.2091, found 350.2092.

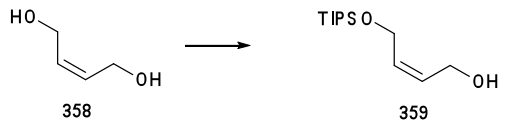
Ethyl *N*-(1′*S*,2′*R*,4′*S*)-bornyloxycarbonyloxamate 357



347 357

To a stirred solution of **347** (716 mg, 5.0 mmol, 1.0 eq) in toluene (5 mL) at 0°C was added (−)-borneol **337** (771 mg, 5.0 mmol, 1.0 eq) and the mixture stirred at 40°C for 1 hr then concentrated *in vacuo* to give **357** as a white solid (1.49 g, quant.); m.p. 61-63 °C; $[\alpha]_D^{25}$ –49.3 (c = 1.0, $CHCl_3$); ν_{max} (KBr) 3280 (N-H), 2955 (C-H), 1795 (C=O), 1740 (C=O), 1715 (C=O), 1500, 1310, 1235, 1190, 1040; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, s, 1 × *Me*), 0.87 (3H, s, 1 × *Me*), 0.89 (3H, s, 1 × *Me*), 1.07 (1H, app dd, *J* 13.9, 3.4, C(3′)H_AH_B), 1.20-1.32 (2H, m, 2 × CH_2), 1.38 (3H, t, *J* 7.2, OCH_2CH_3), 1.68-1.78 (2H, m, C(4′)*H* and 1 × CH_2), 1.93 (1H, ddd, *J* 13.1, 9.2, 4.2, 1 × CH_2), 2.38 (1H, ddt, *J* 9.9, 3.3, 2.2, C(3′)H_AH_B), 4.38 (2H, q, *J* 7.2, OCH_2CH_3), 4.94 (1H, ddd, *J* 9.9, 3.3, 2.2, C(3′)H_AH_B), 8.90 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.4 (1 × *Me*), 13.9 (OCH_2CH_3), 18.8, 19.6 (2 × *Me*), 27.0, 27.9 (*C*(5′) and *C*(6′)), 36.4 (*C*(3′)), 44.7 (*C*(4′)), 47.9, 48.9 (*C*(1′) and *C*(7′)), 64.0 (OCH_2CH_3), 83.4 (O*C*H), 150.5 (NCO_2), 159.6 (2 × *C*=O); *m/z* (ESI^-) 296 ([M–H]$^-$, 100%).

(*Z*)-4-[(Triisopropylsilyl)oxy]but-2-en-1-ol 359[27]

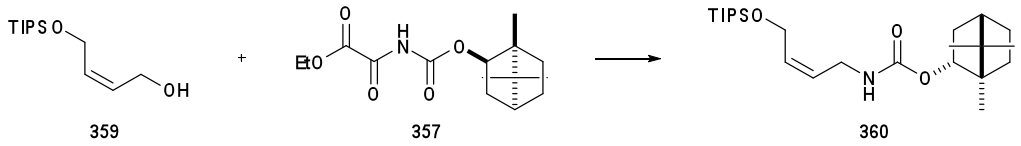


358 359

To a stirred solution of (*Z*)-butene-1,4-diol **358** (14.6 mL, 178 mmol, 10.0 eq) and imidazole (1.36 g, 20 mmol, 1.12 eq) in THF (50 mL) at 0 °C was added TIPSCl (3.8 mL, 17.8 mmol, 1.0 eq) dropwise. The mixture was stirred at RT for 18 hrs, H_2O (50 mL) was added, the organic layer separated and the aqueous layer extracted with

CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol → 20% EtOAc/petrol) to give **359** as a colourless oil (3.68 g, 85%); δ_H (400 MHz, $CDCl_3$) 1.06-1.16 (21H, m, Si(C*H*Me_2)$_3$ and Si(CH*Me*$_2$)$_3$), 4.20-4.23 (2H, m, C(4)*H*$_2$), 4.32-4.36 (2H, m, C(1)*H*$_2$), 5.70-5.74 (2H, m, C(2)*H* and C(3)*H*).

(1′*S*,2′*R*,4′*S*)-Bornyl (*Z*)-4-(triisopropylsilyloxy)but-2-enylcarbamate 360



Following **General Procedure 13**, **359** (489 mg, 2.0 mmol, 1.0 eq), **357** (714 mg, 2.4 mmol, 1.2 eq), PPh_3 (630 mg, 2.4 mmol, 1.2 eq) and DEAD (0.38 mL, 2.4 mmol, 1.2 eq) in THF (20 mL) for 48 hrs, followed by $LiOH{\cdot}H_2O$ (256 mg, 6.0 mmol, 3.0 eq) and H_2O (20 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **360** as a colourless oil (663 mg, 78%); $[\alpha]_D^{25}$ –17.6 (c = 2.0, $CHCl_3$); ν_{max} (KBr) 3335 (N-H), 2945, 2875 (C-H), 1695 (C=O), 1515, 1465, 1390, 1255, 1110, 880, 685; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, s, 1 × *Me*), 0.85 (3H, s, 1 × *Me*), 0.89 (3H, s, 1 × *Me*), 0.97-1.27 (24H, m, C(3′)*H*$_A$H$_B$, 2 × C*H*$_2$, Si(C*H*Me_2)$_3$ and Si(CH*Me*$_2$)$_3$), 1.64-1.72 (2H, m, C(4′)*H* and 1 × C*H*$_2$), 1.84-1.89 (1H, m, 1 × C*H*$_2$), 2.29-2.35 (1H, m, C(3′)H$_A$*H*$_B$), 3.81-3.84 (2H, m, C(1)*H*$_2$), 4.31 (2H, d, *J* 5.9, C(4)*H*$_2$), 4.79-4.85 (2H, m, C(2′)*H* and N*H*), 5.33-5.47 (1H, m, C(2)*H*), 5.66-5.72 (1H, m, *C*(3)*H*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe_2)$_3$), 13.5 (1 × *Me*), 17.9 (Si(CH*Me*$_2$)$_3$), 18.8, 19.7 (2 × *Me*), 27.0, 28.0 (*C*(5′) and *C*(6′)), 36.8 (*C*(3′)), 38.2 (*C*(1)), 44.8 (*C*(4′)), 47.7, 48.7 (*C*(1′) and *C*(7′)), 59.4 (*C*(4)), 80.1

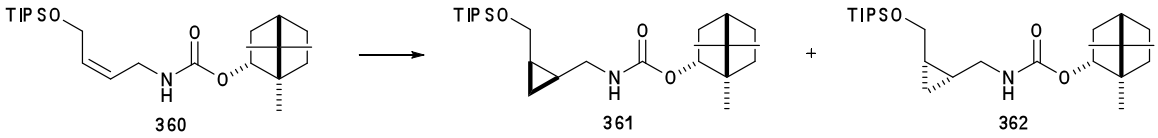
(*C*(2′)), 126.7 (*C*(2)), 132.6 (*C*(3)), 156.9 (*C*=O); *m/z* (ESI$^+$) 446 ([M+Na]$^+$, 60%), 869 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{45}NNaO_3Si$ (M+Na$^+$) requires 446.3061, found 446.3049.

(1′′*S*,2′′*R*,4′′*S*)-Bornyl

[(1′*S*,2′*R*)-2′-[(triisopropylsilyloxy)methyl]cyclopropyl]methylcarbamate 361 and

(1′′*S*,2′′*R*,4′′*S*)-bornyl

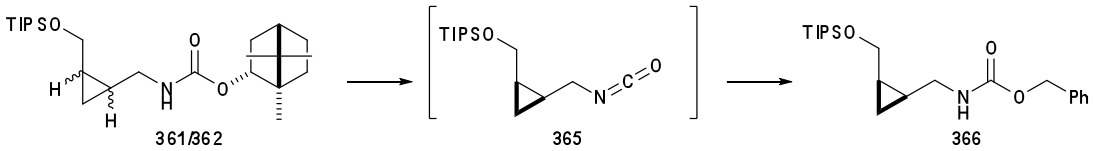
[(1′*R*,2′*S*)-2′-[(triisopropylsilyloxy)methyl]cyclopropyl]methylcarbamate 362



Following **General Procedure 1**, **360** (1.06 g, 2.5 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 5.00 mL, 5.00 mmol, 2.0 eq) and CH_2I_2 (0.81 mL, 10.0 mmol, 4.0 eq) in CH_2Cl_2 (5.0 mL) for 90 mins gave a crude product which was purified by flash column chromatography (silica, petrol → 12% EtOAc/petrol) to give an unknown mixture of **361** and **362** as a white solid (1.00 g, 92%); m.p. 46-48 °C; $[\alpha]_D^{25}$ −16.9 (c = 1.0, $CHCl_3$); ν_{max} (KBr) 3390 (N-H), 2945, 2870 (C-H), 1720 (C=O), 1510, 1230, 1060; δ_H (400 MHz, $CDCl_3$) 0.10 (1H, q, *J* 5.2, cyclopropane C*H*$_A$H$_B$), 0.70 (1H, td, *J* 8.3, 5.2, cyclopropane CH$_A$*H*$_B$), 0.84 (3H, s, 1 × *Me*), 0.86 (3H, s, 1 × *Me*), 0.90 (3H, s, 1 × *Me*), 1.01-1.27 (25H, m, C(1′)*H*, 2 × C*H*$_2$, C(3′)*H*$_A$H$_B$, Si(C*H*Me$_2$)$_3$ and Si(CH*Me*$_2$)$_3$), 1.63-1.75 (2H, m, C(4′′)*H* and 1 × C*H*$_2$), 1.87-1.94 (1H, m, 1 × C*H*$_2$), 2.28-2.36 (1H, m, C(3′′)H$_A$*H*$_B$), 2.49-2.56 (1H, m, C(2′)*H*), 3.21-3.27 (1H, m, C(1)*H*$_A$H$_B$), 3.97-4.03 (1H, m, C(3′)*H*$_A$H$_B$), 4.17 (1H, dd, *J* 11.4, 4.3, C(1)H$_A$*H*$_B$), 4.81-4.87 (1H, m, C(2′′)*H*), 5.75 (1H, d, *J* 9.2, C(3′)H$_A$*H*$_B$); δ_C (100 MHz, $CDCl_3$) 7.6 (cyclopropane *C*H$_2$), 11.9 (Si(*C*HMe$_2$)$_3$), 13.5 (1 × *Me*), 15.6, 15.7 (*C*(1′)$_A$ and

C(1′)$_B$), 17.4 (*C*(2′)), 18.0 (Si(CH*Me*$_2$)$_3$), 18.9, 19.8 (2 × *Me*), 26.9, 28.1 (*C*(5″) and *C*(6″)), 36.8 (*C*(3″)), 40.9 (*C*(1)), 44.9 (*C*(4″)), 47.7, 48.7 (*C*(1″) and *C*(7″)), 63.5 (*C*(3′)), 79.7 and 79.8 (*C*(2″)$_A$ and *C*(2″)$_B$), 157.0 (*C*=O); *m/z* (ESI$^+$) 438 ([M+H]$^+$, 35%), 897 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{47}NNaO_3Si$ (M+Na$^+$) requires 460.3217, found 460.3206.

Benzyl [(1′*R*,2′*S*)-2′-[(triisopropylsilyloxy)methyl]cyclopropyl]methylcarbamate 366 and benzyl [(1′*S*,2′*R*)-2′-[(triisopropylsilyloxy)methyl]cyclopropyl]methyl-carbamate *ent*-366



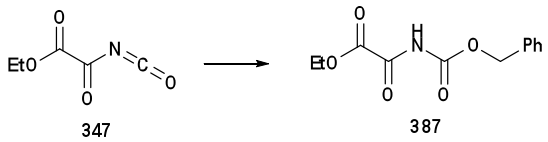
Method A:

To a stirred solution of **361** and **362** (109 mg, 0.25 mmol, 1.0 eq) in toluene (5 mL) at RT was added NEt_3 (0.10 mL, 0.75 mmol, 3.0 eq) followed by BCl_3 (1.0 M in toluene, 0.25 mL, 1.0 eq) dropwise. The resulting solution was stirred at 100 °C for 30 mins then quenched with 1 M aq. NaOH (5 mL) and allowed to stir for 30 mins. The organic layer was separated and the aqueous layer extracted with Et_2O (3 × 5 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give crude isocyanate **365** as a pale yellow oil.

To a stirred solution of BnOH (31 μL, 0.30 mmol, 1.2 eq) and CuCl (25 mg, 0.25 mmol, 1.0 eq) in DMF (0.5 mL) at RT was added a solution of crude isocyanate **365** (assumed 0.25 mmol) in DMF (0.5 mL). The resulting solution was stirred at RT for 16 hrs then diluted wth Et_2O (10 mL) and washed sequentially with H_2O (3 × 10 mL) and brine (2 × 10 mL). The organic layer was dried, filtered and concentrated *in vacuo*

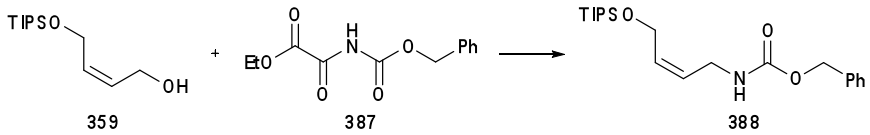
to give a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **366** as a colourless oil (46 mg, 47%); $[\alpha]_D^{25}$ –4.2 (c = 0.5, $CHCl_3$); ν_{max} (film) 3360 (N-H), 2945, 2865 (C-H), 1725 (C=O), 1520, 1465, 1235, 1015, 880; δ_H (400 MHz, $CDCl_3$) 0.13 (1H, q, *J* 5.3, cyclopropane CH_AH_B), 0.72 (1H, td, *J* 8.3, 5.3, cyclopropane CH_AH_B), 1.01-1.22 (23H, m, Si(C*H*Me$_2$)$_3$, Si(CH*Me*$_2$)$_3$, C(1′)*H* and C(2′)*H*), 2.60 (1H, dd, *J* 13.9, 8.8, C(1)H_AH_B), 3.21-3.29 (1H, m, C(3′)H_AH_B), 3.99 (1H, ddd, *J* 13.9, 9.2, 5.0, C(1)H_AH_B), 4.16 (1H, dd, *J* 11.2, 4.7, C(3′)H_AH_B), 5.08 (2H, AB_q, J_{AB} 12.1, OCH_2Ph), 5.95 (1H, d, *J* 9.1, N*H*), 7.27-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.8 (cyclopropane *C*H$_2$), 11.9 (Si(*C*HMe$_2$)$_3$), 15.6, 17.4 (*C*(1′) and *C*(2′)), 18.0 (Si(CH*Me*$_2$)$_3$), 41.1 (*C*(1)), 63.6 (*C*(3′)), 66.4 (O*C*H$_2$Ph), 127.8, 128.0, 128.3 (*Ph*), 136.9 (i-*Ph*), 156.3 (*C*=O); *m/z* (ESI$^+$) 392 ([M+H]$^+$, 20%), 414 ([M+Na]$^+$, 60%), 805 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{37}NNaO_3Si$ (M+Na$^+$) requires 414.2435, found 414.2423; Chiral HPLC, Chiralpak IB; 99:1 hexane:*i*PrOH; 1.3 mL/min; t_r (minor) 5.85, t_r (major) 6.10; 9% e.e.

Ethyl *N*-benzyloxycarbonyloxamate 387[28]



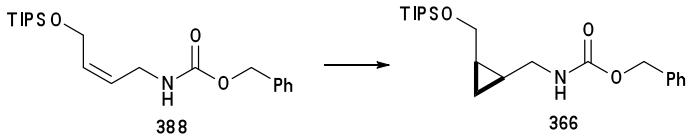
To a stirred solution of **347** (1.43 g, 10.0 mmol, 1.0 eq) in toluene (10 mL) was added BnOH (1.04 mL, 10.0 mmol, 1.0 eq) dropwise and the resulting solution stirred for 1 hr at 40 °C. The reaction mixture was concentrated *in vacuo* to give **387** as a colourless oil (2.51 g, quant.); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 4.36 (1H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.29 (2H, s, OC*H*$_2$Ph), 7.31-7.42 (5H, m, *Ph*).

Benzyl [(2*Z*)-4-[(triisopropylsilyl)oxy]but-2-en-1-yl]carbamate 388



Following **General Procedure 13**, alcohol **359** (244 mg, 1.0 mmol, 1.0 eq), **387** (301 mg, 1.2 mmol, 1.2 eq), PPh_3 (315 mg, 1.2 mmol, 1.2 eq) and DEAD (0.19 mL, 1.2 mmol, 1.2 eq) in THF (10 mL) for 48 hrs followed by $LiOH{\cdot}H_2O$ (126 mg, 3.0 mmol, 3.0 eq) and H_2O (10 mL) gave a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **388** as a colourless oil (248 mg, 66%); ν_{max} (film) 3325 (N-H), 2945, 2865 (C-H), 1705 (C=O), 1530, 1465, 1250, 1095, 885, 690; δ_H (400 MHz, $CDCl_3$) 1.04-1.10 (21H, m, Si(C*H*Me_2)$_3$ and Si(CH*Me*$_2$)$_3$), 3.87 (2H, t, *J* 5.8, C(1)*H*$_2$), 4.33 (2H, d, *J* 5.4, C(4)*H*$_2$), 4.91 (1H, br s, N*H*), 5.11 (2H, s, OC*H*$_2$Ph), 5.47-5.53 (1H, m, C(2)*H*), 5.71 (1H, dt, *J* 10.9, 5.4, C(3)*H*), 7.30-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe_2)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 38.3 (*C*(1)), 59.5 (*C*(4)), 66.7 (O*C*H$_2$Ph), 126.4 (*p*-Ph), 128.1, 128.5 (*o/m-Ph* and *C*(2)), 132.8 (*C*(3)), 136.5 (*i*-Ph), 156.2 (*C*=O); *m/z* (ESI^+) 400 ($[M+Na]^+$, 20%), 436 ($[M+MeCN+NH_4]^+$, 100%); HRMS (ESI^+) $C_{21}H_{35}NNaO_3Si$ ($M+Na^+$) requires 400.2278, found 400.2272.

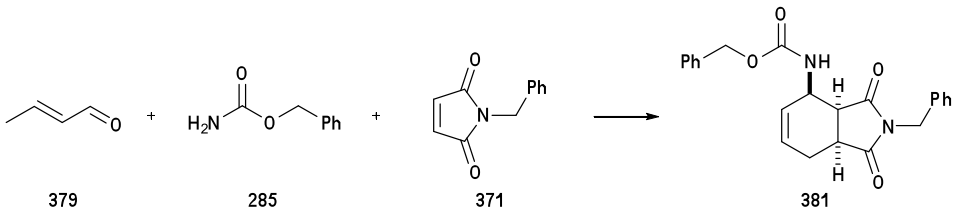
Benzyl [(1′*RS*,2′*SR*)-2′-[(triisopropylsilyloxy)methyl]cyclopropyl]methyl-carbamate 366



Method B:

Following **General Procedure 1**, **388** (241 mg, 0.64 mmol, 1.0 eq), $ZnEt_2$ (1.28 mL, 1.28 mmol, 2.0 eq) and CH_2I_2 (0.21 mL, 2.55 mmol., 4.0 eq) in CH_2Cl_2 (1.5 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 15% EtOAc/petrol) to give **366** as a colourless oil (175 mg, 70%); identical spectroscopic data as above.

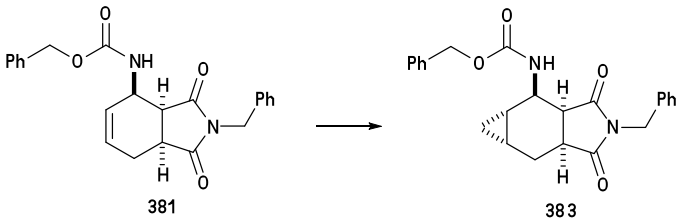
Benzyl (*RS*)-[(3a*SR*,4*RS*7a*SR*)-2-benzyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-2*H*-isoindol-4-yl] carbamate 381



A solution of crotonaldehyde **379** (0.83 mL, 10.0 mmol, 1.0 eq), benzyl carbamate **285** (1.51 g, 10.0 mmol, 1.0 eq), *N*-benzyl maleimide **371** (2.81 g, 15.0 mmol, 1.5 eq), acetic anhydride (0.95 mL, 10.0 mmol, 1.0 eq) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 0.02 eq) in toluene (100 mL) was heated at 120 °C in a sealed tube for 24 hrs. The resulting mixture was concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol → 40% EtOAc/petrol) to give **381** as a pale yellow solid (2.03 g, 53%);

m.p. 68-70 °C, ν_{max} (KBr) 3400 (N-H), 2940 (C-H), 1770 (C=O), 1700 (C=O), 1510, 1400, 1340, 1240, 1055, 700, 665; δ_H (400MHz, $CDCl_3$) 2.16-2.24 (1H, m, C(7)H_AH_B), 2.70 (1H, dd, *J* 15.6, 6.8, C(7)H_AH_B), 3.16 (1H, app t, *J* 8.5, C(7a)*H*), 3.24 (1H, dd, *J* 8.5, 6.4, C(3a)*H*), 4.47 (1H, ddd, *J* 8.5, 6.4, 2.4, C(4)*H*), 4.60 (2H, s, NCH_2Ph), 5.11-5.19 (2H, AB q, OCH_2Ph), 5.75-5.84 (2H, m, C(5)*H* and C(6)*H*), 6.56 (1H, d, *J* 9.3, N*H*), 7.24-7.40 (10H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 24.1 (*C*(7)), 38.8 (*C*(7a)), 42.6 (*C*(3a)), 42.8 (N*C*H_2Ph), 47.3 (*C*(4)), 66.9 (O*C*H_2Ph), 127.2 (*C*(5)), 127.9, 128.1, 128.1, 128.3, 128.5, 128.6 (*Ar*), 133.1, (*C*(6)), 135.4, 136.4 (*i-Ph*), 156.1 (N*C*O_2Bn), 178.5, 179.0 (*C*(1) and *C*(3)); *m/z* (ESI^+) 391 ($[M+H]^+$, 20%), 413 ($[M+Na]^+$, 80%), 449 ($[M+MeCN+NH_4]^+$, 80%), 803 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{22}N_2NaO_4$ ($M+Na^+$) requires 413.1472, found 413.1473.

Benzyl (*RS*)-[3a*SR*,4*RS*,4a*SR*,5a*SR*,6a*SR*)-2-benzyl-1,3-dioxodecahydrocyclopropa[*f*]isoindol-4-yl] carbamate 383

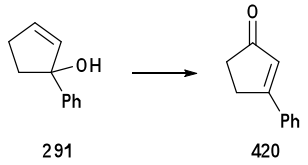


Following **General Procedure 3**, **381** (98 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.75 mL, 0.75 mmol, 3.0 eq), CH_2I_2 (0.12 mL, 1.50 mmol, 6.0 eq) and TFA (57 μL, 0.7 mmol, 3.0 eq) in CH_2Cl_2 (0.75 mL) for 5 hrs gave a crude product. ^1H NMR analysis showed that the reaction conversion was 54%. Following **General Procedure 3**, the crude product, $ZnEt_2$ (1.0M in hexanes, 0.75 mL, 0.75 mmol, 3.0 eq), CH_2I_2 (0.12 mL, 1.50 mmol, 6.0 eq) and TFA (57 μL, 0.7 mmol, 3.0 eq) in CH_2Cl_2 (0.75 mL) for 14 hrs gave a crude product which was purified by flash

column chromatography (silica, 20% EtOAc/petrol) to give **383** as a pale yellow oil (55 mg, 54%); ν_{max} (film) 3405 (N-H), 3035, 2940 (C-H), 1770 (C=O), 1695 (C=O), 1510, 1400, 1345, 1240, 1175, 1070, 1030, 910, 735, 700, 635; δ_H (400MHz, $CDCl_3$) 0.29 (1H, q, *J* 4.6, C(5)H_AH_B), 0.46-0.53 (1H, m, C(4a)*H*), 0.58-0.63 (1H, m, C(5a)*H*), 0.75-0.81 (1H, m, C(5)H_AH_B), 1.06-1.16 (1H, m, C(6)H_AH_B), 2.49-2.55 (1H, m, C(6)H_AH_B), 2.97 (1H, dd, *J* 9.0, 5.0, C(3a)*H*), 3.05-3.08 (1H, m, C(6a)*H*), 3.47-3.53 (1H, m, C(4)*H*), 4.68 (2H, s, NCH_2Ph), 5.13 (2H, s, OCH_2Ph), 6.24 (1H, d, *J* 9.1, N*H*), 7.25-7.40 (10H, m, *Ar*); δ_C (100MHz, $CDCl_3$) 6.1 (*C*(6)), 12.3 (*C*(5)), 13.1 (cyclopropane *C*H_2), 24.6 (*C*(7)), 42.1, 42.1 (*C*(3a), *C*(7a)), 42.6 (N*C*H_2Ph), 50.4 (*C*(4)), 66.9 (O*C*H_2Ph), 128.0, 128.1, 128.5, 128.5, 128.6 (*Ar*), 135.7, 136.4 (*i-Ar*), 155.9 (N*C*O_2Bn), 179.1, 179.7 (*C*(1), *C*(3)); *m/z* (ESI^+) 427 ($[M+Na]^+$, 70%), 463 ($[M+MeCN+NH_4]^+$, 70%), 831 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{24}N_2NaO_4$ $(M+Na)^+$, requires 427.1628, found 427.1635.

5.5 Experimental for Chapter 4

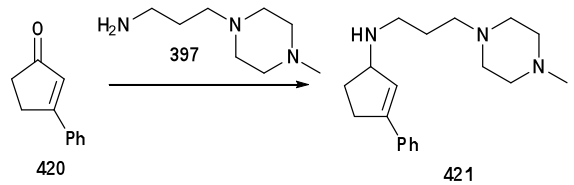
(*RS*)-3-Phenyl-2-cyclopenten-1-one 420[22]



291 420

To a solution of **291** (801 mg, 5.0 mmol, 1.0 eq) in DMSO (25 mL) was added IBX (1.68 g, 12.0 mmol, 1.2 eq) and the mixture stirred at 55°C for 1 hr. The mixture was allowed to cool to RT, H_2O (100 mL) was added, and the mixture extracted with Et_2O (3 × 50 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol → 20% EtOAc/petrol) to give **420** as a colourless oil (270 mg, 34%); δ_H (400 MHz, $CDCl_3$) 2.60-2.63 (2H, m, C(4)H_2), 3.05-3.08 (2H, m, C(5)H_2), 6.59-6.61 (1H, m, C(2)*H*), 7.46-7.49 (3H, m, *Ar*), 7.66-7.68 (2H, m, *Ar*).

(*RS*)-*N*-[3'-(4''-Methylpiperazin-1''-yl)propyl]-3-phenylcyclopent-2-en-1-amine 421



420 421

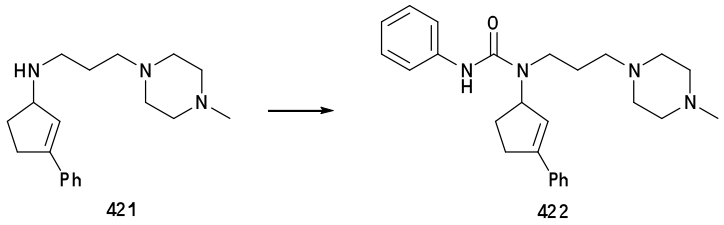
To a stirred solution of **420** (301 mg, 1.90 mmol, 1.0 eq) in MeOH (4.75 mL) was added 3-(4'-methylpiperazin-1'-yl)propan-1-amine **397** (898 mg, 5.71 mmol, 3.0 eq) and $Ti(OiPr)_4$ (0.73 mL, 2.47 mmol, 1.3 eq) and the mixture stirred at RT for 16 hrs. The mixture was then cooled to 0 °C and $NaBH_4$ (86 mg, 2.28 mmol, 1.2 eq) was added portionwise over 5 mins. The resulting mixture was stirred at RT for 2 hrs, then

quenched with water (1 mL). After stirring for 20 mins, the mixture was acidified with 1M aq. HCl (5 mL) and filtered through Celite® [eluent: H_2O (10 mL) and EtOAc (10 mL)]. The organic layer was separated; the aqueous layer was basified to pH 10-12 with 10% aq. NaOH and then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, CH_2Cl_2 → 95:5:0.5 CH_2Cl_2:MeOH:*i*$PrNH_2$) to give **421** as a brown oil (416 mg, 73%); ν_{max} (film) 2935, 2795 (C-H), 1450, 1285 (Ar), 1165, 755, 695, 665; δ_H (400 MHz, $CDCl_3$) 1.65-1.74 (3H, m, C(2')H_2 and C(5)H_AH_B), 2.16-3.02 (8H, br m, N(CH_2CH_2)$_2$N) overlapping [2.22 (3H, s, N*Me*), 2.29-2.48 (3H, m, C(1')H_2 and C(5)H_AH_B), 2.58-2.65 (1H, m, C(4)H_AH_B), 2.70 (2H, t, *J* 6.8, C(3')H_2), 2.76-2.81 (1H, m, C(4)H_AH_B)], 3.92-3.96 (1H, m, C(1)*H*), 5.05 (1H, br s, N*H*), 6.21 (1H, d, *J* 1.8, C(2)*H*), 7.19-7.23 (1H, m, *p-Ph*), 7.26-7.30 (2H, m, *m-Ph*), 7.39-7.43 (2H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 27.1 (*C*(2')), 31.0 (*C*(5)), 31.6 (*C*(4)), 46.0 (N*Me*), 46.2 (*C*(3')), 53.1, 55.0 (N(*C*H_2*C*H_2)$_2$N), 56.9 (*C*(1')), 64.7 (*C*(1)), 125.8, 127.2, 127.5, 128.3 (*Ph*, *C*(2)), 136.0 (*C*(3)), 144.1 (*i-Ph*); *m/z* (ESI^+) 300 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}N_3$ ($[M+H]^+$) requires 300.2434, found 300.2427.

Attempted cyclopropanation of 421

Following **General Procedure 3**, **421** (60 mg, 0.20 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.40 mL, 0.40 mmol, 2.0 eq), CH_2I_2 (64 μL, 0.80 mmol, 4.0 eq) and TFA (30 μL, 0.40 mmol, 2.0 eq) in CH_2Cl_2 (0.5 mL) for 1 hr gave a complex mixture of products. No further purification was attempted.

(*RS*)-1-[3''-(4'''-Methylpiperazin-1'''-yl)propyl]-3-phenyl-1-(3'-phenylcyclopent-2'-en-1'-yl)urea 422



To a stirred solution of **421** (150 mg, 0.50 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) was added DIPEA (94 μL, 0.55 mmol, 1.10 eq) and phenyl isocyanate (57 μL, 0.525 mmol, 1.05 eq) and the mixture stirred at RT for 16 hrs. Sat. aq. $NaHCO_3$ (50 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, CH_2Cl_2 → 95:5:0.5 CH_2Cl_2:MeOH:*i*$PrNH_2$) to give **422** as a yellow oil (199 mg, 95%); ν_{max} (film) 3370 (N-H), 2940, 2700 (C-H), 1650 (C=O), 1595, 1535, 1445, 1310, 1235, 1180, 755, 695; δ_H (400 MHz, $CDCl_3$) 1.72-1.90 (3H, m, C(2'')H_2 and C(5')H_AH_B), 2.23 (3H, s, N*Me*), 2.30-2.62 (11H, m, N(CH_2CH_2)$_2$N, C(3'')H_2 and C(5')H_AH_B), 2.70-2.78 (1H, m, C(4')H_AH_B), 2.86-2.92 (1H, m, C(4')H_AH_B), 3.22-3.29 (1H, m, C(1'')H_AH_B), 3.33-3.40 (1H, m, C(1'')H_AH_B), 5.56 (1H, br s, C(1')*H*), 6.12 (1H, d, *J* 1.8, C(2')*H*), 7.05 (1H, t, *J* 7.3, *Ar*), 7.26-7.31 (3H, m, *Ar*), 7.34-7.42 (4H, m, *Ar*), 7.48 (2H, d, *J* 7.1, *Ar*), 8.51 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 27.4 (*C*(2'')), 29.1 (*C*(4')), 32.0 (*C*(5')), 41.5 (*C*(1'')), 45.9 (N*Me*), 52.8 (*C*(3'')), 54.2, 54.4 (N(CH_2CH_2)$_2$N), 62.6 (*C*(1')), 122.3 (*C*(2')), 123.4, 125.9, 126.0, 128.0, 128.5, 128.6 (*Ar*), 135.5 (*C*(3')), 139.4 (i-*Ph*), 145.5 (i-*Ph*), 157.2 (*C*=O); *m/z* (ESI^+) 419 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{35}N_4O$ ($[M+H]^+$) requires 419.2805, found 419.2805.

Attempted cyclopropanation of 422

Method A:

Following **General Procedure 1**, **422** (14 mg, 0.03 mmol, 1.0 eq), $ZnEt_2$ (0.07 mL, 0.07 mmol, 2.0 eq), CH_2I_2 (11 μL, 0.13 mmol, 4.0 eq) in CH_2Cl_2 (0.10 mL) for 1 hr gave a complex mixture of products. No further purification was attempted.

Method B:

To a stirred solution of **422** (42 mg, 0.10 mmol, 1.0 eq) in CH_2Cl_2 (0.20 mL) at 0 °C was added $ZnEt_2$ (1.0 M in hexanes, 0.11 mL, 0.11 mmol, 1.1 eq) dropwise. The mixture was stirred at 0 °C for 15 mins then CH_2I_2 (10 μL, 0.12 mmol, 4.0 eq) was added and the mixture stirred at RT for 1 hr then quenched with sat. aq. Na_2EDTA (0.2 mL). The resulting mixture was vigorously stirred for 5 mins then diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a complex mixture of products. No further purification was attempted.

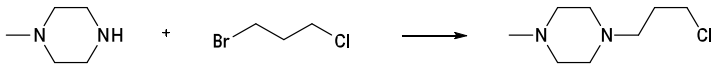
Method C:

Following **General Procedure 3**, **422** (42 mg, 0.10 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.20 mL, 0.20 mmol, 2.0 eq), CH_2I_2 (32 μL, 0.40 mmol, 4.0 eq) and TFA (15 μL, 0.20 mmol, 2.0 eq) in CH_2Cl_2 (0.20 mL) for 1 hr gave a complex mixture of products. No further purification was attempted.

Method D:

Following **General Procedure 3**, **422** (42 mg, 0.10 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 1.00 mL, 1.00 mmol, 10 eq), CH_2I_2 (0.16 mL, 2.00 mmol, 20 eq) and TFA (0.07 mL, 1.00 mmol, 10 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a complex mixture of products. No further purification was attempted.

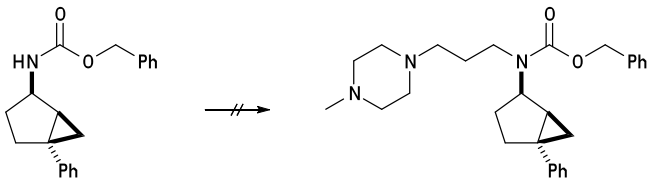
1-(3'-Chloropropyl)-4-methylpiperazine 408[29]



426 427 408

Activated Zn powder (0.65 g, 10.0 mmol, 1.0 eq) was added to a stirred solution of 1-methyl piperazine **426** (1.11 mL, 10.0 mmol, 1.0 eq) and 1-bromo-3-chloropropane **427** (1.02 mL, 10.0 mmol, 1.0 eq) in THF (10 mL) and the mixture stirred at RT for 16 hrs. The mixture was then filtered (eluent: Et_2O), the filtrate washed with sat. aq. $NaHCO_3$ (10 mL), brine (2 × 10 mL), dried, filtered and concentrated *in vacuo*. Bulb-to-bulb distillation (Kugelrohr) under reduced pressure (100 °C, 8 mbar) afforded **408** as a colourless oil (610 mg, 34%); δ_H (400 MHz, $CDCl_3$) 1.91-1.98 (2H, m, C(2)*H*), 2.28 (3H, s, N*Me*), 2.35-2.52 (10H, m, N(CH_2CH_2)$_2$N and C(3)H_2), 3.59 (2H, t, *J* 6.7, C(1)H_2).

Attempted preparation of benzyl (1*SR*,2*RS*5*SR*)-[3'-(4''-methylpiperazin-1''-yl)propyl][5-phenylbicyclo[3.1.0]hex-2-yl]carbamate 425



295 425

(i) NaH (60% dispersion in mineral oil, 15 mg, 0.38 mmol, 2.0 eq) was added portion-wise to a stirred solution of **295** (58 mg, 0.19 mmol, 1.0 eq) in DMF (3 mL) at 0 °C and the mixture was stirred for 10 mins. 1-(3'-Chloropropyl)-4-methylpiperazine **408** (100 mg, 0.56 mmol, 3.0 eq) was added and the mixture heated at 75 °C for 18 hrs. The mixture was allowed to cool to RT and quenched with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers washed with sat. aq. $NaHSO_3$ (10 mL), brine (10 mL), then dried, filtered and concentrated *in vacuo* to give the crude product. ^{1}H NMR spectroscopic analysis showed that no alkylation of **295** had occurred.

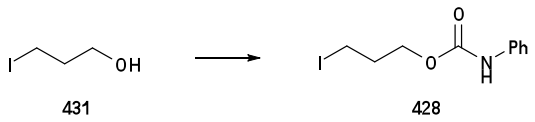
(ii) NaH (60% dispersion in mineral oil, 8 mg, 0.20 mmol, 2.0 eq) was added portion-wise to a stirred solution of **295** (29.3 mg, 0.10 mmol, 1.0 eq) in DMF (2 mL) at 0 °C and thee mixture stirred for 10 mins. 1-(3'-Chloropropyl)-4-methylpiperazine **408** (54 mg, 0.30 mmol, 3.0 eq) and nBu_4NI (111 mg, 0.30 mmol, 3.0 eq) were added and the mixture heated at 75 °C for 18 hrs. The mixture was allowed to cool to RT and quenched with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers washed with sat. aq. $NaHSO_3$ (10 mL), brine (10 mL), then dried, filtered and concentrated *in vacuo* to give the crude product. ^{1}H NMR spectroscopic analysis showed that no alkylation of **295** had occurred.

(iii) To a stirred solution of **295** (29.3 mg, 0.10 mmol, 1.0 eq) in DMF (2 mL) was added Cs_2CO_3 (98 mg, 0.30 mmol, 3.0 eq), nBu_4NI (111 mg, 0.30 mmol, 3.0 eq) and 1-(3'-chloropropyl)-4-methylpiperazine **408** (54 mg, 0.30 mmol, 3.0 eq). The mixture was stirred at RT for 18 hrs then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give the crude product. ^1H NMR spectroscopic analysis showed that no alkylation of **295** had occurred.

(iv) To a stirred solution of **295** (29.3 mg, 0.10 mmol, 1.0 eq) in DMF (2 mL) was added Cs_2CO_3 (98 mg, 0.30 mmol, 3.0 eq), nBu_4NI (111 mg, 0.30 mmol, 3.0 eq) and 1-(3'-chloropropyl)-4-methylpiperazine **408** (54 mg, 0.30 mmol, 3.0 eq). The mixture was stirred at 60 °C for 18 hrs then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give the crude product. ^1H NMR spectroscopic analysis showed that no alkylation of **295** had occurred.

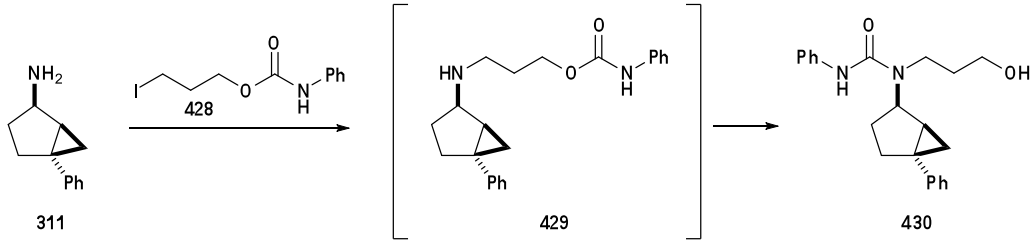
(v) NaH (60% dispersion in mineral oil, 4.8 mg, 0.12 mmol, 1.2 eq) was added to a stirred solution of **295** (29.3 mg, 0.10 mmol, 1.0 eq) in DMF/THF (3:1, v/v, 2 mL) at 0 °C and the mixture stirred for 30 mins. 1-(3'-Chloropropyl)-4-methylpiperazine **408** (21.4 mg, 0.12 mmol, 1.2 eq) and nBu_4NI (44 mg, 0.12 mmol, 1.2 eq) were added and the mixture stirred at RT for 18 hrs. The mixture was quenched with H_2O (5 mL) and then extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL), brine (10 mL), dried, filtered and concentrated *in vacuo* to give the crude product. ^1H NMR spectroscopic analysis showed that no alkylation of **295** had occurred.

3-Iodopropyl phenylcarbamate 428



To a stirred solution of 3-iodopropan-1-ol **431** (1.0 g, 5.38 mmol, 1.0 eq) in toluene (25 mL) was added phenyl isocyanate (0.61 mL, 5.65 mmol, 1.05 eq) and the mixture stirred at reflux for 3 hrs, allowed to cool to RT and concentrated *in vacuo* to give **428** as a pale yellow solid (3.05 g, quant.); m.p. 56-58°C; ν_{max} (KBr) 3315 (N-H), 2960 (C-H), 1710 (C=O), 1600, 1540, 1445, 1315, 1225, 1085, 755, 690, 665; δ_H (400 MHz, $CDCl_3$) 2.19 (2H, app quin, *J* 6.4, C(2)H_2), 3.25 (2H, t, *J* 6.9, C(3)H_2), 4.25 (2H, t, *J* 6.1, C(1)H_2), 6.80 (1H, br s, N*H*), 7.08 (1H, t, *J* 7.3, *p-Ph*), 7.30-7.34 (2H, m, *m-Ph*), 7.39-7.41 (2H, m, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 1.6 (*C*(3)), 32.6 (*C*(2)), 64.8 (*C*(1)), 118.7 (o-*Ph*), 123.6 (p-*Ph*), 129.1 (m-*Ph*), 137.7 (i-*Ph*), 153.3 (*C*=O); *m/z* (CI^+) 306 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{10}H_{13}INO_2$ ($M+H^+$) requires 305.9991, found 305.9995.

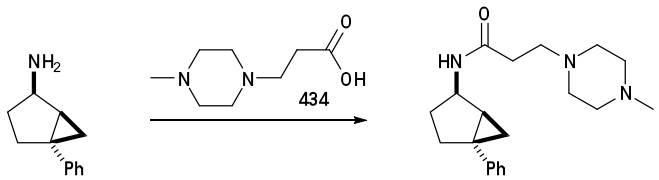
(1'*SR*,2'*RS*,5'*SR*)-1-(3''-Hydroxypropyl)-3-phenyl-1-(5'-phenylbicyclo[3.1.0]hex-2'-yl)urea 430



To a stirred solution of amine **311** (173 mg, 1.0 mmol, 1.0 eq) and **428** (336 mg, 1.1 mmol, 1.1 eq) in anhydrous DMF (5 mL) was added NEt_3 (153 µL, 1.1 mmol, 1.1 eq) and the mixture heated at 50 °C for 30 mins. $AlMe_3$ (2.0 M in toluene, 1.1 mL, 2.2

mmol, 2.0 eq) was added and the mixture heated at 80°C for 2 hrs. The mixture was allowed to cool to RT, quenched with 1 M aq. HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 20% EtOAc/petrol → 40% EtOAc/petrol) to give **430** as a white solid (82 mg, 23%); m.p. 104-106 °C; ν_{max} (KBr) 3300 (O/N-H), 1640 (C=O), 1595, 1550, 1500, 1445 (Ar), 755, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.96 (1H, dd, *J* 7.4, 5.7, C(6')H_AH_B), 1.25-1.36 (2H, m, C(3')H_AH_B and C(6')H_AH_B), 1.65 (1H, app dd, *J* 7.8, 4.2, C(1')*H*), 1.80-1.91 (2H, m, C(2")H_2), 1.94-2.01 (1H, m, C(3')H_AH_B), 2.05-2.18 (2H, m, C(4')H_2), 3.38 (1H, dt, *J* 15.7, 5.8, C(1")H_AH_B), 3.56-3.63 (1H, m, C(1")H_AH_B), 3.70 (2H, m, C(3")H_2), 4.18 (1H, br s, O*H*), 5.00 (1H, ddd, *J* 11.0, 7.0, 4.0, C(2')*H*), 6.98 (1H, t, *J* 7.3, *p-Ph*), 7.15-7.33 (7H, m, *Ar*), 7.46 (2H, d, *J* 7.6, *o-Ph*), 8.25 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 15.1 (*C*(6')), 23.7 (*C*(3')), 27.7 (*C*(1')), 29.3 (*C*(5')), 29.9 (*C*(4')), 38.0 (*C*(2")), 38.6 (*C*(1")), 56.0 (*C*(2')), 58.4 (*C*(3")), 119.9, 122.5, 125.8, 126.3, 128.3, 128.7 (*Ar*), 140.0, 144.2 (i-*Ph*), 157.0 (*C*=O); *m/z* (ESI^+) 351 ($[M+H]^+$, 100%), 373 ($[M+Na]^+$, 40%), 701 ($[2M+H]^+$, 60%); HRMS (ESI^+) $C_{22}H_{26}N_2NaO_2$ ($[M+Na]^+$) requires 373.1886, found 373.1885.

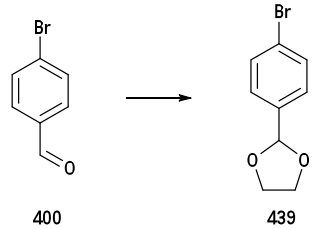
(1*SR*,2*RS*,5*SR*)-*N*-[3'-(4''-Methylpiperazin-1''-yl)propanamide]-5-phenylbicyclo[3.1.0]hexan-2-amine 435



To a stirred solution of **311** (43 mg, 0.25 mmol, 1.0 eq) in $CHCl_3$ (2 mL) was added NEt_3 (0.17 mL, 1.25 mmol, 5.0 eq), HOBt (41 mg, 0.30 mmol, 1.2 eq), 3-(4'-

methylpiperazin-1'-yl)propanoic acid **434** (43 mg, 0.25 mmol, 1.0 eq) and EDCI (58 mg, 0.30 mmol, 1.2 eq). The resulting mixture was stirred at RT for 16 hrs then diluted with EtOAc (20 mL) and washed sequentially with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried, filtered and concentrated *in vacuo* to give **435** as a colourless oil (80 mg, 98%) which was used without further purification; ν_{max} (film) 3280 (N-H), 2935, 2795 (C-H), 1645 (C=O), 1545, 1450, 1285, 1165, 760, 700, 665; δ_H (400MHz, $CDCl_3$) 0.79 (1H, dd, *J* 8.1, 5.1, C(6)H_AH_B), 1.03-1.07 (2H, m, C(3)H_AH_B and C(6)H_AH_B), 1.89 (1H, dt, *J* 8.1, 4.2, C(1)*H*), 2.05-2.20 (3H, m, C(3)H_AH_B and C(4)H_2), 2.32 (3H, s, N*Me*), 2.35-2.69 (8H, br m, N(CH_2CH_2)$_2$N) overlapping 2.36-2.40 (2H, m, C(2′)H_2) and 2.65 (2H, t, *J* 6.2, C(3′)H_2), 4.63-4.66 (1H, m, C(2)*H*), 7.14-7.18 (3H, m, *Ph*), 7.25-7.29 (2H, m, *Ph*), 8.68 (1H, d, *J* 7.6, N*H*); δ_C (100MHz, $CDCl_3$) 14.0 (*C*(6)), 28.1 (*C*(3)), 29.1 (*C*(1)), 31.1 (*C*(4)), 31.8 (*C*(2′)), 45.9 (N*Me*), 50.6, 53.7 (N(CH_2CH_2)$_2$N), 52.1 (*C*(2)), 55.2 (*C*(3′)), 125.8 (*p-Ph*), 126.4, 128.2 (*o/m-Ph*), 144.2 (*i-Ph*), 172.3 (*C*=*O*); *m/z* (ESI^+) 328 ($[M+H]^+$, 80%), 677 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{30}N_3O$ ($M+H^+$) requires 328.2383, found 328.2384.

2-(4'-Bromophenyl)-1,3-dioxolane 439[30]

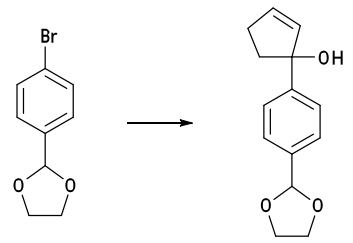


400 439

A solution of ethylene glycol (2.23 mL, 40.0 mmol, 2.0 eq) and $TsOH{\cdot}H_2O$ (380 mg, 2.0 mmol, 0.10 eq) in toluene (40 mL) were heated under N_2 at reflux for 2 hrs in a Dean-Stark apparatus. 4-Bromobenzaldehyde **400** (3.70 g, 20.0 mmol, 1.0 eq) in

toluene (20 mL) was then added and the mixture stirred at reflux for 20 hrs. The reaction was allowed to cool to RT then quenched with sat. aq. $NaHCO_3$ (100 mL) and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 5% EtOAc/petrol) to give **439** as a colourless oil (1.86 g, 41%); δ_H (400 MHz, $CDCl_3$) 4.00-4.12 (4H, m, C(4)H_2 and C(5)H_2), 5.78 (1H, m, C(2)*H*), 7.36 (2H, d, *J* 8.2, C(2')*H* and C(6')*H*), 7.52 (2H, d, *J* 8.2, C(3')*H* and C(5')*H*).

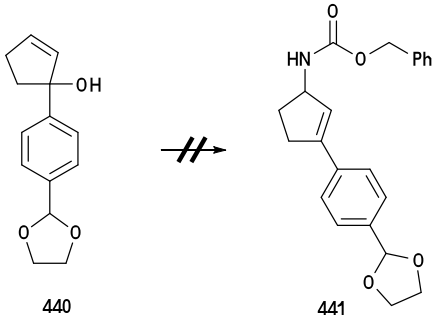
(*RS*)-1-[4'-(1'',3''-Dioxolan-2''-yl)phenyl]cyclopent-2-en-1-ol 440



439 440

To a stirred solution of **439** (504 mg, 2.2 mmol, 1.1 eq) in THF (10 mL) at −78 °C was added *n*BuLi (1.49 M in hexanes, 1.61 mL, 2.40 mmol, 1.2 eq) dropwise and the resulting mixture stirred for 30 mins at −78 °C. 2-Cyclopenten-1-one **290** (0.17 mL, 2.0 mmol, 1.0 eq) was added and the resulting solution stirred at −78 °C for a further 1 hr before being quenched with H_2O (10 mL). The mixture was allowed to warm to RT, the aqueous layer separated and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried, filtered and concentrated *in vacuo* to give crude **440** which was used without further purification; δ_H (400 MHz, $CDCl_3$) 2.24 (2H, t, *J* 6.7, C(5)H_2), 2.42-2.51 (1H, m, C(4)H_AH_B), 2.60-2.68 (1H, m, C(4)H_AH_B), 4.02-4.16 (4H, m, OCH_2CH_2O), 5.82 (1H, s, OC*H*O), 5.84-5.87 (1H, m, C(2)*H*), 6.10-6.13 (1H, m, C(3)*H*), 7.37-7.50 (4H, m, *Ar*).

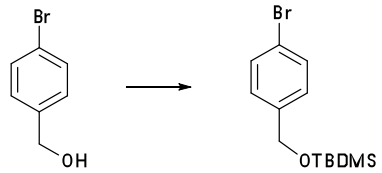
Attempted synthesis of benzyl (*RS*)-1-[4'-(1'',3''-dioxolan-2''-yl)phenyl]cyclopent-2-en-1-yl carbamate 441



440 441

Following **General Procedure 9**, crude **440** (468 mg, 2.0 mmol, 1.0 eq), $Bi(OTf)_3$ (66 mg, 0.10 mmol, 0.05 eq), KPF_6 (18 mg, 0.10 mmol, 1.0 eq), benzyl carbamate **285** (453 mg, 3.0 mmol, 1.5 eq) and $MgSO_4$ (~300 mg) were reacted in THF (7 mL) for 10 mins to give a complex mixture of unidentified products. No further purification was attempted.

4-(*tert*-Butyldimethylsilyloxymethyl)bromobenzene 444[22]

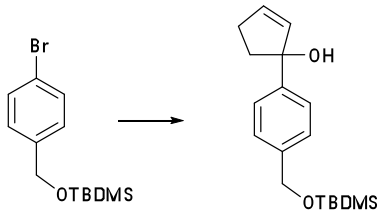


443 444

To a stirred solution of 4-bromobenzylalcohol **443** (4.68 g, 25.0 mmol, 1.0 eq) in anhydrous DMF (70 mL) was added imidazole (2.04 g, 30.0 mmol, 1.2 eq) and TBDMSCl (4.52 g, 30.0 mmol, 1.2 eq) and the resulting mixture stirred at RT for 16 hrs. The mixture was then poured into ice-cold H_2O (250 mL) and extracted with Et_2O (5 × 50 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica,

5%EtOAc/petrol) to give **444** as a colourless oil (7.18 g, 95%); δ_H (400 MHz, $CDCl_3$) 0.10 (6H, s, Si*Me*$_2$t-Bu), 0.95 (9H, s, SiMe$_2$t*Bu*), 4.69 (2H, s, C*H*$_2$OSi), 7.21 (2H, d, *J* 8.5, C(2)*H* and C(6)*H*), 7.46 (2H, d, *J* 8.5, C(3)*H* and C(5)*H*).

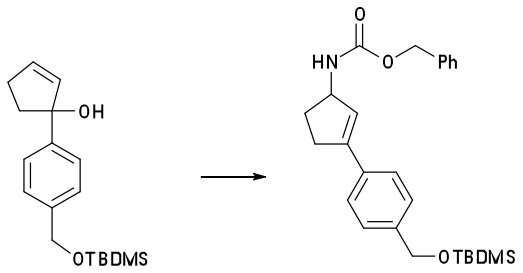
(*RS*)-1-[4'-(*tert*-Butyldimethylsilyloxymethyl)phenyl]cyclopent-2-en-1-ol 445



444 445

Following **General Procedure 10**, 2-cyclopenten-1-one **290** (0.42 mL, 5.0 mmol, 1.0 eq), **444** (1.81 g, 6.0 mmol, 1.2 eq) and ^{t}BuLi (1.7M in pentane, 7.06 mL, 12.0 mmol, 2.4 eq) were reacted in THF (25 mL) for 1 hr to give crude **445** which was used without further purification; δ_H (400 MHz, $CDCl_3$) 0.11 (6H, s, Si*Me*$_2$tBu), 0.95 (9H, s, SiMe$_2$t*Bu*), 2.26 (2H, t, *J* 6.1, C(5)*H*$_2$), 2.42-2.51 (1H, m, C(4)*H*$_A$H$_B$), 2.60-2.68 (1H, m, C(4)H$_A$*H*$_B$), 4.74 (2H, s, C*H*$_2$OSi), 4.76 (1H, s, O*H*), 5.88 (1H, dt, *J* 5.4, 2.0, C(2)*H*), 6.11 (1H, dt, *J* 5.4, 2.5, C(3)*H*), 7.30 (2H, d, *J* 8.2, C(3')*H* and C(5')*H*), 7.41 (2H, d, *J* 8.2, C(2')*H* and C(6')*H*).

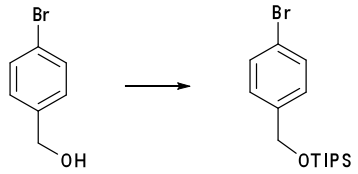
Benzyl [(*RS*)-3-(4'-*tert*-butyldimethylsilyloxymethyl)phenyl]cyclopent-2-en-1-yl]carbamate 446



445 446

Following **General Procedure 9**, crude **445** (1.52 g, 5.0 mmol, 1.0 eq), $Bi(OTf)_3$ (164 mg, 0.25 mmol, 0.05 eq), KPF_6 (46 mg, 0.25 mmol, 1.0 eq), benzyl carbamate **285** (1.13 g, 7.5 mmol, 1.5 eq) and $MgSO_4$ (~750 mg) were reacted in THF (20 mL) for 1 hr to give a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **446** as a white solid (482 mg, 22%); m.p. 52-53°C; ν_{max} (KBr) 3325 (N-H), 2955, 2930, 2855 (C-H), 1700 (C=O), 1515, 1250, 1090, 840, 775, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.13 (6H, s, Si*Me*$_2$tBu), 0.97 (9H, s, SiMe$_2$t*Bu*), 1.72-1.79 (1H, m, C(5)*H*$_A$H$_B$), 2.47-2.59 (1H, m, C(5)H$_A$*H*$_B$), 2.62-2.71 (1H, m, C(4)*H*$_A$H$_B$), 2.78-2.88 (1H, m, C(4)H$_A$*H*$_B$), 4.76 (2H, s, C*H*$_2$OSi), 4.96 (2H, br s, N*H* and C(1)*H*), 5.13 (2H, s, OC*H*$_2$Ph), 6.08 (1H, s, C(2)*H*), 7.30-7.44 (9H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 18.4 (*C*Me$_3$), 26.0 (C*Me*$_3$), 31.6, 32.0 (*C*(4) and *C*(5)), 57.7 (*C*(1)), 64.7 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 125.0 (*C*(2)), 125.9, 126.1, 128.1, 128.2, 128.5 (*Ar*), 134.2 (*C*(3)), 136.6 (*C*(4')), 141.3 (*C*(1')), 145.3 (*i-Ph*), 155.8 (*C*=O); *m/z* (ESI$^+$) 496 ([M+MeCN+NH$_4$]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{35}NNaO_3Si$ (M+Na$^+$) requires 460.2278, found 460.2272.

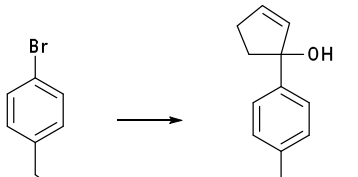
4-(tri-*iso*-propylsilyloxymethyl)bromobenzene 447[31]



443 447

To a stirred solution of 4-bromobenzylalcohol **443** (2.25 g, 12.0 mmol, 1.0 eq) in anhydrous DMF (30 mL) was added imidazole (0.98 g, 14.4 mmol, 1.2 eq) and TIPSCl (2.78 g, 14.4 mmol, 1.2 eq) and the resulting mixture stirred at RT for 16 hrs. The mixture was poured into ice-cold H_2O (100 mL) and extracted with Et_2O (5 × 20 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, 10% EtOAc/petrol) to give **447** as a colourless oil (4.09 g, 99%); δ_H (400 MHz, $CDCl_3$) 1.11 (18H, s, Si(CH*Me*$_2$)$_3$), 1.14-1.21 (3H, m, Si(C*H*Me$_2$)$_3$), 4.79 (2H, s, CH_2OSi), 7.24 (2H, d, *J* 8.5, C(2)*H* and C(6)*H*), 7.46 (2H, d, *J* 8.5, C(3)*H* and C(5)*H*).

(*RS*)-1-[4'-(tri-*iso*-propylsilyloxymethyl)phenyl]cyclopent-2-en-1-ol 448

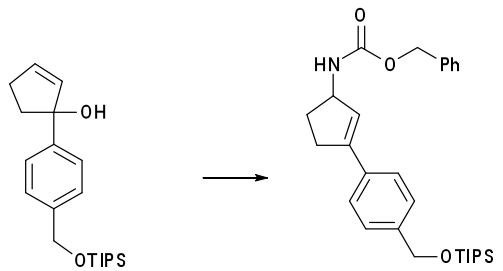


447 448

Following **General Procedure 10**, 2-cyclopenten-1-one **290** (0.31 mL, 3.77 mmol, 1.0 eq), **447** (1.55 g, 4.50 mmol, 1.2 eq) and ^{t}BuLi (1.7 M in pentane, 5.20 mL, 9.0 mmol, 2.4 eq) were reacted in THF (20 mL) for 1 hr to give a crude product which was either purified by flash column chromatography (silica, petrol → 10%

EtOAc/petrol) to give **448** as a colourless oil (815 mg, 62%) or used without further purification; ν_{max} (film) 3385 (O-H), 2940, 2865 (C-H), 1510, 1460, 1095, 920, 800, 680; δ_H (400 MHz, $CDCl_3$) 1.11 (18H, s, Si(CH*Me*$_2$)$_3$), 1.15-1.21 (3H, m, Si(C*H*Me$_2$)$_3$), 2.25-2.28 (2H, m, C(5)*H*$_2$), 2.42-2.51 (1H, m, C(4)*H*$_A$H$_B$), 2.60-2.68 (1H, m, C(4)H$_A$*H*$_B$), 4.84 (2H, s, C*H*$_2$OSi), 5.89 (1H, dt, *J* 5.5, 2.2, C(2)*H*), 6.10 (1H, dt, *J* 5.5, 2.5, C(3)*H*), 7.33-7.36 (2H, m, C(3')*H* and C(5')*H*), 7.40-7.42 (2H, m, C(2')*H* and C(6')*H*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 31.5 (*C*(4)), 41.9 (*C*(5)), 64.8 (*C*H$_2$OSi), 86.9 (*C*(1)) 124.7 (*C*(3') and *C*(5')), 125.6 (*C*(2') and *C*(6')), 134.7 (*C*(3)), 136.7 (*C*(2)), 140.2 (*C*(4')), 145.5 (*C*(1')); *m/z* (ESI$^+$) 329 ([M-OH]$^+$, 100%), 715 ([2M+Na]$^+$, 80%); HRMS (ESI$^+$) $C_{21}H_{34}NaO_2Si$ (M+Na$^+$) requires 369.2220, found 369.2214.

Benzyl {(*RS*)-3-[4'-(tri-*iso*-propylsilyloxymethyl)phenyl]cyclopent-2-en-1-yl}carbamate 449

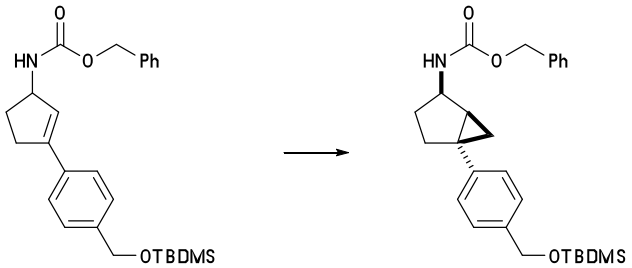


448 449

Following **General Procedure 9**, crude **448** (1.74 g, 5.0 mmol, 1.0 eq), Bi(OTf)$_3$ (164 mg, 0.25 mmol, 0.05 eq), KPF_6 (46 mg, 0.25 mmol, 1.0 eq), benzyl carbamate **285** (1.13 g, 7.5 mmol, 1.5 eq) and $MgSO_4$ (~750 mg) were reacted in THF (20 mL) for 1 hr to give a crude product which was purified by flash column chromatography (silica, petrol → 10% EtOAc/petrol) to give **449** as a white solid (1.04 g, 43%); m.p. 78-80 °C; ν_{max} (KBr) 3325 (N-H), 2945, 2865 (C-H), 1700 (C=O), 1510, 1460, 1235,

1095, 1050, 880, 795, 685; δ_H (400 MHz, $CDCl_3$) 1.12 (18H, s, Si(CH*Me*$_2$)$_3$), 1.17-1.24 (3H, m, Si(C*H*Me$_2$)$_3$), 1.74-1.81 (1H, m, C(5)H_AH_B), 2.53-2.59 (1H, m, C(5)H$_A$*H*$_B$), 2.64-2.71 (1H, m, C(4)H_AH_B), 2.80-2.88 (1H, m, C(4)H$_A$*H*$_B$), 4.85 (2H, s, C*H*$_2$OSi), 4.87-4.91 (1H, d, *J* 8.6, N*H*), 4.94-5.00 (1H, m, C(1)*H*), 5.14 (2H, s, OC*H*$_2$Ph), 6.09 (1H, s, C(2)*H*), 7.32-7.44 (9H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 31.6 (*C*(4)), 32.1 (*C*(5)), 57.7 (*C*(1)), 64.8 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 124.9 (*C*(2)), 125.7, 125.8, 128.1, 128.1, 128.5 (*Ar*), 134.0 (*C*(3)), 136.6 (*C*(4')), 141.6 (*C*(1')), 145.4 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI$^+$) 480 ([M+H]$^+$, 30%), 502 ([M+Na]$^+$, 70%), 976 ([2M + NH_4]$^+$, 100%), 981 ([2M+Na]$^+$, 90%); HRMS (ESI$^+$) $C_{29}H_{42}N_1O_3Si$ ([M+H]$^+$) requires 480.2928, found 480.2928.

Benzyl [(1*SR*,2*RS*,5*SR*)-5-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hex-2-yl]carbamate 450

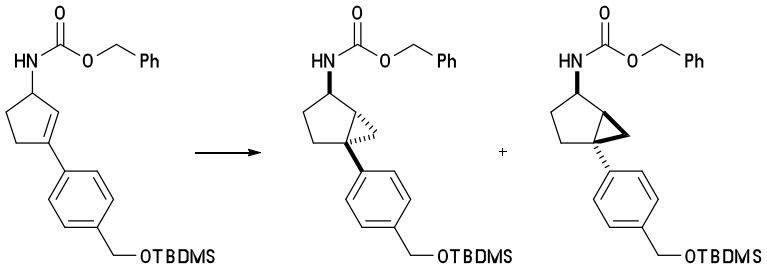


446 450

Following **General Procedure 1**, substrate **446** (109 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0 M in hexanes, 0.50 mL, 0.50 mmol, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10%EtOAc/petrol) to give **450** as a colourless oil (93 mg, 82%); ν_{max} (film) 3325 (N-H), 2955, 2930, 2855 (C-H), 1705 (C=O), 1515, 1250, 1090, 840, 775; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, Si*Me*$_2$tBu), 0.79 (1H, dd, *J* 7.8, 5.3, C(6)H_AH_B), 0.97 (9H, s, SiMe$_2$t*Bu*), 1.05 (1H, app t, *J* 4.6, C(6)H$_A$*H*$_B$), 1.10-1.16 (1H, m, C(4)H_AH_B), 1.91-1.95 (1H, m, C(1)*H*), 2.05-2.21 (3H, m, C(3)H_2 and

C(4)H_AH_B), 4.47-4.55 (1H, m, C(2)*H*), 4.73 (2H, s, CH_2OSi), 4.92 (1H, d, *J* 7.8, N*H*), 5.14 (2H, s, OCH_2Ph), 7.15 (2H, d, *J* 8.2, C(2')*H* and C(6')*H*), 7.27 (2H, d, *J* 8.2, C(3')*H* and C(5')*H*), 7.32-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 13.7 (*C*(6)), 18.4 (*C*Me$_3$), 26.0 (C*Me*$_3$), 28.1 (*C*(4)), 29.2 (*C*(1)), 30.9 (*C*(3)), 31.1 (*C*(5)), 53.0 (*C*(2)), 64.8 (*C*H$_2$OSi), 66.7 (OCH_2Ph), 126.1, 126.2, 128.2, 128.2, 128.6 (*Ar*), 136.6 (*C*(4')), 139.0 (*C*(1')), 142.8 (*i-Ph*), 156.0 (*C*=O); *m/z* (ESI$^+$) 452 ([M+H]$^+$, 25%), 469 ([M+NH$_4$]$^+$, 40%), 920 ([2M+NH$_4$]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{38}NO_3Si$ (M+H$^+$) requires 452.2615, found 452.2615.

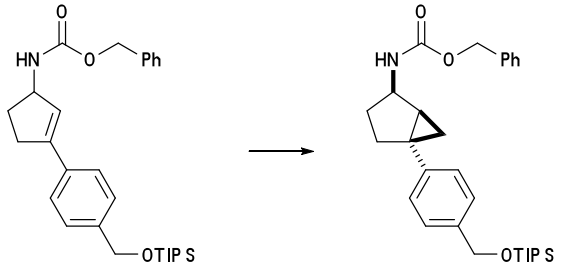
Benzyl [(1*RS*,2*RS*,5*RS*)-5-[4'-(*tert*-butyldimethylsilyloxymethyl)phenyl]bicyclo[3.1.0]hex-2-yl]carbamate 451 and benzyl [(1*SR*,2*RS*,5*SR*)-5-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hex-2-yl]carbamate 450



Following **General Procedure 3**, **446** (109 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.75 mL, 0.75 mmol, 3.0 eq), CH_2I_2 (121 µL, 1.5 mmol, 6.0 eq) and TFA (56 µL, 0.75 mmol, 3.0 eq) in CH_2Cl_2 (1.0 mL) for 4 hrs gave a crude product which was purified by flash column chromatography (silica, petrol→15% EtOAc/petrol) to give an 83:17 mixture of **451**:**450** as a colourless oil (55 mg, 49% combined yield); data for **451**; ν_{max} (film) 3325 (N-H), 2955, 2930, 2855 (C-H), 1705 (C=O), 1520, 1470, 1250, 1090, 840, 775, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, Si*Me*$_2$tBu), 0.88-0.94 (1H, m, C(6)H_AH_B), 0.96 (9H, s, SiMe$_2$t*Bu*), 1.59-1.78 (4H, m, C(1)*H*, C(3)H_2,

C(6)H_AH_B), 2.08-2.20 (2H, m, C(4)H_2), 4.22 (1H, t, *J* 6.7, C(2)*H*), 4.73 (2H, s, CH_2OSi), 4.92 (1H, br s, N*H*), 5.11 (2H, s, OCH_2Ph), 7.14 (2H, d, *J* 8.2, C(2')*H* and C(6')*H*), 7.26 (2H, d, *J* 8.2, C(3')*H* and C(5')*H*), 7.31-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 17.3 (*C*(6)), 18.4 (*C*Me$_3$), 26.0 (C*Me*$_3$), 29.4, 29.5 (*C*(3) and *C*(4)), 31.3 (*C*(1)), 31.8 (*C*(5)), 53.9 (*C*(2)), 64.7 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 126.0, 126.1, 128.1, 128.2, 128.6 (*Ar*), 136.5 (*C*(4')), 138.9 (*C*(1')), 142.6 (*i-Ph*), 155.4 (*C*=O); *m/z* (ESI$^+$) 510 ([M+NH$_4$+MeCN]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{37}NNaO_3Si$ ([M+Na]$^+$) requires 474.2435, found 474.2427.

Benzyl [(1*SR*,2*RS*,5*SR*)-(4'-{[(tri-*iso*-propylsilyl)oxy]methylphenyl}bicyclo[3.1.0]hex-2-yl]carbamate 452

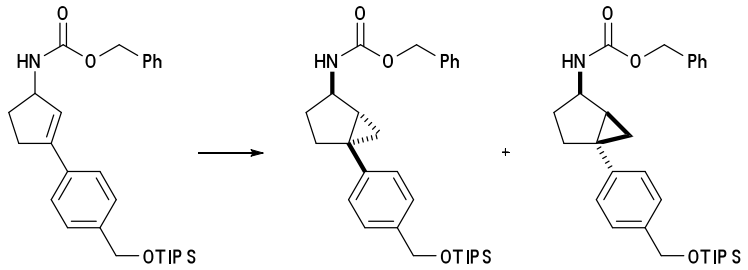


449 452

Following **General Procedure 1**, **449** (120 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.50 mL, 0.50 mmol, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 5% EtOAc/petrol) to give **452** as a colourless oil (111 mg, 90%, >98% d.e.); ν_{max} (film) 3330 (N-H), 2945, 2865 (C-H), 1705 (C=O), 1520, 1465, 1245, 1095, 1065, 1020, 880, 800, 685; δ_H (400 MHz, $CDCl_3$) 0.80 (1H, dd, *J* 7.8, 5.3, C(6)H_AH_B), 1.06 (1H, app t, *J* 4.6, C(6)H_AH_B), 1.13 (18H, d, *J* 6.3, Si(CH*Me*$_2$)$_3$), 1.14-1.23 (4H, m, Si(C*H*Me$_2$)$_3$, C(3)H_AH_B), 1.92-1.96 (1H, m, C(1)*H*), 2.07-2.21 (3H, m, C(3)H_AH_B, C(4)H_2), 4.49-4.56 (1H, m, C(2)*H*), 4.84 (2H, s, CH_2OSi), 4.94 (1H, d, *J* 7.6, N*H*), 5.15 (2H, s, CH_2Ph), 7.16 (2H, d, *J* 8.1, C(2')*H*,

C(6')*H*), 7.31 (2H, d, *J* 8.1, C(3')*H*, C(5')*H*), 7.36-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*H$(CH_3)_2)_3$), 13.7 (*C*(6)), 18.1 (Si(CH(*C*$H_3)_2)_3$), 28.1 (*C*(3)), 29.2 (*C*(1)), 30.9 (*C*(4)), 31.1 (*C*(5)), 53.0 (*C*(2)), 64.8 (*C*H_2OSi), 66.6 (*C*H_2Ph), 125.7, 126.1, 128.1, 128.2, 128.6 (*Ar*), 136.6 (*C*(4')), 139.2 (*i-Ph*), 142.6 (*C*(1')), 156.0 (*C*=O); *m/z* (ESI$^+$) 494 ([M+H]$^+$, 30%), 557 ([M+MeCN+Na]$^+$, 100%), 988 ([2M+H]$^+$, 20%); HRMS (ESI$^+$) $C_{30}H_{44}NO_3Si$ ([M+H]$^+$) requires 494.3085, found 494.3084.

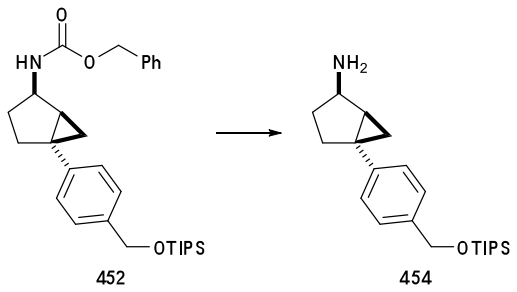
Benzyl [(1*RS*,2*RS*,5*RS*)-5-(4'-{[(tri-*iso*-propylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hex-2-yl]carbamate 453 and benzyl [(1*SR*,2*RS*,5*SR*)-(4'-{[(tri-*iso*-propylsilyl)oxy]methylphenyl}bicyclo[3.1.0]hex-2-yl]carbamate 452



Following **General Procedure 3**, **449** (113 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.75 mL, 0.75 mmol, 3.0 eq), CH_2I_2 (121 µL, 1.5 mmol, 6.0 eq) and TFA (56 µL, 0.75 mmol, 3.0 eq) in CH_2Cl_2 (1.0 mL) for 3 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10%EtOAc/petrol) to give a 91:9 mixture of **453**:**452** as a colourless oil (108 mg, 88%); data for **453**; ν_{max} (film) 3325 (N-H), 2945, 2865 (C-H), 1705 (C=O), 1520, 1465, 1240, 1095, 885, 805, 665; δ_H (400MHz, $CDCl_3$) 0.87-0.96 (2H, m, C(6)H_2), 1.11 (18H, d, *J* 6.4, Si(CH*Me*$_2)_3$), 1.14-1.23 (3H, m, Si(C*H*$Me_2)_3$), 1.63-1.75 (3H, m, C(1)*H* and C(3)H_2), 2.09-2.17 (2H, m, C(4)H_2), 4.21 (1H, app t, *J* 6.7, C(2)*H*), 4.82 (2H, s, *C*H_2OSi), 4.88 (1H, d, *J*

7.0, N*H*), 5.10 (2H, s, OCH_2Ph), 7.14 (2H, d, *J* 8.1, C(2′)*H* and C(6′)*H*), 7.29 (2H, d, *J* 8.1, C(3′)*H* and C(5′)*H*), 7.32-7.39 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$, 17.3 (*C*(6)), 18.1 (Si(CH*Me*$_2$), 29.4, 29.5 (*C*(3) and *C*(4)), 31.3 (*C*(1)), 31.9 (*C*(5)), 53.9 (*C*(2)), 64.8 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 125.7, 125.9, 128.1, 128.2, 128.5 (*Ar*), 136.5, (*C*(4′)), 139.2 (*i-Ph*), 142.4 (*C*(1′)), 155.4 (*C*=O); *m/z* (ESI$^+$) 595 ([M+NEt$_3$+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{43}NNaO_3Si$ (M+Na$^+$) requires 516.2904, found 516.2886.

(1*SR*,2*RS*,5*SR*)-5-(4'-{[(tri-*iso*-propylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hexan-2-amine 454

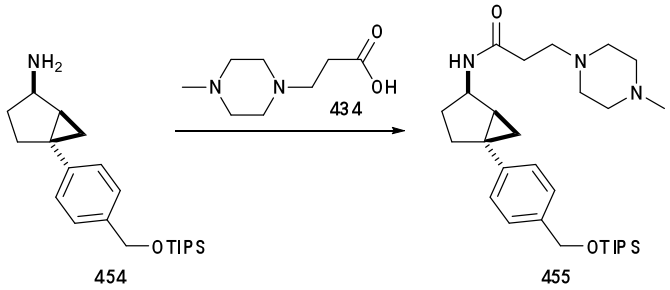


452 454

Following **General Procedure 11**, **452** (313 mg, 0.63 mmol, 1.0 eq) and Pd/C (94 mg) in MeOH (6 mL) gave **454** as a colourless oil (226 mg, quant.); ν_{max} (film) 3340 (N-H), 2945, 2865 (C-H), 1520, 1465, 1385 (Ar), 1095, 1015, 882, 810, 730, 685; δ_H (400 MHz, $CDCl_3$) 0.76 (1H, dd, *J* 8.1, 5.0, C(6)H_AH_B), 1.05-1.13 (2H, m, C(3)H_AH_B and C(6)H_AH_B) overlapping 1.12 (18H, s, Si(CH*Me*$_2$)$_3$), 1.15-1.24 (3H, m, Si(C*H*Me$_2$)$_3$), 1.77 (1H, app dt, *J* 9.2, 4.2, C(1)*H*), 1.84-1.94 (2H, br s, NH_2), 1.94-2.01 (1H, m, C(3)H_AH_B), 2.02-2.17 (2H, m, C(4)H_2), 3.74 (1H, ddd, *J* 9.8, 7.2, 4.4, C(2)*H*), 4.82 (2H, s, CH_2OSi), 7.13 (2H, d, *J* 8.5, C(2')*H* and C(6')*H*), 7.29 (2H, d, *J* 8.5, C(3')*H* and C(5')*H*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 13.5 (*C*(6)), 18.1 (Si(CH*Me*$_2$)$_3$), 30.9, 31.2 (*C*(3) and *C*(4)), 31.6 (*C*(5)), 32.8 (*C*(1)), 53.5 (*C*(2)), 64.8 (*C*H$_2$OSi), 125.7, 125.8 (*C*(2'), *C*(3'), *C*(5') and *C*(6')), 138.8 (*C*(4')), 143.3 (*C*(1')); *m/z*

(ESI^+) 343 ($[M\text{-}NH_2]^+$, 100%), 719 ($[2M+H]^+$, 80%); HRMS (ESI^+) $C_{22}H_{38}NOSi$ ($[M+H]^+$) requires 360.2717, found 360.2720.

(1*SR*,2*RS*,5*SR*)-*N*-[3''-(4'''-methylpiperazin-1'''-yl)propanamide]-5-(4'-{[(tri-*iso*-propylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hexan-2-amine 455

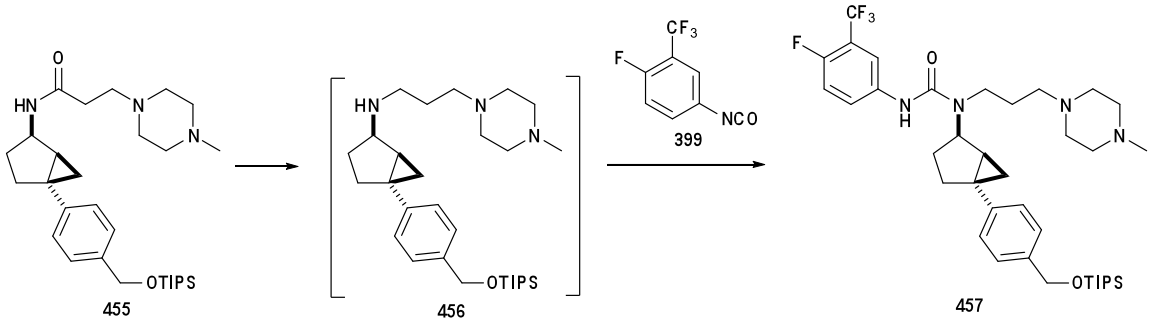


454 455

To a stirred solution of amine **454** (226 mg, 0.63 mmol, 1.0 eq) in $CHCl_3$ (6 mL) was added NEt_3 (0.44 mL, 3.15 mmol, 5.0 eq), HOBt (103 mg, 0.76 mmol, 1.2 eq), 3-(4'-methylpiperazin-1'-yl)propanoic acid **434** (131 mg, 0.76 mmol, 1.2 eq) and EDCI (146 mg, 0.76 mL, 1.2 eq). The resulting mixture was stirred at RT for 16 hrs then diluted with EtOAc (25 mL), washed with sat. aq. $NaHCO_3$ (15 mL), brine (15 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, CH_2Cl_2 → 10% MeOH/CH_2Cl_2) to give **455** as a colourless oil (252 mg, 80%); ν_{max} (film) 3315 (N-H), 2940, 2865 (C-H), 1645 (C=O), 1545, 1460, 1095, 1015, 880, 795, 685; δ_H (400 MHz, $CDCl_3$) 0.77 (1H, dd, *J* 7.8, 5.0, C(6)H_AH_B), 1.01-1.10 (2H, m, C(6)H_AH_B and C(3)H_AH_B) overlapping 1.08 (18H, s, Si(CH*Me*$_2$)$_3$), 1.11-1.20 (3H, m, Si(C*H*Me$_2$)$_3$), 1.87 (1H, dd, *J* 8.2, 4.2, C(1)*H*), 2.03-2.10 (1H, m, C(4)H_AH_B), 2.11-2.19 (2H, m, C(3)H_AH_B and C(4)H_AH_B), 2.30 (3H, s, N*Me*), 2.33-2.67 (8H, br m, N(CH_2CH_2)$_2$N) overlapping 2.36-2.38 (2H, m, C(2'')H_2) and 2.62-2.65 (2H, m, C(3'')H_2), 4.62-4.68 (1H, m, C(2)*H*), 4.78 (2H, s, CH_2OSi), 7.13 (2H, d, *J* 8.3, C(2')*H* and C(6')*H*), 7.26 (2H, d, *J* 8.3, C(3')*H* and C(5')*H*), 8.71 (1H, d, *J* 7.6, N*H*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 13.9

(*C*(6)), 18.0 (Si(CH*Me*$_2$)$_3$), 28.2 (*C*(3)), 29.2 (*C*(1)), 31.2 (*C*(4)), 31.2 (*C*(5)), 31.9 (*C*(2")), 46.0 (N*Me*), 50.6 (*C*(2)), 52.2, 55.2 (N(*C*H$_2$*C*H$_2$)$_2$N), 53.8 (*C*(3")), 64.8 (*C*H$_2$OSi), 125.7, 126.2 (*C*(2'), *C*(3'), *C*(5') and *C*(6')), 139.2 (*C*(4')), 142.7 (*C*(1')), 172.1 (*C*=O); *m/z* (ESI$^+$) 514 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{52}N_3O_2Si$ (M+H$^+$) requires 514.3823, found 514.3824.

(1'*SR*,2'*RS*,5'*SR*)-3-[4''''-fluoro-3''''-(trifluoromethyl)phenyl]-1-[3'''-(4''''-methylpiperazin-1''''-yl)propyl]-1-[5'-(4''-{[(tri-*iso*-propylsilyl)oxy]methyl}phenyl)bicyclo[3.1.0]hex-2'-yl]urea 457

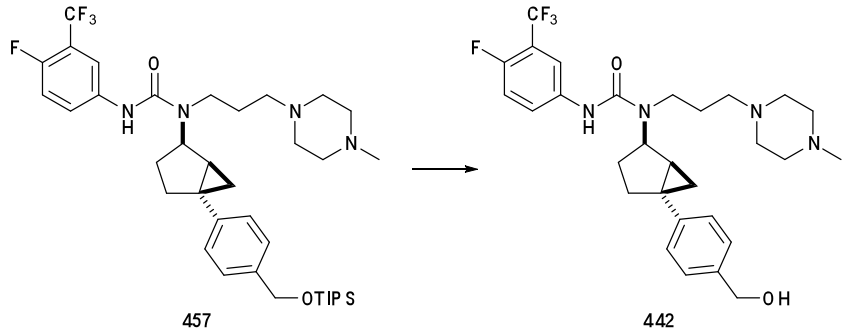


To a stirred solution of **455** (51 mg, 0.10 mmol, 1.0 eq) in THF (5 mL) was added $LiAlH_4$ (9.5 mg, 0.25 mmol, 2.5 eq) and the resulting mixture stirred at reflux for 16 hrs. The mixture was then cooled to 0 °C and H_2O (0.01 mL), 15% aq. NaOH (0.01 mL) and H_2O (0.03 mL) were added sequentially. The mixture was vigorously stirred for 20 mins then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo* to give a crude product which was used without further purification.

The crude product was dissolved in CH_2Cl_2 (1 mL) and DIPEA (21 μL, 0.12 mmol, 1.2 eq) and 4-fluoro-3-(trifluoromethyl)phenyl isocyanate **399** (25 mg, 0.12 mmol, 1.2 eq) were added. The resulting mixture was stirred at RT for 16 hrs and then sat. aq. $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and

the combined organic layers dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, CH_2Cl_2 → 5% MeOH/CH_2Cl_2) to give **457** as a pale yellow oil (50 mg, 71%); ν_{max} (film) 3330 (N-H), 2945, 2865 (C-H), 1635 (C=O), 1560, 1505, 1425, 1325, 1140, 1055, 885, 815, 740; δ_H (400 MHz, $CDCl_3$) 0.95-1.00 (1H, m, C(6')H_AH_B), 1.05-1.37 (5H, m, Si(C*H*Me$_2$)$_3$, C(3')H_AH_B and C(6')H_AH_B) overlapping 1.10 (18H, s, Si(CH*Me*$_2$)$_3$), 1.66 (1H, dd, *J* 8.0, 4.2, C(1')*H*), 1.91-2.06 (4H, m, C(3')H_AH_B, C(4')H_2 and C(2''')H_AH_B), 2.11-2.16 (1H, m, C(2''')H_AH_B), 2.23 (3H, s, N*Me*), 2.27-2.72 (8H, br m, N(CH_2CH_2)$_2$N) overlapping 2.55-2.72 (2H, m, C(3''')H_2), 3.39-3.45 (1H, m, C(1''')H_AH_B), 3.50-3.57 (1H, m, C(1''')H_AH_B), 4.81 (2H, s, CH_2OSi), 5.03-5.08 (1H, m, C(2')*H*), 7.00 (1H, t, *J* 9.2, *Ar*), 7.09-7.12 (2H, m, C(2'')*H* and C(6'')*H*), 7.27-7.29 (2H, m, C(3'')*H* and C(5'')*H*), 7.57 (1H, dd, *J* 6.2, 2.4, *Ar*), 7.65-7.69 (1H, m, *Ar*), 9.70 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.7 (*C*(6')), 18.0 (Si(CH*Me*$_2$)$_3$), 23.2 (*C*(2''')), 26.5 (*C*(3')), 27.4 (*C*(1')), 29.3 (*C*(5')), 30.0 (*C*(4')), 39.9 (*C*(1''')), 45.7 (N*Me*), 53.5 (*C*(3''')), 54.4 (N(*C*H$_2$*C*H$_2$)$_2$N), 56.4 (*C*(2')), 64.7 (*C*H$_2$OSi) 116.9 (d, *J* 20.8, *Ar*), 121.1 (*Ar*), [C_{Ar}F, $C_{Ar}CF_3$ and *C*F$_3$ not observed]; δ_F (376MHz, $CDCl_3$) -122.0 (br s, $C_{Ar}F$), -61.4 (d, *J* 13.8, CF_3); *m/z* (ESI$^+$) 705 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{57}F_4N_4O_2Si$ ([M+H]$^+$) requires 705.4181, found 705.4181.

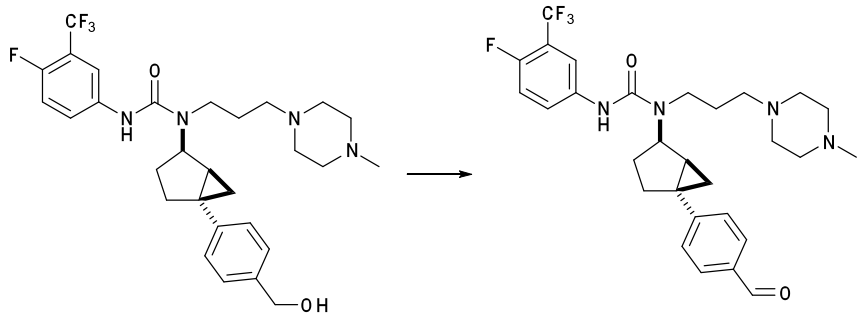
(1'*SR*,2'*RS*,3'*SR*)-3-[4''''-fluoro-3''''-(trifluoromethyl)phenyl]-1-{5'-[4''-(hydroxymethyl)phenyl]bicyclo[3.1.0]hex-2'-yl}-1-[3'''-(4''''-methylpiperazin-1''''-yl)propyl]urea 442



To a stirred solution of **457** (40 mg, 57 μmol, 1.0 eq) in THF (1.0 mL) at 0 °C was added TBAF (68 μL, 1.0M in THF, 68 μmol, 1.2 eq) and the mixture stirred for 1 hr at 0 °C. H_2O (1 mL) was added and the mixture extracted with Et_2O (5 × 1 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give **442** as a colourless oil (34 mg, quant.); ν_{max} (film) 3240 (N-H), 3060, 2925 (C-H), 1630 (C=O), 1605, 1545, 1500, 1445, 1255, 1205, 750, 695; δ_H (400 MHz, $CDCl_3$) 0.92-0.96 (1H, m, C(6')H_AH_B), 1.23-1.34 (3H, m, C(3')H_AH_B, C(6')H_AH_B and O*H*), 1.66 (1H, app dt, *J* 8.0, 4.1, C(1')*H*), 1.86-2.04 (3H, m, C(2''')H_2 and C(3')H_AH_B), 2.05-2.18 (2H, m, C(4')H_2), 2.21-2.70 (10H, br m, N(CH_2CH_2)$_2$N and C(3''')H_2) overlapping 2.24 (3H, s, N*Me*), 3.37 (1H, dt, *J* 15.7, 5, C(1''')H_AH_B), 3.46-3.51 (1H, m, C(1''')H_AH_B), 4.65 (2H, s, CH_2OH), 5.07 (1H, ddd, *J* 11.0, 7.0, 4.2, C(2')*H*), 7.13 (1H, t, *J* 9.5, *Ar*), 7.19 (2H, d, *J* 8.2, C(2'')*H* and C(6'')*H*), 7.29 (2H, d, *J* 8.2, C(3'')*H* and C(5'')*H*), 7.60 (1H, dd, *J* 6.3, 2.5, *Ar*), 7.75-7.79 (1H, m, *Ar*), 9.41 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.8 (*C*(6')), 23.0 (*C*(2''')), 26.5 (*C*(3')), 27.5 (*C*(1')), 29.3 (*C*(5')), 30.1 (*C*(4')), 39.8 (*C*(1''')), 45.7 (N*Me*), 53.6 (*C*(3''')), 54.4 (N(*C*H_2*C*H_2)$_2$N), 56.1 (*C*(2')), 65.0 (*C*H_2OH), 116.9 (d, *J* 20.8, *Ar*), 121.1 (*Ar*), 126.6, 127.1 (*C*(2''), *C*(3''), *C*(5'') and *C*(6'')), 128.2 (*Ar*), 135.8 (*Ar*), 138.6 (*C*(4'')), 143.7 (*C*(1'')), 157.5 (*C*=O),

[$C_{Ar}F$, $C_{Ar}CF_3$ and CF_3 not observed]; δ_F (376MHz, $CDCl_3$) -61.1 (d, *J* 12.6, $C_{Ar}F$), -121.7 (q, *J* 12.6, CF_3); *m/z* (ESI^+) 549 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{36}F_4N_4O_2$ ($[M+H]^+$) requires 549.2847, found 549.2834.

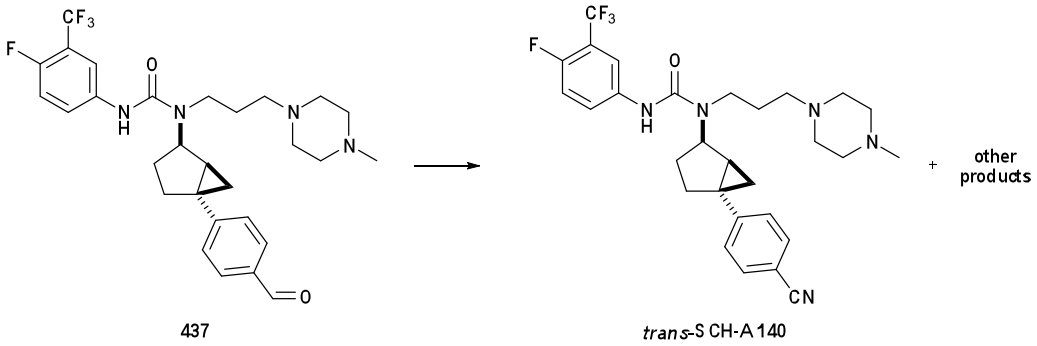
(1'*SR*,2'*RS*,3'*SR*)-3-[4''''-fluoro-3''''-(trifluoromethyl)phenyl]-1-{5'-[4''-formylphenyl]bicyclo[3.1.0]hex-2'-yl}-1-[3'''-(4''''-methylpiperazin-1''''-yl)propyl]urea 437



To a stirred solution of **442** (30 mg, 55 μmol, 1.0 eq) in CH_2Cl_2 (1.0 mL) was added MnO_2 (48 mg, 0.55 mmol, 10.0 eq) and the resulting suspension stirred at RT for 3 hrs. The mixture was concentrated *in vacuo* and purified by flash column chromatography (CH_2Cl_2 → 10% MeOH/CH_2Cl_2) to give **437** (22 mg, 74%) as a colourless oil; ν_{max} (film) 3385 (N-H), 2940, 2360 (C-H), 1700 (aldehyde), 1655 (urea), 1605, 1505, 1325, 1135; δ_H (400 MHz, $CDCl_3$) 1.03 (1H, dd, *J* 7.4, 5.7, C(6')H_AH_B), 1.31-1.40 (2H, m, C(3')H_AH_B and C(6')H_AH_B), 1.73-2.03 (4H, m, C(1')*H*, C(3')H_AH_B, C(2''')H_2), 2.10-2.22 (2H, m, C(4')H_2), 2.24 (3H, s, N*Me*), 2.29-2.70 (10H, br m, N(CH_2CH_2)$_2$N and C(3''')H_2), 3.37 (1H, dt, *J* 15.9, 5.0, C(1''')H_AH_B), 3.48-3.54 (1H, m, C(1''')H_AH_B), 5.04-5.10 (1H, m, C(2')*H*), 7.14 (1H, t, *J* 9.4, *Ar*), 7.30 (2H, d, *J* 8.4, C(2'')*H* and C(6'')*H*), 7.60 (1H, dd, *J* 6.3, 2.8, *Ar*), 7.74-7.79 (1H, m, *Ar*) overlapping 7.80 (2H, d, *J* 8.4, C(3'')*H* and C(5'')*H*), 9.49 (1H, s, N*H*), 9.96 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 17.4 (*C*(6')), 22.8 (*C*(2''')), 26.2 (*C*(3')), 28.9 (*C*(1')),

29.6 (*C*(5')), 29.9 (*C*(4')), 39.9 (*C*(1''')), 45.8 (N*Me*), 51.9 (*C*(1")), 53.6 (*C*(3''')), 54.4 (N(CH_2CH_2)$_2$N), 55.8 (*C*(2')), 117.0 (d, *J* 20.8, *Ar*), 121.2 (*Ar*, 126.6 (*C*(2") and *C*(6")), 128.3 (*Ar*), 129.9 (*C*(3") and *C*(5")), 134.2 (*C*(4")), 135.7 (*Ar*), 157.6 (N*C*=O), 191.8 (*C*HO); δ_F (376MHz, $CDCl_3$) -61.2 (d, *J* 12.6, $C_{Ar}F$), -121.6 (q, *J* 12.6, CF_3); *m/z* (ESI^+) 547 ($[M+H]^+$, 100%), 569 ($[M+Na]^+$, 20%); HRMS (ESI^+) $C_{29}H_{34}F_4N_4O_2$ ($[M+H]^+$) requires 547.2691, found 547.2690.

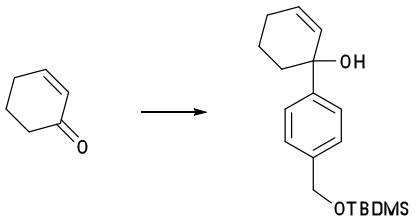
***trans*-SCH-A 140**



To a stirred solution of **437** (7.9 mg, 14.4 μmol, 1.0 eq) in NH_4OH (0.5 mL) and MeCN (0.1 mL) was added IBX (6.1 mg, 21.7 μmol, 1.0 eq) and the mixture stirred for 16 hrs at RT. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 mL), dried, filtered and concentrated *in vacuo* to give a crude product which was purified by flash column chromatography (silica, CH_2Cl_2 → 5 % MeOH/CH_2Cl_2) to give a 33:67 mixture of **437**:**140**, containing other unidentified products, as a pale yellow oil (4.5 mg); Data for **140**; ν_{max} (film) 3585, 3355 (N-H), 2920, 2850 (C-H), 2225 (nitrile), 1660 (urea), 1605, 1505, 1425, 1325, 1135; δ_H (500 MHz, $CDCl_3$) 0.99-1.01 (1H, m, C(6)H_AH_B), 1.29-1.40 (2H, m, C(3)H_AH_B and C(6)H_AH_B), 1.70-2.69 (16H, m, C(1)*H*, C(3)H_AH_B, C(4)H_2, C(2′′)H_2, C(3′′)H_2 and N(CH_2CH_2)$_2$N) overlapping 2.26 (3H, s, N*Me*), 3.34-3.40 (1H, m, C(1′′)H_AH_B), 3.48-3.54 (1H, m, C(1′′)H_AH_B), 5.05-5.09

(1H, m, C(2)*H*), 7.14 (1H, t, *J* 9.4, *Ar*), 7.25 (2H, d, *J* 8.6, C(2′)*H* and C(6′)*H*), 7.57 (1H, d, *J* 8.6, C(3′)*H* and C(5′)*H*), 7.60-7.61 (1H, m, *Ar*), 7.75-7.78 (1H, m, *Ar*), 9.45 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 16.1 (*C*(6)), 22.7 (*C*(2′′)), 26.6 (*C*(3)), 28.7 (*C*(1)), 29.1 (*C*(5)), 29.4 (*C*(4)), 40.0 (*C*(1′′)), 45.7 (N*Me*), 53.6 (*C*(3′′)), 54.4 (N(*C*H_2*C*H_2)$_2$N), 55.8 (*C*(2)), 109.4 (*C*(4′)), 117.0 (d, *J* 21.7, *Ar*), 119.0 (Ar*C*N), 121.2 (*Ar*), 126.8 (*C*(2′) and *C*(6′)), 128.2 (*Ar*), 132.1 (*C*(3′) and *C*(5′)), 135.6 (*Ar*), 150.1 (*C*(1′)), 157.5 (*C*=O)); δ_F (470MHz, $CDCl_3$) -61.2 (d, *J* 12.4, $C_{Ar}F$), -121.6 (m, CF_3); *m/z* (ESI$^+$) 544 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{33}F_4N_5O$ ([M+H]$^+$) requires 544.2694, found 544.2687.

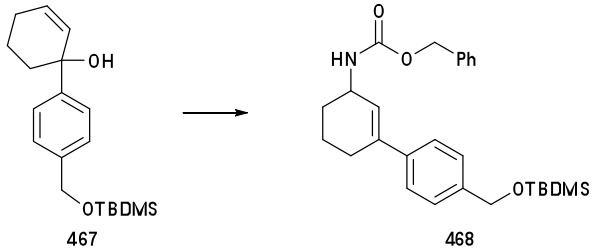
(*RS*)-1-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)cyclohex-2-en-1-ol 467



248 467

Following **General Procedure 10**, 2-cyclohexen-1-one **248** (1.51 mL, 18 mmol, 1.0 eq), **444** (6.51 g, 21.6 mmol, 1.2 eq) and ^{t}BuLi (1.7M in pentane, 25.4 mL, 43.2 mmol, 2.4 eq) were reacted in THF (75 mL) for 1 hr to give crude **467** which was used without further purification; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, Si*Me*$_2$tBu), 0.96 (9H, s, SiMe$_2$t*Bu*), 1.59-1.70 (1H, m, 1 × CH_2), 1.75-1.90 (2H, m, 2 × CH_2), 1.96-2.01 (2H, m, O*H* and 1 × CH_2), 2.06-2.19 (2H, m, 2 × CH_2), 4.75 (2H, s, CH_2OSi), 5.79 (1H, d, *J* 10.2, C(2)*H*), 6.04 (1H, dt, *J* 10.2, 3.8, C(3)*H*), 7.30-7.35 (2H, m, C(2')*H* and C(6')*H*), 7.46 (2H, d, *J* 8.2, C(3')*H* and C(5')*H*).

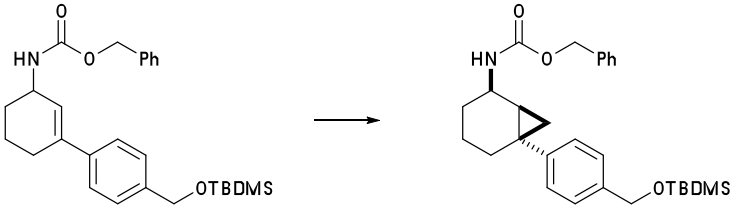
Benzyl [(*RS*)-3-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)cyclohex-2-en-1-yl]carbamate 468



467 468

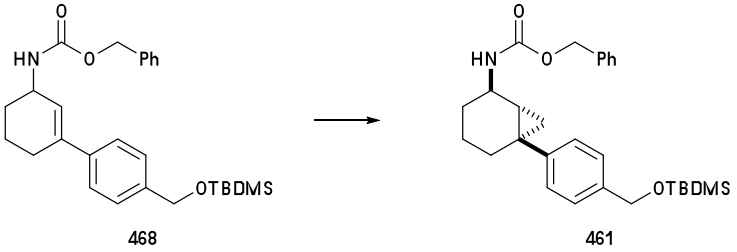
Following **General Procedure 9**, crude **467** (1.85 g, 5.0 mmol, 1.0 eq), $Bi(OTf)_3$ (164 mg, 0.25 mmol, 0.05 eq), KPF_6 (46 mg, 0.25 mmol, 1.0 eq), benzyl carbamate **285** (1.13 g, 7.5 mmol, 1.5 eq) and $MgSO_4$ (~750 mg) were reacted in THF (20 mL) for 16 hrs to give a crude product which was purified by flash column chromatography (silica, petrol → 20% EtOAc/petrol) to give **468** as a white solid (340 mg, 15%); m.p. 63-65°C; ν_{max} (KBr) 3330 (N-H), 2930, 2855 (C-H), 1695 (C=O), 1515, 1460, 1310, 1250, 840, 780, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, Si*Me*$_2$tBu), 0.97 (9H, s, SiMe$_2$t*Bu*), 1.56-1.64 (1H, m, C(6)*H*$_A$H$_B$), 1.75-1.87 (2H, m, C(5)*H*$_2$), 1.97-2.04 (1H, m, C(6)H$_A$*H*$_B$), 2.34-2.50 (2H, m, C(4)*H*$_2$), 4.46 (1H, br s, C(1)*H*), 4.75 (2H, s, C*H*$_2$OSi), 4.89 (1H, br s, N*H*), 5.14 (2H, s, OC*H*$_2$Ph), 6.01 (1H, s, C(2)*H*), 7.27-7.41 (9H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 18.4 (*C*(5)), 20.2 (*C*Me$_3$), 26.0 (C*Me*$_3$), 27.2 (*C*(4)), 29.4 (*C*(6)), 47.2 (*C*(1)), 64.7 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 124.2 (*C*(2)), 125.1, 126.0, 128.1, 128.5 (*Ar*), 136.6 (*C*(3)), 139.9, 140.0, 140.7 (*C*(1'), *C*(4') and *i-Ph*), 155.7 (*C*=O); *m/z* (ESI^+) 510 ([M+NH_4+MeCN]$^+$, 100%); HRMS (ESI^+) $C_{27}H_{37}NNaO_3Si$ ([M+Na]$^+$) requires 474.2435, found 474.2436.

Benzyl [(1*SR*,2*RS*,6*SR*)-6-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)bicyclo[4.1.0]hept-2-yl]carbamate 458



Following **General Procedure 1**, **468** (113 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.50 mL, 0.50 mmol, 2.0 eq) and CH_2I_2 (81 μL, 1.0 mmol, 4.0 eq) in CH_2Cl_2 (1.0 mL) for 1 hr gave a crude product which was purified by flash column chromatography (silica, petrol → 10%EtOAc/petrol) to give **458** as a colourless oil (100 mg, 86%, >98:2 d.r.); ν_{max} (film) 3330 (N-H), 2930, 2855 (C-H), 1710 (C=O), 1515, 1465, 1250, 1090, 840, 775, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.12 (6H, s, Si*Me*$_2$tBu), 0.69 (1H, app t, *J* 5.3, C(7)*H*$_A$H$_B$), 0.93 (1H, dd, *J* 9.4, 4.6, C(7)H$_A$*H*$_B$), 0.97 (9H, s, SiMe$_2$t*Bu*), 1.08-1.17 (1H, m, C(3)*H*$_A$H$_B$), 1.39-1.47 (2H, m, C(4)*H*$_2$), 1.59 (1H, dt, *J* 9.1, 6.1, C(1)*H*), 1.79-1.92 (2H, m, C(3)H$_A$*H*$_B$ and C(5)*H*$_A$H$_B$), 1.96-2.03 (1H, m, C(5)H$_A$*H*$_B$), 4.29-4.36 (1H, m, C(2)*H*), 4.73 (2H, s, C*H*$_2$OSi), 4.87 (1H, d, *J* 7.6, N*H*), 5.14 (2H, s, OC*H*$_2$Ph), 7.22-7.27 (4H, m, *Ar*), 7.32-7.42 (5H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 14.5 (*C*(7)), 18.4 (*C*Me$_3$), 20.7 (*C*(4)), 23.9 (*C*(1)), 26.0 (C*Me*$_3$), 27.1 (*C*(6)), 27.5 (*C*(3)), 31.5 (*C*(5)), 46.4 (*C*(2)), 64.8 (*C*H$_2$OSi), 66.6 (O*C*H$_2$Ph), 126.2, 127.3, 128.1, 128.2, 128.6 (*Ar*), 136.6 (*C*(4')), 139.1 (*C*(1')), 146.8 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI$^+$) 524 ([M+NH$_4$+MeCN]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{39}NNaO_3Si$ ([M+Na]$^+$) requires 488.2591, found 488.2588.

Benzyl [(1*RS*,2*RS*,6*RS*)-6-(4'-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)bicyclo[4.1.0]hept-2-yl]carbamate 461



Following **General Procedure 3**, **468** (113 mg, 0.25 mmol, 1.0 eq), $ZnEt_2$ (1.0M in hexanes, 0.75 mL, 0.75 mmol, 3.0 eq), CH_2I_2 (121 μL, 1.5 mmol, 6.0 eq) and TFA (56 μL, 0.75 mmol, 3.0 eq) in CH_2Cl_2 (1.0 mL) for 4 hrs gave a crude product which was purified by flash column chromatography (silica, petrol → 10%EtOAc/petrol) to give **461** as a colourless oil (66 mg, 57%, >98:2 d.r.); ν_{max} (film) 3330 (N-H), 2930, 2855 (C-H), 1700 (C=O), 1515, 1455, 1310, 1250, 1095, 835, 775, 695, 665; δ_H (400 MHz, $CDCl_3$) 0.11 (6H, s, Si*Me*$_2$tBu), 0.74 (1H, app t, *J* 5.0, C(7)H_AH_B), 0.96 (9H, s, SiMe$_2$t*Bu*), 1.05 (1H, dd, *J* 9.5, 4.9, C(7)H$_A$$H_B$), 1.19-1.29 (3H, m, C(1)*H*, C(3)H_AH_B and C(4)H_AH_B), 1.56-1.62 (1H, m, C(4)H$_A$$H_B$), 1.76-1.82 (1H, m, C(3)H$_A$$H_B$), 1.89-1.96 (1H, m, C(5)H_AH_B), 2.05-2.11 (1H, m, C(5)H$_A$$H_B$), 3.96-4.00 (1H, m, C(2)*H*), 4.72 (2H, s, CH_2OSi), 5.04 (1H, d, *J* 5.8, N*H*), 5.13 (2H, s, OCH_2Ph), 7.20 (2H, AB d, *J* 8.3, C(2')*H* and C(6')*H*), 7.25 (2H, AB d, *J* 8.3, C(3')*H* and C(5')*H*), 7.31-7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) -5.2 (Si*Me*$_2$tBu), 16.9 (*C*(7)), 18.0 (*C*(4)), 18.4 (*C*Me$_3$), 25.2 (*C*(6)), 25.8 (*C*(1)), 26.0 (C*Me*$_3$), 28.8 (*C*(3)), 30.6 (*C*(5)), 47.7 (*C*(2)), 64.7 (*C*H$_2$OSi), 66.6 (OCH$_2$Ph), 126.1, 127.1, 128.1, 128.2, 128.5 (*Ar*), 136.6 (*C*(4')), 139.0 (*C*(1')), 146.6 (*i-Ph*), 155.7 (*C*=O); *m/z* (ESI$^+$) 524 ([M+NH$_4$+MeCN]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{39}NNaO_3Si$ ([M+Na]$^+$) requires 488.2591, found 488.2588.

5.6 References and notes

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