TOWARDS THE DEVELOPMENT OF DIRECT METHODOLOGY TO ENANTIOENRICHED α-ALKYLATED ALDEHYDES

ANDREW CHARLTON

A thesis submitted to the
Board of the Faculty of Physical Sciences
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
at the University of Oxford

TRINITY COLLEGE
UNIVERSITY OF OXFORD

CHEMISTRY RESEARCH LABORATORY
HILARY TERM, 2013

ABSTRACT

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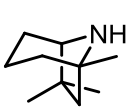
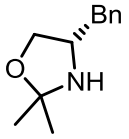
ANDREW CHARLTON **DPHIL**
TRINITY COLLEGE **HILARY TERM, 2013**

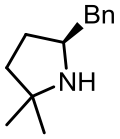
Enantiopure α-alkyl-substituted aldehydes are widely recognised as important building blocks in synthesis. Despite this, methods to prepare such substrates are limited. Strategically, asymmetric intermolecular S_N2 α-alkylation represents a highly straightforward transformation, but still remains an elusive feat. This thesis describes efforts to address this challenge, with attempted access to enantioenriched α-alkyl aldehydes by way of *C*-alkylation of chiral, non-racemic, hindered aldenamines using simple alkyl halides. Enamines derived from four types of auxiliary (a tropane, an oxazolidine, a pyrrolidine and a homotropane) have been prepared, and their alkylation profile examined.



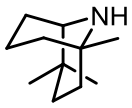
Tropane



Oxazolidine

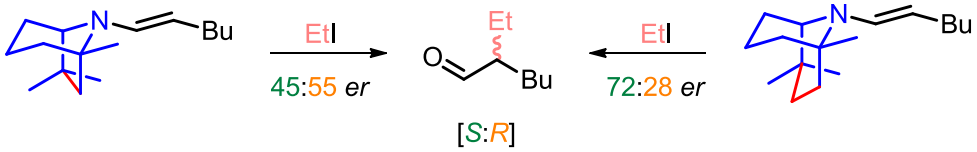


Pyrrolidine



Homotropane

While the desired levels of asymmetric induction were not attained, use of the tropane and homotropane auxiliaries, which differ only by a single methylene group, interestingly, gave complimentary diastereocontrol during alkylation with EtI. The observed stereoselectivity is supported by density functional studies performed for ethylation of both enamines.



Additionally, in the course of preparing the homotropane a highly efficient asymmetric synthesis of a homotropinone bearing *gem*-α-substitution has been developed.

ACKNOWLEDGEMENTS

Firstly, I would like to thank Dave Hodgson for giving me the opportunity to work in his group, and on such an interesting project. I am grateful for his continued support, guidance and most of all patience (particularly in those moments when I approached with the impending news of yet another low *er*).

I would also like to thank Rob Paton for providing computational support that has provided much needed insight into the origins of asymmetric induction with our alkylations, and will, I'm sure, assist in the design of even better chiral auxiliaries in the future.

Thanks must also go to all Hodgson group members, both past (Ruth, Tom, Becky, Charmaine, Tanzeel, Sophie, Matt, Stan, Serdar, Eric, Saifullah and Rosanne) and present (Claire, Chris and Elena), for their helpful suggestions and for providing a good lab atmosphere, though arguably with some questionable tastes in music! Additionally, I wish to thank Chris Bray and Naeem Kaka, for providing much needed advice in the handling of hindered aldenamines, amongst other things!

In terms of analysis, I would like to thank the NMR staff, particularly Tim Claridge and Barbara Odell, for their guidance and training. Thanks, also, to Amber Thompson for providing crucial X-ray data, and to Gus (JWB group), SJ and Rob (MCW group) for their assistance with HPLC. Additionally, I wish to thank all the other support staff in the CRL for their much appreciated services.

Also, thanks to my industrial supervisor, Andrew Whitehead, for useful discussion, and to GlaxoSmithKline and the EPSRC for generous funding.

Lastly, I would like to thank my friends and family for their unconditional love and support throughout, and to Mary Hartley, my wife to be, who has been there for me entirely, through all the lows, as well as the highs.

STATEMENT OF AUTHORSHIP

The work described in this thesis is entirely my own, with the following exceptions:

- computational analyses and data (performed and provided by Dr Robert S. Paton)
- X-ray analyses and data (performed and provided by Dr Amber L. Thompson).
- where reference is given to a published source or thesis
- Additionally, work from a collaborative paper has been:

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Signature: Date:

ABBREVIATIONS

$( )_n$	number of repeat units
(±)	racemic
α	alpha
Å	angstrom(s)
β	beta
°C	degrees Celsius
γ	gamma
δ	chemical shift
Δ	reflux
Δ*δ*	difference in chemical shift
λ	wavelength
µ	micro
µL	microlitre
µmol	micromole(s)
υ	frequency
$A^{1,3}$	1,3-allylic
Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
aq	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
ca.	*circa* (approximately)
cat.	catalytic
CDA	chiral derivatizing agent
CDMT	2-chloro-4,6-dimethyoxy-1,3,5-triazine
CIDR	crystallisation-induced dynamic resolution
cf.	*confer* (compared with)
conc	concentrated
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CTAP	cetyltrimethylammonium permanganate
d	day(s)
d_n-	deuterated (*n* = number of D atoms)
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DEG	diethylene glycol
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory

DIAD	diisopropyl azodicarboxylate
DIBAL–H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethyoxyethane
DMF	*N*,*N*-dimethylformamide
DMPO	5,5-dimethyl-1-pyrroline-*N*-oxide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC	*N*-(3-dimethylamino propyl)-*N′*-ethyl carbodiimide hydrochloride
eq	equivalent(s)
er	enantiomeric ratio
ET	electron transfer
et al.	*et alii* (and others)
Et	ethyl
FG	functional group
FID	flame ionization detector
GC	gas chromatography
gem	geminal
GS	ground state
h	hour(s)
HATU	1-[bis(dimethylamino) methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate
HMQC	heteronuclear multiple-quantum coherence
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i	iso
IBA	isobutyraldehyde
IBX	2-iodoxybenzoic acid
Im	imidazole
in situ	in the reaction mixture
IR	infra-red
J	coupling constant
^{4}J	long range coupling constant (over 4 bonds)
K	Kelvin
kJ mol^{-1}	kilo-Joule(s) per mole
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide

LiHMDS	lithium hexamethyldisilazide
lit.	literature
LTMP	lithium tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
M	molar
MBH	Morita-Baylis-Hillman
Me	methyl
(m)g	(milli)gram
MHz	mega-Hertz
min	minute(s)
mL	millilitre
mm	millimetres (of Hg)
(m)mol	(milli)mole(s)
MOFs	metal-organic frameworks
mp	melting point
MS	molecular sieves
MVK	methyl vinyl ketone
m/*z*	mass-to-charge ratio
n	normal (primary)
NaTCA	sodium trichloroacetate
nm	nanometre(s)
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p	*para*
PCC	pyridinium chlorochromate
pH	potential of hydrogen
Ph	phenyl
Phe	phenylalanine
*p*Ka	acid dissociation constant
PMHS	poly(methylhydrosiloxane)
ppm	parts per million
Pr	propyl
Pyr	pyridine
PPTS	pyridinium *p*-toluenesulfonate
quant	quantitative
rbf	round-bottom flask
R_f	retention factor
Ra	Raney
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
rt	room temperature
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat.	saturated
sec	secondary
SET	single electron transfer
SM	starting material
S_N1	unimolecular nucleophilic substitution

S_N2	bimolecular nucleophilic substitution
SOMO	singly occupied molecular orbital
t / *tert*	tertiary
T	temperature
TBAF	tetrabutylamonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEBA	triethylbenzylammonium chloride
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMDS	1,1,3,3-tetramethyldisiloxane
TMS	trimethylsilyl
TOF	time of flight
TS	transition state
TSA	toluenesulfonic acid
TMP	tetramethylpiperidine
TriMP	trimethylpiperidine
TRIP	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′ binaphthyl-2,2′-diylhydrogenphosphate
Val	valine
vide infra	see below
vide supra	see above

STEREOCHEMISTRY

Throughout this thesis the following schematic nomenclature is used to distinguish between relative and absolute configurations:[*]

relative **absolute**

For stereogenic centres that are non-racemic, and where the *R* : *S* ratio is undefined, the following schematic nomenclature is used:

non-racemic (undefined)

[*] Maehr, H. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 894–902.

CONTENTS

1. INTRODUCTION

Chiral α-alkyl-substituted aldehydes are valuable building blocks that have found widespread use in synthesis. The broad range of transformations available with such aldehydes [addition reactions – with a catalogue of nucleophiles (notably C–C formation) – generating alcohols, imines, amines (by reductive amination), olefins, etc.] provides attractive possibilities for introducing asymmetry into more complex molecular architecture. These compounds also find direct application in the cosmetic industry for their fragrance properties.[1] However, despite long-standing interest by the synthetic community,[2] present strategies to generate chiral α-alkyl-substituted aldehydes '*directly*' are limited.[3] This thesis describes efforts to improve on the current methods used to access enantioenriched α-alkyl aldehydes by way of intermolecular nucleophilic substitution between chiral non-racemic hindered aldenamines and simple alkyl halides. Specifically, this thesis discusses the synthesis of four types of chiral auxiliary (a tropane, an oxazolidine, a pyrrolidine and a homotropane). Subsequent synthesis and alkylation of enamines derived from these auxiliaries was examined. In the case of the bicyclic auxiliaries (tropane and homotropane), a collaborative computational study has shown remarkable consistency with laboratory experimental findings.

The following introduction serves to familiarise the reader with the synthesis and alkylation chemistry of aldenamines. Additionally, a review of the most significant advances for achieving asymmetric α-alkylation of aldehydes highlights the limitations of these methods and the need to develop more robust methodology.

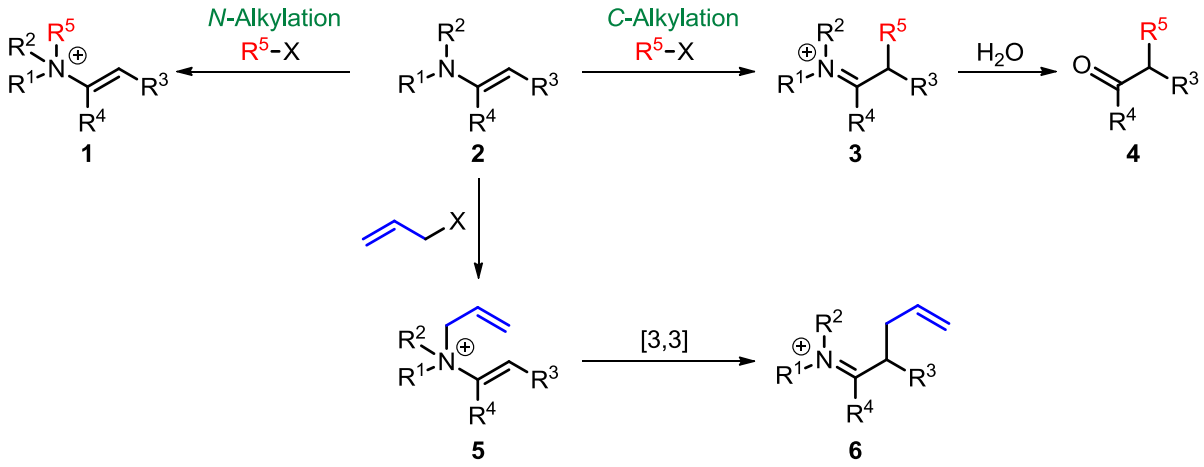
1.1 Aldenamine Synthesis and Alkylation: A Classical Approach

The first convenient method of enamine preparation, pioneered by Mannich and Davidsen, condenses aldehydes and ketones with secondary amines by a process of destructive distillation.[4] While this method is still in widespread use, aldehyde enamine (aldenamine) synthesis can often be problematic, because such enamines are readily hydrolysed, oxidised and polymerised.[5] Alternative methods have been developed attempting to address this problem. Notable examples employ $TiCl_4$[6] and, more recently, molecular sieves[5] to achieve dehydration in high yields.

While a knowledge of enamines dates back as early as 1884,[7] their synthetic use was not exploited until the groundbreaking work of Stork *et al.*,[8] which highlighted their true synthetic utility, as non-charged enolate equivalents. Enamines are capable of α-alkylation and α-acylation of carbonyl compounds without suffering from the common problems associated with enolate alkylations [i.e. polyalkylation and competing side-reactions (e.g. aldol addition / condensation, Cannizzaro, Tishchenko)[2,9]] and do not require the harsh bases typically employed for generation of enolates. Since Stork's discovery, this functional group has found extensive application in synthesis.[10] Enamines derived from ketones (ketenamines) readily undergo *C*-alkylation with a range of electrophiles (**2**→**3** {R^4 = alkyl / aryl}, Scheme 1.1). By contrast, the alkylation of aldenamines is somewhat more limited. While activated electrophiles (e.g. benzylic / allylic halides) are suitable reaction partners for aldenamines (since *N*-alkylation is reversible with activated electrophiles such as benzylic halides, and in the case of allylic halides *C*-alkylation can be achieved by 3,3-sigmatropic rearrangement (**2**→**6**, Scheme 1.1)[11]), the less hindered nature of aldenamines compared with their

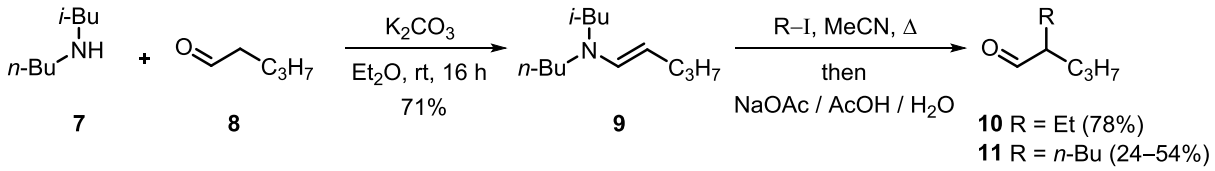
ketenamine counterpart invariably results in irreversible *N*-alkylation (**2**→**1** {R^4 = H}, Scheme 1.1) with weaker electrophiles (i.e. with simple alkyl halides).

SCHEME 1.1



Curphey *et al*. were the first to demonstrate that sterically hindered (about N) aldenamines can circumvent the problem of *N*-alkylation.[12] For example, ethylation of enamine **9** (prepared by K_2CO_3-mediated condensation from amine **7** and valeraldehyde (**8**) in uncommonly high yield for aldenamine synthesis; Scheme 1.2) gave the desired α-ethylated aldehyde **10** in good yield (Scheme 1.2). By contrast, a comparatively weaker electrophile, BuI, provided the desired aldehyde **11** in considerably lower yield (24%, Scheme 1.2). It is noteworthy that the Hodgson group have independently shown the efficiency for this latter alkylation to be higher, though aldehyde **11** was still generated in only a modest yield (54%).[13] Further work by the Hodgson group has expanded upon this chemistry to demonstrate that severely hindered aldenamines provide an excellent solution to the non-trivial task of mono-alkylation at the α-position of aldehydes (see below, p. 13).

SCHEME 1.2



7 **8** **9**

10 R = Et (78%)
11 R = *n*-Bu (24–54%)

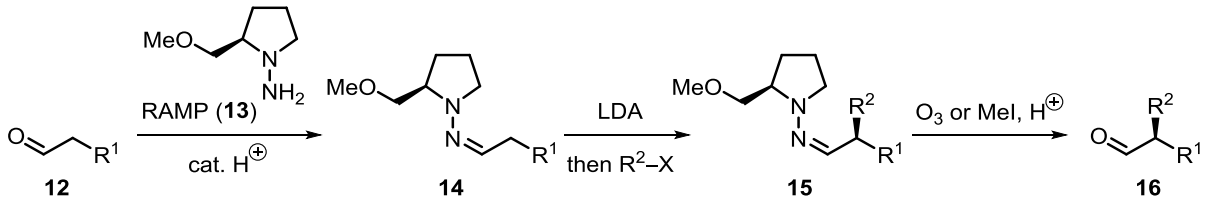
A final point worthy of discussion with regard to the alkylation chemistry of enamines is the reaction solvent. Alkylations of enamines have been performed in all classes of solvent: non-polar (C_6H_6, dioxane and CH_2Cl_2),[8,12] polar protic (MeOH, EtOH and DMF)[8,14] and polar aprotic (MeCN).[8,12] Solvent mixtures have also been employed. For example, Yamada *et al*. alkylated aldenamines in a variety of alcohols (MeOH, EtOH and *t*-BuOH) mixed with varying ratios of polar aprotic (THF, DMSO) / non-polar (C_6H_6, $CHCl_3$ and CCl_4) solvents.[14] Of interest to the current project are alkylations between aldenamines and simple alkyl halides. For such alkylations in the literature MeCN seems to be the preferred solvent.[12,15] As suggested by Kaka,[16] this is likely chosen for its ability to stabilise the transition state, which will have significant charge separation. The use of polar protic solvents, while theoretically suitable, is disfavoured due to potential protonation of the enamine (presumably alkylations with more reactive electrophiles do not suffer this problem due to rate). Therefore a polar aprotic solvent is the obvious choice; MeCN was presumably chosen on the basis of its boiling point, which, while high enough to allow heating that assists slower alkylations, is still sufficiently low to be removed easily post-reaction by evaporation.

1.2 Existing Methodology to Access Enantioenriched α-Alkyl Aldehydes

Owing to the often challenging formation and problematic *N*-alkylation, the application of aldenamines to achieve asymmetric α-alkylation of aldehydes has received little attention. Arguably, the most common method in use at present to access enantioenriched α-alkyl

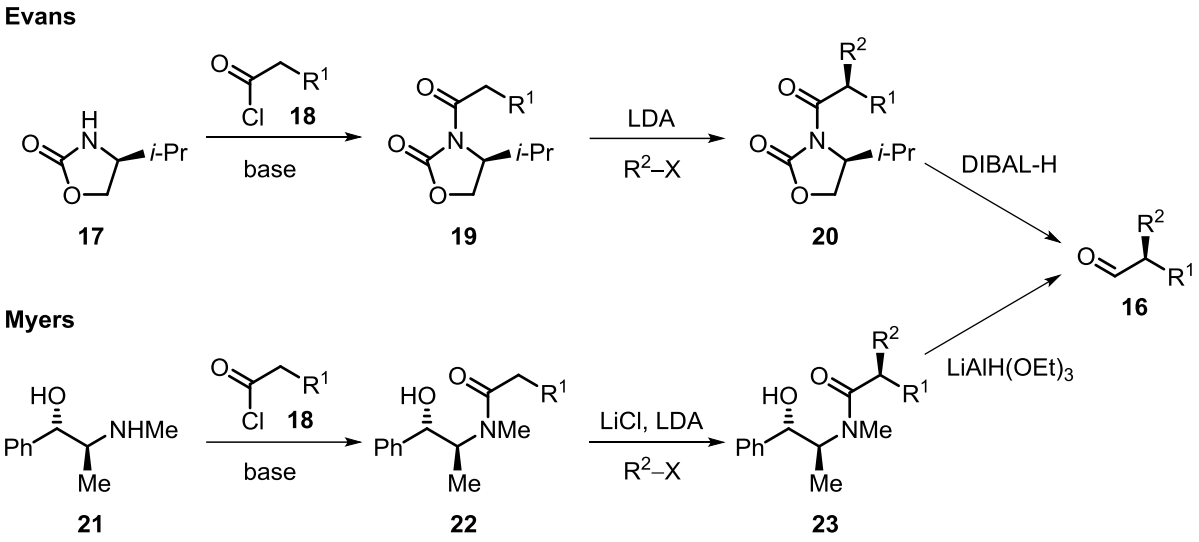
aldehydes is Enders' SAMP / RAMP hydrazone chemistry (Scheme 1.3).[17] However, while this chemistry is capable of attaining very high levels of asymmetric induction, it is not without limitation. A significant drawback of the chemistry is the requirement for very low reaction temperatures (typically between –80 ºC and –120 ºC). Furthermore, an additional step (e.g. ozonolysis / hydrolytic cleavage mediated by MeI and acid; Scheme 1.3) is required to retrieve the aldehyde **16** from hydrazone **15**. The by-product of this cleavage (e.g. a toxic nitrosamine when ozone is used) also requires further manipulation to regenerate the auxiliary **13**, which is often only recovered in poor yield. This chemistry and subsequent modifications have been recently reviewed.[18]

SCHEME 1.3



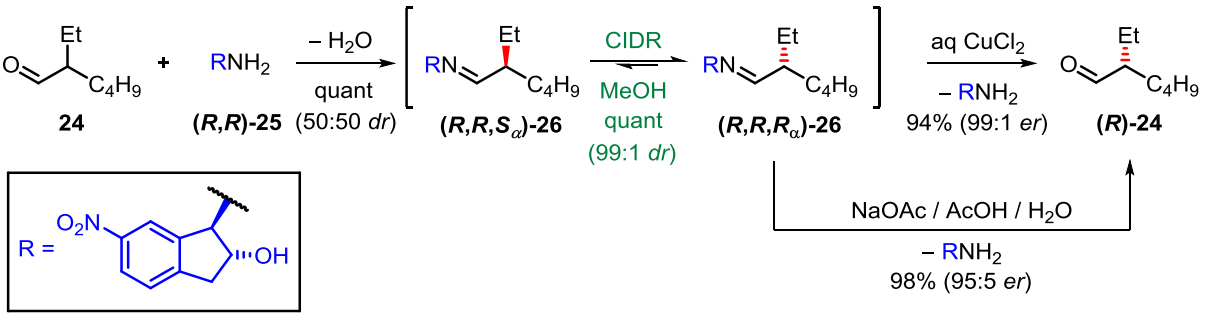
Alternative approaches involving alkylations at a higher (amide) oxidation level have been developed in the laboratories of Evans[19] and Myers[20] (Scheme 1.4). These approaches consistently produce high levels of chirality transfer, and both oxazolidinone (Evans) and pseudoephedrine (Myers) are readily accessible. The indirect nature of these approaches is an obvious drawback, requiring an additional reduction step to access the desired aldehyde.

SCHEME 1.4



Further studies by Evans *et al.* have led to a process to prepare enantioenriched unfunctionalised α-alkyl aldehydes using crystallisation-induced dynamic resolution (CIDR) of diastereomeric imines.[3] For instance, (±)-2-ethylhexanal (**(±)-24**) was condensed with enantiopure amine **(*R*,*R*)-25**, which gave a 50:50 mixture of diastereomeric imines **(*R*,*R*,*S*$_\alpha$)-26** and **(*R*,*R*,*R*$_\alpha$)-26** that was subsequently enriched by CIDR in MeOH to provide essentially enantiopure imine **(*R*,*R*,*R*$_\alpha$)-26** (Scheme 1.5). Following mild hydrolysis this gave (*R*)-2-ethylhexanal **(*R*-24)** in excellent *er* (99:1 or 95:5, depending on the method used). While this represents a highly efficient strategy to chiral non-racemic α-alkyl aldehydes, it should be recognised that this chemistry is very much substrate dependent.

SCHEME 1.5



1.3 Organocatalysis

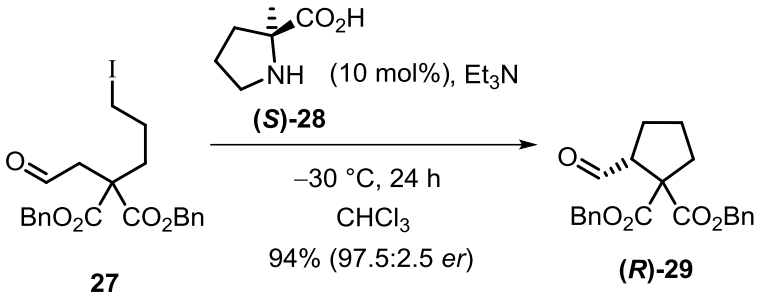
Toward the latter part of last century, a previously neglected field in organic chemistry resurfaced. Organocatalysis, which uses small molecules to catalyse organic transformations, has since emerged as one of the main branches of enantioselective synthesis.[21] The seminal work of Macmillan (iminium catalysis)[22] and List (enamine catalysis)[23] for α- and *β*-functionalisation of aldehydes led to an explosion of interest in this area of research.[24] However, while this surge of work has led to several significant breakthroughs, organocatalytic intermolecular asymmetric α-alkylation of aldehydes with simple alkyl halides still remains elusive, and has been fittingly termed a 'Holy Grail' of organocatalysis.[25] Organocatalytic alkylations with alternative electrophiles have been extensively reviewed in recent years.[25–26] With this in mind, the following discussion aims only to provide the reader with notable highlights relevant to the present work, and to underscore the limits of these methodologies.

1.3.1 *S_N2 Alkylation*

Asymmetric aldenamine catalysis has found utility for a wide range of transformations.[27] In 2004, List and Vignola reported a method for organocatalytic intramolecular α-alkylation of aldehyde **27** facilitated by catalytic (*S*)-α-methyl proline (**(*S*)-28**, Scheme 1.6).[28] While this is a noteworthy achievement, and consistently worked intramolecularly with a variety of substrates and proline derivatives, attempts to mimic this reactivity intermolecularly failed. Attempted alkylation of propionaldehyde with BnBr in the presence of Et_3N, as anticipated, resulted in *N*-benzylation of the catalyst. Presumably the intramolecular reaction does not suffer *N*-alkylation because of geometric limitations (a seven-membered ring TS with a *trans* double bond is highly unstable at rt).[29] Several subsequent examples of intramolecular

alkylations have been reported, generally using proline-derived catalysts, but so far asymmetric intermolecular alkylation with a simple alkyl halide has not been achieved.[25,26d]

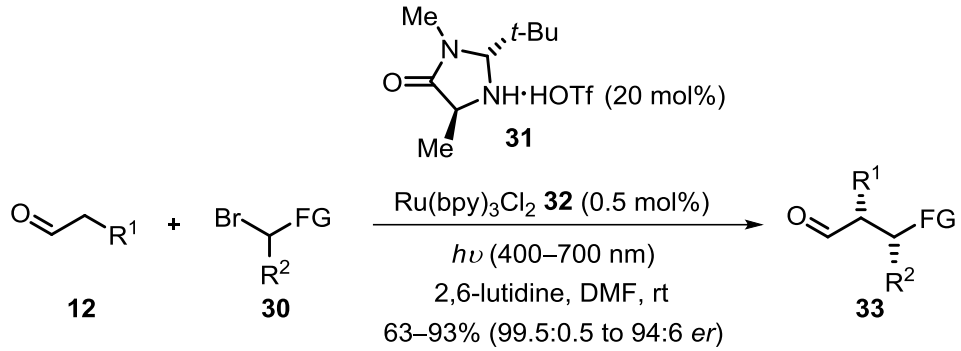
SCHEME 1.6



1.3.2 *Cooperative Catalysis*

In 2007, MacMillan and Nicewitz reported a novel mode of activation for organocatalytic reactions of aldehydes.[30] Typically, such reactions are catalysed by either LUMO lowering iminium catalysis, or HOMO raising enamine catalysis. By comparison, McMillan's chemistry involves a mechanism at the boundary of these two reaction modes utilising SOMO catalysis. Expanding on this concept, in 2008 the MacMillan lab facilitated a series of α-alkylations by way of single electron transfer (SET) using a dual catalytic system of imidazolidinone salt **31** and photoredox catalyst **32**, which is widely recognised as a landmark achievement in the field of organocatalysis (Scheme 1.7).[31] While this chemistry offers an elegant and efficient strategy for α-alkylation (high yields and *er*s, synthetic simplicity, and compatibility with a wide range of substrates), it is important to recognise that the method's applicability is confined to electrophilic partners that contain a functional group capable of stabilising the transient radical species.

SCHEME 1.7

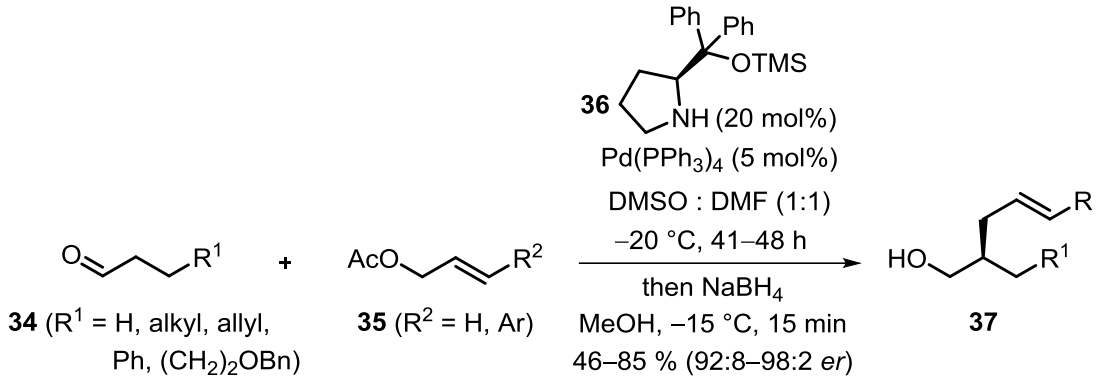


R^1 = any organic substituent
R^2 = H, Me, carbonyl
FG = radical stabilising functional group

Of several modifications to MacMillan's original procedure that have been reported, the development by Cheng He *et al*. of chiral metal-organic frameworks (MOFs) that house the organocatalyst (L- or D-pyrrolidine-2-ylimidazole) and photoactive unit (nitrilotribenzoate) is of particular merit.[32] These heterogeneous reaction systems simplify recovery and re-use of the catalysts (since they are embedded within a Zn-based solid support), and help to reduce heavy metal contamination of the product. Additional benefits of MOFs are the reduced hazards and costs, not only in the reactions themselves but also for disposal. A 'greener' method has also been reported recently by Ferroud *et al*., where the ruthenium based catalyst was replaced with Rose Bengal, an organic dye sensitizer.[33] However, both research groups examined only a malonate as the electrophilic partner.

Córdova and Ibrahem have used a combination of palladium and enamine catalysis to achieve intermolecular α-allylation of aldehydes.[34] Using a chiral, non-racemic, proline catalyst **36**, they were able to allylate aldehydes with high levels of asymmetric induction (up to 98:2 *er*) in moderate to high yields (Scheme 1.8).[34b]

SCHEME 1.8



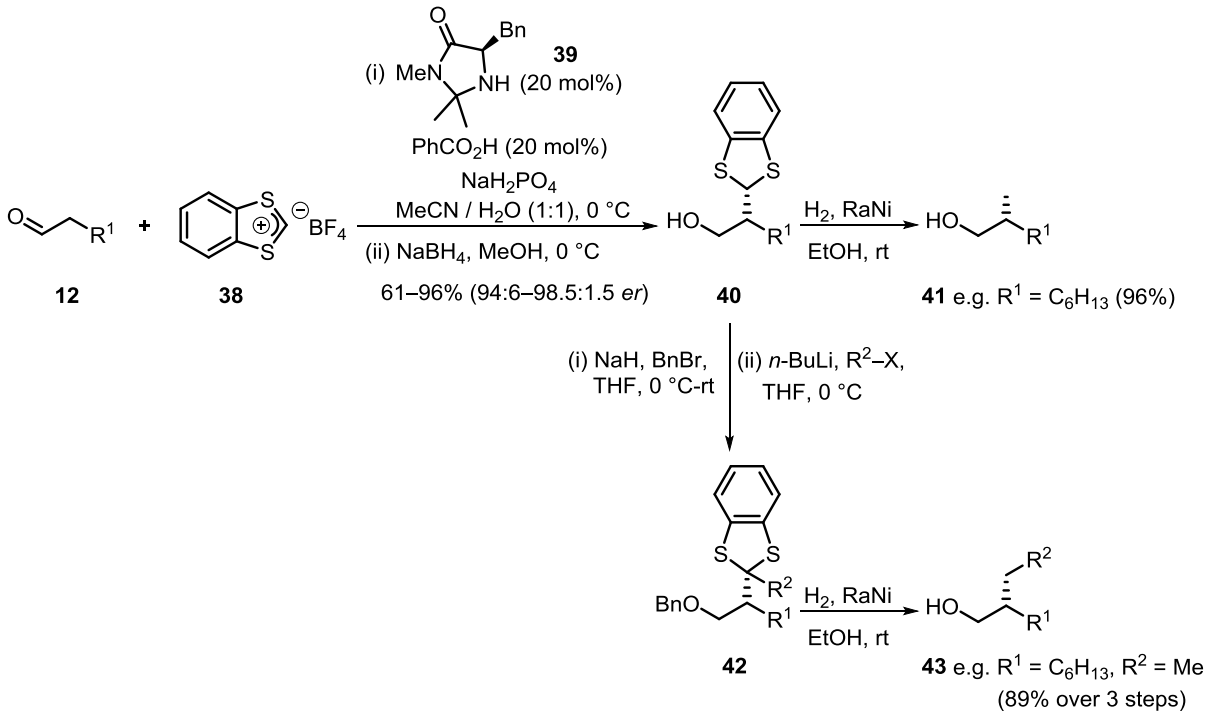
Mukherjee and List have since published an alternative route to such allylic compounds employing a chiral phosphoric acid catalyst ((*R*)-TRIP) with palladium, which together mediate high enantioselectivity through a Tsuji-Trost-type mechanism.[35] However, while promising *er*s have been achieved by both Córdova and List, since these reactions proceed *via* a palladium π-allyl complex, they are restricted to allylic electrophiles.

1.3.3 *S_N1 Alkylation*

In addition to the ET-mediated and enamine-catalysed S_N2 α-alkylation reactions described above, S_N1 processes have also received considerable interest. Initial findings in the laboratories of Petrin and Melchiorre, namely alkylation of an L-proline enamine by a carbocation formed *in situ* from a bisaryl sulfonate, have led to an increase of work in this area.[36] Of particular relevance to the present work is an extension of this chemistry by Cozzi *et al.*, who succeeded in formal asymmetric α-methylation of aldehydes using a similar strategy (Scheme 1.9).[37] In this work, enamines derived from imidazolinone **39** undergo highly stereoselective addition to the carbenium ion of benzodithiolylium tetrafluoroborate **38** in good yield. Subsequent reduction with Raney Ni of the 1,3-benzodithiol group provides a means to access the enantioenriched α-methylated aldehyde. Furthermore the benzodithiol

group of the product from alkylation-reduction, **40**, can be easily metalated and then alkylated (with alkyl halides) to provide longer chain alkyl groups in the α-position, without degrading the enantiopurity of the aldehyde. While this is a noteworthy advance towards the 'Holy Grail', it is still an indirect approach (i.e. the α-alkylated aldehyde is not directly accessed from the alkylation step).

SCHEME 1.9

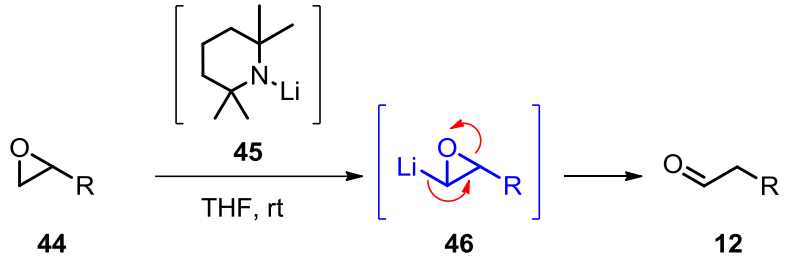


1.4 Previous Hodgson Research

1.4.1 *Hindered Aldenamine Synthesis and Alkylation*

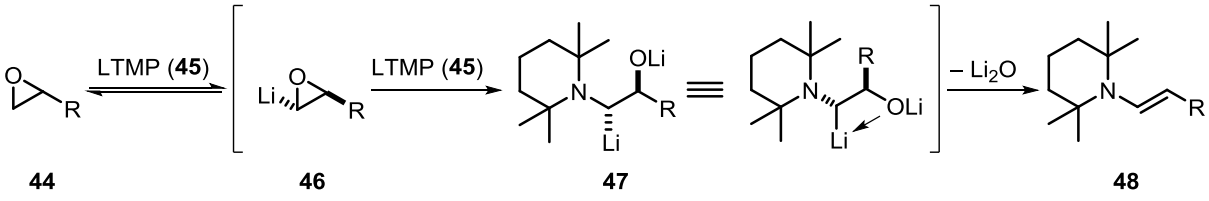
In 1994, Yamamoto *et al*. reported a method for rearranging terminal epoxides **44** to aldehydes **12** using lithium tetramethylpiperidide (LTMP, **45**; Scheme 1.10).[38] It was suggested that the reaction proceeded by way of α-lithiation, followed by isomerisation to an enolate, which upon work-up delivers the aldehyde. On testing an array of hindered lithium amides, it was observed that more hindered lithium amides provided greater yields of aldehyde.

SCHEME 1.10



This suggested mechanism was subsequently disproven by Hodgson *et al.*[39] During an investigation into the synthesis of trans-α,*β*-epoxysilanes from terminal epoxides, the work of Yamamoto was repeated. While aldehydes were isolated following chromatography, ^{1}H NMR analysis of the crude products revealed that the reaction between the epoxide and lithium amide had in fact generated an aldenamine. Further studies elucidated an unusual mechanism. Contrary to the logical epoxide ring opening-elimination pathway, an alternate mechanism was proposed involving insertion of the lithium amide into the α-lithiated epoxide (Scheme 1.11). This mechanism is in agreement with the requirement for at least 2 eq of lithium amide to achieve optimal yields, and the presence of a lithium by-product, which was consistently formed with varied substrates (identified by ^{7}Li NMR to be Li_2O).

SCHEME 1.11



Expanding the epoxide substrate scope to include a range of additional functionalities (e.g. acetal, arene, carbamate and olefin) firmly established this chemistry as a general route to hindered aldenamines.[39] Recognising the importance of this discovery in relation to the original work of Curphey *et al.*[12] (*vide supra*) prompted Hodgson to investigate alkylation (with simple alkyl halides) of enamines prepared using this methodology. Preliminary

examination with enamines derived from LTMP (**45**) gave low yields of the desired aldehydes [e.g. reaction of enamine **48** (R = C_3H_7) with MeI in MeCN, Δ, gave 2-methylpentanal in 30% yield]. Closer inspection of the ^{1}H NMR spectrum for enamine **48** (R = C_3H_7) identified that the difference in the chemical shifts of the vinylic protons ($\Delta\delta$ = 0.48 ppm) was indicative of an unconjugated alkene.[8a,40,41] Molecular modelling studies support orthogonal alignment of the N lone pair and π-bond (**48****, Figure 1.1), owing to inherent $A^{1,3}$ strain present when the orbitals are aligned (**48***, Figure 1.1).[13]

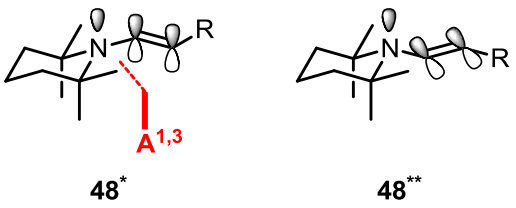
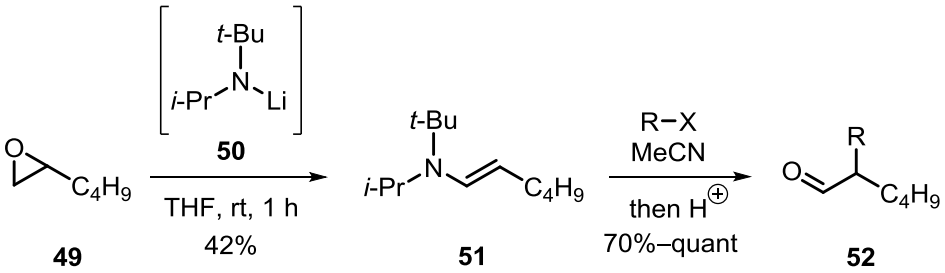


FIGURE 1.1

Alkylation of an alternative enamine **51** [prepared by reaction of lithium amide **50** with 1,2-epoxyhexane (**49**)] showed a substantial improvement in yield with a range of different electrophiles, importantly including simple alkyl halides (Scheme 1.12). Analysis by ^{1}H NMR showed a much greater difference in the olefinic resonance frequencies, showing a value ($\Delta\delta$ = 1.45 ppm) more typical of enamine double bond character.

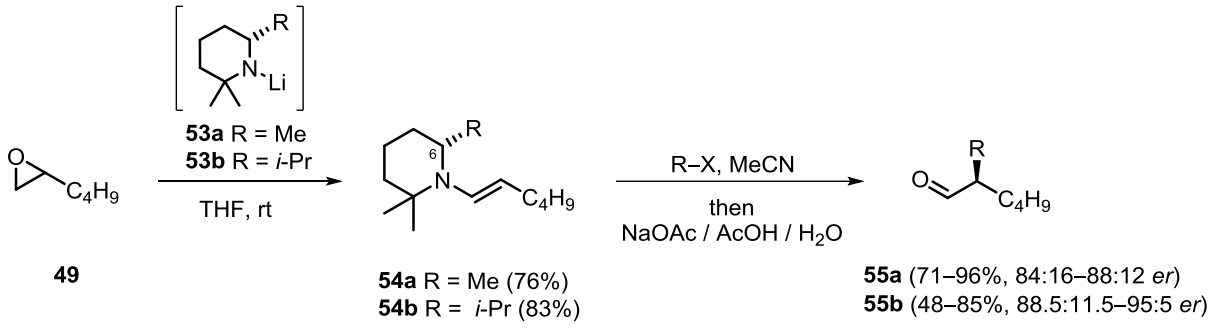
SCHEME 1.12



1.4.2 *Asymmetric α-Alkylation*

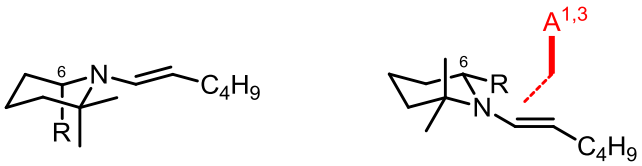
The above work prompted an investigation into the possibility of chiral, non-racemic, hindered enamines for asymmetric intermolecular S_N2 alkylation. In 2008, Hodgson and Kaka reported the first direct synthesis of enantioenriched mono-α-alkyl-substituted aldehydes **55a**–**b** by way of *C*-alkylation of chiral piperidine-derived enamines **54a**–**b** (Scheme 1.13).[42]

SCHEME 1.13



In this work, 2,2,6-trimethylpiperidine-derived enamine **54a** gave high yields and significant levels of enantioenrichment on alkylation.[42] Diastereocontrol of enamine alkylation was enhanced by moving to a sterically more demanding substituent on the piperidine (Me→*i*-Pr, **54b**→**55b**, Scheme 1.13), albeit at the expense of lower alkylation yields. These experimental observations were rationalized through a computational study,[43] which indicates that in enamine **54a** the C-6 Me substituent resides axial in the ground state conformation (**54 (ax)** {R = Me}, Figure 1.2) so as to minimize $A^{1,3}$ strain (**54 (eq)**, Figure 1.2). In contrast, the C-6 *i*-Pr substituent in enamine **54b** is equatorial in the ground state (**54 (eq)** {R = *i*-Pr}, Figure 1.2), with the reactive axial conformation (where *N* lone pair–π^* overlap becomes possible) only being attainable at elevated temperatures; in this case 1,3-diaxial interactions, exacerbated by the larger isopropyl substituent, outweigh allylic strain present in the conformer with the C-6 *i*-Pr group equatorial. When the C-6 substituent is equatorial, the

olefinic component of the enamine twists orthogonal to the nitrogen lone pair rendering the enamine inactive to *C*-alkylation.[8a,40–41] The reactive conformation (C-6 substituent axial) which is achieved in the transition state for enamine **54b** alkylation despite the ground state preference, is expected to be less accessible for enamines derived from piperidines with larger C-6 substituents.



54 (ax) **54 (eq)**

FIGURE 1.2

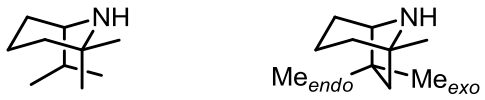
1.5 Research Aims

To summarize, present strategies to access enantioenriched α-alkyl aldehydes are limited; typically they employ very low temperatures (Enders) and are indirect, necessitating additional post-alkylation manipulation [e.g. ozonolysis (Enders) or reduction (Evans / Myers)]. While organocatalysis has been used to great effect for α-functionalisation of aldehydes, alkylation with simple alkyl halides still remains elusive. Previous work in the Hodgson group has attempted to tackle the problem by way of diastereoselective *C*-alkylation of chiral hindered aldenamines (prepared from terminal epoxides). While the trialkyl piperidine auxiliaries developed show high levels of *er* and good yields, computational and empirical evidence suggests that desired improvement to the *er* by expansion of the C-6 substituent will lead to decreased reactivity of the enamine at the C-*β* position. In view of this, the aim of the current project was to develop a new class of chiral amine auxiliaries, hopefully capable of attaining elevated *er* levels while also retaining a high degree of reactivity.

2. A TROPANE AUXILIARY FOR ASYMMETRIC α-ALKYLATION

2.1 Design Principle

As a starting point in the exploration for more reactive enamines, the design of a new auxiliary centered around modification to the scaffold of the precursor to lithium amide **54b**, piperidine **56** (Figure 2.1). Tropane **57**, which is conformationally locked, thus alleviating the problems associated with unfavourable conformers, could generate enamines with enhanced reactivity. At the outset, it was considered that the *gem*-dimethyl substitution in tropane **57** (Figure 2.1) would mimic the isopropyl steric encumberment of enamine **54b** (albeit without the ability to splay outward[43]), thereby providing effective facial discrimination. While a single *exo*-methyl substituent would also potentially suffice [i.e., tropane **57** (Me_{endo} = H), Figure 2.1], this was not considered further, due to the potential greater synthetic complexity associated with inclusion of an additional stereocentre.



56 **57**

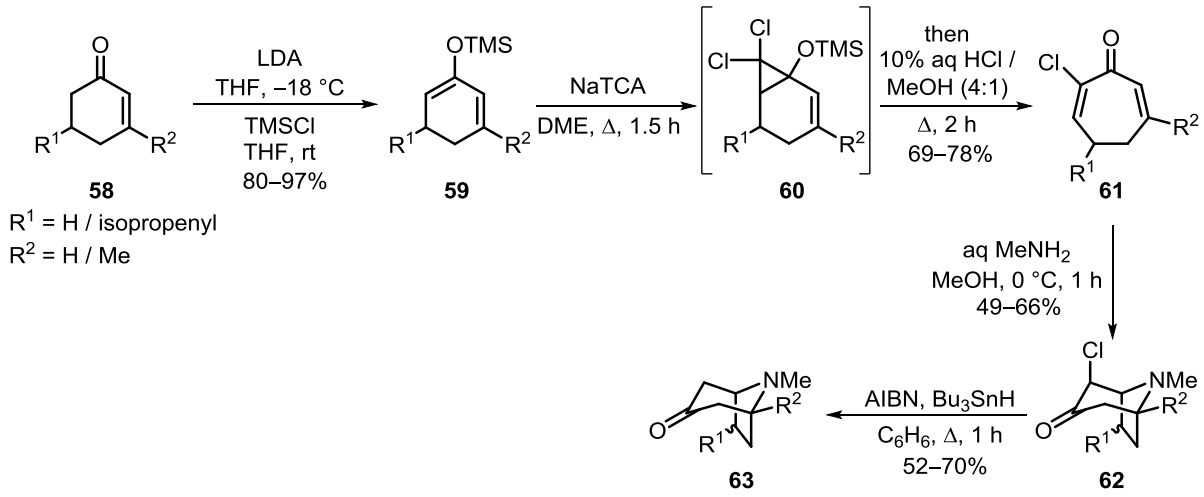
FIGURE 2.1

2.2 First Approach to Tropane 57 Using Macdonald's Methodology

Before meeting the more demanding challenge of preparing tropane **57** as a single enantiomer (necessary for asymmetric alkylation), we chose to prepare the racemate, which is more straightforward synthetically, to examine the alkylation profile of this auxiliary. While there are several methods reported for the synthesis of tropanes and their typical parent, tropinones,[44] there are limited examples[45] of tropanes / tropinones containing the desired

substitution pattern (bridgehead alkyl and *gem*-dialkyl α- to a CH bridgehead). At the outset, we were attracted to methodology developed by Macdonald and Dolan for the construction of tropinone scaffolds (Scheme 2.1).[46] This chemistry was appealing since it offered the potential to synthesise tropane (±)-**57** in a small number of steps from readily available and inexpensive materials. At the root of this strategy is a regioselective dichlorocyclopropanation of silyl enol ether **59**, which generates an α,α-dichlorocyclopropane intermediate **60** that upon hydrolysis readily undergoes thermal rearrangement to α-chlorodienone **61**. Subsequent bisconjugate addition to the ring-expanded product gives the α-chlorotropinone **62**. Dechlorination, facilitated with Bu_3SnH, gives the corresponding tropinone **63**.

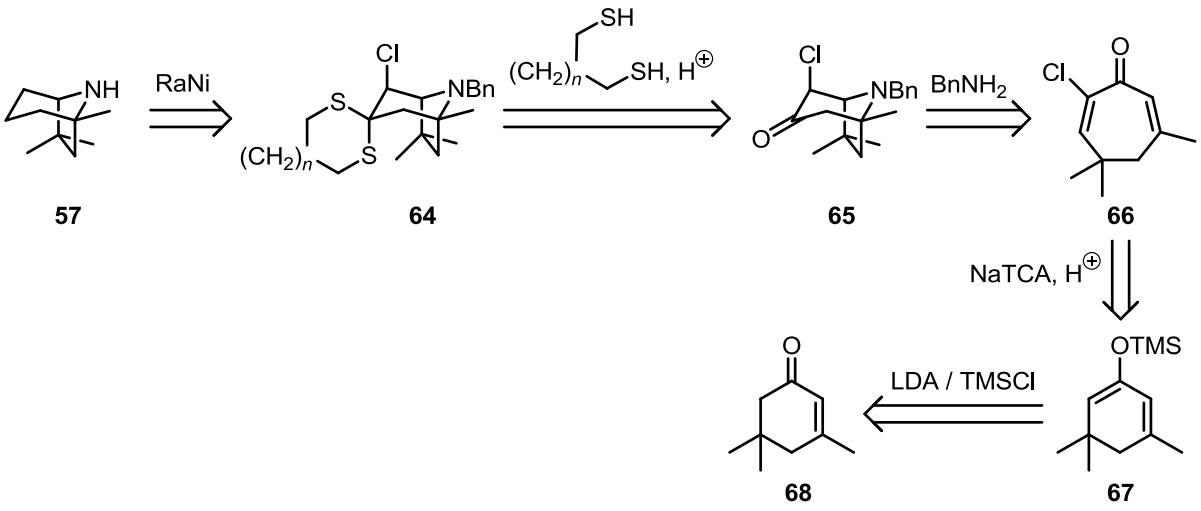
SCHEME 2.1



The retrosynthesis for tropane **57** based on Macdonald and Dolan's protocol is illustrated in Scheme 2.2 below. Rubottom *et al*. have reported syntheses of silyl enol ether **67** in both THF[47] and DME[48] in excellent yield. For our purposes, NH_3 would be the ideal nucleophile for bisconjugate addition to α-chlorodienone. However, given that additions on similar substrates using NH_3 have led to competing polymerisation reactions, we looked to alternative amines.[49] While demethylation of tertiary amines is feasible,[50] we believed that

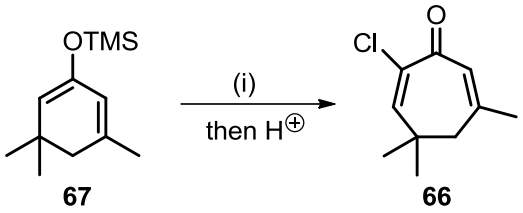
exchanging $MeNH_2$ (employed by Macdonald and Dolan) for $BnNH_2$ would provide more straightforward access to the free amine. For example, a possible strategy to remove the unwanted functionality present in α-chlorobenzyltropinone **65** would be to synthesise the corresponding thioketal **64** and perform global reduction of all functionality with Raney-Ni.

SCHEME 2.2



Silyl enol ether **67** was prepared in excellent yield (88%), using the method of Rubottom *et al*. (Scheme 2.3).[48] However, following Macdonald and Dolan's method, dihalocyclopropanation-hydrolysis reactions employing silyl enol ether **67** proved low yielding (Entry 1, Table 2.1). Despite substantial examination of alternative conditions, which included longer reaction times (Entries 2–3, Table 2.1), purification of NaTCA with NaH (Entry 4, Table 2.1),[46] attempted (but unsuccessful) reaction in chloroform (Entry 5, Table 2.1), incorporation of a phase-transfer catalyst (TEBA) in chloroform (Entries 6–8, Table 2.1), NaOH-mediated dichlorocarbene synthesis (Entry 8, Table 2.1),[51] and dibromocyclopropanation (Entry 9, Table 2.1),[52] little improvement in the reaction outcome was achieved.

TABLE 2.1



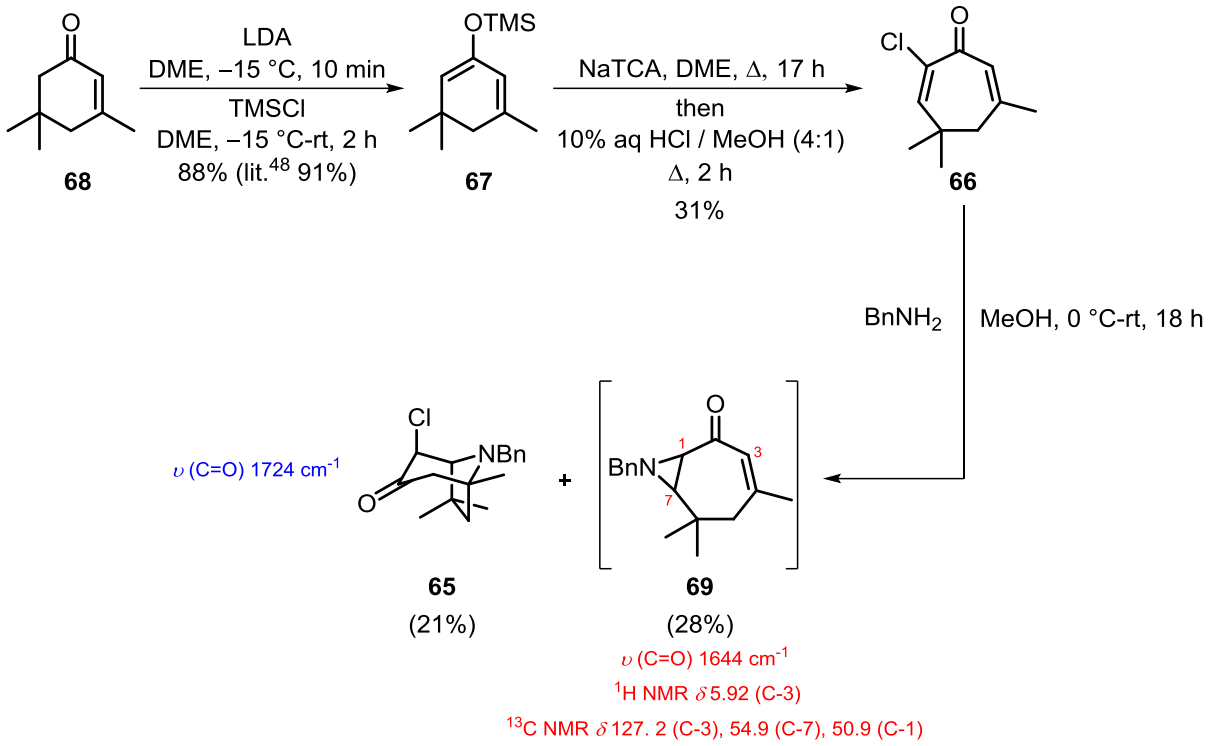
Entry	Reagent(s) for (i)	Solvent for (i)	Reaction Time for (i) (h)	Reaction Temperature for (i)	Yield (%)[b]
1	NaTCA	DME	1.5	reflux	27
2	NaTCA	DME	2	reflux	23
3	NaTCA	DME	17	reflux	31
4	NaTCA[a]	DME	2	reflux	43[c]
5	NaTCA	$CHCl_3$	17	reflux	[d]
6	NaTCA / TEBA	$CHCl_3$	17	reflux	[d]
7	NaTCA / TEBA	$CHCl_3$	48	reflux	[d]
8	NaOH / $CHCl_3$ / TEBA	$CHCl_3$	17	4 °C to rt	[d]
9	*t*-BuOK / $CHBr_3$	pentane	18	–10 °C to rt	[d]

[a] NaTCA purified according to Macdonald and Dolan [see Ref 46].
[b] Yield following hydrolysis.
[c] Crude yield.
[d] No product isolated / observed by crude NMR and TLC analysis.

As significant quantities of unreacted isophorone (**68**) were recovered, it is likely that the dihalocarbene either did not form or was quenched before reaction with silyl enol ether **67**. The more hindered nature of silyl enol ether **67** compared with the substrates employed by Macdonald and Dolan could also explain the low yield. Addition of $BnNH_2$ to α-chlorodienone **66** gave a complex mixture of products from which the desired 2*β*-chlorotropin-3-one **65** was isolated as a single epimer† in low yield (21%, Scheme 2.3); chromatographic purification also eluted aziridine **69** (diagnostic features are shown in Scheme 2.3) as a significant by-product (28%).[53] Given the low yields for the second and third steps, and the competing aziridination, it was decided to abandon this approach to make tropane **57**.

† The stereochemistry of the Cl-bearing carbon in 2*β*-chlorotropin-3-one **65** has been assigned by analogy with the work of Macdonald and Dolan [see Ref. 46 (and Ref. 9 within)].

SCHEME 2.3

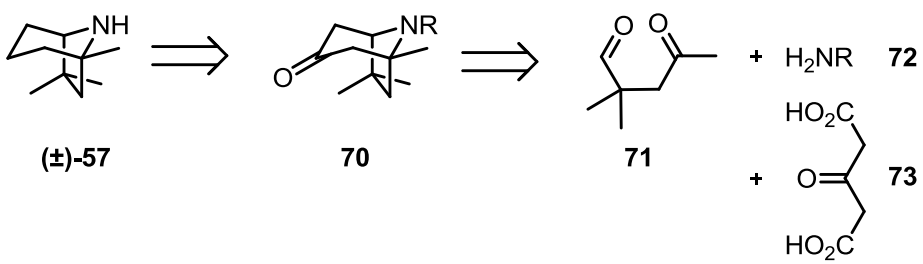


2.3 Second Approach to Tropane 57 – Utilising the Robinson-Schöpf Reaction

2.3.1 *Retrosynthetic Analysis*

Our second envisaged sequence to tropane **(±)-57** projected quick access using a Robinson-Schöpf strategy to first construct tropinone **70** from condensation of an appropriate amine **72** with acetone-1,3-dicarboxylic acid (**73**) and ketoaldehyde **71** (Scheme 2.4). Depending on the amine employed in the Robinson-Schöpf step, there are a number of options available for reduction of tropinone **70** to tropane **(±)-57**.

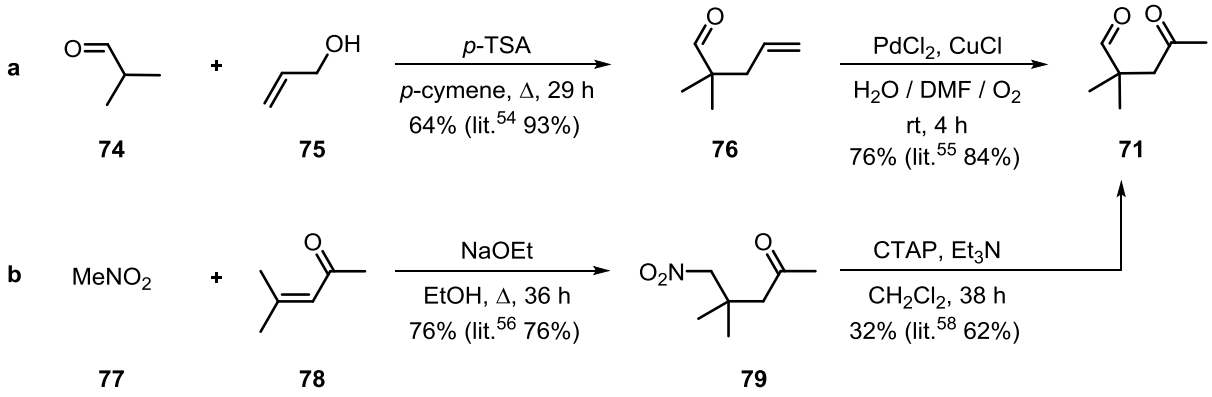
SCHEME 2.4



2.3.2 *Synthesis of Ketoaldehyde **71***

For the synthesis of ketoaldehyde **71**, we initially investigated oxidation of unsaturated aldehyde **76** (Scheme 2.5a). This olefin is commercially available but in the interest of cost was conveniently prepared by condensation and [3,3]-sigmatropic rearrangement between isobutyraldehyde (IBA, **74**) and allyl alcohol (**75**).[54] Subsequent Wacker oxidation using 20 mol% catalyst loading gave the desired ketoaldehyde **71** in a pleasing yield.[55] Due to the expense of $PdCl_2$ (~£10 $mmol^{-1}$, Sigma Aldrich), an alternative synthesis of ketoaldehyde **71** was also examined (Scheme 2.5b). Nitroketone **79** was prepared by NaOEt-mediated Michael addition between nitromethane (**77**) and mesityl oxide (**78**) in a yield consistent with that in the literature.[56] Attempted Nef reaction employing the mild oxidant, cetyltrimethylammonium permanganate (CTAP; synthesised by ion exchange with the corresponding bromide salt[57]), according to the method of Chandrasekaran *et al*.,[58] proved low yielding (32% {90% brsm}), despite a reported yield of 62%. It is noteworthy that Lui and Sammes observed a low yield (35% cf. 32%) when performing the same reaction using MeOH-KOH, followed by $KMnO_4$-$MgSO_4$ at pH 7.[56] Given the low yield of the Nef reaction, ketoaldehyde **71** was scaled-up using the previously established chemistry. Pleasingly, it was found that the $PdCl_2$ catalyst loading could be reduced to 0.4 mol% on scale (~ 1 mol), which significantly reduced the cost of this transformation.

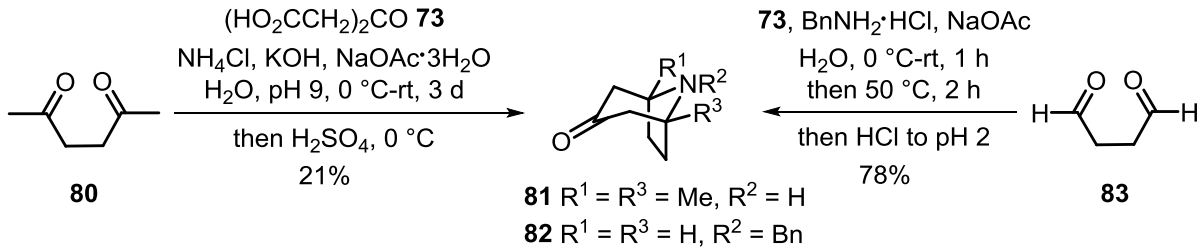
SCHEME 2.5



2.3.3 *Robinsion-Schöpf Reaction with Ketoaldehyde **71** and Endgame to Tropane **(±)-57***

Keana *et al*. have previously reacted 2,5-hexanedione (**80**), which is structurally similar to ketoaldehyde **71**, with acetone-1,3-dicarboxylic acid (**73**) and NH_3 under pH-controlled conditions to give tropinone **81** (isolated as the oxalate salt), albeit in low yield (Scheme 2.6).[59]

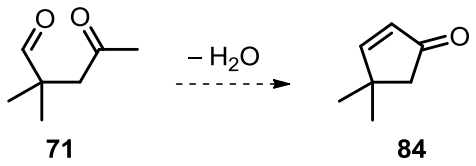
SCHEME 2.6



Despite the low yield, we were encouraged to try the conditions of Keana, since, ignoring the *gem*-dimethyl group, dione **80** is arguably more hindered than ketoaldehyde **71**, and if feasible this would directly access the secondary amine. However, efforts to achieve Robinson cyclisation using this classical aq method did not lead to any of the desired tropinone being isolated. Using similar aq conditions, Momose *et al*.[60] prepared tropinone **82** from dialdehyde **83** in good yield following a procedure, adapted from earlier work by Nádor *et al*.,[61] employing $BnNH_2$. Equally, this chemistry proved unrewarding with ketoaldehyde **71**. While enone **84** was not isolated, it is likely under the basic reaction conditions that

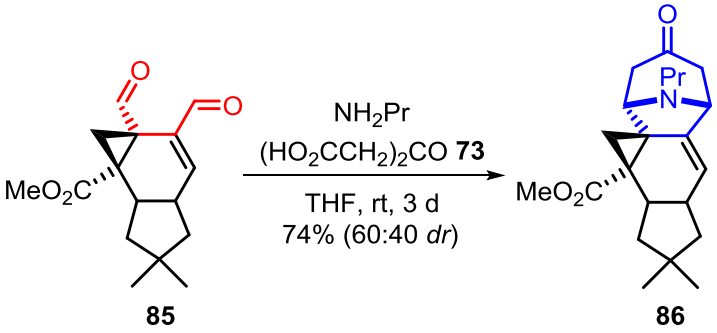
ketoaldehyde **71** suffered intramolecular-aldol condensation (Scheme 2.7; also, see Ch. 4, p. 83).[62]

SCHEME 2.7



Looking to alternative procedures, Sterner *et al*. have demonstrated that impressive yields can be obtained performing Robinson-Schöpf reactions of dialdehydes in THF (Scheme 2.8).[63]

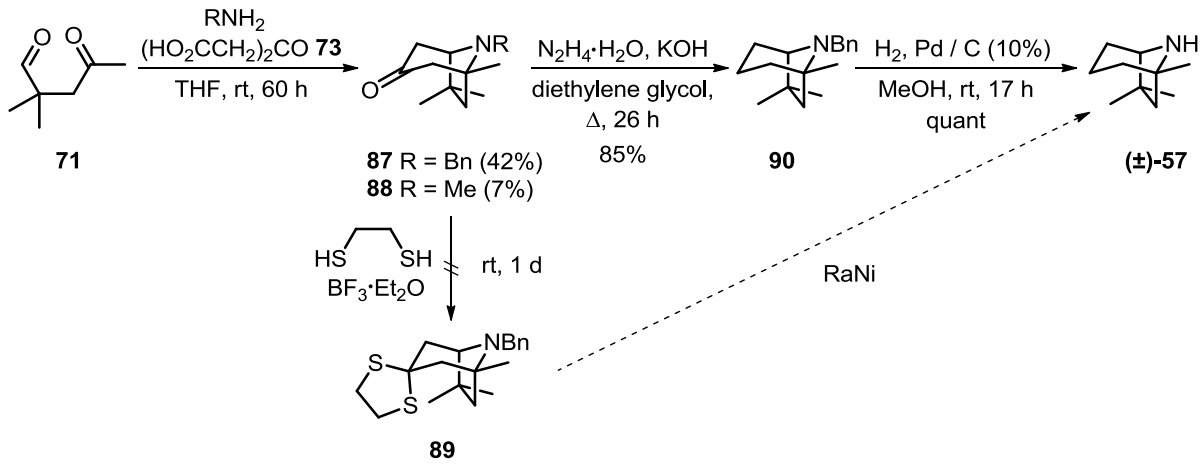
SCHEME 2.8



Following Sterner's protocol, but using $BnNH_2$ (chosen for its greater nucleophilicity compared with NH_3,[64] and projected reduction to access the free amine) gave *N*-benzyl tropinone **87** in satisfactory yield (42%) from ketoaldehyde **71** (Scheme 2.9). Exchanging $BnNH_2$ for $MeNH_2$ gave a significantly lower yield of the corresponding *N*-methyltropinone **88** (7%). Initially, a Mozingo process was considered for removal of the ketone and benzyl functionality of tropinone **87** (Scheme 2.9). However, a test reaction failed to isolate the requisite benzylthioketal **89**. Microwave-assisted Huang-Minlon reduction of *N*-benzyltropinone **87** according to the procedure of Giri *et al*.[65] was examined, but simply returned starting material. More classical Wolff-Kishner reaction conditions prescribed by

Murray *et al.*[66] also proved low yielding (8% {quant brsm}). Fortunately, reduction to *N*-benzyltropane **90** was eventually achieved following the method of O'Brien *et al.* (Scheme 2.9); this procedure involves distillation part-way through the reaction to help increase the internal temperature and thus facilitate more successful decomposition of the hydrazone intermediate.[67] Pleasingly, hydrogenolysis[68] proved an effective strategy for removal of the benzyl group present in **90**, providing the desired tropane **(±)-57** in excellent yield (Scheme 2.9). It is noteworthy that tropane **57** is particularly volatile and had to first be isolated from the methanolic solution as its hydrochloride salt.[69]

SCHEME 2.9



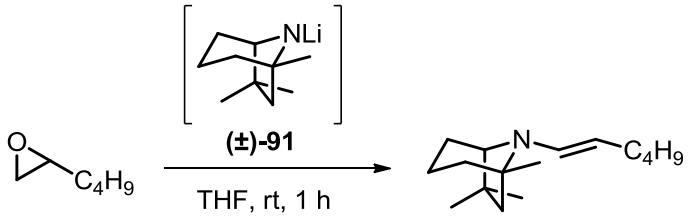
2.4 Attempted Enamine Synthesis from Tropane (±)-57 Using Hodgson Lithium Amide-Epoxide Methodology

Having developed an effective route to tropane **(±)-57**, we examined the feasibility of synthesising enamine **(±)-92**‡ using the earlier mentioned lithium amide-epoxide methodology (cf., **49**→**54**, Scheme 1.13; Ch. 1, p. 14).[39] Previous studies in our laboratory indicated that enamine formation from lithium 2,2,5,5-tetramethylpyrrolidide and 1,2-

‡ The exocyclic alkyl tether in enamine **(±)-92** was chosen for consistency with previous studies in the Hodgson group (see Scheme 1.13, and Refs 13, 16, 39, 42 and 43).

epoxyoctadecane was slow at rt and generated unsatisfactory yields at higher temperatures, which was likely due to instability of the intermediate lithiated epoxide in refluxing THF.[39b] Therefore, we were aware that formation of enamine **(±)-92**, with its embedded pyrrolidine, might show similar poor reactivity. In the event (Scheme 2.10), attempted formation of enamine **(±)-92** from *N*-lithio tropane **(±)-91** and epoxide **49** led to a complex mixture of products, and, due to hydrolytic sensitivity, the desired enamine could not be isolated. While a pure sample of enamine **(±)-92** could not be isolated, it was noteworthy that the ^{1}H NMR spectrum showed separation between the olefinic signals attributed to the enamine of 1.68 ppm, indicative of alignment of the *N*-lone pair and alkene π-orbital, and suggesting a strong *C*-alkylation profile.[8a,40–41]

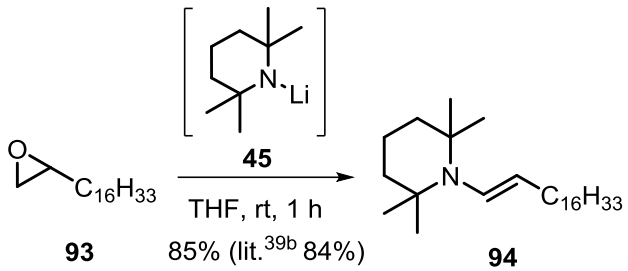
SCHEME 2.10



49 **(±)-92**

As a test of the experimental procedure in my hands, LTMP (**45**) was reacted with 1,2-epoxyoctadecane (**93**), which pleasingly gave the desired enamine **94** in consistent yield with that obtained by Bray[39b] (Scheme 2.11).

SCHEME 2.11

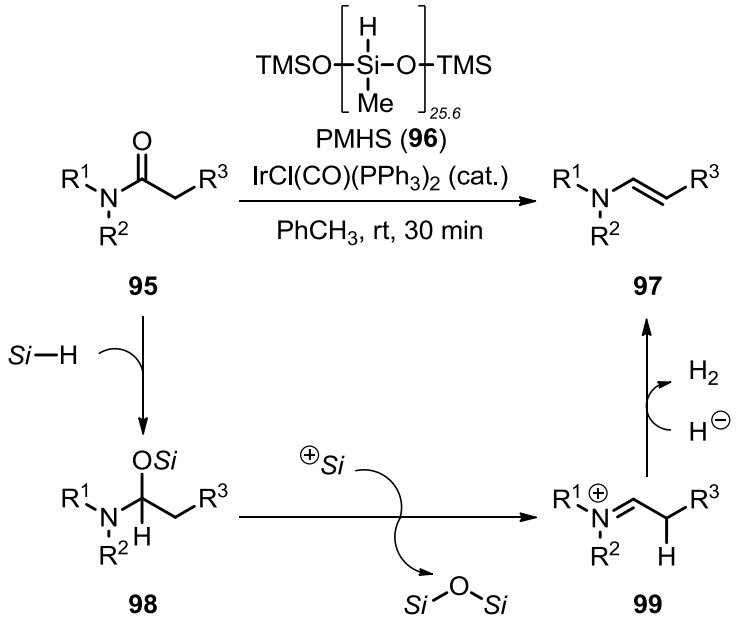


93 **94**

2.5 Examination of Nagashima's Reduction-Dehydration Methodology for Preparation of Hindered Aldenamines

Given the observed incompatibility of *N*-lithio tropane **(±)-91** using the Hodgson approach to hindered aldenamines, our attention turned to alternative methods to access enamine **92**. We were attracted to the work of Nagashima *et al*., who recently reported a novel route to aldenamines from amides using a combination of $IrCl(CO)(PPh_3)_2$ (Vaska's catalyst) and poly(methylhydrosiloxane) (**96**, PMHS, n = 25.6; Scheme 2.12).[70] The proposed mechanism for this transformation, depicted in Scheme 2.11 below, involves initial reduction of amide **95** followed by dehydration, *via* elimination of the siloxy group in hemiaminal ether **98**, followed by deprotonation of the α proton of iminium ion **99**, to give aldenamine **97**.

SCHEME 2.12



Nagashima's methodology had not been examined with sterically hindered amides, but offered potential benefits over the lithium amide-epoxide methodology. Limitations of the latter include: (i) a requirement for at least 2 eq of the lithium amide; (ii) restriction to low molecular weight substrates (since distillation is necessary for purification of the enamine);

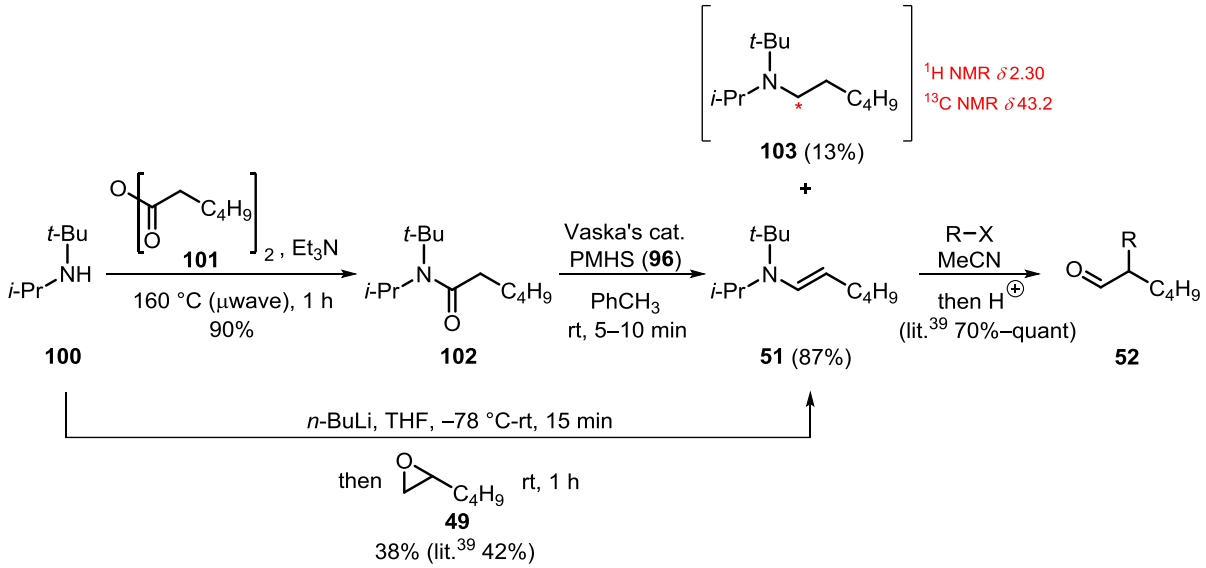
(iii) the strongly basic lithium amide intermediate, which narrows the functional group tolerance. The potential benefits of Nagashima's chemistry were the moderate conditions, the high catalyst turnover frequency [> 20 000 {mol (amide) / mol (Ir)·h}],[70] and most importantly the apparent simplicity of purification, which reportedly requires only filtration through Celite®, thus allowing the use of higher molecular weight substrates. Additionally, the mild conditions allow compatibility with a wider variety of functional groups. Considering this, while our principal interest in Nagashima's chemistry was concerned with its application to synthesise enamine **(±)-92**, we were encouraged to investigate the possiblity of applying this chemistry to the broader problem of preparing hindered aldenamines, which are useful for *C*-alkylation, something that Nagashima appeared to have overlooked. The following discussion details the results of this investigation.

2.5.1 *Application of Nagashima's Chemistry to the Synthesis of Enamine **51***

As a starting point, we chose to examine the synthesis of enamine **51** (Scheme 2.13), which can be formed in only modest yield [38% (lit.[39] 42%), Scheme 2.13; also see Ch. 1, p. 13] using lithium amide-epoxide methodology, but has been shown to monoalkylate with a variety of simple alkyl halides in excellent yield (as previously discussed {Ch. 1, p. 3}, a synthetically non-trivial transformation).[39] The requisite amide **102** was first prepared in high yield by acylation of amine **100** with hexanoic anhydride (**101**),[71] promoted by microwave irradiation using a method employed by Hulme *et al*. for synthesis of comparably hindered amides (Scheme 2.13).[72] Enamine synthesis proceeded rapidly in promising yield, but was hampered by the presence of an inseparable impurity. The impurity was assigned to the product from over-reduction, amine **103** (Scheme 2.13), by analogy with observations made for tropamide **147** (Scheme 2.21; p. 38) and based on diagnostic spectral features [^{1}H NMR δ

2.30 (t, J = 8 Hz, NCH_2) and ^{13}C NMR δ 43.2 (NCH_2)]. Amine by-products were also observed by Nagashima for aldenamine synthesis using 1,1,3,3-tetramethyldisiloxane (TMDS).[70]

SCHEME 2.13



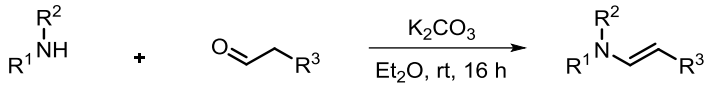
Nagashima's reported method dictates that the reaction be left to stand for 15 min upon completion, where reaction completion is judged by formation of a gel, which typically takes 15 min to appear. From my own observations, the rate at which the gel formed appeared to be dependent on the rate of stirring, typically forming between 5–10 min. For synthesis of enamine **51**, it was found that extracting the gel immediately following its formation gave a significantly improved ratio of enamine : amine (~7:1 cf. ~2:1; the former being the ratio reported in Scheme 2.13). Given this observation, this modification was applied to all subsequent enamine syntheses, with the exception of enamines **(±)-54a** and **145** (Scheme 2.20; p. 37), which were left for the same duration as that used by Nagashima.

Attempted distillations (both directly from the gel and following extraction with Et_2O) were not effective for removing amine **103**, and, owing to the hydrolytic instability of hindered

aldenamines, no alternative manipulation was possible. Dilution of the reaction concentration by half proved equally ineffective, giving no improvement of enamine **51** : amine **103** ratio (see below for further attempts to modify the procedure with amide **127**). However, despite the limitation of the unwanted by-product, amine **103**, Nagashima's method still represents a marked improvement for synthesis of *N*-*tert*-butyl-*N*-*iso*propylamine (**100**)-derived enamines compared with the lithium amide-epoxide approach.

While classic condensation as a means to prepare hindered aldenamines is widely known to be problematic (see Ch. 1, p. 2), we wished to assess the veracity of this for synthesis of enamine **51**, and thus determine the true synthetic benefit (if any) of the above chemistry. Given the hydrolytic sensitivity of sterically hindered aldenamines, acidic methods, such as the previously discussed procedure developed in the Bélanger laboratory,[5] would inevitably lead to hydrolysis of enamine **51**. Therefore, to investigate classical condensation conditions for hindered aldenamines we considered basic conditions prescribed by Curphey *et al*.[12] As anticipated, attempted condensation of amine **100** with hexanal (**104**) failed, in this case simply returning starting materials (Scheme 2.14). To authenticate this result, valeraldehyde (**8**) was reacted with *N*-isobutyl-*N*-butylamine (**7**),[12b] which gave enamine **9** in a yield (66%) consistent with that obtained by Curphey (Scheme 2.14). A parallel reaction between valeraldehyde (**8**) and *N*-*tert*-butyl-*N*-isopropylamine (**100**) gave, as anticipated, none of the desired enamine **106**, but returned mainly starting material and several trace impurities, which by crude NMR showed resonances in the aldehydic and olefinic regions indicative of aldol by-products (Scheme 2.14). Given the observation of aldol impurities, reactions at elevated temperatures were not attempted.

SCHEME 2.14



100 R^1 = *i*-Pr, R^2 = *t*-Bu
7 R^1 = *n*-Bu, R^2 = *i*-Bu

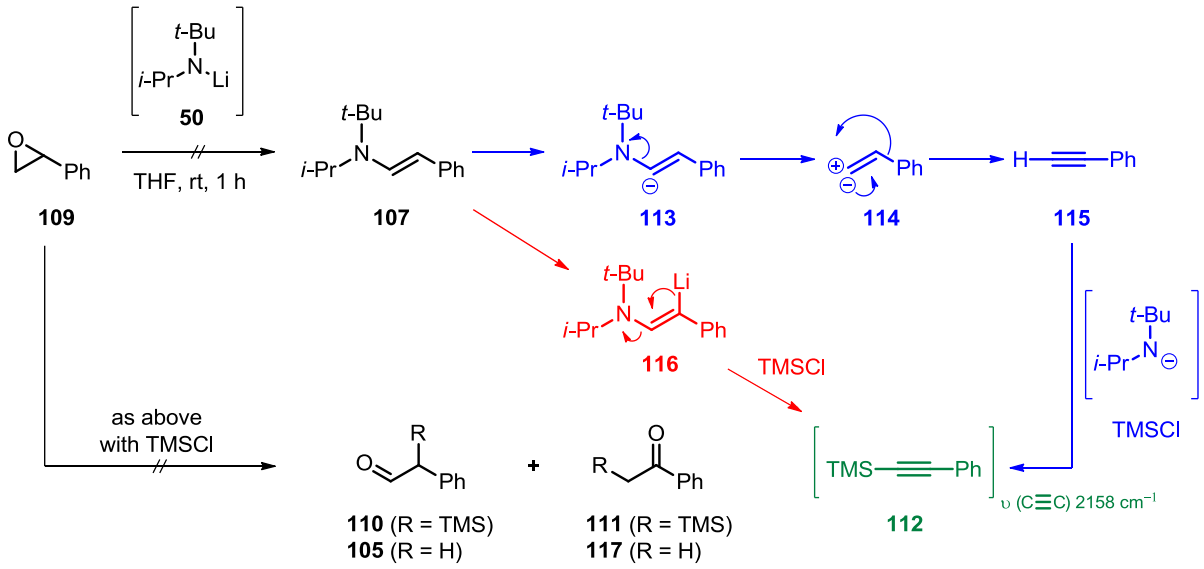
104 R^3 = C_4H_9
8 R^3 = C_3H_7
105 R^3 = Ph

51 R^1 = *i*-Pr, R^2 = *t*-Bu, R^3 = C_4H_9
9 R^1 = *n*-Bu, R^2 = *i*-Bu, R^3 = C_3H_7 [66% (lit.[12b,13] 71–73%)]
106 R^1 = *i*-Pr, R^2 = *t*-Bu, R^3 = C_3H_7
107 R^1 = *i*-Pr, R^2 = *t*-Bu, R^3 = Ph
108 R^1 = *n*-Bu, R^2 = *i*-Bu, R^3 = Ph (54%)

2.5.2 *Application of Nagashima's Chemistry to the Synthesis of β-Aryl-Subsituted Enamines*

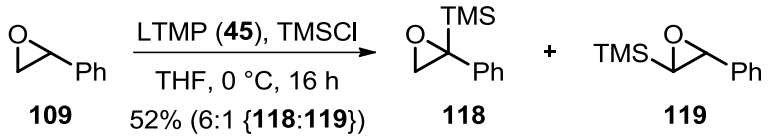
Due to the relative success observed using Nagashima's chemistry for preparation of enamine **51**, we were encouraged to examine possible extension of this chemistry to the synthesis of *β*-aryl-substituted enamines, which are not accessible using Hodgson lithium amide-epoxide methodology – confirmed by attempted synthesis of enamine **107** from reaction of styrene oxide (**109**) with lithium amide **50** using Bray's conditions (Scheme 2.15);[39] this reaction gave a complex mixture of products. Attempted distillation resulted in low mass recovery, with only trace amounts of enamine observed in the ^{1}H NMR spectrum of the isolated residue.

SCHEME 2.15



A series of trapping experiments with TMSCl were performed, as we believed hydrolytic instability of the enamine could be affecting the outcome of the reaction (Scheme 2.15). Earlier work in the Hodgson group by Reynolds showed that lithiation of both the α- and *β*-positions of the epoxide occurs at 0 °C (Scheme 2.16).[73]

SCHEME 2.16

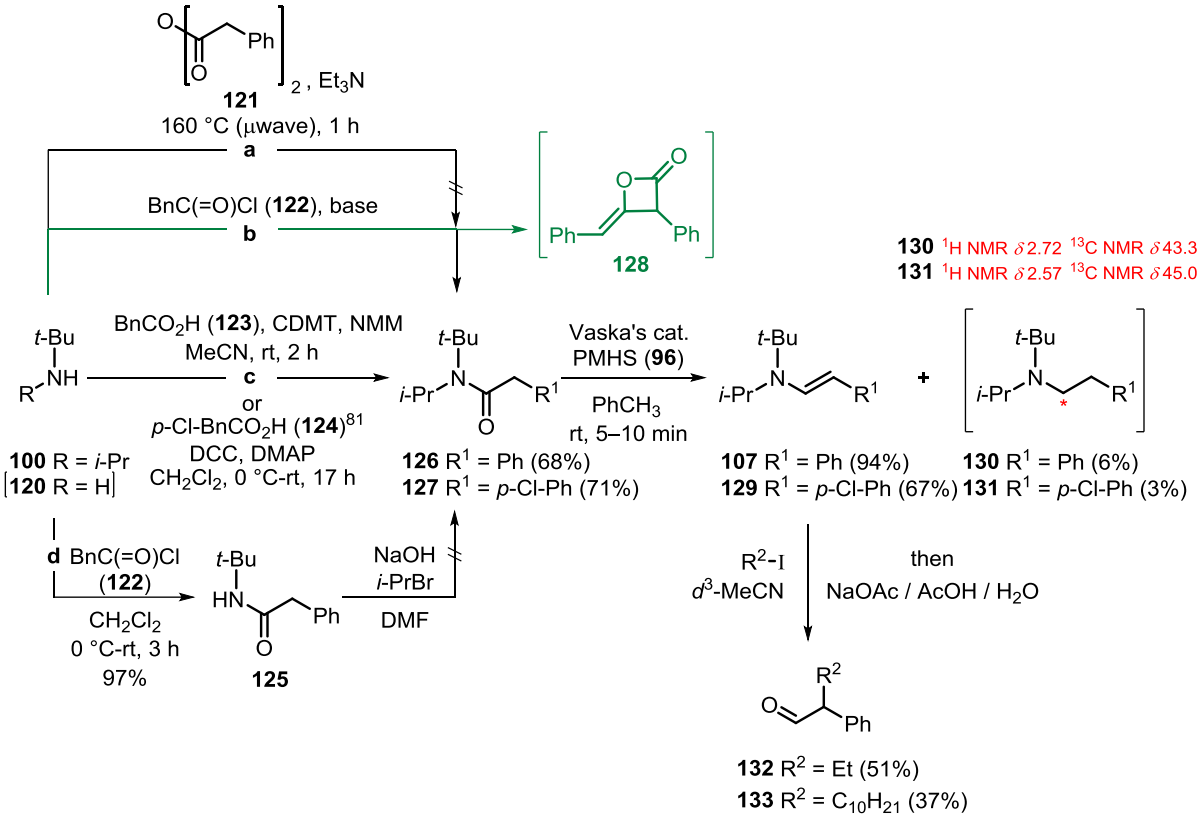


As enamine synthesis *via* the lithium amide-epoxide methodology requires reaction at rt, it was believed, from Reynolds work, that enamine silylation would likely lead to a mixture of aldehyde **110** and ketone **111**, or their subsequently desilylated congeners **105** and **117** (Scheme 2.15). Interestingly, reaction of lithium amide **50** with styrene oxide (**109**) gave neither of the predicted products (Scheme 2.15). Instead, NMR analysis identified TMS-substituted alkyne **112** as the only identifiable by-product (Scheme 2.15). An initial reaction performed used the typical 2.5 eq of lithium amide **50**, which gave TMS-substituted alkyne **112** in 49% crude yield. Two possible mechanisms might account for formation of **112**: (i) the excess lithium amide **50** present (of which there is theoretically 0.5 eq) could deprotonate enamine **107** to give carbanion **113**. Subsequent α-elimination of the amino group would generate carbene **114**, which could rearrange by a mechanism comparable to a Fritsch-Buttenberg-Wiechell isomerisation, resulting in terminal alkyne **115**, which could then be deprotonated-silylated to give TMS-substituted alkyne **112**; (ii) lithiation at the enamine *β*-C would give **116**, which could expel the amino group and subsequently silylate, giving the TMS-substituted alkyne **112**. An effort to attain a quantitative recovery of TMS-substituted alkyne **112** using 3 eq of lithium amide gave a complex mixture from which the TMS-substituted alkyne **112** was obtained in low yield (17%).

Following the findings above, we set about testing Nagashima's chemistry for synthesis of *β*-aryl-substituted enamines. We first wished to examine reduction-dehydration of aryl-amide **126**, which actually proved more difficult to prepare than initially envisaged. Synthesis of amide **126** *via* acylation with phenylacetic anhydride (**121**)[74] failed (Scheme 2.17a). Acylation of amine **100** with phenylacetyl chloride (**122**) was attempted using a variety of bases (Et_3N, KOH,[75] Pyr[76] and **100** (2.1 eq)[77]), but all gave low yields (≤ 20%) of amide **126** or complex mixtures, likely suffering from competing ketene formation (Scheme 2.17b).[78] For example, where 2 eq of amine **100** were employed, ^{1}H [δ 5.99 ppm (PhC*H*=C–CHPh) and 5.02 ppm (PhCH=C–C*H*Ph)] and ^{13}C [δ 169.5 ppm (C=O) and 148.5 ppm (CH=*C*)] resonances in crude NMR spectra indicated possible formation of ketene dimer **128,** though no scalar coupling was observed, which is contrary to observations by Baldwin and Roberts.[79] Equally, attempted alkylation of amide **125**, prepared by reaction of *tert*-butylamine **120** and phenylacetyl chloride (**122**) according to the method of Baumgarten *et al*.,[80] returned only starting materials (Scheme 2.17d).[81] Eventual synthesis of the required amide was achieved by 2-chloro-4,6-dimethyoxy-1,3,5-triazine (CDMT)-mediated coupling between phenylacetic acid (**123**) and amine **100** following the method of Garrett *et al*. (Scheme 2.17c).[82] Pleasingly, treatment of amide **126** with Nagashima's conditions gave a mixture of enamine **107** : amine **130** (94:6) in excellent yield and improved ratio compared to that obtained for preparation of enamine **51** by this method (Scheme 2.17). Similarly, amide **127** (prepared by amide coupling of amine **100** and acid **124**[83] using DCC / DMAP;[84] Scheme 2.17c) gave a mixture of enamine **129** : amine **131** in reasonable ratio and yield [96:4, 70% (after distillation); Scheme 2.17]. Assessment of the alkylation profile for enamine **107** was performed with EtI and $C_{10}H_{21}I$, using conditions adapted from Kaka (85 °C, 20 h)[16] and Bray (82 °C, 22 h),[39] respectively (Scheme 2.17). Unfortunately, enamine **107** gave poor yields of the respective α-alkyl aldehydes **132** and **133**. Attempted ethylation following

Bray's conditions (50 °C, 16 h) also gave a low yield of aldehyde **132** (< 6%). Increasing the temperature to 100 °C for alkylation with $C_{10}H_{21}I$ also gave poor recovery of aldehyde **133** (~17%). *C*-alkylation activity may be lowered by conjugation of the enamine with the Ph group.

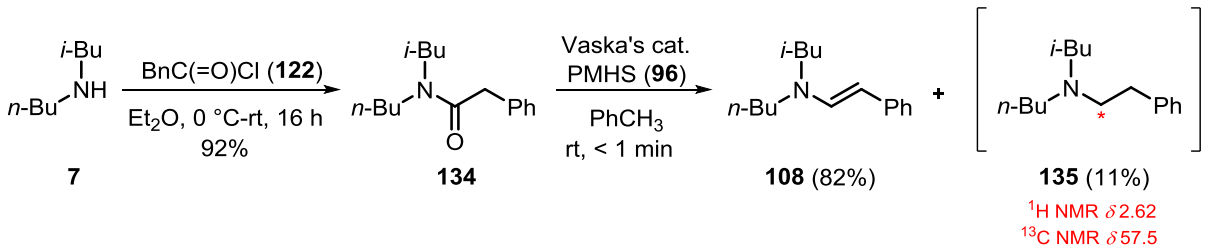
SCHEME 2.17



Despite low yields of alkylation with enamine **107**, such hindered aryl enamines may find utility for other desirable transformations (e.g. cyclopropanation), and thus still represent a potentially important class of compounds that are not easily accessible. For instance, it was determined by attempts to react amine **100** with phenylacetaldehyde (**105**) in the presence of K_2CO_3 that enamine **107** could not be prepared *via* classical condensation (Scheme 2.14).

In contrast to attempted alkylation of enamine **107**, Curphey *et al*. have shown that enamine **108** undergoes facile *C*-alkylation (e.g. reaction with MeI gave 2-phenylpropanal in 77% yield).[12b] A yield was not reported for the classic condensation used by Curphey *et al*. for synthesis of this enamine. We supposed this condensation might be low yielding, and thus were encouraged to examine whether Nagashima's chemistry could offer any advantage. In my hands, condensation of amine **7**[12b] with phenylacetaldehyde (**105**) provided enamine **108** in moderate yield (54%, Scheme 2.14). By contrast, enamine **108** was formed in 82% yield by reaction of amide **134** (prepared by acylation of amine **7** with phenylacetyl chloride (**122**)) under Nagashima's conditions (Scheme 2.18). However, this synthesis was still limited by the presence of amine **135** (11%; Scheme 2.18). It was noteworthy that formation of the polymer gel was extremely rapid in this case (< 1 min). This suggests the rate of gel formation has little impact on the outcome of the reaction, since the enamine / amine ratio is similar to that obtained for reduction of amide **102** (p. 28).

SCHEME 2.18

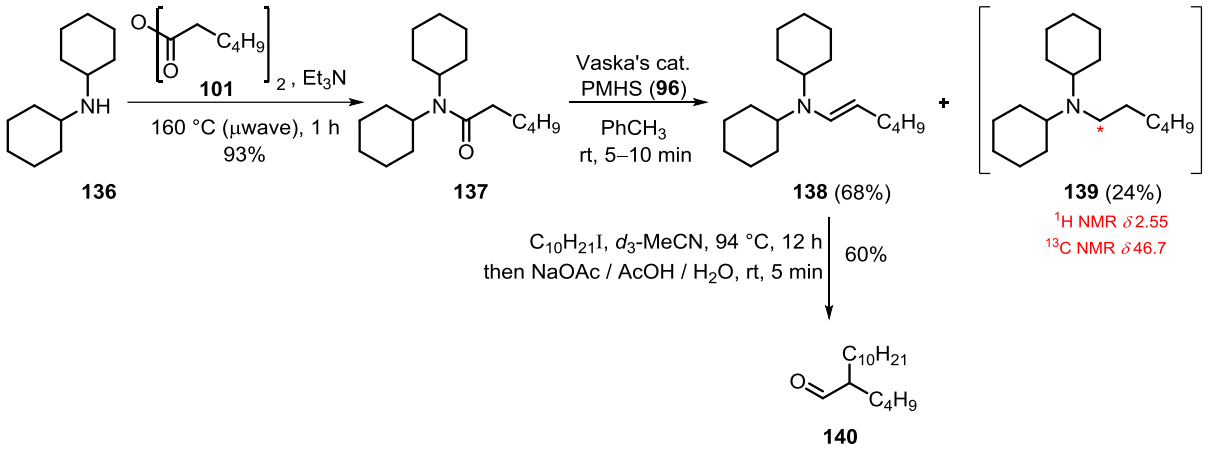


2.5.3 *Attempts to Eliminate / Reduce Amine By-products Using Nagashima's Method*

Given the issue of over-reduction that had been observed for all the above reactions, we decided to examine some alternative amines in the hope of eliminating this unwanted by-product. Dicyclohexylamine (**136**) was chosen for its commercial availability, low cost and structural similarity (α- to N) to amine **100**. Preparation of the requisite amide **137** proceeded in pleasing yield (Scheme 2.19). Unfortunately, under Nagashima's conditions amide **137**

generated an inseparable 3:1 mixture of enamine **138** and amine **139**. An alkylation was attempted with decyl iodide (chosen to give a non-volatile product), following the conditions of Kaka.[16] ^{1}H NMR analysis showed the alkylation was complete after only 12 h, although subsequent hydrolysis gave aldehyde **140** in only moderate yield (60%) – rather lower than that obtained by Bray for decylation of enamine **51** (95%).

SCHEME 2.19



136 **137** **138** (68%) **139** (24%)

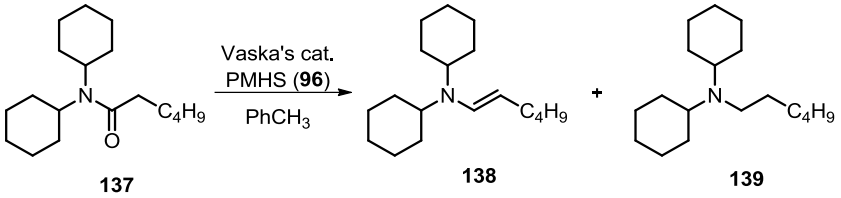
^{1}H NMR δ 2.55

^{13}C NMR δ 46.7

140

It was considered that the less hindered nature of dicyclohexylamine (**136**) compared with amine **100** could mean that enamine **138** was simply suffering from *N*-alkylation. However, in order to truthfully compare the effectiveness of dicyclohexyl-*N*-substituted enamines, we wished to obtain a clean sample of enamine **138**. But, despite efforts to minimise the ratio of enamine **138** : amine **139** (Table 2.2), the impurity could not be removed / reduced.

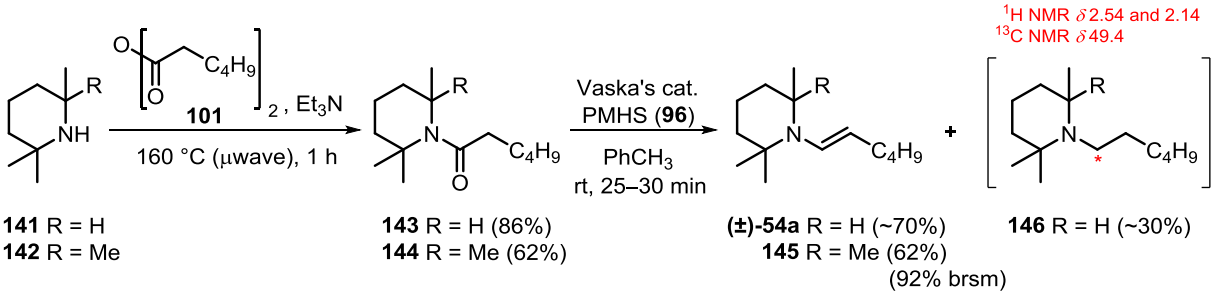
TABLE 2.2



Entry	Vaska's cat. eq	Si–H eq	Reaction Time (min)	Reaction Temperature (°C)	Amide **137**: Enamine **138** : Amine **139**
1	0.01	4	5−10	rt	- : 1.0 : 0.7
2	0.02	4	5−10	rt	- : 1.0 : 0.6
3	0.005	4	5−10	rt	- : 1.0 : 0.7
4	0.01	2	5−10	rt	0.9 : 1.0 : 0.5
5	0.01	4	70	0 °C (1 h) - rt	0.3 : 1.0 : 0.8

We next investigated preparation of the earlier discussed trialkylpiperidine derived enamines (see Ch. 1, p. 14), since access *via* Nagashima's method would be advantageous over formation of these enamines *via* Hodgson lithium amide-epoxide methodology. As discussed above (p. 26), the latter requires distillation to purify product enamines, limiting the molecular weight for substrates, whereas the former reportedly necessitates only simple filtration. TriMP (**141**) was kindly supplied by Kaka, who prepared it by demethylation of TMP (**142**) in three steps.[16] Synthesis of the corresponding amide **143** proceeded in excellent yield using the Hulme protocol[72] (Scheme 2.20). However, subjecting amide **143** to Nagashima's conditions returned a mixture of enamine **(±)-54a** and an impurity believed to be amine **146** (Scheme 2.20). By contrast, amide **144** derived from the more hindered TMP (**142**) failed to fully reduce, returning a 2:1 mixture of enamine **145** : starting material **144** (Scheme 2.20).

SCHEME 2.20



141 R = H
142 R = Me

143 R = H (86%)
144 R = Me (62%)

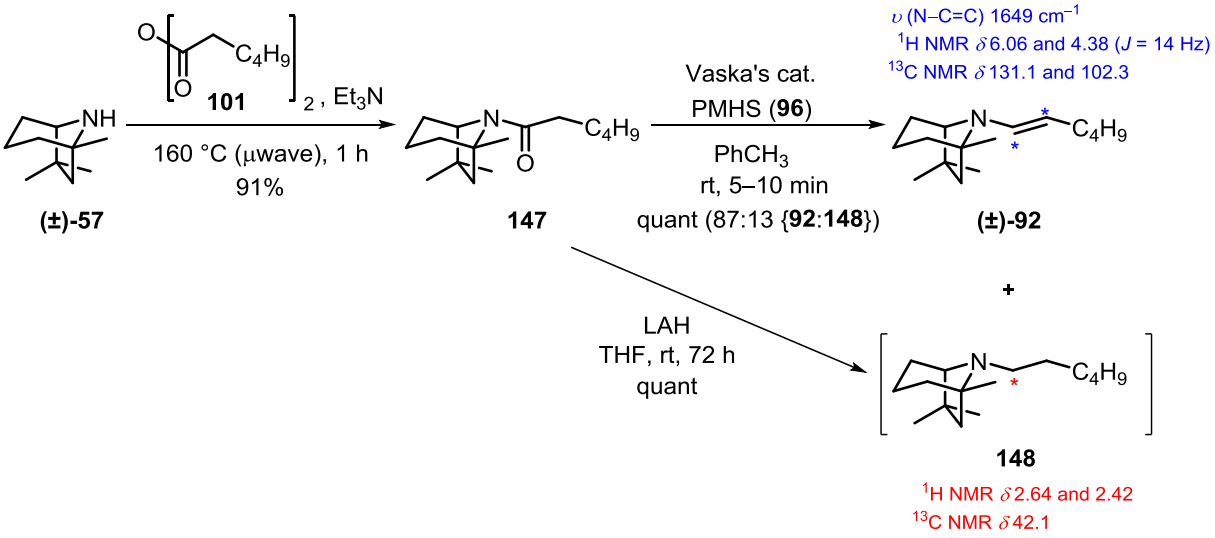
(±)-54a R = H (~70%)
145 R = Me (62%)
(92% brsm)

146 R = H (~30%)

2.6 Enamine Synthesis from Tropane (±)-57 Using Nagashima Amide Reduction-Dehydration Methodology and Alkylation

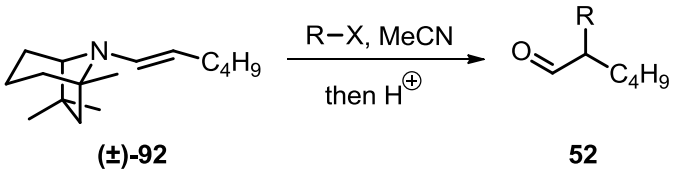
Having performed extensive investigation of Nagashima's method on more hindered amides, it was clear that a limitation of this chemistry is over-reduction to the saturated amine. Despite this limitation, we proceeded to investigate this chemistry for synthesis of our desired tropane-derived enamine **(±)-92** (Scheme 2.21). Synthesis of the necessary amide **147** was accomplished in excellent yield. As expected, the enamine was prepared in high yield but again suffered from the presence of an inseparable impurity believed to be the saturated amine. In this case, the presence of amine **148** was confirmed by LAH reduction of amide **147**, following literature conditions used for reduction of a similarly hindered amide (Scheme 2.21).[85]

SCHEME 2.21



Alkylation of enamine **(±)-92** prepared *via* Nagashima's method was assessed using a similar set of electrophiles as used by Bray[39] and Kaka.[16] As can be seen from Table 2.3, the yields returned from alkylation were disappointing. Following the conditions of Kaka,[16] reaction with EtI, decyl iodide and allyl bromide were all low yielding (Entries 1–3, Table 2.3). Reaction with BnBr gave a more promising yield, but was still lower than would be predicted based on the previously noted (Ch. 1, p. 13) separation of the olefinic signals (Entry 4, Table 2.3).

TABLE 2.3

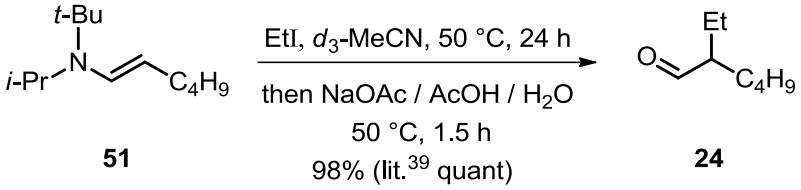


Entry	Electrophile R–X	Reaction Temperature	Reaction Time (h)	Product	Yield [a] (%)
1	EtI	65 °C	16	**24**	52[b]
2	$C_{10}H_{21}I$	95 °C	20	**140**	40
3	AllylBr	rt-50 °C	16	**149**	36[b]
4	BnBr	rt	16	**150**	67

[a] Uncorrected for amine **148** present in starting material; [b] Corrected for residual solvent

In order to validate the alkylation procedure used in the present case, enamine **51** [prepared using Hodgson methodology (Scheme 2.13; p. 28)] was alkylated with EtI[§] to give 2-ethylhexanal (**24**) in a yield consistent with that obtained by Bray (Scheme 2.22). This result, coupled with the inconsistencies in yields obtained from alkylation of enamine **(±)-92**, suggested that inseparable amine **148** or an unidentified contaminant from Nagashima's chemistry could be interfering with alkylation.

SCHEME 2.22



51 **24**

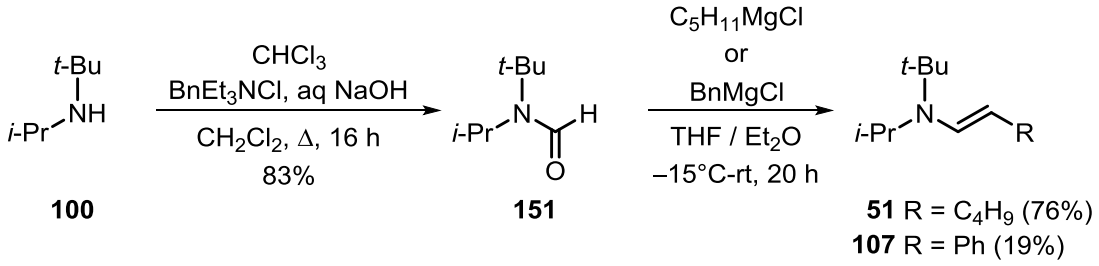
2.7 Examination of Hansson and Wickberg Addition-Elimination Methodology for Preparation of Hindered Aldenamines

Piperidine-derived enamines have previously been prepared in the Hodgson group by way of an addition-elimination reaction between Grignard reagents and formamides, first reported by Hansson and Wickberg,[86] albeit in low yield and prolonged reaction time (e.g., reaction between *N*-formyl-2,2,6,6-tetramethylpiperidine with *n*-BuMgCl proceeded in only 32% yield after 7 d).[13] As with Nagashima's chemistry, we decided first to investigate this chemistry with the hope of improving the synthesis of enamine **51** (Scheme 2.23). The requisite formamide **151** was synthesized in good yield from amine **100**, using the method of Blum and Nyberg (Scheme 2.23).[87] The original Hansson and Wickberg enamine work prescribes excess formamide relative to Grignard reagent; however, it was found that this

[§] Alkylation was performed with EtI, since 2-ethylhexanal (**24**) represents one of the most challenging products to isolate, owing to its volatility.

inevitably resulted in some inseparable formamide contaminating the product enamine. Modification, using a slight excess (1.25 eq) of pentylmagnesium chloride, generated the desired enamine **51** in modest yield (45%). Further adaptation of the procedure, involving addition of an extra 1.1 eq of Grignard reagent after 3 h, improved the yield (76%, Scheme 2.23); a minor unidentified impurity was also present, which could not be removed by distillation. Synthesis of aryl enamine **107** using BnMgCl proved much lower yielding (Scheme 2.23).

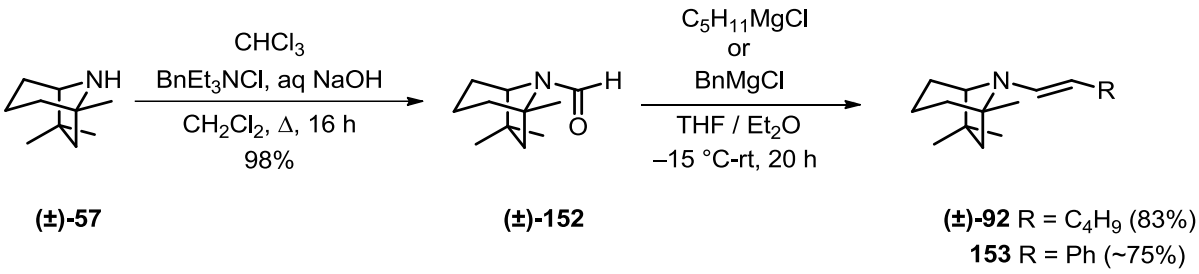
SCHEME 2.23



2.8 Enamine Synthesis from Tropane (±)-57 Using Adapted Hannson and Wickberg Addition-Elimination Methodology and Alkylation

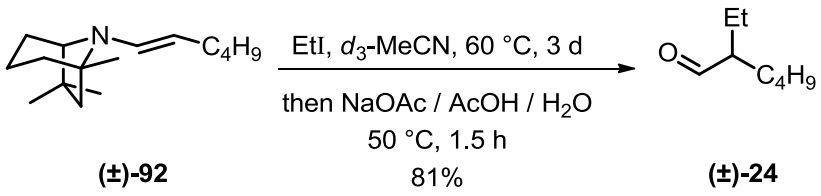
To examine this strategy for synthesis of enamine **(±)-92**, formamide **(±)-152** was synthesized from tropane **(±)-57** in excellent yield (Scheme 2.24).[87] Pleasingly, applying the modified Hansson and Wickberg procedure (employing 1.25 eq of Grignard reagent), enamine **(±)-92** was prepared in excellent yield, and, importantly, was isolated pure after distillation (Scheme 2.24). Furthermore, addition of benzylmagnesium chloride to formamide **(±)-152** gave the corresponding aryl-tethered enamine **153**, also in good yield, though unidentified impurities were present in this case, and thus alkylation of this enamine was not assessed (Scheme 2.24).

SCHEME 2.24



Pleasingly, *C*-ethylation of the pure enamine **(±)-92** with EtI gave, after hydrolysis of the resulting iminium, 2-ethylhexanal (**(±)-24**) in excellent yield (Scheme 2.25). By comparison, enamine **54b** (Ch. 1, p. 14) generated the same aldehyde in only 58% yield under similar conditions. The high yield of aldehyde **24** using formamide-derived enamine **92** supports the idea that impurities in Nagashima's route interfere with alkylation efficiency.

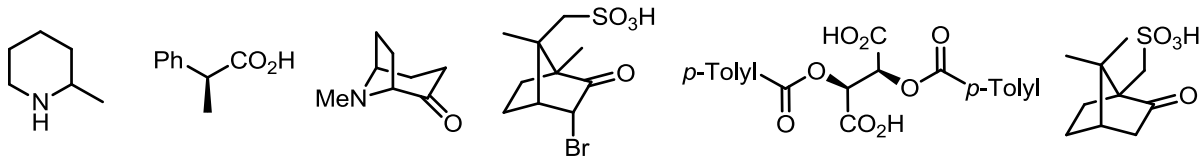
SCHEME 2.25



2.9 Resolution of Tropane (±)-57

Having achieved a good yield for ethylation of enamine **(±)-92**, we pursued the more demanding challenge of asymmetric α-alkylation, which necessitated an enantiopure source of tropane **57**. To separate the enantiomers of tropane **(±)-57**, we first considered crystallisation of an appropriate diastereomeric salt. Aggarwal *et al*. previously separated the diastereomeric salts formed upon neutralisation of (±)-2-methylpiperidine (**(±)-154**) and (–)-mandelic acid (**(–)-155**; Figure 2.2).[88] Pinder *et al*. successfully resolved (±)-tropan-2-one (**(±)-156**) employing first D-(+)-bromocamphor-π-sulfonic acid (**(+)-157**), then (+)-di-*p*-toluoyl-D-tartaric acid (**(+)-158**; Figure 2.2).[89] Unfortunately, these procedures proved

ineffective for resolution of tropane **(±)-57**. Employing (–)-mandelic acid (**(–)-155**) or camphor sulfonic acid (CSA, **(–)-159**; chosen for availability over **(+)-157**) gave no crystallisation using either procedure.

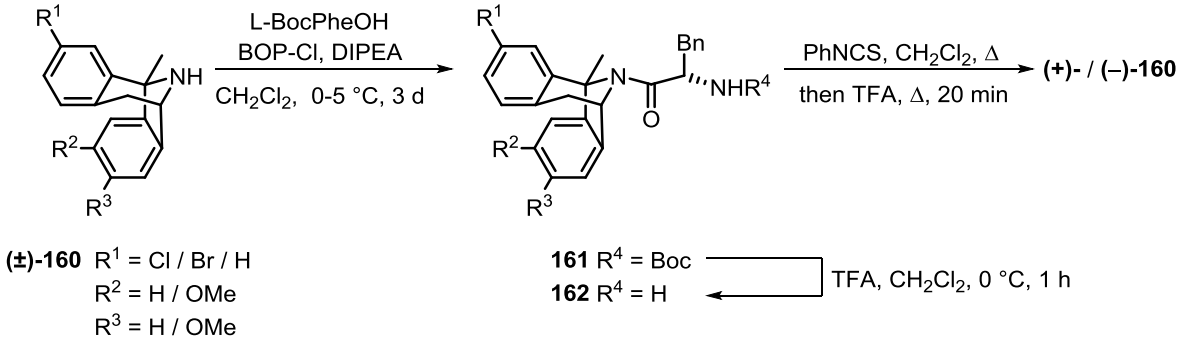


(±)-154 **(–)-155** **(±)-156** **(+)-157** **(+)-158** **(–)-159**

FIGURE 2.2

Considering that a suitable acidic partner could potentially take substantial time to find, we looked to the literature for alternative resolution strategies. Thompson *et al*. have resolved structurally analogous tropanes **160** by chromatographic separation of amino acid derived diastereomers **162**, with subsequent Edman degradation, to retrieve the enantiopure tropane (Scheme 2.26).[90]

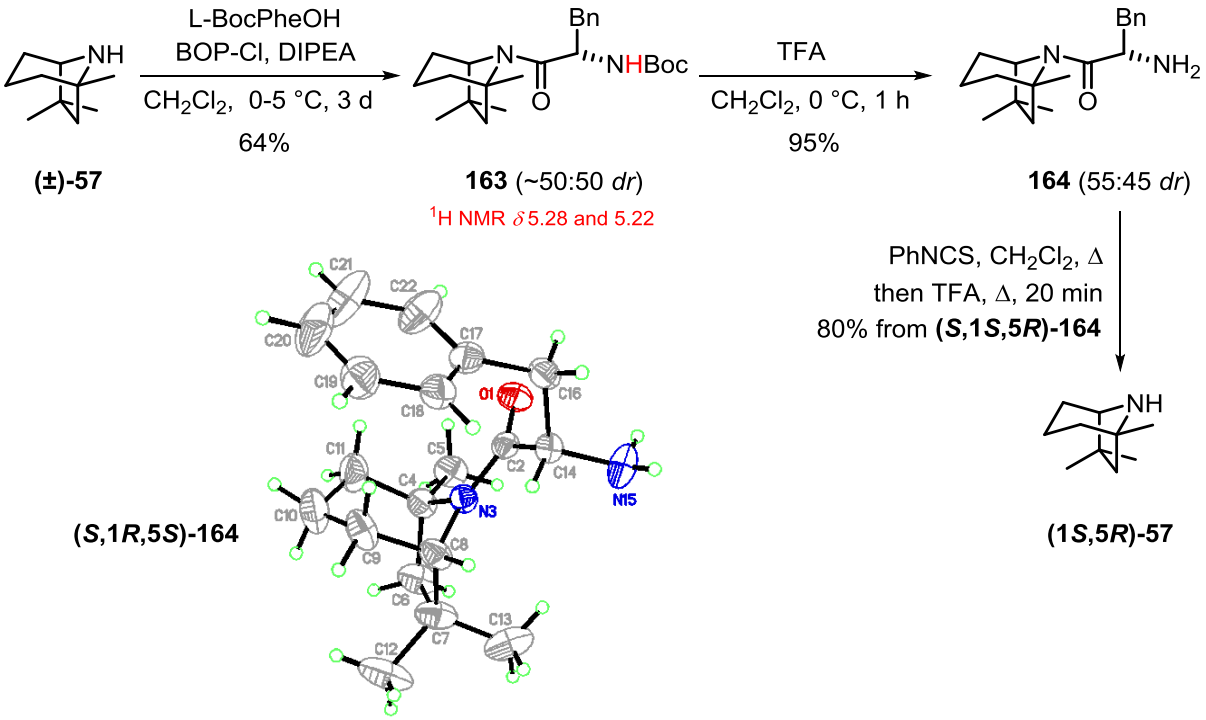
SCHEME 2.26



Applying this strategy, tropane **(±)-57** was resolved by coupling with *N*-Boc-L-phenylalanine to give Boc-protected α-amino amides **163**, followed by deprotection and chromatographic separation of the diastereomeric α-amino amides **164**, then Edman degradation (Scheme

2.27).** The absolute configuration of tropane **(+)-57** was determined to be (1*R*,5*S*) by X-ray crystallographic analysis of the precursor α-amino amide **(*S*,1*R*,5*S*)-164** (Scheme 2.27).[91]

SCHEME 2.27



2.10 Asymmetric Alkylation

2.10.1 *Determination of er*

Measuring enantioenrichment of α-alkyl aldehydes that have comparable (alkyl) substituents at the stereocentre is predicted to be difficult by conventional methods (e.g. chiral HPLC / optical rotation). While Gellman[92] and Meyers[93] have previously determined *er*s of α-substituted aldehydes by observed differentiation of NMR resonances for transient diastereomeric iminium ions, this technique was found to be unsuitable in Kaka's work on piperidine systems (Figure 2.3).[16]

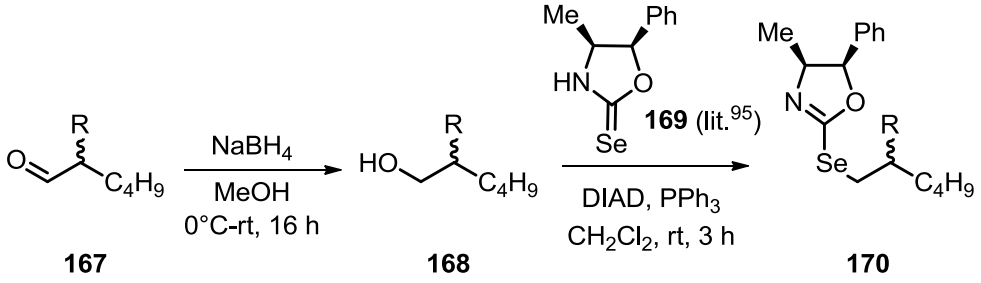
** For clarity, Edman degradation of only one diastereomer has been shown.

165 **166**

FIGURE 2.3

Kaka considered chiral GC might be able to resolve alcohols **168** derived from the enantioenriched α-substituted aldehydes **167**. However, evaluation of this method showed separation of the corresponding alcohol enantiomers was not possible.[16] In light of this, a more convoluted approach was employed, which involved further derivatisation of the alcohols **168** with a selenone auxiliary **169**, and NMR analysis of the resulting selenium adducts **170**, using a method pioneered by Silks *et al*. (Scheme 2.28).[94] The benefit of using a selenium chiral derivatizing agent (CDA) is the high chemical shift sensitivity of the ^{77}Se nucleus. For example, Silks *et al*. have demonstrated that selenone CDA **169** is capable of detecting $\Delta\delta$-values as low as 0.119 ppm, which was observed for diastereomers of the selenium adduct resulting from derivatisation of (*R*,*S*)-lipoic acid.[95] Indeed, Kaka observed a $\Delta\delta$-value of just 0.13 ppm for diastereomers of selenium adduct **170** [R = $C_{10}H_{21}$ ≡ **223** (Scheme 3.20; Ch. 3, p. 71)] derived from 2-butyldodecanal (**140**).[16] Disadvantages of this approach are the inconvenience of having to prepare the selenone CDA **169**, and the toxicity hazards from working with selenium compounds.

SCHEME 2.28



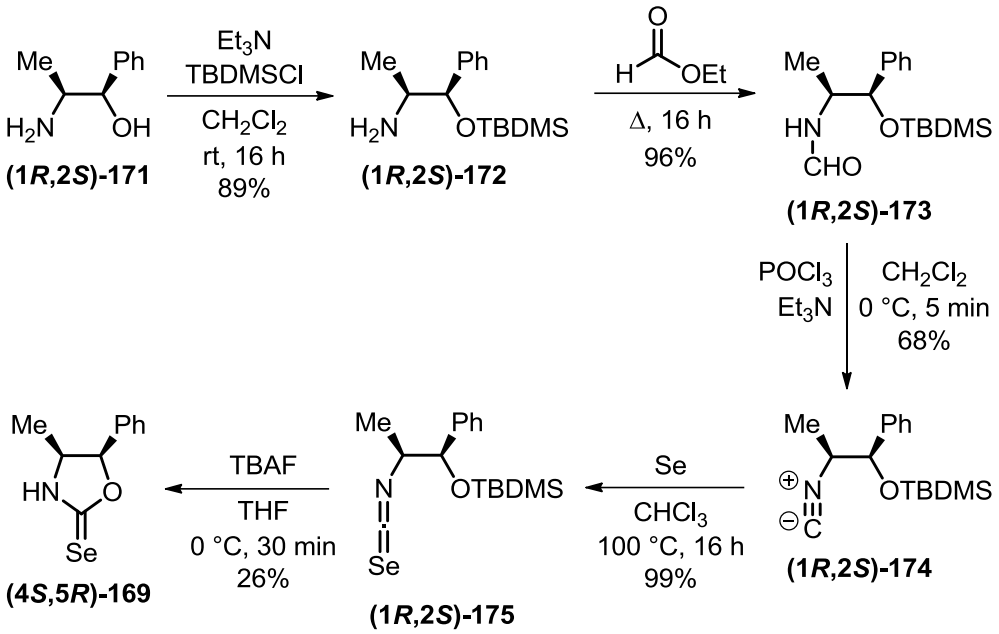
167 **168** **170**

While Kaka's efforts to separate alcohols **168** directly had proved unrewarding, Evans *et al*. have reported that separation of (±)-2-ethylhexanal (**24**) can be achieved using chiral GC.[3] Since α-ethylation of hexanal had been extensively examined, both computationally and synthetically, with the trialkylpiperidine auxiliaries, this was the first reaction we wished to examine with chiral enamine **(1*S*,5*R*)-** / **(1*R*,5*S*)-92**. Evans conditions [Column: Supelco *β*-DEX 225 (0.25 mm x 30 m, thickness 0.25 μm); Carrier gas: He (1 mL / min); Detector: FID @ 250 °C; Injection: 1 μL @ 1–3 mg / mL, Split ratio: 100 : 1, 250 °C] were examined for separation of (±)-2-ethylhexanal (**24**) using the departmental chiral GC. However, following extensive investigation, it was determined that sufficient separation could not be achieved, likely due to differences in the chiral column used [Column: unknown manufacturer, *β*-cyclodextrin (0.22 mm x 30 m, thickness 0.25 μm)]. Replacement of the column was financially unfeasible, and so a CDA approach would be required. The well-known and popular α-methoxy-α-(trifluoromethyl)phenylacetic acid / chloride CDA, developed by Mosher,[96] was a potential substitute for selenone **169**. However, this had initially been disregarded by Kaka, believing it would not give sufficient separation to determine the *er* accurately. Since Kaka had demonstrated successful *er* determination using selenone **169** for a range of asymmetric alkylations, we decided to employ this method to establish the *er* of asymmetric alkylation with enamine **(1*S*,5*R*)-** / **(1*R*,5*S*)-92**. Importantly, this method does not result in any kinetic resolution.[16,94]

Selenone **169** was prepared using a sequence based on the procedures used by Silks[95] and Kaka[16] (Scheme 2.29). Reaction of (1*R*,2*S*)-norephedrine **(1*R*,2*S*)-171** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and Et_3N provided *O*-protected norephedrine **(1*R*,2*S*)-172** in consistent yield with the literature. Formylation using Kaka's conditions (which are based on formylations performed in the laboratories of Ueda[97a] and Yu[97b]), but

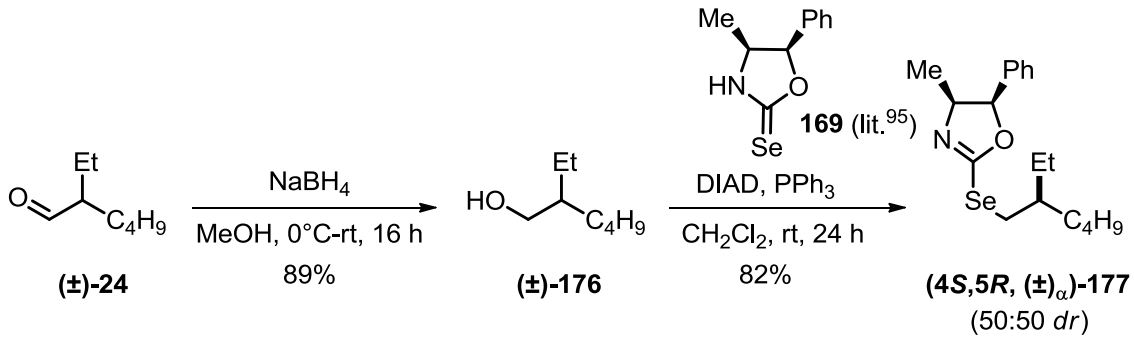
with a prolonged reaction time, gave formamide **(1*R*,2*S*)-173** in excellent yield (96% cf. lit.[16] 58%). Dehydration, mediated by $POCl_3$, proceeded in similar yield to that obtained by Silks *et al*.[95] to give isocyanide **(1*R*,2*S*)-174** in reasonable yield. Formation of isoselenocyanate **(1*R*,2*S*)-175** initially proved difficult. Treatment of **(1*R*,2*S*)-174** with 2 eq of selenium, as suggested by both Kaka and Silks, gave only partial conversion after overnight reflux in $CHCl_3$. This seemed strange, as Silks had suggested the yield was quantitative after only 5 h, and Kaka had obtained the same result after 20 h. After a further 24 h at reflux with 5 eq of Se, the reaction still had not reached completion. It was considered that pressure might assist the reaction. Indeed, heating an aliquot of the mixture in a sealed tube at 100 °C for 3 h in $CHCl_3$ with 2 eq of selenium gave a significant improvement in selenium incorporation. Subjecting the bulk mixture to the same conditions for 16 h gave the desired isoselenocyanate **(1*R*,2*S*)-175** in excellent yield (99%). Presumably, the requirement for higher pressure was due to the age of the selenium used. Being several years old, it is likely that the surface of the selenium had oxidised. Disappointingly, the final step of the sequence was hampered by product decomposition during purification. On loading the crude selenone onto silica gel, a strong red band appeared, indicative of the elemental Se allotrope. Attempts to improve the yield of this reaction gave similar results. Nevertheless, sufficient selenone **(4*S*,5*R*)-169** was prepared by this method for our needs.

SCHEME 2.29



To validate the procedure for installation of selenone **(4*S*,5*R*)-169**, 2-ethylhexanal (**(±)-24**) was first reduced to give 2-ethylhexan-1-ol (**(±)-176**), which was then treated with Silks' conditions, which furnished selenium adduct **(4*S*,5*R*,(±)$_{\alpha}$)-177** in high yield (Scheme 2.30). Subsequent ^{77}Se NMR analysis of **(4*S*,5*R*,(±)$_{\alpha}$)-177** displayed two resonances of equal integration at δ 228.99 and δ 228.26 ppm.[91]

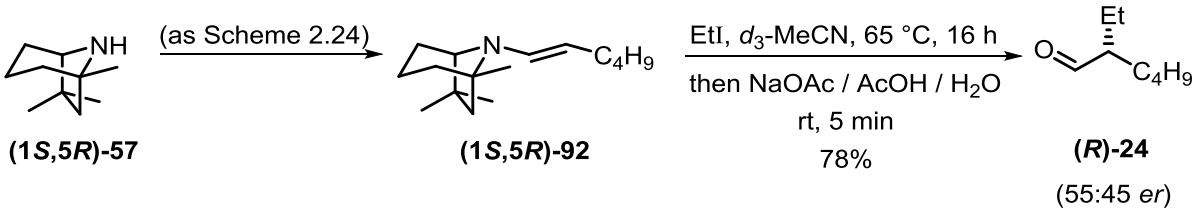
SCHEME 2.30



2.10.2 *Enamine Synthesis from Tropanes **(1S,5R)-** / **(1R,5S)-57** and Alkylation*

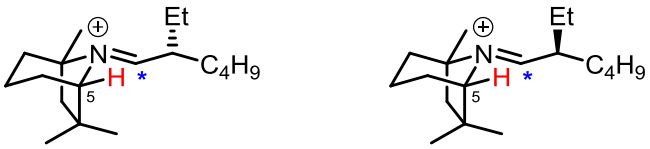
Enamines **(1*S*,5*R*)-92** and **(1*R*,5*S*)-92** were prepared following the strategy outlined in Scheme 2.24 (p. 41). Chiral HPLC analysis of the intermediate formamides **(1*S*,5*R*)-152** and **(1*R*,5*S*)-152** confirmed the enantiopurity of resolved tropanes **(1*S*,5*R*)-57** and **(1*R*,5*S*)-57**, respectively.[91] Surprisingly, the enamine derived from tropane **(1*S*,5*R*)-57** underwent alkylation with EtI to give aldehyde **(*R*)-24** in low *er* (55:45, Scheme 2.31) with a preference for the opposite sense of asymmetric induction (i.e. the opposite enantiomer) to that seen with piperidine-derived enamines **54a–b** (Scheme 1.13; Ch. 1, p. 14); similarly, enantiopure enamine **(1*R*,5*S*)-92** gave aldehyde **(*S*)-24** in 58:42 *er*). The procedure illustrated in Scheme 2.30 was used to measure the *er*.[91]

SCHEME 2.31



Closer analysis of the recorded *in situ* ^{1}H NMR spectra for ethylation of enamine **(1*R*,5*S*)-92** (recorded on a 500 MHz spectrometer) showed that resonances attributed to the protons (C5-H) α- to N on both diastereomers of the transient iminium ion **(1*R*,5*S*,*R*$_\alpha$)-178** and **(1*R*,5*S*,*S*$_\alpha$)-178** (Figure 2.4) were in fact resolved.[91] [Note: resonances attributed to the iminum protons (C*-H) themselves did not resolve.] Inspection of other ethylations performed (i.e. with enamines **(±)-92** and **(1*S*,5*R*)-92**) showed a similar intensity ratio (although resolution was poor for these spectra as they were recorded at lower frequency {400 MHz}), confirming that these signals were in fact due to diastereomers **178**.

Importantly the *in situ* ^{1}H NMR spectra recorded for ethylation of enamine **(1*R*,5*S*)-92** showed no degradation of *dr* with time.

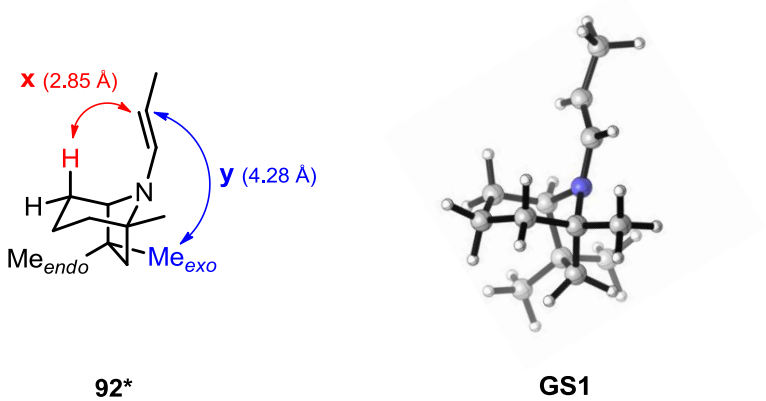


(1*R*,5*S*,R_α)-178 **(1*R*,5*S*,S_α)-178**

FIGURE 2.4

2.11 DFT Studies of Enamine 92*

The origin of the low *er* and unanticipated reversal of asymmetric induction was examined by Dr R. S. Paton using quantum mechanical calculations. Density functional studies of enamine **92*** (a truncated analogue of enamine **92**, Figure 2.5) at the B3LYP / 6-31G(d) level determined that in the ground state the lowest energy conformation **GS1** (Figure 2.5) has the exocyclic C–N bond pseudoaxial with respect to the six-membered ring.



92* **GS1**

FIGURE 2.5 Computed Ground State Conformation for Enamine 92*

Computed transition states **TS1−4** originating from **GS1**, for reaction of enamine **92*** with EtI in MeCN at 65 °C (Figure 2.6), suggest a preference for *Re*-face attack (with **(1*S*,5*R*)-92**). The methylene group α- to the CH bridgehead influences facial selectivity of the approaching

electrophile slightly more than that of the *exo*-methyl substituent (x < y, Figure 2.5; and similarly in the transition states **TS1**–**4**[91]). Transition states **TS1** and **TS2**, which differ only in the approach orientation of EtI to the *Si*-face, lie 1.2 and 2.7 kJ mol^{-1} higher in energy than **TS3**, respectively. The computationally determined face selectivity and calculated 62:38 *er* are in good agreement with the experimental findings.

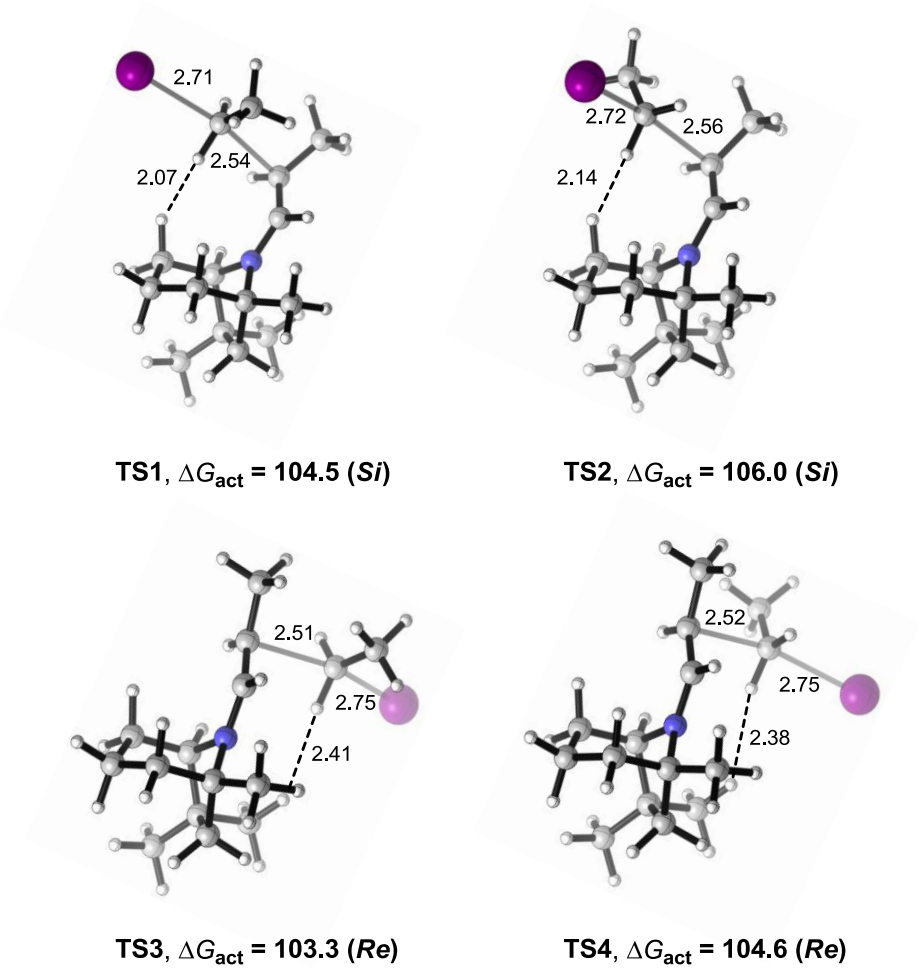


FIGURE 2.6. Computed TS Geometries for Reaction of Enamine 92* with EtI. B3LYP / 6-31G(d) Free Energies in kJ mol^{-1}; Selected Distances Shown in Å

2.12 Chapter Summary

Work encompassing the synthesis and α-alkylation of a racemic and enantiopure tropane-derived enamine **92** has been discussed. The desired substitution pattern (bridgehead alkyl and *gem*-dialkyl α- to a CH bridgehead) on the tropane scaffold proved non-trivial to construct. Initially, a method reported by Macdonald and Rubbotom, involving ring-expansion followed by a bis-conjugate addition, was investigated.[46] Low yields led us to abandon this approach in favour of a Robinson-Scöpf reaction. Using the conditions of Sterner *et al*.[63] gave tropinone **87** in modest yield (42%) from readily available ketoaldehyde **71**. Subsequent reduction provided tropane **57** in excellent yield (85% in two steps).

Tropane **57** proved incompatible with Hodgson lithium amide-epoxide methodology for preparation of the desired enamine **92**. Consequently, an alternative strategy by Nagashima was examined.[70] Extensive investigation of Nagashima's chemistry, not only for preparation of enamine **92** but also in the hope of demonstrating a new method to construct hindered aldenamines, showed a limitation in over-reduction of the precursor amides. While good yields of the enamines were returned, the amine impurity could not be eliminated. Believing the amine impurity could be affecting alkylation of enamine **92**, an alternative method originally reported by Hannson and Wickberg was investigated.[86] Adaptation of this methodology proved most effective and provided enamine **92** in good yield and high purity. Subsequent ethylation of enamine **92** was achieved in excellent yield.

For examination of the asymmetric profile of enamine **92**, enantiopure tropanes **(1*S*,5*R*)-57** and **(1*R*,5*S*)-57** were accessed through resolution by derivatisation with L-Boc phenylalanine

and cleavage utilising an Edman degradation, a similar strategy to that used by Thompson and co-workers.[90] Synthesis of both enantiomers of the chiral non-racemic enamine **(1*S*,5*R*)-92** and **(1*R*,5*S*)-92** showed low *er* (determined by ^{77}Se NMR analysis of a derived selenium adduct), interestingly with unanticipated reversal of diastereoselectivity. DFT studies by Dr R. S. Paton were in agreement with our findings.

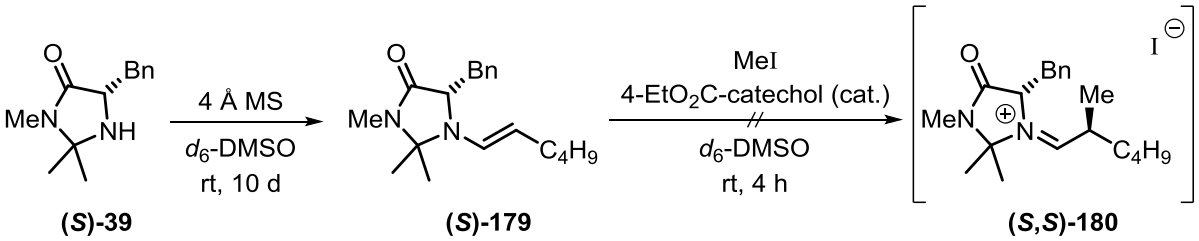
3. 5-MEMBERED RING AUXILIARIES FOR ASYMMETRIC α-ALKYLATION

3.1 Design Principle

Despite the disappointing *er* observed for alkylation with tropane-derived enamine **92**, we were encouraged by the improved yields obtained compared with similar alkylations performed using piperidine-derived enamine **54b**. We believed that the improved yields could be a consequence of the pyrrolidine component of the tropane. Crystallographic studies have shown that pyrrolidine enamines exhibit greater planarity around N than piperidine enamines.[98] From an alkylation perspective this improved N lone pair–π^* overlap leads to superior β-alkylation of pyrrolidine-derived enamines compared with their piperidine analogues.[40] Considering this, we were attracted to the possibility of an enamine derived from a chiral 5-membered ring auxiliary, such as a pyrrolidine, to access highly enantioenriched α-alkyl aldehydes directly from hindered aldenamines. Indeed, many of the recent organocatalytic advances towards α-substitution of aldehydes incorporate the use of a five-membered ring auxiliary.[25–27] For transformations mediated through enamines, many of the auxiliaries used to promote α-substitution are proline-based and sterically unhindered about N. As previously discussed, it is a prerequisite for alkylation with simple alkyl halides that the enamine be sufficiently hindered about N, so as to avoid problematic *N*-alkylation. In light of this, we set about designing a 5-membered ring auxiliary that could meet the steric criteria necessary for successful alkylation, and which could hopefully provide high levels of diastereocontrol.

MacMillan's well-known imidazolidinone **39** (Scheme 3.1) facilitates (through enamine catalysis) α-chlorination[99] and α-fluorination[100] of aldehydes in excellent yields and with exceptional levels of enantioenrichment. We were attracted to imidazolidinone **39**, since it is significantly hindered about N. However, although imidazolidinone **39** functions exceptionally well as an asymmetric enamine catalyst, its use for α-alkylation is limited. For example, while Gellman *et al*. have shown that enamines derived from imidazolidinones react in high yields and *er*s with a series of Michael acceptors,[101] attempted α-alkylation of enamine **(*S*)-179** (prepared according to Gellman's method from imidazolidinone **(*S*)-39**) with MeI by Kaka[16] failed to generate the desired iminium salt **(*S*,*S*)-180** (Scheme 3.1), despite the fact that enamine **(*S*)-179** showed a resonance separation between olefinic protons of 1.48 ppm by ^{1}H NMR, indicative of a strong *C*-alkylation profile (see Ch. 1, p. 13). In this reaction, the predisposition of the auxiliary amide group to undergo *O*-alkylation likely leads to quenching of the reaction.

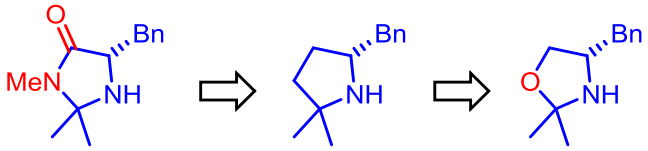
SCHEME 3.1



Disregarding the amide component of imidazolidinone **39**, we believed the latent features necessary for asymmetric α-alkylation with simple alkyl halides were present in this auxiliary. Specifically, the *gem*-dimethyl substitution and benzyl group α to N should provide the necessary steric encumberment to prevent *N*-alkylation of enamines derived from **39**, while also dictating the diastereoselectivity of enamine alkylation. The design principle behind this stereocontrol is closely related to the piperidine and tropane auxiliaries previously discussed. The *gem* dimethyl substituent forces the enamine to adopt one rotameric form, and

the benzyl arm confers facial discrimination of the approaching electrophile. There is still ambiguity as to the exact origin of asymmetric induction, with conflicting hypotheses as to which conformation is responsible for augmenting chirality. To date, models for iminum systems derived from imidazolidinone **39**, incorporating π–π interactions, C–H–π interactions, and oscillatory motion of the benzyl directing group have all been proposed, though a precise model has yet to be established.[22,102] Despite the uncertainty surrounding the exact function of the benzyl arm, which may differ with different substrates, we believed that there was sufficient precedent to suggest that a 5-membered ring auxiliary containing these key features could provide high diastereoselectivity.

Considering the above discussion, in order to generate an auxiliary capable of successful alkylation with simple alkyl halides, the most obvious progression from imidazolidinone **39** is to remove the amide functionality, resulting in pyrrolidine **181** (Figure 3.1). However, given that the preparation of the novel pyrrolidine **181** would involve a more circuitous synthesis, we envisaged that enamines derived from oxazolidine **182** (Figure 3.1), which would be considerably simpler to prepare, might serve the same function. We were aware that the hemiaminal ether present in oxazolidine **182** could present problems for alkylation of derived enamines, but the potential benefits (direct asymmetric synthesis of the auxiliary in a single step from cheap commercially available materials) prompted us to examine this auxiliary first.



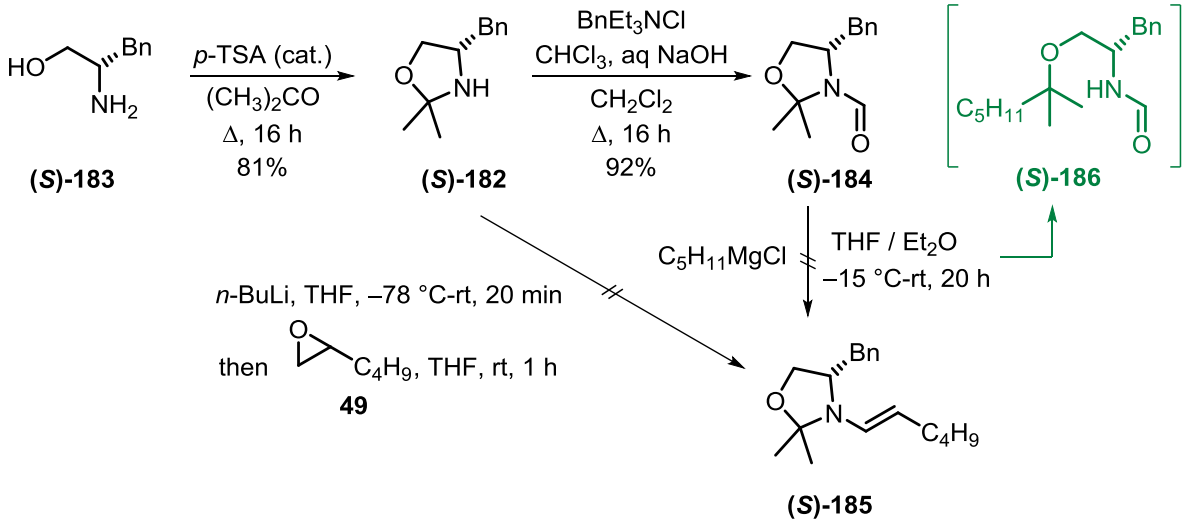
(*S*)-39 (*R*)-181 (*S*)-182

FIGURE 3.1

3.2 Synthesis of Enamines Derived from Oxazolidine (*S*)-182 and Attempted Alkylation

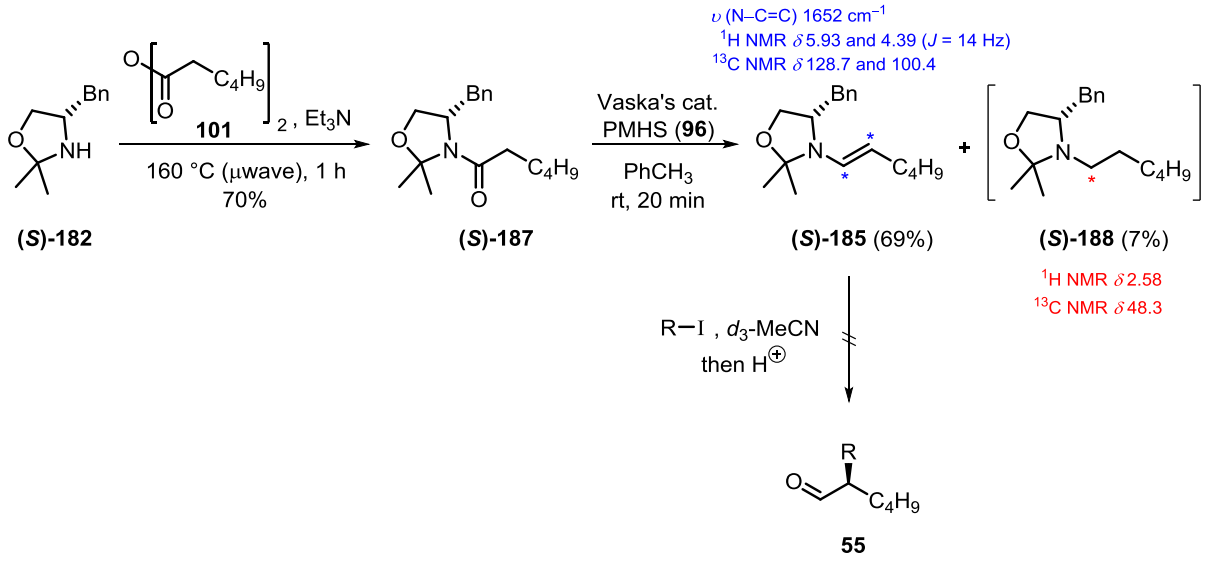
Enantiopure chiral oxazolidine **(*S*)-182** was synthesised according to literature conditions in excellent yield from L-phenylalaninol (**(*S*)-183**) (Scheme 3.2).[103] For consistency with our earlier studies, we wished to prepare the corresponding enamine of hexanal, enamine **185** (Scheme 3.2). Given the success of the modified Wickberg procedure for formation of tropane enamine **92**, we hoped these conditions could facilitate the synthesis of oxazolidine derived enamine **(*S*)-185**. Unfortunately, while formamide **(*S*)-184** could be prepared in excellent yield using Blum and Nyberg's conditions,[87] attempted addition of pentylmagnesium chloride failed to give enamine **(*S*)-185**, instead returning a complex mixture of which formamide **(*S*)-184** was the major constituent (Scheme 3.2). This result suggested that a significant amount of formamide **(*S*)-184** had not reacted with the Grignard reagent, likely due to decreased electrophilicity of the amide carbonyl (resulting from electron donation by the ether present) compared with tropane formamide **152**. Owing to the complexity of the returned mixture, the side-products could not be identified by NMR analysis. However, it is possible they result from Grignard addition to the hemiaminal ether centre of the oxazolidine (i.e. formamido ether **(*S*)-186**).

SCHEME 3.2



Unsurprisingly, given what Bray had observed (see Ch. 2, pp. 24–25), attempted formation of enamine **(*S*)-185** using Hodgson epoxide methodology also proved unsuccessful (Scheme 3.2). As a final resort, we applied the chemistry of Nagashima *et al.*,[70] and were pleased to generate the desired enamine **(*S*)-185** in good yield (albeit contaminated with amine **(*S*)-188**) from amide **(*S*)-187**, the latter being prepared using Hulme's protocol[72] (Scheme 3.3). It should be noted that distillation of the enamine was required to obtain a pure sample to test alkylation. The ^{1}H NMR spectrum for enamine **(*S*)-185** showed separation between the olefinic signals of δ 1.54 ppm, indicative of enamine double bond character (see earlier discussion, Ch. 1, p. 13).

SCHEME 3.3



Disappointingly, efforts to alkylate enamine **(*S*)-185** with a range of simple alkyl iodides (R = Me, Et and $C_{10}H_{21}$, under standard alkylation conditions for each electrophile,[39] Scheme 3.3) proved unrewarding. In all reactions, the iminium proton resonance, indicative of successful alkylation, was not observed by *in situ* ^{1}H and ^{13}C NMR monitoring. However, loss of the olefinic resonances of enamine **(*S*)-185** signified that the enamine had indeed reacted. Given the multitude of by-products observed by crude NMR, it is probable that ring-chain

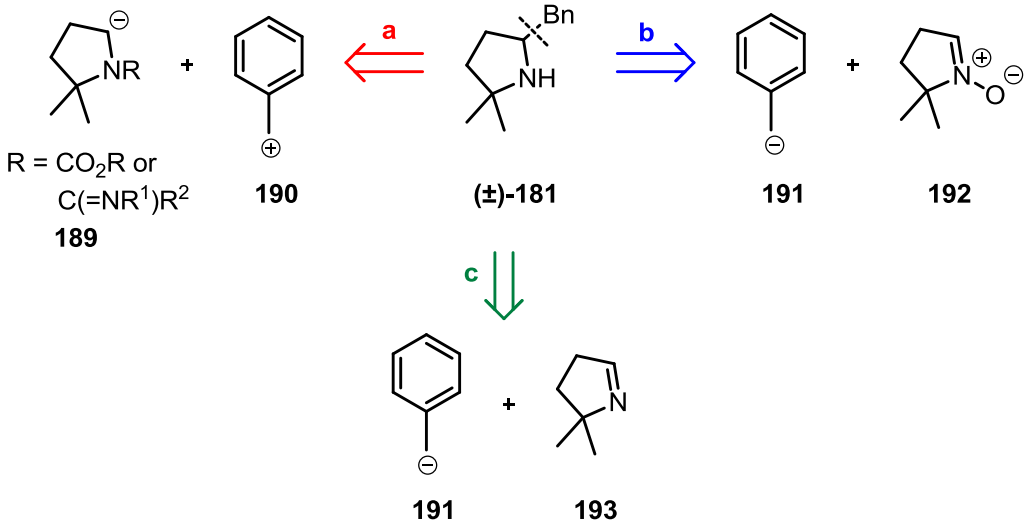
tautomerisation of the oxazolidine creates problems for exclusive *C*-alkylation of enamine **(*S*)-185**. In light of these issues, we decided to proceed with the synthesis of pyrrolidine **181** (Figure 3.1).

3.3 Racemic Synthesis of Pyrrolidine 181

3.3.1 *Retrosynthetic Analysis*

Before committing to an asymmetric synthesis of pyrrolidine **181**, we wished to examine the alkylation profile of an enamine derived from the racemic auxiliary. Retrosynthetic analysis and literature precedent suggested one of three routes could provide an expedient strategy to pyrrolidine **(±)-181** (Scheme 3.4).

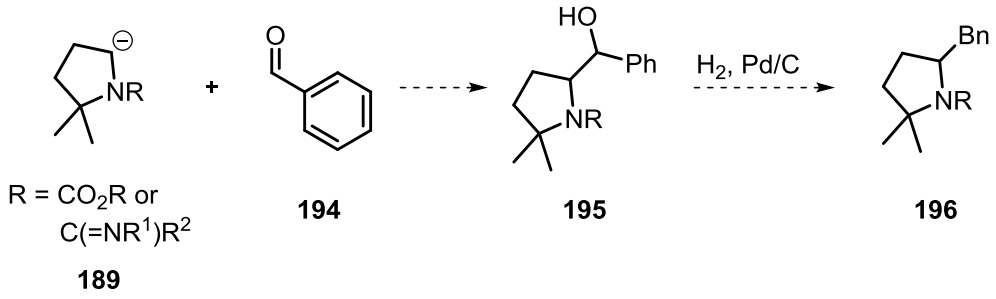
SCHEME 3.4



The first route envisaged (Scheme 3.4a) would involve metallation of an appropriately protected 2,2-dimethyl pyrrolidine to give α-aminoorganometallic **189**, which should then undergo substitution with a suitable electrophile **190**. A recognised limitation of this approach is the tendency for single electron transfer (SET) processes to interfere and diminish

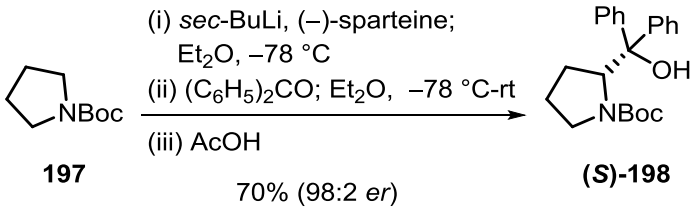
efficiency in reactions between α-aminoorganometallics and alkyl halides, thus benzyl halides should not be used.[104] However, for our purposes we believed this problem could possibly be avoided by reaction of an α-aminoorganometallic **189** with benzaldehyde (**194**), which by hydrogenolysis of the product secondary alcohol **195** should give protected pyrrolidine **196** (Scheme 3.5).

SCHEME 3.5



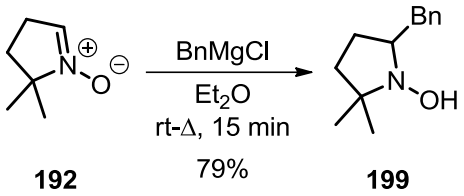
An attractive feature of this approach was the potential to utilise the methodology of Beak and Kerrick[105] and incorporate asymmetry by asymmetric deprotonation (Scheme 3.6).

SCHEME 3.6



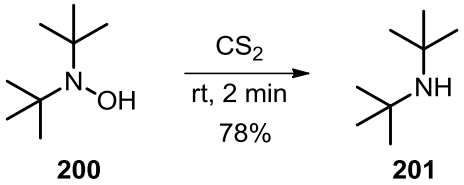
In contrast to the first approach, by reversing the polarity of the disconnection, we considered addition to 5,5-dimethyl-1-pyrroline-*N*-oxide (**192**, DMPO) by a benzyl organometallic **191** could be used to prepare pyrrolidine **(±)-181** (Scheme 3.4b). Indeed, Black and Bosacci have previously reported addition of benzylmagnesium chloride to commercially available DMPO (**192**) in good yield (Scheme 3.7).[106]

SCHEME 3.7



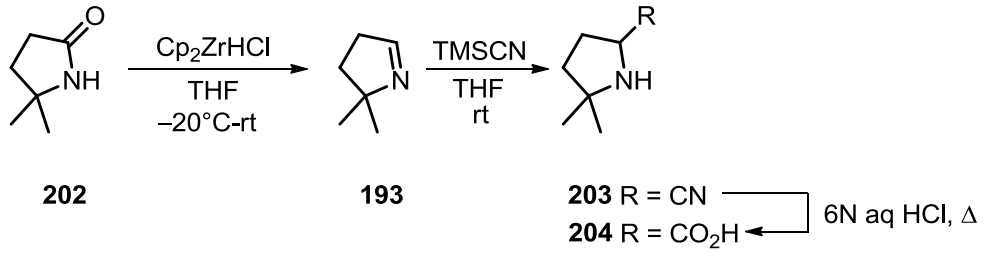
Several strategies exist for deoxygenation of *N*,*N*-disubstituted hydroxylamines: typical reagents used include Zn / HCl,[107] H_2 / Pd,[108] Raney Ni,[109] aq $TiCl_3$,[110] Zn / $Cu(OAc)_2$ / AcOH,[111] Ni boride[112] and In.[113] We were particularly attracted to the work of Schwartz *et al.*, who have described a synthetically mild and practically straightforward method for reduction of sterically hindered *N*,*N*-disubstituted hydroxylamines to secondary amines mediated by CS_2 (Scheme 3.8).[114] For example, reaction between CS_2 and hydroxylamine **200** in CS_2 was rapid and gave amine **201**, by simple evaporation of volatiles under reduced pressure, without the need for further purification.

SCHEME 3.8



Our final retrosynthetic route comprised addition of a benzyl organometallic **191** to imine **193** to give pyrrolidine **(±)-181** (Scheme 3.4c). Ganem and Xia have shown that lactam **202** undergoes reduction to imine **193** in the presence of Cp_2ZrHCl (Schwartz's reagent; Scheme 3.9).[115] Subsequent cyanation, conveniently in the same pot, furnished nitrile **203**, which in this case was hydrolysed to give α-amino acid **204** in reasonable yield (52% over 3 steps).

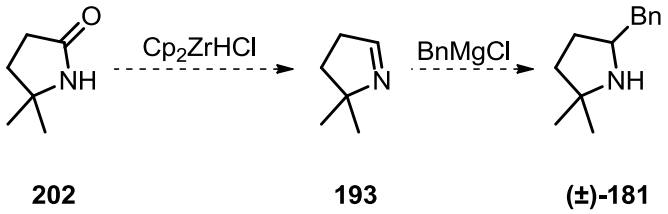
SCHEME 3.9



3.3.2 *Attempted Synthesis of Pyrrolidine (±)-181 Using Retrosynthetic Approach C*

Given the apparent synthetic ease (compared to the alternative methods described) of our projected strategy involving imine addition (Scheme 3.4c), we decided to examine this first. The envisaged approach required preparation of lactam **202**, which should undergo reduction to the imine, with benzylmagnesium chloride then being a suitable organometallic for the addition step (Scheme 3.10).

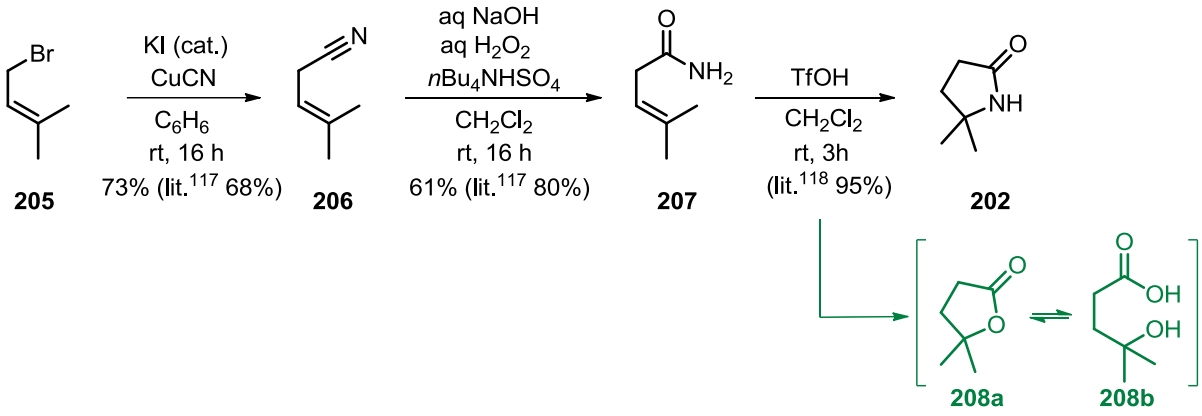
SCHEME 3.10



Attempted preparation of lactam **202** employed a 3-step sequence using literature conditions (Scheme 3.11).[116–118] Finkelstein-mediated nucleophilic substitution of prenyl bromide **205** with copper(I) cyanide gave nitrile **206**, in slightly improved yield compared with the literature. Hydrolysis of nitrile **206** provided *β*,γ-ene amide **207** in modest yield, possibly attributable to the age of the peroxide used. Cyclisation of *β*,γ-ene amide **207** to lactam **202**, facilitated by activation of the double bond with triflic acid, appeared to proceed in excellent yield (quant recovery, based on lactam **202** product). However, physical and spectral data

[white solid, mp 89–91 °C [lit.[119] for lactam **202** 42–43 °C]; IR (neat) (cm^{-1}) 3251brm, 2971m, 1759m, 1540s, 1380m, 1254m, 1150s, 911m; ^{1}H NMR (400 MHz) δ 3.01 (br s, 1H), 2.96 (t, 2H, J = 8 Hz), 1.96 (t, 2H, J = 8 Hz), 1.26 (s, 6H); ^{13}C NMR (101 MHz) δ 179.2, 70.3, 40.5, 33.9, 29.4; m/z (ESI^+) 114.2 ($M + H^+$, 11); HRMS *m/z* (M^+) found 113.0840, $C_6H_{11}NO$ requires 113.0841] are inconsistent with data reported in the literature for lactam **202**.[120] The recorded ^{1}H and ^{13}C NMR shifts also do not match those of the obvious by-product, lactone **208a** (Scheme 3.11).[121] Specifically, the ^{13}C NMR spectrum of the reaction product shows a quaternary carbon resonance at δ 70.3 ppm, which lies in-between those shifts reported for the quaternary carbon α- to N for lactam **202** (δ 56.8 ppm), and the carbon α- to O for lactone **208a** (δ 84.6 ppm). Furthermore, the ^{1}H NMR spectrum shows a methylene group lying downfield (at δ 2.96 ppm), compared to corresponding methylene resonances for lactone **208a** (δ 2.62 ppm) and lactam **202** (δ 2.42 ppm). Unfortunately, mass spectrometry provided ambiguous data. While the mass of lactam **202** was found, the mass corresponding to lactone **208a** was also identified (HRMS *m/z* (M^+) found 114.0679, $C_6H_{10}O_2$ (**208a**) requires 114.0681). Interestingly, the low resolution mass spectrum showed a base peak at *m/z* 149, which corresponds to the mass of the ammonium salt of ring-opened hydroxy acid **208b** (Scheme 3.11). From the IR spectrum, a characteristic broad stretch at υ 3251 cm^{-1} is indicative of a free NH or OH being present, ruling out lactone **208a**. Additionally, a medium absorption at υ 1750 cm^{-1} suggests that an amide is not present. The collective data points to ring-opened hydroxy acid **208b**, though this is a tentative assignment, given that the carboxylic O–H resonance was not observed by NMR, and HRMS did not identify this product. While it is recognised that the lactone is the more stable form, the data suggests that, under the strongly acidic conditions, the lactone formed, then hydrolysed. Attempted repeat reactions returned similar results, contrary to the findings of Marson and Fallah.

SCHEME 3.11



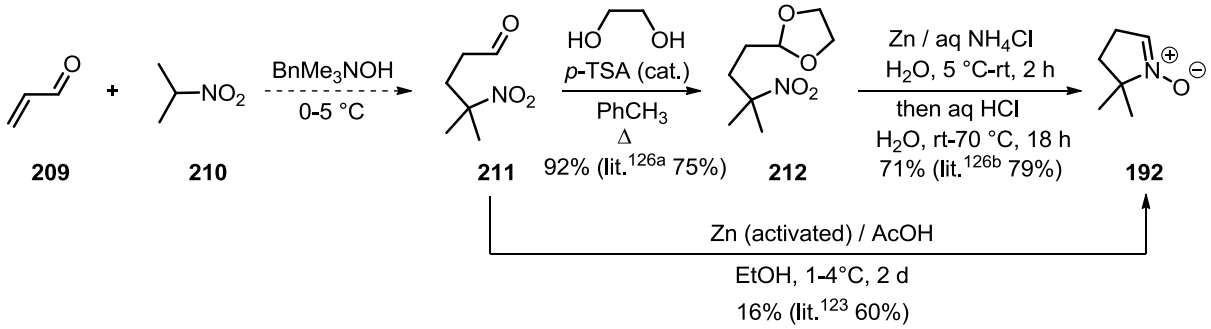
Given the unknown identity of the by-product from attempted cyclisation of **207**, the projected expense of Schwartz reagent (which is used in stoichiometric excess, and for which the synthetic precursor zirconocene dichloride is also costly) and the lack of literature precedent for Grignard additions into pyrrolidine imines, we decided to abandon this approach.

3.3.3 *Synthesis of Pyrrolidine* ***(±)-181*** *Using Retrosynthetic Approach B*

Assessment of the two alternative retrosynthetic approaches (Scheme 3.4a / b) showed stronger precedent for successful formation of pyrrolidine **(±)-181** using route B. One of the reasons for initially avoiding this sequence was that the requisite nitrone, DMPO (**192**), is prohibitively expensive (~£30 $mmol^{-1}$, Sigma Aldrich). DMPO (**192**) can be prepared by a variety of methods, which commonly originate from nitroaldehyde **211** (Scheme 3.12). Given its structural simplicity, nitroaldehyde **211** is also relatively expensive (~£2 $mmol^{-1}$, TCI). However, while nitroaldehyde **211** can be accessed through Michael addition of acrolein (**209**) with 2-nitropropane (**210**), violent explosions have been observed during its synthesis,[122] another reason for originally avoiding this strategy. Given the associated hazards

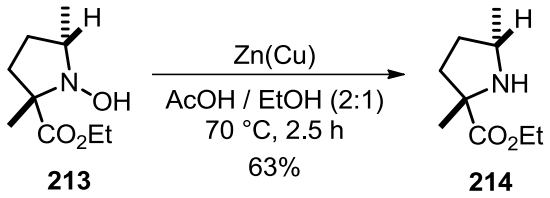
for preparation of nitroaldehyde **211**, we decided to source this commercially. Janzen *et al*. have demonstrated a one-step procedure for cyclisation of nitroaldehyde **211** to DMPO (**192**).[123] The literature procedure prescribes the use of activated Zn to effect the transformation, but unfortunately no instruction was given for the activation procedure. Methods of Zn activation have been well summarised.[124] In the present case, a standard acidic activation was applied to Zn dust directly before the reaction was carried out.[125] Unfortunately, attempted application of these conditions returned a crude mixture of DMPO (**192**) and nitroaldehyde **211** (Scheme 3.12). Purification by distillation isolated DMPO (**192**) in a mere 16% yield. Given the uncertainty surrounding Zn activation we settled with a substitute three-step procedure, [122b,126] which gave DMPO (**192**) in reasonable overall yield (Scheme 3.12).

SCHEME 3.12



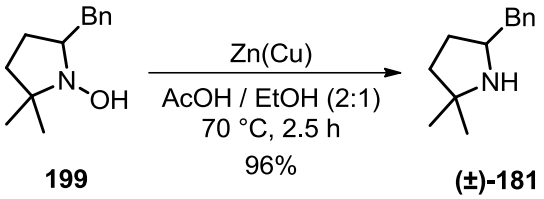
Treatment of DMPO (**192**) with benzylmagnesium chloride according to the method of Black and Bosacci[106] gave the desired hydroxylamine **199** in excellent yield (99%, Scheme 3.7). Deoxygenation by the procedure of Schwartz *et al*.[114] was attempted, but after stirring hydroxylamine **199** in CS_2 for 30 min at rt, removal of the reaction volatiles simply returned starting material (quant). Duvall *et al*. have previously reduced a pyrrolidinol with a similar substitution pattern to hydroxylamine **199** mediated by Zn(Cu) (Scheme 3.13).[127]

SCHEME 3.13



Pleasingly, using the conditions of Duval *et al*., hydroxylamine **199** was successfully reduced to the desired pyrrolidine **(±)-181** in excellent yield (Scheme 3.14).

SCHEME 3.14

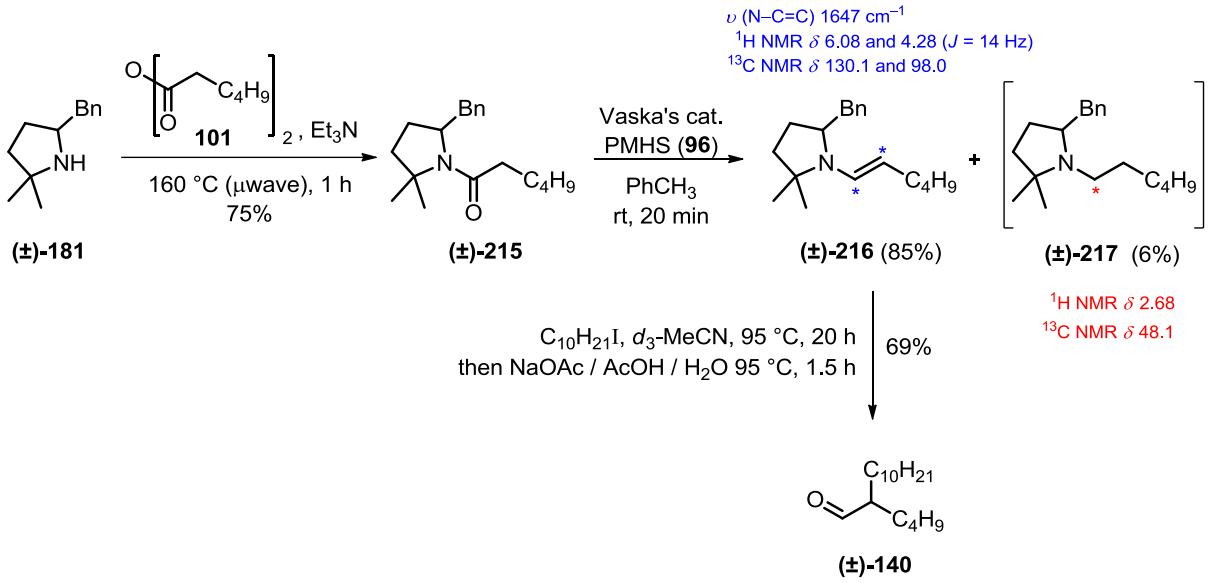


3.4 Enamine Synthesis from Pyrrolidine (±)-181 and Alkylation

With pyrrolidine **(±)-181** in hand, we set about testing the alkylation profile of this auxilliary. Again, for consistency, we wished to make the corresponding enamine of hexanal, enamine **(±)-216** (Scheme 3.15). Given Nagashima's protocol had generated enamine **(*S*)-185** in good yield (p. 57), we decided to examine the feasibility of using this chemistry for formation of enamine **(±)-216**. Pleasingly, enamine **(±)-216** synthesis proceeded in good yield from the corresponding amide **(±)-215**, which was prepared according to Hulme's method (Scheme 3.15). It should be noted that, as with oxazolidine derived enamine **(*S*)-185,** distillation was required to purify enamine **(±)-216**. Some (~6%) of the over-reduction product, amine **(±)-217**, was observed as with previous Nagashima reactions performed, but the enamine following distillation was deemed sufficiently clean to test alkylation. The ^{1}H NMR spectrum for enamine **(±)-216** showed separation between the olefinic signals ($\Delta\delta$) of 1.80 ppm,

suggestive of a strong *C*-alkylation profile (see earlier discussion, Ch. 1, p. 13). It was decided to examine alkylation using decyl iodide given the substantial difficulty in handling 2-ethylhexanal (see footnote, Ch. 2, p. 39). Pleasingly, alkylation with decyl iodide, which represents one of the more challenging, less reactive alkyl halides, given the length of the alkyl chain, furnished the desired aldehyde in reasonable yield (69%, uncorrected for amine **(±)-217**; Scheme 3.15), consistent with TriMP-derived enamine **54a** (see Ch. 1, p. 14).

SCHEME 3.15

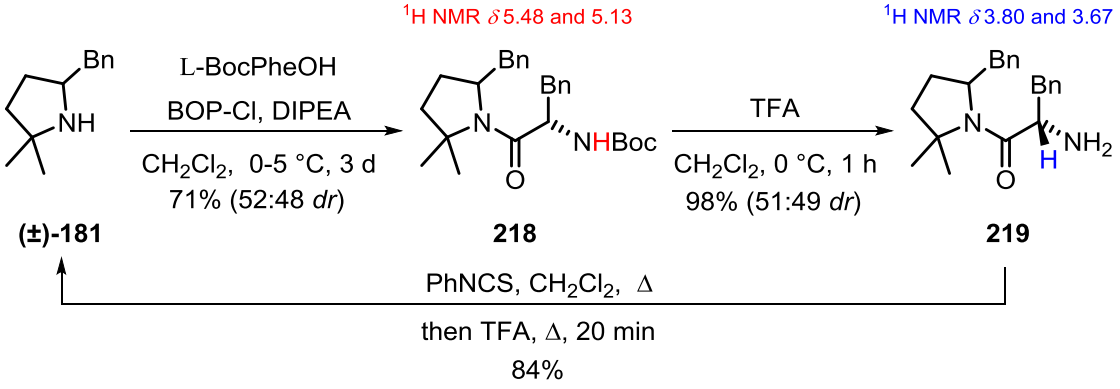


3.5 Resolution of Pyrrolidine (±)-181

Having established racemic alkylation with enamine **(±)-216**, work began to resolve pyrrolidine **(±)-181** to allow examination of the asymmetric profile of this auxiliary. We believed that a similar strategy to that used for resolution of tropane **57** (see earlier discussion, Ch. 2, pp. 42–43) could be adopted for accessing enantiopure pyrrolidine **181**.[90] In the event, pyrrolidine **(±)-181** was coupled with *N*-Boc-L-phenylalanine, which gave an (anticipated) inseparable mixture of Boc-protected α-amino-amides **218** in good yield (71%, Scheme 3.16). Deprotection occurred smoothly, giving an excellent yield of α-amino amides **219** (Scheme

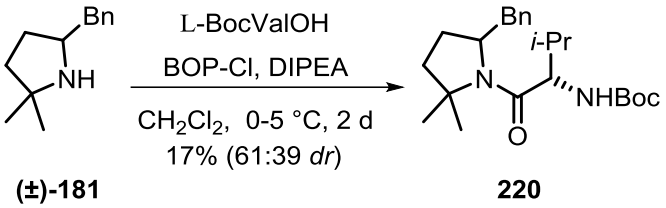
3.16). Unfortunately, after investigation of several different eluents, this diastereomeric mixture was deemed inseparable by chromatography. Edman degradation was used to retrieve the valuable pyrrolidine **(±)-181** (Scheme 3.16).

SCHEME 3.16



After consideration of several amino acids readily available in our laboratory, we next chose to examine possible resolution using *N*-Boc-L-valine. It was believed that the more hindered nature of the α-substitent (i.e. isopropyl versus benzyl) could help chromatographic discrimination of diastereomers derived from this amino acid compared with *N*-Boc-L-phenylalanine. Gratifyingly, chromatography following amide coupling of pyrrolidine **(±)-181** and *N*-Boc-L-valine (Scheme 3.17) on test scale (0.5 mmol of limiting reagent) showed that Boc protected α-amino-amides **220** could be separated. Unfortunately, the diastereomers were isolated in low yield (16%). It was considered the low yield could be due to scale; however, repeating the coupling experiment on a larger scale (6 mmol of limiting reagent) confirmed that the reaction was low yielding. Extending the reaction time also failed to improve the yield; after 4 d (cf. 2 d previously) only a marginal improvement in yield was observed (19% {78% brsm} cf. 16%).

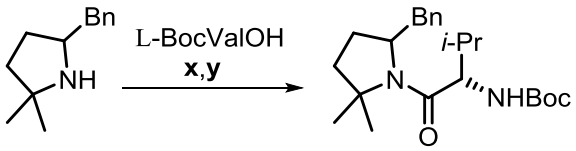
SCHEME 3.17



(±)-181 **220**

In response to the poor yields obtained using the conditions of Thompson *et al.*, we investigated alternative coupling reagents and conditions (Table 3.1).

TABLE 3.1



(±)-181 **220**

Entry	Reagents **x**/**y**	Equivalents **x**/**y**	Solvent	Reaction Time (h)	Reaction Temperature	Yield (%)
1	BOP-Cl/DIPEA	1.1/2.2	CH_2Cl_2	48	0-4 °C	17
2	BOP-Cl/DIPEA	1.1/2.2	CH_2Cl_2	96	0-4 °C	19
3	BOP-Cl/DIPEA	1.1/2.2	CH_2Cl_2	16	rt	34
4	BOP-Cl/DIPEA	1.1/2.2	CH_2Cl_2	64	rt	53
5	EDC/HOBT	1.1/1.1	CH_2Cl_2	96	rt	[a]
6	CDMT/NMM	1.1/1.5	CH_3CN	16	rt	55
7	HBTU/NEt_3	1.2/2	CH_2Cl_2	16	rt	92
8	HBTU/NEt_3	1.2/2	CH_2Cl_2	20	rt	73

[a] No product isolated (42% of SM returned)

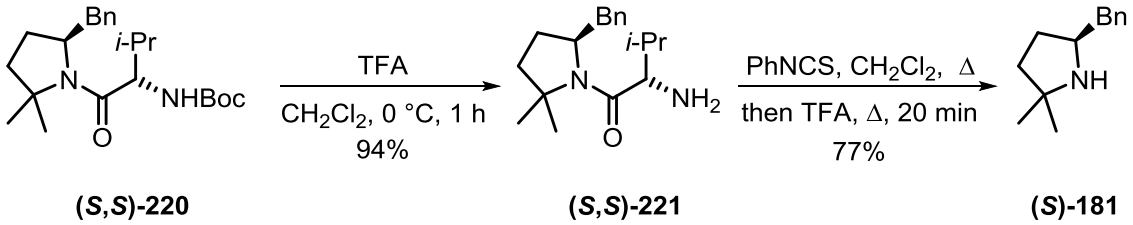
The low temperature conditions used by Thompson *et al.*[90] were most likely prescribed to avoid loss of configurational integrity (i.e. *via* formation of the oxazolone[128]) at the remotely disposed stereocentre α- to the carbamate. However, given the hindered nature of pyrrolidine **(±)-181**, we believed the propensity for racemisation would be small. Thus, couplings using a combination of BOP-Cl and DIPEA at rt for varying lengths of time were attempted (Entries 3 and 4, Table 3.1). This showed some improvement in the yield compared with analogous

reactions performed at 0 °C (Entries 1 and 2, Table 3.1). Given that the yield had only marginally improved with longer reaction times (compare Entries 3 and 4, Table 3.1), we decided to investigate some alternative coupling reagents. While thought unlikely, it was not desirable to leave the reaction mixture at ambient temperature for extensive periods, given the 'possiblity' of racemisation.

Driven by what was available in our laboratory, attempted amide coupling with EDC and HOBT at room temperature proved unrewarding (Entry 5, Table 3.1). After 4 d, TLC analysis showed that no reaction had occurred. This was confirmed by examination of the crude ^{1}H and ^{13}C NMR spectra, which simply showed that starting materials had been returned. A combination of CDMT and NMM generated a modest yield of product, in reasonable time, following conditions reported by Garrett *et al.*[82] (Entry 6, Table 3.1). The uronium salt HATU is known to undergo facile amide coupling with pyrrolidine.[129] Applying a combination of the structurally related HBTU and Et_3N gave a major improvement in yield compared with the other reagents tested (92%, Entry 7, Table 3.1). As such, these coupling reagents were adopted for scale-up (16 mmol of limiting reagent), which returned a good, albeit lower, yield (73%, Entry 8, Table 3.1) of Boc-protected α-amino-amides **220**.

X-ray diffraction of a crystal (grown by slow evaporation from EtOAc) of the lower R_f diastereomer of Boc-protected α-amino-amides **220** detetermined the absolute configuration to be (*R*,*S*).[91] Deprotection of *N*-Boc α-amino-amide **(*S*,*S*)-220**, the upper R_f diastereomer, followed by Edman degradation of the resulting α-amino-amide **(*S*,*S*)-221**, gave pyrrolidine **(*S*)-181** in good yield (72% over 2 steps, Scheme 3.18).

SCHEME 3.18

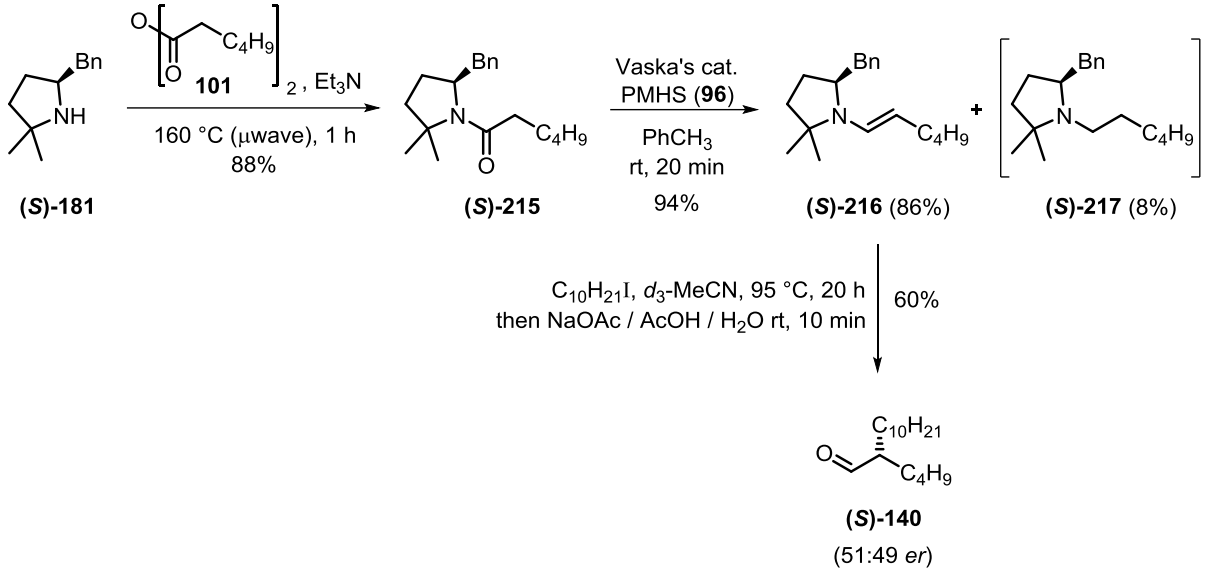


(*S*,*S*)-220 **(*S*,*S*)-221** **(*S*)-181**

3.6 Enamine Synthesis from Pyrrolidine (*S*)-181 and Alkylation

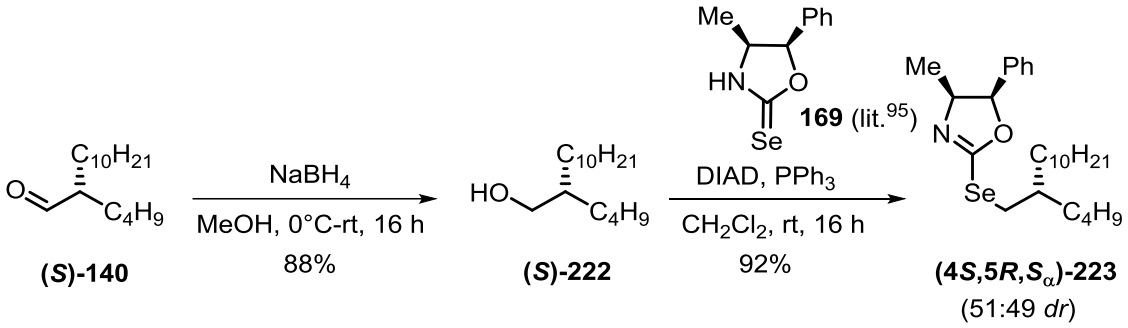
Chiral pyrrolidine **(*S*)-181** was acylated with hexanoic anhydride (**101**), which gave amide **(*S*)-215** in excellent yield (Scheme 3.19). HPLC analysis of amide **215** confirmed the enantiopurity of the auxiliary.[91] Enamine **(*S*)-216** was prepared from amide **(*S*)-215** using the established reduction-dehydration chemistry (Scheme 3.19). Enamine **(*S*)-216** was then reacted with decyl iodide using the same conditions as Kaka, except with d_3-MeCN for *in situ* NMR analysis.[16] As with alkylation of chiral enamines **(1*S*,5*R*)-92** and **(1*R*,5*S*)-92**, hydrolysis of the product iminum was performed at rt for a short period, so as to avoid possible post-reaction epimerisation of the stereogenic centre. Pleasingly, despite the milder hydrolysis conditions, the yield for this reaction was comparable to that previously obtained with enamine **(±)-216** (60% cf. 69%). It is also noteworthy that this was a significant improvement on the yield (34%) obtained by Kaka for asymmetric decylation with chiral piperidine derived enamine **54b** (Ch. 1, p. 13).

SCHEME 3.19



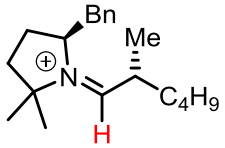
While enamine **(*S*)-216** had shown promise from a productivity point of view, disappointingly the *er* was determined, by ^{77}Se NMR analysis of selenium adduct **(4*S*,5*R*,*S*$_\alpha$)-223** (Scheme 3.20), to be essentially racemic.[91]

SCHEME 3.20

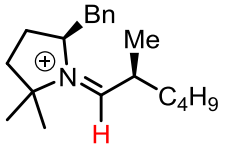


We considered that the high temperature (95 °C) used for alkylation with decyl iodide could have reduced asymmetric induction. In order to rule out this possibility, it was decided to react enamine **(*S*)-216** with an alkyl halide at lower temperature, and see if there was any significant change in the *er* obtained. From alkylations performed by Bray[39] and Kaka,[16] decyl iodide would not be expected to react at a reasonable rate at rt. Methylation of chiral

piperidine enamines **54** with MeI proceeded at a much more moderate temperature, 40 °C, overnight. Thus, despite the obvious volatility issue of the expected product, alkylation of enamine **(*S*)-216** with MeI was examined (Scheme 3.21). Hoping that alkylation could be achieved without external heating, reaction between enamine **(*S*)-216** and MeI in d_3-MeCN was closely monitored by ^{1}H NMR at rt for 1 h; however, no change was observed. Raising the temperature to 40 °C and reacting for 16 h showed complete conversion by NMR. Unfortunately, this also showed two doublet resonances of approximately equal integration in the iminum region of the spectrum.[91] These signals are attributed to the diastereomeric iminium ions **(*S*,*R*)-224** and **(*S*,*S*)-224** formed following methylation of enamine **(*S*)-216** with no asymmetric bias. While this result was disappointing, it affirmed that no enantiodegradation was occurring during manipulation of the aldehyde post-reaction.



(*S*,*R*)-224



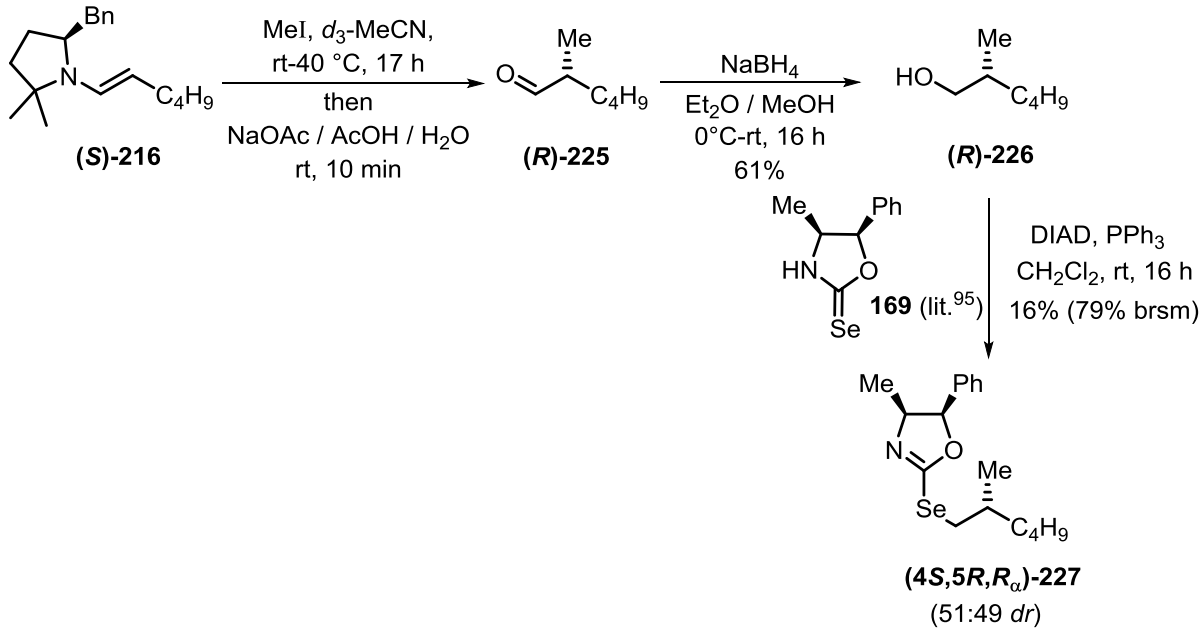
(*S*,*S*)-224

FIGURE 3.2

Following the mild hydrolysis procedure, it was decided (given the volatility of 2-methylhexanal (**225**)) to reduce an aliquot of the organic extracts containing the aldehyde directly to the alcohol, which is easier to handle. The ethereal extracts that were directly reduced afforded a 61% yield of alcohol **(*R*)-226**. This would suggest a comparable yield for methylation of enamine **(*S*)-216**, assuming quantitative reduction of the starting aldehyde. The yield of alkylation is likely to have been higher because, in practice, such reductions do not run quantitatively, and this yield is uncorrected for amine **(*S*)-217**. The isolated alcohol **(*R*)-226** was subjected to the usual Mitsunobu conditions for installation of the selenone auxiliary (Scheme 3.21). Despite leaving this reaction for a prolonged period (16 h cf. 3 h {see

conditions of Kaka[16]}), it gave selenium adduct **(4*S*,5*R*,*R*$_\alpha$)-227** in low yield. It was noted that another Hodgson group member had also found the batch of DIAD reagent used in this case to be unproductive for his work. Nevertheless, a sufficient quantity of selenide **(4*S*,5*R*,*R*$_\alpha$)-227** was generated to examine the *er*. Unfortunately, ^{77}Se NMR analysis confirmed that alkylation had indeed proceeded with essentially no facial preference.[91]

SCHEME 3.21



3.7 Possible Explanation for Low *er*s

The proposed origins of asymmetric induction for reactions employing MacMillan's imidazolidinone **39**, which bears close structural resemblance to pyrrolidine **181**, may provide some rationalization for the low *er*s attained. As previously mentioned (p. 55), there has been extensive enquiry to determine the key steric interactions of intermediates derived from imidazolidinone **39**. For our needs, the current literature is somewhat limited, in that studies performed mainly are focussed in the area of iminium catalysis. The following discussion is an extrapolation of those arguments to the present enamine system.

The classic (and logical) organic chemist's interpretation of how MacMillan's catalyst induces asymmetry is that the benzyl arm of **39** orientates itself over the π-system of the iminium ion (or enamine) to gain a favourable π-stacking interaction (Conformer **A**, Figure 3.3).[22] Computational analyses by Houk *et al*. dispute this theory.[102a] In Houk's study, the most stable iminium ion (e.g. for $R^1 = R^2 = R^3 = Me$) conformation is suggested to be that which adopts an orientation of the benzyl arm over the 5-membered ring, stabilised by a favourable C–H-π interaction between the *cis*-methyl substituent and the aromatic ring (Conformer **B**, Figure 3.3). Later studies by Tominkson[102d] and Seebach[102c,e–f] also support this. While conformer **B** has been calculated as the lowest energy conformer, it should be recognised that the calculated barrier to conformer **A** is low (1.3 kJ mol^{-1} for $R^1 = R^2 = R^3 = Me$, Figure 3.3), and thus can be easily overcome. Indeed, in Seebach's most recent study in this area, it is suggested that the benzyl group is, in fact, free to rotate at ambient temperature, leading to a so-called 'windshield-wiper' effect.[102f] Interestingly, in Houk's original study conformer **C** was found to be the least stable conformer (14.7 kJ mol^{-1} for $R^1 = R^2 = R^3 = Me$, Figure 3.3). This was attributed to an unfavourable 1,5 steric interaction between the oxygen of the amide carbonyl and the *ipso* carbon of the phenyl ring. In the case of enamine **216**, no carbonyl is present, and as such this could substantially lower the energy of this conformer. If, in fact, this conformation was dominant for alkylation of enamine **216**, it provides a viable explanation for the poor *er*s obtained, since the steric impediment (i.e. benzyl group) would be substantially remote from the *β*-carbon of an enamine adopting this conformation.

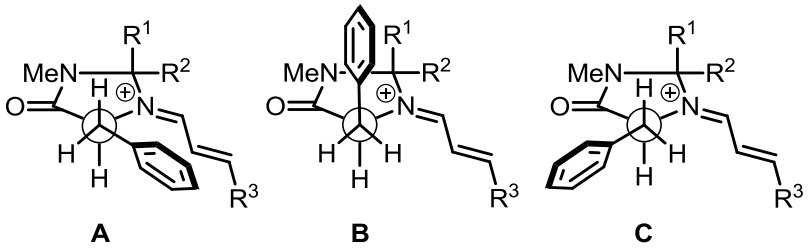


FIGURE 3.3 (Adapted from: Seebach, D. *et al*.[102f])

^{1}H NMR studies by Seebach *et al.*[102c,e] and Tomkinson *et al.*[102d] highlight an additional point of interest. Specifically, ^{1}H NMR chemical shift differences ($\Delta\delta$) between the resonances attributed to the geminal methyl substituents in imidazolidinone **39** salts and the corresponding signals in the spectra of iminium ions derived from **39** were found to be consistent with shielding of one of the *geminal* methyl substituents by a benzene ring, suggesting a large contribution from conformer **B** (Figure 3.3). For example, the diastereotopic methyl group resonances for imidazolidinone **39** have almost the same chemical shift (δ ~ 1.6 ppm), whereas for the corresponding iminium salt (R^1 = R^2 = Me and R^3 = Ph, Figure 3.3) one methyl resonance is shifted significantly upfield ($\Delta\delta$ ~ 0.8 ppm), indicative of a shielding effect.[102e] Interestingly, comparison of ^{1}H NMR spectra recorded for pyrrolidine **181** and enamine **216** determined only a slight shift deviation of a single methyl for enamine **216** ($\Delta\delta$ = 0.1 ppm), suggesting conformer **B** (Figure 3.3) is not a significant contributor. If conformer **A**'s contribution is seen as minimal on the basis of the low *er*s obtained, then this result would be consistent with the postulate that conformer **C** (Figure 3.3) dominates for pyrrolidine-derived enamine **216**.

3.8 Chapter Summary

Work surrounding the synthesis and asymmetric alkylation of an oxazolidine **182-** and a pyrrolidine **181**-derived enamine has been discussed. Oxazolidine **(*S*)-182** was prepared in a single step by simple condensation of L-phenylalaninol **(*S*)-183** and acetone. Pyrrolidine **(±)-181** was constructed by addition of benzylmagnesium chloride to DMPO (**192**) followed by dehydroxylation. Enantiopure pyrrolidine **(*S*)-181** was accessed in a similar manner as that used to resolve tropane **(±)-57**, although it was necessary to exchange the resolving agent to L-BOC valine in this case, to achieve separation of the derived diastereomers. Nagashima's

chemistry gave the desired enamine from amides derived from both auxiliaries in reasonable yield, though again some overreduction was observed. Alkylation of oxazolidine-based enamine **(*S*)-185** proved unsuccessful. Alkylation of pyrrolidine-derived enamine **(*S*)-216** provided the α-alkyl aldehydes in reasonable yield but proved ineffective for inducing asymmetry, returning essentially racemic products. It was confirmed by *in situ* NMR analysis that no degradation of *er* was occuring through integration of resonances attributed to resolved diastereomeric iminium ions. The lack of stereoselectivity has been rationalised based on observations from in-depth literature studies of MacMillan's imidazolidinone **39**, which is structurally similar to pyrrolidine **181**. Further insight is likely to be gained by computational analysis of the same kind as that performed for tropane- and homotropane-derived enamines **92** and **228**, respectively (see Ch. 2, pp. 49–50 and Ch. 4, p. 77–78).

4. A HOMOTROPANE AUXILIARY FOR ASYMMETRIC α-ALKYLATION

4.1 Design Principle

From the DFT studies performed on tropane-derived enamine **92*** (Figures 2.5 and 2.6, Ch. 2, pp. 49–50), it is clear that the presence of the embedded pyrrolidine places an undesired bias on the orientation of the exocyclic double bond. In response to this, we considered that formal expansion of the 2-carbon bridge of the tropane scaffold by a methylene group to generate two rings of equal size (homotropane {6,6}, cf. tropane {6,5}) could give improved *er*, since facial discrimination should now be solely dependent on the presence of the *gem*-dimethyl group on one ring. Comparison of the computed ground state conformations for tropane-derived (**GS1**) and homotropane-derived (**GS2**) enamines shows similar orientation of the common *N*-propenyl group (similar values of x and y, Figures 2.5 and 4.1). However, in contrast to **TS3** and **TS4** (Figure 2.6), the computed transition structures **TS5** and **TS6** for alkylation of homotropane-derived enamine **228*** [a truncated analogue of enamine **228** (Scheme 4.35; p. 105)] with EtI (Figure 4.2) show that the exocyclic C–N bond moves to being essentially equidistant from each piperidine ring of the homotropane ($x \approx y$).[91] Furthermore, the calculated energies of transition states **TS5−8** predicted significant improvement in *er* (85:15), with *Si*-face selectivity (with enamine (**1*S*,5*R*)-228**). Therefore, we decided to examine this homotropane system, which first required synthesis of the corresponding homotropane **229** (*vide infra*).

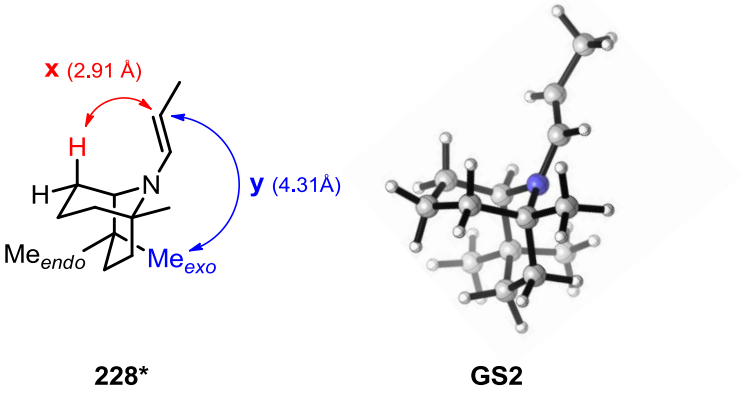


FIGURE 4.1. Computed Ground State Conformation for Enamine 228*

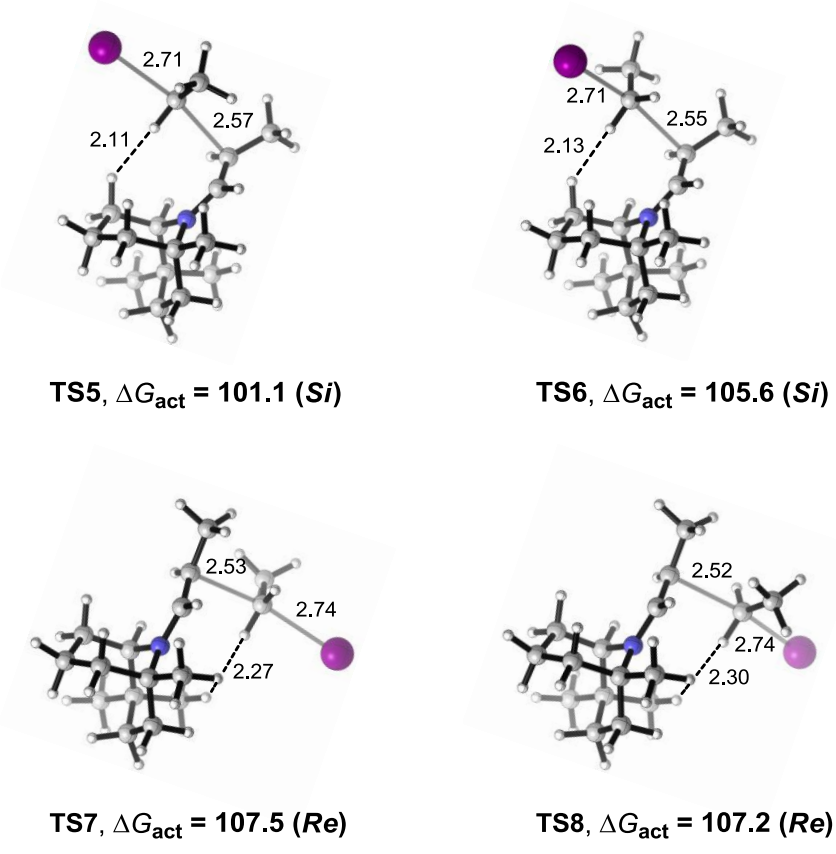


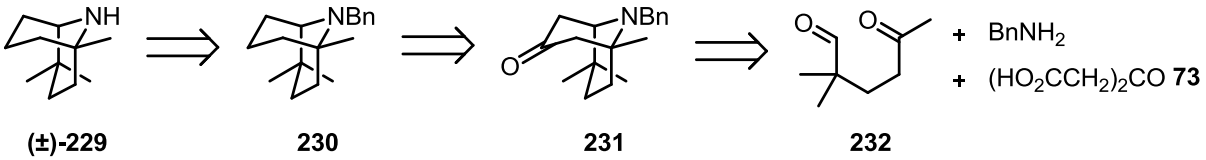
FIGURE 4.2. Computed TS Geometries for Reaction of Enamine 228* with EtI. B3LYP / 6-31G(d) Free Energies in kJ mol^{-1}; Selected Distances Shown in Å

4.2 Synthesis of Homotropane (±)-229

4.2.1 *Retrosynthetic Analysis*

For synthesis of the requisite auxiliary, homotropane **229**, we envisaged quick access to the racemate **(±)-229** [and then resolution (*vide supra*)] through a similar Robinson-Schöpf strategy to that used to prepare tropane **(±)-57** (Scheme 4.1).

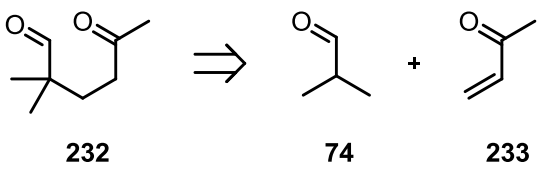
SCHEME 4.1



4.2.2 *Synthesis of Ketoaldehyde **232***

There are several methods described in the literature for the preparation of ketoaldehyde **232**: the majority involve synthesis of an enol equivalent of IBA (**74**), with subsequent 1,4-addition to methyl vinyl ketone (MVK, **233**), often activated by means of a Lewis acid (Scheme 4.2). More specifically, accompanying reaction partners to MVK (**233**) have included aza enolate,[130] enamine,[131] imine[132] and enol ether[133] derivatives of IBA (**74**), used with varying levels of success. More circuitous procedures have also been described by Duhamel[134] and by Baldwin.[135]

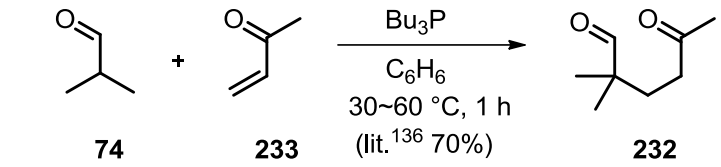
SCHEME 4.2



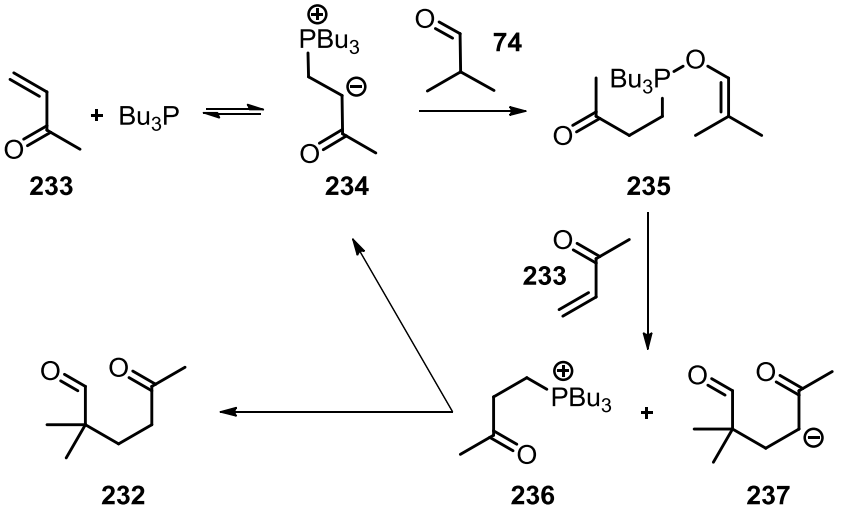
We were first attracted to the procedure of Miyakoshi *et al.*,[136] who have demonstrated an efficient synthesis of ketoaldehyde **232**, in a single step from IBA (**74**) and MVK (**233**)

catalysed by Bu_3P (Scheme 4.3). Interestingly, reaction of these reagents does not follow a Morita-Baylis-Hillman (MBH) reaction pathway. Rather, the proposed mechanism suggests zwitterion **234** undergoes preferential formation of phosphorane **235** (Scheme 4.3).[136] Presumably, the allylic alcohol is not formed, due to the notoriously slow rate associated with MBH reactions.[137]

SCHEME 4.3

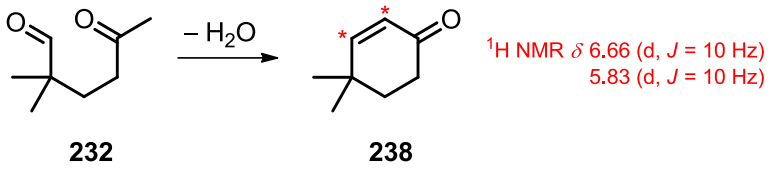


Proposed Mechanism:



Despite extensive investigation, in my hands, ketoaldehyde **232** could only be prepared in 20% yield using Miyakoshi's method. For reactions attempted on scale (0.24 mol of limiting reagent), self-aldolisation completely dominated (Scheme 4.4), and enone **238**[138] was the only identifiable product by crude ^1H NMR analysis.

SCHEME 4.4



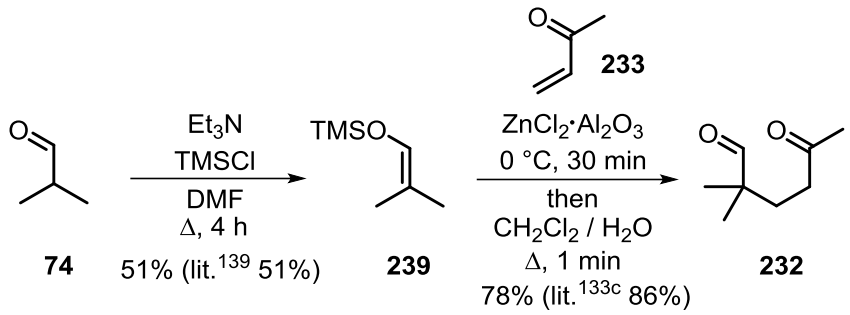
232 **238**

A notable peculiarity with Miyakoshi's procedure is the optimum reaction temperature, which is cited as a range (30~60 °C) rather than a definitive value. Investigation found the reaction to be highly exothermic. Addition of only a small quantity of catalyst to the aldehyde-enone mixture led to a rapid increase of the internal temperature (~120 °C). Furthermore, pre-cooling with an ice-bath did little to control the temperature of the reaction, following initiation with Bu_3P. The high temperature of the reaction inevitably promotes ring closure to generate enone **238**. Additionally, cyclisation is likely also facilitated by an associated Thorpe-Ingold effect from the *gem*-dimethyl group. Given that the reaction was considerably exothermic, it was considered that addition of the aldehyde-enone to Bu_3P (i.e. reversing the prescribed addition of Miyakoshi) could help control the temperature. However, while this did mitigate temperature regulation, which was kept at the midpoint of the range specified by Miyakoshi (45 °C), the major product was still determined by analysis of the crude ^{1}H NMR spectrum to be enone **238**. Given the complications discussed above, we looked to an alternative method for preparation of ketoaldehyde **232**.

Ranu *et al*. have reported a synthesis of ketoaldehyde **232** from reaction of silyl enol ether **239** with MVK (**233**), mediated by Al_2O_3 impregnated with $ZnCl_2$ (Scheme 4.5).[133b–c] In my hands, silyl enol ether **239** was prepared in consistent yield to that obtained by Conia and Girard.[139] On test scale (5 mmol of limiting reagent), synthesis of ketoaldehyde **232** was achieved in pleasing yield (78%) using Ranu's procedure. However, for large scale reactions

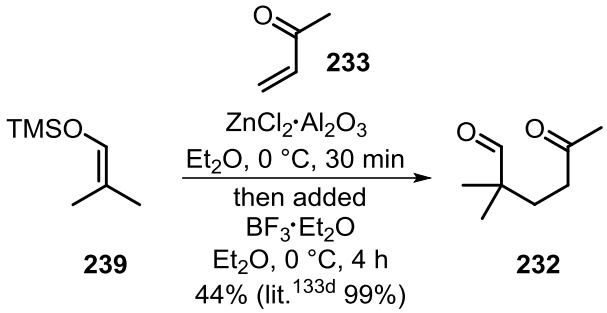
(0.1 mol), the solvent-free procedure and large quantities of $ZnCl_2 \cdot Al_2O_3$ required became severely limiting factors, causing poor mixing of the reagents, which resulted in much lower yields (16%).

SCHEME 4.5



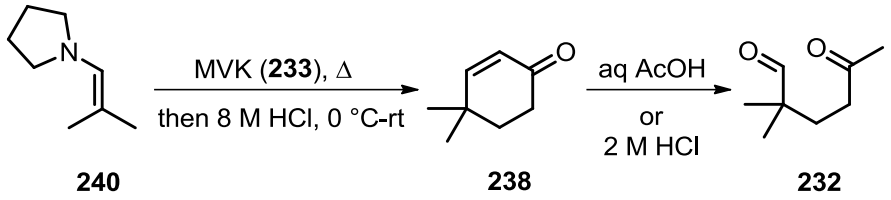
Application of a co-activator ($BF_3 \cdot Et_2O$) according to Fang's protocol[133d] also returned poor yields of the desired ketoaldehyde **232** (Scheme 4.6). However, this sequence did generate a sufficient amount of ketoaldehyde **232** to examine the rest of the envisaged sequence to homotropane **(±)-229**.

SCHEME 4.6



We imagined that if the envisaged route to homotropane **(±)-229** proved viable, enone **238** could be synthesised and subsequently hydrolysed with AcOH according to Fleming and Epstein's procedures (Scheme 4.7).[131]

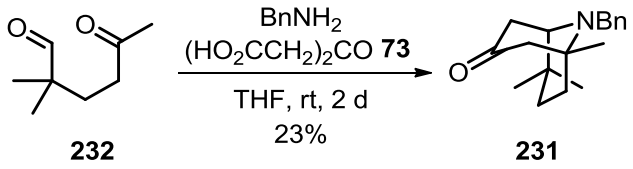
SCHEME 4.7



4.2.3 *Robinson-Schöpf Reaction with Ketoaldehyde **232***

Ketoaldehyde **232** was treated with the same conditions as those used for the synthesis of tropinone **87** (Ch. 2, p. 24), adapted from Sterner *et al*.[63] Unfortunately, despite significant endeavour, homotropinone **231** could only be isolated in low yield (Scheme 4.8). There appeared to be a notable difference between the reactivities of ketoaldehydes **71** and **232**. When the former was reacted under analogous conditions, rapid loss of CO_2 was observed a short time after addition of $BnNH_2$ (though not with $MeNH_2$), but with the latter this did not occur. Indeed, the majority of acetone-1,3-dicarboxylic acid was returned unreacted (hence no significant decarboxylation), as the major by-product formed in the reaction was identified by NMR analysis as enone **238**. Most probably condensation proceeds through the ketenamine under these conditions.

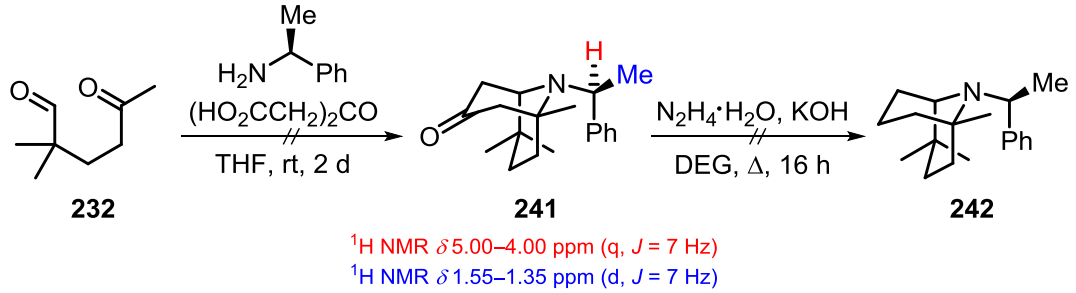
SCHEME 4.8



Further adaptations of Sterner's procedure also proved unrewarding. Substituting $BnNH_2$ for NH_3 (0.5 M in dioxane) simply returned the ketoaldehyde **232** after 2 d at rt. Equally, changing the solvent failed to provide homotropinone **231**. A variety of solvents were examined: d_6-$(Me)_2CO$, CH_2Cl_2, $CDCl_3$, Et_2O, H_2O, MeCN and MeOH. In H_2O, starting

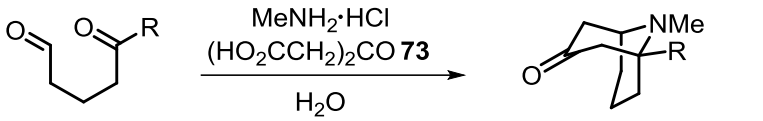
materials were returned. In CH_2Cl_2, $CDCl_3$, Et_2O (at rt and reflux) and MeCN, enone **238** was the only identifiable product. MeOH and d_6-$(Me)_2CO$ led to complex mixtures. Attempted preparation of α-methyl benzyl homotropinone **241** (Scheme 4.9), which if viable could have potentially been used as a strategy to resolve homotropane **(±)-229**, encouragingly showed signs of the product **241** by crude ^{1}H NMR analysis (a series of quartets and doublets, two of greater integration possibly corresponding to diastereomers of **241**, Scheme 4.9). However, chromatography led to decomposition of the product. Efforts to carry through the crude material to the Wolff-Kishner step failed to provide the desired α-methyl benzyl homotropane **242** (Scheme 4.9). This was a somewhat predictable result, given the level of impurities present and the high temperature required for Wolff-Kishner reduction, which increases the propensity for side-reactions.

SCHEME 4.9



The labs of Alder[140] and Howell[141] have demonstrated efficient syntheses of structurally similar homotropinones to **231** (Scheme 4.10). Howell reported the use of aq NaOH and Na_2HPO_4 to prepare pseudopelletierine (**245**); initially, this mixture is reacted at rt for 24 h, then conc HCl is added and the resulting mixture refluxed for 1 h (to force decarboxylation). Alder documented analogous phosphate buffer conditions, without the use of NaOH and HCl, reacted at rt for 5 d to construct 2-methyl-pseudopelletierine (**246**).

SCHEME 4.10

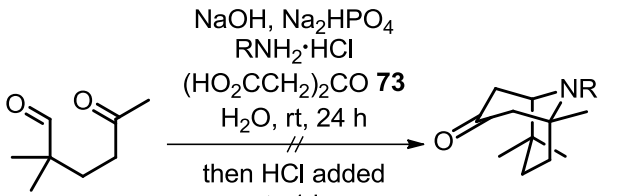


243 R = H
244 R = CH_3

245 R = H (65–68%)
246 R = CH_3 (58–68%)

Ketoaldehyde **232** was subjected to Howell's conditions employing both $MeNH_2$·HCl and $BnNH_2$·HCl in two parallel reactions (Scheme 4.11). Unsurprisingly, given the acid-base conditions, neither reaction generated the desired product, instead, each reaction produced enone **238**, identified by crude ^{1}H NMR. Again, angle compression α- to the aldehyde likely facilitates intramolecular condensation.

SCHEME 4.11



232

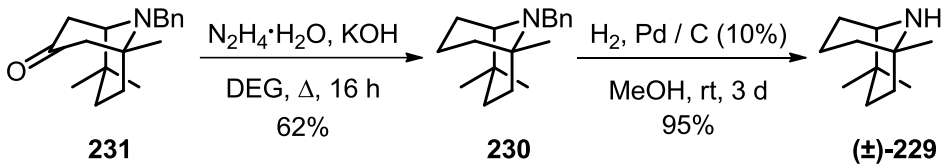
231 R = Bn
247 R = CH_3

4.2.4 *Endgame to Homotropane **(±)-229***

With a small quantity of homotropinone **231** in hand we envisaged the same reduction strategy for removal of the ketone and benzyl groups to that used for the synthesis of tropane **57**, which would complete the synthesis of homotropane **(±)-229**. Wolff-Kishner reaction to *N*-benzyl homotropane **230**[67] and then hydrogenolysis[68] gave the desired homotropane **(±)-229** in satisfactory yield (59% in two steps, Scheme 4.12). It was noted that Wolff-Kishner reduction of homotropinone **231** proved less efficient than with the structurally analogous tropinone **87** (62% cf. 85% {Ch. 2, p. 24}). Additionally, a higher catalyst loading and longer

reaction time were required for successful hydrogenolysis (24 mol% and 3 d cf. 10 mol% and 17 h).

SCHEME 4.12



Despite eventual synthesis of homotropane **(±)-229**, the sequence described above had a major limitation: 5% overall yield. Ketoaldehyde **232**, which shows a strong inclination for intramolecular condensation to enone **238** severely hampered the Robinson-Schöpf reaction, with no foreseeable solution to improve on the yield. The added combination of a less productive Wolff-Kishner reduction and arduous hydrogenolysis persuaded us to examine other possible routes to homotropane **229**.

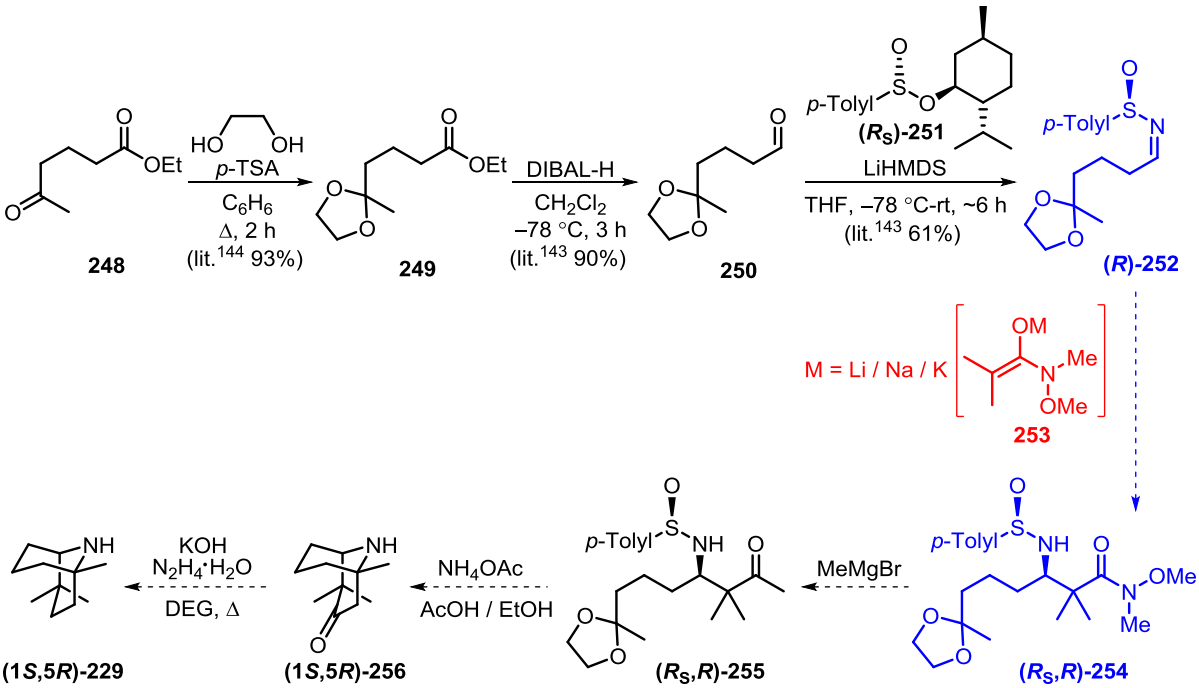
4.3 Asymmetric Synthesis of Homotropane 229

4.3.1 *Davis Approach to Homotropane 229*

In our search for an alternative strategy to homotropane **229**, we were attracted to the work of Davis and Edupuganti,[142] who have recently reported a novel and expedient method to access chiral homotropinones. This chemistry involves diastereoselective additions to chiral sulfinimine ketals, followed by Mannich cyclisation, which assembles chiral homotropinone scaffolds in excellent yields and *er*s. Projected use of this methodology to construct homotropane **229** envisaged a 7-step sequence (Scheme 4.13). Not only did this approach give the prospect of accessing chiral homotropane **229** without the need for resolution but, as

an additional benefit, the first three steps to sulfinimine **(*S*)-252** are described in the literature.[143–144]

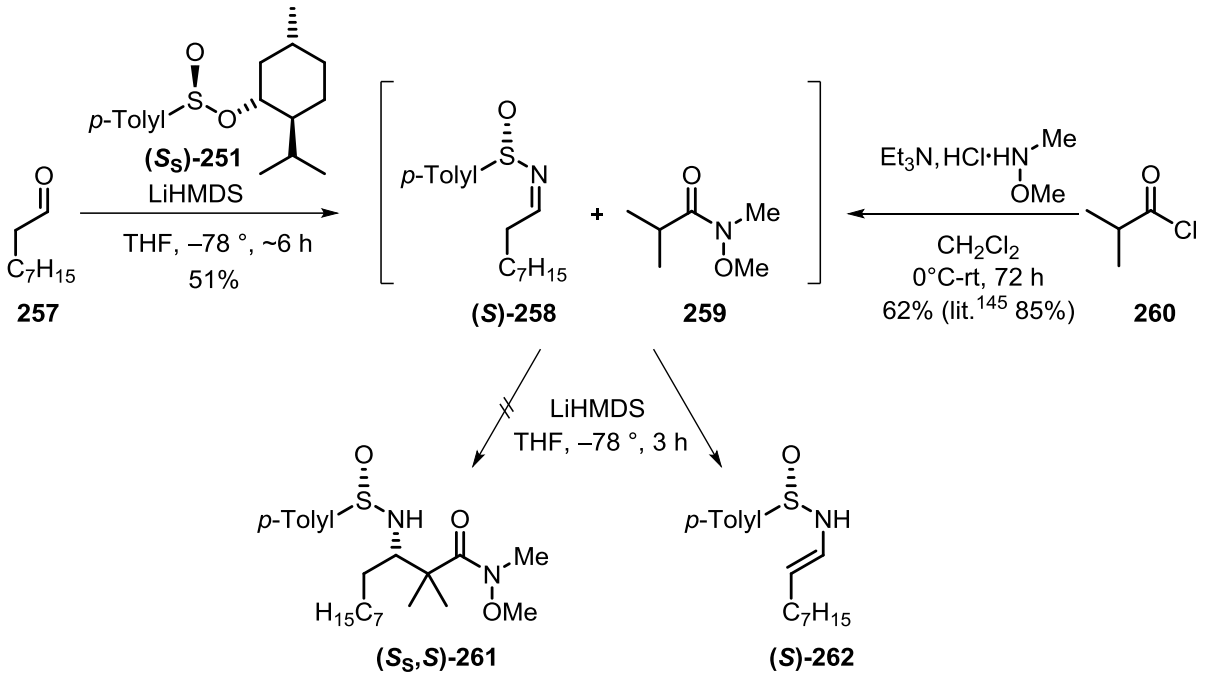
SCHEME 4.13



Before committing to this sequence, we wished to examine the viability of the key unknown step: the addition of Weinreb enolate **253** to chiral sulfinimine **252** (Scheme 4.13). Following Davis' protocol,[142] reaction of nonanal (**257**) with commercially available sulfinate ester **(*S*S)-251** in the presence of LiHMDS gave sulfinimine **(*S*)-258** in satisfactory yield (Scheme 4.14). The precursor to enolate **253**, Weinreb amide **259**, was prepared according to literature conditions in moderate yield (Scheme 4.14).[145] Disappointingly, reaction of sulfinimine **(*S*)-258** and Weinreb amide **259** under the addition conditions described by Davis and Edupuganti.[142] showed no sign of amido-ketal sulfinamide **(*S*S,*S*)-261**, following work-up (Scheme 4.14). From analysis of the crude ^{1}H NMR spectrum, the major by-product was tentatively assigned to enamine **(*S*)-262**, determined from signals in the olefinic region [^{1}H NMR δ 5.77 (d, 1H, NC*H*=CH), 4.55 – 4.41 (m, 1H, NCH=C*H*)]. Attempted isolation of

enamine **(*S*)-262** was not possible, but mass recovery suggested a near quantitative transformation.

SCHEME 4.14

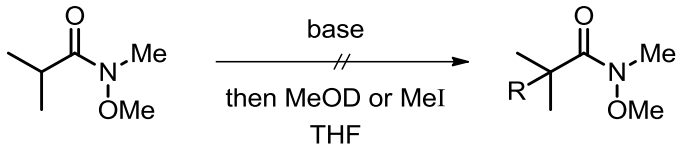


Two plausible explanations were considered for the origin of enamine **(*S*)-262**. Firstly, it is feasible that the enolate of the more hindered amide did not form, and, as such, that the LiHMDS present simply deprotonated sulfinimine **(*S*)-258** to give enamine **(*S*)-262**. Second, the enolate itself, which is more hindered than those enolates added to sulfinimines by Davis and Edupuganti, acts as a base rather than a nucleophile in this reaction.

The obvious reaction to perform next was an electrophile trapping experiment, to see if enolate **253** (M = Li) is actually generated under Davis' conditions. It was decided to perform two reactions in tandem, using MeOD and MeI as electrophiles (Scheme 4.15). The Weinreb amide **259** was treated with LiHMDS at –78 °C for 3 h. The procedure differed from that

described by Davis only in the length of the reaction time (3 h cf. 2 h); a longer time was used – to account for the greater steric hindrance of amide **259**. Electrophiles were added at –78 °C and allowed 30 min to react before the quench (sat. aq NH_4Cl). The same work-up was employed as used by Davis, and, after evaporation under reduced pressure, both reactions returned only starting material, suggesting that indeed no enolate had formed.

SCHEME 4.15



259

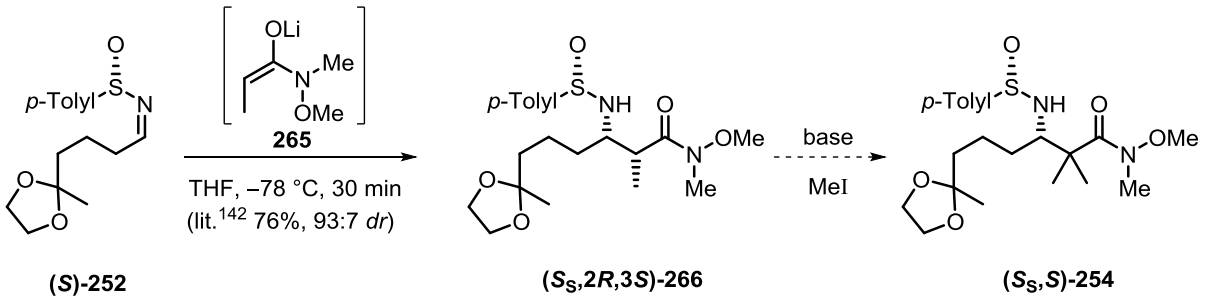
263 R = D
264 R = Me

It was realised that a stronger base may be required for formation of the Weinreb enolate **253**. To the best of our knowledge enolate **253** has not been previously prepared. Given the lack of literature precedent, and the limited bases available, since most strong bases are also partially nucleophilic and would add to the Weinreb amide, it was decided to examine LDA (pK_a ~36 cf. LiHMDS, pK_a ~30), to try to promote deprotonation of amide **259** (Scheme 4.15). We also noted that the low temperature employed (–78 °C) could impede enolate **253** formation, and so a reaction at –20 °C, using LDA, was also investigated. In the elevated temperature reaction, amide **259** was treated with LDA (preformed by reaction of *n*-BuLi with freshly distilled DIPA) for 2.5 h at –20 °C. Following addition of MeI, the reaction was left to stir for 45 min at –20 °C. Following the quench and work-up (according to Davis' prescription), the residue returned showed a complex ^1H NMR spectrum; however, none of the resonances corresponded to amide **264**. In the experiment performed at –78 °C, the mixture of amide **259** and LDA were left for 3 h before addition of MeI. This mixture was left to react for 1.5 h before the typical quench and work-up. The crude returned a similar but cleaner spectrum

(likely a consequence of the lower temperature) to that seen for the previous reaction. From these studies, we decided to investigate a different approach.

Davis and Edupuganti[142] prepared sulfinamide **(*S*S,2*R*,3*S*)-266**, which is structurally analogous to the desired amido-ketal sulfinamide **254**, by reaction of Weinreb enolate **265** with sulfinimine **(*S*)-252** in good yield (76%) and excellent *dr* (Scheme 4.16). Though unlikely, given the unsuccessful formation of enolate **253** (M = Li), we believed it might be possible to form and methylate the enolate of amido-ketal sulfinamide **266** (Scheme 4.16).

SCHEME 4.16

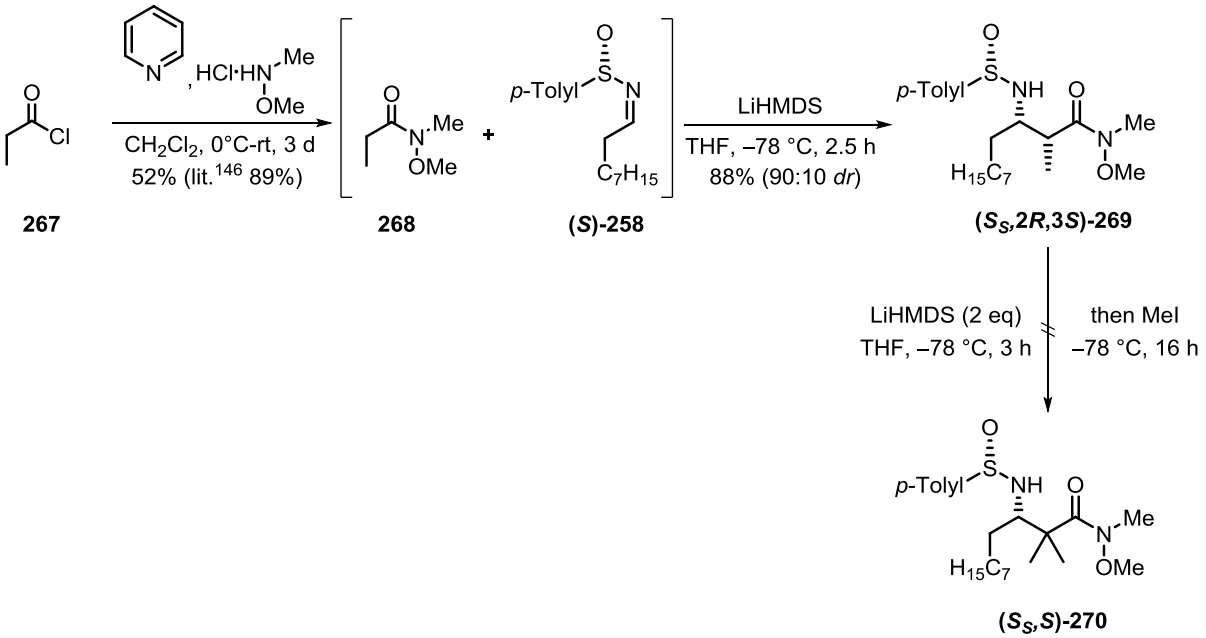


(*S*)-252 **(*S*S,2*R*,3*S*)-266** **(*S*S,*S*)-254**

It was decided, again, to test this chemistry on sulfinimine **(*S*)-258**, before committing to the three-step preparation of sulfinimine **252**. Preparation of the requisite Weinreb amide **268** proceeded in satisfactory yield, following literature conditions (Scheme 4.17).[146] Pleasingly, sulfinimine **(*S*)-258** underwent addition with lithium enolate **265** in excellent yield (88%) and similar *dr* (90:10 cf. 93:7) to that observed by Davis with sulfinimine **(*S*)-252** (Scheme 4.17). The product diastereomers were separable in the present case. Somewhat predictably, attempted methylation of amido sulfinamide **(*S*S,2*R*,3*S*)-269** failed (Scheme 4.17); following work-up, the starting materials were returned. The period allowed for enolate formation in this case was 3 h. Presumably this period is either too short, or, more likely, the amide is simply too hindered to form the enolate. Another possibility is that the anion formed by

deprotonation of the amino group, which must be deprotonated first due to its lower *p*Ka, prevents enolate formation by the electronic repulsion that would be caused in forming a dianion.

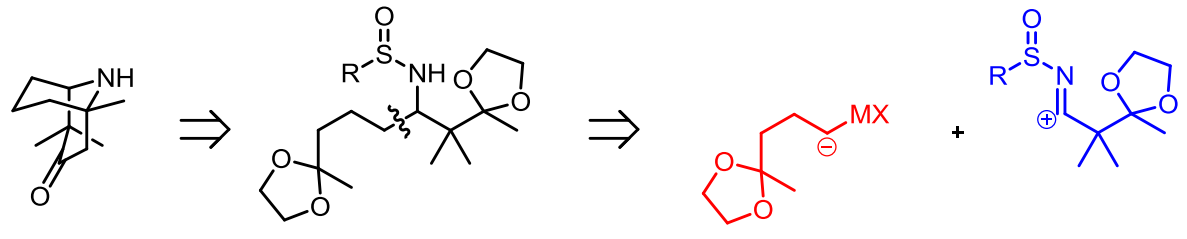
SCHEME 4.17



267 **268** **(*S*)-258** **(*S*$_S$,2*R*,3*S*)-269** **(*S*$_S$,*S*)-270**

Given the above findings, we decided to try an alternative retrosynthetic approach to the necessary cascade substrate, keto-ketal sulfinamide **255**. This involved reversing the polarity of our coupling partners, with envisaged organometallic **272** addition to sulfinimine **273**, to give bisketal sulfinamide **271**, which we believed should undergo the Mannich cascade, using Davis' conditions, to give homotropinone **256** (Scheme 4.18).

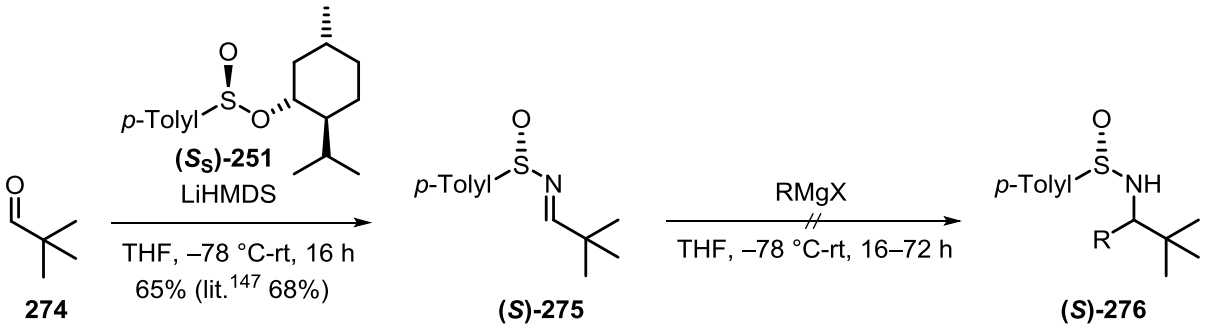
SCHEME 4.18



256 **271** **272** **273**

To test this strategy, we synthesised a Davis-type sulfinimine structurally analogous to sulfinimine **273**. Sulfinimine **(*S*)-275** was prepared from pivaldehyde (**274**) using Davis' conditions in comparable yield (Scheme 4.19).[147] A series of readily available alkyl Grignard reagents (R = Me, C_5H_{11}, $(CH_2)_{17}CH_3$; X = Br, Cl, Cl, respectively) were reacted with sulfinimine **(*S*)-275**, all of which generated complex mixtures with no imine addition product identified.

SCHEME 4.19



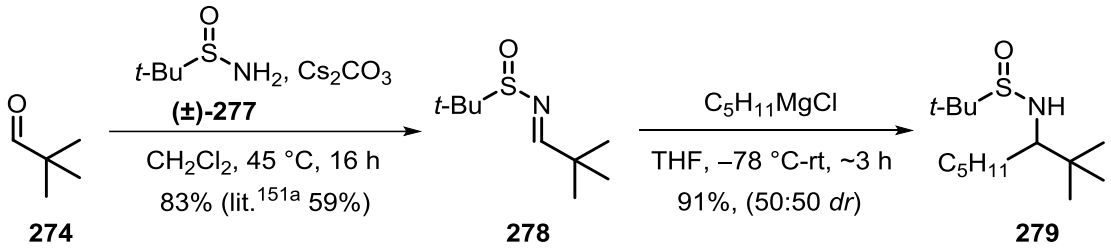
In hindsight, choosing to use a Davis-type sulfinimine for this addition had been an oversight, given the well-known issue of competing *S*- and 1,2-addition with these substrates and organometallics.[148] Chan *et al*. have shown organocuprates can give preferential 1,2-addition to the imine rather than addition at sulfur, but this chemistry seems to be fairly substrate specific.[149]

4.3.2 *Examination of Ellman's Auxiliary for Diastereoselective Addition to Sulfinimine **273***

From exploration of alternative sulfinyl groups known to undergo successful organometallic 1,2-addition, the obvious substitute was Ellman's *tert*-butanesulfinyl group. Sulfinimines comprised of this moiety are known to undergo highly chemo- and stereoselective transformations with an array of nucleophiles, importantly including organometallics.[150]

Typically such sulfinimines are prepared by condensation under Lewis-acidic dehydrating conditions (PPTS / $MgSO_4$, $CuSO_4$ and $Ti(OEt)_4$, for progressively more hindered aldehydes).[151] In the present case, the ketal of sulfinimine **273** would most certainly hydrolyse under these conditions. Fortunately, base-mediated condensations of aldehydes and *tert*-butane sulfinamide (**277**; Scheme 4.20) have also been developed.[152] Following the conditions of Nakata *et al.*,[152a] Cs_2CO_3-mediated condensation of pivalaldehyde (**274**) with sulfinamide **277** to give sulfinimine **278** proceeded in excellent yield (Scheme 4.20). Subsequent addition with pentylmagnesium chloride gave the α-substituted sulfinamide **279** in anticipated high yield (Scheme 4.20). THF had been used merely for convenience and inevitably actuated no *dr*. It was anticipated, by analogy with Ellman's findings,[153] that the *dr* could be increased by exchanging the reaction solvent for CH_2Cl_2 in the addition to sulfinimine **273** [R = *t*-Bu ≡ **285** (Scheme 4.21; p. 94)].

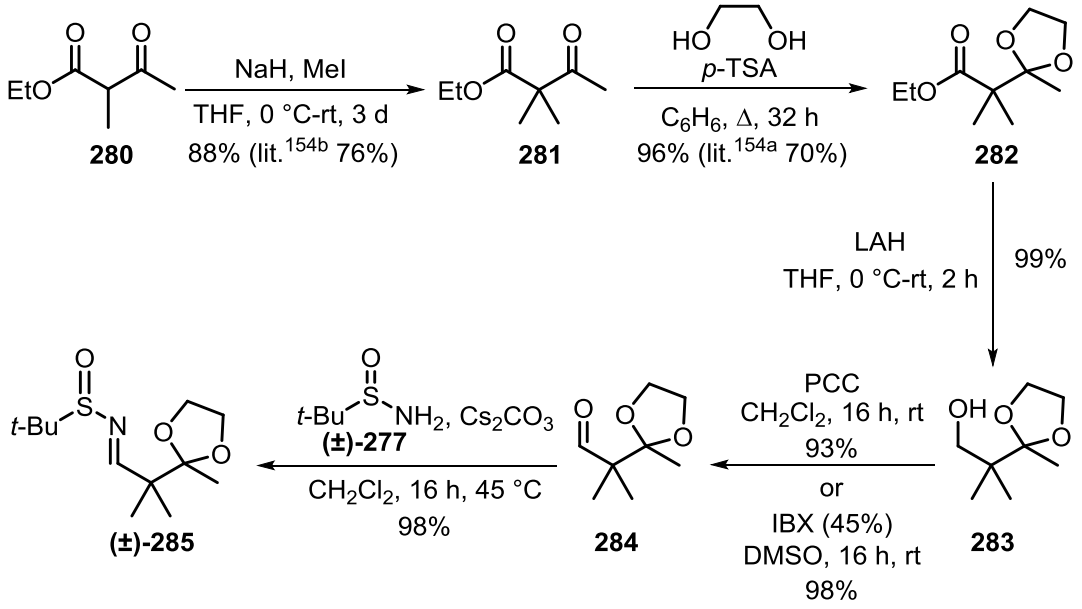
SCHEME 4.20



Having successfully established high yields for the condensation and Grignard addition, we proceeded to prepare the requisite sulfinimine for homotropinone synthesis (Scheme 4.21). Methylation of ethyl α-methylacetoacetate (**280**) and subsequent protection gave ketal ester **282** in excellent yield using literature conditions.[154] DIBAL-H reduction of ketal ester **282** was attempted using Davis' conditions (T < –65 °C).[143] By contrast with Davis' substrates, ketal ester **282** was slow to reduce. Overnight stirring at –78 °C (cryostat controlled) led to a mixture of ketal ester **282**, ketal alcohol **283** and ketal aldehyde **284**. Presumably the rate was

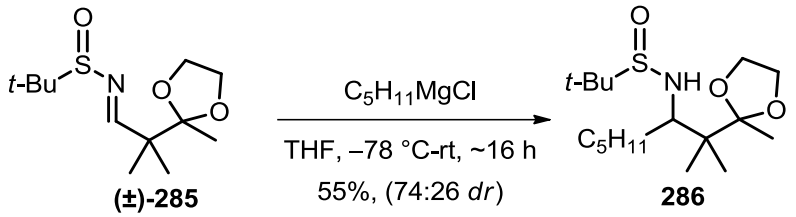
influenced by the α-*gem*-dimethyl substitution (not present in Davis' ester). As a workaround, ketal ester **282** was reduced to ketal alcohol **283** with LAH[155] and then oxidised using PCC,[156] which provided ketal aldehyde **284** in high yield (92% in two steps). IBX was equally effective on test-scale, giving ketal aldehyde **284** in excellent yield (98%), but was not used for scale-up due its expense. Pleasingly, sulfinimine **(±)-285** was prepared in good yield following Nakata's conditions.

SCHEME 4.21



Before preparing the necessary organometallic **272** for preparation of homotropinone **256**, the diastereoselectivity of Grignard addition to sulfinimine **(±)-285** was examined in a test reaction with pentylmagnesium chloride. Unfortunately, hopes of improving the *dr* by replacing THF with CH_2Cl_2 were short-sighted. In the event, reactions performed in CH_2Cl_2 showed only trace amounts of product by TLC, and NMR showed significant recovery of sulfinimine **(±)-285**. Following purification by column chromatography, no product was isolated and 67% of sulfinimine **(±)-285** was returned unreacted. Reaction in THF afforded only a satisfactory 55% yield of sulfinamide **286**, as a separable mixture of diastereomers with modest *dr* (74:26, Scheme 4.22).

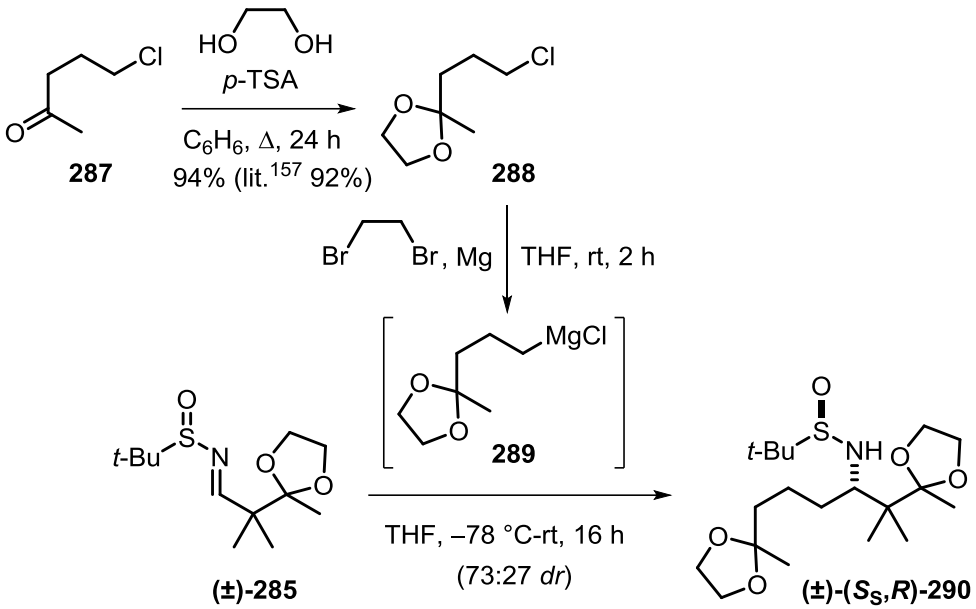
SCHEME 4.22



(±)-285 **286**

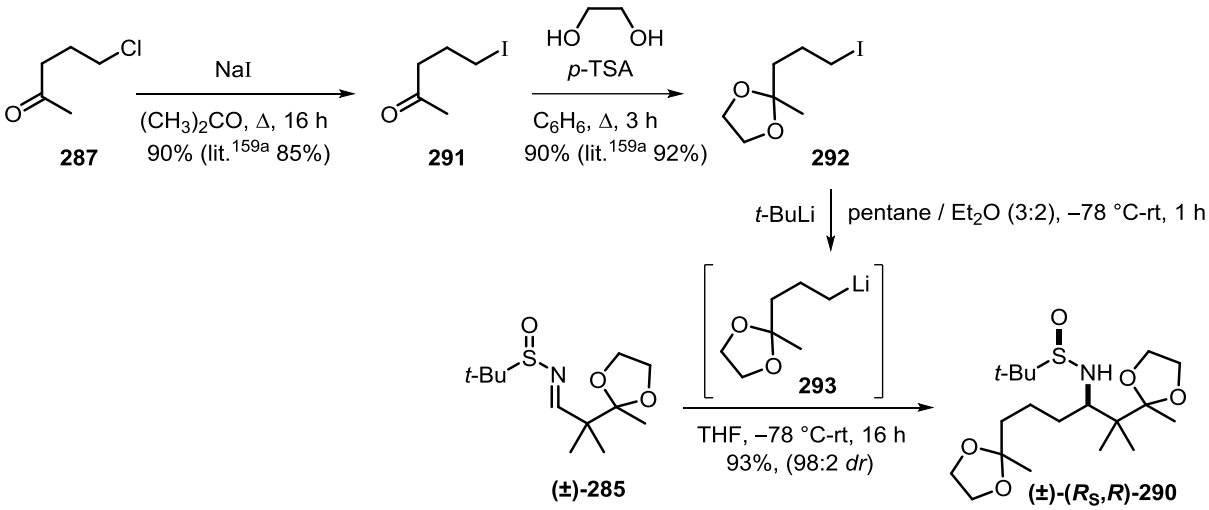
While both results were disappointing, there was hope that the yield and / *dr* could be improved for addition of organometallic **272** [M = Mg, X = Cl ≡ **289** (Scheme 4.23)]. The precursor to Grignard reagent **289** was prepared from a simple protection of commercially available ketochloride **287**.[157] Grignard **289** preparation utilised Brown's method of mechanical activation of the magnesium,[158] and 1,2-dibromoethane to help initiate oxidative insertion. Grignard **289** addition generated bisketal sulfinamide in moderate *dr* (73:27) and from the mass balance a crude yield of 98%. After examination of several eluents, the diastereomers were deemed inseparable by chromatography, and, additionally, an unknown significant impurity could not be separated. However, it was possible to partly extract a pure sample of the major diastereomer by precipitation (45%). The relative configuration of the major diastereomer has been assigned (Scheme 4.23), based on findings discussed below.

SCHEME 4.23



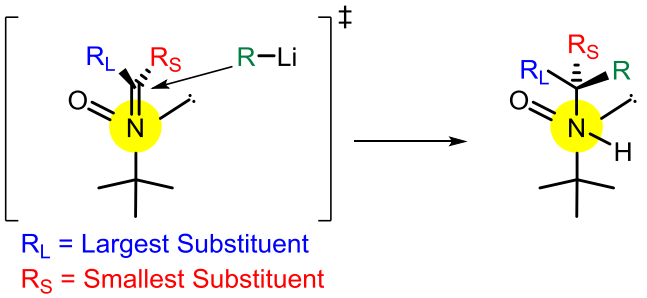
We believed the purity of Grignard reagent **289** may have been jeopardising the outcome of the reaction, and thus decided to examine addition with the corresponding organolithium **293** (Scheme 4.24). The necessary ketaliodide **292** was prepared in 2 steps in consistent yield with the literature, starting from chloride **287**.[159] Organolithium **293** was formed by lithium-halogen exchange according to the prescription of Bailey and Punzalan.[160] To our delight, this effected addition in excellent yield (93%) and outstanding *dr* (98:2).

SCHEME 4.24



The observed reversal of diastereoselectivity is consistent with that found for reactions of other organolithiums and *tert*-butanesulfinylaldimines, which are suggested as proceeding through an open transition state (Scheme 4.25).[150]

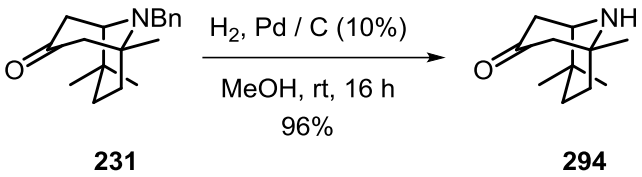
SCHEME 4.25 (Adapted from Plobeck and Powell[161])



4.3.3 *Mannich Cascade with Sulfinamide (±)-(RS,R)-290 and (RS,R)-290*

Having found a productive route to bisketal sulfinamide **290**, we pursued the next key step of the sequence to homotropane **256**, the Mannich cascade. To assist with TLC analysis of the cascade reaction, previously prepared racemic benzyl homotropinone **231** was reduced, generating homotropinone **294**, which provided a good reference sample (Scheme 4.26).

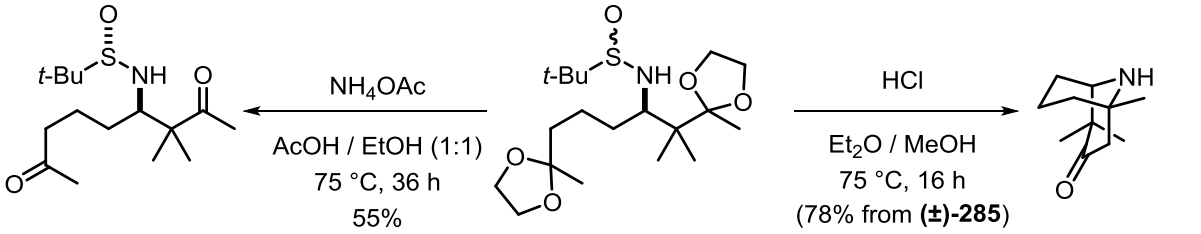
SCHEME 4.26



231 **294**

Subjecting bisketal sulfinamide **(±)-(*S*S,*R*)-290** (prepared from Grignard **289** addition to sulfinimine **(±)-285**) to Davis' buffer conditions (NH_4OAc [25 eq], AcOH : EtOH [1:1], 36 h 75 °C) led to deprotection of both ketals, but left the sulfinamide group intact (Scheme 4.27). Following chromatography, bisketosulfinamide **(±)-(*S*S,*R*)-295** was returned in modest yield; the remaining mass balance was a complex inseparable mixture, with no notable contribution at the same R_f as homotropinone **294**. It was considered that these conditions may not be acidic enough for removal of the *tert*-butylsulfinyl group. Indeed, heating bisketal sulfinamide **(±)-(*R*S,*R*)-290** in a methanolic-ethereal solution of HCl gave the desired homotropinone **(±)-256** in good yield (78% in two steps, Scheme 4.27). For this reaction, a crude supply of bisketal sulfinamide **(±)-(*R*S,*R*)-290**, which was sufficiently pure by NMR, was carried through to the cascade, to test the efficiency over two steps without purification of the addition product.

SCHEME 4.27



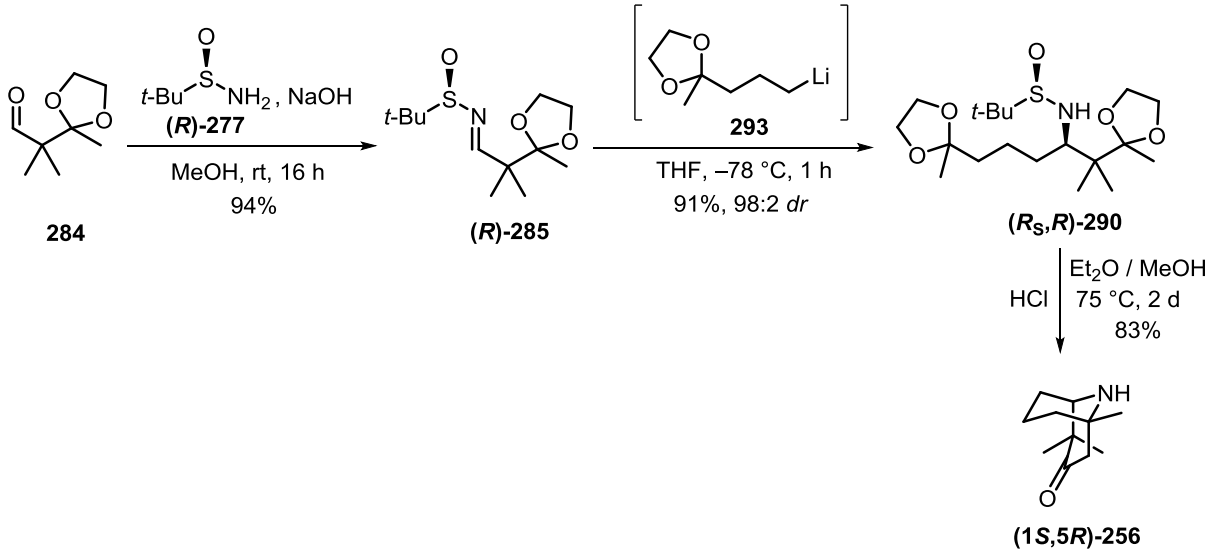
(±)-(*S*S,*R*)-295
υ (2 x C=O) 1705 cm^{-1}
^{13}C NMR δ 212.6 and 209.0

(±)-(*S*S,*R*)- / (±)-(*R*S,*R*)-290

(±)-256
υ (C=O) 1699 cm^{-1}
^{13}C NMR δ 216.2

Now possessing an efficient route to homotropinone **256**, the sequence was re-run on scale, using commercially available (*R*)-*tert*-butane sulfinamide (**(*R*)-277**). On scale (25 mmol), NaOH-mediated condensation using the conditions of Kawęcki *et al*.[152b] proved more reliable than Nakata's procedure[152a] (Scheme 4.28). Organolithium addition proceeded in similarly excellent yield and *dr*, providing bisketalsulfinamide **(R_S,*R*)-290** as essentially a single diastereomer. In the hope of quantitative cyclisation to the homotropinone, the reaction time for the cascade transformation was increased, but this gave no significant improvement. Nevertheless, the reaction proceeded in high yield to give the desired chiral homotropinone **(1*S*,5*R*)-256**, as a single enantiomer (by chiral HPLC analysis), whose absolute configuration was established by X-ray crystallographic analysis.[91]

SCHEME 4.28

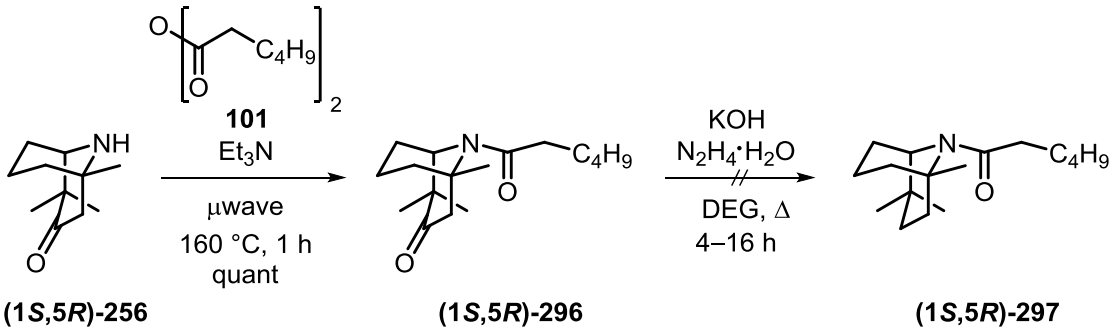


4.3.4 *Deoxygenation of Homotropinone **(1S,5R)-256** to give Homotropane **(1S,5R)-229***

At the outset, we had envisaged removal of the ketone of homotropinone **256** *via* Wolff-Kishner reaction (Scheme 4.13; p. 87). Unfortunately, despite several attempts with varying time frames, hydrazine-mediated reduction failed and led to decomposition of the

homotropinone **(1*S*,5*R*)-256**. We considered that the corresponding amide **(1*S*,5*R*)-296** (Scheme 4.29) *en route* to our desired enamine target using Nagashima's method might be more stable to the harsh conditions of Wolff-Kishner reduction; we imagined formamide **(1*S*,5*R*)-309** (Scheme 4.37; p. 108), the precursor for Wickberg and Hansson's enamine protocol, would be less stable to these conditions. Amide **(1*S*,5*R*)-296** was prepared in excellent yield using Hulme's procedure (Scheme 4.29). However, attempts to reduce amide **(1*S*,5*R*)-296** gave low mass recovery, and the material obtained showed no sign of product.

SCHEME 4.29

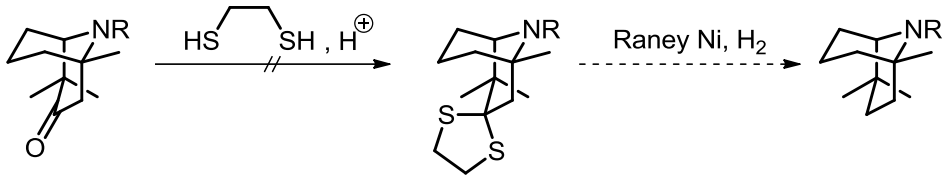


Fitjer *et al*.,[162] and similarly Möhrle and Class,[163] have facilitated deoxygenation on severely hindered cyclic ketones using methods adapted from Barton's earlier work, employing neat hydrazine.[164] However, the practical difficulty and potential hazard in generating pure hydrazine led us to examine alternative methods first.

An obvious substitute was a Mozingo-type strategy (Scheme 4.30). However, despite significant effort, the requisite thioketal **(1*S*,5*R*)-298** would not form. Several different carbonyl activators were employed [$BF_3{\cdot}Et_2O$ (in CH_2Cl_2 at rt and Δ),[165] *p*-TSA (in C_6H_6 with Dean-Stark), Amberlyst-15® (in $CHCl_3$ at rt and Δ)[166]], for varying lengths of time (16 h−5 d), but all reactions simply returned un-reacted homotropinone **(1*S*,5*R*)-256**. Equally,

attempts to form thioketal **(1*S*,5*R*)-299** from amide **(1*S*,5*R*)-296** gave the same result. The resistance of homotropinone **(1*S*,5*R*)-256** to form a thioketal was perhaps unsurprising, given the hindered nature of the ketone in this case.

SCHEME 4.30



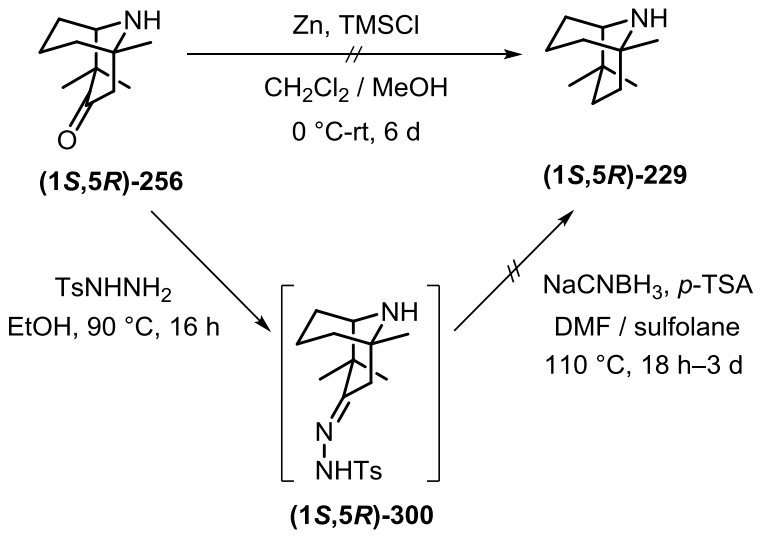
(1*S*,5*R*)-256 R = H
(1*S*,5*R*)-296 R = C(=O)C_5H_{11}

(1*S*,5*R*)-298 R = H
(1*S*,5*R*)-299 R = C(=O)C_5H_{11}

(1*S*,5*R*)-229 R = H
(1*S*,5*R*)-297 R = C(=O)C_5H_{11}

Since attempted Wolff-Kishner reduction had led to decomposition of homotropinone **(1*S*,5*R*)-256**, we hoped strategies operating under more temperate conditions could give successful deoxygenation, and, importantly, if unsuccessful would allow retrieval of the valuable homotropinone **(1*S*,5*R*)-256**. However, application of Arimoto's mild Clemmensen procedure[167] and a Caglioti-type reduction prescribed by Hutchins *et al*.[168] proved ineffective for deoxygenation of homotropinone **(1*S*,5*R*)-256**, both returning the unreduced ketone (Scheme 4.31).

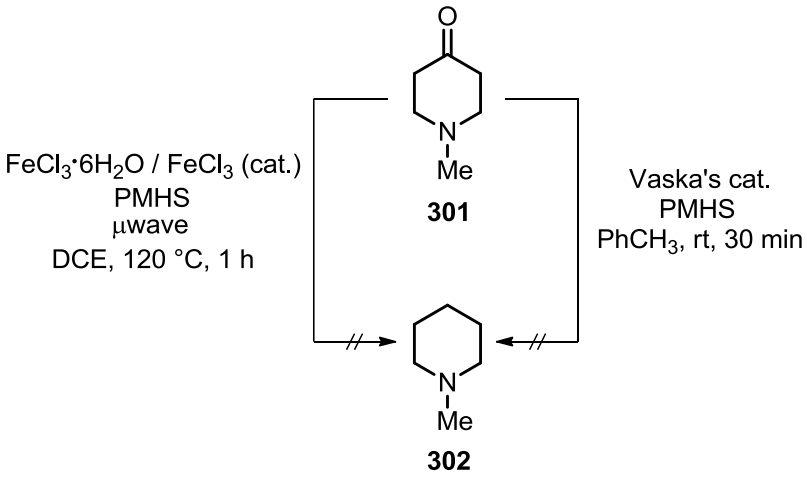
SCHEME 4.31



It was considered that more powerful hydride donors could be employed to reduce tosyl hydrazone **(1*S*,5*R*)-300** (Scheme 4.31), which was identified as having been formed by crude NMR, to the necessary hydrazide for decomposition. For example, Caglioti's original work describes the use of both $NaBH_4$ and LAH to achieve tosyl hydrazone reduction.[169] Given the possibility of undesired Bamford-Stevens by-products,[169] which if formed could have proved difficult to reduce further or separate, this strategy was disregarded.

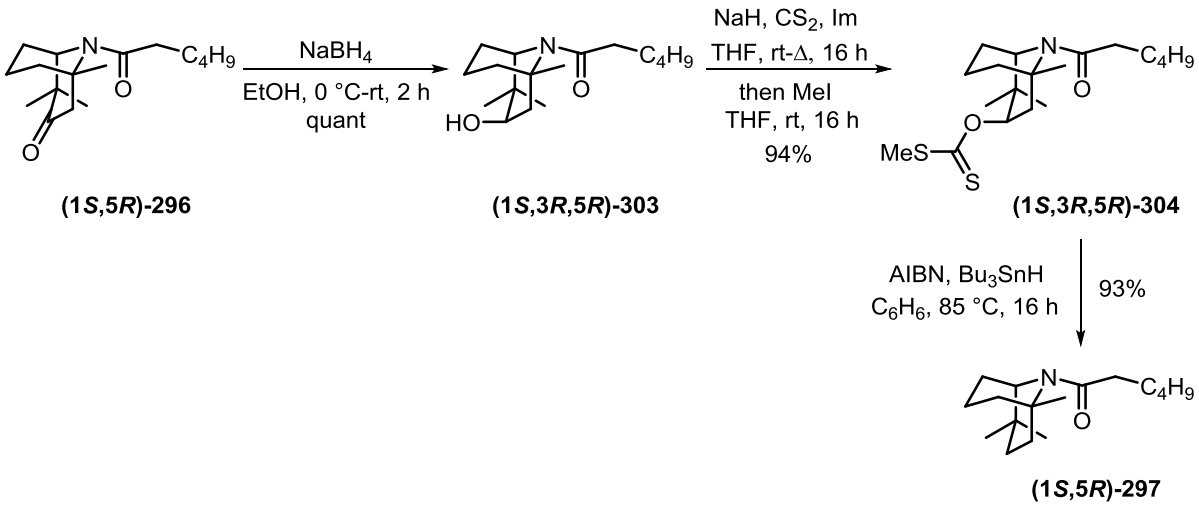
Recently, Campagne *et al*. have demonstrated deoxygenation for a range of ketones and aldehydes to methylenes, using a combination of catalytic Fe(III) and PMHS.[170] While the yields reported are high (81−98%), we realised that none of the examined substrates were significantly hindered, nor did any contain amino functionality. In order to avoid further loss of our valuable intermediate, it was decided to test these unusual conditions using a commercial ketone that was somewhat structurally analogous to homotropinone **256**. Piperidinone **301** was chosen for its availability in the lab. However, subjecting piperdinone **301** to Campagne's conditions (using both $FeCl_3{\cdot}6H_2O$ and $FeCl_3$ in separate reactions) disappointingly returned only starting material (Scheme 4.32). Equally, an attempt (out of curiosity) to utilise Nagashima's conditions[70] also proved ineffective, returning a complex mixture with no resonances easily attributable to *N*-methyl piperidine (**302**, Scheme 4.32).

SCHEME 4.32



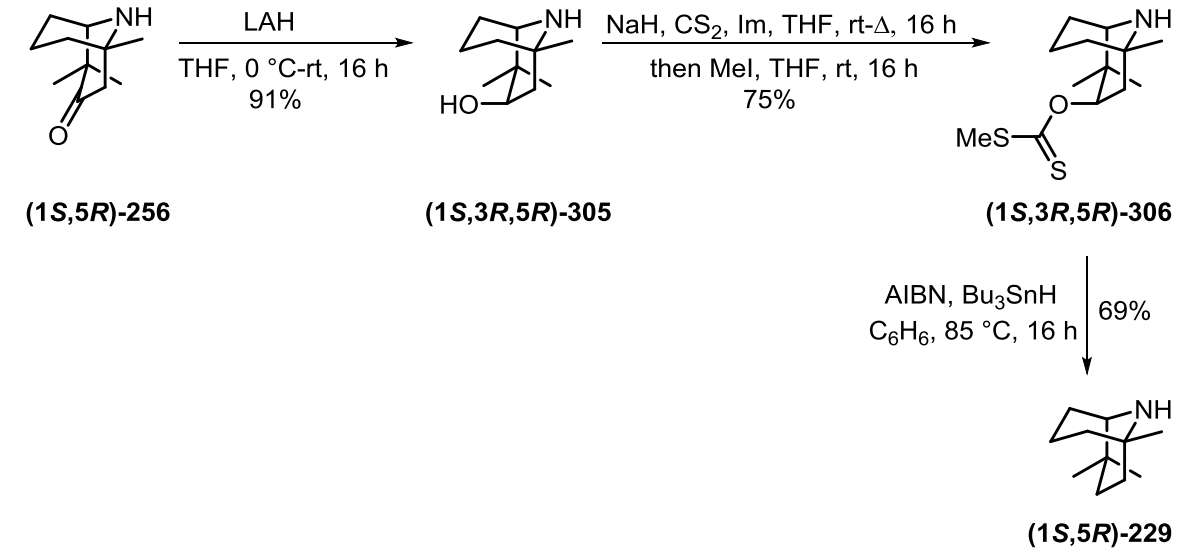
As a more convoluted approach, we postulated that deoxygenation of homotropinone **(1*S*,5*R*)-256** could be accomplished by Barton-McCombie reaction with a derived xanthate. In order to test this strategy, it was decided to use amide **(1*S*,5*R*)-296**, which was available in reasonable quantity from attempted Wolff-Kishner deoxygenation, and whose reduction product would be non-volatile, and thus easier to handle. $NaBH_4$-mediated reduction gave alcohol **(1*S*,3*R*,5*R*)-303** in quantitative yield, with *exo*-face hydride delivery[91] (Scheme 4.33). Gratifyingly, formation of xanthate **(1*S*,3*R*,5*R*)-304** and reduction to amide **(1*S*,5*R*)-297** also proceeded in excellent yield, using conditions adapted from d'Angelo *et al*. (Scheme 4.33).[171] Amide **(1*S*,5*R*)-297** gave identical spectra to that of racemic amide **(±)-297**, prepared from homotropane **(±)-229** using Hulme's protcol.[69]

SCHEME 4.33



Having established deoxygenation for amide **(1*S*,5*R*)-296**, we were encouraged to examine this chemistry for deoxygenation of homotropinone **(1*S*,5*R*)-256**. While $NaBH_4$ was suitable for reduction of homotropinone **(1*S*,5*R*)-256** on test scale (again showing *exo*-face hydride addition[91]), LAH was required to achieve complete reduction to alcohol **(1*S*,5*R*)-305** on gram scale (Scheme 4.34). Xanthate **(1*S*,3*R*,5*R*)-306** formed in good yield, and, pleasingly, when treated to Barton-McCombie conditions, gave homotropane (**1*S*,5*R*)-229** in reasonable yield (Scheme 4.34).

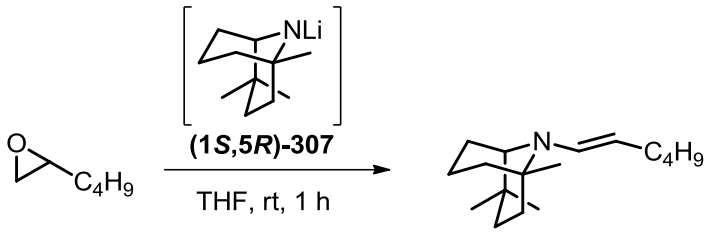
SCHEME 4.34



4.4 Enamine Synthesis Using Nagashima's Protocol with Homotropane (1*S*,5*R*)-229 and Alkylation

With the highly sought after chiral homotropane **(1*S*,5*R*)-229** now in hand, Hodgson lithium amide-epoxide methodology was initially examined for synthesis of enamine **(1*S*,5*R*)-228** (Scheme 4.35). Unfortunately, following the standard conditions returned only the starting amine **(1*S*,5*R*)-229** (45%). The low recovery and purity of the recovered amine suggested that the enamine had formed but then hydrolysed, the products of which (i.e. homotropane **(1*S*,5*R*)-229** and hexanal (**104**)) could then have been evaporated under the high vacuum employed for distillation of the crude reaction product. If hydrolysis could be prevented, the enamine should be accessible *via* this method. However, given the unpredictability of this reaction, and the high eq of amine required (2.5 eq), it was decided to examine alternative approaches, for fear of losing the precious homotropane **(1*S*,5*R*)-229**.

SCHEME 4.35

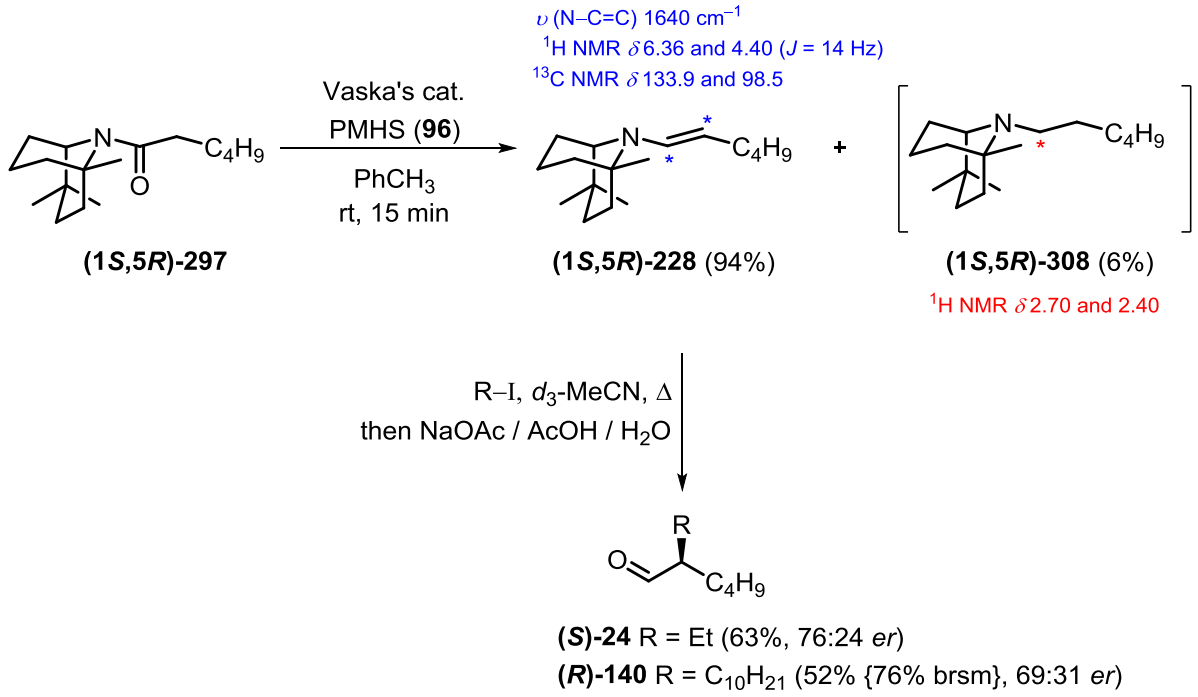


49 **(1*S*,5*R*)-228**

Since amide **(1*S*,5*R*)-297** had been prepared in reasonable quantity, it was decided (despite the above-mentioned limitation, Ch. 2, p. 51) that Nagashima's chemistry was worthy of investigation, since enamine synthesis could be achieved in a single step. In contrast, the substitute Hansson and Wickberg route would necessitate synthesis of the corresponding formamide of homotropane **(1*S*,5*R*)-229.** Initially, amide **(1*S*,5*R*)-297** showed incomplete reduction using Nagashima's chemistry, returning a mixture of enamine **(1*S*,5*R*)-228** and

starting material (quant {2:1 (**(1*S*,5*R*)-228**:**(1*S*,5*R*)-297**)}, Scheme 4.36). Despite this, we were encouraged to examine enamine alkylation using the impure enamine. Alkylation of the impure enamine with decyl iodide (chosen to provide a non-volatile aldehyde) returned the desired product in reasonable yield (52% {76% brsm}), with improved enantioselectivity (69:31 *er*) compared with that observed for alkylation of tropane-derived enamine **(1*S*,5*R*)-92**, and, importantly, with the anticipated sense of asymmetric induction (Scheme 4.36). Promisingly, the *er* obtained was a marginal improvement over that attained by Kaka for decylation of trialkyl piperidine-derived enamine **54b** (69:31 cf. 65:35), suggesting that *er*s equivalent to those of Kaka would be established for alkylations with less demanding electrophiles. However, contrary to what was anticipated, when ethylation was attempted the *er* did not improve (Scheme 4.36). It was considered that the excess amide **(1*S*,5*R*)-297** in the mixture could be affecting the *er*. Through further experimentation, it was found that full conversion could actually be achieved by using a smaller reaction vessel (vial cf. rbf). While this gave the enamine in excellent yield, an impurity considered to be the over-reduction product, amine **(1*S*,5*R*)-308**, was also present. We were concerned that the amine present during alkylation could also influence the *er*, and thus decided to prepare enamine **(1*S*,5*R*)-228**, using the modified Hannson and Wickberg procedure.

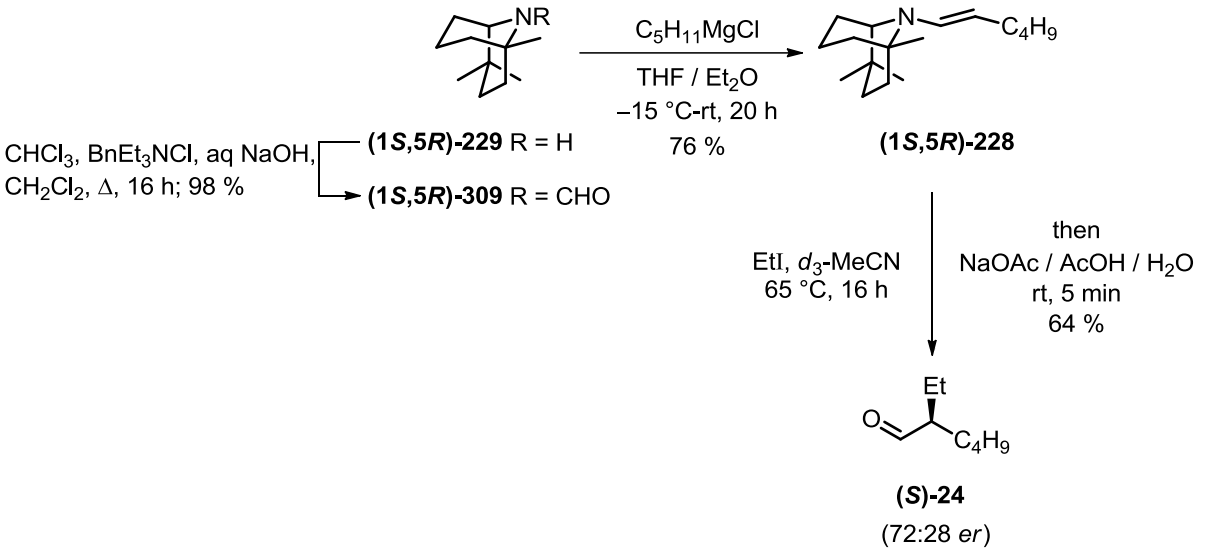
SCHEME 4.36



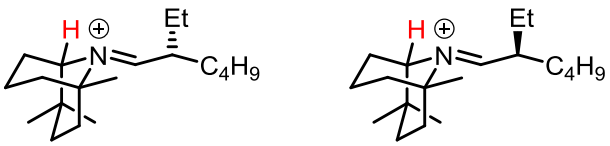
4.5 Enamine Synthesis Using the Adapted Hansson and Wickberg Protocol with Homotropane (1*S*,5*R*)-229 and Alkylation

Formamide **(1*S*,5*R*)-309** was prepared in excellent yield, using Blum and Nyberg's procedure (Scheme 4.37). Using the modified Hansson and Wickberg method gave enamine **(1*S*,5*R*)-228** in good yield, importantly free of impurities (Scheme 4.37). Unfortunately, despite improving the purity of enamine **(1*S*,5*R*)-228**, no improvement in *er* was observed for ethylation, confirming the original result.

SCHEME 4.37



As for ethylation of tropane-derived enamine **92**, the *dr* measured (from resonances attributed to iminium ions **(1*S*,5*R*,*R*$_\alpha$)-310** and **(1*S*,5*R*,*S*$_\alpha$)-310**; Figure 4.3) by *in situ* ^{1}H NMR monitoring of the reaction translated to the *er* established by ^{77}Se NMR of the derived selenium adduct.[91]



(1*S*,5*R*,*R*$_\alpha$)-310 **(1*S*,5*R*,*S*$_\alpha$)-310**

FIGURE 4.3

4.6 Chapter Summary

Based on a computational prediction provided by Dr Robert S. Paton, a homotropane-derived enamine **228** was synthesised and subsequently alkylated. At the outset, to prepare the requisite homotropane **229**, we adopted a Robinson-Schöpf strategy similar to that used to make tropane **57**. However, this strategy was severely compromised by the propensity of the precursor ketoaldehyde **232** to undergo self-condensation to enone **238**. In light of this, we embarked on an asymmetric synthesis, based on earlier work by Davis and Edupuganti.[142]

Unfortunately, Davis' work showed a limitation for our needs, in that the necessary Weinreb enolate **253** could not be generated. Using a reversed disconnection, we prepared an Ellman sulfinimine **285**, to which the required organolithium added in excellent yield and diastereoselectivity. A subsequent Mannich cascade provided the racemic and chiral homotropinone **(±)-256** and **(1*R*,5*S*)-256**, demonstrating a novel route to such compounds. Deoxygenation of homotropinone **256** proved difficult, owing to the *gem*-dimethyl substitution α- to the carbonyl group present. Eventual reduction was achieved using a Barton-McCombie approach. To prepare enamine **228**, both Nagashima's and Wickberg's chemistry proved productive, though Nagashima's chemistry showed conversion problems initially. Subsequent alkylation of enamines derived *via* both methods provided modestly enantioenriched aldehydes, with the anticipated sense of facial selectivity.

4.7 Further Insight into Asymmetric Induction of Bicyclic Auxiliaries

In contrast with tropane enamine **(1*S*,5*R*)-92**, the sense of asymmetric induction seen with homotropane enamine **(1*S*,5*R*)-228** is as originally envisaged, with the *gem*-dimethyl group providing modest steric encumbrance to electrophile approach of the enamine. This is illustrated in Figure 4.4, where the most important competing diastereomeric TS geometries have been superimposed. Approach of the electrophile towards the *Re*-face of enamine **228*** is hindered by the *gem*-dimethyl group, and, as a result, the enamine is appreciably non-planar in the TS, and thus less nucleophilic. Later TS geometries with greater C–I distances are found for this minor pathway, lending further support to this interpretation. In contrast, approach towards the *Si*-face of enamine **228*** is unhindered, and the TS displays a planar enamine geometry, and is thus energetically preferred. However, there is a significant reduction in the *er* for alkylation with enamine **(1*S*,5*R*)-228**, compared with superficially

analogous enamine **54b**. The lower *er* may be a consequence of the rigidity the cyclohexyl ring imposes on the carbon bearing *gem*-dimethyl substitution. For enamine **54b**, the corresponding axial isopropyl group is able to splay slightly away from the idealized chair, thus relieving 1,3-diaxial interactions and providing increased steric shielding of the enamine *Re*-face.[43] Comparison of TS geometries for attack of enamine **92*** (Figures 2.6 and 4.4) highlights the fact that the *gem*-dimethyl substituent is now more remote from the *Re*-face; the combination of these effects leads to a modest inversion in the sense of facial selectivity.

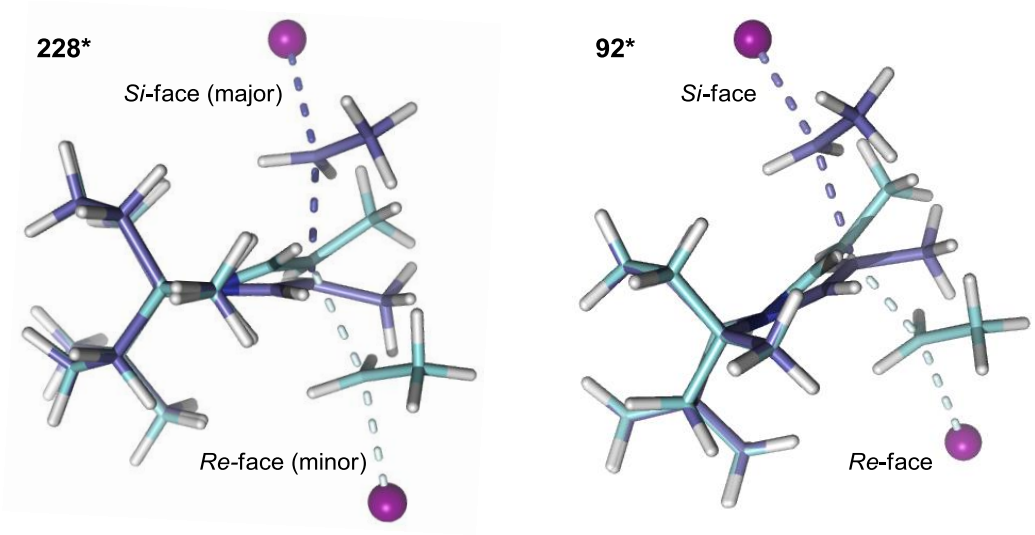


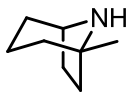
FIGURE 4.4 Superimposed TS Geometries for Homotropane-Derived (228*) and Tropane-Derived (92*) Enamine Alkylation

4.8 Thesis Summary and Future Work

The synthesis and asymmetric alkylation profile of enamines derived from a tropane **57**, an oxazolidine **182**, a pyrrolidine **181** and finally a homotropane **229** have been examined. Oxazolidine **182** alkylation proved unsuccessful. Pyrrolidine **181** gave moderate yields of alkylation and provided no enantioselectivity. Tropane derived enamines **(1*S*,5*R*)-** and **(1*R*,5*S*)-92** showed low and interestingly reverse diastereofacial selectivity to that initially

envisaged. In contrast, homotropane-derived enamine **(1*S*,5*R*)-228**, alkylated with the anticipated sense of (and with significantly improved) diastereoselectivity. The experimental findings are in good agreement with DFT studies for both enamines, where the latter provide insight into the origins of asymmetric induction. While tropane-derived enamine **92** gave a significantly improved yield of ethylation compared with enamine **54b**, all auxiliaries failed to provide high levels of asymmetric induction. However, despite the modest *er*s, the congruence between theory and practical experiment, coupled with an ability to modify and, importantly, improve the *er* through computational design, is central to this chemistry, and should assist future design of chiral auxiliaries and other asymmetric targets. Additionally, the described synthesis of α,α-disubstituted homotropinone **(1*S*,5*R*)-256** demonstrates an efficient strategy to this biologically significant class of chiral compounds that are otherwise difficult to access. Investigations are ongoing to improve on the *er*s obtained.

From the abovementioned computational study, an obvious auxiliary to examine next is tropane **311** (Figure 4.5). Given the observed reversed selectivity with tropane **57**, it seems feasible to suggest that a substantial improvement in *er* would be anticipated by removal of the *gem*-dimethyl substituents from the favoured face for electrophilic attack.



311

FIGURE 4.5

5. EXPERIMENTAL

5.1 General Details

5.1.1 *Reaction Conditions and Materials*

Where anhydrous conditions were required, reactions were performed using flame-dried glassware under an atmosphere of argon. Where necessary, C_6H_6, CH_2Cl_2, Et_2O, MeOH, pentane, THF and toluene were dried over 4 Å MS, then degassed and dried over activated alumina under nitrogen. Dry DMF was purchased from Sigma Aldrich. Dry DME was distilled over LAH immediately prior to use. Dry MeCN was obtained from a communal MBraun SPS800 solvent drying system. d_3-MeCN was purchased in glass ampules (0.75 mL) from Sigma Aldrich, and opened under an atmosphere of Ar. Where required, amines were distilled over CaH_2 immediately prior to use. Alkyl halides were passed through basic alumina immediately prior to use. Titration of *n*-BuLi was performed with diphenylacetic acid.[172] Where necessary, sensitive reagents were distilled before use, or purified according to Perrin and Armarego.[173] Hyrgoscopic solids were dried under high vacuum (0.1 mm Hg) at rt overnight before use. PMHS was purchased from Gelest (mw = 1700.00, *n* = 25.6). Vaska's catalyst was purchased from Strem Chemicals Inc. All other reagents were used as received.

5.1.2 *Chromatography*

Reactions were monitored by TLC (thin layer chromatography), using silica gel aluminium-backed plates (Kieselgel 60 F_{254}). The plates were visualised using ultraviolet light, and developed in basic potassium permanganate, phosphomolybdic acid or ninhydrin solutions. Column chromatography was performed using the solvent systems indicated. The stationary phase used was silica gel (SiO_2, 0.04–0.06 mm particle size, Kieselgel 60), or as otherwise indicated [neutral alumina (Al_2O_3) or Florisil®]. Where specified that silica gel was deactivated, this was done by stirring the silica overnight in 20% Et_3N in petroleum ether. Petroleum ether refers to the fraction of light petrol boiling between 30–40 ºC. HPLC was performed using Daicel chiral columns and HPLC grade solvents.[91]

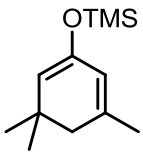
5.1.3 *Analysis*

Melting points are uncorrected. Specific rotations $[\alpha]_{\lambda}^{T}$ were measured using a cell of path length 10 cm, at T = 25 °C, with λ = 589 nm (sodium D line), in the stated solvent, at a concentration (*c*) given in g / 100 mL, and are recorded in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded as either neat samples, thin films in CH_2Cl_2 / $CHCl_3$ or as a KBr disc. The intensity of the peaks are recorded as strong (s), medium (m) or weak (w), and pre-fixed with broad (br) where appropriate. ^{1}H, ^{13}C and ^{77}Se NMR spectra were recorded in $CDCl_3$ at ambient temperature (unless stated otherwise), using either 500 MHz, 400 MHz, 300 MHz or 250 MHz spectrometers. Data are expressed as chemical shifts in parts per million (ppm) relative to residual $CHCl_3$ (^{1}H δ 7.27, ^{13}C δ 77.0 respectively), or where stated that C_6D_6 was used relative to residual C_6H_6 (^{1}H δ 7.16, ^{13}C δ 128.4 respectively), and where d_6-DMSO was used relative to residual DMSO (^{1}H δ 2.54, ^{13}C δ 40.5 respectively), as the internal standard on the δ scale. The multiplicity of each signal is designated using the following abbreviations: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; t, triplet; td, triplet of doublets; tdd, triplet of doublet of doublets; tt, triplet of triplets; q, quartet; qd, quartet of doublets; quin, quintet; sxt, sextet; spt, septet; sptd, septet of doublets; m, multiplet. Where diastereoselectivity is quoted, this was determined from isolated, corresponding signals of each diastereomer in the crude ^{1}H NMR. ^{1}H and ^{13}C NMR peak assignments were made using variations of standard techniques (COSY, DEPT, HMQC, HSQC and NOE[91]). High resolution mass spectra were obtained by field ionization (FI; Micromass GC-TOF {fitted with a temperature-programmed solid state probe}) or by electrospray ionization (ESI; MicroTOF); values are quoted as ratio of mass to charge (*m/z*) in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value.

5.2 Procedures for Chapter 2

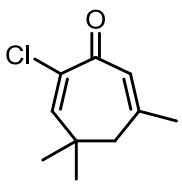
Synthesis of Tropane (±)-57:

Trimethyl((3,3,5-trimethylcyclohexa-1,5-dien-1-yl)oxy)silane (67):[48]



A solution of *n*-BuLi (1.39 M in hexanes, 58.0 mL, 80.6 mmol) was added dropwise, with stirring, to a solution of DIPA (8.13 g, 80.3 mmol) in DME (150 mL) at –15 ºC. After 15 min, isophorone (**68**; 9.99 g, 72.3 mmol) was added dropwise, over 10 min. This resulted in a bright yellow coloration. The solution was stirred at –15 ºC for 15 min, then TMSCl (14.98 g, 137.9 mmol) rapidly added. The resulting white slurry was warmed to rt and stirred for 17 h. After this time, the mixture was concentrated under reduced pressure. Pentane (100 mL) was added to the residue, and the resultant suspended precipitate removed by filtration. The filtrate was evaporated under reduced pressure, and the residue purified by fractional distillation, which gave silyl enol ether **67** as a clear, colourless oil (13.32 g, 88%); bp 45–47 °C (0.05 mm Hg) [lit.[48] bp 54–57 °C (1.5 mm Hg)]; IR (film) (cm^{-1}) 3038w, 2958s, 2865m, 1662s (O–C=C), 1609m (C=C), 1445w, 1361s, 1251s; ^{1}H NMR (400 MHz) δ 5.45 – 5.40 (m, 1H, CH=C–O), 4.54 (s, 1H, C*H*=CCH_3), 1.94 (s, 2H, CH_2), 1.77 (s, 3H, CH_3C=C), 0.98 (s, 6H, C(CH_3)$_2$), 0.19 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (101 MHz) δ 147.2 (*C*–OTMS), 137.4 (C=*C*CH_3), 119.7 (*C*=CCH_3), 111.8 (*C*=COTMS), 44.0 (CH_2), 32.3 (*C*(CH_3)$_2$), 28.9 (C(*C*H_3)$_2$), 23.2 (CH_3), 0.2 (Si(CH_3)$_3$); HRMS *m/z* (M^+) found 210.1440, $C_{12}H_{22}OSi$ requires 210.1440

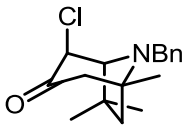
2-Chloro-4,4,6-trimethylcyclohepta-2,6-dienone (66):



A solution of silyl enol ether **67** (0.54 M in DME, 8.85 mL, 4.78 mmol) was added to sodium trichloroacetate (NaTCA; 1.42 g, 7.66 mmol). The resulting suspension was diluted with

DME (12 mL) and heated under reflux for 17 h. The mixture was cooled to rt and 10% aq HCl (20 mL) : MeOH (80 mL) added. After 2 h the aq layer was extracted with Et_2O (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 0–10% EtOAc in cyclohexane), which gave α-chloro dienone **66** (276 mg, 31%); R_f 0.28 (10% EtOAc in cyclohexane); IR (film) (cm^{-1}) 2965m, 2929m, 2871w, 1722w, 1651s (C=O), 1633s (C=C), 1376m, 917s, 889m; ^{1}H NMR (400 MHz) δ 6.80 (s, 1H, CH=CCl), 6.23 (s, 1H, C*H*=CCH_3), 2.41 (s, 2H, CH_2), 2.00 (s, 3H, CH_3), 1.21 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 183.2 (C=O), 153.2 (C=*C*CH_3), 150.6 (*C*=CCl), 133.0 (C=*C*Cl), 128.1 (*C*=CCH_3), 45.9 (CH_2), 36.8 (*C*$(CH_3)_2$), 28.6 (CH_3), 28.2 (C(*C*$H_3)_2$); m/z (ESI$^+$) 185.1 (M + H$^+$, 10); HRMS *m/z* (M$^+$) found 184.0661, $C_{10}H_{13}O^{35}Cl$ requires 184. 0655

(±)-(4*S*)-8-Benzyl-4-chloro-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-3-one ((±)-(4*S*)-65):

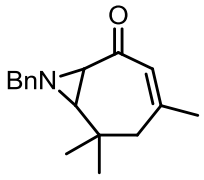


$BnNH_2$ (311 mg, 2.90 mmol) was added to a solution of α-chloro dienone **66** (108 mg, 0.58 mmol) in MeOH (5 mL) with stirring at 0 ºC. After 5 h, the mixture was warmed to rt, left to stir overnight (17 h), then evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (30 mL). The organic layer was separated, and the aq layer extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (Florisil®, gradient elution: 0–10% EtOAc in petroleum ether). First, eluted 2β-chlorotropin-3-one **65** (35 mg, 21%), then aziridine **69** (40 mg, 28%), both as clear, pale-yellow oils;

Data for 2β-chlorotropin-3-one **65**:

R_f 0.33 (10% EtOAc in cyclohexane); IR (film) (cm^{-1}) 2961m, 2930m, 2873w, 1778w, 1724s (C=O), 1455m, 737m, 699m; ^{1}H NMR (500 MHz) δ 7.46 – 7.28 (m, 5H, Ph), 4.85 (d, 1H, J = 4 Hz, CH(Cl)), 4.12 (d, 1H, J_{AB} = 14 Hz, PhCH_AH$_B$CN), 3.78 (d, 1H, J_{AB} = 14 Hz, PhCH$_A$$H_B$CN), 3.11 (d, 1H, J = 4 Hz, NCH), 2.73 (d, 1H, J_{AB} = 15 Hz, CH_AH$_B$C=O), 2.51 (d,

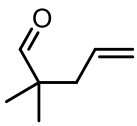
1H, J_{AB} = 15 Hz, $CH_AH_BC=O$), 1.65 – 1.60 (m, 2H, $CH_2C(CH_3)_2$), 1.29 (s, 3H, $NC(CH_3)$), 1.18 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 200.2 (C=O), 138.7 (Ar (*ipso*)), 128.6 (Ar (*ortho*)), 128.3 (Ar (*meta*)), 127.4 (Ar (*para*)), 72.7 (CH(Cl)), 64.3 ($NC(CH_3)$), 61.1 (NCH), 53.1 ($CH_2(CH_3)_2$), 51.2 ($CH_2C=O$), 47.6 ($PhCH_2N$), 40.4 ($C(CH_3)_2$), 33.5 (CH_3), 25.2 ($NC(CH_3)$), 25.0 (CH_3); m/z (ESI^+) 292.2 ($M + H^+$, 59); HRMS *m/z* ($M + H^+$) found 292.1460, $C_{17}H_{22}{}^{35}ClNO$ requires 292.1463



Data for aziridine **69**:

R_f 0.25 (10 % EtOAc in cyclohexane); IR (film) (cm^{-1}) 2959m, 1644s (C=O), 1454m, 1377m, 1331m, 1099m, 884w, 748m, 698m; ^{1}H NMR (400 MHz) δ 7.37 – 7.24 (m, 5H, Ar), 5.92 (br s, 1H $CH=C(CH_3)$), 4.06 (d, 1H, J_{AB} = 13 Hz, $PhCH_AH_BN$), 3.09 (d, 1H, J_{AB} = 13 Hz, $PhCH_AH_BN$), 2.70 (d, 1H, J_{AB} = 18 Hz, $CH_AH_BC(CH_3)_2$), 2.33 (dd, 1H, J_1 = 7 Hz, J_2 = 2 Hz, NCHC=O), 1.88 (s, 3H, $CH=C(CH_3)$), 1.74 (d, 1H, J_{AB} = 18 Hz, $CH_AH_BC(CH_3)_2$), 1.81 (dd, 1H , J_1 = 7 Hz, J_2 = 2 Hz, $CHCHC=O$), 0.92 (s, 3H, CH_3), 0.85 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 199.3 (C=O), 155.0 ($CH=C(CH_3)$), 138.4 (Ar (*ipso*)), 128.4 (Ar (*ortho*)), 128.4 (Ar (*meta*)), 127.4 (Ar (*para*)), 127.2 ($CH=C(CH_3)$), 65.0 (NCH_2Ph), 54.9 ($CHCHC=O$), 50.9 ($CHC=O$), 46.9 ($CH_2C(CH_3)_2$), 33.7 ($C(CH_3)_2$), 30.8 (CH_3), 29.2 ($CH=C(CH_3)$), 23.3 (CH_3); m/z (ESI^+) 256.3 ($M + H^+$, 100); HRMS *m/z* ($M + Na^+$) found 278.1516, $C_{17}H_{21}NNaO$ requires 278.1515

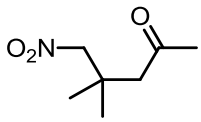
2,2-Dimethylpent-4-enal (76):[54]



IBA (**74**; 108.0 g, 1.50 mol), allyl alcohol (**75**; 58.0 g, 1.00 mol) and *p*-TSA·H_2O (400 mg, 2.10 mmol) in *p*-cymene (230 mL) were heated under reflux for 32 h, under a 50 cm Vigreux fractionating column, topped with a Dean-Stark receiver. After this time, the H_2O that had collected in the Dean-Stark reservoir was separated. The resulting solution was then distilled

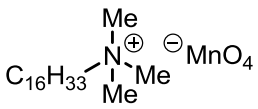
under reduced pressure (through the fractionating column), which gave unsaturated aldehyde **76** as a clear, pale-yellow oil (71.6 g, 64%); bp 60–65 °C (76 mm Hg) [lit.[54] bp 120–126 °C (760 mm Hg)]; R_f 0.17 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2961s, 2926s, 2871s, 1896w, 1729s (C=O), 1706m, 1642w, 1515s, 1464s, 1382m, 1364m, 1057m, 918m, 815s, 721m, 543m; ^{1}H NMR (400 MHz) δ 9.48 (s, 1H, CHO), 5.77 – 5.65 (m, 1H, C*H*=CH_2), 5.11 – 5.03 (m, 2H, CH=C*H*$_2$), 2.22 (dt, 2H, J_1 = 7 Hz, J_2 = 1 Hz, CH_2), 1.06 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 205.9 (C=O), 133.1 (*C*H=CH_2), 118.4 (CH=*C*H_2), 45.7 (*C*$(CH_3)_2$), 41.4 (CH_2), 21.1 ($C(CH_3)_2$); HRMS *m/z* (M^+) found 112.0867, $C_7H_{12}O$ requires 112.0888

4,4-Dimethyl-5-nitropentan-2-one (79):[56]



NaOEt (134 mg, 1.97 mmol) was added in one portion to a refluxing solution of $MeNO_2$ (**77**; 1.00 g, 16.4 mmol) and mesityl oxide (**78**; 1.93 g, 19.7 mmol) in EtOH (8 mL). After 36 h, the mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL) and washed with H_2O (30 mL), dried ($MgSO_4$) and then evaporated under reduced pressure, which gave nitroketone **79** as a clear, colourless oil (1.98 g, 76%); IR (neat) (cm^{-1}) 3060w, 2971s, 2936m, 2917m, 2883w, 1716s (C=O), 1619w, 1549s (C–NO_2), 1474m, 1450m, 1435m, 1408m, 1370s (C–NO_2), 1326w, 1269s, 1221w, 1177m, 1160m, 974w, 907w, 737s, 703w; ^{1}H NMR (400 MHz) δ 4.54 (s, 2H, CH_2NO_2), 2.56 (s, 2H, CH_2C=O), 2.13 (s, 3H, CH_3), 1.11 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 207.0 (C=O), 83.1 (CH_2NO_2), 50.2 (*C*H_2C=O), 34.1 (*C*$(CH_3)_2$), 31.3 (CH_3), 25.8 ($C(CH_3)_2$); m/z (ESI^+) 182.1 (M + Na^+, 45); HRMS *m/z* (M + Na^+) found 182.0789, $C_7H_{13}NNaO_3$ requires 182.0788

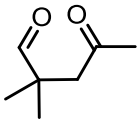
Cetyltrimethylammonium permanganate (CTAP):[57]



Cetyltrimethylammonium bromide (8.02 g, 22.0 mmol) in H_2O (150 mL) was added dropwise, over 20 min, to $KMnO_4$ (3.17 g, 20.1 mmol) in water (100 mL) at rt with stirring.

After 30 min, the violet suspension was filtered, and the filtrand washed thoroughly with water, then dried under high vacuum (0.1 mm Hg) for 3 d, which gave CTAP as a fluffy violet solid (7.18 g, 89%); mp 95–100 (decomp.) [lit.[174] mp 98 °C (decomp)]; m/z (ESI^-) 402.4 ($M - H^+$, 100)

2,2-Dimethyl-4-oxopentanal (71):



By Wacker Oxidation:[55]

A mixture of CuCl (13.9 g, 0.14 mol) and $PdCl_2$ (504 mg, 0.4 mol%) in DMF (355 mL) and H_2O (142 mL) was purged with O_2 for 3 h, with stirring at rt. Unsaturated aldehyde **76** (80.4 g, 0.72 mol) was then added to the mixture, and the resulting suspension stirred at rt under an atmosphere of O_2 for 1 h. After this time, the mixture was poured into H_2O (300 mL), and the resulting slurry filtered. The filtrand was washed with H_2O (500 mL total). The combined aq layers were extracted with pentane (5 x 150 mL). The combined organic layers were dried (Na_2SO_4), then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–50% Et_2O in petroleum ether) gave ketoaldehyde **71** as a clear, colourless oil (70.2 g, 76%); R_f 0.52 (20% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2973s, 2935s, 2875m, 2715w, 1740s (C=O), 1723s (C=O), 1473m, 1388m,1364m, 1270m, 1208m, 1181m, 1135m, 1063m, 948m, 909m, 737m, 704w; ^1H NMR (400 MHz) δ 9.49 (s, 1H, CHO), 2.68 (s, 2H, CH_2), 2.06 (s, 3H, CH_3), 1.04 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 206.3 ($CH_2C(=O)CH_3$), 204.7 (CHO), 51.3 (CH_2), 43.6 ($C(CH_3)_2$), 30.3 (CH_3), 21.9 ($C(CH_3)_2$); HRMS *m/z* (M^+) found 128.0841, $C_7H_{12}O_2$ requires 128.0837

By Nef Reaction:[58]

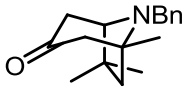
A solution of Et_3N (64 mg, 0.63 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise to nitroketone **79** (100 mg, 0.63 mmol) in CH_2Cl_2 (5 mL), with stirring at rt. After 10 min, a solution of CTAP (380 mg, 0.94 mmol) in CH_2Cl_2 (16 mL) was added dropwise, over 5 min. After stirring for 38 h at rt, the mixture was concentrated to half its original volume by

evaporation under reduced pressure. The residue was diluted with Et_2O (50 mL), and then filtered through a pad of Celite® : $MgSO_4$ (~1 : 1). The filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, gradient elution: 20–100% EtOAc in petroleum ether), which gave gave ketoaldehyde **71** as a clear, colourless oil (26 mg, 32%); other data as above.

(±)-1,6,6,8-Tetramethyl-8-azabicyclo[3.2.1]octan-3-one (88):

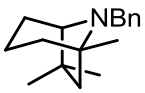
$MeNH_2$ (2.0 M in THF, 4.29 mL, 8.58 mmol) was added dropwise, to a solution of ketoaldehyde **71** (1.00 g, 7.80 mmol) in THF (10 mL) at rt, with stirring. This was followed by addition of acetone-1,3-dicarboxylic acid (**73**; 1.25 g, 8.56 mmol). After 16 h, the mixture was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, gradient elution: 0–30% EtOAc in petroleum ether) to give *N*-methyltropinone **88** as a clear, yellow oil (102 mg, 7%); R_f 0.31 (30% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2942s, 1710s (C=O), 1458m, 1412m, 1347w, 1311m, 1269w, 1175m; ^{1}H NMR (400 MHz) δ 2.97 (d, 1H, J = 5 Hz, NCH), 2.53 (dd, 1H, J_{AB} = 16.2 Hz, J = 5 Hz, NCHCH_AH_B), 2.45 (s, 3H, NCH_3), 2.43 (d, 1H, J_{AB} = 15.9 Hz, NC(CH_3)CH_AH_BC=O), 2.29 (d, 1H, J_{AB} = 16.2 Hz, NCHCH_AH_B), 2.03 (d, 1H, J_{AB} = 15.9 Hz, NC(CH_3)CH_AH_BC=O), 1.51 (dd, 1H, J_{AB} = 13 Hz, J = 3 Hz, CH_AH_BC(CH_3)$_2$), 1.43 (d, 1H, J_{AB} = 13 Hz, CH_AH_BC(CH_3)$_2$), 1.16 (d, 6H, J = 3 Hz, C(CH_3)$_2$), 0.93 (s, 3H, NC(CH_3)); ^{13}C NMR (101 MHz) δ 210.3 (C=O), 71.0 (NCH), 62.3 (N*C*(CH_3)), 52.9 (*C*H_2C(CH_3)$_2$), 48.1 (NC(CH_3)*C*H_2CO), 39.0 (NCH*C*(CH_3)$_2$), 37.6 (NCH*C*H_2), 32.7 (CH_3), 30.5 (NCH_3), 25.2 (CH_3), 24.9 (NC(*C*H_3)); m/z (ESI^+) 182.2 (M + H^+, 100); HRMS *m/z* (M + H^+) found 182.1539, $C_{11}H_{20}NO$ requires 182.1539

8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-3-one (87):



$BnNH_2$ (18.0 g, 0.17 mol) was added to a solution of ketoaldehyde **71** (19.4 g, 0.15 mol) in THF (500 mL) at rt, followed by portionwise addition of acetone-1,3-dicarboxylic acid (**73**; 24.4 g, 0.17 mol), which resulted in immediate gas evolution (CO_2). [Care! Ensure suitable exhaust!] After stirring for 60 h at rt, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (deactivated SiO_2, gradient elution: 0–4% EtOAc in petroleum ether, with 2% Et_3N also in the eluent) gave *N*-benzyltropinone **87** as a yellow oil (16.3 g, 42%); R_f 0.37 (4% EtOAc in petroleum ether); IR (film) (cm^{-1}) 2958m, 1708s (C=O), 1495w, 1455m, 1267m, 1225m, 1177m; ^{1}H NMR (400 MHz) δ 7.44 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.34 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.30 – 7.23 (m, 1H, Ar (*para*)), 4.04 (d, 1H, J_{AB} = 14 Hz, PhCH_AH$_B$N), 3.66 (d, 1H, J_{AB} = 14 Hz, PhCH$_A$$H_B$N), 2.85 (d, 1H, J = 4 Hz, NCH), 2.55 (dd, 1H, J_{AB} = 16.3 Hz, J = 4 Hz, CH_AH$_B$CH), 2.50 (d, 1H, J_{AB} = 15.8 Hz, C(=O)CH_AH$_B$CCH$_3$), 2.26 (d, 1H, J_{AB} = 16.3 Hz, CH$_A$$H_B$CH), 2.16 (d, 1H, J_{AB} = 15.8 Hz, C(=O)CH$_A$$H_BCCH_3$), 1.61 (dd, 1H, J_{AB} = 13 Hz, J = 2 Hz, CH_AH$_B$C(CH$_3$)$_2$), 1.49 (d, 1H, J_{AB} = 13 Hz, CH$_A$$H_B$C(CH$_3$)$_2$) 1.28 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 210.4 (C=O), 139.8 (Ar (*ipso*)), 128.3 (Ar), 128.2 (Ar), 126.9 (Ar (*para*)), 66.1 (NCH), 62.6 (N*C*(CH$_3$)), 52.9 (*C*H$_2$C(CH$_3$)$_2$), 49.6 (NC(CH$_3$)*C*H$_2$C=O), 47.3 (Ph*C*H$_2$N), 39.0 (*C*(CH$_3$)$_2$), 37.4 (CH*C*H$_2$), 32.4 (CH$_3$), 25.5 (CH$_3$), 24.9 (CH$_3$); m/z (ESI$^+$) 258.2 (M + H$^+$, 100); HRMS *m/z* (M + H$^+$) found 258.1851, $C_{17}H_{24}NO$ requires 258.1852

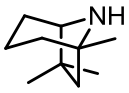
8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane (90):



A mixture of *N*-benzyltropinone **87** (4.54 g, 17.6 mmol), hydrazine monohydrate (4.60 g, 0.09 mol) and KOH (14.99 g, 0.27 mol) in diethylene glycol (36 mL) was heated to 190 °C (oil bath) for 24 h. The volatile components were then removed by distillation for 2 h at 200 °C. The reaction mixture was cooled to rt and combined with the distillate. The mixture was

diluted with water (300 mL), and the aq layer extracted with Et_2O (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–2% EtOAc in petroleum ether) gave *N*-benzyltropane **90** as a clear oil (3.66 g, 85%); R_f 0.50 (2% EtOAc in petroleum ether); IR (film) (cm^{-1}) 3064w, 3027m, 2933s, 2867s, 1494m, 1451s, 1360m, 1279m, 1131m; ^{1}H NMR (400 MHz) δ 7.54 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.40 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.35 – 7.28 (m, 1H, J = 7 Hz, Ar), 3.91 (s, 1H, J_{AB} = 14 Hz, PhCH_AH$_B$N), 3.86 (s, 1H, J_{AB} = 14 Hz, PhCH$_A$$H_B$N), 2.49 (br s, 1H, NCH), 1.96 – 1.69 (m, 6H, 3 x CH_2), 1.72 (d, 1H, J_{AB} = 13 Hz, CH_AH$_B$C(CH$_3$)$_2$), 1.60 (d, 1H, J_{AB} = 13 Hz, CH$_A$$H_B$C(CH$_3$)$_2$), 1.29 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.17 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 141.6 (Ar (*ipso*)), 128.3 (Ar (*ortho*)), 127.9 (Ar (*meta*)), 126.3 (Ar (*para*)), 64.6 (CHN), 60.0 (N*C*(CH$_3$)), 51.9 (*C*H$_2$C(CH$_3$)$_2$), 46.7 (Ph*C*H$_2$N), 37.8 (*C*(CH$_3$)$_2$), 33.2 (CH_3), 28.9 (CH_2), 26.8 (CH_3), 23.7 (CH_3), 18.6 (CH_2), 16.6 (CH_2); m/z (ESI$^+$) 244.2 (M + H$^+$, 71); HRMS *m/z* (M + H$^+$) found 244.2067, $C_{17}H_{26}N$ requires 244.2060

(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((±)-57):

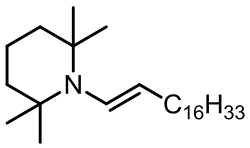


A vigorously stirred solution of *N*-benzyltropane **(±)-90** (2.44 g, 10.0 mmol) in MeOH was hydrogenated at 1 atm, in the presence of 10% palladium on activated carbon (1.06 g, 10 mol %) for 17 h. After this time, the catalyst was removed by filtration through Celite®. To the filtrate was added 1 M HCl in Et_2O (ca. 25 mL). The mixture was evaporated under reduced pressure to give the crude hydrochloride salt, which was recrystallized from EtOAc to give the tropane hydrochloride as a white crystalline solid (1.9 g, quant). [mp 201–203 °C; IR (KBr) (cm^{-1}) 3426brm (N–H), 2957s, 2782s ($R_2NH_2^+$ stretch), 2744s, 2712s, 2687s, 2657m, 2629m, 2478m, 1601s ($R_2NH_2^+$ bend), 1457m, 1380m, 1200w, 1110m, 568m; ^{1}H NMR (700 MHz) δ 9.66 (br s, 1H, NH), 9.53 (br s, 1H, NH), 3.37 (s, 1H, NCH), 2.49 – 2.40 (m, 1H, NC(CH$_3$)CH_AH$_B$), 2.33 – 2.24 (m, 1H, NCHCH_AH$_B$), 1.80 – 1.69 (m, 5H, CH_2CH$_A$$H_B$CHN and C$H_2$C(CH$_3$)$_2$), 1.65 (s, 3H, CH_3), 1.49 (d, 1H, J_{AB} = 14 Hz, NC(CH$_3$)CH$_A$$H_B$), 1.44 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 65.0 (N*C*(CH$_3$)), 64.9 (NCH), 48.2 (*C*H$_2$C(CH$_3$)$_2$), 40.3 (*C*(CH$_3$)$_2$), 35.4 (NC(CH$_3$)*C*H$_2$), 31.9 (CH_3), 25.2 (CH_3), 24.1

(NCH*C*H$_2$), 22.6 (CH$_3$), 17.3 (NCHCH$_2$*C*H$_2$); m/z (ESI$^+$) 154.2 ([M – Cl]$^+$, 100); HRMS *m/z* ([M – HCl]$^+$) found 153.1518, $C_{10}H_{19}N$ requires 153.1517] This salt (1.90 g, 10.0 mmol) was suspended in Et$_2$O (20 mL) and washed with 3 M aq NaOH (20 mL). The ethereal layer was separated and the aq phase back extracted with Et$_2$O (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave tropane **(±)-57** as a clear oil (1.54 g, quant); bp 50–60 °C (14 mm Hg); IR (neat) (cm^{-1}) 3267w (N–H), 2929s, 2868s, 1730m, 1641w, 1599w, 1453s, 1374s, 1277s, 1183m, 822s, 739s; ^{1}H NMR (400 MHz) δ 2.71 – 2.63 (m, 1H, NCH), 1.83 (br s, 1H, NH), 1.77 – 1.35 (m, 7H, 3 x CH$_2$ and 1 x C*H*$_A$H$_B$), 1.23 (d, 1H, J_{AB} = 13 Hz, CH$_A$*H*$_B$), 1.15 (s, 3H, NC(CH$_3$)), 1.12 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 65.6 (NCH), 60.3 (N*C*(CH$_3$)), 50.6 (CH$_2$), 42.9 (*C*(CH$_3$)$_2$), 39.1 (CH$_2$), 33.0 (CH$_3$), 28.7 (CH$_3$), 27.4 (CH$_2$), 23.0 (CH$_3$), 19.0 (CH$_2$); m/z (ESI$^+$) 154.1 (M + H$^+$, 100); HRMS *m/z* (M + H$^+$) found 154.1590, $C_{10}H_{20}N$ requires 154.1590

Test of Enamine Synthesis *via* Lithium Amide-Epoxide Methodology:

(*E*)-2,2,6,6-Tetramethyl-1-(octadec-1-enyl)piperidine (94):[39]

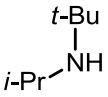


A solution of *n*-BuLi (1.6 M in hexanes, 1.84 mL, 2.94 mmol) was added dropwise, with stirring, to a solution of 2,2,6,6-TMP (**142**; 0.5 mL, 2.96 mmol) in THF (6 mL) at 0 °C. The solution was warmed to rt over 20 min whereby a solution of 1,2-epoxyoctadecane (**93**, 307 mg, 1.14 mmol) in THF (2 mL) was added in one portion. The mixture was stirred for 1 h at rt, then filtered through a pad of deactivated silica, washing the filter cake with 5% Et$_3$N in petroleum ether (350 mL). The filtrate was evaporated under reduced pressure [45 °C (0.05 mm Hg)], which gave enamine **94** as a clear, yellow oil (380 mg, 85%); IR (film) (cm^{-1}) 2925s, 2854s, 1640w (N–C=C), 1466m, 1377w, 1363w, 1265s, 1175w, 1131w, 1034w, 957w, 896w, 741s, 706m; ^{1}H NMR (400 MHz) δ 5.66 (d, 1H, J = 14 Hz, NC*H*=CH), 5.17 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 2.08 – 1.95 (m, 2H, C*H*$_2$CH=CN), 1.64 – 1.16 (m, 34H, 17 x CH$_2$), 1.07 (s, 12H, 2 x C(CH$_3$)$_2$), 0.90 (t, 3H, J = 7 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz) δ 131.1 (N*C*H=CH), 125.8 (NCH=*C*H), 53.6 (2 x *C*(CH$_3$)$_2$), 41.0 (2 x C(CH$_3$)$_2$*C*H$_2$), 31.9

(*C*H_2CH=CHN), 30.5 (CH_2), 30.3 (CH_2), 29.7 – 29.1 (13 x CH_2), 27.6 (2 x C(CH_3)$_2$), 22.6 (CH_2), 17.6 (CH_2), 14.1 (CH_2*C*H_3); m/z (ESI$^+$) 392.4 (M + H^+, 70); HRMS *m/z* (M + H^+) found 392.4244, $C_{27}H_{54}N$ requires 392.4251

Enamine Synthesis Using Nagashima's Methodology:

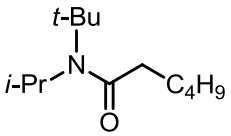
***N*-*tert*-Butyl-*N*-isopropylamine (100):**[71]



A mixture of *tert*-butylamine (**120**; 33.0 g, 0.45 mol), isopropyl bromide (36.9 g, 0.30 mol), tetrabutylammonium iodide (5.55 g, 15.0 mmol) and adiponitrile (32.4 g, 0.30 mol) was heated under reflux, with stirring, for 30 h. After cooling to rt 5 M aq KOH (90 mL, 0.45 mol) and pentane (100 mL) were added. The resulting three layers were separated: Adiponitrile was the middle layer. The organic (top) layer was dried (Na_2SO_4) and concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by fractional distillation gave amine **100** as a clear, colourless oil (19.0 g, 53%); bp 95–100 °C (760 mm Hg) [lit.[71] bp 97–99 °C (760 mm Hg)]; ^{1}H NMR (400 MHz) δ 2.87 (spt, 1H, J = 6 Hz, NCH), 1.03 (s, 9H, NC(CH_3)$_3$), 0.99 (d, 6H, J = 6 Hz, NCH(CH_3)$_2$); ^{13}C NMR (101 MHz) δ 50.7 (N*C*(CH_3)$_3$), 42.7 (NCH), 29.8 (NC(*C*H_3)$_3$), 26.2 (NCH(*C*H_3)$_2$); m/z (ESI$^+$) 154.2 (M + K^+, 100)

General Procedure for Amide Synthesis Using Hulme's Protocol:[72]

***N*-*tert*-Butyl-*N*-isopropylhexanamide (102):**

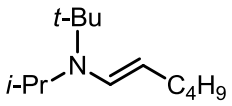


Amine **100** (810 mg, 7.03 mmol), hexanoic anhydride (**101**; 3.02 g, 14.09 mmol) and Et_3N (1.11 g, 10.97 mmol) were irradiated with microwave energy at a temperature of 160 °C for 1 h, with stirring in a sealed tube. The mixture was cooled to rt, then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution:

0–4% EtOAc in petroleum ether) to give amide **102** as a clear, colourless oil (1.35 g, 90%); R_f 0.50 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2960s, 2873s, 1723w, 1644s (C=O), 1458s, 1426s, 1368s, 1324m, 1278s, 1203s, 1179s, 1128m, 736w; ^{1}H NMR (400 MHz) δ 4.00 – 3.82 (m, 1H, NCH), 2.35 – 2.24 (m, 2H, CH_2CO), 1.73 – 1.54 (m, 2H, CH_2CH_2CO), 1.41 (s, 9H, $C(CH_3)_3$), 1.35 (d, 6H, J = 7 Hz, $CH(CH_3)_2$), 1.32 – 1.24 (m, 4H, 2 x CH_2), 0.88 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 175.9 (C=O), 58.1 ($C(CH_3)_3$), 46.2 (NCH), 38.3 (CH_2CO), 31.5 (CH_2), 29.5 ($C(CH_3)_3$), 26.2 (CH_2), 23.4 ($CH(CH_3)_2$), 22.4 (CH_2), 13.8 (CH_2CH_3); m/z (ESI^+) 214.2 ($M + H^+$, 53); HRMS *m/z* ($M + H^+$) found 214.2174, $C_{13}H_{28}NO$ requires 214.2165

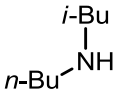
General Procedure for Enamine Synthesis Using Nagashima's Protocol:[70]

(*E*)-*N*-*tert*-Butyl-*N*-isopropylhex-1-en-1-amine (51):



PMHS (**96**; 200 mg, Si–H = 4.00 mmol) was added to a stirred solution of $IrCl(CO)(PPh_3)_2$ (Vaska's complex; 6.0 mg, 7.69 µmol) and amide **102** (160 mg, 0.75 mmol) in toluene (375 µL). H_2 evolution was immediate, and, within 5–10 min, the mixture had formed a gel. The gel was washed with Et_2O (25 mL total) and filtered through a small plug of Celite® under Ar. The solution was evaporated under reduced pressure, which gave a mixture of enamine **51** and amine **103** as a clear, colourless oil (148 mg, quant, 87:13 {**51**:**103**}); IR (neat) (cm^{-1}) 3073w, 2970s, 2925s, 2873m, 1646s (N–C=C), 1465w, 1377m, 1364m, 1302m, 1221s, 1174w, 1118w, 1098w, 956w; ^{1}H NMR (400 MHz, C_6D_6) δ6.02 (d, 1H, J = 14 Hz, NC*H*=CH), 4.69 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.40 (spt, 1H, J = 7 Hz, $NCH(CH_3)_2$), 2.14 (dt, 2H, J = 7 Hz, $NCH=CHCH_2$), 1.50 – 1.35 (m, 4H, 2 x CH_2), 1.22 (d, 6H, J = 7 Hz, $NCH(CH_3)_2$), 1.07 (s, 9H, $(NC(CH_3)_3$), 0.94 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 130.7 (N*C*H=CH), 107.1 (NCH=*C*H), 55.7 ($NC(CH_3)_3$), 46.7 ($NCH(CH_3)_2$), 34.7 (CH_2), 32.5 ($NCH=CHCH_2$), 29.6 ($NC(CH_3)_3$), 23.0 (CH_2), 21.6 ($NCH(CH_3)_2$), 14.7 (CH_2CH_3); m/z (ESI^+) 198.21 ($M + H^+$, 75); HRMS *m/z* ($M + H^+$) found 198.2214, $C_{13}H_{28}N$ requires 198.2216

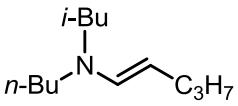
_N_-Isobutylbutan-1-amine (7):[12b]



Isobutylamine (30.0 g, 0.41 mol) was heated to reflux, with stirring. *n*-Butyl bromide (19.6 g, 0.14 mol) was added at a rate sufficient to maintain reflux without external heating. Following addition of the electrophile, the mixture was refluxed for a further 30 min, resulting in precipitation of a white solid. H_2O (10 mL) followed by 8 M aq NaOH (22 mL) were added, forming two layers. The upper layer was separated and treated with KOH, until aq partitioning ceased. The organic (top) layer was separated and stirred vigorously over KOH for 10 min, then decanted and fractionally distilled, to give amine **7** as a clear, colourless oil (13.1 g, 71%); bp 74–79 °C (76 mm Hg) [lit.[12b] bp 147–152 °C (760 mm Hg)]; IR (neat) (cm^{-1}) 2986m, 2932m, 1551m, 1381w, 1367w, 1258s, 1150m; ^1H NMR (400 MHz) δ 2.54 (t, 2H, J = 7 Hz, NHCH_2CH$_2$), 2.37 (d, 2H, J = 7 Hz, NHCH_2CH$(CH_3)_2$), 1.77 – 1.64 (m, 1H, NHCH_2C$H(CH_3)_2$), 1.49 – 1.38 (m, 2H, NHCH$_2$CH_2), 1.36 – 1.23 (m, 2H, CH_2CH$_3$), 0.94 – 0.79 (m, 9H, 3 x CH_3); ^{13}C NMR (101 MHz) δ 58.1 (NHCH_2CH$(CH_3)_2$), 49.8 (NCH_2CH$_2$), 32.3 (NCH$_2$$CH_2$), 28.2 (NCH$_2$$CH(CH_3)_2$), 20.6 (NCH$_2$CH($CH_3)_2$), 20.4 ($CH_2CH_3$), 13.9 (CH$_2$$CH_3$); m/z (ESI$^+$) 130.14 (M + H$^+$, 21); HRMS *m/z* (M + H$^+$) found 130.1592, $C_8H_{20}N$ requires 130.1590

General Procedure for Enamine Synthesis Using Curphey's Protocol:

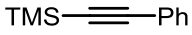
(*E*)-*N*-Butyl-*N*-isobutylpent-1-en-1-amine (9):[12b]



K_2CO_3 (3.21 g, 23.2 mmol) was added to a stirred solution of amine **7** (3.05 g, 23.6 mmol) in Et_2O (5.9 mL). The resulting slurry was cooled to 0 °C, and valeraldehyde (**8**; 2.03 g, 23.6 mmol) added dropwise. After 15 min, the mixture was warmed to rt and stirred for 16 h. After this time, the slurry was filtered through Celite®, and the filtrate evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation, which gave enamine **9** as a clear, colourless oil (3.01 g, 66%); bp 90–95 °C (7.6 mm Hg) [lit.[12b] 63–67 °C (1.5 mm Hg)]; IR (neat) (cm^{-1}) 3050w, 2957s, 2871s, 1653s (N–C=C), 1466s, 1378s, 1335m, 1292m,

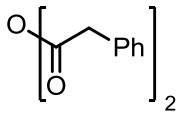
1234m, 1207m, 1190m, 1114s, 936s, 877w, 760w; ^{1}H NMR (400 MHz, C_6D_6) δ 5.91 (d, 1H, J = 14 Hz, NC*H*=CH), 4.22 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 2.80 (t, 2H, J = 7 Hz, NC*H*$_2$CH$_2$), 2.56 (d, 2H, J = 7 Hz, NCH$_2$C*H*$_2$), 2.12 (dt, 2H, J = 7 Hz, NCH=CHC*H*$_2$), 1.81 (spt, 1H, J = 7 Hz, NCH$_2$C*H*(CH$_3$)$_2$), 1.53 – 1.36 (m, 4H, J = 7 Hz, NCH$_2$C*H*$_2$ and NCH=CHCH$_2$C*H*$_2$), 1.24 – 1.12 (m, 2H, J = 7 Hz, N(CH$_2$)$_2$C*H*$_2$CH$_3$), 1.00 (t, 3H, J = 7 Hz, N(CH$_2$)$_2$CH$_2$C*H*$_3$), 0.85 (t, 3H, J = 8 Hz, NCH=CH(CH$_2$)$_2$C*H*$_3$), 0.81 (d, 6H, J = 7 Hz, NCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, C_6D_6) δ 139.2 (N*C*H=CH), 96.1 (NCH=*C*H), 60.7 (N*C*H$_2$CH(CH$_3$)$_2$), 52.4 (N*C*H$_2$CH$_2$), 34.1 (NCH=CH*C*H$_2$), 30.1 (NCH=CHCH$_2$*C*H$_2$), 27.9 (NCH$_2$*C*H(CH$_3$)$_2$), 25.9 (NCH$_2$*C*H$_2$), 21.1 (N(CH$_2$)$_2$*C*H$_2$CH$_3$), 20.9 (NCH$_2$CH(*C*H$_3$)$_2$), 14.6 (NCH=CH(CH$_2$)$_2$*C*H$_3$), 14.2 (N(CH$_2$)$_2$CH$_2$*C*H$_3$); m/z (ESI$^+$) 198.21 (M + H$^+$, 55); HRMS *m/z* (M + H$^+$) found 198.2217, $C_{13}H_{28}N$ requires 198.2216

Representative Procedure for Formation of Trimethyl(phenylethynyl)silane (112):



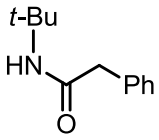
A solution of *n*-BuLi (1.6 M in hexanes, 2.71 mL, 4.34 mmol) was added dropwise, with stirring, to amine **100** (500 mg, 4.34 mmol) in THF (5 mL) at –78 °C. The solution was warmed to rt over 20 min, whereby a solution of styrene oxide (**109**, 174 mg, 1.45 mmol) in THF (2 mL) was added in one portion. The mixture was stirred for 1 h at rt, then cooled to 0 °C. TMSCl (184 µL, 1.45 mmol) was added, and the mixture allowed to warm to rt. After 16 h, the reaction was re-cooled to 0 °C and quenched with sat. aq NH_4Cl (10 mL). After warming to rt, the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, petroleum ether) gave TMS-substituted alkyne **112**[175] as a clear, colourless oil (43 mg, 17%); R_f 0.37 (petroleum ether); IR (neat) (cm^{-1}) 3054m, 2963m, 2158m (C≡C), 1598w, 1488m, 1422w, 1265s, 1015m, 864s; ^{1}H NMR (400 MHz) δ 7.52 – 7.44 (m, 2H, Ar), 7.34 – 7.28 (m, 3H, Ar), 0.28 (s, 9H, Si(CH$_3$)$_3$); ^{13}C NMR (101 MHz) δ 131.9 (Ar), 128.5 (Ar), 128.2 (Ar), 123.1 (Ar), 105.1 (Ph*C*≡CTMS), 94.1 (PhC≡*C*TMS), 0.0 (Si(CH$_3$)$_3$)

2-Phenylacetic anhydride (121):[74]



Phenylacetic acid (1.00 g, 7.34 mmol), and Et_3N (744 mg, 7.35 mmol) in EtOAc (143 mL) were stirred for 10 min at 0 °C. Triphosgene (371 mg, 1.25 mmol) was added in one portion, which resulted in immediate formation of a white precipitate ($Et_3N{\cdot}HCl$). After 10 min, external cooling was removed, and stirring continued for 15 min. The suspension was filtered, and the filtrate evaporated under reduced pressure. Purification of the residue by crystallization from EtOAc / hexane at rt gave anhydride **121** (900 mg, 48%) as clear, white crystals; mp 72–73 °C [lit.[74] 71–72 °C] R_f 0.61 (4% EtOAc in petroleum ether); ^{1}H NMR (400 MHz) δ 7.40 – 7.18 (m, 10H, Ar), 3.74 (s, 4H, 2 x CH_2Ph); ^{13}C NMR (101 MHz) δ 166.9 (2 x C=O), 131.9 (2 x Ar (*ipso*)), 129.4 (4 x Ar), 128.7 (4 x Ar), 127.6 (2 x Ar), 42.0 (2 x CH_2Ph); m/z (ESI$^+$) 277.1 (M + Na^+, 71)

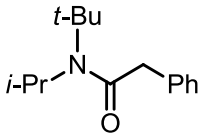
***N-tert*-Butylbenzamide (125):**[80]



Phenylacetyl chloride (**122**; 1.00 g, 6.47 mmol) was added dropwise, over 15 min, to a solution of *tert*-butylamine (**120**; 946 mg, 12.93 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After 1 h, the resultant slurry was warmed to rt, and stirring continued for 2 h. The mixture was then partitioned between H_2O (20 mL) and CH_2Cl_2 (25 mL). The organic layer was separated and the aq layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give amide **125** as an off-white solid (1.20 g, 97%); mp 114–116 °C [lit.[80] mp 114–115 °C]; R_f 0.26 (20% EtOAc in petroleum ether); IR (film) (cm^{-1}) 3421w (N–H), 3055m, 2985m, 1670s (C=O), 1603w, 1515m, 1497w, 1454m, 1422m, 1393w, 1365w, 1265s, 1224w, 896m, 747s; ^{1}H NMR (400 MHz) δ 7.39 – 7.21 (m, 5H, Ar), 5.26 (br s, 1H, NH), 3.48 (s, 2H, CH_2Ph), 1.29 (s, 9H, C(CH_3)$_3$); ^{13}C (101 MHz) δ 170.2 (C=O), 135.4 (Ar (*ipso*)), 129.2 (Ar), 128.8 (Ar), 127.0 (Ar), 51.1 (*C*(CH_3)$_3$),

44.8 (CH_2Ph), 28.6 ($C(CH_3)_3$); m/z (ESI^+) 192.1 ($M + H^+$, 41); HRMS *m/z* ($M + Na^+$) found 214.1202, $C_{12}H_{17}NNaO$ requires 214.1202

***N*-*tert*-Butyl-*N*-isopropyl-2-phenylacetamide (126):**



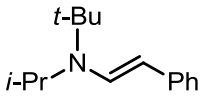
*Example synthesis with phenylacetyl chloride (**122**):*

Phenylacetyl chloride (**122**; 265 mg, 1.71 mmol) was added dropwise to a solution of amine **100** (415 mg, 3.60 mmol) in CH_2Cl_2 (30 mL), with stirring at 0 °C. The reaction was warmed to rt, and stirred for 16 h. The mixture was partitioned with H_2O (10 mL). The organic layer was separated, and the aq layer washed with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–6% EtOAc in petroleum ether then CH_2Cl_2) gave amide **126** (80 mg, 20%); R_f 0.12 (4% EtOAc in petroleum ether); ^1H NMR (400 MHz) δ 7.35 – 7.19 (m, 5H, Ar), 4.05 (br s, 1H, $CH(CH_3)_2$), 3.73 (s, 2H, CH_2Ph), 1.47 (s, 9H, $C(CH_3)_3$), 1.39 (d, 6H, J = 5 Hz, $CH(CH_3)_2$); ^{13}C NMR (101 MHz) δ 173.3 (C=O), 136.7 (Ar (*ipso*)), 128.8 (Ar), 128.3 (Ar), 126.2 (Ar), 58.5 ($C(CH_3)_2$), 47.0 (NCH), 45.0 (CH_2Ph), 29.6 ($C(CH_3)_3$), 23.6 ($CH(CH_3)_2$); m/z (ESI^+) 234.2 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 234.1851, $C_{15}H_{24}NO$ requires 234.1852

Using CDMT:

NMM (2.11 g, 20.9 mmol) was added dropwise, over 10 min, to a mixture of phenylacetic acid (**123**; 1.88 g, 13.8 mmol), amine **100** (1.59 g, 13.8 mmol) and CDMT (2.67 g, 15.2 mmol) in MeCN (15 mL), with stirring at rt. After 2 h, H_2O (50 mL) was added, whereby a yellow oil separated, which was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 0–4% EtOAc in petroleum ether) gave amide **126** as a clear, colourless oil (2.18 g, 68%); other data as above.

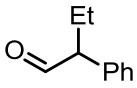
(*E*)-*N*-Isopropyl-2-methyl-*N*-styrylpropan-2-amine (107):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **126** (233 mg, 1.00 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (266 mg, Si–H = 4.01 mmol) at rt for 5–10 min gave a mixture of enamine **107** and amine **130** as a clear, pale-yellow oil (217 mg, quant, 94:6 {**107**:**130**}); IR (film) (cm^{-1}) 3235w, 3059w, 2975s, 2934m, 2875w, 2280s, 1864w, 1627s (N–C=C), 1597s, 1571w, 1495w, 1450m, 1374s, 1355m, 1330s, 1208s, 1187m, 1165m, 1027m, 938m, 812s, 694m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.31 – 6.95 (m, 5H, Ph), 6.99 (d, 1H, *J* = 14 Hz, NC*H*=CHPh), 5.49 (d, 1H, *J* = 14 Hz, NCH=C*H*Ph), 3.39 (spt, 1H, *J* = 7 Hz, NC*H*$(CH_3)_2$), 1.26 (d, 6H, *J* = 7 Hz, CH(C*H*$_3)_2$), 0.97 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (101 MHz, C_6D_6) δ 142.5 (Ar (*ipso*)), 131.6 (N*C*H=CHPh), 129.2 (Ar (*meta*)), 123.9 (Ar (*ortho*)), 123.2 (Ar (*para*)), 99.5 (NCH=*C*HPh), 57.6 (N*C*$(CH_3)_3$), 46.9 (N*C*H$(CH_3)_2$), 29.6 (NC(CH$_3)_3$), 20.5 (NCH(CH$_3)_2$); m/z (ESI$^+$) 218.2 (M + H$^+$, 34); HRMS *m/z* (M + H$^+$) found 218.1903, $C_{15}H_{24}N$ requires 218.1903

General Procedure for Alkylation:

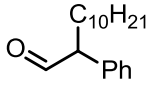
2-Phenylbutanal (132):



Enamine **107** (160 mg, 0.74 mmol), d_3-MeCN (750 µL) and EtI (231 mg, 1.48 mmol) were placed in an NMR tube fitted with a PTFE valve. This mixture was heated at 85 °C for 20 h, with occasional shaking, until consumption of the enamine was complete by ^{1}H NMR spectroscopy. Buffer solution [{AcOH (0.5 g), AcONa (0.5 g), and H_2O (1 mL)}, 0.5 mL] was then added, and the mixture heated at 85 °C. After 1 h, the mixture was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and carefully reduced under vacuum (152 mm, 0 °C). Purification of the residue by column chromatography (SiO_2, 0–4% Et_2O in petroleum ether) gave α-alkyl

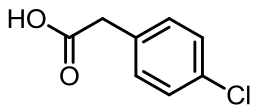
aldehyde **132**[176] as a clear, colourless oil (57 mg, 51%); R_f 0.59 (4% Et_2O in petroleum ether); IR (film) (cm^{-1}) 3155m, 3053m, 2972m, 2936w, 1721s (C=O), 1602w, 1493w, 1454m, 1422m, 1382m, 1265s, 911s, 742s; ^1H NMR (400 MHz) δ 9.69 (d, 1H, J = 2 Hz, CHO), 7.42 – 7.16 (m, 5H, Ar), 3.42 (td, 1H, J_1 = 7 Hz, J_2 = 2 Hz, C*H*CHO), 2.19 – 2.06 (m, 1H, CHCH_AH_B), 1.84 – 1.70 (m, 1H, CHCH_AH_B), 0.92 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 200.9 (C=O), 136.3 (Ar (*ipso*)), 129.0 (Ar), 128.8 (Ar), 127.5 (Ar), 60.8 (*C*HCHO), 22.9 (CH_2), 11.7 (CH_3); m/z (ESI^-) 147.1 ($M - H^+$, 31)

2-Phenyldodecanal (133):



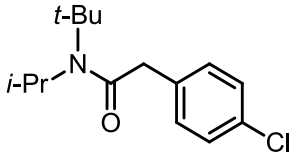
According to the general procedure for enamine alkylation, reaction of enamine **107** (113 mg, 0.52 mmol) with decyl iodide (279 mg, 1.04 mmol) in d_3-MeCN (520 µL) at 82 °C for 22 h gave, following hydrolysis with acidic buffer (250 µL) at 82 °C for 1 h, α-alkyl aldehyde **133** as a clear, colourless oil (49 mg, 37%); R_f 0.40 (2% Et_2O in petroleum ether); 3692w, 3055s, 2987m, 2929s, 2856m, 2686w, 1721s (C=O), 1602w, 1551w, 1493w, 1422s, 1265s, 1157w, 896s, 740s; ^1H NMR (400 MHz) δ 9.68 (d, 1H, J = 2 Hz, CHO), 7.38 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.31 (t, 1H, J = 7 Hz, Ar (*para*)), 7.21 (d, 2H, J = 7 Hz, Ar (*ortho*)), 3.49 (td, 1H, J_1 = 7 Hz, J_2 = 2 Hz, C*H*CHO), 2.14 – 1.99 (m, 1H, CHCH_AH_B), 1.80 – 1.68 (m, 1H, CHCH_AH_B), 1.43 – 1.15 (m, 16H, 8 x CH_2), 0.89 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 201.1 (C=O), 136.5 (Ar (*ipso*)), 129.0 (Ar), 128.8 (Ar), 127.5 (Ar), 59.2 (*C*HCHO), 31.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.44 (CH_2), 29.36 (CH_2), 29.28 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3); m/z (ESI^-) 259.2 ($M - H^+$, 100); HRMS *m/z* (M^+) found 260.2133, $C_{18}H_{28}O$ requires 260.2140

2-(4-Chlorophenyl)acetic acid (124):[83]



A mixture of 2 M aq NaOH (7 mL) and methyl 2-(4-chlorophenyl)acetate (2.00 g, 10.8 mmol) were heated under reflux for 2 h. Conc aq HCl was added, and the resulting suspension partitioned with Et_2O (10 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure, which gave 2-(4-chlorophenyl)acetic acid (**124**) as a white solid (1.85 g, quant); mp 101–103 °C [lit.[177] 105.4–106 °C]; IR (neat) (cm^{-1}) 3017w, 2916w, 2732w, 2637w, 2559w, 1694s (C=O), 1600w, 1493m, 1413m, 1337m, 1249m, 1174m, 1089m, 806m; ^{1}H NMR (400 MHz) δ 11.22 (br s, 1H, CO_2H), 7.32 (d, 2H, J = 8 Hz, Ar), 7.23 (d, 2H, J = 8 Hz, Ar), 3.63 (s, 2H, CH_2); ^{13}C NMR (101 MHz) δ 177.6 (C=O), 133.4 (CCl), 131.5 (*C*CH_2), 130.7 (Ar), 128.8 (Ar), 40.3 (CH_2); m/z (ESI^-) 169.01 ($M - H^+$, 100); HRMS *m/z* ($M - H^+$) found 169.0057, $C_8H_6{}^{35}ClO_2$ requires 169.0062

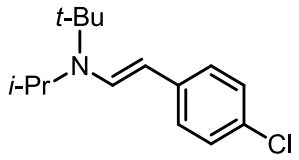
***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-N-isopropylacetamide (127):**



A mixture of 2-(4-chlorophenyl)acetic acid (**124**; 1.00 g, 5.86 mmol), amine **100** (563 mg, 4.89 mmol) and DMAP (120 mg, 0.98 mmol) in CH_2Cl_2 (22 mL) were stirred at 0 °C (ice bath) for 30 min. A solution of DCC (0.6 M in CH_2Cl_2, 11.4 mL, 6.84 mmol) was then added, dropwise. After 30 min, the reaction was warmed to rt, and stirring continued for 16 h, resulting in an orange coloration. The mixture was filtered through a thin pad of Celite®, and the filtrate evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 10% EtOAc in petroleum ether) gave amide **127** as a clear, yellow oil (935 mg, 71%); R_f 0.29 (10% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2970w, 2933w, 1718w, 1637s (C=O), 1492m, 1422m, 1362m, 1323m, 1111s, 1060m, 791m; ^{1}H NMR (400 MHz) δ 7.27 (d, 2H, J = 8 Hz, Ar), 7.20 (d, 2H, J = 8 Hz, Ar), 4.02 (m, 1H, NCH), 3.67 (s, 2H, CH_2), 1.45 (s, 9 H, $C(CH_3)_3$), 1.39 (d, 6H, J = 7 Hz, $CH(CH_3)_2$); ^{13}C NMR (101 MHz) δ

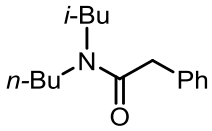
172.9 (C=O), 135.2 (CCl), 132.2 (*C*CH_2CO), 130.3 (2 x Ar), 128.4 (2 x Ar), 58.7 (N*C*$(CH_3)_3$), 46.9 (N*C*H), 44.2 (CH_2), 29.6 (C(*C*$H_3)_3$), 23.7 (CH(*C*$H_3)_2$); m/z (ESI$^+$) 267.27 (M^+, 26); HRMS *m/z* (M + H^+) found 268.1459, $C_{15}H_{23}{}^{35}ClNO$ requires 268.1463

(*E*)-*N*-(4-Chlorostyryl)-*N*-isopropyl-2-methylpropan-2-amine (129):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **127** (268 mg, 1.00 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (266 mg, Si–H = 4.01 mmol) at rt for 5 min gave, following purification by distillation, a mixture of enamine **129** and amine **131** as a clear, pale-yellow oil (177 mg, 70%, 96:4 {**129**:**131**}); bp 150–155 °C (0.08 mm Hg); IR (neat) (cm^{-1}) 2973w, 2934w, 1707w, 1622s (N–C=C), 1586m, 1490m, 1372m, 1320m, 1204m, 1181m, 1092m, 1015w, 823s; ^{1}H NMR (400 MHz ,C_6D_6) δ 7.19 (d, 2H, *J* = 9 Hz, Ar), 6.97 (d, 2H, *J* = 9 Hz, Ar), 6.86 (dd, 1H, J_1 = 15 Hz, J_2 = 1 Hz, ArCH=C*H*N), 5.31 (d, 1H, *J* = 15 Hz, ArC*H*=CHN), 3.36 (sptd, 1H, J_1 = 7 Hz, J_2 = 1 Hz, NC*H*$(CH_3)_2$), 1.22 (d, 6H, *J* = 7 Hz, NCH(C*H*$_3)_2$), 0.93 (s, 9H, C$(CH_3)_3$); ^{13}C NMR (101 MHz, C_6D_6) δ 141.1 (N*C*H=CHAr), 132.1 (Ar), 131.5 (Ar), 129.2 (Ar), 124.8 (Ar), 97.8 (NCH=*C*HAr), 57.7 (*C*$(CH_3)_3$), 46.9 (N*C*H$(CH_3)_2$), 29.5 (C(*C*$H_3)_3$), 20.3 (NCH(*C*$H_3)_2$); m/z (FI$^+$) 251.2 (M + H^+, 100); HRMS *m/z* (M^+) found 251.1445, $C_{15}H_{22}N^{35}Cl$ requires 251.1441

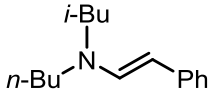
***N*-Butyl-*N*-isobutyl-2-phenylacetamide (134):**



Phenylacetyl chloride (**122**; 598 mg, 3.87 mmol) was added dropwise to a solution of amine **7** (1.00 g, 7.74 mmol) in Et_2O (10 mL) at 0 °C. The resultant slurry was warmed to rt, and stirring continued for 16 h. The mixture was then filtered, and the filter cake washed with Et_2O (50 mL). The combined organic layers were evaporated under reduced pressure.

Purification of the residue by column chromatography (SiO_2, 10% Et_2O in petroleum ether) gave amide **134** as a clear, pale-yellow oil (878 mg, 92%); R_f 0.26 (10% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3053w, 2961s, 2933s, 2873s, 1725w, 1638s (C=O), 1604m, 1584w, 1496m, 1466s, 1458s, 1424s, 1387m, 1370m, 1341w, 1203w, 1138m; ^{1}H NMR (400 MHz, 293K) two rotamers {~ 1:1} δ 7.35 – 7.18 (m, 5H, Ar), 3.72 (3.70) (s, 2H, CH_2Ph), 3.34 (3.22) (t, 2H, J = 8 Hz, NCH_2CH$_2$), 3.18 (3.06) (d, 2H, J = 8 Hz, NCH_2CH), 2.07 – 1.87 (m, 1H, CH(CH$_3$)$_2$), 1.57 – 1.41 (m, 2H, NCH$_2$CH_2), 1.34 – 1.22 (m, 2H, CH_2CH$_3$), 0.94 – 0.82 (m, 9H, J = 8 Hz, CH$_2$CH_3 and CH(CH_3)$_2$); ^{13}C NMR (101 MHz, 293K) two rotamers {~ 1:1} δ 170.9 (170.8) (C=O), 135.54 (135.48) (Ar (*ipso*)), 128.7 (128.6) (Ar (*meta*)), 128.49 (128.48) (Ar (*ortho*)), 126.6 (126.5) (Ar (*para*)), 55.2 (52.6) (NCH$_2$CH$_2$), 48.4 (46.0) (NCH$_2$CH(CH$_3$)$_2$) 41.1 (40.8) (CH$_2$Ph), 30.8 (29.2) (NCH$_2$$CH_2$), 27.8 (26.7) (NCH$_2$$C$H(CH$_3$)$_2$), 20.2 (20.02) ($CH_2CH_3$), 20.1 (19.96) (CH($CH_3$)$_2$), 13.8 (13.7) (CH$_2$$CH_3$); m/z (ESI$^+$) 248.2 (M + H$^+$, 66); HRMS *m/z* (M + Na$^+$) found 270.1828, $C_{16}H_{25}NNaO$ requires 270.1828

(*E*)-*N*-Isobutyl-*N*-styrylbutan-1-amine (108):



Using Curphey's Protocol:[12]

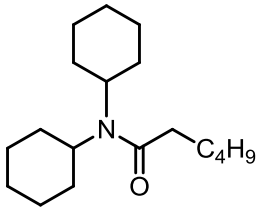
According to the general procedure for enamine synthesis following Curphey's protocol, reaction of amine **7** (2.14 g, 16.6 mmol), K_2CO_3 (2.30 g, 16.6 mmol) and phenylacetaldehyde (**105**; 2.00 g, 16.6 mmol) at 0 °C–rt for 16 h gave enamine **108** as a clear, pale-yellow oil (2.08 g, 54%); bp 175–180 °C (7.6 mm Hg); IR (neat) (cm^{-1}) 3056w, 3026s, 2958m, 2870m, 1677s (C=C), 1634m, 1595s, 1495m, 1466m, 1384m, 1310w, 1249w, 1180w, 1121m, 1027w, 937w; ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 – 7.19 (m, 4H, Ar (*ortho* and *meta*)), 6.99 (t, 1H, J = 7 Hz, Ar), 6.70 (d, 1H, J = 14 Hz, NCH=CH), 5.27 (d, 1H, J = 14 Hz, NCH=CH), 2.82 (t, 2H, J = 7 Hz, NCH_2CH$_2$), 2.60 (d, 2H, J = 7 Hz, NCH_2CH), 1.76 (spt, 1H, J = 7 Hz, CH(CH$_3$)$_2$), 1.37 (quin, 2H, J = 7 Hz, NCH$_2$CH_2), 1.13 (sxt, 2H, J = 7 Hz, CH_2CH$_3$), 0.83 (t, 3H, J = 7 Hz, CH$_2$CH_3), 0.76 (d, 6H, J = 7 Hz, CH(CH_3)$_2$); ^{13}C NMR (101 MHz, C_6D_6) δ 141.4 (Ar (*ipso*)), 139.3 (NCH=CH), 129.2 (Ar (*meta*)), 124.2 (Ar (*ortho*)), 123.5 (Ar (*para*)), 97.1 (NCH=CH), 60.8 (NCH$_2$CH), 52.0 (NCH$_2$CH$_2$), 30.2 (NCH$_2$$CH_2$), 28.0 (NCH$_2$$C$H(CH$_3$)$_2$, 20.9 ($CH_2CH_3$),

20.6 ($NCH_2CH(CH_3)_2$), 14.5 (CH_2CH_3); m/z (ESI^+) 232.2 ($M + H^+$, 24); HRMS *m/z* ($M + H^+$) found 232.2059, $C_{16}H_{26}N$ requires 232.2060

Using Nagashima's Protocol:

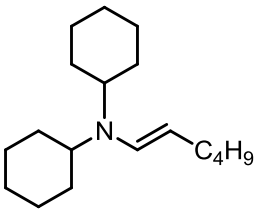
According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **134** (252 mg, 1.02 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (266 mg, Si–H = 4.01 mmol) at rt for 5 min gave a mixture of enamine **108** and amine **135** as a clear, pale-yellow oil (219 mg, 93%, 88:12 {**108**:**135**}); other data as above.

***N,N*-Dicyclohexylhexanamide (137):**



According to the general procedure for amide synthesis using Hulme's protocol, reaction of dicyclohexylamine (**136**; 1.00 g, 5.52 mmol) with hexanoic anhydride (**101**; 1.80 g, 8.40 mmol) and Et_3N (5 mL, 35.9 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, gradient elution: 2–4% EtOAc in petroleum ether), amide **137** as a clear, colourless oil (1.44 g, 93%); R_f 0.26 (4% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2927s, 2853m, 1638s (C=O), 1435 m, 1366m, 1301m, 1185m, 1052w, 997m, 895m, 730m; ^1H NMR (500 MHz, d_6-DMSO, 363K) δ 3.30 (br s, 2H, 2 x NCH), 2.28 (t, 2H, J = 7 Hz, $CH_2C=O$), 1.78 (d, 4H, J_{AB} = 13 Hz, 4 x $NCHCH_2CH_AH_B$), 1.66 – 1.48 (m, 6H, CH_2CH_2CO and 4 x $NCHCH_AH_B$), 1.63 (d, 2H, J_{AB} = 13 Hz, 2 x $NCH(CH_2)_2CH_AH_B$), 1.39 – 1.26 (m, 12H, 4 x $NCHCH_AH_BCH_AH_B$ and $CH_2CH_2CH_3$), 1.20 – 1.08 (m, 2H, 2 x $NCH(CH_2)_2CH_AH_B$), 0.92 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, d_6-DMSO, 363K) δ 171.6 (C=O), 56.3 (2 x NCH), 35.0 ($CH_2C=O$), 31.5 ($CH_3CH_2CH_2$), 31.2 (4 x $NCHCH_2$), 26.3 (4 x $NCHCH_2CH_2$), 25.5 (2 x $NCH(CH_2)_2CH_2$), 25.3 ($CH_2CH_2C=O$), 22.3 (CH_2CH_3), 14.1 (CH_2CH_3); m/z (ESI^+) 280.3 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 280.2627, $C_{18}H_{34}NO$ requires 280.2635

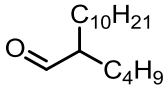
(*E*)-*N*-Cyclohexyl-*N*-(hex-1-en-1-yl)cyclohexanamine (138):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **137** (210 mg, 0.75 mmol) with a solution of Vaska's complex (0.02 M in toluene, 375 µL, 7.5 µmol) and PMHS (200 mg, Si–H = 3.01 mmol) at rt for 5 min gave a mixture of enamine **138** and amine **139** as a clear, pale-yellow oil (180 mg, 92%, 74:26 {**138**:**139**}); IR (neat) (cm^{-1}) 2926s, 2852s, 1645s (C=O), 1450m, 1339m, 1279m, 1258m, 1215m, 1167m, 1138m, 985w, 938m, 891m, 728w; ^{1}H NMR (400 MHz, C_6D_6) δ 6.18 (d, 1H, J = 14 Hz, NC*H*=CH), 4.37 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.00 (tt, 2H, J_1 = 12 Hz, J_2 = 4 Hz, 2 x NC*H*CH_2), 2.25 (dt, 2H, J = 7 Hz, CH=CHC*H*$_2$), 1.73 (d, 4H, J_{AB} = 13 Hz, 4 x NCHC*H*$_A$$CH_B$), 1.66 (d, 4H, J_{AB} = 13 Hz, 4 x NCHCH_2C*H*$_A$$CH_B$), 1.57 – 1.42 (m, 6H, C*H*$_2$C*H*$_2$$CH_3$ and 2 x NC$H(CH_2)_2$C*H*$_A$$CH_B$), 1.39 – 1.11 (m, 8H, 4 x NCHCH_AC*H*$_B$CH_A*H*$_B$), 1.01 – 0.91 (m, 2H, 2 x NC$H(CH_2)_2$CH_AC*H*$_B$), 0.97 (t, 3H, J = 7 Hz, CH_2C*H*$_3$); ^{13}C NMR (101 MHz, C_6D_6) δ 133.1 (N*C*H=CH), 95.0 (NCH=*C*H), 55.8 (2 x N*C*HCH_2), 35.4 (*C*$H_2CH_2CH_3$), 33.2 (4 x NCH*C*H_2), 32.2 (NCH=CH*C*H_2), 27.2 (4 x NCHCH_2*C*H_2), 26.6 (2 x NC$H(CH_2)_2$*C*H_2), 23.0 (*C*H_2CH_3), 14.8 (CH_2*C*H_3)

Alkylation of Enamine 138:

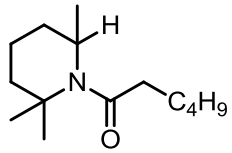
2-Butyldodecanal (140):



According to the general procedure for enamine alkylation, reaction of enamine **138** (124 mg, 0.47 mmol) with decyl iodide (361 mg, 1.35 mmol) in d_3-MeCN (0.5 mL) at 94 °C for 12 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, α-alkyl aldehyde **140**[16,39] as a clear, colourless oil (67 mg, 60%); R_f 0.15 (1% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2957m, 2924s, 2855m, 2692w, 1727s (C=O), 1465m, 1378w, 724w; ^{1}H NMR (400 MHz) δ 9.56 (d, 1H, J = 3 Hz, CHO), 2.27 – 2.17 (m, 1H, C*H*CHO), 1.69 – 1.18 (m,

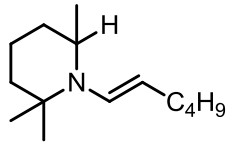
24H, 12 x CH_2), 0.90 (t, 3H, J = 7 Hz, CH_3), 0.88 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 205.8 (C=O), 52.0 (*C*HCHO), 31.9 (CH_2), 29.7 (CH_2), 29.57 (CH_2), 29.56 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 13.9 (CH_3); m/z (ESI$^+$) 263.3 (M + Na$^+$, 18); HRMS *m/z* (M$^+$) found 240.2541, $C_{16}H_{32}O$ requires 240.2453

1-(2,2,6-Trimethylpiperidin-1-yl)hexan-1-one (143):



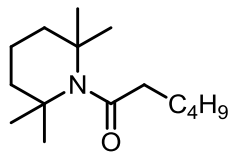
According to the general procedure for amide synthesis using Hulme's protocol, reaction of 2,2,6-TriMP[16] (**141**; 584 mg, 4.59 mmol) with hexanoic anhydride (**101**; 2.06 g, 9.61 mmol) and Et_3N (712 mg, 7.04 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, gradient elution: 0–4% EtOAc in petroleum ether), amide **143** as a clear, colourless oil (893 mg, 86%); R_f 0.25 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2957s, 2872s, 1647s (C=O), 1463s, 1399s, 1363s, 1273s, 1147s, 1111w, 1064w, 1027m, 734w, 640w; ^{1}H NMR (400 MHz) δ 3.97 (quin, 1H, J = 7 Hz, C*H*(CH_3)), 2.40 – 2.11 (m, 2H, CH_2C=O), 1.89 – 1.52 (m, 7H, 3 x CH_2 and 1 x C*H*$_A$H$_B$) 1.48 – 1.36 (m, 1H, CH$_A$*H*$_B$), 1.45 (s, 3H, CH_3) 1.42 (s, 3H, CH_3) 1.34 – 1.19 (m, 4H, 2 x CH_2), 1.25 (d, 3H, J = 7 Hz, CH(C*H*$_3$)), 0.86 (t, 3H, J = 7 Hz, CH_2C*H*$_3$); ^{13}C NMR (101 MHz) δ 173.9 (C=O), 55.1 (*C*(CH_3)$_2$), 48.3 (NCH), 38.1 (C(CH_3)$_2$*C*H$_2$), 35.5 (*C*H$_2$C=O), 31.6 (CH(CH_3)*C*H$_2$), 28.0 (CH_3), 27.7 (CH_3), 27.6 (CH_2), 25.4 (CH_2), 22.9 (CH(*C*H$_3$)), 22.5 (*C*H$_2$CH$_3$), 14.0 (*C*H$_2$CH$_2$C(CH_3)$_2$), 13.9 (CH_2*C*H$_3$); HRMS *m/z* (M$^+$) found 225.2094 $C_{14}H_{27}NO$ requires 225.2093

(±)-(*E*)-1-(Hex-1-enyl)-2,2,6-trimethylpiperidine ((±)-54a):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **143** (225 mg, 1.00 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (266 mg, Si–H = 4.01 mmol) at rt for 25 min gave a mixture of enamine **(±)-54a**[16] and amine **146** as a clear, colourless oil (221 mg, quant, 70:30 {**(±)-54a**:**146**}); IR (film) (cm^{-1}) 1642s (N–C=C), 1459s, 1331s, 1268s, 1245s, 1148s, 1088m, 977w; ^{1}H NMR (400 MHz, C_6D_6) δ 6.05 (d, 1H, J = 14 Hz, NC*H*=CH), 4.65 (dt, 1H, J_1= 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.35 – 3.23 (m, 1H, NC*H*(CH_3)), 2.18 – 2.09 (m, 2H, NCH=CHC*H*$_2$), 1.64 – 1.21 (m, 10H, 5 x CH_2), 1.11 (s, 3H, CH_3) 1.11 (d, 3H, J = 6 Hz, NCH(C*H*$_3$)), 1.09 (s, 3H, CH_3), 0.96 (t, 3H, J = 7 Hz, CH_2C*H*$_3$); ^{13}C NMR (101 MHz, C_6D_6) 134.0 (N*C*=CH), 108.5 (NC=*C*H), 54.0 (*C*(CH_3)$_2$), 48.4 (*C*H(CH_3)), 40.8 (CH_2), 34.5 (CH_2), 33.2 (CH_2), 31.8 (NCH=CH*C*H$_2$), 29.0 (CH_3), 27.3 (CH_3), 23.0 (CH_2), 18.8 (CH(*C*H$_3$)), 18.3 (CH_2), 14.7 (CH_2*C*H$_3$); m/z (ESI$^+$) 210.2 (M + H$^+$, 20)

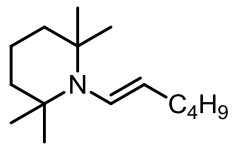
1-(2,2,6,6-Tetramethylpiperidin-1-yl)hexan-1-one (144):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of 2,2,6,6-TMP (**142**; 614 mg, 4.35 mmol) with hexanoic anhydride (**101**; 1.82 g, 8.49 mmol) and Et_3N (678 mg, 6.70 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, gradient elution: 0–4% EtOAc in petroleum ether) and base wash [The chromatographed residue was dissolved in CH_2Cl_2 (20 mL) and washed with 5% aq Na_2CO_3 (10 mL). The aq layer was back-extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure.], amide **144** as a clear, colourless oil (642 mg, 62%); R_f 0.25 (4% EtOAc in petroleum ether); R_f 0.35 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2957s, 2872s, 1731w, 1642s (C=O), 1466s, 1372s, 1305m, 1280s, 1264s, 1244m, 1210w, 1168s, 1140s,

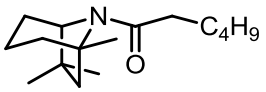
1096m, 1065w, 1030w, 979m, 924w, 733w, 646w; ^{1}H NMR (400 MHz, 293 K) two rotamers {~1:1} δ 2.37 – 2.27 (m, 2H, CH_2C=O), 1.77 – 1.69 (m, 6H, 2 x C*H*$_2$C(CH$_3$)$_2$ and C*H*$_2$CH$_2$C(CH$_3$)$_2$), 1.69 – 1.60 (m, 2H, C*H*$_2$CH$_2$C=O), 1.43 (1.42) (s, 12H, 2 x C(CH$_3$)$_2$), 1.35 – 1.25 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 0.93 – 0.82 (m, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz) δ 178.0 (C=O), 55.6 (2 x *C*(CH$_3$)$_2$), 40.3 (*C*H$_2$C=O), 36.5 (2 x *C*H$_2$C(CH$_3$)$_2$), 31.7 (CH$_2$), 30.1 (2 x C(*C*H$_3$)$_2$), 26.8 (*C*H$_2$CH$_2$C=O), 22.5 (CH$_2$), 14.4 (*C*H$_2$CH$_2$C(CH$_3$)$_2$) 13.9 (CH$_2$*C*H$_3$); m/z (ESI$^+$) 240.3 (M + H$^+$, 4); HRMS *m/z* (M$^+$) found 239.2240, $C_{15}H_{29}NO$ requires 239.2249

(*E*)-1-(Hex-1-enyl)-2,2,6,6-tetramethylpiperidine (145):



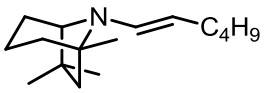
According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **144** (170 mg, 0.71 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (267 mg, Si–H = 2.85 mmol) at rt for 25 min gave a mixture of enamine **145** and amide **144** as a clear, colourless oil (150 mg, 92%, 68:32 {**145**:**144**}); IR (film) (cm^{-1}) 2927s, 2872s, 1731w, 1644s (N–C=C), 1465s, 1375s, 1266s, 1247s, 1201m, 1169m, 1132s, 1063m, 1034m, 957m, 908w, 794w, 700w; ^{1}H NMR (400 MHz, C_6D_6) δ 5.79 (d, 1H, *J* = 14 Hz, NC*H*=CH), 5.32 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 2.05 (dt, 2H, *J* = 7 Hz, C*H*$_2$CH=CHN), 1.52 – 1.27 (m, 10H, 5 x CH$_2$), 1.13 (s, 12H, 2 x C(CH$_3$)$_2$), 0.90 (t, 3H, *J* = 7 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, C_6D_6) δ 132.1 (N*C*H=CH), 126.6 (NCH=*C*H), 54.1 (2 x N*C*(CH$_3$)$_2$) 41.9 (2 x NC(CH$_3$)$_2$*C*H$_2$), 33.4 (CH$_2$), 31.1 (NCH=CHC*H*$_2$), 28.3 (2 x NC(*C*H$_3$)$_2$), 23.1 (CH$_2$), 18.5 (*C*H$_2$CH$_2$C(CH$_3$)$_2$), 14.6 (CH$_2$*C*H$_3$); m/z (ESI$^+$) 224.2 (M + H$^+$, 65); HRMS *m/z* (M + H$^+$) found 224.2374, $C_{15}H_{30}N$ requires 224.2373

1-((±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octan-8-yl)hexan-1-one (147):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of tropane (**57**; 676 mg, 4.41 mmol) with hexanoic anhydride (**101**; 1.85 g, 8.63 mmol) and Et_3N (654 mg, 6.46 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, gradient elution: 0–4% EtOAc in petroleum ether) and base wash [The chromatographed residue was dissolved in CH_2Cl_2 (10 mL) and washed with 5% aq Na_2CO_3 (5 mL). The aq layer was back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure.], amide **147** as a clear, colourless oil (1.01 g, 91%); R_f 0.30 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2957s, 1649s (C=O), 1404s, 1260m, 1159w, 1121m, 924w; ^{1}H NMR (400 MHz, C_6D_6) δ 3.06 (br s, 1H, NCH), 2.27 – 2.10 (m, 2H, NC(CH_3)CH_AH$_B$ and CH_AH$_B$C=O), 2.09 – 1.97 (m, 1H, CH$_A$$H_B$C=O), 1.87 – 1.69 (m, 5H, NC(CH_3) and CH_2CH$_2$CO), 1.56 – 1.41 (m, 1H, CH_AH$_B$CH$_2$CHN), 1.41 – 1.17 (m, 9H, CH$_A$$H_BCH_2$CHN and 4 x CH_2), 1.08 (dd, 1H, J_{AB} = 13 Hz, J = 6 Hz, NC(CH_3)CH$_A$$H_B$), 0.95 (s, 3H, CH_3), 0.89 (t, 3H, J = 7 Hz, CH_2CH_3), 0.82 (s, 3H, CH_3); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0 (C=O), 67.9 (NCH), 63.6 (NC(CH_3)), 52.3 (CH_2C(CH_3)$_2$), 38.3 (C(CH_3)$_2$), 36.4 (CH_2C=O), 35.2 (CH_2C(CH_3)N), 32.7 (CH_3), 32.5 (CH_2), 28.4 (NC(CH_3)), 27.6 (CH_2CHN), 25.7 (CH_2CH_2C=O), 23.4 (CH_3), 23.0 (CH_2), 19.3 (CH_2CH_2C(CH_3)N), 14.7 (CH_2CH_3); m/z (ESI^+) 252.2 (M^+, 100); HRMS *m/z* (M + Na^+) found 274.2137, $C_{16}H_{29}NNaO$ requires 274.2141

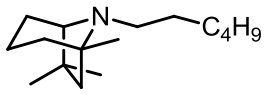
(±)-8-((*E*)-Hex-1-enyl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-92):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **147** (292 mg, 1.16 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (293 mg, Si–H = 4.41 mmol) at rt for 25 min gave a mixture of enamine **(±)-92** and amine **148** as a clear, colourless oil (277 mg, quant, 87:13 {**(±)-92**:**148**}); IR (neat) (cm^{-1}) 2932s, 2870s, 1649s (N–C=C), 1332s, 1247s, 1139m, 936s;

^{1}H NMR (400 MHz, C_6D_6) δ 6.06 (d, 1H, J = 14 Hz, NC*H*=CH), 4.38 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.09 (br s, 1H, NC*H*C$(CH_3)_2$), 2.29 – 2.10 (m, 3H, NCH=CHCH_2 and CH_AH$_B$), 1.69 – 1.36 (m, 8H, 3 x CH_2 and 2 x CH_AH$_B$), 1.31 (d, 1H, J_{AB} = 13 Hz, CH$_A$$H_B$), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.04 – 0.92 (m, 2H, 2 x CH$_A$$H_B$), 1.01 (s, 3H, CH_3), 0.95 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 131.1 (N*C*H=CH), 102.3 (NCH=*C*H), 65.2 (N*C*HC$(CH_3)_2$), 61.3 (N*C*(CH_3)), 51.7 (CH_2), 38.6 (*C*$(CH_3)_2$), 35.5 (CH_2), 34.9 (CH_2), 33.6 (CH_3), 32.0 (NCH=CH*C*H_2), 26.1 (CH_3), 23.5 (CH_3), 23.0 (CH_2), 20.1 (CH_2), 18.1 (CH_2), 14.7 (CH_2*C*H_3); m/z (ESI$^+$) 236.2 (M + H$^+$, 100); HRMS *m/z* (M + H$^+$) found 236.2374, $C_{16}H_{30}N$ requires 236.2373

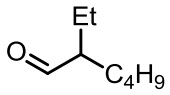
(±)-8-Hexyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane (148):



LAH (46 mg, 1.21 mmol) in THF (5 mL) was transferred dropwise *via* cannula to a solution of amide **147** (106 mg, 0.42 mmol) in THF (5 mL) with stirring at rt. The mixture was heated under reflux for 3 d. After this time, the reaction was cooled to 0 °C and quenched with sat. aq NH_4Cl, then extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), then evaporated under reduced pressure, which gave amine **148** as a clear, colourless oil (100 mg, quant); R_f 0.64 (10% EtOAc in petroleum ether, with 2% NEt_3 also in the eluent); IR (film) (cm^{-1}) 3055m, 2987w, 2957w, 2931w, 2859w, 2686w, 1422w, 1265s, 896m, 740s, 706s; ^{1}H NMR (400 MHz, C_6D_6) δ 2.68 – 2.59 (m, 1H, CH_AH$_B$N), 2.56 (s, 1H, NCH), 2.46 – 2.37 (m, 1H, CH$_A$$H_B$N), 1.71 – 1.26 (m, 14H, 6 x CH_2 and 2 x CH_AH$_B$), 1.31 (s, 3H, NC(CH_3)), 1.09 – 0.98 (m, 1H, CH$_A$$H_B$) 1.07 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.94 (t, 3H, J = 7 Hz, CH_2CH_3), 0.88 – 0.81 (m, 1H, CH$_A$$H_B$); ^{13}C NMR (101 MHz, C_6D_6) δ 65.5 (NCH), 60.3 (N*C*(CH_3)), 52.5 (CH_2), 42.1 (NCH_2), 38.3 (*C*$(CH_3)_2$), 34.2 (NC(*C*H_3)), 32.7 (CH_2), 29.9 (CH_2), 29.1 (CH_2), 27.9 (CH_2), 27.4 (CH_3), 24.3 (CH_3), 23.6 (CH_2), 19.4 (CH_2), 17.0 (CH_2), 14.8 (CH_2*C*H_3); m/z (ESI$^+$) 238.2 (M + H$^+$, 64); HRMS *m/z* (M + H$^+$) found 238.2533, $C_{16}H_{32}N$ requires 238.2529

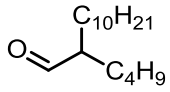
Alkylation of Enamine (±)-92 Prepared Using Nagashima's Protocol:

(±)-2-Ethylhexanal ((±)-24):



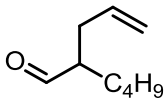
According to the general procedure for enamine alkylation, reaction of enamine **(±)-92** (274 mg, 1.16 mmol) with EtI (362 mg, 2.32 mmol) in MeCN (1.0 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at 65 °C for 1 h, α-alkyl aldehyde **(±)-24**[16,39] as a clear, colourless oil (77 mg, 52%); R_f 0.41 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2961m, 2930m, 2861m, 2694w, 1725s (C=O), 1461m, 1381w, 1154w, 899w; ^1H NMR (400 MHz) δ 9.56 (d, 1H, J = 3 Hz, CHO), 2.23 – 2.10 (m, 1H, C*H*CHO), 1.71 – 1.20 (m, 8H, 4 x CH_2), 0.91 (t, 3H, J = 7 Hz, CH_3), 0.88 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 205.7 (C=O), 53.4 (*C*HCHO), 29.2 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 13.9 (CH_3), 11.4 (CH_3)

(±)-2-Butyldodecanal ((±)-140):



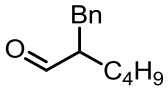
According to the general procedure for enamine alkylation, reaction of enamine **(±)-92** (209 mg, 0.89 mmol) with decyl iodide (477 mg, 1.78 mmol) in MeCN (0.5 mL) at 95 °C for 20 h gave, following hydrolysis with acidic buffer (0.5 mL) at 95 °C for 1 h, α-alkyl aldehyde **(±)-140**[16,39] as a clear, colourless oil (86 mg, 40%); R_f 0.60 (2% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2957m, 2924s, 2855s, 1727s (C=O), 1465m, 1378w, 1073w, 724m; ^1H NMR (400 MHz) δ 9.56 (d, 1H, J = 3 Hz, CHO), 2.27 – 2.17 (m, 1H, C*H*CHO), 1.69 – 1.18 (m, 24H, 12 x CH_2), 0.90 (t, 3H, J = 7 Hz), 0.88 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 205.8 (C=O), 52.0 (*C*HCHO), 31.9 (CH_2), 29.7 (CH_2), 29.57 (CH_2), 29.56 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 13.9 (CH_3); m/z (ESI^+) 263.3 ($M + Na^+$, 18)

(±)-2-Allylhexanal ((±)-149):



According to the general procedure for enamine alkylation, reaction of enamine **(±)-92** (65 mg, 0.28 mmol) with allyl bromide (70 mg, 0.58 mmol) in d_3-MeCN (0.5 mL) at rt for 24 h then 50 °C for 24 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, α-alkyl aldehyde **(±)-149**[16,39] as a clear, colourless oil (14 mg, 36%); R_f 0.19 (2% Et_2O in petroleum ether); IR (film) (cm^{-1}) 3080m, 2959s, 2932s, 2861s, 1728s (C=O), 1642m, 1467m, 1444m, 1418w, 1380w, 1290w, 1212w, 1138w, 993m, 916s; ^{1}H NMR (400 MHz) 9.61 (d, 1H, J = 2 Hz, CHO), 5.82 – 5.67 (m, 1H, C*H*=CH_2), 5.14 – 5.00 (m, 2H, CH=C*H*$_2$), 2.47 – 2.31 (m, 2H, C*H*$_A$H$_B$CH=CH_2 and C*H*CHO), 2.30 – 2.18 (m, 1H, CH_AH_BCH=CH_2), 1.74 – 1.56 (m, 1H, C*H*$_A$H$_B$(CH_2)$_2$$CH_3$), 1.55 – 1.42 (m, 1H, CH_AH_B(C*H*$_2$)$_2$$CH_3$), 1.40 – 1.22 (m, 4H, (C*H*$_2$)$_2$$CH_3$), 0.90 (t, 3H, J = 7 Hz, CH_3); ^{13}C NMR (101 MHz), 204.9 (C=O), 135.0 (*C*H=CH_2), 117.1 (CH=*C*H$_2$), 51.2 (*C*HCHO), 33.0 (*C*H$_2$CH=CH_2), 29.1 (CH_2), 28.1 (*C*H$_2$(CH_2)$_2$$CH_3$), 22.7 ($CH_2$), 13.9 ($CH_2$*C*H$_3$); m/z (ESI$^-$) 139.13 (M – H$^+$, 16); HRMS *m/z* (M – H$^+$) found 139.1129, $C_9H_{15}O$ requires 139.1128

(±)-2-Benzyl hexanal ((±)-150):

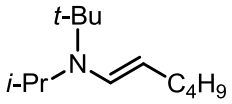


According to the general procedure for enamine alkylation, reaction of enamine **(±)-92** (243 mg, 1.03 mmol) with BnBr (353 mg, 2.06 mmol) in MeCN (1.1 mL) at 82 °C for 22 h gave, following hydrolysis with acidic buffer (250 μL) at 82 °C for 1 h, α-alkyl aldehyde **(±)-150**[16,39] as a clear, colourless oil (132 mg, 67%); R_f 0.25 (2% Et_2O in petroleum ether); IR (film) (cm^{-1}) 3087w, 3064w, 3028m, 3003s, 2931s, 2860s, 2712w, 1726s (C=O), 1604w, 1497m, 1455s, 1380w, 1030w, 745m, 700s; ^{1}H NMR (400 MHz) δ 9.67 (d, 1H, J = 3 Hz, CHO), 7.29 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.21 (t, 1H, J = 7 Hz, Ar (*para*)), 7.16 (d, 2H, J = 7 Hz, Ar (*ortho*)), 3.00 (dd, 1H, J_{AB} = 14 Hz, J = 7 Hz, PhC*H*$_A$H$_B$), 2.73 (dd, 1H, J_{AB} = 14 Hz, J = 7 Hz, PhCH_A*H*$_B$), 2.66 – 2.57 (m, 1H, C*H*CHO), 1.73 – 1.20 (m, 6H, 3 x CH_2), 0.88 (t, 3H, J = 7 Hz, CH_2C*H*$_3$); ^{13}C NMR (101 MHz) δ 204.8 (C=O), 138.9 (Ar (*ipso*)), 128.9 (Ar

(*ortho*)), 128.5 (Ar (*meta*)), 126.3 (Ar (*para*)), 53.4 (*C*HCHO), 35.0 (Ph*C*H_2), 29.1 (CH_2), 28.3 (CH_2), 22.7 (CH_2), 13.8 (CH_3); m/z (ESI$^+$) 213.1 (M + Na^+, 2); HRMS *m/z* (M^+) found 190.1361, $C_{13}H_{18}O$ requires 190.1358

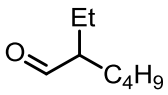
Validation of Alkylation Procedure:

(*E*)-*N*-*tert*-Butyl-*N*-isopropylhex-1-en-1-amine (51):[39]



A solution of *n*-BuLi (1.6 M in hexanes, 16.3 mL, 26.1 mmol) was added dropwise, with stirring, to a solution of amine **100** (3.00 g, 26.0 mmol) in THF (41 mL) at –78 °C. The solution was warmed to rt over 15 min, whereby a solution of 1,2-epoxyhexane (**49**, 1.04 g, 10.4 mmol) in THF (14 mL) was added in one portion. The mixture was stirred for 1 h at rt, then filtered through a pad of deactivated silica, washing the filter cake with Et_2O (300 mL). The filtrate was evaporated under reduced pressure, and the residue purified by bulb-to-bulb distillation, which gave enamine **51** as a clear, colourless oil (788 mg, 38%); bp 90−95 °C (0.1 mm Hg) [lit.[39] 90 °C (0.1 mm Hg)]; other data as above.

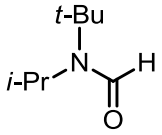
(±)-2-Ethylhexanal ((±)-24):[39]



According to the general procedure for enamine alkylation, reaction of enamine **51** (prepared using Bray's method; 177 mg, 0.90 mmol) with EtI (281 mg, 1.80 mmol) in d_3-MeCN (1.0 mL) at 50 °C for 24 h gave, following hydrolysis with acidic buffer (0.5 mL) at 50 °C for 1 h, α-alkyl aldehyde **(±)-24** as a clear, colourless oil (113 mg, 98%); other data as above.

General Procedure for Formamide Synthesis Using Blum and Nyberg's Protocol:[87]

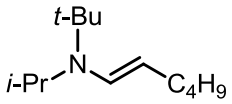
***N*-*tert*-Butyl-*N*-isopropylformamide (151):**



A mixture of amine **100** (2.00 g, 17.4 mmol), $BnEt_3NCl$ (1.78 g, 7.8 mmol), $CHCl_3$ (12.8 mL, 0.16 mol), CH_2Cl_2 (56 mL) and 12.5 M aq NaOH (43 mL) were stirred under reflux for 16 h, then diluted with water (300 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (150 mL), then 10% aq HCl (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave formamide **151** as a white solid (2.07 g, 83%); bp 110 °C (7.6 mm Hg); mp 39–42 °C; IR (film) (cm^{-1}) 3054w, 2981m, 2937w, 1650s (C=O), 1404m, 1334m, 1266s, 1226m, 1117w, 1052w, 739s; ^{1}H NMR (400 MHz, 293K) two rotamers {~ 12:1} δ 8.32 (s, 1H, NCHO (*maj*)), 8.30 (s, 1H, NCHO (*min*)), 3.75 (spt, 1H, J = 7 Hz, NC*H*$(CH_3)_2$ (*min*)), 3.51 (spt, 1H, J = 7 Hz, NC*H*$(CH_3)_2$ (*maj*)), 1.42 (d, 6H, J = 7 Hz, NCH(C*H*$_3)_2$), 1.33 (s, 9H, J = 7 Hz, NC(C*H*$_3)_3$); ^{13}C NMR (101 MHz) δ 161.1 (C=O), 56.4 (N*C*$(CH_3)_3$), 47.1 (N*C*H$(CH_3)_2$), 29.1 (NC(*C*H$_3)_3$), 20.0 (NCH(*C*H$_3)_2$); m/z (ESI$^+$) 166.1 (M + Na$^+$, 47); HRMS *m/z* (M + Na$^+$) found 166.1203, $C_8H_{17}NNaO$ requires 166.1202

General Procedure for Enamine Synthesis Using Adapted Hansson and Wickberg Protocol:[86]

(*E*)-*N*-*tert*-Butyl-*N*-isopropylhex-1-en-1-amine (51):



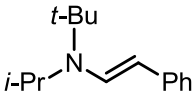
Pentylmagnesium chloride (2.0 M in THF, 320 µL, 0.64 mmol) was added dropwise to a stirred solution of formamide **151** (73 mg, 0.51 mmol) in Et_2O (0.5 mL), while maintaining a temperature between –15 and –20°C. The mixture was kept within this temperature range for 15 min, then warmed to rt. After 16 h, the mixture was evaporated under reduced pressure,

and the crude product purified by bulb-to-bulb distillation, which gave enamine **51**[39] as a clear oil (46 mg, 45%); other data as above.

Alternative Prescription used for (*E*)-*N*-*tert*-Butyl-*N*-isopropylhex-1-en-1-amine (51):

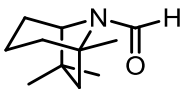
Pentylmagnesium chloride (2.0 M in THF, 875 µL, 1.75 mmol) was added dropwise to a stirred solution of formamide **151** (200 mg, 1.40 mmol) in Et_2O (1 mL), while maintaining a temperature between –15 and –20 °C. The mixture was kept within this temperature range for 15 min, then warmed to rt. After 3 h, the reaction was re-cooled to –20 °C, and excess pentylmagnesium chloride (2.0 M in THF, 800 µL, 1.6 mmol) added dropwise, maintaining the previous temperature range. The reaction was warmed to rt, and stirring continued for 17 h. After this time, the mixture was evaporated and pentane (~ 10 mL) added to the residue. The supernatant was passed through a syringe filter, and then evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave enamine **51**[39] as a clear oil (210 mg, 76%); other data as above.

(*E*)-*N*-Isopropyl-2-methyl-*N*-styrylpropan-2-amine (107):



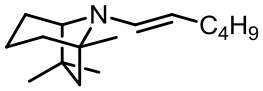
Benzylmagnesium chloride (1.5 M in THF, 1.17 mL, 1.75 mmol) was added dropwise to a stirred solution of formamide **151** (200 mg, 1.40 mmol) in Et_2O (1 mL), while maintaining a temperature between –15 and –20 °C. The mixture was kept within this temperature range for 15 min, then warmed to rt. After 20 h, the reaction was re-cooled to –20 °C, and excess benzylmagnesium chloride (1.5 M in THF, 1.00 mL, 1.50 mmol) added dropwise, maintaining the previous temperature range. The reaction was warmed to rt, and stirring continued for 3 h. After this time, the mixture was evaporated, and pentane (~ 10 mL) added to the residue. The supernatant was passed through a syringe filter, and then evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave enamine **107** as a clear oil (59 mg, 19%); bp 120–125°C (7.6 mm Hg); other data as above.

(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((±)-152):



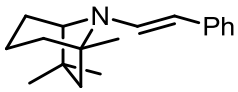
According to the general procedure for formamide synthesis, reaction of tropane **(±)-57** (1.54 g, 10.0 mmol), $BnEt_3NCl$ (1.03 g, 4.5 mmol), $CHCl_3$ (7 mL, 0.09 mol), and 12.5 M aq NaOH (25 mL) in CH_2Cl_2 (32 mL) at reflux for 16 h gave formamide **(±)-152** as a clear, colourless oil (1.78 g, 98%); bp 140–150 °C (7.6 mm Hg); IR (film) (cm^{-1}) 3054m, 2962m, 2875w, 1649s (C=O), 1426m, 1393m, 1375m, 1266s, 740s; ^1H NMR (400 MHz, 293K) two rotamers {~ 13:1} δ 8.15 (s, 1H, NCHO (*min*)), 8.14 (s, 1H, NCHO (*maj*)), 3.96 (br s, 1H, NCH (*maj*)), 3.24 (br s, 1H, NCH (*min*)), 1.85 – 1.40 (m, 8H, 4 x CH_2), 1.38 (s, 3H, CH_3 (*maj*)), 1.12 (s, 3H, CH_3 (*maj*)), 1.10 (s, 3H, CH_3 (*min*)), 1.05 (s, 3H, CH_3 (*min*)), 0.96 (s, 3H, CH_3 (*maj*)); ^{13}C NMR (101 MHz, 293K) two rotamers {~ 13:1} δ 159.2 (C=O (*min*)), 156.7 (C=O (*maj*)), 67.5 (NCH (*min*)), 62.6 (N*C*(CH_3) (*min*)), 61.3 (NCH (*maj*)), 61.1 (N*C*(CH_3) (*maj*)), 52.1 (CH_2 (*min*)), 50.6 (CH_2 (*maj*)), 40.8 (CH_2 (*maj*)), 38.7 (NCH*C*(CH_3)$_2$ (*maj*)), 38.3 (NCH*C*(CH_3)$_2$ (*min*)), 36.6 (CH_2 (*min*)), 32.1 (CH_3 (*maj*)), 31.8 (CH_3 (*min*)), 29.2 (CH_2 (*min*)), 25.8 (CH_3 (*min*)), 25.5 (CH_2 (*maj*)), 24.4 (CH_3 (*maj*)), 22.4 (CH_3 (*min*)), 22.1 (CH_3 (*maj*)), 18.5 (CH_2 (*min*)), 18.4 (CH_2 (*maj*)); m/z (ESI^+) 204.1 (M + Na^+, 31); HRMS *m/z* (M + H^+) found 182.1537, $C_{11}H_{20}NO$ requires 182.1539

(±)-8-((*E*)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-92):



According to the general procedure for enamine synthesis, reaction of formamide **(±)-152** (200 mg, 1.10 mmol) with pentylmagnesium chloride (2.0 M in THF, 690 µL, 1.38 mmol) in Et_2O (1 mL) at rt for 16 h gave, after distillation, enamine **(±)-92** (214 mg, 83%); bp 125–135 °C (0.1 mm Hg); other data as above.

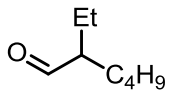
(±)-1,6,6-Trimethyl-8-styryl-8-azabicyclo[3.2.1]octane ((±)-153):



According to the general procedure for enamine synthesis, reaction of formamide **(±)-152** (200 mg, 1.10 mmol) with benzylmagnesium chloride (1.5 M in THF, 920 µL, 1.38 mmol) in Et_2O (1 mL) at rt for 16 h gave, after distillation, enamine **(±)-153** (212 mg, 75%); IR (neat) (cm^{-1}) 3054m, 2959m, 2872w, 1627s (N–C=C), 1596s, 1449m, 1422w, 1380m, 1330m, 1265s, 1180w, 1134w, 939w, 896w, 738s; ^{1}H NMR (400 MHz, C_6D_6) δ 7.36 (d, 2H J = 7 Hz, Ar (*ortho*)), 7.26 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.03 (t, 1H, J = 7 Hz, Ar (*para*)), 6.90 (d, 1H, J = 14 Hz, NC*H*=CH), 5.42 (d, 1H, J = 14 Hz, NCH=C*H*), 3.13 (br s, 1H, NCH), 2.04 – 1.90 (m, 1H, CH_AH_B), 1.60 – 1.45 (m, 1H, CH_AH_B), 1.42 – 1.19 (m, 5H, 2 x CH_2 and 1 x CH_AH_B), 1.04 (s, 6H, 2 x CH_3), 1.02 – 0.96 (m, 1H, CH_AH_B), 0.95 (s, 3H, CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 141.4 (Ar (*ipso*)), 131.5 (N*C*H=CH), 129.3 (Ar (*meta*)), 124.2 (Ar (*ortho*)), 123.9 (Ar (*para*)), 102.1 (NCH=*C*H), 65.1 (NCH), 62.3 (N*C*(CH_3)), 51.3 (CH_2), 38.7 (*C*(CH_3)$_2$), 37.4 (CH_2), 33.3 (CH_3), 25.5 (CH_3), 23.2 (CH_3), 19.90 (CH_2), 19.87 (CH_2); m/z (ESI$^+$) 255.3 (M^+, 95); HRMS *m/z* (M + H^+) found 256.2057, $C_{18}H_{26}N$ requires 256.2060

Alkylation of Enamine (±)-92 Prepared Using Hannson and Wickberg Protocol:

(±)-2-Ethylhexanal ((±)-24):

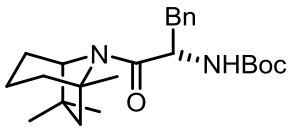


According to the general procedure for enamine alkylation, reaction of enamine **(±)-92** (211 mg, 0.90 mmol) with EtI (281 mg, 1.80 mmol) in d_3-MeCN (1.0 mL) at 60 °C for 3 d gave, following hydrolysis with acidic buffer (0.5 mL) at 50 °C for 1.5 h, α-alkyl aldehyde **(±)-24**[16,39] as a clear, colourless oil (93 mg, 81%); other data as above.

Resolution of Tropane (±)-57:

General Procedure for Coupling with BOP-Cl:

***tert*-Butyl-((*S*)-1-oxo-3-phenyl-1-((1*R*,5*S*)- and *tert*-butyl-((*S*)-1-oxo-3-phenyl-1-((1*S*,5*R*)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-2-yl)carbamate ((*S*,1*R*,5*S*)-163) / (*S*,1*S*,5*R*)-163):**

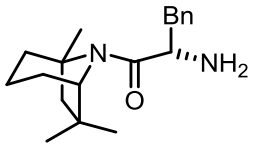


To a stirred solution of tropane **(±)-57** (1.50 g, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DIPEA (2.78 g, 21.5 mmol), *N*-Boc-L-PheOH (2.86 g, 10.8 mmol) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.74 g, 10.8 mmol). The reaction mixture was kept in a refrigerator at 0–4 °C for 3 d [TLC monitoring (50% EtOAc in petroleum ether)]. After this time, the reaction mixture was diluted with ice-cold EtOAc (750 mL), washed with ice-cold 5% aq HCl (500 mL) and 5% aq $NaHCO_3$ (500 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–10% EtOAc in petroleum ether) gave an inseparable mixture of Boc-protected α-amino amides **(*S*,1*R*,5*S*)-163** and **(*S*,1*S*,5*R*)-163** as a white foam (~50:50 *dr*, 2.50 g, 64%); R_f 0.29 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3429w, 3294w, 3055m, 3030w, 2962s, 2873m, 1707s (C=O), 1635s (C=O), 1495s, 1444s, 1266s, 1170s, 1044m, 739s; ^{1}H NMR (400 MHz) two diastereomers {~50:50} δ 7.32 – 7.14 (m, 10H, 2 x Ph), 5.28 (5.22) (d, 2H, J = 9 (10) Hz, 2 x NH), 4.72 – 4.59 (m, 2H, 2 x NHC*H*), 3.67 (3.62) (br s, 2H, 2 x NCH), 3.24 – 3.06 (m, 2H, 2 x PhCH_AH_B), 2.93 – 2.75 (m, 2H, 2 x PhCH_AH_B), 2.14 – 2.02 (m, 1H, CH_AH_B), 1.95 – 1.19 (m, 14H, 6 x CH_2 and 2 x CH_AH_B), 1.63 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$), 1.07 (s, 3H, CH_3), 1.012 (s, 3H, CH_3), 1.006 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.49 – 0.30 (m, 1H, CH_AH_B); ^{13}C NMR (101 MHz) two diastereomers δ 170.9 (169.8) (NHCH*C*=O), 155.0 (154.8) (NH*C*=O), 137.4 (136.8) (Ar (*ipso*)), 129.9 (129.5) (Ar (*ortho*)), 128.3 (128.2) (Ar (*meta*)), 126.6 (126.5) (Ar (*para*)), 79.5 (79.4) (*C*$(CH_3)_3$), 68.7 (67.6) (N*C*HC$(CH_3)_2$), 64.6 (64.3) (N*C*(CH_3)), 53.5 (53.4) (NH*C*H), 51.6 (2 x *C*H_2C$(CH_3)_2$), 39.8 (39.3) (Ph*C*H_2), 38.0 (37.9) (*C*$(CH_3)_2$), 36.7 (CH_2), 35.0 (CH_2), 32.0 (CH_3), 31.8 (CH_3), 28.29 (CH_2), 28.27 (C(*C*$H_3)_3$), 28.23 (C(*C*$H_3)_3$), 27.4 (CH_3), 27.1 (CH_2), 27.0 (CH_3), 22.6 (CH_3), 22.4 (CH_3), 18.4 (2 x CH_2); m/z (ESI^+) 401.3 ($M + H^+$, 79); HRMS *m/z* ($M + H^+$) found 401.2799, $C_{24}H_{37}N_2O_3$ requires 401.2799

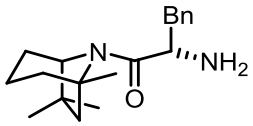
General Procedure for Boc-Deprotection:

(+)-(*S*)-2-Amino-3-phenyl-1-((1*R*,5*S*)- and (+)-(*S*)-2-amino-3-phenyl-1-((1*S*,5*R*)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-1-one ((+)-(*S*,1*R*,5*S*)-164) / (+)-(*S*,1*S*,5*R*)-164):

Anhydrous TFA (62 mL) was added to a stirred solution of Boc-protected α-amino amides **(*S*,1*R*,5*S*)-163** and **(*S*,1*S*,5*R*)-163** (9.35 g, 23.3 mmol) in CH_2Cl_2 (280 mL) at rt. After 1 h, the mixture was evaporated under reduced pressure, and the residue dissolved in $CHCl_3$ (300 mL). The resulting solution was washed with 10% aq Na_2CO_3 (500 mL). The aq layer was separated and back-extracted with $CHCl_3$ (2 x 300 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue purified by column chromatography (SiO_2, gradient elution: 5–10% MeOH in EtOAc). First, eluted α-amino amide **(*S*,1*R*,5*S*)-164** (*minor diastereomer*, 2.96 g), followed by a mixed fraction (747 mg); last eluted α-amino amide **(*S*,1*S*,5*R*)-164** (*major diastereomer*, 2.94 g), all white solids (55:45 *dr*, 6.65 g total product, 95%);



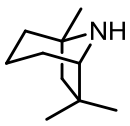
Data for *minor diastereomer* **(*S*,1*R*,5*S*)-164**: mp 69–71 °C; R_f 0.52 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +23.4 (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3390w, 2999m, 2940s, 1631s (C=O), 1493m, 1442s, 1341m, 928m, 750s, 704s; ^{1}H NMR (400 MHz) δ 7.33 – 7.10 (m, 5H, Ar), 3.68 (t, 1H, *J* = 7 Hz, NH_2CH), 3.49 (br s, 1H, C(=O)NCH), 3.09 (dd, 1H, J_{AB} = 13 Hz, *J* = 7 Hz, CH_AH_BPh), 2.72 (dd, 1H, J_{AB} = 13 Hz, *J* = 7 Hz, CH_AH_BPh), 1.89 (td, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH_B), 1.77 – 1.21 (m, 8H, NH_2, 2 x CH_2, 1 x CH_AH_B and 1 x CH_AH_B), 1.64 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.77 – 0.58 (m, 1H, CH_AH_B); ^{13}C NMR (101 MHz) δ 173.4 (C=O), 138.5 (Ar (*ipso*)), 129.6 (Ar), 128.4 (Ar), 126.4 (Ar), 67.5 (C(=O)N*C*H), 64.2 (N*C*(CH_3)), 55.2 (NH_2CH), 51.3 (CH_2), 41.5 (CH_2Ph), 38.1 (NCH*C*(CH_3)$_2$), 36.1 (CH_2), 32.2 (CH_3), 27.4 (CH_3), 27.4 (CH_2), 22.5 (CH_3), 18.5 (CH_2); m/z (ESI^+) 301.2 (M + H^+, 72); HRMS *m/z* (M + H^+) found 301.2277, $C_{19}H_{29}N_2O$ requires 301.2274



Data for *major diastereomer* **(*S*,1*S*,5*R*)-164**: mp 33–35 °C R_f 0.45 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +66.0 (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3347brm (NH_2), 2927s, 1638s (C=O), 1560m, 1443s, 1367m, 1288m, 1120m, 927m, 744s, 703s; ^{1}H NMR (400 MHz) δ 7.35 – 7.13 (m, 5H, Ar), 3.75 (br s, 1H, NH_2CH), 3.57 (br s, 1H, $NCHC(CH_3)_2$), 3.07 (dd, 1H, J_{AB} = 13.4 Hz, *J* = 5 Hz, CH_AH_BPh), 2.72 (dd, 1H, J_{AB} = 13.4 Hz, *J* = 8 Hz, CH_AH_BPh), 2.12 (td, 1H, J_{AB} = 12.9 Hz, *J* = 6 Hz, CH_AH_B), 2.00 (br s , 2H, NH_2), 1.90 – 1.55 (m, 5H, 2 x CH_2 and 1 x CH_AH_B), 1.62 (s, 3H, CH_3), 1.46 (d, 1H, J_{AB} = 13 Hz, CH_AH_B), 1.32 (dd, 1H, J_{AB} = 12.9 Hz, *J* = 6 Hz, CH_AH_B), 1.12 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 174.1 (C=O), 137.9 (Ar (*ipso*)), 129.3 (Ar), 128.5 (Ar), 126.6 (Ar), 68.3 ($NCHC(CH_3)_2$), 64.4 ($NC(CH_3)$), 54.9 (NH_2CH), 51.6 (CH_2), 42.9 (CH_2Ph), 38.0 ($C(CH_3)_2$), 35.1 (CH_2), 32.3 (CH_3), 28.4 (CH_2), 27.4 (CH_3), 22.6 (CH_3), 18.5 (CH_2); m/z (ESI^+) 301.2 ($M + H^+$, 75); HRMS *m/z* ($M + H^+$) found 301.2277, $C_{19}H_{29}N_2O$ requires 301.2274

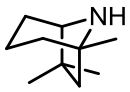
General Procedure for Edman Degradation:

(+)-(1*R*,5*S*)- and (–)-(1*S*,5*R*)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((+)-(1*R*,5*S*)-57 / (–)-(1*S*,5*R*)-57):



PhNCS (340 mg, 2.51 mmol) was added to a stirred solution of α-amino amide **(*S*,1*R*,5*S*)-164** (686 mg, 2.28 mmol) in CH_2Cl_2 (40 mL) at rt. A distillation head, condenser and receiver flask were connected to the reaction vessel, and CH_2Cl_2 removed over an oil bath (100 °C). The distillate was recombined with the contents of the reaction vessel, and the distillation procedure was repeated until α-amino amide **(*S*,1*R*,5*S*)-164** had been consumed [determined by TLC (10% MeOH in EtOAc)]. Upon completion, the mixture was concentrated to dryness, and TFA (20 mL) added to the residue. The resulting solution was heated at 50 °C for 20 min. After this time, the reaction mixture was evaporated under reduced pressure, and the residue dissolved in $CHCl_3$ (100 mL). This solution was partitioned with H_2O (100 mL), the aq layer

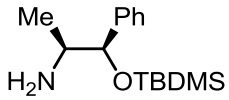
separated and basified with 3 M aq NaOH. The resulting suspension was washed with Et_2O (5 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation [bp 50–60 °C (14 mm Hg)], to give tropane **(1*R*,5*S*)-57** as a clear, colourless oil (316 mg, 90%); $[\alpha]_D^{25}$= + 85.7 (*c* = 1.4, $CHCl_3$); other data as above.



Following the same procedure, reaction of α-amino amide **(*S*,1*S*,5*R*)-164** (3.27 g, 10.9 mmol) with PhNCS (1.62 g, 12.0 mmol) in CH_2Cl_2 (170 mL) gave, after treatment with TFA (85 mL), tropane **(1*S*,5*R*)-57** as a clear, colourless oil (1.34 g, 80%); $[\alpha]_D^{25}$= – 89.6 (*c* = 1.4, $CHCl_3$); other data as above.

Synthesis of Selenone (4*S*,5*R*)-169:

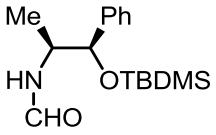
(–)-(1*R*,2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-amine ((–)-(1*R*,2*S*)-172):[95]



Et_3N (8.03 g, 79.4 mmol) was added to a solution of (1*R*,2*S*)-norephedrine (**(1*R*,2*S*)-171**; 12.00 g, 79.4 mmol) and TBDMSCl (11.96 g, 79.4 mmol) in CH_2Cl_2 (120 mL) at rt, with stirring. After 16 h, the mixture was evaporated under reduced pressure. Brine (250 mL) was added to the residue, and the resultant aq mixture extracted with Et_2O (3 x 250 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure, which gave *O*-protected norephedrine **(1*R*,2*S*)-172)** as a clear, pale-yellow oil (18.65 g, 89%); $[\alpha]_D^{25}$ = –45.8 (*c* = 1.2, $CHCl_3$) [lit.[178] $[\alpha]_D^{20}$ = –44.1 (*c* = 1.0, $CHCl_3$)]; IR (neat) (cm^{-1}) 2955w, 2929w, 2886w, 1493w, 1252m, 1088m, 1063m, 862s, 834s, 774s; ^{1}H NMR (400 MHz) δ 7.35 – 7.19 (m, 5H, Ar), 4.38 (d, 1H, *J* = 5 Hz, C*H*Ph), 3.04 – 2.91 (m, 1H, *J* = 7 Hz, C*H*CH_3), 1.42 (br s, 2H, NH_2), 0.98 (d, 3H, *J* = 7 Hz, CHC*H*$_3$), 0.87 (s, 9H, C(C*H*$_3$)$_3$), 0.01 (s, 3H, $SiCH_3$), –0.21 (s, 3H, $SiCH_3$); ^{13}C NMR (101 MHz) δ 141.9 (Ar (*ipso*)), 127.8 (Ar), 127.2 (Ar), 127.0 (Ar), 80.0 (*C*HPh), 53.4 (*C*HCH$_3$), 25.8 (C(*C*H$_3$)$_3$), 18.8 (CH*C*H$_3$), 18.1

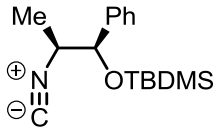
(*C*(CH_3)$_3$), –4.7 ($SiCH_3$), –5.1 ($SiCH_3$); m/z (ESI$^+$) 266.2 (M + H$^+$, 47); HRMS *m/z* (M + H$^+$) found 266.1932, $C_{15}H_{28}NOSi$ requires 266.1935

(–)-*N*-((1*R*,2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)formamide ((–)-(1*R*,2*S*)-173):[16]



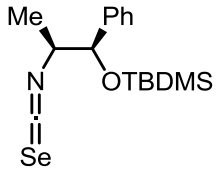
A mixture of ethyl formate (185 mL, 2.30 mol) and *O*-protected norephedrine **(1*R*,2*S*)-172** (17.0 g, 64.0 mmol) was stirred under reflux for 16 h. After this time, the mixture was evaporated under reduced pressure, which gave formamide **(1*R*,2*S*)-173** as a clear, pale-yellow oil (18.1 g, 96%); $[\alpha]_D^{25}$ = –59.4 (*c* = 1.1, $CHCl_3$); R_f 0.19 (50% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3280brw, 3033w, 2955w, 2930w, 2857w, 1658s (C=O), 1382m, 1254m, 1029m, 833s, 775s, 700s; ^{1}H NMR (400 MHz, 293 K) two rotamers {~ 3:1} δ 8.16 (s, 1H, NHC*H*O (*maj*)), 7.98 (d, 1H, *J* = 12 Hz, NHC*H*O (*min*)), 7.39 – 7.20 (m, 5H, Ar), 5.70 (d, 1H, *J* = 8 Hz, NH (*maj*)), 5.53 (t, 1H, *J* = 10 Hz, NH (*min*)), 4.89 (d, 1H, *J* = 3 Hz, C*H*Ph (*maj*)), 4.57 (d, 1H, *J* = 4 Hz, C*H*Ph (*min*)), 4.29 – 4.18 (m, 1H, C*H*CH_3 (*maj*)), 3.74 – 3.60 (m, 1H, C*H*CH_3 (*min*)), 1.08 (d, 3H, *J* = 7 Hz, CHC*H*$_3$ (*min*)), 0.97 (d, 3H, *J* = 7 Hz, CHC*H*$_3$ (*maj*)), 0.96 (s, 9H, C(CH_3)$_3$ (*maj*)), 0.91 (s, 9H, C(CH_3)$_3$ (*min*)), 0.10 (s, 3H, $SiCH_3$ (*min*)), 0.05 (s, 3H, $SiCH_3$ (*maj*)), –0.14 (s, 3H, $SiCH_3$ (*maj*)), –0.17 (s, 3H, $SiCH_3$ (*min*)); ^{13}C NMR (101 MHz, 293 K) two rotamers δ 164.0 (C=O (*min*)), 160.3 (C=O (*maj*)), 141.3 (Ar (*ipso*)(*maj*)), 139.9 (Ar (*ipso*)(*min*)) 128.2 (2 x Ar (*min*)), 128.0 (2 x Ar (*maj*)), 127.9 (1 x Ar (*min*)), 127.3 (1 x Ar (*maj*)), 126.9 (2 x Ar (*min*)), 126.2 (2 x Ar (*maj*)), 77.8 (*C*HPh (*min*)), 75.9 (*C*HPh (*maj*)), 54.2 (*C*HCH$_3$ (*min*)), 50.1 (*C*HCH$_3$ (*maj*)), 25.8 (C(*C*H$_3$)$_3$ (*maj*)), 25.7 (C(*C*H$_3$)$_3$ (*min*)), 18.2 (*C*(CH_3)$_3$ (*maj*)), 18.1 (*C*(CH_3)$_3$ (*min*)), 16.6 (CH*C*H$_3$ (*min*)), 13.2 (CH*C*H$_3$ (*maj*)), –4.66 ($SiCH_3$ (*min*)), –4.69 ($SiCH_3$ (*maj*)), –5.14 ($SiCH_3$ (*maj*)), –5.19 ($SiCH_3$ (*min*)); m/z (ESI$^-$) 292.2 (M – H$^+$, 100); HRMS *m/z* (M – H$^+$) found 292.1725, $C_{16}H_{26}NO_2Si$ requires 292.1738

(–)-*tert*-Butyl((1*R*,2*S*)-2-isocyano-1-phenylpropoxy)dimethylsilane ((–)-(1*R*,2*S*)-174):[95]



$POCl_3$ (5.65 mL, 60.62 mmol) and Et_3N (18.40 g, 0.18 mol) were sequentially added to solution of formamide **(1*R*,2*S*)-173** (17.80 g, 60.62 mmol) in CH_2Cl_2 (120 mL) at 0 °C. The mixture was stirred for 5 min, then poured onto a pad of silica gel and eluted with Et_2O (~ 700 mL). The filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, 0–5% Et_2O in petroleum ether), which gave isocyanide **(1*R*,2*S*)-174** as a clear, pale-yellow oil (11.35 g, 68%); $[\alpha]_D^{25} = -46.7$ (*c* = 1.1, $CHCl_3$); R_f 0.48 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2930w, 2858w, 2136s (C≡N), 1453w, 1255m, 1071m, 1026m, 862s, 834s, 776s; ^1H NMR (400 MHz) δ 7.42 – 7.27 (m, 5H, Ar), 4.76 (d, 1H, *J* = 5 Hz, C*H*Ph), 3.78 – 3.68 (m, 1H, J_1 = 7 Hz, J_2 = 2 Hz, C*H*CH_3), 1.31 (dt, 3H, J_1 = 7 Hz, J_2 = 2 Hz, CHC*H*$_3$), 0.94 (s, 9H, C(C*H*$_3$)$_3$), 0.13 (s, 3H, $SiCH_3$), –0.12 (s, 3H, $SiCH_3$); ^{13}C NMR (101 MHz), 156.0 (t, $J_{C–N}$ = 5 Hz, *C*≡NCH), 140.0 (Ar (*ipso*)), 128.2 (2 x Ar), 128.1 (Ar), 126.6 (2 x Ar), 76.5 (*C*HPh), 56.8 (t, $J_{C–N}$ = 6 Hz, C≡N*C*H)), 25.7 (C(*C*H_3)$_3$), 18.1 (*C*(CH$_3$)$_3$), 16.2 (CH*C*H_3), –4.7 ($SiCH_3$), – 5.1 ($SiCH_3$); m/z (ESI$^+$) 276.2 (M + H$^+$, 87); HRMS *m/z* (M + H$^+$) found 276.1788, $C_{16}H_{26}NOSi$ requires 276.1788

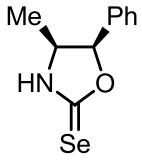
(–)-*tert*-Butyl((1*R*,2*S*)-2-isoselenocyanato-1-phenylpropoxy)dimethylsilane ((–)-(1*R*,2*S*)-175):[95]



Se powder (100 mesh, 2.00 g, 25.33 mol) and isocyanide **(1*R*,2*S*)-174** (1.83 g, 6.63 mmol) in $CHCl_3$ (10 mL) were heated at 100 °C in a sealed tube for 16 h. After this time, the excess Se powder was removed by filtration, and the filtrate evaporated under reduced pressure, which gave isoselenocyanate **((1*R*,2*S*)-175)** as a red-orange oil (2.33 g, 99%); $[\alpha]_D^{25} = -6.1$ (*c* = 1.2, $CHCl_3$); IR (film) (cm^{-1}) 2929w, 2857w, 2118s (N=C=Se); 1472w, 1336w, 1255m, 1200w, 1101s, 1026s, 856s, 838s, 778s, 701s; ^1H NMR (400 MHz) δ 7.41 – 7.24 (m, 5H, Ar), 4.77

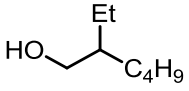
(d, 1H, *J* = 5 Hz, C*H*Ph), 3.93 (qd, 1H, J_1 = 7 Hz, J_2 = 5 Hz, C*H*CH_3), 1.32 (d, 3H, *J* = 7 Hz, CHC*H*$_3$), 0.93 (s, 9H, C$(CH_3)_3$), 0.13 (s, 3H, SiCH_3), –0.13 (s, 3H, SiCH_3); ^{13}C NMR (101 MHz) δ 139.9 (Ar (*ipso*)), 128.3 (Ar), 128.2 (Ar), 126.6 (Ar), 123.4 (N=C=Se), 76.7 (*C*HPh), 60.5 (*C*HCH_3), 25.7 (C(*C*H$_3$)$_3$), 18.1 (*C*$(CH_3)_3$), 16.0 (CH*C*H$_3$), –4.7 (SiCH_3), –5.1 (SiCH_3)

(–)-(4*S*,5*R*)-4-Methyl-5-phenyloxazolidine-2-selenone ((–)-(4*S*,5*R*)-169):[95]



TBAF (1.0 M in THF, 32.8 mL, 32.8 mmol) was added dropwise to a solution of isoselenocyanate **(1*R*,2*S*)-175** (11.62 g, 32.8 mmol) in THF (80 mL) at 0 °C, with stirring. After 30 min, the mixture was loaded onto a silica gel pad and eluted with dry, degassed Et_2O. The filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, CH_2Cl_2), which gave selenone **(4*S*,5*R*)-169** as a pale yellow solid (2.01 g, 26%); mp 120–122 °C [lit.[179] 119–120 °C]; $[\alpha]_D^{25}$ = –164.5 (*c* = 1.0, $CHCl_3$) [lit.[179] –166.0 (*c* = 1.0, $CHCl_3$); R_f 0.15 (CH_2Cl_2); ^{1}H NMR (400 MHz) δ 9.13 (br s, 1H, NH), 7.45 – 7.20 (m, 5H, Ph), 5.98 (d, 1H, *J* = 9 Hz, C*H*Ph), 4.47 – 4.38 (m, 1H, C*H*CH_3), 0.89 (3H, d, *J* = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 187.8 (C=Se), 133.0 (Ar (*ipso*)), 129.0 (Ar), 128.7 (2 x Ar), 126.2 (2 x Ar), 88.2 (*C*HPh), 56.8 (*C*HCH$_3$), 16.4 (CH_3); m/z (FI^-) 240.0 (M^-, 100); HRMS *m/z* (M^-) found 239.9924, $C_{10}H_{10}NOSe$ requires 239.9933

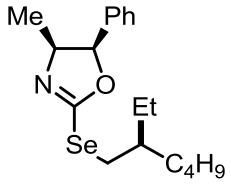
Representative Procedure for Reduction of 2-Ethylhexanal (24) to 2-Ethylhexan-1-ol (176):[16]



$NaBH_4$ (25.0 mg, 0.661 mmol) was added to a solution of (±)-2-ethylhexanal (**(±)-24**; 17.0 mg, 0.133 mmol) in MeOH (1 mL) at 0 °C. The reaction was allowed to warm to rt slowly and stirred for 16 h. The reaction mixture was then poured into a cold solution of Et_2O (10 mL) and 2 M aq HCl (1 mL). The resultant biphasic solution was stirred for 15 min, and then

partitioned between H_2O (10 mL) and Et_2O (10 mL). The organic layers was separated and the aq layer back-extracted with Et_2O (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 0–20% Et_2O in petroleum ether) gave 2-ethylhexan-1-ol (**(±)-176**) as a clear, colourless oil (15.5 mg, 89%); R_f 0.06 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3321brm (O–H), 2958s, 2926s, 2873s, 2860s, 1461s, 1379m, 1228w, 1119m, 1037s, 959m; ^{1}H NMR (400 MHz) δ 3.55 (d, 2H, J = 5 Hz, CH_2OH), 1.46 – 1.21 (m, 10H, CH, OH and 4 x CH_2), 0.90 (t, 6H, J = 7 Hz, 2 x CH_3); ^{13}C NMR (101 MHz) δ 65.3 (*C*H_2OH), 42.0 (*C*HCH$_2$OH), 30.1 (CH_2), 29.1 (CH_2), 23.3 (CH_2), 23.1 (CH_2), 14.1 (CH_3), 11.1 (CH_3)

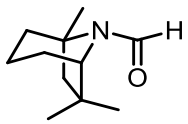
Representative Procedure for Synthesis of (4*S*,5*R*)-2-((2-Ethylhexyl)selanyl)-4-methyl-5-phenyl-4,5-dihydrooxazole ((4*S*,5*R*,(±)$_\alpha$)-177):[16]



DIAD (52 µL, 0.26 mmol) was added dropwise to a mixture of selenone **(4*S*,5*R*)-169** (63 mg, 0.26 mmol), **(±)**-2-ethylhexan-1-ol (**(±)-176**) (23 mg, 0.18 mmol) and PPh_3 (68 mg, 0.26 mmol) in CH_2Cl_2 (3.1 mL), with stirring, at rt. After 24 h, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–4% EtOAc in petroleum ether) gave selenium adduct **(4*S*,5*R*,(±)$_\alpha$)-177** as a clear, pale yellow oil (50:50 *dr*, 52 mg, 82%); R_f 0.19 (4% EtOAc in petroleum ether); IR (film) (cm^{-1}) 2959s, 2928s, 2858m, 1605s (C=N), 1456m, 1378w, 1290w, 1216m, 1110s, 957m, 753s; ^{1}H NMR (400 MHz) δ 7.38 – 7.11 (m, 5H, Ar), 5.58 (d, 1H, J = 9 Hz, C*H*Ph), 4.46 – 4.33 (m, 1H, J_1 = 9 Hz, J_2 = 7 Hz, C*H*CH$_3$), 3.20 – 3.04 (m, 2H, SeCH$_2$), 1.60 (sept, 1H, J = 6 Hz, SeCH$_2$C*H*), 1.42 – 1.10 (m, 8H, 4 x CH_2), 0.88 – 0.77 (m, 6H, 2 x CH_3), 0.72 (d, 3H, J = 7 Hz, CH(C*H*$_3$)); ^{13}C NMR (101 MHz) δ 160.0 (C=N), 136.4 (Ar (*ipso*)), 128.2 (Ar), 127.9 (Ar (*para*)), 126.1 (Ar), 85.5 (*C*HPh), 65.6 (*C*HCH$_3$), 39.6 (SeCH$_2$*C*H), 33.1 (CH_2), 32.4 (SeCH$_2$), 28.8 (CH_2), 26.4 (CH_2), 22.9 (CH_2), 17.7 (CH*C*H$_3$), 14.0 (CH$_2$*C*H$_3$), 10.9 (CH$_2$*C*H$_3$); ^{77}Se NMR (48 MHz) two diastereomers {50:50} δ 228.9, 228.3; m/z (FI$^+$) 353.1 (M$^+$, 100); HRMS *m/z* (M$^+$) found 353.1253, $C_{18}H_{27}NOSe$ requires 353.1258

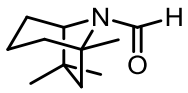
Synthesis of Chiral Formamides (1*R*,5*S*)-152 and (1*S*,5*R*)-152:

(+)-(1*R*,5*S*)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((+)-(1*R*,5*S*)-152):



According to the general procedure for formamide synthesis, reaction of tropane **(1*R*,5*S*)-57** (597 mg, 3.90 mmol), $BnEt_3NCl$ (399 mg, 1.75 mmol), $CHCl_3$ (2.9 mL, 0.04 mol) and 12.5 M aq NaOH (9.7 mL) in CH_2Cl_2 (12.7 mL) at reflux for 17 h gave formamide **(1*R*,5*S*)-152** as a clear, colourless oil (656 mg, 93%); $[\alpha]_D^{25}$ = + 88.0 (*c* = 1.0, MeOH); other data as above.

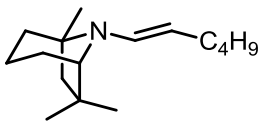
(–)-(1*S*,5*R*)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((–)-(1*S*,5*R*)-152):



According to the general procedure for formamide synthesis, reaction of tropane **(1*S*,5*R*)-57** (1.28 g, 8.4 mmol), $BnEt_3NCl$ (856 mg, 3.8 mmol), $CHCl_3$ (6.2 mL, 0.08 mol) and 12.5 M aq NaOH (20.7 mL) in CH_2Cl_2 (27 mL) at reflux for 17 h gave formamide **(1*S*,5*R*)-152** as a clear, colourless oil (1.25 g, 82%); $[\alpha]_D^{25}$ = – 69.0 (*c* = 0.9, MeOH); other data as above.

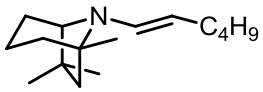
Synthesis of Chiral Enamines (1*R*,5*S*)-92 and (1*S*,5*R*)-92:

(1*R*,5*S*)-8-((*E*)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((1*R*,5*S*)-92):



According to the general procedure for enamine synthesis, reaction of formamide **(1*R*,5*S*)-152** (621 mg, 3.43 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.14 mL, 4.28 mmol) in Et_2O (2.5 mL) at rt for 17 h gave, after distillation, enamine **(1*R*,5*S*)-92** as a clear, colourless oil (676 mg, 84%);[180] other data as above.

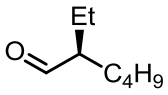
(1*S*,5*R*)-8-((*E*)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((1*S*,5*R*)-92):



According to the general procedure for enamine synthesis, reaction of formamide **(1*S*,5*R*)-152** (684 mg, 3.77 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.42 mL, 4.84 mmol) in Et_2O (5 mL) at rt for 17 h gave, after distillation, enamine **(1*S*,5*R*)-92** as a clear colourless oil (504 mg, 57%);[180] other data as above.

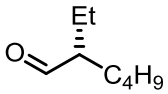
Asymmetric Alkylation of Enamines (1*R*,5*S*)-92 and (1*S*,5*R*)-92 with EtI:

(*S*)-2-ethylhexanal ((*S*)-24):



According to the general procedure for enamine alkylation, reaction of enamine **(1*R*,5*S*)-92** (151 mg, 0.64 mmol) with EtI (200 mg, 1.28 mmol) in d_3-MeCN (690 µL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde **(*S*)-24**[16] (58:42 *er*,[16,95] 60 mg, 73%); other data as above.

(*R*)-2-ethylhexanal ((*R*)-24):

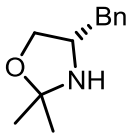


According to the general procedure for enamine alkylation, reaction of enamine **(1*S*,5*R*)-92** (214 mg, 0.91 mmol) with EtI (284 mg, 1.82 mmol) in d_3-MeCN (1 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde **(*R*)-24**[16] (55:45 *er*,[16,95] 91 mg, 78%); other data as above.

5.3 Procedures for Chapter 3

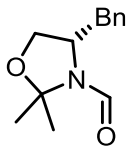
Synthesis of Oxazolidine-Derived Enamine (*S*)-185:

(+)-(*S*)-4-Benzyl-2,2-dimethyloxazolidine ((+)-(*S*)-182):[103]



L-phenylalaninol (**(*S*)-183**; 5.00 g, 33.1 mmol) and *p*-TSA·H_2O (630 mg, 3.3 mmol) in acetone (220 mL) were stirred under reflux for 16 h. After this time, the volatiles were removed by evaporation under reduced pressure, and the residue dissolved in CH_2Cl_2 (100 mL). The resulting solution was washed with sat. aq $NaHCO_3$ (100 mL). The organic layer was separated, and the aq layer back-extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation to give oxazolidine (**(*S*)-182**) as a clear, colourless oil (5.12 g, 81%); bp 100–105 °C (0.3 mm Hg); $[\alpha]_D^{25}$ = +37.1 (*c* = 1.1, $CHCl_3$) [lit.[181] $[\alpha]_{435}^{25}$= +20.4 (*c* = 1.0, THF)]; IR (neat) (cm^{-1}) 2979w, 2931w, 2858w, 1665w, 1497w, 1454m, 1379m, 1256m, 1145m, 1031s, 751m, 699s; ^{1}H NMR (400 MHz) δ 7.34 – 7.28 (m, 2H, Ar), 7.26 – 7.18 (m, 3H, Ar), 3.87 (dd, 1H, J_1 = 8 Hz, J_2 = 7 Hz, OC$H_A$$H_B$), 3.74 – 3.65 (m, 1H, *J* = 7 Hz, NHC*H*), 3.40 (t, 1H, *J* = 8 Hz, OC$H_A$$H_B$), 3.00 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, C$H_A$$H_B$Ph), 2.72 (dd, 1H, J_{AB} = 14 Hz, *J* = 8 Hz, C$H_A$$H_B$Ph), 1.76 (br s, 1H, NH), 1.45 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 138.2 (Ar (*ipso*)), 128.8 (Ar), 128.5 (Ar), 126.5 (Ar), 95.1 (N*C*$(CH_3)_2$), 70.3 (OCH_2), 59.2 (NCH), 39.6 (*C*H_2Ar), 27.8 (CH_3), 26.6 (CH_3); m/z (ESI^+) 192.1 (M + H^+, 43); HRMS *m/z* (M + H^+) found 192.1385, $C_{12}H_{18}NO$ requires 192.1383

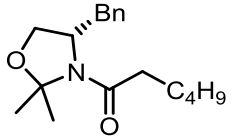
(–)-(*S*)-4-Benzyl-2,2-dimethyloxazolidine-3-carbaldehyde ((–)-(*S*)-184):



According to the general procedure for formamide synthesis, reaction of oxazolidine **(*S*)-182** (1.00 g, 5.2 mmol) with $BnEt_3NCl$ (536 mg, 2.35 mmol), $CHCl_3$ (3.9 mL, 0.05 mol), and aq

NaOH (12.5 M, 16 mL) in CH_2Cl_2 (17 mL) at reflux for 17 h gave, after purification by bulb-to-bulb distillation, the desired formamide **(*S*)-184** as a white solid (1.06 g, 92%); mp 110–113 °C; bp 145–150 °C (0.3 mm Hg); $[\alpha]_D^{25} = -38.9$ (*c* = 1.2, $CHCl_3$); IR (neat) (cm^{-1}) 3029w, 2886w, 1662s (C=O (*min*)), 1640s (C=O (*maj*)), 1409s, 1389s, 1311s, 1070m, 850s, 763s, 702s; ^{1}H NMR (400 MHz, 293K) two rotamers {~ 2:1} δ 8.28 (s, 1H, NCHO (*maj*)), 7.85 (s, 1H, NCHO (*min*)), 7.37 – 7.15 (m, 5H, Ar), 4.39 – 4.31 (m, 1H, *J* = 3 Hz, NCH (*maj*)), 4.06 – 3.96 (m, 2H, J_1 = 7 Hz, J_2 = 6 Hz, NCH (*min*) and OCH_AH$_B$ (*min*)), 3.92 – 3.81 (m, 3H, J_1 = 7 Hz, J_2 = 6 Hz, OCH$_A$$H_B$ (*min*) and OCH_2 (*maj*)), 3.31 (dd, 1H, J_{AB} = 13 Hz, *J* = 3 Hz, CH_AH$_B$Ph (*maj*)), 2.93 (d, 2H, *J* = 7 Hz, CH_2Ph (*min*)), 2.68 (dd, 1H, J_{AB} = 13 Hz, *J* = 10 Hz, CH$_A$$H_B$Ph (*maj*)), 1.72 (s, 3H, CH_3 (*min*)), 1.55 (s, 3H, CH_3 (*min*)), 1.52 (s, 3H, CH_3 (*maj*)), 1.49 (s, 3H, CH_3 (*maj*)); ^{13}C NMR (101 MHz, 293K) two rotamers δ 158.7 (C=O (*min*)), 158.2 (C=O (*maj*)), 137.6 (Ar (*ipso*)(*maj*)), 136.7 (Ar (*ipso*)(*min*)), 129.5 (2 x Ar (*maj*)), 129.4 (2 x Ar (*min*)), 128.9 (2 x Ar (*min*)), 128.5 (2 x Ar (*maj*)), 127.1 (Ar (*min*)), 126.6 (Ar (*maj*)), 94.3 (*C*$(CH_3)_2$ (*min*)), 92.6 (*C*$(CH_3)_2$ (*maj*)), 67.6 (OCH_2 (*min*)), 66.7 (OCH_2 (*maj*)), 58.7 (NCH (*min*)), 56.6 (NCH (*maj*)), 41.9 (NCH*C*H_2 (*min*)), 37.8 (NCH*C*H_2 (*maj*)), 28.9 (CH_3 (*maj*)), 27.5 (CH_3 (*maj*)), 26.3 (CH_3 (*min*)), 23.3 (CH_3 (*min*)); m/z (ESI^+) 220.1 (M + H^+, 62); HRMS *m/z* (M^+) found 219.1262, $C_{13}H_{17}NO_2$ requires 219.1259

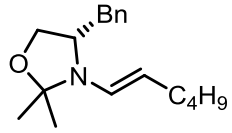
(–)-(*S*)-1-(4-Benzyl-2,2-dimethyloxazolidin-3-yl)hexan-1-one ((–)-(*S*)-187):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of oxazolidine **(*S*)-183** (1.00 g, 5.23 mmol) with hexanoic anhydride (**101**; 2.24 g, 10.5 mmol) and Et_3N (794 mg, 7.85 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (Al_2O_3, 2% EtOAc in petroleum ether), amide **(*S*)-187** as a yellow solid (1.06 g, 70%); mp 53–55 °C; $[\alpha]_D^{25} = -59.3$ (*c* = 0.2, $CHCl_3$); R_f 0.40 (Al_2O_3, 4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2955w, 2931w, 2871w, 1643s (C=O), 1409s, 1245s, 1207m, 1044m, 848s, 700s; ^{1}H NMR (400 MHz) δ 7.39 – 7.16 (m, 5H, Ar), 4.04 – 3.95 (m, 1H, NCH), 3.87 – 3.78 (m, 2H, NCHCH_2CO), 2.97 (dd, 1H, J_{AB} = 14 Hz, *J* = 4 Hz, NCHCH_AH$_B$Ph), 2.87 (dd, 1H, J_{AB} = 14 Hz, *J* = 10 Hz, NCHCH$_A$$H_B$Ph), 2.42 –

2.20 (m, 2H, CH_2C=O), 1.73 (s, 3H, NCCH_3), 1.72 – 1.60 (m, 2H, CH_2CH_2C=O), 1.55 (s, 3H, NCCH_3), 1.40 – 1.27 (m, 4H, (CH_2)$_2CH_3$), 0.92 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 169.9 (C=O), 137.5 (Ar (*ipso*)), 129.1 (Ar), 128.9 (Ar), 126.9 (Ar), 95.4 (N*C*(CH$_3$)$_2$), 66.3 (OCH_2), 59.4 (NCH), 40.5 (NCH*C*H$_2$Ph), 35.5 (*C*H$_2$C=O), 31.6 (*C*H$_2$(CH$_2$)$_2$C=O), 26.9 (NC*C*H$_3$), 24.8 (*C*H$_2$CH$_2$C=O), 23.1 (NC*C*H$_3$), 22.5 (*C*H$_2$CH$_3$), 13.9 (CH_2CH_3); m/z (ESI$^+$) 290.2 (M + H$^+$, 34); HRMS *m/z* (M$^+$) found 289.2038, $C_{18}H_{27}NO_2$ requires 289.2042

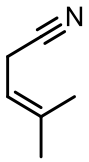
(*S*,*E*)-4-Benzyl-3-(hex-1-en-1-yl)-2,2-dimethyloxazolidine ((*S*)-185):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **(*S*)-187** (289 mg, 1.00 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.5 mL, 0.01 mmol) and PMHS (266 mg, Si–H = 4.00 mmol) at rt for 20 min gave, after purification by bulb-to-bulb distillation, enamine **(*S*)-185** and amine **(*S*)-188** as a clear, colourless oil (206 mg, 76%, 91:9 {**185**:**188**}); bp 140–145 °C (0.6 mm Hg); IR (neat) (cm^{-1}) 2955w, 2927w, 2857w, 1716w, 1652m (N–C=C), 1496w, 1454w, 1378w, 1364w, 1032s, 699s; ^{1}H NMR (400 MHz) δ 7.35 – 7.18 (m, 5H, Ar), 5.93 (d, 1H, J = 14 Hz, NC*H*=CH), 4.39 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.92 – 3.80 (m, 2H, OCH_2), 3.67 – 3.59 (m, 1H, NC*H*CH$_2$), 3.19 (dd, 1H, J_{AB} = 14 Hz, J = 3 Hz, CH_AH_BPh), 2.55 (dd, 1H, J_{AB} = 14 Hz, J = 10 Hz, CH_AH_BPh), 2.09 – 1.99 (m, 2H, NCH=CHCH_2), 1.43 – 1.31 (m, 4H, (CH_2)$_2CH_3$), 1.40 (s, 3H, NCCH_3) 1.25 (s, 3H, NCCH_3), 0.96 – 0.89 (m, 3H, CH_2CH_3); ^{13}C NMR (101 MHz) δ 139.0 (Ar (*ipso*)), 129.2 (2 x Ar), 128.7 (N*C*H=CH), 128.4 (2 x Ar), 126.2 (Ar), 100.4 (NCH=*C*H), 94.4 (N*C*(CH$_3$)$_2$), 67.7 (OCH_2), 58.7 (N*C*HCH$_2$), 37.8 (*C*H$_2$Ph), 33.8 (*C*H$_2$C$_2$H$_5$), 30.6 (NCH=CH*C*H$_2$), 27.5 (NC*C*H$_3$), 24.5 (NC*C*H$_3$), 22.1 (*C*H$_2$CH$_3$), 14.0 (CH_2CH_3); m/z (FI$^+$) 273.2 (M$^+$, 100); HRMS *m/z* (M$^+$) found 273.2084, $C_{18}H_{27}NO$ requires 273.2093

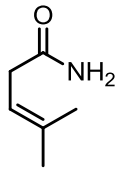
Synthesis of Pyrrolidine (±)-181:

4-Methylpent-3-enenitrile (206):[116]



Prenyl bromide (**205**) (2.00 g, 13.4 mmol), CuCN (1.20 g, 13.4 mmol) and KI (11 mg, 0.07 mmol) in benzene (1 mL) were stirred for 16 h at rt. After this time, nitrile **206** was isolated by bulb-to-bulb distillation as a clear, colourless oil (933 mg, 73%); bp 65–70 °C (15 mm Hg) [lit.[116] bp 62–63 °C (15 mm Hg)]; R_f 0.76 (20% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2974s, 2937s, 2918s, 2249s (C≡N), 1675w, 1450s, 1420s, 1379s, 1102s, 982w, 915s, 821s, 770s; ^{1}H NMR (400 MHz) δ 5.19 – 5.12 (m, 1H, C=CH), 3.03 (d, 2H, J = 7 Hz, CH_2), 1.76 (s, 3H, CH_3), 1.68 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 138.7 (C≡N), 118.5 ($C(CH_3)_2$), 111.7 (CH=C), 25.3 (CH_3), 17.8 (CH_3), 16.2 (CH_2); m/z (FI^+) 95.1 (M^+, 100); HRMS *m/z* (M^+) found 95.0737, C_6H_9N requires 95.0735

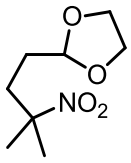
4-Methylpent-3-enamide (207):[117]



Nitrile **206** (6.34 g, 66.6 mmol) was dissolved in CH_2Cl_2 (58 mL) at rt, with stirring. The resulting solution was cooled to 0 °C, and the following added sequentially: 35% aq H_2O_2 (30.05 g, 0.31 mol), nBu$_4$NHSO$_4$ (4.53 g, 13.3 mmol) and 20% aq NaOH (25 mL). After 16 h, the reaction was partitioned with CH_2Cl_2 (150 mL), the organic layer separated, and the aq layer back-extracted CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc), which gave β,γ-ene amide (**207**) as a white solid (4.59 g, 61%); mp 80–82 °C (lit.[182] 81–82 °C); R_f 0.10 (EtOAc); IR (neat) (cm^{-1}) 3347m (N–H), 3171m (N–H), 2974w, 2930w, 2914w, 1660s (C=O stretch), 1627s (N–H bend), 1408s, 1275m, 1229w, 1109w, 938w, 830m; ^{1}H NMR (400 MHz) δ 6.28 (br s, 1H, NH_AH$_B$), 5.79 (br

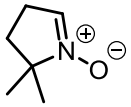
s, 1H, NH_AH_B), 5.33 – 5.25 (m, 1H, J_1 = 8 Hz, J_2 = 3 Hz, J_3 = 1 Hz, C=C*H*CH_2), 2.94 (d, 2H, J = 8 Hz, CH_2), 1.75 (d, 3H, J = 1 Hz, CH_3), 1.64 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 174.7 (C=O), 137.2 (CH=*C*$(CH_3)_2$), 116.7 (*C*H=C$(CH_3)_2$), 35.4 (CH_2), 25.6 (CH_3), 17.8 (CH_3); HRMS *m/z* (M^+) found 113.0835, $C_6H_{11}NO$ requires 113.0841

2-(3-Methyl-3-nitrobutyl)-1,3-dioxolane (212):[122b]



Nitroaldehyde **211** (10.0 g, 68.9 mmol), ethylene glycol (5.0 g, 80.6 mmol) and *p*-TSA·H_2O (130 mg, 0.68 mmol) in $PhCH_3$ (25 mL) were heated under reflux, until the calculated volume (~1.2 mL) of water had been removed, by means of a Dean-Stark trap. The resulting mixture was cooled to rt and diluted with Et_2O (150 mL), then washed with sat. aq $NaHCO_3$ (100 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation, which gave nitroacetal **212** as a clear, colourless oil (12.0 g, 92%); bp 95–100 °C (0.4 mm Hg) [lit.[126a] bp 105 °C (0.5 mm Hg)]; R_f 0.48 (10% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2883w, 1535s (C–NO_2), 1473w, 1399w, 1373w, 1348m (C–NO_2), 1131m, 1034m, 857m; ^{1}H NMR (400 MHz) δ 4.86 (t, 1H, J = 4 Hz, CH_2CHO_2), 3.99 – 3.79 (m, 4H, OC_2H_4O), 2.06 – 1.97 (m, 2H, CH_2CNO_2), 1.63 (dt, 2H, J_1 = 13 Hz, J_2 = 4 Hz, CH_2CHO_2), 1.58 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 103.4 (CH_2CHO_2), 87.7 ($C(CH_3)_2$), 64.9 (OC_2H_4O), 34.6 (CH_2CHO_2), 28.6 (CH_2CNO_2), 25.7 ($C(CH_3)_2$)

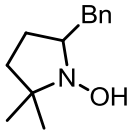
2,2-Dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (192):[122a]



Nitroacetal **212** (12.0 g, 63.4 mmol) was added to a stirred solution of NH_4Cl (3.53 g, 66.0 mmol) in water (70 mL). The resulting mixture was cooled to 5 °C (ice bath), and Zn dust

(16.6 g, 0.25 mol) added with vigorous stirring, maintaining a temperature between 10–15 °C. After 2 h, it was noted that the mixture had changed colour from dark grey to light grey. The zinc salts were filtered under low vacuum, and the filter cake washed with warm (70 °C) water (1 L). The aq washings were combined with the filtrate and acidified with conc HCl (138 mL). The aq solution was stirred for 16 h at rt, then heated to 70 °C for 2 h. The mixture was cooled and concentrated by evaporation under reduced pressure (70 mbar, 50 °C) to ~ one third of the starting volume, then aq NaOH (2 M) was added until a neutral pH (7) was established. The solution was saturated with borax, and then extracted with $CHCl_3$ (5 x 150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to generate DMPO (**192**) as a white solid, which rapidly turned to a clear, colourless oil, as the collection flask was brought back to rt (5.1 g, 71%); bp 50–60 °C (0.4 mm Hg) [lit.[122a] bp 45–53 °C (0.2 mm Hg)]; IR (neat) (cm^{-1}) 2971w, 2934w, 2868w, 1668w, 1572s (C=N), 1458w, 1382w, 1273m, 1236s (N–O), 1144m, 1026s, 688m; ^{1}H NMR (400 MHz) δ 6.74 (t, 1H, J = 3 Hz, CHN), 2.53 (td, 2H, J_1 = 7 Hz, J_2 = 3 Hz, CH_2C=N), 2.08 (t, 2H, J = 7 Hz, CH_2CH_2C=N), 1.38 (s, 6H, C(CH_3)$_2$); ^{13}C NMR (101 MHz) δ 131.6 (CHN), 73.3 (N*C*(CH_3)$_2$), 34.0 (NCHCH_2*C*H_2), 25.2 (NC(*C*H_3)$_2$), 24.2 (NCH*C*H_2); HRMS *m/z* (M^+) found 113.0841, $C_6H_{11}NO$ requires 113.0841

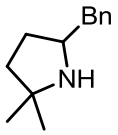
5-Benzyl-2,2-dimethylpyrrolidin-1-ol (199):[106]



A solution of DMPO (**192**) (3.00 g, 26.5 mmol) in Et_2O (24 mL) was added dropwise to a vigorously stirred solution of BnMgCl (1.0 M in Et_2O, 34.5 mL, 34.5 mmol) at such a rate that the mixture boiled under reflux. Following complete addition, stirring was continued for 15 min. The mixture was then quenched by pouring directly onto a mixture of ice and sat. aq NH_4Cl (~200 mL). The aq layer was then extracted with Et_2O (3 x 150 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation to give hydroxylamine **199** as clear, pale yellow crystals (5.37 g, 99%); mp 73–75 °C [lit.[106] 74–76 °C]; bp 125–135 °C; IR (neat) (cm^{-1}) 3270brm (O–H), 2965s, 1603m, 1496m, 1454s, 1377m, 1358m, 1230m, 1192m, 1166m, 996m, 740m, 699s; ^{1}H NMR (400 MHz) δ 7.34 – 7.17 (m, 5H, Ar), 5.77 (br s, 1H, OH), 3.29 (dd, 1H, J_{AB} =

13 Hz, J = 4 Hz, CH_AH$_B$Ph), 3.26 – 3.19 (m, 1H, J_1 = 10 Hz, J_2 = 4 Hz, NCH), 2.59 (dd, 1H, J_{AB} = 13 Hz, J = 10 Hz, CH$_A$$H_B$Ph), 1.76 – 1.63 (m, 1H, NCHCH_AH$_B$), 1.63 – 1.52 (m, 2H, NCHCH$_2$CH_2), 1.48 – 1.37 (m, 1H, NCHCH$_A$$H_B$), 1.26 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 139.8 (Ar (*ipso*)), 129.1 (Ar), 128.2 (Ar), 125.9 (Ar (*para*)), 65.7 (NCH), 63.5 (N*C*(CH$_3$)$_2$), 41.5 (*C*H$_2$Ph), 34.0 (NCHCH$_2$*C*H$_2$), 27.7 (CH$_3$), 24.2 (NCH*C*H$_2$), 19.0 (CH$_3$); m/z (ESI$^+$) 206.2 (M + H$^+$, 23); HRMS *m/z* (M + H$^+$) found 206.1534, C$_{13}$H$_{20}$NO requires 206.1539

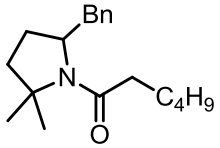
(±)-5-Benzyl-2,2-dimethylpyrrolidine ((±)-181):[127]



A mixture of Zn dust (6.4 g, 0.10 mol) and Cu(OAc)$_2$ (354 mg, 1.95 mmol) in glacial AcOH (20 mL) was stirred, under Ar at rt, for 15 min. A solution of hydroxylamine **199** (4.00 g, 19.5 mmol) in EtOH (12 mL) and glacial AcOH (20 mL) was added, and the resulting mixture stirred at 70 °C for 2.5 h. The mixture was then cooled to rt, and EDTA (20.5 g, 0.07 mol) added. Aq NaOH (2 M) was added to adjust the solution to pH 10, and the resulting basic solution then extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation, which gave pyrrolidine **(±)-(181)** as a clear, colourless oil (3.55 g, 96%); bp 125–135 °C (10 mm Hg); IR (neat) (cm^{-1}) 2957m, 2866w, 1603w, 1496w, 1454w, 1399w, 1157w, 744m, 698s; ^{1}H NMR (400 MHz) δ 7.32 – 7.17 (m, 5H, Ar), 3.50 – 3.39 (m, 1H NCH), 2.89 (dd, 1H, J_{AB} = 13 Hz, J = 6 Hz, CH_AH$_B$Ph), 2.65 (dd, 1H, J_{AB} = 13 Hz, J = 8 Hz, CH$_A$$H_B$Ph), 1.99 (br s, 1H, NH), 1.91 – 1.81 (m, 1H, CH_AH$_B$), 1.66 – 1.39 (m, 3H, 1 x CH$_2$ and CH$_A$$H_B$), 1.21 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 139.8 (Ar (*ipso*)), 129.0 (Ar (*ortho*)), 128.2 (Ar (*meta*)), 126.0 (Ar (*para*)), 59.7 (NCH), 58.8 (N*C*(CH$_3$)$_2$), 43.0 (*C*H$_2$Ph), 39.3 (CH$_2$), 31.8 (CH$_2$), 30.5 (CH$_3$), 29.3 (CH$_3$); m/z (ESI$^+$) 190.16 (M + H$^+$, 47); HRMS *m/z* (M + H$^+$) found 190.1595, C$_{13}$H$_{20}$N requires 190.1590

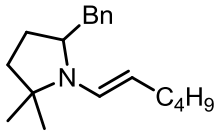
Synthesis and Alkylation of Pyrrolidine-Derived Enamine (±)-216:

1-(5-Benzyl-2,2-dimethylpyrrolidin-1-yl)hexan-1-one ((±)-215):



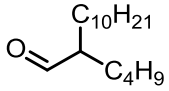
According to the general procedure for amide synthesis using Hulme's protocol, reaction of pyrrolidine **(±)-181** (190 mg, 1.00 mmol) with hexanoic anhydride (**101**; 429 mg, 2.00 mmol) and Et_3N (152 mg, 1.50 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, 20% EtOAc in petroleum ether), amide **(±)-215** as a pale yellow oil (215 mg, 75%); bp 130–135 °C (0.4 mm Hg); R_f 0.26 (20% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2957m, 2928m, 2872w, 1638s (C=O), 1454m, 1400s, 1376m, 1359m, 1171m, 983w,742s, 297s; ^1H NMR (400 MHz, 293 K) two rotamers {~ 6:1} δ 7.38 – 7.14 (m, 5H, Ar), 4.50 – 4.40 (m, 1H, J = 8 Hz, NCH (*min*)), 4.09 – 3.98 (m, 1H, J_1 = 10 Hz, J_2 = 7 Hz, J_3 = 4 Hz, NCH (*maj*)), 3.23 (dd, 1H, J_{AB} = 13 Hz, J = 3 Hz, CH_AH$_B$Ph (*min*)), 2.93 (dd, 1H, J_{AB} = 14 Hz, J = 4 Hz, CH_AH$_B$Ph (*maj*)), 2.65 (dd, 1H, J_{AB} = 14 Hz, J = 10 Hz, CH$_A$$H_B$Ph (*maj*)), 2.46 (dd, 1H, J_{AB} = 13 Hz, J = 10 Hz, CH$_A$$H_B$Ph (*min*)), 2.43 – 2.23 (m, 2H, CH_2C=O), 2.10 – 1.93 (m, 1H, NCHCH_AH$_B$), 1.89 – 1.61 (m, 5H, NCHCH$_A$$H_BCH_2$, and C$H_2$$CH_2$C=O), 1.63 (s, 3H, NC$CH_3$ (*maj*)), 1.50 (s, 3H, NCCH_3 (*min*)), 1.40 (s, 3H, NCCH_3 (*maj*)), 1.39 – 1.29 (m, 4H, CH_2C$H_2$$CH_3$), 1.36 (s, 3H, NC$CH_3$ (*min*)), 0.92 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) two rotamers δ 171.5 (C=O), 139.7 (Ar (*ipso*)(*min*)), 138.4 (Ar (*ipso*)(*maj*)), 129.5 (2 x Ar (*min*)), 129.0 (2 x Ar (*maj*)), 128.7 (2 x Ar (*maj*)), 128.2 (2 x Ar (*min*)), 126.6 (Ar (*para*)(*maj*)), 126.0 (Ar (*para*)(*min*)), 62.7 (N*C*$(CH_3)_2$ (*maj*)), 62.1 (NCH (*min*)), 61.5 (NCH (*maj*)), 60.4 (N*C*$(CH_3)_2$ (*min*)), 41.9 (NCH*C*H_2CH_2 (*min*), 41.4 (*C*H_2Ph (*maj*)), 39.2 (NCH*C*H_2CH_2 (*maj*)), 39.0 (*C*H_2Ph (*min*)), 35.6 (*C*H_2C=O (*maj*)), 35.1 (CH_2 (*min*)), 31.8 (CH_2 (*min*)), 31.7 (CH_2 (*maj*)), 30.0 (NC(*C*H_3)(*min*)), 28.6 (NC(*C*H_3)(*maj*)), 27.8 (NC(*C*H_3)(*min*)), 26.0 (CH_2 (*maj*)), 25.7 (CH_2 (*min*)), 25.1 (CH_2 (*maj*)), 24.8 (NC(*C*H_3)(*maj*)), 24.3 (CH_2 (*min*)), 22.6 (CH_2 (*maj*)), 14.0 (CH_2*C*H_3); m/z (ESI^+) 288.3 ($M + H^+$, 40); HRMS *m/z* (M^+) found 287.2245, $C_{19}H_{29}NO$ requires 287.2249

(±)-(*E*)-5-Benzyl-1-(hex-1-en-1-yl)-2,2-dimethylpyrrolidine ((±)-216):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **(±)-215** (133 mg, 0.46 mmol) with a solution of Vaska's complex (0.02 M in toluene, 0.25 mL, 5.0 µmol) and PMHS (138 mg, Si–H = 2.08 mmol) at rt for 20 min gave, after purification by bulb-to-bulb distillation, enamine **(±)-216** and amine **(±)-217** as a clear, colourless oil (115 mg, 91%, 93:7 {**216**:**217**}); bp 100–105 °C (1.0 mm Hg); IR (neat) (cm^{-1}) 2959s, 2924m, 1647s (N–C=C), 1454m, 1363s, 1291m, 938m, 737m, 699s; ^{1}H NMR (400 MHz) δ 7.37 – 7.14 (m, 5H, Ar), 6.08 (d, 1H, J = 14 Hz, NC*H*=CH), 4.28 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.59 (t, 1H, J = 9 Hz, NC*H*CH_2), 3.06 (dd, 1H, J_{AB} = 13 Hz, J = 3 Hz, C*H*$_A$H$_B$Ph), 2.47 (dd, 1H, J_{AB} = 13 Hz, J = 9 Hz, CH$_A$*H*$_B$Ph), 2.15 – 1.99 (m, 2H, NCH=CHC*H*$_2$), 1.94 – 1.79 (m, 1H, NCHC*H*$_A$H$_B$CH$_2$), 1.68 – 1.62 (m, 1H, NCHCH$_A$*H*$_B$CH$_2$), 1.59 – 1.50 (m, 2H, NCHCH$_2$C*H*$_2$), 1.41 – 1.34 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 1.22 (s, 3H, NCCH$_3$), 1.04 (s, 3H, NCCH$_3$), 0.96 – 0.92 (m, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz) δ 140.1 (Ar (*ipso*)), 130.1 (N*C*H=CH), 129.5 (Ar), 128.1 (Ar), 125.8 (Ar (*para*)), 98.0 (NCH=*C*H), 61.1 (N*C*(CH$_3$)$_2$), 60.0 (N*C*HCH$_2$), 38.6 (*C*H$_2$Ph), 38.3 (NCHCH$_2$*C*H$_2$), 34.3 (CH$_2$), 31.0 (NCH=CH*C*H$_2$), 28.4 (NC*C*H$_3$), 26.5 (NCH*C*H$_2$CH$_2$), 26.0 (NC*C*H$_3$), 22.1 (CH$_2$), 14.1 (CH$_2$*C*H$_3$); m/z (ESI$^+$) 272.3 (M + H$^+$, 11); HRMS *m/z* (M$^+$) found 271.2310, $C_{19}H_{29}N$ requires 271.2300

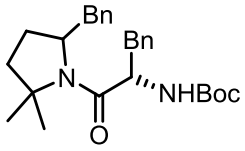
(±)-2-Butyldodecanal ((±)-140):



According to the general procedure for enamine alkylation, reaction of enamine **(±)-216** (78 mg, 0.29 mmol) with decyl iodide (154 mg, 0.57 mmol) in d_3-MeCN (1 mL) at 95 °C for 20 h gave, following hydrolysis with acidic buffer (0.5 mL) at 95 °C for 1.5 h, and purification of the residue from work-up by column chromatography (SiO_2, 1% Et_2O in petroleum ether), aldehyde **(±)-140**[16,39] as a clear, colourless oil (47 mg, 69%); R_f 0.15 (1% Et_2O in petroleum ether); other data as above.

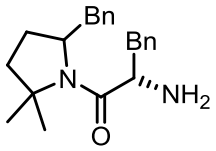
Resolution of Pyrrolidine (±)-181:

***tert*-Butyl ((*S*)-1-((*S*)- and *tert*-butyl ((*S*)-1-((*R*)-5-benzyl-2,2-dimethylpyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate ((*S*,*S*)-218) / ((*S*,*R*)-218):**



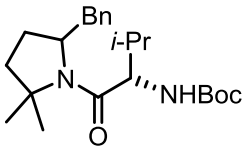
According to the general procedure for amide coupling with BOP-Cl, reaction of pyrrolidine **(±)-181** (600 mg, 3.17 mmol) with DIPEA (901 mg, 6.97 mmol), *N*-Boc-L-PheOH (926 mg, 3.49 mmol) and BOP-Cl (888 mg, 3.49 mmol) in CH_2Cl_2 (33 mL) at 0–4 °C for 3 d gave, following purification of the residue from work-up by column chromatography (SiO_2, 10% EtOAc in petroleum ether), inseparable Boc protected α-amino-amides **218** as a white solid (52:48 *dr*, 981 mg, 71%); mp 82–85 °C; R_f 0.73 (20% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3293w, 3063w, 2966w, 2929w, 1702s (C=O, urethane), 1630s (C=O, 3° amide), 1495m, 1454m, 1335m, 1246m, 1170s, 743m, 700m; ^{1}H NMR (500 MHz) two diastereomers {52:48} δ 7.38 – 7.04 (m, 20H, Ar), 5.48 (d, 1H, J = 9 Hz, NH (*min*)), 5.13 (d, 1H, J = 9 Hz, NH (*maj*)), 4.88 – 4.79 (m, 1H, J = 9 Hz, NHC*H* (*min*)), 4.78 – 4.69 (m, 1H, J = 9 Hz, NHC*H*CH_2 (*maj*)), 4.45 – 4.31 (m, 1H, NC*H*CH_2 (*maj*)), 3.41 – 3.30 (m, 1H, NC*H*CH_2 (*min*)), 3.18 (dd, 1H, J_{AB} = 13 Hz, J = 8 Hz, NHCHC*H*$_A$H$_B$Ph (*maj*)), 3.10 (dd, 1H, J_{AB} = 13 Hz, J = 4 Hz, NHCHC*H*$_A$H$_B$Ph (*min*)), 3.02 – 2.88 (m, 3H, 2 x NHCHCH$_A$*H*$_B$Ph and NCHC*H*$_A$H$_B$Ph (*min*)), 2.51 (t, 1H, J = 12 Hz, NCHCH$_A$*H*$_B$Ph (*min*)), 2.26 – 2.08 (m, 2H, NCHC*H*$_2$Ph (*maj*)), 2.00 – 1.05 (m, 38H, 2 x NCHC*H*$_2$C*H*$_2$, 2 x NC(CH$_3$)$_2$ and 2 x C(CH$_3$)$_3$); ^{13}C NMR (125 MHz) two diastereomers δ 170.3 (C=O, 3° amide (*maj*)), 169.8 (C=O, 3° amide (*min*)), 155.2 (C=O, urethane (*maj*)), 154.9 (C=O, urethane (*min*)), 138.11 (Ar (*ipso*)), 138.06 (Ar (*ipso*)), 137.2 (Ar (*ipso*)), 136.7 (Ar (*ipso*)), 129.7 (Ar), 129.6 (Ar), 129.24 (Ar), 129.20 (Ar), 128.6 (Ar), 128.5 (Ar), 128.42 (Ar), 128.37 (Ar), 126.8 (Ar), 126.7 (Ar), 126.5 (Ar), 126.4 (Ar), 79.6 (O*C*(CH$_3$)$_3$ (*maj*)), 79.4 (O*C*(CH$_3$)$_3$ (*min*)), 63.24 (N*C*(CH$_3$)$_2$ (*maj*)), 63.20 (N*C*(CH$_3$)$_2$ (*min*)), 61.3 (NCH(CH$_2$)$_2$ (*min*)), 60.9 (N*C*H(CH$_2$)$_2$ (*maj*)), 54.1 (NHCH (*maj*)), 54.0 (NHCH (*min*)), 41.3 (NHCH*C*H$_2$Ph (*min*)), 40.9 (NCH*C*H$_2$Ph (*min*)), 40.8 (NCH*C*H$_2$Ph (*maj*)), 39.5 (NHCH*C*H$_2$Ph (*maj*)), 39.0 (CH_2), 38.8 (CH_2), 28.4 (NC*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$ (*maj*)), 28.2 (C(*C*H$_3$)$_3$ (*min*)), 27.8 (NC*C*H$_3$), 25.6 (CH_2), 25.0 (CH_2), 24.5 (NC*C*H$_3$), 24.4 (NC*C*H$_3$); m/z (ESI$^+$) 437.3 (M + H$^+$, 100); HRMS *m/z* (M + H$^+$) found 437.2780, $C_{27}H_{37}N_2O_3$ requires 437.2799

(*S*)-2-Amino-1-((*S*)- and (*S*)-2-amino-1-((*R*)-5-benzyl-2,2-dimethylpyrrolidin-1-yl)-3-phenylpropan-1-one ((*S*,*S*)-219) / ((*S*,*R*)-219):



According to the general procedure for Boc-deprotection, reaction of Boc protected α-amino amides **218** (821 mg, 1.88 mmol) with TFA (5 mL, 0.07 mol) in CH_2Cl_2 (23 mL) at rt for 1 h gave, following purification of the residue from work-up by column chromatography (SiO_2, 10% MeOH in EtOAc), inseparable α-amino amides **219** as a clear, pale yellow oil (51:49 *dr*, 624 mg, 98%); R_f 0.34 (10% MeOH in EtOAc); IR (neat) (cm^{-1}) 3368w, 3062w, 3026w, 2963w, 2878w, 1737w, 1631s (C=O), 1495w, 1359m, 1166w, 847w, 796w; ^{1}H NMR (500 MHz) two diastereomers {51:49} δ 7.36 – 7.01 (m, 20H, Ar), 4.17 – 4.09 (m, 1H, J_1 = 7 Hz, J_2 = 9 Hz, NC*H*CH_2), 3.80 (t, 1H, J = 7 Hz, NH_2C*H* (*min*)), 3.67 (t, 1H, J = 7 Hz, NH_2C*H* (*maj*)), 3.58 – 3.49 (m, 1H, NC*H*CH_2), 3.18 (dd, 1H, J_{AB} = 13 Hz, J = 7Hz, $NH_2CHCH_AH_B$ (*min*)), 2.87 – 2.77 (m, 4H, $NH_2CHCH_AH_B$ (*min*), NH_2CHCH_2 (*maj*) and $NCHCH_AH_B$), 2.59 (dd, 1H, J_{AB} = 14 Hz, J = 9 Hz, $NCHCH_AH_B$), 2.40 – 2.26 (m, 2H, $NCHCH_2$), 2.09 – 1.19 (m, 12H, 2 x $NCHCH_2CH_2$ and 2 x NH_2), 1.63 (CH_3), 1.60 (CH_3), 1.44 (CH_3), 1.31 (CH_3); ^{13}C NMR (125 MHz) two diastereomers δ 173.3 (172.8) (C=O), 138.3 (Ar (*ipso*)), 138.14 (Ar (*ipso*)), 138.06 (Ar (*ipso*)), 137.7 (Ar (*ipso*)), 129.6 (Ar), 129.4 (Ar), 129.1 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 126.72 (Ar (*para*)), 126.66 (Ar (*para*)), 126.61 (Ar (*para*)), 126.57 (Ar (*para*)), 63.12 (63.07) ($NC(CH_3)_2$), 61.0 (60.5) (NCH), 55.8 (55.4) (NH_2C*H*), 43.3 (42.6) (NH_2CHCH_2), 41.6 (41.1) ($NCHCH_2$), 38.98 (38.95) (CH_2), 28.7 (CH_3), 28.0 (CH_3), 26.3 (25.8) (CH_2), 24.7 (CH_3), 24.6 (CH_3); m/z (ESI^+) 337.24 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 337.2260, $C_{22}H_{29}N_2O$ requires 337.2274

(+)-*tert*-Butyl ((*S*)-1-((*S*)- and (–)-*tert*-butyl ((*S*)-1-((*R*)-5-benzyl-2,2-dimethylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate ((+)-(*S*,*S*)-220) / ((–)-(*R*,*S*)-220):



Using BOP-Cl:

According to the general procedure for amide coupling with BOP-Cl, reaction of pyrrolidine **(±)-181** (100 mg, 0.53 mmol) with DIPEA (151 mg, 1.17 mmol), *N*-Boc-L-ValOH (154 mg, 0.71 mmol) and BOP-Cl (148 mg, 0.58 mmol) in CH_2Cl_2 (5.5 mL) at rt for 64 h gave, following purification of the residue from work-up by column chromatography (SiO_2, gradient elution: 5–10% EtOAc in petroleum ether) Boc protected α-amino amides **220** as a white solid (61:39 *dr*, 109 mg, 53%); other data as below.

Using CDMT:

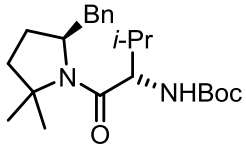
Pyrrolidine **(±)-181** (100 mg, 0.53 mmol), *N*-Boc-L-ValOH (115 mg, 0.53 mmol), CDMT (59 mg, 0.58 mmol) and NMM (81 mg, 0.80 mmol) in MeCN (1 mL) were stirred at rt for 16 h. After this time, the mixture was partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was separated, and the aq layer back-extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, gradient elution: 5–10% EtOAc in petroleum ether), which gave Boc protected α-amino amides **220** as a white solid (111 mg, 55%); other data as below.

Using HBTU:

Pyrrolidine **(±)-181** (3.00 g, 15.8 mmol), *N*-Boc-L-ValOH (3.44 g, 15.8 mmol), HBTU (7.21 g, 19.0 mmol) and NEt_3 (3.21 g, 31.7 mmol) in CH_2Cl_2 (100 mL) were stirred at rt for 20 h, resulting in a pink coloration. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer back-extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and

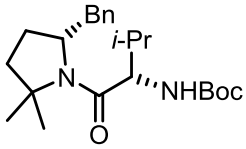
evaporated under reduced pressure. The residue was purified by chromatography (SiO_2, gradient elution: 5–10% EtOAc in petroleum ether). First, eluted Boc protected α-amino amide **(*S*,*S*)-220** (2.01 g), followed by a mixed fraction (0.91 g); last, eluted α-amino amide **(*R*,*S*)-220** (1.58 g), all as white solids (~50:50 *dr*, 4.50 g total product, 73%);

Data for upper R_f diastereomer **(*S*,*S*)-220**:



mp 55–57 °C; $[\alpha]_D^{25}$ = +102.7 (*c* = 1.3, $CHCl_3$); R_f 0.31 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3274m 2967m, 2930w, 1688m (C=O, urethane), 1631s (C=O, 3° amide), 1524m, 1524m, 1422m, 1365m, 1216m, 1169s, 759m, 742m; ^{1}H NMR (400 MHz) δ 7.41 – 7.14 (m, 5H, Ar), 5.35 (d, 1H, *J* = 9 Hz, NH), 4.52 (dd, 1H, J_1 = 9 Hz, J_2 = 7 Hz, NHC*H*), 4.13 – 4.04 (m, 1H, NCH), 3.06 (dd, 1H, J_{AB} = 12 Hz, *J* = 2 Hz, NCHCH_AH_B), 2.68 (t, 1H, J_{AB} = 12 Hz, NCHCH$_A$$H_B$), 2.11 – 1.69 (m, 5H, NHCHC*H* and NCHCH_2CH_2), 1.64 (s, 3H, $NCCH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 1.38 (s, 3H, $NCCH_3$), 1.04 – 0.93 (m, 6H, *J* = 7 Hz, $CH(CH_3)_2$); ^{13}C NMR (125 MHz) δ 170.6 (C=O, 3° amide), 155.7 (C=O, urethane), 138.3 (Ar (*ipso*)), 129.5 (Ar), 128.7 (Ar), 126.6 (Ar (*para*)), 79.2 ($C(CH_3)_3$), 63.1 ($NC(CH_3)_2$), 61.8 (NCH), 57.2 (NHCH), 41.3 (CH_2Ph), 38.8 (CH_2), 32.9 ($CH(CH_3)_2$), 28.6 ($NCCH_3$), 28.4 ($C(CH_3)_3$), 25.2 (CH_2), 24.5 ($NCCH_3$), 19.4 ($CHCH_3$), 17.7 ($CHCH_3$); m/z (ESI^+) 411.3 (M + Na^+, 100); HRMS *m/z* (M^+) found 388.2708, $C_{23}H_{36}N_2O_3$ requires 388.2726

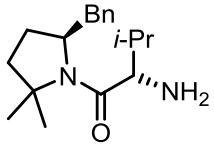
Data for lower R_f diastereomer **(*R*,*S*)-220**:



mp 149–151 °C; $[\alpha]_D^{25}$ = –27.6 (*c* = 0.8, $CHCl_3$); R_f 0.25 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3306w, 2963m, 1710s (C=O, urethane), 1638s (C=O, 3° amide), 1496m, 1413s, 1365m, 1247w, 1168s, 1017w, 745w, 697w; ^{1}H NMR (400 MHz) δ 7.41 – 7.14 (m, 5H, Ar),

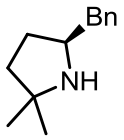
5.00 (d, 1H, *J* = 10 Hz, NH), 4.62 – 4.52 (m, 1H, NCH), 4.30 (t, 1H, *J* = 10 Hz, NHC*H*), 3.08 (dd, 1H, J_{AB} = 13 Hz, *J* = 3 Hz, C$H_A$$H_B$Ph), 2.65 (t, 1H, *J* = 13 Hz, C$H_A$$H_B$Ph), 2.19 – 1.69 (m, 5H, C*H*(CH_3)$_2$ and NCHCH_2CH_2), 1.60 (s, 3H, NCCH_3), 1.45 (s, 9H, C(CH_3)$_3$), 1.41 (s, 3H, NCCH_3), 1.06 (d, 3H, *J* = 7 Hz, CHCH_3), 1.00 (d, 3H, *J* = 7 Hz, CHCH_3); ^{13}C NMR (125 MHz) δ 171.0 (C=O, 3° amide), 155.8 (C=O, urethane), 138.0 (Ar (*ipso*)), 129.3 (Ar), 128.7 (Ar), 126.6 (Ar (*para*)), 79.4 (*C*(CH_3)$_3$), 63.3 (N*C*(CH_3)$_2$), 60.6 (NCH,) 58.1 (NHCH), 42.1 (*C*H_2Ph), 39.2 (CH_2), 31.6 (*C*H(CH_3)$_2$), 28.3 (C(*C*H_3)$_3$), 28.0 (NC*C*H_3), 25.6 (CH_2), 24.4 (NC*C*H_3), 20.3 (CH*C*H_3), 18.3 (CH*C*H_3); m/z (ESI$^+$) 411.3 (M + Na^+, 100); HRMS *m/z* (M^+) found 388.2721, $C_{23}H_{36}N_2O_3$ requires 388.2726

(+)-(*S*)-2-Amino-1-((*S*)-5-benzyl-2,2-dimethylpyrrolidin-1-yl)-3-methylbutan-1-one ((+)-(*S,S*)-221):



According to the general procedure for Boc-deprotection, reaction of Boc protected α-amino amide **(*S,S*)-220** (1.98 g, 5.1 mmol) with TFA (14 mL, 0.18 mol) in CH_2Cl_2 (62 mL) at rt for 1 h gave, following purification of the residue from work-up by column chromatography (SiO_2, 10% MeOH in EtOAc), α-amino amide **(*S,S*)-221** as a clear, pale yellow oil (1.38 g, 94%); $[\alpha]_D^{25}$ = +100.0 (*c* = 1.7, $CHCl_3$); R_f 0.34 (10% MeOH in EtOAc); IR (neat) (cm^{-1}) 2960m, 1632s (C=O), 1495w, 1454m, 1417m, 1360s, 1167m, 924m, 734s, 698s; ^{1}H NMR (400 MHz) δ 7.37 – 7.12 (m, 5H, Ar), 4.13 – 4.02 (m, 1H, NC*H*CH_2Ph), 3.17 (d, 1H, *J* = 6 Hz, C*H*NH_2), 2.91 (dd, 1H, J_{AB} = 14 Hz, *J* = 5 Hz, NCHC$H_A$$H_B$Ph), 2.69 (dd, 1H, J_{AB} = 14 Hz, *J* = 10 Hz, NCHC$H_A$$H_B$Ph), 2.11 – 1.66 (m, 5H, NCH(CH_2)$_2$ and C*H*(CH_3)$_2$), 1.68 (s, 3H, $NCCH_3$), 1.58 (br s, 2H, NH_2) 1.38 (s, 3H, $NCCH_3$), 0.95 (d, 3H, *J* = 10 Hz, CHCH_3), 0.93 (d, 3H, *J* = 10 Hz, CHCH_3); ^{13}C NMR (101 MHz) δ 173.9 (C=O), 138.1 (Ar (*ipso*)), 129.1 (Ar), 128.7 (Ar), 126.7 (Ar), 62.9 (N*C*(CH_3)$_2$), 60.9 (N*C*HCH_2Ph), 58.7 (*C*HNH_2), 41.9 (*C*H_2Ph), 38.9 (CH_2), 32.8 (*C*H(CH_3)$_2$), 28.8 (NC*C*H_3), 26.3 (CH_2), 24.6 (NC*C*H_3), 19.9 (CH*C*H_3), 17.2 (CH*C*H_3); m/z (ESI$^+$) 289.24 (M + H^+, 100); HRMS *m/z* (M + H^+) found 289.2277, $C_{18}H_{29}N_2O$ requires 289.2274

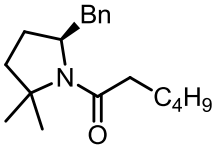
(–)-(*S*)-5-Benzyl-2,2-dimethylpyrrolidine ((–)-(*S*)-181):



According to the general procedure for Edman degradation, reaction of α-amino amide **(*S*,*S*)-221** (1.27 g, 4.4 mmol) with PhNCS (654 mg, 4.84 mmol) in CH_2Cl_2 (15 mL) at 100 °C until consumption of **(*S*,*S*)-221** (monitored by TLC), followed by treatment with TFA (15 mL) at 50 °C for 20 min, gave, after purification of the residue from work-up by bulb-to-bulb distillation, enantiopure pyrrolidine **(*S*)-181** as a clear, colourless oil (640 mg, 77%); $[\alpha]_D^{25}$ = –1.6 (*c* = 1.0, $CHCl_3$); other data as above.

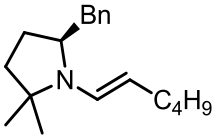
Synthesis and Alkylation of Pyrrolidine-Derived Enamine (*S*)-216:

(+)-(*S*)-1-(5-Benzyl-2,2-dimethylpyrrolidin-1-yl)hexan-1-one ((+)-(*S*)-215):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of pyrrolidine **(*S*)-181** (230 mg, 1.22 mmol) with hexanoic anhydride (**101**; 521 mg, 2.43 mmol) and Et_3N (2 mL, 14.35 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, 20% EtOAc in petroleum ether), amide **(*S*)-215** as a pale yellow oil (307 mg, 88%); $[\alpha]_D^{25}$ = +57.8 (*c* = 1.1, $CHCl_3$); other data as above.

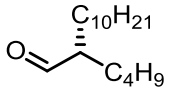
(*S*,*E*)-5-Benzyl-1-(hex-1-en-1-yl)-2,2-dimethylpyrrolidine ((*S*)-216):



According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **(*S*)-215** (220 mg, 0.77 mmol) with a solution of Vaska's complex (0.02 M

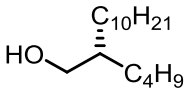
in toluene, 0.39 mL, 7.8 µmol) and PMHS (205 mg, Si–H = 3.09 mmol) at rt for 20 min gave, after purification by bulb-to-bulb distillation, enamine **(*S*)-216** and amine **(*S*)-217** as a clear, colourless oil (195 mg, 94%, 91:9 {**216**:**217**});[180] other data as above.

(*S*)-2-Butyldodecanal ((*S*)-140):



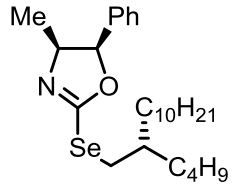
According to the general procedure for enamine alkylation, reaction of enamine **(*S*)-216** (118 mg, 0.43 mmol) with decyl iodide (233 mg, 0.87 mmol) in d_3-MeCN (0.5 mL) at 95 °C for 20 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 10 min, and purification of the residue from work-up by column chromatography (SiO_2, 1% Et_2O in petroleum ether), aldehyde **(*S*)-140**[16] as a clear, colourless oil (51:49 *er*, 63 mg, 60%); $[\alpha]_D^{25} = -0.5$ (*c* = 0.8, $CHCl_3$) [lit.[16] $[\alpha]_D^{22} = -2.4$ (*c* = 0.5, Et_2O)]; other data as above.

(*S*)-2-Butyldodecan-1-ol ((*S*)-222):[16]



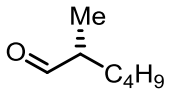
According to the general procedure for aldehyde reduction, reaction of aldehyde **(*S*)-140** (42 mg, 0.17 mmol) with $NaBH_4$ (33 mg, 0.87 mmol) in MeOH / Et_2O (2 mL / 2 mL) at 0 °C–rt for 16 h gave, following purification of the residue from work-up by column chromatography (SiO_2, 15% Et_2O in petroleum ether), alcohol **(*S*)-222** as a clear, colourless oil (36 mg, 88%); $[\alpha]_D^{25} = -1.25$ (*c* = 0.4, $CHCl_3$) [lit.[16] $[\alpha]_D^{22} = -1.5$ (*c* = 0.9, CH_2Cl_2)]; R_f 0.25 (15% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3352br (O–H), 2922s, 2854s, 1743w, 1465m; 1415w, 1377w, 1334m, 1262w, 1200w, 1122w, 1041m, 894w, 723w; ^{1}H NMR (400 MHz) δ 3.54 (d, 2H, *J* = 5 Hz, C*H*$_2$OH), 1.51 – 1.18 (m, 26H, 1 x CH, 1 x OH and 12 x CH_2), 0.95 – 0.84 (m, 6H, 2 x CH_3); ^{13}C NMR (101 MHz) δ 65.7 (CH_2OH), 40.5 (C*H*CH_2OH), 31.9 (CH_2), 30.9 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 29.63 (CH_2), 29.62 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 23.1 (CH_2), 22.7 (CH_2), 14.08 (CH_3), 14.06 (CH_3)

(4*S*,5*R*)-2-((2-Butyldodecyl)selanyl)-4-methyl-5-phenyl-4,5-dihydrooxazole ((4*S*,5*R*,*S*$_\alpha$)-223):[16]



According to the general procedure for Mitsunobu reaction, reaction of alcohol **(*S*)-222** (30 mg, 0.12 mmol) with chiral selenone **(4*S*,5*R*)-169** (43 mg, 0.18 mmol), PPh_3 (50 mg, 0.19 mmol) and DIAD (37 µL, 0.19 mmol) in CH_2Cl_2 (2 mL) at rt for 16 h gave, following purification of the residue from work-up by column chromatography (SiO_2, CH_2Cl_2), selenium adduct **(4*S*,5*R*,*S*$_\alpha$)-223** as a clear, yellow oil (51:49 *dr*, 53 mg, 92%); $[\alpha]_D^{25}$ = –129.4 (*c* = 0.9, $CHCl_3$) [lit.[16] $[\alpha]_D^{22}$ = –117.0 (*c* = 0.8, CH_2Cl_2)]; R_f 0.50 (CH_2Cl_2); IR (neat) (cm^{-1}) 2955m, 2924s, 2854s, 1606s (C=N), 1495w, 1456m, 1377w, 1109s, 957s, 699s; ^{1}H NMR (400 MHz) δ 7.41 – 7.15 (m, 5H, Ar), 5.64 (d, 1H, *J* = 9 Hz, C*H*Ph), 4.46 (dq, 1H, J_1 = 9 Hz, J_2 = 7 Hz, C*H*CH_3), 3.27 – 3.11 (m, 2H, $SeCH_2$), 1.82 – 1.65 (m, 1H, $SeCH_2CH$), 1.49 – 1.20 (m, 24H, 12 x CH_2), 0.96 – 0.85 (m, 6H, 2 x CH_2CH_3), 0.79 (d, 3H, *J* = 7 Hz, $CHCH_3$); ^{13}C NMR (101 MHz) δ 159.8 (Se–C=N), 136.5 (Ar (*ipso*)), 128.2 (Ar), 127.9 (Ar (*para*)), 126.1 (Ar), 85.4 (*C*HPh), 65.8 (*C*HCH_3), 38.1 ($SeCH_2CH$), 33.9 (CH_2), 33.6 (CH_2), 32.9 ($SeCH_2$), 31.9 (CH_2), 29.8 (CH_2), 29.63 (CH_2), 29.60 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.6 (CH_2), 23.7 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 17.7 ($CHCH_3$), 14.09 (CH_2CH_3), 14.05 (CH_2CH_3); ^{77}Se NMR (48 MHz) two diastereomers {51:49} δ 228.2 (*maj*), 228.1 (*min*); m/z (ESI^+) 466.3 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 466.2565, $C_{26}H_{44}NOSe$ requires 466.2584

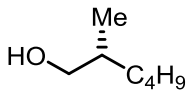
(*R*)-2-Methylhexanal ((*R*)-225):



According to the general procedure for enamine alkylation, reaction of enamine **(*S*)-216** (182 mg, 0.67 mmol) with MeI (190 mg, 1.34 mmol) in d_3-MeCN (1.0 mL) at rt for 1 h, then 40 °C for 16 h, gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 10 min and work-up,

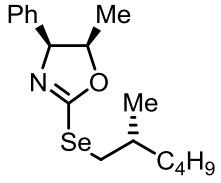
the crude aldehyde in Et_2O. This solution was diluted to 25 mL with Et_2O, and a 15 mL aliquot directly reduced (*vide infra*). The remaining 10 mL aliquot was evaporated under reduced pressure and purified by chromatography (SiO_2, 2% Et_2O in petroleum ether) , which gave aldehyde **(*R*)-225**[16] (51:49 *er*, 2 mg, 3%); R_f 0.44 (2% Et_2O in petroleum ether); ^{1}H NMR (400 MHz) δ 9.62 (d, 1H, J = 2 Hz, CHO), 2.39 – 2.29 (m, 1H, C*H*CH_3), 1.76 – 1.68 (m, 1H, CHC$H_A$$H_B$), 1.46 – 1.22 (m, 5H, CHC$H_A$$H_B$ and 2 x CH_2), 1.10 (d, 3H, J = 7 Hz, CHCH_3), 0.92 (t, 3H, J = 7 Hz, CH_2CH_3)

(*R*)-2-Methylhexan-1-ol ((*R*)-226):[16]



According to the general procedure for aldehyde reduction, reaction of a solution of aldehyde **(*R*)-225** (0.027 M, 15 mL, 0.41 mmol) with $NaBH_4$ (76 mg, 2.01 mmol) in MeOH (5 mL) at 0 °C–rt for 16 h gave, following purification of the residue from work-up by column chromatography (SiO_2, 20% Et_2O in petroleum ether), alcohol **(*R*)-226** as a clear, colourless oil (29 mg, 61%); R_f 0.16 (20% Et_2O in petroleum ether); ^{1}H NMR (300 MHz) δ 3.52 (dd, 1H, J_{AB} = 10 Hz, J = 6 Hz, C$H_A$$H_B$OH), 3.44 (dd, 1H, J_{AB} = 10 Hz, J = 7 Hz, $CH_A$$H_B$OH), 1.70 – 1.49 (m, 1H, C*H*CH_2OH), 1.42 – 1.03 (m, 6H, 3 x CH_2), 0.97 – 0.83 (m, 6H, 2 x CH_3); ^{13}C NMR (75 MHz) δ 68.4 (CH_2OH), 35.7 (*C*HCH_2OH), 32.8 (CH_2), 29.2 (CH_2), 23.0 (CH_2), 16.6 (CH_3), 14.1 (CH_3) m/z (ESI$^-$) 115.2 (M – H^+, 13)

(4*S*,5*R*)-5-Methyl-2-(((*R*)-2-methylhexyl)selanyl)-4-phenyl-4,5-dihydrooxazole ((4*S*,5*R*,*R*$_\alpha$)-227):[16]



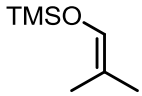
According to the general procedure for Mitsunobu reaction, reaction of alcohol **(*R*)-226** (17 mg, 0.146 mmol) with chiral selenone **(4*S*,5*R*)-169** (53 mg, 0.221 mmol), PPh_3 (58 mg, 0.221 mmol) and DIAD (43 µL, 0.218 mmol) in CH_2Cl_2 / $CDCl_3$ (1 mL / 0.5 mL) at rt for 16 h

gave, following purification of the residue from work-up by column chromatography (SiO_2, CH_2Cl_2), selenium adduct **(4*S*,5*R*,R_α)-227** as a clear, yellow oil (51:49 *dr*, 8 mg, 16%{79% brsm}); R_f 0.41 (CH_2Cl_2); IR (neat) (cm^{-1}) 2957s, 2927s, 2858m, 1760m, 1607s (C=N), 1496w, 1456m, 1377m, 1290w, 1200w, 1110s, 956m, 748w, 700m; ^{1}H NMR (400 MHz) δ 7.38 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.33 (t, 1H, J = 7 Hz, Ar (*para*)), 7.22 (d, 2H, J = 7 Hz, Ar (*ortho*), 5.71 (d, 1H, J = 9 Hz, C*H*Ph), 4.56 – 4.47 (m, 1H, O–C*H*CH_3), 3.29 – 3.04 (m, 2H, $SeCH_2$); 1.91 – 1.80 (m, 1H, $SeCH_2CH$), 1.50 – 1.44 (m, 1H, CH_AH_B), 1.38 – 1.20 (m, 5H, 2 x CH_2 and 1 x CH_AH_B), 1.04 (d, 3H, J = 7 Hz, CH_2CHCH_3), 0.90 (t, 3H, J = 7 Hz, CH_2CH_3), 0.83 (d, 3H, J = 7 Hz, O–$CHCH_3$); ^{13}C NMR (101 MHz) δ 159.7 (C=N), 136.2 (Ar (*ipso*)), 128.4 (Ar (*meta*)), 128.2 (Ar (*para*)), 126.2 (Ar (*ortho*)), 86.1 (*C*HPh), 64.6 (O–*C*HCH_3), 36.3 (CH_2), 35.4 ($SeCH_2$), 33.6 ($SeCH_2CH$), 29.2 (CH_2), 22.8 (CH_2), 19.9 (CH_2CHCH_3), 17.5 (O–$CHCH_3$), 14.0 (CH_2CH_3); ^{77}Se NMR (48 MHz) two diastereomers {51:49} δ 237.3 (*maj*), 236.7 (*min*); m/z (ESI^+) 340.1 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 340.1170, $C_{17}H_{26}NOSe$ requires 340.1175

5.4 Procedures for Chapter 4

Robinson-Schöpf Route to Homotropane (±)-229:

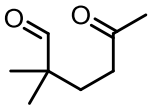
Trimethyl((2-methylprop-1-en-1-yl)oxy)silane (239):[133d]



IBA (**74**, 25.0 g, 0.35 mol), TMSCl (41.4 g, 0.38 mol) and Et_3N (70.2 g, 0.69 mol) in DMF (200 mL) were heated under reflux, with stirring for 4 h. After this time, the mixture was cooled, then quenched with ice-cold sat. aq $NaHCO_3$ (500 mL). [Care! Add slowly and ensure suitable exhaust!] The resultant slurry was partitioned with pentane (500 mL), and the organic layer washed several times with ice-cold sat. aq $NaHCO_3$ (5 x 300 mL). The separated organic layer was dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation, to give silyl enol ether **239** as a clear, colourless oil (25.6 g, 51%); bp 70–80 °C (127 mm Hg) [lit.[183] bp 69 °C (120 mm Hg)]; IR (neat) (cm^{-1}) 2960w, 2922w, 1684m (O–C=C), 1253m, 1169s, 1039w, 877s, 839s, 750m; ^{1}H NMR (400 MHz) δ 6.03 – 5.99 (m, 1H, J = 1 Hz, OCH), 1.60 (d, 3H, J = 1 Hz, CCH_3), 1.55 (d, 3H, J = 1 Hz,

CCH_3), 0.17 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (101 MHz) δ 132.8 (C–O), 114.1 (*C*=C–O), 19.3 (C*C*H_3), 14.7 (C*C*H_3), –0.5 ($Si(CH_3)_3$)

2,2-Dimethyl-5-oxohexanal (232):



By Protocol of Miyakoshi *et al.*:[136]

Bu_3P (250 µL, 1.00 mmol) was added dropwise to a solution of IBA (**74**, 3.61 g, 50.1 mmol) and MVK (**233**, 3.50 g, 49.9 mmol) in benzene (5 mL), with stirring at rt, resulting in a yellow coloration. The mixture was heated at 45 °C for 30 min, then 60 °C for 1 h. After this time, H_2O (50 mL) was added. [Care! Add slowly!] The mixture was washed with Et_2O (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), and then evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% EtOAc in petroleum ether), to give ketoaldehyde **232** as a clear, colourless oil (1.40 g, 20%); R_f 0.19 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2967w, 2933w, 2874w, 2811w, 2706w, 1714s (2 x C=O), 1471w, 1365m, 1173w, 882m; ^1H NMR (400 MHz) δ 9.40 (s, 1H, CHO), 2.35 (t, 2H, J = 8 Hz, CH_2), 2.11 (s, 3H, $CH_2C(=O)CH_3$), 1.74 (t, 2H, J = 8 Hz, CH_2), 1.03 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 207.8 (C=O), 205.5 (CHO), 45.1 (*C*$(CH_3)_2$), 38.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2COCH_3), 21.3 ($C(CH_3)_2$); m/z (ESI^+) 165.1 (M + Na^+, 47); HRMS *m/z* (M + Na^+) found 165.0889, $C_8H_{14}NaO_2$ requires 165.0886

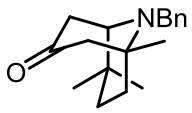
By Protocol of Ranu *et al.*:[133b–c]

Activated alumina (5.00 g) and $ZnCl_2$ (681 mg, 5.00 mmol) were stirred in THF (25 mL) for 5 min. The slurry was then evaporated under reduced pressure, which gave $ZnCl_2$-impregnated alumina as a white solid, which was added to a stirred mixture of silyl enol ether **239** (721 mg, 5.00 mmol) and MVK (**233**, 421 mg, 6.01 mmol) at 0 °C. After 30 min at 0 °C, the solid mass was eluted with CH_2Cl_2 (125 mL). The eluent was then boiled with a few drops of water for 1 min, dried (Na_2SO_4) and evaporated under reduced pressure, which gave ketoaldehyde **232** as a clear, colourless oil (558 mg, 78%); other data as above.

By Protocol of *Fang and Hsu*:[133d]

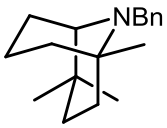
A mixture of silyl enol ether **239** (10.00 g, 69.3 mmol) and MVK (**233**, 8.26 g, 117.8 mmol) was added to a stirred slurry of activated alumina (10.00 g) and $ZnCl_2$ (13.22 g, 97.0 mmol) in Et_2O (300 mL) at 0 °C. After 30 min at 0 °C, $BF_3{\cdot}Et_2O$ (14.6 mL, 118.2 mmol) was added. After 4 h at 0 °C, the reaction was quenched with H_2O (10 mL). The resultant mixture was loaded onto a short pad of silica gel and eluted with 20% EtOAc / petroleum ether. The eluent was concentrated under reduced pressure, and the residue purified by column chromatography (SiO_2, 10% EtOAc in petroleum ether), to give ketoaldehyde **232** as a clear, colourless oil (4.38 g, 44%); other data as above.

(±)-9-Benzyl-1,6,6-trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((±)-231):



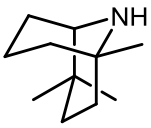
$BnNH_2$ (1.66 g, 15.5 mmol) was added to a stirred solution of ketoaldehyde **232** (2.00 g, 14.1 mmol) and acetone-1,3-dicarboxylic acid (**73**; 2.26 g, 15.5 mmol) in THF (150 mL) at rt. After stirring for 48 h at rt, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–10% EtOAc in petroleum ether) gave homotropinone **(±)-231** as a yellow oil (893 mg, 23%); R_f 0.30 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2934m, 1703s (C=O), 1453m, 1357m, 1201m, 1095m, 903w, 737s, 697s; ^{1}H NMR (400 MHz) δ 7.41 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.33 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.25 (t, 1H, J = 7 Hz, Ar (*para*)), 4.23 (d, 1H, J_{AB} = 14 Hz, PhCH_AH$_B$), 3.53 (d, 1H, J_{AB} = 14 Hz, PhCH$_A$$H_B$), 2.67 (d, 1H, J = 7 Hz, NCH), 2.50 (dd, 1H, J_{AB} = 16 Hz, J = 7 Hz, NCHCH_AH$_B$), 2.45 – 2.35 (m, 2H, NCHCH$_A$$H_B$ and COCH_AH$_B$CCH$_3$), 2.20 (dd, 1H, J_{AB} = 16 Hz, ^4J = 2 Hz, COCH$_A$$H_BCCH_3$), 1.88 (tdd, 1H, J_{AB} = 14 Hz, J = 6 Hz, ^4J = 2 Hz, C(CH$_3$)CH_AH$_B$CH$_2$), 1.47 – 1.16 (m, 3H, C(CH$_3$)CH$_A$$H_B$ and CH_2C(CH$_3$)$_2$), 1.24 (s, 3H, CH$_3$), 1.08 (s, 3H, CH$_3$), 0.80 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 211.1 (C=O), 140.4 (Ar (*ipso*)), 128.3 (2 x Ar), 128.1 (2 x Ar), 126.8 (Ar (*para*)), 63.6 (NCH), 57.3 (N*C*CH$_3$), 51.7 (*C*H$_2$Ph), 47.6 (C(=O)*C*H$_2$CCH$_3$), 37.2 (C(CH$_3$)*C*H$_2$), 35.2 (NCH*C*H$_2$), 34.6 (*C*(CH$_3$)$_2$), 31.8 (*C*H$_2$(CH$_3$)$_2$), 29.2 (CH$_3$), 28.4 (CH$_3$), 26.7 (CH$_3$); m/z (ESI$^+$) 272.2 (M + H$^+$, 82); HRMS *m/z* (M + H$^+$) found 272.2010, $C_{18}H_{26}NO$ requires 272.2009

(±)-9-Benzyl-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonane ((±)-230):



A mixture of homotropinone **(±)-231** (80 mg, 0.29 mmol), hydrazine monohydrate (78 mg, 1.56 mmol) and KOH (262 mg, 4.67 mmol) in diethylene glycol (632 µL) was heated at 200 °C (oil bath) for 16 h. The mixture was cooled to rt, diluted with water (25 mL), and the aq layer extracted with Et_2O (4 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–4% EtOAc in petroleum ether) gave *N*-benzylhomotropane **(±)-230** as a colourless, clear oil (46 mg, 62%); R_f 0.50 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2949m, 2926m, 2869m, 1487m, 1452m, 1360m, 1107m, 1058m, 908m, 744s, 696s; ^1H NMR (400 MHz) δ 7.40 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.29 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.20 (t, 1H, J = 7 Hz, Ar (*para*)), 4.06 (d, 1H, J_{AB} = 14 Hz, PhCH_AH$_B$), 3.63 (d, 1H, J_{AB} = 14 Hz, PhCH$_A$$H_B$), 2.13 (d, 1H, J = 5 Hz, NCH), 2.10 – 1.25 (m, 10H, 5 x CH_2), 1.07 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.82 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 142.4 (Ar (*ipso*)), 128.6 (Ar (*ortho*)), 127.8 (Ar (*meta*)), 126.2 (Ar (*para*)), 60.5 (NCH), 51.7 (N*C*CH_3), 51.1 (*C*H_2Ph), 37.6 (CH_2), 35.8 (CH_2), 34.7 (*C*(CH_3)$_2$), 31.2 (CH_3), 29.7 (CH_2), 29.2 (CH_3), 28.7 (CH_3), 20.6 (CH_2), 16.1 (CH_2); m/z (ESI$^+$) 258.8 (M + H$^+$, 47); HRMS *m/z* (M + H$^+$) found 258.2221, $C_{18}H_{28}N$ requires 258.2216

(±)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane ((±)-229):



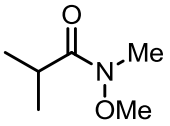
A vigorously stirred solution of *N*-benzylhomotropane **(±)-230** (223 mg, 0.87 mmol) in MeOH was hydrogenated at 1 atm in the presence of 10% palladium on activated carbon (219 mg, 24 mol %) for 3 d. After this time, the catalyst was removed by filtration through Celite®. $HCl_{(g)}$ was bubbled through the methanolic filtrate for 15 min, with stirring at 0 °C. The mixture was evaporated under reduced pressure to give the crude hydrochloride salt. This salt was suspended in Et_2O (10 mL) and washed with 3 M aq NaOH (10 mL). The ethereal layer

was separated, and the aq phase back-extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave homotropane **(±)-229** as a colourless, clear oil (138 mg, 95%); bp 75–85 °C (10 mm Hg); R_f 0.59 (20% MeOH in EtOAc); IR (neat) (cm^{-1}) 2949s, 1486m, 1450m, 1361m, 1196m, 1061m, 945m, 865m, 753s; ^{1}H NMR (500 MHz) δ 2.55 (d, 1H, J = 5 Hz, NCH), 2.02 – 1.87 (m, 3H, 3 x CH_AH_B), 1.74 – 1.29 (m, 8H, 3 x CH_AH_B, 2 x CH_2 and NH), 1.08 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 58.2 (NCH), 47.7 (N*C*CH_3), 37.6 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.2 (CH_3), 32.1 (*C*$(CH_3)_2$), 28.9 (CH_3), 28.3 (CH_3), 26.6 (NCH*C*H_2), 20.4 (CH_2*C*H_2CH_2); m/z (ESI$^+$) 168.6 (M + H$^+$, 42); HRMS *m/z* (M + H$^+$) found 168.1744, $C_{11}H_{22}N$ requires 168.1747

Asymmetric Synthesis of Homotropane (1*S*,5*R*)-229:

Investigation with Davis Auxiliary:

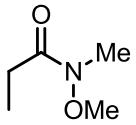
***N*-Methoxy-*N*-methylisobutyramide (259):**[145]



Et_3N (17.6 mL, 126.5 mmol), followed by isobutyryl chloride (**260**; 6.0 mL, 57.3 mmol) were added dropwise to a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (5.61 g, 57.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The ice bath was removed, and the mixture stirred for 72 h at rt. The precipitated Et_3N·HCl was removed by vacuum filtration, and the filtrate concentrated under reduced pressure. The residue was diluted with EtOAc (100mL), and additional Et_3N·HCl removed by vacuum filtration, washing the filter cake several times with EtOAc (100 mL total). The filtrate was then washed with 1 N aq HCl (100 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by first column chromatography (SiO_2, 20% Et_2O in petroleum ether), and then bulb-to-bulb distillation, which gave Weinreb amide **259** as a clear, colourless oil (4.66 g, 62%); bp 75–85 °C (10 mm Hg); R_f 0.22 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2972m, 2938w, 2875w, 1727w, 1657s (C=O), 1472m, 1446m, 1385m, 1303w, 1178m, 1093m, 998s; ^{1}H NMR (400 MHz) δ 3.68 (s, 3H, OCH_3), 3.17 (s, 3H, NCH_3), 3.03 – 2.85 (m, 1H, J = 7 Hz, C*H*$(CH_3)_2$),

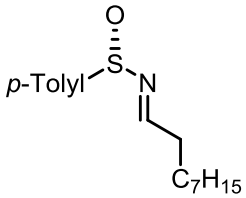
1.11 (d, 6H, J = 7 Hz, CH(CH_3)$_2$); ^{13}C NMR (101 MHz) δ 181.6 (C=O), 61.3 (OCH$_3$), 33.7 (NCH$_3$), 29.7 (*C*H(CH$_3$)$_2$), 19.0 (CH(*C*H$_3$)$_2$); m/z (ESI$^+$) 132.1 (M + H$^+$, 24); HRMS *m/z* (M$^+$) found 131.0948, $C_6H_{13}NO_2$ requires 131.0946

_N_-Methoxy-_N_-methylpropionamide (268):[146]



Pyridine (9.3 mL, 115.1 mmol) was added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (5.61 g, 57.5 mmol) and propionyl chloride (**267**; 5.07 g, 54.8 mmol) in CH_2Cl_2 (150 mL) at 0 °C, with stirring. The solution was then warmed to rt and left to stir for 3.5 h. After this time, the mixture was washed with 0.5 M aq HCl (2 x 100 mL), and then concentrated under reduced pressure to approximately one third of the original volume. Et_2O (100 mL) was added, and the resulting solution was washed with 5% aq $NaHCO_3$ (100 mL), and then brine (100 mL). The separated organic layer was then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation which gave Weinreb amide **268** as a colourless, clear oil (3.33 g, 52%); bp 70–80 °C (10 mm Hg); R_f 0.20 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2941w, 1663s (C=O), 1463m, 1417m, 1379m, 1304w, 1178m, 1116m, 1010m, 986m, 730m; ^{1}H NMR (400 MHz) δ 3.66 (s, 3H, OCH$_3$), 3.16 (s, 3H, NCH$_3$), 2.42 (q, 2H, J = 8 Hz, CH$_2$), 1.11 (t, 3H, J = 8 Hz, CH$_2$CH_3); ^{13}C NMR (101 MHz) δ 175.3 (C=O), 61.1 (OCH$_3$), 32.2 (NCH$_3$), 25.1 (CH$_2$), 8.7 (CH$_2$*C*H$_3$); m/z (ESI$^+$) 118.1 (M + H$^+$, 5); HRMS *m/z* (M$^+$) found 117.0787, $C_5H_{11}NO_2$ requires 117.0790

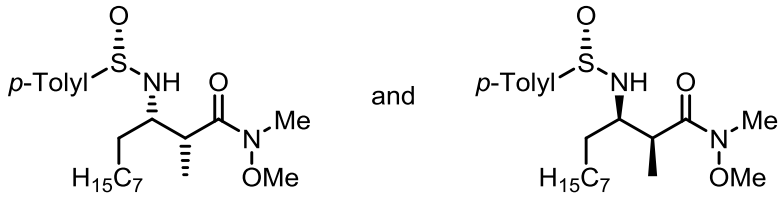
(+)-(*S*)-4-Methyl-N-nonylidenebenzenesulfinamide ((+)-(*S*)-258):



LiHMDS (1.0 M in THF, 2.0 mL, 2.0 mmol) was added dropwise to a solution of (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p* toluenesulfinate (**(*S*S)-251**; 488 mg, 1.66 mmol) in THF (20 mL) at –78 °C,

with stirring. After 15 min, the mixture was warmed to rt, and stirring continued for 1.5 h. The mixture was re-cooled to –78 °C, and nonanal (**257**; 259 mg, 1.82 mmol) added. After 4 h at –78 °C, the reaction was quenched with sat. aq NH_4Cl (0.6 mL). The mixture was warmed to rt, diluted with H_2O (30 mL) and then extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 5–10% EtOAc in petroleum ether), to give sulfinimine **(*S*)-258** as a clear, colourless oil (234 mg, 51%); $[\alpha]_D^{25}$ = +238.9 (*c* = 0.5, $CHCl_3$); R_f 0.19 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2925s, 2855m, 1620s (C=N), 1459w, 1097s (S=O), 1073s, 809s; ^{1}H NMR (400 MHz) δ 8.22 (t, 1H, *J* = 5 Hz, N=CH), 7.56 (d, 2H, *J* = 8 Hz, Ar (*ortho*)), 7.30 (d, 2H, *J* = 8 Hz, Ar (*meta*)), 2.48 (dt, 2H, J_1 = 7 Hz, J_2 = 5 Hz, CH_2CHN), 2.40 (s, 3H, $SC_6H_4CH_3$), 1.60 (quin, 2H, *J* = 7 Hz, CH_2CH_2CHN), 1.37 – 1.20 (m, 10H, 5 x CH_2), 0.88 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 167.3 (C=N), 141.9 (Ar (*para*)), 141.6 (Ar (*ipso*)), 129.7 (Ar (*meta*)), 124.5 (Ar (*ortho*)), 35.9 (*C*H_2CHN), 31.7 (CH_2), 29.2 (CH_2), 29.07 (CH_2), 29.05 (CH_2), 25.3 (*C*H_2CH_2CHN), 22.6 (CH_2), 21.4 ($C_6H_4CH_3$), 14.0 (CH_2CH_3); m/z (ESI^-) 278.16 ($M - H^+$, 22); HRMS *m/z* (M^+) found 279.1660, $C_{16}H_{25}NOS$ requires 279.1657

(+)-(2*R*,3*S*)-*N*-Methoxy-*N*,2-dimethyl-3- and (+)-(2*S*,3*R*)-*N*-methoxy-*N*,2-dimethyl-3-((*S*)-4-methylphenylsulfinamido)undecanamide ((+)-(*S*s,2*R*,3*S*)-269) / ((+)-(*S*s,2*S*,3*R*)-269):



A solution of Weinreb amide **268** (126 mg, 0.96 mmol) in THF (1 mL) was added dropwise to LiHMDS (1.0 M solution in THF, 960 µL, 0.96 mmol) at –78 °C, with stirring. After 2 h, a pre-cooled (to –78 °C) solution of sulfinimine **(*S*)-258 (**114 mg, 0.41 mmol) in THF (2 mL) was added. After 30 min, sulfinimine **(*S*)-258** had been consumed [determined by TLC (10% EtOAc in petroleum ether)]. The reaction was quenched with sat. aq NH_4Cl (1 mL), and then warmed to rt. The mixture was poured into H_2O (1 mL), and the aq layer extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by chromatography (SiO_2, gradient elution: 10–80%

EtOAc in petroleum ether). First, eluted amido sulfinamide **(*S*s,2*S*,3*R*)-269** (*minor diastereomer*, 5 mg), followed by a mixed fraction (37 mg); last, eluted amido sulfinamide **(*S*s,2*R*,3*S*)-269** (*major diastereomer*, 100 mg), all colourless, clear oils (90:10 *dr*, 142 mg total product, 88%);

Major Diastereomer:

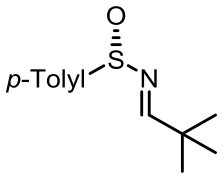
$[\alpha]_D^{25}$ = +94.4 (*c* = 0.6, $CHCl_3$); R_f 0.50 (80% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2927m, 2856w, 1649m (C=O), 1492w, 1387w, 1089m, 1060m, 995m, 908s; ^{1}H NMR (500 MHz) δ 7.59 (d, 2H, *J* = 8 Hz, Ar (*ortho*)), 7.28 (d, 2H, *J* = 8 Hz, Ar (*meta*)), 4.48 (d, 1H, *J* = 7 Hz, NH), 3.68 (s, 3H, OCH_3), 3.55 – 3.45 (m, 1H, *J* = 7 Hz, NHC*H*), 3.21 – 3.15 (m, 1H, C*H*CH_3), 3.14 (s, 3H, NCH_3), 2.41 (s, 3H, $C_6H_4CH_3$), 1.84 – 1.74 (m, 1H, NHCHCH_AH_B), 1.66 – 1.59 (m, 1H, NHCHCH_AH_B), 1.55 – 1.45 (m, 1H, CH_AH_B), 1.39 – 1.23 (m, 11H, CH_AH_B and 5 x CH_2), 1.16 (d, 3H, *J* = 7 Hz, CHCH_3), 0.89 (t, 3H, *J* = 8 Hz, CH_2CH_3); ^{13}C NMR (125 MHz) δ 175.7 (C=O), 142.9 (Ar (*ipso*)), 141.1 (Ar (*para*)), 129.4 (Ar (*meta*)), 125.5 (Ar (*ortho*)), 61.4 (OCH_3), 57.5 (NH*C*H), 39.1 (*C*HCH_3), 32.8 (NHCH*C*H_2), 31.8 (NCH_3), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 22.7 (CH_2), 21.3 ($C_6H_4CH_3$), 14.1 (CH_2CH_3), 12.9 (CH*C*H_3); m/z (ESI$^-$) 395.2 (M – H^+, 76); HRMS *m/z* (M + H^+) found 397.2512, $C_{21}H_{37}N_2O_3S$ requires 397.2519

Minor Diastereomer:

$[\alpha]_D^{25}$ = +100.7 (*c* = 0.2, $CHCl_3$); R_f 0.57 (80% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2926m, 2855w, 1652m (C=O), 1460w, 1385w, 1089m, 1059m, 995m, 909m, 755s, 733s; ^{1}H NMR (500 MHz) δ 7.66 (d, 2H, *J* = 8 Hz, Ar (*ortho*)), 7.30 (d, 2H, *J* = 8 Hz, Ar (*meta*)), 4.04 (d, 1H, *J* = 8 Hz, NH), 3.75 (s, 3H, OCH_3), 3.66 – 3.58 (m, 1H, NHC*H*), 3.23 (s, 3H, NCH_3), 3.16 – 3.11 (m, 1H, C*H*CH_3), 2.41 (s, 3H, $C_6H_4CH_3$), 1.56 – 1.51 (m, 2H, NHCHCH_2), 1.46 – 1.38 (m, 1H, CH_AH_B), 1.35 – 1.19 (m, 11H, CH_AH_B and 5 x CH_2), 1.16 (d, 3H, *J* = 7 Hz, CHCH_3), 0.88 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (125 MHz) δ 175.8 (C=O), 142.7 (Ar (*ipso*)), 141.1 (Ar (*para*)), 129.4 (Ar (*meta*)), 125.8 (Ar (*ortho*)), 61.5 (OCH_3), 57.1 (NH*C*H), 40.6 (*C*HCH_3), 33.6 (NHCH*C*H_2), 31.8 (CH_2 and NCH_3), 29.4 (CH_2), 29.30 (CH_2), 29.27

(CH_2), 26.1 (CH_2), 22.7 (CH_2), 21.3 ($C_6H_4CH_3$), 14.1 (CH_2CH_3), 12.7 ($CHCH_3$); m/z (ESI^-) 395.2 ($M - H^+$, 100); HRMS *m/z* ($M + H^+$) found 397.2516, $C_{21}H_{37}N_2O_3S$ requires 397.2519

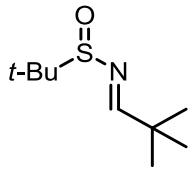
(+)-(*S*)-*N*-(2,2-Dimethylpropylidene)-4-methylbenzenesulfinamide ((+)-(*S*)-275):[147]



LiHMDS (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise to a solution of (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p* toluenesulfinate (**(*S*s)-251**, 976 mg, 3.31 mmol) in THF (40 mL) at –78 °C, with stirring. After 15 min, the mixture was warmed to rt, and stirring continued for 1.5 h. The mixture was re-cooled to –78 °C, and pivalaldehyde (**274**, 314 mg, 3.65 mmol) added dropwise. The reaction was then warmed to rt. After 16 h, the reaction was quenched with sat. aq NH_4Cl (1.2 mL) at –78 °C. The mixture was re-warmed to rt, diluted with H_2O (60 mL) and then extracted with EtOAc (4 x 60 mL). The combined organic extracts were washed with brine (60 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 10% EtOAc in petroleum ether), to give sulfinimine **(*S*)-275** as a white solid (481 mg, 65%); mp 74–75 °C [lit.[147] mp 73–75 °C]; $[\alpha]_D^{25}$ = +513.2 (*c* = 0.3, $CHCl_3$) [lit.[147] $[\alpha]_D^{20}$ = +371.5 (*c* = 1.94, $CHCl_3$)]; R_f 0.50 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2966m, 2931w, 2871w, 1618s (C=N), 1492w, 1366w, 1145w, 1095s (S=O), 1071s, 909s, 809s, 730s; ^1H NMR (400 MHz) δ 8.09 (s, 1H, HC=N), 7.55 (d, 2H, *J* = 8 Hz, Ar (*ortho*)), 7.29 (d, 2H, *J* = 8 Hz, Ar (*meta*)), 2.40 (s, 3H, $C_6H_4CH_3$), 1.14 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz) δ 173.4 (C=N), 142.1 (Ar (*para*)), 141.5 (Ar (*ipso*)), 129.7 (Ar (*meta*)), 124.7 (Ar (*ortho*)), 37.7 ($C(CH_3)_3$), 26.5 ($C(CH_3)_3$), 21.4 ($C_6H_4CH_3$); m/z (ESI^+) 246.1 ($M + Na^+$, 31); HRMS *m/z* ($M + Na^+$) found 246.0929, $C_{12}H_{17}NNaOS$ requires 246.0923

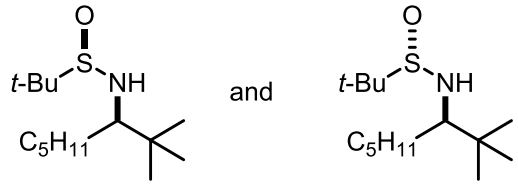
Investigation with Ellman Auxiliary:

***N*-(2,2-Dimethylpropylidene)-2-methylpropane-2-sulfinamide (278):**[152a]



Cs_2CO_3 (168 mg, 0.52 mmol), sulfinamide (**(±)-277**, 63 mg, 0.52 mmol) and pivalaldehyde (**274**, 44 mg, 0.52 mmol) in CH_2Cl_2 (2.6 mL) were stirred vigorously at 45 °C for 16 h. After this time, the reaction mixture was cooled and filtered through a pad of Celite®, and the filter cake washed with CH_2Cl_2 (50 mL). The filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, 10% EtOAc in petroleum ether), to give sulfinimine **278** as a colourless, clear oil (81 mg, 83%); R_f 0.56 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2963m, 2871w, 1620s (C=N), 1476w, 1460w, 1364m, 1096s (S=O), 708w; ^{1}H NMR (400 MHz) δ 7.90 (s, 1H, HC=N), 1.17 (s, 9H, $SC(CH_3)_3$), 1.14 (s, 9H, $CHNC(CH_3)_3$); ^{13}C NMR (101 MHz) δ 175.6 (C=N), 56.4 ($SC(CH_3)_3$), 37.9 ($CHNC(CH_3)_3$), 26.6 ($CHNC(CH_3)_3$), 22.2 ($SC(CH_3)_3$); m/z (ESI$^+$) 212.10 (M + Na^+, 27); HRMS *m/z* (M + Na^+) found 212.1083, $C_9H_{19}NNaOS$ requires 212.1080

(±)-(*R*)- and (±)-(*S*)-*N*-((*R*)-2,2-Dimethyloctan-3-yl)-2-methylpropane-2-sulfinamide ((±)-(*R*S,*R*)-279) / ((±)-(*S*S,*R*)-279):



Pentylmagnesium chloride (2.0 M in THF, 375 µL, 0.75 mmol) was diluted with THF (0.5 mL), and then cooled to –78 °C. A solution of sulfinimine **278** (40 mg, 0.21 mmol) in THF (1.0 mL) was added dropwise to the Grignard reagent with stirring. After 15 min, the mixture was warmed to rt and stirring continued for 2.5 h. The reaction was quenched with sat. aq NH_4Cl (2 mL) at –78 °C, warmed to rt and poured into H_2O (15 mL). Then aq mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography

(SiO_2, gradient elution: 10–80% EtOAc in petroleum ether). First, eluted sulfinamide **279** (*diastereomer A*, 22 mg), followed by a mixed fraction (16 mg); last, eluted sulfinamide **279** (*diastereomer B*, 12 mg), all white solids (50:50 *dr*, 50 mg total product, 91%);

Diastereomer A:

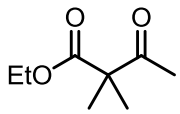
mp 75–77 °C, R_f 0.83 (80% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2956m, 2869w, 1467w, 1363w, 1056s, 907s; ^{1}H NMR (400 MHz) δ 2.88 – 2.72 (m, 2H, NHCH), 1.76 – 1.55 (m, 2H, NHCHC*H*$_2$), 1.40 – 1.12 (m, 6H, 3 x CH_2), 1.24 (s, 9H, SC(CH_3)$_3$), 0.88 (t, 3H, *J* = 7 Hz, CH_2CH_3), 0.88 (s, 9H, CH(=N)C(C*H*$_3$)$_3$); ^{13}C NMR (101 MHz) δ 65.7 (NHCH), 56.3 (S*C*(CH_3)$_3$), 35.7 (NHC*C*(CH_3)$_3$), 31.8 (CH_2), 31.7 (CH_2), 26.6 (SC(*C*H_3)$_3$), 26.1 (CH_2), 23.1 (CHNC(*C*H_3)$_3$), 22.4 (CH_2), 14.1 (CH_2*C*H_3); m/z (ESI$^+$) 262.2 (M + H$^+$, 34); HRMS *m/z* (M + H$^+$) found 262.2202, $C_{14}H_{32}NOS$ requires 262.2199

Diastereomer B:

mp 50–52 °C, R_f 0.69 (80% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2956m, 2870w, 1469w, 1365w, 1055s, 907s; ^{1}H NMR (400 MHz) δ 3.17 (d, 1H, *J* = 7 Hz, NH), 2.90 – 2.80 (m, 1H, *J* = 7 Hz, NHC*H*), 1.66 – 1.47 (m, 2H, NHCHC*H*$_2$), 1.37 – 1.18 (m, 6H, 3 x CH_2), 1.24 (s, 9H, SC(CH_3)$_3$), 0.96 (s, 9H, CH(=N)C(C*H*$_3$)$_3$), 0.89 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 65.7 (NHCH), 56.3 (S*C*(CH_3)$_3$), 34.7 (NHC*C*(CH_3)$_3$), 32.2 (CH_2), 31.8 (CH_2), 27.1 (CH_2), 27.0 (NHCC(*C*H_3)$_3$), 23.0 (SC(*C*H_3)$_3$), 22.6 (CH_2), 14.0 (CH_2*C*H_3); m/z (ESI$^+$) 262.2 (M + H$^+$, 4); HRMS *m/z* (M + H$^+$) found 262.2199, $C_{14}H_{32}NOS$ requires 262.2199

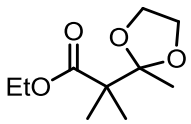
Aldehyde Synthesis:

Ethyl 2,2-dimethyl-3-oxobutanoate (281):[154b]



Ethyl α-methylacetoacetate (**280**; 17.17 g, 0.119 mol) was added dropwise to a suspension of NaH (3.46 g, 0.144 mol) in THF (35 mL) at 0 °C, with stirring. The mixture was warmed to rt, and stirring continued for 1 h. The resulting near-homogeneous mixture was re-cooled to 0 °C, and MeI (22.15 g, 0.156 mol) added dropwise. The mixture was warmed back to rt and stirred for 16 h. After this time, a yellow solution had formed. This was cooled to 0 °C and H_2O (50 mL) added. [Care! Add slowly!] The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 2–10% EtOAc in petroleum ether), to give ketoester **281** as a colourless, clear oil (16.61 g, 88%); R_f 0.38 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2984w, 1712s (2 x C=O), 1386w, 1264m, 1153s, 1116s, 1026m, 859w; ^{1}H NMR (400 MHz) δ 4.16 (q, 2H, J = 7 Hz, CH_2CH$_3$), 2.13 (s, 3H, CH$_3$C=O), 1.33 (s, 6H, C(CH$_3$)$_2$), 1.23 (t, 3H, J = 7 Hz, CH$_2$CH_3); ^{13}C NMR (101 MHz) δ 205.8 (CH$_3$*C*=O), 173.5 (*C*O$_2$C$_2$H$_5$), 61.2 (CH$_2$), 55.6 (*C*(CH$_3$)$_2$), 25.6 (*C*H$_3$C=O), 21.7 (C(*C*H$_3$)$_2$), 13.9 (CH$_2$*C*H$_3$); HRMS *m/z* (M^+) found 158.0937, $C_8H_{14}O_3$ requires 158.0943

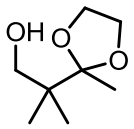
Ethyl 2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (282):[154a]



Ketoester **281** (9.50 g, 60.05 mmol)**,** ethylene glycol (4.65 g, 74.9 mmol) and *p*-TSA·H_2O (114 mg, 0.60 mmol) in benzene (90 mL) were heated under reflux, until the calculated volume (~1.1 mL) of water had been removed, by means of a Dean-Stark trap. The resulting mixture was cooled to rt and diluted with Et_2O (400 mL), then washed with sat. aq $NaHCO_3$ (250 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (3 x 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced

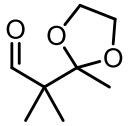
pressure, to give ketal ester **282** as a clear, colourless oil (11.64, 96%); R_f 0.36 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2984w, 2884w, 1723s (C=O), 1475w, 1375w, 1271s, 1168s, 1124s, 1097s, 1044s, 889m; ^{1}H NMR (400 MHz) δ 4.14 (q, 2H, J = 7 Hz, CH_2CH$_3$), 4.00 – 3.89 (m, 4H, OC$_2H_4$O), 1.35 (s, 3H, C(CH$_3$)$_2$CCH_3), 1.25 (t, 3H, J = 7 Hz, CH$_2$CH_3), 1.23 (s, 6H, C(CH$_3$)$_2$); ^{13}C NMR (101 MHz) δ 175.2 (C=O), 111.5 (O–C–O), 65.2 (OC_2H$_4$O), 60.5 (CH$_2$), 50.8 (C(CH$_3$)$_2$), 21.1 (C(CH$_3$)$_2$), 20.6 (C(CH$_3$)$_2$CCH$_3$), 14.1 (CH$_2$$CH_3$); m/z (ESI$^+$) 225.1 (M + Na$^+$, 30); HRMS *m/z* (M + H$^+$) found 225.1101, $C_{10}H_{18}NaO_4$ requires 225.1097

2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol (283):



LAH (1.61 g, 42.5 mmol) was dissolved in THF (58 mL), with stirring and external cooling (ice-bath). Ketal ester **282** (7.48 g, 37.0 mmol) in THF (10 mL) was added, dropwise, with stirring at 0 °C. After 30 min, the reaction was warmed to rt and stirred overnight (16 h). The mixture was re-cooled to 0 °C and quenched: H_2O (1.6 mL), then 15% aq NaOH (1.6 mL), then H_2O (4.8 mL). [Care! Add slowly!] The resulting suspension was filtered, and the filter cake washed with Et_2O (500 mL). The filtrate was concentrated under reduced pressure, to give ketal alcohol **283**[154a] as a clear, colourless oil (5.84 g, 99%); R_f 0.08 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3456brm (O–H), 2973m, 2882m, 1476m, 1419m, 1150m, 1048s (O–C–O), 876m; ^{1}H NMR (400 MHz) δ 4.04 – 3.92 (m, 4H, OC$_2$H$_4$O), 3.49 (d, 2H, J = 6 Hz, CH_2OH), 2.95 (t, 1H, J = 6 Hz, CH$_2$OH), 1.27 (s, 3H, CH$_3$CO$_2$), 0.99 (s, 6H, C(CH$_3$)$_2$); ^{13}C NMR (101 MHz) δ 114.5 (O–C–O), 69.7 (CH$_2$OH), 64.6 (OC$_2$H$_4$O), 42.2 (C(CH$_3$)$_2$), 20.6 (C(CH$_3$)$_2$), 19.2 (CH$_3$CO$_2$); m/z (ESI$^+$) 183.1 (M + Na$^+$, 100); HRMS *m/z* (M + Na$^+$) found 183.0993, $C_8H_{16}NaO_3$ requires 183.0992

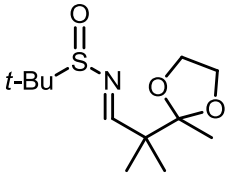
2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propanal (284):



Ketal alcohol **283** (7.2 g, 44.9 mmol) was dissolved in CH_2Cl_2 (40 mL) at rt. The resulting solution was added rapidly to a suspension of PCC (14.5 g, 67.3 mmol) in CH_2Cl_2 (70 mL) at rt, with stirring. The mixture immediately turned black on addition of the alcohol. After overnight stirring at rt, the mixture was diluted with anhydrous Et_2O (200 mL), the solvent decanted and the residual black solid washed with Et_2O (3 x 100 mL). The combined organic layers were passed through a small pad of Florisil®, and the filtrate concentrated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave aldehyde **284**[184] as a clear oil (6.6 g, 93%); bp 75–80 °C (11 mm Hg) [lit.[184] 90–95 °C (7 mm Hg)]; R_f 0.44 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2984m, 2888m; 1725s (C=O), 1471w, 1376m, 1215m, 1163m, 1099m, 1045s (O–C–O), 755s; ^{1}H NMR (400 MHz) δ 9.69 (s, 1H, CHO), 4.07 – 3.86 (m, 4H, C_2H_4), 1.23 (s, 3H, CH_3CO_2), 1.10 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 205.3 (C=O), 111.8 (O–C–O), 64.9 (C_2H_4), 53.7 ($C(CH_3)_2$), 20.2 (CH_3CO_2), 17.8 ($C(CH_3)_2$); m/z (ESI^+) 181.1 (M + Na^+, 6); HRMS *m/z* (M + Na^+) found 181.0831, $C_8H_{14}NaO_3$ requires 181.0835

Sulfinimine Synthesis Using Nakata's Method:[152a]

(±)-2-Methyl-*N*-(2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)propylidene)propane-2-sulfinamide ((±)-285):

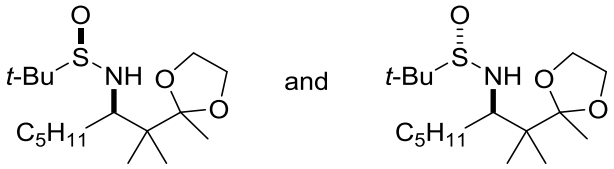


Cs_2CO_3 (97 mg, 0.297 mmol), sulfinamide (**(±)-277**, 36 mg, 0.297 mmol) and ketal aldehyde (**284**, 47 mg, 0.297 mmol) in CH_2Cl_2 (1.5 mL) were stirred vigorously at 45 °C for 16 h. After this time, the reaction mixture was cooled and filtered through a pad of Celite®, and the filter cake washed with CH_2Cl_2 (50 mL). The filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (SiO_2, 10% EtOAc in petroleum ether), to

give sulfinimine **(±)-285** as a colourless, clear oil (77 mg, 98%); R_f 0.10 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2981m, 2885m, 1620m (C=N), 1474m, 1459m, 1363m, 1163m, 1143m, 1084s and 1042s (S=O and O–C–O), 949m, 886m; ^{1}H NMR (400 MHz) δ 8.14 (s, 1H, HC=N), 4.05 – 3.85 (m, 4H, C_2H_4), 1.27 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.19 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz) δ 173.4 (C=N), 112.2 (O–C–O), 65.1 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 56.8 ($C(CH_3)_3$), 49.5 ($C(CH_3)_2$), 22.3 ($C(CH_3)_3$), 20.7 (CH_3), 20.6 (CH_3), 20.1 (CH_3); m/z (ESI^+) 284.1 (M + Na^+, 100); HRMS *m/z* (M + Na^+) found 284.1288, $C_{12}H_{23}NNaO_3S$ requires 284.1291

Commercial Grignard Addition to Sulfinimine (±)-285:

(±)-(*R*S)- and (±)-(*S*S)-2-Methyl-*N*-((*R*)-2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)octan-3-yl)propane-2-sulfinamide ((±)-(*R*S,*R*)-286) / ((±)-(*S*S,*R*)-286):



Pentylmagnesium chloride (2.0 M in THF, 575 µL, 1.15 mmol) was added dropwise to a solution of sulfinimine (100 mg, 0.38 mmol) in THF (3.5 mL), with stirring at –78 °C. After 30 min, the mixture was warmed to rt, and stirring continued for 16 h. The reaction was quenched with sat. aq NH_4Cl (2 mL), diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 30–50% Et_2O in petroleum ether). First, eluted ketal sulfinamide **286** (*major diastereomer*, 51 mg), followed by a mixed fraction (11 mg); last, eluted ketal sulfinamide **286** (*minor diastereomer*, 9 mg), all colourless, clear oils (74:26 *dr*, 71 mg total product, 55%);

Major Diastereomer:

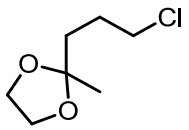
white solid; mp 44–52 °C; R_f 0.32 (50% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3492m (N–H), 3420m (S(=O)N–H), 3179m (S(=O)N–H), 2951m, 2870m, 1637w, 1457m, 1373m, 1123m, 1098s, 1024s (S=O), 949s, 875s; ^{1}H NMR (500 MHz) δ 3.98 – 3.84 (m, 4H,

OC_2H_4O), 3.48 (d, 1H, *J* = 6 Hz, NH), 3.11 – 3.03 (m, 1H, *J* = 6 Hz, NHC*H*), 2.10 – 1.98 (m, 1H, NHCHCH_AH_B), 1.75 – 1.63 (m, 1H, CH_AH_B), 1.38 – 1.18 (m, 6H, 2 x CH_2 and 2 x CH_AH_B), 1.234 (s, 9H, $C(CH_3)_3$), 1.227 (s, 3H, CH_3CO_2), 1.00 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.88 (t, 3H, CH_2CH_3); ^{13}C NMR (125 MHz) δ 113.8 (O–C–O), 64.5 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 63.5 ($C(CH_3)_3$), 56.4 (NHCH), 46.6 ($C(CH_3)_2$), 32.3 (NHCHCH_2), 31.9 (CH_2), 26.9 (CH_2), 23.1 ($C(CH_3)_3$), 22.5 (CH_2), 21.9 (CH_3), 19.9 (CH_3CO_2), 19.3 (CH_3), 14.1 (CH_2CH_3); m/z (ESI$^+$) 356.3 (M + Na^+, 27); HRMS *m/z* (M + Na^+) found 356.2222, $C_{17}H_{35}NNaO_3S$ requires 356.2230

Minor Diastereomer:

pale-yellow, clear oil; R_f 0.13 (50% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 3392brw (N–H), 2956m, 2930m, 1701m, 1625w, 1529w, 1188s, 1027s (S=O), 916w, 731m; ^{1}H NMR (400 MHz) δ 5.27 (br s, 1H, NH), 4.13 – 3.86 (m, 4H, OC_2H_4O), 3.29 – 3.22 (m, 1H, NHC*H*), 1.75 – 1.66 (m, 1H, NHCHCH_AH_B), 1.60 – 1.53 (m, 1H, CH_AH_B), 1.40 – 0.99 (m, 6H, 2 x CH_2, NHCHCH_AH_B and CH_AH_B), 1.34 (s, 3H, CH_3CO_2), 1.23 (s, 9H, $C(CH_3)_3$), 1.06 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.90 (t, 3H, CH_2CH_3); ^{13}C NMR (101 MHz) δ 114.7 (O–C–O), 65.3 (OCH_2CH_2O), 63.6 (OCH_2CH_2O), 58.6 (NHCH), 55.4 ($C(CH_3)_3$), 45.4 ($C(CH_3)_2$), 32.9 (NHCHCH_2), 32.2 (CH_2), 28.3 (CH_2), 23.1 (CH_3), 22.9 ($C(CH_3)_3$), 22.5 (CH_2), 19.3 (CH_3CO_2), 16.6 (CH_3), 14.1 (CH_2CH_3); m/z (ESI$^+$) 356.3 (M + Na^+, 62); HRMS *m/z* (M + Na^+) found 356.2219, $C_{17}H_{35}NNaO_3S$ requires 356.2230

2-(3-Chloropropyl)-2-methyl-1,3-dioxolane (288):[157]

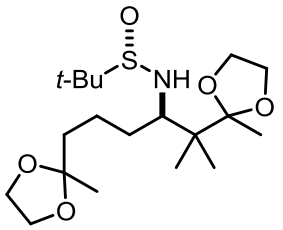


Chloroketone **287** (5.10 g, 42.3 mmol)**,** ethylene glycol (13.1 g, 0.21 mol) and *p*-TSA·H_2O (76 mg, 0.40 mmol) in benzene (70 mL) were heated under reflux, until the calculated volume (~0.8 mL) of water had been removed, by means of a Dean-Stark trap. The resulting mixture was cooled to rt and diluted with Et_2O (100 mL), then washed with sat. aq $NaHCO_3$ (100 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (3 x 100

mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give chloroketal **288** as a clear, colourless oil (6.57 g, 94%); bp 85–90 °C (17 mm Hg) [lit.[185] bp 95–99 °C (21 mm Hg)]; IR (neat) (cm^{-1}) 2960m, 2882m, 1446m, 1377m, 1311m, 1212m, 1122m, 1045s (O–C–O), 870m; ^{1}H NMR (400 MHz) δ 3.99 – 3.89 (m, 4H, OC_2H_4O), 3.56 (t, 2H, CH_2Cl), 1.94 – 1.75 (m, 4H, C*H*$_2$C*H*$_2$CH$_2$Cl), 1.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 109.5 (O–C–O), 64.7 (OC_2H_4O), 45.2 (CH_2Cl), 36.3 (*C*H$_2$CO$_2$), 27.3 (*C*H$_2$CH$_2$Cl), 23.9 (CH_3)

Grignard 289 Addition to Sulfinimine (±)-285:

(±)-(*S*)-2-Methyl-*N*-((*R*)-2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamide ((±)-(*S*$_S$,*R*)-290):



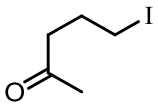
Magnesium turnings were stirred vigorously under argon overnight,[158] resulting in a colour change from grey to black. THF (1.3 mL) was added, followed by 1,2-dibromoethane (2–3 drops), at which point the mixture started to bubble. With close monitoring of the reaction mixture, ketalchloride **288** (1.05 g, 6.4 mmol) was added dropwise, ensuring the temperature did not exceed 50 °C (ice-bath). After addition, the mixture was stirred for 2 h at rt, then diluted with THF (1.9 mL). A portion of the freshly prepared solution of Grignard reagent **289** (190 µL) was added to a stirred solution of sulfinimine **(±)-285** (50 mg, 0.19 mmol) in THF (1.7 mL) at –78 °C, and the resultant mixture warmed to rt after 30 min. After 16 h, the reaction was quenched with sat. aq NH_4Cl (2 mL), diluted with H_2O (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 10–100% Et_2O in petroleum ether) gave inseparable diastereomers of bisketal sulfinamide **(±)-290** (73:27 *dr*), and an unknown, inseparable impurity. From this mixture, it was possible, by precipitation with petroleum ether, to partially extract the racemic major

diastereomer **(±)-(*S*s,*R*)-290** as a white solid (34 mg, 45%); the rest of the material was obtained as a crude mixture (39 mg);

Major Diastereomer:

mp 75–79 °C; R_f 0.12 (50% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3444w, 3297w (N–H), 2981m, 2880m, 1707w, 1650w, 1474m, 1373m, 1128m, 1045s (S=O and O–C–O), 876m; ^{1}H NMR (400 MHz) δ 4.05 – 3.82 (m, 8H, 2 x OC_2H_4O), 3.61 (d, 1H, J = 6 Hz, NH), 3.15 – 3.00 (m, 1H, J = 6 Hz, NHC*H*), 2.10 – 1.98 (m, 1H, NHCHCH_AH_B), 1.88 – 1.78 (m, 1H, $CHCH_2CH_AH_B$), 1.77 – 1.66 (m, 1H, J_{AB} = 14 Hz, $CH(CH_2)_2CH_AH_B$), 1.65 – 1.54 (m, 1H, J_{AB} = 14 Hz, $CH(CH_2)_2CH_AH_B$), 1.50 – 1.36 (m, 2H, $NHCHCH_AH_B$ and $CHCH_2CH_AH_B$), 1.34 (s, 3H, CH_3), 1.243 (s, 9H, $C(CH_3)_3$), 1.235 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 113.8 (O–C–O), 110.2 (O–C–O), 64.7 (OCH_2), 64.6 (OCH_2), 64.5 (OCH_2), 64.2 (OCH_2), 63.6 (NHCH), 56.5 ($C(CH_3)_3$), 46.6 ($C(CH_3)_2$), 39.1 ($CHCH_2CH_2$), 32.3 ($NHCHCH_2$), 23.9 (CH_3), 23.1 ($C(CH_3)_3$), 22.0 ($CH(CH_2)_2CH_2$), 21.7 (CH_3), 19.9 (CH_3), 19.6 (CH_3); m/z (ESI^+) 414.2 (M + Na^+, 100); HRMS *m/z* (M + H^+) found 392.2470, $C_{19}H_{38}NO_5S$ requires 392.2465

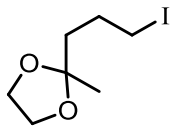
5-Iodopentan-2-one (291):[159a]



Chloroketone **287** (10.70 g, 88.7 mmol) and NaI (62.20 g, 0.41 mol) in acetone (500 mL) were stirred at 90 °C for 16 h. After this time, the mixture was cooled to rt and diluted with Et_2O (500 mL). The suspension was washed with sat aq NH_4Cl : 20% aq $Na_2S_2O_3$ (1:1, 500 mL), which resulted in a colour change (yellow → colourless). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure, which gave iodoketone **291** as a yellow oil (17.02 g, 90%); R_f 0.29 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2959w, 2916w, 2849w, 1712s (C=O), 1425m, 1364m, 1286w, 1220m, 1174m, 832w, 729m; ^{1}H NMR (400 MHz) δ 3.07 (t, 2H, J = 7 Hz, CH_2I), 2.45 (t, 2H, J = 7 Hz, CH_2C=O), 2.01 (s, 3H, CH_3), 1.91 (quin, 2H, CH_2CH_2I); ^{13}C NMR (101 MHz) δ 206.6 (C=O), 43.4 (CH_2C=O), 29.8 (CH_3), 26.7

(CH_2CH_2I), 6.3 (CH_2I); m/z (FI^+) 212.0 (M^+, 100); HRMS *m/z* (M^+) found 211.9700, C_5H_9OI requires 211.9698

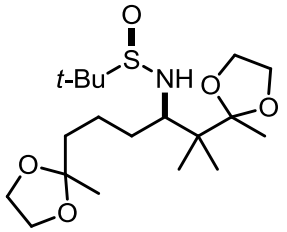
2-(3-Iodopropyl)-2-methyl-1,3-dioxolane (292):[159a]



Iodoketone **291** (3.67 g, 17.31 mmol), ethylene glycol (3.22 g, 51.93 mmol) and *p*-TSA·H_2O (33 mg, 0.17 mmol) in benzene (125 mL) were heated under reflux, until the calculated volume (~0.3 mL) of water had been removed, by means of a Dean-Stark trap. The resulting mixture was cooled to rt and diluted with Et_2O (100 mL), then washed with sat. aq $NaHCO_3$ (100 mL). The organic layer was separated, and the aq layer back-extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, to give iodoketal **292** as a yellow-brown oil (3.99 g, 90%); R_f 0.34 (10% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2981m, 2956m, 2879m, 1448w, 1376m, 1251m, 1234m, 1221m, 1113m, 1041s (O–C–O), 947m, 861m; ^1H NMR (400 MHz) δ 3.99 – 3.88 (m, 4H, OC_2H_4O), 3.21, (t, 2H, J = 7 Hz, CH_2I), 2.00 – 1.70 (m, 4H, $CH_2CH_2CH_2I$), 1.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 109.4 (O–C–O), 64.7 (OC_2H_4O), 39.8 (CH_2CO_2), 28.2 (CH_2CH_2I), 24.0 (CH_3), 6.99 (CH_2I); m/z (FI^+) 256.0 (M^+, 100); HRMS *m/z* (M^+) found 255.9961, $C_7H_{13}O_2I$ requires 255.9960

Organolithium 293 Addition to Sulfinimine (±)-285:

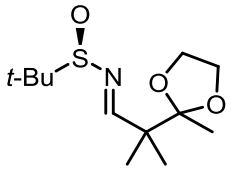
(±)-(*R*)-2-Methyl-*N*-((*R*)-2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamide ((±)-(*R*s,*R*)-290):



Iodoketal **292** (784 mg, 3.06 mmol) was dissolved in pentane / Et_2O (3:2, 30 mL) at rt with stirring. The resulting solution was cooled to – 78 °C, and *t*-BuLi (1.7 M in pentane, 3.78 mL, 6.43 mmol) was added dropwise. The mixture was stirred at –78 °C for 5 min, then warmed to rt. The mixture was stirred at rt for 1 h, and then re-cooled to –78 °C, which resulted in a white slurry. A portion of the freshly prepared organolithium **293** (17 mL) was added dropwise to a solution of sulfinimine **(±)-285** (200 mg, 0.77 mmol) in THF (3.85 mL) at –78 °C. [TLC showed the reaction was essentially complete after the addition.] The reaction was stirred at –78 °C for 1 h, then quenched with MeOH (5 mL), warmed to rt and diluted with H_2O (100 mL). The organic layer was separated, and the aq layer extracted with Et_2O (4 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 50–80% EtOAc in petroleum ether), which gave bisketal sulfinamide **(±)-(*R*s,*R*)-290** as a colourless, clear oil (98:2 *dr*, 279 mg, 93%); R_f 0.12 (50% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3275w (N–H stretch), 2979m, 2881m, 1474m, 1377m, 1217m, 1157m, 1062s and 1041s (S=O and O–C–O), 949m, 874m; ^{1}H NMR (400 MHz) δ 5.25 (br s, 1H, NH), 4.07 – 3.84 (m, 8H, 2 x OC_2H_4O), 3.24 (br s, 1H, NHC*H*), 1.77 – 1.55 (m, 4H, 1 x CH_2 and 2 x CH_AH_B), 1.50 – 1.36 (m, 2H, 2 x CH_AH_B), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.21 (s, 9H, $C(CH_3)_3$), 1.05 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 114.6 (O–C–O), 109.9 (O–C–O), 65.2 (OCH_2), 64.6 (2 x OCH_2), 63.6 (OCH_2), 58.7 (NHCH), 55.4 ($C(CH_3)_3$), 45.3 ($C(CH_3)_2$), 39.4 (CH_2), 33.1 (NHCHCH_2), 23.8 (CH_3), 23.2 (CH_3), 22.9 ($C(CH_3)_3$), 22.8 (CH_2), 19.3 (CH_3), 16.8 (CH_3); m/z (ESI^+) 392.2 (M + H^+, 100); HRMS *m/z* (M + Na^+) found 414.2275, $C_{19}H_{37}NNaO_5S$ requires 414.2285

Sulfinimine Synthesis Using Kawęcki's Method:[152b]

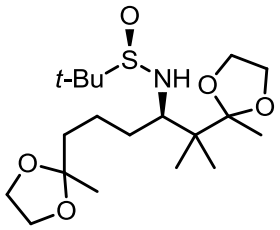
(–)-(*R*)-2-Methyl-*N*-(2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)propylidene)propane-2-sulfinamide ((–)-(*R*)-285):



Finely ground NaOH (1.01 g, 25.3 mmol) was added to a stirred solution of sulfinamide **(*R*)-277** (3.06 g, 25.2 mmol) in MeOH (125 mL) at rt. After 15 min, aldehyde **284** (4.00 g, 25.3 mmol) was added. After 16 h, the reaction mixture was evaporated under reduced pressure, and the residue dissolved in Et_2O (100 mL) and washed with sat. aq NH_4Cl (100 mL). The aq layer was separated and back-extracted with Et_2O (4 x 100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure, to give chiral sulfinimine **(*R*)-285** as a colourless, clear oil (6.19 g, 94%); $[\alpha]_D^{25}$ = –246.5 (*c* = 0.3, $CHCl_3$); other data as above.

Organolithium 293 Addition to Sulfinimine (*R*)-285:

(–)-(*R*)-2-Methyl-*N*-((*R*)-2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamide ((–)-(*R*S,*R*)-290):



Iodoketal **292** (5.88 g, 23.0 mmol) was dissolved in pentane / Et_2O (3:2, 225 mL) at rt with stirring. The resulting solution was cooled to –78 °C, and *t*-BuLi (1.7 M in pentane, 28.4 mL, 48.3 mmol) was added dropwise. The mixture was stirred at –78 °C for 5 min, then warmed to rt, which resulted in formation of a white slurry. The mixture was stirred at rt for 1 h, then re-cooled to –78 °C. The freshly prepared organolithium **293** was transferred, dropwise *via* cannula, to a solution of sulfinimine **(*R*)-285** (3.00 g, 11.5 mmol) in THF (57 mL) at –78 °C.

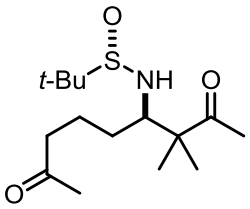
After 16 h at –78 °C, the mixture was quenched with MeOH (100 mL), warmed to rt, then diluted with H_2O (400 mL). The organic layer was separated, and the aq layer extracted with Et_2O (4 x 250 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 50–80% EtOAc in petroleum ether) gave bisketal sulfinamide **(*R*s,*R*)-290** as a colourless, clear oil (98:2 *dr*, 4.09 g, 91%); $[\alpha]_D^{25}$ = –78.8 (*c* = 2.2, $CHCl_3$); other data as above.

Examination of Cascade Reaction:

(±)-1,6,6-Trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((±)-294):

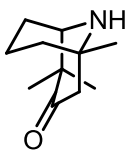
A vigorously stirred solution of *N*-benzylhomotropinone **(±)-231** (28 mg, 0.103 mmol) in MeOH (3 mL) was hydrogenated at 1 atm in the presence of 10% palladium on activated carbon (29 mg, 25 mol %) for 16 h. After this time, the catalyst was removed by filtration through Celite®. The filter cake was washed with CH_2Cl_2 (25 mL), and the filtrate evaporated under reduced pressure, to give homotropinone **(±)-294** as a colourless, clear oil (18 mg, 96%); R_f 0.15 (6% MeOH in CH_2Cl_2); IR (neat) (cm^{-1}) 2958m, 2930m, 2869m, 1703s (C=O), 1464w, 1415w, 1402w, 1377w, 1354w, 1299w, 1238w, 1192m, 909s, 731s; ^{1}H NMR (500 MHz) δ 3.01 (d, 1H, J = 7 Hz, NCH), 2.67 (d, 1H, J_{AB} = 15.9 Hz, NCHCH_AH$_B$), 2.40 (dd, 1H, J_{AB} = 15.9 Hz, J = 7 Hz, NCHCH$_A$$H_B$), 2.30 (dd, 1H, J_{AB} = 15.8 Hz, J = 2 Hz, NC(CH$_3$)CH_AH$_B$C=O), 2.16 (d, 1H, J_{AB} = 15.8 Hz, NC(CH$_3$)CH$_A$$H_B$C=O), 1.66 (br s, 1H, NH), 1.60 (tdd, 1H, J_{AB} = 14 Hz, J_1 = 6 Hz, J_2 = 2Hz, NC(CH$_3$)CH_AH$_B$CH$_2$), 1.49 – 1.42 (m, 1H, NC(CH$_3$)CH$_A$$H_BCH_2$), 1.39 – 1.23 (m, 2H, NC(CH$_3$)CH$_2$CH_2), 1.18 (s, 3H, CH$_3$), 1.09 (s, 3H, CH$_3$), 0.89 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 211.0 (C=O), 59.6 (NCH), 53.6 (NC(CH$_3$)CH$_2$C=O), 52.2 (NC(CH$_3$)), 43.3 (NCHCH$_2$), 34.9 (NC(CH$_3$)CH$_2$CH$_2$), 32.6 (C(CH$_3$)$_2$), 31.5 (NC(CH$_3$)CH$_2$$CH_2$), 31.4 (CH$_3$), 28.4 (CH$_3$), 26.3 (CH$_3$); m/z (ESI$^+$) 182.1 (M + H$^+$, 49); HRMS *m/z* (M + H$^+$) found 182.1534, $C_{11}H_{20}NO$ requires 182.1539

(±)-(*S*)-*N*-((*R*)-3,3-Dimethyl-2,8-dioxononan-4-yl)-2-methylpropane-2-sulfinamide ((±)-(*S*S,*R*)-295):



Bisketal sulfinamide **(±)-(*S*S,*R*)-290** (35 mg, 0.089 mmol) and NH_4OAc (172 mg, 2.23 mmol) in EtOH / AcOH (1:1, 7.8 mL) were stirred at 75 °C for 36 h. After this time, the mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL). Sat. aq Na_2CO_3 was added until the aq layer reached basic pH. The organic layer was separated and the aq layer washed with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0–10% MeOH in CH_2Cl_2), to give bisketone sulfinamide **(±)-(*S*S,*R*)-295** as a pale-yellow, clear oil (15 mg, 55%); R_f 0.29 (6% MeOH in CH_2Cl_2); IR (neat) (cm^{-1}) 3399w, 3291w, 2961m, 2930m, 1705s (2 x C=O), 1466m, 1417m, 1364m, 1247m, 1166w, 1050s, 910m, 731s; ^1H NMR (400 MHz) δ 3.40 (br s, 1H, NHC*H*), 2.57 – 2.38 (m, 2H, CH_2C=O), 2.141 (s, 3H, CH_3), 2.138 (s, 3H, CH_3), 2.08 – 1.98 (m, 1H, $CH_2CH_AH_BCH_2$), 1.68 – 1.56 (m, 1H, $CH_2CH_AH_BCH_2$), 1.66 (br s, 1H, NH), 1.52 – 1.44 (m, 1H, CH_AH_BCH), 1.29 – 1.19 (m, 1H, CH_AH_BCH), 1.24 (s, 9H, $C(CH_3)_3$), 1.12 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 212.6 (C=O), 209.0 (C=O), 62.1 (NHCH), 56.6 ($C(CH_3)_3$), 53.0 ($C(CH_3)_2$), 42.7 (CH_2C=O), 31.6 ($CHCH_2$), 29.9 (CH_3), 26.0 (CH_3), 23.0 ($C(CH_3)_3$), 21.7 (CH_3), 20.8 (CH_3), 20.2 ($CH_2CH_2CH_2$); m/z (ESI^+) 326.2 (M + Na^+, 91); HRMS *m/z* (M + Na^+) found 326.1767, $C_{15}H_{29}NNaO_3S$ requires 326.1760

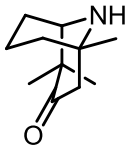
(±)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((±)-256):



Iodoketal **292** (784 mg, 3.06 mmol) was dissolved in pentane / Et_2O (3:2, 30 mL) at rt, with stirring. The resulting solution was cooled to – 78 °C, and *t*-BuLi (1.7 M in pentane, 3.78 mL,

6.43 mmol) was added dropwise. The mixture was stirred at –78 °C for 5 min, then warmed to rt. The mixture was stirred at rt for 1 h, and then re-cooled to –78 °C, which resulted in a white slurry. A portion of the freshly prepared organolithium **293** (17 mL) was added dropwise to a solution of sulfinimine **(±)-285** (200 mg, 0.77 mmol) in THF (3.85 mL) at –78 °C. [TLC showed the reaction was essentially complete after the addition.] The reaction was stirred at –78 °C for 1 h, then quenched with MeOH (5 mL), warmed to rt and diluted with H_2O (100 mL). The organic layer was separated, and the aq layer extracted with Et_2O (4 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude bisketal sulfinamide **(±)-(*R*s,*R*)-290** (pale-yellow, clear oil; 98:2 *dr*, 337 mg) were dissolved in MeOH (250 mL) with stirring at rt. HCl (2 M in Et_2O, 86 mL) was added, and the resulting mixture heated at 75 °C for 16 h. After this time, the mixture was cooled to rt, and the volatiles removed by evaporation under reduced pressure. Aq NaOH (3 M) was added to the residue, until a strongly basic pH was established. The aq layer was then washed with Et_2O (4 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0−10% MeOH in EtOAc) and bulb-to-bulb distillation gave homotropinone **(±)-256** as a clear crystalline solid (108 mg, 78%); bp 90–95 °C (0.5 mm Hg); mp 40–42 °C; R_f 0.36 (10% MeOH in EtOAc); IR (neat) (cm^{-1}) 3310w (N–H), 2953m, 2930m, 1699s (C=O), 1655w, 1457m, 1380m, 1201m, 909m, 730s; ^{1}H NMR (400 MHz) δ 2.93 (br s, 1H, NCH), 2.35 (d, 1H, J_{AB} = 16 Hz, CH_AH$_B$C=O), 2.17 (d, 1H, J_{AB} = 16 Hz, CH$_A$$H_B$C=O), 1.88 (br s, 1H, NH), 1.82 (d, 1H, J_{AB} = 13 Hz, NCHCH_AH$_B$), 1.57 – 1.32 (m, 4H, CH_2, CH_AH$_B$ and CH$_A$$H_B$), 1.31 – 1.15 (m, 1H, CH$_A$$H_B$), 1.22 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 216.2 (C=O), 60.8 (NCH), 53.7 (N*C*CH$_3$), 50.0 (*C*H$_2$C=O), 46.8 (*C*(CH$_3$)$_2$), 38.6 (CH(CH$_2$)$_2$*C*H$_2$), 31.5 (CH_3), 27.7 (CH_3), 27.2 (NCH*C*H$_2$), 21.3 (CH_3), 17.9 (CH$_2$*C*H$_2$CH$_2$); m/z (ESI$^+$) 182.1 (M + H$^+$, 52); HRMS *m/z* (M + H$^+$) found 182.1534, $C_{11}H_{20}NO$ requires 182.1539

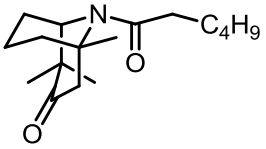
(–)-(1*S*,5*R*)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((–)-(1*S*,5*R*)-256):



HCl (2 M in Et_2O, 86 mL) was added to a stirred solution of bisketal sulfinamide **(*R*S,*R*)-290** (2.69 g, 6.9 mmol) in MeOH (250 mL) at rt. The resulting mixture was heated at 75 °C for 2 d. After this time, the mixture was cooled to rt, and the volatiles removed by evaporation under reduced pressure. Aq NaOH (3 M, 100 mL) was added to the residue and the resulting suspension stirred for 15 min, then washed with CH_2Cl_2 (5 x 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–10% MeOH in EtOAc) gave homotropinone **(1*S*,5*R*)-256** as a clear, crystalline solid (1.04 g, 83%); $[\alpha]_D^{25}$ = –94.4 (*c* = 0.3, $CHCl_3$); other data as above.

Synthesis and Deoxygenation of Amide (1*S*,5*R*)-296:

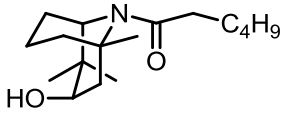
(–)-(1*S*,5*R*)-9-Hexanoyl-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((–)-(1*S*,5*R*)-296):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of homotropinone **(1*S*,5*R*)-256** (300 mg, 1.65 mmol) with hexanoic anhydride (**101**; 709 mg, 3.31 mmol) and Et_3N (5 mL, 35.87 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, gradient elution: 3–10% EtOAc in petroleum ether), ketoamide **(1*S*,5*R*)-296** as a colourless, clear oil (461 mg, quant); $[\alpha]_D^{25}$ = –72.2 (*c* = 1.0, $CHCl_3$); R_f 0.22 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2954m, 2929m, 2873w, 1708s (C=O, ketone), 1655s (C=O, amide), 1457m, 1393s, 1382s, 1333m, 1281m, 1122m, 920w, 753w; ^{1}H NMR (400 MHz) δ 3.94 (br s, 1H, NCH), 2.82 (dd, 1H, J_{AB} = 16 Hz, *J* = 1 Hz, $C(CH_3)CH_AH_BC{=}O$), 2.38 (t, 2H, *J* = 7 Hz, $CH_2C(=O)N$), 2.15 (d, 1H, J_{AB} = 16 Hz, $C(CH_3)CH_AH_BC{=}O$), 1.99 – 1.92 (m, 1H, $NCHCH_AH_B$), 2.00 – 1.82 (m, 1H,

NC(CH_3)CH_AH$_B$CH_2), 1.75 (s, 3H, NC(CH_3)), 1.71 – 1.61 (m, 2H, CH_2CH_2C=O), 1.61 – 1.49 (m, 3H, NC(CH_3)C$H_A$$H_BCH_2$, NC($CH_3$)C$H_2CH_AH_B$ and NCHC$H_A$$H_B$), 1.49 – 1.40 (m, 1H, NC(CH_3)CH_2C$H_A$$H_B$), 1.40 – 1.30 (m, 4H, C$H_2CH_2CH_3$), 1.27 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 0.92 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 214.2 (C(CH_3)$_2$*C*=O), 174.6 (N–C=O), 62.0 (NCH), 59.5 (N*C*(CH_3)), 50.4 (NC(CH_3)*C*H$_2$C=O), 47.9 (*C*(CH_3)$_2$), 38.6 (NC(CH_3)*C*H$_2$CH_2), 36.3 (*C*H$_2$C(=O)N), 31.6 (CH_2), 31.0 (NC(*C*H_3)), 27.14 (NCH*C*H$_2$), 27.10 (CH_3), 25.3 (NC(=O)CH$_2$*C*H$_2$), 22.6 (CH_2), 21.0 (CH_3), 18.0 (NC(CH_3)CH$_2$*C*H$_2$), 14.0 (CH$_2$*C*H_3); m/z (ESI$^+$) 302.2 (M + Na$^+$, 100); HRMS *m/z* (M + Na$^+$) found 302.2083, $C_{17}H_{29}NNaO_2$ requires 302.2091

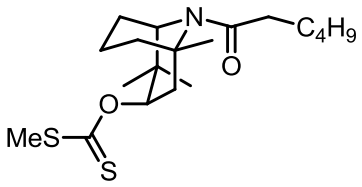
(–)-1-((1*S*,3*R*,5*R*)-3-Hydroxy-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-9-yl)hexan-1-one ((–)-(1*S*,3*R*,5*R*)-303):



$NaBH_4$ (132 mg, 3.50 mmol) was added to a solution of ketoamide **(1*S*,5*R*)-296** (98 mg, 0.35 mmol) in EtOH (5 mL) at 0 °C with stirring. After 30 min, the reaction was warmed to rt, and stirring continued for 1.5 h. The reaction was quenched with H_2O (10 mL) at 0 °C, then warmed to rt and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure, to give amidoalcohol **(1*S*,3*R*,5*R*)-303** as a white solid (99 mg, quant); mp 61–65 °C; $[\alpha]_D^{25}$ = –17.0 (*c* = 0.3, $CHCl_3$); R_f 0.21 (20% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3458m (O–H), 2907m, 1632s (C=O), 1463m, 1406m, 1381m, 1333m, 1279m, 1226w, 1162m, 1103m, 1046m, 956m, 836w, 725w; ^{1}H NMR (500 MHz) δ 3.60 (br s, 1H, NCH), 3.58 (dd, 1H, J_1 = 6 Hz, J_2 = 3 Hz, C*H*OH), 2.72 – 2.60 (m, 1H, NCHCH$_2$CH_AH$_B$), 2.27 (t, 2H, J = 8 Hz, NC(=O)CH_2), 2.17 (ddd, 1H, J_{AB} = 15 Hz, J_1 = 6 Hz, J_2 = 1 Hz, CHOHCH_AH$_B$), 1.98 (br s, 1H, OH), 1.91 – 1.81 (m, 2H, NCHCH_AH$_B$ and NC(CH_3)CH_AH$_B$CH$_2$), 1.66 (s, 3H, NC(CH_3)), 1.64 – 1.56 (m, 2H, NC(=O)CH$_2$CH_2), 1.56 – 1.23 (m, 8H, CHOHCH$_A$$H_B$, NCHCH$_2CH_A$$H_B$, NCHCH$_A$$H_B$, NC($CH_3$)CH$_A$$H_BCH_2$ and CH_2CH_2CH$_3$), 1.07 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.89 (t, 3H, J = 7 Hz, CH$_2$CH_3); ^{13}C NMR (125 MHz) δ 174.0 (C=O), 71.4 (CHOH), 59.8 (NCH), 55.4 (N*C*(CH_3)), 43.7 (CHOH*C*H$_2$), 38.2 (*C*(CH_3)$_2$), 36.2 (NC(CH_3)*C*H$_2$CH$_2$), 35.8 (NC(=O)*C*H$_2$), 32.6 (NC(*C*H_3)), 31.7 (CH_2), 29.2 (CH_3), 25.8 (NCH*C*H$_2$), 25.3 (NC(=O)CH$_2$*C*H$_2$), 22.5

(CH_2), 22.0 (CH_3), 17.4 ($NCHCH_2CH_2$), 14.0 (CH_2CH_3); m/z (ESI^+) 282.3 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 282.2426, $C_{17}H_{32}NO_2$ requires 282.2428

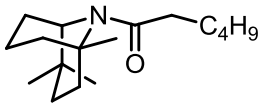
(–)-*O*-((1*S*,3*R*,5*R*)-9-Hexanoyl-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-3-yl) *S*-methyl carbonodithioate ((–)-(1*S*,3*R*,5*R*)-304):



Amidoalcohol **(1*S*,3*R*,5*R*)-303** (944 mg, 3.35 mmol) was dissolved in THF (10 mL) with stirring at rt. Imidazole (50 mg, 0.73 mmol) and NaH (419 mg, 17.46 mmol) were added, and the resulting mixture stirred at rt for 30 min. CS_2 (1.3 mL, 21.62 mmol) was added, dropwise, resulting in an orange coloration. The mixture was heated at 70 °C for 16 h, then cooled to rt, and MeI (952 mg, 6.71 mmol) added, dropwise. The resulting mixture was stirred at rt for 16 h, then cooled to 0 °C and quenched with brine (10 mL). After warming to rt, the mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 3–10% EtOAc in petroleum ether) gave amidoxanthate **(1*S*,3*R*,5*R*)-304** as an orange solid (1.17 g, 94%); mp 50–52°C; $[\alpha]_D^{25}$ = –19.3 (*c* = 1.0, $CHCl_3$); R_f 0.56 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2954m, 2924m, 2872w, 1656s (C=O), 1466w, 1399m, 1386m, 1278w, 1227s (C=S), 1209s, 1183m, 1055s (MeS–CS–O–R), 969m; ^{1}H NMR (500 MHz) δ 5.55 (d, 1H, *J* = 6 Hz, O–CH), 3.65 (d, 1H, *J* = 4 Hz, NCH), 2.60 (s, 3H, SMe), 2.46 – 2.32 (m, 1H, $NCHCH_2CH_AH_B$), 2.30 (t, 2H, *J* = 8 Hz, $NC(=O)CH_2$), 2.26 (dd, 1H, J_{AB} = 16 Hz, *J* = 6 Hz, O–$CHCH_AH_B$), 2.01–1.87 (m, 2H, $NCHCH_AH_BCH_2CH_AH_B$), 1.73 (d, 1H, J_{AB} = 16 Hz, O–$CHCH_AH_B$), 1.67 (s, 3H, $NC(CH_3)$), 1.66 – 1.57 (m, 3H, $NCHCH_AH_B$ and $NC(=O)CH_2CH_2$), 1.54 – 1.46 (m, 1H, $NCHCH_2CH_AH_B$), 1.45 – 1.38 (m, 1H, $NC(CH_3)CH_AH_BCH_2$), 1.38 – 1.26 (m, 4H, $CH_2CH_2CH_3$), 1.20 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.90 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (125 MHz) δ 215.5 (C=S), 174.1 (C=O), 83.0 (O–CH), 59.3 (NCH), 54.8 ($NC(CH_3)$), 40.2 ($O–CHCH_2$), 37.9 ($C(CH_3)_2$), 35.8 ($NC(=O)CH_2$), 35.7 ($NC(CH_3)CH_2CH_2$), 32.4 ($NC(CH_3)$), 31.6 (CH_2), 28.6 (CH_3), 25.23 ($NCHCH_2$), 25.15 ($NC(=O)CH_2CH_2$), 22.5 (CH_2),

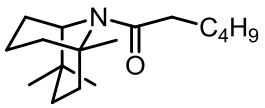
22.4 (CH_3), 19.0 (SMe), 17.1 ($NCHCH_2\mathit{C}H_2$), 14.0 ($CH_2\mathit{C}H_3$); m/z (ESI^+) 372.2 ($M + H^+$, 100); HRMS *m/z* ($M + Na^+$) found 394.1833, $C_{19}H_{33}NNaO_2S_2$ requires 394.1845

(±)-1-(1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-9-yl)hexan-1-one ((±)-297):



According to the general procedure for amide synthesis using Hulme's protocol, reaction of homotropane **(±)-356** (76 mg, 0.45 mmol) with hexanoic anhydride (**101**; 195 mg, 0.91 mmol) and Et_3N (3 mL, 21.52 mmol) irradiated with microwave energy at 160 °C for 1 h gave, after purification by column chromatography (SiO_2, 4% EtOAc in petroleum ether), amide **(±)-297** as a colourless, clear oil (103 mg, 87%); R_f 0.09 (4% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2954m, 2928m, 2870m, 1651s (C=O), 1452m, 1395m, 1383m, 1279m, 1178w, 1148w, 1105m, 951w, 730w; ^{1}H NMR (400 MHz) δ 3.49 (d, 1H, J = 3 Hz, NCH), 2.26 (t, 2H, J = 8 Hz, CH_2C=O), 2.13 – 1.80 (m, 5H, 3 x CH_AH_B and 1 x CH_2), 1.66 – 1.26 (m, 11 H, 3 x CH_AH_B and 4 x CH_2), 1.63 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.89 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz) δ 174.0 (C=O), 60.0 (NCH), 55.5 (N*C*CH_3), 37.4 (CH_2), 36.7 (CH_2), 36.0 (*C*H_2C=O), 34.7 (CH_2), 34.5 (*C*$(CH_3)_2$), 32.1 (CH_3), 31.7 (CH_2), 28.5 (CH_3), 27.5 (CH_3), 26.3 (CH_2), 25.3 (CH_2), 22.5 (CH_2), 20.3 (CH_2), 14.0 (CH_3); m/z (ESI^+) 266.3 ($M + H^+$, 81); HRMS *m/z* ($M + H^+$) found 266.2479, $C_{17}H_{32}NO$ requires 266.2478

(–)-1-((1*S*,5*R*)-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-9-yl)hexan-1-one ((–)-(1*S*,5*R*)-297):

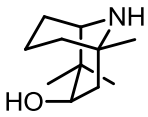


Amidoxanthate **(1*S*,3*R*,5*R*)-304** (48 mg, 0.13 mmol) and AIBN (6.5 mg, 0.040 mmol) were dried under vacuum (0.1 mm Hg) for 1 h. Benzene (degassed under Ar for 1 h, 1.1 mL) was added, followed by Bu_3SnH (35 µL, 0.13 mmol), dropwise with stirring at rt. The mixture was heated at 85 °C for 16 h, then cooled to rt and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: 0–10% EtOAc in petroleum

ether), to give amide **(1*S*,5*R*)-297** as a colourless, clear oil (32 mg, 93%); $[\alpha]_D^{25}$ = –11.2 (*c* = 1.0, $CHCl_3$); other data as above.

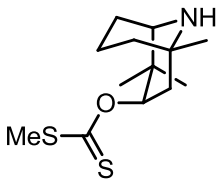
Deoxygenation of Homotropinone (1*S*,5*R*)-256:

(–)-(1*S*,3*R*,5*R*)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-ol ((–)-(1*S*,3*R*,5*R*)-305):



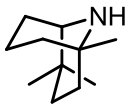
LAH (361 mg, 9.5 mmol) was dissolved in THF (10 mL) with stirring and external cooling (ice-bath). Homotropinone **(1*S*,5*R*)-256** (1.50 g, 8.3 mmol) in THF (10 mL) was added, dropwise, with stirring at 0 °C. The reaction temperature was maintained at 0 °C for 30 min, then warmed to rt and stirred overnight. After this time, the mixture was re-cooled to 0 °C and quenched: H_2O (360 µL), then 15% aq NaOH (360 µL), then H_2O (1.1 mL). [Care! Add slowly!] The resulting suspension was filtered, and the filter cake washed with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure, to give homotropinol **(1*S*,3*R*,5*R*)-305** as a white solid (1.38 g, 91%); mp 105–110 °C; R_f 0.10 (20% MeOH in EtOAc); $[\alpha]_D^{25}$ = –22.4 (*c* = 1.9, $CHCl_3$); IR (neat) (cm^{-1}) 3130brm (O–H and N–H), 2898m, 1459m, 1418m, 1287m, 1106m, 1047s, 968s, 821s; ^{1}H NMR (500 MHz) δ 3.62 (dd, 1H, J_1 = 6 Hz, J_2 = 3 Hz, C*H*OH), 2.70 (d, 1H, *J* = 4 Hz, NCH), 2.59 – 2.41 (m, 1H, $CH_2CH_AH_BCH_2$), 2.12 (br s, 2H, NH and OH), 1.84 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, CH_AH_BCHOH), 1.77 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, $NCHCH_AH_B$), 1.59 – 1.45 (m, 3H, CH_AH_BCHOH, $NCHCH_AH_B$ and $CH(CH_2)_2CH_AH_B$), 1.43 – 1.32 (m, 2H, $CHCH_2CH_AH_BCH_AH_B$), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 71.7 (CHOH), 58.2 (NCH), 47.9 ($NC(CH_3)$), 41.0 (CH_2CHOH), 36.8 ($CH(CH_2)_2CH_2$), 36.0 ($C(CH_3)_2$), 33.3 (CH_3), 30.4 (CH_3), 25.9 ($NCHCH_2$), 21.8 (CH_3), 17.2 ($CH_2CH_2CH_2$); m/z (ESI^+) 184.2 ($M + H^+$, 32); HRMS *m/z* ($M + H^+$) found 184.1695, $C_{11}H_{22}NO$ requires 184.1696

(–)-*S*-Methyl *O*-((1*S*,3*R*,5*R*)-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonan-3-yl) carbonodithio ate ((–)-(1*S*,3*R*,5*R*)-306):



Homotropinol **(1*S*,3*R*,5*R*)-305** (299 mg, 1.63 mmol) was dissolved in THF (5 mL), with stirring at rt. Imidazole (25 mg, 0.36 mmol) and NaH (203 mg, 8.46 mmol) were added, and the resulting mixture stirred at rt for 30 min. CS_2 (647 µL, 10.76 mmol) was added, dropwise, resulting in an orange coloration. The mixture was heated at 70 °C for 16 h, then cooled to rt and MeI (203 µL, 3.26 mmol) added, dropwise. The resulting mixture was stirred at rt for 16 h, then cooled to 0 °C and quenched with brine (5 mL). After warming to rt, the mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: 0–20% MeOH in EtOAc) gave xanthate **(1*S*,3*R*,5*R*)-306** as an orange solid (336 mg, 75%); mp 40–44 °C; $[\alpha]_D^{25} = -17.3$ (*c* = 0.8, $CHCl_3$); R_f 0.21 (20% MeOH in EtOAc); IR (neat) (cm^{-1}) 2920m, 1704w, 1592w, 1424m, 1374m, 1226s (C=S), 1049s (MeS–C(=S)–O–R), 965m, 753m; ^{1}H NMR (500 MHz) δ 5.60 (dd, 1H, J_1 = 6 Hz, J_2 = 2 Hz, C*H*–O–CS_2Me), 2.75 (d, 1H, *J* = 5 Hz, NCH), 2.60 (s, 3H, SCH_3), 2.39 – 2.25 (m, 1H, $CH_2CH_AH_BCH_2$), 2.00 – 1.86 (m, 2H, O–CHCH_AH_B and NCHCH_AH_B), 1.77 (dd, 1H, J_{AB} = 16 Hz, *J* = 2 Hz, O–CHCH_AH_B), 1.71–1.57 (m, 1H, NCHCH_AH_B), 1.55–1.39 (m, 3H, $CHCH_2CH_AH_BCH_2$), 1.23 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 215.7 (C=S), 83.9 (*C*H–OCS_2Me), 57.7 (NCH), 47.4 (N*C*(CH_3)), 37.8 (O–CH*C*H_2), 36.4 (*C*(CH_3)$_2$), 35.9 (CH(CH_2)$_2$*C*H_2), 33.3 (CH_3), 29.9 (CH_3), 25.5 (NCH*C*H_2), 22.5 (CH_3), 18.9 (SMe), 16.9 (CH_2*C*H_2CH_2); m/z (ESI^+) 274.2 (M + H^+, 100); HRMS *m/z* (M + H^+) found 274.1286, $C_{13}H_{24}NOS_2$ requires 274.1294

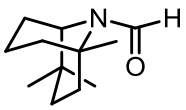
(–)-(1*S*,5*R*)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane ((–)-(1*S*,5*R*)-229):



Xanthate **(1*S*,3*R*,5*R*)-306** (750 mg, 2.74 mmol) and AIBN (135 mg, 0.82 mmol) were dried under vacuum (0.1 mm Hg) for 1 h. Benzene (degassed under Ar for 1 h, 24 mL) was added, followed by Bu_3SnH (740 µL, 2.75 mmol), dropwise with stirring at rt. The mixture was heated at 85 °C for 16 h, then cooled to rt and diluted with 5% aq HCl (20 mL). The aq layer was washed with CH_2Cl_2 (20 mL), and the organic layer separated. The aq layer was basified with 3 M aq NaOH, and the resulting suspension extracted with Et_2O (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), and the mixture concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave homotropane **(1*S*,5*R*)-229** as a clear oil (316 mg, 69%); bp 75–85 °C (10 mm Hg); $[\alpha]_D^{25}$ = –2.2 (*c* = 1.0, $CHCl_3$); other data as above.

Synthesis of Enamine (1*S*,5*R*)-228 and Alkylation:

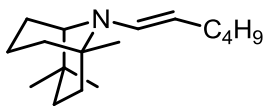
(–)-(1*S*,5*R*)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane-9-carbaldehyde ((–)-(1*S*,5*R*)-309):



According to the general procedure for formamide synthesis, reaction of homotropane **(1*R*,5*S*)-229** (156 mg, 0.93 mmol), $BnEt_3NCl$ (104 mg, 0.46 mmol), $CHCl_3$ (749 µL, 9.36 mmol), and 12.5 M aq NaOH (2.5 mL) in CH_2Cl_2 (3.3 mL) at reflux for 16 h gave formamide **(1*S*,5*R*)-309** as a clear oil (178 mg, 98%); bp 130–140 °C (1.5 mm Hg); R_f 0.33 (Et_2O); $[\alpha]_D^{25}$ = –0.6 (*c* = 1.0, $CDCl_3$); IR (film) (cm^{-1}) 2935m, 1644s (C=O), 1450m, 1391s, 1358m, 1280m, 1139m, 1110m, 910w, 752w; ^1H NMR (400 MHz) δ 8.34 (s, 1H, *J* = 5 Hz, CHO), 4.26 (d, 1H, *J* = 5 Hz, NCH), 2.12 – 1.86 (m, 3H, 3 x CH_AH_B), 1.83 – 1.71 (m, 2H, 2 x CH_AH_B), 1.67 – 1.48 (m, 4H, 4 x CH_AH_B), 1.36 (s, 3H, CH_3), 1.31 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, CH_AH_B), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 158.8 (C=O), 53.3 (N*C*(CH_3)), 52.4 (NCH), 39.3 (CH_2), 36.2 (CH_2), 34.5 (CH_2), 33.8 (*C*(CH_3)$_2$), 28.7 (CH_3),

27.7 (CH_3), 27.1 (CH_3), 25.2 (CH_2), 19.9 (CH_2); m/z (ESI^+) 196.2 ($M + H^+$, 7); HRMS *m/z* ($M + H^+$) found 196.1697, $C_{12}H_{22}NO$ requires 196.1696

(1*S*,5*R*)-9-((*E*)-Hex-1-en-1-yl)-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonane ((1*S*,5*R*)-228):

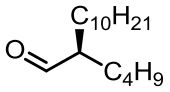


According to the general procedure for enamine synthesis following Nagashima's protocol, reaction of amide **(1*S*,5*R*)-297** (200 mg, 0.75 mmol) with a solution of Vaska's complex (0.02 M in toluene, 375 µL, 7.50 µmol) and PMHS (200 mg, Si–H = 3.01 mmol) at rt for 20 min gave, after purification by bulb-to-bulb distillation, a mixture of enamine **(1*S*,5*R*)-228** and amine **(1*S*,5*R*)-308** as a clear, colourless oil (187 mg, quant, 94:6 {**228**:**308**}); bp 125–130 °C (0.1 mm Hg);[180] IR (neat) (cm^{-1}) 3059w, 2952s, 2918s, 2871m, 1640s (N–C=C), 1451m, 1258s, 1108s, 936s, 903s, 768m; ^1H NMR (400 MHz, C_6D_6) δ 6.36 (d, 1H, J = 14 Hz, NC*H*=CH), 4.40 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH=C*H*), 3.13 (d, 1H, J = 5 Hz, NC*H*CH_2), 2.21 (dt, 2H, $J_1 = J_2$ = 7 Hz, CH=CHCH_2), 2.05 – 1.64 (m, 4H, 4 x C$H_A H_B$), 1.53 – 1.16 (m, 10H, 4 x C$H_A H_B$ and 3 x CH_2), 1.15 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.96 (t, 3H, CH_2CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 133.9 (N*C*H=CH), 98.5 (NCH=*C*H), 58.0 (NCH), 53.3 (N*C*(CH_3)), 37.1 (CH_2), 36.4 (CH_2), 35.8 (CH_2), 35.0 (CH_2), 34.7 (*C*(CH_3)$_2$), 32.0 (CH=CH*C*H_2), 30.4 (CH_3), 29.2 (CH_3), 28.8 (CH_3), 23.0 (CH_2), 21.7 (CH_2), 19.5 (CH_2), 14.7 (CH_2*C*H_3); m/z (ESI^+) 250.3 ($M + H^+$, 100); HRMS *m/z* ($M + H^+$) found 250.2528, $C_{17}H_{32}N$ requires 250.2529

According to the general procedure for enamine synthesis following the adapted Wickberg and Hansson protocol, reaction of formamide **(1*S*,5*R*)-309** (174 mg, 0.89 mmol) with pentylmagnesium chloride (2.0 M in THF, 557 µL, 1.11 mmol) in Et_2O (810 µL) at rt for 16 h gave, after distillation, enamine **(1*S*,5*R*)-228** (170 mg, 76%); other data as above.

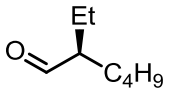
Asymmetric Alkylations of Enamine (1*S*,5*R*)-228 Prepared Using Nagashima's Protocol:

(*R*)-2-Butyldodecanal ((*R*)-140):



According to the general procedure for enamine alkylation, reaction of a mixture of enamine **(1*S*,5*R*)-228** and amide **(1*S*,5*R*)-297** (0.21 mmol, 66:34 {**228**:**297**}) with decyl iodide (102 mg, 0.38 mmol) in d_3-MeCN (0.6 mL) at 94 °C for 14 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde **(*R*)-140**[16] (69:31 *er*,[16,95] 26 mg, 52% {76% brsm}); other data as above.

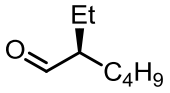
(*S*)-2-Ethylhexanal ((*S*)-24):



According to the general procedure for enamine alkylation, reaction of a mixture of enamine **(1*S*,5*R*)-228** and amide **(1*S*,5*R*)-297** (0.68 mmol, 85:15 {**228**:**297**}) with EtI (212 mg, 1.36 mmol) in d_3-MeCN (0.6 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde **(*S*)-24**[16] (76:24 *er*,[16,95] 55 mg, 63%); other data as above.

Asymmetric Alkylation of Enamine (1*S*,5*R*)-228 Prepared Using the Adapted Hansson and Wickberg Protocol:

(*S*)-2-Ethylhexanal ((*S*)-24):

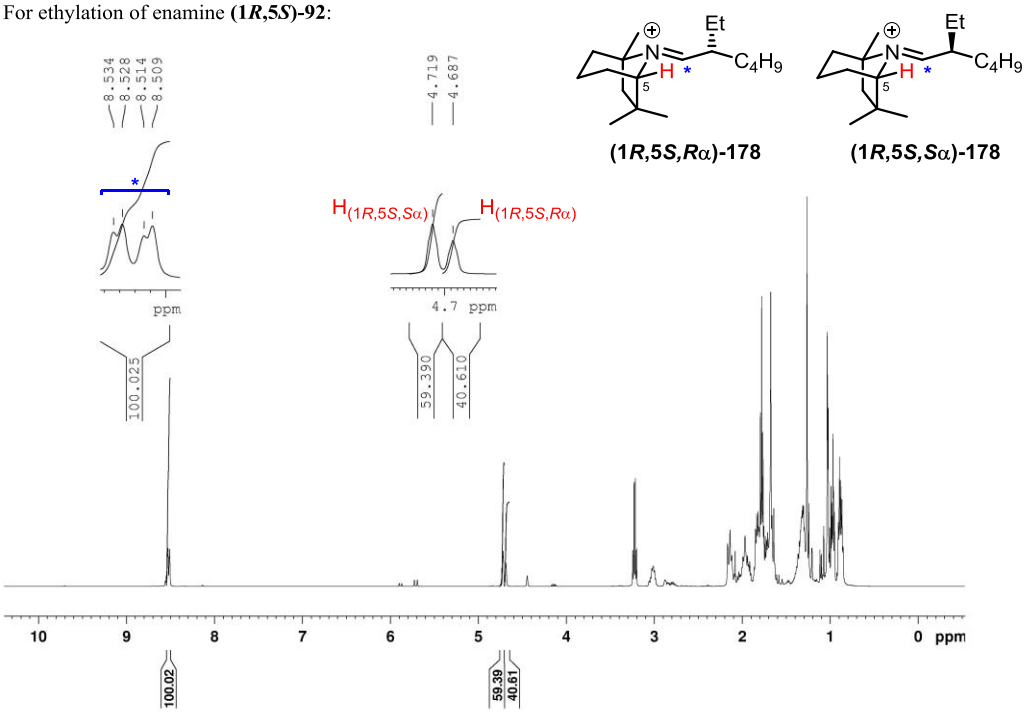


According to the general procedure for enamine alkylation, reaction of enamine **(1*S*,5*R*)-228** (125 mg, 0.50 mmol) with EtI (156 mg, 1.00 mmol) in d_3-MeCN (536 µL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at rt for 5 min, aldehyde **(*S*)-24**[16] (72:28 *er*,[16,95] 41 mg, 64%); other data as above.

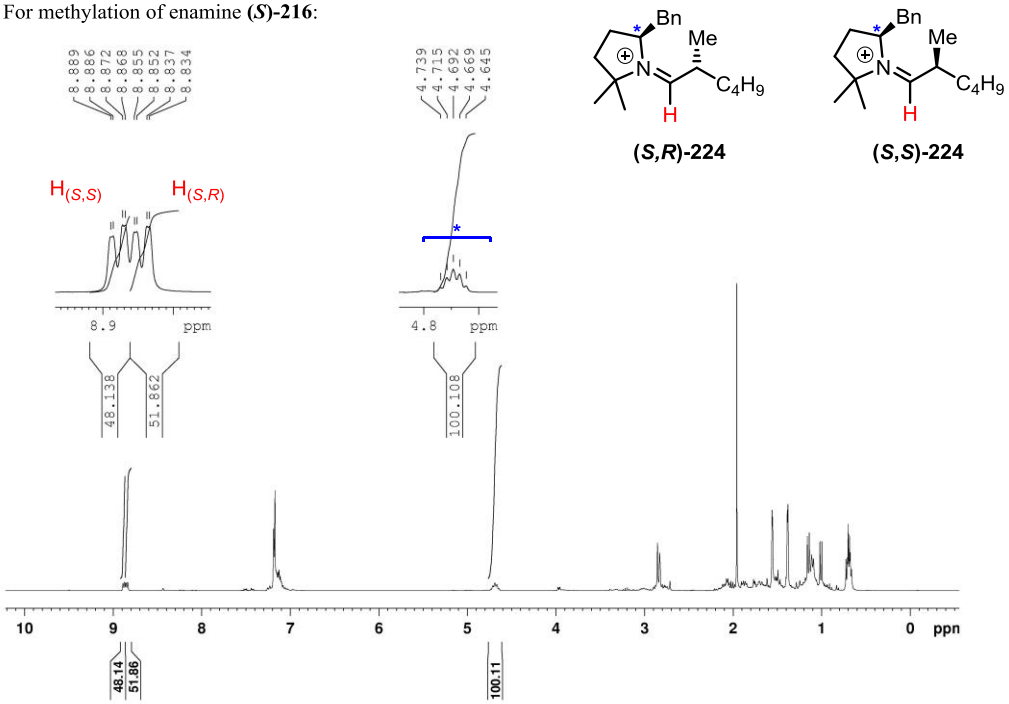
APPENDIX

A.1 Measurement of Alkylation Diastereoselectivity by *in situ* NMR

For ethylation of enamine **(1*R*,5*S*)-92**:

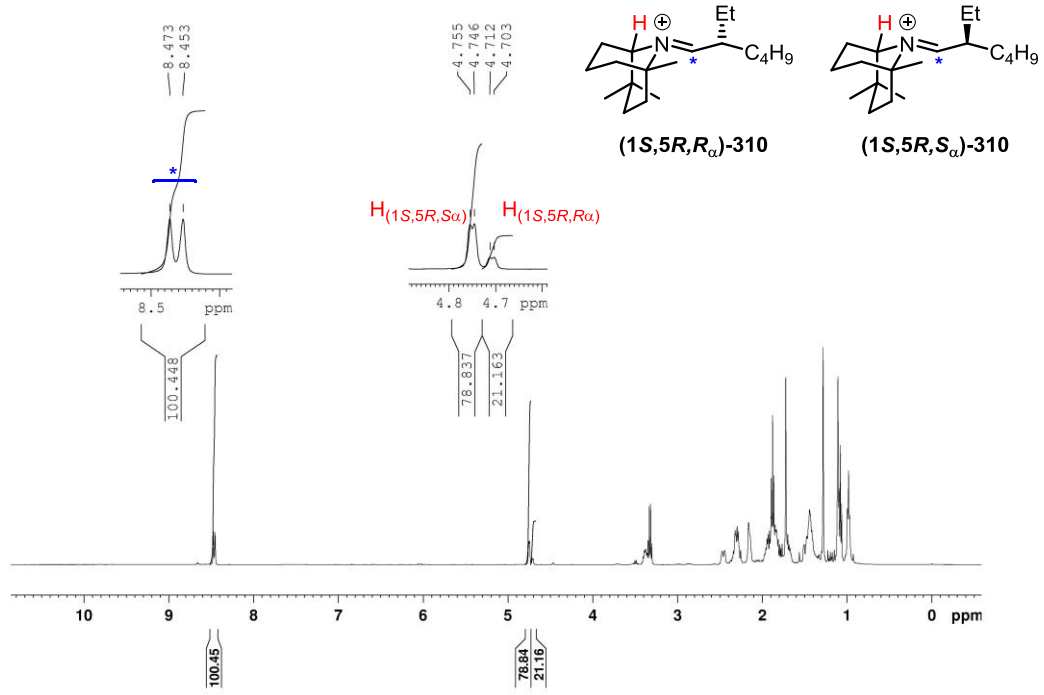


For methylation of enamine **(*S*)-216**:



A.1 Measurement of Alkylation Diastereoselectivity by *in situ* NMR

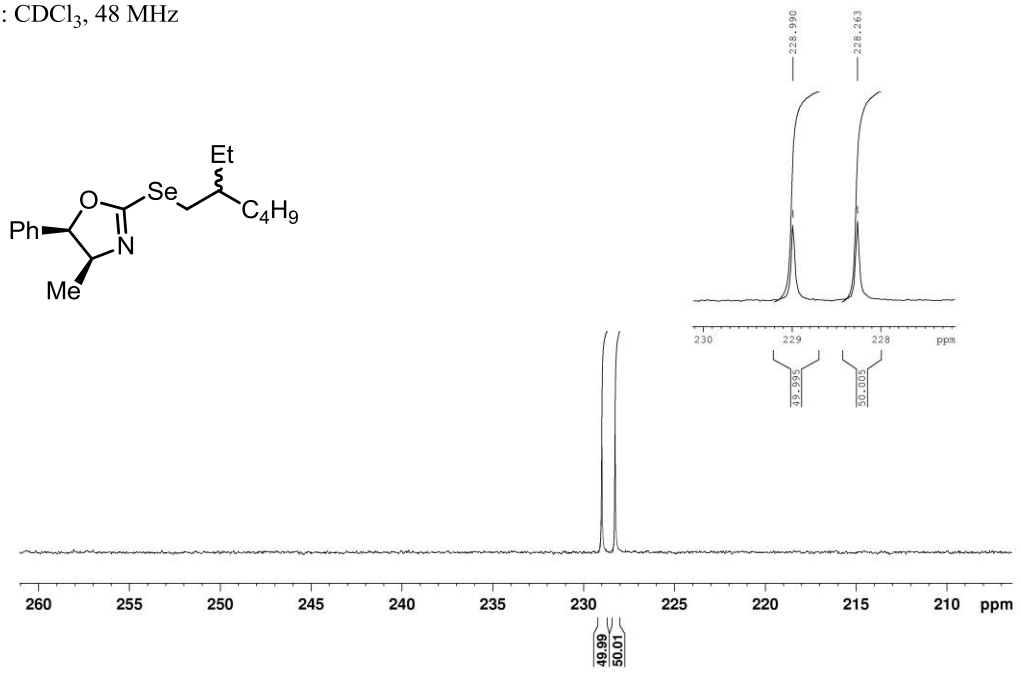
For ethylation of enamine **(*S*)-228**:



A.2 Measurement of Alkylation Enantioselectivity by ^{77}Se NMR

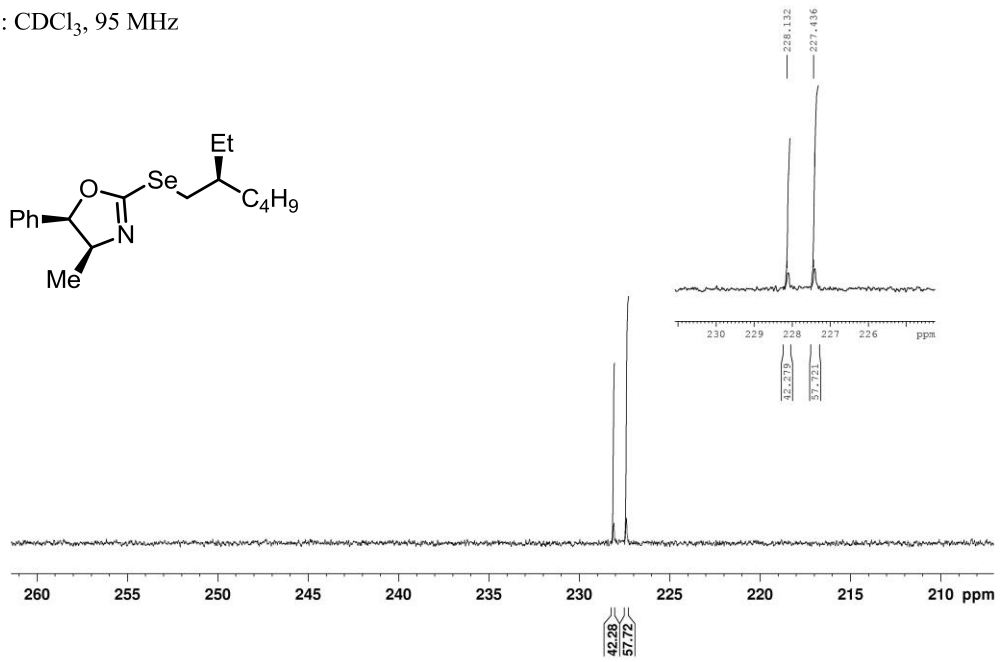
Selenide **(4*S*,5*R*,(±)$_\alpha$)-177** from ethylation of enamine **(±)-92:**

^{77}Se: $CDCl_3$, 48 MHz



Selenide **(4*S*,5*R*,*S*$_\alpha$)-177** from ethylation of enamine **(1*R*,*5S*)-92:**

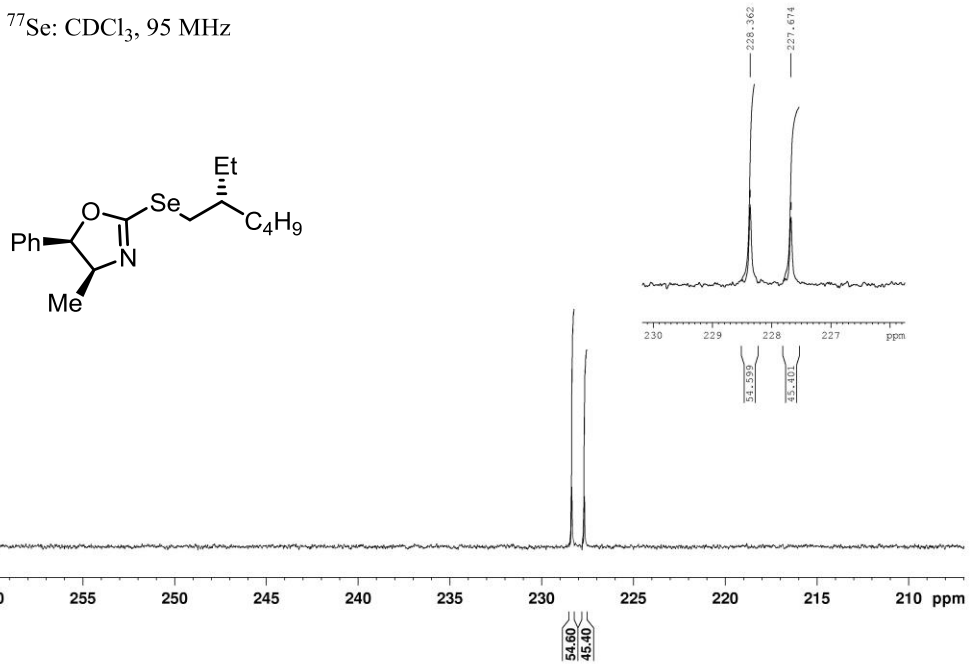
^{77}Se: $CDCl_3$, 95 MHz



A.2 Measurement of Alkylation Enantioselectivity by ^{77}Se NMR

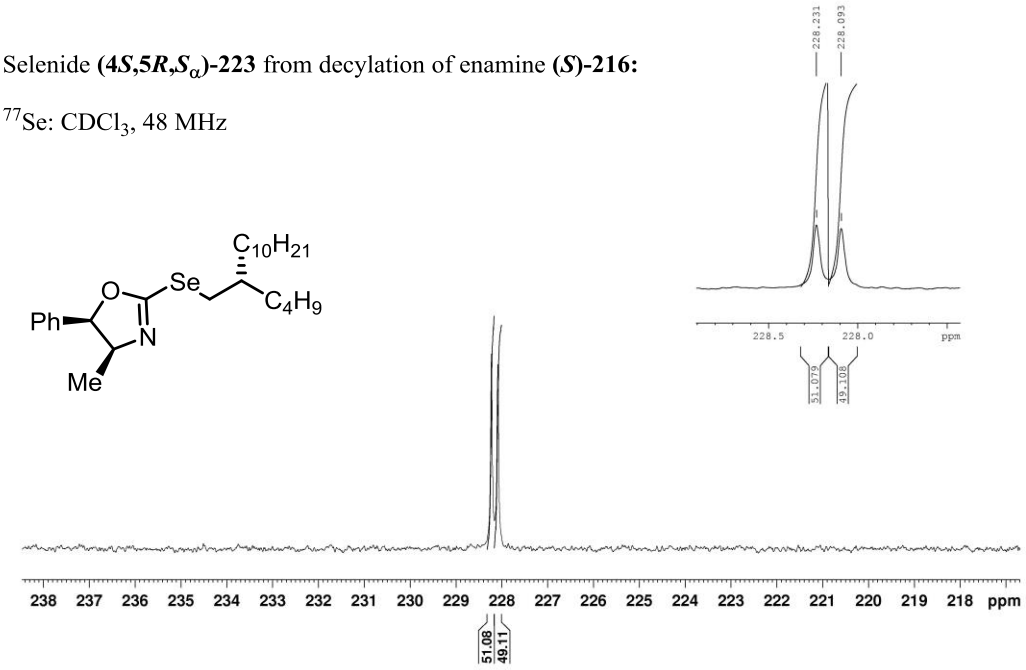
Selenide **(4*S*,5*R*,*R*$_\alpha$)-177** from Enamine **(1*S*,5*R*)-92:**

^{77}Se: $CDCl_3$, 95 MHz



Selenide **(4*S*,5*R*,*S*$_\alpha$)-223** from decylation of enamine **(*S*)-216:**

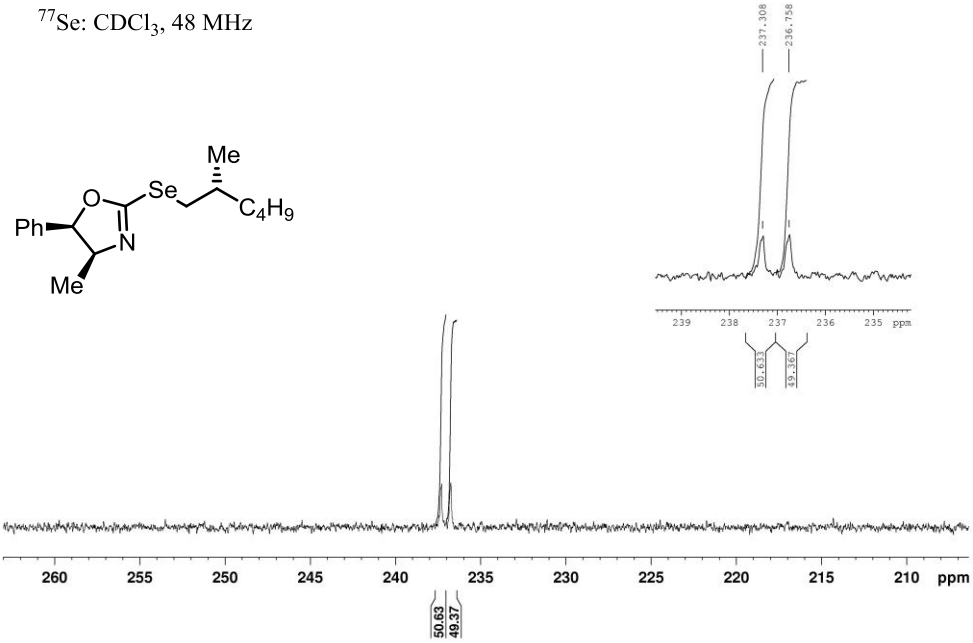
^{77}Se: $CDCl_3$, 48 MHz



A.2 Measurement of Alkylation Enantioselectivity by ^{77}Se NMR

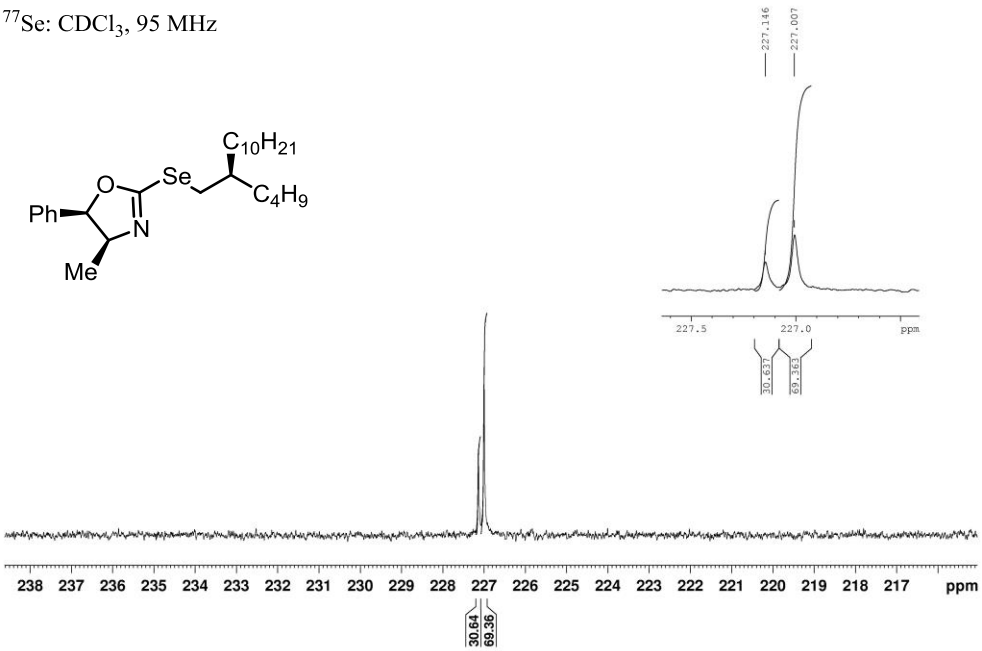
Selenide **(4*S*,5*R*,R_α)-227** from Enamine **(*S*)-216:**

^{77}Se: $CDCl_3$, 48 MHz



Selenide **(4*S*,5*R*,R_α)-223** from decylation of enamine **(1*S*,5*R*)-228:**

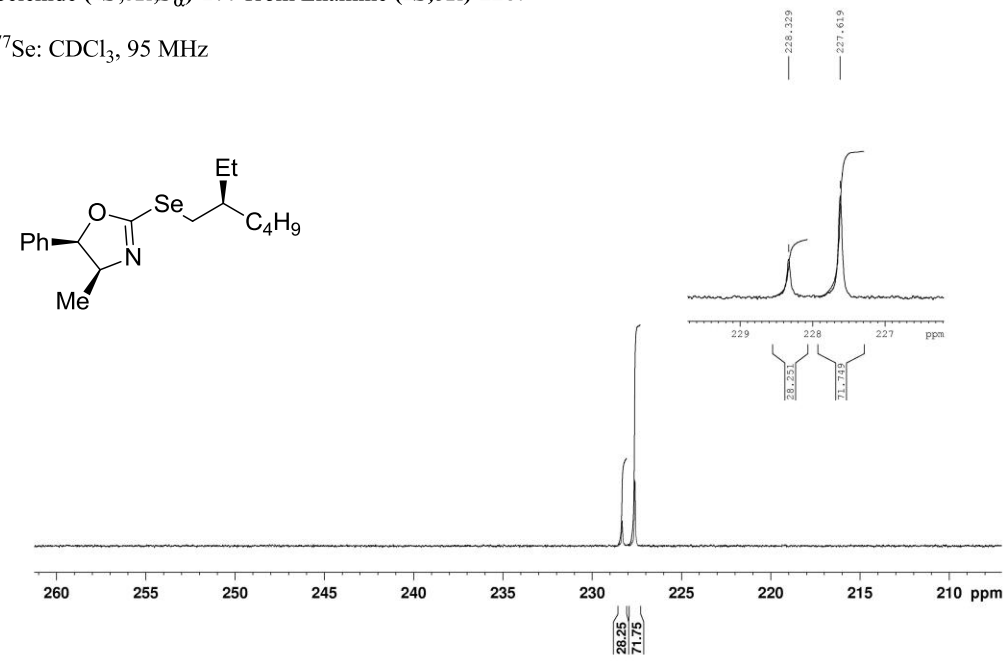
^{77}Se: $CDCl_3$, 95 MHz



A.2 Measurement of Alkylation Enantioselectivity by ^{77}Se NMR

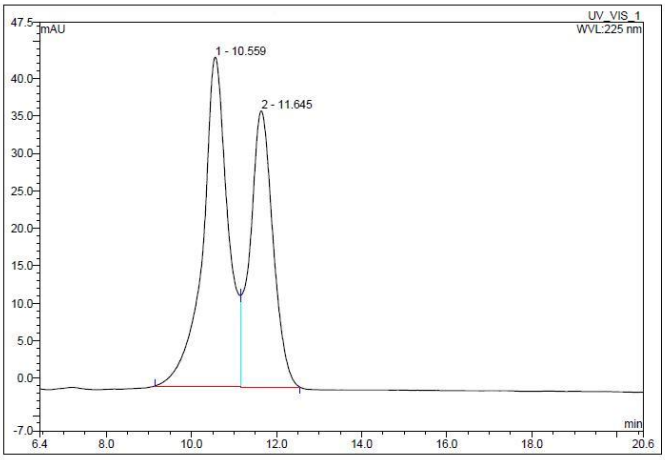
Selenide **(4*S*,5*R*,*S*$_\alpha$)-177** from Enamine **(1*S*,*5R*)-228:**

^{77}Se: $CDCl_3$, 95 MHz



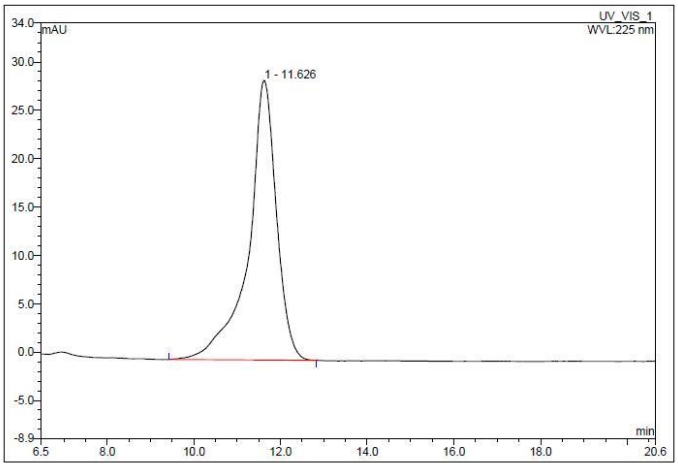
A.3 Measurement of Enantiopurity of Auxiliaries by HPLC

A.3.1 *Traces for Formamide **152***



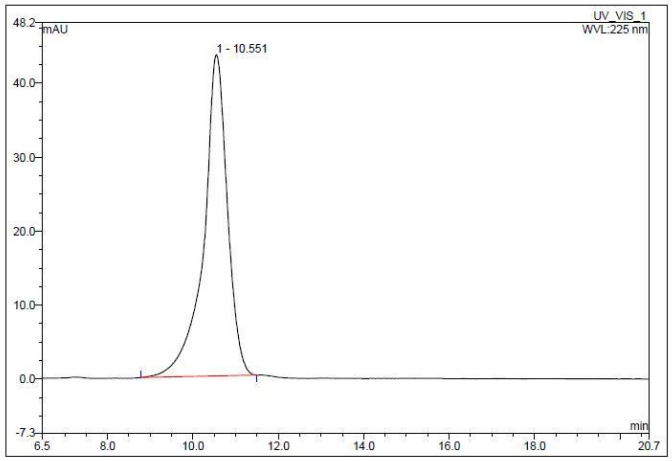
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.56	n.a.	43.891	29.766	56.45	n.a.	BM *
2	11.64	n.a.	36.873	22.966	43.55	n.a.	MB*
Total:			80.764	52.731	100.00	0.000	

Formamide (±)-152



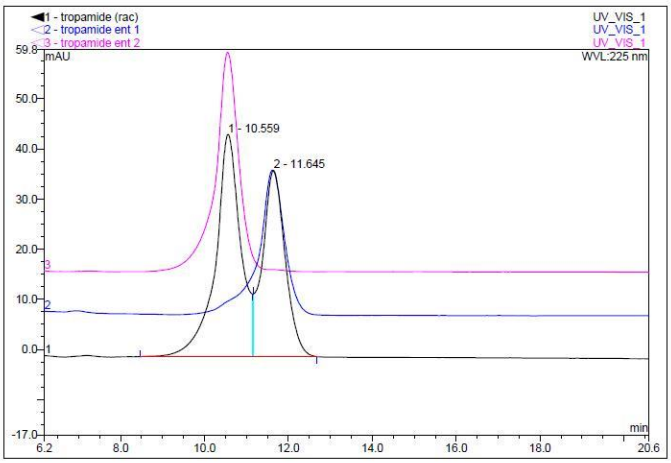
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.63	n.a.	28.900	21.573	100.00	n.a.	BMB*
Total:			28.900	21.573	100.00	0.000	

Formamide (+)-152



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.55	n.a.	43.413	27.869	100.00	n.a.	BMB*
Total:			43.413	27.869	100.00	0.000	

Formamide (–)-152



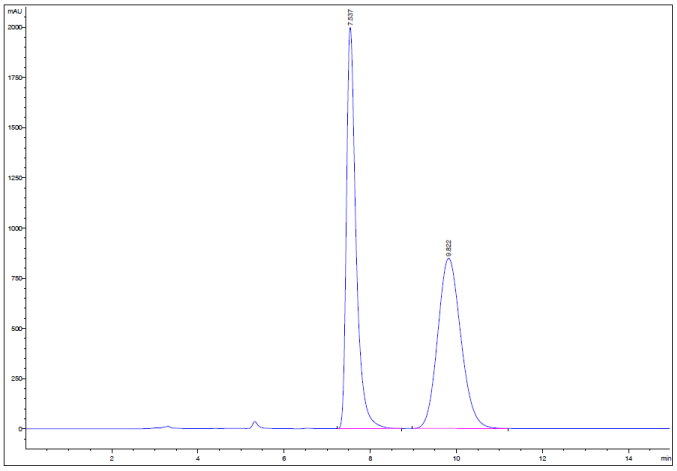
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.56	n.a.	44.290	30.660	56.78	n.a.	BM *
2	11.64	n.a.	37.128	23.337	43.22	n.a.	MB*
Total:			81.418	53.997	100.00	0.000	

Overlay of Racemate and Enantiopure Formamides

Conditions:

Chiral column: Chiralcel® OD; Eluent: 5% IPA in hexane; Flow rate: 1 mL min^{-1}; Detector: UV-Vis (λ=225 nm)

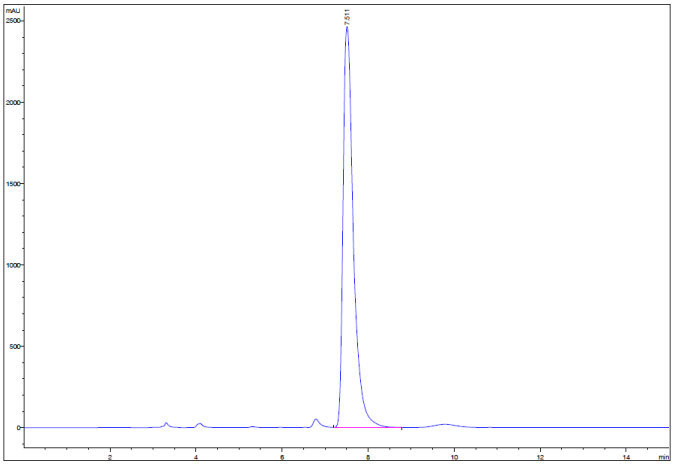
A.3.2 *Traces for Amide **215***



Signal : DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.537	BB	0.2323	3.08994e4	1999.59802	49.4236
2	9.822	BB	0.5789	3.16201e4	848.20856	50.5764
Totals :				6.25195e4	2847.80658	

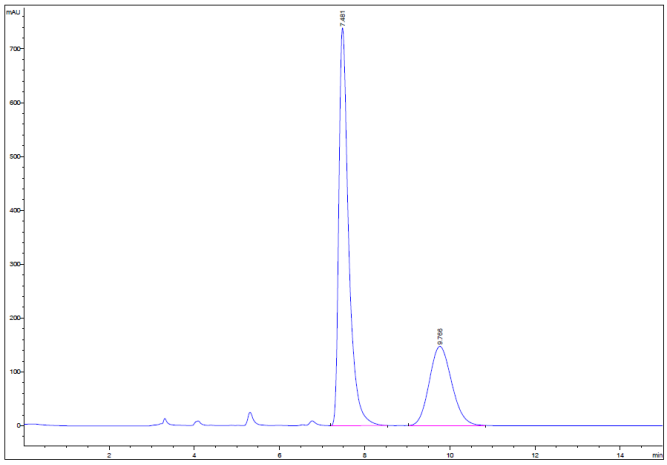
Amide (±)-215



Signal : DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.511	VB	0.2522	4.09924e4	2462.72290	100.0000
Totals :				4.09924e4	2462.72290	

Amide (+)-215



Signal : DAD1 D, Sig=230,16 Ref=360,100

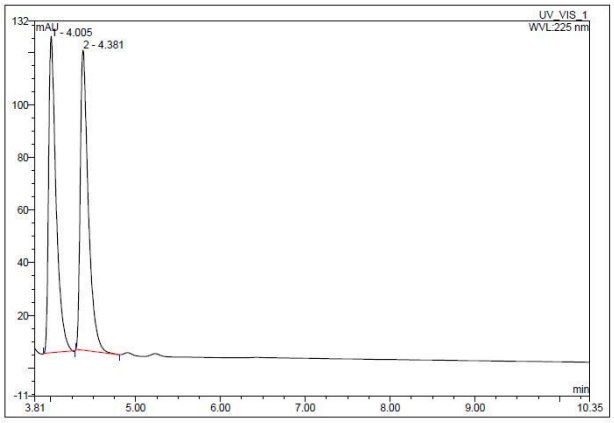
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.481	BB	0.2388	1.18279e4	738.75861	68.6854
2	9.766	BB	0.5697	5392.48389	147.11031	31.3146
Totals :				1.72204e4	885.86891	

Amide (±)-215 Spiked with Amide (+)-215

Conditions:

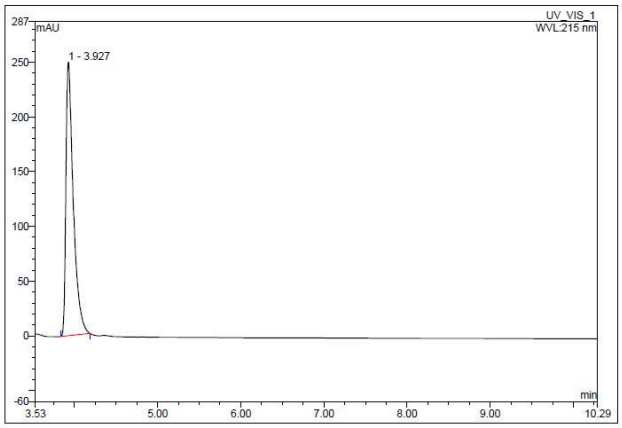
Chiral column: Chiralpak® AD-H; Eluent: 1% IPA in hexane; Flow rate: 1 mL min^{-1}; Detector: UV-Vis (λ= 211 and 230 nm)

A.3.3 *Traces for Homotropinone* ***256***



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.01	n.a.	120.134	12.280	49.47	n.a.	BMB*
2	4.38	n.a.	113.915	12.542	50.53	n.a.	BMB*
Total:			234.049	24.821	100.00	0.000	

Homotropinone (±)-256



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.93	n.a.	249.979	25.722	100.00	n.a.	BMB*
Total:			249.979	25.722	100.00	0.000	

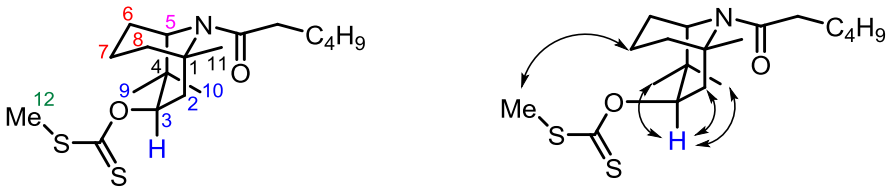
Homotropinone (–)-256

Conditions:

Chiral column: Chiralpak® AS-H; Eluent: 40% IPA in hexane; Flow rate: 1 mL min^{-1}; Detector: UV-Vis (λ=215 and 225 nm)

A.4 NOEs for Determining Facial Selectivity of Homotropinone Reductions

A.4.1 *For Xanthate* ***(1S,3R,5R)-304***



Irradiation of C3-H gave enhancements at C2-H_2 / C9-H_3 / C10-H_3

NOESY of C12-H_3 showed coupling to C7-$H_A$$H_B$

A.4.2 *For Xanthate* ***(1S,3R,5R)-306***

Irradiation of C3-H gave enhancements at C2-H_2 / C9-H_3 / C10-H_3

Irradiation of C10-H_3 gave enhancements at C3-H / C2-$H_A$$H_B$ / C5-H

Irradiation of C9-H_3 gave enhancements at C3-H / C5-H / C6-$H_A$$H_B$ / C7-$H_A$$H_B$ / C10-H_3 / C12-H_3

Irradiation of C7-H_2 and C8-H_2 gave no enhancement at C3-H and C7-$H_A$$H_B$ gave a weak enhancement at C12-H_3

A.5 X-Ray Data for Determining Absolute Configuration of Auxiliaries

A.5.1 *Single Crystal Diffraction Results For* ***(S,1R,5S)-164***

Table 1. Crystal data and structure refinement for **(*S*,1*R*,5*S*)-164**.

Identification code	6314	
Empirical formula	C19 H28 N2 O1	
Formula weight	300.44	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.3133(1) Å	α= 90°.
	b = 10.4410(1) Å	β= 90°.
	c = 18.1294(2) Å	γ = 90°.
Volume	1762.91(3) $Å^3$	
Z	4	
Density (calculated)	1.132 Mg/m^3	
Absorption coefficient	0.539 mm^{-1}	
F(000)	656	
Crystal size	0.060 x 0.050 x 0.040 mm^3	
Theta range for data collection	4.879 to 76.211°.	
Index ranges	-11<=h<=11, -13<=k<=12, -22<=l<=22	
Reflections collected	40256	
Independent reflections	3679 [R(int) = 0.034]	
Completeness to theta = 76.211°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.89	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3678 / 0 / 200	
Goodness-of-fit on F^2	0.9918	
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0827	
R indices (all data)	R1 = 0.0331, wR2 = 0.0855	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.14 and -0.13 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **(*S*,1*R*,5*S*)-164**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8962	2611	2788	40
C(2)	9269	3739	2917	29
N(3)	9211	4258	3596	30
C(4)	8671	3618	4278	36
C(5)	8931	2187	4330	43
C(6)	9525	4346	4882	48
C(7)	10090	5594	4524	48
C(8)	9266	5632	3785	36
C(9)	7715	6124	3816	48
C(10)	6777	5359	4353	59
C(11)	7063	3922	4309	51
C(12)	9840	6790	4997	71
C(13)	11690	5461	4359	67
C(14)	9854	4563	2281	31
N(15)	11321	4112	2137	51
C(16)	8873	4431	1608	36
C(17)	7426	5036	1731	37
C(18)	7259	6359	1709	42
C(19)	5926	6925	1833	53
C(20)	4752	6178	1990	68
C(21)	4911	4871	2022	78
C(22)	6237	4297	1889	57

Table 3. Bond lengths [Å] and angles [°] for **(*S*,1*R*,5*S*)-164**.

O(1)-C(2)	1.234	C(10)-H(101)	0.983
C(2)-N(3)	1.345	C(10)-H(102)	0.989
C(2)-C(14)	1.538	C(11)-H(111)	0.962
N(3)-C(4)	1.494	C(11)-H(112)	0.978
N(3)-C(8)	1.476	C(12)-H(121)	1.011
C(4)-C(5)	1.516	C(12)-H(122)	0.968
C(4)-C(6)	1.551	C(12)-H(123)	0.968
C(4)-C(11)	1.531	C(13)-H(131)	0.976
C(5)-H(51)	1.007	C(13)-H(132)	0.984
C(5)-H(52)	0.979	C(13)-H(133)	0.998
C(5)-H(53)	1.007	C(14)-N(15)	1.469
C(6)-C(7)	1.548	C(14)-C(16)	1.531
C(6)-H(61)	0.964	C(14)-H(141)	0.968
C(6)-H(62)	0.999	N(15)-H(151)	0.858
C(7)-C(8)	1.544	N(15)-H(152)	0.894
C(7)-C(12)	1.533	C(16)-C(17)	1.505
C(7)-C(13)	1.526	C(16)-H(161)	0.989
C(8)-C(9)	1.534	C(16)-H(162)	0.972
C(8)-H(81)	0.974	C(17)-C(18)	1.391
C(9)-C(10)	1.533	C(17)-C(22)	1.380
C(9)-H(91)	1.025	C(18)-C(19)	1.393
C(9)-H(92)	0.985	C(18)-H(181)	0.980
C(10)-C(11)	1.526	C(19)-C(20)	1.373

C(19)-H(191)	0.935	C(11)-C(10)-H(102)	113.6
C(20)-C(21)	1.374	H(101)-C(10)-H(102)	107.9
C(20)-H(201)	0.923	C(4)-C(11)-C(10)	112.128
C(21)-C(22)	1.394	C(4)-C(11)-H(111)	108.7
C(21)-H(211)	0.947	C(10)-C(11)-H(111)	110.1
C(22)-H(221)	0.966	C(4)-C(11)-H(112)	108.1
		C(10)-C(11)-H(112)	108.4
O(1)-C(2)-N(3)	123.277	H(111)-C(11)-H(112)	109.5
O(1)-C(2)-C(14)	118.284	C(7)-C(12)-H(121)	108.8
N(3)-C(2)-C(14)	118.275	C(7)-C(12)-H(122)	108.6
C(2)-N(3)-C(4)	126.183	H(121)-C(12)-H(122)	109.3
C(2)-N(3)-C(8)	127.132	C(7)-C(12)-H(123)	111.8
C(4)-N(3)-C(8)	104.670	H(121)-C(12)-H(123)	108.9
N(3)-C(4)-C(5)	115.977	H(122)-C(12)-H(123)	109.4
N(3)-C(4)-C(6)	101.068	C(7)-C(13)-H(131)	113.2
C(5)-C(4)-C(6)	110.928	C(7)-C(13)-H(132)	111.9
N(3)-C(4)-C(11)	105.442	H(131)-C(13)-H(132)	107.6
C(5)-C(4)-C(11)	111.017	C(7)-C(13)-H(133)	109.9
C(6)-C(4)-C(11)	111.982	H(131)-C(13)-H(133)	104.7
C(4)-C(5)-H(51)	105.4	H(132)-C(13)-H(133)	109.1
C(4)-C(5)-H(52)	111.7	C(2)-C(14)-N(15)	106.470
H(51)-C(5)-H(52)	109.5	C(2)-C(14)-C(16)	109.602
C(4)-C(5)-H(53)	110.3	N(15)-C(14)-C(16)	112.628
H(51)-C(5)-H(53)	109.9	C(2)-C(14)-H(141)	112.7
H(52)-C(5)-H(53)	110.0	N(15)-C(14)-H(141)	107.5
C(4)-C(6)-C(7)	106.950	C(16)-C(14)-H(141)	108.0
C(4)-C(6)-H(61)	109.0	C(14)-N(15)-H(151)	113.3
C(7)-C(6)-H(61)	110.7	C(14)-N(15)-H(152)	111.2
C(4)-C(6)-H(62)	109.5	H(151)-N(15)-H(152)	111.2
C(7)-C(6)-H(62)	111.6	C(14)-C(16)-C(17)	112.232
H(61)-C(6)-H(62)	109.1	C(14)-C(16)-H(161)	107.6
C(6)-C(7)-C(8)	102.473	C(17)-C(16)-H(161)	109.9
C(6)-C(7)-C(12)	113.547	C(14)-C(16)-H(162)	107.6
C(8)-C(7)-C(12)	112.885	C(17)-C(16)-H(162)	109.8
C(6)-C(7)-C(13)	109.738	H(161)-C(16)-H(162)	109.6
C(8)-C(7)-C(13)	108.525	C(16)-C(17)-C(18)	120.881
C(12)-C(7)-C(13)	109.407	C(16)-C(17)-C(22)	120.934
C(7)-C(8)-N(3)	101.200	C(18)-C(17)-C(22)	118.160
C(7)-C(8)-C(9)	116.468	C(17)-C(18)-C(19)	121.111
N(3)-C(8)-C(9)	107.528	C(17)-C(18)-H(181)	118.1
C(7)-C(8)-H(81)	109.3	C(19)-C(18)-H(181)	120.8
N(3)-C(8)-H(81)	111.0	C(18)-C(19)-C(20)	120.118
C(9)-C(8)-H(81)	110.8	C(18)-C(19)-H(191)	119.1
C(8)-C(9)-C(10)	112.659	C(20)-C(19)-H(191)	120.7
C(8)-C(9)-H(91)	109.0	C(19)-C(20)-C(21)	119.155
C(10)-C(9)-H(91)	111.2	C(19)-C(20)-H(201)	121.6
C(8)-C(9)-H(92)	107.1	C(21)-C(20)-H(201)	119.2
C(10)-C(9)-H(92)	110.9	C(20)-C(21)-C(22)	121.055
H(91)-C(9)-H(92)	105.7	C(20)-C(21)-H(211)	118.7
C(9)-C(10)-C(11)	112.255	C(22)-C(21)-H(211)	120.2
C(9)-C(10)-H(101)	109.4	C(21)-C(22)-C(17)	120.390
C(11)-C(10)-H(101)	108.6	C(21)-C(22)-H(221)	121.8
C(9)-C(10)-H(102)	104.9	C(17)-C(22)-H(221)	117.8

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(*S*,1*R*,5*S*)-164**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	49	30	40	-4	-3	-4
C(2)	24	29	35	-2	-2	2
N(3)	32	26	32	-1	4	-2
C(4)	41	32	34	1	6	-5
C(5)	53	33	43	6	3	-6
C(6)	73	38	34	2	-3	-13
C(7)	68	36	39	0	-7	-16
C(8)	48	27	33	-2	6	-3
C(9)	59	37	47	-4	11	13
C(10)	55	51	71	-4	26	9
C(11)	43	46	62	0	21	-4
C(12)	128	44	42	-8	-5	-27
C(13)	61	62	77	8	-20	-25
C(14)	28	33	33	-2	1	2
N(15)	30	63	60	13	12	6
C(16)	39	39	29	-4	1	2
C(17)	36	49	28	1	-6	1
C(18)	40	49	38	-6	-4	4
C(19)	49	62	48	-3	-7	18
C(20)	36	100	68	21	-3	21
C(21)	32	99	105	44	-5	0
C(22)	38	62	70	24	-11	-3

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(*S*,1*R*,5*S*)-164**.

	x	y	z	U(eq)
H(51)	8725	1955	4858	63
H(52)	8289	1707	4004	61
H(53)	9961	1984	4208	62
H(61)	8891	4537	5287	58
H(62)	10328	3795	5063	58
H(81)	9824	6110	3424	42
H(91)	7724	7078	3948	56
H(92)	7329	6075	3311	55
H(101)	6967	5647	4860	70
H(102)	5780	5598	4227	70
H(111)	6610	3569	3877	61
H(112)	6665	3517	4750	59
H(121)	8793	6825	5143	104
H(122)	10424	6725	5437	105
H(123)	10084	7567	4735	104
H(131)	12274	5341	4801	99
H(132)	11888	4740	4025	98
H(133)	12059	6268	4132	98
H(141)	9912	5462	2407	33

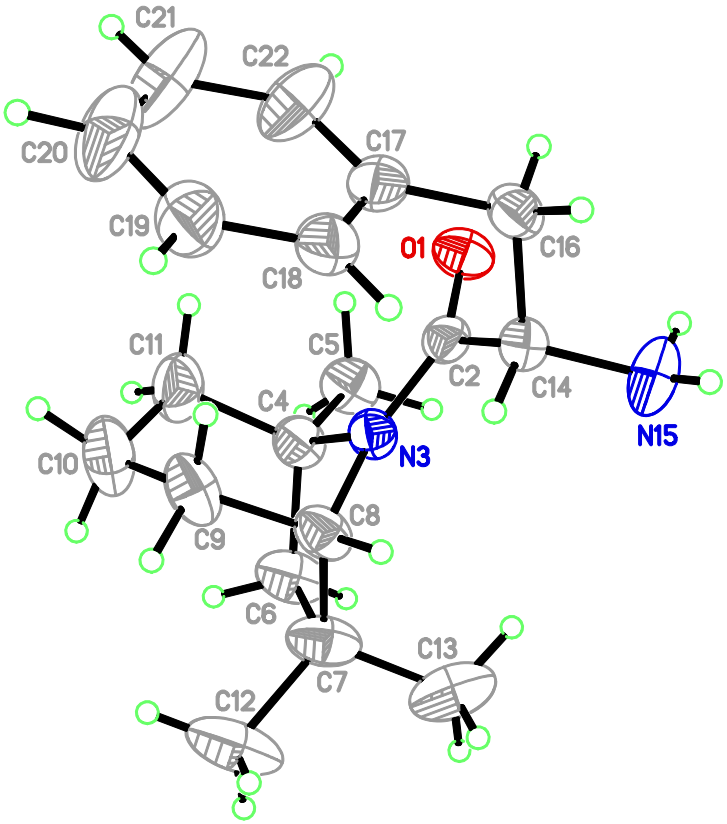
H(151)	11739	4518	1787	65
H(152)	11338	3267	2059	64
H(161)	8758	3506	1506	43
H(162)	9351	4841	1194	43
H(181)	8105	6884	1602	49
H(191)	5839	7815	1792	62
H(201)	3854	6531	2061	82
H(211)	4104	4363	2145	95
H(221)	6361	3378	1905	69

Table 6. Hydrogen bonds for **(*S*,1*R*,5*S*)-164** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(14)#1-H(141)...O(1)#2	0.97	2.50	3.371(2)	149

Symmetry transformations used to generate equivalent atoms:

#1 _____ #2 -x+2,y+1/2,-z+1/2



A.5.2 *Single Crystal Diffraction Results For* ***(R,S)-220***

Table 1. Crystal data and structure refinement for **(*R*,*S*)-220**.

Identification code	6379	
Empirical formula	C23 H36 N2 O3	
Formula weight	388.55	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Tetragonal	
Space group	P 41 21 2	
Unit cell dimensions	a = 10.39650(10) Å	α= 90°.
	b = 10.39650(10) Å	β= 90°.
	c = 42.82080(10) Å	γ = 90°.
Volume	4628.38(6) $Å^3$	
Z	8	
Density (calculated)	1.115 Mg/m^3	
Absorption coefficient	0.579 mm^{-1}	
F(000)	1696	
Crystal size	0.260 x 0.190 x 0.030 mm^3	
Theta range for data collection	4.130 to 76.609°.	
Index ranges	-13<=h<=13, -13<=k<=13, -53<=l<=53	
Reflections collected	180066	
Independent reflections	4867 [R(int) = 0.030]	
Completeness to theta = 76.609°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.79	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4864 / 0 / 254	
Goodness-of-fit on F^2	1.0083	
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0731	
R indices (all data)	R1 = 0.0281, wR2 = 0.0737	
Absolute structure parameter	-0.01(13)	
Largest diff. peak and hole	0.14 and -0.16 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **(*R*,*S*)-220**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4641(1)	6055(1)	3974(1)	34
C(2)	4264(1)	6139(1)	4244(1)	25
O(3)	3171(1)	6722(1)	4336(1)	30
C(4)	2329(1)	7389(1)	4112(1)	28
C(5)	1255(1)	7884(1)	4319(1)	41
C(6)	3038(1)	8497(1)	3959(1)	42
C(7)	1799(1)	6457(1)	3873(1)	44
N(8)	4877(1)	5645(1)	4494(1)	27
C(9)	6115(1)	5009(1)	4462(1)	25
C(10)	6019(1)	3680(1)	4617(1)	27
O(11)	5976(1)	3623(1)	4904(1)	38
N(12)	6008(1)	2623(1)	4436(1)	25
C(13)	5934(1)	1298(1)	4575(1)	30
C(14)	5937(1)	456(1)	4282(1)	32
C(15)	5238(1)	1271(1)	4040(1)	29
C(16)	5802(1)	2612(1)	4093(1)	24
C(17)	7048(1)	2810(1)	3904(1)	26
C(18)	6776(1)	2764(1)	3558(1)	26
C(19)	7297(1)	1796(1)	3371(1)	31
C(20)	7003(1)	1720(1)	3055(1)	40
C(21)	6183(1)	2612(1)	2922(1)	43
C(22)	5670(1)	3588(1)	3103(1)	39
C(23)	5958(1)	3663(1)	3420(1)	31
C(24)	4675(1)	1116(1)	4754(1)	42
C(25)	7092(1)	1034(1)	4783(1)	42
C(26)	7238(1)	5757(1)	4613(1)	31
C(27)	8508(1)	5077(1)	4544(1)	45
C(28)	7278(1)	7147(1)	4502(1)	44

Table 3. Bond lengths [Å] and angles [°] for **(*R*,*S*)-220**.

O(1)-C(2)	1.2200(11)	N(8)-C(9)	1.4535(12)
C(2)-O(3)	1.3475(11)	N(8)-H(81)	0.906
C(2)-N(8)	1.3508(12)	C(9)-C(10)	1.5358(13)
O(3)-C(4)	1.4735(11)	C(9)-C(26)	1.5443(13)
C(4)-C(5)	1.5155(15)	C(9)-H(91)	0.990
C(4)-C(6)	1.5155(14)	C(10)-O(11)	1.2339(11)
C(4)-C(7)	1.5121(14)	C(10)-N(12)	1.3431(12)
C(5)-H(51)	0.984	N(12)-C(13)	1.5023(12)
C(5)-H(52)	0.990	N(12)-C(16)	1.4866(11)
C(5)-H(53)	0.968	C(13)-C(14)	1.5312(14)
C(6)-H(61)	0.982	C(13)-C(24)	1.5282(15)
C(6)-H(62)	0.933	C(13)-C(25)	1.5214(15)
C(6)-H(63)	0.988	C(14)-C(15)	1.5231(13)
C(7)-H(71)	0.984	C(14)-H(141)	0.994
C(7)-H(72)	0.937	C(14)-H(142)	0.975
C(7)-H(73)	0.994	C(15)-C(16)	1.5304(13)

C(15)-H(151)	0.974	C(4)-C(7)-H(71)	108.5
C(15)-H(152)	0.986	C(4)-C(7)-H(72)	111.4
C(16)-C(17)	1.5404(12)	H(71)-C(7)-H(72)	108.8
C(16)-H(161)	0.989	C(4)-C(7)-H(73)	110.3
C(17)-C(18)	1.5121(12)	H(71)-C(7)-H(73)	110.1
C(17)-H(172)	0.992	H(72)-C(7)-H(73)	107.7
C(17)-H(171)	0.999	C(2)-N(8)-C(9)	120.95(8)
C(18)-C(19)	1.3944(14)	C(2)-N(8)-H(81)	121.3
C(18)-C(23)	1.3938(14)	C(9)-N(8)-H(81)	117.4
C(19)-C(20)	1.3905(14)	N(8)-C(9)-C(10)	108.06(8)
C(19)-H(191)	1.000	N(8)-C(9)-C(26)	113.60(8)
C(20)-C(21)	1.3824(19)	C(10)-C(9)-C(26)	108.74(8)
C(20)-H(201)	0.985	N(8)-C(9)-H(91)	107.8
C(21)-C(22)	1.3846(18)	C(10)-C(9)-H(91)	111.5
C(21)-H(211)	0.999	C(26)-C(9)-H(91)	107.3
C(22)-C(23)	1.3916(14)	C(9)-C(10)-O(11)	118.44(8)
C(22)-H(221)	0.957	C(9)-C(10)-N(12)	119.30(7)
C(23)-H(231)	0.949	O(11)-C(10)-N(12)	122.25(9)
C(24)-H(243)	0.996	C(10)-N(12)-C(13)	121.61(7)
C(24)-H(241)	0.985	C(10)-N(12)-C(16)	125.14(8)
C(24)-H(242)	0.938	C(13)-N(12)-C(16)	112.16(7)
C(25)-H(251)	0.980	N(12)-C(13)-C(14)	101.49(7)
C(25)-H(252)	0.964	N(12)-C(13)-C(24)	110.79(8)
C(25)-H(253)	0.959	C(14)-C(13)-C(24)	110.05(9)
C(26)-C(27)	1.5265(15)	N(12)-C(13)-C(25)	110.84(9)
C(26)-C(28)	1.5208(15)	C(14)-C(13)-C(25)	111.97(9)
C(26)-H(261)	1.027	C(24)-C(13)-C(25)	111.32(8)
C(27)-H(272)	0.982	C(13)-C(14)-C(15)	103.89(8)
C(27)-H(271)	0.981	C(13)-C(14)-H(141)	110.5
C(27)-H(273)	0.977	C(15)-C(14)-H(141)	109.7
C(28)-H(282)	1.012	C(13)-C(14)-H(142)	112.4
C(28)-H(283)	0.970	C(15)-C(14)-H(142)	113.7
C(28)-H(281)	0.971	H(141)-C(14)-H(142)	106.7
		C(14)-C(15)-C(16)	102.83(8)
O(1)-C(2)-O(3)	125.53(8)	C(14)-C(15)-H(151)	112.7
O(1)-C(2)-N(8)	124.90(9)	C(16)-C(15)-H(151)	109.5
O(3)-C(2)-N(8)	109.56(8)	C(14)-C(15)-H(152)	114.8
C(2)-O(3)-C(4)	121.38(7)	C(16)-C(15)-H(152)	110.0
O(3)-C(4)-C(5)	102.46(7)	H(151)-C(15)-H(152)	106.9
O(3)-C(4)-C(6)	110.44(8)	C(15)-C(16)-N(12)	102.09(7)
C(5)-C(4)-C(6)	110.63(9)	C(15)-C(16)-C(17)	111.45(7)
O(3)-C(4)-C(7)	110.86(8)	N(12)-C(16)-C(17)	113.39(7)
C(5)-C(4)-C(7)	110.15(9)	C(15)-C(16)-H(161)	110.6
C(6)-C(4)-C(7)	111.92(9)	N(12)-C(16)-H(161)	111.0
C(4)-C(5)-H(51)	107.7	C(17)-C(16)-H(161)	108.3
C(4)-C(5)-H(52)	110.1	C(16)-C(17)-C(18)	110.66(7)
H(51)-C(5)-H(52)	109.9	C(16)-C(17)-H(172)	110.8
C(4)-C(5)-H(53)	109.8	C(18)-C(17)-H(172)	109.1
H(51)-C(5)-H(53)	110.3	C(16)-C(17)-H(171)	109.9
H(52)-C(5)-H(53)	109.0	C(18)-C(17)-H(171)	109.6
C(4)-C(6)-H(61)	109.9	H(172)-C(17)-H(171)	106.7
C(4)-C(6)-H(62)	111.6	C(17)-C(18)-C(19)	120.80(9)
H(61)-C(6)-H(62)	107.4	C(17)-C(18)-C(23)	120.54(9)
C(4)-C(6)-H(63)	112.3	C(19)-C(18)-C(23)	118.62(9)
H(61)-C(6)-H(63)	108.8	C(18)-C(19)-C(20)	120.84(10)
H(62)-C(6)-H(63)	106.7	C(18)-C(19)-H(191)	117.7

C(20)-C(19)-H(191)	121.4	C(13)-C(25)-H(253)	114.8
C(19)-C(20)-C(21)	119.97(10)	H(251)-C(25)-H(253)	106.6
C(19)-C(20)-H(201)	120.7	H(252)-C(25)-H(253)	105.4
C(21)-C(20)-H(201)	119.3	C(9)-C(26)-C(27)	109.86(8)
C(20)-C(21)-C(22)	119.84(9)	C(9)-C(26)-C(28)	111.62(9)
C(20)-C(21)-H(211)	120.0	C(27)-C(26)-C(28)	110.91(10)
C(22)-C(21)-H(211)	120.1	C(9)-C(26)-H(261)	105.5
C(21)-C(22)-C(23)	120.32(11)	C(27)-C(26)-H(261)	108.1
C(21)-C(22)-H(221)	120.5	C(28)-C(26)-H(261)	110.7
C(23)-C(22)-H(221)	119.2	C(26)-C(27)-H(272)	107.3
C(18)-C(23)-C(22)	120.40(10)	C(26)-C(27)-H(271)	109.0
C(18)-C(23)-H(231)	118.6	H(272)-C(27)-H(271)	105.8
C(22)-C(23)-H(231)	121.0	C(26)-C(27)-H(273)	111.2
C(13)-C(24)-H(243)	111.4	H(272)-C(27)-H(273)	112.0
C(13)-C(24)-H(241)	111.1	H(271)-C(27)-H(273)	111.4
H(243)-C(24)-H(241)	104.1	C(26)-C(28)-H(282)	108.9
C(13)-C(24)-H(242)	114.1	C(26)-C(28)-H(283)	109.5
H(243)-C(24)-H(242)	108.3	H(282)-C(28)-H(283)	109.1
H(241)-C(24)-H(242)	107.4	C(26)-C(28)-H(281)	110.4
C(13)-C(25)-H(251)	112.6	H(282)-C(28)-H(281)	108.9
C(13)-C(25)-H(252)	111.9	H(283)-C(28)-H(281)	109.9
H(251)-C(25)-H(252)	104.8		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(*R*,*S*)-220**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	39(1)	41(1)	21(1)	3(1)	1(1)	9(1)
C(2)	28(1)	24(1)	23(1)	0(1)	-1(1)	1(1)
O(3)	30(1)	37(1)	24(1)	2(1)	-2(1)	9(1)
C(4)	27(1)	26(1)	30(1)	5(1)	-4(1)	1(1)
C(5)	34(1)	45(1)	44(1)	9(1)	3(1)	11(1)
C(6)	36(1)	32(1)	57(1)	12(1)	3(1)	-1(1)
C(7)	45(1)	37(1)	51(1)	-3(1)	-22(1)	2(1)
N(8)	30(1)	32(1)	19(1)	0(1)	1(1)	8(1)
C(9)	30(1)	25(1)	19(1)	-1(1)	0(1)	5(1)
C(10)	31(1)	28(1)	22(1)	0(1)	1(1)	6(1)
O(11)	62(1)	33(1)	18(1)	0(1)	3(1)	9(1)
N(12)	32(1)	24(1)	19(1)	2(1)	3(1)	4(1)
C(13)	39(1)	25(1)	26(1)	4(1)	5(1)	6(1)
C(14)	39(1)	25(1)	31(1)	1(1)	3(1)	4(1)
C(15)	32(1)	26(1)	28(1)	0(1)	2(1)	-2(1)
C(16)	25(1)	25(1)	20(1)	-1(1)	1(1)	2(1)
C(17)	26(1)	30(1)	23(1)	-2(1)	2(1)	-1(1)
C(18)	28(1)	27(1)	22(1)	-1(1)	4(1)	-7(1)
C(19)	34(1)	32(1)	27(1)	-3(1)	5(1)	-4(1)
C(20)	51(1)	41(1)	28(1)	-9(1)	7(1)	-7(1)
C(21)	57(1)	48(1)	23(1)	-2(1)	-2(1)	-15(1)
C(22)	47(1)	37(1)	33(1)	6(1)	-9(1)	-7(1)
C(23)	38(1)	28(1)	29(1)	0(1)	0(1)	-3(1)
C(24)	51(1)	38(1)	37(1)	9(1)	17(1)	2(1)

C(25)	54(1)	39(1)	32(1)	4(1)	-8(1)	13(1)
C(26)	36(1)	31(1)	27(1)	-2(1)	-5(1)	2(1)
C(27)	33(1)	51(1)	52(1)	-9(1)	-10(1)	3(1)
C(28)	54(1)	33(1)	46(1)	2(1)	-8(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(*R*,*S*)-220**.

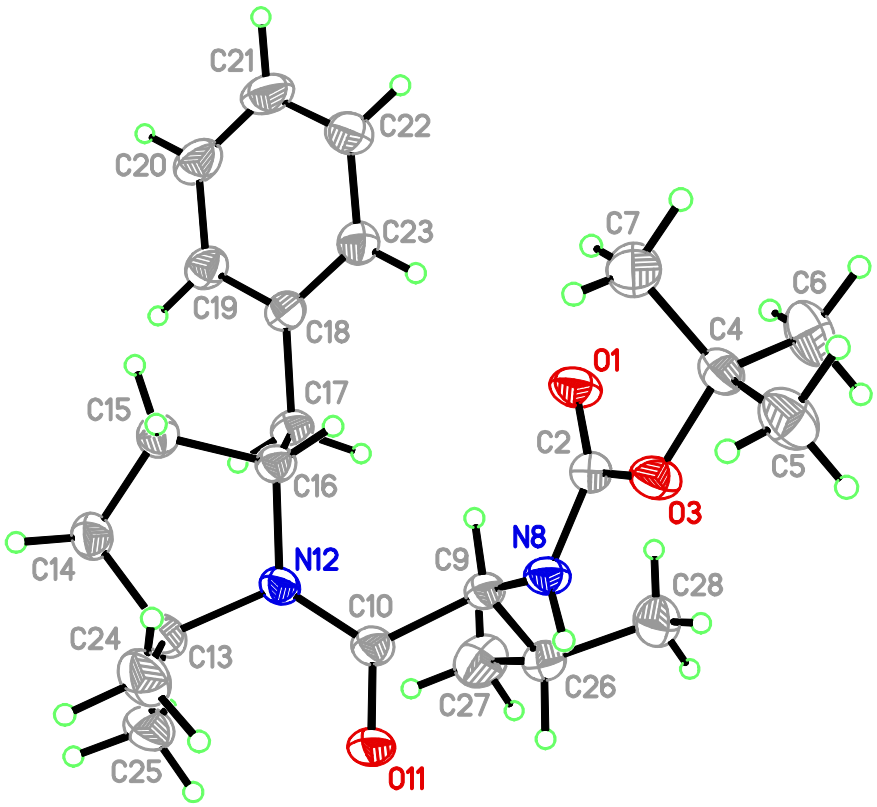
	x	y	z	U(eq)
H(51)	630	8329	4184	61
H(52)	1604	8488	4476	62
H(53)	848	7171	4425	61
H(61)	2448	8984	3825	63
H(62)	3366	9068	4107	64
H(63)	3775	8203	3832	64
H(71)	1180	6917	3740	65
H(72)	1377	5765	3969	65
H(73)	2507	6099	3744	65
H(91)	6305	4937	4236	29
H(141)	6834	290	4211	39
H(142)	5542	-382	4317	39
H(151)	4311	1295	4073	32
H(152)	5377	1004	3821	33
H(161)	5179	3284	4030	26
H(172)	7452	3648	3956	31
H(171)	7687	2129	3960	31
H(191)	7881	1157	3473	36
H(201)	7380	1042	2923	48
H(211)	5967	2556	2695	49
H(221)	5093	4203	3014	47
H(231)	5606	4323	3547	37
H(243)	4624	245	4850	63
H(241)	4623	1709	4933	62
H(242)	3934	1243	4633	63
H(251)	7124	141	4856	60
H(252)	7074	1544	4970	61
H(253)	7909	1209	4688	61
H(261)	7076	5714	4849	36
H(272)	9176	5508	4668	65
H(271)	8462	4194	4625	65
H(273)	8703	5090	4321	65
H(282)	8009	7606	4612	66
H(283)	6473	7569	4554	66
H(281)	7420	7183	4278	66
H(81)	4574	5766	4691	33

Table 6. Hydrogen bonds for **(*R*,*S*)-220** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(8)-H(81)...O(11)#1	0.906	2.008	2.9067(15)	170.79

Symmetry transformations used to generate equivalent atoms:

#1 y,x,-z+1



A.5.3 *Single Crystal Diffraction Results For* ***(1S,5R)-256***

Initially, data were collected on a single crystal using copper radiation at 150 K. However, due to cooling difficulties the data collection was contaminated with diffraction from ice. Best efforts were made to reduce the impact this had on the reduced data, however, although the connectivity was not in question, the refined value of the Flack x parameter[186] was 0.228(263) which improved to 0.058(27) with the application of Friedel difference restraints.[187] Bayesian analysis of the Friedel pairs for the unrestrained refinement gave a Hooft y parameter[188] of 0.364(126) and probabilities of:

P2(correct) 0.9998
P3(correct) 0.0270
P3(racemic) 0.9729

Data were re-collected at 150 K and 100 K and the results for all three datasets are given below:

	1	2	3
Flack x	0.228(263)	0.041(193)	0.007(209)
Flack x (restrained)	0.058(27)	0.013(16)	0.057(15)
Hooft y	0.364(126)	0.031(47)	0.082(64)
P2(correct)	0.9998	1.000	1.000
P3(correct)	0.0270	>0.999	>0.999
P3(racemic)	0.9729	0.144x10^-21	0.198x10^-8

Although none of these results is 100% conclusive alone,[189] the combination of all three together make a compelling case that the absolute configuration of the bulk sample is as presented. The results for the second and third data-sets are included in the CIF; the numbering scheme is the same for both.

Table 1. Crystal data and structure refinement for **(1*S*,5*R*)-256-1**.

Identification code	6441-1	
Empirical formula	C11 H19 N1 O1	
Formula weight	181.28	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.9051(1) Å	α= 90°.
	b = 8.2653(3) Å	β= 90°.
	c = 21.5096(7) Å	γ = 90°.
Volume	1049.83(5) $Å^3$	
Z	4	
Density (calculated)	1.147 Mg/m^3	
Absorption coefficient	0.563 mm^{-1}	
F(000)	400	
Crystal size	0.19 x 0.18 x 0.02 mm^3	
Theta range for data collection	4.110 to 77.332°.	
Index ranges	-7<=h<=7, -10<=k<=10, -26<=l<=27	
Reflections collected	30705	
Independent reflections	2211 [R(int) = 0.046]	
Completeness to theta = 75.785°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.55	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2204 / 0 / 119	
Goodness-of-fit on F^2	1.0324	
Final R indices [I>2sigma(I)]	R1 = 0.0318, wR2 = 0.0755	
R indices (all data)	R1 = 0.0338, wR2 = 0.0765	
Absolute structure parameter	0.2(3)	
Largest diff. peak and hole	0.19 and -0.14 e.$Å^{-3}$	

Table 2. Crystal data and structure refinement for **(1*S*,5*R*)-256-2**.

Identification code	6441-2	
Empirical formula	C11 H19 N1 O1	
Formula weight	181.28	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.9046(1) Å	α= 90°.
	b = 8.2614(1) Å	β= 90°.
	c = 21.5105(1) Å	γ = 90°.
Volume	1049.29(2) $Å^3$	
Z	4	
Density (calculated)	1.147 Mg/m^3	
Absorption coefficient	0.564 mm^{-1}	
F(000)	400	
Crystal size	0.29 x 0.04 x 0.03 mm^3	
Theta range for data collection	4.110 to 76.640°.	
Index ranges	-7<=h<=7, -10<=k<=10, -27<=l<=26	
Reflections collected	50455	
Independent reflections	2205 [R(int) = 0.032]	
Completeness to theta = 76.640°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.61	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2198 / 0 / 119	
Goodness-of-fit on F^2	1.0060	
Final R indices [I>2sigma(I)]	R1 = 0.0252, wR2 = 0.0674	
R indices (all data)	R1 = 0.0254, wR2 = 0.0676	
Absolute structure parameter	0.04(19)	
Largest diff. peak and hole	0.20 and -0.11 e.$Å^{-3}$	

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-2**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-1201(1)	4389(1)	6424(1)	25
C(2)	-34(2)	5543(1)	6013(1)	24
C(3)	1434(2)	4639(1)	5528(1)	24
C(4)	2883(2)	3308(1)	5793(1)	21
C(5)	1828(2)	2255(1)	6298(1)	21
C(6)	382(2)	3317(1)	6749(1)	24
C(7)	-1812(2)	6551(1)	5673(1)	36
O(8)	4787(1)	3050(1)	5595(1)	29
C(9)	241(2)	1048(1)	5967(1)	28
C(10)	3668(2)	1305(1)	6641(1)	30
C(11)	1782(2)	4372(1)	7192(1)	30
C(12)	3036(2)	5711(1)	6845(1)	29
C(13)	1420(2)	6649(1)	6424(1)	28

Table 4. Bond lengths [Å] and angles [°] for **(1*S*,5*R*)-256-2**.

N(1)-C(2)	1.4707(11)	C(13)-H(131)	0.979
N(1)-C(6)	1.4649(11)	C(13)-H(132)	0.994
N(1)-H(11)	0.868		
C(2)-C(3)	1.5491(12)	C(2)-N(1)-C(6)	112.30(7)
C(2)-C(7)	1.5265(13)	C(2)-N(1)-H(11)	109.3
C(2)-C(13)	1.5333(12)	C(6)-N(1)-H(11)	108.4
C(3)-C(4)	1.5062(12)	N(1)-C(2)-C(3)	110.75(7)
C(3)-H(31)	0.988	N(1)-C(2)-C(7)	108.59(8)
C(3)-H(32)	0.974	C(3)-C(2)-C(7)	108.95(8)
C(4)-C(5)	1.5236(11)	N(1)-C(2)-C(13)	107.64(7)
C(4)-O(8)	1.2209(11)	C(3)-C(2)-C(13)	111.25(7)
C(5)-C(6)	1.5620(12)	C(7)-C(2)-C(13)	109.62(8)
C(5)-C(9)	1.5425(12)	C(2)-C(3)-C(4)	114.46(7)
C(5)-C(10)	1.5302(12)	C(2)-C(3)-H(31)	110.8
C(6)-C(11)	1.5339(13)	C(4)-C(3)-H(31)	109.4
C(6)-H(61)	0.994	C(2)-C(3)-H(32)	108.9
C(7)-H(71)	1.001	C(4)-C(3)-H(32)	106.4
C(7)-H(72)	0.984	H(31)-C(3)-H(32)	106.6
C(7)-H(73)	0.999	C(3)-C(4)-C(5)	117.01(7)
C(9)-H(91)	0.974	C(3)-C(4)-O(8)	121.21(8)
C(9)-H(92)	0.967	C(5)-C(4)-O(8)	121.72(8)
C(9)-H(93)	0.974	C(4)-C(5)-C(6)	110.21(7)
C(10)-H(101)	0.982	C(4)-C(5)-C(9)	106.80(7)
C(10)-H(102)	0.979	C(6)-C(5)-C(9)	108.53(7)
C(10)-H(103)	0.989	C(4)-C(5)-C(10)	110.21(8)
C(11)-C(12)	1.5264(14)	C(6)-C(5)-C(10)	112.13(7)
C(11)-H(111)	0.976	C(9)-C(5)-C(10)	108.79(7)
C(11)-H(112)	0.964	C(5)-C(6)-N(1)	113.06(7)
C(12)-C(13)	1.5271(13)	C(5)-C(6)-C(11)	114.25(7)
C(12)-H(121)	0.990	N(1)-C(6)-C(11)	107.27(8)
C(12)-H(122)	0.999	C(5)-C(6)-H(61)	105.7

N(1)-C(6)-H(61)	108.3	H(102)-C(10)-H(103)	106.6
C(11)-C(6)-H(61)	108.0	C(6)-C(11)-C(12)	111.68(8)
C(2)-C(7)-H(71)	110.6	C(6)-C(11)-H(111)	106.4
C(2)-C(7)-H(72)	110.6	C(12)-C(11)-H(111)	109.2
H(71)-C(7)-H(72)	108.9	C(6)-C(11)-H(112)	109.9
C(2)-C(7)-H(73)	110.2	C(12)-C(11)-H(112)	110.3
H(71)-C(7)-H(73)	108.2	H(111)-C(11)-H(112)	109.2
H(72)-C(7)-H(73)	108.3	C(11)-C(12)-C(13)	110.76(8)
C(5)-C(9)-H(91)	108.8	C(11)-C(12)-H(121)	109.3
C(5)-C(9)-H(92)	112.5	C(13)-C(12)-H(121)	109.5
H(91)-C(9)-H(92)	110.0	C(11)-C(12)-H(122)	109.8
C(5)-C(9)-H(93)	109.3	C(13)-C(12)-H(122)	110.5
H(91)-C(9)-H(93)	107.1	H(121)-C(12)-H(122)	106.9
H(92)-C(9)-H(93)	109.0	C(2)-C(13)-C(12)	112.92(8)
C(5)-C(10)-H(101)	109.1	C(2)-C(13)-H(131)	107.6
C(5)-C(10)-H(102)	110.3	C(12)-C(13)-H(131)	109.2
H(101)-C(10)-H(102)	110.2	C(2)-C(13)-H(132)	109.1
C(5)-C(10)-H(103)	111.2	C(12)-C(13)-H(132)	110.1
H(101)-C(10)-H(103)	109.6	H(131)-C(13)-H(132)	107.7

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-2**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	20(1)	23(1)	32(1)	2(1)	1(1)	0(1)
C(2)	24(1)	19(1)	28(1)	2(1)	-2(1)	0(1)
C(3)	31(1)	21(1)	20(1)	2(1)	-2(1)	-3(1)
C(4)	24(1)	20(1)	19(1)	-5(1)	-1(1)	-2(1)
C(5)	23(1)	19(1)	22(1)	2(1)	-1(1)	2(1)
C(6)	25(1)	24(1)	22(1)	2(1)	3(1)	1(1)
C(7)	34(1)	25(1)	49(1)	9(1)	-10(1)	2(1)
O(8)	27(1)	33(1)	27(1)	-5(1)	6(1)	-1(1)
C(9)	32(1)	19(1)	31(1)	1(1)	-3(1)	-2(1)
C(10)	29(1)	29(1)	31(1)	6(1)	-3(1)	6(1)
C(11)	37(1)	33(1)	20(1)	-4(1)	0(1)	4(1)
C(12)	31(1)	29(1)	27(1)	-8(1)	-5(1)	-2(1)
C(13)	31(1)	20(1)	34(1)	-5(1)	-1(1)	0(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-2**.

	x	y	z	U(eq)
H(31)	2400	5405	5295	30
H(32)	439	4129	5224	30
H(61)	-511	2542	7003	27
H(71)	-1073	7315	5375	52
H(72)	-2723	7178	5971	53
H(73)	-2852	5830	5433	52
H(91)	-371	302	6274	41

H(92)	-980	1581	5748	41
H(93)	1114	406	5672	40
H(101)	2980	729	6992	43
H(102)	4853	2040	6788	42
H(103)	4416	520	6361	43
H(111)	709	4859	7482	37
H(112)	2838	3708	7420	36
H(121)	3730	6460	7150	35
H(122)	4303	5235	6597	33
H(131)	392	7294	6681	35
H(132)	2285	7406	6154	33
H(11)	-2117	3797	6204	33

Table 7. Hydrogen bonds for **(1*S*,5*R*)-256-2** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(32)...O(8)#1	0.974	2.549	3.4228(13)	149.31(3)
N(1)-H(11)...O(8)#2	0.868	2.332	3.1637(13)	160.47(3)

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,-z+1 #2 x-1,y,z

Table 8. Crystal data and structure refinement for **(1*S*,5*R*)-256-3**.

Identification code	6441-3	
Empirical formula	C11 H19 N1 O1	
Formula weight	181.28	
Temperature	100 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.8855(2) Å	α= 90°.
	b = 8.2344(2) Å	β= 90°.
	c = 21.4492(7) Å	γ = 90°.
Volume	1039.50(6) $Å^3$	
Z	4	
Density (calculated)	1.158 Mg/m^3	
Absorption coefficient	0.569 mm^{-1}	
F(000)	400	
Crystal size	0.28 x 0.09 x 0.03 mm^3	
Theta range for data collection	4.122 to 76.296°.	
Index ranges	-7<=h<=7, -10<=k<=10, -26<=l<=26	
Reflections collected	28323	
Independent reflections	2173 [R(int) = 0.034]	
Completeness to theta = 76.296°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.55	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2166 / 0 / 119	
Goodness-of-fit on F^2	1.0061	
Final R indices [I>2sigma(I)]	R1 = 0.0253, wR2 = 0.0693	
R indices (all data)	R1 = 0.0256, wR2 = 0.0696	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.18 and -0.13 e.$Å^{-3}$	

Table 9. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-3**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-1222(2)	4377(1)	6429(1)	18
C(2)	-61(2)	5542(1)	6018(1)	17
C(3)	1408(2)	4642(1)	5528(1)	18
C(4)	2872(2)	3305(1)	5791(1)	16
C(5)	1823(2)	2240(1)	6296(1)	16
C(6)	374(2)	3297(1)	6752(1)	17
C(7)	-1852(2)	6555(1)	5680(1)	25
O(8)	4784(1)	3050(1)	5591(1)	21
C(9)	229(2)	1030(1)	5963(1)	20
C(10)	3678(2)	1285(1)	6637(1)	21
C(11)	1779(2)	4354(1)	7197(1)	21
C(12)	3031(2)	5703(1)	6849(1)	20
C(13)	1403(2)	6648(1)	6430(1)	20

Table 10. Bond lengths [Å] and angles [°] for **(1*S*,5*R*)-256-3**.

N(1)-C(2)	1.4709(13)	C(13)-H(131)	0.977
N(1)-C(6)	1.4672(13)	C(13)-H(132)	1.005
N(1)-H(11)	0.867		
C(2)-C(3)	1.5496(14)	C(2)-N(1)-C(6)	112.38(8)
C(2)-C(7)	1.5266(14)	C(2)-N(1)-H(11)	109.1
C(2)-C(13)	1.5346(14)	C(6)-N(1)-H(11)	107.9
C(3)-C(4)	1.5079(14)	N(1)-C(2)-C(3)	110.71(8)
C(3)-H(31)	0.984	N(1)-C(2)-C(7)	108.66(8)
C(3)-H(32)	0.981	C(3)-C(2)-C(7)	108.96(8)
C(4)-C(5)	1.5234(13)	N(1)-C(2)-C(13)	107.62(8)
C(4)-O(8)	1.2227(13)	C(3)-C(2)-C(13)	111.16(8)
C(5)-C(6)	1.5623(13)	C(7)-C(2)-C(13)	109.69(8)
C(5)-C(9)	1.5438(13)	C(2)-C(3)-C(4)	114.45(8)
C(5)-C(10)	1.5312(14)	C(2)-C(3)-H(31)	111.2
C(6)-C(11)	1.5346(14)	C(4)-C(3)-H(31)	108.8
C(6)-H(61)	1.004	C(2)-C(3)-H(32)	108.9
C(7)-H(71)	1.005	C(4)-C(3)-H(32)	106.1
C(7)-H(72)	0.980	H(31)-C(3)-H(32)	107.0
C(7)-H(73)	1.002	C(3)-C(4)-C(5)	117.08(8)
C(9)-H(91)	0.987	C(3)-C(4)-O(8)	121.30(9)
C(9)-H(92)	0.973	C(5)-C(4)-O(8)	121.56(9)
C(9)-H(93)	0.983	C(4)-C(5)-C(6)	110.18(8)
C(10)-H(101)	0.977	C(4)-C(5)-C(9)	106.81(8)
C(10)-H(102)	0.983	C(6)-C(5)-C(9)	108.48(8)
C(10)-H(103)	0.983	C(4)-C(5)-C(10)	110.25(8)
C(11)-C(12)	1.5278(15)	C(6)-C(5)-C(10)	112.14(8)
C(11)-H(111)	0.983	C(9)-C(5)-C(10)	108.81(8)
C(11)-H(112)	0.969	C(5)-C(6)-N(1)	113.06(8)
C(12)-C(13)	1.5270(15)	C(5)-C(6)-C(11)	114.28(8)
C(12)-H(121)	0.974	N(1)-C(6)-C(11)	107.21(8)
C(12)-H(122)	0.994	C(5)-C(6)-H(61)	106.1

N(1)-C(6)-H(61)	108.4	H(102)-C(10)-H(103)	106.7
C(11)-C(6)-H(61)	107.6	C(6)-C(11)-C(12)	111.59(8)
C(2)-C(7)-H(71)	109.5	C(6)-C(11)-H(111)	105.8
C(2)-C(7)-H(72)	109.5	C(12)-C(11)-H(111)	108.8
H(71)-C(7)-H(72)	109.3	C(6)-C(11)-H(112)	110.1
C(2)-C(7)-H(73)	110.3	C(12)-C(11)-H(112)	110.6
H(71)-C(7)-H(73)	109.0	H(111)-C(11)-H(112)	109.8
H(72)-C(7)-H(73)	109.1	C(11)-C(12)-C(13)	110.81(9)
C(5)-C(9)-H(91)	108.9	C(11)-C(12)-H(121)	109.4
C(5)-C(9)-H(92)	111.8	C(13)-C(12)-H(121)	109.4
H(91)-C(9)-H(92)	109.5	C(11)-C(12)-H(122)	110.3
C(5)-C(9)-H(93)	109.8	C(13)-C(12)-H(122)	110.0
H(91)-C(9)-H(93)	107.8	H(121)-C(12)-H(122)	106.8
H(92)-C(9)-H(93)	108.9	C(2)-C(13)-C(12)	112.92(8)
C(5)-C(10)-H(101)	108.9	C(2)-C(13)-H(131)	107.5
C(5)-C(10)-H(102)	110.8	C(12)-C(13)-H(131)	108.9
H(101)-C(10)-H(102)	111.0	C(2)-C(13)-H(132)	109.5
C(5)-C(10)-H(103)	110.4	C(12)-C(13)-H(132)	110.2
H(101)-C(10)-H(103)	109.1	H(131)-C(13)-H(132)	107.6

Symmetry transformations used to generate equivalent atoms:

Table 11. Anisotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-3**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	14(1)	18(1)	22(1)	1(1)	0(1)	0(1)
C(2)	16(1)	16(1)	19(1)	2(1)	-2(1)	0(1)
C(3)	21(1)	17(1)	15(1)	2(1)	-1(1)	-1(1)
C(4)	17(1)	16(1)	14(1)	-4(1)	-2(1)	-2(1)
C(5)	16(1)	16(1)	15(1)	1(1)	-1(1)	1(1)
C(6)	16(1)	19(1)	15(1)	2(1)	2(1)	0(1)
C(7)	23(1)	20(1)	33(1)	5(1)	-7(1)	2(1)
O(8)	19(1)	25(1)	19(1)	-3(1)	3(1)	-1(1)
C(9)	23(1)	17(1)	21(1)	0(1)	-3(1)	-1(1)
C(10)	20(1)	22(1)	22(1)	3(1)	-1(1)	4(1)
C(11)	24(1)	24(1)	15(1)	-2(1)	0(1)	3(1)
C(12)	20(1)	22(1)	19(1)	-5(1)	-3(1)	-1(1)
C(13)	20(1)	17(1)	23(1)	-3(1)	-1(1)	0(1)

Table 12. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for **(1*S*,5*R*)-256-3**.

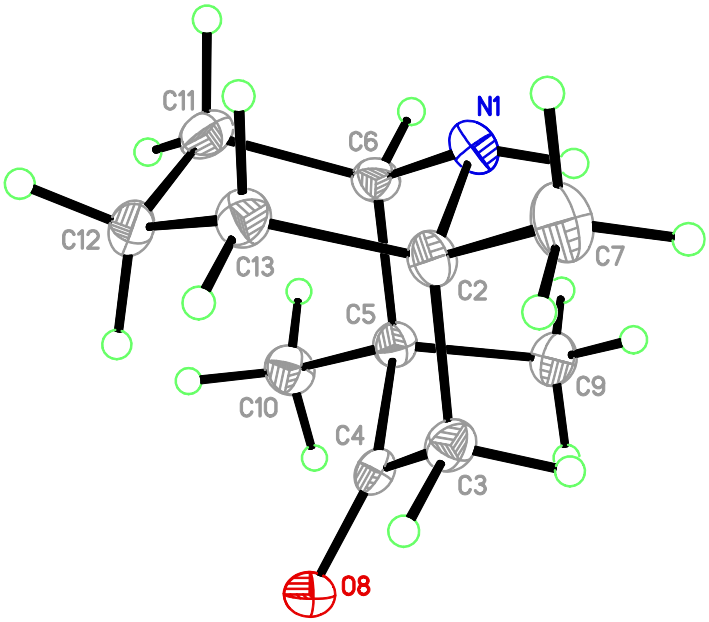
	x	y	z	U(eq)
H(31)	2382	5405	5297	22
H(32)	403	4124	5222	22
H(61)	-524	2512	7012	19
H(71)	-1085	7325	5384	37
H(72)	-2735	7176	5985	38
H(73)	-2904	5833	5439	38
H(91)	-394	268	6274	30
H(92)	-1014	1581	5751	30
H(93)	1093	394	5656	29
H(101)	2988	695	6984	31
H(102)	4884	2015	6785	30
H(103)	4400	504	6352	31
H(111)	679	4849	7485	26
H(112)	2841	3684	7428	25
H(121)	3721	6442	7149	24
H(122)	4290	5241	6597	24
H(131)	375	7283	6692	25
H(132)	2271	7430	6161	24
H(11)	-2127	3778	6207	26

Table 13. Hydrogen bonds for **(1*S*,5*R*)-256-3** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(32)...O(8)#1	0.981	2.526	3.4046(15)	148.98(3)
N(1)-H(11)...O(8)#2	0.867	2.326	3.1531(15)	159.65(3)

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,-z+1 #2 x-1,y,z



A.6 Computation

Density functional theory (DFT) calculations were performed using the *Gaussian 09* package.[190] Optimizations of the enamine ground state structures and of transition state structures for alkylation were performed with the B3LYP density functional[191] using the default (fine) grid density for numerical integration. Harmonic vibrational frequencies were computed for all optimized structures to verify that they were either minima or transition states, possessing zero imaginary frequencies and one imaginary frequency, respectively. This level of DFT calculation has been shown in previous studies to compute relative TS energies in quantitative accord with experimental selectivities.[190] The Pople 6-31G(d) basis set was used for all elements except I, which was described with the LANL2DZ effective core potential and associated valence basis of Hay and Wadt.[192] Effects of solvation due to acetonitrile were implicitly included in all geometry optimizations and in the evaluation of energies using a conductor-like polarizable continuum model (CPCM).[193] Free energies were evaluated at the reaction temperature of 65 °C employing the so-called quasiharmonic approximation, where all vibrational frequencies lower than 100 cm^{-1} were raised to 100 cm^{-1} as a way to correct for the well-known breakdown of the harmonic oscillator model for the free energies of low-frequency vibrational modes.[194] All possible conformational isomers of the diastereomeric transition structures arising from rotation about the incipient C−C bond were considered and optimized for each enamine: in each case there are two TS geometries for attack from either enamine diastereoface lying within 10 kJ / mol of the global minimum energy structure, and thus are the major contributors to the selectivity.

A.6.1 *Cartesian Coordinates*

Optimized at the B3LYP/6-31G(d) (with LANL2DZ for I) level of theory; absolute energies, vibrational zero-point energies, enthalpies and free energies (at 338K) in Hartrees.

92* (GS1)

E(SCF) –563.976206931

E(ZPE) 0.337395

H –563.619226

G(338K) –563.685457

C –0.285904 –0.952277 0.304762
C –0.25135 1.271831 –0.434757
C –0.149417 1.86357 0.993657
C –0.677297 0.884534 2.061634
C –0.235973 –0.572647 1.803165
H 0.105052 –1.981789 0.168488
H 0.90937 2.098843 1.183855
H –0.70407 2.812773 1.048448
H –0.3425 1.203204 3.057812
H –1.772602 0.939819 2.082476
H 0.802412 –0.704044 2.137657
H –0.846874 –1.26747 2.397101
C –1.688021 0.743279 –0.725203
H –1.941518 0.901342 –1.782221
C –1.672937 –0.785572 –0.388449
C –1.677548 –1.608412 –1.693481
H –2.58478 –1.404955 –2.276552
H –0.811417 –1.359317 –2.316064
H –1.64847 –2.685256 –1.481723
C –2.866758 –1.235106 0.467637
H –3.800435 –1.121683 –0.097912
H –2.776444 –2.294112 0.742688
H –2.968259 –0.655422 1.38992
C 0.213697 2.283613 –1.483445
H –0.492634 3.122545 –1.523414
H 1.203181 2.696671 –1.250808
H 0.253878 1.821 –2.477958
N 0.528186 0.002052 –0.469982
C 1.916402 0.003103 –0.404615
C 2.732691 –0.968262 0.05525
H 2.367774 0.893074 –0.852417
H 2.31504 –1.867522 0.510406
C 4.233181 –0.896588 –0.05441
H 4.723661 –0.977951 0.928446
H 4.645126 –1.711618 –0.671239
H 4.554655 0.051204 –0.506705
H –2.432043 1.289915 –0.130889

TS1

E(SCF) –654.575972779

E(ZPE) 0.402955

H –654.146579

G(338K) –654.232872

Imaginary Frequencies (1): –358.7 cm^{-1}

C –2.108921 –0.386811 –0.93435
C –2.570889 0.102572 1.325243
C –1.653798 –1.028051 1.861429
C –1.443553 –2.143869 0.818893
C –1.206635 –1.596975 –0.605284
H –1.842937 0.024258 –1.929664
H –0.689826 –0.573273 2.13756
H –2.088823 –1.450545 2.779889
H –0.59798 –2.776644 1.117629
H –2.323468 –2.798178 0.818597
H –0.163952 –1.260917 –0.703864
H –1.352201 –2.392765 –1.349538
C –3.888975 –0.478037 0.727007
H –4.723903 0.209653 0.91713
C –3.647183 –0.634608 –0.811606
C –4.387347 0.484857 –1.572512
H –5.469285 0.412462 –1.405685
H –4.062182 1.477044 –1.239409
H –4.206612 0.412367 –2.652579
C –4.112128 –1.988164 –1.369242
H –5.202615 –2.075101 –1.28398
H –3.856666 –2.083205 –2.432512
H –3.672154 –2.838228 –0.839184
C –2.827652 1.158577 2.397253
H –3.427221 0.711855 3.199705
H –1.896521 1.52887 2.844439
H –3.385677 2.010909 1.989238
N –1.90679 0.633739 0.105285
C –1.116231 1.723592 0.027297
C –0.28221 2.101857 –1.001418
H –1.17244 2.377802 0.9021
C 0.209014 3.523481 –1.127579
H 1.234362 3.572825 –1.51917
H –0.420515 4.110591 –1.815587
H 0.192799 4.040572 –0.15881
H –4.140844 –1.434022 1.203843
H –0.23098 1.482582 –1.897404
C 1.815303 1.014976 –0.059143
H 1.161077 0.15817 0.016306
H 2.082313 1.35683 –1.051233
C 2.144262 1.846842 1.144761
H 1.414177 2.660438 1.254594
H 2.118322 1.248134 2.061127
H 3.13295 2.307645 1.050086
I 3.913207 –0.699203 –0.144813

TS2

E(SCF)	–654.575818625
E(ZPE)	0.403055
H	–654.146454
G(338K)	–654.231947

Imaginary Frequencies (1): –357.2 cm^{-1}

C	–2.339621	0.230134	–0.899918
C	–2.201122	–0.728482	1.250757
C	–1.277467	–1.884172	0.784586
C	–1.41147	–2.158786	–0.726619
C	–1.481034	–0.866272	–1.56815
H	–2.293128	1.164984	–1.495312
H	–0.242171	–1.604912	1.033691
H	–1.514007	–2.795924	1.35376
H	–0.570636	–2.776847	–1.0666
H	–2.314024	–2.757113	–0.899543
H	–0.470116	–0.452658	–1.698235
H	–1.86313	–1.086071	–2.575211
C	–3.667301	–0.95022	0.769289
H	–4.371436	–0.565688	1.519312
C	–3.816482	–0.162694	–0.575587
C	–4.62442	1.128916	–0.333702
H	–5.636005	0.89001	0.017404
H	–4.146998	1.76102	0.423681
H	–4.717011	1.715241	–1.256859
C	–4.509985	–0.969328	–1.683377
H	–5.548841	–1.179843	–1.399983
H	–4.533743	–0.404331	–2.624181
H	–4.020727	–1.92845	–1.878206
C	–2.100395	–0.517791	2.759274
H	–2.520141	–1.393507	3.269114
H	–1.060758	–0.406191	3.091865
H	–2.668721	0.366081	3.075679
N	–1.809461	0.463983	0.452109
C	–0.969726	1.447578	0.830014
C	–0.381665	2.414388	0.044282
H	–0.745356	1.455031	1.900804
C	0.199849	3.664343	0.659011
H	1.097593	4.008086	0.126686
H	–0.515704	4.502108	0.635144
H	0.473765	3.500987	1.7101
H	–3.876516	–2.020758	0.646873
H	–0.62088	2.449691	–1.018976
C	1.80239	1.122172	–0.320516
H	1.956934	1.455965	0.697319
H	1.123804	0.2961	–0.481592
C	2.317012	1.930346	–1.473894
H	1.652657	2.784324	–1.667955
H	3.311376	2.336997	–1.261375
H	2.365681	1.331017	–2.388951
I	3.805719	–0.681019	0.036869

TS3

E(SCF)	–654.575878047
E(ZPE)	0.402603
H	–654.14672
G(338K)	–654.233417

Imaginary Frequencies (1): –389.2 cm^{-1}

C	2.001664	–0.470251 –0.946339
C	2.759054	0.210214 1.183016
C	4.073372	0.826181 0.640163
C	4.467215	0.229358 –0.726846
C	3.262644	0.046604 –1.676651
H	1.146374	–0.516258 –1.651057
H	3.923001	1.913696 0.555404
H	4.885036	0.667851 1.366118
H	5.2218	0.866407 –1.206019
H	4.953352	–0.739525 –0.561466
H	2.996707	1.013425 –2.129329
H	3.527649	–0.626121 –2.504555
C	2.817971	–1.345065 1.174057
H	2.262887	–1.748155 2.031605
C	2.16326	–1.811864 –0.168916
C	0.765853	–2.401522 0.109689
H	0.843214	–3.284291 0.756623
H	0.119347	–1.672833 0.611778
H	0.274257	–2.707425 –0.822523
C	2.989097	–2.870492 –0.915499
H	3.036087	–3.793552 –0.324335
H	2.526936	–3.120213 –1.879239
H	4.01684	–2.549157 –1.107549
C	2.405428	0.772266 2.559163
H	3.144015	0.423341 3.291548
H	2.417846	1.869173 2.575676
H	1.414391	0.42733 2.88026
N	1.709744	0.472208 0.153946
C	1.117891	1.680036 –0.014083
C	0.334162	2.099425 –1.064081
H	1.250783	2.365892 0.828299
C	–0.057718	3.547099 –1.227105
H	0.588043	4.054093 –1.961267
H	–1.090446	3.659818 –1.585349
H	0.033721	4.09731 –0.281433
H	3.855863	–1.689492 1.269808
H	0.246391	1.465802 –1.946573
C	–1.77077	1.129808 –0.101575
H	–2.030017	1.320757 –1.136168
H	–1.123371	0.291094 0.110463
C	–2.167036	2.096074 0.972978
H	–1.483294	2.956003 0.983597
H	–3.174652	2.488399 0.800394
H	–2.131116	1.628426 1.962136
I	–3.860234	–0.6565 –0.014949

TS4

E(SCF)	–654.575786901
E(ZPE)	0.402757
H	–654.146583
G(338K)	–654.232747

Imaginary Frequencies (1): –385.8 cm^{-1}

C	2.111686	–0.089025	–0.989474
C	2.569935	–0.20147	1.32439
C	3.910032	0.569796	1.204429
C	4.495644	0.49068	–0.220435
C	3.427081	0.652124	–1.324215
H	1.349745	0.11521	–1.769864
H	3.718365	1.61771	1.482636
H	4.63341	0.168675	1.930142
H	5.27116	1.257737	–0.343699
H	5.006132	–0.472385	–0.340601
H	3.175248	1.716203	–1.443935
H	3.822061	0.311098	–2.291536
C	2.706925	–1.65314	0.780997
H	2.074055	–2.335809	1.363693
C	2.242578	–1.618719	–0.713169
C	0.852348	–2.274196	–0.837595
H	0.897005	–3.328577	–0.537848
H	0.117882	–1.773618	–0.196622
H	0.487082	–2.232097	–1.871673
C	3.201917	–2.345006	–1.668334
H	3.220655	–3.417056	–1.436022
H	2.872722	–2.239716	–2.710113
H	4.22903	–1.975054	–1.600161
C	2.023146	–0.15892	2.750155
H	2.679473	–0.746268	3.404169
H	1.98479	0.861472	3.151191
H	1.016322	–0.593084	2.79514
N	1.645078	0.404521	0.320739
C	1.00391	1.580675	0.511573
C	0.384304	2.375487	–0.425897
H	0.935893	1.884654	1.560699
C	–0.09706	3.759649	–0.063138
H	0.631051	4.53037	–0.361845
H	–1.041707	4.016985	–0.561901
H	–0.252032	3.856575	1.01955
H	3.741725	–2.004247	0.884249
H	0.530061	2.161241	–1.48441
C	–1.799389	1.116469	–0.444781
H	–1.135941	0.267281	–0.525491
H	–1.914786	1.573033	0.53047
C	–2.402931	1.747673	–1.662291
H	–1.770944	2.573264	–2.019782
H	–2.497876	1.024761	–2.479001
H	–3.388832	2.17026	–1.442272
I	–3.767699	–0.670429	0.2588

228* GS2

E(SCF)	–603.285692491
E(ZPE)	0.367324
H	–602.897529
G(338K)	–602.966571

C –0.253363 –0.870239 0.372319
C 0.065564 1.467003 –0.355707
C 0.032166 1.961928 1.117527
C –0.65908 1.00392 2.106182
C –0.251272 –0.460496 1.865361
H 0.221991 –1.868552 0.302274
H 1.079507 2.093029 1.432464
H –0.437273 2.956475 1.159653
H –0.388336 1.292128 3.131419
H –1.746927 1.112361 2.045774
H 0.779249 –0.599647 2.223564
H –0.878752 –1.13803 2.459664
C –1.328303 1.439249 –1.037057
C –1.639061 –1.019322 –0.332606
C –1.416338 –1.693655 –1.7045
H –2.368486 –1.798379 –2.239564
H –0.732295 –1.115678 –2.333165
H –0.9898 –2.69739 –1.580662
C –2.5724 –1.924234 0.49237
H –3.504509 –2.1075 –0.057416
H –2.107568 –2.898716 0.692464
H –2.841082 –1.473522 1.454056
C 0.935817 2.435392 –1.175396
H 0.4068 3.392009 –1.266591
H 1.903373 2.638941 –0.70322
H 1.11365 2.049308 –2.187218
N 0.598269 0.070014 –0.389724
C 1.978567 –0.138112 –0.376628
C 2.6834 –1.185181 0.102873
H 2.537749 0.645148 –0.889052
C 4.172911 –1.312996 –0.087312
H 4.703594 –1.410121 0.87298
H 4.443166 –2.203064 –0.678414
H 4.586492 –0.438033 –0.606599
H 2.191641 –1.998772 0.636016
C –2.302487 0.364064 –0.530595
H –1.788638 2.432743 –0.9311
H –1.154841 1.28796 –2.112756
H –2.762225 0.68659 0.409372
H –3.131097 0.266683 –1.246859

TS5

E(SCF)	–693.886550007
E(ZPE)	0.432717
H	–693.426039
G(338K)	–693.517577

Imaginary Frequencies (1): –362.1 cm^{-1}

C	–1.796172	–0.49154 –0.781961
C	–2.349053	0.257343 1.522027
C	–1.643782	–0.997239 2.110648
C	–1.506203	–2.187554 1.147075
C	–1.05006	–1.735835 –0.248267
H	–1.258544	–0.160463 –1.69096
H	–0.63705	–0.676774 2.421224
H	–2.176465	–1.304116 3.022765
H	–0.773071	–2.895293 1.556886
H	–2.449071	–2.739727 1.082529
H	0.014834	–1.461649 –0.200193
H	–1.125009	–2.562032 –0.967383
C	–3.85886	0.049979 1.224341
C	–3.296134	–0.668303 –1.193365
C	–3.753699	0.609593 –1.931336
H	–4.805867	0.518998 –2.228363
H	–3.656185	1.503758 –1.307556
H	–3.160912	0.769743 –2.840616
C	–3.451508	–1.85619 –2.160514
H	–4.486658	–1.915414 –2.520043
H	–2.800869	–1.742738 –3.037471
H	–3.213601	–2.812558 –1.682419
C	–2.228886	1.384932 2.555558
H	–2.746692	1.066673 3.468183
H	–1.18551	1.595105 2.820064
H	–2.70029	2.313441 2.211196
N	–1.681968	0.585864 0.225633
C	–0.984763	1.72695 0.003062
C	–0.204583	2.082433 –1.075303
H	–1.049983	2.456007 0.810467
C	0.222045	3.515409 –1.282547
H	1.243233	3.588813 –1.681899
H	–0.43436	4.03399 –1.999929
H	0.186221	4.08569 –0.344651
H	–0.144252	1.429902 –1.944891
C	1.938076	1.055256 –0.152961
H	1.266413	0.242071 0.082351
H	2.147213	1.247448 –1.198316
C	2.371641	2.030809 0.899762
H	1.674862	2.879162 0.93897
H	2.388162	1.565704 1.890762
H	3.365215	2.435807 0.680738
I	3.979335	–0.733468 –0.120304
C	–4.182812	–0.896325 0.055571
H	–4.350669	–0.31107 2.139603
H	–4.280921	1.043241 1.011573
H	–4.096205	–1.937969 0.380622
H	–5.236418	–0.761324 –0.22731

TS6

E(SCF)	–693.886348036
E(ZPE)	0.43271
H	–693.426949
G(338K)	–693.512503

Imaginary Frequencies (1): –357.0 cm^{-1}

C	–1.997495	0.193709 –0.865219
C	–1.943822	–0.934829 1.348378
C	–1.225373	–2.161204 0.717074
C	–1.410646	–2.323918 –0.800702
C	–1.254311	–0.984195 –1.536442
H	–1.657652	1.117983 –1.370356
H	–0.151402	–2.042231 0.929245
H	–1.555668	–3.070214 1.241015
H	–0.661349	–3.033302 –1.17694
H	–2.384081	–2.772344 –1.022791
H	–0.187937	–0.711165 –1.548312
H	–1.561911	–1.079368 –2.586092
C	–3.493621	–1.036492 1.331085
C	–3.560692	0.201154 –0.935497
C	–4.066047	1.572032 –0.433047
H	–5.161898	1.607611 –0.46941
H	–3.756768	1.772663 0.597443
H	–3.682599	2.385554 –1.061501
C	–4.033287	0.024613 –2.390301
H	–5.124506	0.126344 –2.446864
H	–3.593606	0.787079 –3.04661
H	–3.772538	–0.960373 –2.792437
C	–1.498308	–0.837219 2.813671
H	–1.822859	–1.748757 3.329557
H	–0.40824	–0.768241 2.911789
H	–1.954794	0.017109 3.328122
N	–1.566194	0.269235 0.547591
C	–0.850808	1.309704 1.036658
C	–0.310274	2.391727 0.376779
H	–0.663172	1.260009 2.108896
C	0.189071	3.586538 1.152182
H	1.093952	4.021681 0.704377
H	–0.559177	4.395067 1.184131
H	0.424497	3.319473 2.191221
H	–0.513969	2.546459 –0.681711
C	1.906937	1.209806 –0.151379
H	2.04283	1.340337 0.914827
H	1.22289	0.438497 –0.477577
C	2.450721	2.217779 –1.118116
H	1.783505	3.089852 –1.174357
H	3.433775	2.582051 –0.801718
H	2.533608	1.79708 –2.125545
I	3.887898	–0.650384 –0.126454
C	–4.151171	–0.927237 –0.055618
H	–3.78727	–1.983777 1.806553
H	–3.873851	–0.230391 1.975729
H	–4.072528	–1.881981 –0.585061
H	–5.227768	–0.748843 0.076276

TS7

E(SCF)	–693.884648529
E(ZPE)	0.432916
H	–693.424088
G(338K)	–693.512675

Imaginary Frequencies (1): –371.7 cm^{-1}

C	2.151427	–0.39456 –0.982196
C	2.602323	0.581055 1.259842
C	4.018201	1.034502 0.80849
C	4.584137	0.284635 –0.412252
C	3.524928	0.089292 –1.509622
H	1.437697	–0.32903 –1.825518
H	3.941157	2.104351 0.558234
H	4.710531	0.956012 1.659825
H	5.42647	0.85833 –0.821855
H	5.002028	–0.680791 –0.109184
H	3.33809	1.057321 –2.000082
H	3.89732	–0.587125 –2.290014
C	2.559906	–0.846388 1.867209
H	1.5653	–0.973404 2.319793
C	2.055626	–1.856733 –0.446614
C	2.628174	–2.841484 –1.483003
H	2.470364	–3.873617 –1.145906
H	2.131367	–2.728928 –2.455541
H	3.704373	–2.704745 –1.633835
C	2.822458	–2.001476 0.889064
C	2.101019	1.54183 2.35002
H	2.688955	1.369079 3.259419
H	2.223657	2.596154 2.077329
H	1.045631	1.359431 2.588294
N	1.713072	0.577729 0.053473
C	0.984343	1.673889 –0.293587
C	0.18184	1.874201 –1.395164
H	1.018641	2.488994 0.4298
C	–0.276969	3.257826 –1.787398
H	0.36522	3.68028 –2.576243
H	–1.302391	3.256681 –2.181838
H	–0.241075	3.952611 –0.938131
H	3.286445	–0.888877 2.691493
H	0.124209	1.110843 –2.17067
C	–1.902173	1.069881 –0.22644
H	–2.148444	1.08008 –1.280524
H	–1.265377	0.277158 0.137505
C	–2.287095	2.210318 0.666068
H	–2.352798	1.889863 1.710867
H	–1.531992	3.00665 0.611427
H	–3.245407	2.645949 0.365562
I	–4.022202	–0.638302 0.126195
H	3.894987	–2.088044 0.688888
H	2.531181	–2.946971 1.367679
C	0.568377	–2.208484 –0.231394
H	0.00703	–2.129807 –1.170845
H	0.468431	–3.237751 0.134506
H	0.094483	–1.544619 0.498802

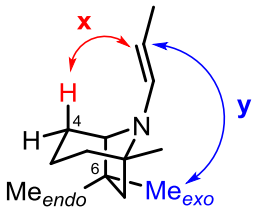
TS8

E(SCF)	–693.884797827
E(ZPE)	0.432928
H	–693.424211
G(338K)	–693.513072

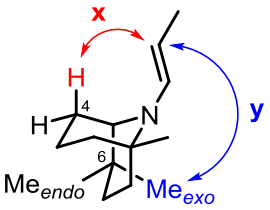
Imaginary Frequencies (1): –383.0 cm^{-1}

C	2.257206	0.073542 –0.952303
C	2.311581	0.057917 1.53472
C	3.736935	0.680454 1.528439
C	4.521886	0.513711 0.21363
C	3.640183	0.764656 –1.021432
H	1.655187	0.452744 –1.800144
H	3.609041	1.756357 1.726105
H	4.311987	0.268775 2.371175
H	5.359964	1.223705 0.209362
H	4.975737	–0.481083 0.160938
H	3.439088	1.844126 –1.102891
H	4.170137	0.477258 –1.938828
C	2.298032	–1.49241 1.509558
H	1.261187	–1.808191 1.697584
C	2.219381	–1.4836 –1.062889
C	3.019672	–1.947502 –2.294205
H	2.91027	–3.031317 –2.425352
H	2.658243	–1.462976 –3.210702
H	4.089523	–1.733852 –2.196202
C	2.798236	–2.142515 0.21148
C	1.594679	0.490745 2.822878
H	2.076063	–0.012873 3.669606
H	1.660615	1.56969 3.003645
H	0.537204	0.198207 2.811447
N	1.602575	0.528615 0.300937
C	0.836768	1.652003 0.307979
C	0.248418	2.314393 –0.745572
H	0.622602	2.044825 1.301979
C	–0.341627	3.691748 –0.558086
H	0.364741	4.478493 –0.867273
H	–1.249961	3.83636 –1.159734
H	–0.5999	3.878368 0.49279
H	2.895447	–1.854918 2.358566
H	0.470367	2.016419 –1.769306
C	–1.90414	0.984335 –0.61545
H	–1.231673	0.167547 –0.406854
H	–2.110873	1.679978 0.188421
C	–2.394437	1.260968 –2.004674
H	–1.784434	2.043983 –2.477087
H	–2.340923	0.365936 –2.632909
H	–3.426712	1.626322 –1.992256
I	–3.899731	–0.616646 0.37161
H	3.891862	–2.116315 0.175425
H	2.525699	–3.207263 0.21805
C	0.753967	–1.932011 –1.254568
H	0.321002	–1.484045 –2.157977
H	0.701554	–3.022342 –1.362479
H	0.124261	–1.650573 –0.404035

A.6.2 *X / Y Distances for* ***TS1–8***



92*



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[**x** = the distance between C4-H_{ax} and the C-β of the enamine
y = the distance between C6-Me_{exo} and the C-β of the enamine]

TS1 **x** = 3.38 **y** = 3.84
TS2 **x** = 3.35 **y** = 3.84
TS3 **x** = 3.07 **y** = 4.13
TS4 **x** = 3.04 **y** = 4.16

TS5 **x** = 3.65 **y** = 3.66
TS6 **x** = 3.66 **y** = 3.69
TS7 **x** = 3.24 **y** = 3.98
TS8 **x** = 3.32 **y** = 4.01

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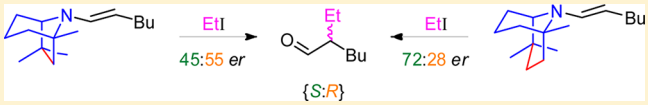
C-Alkylation of Chiral Tropane- and Homotropane-Derived Enamines

David M. Hodgson,* Andrew Charlton, Robert S. Paton,* and Amber L. Thompson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

ABSTRACT: The synthesis and alkylation of chiral, nonracemic tropane- and homotropane-derived enamines is examined as an approach to enantioenriched α-alkylated aldehydes. The two bicyclic N auxiliaries, which differ by a single methylene group, give opposite senses of asymmetric induction on alkylation with EtI and provide modestly enantioenriched 2-ethylhexanal (following hydrolysis of the alkylated iminium). The observed stereoselectivity is supported by density functional studies of ethylation for both enamines.

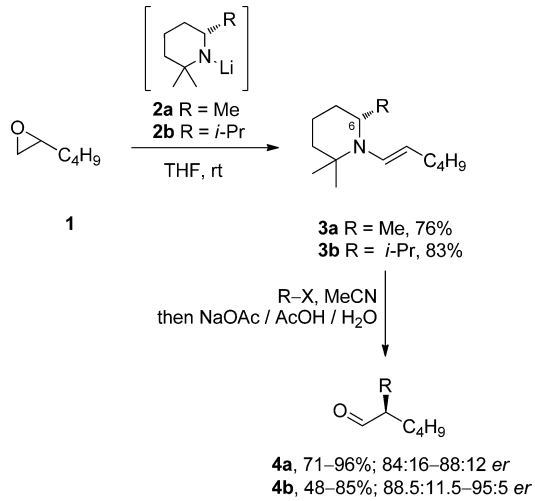


INTRODUCTION

Chiral α-alkyl-substituted aldehydes are widely recognized as valuable materials for synthesis. The aldehyde functional group provides a variety of attractive possibilities for introduction of asymmetry into more complex molecular scaffolds. Chiral α-alkyl-substituted aldehydes have also found direct application in the fragrance industry.[1] Despite longstanding interest by the synthetic community in the development of methodology to access such species directly,[2] success has so far been limited.[3] Currently, one of the most commonly used strategies to generate enantioenriched α-alkyl-substituted aldehydes employs Enders' lithiated SAMP/RAMP hydrazone chemistry.[4] Also effective are alkylations carried out at a higher oxidation level, typically involving Evans' oxazolidinone[5] or Myers' pseudoephedrine auxiliaries.[6] While these methods are robust and normally provide high levels of asymmetric induction, they are not without limitations: Enders' chemistry usually involves very low temperatures (−80 to −120 °C), and all three methods require further manipulation, e.g., ozonolysis (Enders) or reduction (Evans/Myers), to cleave the auxiliary and obtain the aldehyde. Recent years have seen the development of a variety of organocatalytic approaches to achieve direct, asymmetric α-alkylation of aldehydes.[7] Despite this, alkylation involving simple alkyl halides via intermolecular nucleophilic substitution has yet to be achieved organocatalytically. Difficulties with the organocatalytic approach include direct reaction of the amine catalyst with the alkyl halide and/or irreversible *N*-alkylation of the enamine intermediate.[8,9] In the case of MacMillan's elegant combination of photoredox and organocatalysis, a radical stabilizing group is required on the electrophile.[10]

Curphey et al. originally showed that aldenamines which are sterically crowded about N undergo preferential *C*-alkylation with simple alkyl halides.[11] This led us to investigate the possibility of chiral, nonracemic, hindered enamines for asymmetric intermolecular S_N2 alkylation. We previously reported a direct synthesis of enantioenriched mono-α-alkyl-substituted aldehydes **4a,b** by way of *C*-alkylation of chiral piperidine-derived enamines **3a,b** (Scheme 1).[12] These hindered about N enamines were prepared by reaction of the hindered lithium amides **2a,b** with terminal epoxides **1**.[13] The preparation of such enamines by classical condensation techniques is not possible.

Scheme 1. Synthesis and Asymmetric Alkylation of Trialkyl-Substituted Piperidine Enamines 3a,b



In our earlier work, 2,2,6-trimethylpiperidine-derived enamine **3a** gave high yields and significant levels of enantioenrichment on alkylation.[12] Diastereocontrol of enamine alkylation was enhanced by moving to a sterically more demanding substituent on the piperidine (Me → *i*-Pr, Scheme 1, **3b** → **4b**), albeit at the expense of lower alkylation yields. These experimental observations were rationalized through a computational study,[14] which indicates that in enamine **3a** the C-6 Me substituent resides axial in the ground-state conformation (Figure 1; **3(ax)**, R = Me) so as to minimize $A^{1,3}$ strain (Figure 1, **3(eq)**). In contrast, the C-6 *i*-Pr substituent in enamine **3b** is equatorial in the ground state (Figure 1; **3(eq)**, R = *i*-Pr), with the reactive axial conformation (where N lone

Received: November 28, 2012
Published: January 29, 2013

   dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

pair–π^* overlap becomes possible) only being attainable at elevated temperatures; in this case 1,3-diaxial interactions, exacerbated by the larger isopropyl substituent, outweigh allylic strain present in the conformer with the C-6 *i*-Pr group equatorial. When the C-6 substituent is equatorial, the olefinic component of the enamine twists orthogonal to the nitrogen lone pair, rendering the enamine inactive to *C*-alkylation.[15] The reactive conformation (C-6 substituent axial) which is achieved in the transition state for enamine **3b** alkylation, despite the ground-state preference, is expected to be less accessible for enamines derived from piperidines with larger C-6 substituents.

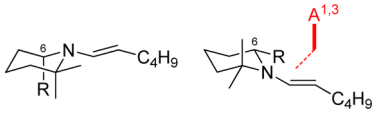


Figure 1. Enamine **3** conformers.

The above findings led to the present study concerning the development of a new class of chiral amine auxiliaries, hopefully capable of attaining elevated er levels while also retaining a high degree of reactivity.

RESULTS AND DISCUSSION

As a starting point in the exploration of more reactive enamines, the design of a new auxiliary centered around modification to the scaffold of the precursor to lithium amide **2b**, piperidine **5** (Figure 2). Tropane **6**, which is conformationally locked, thus alleviating the problems associated with unfavorable conformers, could generate enamines with enhanced reactivity. At the outset, it was considered that the *gem*-dimethyl substitution in tropane **6** (Figure 2) would mimic the isopropyl steric encumberment of enamine **3b** (albeit without the ability to splay outward[14]), thereby providing effective facial discrimination. While a single *exo*-methyl substituent would also potentially suffice (i.e., tropane **6** (Me_{endo} = H); Figure 2), this was not considered further due to the potential greater synthetic complexity associated with inclusion of an additional stereocenter.

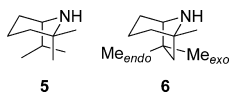
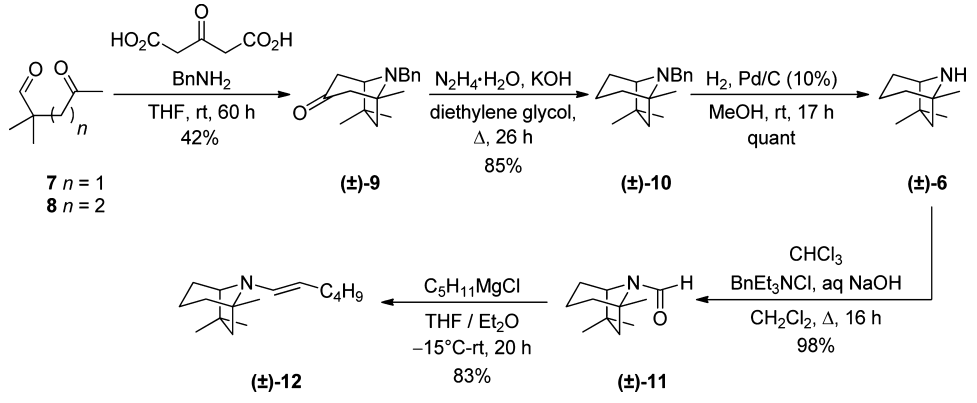


Figure 2. Piperidine **5** and tropane **6**.

We first examined the synthesis and alkylating ability of an enamine derived from racemic tropane (±)-**6**. While there are several methods for the synthesis of tropanes and their typically parent tropinones,[16] there are limited examples[17] of tropanes/tropinones containing the desired substitution pattern (bridgehead alkyl and *gem*-dialkyl α to a CH bridgehead). We envisaged a synthetic sequence using a classical Robinson–Schöpf reaction to construct the azabicyclic core (Scheme 2). Sterner et al. have demonstrated that impressive yields can be obtained by performing Robinson–Schöpf reactions of dialdehydes in THF.[18] Following Sterner's protocol, but using benzylamine (chosen for its greater nucleophilicity compared with ammonia[19] and projected reduction to access the free amine), gave tropinone (±)-**9** in satisfactory yield from readily available (one to two steps) ketoaldehyde **7**.[20] A subsequent Wolff–Kishner reaction to *N*-benzyltropane (±)-**10**[21] and then hydrogenolysis[22] gave the desired tropane (±)-**6** in excellent yield (85% from (±)-**9**).

With tropane (±)-**6** in hand, we examined the feasibility of synthesizing enamine (±)-**12** using the lithium amide–epoxide methodology (cf., **1** → **3**, Scheme 1).[13a] Previous studies in our laboratory indicated that enamine formation from lithium 2,2,5,5-tetramethylpyrrolidide and 1,2-epoxyoctadecane was slow at room temperature and generated unsatisfactory yields at higher temperatures, the latter being due to instability of the intermediate lithiated epoxide in refluxing THF.[23] In the event, attempted formation of enamine (±)-**12** from *N*-lithiotropane **6** and epoxide **1** led to a complex mixture of products from which the enamine could not be isolated by distillation or, due to its hydrolytic sensitivity, by chromatography. Attention turned to alternative methods of hindered aldenamine preparation. We have previously prepared trialkylpiperidine enamines using the unusual reaction of Grignard addition–elimination with formamides reported by Hansson and Wickberg,[24] albeit in low yield and with prolonged reaction time (e.g., reaction between *N*-formyl-2,2,6,6-tetramethylpiperidine and *n*-BuMgCl proceeded in only 32% yield after 7 days).[13b] To examine this strategy in the current work, formamide (±)-**11** was synthesized from tropane (±)-**6** using the method of Blum and Nyberg (Scheme 2).[25] The original Hansson and Wickberg enamine work prescribes excess formamide relative to Grignard reagent; however, we found this inevitably resulted in some inseparable formamide contaminating the product enamine. Modification, using a slight excess

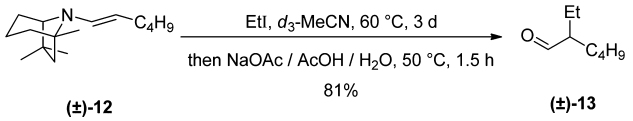
Scheme 2. Synthesis of Tropane-Derived Enamine (±)-12



dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508–1518

(1.25 equiv) of pentylmagnesium chloride, generated the desired enamine (±)-**12** in excellent yield (Scheme 2). The ^{1}H NMR spectrum of enamine (±)-**12** showed separation between the olefinic signals of 1.67 ppm, indicative of alignment of the N lone pair and alkene π orbital, and suggesting a strong *C*-alkylation profile.[15] Indeed, *C*-ethylation of enamine (±)-**12** with EtI gave, after hydrolysis of the resulting iminium, 2-ethylhexanal (±)-**13** in excellent yield (Scheme 3). By comparison, enamine **3b** generated the same aldehyde in only 58% yield under similar conditions.

Scheme 3. Ethylation of Enamine (±)-12



To examine asymmetric alkylation, tropane (±)-**6** was resolved by coupling with *N*-Boc-L-phenylalanine to give Boc-protected α-amino amides **14**, followed by deprotection and chromatographic separation of the diastereomeric α-amino amides **15** and then Edman degradation (Scheme 4).[26] The absolute configuration of tropane (+)-**6** was determined to be 1*R*,5*S* by X-ray crystallographic analysis of the precursor α-amino amide (**S**,**1R**,**5S**)-**15**. Surprisingly, the enamine derived from tropane (−)-(**1S**,**5R**)-**6** underwent alkylation with EtI to give aldehyde (**R**)-**13** in low er (55:45; Scheme 4) with a preference for the opposite sense of asymmetric induction (i.e. the opposite enantiomer) to that seen with piperidine-derived enamines **3a**,**b** (Scheme 1); similarly, enantiopure enamine (**1R**,**5S**)-**12** gave aldehyde (**S**)-**13** in 58:42 er).

The origin of the low er and unanticipated reversal of asymmetric induction was examined using quantum mechanical calculations. Density functional studies of enamine **12*** (Figure 3) at the B3LYP/6-31G(d) level determined that in the ground state the lowest energy conformation **GS1** (Figure 3) has the exocyclic C−N bond pseudoaxial with respect to the six-membered ring.

Computed transition states **TS1**−**TS4** originating from **GS1**, for the reaction of enamine **12*** with EtI in MeCN at 65 °C (Figure 4), suggest a preference for *Re*-face attack (with (**1S**,**5R**)-**12**). The methylene group α to the CH bridgehead influences the facial selectivity of the approaching electrophile

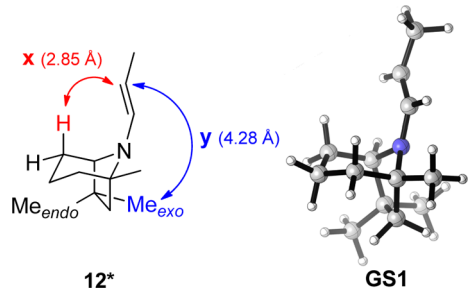


Figure 3. Computed ground-state conformation for enamine **12***.

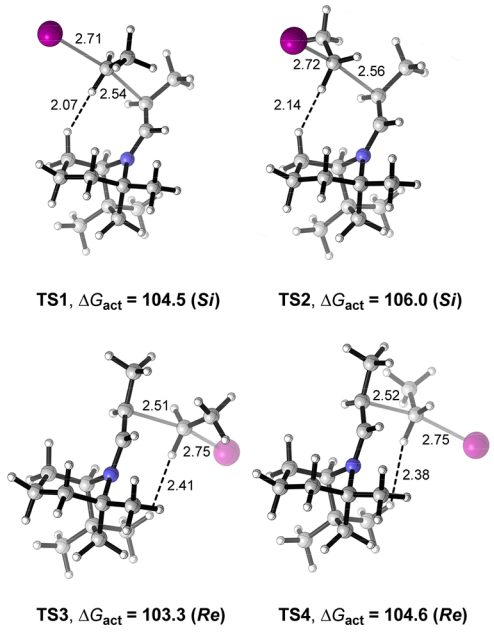
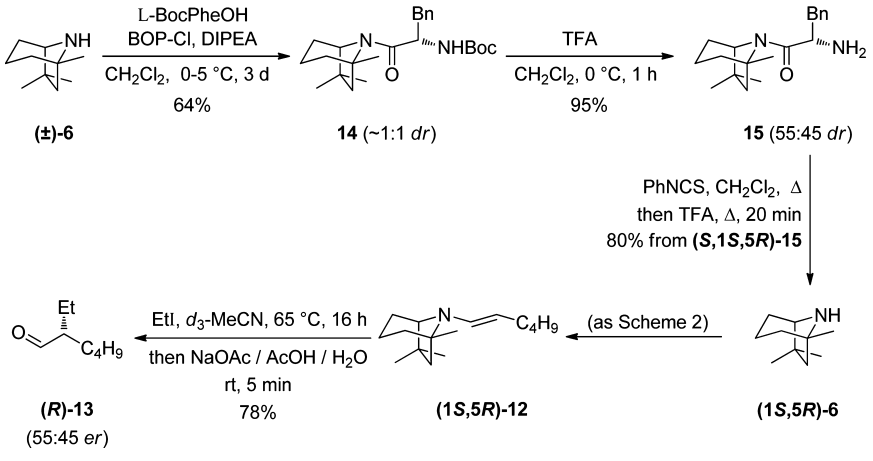


Figure 4. Computed TS geometries for reaction of enamine **12*** with EtI. B3LYP/6-31G(d) free energies in kJ/mol; selected distances shown in Å.

slightly more than that of the *exo*-methyl substituent ($x < y$, Figure 3; and similarly in the transition states **TS1**−**TS4**[35]). Transition states **TS1** and **TS2**, which differ only in the approach orientation of EtI to the *Si* face, lie 1.2 and 2.7 kJ mol^{-1} higher in energy than **TS3**, respectively. The computa-

Scheme 4. Synthesis and Ethylation of Enamine (1S,5R)-12



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tionally determined face selectivity and calculated 62:38 er are in good agreement with the experimental findings.

From Figures 3 and 4 it is clear that the presence of the embedded pyrrolidine places an undesired bias on the orientation of the exocyclic double bond. In response to this, we considered that formal expansion of the two-carbon bridge of the tropane scaffold by a methylene group to generate two rings of equal size (homotropane {6,6}, cf. tropane {6,5}), could give an improved er, since facial discrimination should now be solely dependent on the presence of the *gem*-dimethyl group on one ring. Comparison of the computed ground-state conformations for tropane-derived (**GS1**) and homotropane-derived (**GS2**) enamines shows similar orientations of the common *N*-propenyl group (similar values of *x* and *y*, Figures 3 and 5). However, in contrast to **TS3** and **TS4** (Figure 4), the

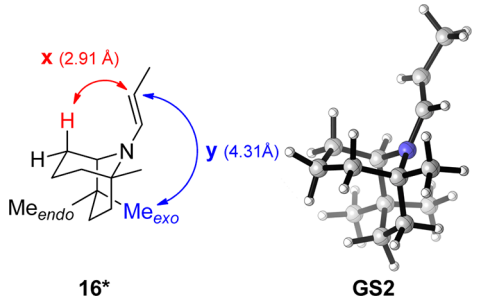

Figure 5. Computed ground-state conformation for enamine **16***.

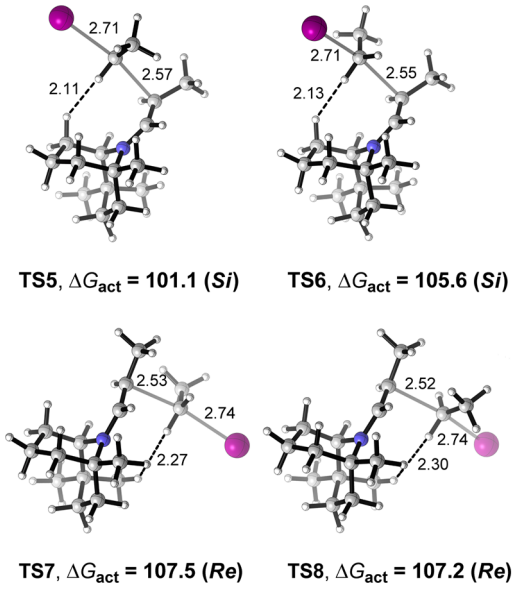

Figure 6. Computed TS geometries for reaction of enamine **16*** with EtI. B3LYP/6-31G(d) free energies in kJ/mol; selected distances shown in Å.

computed transition structures **TS5** and **TS6** for alkylation of homotropane-derived enamine **16*** with EtI (Figure 6) show that the exocyclic C–N bond moves to being essentially equidistant from each piperidine ring of the homotropane ($x \approx y$).[35] Furthermore, the calculated energies of transition states **TS5**–**TS8** predicted significant improvement in er (85:15), with *Si*-face selectivity (with enamine (**1***S*,**5***R*)-**16**).

For preparation of the required homotropane **17**, we initially investigated a Robinson–Schöpf strategy similar to that used for preparing tropane **6**. However, the propensity for intramolecular aldol condensation of the required ketoaldehyde **8** led to poor yields in the early stages of the synthetic sequence and consequently generated insufficient quantities of homotropane **17** for subsequent enamine studies. Therefore, it was decided to examine an asymmetric synthesis of homotropane **17**. We were attracted to the elegant chemistry of Davis et al.,[27] which involves enolate addition to chiral ketal sulfinimines followed by Mannich cyclization to construct chiral homotropinones in excellent yields and ers. However, and despite significant experimentation, the envisaged Davis approach (Scheme 5) was hampered by an inability to form the requisite novel Weinreb enolate **21** (M = Li). We therefore investigated constructing a Mannich cyclization substrate by addition of an organometallic rather than an enolate to a sulfinimine (Scheme 5). As sulfinimines prepared from Davis' auxiliary are known to undergo competing *S*- and 1,2-addition using Grignard reagents,[28] we switched to Ellman's *tert*-butyl sulfur analogue.[29] Although the revised strategy relied heavily on addition of an organometallic **23** to a severely hindered sulfinimine **24**, literature precedent suggested that promising yields and diastereoselectivity could be achieved.[30]

Aldehyde **25** (Scheme 6), prepared in four steps from ethyl α-methylacetoacetate (78% overall yield),[31] underwent NaOH-mediated[32] condensation with sulfinamide (***R***)-**26** to give sulfinimine (***R***)-**24** in excellent yield. Addition of Grignard reagent **23** to racemic sulfinimine **24** generated the crude bis-ketal sulfinamide **20** in moderate dr (73:27).[33] Due to the low yield and dr from Grignard approach, we examined addition of organolithium **27** to sulfinimine (***R***)-**24**, which gave the bis-ketal sulfinamide (***R***$_S$,***R***)-**20** in excellent yield (91%) and dr (98:2), with the configuration later being determined by correlation with homotropinone (**1***S*,**5***R*)-**18**. The diastereoselectivity observed using organolithium **27** (opposite to that seen with Grignard reagent **23**) is consistent with that found for reactions of other organolithiums and *tert*-butanesulfinyl aldimines, which are suggested as proceeding through an open transition state.[34] Treatment of bis-ketal sulfinamide (***R***$_S$,***R***)-**20** under the same conditions used by Davis[27] to promote cascade through to the homotropinone (NH_4OAc (25 equiv), AcOH:EtOH (1:1), 36 h, 75 °C) led to deprotection of both ketals but left the sulfinamide group intact. It was considered that stronger acidic conditions would be required for removal of the *tert*-butyl sulfinyl group. Indeed, heating (***R***$_S$,***R***)-**20** in a methanolic–ethereal solution of HCl gave the desired homotropinone (***R***$_S$,***R***)-**18** as a single enantiomer (by chiral HPLC analysis), whose absolute configuration was established by X-ray crystallographic analysis.[35] Wolff–Kishner reaction (and other common deoxygenation strategies) proved unsuccessful for reduction of homotropinone (**1***S*,**5***R*)-**18**, but conversion to homotropane (**1***S*,**5***R*)-**17** was eventually achieved by reduction to the homotropinol (**1***S*,**3***R*,**5***R*)-**28** and deoxygenation of the derived xanthate (**1***S*,**3***R*,**5***R*)-**29** under Barton–McCombie conditions.[36] NOE studies[35] on xanthate (**1***S*,**3***R*,**5***R*)-**29** indicated that reduction of homotropinol (**1***S*,**3***R*,**5***R*)-**28** had proceeded with *exo*-face hydride delivery.

Ethylation of enamine (**1***S*,**5***R*)-**16**, prepared similarly to tropane enamine **12**, proceeded in reasonable yield (Scheme 7), showed a significant improvement in er compared with tropane enamine (**1***R*,**5***S*)-**12**, and gave the same sense of asymmetric induction seen with piperidine derived enamines **3a**,**b** (Scheme 1).

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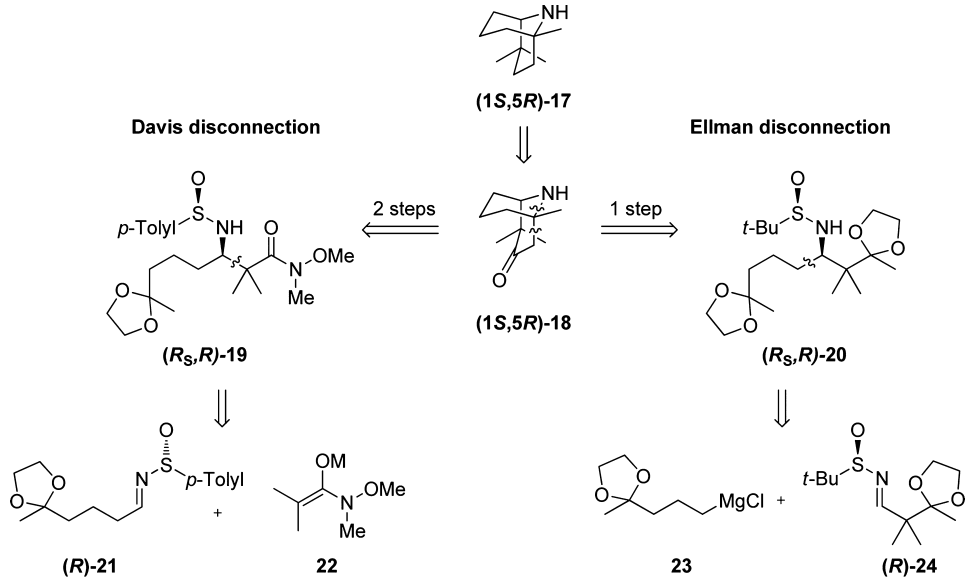
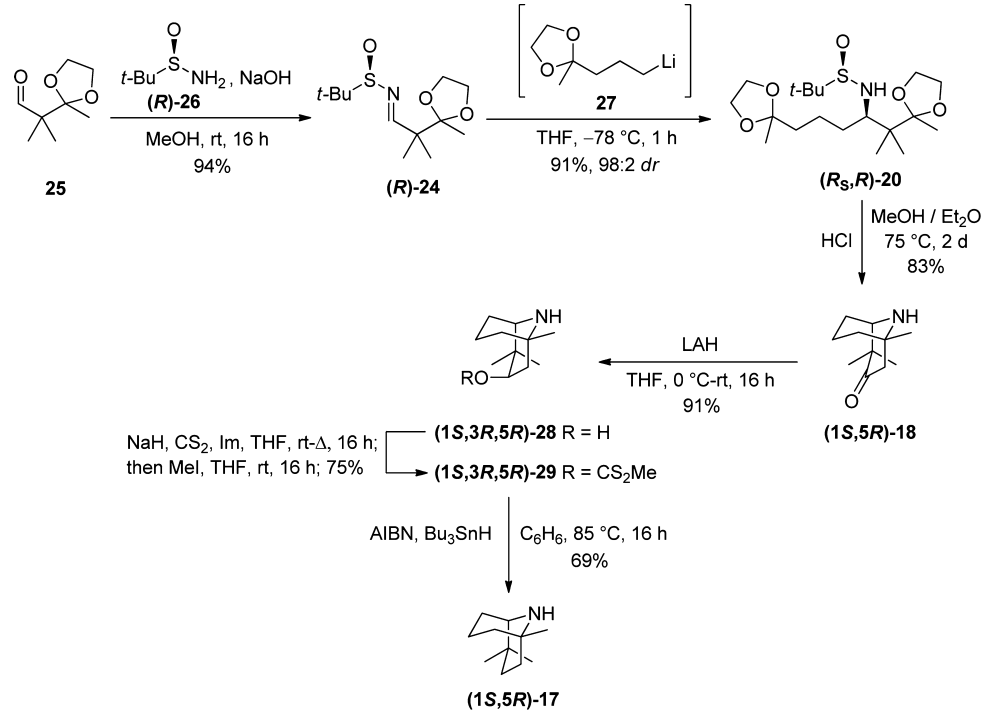
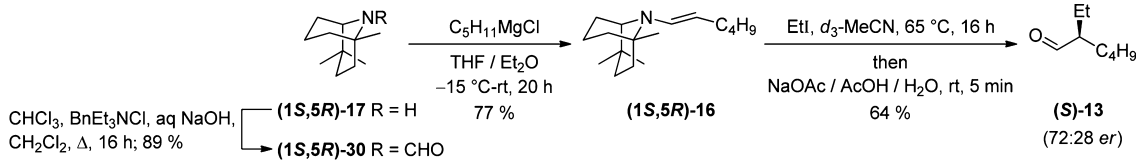
Scheme 5. Retrosynthetic Analyses for Homotropane (1*S*,5*R*)-17



Scheme 6. Synthesis of Homotropane (1*S*,5*R*)-17



Scheme 7. Synthesis and Ethylation of Enamine (1*S*,5*R*)-16



In contrast with tropane enamine (1*R*,5*S*)-12, the sense of asymmetric induction seen with homotropane enamine (1*S*,5*R*)-16 is as originally envisaged, with the *gem*-dimethyl group providing effective steric encumbrance to electrophile approach of the enamine. This is illustrated in Figure 7, where the most important competing diastereomeric TS geometries have been superimposed. Approach of the electrophile toward the *Re* face of enamine **16*** is hindered by the *gem*-dimethyl group, and as a result, the enamine is appreciably nonplanar in the TS and thus less nucleophilic. Later TS geometries with greater C−I distances are found for this minor pathway, lending further support to this interpretation. In contrast, approach

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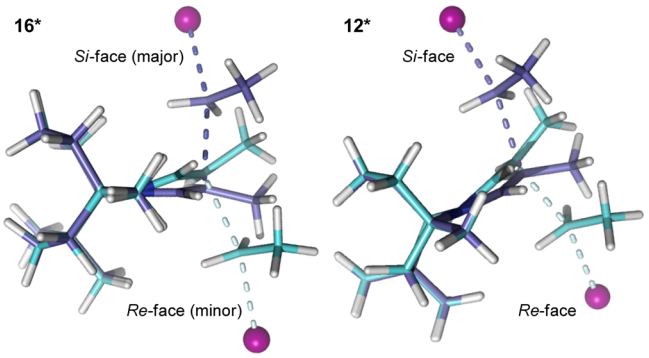

Figure 7. Superimposed TS geometries for homotropane-derived (**16***) and tropane-derived (**12***) enamine alkylation.

toward the *Si* face of enamine **16*** is unhindered and the TS displays a planar enamine geometry and is thus energetically preferred. However, there is a significant reduction in the er for alkylation with enamine (**1*S*,5*R*)-16** in comparison with superficially analogous enamine **3b**. The lower er may be a consequence of the rigidity the cyclohexyl ring imposes on the carbon bearing *gem*-dimethyl substitution. For enamine **3b**, the corresponding axial isopropyl group is able to slightly splay away from the idealized chair, thus relieving 1,3-diaxial interactions and providing increased steric shielding of the enamine *Re* face.[14] Comparison of TS geometries for attack of enamine **12*** (Figures 4 and 7) highlights the fact that the *gem*-dimethyl substituent is now more remote from the *Re* face; the combination of these effects leads to a modest inversion in the sense of facial selectivity.

■ CONCLUSION

The synthesis and asymmetric alkylation profile of enamines derived from chiral tropane **6** and homotropane **17** have been examined. Tropane-derived enamines (**1*S*,5*R***)- and (**1*R*,5*S***)-**12** showed low but reverse diastereofacial selectivity to that initially envisaged. In contrast, homotropane-derived enamine (**1*S*,5*R***)-**16** alkylated with the anticipated sense of (and with significantly improved) diastereoselectivity. The experimental findings are in good agreement with DFT studies for both enamines, where the latter provide insight into the origins of asymmetric induction. While tropane-derived enamine **12** gave a significantly improved yield of ethylation in comparison with enamine **3b**, both auxiliaries failed to provide high levels of asymmetric induction. However, despite the modest ers, the congruence between theory and practical experiment coupled with an ability to modify and, importantly, improve the er through computational studies should assist the future design of chiral auxiliaries and other asymmetric targets. Additionally, the described synthesis of α,α-disubstituted homotropinone (**1*S*,5*R*)-18** demonstrates an efficient strategy to this biologically significant class of chiral compounds that are otherwise difficult to access. Investigations are ongoing to improve on the ers obtained.

■ EXPERIMENTAL SECTION[35]

Tropane (±)-6 Synthesis. *(±)-8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-3-one ((±)-9).* Benzylamine (18.0 g, 0.17 mol) was added to a solution of ketoaldehyde 7[20] (19.4 g, 0.15 mol) in THF (500 mL) at room temperature, followed by portionwise addition of acetone-1,3-dicarboxylic acid (24.4 g, 0.17 mol), which resulted in immediate gas evolution (CO_2). (*Caution!* Ensure suitable exhaust!) After stirring for 60 h at room temperature, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (deactivated SiO_2, gradient elution 0−4% EtOAc in petroleum ether, with 2% Et_3N also in the eluent) gave tropinone (±)-**9** as a yellow oil (16.3 g, 42%): R_f = 0.37 (4% EtOAc in petroleum ether); IR (film) (cm^{-1}) 2958 m, 1708 s (C═O), 1495 w, 1455 m, 1267 m, 1225 m, 1177 m; ^{1}H NMR (400 MHz) δ 7.44 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.34 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.30−7.23 (m, 1H, Ar (*para*)), 4.04 and 3.66 (AB, 2H, J_{AB} = 14 Hz, PhCH_2N), 2.85 (d, 1H, J = 4 Hz, COCH$_2$CH), 2.54 and 2.27 (AB, 2H, J_{AB} = 16 Hz, J = 4 Hz, COCH_2CH), 2.50 and 2.16 (AB, 2H, J_{AB} = 16 Hz, COCH_2CCH$_3$), 1.61 and 1.49 (AB, 2H, J_{AB} = 13 Hz, J = 2 Hz, C(CH$_3$)$_2$CH_2) 1.28 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 210.4 (C═O), 139.8 (Ar (*ipso*)), 128.3 (Ar), 128.2 (Ar), 126.9 (Ar (*para*)), 66.1 (C(CH$_3$)$_3$CH), 62.6 (NCCH$_3$), 52.9 (CH$_2$C(CH$_3$)$_2$), 49.6 (NC(Me)CH$_2$CO), 47.3 (PhCH$_2$N), 39.0 (C(CH$_3$)$_2$), 37.4 (CHCH$_2$CO), 32.4 (CH$_3$), 25.5 (CH$_3$), 24.9 (CH$_3$); MS m/z (ESI$^+$) 258.2 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 258.1851, calcd for $C_{17}H_{24}NO$ 258.1852.

(±)-8-Benzyl-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-10). A mixture of tropinone (±)-**9** (4.54 g, 17.6 mmol), hydrazine monohydrate (4.60 g, 0.09 mol), and KOH (14.99 g, 0.27 mol) in diethylene glycol (36 mL) was heated to 190 °C (oil bath) for 24 h. The volatile components were then removed by distillation for 2 h at 200 °C. The reaction mixture was cooled to room temperature and combined with the distillate. The mixture was diluted with water (300 mL) and the aqueous layer extracted with Et_2O (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−2% EtOAc in petroleum ether) gave *N*-benzyltropane (±)-**10** as a clear oil (3.66 g, 85%): R_f = 0.50 (2% EtOAc in petroleum ether); IR (film) (cm^{-1}) 3064 w, 3027 m, 2933 s, 2867 s, 1494 m, 1451 s, 1360 m, 1279 m, 1131 m; ^{1}H NMR (400 MHz) δ 7.54 (d, 2H, J = 7 Hz, Ar (*ortho*)), 7.40 (t, 2H, J = 7 Hz, Ar (*meta*)), 7.35−7.28 (m, 1H, J = 7 Hz, Ar), 3.91 and 3.86 (AB, 2H, J_{AB} = 14 Hz, PhCH_2N), 2.49 (br s, 1H, NCH), 1.96−1.69 (m, 6H, 3 × CH$_2$), 1.72 and 1.60 (AB, 2H, J_{AB} = 13 Hz, CH_2C(CH$_3$)$_2$), 1.29 (s, 3H, CH$_3$), 1.24 (s, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz) δ 141.6 (Ar (*ipso*)), 128.4 (Ar (*ortho*)), 127.9 (Ar (*meta*)), 126.3 (Ar (*para*)), 64.6 (CHN), 60.0 (NC(CH$_3$)), 51.9 (CH$_2$C(CH$_3$)$_2$), 46.7 (PhCH$_2$N), 37.8 (C(CH$_3$)$_2$), 33.2 (CH$_3$), 28.9 (CH$_2$), 26.8 (CH$_3$), 23.7 (CH$_3$), 18.6 (CH$_2$), 16.6 (CH$_2$); MS m/z (ESI$^+$) 244.2 (M + H$^+$, 71); HRMS m/z (M + H$^+$) found 244.2067, calcd for $C_{17}H_{26}N$ 244.2060.

(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((±)-6). A vigorously stirred solution of *N*-benzyltropane (±)-**10** (2.44 g, 10.0 mmol) in MeOH was hydrogenated at 1 atm in the presence of 10% palladium on activated carbon (1.06 g, 10 mol %) for 17 h. After this time, the catalyst was removed by filtration through Celite. To the filtrate was added 1 M HCl in Et_2O (ca. 25 mL). The mixture was evaporated under reduced pressure to give the crude hydrochloride salt, which was recrystallized from EtOAc to give the tropane hydrochloride as a white crystalline solid (1.9 g, quant) (mp 201−203 °C). This salt (1.90 g, 10.0 mmol) was suspended in Et_2O (20 mL) and washed with 3 M aqueous NaOH (20 mL). The ethereal layer was separated and the aqueous phase back-extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave tropane (±)-**6** as a clear oil (1.54 g, quant): bp 50−60 °C (14 mm); IR (neat) (cm^{-1}) 3267 w (N−H stretch), 2929 s, 2868 s, 1730 m, 1641 w, 1599 w, 1453 s, 1374 s, 1277 s, 1183 m, 822 s, 739 s; ^{1}H NMR (400 MHz) δ 2.71−2.63 (m, 1H, NCH), 1.83 (br s, 1H, NH), 1.77−1.35 (m, 7H, 3 × CH$_2$ and 1 × CH_AH$_B$), 1.23 (d, 1H, J_{AB} = 13 Hz, CH$_A$$H_B$), 1.15 (s, 3H, NC(CH$_3$)), 1.12 (s, 3H, C(CH$_3$)$_2$), 1.07 (s, 3H, C(CH$_3$)$_2$); ^{13}C NMR (101 MHz) δ 65.6 (NCH), 60.3 (NC(CH$_3$)), 50.6 (CH$_2$), 42.9 (C(CH$_3$)$_2$), 39.1 (CH$_2$), 33.0 (CH$_3$), 28.7 (CH$_3$), 27.4 (CH$_2$), 23.0 (CH$_3$), 19.0 (CH$_2$); MS m/z (ESI$^+$) 154.1 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 154.1590, calcd for $C_{10}H_{20}N$ 154.1590.

General Procedure for Formamide Synthesis. *(±)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((±)-11).* A

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

mixture of tropane (±)-**6** (1.54 g, 10.0 mmol), $BnEt_3NCl$ (1.03 g, 4.5 mmol), $CHCl_3$ (7 mL, 0.09 mol), CH_2Cl_2 (32 mL), and 12.5 M aqueous NaOH (25 mL) was stirred under reflux for 16 h, then diluted with water (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL), then 10% aqueous HCl (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave formamide (±)-**11** as a clear oil (1.78 g, 98%): bp 140−150 °C (7.6 mm); IR (film) (cm^{-1}) 3054 m, 2962 m, 2875 w, 1649 s (C═O), 1426 m, 1393 m, 1375 m, 1266 s, 740 s; ^{1}H NMR (400 MHz, 293 K) two rotamers (~13:1) δ 8.15 (s, 1H, NCHO (*min*)), 8.14 (s, 1H, NCHO (*maj*)), 3.96 (br s, 1H, NCH (*maj*)), 3.24 (br s, 1H, NCH (*min*)), 1.85−1.40 (m, 8H, 4 × CH_2), 1.38 (s, 3H, CH_3 (*maj*)), 1.12 (s, 3H, CH_3 (*maj*)), 1.10 (s, 3H, CH_3 (*min*)), 1.05 (s, 3H, CH_3 (*min*)), 0.96 (s, 3H, CH_3 (*maj*)); ^{13}C NMR (101 MHz, 293K) two rotamers {~ 13:1} δ 159.2 (C═O (*min*)), 156.7 (C═O (*maj*)), 67.5 (NCH (*min*)), 62.6 (NC(CH_3) (*min*)), 61.3 (NCH (*maj*)), 61.1 (NC(CH_3) (*maj*)), 52.1 (CH_2 (*min*)), 50.6 (CH_2 (*maj*)), 40.8 (CH_2 (*maj*)), 38.7 (NCHC(CH_3)$_2$ (*maj*)), 38.3 (NCHC(CH_3)$_2$ (*min*)), 36.6 (CH_2 (*min*)), 32.1 (CH_3 (*maj*)), 31.8 (CH_3 (*min*)), 29.2 (CH_2 (*min*)), 25.8 (CH_3 (*min*)), 25.5 (CH_2 (*maj*)), 24.4 (CH_3 (*maj*)), 22.4 (CH_3 (*min*)), 22.1 (CH_3 (*maj*)), 18.5 (CH_2 (*min*)), 18.4 (CH_2 (*maj*)); MS *m*/*z* (ESI^+) 204.1 (M + Na^+, 31); HRMS *m*/*z* (M + H^+) found 182.1537, calcd for $C_{11}H_{20}NO$ 182.1539.

General Procedure for Enamine Synthesis. *(±)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octane ((±)-12).* Pentylmagnesium chloride (2.0 M in THF, 690 μL, 1.38 mmol) was added dropwise to a stirred solution of tropamide (±)-**11** (200 mg, 1.10 mmol) in Et_2O (1 mL) while the temperature was maintained between −15 and −20 °C. The mixture was kept within this temperature range for 15 min and then warmed to room temperature. After 16 h, the mixture was evaporated under reduced pressure and the crude product purified by bulb-to-bulb distillation to give enamine (±)-**12** as a clear oil (214 mg, 83%): bp 125−135 °C (0.1 mm); IR (neat) (cm^{-1}) 2932 s, 2870 s, 1649 s (C═CNR^{1}R^2), 1332 s, 1247 s, 1139 m, 936 s; ^{1}H NMR (400 MHz, C_6D_6) δ 6.06 (d, 1H, *J* = 14 Hz, NC*H*=CH), 4.38 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH═C*H*), 3.09 (br s, 1H, NC*H*C(CH_3)$_2$), 2.29−2.10 (m, 3H, NCH═CHCH_2 and CH_AH$_B$), 1.69−1.36 (m, 8H, 3 × CH_2 and 2 × CH_AH$_B$), 1.31 (d, 1H, J_{AB} = 13 Hz, CH_AH_B), 1.14 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.04−0.92 (m, 2H, 2 × CH_AH_B), 1.01 (s, 3H, CH_3), 0.95 (t, 3H, *J* = 7 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 131.1 (NCH═CH), 102.3 (NCH=CH), 65.2 (NCHC(CH_3)$_2$), 61.3 (NC(CH_3)), 51.7 (CH_2), 38.6 (C(CH_3)$_2$), 35.5 (CH_2), 34.9 (CH_2), 33.6 (CH_3), 32.0 (NCH═CHCH_2), 26.1 (CH_3), 23.5 (CH_3), 23.0 (CH_2), 20.1 (CH_2), 18.1 (CH_2), 14.7 (CH_2CH_3); MS *m*/*z* (ESI^+) 236.2 (M + H^+, 100); HRMS *m*/*z* (M + H^+) found 236.2374, calcd for $C_{16}H_{30}N$ 236.2373.

General Procedure for Enamine Alkylation. *(±)-2-Ethylhexanal ((±)-13).* Enamine (±)-**12** (211 mg, 0.90 mmol), d_3-MeCN (1 mL), and EtI (281 mg, 1.80 mmol) were placed in an NMR tube fitted with a PTFE valve. This mixture was heated at 60 °C for 3 days with occasional shaking until consumption of the enamine was complete by ^{1}H NMR spectroscopy. Buffer solution (AcOH (0.5 g), AcONa (0.5 g), and H_2O (1 mL); 0.5 mL) was then added and the mixture heated at 50 °C. After 1.5 h, the mixture was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer back-extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and carefully reduced under vacuum (152 mm, 0 °C). Purification of the residue by column chromatography (SiO_2, 5% Et_2O in petroleum ether) gave 2-ethylhexanal ((±)-**13**)[13] as a clear oil (93 mg, 81%): R_f = 0.41 (5% Et_2O in petroleum ether); IR (neat) (cm^{-1}) 2961 m, 2930 m, 2861 m, 2694 w, 1725 s (C═O), 1461 m, 1381 w, 1154 w, 899 w; ^{1}H NMR (400 MHz) δ 9.56 (d, 1H, *J* = 3 Hz, CHO), 2.23−2.10 (m, 1H, C*H*CHO), 1.71−1.20 (m, 8H, 4 × CH_2), 0.91 (t, 3H, *J* = 7 Hz, CH_3), 0.88 (t, 3H, *J* = 7 Hz, CH_3); ^{13}C NMR (101 MHz) δ 205.7 (C═O), 53.4 (CHCHO), 29.2 (CH_2), 28.1 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 13.9 (CH_3), 11.4 (CH_3).

Resolution of Tropane (±)-6. *tert-Butyl((S)-1-oxo-3-phenyl-1-((1R,5S)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-2-yl)-carbamate ((S,1R,5S)-14) and tert-Butyl((S)-1-oxo-3-phenyl-1-((1S,5R)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-2-yl)-carbamate ((S,1S,5R)-14).* To a stirred solution of tropane (±)-**6** (1.50 g, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DIPEA (2.78 g, 21.5 mmol), *N*-Boc-L-PheOH (2.86 g, 10.8 mmol), and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.74 g, 10.8 mmol). The reaction mixture was kept in a refrigerator at 0−4 °C for 3 days (TLC monitoring (50% EtOAc in petroleum ether)). After this time, the reaction mixture was diluted with ice-cold EtOAc (750 mL), washed with ice-cold 5% aqueous HCl (500 mL) and 5% aqueous $NaHCO_3$ (500 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−10% EtOAc in petroleum ether) gave an inseparable mixture of Boc-protected α-amino amides (**S,1R,5S**)-**14** and (**S,1S,5R**)-**14** as a white foam (~1:1 dr, 2.50 g, 64%): R_f = 0.29 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3429 w, 3294 w, 3055 m, 3030 w, 2962 s, 2873 m, 1707 s (C═O), 1635 s (C═O), 1495 s, 1444 s, 1266 s, 1170 s, 1044 m, 739 s; ^{1}H NMR (400 MHz) two diastereomers (~1:1) δ 7.32−7.14 (m, 10H, 2 × Ph), 5.28 (5.22) (d, 2H, *J* = 9 (10) Hz, 2 × N*H*), 4.72−4.59 (m, 2H, 2 × NHC*H*), 3.67 (3.62) (br s, 2H, 2 × NC*H*), 3.24−3.06 (m, 2H, 2 × PhCH_AH$_B$), 2.93−2.75 (m, 2H, 2 × PhCH_AH$_B$), 2.14−2.02 (m, 1H, CH_AH$_B$), 1.95−1.19 (m, 14H, 6 × CH_2 and 2 × CH_AH_B), 1.63 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.40 (s, 9H, *t*-Bu), 1.38 (s, 9H, *t*-Bu), 1.07 (s, 3H, CH_3), 1.012 (s, 3H, CH_3), 1.006 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.49−0.30 (m, 1H, CH_AH$_B$); ^{13}C NMR (101 MHz) two diastereomers (~1:1) δ 170.9 (169.8) (NHCHC═O), 155.0 (154.8) (NHC═O), 137.4 (136.8) (Ar (*ipso*)), 129.9 (129.5) (Ar (*ortho*)), 128.3 (128.2) (Ar (*meta*)), 126.6 (126.5) (Ar (*para*)), 79.5 (79.4) (C(CH_3)$_3$), 68.7 (67.6) (NCHC(CH_3)$_2$), 64.6 (64.3) (NC(CH_3)), 53.5 (53.4) (NHCH), 51.6 (2 × CH_2C(CH_3)$_2$), 39.8 (39.3) (PhCH_2), 38.0 (37.9) (C(CH_3)$_2$), 36.7 (CH_2), 35.0 (CH_2), 32.0 (CH_3), 31.8 (CH_3), 28.29 (CH_2), 28.27 (C(CH_3)$_3$), 28.23 (C(CH_3)$_3$), 27.4 (CH_3), 27.1 (CH_2), 27.0 (CH_3), 22.6 (CH_3), 22.4 (CH_3), 18.4 (2 × CH_2); MS *m*/*z* (ESI^+) 401.3 (M + H^+, 79); HRMS *m*/*z* (M + H^+) found 401.2799, calcd for $C_{24}H_{37}N_2O_3$ 401.2799.

(+)-(S)-2-Amino-3-phenyl-1-((1R,5S)-1,6,6-trimethyl-8-azabicyclo[3.2.1]octan-8-yl)propan-1-one ((+)-(S,1R,5S)-15) and (+)-(S)-2-Amino-3-phenyl-1-((1S,5R)-1,6,6-trimethyl-8-azabicyclo-[3.2.1]octan-8-yl)propan-1-one ((+)-(S,1S,5R)-15). Anhydrous TFA (62 mL) was added to a stirred solution of Boc-protected α-amino amides (**S,1R,5S**)-**14** and (**S,1S,5R**)-**14** (9.35 g, 23.3 mmol) in CH_2Cl_2 (280 mL) at room temperature. After 1 h, the mixture was evaporated under reduced pressure and the residue dissolved in $CHCl_3$ (300 mL). The resulting solution was washed with 10% aqueous Na_2CO_3 (500 mL). The aqueous layer was separated and back-extracted with $CHCl_3$ (2 × 300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (SiO_2, gradient elution 5−10% MeOH in EtOAc). The α-amino amide (**S,1R,5S**)-**15** eluted first (*minor diastereomer*, 2.96 g), followed by a mixed fraction (747 mg); the α-amino amide (**S,1S,5R**)-**15** eluted last (*major diastereomer*, 2.94 g), all white solids (55:45 dr, 6.65 g total product, 95%);

Data for minor diastereomer (**S,1R,5S**)-**15**: mp 69−71 °C; R_f = 0.52 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +23.4° (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3390 w, 2999 m, 2940 s, 1631 s (C═O), 1493 m, 1442 s, 1341 m, 928 m, 750 s, 704 s; ^{1}H NMR (400 MHz) δ 7.33−7.10 (m, 5H, Ar), 3.68 (t, 1H, *J* = 7 Hz, NH_2CH), 3.49 (br s, 1H, CONC*H*), 3.09 and 2.72 (AB, 2H, J_{AB} = 13 Hz, *J* = 7 Hz, PhCH_2), 1.89 (td, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH$_B$), 1.77−1.21 (m, 8H, NH_2, 2 × CH_2, 1 × CH_AH_B and 1 × CH_AH$_B$), 1.64 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.77−0.58 (m, 1H, CH_AH_B); ^{13}C NMR (101 MHz) δ 173.4 (C═O), 138.5 (Ar (*ipso*)), 129.6 (Ar), 128.4 (Ar), 126.4 (Ar), 67.5 (CONCH), 64.2 (NC(CH_3)), 55.2 (NH_2CH), 51.3 (CH_2), 41.5 (PhCH_2), 38.1 (NCHC(CH_3)$_2$), 36.1 (CH_2), 32.2 (CH_3), 27.4 (CH_3), 27.4 (CH_2), 22.5 (CH_3), 18.5 (CH_2); MS *m*/*z* (ESI^+) 301.2 (M + H^+, 72); HRMS *m*/*z* (M + H^+) found 301.2277, calcd for $C_{19}H_{29}N_2O$ 301.2274.

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

Data for major diastereomer (**S,1S,5R**)-**15**: mp 33−35 °C, R_f = 0.45 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +66.0° (*c* = 0.5, MeOH); IR (KBr) (cm^{-1}) 3347 br m (NH_2), 2927 s, 1638 s (C═O), 1560 m, 1443 s, 1367 m, 1288 m, 1120 m, 927 m, 744 s, 703 s; ^{1}H NMR (400 MHz) δ 7.35−7.13 (m, 5H, Ar), 3.75 (br s, 1H, NH_2CH), 3.57 (br s, 1H, $NCHC(CH_3)_2$), 3.07 and 2.72 (AB, 2H, J_{AB} = 13 Hz, J_1 = 8 Hz, J_2 = 5 Hz, $PhCH_2$), 2.12 (td, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH_B), 2.00 (br s, 2H, NH_2), 1.90−1.55 (m, 5H, 2 × CH_2 and 1 × CH_AH_B), 1.62 (s, 3H, CH_3), 1.46 (d, 1H, J_{AB} = 13 Hz, CH_AH_B), 1.32 (dd, 1H, J_{AB} = 13 Hz, *J* = 6 Hz, CH_AH_B), 1.12 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 174.1 (C═O), 137.9 (Ar (*ipso*)), 129.3 (Ar), 128.5 (Ar), 126.6 (Ar), 68.3 ($NCHC(CH_3)_2$), 64.4 ($NC(CH_3)$), 54.9 (NH_2CH), 51.6 (CH_2), 42.9 ($PhCH_2$), 38.0 ($C(CH_3)_2$), 35.1 (CH_2), 32.3 (CH_3), 28.4 (CH_2), 27.4 (CH_3), 22.6 (CH_3), 18.5 (CH_2); MS *m*/*z* (ESI$^+$) 301.2 (M + H$^+$, 75); HRMS *m*/*z* (M + H$^+$) found 301.2277, calcd for $C_{19}H_{29}N_2O$ 301.2274.

(+)-(1R,5S)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane ((+)-(1R,5S)-6) and (−)-(1S,5R)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((−)-(1S,5R)-6). PhNCS (340 mg, 2.51 mmol) was added to a stirred solution of α-amino amide (**S,1R,5S**)-**15** (686 mg, 2.28 mmol) in CH_2Cl_2 (40 mL) at room temperature. A distillation head, condenser, and receiver flask were connected to the reaction vessel, and CH_2Cl_2 was removed over an oil bath (100 °C). The distillate was recombined with the contents of the reaction vessel, and the distillation procedure was repeated until α-amino amide (**S,1R,5S**)-**15** had been consumed (determined by TLC (10% MeOH in EtOAc)). Upon completion, the mixture was concentrated to dryness and TFA (20 mL) added to the residue. The resulting solution was heated at 50 °C for 20 min. After this time, the reaction mixture was evaporated under reduced pressure and the residue dissolved in $CHCl_3$ (100 mL). This solution was partitioned with H_2O (100 mL), and the aqueous layer was separated and basified with 3 M aqueous NaOH. The resulting suspension was washed with Et_2O (5 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (bp 50−60 °C (14 mm)) to give tropane (**1R,5S**)-**6** as a clear oil (316 mg, 90%): $[\alpha]_D^{25}$ = +85.7° (*c* = 1.4, $CHCl_3$); other data as above.

Following the same procedure, reaction of the α-amino amide (**S,1S,5R**)-**15** (3.27 g, 10.9 mmol) with PhNCS (1.62 g, 12.0 mmol) in CH_2Cl_2 (170 mL) gave, after treatment with TFA (85 mL), tropane (**1S,5R**)-**6** (1.34 g, 80%): $[\alpha]_D^{25}$ = −89.6° (*c* = 1.4, $CHCl_3$); other data as above.

Synthesis of Chiral Formamides (1*R*,5*S*)-11 and (1*S*,5*R*)-11. *(+)-(1R,5S)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((+)-(1R,5S)-11).* According to the general procedure for formamide synthesis, reaction of tropane (**1R,5S**)-**6** (597 mg, 3.90 mmol), $BnEt_3NCl$ (399 mg, 1.75 mmol), $CHCl_3$ (2.9 mL, 0.04 mol), and 12.5 M aqueous NaOH (9.7 mL) in CH_2Cl_2 (12.7 mL) at reflux for 17 h gave formamide (**1R,5S**)-**11** as a clear oil (656 mg, 93%): $[\alpha]_D^{25}$ = +88.0° (*c* = 1.0, MeOH); other data as above.

(−)-(1S,5R)-1,6,6-Trimethyl-8-azabicyclo[3.2.1]octane-8-carbaldehyde ((−)-(1S,5R)-11). According to the general procedure for formamide synthesis, reaction of tropane (**1S,5R**)-**6** (1.28 g, 8.4 mmol), $BnEt_3NCl$ (856 mg, 3.8 mmol), $CHCl_3$ (6.2 mL, 0.08 mol), and 12.5 M aqueous NaOH (20.7 mL) in CH_2Cl_2 (27 mL) at reflux for 17 h gave formamide (**1S,5R**)-**11** as a clear oil (1.25 g, 82%): $[\alpha]_D^{25}$ = −69.0° (*c* = 0.9, MeOH); other data as above.

Synthesis of Chiral Enamines (1*R*,5*S*)-12 and (1*S*,5*R*)-12. *(1R,5S)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((1R,5S)-12).* According to the general procedure for enamine synthesis, reaction of formamide (**1R,5S**)-**11** (621 mg, 3.43 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.14 mL, 4.28 mmol) in Et_2O (2.5 mL) at room temperature for 17 h gave, after distillation, enamine (**1R,5S**)-**12** (676 mg, 84%):[37] other data as above.

(1S,5R)-8-((E)-Hex-1-en-1-yl)-1,6,6-trimethyl-8-azabicyclo[3.2.1]-octane ((1S,5R)-12). According to the general procedure for enamine synthesis, reaction of formamide (**1S,5R**)-**11** (684 mg, 3.77 mmol) with pentylmagnesium chloride (2.0 M in THF, 2.42 mL, 4.84 mmol) in Et_2O (5 mL) at room temperature for 17 h gave, after distillation, enamine (**1S,5R**)-**12** (504 mg, 57%):[37] other data as above.

Asymmetric Alkylation of Enamines (1*R*,5*S*)-12 and (1*S*,5*R*)-12 with EtI. According to the general procedure for enamine alkylation, reaction of enamine (**1R,5S**)-**12** (151 mg, 0.64 mmol) with EtI (200 mg, 1.28 mmol) in d_3-MeCN (690 μL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde (**S**)-**13**[12] (58:42 *er*,[12,38] 60 mg, 73%).

According to the general procedure for enamine alkylation, reaction of enamine (**1S,5R**)-**12** (214 mg, 0.91 mmol) with EtI (284 mg, 1.82 mmol) in d_3-MeCN (1 mL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde (**R**)-**13**[12] (55:45 er,[12,38] 91 mg, 78%).

Homotropane (1*S*,5*R*)-17 Synthesis. *2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propanal (25).* 2-Methyl-2-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol[31] (7.2 g, 44.9 mmol) was dissolved in CH_2Cl_2 (40 mL) at room temperature. The resulting solution was added rapidly to a suspension of PCC (14.5 g, 67.3 mmol) in CH_2Cl_2 (70 mL) at room temperature with stirring. The mixture immediately turned black on addition of the alcohol. After stirring overnight at room temperature, the mixture was diluted with anhydrous Et_2O (200 mL), the solvent decanted, and the residual black solid washed with Et_2O (3 × 100 mL). The combined organic layers were passed through a small pad of Florisil, and the filtrate was concentrated under reduced pressure. Purification of the residue by bulb-to-bulb distillation gave aldehyde **25**[39] as a clear oil (6.6 g, 93%): bp 75−80 °C (11 mm) (lit.[39] bp 90−95 °C (7 mm)); R_f = 0.44 (10% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 2984 m, 2888 m, 1725 s (C═O), 1471 w, 1376 m, 1215 m, 1163 m, 1099 m, 1045 s (O−C−O), 755 s; ^{1}H NMR (400 MHz) δ 9.69 (s, 1H, CHO), 4.07−3.86 (m, 4H, C_2H_4), 1.23 (s, 3H, CH_3CO), 1.10 (s, 6H, $C(CH_3)_2$); ^{13}C NMR (101 MHz) δ 205.3 (C═O), 111.8 (O−C−O), 64.9 (C_2H_4), 53.7 ($C(CH_3)_2$), 20.2 ($CH_3C\{OC_2H_4O\}$), 17.8 ($C(CH_3)_2$); MS *m*/*z* (ESI$^+$) 181.1 (M + Na$^+$, 6); HRMS *m*/*z* (M + Na$^+$) found 181.0831, calcd for $C_8H_{14}NaO_3$ 181.0835.

(−)-(R,E)-2-Methyl-N-(2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)-propylidene)propane-2-sulfinamide ((−)-(R)-24). Finely ground NaOH (28 mg, 0.70 mmol) was added to a stirred solution of sulfinamide (**R**)-**26** (86 mg, 0.71 mmol) in MeOH (3.5 mL) at room temperature. After 15 min, aldehyde **25** (112 mg, 0.71 mmol) was added. After 16 h, the reaction mixture was evaporated under reduced pressure and the residue dissolved in Et_2O (2 mL) and washed with saturated aqueous NH_4Cl (2 mL). The aqueous layer was separated and back-extracted with Et_2O (4 × 2 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure, to give chiral sulfinimine (**R**)-**24** as a clear oil (175 mg, 94%): R_f = 0.10 (10% EtOAc in petroleum ether); $[\alpha]_D^{25}$ = −246.5° (*c* = 0.3, $CHCl_3$); IR (neat) (cm^{-1}) 2981 m, 2885 m, 1620 m (C═N), 1474 m, 1459 m, 1363 m, 1163 m, 1143 m, 1084 s and 1042 s (S═O and O−C−O), 949 m, 886 m; ^{1}H NMR (400 MHz) δ 8.14 (s, 1H, HC═N), 4.05−3.85 (m, 4H, C_2H_4), 1.27 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.19 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz) δ 173.4 (C═N), 112.2 (O−C−O), 65.1 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 56.8 ($C(CH_3)_3$), 49.5 ($C(CH_3)_2$), 22.3 ($C(CH_3)_3$), 20.7 (CH_3), 20.6 (CH_3), 20.1 (CH_3); MS *m*/*z* (ESI$^+$) 284.1 (M + Na$^+$, 100); HRMS *m*/*z* (M + Na$^+$) found 284.1288, calcd for $C_{12}H_{23}NNaO_3S$ 284.1291.

Grignard Addition to Sulfinimine (±)-24. (±)-2-Methyl-N-(2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamides ((±)-(S_S,R)-20 and (±)-(R_S,S)-20). Magnesium turnings were stirred vigorously under argon overnight,[40] resulting in a color change from gray to black. THF (1.3 mL) was added, followed by 1,2-dibromoethane (2−3 drops), at which point the mixture started to bubble. With close monitoring of the reaction mixture, 2-(3-chloropropyl)-2-methyl-1,3-dioxolane[41] (1.05 g, 6.4 mmol) was added dropwise, ensuring the temperature did not exceed 50 °C (ice bath). After addition, the mixture was stirred for 2 h at room temperature and then diluted with THF (1.9 mL). A portion of the freshly prepared solution of Grignard reagent **23** (190 μL) was added to a stirred solution of sulfinimine (±)-**24** (50 mg, 0.19 mmol) in THF (1.7 mL) at −78 °C and the resultant mixture warmed to room temperature after 30 min. After 16 h the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with Et_2O (3 × 5 mL). The combined organic

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 10−100% Et_2O in petroleum ether) gave inseparable diastereomers of bis-ketal sulfinamide (±)-**20** (73:27 dr) and an unknown, inseparable impurity. From this mixture it was possible, by precipitation with petroleum ether, to partially extract the racemic major diastereomers (±)-(**S_S,R**)-**20** and (±)-(**R_S,S**)-**20** as a white solid (34 mg, 45%); the rest of the material was obtained as a crude mixture (39 mg): mp 75−79 °C; R_f = 0.12 (50% EtOAc in petroleum ether); IR (neat) (cm^{-1}) 3444 w, 3297 w (N−H stretch), 2981 m, 2880 m, 1707 w, 1650 w, 1474 m, 1373 m, 1128 m, 1045 s (S═O and O−C−O), 876 m; ^{1}H NMR (400 MHz) δ 4.05−3.82 (m, 8H, 2 × OC_2H_4O), 3.61 (d, 1H, J = 6 Hz, NH), 3.15−3.00 (m, 1H, J = 6 Hz, NHC*H*), 2.10−1.98 (m, 1H, NHCHCH_AH_B), 1.88−1.78 (m, 1H, CHCH$_2$CH_AH_B), 1.77−1.66 (m, 1H, J_{AB} = 14 Hz, CH-(CH$_2$)$_2$CH_AH_B), 1.65−1.54 (m, 1H, J_{AB} = 14 Hz, CH(CH$_2$)$_2$CH$_A$H$_B$), 1.50−1.36 (m, 2H, NHCHCH$_A$H$_B$ and CHCH$_2$CH$_A$H$_B$), 1.34 (s, 3H, CH_3), 1.243 (s, 9H, C(CH_3)$_3$), 1.235 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 113.8 (O−C−O), 110.2 (O−C−O), 64.7 (OCH_2), 64.6 (OCH_2), 64.5 (OCH_2), 64.2 (OCH_2), 63.6 (NHCH), 56.5 (C(CH_3)$_3$), 46.6 (C(CH_3)$_2$), 39.1 (CHCH$_2$CH$_2$), 32.3 (NHCHCH$_2$), 23.9 (CH_3), 23.1 (C(CH_3)$_3$), 22.0 (CH-(CH$_2$)$_2$CH$_2$), 21.7 (CH_3), 19.9 (CH_3), 19.6 (CH_3); MS m/z (ESI$^+$) 414.2 (M + Na$^+$, 100); HRMS m/z (M + H$^+$) found 392.2470, calcd for $C_{19}H_{38}NO_5S$ 392.2465.

Organolithium ***27*** *Addition to Sulfinimine* ***(R)-24****. (−)-(R)-2-Methyl-N-((R)-2-methyl-2,6-bis(2-methyl-1,3-dioxolan-2-yl)hexan-3-yl)propane-2-sulfinamide (*(−)-(**R_S,R**)-**20***).* 2-(3-Iodopropyl)-2-methyl-1,3-dioxolane[42] (5.88 g, 23.0 mmol) was dissolved in pentane/Et_2O (3:2, 225 mL) at room temperature with stirring. The resulting solution was cooled to −78 °C, and *t*-BuLi (1.7 M in pentane, 28.4 mL, 48.3 mmol) was added dropwise. The mixture was stirred at −78 °C for 5 min and then warmed to room temperature, which resulted in formation of a white slurry. The mixture was stirred at room temperature for 1 h and then recooled to −78 °C. The freshly prepared organolithium **27** was transferred, dropwise via cannula, to a solution of sulfinimine (**R**)-**24** (3.00 g, 11.5 mmol) in THF (57 mL) at −78 °C. After 16 h at −78 °C the mixture was quenched with MeOH (100 mL), warmed to room temperature, and then diluted with H_2O (400 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (4 × 250 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 50−80% EtOAc in petroleum ether) gave bis-ketal sulfinamide (**R_S,R**)-**20** (98:2 dr, 4.09 g, 91%): R_f = 0.12 (50% EtOAc in petroleum ether); $[\alpha]_D^{25}$ = −78.8° (c = 2.2, $CHCl_3$); IR (neat) (cm^{-1}) 3275 w (N−H stretch), 2979 m, 2881 m, 1474 m, 1377 m, 1217 m, 1157 m, 1062 s and 1041 s (S═O and O−C−O), 949 m, 874 m; ^{1}H NMR (400 MHz) δ 5.25 (br s, 1H, NH), 4.07−3.84 (m, 8H, 2 × OC_2H_4O), 3.24 (br s, 1H, NHC*H*), 1.77−1.55 (m, 4H, 1 × CH_2 and 2 × CH_AH_B), 1.50−1.36 (m, 2H, 2 × CH$_A$H$_B$), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.21 (s, 9H, C(CH_3)$_3$), 1.05 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 114.6 (O−C−O), 109.9 (O−C−O), 65.2 (OCH_2), 64.6 (2 × OCH_2), 63.6 (OCH_2), 58.7 (NHCH), 55.4 (C(CH_3)$_3$), 45.3 (C(CH_3)$_2$), 39.4 (CH_2), 33.1 (NHCHCH$_2$), 23.8 (CH_3), 23.2 (CH_3), 22.9 (C(CH_3)$_3$), 22.8 (CH_2), 19.3 (CH_3), 16.8 (CH_3); MS m/z (ESI$^+$) 392.2 (M + H$^+$, 100); HRMS m/z (M + Na$^+$) found 414.2275, calcd for $C_{19}H_{37}NNaO_5S$ 414.2285.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-one ((−)-(**1S,5R**)-**18***).* HCl (2 M in Et_2O, 86 mL) was added to a stirred solution of bis-ketal sulfinamide (**R_S,R**)-**20** (2.69 g, 6.9 mmol) in MeOH (250 mL) at room temperature. The resulting mixture was heated at 75 °C for 2 days. After this time, the mixture was cooled to room temperature, and the volatiles were removed by evaporation under reduced pressure. Aqueous NaOH (3 M, 100 mL) was added to the residue and the resulting suspension stirred for 15 min and then washed with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−10% MeOH in EtOAc) gave homotropinone (**1S,5R**)-**18** as a clear crystalline solid (1.04 g, 83%); mp 40−42 °C; R_f = 0.36 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = −94.4° (c = 0.3, $CHCl_3$); IR (neat) (cm^{-1}) 3310 w (N−H stretch), 2953 m, 2930 m, 1699 s (C═O), 1655 w, 1457 m, 1380 m, 1201 m, 909 m, 730 s; ^{1}H NMR (400 MHz) δ 2.93 (br s, 1H NCH), 2.35 and 2.17 (AB, 2H, J_{AB} = 16 Hz, CH_2C═O), 1.88 (br s, 1H, NH), 1.82 (d, 1H, J_{AB} = 13 Hz, NCHCH_AH_B), 1.57−1.32 (m, 4H, CH_2, CH_AH_B and CH$_A$H$_B$), 1.31−1.15 (m, 1H, CH$_A$H$_B$), 1.22 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 216.2 (C═O), 60.8 (NCH), 53.7 (NCCH$_3$), 50.0 (*C*H$_2$C═O), 46.8 (C(CH_3)$_2$), 38.6 (CH(CH$_2$)$_2$CH$_2$), 31.5 (CH_3), 27.7 (CH_3), 27.2 (NCHCH$_2$), 21.3 (CH_3), 17.9 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 182.1 (M + H$^+$, 52); HRMS m/z (M + H$^+$) found 182.1534, calcd for $C_{11}H_{20}NO$ 182.1539.

(−)-(1S,3R,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonan-3-ol ((−)-(**1S,3S,5R**)-**28***).* LAH (361 mg, 9.5 mmol) was dissolved in THF (10 mL) with stirring and external cooling (ice bath). Homotropinone (**1S,5R**)-**18** (1.50 g, 8.3 mmol) in THF (10 mL) was added, dropwise, with stirring at 0 °C. The reaction temperature was maintained at 0 °C for 30 min and then warmed to room temperature and stirred overnight. After this time, the mixture was recooled to 0 °C and quenched: H_2O (360 μL), then 15% aqueous NaOH (360 μL), and then H_2O (1.1 mL). (*Caution!*) The resulting suspension was filtered and the filter cake washed with CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure, to give homotropinol (**1S,3R,5R**)-**28** as a white solid (1.38 g, 91%): mp 105−110 °C; R_f = 0.10 (20% MeOH in EtOAc); $[\alpha]_D^{25}$ = −22.4° (c = 1.9, $CHCl_3$); IR (neat) (cm^{-1}) 3130 br m (O−H and N−H), 2898 m, 1459 m, 1418 m, 1287 m, 1106 m, 1047 s, 968 s, 821 s; ^{1}H NMR (500 MHz) δ 3.62 (dd, 1H, J_1 = 6 Hz, J_2 = 3 Hz, C*H*OH), 2.70 (d, 1H, J = 4 Hz, NCH), 2.59−2.41 (m, 1H, CH$_2$CH_AH_BCH$_2$), 2.12 (br s, 2H, NH and OH), 1.84 (dd, 1H, J_{AB} = 14 Hz, J = 6 Hz, CH_AH_BCHOH), 1.77 (dd, 1H, J_{AB} = 14 Hz, J = 6 Hz, NCHCH_AH_B), 1.59−1.45 (m, 3H, CH$_A$H$_B$CHOH, NCHCH$_A$H$_B$ and CH(CH$_2$)$_2$CH_AH_B), 1.43−1.32 (m, 2H, CHCH$_2$CH$_A$H$_B$CH$_A$H$_B$), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 71.7 (CHOH), 58.2 (NCH), 47.9 (NC(CH_3)), 41.0 (CH_2CHOH), 36.8 (CH(CH$_2$)$_2$CH$_2$), 36.0 (C(CH_3)$_2$), 33.3 (CH_3), 30.4 (CH_3), 25.9 (NCHCH$_2$), 21.8 (CH_3), 17.2 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 184.2 (M + H$^+$, 32); HRMS m/z (M + H$^+$) found 184.1695, calcd for $C_{11}H_{22}NO$ 184.1696.

(−)-S-Methyl O-((1S,3R,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]-nonan-3-yl)carbonodithioate ((−)-(**1S,3R,5R**)-**29***).* Homotropinol (**1S,3R,5R**)-**28** (299 mg, 1.63 mmol) was dissolved in THF (5 mL) with stirring at room temperature. Imidazole (25 mg, 0.36 mmol) and NaH (203 mg, 8.46 mmol) were added, and the resulting mixture was stirred at room temperature for 30 min. CS_2 (647 μL, 10.76 mmol) was added, dropwise, resulting in an orange coloration. The mixture was heated at 70 °C for 16 h, then cooled to room temperature and MeI (203 μL, 3.26 mmol) added, dropwise. The resulting mixture was stirred at room temperature for 16 h, then evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution 0−20% MeOH in EtOAc) gave xanthate (**1S,3R,5R**)-**29** as an orange solid (336 mg, 75%): mp 40−44 °C; $[\alpha]_D^{25}$ = −17.3° (c = 0.8, $CHCl_3$); R_f = 0.21 (20% MeOH in EtOAc); IR (neat) (cm^{-1}) 2920 m, 1704 w, 1592 w, 1424 m, 1374 m, 1226 s (C═S), 1049 s (MeS−CS−O−R), 965 m, 753 m; ^{1}H NMR (500 MHz) δ 5.60 (dd, 1H, J_1 = 6 Hz, J_2 = 2 Hz, C*H*−O−CS$_2$Me), 2.75 (d, 1H, J = 5 Hz, NCH), 2.60 (s, 3H, SCH_3), 2.39−2.25 (m, 1H, CH$_2$CH_AH_BCH$_2$), 2.00−1.86 (m, 2H, O−CHCH_AH_B and NCHCH_AH_B), 1.77 (dd, 1H, J_{AB} = 16 Hz, J = 2 Hz, O−CHCH$_A$H$_B$), 1.71−1.57 (m, 1H, NCHCH$_A$H$_B$), 1.55−1.39 (m, 3H, CHCH$_2$CH$_A$H$_B$CH$_2$), 1.23 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 215.7 (C═S), 83.9 (CH−OCS$_2$Me), 57.7 (NCH), 47.4 (NC(CH_3)), 37.8 (O−CHCH$_2$), 36.4 (C(CH_3)$_2$), 35.9 (CH(CH$_2$)$_2$CH$_2$), 33.3 (CH_3), 29.9 (CH_3), 25.5 (NCHCH$_2$), 22.5 (CH_3), 18.9 (SMe), 16.9 (CH$_2$CH$_2$CH$_2$); MS m/z (ESI$^+$) 274.2 (M + H$^+$, 100); HRMS m/z (M + H$^+$) found 274.1286, calcd for $C_{13}H_{24}NOS_2$ 274.1294.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane ((−)-(**1S,5R**)-**17***).* Xanthate (**1S,3R,5R**)-**29** (750 mg, 2.74 mmol) and AIBN (135 mg, 0.82 mmol) were dried under vacuum (0.1 mm) for 1 h. Benzene (degassed under Ar for 1 h, 24 mL) was added, followed by

dx.doi.org/10.1021/jo3025972 | J. Org. Chem. 2013, 78, 1508−1518

Bu_3SnH (740 μL, 2.75 mmol), dropwise with stirring at room temperature. The mixture was heated at 85 °C for 16 h, then cooled to room temperature and diluted with 5% aqueous HCl (20 mL). The aqueous layer was washed with CH_2Cl_2 (20 mL) and the organic layer separated. The aqueous layer was basified with 3 M aqueous NaOH and the resulting suspension extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the mixture concentrated by careful evaporation (228 mm, 35 °C). Purification of the residue by bulb-to-bulb distillation gave homotropane **(1*S*,5*R*)-17** as a clear oil (316 mg, 69%): bp 75−85 °C (10 mm); R_f = 0.59 (20% MeOH in EtOAc); $[\alpha]_D^{25}$ = −2.2° (*c* = 1.0, $CHCl_3$); IR (neat) (cm^{-1}) 2949 s, 1486 m, 1450 m, 1361 m, 1196 m, 1061 m, 945 m, 865 m, 753 s; ^{1}H NMR (500 MHz) δ 2.55 (d, 1H, *J* = 5 Hz, NC*H*), 2.02−1.87 (m, 3H, 3 × CH_AH_B), 1.74−1.29 (m, 8H, 3 × CH$_A$*H*$_B$, 2 × CH_2 and NH), 1.08 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (125 MHz) δ 58.2 (NCH), 47.7 ($NCCH_3$), 37.6 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.3 (CH_3), 32.1 ($C(CH_3)_2$), 28.9 (CH_3), 28.3 (CH_3), 26.6 ($NCHCH_2$), 20.4 ($CH_2CH_2CH_2$); MS *m*/*z* (ESI$^+$) 168.6 (M + H$^+$, 42); HRMS *m*/*z* (M + H$^+$) found 168.1744, calcd for $C_{11}H_{21}N$ 168.1747.

(−)-(1S,5R)-1,4,4-Trimethyl-9-azabicyclo[3.3.1]nonane-9-carbaldehyde ((−)-(1S,5R)-30). According to the general procedure for formamide synthesis, reaction of homotropane **(1*S*,5*R*)-17** (156 mg, 0.93 mmol), $BnEt_3NCl$ (104 mg, 0.46 mmol), $CHCl_3$ (749 μL, 9.36 mmol), and 12.5 M aqueous NaOH (2.5 mL) in CH_2Cl_2 (3.3 mL) at reflux for 16 h gave formamide **(1*S*,5*R*)-30** as a clear oil (178 mg, 98%): bp 130−140 °C (1.5 mm); R_f = 0.33 (Et_2O); $[\alpha]_D^{25}$ = −0.6° (*c* = 1.0, $CDCl_3$); IR (film) (cm^{-1}) 2935 m, 1644 s (C═O), 1450 m, 1391 s, 1358 m, 1280 m, 1139 m, 1110 m, 910 w, 752 w; ^{1}H NMR (400 MHz) δ 8.34 (s, 1H, *J* = 5 Hz, CHO), 4.26 (d, 1H, *J* = 5 Hz, NCH), 2.12−1.86 (m, 3H, 3 × CH_AH_B), 1.83−1.71 (m, 2H, 2 × CH_AH_B), 1.67−1.48 (m, 4H, 4 × CH$_A$*H*$_B$), 1.36 (s, 3H, CH_3), 1.31 (dd, 1H, J_{AB} = 14 Hz, *J* = 6 Hz, CH$_A$*H*$_B$), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (101 MHz) δ 158.8 (C═O), 53.3 ($NC(CH_3)$), 52.4 (NCH), 39.3 (CH_2), 36.2 (CH_2), 34.5 (CH_2), 33.8 ($C(CH_3)_2$), 28.7 (CH_3), 27.7 (CH_3), 27.1 (CH_3), 25.2 (CH_2), 19.9 (CH_2); MS *m*/*z* (ESI$^+$) 196.2 (M + H$^+$, 7); HRMS *m*/*z* (M + H$^+$) found 196.1697, calcd for $C_{12}H_{22}NO$ 196.1696.

(1S,5R)-9-((E)-Hex-1-en-1-yl)-1,4,4-trimethyl-9-azabicyclo[3.3.1]nonane ((1S,5R)-16). According to the general procedure for enamine synthesis, reaction of formamide **(1*S*,5*R*)-30** (174 mg, 0.89 mmol) with pentylmagnesium chloride (2.0 M in THF, 557 μL, 1.11 mmol) in Et_2O (810 μL) at room temperature for 16 h gave, after distillation, enamine **(1*S*,5*R*)-16** (170 mg, 77%): bp 125−130 °C (0.1 mm); IR (neat) (cm^{-1}) 3059 w, 2952 s, 2918 s, 2871 m, 1640 s (C═CNR^{1}R^2), 1451 m, 1258 s, 1108 s, 936 s, 903 s, 768 m; ^{1}H NMR (400 MHz, C_6D_6) δ 6.36 (d, *J* = 14 Hz, NC*H*═CH), 4.40 (dt, 1H, J_1 = 14 Hz, J_2 = 7 Hz, NCH═C*H*), 3.13 (d, 1H, *J* = 5 Hz, NC*H*CH_2), 2.21 (dt, 2H, J_1 = J_2 = 7 Hz, CH═CHCH_2), 2.05−1.64 (m, 4H, 4 × CH_AH_B), 1.53−1.16 (m, 10H, 4 × CH$_A$*H*$_B$ and 3 × CH_2), 1.15 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.96 (t, 3H, CH_2CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR (101 MHz, C_6D_6) δ 133.9 (NCH═CH), 98.5 (NCH═CH), 58.0 (NCH), 53.3 ($NC(CH_3)$), 37.1 (CH_2), 36.4 (CH_2), 35.8 (CH_2), 35.0 (CH_2), 34.7 ($C(CH_3)_2$), 32.0 (CH═CHCH_2), 30.4 (CH_3), 29.2 (CH_3), 28.8 (CH_3), 23.0 (CH_2), 21.7 (CH_2), 19.5 (CH_2), 14.7 (CH_2CH_3); MS *m*/*z* (ESI$^+$) 250.3 (M + H$^+$, 100); HRMS *m*/*z* (M + H$^+$) found 250.2528, calcd for $C_{17}H_{32}N$ 250.2529.[37]

Asymmetric Alkylation of Enamine (1*S*,5*R*)-16 with EtI. According to the general procedure for enamine alkylation, reaction of enamine **(1*S*,5*R*)-16** (125 mg, 0.50 mmol) with EtI (156 mg, 1.00 mmol) in d_3-MeCN (536 μL) at 65 °C for 16 h gave, following hydrolysis with acidic buffer (0.5 mL) at room temperature for 5 min, aldehyde **(*S*)-13**[12] (72:28 er,[12,38] 41 mg, 64%).

Computational Methodology. Density functional theory (DFT) calculations were performed using the Gaussian 09 package.[43] Optimizations of the enamine ground-state structures and of transition-state structures for alkylation were performed with the B3LYP density functional[44] using the default (fine) grid density for numerical integration. Harmonic vibrational frequencies were computed for all optimized structures to verify that they were either minima or transition states, possessing zero imaginary frequencies and one imaginary frequency, respectively. This level of DFT calculation has been shown in previous studies to compute relative TS energies in quantitative accord with experimental selectivities.[14] The Pople 6-31G(d) basis set was used for all elements except I, which was described with the LANL2DZ effective core potential and associated valence basis of Hay and Wadt.[45] Effects of solvation due to acetonitrile were implicitly included in all geometry optimizations and in the evaluation of energies using a conductor-like polarizable continuum model (CPCM).[46] Free energies were evaluated at the reaction temperature of 65 °C employing the so-called quasi-harmonic approximation, where all vibrational frequencies lower than 100 cm^{-1} were raised to 100 cm^{-1} as a way to correct for the well-known breakdown of the harmonic oscillator model for the free energies of low-frequency vibrational modes.[47] All possible conformational isomers of the diastereomeric transition structures arising from rotation about the incipient C−C bond were considered and optimized for each enamine: in each case there are two TS geometries for attack from either enamine diastereoface lying within 10 kJ/mol of the global minimum energy structure and thus are the major contributors to the selectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and CIF files giving ^{1}H and ^{13}C NMR spectra for all new compounds, ^{77}Se NMR for determination of er, NOEs of xanthate **(1*S*,3*R*,5*R*)-29** for assignment of stereochemistry, HPLC traces showing enantiopurity, X-ray diffraction data for determination of absolute configuration, Cartesian coordinates, imaginary frequencies, computed energies, and *x*,*y* distances for **TS1**−**TS8**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david.hodgson@chem.ox.ac.uk (D.M.H.); robert.paton@chem.ox.ac.uk (R.S.P.; computational studies).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC and GlaxoSmithKline for an Organic Synthesis Studentship (A.C.), Oxford University Press John Fell Fund (R.S.P.), and the Royal Society (RG 110617; R.S.P.). Additionally, we wish to thank Dr. Arne Dieckmann (UCLA) for helpful discussions and for sharing computer code, Dr. Barbara Odell for NOE 1D NMR analysis, and Dr. Andrew J. Whitehead for helpful discussions.

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