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Acyclic Stereocontrol in the Claisen Rearrangement

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Abstract

This thesis examines the issues of acyclic stereocontrol in the Claisen rearrangement, with particular emphasis on the effects of exopericyclic stereocentres – i.e. those adjacent to the array of atoms directly involved in the sigmatropic process. It is divided into three main parts:

The first section provides a review of the field of acyclic stereocontrol. The models used to explain the development of relationships between stereocenters in systems lacking well-defined conformational constraints are discussed. This is an established field and particular emphasis is given to recent developments in the modelling of such systems.

The second section discusses the results of our studies. Previous examples of exopericyclic stereocontrol in sigmatropic rearrangements are shown. Studies are presented that explore the importance of heteroatom-bearing stereocenters and effects of olefin substitution pattern on the manner and extent of stereoselectivity. Our efforts to exploit these stereochemical effects in the synthesis of small molecules are then presented. A novel reaction sequence is presented in which equilibrating mixtures of allylic azides undergo stereoselective Claisen rearrangements and further chemistry of the products of this transformation is then explored. These studies, and attempts to deploy them in synthesis allow us to draw conclusions on the nature of acyclic stereocontrol in the Claisen rearrangement.

The third section contains experimental procedures and characterisation data for all compounds prepared.

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Declaration

I certify that all work in this thesis is solely my own, except where explicitly stated and appropriately referenced. No part of this thesis has been submitted previously for a degree at this, or any other university.

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I am grateful to Pete Haycock and Dick Sheppard for their expert NMR analysis, Dr. Andrew White for crystallography studies, John Barton for mass spectrometry and Professor Henry Rzepa for helpful discussions.

List of abbreviations

Ac	acetyl
aq	aqueous
Ar	aryl
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
br	broad
BRSM	based on recovered starting material
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bu	butyl
Bz	benzoyl
cat.	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionisation
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
d	doublet

dCr	decarboxylative Claisen rearrangement
Deoxofluor	bis(2-methoxyethyl)aminosulfur trifluoride
DFT	density functional theory
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EI	electrical ionisation
equiv	equivalents
E _{rel}	relative energy
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
h	hours
Hex	hexyl
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
<i>i</i> -	ipso

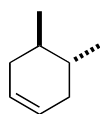
IPA	isopropanol
K _a	acid dissociation constant
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
Lig	ligand
LUMO	lowest occupied molecular orbital
m	multiplet
M	mol dm ⁻³
<i>m</i> -	meta
m/w	microwave
MCPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
Met	metal
min	minutes
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy
NBSH	<i>ortho</i> -nitrobenzenesulfonylhydrazide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
<i>o</i> -	ortho

<i>p</i> -	para
PDC	pyridinium dichromate
Ph	phenyl
PNB	<i>para</i> -nitrobenzyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
py	polystyrene
q	quartet
RHF	restricted Hartree–Fock
rt	room temperature
s	singlet
SCX	silica cation exchange
sept	septet
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBME	<i>tert</i> -butylmethyl ether
TEA	triethylamine
TES	triethylsilyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

THP	tetrahydropyran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl
TS	transition state
v	volume
w	weight

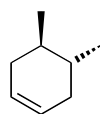
Stereochemical notation

The Maehr convention for indicating relative and absolute stereochemistry has been used throughout this thesis.¹ Solid and broken lines are used to denote racemates, while solid and broken wedges denote absolute configuration. Narrowing of the wedges implies increasing distance from the reader in the latter case.



Racemate

Relative stereochemistry



Single enantiomer

Absolute stereochemistry

Chapter 1

Recent advances in acyclic stereocontrol

1.1 Introduction

1.1.1 Background and scope of the review

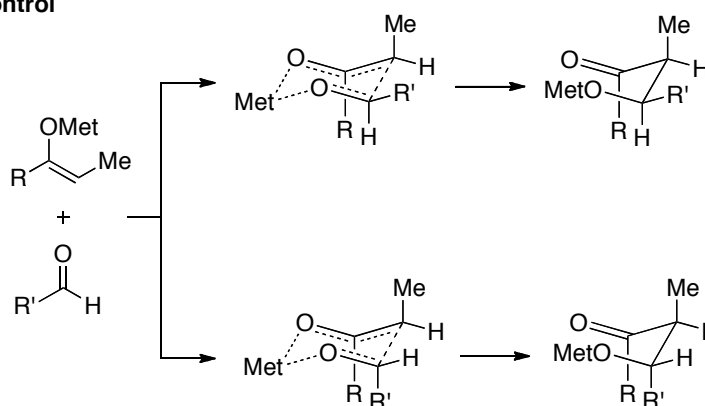
The issue of stereochemical control is central to the development of organic synthesis; in particular, the influence of a pre-existing stereocentre upon the new stereocentres established during a reaction is of key importance. Control of the relationship between two or more stereocentres is readily achieved in cyclic systems in which rigorous conformational constraints are imposed; while control of the relationship between stereocentres is more difficult to achieve in acyclic systems that lack such conformational rigidity. Nevertheless, in the 115 years since Fischer's original report on the stereoselective addition of hydrogen cyanide to aldoses,² the patterns governing acyclic stereocontrol have been intensely investigated and modelled. As a consequence of the continuing development of new stereoselective reactions and advances in computational techniques this remains an active area of interest in organic synthesis, with direct relevance to both the synthesis of small molecules and complex biologically active targets.

Although the work presented in this thesis concentrates on particular aspects of acyclic stereocontrol in the Claisen rearrangement, it is appropriate to give a review of the state of the art in this whole field. This review concentrates on the development of models for predicting the sense of acyclic stereocontrol, particularly over the last 10 years. Three major classes of reaction have been reviewed: addition of nucleophiles to carbonyls, addition of both electrophiles and nucleophiles to C=C double bonds, and pericyclic reactions. A brief account of acyclic stereocontrol in reactions of functional groups adjacent to organometallic complexes is given. We concentrate only on the relationships between adjacent stereocentres. Remote acyclic stereocontrol is beyond the scope of this review. Reactions involving chiral auxiliaries, and strategies for establishing absolute asymmetric induction are not covered. Individual examples of acyclic stereocontrol in the Claisen rearrangement are given a more detailed treatment in Chapter 2 of this thesis.

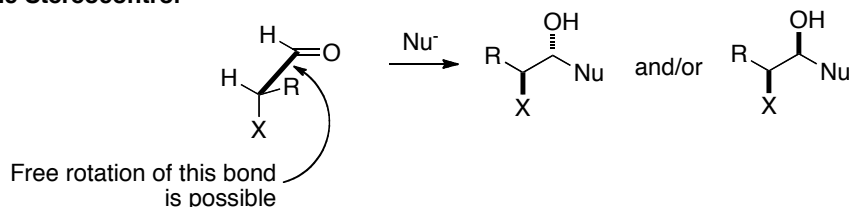
1.1.2 Stereochemical definitions

The term ‘acyclic stereocontrol’ appears to have a somewhat flexible definition in the literature, and below is an attempt to define the term. While a particular reaction may establish a relationship between stereocentres in an acyclic molecule, this can be a result of highly ordered cyclic transition states. As an example, the relationships between pseudoequatorial and pseudoaxial substituents in cyclic Zimmerman–Traxler transition states that determine stereoselectivity in the aldol reaction are an example of cyclic stereocontrol;³ while the stereoselectivity of nucleophilic addition to a carbonyl adjacent to a stereocentre is an example of acyclic stereocontrol (Scheme 1).

Cyclic Stereocontrol

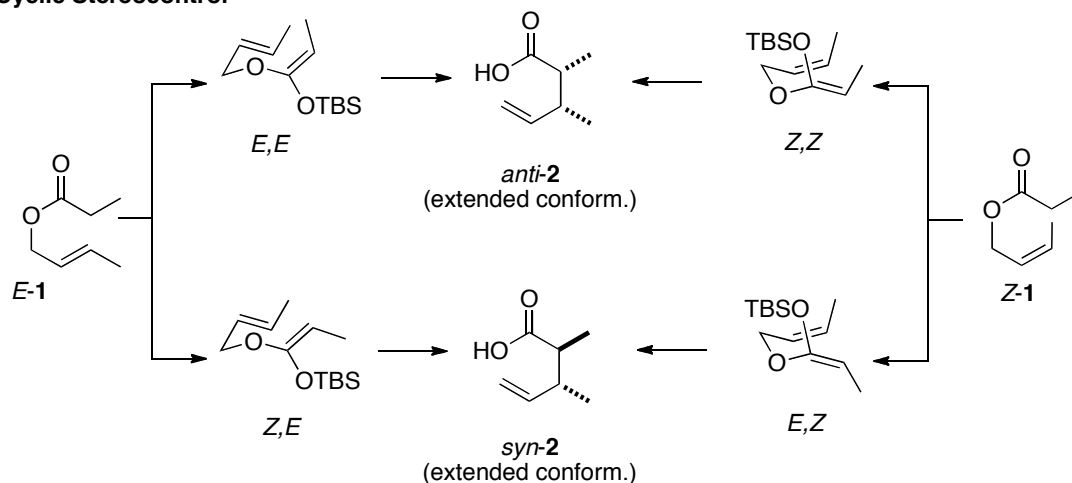
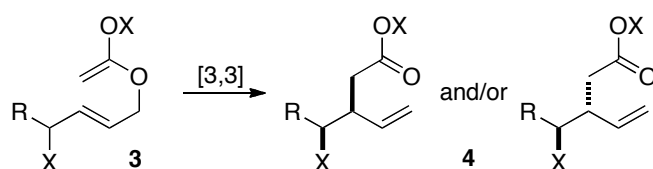


Acyclic Stereocontrol



Scheme 1

A similar dichotomy is shown in the two Claisen rearrangements below (Scheme 2). Although both cases result in acyclic products, in the Ireland–Claisen rearrangement the relative configuration of the two new stereocentres formed during the sigmatropic process is controlled by the relative geometries of the vinylic and allylic portions of the ketene acetal, because the reaction occurs *via* a cyclic transition state.^{87a} Conversely, as will be discussed in depth in this thesis, the relationship between a stereocentre outside the pericyclic array and the new C—C bond formed during a Claisen rearrangement **3**→**4** is a function of acyclic stereocontrol.

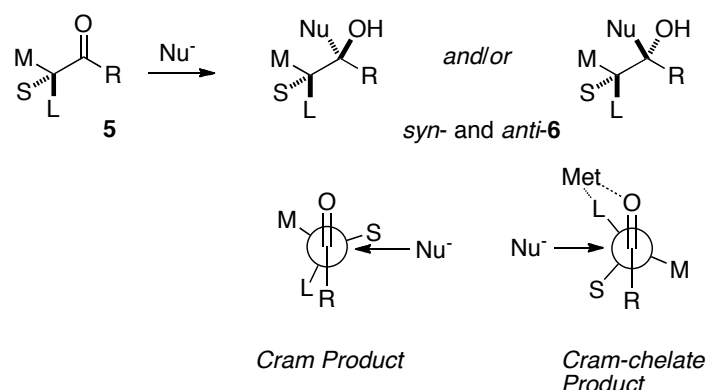
Cyclic Stereocontrol**Acyclic Stereocontrol****Scheme 2**

Therefore, acyclic stereocontrol refers to reactions where the reacting moiety is free to undergo rotation relative to a pre-existing stereocentre but adopts a preferred reactive conformation. Reaction can then occur from either one of two diastereotopic faces as determined by transition state interactions.

1.2 Nucleophilic addition to carbonyls with an adjacent stereocentre

1.2.1 Historical basis of models

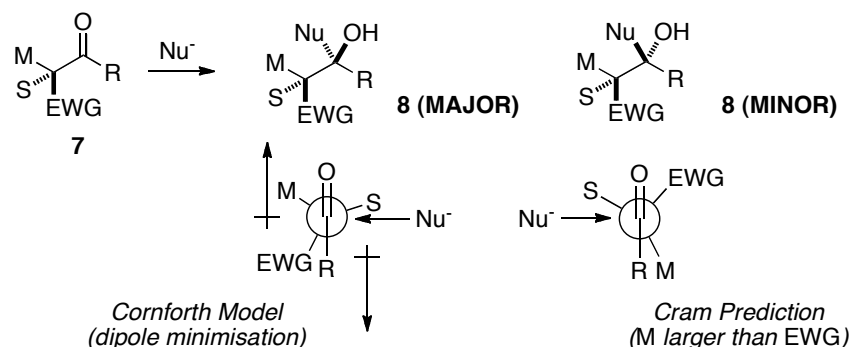
Although the historical development of this area has been comprehensively reviewed,⁴ a brief overview is given here to aid further discussion, particularly as recent discussions of stereocontrol remain based on these models. In 1952, Cram reported an analysis of 1,2-asymmetric induction in the addition of nucleophiles to carbonyl compounds bearing an adjacent stereocentre **5**.⁵ In this case, the largest (L) group adopts a conformation *anti* to the carbonyl group for steric reasons. The nucleophile then attacks preferentially from the side of the small (S) substituent. The outcome of the reaction is modified if chelation (usually mediated by a metal) between the carbonyl oxygen and one of the substituents on the adjacent stereocentre is possible. The large (L) substituent now eclipses the carbonyl group, yet attack still preferentially occurs from the side of the small (S) substituent (Scheme 3).



Scheme 3

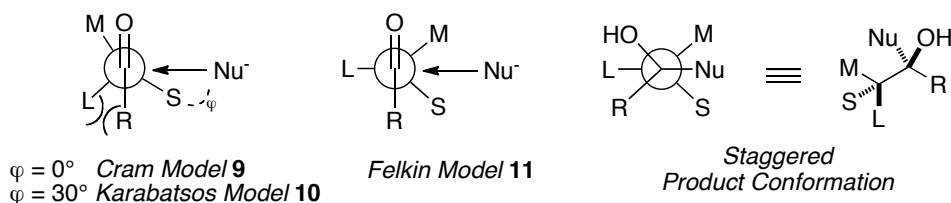
The Cram model is generally reliable in its explanation for the diastereoselectivity of carbonyl addition reactions unless polar substituents are present on the adjacent stereocentre. Cornforth, studying the reaction of Grignard reagents and alkyllithiums with α -chloroketones **7** noted that the α -chloro group took the role of the large substituent, even if more sterically demanding substituents were also present.⁶ In a Cram-type model, this represents a nearly eclipsing arrangement between the carbonyl dipole and the C—Cl bond. The conformation with antiparallel alignment of the C=O and C—Cl dipoles was suggested. In the same fashion as the Cram model,

attack of the nucleophile then occurs from the side of the smaller substituent (Scheme 4).



Scheme 4

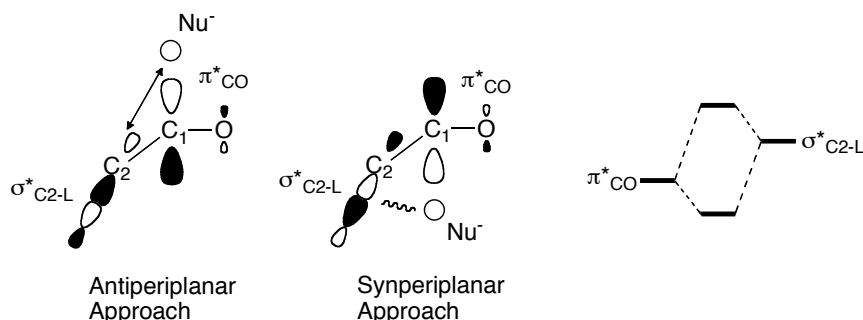
Karabatsos suggested a transition state model **10** and highlighted the importance of the nucleophile attacking along the less hindered trajectory.⁷ An alternative interpretation was given by Felkin,⁸ who suggested that if a either Karabatsos or Cram-type transition state was assumed, increasing the size of the large group would lead to a reduction in stereoselectivity due to strain between the L and R substituents. This is not born out experimentally and an investigation into lithium aluminium hydride reduction of ketones adjacent to a stereocentre, in combination with an examination of polar effects suggested the reaction was best described by a staggered transition state **11**. In this case, the largest, or most electronegative group lies perpendicular to the plane of the carbonyl, antiparallel to the approach of the nucleophile. Additionally, the staggered Felkin transition state **11** is preferable to the analogous Cram transition state **9** in that it leads directly to the more stable staggered conformation of the product (Scheme 5).



Scheme 5

Refinements to the model were made by Anh and Eisenstein,⁹ who investigated the individual factors involved in attack of the nucleophile antiperiplanar to the largest or most donating group. Arrangement of the C2—L bond perpendicular to the carbonyl group results in overlap of the C2—L σ^* and C=O π^* orbitals, lowering the energy of

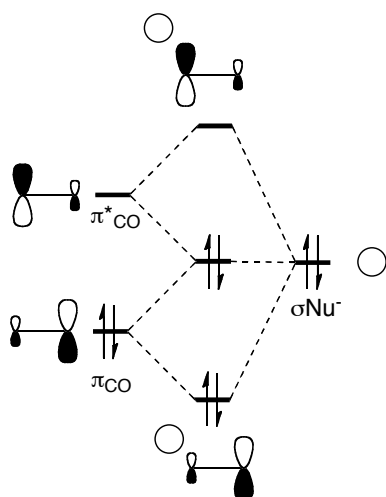
the LUMO. Antiperiplanar attack of the nucleophile then gives a more favourable overlap with the combination of orbitals than synperiplanar attack (Scheme 6).



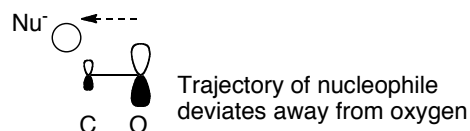
Scheme 6

Computational evidence suggested that the Bürgi–Dunitz angle¹⁰ should be taken into account (Scheme 7) in agreement with approach of the nucleophile along the least hindered trajectory, reconciling the model with those of Cram and Karabatsos. The combination of the above refinements is now referred to as the polar Felkin–Anh model, and it persists as a widely accepted explanation for acyclic stereocontrol in addition of nucleophiles to carbonyls with adjacent stereocenters.

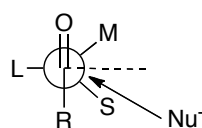
*Linear Combination of Orbitals
(Bürgi/Dunitz):*



Overall result:



Polar Felkin–Anh Model:



Scheme 7

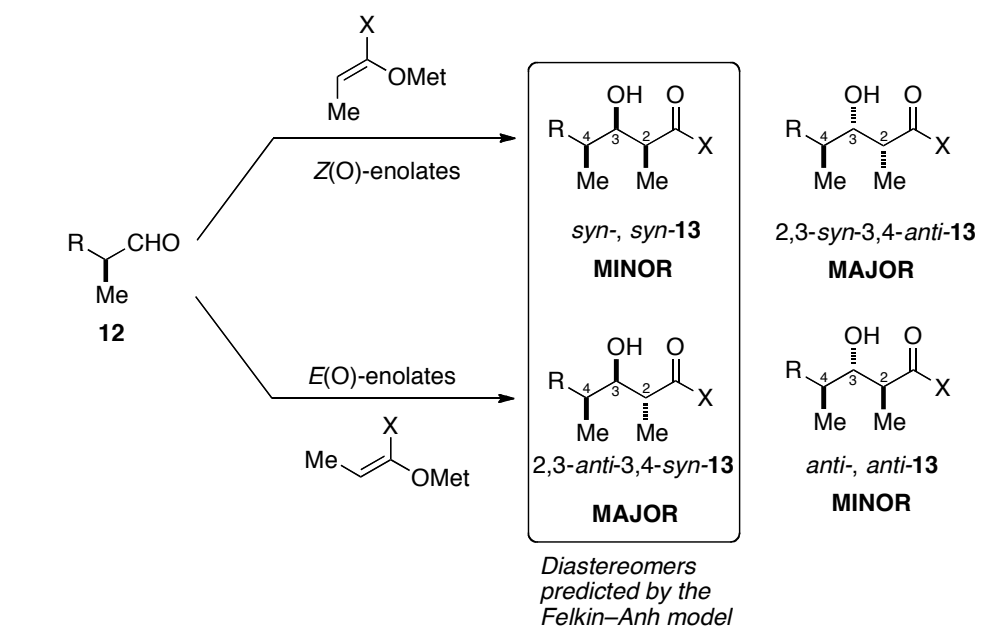
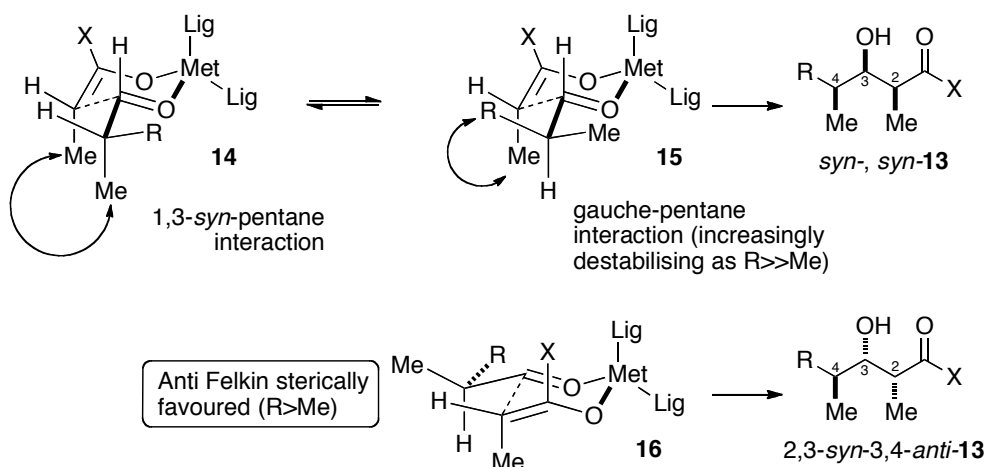
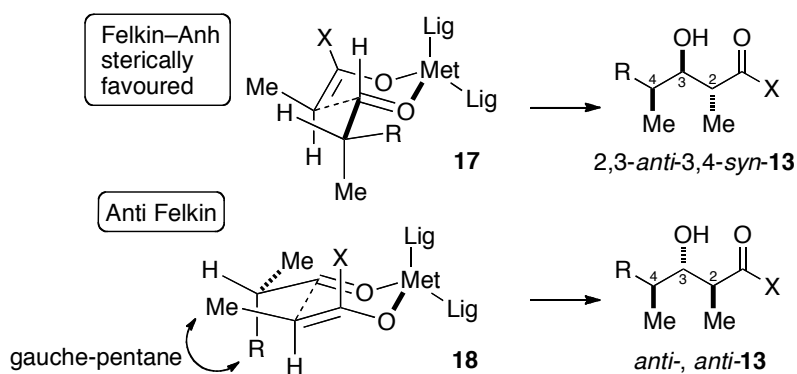
1.2.2 Acyclic stereocontrol adjacent to a cyclic transition state

The most important recent developments in attack on carbonyls with an adjacent stereocentre have arisen from investigations into allylboration of aldehydes with an

adjacent stereocentre, and aldol reactions of boron enolates derived from ketones with aldehydes bearing an adjacent stereocentre. Mengel and Reiser have reviewed earlier work in this area.^{4d} In these reactions, stereoselectivity has been rationalised using a combination of the Zimmerman–Traxler and Felkin–Anh models. This is an example of acyclic stereocontrol occurring adjacent to a well-defined, cyclic transition state. Parallels can be drawn with exopericyclic stereocontrol in sigmatropic rearrangements, for which similar transition states are proposed; therefore a discussion of the literature in this area is highly relevant to our studies.

Both Roush¹¹ and Gennari¹² have discussed this area. A transition state analysis is presented in Scheme 8. For each reaction with *E*- or *Z*-enolates, Zimmerman–Traxler transition states establish the relationship between C2 and C3 in line with the prediction. The relationship between C3 and C4 is determined by acyclic stereocontrol. While reactions of *E*-enolates give the product predicted by the Felkin–Anh model, the opposite ‘anti Felkin’ diastereomer is the major product of reaction of *Z*-enolates. According to Roush, the dominant stereocontrol element determining aldehyde diastereofacial selectivity is the minimisation of gauche-pentane interactions in the competing transition states. For *Z*-enolates the Felkin–Anh transition state **14** contains an unfavourable *syn*-pentane interaction. A rotation of the aldehyde bond to the adjacent stereocentre of 120° partially relieves this interaction (transition state **15**), but this is still destabilised relative to the anti Felkin transition state **16** by a gauche pentane interaction. The case for *E*-enolates is somewhat simpler, since the Felkin–Anh transition state **17** contains the fewest gauche pentane interactions and also benefits stereoelectronically from the antiperiplanar alignment of the forming C—C and aldehyde C—R bonds. Hoffmann and Roush have reported similar diastereoselectivity patterns in allylation reactions.¹³

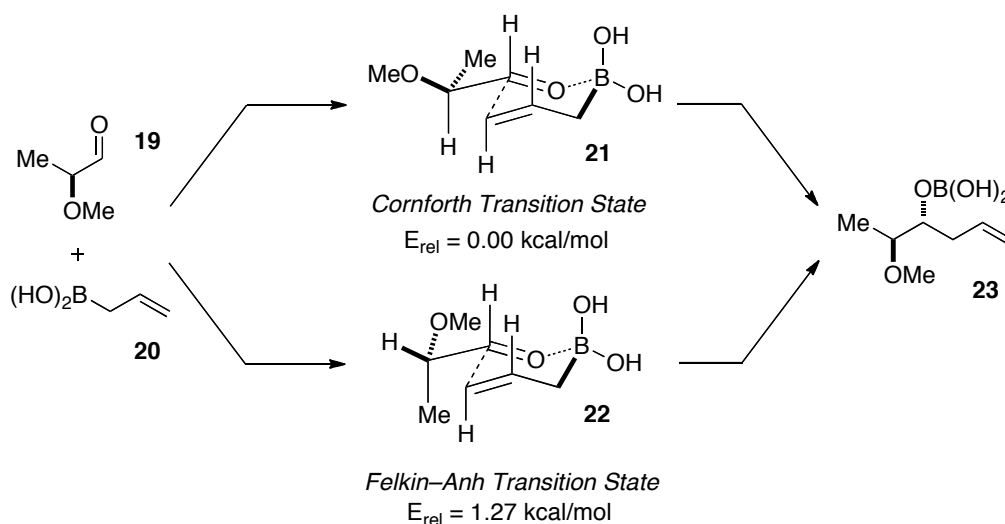
There have been recent reports of additions of nucleophiles to carbonyls adjacent to a polar stereocentre, where the stereoselectivity is also poorly rationalised by the polar Felkin–Anh model. Indeed, numerous authors have suggested that Cornforth-type transition states, where the polar substituent is orientated antiparallel to the carbonyl group, minimising dipolar interactions might better explain such reactions.¹⁴

Transition States for $\text{Z}(\text{O})$ -Enolate Aldol ReactionsTransition States for $\text{E}(\text{O})$ -Enolate Aldol Reactions

Scheme 8

1.2.3 Recent evidence for the Cornforth model

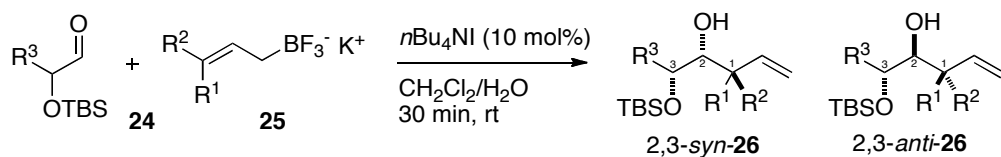
The dichotomy between Felkin–Anh and Cornforth transition states in the context of allylation reactions was investigated by Gung in 2001 using *ab initio* computational methods.¹⁵ For the reaction of allylboronic acid **20** with 2-methoxypropanal **19**, the relative energies of the Felkin–Anh **22** and Cornforth **21** transition states (which both lead to the same product **23**) were calculated, with the former being higher in energy by 1.27 kcal/mol (Scheme 9). The criterion for the Felkin–Anh model, that the nucleophile approaches antiperiplanar to the $\alpha\text{C}—\text{O}$ bond is poorly satisfied in this case. This deviation is attributed to conformational factors, particularly a *syn*-pentane interaction between the axial vinyl protons of the allylboron moiety and the α -methyl group of the aldehyde. In light of these results the authors calculated the energies of individual fragments of the transition states with frozen geometry. However, they did not find any evidence of charge separation between the $\alpha\text{C}—\text{O}$ and carbonyl groups that would be expected for a Cornforth transition state. They concluded that the relative energies of the Felkin–Anh and Cornforth transition states were a function of conformational constraints only.



Scheme 9

Cornforth transition state models have found continued use in the study of diastereoselective allylation and crotylation reactions. In 2003, Batey reported the diastereoselective allylation and crotylation of α - and β -siloxy substituted aldehydes under phase transfer conditions, which was used in a total synthesis of the anti-obesity drug tetrahydrolipstatin.¹⁶ Both *E*- and *Z*- potassium allyl- and crotyltrifluoroborates

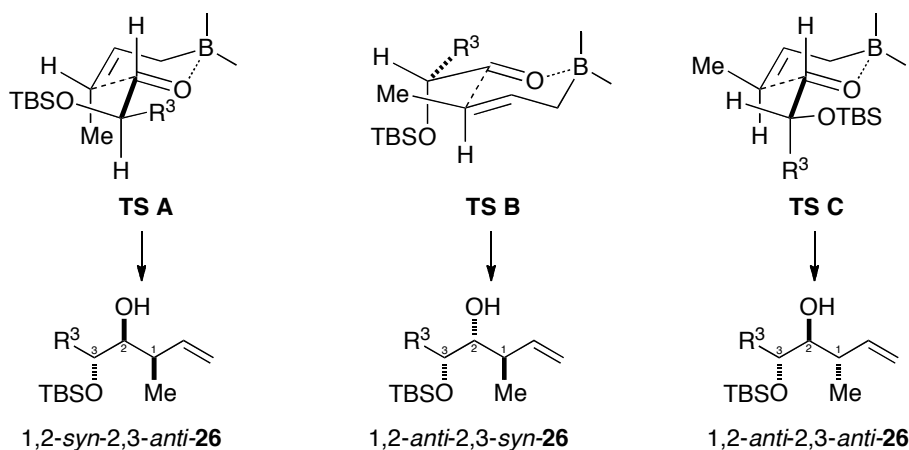
25 reacted with α -*tert*-butyldimethylsiloxy aldehydes **24** to give, in all but one case, the 2,3-*anti* product **26** in uniformly high yield (Scheme 10, Table 1).



Scheme 10

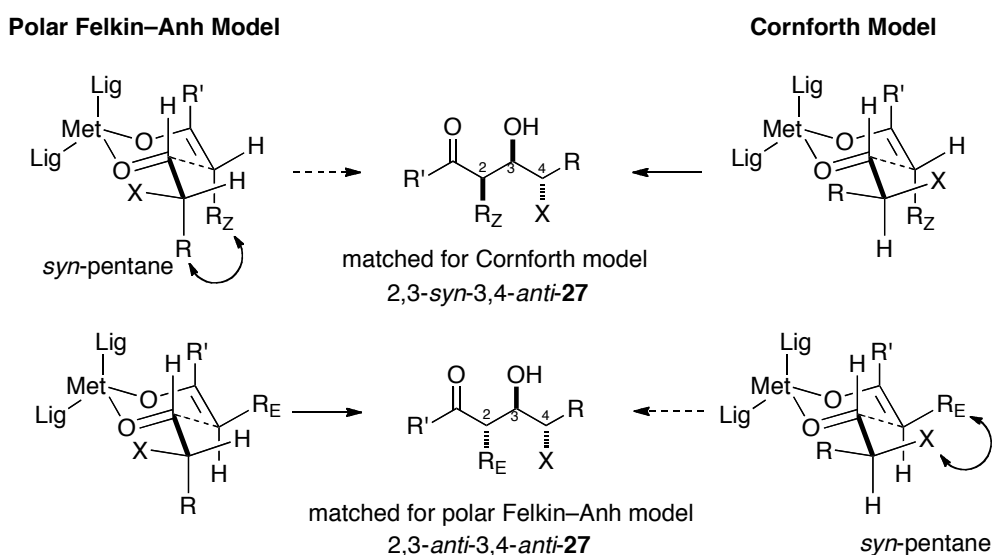
Table 1						
Entry	R ¹	R ²	R ³	<i>E/Z</i>	Ratio of 2,3- <i>syn</i> : 2,3- <i>anti</i> 26	Yield (%)
1	H	H	Me	-	30 : 70	95
2	H	H	Ph	-	35 : 65	94
3	Me	H	Me	<i>Z</i>	5 : 95	95
4	H	Me	Me	<i>E</i>	75 : 25	95
5	Me	H	Ph	<i>Z</i>	10 : 90	97
6	H	Me	Ph	<i>E</i>	10 : 90	99

The major product 2,3-*anti*-**26** derived from a Cornforth transition state (**TS A**) for reactions of *Z*-crotyl trifluoroborates (entries 3 and 5), while the same product derived from a Felkin–Anh type transition state (**TS C**) in the reactions of an *E*-crotyl trifluoroborate (entry 6) in agreement with the predictions of Roush.^{11,13a} The analogous behaviour when R³=Me was unexplained by the authors, but would suggest a greater gauche-pentane interaction between the allyl group and the aldehyde α -methyl than between the allyl group and the α -siloxy substituent. Lower selectivity was observed in allylation reactions (entries 1 and 2), presumably resulting from less significant *syn*-pentane interactions in the transition state leading to 2,3-*syn*-**26** (**TS B**) (Scheme 11).



Scheme 11

Detailed studies of Cornforth transition states for the aldol reaction which combine experimental and computational data, have been performed. However, experimental discrimination between Cornforth and polar Felkin–Anh models is difficult, particularly as both often predict the same product. An experiment which would differentiate between the two models¹⁷ was proposed by Evans. As shown in the above examples of allylation and aldol reactions, such discrimination is possible when the nucleophile imposes a conformational constraint on the orientation of the stereocentre adjacent to the electrophilic carbonyl. For reactions of *E*- and *Z*-enolates, both Felkin–Anh and Cornforth transition states were proposed that lead to the 3,4-*anti* product **27**. The 2,3-relationship was set by the choice of *E*- or *Z*-boron enolate, the geometries of which are reliably reflected in the product stereochemistry. Lithium enolates were also included for generality, although they are inherently less diastereoselective (in defining the 2,3-relationship) (Scheme 12).

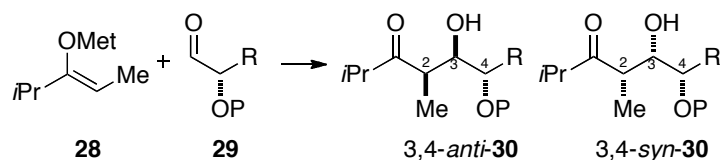


Scheme 12

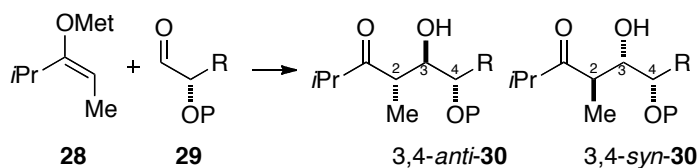
In the prediction of the polar Felkin–Anh model, the *Z*-enolate substituent causes a destabilising *syn*-pentane interaction, while the *E*-enolate substituent experiences no such interaction. Therefore, *E*-enolates are predicted to give superior 3,4-*anti* selectivity relative to *Z*-enolates. Conversely, in the prediction of the Cornforth model, *E*-enolate substituent causes a destabilising *syn*-pentane interaction, while the *Z*-enolate substituent experiences no such interaction. Therefore, *Z*-enolates are predicted to give superior 3,4-*anti* selectivity relative to *E*-enolates. Thus, the *E*- and *Z*-boron and lithium enolates of 2-methyl-3-pentanone **28** were combined with a

representative set of α -oxy-substituted aldehydes **29** (Scheme 13, Table 2). In general, relative to *Z*-enolates, the *E*-isomers showed greatly diminished selectivity for the 3,4-*anti* diastereomer, in support of the Cornforth model.

Aldol reactions of *Z*-enolates



Aldol reactions of *E*-enolates

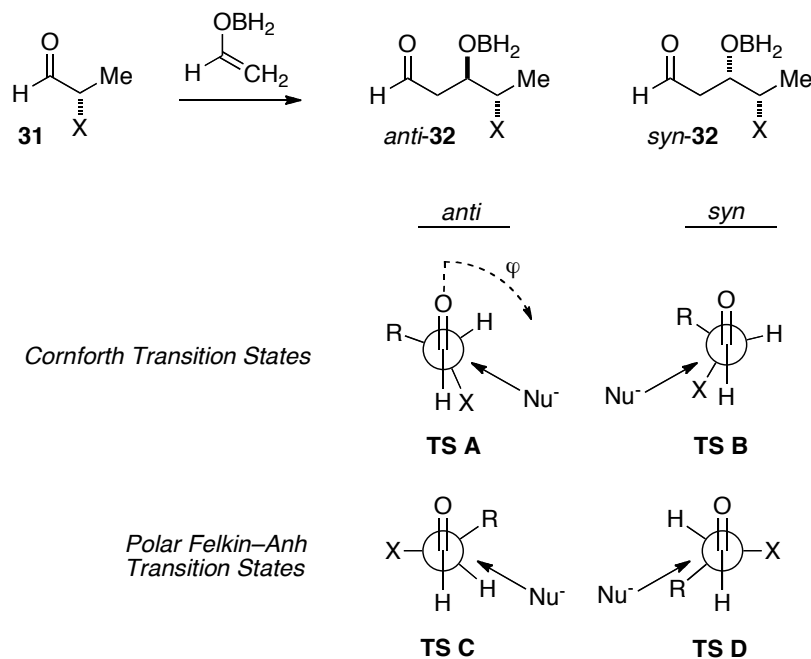


Scheme 13

Table 2									
Aldol reactions of <i>Z</i> -enolates					Aldol reactions of <i>E</i> -enolates				
Met	P	R	3,4- <i>anti</i> - : 3,4- <i>syn</i> -30	Yield (%)	Met	P	R	3,4- <i>anti</i> - : 3,4- <i>syn</i> -30	Yield (%)
9-BBN	Bn	Me	89 : 11	95	(cHex) ₂ B	Bn	Me	33 : 67	59
9-BBN	Bn	<i>i</i> Pr	98 : 2	73	(cHex) ₂ B	Bn	<i>i</i> Pr	67 : 33	77
9-BBN	TBS	Me	98 : 2	77	(cHex) ₂ B	TBS	Me	21 : 79	77
9-BBN	TBS	<i>i</i> Pr	98 : 2	72	(cHex) ₂ B	TBS	<i>i</i> Pr	43 : 57	85
Li	Bn	Me	89 : 11	67	Li	Bn	Me	93 : 7	92
Li	Bn	<i>i</i> Pr	98 : 2	77	Li	Bn	<i>i</i> Pr	80 : 20	78
Li	TBS	Me	95 : 5	65	Li	TBS	Me	85 : 15	78
Li	TBS	<i>i</i> Pr	99 : 1	71	Li	TBS	<i>i</i> Pr	88 : 12	80

More recently, Evans has performed a theoretical investigation of boron enolate addition to α -heteroatom-substituted aldehydes, comparing polar Felkin–Anh and Cornforth transition state models using DFT methods.^{18,19} Highly electronegative substituents (F, OMe, Cl) and less electronegative substituents (PMe₂, SMe, NMe₂) were assessed. For the halopropanals **31** (X=F, Cl) transition states leading to both *anti*- (TS A and C) and *syn*-**32** (TS B and D) were calculated. For di- and tri-valent heteroatoms, where rotamers of the C—X bond are possible, only the transition states leading to the *anti* product were calculated (Scheme 14, Table 3). The relative energies of Cornforth and Felkin–Anh transition state structures are highly dependent on the nature of the heteroatom substituent, with chlorine, fluorine and oxygen

substituents favouring the Cornforth arrangement and nitrogen, sulfur and phosphorus substituents favouring the polar Felkin–Anh arrangement.



Scheme 14

Table 3					
X		Cornforth		Polar Felkin–Anh	
		TS A	TS B	TS C	TS D
F	φ (deg)	166	196	264	76
	E_{rel}^a	0.0	0.8	2.4	3.7
Cl	φ (deg)	175	186	267	76
	E_{rel}^a	0.0	0.6	0.4	2.4
OMe	φ (deg)	171	-	267	-
	E_{rel}^a	0.0	-	1.7	-
SMe	φ (deg)	174	-	271	-
	E_{rel}^a	3.3	-	0	-
NMe ₂	φ (deg)	172	-	272	-
	E_{rel}^a	0.8	-	0.0	-
PMe ₂	φ (deg)	175	-	276	-
	E_{rel}^a	3.5	-	0.0	-

^aCalculated using the B3LYP method with the 6-31G(d) basis set. Energies are given in kcal/mol.

Further analysis suggested that the nucleophile→ $\sigma^*_{\text{C-X}}$ interaction central to the polar Felkin–Anh model was energetically insignificant in reactions of carbonyls with boron enolate nucleophiles. However, it was shown that when X=SMe and X=PMe₂

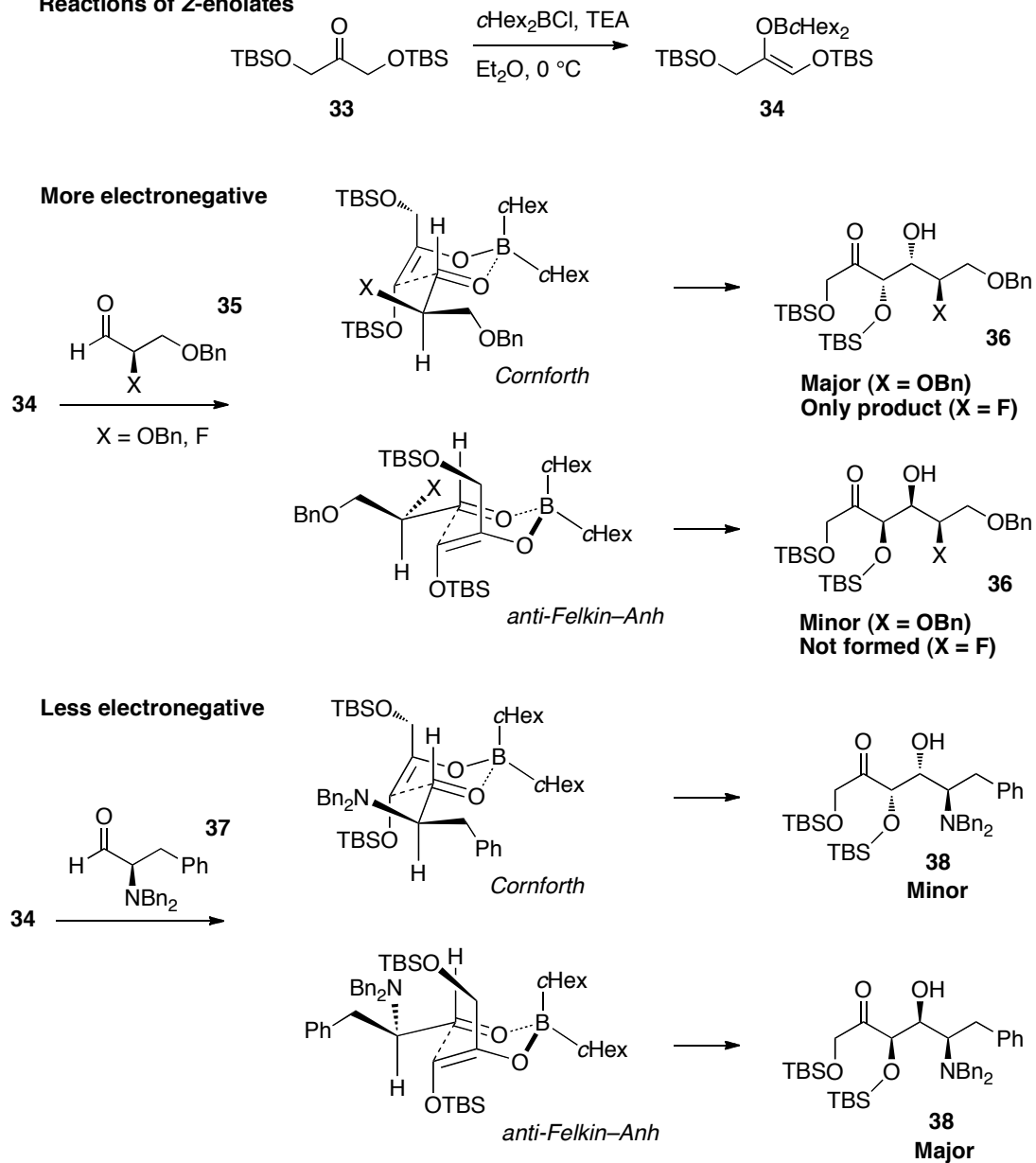
perpendicular alignment of the C—X bond with the carbonyl group (as in the Felkin–Anh model) was favoured due to $\sigma^*_{\text{C-X}} \rightarrow \pi^*_{\text{C=O}}$ delocalisation. Transition states were also calculated for the above aldol reactions¹⁷ in good agreement with experimental data. This work by Evans represents perhaps the most in-depth study in this area to date, and aspects of this methodology have been recently employed in the synthesis of the natural product (+)-peluroside A.²⁰

Similar relationships of Cornforth models with heteroatom electronegativity are evident in the investigations of Marco into doubly diastereoselective aldol reactions²¹ of L-erythulose derivatives with aldehydes bearing an adjacent stereocentre.²² In the most striking case, aldehydes bearing α -fluoro- and α -benzyloxy groups reacted *via* Cornforth transition states, while α -amino aldehydes reacted *via anti*-Felkin–Anh transition states. In these cases, the non-stereogenic ketone **33** was used to form the corresponding *Z*-boron enolate **34**. Additional conformational constraints are placed on the transition states by the dipolar repulsion between the enolate C—O and remaining α -C—OTBS bonds resulting in an antiperiplanar alignment (Scheme 15). Aldehydes bearing α -methyl groups were also studied, which reacted *via* Felkin–Anh transition states as predicted, although computational investigations by other groups have recently suggested that Felkin–Anh models might not be as generally applicable for attack on carbonyls adjacent to non-heteroatomic stereocentres.²³

1.2.4 Conclusions

As the above discussion demonstrates, modelling of nucleophilic addition to carbonyls adjacent to a stereocentre is still a highly active area of development, with numerous studies over the last 10 years that challenge the dominance of the Felkin–Anh model.²⁴ Additional factors must be taken into account when the acyclic stereocontrol arises from the presence of stereocentres adjacent to well-defined transition states. In short, the rotational conformation around the α -stereocentre is dependent on the nature of the nucleophile. Additionally, although the Felkin–Anh model is still useful, its theoretical basis remains in question.²⁵ There is no one model that reliably describes all cases. However, in the case of polar stereocentres, there has been a resurgence in use of the Cornforth model to describe diastereoselectivity.²⁶

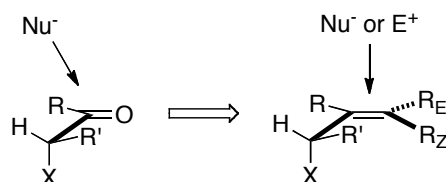
Reactions of Z-enolates



Scheme 15

1.3 Addition to C=C double bonds with an adjacent stereocentre

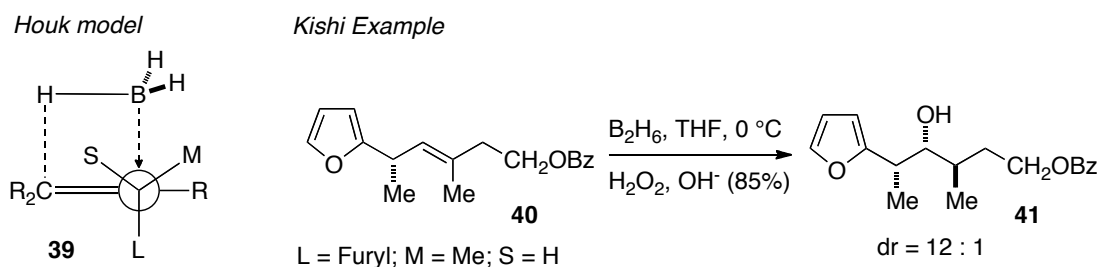
The case for addition of both nucleophiles and electrophiles to olefins is somewhat more complicated than for analogous reactions with carbonyls. Felkin–Anh-type models provide a theoretical basis for these reactions where the carbonyl group is replaced by a C=C double bond (Scheme 16).²⁷ However, additional conformational constraints are imposed by the double bond substituents and the level of acyclic stereocontrol is often highly dependent on the double bond substitution pattern. As for the previous section, this area has been reviewed relatively recently by both Reiser^{4d} and Fleming³⁶ (*vide infra*). A brief historical treatment is given, followed by accounts of recent developments.



Scheme 16

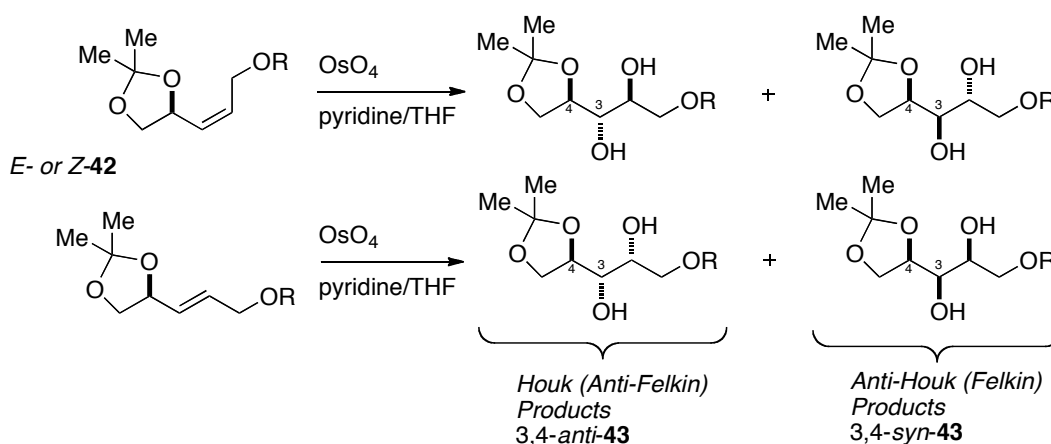
1.3.1 Electrophilic Addition

Calculations of torsional effects in additions of electrophiles to substituted butenes by Houk suggested that staggered transition states were preferred in additions of electrophiles to C=C double bonds adjacent to a stereocentre.²⁸ Attack of the electrophile in these systems occurs perpendicular to the double bond; deviations from this trajectory suffered large energy penalties. Therefore, the lowest-energy structure is that in which the stereocentre exerts the least hindrance to the incoming electrophile, or in an alternative view, that which interacts least with the forming bond. For hydroboration,²⁹ this corresponds to the staggered transition state **39** with the smaller (S) substituent pointing ‘inside’ the double bond, and attack *anti* to the L group. This conformation has the additional advantage of minimising 1,3-allylic strain. Notably, this corresponds to the *anti*-Felkin product **41**, as in the example of Kishi (Scheme 17).³⁰



Scheme 17

Kishi reported similar results in the osmylation of protected and unprotected allylic alcohols **42** (Scheme 18, Table 4, showing selected examples).³¹ The selectivity is rationalised by invoking the Houk model. The increased selectivity upon switching from *E*- to *Z*-allylic double bond geometry is clear indication of the importance of 1,3-allylic strain in this model. As we will see, 1,3-allylic strain is perhaps the most important control element in additions to C=C double bonds, and is a component of most models. This subject has been reviewed in detail by Hoffmann.³²

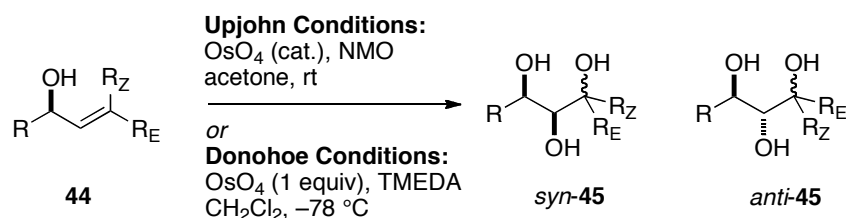


Scheme 18

Table 4			
Entry	R	<i>E/Z</i>	Ratio 3,4- <i>anti</i> - : 3,4- <i>syn</i> - 43
1	H	<i>E</i>	3.3 : 1
2	C(O)CMe ₃	<i>E</i>	4.2 : 1
3	TBDPS	<i>E</i>	3.1 : 1
4	H	<i>Z</i>	6.1 : 1
5	C(O)CMe ₃	<i>Z</i>	6.3 : 1
6	TBDPS	<i>Z</i>	8.0 : 1

In a more recent example Donohoe has reported that *syn* selectivity is possible in osmylations of unsaturated alcohols **44** in the presence of TMEDA, which further illustrates the importance of 1,3-allylic strain for acyclic stereocontrol in additions to

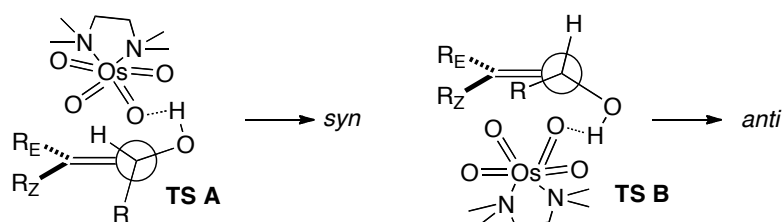
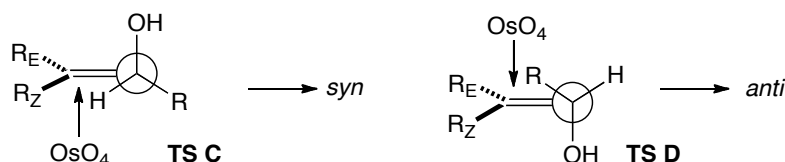
C=C double bonds.³³ The OsO₄–TMEDA conditions, which exploit OH⋯O=Os hydrogen-bonding³⁴ were compared with the substoichiometric OsO₄–NMO ‘Upjohn’ conditions (Scheme 19, Table 5).



Scheme 19

Table 5							
Entry	R	R _E	R _Z	Upjohn Conditions		Donohoe Conditions	
				Ratio <i>syn</i> - <i>anti</i> -45	Yield (%)	Ratio <i>syn</i> - <i>anti</i> -45	Yield (%)
1	<i>n</i> Pr	H	H	25 : 75	80	60 : 40	74
2	<i>n</i> Pr	<i>n</i> Pr	H	25 : 75	85	75 : 25	83
3	<i>n</i> Pr	<i>t</i> Bu	H	17 : 83	83	80 : 20	75
4	<i>i</i> Pr	<i>n</i> Pr	H	20 : 80	75	75 : 25	84
5	<i>n</i> Pr	H	<i>n</i> Pr	62 : 38	76	96 : 4	74
6	<i>t</i> Bu	H	<i>n</i> Pr	80 : 20	85	96 : 4	79
7	<i>n</i> Bu	Me	Me	66 : 34	96	96 : 4	78

Transition states were proposed to account for these selectivity patterns (Scheme 20). The increase in magnitude of the observed *syn* selectivity on switching from *E*- to *Z*-isomers under Donohoe conditions is explained by **TS A** and **TS B**. In both, the hydrogen-bonding interaction is maintained that leads to attack of the oxidant from the same face as the alcohol. However, although **TS B**, which leads to the *anti* product satisfies the conditions for hydrogen-bonding, it is disfavoured by 1,3-allylic strain between the R and R_Z groups. Therefore, when the R_Z substituent is non-hydrogen, reaction *via* **TS A**, which leads to the *syn* product is favoured. Similar transition states **TS C/D** can be proposed to account for the reversal in selectivity under Upjohn conditions. Although selectivity is comparatively low under these conditions, the preferred *anti* products from reaction of *E*-allylic alcohols can be formed *via* **TS C** in which the R group eclipses the double bond. Conversely, **TS D** must be invoked for oxidation of *Z*-allylic alcohols to minimise 1,3-allylic strain.³⁵

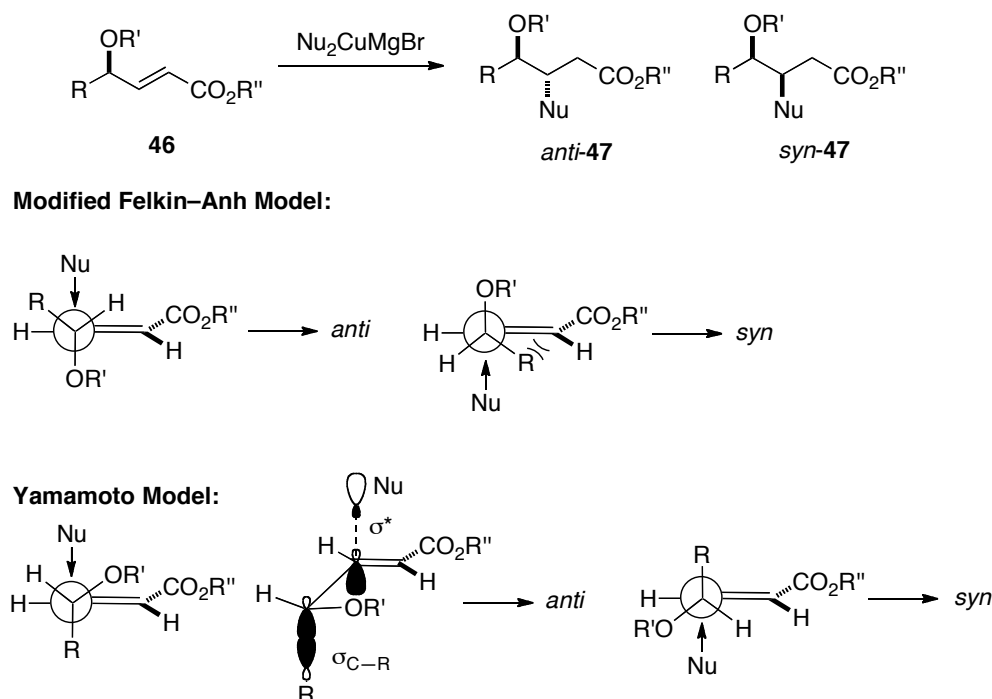
Donohoe Conditions**Upjohn Conditions****Scheme 20**

This is defined by in a recent review by Fleming as the ‘inside methyl’ effect:³⁶ where, in systems lacking a significant 1,3-allylic strain component, the major product can arise from a transition state in which the smallest group does not eclipse the double bond (cf. **TS B/D**, Scheme 20). Its occurrence is highly dependent upon both the substrate and reaction in question. The effect is also observed in nucleophilic additions.

1.3.2 Nucleophilic additions

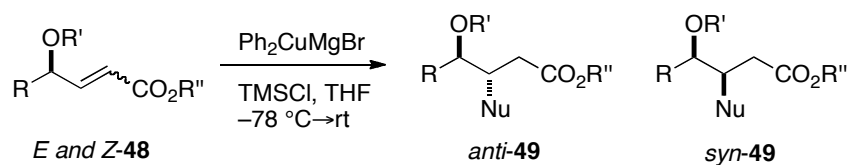
The majority of studies in this area have concentrated on the conjugate addition of organocuprate nucleophiles to enoates **46** bearing a γ -stereocentre, in particular due to the use of this method in the synthesis of polypropionate building blocks for natural products.³⁷ A summary of models for describing this reaction has recently been published by Kornienko.³⁸ In the case of γ -alkoxy and γ -siloxy stereocentres, the *anti* product *anti-47* generally predominates.³⁹ The two most prevalent models for this selectivity are the ‘modified Felkin–Anh’ originally described by Roush,⁴⁰ which parallels that for electrophilic addition to C=C double bonds, and the Yamamoto model,⁴¹ which has many features in common with the Cieplak⁴² and Houk ‘inside-alkoxy’⁵⁷ models *vide infra* (Scheme 21). Yamamoto argued that the reactive conformation is stabilised by overlap of the electron rich C—R bond with the developing C—Nu σ^* orbital. The model correctly predicts a reversal from *anti* to *syn*

selectivity in reactions of *Z*-enoates, as increased 1,3-allylic strain favours the conformation with the hydrogen roughly eclipsing the double bond.



Scheme 21

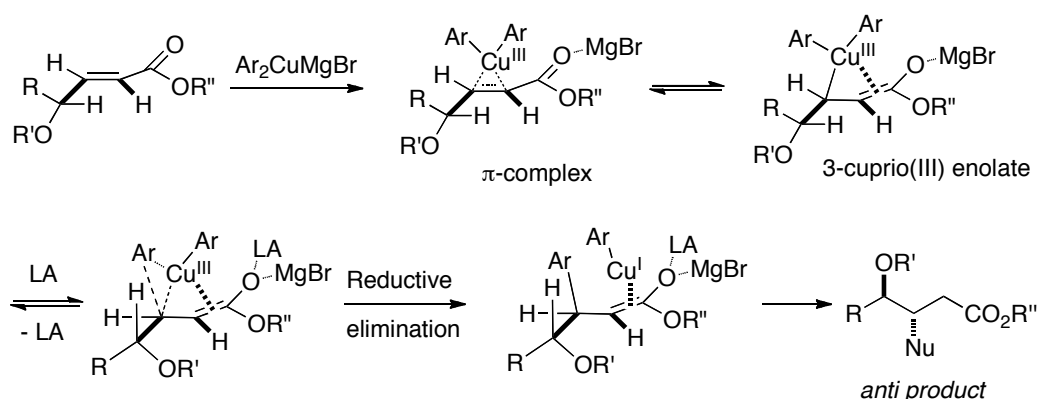
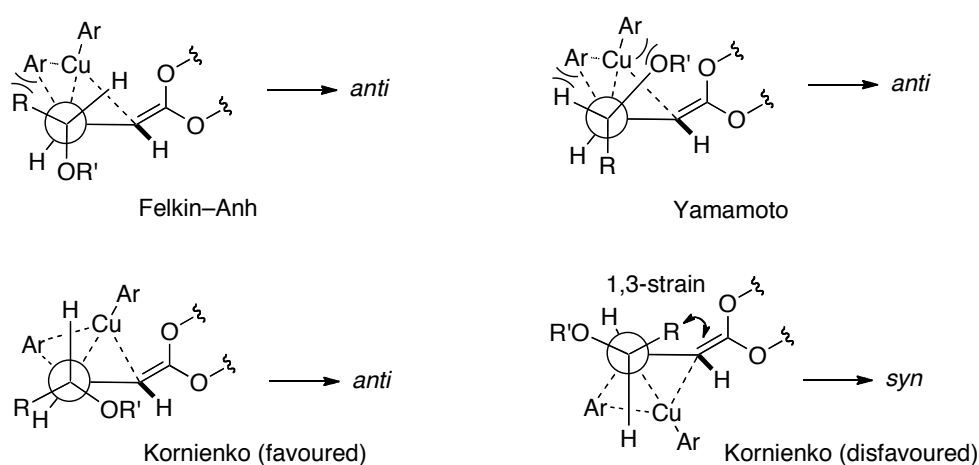
Kornienko studied the addition of various diarylcuprates⁴³ to a representative set of γ -alkoxyenolates **48**, with variations in the alkoxy group, R group and enolate geometry (Scheme 22, Table 6). The high selectivities in addition to *E*-enoates are consistent with the modified Felkin–Anh model, as the selectivity is independent of the size of the R' group (Entry 1,2) which is orientated antiperiplanar to the incoming nucleophile. The reduction in selectivity with reducing size of the R group is also consistent with this model (Entry 2,3,4). The Yamamoto model leads to the opposite prediction: that selectivity should be highly dependent on the size of the R' group (OR' eclipses the enoate in the transition state leading to the *anti* product); and that selectivity should be largely independent of the R group. The moderate selectivities for addition to *Z*-enoates are poorly explained by both models. The modified Felkin–Anh model suggests *anti* selectivity should be higher for *Z*-enoates, while the Yamamoto model suggests that *syn* products should predominate.



Scheme 22

Table 6						
Entry	R	R'	R''	E/Z	Yield (%)	Ratio <i>anti</i> - : <i>syn</i> -49
1	CH_2OTBDPS	MOM	Et	<i>E</i>	80	>50 : 1
2	CH_2OTBDPS	Bn	Me	<i>E</i>	88	>50 : 1
3	CH_2OBn	Bn	Me	<i>E</i>	94	14.6 : 1
4	Me	Bn	Me	<i>E</i>	89	5.4 : 1
5	CH_2OTBDPS	Bn	Me	<i>Z</i>	87	1.6 : 1
6	CH_2OBn	Bn	Me	<i>Z</i>	72	2.8 : 1
7	Me	Bn	Me	<i>Z</i>	65	3.4 : 1

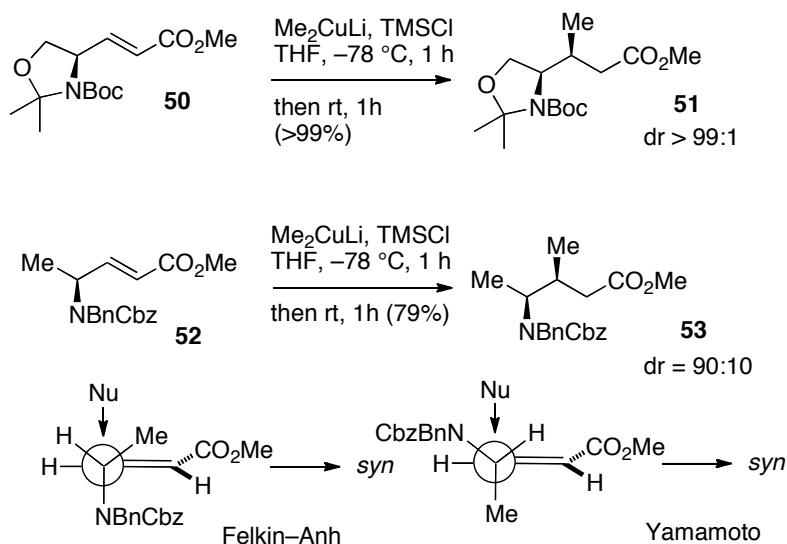
A revised model was suggested that takes into account recent mechanistic studies in the conjugate additions of organocuprates,⁴⁴ with the assumption that the reductive elimination step of the reaction is both rate- and stereochemistry-determining. This contrasts with the Yamamoto and modified Felkin–Anh models, which assume complexation with the enoate to be the step controlling facial selectivity (Scheme 23).

Mechanism of cuprate addition:**Reductive elimination transition states:****Scheme 23**

Both Felkin–Anh and Yamamoto transition states for the reductive elimination step contain eclipsing interactions with the complexed and almost planar organocuprate. The transition states proposed by Kornienko position the R and OR' groups away from the large cuprate moiety.⁴⁵ Also notable are the two roughly antiperiplanar relationships in this transition state: firstly between the C_γ—OR' and forming C_β—Ar bonds; and secondly between the C_γ—R and breaking C_β—Cu bonds. In the former, favourable mixing of the σ_{C_β—Ar} and low-lying σ*_{C_γ—OR'} orbitals is maintained; while in the latter case overlap of the electron rich σ_{C_γ—R} and σ*_{C_β—Cu} orbitals assists the departure of copper. These transition states are consistent with the experimental data.

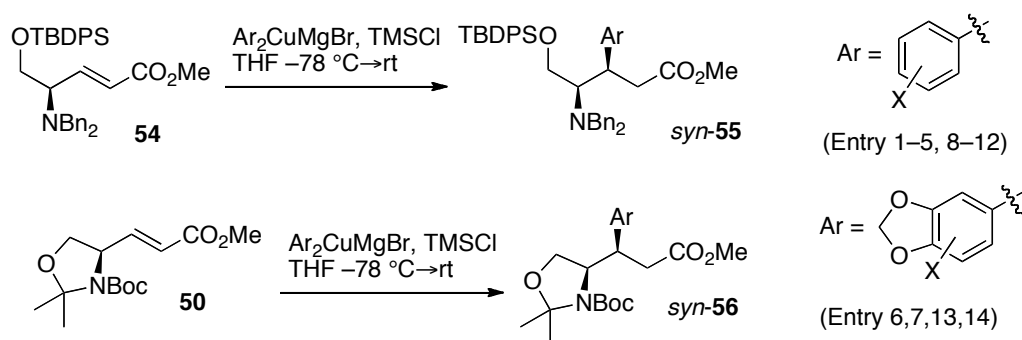
The sense of selectivity is reversed in the presence of γ-amino stereocentres, and the *syn* product predominates. This stereochemical divergence was discussed as early as 1991 by Hanessian.⁴⁶ Two substrates **50**, derived from Garner's aldehyde⁴⁷ and **52** underwent *syn*-selective addition with dimethylcuprate–TMSCl (Scheme 24).

According to Hanessian, the *syn*-products **51** and **53** could derive from either Felkin–Anh or Yamamoto transition states, although neither of these give a convincing explanation of the reversal of selectivity in changing from oxygen to nitrogen.



Scheme 24

A more recent treatment of this dichotomy has been given by Kornienko.⁴⁸ Substrates similar to those investigated by Hanessian were treated with a variety of diarylcuprates (Scheme 25, Table 7). Although diastereoselectivity was effectively absolute in all cases, much lower yields were observed for the bulkier substrate **54**.

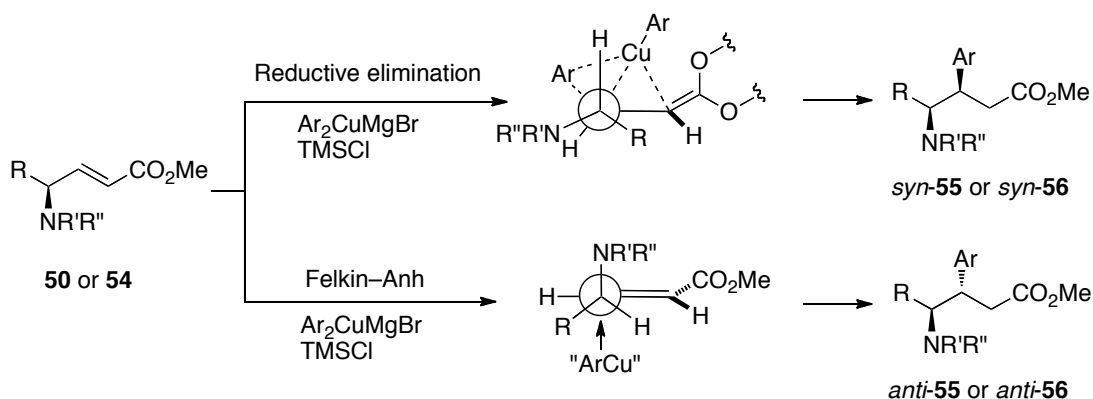


Scheme 25

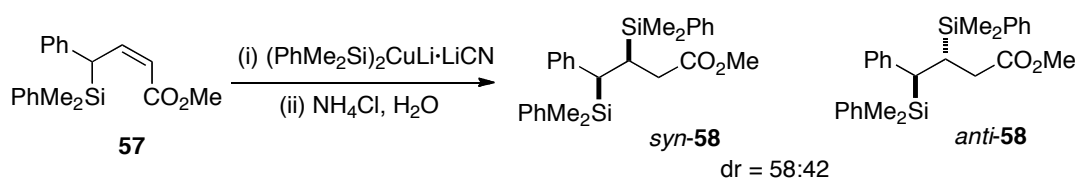
Table 7

Reaction of 54				Reaction of 50			
Entry	X	Yield (%)	Ratio <i>syn</i> - : <i>anti</i> - 55	Entry	X	Yield (%)	Ratio <i>syn</i> - : <i>anti</i> - 56
1	H	58	>20 : 1	8	H	95	>20 : 1
2	4-OMe	50	>20 : 1	9	4-OMe	87	>20 : 1
3	4-F	55	>20 : 1	10	4-F	92	>20 : 1
4	4-Cl	58	>20 : 1	11	4-Cl	83	>20 : 1
5	3,4-OMe	49	>20 : 1	12	3,4-OMe	70	>20 : 1
6	H	52	>20 : 1	13	H	92	>20 : 1
7	5-OMe	0	-	14	5-OMe	70	>20 : 1

In common with the previous study, considering that the Felkin–Anh model predicts predominance of the *anti* product, a ‘reductive-elimination’ transition state was proposed to account for the observed *syn* selectivity (Scheme 26). Although the reduced yields in the case of bulkier R groups (increased 1,3-allylic strain) agree with this model, it is unclear whether this transition state benefits from the favourable orbital interactions of the transition state leading to the *anti* product.

**Scheme 26**

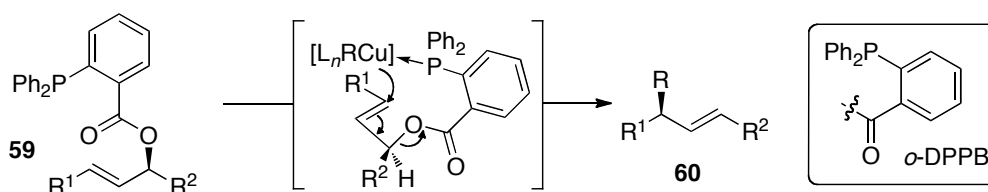
In additions of organocuprates to C=C double bonds adjacent to a silicon-containing stereocentre, diastereoselectivity is somewhat lower. Fleming reported the 1,4-addition of silylcuprates to enoates with silicon stereocentres at either the α- or β-position.⁴⁹ Attack occurred predominantly *syn* to the silicon substituent, with the hydrogen eclipsing the double bond. It is difficult to rationalise this result using the above reductive elimination transition states above, although it may be consistent with a Yamamoto-type model in which the *anti* product is disfavoured by the silicon group roughly eclipsing the double bond (Scheme 27).



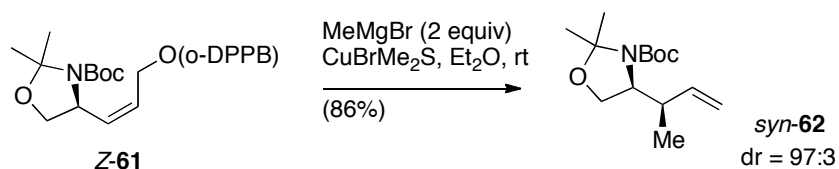
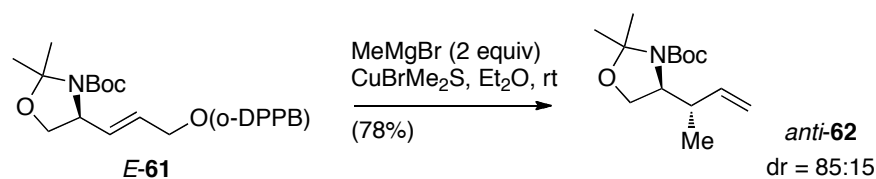
Scheme 27

Further recent examples of acyclic stereocontrol in organocuprate additions have been reported by Breit, who used phosphine substituents for directed delivery of the cuprate.⁵⁰ While *E*-configured substrates **E-61** afforded *anti* products, the *syn* products were obtained from the isomeric *Z*-configured substrates **Z-61**. The level of selectivity was independent of the size of the nucleophile (Scheme 28).

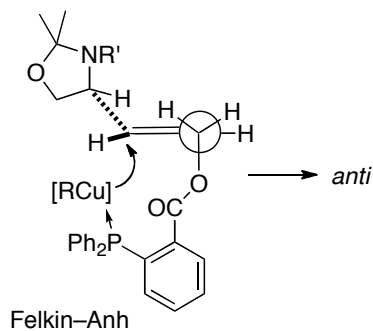
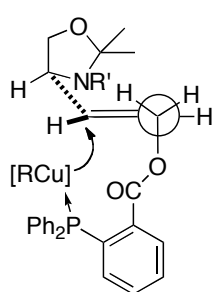
α -DPPB-directed allylic substitution



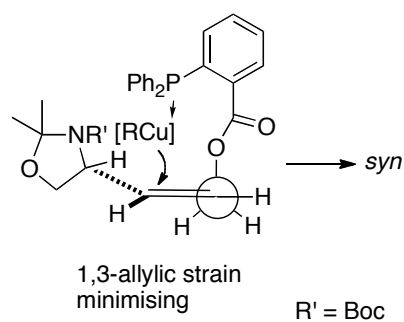
Stereospecific examples:



E-substrate



Z-substrate



Scheme 28

Carbon nucleophiles undergo stereoselective addition to enoates with a γ -stereocentre, and similar models have been used to explain these reactions. The sense of addition of lithium amides varies between *syn* and *anti* depending on substrate,^{51,52} while hydroxylamine nucleophiles generally give the *syn* product.⁵³ Alkoxide nucleophiles have also been studied.⁵⁴ The *anti* sense of rhodium-catalysed conjugate addition of boronic acids to γ,δ -alkoxy enoates has been recently explained using a reductive elimination model.⁵⁵

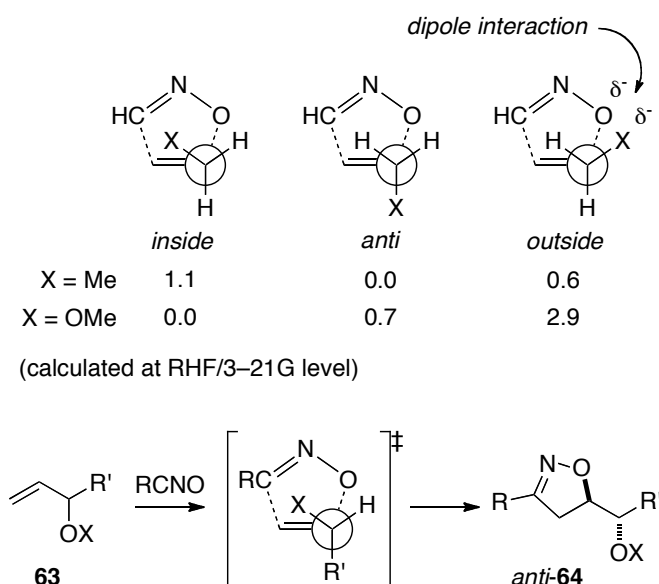
1.3.3 Conclusions

Compared to analogous reactions of carbonyls, addition to double bonds adjacent to a stereocentre is less well defined. Although the Houk model correctly predicts the results of electrophilic addition in many cases, there are exceptions in which the major product arises from seemingly hindered transition states (cf. the inside-methyl effect). For nucleophilic additions, in particular 1,4-addition to enoates with γ -stereocentres, the sense of diastereoselectivity follows clear trends. However, neither the modified Felkin–Anh, Yamamoto or reductive elimination models give conclusive explanations for the changing sense of selectivity with changing γ -heteroatom. Above all, 1,3-allylic strain dominates as an essential control element.

1.4 Pericyclic reactions

1.4.1 [3+2] Cycloadditions

Models for [3+2] cycloadditions follow naturally from those for addition to C=C double bonds, although they differ significantly from Felkin–Anh type models. The case for 1,3-dipolar addition to a C=C double bond adjacent to a stereocentre has been extensively investigated, particularly for chiral allyl ethers **63**. This area has been most recently reviewed in 2001, in which the authors highlight the accuracy with which the established theories predict the observed stereoselectivity.⁵⁶ The two key factors at work are 1,3-allylic strain and the ‘inside-alkoxy’ effects first postulated by Houk (Scheme 29).⁵⁷

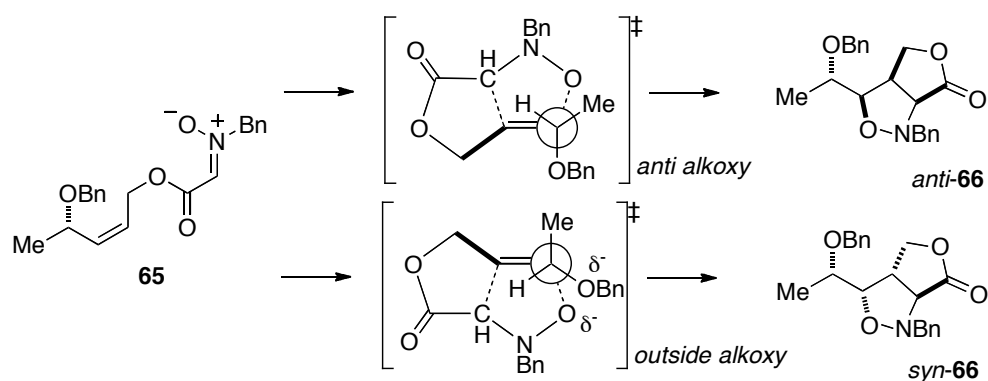


Scheme 29

Houk calculated the relative energies of methyl and methoxy substituents at each of the staggered positions in the cycloaddition transition state. The methyl group preferentially adopted the *anti* configuration, avoiding the *inside* conformation on steric grounds, and allowing hyperconjugation of the $\sigma_{\text{C-Me}}$ and electron-deficient $\pi^*_{\text{C=C}}$ bonds. The methoxy group was situated *inside* in the lowest energy transition state. In the *anti* OMe position, overlap between the $\pi_{\text{C=C}}$ and $\sigma^*_{\text{C-O}}$ orbitals removes electron density from the reacting olefin, disfavours this transition state. Notably, the *anti* disposition of alkoxy groups relative to reacting olefins is shown to be a

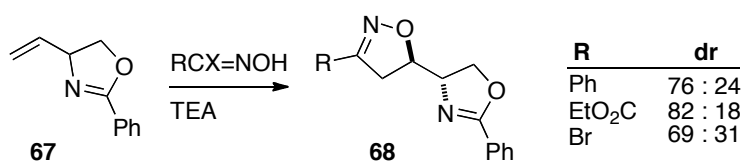
stabilising interaction in other pericyclic reactions, particularly sigmatropic rearrangements, due to a $\pi^*_{C=C}/\sigma^*_{C-O}$ interaction (see Section 2.1). Overall, the most unfavourable orientation is OMe *outside*, which is electrostatically destabilised by interaction of the partial negative charges of the approaching oxygen atoms.

In the case of *Z*-configured substrates where 1,3-allylic strain is greater, the alkoxy group adopts the *anti* position, with the smallest substituent lying *inside*. An example of this is shown in the intramolecular cycloaddition of *Z*-allylic ether **65** (Scheme 30).⁵⁸ Two possible allylic strain-minimising conformations are possible, yet the *outside* alkoxy/*anti* methyl transition state leading to *syn*-**66** is electrostatically disfavoured.



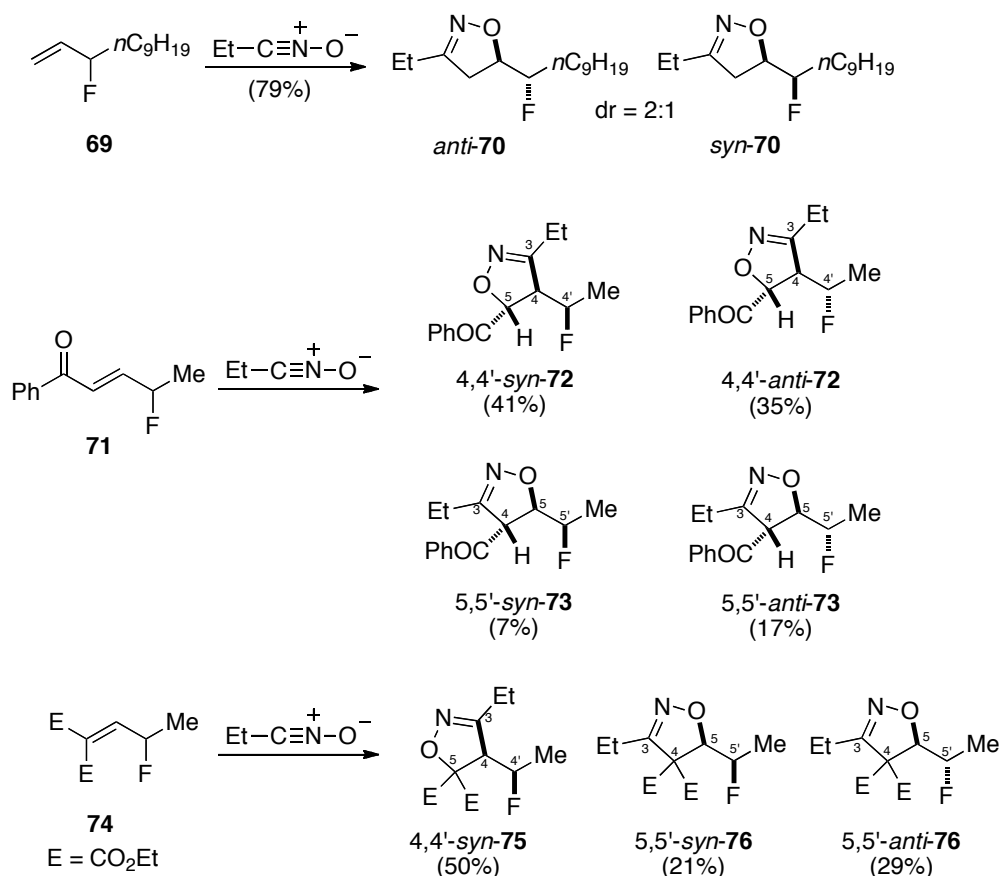
Scheme 30

In contrast to the examples shown above of conjugate nucleophilic addition to enoates, alteration of the heteroatom causes little variation in the sense of the selectivity although some exceptions have been reported. Cycloadditions of nitrile oxides with allylic isoxazoles **67** occur in the inside alkoxy sense and the *anti* product **68** predominates (Scheme 31).⁵⁹ Selectivities are slightly lower than those for allylic ethers, which correlates with the lower electronegativity of nitrogen, causing less destabilisation in *anti* and *outside* transition states. Selectivities for the *anti* product are lower still for acyclic allylic amines.^{59a,60}



Scheme 31

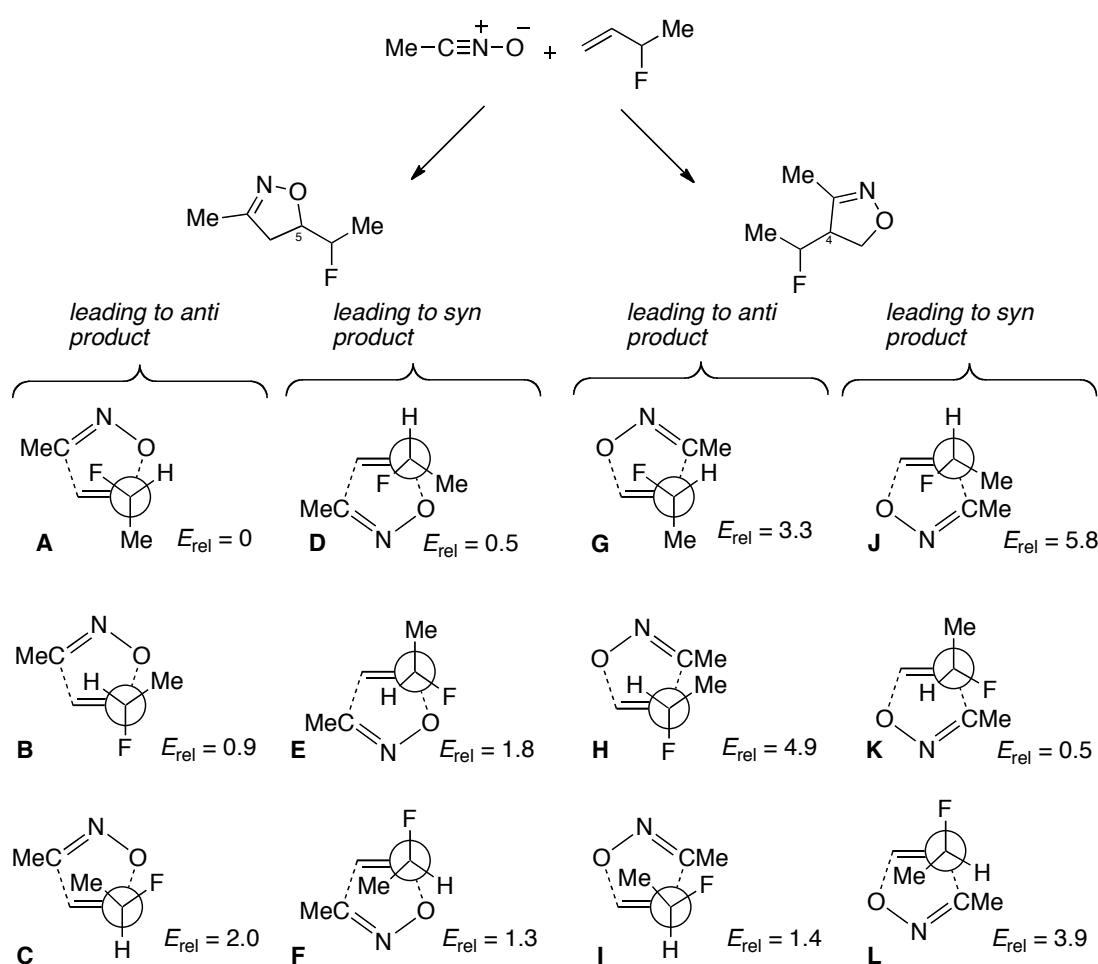
More recently, the preferred conformations of allylic fluorides in transition states for their nitrile oxide cycloadditions have been studied and compared with experimental data.⁶¹ Allylic fluorides were found to react in the sense predicted by the inside alkoxy model, with fluorine taking the place of the alkoxy substituent.⁶² Three allylic fluorides **69**, **71** and **74** were treated with propionitrile oxide to give the corresponding cycloadducts (Scheme 32). **69** reacted in favour of the *anti* adduct. Reaction of **71** and **74** both afforded mixtures of regio- and stereoisomers. For **71** in the series with the stereocentre at the isoxazole 4 position **72**, there was a slight preference for the *syn* cycloadduct. For the series with the stereocentre at the isoxazole 5 position **73** (in common with the above examples), a distinct preference for the *anti* cycloadduct was observed. For **74** in the series with the stereocentre at the isoxazole 4 position **75**, only the *syn* cycloadduct was observed; while with the stereocentre at the 5 position **76**, there was a slight bias for the *anti* product.



Scheme 32

These observations were explained using transition state searches (Scheme 33, calculated at the B3LYP/6-31G* level). For the 5-substituted regioisomer, the lowest

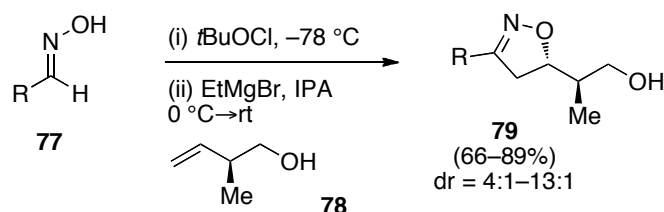
energy transition state (**A**) has fluorine *inside*, with the methyl group in the *anti* position. The second lowest transition state (**D**), which leads to the *syn* product also has fluorine *inside*, but in this case, methyl is *outside* and overlaps poorly with the double bond. However, for transition states leading to the 4-substituted regioisomer, an *inside* fluorine is destabilising due to electrostatic interactions with the oxygen of the 1,3-dipole (transition states **G** and **J**), and the sense of selectivity is reversed. The lowest energy transition state, from which the *syn* product is formed (**K**) has fluorine *outside*, pointing away from the 1,3-dipole and methyl *anti* in good overlap with the dipolarophile double bond. These transition states are in good agreement with the above data.



Scheme 33

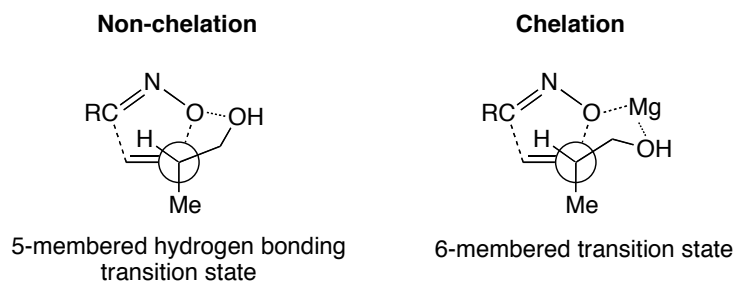
Recent progress has also been made in the study of 1,3-dipolar cycloadditions of homoallylic alcohols, a class of substrates for which stereoselectivity is often low. Carreira has recently shown good *anti* selectivity for cycloaddition of nitrile oxides

derived from oximes **77** with homoallylic alcohol **78** in the presence of a metal counterion (Scheme 34).⁶³



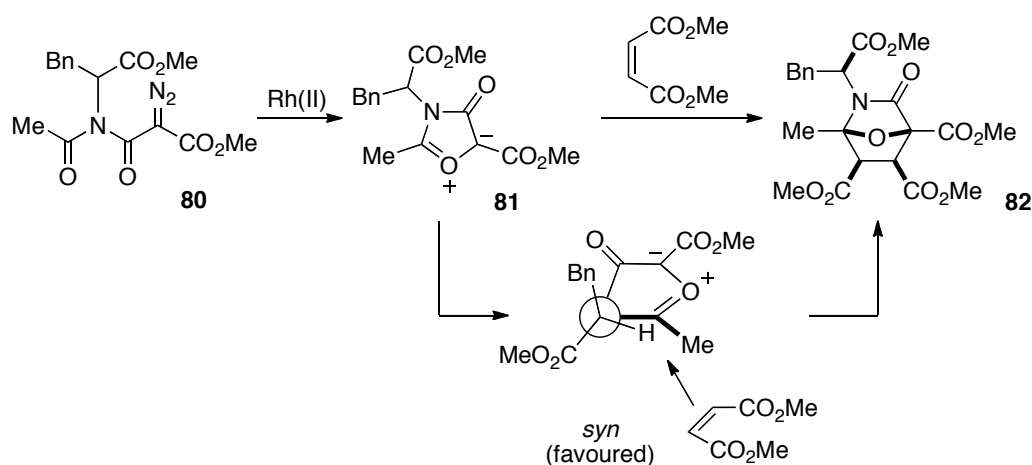
Scheme 34

Houk has proposed transition states to account for this selectivity, which are based on the inside alkoxy model (Scheme 35).⁶⁴ Reactions with and without a chelating magnesium atom between the two oxygens were compared. For both, the lowest energy transition state had the alcohol in the *outside* position and the methyl group *anti*. This leads to the *anti* isoxazole product as observed. In the non-chelation case, a hydrogen-bonding interaction between the 1,3-dipole oxygen and the homoallylic alcohol was observed. The next lowest transition state, which leads to the *syn* product was destabilised by 1 kcal/mol. For the chelated transition state, the lowest *syn* transition state was destabilised relative to the lowest energy *anti* transition state by 3 kcal/mol; consistent with the observed selectivities. Conformations placing the magnesium ether in an *inside* arrangement were further destabilised by around 7–8 kcal/mol. For both cases, hydrogen-bonding or chelation withdraw electron density from the 1,3-dipole, contributing to electron deficiency in the transition state. Thus, it is important that the methyl group lies in the *anti* position, in hyperconjugation with the olefin, which is even more electron deficient in this reaction compared to cycloadditions of chiral allylic ethers. Similar chelation models have been reported for allylic alcohol substrates.⁶⁵



Scheme 35

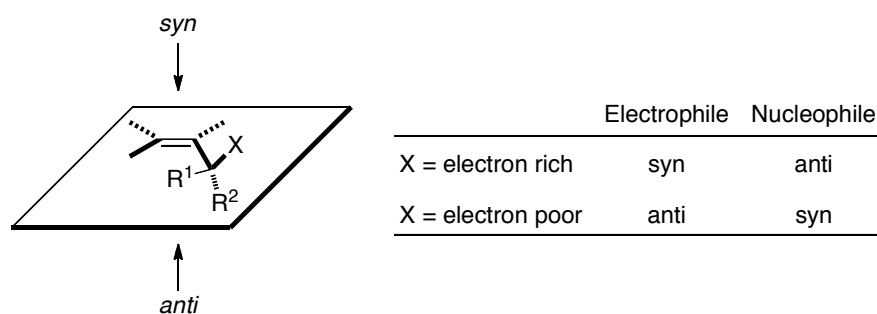
Only a very small section of the literature on [3+2] cycloadditions has been discussed here, and acyclic stereocontrol is certainly not limited to nitrile oxide additions to olefins with adjacent stereocentres. There are many other examples of diastereoselective [3+2] cycloadditions that are beyond the scope of this review. As a representative example, Padwa has reported acyclic stereocontrol in the rhodium-catalysed [3+2] cycloaddition of isomünchone dipoles with a variety of dipolarophiles (Scheme 36).⁶⁶ The conformation of the acyclic amide substituent of **81** determined the sense of diastereoselectivity,⁶⁷ with the hydrogen eclipsing the oxonium of the 1,3-dipole to minimise 1,3-allylic strain. Attack of the electrophilic dipolarophile occurred on the most electron rich face of the 1,3-dipole. This effect, discussed by Kahn and Hehre,⁶⁸ is also observed in [4+2] cycloadditions.



Scheme 36

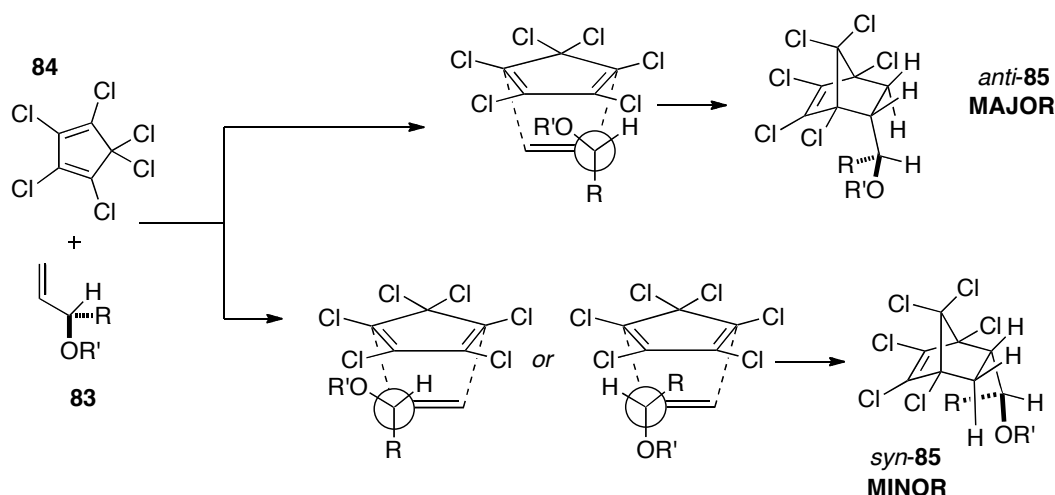
1.4.2 [4+2] Cycloadditions

Similarly well investigated and modelled are [4+2] cycloadditions; particularly the Diels–Alder and hetero-Diels–Alder reactions.⁶⁹ Electrostatic interactions between the diene and dienophile have been shown to play an important role (cf. Scheme 36 above). Diels–Alder reactions of electron-rich dienes and electron-poor dienophiles should occur preferentially onto the more nucleophilic diene face, and onto the face of the dienophile which exhibits greater electrophilicity (Scheme 37).⁶⁸



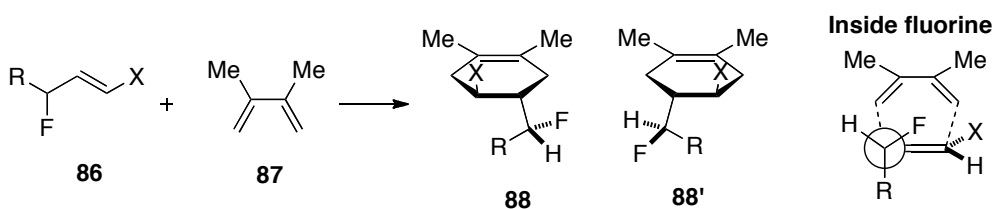
Scheme 37

Houk has suggested an inside alkoxy-type effect (which has an electrostatic component) to explain the stereoselective reactions of chiral allylic alcohols and ethers **83** with highly electron-deficient hexachlorocyclopentadiene **84**, which is in good agreement with experimental data.⁷⁰ In the analogous sense to [3+2] cycloadditions of nitrile oxides with chiral allylic ethers, the alkoxy group lies *inside*, avoiding electrostatic interactions with chlorine, while the alkyl group prefers *anti* alignment with the olefin (Scheme 38).



Scheme 38

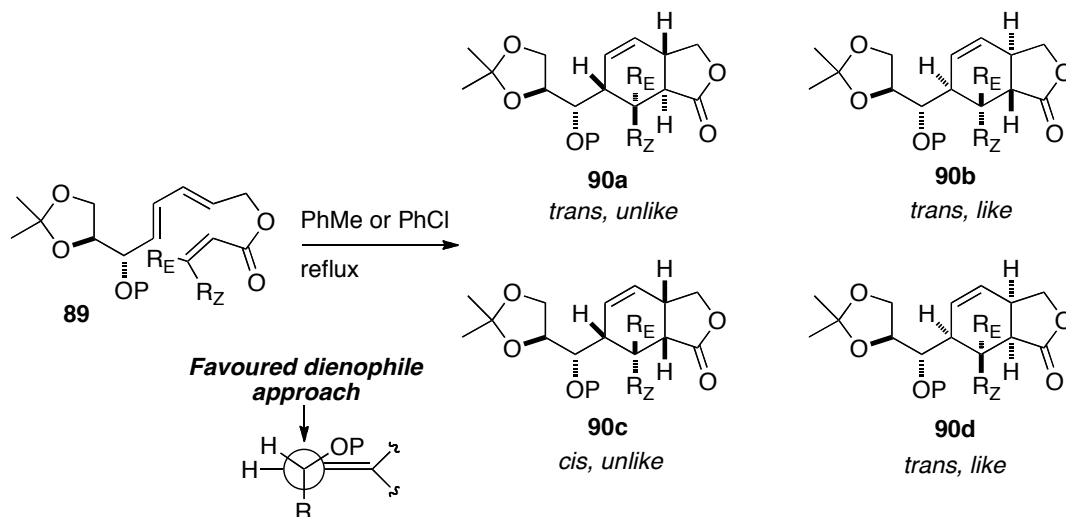
Like [3+2] cycloaddition reactions of nitrile oxides with chiral allylic fluorides, Diels–Alder reactions of chiral allylic fluorides can be described by the inside alkoxy model.⁷¹ Grée *et al.* studied the Diels–Alder reactions of allylic fluorides **86** with 2,3-dimethyl-1,3-butadiene **87** (Scheme 39, Table 8). Where observed (entries 2 and 3), selectivities were in the inside fluorine sense. The reaction was unselective when a nitrile substrate was used (entry 1), although the reason is not clear.



Scheme 39

Table 8				
Entry	R	X	Yield (%)	Ratio 88 : 88'
1	Me	CN	40	50 : 50
2	Me	COPh	85	76 : 24
3	<i>t</i> Bu	COPh	90	81 : 19

Acyclic stereocontrol in the intramolecular Diels–Alder (IMDA) reaction has also been of recent interest.⁷² The reaction can be controlled by stereocentres adjacent to the dienophile moiety. Sherburn studied the IMDA reactions of various ascorbate-derived substrates **89**. The level of selectivity varied greatly with the group P. Based on computational studies, a model was proposed to account for these selectivities, which is in agreement with both the inside alkoxy and Kahn/Hehre models (Scheme 40, Table 9).

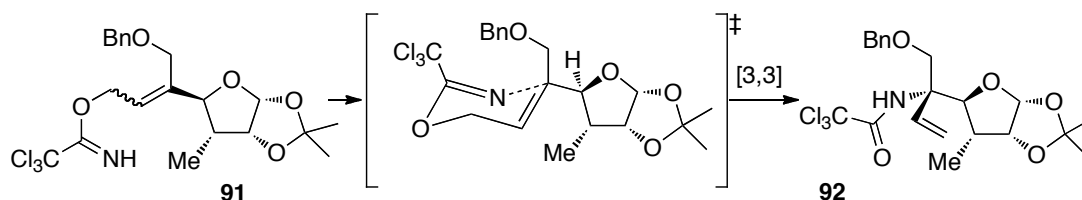


Scheme 40

Table 9						
Entry	P	R _E	R _Z	t (h)	Yield (%)	Ratio 90 a : b : c : d
1	H	H	CO ₂ Me	5	86	56 : 32 : 8 : 4
2	TMS	H	CO ₂ Me	12	67	80 : 14 : 4 : 2
3	TBS	H	CO ₂ Me	15	80	86 : 9 : 4 : 1
4	TIPS	H	CO ₂ Me	18	68	92 : 7 : 1 : 0
5	PNB	H	CO ₂ Me	12	95	49 : 39 : 6 : 6
6	TBS	CO ₂ Me	H	53	62	12 : 3 : 82 : 3

1.4.3 [3,3]-Sigmatropic rearrangements

Numerous examples have been reported of acyclic stereocontrol in the Claisen rearrangement. A complete discussion of this area and the models for observed selectivity is given in Section 2.1, as it is directly relevant to our work in this area. However, in addition to the Claisen rearrangement, acyclic stereocontrol has also been reported in the related Overman rearrangement.⁷³ Chida reports an example of such a reaction during the synthesis of (+)-lactacystin.⁷⁴ Trichloroacetimidate **91** underwent rearrangement upon heating in toluene to give the product **92** with good diastereoselectivity. The product is derived from a transition state that shares many common features with those of Claisen rearrangement, in particular the antiperiplanar alignment of the incipient C—N and furanose C—O bonds (Scheme 41).

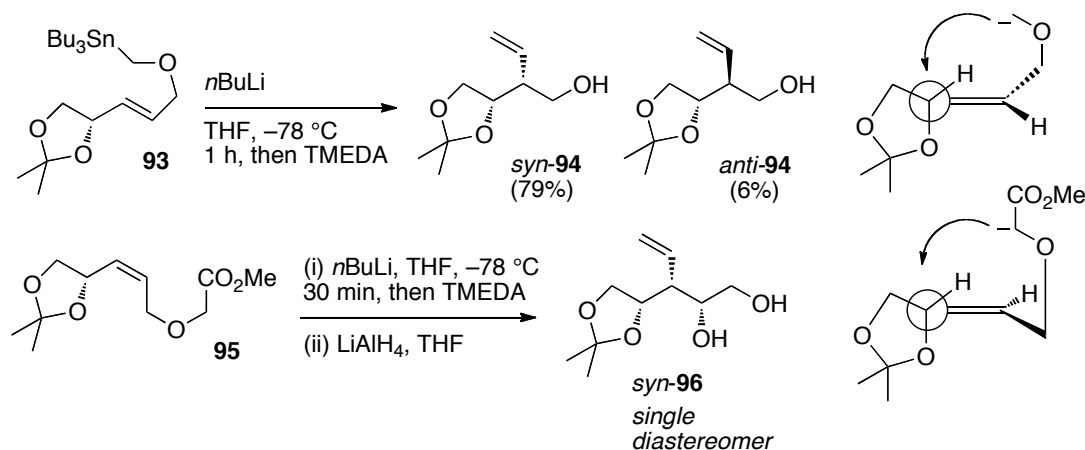


Scheme 41

1.4.4 [2,3]-Sigmatropic rearrangements

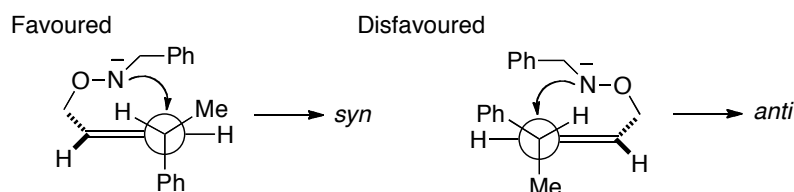
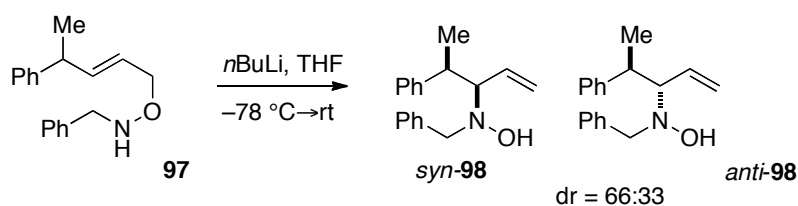
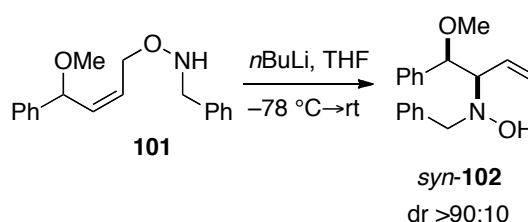
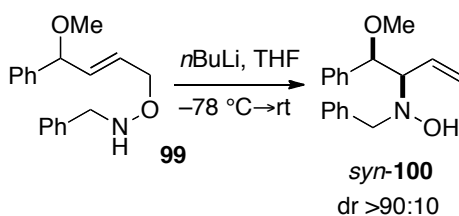
Examples of acyclic stereocontrol in [2,3]-sigmatropic rearrangements are comparatively scarce compared to the related [3,3]-sigmatropic case. The seminal contribution to this area was made in 1988 by Brückner, who studied the [2,3]-Wittig rearrangement of allylic dioxolanes **93** and **95**.⁷⁵ The rearrangement occurred in the *syn* sense, in the same fashion as analogous Claisen rearrangements of allylic dioxolanes. In the transition state leading to the major *syn* product, the dioxolane C—O bond lies perpendicular to the allylic C=C bond, maintaining a favourable $\sigma^*_{\text{C—O}}$

$\sigma/\pi^*_{C=C}$ overlap, which contributes to overall lowering of the LUMO. As shown by the complete *syn* selectivity in the rearrangement of *Z*-allylic substrate **96**, 1,3-allylic strain is a component of this model (Scheme 42).

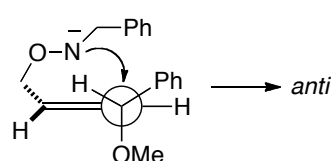


Scheme 42

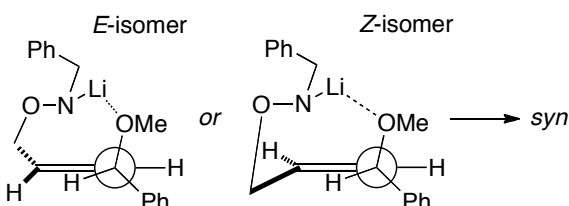
Other examples have been reported of acyclic stereocontrol in similar [2,3]-Wittig rearrangements, and the above model explains these well.⁷⁶ More recently, Davies has reported stereoselective [2,3]-sigmatropic rearrangements of lithium *N*-benzyl-*O*-allylhydroxylamides.⁷⁷ The substrates studied possessed both all-hydrocarbon stereocentres **97** and heteroatom-bearing stereocentres **99/101**. In the latter case, both *E*- and *Z*-configured substrates were compared. All substrates underwent rearrangement to give the *syn* product. For all-hydrocarbon stereocentres, this can be explained using the same transition state model as Brückner, with attack of the anion antiperiplanar to the phenyl group. For heteroatom-bearing stereocentres, this model predicts the opposite *anti* product, and a chelation transition state was proposed to explain formation of the *syn* product (Scheme 43).

All-hydrocarbon stereocentres**Heteroatom bearing stereocentres**

Non-chelation model
predicts opposite product



Chelation model correctly
predicts *syn* product



Scheme 43

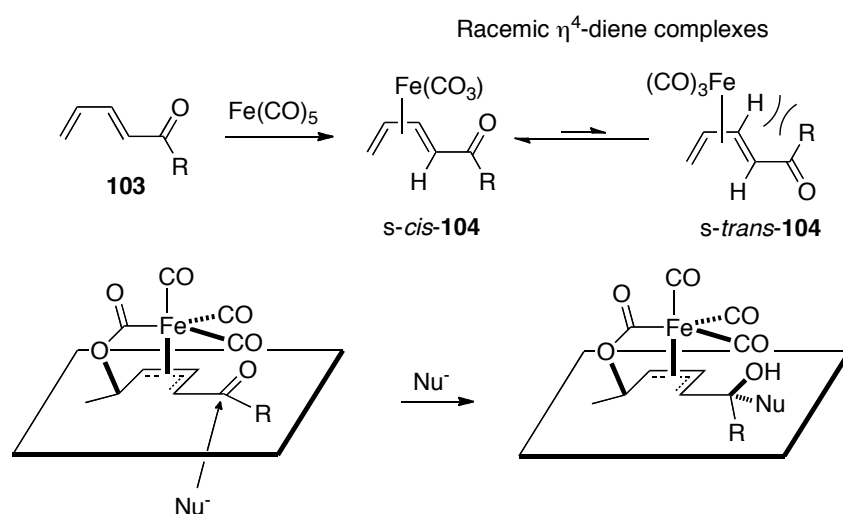
1.4.5 Conclusions

The models presented for describing acyclic stereocontrol in pericyclic reactions have seen less recent development compared to those for acyclic stereocontrol in additions to carbonyls and double bonds. However, for both [3+2] and [4+2] cycloadditions the patterns of stereoselectivity are well defined. The inside alkoxy model developed by Houk is widely applied. The model holds well for other heteroatomic groups, particularly fluorides. Exceptions to the rule occur when chelation or hydrogen-bonding interactions are possible between the heteroatom on the stereocentre and the approaching reactant. Although models have been proposed that explain [3,3]- and [2,3]-sigmatropic rearrangements, there are comparatively few examples in the

literature. In common with reactions of C=C double bonds adjacent to a stereocentre, 1,3-allylic strain is an important factor in influencing acyclic stereocontrol.

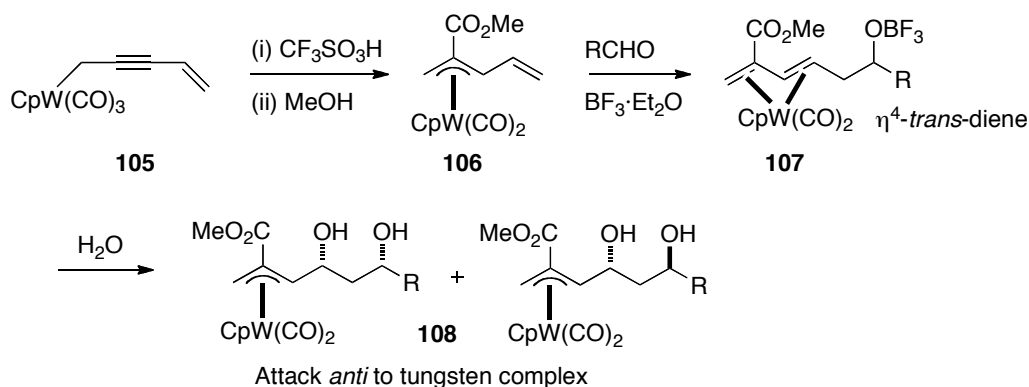
1.5 Reactions adjacent to a metal stereocentre

In addition to reactions of functional groups adjacent to carbon or sulfur stereocentres, acyclic stereocontrol is also possible for reactions of prochiral organic ligands on organometallic complexes. Widely explored in this sense are tricarbonyliron complexes. The subject has been comprehensively reviewed by Cox and Ley.⁷⁸ A diene tricarbonyliron complex exhibits planar chirality. If the diene ligand contains an adjacent functional group, for example in **103** a carbonyl group, this may adopt a preferred reactive conformation with its two diastereotopic faces sterically differentiated by the tricarbonyliron moiety.⁷⁹ *S-cis* and *s-trans* conformations of **104** are possible, but the latter is disfavoured by 1,3-allylic strain. Attack of approaching nucleophiles occurs *anti* to the bulky tricarbonyliron moiety. Aldehydes react with lower diastereoselectivity due to the diminished interaction of the diene with the aldehydic hydrogen reducing the level of 1,3-allylic strain in the *s-trans* conformation (Scheme 44). Similar methodology has recently been used for the synthesis of 2-dienyl piperidines⁸⁰ and for controlling the sense of intramolecular pinacol couplings.⁸¹ Other stereogenic iron complexes have been used to attain acyclic stereocontrol: substituted diphosphaferrocenes have recently been reported to control the sense of addition of phosphorus⁸² and organometallic⁸³ nucleophiles to an adjacent aldehyde.



Scheme 44

This chemistry is not limited to iron complexes; tungsten-*syn*- π -pentadienyl complexes have been used to effect acyclic stereocontrol in the preparation of adjacent 1,3-diols. The Lewis-acid promoted Prins reaction of the tungsten complex **106** with an aldehyde affords a η^4 -*trans*-diene cationic intermediate **107**, which undergoes hydrolysis with water *anti* to the bulky complex (Scheme 45).⁸⁴ This class of reaction is emerging as an interesting new area for investigations into acyclic stereocontrol.



Scheme 45

1.6 Summary

Recent developments in models for acyclic stereocontrol have been discussed in the context of three important classes of organic reaction and some recent organometallic reactions. For additions of nucleophiles to carbonyls with an adjacent stereocentre, both computational and experimental evidence have challenged the predominance of the Felkin–Anh and Cram models for predicting stereoselectivity. Various models for describing electrophilic and nucleophilic addition to double bonds have been proposed that account for variations in selectivity. However, these are often very specific to each particular reaction. In some cases, the major product arises from a seemingly high-energy transition state, for example in examples of the inside-methyl effect. Above all, 1,3-allylic strain appears to be the most important control element in reactions of C=C double bonds adjacent to a stereocentre. Many of the same models have been extended to explain acyclic stereocontrol in pericyclic reactions. In these cases, both stereoelectronic effects, again 1,3-allylic strain in particular, and electrostatic effects must be taken into account. Stereoselective reactions of unsaturated functional groups adjacent to organometallic complexes are also emerging as useful tools for establishing acyclic stereocontrol.

Taking into account the above examples, some general conclusions can be drawn. There is no unified theory that explains all modes of acyclic stereocontrol. Rather, it appears that models are very specific to the individual reaction mechanism and the nature of the incoming electrophile or nucleophile must be considered. Additional complexity is encountered when stereoselectivity is a function of both acyclic and cyclic stereocontrol (double diastereoselection). These cannot be considered in isolation and models must take into account interactions between cyclic and acyclic transition states. Developments in computational methods have contributed to our ability to predict the sense of acyclic stereocontrol, although exceptions to these predictions are often encountered in experiment. Development of models and methods for establishing acyclic stereocontrol remains a highly active area of interest in synthetic chemistry.

Chapter 2

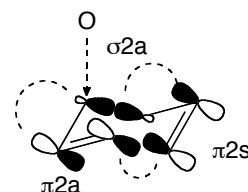
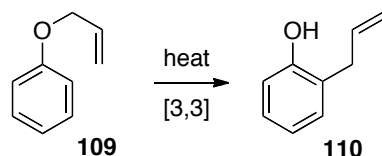
Results and Discussion

2.1 Background

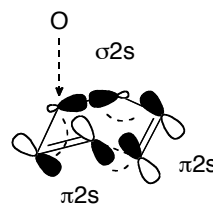
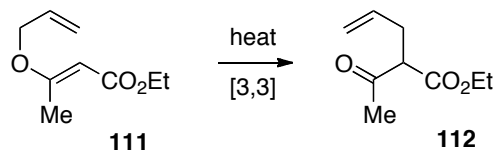
2.1.1 Historical background

The sigmatropic rearrangement of allyl phenyl ether **109** to give *ortho*-allyl phenol **110** was first reported by Claisen in 1912.⁸⁵ The paper contained an additional report of a rearrangement of *O*-allylated ethylacetoacetate **111** to **112**; a reaction that is now generally referred to as the aliphatic Claisen rearrangement. The reaction, containing two $\pi 2_s$ components and one $\sigma 2_s$ component is thermally allowed under Woodward–Hoffmann rules,⁸⁶ whether it proceeds *via* a chair or boat transition state (Scheme 46).

Aromatic Claisen Rearrangement



Aliphatic Claisen Rearrangement

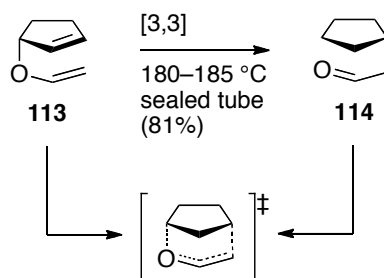


Scheme 46

Nearly a century later, the Claisen rearrangement has become a well-established and general method for the synthesis of γ,δ -unsaturated carbonyl compounds.⁸⁷ When the ketene acetal precursor is disubstituted, diastereomeric products are possible. Nevertheless, the stereochemical patterns governing the rearrangement are similarly well investigated. This statement is more appropriate for cases when substituents are bound directly to the pericyclic array. Explanations of stereoselectivity are generally rationalised by considering well-defined transition state models.⁸⁸

In addition to the case previously shown, in which the relative geometries of the vinylic and allylic portions of the ketene acetal determine the relationship between the two new stereocentres formed (Chapter 1, Scheme 2), stereochemical information is reliably transferred around the pericyclic array. As an example, Hill and Edwards

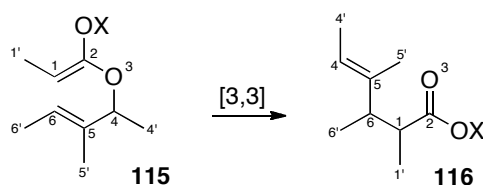
reported 1,3-transfer of the ether stereocentre in the reaction of **113** (Scheme 47).⁸⁹ As we have previously defined, this represents *cyclic stereocontrol*.



Scheme 47

2.1.2 The effects of exopericyclic stereocentres: acyclic stereocontrol

Less investigated has been the manner and extent to which stereocentres outside of the pericyclic array – which we shall refer to as ‘exopericyclic stereocentres’ – affect the stereochemistry of the new bonds formed during the sigmatropic process. This represents *acyclic stereocontrol*. In a generic ketene acetal Claisen precursor **115** (Scheme 48), 1,2-induction of the newly formed C1—C6 bond *via* acyclic stereocontrol is possible when stereocentres are positioned adjacent to the C1 and C5–6 positions. This area has been previously reviewed in the context of the Ireland–Claisen rearrangement,^{87a} and asymmetric [3,3]-sigmatropic rearrangements⁹⁰ and although many of the same examples are cited, it is important that we highlight them here. During the rearrangement C4 becomes, and C5 remains, sp^2 -hybridised, and although stereocentres adjacent to these positions can affect stereochemistry in a similar sense,⁹¹ it is beyond the scope of this work.

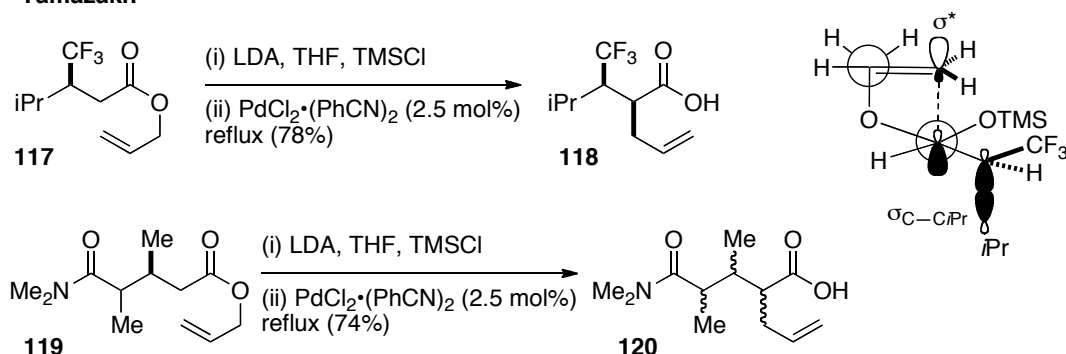


Scheme 48

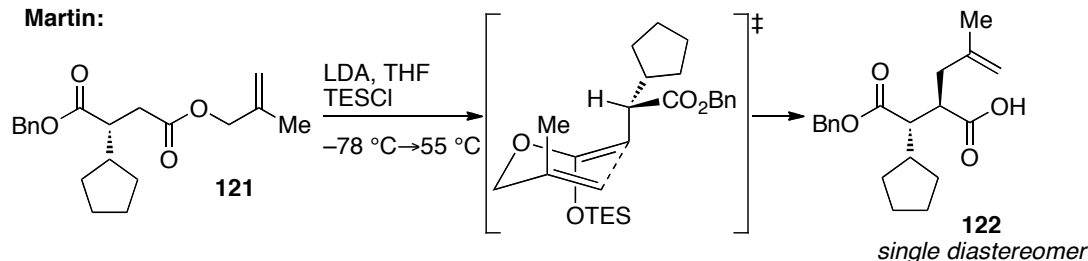
2.1.2.1 Effects of stereocentres adjacent to C1

Yamazaki⁹² and Martin⁹³ have shown examples of C1 exopericyclic stereocontrol using trifluoromethyl and CO₂Bn substituents respectively (Scheme 49). In both cases, the observed stereoselectivity is rationalised by invoking the Cieplak model in which attack occurs antiperiplanar to the more electron rich C—C σ bond. This allows for hyperconjugation between the C—R (or C—cyclopentyl) groups and the electron-deficient σ^* orbital of the incipient C1—C6 bond. In the Yamazaki example, isosteric *i*Pr and CF₃ substituents on **117** were used to remove steric bias from the transition state model. Replacement of the CF₃ group by methyl gave significantly reduced selectivity.⁹⁴ Although deriving from different effects, this corresponds to reaction in the same sense as predicted by the Felkin–Anh model.⁹⁵ Similar examples that occur in a Cieplak sense have been reported by Knight.⁹⁶ Other examples have been described of Johnson–Claisen rearrangements with chiral ortholactones, although the selectivity in these processes is controlled by the relative energies of chair and boat transition states.⁹⁷

Yamazaki:



Martin:

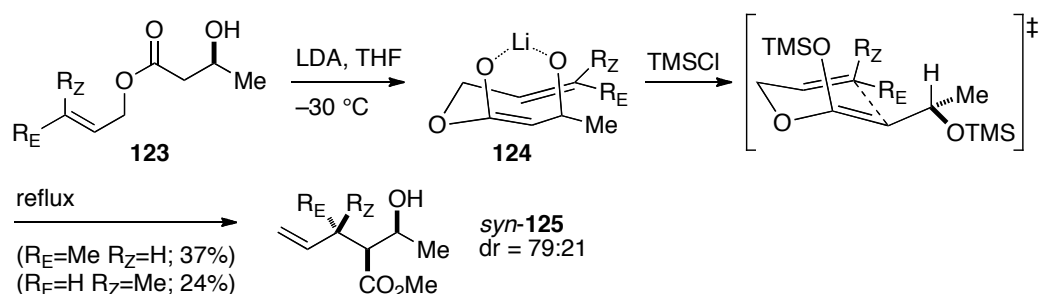


Scheme 49

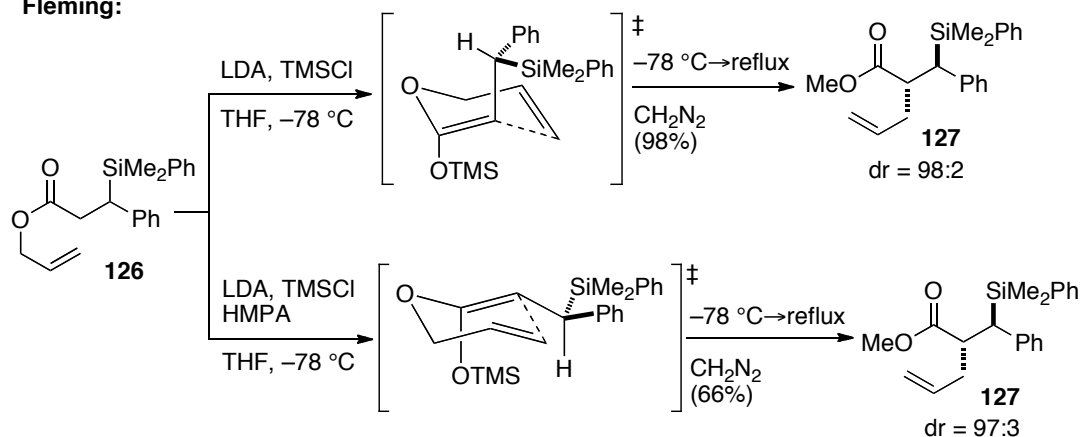
Attack in the opposite (non-Cieplak, anti-Felkin) sense has been reported by Fujisawa⁹⁸ and Fleming (Scheme 50).¹¹² In these examples,⁹⁹ attack occurs preferentially anti to the most electronegative group, with the smallest substituent

eclipsing the vinylic double bond to minimise 1,3-allylic strain: a reactive conformation that is commonplace in examples of C6 exopericyclic stereocontrol *vide infra*.

Fujisawa:



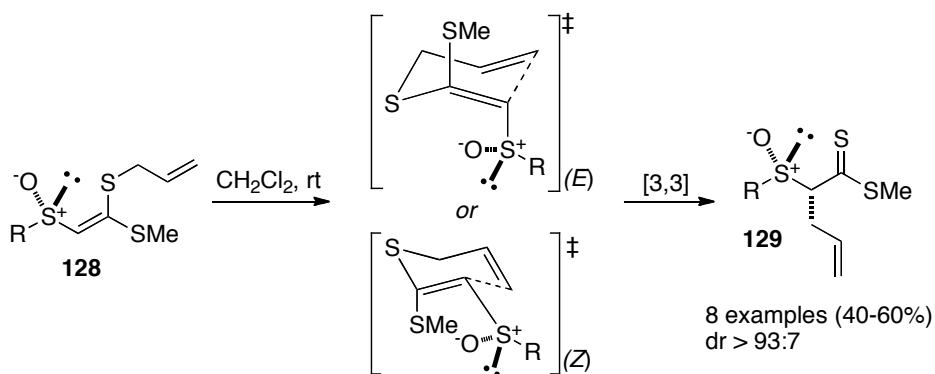
Fleming:



Scheme 50

In addition to rearrangements with carbon stereocentres, C1-sulfur substituents have been used for exopericyclic stereocontrol. The first reactions of this type were reported by Metzner, in which thioketene acetals **128** underwent thio-Claisen rearrangement to give thioesters **129** in very high diastereoselectivity (Scheme 51).¹⁰⁰ The transition states proposed to account for the sense of the selectivity were derived from the original Felkin model in which the best donor (in this case the sulfur lone pair) is placed antiperiplanar to the incipient bond. The oxygen is the smallest substituent and eclipses the ketene acetal (cf. hydrogen eclipsing in the above examples). Both *E*- and *Z*-transition states lead to the same product. Similar examples have been reported from our own laboratories in which C1-sulfoximine stereocentres are used for exopericyclic stereocontrol.¹⁰¹ Recently, we have used this methodology

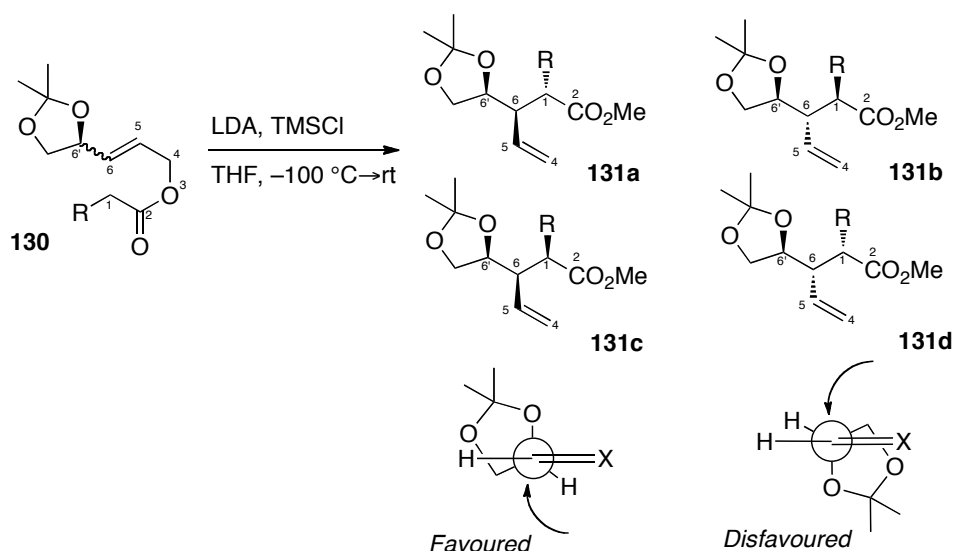
for the stereoselective formation of cyclopropanes *via* decarboxylative Claisen rearrangement (dCr).¹⁰²



Scheme 51

2.1.2.1 Effects of stereocentres adjacent to C6

The earliest examples of exopericyclic stereocontrol adjacent to C6 used C6' dioxolane substituents. *Syn*-selective Ireland–Claisen rearrangements of **130** were reported by Cha,¹⁰³ with variations in allylic *E/Z* geometry and C1 substituent (Scheme 52, Table 10). The transition states proposed to account for the selectivity follow a similar pattern to those described for rearrangements with C1 stereocentres.¹⁰⁴ In this case the vinylic portion of the ketene acetal attacks antiperiplanar to the dioxolane C6'—O bond in the conformation where the C6'—H bond eclipses the allylic moiety. Similar, although significantly less selective Johnson–Claisen rearrangements featuring C6' dioxolane substituents have also been reported by Suzuki¹⁰⁵ and Takano.¹⁰⁶

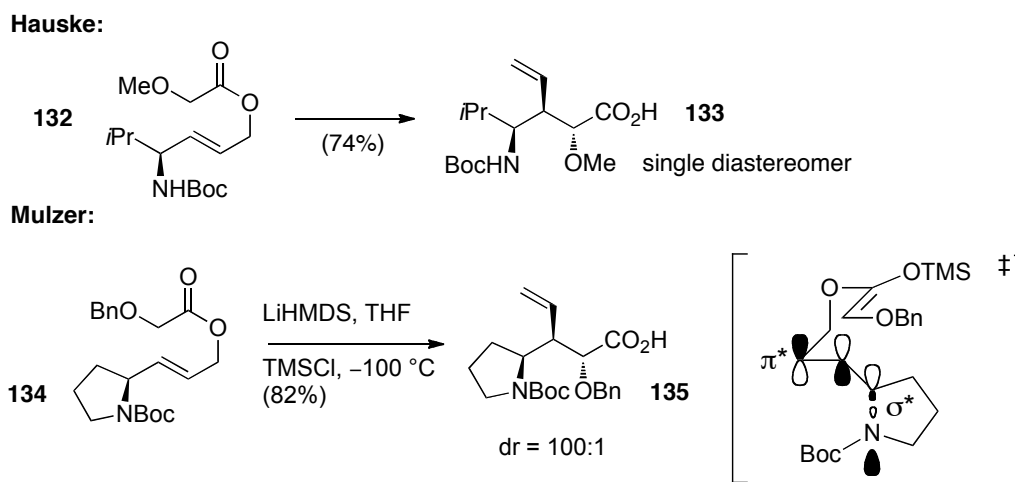


Scheme 52

Table 10				
Entry	<i>E/Z</i>	R	Yield (%)	Ratio 131a : b : c : d
1	<i>E</i>	H	54	1 : 1.3
2	<i>E</i>	OCH ₃	59	4.4 : 1 : 0.2 : 0.3
3	<i>E</i>	OCH ₂ OCH ₃	50	4.0 : 1 : 0.3 : 0.2
4	<i>E</i>	OBn	48	4.2 : 1 : 0.3 : 0.1
5	<i>Z</i>	H	50	1 : 1.4
6	<i>Z</i>	OCH ₃	48	0.5 : 0.3 : 9 : 1
7	<i>Z</i>	OCH ₂ OCH ₃	51	0.1 : 0.2 : 1 : 0.2
8	<i>Z</i>	OBn	56	0.3 : 0.3 : 5 : 1

Notable in this case is the slight increase in selectivity upon changing the allylic geometry from *E* to *Z*, which is consistent with an allylic strain model; and the significantly reduced selectivity in the absence of a C1 substituent. Similar rearrangements have been rationalised in terms of Houk's inside-alkoxy rule although the sense of selectivity is the same^{107, 108}

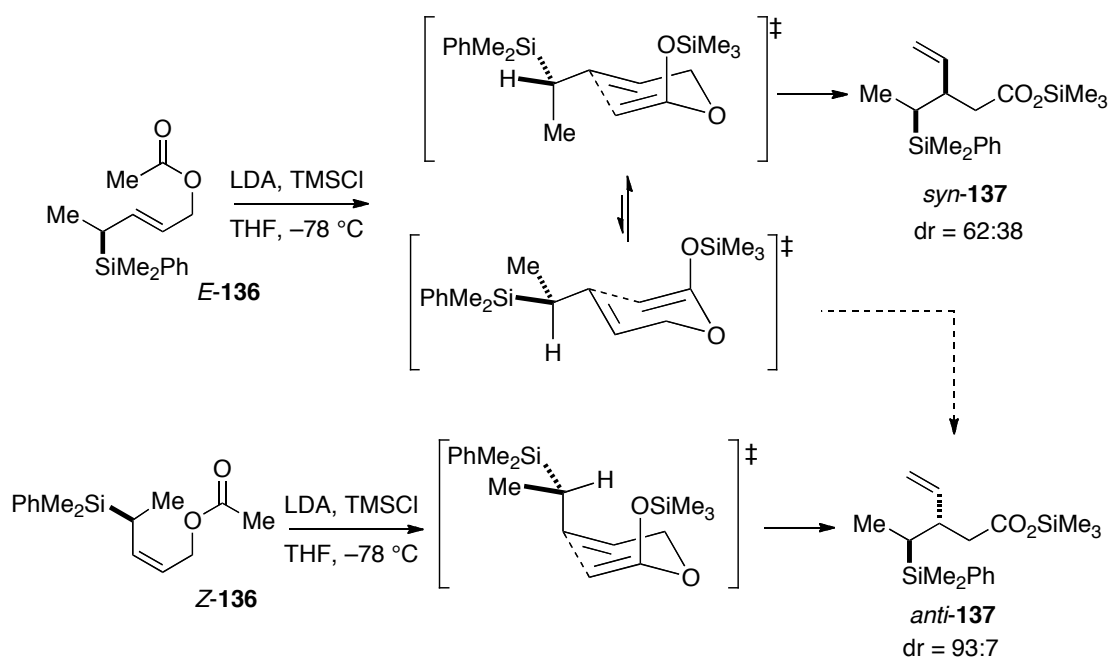
Highly diastereoselective rearrangements, in the same sense as those described by Cha and others above have been reported with C6' nitrogen substituents. Hauske¹⁰⁹ and Mulzer¹¹⁰ studied the Ireland–Claisen rearrangements of the BOC-protected valine- and proline-derived substrates **132** and **134** respectively (Scheme 53).



Scheme 53

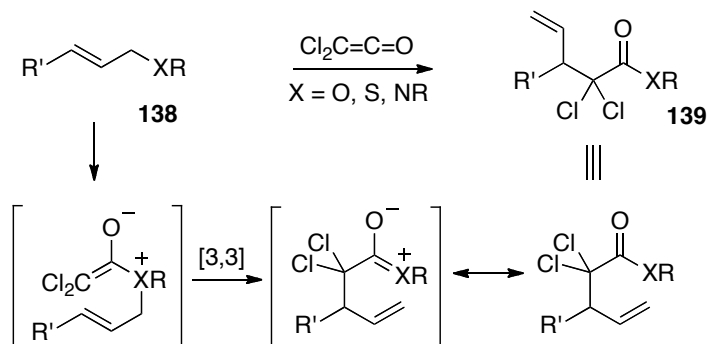
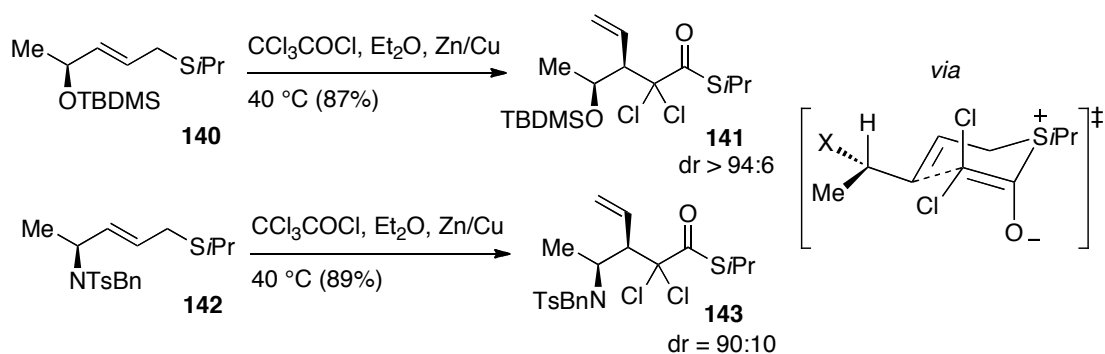
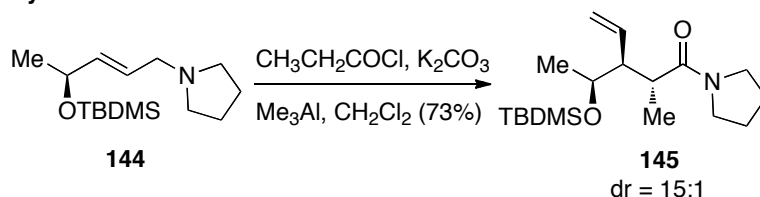
Two complementary explanations were for the high stereoselectivity were provided by Mulzer. The proposed transition state features, in common with other examples, antiperiplanar alignment of the C6'—N and the incipient C1—C6 bond, with the proline residue positioned in such a way that minimises 1,3-allylic strain. An additional explanation is given according to the model of Kahn and Hehre⁶⁸ (modified for the Claisen rearrangement) in which the most electrophilic face of the allylic moiety approaches the most nucleophilic face of the vinylic moiety.¹¹¹ The energy of the allylic LUMO is lowered *via* mixing of $\sigma^*_{\text{C6}'-\text{N}}$ and $\pi^*_{\text{C}=\text{C}}$ orbitals, while the vinylic π orbital (HOMO) is raised in energy by the two electron donating OTMS and OBn residues. Overall, this leads to a strong HOMO-LUMO interaction, lowering the activation barrier of the rearrangement.

Fleming, in the same report that presented the effects of C1' silicon stereocentres, also investigated the effects of C6' silicon stereocentres (Scheme 54).¹¹² Attack of the vinylic moiety antiperiplanar to the silicon substituent is maintained in all cases. Evidence for 1,3-allylic strain as a control element was shown by the high selectivity of *Z* substrates. The isomeric *E* substrates underwent rearrangement with moderate selectivity for the opposite diastereomer, which arises from a reactive conformation in which the methyl group is 'inside'. Calculations showed this conformation to be more populated than the alternative in which the hydrogen is 'inside'. This conformation is accessible in the absence of significant 1,3-allylic strain effects.¹²⁷

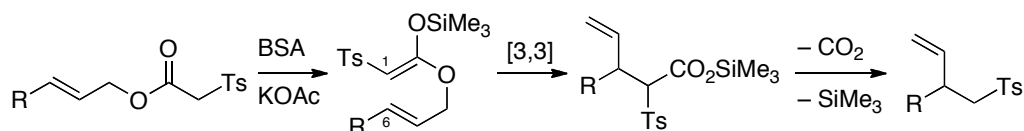
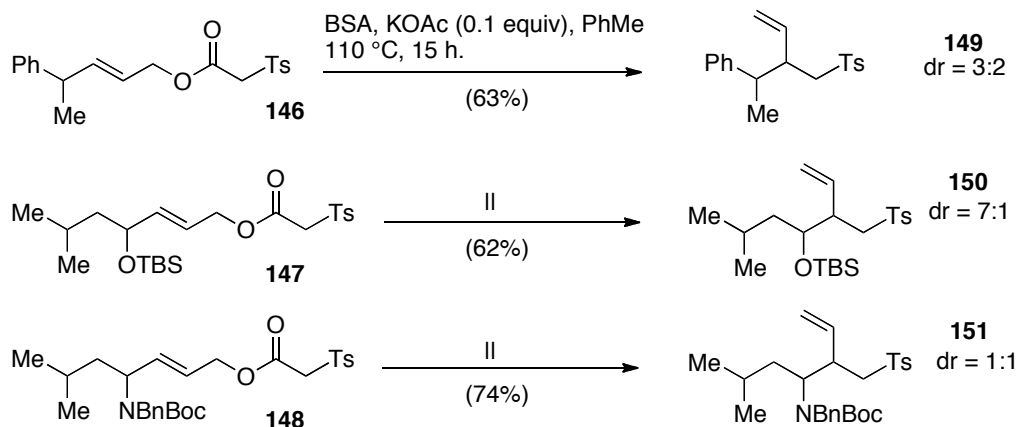


Scheme 54

Thio-Claisen rearrangements have also been used to study the effects of C6' stereocentres.¹¹³ In particular, numerous examples of exo-pericyclic stereocontrol from C6' substituents in Belluś–Claisen¹¹⁴ (ketene Claisen) rearrangements of allylic sulfides have been reported, which follow the established patterns.¹¹⁵ The aza-analogues of these reactions have also been investigated and reduced selectivity was reported for rearrangements lacking a C1 substituent on the pericyclic array (Scheme 55).¹¹⁶ During the course of our studies, an additional example of a thio-Claisen rearrangement in the same sense was reported by Porter.¹¹⁷

Ketene Claisen rearrangement:**Allylic thioethers:****Allylic amines:****Scheme 55**

Recent work in our own laboratories, in the context of the decarboxylative Claisen rearrangement reaction has stimulated our interest in this area.¹¹⁸ Esters **146–148**, when treated with a silylating agent and sub-stoichiometric quantities of acetate underwent Claisen rearrangement followed by concomitant desilylation and decarboxylation to give the homoallylic sulfones **149–151** in varying diastereoselectivity (Scheme 56). Although the sense of selectivity was not assigned, we were interested in the variable selectivities and particularly in the effect of changing the heteroatom.

Decarboxylative Claisen rearrangement:**Examples with stereocentres adjacent to C6:**

Scheme 56

2.1.3 Focus of the current work

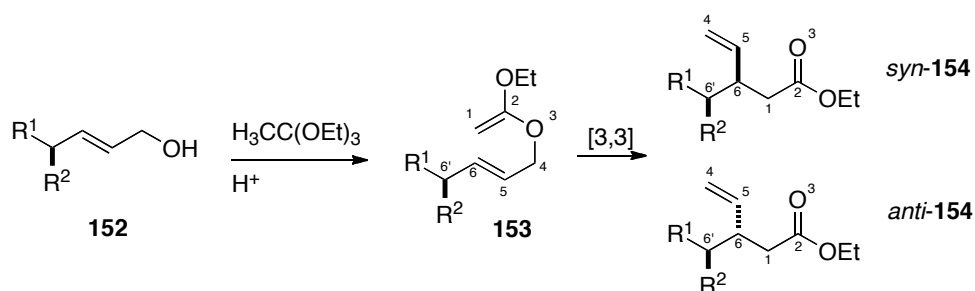
The work presented herein covers two areas. Firstly, concentrating exclusively on Claisen rearrangements with C6' stereocentres, we have performed investigations into the importance of the exopericyclic heteroatom in determining selectivity. We have also investigated in depth the relationship between allylic substitution pattern and stereoselectivity.

Secondly, drawing on our own evidence and that already presented in the literature, we have attempted to exploit exopericyclic stereocontrolled Claisen rearrangements for the synthesis of small, stereochemically complex molecules. During investigations into the effects of C6' azide stereocentres, we have uncovered a novel reaction in which equilibrating mixtures of allylic azides undergo Claisen rearrangements with exopericyclic stereocontrol.

2.2 Effects of hydrocarbon substituents

2.2.1 Background

As an initial investigation, we decided to study the effects of C6' hydrocarbon exopericyclic substituents on stereoselectivity (Scheme 57). This is relatively poorly explored in the literature, compared to rearrangements where the exopericyclic substituents are heteroatomic.



Scheme 57

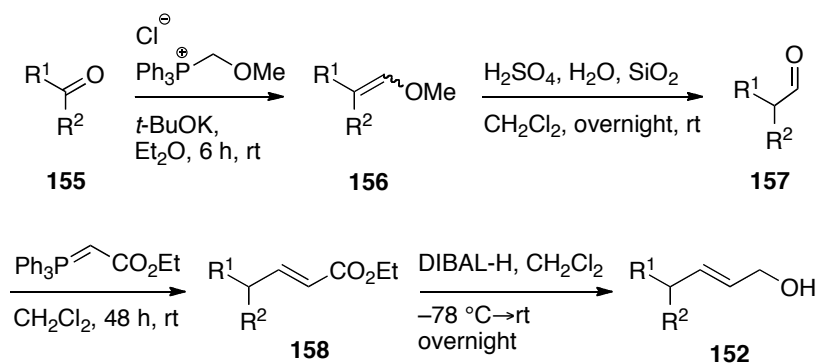
Numerous different variants of the Claisen rearrangement have been used in preceding studies. Most attractive to us was the Johnson orthoester variant.¹¹⁹ Treatment of an allylic alcohol **152** with an orthoester and sub-stoichiometric acid generates a ketene acetal **153** *in situ* with loss of ethanol, which can undergo Claisen rearrangement to give either of the esters *syn*- and/or *anti*-**154**. The lack of substitution at C1 removes the complication of setting a third stereocentre. Relative control of the C1 and C6 stereocentres is difficult to attain in the Johnson–Claisen rearrangement when a higher homologue of the orthoester is used, caused by rapid *E/Z* ketene acetal isomerisation.¹²⁰ This should be taken into account if the process is extended to control more than one stereocentre.

Various orthoesters and acid catalysts have been used in the Johnson–Claisen rearrangement.^{87a} In our case, we chose triethyl orthoacetate as the orthoester, which was used as the solvent, and propionic acid as catalyst. These conditions remained constant throughout our studies.

2.2.2 Synthesis and rearrangement of allylic alcohols

Our strategy for the synthesis of allylic alcohols followed the previous example of Cha,¹⁰³ in which aldehydes bearing an adjacent stereocentre were subjected to Wittig olefination to give the α,β -unsaturated ester, which in turn was reduced to the corresponding allylic alcohol using DIBAL-H. A variety of alkyl groups of increasing size were chosen as the group R. Both aliphatic and branched alkyl groups were studied. Phenyl substituents were also investigated. α,β -Unsaturated ester intermediates **158a** and **158f** were prepared by Horner–Wadsworth–Emmons reaction of commercially available aldehydes.¹²¹ The preparation of non-commercially available aldehydes was attempted using the Levine method,¹²² in which Wittig olefination of a ketone **155** affords a methyl enol ether **156**, which is in turn hydrolysed with perchloric acid to give the aldehyde **157**. The volatility of enol ether and aldehyde intermediates **156** and **157** was problematic, and therefore we sought a method for the synthesis of α,β -unsaturated esters in which isolation of the intermediates was not required.

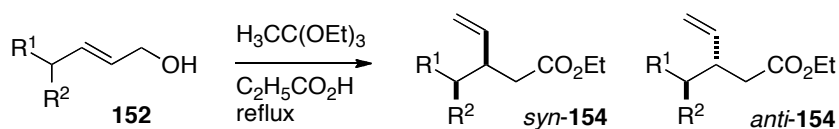
To this end, Wittig reaction¹²³ of a representative set of ketones afforded the enol ethers **156b–e** and **156g** as solutions in diethyl ether. As a heterogeneous alternative to perchloric acid for the hydrolysis, sulfuric acid supported on wet silica gel was used,¹²⁴ affording a dichloromethane solution of the aldehyde **157** after removal of the silica gel by filtration. To this solution was added the phosphorane to afford esters **158b–e** and **158f**. Reduction of the esters **158a–g** with DIBAL-H⁷⁷ afforded the corresponding allylic alcohols **152a–g** (Scheme 58, Table 11). The moderate yields of this process are attributed to the high volatility of the products.



Scheme 58

Table 11				
Entry	R ¹	R ²	Yield of 158 (%)	Yield of 152 (%)
a	Me	Et	72	30
b	Me	cyclopropyl	7	96
c	Me	cHex	37	83
d	Me	<i>n</i> C ₅ H ₁₁	22	35
e	Me	<i>t</i> Bu	15	66
f	Me	Ph	80	20
g	Et	Ph	24	44

Exclusively *E*-configured esters were obtained by this method. The isomeric *Z*-esters and allylic alcohols were not studied. Treatment of allylic alcohols **152a–g** under Johnson–Claisen conditions afforded the γ,δ -unsaturated ester products **154a–g** in high yield and widely ranging diastereoselectivity (Scheme 59, Table 12).

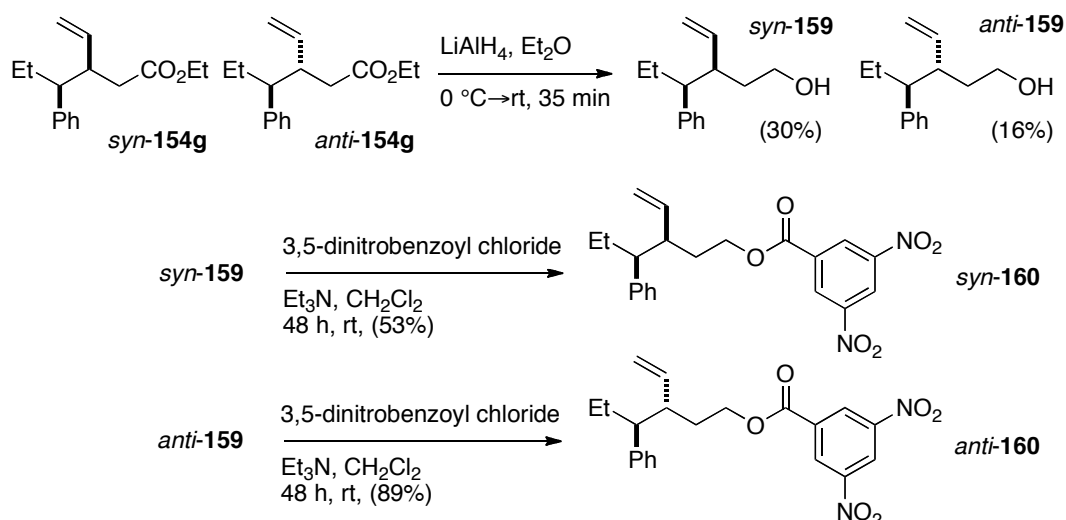


Scheme 59

Table 12				
Entry	R ¹	R ²	Yield (%)	Ratio <i>anti</i> - : <i>syn</i> - 154 ^a
a	Me	Et	98	50 : 50
b	Me	cyclopropyl	89	50 : 50
c	Me	cHex	91	83 : 17
d	Me	<i>n</i> C ₅ H ₁₁	98	50 : 50
e	Me	<i>t</i> Bu	67	67 : 33
f	Me	Ph	99	68 : 32
g	Et	Ph	99	68 : 32

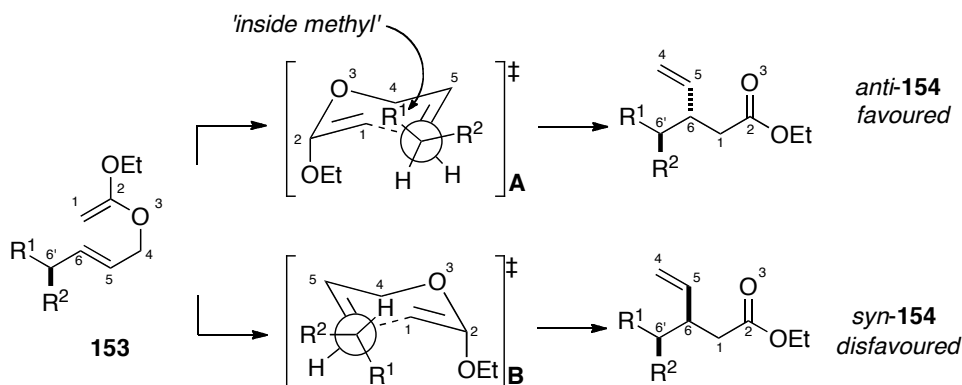
^aDetermined by ¹H-NMR analysis of crude reaction mixtures

The structure of *anti*-**154g** was established by preparation of a derivative. Reduction (LiAlH₄–Et₂O) of the 68:32 mixture of diastereomeric products of Johnson–Claisen rearrangement of **152f** gave a mixture of isomeric alcohols **159**, which were separated and converted into the corresponding 3,5-dinitrobenzoyl esters **160** by treatment with 3,5-dinitrobenzoyl chloride–TEA (Scheme 60).¹²⁵ The *anti* stereochemistry of the major diastereoisomer *anti*-**160** was assigned by X-ray crystallography (see Appendix).¹²⁶ The same *anti* stereochemistry was inferred for the major products of Johnson–Claisen rearrangement **154c** and **154e–f**.



Scheme 60

As shown previously, the stereoselectivity in the Johnson–Claisen rearrangement of **152c** and **152e–g**, can be rationalised by invoking a modified Felkin–Anh model in which the $\text{C}=\text{O}$ group is replaced with the allylic portion of the ketene acetal **153** (Scheme 61). Such a model has been used to describe explain the diastereoselectivity of conjugate organocuprate addition to γ -alkyl- α,β -unsaturated esters.¹²⁷ Rearrangement is more likely to occur through the staggered conformation of the C6' stereocentre in relation to the 6-membered chair transition state and the major product arises from transition state **A**, in an example of the ‘inside methyl’ effect.³⁶ Such transition states are easily accessible in *E*-configured systems. This is also the product that would be predicted by the Felkin–Anh model. However, the generally moderate selectivity points to a low difference in energy between transition states **A** and **B**.



Scheme 61

2.3 The relationship between the heteroatom and stereoselectivity

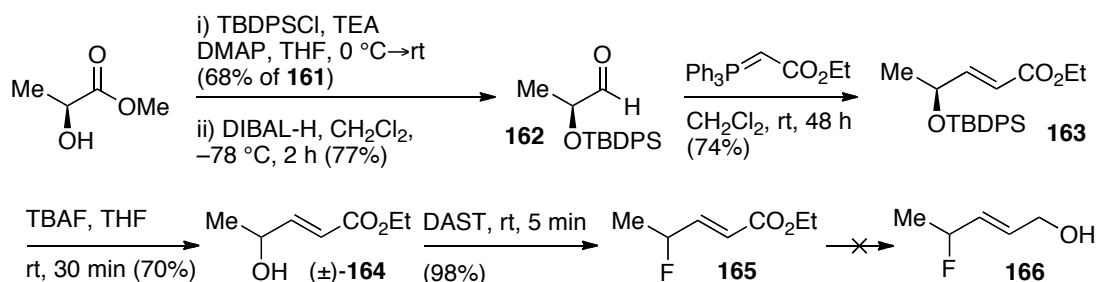
2.3.1 Background

In comparison with literature examples of Claisen rearrangements where the C6' stereocentre bears a heteroatomic substituent, selectivities in the Johnson–Claisen rearrangements of **152a–g** are non-existent or low. The next phase of our study concentrated on rearrangement of substrates where the exopericyclic stereocentre bears a heteroatomic substituent. The role of the heteroatom is clearly apparent from studies of Claisen rearrangements of dioxolanes and proline derived systems shown above. The *syn* product generally predominates, its formation explained in terms of favourable antiperiplanar alignment of the C—X and incipient C—C bond in the reactive conformation, with the allylic exopericyclic C—H bond eclipsing the adjacent C=C bond.

From examination of the literature, exopericyclic oxygen, nitrogen and silicon substituents appear well studied. Relatively unexplored, however are the effects of exopericyclic halogen groups. We decided to investigate the effects of exopericyclic fluorine substituents, inspired both by the analogous Diels–Alder studies of Grée⁷¹ and also Evans' computational studies of aldol reactions of boron enolates¹⁸ (see Section 1). Additionally, since Evans showed a change from Cornforth to Felkin–Anh models upon reducing the electronegativity of the heteroatom, we decided to perform a similar study into the comparative effects of exopericyclic (C6') thiophenyl substituents.

2.3.2 Preparation and rearrangement of γ -fluorinated allylic alcohols

We anticipated that the required fluorinated allylic alcohol **166** could be prepared by reduction of the corresponding γ -fluoro- α,β -unsaturated ester **165**. A synthesis of **165** from methyl lactate has been reported by Grée,⁷¹ in which fluorine is introduced by dehydroxyfluorination of the γ -hydroxy- α,β -unsaturated ester **164**.



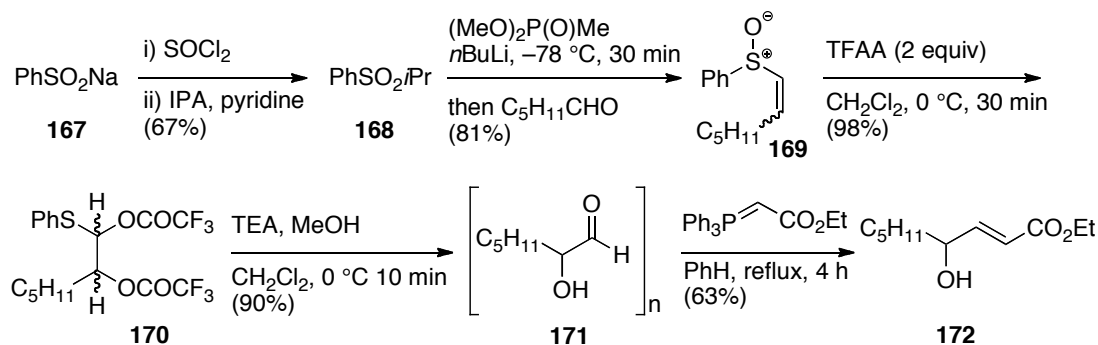
Scheme 62

In our case, we chose the more acid-stable TBDPS group for protection of (*S*)-methyl lactate.¹²⁸ Treatment of the product **161** with DIBAL-H afforded the *O*-protected aldehyde **162**, which was subjected to Wittig reaction to afford the *O*-protected α,β -unsaturated ester **163**.¹²⁹ Deprotection was attempted with both acetic acid and hydrochloric acid, but the reaction was very slow. Instead, TBAF¹³⁰ was used to deprotect the alcohol, affording the desired γ -hydroxy- α,β -unsaturated ester **164**. Racemisation of **164** occurred under these conditions, though this was inconsequential as the enantiopure compound was not required. Dehydroxyfluorination¹³¹ of **164** mediated by DAST gave **165** in excellent yield, without the need for purification. However, reduction of **165** to the corresponding allylic alcohol **166** could not be achieved using either DIBAL-H or lithium aluminium hydride. Only low yields of unidentifiable decomposition products were observed (Scheme 62).

Considering that **166** was likely to be relatively volatile at atmospheric pressure we prepared the higher homologue, exchanging the terminal methyl group for an *n*-pentyl chain. From earlier experiments, we predicted that this alteration would have no effect on the stereoselectivity of Johnson–Claisen rearrangement of the target allylic alcohol **179**.

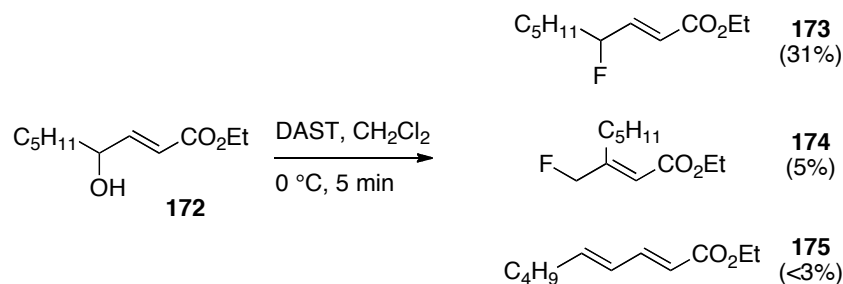
The homologous γ -hydroxy- α,β -unsaturated ester intermediate **172** was prepared using an additive Pummerer-type strategy developed in our own laboratory (Scheme 63).¹³² Isopropyl benzenesulfinate **168** was prepared from sodium benzenesulfinate **167** and subjected to a one-pot Horner–Wadsworth–Emmons procedure to afford the vinyl sulfoxide **169** in good yield. Addition of trifluoroacetic anhydride to **169** effected the Pummerer rearrangement to give **170** in excellent yield, without the need for purification. Base-catalysed methanolysis of **170** gave the lactide **171**, which was

shown by mass spectrometry to exist as a mixture of the monomer, dimer and trimer. Finally, Wittig reaction of **171** in refluxing benzene afforded ester **172**.



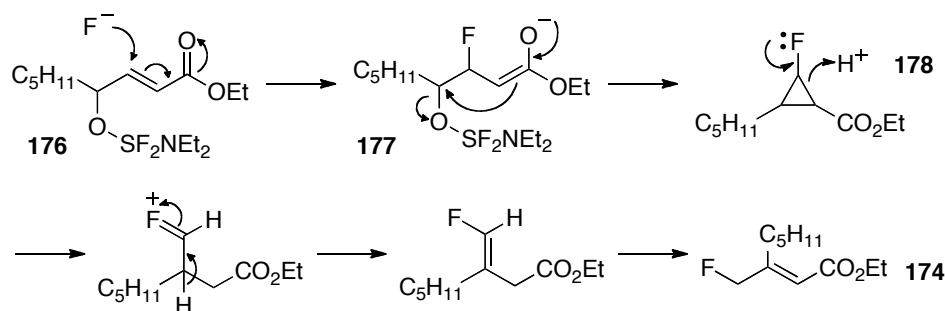
Scheme 63

In contrast to **164**, dehydroxyfluorination of **172** gave a mixture of products. In addition to the desired γ -fluoro compound **173**, the isomeric product **174** and the eliminated product **175** were observed (Scheme 64).



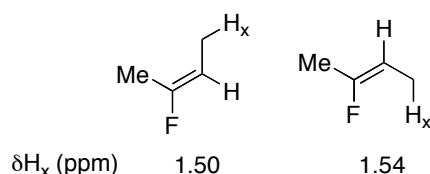
Scheme 64

A mechanism was proposed to explain the formation of the rearranged side product **174** (Scheme 65). It is presumed that the first step of this reaction is in common with the first step of the DAST dehydroxyfluorination mechanism¹³³ involving formation of an O—S bond. 1,4-Attack of the liberated fluoride on the enoate system **176** gives the ester enolate **177** which, through ring closing expulsion of the diethylaminodifluorothiolate group generates the fluorinated cyclopropane **178**. Collapse of **178**, followed by double bond isomerisation gives the side product **174**. The *E*-stereochemistry of the olefin was confirmed by NOESY-NMR.



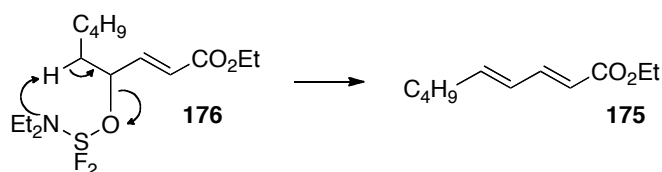
Scheme 65

This mechanism relies on the ability of fluorine to act as a π -donor (even though it is strongly σ -withdrawing); a property exhibited in the *ortho/para*-directing nature of fluorine in electrophilic aromatic substitution¹³⁴ and shown by the reported upfield ^1H -NMR shifts of the allylic protons H_x in fluoroolfefeins (Scheme 66).¹³⁵



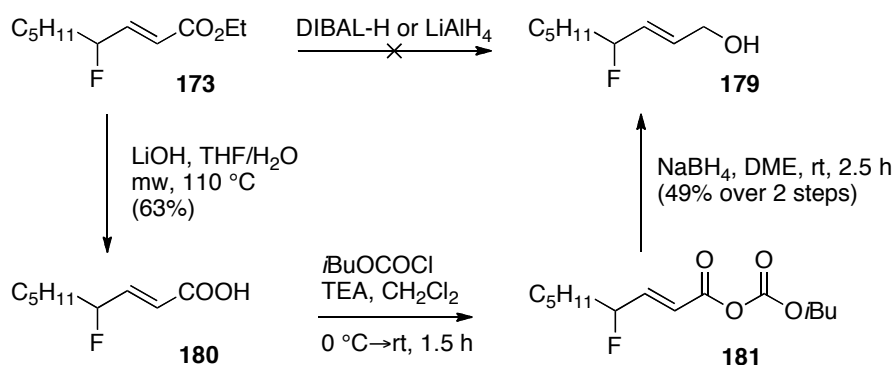
Scheme 66

The elimination product **175** was inseparable from **173** by both chromatography and distillation; although as it was only produced in small quantities, the mixture was carried through to the next step. We propose that the product forms *via* an intramolecular elimination of the intermediate **176** (Scheme 67).



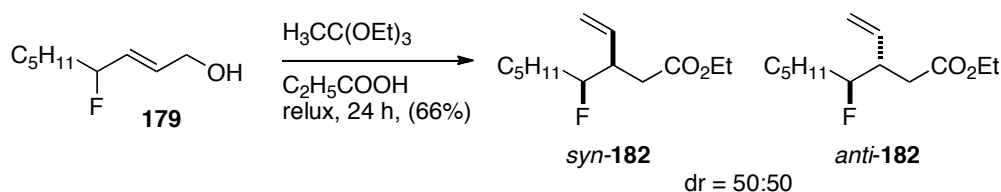
Scheme 67

Reduction of **173** was attempted using DIBAL-H and lithium aluminium hydride, although, similarly to reactions of **165**, only decomposition products were observed. Analysis of the decomposition product showed no signals in the ^{19}F -NMR spectrum. Instead, **179** was prepared by saponification of **173** to give **180**, followed by sodium borohydride reduction of the corresponding mixed anhydride **181** (Scheme 68).¹³⁶ The allylic alcohol **179** was used in the next step directly following purification. Samples of **179** decomposed to an intractable tar overnight, even when refrigerated.



Scheme 68

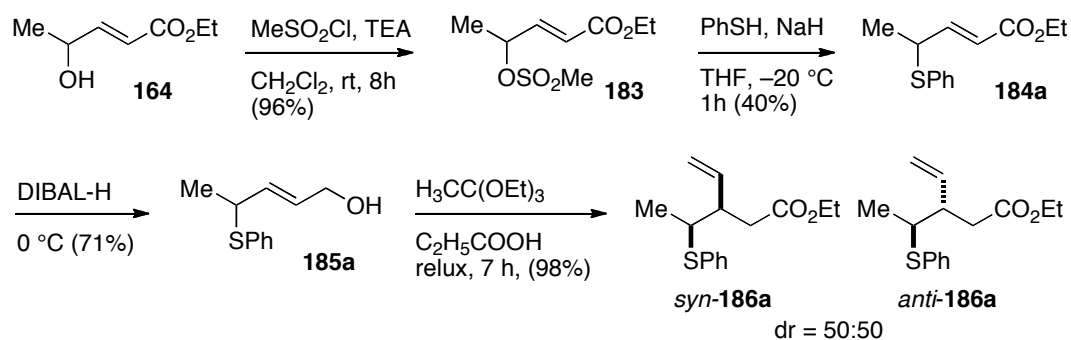
Johnson–Claisen rearrangement of **179** afforded a 50:50 mixture of *syn*- and *anti*-**182** (Scheme 69). This lack of selectivity stands in contrast to that observed in the rearrangements of the proline- and dioxolane-containing substrates reported by Mulzer¹¹⁰ and Cha¹⁰³ respectively. The lower yield for this substrate was attributed to its poor stability.



Scheme 69

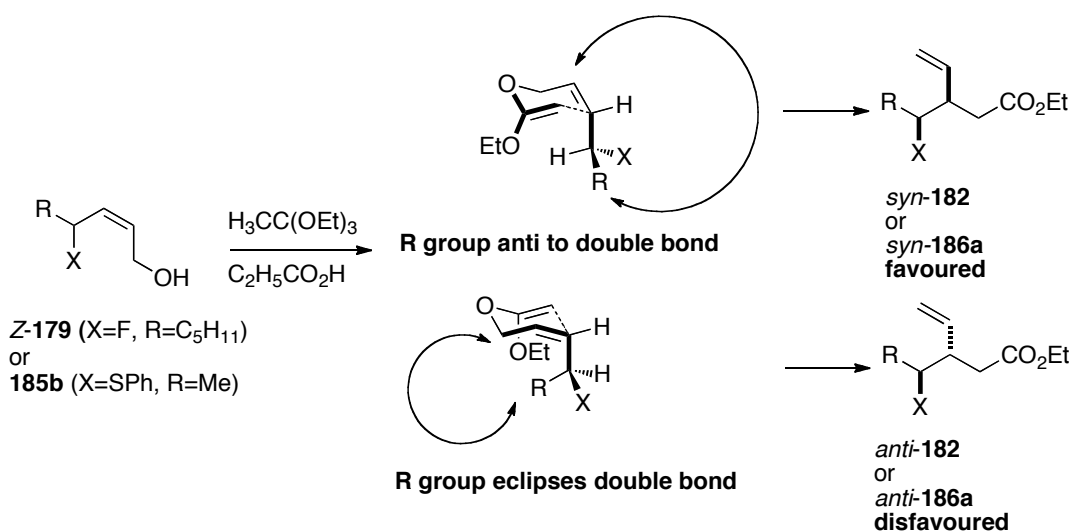
2.3.3 Preparation and rearrangement of γ -thiophenyl allylic alcohols

The Johnson–Claisen rearrangement of the analogous γ -thiophenyl allylic alcohol was then investigated. The previously prepared ester **164** was treated with methanesulfonyl chloride to give methanesulfonate **183**, which was treated with sodium thiophenolate to give ester **184a**. DIBAL-H reduction of **184a** using the procedure of Bach^{147a} afforded **185a** (Scheme 70). Other routes towards substrates of this type have been reported, and a full discussion of these is given later. Johnson–Claisen rearrangement of **185a** was high-yielding, but like rearrangement of **179**, unselective. Rigorously degassed triethyl orthoacetate was required in this reaction to prevent the formation of *S*-oxidation products.



Scheme 70

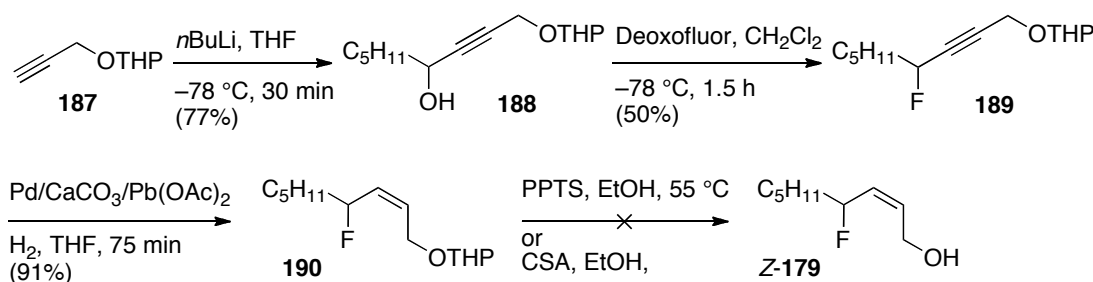
Considering the many previous examples in both nucleophilic and electrophilic addition to C=C double bonds, we predicted that the olefin substitution pattern would play a role in stereoselectivity. This remains comparatively poorly investigated for Claisen rearrangements,¹¹² but we expected *a priori* that the *Z*-isomers would show enhanced selectivity for the *syn* product *via* a transition state in which 1,3-allylic strain was minimised (Scheme 71). Therefore, the behaviour of (*E*)- and (*Z*)-allylic alcohols in the Johnson–Claisen rearrangement were compared using the isomers of the thiophenyl- and fluoro- compounds **185a** and **179** as substrates.



Scheme 71

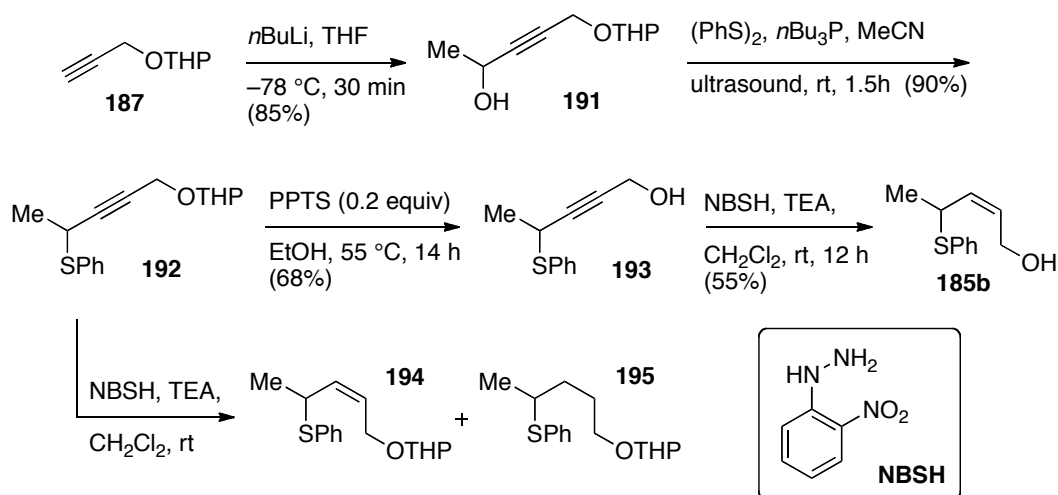
Although no syntheses of (*Z*)- γ -fluoroallylic alcohols have been reported, the dehydroxylfluorination of terminally protected propargyl diols has been demonstrated.¹³⁷ Additionally, fluoroalkynes undergo *cis*-selective hydrogenation to the corresponding fluoroolefin in the presence of Lindlar's catalyst.¹³⁸ We predicted that the required Johnson–Claisen substrate *Z*-**179** could be prepared by such a route (Scheme 72). The carbanion of THP-protected propargyl alcohol **187**¹³⁹ reacted with

hexanal to afford alcohol **188**,¹⁴⁰ which was treated with Deoxofluor [(CH₃OCH₂CH₂)₂NSF₃] (a more thermally stable alternative to DAST)^{141, 131b} to afford propargyl fluoride **189**. The yield was moderate for this step, although no side products were identified. Hydrogenation of **189** afforded the protected allylic alcohol **190** in high purity and yield, without the need for further purification. The reaction time was carefully controlled. Longer times resulted in over-reduction to the fully saturated compound, which was inseparable from **190**. Deprotection of the alcohol was attempted with CSA and PPTS. In both cases the product decomposed upon isolation. This result, in conjunction with studies on *E*-**179** points to the poor stability of these compounds, though analysis by ¹H-NMR of the decomposed material did not show the formation of a discrete product. We concluded that the fluorinated system above was too unstable for its behaviour in the Johnson–Claisen rearrangement to be studied.



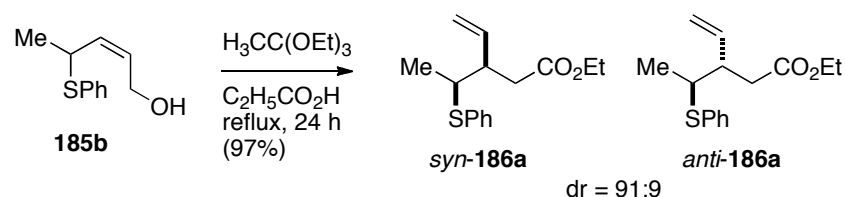
Scheme 72

In light of this setback our attention turned towards looking at the behaviour of (*Z*)-thiophenyl allylic alcohols in the Johnson Claisen rearrangement. We attempted to prepare the *Z*-configured allylic alcohol **185b** via a route similar to that above (Scheme 73). Again, the monoprotected diol **191** was prepared from THP-protected propargyl alcohol **187**. Ultrasound-assisted Mitsunobu reaction¹⁴² installed the sulfide **192**, which could not be reduced under Lindlar conditions. We attribute this to poisoning of the catalyst by the sulfide.¹⁴³ Instead, diimide,¹⁴⁴ generated *in situ* from decomposition of NBSH¹⁴⁵ was used. Tracking of this reaction proved difficult, owing to the very low polarity of **192**. Prior deprotection increased the polarity of the system, and the propargyl alcohol **193** was reduced to give **185b**. Although yields were generally low and this is clearly an inefficient route, a sufficient quantity of **185b** was prepared for further investigation.



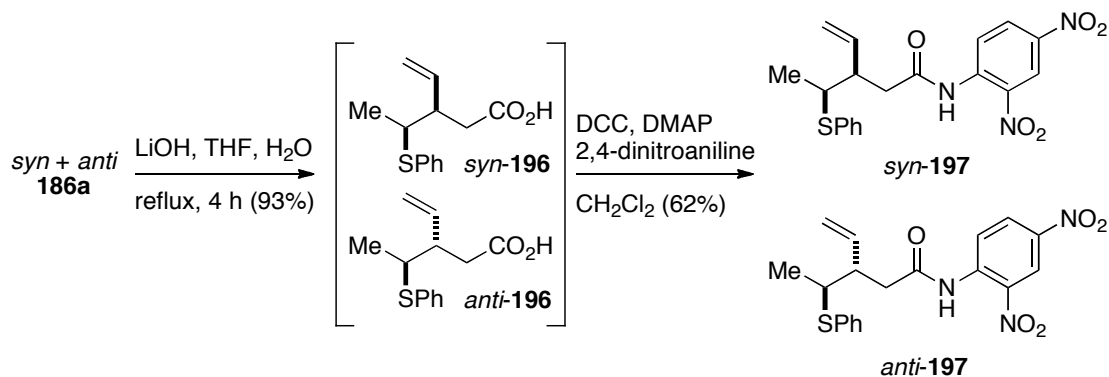
Scheme 73

In contrast to **185a**, Johnson–Claisen rearrangement of **185b** gave a 91:9 mixture of products **186a** in excellent yield. As expected, the reaction time was longer for the *Z*-isomer¹⁴⁶ (Scheme 74). In the same manner as before, the structure of the major diastereomer was established by the synthesis of a derivative.



Scheme 74

The 3,5-dinitrobenzoyl esters of the alcohols derived from Johnson–Claisen products **186a** were prepared in the same fashion as **160**. The corresponding esters were obtained as a viscous liquid, and therefore it was not possible to prepare pure samples suitable for crystallographic analysis. Instead, hydrolysis of the 91:9 mixture of isomers **186a** gave a mixture of isomeric acids **196**, which were converted to the corresponding highly crystalline 2,4-dinitroanilides **197** (Scheme 75). Separation of this mixture gave a pure sample of the major isomer *syn*-**197**, whose stereochemistry was assigned by X-ray crystallography (see Appendix).



Scheme 75

2.4 The effects of olefin substitution pattern on stereoselectivity

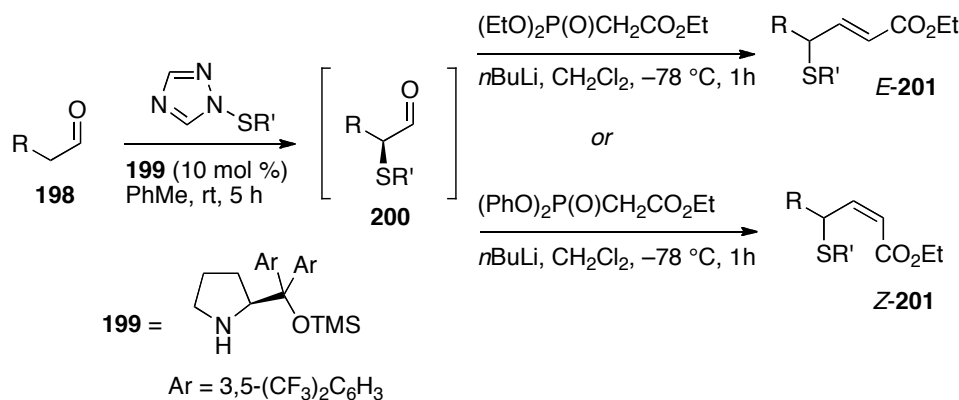
2.4.1 Substrate synthesis

Encouraged by the above result, we sought other examples of selectivity in this reaction. We decided to investigate the effects of larger ($n\text{C}_5\text{H}_{11}$) and branched (*i*Pr) alkyl substituents on the stereoselectivity of the rearrangement. A route was required in which both the alkyl substituent and olefin geometry could be easily varied. The most commonly used route for synthesis of these compounds involves olefination of an α -sulfenyl aldehyde **200**, followed by reduction of the resulting α,β -unsaturated ester **201** (Scheme 76). The α -sulfenyl aldehyde itself is typically generated either from methyl lactate (Bach/Armstrong)¹⁴⁷ or the sulfide **205** (Yadav).¹⁴⁸ With the former, variation of the nature of the alkyl chain would be difficult.

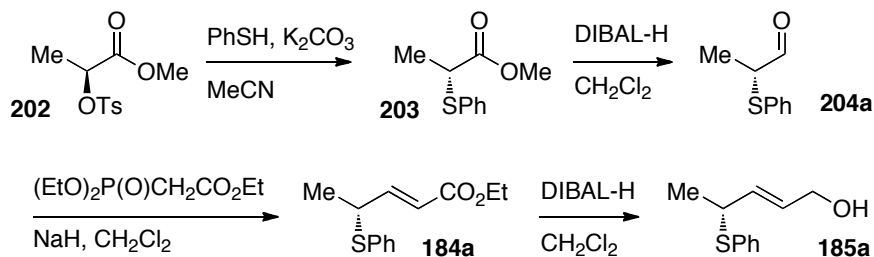
More recently, Armstrong has reported a route to both *E*- and *Z*- γ -sulfenyl- α,β -unsaturated esters **201** by variation of the phosphonate anion.¹⁴⁹ The α -sulfenyl aldehyde **200** was prepared in an organocatalytic, enantioselective fashion using the chemistry of Jørgensen.¹⁵⁰ In the same pot (α -sulfenyl aldehydes racemised during purification over silica gel), use of triethyl phosphonoacetate in a Horner–Wadsworth–Emmons reaction gave the *E*- γ -sulfenyl- α,β -unsaturated esters **201**, while use of the Ando phosphonate¹⁵¹ gave the *Z*-isomers. DIBAL-H reduction of these esters would provide access to the required allylic alcohol substrates **185** and we chose to use a route of this type for our work. Other routes to compounds of this type

via radical isomerisation¹⁵² and Peterson¹⁵³ olefination have also been reported, although these examples were deemed too specific for our work.

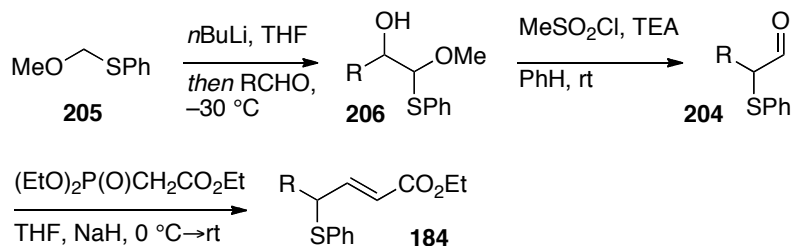
Armstrong Route



Bach Route



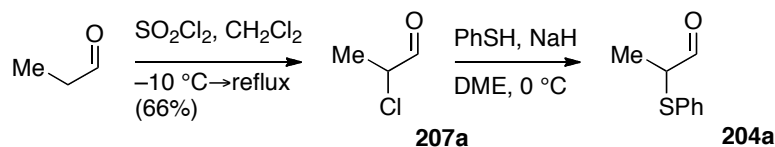
Yadav Route



Scheme 76

As enantiopure substrates were not required we explored other methods of α -sulfenylation of aldehydes. The reaction was optimised with the substrates **185a** and **185b**, where R=Me was the ultimate targets. We did not attempt to reproduce the chemistry of Yadav¹⁴⁸ for the synthesis of these intermediates. The preparation of α -sulfenyl aldehydes by treatment of α -haloaldehydes with thiolates has been reported,¹⁵⁴ and our attention turned to this method for the preparation of **204**. Treatment of propanal with sulfonyl chloride afforded the α -chloroaldehyde **207a**,¹⁵⁵ which existed in a stable oligomeric form at sub-ambient temperatures.¹⁵⁶ Gentle

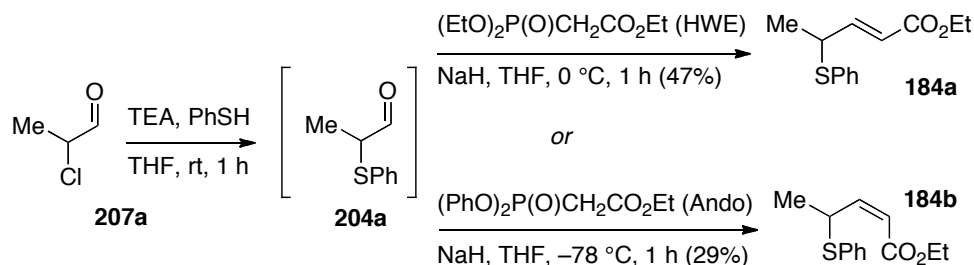
warming of the oligomeric material to room temperature revealed the monomeric aldehyde,¹⁵⁷ which reacted with sodium thiophenolate, generated *in situ* from thiophenol and sodium hydride to afford the α -sulfenyl aldehyde **204a** (Scheme 77).



Scheme 77

However, the isolated material decomposed, to some extent, to thiophenol, which quenched the phosphonate in the subsequent olefination reactions. Pre-washing of the aldehyde with sodium carbonate failed to alleviate this problem. We attempted a one-pot sulfenylation/olefination approach similar to that of Armstrong.

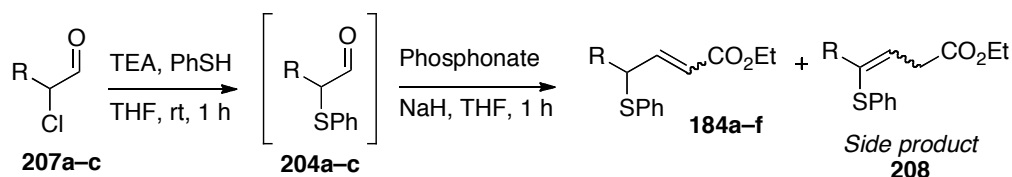
Reasoning that such a strong base as sodium hydride was not required for formation of the thiolate, we found that the α -chloroaldehyde **207a** reacted rapidly at room temperature with triethylammonium thiophenolate in THF, generated *in situ* from TEA–thiophenol, to give a solution of **204a**. The lower-temperature conditions for use of sodium hydride were not required. The solution of the α -sulfenyl aldehyde was filtered under nitrogen and added *via* cannula to a solution of the appropriate phosphonate anion. In common with Armstrong, use of triethyl phosphonoacetate in a Horner–Wadsworth–Emmons (HWE) reaction at 0 °C gave the *E*- γ -sulfenyl- α,β -unsaturated ester **184a** exclusively. Reaction with the anion of the Ando phosphonate¹⁵¹ at the lower temperature of –78 °C gave the esters **184b** and **184a** in a 10:1 ratio respectively (Scheme 78).



Scheme 78

We extended this route to other substrates. The analogous chloroaldehydes were prepared using the organocatalytic method of Jørgensen;^{150b,158} **207b** using proline and **207c** using prolinamide as the catalyst. Yields for the olefination were moderate,

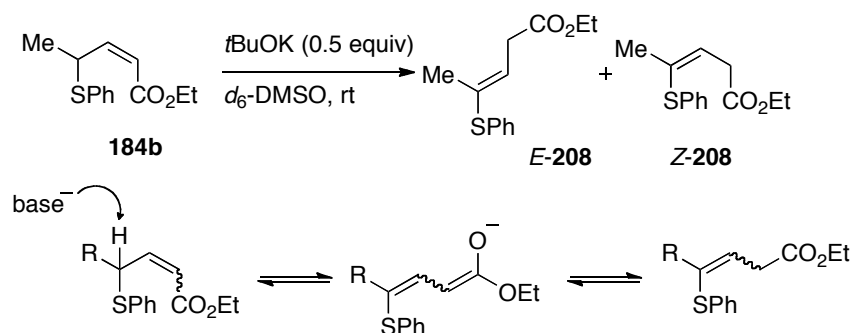
although the reaction was easily scalable and sufficient material was prepared for further investigation (Scheme 79, Table 13).



Scheme 79

Table 13					
Entry	Substrate	R	Phosphonate	E/Z	Yield (%)
a	207a	Me	HWE	<i>E</i>	47
b	207a	Me	Ando	<i>Z</i>	29
c	207b	<i>n</i> C ₅ H ₁₁	HWE	<i>E</i>	57
d	207b	<i>n</i> C ₅ H ₁₁	Ando	<i>Z</i>	73
e	207c	<i>i</i> Pr	HWE	<i>E</i>	60
f	207c	<i>i</i> Pr	Ando	<i>Z</i>	27

During the synthesis of these substrates, particularly when the reaction time was extended, formation of the isomeric product **208** was observed as a 30:70 (unassigned) mixture of *E* and *Z* stereoisomers, which was inseparable from **184**. An NMR experiment suggested a base-catalysed mechanism for the formation of **208** (Scheme 80, Table 14). The ratio of stereoisomers remained constant over time.



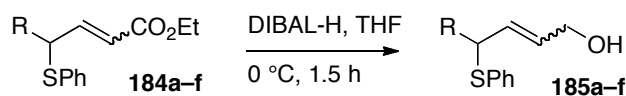
Scheme 80

Table 14	
Time	Conversion to 208 (%)
10 min	38
1 h	67
16 h	100

Reducing the amount of base used for the olefination reaction, reduced the yield. The milder Masamune–Roush (DBU–LiCl) conditions for the synthesis of *E*-isomers¹²¹

and modified Ando (DBU–NaI) conditions^{151b} for the synthesis of *Z*-isomers, might be used in future work.

The esters **184a–f** were reduced to the corresponding allylic alcohols **185a–f** with DIBAL-H (Scheme 81, Table 15). Much lower (ca. 20%) yields were observed upon switching the chromatography eluent from TBME/heptane to ether/heptane, which may be related to the lower level of ether peroxides present in TBME.

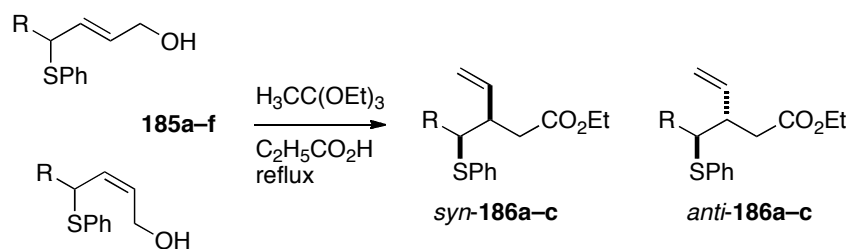


Scheme 81

Table 15			
Entry	R	<i>E/Z</i>	Yield (%)
a	Me	<i>E</i>	71
b	Me	<i>Z</i>	70
c	<i>n</i> C ₅ H ₁₁	<i>E</i>	83
d	<i>n</i> C ₅ H ₁₁	<i>Z</i>	60
e	<i>i</i> Pr	<i>E</i>	83
f	<i>i</i> Pr	<i>Z</i>	54

2.4.2 Rearrangements of *E*- and *Z*-allylic alcohols

Allylic alcohols **185a–f** were subjected to Johnson–Claisen rearrangement conditions (Scheme 82, Table 16) to give **186a–c**. The contrasting behaviour observed for **185a,b** was also observed with the geometric isomers **185c,d** and **185e,f**; yields were uniformly excellent. Reaction times followed the expected pattern, with the more hindered substrates undergoing rearrangement more slowly. In light of the results of the X-ray crystallography studies on **186b** above, *syn* stereochemistry was inferred also for the major products of the Johnson–Claisen rearrangements of **185d** and **185e,f**.

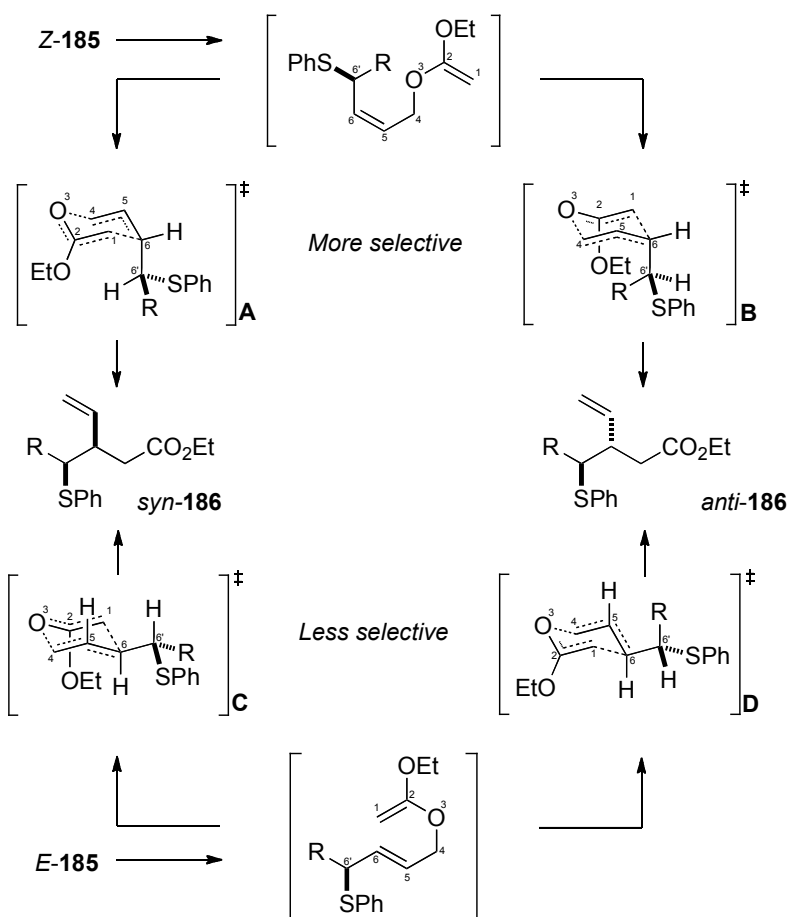


Scheme 82

Table 16							
Entry	Substrate	R	<i>E/Z</i>	time (h)	Product	Yield (%)	Ratio <i>syn-anti-186</i> ^a
1	185a	Me	<i>E</i>	7	186a	98	50 : 50
2	185b	Me	<i>Z</i>	24	186a	97	91 : 9
3	185c	<i>n</i> C ₅ H ₁₁	<i>E</i>	12	186b	98	50 : 50
4	185d	<i>n</i> C ₅ H ₁₁	<i>Z</i>	48	186b	94	90 : 10
5	185e	<i>i</i> Pr	<i>E</i>	24	186c	93	60 : 40
6	185f	<i>i</i> Pr	<i>Z</i>	48	186c	87	90 : 10

^aDetermined by ¹H-NMR analysis of the crude reaction mixture

We rationalise the marked difference in behaviour of *E*- and *Z*-**185** by comparison of the diastereomeric transition states **A–D** for the rearrangement (Scheme 83). In all cases there is antiperiplanar alignment of the C6'–SPh and incipient C1–C6 bond. For *Z*-**185**, the major product *syn*-**186** arises from an orientation in which the C6'–H bond (transition state **A**) rather than the C6'–R bond (transition state **B**) eclipses the allylic C4–C5 double bond. For *E*-**185**, the corresponding allylic 1,3-interactions are between C5–H and the C6'–H (transition state **C** leading to *syn*-**186**) or C6'–R (transition state **D** leading to *anti*-**186**) bonds; the lesser steric bulk associated with C5–H compared to C4–C5 leads to lower selectivity for the *E*-substrates. This lack of discrimination is in contrast to that observed in the rearrangement reactions of analogous dioxolane- and proline-containing systems reported by Cha¹⁰³ and Mulzer¹¹⁰ respectively, and taking into account the results presented in the next chapter, may be a consequence of the lack of substitution at C1 in our acetate-derived substrates.



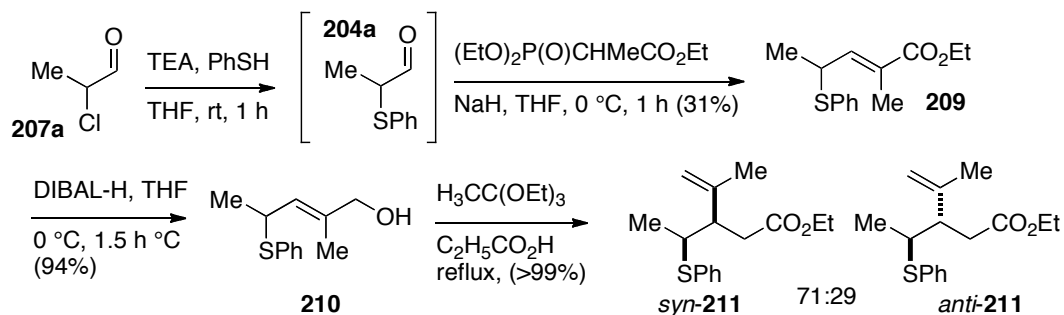
Scheme 83

2.4.3 Preparation and rearrangement of a trisubstituted allylic alcohol

In light of the transition state analysis presented above an additional substrate was prepared and its Johnson–Claisen rearrangement investigated. We reasoned that rearrangement of an *E*-configured substrate possessing a substituent at C5 would be more selective than those of **E-185**, since, upon introducing an unfavourable 1,3-diaxial interaction, there would be a disproportionately greater energy penalty associated with the transition state corresponding to **D** in Scheme 83, which leads to the *anti* product.

The allylic alcohol **210** bearing an additional olefinic methyl group was prepared in the same manner as **185**: addition of the α -sulfenyl aldehyde **204a** to the anion of the appropriate phosphonate afforded ester **209**, which was subsequently reduced with DIBAL-H to afford **210**. Subjection of **210** to the previously established Johnson–Claisen conditions gave in quantitative yield a 71:29 mixture of rearrangement

products **211** (Scheme 84). From prior evidence, we tentatively assigned the major product as the *syn* isomer. Additional evidence in support of this assignment is given by the similar rearrangements of azide-bearing systems shown later. This result is in contrast with those of Takano, who observed no selectivity increase in rearrangements of trisubstituted allylic systems.¹⁰⁶ In summary, we have shown that in the case of C6' thiophenyl substituents, the level of selectivity is highly dependent on the allylic substitution pattern.



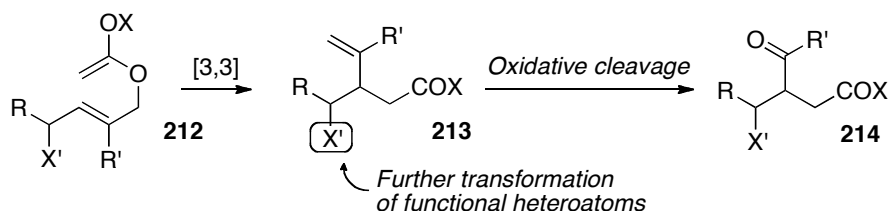
Scheme 84

2.5 Synthetic applications of exopericyclic control in Claisen rearrangements

2.5.1 Background

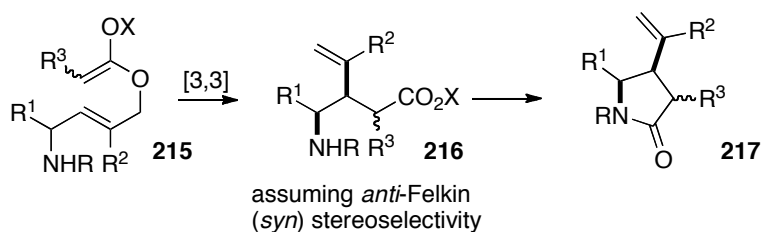
With reliable patterns of stereoselectivity emerging, we wished to exploit these effects in the synthesis of small molecules. We had shown the importance of a heteroatom-bearing stereocentre in attaining stereoselectivity and now wished to explore reactions of the heteroatomic group. This section details our efforts in this area, concentrating on further transformations of rearrangement products. Also described is initial work on elaboration of the new olefin furnished by the Claisen rearrangement.

We envisaged that oxidative cleavage of the olefin of **213** to give the corresponding aldehyde or ketone **214** would provide scope for further transformations of this system (Scheme 85).



Scheme 85

In particular, we became interested in Claisen rearrangements of allylic systems bearing nitrogenous *exo*-pericyclic stereocentres, envisaging that the Claisen rearrangement product **216** of a ketene acetal bearing an exopericyclic amine **215** could be converted into the corresponding γ -lactam **217** (Scheme 86).



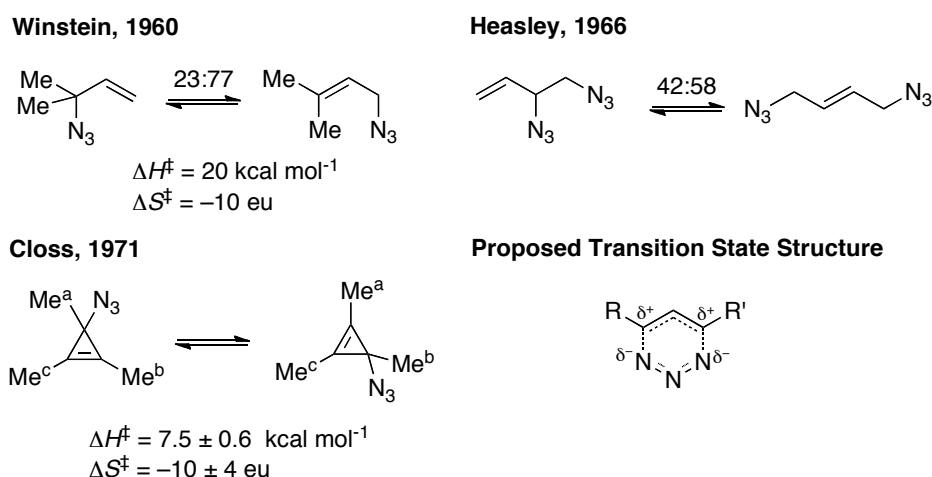
Scheme 86

Free amines are poorly tolerated by the Claisen rearrangement and prior examples of this reaction typically use protecting groups to overcome this problem. In our case, introducing the stereoelectronic complication of a bulky protecting group was

unattractive. Instead, we decided to use the azide group as a surrogate amine, encouraged by its small steric profile and its potential for use in a wide variety of subsequent reactions.¹⁵⁹ We quickly realised that this process would be complicated by a second rearrangement – that of the allylic azide itself; a reaction that has previously been viewed as a synthetic limitation of this functional group.

2.5.2 Sigmatropic rearrangements of allylic azides

The rearrangement of allylic azides was discovered in 1960, when Winstein and co-workers found that treatment of γ,γ -dimethallyl chloride with sodium azide in acetone gave an equilibrating mixture of α,α -dimethallyl and γ,γ -dimethallyl azides.¹⁶⁰ The rearrangement was rapid at room temperature, although the isomers could be separated by fractional crystallisation at $-80\text{ }^{\circ}\text{C}$. Similar rearrangements of allylic diazides were observed by Heasley, who noted that tertiary and secondary allylic azides rearrange faster than primary allylic azides.¹⁶¹ A very small solvent effect on the rate of rearrangement was reported by Winstein; which, in addition to NMR studies by Closs indicates charge separation in the transition state.¹⁶² Nevertheless, the stereospecific nature of the rearrangement, as explored by Padwa,¹⁶³ suggests a cyclic, concerted transition state and the reaction may be viewed as a [3,3]-sigmatropic rearrangement (Scheme 87).

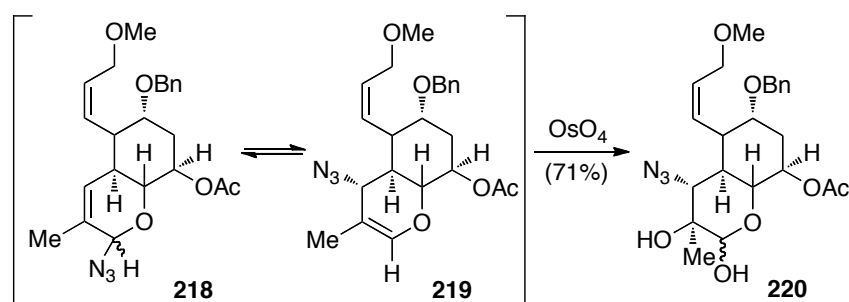


Scheme 87

Allylic azides are generally obtained as thermodynamic mixtures. For acyclic allylic azides the rearrangement is rapid at room temperature, while cyclic allylic azides

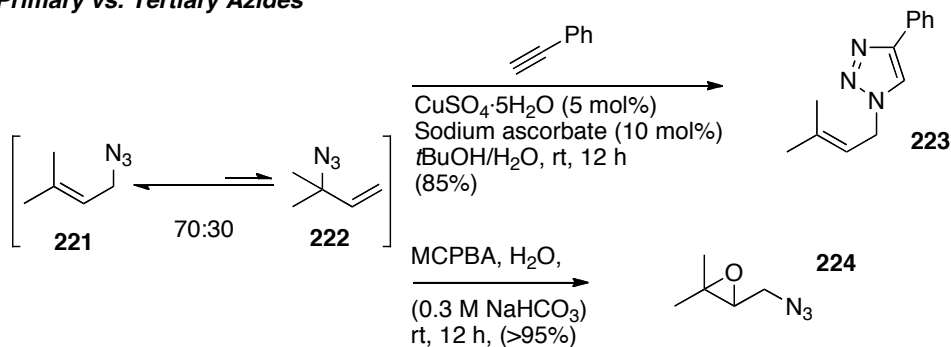
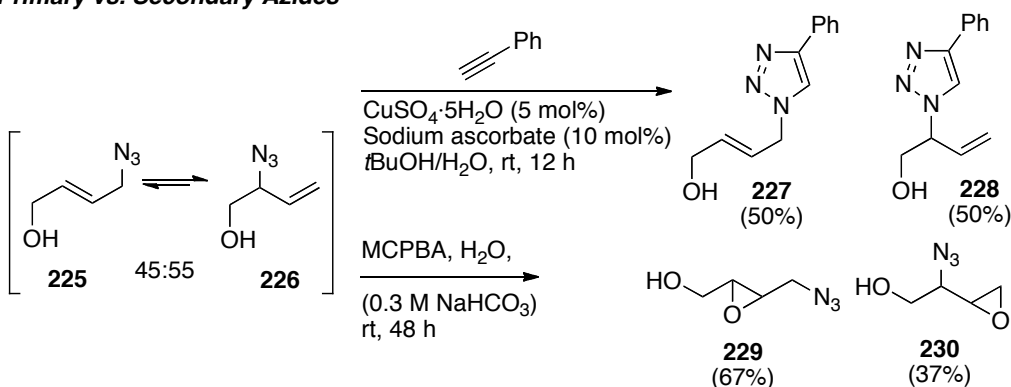
often rearrange more slowly.¹⁶⁴ The vast majority of allylic azides described in the literature exist as a single regioisomer in which the olefin is in conjugation with an arylene,^{172,165} carbonyl or nitrile.¹⁶⁶ Recently, steric factors have been found to influence the equilibrium.

Of key importance for our studies is the small class of reactions in which equilibrating mixtures of allylic azides are transformed into a single product. The earliest report of this reactivity mode is described by Danishefsky in the synthesis of *N*-acetylactinobolamine.¹⁶⁷ Osmylation of the mixture **218** and **219** occurred exclusively *via* the more nucleophilic glycal **219** to give **220** exclusively (Scheme 88).



Scheme 88

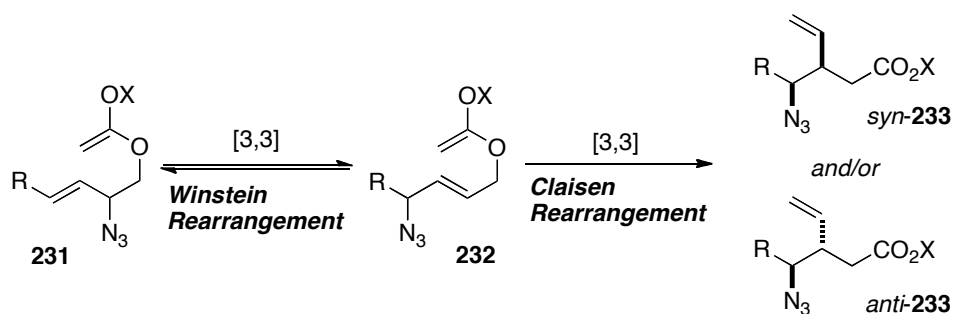
More recently, Sharpless and Fokin studied the behaviour of mixtures of allylic azides in the Cu(I)-catalysed cycloaddition with phenylacetylene and in MCPBA-mediated epoxidation reactions.¹⁶⁸ The differences between primary, secondary and tertiary allylic azides were explored. Mixtures of primary and tertiary (**221,222**), and secondary and tertiary azides reacted selectively *via* the most reactive isomer (the less hindered azide, or the more electron-rich olefin), while dramatically reduced selectivity was observed with mixtures of primary and secondary azides **225,226** (Scheme 89). Notably, in all but one example, the most abundant isomer of the mixture was also the most reactive.

Primary vs. Tertiary Azides**Primary vs. Secondary Azides**

Scheme 89

2.5.3 Development of a tandem rearrangement process

In light of these examples, we proposed a reaction in which a ketene acetal bearing an allylic azide **231** undergoes a pair of [3,3]-sigmatropic rearrangements *via* **232** to give the product **233** (Scheme 90). Conceptually related are the isomerisation-Claisen rearrangements most recently explored by Nelson *et al.*¹⁶⁹ and other examples in the literature of tandem conjugate addition/enolate Claisen rearrangements.¹⁷⁰ However, in these prior examples an isomerisation establishes the vinylic portion of the ketene acetal Claisen precursor. To the best of our knowledge, the studies presented herein represent the only example of isomerisation establishing exclusively the allylic portion of a ketene acetal.¹⁷¹



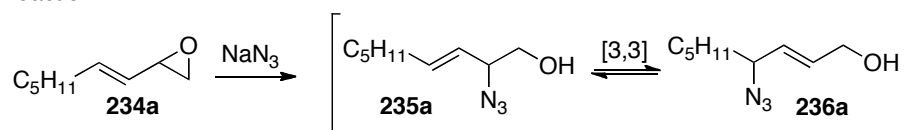
Scheme 90

The work presented in this section describes our work into the development, scope and limitations of this reaction. We have continued to explore the stereochemical patterns previously discussed.

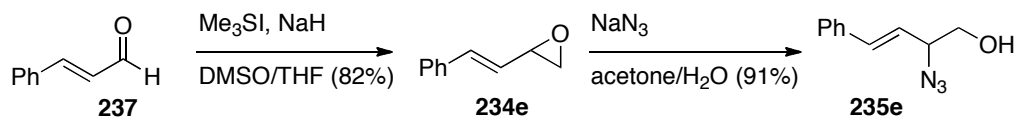
2.5.4 Synthesis and initial rearrangements of allylic azidoalcohol substrates

We decided to study this reaction using a Johnson–Claisen rearrangement of the mixture of allylic azidoalcohols **235a** and **236a**, which would be converted into the required mixture of equilibrating ketene acetals *in situ*. In particular, for this initial study we chose compounds bearing an *n*-pentyl chain, in order to reduce volatility and improve thermal stability. A similar compound **235e**, reported by Whitesides *et al.*¹⁷² was prepared by reaction of oxirane **234e** with sodium azide. The oxirane was prepared by sulfur-ylide epoxidation of *trans*-cinnamaldehyde **237** (Scheme 91).

Proposed Reaction:



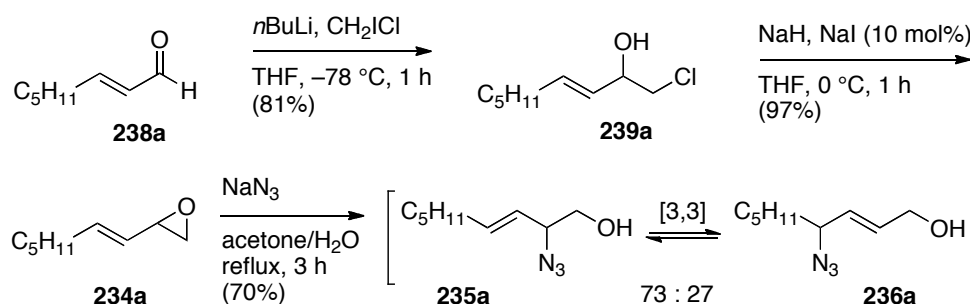
Literature precedent:



Scheme 91

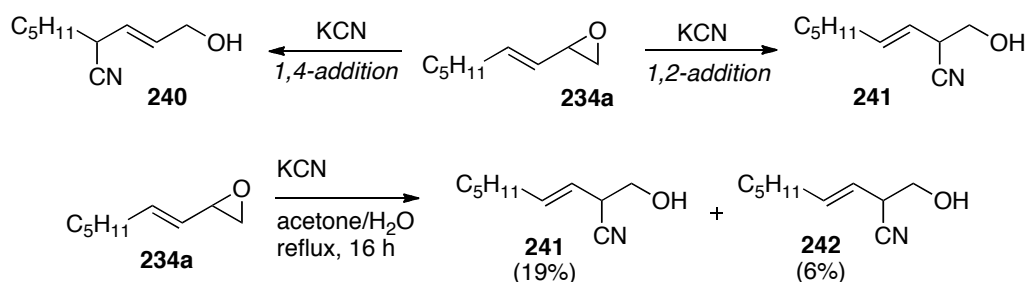
Our initial attempts to form oxirane **234a** from *trans*-2-octenal **238a** under these conditions failed. The oxirane was unstable to chromatography over silica gel and was difficult to separate from the DMSO reaction solvent by distillation. Instead, **234a** was prepared *via* the chlorohydrin **239a** (Scheme 92).¹⁷³ Addition of

lithiochloromethane to **238a** gave the chlorohydrin **239a**, which was then converted into **234a** by treatment with sodium hydride and sub-stoichiometric sodium iodide. When the precursor chlorohydrin was of high purity no purification of the oxirane was required, allowing its use directly in the next step. Reaction of **234a** with sodium azide in refluxing acetone/water gave a 73:27 (by $^1\text{H-NMR}$) mixture of **235a** and **236a** respectively in good yield. The regioisomers were partially separable by column chromatography, although they equilibrated prior to analysis to give a mixture having the same ratio as the crude mixture. Assignment of each isomer was performed using COSY and ^{15}N -HMBC NMR techniques. Notably, the more abundant isomer **235a** is that which requires a further isomerisation to participate in the Claisen rearrangement.



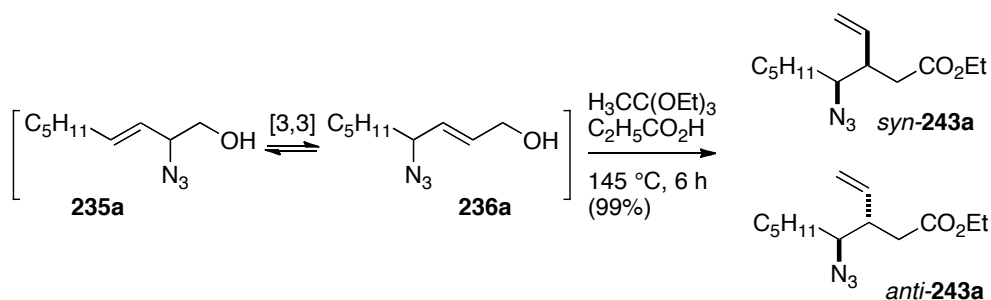
Scheme 92

To eliminate the possibility that the regioisomeric distribution was controlled by relative rates of 1,2- and 1,4-opening of the oxirane rather than an equilibration process, we studied the ring-opening of **234a** with potassium cyanide, which could potentially give a mixture of the non-equilibrating allylic nitriles **240** and **241** (Scheme 93).¹⁷⁴ Although opening of the oxirane by water competed with opening by cyanide,¹⁷⁵ only the 1,2-opening products **241** and **242** were observed. This indicated that in the reaction of **234a** with sodium azide, the 1,2-product **235a** is initially formed, followed by isomerisation *via* reversible sigmatropic rearrangement to give the observed mixture of regioisomers. The low yield may be attributed to the poor stability of the oxirane at elevated temperature over long periods of time.



Scheme 93

The mixture of **235a** and **236a** was then treated under the Johnson–Claisen conditions used previously (Scheme 94). Complete conversion of the mixture was observed in 6 h and the product was isolated in very high yield. This represents the first example of a reaction that discriminates between two *acyclic* secondary allylic azides. It is also the first example of any such transformation of allylic azides where the product arises from the significantly less abundant component of the equilibrium mixture.

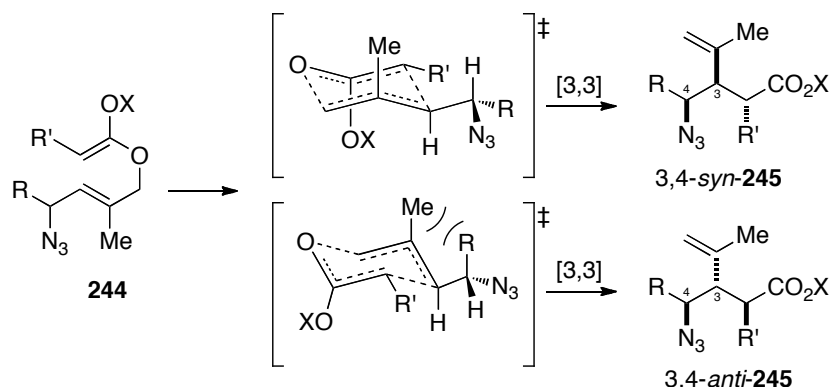


Scheme 94

2.5.5 Attempts to develop a stereoselective rearrangement

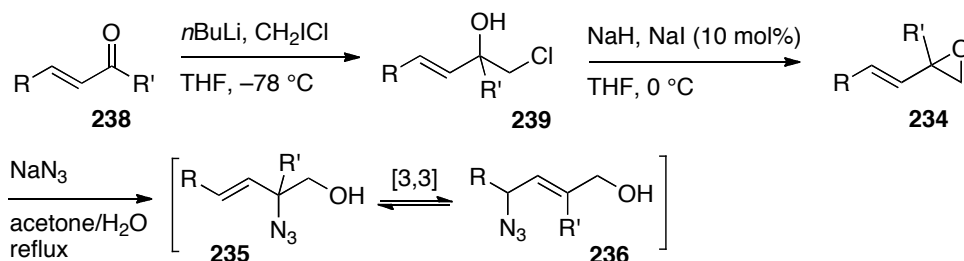
In the initial reactions described above, no stereoselectivity was observed, although this was not unexpected considering our previous investigations into the effects of olefin substitution pattern. Although we have shown that *Z*-allylic alcohols undergo selective Claisen rearrangements, we predicted that *Z*-allylic azidoalcohols might undergo olefin isomerisation during Winstein rearrangement. Given that the rate of Claisen rearrangement of an *E*-allylic system is faster than the *Z*-isomer,¹⁴⁶ we predicted that equilibrating mixtures of *Z*-allylic azidoalcohols would undergo Claisen rearrangement with significantly reduced stereoselectivity. Thus, in the course of our studies into the scope and limitations of this process, our interest turned to other methods of attaining selectivity in the Claisen rearrangement of *E*-allylic alcohols.

Specifically, we wished to study trisubstituted allylic systems **244**, which we predicted would favour the *anti*-Felkin product 3,3-*syn*-**245** (Scheme 95).



Scheme 95

The generality of this tandem process was tested using variations of the R and R' groups. Substrates were prepared by a general route, in the same manner as that reported by Whitesides¹⁷² (Scheme 96). Variations of the R group enabled the study of the relative effects of straight chain and branched alkyl groups, and this was examined both for R'=H and R'=Me where possible. In addition, we chose to explore the case where R=aryl, with regard to its effects on product distribution in both the Winstein and Claisen rearrangements.

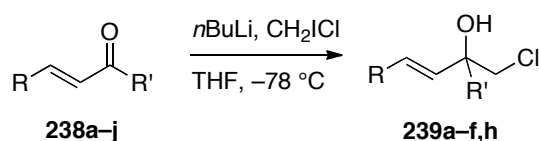


Scheme 96

As shown above, where R=Ph the allylic azidoalcohol **235e** exists as a single isomer which would require isomerisation to participate in the Claisen rearrangement. Aromaticity decreases across the series benzene>pyridine>furan¹⁷⁶ so we proposed the series R=Ph, 2-pyridyl and 2-furyl to investigate the effects of lowering aromaticity, and therefore conjugative stabilisation of **235** on the system. In doing so, we predicted that the barrier to isomerisation might be lowered, increasing the rate with which mixtures of these compounds undergo Claisen rearrangement. Conversely, we reasoned that if R'=Ph, then the allylic azidoalcohol would be stabilized as the

reactive form **236**. Indeed, we were interested to explore whether under appropriate conditions, allylic azidoalcohols that exist exclusively in the unreactive form might still undergo Claisen rearrangement.

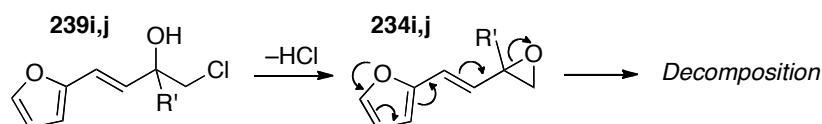
Chlorohydrins **239a–f** and **239h** were prepared using the conditions shown above (Scheme 97, Table 17). In each case, the reaction was complete within 1 h. Where the precursor ketone or aldehyde **238** was not commercially available, it was prepared *via* Wittig olefination of the corresponding aldehyde. Ketone **238f** was prepared by addition of phenylmagnesium chloride to crotonaldehyde and PDC oxidation of the alcohol intermediate.



Scheme 97

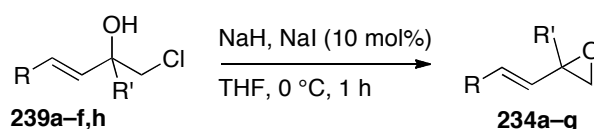
Table 17							
Entry	R	R'	Yield (%)	Entry	R	R'	Yield (%)
a	<i>n</i> C ₅ H ₁₁	H	81	f	Me	Ph	52
b	<i>n</i> C ₅ H ₁₁	Me	92	g	2-pyridyl	H	0
c	Me	Me	35	h	2-pyridyl	Me	88
d	<i>c</i> Hex	Me	84	i	2-furyl	H	0
e	Ph	H	99	j	2-furyl	Me	0

Yields were generally high, with some exceptions. The low yield of **239c** was attributed to its volatility. The furans **239i** and **239j** decomposed violently upon isolation to give an intractable tar. A similar, albeit slower decomposition of the pyridine **239g** was observed. A mechanism is proposed involving formation of the oxirane **234** with loss of HCl. This could be followed by ring-opening of **234** and subsequent acid-assisted decomposition, with the furyl group stabilising the developing partial positive charge on the more substituted oxirane carbon (Scheme 98).



Scheme 98

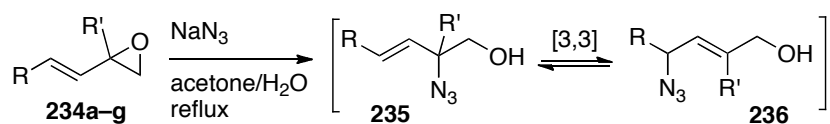
Treatment of the chlorohydrins **239a–f** and **239h** with sodium hydride and substoichiometric sodium iodide afforded the oxiranes **234a–g** (Scheme 99, Table 18). No further purification was required and these compounds were used directly in the next step. **234c** (R=Me) was highly volatile, and could only be isolated as a solution in THF. The concentration of the solution was determined by $^1\text{H-NMR}$ analysis.



Scheme 99

Table 18							
Entry	R	R'	Yield (%)	Entry	R	R'	Yield (%)
a	$n\text{C}_5\text{H}_{11}$	H	97	e	Ph	H	>99
b	$n\text{C}_5\text{H}_{11}$	Me	40	f	Me	Ph	98
c	Me	Me	46	g	2-pyridyl	Me	66
d	$c\text{Hex}$	Me	98				

Treatment of the oxiranes **234a–g** with sodium azide in acetone/water gave the allylic azidoalcohols **235/236a–f** (Scheme 100, Table 19). The reaction was performed under reflux with the exception of **236f**, which was isolated in low (<14%) yield under these conditions. Stabilisation of the developing partial positive charge by both phenyl and vinyl groups bound directly to the quaternary carbon enhance the rate of opening of the oxirane **234f**. Elevated temperatures are therefore not required and only cause decomposition of the starting material. The reaction was repeated at room temperature, affording the allylic azidoalcohol **236f** in good yield.



Scheme 100

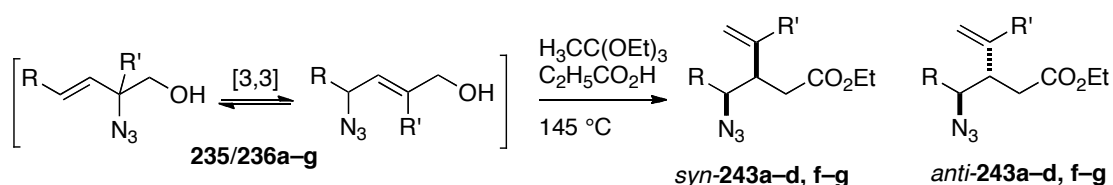
Table 19

Entry	R	R'	Yield (%)	Ratio 235 : 236 ^a
a	<i>n</i> C ₅ H ₁₁	H	70	73 : 27
b	<i>n</i> C ₅ H ₁₁	Me	25	61 : 39
c	Me	Me	71	64 : 36
d	<i>c</i> Hex	Me	59	63 : 37
e	Ph	H	60	100 : 0
f ^b	Me	Ph	74	0 : 100 ^c
g	2-pyridyl	Me	79	100 : 0

^aRatio determined by ¹H-NMR analysis; ^bat room temperature, 4 h; ^cas a 3:1 *E*:*Z* mixture

Mixtures of trisubstituted allylic azidoalcohols **235/236b–d** were obtained in similar ratios, favouring the tertiary (vicinal) azidoalcohol. This isomer was less favoured compared to **235a**. Azidoalcohols **235e** and **235g** were obtained as single isomers with the olefin in conjugation with the aryne as predicted. **236f** was obtained as an inseparable 3:1 *E*:*Z* mixture of isomers (determined by NOESY-NMR), both secondary azides as predicted. A full discussion of the individual factors affecting ratios of allylic azides is given later.

Allylic azidoalcohols **235/236a–g** were exposed to Johnson–Claisen conditions. (Scheme 101, Table 20). In addition to the rearrangement product **243a**, **243b–d** and **f** were obtained in good yield, although extended reaction times were required for these more sterically demanding substrates.



Scheme 101

Table 20

Entry	R	R'	t (h)	Yield (%)	Ratio <i>syn</i> - : <i>anti</i> - 243 ^a
a	<i>n</i> C ₅ H ₁₁	H	6	99	50 : 50
b	<i>n</i> C ₅ H ₁₁	Me	24	72	59 : 41
c	Me	Me	12	86	60 : 40
d	<i>c</i> Hex	Me	26	94	63 : 37
e	Ph	H	48	0	-
f	Me	Ph	24	75	50 : 50
g	2-pyridyl	Me	48	<4	(77 : 23)

^aBy ¹H-NMR analysis

Trisubstituted allylic systems **235/236b–d** rearranged with moderate stereoselectivity; of lower magnitude than analogous sulfide systems. **236f** was the only example of a

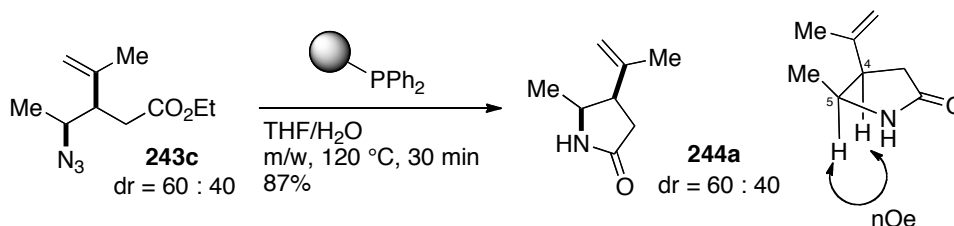
Z-configured allylic system undergoing rearrangement. Interestingly, in contrast to previous examples, no stereoselectivity was observed. **235e** did not rearrange under these conditions. **243g** was obtained as an impure compound in very low yield, thus the magnitude of this selectivity is likely to be invalid. To exclude the effects of neutralisation of the propionic acid catalyst by the 2-pyridyl substituent (examination of pKa values suggests the pyridine would be fully protonated), the reaction was repeated using 1.2 equivalents of propionic acid. The yield was unaffected. Clearly, substrates where R=Ar do not participate in this tandem sigmatropic process.

2.5.6 Synthesis of γ -lactams

In the next phase of the work, the conversion of Claisen products into the corresponding lactams was investigated. The intention was both to demonstrate the synthetic utility of the preceding reaction and to impose a conformational constraint, such that the sense of stereoinduction could be assigned by spectroscopic methods. The transformation of azidoesters into lactams *via* Staudinger reduction¹⁷⁷ of the azide and *in situ* cyclisation of the intermediate aminoester is well preceded.¹⁷⁸ Triphenyl-, tributyl- and trimethylphosphine are commonly used to generate the iminophosphorane intermediate, which is intercepted by water. This technique has been used previously for the cyclisation of Claisen rearrangement products bearing azide groups.^{178c} We chose the mixture of stereoisomers **243c** to investigate this process.

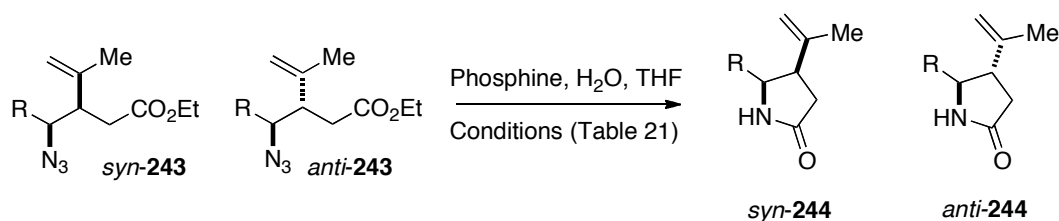
Treatment of **243c** with triphenylphosphine in water under microwave irradiation afforded the lactam **244a**, although due to its high polarity it was difficult to separate from the triphenylphosphine oxide by-product. Switching to polystyrene resin-supported diphenylphosphine¹⁷⁹ alleviated this problem as the reagent and by-products could be removed by filtration. Under these conditions the mixture of lactams *syn*- and *anti*-**244a** was obtained in good yield and with no change in diastereomeric ratio (Scheme 102). The starting material was not consumed when the reaction was performed at room temperature, indicating that heat was required to generate the iminophosphorane intermediate. NOESY-NMR of the product mixtures showed an nOe enhancement between H4-H5 in the major product, confirming its

identity as the predicted *syn*-diastereomer. Separation of the diastereomers was not attempted.



Scheme 102

The products of other moderately selective rearrangements **243b** and **243d** were unreactive under these conditions; neither the lactam product nor the intermediate amine was observed. Reasoning that the lack of reactivity was caused by steric crowding around the internal azide nitrogen, smaller and more nucleophilic trimethylphosphine was used to generate the intermediate iminophosphorane.¹⁸⁰ Neat samples of **243b** and **243d** were treated with water and a solution of trimethylphosphine in THF at room temperature to give the lactams *syn*- and *anti*-**244b** and **244c** respectively (Scheme 103, Table 21). Inspection of ¹H-NMR spectra and NOE enhancements showed a change in the product distribution; the *anti*-diastereomer becoming more abundant. When the reaction of **243c** (R=Me) was repeated using trimethylphosphine a similar change in ratio was observed. **243f** was also converted into the corresponding lactam **244d**.



Scheme 103

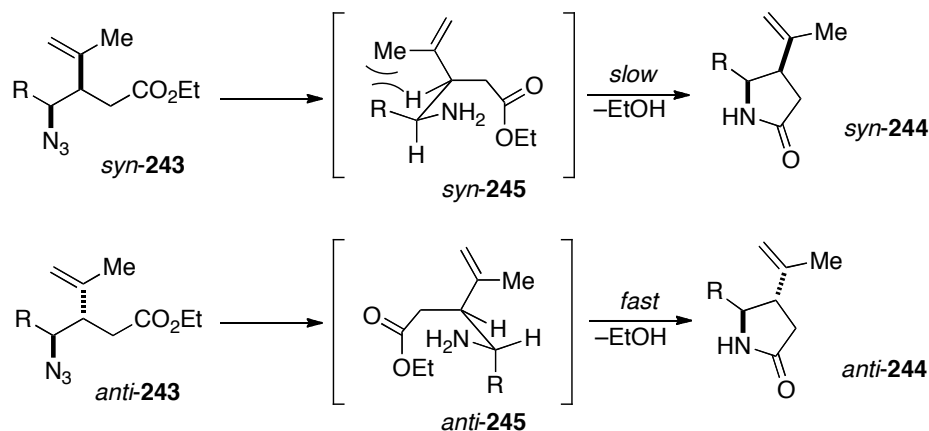
Table 21						
R	R'	Phosphine	Conditions	Product	Yield (%)	Ratio <i>syn</i> - : <i>anti</i> - 244 ^a
Me	Me	py-PPh ₂	30 min, 120 °C (m/w)	244a	87	60 : 40
Me	Me	PMe ₃	40 min, rt	244a	59	45 : 55
<i>n</i> C ₅ H ₁₁	Me	PMe ₃	40 min, rt	244b	75	56 : 44
<i>c</i> Hex	Me	PMe ₃	18 h, rt	244c	59	33 : 66
Me	Ph	PMe ₃	8 h, rt	244d	80	50 : 50

^aBy ¹H-NMR analysis

The change in product distribution may be rationalised by considering the relative rates of cyclisation of aminoester intermediates *syn*-**245** and *anti*-**245** (Scheme 104). The reactive conformation of *syn*-**245** exhibits an unfavourable interaction between the R and methallyl groups not present in the reactive conformation of *anti*-**245**. The yields and product ratios are consistent with this difference in reactivity: in each case,¹⁸¹ the yields of the *syn* and *anti* products are consistent with the ratio of *syn* and *anti* isomers in the starting material (Table 22). As this model suggests, the *syn* cyclohexyl substrate **243d** appears to be the least reactive, and overall, *syn* azidoesters are significantly less reactive than their *anti* isomers.

Table 22

R=Me, Yield 59%	60 <i>syn</i> : 40 <i>anti</i> → 45 <i>syn</i> : 55 <i>anti</i>
	Yield (<i>syn</i>) = (45 x 59%) = 27% (27<60)
	Yield (<i>anti</i>) = (55 x 59%) = 32% (33<40)
R=nC ₅ H ₁₁ , Yield 75%	59 <i>syn</i> : 41 <i>anti</i> → 56 <i>syn</i> : 44 <i>anti</i>
	Yield (<i>syn</i>) = (56 x 75%) = 42% (42<59)
	Yield (<i>anti</i>) = (44 x 75%) = 33% (33<41)
R=cHex, Yield 59%	63 <i>syn</i> : 37 <i>anti</i> → 33 <i>syn</i> : 66 <i>anti</i>
	Yield (<i>syn</i>) = (33 x 59%) = 19% (19<63)
	Yield (<i>anti</i>) = (66 x 59%) = 39% (39>37)

**Scheme 104**

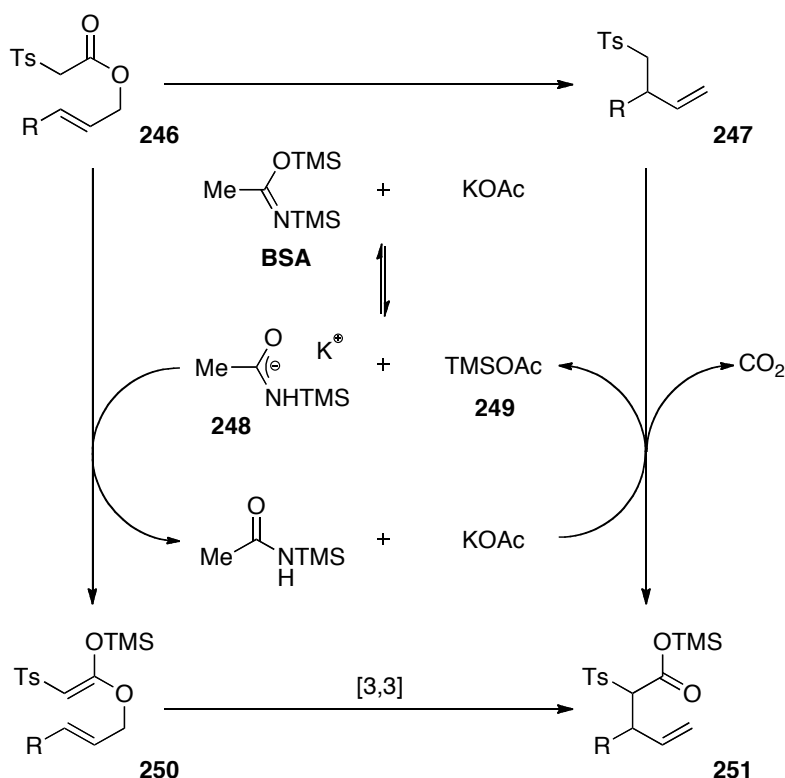
2.5.7 Decarboxylative Claisen rearrangements of allylic azides

Our interest returned to the low stereoselectivity of these rearrangements. Considering that further exploration of the effects of olefin substitution pattern would be difficult using this particular system, we decided to investigate the previously unexplored effects of substitution on the vinylic portion (C1) of the ketene acetal.

Examples from our own laboratory and others^{103,110,118} are reported of *trans*-allylic esters bearing substituents adjacent to the carbonyl undergoing stereoselective Ireland–Claisen rearrangements. We proposed that increased steric bulk at C1 would increase the diastereofacial selectivity of attack on the allylic portion of the ketene acetal.

The dCr reaction developed in our own laboratory¹⁸² appeared particularly attractive for further study of the tandem Winstein–Claisen rearrangement process. α -Tosyl esters of the type **246**, when treated with a silylating agent (typically BSA, although TBDMSOTf–DBU has been used for tosylmalonate substrates) and substoichiometric KOAc undergo Claisen rearrangement followed by concomitant desilylation and decarboxylation to afford homoallylic sulfones **247**. Heating of the ester substrate with BSA in the absence of KOAc affords the non-decarboxylated product, and a catalytic cycle has been proposed which accounts for this (Scheme 105). Reaction of BSA with KOAc gives TMSOAc **249** and the acetamide salt **248**, which together effect silylation and enolisation of the substrate, giving **250**. Following [3,3]-sigmatropic rearrangement, the nucleophilic acetate anion abstracts the TMS group from the product silyl ester **251** with concomitant loss of carbon dioxide. Abstraction of a proton of the resulting α -sulfonyl anion regenerates the active system **248/249** and gives the homoallylic sulfone product **247**.

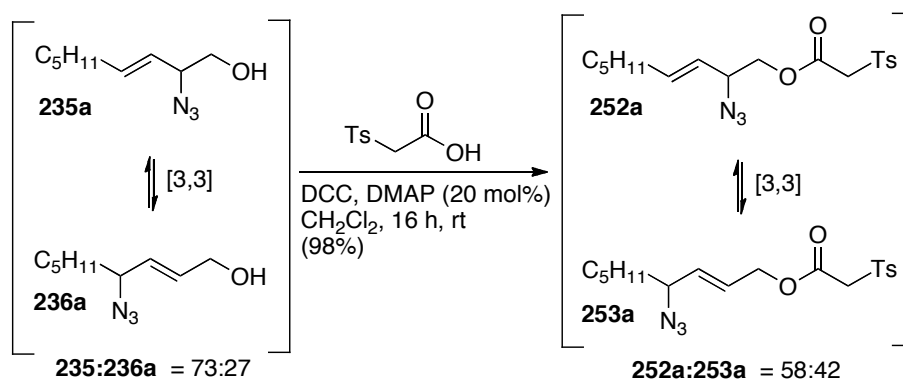
The dCr reaction is a very active area of interest in the Craig group. The reaction has been applied to the synthesis of both small molecules (among which are phenols,¹⁸³ pyridines,¹⁸⁴ vinylcyclopropanes,^{185,102} dearomatised furans¹²⁵ and other heteroaromatic substrates¹⁸⁶) and complex natural products.¹⁸⁷ We have also performed NMR kinetic studies of the reaction.¹⁸⁸ We are currently developing total syntheses of several natural products based on this methodology and are developing base-free variants of the reaction.



Scheme 105

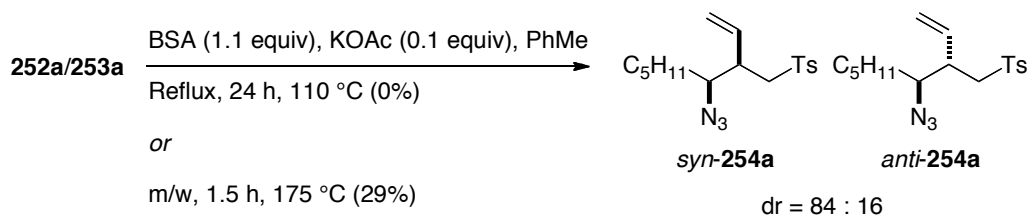
As with other Claisen rearrangements, the rate of reaction is highly substrate-dependent. Tosylmalonate substrates undergo dCr reaction under mild conditions,¹⁸⁹ while microwave heating has been extensively used to trigger rearrangement of less reactive substrates. Nevertheless, the scope of the transformation is very wide. Indeed, we were very interested to explore the behaviour of equilibrating mixtures of allylic azides in this reaction. The attractiveness of the dCr reaction for this study lies in two factors: the steric bulk of the C1 tosyl group should enhance selectivity; and the subsequent decarboxylation process removes the complication of a third stereocentre. Thus, any observed stereoselectivity in the reaction of the substrates presented herein results exclusively from exopericyclic stereocontrol.

In common with previous studies, the system **235a/236a** was used for initial investigation and optimisation of this reaction. Esterification of the mixture of allylic azidoalcohols **235a/236a** with DCC and substoichiometric DMAP gave the mixture of esters **252a/253a** (Scheme 106). The ratio of allylic azide isomers changed slightly, with the vicinal oxy-azido isomer **252a** less abundant than in the corresponding mixture of allylic azidoalcohols.



Scheme 106

Treatment of the azidoesters **235a/236a** with BSA and sub-stoichiometric potassium acetate in toluene under reflux resulted in no reaction taking place. However under microwave conditions, the homoallylic sulfone **254a** was obtained in low yield but good diastereoselectivity; particularly when compared to the non-selective rearrangement of the analogous allylic azidoalcohol to give **243a**. The diastereomers were separable, and X-ray crystallography (see Appendix) showed the major product to be the predicted *syn* diastereomer (Scheme 107).



Scheme 107

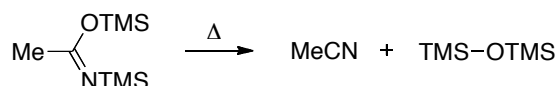
We performed studies to optimise this reaction and increase its yield. More forcing conditions and removal of the solvent from the reaction mixture gave only a slight increase in yield (Table 23, entry 2). Complete decomposition of the starting material was observed upon increasing the reaction temperature to 200 °C (entry 3). Noting that potassium acetate is required for decarboxylation, the reaction was run in non-decarboxylative mode¹¹⁸ using TEA as an alternative base (entry 4). Under these conditions complete conversion to the silyl ester was observed, which was hydrolysed to the acid **255** upon workup, confirming that the Claisen rearrangement was occurring under these conditions. In the presence of sub-stoichiometric quantities of TEA, the reaction was sluggish and required high temperatures (only achievable in DMF) to achieve modest conversion.

Table 23

Entry	BSA (equiv)	Additive	Solvent ^a	Microwave Heating Conditions	Yield (%)
1	1.2	KOAc (0.1 equiv)	PhMe	1.5 h, 175 °C	28%
2	5.0	KOAc (0.1 equiv)	none	2 x 175 °C 5 min	32%
3	5.0	KOAc (0.1 equiv)	none	2 x 200 °C, 5 min	0% ^b
4	3.0	TEA (1.1 equiv)	PhMe	160 °C, 15 min	0% (100%) ^c
5	3.0	TEA (0.1 equiv)	DMF	2 x 180 °C, 15 min	0% (62%) ^c
6	3.0	TEA (0.1 equiv), KOAc, (0.1 equiv)	DMF	180 °C, 15 min	20 %

^aAll reactions, unless solvent-free were performed at 1.0 M. ^bComplete decomposition was observed.
^cConversion to acid intermediate **255** by ¹H-NMR.

Inspection of the dCr reaction mechanism (Scheme 105) shows the reaction should be catalytic in BSA, so we investigated why such an excess was required in this case. The thermal decomposition of BSA to acetonitrile (and also its stabilisation by 2-mercaptobenzothiazole) has been reported (Scheme 108).¹⁹⁰



Scheme 108

Samples of BSA in *d*₈-toluene were heated in a microwave for various periods of time at different temperatures and then analysed by ¹H-NMR. No decomposition was observed, even when heating BSA under solvent-free conditions for extended times. Additionally, no decomposition of BSA was observed in the presence of potassium acetate, indicating that BSA is stable under the dCr reaction conditions (Figure 1).

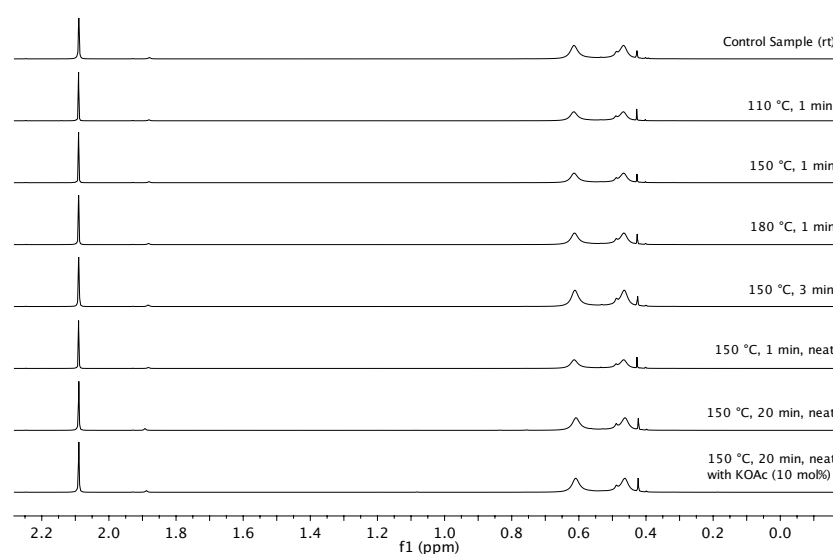
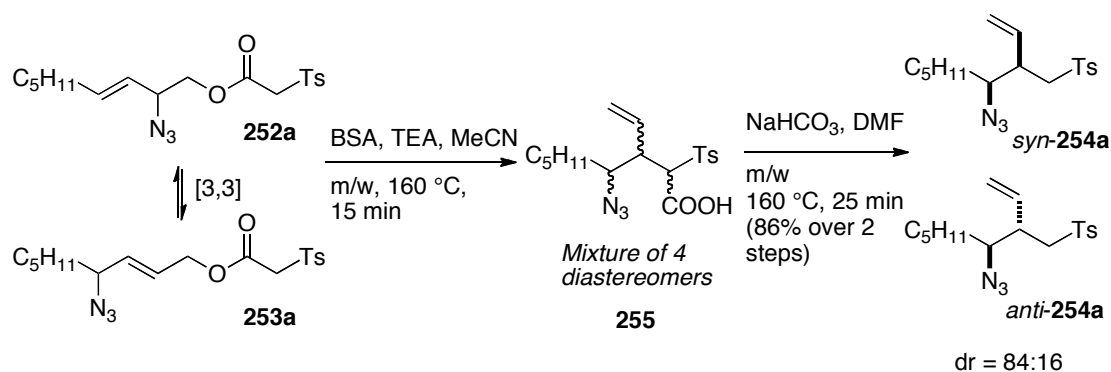


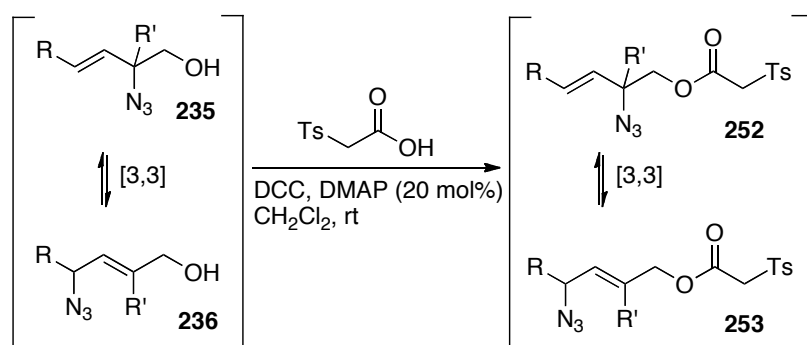
Figure 1

Taking into account the above observations, we concluded that the low yield for the dCr reaction was caused by the forcing conditions required for the decarboxylation step. Alternative conditions have been reported for the decarboxylation of α -tosyl acids,¹⁰² and we reasoned that the dCr reaction could be performed over two separate steps (Scheme 109). Treatment of the mixture of esters **252a/253a** with BSA and TEA followed by microwave heating afforded the acid **255** upon hydrolytic workup as a mixture of four stereoisomers. The purity of the intermediate acid on isolation and the efficiency of microwave heating were improved by changing the reaction solvent to acetonitrile. Residual BSA and TEA were removed by passing a solution of the crude acid through an SCX ion-exchange column. Decarboxylation with sodium carbonate in DMF gave the dCr products *syn*- and *anti*-**254a** in 86% yield over two steps, with the same diastereoselectivity as was observed previously.



Scheme 109

Having optimised the conditions for rearrangement of **252a/253a**, the behaviour of the other previously prepared allylic azides under dCr conditions was investigated. We were particularly interested to explore whether the effects of the olefin substitution pattern would reinforce those of increased steric bulk on the vinylic moiety of the ketene acetal. Treatment of mixtures of allylic azidoalcohols under the same conditions as **235a/236a** gave the corresponding allylic azidoesters **252/253b–g** (Scheme 110, Table 24). In addition to the change in allylic azide ratio for **252a/253a**, an inversion in the position of the equilibrium for substrates **252/253b–d** was observed.



Scheme 110

Table 24

Entry	R	R'	Ratio of azidoalcohol substrates 235 : 236 ^a	Yield of 252/253 (%)	Ratio of azidoester products 252 : 253 ^a
a	<i>n</i> C ₅ H ₁₁	H	73 : 27	99	58 : 42
b	<i>n</i> C ₅ H ₁₁	Me	61 : 39	69	32 : 68
c	Me	Me	64 : 36	97	30 : 70
d	<i>c</i> Hex	Me	63 : 37	92	36 : 65
e	Ph	H	100 : 0	97	100 : 0
f	Me	Ph	0 : 100	75	0 : 100
g	2-pyridyl	Me	100 : 0	52	100 : 0

^aBy ¹H-NMR analysis

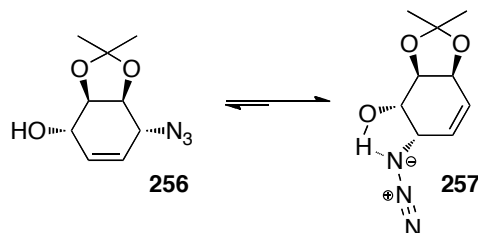
2.5.8 The equilibrium position of allylic azides

We propose that the equilibrium position for the interconversion of allylic azides *via* [3,3]-sigmatropic rearrangement depends on the subtle interplay of numerous factors, including olefin substitution pattern, azide–alcohol hydrogen-bonding, conjugation with aromatic groups and to a lesser extent, 1,3-allylic strain. These factors are discussed below:

For equilibrating mixtures of a secondary and tertiary allylic azide the regioisomer containing the more substituted olefin would be expected to predominate. Recent computational studies on the theoretical basis of Saytzeff's rule show that each additional alkyl substituent contributes 1–2 kcal/mol to the stability of the olefin.¹⁹¹ However, with the exception of isomers stabilised by conjugation with an aromatic group (*vide infra*), this is not the case, and the vicinal azidoalcohol **253** (bearing the less substituted olefin) predominates.

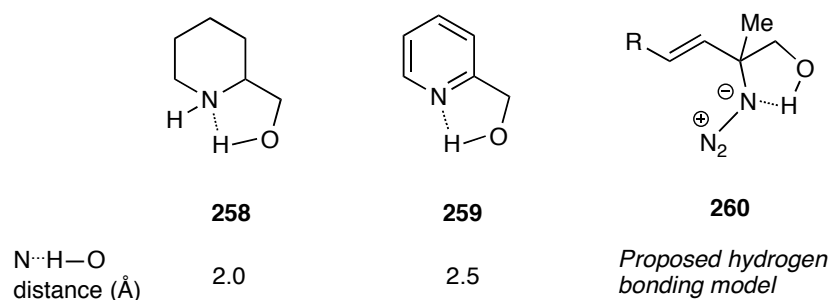
Other effects must therefore contribute to the stability of this isomer. Sharpless *et al.* speculated¹⁶⁸ that an azide–alcohol hydrogen-bonding interaction might exist in

vicinal azidoalcohols. A similar explanation was given by Trost *et al.* for the position of equilibrium between the cyclic allylic azides **256** and **257** (Scheme 111).^{164a}



Scheme 111

We decided to investigate this in depth, assuming that the interaction would take the form of a 5-membered ring incorporating a hydrogen bond between the internal nitrogen of the azide and the alcohol hydrogen **260**. Hydrogen bonds of this type are reported (supported by extensive spectroscopic evidence) in 2-hydroxyalkylpiperidines **258** and 2-hydroxyalkylpyridines **259** (Scheme 112).¹⁹²



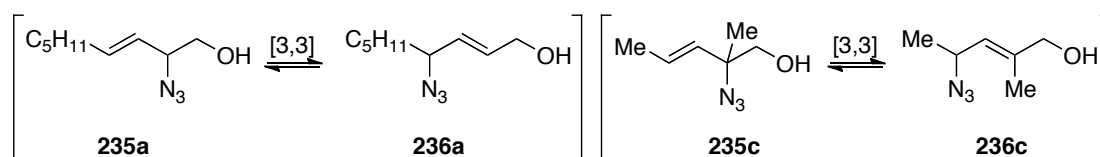
Scheme 112

Although the azide ion is reportedly a very strong hydrogen bond acceptor,¹⁹³ studies on the hydrogen-bonding nature of organic azides are scarce. However, a search of the Cambridge X-ray structure database for distances between the internal azide nitrogen and an alcohol hydrogen less than 2.50 Å revealed some examples of hydrogen-bonding interactions **261–264** (Scheme 113).¹⁹⁴

261 ^{194a}	262 ^{194b}	263 ^{194c}	264 ^{194d}	
Internal N···H—O distance (Å)	2.295	2.383	2.468	2.414
N···H—O angle (deg)	113	110	101	114

Scheme 113

Enthalpies of hydrogen-bonding are typically within the range 2–10 kcal/mol;¹⁹⁵ and although the reported interactions in **261**–**264** are relatively long-range and the N···H—O angle deviates from linearity, a hydrogen-bonding interaction could make a significant contribution to the stability of vicinal azidoalcohols **235**. An NMR experiment was carried out to explore the effect of hydrogen-bonding on the equilibrium position. We predicted that *d*₄-methanol would compete with the dissolved azidoalcohol for hydrogen-bonding interactions, perturbing the equilibrium away from the vicinal regioisomer **235** (Scheme 114, Table 25). No change in ratio was observed for the mixture of secondary allylic azidoalcohols **235a**/**236a** when spectra were measured on CD₃OD rather than CDCl₃ solutions. For the mixture of secondary and tertiary allylic azidoalcohols **235c**/**236c** however, a small shift in the equilibrium position towards **236c** was observed, suggesting a weak hydrogen-bonding interaction.



Scheme 114

Table 25		
Solvent	Ratio 235a : 236a ^a	Ratio 235c : 236c ^a
CDCl ₃	73 : 27	64 : 36
CD ₃ OD	73 : 27	58 : 42

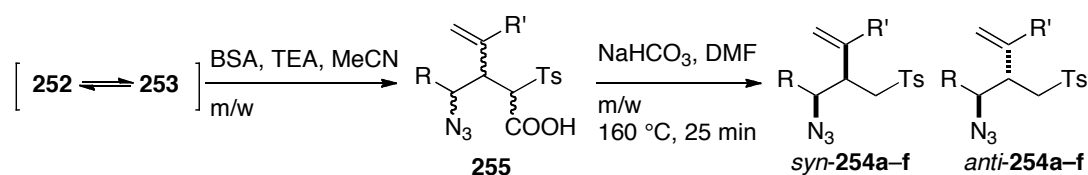
^aBy ¹H-NMR analysis

Esterification of azidoalcohols **235**/**236** removes the possibility of hydrogen-bonding, leaving olefin stability as the dominant effect. Thus, in the absence of hydrogen-

bonding interactions, the isomer containing the more substituted double bond predominates. Furthermore, in the absence of hydrogen-bonding interactions, it appears that 1,3-allylic strain has less effect on the equilibrium position than olefin substitution. A greater, energetically unfavourable 1,3-allylic strain component would be predicted for the more abundant regioisomer in mixtures of allylic azidoesters **252/253b–d** and **252/253f–g**.¹⁹⁶ These combined effects in total are small compared to those of conjugative stabilisation. Indeed, for both allylic azidoalcohols and their ester equivalents, whenever the olefin can lie in conjugation with an aromatic group, this is the only regioisomer observed.

2.5.9 Further examples of allylic azides in the dCr reaction

Esters **252/253a–g** were exposed to the optimised dCr conditions. With the exception of **252g**, all underwent Claisen rearrangement (Scheme 115, Table 26). More hindered substrates required increased amounts of BSA and TEA to react efficiently. Aside from conjugatively stabilised substrates there appeared to be no correlation between azide ratios and yields. *Syn* stereochemistry for the major products **254b–f** was inferred from the X-ray crystallography studies carried out previously on *syn*-**254a**.



Scheme 115

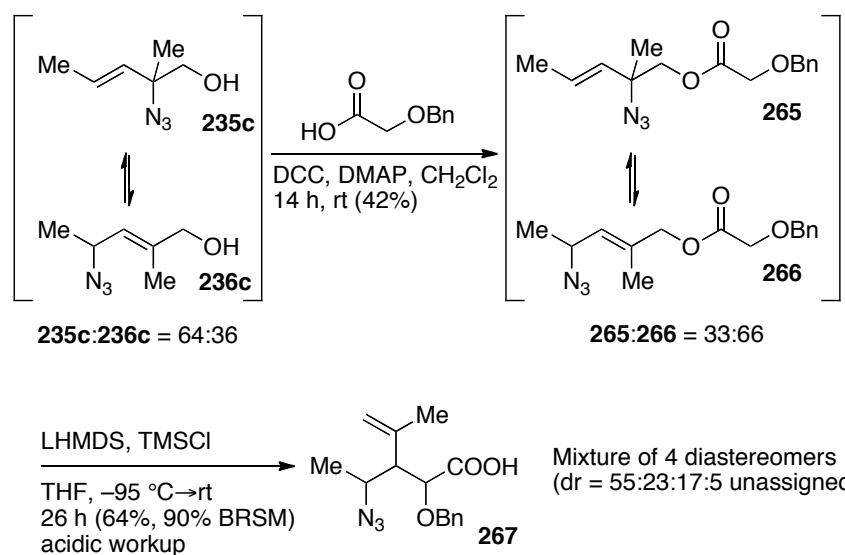
Table 26							
Entry	R	R'	BSA (equiv)	TEA (equiv)	t (min)	Yield (%)	Ratio <i>syn</i> - : <i>anti</i> - 254 ^a
a	<i>n</i> C ₅ H ₁₁	H	3.0	1.2	15	86	84 : 16
b	<i>n</i> C ₅ H ₁₁	Me	5.0	2.0	30	68	68 : 32
c	Me	Me	3.0	1.2	30	82	91 : 9
d	<i>c</i> Hex	Me	5.0	2.0	30	44	82 : 18
e	Ph	H	5.0	2.0	90	22	75 : 25
f	Me	Ph	3.0	1.2	40	32	73 : 27 ^b
g	2-pyridyl	Me	3.0	1.2	30	0	-

^aBy ¹H-NMR analysis; ^bThis substrate partially decarboxylated during first step.

In each case, stereoselectivity was more pronounced than that observed for Johnson–Claisen rearrangement of the corresponding allylic azidoalcohol. We conclude that the effects of C1 substitution and olefin substitution pattern are reinforcing. In contrast to the unreactive phenyl-bearing azidoalcohol **235e**, the single-regioisomer azidoester **252e** underwent rearrangement and decarboxylation to give **254e** in low yield. The pyridyl-bearing substrate **252g** decomposed under these conditions, possibly caused by *N*-silylation of the pyridine moiety with BSA. We therefore conclude that this reaction works generally when R=alkyl. Selectivities are higher, but yields lower (except in the case of **254e**) than the related Johnson–Claisen rearrangements of allylic azidoalcohols bearing the same R and R' groups.

2.5.10 Ireland–Claisen Rearrangements: Control of 3 contiguous stereocentres

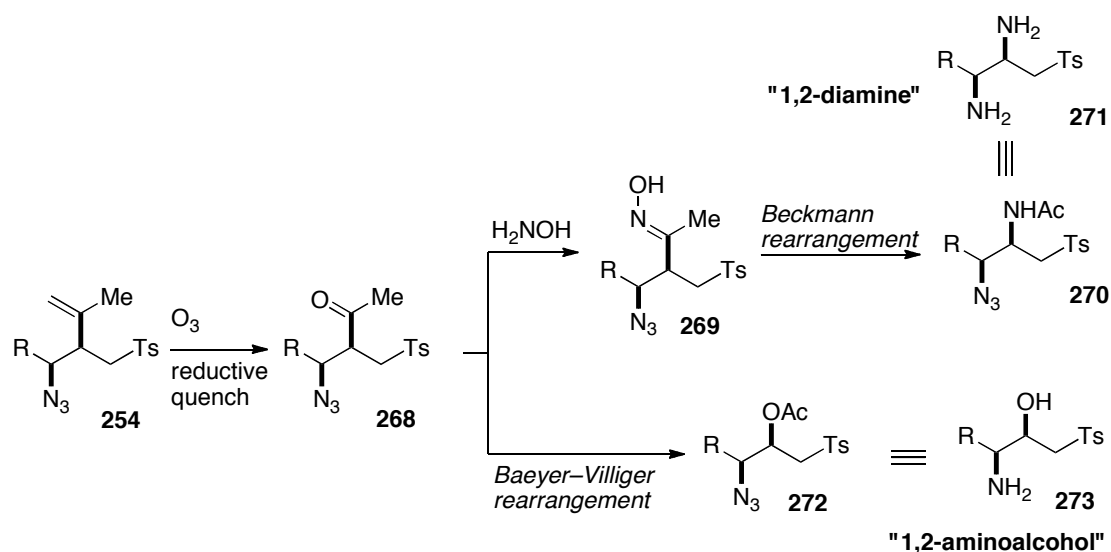
Our interest returned to the chelate-controlled Ireland–Claisen rearrangements of Mulzer,¹¹⁰ in which three contiguous stereocentres are established. We decided to study the behaviour of allylic azidoesters in this process, allowing us to probe the effects of temperature on both the rate of rearrangement and stereoselectivity. The mixture of esters **265/266** was prepared from **235c/236c** by reaction with benzyloxyacetic acid. The ratio of allylic azide isomers was consistent with the analogous α -tosyl ester **252c/253c**; and a similar reversal in the position of equilibrium was observed. Ireland–Claisen rearrangement of **265/266** under the reported conditions gave the product **267** as a mixture of 4 diastereomers, accompanied by unreacted starting material (Scheme 116). The structures of the individual diastereomers were not assigned, although the ratio of products shows incomplete stereocontrol at C1. Clearly, further optimisation of this reaction is required.



Scheme 116

Nevertheless, although we remain unable to control three contiguous stereocentres using this methodology, our results clearly show that a wide variety of equilibrating allylic azidoesters may be converted to azide-bearing γ,δ -unsaturated esters or homoallylic sulfones *via* a pair of sigmatropic rearrangements. In the latter case, the reaction occurs with good stereoselectivity in the predicted *syn* sense.

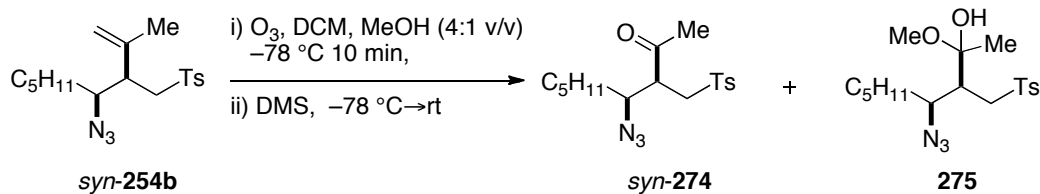
The work presented in this section demonstrates our investigations into further transformations of dCr products **254**. From the outset, we wished to subject these rearranged products to ozonolytic cleavage to form β -azidoketones **268**. We envisaged a sequence in which these β -azidoketones are subjected to either Beckmann or Baeyer–Villiger rearrangement. In the former reaction, stereospecific migration of the bulkier moiety would give the 1,2-azidoamide **270**, while the same migratory pattern for the latter reaction would give the 1,2-azidoacetate **272**. These represent differentially protected 1,2-diamines **271**^{197,198} and 1,2-amino alcohols **273**¹⁹⁹ respectively, which are useful synthetic intermediates (Scheme 117).



2.6.2 Ozonolysis of dCr products

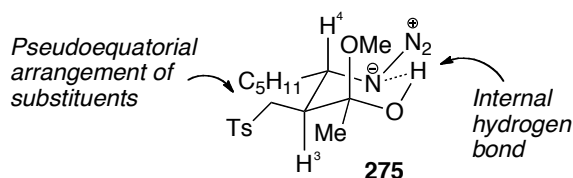
We were concerned that commonly used reagents for reductive quench of the intermediate ozonide such as phosphines might also reduce the azide group. However, examples of reductive quench of ozonides in the presence of azides using dimethylsulfide are reported.²⁰⁰ These reactions are typically performed in a mixture of dichloromethane and methanol. A diastereomerically pure sample of *syn*-**254b** was

treated with ozone at $-78\text{ }^{\circ}\text{C}$ for 10 min under the reported conditions (Scheme 118) to give not only the ketone *syn*-**274** but also the hemiacetal **275** as the major product, both as single diastereomers.



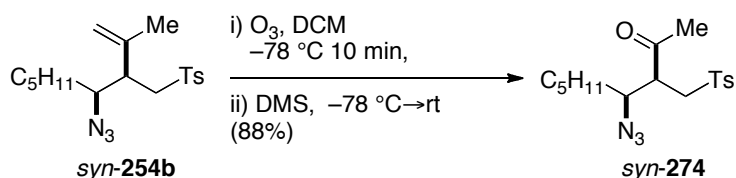
Scheme 118

The hemiacetal **275** was unusually stable and we propose a cyclic, internally hydrogen-bonded structure (Scheme 119) to support this. In addition to the previously discussed examples of $\text{N}_3 \cdots \text{H}-\text{O}$ hydrogen-bonding, there is strong spectroscopic evidence for this assignment. Firstly the coupling constant $J_{\text{H}3-\text{H}4}$ is large (10.0 Hz) compared to ketone *syn*-**274** ($J_{\text{H}3-\text{H}4}$, 6.5 Hz). Addition of D_2O to the NMR sample caused disappearance of the OH signal and a reduction of $J_{\text{H}3-\text{H}4}$ suggesting inhibition of hydrogen-bonding and conversion into an acyclic structure. Additionally, sharp OH signals in both the ^1H -NMR and infrared spectra support this evidence for hydrogen-bonding.



Scheme 119

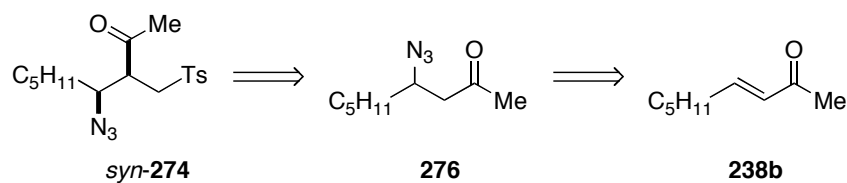
Presuming that **275** could only be formed by addition of methanol to either the intermediate ozonide or the ketone product, the reaction was repeated in its absence, affording solely the diastereomerically pure ketone *syn*-**274** in 88% yield (Scheme 120). We have therefore shown that this methodology may be used for the synthesis of β -azidoketones in good yield and without epimerization of the rearranged product.



Scheme 120

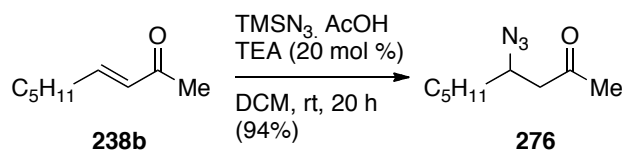
2.6.3 Synthesis of a model system

Before studying further chemistry of the ketone *syn*-**274** directly, we chose to study and optimise this work using the model system **276**. Although the chemistry described here was not eventually applied to the dCr products, it provides an interesting area for further investigation. We envisaged that **276** could be easily prepared *via* conjugate addition of hydrazoic acid to the enone **238b** (Scheme 121).



Scheme 121

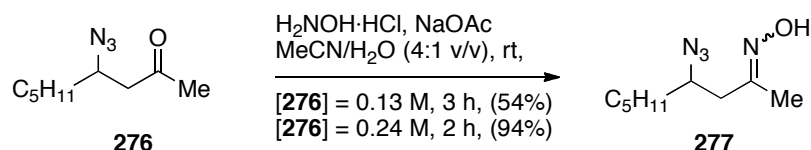
Highly toxic and explosive hydrazoic acid is typically generated *in situ* from the disproportionation of an azide source (typically sodium azide or azidotrimethylsilane) and an acid (acetic acid or strong mineral acid).²⁰¹ The reaction may be performed in the presence of a sub-stoichiometric amount of a Lewis-basic amine or phosphine, which accelerates the disproportionation step.²⁰² Under these conditions, the azide anion does not undergo conjugate addition to the enone and an acid is still required. The transformation can also be carried out in enantioselectively in the presence of a salen/aluminium catalyst.²⁰³ Using the conditions of Miller *et al*,^{202a} **238b** was converted in very high yield into the β -azidoketone **276** (Scheme 122).



Scheme 122

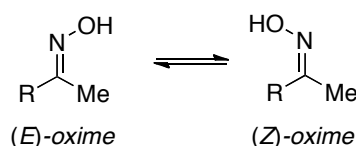
2.6.4 Beckmann rearrangements of β -azidoketones

With β -azidoketone **276** in hand, we investigated the Beckmann rearrangement of the corresponding oxime **277**.²⁰⁴ Treatment of **276** with hydroxylamine hydrochloride and sodium acetate²⁰⁵ afforded the oxime **277** (Scheme 123). Increasing the concentration of the reaction mixture from the reported procedure significantly improved the yield. It should be noted that these conditions may require alteration if used to form the oxime of **274**; base-mediated epimerization of the stereocentre adjacent to the ketone is possible.



Scheme 123

The product was isolated as a 2:1 mixture of *E* and *Z* isomers. This assignment was based on the relative chemical shifts of the methylene group adjacent to the ketoxime, which appeared at lower field for the *Z* (*syn*) isomer than the *E* (*anti*) isomer.²⁰⁶ Examination of literature data for analogous ketoximes suggests interconversion of these isomers is likely to be facile at room temperature, favouring the desired migration of the *E* isomer (Scheme 124, Table 27) in the Beckmann rearrangement. A preference for *E*-geometry in the oxime of **274** would be strongly expected.



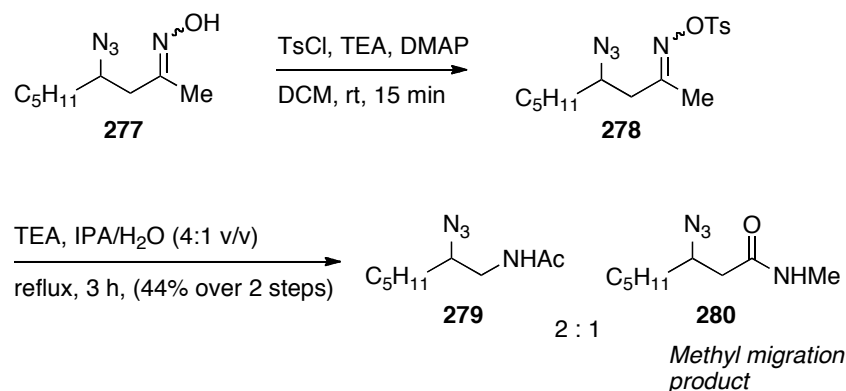
Scheme 124

Table 27²⁰⁶

R	(<i>E</i>)-oxime	(<i>Z</i>)-oxime	$\Delta G_{\text{isomerisation}}$
Et	74	26	0.64
<i>i</i> Pr	91	9	1.41
<i>t</i> Bu	100	0	>2.7
Bn	74	26	0.64
Ph	94	6	1.68

We chose to investigate the Beckmann rearrangement using an intermediate *O*-tosyloxime, envisaging that *E*-oxime would be more sterically favoured in this

system.^{204,205} Formation of the *O*-tosyloxime **278** under the reported conditions was slow. Addition of sub-stoichiometric DMAP accelerated the reaction. No rearranged product was observed at this stage. Heating of **278** in IPA/water afforded a mixture of both the desired acetamide **279** and the amide **280**: the product of methyl migration (Scheme 125).

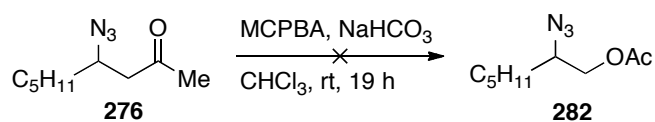


Scheme 125

The product distribution is related to a subtle combination of effects and it is unclear whether the presence of the methyl migration product **280** is a result of slow *E/Z* oxime interconversion, or a surprisingly high migratory aptitude of the methyl group in this system. We predict that the branched Claisen products would migrate with higher selectivity under this process.²⁰⁷ However, the reaction clearly requires further development. This transformation of β -azidoketones could also be carried out under Schmidt rearrangement conditions, although we have not investigated this.²⁰⁸

2.6.5 Baeyer–Villiger rearrangements of β -azidoketones

The Baeyer–Villiger rearrangement²⁰⁹ of the model ketone **276** was also briefly investigated. The ketone was treated with MCPBA in the presence of sodium bicarbonate in chloroform,²¹⁰ but no oxidised product was formed and only starting material was recovered (Scheme 126). The reaction may be possible with a more powerful peracid (e.g. trifluoroperacetic acid). It is unlikely that reactions of the ketone **276** will be complicated by acid-mediated intramolecular Schmidt-type processes due to the short distance between the ketone and azide.²¹¹



Scheme 126

In summary, although the above studies on the model ketone **276** were not applied to a ketone derived from a dCr reaction, we have shown from preliminary results that a Beckmann rearrangement of this substrate will be possible. Further investigation of Beckmann, Baeyer–Villiger and Schmidt processes will allow us to further develop a synthesis of differentially-protected 1,2-aminoalcohols and 1,2-diamines based on a Claisen rearrangement strategy.

2.7 Conclusions

Numerous contributions have been made to the area of acyclic stereocontrol in Claisen rearrangements. Our conclusions are divided into two sections: the former covering contributions to the nature of stereoselectivity in the reaction; and the latter summarising our attempts to exploit these selectivity patterns in synthesis.

2.7.1 Investigations into acyclic stereocontrol

The Johnson–Claisen rearrangements of substrates bearing all-hydrocarbon C6' stereocentres were investigated. Moderate *anti* selectivities were observed in the opposite sense to cases where the C6' stereocentre possessed a heteroatom. The major product arose from a transition state in which the medium-sized group was roughly eclipsing the double allylic double bond of the ketene acetal. Only examples of *E*-configured substrates were investigated; study and comparison of the *Z*-isomers would be recommended for future work.

An investigation was proposed to compare the effects of C6' fluorine and thiophenyl substituents. No stereoselectivity was observed in either case for *E*-configured substrates, while high *syn* selectivity, in line with prediction, was observed in the Johnson–Claisen rearrangement of the isomeric *Z*-allylic alcohols in the thiophenyl-substituted series. Work on the fluorine system was hampered by the instability of rearrangement substrates.

Stereoselectivity in rearrangements of *E*-configured allylic systems may be achieved in two ways. Moderate selectivity was observed in the Johnson–Claisen rearrangements of trisubstituted allylic systems and disubstituted allylic systems bearing a C1 substituent on the ketene acetal. Studies in the context of the dCr reaction showed these effects to be reinforcing.

Although attempts were made to combine cyclic and acyclic stereocontrol modes, they form only a small part of this work and were largely unsuccessful. Further work in this area is also recommended.

2.7.2 Synthetic applications of acyclic stereocontrol in Claisen rearrangements

In the course of work to prepare disubstituted γ -lactams *via* a Claisen rearrangement route, we discovered a novel process where equilibrating mixtures of allylic azides can undergo a pair of sigmatropic rearrangements in a tandem process. This was investigated in the context of the Johnson–Claisen and dCr reactions. Our work in this area studied the factors contributing to the equilibrium position of various mixtures of allylic azides. NMR studies, synthetic studies and examination of crystallographic data showed evidence for an intramolecular hydrogen bond between the azide and alcohol functionalities.

Studies were performed to show that the products of allylic azide Claisen rearrangements could be converted into useful compounds. Products of Johnson–Claisen rearrangement of allylic azidoalcohols were converted into γ -lactams *via* Staudinger reduction and cyclisation, although the differing rates of cyclisation of *syn* and *anti* substrates lead to varying product distributions. We have also shown that products of dCr reaction of allylic tosylazidoesters may be converted into β -azidoketones *via* ozonolytic cleavage. Finally, the Baeyer–Villiger and Beckmann chemistry of a model β -azidoketone was investigated in an effort to convert oxidised dCr products into differentially-protected 1,2-aminoalcohol and 1,2-diamine equivalents respectively. This represents an additional interesting area for future studies.

Chapter 3

Experimental

3.1 General laboratory procedures

All reactions were performed under nitrogen unless otherwise stated. Melting points were determined using Stuart Scientific SMP1 melting point apparatus and are uncorrected. Infrared spectra were recorded on Mattson 5000 FT-IR or Perkin-Elmer Spectrum RX FT-IR System spectrometers. Proton nuclear magnetic resonance (^1H NMR), carbon nuclear magnetic resonance (^{13}C NMR) and fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded in CDCl_3 unless otherwise stated on a Brüker AV-400 or Brüker AV-500 spectrometer. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent (^1H NMR: 7.26 ppm for CDCl_3 ; ^{13}C NMR: 77.0 ppm for CDCl_3). Coupling constants are given in Hertz (Hz). Mass spectra (CI, EI and ESI) were recorded using Micromass AutoSpec-Q, Micromass Platform II or Micromass AutoSpec Premier instruments. Elemental analyses were performed at the microanalytical laboratories of the London Metropolitan University. Optical rotations were measured on an Optical Activity Ltd. instrument. Analytical thin layer chromatography (TLC) was performed on pre-coated glass-backed Merck Kieselgel 60 F254 plates. Visualisation was effected with ultraviolet light, potassium permanganate or vanillin as appropriate. Flash column chromatography was performed using a Biotage Flash+ reservoir system with Biotage SNAP HP-Sil (30 μm) silica gel cartridges or using a Teledyne Isco Companion system fitted with RediSep (35–70 μm) silica gel cartridges. Kugelrohr distillations were performed using a Büchi D56 Kugelrohr oven and controller system. The quoted boiling point corresponds to the internal oven temperature. Standard solvents were distilled under nitrogen prior to use; ether and THF from sodium-benzophenone ketyl, CH_2Cl_2 and acetonitrile from CaH_2 and toluene from sodium. All other solvents were distilled prior to use. Petrol refers to petroleum ether of the fraction bp 40–60 $^\circ\text{C}$. Ether refers to diethyl ether. All liquid reagents were distilled prior to use with the exception of TMS-azide, DAST and Deoxofluor which are thermally unstable. Potassium acetate was oven-dried at 120 $^\circ\text{C}$ for several days prior to use. Microwave reactions were performed in a Biotage Initiator upgraded to version 2.5 and cooled using compressed air (4 bar). Ozone gas was generated from oxygen gas using a Triogen LAB2B ozone generator.

3.2 Safety note

The preparation of numerous potentially explosive low molecular weight organic azides is reported herein. Although we did not experience any explosive behaviour during the course of our studies, all reactions involving azides were carried out behind a blast shield. Particular care was taken during the concentration and purification of organic azides. Sodium azide was handled using non-metallic utensils.

3.3 General synthetic procedures

General procedure A, for the preparation of α,β -unsaturated esters **158b–e,g**

Part 1

To a stirred suspension of (methoxymethylene)triphenylphosphonium chloride (18.8 g, 55.0 mmol, 1.12 equiv) in dichloromethane (75 mL) was added potassium *tert*-butoxide (6.18 g, 55.0 mmol, 1.12 equiv) in three portions at rt. A deep red colour resulted almost immediately upon complete addition. The resulting suspension was stirred at rt for 90 min to complete the formation of the ylide. Ketone **155** (49.0 mmol, 1.0 equiv) was added dropwise at rt over 15 min. The reaction mixture was stirred for 6 h, after which the deep red colour had dissipated and FT-IR showed disappearance of the ketone, and water (60 mL) was added. The phases were separated and the organic layer was washed with water (70 mL) and brine (50 mL). The organic layer was dried (MgSO_4), filtered and partially concentrated under reduced pressure (until ca. 10 mL of solvent remained) to afford a solution of the enol ether **156** in dichloromethane.

Part 2

To a suspension of silica gel (18.8 g) in dichloromethane (15 mL) was added water (1.88 mL, 10% by mass of silica gel). After stirring for 5 min, sulfuric acid (98%, 2 mL) was added dropwise. The enol ether **156** solution from Part 1 was added and the resulting suspension was stirred overnight at rt. ^1H -NMR analysis of a filtered sample

of the reaction mixture showed formation of the aldehyde. Excess solid sodium hydrogencarbonate was added to neutralise the reaction. The resulting suspension was filtered to give a solution of the aldehyde **157** in dichloromethane, to which carbethoxymethylenetriphenylphosphorane (17.07 g, 49.0 mmol, 1.0 equiv) was added in one portion. The resulting suspension was stirred for 48 h and poured onto water (60 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 60 mL). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. The crude product was passed through a silica gel plug (15% EtOAc/petrol) to remove triphenylphosphine oxide. Further purification (if required) over silica gel or by distillation under reduced pressure afforded the ester **158**.

General procedure B, for the preparation of allylic alcohols 152a–g

To a solution of ester **158** (2.60 mmol, 1.0 equiv) in dichloromethane (15 mL) at –78 °C was added diisobutylaluminium hydride (6.50 mL of a 1.0 M solution in toluene, 6.50 mmol, 2.5 equiv) dropwise *via* syringe. The resulting mixture was stirred at –78 °C for 1 h, warmed to rt and stirred overnight. MeOH (1.5 mL) was added, followed by sodium sulfate decahydrate (10.0 g). The resulting slurry was stirred for 1 h and filtered over Celite, washing with dichloromethane. The filtrate was washed with aqueous HCl (1 M, 2 x 50 mL) followed by saturated aqueous sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give the allylic alcohol **152** as a colourless oil after purification over silica gel or by Kugelrohr distillation as appropriate.

General procedure C, for the preparation of esters 154a–g, 182 and 243a–g

To a solution of the allylic alcohol (1.57 mmol, 1.0 equiv) in triethyl orthoacetate (20.4 mmol, 13.0 equiv) was added propionic acid (0.314 mmol, 0.2 equiv) dropwise *via* syringe. After heating under reflux until the starting material had been consumed, the reaction mixture was cooled to rt and concentrated under reduced pressure to give the ester **154**, **182**, or **243**.

General procedure D, for the preparation of (*E*)- γ -sulfenyl- α,β -unsaturated esters 184a,c,e

To a solution of TEA (3.90 mL, 28.0 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.05 mL, 20.0 mmol, 1.0 equiv) dropwise *via* syringe. The colourless solution was stirred at rt for 10 min and a solution of chloroaldehyde **207** (20.0 mmol, 1.0 equiv) in THF (20 mL) was added dropwise *via* syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of triethyl phosphonoacetate (4.80 mL, 24.0 mmol, 1.2 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) in THF (40 mL) at 0 °C *via* cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenyl-aldehyde solution was filtered under nitrogen and added *via* cannula to the phosphonate anion solution at 0 °C. After stirring for 1 h at 0 °C saturated aqueous NH₄Cl (100 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel afforded the ester *E*-**184**.

General procedure E, for the preparation of (*Z*)- γ -sulfenyl- α,β -unsaturated esters 184b,d,f

To a solution of TEA (3.90 mL, 28.0 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.05 mL, 20.0 mmol, 1.0 equiv) dropwise *via* syringe. The colourless solution was stirred at rt for 10 min and a solution of chloroaldehyde **207** (20.0 mmol, 1.0 equiv) in THF (20 mL) was added dropwise *via* syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of 2-(diphenylphosphoryl)acetate (6.41 g, 20.0 mmol, 1.0 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.20 g, 30.0 mmol, 1.5 equiv) in THF (40 mL) at 0 °C *via* cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenyl-aldehyde solution was filtered under nitrogen and added *via* cannula to the phosphonate anion solution at –78 °C. After

stirring for 1 h at $-78\text{ }^{\circ}\text{C}$ saturated aqueous NH_4Cl (150 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO_4) and concentrated under reduced pressure. Purification over silica gel afforded the ester **Z-184**.

General procedure F, for the preparation of allylic alcohols **185a–f**

To a solution of ester **184** (4.91 mmol, 1.0 equiv) in THF (50 mL) at $0\text{ }^{\circ}\text{C}$ was added diisobutylaluminium hydride (14.7 mL of a 1.0 M solution in toluene, 14.7 mmol, 3.0 equiv) dropwise *via* syringe. The resulting colourless solution was warmed to rt and stirred for 1.5 h. The reaction mixture was diluted with dichloromethane (60 mL) and quenched with MeOH (5 mL). Water (10 mL) was added, followed by saturated aqueous sodium hydrogencarbonate (20 mL) and the mixture was filtered. The filtrate was extracted with dichloromethane (3 x 65 mL), dried (MgSO_4) and concentrated under reduced pressure. Purification over silica gel (5–75 % TBME/heptane) afforded the allylic alcohol **185**.

General procedure G, for the preparation of esters **186a–c**

The general procedure C was followed; with the exception that triethyl orthoacetate was degassed by three freeze-vacuum pump-thaw cycles prior to use.

General procedure H, for the preparation of α,β -unsaturated ketones **238b,d,h,j**

To a solution of 1-(triphenylphosphanylidene)propan-2-one (22.5 mmol, 1.5 equiv) in dichloromethane (15 mL) was added the aldehyde (15.0 mmol, 1.0 equiv) dropwise *via* syringe at rt. The resulting mixture was stirred until TLC (20% EtOAc/petrol) confirmed the consumption of starting material. Aqueous HCl (2 M, 15 mL) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. The residue was taken up in ether, filtered and purified by Kugelrohr distillation to afford the α,β -unsaturated ketone **238**.

General procedure I, for the preparation of chlorohydrins 239a–g

To a solution of α,β -unsaturated carbonyl **238** (10.0 mmol, 1.0 equiv) in THF (20 mL) at $-78\text{ }^{\circ}\text{C}$ was added chloriodomethane (15.0 mmol, 1.5 equiv), followed by slow addition of *n*-butyllithium (6.0 mL of a 2.50 M solution in hexanes, 15.0 mmol, 1.5 equiv) over 30 min. The resulting yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and quenched with saturated aqueous NH_4Cl (25 mL). The mixture was warmed to rt and ether (50 mL) was added. The phases were separated and the aqueous layer was extracted with ether (2 x 50 mL), dried (MgSO_4) and concentrated. Purification over silica gel afforded the chlorohydrin **239**.

General procedure J, for the preparation of oxiranes 234a–g

To a suspension of pentane-washed sodium hydride (60% w/w in mineral oil, 10.2 mmol, 1.3 equiv) and sodium iodide (0.78 mmol, 0.1 equiv) in THF (11 mL) was added a solution of the chlorohydrin **239** (7.8 mmol, 1.0 equiv) in THF (11 mL) at $0\text{ }^{\circ}\text{C}$. The resulting white suspension was stirred at $0\text{ }^{\circ}\text{C}$ for 1 h and quenched with saturated aqueous NH_4Cl (30 mL). The phases were separated and the aqueous layer was extracted with ether (30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the oxirane **234**, which were used without further purification.

General procedure K, for the preparation of allylic azidoalcohols 235/236a–g

To a solution of oxirane **234** (31.5 mmol, 1.0 equiv) in acetone (45 mL) and water (19 mL) was added sodium azide (94.5 mmol, 3.0 equiv) in one portion. After heating the resulting solution under reflux for 8 h, the reaction mixture was cooled to rt and NH_4Cl (5.0 g) was added. Water (50 mL) was added and the reaction mixture was concentrated under reduced pressure to remove acetone. The remaining aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified over silica gel to give a mixture of the allylic azidoalcohols **235/236**.

General procedure L, for the preparation of pyrrolidin-2-ones 244a–d

To a mixture of ester **243** (0.44 mmol, 1.0 equiv) and water (0.66 mmol, 1.5 equiv) was added trimethylphosphine (0.66 mL of a 1 M solution in THF, 0.66 mmol, 1.5 equiv) dropwise *via* syringe at rt. The resulting solution was stirred until TLC (20% ether/petrol) confirmed consumption of the starting material. Water (5 mL) was added and the mixture was extracted with ether (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford the pyrrolidin-2-one **244** after purification over silica gel.

General procedure M, for the preparation of allylic azidoesters 252/253a–g

To a solution of azidoalcohols **235/236** (5.46 mmol, 1.0 equiv) in dichloromethane (10 mL) was added DMAP (0.546 mmol, 0.1 equiv), followed by a solution of DCC (6.01 mmol, 1.1 equiv) in dichloromethane (10 mL) at rt. The mixture was stirred for 5 min before addition of 2-*p*-toluenesulfonylacetic acid (1.29 g, 6.01 mmol, 1.1 equiv). After stirring the colourless suspension for 16 h, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. Purification of the residue over silica gel afforded mixtures of the esters **252/253**.

General procedure N, for the preparation of homoallylic sulfones 254a,c,f

To a solution of the azidoesters **252/253** (0.132 mmol 1.0 equiv) in acetonitrile (1.0 M) was added *N,O*-bistrimethylsilylacetamide (0.396 mmol, 3.0 equiv) and TEA (0.158 mmol, 1.2 equiv) in a capped microwave vial. The mixture was heated by microwave at 160 °C until TLC showed consumption of the starting material. The reaction mixture was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were passed through an SCX ion exchange column (conditioned with 10% MeOH/dichloromethane) and concentrated under reduced pressure to afford the acid **255** without further purification. To solution of the crude acid **255** (1.0 equiv) in DMF (1.0 M) was added sodium hydrogencarbonate (1.2 equiv) in a microwave vial. The mixture was heated by microwave at 160 °C for 35 min and cooled to rt. Water (10

mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel afforded sulfone **254**.

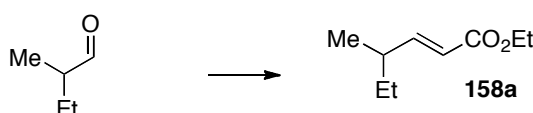
General procedure O, for the preparation of homoallylic sulfones 254b,d,e

To solution of the azidoesters **252/253** (0.132 mmol 1.0 equiv) in acetonitrile (1.0 M) was added *N,O*-bistrimethylsilylacetamide (0.660 mmol, 5.0 equiv) and TEA (0.264 mmol, 2.0 equiv) in a capped microwave vial. The mixture was heated by microwave at 160 °C until TLC showed consumption of the starting material. The reaction mixture was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were passed through an SCX ion exchange column (conditioned with 10% MeOH/dichloromethane) and concentrated under reduced pressure to afford the acid **255** without further purification. To solution of the crude acid **255** (1.0 equiv) in DMF (1.0 M) was added sodium hydrogencarbonate (1.2 equiv) in a microwave vial. The mixture was heated by microwave at 160 °C for 35 min and cooled to rt. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel afforded sulfone **254**.

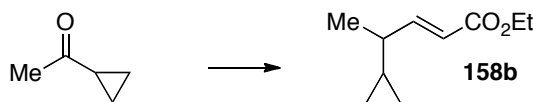
3.4 Individual procedures

3.4.1 Compounds relevant to section 2.2

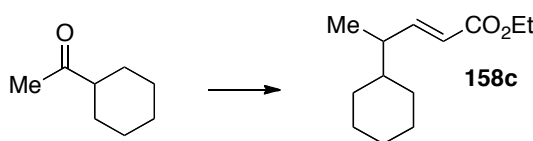
(*E*)-Ethyl 4-methylhex-2,3-enoate (**158a**)



Lithium chloride (0.509 g, 12.0 mmol, 1.2 equiv) was placed in a 20 mL microwave vial, which was capped and purged with argon. Acetonitrile (10 mL) was added *via* syringe, followed by DBU (1.79 mL, 12.0 mmol, 1.2 equiv). Triethyl phosphonoacetate (2.38 mL, 12.0 mmol, 1.2 equiv) was added dropwise at rt and the resulting solution was stirred for 5 min. 2-Methylbutyraldehyde (1.05 mL, 10.0 mmol, 1.0 equiv) was added dropwise, resulting in a slightly exothermic reaction, to give a cloudy mixture. After heating by microwave to 100 °C for 5 min, the reaction was cooled to rt, quenched with aqueous HCl (2 M, 10 mL) and poured onto ether (20 mL). The phases were separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure. Distillation of the residue under reduced pressure afforded (*E*)-ethyl 4-methylhex-2,3-enoate **158a** (1.18 g, 76%) as a colourless oil: bp₃₀ 120–125 °C; ν_{max} (film) 1720, 1652, 1461, 1269, 1186, 1041, 986 cm⁻¹; δ_H (400 MHz, CDCl₃) 6.88 (1H, dd, *J* 15.5, 7.0, H-3), 5.80 (1H, d, *J* 15.5, H-2), 4.21 (2H, q, *J* 7.0, OCH₂), 2.23 (1H, sept, *J* 7.0, H-4), 1.42 (2H, dq, *J* 7.5, 7.0, H-5), 1.31 (3H, t, *J* 7.0, OCH₂CH₃), 1.06 (3H, d, *J* 7.0, 4-CH₃), 0.90 (3H, t, *J* 7.5, H-6); δ_C (101 MHz, CDCl₃) 167.0 (C-1), 154.5 (C-3), 119.7 (C-2), 60.2 (OCH₂), 38.1 (C-4), 28.8 (C-5), 18.9 (4-Me), 14.3 (OCH₂CH₃), 11.6 (C-6); in agreement with published data.²¹²

(E)-Ethyl 4-cyclopropylpent-2-enoate (158b)

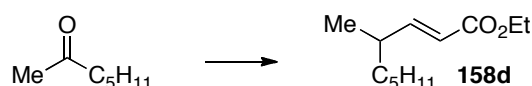
1-Cyclopropylethanone (2.31 g, 23.8 mmol, 1.0 equiv) was reacted according to general procedure **A** to afford (*E*)-ethyl 4-cyclopropylpent-2-enoate **158b** (0.247 g, 7%) as a colourless oil without further purification: $\nu_{\max}$ (film) 1721, 1652 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 6.54 (1H, dd, J 16.0, 6.5, H-3), 5.86 (1H, d, J 16.0, H-2), 4.22 (2H, q, J 7.0, OCH_2), 1.58–1.55 (1H, m, H-4), 1.32 (3H, t, J 7.0, OCH_2CH_3), 1.16 (3H, d, J 7.0, H-5), 0.72–0.63 (1H, m, $\text{CH}(\text{CH}_2)_2$) 0.49–0.54 (2H, m, $\text{CH}(\text{CHH})_2$) 0.14–0.18 (2H, m, $\text{CH}(\text{CHH})_2$); δ_{C} (101 MHz, CDCl_3) 167.1 (C-1), 153.6 (C-3), 119.3 (C-2) 60.2 (OCH_2), 41.3 (C-4), 18.9 (C-5), 16.4 ($\text{CH}(\text{CH}_2)_2$), 14.3 (OCH_2CH_3), [4.0 and 3.8 ($\text{CH}(\text{CH}_2)_2$); m/z (CI) 186 $[\text{MNH}_4]^+$, 169 $[\text{MH}]^+$, 100 (Found: $[\text{MNH}_4]^+$, 186.1494. $\text{C}_{10}\text{H}_{16}\text{O}_2$ requires $[\text{MNH}_4]^+$, 186.1494).

(E)-Ethyl 4-cyclohexylpent-2-enoate (158c)

1-Cyclohexylethanone (3.00 g, 23.8 mmol, 1.0 equiv) was reacted according to general procedure **A** to afford (*E*)-ethyl 4-cyclohexylpent-2-enoate **158c** (1.36 g, 37%) as a colourless oil after purification over silica gel (5% EtOAc/petrol): $\nu_{\max}$ (film) 1722, 1650, 1452, 1140, 1086 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 6.91 (1H, dd, J 15.5, 8.5, H-3), 5.77 (1H, d, J 15.5, H-2), 4.21 (2H, q, J 7.0, OCH_2), 2.20–2.11 (1H, m, H-4), 1.76–1.62 (6H, m, cyclohexyl), 1.32 (3H, t, J 7.0, OCH_2CH_3), 1.03 (3H, d, J 7.0, H-5)

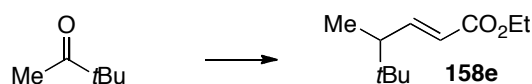
1.25–0.89 (5H, m, cyclohexyl); δ_{C} (101 MHz, CDCl_3) 166.9 (C-1), 153.9 (C-3), 120.3 (C-2) 60.2 (OCH_2CH_3), 42.6 (C-3), 30.5, 26.5, 16.4, (cyclohexyl), 14.3 (C-5 and OCH_2CH_3); m/z (ESI) 214, 211 $[\text{MH}]^+$, 165 $[\text{M}-\text{CO}_2\text{Et}]^+$ (Found: $[\text{MH}]^+$, 211.1708. $\text{C}_{13}\text{H}_{22}\text{O}_2$ requires $[\text{MH}]^+$, 211.1698).

(E)-Ethyl 4-methylnon-2-enoate (158d)



2-Heptanone (2.72 g, 23.8 mmol 1.0 equiv) was reacted according to general procedure **A** to afford (*E*)-ethyl 4-methylnon-2-enoate **158d** (1.13 g, 22%) as a colourless oil after purification over silica gel (5% EtOAc/petrol): ν_{max} (film) 1720, 1650 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 6.68 (1H, dd, J 15.5, 8.0, H-3), 5.76 (1H, d, J 15.5, H-2), 4.20 (2H, q, J 7.0, OCH_2), 2.31 (1H, m, H-4), 1.37–1.26 (8H, m, H-5,6,7,8), 1.05 (3H, d, J 6.5, 4-Me), 0.90 (3H, t, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 167.0 (C-1), 154.8 (C-3), 119.5 (C-2), 60.2 (OCH_2), 36.5, 36.0, 31.9, 26.9, 22.6, 19.4, 14.3, 14.1; in agreement with published data.²¹³

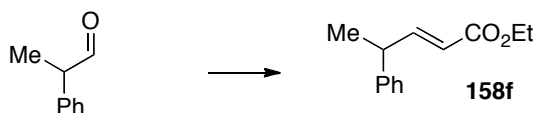
(E)-Ethyl 4,5,5-trimethylhex-2-enoate (158e)



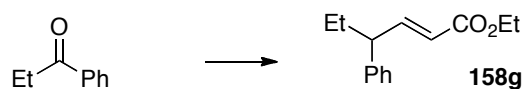
3,3-Dimethyl-2-butanone (4.91 g, 49.0 mmol, 1.0 equiv) was reacted according to general procedure **A** to afford (*E*)-ethyl 4,5,5-trimethylhex-2-enoate **158e** (1.35 g, 15%) as a yellow oil after Kugelrohr distillation: bp_{0.5} 100–105 °C; ν_{max} (film) 1722, 1650, 1463, 1367, 1039, 985, 865 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 6.95 (1H, dd, J 14.0,

15.5, H-3), 5.80 (1H, d, J 15.5, H-2), 4.15 (2H, q, J 7.0, OCH₂), 2.10 (1H, dq, J 14.0, 7.0, H-4), 1.30 (3H, t, J 7.0, OCH₂CH₃), 1.05 (3H, d, J 7.0, 4-Me), 0.85 (9H, s, C(CH₃)₃); δ_C (101 MHz, CDCl₃), 152.7 (C-1), 128.5 (C-3), 120.9 (C-2), 60.1 (OCH₂), 47.0 (C-4) 33.2 (C(CH₃)₃), 27.5 (C(CH₃)₃), 14.6 (OCH₂CH₃), 14.3 (4-CH₃); m/z (CI) 202 [MNH₄]⁺, 185 [MH]⁺ (Found: [MNH₄]⁺, 202.1805. C₁₁H₂₀O₂ requires [MNH₄]⁺, 202.1807).

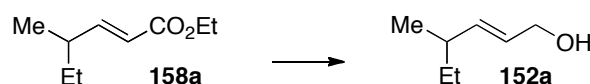
(*E*)-Ethyl 4-phenylpent-2,3-enoate (**158f**)



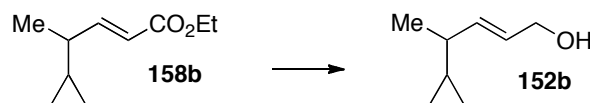
To a solution of 2-phenylpropanal (1.49 mL, 11.0 mmol, 1.0 equiv) in dry dimethylsulfoxide (10 mL) in a microwave vial was added carbethoxymethylenetriphenylphosphorane (3.83 g, 11.0 mmol, 1.0 equiv) and lithium chloride (0.510 g, 12.0 mmol, 1.09 equiv). The reaction mixture was heated by microwave for 30 min at 120 °C to give a colourless solution upon cooling. The reaction mixture was poured onto water (70 mL) and ether (150 mL) was added. The phases were separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford (*E*)-ethyl 4-phenylpent-2,3-enoate **158f** (1.79 g, 80%) as a colourless oil after purification over silica gel (8% EtOAc/petrol): $\nu_{\max}$ (film) 1732, 1651, 1446, 1266, 1177, 1028, 699 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.40–7.20 (5H, m, Ph), 7.16 (1H, dd, J 15.5, 7.0, H-3), 5.85 (1H, d, J 15.5, H-2), 4.22 (2H, q, J 7.0, OCH₂), 3.65 (1H, dq, J 7.0, 7.0, H-4), 1.47 (3H, d, J 7.0 H-5), 1.21 (3H, t, J 7.0, OCH₂CH₃); δ_C (101 MHz, CDCl₃) 166.7 (C-1), 152.6 (C-3), 143.4 (*i*-Ph), 128.7 (*m*-Ph), 127.3 (*o*-Ph), 126.7 (*p*-Ph), 120.2 (C-2), 60.3 (OCH₂), 42.1 (C-4), 20.2 (C-5), 14.3 (OCH₂CH₃); in agreement with published data.⁷⁷

(E)-Ethyl 4-methylhex-2-enoate (158g)

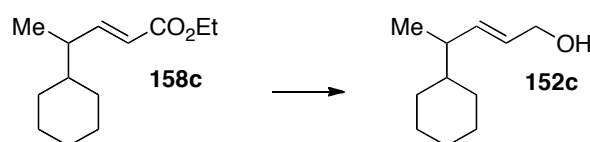
1-Phenylpropanone (3.35 g, 25.0 mmol, 1.0 equiv) was reacted according to general procedure **A** to afford (*E*)-ethyl 4-methylhex-2-enoate **158g** (1.28 g, 24%) as a colourless oil after purification by Kugelrohr distillation: bp₅ 170–175 °C; ν_{max} (film) 1716, 1650, 1454 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.15–7.35 (5H, m, Ph) 7.09 (1H, dd, J 15.5, 8.0, H-3), 5.81 (1H, d, J 15.5, H-2), 4.19 (2H, q, J 7.0, OCH_2), 3.31 (1H, dt, J 8.0, 7.0, H-4), 1.29 (3H, t, J 7.0, OCH_2CH_3), 1.83 (2H, m, H-5), 0.90 (3H, t, J 7.5, H-6); δ_{C} (101 MHz, CDCl_3) 166.7 (C-1), 151.7 (C-3), 142.1, 128.6, 127.9, 126.7 (Ph), 120.8 (C-2), 60.2 (OCH_2), 50.2 (C-4), 27.9, 14.2, 12.1; in agreement with published data.²¹⁴

(E)-4-Methylhex-2-en-1-ol (152a)

Ester **158a** (809 mg, 5.20 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4-methylhex-2-en-1-ol **152a** (176 mg, 30%) as a colourless oil after purification over silica gel (20% EtOAc/petrol): ν_{max} (film) 3392, 1641, 1461 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.66–5.57 (2H, m, H-2,3), 4.91 (2H, d, J 5.0, H-1), 2.11–2.04 (1H, m, H-4), 1.34 (2H, dq, J 7.5, 7.0, H-5), 1.01 (3H, d, J 7.0, 4-Me), 0.87 (3H, t, J 7.5, H-6); δ_{C} (101 MHz, CDCl_3) 139.1 (C-3), 127.2 (C-2), 63.9 (C-1), 38.0 (C-4), 29.5 (C-5), 19.9 (4-Me), 11.8 (C-6); m/z (CI) 114 $[\text{M}]^+$, 103; in agreement with published data.²¹⁵

(E)-4-Cyclopropylpent-2-en-1-ol (152b)

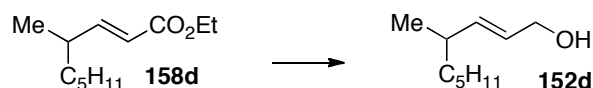
Ester **158b** (224 mg, 1.33 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4-cyclopropylpent-2-en-1-ol **152b** (162 mg, 96%) as a colourless oil, which was used without further purification: $\nu_{\max}$ (film) 3336, 1668 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.76 (1H, dd, J 15.5, 6.0, H-3), 5.67 (1H, dt, J 15.5, 6.0, H-2), 4.14 (2H, d, J 6.0, H-1), 1.45–1.43 (2H, m, H-4, OH), 1.10 (3H, d, J 6.0, H-5), 0.63–0.61 (1H, m, $\text{CH}(\text{CH}_2)_2$), 0.46–0.44 (2H, m, $\text{CH}(\text{CHH})_2$), 0.13–0.12 (2H, m, $\text{CH}(\text{CHH})_2$); δ_{C} (101 MHz, CDCl_3) 138.0 (C-3), 126.8 (C-2), 64.0 (C-1) 41.0 (C-5), 19.7, 17.1, [3.7 and 3.6 (cyclopropyl)]; m/z (CI) 126 $[\text{M}]^+$, 109 (Found: $[\text{MNH}_4]^+$, 144.1388. $\text{C}_8\text{H}_{14}\text{O}$ requires $[\text{MNH}_4]^+$, 144.1387).

(E)-4-Cyclohexylpent-2-en-1-ol (152c)

Ester **158c** (1.14 g, 5.41 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford the (*E*)-4-cyclohexylpent-2-en-1-ol **152c** (0.757 g, 83%) as a colourless oil after purification by Kugelrohr distillation: bp_{10} 175 $^{\circ}\text{C}$; $\nu_{\max}$ (film) 3388, 1641 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.62–5.51 (2H, m, H-2,3), 4.08 (2H, d, J 4.5, H-1), 1.99–1.94 (1H, m, H-4), 1.85 (1H, s (br), OH), 1.73–1.61 (6H, m, cyclohexyl), 1.23–1.12 (5H, m, cyclohexyl), 0.96 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 137.8 (C-3), 127.8 (C-2), 63.8 (C-1) 43.0 (C-4), 42.0, 32.0, 30.3, 26.6 (cyclohexyl), 17.3 (C-5); m/z (CI)

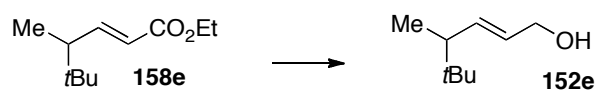
186 $[\text{MNH}_4]^+$, 169 $[\text{MH}]^+$ (Found: $[\text{MNH}_4]^+$, 186.1863. $\text{C}_{11}\text{H}_{20}\text{O}$ requires $[\text{MNH}_4]^+$, 186.1858).

(*E*)-4-Methylnon-2-en-1-ol (152d)



Ester **158d** (1.14 g, 5.73 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4-methylnon-2-en-1-ol **152d** (0.313 g, 35%) as a colourless oil after purification by Kugelrohr distillation: bp₄ 95 °C; ν_{max} (film) 3318, 1668, 1457, 1378, 971 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.61–5.58 (2H, m, H-2,3), 4.10 (2H, d, J 4.5, H-1), 2.14 (1H, m, H-4), 1.40 (1H, s (br), OH), 1.29–1.27 (8H, m, H-5,6,7,8), 0.99 (3H, d, J 7.0, 4-Me), 0.89 (3H, t, J 7.0, H-9); δ_{C} (400 MHz, CDCl_3) 139.4 (C-3), 127.0 (C-2), 63.9 (C-1), 36.8, 36.3, 32.0, 26.9, 22.7, 20.4, 14.1; m/z (ESI) 155 $[\text{M}-\text{H}]^+$, 151, 137.

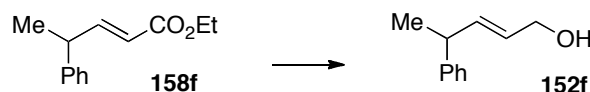
(*E*)-4,5,5-Trimethylhex-2-en-1-ol (152e)



Ester **158e** (568 mg, 3.10 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4,5,5-trimethylhex-2-en-1-ol **152e** (290 mg, 66%) as a colourless oil after purification by Kugelrohr distillation: bp₅ 150 °C; ν_{max} (film) 3450, 1639 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.70–5.57 (2H, m, H-2,3), 4.12 (2H, d, J 5.0, H-1), 1.95 (1H, dq, J 8.0, 6.5, H-4), 1.42 (1H, s (br), OH), 0.96 (3H, d, J 6.5, 4-Me), 0.87 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (101 MHz, CDCl_3) 136.6 (C-3), 128.6 (C-2), 64.0 (C-1),

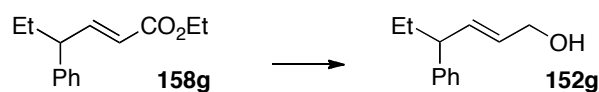
46.8 (C-5) 32.8 (C-4), 27.5 (C(CH₃)₃), 15.4 (4-CH₃); m/z (CI) 142 [M]⁺, 125 [M-OH]⁺ (Found: [M]⁺, 142.1595. C₉H₁₈O requires [M]⁺, 142.1358).

(*E*)-4-Phenylpent-2-en-1-ol (152f)



Ester **158f** (527 mg, 2.58 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4-phenylpent-2-en-1-ol **152f** (303 mg, 77%) as a colourless oil after purification over silica gel (25% EtOAc/petrol): $\nu_{\max}$ (film) 3420, 1638 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.35–7.23 (5H, m, Ph), 5.91 (1H, dd, J 15.5, 7.0, H-3) 5.70 (1H, dt, J 15.5, 6.0, H-2), 4.15 (2H, d, J 6.0, H-1), 3.53 (1H, m, H-4), 1.44 (1H, s (br), OH) 1.41 (3H, d, J 7.0, 4-Me); δ_{C} (101 MHz, CDCl₃) 145.5 (*i*-Ph), 137.5 (C-3), 128.5, 127.7, 127.2 (Ph), 126.3 (C-2), 63.7 (C-1), 42.0 (C-4), 21.1 (C-5); in agreement with published data.⁷⁷

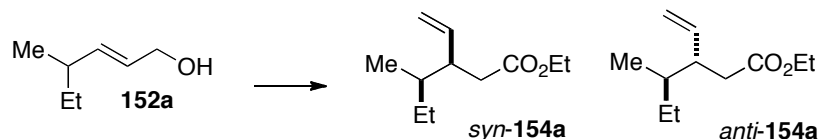
(*E*)-4-Phenylhex-2-en-1-ol (152g)



Ester **158g** (1.03 g, 5.04 mmol, 1.0 equiv) was reacted according to general procedure **B** to afford (*E*)-4-phenylhex-2-en-1-ol **152g** (0.361 g, 45%) as a colourless oil after purification by Kugelrohr distillation: bp₅ 175 °C; $\nu_{\max}$ (film) 3401, 1641, 1492, 1080, 972 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 5.85 (1H, dd, J 15.5, 7.0, H-3), 5.66 (1H, dt, J 15.5, 6.0, H-2), 4.13 (2H, d, J 6.0, H-1), 3.18 (1H, dt, J 7.5, 7.0, H-4), 1.77 (2H, dq, J 7.5, 7.5, H-5), 0.88 (3H, t, J 7.5, H-6), 1.44 (1H, s (br), OH); δ_{C} (101 MHz, CDCl₃) 144.4

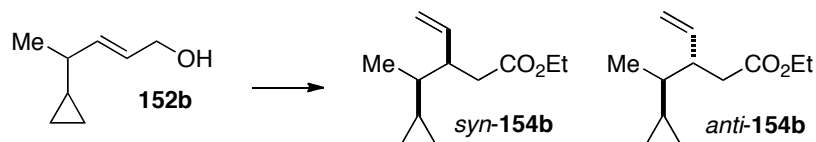
(C-3), 136.5 (C-2), 128.5 (*i*-Ph), 126.0 (*p*-Ph), 126.2 (*m*-Ph), 127.6 (*o*-Ph), 63.7 (C-1), 50.39 (C-4), 12.2 (C-5), 28.6 (C-6); m/z (CI) 194 $[\text{MNH}_4]^+$, 176 $[\text{M}]^+$, 159 $[\text{M-OH}]^+$ (Found: $[\text{MNH}_4]^+$, 194.1539. $\text{C}_{12}\text{H}_{16}\text{O}$ requires $[\text{MNH}_4]^+$, 194.1545).

Ethyl 3-ethenyl-4-methylhexanoate (**154a**)



Allylic alcohol **152a** (147 mg, 1.57 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-methylhexanoate* **154a** (285 mg, 98%, 50:50 *syn:anti* mixture of diastereomers) as a colourless oil: ν_{max} (film) 1736, 1639, 1463, 1374, 1249, 1035 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.73–5.65 (2H, m, *syn+anti* CHCH_2), 5.06–5.00 (4H, m, *syn+anti* CHCH_2), 4.19–4.09 (4H, m, *syn+anti* OCH_2), 2.80–2.04 (4H, m, *syn+anti* H-3,4), [1.40–1.30 (5H, m) and 0.90–0.80 (6H, m) *syn+anti* H-5,6,4-Me and OCH_2CH_3]; δ_{C} (101 MHz, CDCl_3) 182.3 (C-1), 127.9 (CHCH_2), 116.1 (CHCH_2), 60.1 (OCH_2), 57.4, 26.0, 15.2, 14.3; m/z (CI) 202 $[\text{MNH}_4]^+$, 185 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 185.1490. $\text{C}_{11}\text{H}_{20}\text{O}_2$ requires $[\text{MH}]^+$, 185.1497).

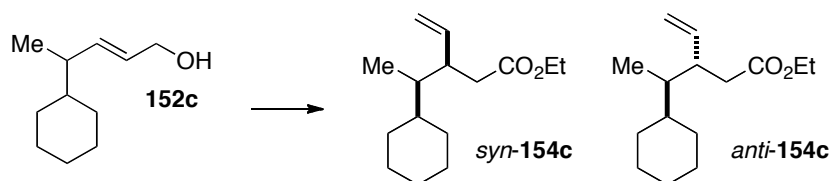
Ethyl 3-ethenyl-4-cyclopropylpentanoate (**154b**)



Allylic alcohol **152b** (156 mg, 1.23 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-cyclopropylpentanoate* **154b** (217 mg, 89%, 50:50 *syn:anti* mixture of diastereomers) as a yellow oil: ν_{max} (film) 1737, 1639,

1461 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [5.81 (1H, ddd, J 17.0, 11.0, 8.5) and 5.73 (1H, ddd, J 17.0, 10.5, 8.5), *syn+anti* CHCH_2], [5.09–5.07 (2H, m) and 5.05–5.04 (2H, m), *syn+anti* CHCH_2], [4.13 (2H, q, J 7.0) and 4.12 (2H, q, J 7.0), *syn+anti* OCH_2], 2.69–2.20 (2H, m, *syn+anti* H-3), [2.59–2.45 (2H, m, H-2) and 2.35 (2H, dd, J 14.0, 7.0), *syn+anti* H-2), [1.26 (3H, d, J 7.0) and 1.25 (3H, d, J 7.0), *syn+anti* OCH_2CH_3], 0.96 (6H, d, J 7.0, *syn+anti* H-5), 0.85–0.64 (4H, m, *syn+anti* H-4), 0.58–0.40 (10H, m, *syn+anti* cyclopropyl); δ_{C} (101 MHz, CDCl_3) [173.1 and 173.0, (C-1)], [139.1 and 139.0, (CHCH_2)], [115.9 and 115.7, (CHCH_2)], 60.1 (OCH_2), [57.6 and 57.4, (C-4)], 46.3, 42.47, 38.0 (C-2), 20.1, 16.3, 3.5, 3.6; m/z (CI) 214 $[\text{MNH}_4]^+$, 197 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 197.1541. $\text{C}_{12}\text{H}_{20}\text{O}_2$ requires $[\text{MH}]^+$, 197.1541).

Ethyl 3-ethenyl-4-cyclohexylpentanoate (**154c**)



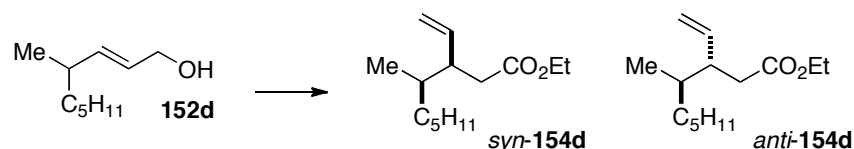
Allylic alcohol **152c** (300 mg, 1.78 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-cyclohexylpentanoate* **154c** (385 mg, 91%, 17:83 *syn:anti* mixture of diastereomers) as a colourless oil.

Data for the mixture: ν_{max} (film) 1738, 1639, 1448, 1368, 1256 cm^{-1} ; m/z (CI) 239 $[\text{MNH}_4]^+$, 256 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 239.2021. $\text{C}_{15}\text{H}_{26}\text{O}_2$ requires $[\text{MH}]^+$, 239.2011).

NMR data for *syn*-**154c**: δ_{H} (400 MHz, CDCl_3) 5.71–5.62 (1H, m, CHCH_2), 5.01–4.99 (2H, m, CHCH_2), 4.11 (2H, q, J 7.0, OCH_2), 2.65–2.58 (1H, m, H-3), 2.48–2.07 (1H, m, H-4), 1.75–1.66 (11H, m, cyclohexyl), 1.28–1.21 (5H, m, H-2, OCH_2CH_3), 0.99 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 174.3 (C-1), 138.2 (CHCH_2), 115.1 (CHCH_2), 60.2 (OCH_2), 57.4 (C-4); 43.0, 41.4, 36.5, 26.7, 20.0, 17.2, 14.0.

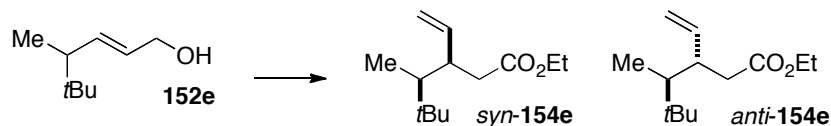
NMR data for *anti*-**154c**: δ_{H} (400 MHz, CDCl_3) 5.71–5.62 (1H, m, CHCH_2), 5.06–5.03 (2H, m, CHCH_2), 4.13 (2H, q, J 7.0, OCH_2), 2.79–2.72 (1H, m, H-3), 2.48–2.07 (1H, m, H-4), 1.75–1.66 (11H, m, cyclohexyl), 1.28–1.21 (5H, m, H-2, OCH_2CH_3), 0.97 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 174.6 (C-1), 138.6 (CHCH_2), 116.0 (CHCH_2), 60.2 (OCH_2), 57.6 (C-4), 43.2, 41.8, 38.7, 26.9, 19.4, 17.4, 14.5.

Ethyl 3-ethenyl-4-methylnonate (**154d**)



Allylic alcohol **152d** (200 mg, 1.28 mmol, 1.0 equiv) reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-methylnonate* **154d** (285 mg, 98%, 50:50 *syn:anti* mixture of diastereomers) as a yellow oil: ν_{max} (film) 1739, 1640, 1463, 1337 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.73–5.63 (2H, m, *syn+anti* CHCH_2), 5.07–4.99 (4H, m, *syn+anti* CHCH_2) [4.12 (2H, q, J 7.0) and 4.13 (2H, q, J 7.0), *syn+anti* OCH_2], [2.58 (1H, dt, J 9.0, 5.0) and 2.50 (1H, dt, J 9.0, 4.0), *syn+anti* H-3], 2.41–2.25 (4H, m, *syn+anti* H-2), 1.37–1.14 (20H, m, *syn+anti* H-4,5,6,7,8), 0.92–0.83 (12H, m, *syn+anti* OCH_2CH_3 and H-9); δ_{C} (101 MHz, CDCl_3) 173.1 (*syn+anti* C-1), [139.6 and 138.2 (CHCH_2)], [116.1 and 113.4 (CHCH_2)], 60.2 (OCH_2), [45.7 and 44.7 (*syn+anti* C-2)], 37.8, 36.6, 34.6, 33.3, 32.1, 27.0, 22.7, 16.7, 15.5, 14.3, 14.1; m/z (CI) 245 $[\text{MH}+\text{NH}_4]^+$, 187, 169 (Found: $[\text{MH}+\text{NH}_4]^+$, 245.2359. $\text{C}_{14}\text{H}_{26}\text{O}_2$ requires $[\text{MH}+\text{NH}_4]^+$, 245.2355).

Ethyl 3-ethenyl-4,5,5-trimethyl-hexanoate (**154e**)



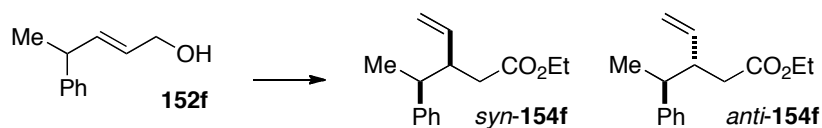
Allylic alcohol **152e** (279 mg, 1.96 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4,5,5-trimethyl-hexanoate* **154e** (280 mg, 67%, 33:67 *syn:anti* mixture of diastereomers) as a yellow oil.

Data for the mixture: $\nu_{\max}$ (film) 1738, 1637, 1466, 1366, 1267, 1176 cm^{-1} ; δ_{C} (101 MHz, CDCl_3); 142.8 (*anti* C-1), 142.7 (*syn* C-1), 134.0 (*syn+anti* CHCH₂), 129.6 (*anti* CHCH₂), 129.2 (*syn* CHCH₂), 60.2 (OCH₂), 41.7, 41.6, 21.5, 23.3, 14.4, 12.7; *m/z* (CI) 230 $[\text{MNH}_4]^+$, 213 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 213.1859. $\text{C}_{13}\text{H}_{24}\text{O}_2$ requires $[\text{MH}]^+$, 213.1855).

^1H -NMR data for *syn-154e*: δ_{H} (400 MHz, CDCl_3) 5.87–5.77 (1H, m, CHCH₂) 4.98–4.95 (2H, m, CHCH₂), 4.12 (2H, q, *J* 7.0, OCH₂), 2.50–2.20 (3H, m, H-2,3), 1.31–1.52 (1H, m, H-4), 1.20 (3H, d, *J* 7.0, 4-Me), 0.95 (2H, d, *J* 7.0, OCH₂CH₃), 0.85 (9H, s, *t*Bu).

^1H -NMR data for *anti-154e*: δ_{H} (400 MHz, CDCl_3) 5.87–5.77 (1H, m, CHCH₂) 5.07–5.01 (2H, m, CHCH₂), 4.13 (2H, q, *J* 7.0, OCH₂), 2.50–2.20 (3H, m, H-2,3), 1.31–1.52 (1H, m, H-4), 1.30 (3H, d, *J* 7.0, 4-Me), 0.96 (2H, d, *J* 7.0, OCH₂CH₃), 0.92 (9H, s, *t*Bu).

Ethyl 3-ethenyl-4-phenylpentanoate (**154f**)



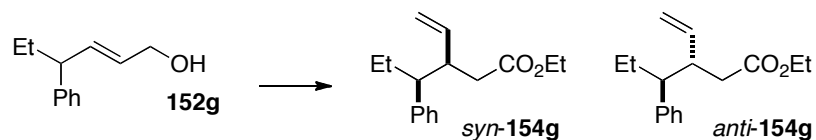
Allylic alcohol **152f** (200 mg, 1.25 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-phenylpentanoate* **154f** (280 mg, 97%, 32:68 *syn:anti* mixture of diastereomers) as a yellow oil.

Data for the mixture: $\nu_{\max}$ (film) 1734, 1640, 1494, 1374, 1176, 1032 cm^{-1} ; m/z (CI) 250 $[\text{MNH}_4]^+$, 233 $[\text{MH}]^+$ (Found $[\text{MH}]^+$, 233.1463. $\text{C}_{15}\text{H}_{20}\text{O}_2$ requires $[\text{MH}]^+$, 233.1463).

NMR data for *syn*-**154f**: δ_{H} (400 MHz, CDCl_3) 7.33–7.15 (5H, m, Ph), 5.56 (1H, ddd, J 17.0, 11.0, 9.0, CHCH_2), 5.03–4.96 (2H, m, CHCH_2), 4.11 (2H, q, J 7.0, OCH_2), 2.90–2.83 (1H, m, H-4), 2.83–2.77 (1H, m, H-3), [2.42 (1H, dd, J 15.0, 5.0) and 2.34 (1H, dd, J 15.0, 7.0), H-2], 1.31 (3H, d, J 7.0, H-5), 1.21 (1H, d, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 172.6 (C-1), 138.4 (CHCH_2), 128.3, 128.1, 126.2, 116.4 (CHCH_2), 60.1 (OCH_2), 46.6, 43.1, 37.5, 18.5, 14.3.

NMR data for *anti*-**154f**: δ_{H} (400 MHz, CDCl_3) 7.33–7.15 (5H, m, Ph), 5.68 (1H, ddd, J 17.5, 10.0, 8.0, CHCH_2), 5.12–5.08 (2H, m, CHCH_2), 4.05 (2H, q, J 7.0, OCH_2), 2.73–2.68 (1H, m, H-4), 2.67–2.61 (1H, m, H-3), [2.24 (1H, dd, J 14.5, 9.0) and 2.10 (1H, dd, J 14.5, 6.0), H-2], 1.25 (3H, d, J 7.0, H-5), 1.21 (1H, d, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 172.6 (C-1), 139.4 (CHCH_2), 128.5, 127.6, 126.3, 116.7 (CHCH_2), 60.1 (OCH_2), 47.5, 43.7, 38.6, 19.8, 14.3.

Ethyl 3-ethenyl-4-phenylhexanoate (**154g**)



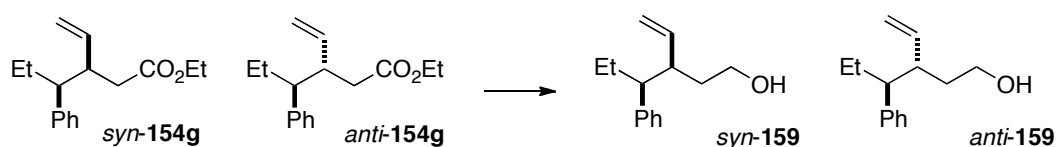
Allylic alcohol **152g** (307 mg, 1.87 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-ethenyl-4-phenylhexanoate* **154g** (460 mg, 99%, 32:68 *syn:anti* mixture of diastereomers) as a yellow oil.

Data for the mixture: $\nu_{\max}$ (film) 1734, 1640, 1494, 1453 cm^{-1} ; m/z (CI) 264 $[\text{MNH}_4]^+$, 247 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 247.1698. $\text{C}_{16}\text{H}_{22}\text{O}_2$ requires $[\text{MH}]^+$, 247.1698).

NMR data for *syn*-**154g**: δ_{H} (400 MHz, CDCl_3) 7.34–7.16 (5H, m, Ph), 5.56 (1H, ddd, J 17.0, 9.0, 8.0, CHCH_2), 5.04–5.01 (2H, m, CHCH_2), 4.13 (2H, q, J 7.0, OCH_2), 2.87 (1H, ddt, J 8.0, 5.5, 3.5, H-3), 2.44–2.30 (1H, m, H-4), 2.22–2.13 (2H, m, H-2), 1.93–1.83 (2H, m, H-5), 1.20 (3H, d, J 7.0, OCH_2CH_3), 0.81 (3H, t, J 7.5, H-6); δ_{C} (101 MHz, CDCl_3) 172.7 (C-1), 141.6 (*i*-Ph), 138.0 (CHCH_2), 129.1, 127.9, 126.5, 116.4 (CHCH_2), 60.2 (OCH_2), 51.1 (C-4), 38.1 (C-2), 25.9 (C-5), 14.9 (OCH_2CH_3), 12.3 (C-6).

NMR data for *anti*-**154g**: δ_{H} (400 MHz, CDCl_3) 7.34–7.16 (5H, m, Ph), 5.69 (1H, ddd, J 17.0, 9.0, 8.0, CHCH_2), 5.16–5.10 (2H, m, CHCH_2), 4.04 (2H, q, J 7.0, OCH_2), 2.75 (1H, ddt, J 8.0, 6.0, 4.0, H-3), 2.44–2.30 (1H, m, H-4), 2.08–2.01 (2H, m, H-2), 1.79–1.69 (2H, m, H-5), 1.26 (3H, d, J 7.0, OCH_2CH_3), 0.70 (3H, t, J 7.5, H-6); δ_{C} (101 MHz, CDCl_3) 172.6 (C-1), 142.9 (*i*-Ph), 139.1 (CHCH_2), 128.5, 126.8, 126.5, 116.6 (CHCH_2), 60.1 (OCH_2), 51.7 (C-4), 38.7 (C-2), 26.8 (C-5), 15.2 (OCH_2CH_3), 12.1 (C-6).

4-Phenyl-3-ethenylhexan-1-ol (**159**)



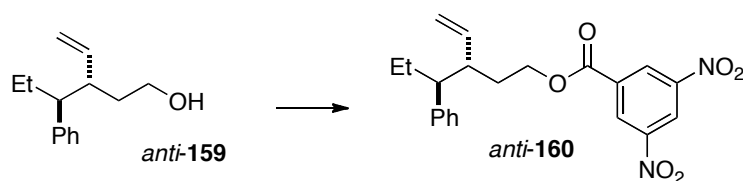
To a stirred solution of lithium aluminium hydride (74 mg, 1.95 mmol, 1.2 equiv) in THF (10 mL) was added a solution of ester **154g** (400 mg, 1.62 mmol, 1.0 equiv) in THF (5 mL) at 0 °C. Slight effervescence was observed. The reaction mixture was warmed to rt and stirred for 35 min before quenching with ethanol (1.5 mL), water (3 mL) and aqueous HCl (2 M, 3 mL). The mixture was taken up in EtOAc (25 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 25 mL) and the combined organic extracts were washed with brine (25 mL) before drying

(MgSO₄) and concentration under reduced pressure. Repeated chromatography over silica gel (50% ether/petrol) afforded analytical samples of the separated diastereoisomers of *4-phenyl-3-ethenylhexan-1-ol* **159**:

Less polar *syn*-**159** (99 mg, 30%): $\nu_{\max}$ (film) 3335, 1630 cm⁻¹; δ_{H} (400 MHz CDCl₃) 7.32 (2H, m, *m*-Ph), 7.22–7.20 (1H, m, *p*-Ph), 7.15–7.13 (2H, m, *o*-Ph), 5.63 (1H, ddd, *J* 17.0, 9.5, 7.5, CHCH₂), 5.13 (2H, m, CHCH₂), [3.59 (1H, ddd, *J* 11.0, 7.0, 5.0) and 3.50 (1H, ddd, *J* 11.0, 8.0, 6.5), H-1], 2.40–2.27 (2H, m, H-2), 1.92–1.82 (1H, m, H-4), 1.53–1.41 (2H, m, H-5), 1.34–1.24 (1H, m, H-3), 0.69 (3H, t, *J* 7.5, H-6); δ_{C} (101 MHz CDCl₃) 143.7, 141.9 (CHCH₂), 128.5, 128.3, 126.1, 116.3, 61.5 (C-1), 52.4, 47.5, 35.6 (C-3), 26.9 (C-4), 12.2 (C-6) *m/z* (CI), 222 [MNH₄]⁺ (Found: [MNH₄]⁺, 222.1856. C₁₄H₂₀O requires [MNH₄]⁺, 222.1858).

More polar *anti*-**159** (54 mg, 16%): $\nu_{\max}$ (film) 3336, 1630 cm⁻¹; δ_{H} (400 MHz CDCl₃) 7.38 (2H, m, *m*-Ph), 7.22–7.20 (1H, m, *p*-Ph), 7.12–7.11 (2H, m, *o*-Ph), 5.49 (1H, ddd, *J* 17.0, 10.0, 7.0, CHCH₂), 5.06–4.98 (2H, m, CHCH₂), [3.65 (1H, ddd, *J* 11.0, 7.0, 5.0) and 3.57 (1H, ddd, *J* 11.0, 7.0 and 5.0), H-1], 2.58–2.43 (2H, m, H-2), 1.82–1.69 (1H, m, H-4), 1.53–1.48 (2H, m, H-5), 1.39–1.32 (1H, m, H-3), 0.81 (3H, t, *J* 7.5, H-6); δ_{C} (101 MHz CDCl₃) 143.7, 139.8 (CHCH₂), 128.7, 128.4, 126.2, 116.3, 61.4 (C-1), 52.1, 45.9, 35.6 (C-3), 25.9 (C-4), 12.1 (C-6); *m/z* (CI), 222 [MNH₄]⁺ (Found: [MNH₄]⁺, 222.1856. C₁₄H₂₀O requires [MNH₄]⁺, 222.1858).

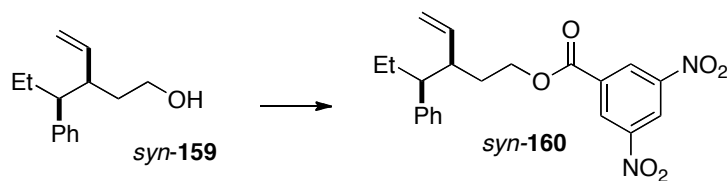
Anti-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate (*anti*-**160**)



To a solution of alcohol *anti*-**159** (90 mg, 0.44 mmol, 1.0 equiv) in dichloromethane (1 mL) was added TEA (0.19 mL, 1.32 mmol, 3.0 equiv) followed by a solution of 3,5-dinitrobenzoyl chloride (112 mg, 0.49 mmol, 1.1 equiv) in dichloromethane (1.2

mL) at 0 °C. The resulting orange solution was warmed to rt and stirred for 48 h before quenching with aqueous HCl (2 M, 2 mL). The mixture was partitioned between dichloromethane (7 mL) and water (15 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 7 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (20% ether/petrol) and recrystallisation (EtOAc/60–80 petrol) afforded anti-(±)-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate *anti*-**160** (145 mg, 89%) as yellow crystalline plates: mp 58–60 °C; ν_{max} (film) 3085, 3026, 1723, 1629, 1546, 1462, 1344, 1280, 1172, 1078 cm⁻¹; δ_{H} (500 MHz CDCl₃) 9.24 (1H, s, Ar), 9.10 (2H, s, Ar), 7.35 (2H, t, *J* 7.5, *m*-Ph), 7.22 (1H, t, *J* 7.5, *p*-Ph), 7.17–7.16 (2H, m, *o*-Ph), 5.62 (1H, ddd, *J* 17.0, 10.0, 9.0, CHCH₂), 5.20 (1H, d, *J* 10.0, *trans*-CHCH₂), 5.12 (1H, d, *J* 17.0, *cis*-CHCH₂), 4.31 (1H, dddd, *J* 6.0, 8.0, 11.0, 15.0, H-1), 2.36 (2H, m, H-2), 1.86 (1H, m, H-4), 1.75 (1H, m, H-3), 1.48 (2H, m, H-5), 0.68 (3H, t, *J* 7.5, H-6); δ_{C} (126 MHz CDCl₃) 162.3 (C-1), 148.6, 143.3, 140.6, 134.1, 128.4, 126.4, 122.3, 117.1, 65.5, 52.3, 47.6, 31.3 (C-3), 27.1 (C-4), 12.1 (C-6); *m/z* (ESI) 399 [MH]⁺, 391, 217 (Found: C, 63.39; H, 5.52; N, 6.95. C₂₁H₂₂N₂O₆ requires C, 63.31; H, 5.57; N, 7.03).

Syn-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate (*syn*-160)

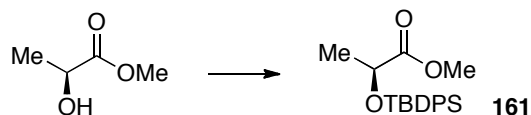


To a solution of alcohol *syn*-**159** (23 mg, 0.11 mmol, 1.0 equiv) in dichloromethane (1 mL) was added TEA (0.046 mL, 0.33 mmol, 3.0 equiv) followed by a solution of 3,5-dinitrobenzoyl chloride (32 mg, 0.14 mmol, 1.1 equiv) in dichloromethane (0.5 mL) at 0 °C. The resulting orange solution was warmed to rt and stirred overnight before quenching with aqueous HCl (2 M, 2 mL). The mixture was partitioned between dichloromethane (7 mL) and water (15 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 7 mL). The combined

organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (20% ether/petrol) afforded syn-(±)-4-phenyl-3-ethenylhexyl 3,5-dinitrobenzoate syn-**160** (24 mg, 53%) as a yellow gum: $\nu_{\max}$ (film) 3084, 3026, 2958, 1722, 1629, 1546, 1462, 1344, 1280, 1172, 1078 cm⁻¹; δ_{H} (500 MHz CDCl₃) 9.22 (1H, s, Ar), 9.12 (2H, s, Ar), 7.29 (2H, t, *J* 7.5, *m*-Ph), 7.20 (1H, t, *J* 7.5, *p*-Ph), 7.14 (2H, m, *o*-Ph), 5.52 (1H, ddd, *J* 17.0, 10.0, 7.0, CHCH₂), 5.10 (1H, d, *J* 10.0, *trans*-CHCH₂), 5.02 (1H, d, *J* 17.0, *cis*-CHCH₂), 4.43–4.34 (1H, m, H-1), 2.48–2.43 (2H, m, H-2), 2.01–2.00 (1H, m, H-4), 1.77 (1H, m, H-3), 1.41 (2H, m, H-5), 0.81 (3H, t, *J* 7.5, H-6); δ_{C} (126 MHz CDCl₃) 162.4 (C-1), 148.6 143.3, 140.6, 134.1, 128.4, 126.4, 122.3, 117.1, 65.7 (C-1), 52.0, 45.9, 31.5 (C-3), 25.7 (C-4), 12.2 (C-6); *m/z* (ESI) 399 [MH]⁺, 391, 217.

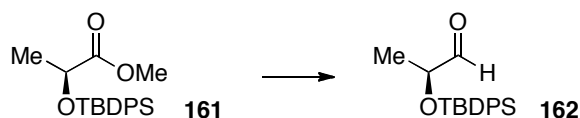
3.4.2 Compounds relevant to sections 2.3 and 2.4

Methyl (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propanoate (**161**)



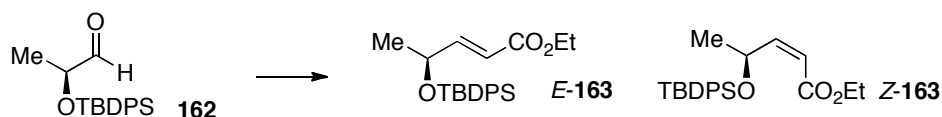
(*S*)-Methyl lactate (5.67 g, 54.5 mmol, 1.0 equiv) was added dropwise *via* syringe to a solution of *tert*-butyldiphenylchlorosilane (16.5 g, 60.0 mmol, 1.1 equiv), TEA (19.0 mL, 136.4 mmol, 2.5 equiv) and DMAP (0.67 g, 5.45 mmol, 0.1 equiv) in THF (50 mL) at 0 °C, to give a white suspension. The reaction mixture was warmed to rt overnight and concentrated under reduced pressure. The remaining white residue was triturated with ether (100 mL) and the solids were removed by filtration. The filtrate was sequentially washed with acetic acid (15% w/w in water, 150 mL), water (150 mL), saturated sodium hydrogencarbonate solution (100 mL) and water (100 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification over silica gel (50% dichloromethane/petrol) afforded methyl (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propanoate **161** (12.61 g, 68%) as a colourless oil: $[\alpha]_{\text{D}}^{20}$ –34.1 (*c* 0.82, CHCl₃), lit –51.8 (*c* 0.78, EtOH); ν_{max} (film) 1762, 1281, 1137, 1113 cm^{–1}; δ_{H} (400 MHz CDCl₃) 7.69–7.68 (4H, m, *o*-Ph), 7.47–7.38 (6H, m, *m,p*-Ph), 4.30 (1H, q, *J* 7.0, H-2), 3.58 (3H, s, OMe), 1.39 (3H, d, *J* 7.0, H-3), 1.12 (9H, s, C(CH₃)₃); δ_{C} (101 MHz CDCl₃) 174.2 (C-1), 135.8, 129.8, 127.6 (Ph), 68.9 (OMe), 51.6 (C-2), 26.8 (C(CH₃)₃), 21.3, 19.3; in agreement with published data.²¹⁶

(2*S*)-2-(*Tert*-butyldiphenylsilyloxy)propanal (**162**)



Diisobutylaluminium hydride (15.45 mL of a 1.5 M solution in toluene, 18.54 mmol, 1.0 equiv) was added dropwise *via* syringe to a solution of ester **161** (6.35 g, 18.54 mmol, 1.0 equiv) in dichloromethane (25 mL) at $-78\text{ }^{\circ}\text{C}$ over 15 min. The reaction mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$ before the addition of water (16 mL) with vigorous stirring. The reaction mixture was allowed to warm to rt and solid sodium hydrogen carbonate was added to bind the resultant precipitate. The precipitate was filtered and washed with ether (100 mL) before separation of excess water from the filtrate, drying (MgSO_4) and concentration under reduced pressure. Purification over silica gel (40% dichloromethane/petrol) afforded (2*S*)-2-(*tert*-butyldiphenylsiloxy)propanal **162** (4.43 g, 77%) as a colourless oil: $[\alpha]_{\text{D}}^{20} -15.2$ (c 0.56, CHCl_3); ν_{max} (film) 1739, 1445, 1112, 1007, 740 cm^{-1} ; δ_{H} (400 MHz CDCl_3) 9.68 (1H, s, H-1), 7.67–7.65 (4H, m, *o*-Ph), 7.43–7.41 (6H, m, *m,p*-Ph), 4.12 (1H, q, *J* 7.0, H-2), 1.25 (3H, d, *J* 7.0, H-3), 1.14 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (101 MHz CDCl_3) 203.9 (C-1), 135.9, 130.1, 127.8, 76.7 (C-2), 26.9 ($\text{C}(\text{CH}_3)_3$), 19.2, 18.4; m/z (CI) 330 $[\text{MNH}_4]^+$, 312 $[\text{M}]^+$, 235; in agreement with published data.²¹⁶

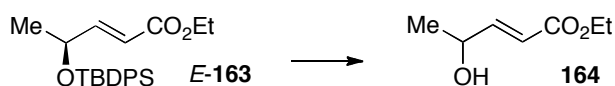
Ethyl [4*S*]-2(*E*)-4-(*tert*-butyldiphenylsilyloxy)-2-pentenoate (*E*-163) and ethyl [4*S*]-2(*Z*)-4-(*tert*-butyldiphenylsilyloxy)-2-pentenoate (*Z*-163)



To a solution of aldehyde **162** (4.43 g, 14.16 mmol, 1.0 equiv) in dichloromethane (14 mL) was added carbethoxymethylenetriphenylphosphorane (4.47 g, 14.16 mmol, 1.0 equiv) over 3 min at rt. After stirring for 48 h the reaction mixture was concentrated under reduced pressure. The resultant solid triphenyl phosphine oxide was removed by filtration and the residue was washed extensively with ether. The filtrate was concentrated under reduced pressure and purified over silica gel (5% ether/petrol) to afford the separated esters: desired ethyl [4*S*]-2(*E*)-4-(*tert*-butyldiphenylsilyloxy)-2-pentenoate *E*-**163** (3.81 g, 74%) as a colourless oil: $[\alpha]_{\text{D}}^{20} -38.8$ (c 0.43, CHCl_3); ν_{max}

(film) 1720, 1660, 1590, 1427, 1118 cm^{-1} ; δ_{H} (400 MHz CDCl_3) 7.71–7.64 (4H, m, *o*-Ph), 7.46–7.36 (6H, m, *m,p*-Ph), 6.91 (1H, dd, *J* 15.5, 4.5, H-3), 6.02 (1H, d, *J* 15.5, H-2), 4.45–4.47 (1H, m, H-4), 4.21 (2H, q, *J* 7.0, OCH_2), 1.32 (3H, t, *J* 7.0, OCH_2CH_3), 1.15 (3H, d, *J* 6.5, H-5), 1.10 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (101 MHz CDCl_3) 190.8 (C-1), 151.5, 135.8, 134.0 129.8, 127.6, 119.13, 68.7, 60.3, 26.9, 23.3, 19.2, 14.3; *m/z* (CI), 400 $[\text{MNH}_4]^+$; and undesired ethyl [4*S*]-(*Z*)-4-(*tert*-butyldiphenylsilyloxy)-2-pentenoate **Z-163** (0.347 g, 7%) as a colourless oil: ν_{max} (film) 1728, 1660, 1591, 1427, 1118 cm^{-1} ; δ_{H} (400 MHz CDCl_3) 7.68–7.63 (2H, m, *o*-Ph), 7.40–7.33 (3H, m, *m,p*-Ph), 6.27 (1H, dd, *J* 8.0, 11.5, H-3), 5.50 (1H, d, *J* 11.5, H-2), 5.43–5.41 (1H, m, H-4), 4.00 (2H, q, *J* 7.0, OCH_2), 1.27 (3H, d, *J* 6.5, H-5), 1.16 (3H, t, *J* 7.0, OCH_2CH_3), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (101 MHz CDCl_3) 190.9, 153.7, 135.8, 134.0 129.8, 127.4, 117.0, 66.8, 60.0, 27.0, 23.3, 19.2, 14.1; *m/z* (CI), 400 $[\text{MNH}_4]^+$; as colourless oils, in agreement with literature data.¹²⁹

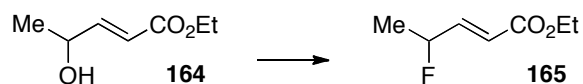
Ethyl (*E*)-4-hydroxypent-2-enoate (**164**)



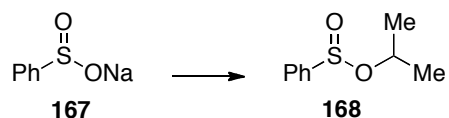
To a solution of TBAF trihydrate (2.58 g, 8.17 mmol, 3.0 equiv) in THF (15 mL) at 0 °C was added a solution of ester **E-163** (1.00 g, 2.61 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was warmed to rt and stirred for 30 min before addition of acetic acid (2.5 mL) and filtration of the mixture over a pad of silica gel (1 cm x 10 cm, 50 % EtOAc/petrol). The filtrate was washed with saturated aqueous sodium hydrogencarbonate (2 x 75 mL) and brine (50 mL) before drying (MgSO_4) and concentration under reduced pressure. Purification over silica gel (25% EtOAc in 40/60 petrol) afforded the ester ($\pm$)-**164** (264 mg, 70%) as a colourless oil: ν_{max} (film) 3345, 1716, 1653 cm^{-1} ; δ_{H} (400 MHz CDCl_3) 6.99 (1H, dd, *J* 15.4, 4.5, H-3), 6.04 (1H, d, *J* 15.5, H-2), 4.51–4.49 (1H, m, H-4), 4.22 (2H, q, *J* 7.0, OCH_2), 1.79 (1H, s (br), OH), 1.36 (3H, d, *J* 6.5, H-5), 1.32 (3H, t, *J* 7.0, OCH_2CH_3); δ_{C} (101 MHz CDCl_3) 166.5 (C-1) 150.9 (C-3), 119.6 (C-2), 67.2 (C-4), 60.5 (OCH_2), 22.8

(OCH₂CH₃), 14.1 (C-5); m/z (CI) 162 [MNH₄]⁺, 145 [MH]⁺, 127 [M-OH]⁺ (Found: [MH]⁺, 145.0873. C₇H₁₃O₃ requires [MH]⁺, 145.0865); in agreement with published data.⁷¹

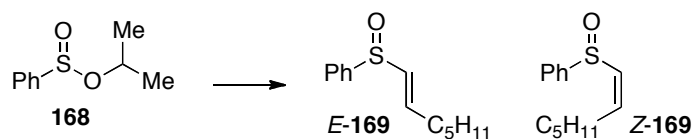
Ethyl (*E*)-4-fluoropent-2-enoate (**165**)



To a solution of DAST (1.80 mL, 14.6 mmol, 1.4 equiv) in dichloromethane (10 mL) at rt was added a solution of ester **164** (1.50 g, 10.4 mmol, 1.0 equiv) in dichloromethane (10 mL) *via* syringe. The resultant solution was stirred at rt for 5 min before sodium carbonate (2.6 g) was carefully added *via* a wide-bore needle. The mixture was stirred for 25 min and filtered. The filtrate was washed with saturated aqueous sodium carbonate (50 mL), dried (MgSO₄) and concentrated using a rotary evaporator at atmospheric pressure (water bath temperature 40 °C) to give ethyl (*E*)-4-fluoropent-2-enoate **165** (1.19 g, 98%) as a yellow oil without further purification: ν_{max} (film) 1722, 1641, 1305 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 6.94 (1H, ddd, J 20.0, 15.5, 8.0, H-3), 6.07 (1H, dt, J 15.5, 2.0, H-2), 5.26 (1H, ddt, J 48.0, 8.0, 6.5, H-4), 4.24 (2H, q, J 7.0, OCH₂), 1.50 (3H, dd, J 23.5, 6.5, H-5), 1.33 (3H, t, J 7.0, OCH₂CH₃); δ_{F} (376 MHz, CDCl₃) -176.7 (ddt, J 48.0, 22.0, 20.0); δ_{C} (101 MHz, CDCl₃) 166.1 (C-1), 146.0, 145.8 (C-3), 120.7 (C-2), 88.7, 87.0 (C-4), 60.7 (OCH₂), 20.8, 20.6 (C-5), 14.2 (OCH₂CH₃); m/z (EI) 124 [M-HF]⁺; in agreement with published data.⁷¹

Isopropyl benzenesulfinate (**168**)

To a suspension of sodium benzenesulfinate **167** (73.87 g, 450 mmol, 1.0 equiv) in 1,2-dichloroethane (120 mL) was added thionyl chloride (80.31 g, 49.0 mL, 675 mmol, 1.5 equiv) dropwise *via* syringe at 0 °C. The resulting mixture was warmed to rt and stirred for 2 h before removal of excess thionyl chloride by distillation under reduced pressure. The residue was taken up in ether (200 mL) and added *via* a syringe fitted with a wide-bore needle to a solution of IPA (42.4 mL, 540 mmol, 1.2 equiv) in pyridine (72.5 mL, 900 mmol, 2.0 equiv) at 0 °C. The solution was warmed to rt, stirred for 2.5 h and water (200 mL) was added. The mixture was poured onto ether (200 mL) and the phases were separated. The organic phase was washed with aqueous HCl (2 M, 4 x 100 mL) followed by brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. Distillation of the residue under reduced pressure afforded isopropyl benzenesulfinate **168** (55.2 g, 67%) as a colourless oil: bp₁ 88–90 °C; ν_{max} (film) 1444, 1384, 1139, 912, 840, 734 cm⁻¹; δ_{H} (400 MHz CDCl₃) 7.76–7.73 (2H, m, Ph), 7.57–7.55 (3H, m, Ph), 4.64 (1H, hept, *J* 6.5, CH(CH₃)₂), [1.42 (3H, d, *J* 6.5) and 1.28 (3H, d, *J* 6.5), CH(CH₃)₂]; δ_{C} (101 MHz, CDCl₃) 145.7 (*i*-Ph), 131.9 (*p*-Ph), 129.0 (*m*-Ph), 125.1 (*o*-Ph), 73.0 (CH(CH₃)₃), 24.0, 23.8 (CH(CH₃)₃); *m/z* (CI) 185 [MH]⁺, 202 [MNH₄]⁺; in agreement with published data.¹³²

(E)-(Hept-1-enylsulfinyl)benzene and (Z)-(hept-1-enylsulfinyl)benzene (169)

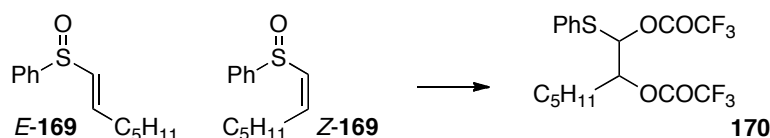
To a solution of dimethyl methylphosphonate (6.46 mL, 59.5 mmol, 2.2 equiv) in THF (60 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (25.7 mL of a 2.21 M solution in hexanes, 56.8 mmol 2.1 equiv) dropwise *via* syringe. The resultant colourless anion solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min before dropwise addition of isopropyl benzenesulfinate **168** (5.00 g, 27.0 mmol, 1.0 equiv). The cloudy white reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, and hexanal (3.90 mL, 32.4 mmol, 1.2 equiv) was added dropwise *via* syringe to give a clear, colourless solution. The reaction mixture was warmed immediately to room temperature and quenched with saturated aqueous NH_4Cl (100 mL). The mixture was partitioned between dichloromethane (150 mL) and water (75 mL), and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried (MgSO_4), concentrated under reduced pressure and purified over silica gel (20–50% ether/petrol) to afford a mixture of (*E*)-(*hept-1-enylsulfinyl*)benzene and (*Z*)-(*hept-1-enylsulfinyl*)benzene **169** (3.56 g, 60%, 1:1 *E*:*Z* mixture of isomers) as a colourless oil.

Data for the mixture: ν_{max} (film) 1651, 1622, 1583, 1468, 1304, 1050, 922, 775, 701 cm^{-1} ; m/z (EI) 222 $[\text{M}]^+$, 205 $[\text{M}-\text{OH}]^+$ (Found: $[\text{M}]^+$, 222.1074. $\text{C}_{13}\text{H}_{18}\text{OS}$ requires $[\text{M}]^+$, 222.1078).

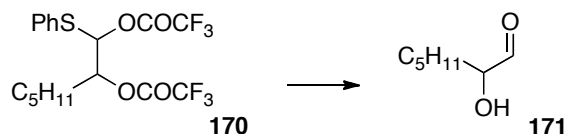
NMR data for *E*-**169**: δ_{H} (400 MHz, CDCl_3) 7.65–7.63 (2H, m, SPh), 7.53–7.51 (3H, m, SPh), 6.65 (1H, dt, J 15.0, 7.0, H-2), 6.25 (1H, dt, J 15.0, 1.5, H-1), 2.24 (2H, AB quartet, J 7.0, 1.5, H-3), 1.55–1.47 (2H, m, H-4), 1.33–1.29 (4H, m, H-5,6), 0.92–0.88 (3H, m, H-7); δ_{C} (101 MHz, CDCl_3) 144.7 142.5, 136.7, 130.8, 128.9, 124.5, 123.7, 31.23, 22.4, 21.6, 13.6, 13.2.

NMR data for **Z-169**: δ_{H} (400 MHz, CDCl_3) 7.64 (2H, d, J 6.5, *o*-SPh), 7.56–7.50 (3H, m, *m,p*-SPh), 6.26–6.23 (2H, m, H-1,2), 2.72–2.52 (2H, m, H-3), 1.57–1.52 (2H, m, H-4), 1.42–1.39 (4H, m, H-5,6), 0.95 (3H, t, J 7.0, H-7); δ_{C} (400 MHz, CDCl_3) 144.6, 142.5, 136.8, 130.7, 129.3, 124.1, 31.3, 29.4, 28.8, 22.4, 14.0.

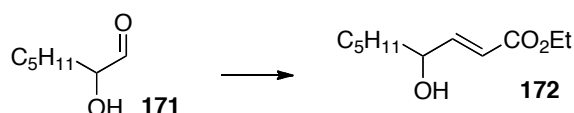
1,2-Bis(trifluoroacetoxy)-1-(phenylsulfenyl)heptane (**170**)



To a solution of vinyl sulfinate **169** (3.58 g, 16.1 mmol, 1.0 equiv, 1:1 *E:Z* mixture of isomers) in dichloromethane (30 mL) at 0 °C under was added TFAC (2.27 mL, 16.10 mmol, 1.0 equiv) dropwise *via* syringe. The resulting colourless solution was stirred at 0 °C for 10 min before further addition of TFAC (3.39 g, 2.27 mL, 16.10 mmol, 1.0 equiv) dropwise *via* syringe. The reaction mixture was stirred for 30 min at 0 °C before quenching with saturated aqueous sodium hydrogencarbonate (75 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure to afford 1,2-bis(trifluoroacetoxy)-1-(phenylsulfenyl)heptane **170** (6.68 g, 96%, 1:1 *syn:anti* mixture of diastereomers) as a colourless oil without further purification: ν_{max} (film) 1787, 1641, 1226 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.53–7.39 (10H, m, *syn+anti* SPh), 6.35 (1H, d, J 4.0, *anti* H-1), 6.19 (1H, d, J 8.5, *syn* H-1), 5.42 (1H, AB quartet, J 4.0, 2.0, *anti* H-2), 5.26 (1H, AB quartet, J 8.5, 3.5, *syn* H-2), 2.01–1.83 (4H, m, *syn+anti* H-3), 1.45–1.27 (12H, m, *syn+anti* H-4,5,6), 0.94–0.90 (6H, m, *syn+anti* H-7); δ_{C} (101 MHz, CDCl_3) 134.8, 134.3, 130.1, 129.8, 129.7, 129.6, 129.5, 127.8, 86.1, 83.8, 31.1, 30.2, 29.2, 24.5, 23.9, 22.3, 22.2, 13.8; m/z (ESI) 432 $[\text{M}]^+$, 276, 203 (Found: $[\text{M}]^+$, 432.0885. $\text{C}_{17}\text{H}_{18}\text{F}_6\text{O}_4\text{S}$ requires $[\text{M}]^+$, 432.0830).

2-Hydroxyheptanal (171)

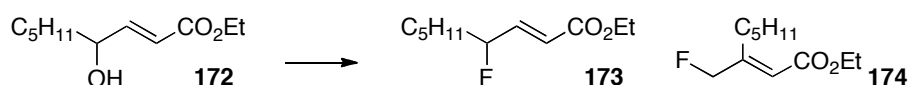
To a solution of **170** (6.67 g, 15.44 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C were added, consecutively, dropwise *via* syringe; MeOH (1.56 mL, 38.6 mmol, 2.50 equiv) and TEA (0.22 mL, 1.54 mmol, 0.1 equiv). The resulting solution was stirred at 0 °C for 15 min and concentrated under reduced pressure. The residue was purified over silica gel (40–50% ether/petrol) to afford *2-hydroxyheptanal* **171** (1.34 g, 67%) as a white solid: mp 86–88 °C; NMR data were complicated as the aldehyde existed as a mixture of oligomeric forms; *m/z* (ESI) 413 $[M_3Na]^+$, 283 $[M_2Na]^+$, 131 $[M]^+$ (Found: $[M]^+$, 131.1076. $C_7H_{15}O_2$ requires $[M]^+$ 131.1027).

Ethyl (*E*)-4-hydroxynon-2-enoate (172)

To a refluxing solution of aldehyde **171** (1.30 g, 10.0 mmol, 1.0 equiv) in benzene (15 mL) was added a suspension of carbethoxymethylenetriphenylphosphorane (3.83 g, 11.0 mmol, 1.1 equiv) in benzene (20 mL) dropwise *via* a pressure-equalised dropping funnel. After refluxing for 5.5 h, the reaction mixture was cooled and concentrated under reduced pressure. The residue was purified over silica gel (30% ether/petrol) to afford the ethyl (*E*)-4-hydroxynon-2-enoate **172** (1.61 g, 81%) as a colourless oil: $\nu_{\max}$ (film) 3345, 1717, 1652; δ_H (400 MHz, $CDCl_3$) 6.97 (1H, dd, *J* 15.5, 5.0, H-3), 6.07 (1H, d, *J* 15.5, H-2), 4.35–4.32 (1H, m, H-4), 4.23 (2H, q, *J* 7.0, OCH_2), 1.65–1.58 (4H, m, H-5,6), 1.37–1.31 (7H, m, H-7,8,9), 0.92 (3H, t, *J* 7.0,

OCH₂CH₃); δ_C (101 MHz, CDCl₃) 166.5 (C-1), 150.1 (C-3), 120.2 (C-2), 71.2 (C-4), 60.5 (OCH₂), 36.6 (C-5), 31.7 (C-6), 24.9 (C-7), 22.5 (C-8), 14.2, 14.0; m/z (CI) 218 [MNH₄]⁺, 201 [MH]⁺ (Found: [MH]⁺, 201.1485. C₁₁H₂₀O₃ requires [MH]⁺, 201.1491); in agreement with published data.^{129a}

Ethyl (*E*)-4-fluoronon-2-enoate (**173**) and ethyl (*E*)-3-(fluoromethyl)oct-2-enoate (**174**)



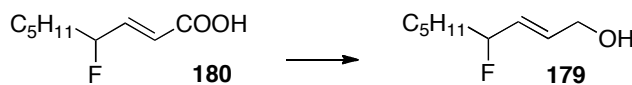
To a solution of DAST (367 μ L, 3.00 mmol, 1.2 equiv) in dichloromethane (2.5 mL) at -78°C under a dry nitrogen atmosphere was added ester **172** (500 mg, 2.50 mmol, 1.0 equiv) *via* syringe. The reaction mixture was allowed to warm to 0°C over 15 min and was cooled to -78°C . MeOH (4 mL) was added and the mixture was allowed to warm to rt. Water (6 mL) was poured on and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel (5% EtOAc/20% dichloromethane/petrol) to afford the separated esters: Less polar *ethyl (E)*-3-(*fluoromethyl*)oct-2-enoate **174** (25 mg, 5%) as a colourless oil: ν_{max} (film) 1718, 1662, 1462 cm^{-1} ; δ_H (400 MHz, CDCl₃) 5.93 (1H, s, H-2), 4.87 (2H, dd, J_{HF} 47.0, $J_{\text{H}_2\text{H}_4}$ 1.5, CH₂F), 4.20 (2H, q, J 7.0, OCH₂), 2.56 (2H, dt, J 8.0, 1.5, H-4), 1.59–1.49 (2H, m, H-5), 1.38–1.32 (7H, m, H-6,7,8), 0.93 (3H, t, J 7.0, OCH₂CH₃); δ_F (376 MHz, CDCl₃) -219.5 (t, J_{HF} 47.0, CH₂F); δ_C (101 MHz, CDCl₃) 166.0 (C-1), 156.5 (C-3), 114.6 (C-2), 84.0 (d, J_{CF} 177, CH₂F), 59.9 (OCH₂), 32.0 (C-4), 29.7 (C-5), 28.4 (C-6), 22.4 (C-7), [14.3 and 14.0 (C-8 and OCH₂CH₃)]; m/z (ESI) 203 [MH]⁺, 183 [M-F]⁺ (Found: [MH]⁺, 203.1442. C₁₁H₁₉FO₂ requires [MH]⁺, 203.1447); and more polar *ethyl (E)*-4-fluoronon-2-enoate **173** (154 mg, 31%) as a colourless oil: ν_{max} (film) 1722, 1647 cm^{-1} ; δ_H (400 MHz, CDCl₃) 6.92 (1H, ddd, J_{HF} 25.0, J_{HH} 16.0, 7.0, H-3), 6.07 (1H, d, J 16.0, H-2), 5.11 (1H, dm, J_{HF}

48.0, H-4), 4.20 (2H, q, J 7.0, OCH₂) 1.78–1.60 (2H, m, H-5), 1.46–1.38 (9H, m, H-6,7,8,9), 0.91 (3H, t, J 7.0 OCH₂CH₃); δ_F (376 MHz, CDCl₃) –184.1 (ddt, J 48.0, 25.0, 21.0); δ_C (101 MHz, CDCl₃) 166.1 (C-1), 145.3, 145.1 (C-3), 120.1 (C-2), 91.0 (C-4) 60.6 (OCH₂), 34.8, 31.5, 24.3, 21.7, 14.2; m/z (CI) 220 [MNH₄]⁺, 200, 183 [M-F]⁺, (Found: [MNH₄]⁺, 220.1719. C₁₁H₁₉FO₂ requires [MNH₄]⁺ 220.1713); the fraction contained <3% of the elimination product **175** in agreement with published data.²¹⁷

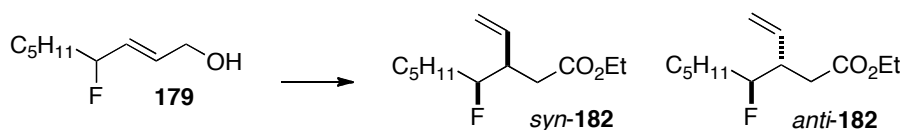
(*E*)-4-Fluoronon-2-enoic acid (**180**)



To a solution of ester **173** (1.00 g, 4.95 mmol, 1.0 equiv) in THF (8 mL) and water (2 mL) in a microwave vial was added lithium hydroxide monohydrate (0.415 g, 9.90 mmol, 2.0 equiv). After heating by microwave at 110 °C for 45 min, the reaction was cooled to rt and aqueous HCl (2 M, 20 mL) was added. The mixture was poured onto dichloromethane (20 mL) and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL), the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to afford (*E*)-4-fluoronon-2-enoic acid **180** (467 mg, 55%) as a white solid which was used without further purification: mp 30–32 °C; δ_H (400 MHz, CDCl₃) 7.04 (1H, ddd, J_{H3F4} 21.0, J 16.0, 9.5, H-3), 6.10 (1H, d, J 16.0, H-2), 5.10 (1H, dm, J_{H4F4} 47.0, H-4), 1.81–1.69 (2H, m, H-5), 1.52–1.34 (6H, m, H-6,7,8), 0.93 (3H, t, J 7.0, H-9); δ_F (376 MHz, CDCl₃) 185.1 (ddt, J_{H4F4} 47.0, J_{H3F4} 21.0, J_{H5F4} 22.5); δ_C (101 MHz, CDCl₃) 170.9 (C-1), 147.1 (d, J 19.0, C-3), 133.9 (d, J 11.0, C-2), 91.2 (C-4), 34.6 (d, J 21.0, C-5), 31.5 (C-6), 24.2 (C-7), 22.5 (C-8), 14.0 (C-9).

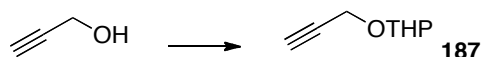
(E)-4-Fluoronon-2-en-1-ol (179)

To a solution of acid **180** (567 mg, 3.26 mmol, 1.0 equiv) in dichloromethane (10 mL) at 0 °C was added TEA (0.489 mL, 3.52 mmol, 1.08 equiv), followed by isobutylchloroformate (0.456 mL, 3.58 mmol, 1.10 equiv). A fine white precipitate of triethylamine hydrochloride developed. The reaction mixture was warmed to rt, stirred for 1.5 h and filtered directly into a suspension of sodium borohydride (492 mg, 13.03 mmol, 4.0 equiv) in dimethoxyethane (10 mL) under nitrogen. The white suspension was stirred for 2.5 h and water (50 mL) was poured on, resulting in vigorous effervescence. The mixture was extracted with dichloromethane (3 x 45 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), concentrated and purified over silica gel (10% EtOAc/petrol) to afford (E)-4-fluoronon-2-en-1-ol **179** (252 mg, 49%) as a colourless oil which decomposed on standing: ν_{max} (film) 3343, 1653, 1461, 1379, 1086, 972 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 5.99–5.92 (1H, m, H-3), 5.86–5.77 (1H, m, H-2), 4.93 (1H, ddt, J_{H4F4} 48.0, J_{HH} 12.5, 6.0, H-4), 4.24–4.21 (2H, m, H-1), 1.79–1.34 (9H, m, OH, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); δ_{F} (376 MHz, CDCl₃) –174.0 (m); δ_{C} (101 MHz, CDCl₃) 132.1 (d, J 11.0, C-3), 129.6 (d, J 19.5, C-2), 93.1 (d, J 165.5, C-4), 62.7 (C-1), 35.4 (d, J 22.0, C-5), 31.6 (C-6), 24.4 (C-7), 22.6 (C-8), 14.0 (C-9); m/z (CI) 178 [MNH₄]⁺, 158 [M-2H]⁺, 140 [M-HF]⁺, 123.

Ethyl 4-fluoro-3-ethenylnonanoate (182)

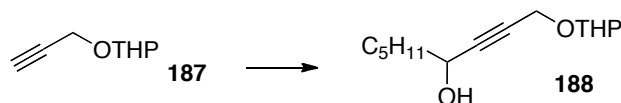
Allylic alcohol **179** (86 mg, 0.538 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 4-fluoro-3-ethenylnonanoate* **182** (82 mg, 66%, 1:1 *syn:anti* mixture of diastereomers) as a yellow oil: $\nu_{\max}$ (film) 1726, 1678, 1456, 1355, 1158, 1120, 1026, 903, 871 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) [5.69 (1H, ddd, J 17.0, 11.0, 9.0) and 5.68 (1H, ddd, J 17.0, 11.0, 9.0), *syn+anti* CHCH_2], 5.17–5.10 (4H, m, *syn+anti* CHCH_2), [4.48 (1H, ddt, J_{HF} 48.5, J_{HH} 9.0, 6.0) and 4.36 (1H, ddt, J_{HF} 48.5, J_{HH} 7.5, 5.0), *syn+anti* H-4], 3.55 (4H, q, J 7.0, *syn+anti* OCH_2), 2.87–2.68 (2H, m, *syn+anti* H-3), [2.64 (1H, dd, J 15.0, 5.0), 2.57 (1H, dd, J 15.0, 5.5), 2.45 (1H, dd, J 15.0, 8.0) and 2.35 (1H, dd, J 15.0, 9.5), *syn+anti* H-2], 1.35–1.27 (12H, m, H-6,7,8), 1.22 (4H, ddt, J_{HF} 22.0, J_{HH} 7.0, 3.0, *syn+anti* H-5), [0.89 (6H, t, J 7.0) and 0.88 (6H, t, J 7.0), *syn+anti* H-9 and OCH_2CH_3]; δ_{F} (376 MHz, CDCl_3) –186.4, –191.4; δ_{C} (126 MHz, CDCl_3) [172.3 and 172.2 (C-1)], [136.3 and 135.0 (CHCH_2)], [118.3 and 117.8 (CHCH_2)], [96.2 (d, J 24.0) and 94.5 (d, J 24.0), C-4], [60.5 and 60.4 (OCH_2)], [45.4 and 44.7 (C-3)], [36.2 and 35.6 (C-2)], 32.9, 32.5, 24.5, 22.3, 14.8, 14.0; m/z (CI) 248 $[\text{MNH}_4]^+$, 231 $[\text{MH}]^+$, 211 $[\text{M-F}]^+$ (Found: $[\text{MNH}_4]^+$, 248.2014. $\text{C}_{13}\text{H}_{23}\text{FO}_2$ requires $[\text{MNH}_4]^+$, 248.2026).

2-(Prop-2-ynyloxy)tetrahydro-2H-pyran (**187**)



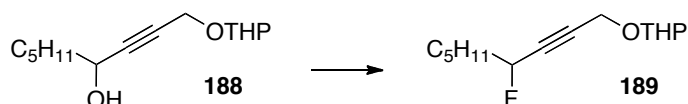
Propargyl alcohol (5.19 mL, 89.2 mmol, 1.0 equiv) was reacted according to the procedure of Larock *et al* to afford 2-(prop-2-ynyloxy)tetrahydro-2H-pyran **187** (9.83 g, 79%) as a colourless oil after distillation under reduced pressure (bp₄ 60–61 °C) in agreement with literature data.¹³⁹

1-(Tetrahydro-2H-pyran-2-yloxy)non-2-yn-4-ol (**188**)



To a solution of propargyl ether **187** (4.00 g, 28.4 mmol, 1.0 equiv) in THF (50 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-butyllithium (11.36 mL of a 2.42 M solution in hexanes, 28.4 mmol, 1.0 equiv) dropwise *via* syringe. The resulting yellow anion solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min before addition of hexanal (3.41 g, 34.08 mmol, 1.2 equiv) dropwise *via* syringe. The colourless reaction mixture was warmed to $0\text{ }^{\circ}\text{C}$ and saturated aqueous NH_4Cl (100 mL) was added. Dichloromethane (100 mL) and water (20 mL) were added and the phases were separated. The aqueous layer was extracted with dichloromethane (2 x 75 mL). The combined organic extracts were dried (MgSO_4), concentrated under reduced pressure and purified over silica gel (25–35% ether/petrol) to afford 1-(tetrahydro-2H-pyran-2-yloxy)non-2-yn-4-ol **188** (5.24 g, 77%) as a colourless oil: ν_{max} (film) 3423, 2360, 2341, 1455, 1388, 1023 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 4.83 (1H, t, J 3.5, OCHO), 4.43 (1H, dt, J 6.5, 2.0, H-4), 4.32 (2H, AB quartet, J 15.5, 2.0, H-1), 3.85 (1H, ddd, J 12.0, 9.0, 6.0, $\text{OCH}_{\text{axial}}$), 3.58–3.55 (1H, m, $\text{OCH}_{\text{equatorial}}$), 1.61 (1H, s (br), OH), 1.83–1.32 (14H, m), 0.91 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 96.8 (OCHO), 87.1 (C-3), 80.8 (C-2), 62.6 (THP- OCH_2), 62.0 (C-4), 54.3 (C-1), 37.7, 31.5, 30.3, 25.4, 24.8, 22.6, 19.1, 14.0; m/z (CI) 258 $[\text{MNH}_4]^+$, 223, 174, 102; in agreement with published data.²¹⁸

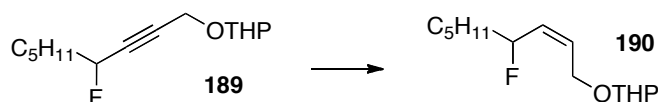
2-(4-Fluoronon-2-ynyloxy)tetrahydro-2H-pyran (**189**)



To a solution of Deoxofluor (2.12 mL of 50% w/w solution in THF, 4.98 mmol, 1.2 equiv) in dichloromethane (20 mL) at $-78\text{ }^{\circ}\text{C}$ was added a solution of propargyl

alcohol **188** (1.00 g, 4.15 mmol, 1.0 equiv). The reaction mixture was stirred at -78°C for 1.5 h, and quenched at -78°C with saturated aqueous potassium carbonate (25 mL) before warming to rt. The phases were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (40 mL), dried (MgSO_4), decolourised with charcoal, concentrated under reduced pressure and purified over silica gel (5% ether/petrol) to afford 2-(4-fluoronon-2-ynyloxy)tetrahydro-2H-pyran **189** (502 mg, 50%) as a colourless oil: ν_{max} (film) 2359, 2342 1462, 1379, 1355, 1202, 1121, 1029, 903 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.16 (1H, dt, J_{HF} 48.5, J_{H4H5} 6.5, H-4), 4.85–4.83 (1H, m, OCHO), 4.35–4.30 (2H, m, H-1), 3.86 (1H, dt, J 11.0, 3.0, $\text{OCH}_{\text{axial}}$), 3.57 (1H, m, $\text{OCH}_{\text{equatorial}}$), 1.84 (4H, m), 1.76 (7H, m), 1.15 (4H, m) 0.92 (3H, t, J 7.0, H-9); δ_{F} (376 MHz, CDCl_3) –172.9 (m, F-4); δ_{C} (101 MHz, CDCl_3) 96.9 (OCHO), 84.3 (d, J 10.0), 82.8 (d, J 25.5), 82.7 (d, J 166.5), 62.0 (d, J 5.0, C-4), 54.1 (C-1), 35.9, 35.7, 31.3, 30.2, 25.3, 24.2, 22.5, 19.0, 18.9, 14.0; m/z (CI) 260 $[\text{MNH}_4]^+$, 235, 219, 102, 85 (Found: 260.2030. $\text{C}_{14}\text{H}_{23}\text{FO}_2$ requires $[\text{MNH}_4]^+$, 260.2026) (Found: C, 69.29; H, 9.51. $\text{C}_{14}\text{H}_{23}\text{FO}_2$ requires C, 69.39; H, 9.57).

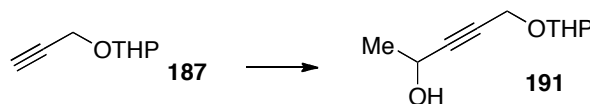
(Z)-2-(4-Fluoronon-2-enyloxy)tetrahydro-2H-pyran (190)



A mixture of propargyl fluoride **189** (480 mg, 1.98 mmol, 1.0 equiv) in THF (3 mL) and Lindlar's catalyst (40 mg) was stirred vigorously under an atmosphere of hydrogen gas for 75 min. The reaction mixture was filtered over a pad of Celite, washing with dichloromethane (20 mL). The filtrate was dried (MgSO_4) and concentrated to afford (Z)-2-(4-fluoronon-2-enyloxy)tetrahydro-2H-pyran **190** (435 mg, 91%) as a colourless oil, without further purification: ν_{max} (film) 1670, 1461, 1380, 1119, 1032, 904 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.78–5.75 (1H, m, H-3), 5.68–5.65 (1H, m, H-2), 5.25 (1H, ddt, J_{HF} 48.0, J_{HH} 7.5, 5.5, H-4), 4.66 (1H, t, J 3.5, OCHO), 4.39–4.27 (1H, m, H-1), 4.18–4.08 (1H, m, H-1), 3.88–3.84 (1H, m,

OCH_{axial}), 3.55 (1H, m, OCH_{equatorial}), 1.80–1.72 (3H, m), 1.63–1.56 (7H, m), 1.39–1.33 (5H, m), 0.92 (3H, t, *J* 6.5, H-9); δ_F (376 MHz, CDCl₃) –172.2 (ddt, *J* 48.0, 27.5, 14.0), δ_C (101 MHz, CDCl₃) 131.1 (d, *J* 22.5, C-3), 131.0 (d, *J* 21.5, C-3), 130.2 (d, *J* 10.0, C-2); 129.8 (d, *J* 10.0, C-2), 98.1 (OCHO), 89.2 (d, *J* 161.5, C-4), 62.9 (d, *J* 23.0, C-1), 62.2 (d, *J* 20.0, C-1), 35.6 (d, *J* 22.5, C-5), 31.6, 30.6, 25.4, 24.4, 22.6, 19.5, 19.3, 14.0; *m/z* (CI) 262 [MNH₄]⁺, 225, 102 [THPNH₄]⁺, 85 [THP]⁺ (Found: [MNH₄]⁺, 262.2178. C₁₄H₂₅FO₂ requires [MNH₄]⁺, 262.2182) (Found: C, 68.76; H, 10.29. C₁₄H₂₅FO₂ requires C, 68.82; H, 10.31).

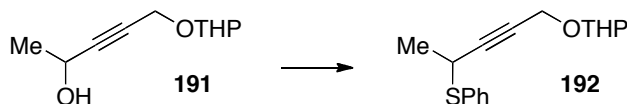
2-(4-(Hydroxyl)pentynyloxy)tetrahydro-2*H*-pyran (**191**)



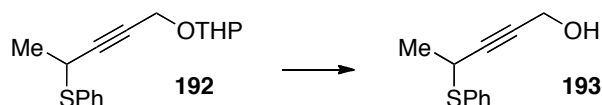
To a solution of propargyl ether **187** (1.00 g, 7.14 mmol, 1.0 equiv) in THF (15 mL) was added *n*-butyllithium (3.15 mL of a 2.27 M solution in hexanes, 7.14 mmol, 1.0 equiv) dropwise *via* syringe at –78 °C. The resulting anion solution was stirred at –78 °C for 10 min before addition of acetaldehyde (0.49 mL, 8.57 mmol, 1.2 equiv) dropwise *via* syringe. The resulting solution was stirred at –78 °C for 30 min and quenched with saturated aqueous NH₄Cl (10 mL) followed by water (10 mL). Ether (30 mL) was poured on and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL). The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (5–40% EtOAc/petrol) to afford 2-(4-(hydroxyl)pentynyloxy)tetrahydro-2*H*-pyran **191** (1.12 g, 85%) as a colourless oil $\nu_{\max}$ (film) 3391, 1647, 1442, 1202 cm^{–1}; δ_H (400 MHz, CDCl₃) 4.82 (1H, t, *J* 3.0, OCHO), 4.59–4.56 (1H, m, H-2), [4.25 (1H, dd, *J* 15.0, 2.0) and 4.35 (1H, dd, *J* 15.0, 2.0), H-5], 3.86 (1H, ddd, *J* 12.0, 9.0, 3.0, OCH_{axial}), 3.51–3.59 (1H, m, OCH_{equatorial}), 1.86 (1H, s, OH), 1.78–1.55 (6H, m, THP), 1.48 (3H, d, *J* 6.5, H-1); δ_C (400 MHz, CDCl₃) 96.9 (OCHO), 87.9 (C-3), 80.0 (C-4), 61.9 (THP OCH₂), 58.4 (C-2), 54.2, 30.23, 25.3, 24.2, 19.0; *m/z* (CI) 202 [MNH₄]⁺, 186 [MH]⁺,

85 [THP]⁺ (Found: [MNH₄]⁺, 202.1440. C₁₀H₁₆O₃ requires [MNH₄]⁺, 202.1443); in agreement with literature data.²¹⁹

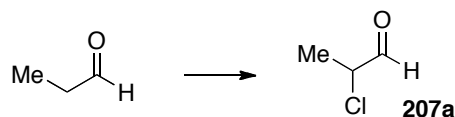
2-(4-(Thiophenyl)pentynyloxy)tetrahydro-2H-pyran (**192**)



To a solution of propargyl alcohol **191** (500 mg, 2.71 mmol, 1.0 equiv) and diphenyl disulfide (774 mg, 3.55 mmol, 1.3 equiv, recrystallised from ether) in acetonitrile (25 mL) was added tri-*n*-butylphosphine (1.56 mL, 6.24 mmol, 2.3 equiv) dropwise *via* syringe at rt to give a biphasic mixture. The reaction mixture was immersed in an ultrasound bath at rt for 1.5 h before dilution with dichloromethane (50 mL) and washing with aqueous NaOH (2 M, 2 x 45 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified over silica gel (10 % ether/petrol) to afford 2-(4-(thiophenyl)pentynyloxy)tetrahydro-2H-pyran **192** (571 mg, 90%) as a yellow oil: ν_{max} (film) 1583, 1480, 1440, 1388, 1346 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.54 (2H, d, *J* 6.5, *o*-SPh), 7.35–7.29 (3H, m, *m,p*-SPh), 4.73 (1H, t, *J* 3.5, OCHO), [4.28 (1H, dd, *J* 15.5, 5.5) and 4.27 (1H, dd, *J* 15.5, 7.5), H-5], 3.99 (1H, q, *J* 7.0, OCH_{axial}), 3.85–3.80 (1H, m OCH_{equatorial}), 3.54–3.50 (1H, m, H-2), 1.84–1.63 (2H, m, THP), 1.52 (3H, d, *J* 7.0, H-1); δ_{C} (101 MHz, CDCl₃) 133.9 (*i*-SPh), 132.2, 128.8, 127.7 (SPh), 96.5 (OCHO), 86.6 (C-3), 79.3 (C-2), 62.0 (OCH₂), 54.3 (C-1), 33.4, 30.2, 25.4, 21.7, 19.1; *m/z* (CI) 294 [MNH₄]⁺, 277 [MH]⁺, 210 [M-THPNH₄]⁺, (Found: [MH]⁺, 277.1273. C₁₆H₂₀O₂S requires [MH]⁺, 277.1262).

4-(Phenylthio)pent-2-yn-1-ol (193)

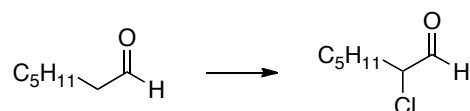
To a solution of propargyl ether **192** (1.76 g, 6.37 mmol, 1.0 equiv), in ethanol (15 mL) was added pyridinium paratoluenesulfonate (160 mg, 0.637 mmol, 0.1 equiv) with stirring. The mixture was heated to 55 °C for 6 h, after which TLC showed some remaining **192**. Pyridinium paratoluenesulfonate (160 mg, 0.637 mmol, 0.1 equiv) was added and heating at 55 °C was continued for a further 9 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was purified over silica gel (20% ether/petrol) to afford 4-(phenylthio)pent-2-yn-1-ol **193** (836 mg, 68%) as a yellow oil: ν_{max} (film) 3357, 2351, 1583, 1479, 1483, 1038, 1009, 744, 691 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.54 (2H, dd, J 8.0, 7.5, m -SPh), 7.38–7.32 (3H, m, o,p -SPh), 4.27 (2H, d, J , 2.5, H-1), 3.97 (1H, ddt, J 14.0, 7.0, 2.5, H-4), 1.61 (1H, s (br), OH), 1.55 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 133.8, 133.0, 128.9, 127.9, 86.6 (C-3), 81.7 (C-2), 51.3 (C-1), 33.4 (C-4), 21.7 (C-5); m/z (CI) 210 $[\text{MNH}_4]^+$, 192 $[\text{M}]^+$ (Found: $[\text{MNH}_4]^+$, 210.0957. $\text{C}_{11}\text{H}_{12}\text{OS}$ requires $[\text{MNH}_4]^+$, 210.0953).

2-Chloropropanal (207a)

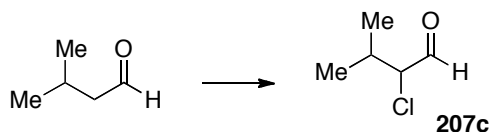
To a solution of propanal (54.6 mL, 750 mmol, 1.0 equiv) in dichloromethane (30 mL) at -10 °C was added sulfuryl chloride (60.3 mL, 750 mmol, 1.0 equiv) dropwise *via* an addition funnel over 30 minutes and the reaction mixture was allowed to warm

to rt overnight. The reaction mixture was heated to reflux for 2 h, cooled and distilled through a 15 cm Vigreux column, collecting the fraction containing 2-chloropropanal **207a** (33.1 g, 66%) as a colourless oil: bp₇₆₀ 82–84 °C; δ_{H} (400 MHz, CDCl₃) 9.54 (1H, s (br), H-1), 4.30 (1H, dq, J 7.0, 2.0 H-2), 1.63 (3H, d, J 7.0, H-3); δ_{C} (101 MHz, CDCl₃) 195.1 (C-1), 58.8 (C-2), 18.3 (C-3), m/z (CI) 388, 294 [(3M)NH₄]⁺, 260, 92 [M]⁺; in agreement with published data.¹⁵⁵

2-Chloroheptanal (207b)



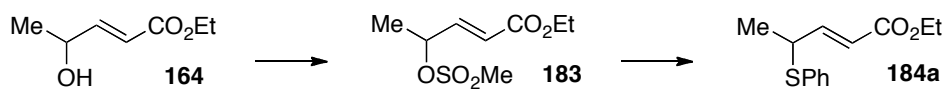
To a solution of heptanal (3.94 mL, 26.8 mmol, 1.0 equiv) at 0 °C was added D,L-proline (313 mg, 2.68 mmol, 0.1 equiv), followed by *N*-chlorosuccinimide (4.85 g, 34.8 mmol, 1.3 equiv). The suspension was warmed to rt, stirred for 16 h and pentane (100 mL) was added. The mixture was filtered and concentrated under reduced pressure. The residue was added to pentane (50 mL), filtered, concentrated under reduced pressure and distilled under reduced pressure to afford 2-chloroheptanal **207b** (3.37 g, 85%) as a colourless oil: bp₉₀ 80–82 °C; ν_{max} (film) 1735, 1466, 1379, 1102 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 9.47 (1H, d, J 2.5, H-1), 4.14 (1H, dt, J 5.5, 2.5, H-2), 2.00–1.78 (2H, m, H-3), 1.36–1.29 (6H, m, H-4,5,6), 0.89 (3H, t, J 7.0, H-7); δ_{C} (101 MHz, CDCl₃) 185.2 (C-1), 64.1 (C-2), 32.3, 31.1, 25.4, 22.5, 14.1; m/z (CI), 148 [M]⁺, 166 [MNH₄]⁺, 462, 428 [(3M)NH₄]⁺; in agreement with published data.²²⁰

2-Chloro-3-methylbutanal (207c)

To a solution of 3-methylbutanal (5.36 mL, 50.0 mmol, 1.0 equiv) at 0 °C was added D,L-prolinamide (571 mg, 5.00 mmol, 0.1 equiv), followed by N-chlorosuccinimide (5.46 g, 65.0 mmol, 1.3 equiv). The reaction mixture was warmed to rt during 16 h and pentane (100 mL) was added. The mixture was filtered and concentrated under reduced pressure. The residue was added to pentane (50 mL), filtered, concentrated under reduced pressure and distilled to afford 2-chloro-3-methylbutanal **207c** (3.88 g, 64%) as a colourless oil: bp₇₆₀ 130–132 °C; ν_{max} (film) 1737, 1465, 1369, 1058, 830 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 9.42 (1H, d, J 3.0, H-1), 3.95 (1H, dd, J 5.5, 3.0, H-2), 2.28 (1H, dsept, J 7.0, 5.5, H-3), [1.00 (3H, d, J 7.0) and 0.98 (3H, d, J 7.0), H-4]; δ_{C} (101 MHz, CDCl_3) 196.1 (C-1), 70.6 (C-2), 31.1 (C-3), 17.8 (C-4); m/z (CI) 120 $[\text{M}]^+$, 138 $[\text{MNH}_4]^+$, 344, 378 $[(3\text{M})\text{NH}_4]^+$; in agreement with published data.¹⁵⁸

Ethyl (*E*)-4-thiophenypent-2-enoate (184a)

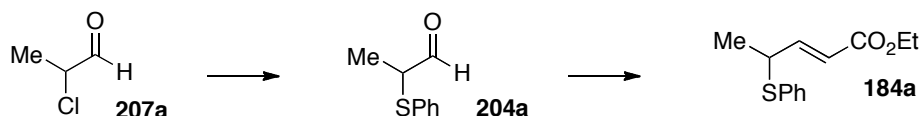
From **164**:



To a solution of ester **164** (1.00 g, 6.94 mmol, 1.0 equiv) in dichloromethane (15 mL) was added TEA (1.95 mL, 13.9 mmol, 1.0 equiv) followed by methanesulfonyl chloride (0.81 mL, 10.4 mmol, 1.5 equiv) at 0 °C. After warming to rt and stirring for 8 h, aqueous HCl (2 M, 30 mL) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined

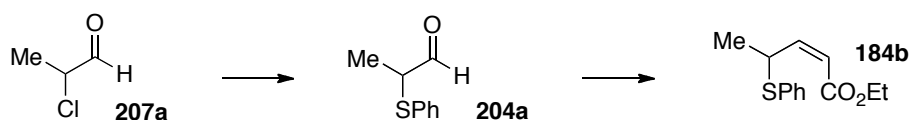
organic extracts were dried (MgSO_4) and concentrated under reduced pressure to give methanesulfonate **183** (1.49 g, 97%) as a colourless oil. To a solution of sodium hydride (60% w/w on mineral oil, 295 mg, 7.38 mmol, 1.1 equiv) in THF (40 mL) at 0 °C was added thiophenol (813 mg, 0.756 mL, 7.38 mmol, 1.1 equiv) dropwise *via* syringe. The reaction mixture was allowed to warm to rt for 5 min before cooling to –20 °C and addition of a solution of methanesulfonate **183** (1.49 g, 6.71 mmol) in THF (5 mL) dropwise *via* syringe. The resulting light orange suspension was stirred at –20 °C for 1 h before warming to 0 °C and quenching with aqueous HCl (2 M, 30 mL). The mixture was partitioned between water (20 mL) and ether (30 mL) and the phases were separated. The aqueous phase was extracted with ether (2 x 30 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (35 mL) and brine (35 mL), dried (MgSO_4) and concentrated under reduced pressure. The residue was purified over silica gel (40% ether in 40/60 petrol) affording ethyl (*E*)-4-thiophenypent-2-enoate **184a** (1.19 g, 75%) as a colourless oil.

From **207a**:



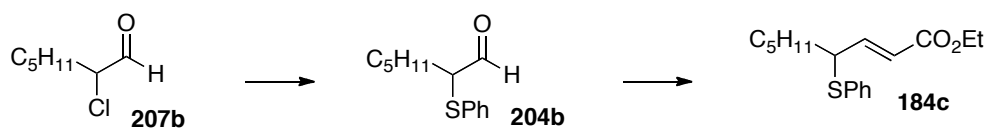
2-Chloropropanal **207a** (2.29 mL, 20.0 mmol, 1.0 equiv) was reacted according to general procedure **D** to afford ethyl (*E*)-4-thiophenypent-2-enoate **184a** (2.38 g, 47%) as a colourless oil after purification over silica gel (5–20% ether/heptane): ν_{max} (film) 1716, 1650, 747, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.42–7.40 (2H, m) and 7.34–7.28 (3H, m), SPh], 6.89 (1H, dd, J 15.5, 8.0, H-3), 5.60 (1H, d, J 15.5, H-2), 4.18 (2H, q, J 7.0, OCH_2), 3.81 (1H, dq, J 8.0, 7.0, H-4), 1.45 (3H, d, J 7.0, H-5), 1.28 (3H, t, J 7.0 OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 166.3 (C-1), 148.4 (C-3), 133.5 (*o*-SPh), 133.3, (*i*-SPh), 128.9 (*m*-SPh), 127.9 (*p*-SPh), 120.5 (C-2), 60.4 (OCH_2), 44.9 (C-4), 19.5 (C-5), 14.2 (OCH_2CH_3); m/z (CI) 254 $[\text{MNH}_4]^+$, 237 $[\text{MH}]^+$, 146 $[\text{M}-(\text{SPh})\text{NH}_4]^+$ (Found: $[\text{MNH}_4]^+$, 254.1219. $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$ requires 254.1215); in agreement with published data.^{147a}

Ethyl (Z)-4-(phenylthio)pent-2-enoate (**184b**)



2-Chloropropanal **207a** (2.29 mL, 20.0 mmol, 1.0 equiv) was reacted according to general procedure **E** to afford *ethyl (E)-5-methyl-4-thiophenylhex-2-enoate* **184b** (1.37 g, 29%) as a colourless oil after purification over silica gel (5–20% ether/heptane): $\nu_{\max}$ (film) 2979, 1715, 1639, 1186, 1029, 826, 744, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.40–7.30 (2H, m) and 7.27–7.21 (3H, m), SPh], 6.02 (1H, dd, J 11.5 10.5, H-3), 5.61 (1H, d, J 11.5, H-2), 5.25 (1H, dq, J 10.5, 7.0, H-4), 4.05 (2H, q, J 7.0, OCH_2), 1.39 (3H, d, J 7.0, H-5), 1.21 (3H, t, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 166.3 (C-1), 150.3 (C-3), 134.1, 133.2, 128.9, 127.5, 118.9 (C-2), 60.2 (OCH_2), 40.4 (C-4), 32.1, 20.0, 14.4; m/z (CI) 254 $[\text{MNH}_4]^+$, 237 $[\text{MH}]^+$ (Found: C, 65.84; H, 6.80. $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$ requires C, 66.07; H, 6.82).

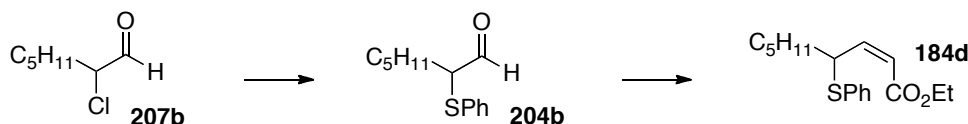
Ethyl (E)-4-thiophenylnon-2-enoate (**184c**)



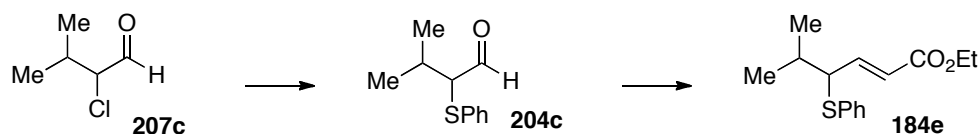
2-Chloroheptanal **207b** (743 mg, 5.0 mmol, 1.0 equiv) was reacted according to general procedure **D** to afford *ethyl (E)-4-thiophenylnon-2-enoate* **184c** (785 mg, 57%) as a colourless oil after purification over silica gel (5–40% ether/heptane): $\nu_{\max}$ (film) 2931, 1720, 1648, 1438, 1160, 746, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.38–7.35 (2H, m) and 7.31–7.23 (3H, m), SPh], 6.77 (1H, dd, J 15.5, 9.0, H-3), 5.50 (1H, dd, J 15.5, 1.0, H-2), 4.15 (2H, q, J 7.0, OCH_2), 3.60 (1H, dt, J 9.0, 6.5, H-4), 1.79–

1.61 (2H, m, H-5), 1.47–1.29 (6H, m, H-6,7,8), 1.26 (3H, t, J 7.0, OCH_2CH_3), 0.89 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 166.4 (C-1), 147.9 (C-3), 133.7, 129.1, 128.0, 124.0, 121.3 (C-2), 60.5 (OCH_2), 51.1 (C-4), 33.8, 31.7, 27.2, 22.7, 14.4, 14.2; m/z (CI) 310 $[\text{MNH}_4]^+$, 293 $[\text{MH}]^+$, 282, 268 (Found: $[\text{MH}]^+$, 293.1581. $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}$ requires $[\text{MH}]^+$ 293.1575) (Found C, 69.63; H, 8.29. $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}$ requires C, 69.82; H, 8.27).

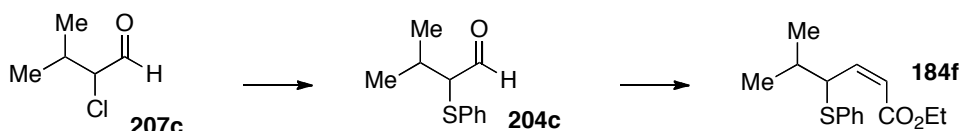
Ethyl (Z)-4-(thiophenyl)non-2-enoate (**184d**)



2-Chloroheptanal **207b** (2.91 ml, 20.0 mmol, 1.0 equiv) was reacted according to general procedure **E** to afford the ester to afford *ethyl (Z)-4-(thiophenyl)non-2-enoate* **184d** (4.35 g, 73%) as a colourless oil after purification over silica gel (5–40% ether/heptane): ν_{max} (film) 2931, 2859, 1717, 1640, 1583, 1178, 1026, 744, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.43–7.41 (2H, m) and 7.29–7.45 (3H, m), SPh], 5.99 (1H, dd, J 11.0, 11.5, H-3), 5.65 (1H, d, J 11.5, H-2), 5.20–5.14 (1H, m, H-4), 4.05 (2H, q, J 7.5, OCH_2), 1.64–1.28 (8H, m, H-5,6,7,8), 1.23 (3H, t, J , 7.5, OCH_2CH_3), 0.93–0.89 (3H, m, H-9); δ_{C} (101 MHz, CDCl_3) 166.1 (C-1), 149.1 (C-3), 133.9, 133.0, 128.6, 127.2, 119.4 (C-2), 60.0 (OCH_2), 45.2, 34.0, 31.5, 26.8, 22.5, 14.2, 14.0; m/z (CI) 310 $[\text{MNH}_4]^+$, 293 $[\text{MH}]^+$, 268 (Found: $[\text{MH}]^+$, 293.1579. $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 293.1575).

Ethyl (*E*)-5-methyl-4-thiophenylhex-2-enoate (**184e**)

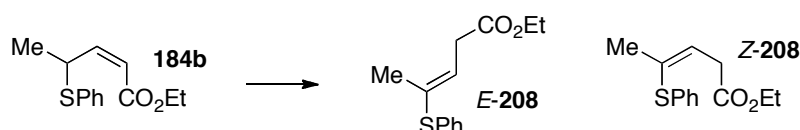
2-Chloro-3-methylbutanal **207c** (551 mg, 5.0 mmol, 1.0 equiv) was reacted according to general procedure **D** to afford *ethyl (E)-5-methyl-4-thiophenylhex-2-enoate* **184e** (795 mg, 60%) as a colourless oil after purification over silica gel (5–40% ether/heptane): ν_{max} (film) 1717, 1682, 1583, 1182, 1026, 744, 690 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.30–7.27 (2H, m) and 7.22–7.16 (3H, m), SPh], 6.75 (1H, dd, J 15.5, 10.0, H-3), 5.40 (1H, d, J 15.5, H-2), 4.07 (2H, q, J 7.0, OCH_2), 3.36 (1H, dd, J 10.0, 6.5, H-5), 1.18 (3H, t, J 7.0, OCH_2CH_3), [1.03 (3H, d, J 6.5) and 0.98 (3H, d, J 6.5), H-6]; δ_{C} (101 MHz, CDCl_3) 166.3 (C-1), 146.2 (C-3), 136.5, 133.5, 129.1, 127.8, 121.8 (C-2), 60.5 (OCH_2), 59.0 (C-4), 32.4 (C-5), [20.8 and 20.1, (C-6)], 14.4 (OCH_2CH_3); m/z (CI) 282 $[\text{MNH}_4]^+$, 265 $[\text{MH}]^+$, 233 (Found: $[\text{MNH}_4]^+$, 282.1357. $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$ requires $[\text{MNH}_4]^+$, 282.1528) (Found: C, 67.49; H, 7.68. $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$ requires C, 68.14; H, 7.62).

Ethyl (*Z*)-5-methyl-4-(thiophenyl)hex-2-enoate (**184f**)

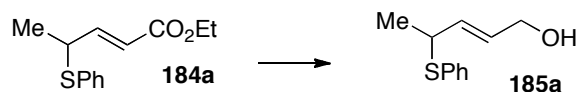
2-Chloro-3-methylbutanal **207c** (2.41 g, 20.0 mmol, 1.0 equiv) was reacted according to general procedure **E** to afford *ethyl (Z)-5-methyl-4-(thiophenyl)hex-2-enoate* **184f** (1.41 g, 27%) as a colourless oil after purification over silica gel (5–20% ether/heptane): ν_{max} (film) 1716, 1683, 1583, 1182, 1026, 744, 691 cm^{-1} ; δ_{H} (400

MHz, CDCl₃) [7.40 (2H, d, *J* 7.0) and 7.28–7.19 (3H, m), SPh], 6.10 (1H, dd, *J* 11.5, 11.0, H-3), 5.68 (1H, d, *J* 11.5, H-2), 5.02 (1H, dd, *J* 11.0, 7.0, H-4), 4.03 (2H, q, *J* 7.0, OCH₂), 1.96 (1H, sext, *J* 7.0, H-5), 1.22 (3H, t, *J* 7.0, OCH₂CH₃), [1.15 (3H, d, *J* 7.0) and 1.06 (3H, d, *J* 7.0), H-6]; δ_C (101 MHz, CDCl₃) 166.2 (C-1), 147.5 (C-3), 134.3 (*i*-SPh) 132.9 (*o*-SPh), 128.6 (*m*-SPh), 127.1 (*p*-SPh), 119.6 (C-2), 59.9 (OCH₂), 32.2 (C-5), [20.5 and 19.8, (C-6)], 14.2 (OCH₂CH₃); *m/z* (CI) 282 [MNH₄]⁺, 265 [MH]⁺ (Found: [MH]⁺, 265.1265. C₁₅H₂₀O₂S requires [MH]⁺, 265.1262) (Found: C, 68.19; H, 7.62. C₁₅H₂₀O₂S requires C, 68.14; H, 7.62).

Ethyl (*E*)-4-(phenylthio)-pent-3-enoate and ethyl (*Z*)-4-(phenylthio)-pent-3-enoate (208**)**



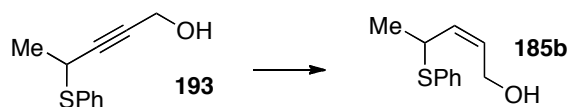
To a solution of ester **184b** (20 mg, 0.09 mmol, 1.0 equiv) in *d*₆-DMSO (0.7 mL) in an NMR tube was added potassium *tert*-butoxide (5 mg, 0.045 mmol, 0.5 equiv) in one portion. The tube was shaken and a red colour developed. The ¹H-NMR spectrum of the mixture was measured at intervals of 10 min, 1 h and 16 h showing conversion to a 70:30 mixture of ethyl (*E*)-4-(phenylthio)-pent-3-enoate *E*-**208** and ethyl (*Z*)-4-(phenylthio)-pent-3-enoate and *Z*-**208**: δ_H (400 MHz, CDCl₃) *inter alia* 7.35–7.02 (10H, m, *E*+*Z* SPh), [6.64 (1H, t, *J* 7.5) and 6.39 (1H, t, *J* 7.0) *E*+*Z* H-3], 4.07–3.95 (4H, m, *E*+*Z* OCH₂), 2.50 (4H, m, *E*+*Z* H-2).

(*E*)-4-(Thiophenyl)pent-2-en-1-ol (185a)

Ester **184a** (1.16 g, 4.91 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford (*E*)-4-(thiophenyl)pent-2-en-1-ol **185a** (676 mg, 71%) as a colourless oil after purification over silica gel (5–75 % TBME/heptane): $\nu_{\max}$ (film) 3378, 1639, 1372, 1196, 750, 693 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.35–7.69 (3H, m,) and 7.43–7.41 (2H, m), SPh], 5.69 (1H, ddt, J 15.5, 9.0, 1.5, H-3), 5.52 (1H, dt, 15.5, 6.0, H-2), 4.05 (2H, m, H-1), 3.80 (1H, dq, J 9.0, 7.5, H-4), 1.42 (3H, d, J 7.5, H-5), 1.15 (1H, s (br), OH); δ_{C} (101 MHz, CDCl_3) 134.6 (C-3), 133.7, 133.15, 129.5, 128.7, 127.4 (C-2), 63.1 (C-1), 45.3 (C-4), 20.3 (C-5); m/z (EI) 194 $[\text{M}]^+$, 163 $[\text{M}-\text{CH}_2\text{OH}]^+$, 110 $[\text{SPh}]^+$, 84 $[\text{M}-\text{SPh}]^+$ (Found: $[\text{M}]^+$, 194.0765. $\text{C}_{11}\text{H}_{14}\text{OS}$ requires $[\text{M}]^+$, 194.0762); in agreement with published data.^{147a}

(*Z*)-4-(Phenylthio)pent-2-en-1-ol (185b)

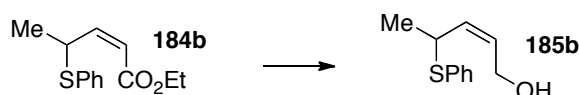
From **193**:



To a solution of propargyl alcohol **193** (377 mg, 1.96 mmol, 1.0 equiv) in dichloromethane (20 mL) was added TEA (1.08 mL, 7.84 mmol, 4.0 equiv) followed by NBSH²²¹ (1.06 g, 4.91 mmol, 2.5 equiv) in one portion. The suspension was stirred for 12 h to give a dark red solution. Saturated aqueous sodium hydrogencarbonate (50 mL) was poured on and the mixture was stirred for 10 min.

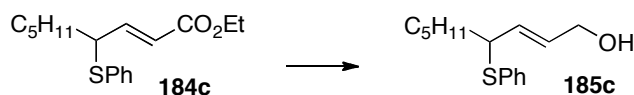
The phases were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (75 mL), dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (25% TBME/petrol) to afford *(Z)*-4-(thiophenyl)pent-2-en-1-ol **185b** (210 mg, 55%) as a colourless oil.

From **184b**:



Ester **184b** (1.16 g, 4.91 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford *(Z)*-4-(thiophenyl)pent-2-en-1-ol **185b** (670 mg, 70%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): ν_{max} (film) 3366, 1651, 1583, 1474, 1438, 1195, 1041, 1013, 750, 692 cm⁻¹; δ_{H} (400 MHz, CDCl₃), [7.52–7.50 (2H, m) and 7.36–7.29 (3H, m), SPh], 5.56–5.50 (1H, m, H-2), 5.44 (1H, dd, J 11.0, 10.5, H-3), 4.10 (1H, dq, J 10.5, 7.0, H-4), [3.83 (1H, dd, J 13.0, 6.0) and 3.73 (1H, dd, J 13.0, 7.0), H-1], 1.60 (1H, s, OH), 1.40 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl₃) 134.8 (SPh), 134.4 (C-3), 132.1 (*i*-SPh), 128.9 (SPh), 128.2, 126.8 (C-2), 58.3 (C-1), 42.0 (C-4), 20.7 (C-5); m/z (CI) 212 [MNH₄]⁺, 194, [M]⁺, 177 [M-OH]⁺, 163 (Found: [MNH₄]⁺, 212.1113. C₁₁H₁₄OS requires [MNH₄]⁺, 212.1109).

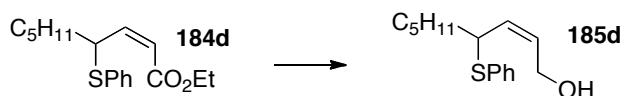
(E)-4-(Thiophenyl)non-2-en-1-ol (**185c**)



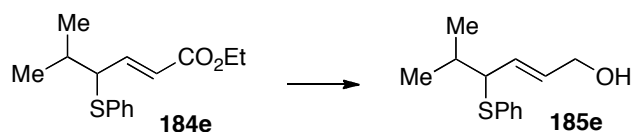
Ester **184c** (746 mg, 2.55 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford *(E)*-4-(thiophenyl)non-2-en-1-ol **185c** (531 mg, 83%) as a

colourless oil after purification over silica gel (5–60% TBME/heptane): $\nu_{\max}$ (film) 3350, 1663, 1583, 1438, 747, 691 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.38–7.36 (2H, m) and 7.29–7.23 (3H, m), SPh], 5.55 (1H, dd, J 15.5, 9.0, H-3), 5.42 (1H, dt, J 15.5, 5.5, H-2), 3.99 (2H, t, J 6.0, H-1), 3.59 (1H, m, H-4), 1.80–1.20 (8H, m, H-5,6,7,8), 0.85 (3H, t, J 7.0, H-9); δ_{C} (400 MHz, CDCl_3) 135.0 (*i*-SPh), 133.5 (C-3), 133.1 (*o*-SPh), 130.6 (*m*-SPh), 128.8 (C-2), 127.4 (*p*-SPh), 62.3 (C-1), 51.5 (C-4), 34.5 (C-5), 31.8 (C-6), 27.2 (C-7), 22.7 (C-8), 14.2 (C-9); m/z (CI) 268 $[\text{MNH}_4]^+$, 251 $[\text{MH}]^+$, 233 $[\text{M-OH}]^+$ (Found: $[\text{MNH}_4]^+$, 268.1738. $\text{C}_{15}\text{H}_{22}\text{OS}$ requires $[\text{MNH}_4]^+$, 268.1735) (Found: C, 71.42; H, 8.81. $\text{C}_{15}\text{H}_{22}\text{OS}$ requires C, 71.95; H, 8.86).

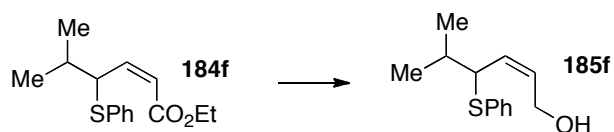
(*Z*)-4-(Thiophenyl)non-2-en-1-ol (**185d**)



Ester **184d** (3.00 g, 10.3 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford (*Z*)-4-(thiophenyl)non-2-en-1-ol **185d** (1.54 g, 60%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): $\nu_{\max}$ (film) 3388, 1651, 1583, 1467, 1438, 1378, 1176, 1025, 747, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.52–7.50 (2H, m) and 7.36–7.33 (3H, m), SPh], 5.57 (1H, dt, J 11.0, 7.0, H-2), 5.39 (1H, dd, J 11.0, 9.0, H-3), 3.91 (1H, dt, J 9.0, 5.5, H-4), 3.80–3.71 (2H, m, H-1), 1.60 (1H, s (br), OH), 1.44–1.40 (2H, m, H-5), 1.37–1.31 (6H, m, H-6,7,8), 0.91 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 134.9, 134.3, 133.5, 129.4, 128.9, 128.2, 58.4 (C-1), 47.4 (C-4), 34.5, 31.5, 31.3, 27.2, 22.5, 14.0; m/z (CI) 268 $[\text{MNH}_4]^+$, 251 $[\text{MH}]^+$, 233, 158 (Found: C, 72.03; H, 8.72. $\text{C}_{15}\text{H}_{22}\text{OS}$ requires C, 71.95; H, 8.86).

(E)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185e)

Ester **184e** (279 mg, 1.06 mmol) was reacted according to general procedure **F** to afford (*E*)-5-methyl-4-(thiophenyl)hex-2-en-1-ol **185e** (195 mg, 83%) as a colourless oil after purification over silica gel (5–75% TBME/heptane): $\nu_{\max}$ (film) 3367, 1663, 1583, 1438, 969, 748, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.38–7.36 (2H, m) and 7.27–7.20 (3H, m), SPh], 5.58 (1H, dd, J 15.0, 9.5, H-3), 5.38 (1H, dt, J 15.0, 6.0, H-2), 3.98 (1H, t, J 6.0, H-1), 3.45 (1H, dd, J 9.50, 6.5, H-4), 1.96 (1H, sext, J 6.5, H-5), [1.06 (3H, d, J 6.5) and 1.03 (3H, d, J 6.64), H-6], 0.93 (1H, t, J 6.0, OH); δ_{C} (400 MHz, CDCl_3) 135.4, 133.4, 131.3, 131.0, 128.8, 127.3, 63.3 (C-1), 59.3 (C-4), 32.3 (C-5), 20.9, 19.8 (C-6); m/z (CI) 240 $[\text{MNH}_4]^+$, 223 $[\text{MH}]^+$, 205 $[\text{M-OH}]^+$ (Found: $[\text{MH}]^+$, 223.1166. $\text{C}_{13}\text{H}_{18}\text{OS}$ requires $[\text{MH}]^+$, 223.1157) (Found: C, 70.28; H, 8.13. $\text{C}_{13}\text{H}_{18}\text{OS}$ requires C, 70.22; H, 8.16).

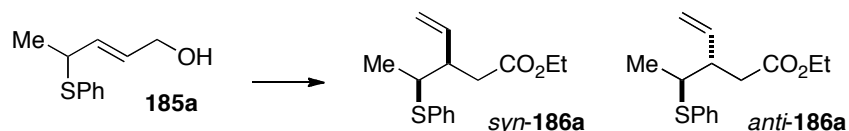
(Z)-5-Methyl-4-(thiophenyl)hex-2-en-1-ol (185f)

Ester **184f** (81 mg, 0.31 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford (*Z*)-5-methyl-4-(thiophenyl)hex-2-en-1-ol **185f** (36 mg, 54%) as a colourless oil after purification over silica gel (5–20% TBME/heptane): $\nu_{\max}$ (film) 3350, 1650, 1583, 750, 690 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.51–7.49 (2H, dd, J 8.0, 2.0) and 7.37–7.29 (3H, m), SPh], 5.62–5.48 (2H, m, H-2,3), 3.77–3.70 (3H, m, H-

1,4), 1.92 (1H, sext, J 6.5, H-5), [1.10 (3H, d, J 6.5) and 1.03 (3H, d, J 6.5), H-6]; δ_{C} (101 MHz, CDCl_3) 134.9 (C-3), 134.7, 131.3, 129.5, 128.9, 128.0, 58.2 (C-1), 54.8 (C-4), 32.0 (C-5), 20.8 (C-6), 19.6 (C-6); m/z (CI) 240 $[\text{MNH}_4]^+$, 223 $[\text{MH}]^+$ (Found: C, 70.34; H, 8.17. $\text{C}_{13}\text{H}_{18}\text{OS}$ requires C, 70.22; H, 8.16).

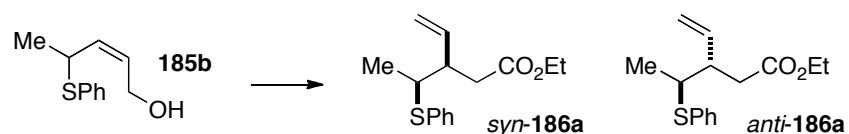
Ethyl 3-ethenyl-4-(phenylthio)-pentanoate (**186a**)

From **185a**:



Allylic alcohol **185a** (100 mg, 0.515 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 3-ethenyl-4-(phenylthio)-pentanoate* **186a** (133 mg, 98%, 1:1 *syn:anti* mixture of diastereomers) as a colourless oil.

From **185b**:



Allylic alcohol **185b** (100 mg, 0.515 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 3-ethenyl-4-(phenylthio)-pentanoate* **186a** (131 mg, 97%, 91:9 *syn:anti* mixture of diastereoisomers) as a colourless oil.

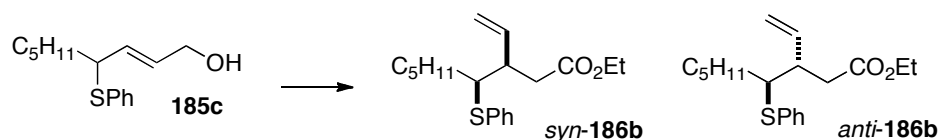
Data for the mixture: ν_{max} (film) 1734, 1639, 1584, 1479, 1176, 1090 cm^{-1} ; m/z (ESI) 454, 391, 265 $[\text{MH}]^+$, 219, 177 $[\text{M-SPhNa}]^+$ (Found: $[\text{MH}]^+$, 265.1269, $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 265.1262).

NMR data for *syn*-**186a**: δ_{H} (400 MHz, d_6 -acetone) [7.46 (2H, d, J 7.0), 7.35 (2H, dd, J 7.5, 7.0) and 7.27 (1H, dd, J 7.5, 7.0), SPh], 5.81 (1H, ddd, J 16.5, 11.0, 8.0, CHCH₂), 5.11 (1H, d, J 11.0, *trans*-CHCH₂), 5.10 (1H, d, J 16.5, *cis*-CHCH₂), 4.06 (2H, q, J 7.0, OCH₂), 3.51 (1H, dq, J 7.0, 3.5, H-4), 2.85–2.80 (1H, m, H-3), [2.75 (1H, dd, J 15.0, 5.5) and 2.43 (1H, dd, J 15.0, 9.0), H-2], 1.27 (3H, d, J 7.0, H-5), 1.18 (3H, t, J 7.0, OCH₂CH₃); δ_{C} (101 MHz, d_6 -acetone) 172.1 (C-1), 138.3 (CHCH₂), 136.1 (*i*-SPh), 132.2, 129.6, 127.4, 117.1 (CHCH₂), 60.3 (OCH₂), 47.9 (C-4), 45.3 (C-3), 36.1 (C-2), 18.5 (C-5), 14.2 (OCH₂CH₃)

NMR data for *anti*-**186a**: δ_{H} (400 MHz, d_6 -acetone) [7.46 (2H, d, J 7.0), 7.35 (2H, dd, J 7.5, 7.0) and 7.27 (1H, dd, J 7.5, 7.0), SPh], 5.83 (1H, ddd, J 17.0, 11.0, 8.0, CHCH₂), 5.10 (1H, d, J 11.0, *trans*-CHCH₂), 5.07 (1H, d, J 17.0, *cis*-CHCH₂), 4.06 (2H, q, J 7.0, OCH₂), 3.41 (1H, dq, J 13.5, 6.5, H-4), 2.82–2.77 (1H, m, H-3), [2.73 (1H, dd, J 15.0, 5.5) and 2.45 (1H, dd, J 15.0, 8.5), H-2], 1.25 (3H, d, J 7.0, H-5), 1.18 (3H, t, J 7.0, OCH₂CH₃); δ_{C} (101 MHz, d_6 -acetone) 172.8 (C-1), 137.9 (CHCH₂), 135.7 (*i*-SPh), 132.2, 129.5, 127.4, 117.1 (CHCH₂), 60.3 (OCH₂), 46.6 (C-4), 45.3 (C-3), 37.7 (C-2), 17.8 (C-5), 14.2 (OCH₂CH₃).

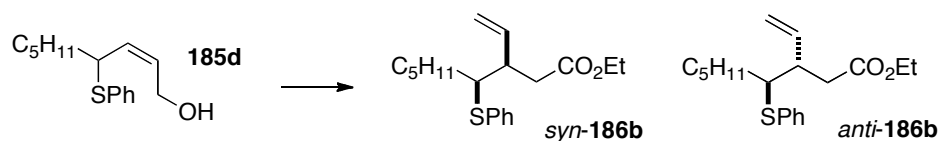
Ethyl 3-ethenyl-4-(phenylthio)-nonate (**186b**)

From **185c**:



Allylic alcohol **185c** (65 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 3-ethenyl-4-(phenylthio)-nonate* **186b** (82 mg, 98%, 50:50 *syn*:*anti* mixture of diastereomers) as a colourless oil.

From **185d**:



Allylic alcohol **185d** (65 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 3-ethenyl-4-(phenylthio)-nonate 186b* (78 mg, 94%, 90:10 *syn:anti* mixture of diastereomers) as a colourless oil.

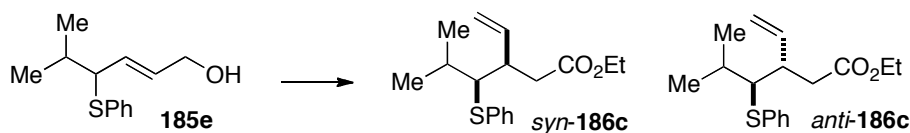
Data for the mixture: $\nu_{\max}$ (film) 1733, 1639, 1584, 1479, 1351, 1173, 745, 692 cm^{-1} ; m/z (CI) 328 $[\text{MNH}_4]^+$, 321 $[\text{MH}]^+$, 264, 233 (Found: $[\text{MH}]^+$, 321.1909. $\text{C}_{19}\text{H}_{28}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 321.1888).

NMR data for *syn-186b*: δ_{H} (400 MHz, d_6 -acetone) [7.47 (2H, d, J 8.0), 7.35 (2H, dd, J 8.0, 6.5) and 7.26 (1H, dd, J 8.0, 6.5), SPh], 5.83 (1H, ddd, J 17.0, 10.0, 8.0, CHCH_2), 5.13 (1H, d, J 10.0, *trans*- CHCH_2), 5.11 (1H, d, J 17.0, *cis*- CHCH_2), 4.07 (2H, q, J 7.0, OCH_2), 3.83–3.33 (1H, m, H-4), 2.92 (1H, m, H-3), [2.79 (1H, dd, J 15.0, 6.0) and 2.46 (1H, dd, J 15.0, 8.0), H-2], 1.75–1.27 (8H, m, H-5,6,7,8), 1.18 (3H, t, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, d_6 -acetone) 171.6 (C-1), 137.6 (CHCH_2), 131.3 (*o*-SPh), 136.5, 129.0 (*m*-SPh), 126.6 (*p*-SPh), 116.6 (CHCH_2), 59.8 (OCH_2), 53.5 (C-4), 43.7 (C-3), 33.0, 31.3, 26.9, 22.3, 13.7, 13.4.

NMR data for *anti-186b*: δ_{H} (400 MHz, d_6 -acetone) [7.47 (2H, d, J 8.0), 7.35 (2H, dd, J 8.0, 6.5) and 7.26 (1H, dd, J 8.0, 6.5), SPh], 5.86 (1H, ddd, J 17.0, 10.0, 8.0, CHCH_2), 5.13 (1H, d, J 10.0, *trans*- CHCH_2), 5.11 (1H, d, J 17.0, *cis*- CHCH_2), 4.08 (2H, q, J 7.0, OCH_2), 3.29–3.24 (1H, m, H-4), 2.90–2.83 (1H, m, H-3), [2.78 (1H, dd, J 15.0, 5.5) and 2.45 (1H, dd, J 15.0, 9.0), H-2], 1.75–1.27 (8H, m, H-5,6,7,8), 1.18 (3H, t, J 7.0, OCH_2CH_3); δ_{C} (101 MHz, d_6 -acetone) 171.4 (C-1), 138.2 (CHCH_2), 136.5, 131.4 (*o*-SPh), 128.9 (*m*-SPh), 127.4 (*p*-SPh), 116.4 (CHCH_2), 59.8 (OCH_2), 52.7 (C-4), 44.5 (C-3), 36.9 (C-2), 36.2 (C-2), 33.0, 31.4, 26.5, 22.3, 13.7, 13.4.

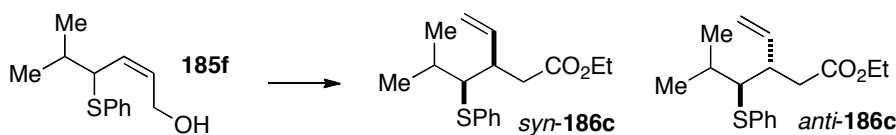
Ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate (186c)

From **185e**:



Allylic alcohol **185e** (58 mg, 0.26 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate* **186c** (71 mg, 93%, 60:40 *syn:anti* mixture of diastereoisomers) as a colourless oil.

From **185f**:



Allylic alcohol **185f** (36 mg, 0.16 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 5-methyl-3-ethenyl-4-(phenylthio)-hexanoate* **186c** (41 mg, 87%, 90:10 *syn:anti* mixture of diastereoisomers) as a colourless oil.

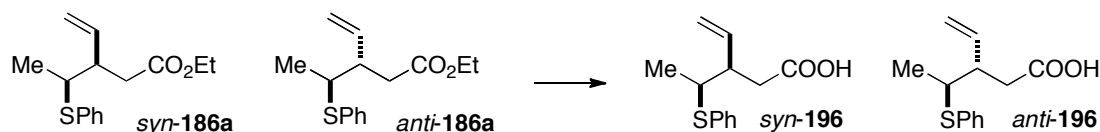
Data for the mixture: $\nu_{\max}$ (film) 1734, 1640, 1582, 1440, 1351, 745, 692 cm^{-1} ; m/z (CI) 310 $[\text{MNH}_4]^+$, 293 $[\text{MH}]^+$, 205, 117 (Found: $[\text{MH}]^+$, 293.1587. $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 293.1575).

NMR data for *syn*-**186c**: δ_{H} (400 MHz, CDCl_3) [7.83–7.80 (2H, m) and 7.67–7.56 (3H, m), SPh], 6.21 (1H, ddd, J 17.0, 10.0, 8.0, CHCH_2), 5.54 (1H, d, J 17.0, *cis*- CHCH_2), 5.48 (1H, d, J 10.0, *trans*- CHCH_2), 3.95–3.87 (2H, m, OCH_2), 3.95–3.87 (1H, m, OCH_2), 3.21–3.13 (1H, m, H-3), [2.74 (1H, dd, J 15.5, 6.0) and 2.51 (1H, dd, J 15.5, 7.0), H-2], 2.00–1.91 (1H, m, H-4), 1.19–1.15 (3H, m, OCH_2CH_3), [1.16 (3H, d, J 7.0) and 1.10 (3H, d, J 7.0), H-6], 1.08–1.02 (2H, m, H-5); δ_{C} (101 MHz, CDCl_3)

171.9 (C-1), 138.3 (CHCH₂), 134.4, 130.9, 129.5, 126.6, 117.1 (CHCH₂), 60.3 (OCH₂), 43.4 (C-3), 38.7 (C-2), 33.1 (C-4), [21.1 and 21.0 (C-6)], 16.1, 14.7.

NMR data for *anti*-**186c**: δ_{H} (400 MHz, CDCl₃) [7.83–7.80 (2H, m) and 7.67–7.56 (3H, m), SPh], 6.36 (1H, ddd, *J* 16.5, 10.0, 7.0, CHCH₂), 5.50 (1H, d, *J* 16.5, *cis*-CHCH₂), 5.42 (1H, d, *J* 10.0, *trans*-CHCH₂), 3.95–3.87 (2H, m, OCH₂), 3.95–3.87 (1H, m, OCH₂), 3.21–3.13 (1H, m, H-3), [2.97 (1H, dd, *J* 14.5, 4.0) and 2.36 (1H, dd, *J* 14.5, 9.5), H-2], 2.00–1.91 (1H, m, H-4), 1.19–1.15 (3H, m, OCH₂CH₃), 1.08–1.02 (2H, m, H-5), [0.95 (3H, d, *J* 7.0) and 0.89 (3H, d, *J* 7.9), H-6]; δ_{C} (101 MHz, CDCl₃) 172.0 (C-1), 138.7 (CHCH₂), 133.3, 130.6, 129.4, 126.5, 116.5 (CHCH₂), 60.2 (OCH₂), 43.4 (C-3), 38.6 (C-2), 33.1 (C-4), [22.2 and 21.9 (C-6)], 16.1, 14.2.

4-(Thiophenyl)-3-ethenyl-pentanoic acid (**196**)



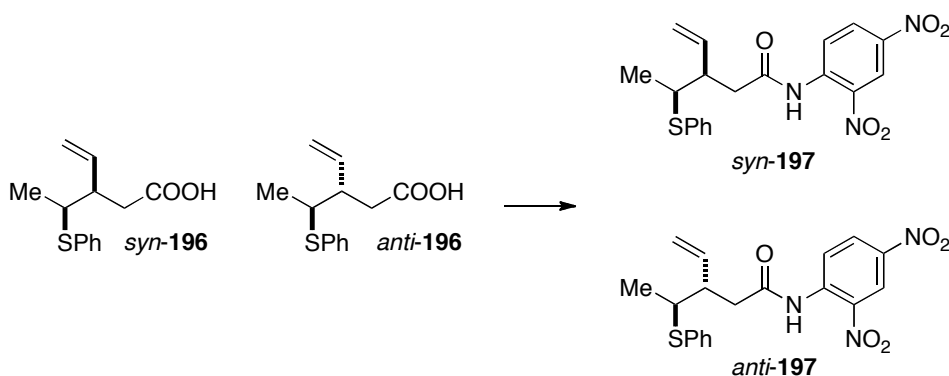
To a solution of ester **186a** (1.20 g, 4.24 mmol, 1.0 equiv, 91:9 mixture of diastereomers) in THF (15 mL) and water (15 mL) was added lithium hydroxide (1.01 g, 42.4 mmol, 10.0 equiv) in one portion at rt. The stirred mixture was heated under reflux for 4 h cooled to rt, quenched with aqueous HCl (2 M, 30 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to afford an inseparable mixture of 4-(thiophenyl)-3-ethenyl-pentanoic acid **196** (0.93 g, 93%, 91:9 mixture of diastereomers) as a colourless oil which was used without further purification.

Data for *syn*-**196**: ν_{max} (film) 3075, 1709, 1639, 1584, 1480, 1438, 1284, 923, 741, 692; δ_{H} (400 MHz, CDCl₃) 7.44 (2H, d, *J* 7.0, *o*-SPh), 7.33–7.24 (3H, m, *m,p*-SPh), 5.79 (1H, ddd, *J* 17.0, 10.0, 8.0, CHCH₂), 5.18 (1H, d, *J* 10.0, *trans*-CHCH₂), 5.14 (1H, d, *J* 17.0, *cis*-CHCH₂), 3.40 (1H, dq, *J* 7.0, 4.0, H-4), 2.91–2.78 (2H, m, H-2,3), 2.51 (1H, dd, *J* 14.0, 8.0, H-2'), 1.29 (3H, d, *J* 7.0, H-5); δ_{C} (101 MHz, CDCl₃), 178.0

(C-1), 137.0 (CHCH₂), 135.0 (*i*-SPh), 132.2 (*o*-SPh), 129.0 (*m*-SPh), 127.1 (*p*-SPh), 117.6 (CHCH₂), 47.9 (C-4), 44.3 (C-3), 35.4 (C-2), 18.2 (C-5).

Characteristic NMR signals for *anti*-**196**: δ_{H} (400 MHz, CDCl₃) *inter alia* 4.12–4.04 (1H, m, H-4), 1.39 (3H, d, *J* 6.5, H-5); δ_{C} (101 MHz, CDCl₃) 46.7 (C-4), 44.7 (C-3), 37.2 (C-2), 18.1 (C-5).

N-(2,4-dinitrophenyl)-4-(thiophenyl)-3-ethenyl-pentamide (**197**)

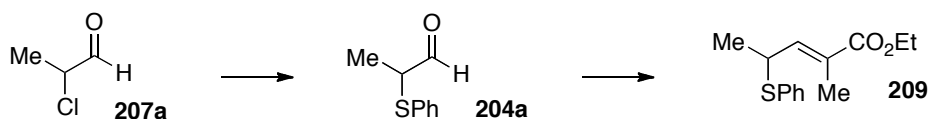


To a solution of acid **196** (919 mg, 3.89 mmol, 1.0 equiv, 91:9 mixture of diastereoisomers) in dichloromethane (20 mL) was added DCC (803 mg, 3.89 mmol, 1.0 equiv) and DMAP (47.5 mg, 0.389 mmol, 0.1 equiv) at rt. The mixture was stirred for 5 min and a solution of 2,4-dinitroaniline (783 mg, 4.28 mmol, 1.1 equiv) in dichloromethane (20 mL) was added dropwise *via* syringe. The resulting yellow mixture was stirred overnight at rt and filtered over Celite. The filtrate was washed with sodium hydrogencarbonate (30 mL) and aqueous HCl (2 M, 30 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue over silica gel (15% ether/hexane) afforded *N*-(2,4-dinitrophenyl)-4-(thiophenyl)-3-ethenyl-pentamide **197** (967 mg, 62%, 91:9 mixture of diastereoisomers) as a yellow solid. Further purification of the mixture over silica gel (5–15% ether/hexane) and recrystallisation (EtOAc) afforded an analytical sample of *syn*-**197** (435 mg, 28%) as a yellow crystalline solid.

Data for *syn*-**197**: mp 82–83 °C; ν_{max} (film) 1712, 1615, 1599, 1499, 1335, 1307, 1141, 748, 696; δ_{H} (400 MHz, CDCl_3) 10.54 (1H, s (br), NH), 9.13 (1H, d, J 2.5, 3-Ar), 9.06 (1H, d, J 9.5, 4-Ar), 8.46 (1H, dd, J 9.5, 2.5, 5-Ar), [7.42 (2H, d, J 8.5), 7.28–7.24 (2H, m) and 7.21–7.16 (1H, m), SPh], 5.87 (1H, ddd, J 17.0, 10.0, 8.5, CHCH₂), 5.22 (1H, d, J 10.0, *trans*-CHCH₂), 5.18 (1H, d, J 17.0 *cis*-CHCH₂), 3.50 (1H, dq, J 9.5, 7.0, H-4), 3.05–2.96 (2H, m, H-2,3), 2.66 (1H, dd, J 14.0, 7.5, H-2), 1.36 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 171.1 (C-1), 141.7, 139.6, 136.5 (CHCH₂), 135.1, 134.8, 131.7 (SPh), 130.1 (5-Ar), 129.1 (SPh), 127.0 (SPh), 122.3 (4-Ar), 122.0 (3-Ar), 118.5 (CHCH₂), 47.7 (C-4), 45.2 (C-3), 40.6 (C-2), 18.8 (C-5); m/z (CI) 419 $[\text{MNH}_4]^+$, 402 $[\text{MH}]^+$, 369, 326, 201 (Found: $[\text{MNH}_4]^+$ 419.1388; $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$ requires $[\text{MNH}_4]^+$ 419.1389) (Found: C, 56.88; H, 4.74; N, 10.41. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$ requires C, 56.85; H, 4.77; N, 10.47).

NMR data for *anti*-**197**: δ_{H} (400 MHz, CDCl_3) 10.68 (1H, s (br), NH), 9.13 (1H, d, J 2.5, 3-Ar), 9.11 (1H, d, J 9.5, 4-Ar), 8.47 (1H, dd, J 9.5, 2.5, 5-Ar), 7.42–7.19 (5H, m, SPh), 5.80 (1H, ddd, J 17.0, 10.5, 8.5, CHCH₂), 5.16 (1H, d, J 10.5, *trans*-CHCH₂), 5.12 (1H, d, J 17.0, *cis*-CHCH₂), 3.49 (1H, dq, J 10.0, 7.0, H-4), 3.01–2.95 (1H, m, H-3), [2.83 (1H, dd, J 15.0, 6.5) and 2.85 (1H, dd, J 15.0, 7.5), H-2], 1.30 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 171.7 (C-1), 153.8, 137.6, 137.2 (CHCH₂), 135.5, 131.9, 131.1, 129.0, 126.9, 126.7, 122.3, 122.0, 117.6 (CHCH₂), 47.4 (C-4), 45.4 (C-3), 37.3 (C-2), 18.4 (C-5).

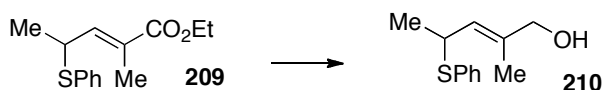
Ethyl (*E*)-4-(phenylthio)-2-methylpent-2-enoate (**209**)



To a solution of TEA (3.97 mL, 28.8 mmol, 1.4 equiv) in THF (40 mL) was added thiophenol (2.1 mL, 20.6 mmol, 1.0 equiv) dropwise *via* syringe. The colourless solution was stirred at rt for 10 min and a solution of 2-chloropropanal **207a** (1.89 g,

20.6 mmol, 1.0 equiv) in THF (20 mL) was added dropwise *via* syringe. The rapid formation of a white precipitate was observed upon addition and the resulting suspension was stirred at rt for 1 h. In a separate flask, a solution of triethyl 2-phosphonopropionate (6.86 g, 28.8 mmol, 1.0 equiv) in THF (80 mL) was added to a suspension of sodium hydride (60% w/w in mineral oil, 1.23 g, 30.9 mmol, 1.5 equiv) in THF (40 mL) at 0 °C *via* cannula. The mixture was allowed to warm to rt with stirring until all sodium hydride had dissolved. The previously prepared sulfenylaldehyde solution was filtered under nitrogen and added *via* cannula to the phosphonate anion solution at –78 °C. After stirring for 2 h at –78 °C saturated aqueous NH₄Cl (150 mL) was added and the mixture extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (10% TBME/petrol) to afford *ethyl (E)-4-(phenylthio)-2-methylpent-2-enoate* **209** (1.57 g, 31%) as a colourless oil: $\nu_{\max}$ (film) 1711, 1646, 1439, 1252, 1110, 753, 693 cm⁻¹; δ_{H} (400 MHz, CDCl₃) [7.46–7.44 (2H, m) and 7.32–7.29 (3H, m), SPh], 6.62 (1H, dd, *J* 10.5, 1.5, H-3), 4.20 (2H, q, *J* 7.0, OCH₂), 4.03 (1H, dq, *J* 10.5, 6.5, H-4), 1.52 (3H, d, *J* 1.5, 2-Me), 1.43 (3H, d, *J* 6.5, H-5), 1.31 (3H, t, *J* 7.0, OCH₂CH₃); δ_{C} (101 MHz, CDCl₃), 167.9 (C-1), 142.3, 134.3, 133.5, 129.2, 128.8, 128.0, 60.7 (OCH₂), 42.4 (C-4), 20.2, 14.2, 12.2; *m/z* (CI) 268 [MNH₄]⁺, 251 [MH]⁺, 205, 141 (Found: [MNH₄]⁺, 251.1096; C₁₄H₁₈O₂S requires [MNH₄]⁺, 251.1106) (Found: C, 67.19; H, 7.25. C₁₄H₁₈O₂S requires C, 67.16; H, 7.25).

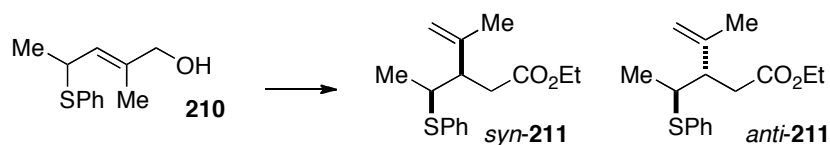
(*E*)-4-(Thiophenyl)-2-methylpent-2-en-1-ol (**210**)



Ester **209** (1.18 g, 4.72 mmol, 1.0 equiv) was reacted according to general procedure **F** to afford (*E*)-4-(thiophenyl)-2-methylpent-2-en-1-ol **210** (924 mg, 94%) as a colourless oil after purification over silica gel (5–20% TBME/heptane): $\nu_{\max}$ (film)

3349, 1582, 1438, 1024, 752, 692 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [7.46–7.44 (2H, m) and 7.33 (3H, m), SPh], 5.36 (1H, dd, J 10.0, 1.5, H-3), 4.05 (1H, dq, J 10.0, 7.0, H-4), 3.96 (2H, s, H-1), 1.45 (3H, d, J 1.5, Me), 1.37 (3H, d, J 7.0, H-5); δ_{C} (101 MHz, CDCl_3) 136.3, 133.8, 129.0, 128.6, 127.9, 127.5, 68.3, 41.7, 21.1, 13.6; m/z (CI) 226 $[\text{MNH}_4]^+$, 209 $[\text{MH}]^+$, 191, 116 (Found: $[\text{MH}]^+$, 209.1008. $\text{C}_{12}\text{H}_{16}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 209.1000).

Ethyl 4-(phenylthio)-3-(prop-1-enyl)pentanoate (**211**)



Allylic alcohol **210** (150 mg, 0.72 mmol, 1.0 equiv) was reacted according to general procedure **G** to afford *ethyl 4-(phenylthio)-3-(prop-1-enyl)pentanoate* **211** (200 mg, >99%, 71:29 *syn:anti* mixture of diastereoisomers) as a colourless oil.

Data for the mixture: ν_{max} (film) 1738, 1646, 1584, 1439, 1376, 1160, 1051, 749, 693 cm^{-1} ; m/z (CI), 296 $[\text{MNH}_4]^+$, 279 $[\text{MH}]^+$, 191, 169, 117 (Found: $[\text{MH}]^+$, 279.1414. $\text{C}_{16}\text{H}_{22}\text{O}_2\text{S}$ requires $[\text{MH}]^+$, 279.1419).

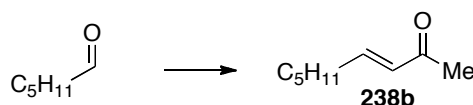
NMR data for *syn*-**211**: δ_{H} (400 MHz, CDCl_3) [7.47–7.43 (2H, m) and 7.34–7.26 (3H, m), SPh], 4.93 (1H, s, *trans*- CMeCH_2), 4.82 (1H, s, *cis*- CMeCH_2), 4.11 (2H, q, J 7.0, OCH_2), 3.60–3.52 (1H, m, H-4), 3.43–3.35 (1H, m, H-3), [2.85–2.77 (1H, m) and 2.53–2.44 (1H, m), H-2], 1.76 (3H, s, CMeCH_2), 1.26–1.22 (6H, m, OCH_2CH_3 , H-5); δ_{C} (101 MHz, CDCl_3) 171.7 (C-1), 144.8 (CMeCH_2), 135.2, 132.0, 129.0, 127.2, 112.2 (CMeCH_2), 60.3 (OCH_2), 46.6 (*syn* + *anti* C-4), 45.0 (C-3), 34.2 (C-2), 21.6, 17.0, 14.2.

NMR data for *anti*-**211**: δ_{H} (400 MHz, CDCl_3) [7.47–7.43 (2H, m) and 7.34–7.26 (3H, m), SPh], 4.87 (1H, s, *trans*- CMeCH_2), 4.82 (1H, s, *cis*- CMeCH_2), 4.14 (2H, q, J 7.0, OCH_2), 3.60–3.52 (1H, m, H-4), 3.43–3.35 (1H, m, H-3), [2.85–2.77 (1H, m) and

2.53–2.44 (1H, m), H-2], 1.73 (3H, s, CMeCH₂), 1.26–1.22 (6H, m, OCH₂CH₃, H-5);
δ_C (101 MHz, CDCl₃) 171.5 (C-1), 144.7 (CMeCH₂), 135.1, 131.0, 128.6, 127.1,
114.3 (CMeCH₂), 60.3 (OCH₂), 46.6 (C-4), 45.0 (C-3), 34.2 (C-2), 21.6, 17.0, 14.2.

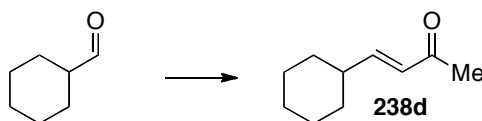
3.4.3 Compounds relevant to section 2.5

(*E*)-Non-3-en-2-one (238b)



Hexanal (1.85 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure **H** to afford (*E*)-non-3-en-2-one **238b** (1.07 g, 51%) as a colourless oil: bp₄ 100–102 °C; ν_{max} (film) 1677, 1628, 1466, 1360, 1253, 1176, 982 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 6.92 (1H, dt, *J* 16.0, 7.0, H-4), 6.08 (1H, d, *J* 16.0, H-3), 2.25 (3H, s, H-1), 2.25–2.21 (2H, m, H-5), 1.52–1.44 (2H, m, H-6), 1.36–1.27 (4H, m, H-7,8), 0.90 (3H, t, *J* 6.5, H-9); δ_{C} (101 MHz, CDCl₃) 198.8 (C-2), 148.7 (C-4), 131.3 (C-3), 32.4, 31.3, 27.8, 26.8, 22.4, 14.0; *m/z* (CI) 158 [MNH₄]⁺, 141 [MH]⁺, 125; in agreement with published data.²²²

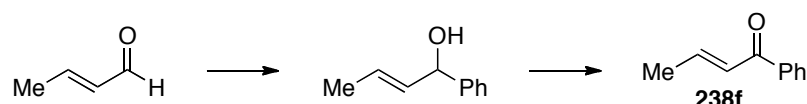
(*E*)-4-(Cyclohexyl)-but-3-en-2-one (238d)



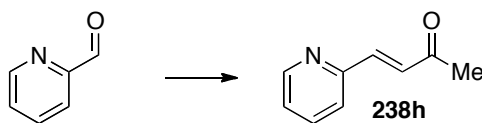
Cyclohexanecarboxaldehyde (1.82 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure **H** to afford (*E*)-4-(cyclohexyl)-but-3-en-2-one **238d** (917 mg, 40%) as a colourless oil: bp₄ 95–100 °C, ν_{max} (film) 1698, 1676, 1624, 1449, 1357, 1253, 980 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 6.73 (1H, dd, *J* 16.0, 7.0, H-4), 6.05 (1H, d, *J* 16.0, H-3), 2.45 (3H, s, H-1), 2.20–2.12 (1H, m, H-5), 1.78 (4H, d, *J* 11.0, cyclohexyl), 1.69 (1H, d, *J* 13.5, cyclohexyl), 1.36–1.15 (5H, m, cyclohexyl); δ_{C} (101

MHz, CDCl₃) 199.2 (C-2), 153.4 (C-4), 128.8 (C-3), 40.6 (C-5), 31.8 (cyclohexyl) 26.8 (C-1), 25.9 (cyclohexyl), 25.7 (cyclohexyl); *m/z* (CI) 170 [MNH₄]⁺, 153 [MH]⁺ (Found: [MH]⁺, 153.1281. C₁₀H₁₆O requires [MH]⁺, 153.1279).

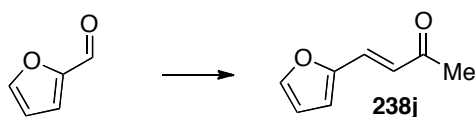
(*E*)-1-Phenylbut-2-en-1-one (238f)



A solution of phenylmagnesium chloride (26.3 mL of a 1.90 M solution in THF, 50.0 mmol, 1.0 equiv) was added to a flask containing THF (150 mL) at 0 °C and crotonaldehyde (4.1 mL, 50.0 mmol, 1.0 equiv) was added. After stirring at 0 °C for 30 min, the reaction was quenched with saturated aqueous NH₄Cl (25 mL). The reaction mixture was warmed to rt, partially concentrated under reduced pressure to remove THF and extracted with ether (2 x 120 mL). The combined organic extracts were washed with aqueous HCl (2 M, 40 mL), water (2 x 40 mL) and brine (40 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was taken up in DMF (10 mL) and added to a stirred solution of pyridinium dichromate (20.4 g, 1.08 equiv) in DMF (40 mL). After 1 h, the reaction mixture was diluted with ether (100 mL) and poured onto water (100 mL). The phases were separated and the organic layer was washed with water (2 x 100 mL) and brine (40 mL). Concentration under reduced pressure and Kugelrohr distillation afforded (*E*)-1-phenylbut-2-en-1-one **238f** (2.02 g, 28%) as a colourless oil: bp₄ 120–125 °C; *v*_{max} (film) 1668, 1624, 1577, 1449, 1296, 1220, 966 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.58–7.42 (5H, m, Ph), 7.10 (1H, dq, *J* 15.0, 7.0, H-3), 6.93 (1H, d, *J* 15.0, H-2), 2.03 (3H, d, *J* 7.0, H-4); δ_C (101 MHz, CDCl₃) 190.1 (C-1), 145.1, 143.5, 137.9, 132.6, 128.5, 128.2, 18.6 (Me); *m/z* (CI) 164 [MNH₄]⁺, 147 [MH]⁺, 131; in agreement with published data.²²³

(E)-4-(Pyridin-2-yl)-but-3-en-2-one (238h)

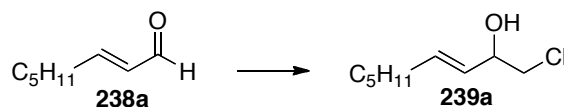
2-Pyridinecarboxaldehyde (1.43 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure **H** to afford (*E*)-4-(pyridin-2-yl)-but-3-en-2-one **238h** (1.41 g, 64%) as a colourless oil: bp₄ 120–125 °C; ν_{max} (film) 1667, 1621, 1583, 1469, 1432, 1359, 1312, 1200, 1152, 980, 766 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 8.57 (1H, s (br), 6-pyridyl), 7.75–7.71 (1H, m, pyridyl), 7.52 (1H, d, *J* 16.5, H-4), 7.50–7.48 (1H, m, pyridyl), 7.30–7.27 (1H, m, pyridyl), 7.14 (1H, d, *J* 16.5, H-3), 2.41 (3H, s, H-1); δ_{C} (101 MHz, CDCl₃) 198.6 (C-2), 153.1 (2-pyridyl), 150.1 (6-pyridyl), 141.9 (C-4), 136.9 (pyridyl), 130.2 (C-3), 124.4, 124.3 (pyridyl), 28.1 (C-1); *m/z* (ESI) 148 [MH]⁺, 130, 120 (Found: [MH]⁺, 148.0754. C₉H₉NO requires [MH]⁺, 148.0762).

(E)-4-(Furan-2-yl)-but-3-en-2-one (238j)

Furfural (1.24 mL, 15.0 mmol, 1.0 equiv) was reacted according to general procedure **H** to afford (*E*)-4-(furan-2-yl)-but-3-en-2-one **238j** (1.16 g, 57%) as white crystals: bp₄ 105–110 °C; mp 37–39 °C; ν_{max} (film) 1657, 1622, 1477, 1272, 1252, 932 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.52 (1H, d, *J* 2.0, 5-furanyl), 7.29 (1H, d, *J* 16.5, H-4), 6.69 (1H, d, *J* 3.0, 3-furanyl), 6.64 (1H, d, *J* 16.5, H-3), 6.51 (1H, dd, *J* 3.0, 2.0, 4-furanyl), 2.38 (3H, s, H-1); δ_{C} (101 MHz, CDCl₃) 197.9 (C-2), 150.9 (C-5), 145.0 (5-furanyl), 129.5 (C-4), 124.3 (C-3), 115.7 (3-furanyl), 112.6 (4-furanyl), 27.9 (C-1); *m/z* (CI)

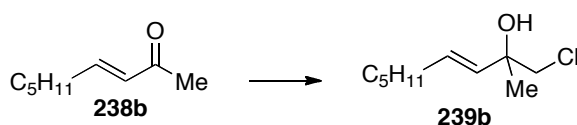
154 $[\text{MNH}_4]^+$, 137 $[\text{MH}]^+$, 121 (Found: $[\text{MH}]^+$, 137.0604. $\text{C}_8\text{H}_8\text{O}_2$ requires $[\text{MH}]^+$, 137.0603).

(*E*)-1-Chloronon-3-en-2-ol (239a)



Octen-2-al **238a** (1.49 mL, 10.0 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloronon-3-en-2-ol **239a** (1.42 g, 81%) as a colourless oil after purification over silica gel (20% ether/petrol): ν_{max} (film) 3354, 1671, 972, 760, 730 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.84 (1H, dt, J 15.5, 7.5, H-4), 5.48 (1H, ddt, J 15.5, 7.5, 1.5, H-3), 4.32 (1H, m, H-2), [3.65 (1H, dd, J 11.0, 3.5) and 3.52 (1H, dd, J 11.0, 7.5), H-1], 2.08 (1H, m, H-5), 1.45–1.29 (6H, m, H-6,7,8), 0.91 (3H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 135.2 (C-4), 127.9 (C-3), 72.4 (C-2), 50.0 (C-1), 32.2 (C-5), 31.3 (C-6), 28.6 (C-7), 22.5 (C-8), 14.0 (C-9); m/z (CI) 194 $[\text{MNH}_4]^+$, 176 $[\text{M}]^+$ (Found: $[\text{MNH}_4]^+$, 194.1313. $\text{C}_9\text{H}_{17}\text{ClO}$ requires $[\text{MNH}_4]^+$, 194.1312) (Found: C, 61.08; H, 9.72. $\text{C}_9\text{H}_{17}\text{ClO}$ requires C, 61.18; H, 9.70).

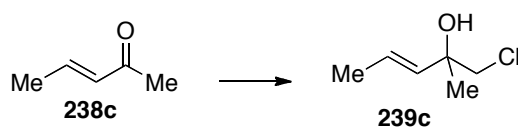
(*E*)-1-Chloro-2-methylnon-3-en-2-ol (239b)



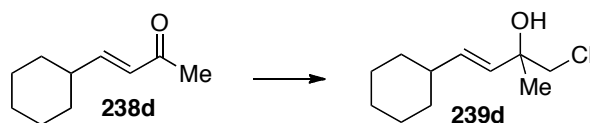
3-Nonen-2-one **238b** (936 mg, 6.68 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-2-methylnon-3-en-2-ol **239b** (1.17 g, 92%) as a colourless oil after purification over silica gel (20% TBME/petrol): ν_{max} (film)

3411, 1669, 1457, 1376, 973, 745 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.80 (1H, dt, J 15.5, 6.5, H-4), 5.53 (1H, dt, J 15.5, 1.0, H-3), 3.55 (2H, AB quartet, J 10.0, H-1), 2.10 (2H, dt, J 13.0, 6.5, H-5), 1.39 (3H, s, 2-Me), 1.40–1.30 (6H, m, H-6,7,8), 0.92 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 132.8 (C-3), 131.3 (C-4), 72.0 (C-2), 54.7 (C-1), 32.2 (C-5), 31.3 (C-6), 28.8 (C-7), 25.6 (2-Me), 14.1 (C-9); m/z (CI) 190 $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 177, 172 $[\text{M--OH}]^+$, 137 (Found: $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 190.1363. $\text{C}_{10}\text{H}_{19}\text{ClO}$ requires $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 190.1357).

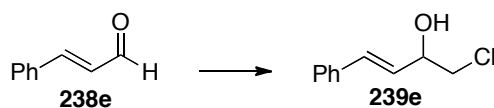
(*E*)-1-Chloro-2-methylpent-3-en-2-ol (**239c**)



3-Penten-2-one **238c** (2.44 mL, 25.0 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-2-methylpent-3-en-2-ol **239c** (1.18 g, 35%) as a colourless oil after purification over silica gel (20% ether/petrol): ν_{max} (film) 3419, 1671, 1450, 968, 801, 743 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.82 (1H, dq, J 15.5, 6.5, H-4), 5.55 (1H, d, J 15.5, H-3), 3.53 (2H, AB quartet, J 15.0, H-1), 2.16 (1H, s (br), OH), 1.74 (3H, dd, J 6.5, 1.5, H-5), 1.38 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 134.1 (C-3), 125.9 (C-4), 72.0 (C-2), 54.6 (C-1), 25.5 (C-5), 17.8 (2-Me); m/z (CI) 136 $[\text{M--H}]^+$, 134 $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 100 (Found: $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 134.0739. $\text{C}_6\text{H}_{11}\text{ClO}$ requires $[\text{MNH}_4\text{--H}_2\text{O}]^+$, 134.0737).

(E)-1-Chloro-4-cyclohexyl-2-methylbut-3-en-2-ol (239d)

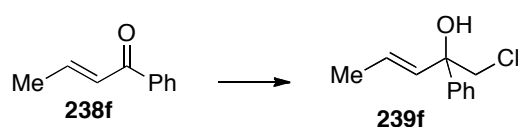
(*E*)-4-(Cyclohexyl)-but-3-en-2-one **238d** (508 mg, 3.94 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-4-cyclohexyl-2-methylbut-3-en-2-ol **239d** (562 mg, 84%) as a colourless oil after purification over silica gel (10% ether/hexane): $\nu_{\max}$ (film) 3430, 1668, 1449, 1373, 1263, 970, 745 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.75 (1H, dd, J 15.5, 7.5, H-4), 5.46 (1H, dd, J 15.5, 1.5, H-3), 3.53 (2H, AB quartet, J 11.0, H-1), 2.18 (1H, s (br), OH), 2.04–1.95 (1H, m, H-5), 1.78–1.65 (5H, m, cyclohexyl), 1.39 (3H, s, 2-Me), 1.38–1.05 (5H, m, cyclohexyl); δ_{C} (101 MHz, CDCl_3) 136.9 (C-4), 130.3 (C-3), 72.0 (C-2), 54.7 (C-1), 40.3 (C-5), 32.8, 26.1, 26.0 (cyclohexyl), 25.7 (2-Me); m/z (CI) 222, 220 $[\text{MNH}_4]^+$, 204, 202 $[\text{M}]^+$, 187, 185 (Found: $[\text{MNH}_4]^+$, 220.1473. $\text{C}_{11}\text{H}_{19}\text{ClO}$ requires $[\text{MNH}_4]^+$, 220.1468) (Found: C, 65.13; H, 9.36. $\text{C}_{11}\text{H}_{19}\text{ClO}$ requires C, 65.17; H, 9.45).

(E)-1-Chloro-4-phenylbut-3-en-2-ol (239e)

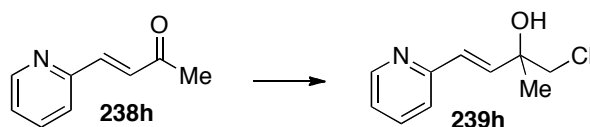
Cinnamaldehyde **238e** (1.50 g, 11.35 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-4-phenylbut-3-en-2-ol **239e** (2.06 g, 99%) as a colourless oil after purification over silica gel (10% ether/petrol): $\nu_{\max}$ (film) 3390, 3026, 1659, 1598, 1578, 1494, 1449, 1296, 1071, 967, 754, 693 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.43 (2H, d, J 7.5, *o*-Ph), 7.37 (2H, dd, J 13.5, 7.5, *m*-Ph), 7.31 (1H, dd, J 13.5, 6.5, *p*-Ph), 6.76 (1H, d, J 15.5, H-4), 6.24 (1H, dd, J 15.5, 6.0, H-3), 4.57 (1H,

dt, J 7.0, 6.0, H-2), [3.57 (1H, dd, J 11.0, 3.5) and 3.64 (1H, dd, J 11.0, 6.5), H-1]; δ_{C} (101 MHz, CDCl_3) 136.1 (*i*-Ph), 132.8 (C-4), 128.7 (*m*-Ph), 128.2 (*p*-Ph), 127.2 (C-3), 126.7 (*o*-Ph), 72.3 (C-2), 49.7 (C-1); m/z (CI) 200 $[\text{MNH}_4]^+$, 182 $[\text{M}]^+$, 165 (Found: $[\text{MNH}_4]^+$, 200.0842. $\text{C}_{10}\text{H}_{11}\text{ClO}$ requires $[\text{MNH}_4]^+$, 200.0842); in agreement with published data.¹⁷²

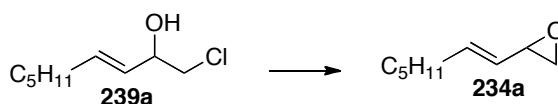
(*E*)-1-Chloro-2-phenyl-pent-3-en-2-ol (239f)



(*E*)-1-Phenylbut-2-en-1-one **238f** (1.89 g, 12.91 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-2-phenyl-pent-3-en-2-ol **239f** (1.31 g, 52%) as a colourless oil after purification over silica gel (10% ether/hexane): ν_{max} (film) 3466, 1667, 1623, 1494, 1448, 1336, 1161, 1050, 967, 724, 699 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.49 (2H, d, J 8.5, *o*-Ph), 7.40 (2H, dd, J 8.5, 7.0, *m*-Ph), 7.32 (1H, dd, J 7.5, 7.0, *p*-Ph), 5.83–5.80 (2H, m, H-3 and H-4), 3.89 (2H, AB quartet, J 11.5, H-1), 2.74 (1H, s, OH), 1.78 (3H, dd, J 5.0, 1.5, H-5); δ_{C} (101 MHz, CDCl_3) 142.8 (*i*-Ph), 133.5, 128.5 (*m*-Ph), 128.4, 127.6, 125.6 (*o*-Ph), 75.9 (C-2), 54.0 (C-1), 17.8 (C-5); m/z (CI) 216, 214 $[\text{MNH}_4]^+$, 198, 196 $[\text{MH}]^+$, 181, 179 (Found: $[\text{MNH}_4]^+$, 214.1003. $\text{C}_{11}\text{H}_{13}\text{ClO}$ requires $[\text{MNH}_4]^+$, 214.0999) (Found: C, 67.24; H, 6.59. $\text{C}_{11}\text{H}_{13}\text{ClO}$ requires C, 67.18; H, 6.66).

(E)-1-Chloro-2-methyl-4-(pyridin-2-yl)but-3-en-2-ol (239h)

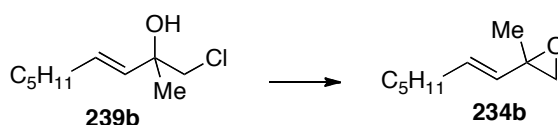
(*E*)-4-(Pyridin-2-yl)-but-3-en-2-one **238h** (1.00 g, 6.80 mmol, 1.0 equiv) was reacted according to general procedure **I** to afford (*E*)-1-chloro-2-methyl-4-(pyridin-2-yl)but-3-en-2-ol **239h** (1.18 g, 88%) as a yellow oil after purification over silica gel (25% EtOAc, 5% TEA/hexane): ν_{max} (film) 3348, 1657, 1589, 1566, 1472, 1432, 1371, 977, 801, 768, 747 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 8.58 (1H, d, J 5.5, 6-pyridyl), 7.66 (1H, ddd, J 9.5, 8.0, 2.0, 4-pyridyl), 7.29 (1H, d, J 8.0, 3-pyridyl), 7.16 (1H, ddd, J 7.5, 5.0, 2.0, 5-pyridyl), 6.84 (2H, d, J 17.0, H-3, H-4), 3.67 (2H, AB quartet, J 11.0, H-1), 2.70 (1H, s (br), OH), 1.29 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 154.7 (2-pyridyl), 149.6 (6-pyridyl), 137.0 (C-4), 136.7 (4-pyridyl), 129.4 (C-3), 122.5 (5-pyridyl), 122.4 (3-pyridyl), 72.6 (C-2), 54.2 (C-1), 25.7 (2-Me); m/z (ESI) 201, 200, 198 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 198.0680. $\text{C}_{10}\text{H}_{12}\text{ClNO}$ requires $[\text{MH}]^+$, 198.0686) (Found: C, 60.69; H, 6.03; N, 6.99. $\text{C}_{10}\text{H}_{12}\text{ClNO}$ requires C, 60.76; H, 6.12; N, 7.09).

(E)-2-(Hept-1-enyl)oxirane (234a)

Chlorohydrin **239a** (1.38 g, 7.82 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford (*E*)-2-(hept-1-enyl)oxirane **234a** (1.06 g, 97%) as a yellow oil: ν_{max} (film) 1669, 1466, 1369, 1245, 964, 835, 771, 727 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.98 (1H, dt, J 15.5, 6.5, H-4), 5.15 (1H, ddt, J 15.5, 8.0, 1.5, H-3), 3.34 (1H, ddd, J 8.0, 4.0, 3.0), [2.95 (1H, dd, J 5.0, 4.0) and 2.67 (1H, dd, J 5.0, 3.0), H-1], 2.09 (2H,

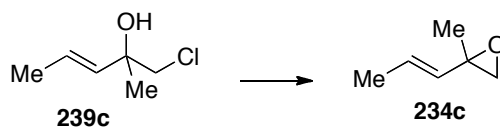
dt, J 7.5, 6.5, H-5), 1.46–1.38 (2H, m, H-6), 1.37–1.28 (4H, m H-7,8), 0.91 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 137.4 (C-4), 127.4 (C-3), 52.7 (C-2), 48.8 (C-1), 32.3 (C-5), 31.3 (C-7), 28.6 (C-6), 22.5 (C-8), 14.0 (C-9); m/z (CI) 158 $[\text{MNH}_4]^+$, 141 $[\text{MH}]^+$, 123 $[\text{M}-\text{OH}]^+$ (Found: $[\text{MNH}_4]^+$, 158.1545. $\text{C}_9\text{H}_{16}\text{O}$ requires $[\text{MNH}_4]^+$, 158.1545).

(*E*)-2-Methyl-2-(hept-1-enyl)oxirane (234b)



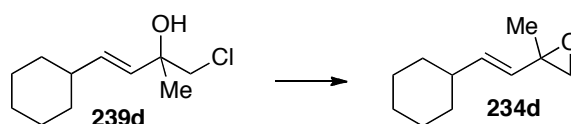
Chlorohydrin **239b** (1.12 g, 5.88 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford (*E*)-2-methyl-2-(hept-1-enyl)oxirane **234b** (1.06 g, 40%) as a colourless oil: ν_{max} (film) 1668, 1585, 1457, 1379, 968, 905 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.81 (1H, dt, J 16.0, 7.0, H-4), 5.27 (1H, dt, J 16.0, 1.5, H-3), [2.82 (1H, d, J 5.0) and 2.75 (1H, d, J 5.0), H-1], 2.06 (2H, dt, J 8.0, 7.0, H-5), 1.46–1.23 (6H, m, H-6,7,8), 0.90 (3H, t, J 7.5, H-9); δ_{C} (101 MHz, CDCl_3) 134.0 (C-4), 130.9, (C-3), 55.8 (C-1), 55.6 (C-2), 32.4 (C-5), 31.4 (C-6), 28.8 (C-7), 22.5 (C-8), 19.7 (2-Me), 14.0 (C-9); m/z (CI) 155 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 155.1434. $\text{C}_{10}\text{H}_{18}\text{O}$ requires $[\text{MH}]^+$, 155.1436).

(*E*)-2-Methyl-2-(prop-1-enyl)oxirane (234c)

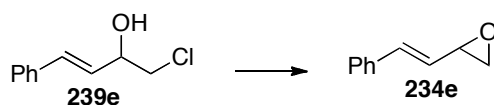


Chlorohydrin **239c** (1.13 g, 8.40 mmol, 1.0 equiv) was reacted according to general procedure **J**. Incomplete concentration under reduced pressure of the combined organic extracts afforded (*E*)-2-methyl-2-(*prop-1-enyl*)oxirane **234c** (1.06 g of a colourless solution, 35% w/w in THF by ^1H -NMR analysis, 46%): δ_{H} (400 MHz, CDCl_3) 5.83 (1H, dq, J 15.5, 6.5, H-4), 5.30 (1H, d, J 15.5, H-3), [2.81 (1H, d, J 5.0) and 2.75 (1H, d, J 5.0), H-1], 1.75 (3H, dd, J 6.5, 1.5, H-5), 1.46 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 132.2 (C-3), 128.5 (C-4), 60.4 (C-2), 55.7 (C-1), 19.7 (2-Me), 17.8 (C-5).

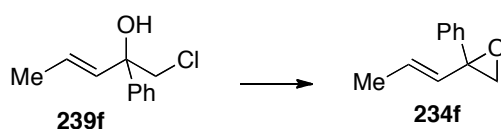
2-[(*E*)-2-Cyclohexylethenyl]-2-methyloxirane (**234d**)



Chlorohydrin **239d** (0.533 g, 2.64 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford 2-[(*E*)-2-Cyclohexylethenyl]-2-methyloxirane **234d** (431 mg, 98%) as a colourless oil: ν_{max} (film) 1677, 1449, 1387, 1064, 968 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.75 (1H, dd, J 16.0, 6.5, H-4), 5.23 (1H, dd, J 16.0, 1.5, H-3), [2.82 (1H, d, J 5.0) and 2.75 (1H, d, J 4.0), H-1], 2.03–1.96 (1H, m, H-5), [1.78–1.61 and 1.35–1.03 (10H, m, cyclohexyl)], 1.46 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 139.5 (C-4), 128.5 (C-3), 55.9 (C-1), 55.7 (C-2), 40.5 (C-5), 32.7, 26.1, 26.0, 19.7 (2-Me); m/z (CI) 184 $[\text{MNH}_4]^+$, 165 $[\text{M}-\text{H}]^+$, 149 (Found: $[\text{MNH}_4]^+$, 184.1700. $\text{C}_{11}\text{H}_{18}\text{O}$ requires $[\text{MNH}_4]^+$, 184.1701).

(E)-2-Styryloxirane (234e)

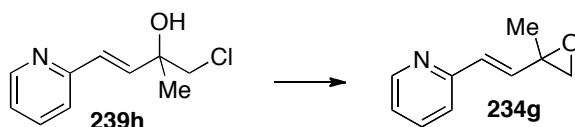
Chlorohydrin **239e** (1.20 g, 6.59 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford (*E*)-2-styryloxirane **234e** (963 mg, >99%) as a yellow oil: $\nu_{\max}$ (film) 3027, 1601, 1578, 1492, 1393, 1244, 1134, 1072, 965 747, 693 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.43–7.27 (5H, m, Ph), 6.85 (1H, d, J 16.5, H-4), 5.91 (1H, dd, J 16.5, 7.5, H-3), 3.56 (1H, ddd, J 7.5, 5.0, 3.0, H-2), [3.10 (1H, dd, J 5.5, 4.0) and 2.81 (1H, dd, J 5.0, 3.0), H-1]; δ_{C} (101 MHz, CDCl_3) 136.3 (*i*-Ph), 134.6 (C-4), 128.7, 128.1 (Ph), 127.0 (C-3), 126.5 (Ph), 52.7 (C-2), 49.3 (C-1); m/z (CI) 164 $[\text{MNH}_4]^+$, 147 $[\text{MH}]^+$, 129 $[\text{M}-\text{H}_2\text{O}]^+$ (Found: $[\text{MH}]^+$, 147.0812. $\text{C}_{10}\text{H}_{10}\text{O}$ requires $[\text{MH}]^+$, 147.0810); in agreement with published data.¹⁷²

(E)-2-Methyl-2-styryloxirane (234f)

Chlorohydrin **239f** (1.26 g, 6.43 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford (*E*)-2-methyl-2-styryloxirane **234f** (1.01 g, 98%): $\nu_{\max}$ (film) 1681, 1598, 1495, 1448, 965, 760, 700 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.44–7.32 (5H, m, Ph), 5.73–5.70 (2H, m, CHCHMe), [3.14 (1H, d, J 5.5) and 3.00 (1H, d, J 5.5), OCH_2], 1.77 (3H, dd, J 5.0, 2.0, Me); δ_{C} (101 MHz, CDCl_3) 153.0 (*i*-Ph), 131.2, 130.4, 128.2 (*o*-Ph), 127.7 (*p*-Ph), 127.0 (*m*-Ph), 60.1 (C-2), 56.7 (OCH_2), 17.8 (Me);

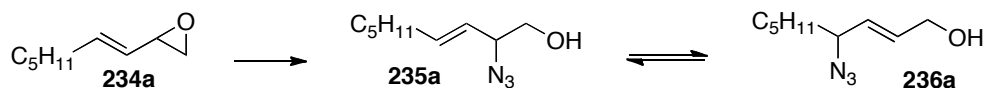
m/z (CI) 178 $[\text{MNH}_4]^+$, 161 $[\text{MH}]^+$, 143, 105 (Found: $[\text{MNH}_4]^+$, 178.1231. $\text{C}_{11}\text{H}_{12}\text{O}$ requires $[\text{MNH}_4]^+$, 178.1232).

2-[(*E*)-2-(2-Methyloxiran-2-yl)ethenyl]pyridine (**234g**)



Chlorohydrin **239h** (1.16 g, 5.87 mmol, 1.0 equiv) was reacted according to general procedure **J** to afford 2-[(*E*)-2-(2-Methyloxiran-2-yl)ethenyl]pyridine **234g** (623 mg, 66%) as yellow oil: ν_{max} (film) 1654, 1555, 1387, 1305, 1150, 1065, 973, 907, 793, 766, 742, 611 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 8.57 (1H, d, J 5.0, 6-pyridyl), 7.65 (1H, ddd, J 9.5, 8.0, 2.0, 4-pyridyl), 7.29 (1H, d, J 8.0, 3-pyridyl), 7.16 (1H, ddd, J 8.0, 5.0, 2.0, 5-pyridyl), [6.77 (1H, d, J 16.0) and 6.57 (1H, d, J 16.0), H-3,4], [2.94 (1H, d, J 5.0) and 2.89 (1H, d, J 5.0), H-1], 1.61 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 154.8 (2-pyridyl), 149.6 (6-pyridyl), 136.6 (4-pyridyl), [135.2 and 131.3 (C-3 and C-4)], 122.4 (5-pyridyl), 121.7 (3-pyridyl), 55.3 (C-1), 55.7 (C-2), 19.7 (2-Me); m/z (ESI) 181, 180, 162 $[\text{MH}]^+$, 130 (Found: $[\text{MH}]^+$, 162.0912. $\text{C}_{10}\text{H}_{11}\text{NO}$ requires $[\text{MH}]^+$, 162.0919).

(*E*)-2-Azidonon-3-en-1-ol (**235a**) and (*E*)-4-azidonon-2-en-1-ol (**236a**)



Oxirane **234a** (4.41 g, 31.5 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford a 73:27 mixture of (*E*)-2-azidonon-3-en-1-ol **235a** and (*E*)-4-

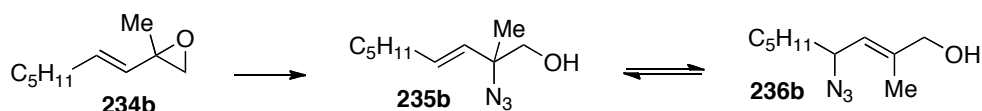
azidonon-2-en-1-ol **236a** respectively (4.04 g, 70%) as a colourless oil after purification over silica gel (30% TBME/petrol).

Data for the mixture: $\nu_{\max}$ (film) 3352, 2101, 1667, 1462, 1240, 1072 cm^{-1} ; m/z (CI) 201 $[\text{MNH}_4]^+$, 191, 158, 126 (Found: $[\text{MNH}_4]^+$, 201.1715. $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 201.1715).

NMR data for **235a**: δ_{H} (500 MHz, CDCl_3) 5.85 (1H, dt, J 15.5, 6.5, H-4), 5.40 (1H, ddt, J 15.5, 8.0, 1.5, H-3), 4.03 (1H, dt, J 11.5, 5.0, H-2), [3.60 (1H, dd, J 11.5, 5.0) and 3.52 (1H, dd, J 11.5, 7.5), H-1], 2.09–2.11 (2H, m, H-5), 1.66 (2H, s (br), OH), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 138.2, 123.4, 66.3, 65.0, 32.3, 31.2, 28.7, 22.4, 14.0.

NMR data for **236a**: δ_{H} (500 MHz, CDCl_3) 5.88 (1H, dt, J 15.0, 5.5, H-2), 5.66 (1H, ddt, J 15.5, 7.5, 1.5, H-3), 4.21 (2H, dd, J 5.5, 1.5, H-1), 3.85 (1H, dt, J 14.0, 7.5, H-4), 1.66 (2H, s (br), OH), 1.56–1.49 (2H, m, H-5), 1.43–1.25 (12H, m, H-6,7,8), 0.89 (6H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 132.9, 128.9, 64.0, 62.6, 34.5, 31.4, 35.5, 22.5, 14.0.

(*E*)-2-Azido-2-methylnon-3-en-1-ol (235b) and (*E*)-4-azido-2-methylnon-2-en-1-ol (236b)



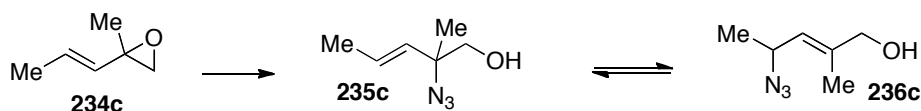
Oxirane **234b** (497 mg, 3.22 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford a 61:39 mixture of (*E*)-2-azido-2-methylnon-3-en-1-ol **235b** and (*E*)-4-azido-2-methylnon-2-en-1-ol **236b** respectively (150 mg, 25%) as a colourless oil after purification over silica gel (20% TBME/hexane).

Data for the mixture: $\nu_{\max}$ (film) 3370, 2102, 1666, 1456, 1379, 1247, 1056 cm^{-1} ; m/z (CI) 215 $[\text{MNH}_4]^+$, 172, 155 $[\text{M}-\text{N}_3]^+$, 137 (Found: $[\text{MNH}_4]^+$, 215.1872. $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 215.1871).

NMR data for **235b**: δ_{H} (400 MHz, CDCl_3) 5.82 (1H, dt, J 16.0, 7.0, H-4), 5.50 (1H, dt, J 16.0, 2.0, H-3), 3.46 (2H, AB quartet, J 11.5, H-1), 2.11 (2H, dt, J 9.0, 7.0, H-5), 1.71–1.55 (1H, s (br), OH), 1.40 (3H, s, 2-Me), 1.38–1.27 (6H, m, H-6,7,8), 0.99 (3H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 134.1 (C-4), 128.5 (C-3), 69.3 (C-1), 66.1 (C-2), 32.5, 31.3, 28.9, 22.4 (2-Me), 20.2, 14.0 (C-9).

NMR data for **236b**: δ_{H} (400 MHz, CDCl_3) 5.44 (1H, d, J 10.0, H-3), 4.22–4.15 (1H, m, H-4), 4.11 (2H, s, H-1), 1.77 (3H, s, 2-Me), 1.71–1.55 (1H, s (br), OH), 1.38–1.27 (8H, m, H-5,6,7,8), 0.99 (3H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 140.3 (C-2), 122.7 (C-3), 67.7 (C-1), 59.4 (C-4), 35.0, 31.5, 25.5, 22.5 (2-Me), 14.3, 14.0 (C-9).

(*E*)-2-Azido-2-methylpent-3-en-1-ol (235c) and (*E*)-4-azido-2-methylpent-2-en-1-ol (236c)



A solution of oxirane **234c** in THF (6.36 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford a 64:36 mixture of (*E*)-2-azido-2-methylpent-3-en-1-ol **235c** and (*E*)-4-azido-2-methylpent-2-en-1-ol **236c** respectively (634 mg, 71%) as a colourless oil after purification over silica gel (20% ether/petrol).

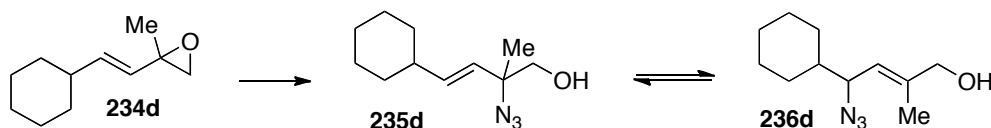
Data for the mixture: $\nu_{\max}$ (film) 3374, 2105, 1652, 1449, 1379, 1250, 1052, 970 cm^{-1} ; m/z (CI) 159 $[\text{MNH}_4]^+$, 116, 114, 96 (Found: $[\text{MNH}_4]^+$, 159.1248. $\text{C}_6\text{H}_{11}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 159.1246).

NMR data for **235c**: δ_{H} (400 MHz, CDCl_3) 5.85 (1H, dq, J 15.5, 6.5, H-4), 5.53 (1H, dd, J 15.5, 1.5, H-3), 3.47 (2H, AB quartet, J 12.0, H-1), 1.80 (3H, dd, J 6.5, 1.5, H-

5), 1.41 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 129.9 (C-3), 128.6 (C-4), 69.2 (C-1), 67.5 (C-2), 20.1 (2-Me), 18.0 (C-5).

NMR data for **236c**: δ_{H} (400 MHz, CDCl_3) 5.46 (1H, dd, J 9.5, 1.5, H-3), 4.37 (1H, dq, J 9.5, 6.5, H-4), 4.10 (2H, s, H-1), 1.77 (3H, s, 2-Me), 1.28 (3H, d, J 6.5, H-5); δ_{C} (101 MHz, CDCl_3) 139.5 (C-2), 123.7 (C-3), 66.0 (C-1), 54.7 (C-4), 20.8 (C-Me), 14.1 (C-5).

(*E*)-2-Azido-4-cyclohexyl-2-methylbut-3-en-1-ol (235d) and (*E*)-4-azido-4-cyclohexyl-2-methylbut-2-en-1-ol (236d)

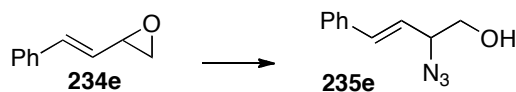


Oxirane **234d** (265 mg, 1.60 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford a 72:28 mixture of (*E*)-2-azido-4-cyclohexyl-2-methylbut-3-en-1-ol **235d** and (*E*)-4-azido-4-cyclohexyl-2-methylbut-2-en-1-ol **236d** respectively (196 mg, 59%) as a colourless oil after purification over silica gel (15% ether/hexane).

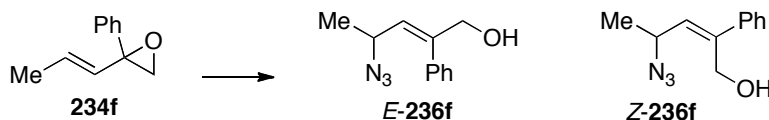
Data for the mixture: ν_{max} (film) 3359, 2103, 1665, 1448, 1250, 1052, 970 cm^{-1} ; m/z (CI) 227 $[\text{MNH}_4]^+$, 210 $[\text{MH}]^+$, 184, 149 (Found: $[\text{MNH}_4]^+$, 227.1870. $\text{C}_{11}\text{H}_{19}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 227.1872).

NMR data for **235d**: δ_{H} (400 MHz, CDCl_3) 5.76 (1H, dd, J 15.5, 6.5, H-4), 5.45 (1H, dd, J 15.5, 1.5, H-3), 3.50 (2H, m, H-1), 2.08–0.85 (11H, m, cyclohexyl), 1.40 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 139.9 (C-4), 125.9 (C-3), 69.3 (C-1), 42.4 (C-2), 40.7, 33.0, 32.9, 25.9, 20.2.

NMR data for **236d**: δ_{H} (400 MHz, CDCl_3) 5.47 (1H, d, J 10.0, H-3), 4.12 (2H, d, J 4.0, H-1), 3.96 (1H, dd, J 10.0, 7.5, H-4), 2.08–0.85 (11H, m, cyclohexyl), 1.75 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 121.2 (C-3), 67.7 (C-1), 65.9 (C-2), 64.6 (C-4), 29.5, 29.3, 26.3, 26.0, 14.3.

(*E*)-2-Azido-4-phenylbut-3-en-1-ol (235e)

Oxirane **234e** (950 mg, 6.50 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford (*E*)-2-azido-4-phenylbut-3-en-1-ol **235e** (739 mg, 60%) as a yellow oil after purification over silica gel (20% EtOAc/hexane): ν_{max} (film) 2109, 1650, 1449, 1246, 1040, 969, 750, 693 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.45 (1H, d, J 8.0, *p*-Ph), 7.38 (2H, dd, J 8.0, 7.5, *m*-Ph), 7.35 (2H, d, J 7.5, *o*-Ph), 6.76 (1H, d, J 17.0, H-4), 6.18 (1H, dd, J 17.0, 8.0, H-3), 4.28 (1H, dt, J 8.0, 4.5, H-2), [3.76 (1H, dd, J 11.0, 4.5) and 3.67 (1H, dd, J 11.0, 7.0), H-1], 1.99 (1H, s (br), OH); δ_{C} (101 MHz, CDCl_3) 135.7 (*i*-Ph), 135.4 (C-4), 128.7 (*o*-Ph), 128.5 (*p*-Ph), 126.7 (*m*-Ph), 122.9 (C-3), 66.3 (C-2), 65.0 (C-1); m/z (CI) 207 $[\text{MNH}_4]^+$, 189 $[\text{M}]^+$, 164, 147 (Found: $[\text{MNH}_4]^+$, 207.1247. $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 207.1246); in agreement with published data.¹⁷²

(*E*)-4-Azido-2-methyl-4-phenylbut-2-en-1-ol (*E*-236f) and (*Z*)-4-azido-2-methyl-4-phenylbut-2-en-1-ol (*Z*-236f)

To a solution of oxirane **234f** (490 mg, 3.06 mmol, 1.0 equiv) in acetone (10 mL) and water (3 mL) was added sodium azide (597 mg, 9.18 mmol, 3.0 equiv) in one portion. The reaction mixture was stirred at rt for 4 h, and ammonium chloride (500 mg) was added. The resulting mixture was stirred at rt for 10 min. Water (10 mL) was added and the mixture was concentrated under reduced pressure to remove acetone. The

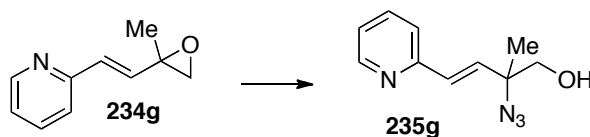
aqueous layer was extracted with dichloromethane (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue over silica gel (10% EtOAc/petrol) afforded a 75:25 mixture of (*E*)-4-azido-2-methyl-4-phenylbut-2-en-1-ol **E-236f** and (*Z*)-4-azido-2-methyl-4-phenylbut-2-en-1-ol **Z-236f** respectively (461 mg, 74%) as a colourless oil.

Data for the mixture: ν_{max} (film) 3366, 2101, 1492, 1446, 1238, 1074, 702 cm^{-1} ; m/z (CI) 221 $[\text{MNH}_4]^+$, 210, 178 $[\text{MNH}_4-\text{N}_3]^+$, 161 $[\text{MH}-\text{N}_3]^+$ (Found: $[\text{MNH}_4]^+$, 221.1411. $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 221.1402).

NMR data for **E-236f**: δ_{H} (500 MHz, CDCl_3) [7.47–7.38 (3H, m) and 7.19–7.17 (2H, m), Ph], 5.71 (1H, dt, J 10.0, 1.5, H-3), 4.36 (2H, s (br), H-1), 4.06 (1H, dq, J 10.0, 6.5, H-4), 1.62 (1H, s (br), OH), 1.24 (3H, d, J 6.5, H-5); δ_{C} (126 MHz, CDCl_3), 144.5, 136.9, 128.6, 128.5, 126.9, 125.6 (C-3), 66.9 (C-1), 55.4 (C-4), 20.6 (C-5).

NMR data for **Z-236f**: δ_{H} (500 MHz, CDCl_3) [7.47–7.38 (3H, m) and 7.19–7.17 (2H, m), Ph], 5.47 (1H, d, J 9.0, H-3), 4.62 (2H, s (br), H-1), 4.59 (1H, dq, J 9.0, 7.0, H-4), 1.57 (1H, s (br), OH), 1.39 (3H, d, J 7.0, H-5); δ_{C} (126 MHz, CDCl_3), 142.7, 139.6, 130.0 (C-3), 128.1, 127.9, 126.7, 60.1 (C-1), 54.7 (C-4), 20.8 (C-5).

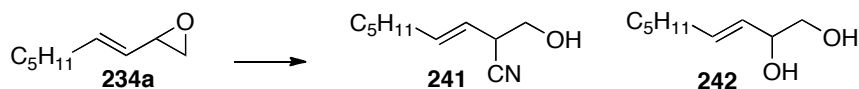
(*E*)-2-Azido-2-methyl-4-(pyridin-2-yl)but-3-en-1-ol (**235g**)



Oxirane **234g** (600 mg, 3.73 mmol, 1.0 equiv) was reacted according to general procedure **K** to afford (*E*)-2-azido-2-methyl-4-(pyridin-2-yl)but-3-en-1-ol **235g** (600 mg, 79%) as a colourless oil after purification over silica gel (20% EtOAc/5% TEA/hexane): ν_{max} (film) 3339, 2105, 1656, 1590, 1473, 1260, 1153, 1061, 975, 766 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 8.55 (1H, d, J 5.0, 6-pyridyl), 7.68 (1H, dt, J 7.5, 1.5, 4-pyridyl), 7.32 (1H, d, J 7.5, 3-pyridyl), 7.19 (1H, dd, J 8.0, 7.5, 5-pyridyl), 6.81 (1H,

d, J 16.0, H-4), 6.77 (1H, d, J 16.0, H-3), 3.64 (2H, dd, J 3.0, 2.5, H-1), 1.55 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 154.4 (2-pyridyl), 149.6 (6-pyridyl), 136.8 (4-pyridyl), [133.3 and 131.2, (C-3) and (C-4)], 122.8 (5-pyridyl), 122.5 (3-pyridyl), 69.1 (C-1), 66.0 (C-2), 20.4 (2-Me); m/z (CI), 205 $[\text{MH}]^+$, 164, 145, 102 (Found: $[\text{MH}]^+$, 205.1081. $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$ requires $[\text{MH}]^+$, 205.1076) (Found: C, 58.88; H, 5.87; N, 27.59. $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$ requires C, 58.81; H, 5.92; N, 27.43).

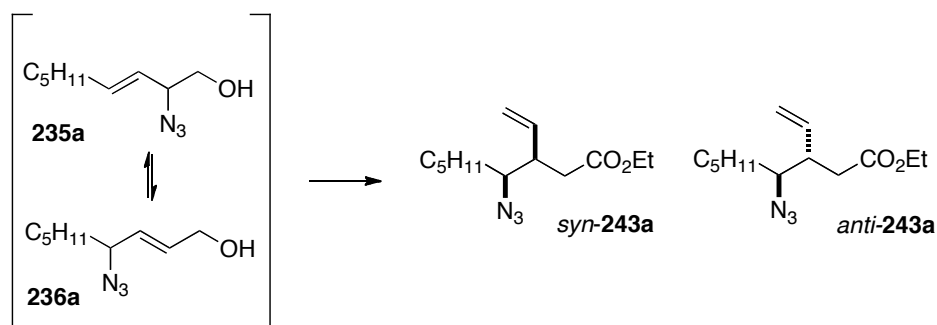
(*E*)-2-(Hydroxymethyl)non-3-enenitrile (241) and (*E*)-non-3-ene-1,2-diol (242)



To a solution of oxirane **234a** (1.19 g, 8.52 mmol, 1.0 equiv) in acetone (10 mL) and water (5 mL) was added potassium cyanide (0.61 g, 9.37 mmol, 1.1 equiv) in one portion at rt. The resulting solution was stirred at rt for 30 min and heated to reflux for 16 h. The reaction mixture was cooled to rt and NH_4Cl (500 mg) was added. After stirring for 10 min, the reaction mixture was concentrated under reduced pressure to remove acetone and the residue was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. Purification of the residue over silica gel (25% ether/petrol) afforded less polar (*E*)-2-(hydroxymethyl)non-3-enenitrile **241** (271 mg, 19%) as a colourless oil: ν_{max} (film) 3435, 2252, 1671, 1467, 1042, 973 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.84 (1H, dt, J 15.5, 6.5, H-4), 5.55 (1H, ddt, J 15.5, 6.5, 2.0, H-3), 4.42 (1H, dt, J 6.5, 6.0, H-2), 2.60 (2H, doublet of AB quartets, J 16.5, 6.0, CH_2), 2.33 (1H, s (br), OH), 2.08 (2H, dt, J 7.5, 6.5, H-5), 1.44–1.27 (6H, m, H-6,7,8), 0.91 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 135.3 (C-4), 129.2 (C-3), 117.4 (CN), 68.7 (C-2), 32.0 (C-5), 31.3 (C-6), 28.5 (C-7), 26.3 (C-1), 22.5 (C-8), 14.0 (C-9); m/z (CI) 185 $[\text{MNH}_4]^+$, 52 (Found: $[\text{MNH}_4]^+$, 185.1660. $\text{C}_{10}\text{H}_{17}\text{NO}$ requires $[\text{MNH}_4]^+$, 185.1654) (Found: C, 71.89; H, 10.26; N, 8.43. $\text{C}_{10}\text{H}_{17}\text{NO}$ requires C, 71.81; H, 10.25; N, 8.37); and more polar (*E*)-non-3-ene-1,2-diol **242** (82 mg, 6%) as a colourless oil: ν_{max}

(film) 3433, 1671, 1456, 1074, 1027, 971 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 5.77 (1H, dt, J 15.5, 6.5, H-4), 5.44 (1H, dd, J 15.5, 6.5, H-3), 4.19 (1H, dt, J 7.0, 3.5, H-2), [3.62 (1H, dd, J 11.0, 3.5) and 3.47 (1H, dd, J 11.0, 8.0), H-1], 3.02 (1H, s (br), OH), 2.04 (2H, dt, J 7.5, 7.0, H-5), 1.42–1.24 (6H, m, H-6,7,8), 0.90 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 134.2 (C-4), 128.2 (C-3), 73.2 (C-2), 66.6 (C-1), 32.3 (C-5), 31.4 (C-6), 28.7 (C-7), 22.5 (C-8), 14.0 (C-9); m/z (CI) 176 $[\text{MNH}_4]^+$, 158 $[\text{MH}]^+$, 96 (Found: $[\text{MNH}_4]^+$, 176.1653. $\text{C}_9\text{H}_{18}\text{O}_2$ requires $[\text{MNH}_4]^+$, 176.1651).

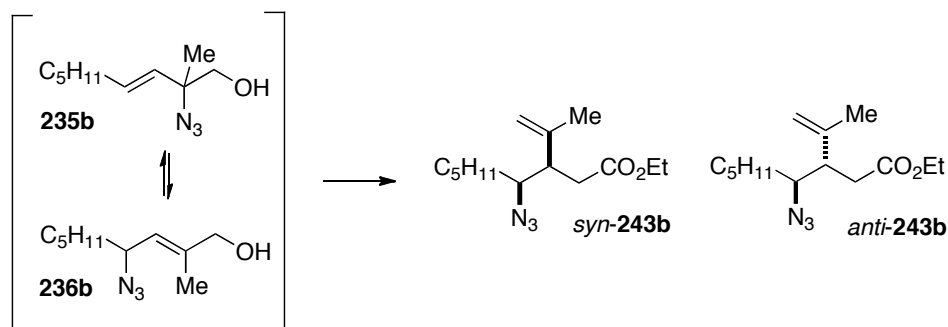
Ethyl 4-azido-3-ethenylnonanoate (**243a**)



A 73:27 mixture of allylic azides **235a** and **236a** respectively (100 mg, 0.546 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 4-azido-3-ethenylnonanoate* **243a** (137 mg, 99%, 50:50 *syn:anti* mixture of diastereomers) as a colourless oil without further purification: ν_{max} (film) 2102, 1736, 1641, 1465, 1257, 923 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) [5.74 (1H, ddd, J 17.0, 10.0, 4.0), and 5.65 (1H, ddd, J 17.0, 10.0, 4.0), *syn+anti* CHCH_2], 5.19–5.13 (4H, m, *syn+anti* CHCH_2), [4.14 (2H, q, J 7.5) and 4.15 (2H, q, J 7.5), *syn+anti* OCH_2], [3.84–3.43 (1H, m) and 3.26–3.06 (1H, m), *syn+anti* H-4], 2.77–2.69 (2H, m, *syn+anti* H-3), [2.56 (2H, dd, J 15.0, 5.0) and 2.41 (2H, dd, J 15.0, 8.0), *syn+anti* H-2], 1.62–1.32 (16H, m, *syn+anti* H-5,6,7,8), [1.27 (3H, t, J 7.5), and 1.26 (3H, t, J 7.5), *syn+anti* OCH_2CH_3], 0.91 (6H, t, J 6.0 *syn+anti* H-9); δ_{C} (101 MHz, CDCl_3) 172.0 (C-1), [137.2 and 135.6, (CHCH_2)], [118.3 and 117.8, (CHCH_2)], [65.8 and 65.3, (C-4)], 60.5 (OCH_2), [44.9 and 44.5, (C-3)], [37.0 and 36.3, (C-2)], 32.2, 32.0, 31.5, 26.0, 25.8, 22.5, 14.2, 14.0; m/z (CI) 271

$[\text{MNH}_4]^+$, 254 $[\text{MH}]^+$, 226 (Found: $[\text{MH}]^+$, 254.1858. $\text{C}_{13}\text{H}_{23}\text{N}_3\text{O}_2$ requires $[\text{MH}]^+$, 254.1869).

Ethyl 4-azido-3-(prop-1-enyl)nonanoate (**243b**)



A 61:39 mixture of allylic azides **235b** and **236b** respectively (88 mg, 0.446 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 4-azido-3-(prop-1-enyl)nonanoate* **243b** (86 mg, 72%, 59:41 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/hexane).

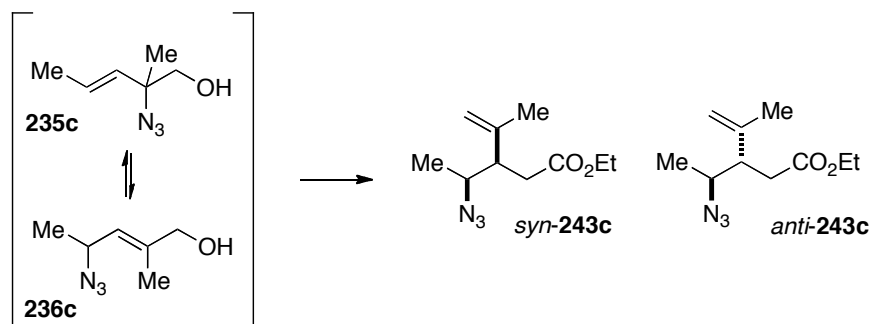
Data for the mixture: ν_{max} (film) 2012, 1733, 1648, 1464, 1379, 1273, 1123, 1073, 899 cm^{-1} ; m/z (CI) 285 $[\text{MNH}_4]^+$, 268 $[\text{MH}]^+$, 240 (Found: $[\text{MH}]^+$, 268.2025 $\text{C}_{14}\text{H}_{25}\text{N}_3\text{O}_2$ requires $[\text{MH}]^+$, 268.2025).

NMR data for *syn-243b*: δ_{H} (400 MHz, CDCl_3) 4.94 (1H, t, J 1.5, *trans*- CMeCH_2), 4.86 (1H, s (br), *cis*- CMeCH_2), 4.15 (2H, q, J 7.0, OCH_2), 3.44–3.39 (1H, m, H-4), 2.81 (1H, dt, J 8.0, 6.0, H-3), 2.49 (2H, dd, J 15.0, 9.0, H-2), 1.80 (3H, s, Me), 1.60–1.25 (8H, m, H-5,6,7,8), 1.27 (3H, t, J 7.0, OCH_2CH_3), 0.93 (6H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 172.1 (C-1), 143.4 (CMeCH_2), 114.5 (CMeCH_2), 65.1 (C-4), 60.5 (OCH_2), 47.0 (C-3), 35.7, 31.7, 31.6, 26.2, 22.5, 21.0, 14.0.

NMR data for *anti-243b*: δ_{H} (400 MHz, CDCl_3) 4.93 (1H, t, J 1.5, *trans*- CMeCH_2), 4.86 (1H, s (br), *cis*- CMeCH_2), 4.13 (2H, q, J 7.0, OCH_2), 3.24 (1H, dt, J 8.0, 3.0, H-4), 2.67 (1H, dt, J 8.0, 5.0, H-3), 2.57 (2H, dd, J 15.0, 6.0, H-2), 1.74 (3H, s, Me), 1.60–1.25 (8H, m, H-5,6,7,8), 1.26 (3H, t, J 7.0, OCH_2CH_3), 0.93 (6H, t, J 6.5, H-9).

9); δ_{C} (101 MHz, CDCl_3) 172.2 (C-1), 143.8 (CMeCH₂), 114.3 (CMeCH₂), 64.6 (C-4), 60.4 (OCH₂), 47.9 (C-3), 36.3, 32.5, 31.5, 25.9, 22.5, 20.1, 14.2.

Ethyl 4-azido-3-(prop-1-enyl)pentanoate (**243c**)



A 64:36 mixture of allylic azides **235c** and **236c** respectively (88 mg, 0.446 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 4-azido-3-(prop-1-enyl)pentanoate* **243c** (86 mg, 86%, 60:40 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/hexane).

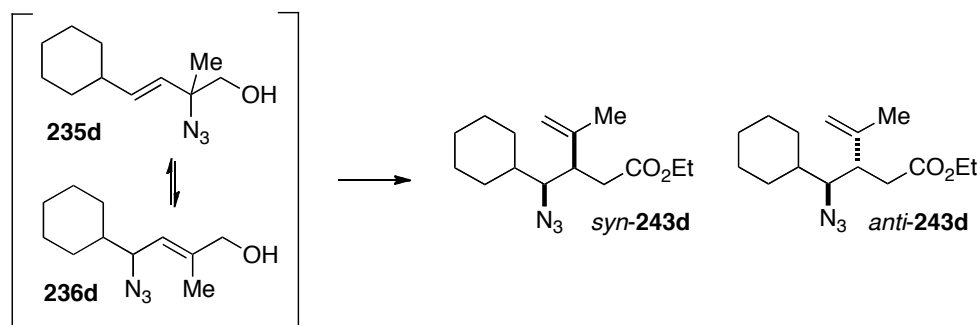
Data for the mixture: ν_{max} (film) 2101, 1736, 1650, 1446, 1378, 1258, 1034 cm^{-1} ; m/z (CI) 229 $[\text{MNH}_4]^+$, 212 $[\text{MH}]^+$, 184, 117 (Found: $[\text{MNH}_4]^+$, 229.1666. $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_2$ requires $[\text{MNH}_4]^+$, 229.1665).

NMR data for *syn-243c*: δ_{H} (400 MHz, CDCl_3) 4.93 (1H, t, J 1.5, *trans*-CMeCH₂), 4.83 (1H, s (br), *cis*-CMeCH₂), 4.13 (2H, q, J 7.0, OCH₂), 3.64 (1H, dq, J 13.0, 6.0, H-4), 2.74–2.69 (1H, m, H-3), 2.56–2.36 (2H, m, H-2), 1.78 (3H, s, CMeCH₂), 1.27 (3H, t, J 7.0, OCH₂CH₃), 1.25 (3H, d, J 6.0, H-5); δ_{C} (101 MHz, CDCl_3) 176.2 (C-1), 139.3 (CMeCH₂), 116.7 (CMeCH₂), 60.1 (OCH₂), 46.6 (C-4), 43.9 (C-3), 34.8 (C-2), 20.3 (CMeCH₂), 14.3 (C-5), 14.0 (OCH₂CH₃).

NMR data for *anti-243c*: δ_{H} (400 MHz, CDCl_3) 4.89 (1H, t, J 1.5, *trans*-CMeCH₂), 4.83 (1H, s (br), *cis*-CMeCH₂), 4.12 (2H, q, J 7.0, OCH₂), 3.40 (1H, dq, J 9.0, 6.5, H-4), 2.74–2.69 (1H, m, H-3), 2.56–2.36 (2H, m, H-2), 1.72 (3H, s, CMeCH₂), 1.26 (3H, t, J 7.0, OCH₂CH₃), 1.24 (3H, d, J 6.5, H-5); δ_{C} (101 MHz, CDCl_3) 176.7 (C-1),

139.9 (CMeCH₂), 116.0 (CMeCH₂), 60.0 (OCH₂), 47.0 (C-4), 44.0 (C-3), 33.4 (C-2), 20.3 (CMeCH₂), 14.3 (C-5), 13.9 (OCH₂CH₃).

Ethyl 4-azido-4-cyclohexyl-3-(prop-1-enyl)pentanoate (**243d**)



A 63:37 mixture of allylic azides **235d** and **236d** respectively (50 mg, 0.239 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 4-azido-4-cyclohexyl-3-(prop-1-enyl)pentanoate* **243d** (86 mg, 94%, 63:37 *syn:anti* mixture of diastereomers) as a colourless oil without further purification.

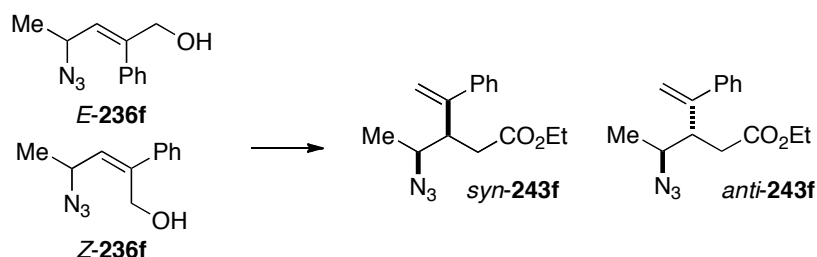
Data for the mixture: $\nu_{\max}$ (film) 2099, 1738, 1647, 1449, 1256, 1156, 1038, 899 cm⁻¹; m/z (CI) 297 [MNH₄]⁺, 280 [MH]⁺, 252 (Found: [MH]⁺, 280.2018 C₁₅H₂₅N₃O₂ requires [MH]⁺, 280.2025).

NMR data for *syn*-**243d**: δ_{H} (400 MHz, CDCl₃) [4.92 (1H, s) and 4.88 (1H, s), CMeCH₂], 4.13 (2H, q, J 7.0, OCH₂), 3.17–3.13 (1H, m, H-4), 2.82 (1H, dt, J 10.0, 4.5, H-3), 2.63–2.42 (2H, m, H-2), 1.75 (3H, s, CMeCH₂), 1.70–1.10 (11H, m, cyclohexyl), 1.28–1.23 (3H, m, OCH₂CH₃); δ_{C} (101 MHz, CDCl₃) 172.2 (=C-1), 143.7 (CMeCH₂), 114.3 (CMeCH₂), 71.4 (C-4), 60.4 (OCH₂), 45.0 (C-3), 40.6 (C-5), 36.0 (C-2), 31.3, 27.1, 26.0, 20.0, 14.2.

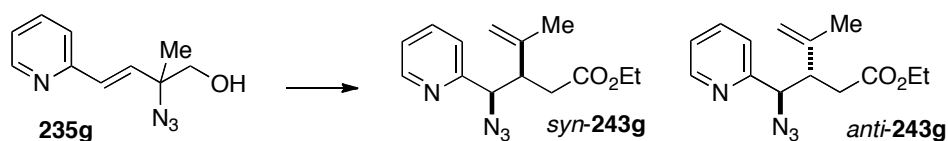
NMR data for *anti*-**243d**: δ_{H} (400 MHz, CDCl₃) [4.93 (1H, s) and 4.90 (1H, s), CMeCH₂], 4.14 (2H, q, J 7.0, OCH₂), 3.17–3.13 (1H, m, H-4), 2.93 (1H, dt, J 9.0, 6.5, H-3), 2.63–2.42 (2H, m, H-2), 1.79 (3H, s, CMeCH₂), 1.70–1.10 (11H, m, cyclohexyl), 1.28–1.23 (3H, m, OCH₂CH₃); δ_{C} (101 MHz, CDCl₃) 171.9 (C-1), 143.6

(CMeCH₂), 115.1 (CMeCH₂), 70.8 (C-4), 60.5 (OCH₂), 44.5 (C-3), 40.3 (C-5), 36.8 (C-2), 31.1, 27.8, 26.3, 26.1, 20.5, 14.2.

Ethyl 3-(1-azidoethyl)-4-phenylpent-4-enoate (**243f**)



A 75:25 mixture of allylic azide *E*-**236** and *Z*-**236** respectively (100 mg, 0.492 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford *ethyl 3-(1-azidoethyl)-4-phenylpent-4-enoate* **243f** (100 mg, 75%, 50:50 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (5% ether/hexane): $\nu_{\max}$ (film) 2105, 1734, 1631, 1256, 1176, 1037 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.46–7.33 (10H, m, *syn+anti* Ph), [5.41 (2H, d, *J* 3.0) and 5.19 (2H, s (br)), *syn+anti* CPhCH₂], [4.17 (2H, q, *J* 7.0) and 4.03 (2H, q, *J* 7.0), *syn+anti* OCH₂], [3.65 (1H, dq, *J* 6.5, 4.5) and 3.54 (1H, dq, *J* 7.0, 6.5), *syn+anti* CHN₃], [3.46 (1H, dt, *J* 6.5, 5.5) and 3.21 (1H, dt, *J* 6.5, 5.5), *syn+anti* CHCPhCH₂], 2.84–2.63 (4H, m, *syn+anti* CH₂CO₂Et), [1.27 (3H, t, *J* 7.0) and 1.24 (3H, t, *J* 7.0), *syn+anti* OCH₂CH₃], [1.27 (3H, d, *J* 6.5) and 1.16 (3H, d, *J* 6.5), *syn+anti* Me]; δ_{C} (101 MHz, CDCl₃) [172.3 and 172.1 (*syn+anti* C=O)], [149.2 and 148.1 (*syn+anti* CPhCH₂)], [142.3 and 142.2 (*syn+anti* *i*-Ph)], [128.5, 128.4, 127.8, 127.7, 126.9 and 126.7 (*syn+anti* Ph)], [115.1 and 114.8 (*syn+anti* CPhCH₂)], [60.7 and 60.6 (*syn+anti* OCH₂)], [60.6 and 58.9 (*syn+anti* CHN₃)], [46.0 and 44.7 (*syn+anti* CHCPhCH₂)], [36.1 and 34.4 (*syn+anti* CH₂CO₂Et)], [18.0 and 15.1 (*syn+anti* Me)], 14.2 (*syn+anti* OCH₂CH₃); *m/z* (CI) 291 [MNH₄]⁺, 274 [MH]⁺, 246, 205 (Found: [MH]⁺, 274.1563. C₁₅H₁₉N₃O₂ requires [MH]⁺, 274.1556).

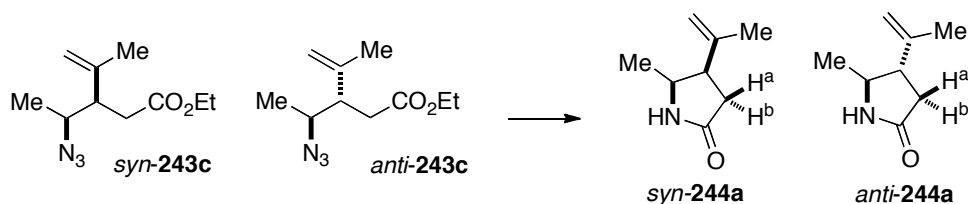
Ethyl 4-azido-4-(pyridin-2-yl)-3-(prop-1-enyl)pentanoate (243g)


Allylic azide **235g** (80 mg, 0.392 mmol, 1.0 equiv) was reacted according to general procedure **C** to afford an impure sample of *ethyl 4-azido-4-(pyridin-2-yl)-3-(prop-1-enyl)pentanoate* **243g** (4 mg, <4%, 77:23 *syn:anti* mixture of diastereomers) as a brown oil after purification over silica gel (10% ether/5% TEA/petrol).

NMR data for *syn-243g* *inter alia*: δ_{H} (400 MHz, CDCl_3) 8.60 (1H, d, J 5.0, 6-pyridyl), 7.78–7.67 (1H, m, 4-pyridyl), 7.34–7.19 (2H, m, 3,5-pyridyl), 4.80 (1H, s, *trans*- CMeCH_2), 4.77 (1H, s, *cis*- CMeCH_2), 4.58 (1H, d, J 8.0, H-4), 4.20–4.05 (2H, m, OCH_2), 3.26, 1H, dd, J 8.0, 5.0, H-3), [2.73 (1H, dd, J 14.5, 4.0) and 2.59 (1H, dd, J 14.5, 9.5), H-2], 1.69 (3H, s, CMeCH_2), 1.31–1.23 (3H, m, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 149.7 (6-pyridyl), 136.8 (4-pyridyl), 114.5 (CMeCH_2), 68.9 (C-4), 60.4 (OCH_2), 47.4 (C-3), 35.5 (C-2), 20.3 (CMeCH_2), 14.0 (OCH_2CH_3).

NMR data for *anti-243g* *inter alia*: δ_{H} (400 MHz, CDCl_3) 8.63 (1H, d, J 5.0, 6-pyridyl), 7.78–7.67 (1H, m, 4-pyridyl), 7.34–7.19 (2H, m, 3,5-pyridyl), 5.00 (1H, s, *trans*- CMeCH_2), 4.96 (1H, s, *cis*- CMeCH_2), 4.51 (1H, d, J 9.5, H-4), 4.20–4.05 (2H, m, OCH_2), 3.35–3.28 (1H, m, H-3), [2.34 (1H, dd, J 15.0, 10.0) and 2.21 (1H, dd, J 15.0, 5.0), H-2], 1.83 (3H, CMeCH_2), 1.31–1.23 (3H, m, OCH_2CH_3); δ_{C} (101 MHz, CDCl_3) 149.5 (6-pyridyl), 136.7 (4-pyridyl), 69.1 (C-4), 60.4 (OCH_2), 47.4 (C-3), 20.9 (CMeCH_2), 14.0 (OCH_2CH_3).

5-Methyl-4-(prop-1-enyl)pyrrolidin-2-one (**244a**)



General procedure (using PMe_3):

Ester **243c** (85 mg, 0.403 mmol, 1.0 equiv, 60:40 *syn:anti* mixture of diastereomers) was reacted according to general procedure **L** to afford 5-methyl-4-(prop-1-enyl)pyrrolidin-2-one **244a** (33 mg, 59% 45:55 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (20–30 % EtOAc/dichloromethane).

Alternative procedure (using polystyrene- PPh_2):

To a solution of ester **243c** (51 mg, 0.242 mmol, 1.0 equiv) in THF (242 μ L) in a 0.2–0.5 mL microwave vial was added polystyrene supported diphenylphosphine (286 mg of a 1.10 mmol/g resin, 0.314 mmol, 1.3 equiv) and water (5.6 μ L, 0.314 mmol, 1.3 equiv). The vial was flushed with nitrogen gas and capped. After heating by microwave at 120 $^{\circ}$ C for 30 min, the mixture was cooled and filtered, washing the resin with dichloromethane (15 mL). The filtrate was concentrated under reduced pressure and the residue purified over silica gel (20–30 % EtOAc/dichloromethane) to afford 5-methyl-4-(prop-1-enyl)pyrrolidin-2-one **244a** (33 mg, 87% 60:40 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel.

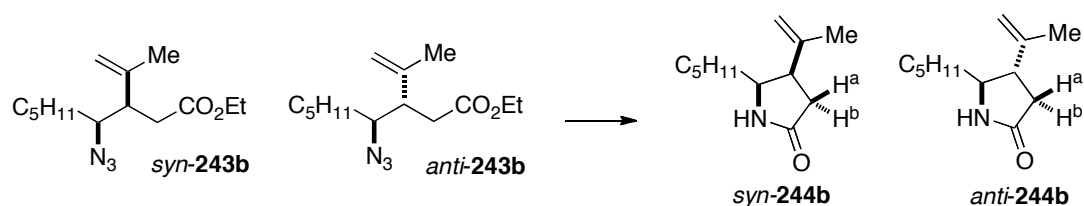
Data for the mixture: $\nu_{\max}$ (film) 3321, 1693, 1652 cm^{-1} ; m/z (CI) 157 $[\text{MNH}_4]^+$, 140 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 140.1081. $\text{C}_8\text{H}_{13}\text{NO}$ requires $[\text{MH}]^+$, 140.1075).

NMR data for *syn*-**244a**: δ_{H} (500 MHz, CDCl_3) 6.83 (1H, s, NH), 4.81 (1H, s, *trans*- CMeCH_2) 4.76 (1H, s, *cis*- CMeCH_2), 3.85 (1H, dq, J 7.0, 6.0, H-5), 3.06 (1H, dt, J 10.0, 7.0, H-4), [2.43 (1H, dd, J 17.0, 4.0) and 2.23 (1H, dd, J 17.0, 8.0), H-3], 1.73

(3H, s, CMeCH₂), 0.97 (3H, d, *J* 6.0, 5-Me); δ_{C} (126 MHz, CDCl₃) 177.5 (C-2), 143.2 (CMeCH₂), 112.5 (CMeCH₂), 51.7 (C-5), 45.6 (C-4), 32.6 (C-3), 21.9 (CMeCH₂), 16.5 (5-Me).

NMR data for *anti*-**244a**: δ_{H} (500 MHz, CDCl₃) 6.83 (1H, s, NH), 4.93 (1H, s, *trans*-CMeCH₂), 4.81 (1H, s, *cis*-CMeCH₂), 3.59 (1H, dq, *J* 7.0, 6.0, H-5), 2.57 (1H, dt, *J* 9.5, 7.0, H-4), [2.45 (1H, dd, *J* 16.5, 4.5) and 2.32 (1H, dd, *J* 16.5, 10.0), H-3], 1.72 (3H, s, CMeCH₂), 1.21 (3H, d, *J* 6.0, 5-Me); δ_{C} (126 MHz, CDCl₃) 176.9 (C-2), 141.9 (CMeCH₂), 112.4 (CMeCH₂), 53.6 (C-5), 50.7 (C-4), 36.0 (C-3), 20.7 (CMeCH₂), 19.7 (5-Me).

5-Pentyl-4-(prop-1-enyl)pyrrolidin-2-one (**244b**)



Ester **243b** (22 mg, 0.082 mmol, 1.0 equiv, 59:41 *syn:anti* mixture of diastereomers) was reacted according to general procedure **L** to afford 5-pentyl-4-(prop-1-enyl)pyrrolidin-2-one **244b** (12 mg, 75%, 56:44 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (20% EtOAc/dichloromethane).

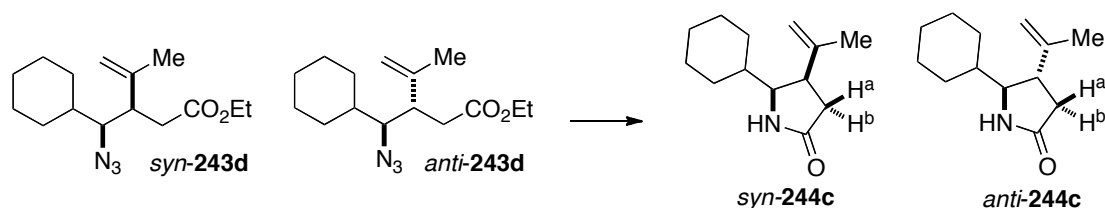
Data for the mixture: ν_{max} (film) 3207, 1697, 1450, 1377, 1073, 892, 728 cm⁻¹; *m/z* (CI) 213 [MNH₄]⁺, 196 [MH]⁺ (Found: [MH]⁺, 196.1694. C₁₂H₂₁NO requires [MH]⁺, 196.1701).

NMR data for *syn*-**244b**: δ_{H} (500 MHz, CDCl₃) 6.04 (1H, s (br), NH), 4.97 (1H, s, *trans*-CMeCH₂), 4.81 (1H, s, *cis*-CMeCH₂), 3.69–3.65 (1H, m, H-5), 3.14 (1H, dt, *J* 9.5, 8.0, H-4), 2.44 (1H, dd, *J* 17.0, 10.5, H^a), 2.28 (1H, dd, *J* 9.5, 8.0, H^b), 1.76–1.74 (3H, s, CMeCH₂), 1.35–1.21 (8H, m, pentyl), 0.90–0.86 (3H, m, CH₃ of pentyl); δ_{C}

(126 MHz, CDCl₃) 177.3 (C-2), 141.9 (CMeCH₂), 112.8 (CMeCH₂), 56.4 (C-5), 45.9 (C-4), 35.5, 31.7, 30.5, 26.2, 22.5, 21.9, 14.0.

NMR data for *anti*-**243b**: δ_{H} (500 MHz, CDCl₃) 5.93 (1H, s (br), NH), 4.84 (2H, s (br), CMeCH₂), 3.49 (1H, dt, *J* 7.0, 6.0, H-5), 2.71 (1H, dt, *J* 8.0, 7.0, H-4), 2.48 (1H, dd, *J* 17.0, 9.0 H^a), 2.29 (1H, dd, *J* 10.0, 8.0, H^b), 1.76–1.74 (3H, s, CMeCH₂), [1.61–1.55 (1H, m) and 1.45–1.39 (1H, m), CH₂ of pentyl], 1.35–1.21 (6H, m, pentyl) 0.90–0.86 (3H, m, CH₃ of pentyl); δ_{C} (126 MHz, CDCl₃) 176.6 (C-2), 144.2 (CMeCH₂), 112.3 (CMeCH₂), 58.0 (C-5), 48.5 (C-4), 35.8, 33.1, 31.7, 25.9, 22.4, 19.6, 14.0.

5-Cyclohexyl-4-(prop-1-enyl)pyrrolidin-2-one (**244c**)



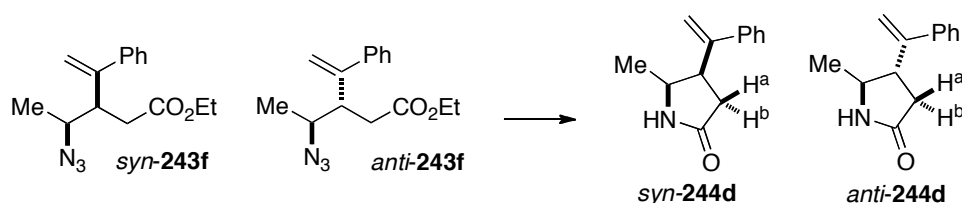
Ester **243d** (122 mg, 0.437 mmol, 1.0 equiv 63:37 *syn:anti* mixture of distereomers) was reacted according to general procedure **L** to afford 5-cyclohexyl-4-(prop-1-enyl)pyrrolidin-2-one **244c** (53 mg, 59%, 33:66 *syn:anti* mixture of diastereomers) as a white solid after purification over silica gel (20–60% EtOAc/dichloromethane).

Data for the mixture: mp 78–82 °C; ν_{max} (film) 3209, 1690, 1652, 1448, 1256, 890, 764 cm⁻¹; *m/z* (CI) 225 [MNH₄]⁺, 208 [MH]⁺ (Found: [MH]⁺, 208.1704. C₁₃H₂₁NO requires [MH]⁺, 208.1701).

NMR data for *syn*-**244c** δ_{H} (500 MHz, CDCl₃) 6.15 (1H, s (br), NH), 4.97 (1H, s, *trans*-CMeCH₂), 4.81 (1H, s, *cis*-CMeCH₂), 3.46 (1H, dd, *J* 7.0, 6.5, H-5), 3.12 (1H, dt, *J* 7.5, 7.0, H-4), [2.39 (1H, dd, *J* 16.5, 8.0) and 2.35 (1H, dd, *J* 16.5, 7.0), H-3], 1.79 (3H, s, CMeCH₂), 1.67–0.84 (11H, m, cyclohexyl); δ_{C} (126 MHz, CDCl₃) 177.9 (C-2), 142.6 (CMeCH₂), 113.5 (CMeCH₂), 61.8 (C-5), 45.3 (C-4), 38.7 (cyclohexyl CH), 33.9 (C-3), 30.5, 28.8, 25.8, 25.6, 24.9, 21.4 (CMeCH₂).

NMR data for *anti*-**244c** δ_{H} (500 MHz, CDCl_3) 6.15 (1H, s (br), NH), 4.80 (1H, s, *cis*- CMeCH_2), 4.77 (1H, s, *trans*- CMeCH_2), 3.25 (1H, dd, J 5.5, 5.0, H-5), 2.83 (1H, dt, J 9.5, 5.0, H-4), 2.51 (1H, dd, J 17.5, 9.5, H^{a}), 2.21 (1H, dd, J 17.5, 5.5, H^{b}), 1.74 (3H, s, CMeCH_2), 1.67–0.84 (11H, m, cyclohexyl); δ_{C} (126 MHz, CDCl_3) 177.0 (C-2), 145.9 (CMeCH_2), 111.5 (CMeCH_2), 63.2 (C-5), 44.6 (C-4), 42.8 (cyclohexyl CH), 35.6 (C-3), 29.6, 28.3, 26.2, 26.0, 25.9, 19.4 (CMeCH_2).

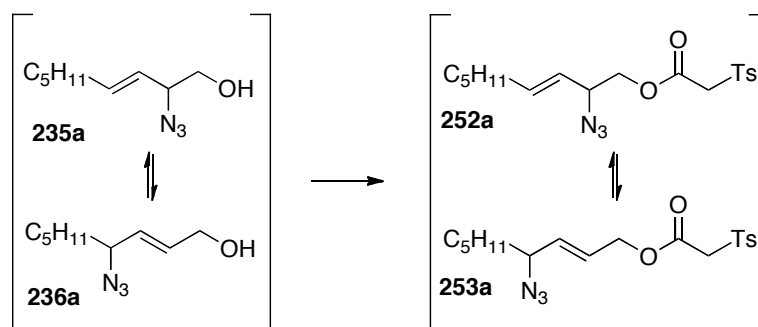
5-Methyl-4-(1-phenylethenyl)pyrrolidin-2-one (**244d**)



Ester **243f** (78 mg, 0.286 mmol, 1.0 equiv, 50:50 *syn:anti* mixture of diastereomers) was reacted according to general procedure **L** to afford 5-methyl-4-(1-phenylethenyl)pyrrolidin-2-one **244d** (46 mg, 80%, 50:50 *syn:anti* mixture of diastereomers) as a white solid after purification over silica gel (20% EtOAc/dichloromethane). Data for the mixture: mp 64–68 °C; ν_{max} (film) 3202, 1694, 1631, 1262, 905, 764, 697 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.40–7.30 (10H, m, *syn+anti* Ph), 6.36 (2H, s (br), *syn+anti* NH), 5.47 (1H, d, J 1.0, *syn trans*- CPhCH_2), 5.32 (1H, s, *anti trans*- CPhCH_2), 5.19 (1H, s, *anti cis*- CPhCH_2), 5.13 (1H, d, J 1.0, *syn cis*- CPhCH_2), 3.85 (1H, dt, J 12.0, 7.5, *syn* H-4), 3.75 (2H, dq, J 12.0, 6.5, *syn+anti* H-5), 3.09 (1H, dt, J 8.0, 7.0, *anti* H-4), 2.65 (1H, dd, J 16.0, 11.5, *anti* H^{a}), 2.62 (1H, dd, J 17.0, 8.5, *syn* H^{b}), 2.41 (1H, dd, J 16.0, 13.5, *anti* H^{b}), 2.39 (1H, dd, J 16.0, 14.0, *syn* H^{a}), 1.24 (3H, d, J 6.5, *anti* 5-Me), 0.84 (3H, d, J 6.5, *syn* 5-Me); δ_{C} (126 MHz, CDCl_3) [176.7 and 176.3 (*syn+anti* C-2)], [148.6 and 145.6 (*syn+anti* CPhCH_2)], [141.3 and 140.7 (*syn+anti* *i*-Ph)], 128.6, 128.4, 127.9, 127.7, 126.7, 126.2, 114.5 (*syn* CPhCH_2), 113.2 (*anti* CPhCH_2), [55.1 and 51.4 (*syn+anti* C-5)], 47.5 (*anti* C-4), 42.8 (*syn* C-4), 37.3 (*anti* C-3), 32.5 (*syn* C-3), 20.1 (*anti* 5-Me), 16.7 (*syn* 5-Me); m/z (CI)

219 $[\text{MNH}_4]^+$, 202 $[\text{MH}]^+$ (Found: $[\text{MH}]^+$, 202.1223. $\text{C}_{13}\text{H}_{15}\text{NO}$ requires $[\text{MH}]^+$, 202.1232).

(*E*)-2-Azidonon-3-enyl 2-tosylacetate (252a) and (*E*)-4-azidonon-2-enyl 2-tosylacetate (253a)



A 73:27 mixture of allylic azides **235a** and **236a** respectively (1.00 g, 5.46 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford a 58:42 mixture of the esters (*E*)-2-azidonon-3-enyl 2-tosylacetate **252a** and (*E*)-4-azidonon-2-enyl 2-tosylacetate **253a** (2.05 g, 99%) respectively as a colourless oil after purification over silica gel (25% ether/petrol).

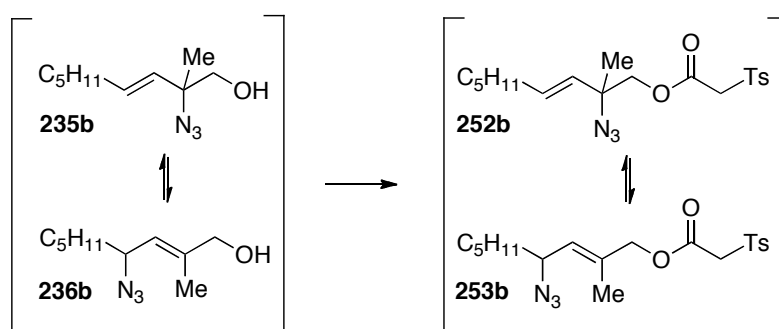
Data for the mixture: ν_{max} (film) 2932, 2099, 1747, 1598, 1455, 1330, 1152, 1085, 975, 814, 728, 646, cm^{-1} ; δ_{C} (126 MHz, CDCl_3) 162.2, 162.1, 138.7, 133.2, 129.9, 128.5, 125.9, 128.5, 125.9, 122.3, 67.1, 65.5, 63.5, 62.0, 60.8, 34.2, 32.2, 31.4, 31.2, 28.5, 25.4, 22.5, 22.4, 21.7, 14.0; m/z (CI) 397 $[\text{MNH}_4]^+$, 352, 243 (Found: $[\text{MNH}_4]^+$, 397.1926. $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$ requires $[\text{MNH}_4]^+$, 397.1910).

^1H -NMR data for **252a**: δ_{H} (500 MHz, CDCl_3) 7.85–7.81 (2H, m, *o*-Ts), 7.39–7.37 (2H, m, *m*-Ts), 5.82 (1H, dt, J 15.0, 7.0, H-4), 5.31 (1H, ddt, J 15.0, 7.0, 1.5, H-3), 4.62 (2H, d, J 5.0, H-1), 4.13 (2H, d, J 5.0, CH_2Ts), 4.10–3.90 (1H, m, H-2), 2.47 (3H, s, TsMe), 2.10–2.15 (2H, m, H-5), 1.57–1.28 (6H, m, H-6,7,8), 0.89 (3H, t, J 7.5, H-9).

^1H -NMR data for **253b**: δ_{H} (500 MHz, CDCl_3) 7.85–7.81 (2H, m, *o*-Ts), 7.39–7.37 (2H, m, *m*-Ts), 5.74–5.65 (2H, m, H-2,3), 4.62 (2H, d, J 5.0, H-1), 4.13 (2H, d, J 5.0,

CH₂Ts), 3.82 (1H, dt, *J* 14.0, 7.0, H-4), 2.47 (3H, s, TsMe), 1.57–1.28 (8H, m, H-5,6,7,8), 0.89 (3H, t, *J* 7.5, H-9).

(*E*)-2-Azido-2-methylnon-3-enyl 2-tosylacetate (252b) and (*E*)-4-azido-2-methylnon-2-enyl 2-tosylacetate (253b)



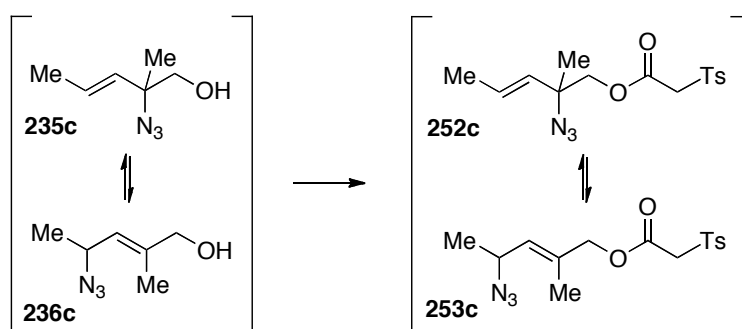
A 61:39 mixture of allylic azides **235b** and **236b** respectively (795 mg, 4.03 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford a 65:35 mixture the esters (*E*)-4-azido-2-methylnon-3-enyl 2-tosylacetate **253b** and (*E*)-2-azido-2-methylnon-2-enyl 2-tosylacetate **252b** respectively (1.09 g, 69%) as a colourless oil after purification over silica gel (20% ether/petrol).

Data for the mixture: ν_{max} (film) 2099, 1745, 1673, 1597, 1454, 1331, 1157, 1085, 831, 727 cm⁻¹; δ_{C} (101 MHz, CDCl₃) 162.2, 162.1, 145.6, 145.5, 135.8, 134.5, 134.1, 130.2, 129.9, 129.34, 129.1, 128.5, 127.7, 127.3, 70.7, 70.4, 62.9, 61.0, 60.8, 59.1, 34.7, 33.6, 32.4, 31.5, 31.2, 28.8, 27.7, 26.1, 25.4, 22.5, 21.7, 20.9, 14.4; *m/z* (CI) 411 [MNH₄]⁺, 366, 207, 137 (Found: [MNH₄]⁺, 411.2074. C₁₉H₂₇N₃O₄S requires [MNH₄]⁺, 411.2066).

¹H-NMR data for **253b**: δ_{H} (400 MHz, CDCl₃), 7.84 (2H, d, *J* 7.5, *o*-Ts), 7.39 (2H, d, *J* 7.5, *m*-Ts), 5.42, (1H, d, *J* 9.5, H-3), 4.16 (2H, s, CH₂Ts), 4.02 (2H, AB quartet, *J* 11.0, H-1), 2.48 (3H, s, TsMe), 1.72 (3H, d, *J* 1.5, 2-Me), 1.63–1.26 (8H, m, H-5,6,7,8), 0.91 (6H, t, *J* 7.0, H-9).

^1H -NMR data for **252b**: δ_{H} (400 MHz, CDCl_3), 7.83 (2H, d, J 7.5, *o*-Ts), 7.40 (2H, d, J 7.5, *m*-Ts), 5.79 (1H, dt, J 15.5, 7.0, H-4), 5.40 (1H, d, J 15.5, H-3), 4.57 (2H, s, CH_2Ts), 4.14–4.11 (2H, m, H-1), 2.48 (3H, s, TsMe), 2.09 (2H, dt, J 7.5, 7.0, H-5), 1.63–1.26 (6H, m, H-6,7,8), 1.35 (3H, s, 2-Me), 0.91 (6H, t, J 7.0, H-9).

(*E*)-2-Azido-2-methylpent-3-enyl 2-tosylacetate (252c) and (*E*)-4-azido-2-methylpent-2-enyl 2-tosylacetate (253c)



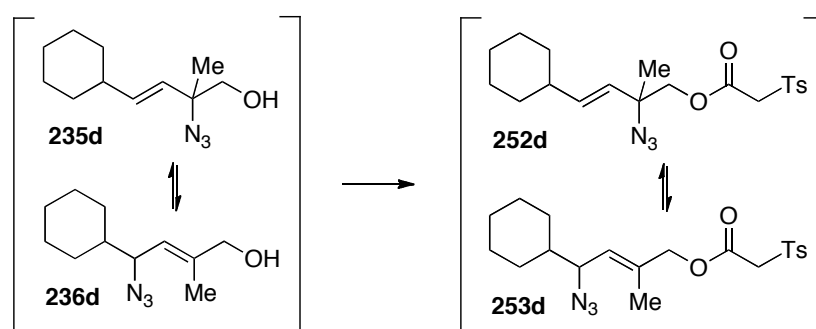
A 64:36 mixture of allylic azides **235c** and **236c** respectively (300 mg, 2.13 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford a 70:30 mixture of (*E*)-4-azido-2-methylpent-3-enyl 2-tosylacetate **253c** and (*E*)-2-azido-2-methylpent-2-enyl 2-tosylacetate **252c** respectively (667 mg, 97%) as a colourless oil after purification over silica gel (30% ether/petrol).

Data for the mixture: ν_{max} (film) 2102, 1744, 1664, 1597, 1450, 1328, 1152, 1085, 813, 727 cm^{-1} ; δ_{C} (101 MHz, CDCl_3) 162.2, 162.1, 145.6, 145.55, 135.9, 133.9, 130.4, 130.0, 129.1, 128.6, 128.3, 70.7, 70.3, 63.0, 61.1, 60.9, 54.5, 32.4, 30.5, 25.9, 24.8, 21.8, 20.8, 20.3, 18.0, 14.3; m/z (CI) 355 $[\text{MNH}_4]^+$, 310, 295, 201 (Found: $[\text{MNH}_4]^+$, 355.1446. $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ requires $[\text{MNH}_4]^+$, 355.1440).

^1H -NMR data for **253c**: δ_{H} (400 MHz, CDCl_3) 7.85 (2H, d, J 7.5, *o*-Ts), 7.00 (2H, d, J 7.5 *m*-Ts), 5.44 (1H, d, J 9.5, H-3), 4.33 (1H, dq, J 9.5, 7.0, H-4), 4.17 (2H, s, CH_2Ts), 3.98 (2H, s, H-1), 2.46 (3H, s, TsMe), 1.68 (3H, d, J 1.5, 2-Me), 1.24 (3H, d, J 7.0, H-5).

¹H-NMR data for **252c**: δ_{H} (400 MHz, CDCl₃) 7.85 (2H, d, *J* 7.5, *o*-Ts), 7.00 (2H, d, *J* 7.5 *m*-Ts), 5.83 (1H, dq, *J* 15.5, 6.5, H-4), 5.45 (1H, d, *J* 15.5, H-3), 4.56 (2H, s, CH₂Ts), 4.16 (2H, s, H-1), 2.46 (3H, s, TsMe), 1.32 (3H, s, 2-Me), 1.21 (3H, d, *J* 6.5, H-5).

(*E*)-2-Azido-4-cyclohexyl-2-methylbut-3-enyl 2-tosylacetate (252d) and (*E*)-4-azido-4-cyclohexyl-2-methylbut-2-enyl 2-tosylacetate (253d).



A 72:28 mixture of allylic azides **235d** and **236d** respectively (618 mg, 2.96 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford a 68:32 mixture of (*E*)-4-azido-4-cyclohexyl-2-methylbut-3-enyl 2-tosylacetate **253d** and (*E*)-2-azido-4-cyclohexyl-2-methylbut-2-enyl 2-tosylacetate **252d** respectively (1.10 g, 92%) as a colourless oil after purification over silica gel (20% ether/petrol).

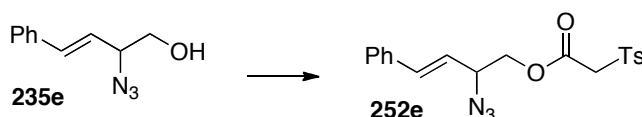
Data for the mixture: ν_{max} (film) 2096, 1742, 1650, 1598, 1450, 1329, 1152, 1085, 813, 727, 697, 603 cm⁻¹; δ_{C} (101 MHz, CDCl₃) 162.2, 145.6, 145.5, 140.1, 135.8, 135.7, 134.6, 129.9, 128.5, 128.4, 128.3, 127.9, 125.9, 125.2, 70.7, 70.5, 64.4, 64.3, 62.9, 61.0, 42.3, 40.6, 32.9, 32.8, 29.5, 26.3, 25.9, 25.8, 21.7, 20.9, 14.5; *m/z* (ESI) 428 [MNa]⁺, 378, 309, 149 (Found: [MNa]⁺, 428.1635. C₂₀H₂₇N₃O₄S requires [MNa]⁺, 428.1620).

¹H-NMR data for **253d**: δ_{H} (400 MHz, CDCl₃) 7.84 (2H, d, *J* 7.5, *o*-Ts), 7.39 (2H, d, *J* 7.5, *m*-Ts), 5.45 (1H, d, *J* 9.5, H-3), 4.16 (2H, s, CH₂Ts), 4.02 (2H, AB quartet, *J*

11.5, H-1), 3.91 (1H, dd, J 9.5, 8.0, H-4), 4.28 (3H, s, TsMe), [1.77–1.58 and 1.45–0.88 (11H, m, cyclohexyl)], 1.71 (3H, s, 2-Me).

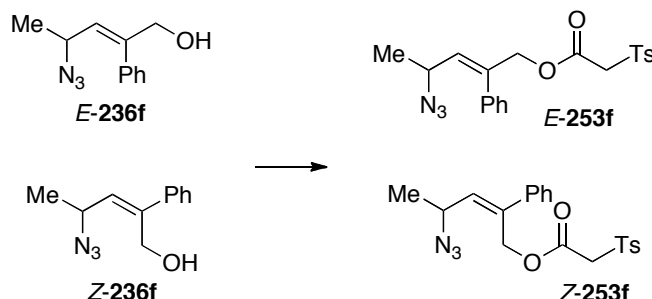
^1H -NMR data for **252d**: δ_{H} (400 MHz, CDCl_3) 7.84 (2H, d, J 7.5, *o*-Ts), 7.39 (2H, d, J 7.5, *m*-Ts), 5.73 (1H, dd, J 16.0, 7.0, H-4), 5.36 (1H, d, J 16.0, H-3), 4.58 (2H, s, CH_2Ts), 4.15–4.12 (2H, m, H-1), 4.28 (3H, s, TsMe), 2.05–1.96 (1H, m, A-5), [1.77–1.58 and 1.45–0.88 (10H, m, cyclohexyl)], 1.34 (3H, s, 2-Me).

(*E*)-2-Azido-4-phenylbut-3-enyl 2-tosylacetate (**252e**)



Allylic azide **235e** (500 mg, 2.64 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford (*E*)-2-azido-4-phenylbut-3-enyl 2-tosylacetate **252e** (1.03 g, 97%) as a colourless oil after purification over silica gel (15% EtOAc/hexane): ν_{max} (film) 2109, 1747, 1598, 1328, 1151, 1085, 971, 814, 754, 695, 646 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.81 (2H, d, J 8.5, *o*-Ts), 7.40–7.28 (5H, m, Ph), 7.34 (2H, d, J 8.5, *m*-Ts), 6.69 (1H, d, J 16.0, H-4), 6.04 (1H, dd, J 16.0, 7.5, H-3), 4.28–4.20 (1H, m, H-2), 4.14 (2H, s, CH_2Ts), 4.13–4.07 (2H, m, H-1), 2.42 (3H, s, TsMe); δ_{C} (101 MHz, CDCl_3) 162.2, 145.6, 135.9 (C-4), 135.7, 135.3, 129.9, 128.8, 128.7, 128.6, 126.8 (*m*-Ts), 121.7 (C-3), 67.0 (C-2), 62.2 (CH_2Ts), 60.9 (C-1), 21.7 (TsMe); m/z (CI) 403 $[\text{MNH}_4]^+$, 355, 244, 212 (Found: $[\text{MNH}_4]^+$, 403.1445. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ requires $[\text{MNH}_4]^+$, 403.1440) (Found: C, 59.26; H, 4.16; N, 10.98. $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$ requires C, 59.21; H, 4.97; N, 10.90).

(*E*)-4-Azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (*E*-236f) and (*Z*)-4-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate (*Z*-236f)

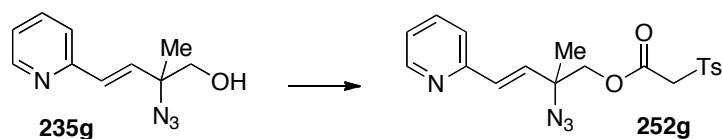


Allylic azide **236f** (212 mg, 1.04 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford a 75:25 mixture of (*E*)-4-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate **E-253f** and (*Z*)-4-azido-2-methyl-4-phenylbut-2-enyl 2-tosylacetate **Z-253f** respectively (313 mg, 75%) as a colourless oil after purification over silica gel (25% ether/hexane).

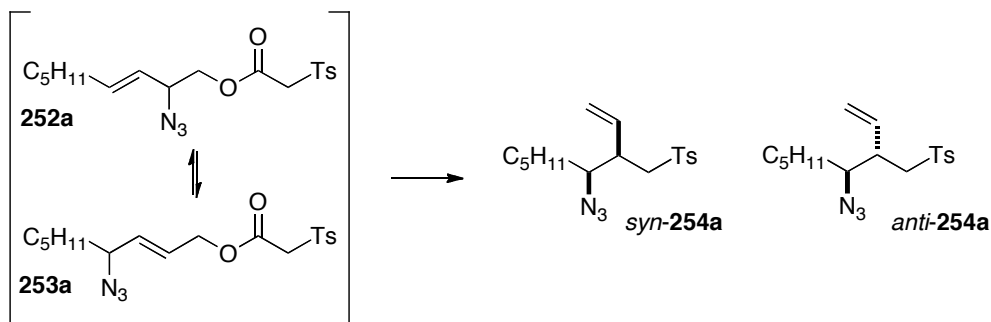
Data for the mixture: ν_{max} (film) 2101, 1742, 1598, 1329, 1151, 1055, 814 cm^{-1} ; δ_{C} (101 MHz, CDCl_3) 162.3 (*Z* C-1), 162.1 (*E* C-1), 148.5, 138.9, 138.4, 136.4, 136.0, 135.8, 135.7, 133.6, 129.9, 129.6, 128.7, 128.6, 128.5, 128.4, 128.2, 126.4, 69.1 (*E* C-1), 62.4 (*Z* C-1), 60.9 (*E* and *Z* CH_2Ts), 55.2 (*E* C-4), 54.9 (*Z* C-4), 21.7 (*E* and *Z* TsMe), 20.7 (*Z* C-5), 20.4 (*E* C-5); m/z (ESI) 423 $[\text{MHNa}]^+$, 422 $[\text{MNa}]^+$, 417, 394, 196, 143 (Found: $[\text{MNa}]^+$, 422.1153. $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$ requires $[\text{MNa}]^+$, 422.1150).

^1H -NMR data for **E-253f**: δ_{H} (400 MHz, CDCl_3) 7.80 (2H, d, J 8.5, *m*-Ts), 7.43–7.35 (5H, m, Ph), 7.17 (2H, d, J 8.5, *o*-Ts), 5.72 (1H, dt, J 9.5, 1.5, H-3), 4.83 (2H, d, J 1.5, H-1), 4.13 (2H, s, CH_2Ts), 4.05 (1H, dq, J 9.5, 6.5, H-4), 2.48 (3H, s, TsMe), 1.25 (3H, d, J 6.5, H-5).

^1H -NMR data for **Z-253f**: δ_{H} (400 MHz, CDCl_3) 7.77 (2H, d, J 8.5, *m*-Ts), 7.43–7.35 (5H, m, Ph), 7.33 (2H, d, J 8.5, *o*-Ts), 5.93 (1H, d, J 9.5, H-3), 5.09 (2H, AB quartet, J 12.5, H-1), 4.54 (1H, dq, J 9.5, 6.5, H-4), 4.10 (2H, s, CH_2Ts), 2.47 (3H, s, TsMe), 1.36 (3H, d, J 6.5, H-5).

(*E*)-2-Azido-2-methyl-4-(pyridin-2-yl)but-3-enyl 2-tosylacetate (252g)

Allylic azide **235g** (532 mg, 1.24 mmol, 1.0 equiv) was reacted according to general procedure **M** to afford (*E*)-2-azido-2-methyl-4-(pyridin-2-yl)but-3-enyl 2-tosylacetate **252g** (259 mg, 52%) as a yellow oil after purification over silica gel (30% EtOAc/5% TEA/hexane): $\nu_{\max}$ (film) 2106, 1748, 1586, 1329, 1151, 1085, 970, 768 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 8.61 (1H, d, J 5.0, 6-pyridyl), 7.85 (2H, d, J 8.0, *o*-Ts), 7.70 (1H, dt, J 7.5, 2.0, 4-pyridyl), 7.38 (2H, d, J 8.0, *m*-Ts), 7.35 (1H, d, J 7.5, 3-pyridyl), 7.22 (1H, dd, J 7.5, 5.0, 5-pyridyl), 6.79 (1H, d, J 16.0, H-4), 6.73 (1H, d, J 16.0, H-3), 4.19 (2H, s, CH_2Ts), 4.17 (2H, d, J 2.0, H-1), 2.47 (3H, s, TsMe), 1.53 (3H, s, 2-Me); δ_{C} (101 MHz, CDCl_3) 162.1 (C=O), 154.0 (2-pyridyl), 149.7 (6-pyridyl), 145.6, 136.8 (4-pyridyl), 135.7, [131.8 and 131.7 (C-3) and [C-4)], 130.0 (*m*-Ts), 128.5 (*o*-Ts), 123.0 (5-pyridyl), 122.7 (3-pyridyl), 7.05 (C-1), 63.1 (C-2), 60.9 (CH_2Ts), 21.7 (TsMe), 21.0 (2-Me); m/z (CI) 401 $[\text{MH}]^+$, 360, 188 (Found: $[\text{MH}]^+$, 401.1276. $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$ requires $[\text{MH}]^+$, 401.1284).

1-[(3-Azido-2-ethenyloctane)sulfonyl]-4-methylbenzene (254a)

A 58:42 mixture of allylic azides **252a** and **253a** respectively (50 mg, 0.132 mmol, 1.0 equiv) was reacted according to general procedure **N** to afford *1-[(3-azido-2-ethenyloctane)sulfonyl]-4-methylbenzene* **254a** (38 mg, 86%, 84:16 *syn:anti* mixture of diastereomers) as a white solid after purification over silica gel (2–10% ether/petrol).

An alternative one-step procedure gave 254a in a lower yield:

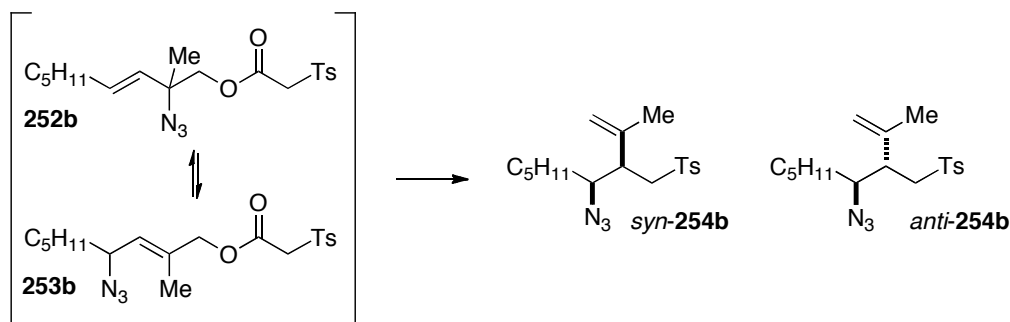
N,N-bis(trimethylsilyl)acetamide (0.484 mL, 1.98 mmol, 5.0 equiv), a 58:42 mixture of allylic azides **252a** and **253a** respectively (150 mg, 0.396 mmol, 1.0 equiv) and potassium acetate (4 mg, 0.396 mmol, 0.1 equiv) were combined in a 0.2–0.5 mL microwave vial. The vial was flushed with nitrogen, sealed and heated under microwave irradiation at 170 °C for two cycles of 5 min. The reaction mixture was concentrated under reduced pressure and the residue was purified over silica gel (2–10% ether/petrol) to afford *1-[(3-azido-2-ethenyloctane)sulfonyl]-4-methylbenzene* **254a** (42 mg, 32%, 84:16 *syn:anti* mixture of diastereomers) as a white solid. Repeated purification over silica gel (2–10% ether/petrol) followed by recrystallisation (EtOAc/petrol) afforded an analytical sample of *syn*-**254a** and an analytical sample enriched in *anti*-**254a**.

Data for *syn*-**254a**: m.p 72–74 °C; ν_{max} (film) 2902, 2100, 1456, 1142, 880, 771, 706, 670 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.81 (2H, d, J 8.5, *o*-Ts), 7.39 (2H, d, J 8.5, *m*-Ts), 5.60 (1H, ddd, J 17.0, 10.0, 8.5, CHCH_2), 5.17 (1H, d, J 10.0, *trans*- CHCH_2), 5.12 (1H, d, J 17.0, *cis*- CHCH_2), 3.70 (1H, ddd, J 8.5, 5.5, 3.0, H-3), [3.40 (1H, dd, J 14.0, 7.0) and 3.15 (1H, dd, J 14.0, 6.0), H-1], 2.90 (1H, dddd, J 12.5, 9.5, 6.0, 3.0, H-2), 2.48 (3H, s, TsMe), 1.62–1.31 (8H, m, H-4,5,6,7), 0.92 (3H, t, J 6.0, H-8); δ_{C} (101 MHz, CDCl_3) 144.9 (Ts), 136.9 (Ts), 133.7 (CHCH_2), 130.0 (*m*-Ts), 128.0 (*o*-Ts), 119.5 (CHCH_2), 64.3 (C-3), 58.1 (C-1), 42.5 (C-2), 32.2 (C-4), 31.5 (C-5), 25.8 (C-6), 22.5 (C-7), 21.7 (TsMe), 14.0 (C-8); m/z (CI) 353 $[\text{MNH}_4]^+$, 310, 226, 174, 152; m/z (CI) 353 $[\text{MNH}_4]^+$, 310, 226, 152 (Found: $[\text{MNH}_4]^+$, 353.2020. $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$ requires $[\text{MNH}_4]^+$, 353.2011) (Found: C, 60.95; H, 7.47; N, 12.48. $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$ requires C, 60.87; H, 7.51; N, 12.53).

NMR data for *anti*-**254a**: δ_{H} (400 MHz, CDCl_3) 7.79 (2H, d, J 8.0, *o*-Ts), 7.38 (2H, d, J 8.0, *m*-Ts), 5.68 (1H, ddd, J 17.5, 10.0, 8.5, CHCH_2), 5.17 (1H, d, J 10.0, *trans*-

CHCH₂), 5.16 (1H, d, *J* 17.5, *cis*-CHCH₂), 3.41–3.36 (1H, m, H-3), [3.31 (1H, dd, *J* 14.5, 3.5) and 3.20 (1H, dd, *J* 14.5, 9.0), H-1], 2.80–2.74 (1H, m, H-2), 2.48 (3H, s, TsMe), 1.63–1.28 (8H, m, H-4,5,6,7), 0.91 (3H, t, *J* 7.0, H-8); δ_{C} (101 MHz, CDCl₃) 144.4 (Ts), 135.9 (Ts), 135.5 (CHCH₂), 129.9 (*m*-Ts), 128.1 (*o*-Ts), 118.9 (CHCH₂), 65.8 (C-3), 56.9 (C-1), 43.0 (C-2), 31.6 (C-4), 31.4 (C-5), 25.3 (C-6), 22.4 (C-7), 21.7 (TsMe), 13.6 (C-8).

1- $\{[3\text{-Azido-2-(prop-1-en-2-yl)octane]sulfonyl}\}$ -4-methylbenzene (**254b**)



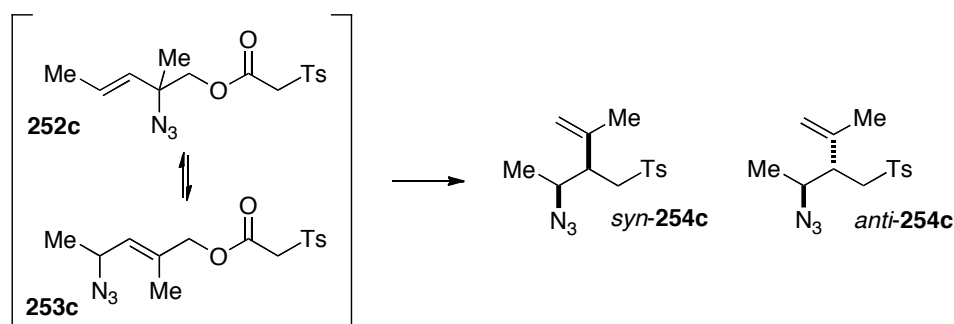
A 68:32 mixture of allylic azides **253b** and **252b** respectively (161 mg, 0.41 mmol, 1.0 equiv) was reacted according to general procedure **O** to afford 1- $\{[3\text{-azido-2-(prop-1-en-2-yl)octane]sulfonyl}\}$ -4-methylbenzene **254b** (97 mg, 68%, 68:32 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (15% ether/petrol). Further purification over silica gel (10% ether/petrol) afforded an analytical sample of *syn*-**254b** and an analytical sample enriched in *anti*-**254b**.

Data for *syn*-**254b**: ν_{max} (film) 2103, 1647, 1597, 1455, 1303, 1142, 1088, 899, 815 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.68 (2H, d, *J* 8.0, *o*-Ts), 7.34 (2H, d, *J* 8.0, *m*-Ts), 4.87 (1H, t, *J* 1.5, *trans*-CMeCH₂), 4.78 (1H, s, *cis*-CMeCH₂), 3.61 (1H, dt, *J* 7.0, 5.0, H-3), [3.37 (1H, dd, *J* 14.5, 6.5) and 3.19 (1H, dd, *J* 14.5, 6.5), H-1], 2.86 (1H, dt, *J* 6.5, 5.0, H-2), 2.43 (3H, s, TsMe), 1.64 (3H, s, CMeCH₂), 1.49–1.23 (8H, m, H-4,5,6,7), 0.87 (3H, t, *J* 6.5, H-8); δ_{C} (101 MHz, CDCl₃) 144.8, 141.4, 136.9, 129.9 (*o*-Ts), 128.0 (*m*-Ts), 116.4 (CMeCH₂), 64.2 (C-3), 57.1 (C-1), 44.7 (C-2), 32.3, 31.5, 26.2,

22.5, 21.0, 14.0 (C-8); m/z (CI) 367 $[\text{MNH}_4]^+$, 350 $[\text{MH}]^+$, 324, 240 (Found: $[\text{MNH}_4]^+$, 367.2172. $\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$ requires $[\text{MNH}_4]^+$, 367.2168).

NMR data for *anti*-**254b**: δ_{H} (400 MHz, CDCl_3) 7.74 (2H, d, J 8.0, *o*-Ts), 7.32 (2H, d, J 8.0, *o*-Ts), 4.89 (1H, t, J 1.5, *trans*- CMeCH_2), 4.83 (1H, s, *cis*- CMeCH_2), [3.94 (1H, dd, J 14.5, 3.0) and 3.27 (1H, dd, J 14.5, 8.0), H-1], 3.17–3.12 (1H, m, H-3), 2.60 (1H, ddd, J 10.0, 8.0, 3.0, H-2), 2.43 (3H, s, TsMe), 1.63 (3H, s, CMeCH_2), 1.49–1.23 (8H, m, H-4,5,6,7), 0.87 (3H, t, J 6.5, H-8); δ_{C} (101 MHz, CDCl_3) 144.7, 141.8, 136.8, 129.8 (*o*-Ts), 128.1 (*m*-Ts), 116.2 (CMeCH_2), 64.7 (C-3), 56.2 (C-1), 45.8 (C-2), 32.1, 31.4, 25.8, 21.6, 19.8, 14.0 (C-8).

1-[2-(1-Azidoethyl)-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene (**254c**)



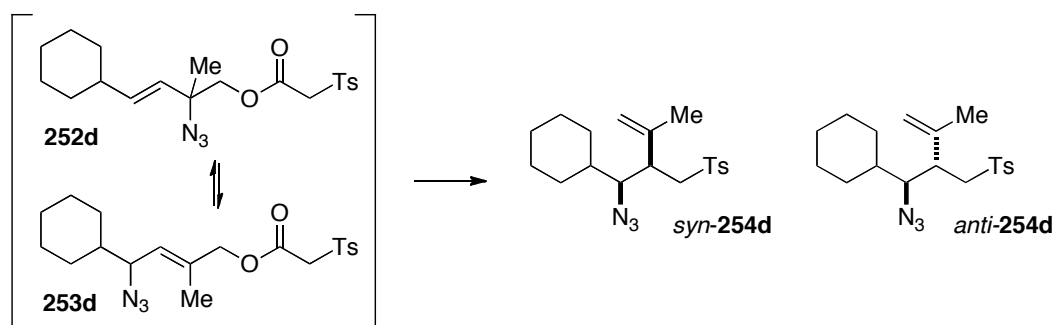
A 70:30 mixture of allylic azides **253c** and **252c** respectively (50 mg, 0.16 mmol, 1.0 equiv) was reacted according to general procedure N to afford 1-[2-(1-azidoethyl)-3-methylbut-3-ene-1-sulfonyl]-4-methylbenzene **254c** (36 mg, 82%, 91:9 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (10% ether/petrol). Further purification over silica gel (10% ether/petrol) afforded an analytical sample of *syn*-**254c** and an analytical sample enriched in *anti*-**254c**.

Data for *syn*-**254c**: ν_{max} (film) 2110, 1648, 1598, 1452, 1304, 1146, 1087, 871, 693 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.81 (2H, d, J 8.0, *o*-Ts), 7.38 (2H, d, J 8.0, *m*-Ts), 4.95 (1H, s, *trans*- CMeCH_2), 4.83 (1H, s, *cis*- CMeCH_2), 3.89 (1H, dq, J 6.5, 5.0, H-3), [3.40 (1H, dd, J 14.0, 6.0) and 3.25 (1H, dd, J 14.0, 7.0), H-1], 2.81 (1H, dt, J 6.0,

5.0, H-2), 2.48 (3H, s, TsMe), 1.70 (3H, s, CMeCH₂), 1.26 (3H, d, *J* 6.5, H-4); δ_{C} (101 MHz, CDCl₃) 144.8, 141.2, 136.8, 129.8 (*m*-Ts), 128.0 (*o*-Ts), 116.5 (CMeCH₂), 58.7 (C-3), 56.8 (C-1), 45.7 (C-2), 21.7 (TsMe), 21.1 (CMeCH₂), 16.9 (C-4); *m/z* (CI), 311 [MNH₄]⁺, 294 [MH]⁺, 268 (Found: [MNH₄]⁺, 311.1542. C₁₄H₁₉N₃O₂S requires [MNH₄]⁺, 311.1542).

NMR data for *anti*-**254c** *inter alia*: δ_{H} (400 MHz, CDCl₃) 7.79 (2H, d, *J* 7.5, *o*-Ts), 7.37 (2H, d, *J* 7.5, *m*-Ts), 4.87 (1H, s, *trans*-CMeCH₂), 4.54 (1H, s, *cis*-CMeCH₂), 2.06–1.93 (1H, m, H-3), 1.05 (3H, d, *J* 7.0, H-4), δ_{C} (101 MHz, CDCl₃) 129.7 (*m*-Ts), 128.1 (*o*-Ts).

1-{2-[Azido(cyclohexyl)methyl]-3-methylbut-3-ene-1-sulfonyl}-4-methylbenzene (254d)



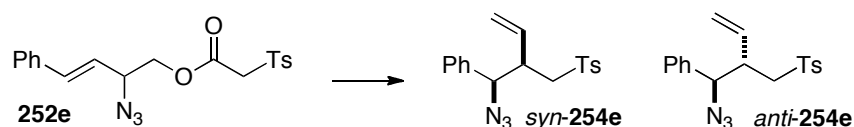
A 65:35 mixture of allylic azides **253d** and **252d** respectively (234 mg, 0.58 mmol, 1.0 equiv) was reacted according to general procedure **O** to afford 1-{2-[azido(cyclohexyl)methyl]-3-methylbut-3-ene-1-sulfonyl}-4-methylbenzene **254d** (92 mg, 44%, 82:18 *syn:anti* mixture of diastereomers) as a colourless gum after purification over silica gel (15% ether/petrol).

Data for the mixture: ν_{max} (film) 2100, 1646, 1597, 1449, 1302, 1143, 1087, 815, 761 cm⁻¹; *m/z* (CI) 379 [MNH₄]⁺, 336, 240, 184, 112 (Found: [MNH₄]⁺, 379.2170. C₁₉H₂₇N₃O₂S requires [MNH₄]⁺, 379.2168).

NMR data for *syn*-**254d**: δ_{H} (400 MHz, CDCl_3) 7.82 (2H, d, J 8.5, *o*-Ts), 7.39 (2H, d, J 8.5, *m*-Ts), 4.90 (1H, t, J 1.5, *trans*- CMeCH_2), 4.85 (1H, s, *cis*- CMeCH_2), 3.85–3.42 (2H, m, H-1 and H-3), 3.21 (1H, dd, J 14.5, 6.0, H-1), 3.08 (1H, dt, J 7.5, 6.0, H-2), 2.49 (3H, s, TsMe), 1.89–1.07 (11H, m, cyclohexyl), 1.67 (3H, s, CMeCH_2); δ_{C} (101 MHz, CDCl_3) 144.8 (*i*-Ts), 141.9 (*p*-Ts), 129.9 (*m*-Ts), 128.1 (*o*-Ts), 116.6 (CMeCH_2), 77.2 (CMeCH_2), 70.1 (C-3), 57.7 (C-1), 42.2 (C-2), 40.6, 30.5, 29.1, 26.1, 25.8, 20.8.

NMR data for *anti*-**254d**: δ_{H} (400 MHz, CDCl_3) 7.79 (2H, d, J 8.5, *o*-Ts), 7.37 (2H, d, J 8.5, *m*-Ts), 4.95 (1H, t, J 1.5, *trans*- CMeCH_2), 4.91 (1H, s, *cis*- CMeCH_2), 3.43–3.29 (2H, m, H-1), 3.08–3.04 (1H, m, H-3), 2.87 (1H, m, H-2), 2.48 (3H, s, TsMe), 1.89–1.07 (11H, m, cyclohexyl), 1.70 (3H, s, CMeCH_2); δ_{C} (101 MHz, CDCl_3) 144.6 (*i*-Ts), 136.9 (*p*-Ts), 129.7 (*m*-Ts), 128.2 (*o*-Ts), 115.8 (CMeCH_2), 77.2 (CMeCH_2), 71.5 (C-3), 56.0 (C-1), 42.6 (C-2), 40.6, 30.8, 27.6, 25.7, 21.7, 20.0.

1-{2-[Azido(phenyl)methyl]but-3-ene-1-sulfonyl}-4-methylbenzene (**254e**)



Allylic azide **252e** (213 mg, 0.55 mmol, 1.0 equiv) was reacted according to general procedure **O** to afford 1-{2-[azido(phenyl)methyl]but-3-ene-1-sulfonyl}-4-methylbenzene **254e** (36 mg, 22%, 75:25 *syn:anti* mixture of diastereomers) after purification over silica gel (10% ether/petrol).

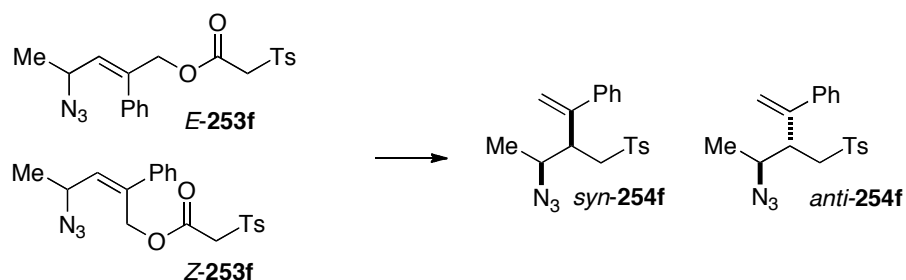
Data for the mixture: ν_{max} (film) 2104, 1640, 1598, 1300, 1146, 1087, 755, 662 cm^{-1} ; m/z (CI) 359 $[\text{MNH}_4]^+$, 342 $[\text{MH}]^+$, 316, 311, 266 (Found: $[\text{MNH}_4]^+$, 359.1546. $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ requires $[\text{MNH}_4]^+$, 359.1542).

NMR data for *syn*-**254e**: δ_{H} (400 MHz, CDCl_3) 7.81 (2H, d, J 8.0, *o*-Ts), 7.38 (2H, d, J 8.0, *m*-Ts), 7.31–7.17 (5H, m, Ph), 5.68 (1H, ddd, J 17.5, 10.0, 7.5, CHCH_2), 5.38

(1H, d, J 17.5, *cis*-CHCH₂), 5.19 (1H, d, J 10.0, *trans*-CHCH₂), 4.96 (1H, d, J 8.5, H-3), [3.41 (1H, dd, J 14.5, 9.5) and 3.38 (1H, dd, J 14.5, 5.5), H-1], 3.24–3.18 (1H, m, H-2), 2.48 (3H, s, TsMe); δ_{C} (101 MHz, CDCl₃) 144.5, 135.3, 129.9, 129.6, 129.4, 128.0, 127.9, 127.4, 127.3, 117.3, 67.8 (C-3), 56.7 (C-1), 45.7 (C-2), 21.7 (TsMe).

NMR data for *anti*-**254e**: δ_{H} (400 MHz, CDCl₃) 7.78 (2H, d, J 8.0, *o*-Ts), 7.37 (2H, d, J 8.0, *m*-Ts), 7.31–7.17 (5H, m, Ph), 5.57 (1H, ddd, J 17.0, 10.0, 8.5, CHCH₂), 5.10 (1H, d, J 10.0, *trans*-CHCH₂), 4.91 (1H, d, J 8.5, H-3), 4.85 (1H, d, J 17.0, *cis*-CHCH₂), [3.26 (1H, dd, J 14.5, 7.0) and 3.10 (1H, dd, J 14.5, 7.0), H-1], 3.03–2.96 (1H, m, H-2), 2.43 (3H, s, TsMe); δ_{C} (101 MHz, CDCl₃) *inter alia* 141.1, 133.9, 130.0, 128.5, 119.7, 65.5 (C-3), 57.3 (C-1), 44.7 (C-2), 21.1 (TsMe).

1-[2-(1-Azidoethyl)-3-phenylbut-3-ene-1-sulfonyl]-4-methylbenzene (**254f**)



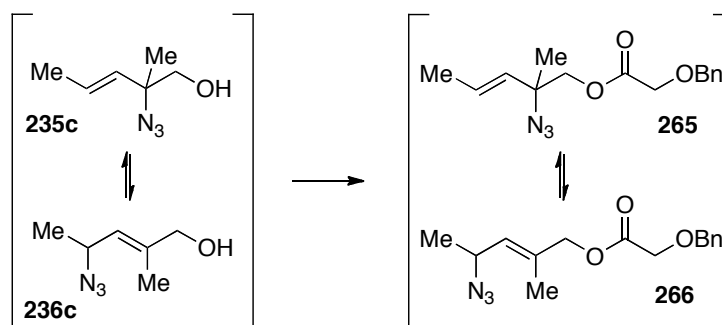
A 75:25 mixture of allylic azides *E*-**253f** and *Z*-**253f** respectively (297 mg, 0.74 mmol, 1.0 equiv) was reacted according to general procedure N to afford 1-[2-(1-azidoethyl)-3-phenylbut-3-ene-1-sulfonyl]-4-methylbenzene **254f** (87 mg, 32%, 73:27 *syn:anti* mixture of diastereomers) as a colourless oil after purification over silica gel (10–40% ether/hexane).

Data for the mixture: ν_{max} (film) 2109, 1626, 1597, 1494, 1317, 1143, 1087, 907, 815, 779 cm⁻¹; m/z (CI) 373 [MNH₄]⁺, 355 [M]⁺, 330, 178 (Found: [MNH₄]⁺, 373.1698). C₁₉H₂₁N₃O₂S requires [MNH₄]⁺, 373.1698).

NMR data for *syn*-**254f**: δ_{H} (400 MHz, CDCl_3) 7.82 (2H, d, J 8.0, *o*-Ts), 7.38–7.32 (7H, *m*-Ts, CPhCH_2), [5.43 (1H, s) and 5.19 (1H, s), CPhCH_2], 3.94 (1H, dq, 6.5, 4.0, H-3), 3.63–3.42 (3H, m, H-1,2), 2.48 (3H, s, TsMe), 1.15 (3H, d, J 6.5, H-4); δ_{C} (101 MHz, CDCl_3) 145.9 (CPhCH_2), 144.9, 142.0, 136.9, 130.0, 129.8, 128.6, 128.1, 128.0, 117.0 (CPhCH_2), 58.8 (C-3), 57.1 (C-1), 42.8 (C-2), 21.7 (TsMe), 16.2 (C-4).

NMR data for *anti*-**254f**: δ_{H} (400 MHz, CDCl_3) 7.75 (2H, d, J 8.0, *o*-Ts), 7.38–7.32 (7H, *m*-Ts, CPhCH_2), [5.12 (1H, s) and 5.39 (1H, s), CPhCH_2], 3.63–3.42 (3H, m, H-1,3), 3.20 (1H, ddd, J 9.0, 6.5, 3.0, H-2), 2.46 (3H, s, TsMe), 1.29 (3H, d, J 6.5, H-4); δ_{C} (101 MHz, CDCl_3) *inter alia* 147.1 (CPhCH_2), 141.1, 128.5, 127.9, 127.0, 126.5, 116.4 (CPhCH_2), 60.3 (C-3), 57.0 (C-1), 44.7 (C-2), 21.7 (TsMe), 17.7 (C-4).

(*E*)-2-Azido-2-methylpent-3-en-1-yl 2-(benzyloxy)acetate (265) and (*E*)-4-azido-2-methylpent-2-en-1-yl 2-(benzyloxy)acetate (266)



To a solution of a 64:36 mixture of allylic azides **235c** and **236c** respectively (82 mg, 0.58 mmol, 1.0 equiv) in dichloromethane (2 mL) was added DCC (132 mg, 0.64 mmol, 1.1 equiv) and DMAP (7 mg, 0.06 mmol, 0.1 equiv) at rt and the resulting solution was stirred for 5 min. Benzyloxyacetic acid (91 μL , 0.64 mmol, 1.1 equiv) was added dropwise *via* syringe to give a white suspension. After stirring for 14 h, the reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure. Purification of the residue over silica gel (10% ether/petrol) afforded a 66:33 mixture of (*E*)-4-azido-2-methylpent-2-en-1-yl 2-(benzyloxy)acetate

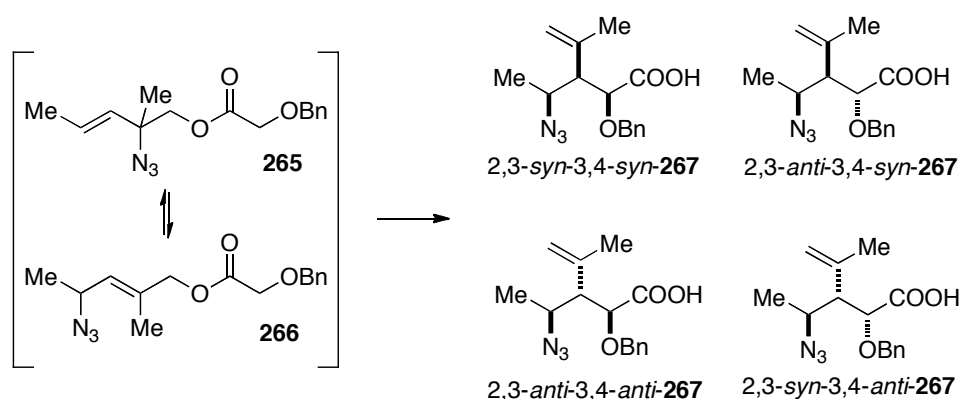
266 and (E)-2-Azido-2-methylpent-3-en-1-yl 2-(benzyloxy)acetate **265** respectively (71 mg, 42%) as a colourless oil.

Data for the mixture: $\nu_{\max}$ (film) 2104, 1757, 1452, 1243, 1192, 1127 cm^{-1} ; δ_{C} (101 MHz, CDCl_3) 170.0 (C-1), 132.2, 134.3, 134.2, 130.1, 129.6, 128.9, 128.7, 128.3, 127.8, 73.6 (CH_2), 69.7 (CH_2), 69.0 (CH_2), 67.3 (CH_2), 67.1 (CH_2), 63.4, 62.3, 54.7, 21.7, 21.3, 20.9, 20.5, 18.1, 14.6; m/z (CI) 307 $[\text{MNH}_4]^+$, 247 (Found: $[\text{MNH}_4]^+$, 307.1774. $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_3$ requires $[\text{MNH}_4]^+$, 307.1770).

^1H -NMR data for **265**: δ_{H} (400 MHz, CDCl_3) 7.41–7.36 (5H, m, Ph), 5.85 (1H, dq, J 15.5, 6.5, H-4), 5.50 (1H, d, J 15.5, H-3), 4.64 (2H, s), 4.19 (2H, s), 4.10 (2H, s), 1.41 (3H, s, 2-Me), 1.27 (3H, d, J 6.5, H-5).

^1H -NMR data for **266**: δ_{H} (400 MHz, CDCl_3) 7.41–7.36 (5H, m, Ph), 5.46 (1H, d, J 9.0, H-3), 4.68 (2H, s), 4.35 (1H, dq, J 9.0, 6.5, H-4), 4.18 (2H, s), 4.07 (2H, s), 1.78 (3H, d, J 1.5, 2-Me), 1.28 (3H, d, J 6.5, H-5).

4-Azido-3-(prop-1-enyl)-2-(benzyloxy)-pentanoic acid (**267**)

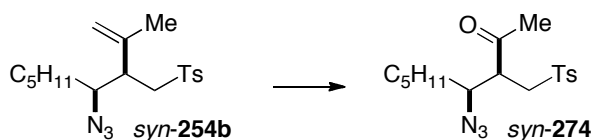


To a solution of a 66:33 mixture of allylic azides **266** and **265** respectively (69 mg, 0.24 mmol, 1.0 equiv) in THF (3.4 mL) at $-95\text{ }^{\circ}\text{C}$ was added LHMDS (0.72 mL of a 1 M solution in THF, 0.72 mmol, 3.0 equiv) dropwise *via* syringe. The resulting solution was stirred for 1 h and base-treated chlorotrimethylsilane (0.18 mL, 1.43 mmol, 6.0 equiv) was added at $-95\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-95\text{ }^{\circ}\text{C}$ for

1 h, warmed to 0 °C over 1 h and warmed to rt during 24 h. Water (10 mL) and aqueous HCl (2 M, 10 mL) were added, the phases were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO₄), concentrated under reduced pressure and purified over silica gel (20% EtOAc/5% formic acid/petrol) to afford recovered starting material **265/266** (20 mg, 29% 66:33 mixture) and *4-azido-3-(prop-1-enyl)-2-(benzyloxy)-pentanoic acid* **267** (44 mg, 64%, 90% BRSM, 55:23:17:5 unassigned mixture of 4 diastereomers) as a colourless oil: ν_{max} (film) 3468, 2104, 1747, 1452, 1379, 1240, 1124, 1029, 743, 699 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 7.43–7.34 (20H, m, Ph), 5.02–4.13 (20H, m, OCH₂, CMeCH₂ and H-2), [4.18 (1H, dq, *J* 7.0, 4.5), 3.93 (1H, dq, *J* 10.0, 6.5), 3.86 (1H, dq, *J* 10.5, 6.5) and 3.78 (1H, dq, *J* 10.0, 6.5), H-4], [2.67 (1H, dd, *J* 10.0, 3.0), 2.59 (1H, dd, *J* 9.5, 4.5), 2.57 (1H, dd, *J* 9.5, 4.0) and (1H, dd, *J* 11.0, 4.0), H-3], [1.89 (3H, s), 1.82 (6H, s), 1.79 (3H, s) and 1.79 (3H, s), CMeCH₂], 1.30–1.22 (12H, m, H-5); δ_{C} (101 MHz, CDCl₃) [177.0, 176.8, 176.7 and 176.4 (C-1)], 166.1, 165.2, 142.8, 142.0, 136.9, 136.8, 136.7, 117.5, 116.7, 115.1, 79.0, 78.9, 78.8, 78.6, 73.6, 73.5, 73.2, 73.1, 56.5, 56.2, 55.9, 55.4, 54.7, 54.6, 54.4, 54.1, 31.9, 29.7, 29.5, 29.4, 29.2, 29.1, [22.7, 22.5, 22.0 and 21.2 (CMeCH₂)], [17.9, 17.7, 17.4 and 17.2 (C-5)]; *m/z* (CI), 321, 307 [MNH₄]⁺, 288 [M–H]⁺, 274, 184 (Found: [MNH₄]⁺, 307.1773. C₁₅H₁₉N₃O₃ requires [MNH₄]⁺, 307.1770).

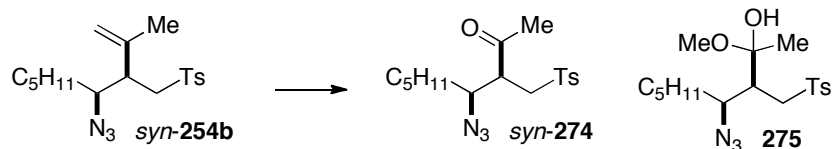
3.4.4 Compounds relevant to section 2.6

Syn-4-azido-3-{[(4-methylbenzene)sulfonyl]methyl}nonan-2-one (*syn*-274)



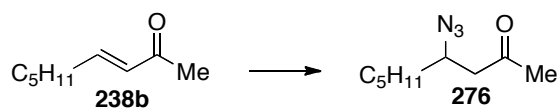
Ozone gas was passed through a stirred solution of sulfone *syn*-254b (24 mg, 0.07 mmol, 1.0 equiv) in dichloromethane (2.5 mL) at $-78\text{ }^{\circ}\text{C}$ for 5 min. The solution was purged with nitrogen and dimethylsulfide (0.10 mL) was added at $-78\text{ }^{\circ}\text{C}$. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, allowed to warm to rt overnight and concentrated under reduced pressure. Purification of the residue over silica gel (10% EtOAc/petrol) afforded *syn*-4-azido-3-{[(4-methylbenzene)sulfonyl]methyl}nonan-2-one *syn*-274 (21 mg, 88%) as a colourless oil: ν_{max} (film) 2106, 1719, 1598, 1316, 1148, 1087, 816 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.80 (2H, d, J 8.0, *o*-Ts), 7.40 (2H, d, J 8.0, *m*-Ts), [3.73 (1H, dd, J 14.0, 9.5) and 3.13 (1H, dd, J 14.0, 3.0), CH_2Ts], 3.59 (1H, dt, J 9.0, 6.5, H-4), 3.54 (1H, dt, J 9.5, 6.5, H-3), 2.49 (3H, s, TsMe), 2.35 (3H, s, H-1), 1.48–1.27 (8H, m, H-5,6,7,8), 0.91 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 206.1 (C-2), 145.3, 136.1, 130.1 (*m*-Ts), 128.0 (*o*-Ts), 63.1 (C-4), 54.8 (CH_2Ts), 49.2 (C-3), 31.5, 31.4, 31.3 (C-1), 25.5, 22.4, 21.7 (TsMe), 13.9 (C-9); m/z (CI) 369 $[\text{MNH}_4]^+$, 342, 326 (Found: C, 58.00; H, 7.13; N, 11.85. $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ requires C, 58.09; H, 7.17; N, 11.96).

Syn-4-azido-3-{[(4-methylbenzene)sulfonyl]methyl}nonan-2-one (*syn*-274) and 4-azido-2-methoxy-3-{[(4-methylbenzene)sulfonyl]methyl}nonan-2-ol (275)



When the above reaction was performed with a mixture of dichloromethane and methanol (4:1 v/v) as the solvent, *syn*-274 (17%) and an additional product 4-azido-2-methoxy-3-{[(4-methylbenzene)sulfonyl]methyl}nonan-2-ol **275** (34%) was isolated as a colourless oil composed of a single diastereomer: ν_{max} (film) 3392, 2105, 1598, 1294, 1143, 815 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.86 (2H, d, J 8.0, *o*-Ts), 7.41 (2H, d, J 8.0, *m*-Ts), 3.65 (1H, dt, J 10.0, 3.5, H-4), [3.59 (1H, dd, J 14.5, 4.0) and 3.14 (1H, dd, J 14.5, 5.0) CH_2Ts], 3.32 (3H, s, OMe), 3.00 (1H, dt, J 10.0, 4.0, H-3), 2.49 (3H, s, TsMe), 1.54 (3H, s, H-1), 1.50–1.25 (8H, m, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 145.0, 136.5, 130.0 (*m*-Ts), 128.1 (*o*-Ts), 106.7 (C-2), 63.3 (C-4), 53.3 (CH_2Ts), 49.8 (OMe), 42.8 (C-3), 31.4 (C-5), 31.3 (C-6), 26.7 (C-7,8), 21.7 (TsMe), 18.4 (C-1), 14.0 (C-9).

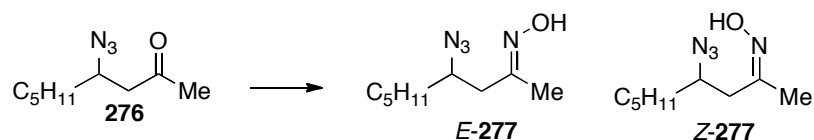
4-Azidononan-2-one (276)



To a solution of azidotrimethylsilane (3.32 mL, 25.0 mmol, 5.0 equiv) in dichloromethane (20 mL) was added acetic acid (1.42 mL, 25.0 mmol, 5.0 equiv) at rt. The solution was stirred for 20 min and 3-nonen-2-one **238b** (0.70 g, 5.0 mmol, 1.0 equiv) was added dropwise. TEA (0.14 mL, 1.0 mmol, 0.2 equiv) was then added and

the solution was stirred for 24 h. The reaction mixture was passed through a silica gel plug (10% ether/petrol) and concentrated under reduced pressure to afford 4-azidononan-2-one **276** (863 mg, 94%) as a colourless oil: $\nu_{\max}$ (film) 2102, 1719, 1362, 1260 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 3.90–3.83 (1H, m, H-4), [2.69 (1H, dd, J 17.0, 8.5) and 2.57 (1H, dd, J 17.0, 5.0), H-3], 2.21 (3H, s, H-1), 1.54–1.26 (8H, m, H-5,6,7,8), 0.92 (3H, t, J 7.0, H-9); δ_{C} (101 MHz, CDCl_3) 205.9 (C-2), 58.2 (C-4), 48.0 (C-3), 34.4 (C-5), 31.8 (C-6), 30.6 (C-1), 25.6 (C-7), 22.5 (C-8), 14.0 (C-9); m/z (CI) 201 $[\text{MNH}_4]^+$, 184 $[\text{MH}]^+$, 156 (Found: $[\text{MNH}_4]^+$, 201.1715. $\text{C}_9\text{H}_{17}\text{N}_3\text{O}$ requires $[\text{MNH}_4]^+$, 201.1715); in agreement with published data.^{202e}

(E)- and (Z)-4-Azidononan-2-one oxime (277)



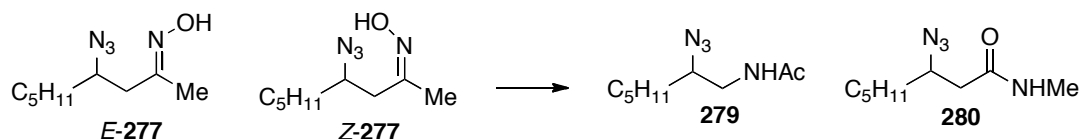
To a solution of azidoketone **276** (2.20 g, 12.0 mmol, 1.0 equiv) in acetonitrile (40 mL) and water (10 mL) was added sodium acetate (1.48 g, 18.0 mmol, 1.50 equiv) at rt. The mixture was stirred for 10 min to give a homogeneous solution and hydroxylamine hydrochloride (0.97 g, 14.0 mmol, 1.17 equiv) was added. The resulting solution was stirred at rt for 2 h and concentrated under reduced pressure to remove acetonitrile. The residue was partitioned between EtOAc (50 mL) and water (50 mL), the phases were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure to afford an inseparable 66:33 mixture of (E)- and (Z)-4-azidononan-2-one oxime **277** respectively (2.23 g, 94%) as a colourless oil after purification over silica gel (15% ether/petrol).

Data for the mixture: $\nu_{\max}$ (film) 3234, 2103, 1664, 1468, 1378, 1248, 961, 727; m/z (CI) 216 $[\text{MNH}_4]^+$, 199 $[\text{MH}]^+$, 177 (Found: $[\text{MH}]^+$, 199.1559. $\text{C}_9\text{H}_{18}\text{N}_4\text{O}$ requires $[\text{MH}]^+$, 199.1559).

NMR data for *E*-**277**: δ_{H} (500 MHz, CDCl_3) 8.06 (1H, s (br), OH), 3.36 (1H, dt, J 13.0, 6.5, H-4), 2.38 (1H, d, J 6.5, H-3), 1.93 (1H, s, H-1), 1.57–1.25 (8H, m, H-5,6,7,8), 0.89 (3H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 155.5 (C-2), 59.9 (C-4), 40.7 (C-3), 34.5, 31.5, 25.6, 22.5, 14.0 (C-9 and C-1).

NMR data for *Z*-**277**: δ_{H} (500 MHz, CDCl_3) 8.06 (1H, s (br), OH), 3.73–3.68 (1H, m, H-4), [2.65 (1H, dd, J 13.0, 5.0) and 2.46 (1H, dd, J 13.0, 9.5), H-3], 1.95 (1H, s, H-1), 1.57–1.25 (8H, m, H-5,6,7,8), 0.90 (3H, t, J 6.5, H-9); δ_{C} (101 MHz, CDCl_3) 155.8 (C-2), 59.6 (C-4), 34.9, 34.5, 33.9 (C-3), 31.5, 22.5, 21.1 (C-1), 14.0 (C-9).

N-(2-Azidoheptyl)acetamide (**279**) and 3-azido-*N*-methyloctanamide (**280**)



To a solution of the oxime **277** (111 mg, 0.56 mmol, 1.0 equiv) in dichloromethane (3.29 mL) was added TEA (0.22 mL, 1.60 mmol, 2.85 equiv), DMAP (14 mg, 0.11 mmol, 0.2 equiv) and *p*-toluenesulfonyl chloride (305 mg, 1.60 mmol, 2.85 equiv) at rt. The mixture was stirred for 15 min and concentrated under reduced pressure. The residue was purified over silica gel (20% ether/petrol) to remove residual *p*-toluenesulfonyl chloride. Then, to a solution of the residue in IPA-water (3.29 mL, 4:1 v/v) was added TEA (0.22 mL, 1.60 mmol, 2.85 equiv) and the mixture was heated to reflux at 90 °C for 3 h. The reaction mixture was cooled to rt and water (25 mL) and EtOAc (25 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. Purification of the residue over silica gel (50–80% EtOAc/petrol) gave an inseparable 2:1 mixture of *N*-(2-azidoheptyl)acetamide **279** and 3-azido-*N*-methyloctanamide **280** respectively (49 mg, 44%) as a yellow oil.

Data for the mixture: $\nu_{\max}$ (film) 3298, 3087, 2107, 1654, 1555, 1462, 1373, 1274 cm^{-1} ; m/z (CI) 216 $[\text{MNH}_4]^+$, 199 $[\text{MH}]^+$, 171, 100 (Found: $[\text{MH}]^+$, 199.1560. $\text{C}_9\text{H}_{18}\text{N}_4\text{O}$ requires $[\text{MH}]^+$, 199.1559).

NMR data for **279**: δ_{H} (400 MHz, CDCl_3) 5.83 (1H, s (br), NH), [3.62 (1H, ddd, J 13.5, 7.0, 3.5) and 3.04 (1H, ddd, 13.5, 8.5, 3.5), H-1], 3.56–3.50 (1H, m, H-2), 2.04 (3H, s, Me), 1.59–1.28 (8H, m, H-3,4,5,6), 0.92 (3H, t, J 7.0, H-7); δ_{C} (101 MHz, CDCl_3) 170.3 (C=O), 62.3 (C-2), 43.0 (C-1), 31.5, 32.2 (C-3), 25.6, 23.2 (Me), 22.5, 14.0 (C-7);

NMR data for **280**: δ_{H} (400 MHz, CDCl_3) 5.72 (1H, s (br), NH), 3.88 (1H, ddt, J 14.0, 6.5, 2.5, H-3), 2.86 (3H, d, J 5.0, NHMe), [2.40 (1H, dd, J 14.0, 4.5) and 2.29 (1H, dd, J 14.0, 8.5), H-2], 1.59–1.28 (8H, m, H-3,4,5,6), 0.92 (3H, t, J 7.0, H-7); δ_{C} (101 MHz, CDCl_3) 170.4 (C-1), 59.6 (C-3), 41.4 (C-2), 35.5 (C-4), 32.0, 29.9, 26.6 (NHMe), 23.0, 14.1 (C-8).

Chapter 4

Appendix

4.1 Crystallographic data for *anti*-160

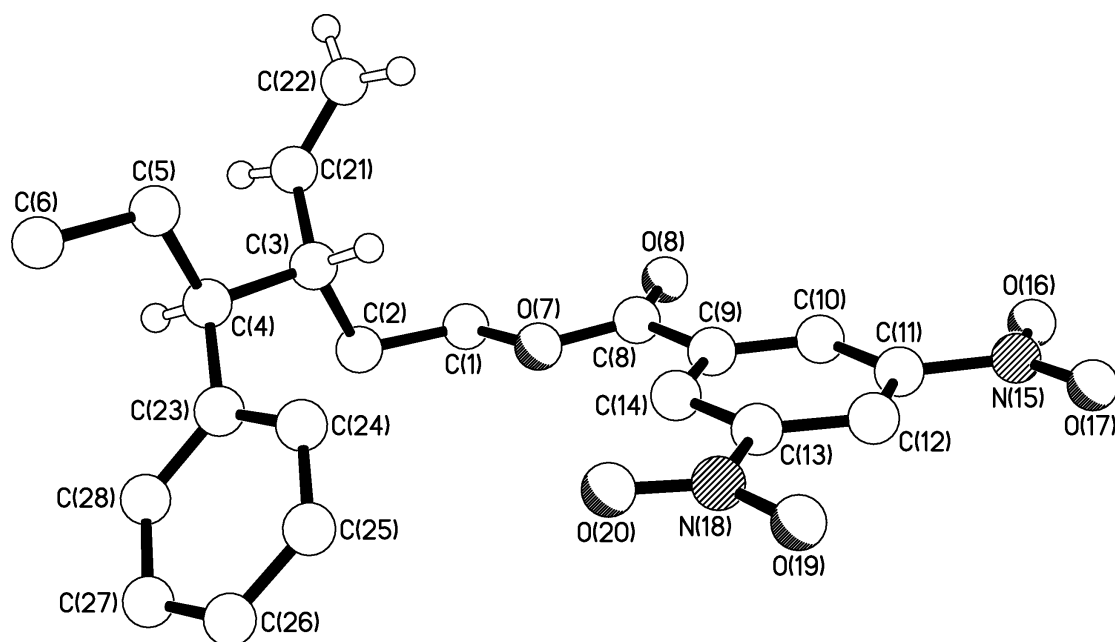


Table 1. Crystal data and structure refinement for DC0703.

Identification code	DC0703
Empirical formula	C ₂₁ H ₂₂ N ₂ O ₆
Formula weight	398.41
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54248 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 9.6435(2) Å α = 90° b = 9.8412(2) Å β = 91.418(2)°
Volume, Z	c = 42.7551(9) Å γ = 90° 4056.37(15) Å ³ , 8
Density (calculated)	1.305 Mg/m ³
Absorption coefficient	0.803 mm ⁻¹
F(000)	1680
Crystal colour / morphology	Colourless plates
Crystal size	0.42 x 0.24 x 0.01 mm ³
θ range for data collection	2.07 to 71.58°
Index ranges	-11 ≤ h ≤ 11, -10 ≤ k ≤ 11, - 51 ≤ l ≤ 52
Reflns collected / unique	55324 / 7825 [R(int) = 0.0676]
Reflns observed [F > 4σ(F)]	4517
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.72928
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7825 / 0 / 523
Goodness-of-fit on F ²	1.041
Final R indices [F > 4σ(F)]	R1 = 0.0547, wR2 = 0.1288
R indices (all data)	R1 = 0.0967, wR2 = 0.1485
Largest diff. peak, hole	0.186, -0.229 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for DC0703.

C(1)-O(7)	1.460(3)
C(1)-C(2)	1.501(3)
C(2)-C(3)	1.535(3)
C(3)-C(21)	1.502(3)
C(3)-C(4)	1.539(3)
C(4)-C(23)	1.515(3)
C(4)-C(5)	1.538(4)
C(5)-C(6)	1.514(3)
O(7)-C(8)	1.327(3)
C(8)-O(8)	1.209(3)
C(8)-C(9)	1.501(3)
C(9)-C(10)	1.379(3)
C(9)-C(14)	1.391(3)
C(10)-C(11)	1.380(3)
C(11)-C(12)	1.379(3)
C(11)-N(15)	1.468(3)
C(12)-C(13)	1.378(3)
C(13)-C(14)	1.379(3)
C(13)-N(18)	1.477(3)
N(15)-O(16)	1.222(2)
N(15)-O(17)	1.228(2)
N(18)-O(20)	1.228(2)
N(18)-O(19)	1.230(2)
C(21)-C(22)	1.304(4)
C(23)-C(24)	1.387(3)
C(23)-C(28)	1.389(3)
C(24)-C(25)	1.379(3)
C(25)-C(26)	1.380(4)
C(26)-C(27)	1.376(3)
C(27)-C(28)	1.380(3)
C(1')-O(7')	1.463(3)
C(1')-C(2')	1.505(3)
C(2')-C(3')	1.530(4)
C(3')-C(21')	1.502(4)
C(3')-C(4')	1.545(3)
C(4')-C(23')	1.512(4)
C(4')-C(5')	1.546(4)
C(5')-C(6')	1.512(4)
O(7')-C(8')	1.329(3)

C(8')-O(8')	1.206(3)
C(8')-C(9')	1.498(3)
C(9')-C(10')	1.378(4)
C(9')-C(14')	1.397(3)
C(10')-C(11')	1.380(3)
C(11')-C(12')	1.389(3)
C(11')-N(15')	1.461(3)
C(12')-C(13')	1.366(4)
C(13')-C(14')	1.375(4)
C(13')-N(18')	1.485(3)
N(15')-O(17')	1.223(2)
N(15')-O(16')	1.233(3)
N(18')-O(19')	1.222(3)
N(18')-O(20')	1.226(4)
C(21')-C(22')	1.307(4)
C(23')-C(24')	1.386(4)
C(23')-C(28')	1.391(4)
C(24')-C(25')	1.382(4)
C(25')-C(26')	1.384(4)
C(26')-C(27')	1.377(4)
C(27')-C(28')	1.380(3)

O(7)-C(1)-C(2)	106.37(18)
C(1)-C(2)-C(3)	113.8(2)
C(21)-C(3)-C(2)	108.4(2)
C(21)-C(3)-C(4)	110.65(19)
C(2)-C(3)-C(4)	112.3(2)
C(23)-C(4)-C(5)	110.3(2)
C(23)-C(4)-C(3)	113.39(19)
C(5)-C(4)-C(3)	111.2(2)
C(6)-C(5)-C(4)	113.6(2)
C(8)-O(7)-C(1)	116.67(17)
O(8)-C(8)-O(7)	125.5(2)
O(8)-C(8)-C(9)	123.1(2)
O(7)-C(8)-C(9)	111.36(19)
C(10)-C(9)-C(14)	120.2(2)
C(10)-C(9)-C(8)	117.8(2)
C(14)-C(9)-C(8)	122.0(2)
C(9)-C(10)-C(11)	119.2(2)
C(12)-C(11)-C(10)	122.5(2)
C(12)-C(11)-N(15)	118.68(19)

C(10)-C(11)-N(15)	118.86(19)
C(13)-C(12)-C(11)	116.7(2)
C(12)-C(13)-C(14)	123.0(2)
C(12)-C(13)-N(18)	118.27(19)
C(14)-C(13)-N(18)	118.7(2)
C(13)-C(14)-C(9)	118.4(2)
O(16)-N(15)-O(17)	124.2(2)
O(16)-N(15)-C(11)	117.82(18)
O(17)-N(15)-C(11)	117.93(18)
O(20)-N(18)-O(19)	124.33(19)
O(20)-N(18)-C(13)	117.87(19)
O(19)-N(18)-C(13)	117.8(2)
C(22)-C(21)-C(3)	125.9(3)
C(24)-C(23)-C(28)	117.5(2)
C(24)-C(23)-C(4)	121.4(2)
C(28)-C(23)-C(4)	120.9(2)
C(25)-C(24)-C(23)	121.0(2)
C(24)-C(25)-C(26)	120.4(3)
C(27)-C(26)-C(25)	119.5(2)
C(26)-C(27)-C(28)	119.8(3)
C(27)-C(28)-C(23)	121.7(2)
O(7')-C(1')-C(2')	106.6(2)
C(1')-C(2')-C(3')	114.1(2)
C(21')-C(3')-C(2')	109.4(2)
C(21')-C(3')-C(4')	111.3(2)
C(2')-C(3')-C(4')	110.9(2)
C(23')-C(4')-C(3')	113.4(2)
C(23')-C(4')-C(5')	109.8(2)
C(3')-C(4')-C(5')	110.8(2)
C(6')-C(5')-C(4')	114.9(2)
C(8')-O(7')-C(1')	116.3(2)
O(8')-C(8')-O(7')	125.0(3)
O(8')-C(8')-C(9')	123.2(2)
O(7')-C(8')-C(9')	111.8(2)
C(10')-C(9')-C(14')	120.3(3)
C(10')-C(9')-C(8')	117.8(2)
C(14')-C(9')-C(8')	121.9(3)
C(9')-C(10')-C(11')	119.2(2)
C(10')-C(11')-C(12')	121.8(3)
C(10')-C(11')-N(15')	118.9(2)
C(12')-C(11')-N(15')	119.3(2)

C(13')-C(12')-C(11') 117.5(3)
C(12')-C(13')-C(14') 123.0(2)
C(12')-C(13')-N(18') 118.2(3)
C(14')-C(13')-N(18') 118.8(3)
C(13')-C(14')-C(9') 118.3(3)
O(17')-N(15')-O(16') 123.5(3)
O(17')-N(15')-C(11') 118.5(2)
O(16')-N(15')-C(11') 118.0(2)
O(19')-N(18')-O(20') 125.3(3)
O(19')-N(18')-C(13') 117.3(3)
O(20')-N(18')-C(13') 117.3(3)
C(22')-C(21')-C(3') 125.5(3)
C(24')-C(23')-C(28') 117.5(3)
C(24')-C(23')-C(4') 121.7(3)
C(28')-C(23')-C(4') 120.7(2)
C(25')-C(24')-C(23') 121.2(3)
C(24')-C(25')-C(26') 120.4(3)
C(27')-C(26')-C(25') 119.1(3)
C(26')-C(27')-C(28') 120.2(3)
C(27')-C(28')-C(23') 121.5(3)

4.2 Crystallographic data for *syn*-197

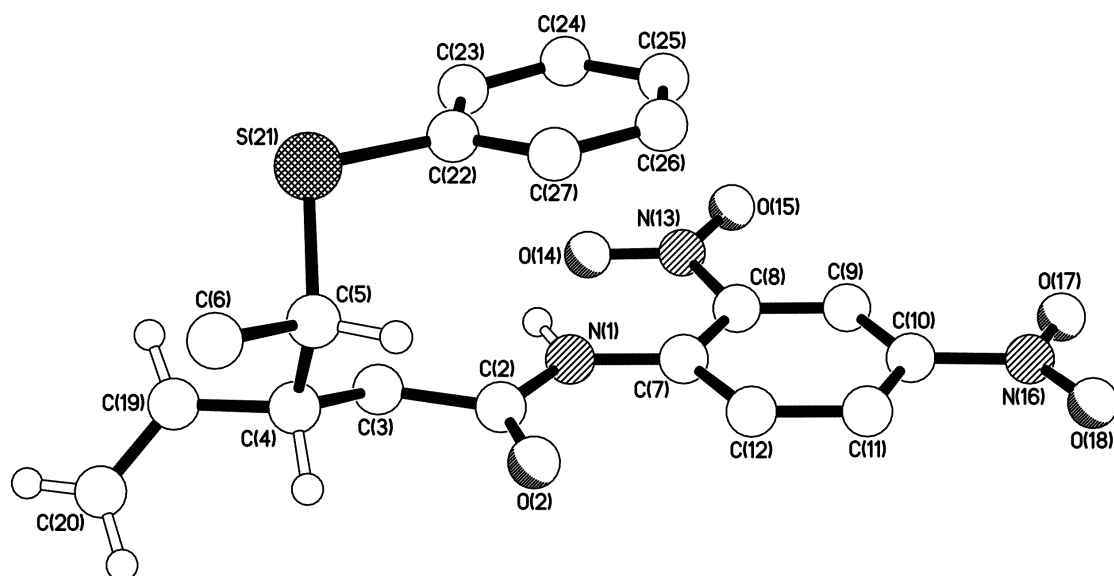


Table 1. Crystal data and structure refinement for DC0901.

Identification code	DC0901
Empirical formula	C ₁₉ H ₁₉ N ₃ O ₅ S
Formula weight	401.43
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.0330(2) Å α =
69.170(3)°	b = 11.6869(4) Å β =
78.712(3)°	c = 12.9973(5) Å γ =
82.731(3)°	
Volume, Z	977.27(6) Å ³ , 2
Density (calculated)	1.364 Mg/m ³
Absorption coefficient	0.201 mm ⁻¹
F(000)	420
Crystal colour / morphology	Yellow tabular needles
Crystal size	0.45 x 0.24 x 0.10 mm ³
θ range for data collection	2.92 to 32.43°
Index ranges	-6 ≤ h ≤ 10, -16 ≤ k ≤ 17, -18 ≤ l ≤ 19
Reflns collected / unique	12052 / 6353 [R(int) = 0.0204]
Reflns observed [F > 4σ(F)]	4267
Absorption correction	Analytical
Max. and min. transmission	0.980 and 0.938
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6353 / 21 / 270
Goodness-of-fit on F ²	1.053
Final R indices [F > 4σ(F)]	R ₁ = 0.0556, wR ₂ = 0.1351
R indices (all data)	R ₁ = 0.0896, wR ₂ = 0.1467
Largest diff. peak, hole	0.424, -0.637 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for DC0901.

N(1)–C(2)	1.3805(18)
N(1)–C(7)	1.3878(16)
C(2)–O(2)	1.2055(18)
C(2)–C(3)	1.5157(19)
C(3)–C(4)	1.527(2)
C(4)–C(19)	1.502(2)
C(4)–C(5)	1.532(2)
C(5)–C(6)	1.541(3)
C(5)–S(21)	1.819(2)
C(7)–C(12)	1.401(2)
C(7)–C(8)	1.4095(19)
C(8)–C(9)	1.3883(19)
C(8)–N(13)	1.465(3)
C(8)–N(13')	1.478(10)
C(9)–C(10)	1.365(2)
C(10)–C(11)	1.380(2)
C(10)–N(16)	1.4636(18)
C(11)–C(12)	1.3754(19)
N(13)–O(15)	1.206(3)
N(13)–O(14)	1.231(3)
N(13')–O(15')	1.218(12)
N(13')–O(14')	1.223(12)
N(16)–O(17)	1.2162(19)
N(16)–O(18)	1.2215(19)
C(19)–C(20)	1.315(2)
S(21)–C(22)	1.7751(17)
C(22)–C(23)	1.378(3)
C(22)–C(27)	1.390(3)
C(23)–C(24)	1.383(3)
C(24)–C(25)	1.383(3)
C(25)–C(26)	1.365(3)
C(26)–C(27)	1.395(3)
C(2)–N(1)–C(7)	127.93(12)
O(2)–C(2)–N(1)	123.64(13)
O(2)–C(2)–C(3)	123.04(13)
N(1)–C(2)–C(3)	113.30(13)
C(2)–C(3)–C(4)	112.97(12)
C(19)–C(4)–C(3)	109.77(13)

C(19)-C(4)-C(5)	112.54(13)
C(3)-C(4)-C(5)	113.22(12)
C(4)-C(5)-C(6)	110.63(16)
C(4)-C(5)-S(21)	114.31(12)
C(6)-C(5)-S(21)	107.74(18)
N(1)-C(7)-C(12)	121.63(12)
N(1)-C(7)-C(8)	121.78(12)
C(12)-C(7)-C(8)	116.59(12)
C(9)-C(8)-C(7)	122.07(13)
C(9)-C(8)-N(13)	114.55(15)
C(7)-C(8)-N(13)	123.33(15)
C(9)-C(8)-N(13')	118.0(5)
C(7)-C(8)-N(13')	119.2(5)
C(10)-C(9)-C(8)	118.38(13)
C(9)-C(10)-C(11)	122.03(13)
C(9)-C(10)-N(16)	119.11(13)
C(11)-C(10)-N(16)	118.85(14)
C(12)-C(11)-C(10)	119.16(14)
C(11)-C(12)-C(7)	121.76(13)
O(15)-N(13)-O(14)	121.3(2)
O(15)-N(13)-C(8)	118.6(2)
O(14)-N(13)-C(8)	120.1(2)
O(15')-N(13')-O(14')	124.1(13)
O(15')-N(13')-C(8)	117.4(9)
O(14')-N(13')-C(8)	117.5(10)
O(17)-N(16)-O(18)	123.44(14)
O(17)-N(16)-C(10)	118.27(14)
O(18)-N(16)-C(10)	118.27(14)
C(20)-C(19)-C(4)	124.11(17)
C(22)-S(21)-C(5)	104.50(8)
C(23)-C(22)-C(27)	119.05(17)
C(23)-C(22)-S(21)	118.00(13)
C(27)-C(22)-S(21)	122.86(17)
C(22)-C(23)-C(24)	120.81(18)
C(23)-C(24)-C(25)	120.3(2)
C(26)-C(25)-C(24)	119.12(18)
C(25)-C(26)-C(27)	121.21(18)
C(22)-C(27)-C(26)	119.5(2)

4.3 Crystallographic data for *syn*-254a

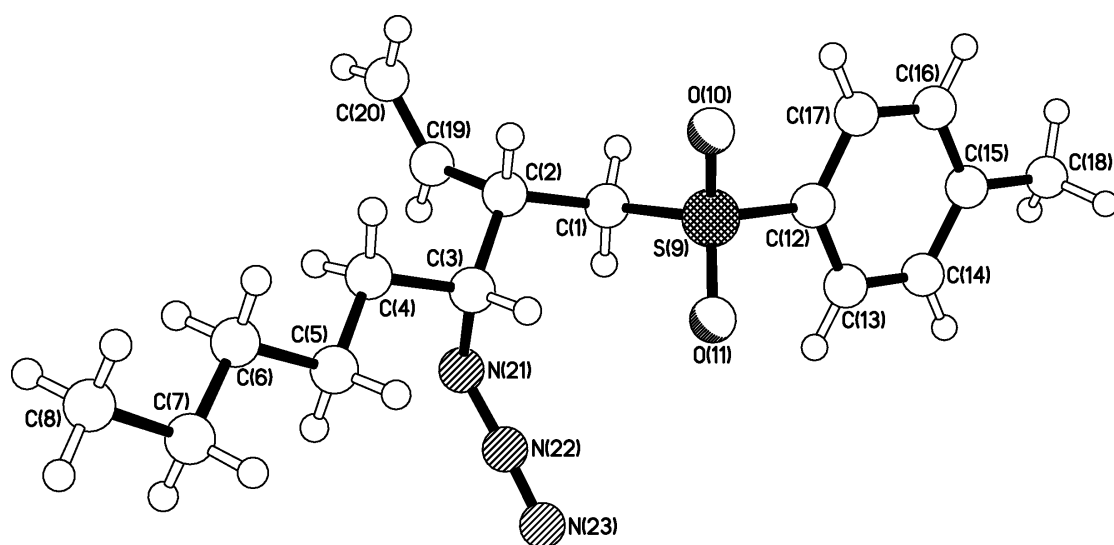


Table 1. Crystal data and structure refinement for DC0808.

Identification code	DC0808
Empirical formula	C ₁₇ H ₂₅ N ₃ O ₂ S
Formula weight	335.46
Temperature	173(2) K
Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 5.48411(17) Å α = 90° b = 8.0007(2) Å β = 90.353(3)° c = 41.2338(12) Å γ = 90°
Volume, Z	1809.17(9) Å ³ , 4
Density (calculated)	1.232 Mg/m ³
Absorption coefficient	0.192 mm ⁻¹
F(000)	720
Crystal colour / morphology	Colourless platy needles
Crystal size	0.45 x 0.15 x 0.02 mm ³
θ range for data collection	3.91 to 31.68°
Index ranges	-8<=h<=7, -11<=k<=11, -59<=l<=59
Reflns collected / unique	22930 / 5800 [R(int) = 0.0666]
Reflns observed [F>4σ(F)]	4035
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.88234
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5800 / 0 / 209
Goodness-of-fit on F ²	1.212
Final R indices [F>4σ(F)]	R1 = 0.1083, wR2 = 0.1913
R indices (all data)	R1 = 0.1493, wR2 = 0.2018
Largest diff. peak, hole	0.450, -0.793 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for DC0808.

C(1)–C(2)	1.550(4)
C(1)–S(9)	1.772(3)
C(2)–C(19)	1.502(5)
C(2)–C(3)	1.531(5)
C(3)–N(21)	1.498(4)
C(3)–C(4)	1.524(5)
C(4)–C(5)	1.513(5)
C(5)–C(6)	1.539(5)
C(6)–C(7)	1.498(6)
C(7)–C(8)	1.515(6)
S(9)–O(11)	1.431(3)
S(9)–O(10)	1.438(3)
S(9)–C(12)	1.766(3)
C(12)–C(13)	1.383(5)
C(12)–C(17)	1.388(5)
C(13)–C(14)	1.387(5)
C(14)–C(15)	1.394(5)
C(15)–C(16)	1.380(5)
C(15)–C(18)	1.518(5)
C(16)–C(17)	1.393(5)
C(19)–C(20)	1.308(6)
N(21)–N(22)	1.225(5)
N(22)–N(23)	1.128(5)
C(2)–C(1)–S(9)	113.1(2)
C(19)–C(2)–C(3)	112.6(3)
C(19)–C(2)–C(1)	108.3(3)
C(3)–C(2)–C(1)	112.5(3)
N(21)–C(3)–C(4)	109.8(3)
N(21)–C(3)–C(2)	107.7(3)
C(4)–C(3)–C(2)	111.9(3)
C(5)–C(4)–C(3)	114.5(3)
C(4)–C(5)–C(6)	111.9(3)
C(7)–C(6)–C(5)	114.7(3)
C(6)–C(7)–C(8)	112.5(4)
O(11)–S(9)–O(10)	118.62(18)
O(11)–S(9)–C(12)	107.89(16)
O(10)–S(9)–C(12)	108.26(15)
O(11)–S(9)–C(1)	109.27(16)

O(10)-S(9)-C(1)	107.75(17)
C(12)-S(9)-C(1)	104.11(16)
C(13)-C(12)-C(17)	121.4(3)
C(13)-C(12)-S(9)	119.8(3)
C(17)-C(12)-S(9)	118.8(3)
C(12)-C(13)-C(14)	119.0(3)
C(13)-C(14)-C(15)	121.0(3)
C(16)-C(15)-C(14)	118.6(3)
C(16)-C(15)-C(18)	120.5(3)
C(14)-C(15)-C(18)	120.9(3)
C(15)-C(16)-C(17)	121.6(3)
C(12)-C(17)-C(16)	118.4(3)
C(20)-C(19)-C(2)	124.3(4)
N(22)-N(21)-C(3)	115.1(3)
N(23)-N(22)-N(21)	173.6(4)

Chapter 5

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