

Studies into Iridium-catalysed Asymmetric Allylic Alkylation Towards the Total Synthesis of a Dolabellane

Lingfan Jiang

Exeter College, University of Oxford

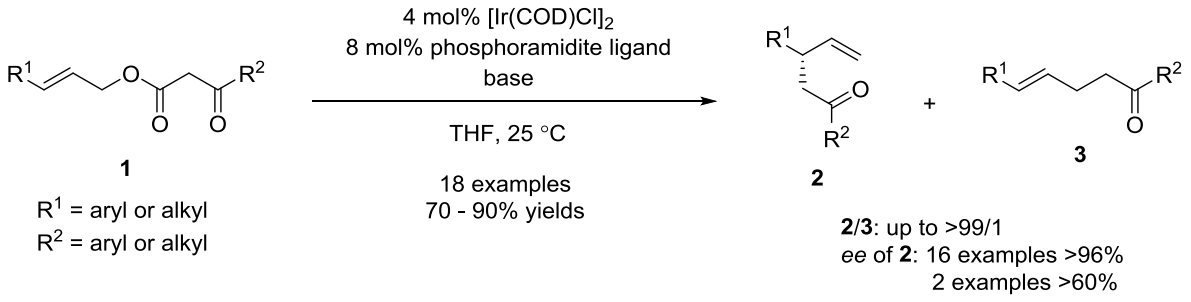
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Abstract

In recent years, iridium-catalysed asymmetric allylic substitution has received considerable attention because it is a valuable tool to selectively synthesise chiral compounds with high *ee* from simple starting materials. This thesis presents an efficient catalytic system for the decarboxylative iridium-catalysed asymmetric allylic alkylation (AAA) in which allylic *β*-ketoester substrates **1** were converted into chiral ketones **2** in good yields with high regio- and enantioselectivities (**Scheme 1**). A wide range of examples are presented in **Section 2.3**. **Section 2.4** describes studies into decarboxylative iridium-catalysed AAA using allylic substrates **1** with R^2 being heteroatoms such as oxygen, sulphur or nitrogen to produce chiral esters and amides products. A possible mechanism for decarboxylative iridium-catalysed AAA is also proposed.



Scheme 1: Synthesis of enantioenriched ketones *via* decarboxylative iridium-catalysed AAA

Chapter 3 reports the investigations towards the total synthesis of a racemic dolabellane natural product. This chapter focuses on the optimisation of the reduction of a carboxylic acid functionality to an alkane in the presence of other functional groups (alkene, nitrile and silyl ether protecting group) in the molecule.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative work.

This thesis has not been previously submitted for a degree, diploma, or any other qualification at the University of Oxford or elsewhere.

Lingfan Jiang

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Finally, I want to express my love and gratitude to my beloved parents for their endless support and encouragement. Thank you for always being there.

Selected abbreviations

$[Cp^*RuCl]_4$	Chloro(pentamethylcyclopentadienyl)ruthenium(II)
$[Ir(COD)Cl]_2$	Bis(1,5-cyclooctadiene)diiridium(I) dichloride
$[Ir(dbcot)Cl]_2$	Dichlorobis(η^4-dibenzo[*a,e*]cyclooctatetraene)diiridium(I)
AAA	Asymmetric allylic alkylation
AAS	Asymmetric allylic substitution
aq.	Aqueous
Ar	Aryl
b : l	Branched to linear ratio
BINOL	1,1’-Bi-2-naphthol
brsm	by recovering starting material
cat.	Catalytic amount
COD	Cyclooctadiene
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
dbcot	Dibenzocyclooctatetraene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	*N*,*N′*-Dimethylpropylene urea
DMSO	Dimethyl sulfoxide
dr	diastereomeric ratio

ee	Enantiomeric excess
ESI	Electrospray ionisation
FC	Flash column chromatography
HMBC	Heteronuclear multiple bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
HWE	Horner-Wadsworth-Emmons
IBX	2-Iodoxybenzoic acid
IR	Infrared
LA	Lewis acid
LDA	Lithium diisopropylamide
LG	Leaving group
LiHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low resolution mass spectrometry
m.p.	Melting point
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MOM	Methoxymethyl
MPO	4-Methoxypyridine *N*-oxide
MS	Molecular sieves
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
RCM	Ring closing metathesis
R_f	Retention factor
RT	Room temperature
sat.	Saturated
T	Temperature

TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDMS	*tert*-Butyldimethylsilyl
TBDPSCl	*tert*-Butyl(chloro)diphenylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMSCl	Chlorotrimethylsilane

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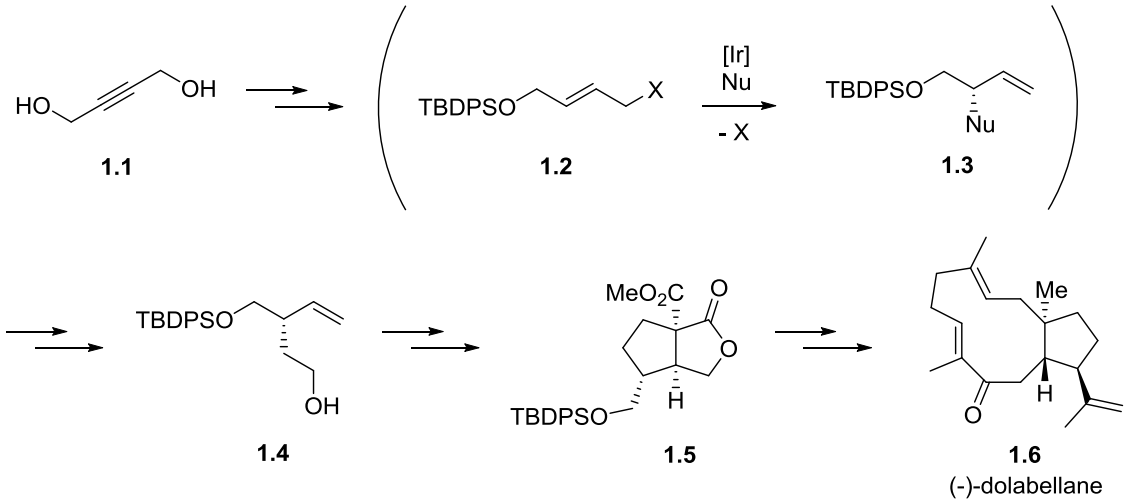
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1 Overview

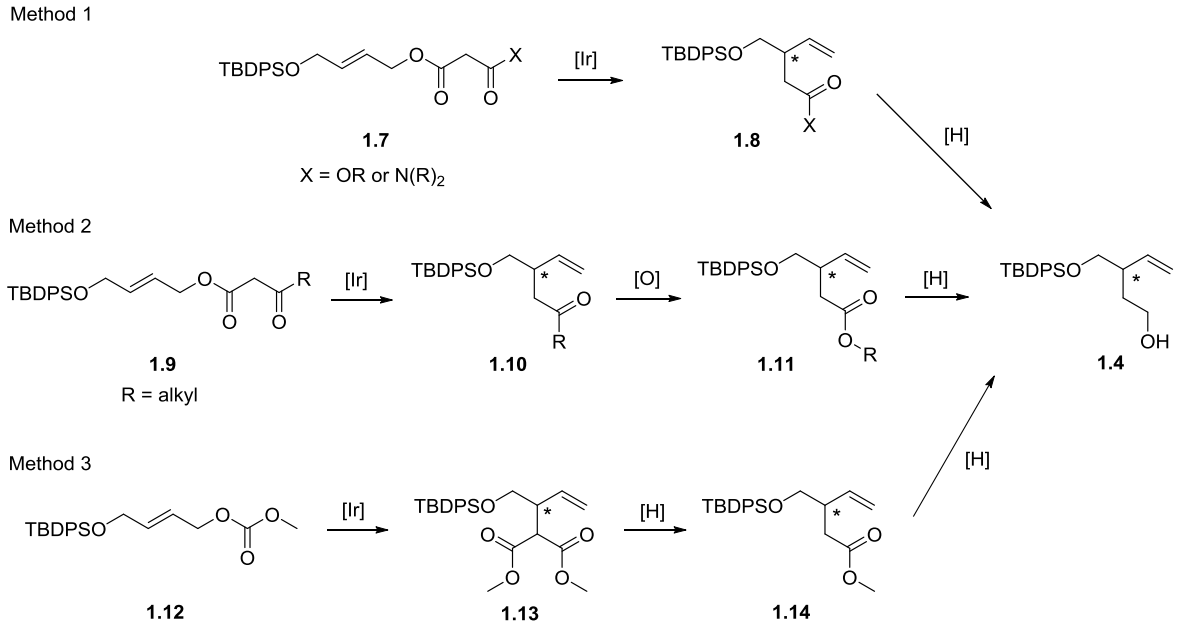
The dolabellanes are a large class of diterpenes many of which exhibit antibacterial, antiviral and cytotoxic activity.[1] The (-)-dolabellane **1.6** shown in **Scheme 1.1** was isolated from the deep water gorgonian octocoral *Convexella magelhaenica* in 2010 and found to be cytotoxic against a human pancreatic adenocarcinoma cell line at micromolar concentrations.[2] The overall aim of this project is to synthesise the (-)-dolabellane **1.6** from the [3.3.0] bicyclic lactone **1.5** which is to be prepared in enantioenriched form using an iridium-catalysed asymmetric allylic alkylation (abbreviated as AAA) reaction (**1.2** -> **1.3**).



Scheme 1.1: Proposed synthetic route to enantioenriched dolabellane 1.6 from butynediol 1.1

Three different synthetic pathways from achiral allylic substrate **1.2** to enantioenriched primary alcohol **1.4** were investigated in this project (**Scheme 1.2**). Firstly, the direct synthesis of enantioenriched ester or amide **1.8** from achiral allylic malonate or *β*-amidoester **1.7** *via* decarboxylative iridium-catalysed AAA was studied (Method 1, **Scheme 1.2**). Ester or amide **1.8** could then be simply reduced

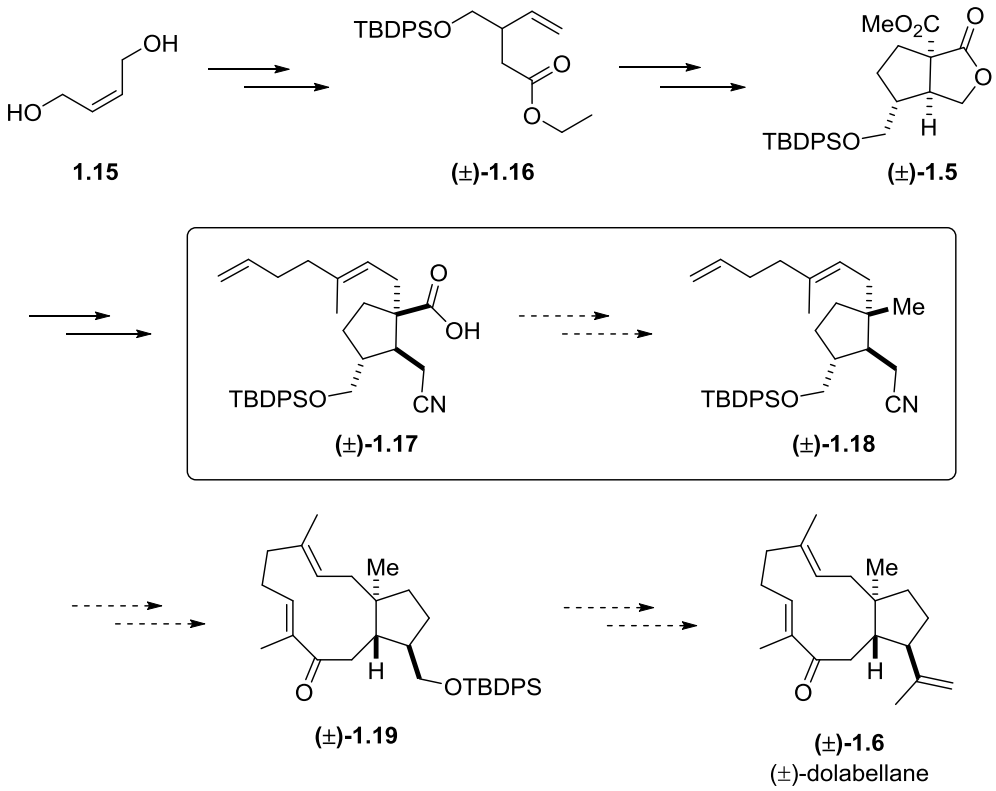
to primary alcohol **1.4**. Secondly, the preparation of enantioenriched ketone **1.10** from achiral allylic *β*-ketoester **1.9** *via* decarboxylative iridium-catalysed AAA was also investigated (Method 2). Attempts were then carried out to convert ketone **1.10** into carboxylic acid derivative **1.11** followed by reduction to form alcohol **1.4**. Thirdly, a literature method which converts allylic carbonate **1.12** into enantioenriched malonate **1.13** *via* iridium-catalysed AAA was followed and attempts were made to convert malonate **1.13** into ester **1.14** followed by reduction to give alcohol **1.4** (Method 3). The above reactions will be described in details in **Chapter 2**.



Scheme 1.2: Different synthetic pathways for the preparation of enantioenriched alcohol 1.4 from achiral allylic substrates

A previous member of the Burton group, Ferrara, has made significant progress in the synthesis of racemic dolabellane **(±)-1.6** (**Scheme 1.3**, more details are given in **Chapter 3**).[3] Ferrara reported that the reduction of carboxylic acid **(±)-1.17** to alkane **(±)-1.18** in the presence of alkene, nitrile and silyl ether group in the molecule is challenging and conversion in a stepwise fashion is probably

required. Attempts were carried out to investigate this key step in this project and details will be elaborated in **Chapter 3**.



Scheme 1.3: Work done by Steve Ferrara on the total synthesis of racemic dolabellane (±)-1.6[3]

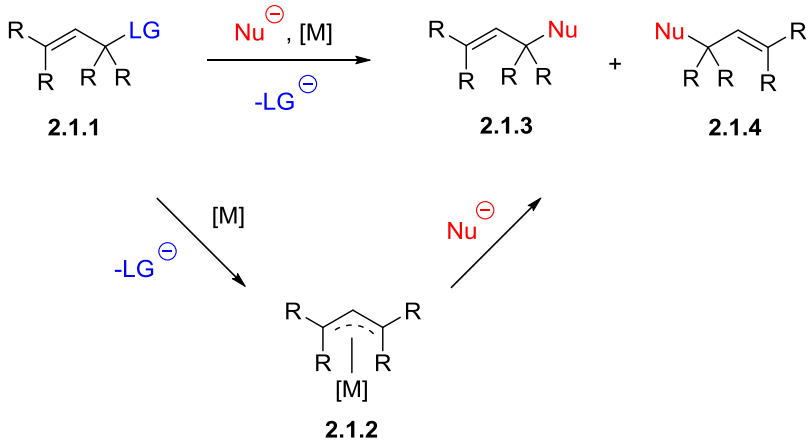
2 Iridium-catalysed asymmetric allylic alkylation

2.1 Introduction

This section briefly introduces the general concept of metal-catalysed allylic substitution, summarises the past development of iridium-catalysed allylic substitution and provides insights into its mechanism and product selectivity.

2.1.1 Metal-catalysed allylic substitution

In a general metal-catalysed allylic substitution reaction (**Scheme 2.1.1**), starting material **2.1.1** contains an alkene and a leaving group at the allylic position. A metal complex coordinates to the alkene and displaces the leaving group to form an η^3-allyl complex **2.1.2** which is subsequently attacked by the nucleophile at one of the termini to form either product **2.1.3** or **2.1.4** or a mixture of both.[4]



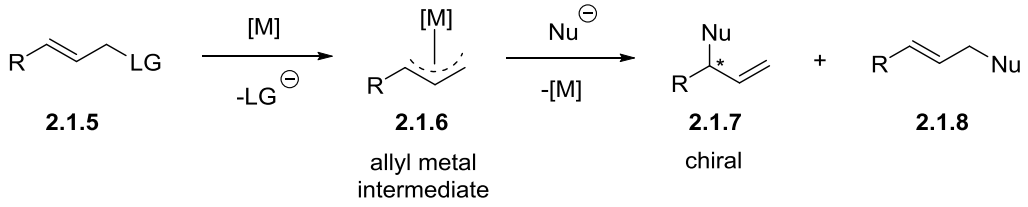
LG: leaving group e.g. ester, carbonate or halide
[M]: metal catalyst
Nu: nucleophile

Scheme 2.1.1: Overall scheme of metal-catalysed allylic substitution (scheme adapted from Hartwig and Pouy's publication)[4]

For starting materials which have different R groups, regioselectivity (i.e. ratio between product **2.1.3** and **2.1.4**, **Scheme 2.1.1**) can frequently be controlled by using a suitable metal catalyst, usually with a ligand. If the nucleophile is directed to attack a substituted terminus, a chiral product will be formed. The enantioselectivity of the reaction can then potentially be controlled by the use of an appropriate chiral ligand. Therefore, metal-catalysed asymmetric allylic substitution (abbreviated as AAS) is a valuable tool to synthesise chiral compounds from simple achiral allylic starting materials *via* stereoselective formation of C-C and C-X bonds (X = heteroatom).

When using a mono-substituted allylic substrate **2.1.5** as the starting material (**Scheme 2.1.2**), substitution at the less sterically hindered terminus of allyl intermediate **2.1.6** to form the linear product **2.1.8** is favoured in the presence of palladium complexes.[4] On the other hand, most other transition metals favourably lead to the formation of the chiral product **2.1.7**. For example, ruthenium[5] and nickel[6] complexes favour the formation of chiral product **2.1.7** but with only moderate regioselectivities. Tungsten[7] and molybdenum[8] complexes lead to the formation of chiral product **2.1.7** with good selectivities (branched to linear ratios up to >99 : 1)[8] but the reactions generally require high catalyst loadings. When using iron[9] and rhodium[10,11] complexes in allylic substitution reactions, the nucleophiles were found to predominantly attack the same terminus where the leaving group was attached. It was believed that the reactions proceed *via* σ-allylmetal rather than π-allylmetal complexes.[9,10] Although a large portion of the d-block transition metals had been investigated in catalytic allylic substitution reactions, the type of nucleophiles was limited to stabilised enolates. Therefore, a suitable catalyst that is

highly active and selective for the formation of chiral products using a variety of nucleophiles was unknown before the discovery of iridium chemistry.



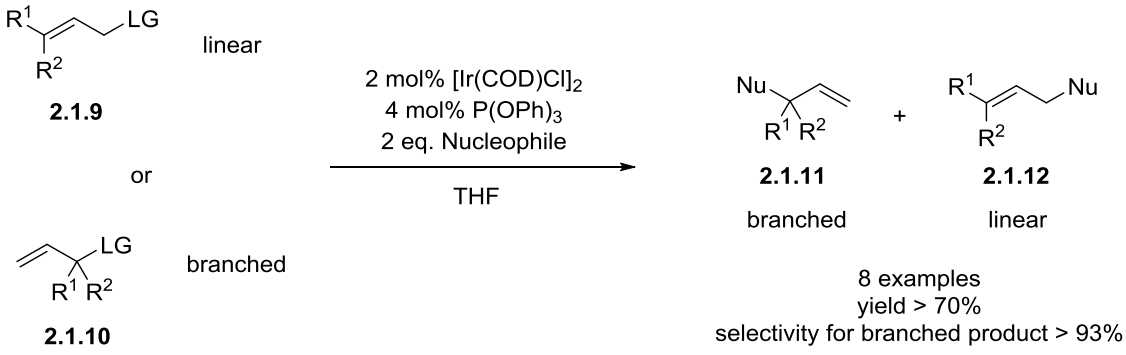
2.1.5 **2.1.6** allyl metal intermediate **2.1.7** chiral **2.1.8**

Scheme 2.1.2: Allylic substitution reaction involving the formation of an η^3-allyl complex that has one unsubstituted terminus[4]

2.1.2 Iridium-catalysed allylic substitution

2.1.2.1 Early work and development of enantioenriched ligands

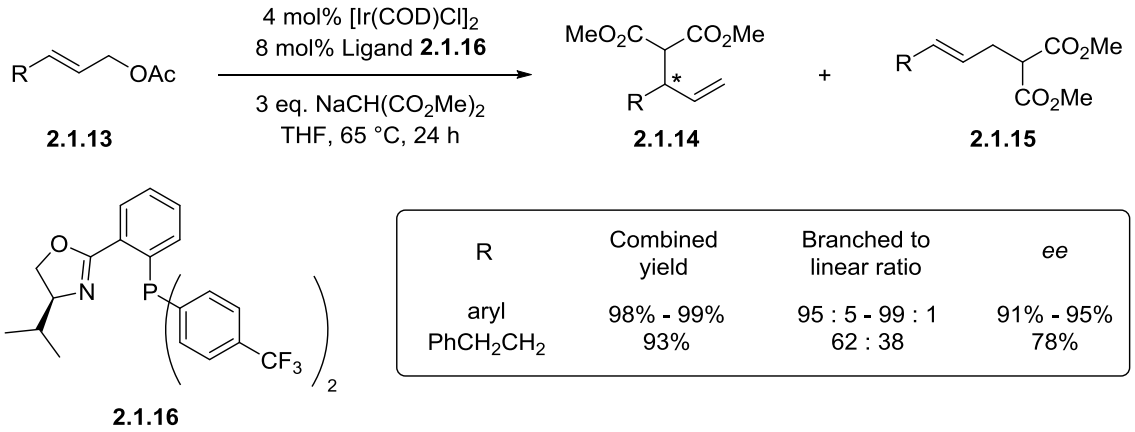
The first iridium-catalysed allylic substitution was introduced by Takeuchi *et al*. in 1997.[12] In this study, an efficient catalyst system using $[Ir(COD)Cl]_2$ and triphenyl phosphite (achiral ligand) was reported (**Scheme 2.1.3**). Under this system, stabilised enolate nucleophiles react with both linear and branched allylic substrates **2.1.9** and **2.1.10** to selectively form the branched product **2.1.11** in high yields with excellent branched to linear ratios. In subsequent studies, Takeuchi *et al.* further demonstrated that both primary and secondary amines can be used as nucleophiles in allylic amination to form branched products in high yields with excellent selectivities (branched to linear ratios up to 99 : 1).[13] $[Ir(COD)Cl]_2$ was also found to be the most active catalyst precursor after a series of catalysts screening as other iridium catalyst precursors required higher temperatures and gave lower yields.[14]



Nu: $NaCH(CO_2Me)_2$ or $NaCH(CO_2Et)_2$
R^1: aryl and alkyl
R^2: alkyl and H
LG: acetate, carbonate or trifluoroacetate

Scheme 2.1.3: Iridium-catalysed allylic alkylation with stabilised carbon nucleophiles by Takeuchi *et al.*[12]

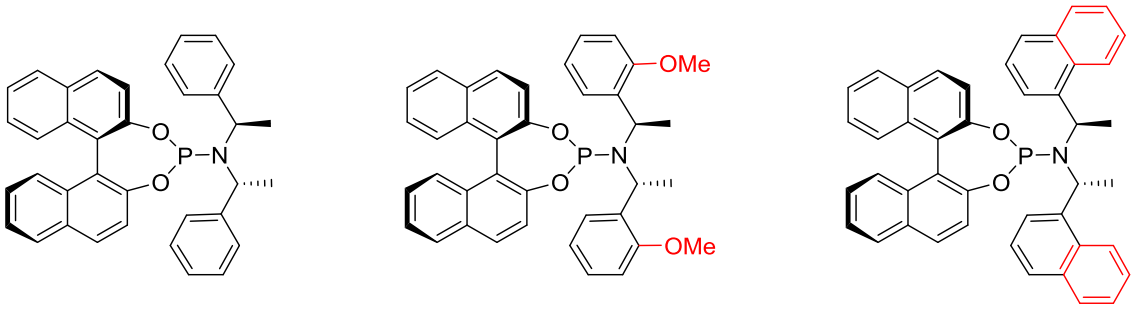
After the work of Takeuchi *et al*. in iridium chemistry in 1997,[12] there has been a growing interest in developing catalyst systems with chiral ligands to control the absolute configurations of products. The first iridium-catalysed asymmetric allylic substitution (abbreviated as AAS) was reported by Helmchen *et al*. in 1997[15] shortly after the initial report by Takeuchi *et al*.. In the presence of $[Ir(COD)Cl]_2$ and the enantioenriched phosphino-oxazoline ligand **2.1.16**, aryl allylic acetates **2.1.13** were reacted with sodium dimethylmalonate to selectively form the aryl branched products **2.1.14** in near quantitative yields with excellent regio- and enantioselectivities (**Scheme 2.1.4**). On the other hand, the limitation with this catalyst system is that the regioselectivity and enantioselectivity of the reaction are much lower for alkyl allylic acetates (R = $PhCH_2CH_2$) in comparison to that of aryl allylic acetates.[16]



R	Combined yield	Branched to linear ratio	*ee*
aryl	98% - 99%	95 : 5 - 99 : 1	91% - 95%
$PhCH_2CH_2$	93%	62 : 38	78%

Scheme 2.1.4: First iridium-catalysed AAS using phosphino-oxazoline ligand by Helmchen *et al.*[15,16]

In the following years, many types of chiral ligands such as phenyl pyridyl bis(oxazoline) (Ph-Pybox),[17] diaminophosphine oxide (DIAPHOX),[18,19] dimethylamine-derived phosphoramidite (monophos)[16] and bisphenethylamine-derived phosphoramidite ligands[20] have been developed to improve the selectivity of the reaction and extend the scope of nucleophiles and allylic substrates. Out of those many types of chiral ligands, phosphoramidite ligands **L1**,[21] **L2**[22,23] and **L3**[24,25] were found to be particularly efficient in terms of reactivity and selectivity (**Figure 2.1.1**).[26]



Ligand **L1** Ligand **L2** Ligand **L3**

Figure 2.1.1: Three particularly efficient phosphoramidite ligands in iridium-catalysed AAS reactions[20]

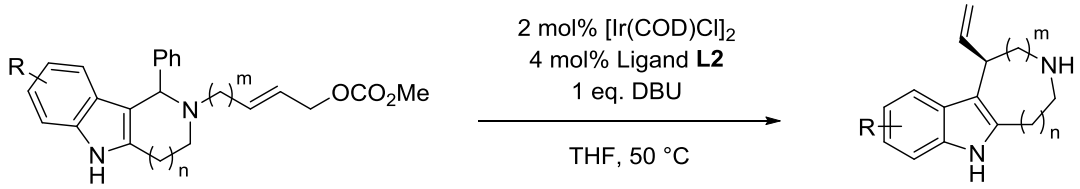
During the past decade, a number of reviews on iridium-catalysed AAS reactions have been published.[27,28,29,30] Since one of the most recent reviews by Tosatti *et al*.,[26] many new advances in the field of iridium-catalysed AAS have been made, especially in expanding the scope of nucleophiles to synthesise compounds with diverse functionalities. This introduction will not cover all of the discoveries that have been achieved so far, but will aim to present some of the most recent examples in the three main groups of nucleophiles – carbon, nitrogen and oxygen nucleophiles.

2.1.2.2 Carbon nucleophiles

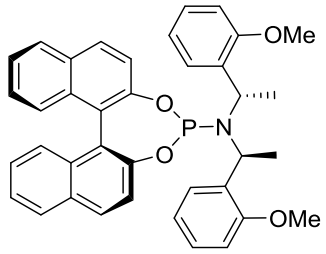
Over the years, considerable attention has been focussed on the use of stabilised carbon nucleophiles, including malonates,[31] nitroacetates,[32] malononitriles,[33] *β*-ketoesters,[34] sulfonyl acetates[35] and anthrones.[36]

Recently in 2016, You *et al*. reported an interesting synthesis of enantioenriched indole-annulated medium-sized-ring compounds *via* an iridium-catalysed allylic dearomatisation/retro-Mannich/hydrolysis cascade reaction.[37] Subjecting a variety of allylic carbonates **2.1.17** to precatalyst $[Ir(COD)Cl]_2$, ligand **L2** and DBU in THF at 50 °C afforded various seven- or eight-membered-ring compounds **2.1.18** in good to excellent yields with excellent enantioselectivities (**Scheme 2.1.5**). You *et al*. postulated that allylic carbonate **2.1.17** firstly undergoes iridium-catalysed AAA at the C3 position of the indole moiety to form the enantioenriched bridged intermediate **2.1.20** which then undergoes a retro-Mannich-type ring opening to give the ring-expansion

intermediate **2.1.21** (**Scheme 2.1.5**). Subsequent hydrolysis of the imine group affords the macrocyclic compound **2.1.18**.



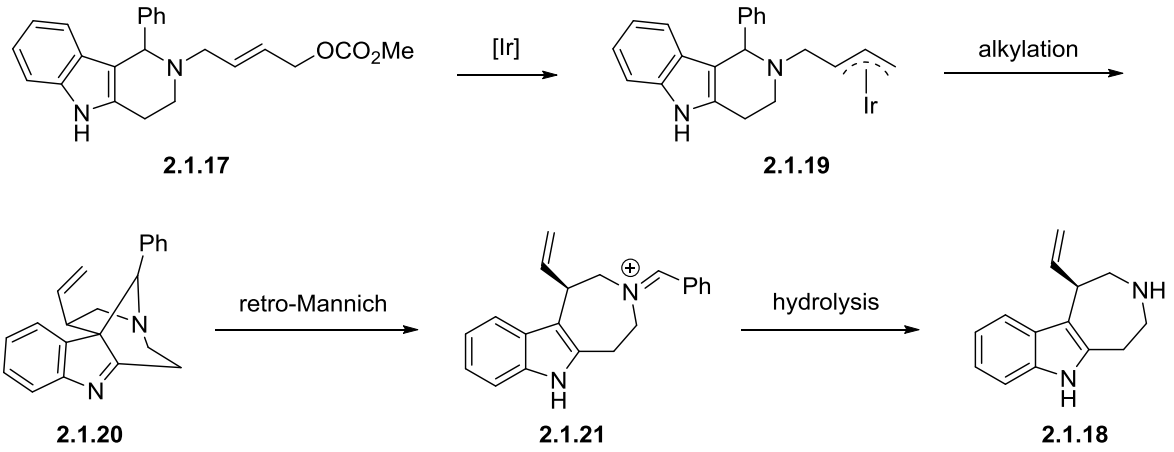
2.1.17 **2.1.18**



Ligand **L2** (*S*,*S*,*S*)

m	n	Yield	*ee*
1	1	47% - 89%	96% - 98%
2	1	57% - 64%	93% - 98%
1	2	75% - 84%	98% - 99%

Proposed mechanism:



2.1.17 **2.1.19** **2.1.20** **2.1.21** **2.1.18**

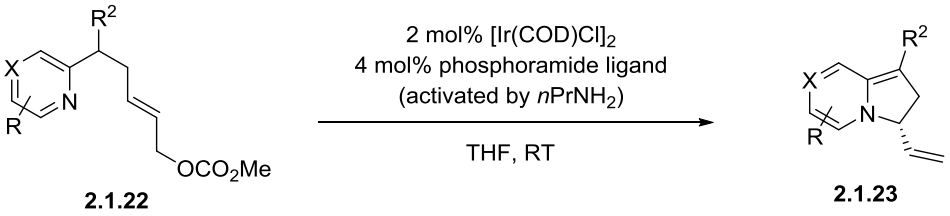
Scheme 2.1.5: Synthesis of enantioenriched macrocyclic compounds *via* iridium-catalysed AAA by You *et al*.[37]

Before discussing iridium-catalysed AAA using unstabilised carbon nucleophiles (which will be described in details in **Section 2.1.4**), nucleophiles from the *N*- and *O*- series are presented in the next two sections.

2.1.2.3 Nitrogen nucleophiles

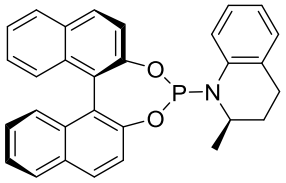
The advances in iridium-catalysed AAS over the past few decades have allowed the use of an increasingly wider scope of nucleophiles. Besides carbon nucleophiles, a broad range of nitrogen nucleophiles, such as primary and secondary amines,[23,25,38] carbamates,[39] imides,[40,41] sulfonamides,[42,43] hydroxylamides[44] and trifluoroacetamides,[45] was also shown to be competent and efficient in iridium-catalysed AAS reactions.

In 2014, You *et al*. demonstrated the application of iridium-catalysed asymmetric allylic amination in the synthesis of heterocyclic compounds.[46] You *et al*. reported the synthesis of dihydroindolizines or dihydropyrrolopyrazines **2.1.23** *via* iridium-catalysed intramolecular asymmetric allylic amination (**Scheme 2.1.6**). A variety of allylic carbonates **2.1.22** (X = C) containing substituted pyridine rings was subjected to precatalyst $[Ir(COD)Cl]_2$ and ligand **L2** in THF at RT; dihydroindolizine products **2.1.23** (X = C) were obtained in very good yields with good to excellent enantioselectivities. A wide scope of allylic carbonates **2.1.22** (X = N) containing substituted pyrazine rings was also subjected to similar reaction conditions using ligand **2.1.24**; dihydropyrrolopyrazine products **2.1.23** (X = N) were also obtained in good yields with good enantioselectivities. You *et al*. postulated that by having an electron-withdrawing group at R^2, the acidic *α*-proton in allyliridium complex **2.1.24** can be easily deprotonated to form intermediate **2.1.25** which contains an electron-rich pyridine or pyrazine moiety (**Scheme 2.1.6**). The nucleophilic nitrogen then attacks the allyliridium moiety intramolecularly to afford the heterobicyclic product **2.1.23**.

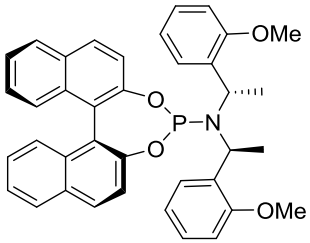


2.1.22 **2.1.23**

R: electron-donating or electron-withdrawing groups
R^2: ester, ketone or sulfonyl



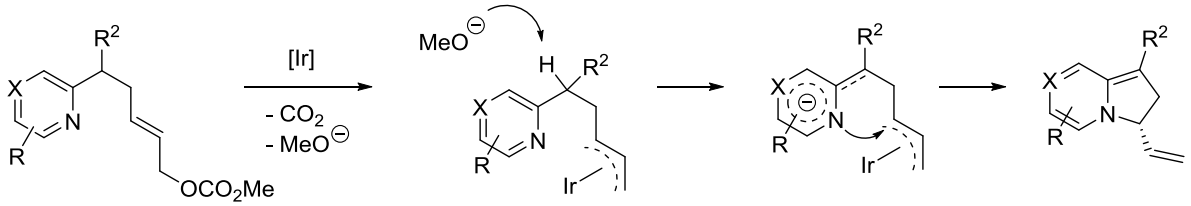
2.1.24 (*R*,*R*)



Ligand **L2** (*S*,*S*,*S*)

X	Ligand	Yield	*ee*
C	**L2**	82% - 99%	83% - 99%
N	**2.1.24**	64% - 95%	86% - 97%

Proposed mechanism:



2.1.22 **2.1.24** **2.1.25** **2.1.23**

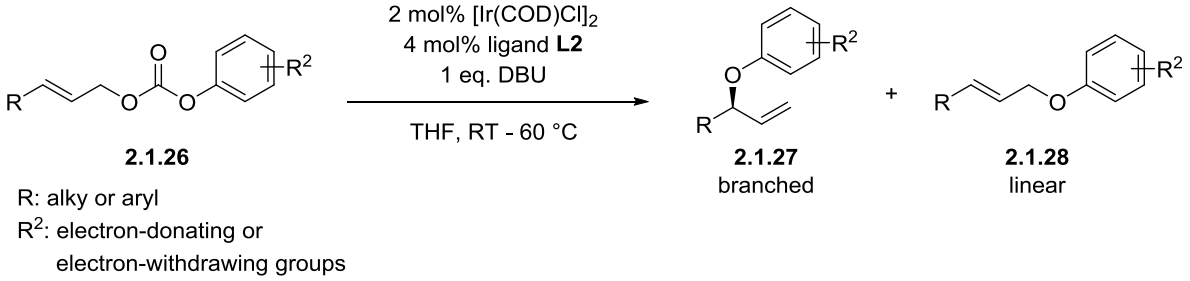
Scheme 2.1.6: Synthesis of enantioenriched dihydroindolizines and dihydropyrrolopyrazines *via* iridium-catalysed intramolecular asymmetric allylic amination by You *et al*.[46]

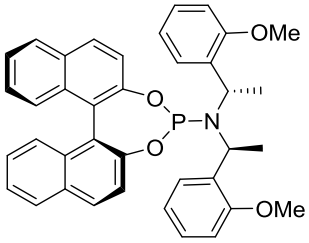
2.1.2.4 Oxygen nucleophiles

Comparing with carbon and nitrogen nucleophiles, there are fewer publications on iridium-catalysed AAS using oxygen nucleophiles. Nevertheless, oxygen nucleophiles such as aryloxides,[47] alkoxides,[48] esters,[49] carbonates[50] and siloxides[51] have been shown to be equally competent in iridium-catalysed AAS

reactions to form enantioenriched ethers, esters or alcohols in good yields with good selectivities.

In 2013, Han *et al*. reported a decarboxylative iridium-catalysed asymmetric allylic etherification.[52] A wide scope of allylic carbonates **2.1.26** was explored using the optimal reaction conditions – $[Ir(COD)Cl]_2$, ligand **L2** and DBU in THF (**Scheme 2.1.7**). Various aryl and alkyl substrates **2.1.26** with different R^2 groups on the aryl carbonate moiety were screened to give the chiral ether products **2.1.27** in overall good yields with good to excellent regio- and enantioselectivities.



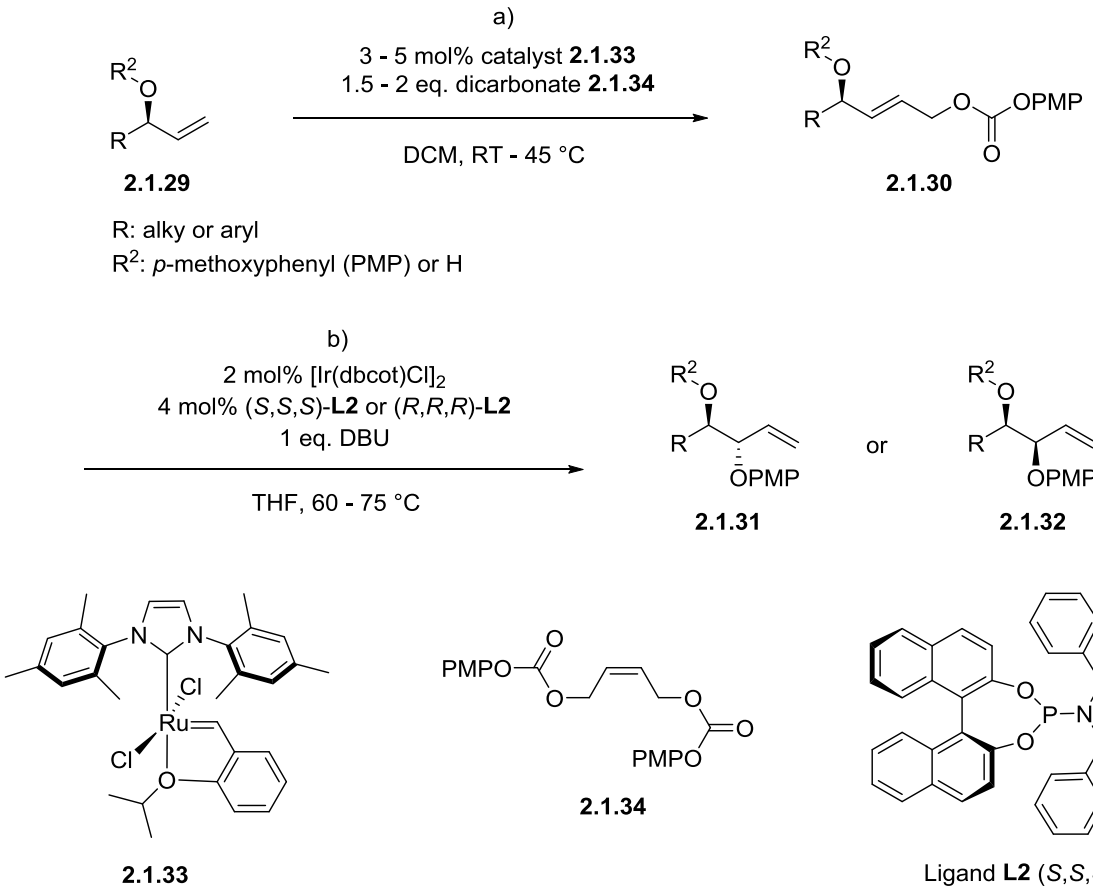


Ligand **L2** (*S*,*S*,*S*)

R	Yield	Branched to linear ratio	*ee*
aryl	56% - 91%	96 : 4 - 99 : 1	76% - 99%
alkyl	70% - 91%	87 : 13 - 98 : 2	74% - 99%

Scheme 2.1.7: Decarboxylative iridium-catalysed asymmetric allylic etherification by Han *et al*.[52]

Later in the same year, Han *et al*. reported the asymmetric synthesis of *syn*- and *anti*-1,2-diols with excellent control of absolute and relative stereochemistry utilising a cross-metathesis/decarboxylative diastereoselective iridium-catalysed asymmetric allylic etherification strategy (**Scheme 2.1.8**).[53] Enantioenriched alcohols **2.1.29** with various R^2 groups were firstly reacted with dicarbonates **2.1.34** *via* cross-metathesis to form allylic carbonates **2.1.30**, which were then subjected to the decarboxylative iridium-catalysed asymmetric allylic etherification to give 1,2-diols **2.1.31** or **2.1.32** in very good yields with excellent diastereoselectivities (**Scheme 2.1.8**). Han *et al*. reported that the diastereoselectivity of the reaction is predominantly controlled by the configuration of the chiral ligand used, i.e. (*S*,*S*,*S*)-**L2** predominantly gives *anti*-1,2-diol **2.1.31** while (*R*,*R*,*R*)-**L2** gives *syn*-1,2-diol **2.1.32**.



R^2	Ligand	Product	Yield (step b)	*dr*	*ee*
PMP	(*S,S,S*)-L**2**	**2.1.31**	84% - 92%	20 : 1 - >25 : 1	-
	(*R,R,R*)-L**2**	**2.1.32**	86% - 94%	1 : 18 - 1 : >25	-
H	(*S,S,S*)-L**2**	**2.1.31**	87% - 90%	>25 : 1	99% - >99%
	(*R,R,R*)-L**2**	**2.1.32**	84% - 93%	1 : 16 - 1 : >25	99% - >99%

Scheme 2.1.8: Synthesis of *syn*- and *anti*-1,2-diols *via* decarboxylative diastereoselective iridium-catalysed asymmetric allylic etherification by Han *et al*.[53]

2.1.3 Mechanistic insights into iridium-catalysed AAS

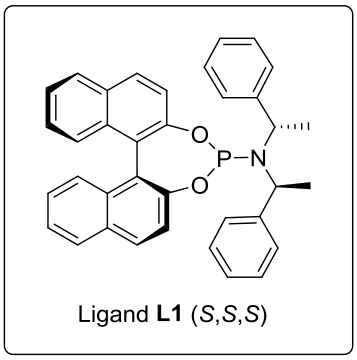
Before presenting other categories of nucleophiles, some of the current mechanistic insights into iridium-catalysed AAS will be discussed in this section. As remarkable results were achieved from iridium-catalysed AAS with phosphoramidite

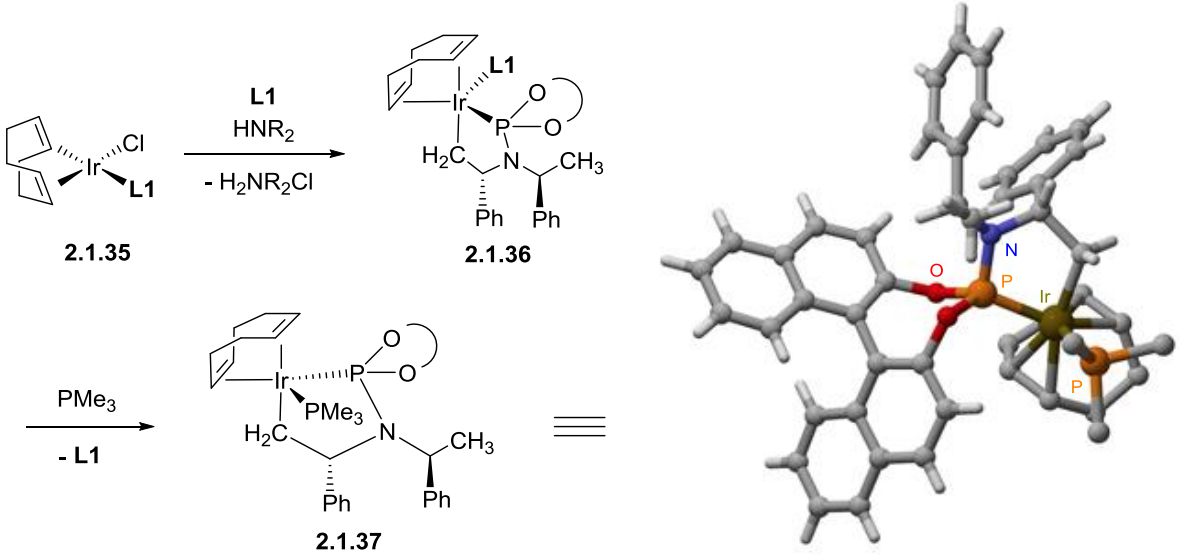
ligands, much effort has been spent over the years in the investigation of the mechanism of this reaction.

2.1.3.1 Identification of the structure of the active catalyst

In 2003, Hartwig *et al*. reported that reacting phosphoramidite ligand **L1** with $[Ir(COD)Cl]_2$ cleaved its chloride bridge and formed a square planar complex [Ir(COD)Cl(**L1**)] **2.1.35** (**Scheme 2.1.9**).[54] However, this square planar Ir(I) complex **2.1.35** did not react with allylic carbonates under standard reaction conditions and thus, it is unlikely to be the active catalyst.

When subjecting square planar complex **2.1.35** to an amine base (bases such as TBD are usually employed in standard reaction conditions of iridium-catalysed AAS), a new complex **2.1.36** was formed (**Scheme 2.1.9**).[54] X-ray crystallography and NMR spectroscopy suggested that the phosphoramidite ligand **L1** underwent cyclometalation at one of the methyl groups of the bis(phenethylamine) component onto the central iridium. This eliminated the chlorine ligand as an amine hydrochloride salt. Another molecule of ligand **L1** coordinated to the last vacant site on the central iridium. This led to a trigonal bipyramidal Ir(I) complex **2.1.36** which consists of a COD ligand, a *P*-bound κ^1-phosphoramidite ligand and a *P,C*-bound κ^2-phosphoramidite ligand. The crystal structure on the right in **Scheme 2.1.9** belongs to complex **2.1.37** which was derived from the initial complex **2.1.36** by displacing the *P*-bound κ^1-phosphoramidite with PMe_3 (which is a more strongly coordinating ligand).

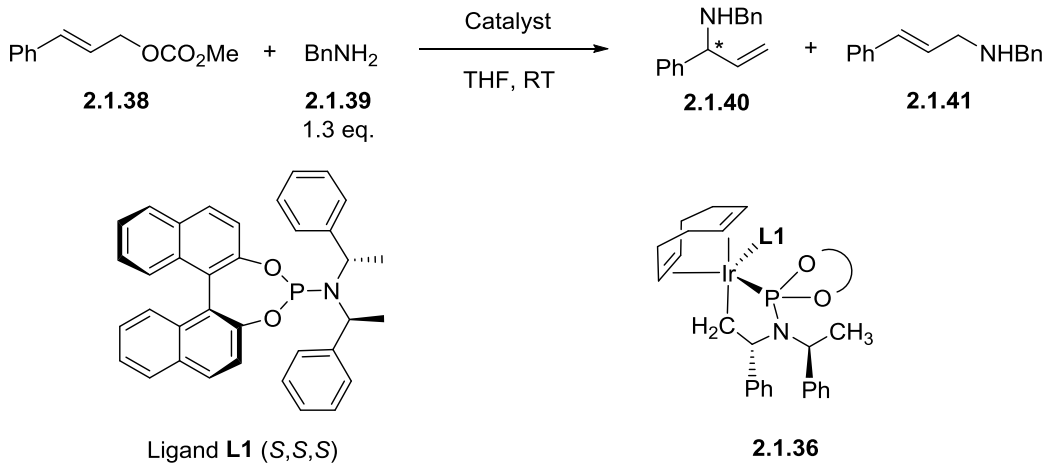




Scheme 2.1.9: Preparation and characterisation of the iridium metalacycle by Hartwig *et al*.[54] (The hydrogen atoms on the COD and PMe_3 ligand of the X-ray structure were removed for clarity)

Experimental results supported the role of complex **2.1.36** as the active catalyst.[54] Yield, regioselectivity and enantioselectivity of allylic amination catalysed by the combination of complex **2.1.36** and $[Ir(COD)Cl]_2$ (some $[Ir(COD)Cl]_2$ were added to trap the *P*-bound κ^1-phosphoramidite dissociated during the reaction) were comparable with those of allylic amination catalysed by the original catalyst system, $[Ir(COD)Cl]_2$ and ligand **L1** (**Scheme 2.1.10**). Besides, the latter took more than 10 hours to go to completion whereas in the presence of complex **2.1.36**, reaction finished within 2 hours. This implied that there was probably an induction

period in the reaction catalysed by the original catalyst system, $[Ir(COD)Cl]_2$ and ligand **L1**, during which the active catalyst complex **2.1.36** was being formed.



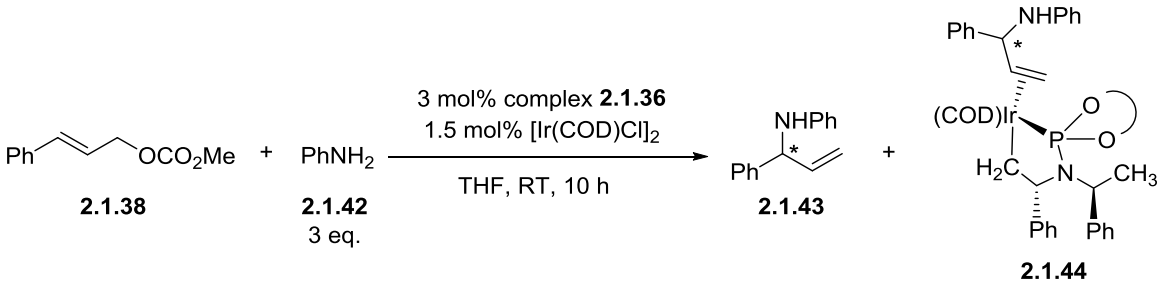
Catalyst	Combined yield	Branched to linear ratio	*ee*	t
2 mol% **2.1.36** + 1 mol% $[Ir(COD)Cl]_2$	81%	98 : 2	97%	2 h
2 mol% **L1** + 1 mol% $[Ir(COD)Cl]_2$	84%	98 : 2	95%	12 h

Scheme 2.1.10: Comparison of performances of the active catalyst 2.1.36 and the original catalyst system[54]

2.1.3.2 Isolation and identification of possible intermediates in the proposed catalytic cycle

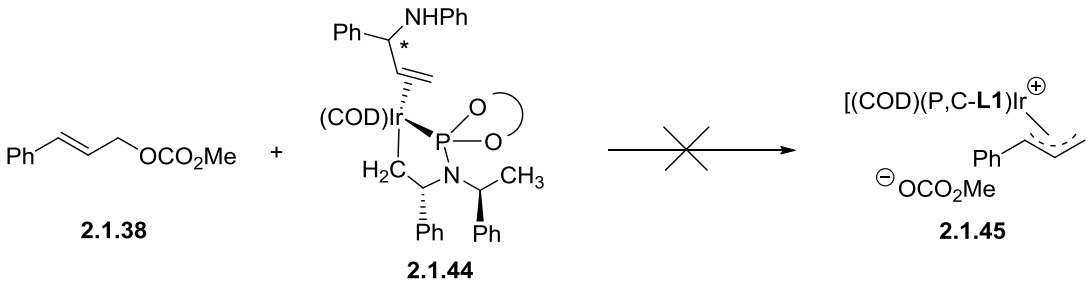
In 2007, Hartwig *et al*. isolated the first intermediate in iridium-catalysed AAS.[55] In a reaction between cinnamyl carbonate **2.1.38** and aniline **2.1.42** in the presence of active catalyst **2.1.36**, an allylic amine complex **2.1.44** was isolated and characterised by NMR spectroscopy (**Scheme 2.1.11**). Reacting complex **2.1.44** alone (without adding more $[Ir(COD)Cl]_2$) with cinnamyl carbonate **2.1.38** and aniline **2.1.42** gave the same allylic amine product **2.1.43** as that generated from the reaction conducted with the original catalyst system, $[Ir(COD)Cl]_2$ and ligand **L1**, or the reaction conducted with the combination of the active catalyst **2.1.36** and

$[Ir(COD)Cl]_2$.[55] Yields, regioselectivities and enantioselectivities were all comparable. Thus, Hartwig *et al*. suggested that allylic amine complex **2.1.44** is probably an intermediate in the catalytic process.



Scheme 2.1.11: Isolation of intermediate 2.1.44 by Hartwig *et al*.[55]

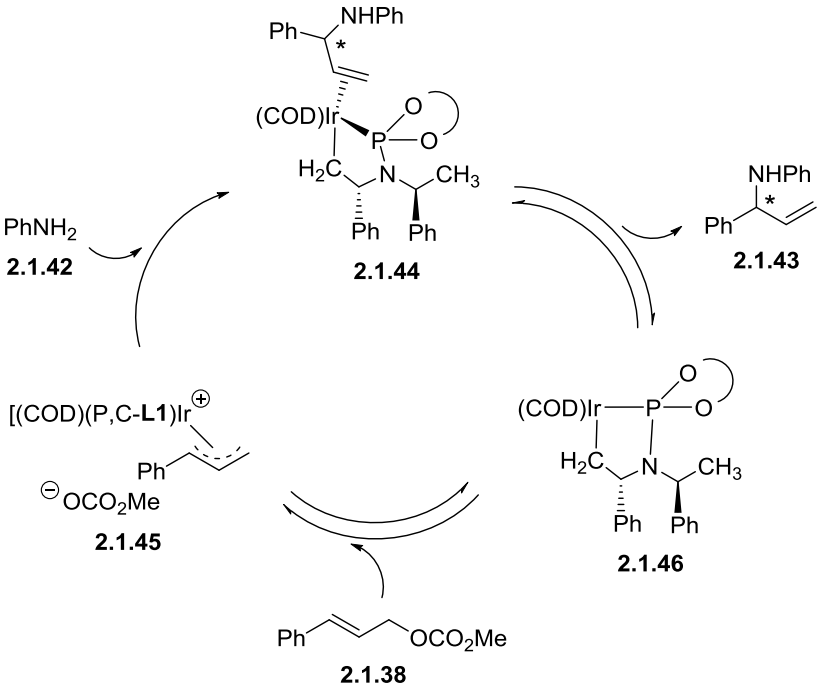
However, attempts to isolate allyliridium complex **2.1.45** (which was believed to be an intermediate) by reacting allylic amine complex **2.1.44** with cinnamyl carbonate **2.1.38** failed (**Scheme 2.1.12**).[55] The reaction did not proceed. As it was elaborated in the previous paragraph that allylic amine complex **2.1.44** is very likely to be an intermediate in the reaction, Hartwig *et al*. suggested that the formation of allyliridium complex **2.1.45** *via* oxidative addition is probably a disfavoured, reversible process.



Scheme 2.1.12: Attempts to isolate allyliridium complex 2.1.45 by Hartwig *et al*.[55]

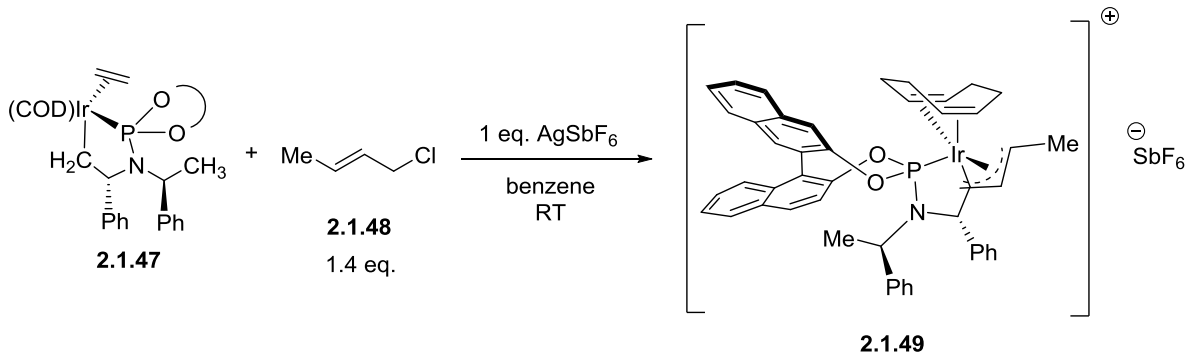
Hartwig *et al*. then proposed a possible mechanism for iridium-catalysed asymmetric allylic amination with ligand **L1** (**Scheme 2.1.13**).[55] Hartwig *et al*.

postulated that allylic amine complex **2.1.44** undergoes an endothermic and reversible addition to allylic carbonate **2.1.38** to form allyliridium complex **2.1.45**. Allyliridium complex **2.1.45** then reacts with aniline **2.1.42** *via* an irreversible reductive elimination to regenerate the allylic amine complex **2.1.44**.



Scheme 2.1.13: Catalytic cycle for iridium-catalysed asymmetric allylic amination proposed by Hartwig *et al*.[55]

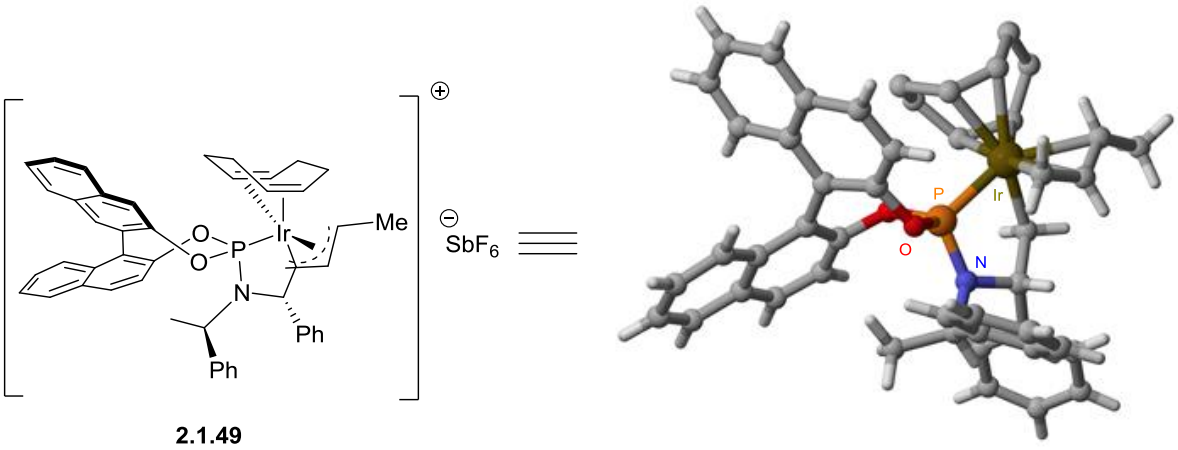
In 2009, Hartwig *et al*. reported an independent synthesis of an allyliridium complex **2.1.49** from active catalyst **2.1.47** and allylic chloride **2.1.48** (**Scheme 2.1.14**).[56] The resulting intermediate was then trapped by $AgSbF_6$ to form a stable allyliridium complex **2.1.49**.



Complex **2.1.47** was made from complex **2.1.36** (**Scheme 2.1.10**) by displacing ligand **L1** with ethylene

Scheme 2.1.14 : Independent synthesis of allyliridium complex 2.1.49 by Hartwig *et al*.[56]

The identity of allyliridium complex **2.1.49** was confirmed by X-ray crystallography (**Figure 2.1.2**).[56] It is a distorted octahedron with the central iridium being coordinated to the COD ligand, phosphorus and methylene group of the phosphoramidite ligand and the two termini of the allyl substrate. This allyliridium complex **2.1.49** was subjected to a variety of nucleophiles and the results were compared with reactions carried out under standard reaction conditions (e.g. **Scheme 2.1.10**, page 18).[56] Similar yields, regioselectivities and enantioselectivities were obtained which suggests that the allyliridium complex **2.1.49** is chemically and kinetically competent to be an intermediate in iridium-catalysed AAS. This further supports the proposed mechanism in **Scheme 2.1.13**.

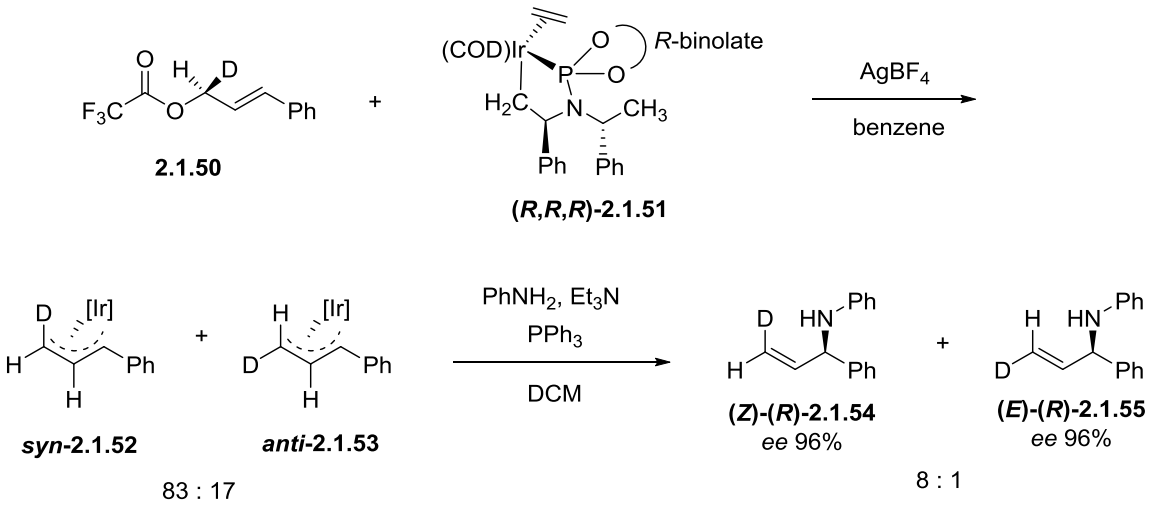


2.1.49

Figure 2.1.2: X-ray crystallography of allyliridium complex 2.1.49[56] (the SbF_6 anion and the hydrogen atoms on the COD ligand of the X-ray structure were removed for clarity)

Later in 2012, Hartwig *et al*. further studied the stereochemistry of the individual steps in the proposed catalytic cycle (**Scheme 2.1.13**, page 20) by firstly reacting the enantioenriched deuterium-labelled linear allylic trifluoroacetate **2.1.50** with a stoichiometric amount of the iridium catalyst **(*R*,*R*,*R*)-2.1.51** followed by subjecting the resulting allyliridium complexes ***syn*-2.1.52** and ***anti*-2.1.53** to aniline which was the nucleophile (**Scheme 2.1.15**).[57] The positions of deuterium in the intermediates/products obtained from each step were monitored. Using complex **(*R*,*R*,*R*)-2.1.51** as the active iridium catalyst, the products obtained from the oxidative addition step were allyliridium complexes ***syn*-2.1.52** and ***anti*-2.1.53** in a ratio of 83 : 17. The ratio was determined by integrating the terminal proton peaks in the ^{1}H NMR spectrum. Hartwig *et al*. explained that the starting material **2.1.50** was partially racemised when it was prepared from the enantioenriched cinnamyl alcohol (*ee* >90%) *via* esterification (the *ee* of substrate **2.1.50** could not be determined directly) and thus, both stereoisomers ***syn*-2.1.52** and ***anti*-2.1.53** were formed in the oxidative addition step. Nonetheless, the fact that allyliridium complex ***syn*-2.1.52** was formed predominantly suggests that the oxidative addition step

likely proceeds with inversion of configuration. After that, the nucleophilic attack by aniline on allyliridium complexes ***syn*-2.1.52** and ***anti*-2.1.53** afforded stereoisomers **(*Z*)-(*R*)-2.1.54** and **(*E*)-(*R*)-2.1.55**, both in *R*-configurations with excellent *ee*s. This result suggests that the reductive elimination step also proceeds with inversion of configuration. Hartwig *et al*. also carried out similar studies using catalytic amount of iridium catalysts and the results were found to be consistent with those illustrated in **Scheme 2.1.15** (with stoichiometric amount of iridium catalysts). Thus, the iridium-catalysed AAS reaction was shown to proceed with overall retention of configuration *via* two inversions of configurations in the oxidative addition step and reductive elimination step respectively.



Scheme 2.1.15: Investigation of the stereochemistry of the intermediates and products in iridium-catalysed AAS by Hartwig *et al*.[57]

2.1.3.3 Enantioselectivity

The structure of the allyliridium complex **2.1.49** (initially mentioned in **Scheme 2.1.14**, page 21)[56] provides insights into the origins of enantioselectivity of iridium-catalysed AAS with phosphoramidite ligands (**Figure 2.1.3**). Based on the

X-ray crystallography diagram (left) and a proposed quadrant diagram (right), Hartwig *et al*. suggested that firstly, the C48 methyl group of the allyl substrate points to the eastern quadrants in order to avoid interactions with the BINOLate and the phenethyl groups in the two western quadrants.[56] Secondly, coordination of one face of the allyl substrate to iridium is favoured over the other. This arises from the difference between the size of the COD ligand and the size of the C21 methylene group. There are fewer steric interactions between the small C21 methylene group and the allyl substrate. Therefore, the allyl substrate coordinates to iridium in such a way that the C48 methyl group occupies the southeastern quadrant, away from the large COD ligand in the northern quadrant.

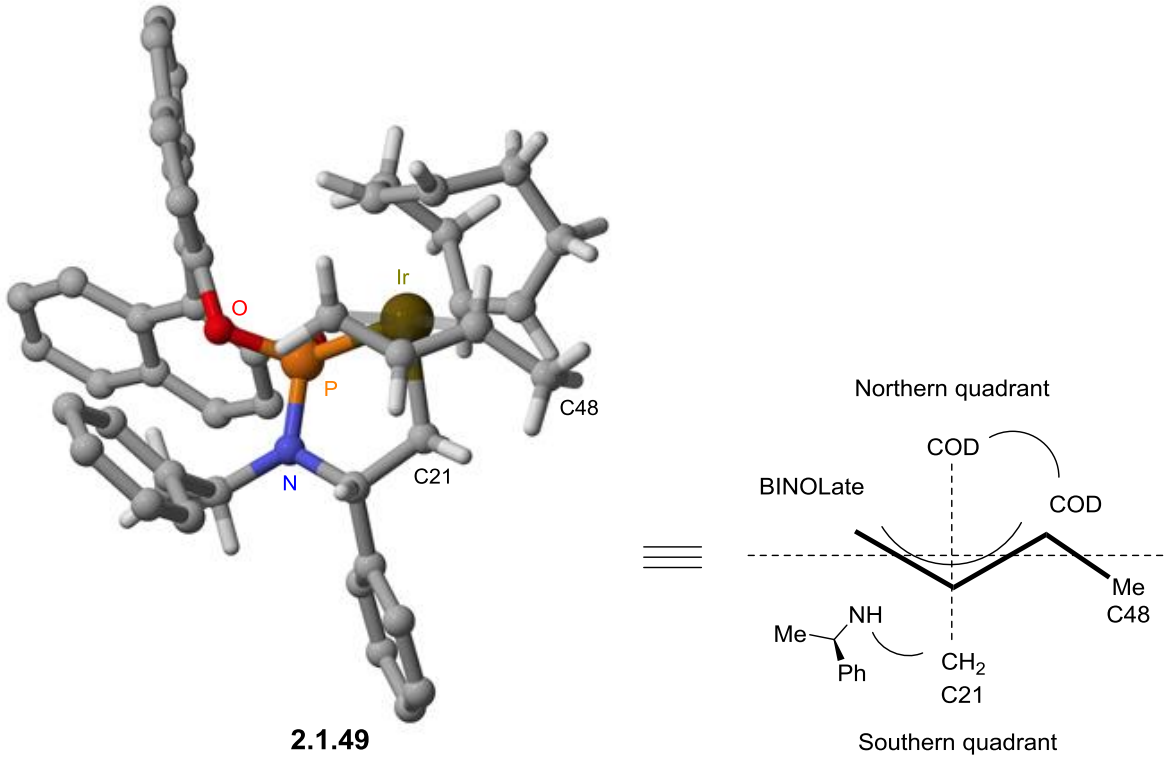
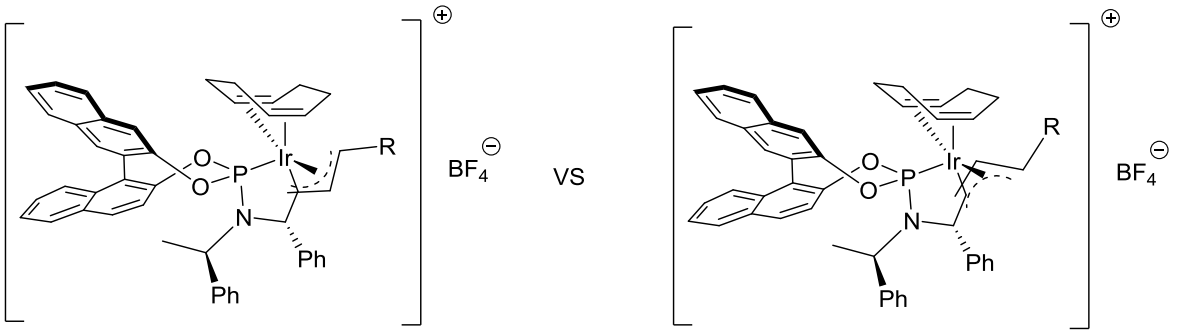


Figure 2.1.3: X-ray crystallography and quadrant diagram of allyliridium complex 2.1.49[56] (the SbF_6 anion and the hydrogen atoms on the aromatic rings of the X-ray structure were removed for clarity)

Later in 2012, Hartwig *et al*. further investigated into the origins of enantioselectivity of the iridium-catalysed AAS utilising phosphoramidite ligands.[57] Hartwig *et al*. reported the preparation of the two diastereomeric allyliridium complexes **2.1.56** and **2.1.57** which would eventually lead to the formation of opposite enantiomers after reacting with nucleophiles (**Figure 2.1.4**). According to previous discussion (**Figure 2.1.3**), complex **2.1.56** is the thermodynamically more stable allyliridium stereoisomer while complex **2.1.57** is the thermodynamically less stable allyliridium stereoisomer due to the unfavourable interaction between the R substituent and the COD ligand.[56] Hartwig *et al*. measured the rate of epimerisation of the less stable stereoisomer **2.1.57** to the more stable stereoisomer **2.1.56** and the rates of nucleophilic attack by amine nucleophiles on both allyliridium stereoisomers **2.1.56** and **2.1.57**. It was found that the rates of nucleophilic attack on both allyliridium stereoisomers **2.1.56** and **2.1.57** are much faster than the rates of interconversion between the two allyliridium stereoisomers **2.1.56** and **2.1.57**. This suggests that the enantioselectivity of the reaction is not controlled by the η^3-η^1-η^3 interconversions. Instead, the enantioselectivity is determined by the stereoselectivity of the oxidative addition step which favours the formation of the more stable allyliridium stereoisomer **2.1.56** using this catalyst system – $[Ir(COD)Cl]_2$ with phosphoramidite ligands.



2.1.56
more stable stereoisomer

2.1.57
less stable stereoisomer

R = 2-bromophenyl

Figure 2.1.4: Diastereomeric allyliridium complexes prepared by Hartwig *et al*.[57]

2.1.3.4 Regioselectivity

The origin of the high regioselectivity of iridium-catalysed allylic substitution reactions for the formation of branched isomers was not well understood until recently. In 2015, Hartwig *et al*. reported detailed computational studies utilising the catalyst system, $[Ir(COD)Cl]_2$ and triphenyl phosphite, which is the first iridium catalyst system discovered to strongly favour the formation of branched isomers as mentioned earlier in **Section 2.1.2.1**.[12,58] Hartwig *et al*. reported that the regioselectivity is unlikely determined by the relative bond lengths between the iridium and the two allyl termini because they were found to be similar in the allyliridium complex. Instead, from the crystal structure of the isolated allyliridium BF_4^- complex **2.1.58** (**Figure 2.1.5**), it was found that the distance between one of the hydrogen atoms in the COD ligand and one of the fluorine atoms in BF_4^- is only 2.43 Å which is shorter than the sum of their Van der Waal radii (2.67 Å). This suggests that there is C-H···F attractive interaction and thus, Hartwig *et al*. believed that there will also be similar interactions between the allyliridium complex and the electronegative atoms in the approaching nucleophile; these attractive interactions

can lower the free energies of various transition states to different extents and therefore, contribute to the regioselectivity of the reaction.

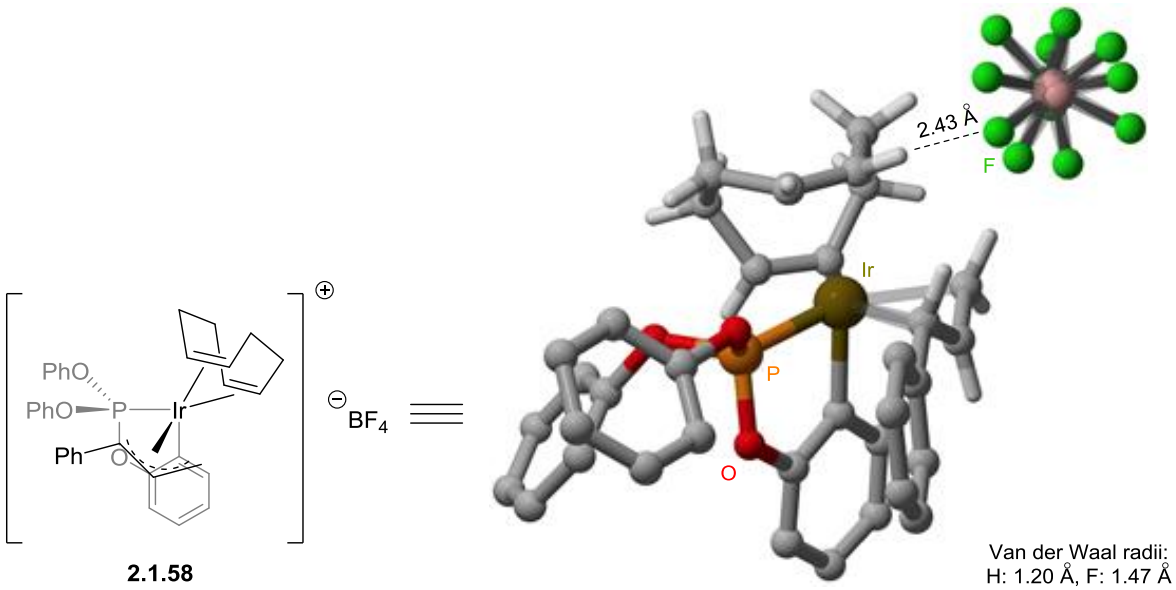


Figure 2.1.5: C-H···F interaction between the BF_4^- anion (disordered) and one of the hydrogen atoms of the COD ligand in complex 2.1.58[58] (the hydrogen atoms on the aromatic rings of the X-ray structure were removed for clarity)

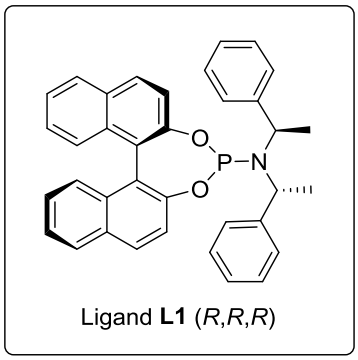
Hartwig *et al*. then performed extensive DFT calculations on reactions between allyliridium complex **2.1.58** and two different nucleophiles – trifluoroacetate and the anion of dimethylmalonate.[58] It was found that there are several C-H···O interactions present between various hydrogen atoms of the allyl moiety or the COD ligand and the oxygen atoms of the incoming nucleophile, and these interactions lower the free energy of the transition state leading to the branched products to a larger extent in comparison to the transition state leading to the linear products. This is in agreement with the experimentally observed regioselectivity. Thus, Hartwig *et al*. suggested that the regioselectivity of the iridium-catalysed allylic substitution reactions is influenced by a series of weak, attractive and noncovalent interactions between the allyliridium complex and the approaching nucleophile.[58]

2.1.4 Iridium-catalysed AAA with unstabilised carbon nucleophiles

Iridium-catalysed AAA involving stabilised carbon nucleophiles such as malonates has been very well established over the years (as discussed in **Section 2.1.2.2**), but reactions using unstabilised enolates are less explored and more challenging. This is because the high reactivity of unstabilised carbon nucleophiles usually limits their compatibility with the functional groups in other reagents. This section will not cover all of the advances in iridium-catalysed AAA using unstabilised carbon nucleophiles, but will aim to present several examples that are more relevant to our work in this thesis, i.e. the asymmetric synthesis of *γ*,*δ*-unsaturated carbonyl compounds.

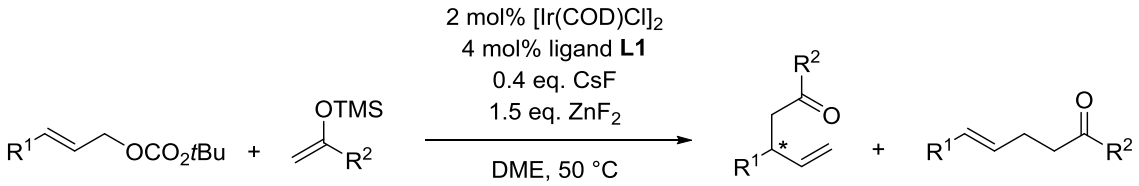
2.1.4.1 Iridium-catalysed AAA with external unstabilised carbon nucleophiles

In 2005 and 2007, Hartwig *et al*. reported two iridium-catalysed AAA reactions using silyl enol ethers **2.1.60**[59] and enamines **2.1.64**[60] as the nucleophiles respectively (**Scheme 2.1.16**). In summary, best results (i.e. yield, regioselectivity and enantioselectivity) were obtained from reactions of aryl allylic substrates and aryl nucleophiles. When one of the reagents was an alkyl compound, either yield or selectivity or both was lowered. The poorest result was obtained when both allylic substrate and nucleophile were alkyl compounds.



Ligand **L1** (*R*,*R*,*R*)

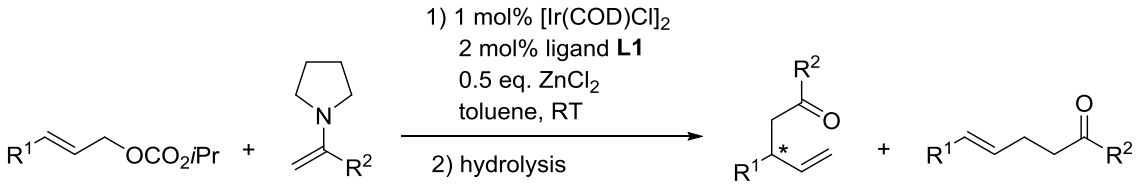
Using silyl enol ethers:



2.1.59 **2.1.60** 1.5 eq. **2.1.61** **2.1.62**

R^1	R^2	Combined yield	Branched to linear ratio	*ee*	t
Ph	Ph	84%	93 : 7	94%	8 h
Ph	CH_2CH_2Ph	54%	99 : 1	94%	18 h
*n*Pr	Ph	92%	87 : 13	92%	8 h

Using enamines:

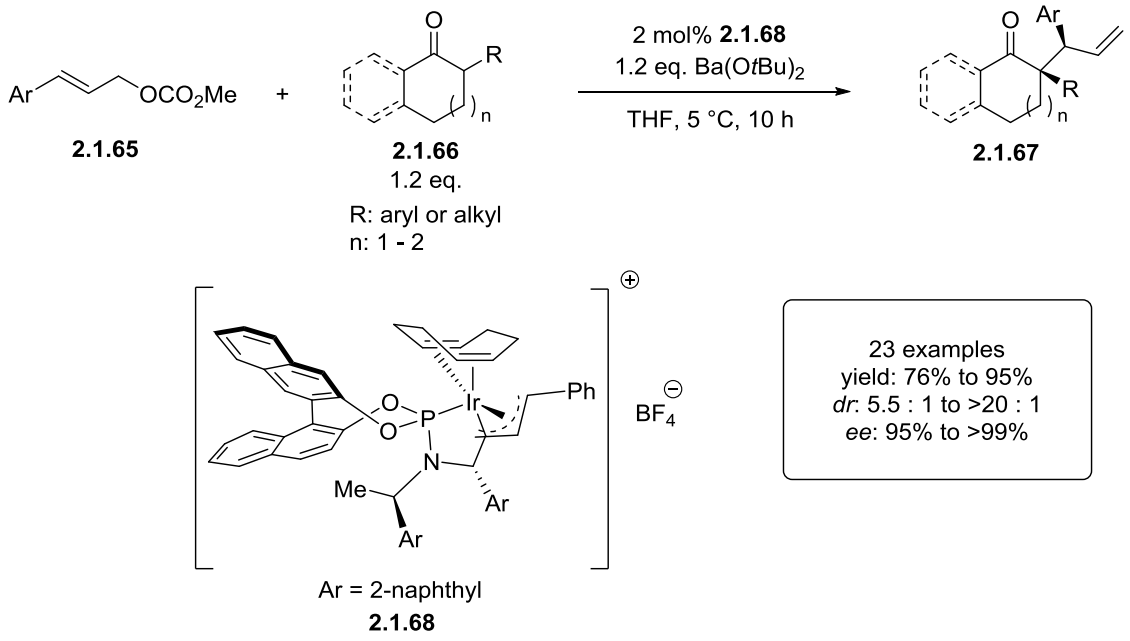


2.1.63 **2.1.64** 1.2 eq. **2.1.61** **2.1.62**

R^1	R^2	Combined yield	Branched to linear ratio	*ee*	t
Ph	Ph	91%	>99 : 1	94%	6 h
Ph	*i*Pr	86%	>99 : 1	95%	5 h
Me	Ph	68%	95 : 5	94%	4 h
*n*Pr	*i*Bu	64%	89 : 11	83%	39 h

Scheme 2.1.16: Iridium-catalysed AAA using silyl enol ether and enamine nucleophiles by Hartwig *et al*.[59,60]

Later in 2014, Hartwig *et al*. reported a diastereo- and enantioselective iridium-catalysed AAA using cyclic ketone enolates as the nucleophiles (**Scheme 2.1.17**).[61] In the reaction, cyclic ketones **2.1.66** were deprotonated by the base, Ba(O*t*Bu)$_2$, to form barium ketone enolates which then reacted with allylic carbonates **2.1.65** in the presence of the active iridium catalyst **2.1.68** to afford alkylated ketones **2.1.67**, generating the vicinal quaternary and tertiary stereocenters in one step. In summary, only aromatic allylic carbonates **2.1.65** were reported; aromatic substrates **2.1.65** containing a variety of Ar groups, including pyridyl group, furyl group and phenyl groups with electron-donating or electron-withdrawing substituents, were reacted with a wide scope of ketone nucleophiles **2.1.66** to give alkylated ketones **2.1.67** in very good yields with good diastereo- and enantioselectivities.

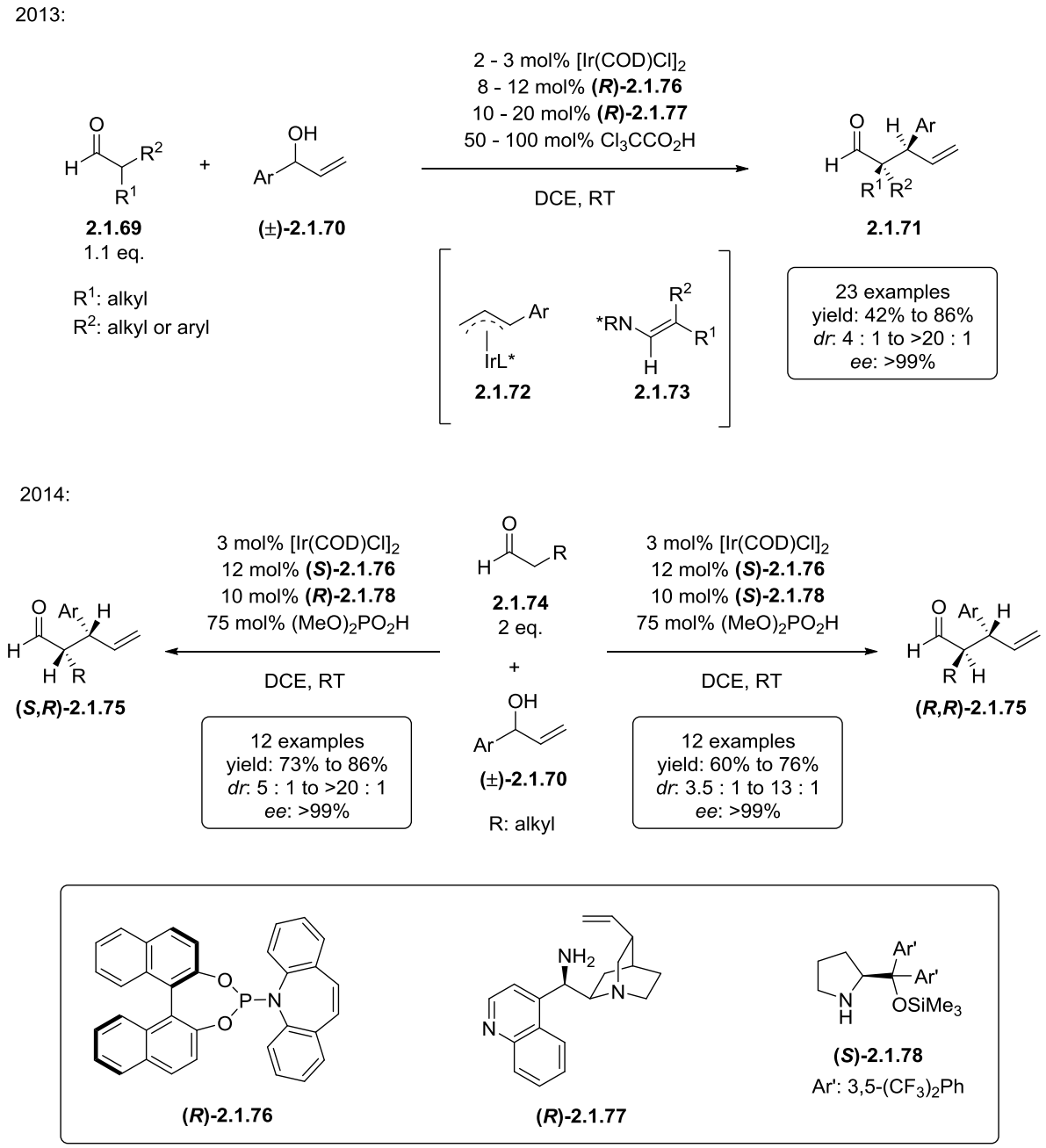


Scheme 2.1.17: Diastereo- and enantioselective iridium-catalysed AAA using barium ketone enolate nucleophiles by Hartwig *et al*.[61]

From 2013 to 2015, Carreira *et al*. reported intensive studies into the diastereo- and enantioselective iridium/amine dual-catalysed AAA that forms *γ*,*δ*-unsaturated aldehydes bearing two vicinal stereogenic centers in one step.[62,63,64] The distinct chiral iridium and amine catalysts operate concurrently and independently to set the configurations of both stereogenic centers in a single transition state. In 2013, Carreira *et al*. reported the asymmetric synthesis of *γ*,*δ*-unsaturated aldehydes **2.1.71** from racemic alcohols **(±)-2.1.70** and *α*-alkyl substituted branched aldehydes **2.1.69** (**Scheme 2.1.18**).[62] The configurations of the two stereogenic centers in the products **2.1.71** were controlled by the transition state involving a chiral allyliridium complex **2.1.72** and a chiral nucleophilic enamine **2.1.73** (formed form aldehyde **2.1.69** and the chiral amine catalyst **(*R*)-2.1.77**). A wide range of substrates (23 examples) was screened; good to excellent yields and *dr*s were obtained and >99% *ee*s were achieved. Carreira *et al*. also showed that by simply using the opposite enantiomer of chiral catalyst **2.1.76** or **2.1.77**, the other three stereoisomeric products **2.1.71** could be obtained in similar yields with comparable *dr*s and *ee*s.

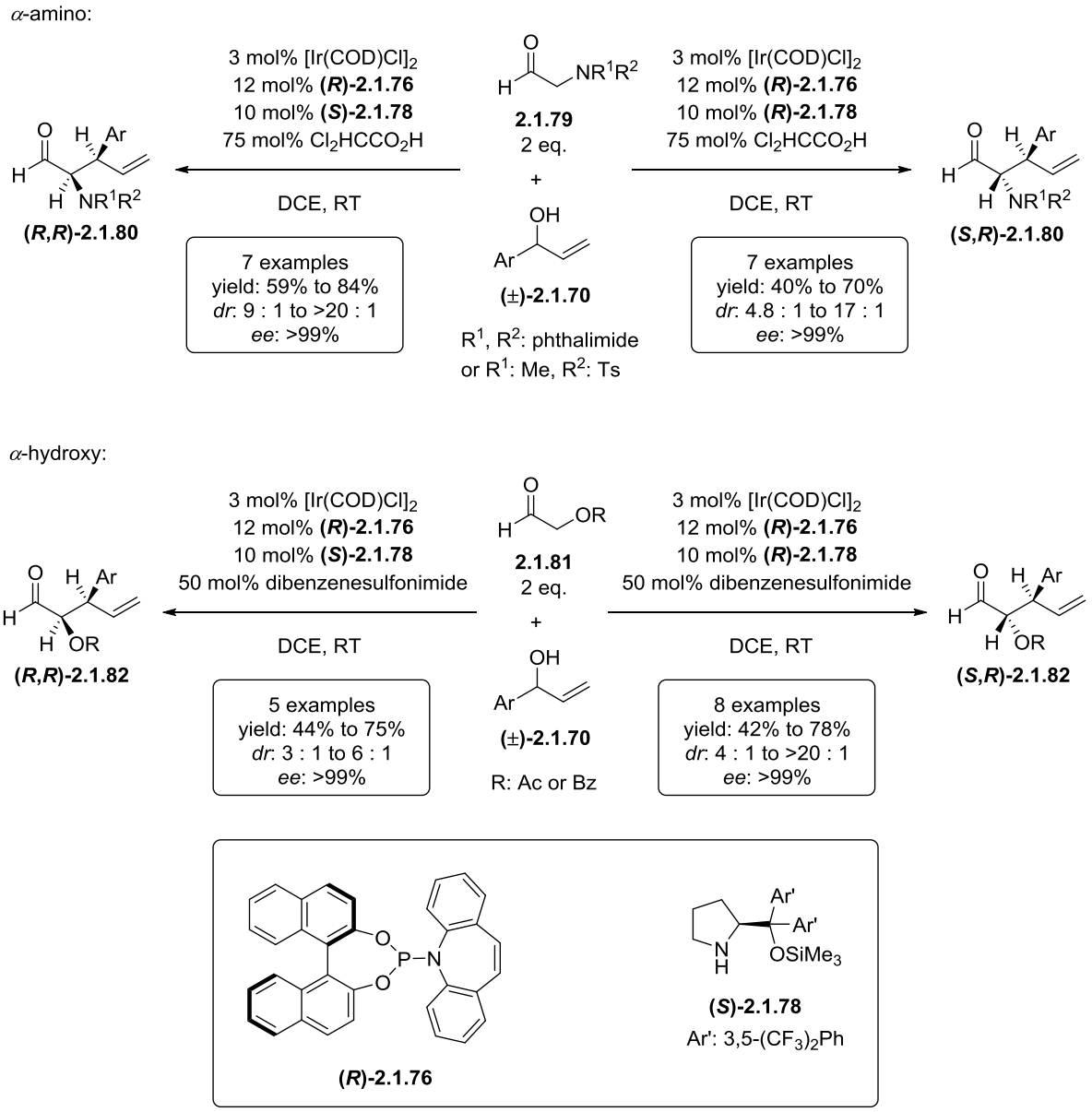
Later in 2014, Carreira *et al*. expanded the substrate scope to include *α*-alkyl substituted linear aldehydes **2.1.74** (**Scheme 2.1.18**).[63] This type of substrate is more challenging to handle as it is prone to self-aldol condensation. Besides this, the product **2.1.75** is also prone to epimerisation as it contains an enolisable stereogenic center at the *α*-position. After extensive screening of various reaction parameters, secondary amine **2.1.78** and phosphoric acid were found to be the optimal amine catalyst and acid promoter. A list of substrates was then explored

which gave good to excellent yields and *dr*s and >99% *ee*s. One limitation is that only aryl alcohol substrates were reported in these two studies.



Scheme 2.1.18: Diastereo- and enantioselective iridium/amine dual-catalysed AAA using branched and linear aldehyde substrates towards the synthesis of *γ*,*δ*-unsaturated aldehydes bearing two vicinal stereogenic centers by Carreira *et al*.[62,63]

In 2015, Carreira *et al*. further expanded the substrate scope to include protected *α*-amino and *α*-hydroxyaldehydes **2.1.79** and **2.1.81** (**Scheme 2.1.19**).[64] It was found that the nature of the acid promoter has significant impact on the yields and selectivities of the reaction (the reason is not well understood). Optimisation studies showed that the use of dichloroacetic acid gave the optimal results for the *α*-aminoaldehyde substrates **2.1.79** while dibenzenesulfonimide gave the optimal results for the *α*-hydroxyaldehyde substrates **2.1.81**. A list of substrates was then screened. Overall, moderate to good yields and synthetically useful *dr*s were obtained. >99% *ee*s were achieved for all substrates screened. In general, the diastereoselectivities of reactions involving *α*-hydroxyaldehydes **2.1.81** are slightly lower than those of reactions involving *α*-aminoaldehydes **2.1.79**. Again, only aryl alcohol substrates were reported in this study.

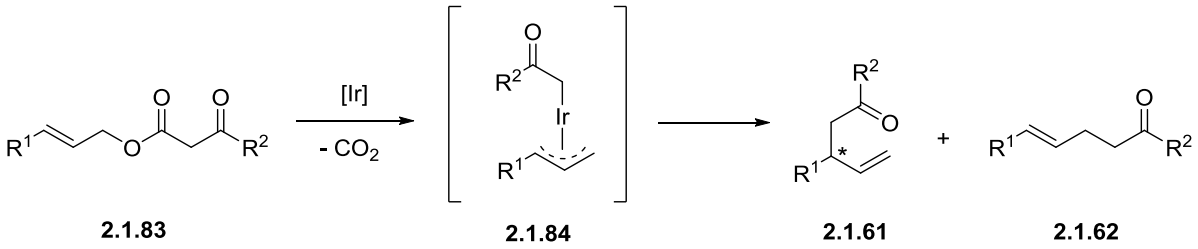


Scheme 2.1.19: Diastereo- and enantioselective iridium/amine dual-catalysed AAA using *α*-amino and *α*-hydroxyaldehyde substrates towards the synthesis of *γ*,*δ*-unsaturated aldehydes bearing two vicinal stereogenic centers by Carreira *et al*.[64]

2.1.4.2 Decarboxylative iridium-catalysed AAA

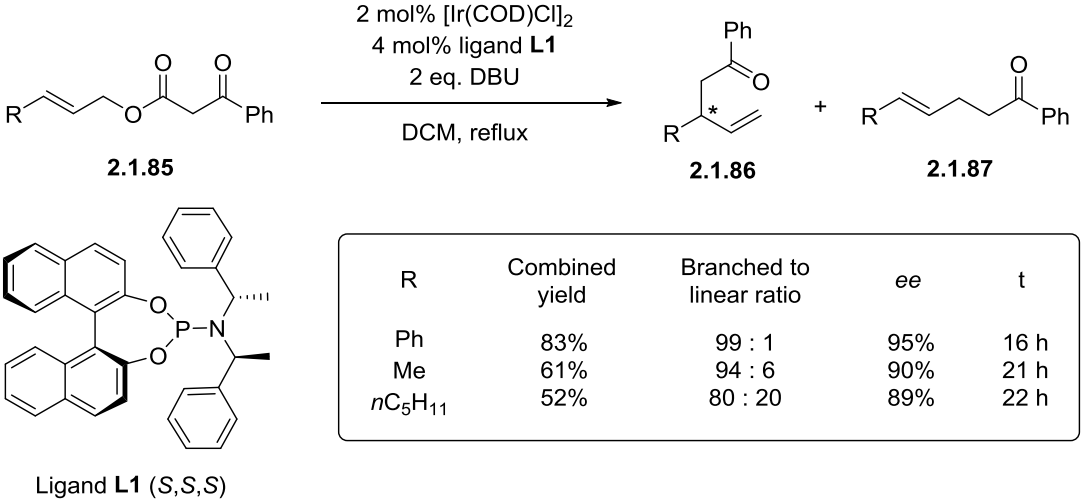
In 2007, You *et al*. reported an interesting decarboxylative iridium-catalysed AAA using substrates with potential nucleophiles built-in (**Scheme 2.1.20**).[65] Instead of having a carbonate as the leaving group, the leaving group was a *β*-ketoester. The starting material **2.1.83** underwent decarboxylation to form a

nucleophilic enolate, which then underwent carbon-carbon bond formation to give the chiral product **2.1.61** or linear product **2.1.62**. In this case, no external nucleophiles were required in the reaction. This reaction can be considered as the asymmetric version of Carroll rearrangement[66] to form enantioenriched ketones.



Scheme 2.1.20: Proposed reaction pathway of decarboxylative iridium-catalysed AAA by You *et al*.[65]

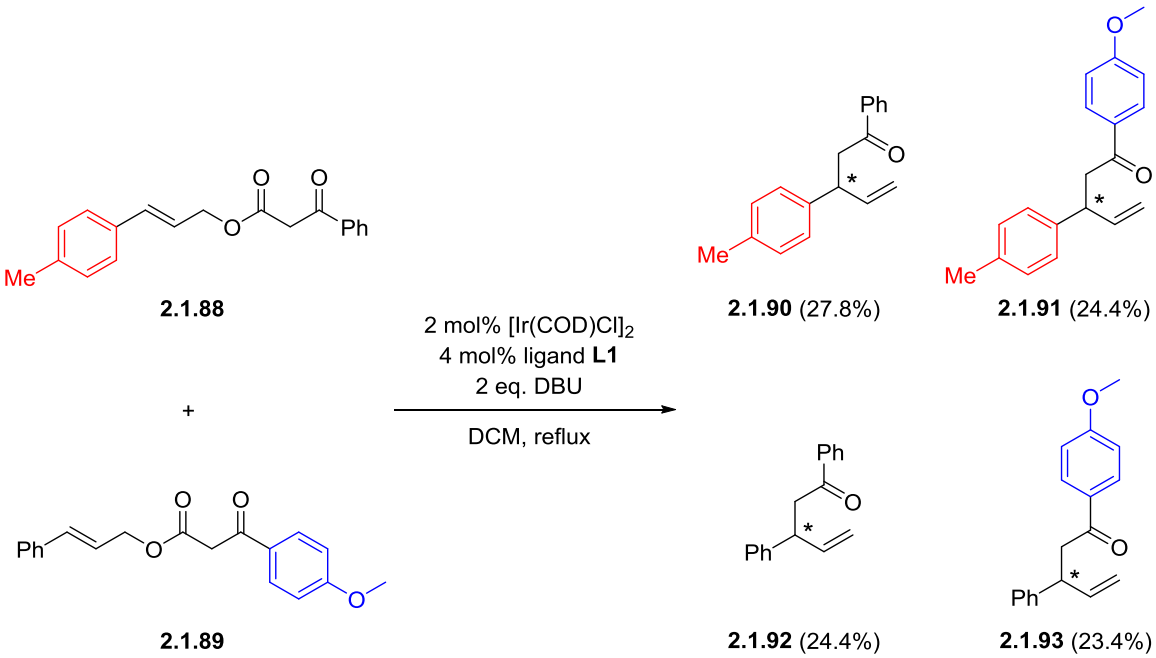
The advantage of this decarboxylative method in comparison to the previous reactions with external unstabilised carbon nucleophiles in **Section 2.1.4.1** is that no additives are required to activate the nucleophiles and no hydrolysis step is required to furnish the products. Aqueous work-up can also be avoided which makes purification step simpler. Nonetheless, there are still limitations. In order to achieve good yields and selectivities, the reactions needed to be slightly heated and two equivalents of base were required (**Scheme 2.1.21**).[65] Furthermore, good results (i.e. yield, regioselectivity and enantioselectivity) were only obtained from reactions involving aryl allylic substrates. Alkyl substrates led to much poorer yields, regioselectivities and enantioselectivities.



R	Combined yield	Branched to linear ratio	*ee*	t
Ph	83%	99 : 1	95%	16 h
Me	61%	94 : 6	90%	21 h
nC_5H_{11}	52%	80 : 20	89%	22 h

Scheme 2.1.21: Decarboxylative iridium-catalysed AAA by You *et al*.[65]

The mechanism of this decarboxylative allylic substitution reaction has not been fully investigated. You *et al*. carried out a crossover experiment which provided some insights into the reaction mechanism (**Scheme 2.1.22**).[65] Two equimolar amounts of allylic substrates **2.1.88** and **2.1.89** were subjected to the standard reaction conditions. All four possible branched products **2.1.90**, **2.1.91**, **2.1.92** and **2.1.93** were formed in nearly equal amounts. This result suggests that the reaction unlikely proceeds *via* intramolecular rearrangement to form alkylated products.



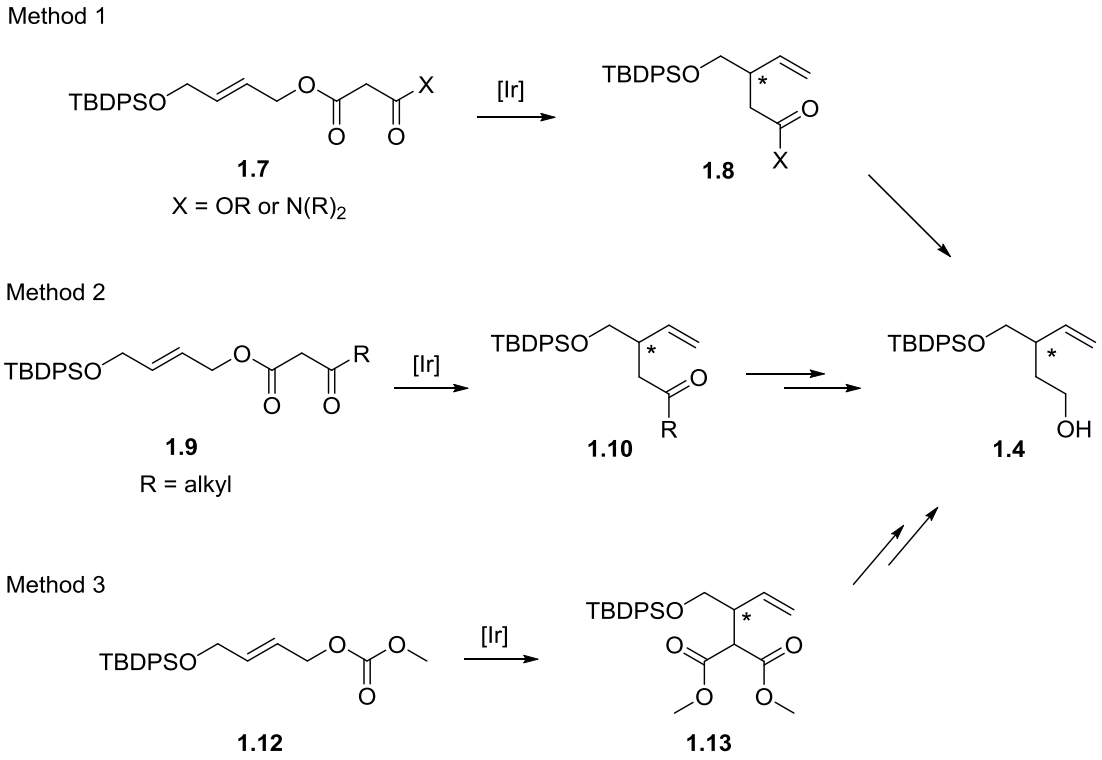
Scheme 2.1.22: Crossover experiment by You *et al*.[65]

In summary, a wide range of ligands has been tested for iridium-catalysed AAS over the years, out of which phosphoramidite ligands **L1**, **L2** and **L3** were found to be particularly efficient in terms of reactivity and selectivity.[20] These enantioenriched ligands are the most commonly used ones in recent research and ligands **L1** and **L2** will be focused in this project.

2.2 Aim

As mentioned in **Chapter 1** (Overview), there are three synthetic pathways to prepare enantioenriched primary alcohol **1.4** (which is an intermediate in the synthesis of dolabellane) from achiral allylic substrates (**Scheme 2.2.1**). All three pathways involve the use of iridium-catalysed AAA. Therefore, this project aims to improve the scope of decarboxylative iridium-catalysed AAA reported by You *et al*.[65] by expanding substrate scope to both aryl and alkyl *β*-ketoesters **1.9**. This project also aims to apply this decarboxylative method to substrates **1.7** containing

heteroatoms at position X, such as allylic malonates and allylic *β*-amidoesters. Those types of substrates have not been reported in literature. They can form chiral esters and amides **1.8** which are synthetically useful precursors for various transformations. This type of reactions is equivalent to the asymmetric Johnson-Claisen[67] and Eschenmoser-Claisen[68] rearrangements. Lastly, the conversion of those enantioenriched alkylated products **1.8**, **1.10** and **1.13** to alcohol **1.4** will be explored.



Scheme 2.2.1: Different synthetic pathways for the preparation of enantioenriched alcohol 1.4 from achiral allylic substrates

2.3 Synthesis of enantioenriched ketones

As mentioned previously in **Section 2.1.4** (page 35), You *et al*. reported a decarboxylative iridium-catalysed AAA to synthesise enantioenriched ketones.[65] One major limitation of the work was that good results (i.e. yield, regioselectivity

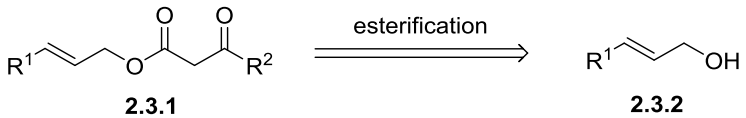
and enantioselectivity) were only obtained from reactions involving aryl allylic substrates. Alkyl substrates led to much poorer yields, regioselectivities and enantioselectivities. Therefore, this section describes further optimisation of reaction conditions for decarboxylative iridium-catalysed AAA reported by You *et al*., application of the optimal reaction condition to a wide range of *β*-ketoester substrates (including a variety of alkyl substrates) and attempts to convert enantioenriched ketone products into carboxylic acid derivatives.

2.3.1 Motivation

Decarboxylative iridium-catalysed AAA is a convenient method to directly synthesise enantioenriched ketones which are useful building blocks in natural product synthesis. Therefore, it would be desirable to find conditions that apply to a large scope of substrates and form products in good yields with good selectivities.

2.3.2 Substrates, iridium pre-catalyst and ligands synthesis

The allylic *β*-ketoester substrates **2.3.1** for decarboxylative iridium-catalysed AAA can be simply prepared from the corresponding allylic alcohols **2.3.2** *via* esterification (**Scheme 2.3.1**).



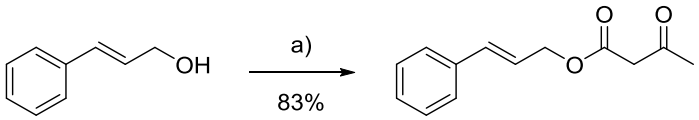
2.3.1 **2.3.2**

Scheme 2.3.1: General preparation of *β*-ketoesters

An aryl and an alkyl substrate were firstly prepared for optimisation of reaction conditions. Cinnamyl *β*-ketoester **2.3.4** (**Scheme 2.3.2**) was chosen as a suitable substrate to start investigations with because aryl substrates usually give

better yields and higher branched to linear ratios in comparison to alkyl substrates (see You's work in **Scheme 2.1.21**, page 36). Therefore, results can be more easily analysed and trends more clearly observed by using aryl substrates.

Cinnamyl *β*-ketoester **2.3.4** was synthesised from commercially available cinnamyl alcohol **2.3.3** *via* esterification[69] (**Scheme 2.3.2**).

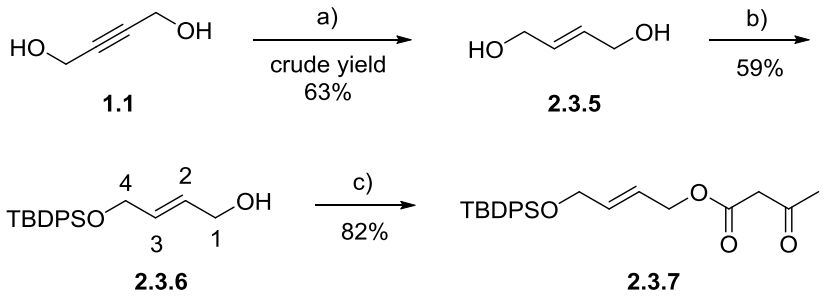


2.3.3 **2.3.4**

Reagents and conditions: a) Ethyl acetoacetate (1 eq.), DMAP (1 eq.), molecular sieves (4 Å), toluene, 130 °C, 16 h.

Scheme 2.3.2: Preparation of cinnamyl *β*-ketoester 2.3.4

Optimisation of reaction conditions for the alkyl substrates were carried out using the allylic *β*-ketoester **2.3.7** with a *tert*-butyldiphenylsilyl (TBDPS) ether protecting group (**Scheme 2.3.3**) because *β*-ketoester **2.3.7** is involved in the total synthesis of dolabellane **1.6** (mentioned in **Chapter 1**). *β*-Ketoester **2.3.7** was synthesised from butynediol **1.1** in three steps (**Scheme 2.3.3**). Butynediol **1.1** was firstly reduced[70] to butenediol **2.3.5** which, without further purification, was monosilylated to form allylic alcohol **2.3.6**.[71] The geometry of the double bond was determined by coupling constants analysis: H-2 is a doublet of triplets of triplets with coupling constants J = 15.4, 5.4, 1.7 Hz and H-3 is also a doublet of triplets of triplets with coupling constants J = 15.4, 4.4, 1.4 Hz. As $J_{H2\text{-}H3}$ is >14 Hz, it should be an *E*-alkene. Allylic alcohol **2.3.6** was then reacted with ethyl acetoacetate in toluene under reflux to form allylic *β*-ketoester **2.3.7** in good yield.[69]



1.1 2.3.5 2.3.6 2.3.7

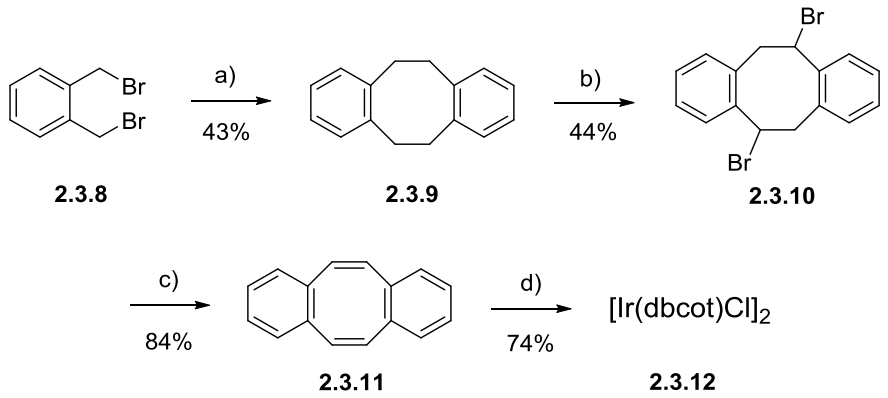
Reagents and conditions: a) $LiAlH_4$ (1.2 eq.), THF, 0 °C to RT, 16 h; b) NaH (1 eq.), TBDPS-Cl (1 eq.), THF, RT, 16 h; c) ethyl acetoacetate (1 eq.), DMAP (1 eq.), molecular sieves (4 Å), toluene, 120 °C, 16 h.

Scheme 2.3.3: Preparation of alkyl allylic *β*-ketoester 2.3.7

The commonly used iridium catalyst precursor, $[Ir(COD)Cl]_2$, is commercially available and has been shown by Takeuchi *et al*. to be one of the best catalyst precursors.[14] Another catalyst precursor, $[Ir(dbcot)Cl]_2$, was also prepared for screening (**Scheme 2.3.4**). In 2008, Helmchen *et al*. reported that using $[Ir(dbcot)Cl]_2$ in iridium-catalysed asymmetric allylic amination and allylic alkylation with stabilised enolates led to better regioselectivities.[72] This improvement in regioselectivity was believed to be due to the stronger bonding between iridium and dbcot ligand as dbcot is a better *π*-acceptor than COD. This would induce a greater cationic character in the η^3-allyl iridium complex.[73] A greater carbonium ion character will more likely be induced at the more substituted allylic terminus, thereby directing the nucleophile to attack this more substituted position.[14]

As $[Ir(dbcot)Cl]_2$ has not been used in decarboxylative allylic alkylation reactions before, its performance was studied in this project. $[Ir(dbcot)Cl]_2$ was synthesised from dibromide **2.3.8** in 4 steps (**Scheme 2.3.4**). Dibromide **2.3.8** was firstly dimerised to aryl octane **2.3.9** which then underwent allylic bromination.[74]

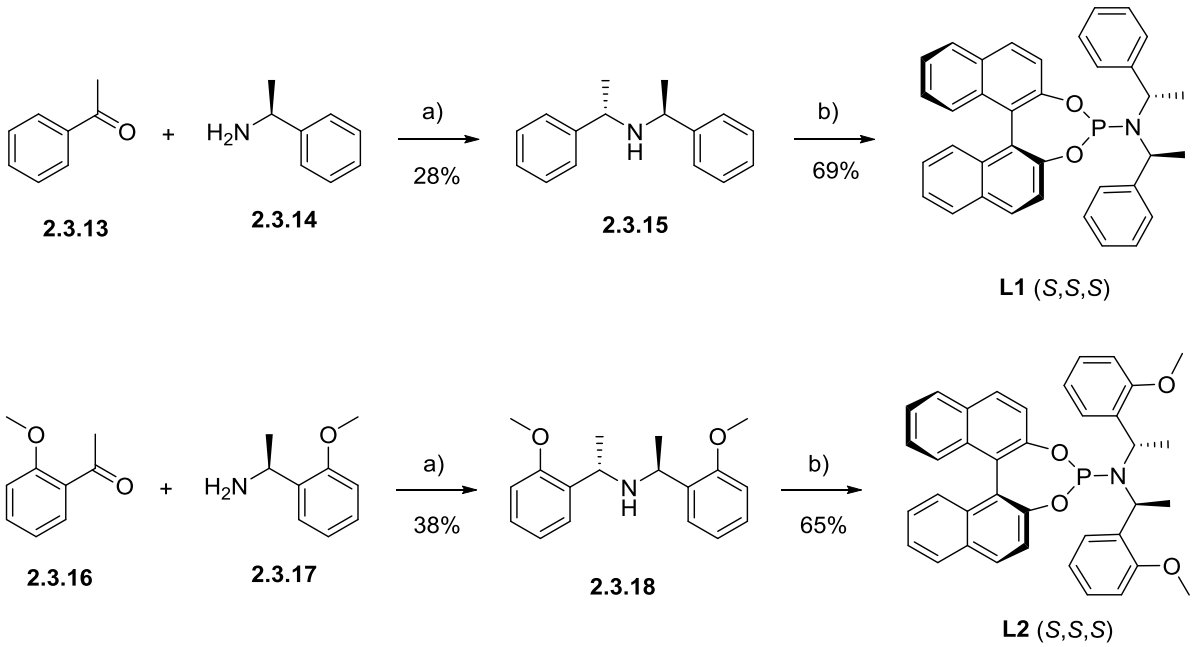
Dibromide **2.3.10** underwent dehalogenation to form dibenzoannulene **2.3.11** which then substituted the COD ligand on iridium to form $[Ir(dbcot)Cl]_2$.[74,75]



Reagents and conditions: a) Li nodules (5.8 eq.), THF, 0 °C to RT, sonication, 4 h; b) NBS (2 eq.), cat. 1,1′-azobis(cyclohexanecarbonitrile), CCl_4, 80 °C, 2.5 h; c) *t*-BuOK (1 M, 16 eq.), THF, 0 °C to RT, 16 h; d) $[Ir(COD)Cl]_2$ (0.5 eq.), DCM, RT, 20 min.

Scheme 2.3.4: Synthesis of $[Ir(dbcot)Cl]_2$[74,75]

Two phosphoramidite ligands **L1** and **L2**, which are particularly efficient in iridium-catalysed allylic substitution reactions (as mentioned in **Section 2.1**), were prepared for screening following literature procedures (**Scheme 2.3.5**).[22,76] Ketone **2.3.13** and chiral amine **2.3.14** were subjected to reductive amination to give the chiral secondary amine **2.3.15** which was then reacted with phosphorus trichloride followed by (*S*)-[1,1'-binaphthalene]-2,2'-diol to form the chiral phosphoramidite ligand **L1**. Phosphoramidite ligand **L2** was prepared in the same way using ketone **2.3.16** and chiral amine **2.3.17** (**Scheme 2.3.5**).



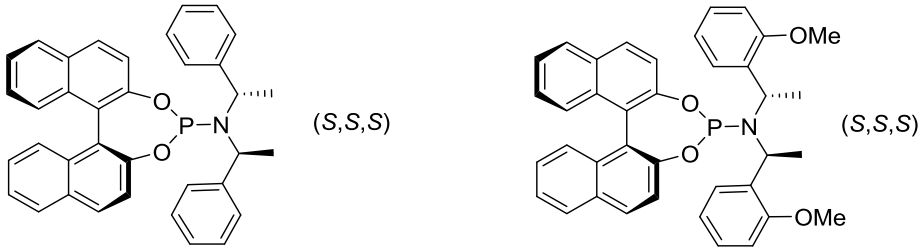
Reagents and conditions: a) $Ti(OiPr)_4$ (4 eq.), EtOAc, RT, 20 min, then 10% Pd/C (0.5 mol%), H_2, 1 atm, RT, 48 h; b) Et_3N (5 eq.), PCl_3 (1 eq.), THF, RT, 3 h, then (*S*)-[1,1'-binaphthalene]-2,2'-diol (1 eq.), RT, 16 h.

Scheme 2.3.5: Synthesis of phosphoramidite ligands L1 and L2[22,76]

2.3.3 Optimisation of reaction conditions

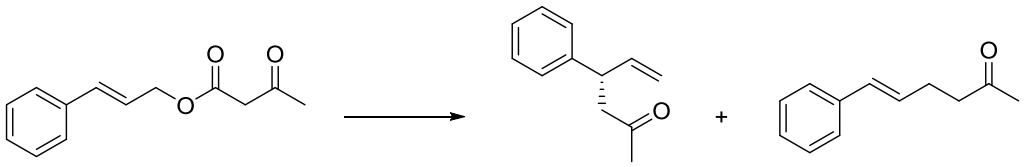
Cinnamyl *β*-ketoester **2.3.4** was subjected to decarboxylative iridium-catalysed AAA (**Table 2.3.1**). Phosphoramidite ligands **L1** and **L2** (**Figure 2.3.1**) and two commonly used bases (TBD and DBU) were screened.[31] THF was chosen as the solvent to start the optimisation with because Helmchen *et al*. obtained very good results from iridium-catalysed AAA using ligands **L1** and **L2** in THF.[31]

Linear isomers **2.3.20** were not formed in the reactions (neither observed in ^{1}H NMR nor isolated). The combination of $[Ir(COD)Cl]_2$ and ligand **L2** (**Table 2.3.1**, entry 2) led to a higher yield and *ee* in comparison to that of $[Ir(COD)Cl]_2$ and ligand **L1** (entry 1). Yield was decreased on changing base from TBD to DBU, but enantioselectivity was not affected (entry 3). On reducing the catalyst (dimer) loading from 4 mol% to 2 mol%, the reaction time was prolonged and yield was decreased (entry 4). Warming the reactions shortened the reaction times and slightly improved the yields with enantioselectivities unaffected (entries 5 and 6). Therefore, entry 2 (4 mol% $[Ir(COD)Cl]_2$, 8 mol% ligand **L2** and 16 mol% TBD at RT) was found to be the optimal set of conditions for decarboxylative iridium-catalysed AAA involving aryl substrates. (Determination of the enantiomeric excess will be discussed in **Section 2.3.4.4**, page 57.)



L1 **L2**

Figure 2.3.1: Phosphoramidite ligands used in optimisation



2.3.4 **2.3.19** **2.3.20**

Reagents and conditions: $[Ir(COD)Cl]_2$, phosphoramidite ligand, base, THF.

Entry[a]	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[b]	Ratio b : l[c]	*ee* (%)[d]
1	4	**L1** (8)	TBD (16)	RT	16	58	>99 : 1	96
2	4	**L2** (8)	TBD (16)	RT	3.5	83	>99 : 1	>99
3	4	**L2** (8)	DBU (16)	RT	2	45	>99 : 1	>99
4	2	**L2** (4)	TBD (8)	RT	6	56	>99 : 1	98
5	2	**L2** (4)	TBD (8)	40	2	63	>99 : 1	99
6	2	**L2** (4)	TBD (8)	50	1	61	>99 : 1	99

[a] All reactions were carried out on a 0.23 mmol scale. [b] Isolated yield of branched isomer **2.3.19**. [c] Branched to linear ratio, estimated from ^{1}H NMR. [d] Determined by chiral HPLC analysis.

Table 2.3.1: Optimisation of reaction conditions for aryl allylic *β*-ketoester 2.3.4

Optimisation for alkyl substrates was carried out separately as alkyl substrates generally give poorer results under the same conditions (**Table 2.3.2**). More bases were screened, also including non-amine inorganic bases which have not been used in the literature before (entries 8 to 11). Reaction time, yield and regioselectivity varied depending on the base, but enantioselectivity was generally unaffected. No desirable products were formed in reactions involving inorganic bases; reaction conversions were low and starting materials were recovered (entries 8 to 11). Amine base, *n*$PrNH_2$,[72] also did not lead to formation of products (entry 7). Using DBU, DABCO and *n*$BuNH_2$ gave poor yields of branched isomer **2.3.21** but branched to linear ratios and *ee*s were good (entries 4 to 6). Overall good results were obtained in the presence of TBD as the base (entries 1 to 3). Similar to the results in **Table 2.3.1**, the combination of $[Ir(COD)Cl]_2$ and ligand **L2** (entry 2) led to a higher yield in comparison to that of $[Ir(COD)Cl]_2$ and ligand **L1** (entry 1) although branched to linear ratios and *ee*s were comparable in both entries. On reducing the catalyst (dimer) loading from 4 mol% to 2 mol%, both yield and branched to linear ratio were slightly decreased (entry 3).



2.3.7 **2.3.21** **2.3.22**

Reagents and conditions: $[Ir(COD)Cl]_2$, phosphoramidite ligand, base, THF.

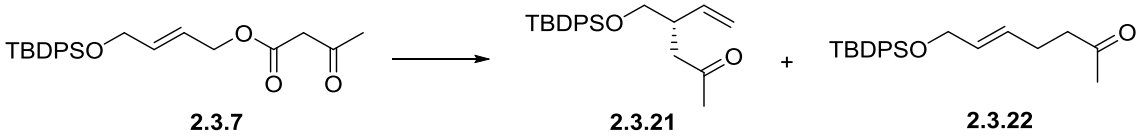
Entry[a]	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[b]	Ratio b : l[c]	*ee* (%)[d]
1	4	**L1** (8)	TBD (16)	RT	3	62	10 : 1	>99
2	4	**L2** (8)	TBD (16)	RT	3	75	10 : 1	>99
3	2	**L2** (4)	TBD (8)	40	2	69	9 : 1	>99
4	4	**L2** (8)	DBU (16)	RT	2.5	32	15 : 1	>99
5	4	**L2** (8)	DABCO (16)	RT	22	21	15 : 1	>99
6	4	**L2** (8)	*n*$BuNH_2$ (16)	RT	22	8[e]	-	94
7	4	**L2** (8)	*n*$PrNH_2$ (16)	RT	22	0[f]	-	-
8	4	**L2** (8)	Cs_2CO_3	RT	22	0[g]	-	-
9	4	**L2** (8)	K_2CO_3	RT	22	0[h]	-	-
10	4	**L2** (8)	K_3PO_4	RT	22	0[i]	-	-
11	4	**L2** (8)	Li_2CO_3	RT	22	0[j]	-	-

[a] All reactions were carried out on a 0.19 mmol scale. [b] Isolated yield of branched isomer **2.3.21**. [c] Branched to linear ratio, estimated from ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] 36% of starting material was recovered. [f] 75% of starting material was recovered. [g] 18% of starting material was recovered. [h] 63% of starting material was recovered. [i] 44% of starting material was recovered. [j] 69% of starting material was recovered.

Table 2.3.2: Optimisation of reaction conditions for alkyl allylic *β*-ketoester 2.3.7 using $[Ir(COD)Cl]_2$

Optimisation for alkyl *β*-ketoester **2.3.7** using another catalyst precursor, $[Ir(dbcot)Cl]_2$, was also carried out, hoping to further improve the regioselectivity of the reaction. The reactions were conducted using 8 mol% Ir/L and 16 mol% TBD in THF (**Table 2.3.3**). Different from observations in **Table 2.3.1** and **Table 2.3.2**, better results were obtained in the presence of ligand **L1** (entry 1) instead of ligand **L2** (entry 3). No desired products were formed on warming the reaction to 50 °C (entry 2). The overall results obtained from using $[Ir(dbcot)Cl]_2$ were not promising;

yield, regioselectivity and enantioselectivity were all lowered in comparison to previous results.



2.3.7 **2.3.21** **2.3.22**

Reagents and conditions: $[Ir(dbcot)Cl]_2$ (4 mol%), phosphoramidite ligand (8 mol%), TBD (16 mol%), THF.

Entry[a]	Ligand	T (°C)	t (h)	Yield (%)[b]	Ratio b : l[c]	*ee* (%)[d]
1	**L1**	RT	22	40	8 : 1	98
2	**L1**	50	22	0[e]	-	-
3	**L2**	RT	22	0[f]	-	-

[a] All reactions were carried out on a 0.19 mmol scale. [b] Isolated yield of branched isomer **2.3.21**. [c] Branched to linear ratio, estimated from ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] Unidentifiable complex mixture. [f] 14% of starting material recovered, the rest are unidentifiable complex mixture.

Table 2.3.3: Optimisation of reaction conditions for alkyl allylic *β*-ketoester 2.3.7 using $[Ir(dbcot)Cl]_2$

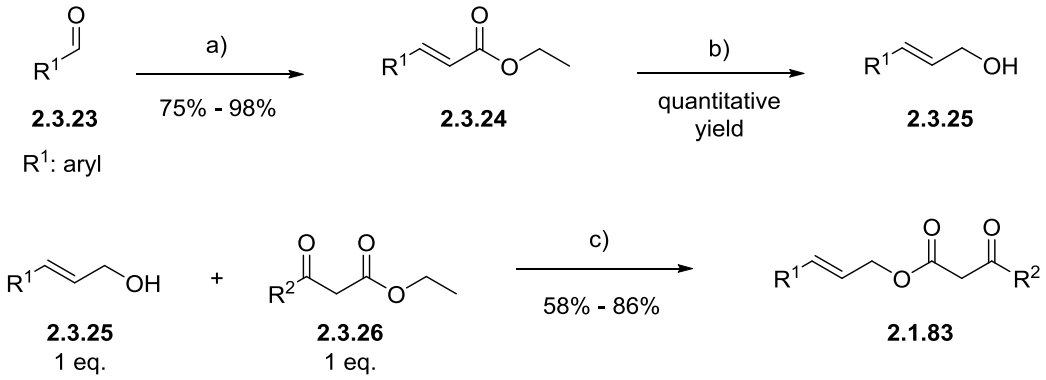
It was exciting to see that the same set of conditions (entry 2, **Table 2.3.1**), which gave the best results for aryl substrate **2.3.4**, was also optimal for alkyl substrate **2.3.7** (entry 2, **Table 2.3.2**) in decarboxylative iridium-catalysed AAA. Therefore, the optimal condition – 4 mol% $[Ir(COD)Cl]_2$, 8 mol% ligand **L2** and 16 mol% TBD in THF at RT was used for substrate screening which is reported in the following section.

2.3.4 Substrates screening

2.3.4.1 Preparation and screening of aryl substrates

The aryl allylic *β*-ketoester substrates **2.1.83** (R^1: aryl, R^2: alkyl) were prepared from various aryl aldehydes **2.3.23** in three steps (**Scheme 2.3.6**).

Aldehydes **2.3.23** firstly underwent Wittig reaction[77] to give (*E*)-*α*,*β*-unsaturated esters **2.3.24** which were reduced[77] by DIBAL-H to form allylic alcohols **2.3.25**. Alcohols **2.3.25** were then reacted with a variety of *β*-ketoesters **2.3.26** to form allylic *β*-ketoesters **2.1.83** in overall good yields.[69]



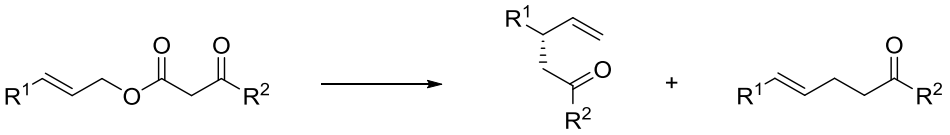
Reagents and conditions: a) (Carbethoxymethylene)triphenylphosphorane (1.1 eq.), THF, RT; b) DIBAL-H (2.2 eq.), DCM, 0 °C to RT; c) DMAP (1 eq.), molecular sieves (4 Å), toluene, 120 °C.

Scheme 2.3.6: General procedure for the preparation of aryl substrates 2.1.83

Using the optimal reaction condition (entry 2, **Table 2.3.1**), the scope of aryl allylic substrates was firstly explored (**Table 2.3.4**). In general, no linear isomers **2.3.28** were formed in reactions involving aryl allylic substrates, in keeping with a number of previous studies.[31,65] All cinnamyl substrates with different alkyl substituents at R^2 gave products in good to very good yields with excellent enantioselectivities (entries 1 to 4). For instance, even a tertiary *t*Bu group was tolerated and gave good results (entry 4). Substrates containing electron-donating groups (entries 6 and 9) and electron-withdrawing groups (entries 7, 8 and 10) on benzene rings were all well-tolerated. The positions of substituents on benzene rings also showed little effect on yields and selectivities except the cases of having bulky substituents at the ortho position of benzene rings (entries 10 and 11). In

these two entries, the *ee*s of the enantioenriched products were greatly decreased. This result is in line with the work published by You *et al*. who also observed a decrease in *ee* with ortho-substituted substrates.[78] It was suggested that this decrease in *ee* was probably due to poor fitting of the ortho-substituted substrate into the ligand pocket.[79,80] This hypothesis was supported by You's work on ligands with larger pockets which led to much better enantioselectivities for ortho-substituted aryl substrates.[79] However, it is interesting that the substrate containing an ortho-methoxy group (entry 9) gives an excellent *ee* of 96% despite OMe (A-value = 0.75 kcalmol^{-1}) being bulkier than Br (A-value = 0.49 kcalmol^{-1}).[81] Nevertheless, this trend is in agreement with You's work on iridium-catalysed AAA (using dimethyl malonate as the nucleophile) which also showed that *o*-OMe substrate gives a higher *ee* than *o*-Br substrate.[79] Besides this, You *et al*. also observed that *o*-Me (A-value = 1.7 kcalmol^{-1})[82] substrate likewise gives a higher *ee* than *o*-Br substrate.[79] The cause of this difference in *ee* values is not well understood; it is probably due to both steric and electronic effects.

Various heterocycles at R^1 were well tolerated as well (entries 11 to 14). (Determination of the absolute configurations of the enantioenriched ketone products **2.3.27** will be discussed in **Section 2.3.4.3**, page 55.)



2.1.83 **2.3.27** **2.3.28**

Reagents and conditions: $[Ir(COD)Cl]_2$ (4 mol%), ligand **L2** (8 mol%), TBD (16 mol%), THF, RT.

Entry	R^1	R^2	t (h)	Yield (%)[a]	Ratio b : l[b]	*ee* (%)[c]
1	Ph	Me	3.5	86	>99 : 1	>99 (*S*)
2	Ph	Et	1.5	74	>99 : 1	99
3	Ph	*n*Pr	3	74	>99 : 1	>99
4	Ph	*t*Bu	4	70	>99 : 1	>99
5	*m*-OMe-C_6H_4-	Me	3	83	>99 : 1	97
6	*p*-OMe-C_6H_4-	Me	3	85	>99 : 1	99
7	*p*-Br-C_6H_4-	Me	1.5	77	>99 : 1	98
8	*p*-NO_2-C_6H_4-	Me	3	74	>99 : 1	97
9	*o*-OMe-C_6H_4-	Me	3	85	>99 : 1	96
10	*o*-Br-C_6H_4-	Me	6	90	>99 : 1	62
11	1-naphthyl	Me	3	76	>99 : 1	70
12	2-naphthyl	Me	3	76	>99 : 1	99
13	2-furyl	Me	3.5	74	>99 : 1	98
14	2-thio	Me	2	73	>99 : 1	99

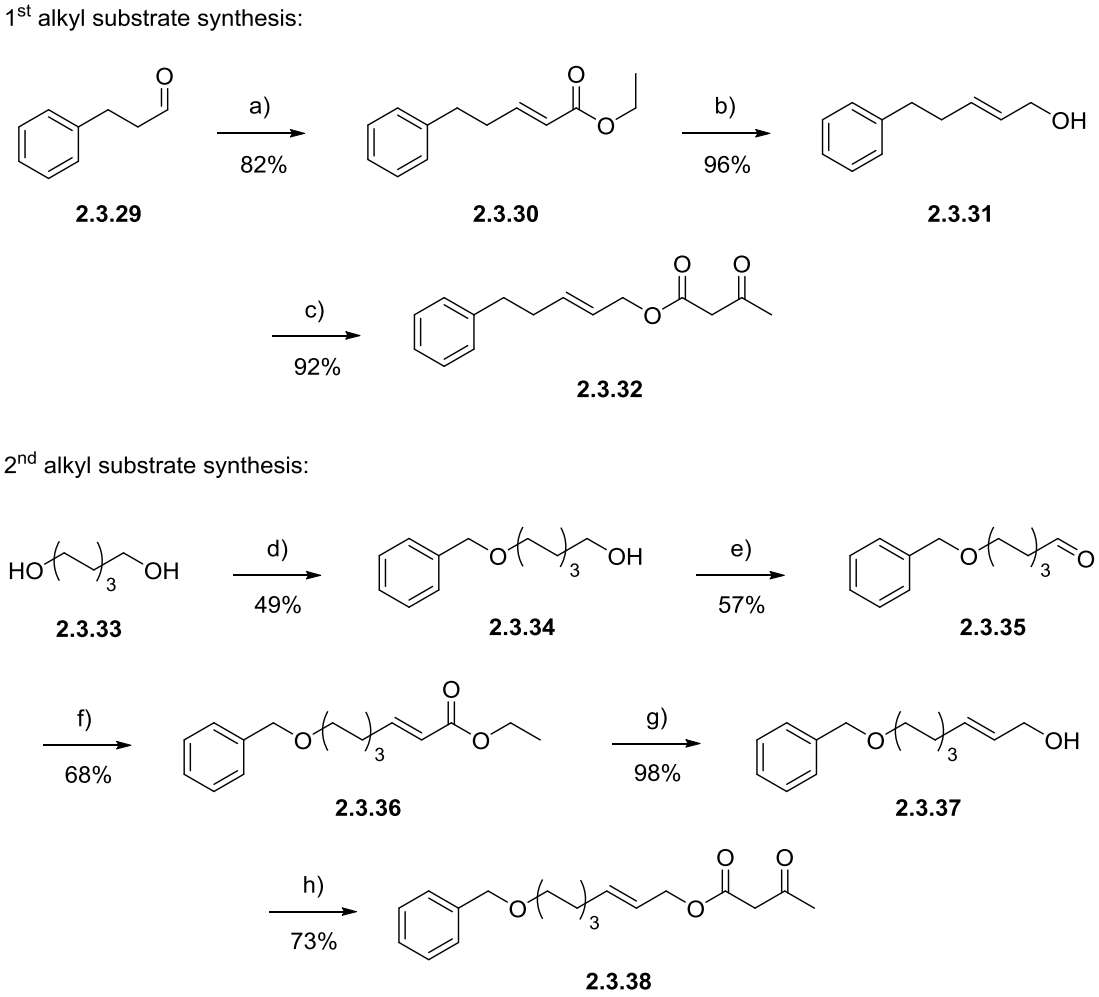
[a] Isolated yield of branched isomer **2.3.27**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Determined by chiral HPLC analysis.

Table 2.3.4: Decarboxylative iridium-catalysed asymmetric allylic alkylation of aryl allylic *β*-ketoesters

2.3.4.2 Preparation and screening of alkyl substrates

Four different alkyl substrates were prepared for screening, two of which are shown in **Scheme 2.3.7**. Alkyl substrate **2.3.32** was prepared from the corresponding aldehyde **2.3.29** *via* Wittig reaction,[77] DIBAL-H reduction[77] and esterification[69] (same as the synthetic route used for the preparation of aryl substrates in **Scheme 2.3.6**) in overall excellent yields. The second alkyl substrate **2.3.38** consists of a six-carbon chain with a benzyl ether group and it was prepared

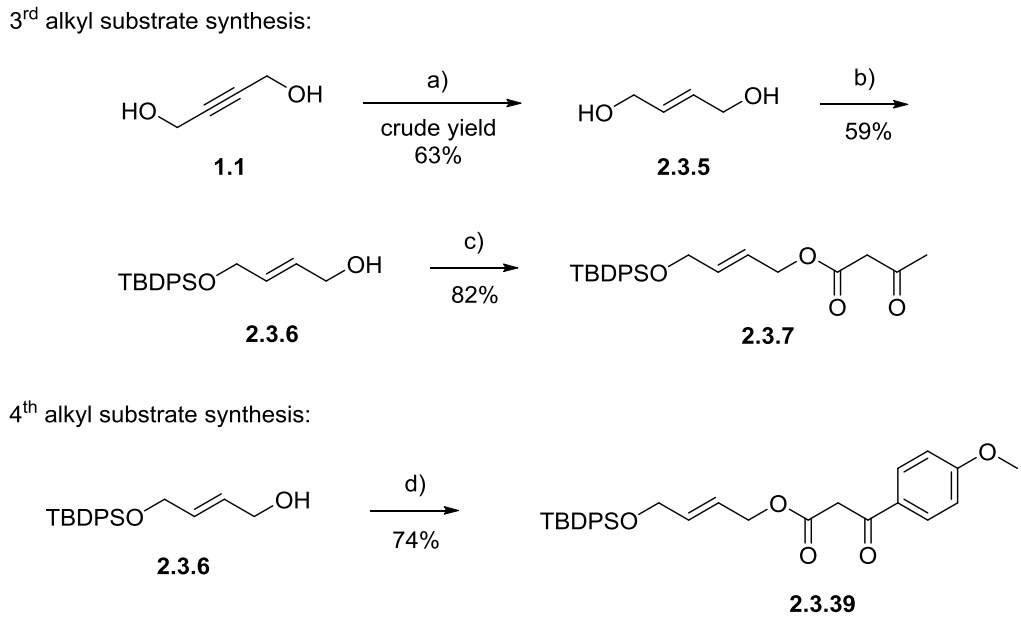
from heptane-1,7-diol **2.3.33** in five steps (**Scheme 2.3.7**). Diol **2.3.33** firstly underwent mono-benzylation to form alcohol **2.3.34** which was oxidised to aldehyde **2.3.35** in moderate yield.[83] Aldehyde **2.3.35** was then converted into alkyl substrate **2.3.38** *via* the standard route, i.e. Wittig reaction, DIBAL-H reduction and esterification.



Reagents and conditions: a) (Carbethoxymethylene)triphenylphosphorane (1.1 eq.), THF, RT, 16 h; b) DIBAL-H (2.2 eq.), DCM, 0 °C to RT, 1 h; c) ethyl acetoacetate (1 eq.), DMAP (1 eq.), molecular sieves (4 Å), toluene, 120 °C, 16 h; d) NaH (1 eq.), BnBr (1 eq.), THF/DMF, RT, 16 h; e) PCC (2.5 eq.), DCM, RT, 2 h; f) (carbethoxymethylene)triphenylphosphorane (1.1 eq.), THF, RT, 16 h; g) DIBAL-H (2.2 eq.), THF, 0 °C to RT, 1 h; h) ethyl acetoacetate (1 eq.), DMAP (1 eq.), molecular sieves (4 Å), toluene, 120 °C, 16 h.

Scheme 2.3.7: Preparation of alkyl substrates 2.3.32 and 2.3.38

The synthesis of the other two alkyl substrates is shown in **Scheme 2.3.8**. Substrate **2.3.7** contains a silyl ether protecting group and was prepared from butynediol **1.1** *via* $LiAlH_4$ reduction,[70] mono-silylation[71] and esterification[69] (mentioned previously in **Scheme 2.3.3**, page 41). The other alkyl substrate, *β*-ketoester **2.3.39**, contains an aryl ketone moiety and was also synthesised from alcohol **2.3.6** *via* esterification (**Scheme 2.3.8**).[69]

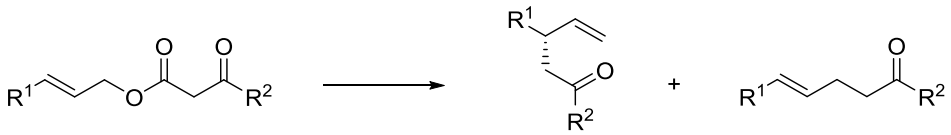


Reagents and conditions: a) $LiAlH_4$ (1.2 eq.), THF, 0 °C to RT, 16 h; b) NaH (1 eq.), TBDPS-Cl (1 eq.), THF, RT, 16 h; c) ethyl acetoacetate (1 eq.), DMAP (1 eq.), molecular sieves (4Å), toluene, 120 °C, 16 h; d) ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (1 eq.), DMAP (1 eq.), molecular sieves (4 Å), toluene, 120 °C, 16 h.

Scheme 2.3.8: Preparation of alkyl substrates 2.3.7 and 2.3.30

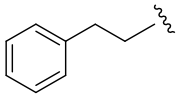
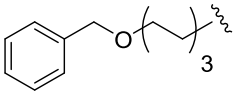
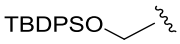
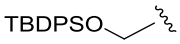
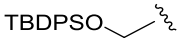
The scope of alkyl allylic substrates was also explored using the optimal reaction condition (**Table 2.3.5**). In general, linear isomers **2.3.28** were formed in reactions involving alkyl substrates and the branched to linear ratios were substrates-dependent. A variety of alkyl substrates was studied, including one with a short carbon chain (entry 1), one with a long carbon chain (entry 2) and ones with

silyl ether protecting groups (entries 3 and 4). It was exciting to see that they all displayed good reactivities to form the branched products **2.3.27** in good yields with good regioselectivities and excellent enantioselectivities. This is an improvement on previous studies (see **Section 2.1.4**) in which alkyl substrates generally behave much poorer than aryl substrates.



2.1.83 **2.3.27** **2.3.28**

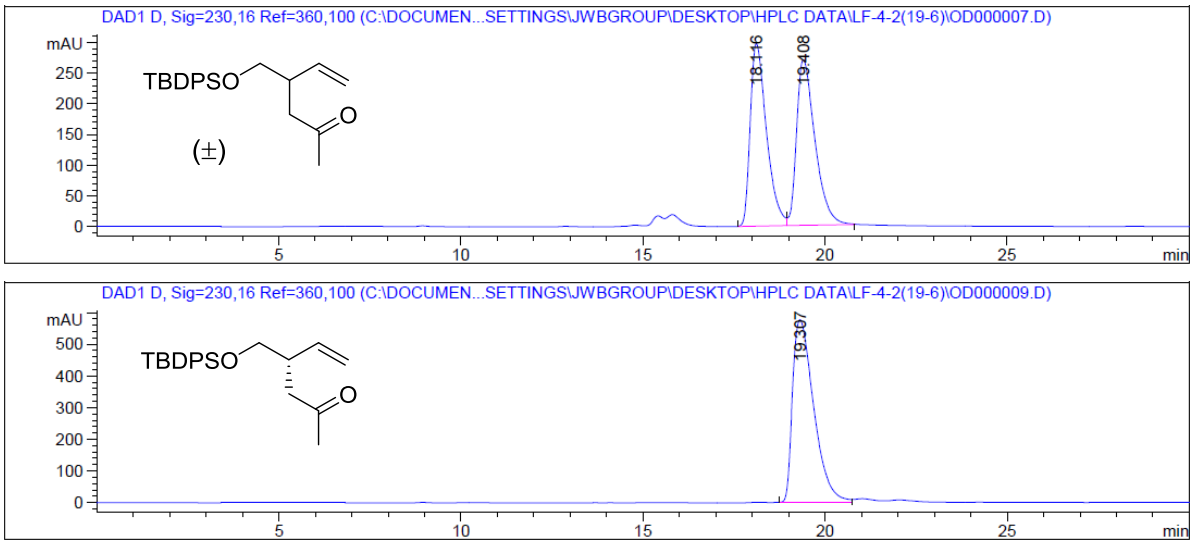
Reagents and conditions: $[Ir(COD)Cl]_2$ (4 mol%), ligand **L2** (8 mol%), TBD (16 mol%), THF.

Entry	R^1	R^2	Time (h)	T (°C)	Yield (%)[a]	Ratio b : l[b]	*ee* (%)[c]
1		Me	3	RT	78	10 : 1	98
2		Me	3	RT	81	15 : 1	97
3		Me	3	RT	84	10 : 1	>99
4		*p*-OMe-C_6H_4-	3	RT	84	14 : 1	>99
5[d]		Me	2	40	73	7 : 1	>99

[a] Combined yield of branched isomer **2.3.27** and liner isomer **2.3.28**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] 4.9 mmol scale, reagents: 2 mol% $[Ir(COD)Cl]_2$, 4 mol% ligand **L2**, 8 mol% TBD, THF.

Table 2.3.5: Decarboxylative iridium-catalysed asymmetric allylic alkylation of alkyl allylic *β*-ketoesters

It should be noted that in entry 5 (**Table 2.3.5**), a large scale (2.0 g) reaction was carried out using only 2 mol% of $[Ir(COD)Cl]_2$. The reaction went to completion quickly under mild conditions. Although branched to linear ratio was slightly decreased, comparable yield and enantioselectivity were obtained. This shows that the reaction is scalable. The HPLC trace diagram of the enantioenriched ketone product in entry 5 is shown in **Figure 2.3.2** which suggests a nearly perfect *ee*.



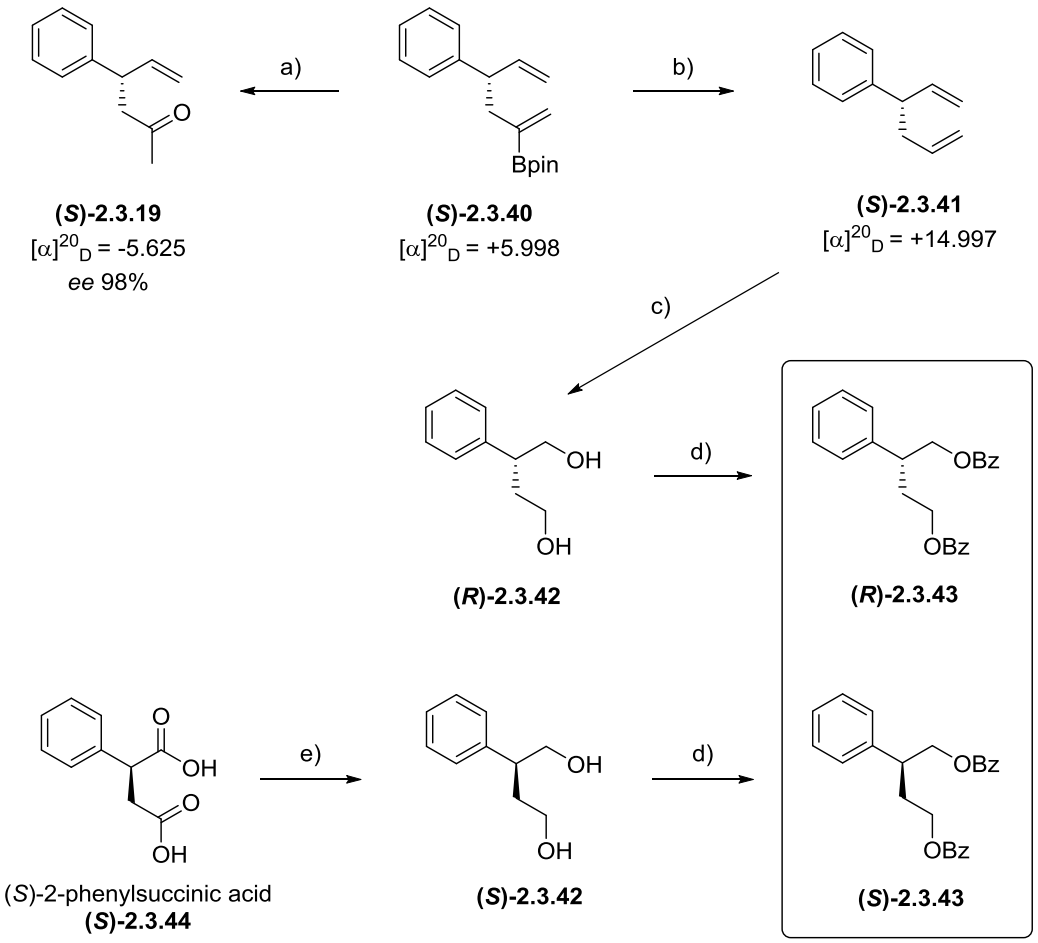
Conditions: Chiralcel OD-H column (4.6 mm x 250 mm), 0.6% 2-propanol in *n*-hexane, flow rate = 0.4 mL / min, detection wavelength = 230 nm.

Figure 2.3.2: HPLC trace of an enantioenriched ketone

2.3.4.3 Determination of absolute configurations

The absolute configuration of the aryl ketone in entry 1 of **Table 2.3.4** (page 51) was assigned to be (*S*) by comparing its optical rotation value, $[\alpha]_D$ (22 °C) = -12.3 (c = 0.80 in $CHCl_3$), with that reported by Morken *et al*., $[\alpha]_D$ (20 °C) = -5.625 (c = 1.07 in $CHCl_3$).[84] Morken *et al*. determined the absolute configuration of aryl ketone **(*S*)-2.3.19** by conducting a few transformations on its precursor, boronic ester **(*S*)-2.3.40** (**Scheme 2.3.9**). Firstly, boronic ester **(*S*)-2.3.40** was reacted with

copper(II) bromide followed by lithium halogen exchange with a protic quench to form diene **(*S*)-2.3.41**. Ozonolysis with reductive work-up was then carried out to give diol **(*R*)-2.3.42** which was reacted with benzoic anhydride to form the (*R*)-dibenzoate **(*R*)-2.3.43**.[85] Using chiral HPLC analysis, the (*R*)-dibenzoate **(*R*)-2.3.43** was compared with the authentic (*S*)-dibenzoate **(*S*)-2.3.43** which was derived from the commercially available (*S*)-2-phenylsuccinic acid **(*S*)-2.3.44** *via* $LiAlH_4$ reduction followed by benzoate protection. Therefore, the absolute configuration of boronic ester **(*S*)-2.3.40** was assigned to be (*S*) and as it could be converted to ketone **(*S*)-2.3.19** *via* H_2O_2 oxidation, the absolute configuration of ketone **(*S*)-2.3.19** was also assigned accordingly. Thus, the absolute configurations of products of decarboxylative iridium-catalysed AAA in this thesis are assigned by analogy.



(*S*)-2.3.19
$[\alpha]^{20}_D$ = -5.625
ee 98%

(*S*)-2.3.40
$[\alpha]^{20}_D$ = +5.998

(*S*)-2.3.41
$[\alpha]^{20}_D$ = +14.997

(*R*)-2.3.42

(*R*)-2.3.43

(*S*)-2.3.42

(*S*)-2.3.43

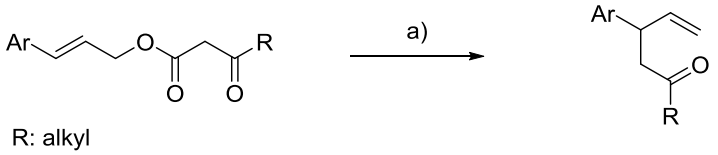
Reagents and conditions: a) H_2O_2, NaOH, THF, RT, 4 h; b) i) $CuBr_2$, MeOH/H_2O, 90 °C, 12 h, ii) *n*BuLi then H_2O; c) i) O_3, DCM/MeOH, -78 °C, ii) $NaBH_4$; d) Bz_2O, DMAP, Et_3N, DCM; e) $LiAlH_4$, THF, reflux.

Scheme 2.3.9: Method of determination of the absolute configuration of aryl ketone (*S*)-2.3.19 developed by Morken *et al.*[84,85]

2.3.4.4 Synthesis of racemic references for the measurement of enantiomeric excesses

The enantiomeric excesses of the enantioenriched aryl and alkyl ketones mentioned in previous sections were measured against the corresponding racemic references by chiral HPLC analysis. (More details about the synthetic procedures and characterisation data of the racemic references can be found in the experimental section, **Section 4.3.5**.)

The aryl racemic ketones **(±)-2.3.46** were prepared from *β*-ketoesters **2.3.45** *via* a decarboxylative ruthenium-catalysed allylic alkylation reaction (**Scheme 2.3.10**).[86]

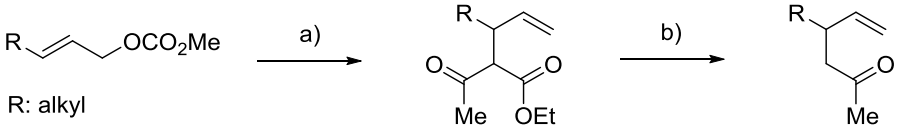


2.3.45 **(±)-2.3.46**

Reagents and conditions: a) $[Cp^*RuCl]_4$ (3 mol%), 2,2'-bipyridine (12 mol%), DCM, RT, 1.5 h.

Scheme 2.3.10: Synthesis of the aryl racemic ketones (±)-2.3.46

The alkyl racemic ketones **(±)-2.3.49** were prepared from the corresponding alkyl allylic carbonates **2.3.47** which firstly underwent iridium-catalysed allylic alkylation with ethyl acetoacetate as the nucleophile to form the racemic *β*-ketoesters **(±)-2.3.48** (**Scheme 2.3.11**).[12] *β*-Ketoesters **(±)-2.3.48** then underwent Krapcho decarboxylation to form the corresponding alkyl racemic ketones **(±)-2.3.49**.[87,88]



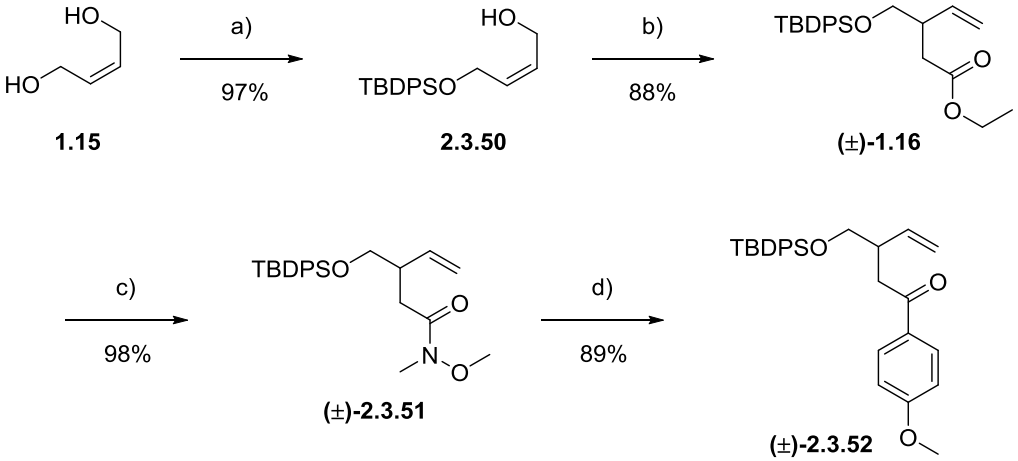
2.3.47 **(±)-2.3.48** **(±)-2.3.49**

Reagents and conditions: a) $[Ir(COD)Cl]_2$ (4 mol%), $P(OPh)_3$ (16 mol%), ethyl acetoacetate (3 eq.), NaH (3 eq.), THF, 70 °C, 16 h; b) LiCl (2 eq.), H_2O (10 eq.), DMSO, 150 °C, 16 h.

Scheme 2.3.11: Synthesis of the alkyl racemic ketones (±)-2.3.49

The racemic reference for the enantioenriched *p*-methoxyphenyl ketone **2.3.52** (**Table 2.3.5**, entry 4, page 54) was synthesised from butenediol **1.15** in four steps (**Scheme 2.3.12**). Butenediol **1.15** was firstly mono-protected[89] with TBDPS group to form allylic alcohol **2.3.50** in nearly quantitative yield, which then

underwent Johnson-Claisen rearrangement[67] to form the racemic ester **(±)-1.16** in very good yield. Ester **(±)-1.16** was then converted into Weinreb amide **(±)-2.3.51** in quantitative yield[90] which was subsequently converted into the racemic *p*-methoxyphenyl ketone **(±)-2.3.52** in 89% yield.[91]



Reagents and conditions: a) NaH (1.05 eq.), TBDPS-Cl (1 eq.), THF, RT, 2 h; b) triethyl orthoacetate (7 eq.), propionic acid (0.06 eq.), 138 °C, 22 h; c) *N*,*O*-dimethylhydroxylamine hydrochloride (1.6 eq.), *i*PrMgCl (2 M in THF, 3.5 eq.), THF, -15 °C, 1.5 h; d) *p*-methoxyphenylmagnesium bromide (1.5 eq.), THF, RT, 22 h.

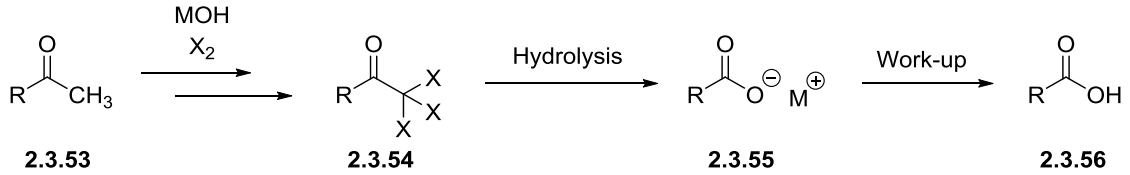
Scheme 2.3.12: Synthesis of the racemic *p*-methoxyphenyl ketone (±)-2.3.52

2.3.5 Conversion of ketone to carboxylic acid *via* Lieben haloform reaction

Having developed a methodology for the efficient synthesis of highly enantioenriched *γ*,*δ*-unsaturated ketones, we turned our attention to being able to convert these ketones into the corresponding carboxylic acid derivatives which would ultimately allow the synthesis of the key alcohol **1.4** (page 1).

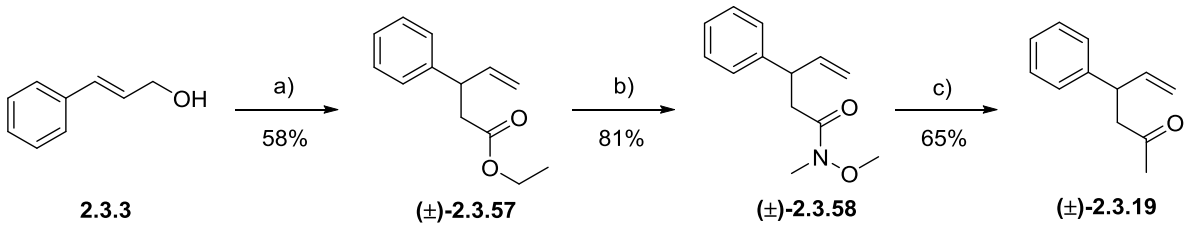
The Lieben haloform reaction was firstly attempted.[92] In a standard Lieben haloform reaction (**Scheme 2.3.13**), a ketone **2.3.53** reacts with a halogen source in the presence of base to form a trihaloketone **2.3.54** which is then rapidly hydrolysed

to a carboxylate **2.3.55**. Acid work up then affords carboxylic acid **2.3.56** which can be reduced to a primary alcohol.



Scheme 2.3.13: Standard Lieben haloform reaction[92]

Racemic branched ketone **(±)-2.3.19** was prepared for Lieben haloform reaction as it was more costly to use enantioenriched ketones as starting materials (**Scheme 2.3.14**). Ketone **(±)-2.3.19** was synthesised from cinnamyl alcohol **2.3.3** in three steps. The first step is the Johnson-Claisen rearrangement which formed ester **(±)-2.3.57**.[92,67] Ester **(±)-2.3.57** was then converted into Weinreb amide **(±)-2.3.58** which was alkylated to give ketone **(±)-2.3.19**.

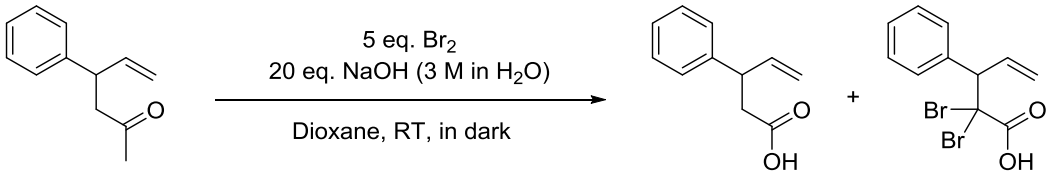


Reagents and conditions: a) Triethyl orthoacetate (5 eq.), propionic acid (0.06 eq.), 140 °C, 22 h; b) *N*,*O*-dimethylhydroxylamine hydrochloride (1.6 eq.), *i*PrMgCl (2 M in THF, 3.5 eq.), THF, -15 °C, 1 h; c) MeLi (1.6 M in Et_2O, 2 eq.), THF, -78 °C, 2.5 h.

Scheme 2.3.14: Synthesis of racemic phenyl substrate (±)-2.3.19

The Lieben haloform reaction was then carried out on ketone **(±)-2.3.19** using standard reaction conditions reported in the literature (**Scheme 2.3.15**).[93] Due to the number of intermediates en route to the formation of the desired product **(±)-2.3.59**, it was difficult to monitor the reaction progress. A poor yield, 45%, of carboxylic acid **(±)-2.3.59** was obtained by leaving the reaction overnight and the

dibromide side product **(±)-2.3.60** was isolated in 19% yield (HRMS: found 331.8971, $C_{11}H_{10}{}^{79}Br_2O_2$ requires 331.9048). The formation of the side product **(±)-2.3.60** was due to the presence of *α*-protons on both side of the carbonyl group. By shortening reaction time to 7 h, the yield of desired carboxylic acid **(±)-2.3.59** was improved to 59% and yield of side product **(±)-2.3.60** was reduced. By comparing the above results, it was initially presumed that formation of carboxylic acid **(±)-2.3.59** was fast and over-bromination occurred afterwards. Therefore, the reaction time was further shortened to 3 h, but the yield of desired product **(±)-2.3.59** was not improved and side product **(±)-2.3.60** was still formed in notable quantities. No further attempts were carried out for this reaction as there were no clear trends observed during optimisation.



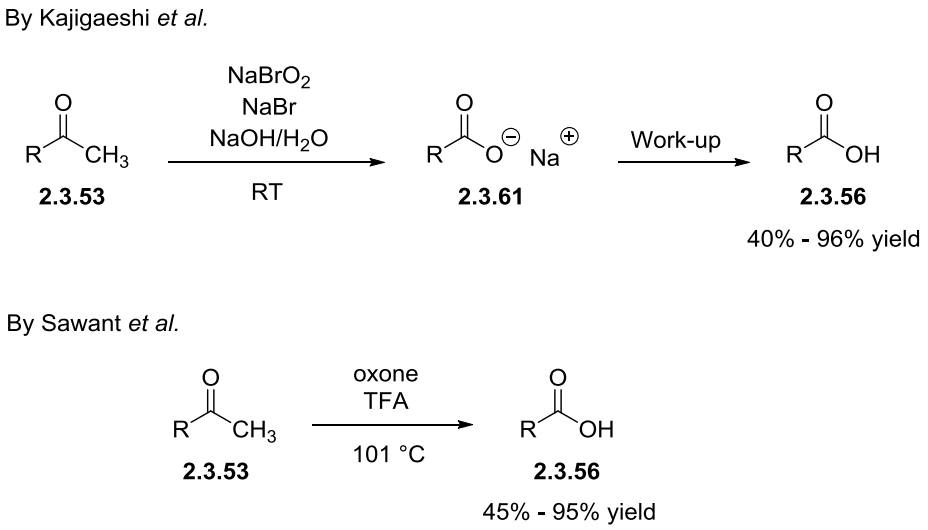
(±)-2.3.19 **(±)-2.3.59** **(±)-2.3.60**

Entry	t (h)	Yield of **(±)-2.3.59**	Yield of **(±)-2.3.60**
1	22	45%	19%
2	7	59%	10%
3	3	45%	10%

Scheme 2.3.15: Lieben haloform reactions on ketone (±)-2.3.19

Other conditions for haloform reaction are also available in literature. Two examples are shown in **Scheme 2.3.16**.[94,95] In general, the use of strong bases (e.g. NaOH) and harsh conditions in many haloform reactions limits the scope of substrates that can be involved. For instance, silyl ether protecting groups will

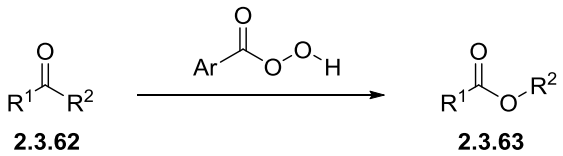
probably not be tolerated under those conditions. Therefore, an alternative method was explored and described in the next section.



Scheme 2.3.16: Examples of haloform reaction by Kajigaeshi *et al.*[94] and Sawant *et al.*[95]

2.3.6 Conversion of ketone to ester *via* Baeyer-Villiger oxidation

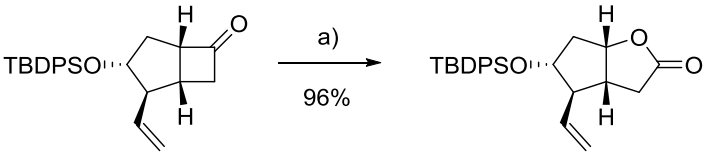
A second method for conversion of the *γ*,*δ*-unsaturated ketones into the corresponding carboxylic acid derivatives would be by the Baeyer-Villiger oxidation, which converts ketone **2.3.62** into ester **2.3.63** in the presence of peroxide source (**Scheme 2.3.17**).[92,96] We required conditions that would allow the Baeyer-Villiger oxidation reaction to occur ultimately in the presence of a terminal alkene.



Scheme 2.3.17: Standard Baeyer-Villiger oxidation reaction[92,96]

Ghosez *et al.* reported a Baeyer-Villiger oxidation reaction using *m*CPBA which converted cyclic ketone **2.3.64** into lactone **2.3.65** in excellent yield (**Scheme**

2.3.18).[97] Although the literature substrate **2.3.64** is not structurally similar to the substrate of interest in this project, it also contains a TBDP silyl ether group and a terminal alkene. Therefore, their literature conditions were followed.



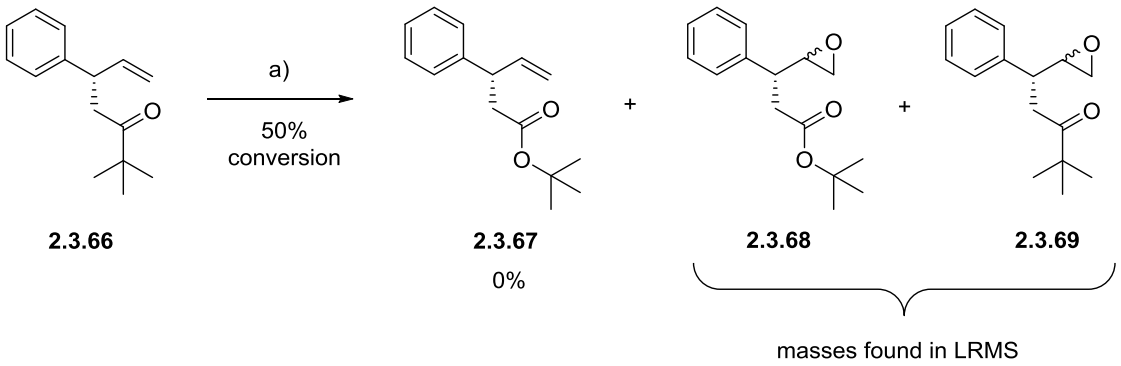
2.3.64 **2.3.65**

regioisomer ratio 3.4 : 1

Reagents and conditions: a) *m*CPBA (4 eq.), $NaHCO_3$ (4 eq.), DCM, 0 °C, 30 min.

Scheme 2.3.18: Baeyer-Villiger oxidation by Ghosez *et al*.[97]

Baeyer-Villiger oxidation was firstly attempted on ketone **2.3.66** (**Scheme 2.3.19**) as it has been previously made during substrates screening (**Table 2.3.4**, entry 4). The rearrangement step is expected to occur with the *t*butyl group migrating to form ester **2.3.67** as tertiary alkyl groups have higher migratory aptitude than primary alkyl groups.[92] However, the desired product **2.3.67** was not formed. Instead, an inseparable mixture of side products, which were believed to be epoxides **2.3.68** and **2.3.69**, were isolated after flash chromatography (FC). The masses of both epoxides **2.3.68** and **2.3.69** were observed on LRMS: *m/z* 271.1 ($[M_{\mathbf{2.3.68}}+Na]^+$, 10%), *m/z* 233.1 ($[M_{\mathbf{2.3.69}}+H]^+$, 90%) and *m/z* 255.1 ($[M_{\mathbf{2.3.69}}+Na]^+$, 95%). More evidence was found from ^1H NMR spectrum which shows disappearance of alkene proton peaks. A few sets of doublet of doublets appear around 2.42 – 2.73 ppm with *J* couplings of around 3.0 Hz and 5.0 Hz which correspond to the ^3J and ^2J couplings of epoxide protons respectively. However, full characterisation was not obtained as the epoxides decomposed during NMR acquisition.

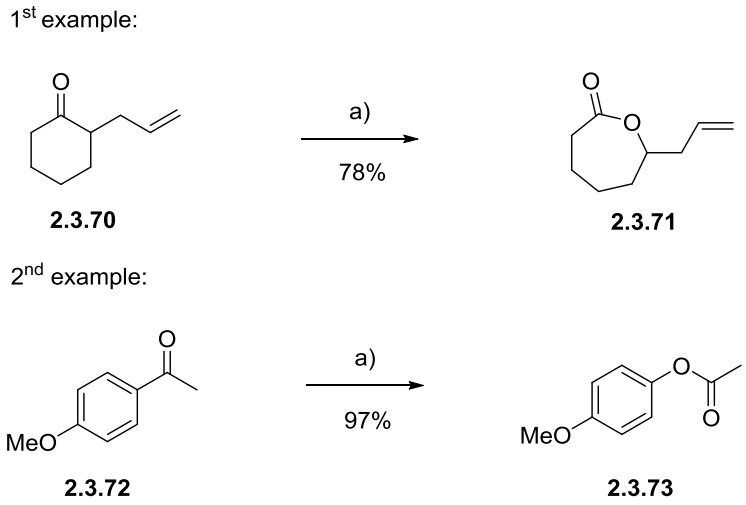


Reagents and conditions: a) *m*CPBA (4 eq.), $NaHCO_3$ (4 eq.), DCM, 0 °C, 5 h.

Scheme 2.3.19: Baeyer-Villiger oxidation using *m*CPBA

Unlike the literature substrate **2.3.64** (**Scheme 2.3.18**) which is a strained four-membered cyclic ketone, our acyclic substrate **2.3.66** lacks the driving force to undergo rapid Baeyer-Villiger oxidation before epoxidation of the terminal alkene. This probably explains the poor chemoselectivity of this reaction.

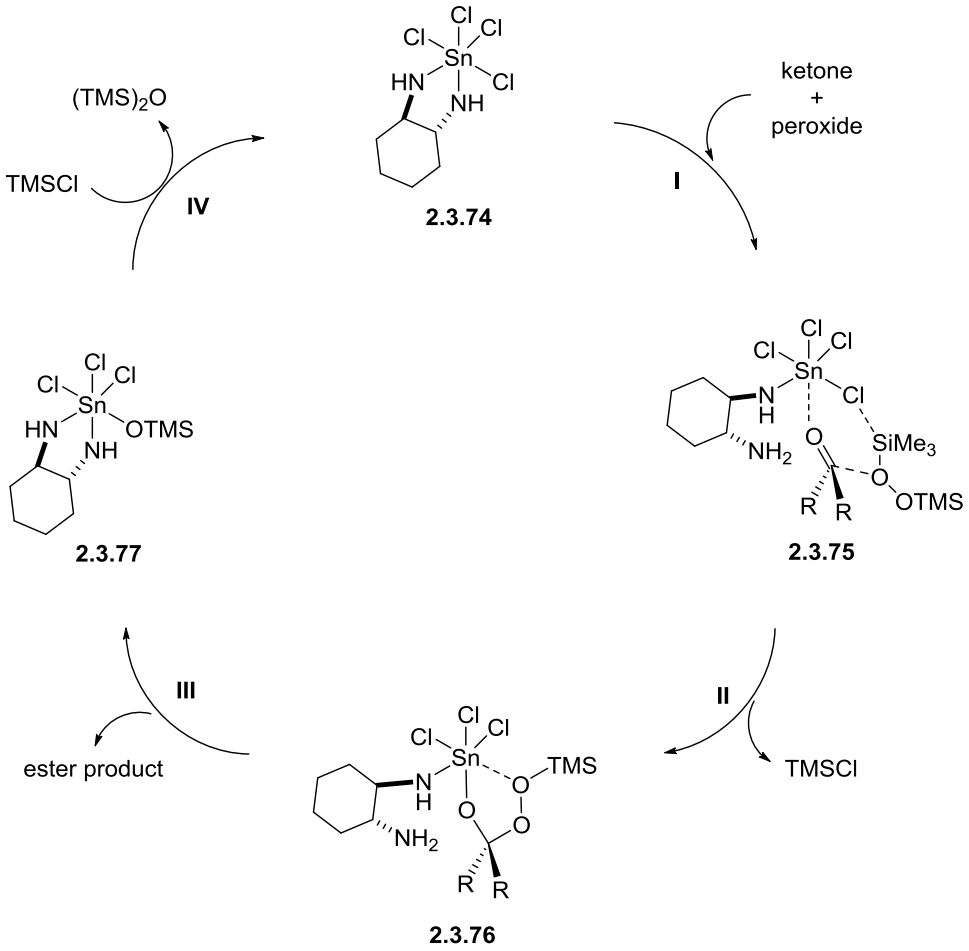
In 1997, Shibasaki *et al*. reported a selective metal-catalysed Baeyer-Villiger oxidation reaction using $SnCl_4$ as the catalyst and bis(trimethylsilyl) peroxide as the oxidant.[98] Two examples in the literature are illustrated in **Scheme 2.3.20**. Using an unstrained six-membered cyclic ketone **2.3.70**, reaction proceeded to selectively form ester **2.3.71** with the terminal alkene intact.



Reagents and conditions: a) Bis(trimethylsilyl) peroxide (2 eq.), $SnCl_4$ (0.25 eq.), *trans*-1,2-(diamino)cyclohexane (0.25 eq.), K_2CO_3 (1.5 eq.), MS (4 Å), DCM, RT, 3 – 24 h.

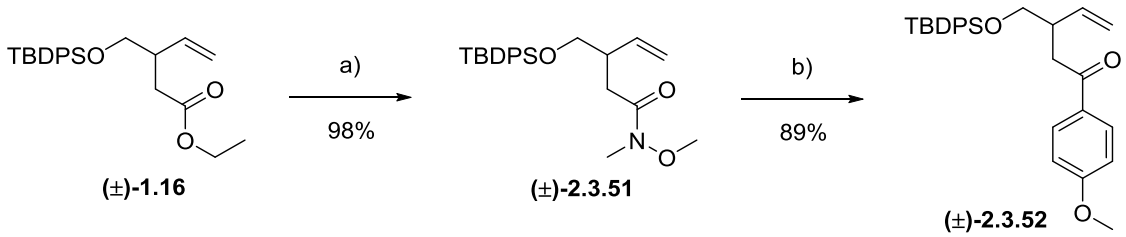
Scheme 2.3.20: Selective metal-catalysed Baeyer-Villiger oxidation by Shibasaki *et al*.[98]

Shibasaki *et al*. proposed a mechanism to explain the chemoselectivity of this reaction (**Scheme 2.3.21**).[98] A diamino ligand (e.g. *trans*-1,2-(diamino)cyclohexane) coordinates to $SnCl_4$ to form complex **2.3.74**. In step **I**, one of the two amino groups dissociates from tin to create a vacant site for the coordination of a ketone substrate. Coordination to a Lewis acid makes the carbonyl carbon more electrophilic and susceptible to be attacked by the peroxide. The high affinity of silicon for electronegative atoms (e.g. chloride) also brings the peroxide closer to the carbonyl group as shown in complex **2.3.75**.[99] The following steps involve nucleophilic attack of peroxide (step **II**), rearrangement to form the ester product (step **III**) and regeneration of catalyst **2.3.74** (step **IV**).



Scheme 2.3.21: Proposed mechanism for metal-catalysed Baeyer-Villiger oxidation by Shibasaki *et al*.[98]

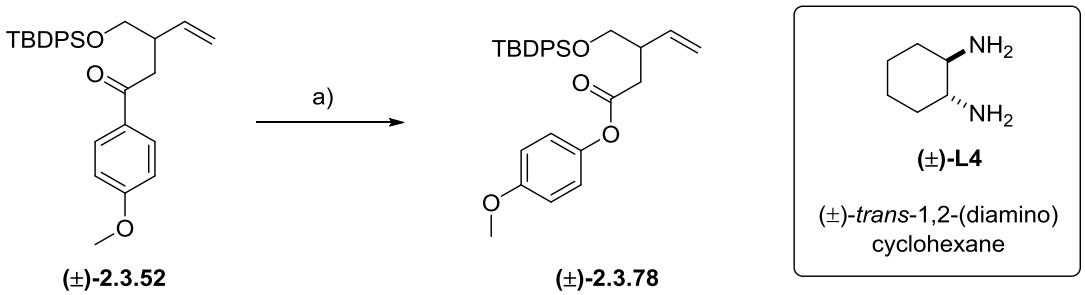
In **Scheme 2.3.20**, the second example used a *p*-methoxyphenyl ketone as the substrate and an excellent yield of product was obtained. As previously described in **Section 2.3.4**, enantioenriched *p*-methoxyphenyl ketone derivative could be easily prepared *via* iridium-catalysed AAA in good yield with excellent selectivities (**Table 2.3.5**, entry 4). Therefore, *p*-methoxyphenyl ketone **(±)-2.3.52** is a promising substrate to start with in tin-catalysed Baeyer-Villiger oxidation (**Scheme 2.3.22**). Racemic ketone **(±)-2.3.52** was synthesised from ester **(±)-1.16** in two steps. Ester **(±)-1.16** was firstly converted into Weinreb amide **(±)-2.3.51** in quantitative yield[90] which was then converted into ketone **(±)-2.3.52** in 89% yield.[91]



Reagents and conditions: a) *N*,*O*-Dimethylhydroxylamine hydrochloride (1.6 eq.), *i*PrMgCl (2 M in THF, 3.5 eq.), THF, -15 °C, 1.5 h; b) *p*-methoxyphenylmagnesium bromide (1.5 eq.), THF, RT, 22 h.

Scheme 2.3.22: Synthesis of racemic *p*-methoxyphenyl ketone

The literature reaction conditions were followed in the first attempt (**Table 2.3.6**, entry 1). Using 0.25 eq. of $SnCl_4$, the reaction did not proceed at RT after 23 h and 93% of ketone starting material **(±)-2.3.52** was recovered. After increasing the catalyst loading to 1 eq. (entry 2), new peaks appeared in ^{1}H NMR spectrum after 23 h and the mass of ester product **(±)-2.3.78** was observed in LRMS. However, there was still starting material present and due to the difficulty in separating starting material and product by FC, the reaction needed to be driven to completion.



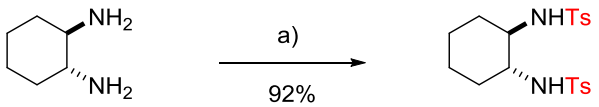
Reagents and conditions: a) Bis(trimethylsilyl) peroxide (2 eq.), $SnCl_4$, **(±)-L4**, K_2CO_3 (1.5 eq.), MS (4 Å), DCM, RT, 23 h.

Entry	$SnCl_4$ (eq.)[a]	(±)-L4 (eq.)	Conversion (%)
1	0.25	0.25	0[b]
2	1	1	≈ 25[c]

[a] 1 M in DCM. [b] 93% of starting material was recovered. [c] Estimated from ^{1}H NMR, starting material to product ratio is ≈ 3 : 1.

Table 2.3.6: Tin-catalysed Baeyer-Villiger oxidation on *p*-methoxyphenyl ketone (±)-2.3.52

It was envisaged that increasing the Lewis acidity of the catalyst would probably expedite the nucleophilic attack of peroxide (**Scheme 2.3.21**, step **II**) as well as the following rearrangement step (step **III**), thereby reducing the reaction time. A few literature articles reported the use of ligand **(±)-L5** (**Scheme 2.3.23**) in the catalyst system and obtained good results in tin-catalysed Baeyer-Villiger oxidation reactions.[100,101] It was believed that the Lewis acidity of the catalyst complex could be increased by introducing electron-withdrawing tosylates onto the amino groups.[98] Ligand **(±)-L5** was synthesised from ligand **(±)-L4** in excellent yield.[102]

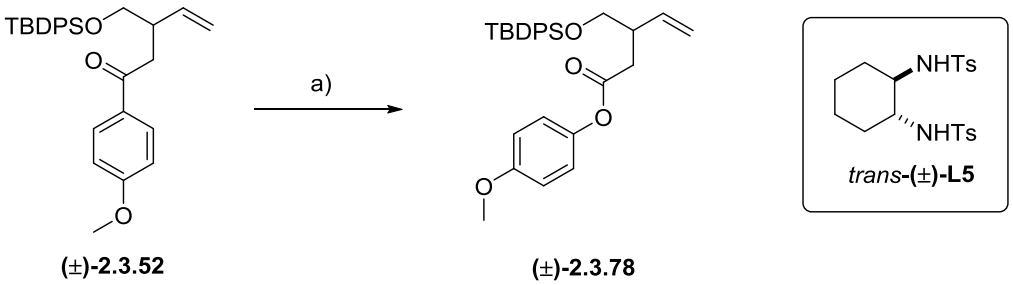


(±)-L4 **(±)-L5**

Reagents and conditions: a) TsCl (2.1 eq.), Et_3N (2.1 eq.), DCM, RT, 22 h.

Scheme 2.3.23: Synthesis of ligand *trans*-(±)-L5

Utilising ligand **(±)-L5** in our reaction system gave promising results (**Table 2.3.7**). In the presence of 1 eq. of $SnCl_4$ and 2 eq. of peroxide (entry 1), the reaction went to completion rapidly at RT to give ester **(±)-2.3.78** in 41% yield. The rest of the mass isolated from column was a messy mixture of unidentifiable compounds, but ^{1}H NMR spectrum of the crude reaction mixture showed absence of alkene proton peaks. Thus, in the next attempt (entry 2), only 1 eq. of peroxide was used in order to prevent over-reaction of ester **(±)-2.3.78** with excess peroxides. It was found that the reaction was still rapid even when conducted at 0 °C. A slightly better yield of 53% was obtained in this case. In entries 1 and 2, the reactions were carried out following the literature procedure exactly, in which ketone **(±)-2.3.52** was added to a mixture of catalyst and peroxide.[98] The rapid rate of reaction indicates that it is probably better to add the mixture of catalyst and peroxide to ketone **(±)-2.3.52** instead (entry 3). As expected, the yield was further improved to 68% (calculated by recovering starting material). Incomplete conversion in entry 3 was probably due to some loss of peroxide during transfer. Therefore, in entry 4, 1.1 eq. of peroxide was added to drive reaction to completion and a good yield of 75% was achieved. Attempts were then carried out to reduce the catalyst loadings (entries 5 – 6). It was surprising to find out that reducing the catalyst loading to 0.5 eq. did not prolong the reaction time and similar yield was achieved (entry 5). However, on reducing the catalyst loading to 0.25 eq. (entry 6), the reaction time was prolonged to 4 h and a much lower yield of 52% was obtained.



(±)-2.3.52 **(±)-2.3.78**

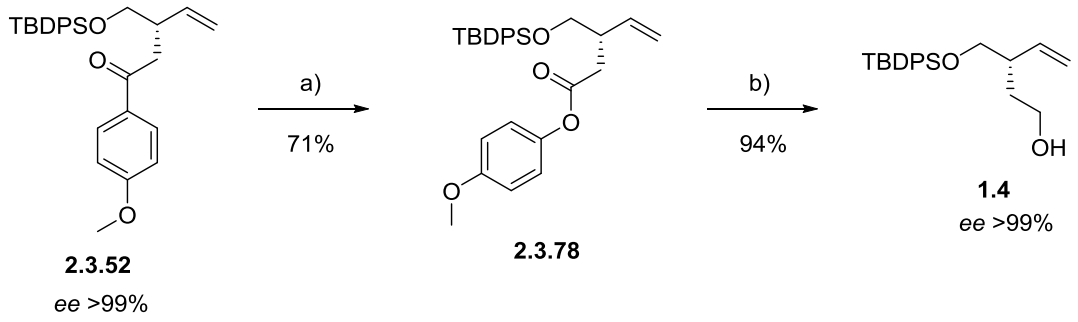
Reagents and conditions: a) Bis(trimethylsilyl) peroxide, $SnCl_4$, **(±)-L5**, K_2CO_3 (1.5 eq.), MS (4 Å), DCM

Entry	$SnCl_4$ (eq.)[a]	(±)-L5 (eq.)	Peroxide (eq.)	Time (h)	T (°C)	Conversion (%)	Yield (%)[b]
1[c]	1	1	2	1	RT	100	41
2[c]	1	1	1	1.5	0	100	53
3[d]	1	1	1	1	0	86	59 (68)[e]
4[d]	1	1	1.1	1	0	100	75
5[d]	0.5	0.5	1.1	1	0	100	72
6[d]	0.25	0.25	1.1	4	0	100	52

[a] 1 M in DCM. [b] Isolated yield of ester product **(±)-2.3.78**. [c] Ketone **(±)-2.3.52** was added to a mixture of catalyst and peroxide. [d] The mixture of catalyst and peroxide was added to a solution of ketone **(±)-2.3.52**. [e] Yield in parenthesis was calculated by recovering starting material.

Table 2.3.7: Tin-catalysed Baeyer-Villiger oxidation on *p*-methoxyphenyl ketone (±)-2.3.52 using ligand (±)-L5

The enantioenriched ketone **2.3.52** could be obtained by iridium-catalysed AAA in good yield with excellent *ee* (**Table 2.3.5**, entry 4). It underwent tin-catalysed Baeyer-Villiger oxidation to form ester **2.3.78** in good yield (**Scheme 2.3.24**). Ester **2.3.78** could then be reduced to form enantioenriched alcohol **1.4** in excellent yield with *ee* unaffected.[88]



2.3.52
ee >99%

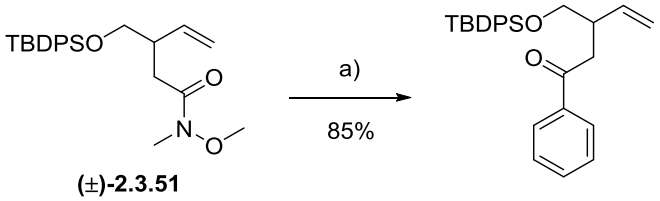
2.3.78

1.4
ee >99%

Reagents and conditions: a) Bis(trimethylsilyl) peroxide (1.1 eq.), $SnCl_4$ (0.5 eq.), **(±)-L5** (0.5 eq.), K_2CO_3 (1.5 eq.), MS (4 Å), DCM, 0 °C, 1 h; b) DIBAL-H (2.3 eq.), THF, 0 °C, 1 h.

Scheme 2.3.24: Synthesis of enantioenriched alcohol 1.4 from enantioenriched ketone 2.3.52 *via* formation of ester 2.3.78

In the meantime, another substrate, phenyl ketone **(±)-2.3.79**, was also prepared and trialled in the tin-catalysed Baeyer-Villiger oxidation. It was synthesised from Weinreb amide **(±)-2.3.51** in very good yield (**Scheme 2.3.25**).[91]



(±)-2.3.51

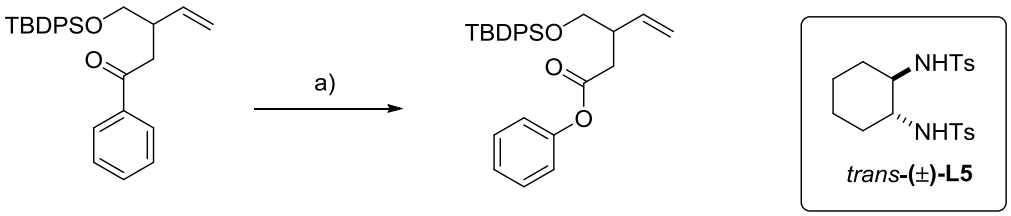
(±)-2.3.79

Reagents and conditions: a) Phenylmagnesium bromide (1.5 eq.), THF, RT, 22 h.

Scheme 2.3.25: Synthesis of phenyl ketone (±)-2.3.79

Unfortunately, subjecting ketone **(±)-2.3.79** to tin-catalysed Baeyer-Villiger oxidation conditions did not yield the desired ester **(±)-2.3.80** (**Table 2.3.8**). In both entries 1 and 2, all ketone starting materials **(±)-2.3.79** were consumed within 4 h, but no product **(±)-2.3.80** masses were seen in LRMS. There was only a mixture of unidentifiable compounds isolated after flash column chromatography which showed messy ^{1}H NMR spectra with no or very small alkene proton peaks. This result probably suggests a poor chemoselectivity and the failure of this reaction is

likely due to the absence of an electron-donating group (e.g. *p*-OMe) on the benzene ring. Without an electron-donating group, the benzene ring is less able to stabilise the electron-deficient oxygen during the migration.[92] As the rearrangement step is normally the rate-determining step in Baeyer-Villiger oxidation reactions,[98] this decrease in reactivity may lead to side reactions. This result is also in agreement with observations made by Lawler *et al*. who reported that the use of phenyl ketone substrates gave around 20% lower yields in comparison to *p*-methoxyphenyl ketone substrates.[100]



(±)-2.3.79 **(±)-2.3.80** ***trans*-(±)-L5**

Reagents and conditions: a) Bis(trimethylsilyl) peroxide (2 eq.), $SnCl_4$, **(±)-L5**, K_2CO_3 (1.5 eq.), MS (4 Å), DCM, RT.

Entry	$SnCl_4$ (eq.)[a]	(±)-L5 (eq.)	Time (h)	Yield (%)[b]
1	0.25	0.25	4	0[c]
2	1	1	2	0[c]

[a] 1 M in DCM. b [b] Isolated yield of ester product **(±)-2.3.80**. [c] Only a mixture of unidentifiable compounds was isolated.

Table 2.3.8: Tin-catalysed Baeyer-Villiger oxidation on phenyl ketone (±)-2.3.79

2.3.7 Summary

In summary, an optimal set of reaction conditions was found for decarboxylative iridium-catalysed AAA to prepare highly enantioenriched ketones from a wide scope of *β*-ketoester substrates. Good yields and excellent selectivities were achieved for both aryl and alkyl substrates. The reaction was also found to work on gram scale. A tin-catalysed Baeyer-Villiger oxidation reaction was then

optimised and conducted to smoothly convert an enantioenriched *p*-methoxyphenyl ketone substrate into an ester. Subsequent DIBAL-H reduction afforded a highly enantioenriched primary alcohol in excellent yield.

2.4 Synthesis of enantioenriched esters or amides

This section describes application of the established optimal reaction conditions on substrates that form enantioenriched esters and amides directly. A wide range of substrates with different carbonyl leaving groups was investigated and a possible mechanism for decarboxylative iridium-catalysed AAA proposed.

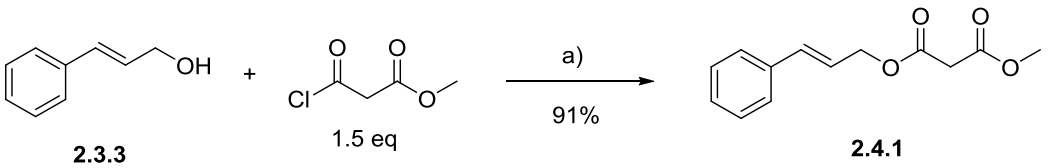
2.4.1 Motivation

Enantioenriched ester or amide compounds are in general more synthetically useful than ketone compounds as the former can be easily converted into enantioenriched aldehydes or alcohols which are useful precursors for various transformations. Moreover, if esters can be directly prepared *via* decarboxylative iridium-catalysed AAA, synthesis of primary alcohols can be shortened by one step as conversion of ketones to esters or malonates to esters is no longer required.

2.4.2 Optimisation of reaction conditions

Optimisation of conditions was firstly carried out on cinnamyl malonate **2.4.1**. It is a suitable substrate to start investigations with because aryl substrates usually lead to much better yields, higher branched to linear ratios and fewer side products than alkyl substrates in metal-catalysed allylic substitutions. Therefore, results can be more easily analysed and trends more clearly observed by using aryl substrates.

Cinnamyl malonate **2.4.1** was synthesised from cinnamyl alcohol **2.3.3** in excellent yield (**Scheme 2.4.1**).[103]



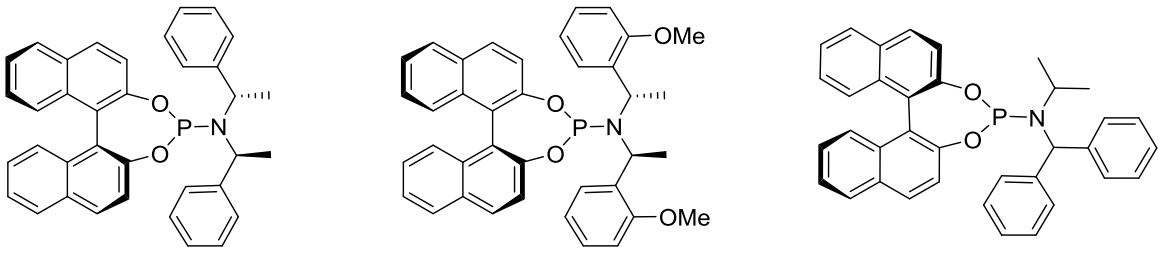
2.3.3 **2.4.1**

Reagents and conditions: a) Pyridine (1.5 eq.), DCM, RT, 2 h.

Scheme 2.4.1: Synthesis of cinnamyl malonate 2.4.1

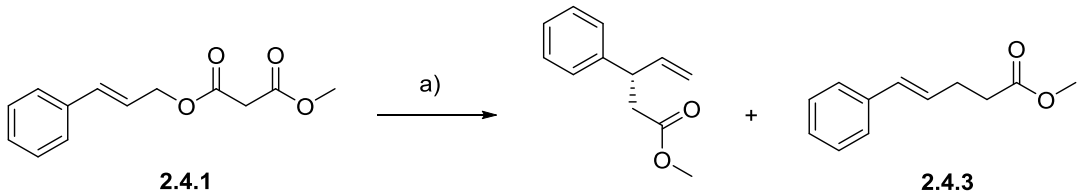
The first set of conditions we attempted was the optimal conditions developed for the allylic *β*-ketoester substrates in **Section 2.3.3** (page 45, **Table 2.3.1**, entry 2). Unfortunately, the reaction did not yield the desired ester product **2.4.2** under this condition even after 22 h (**Table 2.4.1**, entry 1). Around 46% of the malonate starting material **2.4.1** was recovered and the rest was a mixture of unidentifiable compounds. This poor result is probably due to a less favourable decarboxylation process of a malonic acid half-ester in comparison to a *β*-ketoacid as the methoxy group can donate electron density into the system. Therefore, the reaction was repeated at a higher temperature (entry 2), but there was still no formation of product. After increasing the catalyst (dimer) loading to 8 mol% and running the reaction at 60 °C overnight, the reaction went to completion and the product was isolated in 45% yield (entry 3). Similar to the reactions involving the aryl *β*-ketoester substrates **2.3.4**, reactions involving the aryl malonate substrates **2.4.1** did not form any linear isomers **2.4.3** either. After further increasing the catalyst (dimer) loadings to 12 mol% (entry 4) and 16 mol% (entry 5), the yields were improved to around 60% with excellent enantioselectivities but long reaction times were still required. We postulated whether the presence of excess base (2 eq.

of base with respect to iridium was used) at high temperature over prolonged reaction time could cause the formation of side products, thereby lowering the yield. Therefore, only 1.5 eq. of base (with respect to iridium) was used in entry 6. Unfortunately, the reaction was not completed even after 45 h at 60 °C and the ^{1}H NMR spectrum of the crude showed increased number of unidentifiable side products over time. A different base, DBU, was also attempted which afforded similar yield and *ee* (entry 7). Two other phosphoramidite ligands, **L1** and **L6**, were tried (entries 8 – 9) but they both led to poorer results. The conditions in entry 4 gave the best yield and selectivity hitherto, but further optimisation was essential as the catalyst loading required (12 mol% iridium dimer) was too high for this reaction to be useful on large scale.



L1 (*S*,*S*,*S*) **L2** (*S*,*S*,*S*) **L6** (*R*)

Figure 2.4.1: Phosphoramidite ligands used in optimisation



2.4.1 **2.4.2** **2.4.3**

Reagents and conditions: a) $[Ir(COD)Cl]_2$, phosphoramidite ligand, base, THF.

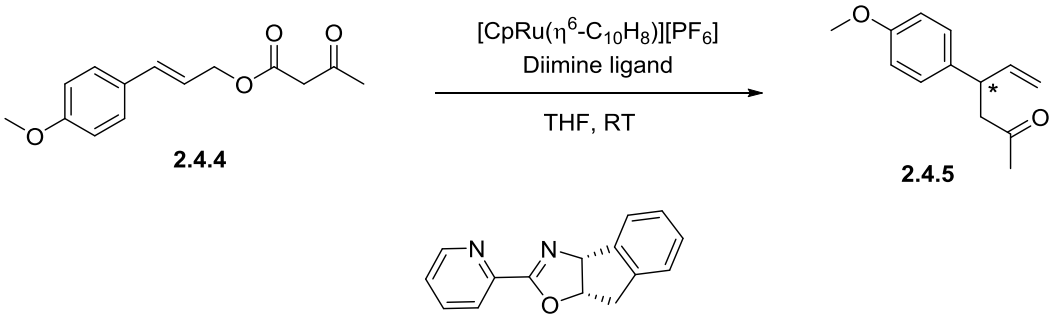
Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]	*ee* (%)[c]
1	4	**L2** (8)	TBD (16)	RT	22	0[d]	-	-
2	4	**L2** (8)	TBD (16)	50	22	0[e]	-	-
3	8	**L2** (16)	TBD (32)	60	22	45	>99 : 1	-
4	12	**L2** (24)	TBD (48)	60	22	61	>99 : 1	98
5	16	**L2** (32)	TBD (64)	60	22	55	>99 : 1	97
6	12	**L2** (24)	TBD (36)	60	45	-[f]	-	-
7	12	**L2** (24)	DBU (48)	60	22	61	>99 : 1	96
8	12	**L1** (24)	TBD (48)	60	22	25[g]	>99 : 1	90
9	12	**L6** (24)[h]	TBD (48)	60	22	0[i]	-	-

[a] Isolated yield of branched isomer **2.4.2**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] 46% of starting material was recovered. [e] Mainly starting material signals were observed in the ^{1}H NMR spectrum of the crude; crude was not purified. [f] Starting material to product ratio was 1 to 4; crude was not purified. [g] Complete conversion; the rest of the mass could not be flushed out of column. [h] Ligand **L6** was synthesised in the Fletcher group. [i] 74% of starting material was recovered.

Table 2.4.1: Optimisation of reaction conditions for cinnamyl malonate 2.4.1 using $[Ir(COD)Cl]_2$

In 2009, Lacour *et al*. reported a Lewis acid (LA)/ruthenium-catalysed decarboxylative allylic alkylation using allylic *β*-ketoesters **2.4.4** (**Scheme 2.4.2**).[104]

Lacour *et al*. proposed that the formation of the allylruthenium complex with the separation of the *β*-ketoester moiety was likely to be the rate-determining step. Therefore, any factors that render the *β*-ketoester moiety a better leaving group will be beneficial to the reaction. As they expected, when using sub-stoichiometric amount of Lewis acid (e.g. $Mg(OTf)_2$) which was believed to coordinate to the 1,3-dicarbonyl moiety thereby aiding the separation and decarboxylation process, the conversion was greatly improved to nearly 100%.

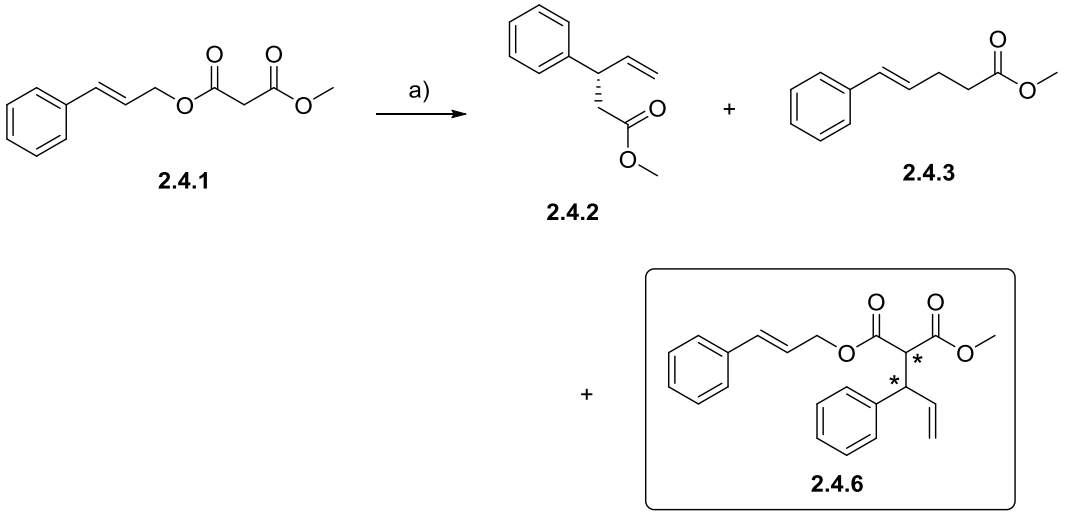


LA	Time	Conversion	*ee*
-	48 h	<3%	-
$Mg(OTf)_2$	24 h	>97%	84%
$Zn(OTf)_2$	54 h	80%	80%
$Cu(OTf)_2$	54 h	95%	84%

Scheme 2.4.2: Ruthenium-catalysed decarboxylative allylic alkylation by Lacour *et al*.[104]

As our substrates are similar to the literature substrate **2.4.4** above, we tried using Lewis acids in our reactions as well. Using the optimal set of conditions developed previously (page 76, **Table 2.4.1**, entry 4), three different Lewis acids were screened (**Table 2.4.2**). Unfortunately, there was neither conversion at RT nor at 50 °C overnight. An interesting side product **2.4.6** was isolated from reactions using $Zn(OTf)_2$ and $Mg(OTf)_2$ (entries 3 – 4). This side product **2.4.6** may be an

intermediate in the reaction and its structure sheds some light on the mechanism which will be discussed in more details in **Section 2.4.4**.



Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), Lewis acid, THF.

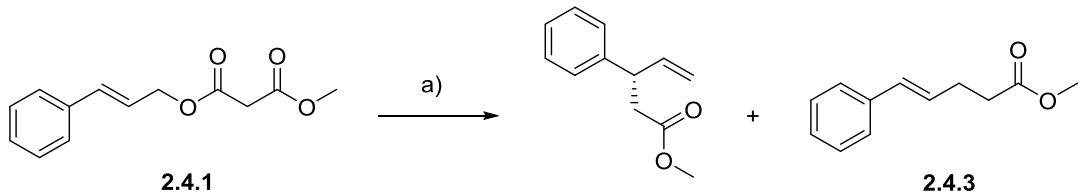
Entry	LA (mol%)	T (°C)	t (h)	Yield of 2.4.2 (%)[a]	Yield of 2.4.6 (%)[b]
1	$Cu(OTf)_2$ (30)	RT	48	0[c]	0
2	$Cu(OTf)_2$ (30)	50	22	0[c]	0
3	$Zn(OTf)_2$ (30)	50	22	0[d]	44
4	$Mg(OTf)_2$ (30)	50	22	0[e]	17

[a] Isolated yield of branched isomer **2.4.2**. [b] Isolated yield of side product **2.4.6**. [c] ^{1}H NMR spectrum of the crude was clean with only starting material peaks; crude was not purified. [d] 26% of starting material was recovered. [e] 28% of starting material was recovered.

Table 2.4.2: Optimisation of reaction conditions for cinnamyl malonate 2.4.1 using $[Ir(COD)Cl]_2$ and Lewis acids

Optimisation was carried out using a different iridium pre-catalyst, $[Ir(dbcot)Cl]_2$, the synthesis of which was described previously in **Scheme 2.3.4** (page 42). The active catalyst generated from $[Ir(dbcot)Cl]_2$ was reported to be able to survive in polar aprotic solvents[105] under elevated temperatures for long reaction times.[52] On the other hand, reactions catalysed by $[Ir(COD)Cl]_2$ in polar aprotic

solvents at high temperatures were reported to give very low conversions.[105] Therefore, we carried out a solvent-screen using $[Ir(dbcot)Cl]_2$ as the catalyst (**Table 2.4.3**). Reactions using $[Ir(dbcot)Cl]_2$ with TBD and DBU in THF (entries 1 – 2) were carried out to compare the yields with reactions using $[Ir(COD)Cl]_2$ under the same conditions (page 76, **Table 2.4.1**, entries 4 and 7). The reaction times were shortened but the yields were lowered. Changing solvent to MeCN further lowered the yield (entry 3) while DMSO and DMF slightly improved the yields (entries 4 – 5). On the whole, the yields were not improved using $[Ir(dbcot)Cl]_2$ as the pre-catalyst. This is in agreement with previous reactions involving the allylic *β*-ketoester substrates in which poorer yields were also obtained when using $[Ir(dbcot)Cl]_2$ (page 48, **Table 2.3.3**). Thus, $[Ir(dbcot)Cl]_2$ is probably not a suitable pre-catalyst in decarboxylative alkylation reactions.



2.4.1 **2.4.2** **2.4.3**

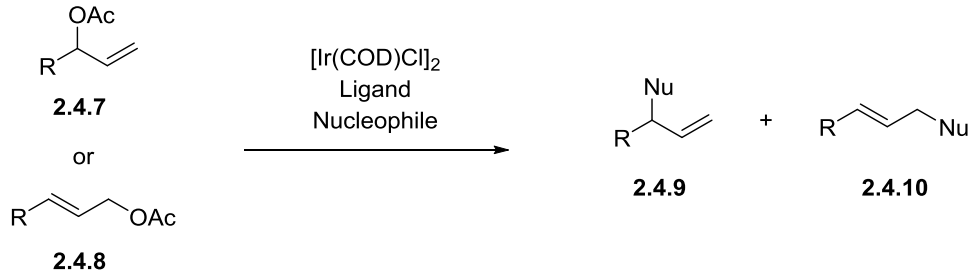
Reagents and conditions: a) $[Ir(dbcot)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), base.

Entry	Base (mol%)	solvent	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]
1	TBD (48)	THF	60	6	43	>99 : 1
2	DBU (48)	THF	60	5	49	>99 : 1
3	TBD (48)	MeCN	60	6	25[c]	>99 : 1
4	TBD (48)	DMSO	60	5	53	>99 : 1
5	TBD (48)	DMF	60	5	57	>99 : 1

[a] Isolated yield of branched isomer **2.4.2**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] The rest of the mass could not be flushed out of column. Enantiomeric excesses (*ee*s) were not measured due to sub-optimal yields.

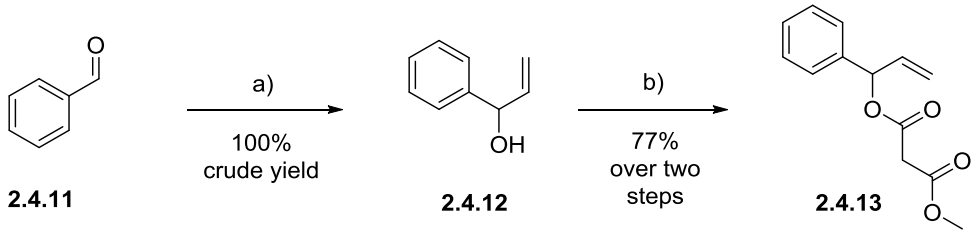
Table 2.4.3: Optimisation of reaction conditions for cinnamyl malonate 2.4.1 using $[Ir(dbcot)Cl]_2$

In 2002, Helmchen *et al*. reported that in a typical iridium-catalysed AAA, the rate of reaction was much faster when using the branched starting material **2.4.7** in comparison to that when using the linear starting material **2.4.8** (**Scheme 2.4.3**).[106] They believed that this was probably due to a faster S_N2' reaction in the oxidative addition step.



Scheme 2.4.3: Iridium-catalysed AAA using branched or linear starting materials by Helmchen *et al*.[106]

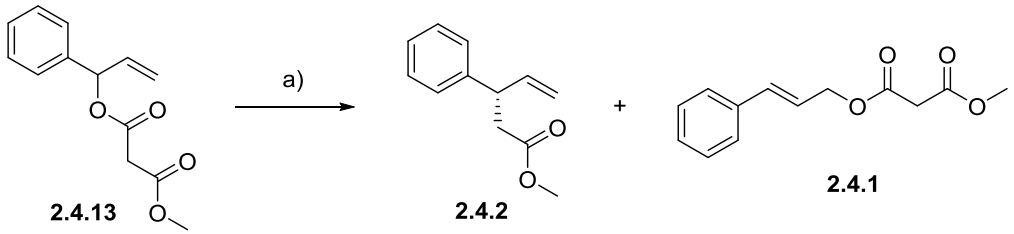
We therefore wondered if decarboxylative iridium-catalysed AAA using branched malonate **2.4.13** could proceed under milder conditions (e.g. lower catalyst loadings or lower reaction temperatures) (**Scheme 2.4.4**). Malonate **2.4.13** was synthesised from benzaldehyde **2.4.11** in two steps – 1,2-addition[107] of vinylmagnesium bromide followed by esterification.[103]



Reagents and conditions: a) Vinylmagnesium bromide (1.2 eq.), THF, 0 °C to RT, 3 h; b) methyl malonyl chloride (1.3 eq.), pyridine (1.3 eq.), DCM, 0 °C to RT, 2 h.

Scheme 2.4.4: Synthesis of branched allylic malonate 2.4.13

Unfortunately, the results obtained were not promising. Attempts were carried out using lower catalyst loadings, 4 mol% of catalyst dimer, with both ligands **L1** and **L2** (**Table 2.4.4**). Both reactions were firstly conducted at RT. As there were no conversions after 3 h, the reactions were warmed to 40 °C for 1.5 h and then to 50 °C for another 1.5 h. As expected, branched malonate **2.4.13** was more reactive than linear malonate **2.4.1** as the former reacted with 4 mol% of catalyst (dimer) at 50 °C while the latter did not react even after 22 h (page 76, **Table 2.4.1**, entry 2). Nonetheless, the results were still not optimal. Only 12% of the desired product **2.4.2** was isolated (entry 1). Linear malonate **2.4.1** was probably formed from thermal or iridium-mediated isomerisation as 1,2-disubstituted alkene is thermodynamically more stable.



Reagents and conditions: a) $[Ir(COD)Cl]_2$ (4 mol%), ligand, TBD (16 mol%), THF, RT -> 40 °C -> 50 °C.

Entry	Ligand (mol%)	t (h)	Yield of 2.4.2 (%)[a]	Yield of 2.4.1 (%)[a]
1	**L2** (8)	6	12[b]	28
2	**L1** (8)	6	0[c]	-

[a] Isolated yields after column. [b] 16% of starting material was recovered. [c] Only starting material peaks and very small **2.4.1** peaks were observed in the ^{1}H NMR spectrum of the crude; crude was not purified. Enantiomeric excesses (*ee*s) were not measured due to sub-optimal yields.

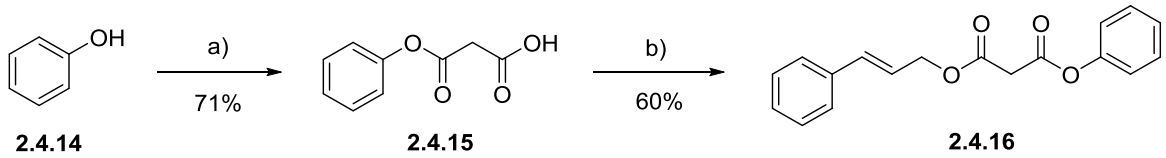
Table 2.4.4: Optimisation of reaction conditions for allylic malonate 2.4.13

2.4.3 Investigation of substrates with different carbonyl leaving groups

We envisaged that the poorer results obtained from the allylic malonate substrates in comparison to those from the allylic *β*-ketoester substrates were probably due to a less favourable decarboxylation process as the heteroatom could donate electron density into the system. Therefore, we next carried out an extensive investigation on a range of substrates with different carbonyl leaving groups. We aimed to find a suitable substrate that could react smoothly with a low catalyst loading to give >70% yield of product under mild conditions.

2.4.3.1 Mono phenylmalonate derivatives

Mono phenylmalonate **2.4.16** was firstly prepared as the benzene ring was expected to withdraw electron density from oxygen. Phenol **2.4.14** reacted with Meldrum's acid to form carboxylic acid **2.4.15**[108] which was then converted into phenylmalonate **2.4.16** *via* formation of acid chloride[109] (**Scheme 2.4.5**).



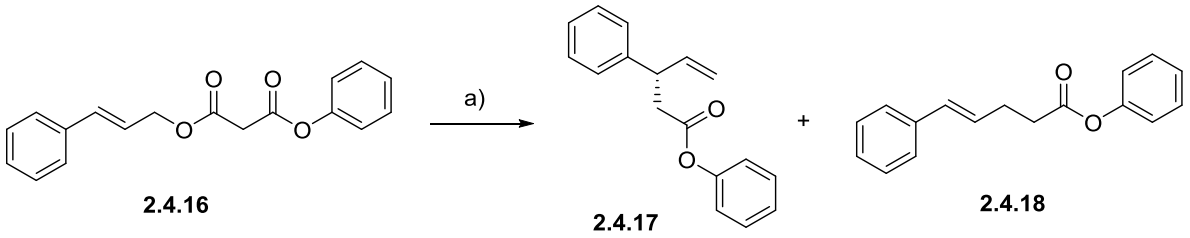
2.4.14 **2.4.15** **2.4.16**

Reagents and conditions: a) Meldrum's acid (1 eq.), toluene, 130 °C, 4 h; b) i) oxalyl chloride (1.2 eq.), DMF (0.1 eq.), DCM, RT, 3 h, ii) cinnamyl alcohol (1 eq.), DMAP (1.2 eq.), DCM, RT, 22 h.

Scheme 2.4.5: Synthesis of phenylmalonate 2.4.16

Optimisation was carried out using 8 mol% or 12 mol% of catalyst (dimer) at different temperatures (**Table 2.4.5**). On the whole, the reactions using phenylmalonate **2.4.16** went to completion in ≈ 3 h while those using methylmalonate **2.4.1** took ≈ 22 h to reach completion, probably due to a more

favourable decarboxylation process with the phenyl esters. However, the yields were not improved. Besides the desired product **2.4.17**, mixtures of unidentifiable cinnamyl fragments and aromatic compounds were isolated in almost all of the reactions (entries 1 – 3). Nonetheless, the higher rate of reaction supported our hypothesis that better carbonyl leaving groups might be beneficial to the reaction.



Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, TBD, THF.

Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]
1	8	**L2** (16)	TBD (32)	50	3	24[c]	>99 : 1
2	12	**L2** (24)	TBD (48)	50	3	56[c]	>99 : 1
3	12	**L2** (24)	TBD (48)	40	3	54[c]	>99 : 1
4	12	**L2** (24)	TBD (48)	RT	22	-[d]	-

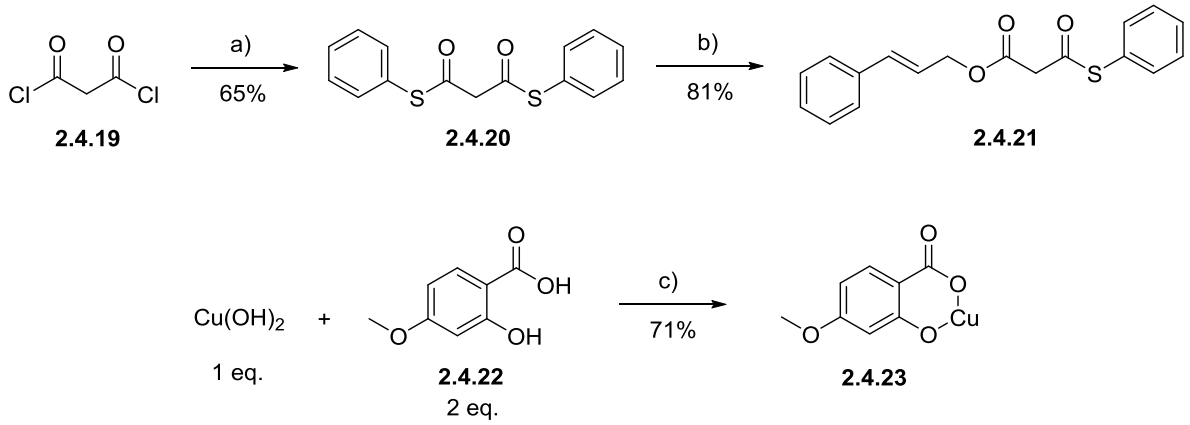
[a] Isolated yield of branched isomer **2.4.17**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Side products are mixtures of unidentifiable cinnamyl fragments and aromatic compounds. [d] Only trace amount of product was observed in a very messy ^{1}H NMR spectrum of the crude; crude was not purified. Enantiomeric excesses (*ee*s) were not measured due to sub-optimal yields.

Table 2.4.5: Optimisation of reaction conditions for phenylmalonate 2.4.16

2.4.3.2 Mono thiomalonate derivatives

We next turned our attention to mono thiophenylmalonate **2.4.21**. Thioesters are more electrophilic than esters due to poorer orbital overlap between the sulphur lone pairs and C=O π^* orbital. Therefore, decarboxylation is expected to be easier to carry out. Following the procedure of Shindo *et al*., malonyl dichloride **2.4.19** was

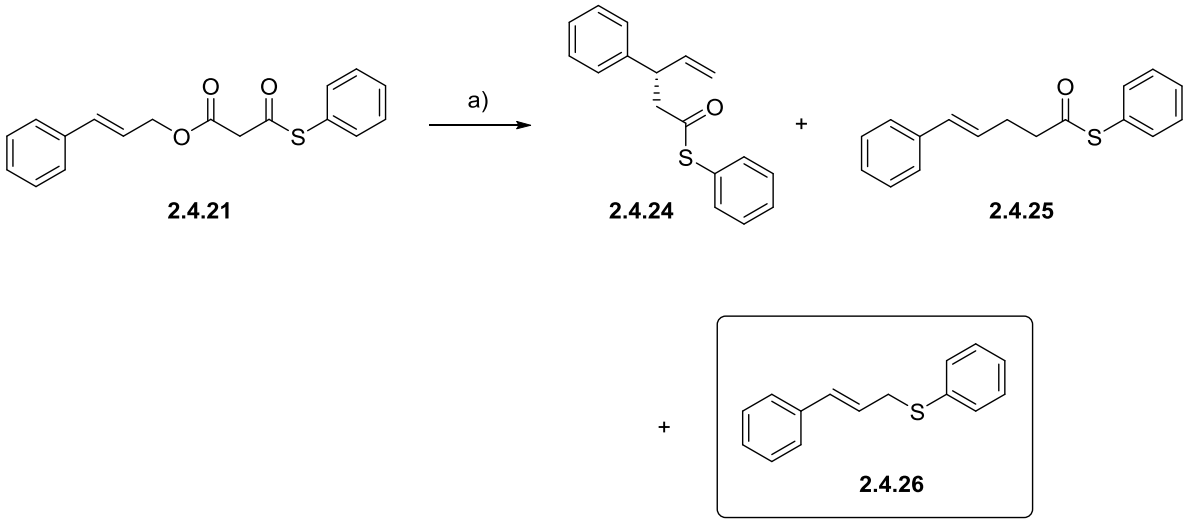
converted into dithiomalonate **2.4.20** which then underwent monoalcoholysis in the presence of catalyst **2.4.23** to form thiophenylmalonate **2.4.21** (**Scheme 2.4.6**).[110]



Reagents and conditions: a) Thiophenol (2.2 eq.), Et_2O, RT, 22 h; b) cinnamyl alcohol (1.2 eq.), catalyst **2.4.23** (1 mol%), MS (4 Å), MeCN, 60 °C, 5 h, air; c) EtOH, 90 °C, 4 h.

Scheme 2.4.6: Synthesis of thiomalonate 2.4.21

Decarboxylative iridium-catalysed AAA of thiophenylmalonate **2.4.21** proceeded to completion at RT with only 4 mol% catalyst (dimer) (**Table 2.4.6**, entry 1). This shows that a more electrophilic leaving group could indeed lead to reactions under milder conditions. However, the desired product thioester **2.4.24** was only formed in around 24% yield. Sulfane **2.4.26** was isolated as a major side product. Using a different ligand and base led to a messy reaction and neither thioester **2.4.24** nor sulfane **2.4.26** was formed (entries 2 – 4).



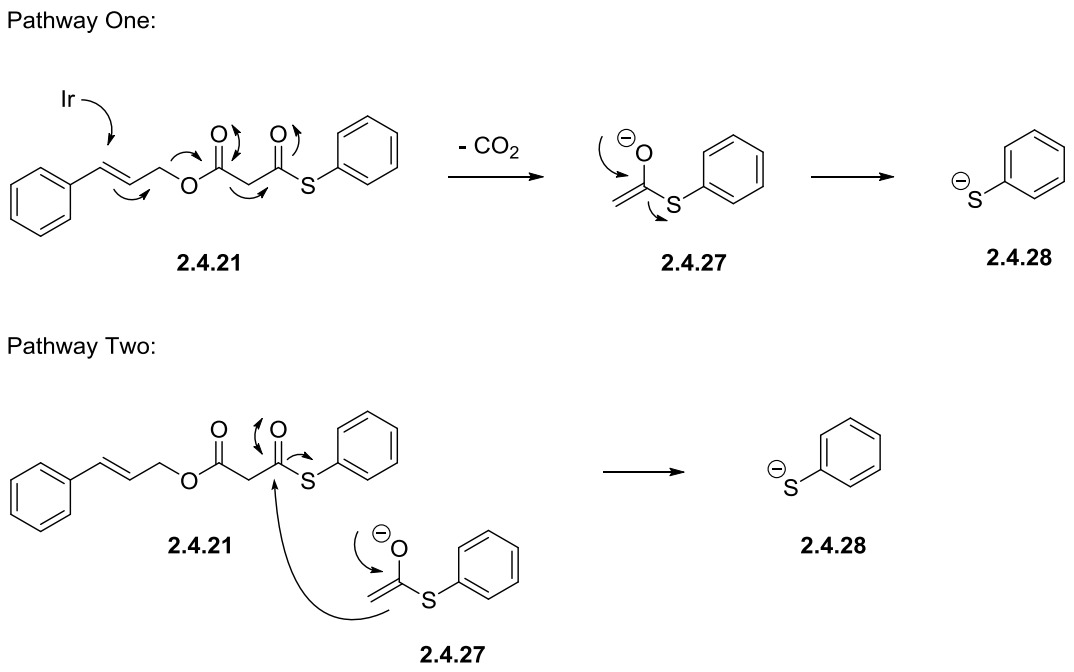
Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, base, THF.

Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]
1	4	**L2** (8)	TBD (16)	RT	5	24[c]	>99 : 1
2	4	**L2** (8)	DBU (16)	RT	22	0[d]	-
3	4	**L1** (8)	TBD (16)	RT	22	0[d]	-
4	4	**L1** (8)	DBU (16)	RT	22	0[d]	-

[a] Isolated yield of branched isomer **2.4.24**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] 28% of sulfane **2.4.26** isolated. [d] Highly complex crude; mixtures of unidentifiable cinnamyl fragments isolated. Enantiomeric excesses (*ee*s) were not measured due to sub-optimal yields.

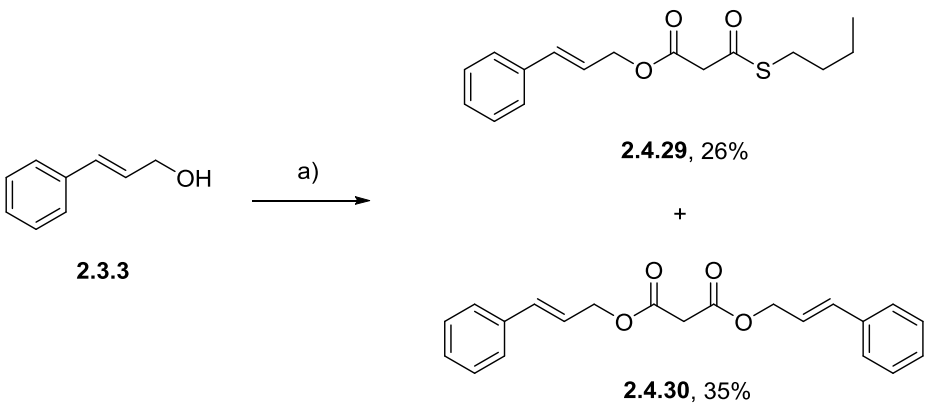
Table 2.4.6: Optimisation of reaction conditions for thiophenylmalonate 2.4.21

From the structure of sulfane **2.4.26**, it could be deduced that its formation is probably caused by the detachment of the thiophenol group from the thioester moiety. There are two possible reaction pathways which could lead to desulphurisation (**Scheme 2.4.7**). Firstly, after the oxidative addition of iridium and decarboxylation, the resulting enolate **2.4.27** may undergo fragmentation to form a ketene and the thiophenol anion **2.4.28** (Pathway One). This is plausible because the C-S bond is weak and thiophenol is a good leaving group. Secondly, it is also possible for enolate **2.4.27** to attack the thioester moiety of starting material **2.4.21** and eliminate the thiophenol anion **2.4.28** (Pathway Two).



Scheme 2.4.7: Two possible reaction pathways that could lead to the formation of thiophenol anion 2.4.28

As the formation of side product sulfane **2.4.26** was probably due to thiophenol being a good leaving group, alkylthiomalonate **2.4.29** was prepared in the next attempt. It was believed that substituting the electron-withdrawing benzene ring with an alkyl group would destabilise negative charge on sulphur, thereby discouraging desulphurisation to occur. The first few attempts on the synthesis of alkylthiomalonate **2.4.29** gave poor yields (**Scheme 2.4.8**) due to formation of side products, but further attempts were not carried out as there was enough material for the next step.



2.3.3

2.4.29, 26%

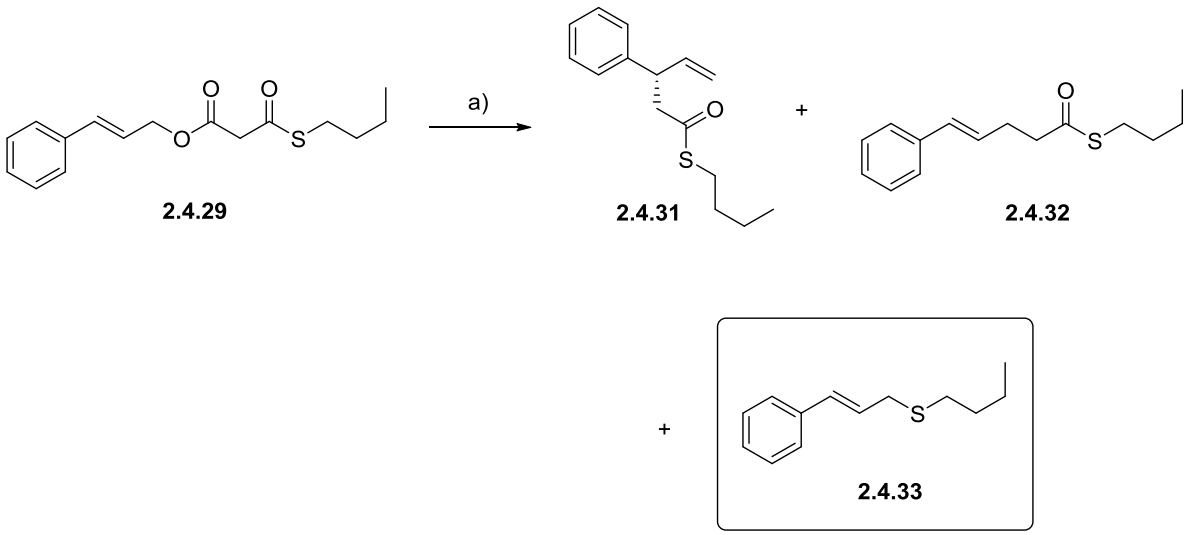
+

2.4.30, 35%

Reagents and conditions: a) i) Malonyl chloride (2.5 eq.), DMAP (1.1 eq.), DCM, RT, 1.5 h, ii) butanethiol (4.5 eq.), DMAP (4.7 eq.), DCM, RT, 2 h.

Scheme 2.4.8: Synthesis of alkylthiomalonate 2.4.29

Harsher conditions were required to drive the reaction to completion when alkylthiomalonate **2.4.29** was used as the starting material (**Table 2.4.7**). For instance, with 4 mol% catalyst (dimer) at 50 °C, the reaction was incomplete even after 22 h (entry 1). This is within expectation as the alkylsulfane substituent is less electron-withdrawing than thiophenol. However, despite a less electrophilic substituent, desulphurisation occurred again to form the side product sulfane **2.4.33** in similar yields as the desired product thioester **2.4.31** (entries 2 – 3). Increasing catalyst loadings increased the yields of both desired product **2.4.31** and side product **2.4.33**.



Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, TBD, THF.

Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]
1	4	**L2** (8)	TBD (16)	50	22	13[c]	>99 : 1
2	8	**L2** (16)	TBD (32)	50	22	24[d]	>99 : 1
2	12	**L2** (24)	TBD (48)	50	7	36[e]	>99 : 1

[a] Isolated yield of branched isomer **2.4.31**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] 25% of starting material was recovered. [d] 18% of sulfane **2.4.33** was isolated. [e] 23% of sulfane **2.4.33** was isolated. Enantiomeric excesses (*ees*) were not measured due to sub-optimal yields.

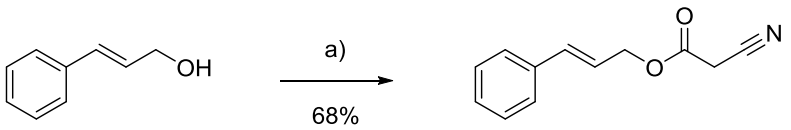
Table 2.4.7: Optimisation of reaction conditions for alkylthiomalonate 2.4.29

From the results obtained so far, it could be concluded that the substituent on the carbonyl leaving group needs to have some electron-withdrawing ability to facilitate decarboxylation but at the same time it cannot be too good a leaving group such that it may detach from the molecule.

2.4.3.3 α-*Cyanoester derivatives*

In the next attempt we prepared a cyanoester derivative **2.4.34**. It was a target of interest because firstly, its synthesis is straightforward – one step synthesis from cinnamyl alcohol **2.3.3** *via* Steglich esterification[111,92,112] (**Scheme**

2.4.9) and secondly, the nitrile product formed from iridium-catalysed AAA can be hydrolysed to form carboxylic acid derivatives.



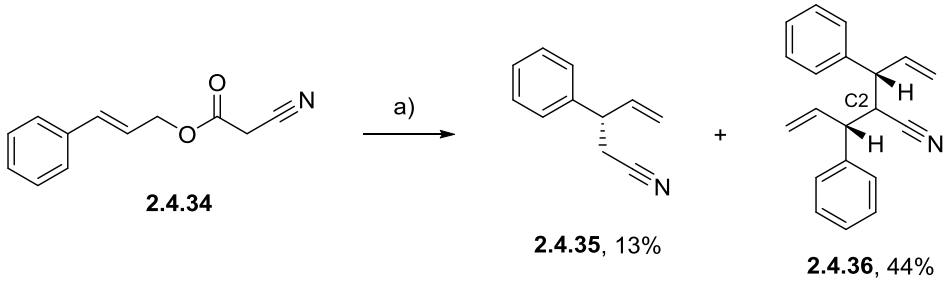
2.3.3 **2.4.34**

Reagents and conditions: a) Cyanoacetic acid (1.1 eq.), DCC (1.1 eq.), DMAP (0.1 eq.), DCM, 0 °C, 3.5 h.

Scheme 2.4.9: Synthesis of cyanoester 2.4.34

Using our standard reaction conditions for malonate type of substrates in decarboxylative iridium-catalysed AAA, although the desired nitrile **2.4.35** was only formed in poor yield, an interesting side product **2.4.36** was isolated (**Scheme 2.4.10**). The structure of the side product **2.4.36** indicates that it was probably formed from over-alkylation of the desired product **2.4.35**. The stereocenters of the side product **2.4.36** were labelled by analogy as ligand **L2** (*S*,*S*,*S*) normally affords products with *S* configurations. The ^{1}H and ^{13}C NMR spectra of the side product **2.4.36**, which only contain one clean set of signals, also show that it was formed as a single diastereomer. This is within expectation considering the excellent *ee*s normally obtained in previous iridium-catalysed AAA reactions. Furthermore, the optical rotation value of the side product **2.4.36** is $[\alpha]_D$ (25 °C) +59.0 (c = 1.00 in $CHCl_3$), showing that the side product **2.4.36** is chiral and not racemic. Therefore, the side product should be compound **2.4.36** and not a mixture of the corresponding meso compounds. According to the nomenclature of Mislow and Siegel,[113] carbon C2 is a chirotopic non-stereogenic center. The formation of the side product **2.4.36** is interesting as it shows that this reaction can be utilised to

prepare a single diastereomer with two stereogenic centers and one pro-stereogenic center all in one step.



2.4.34

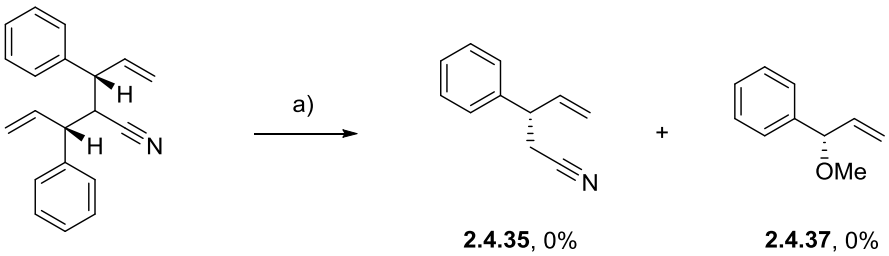
2.4.35, 13%

2.4.36, 44%

Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), THF, 40 °C, 3 h.

Scheme 2.4.10: Decarboxylative iridium-catalysed AAA on cyanoester 2.4.34

Subjecting the side product **2.4.36** to the same reaction conditions above with one drop of MeOH (to trap the allyliridium complex formed) did not afford any products (**Scheme 2.4.11**); the reaction did not proceed and there was only starting material **2.4.36** present in the crude.



2.4.36

2.4.35, 0%

2.4.37, 0%

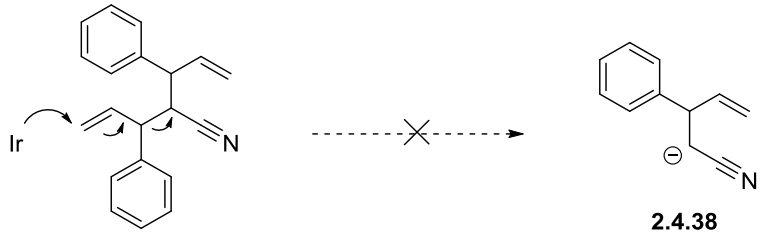
No progress

Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), MeOH (1 drop), THF, 40 °C, 6.5 h.

Scheme 2.4.11: Iridium-catalysed AAA on nitrile 2.4.36

This result indicates that firstly, nitrile **2.4.36** is probably not an intermediate in the reaction. Secondly, its formation is probably not reversible under the iridium-catalysed AAA conditions. Once it is formed, it may not be converted into

the desired product **2.4.35**. This is probably because there is insufficient driving force for iridium to oxidatively add to nitrile **2.4.36** as alkylnitrile anion **2.4.38** may not be a good leaving group (**Scheme 2.4.12**).



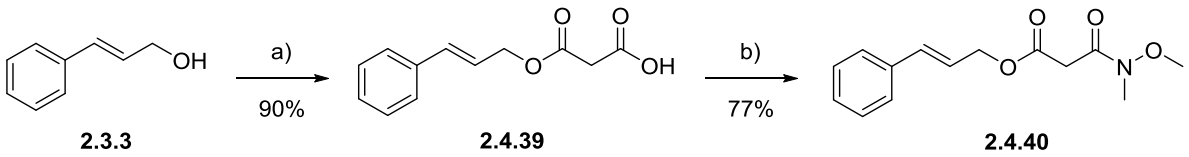
2.4.36 **2.4.38**

Scheme 2.4.12: Unfavourable conversion of nitrile 2.4.36 to the alkylnitrile anion 2.4.38

Further attempts on decarboxylative iridium-catalysed AAA using cyanoester **2.4.34** with different catalyst loadings and temperatures failed to reduce the formation of the side product **2.4.36**. It was not possible to selectively control the formation of the desired nitrile product **2.4.35** under this catalyst system. This probably suggests that under this system, the alkylnitrile anion **2.4.38** (**Scheme 2.4.12**) prefers to react with an allyliridium complex to form the over-alkylation product **2.4.36**, rather than react with an acidic proton to form the desired product **2.4.35**. However, similar over-alkylation products were not isolated in reactions using other types of substrates (e.g. phenyl malonate **2.4.16**, thiomalonate **2.4.21** and substrates to be discussed in the next few sections) under the same catalyst system. This suggests that the reaction pathways and product distributions are largely substrate-dependent.

2.4.3.4 "Weinreb" β-amidoester derivative

Having trialled *O*- and *S*-series of substrates, we next attempted decarboxylative iridium-catalysed AAA on *N*-series of substrates. By analogy, decarboxylation should be less favoured in *β*-amidoester derivatives as nitrogen donates more electron density into the system than oxygen. Therefore, we started the investigation with "Weinreb" *β*-amidoester derivative **2.4.40** because firstly, the oxygen atom was expected to withdraw some electron density from the adjacent nitrogen by inductive effect and secondly, Weinreb amides can be easily converted into ketones and esters afterwards. *β*-Amidoester **2.4.40** was synthesised from cinnamyl alcohol **2.3.3** in overall good yield *via* formation of carboxylic acid **2.4.39** (**Scheme 2.4.13**).[108,114]



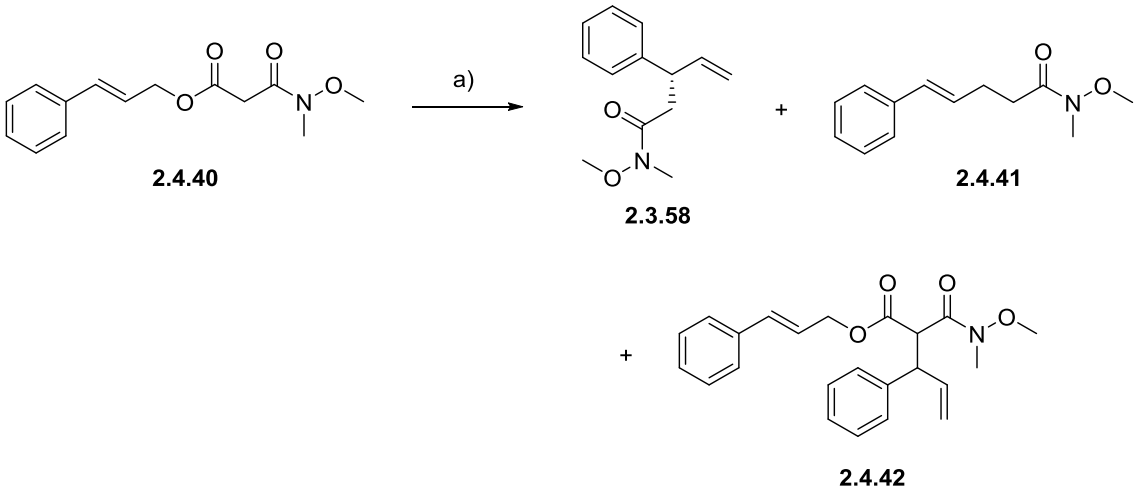
2.3.3 **2.4.39** **2.4.40**

Reagents and conditions: a) Meldrum's acid (1 eq.), toluene, 130 °C, 1 h; b) i) oxalyl chloride (1.2 eq.), DMF (0.1 eq.), DCM, RT, 3 h, ii) *N*,*O*-dimethylhydroxylamine hydrochloride (1 eq.), DMAP (3.2 eq.), DCM, RT, 1 h.

Scheme 2.4.13: Synthesis of *β*-amidoester 2.4.40

β-Amidoester **2.4.40** underwent decarboxylative iridium-catalysed AAA very slowly at RT (**Table 2.4.8**, entry 1) even with 12 mol% of catalyst (dimer). There was no desired amide **2.3.58** formed after 3 h at RT, instead 32% of the starting material **2.4.40** was recovered and around 37% of possible intermediate **2.4.42** was isolated (more details regarding this intermediate will be described in **Section 2.4.4**). After increasing the temperature, the reactions went to completion to selectively

form the branched isomer **2.3.58** in moderate yields (entries 2 – 3). Although the yields and catalyst loadings were still not promising, the results showed that the *β*-amidoester substrates were tolerated under the reaction conditions. In order to further improve the yields of the branched products and lower the catalyst loadings, we moved on to investigate other nitrogen-containing substrates.



Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, TBD, THF.

Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]	*ee* (%)[c]
1	12	**L2** (24)	TBD (48)	RT	3	0[d]	-	-
2	12	**L2** (24)	TBD (48)	40	7	62 (65)[e]	>99 : 1	-
3	12	**L2** (24)	TBD (48)	50	6	65	>99 : 1	>99

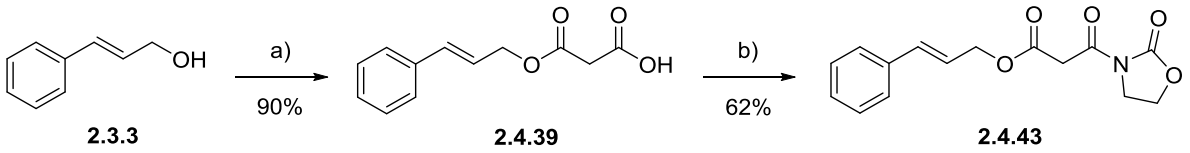
[a] Isolated yield of branched isomer **2.3.58**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Determined by chiral HPLC analysis. [d] 32% starting material was recovered; 37% of intermediate **2.4.42** was isolated. [e] Yield in parenthesis is calculated by recovering starting material.

Table 2.4.8: Optimisation of reaction conditions for *β*-amidoester 2.4.40

2.4.3.5 β-*Imidoester derivatives*

The final type of substrate we attempted was *β*-imidoester **2.4.43**. It was a target of interest because we envisaged that by adding a carbonyl group on nitrogen, the resulting amido group could be more electrophilic than the previous

"Weinreb" amino group. Furthermore, imides can be easily reduced to alcohols afterwards. After a few attempts, the best route was found which converted cinnamyl alcohol **2.3.3** into *β*-imidoester **2.4.43** *via* formation of acid anhydride in 56% yield over two steps (**Scheme 2.4.14**).[108,115]

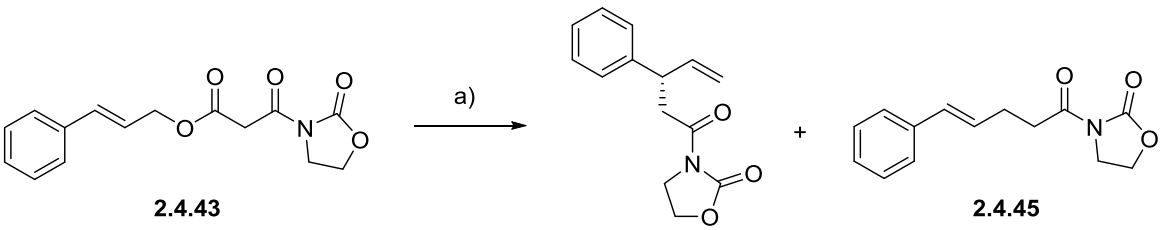


2.3.3 **2.4.39** **2.4.43**

Reagents and conditions: a) Meldrum's acid (1 eq.), toluene, 130 °C, 1 h; b) i) PivCl (1.3 eq.), MS (4 Å), toluene, RT, 1.5 h, ii) 2-oxazolidinone (3 eq.), LiCl (1 eq.), toluene, 130 °C, 3 h.

Scheme 2.4.14: Synthesis of *β*-imidoester 2.4.43

We were pleased to find out that very good results were obtained from decarboxylative iridium-catalysed AAA using *β*-imidoester **2.4.43** (**Table 2.4.9**). In general, there were no linear isomers **2.4.45** formed and the oxazolidinone substituent did not detach from the molecule to form side products. Reactions went to completion within 3 h upon gentle heating to form product **2.4.44** in good yields with excellent selectivities. Varying the catalyst loadings did not change the yields significantly (entries 1 – 3). Conducting the reaction at RT also gave comparable yield but reaction time was prolonged (entry 4). It was surprising to see that good yield and excellent selectivity were achieved even with only 2 mol% of catalyst (dimer) (entry 5). The reaction went to completion smoothly at 40 °C within 3 h.



2.4.43 **2.4.44** **2.4.45**

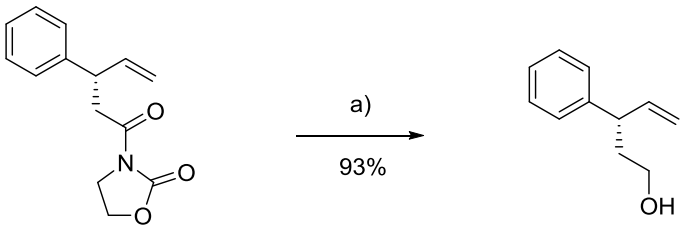
Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, TBD, THF.

Entry	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	T (°C)	t (h)	Yield (%)[a]	Ratio b : l[b]	*ee* (%)[c]
1	12	**L2** (24)	TBD (48)	40	3	73	>99 : 1	-
2	8	**L2** (16)	TBD (32)	40	3	80	>99 : 1	-
3	4	**L2** (8)	TBD (16)	40	3	74	>99 : 1	99
4	4	**L2** (8)	TBD (16)	RT	22	78	>99 : 1	>99
5	2	**L2** (4)	TBD (8)	40	3	72	>99 : 1	99

[a] Isolated yield of branched isomer **2.4.44**. [b] Branched to linear ratio, estimated from ^{1}H NMR. [c] Determined by chiral HPLC analysis.

Table 2.4.9: Optimisation of reaction conditions for *β*-imidoester 2.4.43

Reduction of *β*-imidoester **2.4.44** was then carried out using $LiBH_4$ to afford the primary alcohol **2.4.46** in excellent yield with *ee* unaffected (**Scheme 2.4.15**).[116]



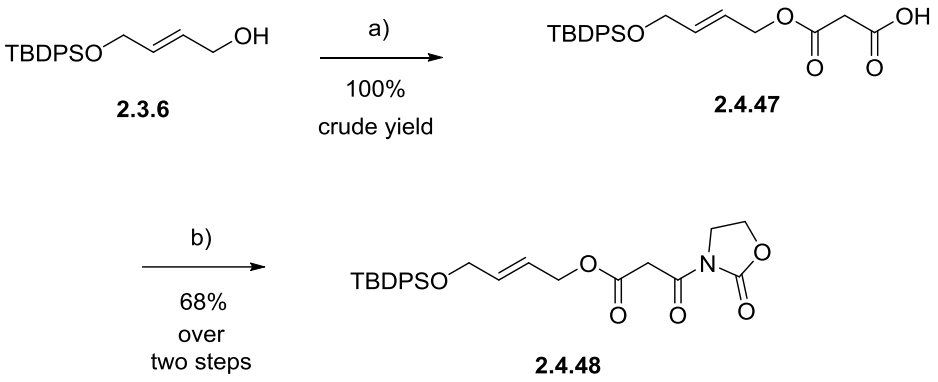
2.4.44 **2.4.46**, *ee* 99%

Reagents and conditions: a) $LiBH_4$ (2 eq.), MeOH (2 eq.), THF, RT, 1 h.

Scheme 2.4.15: Reduction of *β*-imidoester 2.4.44 to alcohol 2.4.46

We then moved on to prepare the alkyl *β*-imidoester **2.4.48** with a silyl ether protecting group as it was the ultimate target of interest in this project. It was

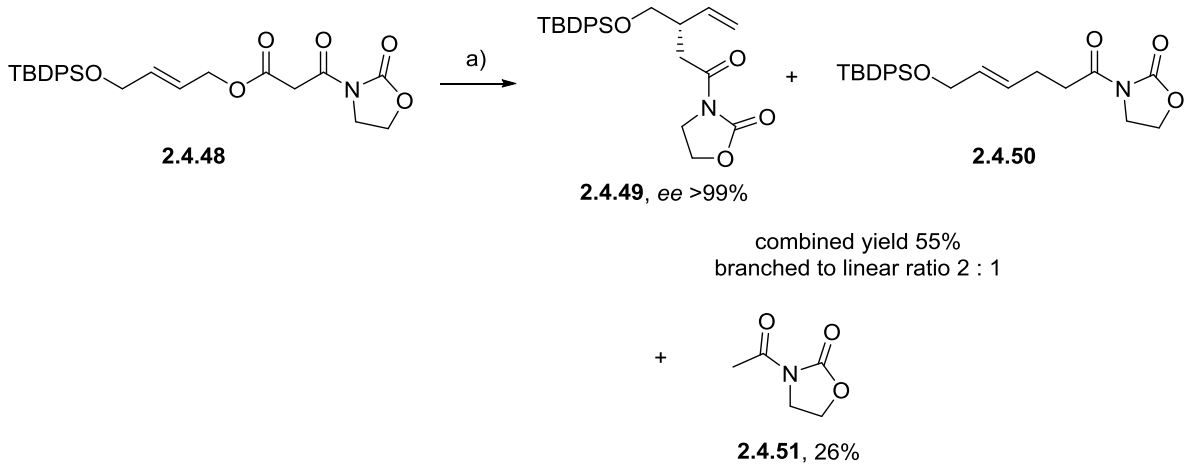
synthesised from allylic alcohol **2.3.6** in the same way as the previous aryl *β*-imidoester **2.4.43** in good yield over two steps (**Scheme 2.4.16**).



Reagents and conditions: a) Meldrum's acid (1 eq.), toluene, 130 °C, 1 h; b) i) PivCl (1.1 eq.), MS (4 Å), toluene, RT, 1.5 h, ii) 2-oxazolidinone (2 eq.), LiCl (1 eq.), toluene, 130 °C, 3 h.

Scheme 2.4.16: Synthesis of alkyl *β*-imidoester 2.4.48

Unfortunately, alkyl *β*-imidoester **2.4.48** did not give promising results in decarboxylative iridium-catalysed AAA under the same reaction conditions established for aryl *β*-imidoester **2.4.43** (**Scheme 2.4.17**). The regioselectivity of this reaction was poor; the branched to linear ratio was only 2 to 1. Furthermore, the branched and linear combined yield was only moderate due to the formation of a side product, acetyloxazolidinone **2.4.51**. The formation of this side product indicates that the enolate formed after decarboxylation is also acting as a base.



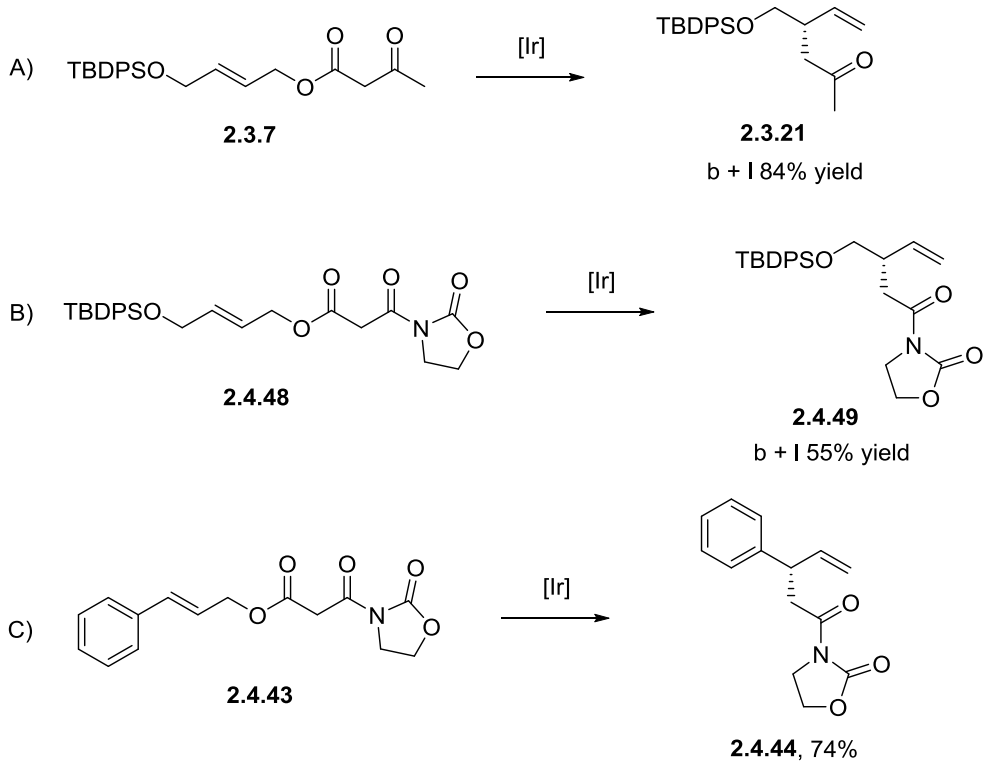
Reagents and conditions: a) $[Ir(COD)Cl]_2$ (4 mol%), ligand **L2** (8 mol%), TBD (16 mol%), THF, 40 °C, 6 h.

Scheme 2.4.17: Decarboxylative iridium-catalysed AAA on alkyl *β*-imidoester 2.4.48

The above reaction was also repeated at RT overnight. Unreacted starting material **2.4.48** was present in large amount. The desired imide **2.4.49** was not formed but trace amount of the side product, acetyloxazolidinone **2.4.51**, was already observed.

Two possible reasons for the formation of acetyloxazolidinone **2.4.51** were proposed by comparing the results with previous reactions (**Scheme 2.4.18**). Firstly, comparing between reactions A and B, the only difference is the substituent on the carbonyl moiety. Therefore, acetyloxazolidinone enolate formed from *β*-imidoester **2.4.48** may be more basic than acetyl enolate formed from *β*-ketoester **2.3.7**. Secondly, the ^{1}H NMR of the crude from reaction C also showed small peaks that corresponded to acetyloxazolidinone **2.4.51** which indicated that acetyloxazolidinone **2.4.51** was also formed in reactions involving aryl *β*-imidoester substrates **2.4.43** but only in small amounts. This probably implies that the alkyl allyliridium complex formed after decarboxylation in reaction B was a poorer

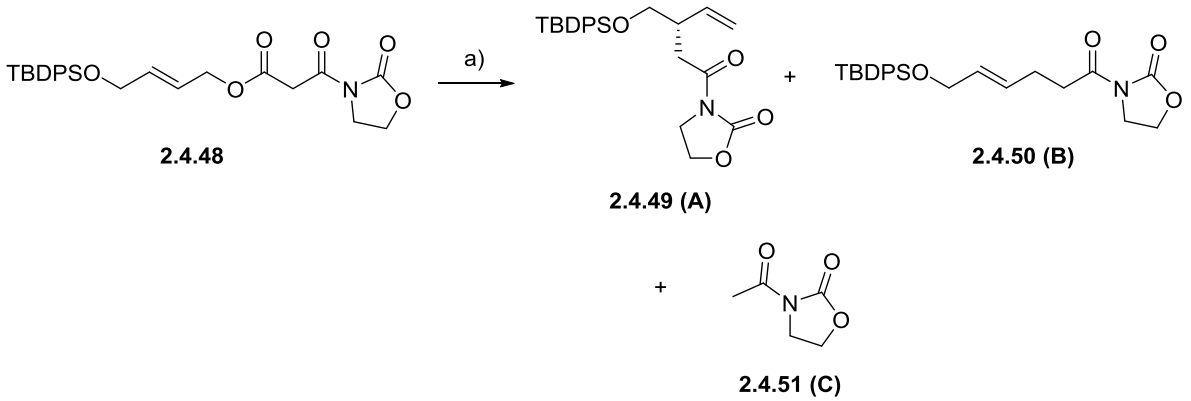
electrophile compared to the aryl allyliridium complex formed in reaction C and therefore, the alkyl allyliridium complex was unable to quickly trap the enolate before it was protonated.



Reagents and conditions: $[Ir(COD)Cl]_2$ (4 mol%), ligand **L2** (8 mol%), TBD (16 mol%), THF.

Scheme 2.4.18: Comparison of decarboxylative iridium-catalysed AAA among different substrates

Attempts were then carried out to optimise the ratio between the three products - branched isomer **2.4.49**, linear isomer **2.4.50** and acetyloxazolidinone **2.4.51** (**Table 2.4.10**). It was found that using ligand **L1** in this substrate system gave a slightly better branched to linear ratio (entries 1 – 2). Increasing the catalyst loading did not change the product distribution (entry 3).



Reagents and conditions: a) $[Ir(COD)Cl]_2$, ligand, TBD, 50 °C.

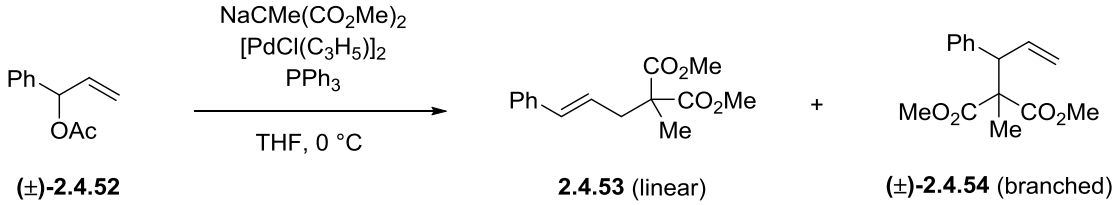
Entry	Ir dimer (mol%)	Ligand (mol%)	Solvent	Additives	Ratio[a]		
					A	B	C
1	4	**L2** (8)	THF	-	1.5	0.7	1
2	4	**L1** (8)	THF	-	2	0.7	1
3	8	**L1** (16)	THF	-	2	0.7	1
4	4	**L1** (8)	THF	LiCl[b]		-[c]	
5	4	**L1** (8)	THF	LiBr[b]		-[c]	
6	4	**L1** (8)	DME	-	1.2	0.15	1
7	4	**L1** (8)	Dioxane	-	0.77	0.15	1

[a] Estimated from the ^{1}H NMR spectra of the crudes. [b] 0.5 eq. of additives added. [c] Only starting material was present in the crude.

Table 2.4.10: Optimisation of reaction conditions for alkyl *β*-imidoester 2.4.48

In entries 4 and 5 (**Table 2.4.10**), the addition of additives, LiCl and LiBr, was attempted as it was reported in a few literature articles that halide ions could influence the selectivities of metal-catalysed allylic substitutions.[16,117] For instance, Hayashi *et al*. reported that the regioselectivity of a palladium-catalysed allylic alkylation reaction was affected by the addition of different halide additives (**Scheme 2.4.19**).[118] It was believed that halide ions could coordinate to the palladium metal center and form new catalyst complexes which led to better regioselectivities.[118] Unfortunately, reactions with the participation of additives did not proceed at all (**Table 2.4.10**, entries 4 – 5). This is probably because LiCl and

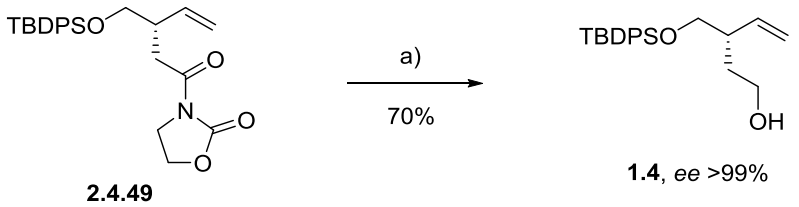
LiBr are also Lewis acids which do not perform well in decarboxylative iridium-catalysed AAA as mentioned previously (page 78, **Section 2.4.2**). Next, as the nucleophilicity of nucleophiles can be affected by the reaction medium, we carried out a solvent screen to see whether the ratio of the products could be changed. Unfortunately, most solvents (e.g. DCM, DCE, chloroform, acetonitrile, DMSO and DMF) led to trace amount of products with messy reactions. The ratios of products obtained from toluene and benzene were similar to that obtained from THF (**Table 2.4.10**, entry 1). Only DME and dioxane led to much better branched to linear ratios but acetyloxazolidinone **2.4.51 (C)** was still formed in large amounts in both solvents (**Table 2.4.10**, entries 6 – 7).



Additives	Combined yield	Linear to branched ratio
-	96%	77 : 23
LiI	99%	100 : 0
LiF	89%	78 : 22
LiCl	96%	82 : 18
LiBr	90%	80 : 20

Scheme 2.4.19: Effects of halide ions on the regioselectivities of a palladium-catalysed allylic alkylation reaction by Hayashi *et al*.[118]

Optimisation on alkyl *β*-imidoester **2.4.48** was stopped here due to time constraint. We attempted the following reduction step and we were happy to see that alcohol **1.4** was achieved in good yield (**Scheme 2.4.20**).[116] The yield could probably be further optimised at lower temperatures as the silyl ether protecting group may be unstable in the presence of strong reducing agent.



2.4.49 **1.4**, *ee* >99%

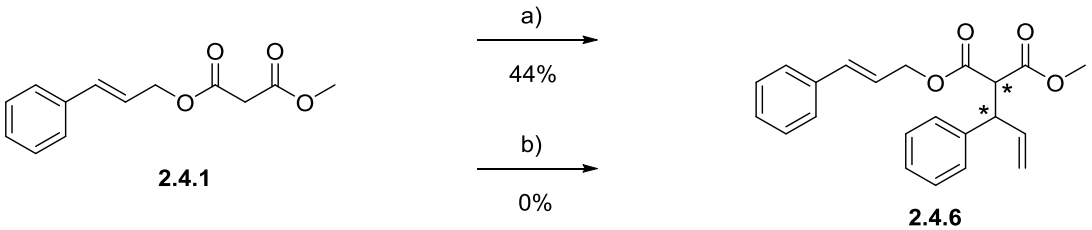
Reagents and conditions: a) $LiBH_4$ (2 eq.), MeOH (2 eq.), THF, RT, 1 h.

Scheme 2.4.20: Reduction of alkyl *β*-imidoester 2.4.49 to alcohol 1.4

2.4.4 Mechanistic insights

The mechanism of decarboxylative iridium-catalysed AAA was not extensively explored in this project but some of the compounds isolated from reactions shed some light on the mechanism.

It was mentioned in **Section 2.4.2** (page 78) that conducting decarboxylative iridium-catalysed AAA on malonate **2.4.1** in the presence of $Zn(OTf)_2$ did not yield any desired ester products but led to the formation of a side product **2.4.6** in 44% yield (**Scheme 2.4.21** a)). To prove that iridium is required for the formation of compound **2.4.6**, the reaction was repeated without adding $[Ir(COD)Cl]_2$ and ligand (**Scheme 2.4.21** b)). As expected, the reaction did not proceed and therefore, the formation of compound **2.4.6** was not a thermally-driven reaction.

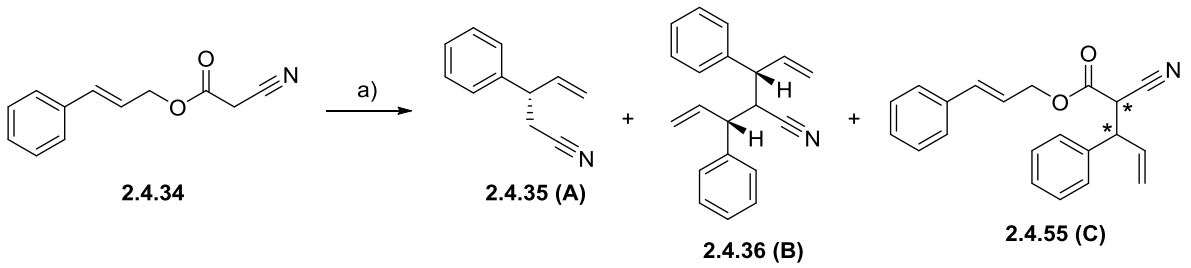


2.4.1 **2.4.6**

Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), $Zn(OTf)_2$ (30 mol%), THF, 50 °C, 22 h; b) TBD (48 mol%), $Zn(OTf)_2$ (30 mol%), THF, 50 °C, 22 h.

Scheme 2.4.21: Conversion of malonate 2.4.1 to possible intermediate 2.4.6

In **Section 2.4.3.3** (page 88), it was shown that cyanoester **2.4.34** underwent decarboxylative iridium-catalysed AAA to form both nitrile **2.4.35** and the over-alkylated product **2.4.36** (**Table 2.4.11**). In fact, if this reaction was stopped prior to completion, another product, cyanoester **2.4.55**, was also isolated which is the analogue of malonate **2.4.6**. By monitoring the reaction progression using ^{1}H NMR, the ratios among starting material **2.4.34** and the three products were tabulated at different time intervals (**Table 2.4.11**). Cyanoester **2.4.55 (C)** was observed in large amounts at the start of the reaction when there was still a lot of starting material **2.4.34** present (entry 1). As the reaction progressed, the amount of cyanoester **2.4.55 (C)** decreased and the amount of products **2.4.35 (A)** and **2.4.36 (B)** increased over time (entry 2). Eventually, after leaving the reaction overnight, cyanoester **2.4.55 (C)** was completely consumed; only products **2.4.35 (A)** and **2.4.36 (B)** were found in the crude (entry 3). These results indicate that cyanoester **2.4.55** is a plausible intermediate in the reaction and thus, the analogous malonate **2.4.6** is probably also an intermediate in the reaction of allylic malonate **2.4.1**.



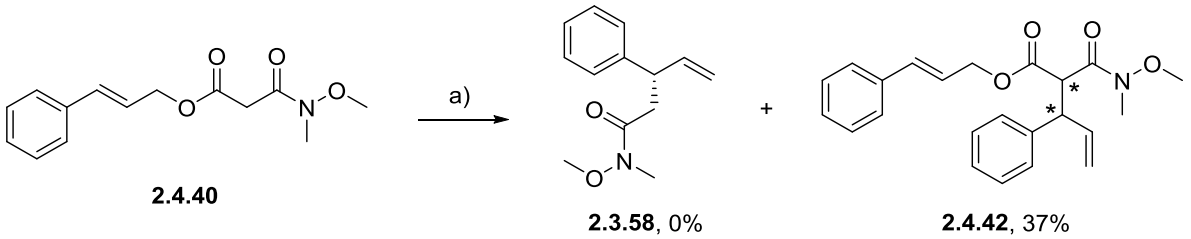
Reagents and conditions: a) $[Ir(COD)Cl]_2$ (4 mol%), ligand **L2** (8 mol%), TBD (16 mol%), THF, 40 °C.

Entry	t (h)[a]	Ratio[b]			
		SM[c]	A	B	C
1	3	1	1	-	2
2	6	-	1	0.4	0.4
3	22	-	1	1.8	-

[a] Number of hours that the reaction had been ran at 40 °C. [b] Estimated from ^{1}H NMR spectrum. [c] Starting material **2.4.34**.

Table 2.4.11: Investigation on the course of reaction

This intermediate analogue was also observed in reactions using "Weinreb" *β*-amidoester derivatives in **Section 2.4.3.4** (page 92). When carrying out decarboxylative iridium-catalysed AAA at RT, there was no desired amide **2.3.58** formed and around 37% of *β*-amidoester **2.4.42** was isolated (**Scheme 2.4.22**).

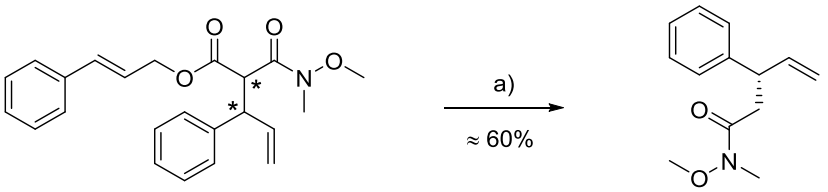


Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), THF, RT, 3 h.

Scheme 2.4.22: Decarboxylative iridium-catalysed asymmetric allylic alkylation of *β*-amidoester 2.4.40

β-Amidoester **2.4.42** alone was then subjected to the same reaction condition above except at 50 °C in order to drive the reaction to completion

(**Scheme 2.4.23**). As expected, the desired product **2.3.58** was formed with the same *ee* as that in the original reactions (page 93, **Section 2.4.3.4**, **Table 2.4.8**). This further implies that these compound analogues are intermediates in decarboxylative iridium-catalysed AAA.



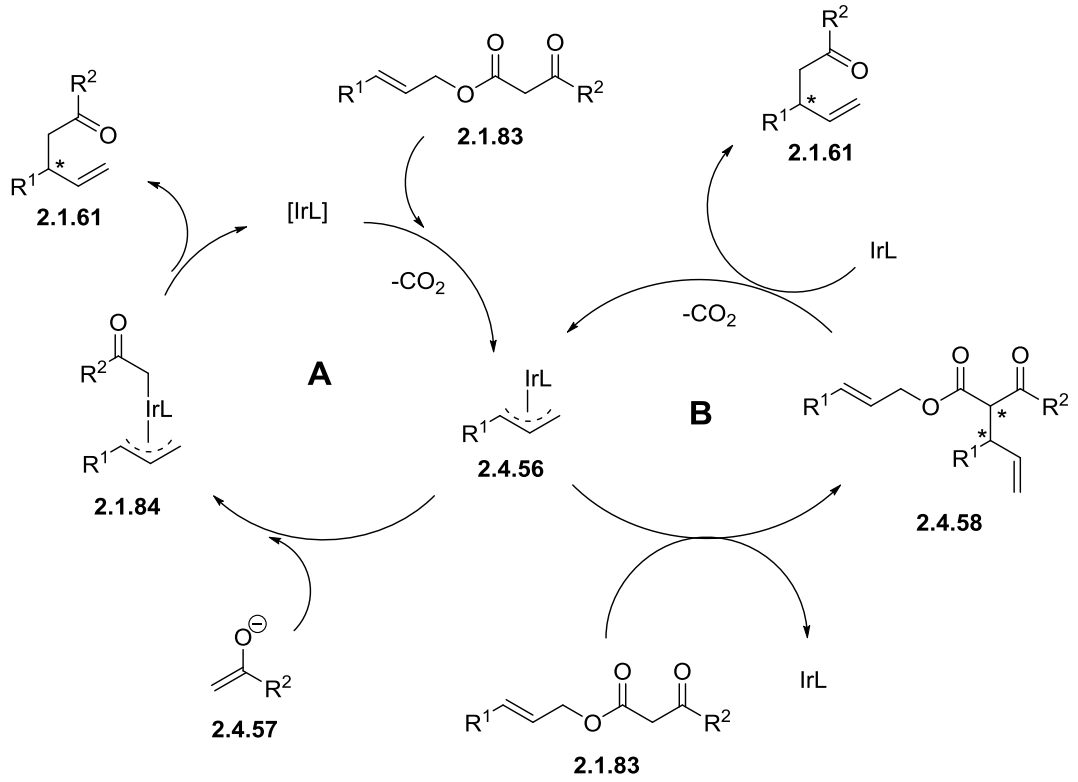
2.4.42 **2.3.58**, *ee* >99%

Reagents and conditions: a) $[Ir(COD)Cl]_2$ (12 mol%), ligand **L2** (24 mol%), TBD (48 mol%), THF, 50 °C, 4 h.

Scheme 2.4.23: Conversion of intermediate 2.4.42 to product 2.3.58

It was previously mentioned in **Section 2.1.4** (page 35, **Scheme 2.1.20**) that You *et al*. proposed a possible reaction pathway for decarboxylative iridium-catalysed AAA (**Scheme 2.4.24**, cycle **A**).[65] It was proposed that the starting material **2.1.83** underwent decarboxylation in the presence of the active iridium catalyst to form nucleophilic enolate **2.4.57**, which then underwent carbon-carbon bond formation with allyliridium complex **2.4.56** to give the chiral product **2.1.61**. You *et al*. also proved that decarboxylative iridium-catalysed AAA is unlikely to be an intramolecular rearrangement by conducting crossover experiments (page 37, **Scheme 2.1.22**).[65] This result probably implies that any nucleophilic species present in the reaction mixture could attack allyliridium complex **2.4.56** and this hypothesis was supported by the isolation of intermediates **2.4.58** in this project. At the beginning of the reaction, as there is far more starting material **2.1.83** than enolate **2.4.57**, it could be that the nucleophilic starting material **2.1.83** competes to

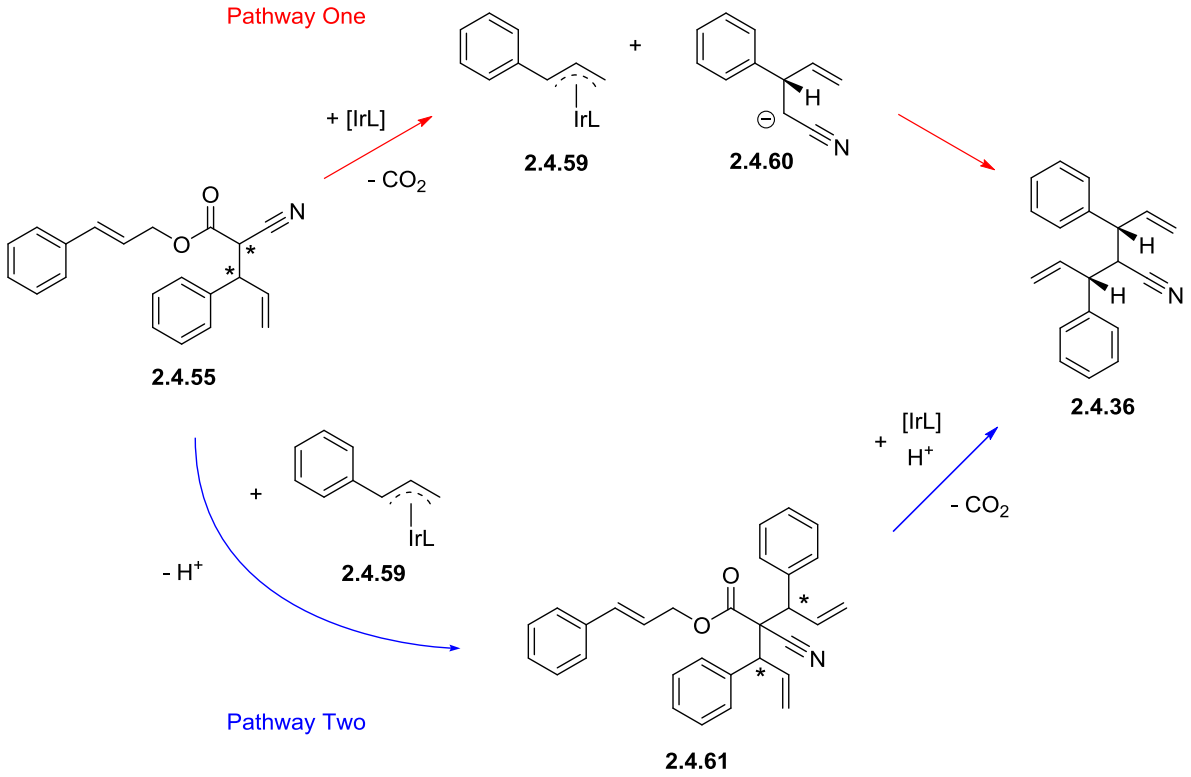
react with allyliridium complex **2.4.56** to form intermediate **2.4.58** which then undergoes another iridium-catalysed decarboxylation to form the final product **2.1.61** (**Scheme 2.4.24**, cycle **B**).



Scheme 2.4.24: Proposed dual pathway catalytic cycle for decarboxylative iridium-catalysed asymmetric allylic alkylation

The mechanistic pathway that leads to the formation of the nitrile side product **2.4.36** was not investigated in this project (**Scheme 2.4.25**). Nonetheless, from its structure, it could be deduced that the side product **2.4.36** is probably caused by the over-alkylation of the acetonitrile moiety. Therefore, two possible pathways were proposed that could lead to the formation of this side product **2.4.36**. Firstly, after intermediate **2.4.55** undergoes iridium-catalysed decarboxylation, instead of being protonated, the alkylnitrile anion **2.4.60** may react with a molecule of the allyliridium complex **2.4.59** present in the reaction medium to form the side

product **2.4.36** (**Scheme 2.4.25**, Pathway One). Secondly, it is also possible that in the presence of excess base, intermediate **2.4.55** loses a proton and reacts with another molecule of the allyliridium complex **2.4.59** to form the quaternary nitrile **2.4.61**, which then undergoes iridium-catalysed decarboxylation to give the side product **2.4.36** (Pathway Two).



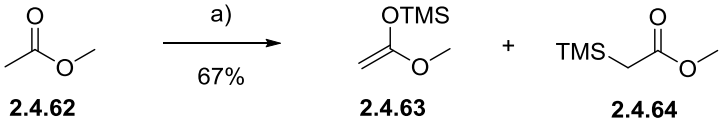
Scheme 2.4.25: Two possible pathways that lead to the formation of the side product 2.4.36

2.4.5 Iridium-catalysed AAA using unstabilised enolate equivalents

It was previously described in **Section 2.1.4** (page 29, **Scheme 2.1.16**) that two examples of iridium-catalysed AAA involving external unstabilised carbon nucleophiles were reported by Hartwig *et al*..[59,60] One of the examples involves the use of silyl enol ethers as the unstabilised nucleophiles which react with allyliridium complexes to form enantioenriched ketones.[59] Inspired by this, we attempted to use

silyl ketene acetals (e.g. TBDMS and TMS ketene acetal) as the nucleophiles to form enantioenriched esters. This type of unstabilised carbon nucleophiles has not been used in iridium-catalysed AAA before.

TMS ketene acetal **2.4.63** is not commercially available and was prepared from methyl acetate **2.4.62** (**Scheme 2.4.26**).[119] A mixture of *O*-silylated and *C*-silylated products was formed and could only be partially separated by distillation. The *C*-silylated product **2.4.64** should not cause any side reactions in iridium-catalysed AAA and thus, the second fraction was used in the following reactions.



2.4.62 **2.4.63** **2.4.64**

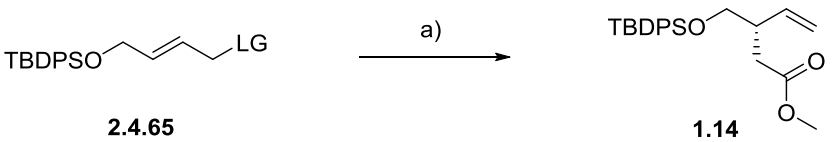
Distillation	Ratio		
	2.4.63	**2.4.64**	
1st fraction	6	1	+ little impurity
2nd fraction	5	1	
3rd fraction	3	1	

Reagents and conditions: a) DIPA (1.1 eq.), *n*BuLi (1.05 eq.), TMSCl (1.2 eq.), THF, -78 °C -> RT, 1.5 h.

Scheme 2.4.26: Synthesis of TMS ketene acetal 2.4.63

Iridium-catalysed AAA using TMS ketene acetal **2.4.63** was carried out using substrates with various leaving groups as different leaving groups often have substantial effect on reaction yields and selectivities (**Table 2.4.12**).[4] Unfortunately, there was none of the desired esters **1.14** formed in any reactions. When using carbonate as the leaving group, all starting materials were consumed and a messy mixture of unidentifiable compounds was formed (entries 1 – 2). The same results

were also obtained when using TBDMS ketene acetal as the nucleophile. This was probably due to the methoxide ions produced after decarboxylation of the carbonate leaving group which might lead to side reactions. When using acetate and bromide as the leaving groups, the reactions did not proceed and only starting materials were observed in the crudes (entries 3 – 4). This result at least indicates that these two substrates do not participate in side reactions. The lack of reaction progress may be because silyl ketene acetals are not reactive enough and fluoride source is probably required to activate them. However, conditions involving fluoride will not be suitable for substrates with silyl ether protecting groups which are the targets of our interest. Therefore, for future work, more research is required to establish a condition for iridium-catalysed AAA using silyl ketene acetals as the nucleophiles. Conditions involving fluoride can be attempted for substrates with other types of alcohol protecting groups such as PMB ethers which are also commonly used in synthesis.



2.4.65 **1.14**

Reagents and conditions: a) Mixture of silyl ketene acetal **2.4.63** and C-silylated product **2.4.64** (2.5 eq.), $[Ir(COD)Cl]_2$, ligand, TBD, THF, 50 , 6 h.

Entry	Leaving group	Ir dimer (mol%)	Ligand (mol%)	Base (mol%)	Yield (%)[a]
1	OCO_2Me	8	**L2** (16)	TBD (32)	0[b]
2	OCO_2Me	8	**L1** (16)	TBD (32)	0[b]
3	OAc	8	**L2** (16)	TBD (32)	0[c]
4	Br	8	**L2** (16)	TBD (32)	0[c]

[a] Isolated yield of ester **1.14**. [b] Messy mixture of unidentifiable side products. [c] No reaction progress.

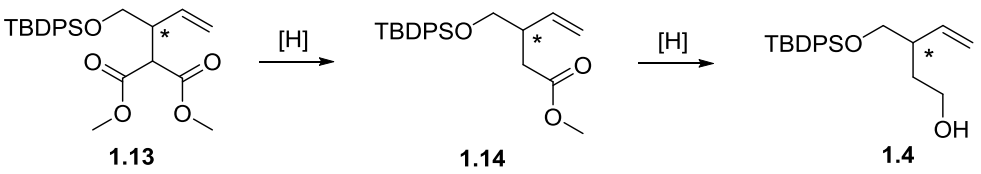
Table 2.4.12: Iridium-catalysed AAA using substrates with different leaving groups

2.4.6 Summary

In summary, decarboxylative iridium-catalysed AAA was attempted using allylic malonate substrates for the synthesis of enantioenriched esters. Unlike allylic *β*-ketoester substrates in **Section 2.3**, allylic malonate substrates required harsher conditions and poorer yields were obtained. A range of substrates with different carbonyl leaving groups were then investigated and very good results were obtained from aryl allylic *β*-imidoester substrates. A possible mechanism for decarboxylative iridium-catalysed AAA was also proposed based on the intermediates isolated during the reactions.

2.5 Synthesis of enantioenriched malonates

As mentioned in **Chapter 1** (page 2), the enantioenriched alcohol **1.4** could also be prepared *via* two-steps reduction from the known malonate **1.13** (**Scheme 2.5.1**).[31]

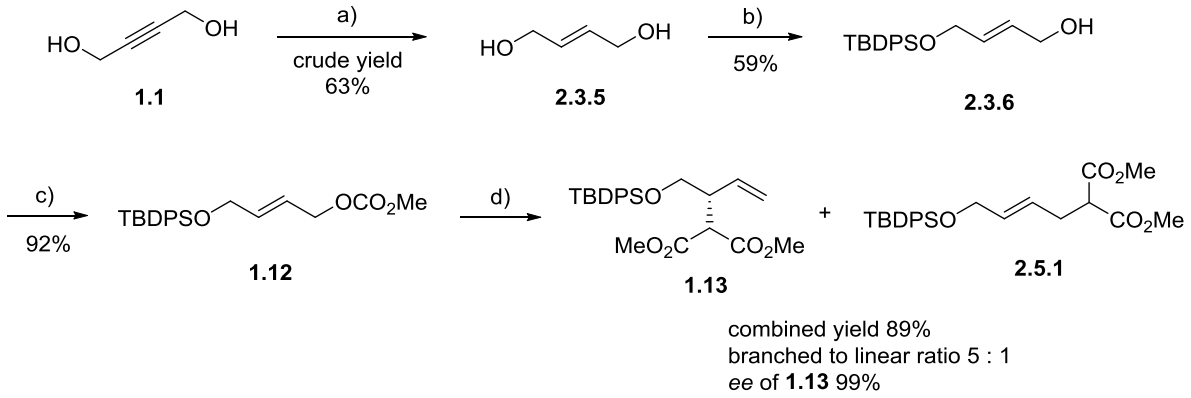


1.13 **1.14** **1.4**

Scheme 2.5.1: Conversion of enantioenriched malonate 1.13 to alcohol 1.4

Malonate **1.13** was synthesised from butynediol **1.1** in four steps (**Scheme 2.5.2**). Butynediol **1.1** was firstly reduced[70] to butenediol **2.3.5** which, without further purification, was monosilylated.[71] Allylic alcohol **2.3.6** was then converted into allylic carbonate **1.12** in excellent yield.[69] Following Helmchen's procedure and conditions,[31] iridium-catalysed AAA was then carried out to form an inseparable

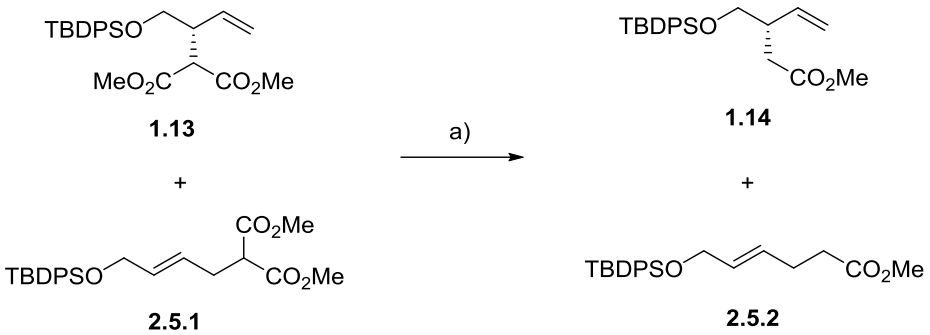
mixture of the enantioenriched malonate **1.13** and the linear isomer **2.5.1**. Both yields and selectivities were comparable to those reported in literature.



Reagents and conditions: a) $LiAlH_4$ (1.2 eq.), THF, 0 °C to RT, 16 h; b) NaH (1 eq.), TBDPS-Cl (1 eq.), THF, RT, 16 h; c) $ClCO_2Me$ (1.5 eq.), pyridine (1.5 eq.), DCM, RT, 2 h; d) $[Ir(COD)Cl]_2$ (4 mol%), ligand **L1** (8 mol%), TBD (16 mol%), dimethyl malonate (1.4 eq.), THF, RT, 22 h.

Scheme 2.5.2: Synthesis of enantioenriched malonate 1.13

Krapcho decarboxylation[87,88] was then carried out to convert the inseparable mixture of malonates **1.13** and **2.5.1** into esters **1.14** and **2.5.2** (**Table 2.5.1**). Initially only a moderate combined yield of 50% was obtained (entry 1). We assumed that this might be due to loss of water during the reaction as the reaction temperature was much higher than the boiling point of water. As water is essential for the formation of esters **1.14** and **2.5.2**, loss of water may cause side reactions to happen. The reaction was then repeated with the addition of another equivalent of water halfway through the reaction and we were happy to see that an excellent yield of 90% was achieved (entry 2).



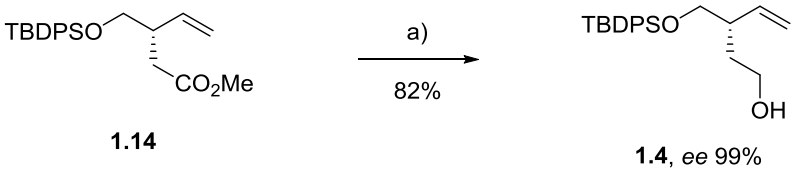
Reagents and conditions: a) LiCl (2 eq.), H_2O, DMSO, 150 °C.

Entry	H_2O (eq.)	t (h)	Yield (%)[a]
1	2	3	50
2	3[b]	4	90

[a] Combined yield of esters **1.14** and **2.5.2**. [b] 2 eq. of water was added at the start of reaction and another eq. of water was added after 2 h.

Table 2.5.1: Optimisation of Krapcho decarboxylation

The mixture of esters **1.14** and **2.5.2** was partially separable. Only the branched ester **1.14** was then subjected to DIBAL-H reduction to form the enantioenriched alcohol **1.4** in very good yield (**Scheme 2.5.3**).[88]



Reagents and conditions: a) DIBAL-H (2.3 eq.), THF, 0 °C, 1 h.

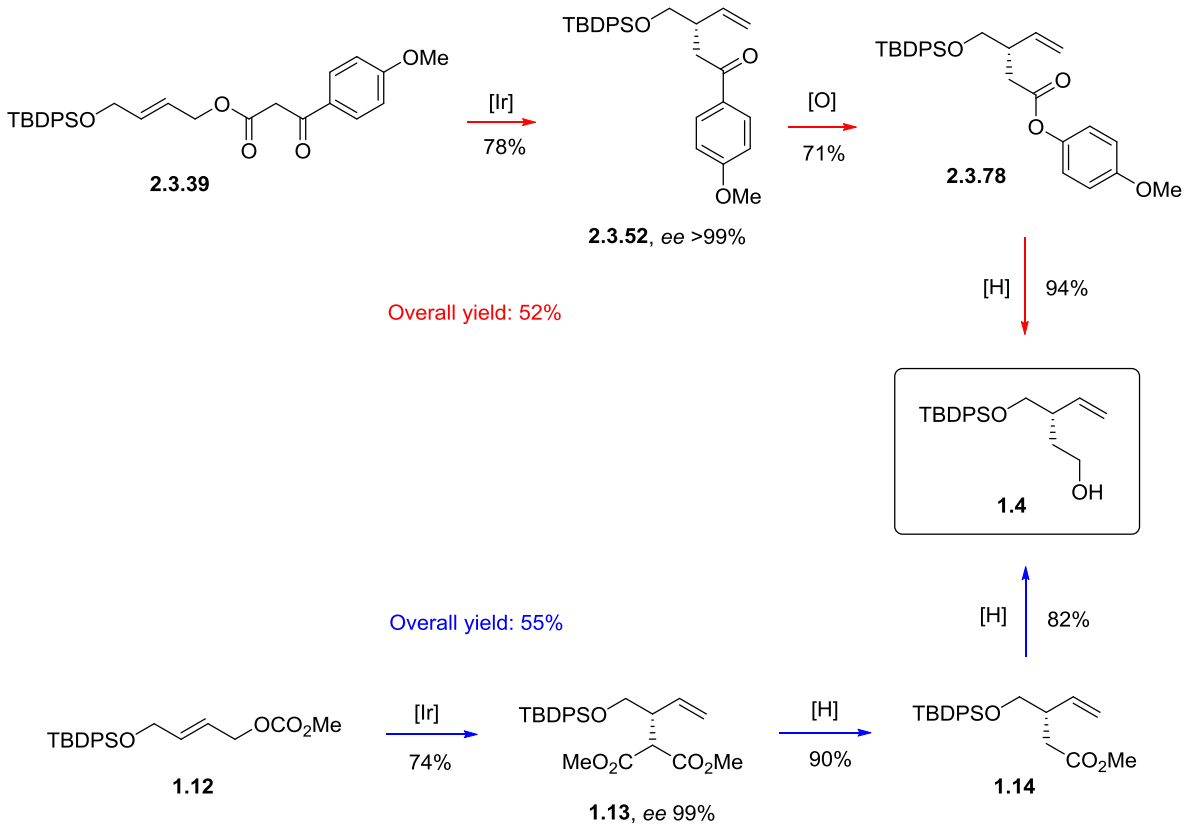
Scheme 2.5.3: DIBAL-H reduction of ester 1.14

2.6 Conclusion and future work

Decarboxylative iridium-catalysed AAA has been shown to be a powerful tool to synthesise highly enantioenriched compounds in good yields. In **Section 2.3**, an optimal reaction condition was found for decarboxylative iridium-catalysed AAA to

prepare highly enantioenriched ketones from a wide scope of *β*-ketoester substrates.

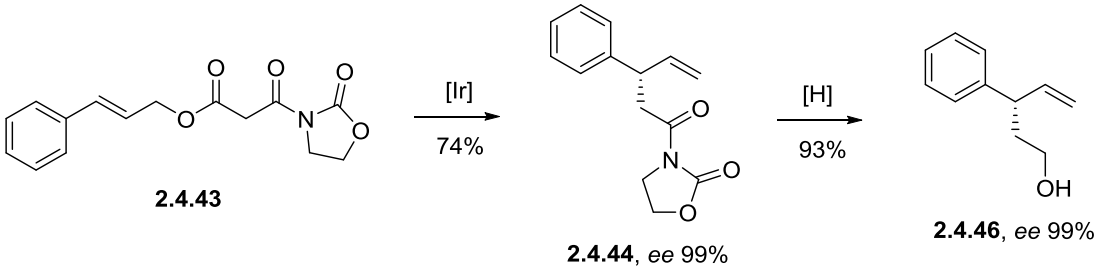
Two reaction pathways have also been established to prepare the enantioenriched alcohol **1.4** from achiral allylic substrates *via* formation of ester derivatives (**Scheme 2.6.1**). Alcohol **1.4** could be prepared by either route in overall good yields with excellent *ee*s.



Scheme 2.6.1: Different synthetic pathways for the preparation of enantioenriched alcohol 1.4 from achiral allylic substrates

In **Section 2.4.3.5**, the direct synthesis of enantioenriched imide **2.4.44** from aryl allylic *β*-imidoester **2.4.43** *via* decarboxylative iridium-catalysed AAA was achieved with good yields and excellent selectivities (**Scheme 2.6.2**). Subsequent

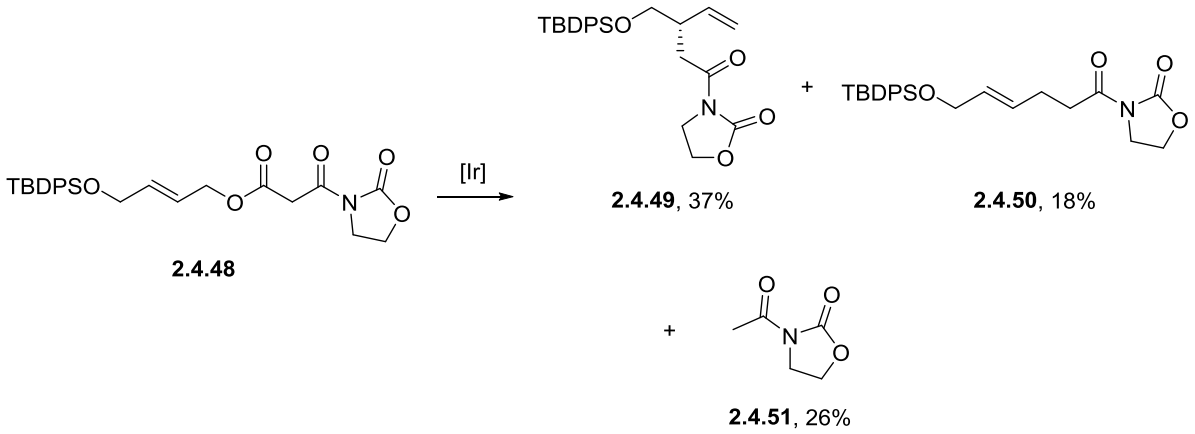
reduction formed aryl alcohol **2.4.46** which is a useful building block for enantioenriched compounds involving aromatic groups.



2.4.43 **2.4.44**, *ee* 99% **2.4.46**, *ee* 99%

Scheme 2.6.2: Preparation of the enantioenriched aryl alcohol 2.4.46 from an achiral substrate in two steps

Utilisation of the above methodology did not give good results for the synthesis of the alkyl imide **2.4.49** due to poor regioselectivity and formation of the side product **2.4.51** (**Scheme 2.6.3**). By comparing with results obtained from other substrates, the nature of the alkyl allyliridium complex could be the cause of the problem. It is frequently shown in literature that by varying the structure of ligands, the nature of the catalyst complex can be altered which often leads to large differences in yields and selectivities.[26,79] Therefore, for future work, a ligand-screen can be attempted to improve the branched to linear ratio as well as to minimise the formation of the side product **2.4.51**. Furthermore, other alkyl *β*-imidoester substrates can also be tried to see whether the poor regioselectivity applies to all alkyl substrates.



Scheme 2.6.3: Decarboxylative iridium-catalysed AAA on an alkyl *β*-imidoester substrate

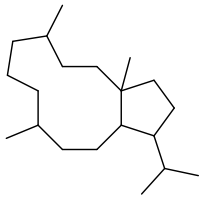
3 Towards the synthesis of a dolabellane

3.1 Introduction

This section briefly introduces the dolabellane family and its biosynthesis. Several recent examples of the total synthesis of dolabellane diterpenoids in the literature will be described. Previous work towards the total synthesis of dolabellane **(±)-1.6** by members of the Burton group will also be discussed.

3.1.1 Overview of the dolabellane family

The dolabellanes belong to a growing class of diterpenes that have been isolated from marine and terrestrial sources such as molluscs (sea hares) and brown algae (seaweeds).[120] The dolabellanes are characterised by a *trans*-bicyclo [9.3.0] tetradecane skeleton **3.1.1** (**Figure 3.1.1**).[120]

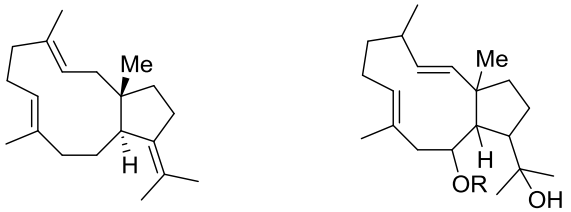


3.1.1

Figure 3.1.1: The dolabellane skeleton[121]

In 1975, Borschberg *et al*. reported the first isolation of a diterpene (**3.1.2**) having this bicyclic skeleton from the mould *Sordaria araneos* (**Figure 3.1.2**).[122] As there was no precedent in the diterpene class of natural products which shared the same bicyclic structure as diterpene **3.1.2**, Borschberg *et al*. suggested that diterpene **3.1.2** belonged to a novel skeletal class and named it the araneosene

family. Later in 1976, this skeletal class was re-named dolabellane after Clardy *et al*. isolated several related diterpenoids (**3.1.3**), which all contained the same carbon framework as araneosene **3.1.2**, from the sea hare *Dolabella californica* (**Figure 3.1.2**).[121]

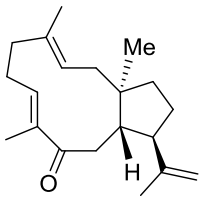


araneosene
3.1.2

R: H or Ac
dolabellane
3.1.3

Figure 3.1.2: The first araneosene and dolabellanes isolated

Until today, more than 160 dolabellanes have been identified and isolated from terrestrial and marine sources.[120,3] As the dolabellane family consists of a wide array of functionalised natural products many of which exhibit antibacterial, antiviral and cytotoxic activity, they have been of synthetic interest to chemists over the years.[1,123] Of particular interest to this project is dolabellane **1.6** which was isolated from the deep water gorgonian octocoral *Convexella magelhaenica* in 2010 and found to be cytotoxic against a human pancreatic adenocarcinoma cell line at micromolar concentrations (**Figure 3.1.3**).[2]

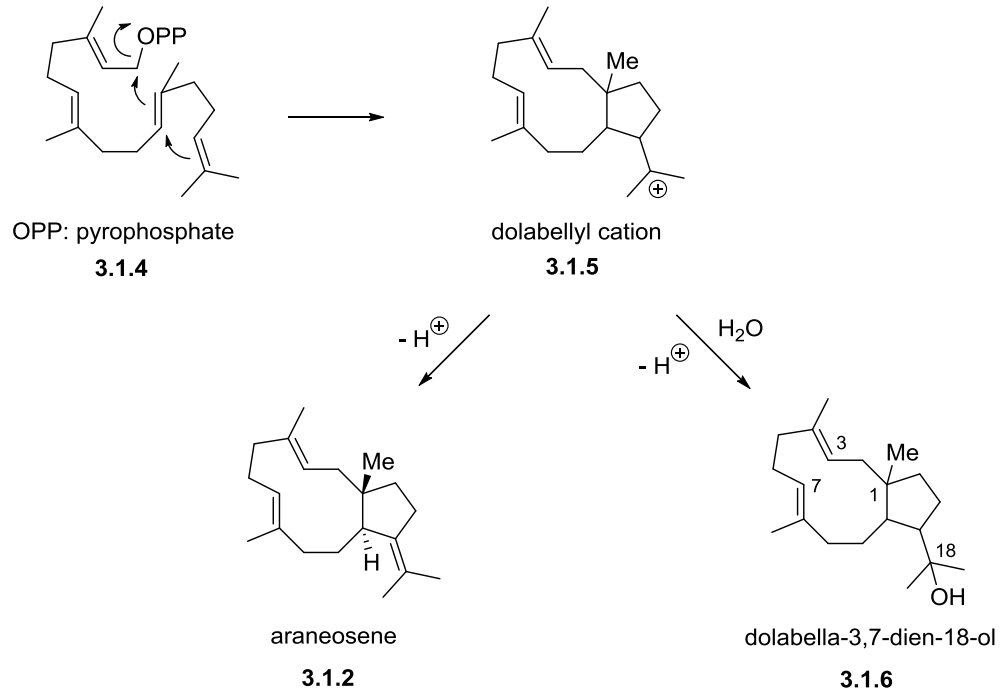


1.6

Figure 3.1.3: Dolabellane 1.6 – the target of interest in this project

3.1.2 Biosynthesis

As it is widely reported in the literature that many different diterpenes are biosynthesised from the achiral substrate – geranylgeranyl pyrophosphate, it was proposed that the dolabellanes were also biosynthesised from the pyrophosphate **3.1.4** (**Scheme 3.1.1**).[124] It is believed that pyrophosphate **3.1.4** undergoes two cyclisations to afford the dolabellyl cation **3.1.5** which after proton loss formed the araneosene **3.1.2** scaffold. The dolabellyl cation **3.1.5** could also react with water to form dolabellane **3.1.6** which could be further converted into other dolabellane diterpenoids.

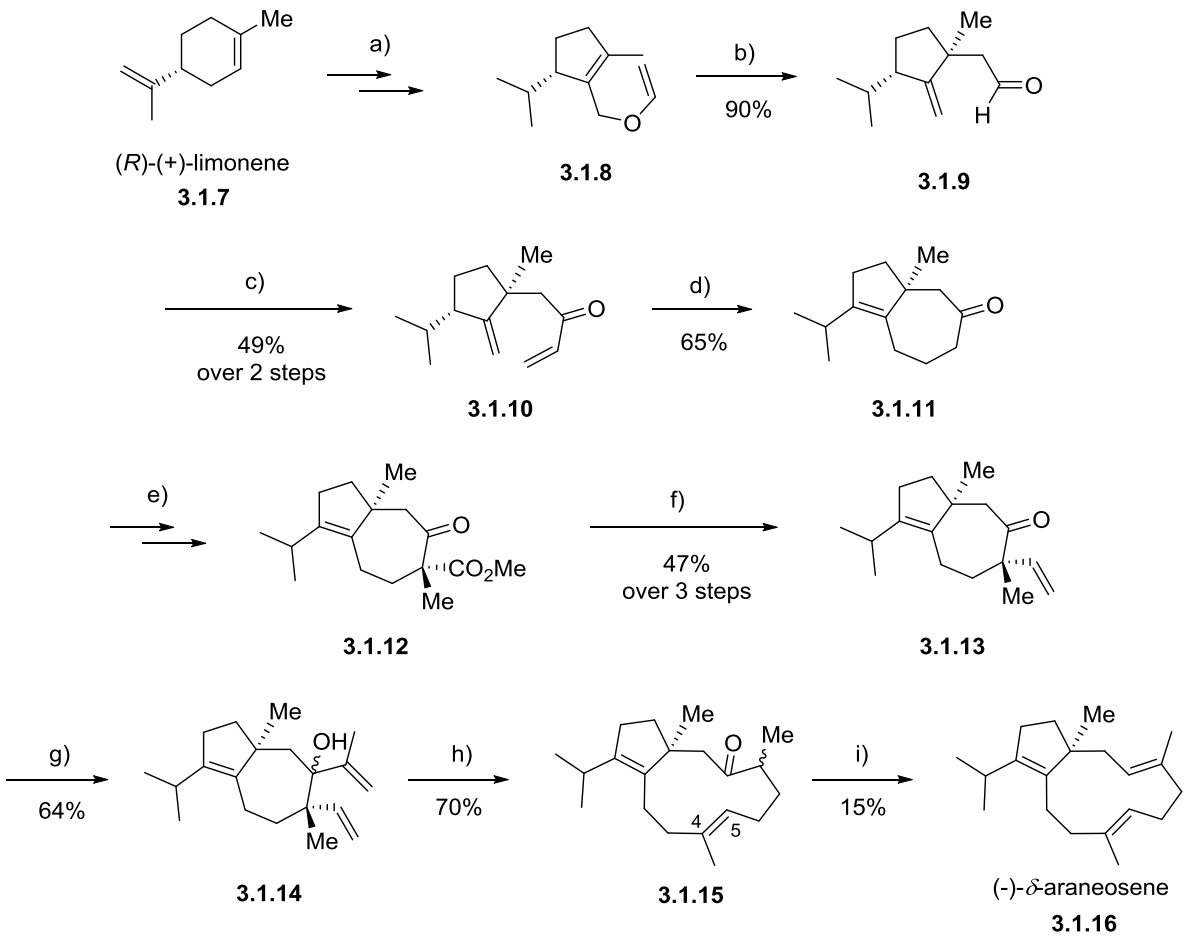


Scheme 3.1.1: Proposed biosynthesis leading to the dolabellane skeletons[120,124]

3.1.3 Total syntheses of dolabellane diterpenoids

In 1990, Mehta *et al*. reported the first enantioselective total synthesis of a dolabellane diterpenoid, (-)-*δ*-araneosene **3.1.16** (**Scheme 3.1.2**).[125] The synthesis

started from enantiomerically pure limonene **3.1.7** which was readily converted into enol ether **3.1.8** using standard transformations.[126] The first key step was a stereoselective Claisen rearrangement leading to the formation of aldehyde **3.1.9** in excellent yield.[127] In the Claisen rearrangement the allyl group selectively attacks the less hindered face of the alkene opposite to the isopropyl group. The second key step was an acid-catalysed olefin-enone cyclisation in step d) which constructed the seven-membered ring **3.1.11**. This was followed by carbomethoxylation and methylation which gave compound **3.1.12**. Subsequent $LiAlH_4$ reduction, Swern oxidation, Wittig olefination and Grignard addition gave diene **3.1.14**. The next key step was an oxy-Cope rearrangement which led to the formation of the eleven-membered ring **3.1.15** and set the (*E*)-geometry of the C(4)=C(5) double bond. The final reduction and elimination step from ketone **3.1.15** gave a low yield due to the formation of a wide range of side products, arising from transannular reactions. Overall, (-)-*δ*-araneosene **3.1.16** was synthesised from limonene **3.1.7** in 19 steps in 0.3% overall yield.



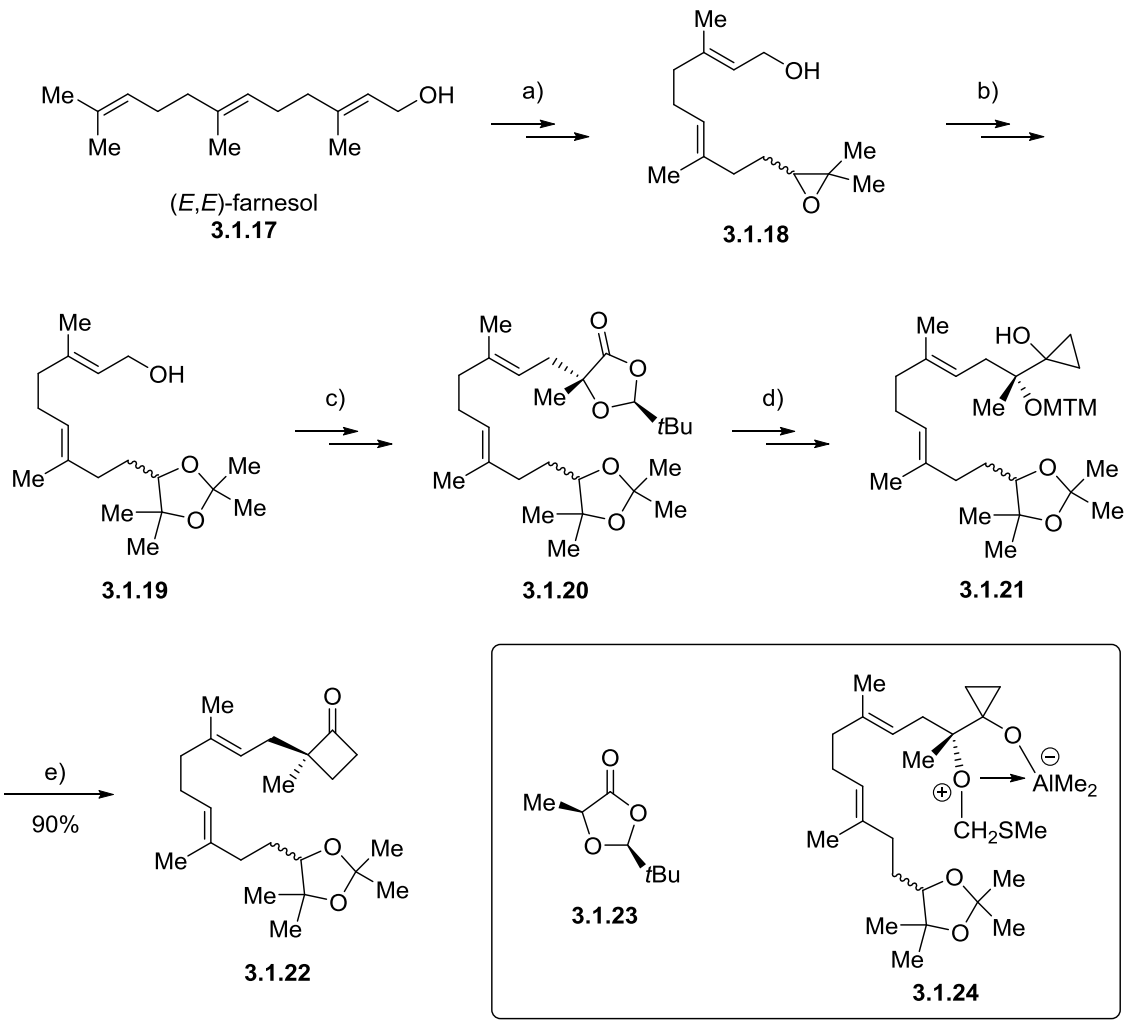
Reagents and conditions: a) i) 5% Pt/C, ii) performic acid then KOH, iii) periodic acid, 78% over 3 steps, iv) AcOH, piperidine, benzene, heat, 2.5 h, 76%, v) $NaBH_4$, MeOH, 0 °C, 90%, vi) ethyl vinyl ether, $Hg(OAc)_2$, RT, 80%; b) 200 °C, 90%; c) i) vinyl bromide, Mg, THF, RT, 0.5 h, 75%, ii) PCC, DCM, RT, 1 h, 65%; d) cat. $HClO_4$, Ac_2O, EtOAc, RT, 25 min, 65%; e) i) NaH, dimethyl carbonate, heat, 6 h, 78%, ii) K_2CO_3, acetone, MeI, heat, 24 h, 85%; f) i) $LiAlH_4$, Et_2O, RT, 1 h, 65%, ii) $(COCl)_2$, DMSO, Et_3N, DCM, -60 °C, iii) $Ph_3P^+CH_3Br^-$, sodium *tert*-amyloxide, RT, 10 min, 72% over 2 steps; g) isopropenylmagnesium bromide, THF, heat, 0.5 h, 64%; h) sealed tube, 170 °C, 1 h, 70%; i) i) $LiAlH_4$, Et_2O, RT, 1 h, 100%, ii) MsCl, pyridine, DCM, 20 h, 15%.

Scheme 3.1.2: Synthesis of (-)-δ-araneosene by Mehta *et al*.[125,126,127]

In the following decades, there have been many new advances in the total synthesis of dolabellane diterpenoids. The latest review was reported by Hiersemann *et al*. in 2005[124] which covers different macrocyclisation strategies towards the construction of the eleven-membered ring of dolabellane diterpenoids,

including intramolecular sulfone alkylation,[128,129] intramolecular Horner-Wadsworth-Emmons (HWE) olefination,[130] ring-closing pinacol coupling[123] and intramolecular Julia condensation.[131] This introduction will not cover those examples discussed in the review of Hiersemann *et al*., but will aim to present the total syntheses of dolabellane diterpenoids published since 2005.

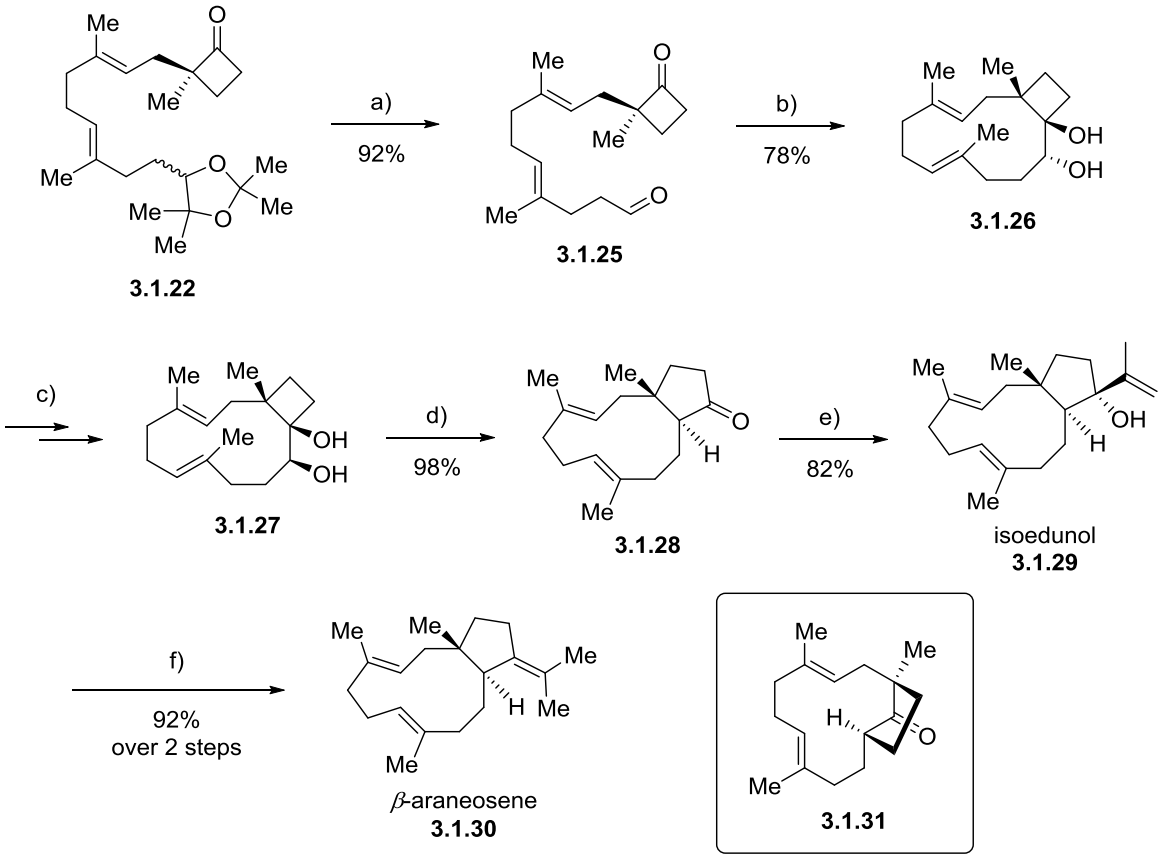
More recently in 2005, Corey *et al*. reported the enantioselective total syntheses of isoedunol **3.1.29** and *β*-araneosene **3.1.30** (**Scheme 3.1.4**).[132] The syntheses utilised pinacol coupling and pinacol rearrangement as key steps in the construction of the *trans*-bicyclo [9.3.0] skeleton. The synthesis started from (*E*,*E*)-farnesol **3.1.17** which was converted into farnesol epoxide **3.1.18** *via* the corresponding bromohydrin (**Scheme 3.1.3**).[133] Epoxide **3.1.18** was then hydrolysed and reacted with acetone to form acetonide **3.1.19** in 80% over two steps.[132] Subsequent transformations involving mesylation, iodination and diastereoselective alkylation with the lithium enolate of dioxolanone **3.1.23** (at the less hindered face) gave acetonide **3.1.20**. Subsequent methanolysis, methylthiomethyl (MTM) ether protection and Kulinkovich reaction[92] afforded cyclopropyl carbinol **3.1.21**. In the following step, cyclopropyl carbinol **3.1.21** underwent ring expansion in the presence of Me_3Al to form cyclobutanone **3.1.22** in excellent yield. Although the enantiomeric excess of cyclobutanone **3.1.22** was not reported in the paper, Corey *et al.* mentioned that the ring expansion reaction (step e) proceeded with good stereochemical control and this was likely enabled by Me_3Al which promoted a concerted rearrangement pathway *via* intermediate **3.1.24**.



Reagents and conditions: a) i) Ac_2O, Et_3N, DMAP, DCM, 0 °C, 5 min, 99%, ii) NBS, THF/H_2O, 0 °C, 1 h, 71%, iii) K_2CO_3, MeOH, RT, 1.5 h, 97%; b) i) (1*R*)-(-)-10-camphorsulfonic acid, H_2O/MeCN, RT, 2 h, ii) (1*R*)-(-)-10-camphorsulfonic acid, acetone, RT, 3 h, 80% over 2 steps; c) i) MsCl, Et_3N, pentane/benzene, 0 °C, 1 h, ii) LiI, THF, 0 °C, 30 min, iii) dioxolanone **3.1.23**, LDA, -78 °C, 8 h, 64% over 3 steps; d) i) NaOMe, MeOH, 50 °C, 30 min, 96%, ii) Ac_2O/DMSO (1 : 1), RT, 24 h, 99%, iii) EtMgBr, $ClTi(OiPr)_3$, THF, 0 °C to RT, 48 h, 60%; e) Me_3Al, toluene/DCM, 4 °C, 72 h, 90%.

Scheme 3.1.3: Synthesis of isoedunol and *β*-araneosene by Corey *et al.* (Part One)[132,133]

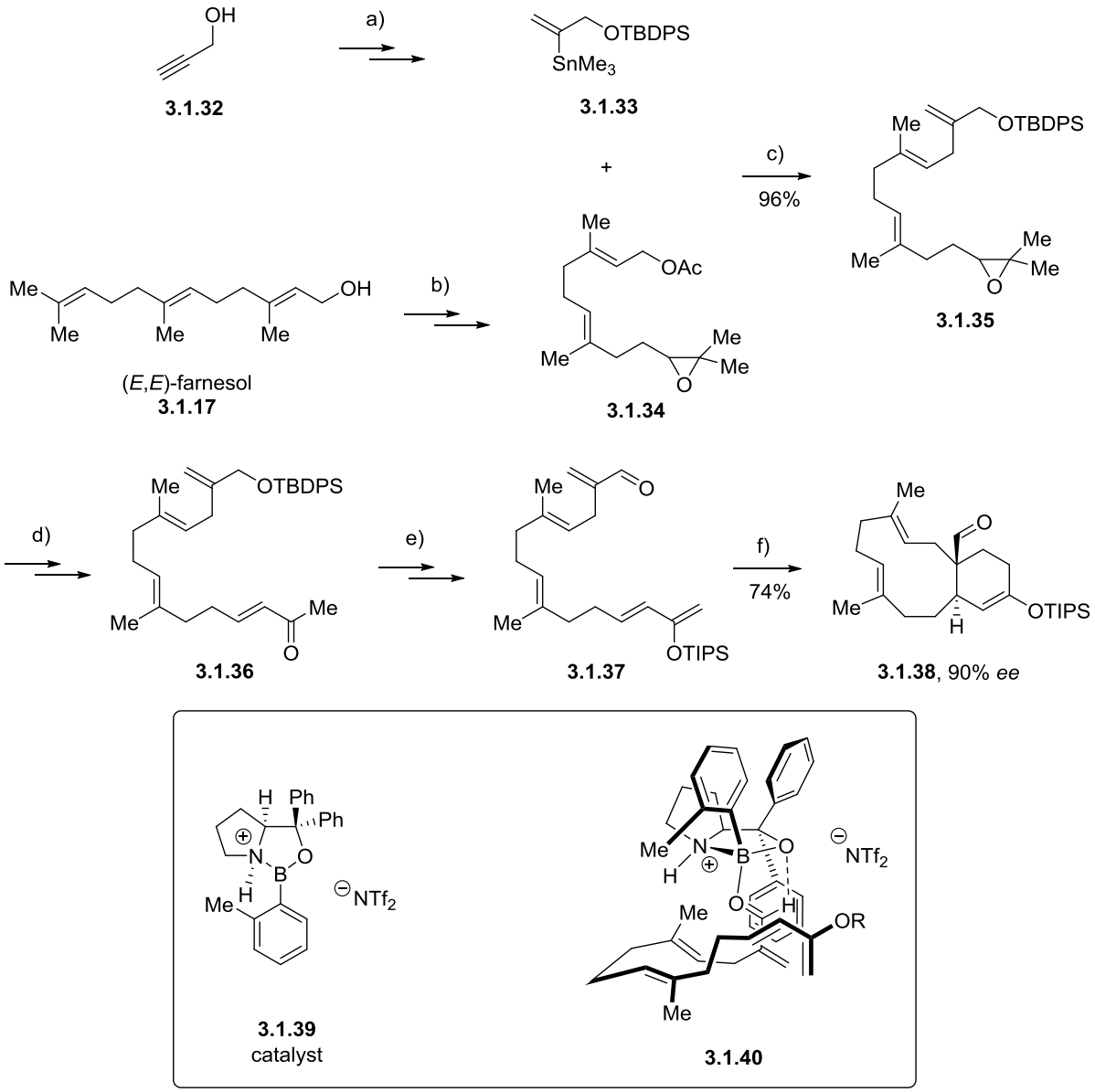
Acetonide **3.1.22** then underwent acid-hydrolysis followed by vicinal diol cleavage to form aldehyde **3.1.25** (**Scheme 3.1.4**).[132] The following step was a samarium-mediated pinacol coupling reaction which formed the macrocyclic compound **3.1.26** with a *trans*-pinacol moiety as a single diastereomer. *Trans*-pinacol **3.1.26** was subsequently converted into *cis*-pinacol **3.1.27** *via* an oxidation/reduction sequence. The next key step was a bond-selective pinacol rearrangement which proceeded smoothly to form the *trans*-bicyclo [9.3.0] skeleton **3.1.28** in near quantitative yield. Corey *et al*. explained that the *cis*-pinacol moiety is necessary for the formation of the desired product **3.1.28** as *trans*-pinacol **3.1.26** exclusively gave the bridged pentanone **3.1.31** as the pinacol rearrangement product. Corey *et al*. suggested that this is due to conformational rigidity of the twelve-membered ring in *trans*-pinacol **3.1.26** that results in a stereoelectronic preference for the migration of the exocyclic bond. Ketone **3.1.28** was then reacted with 2-lithiopropene to form the natural product, isoedunol **3.1.29**, in very good yield. Corey *et al*. explained that the good diastereo-control of the reaction was resulted from a preferred crown-like conformation of the macrocycle. Further transformations involving MOM ether formation followed by dissolving metal reduction converted isoedunol **3.1.29** into the other natural product, *β*-araneosene **3.1.30**, in excellent yield. Overall, isoedunol **3.1.29** was synthesised from (*E*,*E*)-farnesol **3.1.17** in 18 steps in 9.7% overall yield and *β*-araneosene **3.1.30** was synthesised from (*E*,*E*)-farnesol **3.1.17** in 20 steps in 8.9% overall yield.



Reagents and conditions: a) AcOH, H_2O, 55 °C, 3 h, then $NaIO_4$, RT, 30 min, 92%; b) SmI_2, THF, 67 °C, 2 h, 78%; c) i) oxalyl chloride, DMSO, Et_3N, DCM, 4 °C, 12 h, ii) $LiAlH_4$, THF, 67 °C, 5 min, 94% over 2 steps by recovering starting material; d) MsCl, Et_3N, DCM, -30 °C, 1 h, then 4 °C, 72 h, 98%; e) 2-bromopropene, *t*BuLi, Et_2O, -10 °C, 30 min, 82%; f) i) MOMCl, *i*Pr_2NEt, TBAI, THF, 67 °C, 6 h, ii) Li, NH_3, THF, -60 °C, 3 h, 92% over 2 steps.

Scheme 3.1.4: Synthesis of isoedunol and *β*-araneosene by Corey *et al.* (Part Two)[132]

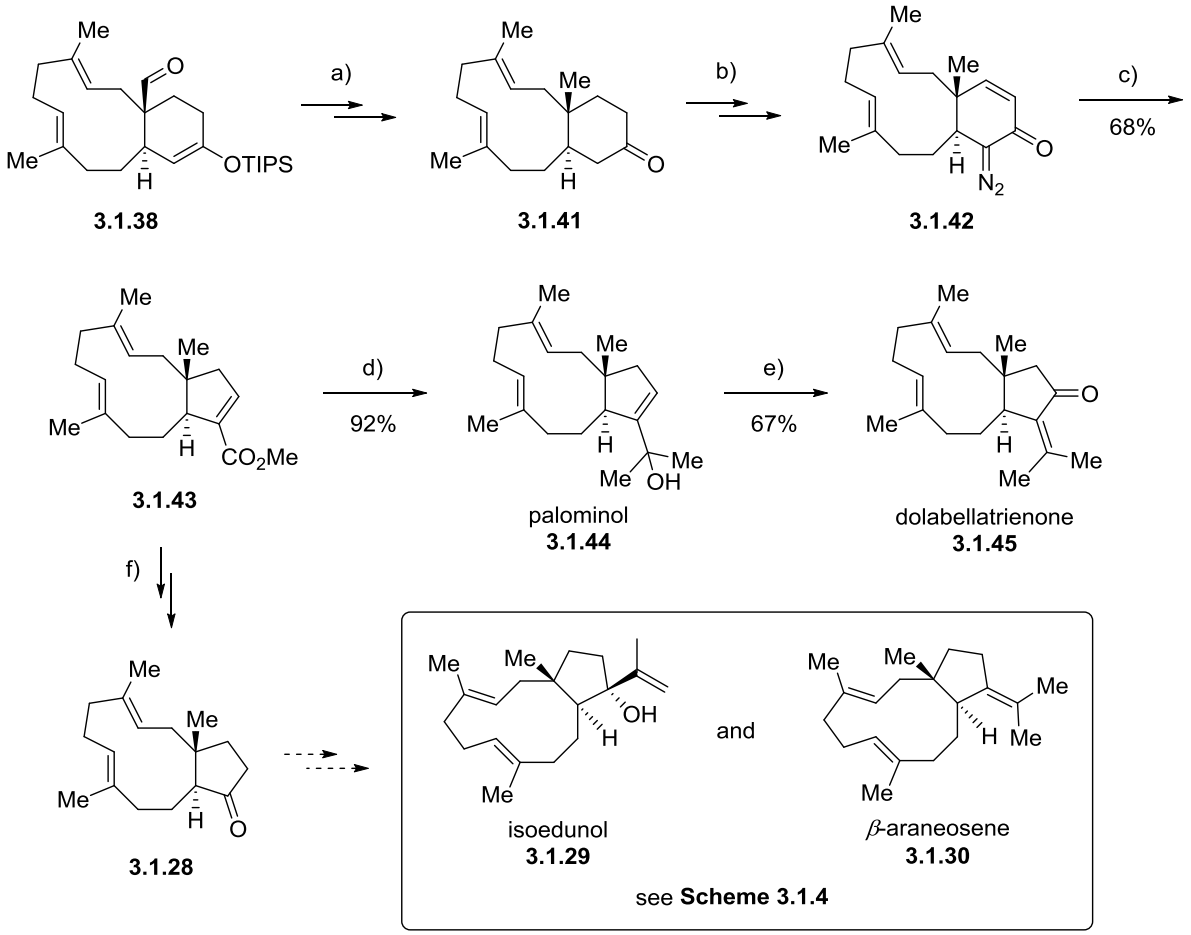
Later in 2006, Corey *et al*. reported the enantioselective total syntheses of another two dolabellane diterpenoids, palominol **3.1.44** and dolabellatrienone **3.1.45** (**Scheme 3.1.6**).[134] The synthetic strategy involved an enantioselective Diels-Alder macrocyclisation as the key step to construct the eleven-membered ring. The synthesis started with a Stille coupling reaction between building blocks **3.1.33** and **3.1.34** to afford the long carbon chain **3.1.35** (**Scheme 3.1.5**).[133] Subsequent transformations involving epoxide opening, 1,2-diol cleavage, HWE olefination, alcohol oxidation and silyl enol ether formation gave the Diels-Alder precursor, *α*,*β*-unsaturated aldehyde **3.1.37**. Corey *et al*. reported that the enantioselective Diels-Alder reaction (step f) proceeded *via* an *endo*-transition state assembly **3.1.40**. A chiral catalyst **3.1.39** was utilised which controlled the stereoselectivity of the reaction by forming a formyl hydrogen bond and *π*-*π* stacking between the dienophile and the phenyl group of catalyst **3.1.39** (see assembly **3.1.40**, **Scheme 3.1.5**). The bicyclic aldehyde **3.1.38** was formed in good yield with good *ee*.



Reagents and conditions: a) i) HBr (g), Et_4NBr, DCM, 45 °C, 2 h, 98%, ii) TBDPS-Cl, imidazole, DMF, RT, 12 h, 78%, iii) hexamethylditin, $Pd(PPh_3)_4$, *i*PrNEt$_2$, benzene, 80 °C, 3 h, 92%; b) i) Ac_2O, Et_3N, DMAP, DCM, 0 °C, 5 min, 99%, ii) NBS, THF/H_2O, 0 °C, 1 h, 71%, iii) K_2CO_3, MeOH, RT, 1.5 h, 97%, iv) Ac_2O, Et_3N, DMAP, DCM, 0 °C, 5 min, 95%; c) Pd_2dba_3, LiCl, *i*Pr$_2$NEt, *N*-methyl-2-pyrrolidone, 35 °C, 1 h, 96%; d) i) HIO_4, $NaIO_4$, THF/H_2O, RT, 45 min, 98%, ii) diethyl (2-oxopropyl)phosphonate, KO*t*Bu, THF, -20 °C, 2 h, 94%; e) i) TBAF, AcOH, THF, RT, 24 h, 94%, ii) MnO_2, DCM, RT, 24 h, 94%, iii) TIPSOTf, *i*Pr$_2$NEt, DCM, -78 °C, 3 min, 83%; f) catalyst **3.1.39**, toluene, -78 °C, 10 h, 74%.

Scheme 3.1.5: Synthesis of palominol and dolabellatrienone by Corey *et al.* (Part One)[134,133]

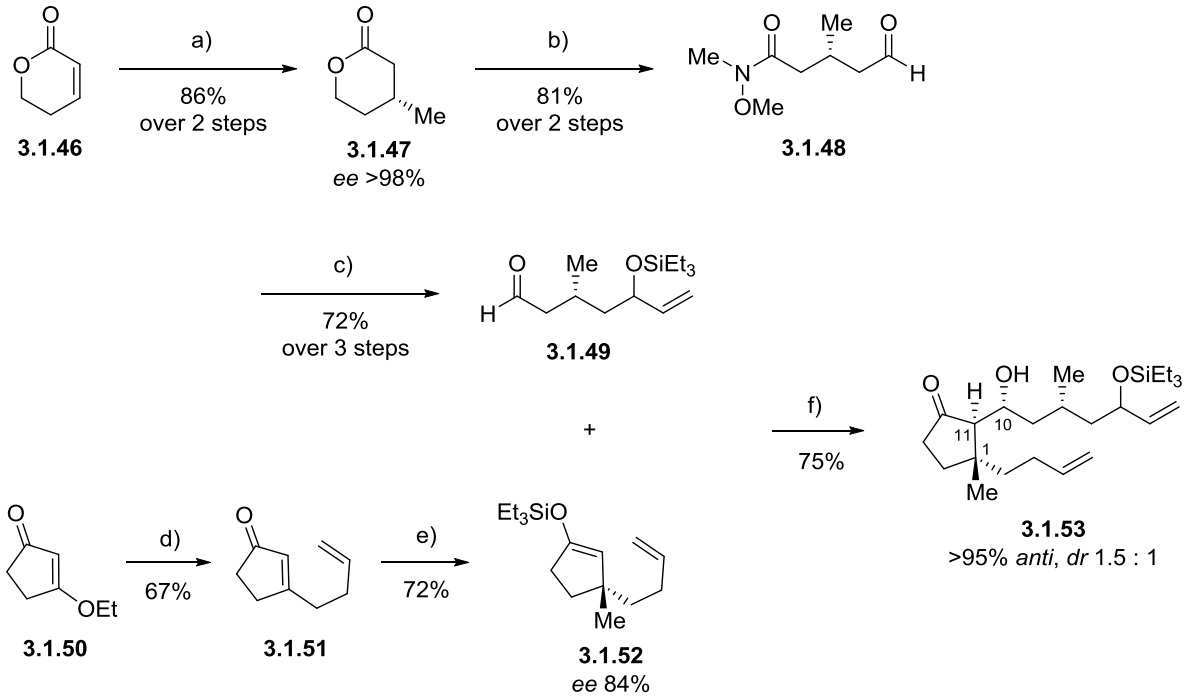
Subsequent transformations involving dithiolane formation, desulphurisation, *α*,*β*-desaturation and diazo transfer converted aldehyde **3.1.38** into the diazo compound **3.1.42** (**Scheme 3.1.6**).[134] The next key step (step c) was a photochemical Wolff rearrangement which resulted in ring contraction to form the *trans*-bicyclo [9.3.0] skeleton **3.1.43**. Ester **3.1.43** was then methylated to give the natural product, palominol **3.1.44**, in excellent yield. Finally, PDC oxidation converted palominol **3.1.44** into the other natural product, dolabellatrienone **3.1.45**, in 67% yield. Overall, palominol **3.1.44** was synthesised from (*E*,*E*)-farnesol **3.1.17** in 17 steps in 7.2% overall yield and dolabellatrienone **3.1.45** was synthesised from (*E*,*E*)-farnesol **3.1.17** in 18 steps in 4.8% overall yield. Notably, ester **3.1.43** could also be converted into ketone **3.1.28** in four steps *via* conjugate reduction, *α*-oxygenation, $LiAlH_4$ reduction and vicinal diol cleavage. As mentioned previously, ketone **3.1.28** is an intermediate compound in the synthesis of the natural products, isoedunol **3.1.29** and *β*-araneosene **3.1.30** (**Scheme 3.1.4**). Therefore, this is an efficient synthetic pathway for the preparation of four different enantioenriched dolabellane diterpenoids.

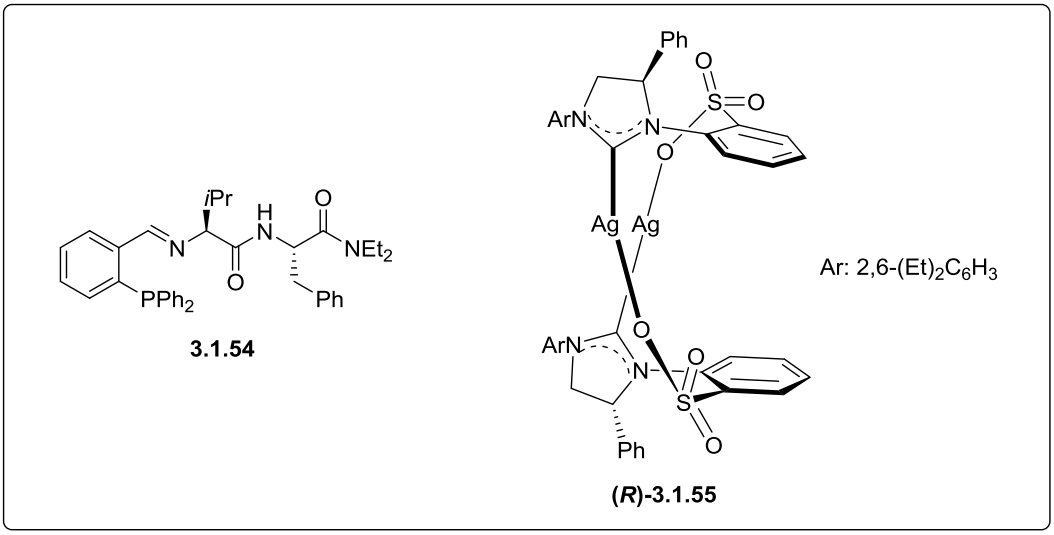


Reagents and conditions: a) i) $Me_2AlSCH_2CH_2SAlMe_2$, DCE, 60 °C, 12 h, then TBAF, THF, RT, 5 min, 71%, ii) Raney Ni, THF, RT, 10 h, 92%, b) i) NaHMDS, TMS-Cl, THF, 0 °C, 10 min, then IBX·MPO, DMSO, RT, 6 h, 79%, ii) trisyl azide, 18-Crown-6, $BnEt_3NCl$, aq. KOH/benzene, 40 °C, 48 h, 72%; c) hv, MeOH, RT, 2 h, then DBU, 115 °C, 18 h; d) MeLi, THF, -20 °C, 1 h, 92%; e) PDC, molecular sieves (4 Å), DCM, RT, 5 h, 67%; f) i) L-Selectride, THF, 0 °C, 1.5 h, 87%, ii) LDA, O_2, THF, 0 °C, 10 min, 81%, iii) $LiAlH_4$, THF, RT, 10 min, iv) $NaIO_4$, DCM, RT, 15 min, 73% over 2 steps.

Scheme 3.1.6: Synthesis of palominol and dolabellatrienone by Corey *et al.* (Part Two)[134]

Later in 2008, Hoveyda *et al*. reported the enantioselective total synthesis of (-)-clavirolide C.[135] This synthesis features two copper-catalysed asymmetric conjugate addition reactions and a ruthenium-catalysed ring closing metathesis. *α*,*β*-Unsaturated lactone **3.1.46** was firstly converted into lactone **3.1.47** in very good yield with excellent enantioselectivity *via* a copper-catalysed asymmetric conjugate addition developed in Hoveyda's group (**Scheme 3.1.7**).[136] Subsequent transformations involving formation of Weinreb amide, Swern oxidation, formation of allylic silyl ether and DIBAL-H reduction converted lactone **3.1.47** into aldehyde **3.1.49**. The enantioenriched cyclic silyl enol ether **3.1.52** was prepared from cyclopentenone **3.1.51** *via* another copper-catalysed asymmetric conjugate addition using chiral ligand **(*R*)-3.1.55**. The two fragments, aldehyde **3.1.49** and silyl enol ether **3.1.52**, were then joined together *via* a diastereoselective aldol addition to give the aldol product **3.1.53** in 75% yield with excellent (>95%) *anti*-aldol (C10-C11) selectivity.[137] However, the diastereomeric ratio (*dr*) with respect to C1-C11 was only 1.5 : 1.

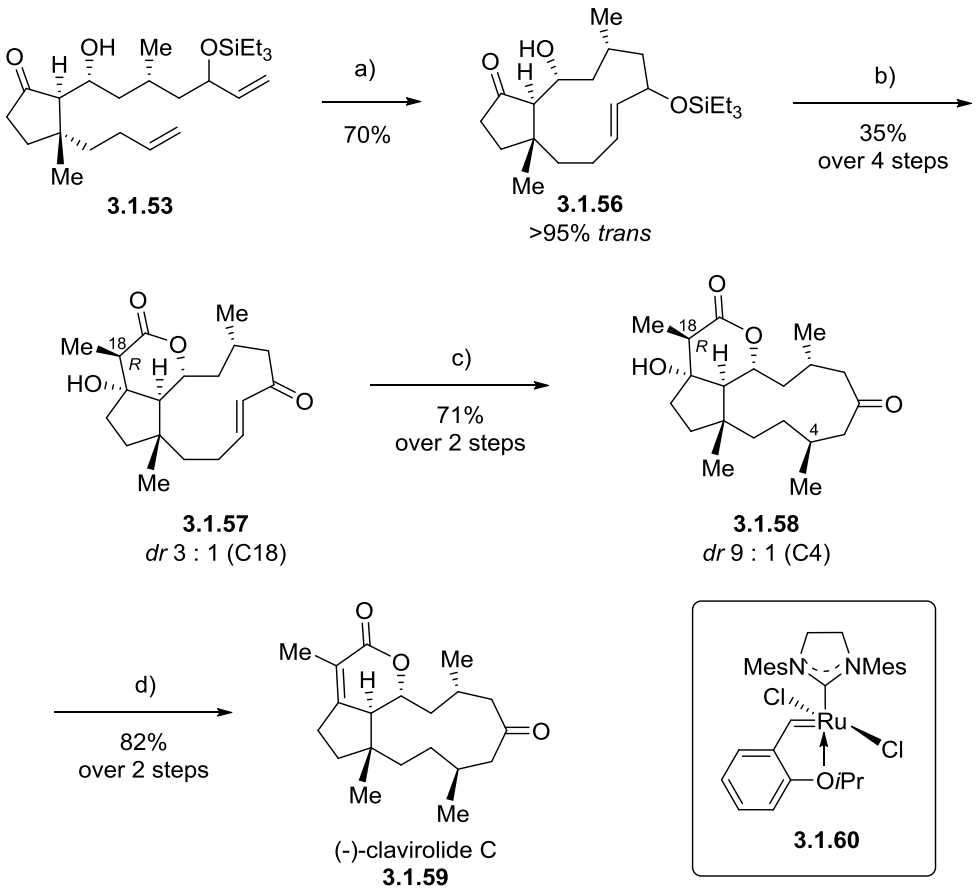




Reagents and conditions: a) i) Ligand **3.1.54**, $Cu(OTf)_2$·toluene, Me_2Zn, benzaldehyde, toluene, -15 °C, 24 h, ii) K_2CO_3, toluene, 120 °C, 2 h, 86% over 2 steps; b) i) Me(OMe)NH·HCl, *i*PrMgCl, THF, RT, 30 min, ii) oxalyl chloride, DMSO, DCM, -78 °C, 30 min, then Et_3N, RT, 30 min, 81% over 2 steps; c) i) vinylmagnesium bromide, THF, 0 °C, 5 min, ii) Et_3SiCl, imidazole, DCM, RT, 30 min, iii) DIBAL-H, THF, -78 °C, 30 min, 72% over 3 steps; d) Mg, 4-bromo-1-butene, THF, reflux, 30 min, 67%; e) ligand **(*R*)-3.1.55**, $Cu(OTf)_2$, Me_3Al, THF, -78 °C, 36 h, then Et_3SiOTf, -78 °C, 4 h, 72%; f) *n*BuLi, BEt_3, THF, -78 °C, 15 min, 75%.

Scheme 3.1.7: Synthesis of (-)-clavirolide C by Hoveyda *et al.* (Part One)[135,138]

The next key step was a catalytic ring-closing metathesis (RCM) using catalyst **3.1.60** (**Scheme 3.1.8**, step a).[135] The reaction proceeded smoothly to form the desired eleven-membered ring **3.1.56** in good yield with >95% (*E*)-alkene selectivity. Subsequent esterification, samarium iodide-mediated Reformatsky reaction, removal of silyl ether protecting group and allylic alcohol oxidation afforded lactone **3.1.57** in 35% yield over 4 steps. Hoveyda *et al*. reported that lactone **3.1.57** was formed with 3 : 1 *dr* with respect to C18*R* : C18*S*, but this is unimportant to the final product. This was followed by conjugate addition and desilylation which provided the methylated product **3.1.58** in good yield with good *dr* (9 : 1). Hoveyda *et al*. suggested that the good *dr* was achieved because firstly, enone **3.1.57** exists as two conformers in equilibrium and secondly, the conformer that leads to the desired product **3.1.58** reacts more rapidly during the conjugate addition reaction than the other conformer that forms the undesired diastereomer. Finally, mesylation followed by elimination provided the natural product, (-)-clavirolide C **3.1.59**, in 82% yield over 2 steps. Overall, (-)-clavirolide C **3.1.59** was synthesised from lactone **3.1.46** in 17 steps in 3.5% overall yield.



Reagents and conditions: a) Catalyst **3.1.60**, DCE, 83 °C, 6 h, 70%; b) i) 2-bromopropionyl bromide, pyridine, DMAP, DCM, RT, 1 h, ii) SmI_2, THF, 0 °C, 5 min, iii) (+)-camphorsulfonic acid, MeOH, 0 °C, 15 min, iv) MnO_2, Et_2O, RT, 1 h, 35% over 4 steps; c) i) MeLi, CuI, TMSCl, THF, -78 °C, 15 min, ii) HF·pyridine, THF, 0 °C, 5 min, 71% over 2 steps; d) i) MsCl, Et_3N, DCM, RT, 15 min, ii) DBU, MeOH, 55 °C, 2 h, 82% over 2 steps.

Scheme 3.1.8: Synthesis of (-)-clavirolide C by Hoveyda *et al.* (Part Two)[135]

3.1.4 Total syntheses of dolabellane diterpenoids in Burton group

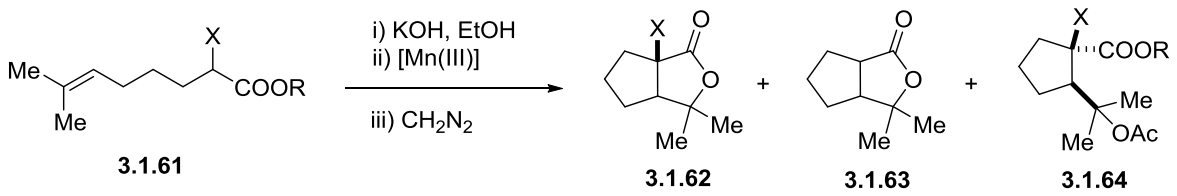
3.1.4.1 Manganese(III) acetate mediated oxidative free-radical cyclisation

As the dolabellane diterpenoids consist of a fused bicyclic system generally with contiguous quaternary and tertiary stereocenters, members of the Burton group sought to utilise the manganese(III) acetate mediated cyclisation in their syntheses.

In 1985, Fristad *et al*. reported an intramolecular *γ*-lactonisation mediated by manganese(III) acetate species.[139] Fristad *et al*. firstly converted esters **3.1.61** into the corresponding potassium carboxylate salts which were then subjected to manganese(III) mediated cyclisation using the manganese(III) complex, $[Mn_3O(OAc)_7(HOAc)]\cdot 5H_2O$ (**Scheme 3.1.9**). Diazomethane was used to esterify the products in order to simplify the purification process. Fristad *et al*. found that manganese(III) mediated cyclisation using cyanoacid **3.1.61** (X = CN) gave a mixture of *γ*-lactone **3.1.62** and monocyclised product **3.1.64** which suggested that there was competitive external trapping of the intermediate radical after the initial C-C bond formation. On the other hand, using half-acid ester **3.1.61** (X = CO_2Me) only produced *γ*-lactone products **3.1.62** and **3.1.63**; monocyclised product **3.1.64** was not obtained. Fristad *et al*. explained that in this case, the intermediate radical could be trapped by both the ester and carboxylate groups to form products with either X = CO_2Me or CO_2H (before diazomethane treatment).

Bicyclo[4.3.0] systems **3.1.66** and **3.1.67** could also be prepared *via* the manganese(III) mediated cyclisation from carboxylates **3.1.65** (**Scheme 3.1.9**).[139] Using this type of substrates, only *γ*-lactone products **3.1.66** and **3.1.67** were produced; monocyclised products were not formed. While cyanoacid **3.1.65** (X = CN) only led to the *cis*-fused *γ*-lactone **3.1.66**, half-acid ester **3.1.65** (X = CO_2Me) led to a mixture of *cis*- and *trans*-fused *γ*-lactones **3.1.66**; the *cis* : *trans* ratio is temperature-dependent.

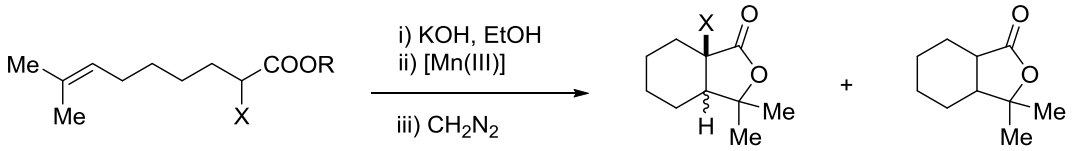
bicyclo[3.3.0] system synthesis:



3.1.61 **3.1.62** **3.1.63** **3.1.64**

step ii)					
				Yield	
X	R	T/°C	**3.1.62**	**3.1.63**	**3.1.64**
CN	Et	RT	14%	-	7%
CO_2Me	Me	RT	41%	3%	-

bicyclo[4.3.0] system synthesis:

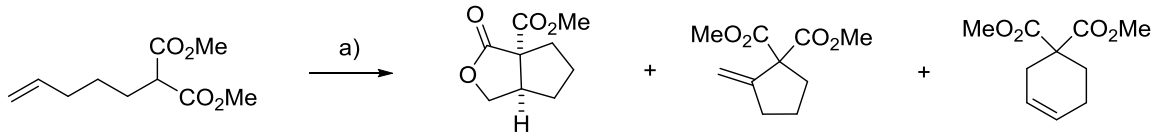


3.1.65 **3.1.66** **3.1.67**

step ii)				
			Yield	
X	R	T/°C	**3.1.66**	**3.1.67**
CN	Et	RT	20% (cis)	-
CO_2Me	Me	RT	40% (cis : trans, 1 : 1)	12%
CO_2Me	Me	70	48% (cis : trans, 4 : 1)	8%

Scheme 3.1.9: Intramolecular free-radical cyclisation mediated by manganese (III) complex by Fristad *et al*.[139]

Later In 1991, Snider *et al*. reported a free-radical cyclisation reaction of dimethyl 4-pentenylmalonate **3.1.68** using manganese(III) acetate and copper(II) acetate in acetic acid which gave a mixture of cyclised products (**Scheme 3.1.10**).[140]

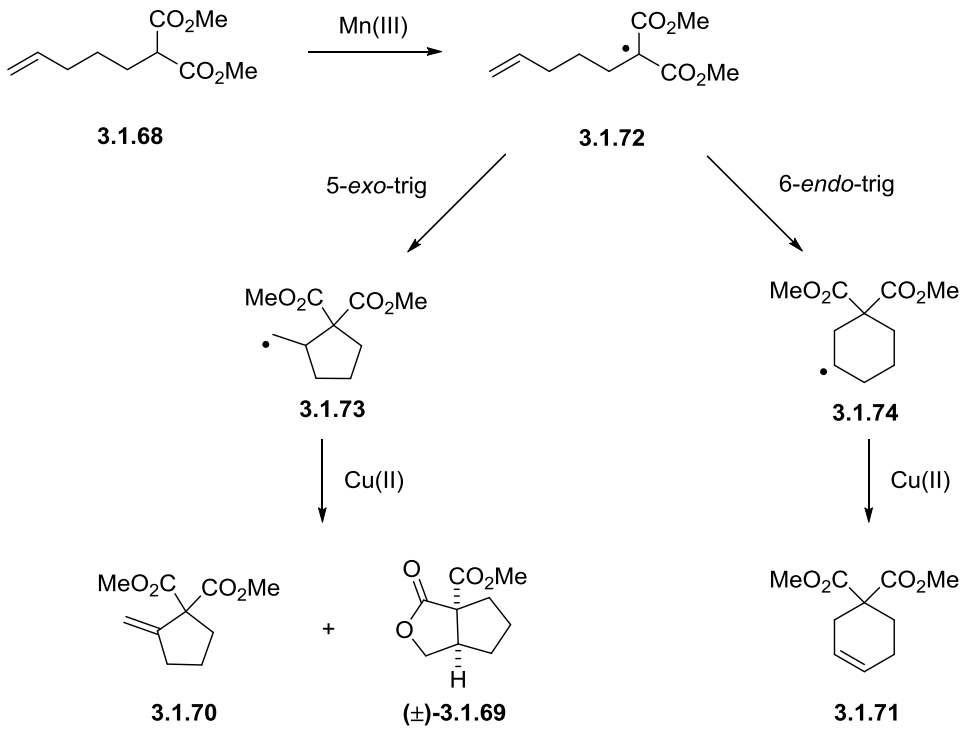


3.1.68 **(±)-3.1.69**, 48% **3.1.70**, 20% **3.1.71**, 7%

Reagents and conditions: a) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OAc)_2 \cdot H_2O$ (1 eq.), AcOH, 55 °C.

Scheme 3.1.10: Manganese(III) acetate mediated oxidative free-radical cyclisation of dimethyl 4-pentenylmalonate 3.1.68 by Snider *et al*.[140]

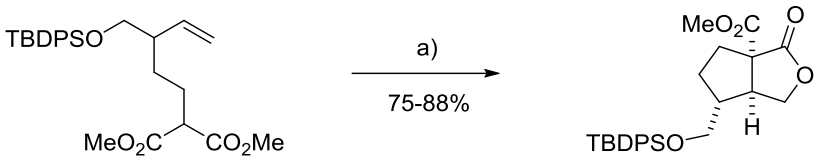
Snider *et al*. proposed that malonate **3.1.68** was firstly oxidised by manganese(III) acetate to form radical **3.1.72** which then underwent either a 5-*exo*-trig or 6-*endo*-trig cyclisation to form cyclopentanemethyl radical **3.1.73** or cyclohexyl radical **3.1.74** respectively (**Scheme 3.1.11**). Cyclopentanemethyl radical **3.1.73** was then oxidised by copper(II) acetate to form an organocopper(III) complex which could either undergo a *β*-hydride elimination to form alkene **3.1.70** or cyclise onto the proximal ester to form the bicyclic *γ*-lactone **(±)-3.1.69**. Cyclohexene **3.1.71** was formed by the oxidation of cyclohexyl radical **3.1.74** by copper(II) acetate followed by *β*-hydride elimination.



Scheme 3.1.11: Proposed mechanism of manganese(III) acetate mediated radical cyclisation by Snider *et al*.[140]

Thus, manganese(III) acetate mediated radical cyclisation is a convenient method to prepare [3.3.0] bicyclic systems, such as *γ*-lactone **(±)-3.1.69**, which are useful intermediates for the synthesis of natural products as they consist of adjacent tertiary and quaternary stereocenters as well as carbonyl moieties which can be converted into other functionalities.

In recent years, Burton *et al*. have further optimised the conditions and expanded the substrate scope for the manganese(III) acetate mediated cyclisation.[141] One example, which is relevant to this project, is the cyclisation of malonate **(±)-3.1.75** to form the [3.3.0] bicyclic *γ*-lactone **(±)-1.5** in good yield with good diastereoselectivity (**Scheme 3.1.12**).[142]

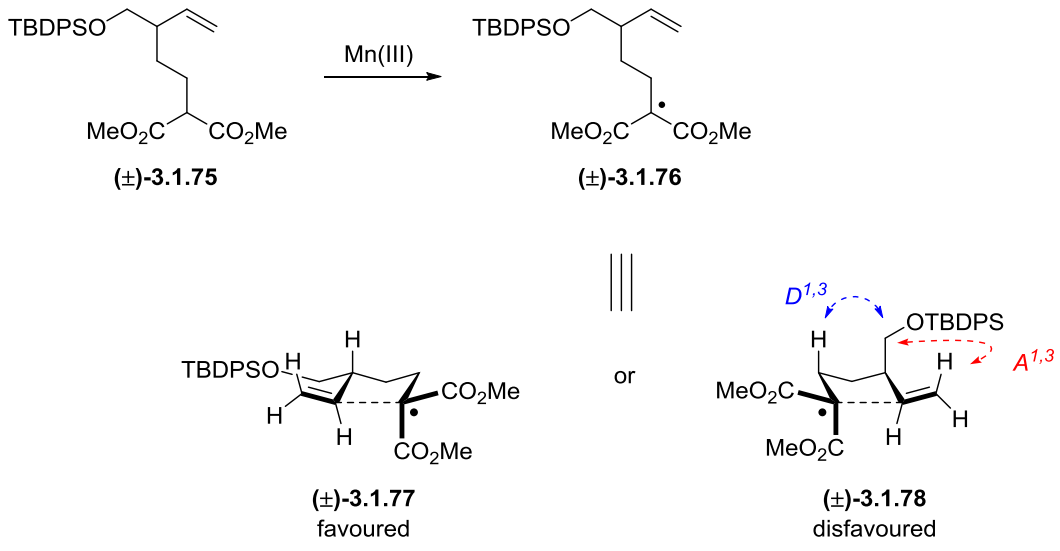


(±)-3.1.75 dr >13 : 1 **(±)-1.5**

Reagents and conditions: a) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 2 h.

Scheme 3.1.12: Synthesis of *γ*-lactone (±)-1.5 *via* manganese(III) acetate mediated radical cyclisation[142]

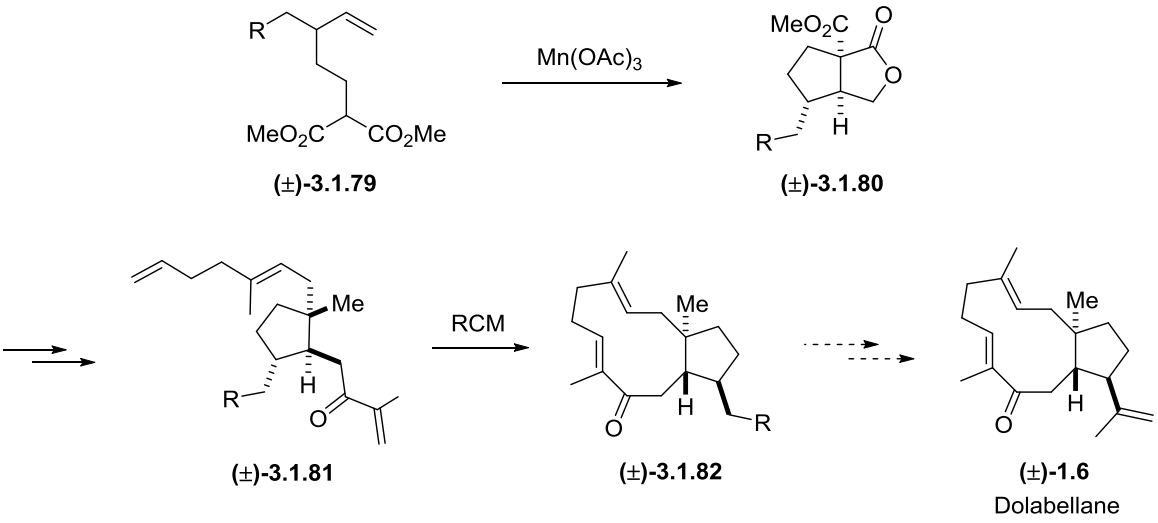
Burton *et al*. proposed that the good diastereoselectivity of the reaction above arises from a chair-like transition state which is in agreement with the Beckwith-Houk model for 5-*exo*-trig radical cyclisation reactions.[143,144] It was postulated that the pre-transition state assembly **(±)-3.1.77** is preferred as it places the $TBDPSOCH_2$ substituent in a *pseudo*-equatorial position and thus, minimises the 1,3-diaxial ($D^{1,3}$) and 1,3-allylic strain ($A^{1,3}$) present in the transition state **(±)-3.1.78** (**Scheme 3.1.13**).



Scheme 3.1.13: Comparison of the two chair-like pre-transition state assemblies in the manganese(III) acetate mediated cyclisation of malonate (±)-3.1.75

3.1.4.2 Towards the total synthesis of dolabellane ***(±)-1.6*** *by Lua*

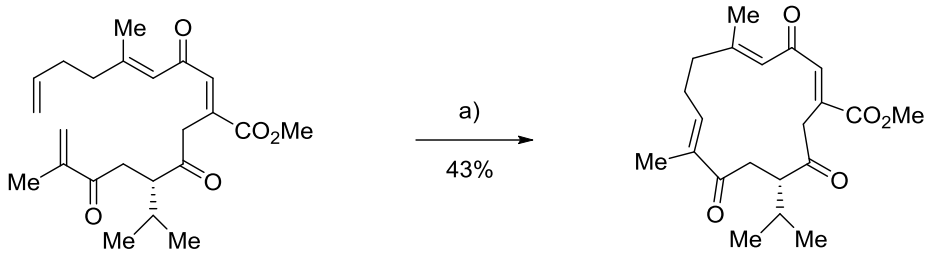
As bicyclic systems with adjacent tertiary and quaternary stereocenters can be conveniently prepared with good diastereoselectivities by the manganese(III) acetate mediated radical cyclisation, members of the Burton group have utilised this methodology in the formal synthesis of a racemic dolabellane diterpenoid **(±)-1.6** to construct the three stereocenters of the natural product (malonate **(±)-3.1.79** -> *γ*-lactone **(±)-3.1.80**, **Scheme 3.1.14**). Another key step utilised in this synthesis was the ring closing metathesis (RCM) for the construction of the eleven-membered ring (enone **(±)-3.1.81** -> enone **(±)-3.1.82**); the full route to compound **3.1.82** with different R groups will be discussed below.



Scheme 3.1.14: Synthetic strategy towards the racemic dolabellane diterpenoid (±)-1.6

The RCM was chosen to construct the eleven-membered ring because it is commonly used in syntheses of natural products containing medium and large rings.[145] Of particular interest to this project was the total synthesis of methyl sarcophytoate by Nakata *et al*. in 2009.[146] The macrocycle **3.1.84** is a fragment of methyl sarcophytoate which was prepared from enone **3.1.83** *via* RCM (**Scheme**

3.1.15). The RCM reaction was carried out with stoichiometric amount of Grubbs catalyst (2nd generation) in toluene at 100 °C to afford macrocycle **3.1.84** as exclusively the (*E*)-alkene in moderate yield without formation of dimers. Similar to macrocycle **3.1.84**, our target of interest, dolabellane **(±)-1.6**, also contains an *α*,*β*-unsaturated ketone with the alkene having an *E* geometry. Therefore, a RCM could be applied to construct the eleven-membered ring in dolabellane **(±)-1.6**.

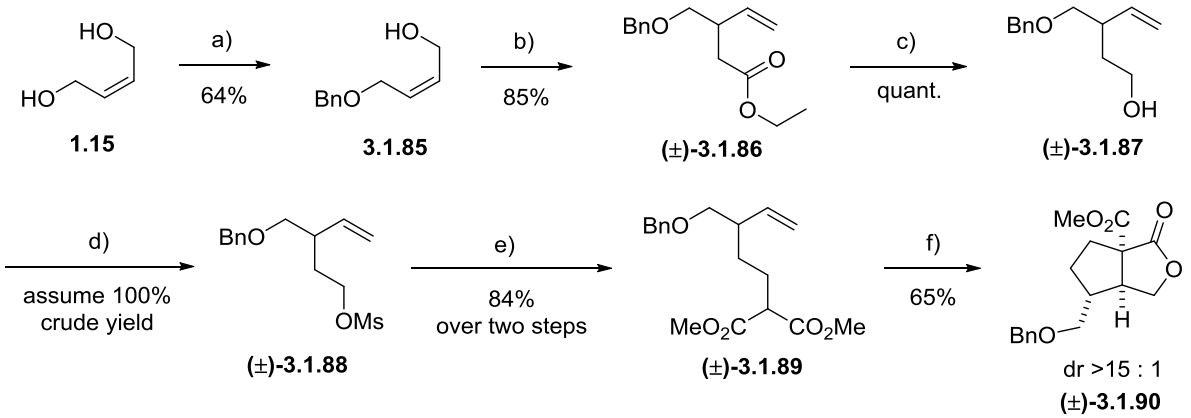


3.1.83 **3.1.84**

Reagents and conditions: a) Grubbs catalyst (2nd generation) (1 eq.), toluene, 100 °C, 0.5 h.

Scheme 3.1.15: Synthesis of macrocycle 3.1.84 *via* RCM by Nakata *et al*.[146]

In 2012, Lua began the investigation of the total synthesis of dolabellane **(±)-1.6** which features two key steps – manganese(III) acetate mediated radical cyclisation (to generate the desired diastereomer) and RCM (to construct the eleven-membered ring) (**Scheme 3.1.16**).[147] The synthesis began with diol **1.15** which underwent mono-benzylation (step a), Johnson-Claisen rearrangement (step b)[67] and $LiAlH_4$ reduction (step c) to form alcohol **(±)-3.1.87**. Subsequent mesylation (step d) and alkylation (step e) afforded malonate **(±)-3.1.89** which then underwent the manganese(III) acetate mediated radical cyclisation to form the bicyclic *γ*-lactone **(±)-3.1.90** in moderate yield with very good diastereoselectivity.

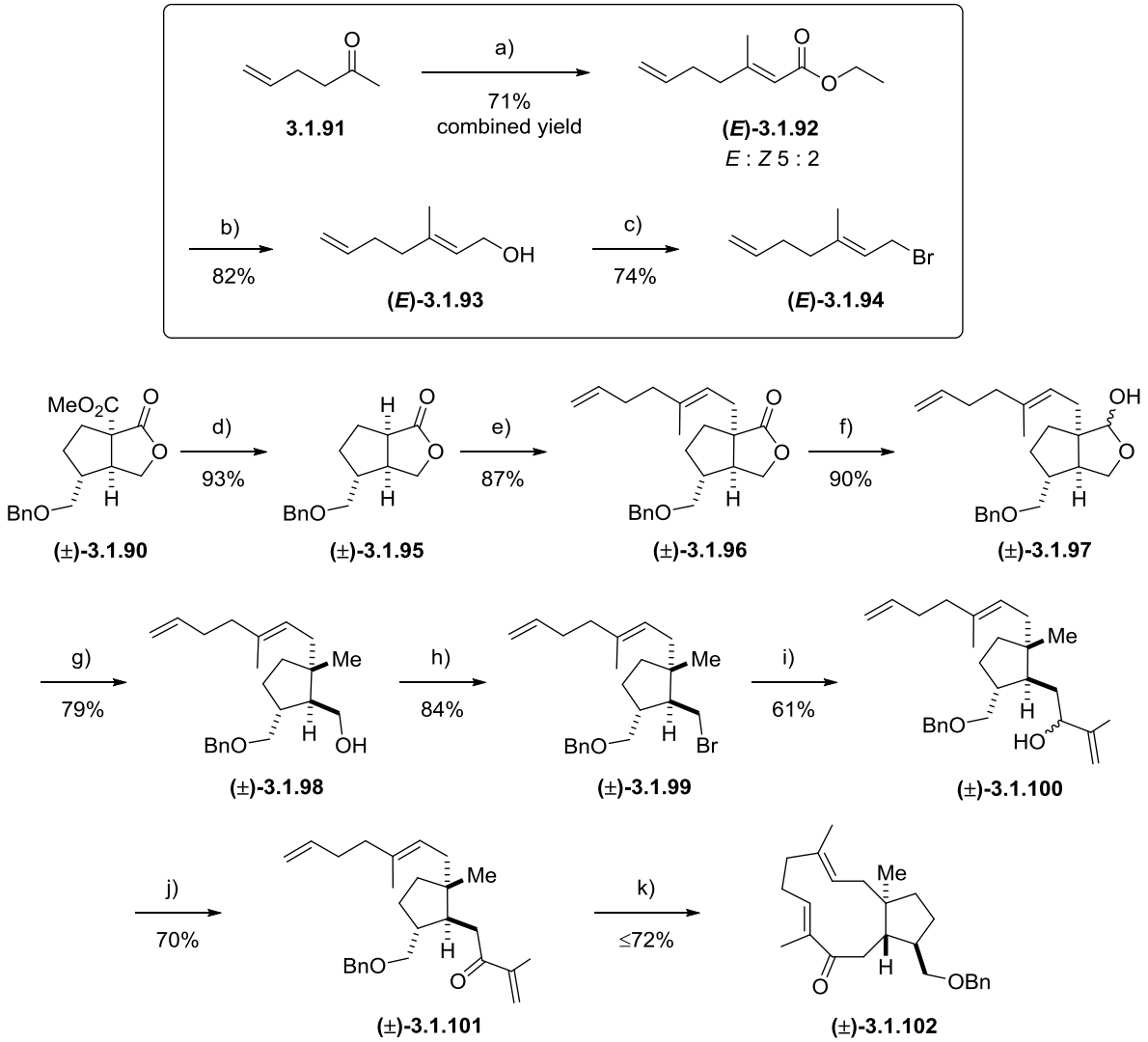


Reagents and conditions: a) NaH, BnBr, tetrabutylammonium iodide, DMF, RT, 45 min; b) triethyl orthoacetate, propionic acid, *p*-xylene 180 °C, 4 h; c) $LiAlH_4$, Et_2O, RT, 1 h; d) Et_3N, MsCl, DCM, RT, 1.5 h; e) NaH, dimethyl malonate, KI, DMF/THF, 80 °C, 21 h; f) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, argon, 80 °C, 2.5 h.

Scheme 3.1.16: Synthesis of the bicyclic *γ*-lactone (±)-3.1.90 by Lua[147]

γ-Lactone **(±)-3.1.90** was then subjected to Krapcho decarboxylation (step d)[87] and the resulting *γ*-lactone **(±)-3.1.95** was reacted with allylic bromide **(*E*)-3.1.94** to give the *γ*-lactone **(±)-3.1.96** with a long carbon chain (**Scheme 3.1.17**). Subsequent transformations, including DIBAL-H reduction (step f), Wolff-Kishner reduction (step g)[148,92] and bromination (step h), afforded bromide **(±)-3.1.99** which was then reacted with methacrolein (step i) followed by IBX oxidation (step j) to form the RCM precursor **(±)-3.1.101**. Lua attempted the RCM reaction following the conditions reported by Nakata *et al*. - stoichiometric amount of Grubbs catalyst (2nd generation) in toluene at 100 °C as mentioned earlier.[146] Due to time constraints, Lua could not obtain a pure sample of enone **(±)-3.1.102** and thus, its actual yield was not determined. Nevertheless, Lua reported that the molecular weight of enone **(±)-3.1.102** was found in HRMS and there was also a good overlap between the chemical shifts of the alkene protons of enone

(±)-3.1.102 and those of the natural product, dolabellane **1.6**, in their ^{1}H NMR spectra.[147,2]

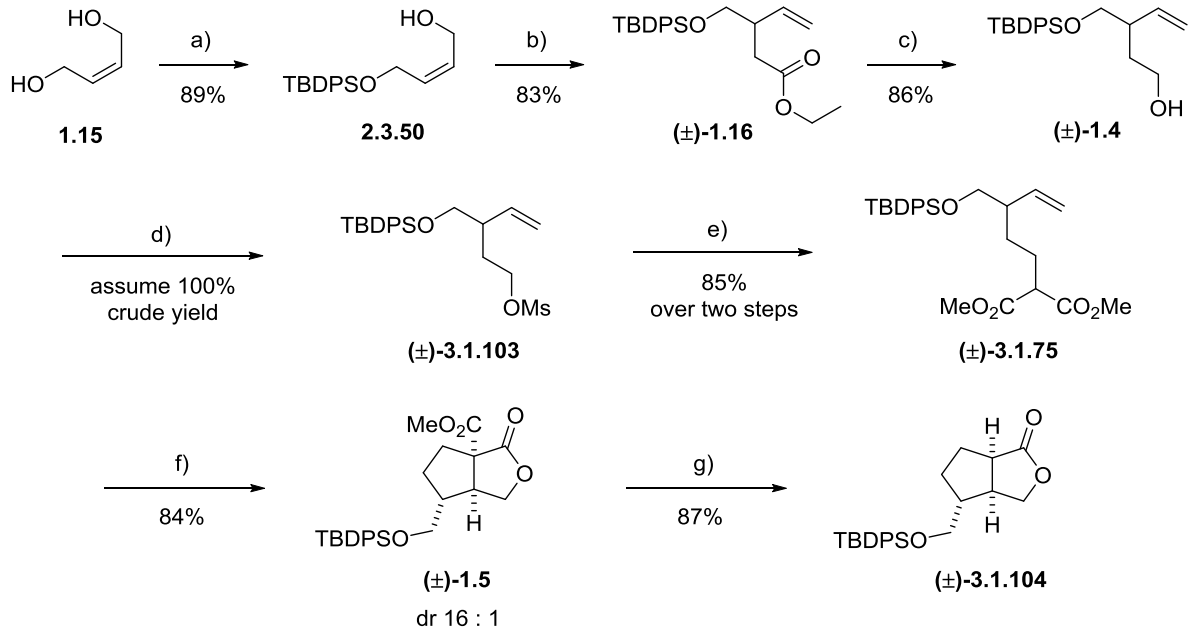


Reagents and conditions: a) NaH, trimethyl phosphonoacetate, THF, 70 °C, 15 h; b) DIBAL-H, hexane, 0 °C, 1 h; c) i) Et_3N, MsCl, THF, 0 °C, 2 h, ii) LiBr, THF, 0 °C, 1 h; d) LiCl, H_2O, DMF, 150 °C, 2 h; e) bromide **(*E*)-3.1.94**, LiHMDS, THF, -20 °C, 1.5 h; f) DIBAL-H, DCM, -60 °C, 3 h; g) hydrazine monohydrate, KOH, diethylene glycol, 180 °C, 4 h; h) i) Et_3N, MsCl, THF, 0 °C, 2 h, ii) LiBr, THF, 0 °C, 1 h; i) *t*BuLi, methacrolein, THF, -78 °C, 2 h; j) IBX, DMSO/THF, RT, 5 h; k) Grubbs catalyst (2nd generation), toluene, 100 °C, 0.5 h.

Scheme 3.1.17: Synthesis of [9.3.0] bicyclic ketone (±)-3.1.102 by Lua[147]

3.1.4.3 Towards the total synthesis of dolabellane ***(±)-1.6*** *by Ferrara*

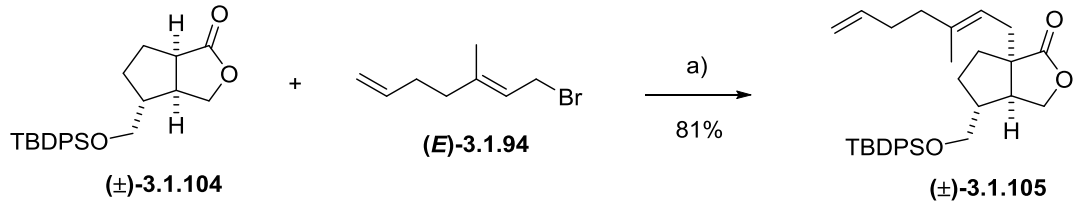
In Lua's synthesis of dolabellane **(±)-1.6**, the manganese(III) acetate mediated radical cyclisation reaction only gave a moderate yield of 65% (**Section 3.1.4.2**, **Scheme 3.1.16**, page 139).[147] Thus, in 2013, Ferrara re-explored the synthesis of dolabellane **(±)-1.6** by using a *tert*-butyldiphenyl silyl ether protecting group in place of the benzyl ether protecting group employed in Lua's synthesis (**Scheme 3.1.18**).[3] Ferrara's synthetic strategy was similar to Lua's during the early stages; diol **1.15** underwent mono-silylation (step a), Johnson-Claisen rearrangement (step b),[67] $LiAlH_4$ reduction (step c), mesylation (step d) and alkylation (step e) to form malonate **(±)-3.1.75** which then underwent the manganese(III) acetate mediated radical cyclisation to form the bicyclic *γ*-lactone **(±)-1.5** in very good yield with very good diastereoselectivity.



Reagents and conditions: a) TBDPSCl, DIPEA, DMF, RT, 1 h; b) triethyl orthoacetate, propionic acid, 138 °C, 18 h; c) $LiAlH_4$, Et_2O, 0 °C, 30 min; d) Et_3N, MsCl, DCM, RT, 1.5 h; e) NaH, dimethyl malonate, DMF/THF, 80 °C, 2 h; f) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, argon, 80 °C, 3 h; g) LiCl, H_2O, DMF, 150 °C, 2 h.

Scheme 3.1.18: Synthesis of the bicyclic *γ*-lactone (±)-3.1.104 by Ferrara[3]

Ferrara prepared the allylic bromide side chain **(*E*)-3.1.94** following Lua's synthetic route (**Scheme 3.1.17**, page 140) and reacted it with *γ*-lactone **(±)-3.1.104** to give *γ*-lactone **(±)-3.1.105** in very good yield (**Scheme 3.1.19**).[3]

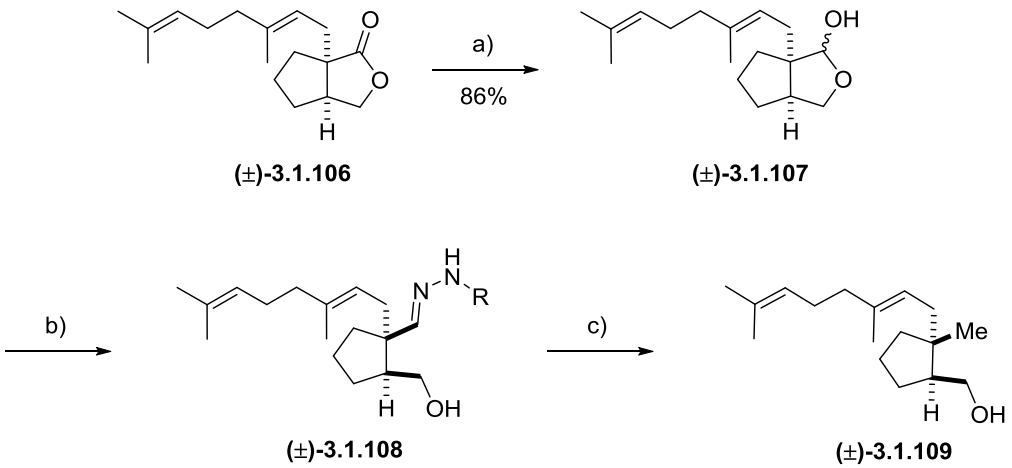


Reagents and conditions: a) LiHMDS, THF, -78 °C, 2.5 h.

Scheme 3.1.19: Synthesis of *γ*-lactone (±)-3.1.105 by Ferrara[3]

In Lua's synthesis (**Scheme 3.1.17**, page 140), *γ*-lactone **(±)-3.1.96** was then reduced to lactol **(±)-3.1.97** which underwent Wolff-Kishner reduction to form alkane **(±)-3.1.98**.[147] As the standard Wolff-Kishner reduction involves the use of strong

base under elevated temperature, the same reaction conditions are not suitable for Ferrara's target molecule because the silyl ether protecting group would be cleaved. Therefore, Ferrara attempted a two-step Wolff-Kishner reduction using milder conditions on a model system **(±)-3.1.107** (**Table 3.1.1**).[3] Following literature precedence, Ferrara attempted two Wolff-Kishner conditions to reduce lactol **(±)-3.1.107** to alkane **(±)-3.1.109** *via* the formation of hydrazone **(±)-3.1.108** (**Table 3.1.1**). In the first attempt, lactol **(±)-3.1.107** was subjected to hydrazine monohydrate in refluxing ethanol to form hydrazone **(±)-3.1.108** (R = H) which was observed in LRMS (entry 1).[149,150] Unfortunately, subjecting hydrazone **(±)-3.1.108** (R = H) to potassium *tert*-butoxide in DMSO at RT only gave a trace amount of alkane **(±)-3.1.109**. Ferrara attributed the low yield to possible dimerisation of hydrazone **(±)-3.1.108** (R = H) to the corresponding azine.[151] In order to prevent hydrazone dimerisation, Ferrara then tried a modified hydrazine derivative, 1,2-bis(*tert*-butyldimethylsilyl)hydrazine, which led to the formation of silylhydrazone **(±)-3.1.108** (R = TBDMS) (entry 2).[152] This type of silylhydrazone was more stable and could be isolated and purified. However, upon treatment with potassium *tert*-butoxide, a trace amount of alkane **(±)-3.1.109** was obtained again.



(±)-3.1.106 **(±)-3.1.107** **(±)-3.1.108** **(±)-3.1.109**

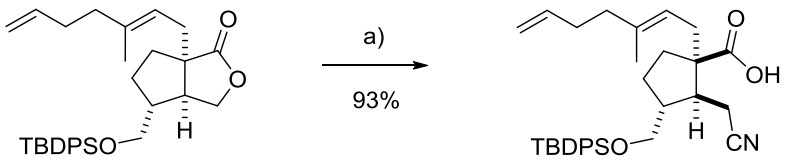
Reagents and conditions: a) DIBAL-H, DCM, -78 °C, 1 h; b) see **Table 3.1.1**; c) KO*t*Bu, DMSO, RT, 24 h.

Entry	Conditions (step b)	R	Yield of (±)-3.1.109 (%)
1	$N_2H_4 \cdot H_2O$, EtOH, 100 °C, 16 h	H	trace[a]
2	1,2-bis(*tert*-butyldimethylsilyl)hydrazine, cat. $Sc(OTf)_3$, 0 – 23 °C, 24 h	TBDMS	trace[a]

[a] Detected by ^{1}H NMR.

Table 3.1.1: Alternative Wolff-Kishner conditions screened by Ferrara for the synthesis of alkane (±)-3.1.109[3]

Ferrara then sought to open the lactone ring of **(±)-3.1.105** by KCN to form acid **(±)-1.17** and reduce the carboxylic acid group of acid **(±)-1.17** to a methyl group afterwards (**Scheme 3.1.20**).[3] Lactone ring-opening by KCN gave acid **(±)-1.17** in excellent yield but reduction of the carboxylic acid to a methyl group was shown to be difficult due to the presence of various functionalities in the molecule.

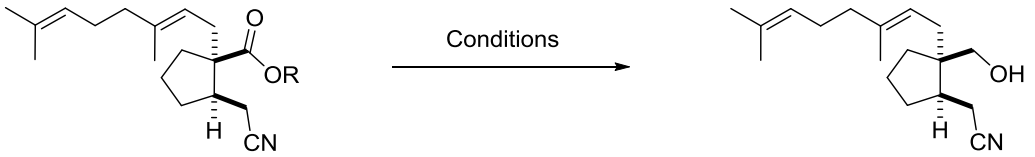


(±)-3.1.105 **(±)-1.17**

Reagents and conditions: a) KCN, DMSO, 185 °C, 1.5 h.

Scheme 3.1.20: Synthesis of acid (±)-1.17 by Ferrara[3]

Utilising a model system, Ferrara carried out a few attempts on the reduction of the carboxylic acid derivative **(±)-3.1.110** to the alcohol **(±)-3.1.111** (**Table 3.1.2**).[3] Reduction of a carboxylic acid group to a hydroxyl group using borane dimethyl sulfide complex led to decomposition of the starting material **(±)-3.1.110** due to competing hydroboration of the alkenes in the molecule (entry 1). Reduction of an ester using $LiBH_4$ gave trace amounts of alcohol **(±)-3.1.111** (entry 2) while reduction of an anhydride using $NaBH_4$ did not form alcohol **(±)-3.1.111** at all (entry 3). Ferrara postulated that those poor results are probably due to steric hindrance at the reaction center as it is next to a quaternary carbon.



(±)-3.1.110 **(±)-3.1.111**

Entry	R	Conditions	Yield (%)
1	H	$BH_3 \cdot SMe_2$, THF, 65 °C, 1 h	0
2	Me	$LiBH_4$, EtOH/THF, RT – 50 °C, 24 h	trace[a]
3	CO_2Me	$NaBH_4$, THF	0

[a] Detected by LRMS.

Table 3.1.2: Conditions screened by Ferrara for the synthesis of alcohol (±)-3.1.111[3]

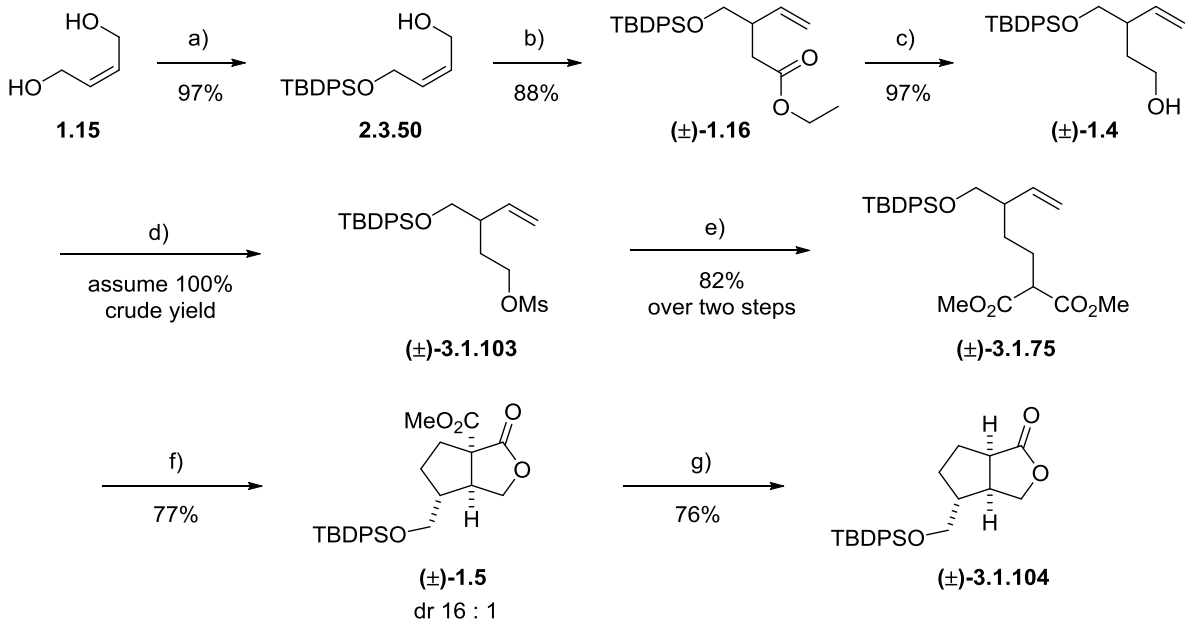
3.2 Aim

This project aims to extend Ferrara's investigation into the total synthesis of the racemic dolabellane **(±)-1.6**. The reduction of acid derivative **(±)-3.1.110** (model system) to alkane **(±)-3.1.111** will be further optimised and the conditions will then be applied to the actual system and ultimately to the preparation of the enantiopure natural product **1.6**.

3.3 Synthesis of carboxylic acid (±)-1.17

The synthesis towards carboxylic acid **(±)-1.17** was carried out following the procedures reported previously by Ferrara with a few modifications.[3,142] Instead of conducting the mono-silylation using TBDPS-Cl with DIPEA in DMF (**Scheme 3.1.18**, step a), butenediol **1.15** was mono-protected with TBDPS using NaH in THF (**Scheme 3.3.1**, step a).[89] The change of solvent simplified the purification and allylic alcohol **2.3.50** was obtained in near quantitative yield. Alcohol **2.3.50** then underwent Johnson-Claisen rearrangement[67] to form the racemic ester **(±)-1.16** in very good yield. In the next step, it was found that the silyl ether group was partially cleaved when using $LiAlH_4$ as the reducing agent. Therefore, DIBAL-H reduction[88] was carried out instead to afford alcohol **(±)-1.4** in near quantitative yield which was then converted into mesylate **(±)-3.1.103**. Mesylate **(±)-3.1.103** was unstable on column and thus, the crude was reacted with dimethyl malonate to form malonate **(±)-3.1.75** in 82% yield over two steps. The manganese-mediated cyclisation was then carried out to convert malonate **(±)-3.1.75** into the [3.3.0] bicyclic *γ*-lactone **(±)-1.5** in good yield with good diastereomeric ratio (*dr*). The

structure of *γ*-lactone **(±)-1.5** was identified by IR and ^{1}H NMR analysis. Firstly, IR spectrum shows a *γ*-lactone C=O stretch at 1777 cm^{-1} and a normal ester C=O stretch at 1743 cm^{-1}.[153] Secondly, ^{1}H NMR spectrum shows two sets of doublet of doublets around 4.49 – 4.25 ppm with ^{2}J coupling of 9.2 Hz which correspond to the diastereotopic *γ*-lactone protons (OCOC*H*$_2$).[153] A triplet of doublets is found at 2.86 ppm which corresponds to the proton (OCOCH$_2$C*H*) at the fused position of the bicyclic system. *γ*-Lactone **(±)-1.5** then underwent Krapcho decarboxylation[87] to form the decarboxylated *γ*-lactone **(±)-3.1.104** in 76% yield.

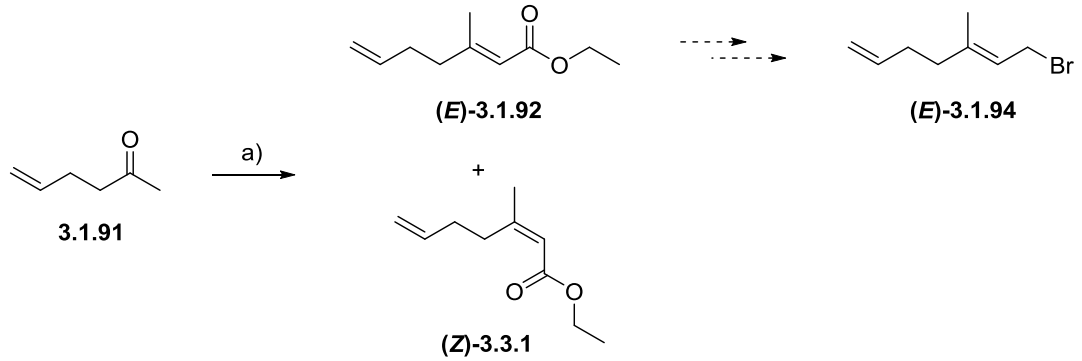


Reagents and conditions: a) NaH (1.05 eq.), TBDPS-Cl (1 eq.), THF, RT, 2 h; b) triethyl orthoacetate (7 eq.), propionic acid (0.06 eq.), 138 °C, 22 h; c) DIBAL-H (2.3 eq.), THF, -78 °C to 0 °C, 1 h; d) Et_3N (1.2 eq.), MsCl (1.2 eq.), DCM, RT, 1.5 h; e) NaH (2.4 eq.), dimethyl malonate (2.5 eq.), KI (0.5 eq.), THF, 80 °C, 9 h; f) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, argon, 80 °C, 5.5 h; g) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 2 h.

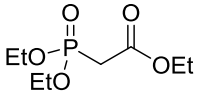
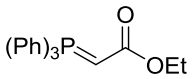
Scheme 3.3.1: Synthesis of the bicyclic *γ*-lactone (±)-3.1.104

The dienyl side chain, bromide **(*E*)-3.1.94**, was prepared from hexenone **3.1.91** *via* an *E*-selective olefination reaction (**Table 3.3.1**).[3] When using

phosphonate carbanions as the HWE reagent, the *E*/*Z* ratios could be changed by using different bases – *n*BuLi (entry 2) gave a better *E*/*Z* ratio than NaH (entry 1). Reaction using the triphenylphosphanylidene[154] reagent did not proceed with only starting material **3.1.91** present in the crude mixture (entry 3).



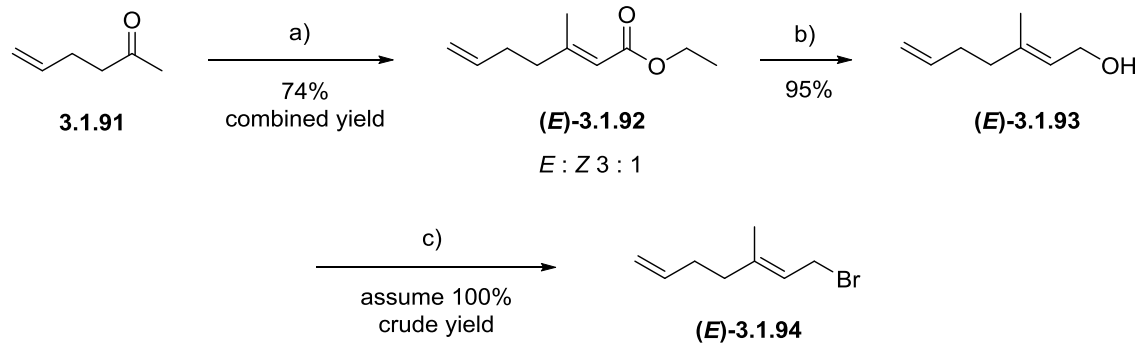
Reagents and conditions: a) Olefination reagent (1.1 eq.), base (1.2 eq.), THF, RT, 22 h.

Entry	Olefination reagent	Base	*E* : *Z* ratio[a]
1		NaH	2 : 1
2		*n*BuLi	3 : 1
3		-	-[b]

[a] Estimated from ^{1}H NMR. [b] Reaction did not proceed.

Table 3.3.1: Optimisation of conditions for the olefination reaction

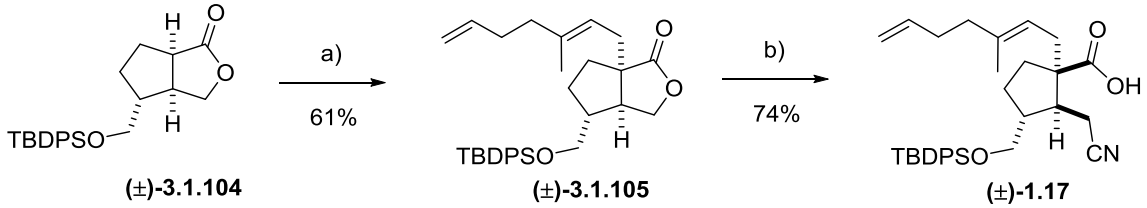
Hexenone **3.1.91** underwent HWE olefination to form the *α*,*β*-unsaturated ester **3.1.92** with an *E*/*Z* ratio of 3 to 1 (**Scheme 3.3.2**). A good *E*/*Z* combined yield of 74% was obtained. The desired *E* isomer **(*E*)-3.1.92** was then reduced to alcohol **(*E*)-3.1.93** using DIBAL-H which was subsequently converted into bromide **(*E*)-3.1.94**. As bromide **(*E*)-3.1.94** was unstable on column, the crude was used in the following step without purification.



Reagents and conditions: a) Triethyl phosphonoacetate (1.1 eq.), *n*BuLi (1.2 eq.), THF, RT, 22 h; b) DIBAL-H (2.3 eq.), THF, -78 °C to 0 °C, 1 h; c) i) Et_3N (2.1 eq.), MsCl (1.4 eq.), THF, 0 °C, 2 h, ii) LiBr (5 eq.), THF, 0 °C, 1.5 h.

Scheme 3.3.2: Synthesis of the dienyl side chain (*E*)-3.1.94

The crude bromide **(*E*)-3.1.94** was then reacted with the lithium enolate of lactone **(±)-3.1.104** to form lactone **(±)-3.1.105** with a dienyl side chain. Finally, reacting lactone **(±)-3.1.105** with KCN at elevated temperature opened the lactone ring to form acid **(±)-1.17** in good yield.[155] The structure of acid **(±)-1.17** was identified by IR and ^{13}C NMR analysis. IR spectrum shows a broad O-H (H-bonded) stretch around 2900 cm^{-1} which corresponds to the carboxylic acid group. ^{13}C NMR spectrum shows a peak at 119.0 ppm which is characteristic of a nitrile carbon.[153]

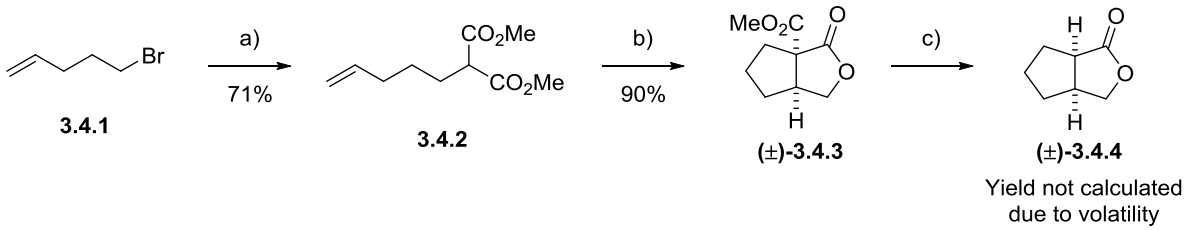


Reagents and conditions: a) Bromide **(*E*)-3.1.94** (2 eq.), LiHMDS (2 eq.), THF, -78 °C, 4 h; b) KCN (5 eq.), DMSO, 185 °C, 1.5 h.

Scheme 3.3.3: Synthesis of acid (±)-1.17

3.4 Model system synthesis

As mentioned in **Section 3.1.4.3** (pg 144), Ferrara had carried out a few attempts on reducing the carboxylic acid group in acid **(±)-1.17** to a methyl group and this step was shown to be challenging due to the presence of other functionalities in the molecule. As further optimisation of this reduction step was required, a model system, which is easier to be prepared, was synthesised in this project following the procedures reported previously in the Burton group (this is the same model system prepared by Ferrara).[3,156] Bromopentene **3.4.1** was alkylated with dimethyl malonate to form malonate **3.4.2** (**Scheme 3.4.1**). The manganese-mediated cyclisation was then carried out to convert malonate **3.4.2** into the [3.3.0] bicyclic *γ*-lactone **(±)-3.4.3** in excellent yield, which then underwent Krapcho decarboxylation to form the decarboxylated *γ*-lactone **(±)-3.4.4**. The yield of step c) was not measured at this stage because the decarboxylated *γ*-lactone **(±)-3.4.4** is highly volatile.



3.4.1 **3.4.2** **(±)-3.4.3** **(±)-3.4.4**

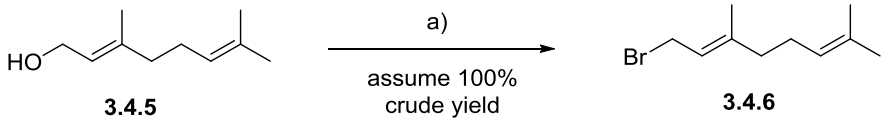
Yield not calculated due to volatility

Reagents and conditions: a) NaH (3 eq.), dimethyl malonate (3 eq.), DMF/THF, 80 °C, 2 h; b) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, argon, 80 °C, 22 h; c) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 6 h.

Scheme 3.4.1: Synthesis of model [3.3.0] bicyclic *γ*-lactone (±)-3.4.4

Geraniol **3.4.5** was chosen as the precursor for the side chain in the model system because it has similar features in comparison to the side chain in the actual

system – firstly, it consists of two *E*-alkenes and secondly, the alkenes are separated by two CH_2 units (**Scheme 3.4.2**). Furthermore, geraniol **3.4.5** is commercially available that simplifies the synthesis on the whole. Thus, geraniol **3.4.5** was reacted with phosphorus tribromide to form the geranyl bromide **3.4.6**. As bromide **3.4.6** was unstable on column, the crude was used in the following step without purification.

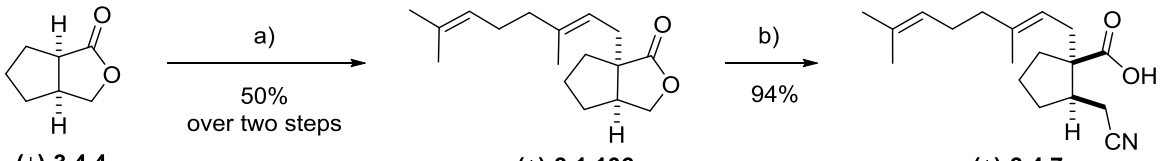


3.4.5 **3.4.6**

Reagents and conditions: a) PBr_3 (0.4 eq.), pyridine (0.1 eq.), Et_2O, 0 °C, 1 h.

Scheme 3.4.2: Synthesis of the geranyl side chain 3.4.6

The crude bromide **3.4.6** was then reacted with the lithium enolate of lactone **(±)-3.4.4** to form lactone **(±)-3.1.106** with the geranyl side chain (**Scheme 3.4.3**). Finally, reacting lactone **(±)-3.1.106** with KCN gave acid **(±)-3.4.7** in an excellent yield.[155] The model acid **(±)-3.4.7** differs from the actual system (acid **(±)-1.17**, page 149) in two ways: 1) the absence of a silyloxymethyl side chain and 2) the presence of a 1,1-dimethyl substituted alkene instead of a terminal alkene in the actual system.



(±)-3.4.4 **(±)-3.1.106** **(±)-3.4.7**

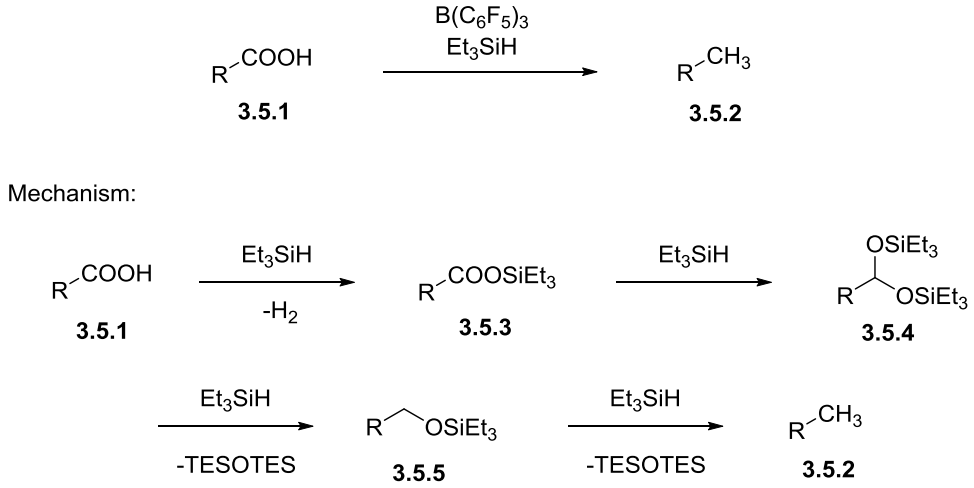
Reagents and conditions: a) Geranyl bromide **3.4.6** (2 eq.), LiHMDS (2 eq.), THF, -78 °C, 3 h; b) KCN (4 eq.), DMSO, 185 °C, 2.5 h.

Scheme 3.4.3: Synthesis of model acid (±)-3.4.7

3.5 Investigations on reduction of a carboxylic acid to a methyl group using the model system

3.5.1 One-step reduction

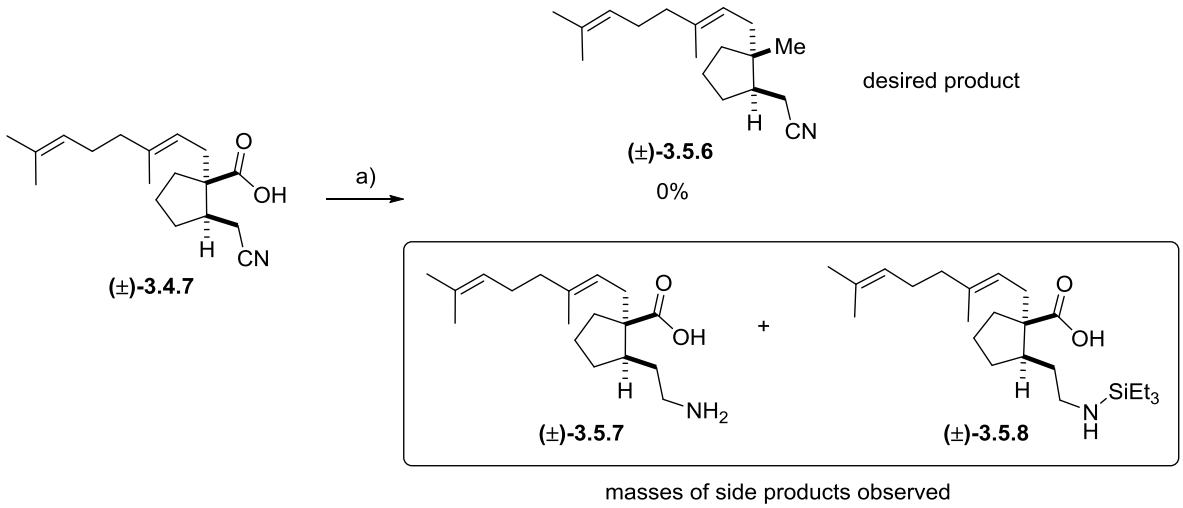
In 2001, Yamamoto *et al*. reported a Lewis acid catalysed reduction of carboxylic acids to alkanes using hydrosilanes (**Scheme 3.5.1**).[157] It was proposed that in the presence of the $B(C_6F_5)_3$ catalyst, carboxylic acid **3.5.1** reacted with 4 equivalents of Et_3SiH to form alkane **3.5.2** in a stepwise fashion. Firstly, carboxylic acid **3.5.1** reacted with one equivalent of Et_3SiH to form silyl ester **3.5.3** with hydrogen given off. Further transformations involved the formation of acetal **3.5.4** followed by silyl ether **3.5.5** which was finally reduced to alkane **3.5.2**.



Scheme 3.5.1: Proposed mechanism for the direct reduction of a carboxylic acid to a methyl group using hydrosilanes[157]

Ferrara had shown that the above reductive method did not work in the actual system **(±)-1.17**.[3] Nevertheless, it was deemed sensible to aim to optimise this reductive method in the model system **(±)-3.4.7** and then re-investigate the reduction in the actual system **(±)-1.17**. Therefore, the above method was

attempted using the model system **(±)-3.4.7** (**Scheme 3.5.2**). Unfortunately, the desired alkane **(±)-3.5.6** was not formed in the reaction. Acid **(±)-3.4.7** was converted into a mixture of highly polar side products. Although the ^{1}H NMR of the crude was too messy to identify any structures, it was clear that the CH_2CN protons disappeared which suggested that the nitrile group might have been reduced. This was further supported by LRMS results in which the masses of amine **(±)-3.5.7** (*m/z* 294.2 $[M+H]^+$) and silyl amine **(±)-3.5.8** (*m/z* 408.3 $[M+H]^+$) were both found. It could thus be concluded that the nitrile group in acid **(±)-3.4.7** was probably reduced prior to the carboxylic acid functionality under the reported reduction conditions.



Reagents and conditions: a) $B(C_6F_5)_3$ (5 mol%), Et_3SiH (6 eq.), DCM, RT, 22 h.

Scheme 3.5.2: Direct reduction of acid (±)-3.4.7 to alkane (±)-3.5.6

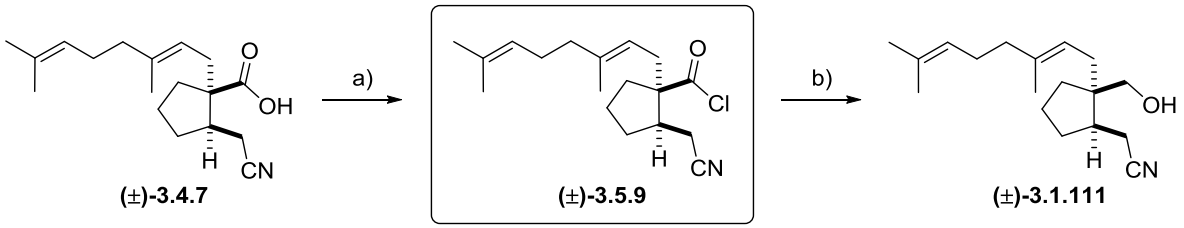
3.5.2 Multi-steps reduction

Chemoselective direct reduction of carboxylic acids to alkanes, especially in the presence of other reducible groups, is rarely found in literature. Therefore, due to the presence of various functionalities (e.g. alkene, nitrile and silyl ether groups)

in the actual system – acid **(±)-1.17**, we decided to reduce the carboxylic acid group to a methyl group in a stepwise fashion.

3.5.2.1 Reduction of a carboxylic acid to an alcohol

We started the stepwise transformation with the reduction of a carboxylic acid to a primary alcohol. Following a procedure reported by Marx *et al*.,[158] the model system, acid **(±)-3.4.7**, was firstly converted into acid chloride **(±)-3.5.9** which was then reduced to alcohol **(±)-3.1.111** in one pot (**Table 3.5.1**). It was found to be difficult to drive the reaction to completion; the starting material **(±)-3.4.7** was still present even after leaving the formation of acid chloride **(±)-3.5.9** (step a) overnight (entry 2). This is probably because of steric effects due to the substituents on the quaternary *α*-carbon which makes it difficult for the chloride anion to attack the carbonyl carbon. In addition, it was also realised that by increasing the reaction time of step a) from 6 h (entry 1) to 22 h (entry 2), although the isolated yield of the product **(±)-3.1.111** was improved, the yield by recovering starting material (in parenthesis) was actually lowered. Therefore, longer reaction times are not beneficial to the reaction, probably due to the instability of acid chlorides.



(±)-3.4.7 (±)-3.5.9 (±)-3.1.111

not isolated

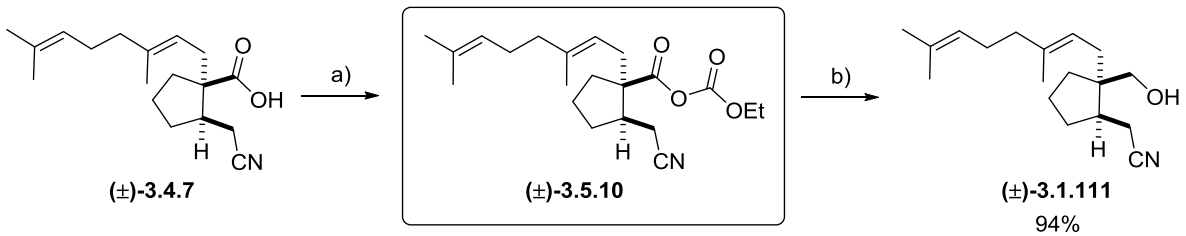
Reagents and conditions: a) Oxalyl chloride (3 eq.), DMF (2 eq.), THF, RT; b) $NaBH_4$ (2 eq.), DMF, RT, 22 h.

Entry	Time (h)[a]	Yield (%)[b]
1	6	53 (93)
2	22	70 (76)

[a] Reaction time of Step a). [b] Isolated yield of alcohol **(±)-3.1.111**; yield in parenthesis was calculated by recovering starting material.

Table 3.5.1: Reduction of a carboxylic acid to an alcohol *via* the formation of an acid chloride

In the next attempt, following the procedure reported by Mulzer *et al*.,[159] acid **(±)-3.4.7** was firstly converted into acid anhydride **(±)-3.5.10** which was then reduced by $NaBH_4$ in one-pot to form alcohol **(±)-3.1.111** (**Scheme 3.5.3**). It was surprising to see that an excellent yield of 94% was achieved with the nitrile untouched.



(±)-3.4.7 (±)-3.5.10 (±)-3.1.111

not isolated

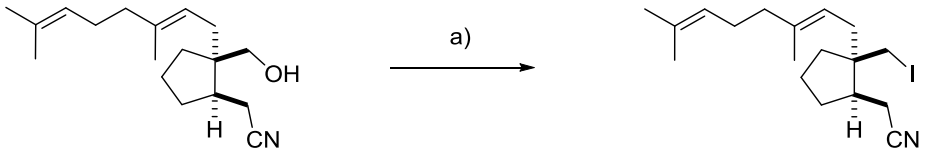
94%
one pot

Reagents and conditions: a) Ethyl chloroformate (1.1 eq.), *N*-methyl morpholine (1.1 eq.), THF, 0 °C, 6 h; b) $NaBH_4$ (3 eq.), THF/MeOH, RT, 6.5 h.

Scheme 3.5.3: Reduction of a carboxylic acid to an alcohol *via* the formation of an acid anhydride

3.5.2.2 Conversion of an alcohol to an iodide

The Appel reaction was then carried out to convert the hydroxyl group into a better leaving group, e.g. an iodide. As there are various types of solvents used in literatures for the Appel reaction,[160,161] a solvent-screening was conducted to find the optimal condition for our substrate (**Table 3.5.2**). The reaction did not proceed in DCM with 70% of the starting material **(±)-3.1.111** recovered (entry 1). Iodide **(±)-3.5.11** was successfully formed in both reactions conducted in MeCN/Et_2O and THF with the highest yield obtained from the reaction in THF (entries 2 to 3).



(±)-3.1.111 **(±)-3.5.11**

Reagents and conditions: a) I_2 (1.5 eq.), PPh_3 (2 eq.), imidazole (2 eq.), RT, 6 h.

Entry	Solvent	Yield (%)[a]
1	DCM	0[b]
2	MeCN/Et_2O	60
3	THF	80

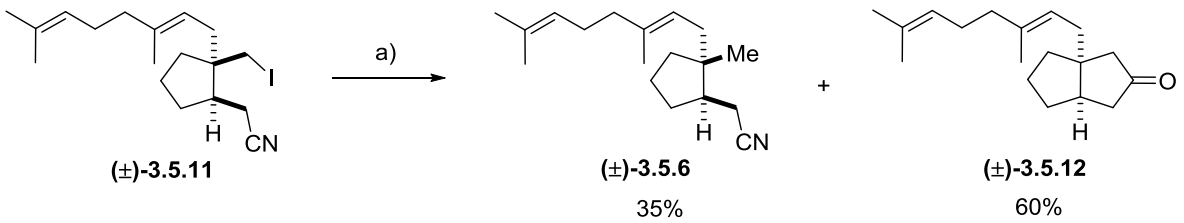
[a] Isolated yield of iodide **(±)-3.5.11**. [b] No reaction progress; 70% of the starting material was recovered.

Table 3.5.2: Solvent screen for the synthesis of iodide (±)-3.5.11

3.5.2.3 Conversion of an iodide to a methyl group

There is a variety of conditions for the conversion of alkyl iodides to the corresponding alkanes reported in the literature. We first attempted the synthesis of alkane **(±)-3.5.6** using the combination of zinc and acetic acid in Et_2O/MeOH (v/v 1:1) (**Scheme 3.5.4**).[162] The desired product **(±)-3.5.6** was only formed in 35% yield due to the formation of a major side product, the cyclic ketone **(±)-3.5.12**. The

structure of ketone **(±)-3.5.12** was identified by a C=O stretch at 1741 cm^{-1} in its IR spectrum and a *C*=O peak at 220.5 ppm in its ^{13}C NMR spectrum; the *C*≡N peak which should be around 119 ppm was also absent. The formation of ketone **(±)-3.5.12** was probably due to an intramolecular cyclisation of the alkylzinc iodide moiety (formed *via* zinc insertion)[163] onto the nitrile group nearby and the resulting imine was then hydrolysed to a ketone during aqueous work-up.



(±)-3.5.11 **(±)-3.5.6** 35% **(±)-3.5.12** 60%

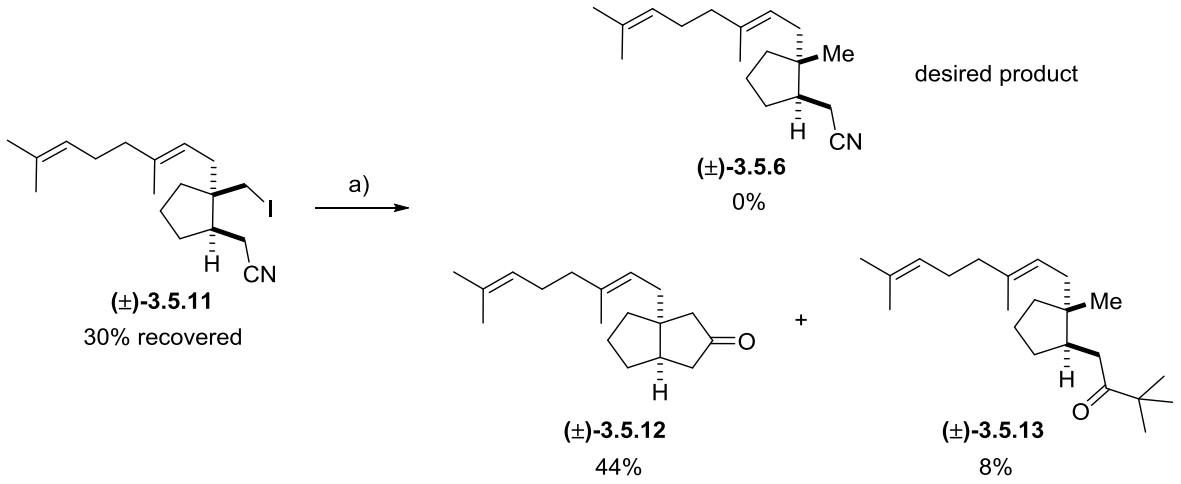
Reagents and conditions: a) Zinc (10 eq.), AcOH (2 eq.), Et_2O/MeOH (v/v 1:1), RT, 4 h.

Scheme 3.5.4: Synthesis of alkane (±)-3.5.6 using zinc and acetic acid

The reaction above was repeated using ten equivalents of acetic acid with more MeOH added (Et_2O/MeOH v/v 1:3) in order to accelerate the protonation of the alkylzinc complex before the intramolecular cyclisation took place. However, similar ratio of alkane **(±)-3.5.6** and ketone **(±)-3.5.12** was obtained.

In 1986, Bailey *et al*. reported a dehalogenation reaction *via* lithium-halogen exchange.[164] In light of this report, iodide **(±)-3.5.11** was subjected to two equivalents of *t*BuLi in the presence of MeOH as the proton source (**Scheme 3.5.5**). The reaction was carried out at -78 °C and closely monitored. It was stopped before completion as the side product, ketone **(±)-3.5.12**, was observed in large quantity again. Another side product, ketone **(±)-3.5.13**, was isolated in 8% yield which was probably formed by the nucleophilic attack of *t*BuLi on the nitrile group. The desired product **(±)-3.5.6** was not observed at all in the

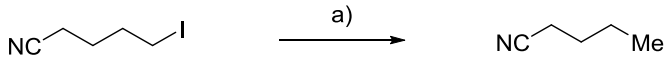
reaction. The formation of ketone **(±)-3.5.12** in these two reactions probably implies that the formation of a nucleophilic carbon species should be avoided in the reaction as it would very likely cyclise onto the nitrile group.



Reagents and conditions: a) *t*BuLi (2 eq.), MeOH (2 eq.), pentane/Et_2O (v/v 3:2), -78 °C, 1.5 h.

Scheme 3.5.5: Synthesis of alkane (±)-3.5.6 using *t*BuLi

In 1978, Hutchins *et al*. reported a reductive dehalogenation reaction using a mild reducing agent, $NaBH_4$, which reduced primary and secondary halides to the corresponding hydrocarbons.[165] 5-Iodopentanenitrile **3.5.14** is one of the examples reported in the literature which was reduced to pentanenitrile **3.5.15** in good yield with the nitrile group untouched (**Scheme 3.5.6**).



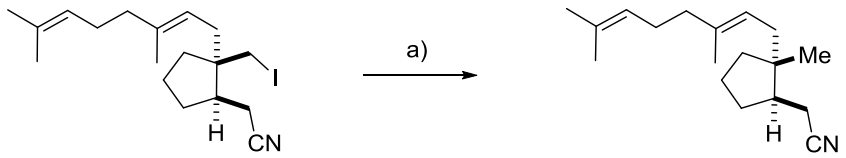
3.5.14 **3.5.15**

Reagents and conditions: a) $NaBH_4$ (6 eq.), sulfolane, 40 °C, 1 h, 70%.

Scheme 3.5.6: Reductive dehalogenation using $NaBH_4$ by Hutchins *et al*.[165]

As our substrate **(±)-3.5.11** also contains a nitrile group, the reaction conditions above were attempted. It was found that it was difficult to drive the reaction to completion in our system (**Table 3.5.3**). The reaction was very slow at

40 °C and was incomplete after 48 h (entry 1). This is probably because the reaction center in iodide **(±)-3.5.11** is much more sterically hindered in comparison to that of the literature molecule **3.5.14** (**Scheme 3.5.6**). Attempts were then carried out to drive the reaction to completion because the starting material **(±)-3.5.11** and the product **(±)-3.5.6** were inseparable by column chromatography. The reaction time could be shortened by increasing the temperature to 60 °C but a full conversion was still not achieved (entry 2). It was postulated that the polar aprotic solvent, sulfolane, might be destroying $NaBH_4$ over prolonged reaction times as the reaction mixture developed a stench on extended reaction times. Therefore, in the next attempt, after the initial addition of $NaBH_4$ at the start of the reaction, another six equivalents of $NaBH_4$ were added after 3 h (entry 3). Disappointingly, the reaction was still incomplete after 6 h at 60 °C. Nonetheless, a good yield of 76% was achieved with the nitrile group untouched (entry 3).



(±)-3.5.11 **(±)-3.5.6**

Reagents and conditions: a) $NaBH_4$, sulfolane.

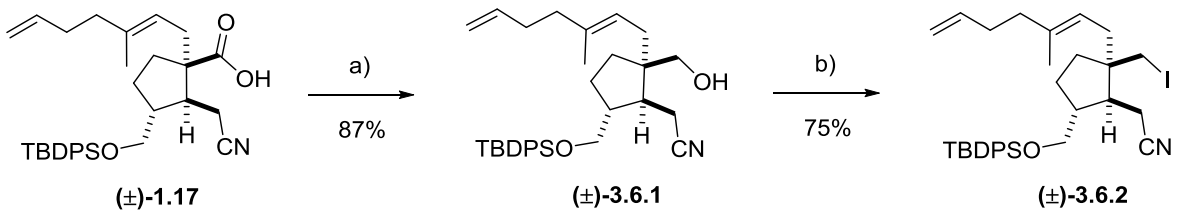
Entry	$NaBH_4$ (eq.)	T (°C)	t (h)	Yield (%)[a]	Ratio SM : P[b]
1	6	40	48	>50[c]	1 : 18
2	6	60	6.5	>50[c]	1 : 14
3	6 + 6[d]	60	6	76	1 : 10

[a] Yield of alkane **(±)-3.5.6**; starting material **(±)-3.5.11** and product **(±)-3.5.6** are inseparable and thus, yield was calculated on basis of the combined mass and the ratio estimated from ^{1}H NMR. [b] Estimated from ^{1}H NMR. [c] Actual yields were higher as reactions were monitored by taking aliquots of reaction mixture every few hours for ^{1}H NMR analysis. [d] 6 eq. of $NaBH_4$ were added at the start of reaction and another 6 eq. of $NaBH_4$ were added after 3 h.

Table 3.5.3: Optimisation of conditions for the synthesis of alkane (±)-3.5.6 using $NaBH_4$

3.6 Application of the multi-steps reduction on the actual system

The stepwise reduction of a carboxylic acid to a methyl group *via* formation of the corresponding alcohol and iodide was then attempted on the actual system. Utilising the reaction conditions developed for the model system in **Section 3.5.2** (page 155), acid **(±)-1.17** was smoothly reduced to alcohol **(±)-3.6.1** in very good yield (**Scheme 3.6.1**). The structure of alcohol **(±)-3.6.1** was identified by a broad O-H stretch at 3504 cm^{-1} in its IR spectrum. The ^1H NMR analysis shows two sets of doublet of doublets around 3.61 – 3.57 ppm which correspond to the diastereotopic CH_2OH protons next to the hydroxyl group. Alcohol **(±)-3.6.1** was then converted into iodide **(±)-3.6.2** in good yield. The structure of iodide **(±)-3.6.2** was identified by an upfield shift of the two sets of doublet of doublets from 3.61 – 3.57 ppm (CH_2OH) to 3.34 – 3.29 ppm (CH_2I) in its ^1H NMR spectrum.



(±)-1.17 **(±)-3.6.1** **(±)-3.6.2**

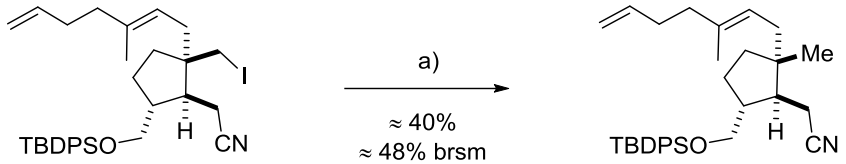
Reagents and conditions: a) i) Ethyl chloroformate (1.1 eq.), *N*-methyl morpholine (1.1 eq.), THF, 0 °C, 6 h, ii) $NaBH_4$ (3 eq.), THF/MeOH, RT, 6.5 h; b) I_2 (1.5 eq.), PPh_3 (2 eq.), imidazole (2 eq.), THF, RT, 5 h.

Scheme 3.6.1: Synthesis of iodide (±)-3.6.2 from acid (±)-1.17 in two steps

3.6.1 Reductive dehalogenation with $NaBH_4$

Using the previously developed conditions (page 159), the reductive dehalogenation reaction was then attempted on iodide **(±)-3.6.2** using $NaBH_4$ in sulfolane at 60 °C (**Scheme 3.6.2**). Unfortunately, this reaction did not work well for

the actual system. A low yield of 40% (48% by recovering starting material) was obtained. The rest of the mass isolated from column chromatography appeared to be derived from the silyl ether protecting group which probably implied that the silyl ether protecting group was unstable in sulfolane in the presence of $NaBH_4$ over prolonged reaction times.



(±)-3.6.2 **(±)-1.18**

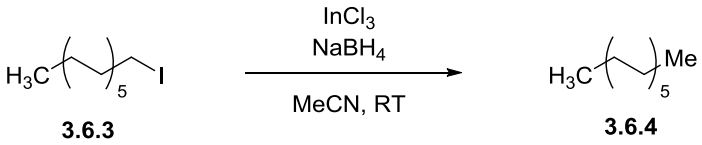
SM : P ratio 1 : 2

Reagents and conditions: a) $NaBH_4$ (12 eq.), sulfolane, 60 °C, 6 h.

Scheme 3.6.2: Synthesis of alkane (±)-1.18 *via* reductive dehalogenation

3.6.2 Reductive dehalogenation *via* a radical pathway

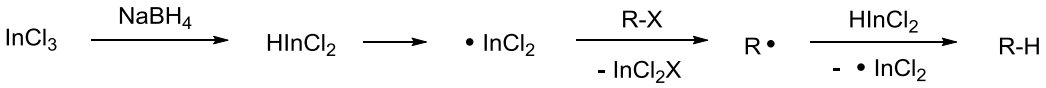
In 2002, Baba *et al*. reported a novel radical reducing system, $InCl_3/NaBH_4$, which could replace the commonly used but toxic Bu_3SnH reagent in reductive dehalogenation reactions.[166] One of the examples reported was the reduction of 1-iododododecane **3.6.3** to hydrocarbon **3.6.4** at ambient temperature which gave an excellent yield of 93% (**Scheme 3.6.3**). Baba *et al*. proposed that $InCl_3$ undergoes transmetalation with $NaBH_4$ to form $HInCl_2$ which then homolytically cleaves to form the $InCl_2$ radical (**Scheme 3.6.3**). The $InCl_2$ radical then abstracts the halogen atom from an aryl/alkyl halide compound, R-X. The resulting aryl/alkyl carbon radical abstracts a hydrogen atom from $HInCl_2$ to form the alkane product, R-H, and regenerates the $InCl_2$ radical.



3.6.3 **3.6.4**

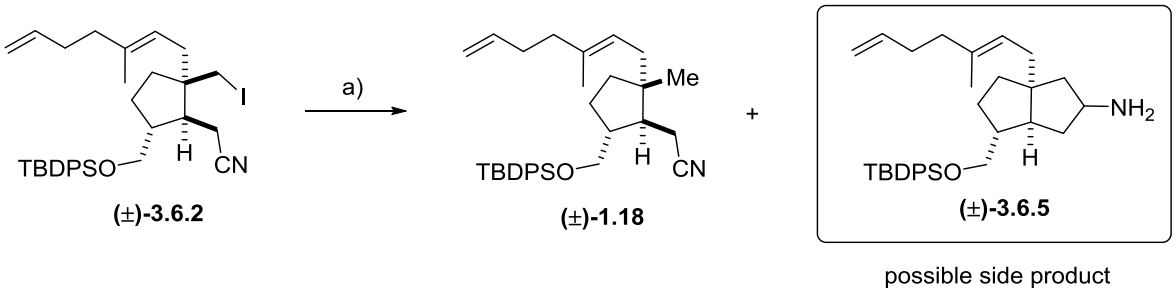
93%

Proposed mechanism:



Scheme 3.6.3: Dehalogenation using a radical reducing agent and its mechanism proposed by Baba *et al*.[166]

The radical reducing system described above was then utilised in the reduction of iodide **(±)-3.6.2** to alkane **(±)-1.18** (**Table 3.6.1**). The reaction was initially conducted at RT which gave a low yield of 41% (entry 1). Decreasing the reaction temperature to 0 °C gave a large range of yields which were irreproducible (entry 2). While compounds formed from the intramolecular cyclisation of the methyl radical onto the alkenes in the side chain were not observed, the molecular weight of the side product **(±)-3.6.5** (*m/z* 502.4 $[M+H]^+$) was found in the LRMS spectrum of the crude mixture. It was probably formed when the methyl radical attacked the nitrile group to form an imine which was then reduced by $NaBH_4$ to the primary amine. Furthermore, polymerisation might have also occurred as the ^1H NMR spectrum of the crude mixture shows messy baseline especially in the alkane region. Due to time constraints, no further investigation was carried out in optimising the reduction of alkyl iodide **(±)-3.6.2** to alkane **(±)-1.18**.



Reagents and conditions: a) $InCl_3$ (1 eq.), $NaBH_4$ (3 eq.), MeCN.

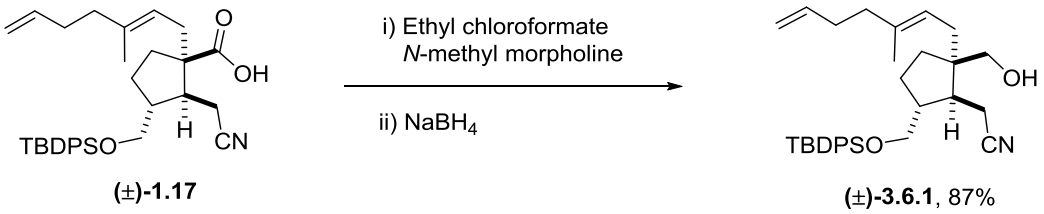
Entry	T (°C)	t (h)	Yield (%)[a]
1	RT	2	41
2	0	1.5	25 – 63

[a] Isolated yield of alkane **(±)-1.18**.

Table 3.6.1: Synthesis of alkane (±)-1.18 using a radical reducing system

3.7 Conclusion and future work

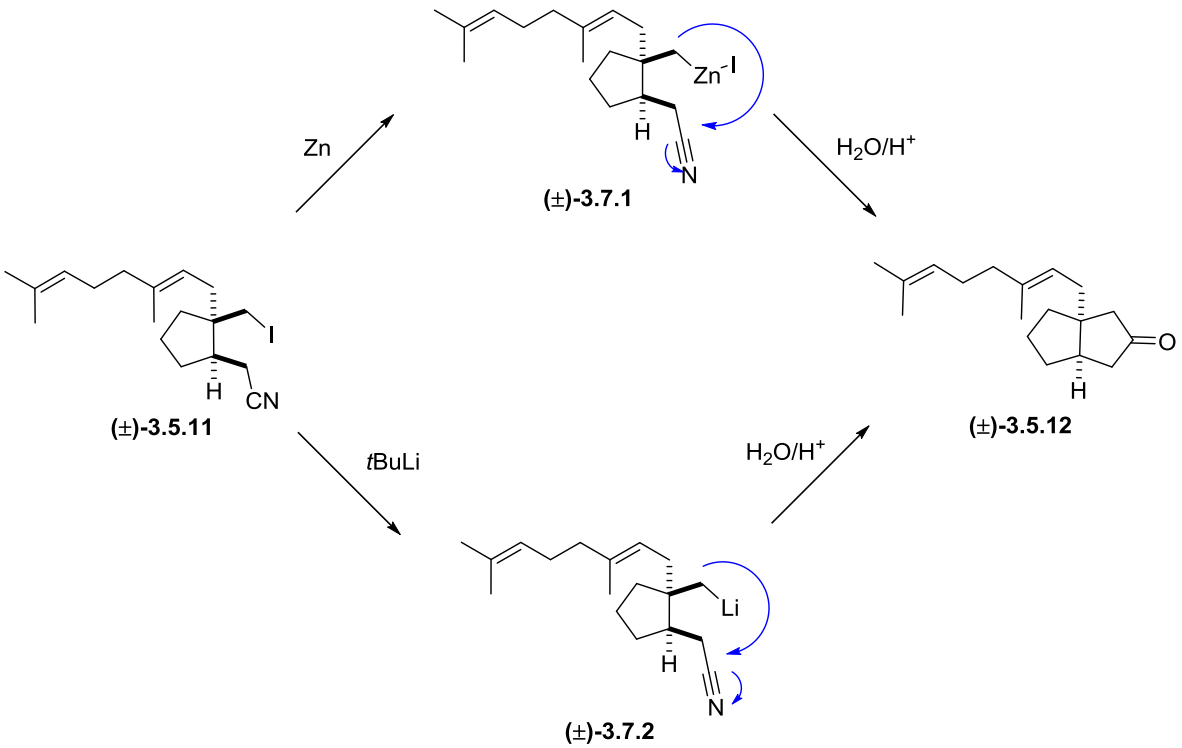
In summary, it was found to be difficult to directly reduce a carboxylic acid to an alkane in the presence of other reducible groups such as alkene and nitrile. In this project, we found a method to smoothly reduce acid **(±)-1.17** to alcohol **(±)-3.6.1** in very good yield with the nitrile group untouched (**Scheme 3.7.1**).



Scheme 3.7.1: One-pot reduction of acid (±)-1.17 to alcohol (±)-3.6.1

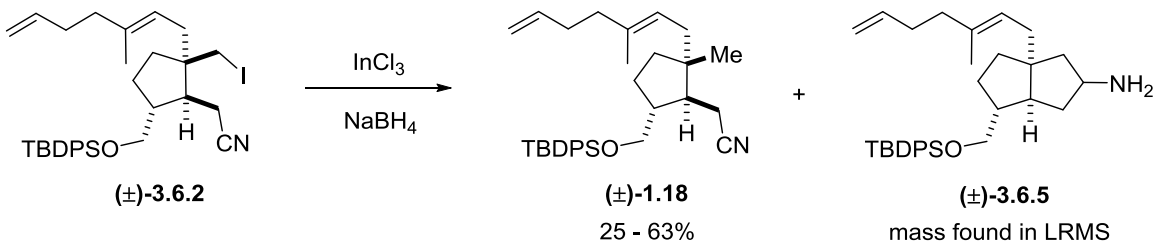
In **Section 3.5.2.3**, it was found that when the conversion of iodide **(±)-3.5.11** to alkane **(±)-3.5.6** proceeded *via* a carbanion type of intermediate (e.g. alkylzinc complex **(±)-3.7.1** or alkyllithium complex **(±)-3.7.2**), the cyclic ketone side product **(±)-3.5.12** would be formed in large quantities (**Scheme 3.7.2**). This is probably

caused by the organometal complex attacking the nearby nitrile group followed by hydrolysis.



Scheme 3.7.2: Possible reaction pathways that lead to the formation of the side product cyclic ketone (±)-3.5.12

Furthermore, in **Section 3.6.2**, the cyclisation was observed again in the reductive radical dehalogenation reaction whereby the methyl radical probably attacked the nitrile triple bond to form an imine which was then reduced to amine **(±)-3.6.5**.

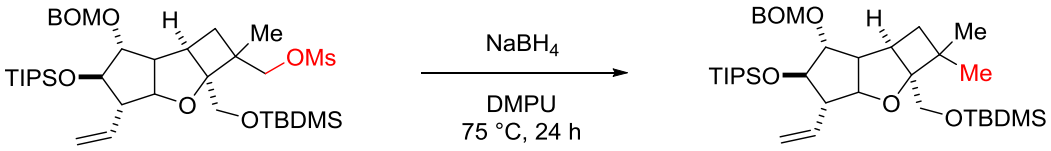


Scheme 3.7.3: Reductive radical dehalogenation

Therefore, it could be concluded that reactions forming nucleophilic carbon species should be avoided in the conversion of (R-X) to (R-H) as cyclisation onto the nitrile group is likely to happen.

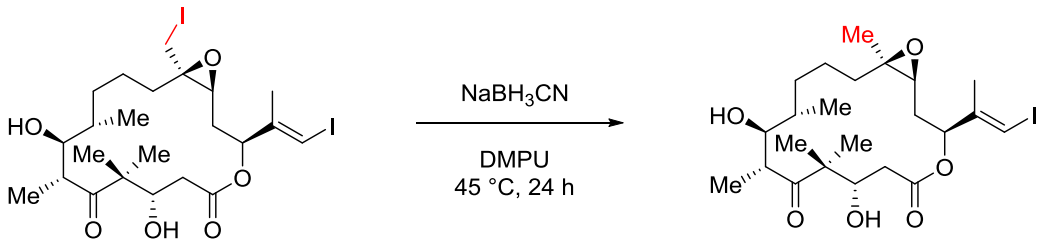
For future work, more efforts can be carried out in the optimisation of nucleophilic hydride reduction reactions. For instance, in 2008, Bach *et al*. reported the reduction of mesylate **3.7.3** using $NaBH_4$ in DMPU to afford alkane **3.7.4** in 77% yield (**Scheme 3.7.4**).[167] Although the structure of mesylate **3.7.3** is not analogous to that of our target of interest (e.g. iodide **(±)-3.6.2**), it also contains a silyl ether protecting group and a terminal alkene. Moreover, mesylate **3.7.3** exhibits similar steric congestion as the reaction center is next to a quaternary carbon. In another literature by Nicolaou *et al*., iodide **3.7.5** was reduced using $NaBH_3CN$ in DMPU to afford alkane **3.7.6** in 70% yield (**Scheme 3.7.4**).[168] Again, although not analogous to our target of interest, compound **3.7.5** contains an easily reducible ketone group which is tolerated under the reaction conditions. This probably indicates that the nitrile group in our compound may be tolerated as well.

By Bach *et al*.



3.7.3 **3.7.4**, 77%

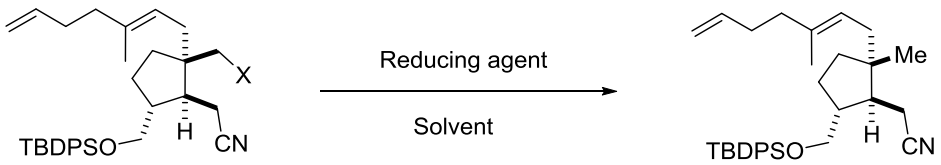
By Nicolaou *et al*.



3.7.5 **3.7.6**, 70%

Scheme 3.7.4: Two examples of the nucleophilic hydride reduction reactions in literature[167,168]

Therefore, for future work, a variety of leaving groups, hydride reducing agents and solvents could be screened to find the optimal reaction conditions to reduce compound **(±)-3.7.7** to alkane **(±)-1.18** (**Scheme 3.7.5**).



(±)-3.7.7 **(±)-1.18**

X = I, OMs or OTs
Reducing agent: $NaBH_4$ or $NaBH_3CN$
Solvent: HMPA, DMSO, DMPU or DMI

Scheme 3.7.5: Optimisation of reaction conditions

4 Experimental

4.1 General experimental

All non-aqueous reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless stated otherwise. THF and DCM were distilled over CaH_2 and stored over molecular sieves (4 Å). Triethylamine was distilled over CaH_2 and stored over KOH. Anhydrous DMSO, DMF, DME, dioxane and benzene were purchased. Water was deionised by Milli-Q purifier with an Ultrapure Organex cartriage. All other solvents were dried using activated alumina columns unless stated otherwise. All other commercially available reagents were purchased and used without additional purification unless stated otherwise.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400 and AV-500 spectrometers with chemical shifts (δ_H and δ_C) reported in parts per million and residual protonated solvent signal as the internal reference. Assignments were made on the basis of chemical shifts, integrals, coupling constants, 2D NMR experiments (COSY, HSQC, HMBC) and analogy by comparing with related compounds. Resonances are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), hept (heptet), oct (octet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets) and so on. Coupling constants (J) were measured in Hz and rounded to 0.1 Hz. H and H’ refer to the diastereotopic protons attached to the same carbon atom; there is no stereochemistry implied.

Low resolution electrospray ionisation (ESI) mass spectra (LRMS) were recorded by a Waters LCT Premier mass spectrometer. High resolution electrospray ionisation (ESI) mass spectra (HRMS) were recorded by the Mass Spectrometry Service at the Chemical Research Laboratory of University of Oxford. Mass values (*m/z*) are reported in Daltons with the relevant fragment ions in parentheses. HRMS values are calculated to four decimal places.

Infrared spectra (IR) were recorded using a Tensor 27 FTIR spectrometer with samples prepared in diethyl ether, dichloromethane or chloroform. Absorption maxima (ν_{max}) are represented in wavenumbers (cm^{-1}) and abbreviated as s (strong), m (medium), w (weak) and br (broad).

Melting points of solids were measured using a Leica Galen III Compound Microscope.

Optical rotations ($°cm^2g^{-1}$) were measured in a cell of 1 dm path length using a Perkin-Elmer 241 polarimeter with a sodium lamp (wavelength of light = 589 nm) at 25 °C (unless stated otherwise). Samples were prepared as solutions in chloroform (unless stated otherwise) with concentrations (expressed in mg/0.1mL) indicated in parentheses.

HPLC analysis was conducted using an Agilent 1200 machine. Chiral columns used are Chiralcel OD-H (4.6 mm x 250 mm) and Chiralpak AD-H (4.6 mm x 250 mm). Compounds were detected by 210 nm, 230 nm and 254 nm wavelengths.

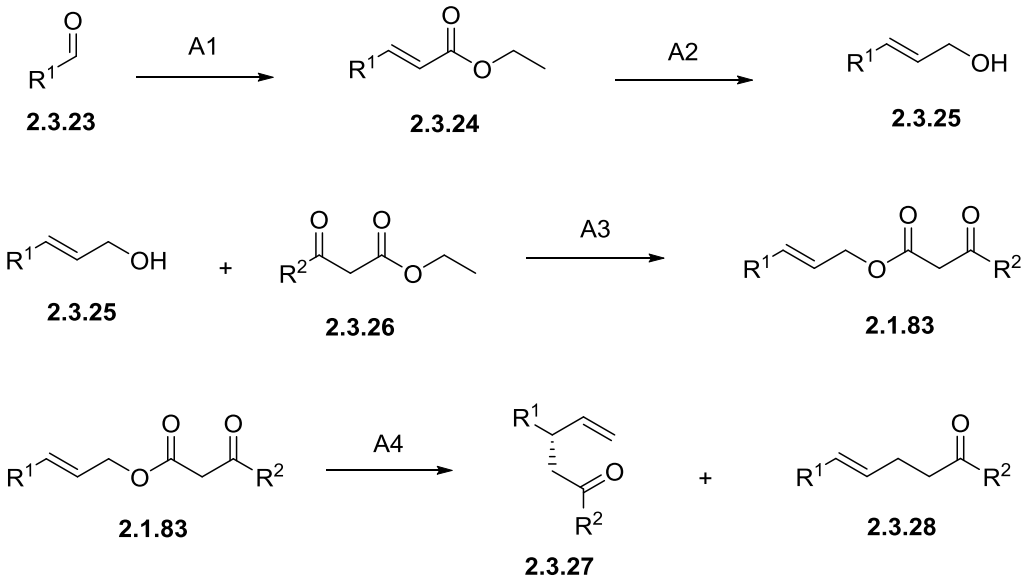
Flash column chromatography (FC) was carried out using Merck Kieselgel 60 F254 230-400 mesh silica gel. Thin layer chromatography was carried out using

Merck 60 F_{254} aluminium-backed silica plates and visualised using a UV lamp, potassium permanganate and vanillin dips. Retention factors (R_f) are reported with the solvent systems used in parentheses.

Names of compounds were generated by ChemBioDraw Ultra 12.0. Compounds titled in *italics* are novel.

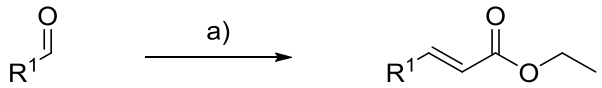
4.2 General procedures

4.2.1 General procedure A



Scheme 4.2.1: General reaction scheme towards the synthesis of enantioenriched carbonyl compounds 2.3.27 (Chapter 2)

4.2.1.1 General procedure A1 – Wittig reaction

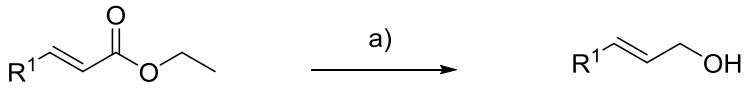


2.3.23 **2.3.24**

Reagents and conditions: a) (Carbethoxymethylene)triphenylphosphorane, THF, RT

According to a modified procedure of Tiekink *et al*.:[77] To a solution of aldehyde **2.3.23** (1.0 eq.) in THF (0.38 M with respective to aldehyde **2.3.23**) at 0 °C was added (carbethoxymethylene)triphenylphosphorane (1.1 eq.). The reaction mixture was stirred at RT and monitored by TLC. Upon completion, the mixture was concentrated *in vacuo* to give the crude ester **2.3.24** which was subsequently purified by FC.

4.2.1.2 General procedure A2 – Reduction



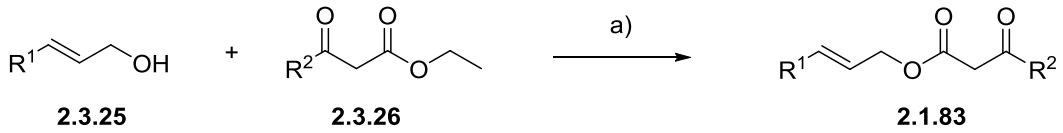
2.3.24 **2.3.25**

Reagents and conditions: a) DIBAL-H, DCM, 0 °C to RT

According to a modified procedure of Tiekink *et al*.:[77] To a solution of ester **2.3.24** (1.0 eq.) in DCM (0.32 M with respective to ester **2.3.24**) at 0 °C was added DIBAL-H (1 M in hexane) (2.2 eq.) slowly. The reaction mixture was stirred at 0 °C for 1 h before being warmed to RT and monitored by TLC. Upon completion, the reaction mixture was quenched with sat. aq. Rochelle's salt solution (4 mL/mmol with respect to ester **2.3.24**) and the biphasic mixture was stirred for 3 h. The two layers were then separated and the aqueous layer was extracted with Et_2O (2 x 10 mL/mmol). The organic layers were combined, dried over $MgSO_4$, filtered and

concentrated *in vacuo* to give the crude alcohol **2.3.25** which was used in the next step without further purification.

4.2.1.3 General procedure A3 – Esterification

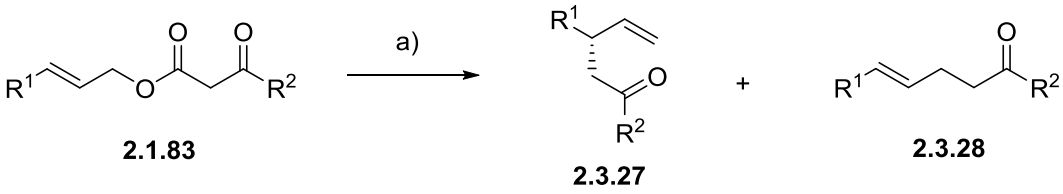


2.3.25 **2.3.26** **2.1.83**

Reagents and conditions: a) DMAP, molecular sieves (4 Å), toluene, 120 °C

According to a modified procedure of Kelly *et al.*:[69] A mixture of allylic alcohol **2.3.25** (1.0 eq.), *β*-ketoester **2.3.26** (1.0 eq.), DMAP (1.0 eq.) and molecular sieves (4 Å) (1.5 g/mmol) in toluene (0.075 M with respective to allylic alcohol **2.3.25**) was stirred at 120 °C under reflux overnight. Upon completion, the molecular sieves were filtered off and the filtrate was washed with sat. aq. NH_4Cl solution (1 x 10 mL/mmol with respect to *β*-ketoester **2.3.25**). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude allylic *β*-ketoester **2.1.83** which was subsequently purified by FC.

4.2.1.4 General procedure A4 – Iridium-catalysed AAA



2.1.83 **2.3.27** **2.3.28**

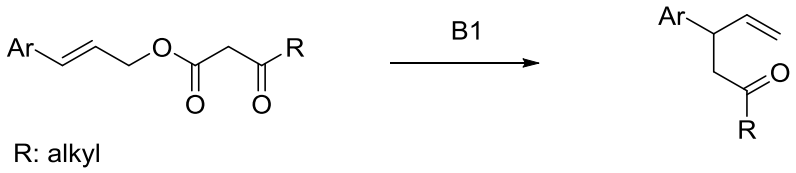
Reagents and conditions: a) $[Ir(COD)Cl]_2$, phosphoramidite ligand **L2**, TBD, THF, RT

To a solution of $[Ir(COD)Cl]_2$ (4 mol%) and ligand **L2** (8 mol%) in THF (0.03 M with respective to $[Ir(COD)Cl]_2$) was added 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (16 mol%) at RT. The mixture was stirred at RT for 5 min followed by the addition of a solution of *β*-ketoester **2.1.83** (1.0 eq.) in THF (0.54 M with respective

to *β*-ketoester **2.1.83**). The reaction mixture was stirred at RT and monitored by TLC. Upon completion, the mixture was concentrated *in vacuo* to give a crude mixture of branched ketone **2.3.27** and linear ketone **2.3.28** which were subsequently purified by FC.

4.2.2 General procedure B

4.2.2.1 General procedure towards the synthesis of aryl racemic references



R: alkyl

2.3.45 **(±)-2.3.46**

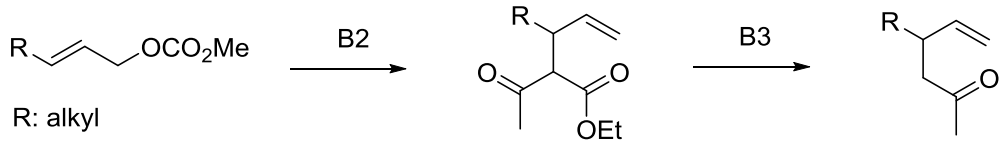
Reagents and conditions: B1) $[Cp^*RuCl]_4$, 2,2'-bipyridine, DCM, RT.

Scheme 4.2.2: General reaction scheme towards the synthesis of aryl racemic references (±)-2.3.46 (Chapter 2)

General procedure B1:

According to a modified procedure of Tunge *et al*.:[86] A solution of $[Cp^*RuCl]_4$ (3 mol%) and 2,2'-bipyridine (12 mol%) in DCM (0.014 M with respect to $[Cp^*RuCl]_4$) was stirred at RT for 5 min. A solution of *β*-ketoester **2.3.45** (1 eq.) in DCM (0.38 M with respect to *β*-ketoester **2.3.45**) was then added to the catalyst suspension at RT. The reaction mixture was stirred at RT and monitored by TLC. Upon completion, the mixture was concentrated *in vacuo* to give crude ketone **(±)-2.3.46** which was subsequently purified by FC.

4.2.2.2 General procedure towards the synthesis of alkyl racemic references

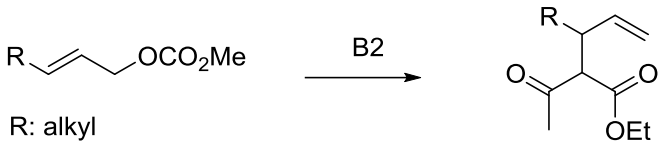


2.3.47 **(±)-2.3.48** **(±)-2.3.49**

Reagents and conditions: B2) $[Ir(COD)Cl]_2$, $P(OPh)_3$, ethyl acetoacetate, NaH, THF, 70 °C; B3) LiCl, H_2O, DMSO, 150 °C.

Scheme 4.2.3: General reaction scheme towards the synthesis of alkyl racemic references (±)-2.3.49 (Chapter 2)

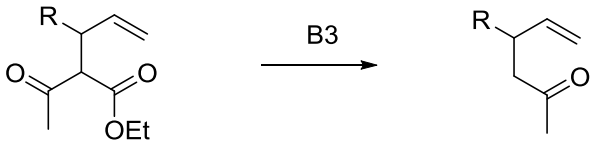
General procedure B2:



2.3.47 **(±)-2.3.48**

According to a modified procedure of Kashio *et al.*:[12] To a slurry of sodium hydride (3 eq.) in THF (1.37 M with respect to ethyl acetoacetate) at RT was added ethyl acetoacetate (3 eq.). The resulting mixture was then added to a solution of carbonate **2.3.47** (1 eq.), triphenyl phosphite (16 mol%) and $[Ir(COD)Cl]_2$ (4 mol%) in THF (0.40 M with respect to carbonate **2.3.47**) at RT. The reaction mixture was stirred at RT overnight and monitored by TLC. Upon completion, water (10 mL/mmol with respect to carbonate **2.3.47**) and Et_2O (10 mL/mmol) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL/mmol). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude *β*-ketoester **(±)-2.3.48** which was subsequently purified by FC.

General procedure B3:



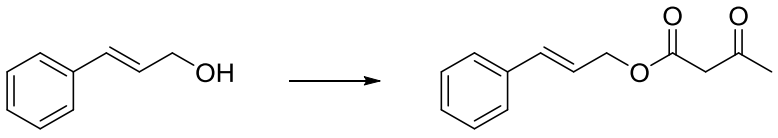
(±)-2.3.48 **(±)-2.3.49**

According to a modified procedure of Davies:[88] To a solution of *β*-ketoester **(±)-2.3.48** (1 eq.) in DMSO (0.5 M with respect to *β*-ketoester **2.3.48**) was added lithium chloride (2 eq.) at RT. Water (10 eq.) was then added and the reaction vessel was degassed. The reaction mixture was then stirred under reflux at 150 °C and monitored by TLC. Upon completion, the reaction mixture was cooled to RT. Et_2O (10 mL/mmol with respect to *β*-ketoester **(±)-2.3.48**) and water (10 mL/mmol) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL/mmol). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude ketone **(±)-2.3.49** which was subsequently purified by FC.

4.3 Compound synthesis: experimental details (Chapter 2)

4.3.1 Experimental details part one (Section 2.3.1 to 2.3.3)

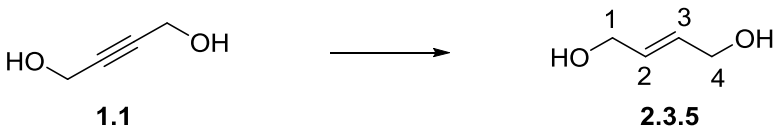
Cinnamyl 3-oxobutanoate (2.3.4)



2.3.3 **2.3.4**

The title compound **2.3.4** was synthesised from allylic alcohol **2.3.3** (300 mg, 2.24 mmol) using ethyl acetoacetate (0.29 mL, 2.2 mmol), DMAP (274 mg, 2.24 mmol) and molecular sieves (4 Å) (4.5 g) in toluene (30 mL) according to general procedure A3. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.4** (406 mg, 1.86 mmol, 83%) as a pale yellow oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.41 – 7.38 (m, 2H, Ar-*H*), 7.35 – 7.31 (m, 2H, Ar-*H*), 7.29 – 7.27 (m, 1H, Ar-*H*), 6.68 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 16.0, 6.6 Hz, PhCH=C*H*), 4.81 (dd, 2H, *J* = 6.6, 1.3 Hz, CH=CHCH_2), 3.51 (s, 2H, OC(O)CH_2), 2.29 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 136.1 (Ar), 135.0 (Ph*C*H=CH), 128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 122.5 (PhCH=*C*H), 66.1 (CH=CH*C*H_2), 50.2 (OC(O)*C*H_2), 30.4 (C(O)*C*H_3); *m/z* (ESI^+): 241.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[169]

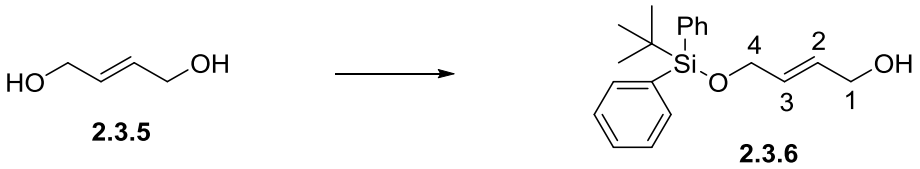
(*E*)-But-2-ene-1,4-diol (2.3.5)



1.1 **2.3.5**

According to the procedure of Crimmins *et al*.:[70] To a solution of $LiAlH_4$ (2.4 M in THF, 100 mL, 240 mmol) in THF (250 mL) at 0 °C was added a solution of but-2-yne-1,4-diol **1.1** (18.0 g, 211 mmol) in THF (100 mL) *via* cannula. The reaction mixture was stirred at 0 °C for 10 min before it was warmed to RT and stirred for 16 h. Upon completion, the reaction mixture was cooled to 0 °C and 10 g of Celite™ was added. Sat. aq. $(NH_4)_2SO_4$ solution (25 mL) was then added dropwise and the mixture was stirred for 30 min at 0 °C. The mixture was filtered through Celite™ (7 g) and the filter cake was washed with Et_2O (3 x 150 mL). The Celite™ was transferred into a 1 L conical flask and stirred in DCM overnight at RT to extract the remaining product. The mixture was filtered through a new layer of Celite™ (1 g) and the filter cake was washed with DCM (3 x 150 mL). The organic layers were combined and concentrated *in vacuo* (> 50 mbar) to give the title crude product **2.3.5** (11.8 g, 134 mmol, 63%) as a colourless oil. The crude diol **2.3.5** was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 5.95 – 5.84 (m, 2H, H-2 and H-3), 4.19 (m, 4H, H-1 and H-4); δ_C (100 MHz, $CDCl_3$): 130.5 (C-2 and C-3), 62.9 (C-1 and C-4). Characterisation data are consistent with literature values.[70]

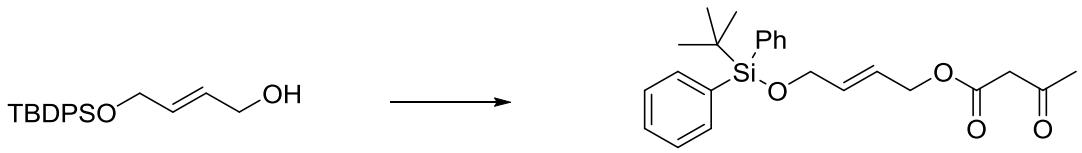
(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-ol (2.3.6)



2.3.5 **2.3.6**

According to the procedure of McDougal *et al*.:[71] To a suspension of sodium hydride (57% - 63% oil dispersion) (920 mg, 22.7 mmol) in THF (35 mL) at RT was slowly added a solution of diol **2.3.5** (2.00 g, 22.7 mmol) in THF (10 mL). The reaction mixture was stirred for 45 min at RT before the addition of *tert*-butylchlorodiphenylsilane (5.9 mL, 23 mmol) at RT. The reaction mixture was stirred at RT for 16 h. Upon completion, Et_2O (50 mL) and 10% aq. K_2CO_3 solution (50 mL) were added to the mixture and the two layers were separated. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.6** (4.40 g, 13.5 mmol, 59%) as a colourless oil. R_f = 0.25 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.70 – 7.67 (m, 4H, Ar-*H*), 7.44 – 7.39 (m, 6H, Ar-*H*), 5.93 (dtt, 1H, *J* = 15.4, 5.4, 1.6 Hz, H-2), 5.80 (dtt, 1H, *J* = 15.4, 4.4, 1.4 Hz, H-3), 4.24 (dq, 2H, *J* = 4.4, 1.6 Hz, H-4), 4.16 (d, 2H, *J* = 5.4 Hz, H-1), 1.07 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 135.6 (Ar), 133.6 (Ar), 130.7 (C-3), 129.7 (Ar), 128.8 (C-2), 127.7 (Ar), 63.8 (C-4), 63.3 (C-1), 26.8 ($SiC(CH_3)_3$), 19.3 ($SiC(CH_3)_3$). Characterisation data are consistent with literature values.[103]

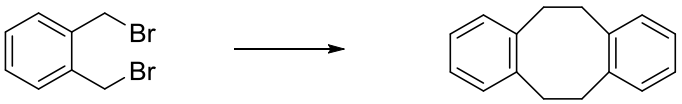
(E)-4-((tert-Butyldiphenylsilyl)oxy)but-2-en-1-yl 3-oxobutanoate (2.3.7)



2.3.6 **2.3.7**

The title compound **2.3.7** was synthesised from allylic alcohol **2.3.6** (100 mg, 0.310 mmol) using ethyl acetoacetate (0.04 mL, 0.31 mmol), DMAP (38 mg, 0.31 mmol) and molecular sieves (4 Å) (1.6 g) in toluene (13 mL) according to general procedure A3. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.7** (100 mg, 0.254 mmol, 82%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.65 (m, 4H, Ar-*H*), 7.43 – 7.36 (m, 6H, Ar-*H*), 5.90 – 5.87 (m, 2H, C*H*=C*H*), 4.67 – 4.65 (m, 2H, CH=CHCH_2OCO), 4.23 – 4.21 (m, 2H, SiOCH_2), 3.48 (s, 2H, OC(O)CH_2CO), 2.28 (s, 3H, COCH_3), 1.07 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 135.6 (Ar), 134.5 (*C*H=*C*H), 133.5 (Ar), 129.9 (Ar), 127.8 (Ar), 122.9 (*C*H=*C*H), 65.5 (C=C*C*H_2OCO), 63.5 (*C*H_2OSi), 50.2 (OC(O)*C*H_2CO), 30.3 (CO*C*H_3), 26.9 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 2932 (m, C-H), 2858 (m, C-H), 1744 (s, C=O, ester), 1719 (s, C=O, ketone), 1428 (m), 1111 (s), 703 (s); *m/z* (ESI$^+$): 433.2 ([M+Na]$^+$, 100%); accurate mass: found 433.1801, $C_{24}H_{30}NaO_4Si$ [M+Na]$^+$ requires 433.1806.

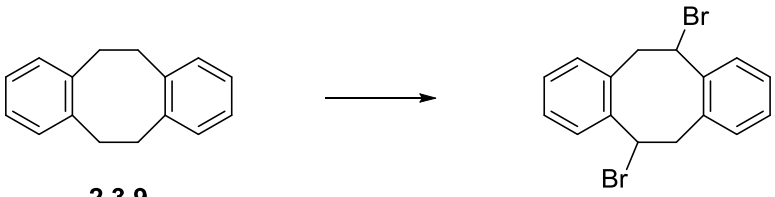
5,6,11,12-Tetrahydrodibenzo[*a,e*][8]annulene (2.3.9)



2.3.8 **2.3.9**

According to a procedure of Wudl *et al*.:[74] In a Schlenk tube Li granules (77 mg, 11 mmol) were stirred vigorously for 16 h at RT under argon. To a suspension of the activated Li granules (77 mg, 11 mmol) in THF (3 mL) at 0 °C was added 1,2-bis(bromomethyl)benzene **2.3.8** (500 mg, 1.89 mmol). The mixture was degassed with argon and then sonicated for 4 h at RT. Upon completion, the organic solvent was decanted and the residue was washed with EtOAc (3 x 5 mL). The filtrates were combined and concentrated *in vacuo*. The crude product was purified by FC (1% Et_2O in $PE_{40\text{-}60}$) to give the title compound **2.3.9** (170 mg, 0.0.813 mmol, 43%) as a white crystalline solid. R_f = 0.3 (1% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.02 – 7.00 (m, 8H, Ar-*H*), 3.08 (s, 8H, ring C*H*$_2$); δ_C (100 MHz, $CDCl_3$): 140.7 (Ar), 129.8 (Ar), 126.2 (Ar), 35.3 (ring *C*H_2). Characterisation data are consistent with literature values.[74]

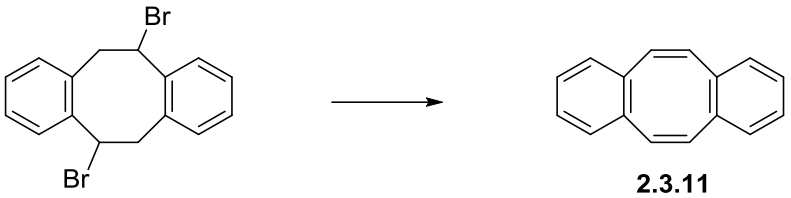
5,11-Dibromo-5,6,11,12-tetrahydrodibenzo[*a,e*][8]annulene (2.3.10)



2.3.9 **2.3.10**

According to a procedure of Wudl *et al*.:[74] To a solution of annulene **2.3.9** (150 mg, 0.816 mmol) in CCl_4 (8 mL) was added *N*-bromosuccinimide (257 mg, 1.63 mmol). The reaction mixture was stirred under reflux at 80 °C for 2.5 h. Upon completion, the mixture was cooled to RT. The mixture was then filtered and the residue was washed by diethyl ether (3 x 5 mL). The filtrates were combined and concentrated *in vacuo*. The crude product was purified by FC (6% Et_2O in $PE_{40\text{-}60}$) to give the title compound **2.3.10** (47 mg, 0.36 mmol, 44%) as a white solid. R_f = 0.3 (6% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.15 – 6.97 (m, 8H, Ar-*H*), 5.33 (dd, 2H, *J* = 11.1, 8.5 Hz, C*H*Br), 4.29 (dd, 2H, *J* = 14.1, 11.1 Hz, PhC*H*), 3.65 (dd, 2H, *J* = 14.1, 8.5 Hz, PhC*H'*); δ_C (100 MHz, $CDCl_3$): 138.5 (Ar), 136.5 (Ar), 131.1 (Ar), 131.0 (Ar), 129.2 (Ar), 128.1 (Ar), 53.1 (*C*HBr), 43.8 (Ph*C*H_2). Characterisation data are consistent with literature values.[74]

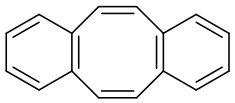
(5*Z*,11*Z*)-Dibenzo[*a,e*][8]annulene (2.3.11)



2.3.10 **2.3.11**

According to a procedure of Wudl *et al*.:[74] To a solution of *t*BuOK (1 M, 2.1 g, 19 mmol) in THF (18.7 mL) was added a solution of bromoannulene **2.3.10** (430 mg, 1.17 mmol) in THF (11 mL) slowly at 0 °C. The reaction mixture was then stirred at RT for 16 h. Upon completion, the reaction mixture was quenched with water (30 mL). The two layers were separated and the aq. layer was extracted with chloroform (2 x 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (1% Et_2O in $PE_{40\text{-}60}$) to give the title compound **2.3.11** (201 mg, 0.983 mmol, 84%) as a white crystalline solid. R_f = 0.3 (1% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.16 (dd, 4H, *J* = 5.8, 3.4 Hz, benzene-*H*), 7.06 (dd, 4H, *J* = 5.8, 3.5 Hz, benzene-*H*), 6.76 (s, 4H, octatetraene-*H*); δ_C (100 MHz, $CDCl_3$): 137.1 (quarternary carbon), 133.2 (*C*-H, octatetraene), 129.1 (*C*-H, benzene), 126.8 (*C*-H, benzene). Characterisation data are consistent with literature values.[74]

Dichlorobis(η^4-dibenzo[*a,e*]cyclooctatetraene)diiridium (2.3.12)



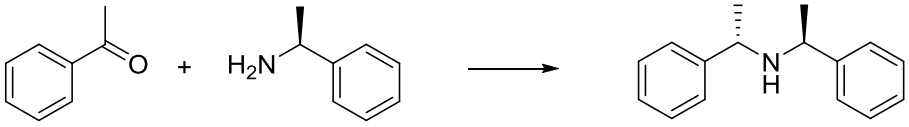
2.3.11

$[Ir(dbcot)Cl]_2$

2.3.12

According to a procedure of Crabtree *et al*.:[75] To a solution of $[Ir(COD)Cl]_2$ (82 mg, 0.12 mmol) in DCM (2 mL) was added a solution of dibenzoannulene **2.3.11** (50 mg, 0.25 mmol) in DCM (2 mL) dropwise over 5 min at RT. The reaction mixture was stirred at RT for 20 min. Upon completion, the solid formed was filtered and washed with DCM (3 x 2 mL). The filtrate was reduced to 1 mL and hexane (1.5 mL) was added. More solid was formed in the suspension which was then filtered and washed with hexane (3 x 2 mL). The solids were combined and dried *in vacuo* for 2 h to give the title compound **2.3.12** (78 mg, 0.090 mmol, 74%) as a yellow solid. δ_H (400 MHz, $CDCl_3$): 6.99 (dd, 4H, *J* = 5.4, 3.5 Hz, benzene-*H*), 7.06 (dd, 4H, *J* = 5.4, 3.0 Hz, benzene-*H*), 6.76 (s, 4H, octatetraene-*H*); ν_{max}/cm^{-1}: 1489 (m), 1096 (m), 1003 (m), 830 (m). Characterisation data are consistent with literature values.[75]

(*S*)-bis((*S*)-1-Phenylethyl)amine (2.3.15)



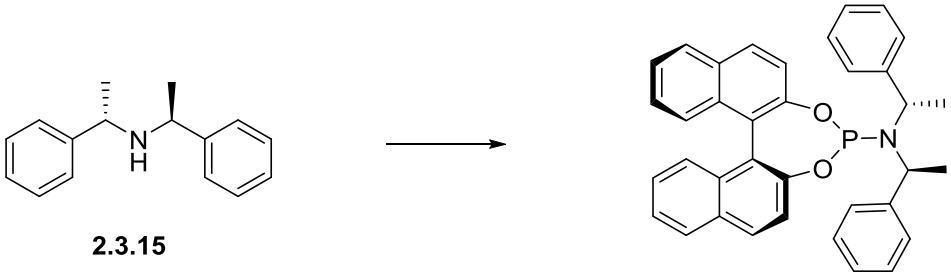
2.3.13 **2.3.14** **2.3.15**

According to a modified procedure of Alexakis *et al*.:[22,76] To a solution of acetophenone **2.3.13** (4.9 mL, 41 mmol) and 1-phenylethanamine **2.3.14** (5.3 mL,

41 mmol) in ethyl acetate (10 mL) at RT was added titanium isopropoxide (49.0 mL, 165 mmol). The reaction mixture was stirred at RT for 20 min before the addition of 10% Pd/C (23 mg, 0.21 mmol). The reaction vessel was purged two times with vacuum-nitrogen sequence followed by five times with vacuum-hydrogen sequence. The reaction mixture was then stirred under one atmosphere of hydrogen for 48 h at RT, compensating the consumption of hydrogen from time to time. Before exposing the reaction mixture to air, the reaction vessel was purged five times with vacuum-nitrogen sequence. The reaction mixture was cooled to 0 °C and 10% aq. NaOH solution (150 mL) was added. The precipitate formed was triturated with EtOAc (6 x 50 mL) and decanted. The organic layers were combined and filtered through Celite™. The filter cake was rinsed with EtOAc (3 x 50 mL). The filtrates were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was dissolved in EtOAc (20 mL) and conc. HCl was added dropwise until no further precipitation was observed. The white precipitate was filtered, rinsed with EtOAc (20 mL) and dried under suction. The white precipitate was then recrystallised from water[170] to give the chloride salt of the title compoud as white crystals. The crystals were dissolved in aq. NaOH solution (2 M, 60 mL) and Et_2O (30 mL) was added. The mixture was stirred for 2 h until the crystals were fully dissolved. The layers were then separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **2.3.15** (2.62 g, 11.5 mmol, 28%) as colourless oil. δ_H (400 MHz, $CDCl_3$): 7.37 – 7.33 (m, 4H, Ar-*H*), 7.28 – 7.23 (m, 6H, Ar-*H*), 3.52 (q, 2H, *J* = 6.1 Hz, C*H*NHC*H*), 1.30 (d, 6H, *J* = 6.1 Hz, CH_3CHNHCHCH_3); δ_C (100 MHz, $CDCl_3$): 128.4 (Ar), 126.8 (Ar), 126.7 (Ar),

55.09 (*C*HNH), 24.92 (*C*H_3CHNH); [α]$_D$ (22 °C) -163 (c = 1.00 in $CHCl_3$), literature value [α]$_D$ (20 °C) -168 (c = 0.72 in $CHCl_3$).[171] Characterisation data are consistent with literature values.[170] 44% of starting material, acetophenone **2.3.13**, (2.20 g, 18.0 mmol) was recovered.

(11b*S*)-*N,N*-bis((*S*)-1-Phenylethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L1)

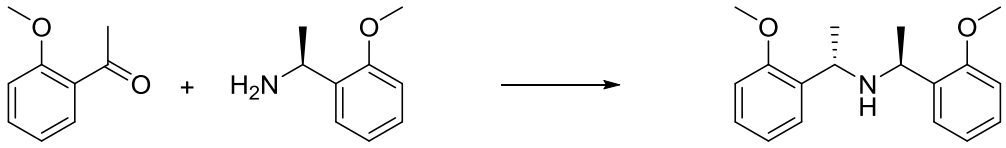


2.3.15 (*S*,*S*,*S*)-**L1**

According to a modified procedure of Alexakis *et al*.:[22] To a solution of triethylamine (1.6 mL, 22 mmol) in THF (7 mL) at 0 °C was added phosphorus trichloride (0.20 mL, 4.4 mmol) dropwise over 5 min. To the above solution at 0 °C was added a solution of (*S*)-bis((*S*)-1-phenylethyl)amine **2.3.15** (500 mg, 4.44 mmol) in THF (3mL) dropwise over 5 min. The reaction mixture was warmed to RT and stirred for 3 h. After cooling the reaction mixture to 0 °C, a solution of (*S*)-binaphthol (640 mg, 4.44 mmol) in THF (5 mL) was slowly added. The resulting mixture was warmed to RT and stirred for 16 h. Upon completion, the mixture was filtered through Celite™ and the filter cake was washed with Et_2O (3 x 30 mL). The organic layers were combined and concentrated *in vacuo*. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **L1** (830 mg, 3.06 mmol, 69%) as a

colourless foam. R_f = 0.3 (20% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 8.09 (d, 1H, *J* = 8.9 Hz, Ar-*H*), 8.00 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 7.90 (d, 1H, *J* = 8.9 Hz, Ar-*H*), 7.82 (d, 1H, *J* = 8.9 Hz, Ar-*H*), 7.66 (dd, 1H, *J* = 8.7, 1.0 Hz, Ar-*H*), 7.45 – 7.18 (m, 17H, Ar-*H*), 4.43 (q, 1H, *J* = 7.1 Hz, NC*H*), 4.40 (q, 1H, *J* = 7.1 Hz, NC*H*), 1.68 (d, 6H, *J* = 7.1 Hz, CH_3CHNHCHCH_3); δ_C (100 MHz, $CDCl_3$): 150.6 (Ar), 150.5 (Ar), 149.8 (Ar), 143.1 (Ar), 132.9 (Ar), 132.8 (Ar), 131.4 (Ar), 130.5 (Ar), 130.4 (Ar), 129.6 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.3 (Ar), 127.2 (Ar), 126.7(Ar), 126.0 (Ar), 125.9 (Ar), 124.8 (Ar), 124.4 (Ar), 124.2 (Ar), 122.6 (Ar), 122.4 (Ar), 121.2 (Ar), 54.6 (*C*HNH), 54.5 (*C*HNH), 23.1 (*C*H_3CHNH), 23.0 (*C*H_3CHNH). $[\alpha]_D$ (22 °C) +22 (c = 1.00 in $CHCl_3$), literature value $[\alpha]_D$ (20 °C) +11 (c = 0.79 in $CHCl_3$).[172] Characterisation data are consistent with literature values.[173]

(*S*)-bis((*S*)-1-(2-Methoxyphenyl)ethyl)amine (2.3.18)

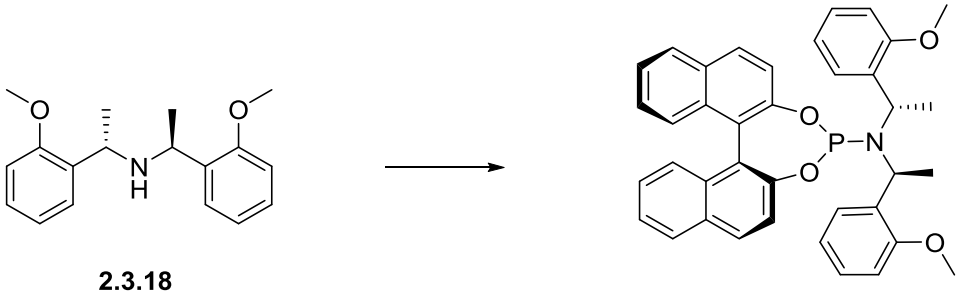


2.3.16 **2.3.17** **2.3.18**

According to a procedure of Alexakis *et al*.:[22] To a mixture of 2-methoxyacetophenone **2.3.16** (0.93 mL, 6.7 mmol) and (*S*)-2-methoxy-*α*-methylbenzylamine **2.3.17** (1.00 g, 6.61 mmol) was added titanium isopropoxide (6.3 mL, 21 mmol) at RT. The reaction mixture was stirred at RT for 20 min before the addition of 10% Pd/C (35 mg, 0.033 mmol). The reaction vessel was sequentially purged two times with vacuum-nitrogen sequence and five times with

vacuum-hydrogen sequence. The reaction mixture was then stirred under one atmosphere of hydrogen for 48 h at RT, compensating the consumption of H_2 from time to time. Upon completion, before exposing the reaction mixture to air, the reaction vessel was purged five times with vacuum-nitrogen sequence. The reaction mixture was cooled to 0 °C and aq. 10% NaOH solution (11 mL) was added, causing the precipitation of titanium salts. The precipitate formed was triturated with EtOAc (3 x 10 mL) and decanted. The organic layers were combined and filtered through Celite™. The filter cake was rinsed with EtOAc (3 x 5 mL). The filtrates were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in EtOAc (8 mL) and aq. 48% HBr solution (0.5 mL) was added dropwise until no further precipitation was observed. The white precipitate was directly recrystallised from a mixture of EtOAc/EtOH (3/1, 20 mL) at RT to give the bromide salt of the title compound as colourless crystals. The crystals were dissolved in aq. NaOH solution (2 M, 0.87 mL) and DCM (5 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound **2.3.18** (715 mg, 2.51 mmol, 38%) as colourless oil. δ_H (400 MHz, $CDCl_3$): 7.32 (dd, 2H, *J* = 7.5, 1.7 Hz, Ar-*H*), 7.20 (td, 2H, *J* = 8.1, 1.7 Hz, Ar-*H*), 6.94 (td, 2H, *J* = 7.5, 1.1 Hz, Ar-*H*), 6.84 (dd, 2H, *J* = 8.1, 1.1 Hz, Ar-*H*), 3.89 (q, 2H, *J* = 6.7 Hz, C*H*CH_3 x 2), 3.72 (s, 6H, OC*H*$_3$ x 2), 1.30 (d, 6H, *J* = 6.7 Hz, CHC*H*$_3$ x 2); δ_C (100 MHz, $CDCl_3$): 157.5 (Ar), 133.9 (Ar), 127.6 (Ar), 127.4 (Ar), 120.7 (Ar), 110.6 (Ar), 55.3 (O*C*H_3), 50.5 (*C*HCH_3), 23.1 (CH*C*H_3); $[\alpha]_D$ (25 °C) -53.2 (c = 1.00 in $CHCl_3$), literature value $[\alpha]_D$ (22 °C) -92 (c = 0.98 in $CHCl_3$). Characterisation data are consistent with literature values.[88]

(11b*S*)-*N*,*N*-bis((*S*)-1-(2-Methoxyphenyl)ethyl)dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (L2)

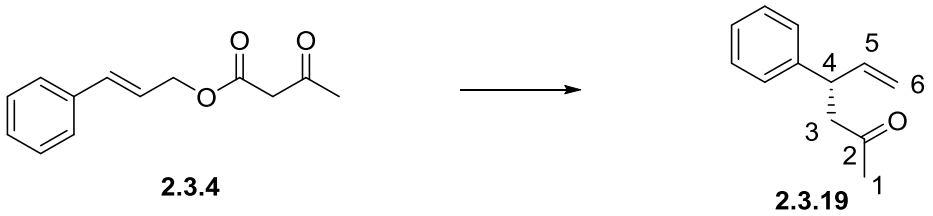


2.3.18 (*S*,*S*,*S*)-**L2**

According to a procedure of Alexakis *et al*.:[22] To a solution of triethylamine (1.1 mL, 7.5 mmol) in THF (4.6 mL) at 0 °C was added phosphorus trichloride (0.11 mL, 1.2 mmol) dropwise over 5 min. To the above solution at 0 °C was added a solution of (*S*)-bis((*S*)-1-(2-methoxyphenyl)ethyl)amine **2.3.18** (348 mg, 1.22 mmol) in THF (1.7 mL) dropwise over 10 min. The reaction mixture was warmed to RT and stirred for 4 h. A solution of (*S*)-binaphthol (349 mg, 1.22 mmol) in THF (3.3 mL) was then slowly added to the above reaction mixture at 0 °C over 1 min. The resulting mixture was warmed to RT and stirred for 16 h. Upon completion, the mixture was filtered through Celite™ and the filter cake was washed with Et_2O (4 x 10 mL). The organic layers were combined and concentrated *in vacuo*. The crude product was purified by FC (17% Et_2O in $PE_{40\text{-}60}$) to give the title compound **L2** (476 mg, 0.794 mmol, 65%) as a white solid. R_f = 0.3 (17% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.98 (d, 1H, *J* = 8.7 Hz, Ar-*H*), 7.91 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.80 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 7.62 – 7.51 (m, 4H, Ar-*H*), 7.42 – 7.32 (m, 3H, Ar-*H*), 7.30 – 7.18 (m, 4H, Ar-*H*), 7.06 (td, 2H, *J* = 7.6, 1.4 Hz, Ar-*H*), 6.81 (td, 2H, *J* = 7.6, 1.1 Hz, Ar-*H*), 6.49 (dd, 2H, *J* = 8.2, 1.1 Hz, Ar-*H*), 4.96 (q, 1H, *J* = 7.0 Hz, C*H*CH_3), 4.94 (q, 1H,

J = 7.3 Hz, C*H*CH_3), 3.54 (s, 6H, OC*H*$_3$ x 2), 1.51 (d, 6H, *J* = 7.1 Hz, CHC*H*$_3$ x 2); δ_C (100 MHz, $CDCl_3$): 156.2 (Ar), 151.5 (Ar), 151.4 (Ar), 150.0 (Ar), 133.1 (Ar), 132.9 (Ar), 132.7 (Ar), 132.6 (Ar), 131.5 (Ar), 130.4 (Ar), 129.3 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.5 (Ar), 127.4 (Ar), 126.0 (Ar), 125.7 (Ar), 124.8 (Ar), 124.6 (Ar), 124.2 (Ar), 122.8 (Ar), 121.6 (Ar), 119.8 (Ar), 109.4 (Ar), 54.7 (O*C*H_3), 50.4 (*C*HCH_3), 50.3 (*C*HCH_3), 22.7 (CH*C*H_3), 22.6 (CH*C*H_3); δ_P (162 MHz, $CDCl_3$): 154.58 (*P*-N); $[\alpha]_D$ (25 °C) +119.2 (c = 1.00 in $CHCl_3$), literature value $[\alpha]_D$ (22 °C) +144.3 (c = 1.10 in $CHCl_3$). Characterisation data are consistent with literature values.[22]

(*S*)-4-Phenylhex-5-en-2-one (2.3.19)

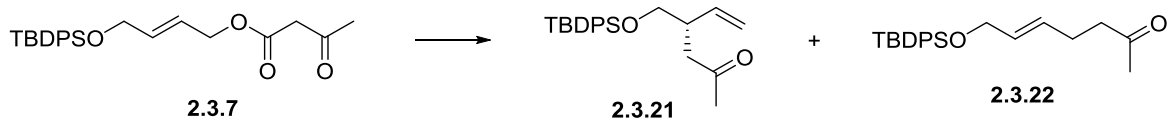


2.3.4 **2.3.19**

The title compound **2.3.19** was synthesised from *β*-ketoester **2.3.4** (200 mg, 0.916 mmol) in THF (1.7 mL) using $[Ir(COD)Cl]_2$ (25 mg, 0.92 mmol), ligand **L2** (44 mg, 1.8 mmol) and TBD (21 mg, 3.7 mmol) in THF (1.4 mL) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.19** (137 mg, 0.788 mmol, 86%) as a yellow oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.23 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.2, 10.4, 6.9 Hz, H-5), 5.06 (dt, 1H, *J* = 10.4, 1.3 Hz, $H_{pro(E)}$-6), 5.02 (dt, 1H, *J* = 17.2, 1.3 Hz, $H_{pro(Z)}$-6), 3.91 (q, 1H, *J* =

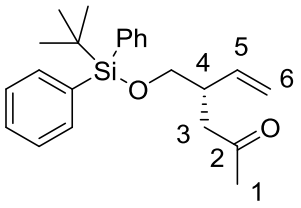
6.9 Hz, H-4), 2.89 (dd, 1H, *J* = 16.2, 7.6 Hz, H-3), 2.82 (dd, 1H, *J* = 16.2, 7.4 Hz, H'-3), 2.09 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.2 (C-2), 142.9 (C-5), 140.7 (Ar), 128.7 (Ar), 127.7 (Ar), 126.7 (Ar), 114.7 (C-6), 49.1 (C-3), 44.7 (C-4), 30.8 (C-1); *m/z* (ESI^+): 197.1 ($[M+Na]^+$, 100%); *ee*: >99% [Chiralcel AD-H column (4.6 mm x 250 mm), 2% 2-propanol in *n*-hexane, flow rate = 0.5 mL / min, detection wavelength = 210 nm] t_R(*R*) = 14.50 min, t_R(*S*) = 16.36 min; $[\alpha]_D$ (22 °C) -12.3 (c = 0.80 in $CHCl_3$), literature value $[\alpha]_D$ (20 °C) -5.63 (c = 1.10 in $CHCl_3$).[84] Characterisation data are consistent with literature values.[86]

(S)-4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hex-5-en-2-one (2.3.21) and **(*E*)-7-((*tert*-butyldiphenylsilyl)oxy)hept-5-en-2-one (2.3.22)**



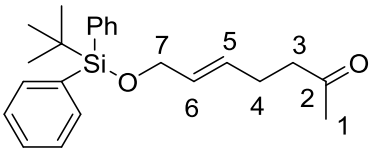
The title compounds **2.3.21** and **2.3.22** were synthesised from *β*-ketoester **2.3.7** (200 mg, 0.507 mmol) in THF (1.7 mL) using $[Ir(COD)Cl]_2$ (14 mg, 0.021 mmol), ligand **L2** (25 mg, 1.0 mmol) and TBD (12 mg, 0.086 mmol) in THF (0.8 mL) according to general procedure A4.

(S)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)hex-5-en-2-one (2.3.21)



The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title branched isomer **2.3.21** (142 mg, 0.385mmol, 76%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.75 (ddd, 1H, *J* = 17.6, 9.8, 7.7 Hz, H-5), 5.06 (ddd, 1H, *J* = 17.6, 1.5, 1.3 Hz, $H_{pro(Z)}$-6), 5.05 (ddd, 1H, *J* = 9.8, 1.5, 0.8 Hz, $H_{pro(E)}$-6), 3.67 (dd, 1H, *J* = 9.8, 5.3 Hz, SiOCH_2), 3.57 (dd, 1H, *J* = 9.8, 6.6 Hz, SiOCH'_2), 2.86 (sext, 1H, *J* = 6.8 Hz, H-4), 2.76 (dd, 1H, *J* = 16.2, 5.6 Hz, H-3), 2.48 (dd, 1H, *J* = 16.2, 8.0 Hz, H'-3), 2.13 (s, 3H, H-1), 1.08 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 207.9 (C-2), 138.3 (C-5), 135.6 (Ar), 133.6 (Ar), 129.7 (Ar), 127.7 (Ar), 116.1 (C-6), 66.5 (*C*H_2OSi), 45.1 (C-3), 41.7 (C-4), 30.5 (C-1), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 2931 (w, C-H), 2858 (w, C-H), 1716 (s, C=O), 1110 (s), 702 (s); *m/z* (ESI$^+$): 389.2 ([M+Na]$^+$, 100%); accurate mass: found 389.1903, $C_{23}H_{30}NaO_2Si$ [M+Na]$^+$ requires 389.1907; *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 0.6% 2-propanol in *n*-hexane, flow rate = 0.4 mL / min, detection wavelength = 230 nm] t_R(*R*) = 17.59 min, t_R(*S*) = 18.77 min; [α]$_D$ (22 °C) +7.5 (c = 0.80 in $CHCl_3$).

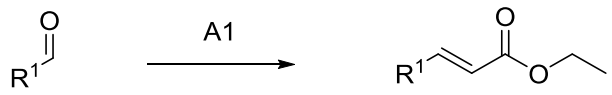
(*E*)-7-((*tert*-Butyldiphenylsilyl)oxy)hept-5-en-2-one (2.3.22)



The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title linear isomer **2.3.22** (14 mg, 0.038 mmol, branched to linear ratio 10 : 1) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.68 – 7.65 (m, 4H, Ar-*H*), 7.42 – 7.36 (m, 6H, Ar-*H*), 5.64 (dtt, 1H, *J* = 15.4, 6.1, 1.4 Hz, H-5), 5.57 (dtt, 1H, *J* = 15.4, 4.9, 1.0 Hz, H-6), 4.15 (dq, 2H, *J* = 4.9, 1.4 Hz, H-7), 2.49 (t, 2H, *J* = 7.5 Hz, H-3), 2.29 (dt, 2H, *J* = 6.1, 7.5 Hz, H-4), 2.14 (s, 3H, H-1), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 208.2 (C-2), 135.5 (Ar), 133.8 (Ar), 129.7 (C-6), 129.6 (Ar), 129.1 (C-5), 127.6 (Ar), 64.4 (C-7), 43.1 (C-3), 30.0 (C-1), 26.8 ($SiC(CH_3)_3$), 26.3 (C-4), 19.2 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2857 (m, C-H), 1718 (m, C=O), 1428 (m), 1112 (s), 703 (s); *m/z* (ESI^+): 389.3 ($[M+Na]^+$, 100%); accurate mass: found 389.1916, $C_{23}H_{30}NaO_2Si$ $[M+Na]^+$ requires 389.1907.

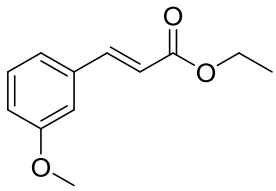
4.3.2 Screening of aryl *β*-ketoester substrates (Section 2.3.4)

4.3.2.1 Preparation of α,β*-unsaturated esters* ***2.3.24***



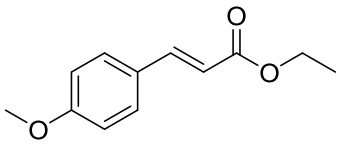
2.3.23 **2.3.24**

(*E*)-Ethyl 3-(3-methoxyphenyl)acrylate



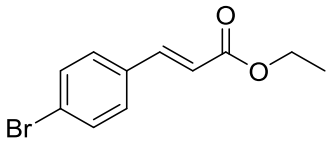
The title compound was synthesised from the corresponding aldehyde (700 mg, 5.14 mmol) according to general procedure A1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (940 mg, 4.56 mmol, 89%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.65 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 7.30 (t, 1H, *J* = 7.9 Hz, Ar-*H*), 7.12 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.05 – 7.04 (m, 1H, Ar-*H*), 6.93 (dd, 1H, *J* = 8.3, 2.5 Hz, Ar-*H*), 6.43 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 4.27 (q, 2H, *J* = 7.3 Hz, OCOCH_2), 3.83 (s, 3H, PhOCH_3), 1.34 (t, 3H, *J* = 7.3 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.1 (*C*=O), 160.0 (Ar), 144.6 (Ph*C*H=CH), 135.9 (Ar), 130.0 (Ar), 120.9 (Ar), 118.7 (PhCH=*C*H), 116.2 (Ar), 113.0 (Ar), 60.7 ($OCOCH_2$), 55.4 ($PhOCH_3$), 14.5 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[174]

(*E*)-Ethyl 3-(4-methoxyphenyl)acrylate



The title compound was synthesised from the corresponding aldehyde (700 mg, 5.14 mmol) according to general procedure A1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (700 mg, 3.39 mmol, 75%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.64 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 7.48 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.90 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.31 (d, 1H, *J* = 15.9 Hz, PhCH=C*H*), 4.25 (q, 2H, *J* = 7.0 Hz, OCOCH_2), 3.84 (s, 3H, OCH_3), 1.33 (t, 3H, *J* = 7.0 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.5 (*C*=O), 161.4 (Ar), 144.4 (Ph*C*H=CH), 129.8 (Ar), 127.3 (Ar), 115.9 (PhCH=*C*H), 114.4 (Ar), 60.5 ($OCOCH_2$), 55.5 (OCH_3), 14.5 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[175]

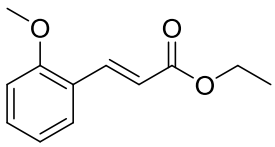
(*E*)-Ethyl 3-(4-bromophenyl)acrylate



The title compound was synthesised from the corresponding aldehyde (2.00 g, 10.8 mmol) according to general procedure A1. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (2.7 g, 10.6 mmol, 98%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.61 (d, 1H,

J = 16.1 Hz, PhC*H*=CH), 7.53 – 7.51 (m, 2H, Ar-*H*), 7.40 – 7.37 (m, 2H, Ar-*H*), 6.42 (d, 1H, *J* = 16.1 Hz, PhCH=C*H*), 4.26 (q, 2H, *J* = 7.3 Hz, OCOCH_2), 1.34 (t, 3H, *J* = 7.3 Hz, OCOCH$_2$CH_3); δ_C (100 MHz, $CDCl_3$): 166.8 (*C*=O), 143.2 (Ph*C*H=CH), 133.5 (Ar), 132.2 (Ar), 129.5 (Ar), 124.5 (Ar), 119.1 (PhCH=*C*H), 60.7 (OCO*C*H$_2$), 14.4 (OCOCH$_2$*C*H$_3$). Characterisation data are consistent with literature values.[176]

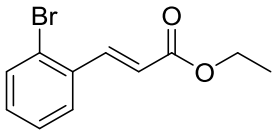
(*E*)-Ethyl 3-(2-methoxyphenyl)acrylate



The title compound was synthesised from the corresponding aldehyde (700 mg, 5.14 mmol) according to general procedure A1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give a mixture of *E* and *Z* isomers (*E* : *Z* ratio 5.6 : 1, 908 mg, 4.42 mmol, 86%). The *Z* isomers were converted to *E* isomers according to a procedure of Argade *et al*.:[177] a mixture of *E* and *Z* isomers (565 mg, 2.74 mmol), *N*-bromosuccinimide (536 mg, 3.01 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (67 mg, 0.27 mmol) in CCl_4 (15 mL) was stirred under reflux for 3.5 h. Upon completion, the mixture was concentrated *in vacuo* and the crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (517 mg, 2.52 mmol, 92%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.99 (d, 1H, *J* = 16.3 Hz, PhC*H*=CH), 7.51 (dd, 1H, *J* = 7.6, 1.6 Hz, Ar-*H*), 7.37 – 7.33 (m, 1H, Ar-*H*), 6.96 (t, 1H, *J* = 7.6 Hz, Ar-*H*), 6.92 (d, 1H, *J* = 6.5 Hz, Ar-*H*), 6.53 (d, 1H, *J* = 16.3 Hz, PhCH=C*H*), 4.26 (q, 2H, *J* = 7.1 Hz, OCOCH_2),

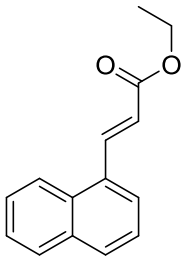
3.89 (s, 3H, OC*H*$_3$), 1.34 (t, 3H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$): 167.6 (*C*=O), 158.5 (Ar), 140.1 (Ph*C*H=CH), 131.5 (Ar), 129.1 (Ar), 123.6 (Ar), 120.8 (Ar), 118.9 (PhCH=*C*H), 111.2 (Ar), 60.5 (OCO*C*H$_2$), 55.6 (O*C*H$_3$), 14.5 (OCOCH$_2$*C*H$_3$). Characterisation data are consistent with literature values.[176]

(*E*)-Ethyl 3-(2-bromophenyl)acrylate



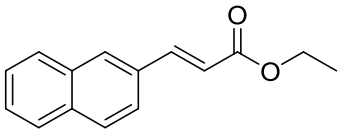
The title compound was synthesised from the corresponding aldehyde (1.00 g, 5.40 mmol) according to general procedure A1. The crude product was purified by FC (8% EtOAc in PE$_{40\text{-}60}$) to give a mixture of *E* and *Z* isomers (*E* : *Z* ratio 4 : 1, 1.24 g, 4.86 mmol, 90%). The *Z* isomers were converted to *E* isomers according to a procedure of Argade *et al*.:[177] a mixture of *E* and *Z* isomers (600 mg, 2.35 mmol), *N*-bromosuccinimide (461 mg, 2.59 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (57 mg, 0.24 mmol) in CCl_4 (12.0 mL) was stirred under reflux for 4.5 h. Upon completion, the mixture was concentrated in vacuo and the crude product was purified by FC (10% EtOAc in PE$_{40\text{-}60}$) to give the title compound (600 mg, 2.35 mmol, 100%) as a colourless oil. R_f = 0.3 (10% EtOAc in PE$_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.05 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 7.62 – 7.59 (m, 2H, Ar-*H*), 7.33 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.23 (td, 1H, *J* = 7.5, 1.7 Hz, Ar-*H*), 6.39 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 4.28 (q, 2H, *J* = 7.1 Hz, OCOC*H*$_2$), 1.35 (t, 3H, *J* = 7.1 Hz, OCOCH$_2$C*H*$_3$). Characterisation data are consistent with literature values.[178]

(*E*)-Ethyl 3-(naphthalen-1-yl)acrylate



The title compound was synthesised from the corresponding aldehyde (1.00 g, 6.40 mmol) according to general procedure A1. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (1.20 g, 5.30 mmol, 83%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.53 (d, 1H, *J* = 15.7 Hz, PhC*H*=CH), 8.21 (d, 1H, *J* = 8.5 Hz, Ar-*H*), 7.89 (t, 2H, *J* = 8.0 Hz, Ar-*H*), 7.76 (d, 1H, *J* = 7.1 Hz, Ar-*H*), 7.61 – 7.47 (m, 3H, Ar-*H*), 6.53 (d, 1H, *J* = 15.7 Hz, PhCH=C*H*), 4.32 (q, 2H, *J* = 7.2 Hz, OCOCH_2), 1.38 (t, 3H, *J* = 7.2 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.0 (*C*=O), 141.7 (Ph*C*H=CH), 133.8 (Ar), 131.9 (Ar), 131.5 (Ar), 130.6 (Ar), 128.8 (Ar), 127.0 (Ar), 126.3 (Ar), 125.6 (Ar), 125.1 (Ar), 123.5 (Ar), 121.0 (PhCH=*C*H), 60.7 ($OCOCH_2$), 14.5 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[179]

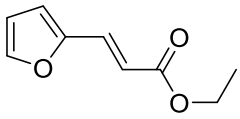
(*E*)-Ethyl 3-(naphthalen-2-yl)acrylate



The title compound was synthesised from the corresponding aldehyde (1.00 g, 6.40 mmol) according to general procedure A1. The crude product was purified by

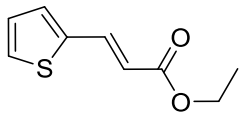
FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (1.27 g, 5.61 mmol, 88%) as a white solid. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.94 (s, 1H, Ar-*H*), 7.87 – 7.83 (m, 4H, Ar-*H* and PhC*H*=CH), 7.67 (dd, 1H, *J* = 8.6, 1.1 Hz, Ar-*H*), 7.53 – 7.50 (m, 2H, Ar-*H*), 6.56 (d, 1H, *J* = 16.0 Hz, PhCH=C*H*), 4.29 (q, 2H, *J* = 7.2 Hz, OCOC*H*$_2$), 1.36 (t, 3H, *J* = 7.2 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.2 (*C*=O), 144.7 (Ph*C*H=CH), 134.3 (Ar), 133.4 (Ar), 132.1 (Ar), 130.0 (Ar), 128.8 (Ar), 128.7 (Ar), 127.9 (Ar), 127.3 (Ar), 126.8 (Ar), 123.6 (Ar), 118.6 (PhCH=*C*H), 60.6 ($OCOCH_2$), 14.5 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[180]

(*E*)-Ethyl 3-(furan-2-yl)acrylate



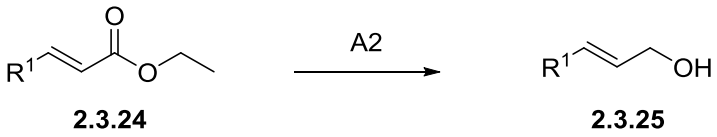
The title compound was synthesised from the corresponding aldehyde (700 mg, 7.28 mmol) according to general procedure A1. The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title compound (1.05 g, 6.26 mmol, 86%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.48 (s, 1H, Ar-*H*), 7.43 (d, 1H, *J* = 15.7 Hz, ArC*H*=CH), 6.60 (d, 1H, *J* = 3.4 Hz, Ar-*H*), 6.46 (dd, 1H, *J* = 3.4, 2.0 Hz, Ar-*H*), 6.31 (d, 1H, *J* = 15.7 Hz, ArCH=C*H*), 4.24 (q, 2H, *J* = 7.1 Hz, OCOC*H*$_2$), 1.32 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.2 (*C*=O), 151.1 (Ar), 144.8 (Ar), 131.1 (ArC*H*=CH), 116.1 (ArCH=C*H*), 114.7 (Ar), 112.3 (Ar), 60.6 ($OCOCH_2$), 14.4 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[181]

(*E*)-Ethyl 3-(thiophen-2-yl)acrylate



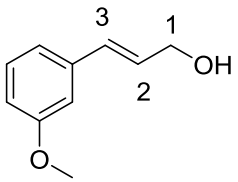
The title compound was synthesised from the corresponding aldehyde (1.00 g, 8.92 mmol) according to general procedure A1. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (1.37 g, 7.52 mmol, 84%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.78 (d, 1H, *J* = 15.7 Hz, ArC*H*=CH), 7.37 (d, 1H, *J* = 5.0 Hz, Ar-*H*), 7.26 – 7.25 (m, 1H, Ar-*H*), 7.05 (dd, 1H, *J* = 5.0, 3.6 Hz, Ar-*H*), 6.24 (d, 1H, *J* = 15.7 Hz, PhCH=C*H*), 4.25 (q, 2H, *J* = 7.2 Hz, OCOCH_2), 1.33 (t, 3H, *J* = 7.2 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.0 (*C*=O), 139.7 (Ar), 137.1 (Ph*C*H=CH), 131.0 (Ar), 128.5 (Ar), 128.2 (Ar), 117.1 (PhCH=*C*H), 60.6 (OCO*C*H_2), 14.4 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[182]

4.3.2.2 Preparation of allylic alcohols ***2.3.25***



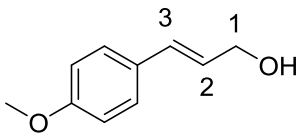
2.3.24 **2.3.25**

(*E*)-3-(3-Methoxyphenyl)prop-2-en-1-ol



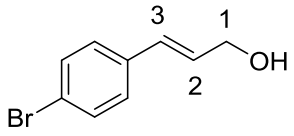
The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (700 mg, 3.39 mmol) according to general procedure A2 to give the crude title compound (550 mg, 3.35 mmol, 99%) as a colourless oil. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.24 – 7.22 (m, 1H, Ar-*H*), 6.99 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 6.93 – 6.92 (m, 1H, Ar-*H*), 6.80 (dd, 1H, *J* = 7.8, 2.5 Hz, Ar-*H*), 6.59 (d, 1H, *J* = 15.9 Hz, H-3), 6.36 (dt, 1H, *J* = 15.9, 5.4 Hz, H-2), 4.33 (dd, 2H, *J* = 5.4, 1.3 Hz, H-1), 3.82 (s, 3H, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$): 159.9 (Ar), 138.3 (Ar), 131.1 (C-3), 129.7 (Ar), 129.0 (C-2), 119.2 (Ar), 113.4 (Ar), 111.9 (Ar), 63.7 (C-1), 55.3 (O*C*H$_3$). Characterisation data are consistent with literature values.[183]

(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (600 mg, 2.91 mmol) according to general procedure A2 to give the crude title compound (469 mg, 2.85 mmol, 98%) as a white solide. The crude alcohol was used in the next step without further purification. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 6.86 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 6.56 (d, 1H, *J* = 15.9 Hz, H-3), 6.24 (dt, 1H, *J* = 15.9, 6.0 Hz, H-2), 4.30 (d, 2H, *J* = 6.0 Hz, H-1), 3.81 (s, 3H, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$): 159.4 (Ar), 131.1 (C-3), 129.5 (Ar), 127.8 (Ar), 126.4 (C-2), 114.1 (Ar), 64.1 (C-1), 55.4 (O*C*H_3). Characterisation data are consistent with literature values.[184]

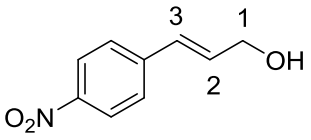
(*E*)-3-(4-Bromophenyl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (1.20 g, 4.70 mmol) according to general procedure A2 to give the crude title compound (1.03 g, 4.83 mmol, 103%) as a white solid. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.44 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.25 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 6.56 (d, 1H, *J* = 15.7 Hz, H-3), 6.35 (dt,

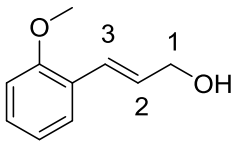
1H, *J* = 15.7, 5.6 Hz, H-2), 4.32 (dd, 2H, *J* = 5.6, 1.4 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 135.7 (Ar), 131.8 (Ar), 129.9 (C-3), 129.4 (C-2), 128.1 (Ar), 121.5 (Ar), 63.6 (C-1). Characterisation data are consistent with literature values.[183]

(*E*)-3-(4-Nitrophenyl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (2.00 g, 9.04 mmol) according to general procedure A2 and purified by FC (65% EtOAc in PE_{40-60}) to give the title compound (1.40 g, 7.81 mmol, 86%) as a yellow solid. R_f = 0.3 (65% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 8.20 – 8.18 (m, 2H, Ar-*H*), 7.53 – 7.50 (m, 2H, Ar-*H*), 6.72 (dt, 1H, *J* = 15.9, 1.8 Hz, H-3), 6.54 (dt, 1H, *J* = 15.9, 5.2 Hz, H-2), 4.40 (dd, 2H, *J* = 5.2, 1.5 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 147.1 (Ar), 143.4 (Ar), 133.7 (C-2), 128.4 (C-3), 127.1 (Ar), 124.2 (Ar), 63.3 (C-1); m.p. = 117 - 122 °C. Characterisation data are consistent with literature values.[185]

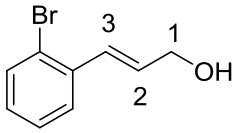
(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (454 mg, 2.20 mmol) according to general procedure A2 to give the crude title

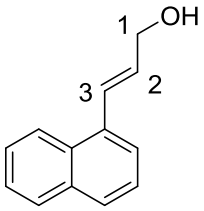
compound (344 mg, 2.10 mmol, 95%) as a colourless oil. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.44 (dd, 1H, *J* = 7.7, 1.5 Hz, Ar-*H*), 7.24 – 7.22 (m, 1H, Ar-*H*), 6.95 – 6.87 (m, 3H, Ar-*H* and H-3), 6.39 (dt, 1H, *J* = 16.0, 5.9 Hz, H-2), 4.33 (dd, 2H, *J* = 5.9, 1.3 Hz, H-1), 3.85 (s, 3H, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$): 156.9 (Ar), 129.4 (C-2), 128.9 (Ar), 127.1 (Ar), 126.3 (C-3), 125.8 (Ar), 120.8 (Ar), 110.9 (Ar), 64.4 (C-1), 55.5 (O*C*H$_3$). Characterisation data are consistent with literature values.[182]

(*E*)-3-(2-Bromophenyl)prop-2-en-1-ol



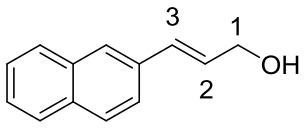
The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (550 mg, 2.16 mmol) according to general procedure A2 to give the crude title compound (435 mg, 2.04 mmol, 95%) as a colourless oil. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.56 – 7.51 (m, 2H, Ar-*H*), 7.30 – 7.28 (m, 1H, Ar-*H*), 7.11 (td, 1H, *J* = 7.7, 1.7 Hz, Ar-*H*), 6.96 (d, 1H, *J* = 15.7 Hz, H-3), 6.31 (dt, 1H, *J* = 15.7, 5.6 Hz, H-2), 4.37 (dd, 2H, *J* = 5.6, 1.0 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 136.7 (Ar), 133.1 (Ar), 131.8 (C-2), 129.8 (C-3), 129.1 (Ar), 127.6 (Ar), 127.3 (Ar), 123.8 (Ar), 63.7 (C-1). Characterisation data are consistent with literature values.[183]

(*E*)-3-(Naphthalen-1-yl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (600 mg, 2.65 mmol) according to general procedure A2 to give the crude title compound (470 mg, 2.55 mmol, 96%) as a cream oil. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 8.13 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.87 – 7.85 (m, 1H, Ar-*H*), 7.79 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.61 (d, 1H, *J* = 7.1 Hz, Ar-*H*), 7.54 – 7.44 (m, 3H, Ar-*H*), 7.39 (d, 1H, *J* = 15.7 Hz, H-3), 6.41 (dt, 1H, *J* = 15.7, 5.6 Hz, H-2), 4.45 (d, 2H, *J* = 5.6 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 134.6 (Ar), 133.7 (Ar), 131.9 (C-2), 131.3 (Ar), 128.7 (Ar), 128.3 (Ar), 128.2 (C-2), 126.2 (Ar), 125.9 (Ar), 125.7 (Ar), 124.1 (Ar), 123.9 (Ar), 64.1 (C-1). Characterisation data are consistent with literature values.[186]

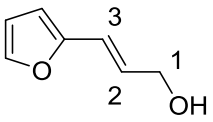
(*E*)-3-(Naphthalen-2-yl)prop-2-en-1-ol



The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (1.17 g, 5.17 mmol) according to general procedure A2 to give the crude title compound (900 mg, 4.89 mmol, 95%) as a white solid. The crude alcohol was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.82 – 7.78 (m,

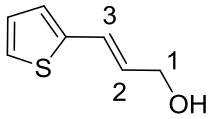
3H, Ar-*H*), 7.74 (s, 1H, Ar-*H*), 7.61 (dd, 1H, *J* = 8.6, 1.4 Hz, Ar-*H*), 7.49 – 7.43 (m, 2H, Ar-*H*), 6.79 (d, 1H, *J* = 16.3 Hz, H-3), 6.50 (dt, 1H, *J* = 16.3, 5.8 Hz, H-2), 4.39 (d, 2H, *J* = 5.8 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 134.3 (Ar), 133.7 (Ar), 133.2 (Ar), 131.4 (C-3), 129.0 (Ar), 128.4 (C-2), 128.1 (Ar), 127.8 (Ar), 126.6 (Ar), 126.4 (Ar), 126.1 (Ar), 123.7 (Ar), 64.0 (C-1). Characterisation data are consistent with literature values.[187]

(*E*)-3-(Furan-2-yl)prop-2-en-1-ol



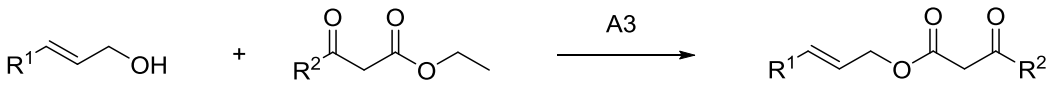
The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (300 mg, 1.80 mmol) according to general procedure A2 and purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound (190 mg, 1.53 mmol, 85%) as a yellow oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 (d, 1H, *J* = 1.8 Hz, Ar-*H*), 6.44 (dt, 1H, *J* = 15.8, 1.6 Hz, H-3), 6.37 (dd, 1H, *J* = 3.3, 1.8 Hz, Ar-*H*), 6.29 (dt, 1H, *J* = 15.8, 5.5 Hz, H-2), 6.24 (d, 1H, *J* = 3.3 Hz, Ar-*H*), 4.29 (dd, 2H, *J* = 5.5, 1.6 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 152.5 (Ar), 142.2 (Ar), 127.3 (C-2), 119.4 (C-3), 111.4 (Ar), 108.1 (Ar), 63.4 (C-1). Characterisation data are consistent with literature values.[188]

(*E*)-3-(Thiophen-2-yl)prop-2-en-1-ol



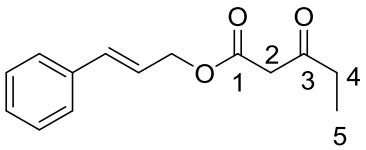
The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester (1.22 g, 6.69 mmol) according to general procedure A2 to give the crude title compound (920 mg, 6.56 mmol, 98%) as a yellow oil. δ_H (400 MHz, $CDCl_3$): 7.17 – 7.16 (m, 1H, Ar-*H*), 6.97 – 6.95 (m, 2H, Ar-*H*), 6.75 (d, 1H, *J* = 15.7 Hz, H-3), 6.30 (dt, 1H, *J* = 15.7, 5.6 Hz, H-2), 4.29 (d, 2H, *J* = 5.6 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 141.9 (Ar), 128.2 (C-2), 127.5 (Ar), 126.0 (Ar), 124.5 (Ar), 124.4 (C-3), 63.5 (C-1). Characterisation data are consistent with literature values.[184]

4.3.2.3 Preparation of β*-ketoesters* ***2.1.83***



2.3.25 **2.3.26** **2.1.83**

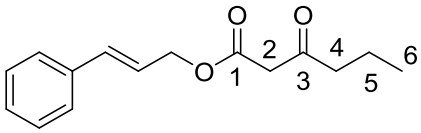
Cinnamyl 3-oxopentanoate



The title compound was synthesised from the corresponding allylic alcohol (500 mg, 3.73 mmol) and methyl 3-oxopentanoate (0.47 mL, 3.73 mmol) according to general

procedure A3. The crude product was purified by FC (20% EtOAc in PE_{40-60}) to give the title compound (699 mg, 3.01 mmol, 81%) as a pale yellow oil. R_f = 0.3 (20% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.42 – 7.37 (m, 2H, Ar-*H*), 7.36 – 7.30 (m, 2H, Ar-*H*), 7.29 – 7.26 (m, 1H, Ar-*H*), 6.67 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.9, 6.5 Hz, PhCH=C*H*), 4.80 (dd, 2H, *J* = 6.5, 1.3 Hz, CH=CHCH_2), 3.50 (s, 2H, H-2), 2.58 (q, 2H, *J* = 7.3 Hz, H-4), 1.09 (t, 3H, *J* = 7.3 Hz, H-5); δ_C (100 MHz, $CDCl_3$): 203.2 (C-3), 167.2 (C-1), 136.1 (Ar), 134.9 (Ph*C*H=CH), 128.7 (Ar), 128.3 (Ar), 126.8 (Ar), 122.6 (PhCH=*C*H), 66.0 (PhCH=CH*C*H_2), 49.1 (C-2), 36.5 (C-4), 7.7 (C-5); ν_{max}/cm^{-1}: 2979 (w, C-H), 1742 (s, C=O, ester), 1714 (s, C=O, ketone), 1307 (m), 1155 (m), 966 (s); *m/z* (ESI^+): 255.1 ($[M+Na]^+$, 80%); accurate mass: found 255.0994, $C_{14}H_{16}NaO_3$ $[M+Na]^+$ requires 255.0992.

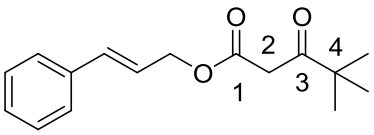
Cinnamyl 3-oxohexanoate



The title compound was synthesised from the corresponding allylic alcohol (500 mg, 3.73 mmol) and ethyl 3-oxohexanoate (0.60 mL, 3.7 mmol) according to general procedure A3. The crude product was purified by FC (15% EtOAc in PE_{40-60}) to give the title compound (705 mg, 2.86 mmol, 77%) as a colourless oil. R_f = 0.3 (15% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.40 – 7.38 (m, 2H, Ar-H), 7.35 – 7.31 (m, 2H, Ar-*H*), 7.28 – 7.25 (m, 1H, Ar-*H*), 6.67 (d, 1H, *J* = 15.8 Hz, PhC*H*=CH), 6.27 (dt, 1H, *J* = 15.8, 6.6 Hz, PhCH=C*H*), 4.79 (dd, 2H, *J* = 6.6, 1.4 Hz, PhCH=CHCH_2),

3.48 (s, 2H, H-2), 2.53 (t, 2H, *J* = 6.9 Hz, H-4), 1.63 (sext, 2H, *J* = 7.3 Hz, H-5), 0.92 (t, 3H, *J* = 7.6 Hz, H-6); δ_C (100 MHz, $CDCl_3$): 202.8 (C-3), 167.2 (C-1), 136.2 (Ar), 134.9 (Ph*C*H=CH), 128.7 (Ar), 128.3 (Ar),126.8 (Ar), 122.6 (PhCH=*C*H), 66.0 (PhCH=CH*C*H_2), 49.4 (C-2), 45.1 (C-4), 17.1 (C-5), 13.7 (C-6); ν_{max}/cm^{-1}: 2964 (w, C-H), 1742 (s, C=O, ester), 1714 (s, C=O, ketone), 1314 (m), 1153 (m), 967 (s); *m/z* (ESI^+): 269.1 ($[M+Na]^+$, 60%); accurate mass: found 269.1158, $C_{15}H_{18}NaO_3$ $[M+Na]^+$ requires 269.1148.

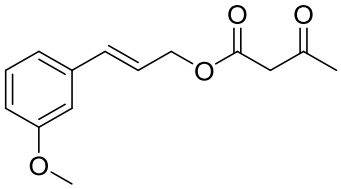
Cinnamyl 4,4-dimethyl-3-oxopentanoate



The title compound was synthesised from the corresponding allylic alcohol (400 mg, 2.98 mmol) and ethyl 4,4-dimethyl-3-oxopentanoate (0.53 mL, 3.0 mmol) according to general procedure A3. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (605 mg, 2.32 mmol, 78%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.40 – 7.38 (m, 2H, Ar-H), 7.34 – 7.30 (m, 2H, Ar-*H*), 7.28 – 7.24 (m, 1H, Ar-*H*), 6.67 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.9, 6.5 Hz, PhCH=C*H*), 4.79 (dd, 2H, *J* = 6.5, 1.2 Hz, PhCH=CHCH_2), 3.60 (s, 2H, H-2), 1.18 (s, 9H, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 208.0 (C-3), 167.7 (C-1), 136.3 (Ar), 134.7 (Ph*C*H=CH), 128.7 (Ar), 128.2 (Ar),126.8 (Ar), 122.9 (PhCH=*C*H), 66.0 (PhCH=CH*C*H_2), 44.0 (C-2), 27.9 (C-4), 26.2 (C(*C*H_3)$_3$); ν_{max}/cm^{-1}: 2971 (w, C-H), 1744 (s, C=O, ester), 1706 (s, C=O,

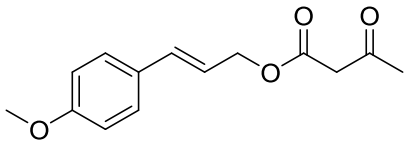
ketone), 1314 (m), 1268 (s), 1200 (m), 1142 (m), 966 (s); *m/z* (ESI^+): 283.1 ($[M+Na]^+$, 40%); accurate mass: found 283.1307, $C_{16}H_{20}NaO_3$ $[M+Na]^+$ requires 283.1305.

(*E*)-3-(3-Methoxyphenyl)allyl 3-oxobutanoate



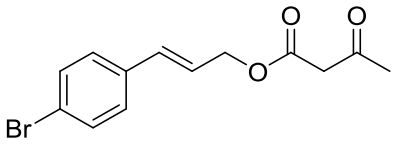
The title compound was synthesised from the corresponding allylic alcohol (450 mg, 2.74 mmol) and ethyl acetoacetate (0.35 mL, 2.7 mmol) according to general procedure A3. The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound (582 mg, 2.34 mmol, 86%) as a yellow oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.24 – 7.22 (m, 1H, Ar-*H*), 6.99 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 6.93 – 6.92 (m, 1H, Ar-*H*), 6.82 (dd, 1H, *J* = 8.3, 2.5 Hz, Ar-*H*), 6.65 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.27 (dt, 1H, *J* = 15.9, 6.6 Hz, PhCH=C*H*), 4.79 (dd, 2H, *J* = 6.6, 0.9 Hz, PhCH=CHC*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 3.51 (s, 2H, OC(O)C*H*$_2$CO), 2.29 (s, 3H, C(O)C*H*$_3$); δ_C (100 MHz, $CDCl_3$): 200.5 (*C*=O, ketone), 167.0 (*C*=O, ester), 159.9 (Ar), 137.6 (Ar), 134.9 (Ph*C*H=CH), 129.8 (Ar), 122.9 (PhCH=*C*H), 119.5 (Ar), 114.1 (Ar), 112.0 (Ar), 66.0 (PhCH=CH*C*H$_2$), 55.4 (O*C*H$_3$), 50.2 (OC(O)*C*H$_2$CO), 30.4 (C(O)*C*H$_3$); ν_{max}/cm^{-1}: 2942 (w, C-H), 1741 (s, C=O, ester), 1714 (s, C=O, ketone), 1315 (m), 1259 (s), 1151 (s), 965 (s); *m/z* (ESI^+): 271.1 ($[M+Na]^+$, 100%); accurate mass: found 271.0943, $C_{14}H_{16}NaO_4$ $[M+Na]^+$ requires 271.0941.

(*E*)-3-(4-Methoxyphenyl)allyl 3-oxobutanoate



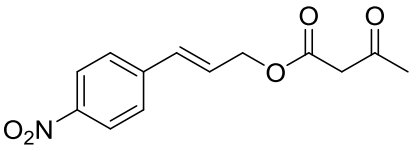
The title compound was synthesised from the corresponding allylic alcohol (200 mg, 1.22 mmol) and ethyl acetoacetate (0.16 mL, 1.2 mmol) according to general procedure A3. The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound (192 mg, 0.773 mmol, 64%) as a yellow oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.36 – 7.30 (m, 2H, Ar-*H*), 6.89 – 6.83 (m, 2H, Ar-*H*), 6.62 (d, 1H, *J* = 15.8 Hz, PhC*H*=CH), 6.14 (dt, 1H, *J* = 15.8, 6.8 Hz, PhCH=C*H*), 4.78 (dd, 2H, *J* = 6.8, 1.2 Hz, PhCH=CHCH_2), 3.81 (s, 3H, OCH_3), 3.49 (s, 2H, OC(O)CH_2CO), 2.28 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 159.8 (Ar), 134.8 (Ph*C*H=CH), 128.8 (Ar), 128.0 (Ar), 120.1 (PhCH=*C*H), 114.1 (Ar), 66.3 (PhCH=CH*C*H_2), 55.4 (O*C*H_3), 50.2 (OC(O)*C*H_2CO), 30.3 (C(O)*C*H_3); ν_{max}/cm^{-1}: 2937 (w, C-H), 1741 (s, C=O, ester), 1714 (s, C=O, ketone), 1513 (s), 1306 (m), 1247 (s), 1174 (s), 1150 (s), 1031 (s); *m/z* (ESI^+): 271.1 ($[M+Na]^+$, 100%); accurate mass: found 271.0939, $C_{14}H_{16}NaO_4$ $[M+Na]^+$ requires 271.0941.

(*E*)-3-(4-Bromophenyl)allyl 3-oxobutanoate



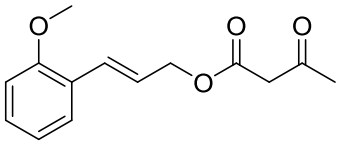
The title compound was synthesised from the corresponding allylic alcohol (400 mg, 1.88 mmol) and ethyl acetoacetate (0.24 mL, 1.9 mmol) according to general procedure A3. The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound (470 mg, 1.58 mmol, 84%) as a colourlesss oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.46 – 7.43 (m, 2H, Ar-*H*), 7.26 – 7.24 (m, 2H, Ar-*H*), 6.61 (d, 1H, *J* = 16.3 Hz, PhC*H*=CH), 6.26 (dt, 1H, *J* = 16.3, 6.3 Hz, PhCH=C*H*), 4.78 (dd, 2H, *J* = 6.3, 1.0 Hz, PhCH=CHCH_2), 3.51 (s, 2H, OC(O)CH_2CO), 2.29 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.5 (*C*=O, ketone), 167.0 (*C*=O, ester), 135.1 (Ar), 133.6 (Ph*C*H=CH), 131.9 (Ar), 128.3 (Ar), 123.4 (PhCH=*C*H), 122.2 (Ar), 65.8 (PhCH=CH*C*H_2), 50.1 (OC(O)*C*H_2CO), 30.4 (C(O)*C*H_3); ν_{max}/cm^{-1}: 1745 (s, C=O, ester), 1713 (s, C=O, ketone), 1487 (m), 1315 (m), 1260 (m), 1146 (s), 1071 (m), 1008 (m), 965 (s); *m/z* (ESI^+): 319.0 ($[M^{79Br}+Na]^+$, 100%), 321.0 ($[M^{81Br}+Na]^+$, 100%); accurate mass: found 318.9940, $C_{13}H_{13}{}^{79}BrNaO_3$ $[M^{79Br}+Na]^+$ requires 318.9940, found 320.9922, $C_{13}H_{13}{}^{81}BrNaO_3$ $[M^{81Br}+Na]^+$ requires 320.9920.

(*E*)-3-(4-Nitrophenyl)allyl 3-oxobutanoate



The title compound was synthesised from the corresponding allylic alcohol (500 mg, 2.79 mmol) and ethyl acetoacetate (0.36 mL, 2.8 mmol) according to general procedure A3. The crude product was purified by FC (40% EtOAc in $PE_{40\text{-}60}$) to give the title compound (507 mg, 1.93 mmol, 69%) as a yellow oil. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.19 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.53 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 6.79 (d, 1H, *J* = 16.1 Hz, PhC*H*=CH), 6.44 (dt, 1H, *J* = 16.1, 5.9 Hz, PhCH=C*H*), 4.85 (dd, 2H, *J* = 5.9, 1.2 Hz, PhCH=CHCH_2), 3.54 (s, 2H, OC(O)CH_2CO), 2.30 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.4 (*C*=O, ketone), 166.8 (*C*=O, ester), 147.4 (Ar), 142.6 (Ar), 131.9 (Ph*C*H=CH), 127.6 (PhCH=*C*H), 127.3 (Ar), 124.2 (Ar), 65.2 (PhCH=CH*C*H_2), 50.1 (OC(O)*C*H_2CO), 30.4 (C(O)*C*H_3). Characterisation data are consistent with literature values.[189]

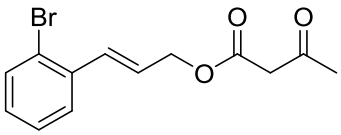
(*E*)-3-(2-Methoxyphenyl)allyl 3-oxobutanoate



The title compound was synthesised from the corresponding allylic alcohol (300 mg, 1.83 mmol) and ethyl acetoacetate (0.23 mL, 1.8 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give

the title compound (300 mg, 1.21 mmol, 66%) as a yellow oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.43 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar-*H*), 7.26 – 7.22 (m, 1H, Ar-*H*), 6.99 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 6.93 (t, 1H, *J* = 7.7 Hz, Ar-*H*), 6.88 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 6.31 (dt, 1H, *J* = 16.0, 6.6 Hz, PhCH=C*H*), 4.81 (dd, 2H, *J* = 6.6, 1.3 Hz, PhCH=CHCH_2), 3.85 (s, 3H, OCH_3), 3.50 (s, 2H, OC(O)CH_2CO), 2.29 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.5 (*C*=O, ketone), 166.9 (*C*=O, ester), 156.9 (Ar), 129.9 (Ph*C*H=CH), 129.3 (Ar), 127.2 (Ar), 124.9 (Ar), 123.0 (PhCH=*C*H), 120.6 (Ar), 110.9 (Ar), 66.5 (PhCH=CH*C*H_2), 55.4 (O*C*H_3), 50.0 (OC(O)*C*H_2CO), 30.1 (C(O)*C*H_3); ν_{max}/cm^{-1}: 2940 (w, C-H), 1742 (s, C=O, ester), 1717 (s, C=O, ketone), 1450 (m), 1316 (m), 1245 (s), 1149 (m), 1027 (m); *m/z* (ESI^+): 271.1 ($[M+Na]^+$, 100%); accurate mass: found 271.0943, $C_{14}H_{16}NaO_4$ $[M+Na]^+$ requires 271.0941.

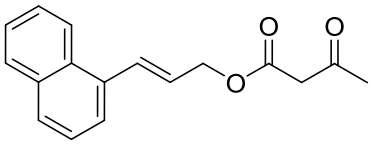
(E)-3-(2-Bromophenyl)allyl 3-oxobutanoate



The title compound was synthesised from the corresponding allylic alcohol (374 mg, 1.76 mmol) and ethyl acetoacetate (0.22 mL, 1.8 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (344 mg, 1.16 mmol, 66%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.56 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.52 (d, 1H, *J* = 7.8 Hz, Ar-*H*), 7.28 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 7.13 (t, 1H, *J* = 7.8 Hz, Ar-*H*), 7.02

(d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.23 (dt, 1H, *J* = 15.9, 6.5 Hz, PhCH=C*H*), 4.84 (d, 2H, *J* = 6.5 Hz, PhCH=CHC*H*$_2$), 3.52 (s, 2H, OC(O)C*H*$_2$CO), 2.30 (s, 3H, C(O)C*H*$_3$); δ_C (100 MHz, $CDCl_3$): 200.5 (*C*=O, ketone), 166.9 (*C*=O, ester), 136.1 (Ar), 133.3 (Ph*C*H=CH), 133.1 (Ar), 129.6 (Ar), 127.7 (Ar), 127.4 (Ar), 125.7 (PhCH=*C*H), 123.9 (Ar), 65.7 (PhCH=CH*C*H$_2$), 50.1 (OC(O)*C*H$_2$CO), 30.4 (C(O)*C*H$_3$); ν_{max}/cm^{-1}: 1742 (s, C=O, ester), 1715 (s, C=O, ketone), 1467 (m), 1360 (m), 1314 (m), 1256 (m), 1147 (s), 1023 (s), 964 (s); *m/z* (ESI$^+$): 319.0 ([M^{79Br}+Na]$^+$, 100%), 321.0 ([M^{81Br}+Na]$^+$, 100%); accurate mass: found 318.9947, $C_{13}H_{13}{}^{79}BrNaO_3$ [M^{79Br}+Na]$^+$ requires 318.9940, found 320.9928, $C_{13}H_{13}{}^{81}BrNaO_3$ [M^{81Br}+Na]$^+$ requires 320.9920.

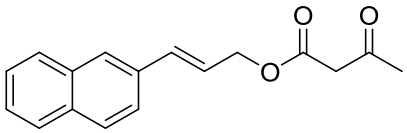
(E)-3-(Naphthalen-1-yl)allyl 3-oxobutanoate



The title compound was synthesised from the corresponding allylic alcohol (400 mg, 2.17 mmol) and ethyl acetoacetate (0.28 mL, 2.2 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in PE$_{40-60}$) to give the title compound (430 mg, 1.60 mmol, 74%) as a colourless oil. R_f = 0.3 (25% EtOAc in PE$_{40-60}$); δ_H (400 MHz, $CDCl_3$): 8.10 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.86 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.81 (d, 1H, *J* = 7.9 Hz, Ar-*H*), 7.60 (d, 1H, *J* = 7.2 Hz, Ar-*H*), 7.55 – 7.43 (m, 4H, Ar-*H* and ArC*H*=CH), 6.31 (dt, 1H, *J* = 15.3, 6.4 Hz, ArCH=C*H*), 4.92 (d, 2H, *J* = 6.4 Hz, ArCH=CHC*H*$_2$), 3.54 (s, 2H, OC(O)C*H*$_2$CO), 2.31 (s, 3H, C(O)C*H*$_3$); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 133.9

(Ar), 133.7 (Ar), 132.1 (Ar*C*H=CH), 131.2 (Ar), 128.7 (Ar), 128.6 (Ar), 126.4 (Ar), 126.0 (Ar), 125.7 (ArCH=*C*H), 125.6 (Ar), 124.3 (Ar), 123.7 (Ar), 66.1 (PhCH=CH*C*H_2), 50.2 (OC(O)*C*H_2CO), 30.4 (C(O)*C*H_3); ν_{max}/cm^{-1}: 3047 (w, C-H), 1741 (s, C=O, ester), 1715 (s, C=O, ketone), 1314 (m), 1253 (m), 1171 (m), 1148 (s), 965 (s); accurate mass: found 268.1099, $C_{17}H_{16}O_3$ requires 268.1100.

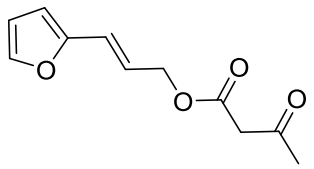
(E)-3-(Naphthalen-2-yl)allyl 3-oxobutanoate



The title compound was synthesised from the corresponding allylic alcohol (400 mg, 2.17 mmol) and ethyl acetoacetate (0.28 mL, 2.2 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (454 mg, 1.69 mmol, 78%) as a creamy white solid. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.82 – 7.79 (m, 3H, Ar-*H*), 7.76 (s, 1H, Ar-*H*), 7.60 (dd, 1H, *J* = 8.5, 1.7 Hz, Ar-*H*), 7.49 – 7.45 (m, 2H, Ar-*H*), 6.84 (d, 1H, *J* = 16.1 Hz, ArC*H*=CH), 6.40 (dt, 1H, *J* = 16.1, 6.5 Hz, ArCH=C*H*), 4.86 (d, 2H, *J* = 6.5 Hz, ArCH=CHC*H*$_2$), 3.53 (s, 2H, OC(O)C*H*$_2$CO), 2.30 (s, 3H, C(O)C*H*$_3$); δ_C (100 MHz, $CDCl_3$): 200.5 (C=O, ketone), 167.0 (C=O, ester), 135.0 (Ar*C*H=CH), 133.5 (Ar), 133.3 (Ar), 128.4 (Ar), 128.2 (Ar), 127.8 (Ar), 127.1 (Ar), 126.5 (Ar), 126.3 (Ar), 123.5 (Ar), 122.8 (ArCH=*C*H), 66.1 (PhCH=CH*C*H_2), 50.1 (OC(O)*C*H_2CO), 30.3 (C(O)*C*H_3); ν_{max}/cm^{-1}: 3056 (w, C-H), 1739 (s, C=O, ester), 1714 (s, C=O, ketone), 1314 (m), 1263 (m), 1146 (s), 962 (s); *m/z* (ESI^+): 291.1

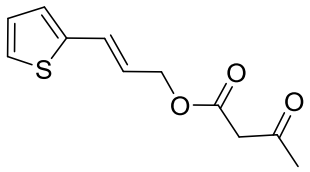
([M+Na]$^+$, 80%); accuate mass: found 291.0993, $C_{17}H_{16}NaO_3$ [M+Na]$^+$ requires 291.0992.

(*E*)-3-(Furan-2-yl)allyl 3-oxobutanoate



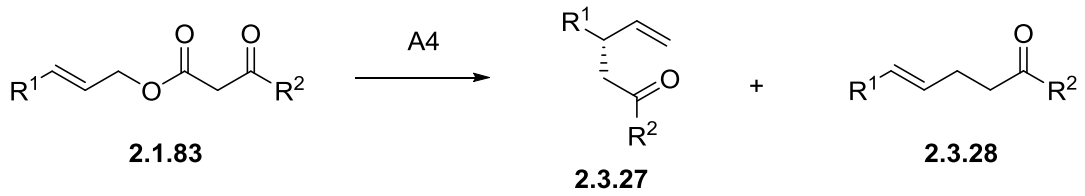
The title compound was synthesised from the corresponding allylic alcohol (445 mg, 3.58 mmol) and ethyl acetoacetate (0.41 mL, 3.6 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (460 mg, 2.43 mmol, 68%) as a yellow oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.36 (d, 1H, *J* = 1.9 Hz, Ar-*H*), 6.48 (dt, 1H, *J* = 15.8, 1.4 Hz, ArC*H*=CH), 6.37 (dd, 1H, *J* = 3.3, 1.9 Hz, Ar-*H*), 6.29 (d, 1H, *J* = 3.3 Hz, Ar-*H*), 6.19 (dt, 1H, *J* = 15.8, 6.5 Hz, ArCH=C*H*), 4.77 (dd, 2H, *J* = 6.5, 1.4 Hz, ArCH=CHCH_2), 3.49 (s, 2H, OC(O)CH_2), 2.28 (s, 3H, OC(O)CH_2C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.7 (*C*=O, ketone), 167.1 (*C*=O, ester), 151.9 (Ar), 142.8 (Ar), 123.1 (Ar*C*H=CH), 121.1 (ArCH=*C*H), 111.7 (Ar), 109.5 (Ar), 65.8 (ArCH=CH*C*H_2), 50.3 (C(O)*C*H_2), 30.5 (C(O)*C*H_3); ν_{max}/cm^{-1}: 3135 (w, C-H), 2936 (w, C-H), 1741 (s, C=O, ester), 1714 (s, C=O, ketone), 1410 (m), 1361 (m), 1315 (s), 1260 (s), 1172 (s), 1148 (s), 1014 (m); *m/z* (ESI$^+$): 231.1 ([M+Na]$^+$, 100%); accurate mass: found 231.0628, $C_{11}H_{12}O_4Na$ [M+Na]$^+$ requires 231.0628.

(*E*)-3-(Thiophen-2-yl)allyl 3-oxobutanoate



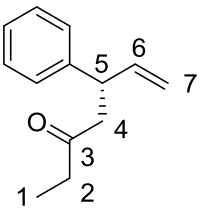
The title compound was synthesised from the corresponding allylic alcohol (820 mg, 5.85 mmol) and ethyl acetoacetate (0.75 mL, 5.9 mmol) according to general procedure A3. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (760 mg, 3.39 mmol, 58%) as a pale yellow oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.19 (d, 1H, *J* = 5.0 Hz, Ar-*H*), 7.01 – 6.96 (m, 2H, Ar-*H*), 6.80 (d, 1H, *J* = 15.9 Hz, ArC*H*=CH), 6.10 (dt, 1H, *J* = 15.9, 6.8 Hz, ArCH=C*H*), 4.76 (d, 2H, *J* = 6.8 Hz, ArCH=CHCH_2), 3.50 (s, 2H, OC(O)CH_2CO), 2.28 (s, 3H, C(O)CH_3); δ_C (100 MHz, $CDCl_3$): 200.5 (*C*=O, ketone), 167.0 (*C*=O, ester), 141.0 (Ar), 128.2 (Ar), 127.6 (Ar*C*H=CH), 126.7 (Ar), 125.3 (Ar), 121.8 (ArCH=*C*H), 65.7 (PhCH=CH*C*H_2), 50.1 (OC(O)*C*H_2CO), 30.3 (C(O)*C*H_3); ν_{max}/cm^{-1}: 3108 (w, C-H), 2934 (w, C-H), 1740 (s, C=O, ester), 1713 (s, C=O, ketone), 1649 (m), 1313 (m), 1262 (m), 1146 (s), 955 (s); *m/z* (ESI^+): 247.1 ($[M+Na]^+$, 100%); accurate mass: found 225.0585, $C_{11}H_{13}O_3S$ $[M+H]^+$ requires 225.0580.

*4.3.2.4 Preparation of enantioenriched ketones **2.3.27***



2.1.83 **2.3.27** **2.3.28**

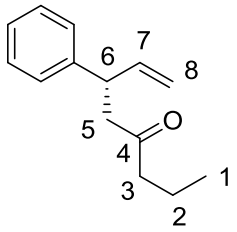
(*S*)-5-Phenylhept-6-en-3-one (Table 2.3.4, entry 2)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.26 mmol) according to general procedure A4. The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title compound (36 mg, 0.19 mmol, 74%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.22 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.1, 10.3, 7.1 Hz, H-6), 5.05 (dt, 1H, *J* = 10.3, 1.0 Hz, $H_{pro(E)}$-7), 5.01 (dt, 1H, *J* = 17.1, 1.0 Hz, $H_{pro(Z)}$-7), 3.93 (dt, 1H, *J* = 7.1, 7.0 Hz, H-5), 2.86 (dd, 1H, *J* = 16.1, 7.0 Hz, H-4), 2.79 (dd, 1H, *J* = 16.1, 7.1 Hz, H'-4), 2.39 (dq, 1H, *J* = 17.9, 7.2 Hz, H-2), 2.30 (dq, 1H, *J* = 17.9, 7.4 Hz, H'-2), 0.98 (t, 3H, *J* = 7.4 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 209.8 (C-3), 143.1 (Ar), 140.8 (C-6), 128.7 (Ar), 127.8 (Ar), 126.7 (Ar), 114.7 (C-7), 47.9 (C-4), 44.7 (C-5), 36.9 (C-2), 7.7 (C-1); *ee*: 99% [Chiralpak AD-H column (4.6 mm x 250 mm), 0.8% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength =

230 nm] $t_R(R)$ = 8.96 min, $t_R(S)$ = 10.34 min; $[\alpha]_D$ (20 °C) -25.0 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[86]

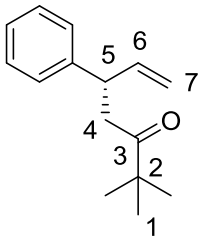
(S)-6-Phenyloct-7-en-4-one **(Table 2.3.4, entry 3)**



The title compound was synthesised from the corresponding *β*-ketoester (80 mg, 0.32 mmol) according to general procedure A4. The crude product was purified by FC (6% EtOAc in $PE_{40\text{-}60}$) to give the title compound (49 mg, 0.24 mmol, 74%) as a colourless oil. R_f = 0.3 (6% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.28 (m, 2H, Ar-*H*), 7.22 – 7.19 (m, 3H, Ar-*H*), 5.96 (ddd, 1H, *J* = 17.2, 10.2, 7.3 Hz, H-7), 5.05 (dt, 1H, *J* = 10.2, 1.3 Hz, $H_{pro(E)}$-8), 5.01 (dt, 1H, *J* = 17.2, 1.3 Hz, $H_{pro(Z)}$-8), 3.93 (dt, 1H, *J* = 7.3, 7.1 Hz, H-6), 2.85 (dd, 1H, *J* = 16.2, 7.5 Hz, H-5), 2.78 (dd, 1H, *J* = 16.2, 7.1 Hz, H'-5), 2.34 (dt, 1H, *J* = 16.7, 7.4 Hz, H-3), 2.27 (dt, 1H, *J* = 16.7, 7.2 Hz, H'-3), 1.53 (sext, 2H, *J* = 7.3 Hz, H-2), 0.84 (t, 3H, *J* = 7.5 Hz, H-1); δ_C (100 MHz, $CDCl_3$): 209.3 (C-4), 143.1 (Ar), 140.8 (C-7), 128.7 (Ar), 127.8 (Ar), 126.7 (Ar), 114.7 (C-8), 48.2 (C-5), 45.6 (C-3), 44.6 (C-6), 17.1 (C-2), 13.8 (C-1); ν_{max}/cm^{-1}: 2962 (w, C-H), 1712 (s, C=O), 1638 (w), 1493 (w), 1453 (w), 1408 (w), 1367 (w), 916 (m); *m/z* (ESI^+): 225.1 ($[M+Na]^+$, 100%); accurate mass: found 225.1251, $C_{14}H_{18}NaO$ $[M+Na]^+$ requires 225.1250; *ee*: >99% [Chiralpak AD-H column (4.6 mm x 250 mm), 0.5% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min,

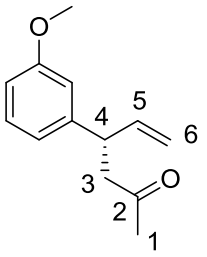
detection wavelength = 210 nm] t_R(*R*) = 9.30 min, t_R(*S*) = 11.01 min; [α]$_D$ (20 °C) -19.9 (c = 1.00 in $CHCl_3$).

(*S*)-2,2-Dimethyl-5-phenylhept-6-en-3-one (Table 2.3.4, entry 4)



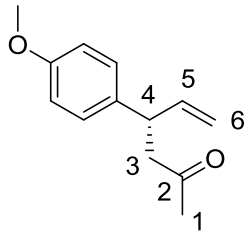
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.23 mmol) according to general procedure A4. The crude product was purified by FC (5% EtOAc in $PE_{40\text{-}60}$) to give the title compound (35 mg, 0.16 mmol, 70%) as a colourless oil. R_f = 0.3 (5% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.27 (m, 2H, Ar-*H*), 7.21 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.2, 10.4, 7.0 Hz, H-6), 5.04 (dt, 1H, *J* = 10.4, 1.5 Hz, $H_{pro(E)}$-7), 5.01 (dt, 1H, *J* = 17.2, 1.5 Hz, $H_{pro(Z)}$-7), 3.99 (dt, 1H, *J* = 7.0, 6.9 Hz, H-5), 2.92 (dd, 1H, *J* = 17.1, 7.0 Hz, H-4), 2.87 (dd, 1H, *J* = 17.1, 7.1 Hz, H'-4), 1.05 (s, 9H, H-1); δ_C (100 MHz, $CDCl_3$): 213.5 (C-3), 143.5 (Ar), 141.1 (C-6), 128.6 (Ar), 127.9 (Ar), 126.6 (Ar), 114.6 (C-7), 44.3 (C-2), 44.1 (C-5), 42.4 (C-4), 26.2 (C-1); *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 0.4% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 210 nm] t_R(*R*) = 19.46 min, t_R(*S*) = 26.49 min; [α]$_D$ (20 °C) -24.6 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[190]

***(S)-4-(3-Methoxyphenyl)hex-5-en-2-one* (Table 2.3.4, entry 5)**



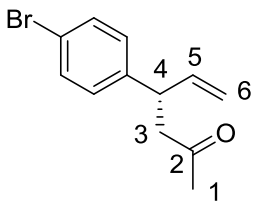
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure A4. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound (41 mg, 0.20 mmol, 83%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.24 – 7.20 (m, 1H, Ar-*H*), 6.81 – 6.74 (m, 3H, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.1, 10.2, 7.2 Hz, H-5), 5.06 (dt, 1H, *J* = 10.2, 1.1 Hz, $H_{pro(E)}$-6), 5.02 (dt, 1H, *J* = 17.1, 1.1 Hz, $H_{pro(Z)}$-6), 3.89 (dt, 1H, *J* = 7.2, 7.0 Hz, H-4), 3.79 (s, 3H, OC*H*$_3$), 2.87 (dd, 1H, *J* = 16.3, 7.6 Hz, H-3), 2.81 (dd, 1H, *J* = 16.3, 7.0 Hz, H'-3), 2.10 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.2 (C-2), 159.9 (Ar), 144.6 (Ar), 140.5 (C-5), 129.7 (Ar), 120.0 (Ar), 114.8 (C-6), 113.7 (Ar), 111.9 (Ar), 55.3 (O*C*H_3), 49.1 (C-3), 44.7 (C-4), 30.8 (C-1); ν_{max}/cm^{-1}: 2957 (w, C-H), 1714 (s, C=O), 1599 (s), 1584 (s), 1488 (s), 1359 (m), 1261 (s), 1159 (s), 1043 (s); *m/z* (ESI^+): 227.1 ($[M+Na]^+$, 100%); accurate mass: found 227.1052, $C_{13}H_{16}NaO_2$ $[M+Na]^+$ requires 227.1043; *ee*: 97% [Chiralpak AD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 210 nm] t_R(*S*) = 21.26 min, t_R(*R*) = 27.37 min; $[\alpha]_D$ (20 °C) -8.6 (c = 1.00 in $CHCl_3$).

(*S*)-4-(4-Methoxyphenyl)hex-5-en-2-one (Table 2.3.4, entry 6)



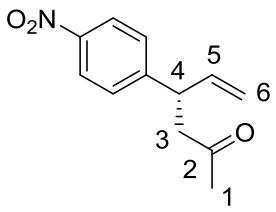
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure A4. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound (42 mg, 0.21 mmol, 85%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.12 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 6.84 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 5.94 (ddd, 1H, *J* = 17.2, 10.4, 6.8 Hz, H-5), 5.04 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-6), 4.99 (dt, 1H, *J* = 17.2, 1.2 Hz, $H_{pro(Z)}$-6), 3.86 (q, 1H, *J* = 7.1 Hz, H-4), 3.78 (s, 3H, OC*H*$_3$), 2.85 (dd, 1H, *J* = 16.0, 7.4 Hz, H-3), 2.79 (dd, 1H, *J* = 16.0, 7.1 Hz, H'-3), 2.08 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.4 (C-2), 158.4 (Ar), 141.0 (C-5), 134.9 (Ar), 128.7 (Ar), 114.4 (C-6), 114.1 (Ar), 55.3 (O*C*H$_3$), 49.3 (C-3), 43.9 (C-4), 30.8 (C-1); *ee*: 99% [Chiralpak AD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 210 nm] t_R(*R*) = 10.96 min, t_R(*S*) = 14.88 min; $[\alpha]_D$ (20 °C) -13.5 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[86]

(S)-4-(4-Bromophenyl)hex-5-en-2-one **(Table 2.3.4, entry 7)**



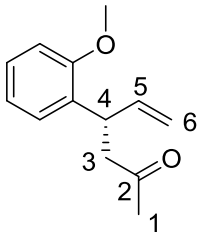
The title compound was synthesised from the corresponding *β*-ketoester (70 mg, 0.24 mmol) according to general procedure A4. The crude product was purified by FC (18% EtOAc in $PE_{40\text{-}60}$) to give the title compound (46 mg, 0.18 mmol, 77%) as a colourless oil. R_f = 0.3 (18% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.41 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.08 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 5.92 (ddd, 1H, *J* = 17.1, 10.4, 6.6 Hz, H-5), 5.07 (dt, 1H, *J* = 10.4, 1.1 Hz, $H_{pro(E)}$-6), 5.00 (dt, 1H, *J* = 17.1, 1.3 Hz, $H_{pro(Z)}$-6), 3.88 (dt, 1H, *J* = 6.6, 7.0 Hz, H-4), 2.87 (dd, 1H, *J* = 16.7, 7.4 Hz, H-3), 2.79 (dd, 1H, *J* = 16.7, 7.3 Hz, H'-3), 2.09 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 206.7 (C-2), 141.9 (Ar), 140.1 (C-5), 131.8 (Ar), 129.6 (Ar), 120.5 (Ar), 115.2 (C-6), 48.8 (C-3), 43.9 (C-4), 30.8 (C-1); ν_{max}/cm^{-1}: 3081 (w, C-H), 3003 (w, C-H), 1714 (s, C=O), 1488 (s), 1405 (m), 1359 (m), 1161 (m), 1105 (m), 1009 (s); *m/z* (ESI^+): 275.0 ($[M^{79Br}+Na]^+$, 100%), 277.0 ($[M^{81Br}+Na]^+$, 100%); accurate mass: found 275.0044, $C_{12}H_{13}{}^{79}BrNaO$ $[M^{79Br}+Na]^+$ requires 275.0042, found 277.0025, $C_{12}H_{13}{}^{81}BrNaO$ $[M^{81Br}+Na]^+$ requires 277.0022; *ee*: 98% [Chiralpak AD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 210 nm] t_R(*R*) = 8.91 min, t_R(*S*) = 14.10 min; $[\alpha]_D$ (20 °C) -5.2 (c = 1.00 in $CHCl_3$).

(*S*)-4-(4-Nitrophenyl)hex-5-en-2-one (Table 2.3.4, entry 8)



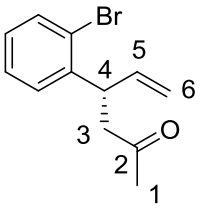
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.23 mmol) according to general procedure A4. The crude product was purified by FC (28% EtOAc in $PE_{40\text{-}60}$) to give the title compound (37 mg, 0.17 mmol, 74%) as a yellow oil. R_f = 0.3 (28% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.16 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.38 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.93 (ddd, 1H, *J* = 17.1, 10.4, 6.9 Hz, H-5), 5.14 (dt, 1H, *J* = 10.4, 1.0 Hz, $H_{pro(E)}$-6), 5.05 (dt, 1H, *J* = 17.1, 1.2 Hz, $H_{pro(Z)}$-6), 4.05 (q, 1H, *J* = 6.9 Hz, H-4), 2.95 (dd, 1H, *J* = 17.0, 6.9 Hz, H-3), 2.87 (dd, 1H, *J* = 17.0, 7.3 Hz, H'-3), 2.12 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 205.9 (C-2), 150.7 (Ar), 146.8 (Ar), 139.2 (C-5), 128.8 (Ar), 124.0 (Ar), 116.1 (C-6), 48.5 (C-3), 44.1 (C-4), 30.7 (C-1); *ee*: 97% [Chiralpak AD-H column (4.6 mm x 250 mm), 8% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 210 nm] t_R(*R*) = 13.10 min, t_R(*S*) = 14.67 min; $[\alpha]_D$ (20 °C) +8.8 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[191]

(*S*)-4-(2-Methoxyphenyl)hex-5-en-2-one (Table 2.3.4, entry 9)



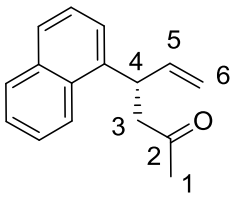
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (42 mg, 0.21 mmol, 85%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.22 – 7.18 (m, 1H, Ar-*H*), 7.13 (dd, 1H, *J* = 7.5, 1.6 Hz, Ar-*H*), 6.91 (t, 1H, *J* = 7.5 Hz, Ar-*H*), 6.86 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 6.02 (ddd, 1H, *J* = 17.2, 10.2, 7.3 Hz, H-5), 5.05 (dt, 1H, *J* = 10.2, 1.3 Hz, $H_{pro(E)}$-6), 5.01 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-6), 4.29 (dt, 1H, *J* = 7.3, 7.0 Hz, H-4), 3.84 (s, 3H, OCH_3), 2.86 (dd, 1H, *J* = 16.0, 8.2 Hz, H-3), 2.80 (dd, 1H, *J* = 16.0, 6.4 Hz, H'-3), 2.12 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.8 (C-2), 156.9 (Ar), 140.0 (C-5), 131.2 (Ar), 128.3 (Ar), 127.8 (Ar), 120.8 (Ar), 114.7 (C-6), 110.9 (Ar), 55.5 (OCH_3), 48.3 (C-3), 38.6 (C-4), 30.3 (C-1); *ee*: 96% [Chiralpak AD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 230 nm] t_R(*R*) = 12.06 min, t_R(*S*) = 15.06 min; $[\alpha]_D$ (20 °C) -17.8 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[86]

(S)-4-(2-Bromophenyl)hex-5-en-2-one **(Table 2.3.4, entry 10)**



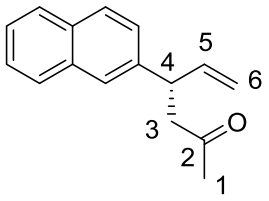
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.20 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (46 mg, 0.18 mmol, 90%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.56 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.29 – 7.25 (m, 1H, Ar-*H*), 7.19 (dd, 1H, *J* = 7.6, 1.4 Hz, Ar-*H*), 7.10 – 7.06 (m, 1H, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.2, 10.5, 6.9 Hz, H-5), 5.14 (dt, 1H, *J* = 10.5, 1.3 Hz, $H_{pro(E)}$-6), 5.03 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-6), 4.44 (q, 1H, *J* = 6.9 Hz, H-4), 2.87 (dd, 1H, *J* = 16.7, 7.7 Hz, H-3), 2.82 (dd, 1H, *J* = 16.7, 6.5 Hz, H'-3), 2.16 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 206.5 (C-2), 141.9 (Ar), 138.8 (C-5), 133.4 (Ar), 128.7 (Ar), 128.3 (Ar), 127.8 (Ar), 124.6 (Ar), 115.8 (C-6), 48.3 (C-3), 43.2 (C-4), 30.1 (C-1); ν_{max}/cm^{-1}: 3081 (w, C-H), 1716 (s, C=O), 1469 (m), 1437 (m), 1359 (m), 1162 (m), 1022 (m); *m/z* (ESI^+): 275.0 ($[M^{79Br}+Na]^+$, 100%), 277.0 ($[M^{81Br}+Na]^+$, 100%); accurate mass: found 275.0049, $C_{12}H_{13}{}^{79}BrNaO$ ($[M^{79Br}+Na]^+$ requires 275.0042, found 277.0031, $C_{12}H_{13}{}^{81}BrNaO$ $[M^{81Br}+Na]^+$ requires 277.0022; *ee*: 62% [Chiralpak AD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 210 nm] t_R(*R*) = 10.97 min, t_R(*S*) = 13.02 min; $[\alpha]_D$ (20 °C) -18.6 (c = 1.00 in $CHCl_3$).

***(S)-4-(Naphthalen-1-yl)hex-5-en-2-one* (Table 2.3.4, entry 11)**



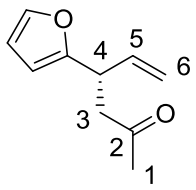
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.22 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (38 mg, 0.17 mmol, 76%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.15 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.86 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.74 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.55 – 7.47 (m, 2H, Ar-*H*), 7.43, (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.35 (d, 1H, *J* = 7.3 Hz, Ar-*H*), 6.11 (ddd, 1H, *J* = 17.1, 10.4, 7.0 Hz, H-5), 5.13 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-6), 5.04 (dt, 1H, *J* = 17.0, 1.4 Hz, $H_{pro(Z)}$-6), 4.80 (dt, 1H, *J* = 7.0, 6.2 Hz, H-4), 3.07 (dd, 1H, *J* = 16.9, 8.8 Hz, H-3), 2.96 (dd, 1H, *J* = 16.9, 5.2 Hz, H'-3), 2.16 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.1 (C-2), 140.2 (C-5), 139.0 (Ar), 134.2 (Ar), 131.3 (Ar), 129.1 (Ar), 127.4 (Ar), 126.3 (Ar), 125.7 (Ar), 125.6 (Ar), 124.4 (Ar), 123.5 (Ar), 115.3 (C-6), 48.8 (C-3), 39.2 (C-4), 30.7 (C-1); ν_{max}/cm^{-1}: 3049 (w, C-H), 1713 (s, C=O), 1396 (m), 1357 (m), 1162 (m); *m/z* (ESI^+): 247.1 ($[M+Na]^+$, 100%); accurate mass: found 247.1098, $C_{16}H_{16}NaO$ $[M+Na]^+$ requires 247.1093; *ee*: 70% [Chiralpak AD-H column (4.6 mm x 250 mm), 2% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 230 nm] t_R(*R*) = 9.65 min, t_R(*S*) = 11.27 min; $[\alpha]_D$ (20 °C) -29.0 (c = 1.00 in $CHCl_3$).

(S)-4-(Naphthalen-2-yl)hex-5-en-2-one **(Table 2.3.4, entry 12)**



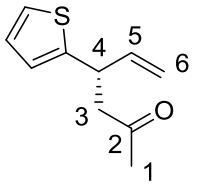
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.22 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (38 mg, 0.17 mmol, 76%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.80 – 7.78 (m, 3H, Ar-*H*), 7.64 (s, 1H, Ar-*H*), 7.48 – 7.41 (m, 2H, Ar-*H*), 7.35 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar-*H*), 6.04 (ddd, 1H, *J* = 17.1, 10.4, 6.7 Hz, H-5), 5.11 (dt, 1H, *J* = 10.4, 1.3 Hz, $H_{pro(E)}$-6), 5.07 (dt, 1H, *J* = 17.1, 1.4 Hz, $H_{pro(Z)}$-6), 4.09 (dt, 1H, *J* = 6.7, 7.2 Hz, H-4), 2.98 (dd, 1H, *J* = 16.3, 7.5 Hz, H-3), 2.93 (dd, 1H, *J* = 16.3, 7.2 Hz, H'-3), 2.11 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.1 (C-2), 140.6 (C-5), 140.3 (Ar), 133.7 (Ar), 132.5 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 126.3 (Ar), 126.2 (Ar), 126.1 (Ar), 125.7 (Ar), 115.0 (C-6), 49.0 (C-3), 44.7 (C-4), 30.9 (C-1); ν_{max}/cm^{-1}: 3055 (w, C-H), 1715 (s, C=O), 1413 (m), 1358 (m); *m/z* (ESI^+): 247.1 ($[M+Na]^+$, 100%); accurate mass: found 225.1266, $C_{16}H_{17}O$ $[M+H]^+$ requires 225.1274; *ee*: 99% [Chiralcel OD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 254 nm] t_R(*R*) = 13.21 min, t_R(*S*) = 15.79 min; $[\alpha]_D$ (20 °C) -11.4 (c = 1.00 in $CHCl_3$).

(S)-4-(Furan-2-yl)hex-5-en-2-one **(Table 2.3.4, entry 13)**



The title compound was synthesised from the corresponding *β*-ketoester (100 mg, 0.480 mmol) according to general procedure A4. The crude product was purified by FC (20% Et_2O in $PE_{30\text{-}40}$) to give the title compound (58 mg, 0.35 mmol, 74%) as a colourless oil. R_f = 0.3 (20% Et_2O in $PE_{30\text{-}40}$); δ_H (400 MHz, $CDCl_3$): 7.32 (s, 1H, Ar-*H*), 6.28 (dd, 1H, *J* = 3.2, 1.8 Hz, Ar-*H*), 6.03 (d, 1H, *J* = 3.2 Hz, Ar-*H*), 5.89 (ddd, 1H, *J* = 17.0, 10.4, 7.4 Hz, H-5), 5.10 (dt, 1H, *J* = 10.4, 1.1 Hz, $H_{pro(E)}$-6), 5.09 (dt, 1H, *J* = 17.0, 1.2 Hz, $H_{pro(Z)}$-6), 4.01 (dt, 1H, *J* = 7.4, 7.1 Hz, H-4), 2.93 (dd, 1H, *J* = 16.5, 6.7 Hz, H-3), 2.77 (dd, 1H, *J* = 16.5, 7.6 Hz, H'-3), 2.14 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 206.6 (C-2), 155.8 (Ar), 141.6 (Ar), 137.7 (C-5), 116.2 (C-6), 110.3 (Ar), 105.5 (Ar), 46.9 (C-3), 38.5 (C-4), 30.6 (C-1); ν_{max}/cm^{-1}: 2922 (w, C-H), 1716 (s, C=O), 1505 (m), 1413 (m), 1360 (m), 1161 (m), 1148 (m), 1010 (m); *m/z* (ESI^+): 187.1 ($[M+Na]^+$, 20%); accurate mass: found 165.0912, $C_{10}H_{13}O_2$ $[M+H]^+$ requires 165.0910; *ee*: 98% [Chiralpak AD-H column (4.6 mm x 250 mm), 0.5% 2-propanol in *n*-hexane, flow rate = 1.0 mL / min, detection wavelength = 210 nm] t_R(*S*) = 15.36 min, t_R(*R*) = 16.83 min; $[\alpha]_D$ (25 °C) +59.5 (c = 1.00 in $CHCl_3$).

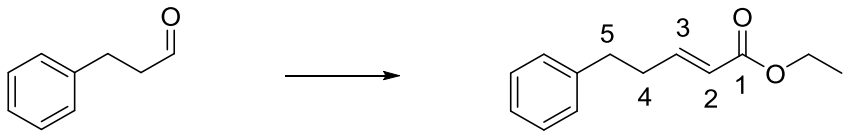
(*S*)-4-(Thiophen-2-yl)hex-5-en-2-one (Table 2.3.4, entry 14)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.27 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (35 mg, 0.19 mmol, 73%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.16 (d, 1H, *J* = 5.1 Hz, Ar-*H*), 6.94 – 6.92 (m, 1H, Ar-*H*), 6.83 – 6.82 (m, 1H, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.3, 10.3, 7.3 Hz, H-5), 5.10 (d, 1H, *J* = 17.3 Hz, $H_{pro(Z)}$-6), 5.09 (d, 1H, *J* = 10.3 Hz, $H_{pro(E)}$-6), 4.21 (q, 1H, *J* = 7.3 Hz, H-4), 2.92 (dd, 1H, *J* = 16.7, 7.0 Hz, H-3), 2.87 (dd, 1H, *J* = 16.7, 7.3 Hz, H'-3), 2.14 (s, 3H, H-1); δ_C (125 MHz, $CDCl_3$): 206.5 (C-2), 146.6 (Ar), 140.1 (C-5), 126.9 (Ar), 124.1 (Ar), 123.8 (Ar), 115.4 (C-6), 50.0 (C-3), 40.0 (C-4), 30.8 (C-1). ν_{max}/cm^{-1}: 3081 (w, C-H), 2980 (w, C-H), 1715 (s, C=O), 1408 (m), 1358 (s), 1232 (m), 1162 (m); *m/z* (ESI^+): 203.1 ($[M+Na]^+$, 80%); accurate mass: found 203.0505, $C_{10}H_{12}NaOS$ $[M+Na]^+$ requires 203.0501; *ee*: 99% [Chiralpak AD-H column (4.6 mm x 250 mm), 0.8% 2-propanol in *n*-hexane, flow rate = 0.8 mL / min, detection wavelength = 254 nm] t_R(*R*) = 13.15 min, t_R(*S*) = 14.19 min; $[\alpha]_D$ (20 °C) +33.6 (c = 1.00 in $CHCl_3$).

4.3.3 Screening of alkyl *β*-ketoester substrates (Section 2.3.4)

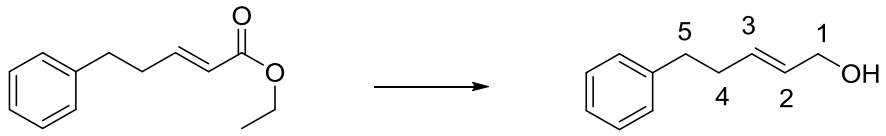
(*E*)-Ethyl 5-phenylpent-2-enoate (2.3.30)



2.3.29 **2.3.30**

The title compound was synthesised from the corresponding aldehyde **2.3.29** (2.00 g, 14.9 mmol) according to general procedure A1. The crude product was purified by FC (7% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.30** (1.56 g, 7.64 mmol, 82%) as a colourless oil. R_f = 0.3 (7% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.28 (m, 2H, Ar-*H*), 7.22 – 7.17 (m, 3H, Ar-*H*), 7.00 (dt, 1H, *J* = 15.5, 6.7 Hz, H-3), 5.84 (dt, 1H, *J* = 15.5, 1.5 Hz, H-2), 4.18 (q, 2H, *J* = 7.1 Hz, OCO*CH*$_2$), 2.78 (t, 2H, *J* = 7.5 Hz, H-5), 2.55 – 2.50 (m, 2H, H-4), 1.28 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$); *m/z* (ESI^+): 227.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[192]

(*E*)-5-Phenylpent-2-en-1-ol (2.3.31)

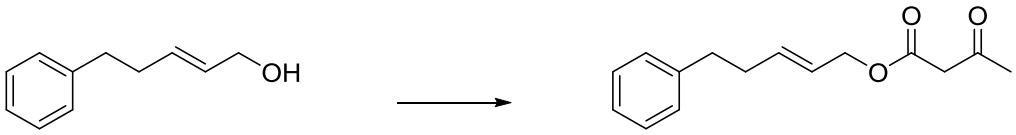


2.3.30 **2.3.31**

The title compound was synthesised from the corresponding *α*,*β*-unsaturated ester **2.3.30** (1.56 g, 7.64 mmol) according to general procedure A2 and purified by FC (40% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.31** (1.19 g, 7.34 mmol, 96%)

as a colourless oil. R_f = 0.3 (40% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.27 (m, 2H, Ar-*H*), 7.21 – 7.17 (m, 3H, Ar-*H*), 5.74 (dt, 1H, *J* = 15.4, 6.4 Hz, H-2), 5.66 (dt, 1H, *J* = 15.4, 5.1 Hz, H-3), 4.09 (t, 2H, *J* = 5.7 Hz, H-1), 2.71 (t, 2H, *J* = 7.4 Hz, H-5), 2.41 – 2.35 (m, 2H, H-4); *m/z* (ESI^+): 185.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[193]

(E)-5-Phenylpent-2-en-1-yl 3-oxobutanoate (2.3.32)

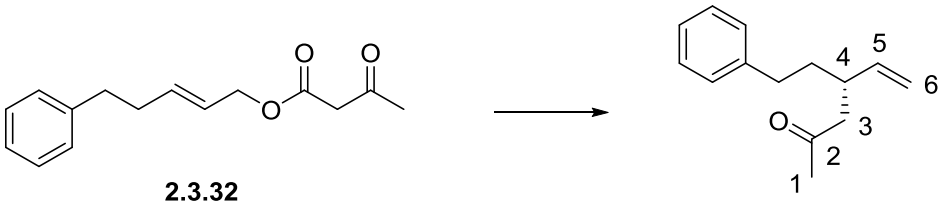


2.3.31 **2.3.32**

The title compound was synthesised from the corresponding allylic alcohol **2.3.31** (400 mg, 2.47 mmol) and ethyl acetoacetate (0.32 mL, 2.5 mmol) according to general procedure A3. The crude product was purified by FC (22% EtOAc in PE_{40-60}) to give the title compound **2.3.32** (557 mg, 2.26 mmol, 92%) as a colourless oil. R_f = 0.3 (22% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.23 – 7.14 (m, 3H, Ar-*H*), 5.84 (dtt, 1H, *J* = 15.5, 7.3, 1.2 Hz, $PhCH_2CH_2CH$=CH), 5.60 (dtt, 1H, *J* = 15.5, 6.7, 1.4 Hz, CH=$CHCH_2OCO$), 4.58 (dd, 2H, *J* = 6.7, 1.2 Hz, CH=$CHCH_2OCO$), 3.46 (s, 2H, $OC(O)CH_2CO$), 2.71 (t, 2H, *J* = 7.3 Hz, $PhCH_2$), 2.39 (q, 2H, *J* = 7.3 Hz, $PhCH_2CH_2$), 2.27 (s, 3H, $C(O)CH_3$); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 141.5 (Ar), 136.3 ($PhCH_2CH_2CH$=CH), 128.5 (Ar), 128.5 (Ar), 126.1 (Ar), 124.0 (CH=$CHCH_2OCO$), 66.1 (CH=$CHCH_2OCO$), 50.2 ($OC(O)CH_2CO$), 35.4 ($PhCH_2$), 34.1 ($PhCH_2CH_2$), 30.3 ($C(O)CH_3$); ν_{max}/cm^{-1}: 2931 (w, C-H), 1740 (s, C=O, ester), 1716 (s, C=O, ketone), 1496 (w), 1454 (w),

1360 (w), 1315 (m), 1265 (m), 1148 (s), 967 (s); *m/z* (ESI^+): 269.1 ($[M+Na]^+$, 100%); accurate mass: found 269.1151, $C_{15}H_{18}NaO_3$ $[M+Na]^+$ requires 269.1148.

(*S*)-4-Phenethylhex-5-en-2-one (Table 2.3.5, entry 1)



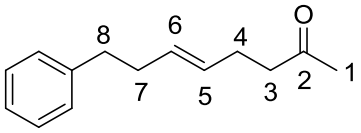
2.3.32

The title compound was synthesised from the corresponding *β*-ketoester **2.3.32** (150 mg, 0.609 mmol) according to general procedure A4. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give a mixture of the title compound and its linear isomer (branched to linear ratio: 10 to 1, 96 mg, 0.47 mmol, combined yield 78%) as a colourless oil. Title compound: R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.29 – 7.25 (m, 2H, Ar-*H*), 7.19 – 7.15 (m, 3H, Ar-*H*), 5.70 – 5.61 (m, 1H, H-5), 5.07 (ddd, 1H, *J* = 10.4, 1.6, 0.5 Hz, $H_{pro(E)}$-6), 5.06 (d, 1H, *J* = 16.8, 1.6, 0.9 Hz, $H_{pro(Z)}$-6), 2.68 – 2.50 (m, 3H, H-4 and PhCH_2), 2.47 (d, 2H, *J* = 6.8 Hz, H-3), 2.10 (s, 3H, H-1), 1.75 (dddd, 1H, *J* = 13.5, 10.5, 6.6, 4.6 Hz, $PhCH_2CH_2$), 1.62 (dddd, 1H, *J* = 13.5, 10.1, 9.3, 5.3 Hz, $PhCH_2CH'_2$); δ_C (100 MHz, $CDCl_3$): 208.0 (C-2), 142.3 (Ar), 141.0 (C-5), 128.5 (Ar), 128.4 (Ar), 125.9 (Ar), 115.7 (C-6), 49.3 (C-3), 39.4 (C-4), 36.5 ($PhCH_2CH_2$), 33.5 ($PhCH_2$), 30.7 (C-1); ν_{max}/cm^{-1}: 3027 (w, C-H), 2922 (w, C-H), 2857 (w, C-H), 1714 (s, C=O), 1496 (m), 1454 (m), 1420 (m), 1359 (m), 1155 (m); *m/z* (ESI^+): 225.1 ($[M+Na]^+$, 100%); accurate mass: found 225.1254, $C_{14}H_{18}NaO$ $[M+Na]^+$ requires 225.1250; *ee*: 98%

[Chiralcel OD-H column (4.6 mm x 250 mm), 0.8% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 230 nm] $t_R(R)$ = 15.03 min, $t_R(S)$ = 16.01 min; $[\alpha]_D$ (20 °C) +2.7 (c = 1.00 in $CHCl_3$).

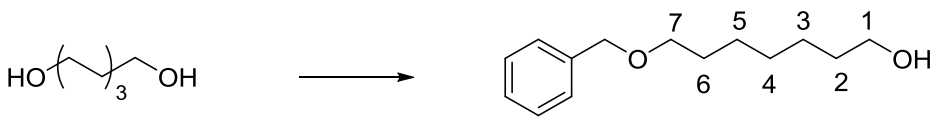
Linear isomer:

(*E*)-8-Phenyloct-5-en-2-one (Table 2.3.5, entry 1)



The title linear isomer is inseparable from the branched isomer (*S*)-4-phenethylhex-5-en-2-one. Non-overlapped ^{1}H signals are reported. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.47 (dt, 1H, *J* = 15.6, 6.3 Hz, H-5 or H-6), 5.41 (dt, 1H, *J* = 15.6, 6.1 Hz, H-5 or H-6), 2.32 – 2.23 (m, 4H, H-4 and H-7), 2.12 (s, 3H, H-1). Characterisation data are consistent with literature values.[194]

7-(Benzyloxy)heptan-1-ol (2.3.34)

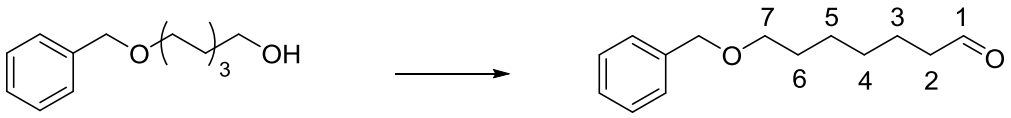


2.3.33 **2.3.34**

According to the procedure of Mohapatra *et al*.:[83] To a solution of heptane-1,7-diol **2.3.33** (5.6 mL, 40 mmol) in THF/DMF (35/15 mL) at 0 °C was slowly added sodium hydride (1.61 g, 40.1 mmol). The reaction mixture was stirred at 0 °C for 3 h. A solution of benzyl bromide (4.9 mL, 40 mmol) in THF (10 mL) was then added dropwise to the above reaction mixture at 0 °C. The reaction mixture was stirred at

0 °C for 30 min followed by warming to RT and stirred for 16 h. Upon completion, the reaction was quenched with H_2O (100 mL). After removing THF *in vacuo*, Et_2O (60 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (40% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.34** (4.20 g, 18.9 mmol, 49%) as a colourless oil. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 – 7.28 (m, 5H, Ar-*H*), 4.50 (s, 2H, PhC*H*$_2$O), 3.63 (t, 2H, *J* = 6.6 Hz, H-1 or H-7), 3.46 (t, 2H, *J* = 6.6 Hz, H-1 or H-7), 1.64 – 1.35 (m, 10H, H-2, H-3, H-4, H-5 and H-6); δ_C (100 MHz, $CDCl_3$): 138.8 (Ar), 128.5 (Ar), 127.8 (Ar), 127.6 (Ar), 73.0 (Ar*C*H$_2$O), 70.5 (C-1 or C-7), 63.1 (C-1 or C-7), 32.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.4 (*C*H$_2$), 26.3 (*C*H$_2$), 25.8 (*C*H$_2$). Characterisation data are consistent with literature values.[83]

7-(Benzyloxy)heptanal (2.3.35)

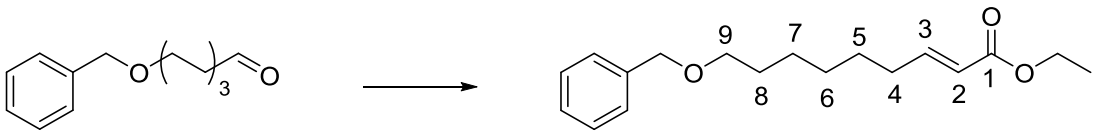


2.3.34 **2.3.35**

According to the procedure of Mohapatra *et al*.:[83] To a stirred solution of 7-(benzyloxy)heptan-1-ol **2.3.34** (4.10 g, 18.4 mmol) in DCM (50 mL) was added pyridinium chlorochromate (8.11 g, 36.9 mmol) at RT. The reaction mixture was stirred at RT for 2 h. Upon completion, the black solid was filtered off using a sintered funnel and Celite™. The Celite™ cake was rinsed with Et_2O (3 x 20 mL). The organic filtrates were combined and concentrated *in vacuo*. The crude product

was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.35** (2.32 g, 10.5 mmol, 57%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 9.76 (t, 1H, *J* = 1.8 Hz, H-1), 7.35 – 7.28 (m, 5H, Ar-*H*), 4.50 (s, 2H, PhCH_2O), 3.46 (t, 2H, *J* = 6.5 Hz, H-7), 2.42 (td, 2H, *J* = 7.3, 1.8 Hz, H-2), 1.66 – 1.34 (m, 8H, H-3, H-4, H-5 and H-6); δ_C (100 MHz, $CDCl_3$): 202.9 (C-1), 138.7 (Ar), 128.5 (Ar), 127.8 (Ar), 127.6 (Ar), 73.0 (ArCH_2O), 70.4 (C-7), 43.9 (C-2), 29.7 (CH_2), 29.1 (CH_2), 26.1 (CH_2), 22.1 (CH_2). Characterisation data are consistent with literature values.[83]

(*E*)-Ethyl 9-(benzyloxy)non-2-enoate (2.3.36)

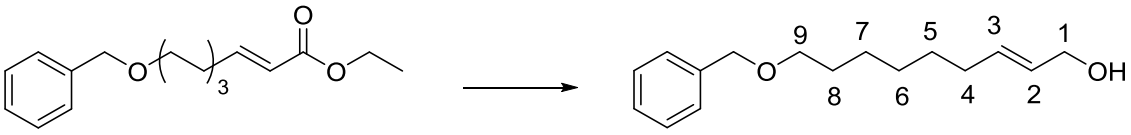


2.3.35 **2.3.36**

The title compound was synthesised from 7-(benzyloxy)heptanal **2.3.35** (1.50 g, 6.81 mmol) according to general procedure A1. The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.36** (1.34 g, 4.61 mmol, 68%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 – 7.27 (m, 5H, Ar-*H*), 6.95 (dt, 1H, *J* = 15.7, 7.1 Hz, H-3), 5.81 (dt, 1H, *J* = 15.7, 1.5 Hz, H-2), 4.50 (s, 2H, PhCH_2O), 4.18 (q, 2H, *J* = 7.1 Hz, OCOC$H_2$$CH_3$), 3.46 (t, 2H , *J* = 6.5 Hz, H-9), 2.19 (dtd, 2H, *J* = 7.1, 7.0, 1.5 Hz, H-4), 1.63 – 1.33 (m, 8H, H-5, H-6, H-7 and H-8), 1.29 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$):166.9 (C-1), 149.4 (C-3), 138.8 (Ar), 128.5 (Ar), 127.8 (Ar), 127.6 (Ar), 121.4 (C-2), 73.0 (ArCH_2O), 70.5 (C-9), 60.3 ($OCOCH_2CH_3$), 32.2 (C-4), 29.8 (CH_2),

29.1 (*C*H_2), 28.1 (*C*H_2), 26.1 (*C*H_2), 14.4 (OCOCH_2*C*H_3). Characterisation data are consistent with literature values.[195]

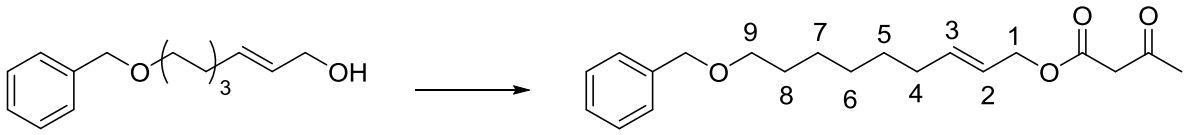
(*E*)-9-(Benzyloxy)non-2-en-1-ol (2.3.37)



2.3.36 **2.3.37**

The title compound was synthesised from (*E*)-ethyl 9-(benzyloxy)non-2-enoate **2.3.36** (700 mg, 2.41 mmol) according to general procedure A2 to give the crude title compound **2.3.37** (590 mg, 2.38 mmol, 98%) as a colourless oil. The crude alcohol was used in the next step without further purification. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 – 7.28 (m, 5H, Ar-*H*), 5.69 (dt, 1H, *J* = 15.5, 6.8 Hz, H-3), 5.62 (dt, 1H, *J* = 15.5, 5.2 Hz, H-2), 4.50 (s, 2H, PhCH_2O), 4.08 (d, 2H, *J* = 5.2 Hz, H-1), 3.46 (t, 2H, *J* = 6.6 Hz, H-9), 2.04 (q, 2H, *J* = 6.8 Hz, H-4), 1.63 – 1.27 (m, 8H, H-5, H-6, H-7 and H-8); δ_C (100 MHz, $CDCl_3$): 138.8 (Ar), 133.5 (C-3), 129.1 (C-2), 128.5 (Ar), 127.7 (Ar), 127.6 (Ar), 73.0 (Ar*C*H_2O), 70.6 (C-9), 63.9 (C-1), 32.3 (C-4), 29.8 (*C*H_2), 29.2 (*C*H_2), 29.1 (*C*H_2), 26.2 (*C*H_2). Characterisation data are consistent with literature values.[195]

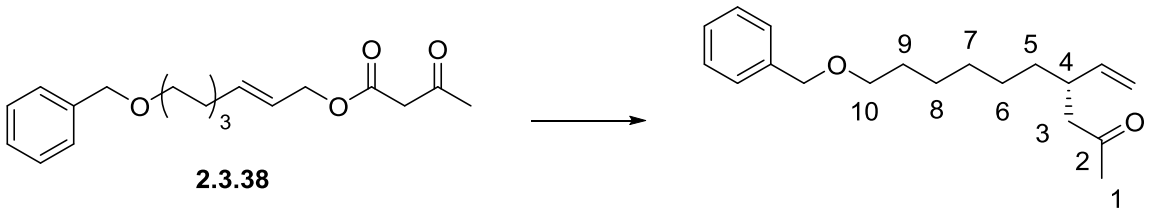
(E)-9-(Benzyloxy)non-2-en-1-yl 3-oxobutanoate (2.3.38)



2.3.37 **2.3.38**

The title compound was synthesised from (*E*)-9-(benzyloxy)non-2-en-1-ol **2.3.37** (514 mg, 2.07 mmol) and ethyl acetoacetate (0.26 mL, 2.1 mmol) according to general procedure A3. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.38** (504 mg, 1.52 mmol, 73%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.37 – 7.27 (m, 5H, Ar-*H*), 5.78 (dt, 1H, *J* = 15.2, 7.0 Hz, H-3), 5.55 (dtt, 1H, *J* = 15.2, 6.6, 1.5 Hz, H-2), 4.58 (d, 2H, *J* = 6.6 Hz, H-1), 4.50 (s, 2H, PhCH_2O), 3.47 (t, 2H, *J* = 6.8 Hz, H-9), 3.46 (s, 2H, OCOCH_2), 2.27 (s, 3H, OC(O)CH_2C(O)CH_3), 2.05 (dt, 2H, *J* = 7.0, 6.7 Hz, H-4), 1.61 (quint, 2H, *J* = 6.5 Hz, H-8), 1.43 – 1.27 (m, 6H, H-5, H-6 and H-7); δ_C (100 MHz, $CDCl_3$): 200.6 (*C*=O, ketone), 167.0 (*C*=O, ester), 138.8 (Ar), 137.5 (C-3), 128.4 (Ar), 127.7 (Ar), 127.6 (Ar), 123.2 (C-2), 72.9 (Ph*C*H_2O), 70.5 (C-9), 66.2 (C-1), 50.2 (OCO*C*H_2), 32.2 (C-4), 30.2 (OC(O)CH_2C(O)*C*H_3), 29.8 (C-8), 29.0 (*C*H_2), 28.8 (*C*H_2), 26.1 (*C*H_2); ν_{max}/cm^{-1}: 2931 (w, C-H), 2855 (w, C-H), 1745 (s, C=O, ester), 1716 (s, C=O, ketone), 1148 (s), 1095 (s), 967 (s), 735 (s); *m/z* (ESI^+): 355.2 ($[M+Na]^+$, 100%); accurate mass: found 355.1874, $C_{20}H_{28}NaO_4$ $[M+Na]^+$ requires 355.1880.

(S)-10-(Benzyloxy)-4-vinyldecan-2-one **(Table 2.3.5, entry 2)**

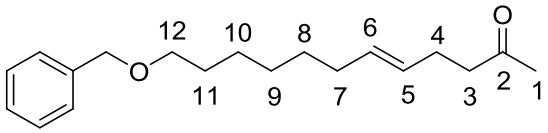


2.3.38

The title compound was synthesised from (*E*)-9-(benzyloxy)non-2-en-1-yl 3-oxobutanoate **2.3.38** (60 mg, 0.18 mmol) according to general procedure A4. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give a mixture of the title compound and its linear isomer (branched to linear ratio: 15 to 1, 42 mg, 0.15 mmol, combined yield 81%) as a yellow oil. The title compound: R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 – 7.33 (m, 4H, Ar-*H*), 7.30 – 7.27 (m, 1H, Ar-*H*), 5.59 (ddd, 1H, *J* = 16.7, 10.8, 8.4 Hz, CHC*H*=CH_2), 4.99 (ddd, 1H, *J* = 16.7, 1.7, 1.0 Hz, CH=$CH_{pro(E)}H_{Pro(Z)}$), 4.98 (ddd, 1H, *J* = 10.8, 1.7, 0.5 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 4.50 (s, 2H, PhCH_2O), 3.45 (t, 2H, *J* = 6.6 Hz, H-10), 2.54 (sext, 1H, *J* = 6.8 Hz, H-4), 2.43 – 2.41 (m, 2H, H-3), 2.12 (s, 3H, H-1), 1.62 – 1.58 (m, 2H, H-9), 1.34 – 1.25 (m, 8H, H-5, H-6, H-7 and H-8); δ_C (100 MHz, $CDCl_3$): 208.4 (C-2), 141.5 (CHCH=CH_2), 138.8 (Ar), 128.5 (Ar), 127.7 (Ar), 127.6 (Ar), 115.0 (CH=CH_2), 73.0 (PhCH_2O), 70.6 (C-10), 49.3 (C-3), 39.7 (C-4), 34.7 (CH_2), 30.7 (C-1), 29.8(CH_2), 29.5 (C-9), 27.1(CH_2), 26.2 (CH_2); ν_{max}/cm^{-1}: 2929 (s, C-H), 2855 (s, C-H), 1714 (s, C=O), 1454 (m), 1359 (s), 1101 (s); *m/z* (ESI^+): 311.2 ($[M+Na]^+$, 100%); accurate mass: found 311.1976, $C_{19}H_{28}NaO_2$ $[M+Na]^+$ requires 311.1982; *ee*: ≈ 97% [Chiralcel OD-H column (4.6 mm x 250 mm), 0.8% 2-propanol in *n*-hexane, flow rate = 0.4 mL / min, detection wavelength = 210 nm] t_R(*S*) = 19.80 min, t_R(*R*) = 22.25 min; $[\alpha]_D$ (20 °C) +1.8 (c = 1.00 in $CHCl_3$).

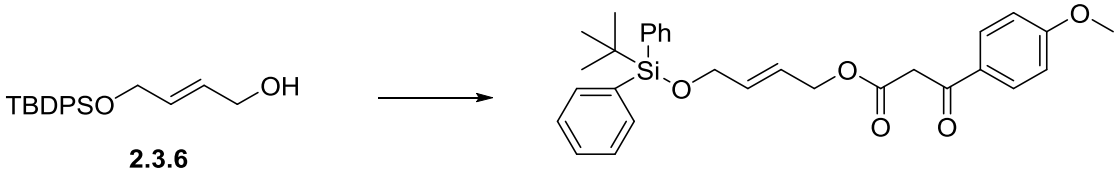
Linear isomer:

***(E)-12-(Benzyloxy)dodec-5-en-2-one* (Table 2.3.5, entry 2)**



The title linear isomer is inseparable from the branched isomer (*S*)-10-(benzyloxy)-4-vinyldecan-2-one. Non-overlapped NMR signals are reported: R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.43 (dt, 1H, *J* = 15.3, 6.3 Hz, H-6), 5.36 (dt, 1H, *J* = 15.3, 6.0 Hz, H-5), 3.46 (t, 2H, *J* = 6.7 Hz, H-12), 2.50 – 2.45 (m, 2H, H-3), 2.27 – 2.22 (m, 2H, H-4), 1.98 – 1.93 (m, 2H, H-7); δ_C (100 MHz, $CDCl_3$): 43.7 (C-3), 32.6 (C-7), 27.0 (C-4). The rest of the characterisation data were measured together with the branched isomer as a mixture.

(E)-4-((tert-Butyldiphenylsilyl)oxy)but-2-en-1-yl 3-(4-methoxyphenyl)-3-oxopropanoate (2.3.39)

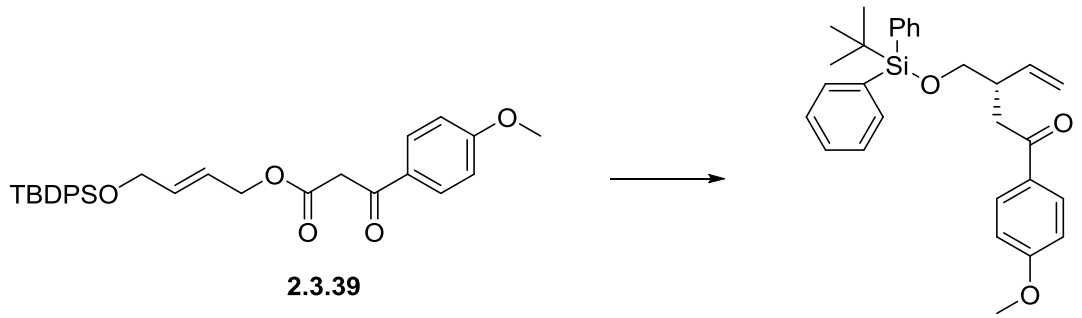


2.3.6 **2.3.39**

The title compound was synthesised from the corresponding allylic alcohol **2.3.6** (1.00 g, 3.06 mmol) and ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (0.53 mL, 3.06 mmol) according to general procedure A3. The crude product was purified by FC (2% EtOAc in DCM) to give the title compound **2.3.39** (1.03 g, 2.05 mmol, 74%)

as a pale yellow oil. R_f = 0.3 (2% EtOAc in DCM); δ_H (500 MHz, $CDCl_3$): 7.93 (d, 2H, *J* = 9.4 Hz, Ar-*H*), 7.67 – 7.63 (m, 4H, Ar-*H*), 7.43 – 7.36 (m, 6H, Ar-*H*), 6.93 (d, 2H, *J* = 9.4 Hz, Ar-*H*), 5.88 (dtt, 1H, *J* = 15.6, 5.7, 0.9 Hz, $SiOCH_2CH=CH$), 5.85 – 5.79 (m, 1H, $SiOCH_2CH=CH$), 4.66 (d, 2H, *J* = 5.7 Hz, $CH=CHCH_2OCO$), 4.20 – 4.18 (m, 2H, $SiOCH_2CH=CH$), 3.98 (s, 2H, $OC(O)CH_2$), 3.86 (s, 3H, OCH_3), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 190.9 (*C*=O, ketone), 167.6 (*C*=O, ester), 164.1 (Ar), 135.6 (Ar), 134.1 ($SiOCH_2CH=CH$), 133.6 (Ar), 131.1 (Ar), 129.8 (Ar), 129.3 (Ar), 127.8 (Ar), 123.1 ($SiOCH_2CH=CH$), 114.1 (Ar), 65.5 ($CH=CHCH_2OCO$), 63.6 ($SiOCH_2CH=CH$), 55.7 (OCH_3), 45.9 ($OC(O)CH_2$), 27.0 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 2932 (m, C-H), 2857 (m, C-H), 1741 (s, C=O, ester), 1678 (s, C=O, ketone), 1601 (s), 1261 (s), 1172 (s), 1111 (s), 703 (s); *m/z* (ESI^+): 525.2 ($[M+Na]^+$, 100%); accurate mass: found 503.2245, $C_{30}H_{35}O_5Si$ $[M+H]^+$ requires 503.2248.

***(S)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pent-4-en-1-one* (2.3.46, Table 2.3.5, entry 4)**



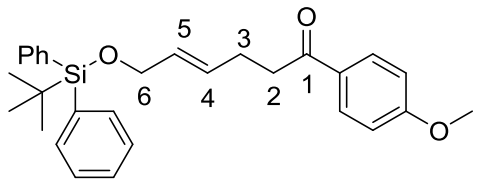
2.3.39

The title compound was synthesised from (*E*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-yl 3-(4-methoxyphenyl)-3-oxopropanoate **2.3.39** (282 mg, 0.561 mmol)

according to general procedure A4. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give a mixture of the title compound and its linear isomer (branched to linear ratio: 14 to 1, 215 mg, 0.469 mmol, combined yield 84%) as a colourless oil. The title compound: R_f = 0.3 (13% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.97 – 7.92 (m, 2H, Ar-*H*), 7.66 – 7.62 (m, 4H, Ar-*H*), 7.46 – 7.31 (m, 6H, Ar-*H*), 6.96 – 6.89 (m, 2H, Ar-*H*), 5.81 (ddd, 1H, *J* = 17.2, 10.5, 7.2 Hz, C*H*=CH_2), 5.03 (dt, 1H, *J* = 17.2, 1.3 Hz, CH=$CH_{pro(E)}$*H*$_{pro(Z)}$), 5.02 (ddd, 1H, *J* = 10.5, 1.5, 0.8 Hz, CH=*H*$_{pro(E)}$$H_{pro(Z)}$), 3.87 (s, 3H, OC*H*$_3$), 3.74 (dd, 1H, *J* = 9.9, 5.0 Hz, SiOC*H*$_2$), 3.65 (dd, 1H, *J* = 9.9, 6.6 Hz, SiOC*H'*$_2$), 3.32 (dd, 1H, *J* = 15.8, 5.3 Hz, ArC(O)C*H*$_2$), 3.01 (sext, 1H, *J* = 6.7 Hz, $SiOCH_2CH$), 2.88 (dd, 1H, *J* = 15.8, 8.0 Hz, ArC(O)C*H'*$_2$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 197.9 (*C*=O), 163.4 (Ar), 138.7 (*C*H=CH_2), 135.7 (Ar), 133.7 (Ar), 130.5 (Ar), 130.4 (Ar), 129.7 (Ar), 127.7 (Ar), 116.0 (CH=*C*H_2), 113.7 (Ar), 66.7 ($SiOCH_2$), 55.6 (OCH_3), 42.2 ($SiOCH_2CH$), 39.6 ($PhC(O)CH_2$), 27.0 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 3071 (w, C-H), 2931 (m, C-H), 2857 (m, C-H), 1677 (s, C=O), 1600 (s), 1576 (m), 1510 (m), 1427 (m), 1255 (s), 1170 (s), 1110 (s); *m/z* (ESI^+): 481.2 ($[M+Na]^+$, 100%); accurate mass: found 481.2169, $C_{29}H_{34}O_3NaSi$ $[M+Na]^+$ requires 481.2169; *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 1.5% 2-propanol in *n*-hexane, flow rate = 1.0 mL / min, detection wavelength = 254 nm] t_R(*R*) = 8.34 min, t_R(*S*) = 10.22 min; $[\alpha]_D$ (25 °C) +27.1 (c = 1.00 in $CHCl_3$).

The linear isomer:

(E)-6-((tert-Butyldiphenylsilyl)oxy)-1-(4-methoxyphenyl)hex-4-en-1-one **(Table 2.3.5, entry 4)**

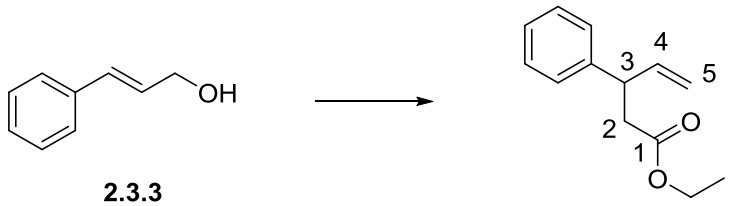


The title linear isomer is inseparable from the branched isomer (*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pent-4-en-1-one.

Non-overlapped NMR signals are reported: R_f = 0.3 (13% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 5.60 (dt, 1H, *J* = 15.1, 4.9 Hz, H-5), 4.16 (d, 2H, *J* = 4.9, H-6), 2.45 (q, 2H, *J* = 7.2 Hz, H-3); δ_C (125 MHz, $CDCl_3$): 130.4 (C-5), 26.9 (C-3). The rest of the characterisation data were measured together with the branched isomer as a mixture.

4.3.4 Experimental details part two (Section 2.3.5 to 2.5)

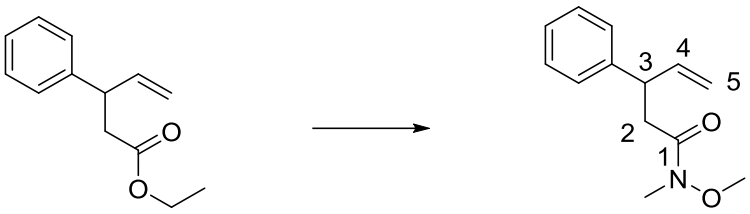
(±)-Ethyl 3-phenylpent-4-enoate ((±)-2.3.57)



2.3.3 **(±)-2.3.57**

According to a procedure of Ferrara *et al*.:[3] A mixture of cinnamyl alcohol **2.3.3** (3.0 g, 22 mmol), triethyl orthoacetate (20.5 mL, 112 mmol) and propionic acid (0.10 mL, 1.3 mmol) was stirred at 145 °C under reflux for 22 h. Upon completion, aq. HCl solution (1 M, 70 mL) was slowly added to the reaction mixture. The mixture was shaken vigorously before separating the two layers. The aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ solution (70 mL) and brine (70 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (4% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.57** (2.7 g, 13 mmol, 58%) as a colourless oil. R_f = 0.3 (4% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.21 (m, 5H, Ar-*H*), 5.98 (ddd, 1H, *J* = 17.2, 10.1, 7.0 Hz, H-4), 5.08 (dt, 1H, *J* = 17.2, 1.3 Hz, $H_{pro(Z)}$-5), 5.07 (dt, 1H, *J* = 10.1, 1.4 Hz, $H_{pro(E)}$-5), 4.07 (q, 2H, *J* = 7.2 Hz, $OCOC\mathit{H}_2CH_3$), 3.91 (q, 1H, *J* = 7.6 Hz, H-3), 2.76 (dd, 1H, *J* = 15.1, 8.2 Hz, H-2), 2.69 (dd, 1H, *J* = 15.1, 7.4 Hz, H'-2), 1.17 (t, 3H, *J* = 7.2 Hz, $OCOCH_2C\mathit{H}_3$); δ_C (100 MHz, $CDCl_3$): 172.0 (C-1), 142.6 (Ar), 140.4 (C-4), 128.7 (Ar), 127.7 (Ar), 126.8 (Ar), 114.9 (C-5), 60.5 ($OCO\mathit{C}H_2CH_3$), 45.7 (C-3), 40.4 (C-2), 14.3 ($OCOCH_2\mathit{C}H_3$). Characterisation data are consistent with literature values.[196]

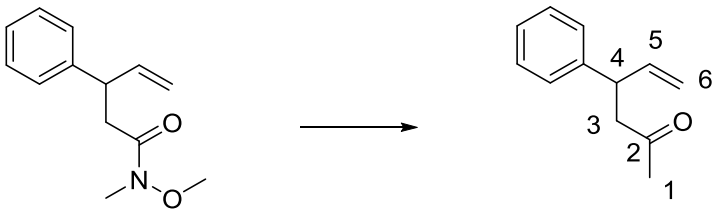
(±)-*N*-Methoxy-*N*-methyl-3-phenylpent-4-enamide ((±)-2.3.58)



(±)-2.3.57 **(±)-2.3.58**

According to a modified procedure of Prunet *et al*.:[90] To a slurry of ester **(±)-2.3.57** (100 mg, 0.490 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (74 mg, 0.76 mmol) in THF (1.2 mL) at -20 °C was added isopropylmagnesium chloride solution (2 M in THF, 0.73 mL, 1.5 mmol) dropwise over 10 min, maintaining the temperature below -5 °C at all times. The reaction mixture was then stirred at -15 °C for 1 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (35% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.58** (87 mg, 0.40 mmol, 81%) as a colourless oil. R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 – 7.21 (m, 5H, Ar-*H*), 6.03 (ddd, 1H, *J* = 16.5, 10.9, 6.9 Hz, H-4), 5.08 (dt, 1H, *J* = 10.9, 1.3 Hz, $H_{pro(E)}$-5), 5.07 (dt, 1H, *J* = 16.5, 1.4 Hz, $H_{pro(Z)}$-5), 3.99 (q, 1H, *J* = 7.4 Hz, H-3), 3.60 (s, 3H, NOCH_3), 3.14 (s, 3H, NCH_3), 2.90 (dd, 1H, *J* = 15.4, 8.2 Hz, H-2), 2.82 (dd, 1H, *J* = 15.4, 7.0 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 172.6 (C-1), 143.3 (Ar), 140.9 (C-4), 128.6 (Ar), 127.9 (Ar), 126.6 (Ar), 114.7 (C-5), 61.4 (NOCH_3), 45.0 (C-3), 37.6 (C-2), 32.2 (NCH_3). Characterisation data are consistent with literature values.[197]

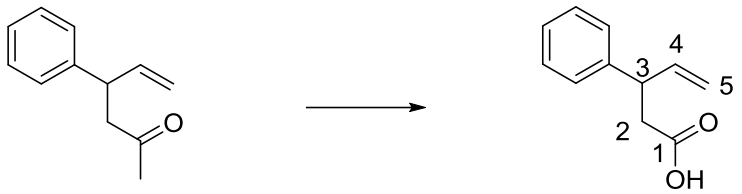
(±)-4-Phenylhex-5-en-2-one ((±)-2.3.19)



(±)-2.3.58 **(±)-2.3.19**

According to a modified procedure of Rychnovsky *et al*.:[91] To a solution of amide **(±)-2.3.58** (60 mg, 0.27 mmol) in THF (0.94 mL) at -78 °C was added MeLi (1.6 M in Et_2O, 0.34 mL, 0.55 mmol) dropwise over 5 min. The reaction mixture was stirred at -78 °C for 2.5 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl (5 mL) at -78 °C. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.19** (31 mg, 0.18 mmol, 65%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.23 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.2, 10.4, 6.8 Hz, H-5), 5.06 (dt, 1H, *J* = 10.4, 1.3 Hz, $H_{pro(E)}$-6), 5.02 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-6), 3.91 (q, 1H, *J* = 7.1 Hz, H-4), 2.89 (dd, 1H, *J* = 16.2, 7.6 Hz, H-3), 2.82 (dd, 1H, *J* = 16.2, 7.4 Hz, H'-3), 2.09 (s, 3H, H-1); δ_C (100 MHz, $CDCl_3$): 207.2 (C-2), 142.9 (C-5), 140.7 (Ar), 128.7 (Ar), 127.7 (Ar), 126.7 (Ar), 114.7 (C-6), 49.1 (C-3), 44.7 (C-4), 30.8 (C-1); *m/z* (ESI^+): 197.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[86]

(±)-3-Phenylpent-4-enoic acid ((±)-2.3.59)

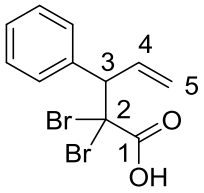


(±)-2.3.19 **(±)-2.3.59**

According to a modified procedure of Javaid *et al*.:[93] To a solution of sodium hydroxide (230 mg, 5.74 mmol) in water (1.9 mL) was added bromine (0.07 mL, 1.4 mmol) at RT. The hypobromite solution was then added dropwise to a solution of ketone **(±)-2.3.19** (50 mg, 0.29 mmol) in dioxane (1.4 mL) over 5 min. The reaction mixture was stirred at RT for 7 h. Upon completion, aq. Na_2SO_3 solution (1 M, 0.56 mL) was added. The dioxane was then removed *in vacuo* and the aqueous layer was extracted with Et_2O (1 x 5 mL). The aqueous layer was acidified with conc. H_2SO_4 to pH 2-3 and extracted with Et_2O (3 x 8 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (35% EtOAc in $PE_{40\text{-}60}$ with 1% acetic acid) to give the title compound **(±)-2.3.59** (30 mg, 0.17 mmol, 59%) as a colourless oil. R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$ with 1% acetic acid); δ_H (400 MHz, $CDCl_3$): 7.34 – 7.29 (m, 2H, Ar-*H*), 7.24 – 7.19 (m, 3H, Ar-*H*), 5.99 (ddd, 1H, *J* = 16.9, 10.1, 6.9 Hz, H-4), 5.10 (dt, 1H, *J* = 10.1, 1.2 Hz, $H_{pro(E)}$-5), 5.09 (dt, 1H, *J* = 16.9, 1.2 Hz, $H_{pro(Z)}$-5), 3.87 (q, 1H, *J* = 7.5 Hz, H-3), 2.81 (dd, 1H, *J* = 15.6, 8.2 Hz, H-2), 2.75 (dd, 1H, *J* = 15.6, 7.1 Hz, H'-2); *m/z* (ESI^+): 199.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[198]

Side product:

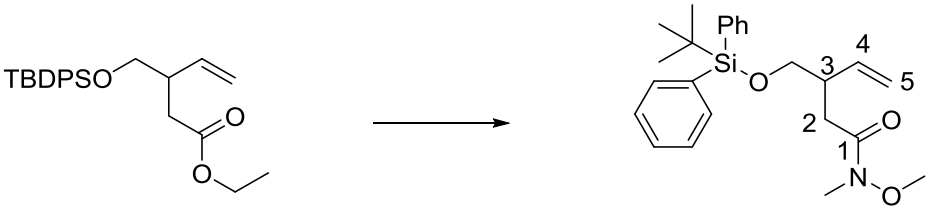
(±)-2,2-Dibromo-3-phenylpent-4-enoic acid ((±)-2.3.60)



(±)-2.3.60

R_f = 0.15 (35% EtOAc in PE_{40-60} with 1% acetic acid); δ_H (400 MHz, $CDCl_3$): 7.50 – 7.46 (m, 2H, Ar-*H*), 7.34 – 7.31 (m, 3H, Ar-*H*), 6.34 (ddd, 1H, *J* = 16.9, 10.2, 8.4 Hz, H-4), 5.36 (d, 1H, *J* = 10.2 Hz, $H_{pro(E)}$-5), 5.29 (d, 1H, *J* = 16.9 Hz, $H_{pro(Z)}$-5), 4.40 (d, 1H, *J* = 8.4 Hz, H-3); accurate mass: found 331.8971, $C_{11}H_{10}{}^{79}Br_2O_2$ requires 331.9048, found 333.9027, $C_{11}H_{10}{}^{79}Br^{81}BrO_2$ requires 333.9027, found 335.8978, $C_{11}H_{10}{}^{81}Br_2O_2$ requires 335.9007. Characterisation data are consistent with literature values.[199]

(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-*N*-methoxy-*N*-methylpent-4-enamide ((±)-2.3.51)

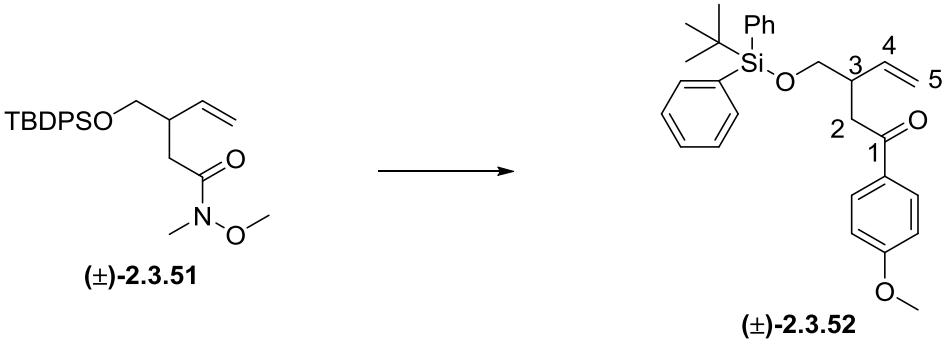


(±)-1.16 **(±)-2.3.51**

According to a modified procedure of Prunet *et al*.:[90] To a solution of ester **(±)-1.16** (2.00 g, 5.04 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (781 mg, 8.07 mmol) in THF (20.8 mL) at -15 °C was added isopropylmagnesium chloride

(2 M in THF, 8.8 mL, 18 mmol) dropwise over 30 min. The reaction mixture was stirred at -15 °C for 2 h. Upon completion, the reaction was quenched by water (10 mL) and brine (10 mL) at -15 °C. EtOAc (10 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.51** (2.04 g, 4.94 mmol, 98%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.63 (m, 4H, Ar-*H*), 7.45 – 7.33 (m, 6H, Ar-*H*), 5.81 (ddd, 1H, *J* = 17.4, 10.4, 7.8 Hz, H-4), 5.09 (dt, 1H, *J* = 17.4, 1.2 Hz, $H_{pro(Z)}$-5), 5.04 (ddd, 1H, *J* = 10.4, 1.7, 0.8 Hz, $H_{pro(E)}$-5), 3.71 (dd, 1H, *J* = 9.8, 5.2 Hz, SiOCH_2), 3.66 (s, 3H, OCNOCH_3), 3.62 (dd, 1H, *J* = 9.8, 6.4 Hz, SiOCH'_2), 3.16 (s, 3H, OCNCH_3), 2.90 (sext, 1H, *J* = 6.0 Hz, H-3), 2.75 (dd, 1H, *J* = 15.5, 5.5 Hz, H-2), 2.52 (dd, 1H, *J* = 15.5, 8.6 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$); *m/z* (ESI^+): 434.2 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[197]

(±)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pent-4-en-1-one ((±)-2.3.52)

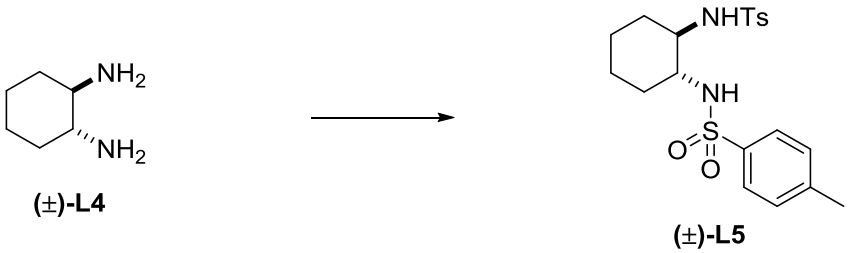


(±)-2.3.51 **(±)-2.3.52**

According to a modified procedure of Rychnovsky *et al*.:[91] To a solution of amide **(±)-2.3.51** (460 mg, 1.12 mmol) in THF (3.7 mL) at 0 °C was added (4-methoxyphenyl)magnesium bromide (0.5 M in THF, 3.4 mL, 1.7 mmol) dropwise over 30 min. The reaction mixture was further stirred at 0 °C for 30 min before warming to RT and stirred for 22 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl (5 mL). EtOAc (3 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 3 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (10% to 13% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.52** (454 mg, 0.990 mmol, 89%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.96 – 7.93 (m, 2H, Ar-*H*), 7.67 – 7.62 (m, 4H, Ar-*H*), 7.44 – 7.32 (m, 6H, Ar-*H*), 6.95 – 6.90 (m, 2H, Ar-*H*), 5.81 (ddd, 1H, *J* = 17.0, 10.6, 7.6 Hz, H-4), 5.04 (dt, 1H, *J* = 17.0, 1.5 Hz, $H_{pro(Z)}$-5), 5.02 (ddd, 1H, *J* = 10.6, 1.3, 0.7 Hz, $H_{pro(E)}$-5), 3.89 (s, 3H, PhOCH_3), 3.74 (dd, 1H, *J* = 9.9, 5.0 Hz, SiOCH_2), 3.64 (dd, 1H, *J* = 9.9, 6.8 Hz, SiOCH'_2), 3.33 (dd, 1H, *J* = 15.8, 5.3 Hz, H-2), 3.02 (sext, 1H, *J* = 6.7 Hz, H-3), 2.88 (dd, 1H, *J* = 15.8, 8.1 Hz, H'-2), 1.06 (s, 9H,

SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 197.9 (*C*=O), 163.4 (Ar), 138.7 (*C*H=CH_2), 135.7 (Ar), 133.7 (Ar), 130.5 (Ar), 130.4 (Ar), 129.7 (Ar), 127.7 (Ar), 116.0 (CH=*C*H_2), 113.7 (Ar), 66.7 (SiO*C*H_2), 55.6 (O*C*H_3), 42.2 (SiOCH_2*C*H), 39.6 (PhCO*C*H_2), 27.0 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2857 (m, C-H), 1677 (s, C=O), 1600 (s), 1255 (s), 1110 (s), 702 (s); *m/z* (ESI$^+$): 481.2 ([M+Na]$^+$, 100%); accurate mass: found 481.2169, $C_{29}H_{34}O_3NaSi$ [M+Na]$^+$ requires 481.2169.

(±)-*N*,*N*'-((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(4-methylbenzenesulfonamide) ((±)-L5)

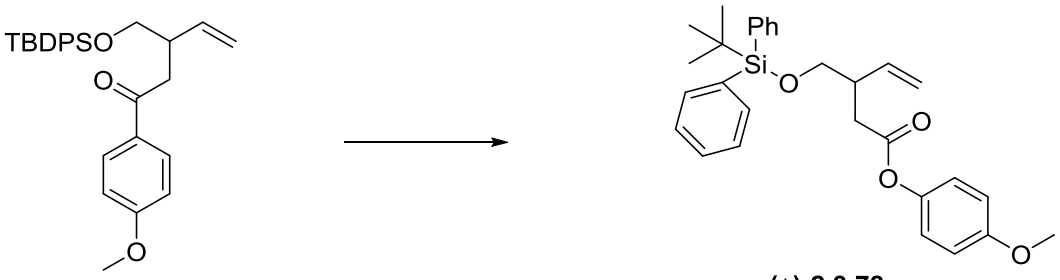


(±)-L4 **(±)-L5**

According to a modified procedure of Aggarwal *et al*.:[102] To a solution of ligand **(±)-L4** (300 mg, 2.63 mmol) in DCM (7.7 mL) at 0 °C was added Et_3N (0.76 mL, 5.5 mmol) followed by *p*-toluenesulfonyl chloride (1.05 g, 5.52 mmol). The reaction mixture was stirred at 0 °C for 1 h followed by warming to RT and stirred for 22 h. Upon completion, the reaction was quenched by water (10 mL) and the two layers were separated. The aqueous layer was extracted with DCM (2 x 7 mL). The organic layers were combined, sequentially washed with aq. HCl solution (1 M, 15 mL), water (15 mL), sat. aq. $NaHCO_3$ solution (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (50% to 60% EtOAc in PE_{40-60}) to give the title compound **(±)-L5** (1.02 g,

2.41 mmol, 92%) as a white solid. R_f = 0.3 (50% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.76 (dt, 4H, *J* = 8.2, 1.7 Hz, Ar-*H*), 7.32 (d, 4H, *J* = 8.2 Hz, Ar-*H*), 4.70 – 4.69 (m, 2H, C*H*NHTs x 2), 2.73 – 2.70 (m, 2H, CH_2CHNHTs), 2.44 (s, 6H, PhCH_3 x 2), 1.89 – 1.85 (m, 2H, CH'_2CHNHTs), 1.13 – 1.07 (m, 4H, CH_2); *m/z* (ESI^+): 423.1 ($[M+Na]^+$, 100%); m.p. = 184 – 187 °C (lit. 186 – 188 °C). Characterisation data are consistent with literature values.[102]

(±)-4-Methoxyphenyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)pent-4-enoate ((±)-2.3.78)



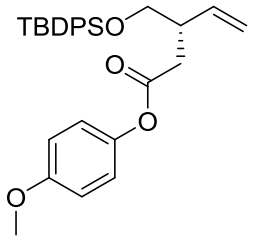
(±)-2.3.52 **(±)-2.3.78**

According to a modified procedure of Shibasaki *et al*.:[98] To a mixture of molecular sieves (4 Å, 100 mg, 200 mg/mmol), ligand **(±)-L5** (46 mg, 0.11 mmol) and K_2CO_3 (45 mg, 0.44 mmol) in DCM (2.6 mL) at RT was added tin(IV) chloride (1 M in DCM, 0.11 mL, 0.11 mmol). To this mixture at 0 °C was added bis(trimethylsilyl)peroxide (60.0 µL, 0.240 mmol) and the resulting mixture was stirred at 0 °C for 10 min. This mixture was then slowly added to a solution of ketone **(±)-2.3.52** (100 mg, 0.218 mmol) in DCM (0.96 mL) at 0 °C over 1 min. The reaction mixture was stirred at 0 °C for 1 h. Upon completion, the reaction was quenched by the addition of solid Na_2SO_3 (50 mg) at 0 °C. The mixture was stirred at 0 °C for 20 min before being

concentrated *in vacuo*. The residue was then dissolved in EtOAc/$PE_{40\text{-}60}$ (1/4, 10 mL) and filtered over 2 cm of silica. The silica cake was washed with EtOAc/$PE_{40\text{-}60}$ (1/4, 2 x 10 mL). The filtrates were then combined and concentrated *in vacuo*. The crude product was purified by FC (12% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.78** (75 mg, 0.16 mmol, 72%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.70 – 7.66 (m, 4H, Ar-*H*), 7.45 – 7.36 (m, 6H, Ar-*H*), 6.97 – 6.92 (m, 2H, Ar-*H*), 6.89 – 6.85 (m, 2H, Ar-*H*), 5.84 (ddd, 1H, *J* = 17.2, 10.4, 7.6 Hz, C*H*=CH_2), 5.18 (dt, 1H, *J* = 17.2, 1.3 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 5.14 (dd, 1H, *J* = 10.4, 1.0 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 3.80 (s, 3H, OCH_3), 3.74 (dd, 1H, *J* = 10.0, 4.9 Hz, SiOCH_2), 3.64 (dd, 1H, *J* = 10.0, 6.7 Hz, SiOCH'_2), 2.97 – 2.88 (m, 2H, $SiOCH_2CH$ and CH_2C(O)O), 2.59 (dd, 1H, *J* = 16.4, 10.2 Hz, CH'_2C(O)O), 1.08 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 171.5 (*C*=O), 157.2 (Ar), 144.2 (Ar), 137.7 (*C*H=CH_2), 135.6 (Ar), 133.4 (Ar), 129.7 (Ar), 127.7 (Ar), 122.3 (Ar), 116.7 (CH=*C*H_2), 114.4 (Ar), 66.3 (SiO*C*H_2), 55.6 (O*C*H_3), 42.9 ($SiOCH_2$*C*H), 36.1 (*C*H_2C(O)O), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); ν_{max}/cm^{-1}: 2932 (m, C-H), 2858 (m, C-H), 1756 (s, C=O), 1506 (s), 1194 (s), 1110 (s), 703 (s); *m/z* (ESI^+): 497.2 ($[M+Na]^+$, 100%); accurate mass: found 497.2115, $C_{29}H_{34}O_4NaSi$ $[M+Na]^+$ requires 497.2119.

The enantioenriched ester:

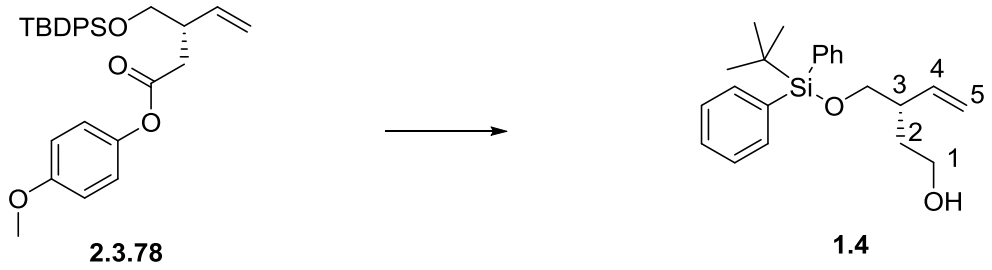
(S)-4-Methoxyphenyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)pent-4-enoate (2.3.78)



2.3.78

ee >99% measured by reducing ester **2.3.78** to alcohol **1.4** and conducting HPLC analysis on alcohol **1.4** (see below); $[\alpha]_D$ (25 °C) +10.1 (c = 1.00 in $CHCl_3$). (The rest of the characterisation see compound **(±)-2.3.78** above.)

(*S*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (1.4)

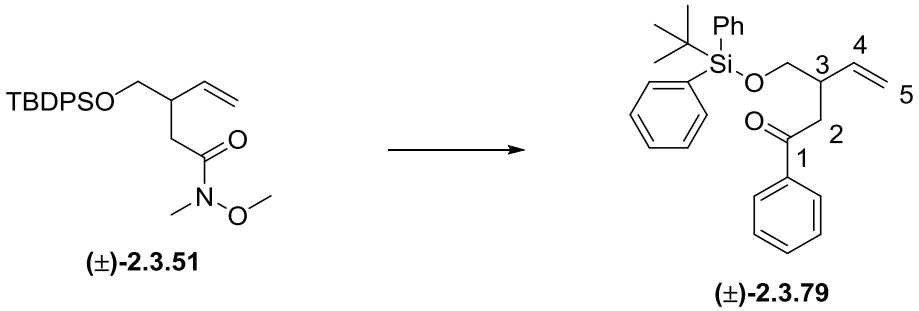


2.3.78 **1.4**

The title compound **1.4** was synthesised from ester **2.3.78** (37 mg, 0.078 mmol) using DIBAL-H (1 M in hexane, 0.18 mL, 0.18 mmol) in THF (0.42 mL) according to general procedure A2. The crude product was purified by FC (22% EtOAc in $PE_{40\text{-}60}$) to give the title compound **1.4** (26 mg, 0.073 mmol, 94%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 –

7.38 (m, 6H, Ar-*H*), 5.70 (ddd, 1H, *J* = 16.8, 10.9, 8.6 Hz, H-4), 5.05 (ddd, 1H, *J* = 16.8, 1.6, 0.8 Hz, $H_{pro(Z)}$-5), 5.04 (dd, 1H, *J* = 10.9, 1.6 Hz, $H_{pro(E)}$-5), 3.73 – 3.64 (m, 2H, H-1), 3.62 (dd, 1H, *J* = 10.1, 5.5 Hz, SiOCH_2), 3.59 (dd, 1H, *J* = 10.1, 6.6 Hz, SiOCH'_2), 2.42 – 2.35 (m, 1H, H-3), 1.82 (ddt, 1H, *J* = 11.9, 7.5, 6.2 Hz, H-2), 1.63 (ddt, 1H, *J* = 11.9, 8.5, 6.0 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 140.2 (C-4), 136.2 (Ar), 134.1 (Ar), 130.3 (Ar), 128.2 (Ar), 116.6 (C-5), 68.0 (*C*H_2OSi), 61.8 (C-1), 44.4 (C-3), 35.0 (C-2), 27.4 (SiC(*C*H_3)$_3$), 19.9 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 3339 (br, O-H), 2858 (w, C-H), 1428 (w), 1112 (m), 702 (m); *m/z* (ESI$^+$): 355.1 ([M+H]$^+$, 90%), 377.3 ([M+Na]$^+$, 100%); accurate mass: found 377.1891, $C_{22}H_{30}NaO_2Si$ [M+Na]$^+$ requires 377.1907; *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 1 mL / min, detection wavelength = 254 nm] t_R(*R*) = 8.86 min, t_R(*S*) = 10.79 min; [α]$_D$ (22 °C) +15.7 (c = 0.60 in ethanol), literature value [α]$_D$ (22 °C) +17.2 (c = 0.51 in ethanol). Characterisation data are consistent with literature values.[88]

(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1-phenylpent-4-en-1-one ((±)-2.3.48)

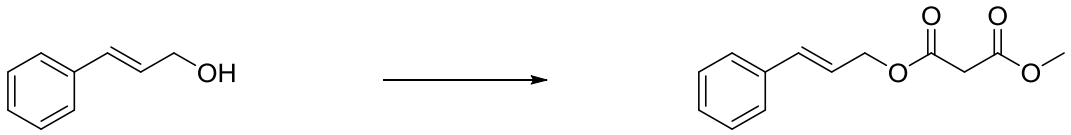


(±)-2.3.51 **(±)-2.3.79**

According to a modified procedure of Rychnovsky *et al*.:[91] To a solution of amide **(±)-2.3.51** (200 mg, 0.486 mmol) in THF (1.6 mL) at 0 °C was added

phenylmagnesium bromide (3 M in Et_2O, 0.24 mL, 0.73 mmol) dropwise over 30 min. The reaction mixture was further stirred at 0 °C for 30 min before warming to RT and stirred for 22 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl solution (5 mL). EtOAc (5 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (7% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.79** (178 mg, 0.425 mmol, 85%) as a colourless oil. R_f = 0.3 (7% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.00 – 7.93 (m, 2H, Ar-*H*), 7.65 (td, 4H, *J* = 8.1, 1.3 Hz, Ar-*H*), 7.57 (tt, 1H, *J* = 7.4, 1.3 Hz, Ar-*H*), 7.49 – 7.32 (m, 8H, Ar-*H*), 5.82 (ddd, 1H, *J* = 16.8, 10.7, 7.5 Hz, H-4), 5.05 (dt, 1H, *J* = 16.8, 1.2 Hz, $H_{pro(Z)}$-5), 5.04 (ddd, 1H, *J* = 10.7, 1.5, 0.7 Hz, $H_{pro(E)}$-5), 3.75 (dd, 1H, *J* = 9.9, 4.9 Hz, SiOC*H*$_2$), 3.66 (dd, 1H, *J* = 9.9, 6.6 Hz, SiOC*H'*$_2$), 3.38 (dd, 1H, *J* = 15.8, 5.1 Hz, H-2), 3.04 (sext, 1H, *J* = 6.2 Hz, H-3), 2.95 (dd, 1H, *J* = 15.8, 8.0 Hz, H'-2), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$): 199.2 (C-1), 138.4 (C-4), 137.2 (Ar), 135.6 (Ar doublet), 133.5 (Ar doublet), 132.9 (Ar), 129.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.6 (Ar doublet), 116.0 (C-5), 66.5 (SiO*C*H$_2$), 41.9 (C-3), 39.9 (C-2), 26.9 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2857 (m, C-H), 1685 (s, C=O), 1427 (m), 1107 (s), 700 (s), 689 (s); *m/z* (ESI$^+$): 451.2 ([M+Na]$^+$, 100%); accurate mass: found 429.2240, $C_{28}H_{33}O_2Si$ [M+H]$^+$ requires 429.2244.

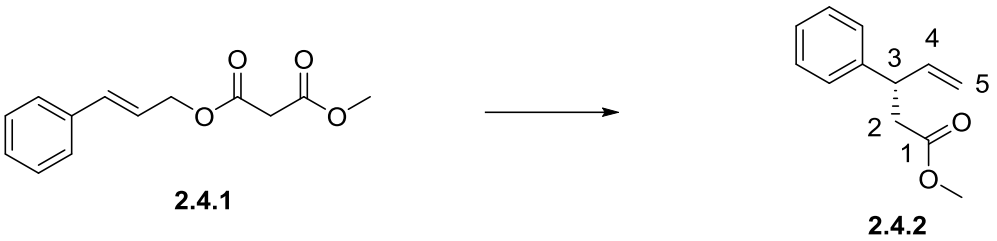
Cinnamyl methyl malonate (2.4.1)



2.3.3 **2.4.1**

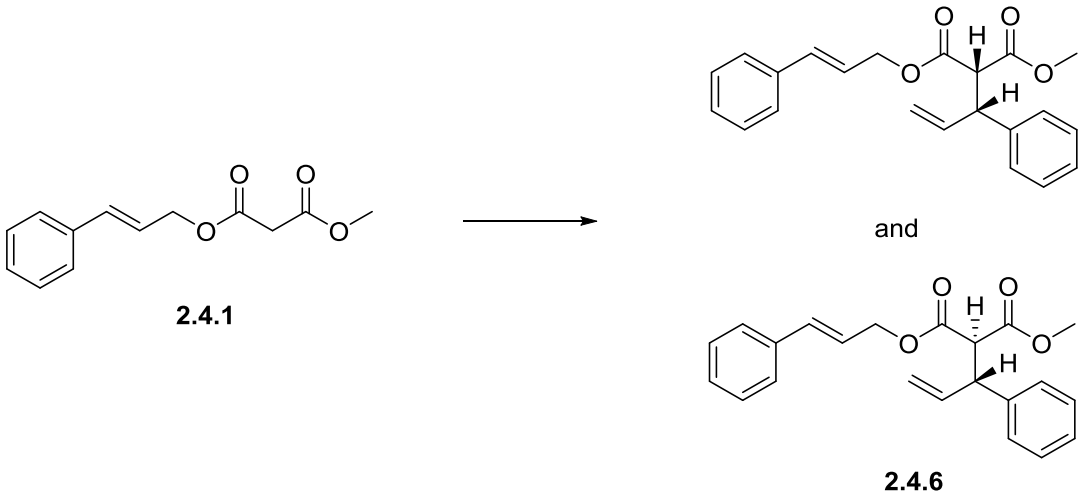
According to a modified procedure of Helmchen *et al*.:[103] To a solution of cinnamyl alcohol **2.3.3** (1.07 g, 7.97 mmol) in DCM (25 mL) was added pyridine (0.97 mL, 12 mmol) followed by methyl 3-chloro-3-oxopropanoate (1.3 mL, 12 mmol) dropwise over 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before it was warmed to RT. The reaction mixture was then stirred at RT for 2 h. Upon completion, water (15 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (3 x 15 mL). The organic layers were combined, washed with sat. aq. $CuSO_4$ solution (15 mL) and sat. aq. NH_4Cl solution (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.1** (1.70 g, 7.31 mmol, 91%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.41 – 7.38 (m, 2H, Ar-*H*), 7.35 – 7.31 (m, 2H, Ar-*H*), 7.29 – 7.27 (m, 1H, Ar-*H*), 6.67 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 16.0, 6.5 Hz, PhCH=C*H*), 4.81 (dd, 2H, *J* = 6.5, 1.3 Hz, CH=CHCH_2), 3.76 (s, 3H, CO_2CH_3), 3.44 (s, 2H, $OCOCH_2CO_2CH_3$); δ_C (100 MHz, $CDCl_3$): 167.0 (CO_2CH_3), 166.4 ($OCOCH_2CO_2CH_3$), 136.1 (Ar), 134.9 (PhCH=CH), 128.8 (Ar), 128.3 (Ar), 126.8(Ar), 122.5 (PhCH=CH), 66.2 ($CH=CHCH_2$), 52.7 (CO_2CH_3), 41.5 ($OCOCH_2CO_2CH_3$); *m/z* (ESI^+): 257.1 ($[M+Na]^+$, 60%).

(*S*)-Methyl 3-phenylpent-4-enoate (2.4.2)



The title compound **2.4.2** was synthesised from malonate **2.4.1** (40 mg, 0.17 mmol) in THF (0.33 mL) using $[Ir(COD)Cl]_2$ (14 mg, 0.021 mmol), ligand **L2** (25 mg, 0.042 mmol) and TBD (12 mg, 0.086 mmol) in THF (0.8 mL) at 60 °C according to a modified general procedure A4. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.2** (20 mg, 0.10 mmol, 61%) as a yellow oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 – 7.29 (m, 2H, Ar-*H*), 7.24 – 7.20 (m, 3H, Ar-*H*), 5.98 (ddd, 1H, *J* = 17.0, 10.1, 6.9 Hz, H-4), 5.08 (dt, 1H, *J* = 10.1, 1.3 Hz, $H_{pro(E)}$-5), 5.07 (dt, 1H, *J* = 17.0, 1.4 Hz, $H_{pro(Z)}$-5), 3.88 (q, 1H, *J* = 7.7 Hz, H-3), 3.62 (s, 3H, CO_2CH_3), 2.77 (dd, 1H, *J* = 15.2, 8.2 Hz, H-2), 2.70 (dd, 1H, *J* = 15.2, 7.3 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 172.5 (C-1), 142.6 (Ar), 140.3 (C-4), 128.7 (Ar), 127.6 (Ar), 126.9 (Ar), 115.0 (C-5), 51.7 ($OCOCH_3$), 45.7 (C-3), 40.2 (C-2); accurate mass: found 213.0890, $C_{12}H_{14}NaO_2$ $[M+Na]^+$ requires 213.0886; *ee*: 98% [Chiralcel OD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 1 mL / min, detection wavelength = 210 nm] $t_R(S)$ = 7.82 min, $t_R(R)$ = 13.22 min; $[\alpha]_D$ (22 °C) -6.2 (c = 0.80 in $CHCl_3$), literature value $[\alpha]_D$ (20 °C) -7.5 (c = 0.50 in $CHCl_3$).[200] Characterisation data are consistent with literature values.[200]

1-Cinnamyl 3-methyl 2-(1-phenylallyl)malonate (2.4.6)

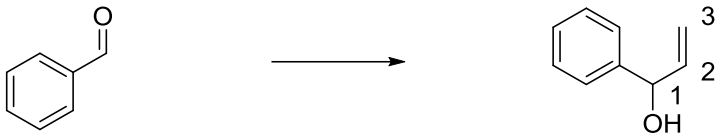


2.4.1 **2.4.6**

To a solution of $[Ir(COD)Cl]_2$ (17 mg, 0.025 mmol) and ligand **L2** (31 mg, 0.050 mmol) in THF (1.0 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (15 mg, 0.10 mmol) at RT. The mixture was stirred at RT for 5 min followed by the addition of a solution of malonate **2.4.1** (50 mg, 0.21 mmol) in THF (0.43 mL). $Zn(OTf)_2$ (23 mg, 0.063 mmol) was quickly added to the above reaction mixture and the reaction mixture was stirred at 50 °C for 22 h. The reaction was stopped before completion. The mixture was concentrated *in vacuo* and purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.6** (16 mg, 0.046 mmol, 44%) as a colourless oil. The title compound **2.4.6** was formed as a mixture of inseparable diastereomers. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.35 – 7.28 (m, 2H, Ar-*H*), 7.30 – 7.16 (m, 10H, Ar-*H*), 7.20 – 7.12 (m, 6H, Ar-*H*), 7.16 – 7.05 (m, 2H, Ar-*H*), 6.58 (d, 1H, *J* = 15.7 Hz, PhC*H*=CHCH$_2$), 6.37 (d, 1H, *J* = 16.0 Hz, PhC*H*=CHCH$_2$ of the other diastereomer), 6.19 (dt, 1H, *J* = 16.0, 6.5 Hz, PhCH=C*H*CH$_2$), 5.98 – 5.89 (m, 2H, C*H*=CH$_2$ x 2), 5.83 (dt, 1H, *J* = 15.7, 6.4 Hz, PhCH=C*H*CH$_2$ of the other diastereomer), 5.07 (dt, 1H, *J* = 17.0, 1.2 Hz,

CH=CH$_{pro(E)}$*H$_{pro(Z)}$*), 5.06 (dt, 1H, *J* = 10.2, 1.2 Hz, CH=C*H$_{pro(E)}$*H$_{pro(Z)}$), 5.03 (dt, 1H, *J* = 15.7, 0.9 Hz, CH=C*H$_E$*H$_Z$ of the other diastereomer), 5.02 (dt, 1H, *J* = 10.2, 0.9 Hz, CH=CH$_E$*H$_Z$* of the other diastereomer), 4.73 (dt, 2H, *J* = 6.4, 1.6 Hz, PhCH=CHC*H$_2$*), 4.46 (dd, 2H, *J* = 6.5, 1.3 Hz, PhCH=CHC*H$_2$* of the other diastereomer), 4.08 – 4.04 (m, 2H, PhC*H*CH=CH$_2$ x 2), 3.84 (d, 2H, *J* = 11.1 Hz, OC(O)C*H* x 2), 3.68 (s, 3H, OCOC*H$_3$*), 3.43 (s, 3H, OCOC*H$_3$* of the other diastereomer); δ_C (125 MHz, $CDCl_3$): 168.3 (*C*=O), 167.9 (*C*=O), 167.7 (*C*=O), 167.3 (*C*=O), 140.1 (Ar), 139.9 (Ar), 138.0 (*C*H=CH$_2$), 137.8 (*C*H=CH$_2$ of the other diastereomer), 136.2 (Ar doublet), 134.9 (Ph*C*H=CHCH$_2$), 134.6 (Ph*C*H=CHCH$_2$ of the other diastereomer), 128.8 (Ar doublet), 128.7 (Ar), 128.3 (Ar), 128.2 (Ar doublet), 128.1 (Ar), 127.3 (Ar doublet), 126.8 (Ar), 122.6 (PhCH=*C*HCH$_2$), 122.4 (PhCH=*C*HCH$_2$ of the other diastereomer), 116.9 (CH=*C*H$_2$), 116.7 (CH=*C*H$_2$ of the other diastereomer), 66.3 (PhCH=CH*C*H$_2$), 66.1 (PhCH=CH*C*H$_2$ of the other diastereomer), 57.5 (OC(O)*C*H doublet), 52.8 (OCO*C*H$_3$), 52.6 (OCO*C*H$_3$), 50.0 (Ph*C*HCH=CH$_2$), 49.9 (Ph*C*HCH=CH$_2$ of the other diastereomer); ν_{max}/cm^{-1}: 3032 (w, C-H), 1756 (s, C=O), 1737 (s, C=O), 1260 (s), 1151 (s); *m/z* (ESI$^+$): 373.1 ([M+Na]$^+$, 100%); accurate mass: found 373.1415, $C_{22}H_{22}NaO_4$ [M+Na]$^+$ requires 373.1410; $[\alpha]_D$ (25 °C) +6.5 (c = 0.50 in $CHCl_3$).

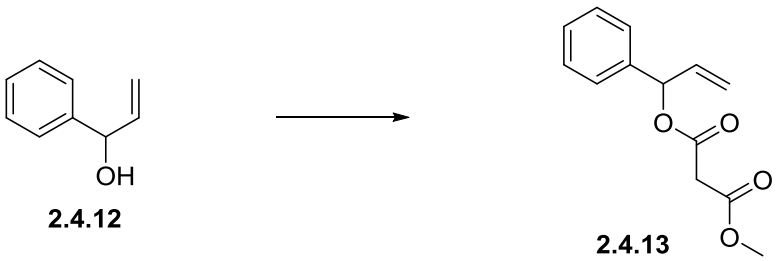
(±)-1-Phenylprop-2-en-1-ol (2.4.12)



2.4.11 **2.4.12**

According to a modified procedure of Cossy *et al*.:[107] To vinylmagnesium bromide (1 M in THF, 56.5 mL, 56.5 mmol) at 0 °C was added a solution of benzaldehyde (4.8 mL, 47 mmol) in THF (63 mL). The reaction mixture was stirred at 0 °C for 30 min before warming to RT. The reaction mixture was stirred at RT for another 3 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl solution (90 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 70 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound **2.4.12** (6.30 g, 47.1 mmol, 100%) as a yellow oil. The crude was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.40 – 7.34 (m, 4H, Ar-*H*), 7.31 – 7.27 (m, 1H, Ar-*H*), 6.06 (ddd, 1H, *J* = 16.7, 10.3, 6.1 Hz, H-2), 5.36 (d, 1H, *J* = 16.7 Hz, $H_{pro(Z)}$-3), 5.23 – 5.19 (m, 2H, H-1 and $H_{pro(E)}$-3); δ_C (100 MHz, $CDCl_3$): 142.7 (Ar), 140.4 (C-2), 128.7 (Ar), 127.9 (Ar), 126.4 (Ar), 115.2 (C-3), 75.5 (C-1). Characterisation data are consistent with literature values.[188]

(±)-Methyl (1-phenylallyl) malonate (2.4.13)

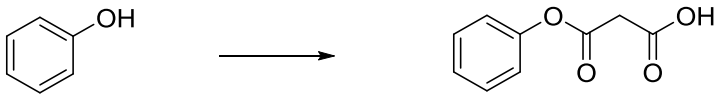


2.4.12 **2.4.13**

According to a modified procedure of Helmchen et al.:[103] To a solution of alcohol **2.4.12** (1.00 g, 7.45 mmol) in DCM (25 mL) at 0 °C was added pyridine (0.78 mL, 9.7 mmol). Methyl malonyl chloride (1.0 mL, 9.7 mmol) was then added to the above mixture dropwise over 5 min. The reaction mixture was stirred at 0 °C for 1 h before warming to RT. The reaction mixture was stirred at RT for 2 h. Upon completion, water (10 mL) and brine (15 mL) were added to the reaction mixture and the two layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, washed sequentially with sat. aq. $CuSO_4$ solution (10 mL) and sat. aq. NH_4Cl solution (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (17% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.13** (1.34 g, 5.72 mmol, 77% over two steps) as a colourless oil. R_f = 0.3 (17% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.39 – 7.29 (m, 5H, Ar-*H*), 6.31 (dt, 1H, *J* = 5.9, 1.1 Hz, PhC*H*), 6.01 (ddd, 1H, *J* = 17.1, 10.5, 5.9 Hz, C*H*=CH_2), 5.33 (dt, 1H, *J* = 17.1, 1.1 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 5.28 (dt, 1H, *J* = 10.5, 1.1 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 3.73 (s, 3H, OCOCH_3), 3.44 (s, 2H, OC(O)CH_2); δ_C (100 MHz, $CDCl_3$): 166.9 (*C*=O), 165.6 (*C*=O), 138.4 (Ar), 135.7 (*C*H=CH_2), 128.7 (Ar), 128.5 (Ar), 127.3 (Ar), 117.6 (CH=*C*H_2), 77.5 (Ph*C*H), 52.6 (OCO*C*H_3), 41.7 (OCO*C*H_2); ν_{max}/cm^{-1}: 2953 (w, C-H), 1733 (s, C=O), 1146 (s),

1017 (m), 984 (m), 700 (s); *m/z* (ESI^+): 257.1 ($[M+Na]^+$, 100%); accurate mass: found 257.0783, $C_{13}H_{14}NaO_4$ $[M+Na]^+$ requires 257.07843.

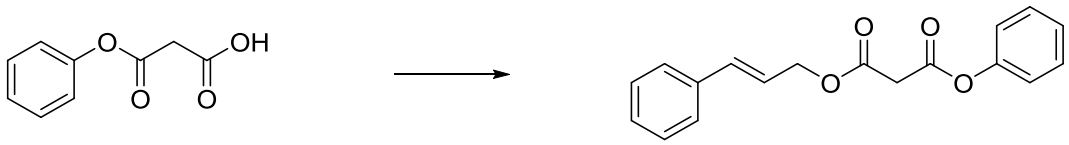
3-Oxo-3-phenoxypropanoic acid (2.4.15)



2.4.14 **2.4.15**

According to a modified procedure of Scott *et al*.:[108] A mixture of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (1.53 g, 10.6 mmol) and phenol **2.4.14** (1.00 g, 10.6 mmol) in toluene (80 mL) was stirred under reflux at 130 °C for 4 h. Upon completion, aq. 5% $NaHCO_3$ solution (1.79 g solid $NaHCO_3$ in 35 mL water) was added to the mixture. The two layers were separated and the organic layer was extracted with water (2 x 20 mL). The aqueous layers were combined. Aq. 18.8% HCl solution (5.3 mL conc. HCl in 5 mL water) was added to the combined aqueous layers and the aqueous layers were extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound **2.4.15** (1.36 g, 7.55 mmol, 71%) as white crystalline solid. The crude was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$): 7.42 – 7.38 (m, 2H, Ar-*H*), 7.29 – 7.25 (m, 1H, Ar-*H*), 7.15 – 7.12 (m, 2H, Ar-*H*), 3.70 (s, 2H, OCOCH_2); *m/z* (ESI^+): 179.0 ($[M-H]^-$, 95%); m.p. = 67 – 71 °C. Characterisation data are consistent with literature values.[201]

Cinnamyl phenyl malonate (2.4.16)

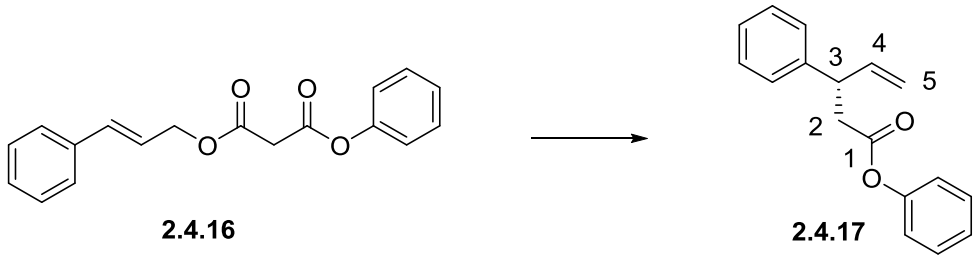


2.4.15 **2.4.16**

According to a modified procedure of Woggon *et al*.:[109] To a solution of acid **2.4.15** (400 mg, 2.22 mmol) in DCM (10 mL) was added DMF (18.0 µL) at 0 °C followed by oxalyl chloride (0.24 mL, 2.8 mmol) dropwise at 0 °C. After stirring the reaction mixture at 0 °C for 30 min, the reaction was warmed to RT and stirred for 3 h. To the reaction mixture was then added a solution of cinnamyl alcohol (0.30 mL, 2.2 mmol) and DMAP (326 mg, 2.66 mmol) in DCM (6 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 22 h. Upon completion, water (20 mL) and Et_2O (20 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 16 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (18% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.16** (395 mg, 1.33 mmol, 60%) as a white solid. R_f = 0.3 (18% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.40 – 7.27 (m, 7H, Ar-*H*), 7.25 – 7.23 (m, 1H, Ar-*H*), 7.14 – 7.11 (m, 2H, Ar-*H*), 6.71 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH), 6.31 (dt, 1H, *J* = 16.0, 6.6 Hz, PhCH=C*H*), 4.87 (dd, 2H, *J* = 6.6, 1.3 Hz, PhCH=CHCH_2), 3.67 (s, 2H, OCOCH_2); δ_C (100 MHz, $CDCl_3$): 166.1 (*C*=O), 165.1 (*C*=O), 150.5 (Ar), 136.1 (Ar), 135.2 (Ph*C*H=CH), 129.6 (Ar), 128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 126.4 (Ar), 122.3 (PhCH=*C*H), 121.5 (Ar), 66.4 (PhCH=CH*C*H_2), 41.8 (OCO*C*H_2); ν_{max}/cm^{-1}: 3028 (w, C-H), 1766 (s, C=O), 1737 (s,

C=O), 1190 (s), 1134 (s); *m/z* (ESI$^+$): 319.1 ([M+Na]$^+$, 100%); accurate mass: found 319.0942, $C_{18}H_{16}NaO_4$ [M+Na]$^+$ requires 319.0941.

(S)-Phenyl 3-phenylpent-4-enoate (2.4.17)

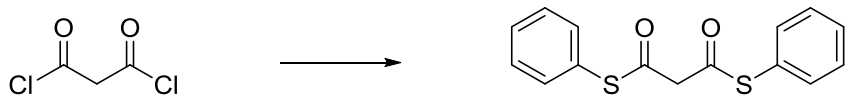


2.4.16 **2.4.17**

The title compound **2.4.17** was synthesised from malonate **2.4.16** (40 mg, 0.13 mmol) in THF (0.30 mL) using $[Ir(COD)Cl]_2$ (11 mg, 0.016 mmol), ligand **L2** (20 mg, 0.033 mmol) and TBD (9 mg, 0.07 mmol) in THF (0.60 mL) at 50 °C according to a modified general procedure A4. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.17** (19 mg, 0.075 mmol, 56%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.38 – 7.25 (m, 7H, Ar-*H*), 7.22 – 7.18 (m, 1H, Ar-*H*), 6.92 – 6.90 (m, 2H, Ar-*H*), 6.08 (ddd, 1H, *J* = 17.1, 10.2, 7.0 Hz, H-4), 5.19 (dt, 1H, *J* = 17.1, 1.3 Hz, $H_{pro(Z)}$-5), 5.16 (dt, 1H, *J* = 10.2, 1.3 Hz, $H_{pro(E)}$-5), 4.00 (q, 1H, *J* = 7.3 Hz, H-3), 3.02 (dd, 1H, *J* = 14.8, 8.1 Hz, H-2), 2.95 (dd, 1H, *J* = 14.8, 7.7 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 170.6 (C-1), 150.7 (Ar), 142.2 (Ar), 140.1 (C-4), 129.5 (Ar), 128.9 (Ar), 127.8 (Ar), 127.1 (Ar), 126.0 (Ar), 121.7 (Ar), 115.3 (C-5), 46.0 (C-3), 40.5 (C-2); ν_{max}/cm^{-1}: 3030 (w, C-H), 1755 (s, C=O), 1492 (m), 1195 (s); *m/z* (ESI$^+$): 275.1 ([M+Na]$^+$, 100%); accurate mass: found 275.1050, $C_{17}H_{16}NaO_2$ [M+Na]$^+$ requires 275.1043;

$[\alpha]_D$ (25 °C) -28.3 (c = 1.00 in $CHCl_3$). Enantiomeric excess was not measured due to sub-optimal yields.

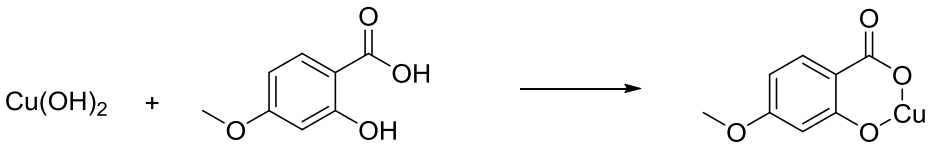
_S_,_S_-Diphenyl propanebis(thioate) (2.4.20)



2.4.19 **2.4.20**

According to a procedure of Shindo *et al*.:[110] To a solution of malonyl chloride **2.4.19** (1.1 mL, 11 mmol) in Et_2O (38 mL) was added thiophenol (2.6 mL, 25 mmol). The reaction mixture was stirred for 22 h at RT. Upon completion, the reaction was quenched with water (20 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (18% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.20** (2.12 g, 7.35 mmol, 65%) as white needles. R_f = 0.3 (18% EtOAc in $PE_{40\text{-}60}$); m.p. = 93 – 95 °C (lit. 94.6 – 95.3 °C); δ_H (400 MHz, $CDCl_3$): 7.48 – 7.42 (m, 10H, Ar-*H*), 3.96 (s, 2H, SC(O)C*H*$_2$). Characterisation data are consistent with literature values.[110]

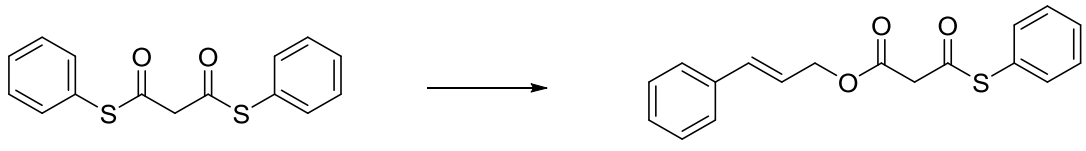
Copper(II) 4-methoxy-2-oxidobenzoate (2.4.23)



2.4.22 **2.4.23**

According to a procedure of Shindo *et al*.:[110] A mixture of $Cu(OH)_2$ (90 mg, 0.92 mmol) and 4-methoxysalicyclic acid **2.4.22** (311 mg, 1.85 mmol) in ethanol (4.5 mL) was stirred under reflux at 90 °C for 4 h. Upon completion, after cooling the reaction mixture to RT, the solid was filtered, washed with water (2 x 5 mL) and ethanol (2 x 5 mL) and air-dried under suction to give the title compound **2.4.23** (150 mg, 0.655 mmol, 71%) as green powders. m.p. = 200 – 210 °C decomposed (lit. m.p. = 210 – 258 °C decomposed);[110] ν_{max}/cm^{-1}: 1600 (s, C=O), 1438 (s), 1371 (s), 1264 (s), 1160 (s, C-O). Characterisation data are consistent with literature values.[110]

Cinnamyl 3-oxo-3-(phenylthio)propanoate (2.4.21)

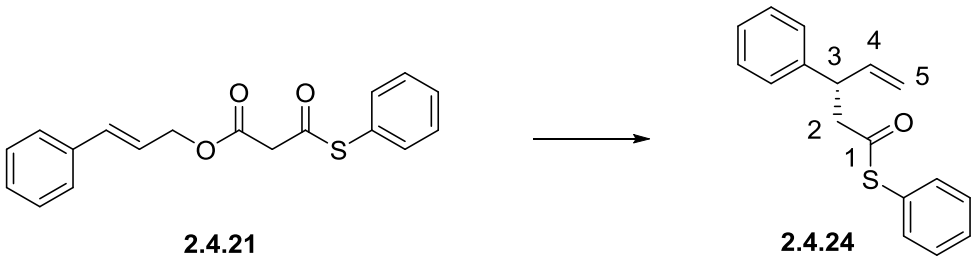


2.4.20 **2.4.21**

According to a modified procedure of Shindo *et al*.:[110] To a solution of thioate **2.4.20** (500 mg, 1.73 mmol) in MeCN (4 mL) was added copper catalyst **2.4.23** (4 mg, 0.02 mmol), cinnamyl alcohol (0.27 mL, 2.1 mmol) and molecular sieves (4 Å, 30 mg). The reaction mixture was stirred at 60 °C under air for 5 h. Upon

completion, after cooling the mixture to RT, it was filtered through Celite™ (100 mg) and the filter cake was washed with EtOAc (20 mL). The filtrates were combined and concentrated *in vacuo*. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.21** (440 mg, 1.41 mmol, 81%) as a pale yellow oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.44 – 7.27 (m, 10H, Ar-*H*), 6.69 (d, 1H, *J* = 15.8 Hz, PhC*H*=CH), 6.29 (dt, 1H, *J* = 15.8, 6.6 Hz, PhCH=C*H*), 4.82 (dd, 2H, *J* = 6.6, 1.3 Hz, CH=CHCH_2), 3.72 (s, 2H, OC(O)CH_2); δ_C (100 MHz, $CDCl_3$): 189.6 (*C*=O, thioester), 165.4 (*C*=O, ester), 136.1 (Ar), 135.0 (Ph*C*H=CH), 134.9 (Ar), 134.6 (Ar), 130.0 (Ar), 129.5 (Ar), 128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 122.4 (PhCH=*C*H), 66.4 (CH=CH*C*H_2), 49.2 (OC(O)*C*H_2); ν_{max}/cm^{-1}: 2998 (w, C-H), 1739 s (C=O, ester), 1703 s (C=O, thioester), 1146 (s), 963 (s), 744 (s); *m/z* (ESI^+): 335.1 ($[M+Na]^+$, 100%); accurate mass: found 335.0715, $C_{18}H_{16}NaO_3S$ $[M+Na]^+$ requires 335.0712.

(S)-S-Phenyl 3-phenylpent-4-enethioate (2.4.24)



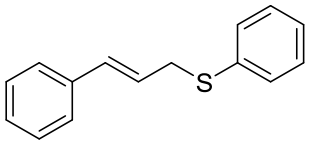
2.4.21 **2.4.24**

The title compound **2.4.24** was synthesised from thiophenylmalonate **2.4.21** (40 mg, 0.13 mmol) in THF (0.25 mL) using $[Ir(COD)Cl]_2$ (3 mg, 0.005 mmol), ligand **L2** (6 mg, 0.01 mmol) and TBD (3 mg, 0.02 mmol) in THF (0.20 mL) according to general procedure A4. The crude product was purified by FC (4% EtOAc in $PE_{40\text{-}60}$)

to give the title compound **2.4.24** (8 mg, 0.03 mmol, 24%) as a yellow oil. R_f = 0.3 (4% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.39 – 7.37 (m, 3H, Ar-*H*), 7.33 – 7.31 (m, 4H, Ar-*H*), 7.24 – 7.22 (m, 3H, Ar-*H*), 6.01 (ddd, 1H, *J* = 16.5, 10.9, 6.9 Hz, H-4), 5.12 (dt, 1H, *J* = 10.9, 1.3 Hz, $H_{pro(E)}$-5), 5.11 (dt, 1H, *J* = 16.5, 1.2 Hz, $H_{pro(Z)}$-5), 3.97 (q, 1H, *J* = 7.5 Hz, H-3), 3.10 (dd, 1H, *J* = 15.0, 7.9 Hz, H-2), 3.03 (dd, 1H, *J* = 15.0, 7.2 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 195.8 (C-1), 142.1 (Ar), 139.8 (C-4), 134.6 (Ar), 129.5 (Ar), 129.3 (Ar), 128.8 (Ar), 127.8 (Ar), 127.7 (Ar), 127.0 (Ar), 115.5 (C-5), 49.1 (C-2), 46.1 (C-3); ν_{max}/cm^{-1}: 2923 (w, C-H), 1706 s (C=O), 1024 (s), 998 (s), 746 (s); *m/z* (ESI^+): 291.1 ($[M+Na]^+$, 100%); accurate mass: found 291.0811, $C_{17}H_{16}NaOS$ $[M+Na]^+$ requires 291.0814; $[\alpha]_D$ (25 °C) -15.2 (c = 0.40 in $CHCl_3$). *ee* was not measured due to the sub-optimal yield.

Side product:

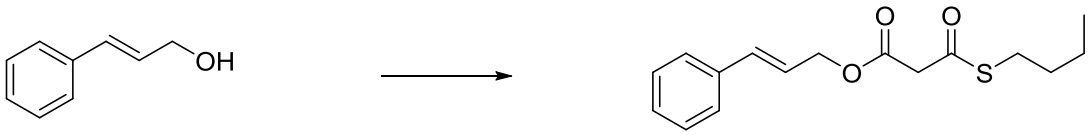
Cinnamyl(phenyl)sulfane (2.4.26)



2.4.26

White crystalline solid (8 mg, 0.04 mmol, 28%); R_f = 0.3 (3% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.39 – 7.37 (m, 2H, Ar-*H*), 7.33 – 7.28 (m, 6H, Ar-*H*), 7.24 – 7.19 (m, 2H, Ar-*H*), 6.3 (d, 1H, *J* = 15.6 Hz, PhC*H*=CH), 6.25 (dt, 1H, *J* = 15.6, 7.1 Hz, PhCH=C*H*), 3.71 (dd, 2H, *J* = 7.1, 1.2 Hz, CH=CHCH_2); δ_C (100 MHz, $CDCl_3$): 136.9 (Ar), 136.0 (Ar), 132.9 (Ph*C*H=CH), 130.4 (Ar), 129.0 (Ar), 128.7 (Ar), 127.7 (Ar), 126.6 (Ar), 126.5 (Ar), 125.2 (PhCH=*C*H), 37.3 (CH=CH*C*H_2). Characterisation data are consistent with literature values.[202]

Cinnamyl 3-(butylthio)-3-oxopropanoate (2.4.29)



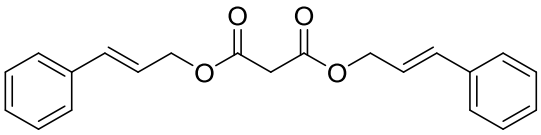
2.3.3 **2.4.29**

To a solution of malonyl dichloride (0.19 mL, 1.9 mmol) in DCM (1 mL) at 0 °C was added a solution of cinnamyl alcohol **2.3.3** (0.10 mL, 0.75 mmol) and DMAP (101 mg, 0.825 mmol) in DCM (4 mL) dropwise over 30 min. The reaction mixture was warmed to RT and stirred for 1.5 h. The reaction mixture was then cooled to 0 °C and a solution of butane-1-thiol (0.36 mL, 3.4 mmol) and DMAP (421 mg, 3.45 mmol) in DCM (7 mL) was added to the reaction mixture. The reaction mixture was warmed to RT and stirred for 2 h. Upon completion, Et_2O (15 mL), water (15 mL) and brine (10 mL) were added to the mixture. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.29** (56 mg, 0.19 mmol, 26%) as a yellow oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.42 – 7.38 (m, 2H, Ar-*H*), 7.34 – 7.28 (m, 3H, Ar-*H*), 6.67 (d, 1H, *J* = 15.8 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.8, 6.5 Hz, PhCH=C*H*), 4.80 (dd, 2H, *J* = 6.5, 1.4 Hz, PhCH=CHCH_2), 3.62 (s, 2H, OCOCH_2), 2.94 (t, 2H, *J* = 7.3 Hz, OCSCH_2), 1.60 – 1.53 (m, 2H, OCSCH_2CH_2), 1.42 – 1.36 (m, 2H, OCSCH_2CH_2CH_2), 0.90 (t, 3H, *J* = 7.3 Hz, OCSCH_2CH_2CH_2CH_3); δ_C (100 MHz, $CDCl_3$): 191.3 (*C*=O, thioester), 166.1 (*C*=O, ester), 136.2 (Ph*C*H=CH), 135.0 (Ar), 128.8 (Ar), 128.3 (Ar), 126.8 (Ar), 122.5 (PhCH=*C*H), 66.3 (PhCH=CH*C*H_2), 49.7

($OCOCH_2$), 31.4 ($OCSCH_2CH_2$), 29.4 ($OCSCH_2$), 22.0 ($OCSCH_2CH_2CH_2$), 13.7 ($OCSCH_2CH_2CH_2CH_3$); ν_{max}/cm^{-1}: 2959 (w, C-H), 2932 (w, C-H), 1741 (s, C=O, ester), 1683 (s, C=O, thioester); *m/z* (ESI^+): 315.1 ($[M+Na]^+$, 100%); accurate mass: found 310.1474, $C_{16}H_{20}O_3SNH_4$ $[M+NH_4]^+$ requires 310.1477.

Side product:

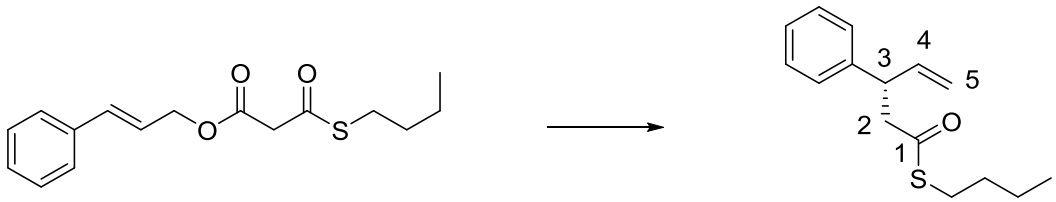
Dicinnamyl malonate (2.4.30)



2.4.30

Colourless oil (75 mg, 0.26 mmol, 35%); R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.39 – 7.35 (m, 4H, Ar-*H*), 7.34 – 7.27 (m, 6H, Ar-*H*), 6.66 (d, 2H, *J* = 15.7 Hz, PhC*H*=CHCH$_2$), 6.28 (dt, 2H, *J* = 15.7, 6.5 Hz, PhCH=C*H*CH$_2$), 4.82 (dd, 4H, *J* = 6.5, 1.4 Hz, PhCH=CHC*H*$_2$), 3.48 (s, 2H, OC(O)C*H*$_2$); δ_C (100 MHz, $CDCl_3$): 166.4 (*C*=O), 136.1 (Ar), 134.9 (Ph*C*H=CHCH$_2$), 128.8 (Ar), 128.3 (Ar), 126.8 (Ar), 122.5 (PhCH=*C*HCH$_2$), 66.3 (PhCH=CH*C*H$_2$), 41.7 (OC(O)*C*H$_2$); *m/z* (ESI^+): 359.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[203]

(S)-S-Butyl 3-phenylpent-4-enethioate (2.4.31)

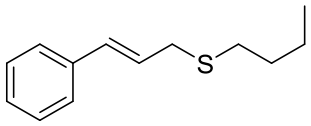


2.4.29 **2.4.31**

The title compound **2.4.31** was synthesised from alkylthiomalonate **2.4.29** (30 mg, 0.10 mmol) in THF (0.20 mL) using $[Ir(COD)Cl]_2$ (8 mg, 0.01 mmol), ligand **L2** (14 mg, 0.025 mmol) and TBD (7 mg, 0.05 mmol) in THF (0.48 mL) at 50 °C according to a modified general procedure A4. The crude product was purified by FC (5% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.31** (9 mg, 0.04 mmol, 36%) as a yellow oil. R_f = 0.3 (5% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.32 – 7.29 (m, 2H, Ar-*H*), 7.23 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 16.7, 10.4, 7.0 Hz, H-4), 5.08 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-5), 5.06 (dt, 1H, *J* = 16.7, 1.3 Hz, $H_{pro(Z)}$-5), 3.94 (q, 1H, *J* = 7.5 Hz, H-3), 2.99 (dd, 1H, *J* = 14.8, 8.1 Hz, H-2), 2.92 (dd, 1H, *J* = 14.8, 7.2 Hz, H'-2), 2.83 (t, 2H, *J* = 7.3 Hz, OCSCH_2), 1.51 – 1.44 (m, 2H, $OCSCH_2CH_2$), 1.34 – 1.29 (m, 2H, $OCSCH_2CH_2CH_2$), 0.88 (t, 3H, *J* = 7.4 Hz, $OCSCH_2CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$): 197.9 (C-1), 142.2 (Ar), 140.0 (C-4), 128.7 (Ar), 127.8 (Ar), 126.9 (Ar), 115.2 (C-5), 49.5 (C-2), 46.1 (C-3), 31.7 ($OCSCH_2CH_2$), 28.8 ($OCSCH_2$), 22.0 ($OCSCH_2CH_2CH_2$), 13.7 ($OCSCH_2CH_2CH_2CH_3$); ν_{max}/cm^{-1}: 2958 (m, C-H), 2926 (m, C-H), 1687 s (C=O), 1045 (m), 992 (m), 699 (s); *m/z* (ESI^+): 249.2 ($[M+H]^+$, 95%), 271.1 ($[M+Na]^+$, 100%); accurate mass: found 271.1131, $C_{15}H_{20}NaOS$ $[M+Na]^+$ requires 271.1127; $[\alpha]_D$ (25 °C) -9.5 (c = 0.80 in $CHCl_3$). *ee* was not measured due to the sub-optimal yield.

Side product:

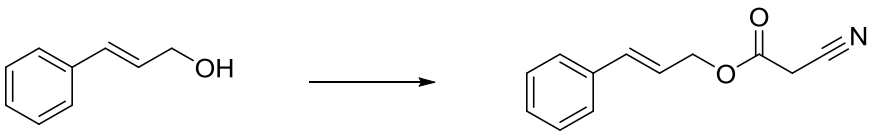
Butyl(cinnamyl)sulfane (2.4.33)



2.4.33

Yellow oil (6 mg, 0.03 mmol, 23%); R_f = 0.5 (5% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.41 – 7.34 (m, 2H, Ar-*H*), 7.34 – 7.30 (m, 2H, Ar-*H*), 7.25 – 7.21 (m, 1H, Ar-*H*), 6.43 (d, 1H, *J* = 15.7 Hz, PhC*H*=CH), 6.19 (dt, 1H, *J* = 15.7, 7.4 Hz, PhCH=C*H*), 3.30 (dd, 2H, *J* = 7.4, 1.2 Hz, PhCH=CHCH_2), 2.49 (t, 2H, *J* = 7.2 Hz, PhCH=CHCH_2SCH_2), 1.62 – 1.52 (m, 2H, SCH_2CH_2), 1.40 (sext, 2H, *J* = 7.3 Hz, $SCH_2CH_2CH_2$), 0.91 (t, 3H, *J* = 7.3 Hz, $SCH_2CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$): 137.0 (Ar), 132.0 (PhCH=CH), 128.7 (Ar), 127.6 (Ar), 126.4 (PhCH=CH), 126.4 (Ar), 34.5 (PhCH=CHCH$_2$), 31.7 (SCH_2CH_2), 30.6 (PhCH=CHCH_2SCH_2), 22.2 ($SCH_2CH_2CH_2$), 13.9 ($SCH_2CH_2CH_2CH_3$). Characterisation data are consistent with literature values.[204]

Cinnamyl 2-cyanoacetate (2.4.34)

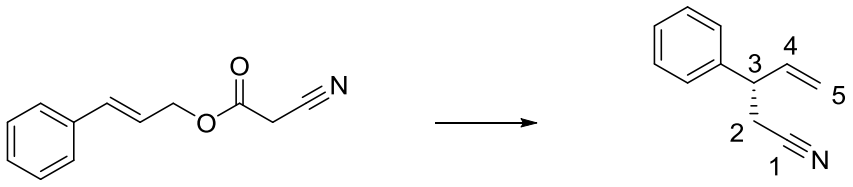


2.3.3 **2.4.34**

According to a procedure of Ducki *et al*.:[111] To a solution of cinnamyl alcohol **2.3.3** (100 mg, 0.745 mmol) and cyanoacetic acid (70 mg, 0.82 mmol) in DCM (4.2 mL) at

0 °C was added DMAP (9 mg, 0.07 mmol) and dicyclohexylcarbodiimide (169 mg, 0.820 mmol). The reaction mixture was stirred at 0 °C for 3.5 h. Upon completion, the mixture was filtered through Celite™ and the filter cake was washed with DCM (2 x 5 mL). The filtrates were combined and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.34** (102 mg, 0.507 mmol, 68%) as white crystals. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.41 – 7.29 (m, 5H, Ar-*H*), 6.71 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.9, 6.7 Hz, PhCH=C*H*), 4.86 (dd, 2H, *J* = 6.7, 1.2 Hz, PhCH=CHCH_2), 3.50 (s, 2H, OCOCH_2); δ_C (100 MHz, $CDCl_3$): 162.9 (*C*=O), 136.1 (Ph*C*H=CH), 135.8 (Ar), 128.9 (Ar), 128.6 (Ar), 126.9 (Ar), 121.4 (PhCH=*C*H), 113.0 (*C*≡N), 67.5 (PhCH=CH*C*H_2), 24.9 (OCO*C*H_2). Characterisation data are consistent with literature values.[111]

(*S*)-3-Phenylpent-4-enenitrile (2.4.35)



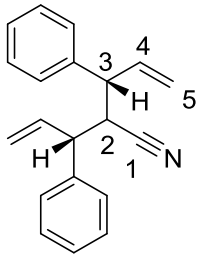
2.4.34 **2.4.35**

The title compound **2.4.35** was synthesised from cyanoester **2.4.34** (50 mg, 0.25 mmol) in THF (0.50 mL) using $[Ir(COD)Cl]_2$ (20 mg, 0.030 mmol), ligand **L2** (36 mg, 0.060 mmol) and TBD (17 mg, 0.12 mmol) in THF (1.2 mL) at 40 °C according to a modified general procedure A4. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.35** (5 mg, 0.03 mmol,

13%) as a yellow oil. R_f = 0.3 (10% EtOAc in PE_{40-60}); δ_H (500 MHz, $CDCl_3$): 7.38 – 7.23 (m, 5H, Ar-*H*), 6.04 (ddd, 1H, *J* = 17.1, 10.0, 7.0 Hz, H-4), 5.26 (dt, 1H, *J* = 10.0, 0.9 Hz, $H_{pro(E)}$-5), 5.21 (dt, 1H, *J* = 17.1, 1.0 Hz, $H_{pro(Z)}$-5), 3.71 (q, 1H, *J* = 7.3 Hz, H-3), 2.76 (dd, 1H, *J* = 16.6, 7.4 Hz, H-2), 2.71 (dd, 1H, *J* = 16.6, 7.1 Hz, H'-2); δ_C (125 MHz, $CDCl_3$): 140.5 (Ar), 137.9 (C-4), 129.1 (Ar), 127.7 (Ar), 127.5 (Ar), 118.3 (C-1), 117.0 (C-5), 45.6 (C-3), 24.1 (C-2); $[\alpha]_D$ (25 °C) +6.0 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[205]

Side product:

(R)-3-Phenyl-2-((R)-1-phenylallyl)pent-4-enenitrile (2.4.36)

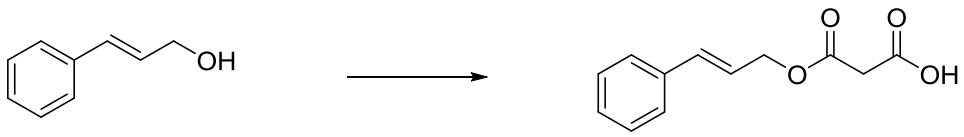


2.4.36

White solid (15 mg, 0.055 mmol, 44%); R_f = 0.3 (8% EtOAc in PE_{40-60}); δ_H (500 MHz, $CDCl_3$): 7.39 – 7.21 (m, 10H, Ar-*H*), 6.16 (ddd, 1H, *J* = 16.9, 10.2, 8.8 Hz, H-4 or C*H*=CH_2), 6.03 (ddd, 1H, *J* = 16.9, 10.2, 8.4 Hz, H-4 or C*H*=CH_2), 5.28 (d, 1H, *J* = 10.2 Hz, $H_{pro(E)}$-5 or CH=C$H_{pro(E)}H_{pro(Z)}$), 5.23 (d, 1H, *J* = 10.2 Hz, $H_{pro(E)}$-5 or CH=C$H_{pro(E)}H_{pro(Z)}$), 5.18 (dt, 1H, *J* = 16.9, 1.1 Hz, $H_{pro(Z)}$-5 or CH=$CH_{pro(E)}H_{pro(Z)}$), 5.15 (dt, 1H, *J* = 16.9, 1.1 Hz, $H_{pro(Z)}$-5 or CH=$CH_{pro(E)}H_{pro(Z)}$), 3.53 (dd, 1H, *J* = 8.4, 6.8 Hz, H-3 or PhC*H*CH=CH_2), 3.44 (t, 1H, *J* = 8.2 Hz, H-3 or PhC*H*CH=CH_2), 3.24 (dd, 1H, *J* = 8.2, 6.8 Hz, H-2); δ_C (125 MHz, $CDCl_3$): 140.3 (Ar), 139.3 (Ar), 138.1 (C-4 or *C*H=CH_2), 136.5 (C-4 or *C*H=CH_2), 129.2 (Ar), 129.0 (Ar), 128.4 (Ar), 127.8

(Ar), 127.6 (Ar), 119.5 (C-1), 119.1 (C-5 or CH=*C*H_2), 117.9 (C-5 or CH=*C*H_2), 49.6 (C-3 or Ph*C*HCH=CH_2), 49.0 (C-3 or Ph*C*HCH=CH_2), 43.6 (C-2); ν_{max}/cm^{-1}: 3059 (w, C-H), 3028 (w, C-H), 2234 (w, C≡N), 1453 (m), 993 (m), 925 (s), 699 (s); *m/z* (ESI^+): 296.1 ([M+Na]$^+$, 100%); accurate mass: found 296.1404, $C_{20}H_{19}NaN$ [M+Na]$^+$ requires 296.1410; $[\alpha]_D$ (25 °C) +59.0 (c = 1.00 in $CHCl_3$).

3-(Cinnamyloxy)-3-oxopropanoic acid (2.4.39)

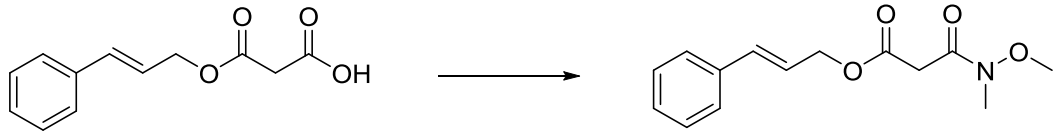


2.3.3 **2.4.39**

According to a modified procedure of Corey *et al*.:[206] A mixture of cinnamyl alcohol **2.3.3** (2.00 g, 14.9 mmol) and Meldrum's acid (2.15 g, 14.9 mmol) in toluene (110 mL) was stirred at 130 °C under reflux for 1 h. Upon completion, aq. $NaHCO_3$ solution (0.6 M, 2.5 g, 30 mmol) was added and the mixture was vigorously shaken. The two layers were separated and the organic layer was extracted with water (3 x 30 mL). The aqueous layers were combined and to the combined aqueous layer was added aq. HCl solution (5 M, 7.4 mL, 75 mmol). The aqueous layer was then extracted with EtOAc (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound **2.4.39** (2.90 g, 13.2 mmol, 90%) as a pale yellow solid. δ_H (400 MHz, $CDCl_3$): 7.41 – 7.28 (m, 5H, Ar-*H*), 6.69 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.9, 6.6 Hz, PhCH=C*H*), 4.84 (dd, 2H, *J* = 6.6, 1.2 Hz, PhCH=CHCH_2), 3.49 (s, 2H, OCOCH_2); δ_C (100 MHz, $CDCl_3$): 171.7 (*C*=O), 166.7 (*C*=O), 136.0 (Ar), 135.3 (Ph*C*H=CH),

128.8 (Ar), 128.4 (Ar), 126.8 (Ar), 122.1 (PhCH=*C*H), 66.6 (PhCH=CH*C*H_2), 40.9 (OCO*C*H_2); ν_{max}/cm^{-1}: 3028 (br, COO-H), 1714 (s, C=O x 2), 1151 (s), 966 (s), 692 (s); *m/z* (ESI^+): 243.1 ($[M+Na]^+$, 100%); accurate mass: found 243.0625, $C_{12}H_{12}NaO_4$ $[M+Na]^+$ requires 243.0628.

Cinnamyl 3-(methoxy(methyl)amino)-3-oxopropanoate (2.4.40)

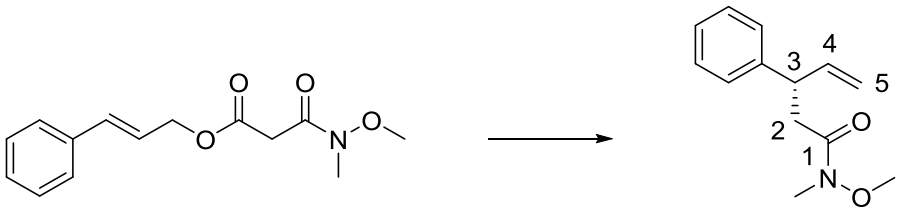


2.4.39 **2.4.40**

According to a modified procedure of Razdan *et al*.:[114] To a solution of acid **2.4.39** (500 mg, 2.27 mmol) in DCM (10 mL) at 0 °C was added DMF (0.02 mL, 0.2 mmol) followed by oxalyl chloride (0.25 mL, 2.7 mmol) dropwise over 3 min. The reaction mixture was stirred at 0 °C for 30 min and then warmed to RT and stirred for 3 h. The acid chloride solution was then added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (222 mg, 2.27 mmol) and DMAP (888 mg, 7.26 mmol) in DCM (10 mL) at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 30 min and then warmed to RT and stirred for another 1 h. Upon completion, the reaction was quenched with sat. aq. $NaHCO_3$ solution (25 mL) and Et_2O (40 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 25 mL). The organic layers were combined, washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (50% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.40** (460 mg, 1.75 mmol, 77%) as a yellow oil. R_f = 0.3 (50% EtOAc in $PE_{40\text{-}60}$);

δ_H (400 MHz, $CDCl_3$): 7.40 – 7.28 (m, 5H, Ar-*H*), 6.67 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.28 (dt, 1H, *J* = 15.9, 6.6 Hz, PhCH=C*H*), 4.80 (dd, 2H, *J* = 6.6, 1.2 Hz, PhCH=CHCH_2), 3.71 (s, 3H, NOCH_3), 3.55 (s, 2H, OCOCH_2), 3.23 (s, 3H, NCH_3); δ_C (100 MHz, $CDCl_3$): 167.3 (*C*=O x 2), 136.2 (Ar), 134.7 (Ph*C*H=CH), 128.7 (Ar), 128.3 (Ar), 126.8 (Ar), 122.8 (PhCH=*C*H), 66.0 (PhCH=CH*C*H_2), 61.5 (NO*C*H_3), 40.9 (OCO*C*H_2), 32.4 (N*C*H_3); ν_{max}/cm^{-1}: 2942 (w, C-H), 1738 (s, C=O, ester), 1664 (s, C=O amide), 1152 (s), 968 (s), 693 (s); *m/z* (ESI^+): 286.0 ($[M+Na]^+$, 40%); accurate mass: found 286.1046, $C_{14}H_{17}NaO_4N$ $[M+Na]^+$ requires 286.1050.

(*S*)-*N*-Methoxy-*N*-methyl-3-phenylpent-4-enamide (2.3.58)

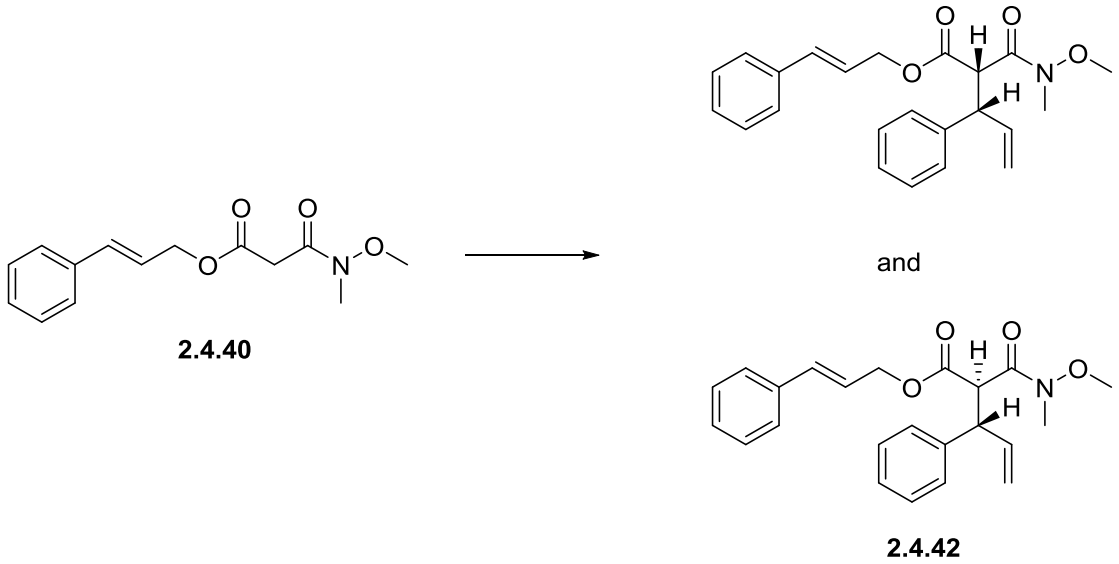


2.4.40 **2.3.58**

The title compound **2.3.58** was synthesised from *β*-amidoester **2.4.40** (50 mg, 0.19 mmol) in THF (0.38 mL) using $[Ir(COD)Cl]_2$ (15 mg, 0.023 mmol), ligand **L2** (27 mg, 0.046 mmol) and TBD (13 mg, 0.091 mmol) in THF (0.89 mL) at 50 °C according to a modified general procedure A4. The crude product was purified by FC (35% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.58** (27 mg, 0.12 mmol, 65%) as a pale yellow oil. R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 – 7.21 (m, 5H, Ar-*H*), 6.03 (ddd, 1H, *J* = 16.5, 10.9, 6.9 Hz, H-4), 5.08 (dt, 1H, *J* = 10.9, 1.3 Hz, $H_{pro(E)}$-5), 5.07 (dt, 1H, *J* = 16.5, 1.4 Hz, $H_{pro(Z)}$-5), 3.99 (q, 1H, *J* = 7.4 Hz, H-3), 3.60 (s, 3H, NOCH_3), 3.14 (s, 3H, NCH_3), 2.90 (dd, 1H, *J* = 15.4,

8.2 Hz, H-2), 2.82 (dd, 1H, J = 15.4, 7.0 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 172.6 (C-1), 143.3 (Ar), 140.9 (C-4), 128.6 (Ar), 127.9 (Ar), 126.6 (Ar), 114.7 (C-5), 61.4 ($NOCH_3$), 45.0 (C-3), 37.6 (C-2), 32.2 (NCH_3); *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 1% 2-propanol in *n*-hexane, flow rate = 1 mL / min, detection wavelength = 254 nm] $t_R(R)$ = 20.04 min, $t_R(S)$ = 21.58 min; $[\alpha]_D$ (25 °C) +12.8 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[197]

Cinnamyl 2-(methoxy(methyl)carbamoyl)-3-phenylpent-4-enoate (2.4.42)



To a solution of $[Ir(COD)Cl]_2$ (15 mg, 0.022 mmol) and ligand **L2** (27 mg, 0.044 mmol) in THF (0.89 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (13 mg, 0.088 mmol) at RT. The mixture was stirred at RT for 5 min followed by the addition of a solution of *β*-ketoester **2.4.40** (50 mg, 0.19 mmol) in THF (0.38 mL). The reaction mixture was stirred at RT and stopped after 3 h. The mixture was concentrated *in vacuo* and purified by FC (35% EtOAc in $PE_{40\text{-}60}$) to

give the title compound **2.4.42** (13 mg, 0.035 mmol, 37%) as a pale yellow oil. The title compound **2.4.42** was formed as a mixture of partially separable diastereomers.

Diastereomer 1:

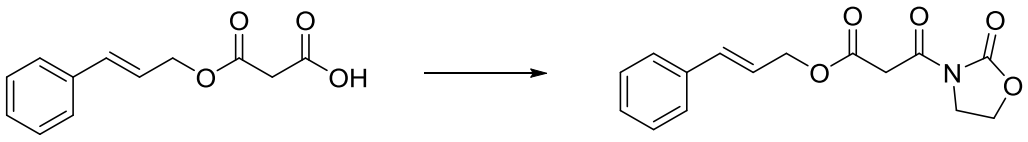
Yellow oil; R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.43 – 7.40 (m, 2H, Ar-*H*), 7.39 – 7.33 (m, 2H, Ar-*H*), 7.32 – 7.28 (m, 6H, Ar-*H*), 6.68 (d, 1H, *J* = 15.8 Hz, PhC*H*=CHCH$_2$), 6.30 (dt, 1H, *J* = 15.8, 6.5 Hz, PhCH=C*H*CH$_2$), 6.06 (ddd, 1H, *J* = 17.1, 10.2, 8.3 Hz, C*H*=CH$_2$), 5.17 (dt, 1H, *J* = 17.1, 1.2 Hz, CH=CH$_{pro(E)}$*H*$_{pro(Z)}$), 5.10 (d, 1H, *J* = 10.2 Hz, CH=C*H*$_{pro(E)}$H$_{pro(Z)}$), 4.82 (dd, 2H, *J* = 6.5, 1.4 Hz, PhCH=CHC*H*$_2$), 4.41 (d, 1H, *J* = 11.1 Hz, OC(O)C*H*), 4.27 (dd, 1H, *J* = 11.1, 8.3 Hz, PhC*H*CH=CH$_2$), 3.65 (s, 3H, OC*H*$_3$), 2.99 (s, 3H, NC*H*$_3$); δ_C (125 MHz, $CDCl_3$): δ 168.2 (*C*=O), 168.0 (*C*=O), 140.8 (Ar), 138.5 (*C*H=CH$_2$), 136.3 (Ar), 134.7 (Ph*C*H=CHCH$_2$), 128.8 (Ar), 128.6 (Ar), 128.3 (Ar), 128.2 (Ar), 127.0 (Ar), 126.8 (Ar), 122.9 (PhCH=*C*HCH$_2$), 116.6 (CH=*C*H$_2$), 66.1 (PhCH=CH*C*H$_2$), 61.7 (O*C*H$_3$), 53.4 (OC(O)*C*H), 49.5 (Ph*C*HCH=CH$_2$), 32.5 (N*C*H$_3$); ν_{max}/cm^{-1}: 3028 (w, C-H), 1736 (s, C=O, ester), 1667 (s, C=O, amide), 1153 (s), 966 (s), 746 (s); *m/z* (ESI$^+$): 402.2 ([M+Na]$^+$, 80%); accurate mass: found 402.1670, $C_{23}H_{25}NaO_4N$ [M+Na]$^+$ requires 402.1676; $[\alpha]_D$ (25 °C) +7.3 (c = 0.50 in $CHCl_3$).

Diastereomer 2:

Yellow oil; R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.36 – 7.26 (m, 8H, Ar-*H*), 7.25 – 7.24 (m, 2H, Ar-*H*), 6.43 (d, 1H, *J* = 15.6 Hz, PhC*H*=CHCH$_2$), 6.00 (ddd, 1H, *J* = 17.3, 10.4, 7.8 Hz, C*H*=CH$_2$), 5.89 (dt, 1H, *J* = 15.6, 6.6 Hz, PhCH=C*H*CH$_2$), 5.10 (dt, 1H, *J* = 17.3, 1.0 Hz, CH=CH$_{pro(E)}$*H*$_{pro(Z)}$), 5.06 (dt, 1H, *J* = 10.4, 0.9 Hz, CH=C*H*$_{pro(E)}$H$_{pro(Z)}$), 4.53 (ddd, 1H, *J* = 12.8, 6.4, 1.3 Hz,

PhCH=CHCH_2), 4.48 (ddd, 1H, J = 12.8, 6.5, 1.3 Hz, PhCH=CHCH'_2), 4.40 (d, 1H, J = 10.9 Hz, OC(O)CH), 4.25 (dd, 1H, J = 10.9, 7.8 Hz, PhCHCH=CH_2), 3.76 (s, 3H, OCH_3), 3.23 (s, 3H, NCH_3); δ_C (125 MHz, $CDCl_3$): 168.4 (*C*=O), 167.7 (*C*=O), 140.3 (Ar), 138.3 (*C*H=CH_2), 136.1 (Ar), 134.5 (Ar), 134.2 (Ph*C*H=CHCH_2), 128.5 (Ar doublet), 128.4 (Ar), 128.0 (Ar), 126.6 (Ar), 122.6 (PhCH=*C*HCH_2), 116.2 (CH=*C*H_2), 65.7 (PhCH=CH*C*H_2), 61.7 (O*C*H_3), 53.0 (OC(O)*C*H), 49.3 (Ph*C*HCH=CH_2), 32.6 (N*C*H_3); ν_{max}/cm^{-1}: 2924 (w, C-H), 1738 (s, C=O, ester), 1667 (s, C=O, amide), 1153 (s), 989 (s), 968 (s), 748 (s); *m/z* (ESI^+): 402.2 ($[M+Na]^+$, 90%); accurate mass: found 402.1676, $C_{23}H_{25}NaO_4N$ $[M+Na]^+$ requires 402.1676; $[\alpha]_D$ (25 °C) +6.0 (c = 0.30 in $CHCl_3$).

Cinnamyl 3-oxo-3-(2-oxooxazolidin-3-yl)propanoate (2.4.43)

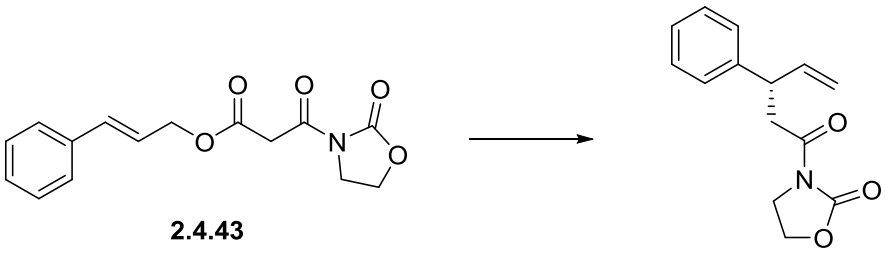


2.4.39 **2.4.43**

According to a modified procedure of Pearson *et al*.:[115] To a mixture of acid **2.4.39** (492 mg, 2.24 mmol) and molecular sieves (4 Å, 100 mg) in toluene (54 mL) at 0 °C was added pivaloyl chloride (0.36 mL, 2.91 mmol). The reaction mixture was stirred at 0 °C for 30 min before warming to RT and stirred for another 1.5 h. LiCl (95 mg, 2.2 mmol) and oxazolidin-2-one (584 mg, 6.71 mmol) were successively added at RT. The reaction mixture was then stirred at 130 °C under reflux for 3 h. Upon completion, the mixture was cooled to RT and filtered through a layer of Celite™. The filter cake was washed with EtOAc (2 x 30 mL). The filtrates were combined

and concentrated *in vacuo*. The crude product was purified by FC (40% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.43** (401 mg, 1.39 mmol, 62%) as a colourless oil. R_f = 0.3 (48% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.41 – 7.24 (m, 5H, Ar-*H*), 6.67 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.27 (dt, 1H, *J* = 15.9, 6.5 Hz, PhCH=C*H*), 4.81 (dd, 2H, *J* = 6.5, 1.3 Hz, PhCH=CHCH_2), 4.46 (t, 2H, *J* = 7.8 Hz, NCH_2CH_2), 4.08 (t, 2H, *J* = 7.8 Hz, NCH_2), 4.02 (s, 2H, $OCOCH_2$); δ_C (125 MHz, $CDCl_3$): 166.8 (*C*=O, imide), 165.9 (*C*=O, ester), 153.7 (*C*=O, carbamate), 136.2 (Ar), 134.9 (Ph*C*H=CH), 128.8 (Ar), 128.3 (Ar), 126.8 (Ar), 122.6 (PhCH=*C*H), 66.3 ($PhCH=CHCH_2$), 62.4 (NCH_2CH_2), 42.7 ($OCOCH_2$), 42.5 (NCH_2); ν_{max}/cm^{-1}: 1776 (s, C=O, ester), 1737 (s, C=O, imide), 1698 (s, C=O, carbamate), 1389 (s), 1170 (s), 966 (s), 694 (s); *m/z* (ESI^+): 312.1 ($[M+Na]^+$, 30%); accurate mass: found 312.0836, $C_{15}H_{15}NaO_5N$ $[M+Na]^+$ requires 312.0842.

(S)-3-(3-Phenylpent-4-enoyl)oxazolidin-2-one (2.4.44)

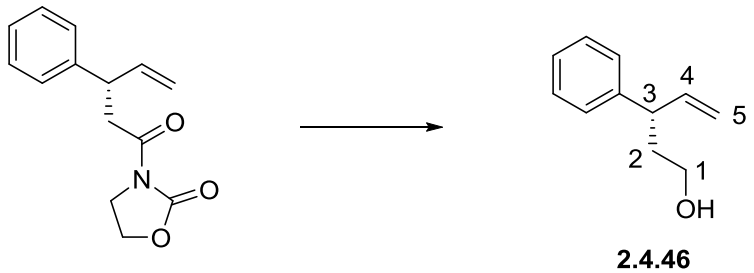


2.4.43 **2.4.44**

The title compound **2.4.44** was synthesised from *β*-imidoester **2.4.43** (50 mg, 0.17 mmol) in THF (0.35 mL) using $[Ir(COD)Cl]_2$ (5 mg, 0.007 mmol), ligand **L2** (8 mg, 0.01 mmol) and TBD (4 mg, 0.03 mmol) in THF (0.29 mL) at 40 °C according to a modified general procedure A4. The crude product was purified by FC (40%

EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.44** (32 mg, 0.13 mmol, 74%) as a colourless oil which crystallised on standing. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.33 – 7.19 (m, 5H, Ar-*H*), 6.03 (ddd, 1H, *J* = 17.0, 10.4, 7.1 Hz, C*H*=CH_2), 5.08 (dt, 1H, *J* = 17.0, 1.3 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 5.07 (dt, 1H, *J* = 10.4, 1.3 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 4.38 (dt, 1H, *J* = 14.0, 9.0 Hz, OCOCH_2), 4.33 (dt, 1H, *J* = 14.0, 9.1 Hz, OCOCH'_2), 4.01 – 3.89 (m, 3H, OCNCH_2 and PhC*H*CH=CH_2), 3.44 (dd, 1H, *J* = 16.7, 7.1 Hz, PhCHCH_2), 3.39 (dd, 1H, *J* = 16.7, 7.7 Hz, PhCHCH'_2); δ_C (125 MHz, $CDCl_3$): 171.7 (*C*=O, imide), 153.6 (*C*=O, carbamate), 142.7 (Ar), 140.5 (*C*H=CH_2), 128.7 (Ar), 127.9 (Ar), 126.8 (Ar), 115.1 (CH=*C*H_2), 62.1 (OCO*C*H_2), 45.3 (Ph*C*HCH=CH_2), 42.6 (OCN*C*H_2), 40.5 (PhCH*C*H_2); ν_{max}/cm^{-1}: 1782 (s, C=O, imide), 1686 (s, C=O, carbamate), 1386 (s), 1221 (s), 756 (s), 676 (s); *m/z* (ESI^+): 268.1 ($[M+Na]^+$, 100%); accurate mass: found 268.0939, $C_{14}H_{15}NaO_3N$ $[M+Na]^+$ requires 268.0944; *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 20% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 210 nm] t_R(*S*) = 20.48 min, t_R(*R*) = 25.06 min; $[\alpha]_D$ (20 °C) +18.9 (c = 1.00 in $CHCl_3$).

(*S*)-3-Phenylpent-4-en-1-ol (2.4.46)

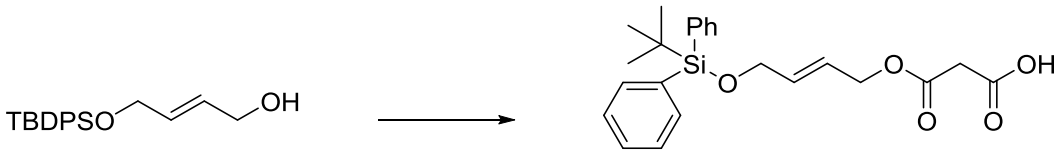


2.4.44 **2.4.46**

According to a modified procedure of Day *et al*.:[116] To a solution of imide **2.4.4** (47 mg, 0.19 mmol) in methanol (16 µL, 0.38 mmol) and THF (0.96 mL) at 0 °C was added lithium borohydride (4 M in THF, 0.10 mL, 0.38 mL) dropwise over 3 min. The reaction mixture was stirred at 0 °C for 20 min before warming to RT and stirred at RT for 1 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (4 mL) and diluted with EtOAc (5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (28% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.46** (29 mg, 0.18 mmol, 93%) as a colourless oil. R_f = 0.3 (28% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.34 – 7.28 (m, 2H, Ar-*H*), 7.24 – 7.19 (m, 3H, Ar-*H*), 5.98 (ddd, 1H, *J* = 17.5, 10.2, 7.6 Hz, H-4), 5.09 (d, 1H, *J* = 17.5 Hz, $H_{pro(Z)}$-5), 5.06 (d, 1H, *J* = 10.2 Hz, $H_{pro(E)}$-5), 3.70 – 3.56 (m, 2H, H-1), 3.48 (q, 1H, *J* = 7.9 Hz, H-3), 2.08 – 1.92 (m, 2H, H-2); δ_C (100 MHz, $CDCl_3$): 143.8 (Ar), 142.0 (C-4), 128.7 (Ar), 127.7 (Ar), 126.6 (Ar), 114.6 (C-5), 61.1 (C-1), 46.5 (C-3), 38.1 (C-2); *ee*: 99% [Chiralcel OD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 1.0 mL / min, detection wavelength = 210 nm] t_R(*S*) = 20.24 min,

$t_R(R)$ = 24.98 min; $[\alpha]_D$ (20 °C) +41.3 (c = 1.00 in $CHCl_3$). Characterisation data are consistent with literature values.[207]

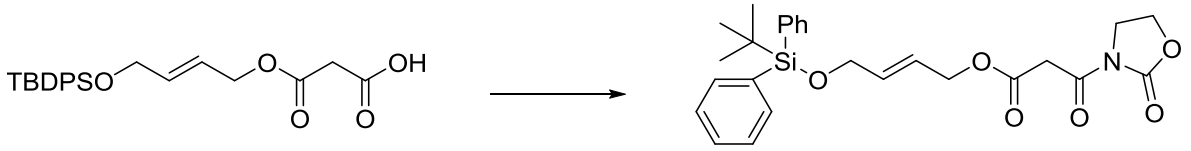
(E)-3-((4-((tert-Butyldiphenylsilyl)oxy)but-2-en-1-yl)oxy)-3-oxopropanoic acid (2.4.47)



2.3.6 **2.4.47**

According to a modified procedure of Corey *et al*.:[206] A mixture of alcohol **2.3.6** (1.00 g, 3.06 mmol) and Meldrum's acid (441 mg, 3.06 mmol) in toluene (23 mL) was stirred at 130 °C under reflux for 1 h. Upon completion, the mixture was concentrated *in vacuo* to give the crude title compound **2.4.47** (1.26 g, 3.06 mmol, 100% crude yield) as a pink oily solid. The crude compound was used in the next step without further purification. δ_H (500 MHz, $CDCl_3$): 7.67 – 7.65 (m, 4H, Ar-*H*), 7.43 – 7.37 (m, 6H, Ar-*H*), 5.89 – 5.88 (m, 2H, C*H*=C*H*), 4.70 – 4.69 (m, 2H, CH=CHCH_2OCO), 4.23 – 4.21 (m, 2H, SiOCH_2), 3.47 (s, 2H, CH_2COOH), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 169.1 (*C*=O), 167.7 (*C*=O), 135.6 (Ar), 135.1 (alkene carbon), 133.5 (Ar), 129.9 (Ar), 127.9 (Ar),122.4 (alkene carbon), 66.2 (CH=CH*C*H$_2$OCO), 63.5 (SiO*C*H$_2$), 40.1 (*C*H$_2$COOH), 26.9 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 2932 (m, C-H), 2858 (m, C-H), 1747 (s, C=O x 2), 1112 (s), 703 (s); *m/z* (ESI$^+$): 435.2 ([M+Na]$^+$, 100%); accurate mass: found 435.1585, $C_{23}H_{28}NaO_5Si$ [M+Na]$^+$ requires 435.1598.

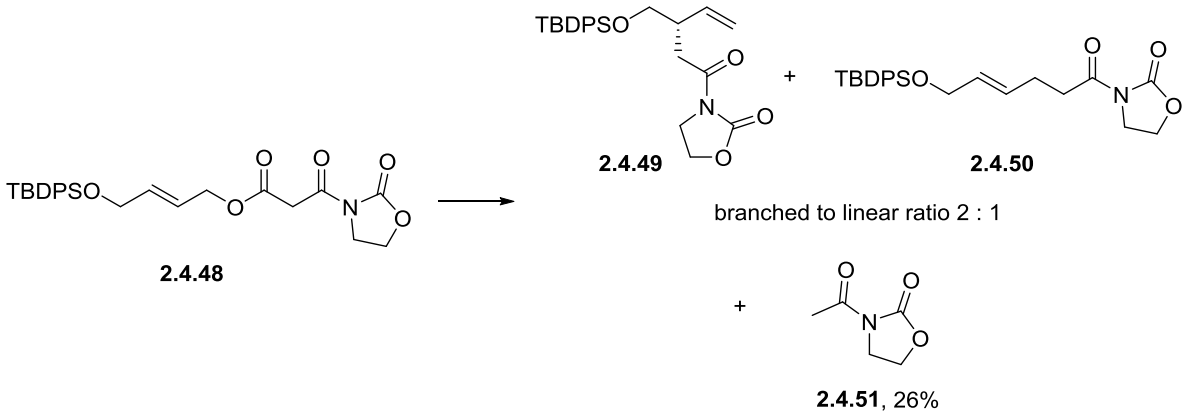
(E)-4-((tert-Butyldiphenylsilyl)oxy)but-2-en-1-yl 3-oxo-3-(2-oxooxazolidin-3-yl)propanoate (2.4.48)



2.4.47 **2.4.48**

According to a modified procedure of Pearson *et al*.:[115] To a mixture of acid **2.4.47** (1.26 g, 3.06 mmol) and molecular sieves (4 Å, 300 mg) in toluene (63 mL) at 0 °C was added pivaloyl chloride (0.42 mL, 3.4 mmol). The reaction mixture was stirred at 0 °C for 30 min before warming to RT and stirred for another 1.5 h. LiCl (129 mg, 3.06 mmol) and oxazolidin-2-one (532 mg, 6.12 mmol) were successively added at RT. The reaction mixture was then stirred at 130 °C under reflux for 3 h. Upon completion, the mixture was cooled to RT and filtered through a layer of Celite^{TM}. The filter cake was washed with EtOAc (2 x 30 mL). The filtrates were combined and concentrated *in vacuo*. The crude product was purified by FC (40% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.48** (1.00 g, 2.08 mmol, 68% over two steps) as a pale yellow oil. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.43 – 7.37 (m, 6H, Ar-*H*), 5.89 – 5.86 (m, 2H, C*H*=C*H*), 4.66 – 4.65 (m, 2H, CH=CHCH_2OCO), 4.44 (t, 2H, *J* = 8.1 Hz, NC(O)OCH_2), 4.22 – 4.20 (m, 2H, TBDPSOCH_2), 4.07 (t, 2H, *J* = 8.1 Hz, OCNCH_2), 3.99 (s, 2H, OC(O)CH_2OCN), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 166.7 (*C*=O, imide), 165.9 (*C*=O, ester), 153.6 (*C*=O, carbamate), 135.7 (Ar), 134.3 (alkene carbon), 133.6 (Ar), 129.9 (Ar), 127.9 (Ar), 122.9 (alkene carbon), 65.7 (CH=CH*C*H_2OCO), 63.6 (SiO*C*H_2), 62.4 (NC(O)O*C*H_2), 42.7 (OC(O)*C*H_2OCN), 42.4 (OCN*C*H_2), 27.0

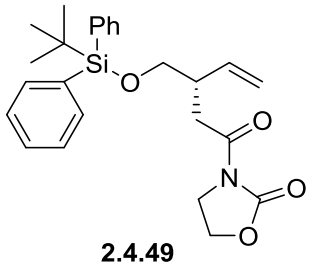
($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2857 (m, C-H), 1782 (s, C=O, ester), 1739 (s, C=O, imide), 1703 (s, C=O, carbamate), 1389 (s), 1109 (s), 702 (s); *m/z* (ESI^+): 504.2 ($[M+Na]^+$, 100%); accurate mass: found 504.1802, $C_{26}H_{31}NaO_6NSi$ $[M+Na]^+$ requires 504.1813.



The compounds **2.4.49**, **2.4.50** and **2.4.51** were synthesised from *β*-imidoester **2.4.48** (100 mg, 0.208 mmol) in THF (0.42 mL) using $[Ir(COD)Cl]_2$ (6 mg, 0.008 mmol), ligand **L2** (10 mg, 0.017 mmol) and TBD (5 mg, 0.03 mmol) in THF (0.35 mL) at 40 °C according to a modified general procedure A4. The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give a mixture of the branched isomer **2.4.49** and linear isomer **2.4.50** (branched to linear ratio 2 : 1, 50 mg, 0.11 mmol, combined yield 55%) and the side product **2.4.51** (7 mg, 0.054 mmol, 26%).

Branched isomer:

(S)-3-(3-(((tert-Butyldiphenylsilyl)oxy)methyl)pent-4-enoyl)oxazolidin-2-one (2.4.49)

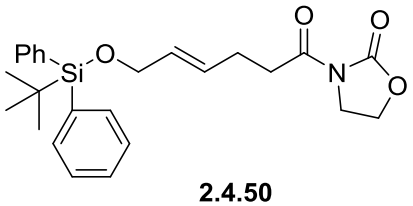


2.4.49

Pale yellow oil; R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.67 – 7.64 (m, 4H, Ar-*H*), 7.44 – 7.36 (m, 6H, Ar-*H*), 5.78 (ddd, 1H, *J* = 17.3, 10.4, 7.9 Hz, C*H*=CH_2), 5.09 (dt, 1H, *J* = 17.3, 1.2 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 5.05 (ddd, 1H, *J* = 10.4, 1.6, 0.7 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 4.38 – 4.34 (m, 2H, OCOCH_2), 3.96 (dt, 1H, *J* = 15.8, 10.8 Hz, OCNCH_2), 3.95 (dt, 1H, J = 15.8, 10.9 Hz, OCNCH'_2), 3.69 (dd, 1H, *J* = 9.9, 5.3 Hz, SiOCH_2), 3.62 (dd, 1H, *J* = 9.9, 6.8 Hz, SiOCH'_2), 3.22 (dd, 1H , *J* = 16.7, 5.8 Hz, CHCH_2C(O)N), 3.10 (dd, 1H , *J* = 16.7, 5.8 Hz, CHCH'_2C(O)N), 2.95 (sext, 1H, *J* = 6.7 Hz, $SiOCH_2CH$), 1.05 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 172.4 (*C*=O, imide), 153.6 (*C*=O, carbamate), 138.3 (*C*H=CH_2), 135.8 (Ar), 133.7 (Ar), 129.7 (Ar), 127.8 (Ar), 116.4 (CH=*C*H_2), 66.6 ($SiOCH_2$), 62.1 (OC(O)*C*H_2), 42.6 (OCN*C*H_2), 42.1 ($SiOCH_2CH$), 36.6 (CH*C*H_2OCN), 27.0 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$); ν_{max}/cm^{-1}: 2930 (m, C-H), 2858 (m, C-H), 1779 (s, C=O, imide), 1700 (s, C=O, carbamate), 1385 (s), 1106 (s), 701 (s); *m/z* (ESI^+): 460.2 ($[M+Na]^+$, 100%); accurate mass: found 460.1907, $C_{25}H_{31}NaO_4NSi$ $[M+Na]^+$ requires 460.1915; *ee* was measured by reducing the title compound to alcohol **1.4** and conducting HPLC analysis on alcohol **1.4** (see below); $[\alpha]_D$ (20 °C) +12.6 (c = 1.00 in $CHCl_3$).

Linear isomer:

(E)-3-(6-((tert-Butyldiphenylsilyl)oxy)hex-4-enoyl)oxazolidin-2-one (2.4.50)

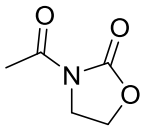


2.4.50

Pale yellow oil; R_f = 0.26 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.68 – 7.63 (m, 4H, Ar-*H*), 7.40 – 7.37 (m, 6H, Ar-*H*), 5.69 (dtt, 1H, *J* = 15.0, 7.0, 1.2 Hz, $SiOCH_2CH{=}CH$), 5.62 (dtt, 1H, *J* = 15.0, 4.9, 0.8 Hz, $SiOCH_2CH{=}CH$), 4.39 (t, 2H, *J* = 8.1 Hz, $NC(O)OCH_2$), 4.15 (dq, 2H, *J* = 4.9, 1.2 Hz, $SiOCH_2$), 4.00 (dd, 2H, *J* = 8.7, 7.6 Hz, NCH_2), 3.00 (t, 2H, *J* = 7.5 Hz, $CH_2CH_2C(O)N$), 2.40 (dt, 2H, *J* = 7.0, 7.5 Hz, $CH_2CH_2C(O)N$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): (aromatic carbons were not assigned as there are many aromatic peaks due to presence of TBDPS derivatives) 130.2 ($SiOCH_2CH{=}CH$), 128.7 ($SiOCH_2CH{=}CH$), 64.4 ($SiOCH_2$), 62.0 ($NC(O)OCH_2$), 42.5 (NCH_2), 34.8 ($CH_2CH_2C(O)N$), 26.8 ($SiC(CH_3)_3$), 26.7 ($CH_2CH_2C(O)N$), 19.2 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 2930 (m, C-H), 2857 (m, C-H), 1778 (s, C=O, imide), 1699 (s, C=O, carbamate), 1428 (s), 1109 (s), 702 (s); *m/z* (ESI^+): 460.2 ($[M+Na]^+$, 100%); accurate mass: found 460.1913, $C_{25}H_{31}NaO_4NSi$ $[M+Na]^+$ requires 460.1915.

Side product:

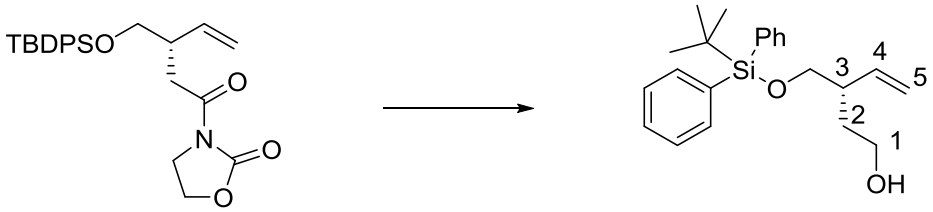
3-Acetyloxazolidin-2-one (2.4.51)



2.4.51

Colourless oil; R_f = 0.3 (50% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 4.41 (t, 2H, *J* = 8.0 Hz, C(O)OCH_2), 4.02 (t, 2H, *J* = 8.0 Hz, NCH_2), 2.53 (s, 3H, CH_3C(O)N); *m/z* (ESI^+): 152.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[208]

(*S*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (1.4)

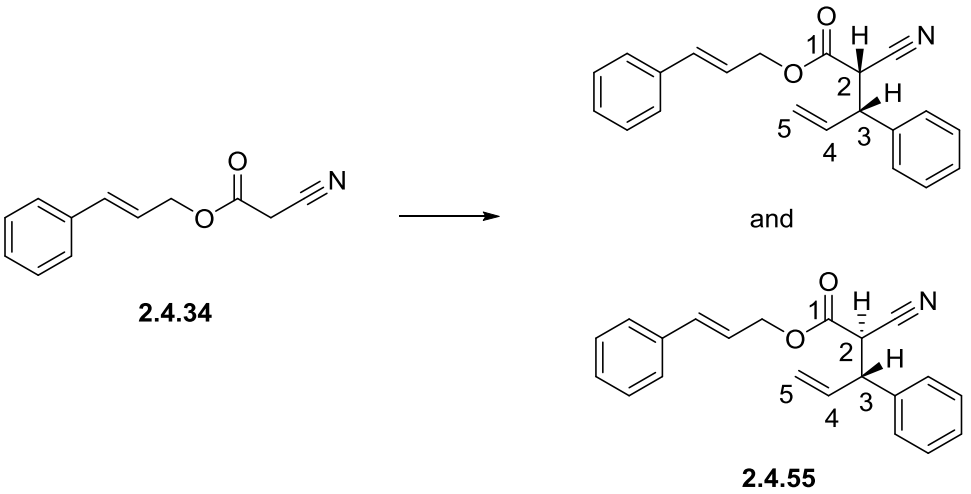


2.4.49 **1.4**

According to a modified procedure of Day *et al*.:[116] To a solution of imide **2.4.49** (55 mg, 0.13 mmol) in methanol (10 µL, 0.25 mmol) and THF (0.63 mL) at 0 °C was added lithium borohydride (4 M in THF, 60 µL, 0.25 mL) dropwise over 3 min. The reaction mixture was stirred at 0 °C for 20 min before warming to RT and stirred at RT for 1 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (4 mL) and diluted with EtOAc (5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layers were

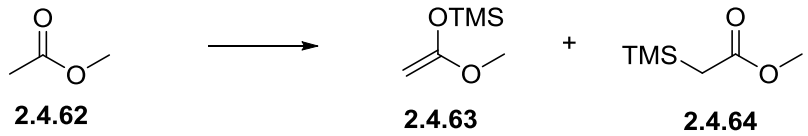
combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (22% EtOAc in $PE_{40\text{-}60}$) to give the title compound **1.4** (31 mg, 0.087 mmol, 70%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.70 (ddd, 1H, *J* = 16.8, 10.9, 8.6 Hz, H-4), 5.05 (ddd, 1H, *J* = 16.8, 1.6, 0.8 Hz, $H_{pro(Z)}$-5), 5.04 (dd, 1H, *J* = 10.9, 1.6 Hz, $H_{pro(E)}$-5), 3.73 – 3.64 (m, 2H, H-1), 3.62 (dd, 1H, *J* = 10.1, 5.5 Hz, SiOCH_2), 3.59 (dd, 1H, *J* = 10.1, 6.6 Hz, SiOCH'_2), 2.42 – 2.35 (m, 1H, H-3), 1.82 (ddt, 1H, *J* = 11.9, 7.5, 6.2 Hz, H-2), 1.63 (ddt, 1H, *J* = 11.9, 8.5, 6.0 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 140.2 (C-4), 136.2 (Ar), 134.1 (Ar), 130.3 (Ar), 128.2 (Ar), 116.6 (C-5), 68.0 (*C*H_2OSi), 61.8 (C-1), 44.4 (C-3), 35.0 (C-2), 27.4 (SiC(*C*H_3)$_3$), 19.9 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 3339 (br, O-H), 2858 (w, C-H), 1428 (w), 1112 (m), 702 (m); *m/z* (ESI$^+$): 355.1 ([M+H]$^+$, 90%), 377.3 ([M+Na]$^+$, 100%); accurate mass: found 377.1891, $C_{22}H_{30}NaO_2Si$ [M+Na]$^+$ requires 377.1907; *ee*: >99% [Chiralcel OD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 0.9 mL / min, detection wavelength = 254 nm] t_R(*R*) = 10.74 min, t_R(*S*) = 12.97 min; [α]$_D$ (22 °C) +15.7 (c = 0.60 in ethanol), literature value [α]$_D$ (22 °C) +17.2 (c = 5.1 in ethanol). Characterisation data are consistent with literature values.[88]

Cinnamyl 2-cyano-3-phenylpent-4-enoate (2.4.55)



To a solution of $[Ir(COD)Cl]_2$ (5 mg, 0.008 mmol) and ligand **L2** (9 mg, 0.02 mmol) in THF (0.31 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (4 mg, 0.03 mmol) at RT. The mixture was stirred at RT for 5 min followed by the addition of a solution of cyanoester **2.4.34** (39 mg, 0.19 mmol) in THF (0.39 mL). The reaction mixture was stirred at RT for 7 h and stopped after 7 h at RT before completion. The mixture was concentrated *in vacuo* and purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.4.55** (15 mg, 0.047 mmol, 49%) as a yellow oil. The title compound **2.4.55** was formed as a mixture of inseparable diastereomers. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.31 – 7.17 (m, 10H, Ar-*H*), 6.55 (d, 1H, *J* = 15.9 Hz, PhC*H*=CH), 6.54 (d, 1H, *J* = 16.0 Hz, PhC*H*=CH of the other diastereomer), 6.15 – 6.00 (m, 2H, PhCH=C*H* and H-4), 5.28 – 5.15 (m, 2H, H-5), 4.68 (dd, 2H, *J* = 6.6, 1.3 Hz, PhCH=CHCH_2), 4.67 (dd, 2H, *J* = 6.8, 1.3 Hz, PhCH=CHCH_2 of the other diastereomer), 4.01 (t, 1H, *J* = 6.9 Hz, H-3), 3.99 (t, 1H, *J* = 7.4 Hz, H-3 of the other diastereomer), 3.84 (d, 1H, *J* = 7.4 Hz, H-2), 3.77 (d, 1H, *J* = 6.9 Hz, H-2 of the other diastereomer);

δ_C (125 MHz, $CDCl_3$): only major peaks are reported as there are many impurity peaks 164.7 (*C*=O), 138.1 (Ar), 137.4 (Ar), 135.8 (Ph*C*H=CH), 134.6 (C-4), 128.9 (Ar), 128.6 (Ar), 128.3 (Ar), 128.0 (Ar), 127.6 (Ar), 126.7 (Ar), 121.3 (PhCH=*C*H), 119.4 (C-5), 116.8 (C-1), 67.1 (PhCH=CH*C*H_2), 49.7 (C-3), 44.3 (C-2); ν_{max}/cm^{-1}: 3030 (w, C-H), 2925 (w, C-H), 2250 (w, C≡N), 1744 (s, C=O), 1231 (s), 967 (s), 699 (s); *m/z* (ESI^+): 340.1 ($[M+Na]^+$, 100%); accurate mass: found 340.1301, $C_{21}H_{19}NaO_2N$ $[M+Na]^+$ requires 340.1308; $[\alpha]_D$ (25 °C) +5.5 (c = 0.50 in $CHCl_3$).



2.4.62 **2.4.63** **2.4.64**

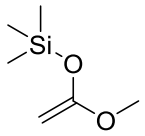
combined yield 67%

According to a procedure of Hesp *et al*.:[209] To a solution of diisopropylamine (13.4 mL, 95.6 mmol) in THF (80 mL) at -30 °C was added *n*BuLi (2.5 M in hexane, 36.5 mL, 91.3 mmol) dropwise over 30 min. The reaction mixture was stirred at -30 °C for 30 min before cooling to -78 °C. To this solution at -78 °C was added a solution of methyl acetate **2.4.62** (7.0 mL, 87 mmol) in THF (20 mL) dropwise over 5 min. The reaction mixture was stirred at -78 °C for 30 min. To this mixture was then added trimethylsilyl chloride (13.2 mL, 104 mmol) over 20 min. The reaction mixture was stirred at -78 °C for 1.5 h and slowly warmed to RT over 1.5 h. Upon completion, the mixture was concentrated *in vacuo* (with no heat as product is volatile). PE_{40-60} (20 mL) was added to the residue and the mixture was filtered through Celite™ on a sintered funnel. The filter cake was washed with PE_{40-60} (1 x 60 mL). The filtrates were combined and concentrated *in vacuo* (with no heat). The

crude product was purified by distillation (40 °C, 68 mbar) to give a mixture of the *O*-silylated compound **2.4.63** and *C*-silylated compound **2.4.64** (8.50 g, 58.1 mmol, combined yield 67%) as colourless oil (there was still some mass left in the crude residue).

O-silylated product:

((1-Methoxyvinyl)oxy)trimethylsilane (2.4.63)

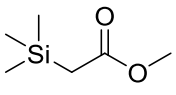


2.4.63

δ_H (400 MHz, $CDCl_3$): 3.55 (s, 3H, OC*H*$_3$), 3.21 (d, 1H, *J* = 2.9 Hz, C=C*H*$_2$), 3.10 (d, 1H, *J* = 2.9 Hz, C=C*H*$_2$), 0.23 (s, 9H, Si(*CH*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$): 162.2 (*C*=CH_2), 60.1 (C=*C*H_2), 55.2 (O*C*H_3), 0.11 (Si(*C*H_3)$_3$). Characterisation data are consistent with literature values.[210]

C-silylated product:

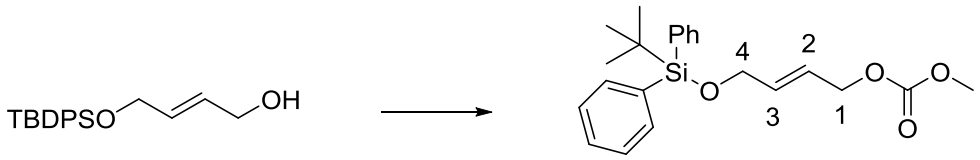
Methyl 2-(trimethylsilyl)acetate (2.4.64)



2.4.64

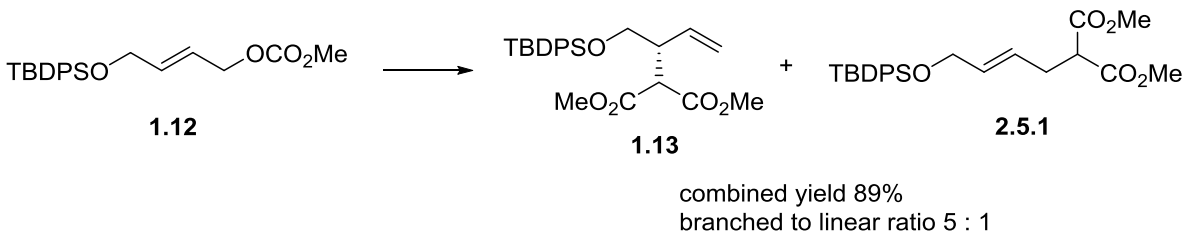
δ_H (400 MHz, $CDCl_3$): 3.63 (s, 3H, OC*H*$_3$), 1.91 (s, 2H, SiC*H*$_2$CO), 0.12 (s, 9H, Si(*CH*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$): 173.6 (*C*=O), 51.3 (O*C*H_3), 26.9 (Si*C*H_2CO). Characterisation data are consistent with literature values.[211]

(*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-yl methyl carbonate (1.12)



2.3.6 **1.12**

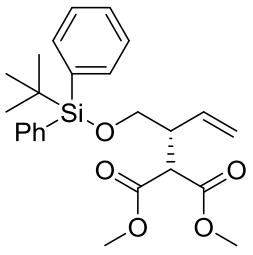
According to the procedure of Helmchen *et al*.:[103] To a solution of alcohol **2.3.6** (1.50 g, 4.60 mmol) in DCM (10 mL) at 0 °C was added pyridine (0.56 mL, 6.9 mmol) followed by methyl chloroformate (0.54 mL, 6.9 mmol) dropwise over 2 min. The reaction mixture was stirred at 0 °C for 1 h before it was warmed to RT. The reaction mixture was then stirred at RT for 2 h. Upon completion, water (10 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic layers were combined, washed sequentially with sat. aq. $CuSO_4$ solution (10 mL) and sat. aq. NH_4Cl solution (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **1.12** (1.63 g, 4.24 mmol, 92%) as a pale yellow oil. R_f = 0.4 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.70 – 7.68 (m, 4H, Ar-*H*), 7.48 – 7.39 (m, 6H, Ar-*H*), 5.94 (dtt, 1H, *J* = 15.3, 5.3, 1.0 Hz, H-2), 5.90 – 5.85 (m, 1H, H-3), 4.68 (d, 2H, *J* = 5.3 Hz, H-1), 4.21 – 4.20 (m, 2H, H-4), 3.82 (s, 3H, OCOCH_3), 1.09 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 155.6 (O*C*OCH_3), 135.5 (Ar), 134.4 (Ar), 133.4 (C-3), 129.7 (Ar), 127.7 (Ar), 122.8 (C-2), 68.0 (C-1), 63.4 (C-4), 54.8 (OCO*C*H_3), 26.8 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH$_3$)$_3$); *m/z* (ESI$^+$): 407.2 ([M+Na]$^+$, 100%); accurate mass: found 407.1642, $C_{22}H_{28}NaO_4Si$ [M+Na]$^+$ requires 407.1649. Characterisation data are consistent with literature values.[88]



According to the procedure of Helmchen *et al*.:[31] To a solution of $[Ir(COD)Cl]_2$ (56 mg, 0.077 mmol) and ligand **L1** (84.0 mg, 0.154 mmol) in THF (3.5 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (42.0 mg, 0.308 mmol) at RT. The mixture was stirred at RT for 2 h followed by the addition of a solution of carbonate **1.12** (700 mg, 1.82 mmol) and dimethyl malonate (0.350 mL, 2.59 mmol) in THF (7 mL). The reaction mixture was stirred at RT for 22 h. Upon completion, the mixture was concentrated *in vacuo* and the crude product was purified by FC (20% Et_2O in $PE_{40\text{-}60}$) to give an inseparable mixture of the branched product **1.13** and linear product **2.5.1** (branched to linear ratio 5 : 1, 715 mg, 1.62 mmol, combined yield 89%) as a yellow oil.

Branched isomer:

(*R*)-Dimethyl 2-(1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-yl)malonate (1.13)



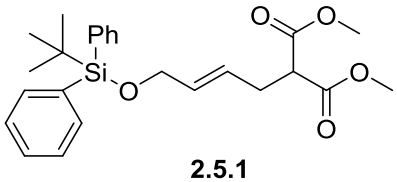
1.13

R_f = 0.3 (20% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.64 – 7.61 (m, 4H, Ar-*H*), 7.42 – 7.35 (m, 6H, Ar-*H*), 5.94 (ddd, 1H, *J* = 17.1, 10.3, 9.1 Hz, C*H*=CH_2), 5.11

(ddd, 1H, *J* = 17.1, 1.7, 0.9 Hz, CH=CH$_{pro(E)}$*H$_{pro(Z)}$*), 5.10 (dd, 1H, *J* = 10.3, 1.7 Hz, CH=C*H$_{pro(E)}$*H$_{pro(Z)}$), 3.91 (d, 1H, *J* = 8.6 Hz, CHC*H*(CO$_2$CH$_3$)$_2$), 3.75 (d, 2H, *J* = 6.0 Hz, SiOC*H$_2$*), 3.72 (s, 3H, CO$_2$C*H*$_3$), 3.70 (s, 3H, CO$_2$C*H*$_3$), 3.02 (tt, 1H, *J* = 8.6, 6.0 Hz, SiOCH$_2$C*H*), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$); δ_C (100 MHz, CDCl$_3$): 168.9 (*C*=O), 168.7 (*C*=O), 135.6 (Ar), 135.5 (*C*H=CH$_2$), 133.2 (Ar), 129.7 (Ar), 127.7 (Ar), 118.2 (CH=*C*H$_2$), 64.7 (SiO*C*H$_2$), 52.6 (CH*C*H(CO$_2$CH$_3$)$_2$), 52.4 (CO$_2$*C*H$_3$), 52.3 (CO$_2$*C*H$_3$), 46.2 (SiOCH$_2$*C*H), 26.8 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$); *ee* was measured by reducing the title compound to alcohol **1.4** and conducting HPLC analysis on alcohol **1.4** (see below); [α]$_D$ (20 °C) +23.9 (c = 1.00 in CHCl$_3$). Lit: [α]$_D$ (27 °C) +20.8 (c = 1.28 in CHCl$_3$).[31] Characterisation data are consistent with literature values.[88]

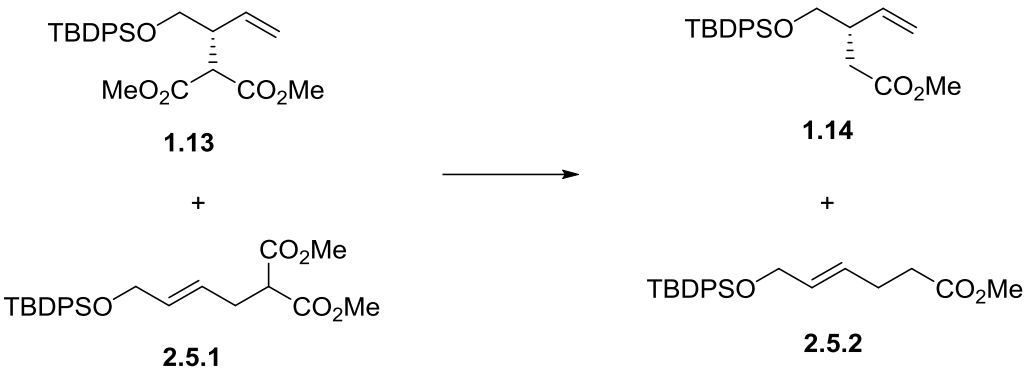
Linear isomer:

(*E*)-Dimethyl 2-(4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-yl)malonate (2.5.1)



2.5.1

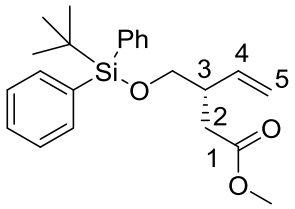
R$_f$ = 0.3 (20% Et$_2$O in PE$_{40\text{-}60}$); δ_H (400 MHz, CDCl$_3$): only non-overlapped signals are reported 5.67 – 5.65 (m, 2H, C*H*=C*H*), 4.14 – 4.12 (m, 2H, SiOC*H$_2$*), 3.71 (2 x singlet, 6H, 2 x CO$_2$C*H$_3$*), 3.44 (t, 1H, *J* = 7.6 Hz, C*H*(CO$_2$CH$_3$)$_2$), 2.66 – 2.62 (m, 2H, SiOCH$_2$CH=CHC*H$_2$*); δ_C (100 MHz, CDCl$_3$): 132.3 (*C*H=CH$_2$), 120.6 (CH=*C*H$_2$), 64.2 (SiO*C*H$_2$), 52.6 (CO$_2$*C*H$_3$), 51.9 (*C*H(CO$_2$CH$_3$)$_2$), 31.6 (SiOCH$_2$CH=CH*C*H$_2$). Characterisation data are consistent with literature values.[88]



According to a modified procedure of Davies:[88] To a solution of malonate **1.13** and **2.5.1** (450 mg, 1.01 mmol) in DMSO (2 mL) at RT was added lithium chloride (90 mg, 2.0 mmol). Water (0.04 mL, 2 mmol) was then added and the reaction mixture was stirred under reflux at 150 °C. After 2 h at 150 °C, another equivalent of water (0.02 mL, 1 mmol) was added to the reaction mixture and the reaction mixture was stirred at 150 °C for another 2 h. Upon completion, the reaction mixture was cooled to RT. Et_2O (10 mL) and water (10 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (10% Et_2O in $PE_{40\text{-}60}$) to give a partially separable mixture of the branched product **1.14** and the linear product **2.5.2** (343 mg, 0.897 mmol, combined yield 90%) as a colourless oil.

Branched isomer:

(*S*)-Methyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate (1.14)

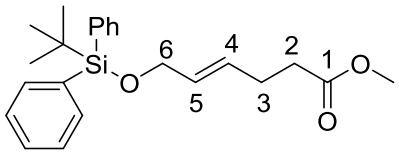


1.14

R_f = 0.3 (10% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.66 – 7.64 (m, 4H, Ar-*H*), 7.44 – 7.37 (m, 6H, Ar-*H*), 5.75 (ddd, 1H, *J* = 17.4, 10.4, 7.8 Hz, H-4), 5.08 (dt, 1H, *J* = 17.4, 1.2 Hz, $H_{pro(Z)}$-5), 5.08 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-5), 3.65 (dd, 1H, *J* = 9.9, 4.9 Hz, H-2), 3.65 (s, 3H, CO_2CH_3), 3.56 (dd, 1H, *J* = 9.9, 6.8 Hz, H'-2), 2.80 (sext, 1H, *J* = 7.2 Hz, H-3), 2.70 (dd, 1H, *J* = 15.2, 5.8 Hz, $SiOCH_2$), 2.38 (dd, 1H, *J* = 15.2, 8.6 Hz, $SiOCH'_2$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 173.1 (C-1), 138.0 (Ar), 135.6 (C-4), 133.5 (Ar), 129.7 (Ar), 127.7 (Ar), 116.3 (C-5), 66.4 (CH_2OSi), 51.5 (CO_2CH_3), 42.6 (C-3), 36.0 (C-2), 26.8 ($SiC(CH_3)_3$), 19.3 ($SiC(CH_3)_3$); *m/z* (ESI^+): 383.1 ($[M+H]^+$, 35%), 405.1 ($[M+Na]^+$, 100%); accurate mass: found 405.1850, $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ requires 405.1856; *ee* was measured by reducing the title compound to alcohol **1.4** and conducting HPLC analysis on alcohol **1.4** (see below); $[\alpha]_D$ (20 °C) +3.4 (c = 0.60 in $CHCl_3$). Characterisation data are consistent with literature values.[88]

Linear isomer:

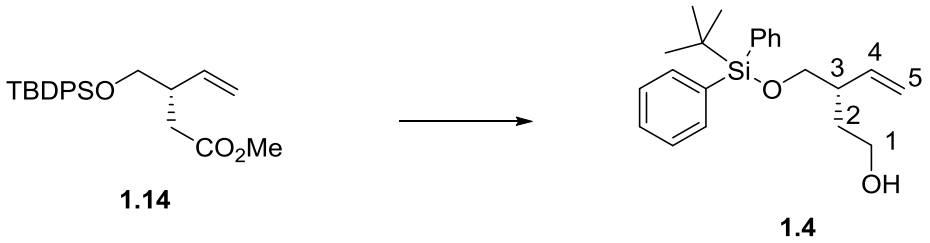
(*E*)-Methyl 6-((*tert*-butyldiphenylsilyl)oxy)hex-4-enoate (2.5.2)



2.5.2

R_f = 0.25 (10% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.72 – 7.63 (m, 4H, Ar-*H*), 7.44 – 7.36 (m, 6H, Ar-*H*), 5.68 – 5.60 (m, 2H, H-4 and H-5), 4.18 – 4.14 (m, 2H, H-6), 3.68 (s, 3H, OCH_3), 2.43 – 2.35 (m, 4H, H-2 and H-3), 1.06 (s, 9H, SiC(CH_3)$_3$); *m/z* (ESI$^+$): 405.2 ([M+Na]$^+$, 100%). Characterisation data are consistent with literature values.[88]

(*S*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (1.4)



1.14 **1.4**

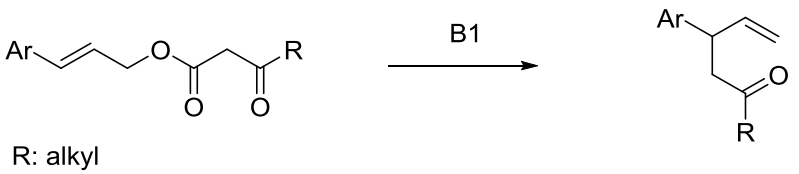
The title compound **1.4** was synthesised from ester **1.14** (100 mg, 0.261 mmol) using DIBAL-H (1 M in hexane, 0.57 mL, 0.574 mmol) in THF (1.2 mL) according to general procedure A2. The crude product was purified by FC (22% EtOAc in $PE_{40\text{-}60}$) to give the title compound **1.4** (76 mg, 0.214 mmol, 82%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.70 (ddd, 1H, *J* = 16.8, 10.9, 8.6 Hz, H-4), 5.05 (ddd, 1H, *J* =

16.8, 1.6, 0.8 Hz, $H_{pro(Z)}$-5), 5.04 (dd, 1H, *J* = 10.9, 1.6 Hz, $H_{pro(E)}$-5), 3.73 – 3.64 (m, 2H, H-1), 3.62 (dd, 1H, *J* = 10.1, 5.5 Hz, SiOCH_2), 3.59 (dd, 1H, *J* = 10.1, 6.6 Hz, SiOCH'_2), 2.42 – 2.35 (m, 1H, H-3), 1.82 (ddt, 1H, *J* = 11.9, 7.5, 6.2 Hz, H-2), 1.63 (ddt, 1H, *J* = 11.9, 8.5, 6.0 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 140.2 (C-4), 136.2 (Ar), 134.1 (Ar), 130.3 (Ar), 128.2 (Ar), 116.6 (C-5), 68.0 (*C*H_2OSi), 61.8 (C-1), 44.4 (C-3), 35.0 (C-2), 27.4 (SiC(*C*H_3)$_3$), 19.9 (Si*C*(CH$_3$)$_3$); ν_{max}/cm^{-1}: 3339 (br, O-H), 2858 (w, C-H), 1428 (w), 1112 (m), 702 (m); *m/z* (ESI$^+$): 355.1 ([M+H]$^+$, 90%), 377.3 ([M+Na]$^+$, 100%); accurate mass: found 377.1891, $C_{22}H_{30}NaO_2Si$ [M+Na]$^+$ requires 377.1907; *ee*: 99% [Chiralcel OD-H column (4.6 mm x 250 mm), 3% 2-propanol in *n*-hexane, flow rate = 1 mL / min, detection wavelength = 254 nm] t_R(*R*) = 8.70 min, t_R(*S*) = 10.13 min; [α]$_D$ (22 °C) +15.7 (c = 0.60 in ethanol), literature value [α]$_D$ (22 °C) +17.2 (c = 5.10 in ethanol). Characterisation data are consistent with literature values.[88]

4.3.5 Synthesis of racemic references

4.3.5.1 Synthesis of aryl racemic references (compounds in Section 2.3.4)

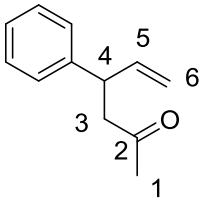
General procedure B1:



R: alkyl

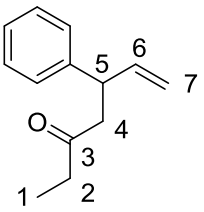
2.3.45 **(±)-2.3.46**

(±)-4-Phenylhex-5-en-2-one ((±)-2.3.19)



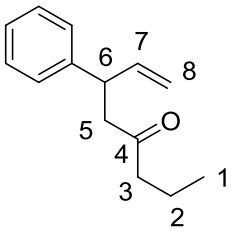
The title compound was synthesised from the corresponding *β*-ketoester (100 mg, 0.458 mmol) according to general procedure B1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.19** (56 mg, 0.321 mmol, 70%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.23 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.2, 10.4, 6.8 Hz, H-5), 5.06 (dt, 1H, *J* = 10.4, 1.3 Hz, $H_{pro(E)}$-6), 5.02 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-6), 3.91 (q, 1H, *J* = 7.1 Hz, H-4), 2.89 (dd, 1H, *J* = 16.2, 7.6 Hz, H-3), 2.82 (dd, 1H, *J* = 16.2, 7.4 Hz, H'-3), 2.09 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone **2.3.19** (page 188).

(±)-5-Phenylhept-6-en-3-one (Table 2.3.4, entry 2)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.26 mmol) according to general procedure B1. The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title compound (36 mg, 0.19 mmol, 74%) as a pale yellow oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.22 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.1, 10.3, 7.1 Hz, H-6), 5.05 (dt, 1H, *J* = 10.3, 1.0 Hz, $H_{pro(E)}$-7), 5.01 (dt, 1H, *J* = 17.1, 1.4 Hz, $H_{pro(Z)}$-7), 3.93 (q, 1H, *J* = 7.1 Hz, H-5), 2.86 (dd, 1H, *J* = 16.1, 7.1 Hz, H-4), 2.79 (dd, 1H, *J* = 16.1, 7.1 Hz, H'-4), 2.39 (dq, 1H, *J* = 18.0, 7.1 Hz, H-2), 2.30 (dq, 1H, *J* = 18.0, 7.4 Hz, H'-2), 0.98 (t, 3H, *J* = 7.2 Hz, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 217).

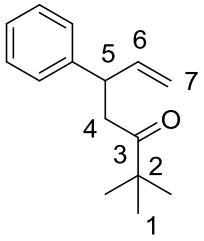
(±)-6-Phenyloct-7-en-4-one (Table 2.3.4, entry 3)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure B1. The crude product was purified by

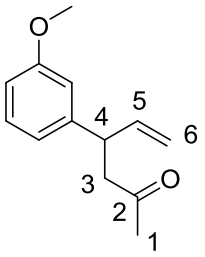
FC (6% EtOAc in $PE_{40\text{-}60}$) to give the title compound (36 mg, 0.18 mmol, 73%) as a yellow oil. R_f = 0.3 (6% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.28 (m, 2H, Ar-*H*), 7.22 – 7.19 (m, 3H, Ar-*H*), 5.96 (ddd, 1H, *J* = 17.2, 10.2, 7.1 Hz, H-7), 5.05 (dt, 1H, *J* = 10.2, 1.3 Hz, $H_{pro(E)}$-8), 5.01 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-8), 3.93 (q, 1H, *J* = 7.1 Hz, H-6), 2.85 (dd, 1H, *J* = 16.2, 7.5 Hz, H-5), 2.78 (dd, 1H, *J* = 16.2, 7.1 Hz, H'-5), 2.34 (dt, 1H, *J* = 16.7, 7.4 Hz, H-3), 2.27 (dt, 1H, *J* = 16.7, 7.2 Hz, H'-3), 1.54 (sext, 2H, *J* = 7.2 Hz, H-2), 0.84 (t, 3H, *J* = 7.5 Hz, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 218).

(±)-2,2-Dimethyl-5-phenylhept-6-en-3-one (Table 2.3.4, entry 4)



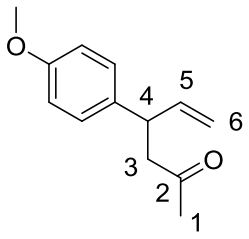
The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.23 mmol) according to general procedure B1. The crude product was purified by FC (5% EtOAc in $PE_{40\text{-}60}$) to give the title compound (20 mg, 0.092 mmol, 40%) as a colourless oil. R_f = 0.3 (5% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.31 – 7.27 (m, 2H, Ar-*H*), 7.21 – 7.19 (m, 3H, Ar-*H*), 5.97 (ddd, 1H, *J* = 17.2, 10.4, 6.7 Hz, H-6), 5.04 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-7), 5.01 (dt, 1H, *J* = 17.2, 1.3 Hz, $H_{pro(Z)}$-7), 3.99 (dt, 1H, *J* = 6.7, 6.9 Hz, H-5), 2.92 (dd, 1H, *J* = 17.1, 7.0 Hz, H-4), 2.87 (dd, 1H, *J* = 17.1, 7.1 Hz, H'-4), 1.05 (s, 9H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 219).

***(±)-4-(3-Methoxyphenyl)hex-5-en-2-one* (Table 2.3.4, entry 5)**



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure B1. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound (29 mg, 0.14 mmol, 59%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.24 – 7.20 (m, 1H, Ar-*H*), 6.81 – 6.74 (m, 3H, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.1, 10.2, 6.9 Hz, H-5), 5.06 (dt, 1H, *J* = 10.2, 1.1 Hz, $H_{pro(E)}$-6), 5.02 (dt, 1H, *J* = 17.1, 1.4 Hz, $H_{pro(Z)}$-6), 3.89 (q, 1H, *J* = 7.1 Hz, H-4), 3.79 (s, 3H, OCH_3), 2.87 (dd, 1H, *J* = 16.3, 7.6 Hz, H-3), 2.81 (dd, 1H, *J* = 16.3, 7.0 Hz, H'-3), 2.10 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 220).

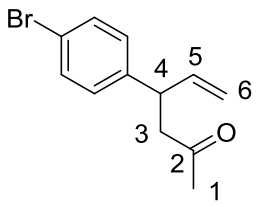
(±)-4-(4-Methoxyphenyl)hex-5-en-2-one (Table 2.3.4, entry 6)



The title compound was synthesised from the corresponding *β*-ketoester (34 mg, 0.14 mmol) according to general procedure B1. The crude product was purified by

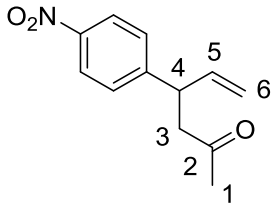
FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound (17 mg, 0.085 mmol, 61%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.11 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 6.84 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 5.94 (ddd, 1H, *J* = 17.2, 10.4, 7.2 Hz, H-5), 5.04 (dt, 1H, *J* = 10.4, 1.2 Hz, $H_{pro(E)}$-6), 4.99 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-6), 3.86 (dt, 1H, *J* = 7.2, 7.0 Hz, H-4), 3.78 (s, 3H, OCH_3), 2.85 (dd, 1H, *J* = 16.0, 7.4 Hz, H-3), 2.79 (dd, 1H, *J* = 16.0, 7.1 Hz, H'-3), 2.08 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 221).

***(±)-4-(4-Bromophenyl)hex-5-en-2-one* (Table 2.3.4, entry 7)**



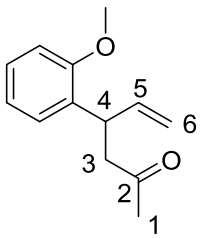
The title compound was synthesised from the corresponding *β*-ketoester (80 mg, 0.27 mmol) according to general procedure B1. The crude product was purified by FC (16% EtOAc in $PE_{40\text{-}60}$) to give the title compound (33 mg, 0.13 mmol, 48%) as a colourless oil. R_f = 0.3 (16% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.42 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.08 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 5.92 (ddd, 1H, *J* = 17.1, 10.4, 6.6 Hz, H-5), 5.07 (dt, 1H, *J* = 10.4, 1.3 Hz, $H_{pro(E)}$-6), 5.00 (dt, 1H, *J* = 17.1, 1.1 Hz, $H_{pro(Z)}$-6), 3.89 (dt, 1H, *J* = 6.6, 7.1 Hz, H-4), 2.87 (dd, 1H, *J* = 16.7, 7.4 Hz, H-3), 2.79 (dd, 1H, *J* = 16.7, 7.3 Hz, H'-3), 2.09 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 222).

(±)-4-(4-Nitrophenyl)hex-5-en-2-one (Table 2.3.4, entry 8)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.23 mmol) according to general procedure B1. The crude product was purified by FC (28% EtOAc in $PE_{40\text{-}60}$) to give the title compound (7 mg, 0.03 mmol, 14%) as a yellow oil. R_f = 0.3 (28% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.16 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 7.38 (d, 2H, *J* = 8.8 Hz, Ar-*H*), 5.93 (ddd, 1H, *J* = 17.1, 10.4, 7.0 Hz, H-5), 5.14 (dt, 1H, *J* = 10.4, 0.7 Hz, $H_{pro(E)}$-6), 5.05 (dt, 1H, *J* = 17.1, 1.1 Hz, $H_{pro(Z)}$-6), 4.05 (q, 1H, *J* = 7.0 Hz, H-4), 2.95 (dd, 1H, *J* = 17.0, 6.9 Hz, H-3), 2.87 (dd, 1H, *J* = 17.0, 7.3 Hz, H'-3), 2.12 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 223).

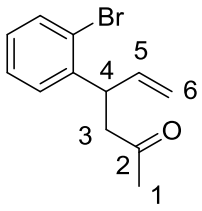
(±)-4-(2-Methoxyphenyl)hex-5-en-2-one (Table 2.3.4, entry 9)



The title compound was synthesised from the corresponding *β*-ketoester (60 mg, 0.24 mmol) according to general procedure B1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (36 mg, 0.18 mmol, 73%) as

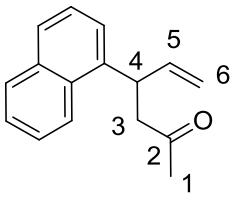
a colourless oil. R_f = 0.3 (15% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.20 (td, 1H, *J* = 7.8, 1.5 Hz, Ar-*H*), 7.13 (dd, 1H, *J* = 7.5, 1.5 Hz, Ar-*H*), 6.91 (t, 1H, *J* = 7.8 Hz, Ar-*H*), 6.86 (d, 1H, *J* = 8.3 Hz, Ar-*H*), 6.02 (ddd, 1H, *J* = 17.2, 10.2, 7.1 Hz, H-5), 5.05 (dt, 1H, *J* = 10.2, 1.8 Hz, $H_{pro(E)}$-6), 5.01 (dt, 1H, *J* = 17.2, 1.8 Hz, $H_{pro(Z)}$-6), 4.29 (dt, 1H, *J* = 7.1, 6.9 Hz, H-4), 3.84 (s, 3H, OC*H*$_3$), 2.86 (dd, 1H, *J* = 16.0, 8.2 Hz, H-3), 2.80 (dd, 1H, *J* = 16.0, 6.4 Hz, H'-3), 2.12 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 224).

***(±)-4-(2-Bromophenyl)hex-5-en-2-one* (Table 2.3.4, entry 10)**



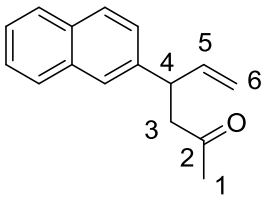
The title compound was synthesised from the corresponding *β*-ketoester (70 mg, 0.24 mmol) according to general procedure B1. The crude product was purified by FC (15% EtOAc in PE_{40-60}) to give the title compound (32 mg, 0.13 mmol, 53%) as a yellow oil. R_f = 0.3 (15% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.56 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.29 – 7.25 (m, 1H, Ar-*H*), 7.19 (dd, 1H, *J* = 7.6, 1.4 Hz, Ar-*H*), 7.08 (td, 1H, *J* = 7.6, 1.7 Hz, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.2, 10.5, 7.0 Hz, H-5), 5.14 (d, 1H, *J* = 10.5 Hz, $H_{pro(E)}$-6), 5.03 (d, 1H, *J* = 17.2 Hz, $H_{pro(Z)}$-6), 4.44 (q, 1H, *J* = 7.0 Hz, H-4), 2.87 (dd, 1H, *J* = 16.7, 7.7 Hz, H-3), 2.82 (dd, 1H, *J* = 16.7, 6.5 Hz, H'-3), 2.16 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 225).

***(±)-4-(Naphthalen-1-yl)hex-5-en-2-one* (Table 2.3.4, entry 11)**



The title compound was synthesised from the corresponding *β*-ketoester (80 mg, 0.30 mmol) according to general procedure B1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (4 mg, 0.02 mmol, 6%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 8.15 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.86 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.74 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 7.55 – 7.47 (m, 2H, Ar-*H*), 7.43, (t, 1H, *J* = 7.3 Hz, Ar-*H*), 7.35 (d, 1H, *J* = 7.2 Hz, Ar-*H*), 6.11 (ddd, 1H, *J* = 17.1, 10.4, 7.2 Hz, H-5), 5.13 (d, 1H, *J* = 10.4 Hz, $H_{pro(E)}$-6), 5.04 (d, 1H, *J* = 17.1 Hz, $H_{pro(Z)}$-6), 4.81 (dt, 1H, *J* = 7.2, 6.2 Hz, H-4), 3.07 (dd, 1H, *J* = 16.9, 8.8 Hz, H-3), 2.96 (dd, 1H, *J* = 16.9, 5.2 Hz, H'-3), 2.16 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 226).

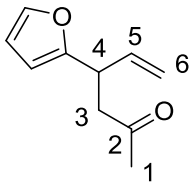
***(±)-4-(Naphthalen-2-yl)hex-5-en-2-one* (Table 2.3.4, entry 12)**



The title compound was synthesised from the corresponding *β*-ketoester (80 mg, 0.30 mmol) according to general procedure B1. The crude product was purified by

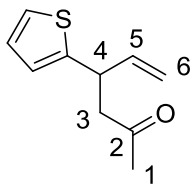
FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (38 mg, 0.17 mmol, 57%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.80 – 7.78 (m, 3H, Ar-*H*), 7.64 (s, 1H, Ar-*H*), 7.48 – 7.41 (m, 2H, Ar-*H*), 7.35 (dd, 1H, *J* = 8.4, 1.5 Hz, Ar-*H*), 6.04 (ddd, 1H, *J* = 17.1, 10.4, 7.0 Hz, H-5), 5.11 (d, 1H, *J* = 10.4 Hz, $H_{pro(E)}$-6), 5.07 (d, 1H, *J* = 17.1 Hz, $H_{pro(Z)}$-6), 4.09 (dt, 1H, *J* = 7.0, 6.8 Hz, H-4), 2.98 (dd, 1H, *J* = 16.3, 7.5 Hz, H-3), 2.93 (dd, 1H, *J* = 16.3, 7.2 Hz, H'-3), 2.11 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 227).

(±)-4-(Furan-2-yl)hex-5-en-2-one **(Table 2.3.4, entry 13)**



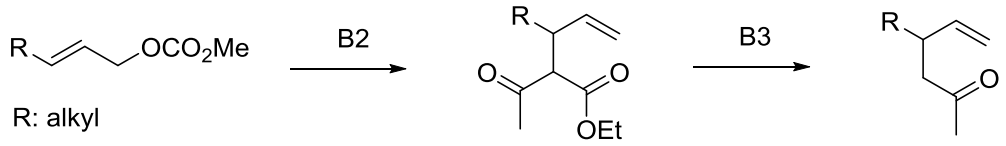
The title compound was synthesised from the corresponding *β*-ketoester (50 mg, 0.24 mmol) according to general procedure B1. The crude product was purified by FC (20% Et_2O in $PE_{30\text{-}40}$) to give the title compound (28 mg, 0.17 mmol, 71%) as a colourless oil. R_f = 0.3 (20% Et_2O in $PE_{30\text{-}40}$); δ_H (400 MHz, $CDCl_3$): 7.32 (s, 1H, Ar-*H*), 6.28 (dd, 1H, *J* = 3.2, 1.8 Hz, Ar-*H*), 6.03 (d, 1H, *J* = 3.2 Hz, Ar-*H*), 5.89 (ddd, 1H, *J* = 17.0, 10.4, 7.4 Hz, H-5), 5.10 (dt, 1H, *J* = 10.4, 1.1 Hz, $H_{pro(E)}$-6), 5.09 (dt, 1H, *J* = 17.0, 1.1 Hz, $H_{pro(Z)}$-6), 4.01 (q, 1H, *J* = 7.4 Hz, H-4), 2.93 (dd, 1H, *J* = 16.5, 6.7 Hz, H-3), 2.77 (dd, 1H, *J* = 16.5, 7.6 Hz, H'-3), 2.14 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 228).

(±)-4-(Thiophen-2-yl)hex-5-en-2-one (Table 2.3.4, entry 14)

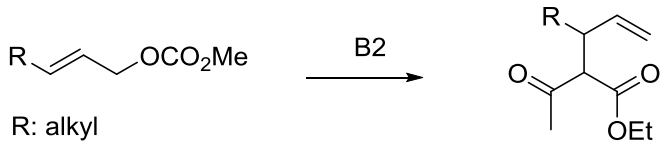


The title compound was synthesised from the corresponding *β*-ketoester (70 mg, 0.31 mmol) according to general procedure B1. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (37 mg, 0.20 mmol, 66%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.16 (d, 1H, *J* = 5.1 Hz, Ar-*H*), 6.93 (dd, 1H, *J* = 5.1, 3.6 Hz, Ar-*H*), 6.83 (d, 1H, *J* = 3.6 Hz, Ar-*H*), 5.95 (ddd, 1H, *J* = 17.3, 10.3, 7.3 Hz, H-5), 5.10 (d, 1H, *J* = 17.3 Hz, $H_{pro(E)}$-6), 5.09 (d, 1H, *J* = 10.3 Hz, $H_{pro(Z)}$-6), 4.21 (q, 1H, *J* = 7.3 Hz, H-4), 2.92 (dd, 1H, *J* = 16.7, 7.0 Hz, H-3), 2.87 (dd, 1H, *J* = 16.7, 7.3 Hz, H'-3), 2.14 (s, 3H, H-1). For the rest of the characterisation data please refer to the enantioenriched ketone (page 229).

4.3.5.2 Synthesis of alkyl racemic references (compounds in Section 2.3.4)



General procedure B2:



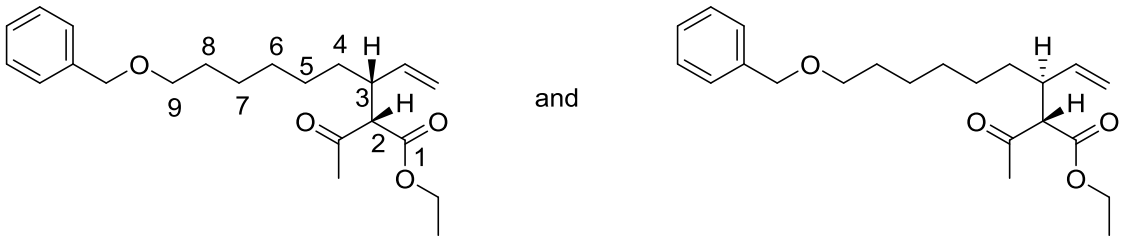
(±)-Ethyl 2-acetyl-3-phenethylpent-4-enoate



The title compound was synthesised from the corresponding carbonate (50 mg, 0.23 mmol) according to general procedure B2. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound (31 mg, 0.11 mmol, 50%) as a colourless oil. The product is an inseparable mixture of diastereomers. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.29 – 7.25 (m, 2H, Ar-*H*), 7.20 – 7.14 (m, 3H, Ar-*H*), 5.72 – 5.53 (m, 1H, H-4), 5.20 – 5.10 (m, 2H, H-5), 4.17 (q, 1H, *J* = 7.1 Hz, OCOCH_2), 4.13 (q, 1H, *J* = 7.2 Hz, OCOCH_2 of the other diastereomer), 3.45 (d, 1H, *J* = 9.2 Hz, H-2), 2.84 (dq, 1H, *J* = 9.2, 9.7 Hz, H-3), 2.83 (dq, 1H, *J* =

10.1, 9.0 Hz, H-3 of the other diastereomer), 2.73 – 2.61 (m, 2H, PhCH_2), 2.56 – 2.44 (m, 2H, PhCH_2 of the other diastereomer), 2.16 (2 x singlet, 3H, CH_3CO), 1.79 (dddd, 1H, J = 13.6, 10.2, 6.6, 3.1 Hz, PHCH_2CH_2), 1.69 (dddd, 1H, J = 13.6, 10.2, 6.9, 3.4 Hz, PHCH_2CH'_2), 1.26 (t, 3H, J = 7.1 Hz, OCOCH_2CH_3), 1.24 (t, 3H, J = 7.2 Hz, OCOCH_2CH_3 of the other diastereomer); *m/z* (ESI$^+$): 297.2 ([M+Na]$^+$, 100%); accurate mass: found 297.1463, $C_{17}H_{22}NaO_3$ [M+Na]$^+$ requires 297.1461. IR and ^{13}C NMR were not recorded due to loss of material.

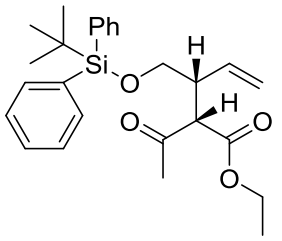
(±)-Ethyl 2-acetyl-9-(benzyloxy)-3-vinylnonanoate



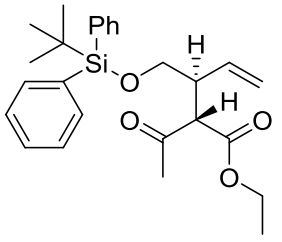
The title compound was synthesised from the corresponding carbonate (100 mg, 0.326 mmol) according to general procedure B2. The crude product was purified by FC (13% EtOAc in $PE_{40\text{-}60}$) to give the title compound (69 mg, 0.19 mmol, 59%) as a colourless oil. The product is an inseparable mixture of diastereomers. R_f = 0.3 (13% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.37 – 7.33 (m, 4H, Ar-*H*), 7.30 – 7.27 (m, 1H, Ar-*H*), 5.59 (ddd, 1H, J = 17.0, 10.3, 9.3 Hz, C*H*=CH_2), 5.11 – 5.00 (m, 2H, CH=CH_2), 4.50 (s, 2H, PhCH_2), 4.49 (s, 2H, PhCH_2 of the other diastereomer), 4.18 (q, 2H, J = 7.2 Hz, OCOCH_2), 4.14 (q, 2H, J = 7.2 Hz, OCOCH_2 of the other diastereomer), 3.47 – 3.40 (m, 3H, H-2 and H-9), 2.80 – 2.74 (m, 1H, H-3), 2.22 (s, 3H, CH_3CO), 2.17 (s, 3H, CH_3CO of the other diastereomer), 1.38 – 1.16 (m, 13H,

H-4, H-5, H-6, H-7, H-8 and $OCOCH_2C\mathit{H_3}$); δ_C (125 MHz, $CDCl_3$): 203.0 (*C*=O, ketone), 202.9 (*C*=O of the other diastereomer, ketone), 169.0 (C-1), 168.8 (C-1 of the other diastereomer), 139.0 (Ar), 138.4 ($\mathit{C}H=CH_2$), 138.3 ($\mathit{C}H=CH_2$ of the other diastereomer), 134.1 (Ar), 128.6 (Ar), 127.9 (Ar), 127.8 (Ar), 125.6 (Ar), 117.9 ($CH=\mathit{C}H_2$), 117.7 ($CH=\mathit{C}H_2$ of the other diastereomer), 73.2 ($Ph\mathit{C}H_2$), 70.7 (C-9 doublet), 65.7 (C-2), 65.5 (C-2 of the other diastereomer), 61.6 ($OCO\mathit{C}H_2$ doublet), 44.4 (C-3), 44.3 (C-3 of the other diastereomer), 32.7 ($\mathit{C}H_2$), 32.6 ($\mathit{C}H_2$), 31.6 ($\mathit{C}H_2$), 30.0 ($\mathit{C}H_2$), 29.7 ($\mathit{C}H_2$), 29.5 ($\mathit{C}H_3CO$ doublet), 29.2 ($\mathit{C}H_2$), 27.2 ($\mathit{C}H_2$), 27.0 ($\mathit{C}H_2$), 26.4 ($\mathit{C}H_2$), 26.3 ($\mathit{C}H_2$), 14.4 ($OCOCH_2\mathit{C}H_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2856 (m, C-H), 1750 (s, C=O, ester), 1715 (s, C=O, ketone), 1160 (s), 1099 (s), 922 (s), 736 (s), 697 (s); *m/z* (ESI^+): 383.2 ($[M+Na]^+$, 100%); accurate mass: found 383.2195, $C_{22}H_{32}NaO_4$ $[M+Na]^+$ requires 383.2193.

(±)-Ethyl 2-acetyl-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate



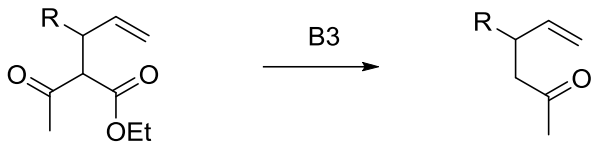
and



The title compound was synthesised from the corresponding carbonate (50 mg, 0.13 mmol) according to general procedure B2. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (16 mg, 0.035 mmol, 27%) as a colourless oil. The product is an inseparable mixture of diastereomers. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.64 – 7.61 (m, 4H, Ar-*H*), 7.51 –

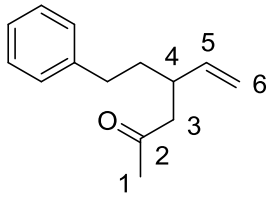
7.32 (m, 6H, Ar-*H*), 5.89 – 5.79 (m, 1H, C*H*=CH_2), 5.13 – 5.06 (m, 2H, CH=C*H*$_2$), 4.15 (q, 2H, *J* = 7.1 Hz, C(O)OC*H*$_2$), 4.11 (q, 2H, *J* = 7.1 Hz, C(O)OC*H*$_2$ of the other diastereomer), 3.89 (d, 1H, *J* = 8.7 Hz, C*H*C(O)OCH_2), 3.87 (d, 1H, *J* = 9.5 Hz, C*H*C(O)OCH_2 of the other diastereomer), 3.73 (dd, 1H, *J* = 10.0, 4.9 Hz, SiOC*H*$_2$), 3.69 (dd, 1H, *J* = 10.0, 4.9 Hz, SiOC*H'*$_2$), 3.03 (hept, 1H, *J* = 5.2 Hz, $SiOCH_2$C*H*), 2.21 (s, 3H, C(O)C*H*$_3$), 2.20 (s, 3H, C(O)C*H*$_3$ of the other diastereomer), 1.24 (t, 3H, *J* = 7.1 Hz, C(O)OCH_2C*H*$_3$), 1.21 (t, 3H, *J* = 7.1 Hz, C(O)OCH_2C*H*$_3$ of the other diastereomer), 1.05 (s, 9H, SiC(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$): 202.8 (*C*=O, ketone), 202.4 (*C*=O of the other diastereomer, ketone), 168.8 (*C*=O, ester), 168.7 (*C*=O of the other diastereomer, ester), 135.9, 135.7 (*C*H=CH_2), 135.6 (Ar), 133.3 (Ar), 129.9 (Ar), 129.8 (Ar), 127.8 (Ar), 118.3 (CH=*C*H_2), 118.1 (CH=*C*H_2 of the other diastereomer), 65.2 (SiO*C*H_2), 65.0 (SiO*C*H_2 of the other diastereomer), 61.5 (OCO*C*H_2), 61.3 (OCO*C*H_2 of the other diastereomer), 60.8 (*C*H_2OCOCH_2), 60.7 (*C*H_2OCOCH_2 of the other diastereomer), 46.1 ($SiOCH_2$*C*H), 45.8 ($SiOCH_2$*C*H of the other diastereomer), 29.9 (*C*H_3CO), 29.8 (*C*H_3CO of the other diastereomer), 26.9 (SiC(*C*H_3)$_3$), 19.4 (Si*C*$(CH_3)_3$), 14.2 ($OCOCH_2$*C*H_3), 14.1 ($OCOCH_2$*C*H_3 of the other diastereomer); ν_{max}/cm^{-1}: 2932 (w, C-H), 2858 (w, C-H), 1750 (s, C=O, ester), 1716 (s, C=O, ketone), 1110 (s), 702 (s); *m/z* (ESI^+): 461.3 ($[M+Na]^+$, 100%); accurate mass: found 461.2133, $C_{26}H_{34}NaO_4Si$ $[M+Na]^+$ requires 461.2119.

General procedure B3:



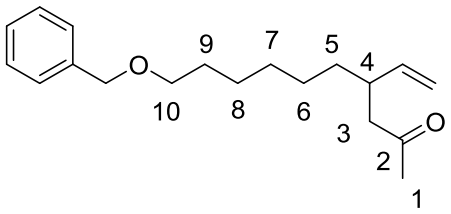
(±)-2.3.48 **(±)-2.3.49**

(±)-4-Phenethylhex-5-en-2-one (Table 2.3.5, entry 1)



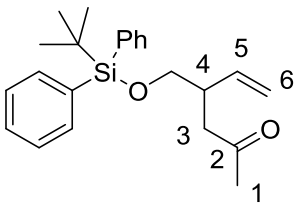
The title compound was synthesised from the corresponding *β*-ketoester (31 mg, 0.11 mmol) according to general procedure B3. The crude product was purified by FC (60% DCM in $PE_{40\text{-}60}$) to give the title compound (14 mg, 0.067 mmol, 61%) as a colourless oil. R_f = 0.3 (60% DCM in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.29 – 7.25 (m, 2H, Ar-*H*), 7.19 – 7.15 (m, 3H, Ar-*H*), 5.70 – 5.61 (m, 1H, H-5), 5.07 (dd, 1H, *J* = 11.2, 1.4 Hz, $H_{pro(E)}$-6), 5.06 (d, 1H, *J* = 16.1 Hz, $H_{pro(Z)}$-6), 2.68 – 2.50 (m, 3H, H-4 and PhCH_2), 2.47 (d, 2H, *J* = 6.8 Hz, H-3), 2.10 (s, 3H, H-1), 1.74 – 1.57 (m, 2H, $PhCH_2CH_2$). For the rest of the characterisation data please refer to the enantioenriched ketone (page 232).

(±)-10-(Benzyloxy)-4-vinyldecan-2-one (Table 2.3.5, entry 2)



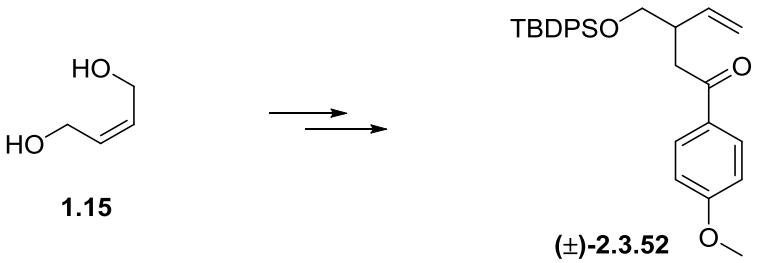
The title compound was synthesised from the corresponding *β*-ketoester (66 mg, 0.18 mmol) according to general procedure B3. The crude product was purified by FC (13% EtOAc in $PE_{40\text{-}60}$) to give the title compound (27 mg, 0.092 mmol, 51%) as a colourless oil. R_f = 0.3 (13% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.35 – 7.33 (m, 4H, Ar-*H*), 7.30 – 7.27 (m, 1H, Ar-*H*), 5.59 (ddd, 1H, *J* = 16.7, 10.8, 8.4 Hz, CHC*H*=CH_2), 4.99 (ddd, 1H, *J* = 16.7, 1.6, 0.8 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 4.98 (dd, 1H, *J* = 10.8, 1.6 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 4.50 (s, 2H, PhCH_2O), 3.45 (t, 2H, *J* = 6.6 Hz, H-10), 2.56 – 2.50 (m, 1H, H-4), 2.43 – 2.41 (m, 2H, H-3), 2.12 (s, 3H, H-1), 1.62 – 1.58 (m, 2H, H-9), 1.34 – 1.25 (m, 8H, H-5, H-6, H-7 and H-8). For the rest of the characterisation data please refer to the enantioenriched ketone (page 238).

(±)-4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hex-5-en-2-one ((±)-2.3.21)



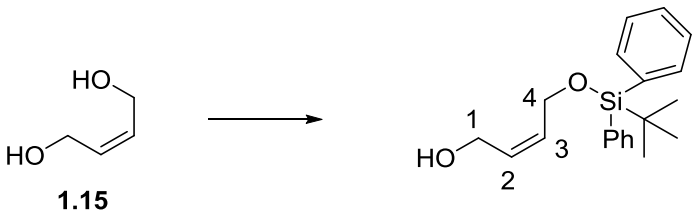
The title compound was synthesised from the corresponding *β*-ketoester (50 mg, 0.11 mmol) according to general procedure B3. The crude product was purified by

FC (80% DCM in PE_{40-60}) to give the title compound (12 mg, 0.031 mmol, 29%) as a colourless oil. R_f = 0.3 (80% DCM in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.72 (ddd, 1H, *J* = 17.6, 10.1, 7.7 Hz, H-5), 5.06 (dt, 1H, *J* = 17.6, 1.1 Hz, $H_{pro(Z)}$-6), 5.05 (dt, 1H, *J* = 10.1, 1.1 Hz, $H_{pro(E)}$-6), 3.65 (dd, 1H, *J* = 9.8, 5.3 Hz, SiOCH_2), 3.55 (dd, 1H, *J* = 9.8, 6.6 Hz, SiOCH'_2), 2.83 (sext, 1H, *J* = 6.8 Hz, H-4), 2.74 (dd, 1H, *J* = 16.2, 5.6 Hz, H-3), 2.46 (dd, 1H, *J* = 16.2, 8.0 Hz, H'-3), 2.13 (s, 3H, H-1), 1.08 (s, 9H, SiC(CH_3)$_3$). For the rest of the characterisation data please refer to the enantioenriched ketone **2.3.21** (page 190).



1.15 **(±)-2.3.52**

(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-ol (2.3.50)

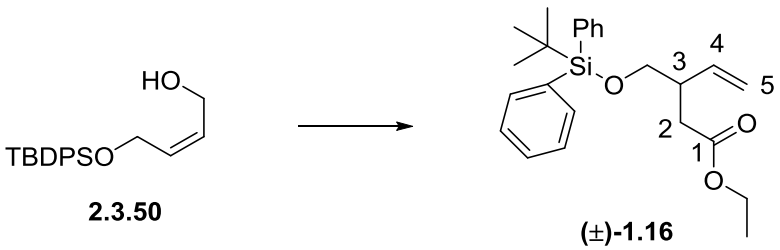


1.15 **2.3.50**

According to the procedure of Ferrara:[3] To a solution of (*Z*)-2-butene-1,4-diol **1.15** (2.9 mL, 34 mmol) in THF (30 mL) at 0 °C was added sodium hydride (1.43 g, 35.8 mmol) slowly. The reaction mixture was warmed to RT and stirred for 45 min. To this mixture at 0 °C was added a solution of *tert*-butyl(chloro)diphenylsilane (8.9 mL, 34 mmol) in THF (12 mL) dropwise over 30 min. After complete addition,

the reaction mixture was warmed to RT and stirred for 2 h. Upon completion, the reaction was quenched with brine (20 mL) and water (80 mL). The mixture was diluted with Et_2O (100 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.50** (10.8 g, 33.1 mmol, 97%) as a pale yellow oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.72 – 7.69 (m, 4H, Ar-*H*), 7.48 – 7.38 (m, 6H, Ar-*H*), 5.73 (dtt, 1H, *J* = 11.2, 5.9, 1.3 Hz, H-3), 5.65 (dtt, 1H, *J* = 11.2, 6.2, 1.3 Hz, H-2), 4.28 (dd, 2H, *J* = 5.9, 1.3 Hz, H-4), 4.03 – 4.01 (m, 2H, H-1), 1.07 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 135.6 (Ar), 133.4 (Ar), 130.9 (C-3), 129.9 (C-2), 129.8 (Ar), 127.7 (Ar), 60.2 (C-4), 58.7 (C-1), 26.8 (SiC(CH_3)$_3$), 19.1 (SiC(CH_3)$_3$). Characterisation data are consistent with literature values.[3]

(±)-Ethyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate ((±)-1.16)

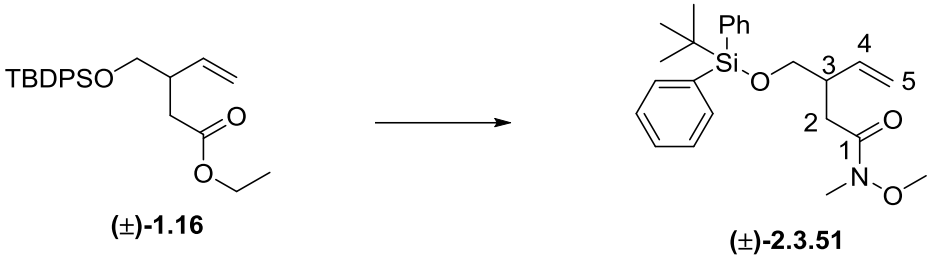


2.3.50 **(±)-1.16**

According to the procedure of Ferrara:[3] A mixture of alcohol **2.3.50** (1.00 g, 3.06 mmol), triethyl orthoacetate (3.9 mL, 21 mmol) and propionic acid (14 µL, 0.18 mmol) was stirred at 138 °C for 22 h, using setup for distillative removal of ethanol. Upon completion, sat. aq. NH_4Cl solution (10 mL) was added and the

biphasic mixture was vigorously stirred for 20 min to hydrolyse the excess triethyl orthoacetate. The two layers were then separated and the aqueous layer was extracted with EtOAc (2 x 7 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (7% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-1.16** (1.07 g, 2.70 mmol, 88%) as a colourless oil. R_f = 0.3 (7% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.72 – 7.63 (m, 4H, Ar-*H*), 7.47 – 7.39 (m, 6H, Ar-*H*), 5.75 (ddd, 1H, *J* = 17.2, 10.4, 7.8 Hz, H-4), 5.07 (dt, 1H, *J* = 17.2, 1.6 Hz, $H_{pro(Z)}$-5), 5.05 (ddd, 1H, *J* = 10.4, 1.6, 0.7 Hz, $H_{pro(E)}$-5), 4.11 (q, 2H, *J* = 7.1 Hz, OCOC*H*$_2$$CH_3$), 3.65 (dd, 1H, *J* = 9.9, 5.3 Hz, SiOC*H*$_2$), 3.56 (dd, 1H, *J* = 9.9, 6.7 Hz, SiOC*H'*$_2$), 2.80 (sext, 1H, *J* = 7.0 Hz, H-3), 2.67 (dd, 1H, *J* = 15.2, 5.7 Hz, H-2), 2.35 (dd, 1H, *J* = 15.2, 8.7 Hz, H'-2), 1.23 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 172.6 (C-1), 138.0 (C-4), 135.6 (Ar), 133.5 (Ar), 129.7 (Ar), 127.7 (Ar), 116.2 (C-5), 66.4 ($SiOCH_2$), 60.3 ($OCOCH_2CH_3$), 42.7 (C-3), 36.2 (C-2), 26.9 ($SiC(CH_3)_3$), 19.3 ($SiC(CH_3)_3$), 14.3 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[3]

(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-*N*-methoxy-*N*-methylpent-4-enamide ((±)-2.3.51)

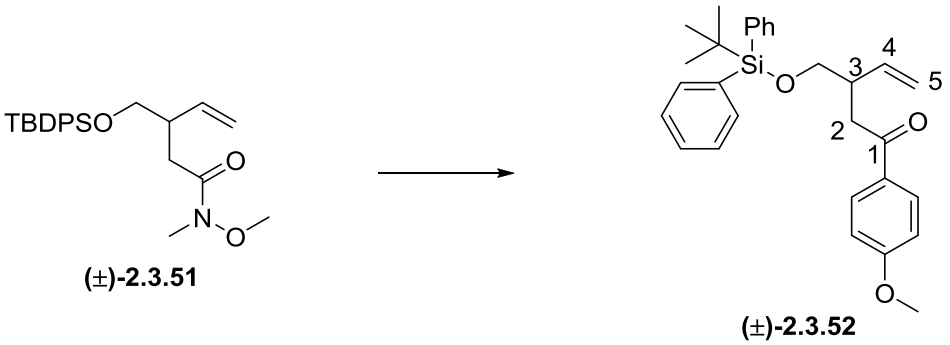


(±)-1.16 **(±)-2.3.51**

According to a modified procedure of Prunet *et al*.:[90] To a solution of ester **(±)-1.16** (2.00 g, 5.04 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (781 mg, 8.07 mmol) in THF (20.8 mL) at -15 °C was added isopropylmagnesium chloride (2 M in THF, 8.8 mL, 18 mmol) dropwise over 30 min. The reaction mixture was stirred at -15 °C for 1.5 h. Upon completion, the reaction was quenched by water (10 mL) and brine (10 mL) at -15 °C. EtOAc (10 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.51** (2.04 g, 4.94 mmol, 98%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.63 (m, 4H, Ar-*H*), 7.45 – 7.33 (m, 6H, Ar-*H*), 5.81 (ddd, 1H, *J* = 17.4, 10.4, 7.8 Hz, H-4), 5.09 (dt, 1H, *J* = 17.4, 1.2 Hz, $H_{pro(Z)}$-5), 5.04 (ddd, 1H, *J* = 10.4, 1.7, 0.8 Hz, $H_{pro(E)}$-5), 3.71 (dd, 1H, *J* = 9.8, 5.2 Hz, SiOCH_2), 3.66 (s, 3H, OCNOCH_3), 3.62 (dd, 1H, *J* = 9.8, 6.4 Hz, SiOCH'_2), 3.16 (s, 3H, OCNCH_3), 2.90 (sext, 1H, *J* = 6.0 Hz, H-3), 2.75 (dd, 1H, *J* = 15.5, 5.5 Hz, H-2), 2.52 (dd, 1H, *J* = 15.5, 8.6 Hz, H'-2), 1.06

(s, 9H, SiC(CH_3)$_3$); *m/z* (ESI$^+$): 434.2 ([M+Na]$^+$, 100%). Characterisation data are consistent with literature values.[197]

(±)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-(4-methoxyphenyl)pent-4-en-1-one ((±)-2.3.52)



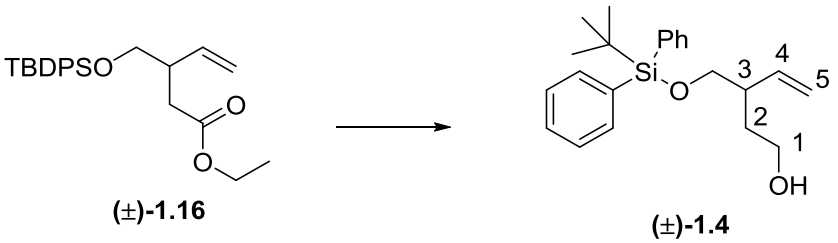
(±)-2.3.51 **(±)-2.3.52**

According to a modified procedure of Rychnovsky *et al*.:[91] To a solution of amide **(±)-2.3.51** (460 mg, 1.12 mmol) in THF (3.7 mL) at 0 °C was added (4-methoxyphenyl)magnesium bromide (0.5 M in THF, 3.4 mL, 1.7 mmol) dropwise over 30 min. The reaction mixture was further stirred at 0 °C for 30 min before warming to RT and stirred for 16 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl (5 mL). EtOAc (3 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 3 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (10% to 13% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.52** (454 mg, 0.990 mmol, 89%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.96 – 7.93 (m, 2H, Ar-*H*), 7.67 – 7.62 (m, 4H, Ar-*H*), 7.44 – 7.32 (m, 6H, Ar-*H*), 6.95 – 6.90 (m, 2H, Ar-*H*), 5.81 (ddd, 1H, *J* = 17.0, 10.6, 7.6 Hz, H-4), 5.04 (dt, 1H, *J* = 17.0, 1.4 Hz, $H_{pro(Z)}$-5), 5.02 (ddd, 1H, *J* = 10.6, 1.4,

0.7 Hz, $H_{pro(E)}$-5), 3.89 (s, 3H, PhOCH_3), 3.74 (dd, 1H, *J* = 9.9, 5.0 Hz, SiOCH_2), 3.64 (dd, 1H, *J* = 9.9, 6.8 Hz, SiOCH'_2), 3.33 (dd, 1H, *J* = 15.8, 5.3 Hz, H-2), 3.02 (sext, 1H, *J* = 6.7 Hz, H-3), 2.88 (dd, 1H, *J* = 15.8, 8.1 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 197.9 (*C*=O), 163.4 (Ar), 138.7 (*C*H=CH_2), 135.7 (Ar), 133.7 (Ar), 130.5 (Ar), 130.4 (Ar), 129.7 (Ar), 127.7 (Ar), 116.0 (CH=*C*H_2), 113.7 (Ar), 66.7 (SiO*C*H_2), 55.6 (O*C*H_3), 42.2 (SiOCH_2*C*H), 39.6 (PhCO*C*H_2), 27.0 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$); ν_{max}/cm^{-1}: 2931 (m, C-H), 2857 (m, C-H), 1677 (s, C=O), 1600 (s), 1255 (s), 1110 (s), 702 (s); *m/z* (ESI$^+$): 481.2 ([M+Na]$^+$, 100%); accurate mass: found 481.2169, $C_{29}H_{34}O_3NaSi$ [M+Na]$^+$ requires 481.2169.

4.3.5.3 Synthesis of racemic references (compounds in Section 2.3.6)

(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol ((±)1.4)

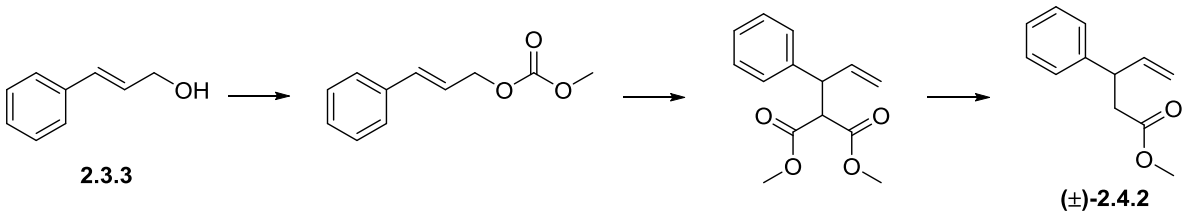


(±)-1.16 **(±)-1.4**

The title compound **(±)-1.4** was synthesised from ester **(±)-1.16** (155 mg, 0.392 mmol) using DIBAL-H (1 M in hexane, 0.87 mL, 0.87 mmol) in THF (2.0 mL) according to general procedure A2. The crude product was purified by FC (25% EtOAc in PE_{40-60}) to give the title compound **(±)-1.4** (92 mg, 0.26 mmol, 66%) as a colourless oil. The yield in this case is low because only the pure fractions after FC were collected; yield does not matter in this case because the title compound

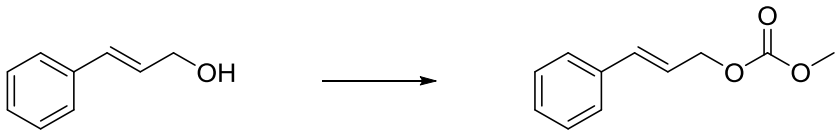
(±)-1.4 was only prepared for *ee* measurement. R_f = 0.3 (25% EtOAc in PE_{40-60}); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.70 (ddd, 1H, *J* = 16.8, 10.9, 8.6 Hz, H-4), 5.05 (ddd, 1H, *J* = 16.8, 1.9, 0.9 Hz, $H_{pro(Z)}$-5), 5.04 (dd, 1H, *J* = 10.9, 1.9 Hz, $H_{pro(E)}$-5), 3.73 – 3.64 (m, 2H, H-1), 3.62 (dd, 1H, *J* = 10.1, 5.5 Hz, SiOCH_2), 3.59 (dd, 1H, *J* = 10.1, 6.6 Hz, SiOCH'_2), 2.43 – 2.36 (m, 1H, H-3), 1.82 (ddt, 1H, *J* = 11.9, 7.2, 5.9 Hz, H-2), 1.63 (ddt, 1H, *J* = 11.9, 8.5, 5.9 Hz, H'-2), 1.06 (s, 9H, SiC(CH_3)$_3$). For the rest of the characterisation data please refer to the enantioenriched alcohol **1.4** (page 253).

4.3.5.4 Synthesis of racemic references (compounds in Section 2.4.2)



2.3.3 **(±)-2.4.2**

Cinnamyl methyl carbonate

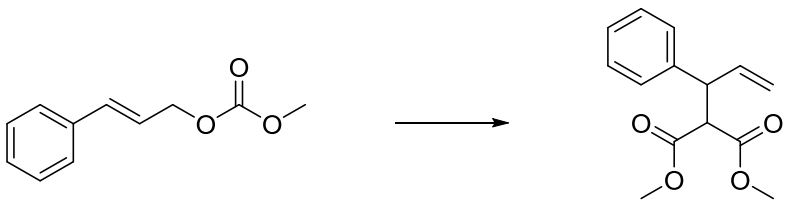


2.3.3

According to a modified procedure of Helmchen et al.:[103] To a solution of cinnamyl alcohol **2.3.3** (1.00 g, 7.45 mmol) in DCM (17 mL) was added pyridine (0.90 mL, 11 mmol) followed by methyl 3-chloro-3-oxopropanoate (0.86 mL, 11 mmol) dropwise over 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 1 h before it was warmed to RT. The reaction mixture was then stirred at RT for 2 h. Upon

completion, water (15 mL) was added. The two layers were separated and the aqueous layer was extracted with DCM (3 x 15 mL). The organic layers were combined, washed with sat. aq. $CuSO_4$ solution (15 mL) and sat. aq. NH_4Cl solution (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound (1.40 g, 7.30 mmol, 98%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.41 – 7.38 (m, 2H, Ar-*H*), 7.35 – 7.31 (m, 2H, Ar-*H*), 7.29 – 7.27 (m, 1H,Ar-*H*), 6.69 (d, 1H, *J* = 16.2 Hz, PhC*H*=CH), 6.30 (dt, 1H, *J* = 16.2, 6.5 Hz, PhCH=C*H*), 4.80 (dd, 2H, *J* = 6.5, 1.3 Hz, CH=CHCH_2), 3.81 (s, 3H, OCO_2CH_3); δ_C (400 MHz, $CDCl_3$): 155.8 (*C*=O), 136.2 (Ar), 134.9 (Ph*C*H=CH), 128.7 (Ar), 128.3 (Ar), 126.8 (Ar), 122.5 (PhCH=*C*H), 68.5 (CH=CH*C*H_2), 55.0 (CO_2CH_3); *m/z* (ESI^+): 215.1 ($[M+Na]^+$, 100%). Characterisation data are consistent with literature values.[212]

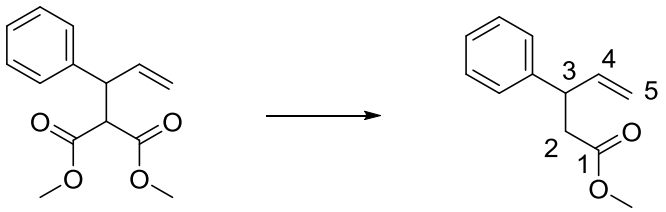
(±)-Dimethyl 2-(1-phenylallyl)malonate



According to a modified procedure of Kashio *et al.*:[12] To a slurry of sodium hydride (300 mg, 12.5 mmol) in THF (24 mL) was added dimethyl malonate (1.4 mL, 12 mmol) at RT. The resulting mixture was added to a solution of cinnamyl methyl carbonate (800 mg, 4.16 mmol), triphenyl phosphite (0.09 mL, 0.3 mmol) and $[Ir(COD)Cl]_2$ (56 mg, 0.083 mmol) in THF (25 mL) at RT. The reaction mixture was

stirred at RT for 16 h. Water (20 mL) and Et_2O (15 mL) were then added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (25% EtOAc in $PE_{40\text{-}60}$) to give the title compound (290 mg, 1.17 mmol, 28%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.28 (m, 2H, Ar-*H*), 7.23 – 7.21 (m, 3H, Ar-*H*), 5.99 (ddd, 1H, *J* = 17.1, 10.3, 8.3 Hz, CHC*H*=CH), 5.15 – 5.07 (m, 2H, CHCH=CH_2), 4.13 – 4.08 (m, 1H, PhC*H*), 3.87 (d, 1H, *J* = 11.1 Hz, C*H*C(O)OCH_3), 3.74 (s, 3H, C(O)OCH_3), 3.49 (s, 3H, C(O)OCH_3); δ_C (100 MHz, $CDCl_3$): 168.4 (*C*=O), 168.0 (*C*=O), 140.1 (Ar), 137.9 (CH*C*H=CH), 128.8 (Ar), 128.0 (Ar), 127.3 (Ar), 116.8 (CHCH=*C*H), 57.5 (*C*HC(O)OCH_3), 52.7 (C(O)O*C*H_3), 52.6 (C(O)O*C*H_3), 49.9 (Ph*C*H). Characterisation data are consistent with literature values.[213]

(±)-Methyl 3-phenylpent-4-enoate ((±)-2.4.2)

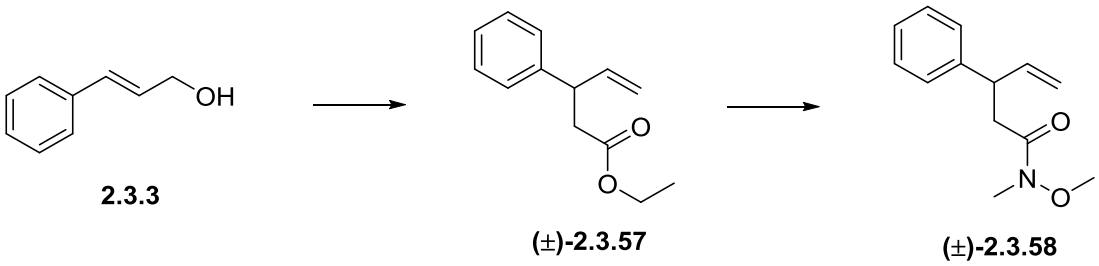


(±)-2.4.2

The title compound **(±)-2.4.2** was synthesised from (±)-dimethyl 2-(1-phenylallyl)malonate (150 mg, 0.604 mmol) according to general procedure B3. The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.4.2** (79 mg, 0.42 mmol, 69%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 – 7.29 (m, 2H, Ar-*H*), 7.24 – 7.20 (m, 3H, Ar-*H*),

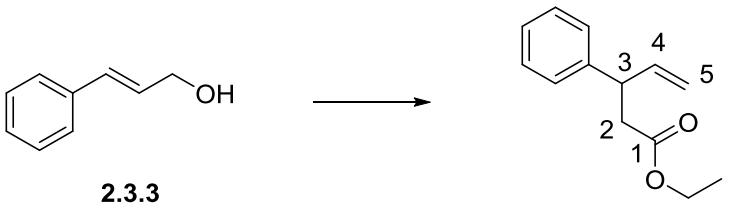
5.97 (ddd, 1H, *J* = 17.0, 10.0, 6.9 Hz, H-4), 5.08 (dt, 1H, *J* = 10.0, 1.4 Hz, $H_{pro(E)}$-5), 5.07 (dt, 1H, *J* = 17.0, 1.4 Hz, $H_{pro(Z)}$-5), 3.88 (q, 1H, *J* = 7.6 Hz, H-3), 3.62 (s, 3H, CO_2CH_3), 2.77 (dd, 1H, *J* = 15.2, 8.3 Hz, H-2), 2.70 (dd, 1H, *J* = 15.2, 7.3 Hz, H'-2). For the rest of the characterisation data please refer to the enantioenriched ester **2.4.2** (page 257).

4.3.5.5 Synthesis of racemic references (compounds in Section 2.4.3)



2.3.3 **(±)-2.3.57** **(±)-2.3.58**

(±)-Ethyl 3-phenylpent-4-enoate ((±)-2.3.57)

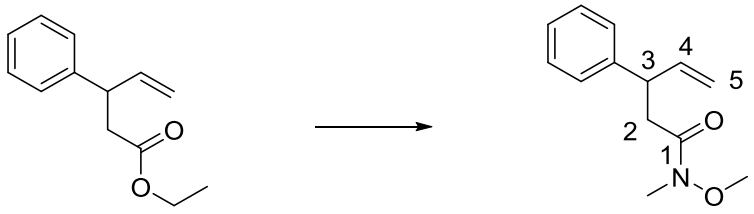


2.3.3 **(±)-2.3.57**

According to a procedure of Ferrara *et al*.:[3] A mixture of cinnamyl alcohol **2.3.3** (3.0 g, 22 mmol), triethyl orthoacetate (20.5 mL, 112 mmol) and propionic acid (0.10 mL, 1.3 mmol) was stirred at 145 °C under reflux for 1 h. Upon completion, aq. HCl (1 M, 70 mL) was slowly added to the reaction mixture. The mixture was shaken vigorously before separating the two layers. The aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with

sat. aq. $NaHCO_3$ (70 mL) and brine (70 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (4% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.57** (2.7 g, 13 mmol, 58%) as a colourless oil. R_f = 0.3 (4% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.32 – 7.21 (m, 5H, Ar-*H*), 5.98 (ddd, 1H, *J* = 17.2, 10.1, 7.0 Hz, H-4), 5.08 (dt, 1H, *J* = 17.2, 1.4 Hz, $H_{pro(Z)}$-5), 5.07 (dt, 1H, *J* = 10.1, 1.4 Hz, $H_{pro(E)}$-5), 4.07 (q, 2H, *J* = 7.2 Hz, OCOC$H_2$$CH_3$), 3.91 (q, 1H, *J* = 7.6 Hz, H-3), 2.76 (dd, 1H, *J* = 15.1, 8.2 Hz, H-2), 2.69 (dd, 1H, *J* = 15.1, 7.4 Hz, H'-2), 1.17 (t, 3H, *J* = 7.2 Hz, $OCOCH_2CH_3$); δ_C (100 MHz, $CDCl_3$): 172.0 (C-1), 142.6 (Ar), 140.4 (C-4), 128.7 (Ar), 127.7 (Ar), 126.8 (Ar), 114.9 (C-5), 60.5 ($OCOCH_2CH_3$), 45.7 (C-3), 40.4 (C-2), 14.3 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[196]

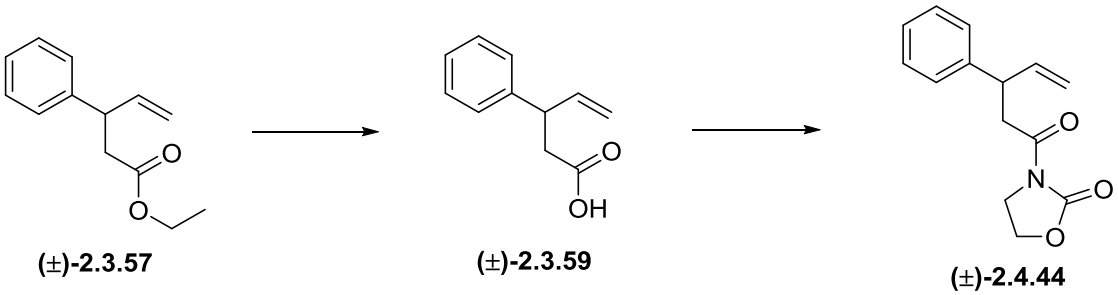
(±)-*N*-Methoxy-*N*-methyl-3-phenylpent-4-enamide ((±)-2.3.58)



(±)-2.3.57 **(±)-2.3.58**

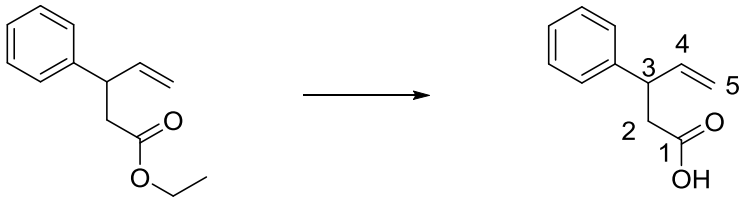
According to a modified procedure of Prunet *et al*.:[90] To a slurry of ester **(±)-2.3.57** (100 mg, 0.490 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (74 mg, 0.76 mmol) in THF (1.2 mL) at -20 °C was added isopropylmagnesium chloride solution (2 M in THF, 0.73 mL, 1.5 mmol) dropwise over 10 min, maintaining the temperature below -5 °C at all times. Upon completion, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The two layers were separated and the aqueous layer

was extracted with Et_2O (2 x 5 mL). The organic layers were combined, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (35% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-2.3.58** (87 mg, 0.40 mmol, 81%) as a colourless oil. R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.33 – 7.21 (m, 5H, Ar-*H*), 6.03 (ddd, 1H, *J* = 16.5, 10.9, 6.9 Hz, H-4), 5.08 (dt, 1H, *J* = 10.9, 1.3 Hz, $H_{pro(E)}$-5), 5.07 (dt, 1H, *J* = 16.5, 1.3 Hz, $H_{pro(Z)}$-5), 3.99 (q, 1H, *J* = 7.4 Hz, H-3), 3.60 (s, 3H, NOC*H*$_3$), 3.14 (s, 3H, NC*H*$_3$), 2.90 (dd, 1H, *J* = 15.4, 8.2 Hz, H-2), 2.82 (dd, 1H, *J* = 15.4, 7.0 Hz, H'-2); δ_C (100 MHz, $CDCl_3$): 172.6 (C-1), 143.3 (Ar), 140.9 (C-4), 128.6 (Ar), 127.9 (Ar), 126.6 (Ar), 114.7 (C-5), 61.4 (NO*C*H_3), 45.0 (C-3), 37.6 (C-2), 32.2 (N*C*H_3). Characterisation data are consistent with literature values.[197]



(±)-2.3.57 **(±)-2.3.59** **(±)-2.4.44**

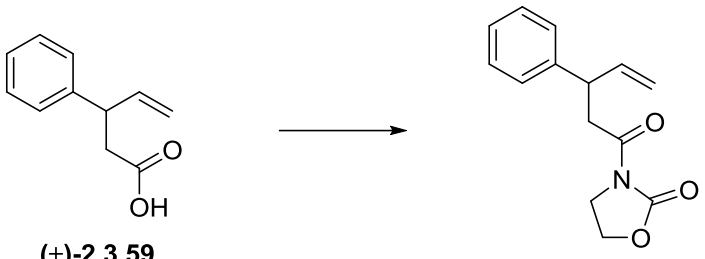
(±)-3-Phenylpent-4-enoic acid ((±)-2.3.59)



(±)-2.3.57 **(±)-2.3.59**

According to a modified procedure of Theodorou *et al*.:[214] A solution of ester **(±)-2.3.57** (300 mg, 1.47 mmol) and NaOH (88 mg, 2.2 mmol) in methanol (3.3 mL) and water (0.83 mL) was stirred at 75 °C under reflux. Upon completion, methanol was removed *in vacuo*. Water (10 mL) was added and the aqueous layer was washed by Et_2O (1 x 7 mL). To the aqueous layer was then added conc. HCl dropwise until pH = 2. The aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound **(±)-2.3.59** (188 mg, 1.07 mmol, 73%) as a pale yellow oil. R_f = 0.3 (35% EtOAc in $PE_{40\text{-}60}$ with 1% acetic acid); δ_H (400 MHz, $CDCl_3$): 7.34 – 7.29 (m, 2H, Ar-*H*), 7.24 – 7.19 (m, 3H, Ar-*H*), 5.98 (ddd, 1H, *J* = 16.9, 10.1, 6.9 Hz, H-4), 5.10 (dt, 1H, *J* = 10.1, 1.2 Hz, $H_{pro(E)}$-5), 5.09 (dt, 1H, *J* = 16.9, 1.2 Hz, $H_{pro(Z)}$-5), 3.86 (dt, 1H, *J* = 6.9, 7.3 Hz, H-3), 2.81 (dd, 1H, *J* = 15.6, 8.2 Hz, H-2), 2.75 (dd, 1H, *J* = 15.6, 7.1 Hz, H'-2). For the rest of the characterisation data please refer to acid **(±)-2.3.59** (page 246).

(±)-3-(3-Phenylpent-4-enoyl)oxazolidin-2-one ((±)-2.4.44)

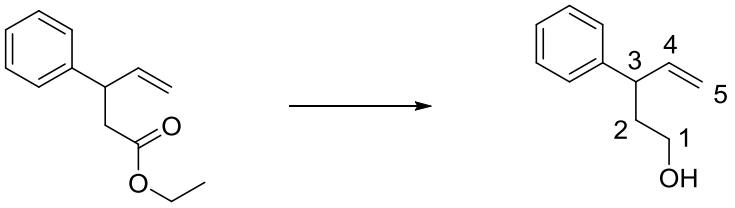


(±)-2.3.59 **(±)-2.4.44**

According to a modified procedure of Razdan *et al*.:[114] To a solution of acid **(±)-2.3.59** (90 mg, 0.51 mmol) in DCM (2.3 mL) at 0 °C was added DMF (cat. amount, 1 drop) followed by oxalyl chloride (0.05 mL, 0.6 mmol) dropwise over 1 min. Reaction mixture was stirred at 0 °C for 20 min and then at RT for 2 h. The mixture was then concentrated by blowing a stream of nitrogen and re-dissolved in THF (1.1 mL). This mixture was then added to a suspension of oxazolidin-2-one (133 mg, 1.53 mmol) in THF (2.2 mL). The reaction mixture was stirred at 75 °C under reflux for 22 h. The reaction was stopped before completion. Unreacted acid **2.3.59** was removed by washing the mixture with aq. NaOH solution (2 M, 1 x 10 mL). EtOAc (5 mL) was then added. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (100% DCM) to give the title compound **(±)-2.4.44** (17 mg, 0.072 mmol, 14%) as a colourless oil. R_f = 0.3 (40% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.33 – 7.19 (m, 5H, Ar-*H*), 6.03 (ddd, 1H, *J* = 17.0, 10.4, 7.1 Hz, C*H*=CH_2), 5.08 (dt, 1H, *J* = 17.0, 1.4 Hz, CH=$CH_{pro(E)}H_{pro(Z)}$), 5.07 (dt, 1H, *J* = 10.4, 1.1 Hz, CH=C$H_{pro(E)}H_{pro(Z)}$), 4.38 (dt, 1H, *J* = 14.0, 9.0 Hz, OCOCH_2), 4.33 (dt, 1H, *J* = 14.0, 9.1 Hz, OCOCH'_2), 4.01 – 3.89 (m, 3H, OCNCH_2 and PhC*H*CH=CH_2), 3.44 (dd, 1H,

J = 16.7, 7.1 Hz, PhCHC*H*$_2$), 3.39 (dd, 1H, *J* = 16.7, 7.7 Hz, PhCHC*H'*$_2$). For the rest of the characterisation data please refer to the enantioenriched imide **2.4.44** (page 281).

(±)-3-Phenylpent-4-en-1-ol ((±) 2.4.46)

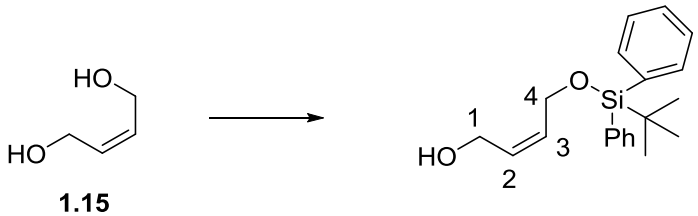


(±)-2.3.57 **(±)-2.4.46**

The title compound **(±)-2.4.46** was synthesised from ester **(±)-2.3.57** (150 mg, 0.734 mmol) using DIBAL-H (1M in hexane, 1.8 mL, 1.8 mmol) in THF (4.0 mL) according to general procedure A3. The crude product was purified by FC (47% Et_2O in $PE_{30\text{-}40}$) to give the title compound **(±)-2.4.46** (47 mg, 0.29 mmol, 39%) as a colourless oil. The yield in this case is low because only the pure fractions after FC were collected; yield does not matter in this case because the title compound **(±)-2.4.46** was only prepared for *ee* measurement. R_f = 0.3 (47% Et_2O in $PE_{30\text{-}40}$); δ_H (400 MHz, $CDCl_3$): 7.34 – 7.28 (m, 2H, Ar-*H*), 7.24 – 7.19 (m, 3H, Ar-*H*), 5.98 (ddd, 1H, *J* = 17.5, 10.2, 7.6 Hz, H-4), 5.09 (d, 1H, *J* = 17.5 Hz, $H_{pro(Z)}$-5), 5.06 (d, 1H, *J* = 10.2 Hz, $H_{pro(E)}$-5), 3.70 – 3.56 (m, 2H, H-1), 3.48 (q, 1H, *J* = 7.9 Hz, H-3), 2.08 – 1.92 (m, 2H, H-2); For the rest of the characterisation data please refer to the enantioenriched alcohol **2.4.46** (page 283).

4.4 Compound synthesis: experimental details (Chapter 3)

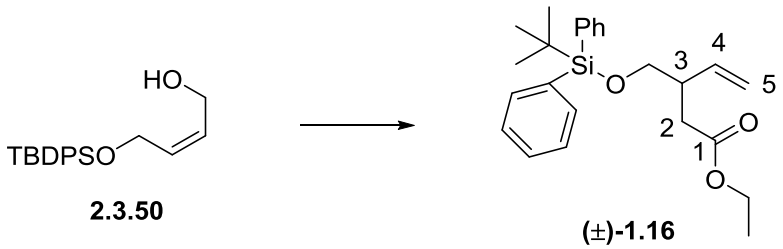
(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-ol (2.3.50)



According to the procedure of Ferrara:[3] To a solution of (*Z*)-2-butene-1,4-diol **1.15** (2.9 mL, 34 mmol) in THF (30 mL) at 0 °C was added sodium hydride (1.43 g, 35.8 mmol) slowly. The reaction mixture was warmed to RT and stirred for 45 min. To this mixture at 0 °C was added a solution of *tert*-butyl(chloro)diphenylsilane (8.9 mL, 34 mmol) in THF (12 mL) dropwise over 30 min. After complete addition, the reaction mixture was warmed to RT and stirred for 2 h. Upon completion, the reaction was quenched with brine (20 mL) and water (80 mL). The mixture was diluted with Et_2O (100 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound **2.3.50** (10.8 g, 33.1 mmol, 97%) as a pale yellow oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.72 – 7.69 (m, 4H, Ar-*H*), 7.48 – 7.38 (m, 6H, Ar-*H*), 5.73 (dtt, 1H, *J* = 11.2, 5.9, 1.3 Hz, H-3), 5.65 (dtt, 1H, *J* = 11.2, 6.2, 1.3 Hz, H-2), 4.28 (dd, 2H, *J* = 5.9, 1.3 Hz, H-4), 4.03 – 4.01 (m, 2H, H-1), 1.07 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 135.6 (Ar), 133.4 (Ar), 130.9 (C-3), 129.9 (C-2), 129.8 (Ar), 127.7 (Ar), 60.2 (C-4), 58.7

(C-1), 26.8 (SiC(CH_3)$_3$), 19.1 (SiC(CH$_3$)$_3$). Characterisation data are consistent with literature values.[3]

(±)-Ethyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate ((±)-1.16)

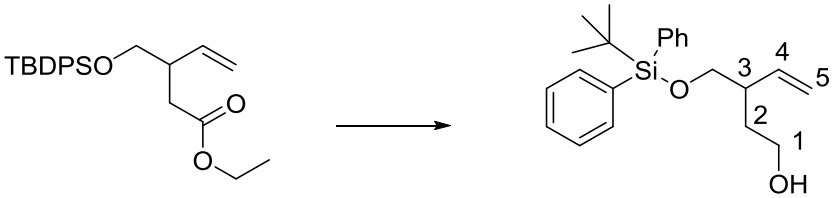


2.3.50 **(±)-1.16**

According to the procedure of Ferrara:[3] A mixture of alcohol **2.3.50** (1.00 g, 3.06 mmol), triethyl orthoacetate (3.9 mL, 21 mmol) and propionic acid (14 µL, 0.18 mmol) was stirred at 138 °C for 22 h, using setup for distillative removal of ethanol. Upon completion, sat. aq. NH_4Cl solution (10 mL) was added and the biphasic mixture was vigorously stirred for 20 min to hydrolyse the excess triethyl orthoacetate. The two layers were then separated and the aqueous layer was extracted with EtOAc (2 x 7 mL). The organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (7% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-1.16** (1.07 g, 2.70 mmol, 88%) as a colourless oil. R_f = 0.3 (7% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.72 – 7.63 (m, 4H, Ar-*H*), 7.47 – 7.39 (m, 6H, Ar-*H*), 5.75 (ddd, 1H, *J* = 17.2, 10.4, 7.8 Hz, H-4), 5.07 (dt, 1H, *J* = 17.2, 1.5 Hz, $H_{pro(Z)}$-5), 5.05 (ddd, 1H, *J* = 10.4, 1.5, 0.7 Hz, $H_{pro(E)}$-5), 4.11 (q, 2H, *J* = 7.1 Hz, OCOCH_2CH$_3$), 3.65 (dd, 1H, *J* = 9.9, 5.3 Hz, SiOCH_2), 3.56 (dd, 1H, *J* = 9.9, 6.7 Hz, SiOC*H'*$_2$), 2.80 (sext, 1H, *J* = 7.0 Hz, H-3), 2.67 (dd, 1H, *J* = 15.2, 5.7 Hz, H-2), 2.35

(dd, 1H, *J* = 15.2, 8.7 Hz, H'-2), 1.23 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 172.6 (C-1), 138.0 (C-4), 135.6 (Ar), 133.5 (Ar), 129.7 (Ar), 127.7 (Ar), 116.2 (C-5), 66.4 ($SiOCH_2$), 60.3 ($OCOCH_2CH_3$), 42.7 (C-3), 36.2 (C-2), 26.9 ($SiC(CH_3)_3$), 19.3 ($SiC(CH_3)_3$), 14.3 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[3]

(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol ((±)-1.4)

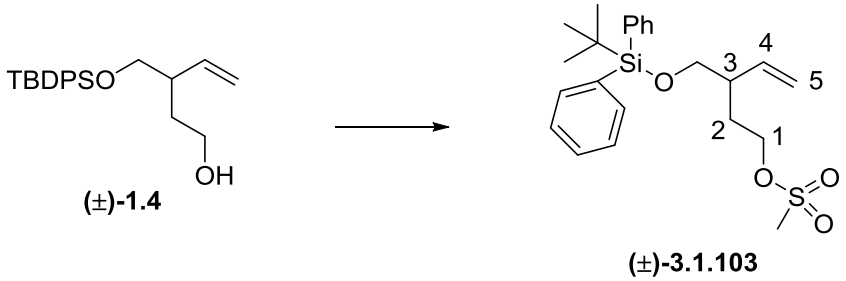


(±)-1.16 **(±)-1.4**

The title compound **(±)-1.4** was synthesised from ester **(±)-1.16** (4.50 g, 11.4 mmol) using DIBAL-H (1 M in hexane, 26.1 mL, 26.1 mmol) in THF (61 mL) according to general procedure A2. The crude product was purified by FC (22% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-1.4** (3.90 g, 11.0 mmol, 97%) as a colourless oil. R_f = 0.3 (25% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4H, Ar-*H*), 7.44 – 7.38 (m, 6H, Ar-*H*), 5.70 (ddd, 1H, *J* = 16.8, 10.9, 8.6 Hz, H-4), 5.05 (d, 1H, *J* = 16.8 Hz, $H_{pro(Z)}$-5), 5.04 (d, 1H, *J* = 10.9 Hz, $H_{pro(E)}$-5), 3.73 – 3.64 (m, 2H, H-1), 3.62 (dd, 1H, *J* = 10.1, 5.5 Hz, $SiOCH_2$), 3.59 (dd, 1H, *J* = 10.1, 6.6 Hz, $SiOCH'_2$), 2.39 (qt, 1H, *J* = 6.1, 5.7 Hz, H-3), 1.82 (ddt, 1H, *J* = 11.9, 7.5, 6.2 Hz, H-2), 1.63 (ddt, 1H, *J* = 11.9, 8.5, 6.0 Hz, H'-2), 1.06 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 140.2 (C-4), 136.2 (Ar), 134.1 (Ar), 130.3 (Ar), 128.2 (Ar), 116.6 (C-5), 68.0 (CH_2OSi), 61.8 (C-1), 44.4 (C-3), 35.0 (C-2), 27.4 ($SiC(CH_3)_3$), 19.9 ($SiC(CH_3)_3$);

ν_{max}/cm^{-1}: 3339 (br, O-H), 2858 (w, C-H), 1428 (w), 1112 (m), 702 (m); *m/z* (ESI$^+$): 355.1 ([M+H]$^+$, 90%), 377.3 ([M+Na]$^+$, 100%); accurate mass: found 377.1891, $C_{22}H_{30}NaO_2Si$ [M+Na]$^+$ requires 377.1907. Characterisation data are consistent with literature values.[3]

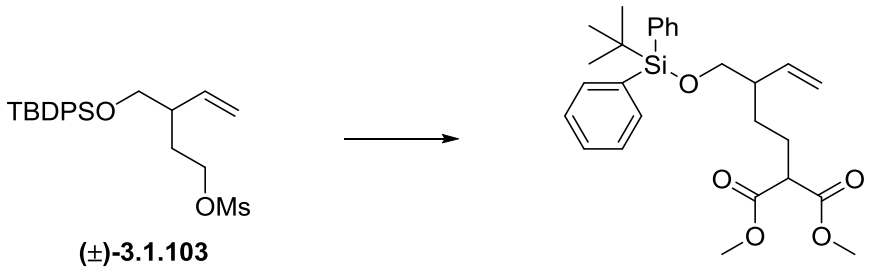
(±)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl methanesulfonate ((±)-3.1.103)



According to the procedure of Ferrara:[3] To a solution of alcohol **(±)-1.4** (5.00 g, 14.1 mmol) in DCM (47 mL) at 0 °C was added triethylamine (2.4 mL, 17 mmol) followed by dropwise addition of methanesulfonyl chloride (1.3 mL, 17 mmol). The reaction mixture was stirred at RT for 1.5 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl solution (50 mL) and aq. HCl solution (1 M, 4 mL). The two layers were separated and the aqueous layer was extracted with DCM (2 x 30 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ solution (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude title compound **(±)-3.1.103** (6.09 g, 14.1 mmol, 100% crude yield) as a colourless oil. The title compound is not stable on silica and thus, the crude was used in the next step without further purification. R_f = 0.5 (100% DCM); δ_H (400 MHz, $CDCl_3$): 7.68 –

7.64 (m, 4H, Ar-*H*), 7.46 – 7.37 (m, 6H, Ar-*H*), 5.67 (ddd, 1H, *J* = 17.1, 10.4, 8.6 Hz, H-4), 5.13 (dd, 1H, *J* = 10.4, 1.5 Hz, $H_{pro(E)}$-5), 5.13 (ddd, 1H, *J* = 17.1, 1.5, 0.9 Hz, $H_{pro(Z)}$-5), 4.33 – 4.18 (m, 2H, H-1), 3.65 (dd, 1H, *J* = 10.0, 5.3 Hz, SiOCH_2), 3.60 (dd, 1H, *J* = 10.0, 6.3 Hz, SiOCH'_2), 2.97 (s, 3H, OSO_2CH_3), 2.41 (sext, 1H, *J* = 5.3 Hz, H-3), 2.11 (dddd, 1H, *J* = 14.1, 8.2, 7.1, 4.5 Hz, H-2), 1.75 (dddd, 1H, *J* = 14.1, 9.8, 6.4, 5.2 Hz, H'-2), 1.07 (s, 9H, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$): 138.2 (C-4), 135.8 (Ar), 133.6 (Ar), 129.9 (Ar), 127.9 (Ar), 117.5 (C-5), 68.6 (C-1), 67.1 (SiOCH_2), 43.0 (C-3), 37.5 (OSO_2CH_3), 30.5 (C-2), 27.0 (SiC(CH_3)$_3$), 19.5 (SiC(CH_3)$_3$). Characterisation data are consistent with literature values.[3]

(±)-Dimethyl 2-(3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl)malonate ((±)-3.1.75)

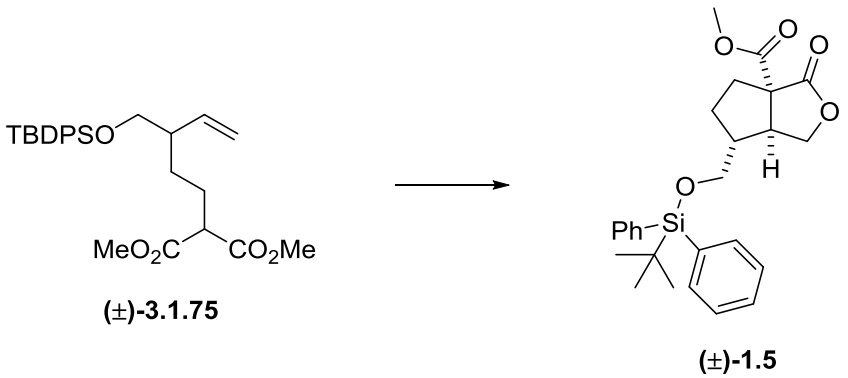


(±)-3.1.103 **(±)-3.1.75**

According to the procedure of Ferrara:[3] To a stirred suspension of sodium hydride (60%, 1.35 g, 33.8 mmol) in THF (40 mL) at 0 °C was added dimethylmalonate (4.0 mL, 35 mmol). The reaction mixture was stirred at RT for 15 min. To this mixture at 0 °C was added a solution of mesylate **(±)-3.1.103** (6.10 g, 14.1 mmol) in THF (35 mL) followed by potassium iodide (1.17 g, 7.05 mmol). The reaction mixture was warmed to RT and then stirred under reflux at 80 °C for 9 h. Upon

completion, the mixture was cooled to RT and quenched with sat. aq. NH_4Cl solution (60 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The organic layers were combined, sequentially washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by FC (13% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.1.75** (5.40 g, 11.5 mmol, 82% over two steps) as a colourless oil. R_f = 0.3 (13% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.66 – 7.63 (m, 4H, Ar-*H*), 7.43 – 7.35 (m, 6H, Ar-*H*), 5.62 (ddd, 1H, *J* = 17.0, 10.6, 8.5 Hz, C*H*=CH_2), 5.09 – 5.00 (m, 2H, CH=C*H*$_2$), 3.72 (s, 6H, OCOC*H*$_3$), 3.59 (dd, 1H, *J* = 9.9, 5.8 Hz, SiOC*H*$_2$), 3.53 (dd, 1H, *J* = 9.9, 6.4 Hz, SiOC*H'*$_2$), 3.34 (t, 1H, *J* = 7.6 Hz, C*H*$(OCOCH_3)_2$), 2.27 – 2.17 (m, 1H, $SiOCH_2CH$), 1.95 (dddd, 1H, *J* = 13.7, 11.2, 7.7, 4.9 Hz, $SiOCH_2CHCH_2$), 1.82 (dddd, 1H, *J* = 13.7, 11.0, 7.4, 5.6 Hz, $SiOCH_2CHCH'_2$), 1.66 – 1.55 (m, 1H, C*H*$_2CH(CO_2CH_3)_2$), 1.34 – 1.28 (m, 1H, C*H'*$_2CH(CO_2CH_3)_2$), 1.04 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 169.8 (*C*=O), 139.1 (*C*H=CH_2), 135.6 (Ar), 133.7 (Ar), 129.6 (Ar), 127.6 (Ar), 116.4 (CH=*C*H_2), 67.0 ($SiOCH_2$), 52.4 ($OCOCH_3$), 51.8 (*C*$H(CO_2CH_3)_2$), 46.3 ($SiOCH_2CH$), 28.4 ($CH_2CH(CO_2CH_3)_2$), 26.8 ($SiC(CH_3)_3$), 26.5 ($SiOCH_2CHCH_2$), 19.3 ($SiC(CH_3)_3$). Characterisation data are consistent with literature values.[3]

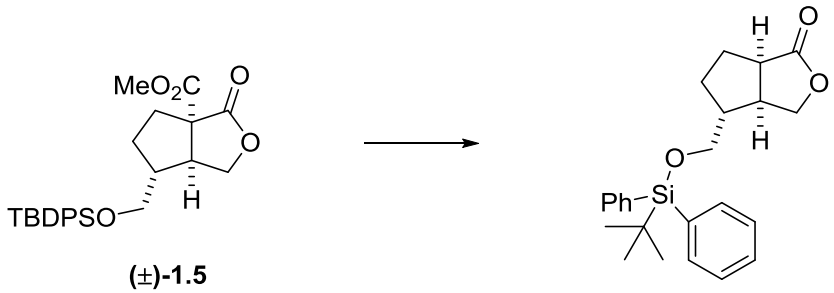
(±)-Methyl (3a*R*,6*R*,6a*S*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3H)-carboxylate ((±)-1.5)



According to the procedure of Ferrara:[3] To a mixture of manganese(III) acetate dihydrate (6.18 g, 23.0 mmol) and copper(II) triflate (4.17 g, 11.5 mmol) under argon at 80 °C was added a solution of malonate **(±)-3.1.75** (5.40 g, 11.5 mmol) in argon-sparged acetonitrile (135 mL). The resulting mixture was stirred at 80 °C for 5.5 h. Upon completion, the mixture was filtered through a silica plug eluting with Et_2O (400 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by FC (15% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-1.5** (4.00 g, 8.84 mmol, 77%) as a colourless oil. R_f = 0.3 (15% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.64 – 7.61 (m, 4H, Ar-*H*), 7.47 – 7.36 (m, 6H, Ar-*H*), 4.49 (dd, 1H, *J* = 9.2, 6.8 Hz, OCOCH_2), 4.25 (dd, 1H, *J* = 9.2, 1.6 Hz, OCOCH'_2), 3.77 (s, 3H, OCOCH_3), 3.70 (dd, 1H, *J* = 10.3, 5.6 Hz, SiOCH_2), 3.55 (dd, 1H, *J* = 10.3, 7.4 Hz, SiOCH'_2), 2.86 (td, 1H, *J* = 7.1, 1.6 Hz, $OCOCH_2CH$), 2.54 (ddd, 1H, *J* = 13.8, 8.2, 5.5 Hz, $CH_3OC(O)CCH_2$), 2.19 – 2.08 (m, 2H, $CH_3OC(O)CCH'_2$ and $SiOCH_2CH$), 1.79 (ddt, 1H, *J* = 14.1, 7.1, 5.5 Hz, $SiOCH_2CHCH_2$), 1.64 – 1.55 (m, 1H, $SiOCH_2CHCH'_2$), 1.05 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 176.4 (*C*=O, lactone), 170.3 (*C*=O, ester), 135.5 (Ar), 133.2 (Ar), 129.8 (Ar), 127.8 (Ar), 72.0 ($OCOCH_2$), 65.7 ($SiOCH_2$),

61.4 ($CH_3OC(O)C$), 53.1 (CH_3OCO), 50.0 ($OCOCH_2CH$), 49.6 ($SiOCH_2CH$), 32.7 ($CH_3OC(O)CCH_2$), 29.1 ($SiOCH_2CHCH_2$), 26.8 ($SiC(CH_3)_3$), 19.2 ($SiC(CH_3)_3$); ν_{max}/cm^{-1}: 2955 (m, C-H), 2858 (m, C-H), 1777 (s, C=O, lactone), 1743 (s, C=O, ester), 1111 (s), 703 (s). Characterisation data are consistent with literature values.[3]

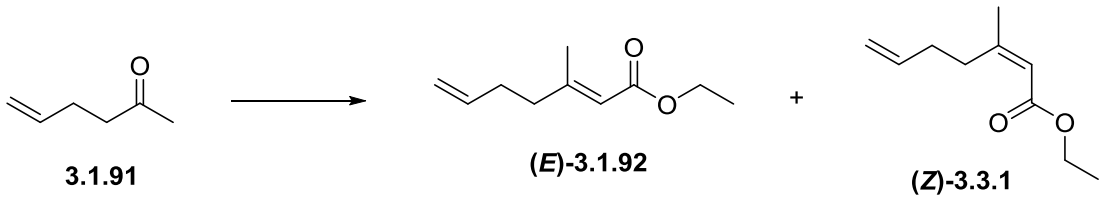
(±)-(3a*S*,4*R*,6a*R*)-4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one ((±)-3.1.104)



(±)-1.5 **(±)-3.1.104**

According to the procedure of Ferrara:[3] A mixture of lactone **(±)-1.5** (2.00 g, 4.42 mmol) and lithium chloride (374 mg, 8.84 mmol) in water (0.48 mL, 27 mmol) and DMF (8.8 mL) was stirred at 150 °C for 2 h. Upon completion, sat. aq. NH_4Cl solution (10 mL) and EtOAc (4 mL) were added. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 6 mL). The organic layers were combined, sequentially washed with water (2 x 10 mL), 30% aq. LiCl solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC (20% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.1.104** (1.33 g, 3.37 mmol, 76%) as a colourless oil. R_f = 0.3 (20% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.66 – 7.62 (m, 4H, Ar-*H*), 7.48 – 7.37 (m, 6H, Ar-*H*), 4.39 (dd, 1H, *J* = 9.4, 7.3 Hz, $OCOCH_2$), 4.18 (dd, 1H, *J* = 9.4, 2.4 Hz,

OCOC*H'*$_2$), 3.67 (dd, 1H, *J* = 10.2, 5.8 Hz, SiOC*H*$_2$), 3.54 (dd, 1H, *J* = 10.2, 7.2 Hz, SiOC*H'*$_2$), 3.00 (td, 1H, *J* = 9.5, 4.3 Hz, C*H*OCO), 2.69 (dtd, 1H, *J* = 9.5, 7.0, 2.4 Hz, OCOCH$_2$C*H*), 2.12 – 2.02 (m, 2H, SiOCH$_2$CHCH$_2$C*H*$_2$ and SiOCH$_2$C*H*), 2.02 – 1.94 (m, 1H, SiOCH$_2$CHCH$_2$C*H'*$_2$), 1.77 (dq, 1H, *J* = 13.6, 7.0 Hz, SiOCH$_2$CHC*H*$_2$), 1.57 – 1.46 (m, 1H, SiOCH$_2$CHC*H'*$_2$), 1.06 (s, 9H, SiC(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$): 180.9 (*C*=O), 135.5 (Ar), 133.4 (Ar), 129.8 (Ar), 127.7 (Ar), 72.3 (OCO*C*H$_2$), 65.9 (SiO*C*H$_2$), 48.9 (SiOCH$_2$*C*H), 44.5 (*C*HCO$_2$), 43.5 (OCOCH$_2$*C*H), 29.1 (SiOCH$_2$CH*C*H$_2$), 28.4 (SiOCH$_2$CHCH$_2$*C*H$_2$), 26.9 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$). Characterisation data are consistent with literature values.[3]



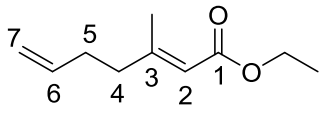
3.1.91 **(*E*)-3.1.92** **(*Z*)-3.3.1**

According to the procedure of Ferrara:[3] To a solution of triethyl phosphonoacetate (18.0 mL, 81.5 mmol) in THF (204 mL) at -78 °C was added *n*BuLi (2.4 M in hexane, 40.8 mL, 97.8 mmol) dropwise over 1 h. The resulting mixture was warmed to RT and stirred for 2 h. After cooling back to -78 °C, a solution of hex-5-en-2-one **3.1.91** (8.00 g, 81.5 mmol) in THF (36 mL) was slowly added to the above reaction mixture. The resulting mixture was warmed to RT and stirred for 22 h. Upon completion, sat. aq. NH_4Cl solution (300 mL) and Et_2O (50 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 200 mL). The organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (no heating, substrate is volatile). The crude

product was purified by FC (4% Et_2O in pentane) to give a partially separable mixture of esters **(*E*)-3.1.92** and **(*Z*)-3.3.1** (*E* to *Z* ratio 3 : 1, 10.1 g, 60.0 mmol, combined yield 74%) as colourless oils. Characterisation of each isomer is reported below.

E-isomer:

(*E*)-Ethyl 3-methylhepta-2,6-dienoate ((*E*)-3.1.92)

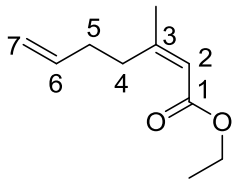


(*E*)-3.1.92

R_f = 0.33 (4% Et_2O in pentane); δ_H (500 MHz, $CDCl_3$): 5.84 – 5.74 (m, 1H, H-6), 5.66 (q, 1H, *J* = 1.3 Hz, H-2), 5.04 (ddt, 1H, *J* = 16.6, 1.6, 1.4 Hz, $H_{pro(Z)}$-7), 4.98 (dd, 1H, *J* = 10.2, 1.6 Hz, $H_{pro(E)}$-7), 4.14 (q, 2H, *J* = 7.1 Hz, OCOCH_2), 2.24 – 2.23 (m, 4H, H-4 and H-5), 2.16 (d, 3H, *J* = 1.3 Hz, $CH_2C(CH_3)$=CH), 1.27 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$); δ_C (125 MHz, $CDCl_3$): 166.8 (C-1), 159.0 (C-3), 137.3 (C-6), 115.9 (C-2), 115.3 (C-7), 59.5 ($OCOCH_2$), 40.1 (C-4), 31.5 (C-5), 18.7 ($CH_2C(CH_3)$=CH), 14.3 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[3]

Z-isomer:

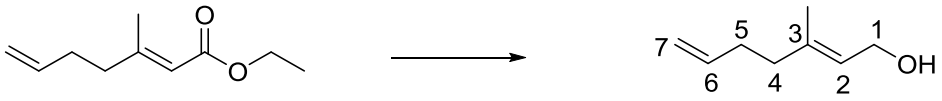
(*Z*)-Ethyl 3-methylhepta-2,6-dienoate ((*Z*)-3.3.1)



(*Z*)-3.3.1

R_f = 0.37 (4% Et_2O in pentane); δ_H (500 MHz, $CDCl_3$): 5.84 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, H-6), 5.67 (s, 1H, H-2), 5.05 (ddt, 1H, *J* = 17.1, 1.8, 1.5 Hz, $H_{pro(Z)}$-7), 4.97 (ddt, 1H, *J* = 10.2, 1.8, 1.3 Hz, $H_{pro(E)}$-7), 4.14 (q, 2H, *J* = 7.1 Hz, OCOCH_2), 2.72 (t, 2H, *J* = 7.4 Hz, H-4), 2.24 (dtt, 2H, *J* = 7.9, 6.6, 1.4 Hz, H-5), 1.89 (d, 3H, *J* = 1.4 Hz, $CH_2C(CH_3)$=CH), 1.27 (t, 3H, *J* = 7.1 Hz, $OCOCH_2CH_3$); δ_C (125 MHz, $CDCl_3$): 166.3 (C-1), 159.5 (C-3), 137.9 (C-6), 116.5 (C-2), 114.8 (C-7), 59.5 ($OCOCH_2$), 32.7 (C-4), 32.2 (C-5), 25.2 ($CH_2C(CH_3)$=CH), 14.3 ($OCOCH_2CH_3$). Characterisation data are consistent with literature values.[3]

(*E*)-3-Methylhepta-2,6-dien-1-ol ((*E*)-3.1.93)

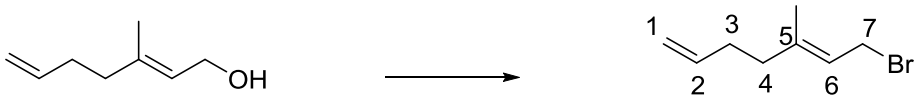


(*E*)-3.1.92 **(*E*)-3.1.93**

According to the procedure of Ferrara[3]: To a solution of ester **(*E*)-3.1.92** (2.10 g, 12.5 mmol) in THF (73 mL) at -78 °C was added DIBAL-H (1 M in hexane, 28.7 mL, 28.7 mmol) dropwise over 1.5 h. The reaction mixture was stirred at -78 °C for 1 h before warming to 0 °C and stirred for a further 1 h. Upon completion, the reaction

was quenched with sat. aq. potassium sodium tartrate solution (70 mL) at 0 °C and diluted with Et_2O (30 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 40 mL). The organic layers were combined, washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* (no heating, substrate is volatile). The crude product was purified by FC (44% to 60% Et_2O in $PE_{30\text{-}40}$) to give the title compound **(*E*)-3.1.93** (1.50 g, 11.9 mmol, 95%) as a colourless oil. R_f = 0.25 (44% Et_2O in $PE_{30\text{-}40}$); δ_H (500 MHz, $CDCl_3$): 5.80 (ddt, 1H, *J* = 16.9, 10.2, 6.5 Hz, H-6), 5.43 (tsext, 1H, *J* = 7.0, 1.3 Hz, H-2), 5.02 (dq, 1H, *J* = 17.1, 1.6 Hz, $H_{pro(Z)}$-7), 4.95 (ddt, 1H, *J* = 10.2, 2.0, 1.3 Hz, $H_{pro(E)}$-7), 4.15 (t, 2H, *J* = 6.0 Hz, H-1), 2.23 – 2.15 (m, 2H, H-5), 2.12 – 2.09 (m, 2H, H-4), 1.68 (s, 3H, $CH_2C(CH_3)$=CH); δ_C (125 MHz, $CDCl_3$): 139.2 (C-3), 138.2 (C-6), 123.6 (C-2), 114.6 (C-7), 59.4 (C-1), 38.8 (C-4), 31.9 (C-5), 16.2 ($CH_2C(CH_3)$=CH). Characterisation data are consistent with literature values.[3]

(*E*)-7-Bromo-5-methylhepta-1,5-diene ((*E*)-3.1.94)

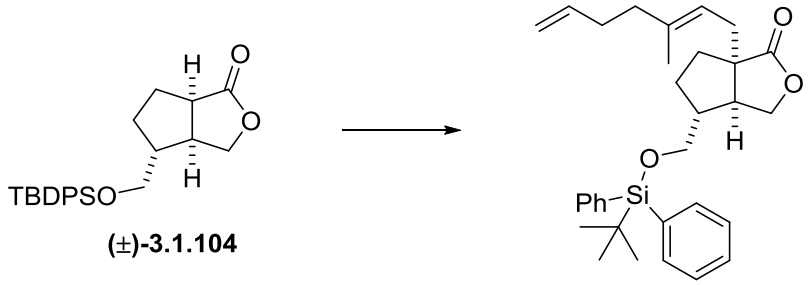


(*E*)-3.1.93 **(*E*)-3.1.94**

According to the procedure of Ferrara:[3] To a solution of **(*E*)-3.1.93** (1.20 g, 9.51 mmol) in THF (32 mL) at 0 °C was added triethylamine (2.8 mL, 20 mmol) followed by dropwise addition of methanesulfonyl chloride (1.0 mL, 13 mmol) over 30 min. The reaction mixture was stirred at 0 °C for another 2 h. To this mixture at 0 °C was added lithium bromide (4.13 g, 47.6 mmol) portionwise. The reaction

mixture was stirred at 0 °C for 1.5 h. Upon completion, the reaction was quenched by sat. aq. NH_4Cl solution (30 mL). Et_2O (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layers were combined, sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (no heating, product is volatile). The title compound **(*E*)-3.1.94** is not stable on silica and thus, the crude product was used in the next step without further purification. R_f = 0.6 (50% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.77 (ddt, 1H, *J* = 17.1, 10.2, 6.4 Hz, H-2), 5.54 (tsext, 1H, *J* = 8.4, 1.3 Hz, H-6), 5.02 (ddt, 1H, *J* = 17.1, 1.9, 1.5 Hz, $H_{pro(Z)}$-1), 4.97 (ddt, 1H, *J* = 10.2, 1.9, 1.1 Hz, $H_{pro(E)}$-1), 4.02 (d, 2H, *J* = 8.4 Hz, H-7), 2.22 – 2.17 (m, 2H, H-3), 2.16 – 2.10 (m, 2H, H-4), 1.73 (d, 3H, *J* = 1.2 Hz, $CH_2C(CH_3)$=CH). Characterisation data are consistent with literature values.[3]

(±)-(3a*S*,4*R*,6a*S*)-4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-6a-((*E*)-3-methylhepta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one ((±)-3.1.105)



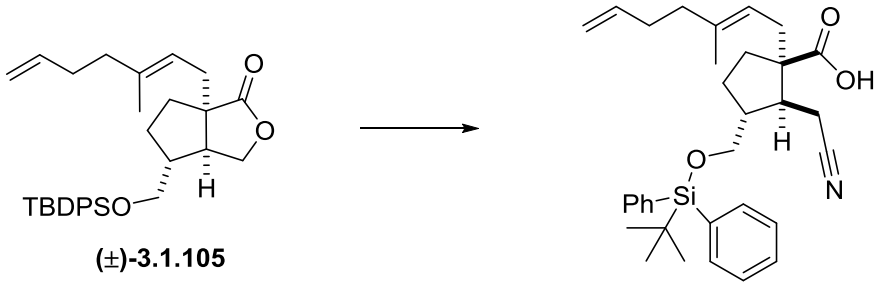
(±)-3.1.104 **(±)-3.1.105**

According to the procedure of Ferrara:[3] To a solution of lactone **(±)-3.1.104** (245 mg, 0.621 mmol) in THF (11 mL) at -78 °C was added a solution of bromide **(*E*)-3.1.94**

(235 mg, 1.24 mmol) in THF (1.5 mL). Lithium bis(trimethylsilyl)amide (1 M in toluene, 1.24 mL, 1.24 mmol) was then added dropwise at -78 °C over 2 h. The reaction mixture was stirred at -78 °C for another 2 h. Upon completion, the reaction mixture was poured over sat. aq. NH_4Cl solution (70 mL). EtOAc (20 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by FC (8% to 10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.1.105** (190 mg, 0.379 mmol, 61%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 7.64 – 7.62 (m, 4H, Ar-*H*), 7.46 – 7.37 (m, 6H, Ar-*H*), 5.76 (ddt, 1H, *J* = 17.1, 10.1, 6.3 Hz, CH_2=C*H*), 5.09 (tsext, 1H, *J* = 7.3, 1.2 Hz, $CH_2(CH_3)C$=C*H*), 5.00 (dq, 1H, *J* = 17.1, 1.6 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 4.93 (ddt, 1H, *J* = 10.1, 2.2, 1.1 Hz, C$H_{pro(E)}H_{pro(Z)}$=CH), 4.24 (dd, 1H, *J* = 9.3, 7.1 Hz, OCOCH_2), 4.09 (dd, 1H, *J* = 9.3, 1.9 Hz, OCOCH'_2), 3.65 (dd, 1H, *J* = 10.2, 5.8 Hz, SiOCH_2), 3.53 (dd, 1H, *J* = 10.2, 7.2 Hz, SiOCH'_2), 2.46 (dd, 1H, *J* = 14.3, 7.2 Hz, C=CHCH_2C(CH_2)CO_2), 2.36 (td, 1H, *J* = 7.0, 1.9 Hz, OCOCH_2C*H*), 2.24 (dd, 1H, *J* = 14.3, 8.2 Hz, C=CHCH'_2C(CH_2)CO_2), 2.18 – 2.00 (m, 6H, SiOCH_2C*H* and 2 x CH_2 side chain and SiOCH_2CHCH_2CH_2), 1.79 – 1.66 (m, 2H, SiOCH_2CHCH_2 and SiOCH_2CHCH_2CH'_2), 1.61 (d, 3H, *J* = 0.7 Hz, CH_2C(CH_3)=CH), 1.49 (dd, 1H, *J* = 12.7, 7.7 Hz, SiOCH_2CHCH'_2), 1.05 (s, 9H, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$): 183.0 (*C*=O), 139.0 (CH_2=*C*H), 138.2 (CH_2*C*(CH_3)=CH), 135.5 (Ar), 133.4 (Ar), 129.8 (Ar), 127.7 (Ar), 118.7 ($CH_2C(CH_3)$=*C*H), 114.6 (*C*H_2=CH), 71.8 (OCO*C*H_2), 65.8 (SiO*C*H_2), 55.7 (CH_2*C*(CH)OCO), 50.3 (SiOCH_2*C*H), 47.2 (OCOCH_2*C*H), 39.2 (CH_2=CHCH_2*C*H_2), 35.4 (SiOCH_2CHCH_2*C*H_2), 34.7 (*C*H_2C(CH_2)OCO), 32.2

(CH_2=CHCH_2), 28.5 (SiOCH_2CHCH_2), 26.8 (SiC(CH_3)$_3$), 19.2 (SiC(CH_3)$_3$), 16.3 (CH_2C(CH_3)=CH). Characterisation data are consistent with literature values.[3]

(±)-(1*S*,2*S*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-(cyanomethyl)-1-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentane-1-carboxylic acid ((±)-1.17)

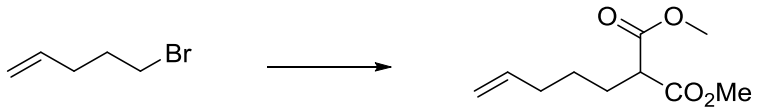


(±)-3.1.105 **(±)-1.17**

According to the procedure of Ferrara:[3] To a stirred solution of lactone **(±)-3.1.105** (900 mg, 1.79 mmol) in DMSO (36 mL) at RT was added potassium cyanide (583 mg, 8.95 mmol). The reaction mixture was stirred at 185 °C for 1.5 h. Upon completion, the reaction mixture was cooled to RT. EtOAc (20 mL) was added and sat. aq. NH_4Cl solution (30 mL) was added dropwise. *CAUTION gaseous HCN given off* The biphasic mixture was vigorously stirred for 20 min before adding aq. HCl solution (1 M, 20 mL). The mixture was gently swirled and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The organic layers were combined and washed with brine (1 x 30 mL). The brine layer was re-extracted with EtOAc (1 x 20 mL). All of the organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by FC (2% - 4% MeOH in DCM) to give the title compound **(±)-1.17** (703 mg, 1.33 mmol, 74%) as a pale yellow oil. R_f = 0.3 (4% MeOH in DCM); δ_H (400 MHz,

$CDCl_3$): 7.67 – 7.63 (m, 4H, Ar-*H*), 7.44 – 7.40 (m, 6H, Ar-*H*), 5.75 (ddt, 1H, *J* = 16.8, 10.2, 6.3 Hz, CH_2=C*H*), 5.13 (t, 1H, *J* = 7.5 Hz, $CH_2C(CH_3)$=C*H*), 4.98 (dq, 1H, *J* = 16.8, 1.5 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 4.92 (d, 1H, *J* = 10.2 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 3.70 (dd, 1H, *J* = 10.2, 4.0 Hz, SiOCH_2), 3.64 (dd, 1H, *J* = 10.2, 4.8 Hz, SiOCH'_2), 2.69 (dd, 1H, *J* = 14.0, 6.8 Hz, $CH_2C(CH_3)$=CHCH_2C), 2.61 (dd, 1H, *J* = 17.5, 5.6 Hz, CH_2CN), 2.53 (dd, 1H, *J* = 17.5, 6.7 Hz, CH'_2CN), 2.23 (dd, 1H, *J* = 14.0, 7.7 Hz, $CH_2C(CH_3)$=CHCH'_2C), 2.17 – 2.05 (m, 7H, 2 x side chain CH_2, $SiOCH_2CH$, C*H*CH_2CN, and $SiOCH_2CHCH_2CH_2$), 1.97 – 1.88 (m, 1H, $SiOCH_2CHCH_2$), 1.63 (s, 3H, $CH_2C(CH_3)$=CH), 1.60 – 1.50 (m, 2H, $SiOCH_2CHCH'_2$ and $SiOCH_2CHCH_2CH'_2$), 1.07 (s, 9H, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$): 180.5 (*C*=O), 138.6 ($CH_2C(CH_3)$=CH), 138.5 (CH_2=*C*H), 135.8 (Ar), 133.5 (Ar), 133.3 (Ar), 130.0 (Ar, doublet), 127.9 (Ar, doublet), 119.5 (*C*≡N), 114.7 (CH_2=CH), 65.7 ($SiOCH_2$), 57.3 (*C*C(O)OH), 46.3 (*C*HCH_2CN), 46.2 ($SiOCH_2CH$), 39.4 ($CH_2C(CH_3)$=CH), 35.7 ($CH_2C(CH_3)$=CHCH_2), 33.5 ($SiOCH_2CHCH_2CH_2$), 32.4 (CH_2=$CHCH_2$), 27.1 ($SiC(CH_3)_3$), 26.2 ($SiOCH_2CHCH_2$), 19.4 ($SiC(CH_3)_3$), 18.3 (CH_2CN), 16.5 ($CH_2C(CH_3)$=CH); ν_{max}/cm^{-1}: 2931 (m, C-H), ≈ 2900 (broad, w, O-H, H-bonded), 2858 (m, C-H), 2248 (w, C≡N), 1696 (s, C=O), 1428 (m), 1112 (s), 702 (s); *m/z* (ESI^+): 528.3 ($[M-H]^-$, 100%). Characterisation data are consistent with literature values.[3]

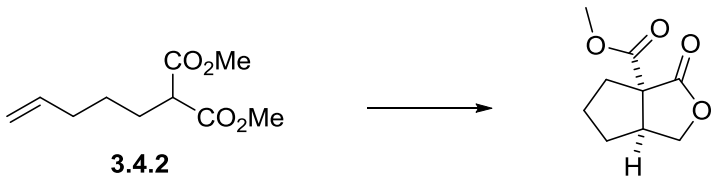
Dimethyl 2-(pent-4-en-1-yl)malonate (3.4.2)



3.4.1 **3.4.2**

According to the procedure of Ferrara:[3] To a suspension of sodium hydride (4.83 g, 121 mmol) in DMF (101 mL) at 0 °C was added dimethyl malonate (13.8 mL, 121 mmol) dropwise over 10 min. The reaction mixture was stirred at 0 °C for 30 min. To the above mixture at 0 °C was added a solution of 5-bromo-1-pentene **3.4.1** (4.8 mL, 40 mmol) in THF (101 mL) *via* cannula. The reaction mixture was stirred at 80 °C for 2 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (150 mL) and water (50 mL) and diluted with $PE_{40\text{-}60}/Et_2O$ (10/1, 100 mL). The two layers were separated and the aqueous layer was extracted with $PE_{40\text{-}60}/Et_2O$ (10/1, 3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (product is volatile). The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **3.4.2** (5.71 g, 29.2 mmol, 71%) as a colourless oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.77 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, CH_2=C*H*), 5.02 (dq, 1H, *J* = 16.9, 1.8 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 5.00 (ddt, 1H, *J* = 10.2, 1.8, 1.2 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 3.74 (s, 6H, OCH_3), 3.37 (t, 1H, *J* = 7.6 Hz, $CHC(O)OCH_3$), 2.08 (q, 1H, *J* = 7.0 Hz, CH_2=CHCH_2), 1.91 (td, 2H, *J* = 8.3, 7.6 Hz, $CH_2CHC(O)OCH_3$), 1.41 (tt, 2H, *J* = 8.3, 7.7 Hz, CH_2=$CHCH_2CH_2$); δ_C (100 MHz, $CDCl_3$): 169.9 (*C*=O), 137.9 (CH_2=*C*H), 115.1 (*C*H_2=CH), 52.5 (OCH_3), 51.6 ($CHC(O)OCH_3$), 33.3 (CH_2=CH*C*H_2), 28.3 ($CH_2CHC(O)OCH_3$), 26.6 (CH_2=$CHCH_2CH_2$). Characterisation data are consistent with literature values.[3]

(±)-Methyl (3a*R*,6a*S*)-3-oxotetrahydro-1H-cyclopenta[*c*]furan-3a(3*H*)-carboxylate ((±)-3.4.3)

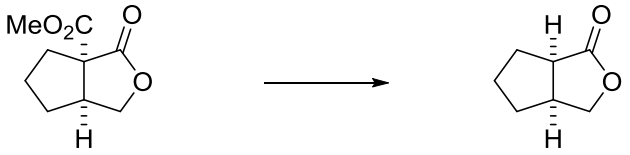


3.4.2 **(±)-3.4.3**

According to the procedure of Ferrara:[3] To a three-neck reaction vessel was added manganese(III) acetate dihydrate (14.5 g, 53.9 mmol) and copper(II) triflate (9.81 g, 27.0 mmol). The reaction vessel was degassed with argon. To the above mixture at RT under argon was added a solution of malonate **3.4.2** (5.39 g, 27.0 mmol) in argon-sparged acetonitrile (135 mL). The resulting mixture was stirred at 80 °C under argon for 22 h. Upon completion, the mixture was cooled to RT. Aq. HCl solution (1 M, 100 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined, sequentially washed with sat. aq. $NaHCO_3$ solution (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (60% Et_2O in $PE_{40\text{-}60}$) to give the title compound **(±)-3.4.3** (4.48 g, 24.3 mmol, 90%) as a colourless oil. R_f = 0.3 (60% Et_2O in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 4.52 (dd, 1H, *J* = 9.2, 7.6 Hz, OCOC*H*$_2$), 4.04 (dd, 1H, *J* = 9.2, 2.5 Hz, OCOC*H'*$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.14 – 3.01 (m, 1H, $OCOCH_2CH$), 2.34 (ddd, 1H, *J* = 13.4, 9.3, 7.3 Hz, $CH_3OC(O)CCH_2$), 2.25 – 2.19 (m, 1H, $CH_3OC(O)CCH'_2$), 2.11 – 1.95 (m, 1H, $OCOCH_2CHCH_2$), 1.86 – 1.74 (m, 1H, $OCOCH_2CHCH_2CH_2$), 1.68 – 1.54 (m, 2H, $OCOCH_2CHCH'_2$ and $OCOCH_2CHCH_2CH'_2$); δ_C (100 MHz, $CDCl_3$): 176.5 (*C*=O, lactone), 170.5 (*C*=O, ester), 73.1 ($OCOCH_2$), 61.6

($CH_3OC(O)C$), 53.1 (OCH_3), 45.6 ($OCOCH_2CH$), 34.7 ($CH_3OC(O)CCH_2$), 34.1 ($OCOCH_2CHCH_2$), 25.9 ($OCOCH_2CHCH_2CH_2$). Characterisation data are consistent with literature values.[3]

(±)-(3a*S*,6a*R*)-Hexahydro-1*H*-cyclopenta[*c*]furan-1-one ((±)-3.4.4)

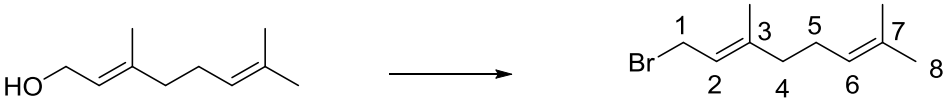


(±)-3.4.3 **(±)-3.4.4**

According to the procedure of Ferrara:[3] To a stirred solution of lactone **(±)-3.4.3** (4.20 g, 22.8 mmol) in DMF (46 mL) at RT was added water (0.82 mL) and LiCl (1.93 g, 45.6 mmol). The reaction mixture was stirred at 150 °C for 6 h. Upon completion, sat. aq. NH_4Cl solution (50 mL) and EtOAc (50 mL) were added. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, sequentially washed with water (2 x 100 mL), 30% aq. LiCl solution (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (do not heat the water bath nor reduce the pressure less than 200 mbar as the title compound **(±)-3.4.4** is very volatile). The crude product was purified by FC (70% Et_2O in $PE_{30\text{-}40}$) to give the title compound **(±)-3.4.4** in a lot of solvent (3.33 g) (yield will be calculated in the next step due to the volatility of title compound **(±)-3.4.4**). R_f = 0.3 (70% Et_2O in $PE_{30\text{-}40}$); δ_H (400 MHz, $CDCl_3$): 4.40 (dd, 1H, *J* = 9.4, 7.7 Hz, $OCOCH_2$), 3.92 (dd, 1H, *J* = 9.4, 3.1 Hz, $OCOCH'_2$), 2.94 (td, 1H, *J* = 9.2, 2.5 Hz, $CHCO_2$), 2.90 – 2.87 (m, 1H, $OCOCH_2CH$), 2.05 – 1.96 (m, 1H, CH_2CHCO_2), 1.91 – 1.78 (m, 2H, CH'_2CHCO_2

and $OCOCH_2CHCH_2$), 1.70 – 1.61 (m, 1H, $OCOCH_2CHCH_2CH_2$), 1.58 – 1.43 (m, 2H, $OCOCH_2CHCH_2CH'_2$ and $OCOCH_2CHCH'_2$); δ_C (100 MHz, $CDCl_3$): 181.1 (*C*=O), 73.6 ($OCOCH_2$), 44.5 ($CHCO_2$), 38.9 ($OCOCH_2CH$), 33.7 ($OCOCH_2CHCH_2$), 30.7 (CH_2CHCO_2), 25.5 ($CH_2CH_2CHCO_2$). Characterisation data are consistent with literature values.[3]

(*E*)-1-Bromo-3,7-dimethylocta-2,6-diene (3.4.6)

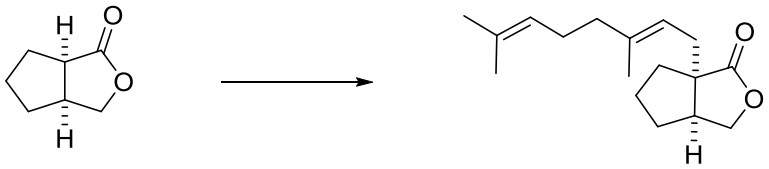


3.4.5 **3.4.6**

According to the procedure of Ferrara:[3] To a stirred solution of geraniol **3.4.5** (16.3 mL, 90.0 mmol) in Et_2O (108 mL) was added pyridine (0.73 mL, 9.0 mmol) dropwise at RT over 3 min. To this mixture at 0 °C was added phosphorus tribromide (3.4 mL, 36 mmol) dropwise over 30 min. After complete addition of phosphorus tribromide, the reaction mixture was stirred at 0 °C for 1 h. Upon completion, the reaction was quenched with water (100 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* (do not heat the water bath nor reduce the pressure less than 200 mbar as the title compound **3.4.6** is very volatile) to give the crude title compound **3.4.6** in Et_2O (yield will be calculated in the next step due to the volatility of title compound **3.4.6**). The crude product was used in the next step without further purification as the title compound **3.4.6** is unstable on silica. δ_H (400 MHz, $CDCl_3$): 5.52 (tsext, 1H,

J = 8.4, 1.3 Hz, H-2), 5.06 (thept, 1H, *J* = 6.1, 1.4 Hz, H-6), 4.01 (d, 2H, *J* = 8.4 Hz, H-1), 2.12 – 2.03 (m, 4H, H-4 and H-5), 1.72 (d, 3H, *J* = 1.4 Hz, CH=C(C*H*$_3$)CH$_2$), 1.67 (s, 3H, CH=C(C*H*$_3$)$_2$), 1.59 (s, 3H, CH=C(C*H*$_3$)$_2$); δ_C (100 MHz, $CDCl_3$): 143.6 (C-3), 132.0 (C-7), 123.5 (C-6), 120.5 (C-2), 39.5 (C-4), 29.6 (C-1), 26.2 (C-5), 25.6 (CH=C(*C*H$_3$)$_2$), 17.7 (CH=C(*C*H$_3$)$_2$), 15.9 (CH=C(*C*H$_3$)CH$_2$). Characterisation data are consistent with literature values.[3]

(±)-(3a*S*,6a*S*)-6a-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one ((±)-3.1.106)

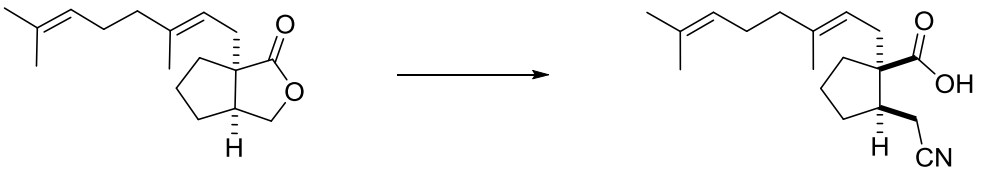


(±)-3.4.4 **(±)-3.1.106**

According to the procedure of Ferrara:[3] To a solution of lactone **(±)-3.4.4** (2.88 g, 22.8 mmol) in THF (220 mL) at -78 °C was slowly added a solution of bromide **3.4.6** (14.2 g, 45.7 mmol) in THF (26 mL). To this mixture at -78 °C was added lithium bis(trimethylsilyl)amide (1 M in toluene, 45.7 mL, 45.7 mmol) dropwise over 3 h. The reaction mixture was further stirred at -78 °C for 20 min. Upon completion, the mixture was poured over sat. aq. NH_4Cl solution (250 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 200 mL). The organic layers were combined, washed with brine (1 x 250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (10% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.1.106** (3.00 g, 11.4 mmol, 50%

over two steps) as a yellow oil. R_f = 0.3 (10% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.08 (tsext, 1H, *J* = 7.8, 1.1 Hz, $CH_2C(CH_3)$=C*H*), 5.02 (thept, 1H, *J* = 6.5, 1.3 Hz, $(CH_3)_2C$=C*H*), 4.30 (dd, 1H, *J* = 9.3, 8.2 Hz, OCOC*H*$_2$), 3.88 (dd, 1H, *J* = 9.3, 3.2 Hz, OCOC*H'*$_2$), 2.58 (tt, 1H, *J* = 8.2, 3.3 Hz, $OCOCH_2$C*H*), 2.48 (dd, 1H, *J* = 14.2, 6.9 Hz, C=CHC*H*$_2$$CCO_2$), 2.25 (dd, 1H, *J* = 14.2, 8.2 Hz, C=CHC*H'*$_2$$CCO_2$), 2.11 – 1.97 (m, 5H, side chain and ring C*H*$_2$), 1.94 – 1.86 (m, 1H, $OCOCH_2CHCH_2$), 1.73 – 1.47 (m, 4H, side chain and ring C*H*$_2$), 1.64 (s, 3H, $(CH_3)_2$C=CH), 1.61 (s, 3H, $CH_2C(CH_3)$=CH), 1.57 (s, 3H, $(CH_3)_2$C=CH); δ_C (100 MHz, $CDCl_3$): 183.1 (*C*=O), 139.4 ($CH_2C(CH_3)$=CH), 131.7 ($(CH_3)_2C$=CH), 124.1 ($(CH_3)_2$C=*C*H), 118.9 ($CH_2C(CH_3)$=*C*H), 73.0 ($OCOCH_2$), 56.0 (C=CCH_2CCO_2), 43.0 ($OCOCH_2CH$), 40.0 (CH_2), 37.7 (CH_2), 34.7 ($OCOCH_2CHCH_2$), 34.6 (CH_3C=$CHCH_2$), 26.6 (CH_2), 25.8 ($(CH_3)_2$C=CH), 25.6 (CH_2), 17.8 ($(CH_3)_2$C=CH), 16.4 ($CH_2C(CH_3)$=CH). Characterisation data are consistent with literature values.[3]

(±)-(1*S*,2*R*)-2-(Cyanomethyl)-1-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentane-1-carboxylic acid ((±)-3.4.7)

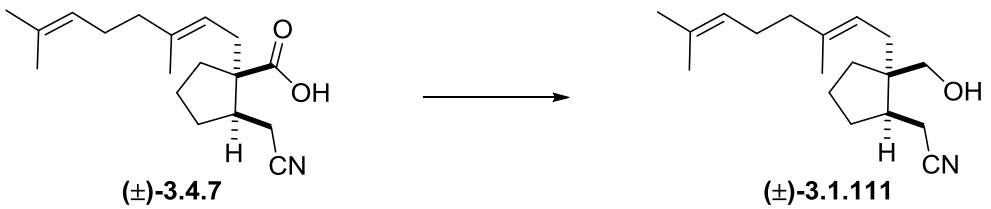


(±)-3.1.106 **(±)-3.4.7**

According to the procedure of Ferrara:[3] To a stirred solution of lactone **(±)-3.1.106** (900 mg, 3.43 mmol) in DMSO (63 mL) at RT was added potassium cyanide (893 mg, 13.7 mmol). The reaction mixture was stirred at 185 °C for 2.5 h. Upon completion, EtOAc (20 mL) was added and sat. aq. NH_4Cl solution (20 mL) was

added dropwise. *CAUTION gaseous HCN given off* The biphasic mixture was vigorously stirred for 20 min before adding aq. HCl solution (1 M, 20 mL). The mixture was gently swirled and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined and concentrated to around 100 mL *in vacuo*. The organic layer was then sequentially washed with water (50 mL) and brine (50 mL). The water and brine layers were combined and extracted with EtOAc (1 x 70 mL). All organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$ with 1.5% acetic acid) to give the title compound **(±)-3.4.7** (930 mg, 3.21 mmol, 94%) as a colourless oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$ with 1.5% acetic acid); δ_H (400 MHz, $CDCl_3$): 5.09 (tsext, 1H, *J* = 7.3, 1.2 Hz, $CH_2C(CH_3)=CH$), 5.05 (thept, 1H, *J* = 6.7, 1.3 Hz, $(CH_3)_2C=CH$), 2.61 (dd, 1H, *J* = 16.8, 4.4 Hz, CH_2CN), 2.56 (dd, 1H, *J* = 14.4, 7.3 Hz, $CH_2C(CH_3)=CHCH_2$), 2.38 (dd, 1H, J = 16.8, 9.8 Hz, CH'_2CN), 2.27 – 2.18 (m, 2H, $CH_2C(CH_3)=CHCH'_2$ and CH_2), 2.15 – 1.99 (m, 6H, $CHCH_2CN$ and CH_2), 1.89 – 1.82 (m, 1H, CH_2), 1.74 – 1.56 (m, 3H, CH_2), 1.67 (s, 3H, $(CH_3)_2C=CH$), 1.62 (s, 3H, $CH_2C(CH_3)=CH$), 1.60 (s, 3H, $(CH_3)_2C=CH$); δ_C (125 MHz, $CDCl_3$): 180.5 (*C*=O), 139.0 ($CH_2C(CH_3)=CH$), 131.6 ($(CH_3)_2C=CH$), 124.0 ($(CH_3)_2C=CH$), 119.1 (*C*≡N), 118.9 ($CH_2C(CH_3)=CH$), 56.2 (CCO_2H), 44.9 ($CHCH_2CN$), 39.9 (CH_2), 35.1 (CH_2), 33.7 (CH_2), 31.0 (CH_2), 26.4 (CH_2), 25.7 ($(CH_3)_2C=CH$), 21.8 (CH_2), 19.1 (CH_2), 17.7 ($(CH_3)_2C=CH$), 16.3 ($CH_2C(CH_3)=CH$). Characterisation data are consistent with literature values.[3]

(±)-2-((1R,2S)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-(hydroxymethyl)cyclopentyl)acetonitrile ((±)-3.1.111)

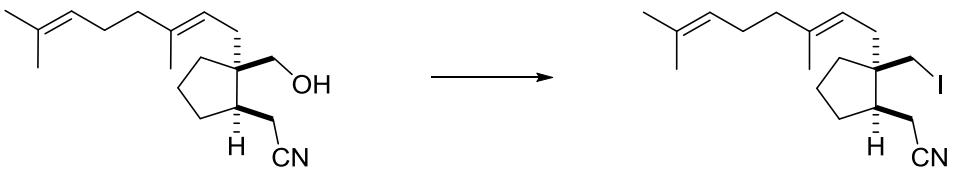


(±)-3.4.7 **(±)-3.1.111**

According to a modified procedure of Mulzer *et al*.:[159] To a solution of acid **(±)-3.4.7** (930 mg, 3.21 mmol) in THF (12 mL) at 0 °C was added 4-methyl morpholine (0.39 mL, 3.5 mmol) followed by ethyl chloroformate (0.34 mL, 3.5 mmol). The reaction mixture was stirred at 0 °C for 6 h. In another flask, sodium borohydride (365 mg, 9.64 mmol) was suspended in THF (8.1 mL). To this suspension at -78 °C was added MeOH (3.4 mL) followed by the above anhydride mixture portionwise. The resulting reaction mixture was then stirred at -78 °C for 15 min. After that, the reaction mixture was warmed to RT and stirred for 6.5 h. Upon completion, the reaction was quenched with aq. sat. NH_4Cl solution (10 mL) and water (5 mL) and diluted with EtOAc (10 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (30% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.1.111** (830 mg, 3.02 mmol, 94%) as a colourless oil. R_f = 0.3 (30% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 5.18 (tsext, 1H, *J* = 7.6, 1.3 Hz, $CH_2C(CH_3)$=C*H*), 5.05 (thept, 1H, *J* = 6.7, 1.4 Hz, $(CH_3)_2C$=C*H*), 3.49 (dd, 1H, *J* = 11.3, 5.8 Hz, CH_2OH), 3.46 (dd, 1H, *J* = 11.3, 5.0 Hz, CH'_2OH), 2.65 (dd, 1H, *J* = 16.8, 5.3 Hz, CH_2CN), 2.39 (dd, 1H, *J* = 16.8, 9.6 Hz, CH'_2CN), 2.30 (dd, 1H, *J* = 14.4, 8.1 Hz, $CH_2(CH_3)$C=CHCH_2), 2.13 –

1.94 (m, 7H, C*H*$_2$), 1.73 – 1.70 (m, 1H, C*H*$_2$), 1.68 (s, 3H, (C*H*$_3$)$_2$C=CH), 1.65 (s, 3H, CH$_2$C(C*H*$_3$)=CH), 1.61 (s, 3H, (C*H*$_3$)$_2$C=CH), 1.59 – 1.45 (m, 4H, C*H*$_2$), 1.39 (t, 1H, *J* = 5.5 Hz, O-*H*); δ_C (125 MHz, $CDCl_3$): 138.2 (*C*=CH), 131.9 (*C*=CH), 124.2 ((CH$_3$)$_2$C=*C*H), 120.5 (CH$_2$C(CH$_3$)=*C*H), 120.3 (*C*≡N), 66.1 (*C*H$_2$OH), 48.6 (*C*H$_2$), 44.2 (*C*H$_2$), 40.2 (*C*H$_2$), 34.9 (CH$_2$(CH$_3$)C=CH*C*H$_2$), 34.1 (*C*H$_2$), 32.1 (*C*H$_2$), 26.6 ((*C*H$_3$)$_2$C=CH), 25.9 (*C*H$_2$), 22.4 (*C*H$_2$), 18.6 (*C*H$_2$CN), 17.9 ((*C*H$_3$)$_2$C=CH), 16.3 (CH$_2$C(*C*H$_3$)=CH); ν_{max}/cm^{-1}: 3502 (br, O-H), 2923 (s, C-H), 2360 (s, C≡N), 1449 (m), 1047 (m); *m/z* LRMS (ESI$^+$): 298.2 ([M+Na]$^+$, 100%); accurate mass: found 298.2140, $C_{18}H_{29}NaON$ [M+Na]$^+$ requires 298.2141.

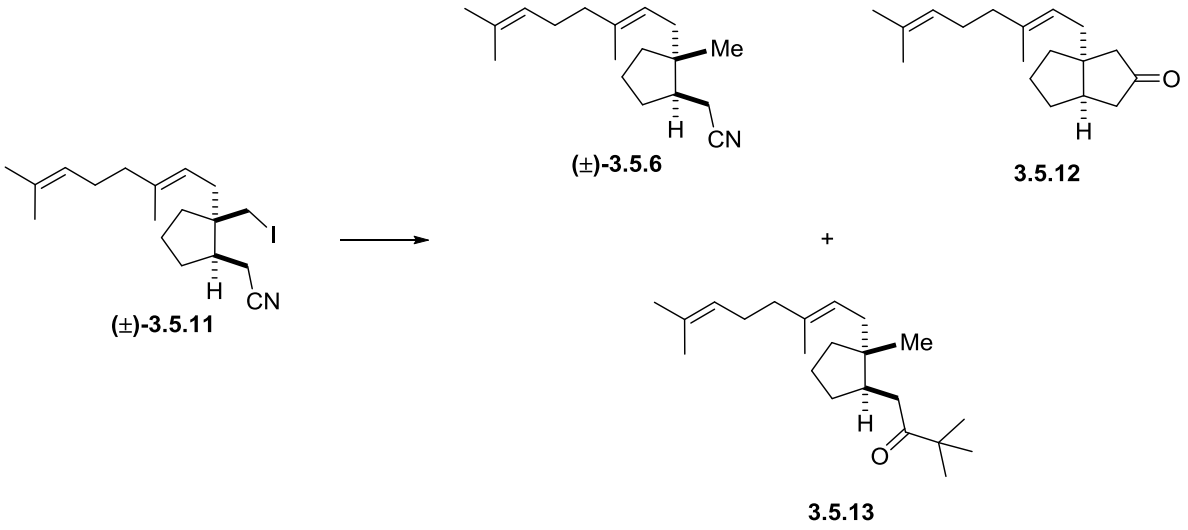
(±)-2-((1R,2S)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-(iodomethyl)cyclopentyl)acetonitrile ((±)-3.5.11)



(±)-3.1.111 **(±)-3.5.11**

According to a modified procedure of Alexanian *et al*.:[161] To a mixture of alcohol **(±)-3.1.111** (300 mg, 1.09 mmol), triphenylphosphine (571 mg, 2.18 mmol) and imidazole (148 mg, 2.18 mmol) in THF (10 mL) at 0 °C was slowly added iodine (415 mg, 1.63 mmol) in small potions in dark. The reaction mixture was stirred at RT in dark for 6 h. Upon completion, the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (10 mL) and diluted with Et_2O (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The

crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.5.11** (334 mg, 0.871 mmol, 80%) as a colourless oil. R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 5.00 (tsext, 1H, *J* = 8.1, 1.0 Hz, $CH_2C(CH_3)=CH$), 4.99 (thept, 1H, *J* = 6.9, 1.4 Hz, $(CH_3)_2C=CH$), 3.23 (d, 1H, *J* = 10.0 Hz, CH_2I), 3.07 (d, 1H, *J* = 10.0 Hz, CH'_2I), 2.55 (dd, 1H, *J* = 16.3, 4.2 Hz, CH_2CN), 2.27 – 2.04 (m, 9H, CH'_2CN and $CHCH_2CN$ and side chain CH_2), 1.68 (s, 3H, $(CH_3)_2C=CH$), 1.67 (s, 3H, $CH_2C(CH_3)=CH$), 1.62 (s, 3H, $(CH_3)_2C=CH$), 1.79 – 1.62 (m, 5H, ring CH_2); δ_C (125 MHz, $CDCl_3$): 139.3 (*C*=CH), 131.9 (*C*=CH), 124.3 ($(CH_3)_2C=CH$), 119.5 (*C*≡N), 118.9 ($CH_2C(CH_3)=CH$), 47.8 (CCH_2I), 42.9 ($CHCH_2CN$), 40.2 (side chain CH_2), 36.8 (side chain CH_2), 36.5 (ring CH_2), 30.7 (side chain CH_2), 26.5 (ring CH_2), 25.9 ($(CH_3)_2C=CH$), 21.9 (ring CH_2), 18.9 (CH_2CN), 17.9 ($(CH_3)_2C=CH$), 16.7 ($CH_2C(CH_3)=CH$), 16.2 (CH_2I); ν_{max}/cm^{-1}: 2959 (s, C-H), 2924 (s, C-H), 2247 (w, C≡N), 1451 (s), 1376 (m), 1206 (m); *m/z* (ESI^+): 408.1 ($[M+Na]^+$, 100%); accurate mass: found 408.1159, $C_{18}H_{28}NaNI$ $[M+Na]^+$ requires 408.1159.



Method One:

According to a modified procedure of Burton *et al.*:[162] To a stirred solution of iodide **3.5.11** (22 mg, 0.057 mmol) in Et_2O (0.22 mL) and methanol (0.22 mL) at RT was added zinc (37 mg, 0.57 mmol) followed by acetic acid (6.0 µL, 0.11 mmol). The reaction mixture was stirred at RT for 4 h. Upon completion, the mixture was diluted with Et_2O (15 mL) and filtered through cotton wool. The filtrate was washed with sat. aq. $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by FC to give a mixture of alkane **3.5.6** (5 mg, 0.02 mmol, 35%, colourless oil) and ketone **3.5.12** (9 mg, 0.03 mmol, 60%, colourless oil).

Method Two:

According to a modified procedure of Bailey *et al.*:[164] To a solution of iodide **3.5.11** (30 mg, 0.078 mmol) and methanol (6.3 µL, 0.16 mmol) in pentane (0.37 mL) and Et_2O (0.31 mL) at -78 °C was added *t*BuLi (1.7 M in pentane, 92.0 µL, 0.156 mmol) dropwise over 2 min. The reaction mixture was stirred at -78 °C for 1.5 h. The

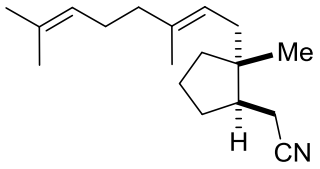
reaction was quenched before completion by methanol (2 mL) at -78 °C. After warming the mixture to RT, the mixture was diluted with Et_2O (15 mL) and washed with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC to give a mixture of cyclic ketone **3.5.12** (9 mg, 0.03 mmol, 44%, colourless oil) and *t*Butyl ketone **3.5.13** (2 mg, 0.006 mmol, 8%, colourless oil). 30% of starting material was recovered.

Method Three:

According to a modified procedure of Hutchins *et al*.:[165] To a solution of iodide **(±)-3.5.11** (80 mg, 0.21 mmol) in sulfolane (2.1 mL) at RT was added sodium borohydride (47 mg, 1.2 mmol) slowly. After stirring the reaction mixture at 60 °C in dark for 3 h, another 6 eq. of sodium borohydride (47 mg, 1.2 mmol) was added and the reaction mixture was further stirred at 60 °C in dark for 3 h. Reaction was stopped before completion. The reaction was quenched with brine (5 mL) and water (5 mL). $PE_{40\text{-}60}$ (15 mL) and Et_2O (1 mL) were then added. The two layers were separated and the aqueous layer was extracted with $PE_{40\text{-}60}$ (3 x 10 mL). The combined organic layers were then washed with brine (1 x 15 mL). The brine layer was extracted with $PE_{40\text{-}60}$ (1 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (8% EtOAc in $PE_{40\text{-}60}$) to give an inseparable mixture of the starting material **(±)-3.5.11** and the title compound **(±)-3.5.6** (starting material to product ratio 1 : 10, 41 mg, 0.160 mmol, 76% by taking into account of the unreacted starting material) as a colourless oil.

Characterisation:

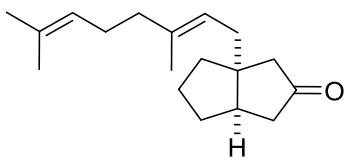
(±)-2-((1R,2R)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-methylcyclopentyl)acetonitrile ((±)-3.5.6)



(±)-3.5.6

R_f = 0.3 (8% EtOAc in $PE_{40\text{-}60}$); δ_H (400 MHz, $CDCl_3$): 5.16 (t, 1H, *J* = 7.7 Hz, $CH_2C(CH_3)=CH$), 5.07 (thept, 1H, *J* = 6.9, 1.3 Hz, $(CH_3)_2C=CH$), 2.38 (dd, 1H *J* = 16.6, 5.0 Hz, CH_2CN), 2.15 – 2.03 (m, 7H, CH'_2CN and CH_2), 1.94 – 1.87 (m, 2H, $CHCH_2CN$ and $CH_2(CH_3)C=CHCH_2$), 1.68 (s, 3H, $(CH_3)_2C=CH$), 1.61 (s, 3H, $(CH_3)_2C=CH$), 1.60 (s, 3H, $CH_2(CH_3)C=CH$), 1.73 – 1.43 (m, 5H, CH_2), 0.79 (s, 3H, $CH_2C(CH_2)(CH)CH_3$); δ_C (125 MHz, $CDCl_3$): 137.4 (*C*=CH), 131.6 (*C*=CH), 124.4 ($(CH_3)_2C=CH$), 120.8 ($CH_2C(CH_3)=CH$), 120.2 (*C*≡N), 44.5 ($CHCH_2CN$), 44.2 ($CH_2C(CH_2)(CH)CH_3$), 40.2 (CH_2), 39.0 ($CH_2(CH_3)C=CHCH_2$), 38.9 (CH_2), 30.9 (CH_2), 26.7 (CH_2), 25.9 ($(CH_3)_2C=CH$), 21.3 (CH_2), 20.3 ($CH_2C(CH_2)(CH)CH_3$), 18.4 (CH_2CN), 17.9 ($(CH_3)_2C=CH$), 16.3 ($CH_2C(CH_3)=CH$); ν_{max}/cm^{-1}: 2959 (s, C-H), 2926 (s, C-H), 2246 (w, C≡N), 1449 (m), 1378 (m); *m/z* (ESI^+): 282.2 ($[M+Na]^+$, 100%); accurate mass: found 282.21924, $C_{18}H_{29}NaN$ $[M+Na]^+$ requires 282.21922.

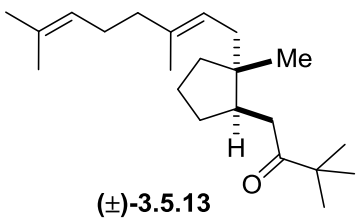
(±)-(3aR,6aR)-3a-((E)-3,7-Dimethylocta-2,6-dien-1-yl)hexahydropentalen-2(1H)-one ((±)-3.5.12)



(±)-3.5.12

Colourless oil; R_f = 0.2 (60% DCM in PE_{30-40}); δ_H (500 MHz, $CDCl_3$): 5.14 (tsext, 1H, *J* = 7.4, 1.1 Hz, $CH_2C(CH_3)=CH$), 5.06 (thept, 1H, *J* = 6.6, 1.4 Hz, $(CH_3)_2C=CH$), 2.52 (ddd, 1H, *J* = 18.9, 9.4, 1.8 Hz, $CHCH_2CO$), 2.37 – 2.30 (m, 1H, $CHCH_2CO$), 2.30 – 2.25 (m, 1H, CH_2), 2.18 – 1.94 (m, 9H, CH_2), 1.76 – 1.68 (m, 3H, CH_2), 1.67 (s, 3H, $(CH_3)_2C=CH$), 1.60 (s, 6H, $CH_2(CH_3)C=CH$ and $(CH_3)_2C=CH$), 1.60 – 1.58 (m, 1H, chain CH_2), 1.44 – 1.39 (m, 1H, CH_2); δ_C (125 MHz, $CDCl_3$): 220.5 (*C*=O), 137.8 (*C*=CH), 131.5 (*C*=CH), 124.1 ($(CH_3)_2C=CH$), 120.7 ($CH_2C(CH_3)=CH$), 51.1 (CH_2), 49.7 (CH_2), 45.1 ($CHCH_2CO$), 44.6 ($CHCH_2CO$), 40.0 (CH_2), 38.4 (CH_2), 38.3 (CH_2), 33.4 (CH_2), 26.5 (CH_2), 25.7 ($(CH_3)_2C=CH$), 24.4 (CH_2), 17.7 (CH_3), 16.2 (CH_3); ν_{max}/cm^{-1}: 2919 (s, C-H), 1741 (s, C=O), 1450 (m), 1403 (m), 1165 (m); *m/z* (ESI^+): 283.2 ($[M+Na]^+$, 100%); accurate mass: found 283.2034, $C_{18}H_{28}NaO$ $[M+Na]^+$ requires 283.2032.

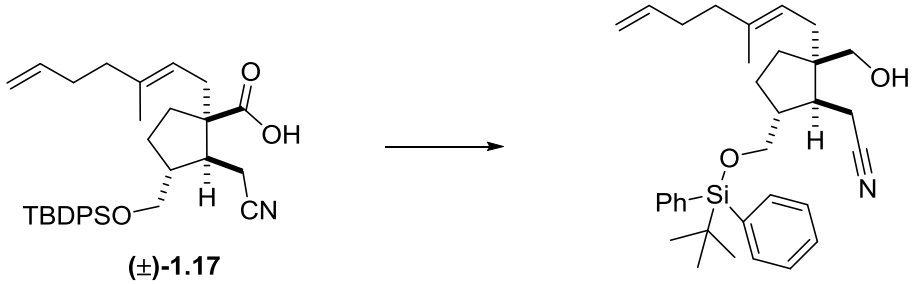
(±)-1-((1R,2R)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-methylcyclopentyl)-3,3-dimethylbutan-2-one ((±)-3.5.13)



(±)-3.5.13

Colourless oil; R_f = 0.5 (50% DCM in PE_{40-60}); δ_H (500 MHz, $CDCl_3$): 5.20 (tsext, 1H, *J* = 7.8, 1.1 Hz, $CH_2(CH_3)C=CHCH_2$), 5.09 (thept, 1H, *J* = 6.9, 1.5 Hz, $(CH_3)_2C=CHCH_2$), 2.45 (dd, 1H, *J* = 16.8, 3.0 Hz, CH_2CO), 2.33 (dd, 1H, *J* = 16.8, 10.3 Hz, CH'_2CO), 2.15 – 1.97 (m, 7H, chain CH_2, ring CH_2 and $CHCH_2CO$), 1.94 – 1.82 (m, 3H, chain CH_2 and ring CH_2), 1.68 (s, 3H, $(CH_3)_2C=CHCH_2$), 1.60 (s, 3H, $(CH_3)_2C=CHCH_2$), 1.58 (s, 3H, $CH_2(CH_3)C=CHCH_2$), 1.54 – 1.43 (m, 3H, ring CH_2), 1.13 (s, 9H, $C(CH_3)_3$), 0.74 (s, 3H, $C(CH)CH_3$); δ_C (125 MHz, $CDCl_3$): 216.0 (*C*=O), 136.2 ($C=CHCH_2$), 131.3 ($C=CHCH_2$), 124.4 ($(CH_3)_2C=CHCH_2$), 121.6 ($CH_2(CH_3)C=CHCH_2$), 44.3 (quarternary carbon doublet), 43.0 (CH_2), 40.1 (CH_2), 38.9 (CH_2), 38.4 (CH_2), 37.5 (CH_2CO), 30.6 (CH_2), 26.7 (CH_2), 26.4 ($C(CH_3)_3$), 25.7 ($(CH_3)_2C=CHCH_2$), 21.2 ($C(CH_3)_3$), 20.2 ($C(CH)CH_3$), 17.7 ($(CH_3)_2C=CHCH_2$), 16.1 ($CH_2(CH_3)C=CHCH_2$); ν_{max}/cm^{-1}: 2957 (s, C-H), 2928 (s, C-H), 2870 (s, C-H), 1707 (s, C=O), 1477 (m), 1375 (m); *m/z* (ESI^+): 341.3 ($[M+Na]^+$, 100%); accurate mass: found 341.2814, $C_{22}H_{38}NaO$ $[M+Na]^+$ requires 341.2815.

(±)-2-((1S,2S,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-(hydroxymethyl)-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile ((±)-3.6.1)

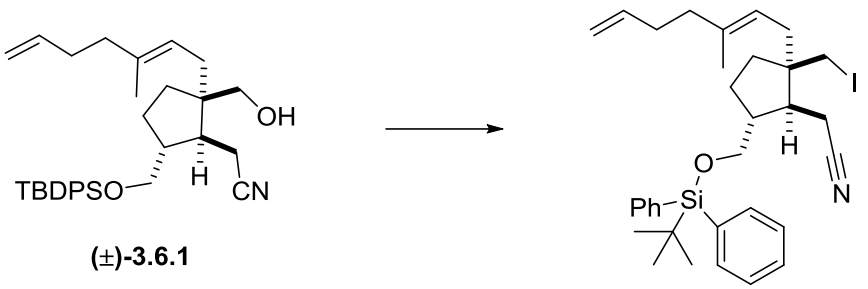


(±)-1.17 **(±)-3.6.1**

According to a modified procedure of Mulzer *et al.*:[159] To a solution of acid **(±)-1.17** (656 mg, 1.24 mmol) in THF (3.1 mL) at 0 °C was added 4-methylmorpholine (0.15 mL, 1.4 mmol) followed by ethyl chloroformate (0.13 mL, 1.4 mmol). The reaction mixture was stirred at 0 °C for 6 h. In another reaction vessel, sodium borohydride (187 mg, 4.95 mmol) was suspended in THF (3.3 mL). To this mixture at -78 °C was added MeOH (1.3 mL) followed by the above anhydride mixture portionwise. The reaction mixture was stirred at -78 °C for 15 min before warming to RT and stirred for 6.5 h. Upon completion, the reaction was quenched with sat. aq. NH_4Cl solution (6 mL) and water (4 mL). EtOAc (4 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (2 x 7 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (20% - 22% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-3.6.1** (553 mg, 1.07 mmol, 87%) as a colourless oil. R_f = 0.3 (22% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.69 – 7.63 (m, 4H, Ar-*H*), 7.47 – 7.36 (m, 6H, Ar-*H*), 5.77 (ddt, 1H, *J* = 16.9, 10.2, 6.4 Hz, CH_2=C*H*), 5.21 (t, 1H, *J* = 7.7 Hz, $CH_2C(CH_3)$=C*H*), 5.00 (dq, 1H, *J* = 16.9, 1.6 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 4.94

(ddt, 1H, *J* = 10.2, 2.1, 1.2 Hz, C*H*$_{pro(E)}$H$_{pro(Z)}$=CH), 3.67 (dd, 1H, *J* = 10.5, 4.9 Hz, SiOC*H*$_2$), 3.63 (dd, 1H, *J* = 10.5, 5.8 Hz, SiOC*H'*$_2$), 3.61 (dd, 1H, *J* = 11.3, 5.0 Hz, C*H*$_2$OH), 3.57 (dd, 1H, *J* = 11.3, 3.3 Hz, C*H'*$_2$OH), 2.60 (dd, 1H, *J* = 17.1, 5.2 Hz, C*H*$_2$CN), 2.55 (dd, 1H, *J* = 17.1, 8.1 Hz, C*H'*$_2$CN), 2.41 (dd, 1H, *J* = 14.4, 8.2 Hz, CH$_2$C(CH$_3$)=CHC*H*$_2$), 2.20 – 2.14 (m, 2H, CH$_2$=CHC*H*$_2$), 2.12 – 2.07 (m, 2H, CH$_2$=CHCH$_2$C*H*$_2$), 2.07 – 1.99 (m, 2H, CH$_2$C(CH$_3$)=CHC*H'*$_2$ and SiOCH$_2$C*H*), 1.85 (ddd, 1H, *J* = 9.6, 8.0, 5.2 Hz, C*H*CH$_2$CN), 1.77 – 1.70 (m, 1H, SiOCH$_2$CHC*H*$_2$), 1.65 (s, 3H, CH$_2$C(C*H*$_3$)=CH), 1.55 – 1.51 (m, 2H, SiOCH$_2$CHCH$_2$C*H*$_2$), 1.46 – 1.40 (m, 1H, SiOCH$_2$CHC*H'*$_2$), 1.07 (s, 9H, SiC(C*H*$_3$)$_3$); δ_C (125 MHz, CDCl$_3$): 138.6 (CH$_2$=*C*H), 137.6 (CH$_2$*C*(CH$_3$)=CH), 135.7 (Ar), 133.6 (Ar), 129.9 (Ar), 127.9 (Ar), 120.6 (CH$_2$C(CH$_3$)=*C*H), 120.5 (*C*≡N), 114.7 (*C*H$_2$=CH), 66.4 (*C*H$_2$OH and *C*H$_2$OSi), 49.9 (*C*CH$_2$OH), 46.8 (SiOCH$_2$*C*H), 45.7 (*C*HCH$_2$CN), 39.5 (*C*H$_2$C(CH$_3$)=CH), 35.2 (CH$_2$C(CH$_3$)=CH*C*H$_2$), 33.1 (SiOCH$_2$CHCH$_2$*C*H$_2$), 32.4 (CH$_2$=CH*C*H$_2$), 27.1 (SiC(*C*H$_3$)$_3$), 26.3 (SiOCH$_2$CH*C*H$_2$), 19.4 (Si*C*(CH$_3$)$_3$), 17.4 (*C*H$_2$CN), 16.4 (CH$_2$C(*C*H$_3$)=CH); ν_{max}/cm^{-1}: 3504 (br, O-H), 2930 (m, C-H), 2857 (m, C-H), 1428 (m), 1111 (s), 702 (s); *m/z* (ESI$^+$): 538.3 ([M+Na]$^+$, 100%); accurate mass: found 538.3109, C$_{33}$H$_{45}$O$_2$NNaSi [M+Na]$^+$ requires 538.3112.

(±)-2-((1S,2S,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-(iodomethyl)-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile ((±)-3.6.2)

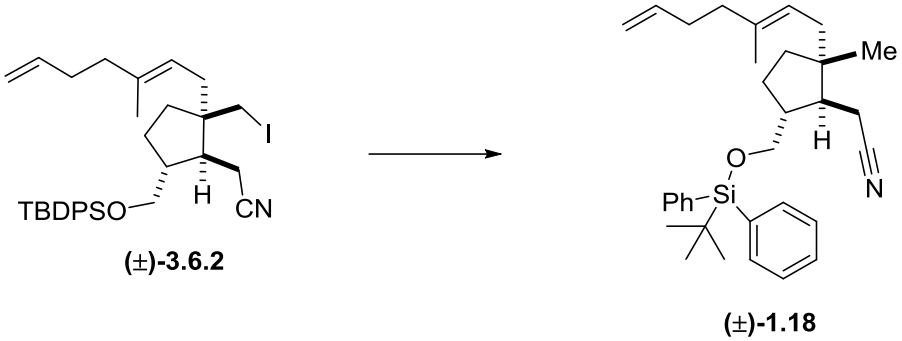


(±)-3.6.1 **(±)-3.6.2**

According to a modified procedure of Alexanian *et al*.:[161] To a mixture of alcohol **(±)-3.6.1** (550 mg, 1.07 mmol), triphenylphosphine (559 mg, 2.13 mmol) and imidazole (145 mg, 2.13 mmol) in THF (9.8 mL) at 0 °C was slowly added iodine (406 mg, 1.60 mmol) in small portions in dark. The reaction mixture was stirred at RT in dark for 5 h. Upon completion, the reaction was quenched with aq. $Na_2S_2O_3$ (14 mL) and diluted with Et_2O (5 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (50% DCM in $PE_{40\text{-}60}$) to give the title compound **(±)-3.6.2** (500 mg, 0.803 mmol, 75%) as a colourless oil. R_f = 0.3 (50% DCM in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.66 – 7.64 (m, 4H, Ar-*H*), 7.47 – 7.37 (m, 6H, Ar-*H*), 5.77 (ddt, 1H, *J* = 17.0, 10.2, 6.3 Hz, CH_2=C*H*), 5.12 (t, 1H, *J* = 8.0 Hz, $CH_2C(CH_3)$=C*H*), 5.00 (ddt, 1H, *J* = 17.0, 1.9, 1.6 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 4.94 (ddt, 1H, *J* = 10.2, 1.9, 1.2 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 3.68 (dd, 1H, *J* = 10.3, 4.8 Hz, SiOCH_2), 3.62 (dd, 1H, *J* = 10.3, 5.8 Hz, SiOCH'_2), 3.34 (d, 1H, *J* = 10.0 Hz, CH_2I), 3.29 (d, 1H, *J* = 10.0 Hz, CH'_2I), 2.49 (dd, 1H, *J* = 17.3, 5.4 Hz, CH_2CN), 2.45 (dd, 1H, *J* = 17.3, 6.3 Hz,

C*H'*$_2$CN), 2.31 (dd, 1H, *J* = 14.8, 8.0 Hz, $CH_2C(CH_3)$=CHC*H*$_2$), 2.22 – 2.03 (m, 7H, CH_2=CHC*H*$_2$ and CH_2=$CHCH_2$C*H*$_2$ and $SiOCH_2$C*H* and C*H*CH_2CN and $CH_2C(CH_3)$=CHC*H'*$_2$), 1.80 – 1.57 (m, 6H, $CH_2C(CH_3)$=CH and ring C*H*$_2$), 1.48 – 1.42 (m, 1H, ring C*H*$_2$), 1.07 (s, 9H, $SiC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 138.6 ($CH_2C(CH_3)$=CH), 138.4 (CH_2=CH), 135.6 (Ar), 133.3 (Ar), 129.8 (Ar), 127.8 (Ar), 119.2 (C≡N), 119.0 ($CH_2C(CH_3)$=CH), 114.7 (CH_2=CH), 66.2 ($SiOCH_2$), 48.4 (CCH_2I), 46.0 ($SiOCH_2CH$), 43.3 ($CHCH_2CN$), 39.4 ($CH_2C(CH_3)$=CH), 37.1 ($CH_2C(CH_3)$=$CHCH_2$), 36.8 (ring CH_2), 32.2 (CH_2=$CHCH_2$), 26.9 ($SiC(CH_3)_3$), 25.4 (ring CH_2), 19.2 ($SiC(CH_3)_3$), 17.8 (CH_2CN), 17.2 (CH_2I), 16.5 ($CH_2C(CH_3)$=CH); ν_{max}/cm^{-1}: 2930 (w, C-H), 2857 (w, C-H), 2245 (w, C≡N), 1471 (m), 1110 (s), 701 (s); *m/z* (ESI$^+$): 648.2 ([M+Na]$^+$, 100%); accurate mass: found 648.2125, $C_{33}H_{44}ONINaSi$ [M+Na]$^+$ requires 648.2129.

(±)-2-((1S,2R,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-methyl-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile ((±)-1.18)



(±)-3.6.2 **(±)-1.18**

Method One:

According to a modified procedure of Hutchins *et al*.:[165] To a solution of iodide **(±)-3.6.2** (43 mg, 0.069 mmol) in sulfolane (0.7 mL) at RT was added sodium borohydride (16 mg, 0.41 mmol) slowly. After stirring the reaction mixture at 60 °C in dark for 3 h, another 6 eq. of sodium borohydride (16 mg, 0.41 mmol) was added and the reaction mixture was further stirred at 60 °C in dark for 3 h. Reaction was stopped before completion. The reaction was quenched with brine (5 mL) and water (5 mL). $PE_{40\text{-}60}$ (10 mL) and Et_2O (0.5 mL) were then added. The two layers were separated and the aqueous layer was extracted with $PE_{40\text{-}60}$ (3 x 10 mL). The combined organic layers were then washed with brine (1 x 15 mL). The brine layer was extracted with $PE_{40\text{-}60}$ (1 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (45% DCM in $PE_{40\text{-}60}$) to give an inseparable mixture of the starting material **(±)-3.6.2** and the title compound **(±)-1.18** (starting material to product ratio 1 : 2, 17 mg, 0.033 mmol, 48% by taking into account of the unreacted starting material) as a colourless oil.

Method Two:

According to a modified procedure of Baba *et al*.:[166] Indium(III) chloride (7 mg, 0.03 mmol) was heated *in vacuo* at 150 °C for 1 h. After cooling to RT, acetonitrile (0.17 mL) was added. To this mixture at -78 °C was then added $NaBH_4$ (4 mg, 0.1 mmol) and the reaction mixture was stirred at -78 °C for 5 min. The reaction mixture was warmed to RT and to the mixture at RT was then added a solution of iodide **(±)-3.6.2** (20 mg, 0.032 mmol) in acetonitrile (0.2 mL). The reaction mixture was stirred at RT for 2 h. Upon completion, the reaction was quenched by water (10 mL) and diluted with Et_2O (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by FC (6% EtOAc in $PE_{40\text{-}60}$) to give the title compound **(±)-1.18** (7 mg, 0.01 mmol, 41%) as a colourless oil.

Characterisation:

R_f = 0.3 (6% EtOAc in $PE_{40\text{-}60}$); δ_H (500 MHz, $CDCl_3$): 7.70 – 7.63 (m, 4H, Ar-*H*), 7.45 – 7.37 (m, 6H, Ar-*H*), 5.78 (ddt, 1H, *J* = 17.0, 10.1, 6.4 Hz, CH_2=C*H*), 5.19 (t, 1H, *J* = 7.7 Hz, $CH_2C(CH_3)$=C*H*), 5.00 (ddt, 1H, *J* = 17.0, 1.9, 1.7 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 4.93 (ddt, 1H, *J* = 10.1, 1.9, 1.2 Hz, $CH_{pro(E)}H_{pro(Z)}$=CH), 3.67 (dd, 1H, *J* = 10.2, 5.1 Hz, SiOCH_2), 3.62 (dd, 1H, *J* = 10.2, 6.0 Hz, SiOCH'_2), 2.40 (dd, 1H, *J* = 17.1, 5.2 Hz, CH_2CN), 2.31 (dd, 1H, *J* = 17.1, 7.9 Hz, CH'_2CN), 2.23 (dd, 1H, *J* = 14.2, 7.7 Hz, $CH_2C(CH_3)$=CHCH_2), 2.19 – 2.13 (m, 2H, CH_2=CHCH_2), 2.12 – 2.06 (m, 2H, CH_2=$CHCH_2CH_2$), 2.02 – 1.92 (m, 2H, $CH_2C(CH_3)$=CHCH'_2 and

ring C*H*), 1.80 – 1.72 (m, 2H, $SiOCH_2CHCH_2$ and ring C*H*), 1.61 (s, 3H, $CH_2C(CH_3)=CH$), 1.54 – 1.48 (m, 1H, $SiOCH_2CHCH_2CH_2$), 1.45 – 1.36 (m, 2H, $SiOCH_2CHCH'_2$ and $SiOCH_2CHCH_2CH'_2$), 1.07 (s, 9H, $SiC(CH_3)_3$), 0.90 (s, 3H, $SiOCH_2CHCH_2CH_2CCH_3$); δ_C (125 MHz, $CDCl_3$): 138.6 ($CH_2=CH$), 136.8 ($CH_2C(CH_3)=CH$), 135.6 (Ar), 133.5 (Ar), 129.7 (Ar), 127.7 (Ar), 120.8 ($CH_2C(CH_3)=CH$), 119.8 ($C\equiv N$), 114.4 ($CH_2=CH$), 66.7 ($SiOCH_2$), 45.9 (ring *C*H) x 2, 45.8 ($SiOCH_2CHCH_2CH_2C$), 39.4 ($CH_2C(CH_3)=CH$), 39.2 ($CH_2C(CH_3)=CHCH_2$), 37.8 ($SiOCH_2CHCH_2CH_2$), 32.3 ($CH_2=CHCH_2$), 26.9 ($SiC(CH_3)_3$), 25.4 ($SiOCH_2CHCH_2$), 20.7 ($SiOCH_2CHCH_2CH_2CCH_3$), 19.2 ($SiC(CH_3)_3$), 17.3 (CH_2CN), 16.2 ($CH_2C(CH_3)=CH$); ν_{max}/cm^{-1}: 2955 (s, C-H), 2931 (s, C-H), 2245 (w, C≡N), 1428 (m), 1111 (s), 823 (m), 702 (s); *m/z* (ESI^+): 522.3 ($[M+Na]^+$, 100%); accurate mass: found 522.3161, $C_{33}H_{45}ONNaSi$ $[M+Na]^+$ requires 522.3163.

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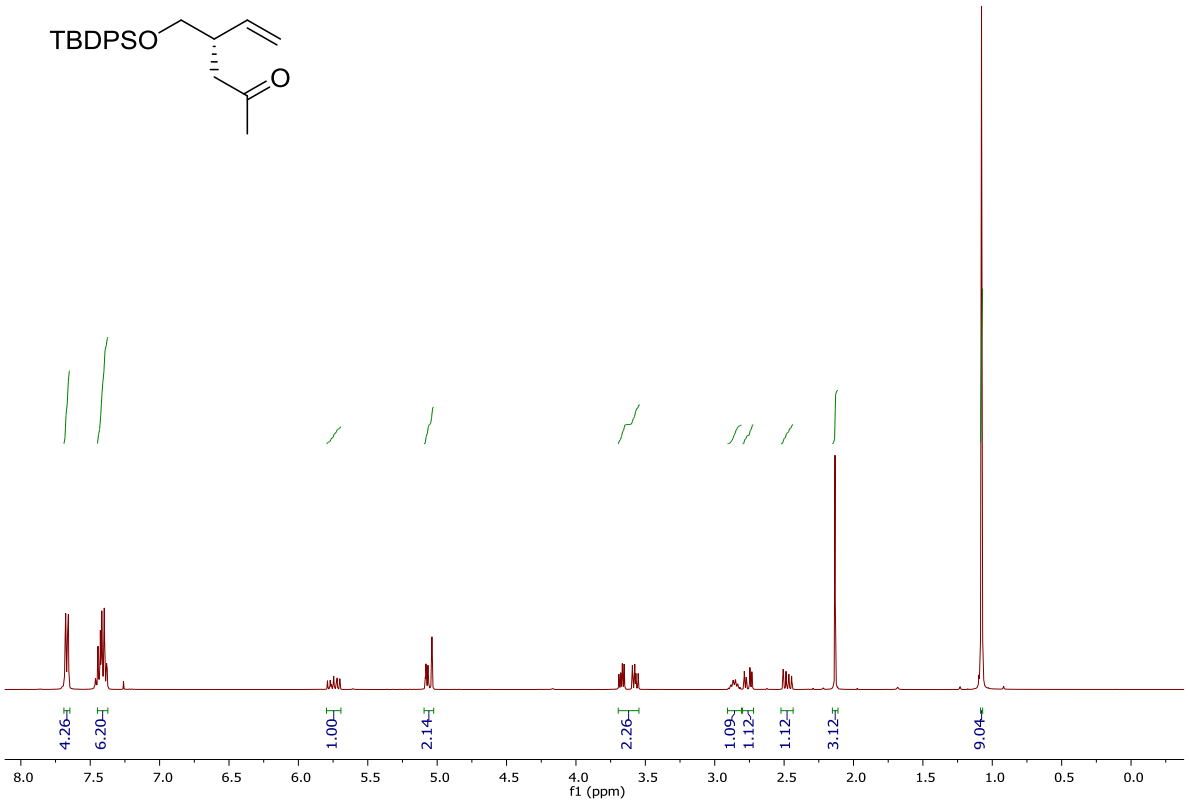
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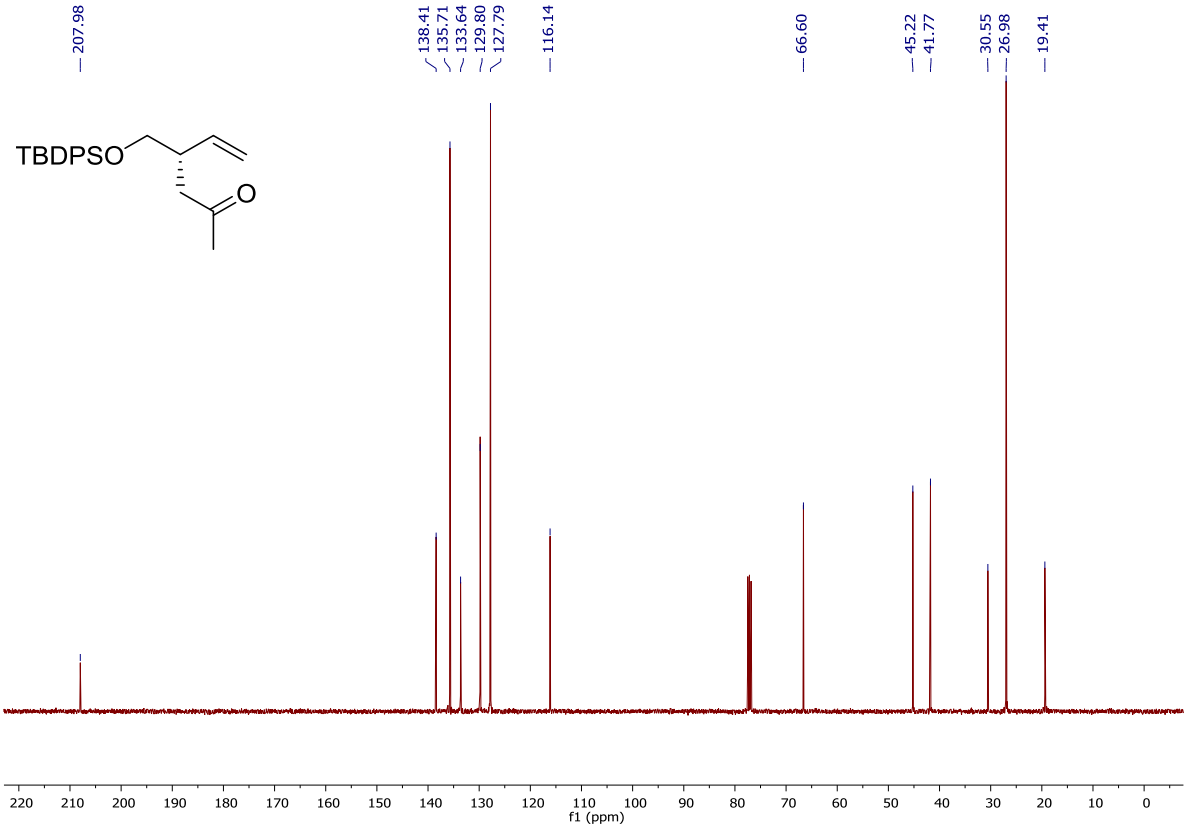
6 Appendix:

6.1 Selected spectra

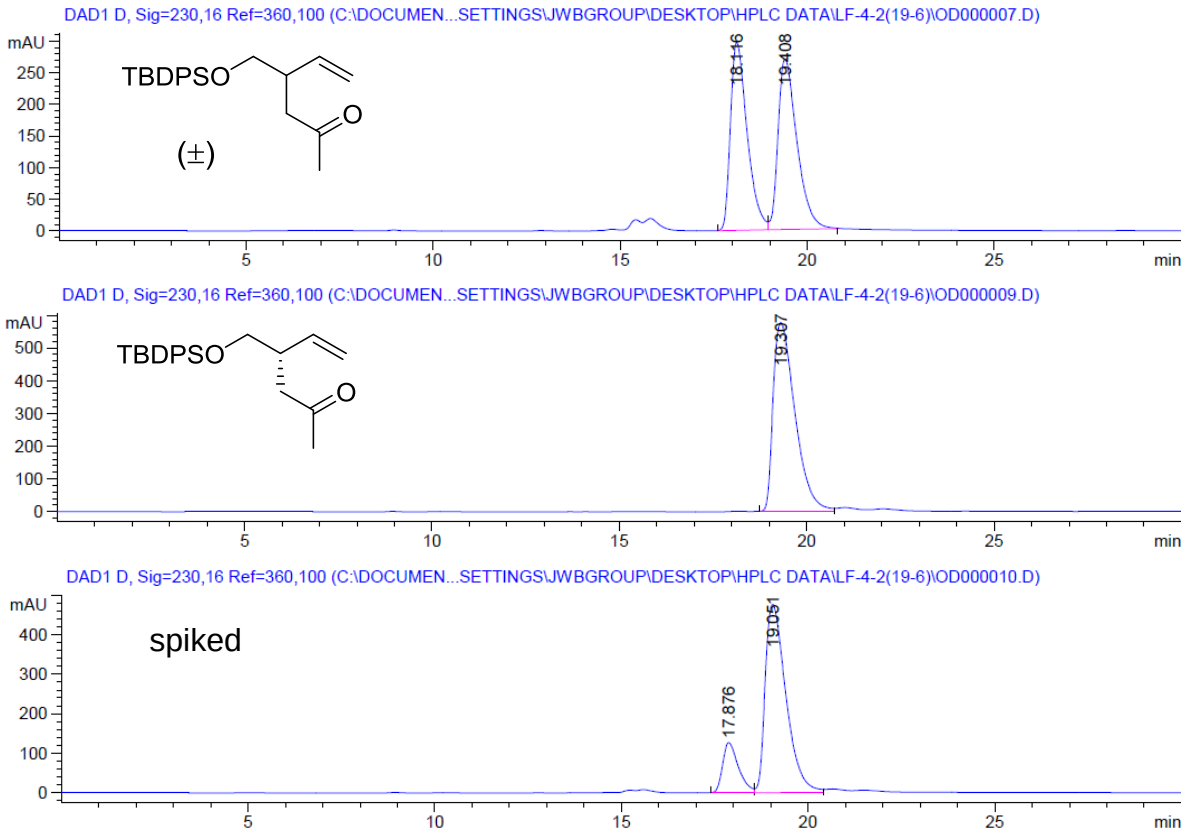
6.1.1 Ketone 2.3.21 (Table 2.3.5, entry 3)

(S)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)hex-5-en-2-one




207.98
138.41
135.71
133.64
129.80
127.79
116.14
66.60
45.22
41.77
30.55
26.98
19.41
TBDPSO
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC traces (Chiralcel OD-H, 0.8% 2-propanol in *n*-hexane, flow rate 0.4 mL/min)



Racemic:

```
Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.116 BV    0.4723 9223.66211  296.99054  49.3366
   2  19.408 VB    0.5359 9471.71582  269.56857  50.6634

Totals :                 1.86954e4   566.55911
```

Enantioenriched:

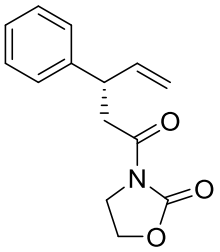
```
Signal 4: DAD1 D, Sig=230,16 Ref=360,100

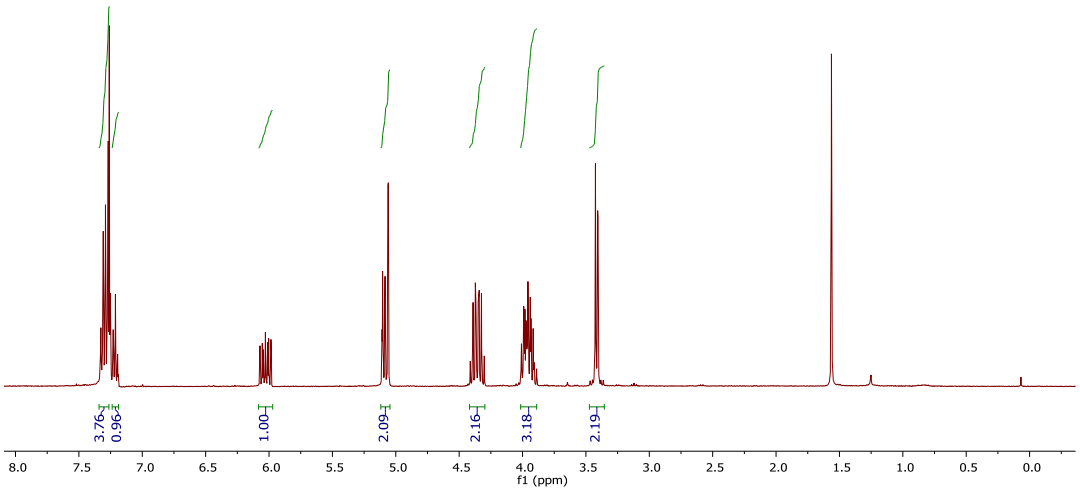
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.307 BB    0.6258 2.33249e4   576.78265 100.0000

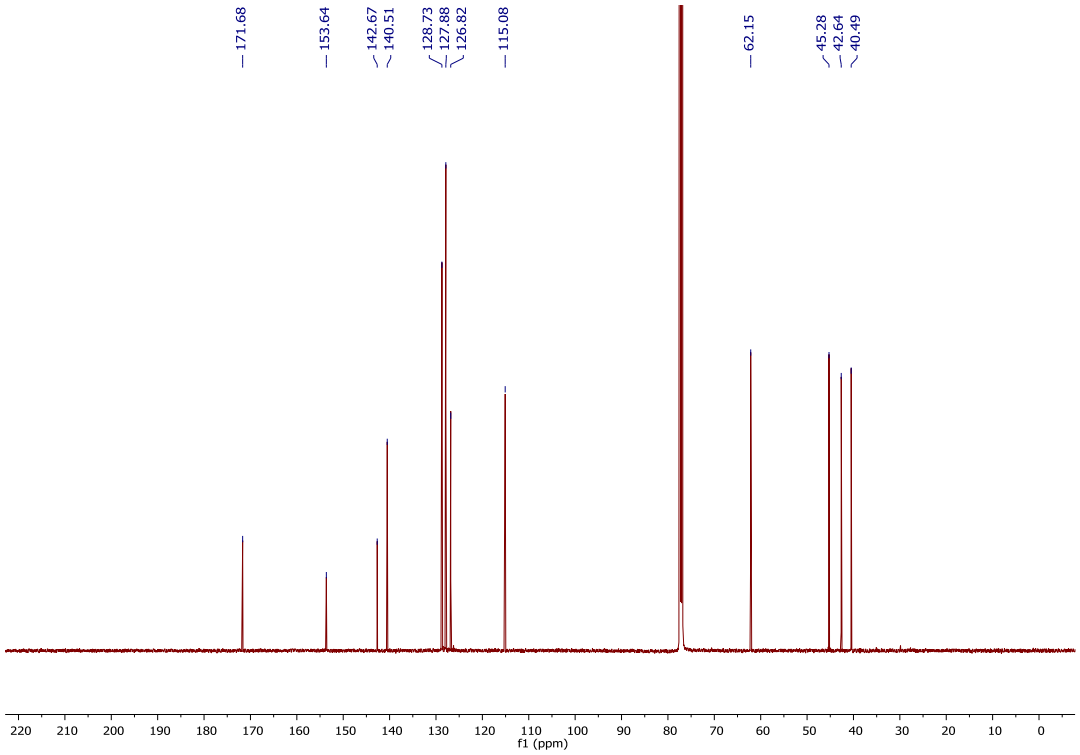
Totals :                 2.33249e4   576.78265
```

6.1.2 Imide 2.4.44

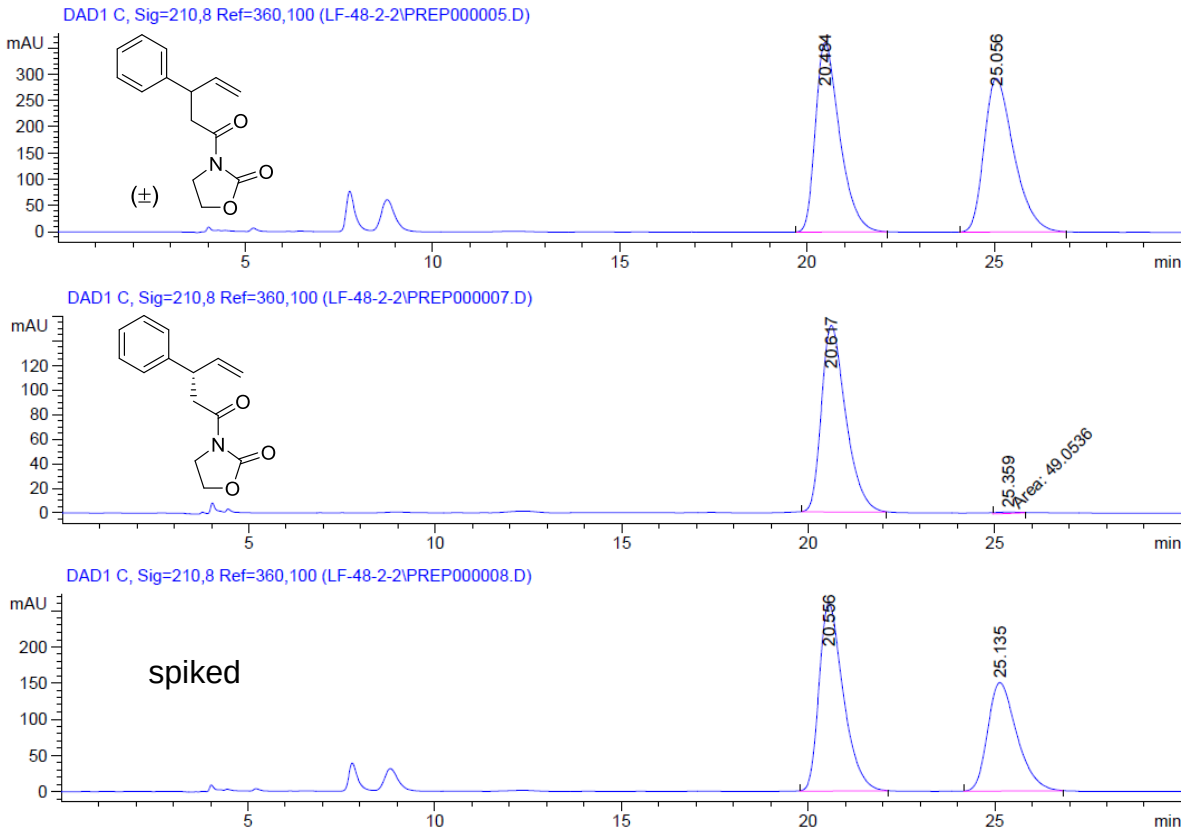
(S)-3-(3-Phenylpent-4-enoyl)oxazolidin-2-one







HPLC traces (Chiralcel OD-H, 20% 2-propanol in *n*-hexane, flow rate 0.9 mL/min)



Racemic:

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.484	BB	0.6847	1.62008e4	360.19159	50.1123
2	25.056	BB	0.8441	1.61282e4	292.11569	49.8877
Totals :				3.23289e4	652.30728	

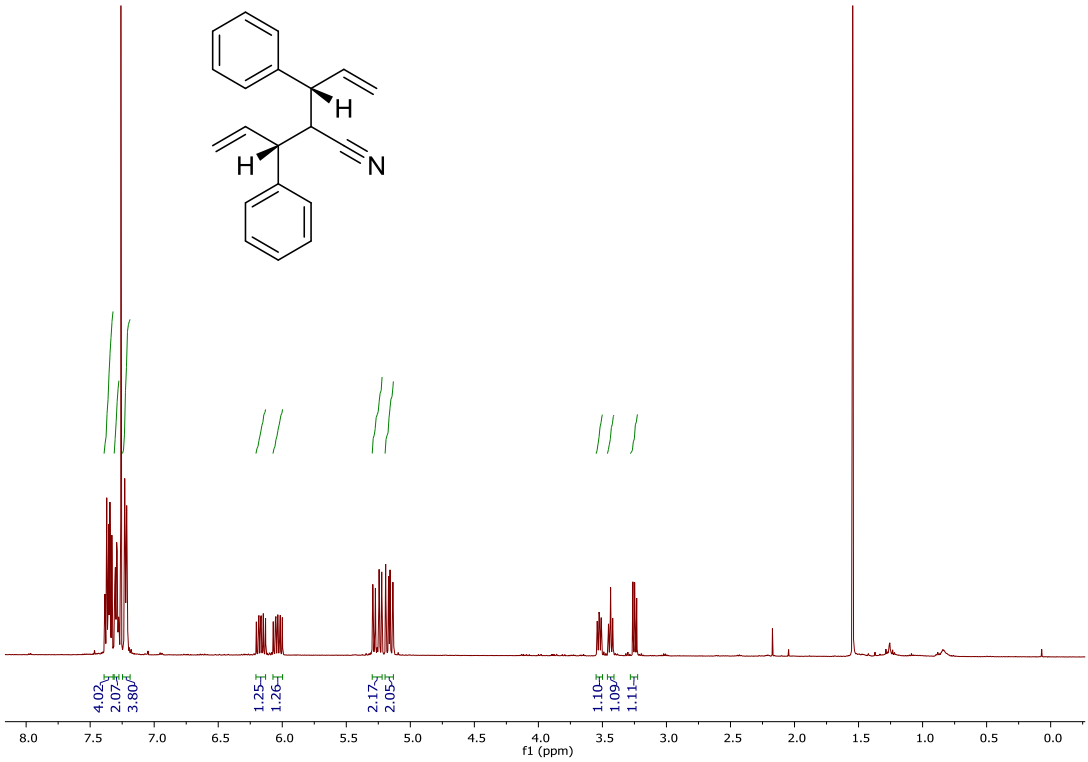
Enantioenriched:

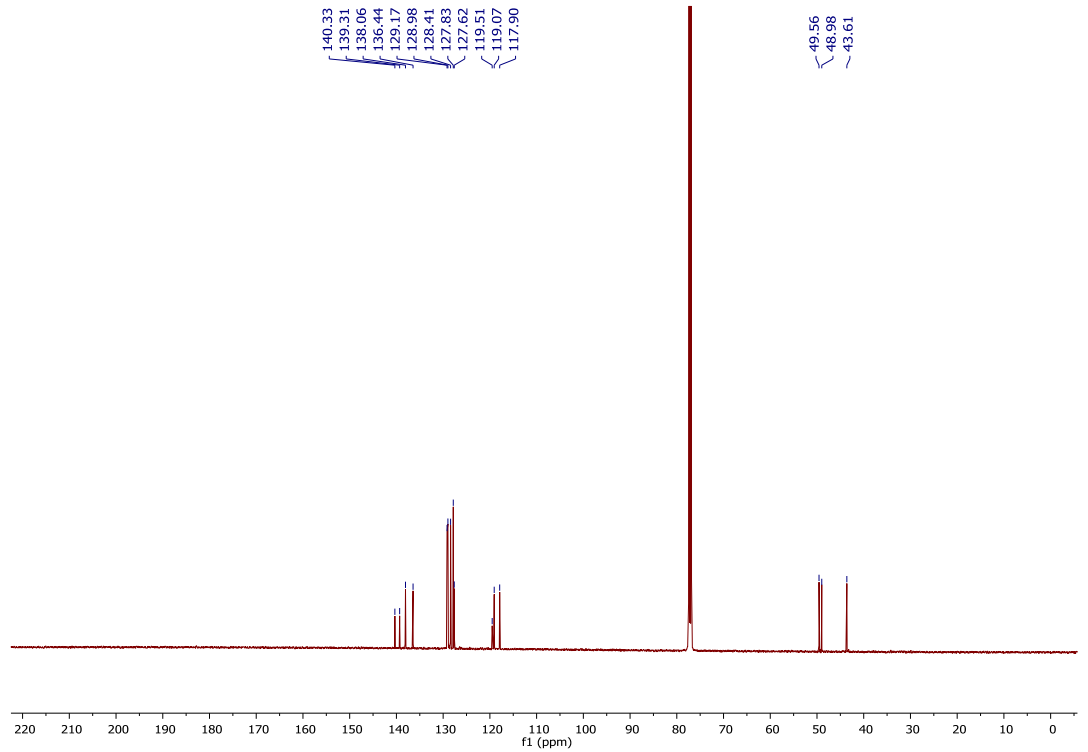
Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.617	BB	0.6942	6903.33789	151.90750	99.2944
2	25.359	MM	0.5382	49.05356	1.09514	0.7056
Totals :				6952.39145	153.00264	

6.1.3 Nitrile 2.4.36

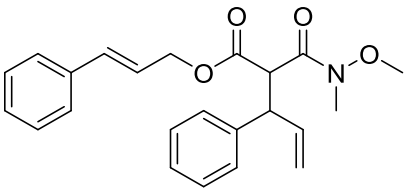
(R)-3-Phenyl-2-((R)-1-phenylallyl)pent-4-enenitrile



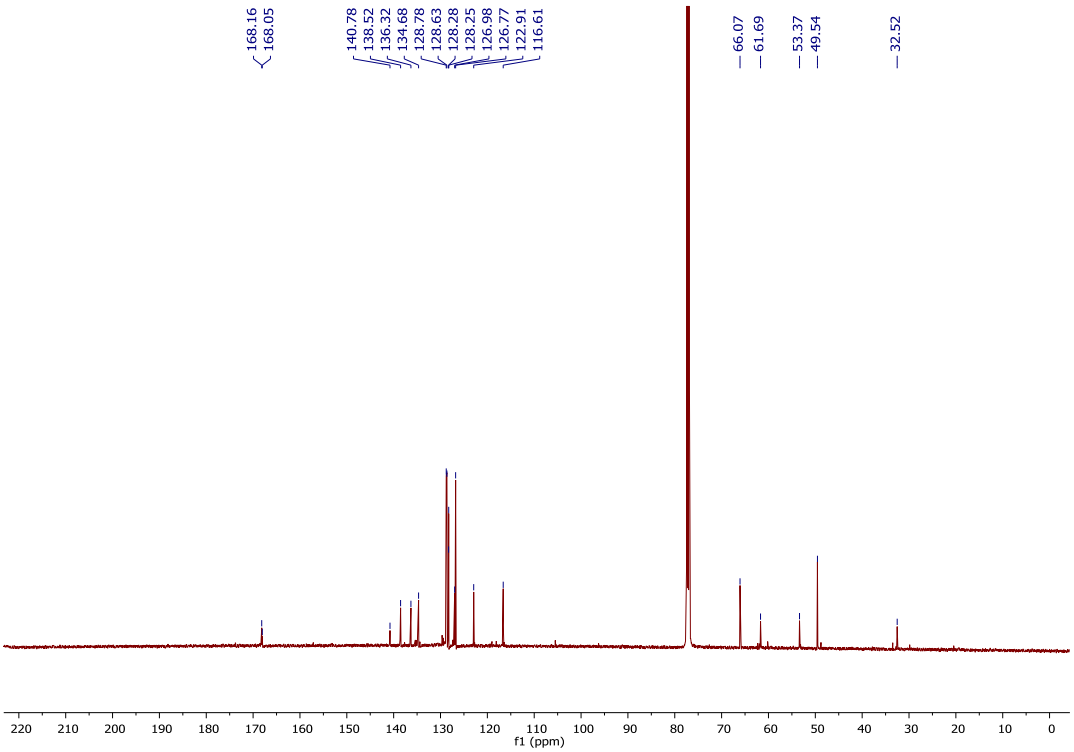


6.1.4 *β*-Amidoester 2.4.42

Cinnamyl 2-(methoxy(methyl)carbamoyl)-3-phenylpent-4-enoate

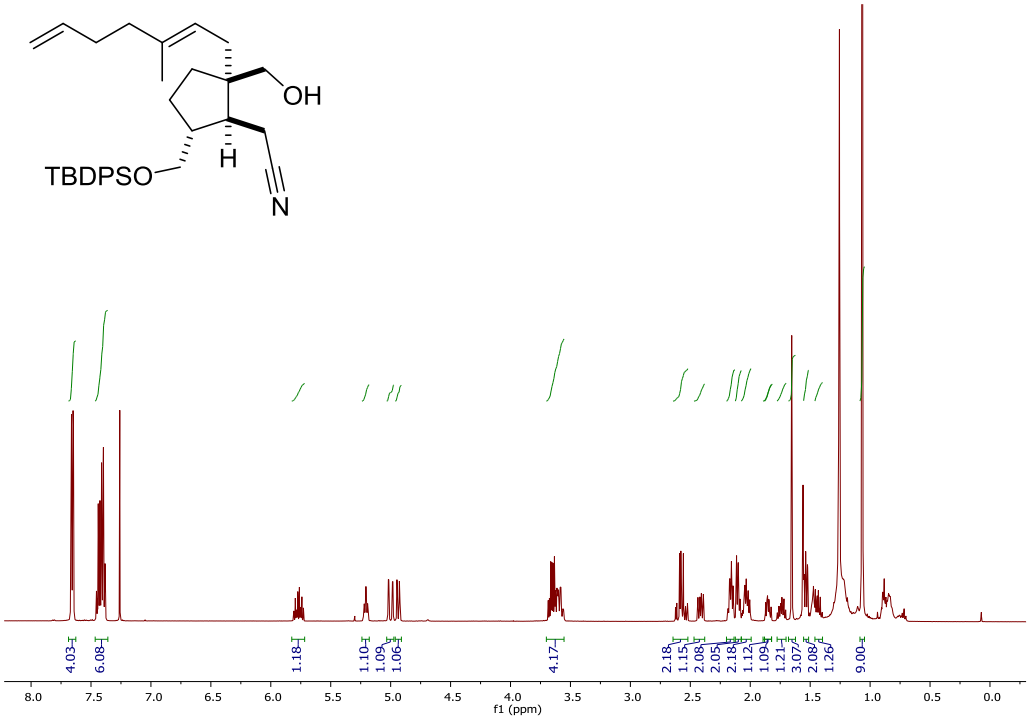


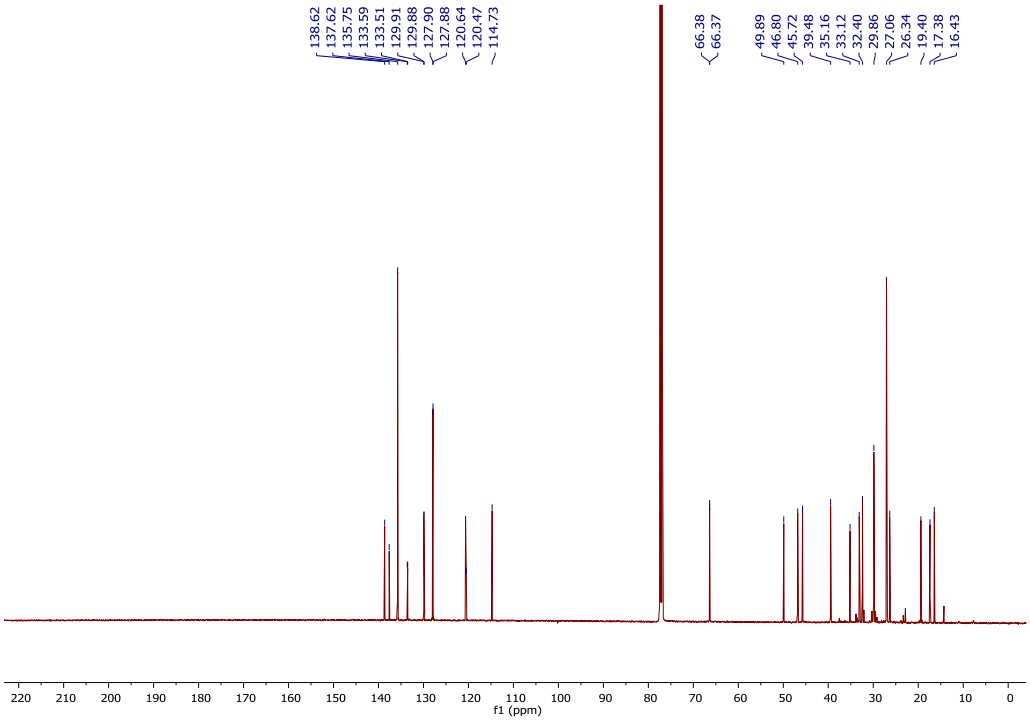
One of the diastereomers

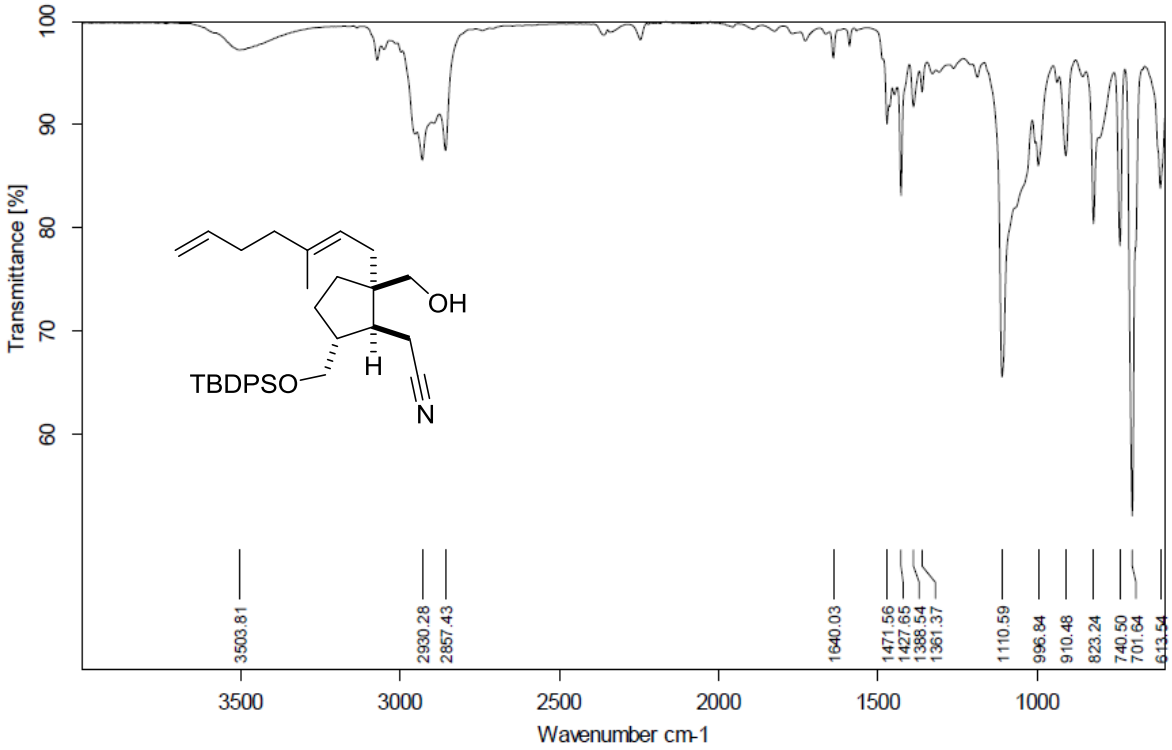


6.1.5 Alcohol (±)-3.6.1

(±)-2-((1S,2S,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-(hydroxymethyl)-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile

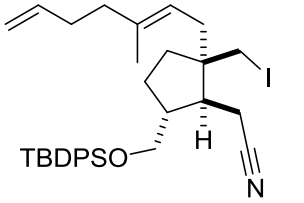


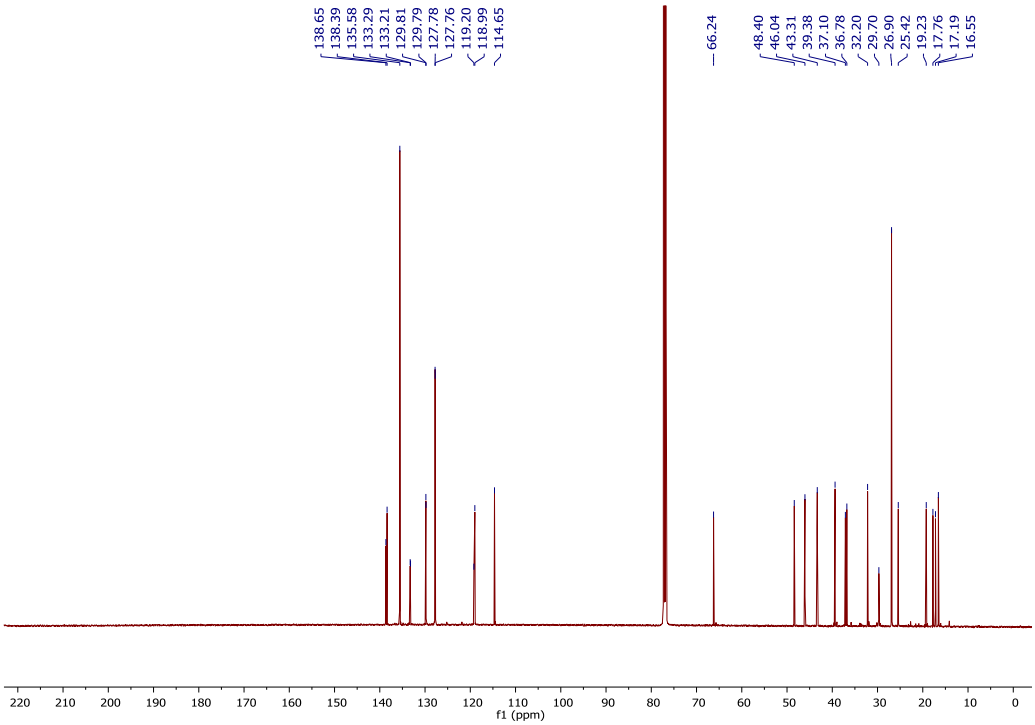



Transmittance [%]
100
90
80
70
60
OH
H
TBDPSO
N
3503.81
2930.28
2857.43
1640.03
1471.56
1427.65
1388.54
1361.37
1110.59
996.84
910.48
823.24
740.50
701.64
613.54
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

6.1.6 Iodide (±)-3.6.2

(±)-2-((1S,2S,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-(iodomethyl)-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile





6.1.7 Alkane (±)-1.18

(±)-2-((1S,2R,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-methyl-2-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile

