Enantioselective desymmetrisation of bis-alkenyltriflates via palladium-catalysed carbonylation

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Enantioselective Desymmetrisation of *bis*-Alkenyltriflates *via* Palladium-Catalysed Carbonylation

Submitted by Simon Joseph Byrne
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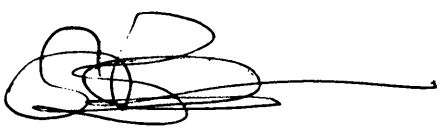

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Abstract

This thesis details studies towards the enantioselective desymmetrisation of *bis*-alkenyltriflate subtrates *via* palladium-catalysed carbonylation. These achiral substrates contain two enantiotopic faces and a mirror plane, which is destroyed upon mono-functionalisation to produce esters that contain a stereodefined chiral quaternary carbon centre.

Chapter 1 comprises a literature review of palladium-catalysed carbonylative chemistry, with mechanistic aspects and reaction scope described.

Chapter 2 discusses the principles of enantioselective desymmetrisation, and also provides a literature review of both the pioneering work and recent advances in this field.

Chapter 3 presents the work undertaken and results obtained throughout the desymmetrisation studies. Chapter 3.1 details initial studies such as the preparation of a simple *bis*-alkenyltriflate, with optimisation of an enantioselective desymmetrisation reaction described in chapter 3.2. Chapter 3.3 details three kinetic experiments performed on a simple *bis*-alkenyltriflate in an attempt to understand more about the specific mechanisms at work in this process. Chapter 3.4 investigates the use of alternative nucleophiles such as alcohols and amines in this carbonylation reaction. The incorporation of polymer supported alcohols as scavenger reagents is covered in chapter 3.5, and the variation of the ligand structure is probed in chapter 3.6. Chapter 3.7 explores the development of alternative substrates with varying core structure, or bearing enantiotopic groups of differing size/electronic nature. Also briefly investigated in chapter 3.8 are substrates with other halide/pseudo-halide activating groups. The work described in chapter 3.9 aims to synthesise a substrate able to undergo an intramolecular desymmetrisation reaction to form a lactone/lactam product.

Chapter 4 provides conclusions to this work, and also future work to be undertaken in this field of study.

Acknowledgements

I would like to firstly thank Dr. Mike Willis not only for giving me the opportunity to do a PhD under his supervision, but also for the enthusiasm and ideas he has given me throughout my studies.

I also have to thank all members of the Willis group who have been present at some point over the past 4 years; Helen who started at the same time as me and suffered my moods for three years, Matt for weekend work and general banter, and Fletch (MAP specialist) for also being rubbish with palladium. The rest, in no particular order; Jimmy and Baxo (the SCS), Ai-san (o-genki desu ka), Nikki, Jay (-Dog), Taddo, Dawn, Gary, Gareth, Rob, Luke, Ana, Ollie, Scott, and Roy. Special thanks goes to those who got stuck with proof-reading.

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I can't forget my friends Dino, Andy, Gareth, Rob, and Sarah amongst others, and the mighty Chemistry FC who are now one goal per season worse off.

Finally thanks to my family. I dedicate this to my mother and father for not letting me give up before I had started, despite situations that made me think twice, and for always telling me I am smarter than I really am.

Contents

Abbreviations and Acronyms

δ	Chemical shift (ppm)
η	Hapacity
ν	Frequency
Å	Angstrom
AAA	Asymmetric allylic alkylation
Ac	Acetyl
Acac	Acetylacetenoate
AcO	Acetate
Alk	Generic alkyl group
^{t}Am	*tert*-Amyl
app.	Apparent
aq.	Aqueous
Ar	Aryl
atm.	Atmosphere
B	Generic Base
BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-napthol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
BOM	Benzyloxymethyl
br	Broad
Bs	Benzenesulfonyl
Bu	*n*-Butyl
^{i}Bu	*iso*-Butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-Butyl
°C	Degrees Celcius
Cbz	Benzyloxycarbonyl
CI	Chemical ionization
cod	Cycloocta-1,5-diene
Cp	Cyclopentadienyl ligand
Cy	Cyclohexyl
d	Doublet

DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	*trans,trans*-Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DET	Diethyltartrate
DIOP	2,3-*ortho*-Isoprpylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) propane
DIPT	Di-*iso*-propyltartrate
DMAP	4-*N,N*-Dimethylaminopyridine
DMA	*N,N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMP	Dimethyl phthalate
DMSO	Dimethylsulfoxide
DPEphos	Bis(2-diphenylphosphino)-phenyl ether
dppe	1,2-Bis(diphenylphosphino)-ethane
DPPF	1,1'-Bis(diphenylphosphino)-ferrocene
dppm	1,1-Bis(diphenylphosphino)-methane
dppp	1,3-Bis(diphenylphosphino)-propane
dr	Diastereomeric ratio
Me-DUPHOS	1,2-Bis(2,5-dimethylphospholano)benzene
E-	Entgegen
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalent
ES	Electrospray ionization
Et	Ethyl
HPLC	High performance liquid chromatography
h	hour
HRMS	High resolution mass spectrum
Hz	Hertz
IR	Infrared
J	Coupling constant
JOSIPHOS	[2-(Diphenylphosphino)ferrocenyl]ethyl dicyclohexyl-phosphine
KHMDS	Potassium bis(trimethylsilyl)amide

L	Ligand
L*	Chiral ligand
LDA	Lithium di-*iso*-proylamide
LRMS	Low resolution mass spectrum
M	Metal (schemes)
M	Molar/molarity (text)
m	Multiplet
m-	*meta*-
Me	Methyl
MeCN	Acetonitrile
MeO-MOP	2-Diphenylphosphino-2'-methoxy-1,1'-binaphthyl
MEPY	Methylpyridine
Mes	Mesityl, 2,4,6-trimethylphenyl
MHz	Megahertz
min	Minute
mmol	Millimole
MOM	Methoxymethyl
mp	Melting point
MS	Mass spectrometry/spectrum (text)
MS	Molecular sieves (schemes)
Ms	Methanesulfonyl/mesyl
m/z	Mass to charge ratio
Nap	Naphthyl
Nf	Nonafluorobutanesulfonyl
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear Magnetic Resonance
Nuc	Nucleophile
o-	*ortho*-
Oct	*n*-Octyl
p-	*para*-
P	Generic protecting group
Ph	Phenyl
PHOX	Phosphine oxazoline
Piv	Pivoyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl

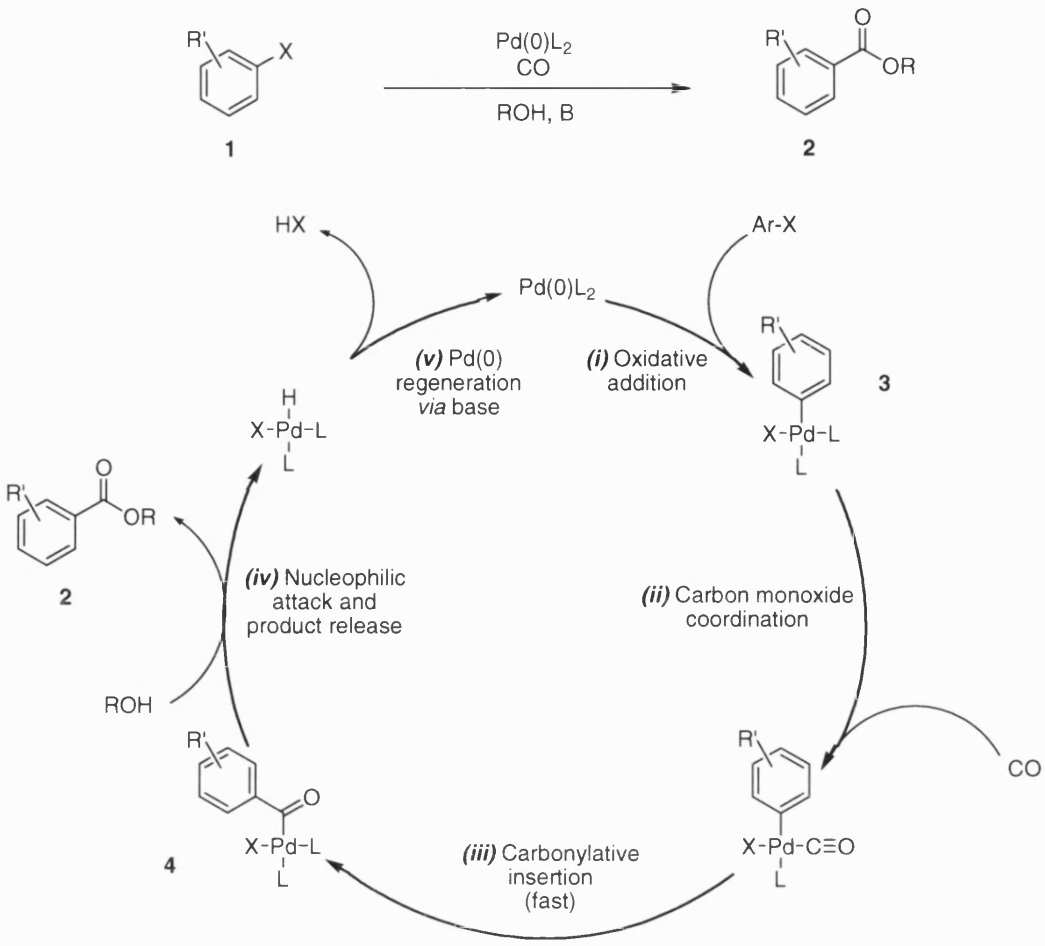
PPh_3	Triphenylphosphine
ppm	Parts per million
Pr	*n*-Propyl
^{i}Pr	*iso*-Propyl
q	Quartet
QUINAP	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
R	Generic group/substituent
RCM	Ring closing metathesis
rt	Room Temperature
Ref(s).	Reference(s)
s	Singlet
SEM	(2-Trimethylsilylethoxy)methyl
t	Triplet
TADDOL	2,2-Dimethyl-α,α,α',α',-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TCE	Trichloroethylene
TFA	Trifluoroacetic acid/trilfluoroacetate
Tf	Trifluromethanesulfonyl
THF	Tetrahydrofuran
THFA	Tetrahydrofurfuryl alcohol
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylene diamine
TMS	Trimethylsilyl
Tol	Tolyl
Tr	Trityl
Ts	*para*-Toluenesulfonyl
TsO	*para*-Toluenesulfonate/tosylate
X	Generic halide or *pseudo*-halide unless otherwise defined
Z-	Zusamen

Chapter 1: Palladium-Catalysed Carbonylation

1.1 - Introduction and mechanism

Palladium-catalysed reactions have come to the forefront of organic synthesis in recent years. Their synthetic utility in a wide range of transformations, both achiral and enantioselective[1] has lead to a great deal of interest in exploiting this in methodology and natural product synthesis. They have been shown to effect a wide range of *C-C* and *C-X* bond forming reactions (*X* = heteroatom), and as such have become commonplace in modern chemistry. The introduction of carbon monoxide into these reaction pathways has also been extensively studied, and by doing so it can be introduced into a number of different sites in organic molecules, leading to products such as esters, amides, carboxylic acids and ketones.[2] This field of research is so vast that no review can be all-encompassing, however the fundamentals of the reaction and some of the major achievements in the field will be covered.

The first examples of such a process were reported by Heck, among others in 1974.[3-7] He investigated the palladium-catalysed reactions of aryl, vinyl and benzyl halides with alcohols under an atmospheric pressure of carbon monoxide. Results were extremely promising, producing the desired esters in up to 96% yield, and the following mechanism for alkoxycarbonylation of an arylhalide was postulated (Scheme 1):



Scheme 1: mechanism of palladium-catalysed alkoxycarbonylation

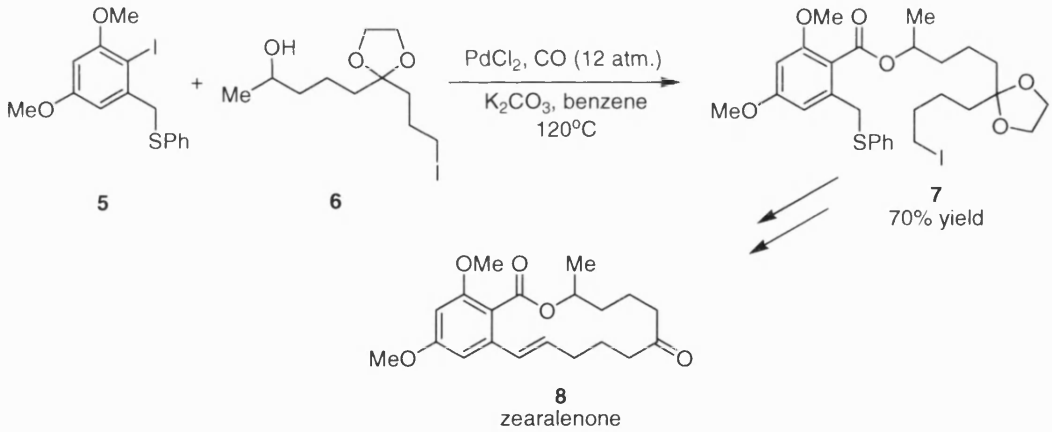
The reaction commences with ***(i)*** oxidative addition of an arylhalide (Ar-X) **1** to a palladium (0) catalyst to form **3**. Carbon monoxide can then coordinate to the catalyst *via* ligand displacement ***(ii)***, and perform an insertion into the *Pd-C* bond ***(iii)*** to form acyl-palladium species **4**. A nucleophile, in this case an alcohol, then attacks this acyl-palladium complex ***(iv)*** to release the coupled product **2** and form a hydrido-palladium adduct which is then treated with base ***(v)*** to regenerate the palladium (0) catalyst.

An alternative to this mechanism involves the addition of organometallic reagents in place of the nucleophile, and follows a *transmetallation-reductive elimination* pathway once the *Pd-C* carbonyl insertion has taken place. Specific types of these reactions will be discussed later. Aryl/vinyl iodides and bromides are the most common halides to undergo this reaction due to ease of oxidative addition into the *C-X* bond, however aryl chlorides have also been known to

react in this manner, often with the aid of electron-rich phosphine ligands to increase electron density at the palladium centre.[8] Aside from halides, the most commonly used activating groups are the *pseudo*-halide aryl/alkenyl triflates which are readily prepared from the parent phenol or ketone.[9] Other *pseudo*-halides are also known to be useful for palladium-catalysed carbonylations including fluorosulfonates,[10] iodonium salts,[11, 12] iodoxyaryl compounds[13] and aryl diazonium salts.[14]

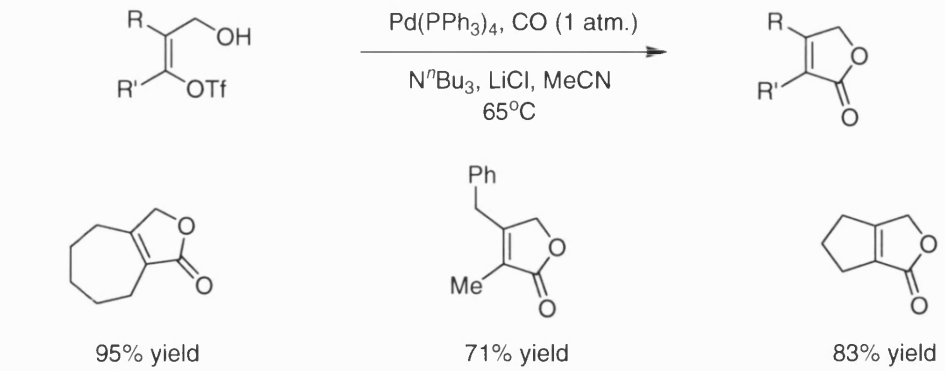
1.2 - The nature of nucleophiles in carbonylations

A good example of this carbonylation process is the intermolecular reaction between hindered aryliodide **5** and alcohol **6**.[15] The palladium-catalysed reaction under carbon monoxide pressure yielded ester **7** in 70% yield, as an intermediate in the synthesis of zearalenone **8** (Scheme 2). The selectivity of this reaction is of note, as the alkyliodide present in the alcohol fragment remains untouched.



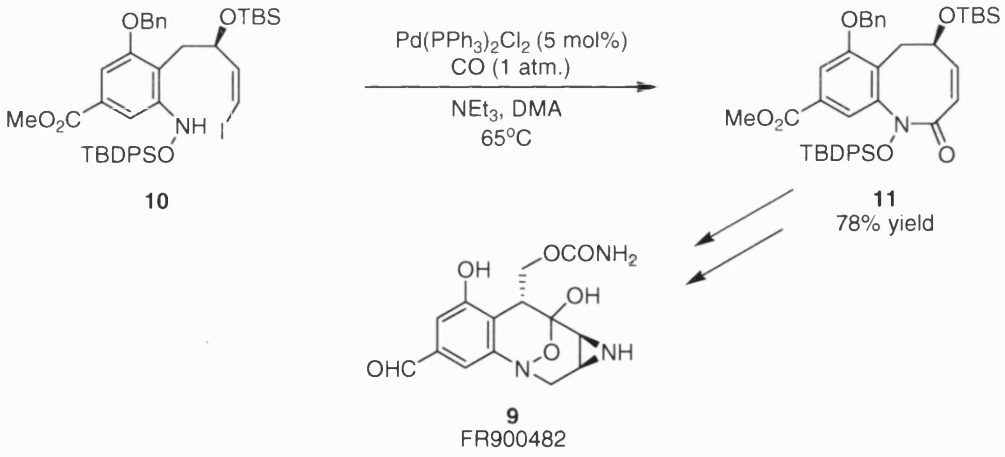
Scheme 2: intermolecular carbonylation in the synthesis of zearalenone

Intramolecular palladium-catalysed carbonylations have also found substantial use in organic synthesis. Crisp has demonstrated this in the synthesis of substituted α,β-butenolides from alkenyltriflates.[16] Reaction of the alkenyltriflates with the proximal primary alcohols in the presence of a palladium (0) catalyst generated the lactone products in good yields (Scheme 3). The reactions were also run under a carbon monoxide pressure of 1 atmosphere, making them more attractive than procedures that require high pressures.



Scheme 3: intramolecular carbonylative cyclisation of alkenyltriflates

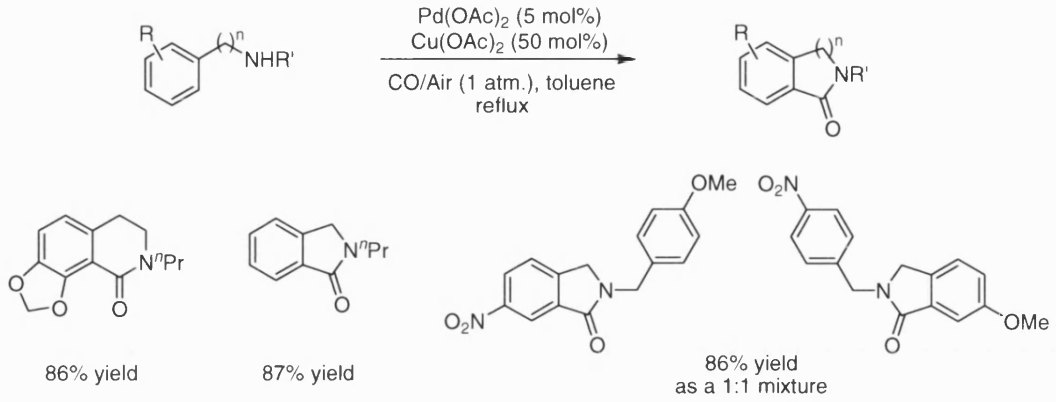
Amines are also effective nucleophiles for this chemistry, and react readily to give the corresponding aryl or α,β-unsaturated amides. This is well illustrated in Trost's recent synthesis of the mitomycin C analogue FR900482 (**9**) in which a palladium-catalysed carbonylation of vinyliodide **10** results in lactamisation to form **11**, which contains an 8-membered ring (Scheme 4).[17] Amines have been shown to react preferentially in couplings of chiral amino alcohols and aryl triflates, followed by cyclisation to produce oxazoline ligands.[18]



Scheme 4: palladium catalysed lactamisation in the synthesis of **9**

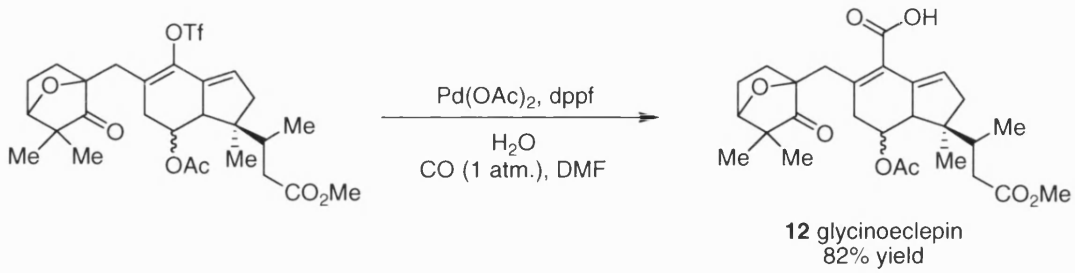
More recently, the formation of amides by carbonylation of unactivated aryl systems has been reported by Orito *et al.* in a atmosphere containing a mixture of carbon monoxide and air.[19] In this reaction, *ortho*-palladation of a phenyl alkylamine is followed by carbonyl insertion and nucleophilic attack of the amine

to produce the amide products in good yields (Scheme 5). A copper (II) acetate co-catalyst is used for reductive regeneration of the palladium (0) species *via* a Wacker-type process. Substrates bearing two different aryl groups were also tested, but provided mixtures of isomers.



Scheme 5: aminocarbonylation of unactivated aryl systems

The use of water as a nucleophile is also well-established, producing the aryl or α,β-unsaturated carboxylic acids. This is utilised in the synthesis of glycinoeclepin **12**, which exemplifies the mildness of this process by leaving numerous other functionalities untouched throughout the reaction(Scheme 6).[20]



Scheme 6: water as a nucleophile in carbonylation chemistry

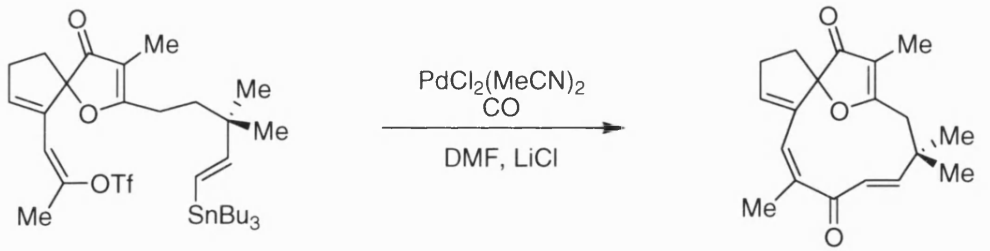
Under specific conditions other nucleophiles such as alkoxides (ester products)[21] and fluorides (acyl fluorides)[22] have been shown to be effective, whilst carbon nucleophiles including malonates (ketones)[23] and cyanides[24] have also displayed good reactivity. The carbonylation of benzaldehyde has also been reported in reactions incorporating hydrogen chloride, however this is thought to proceed through chloride attack of the aldehyde to form a benzyl chlorohydrin. This then undergoes carbonylation, followed by further chloride

attack, a second carbonylation and then decarboxylation.[25] It is also possible to use enolates as nucleophiles, with attack of the oxyanion generally favoured over that of the corresponding carbanion.[26, 27]

Double insertion of carbon monoxide is occasionally observed in this chemistry. Nucleophilic attack of alcohols and amides on these substrates yields the respective glyoxylate and α-keto amides.[28-30] This process is generally reserved for those reactions that require high pressures of carbon monoxide, however there are limited reports of it at atmospheric pressure.[31]

1.3 - Organometallic and related reagents in carbonylation chemistry

As alternatives to simple nucleophiles such as alcohols and amines, there are numerous options available to produce ketone and aldehyde products. Stannanes have been widely used in the preparation of ketones *via* this methodology. This can been seen in the reaction of alkenyltriflate **13** to produce the macrocyclic doubly α,β-unsaturated ketone **14** by intramolecular Stille reaction (Scheme 7).[32] Although the yield of this reaction is not spectacular, the formation of such a large ring system by such a macrocyclisation is a notable achievement.

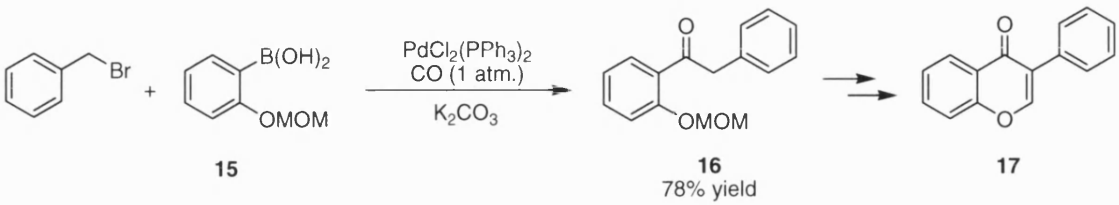


13 **14**
53% yield

Scheme 7: ketone formation by carbonylative Stille reaction

In similar fashion, reaction with alkyl tin hydrides produces the corresponding aldehyde.[33] Alternative preparations of aldehydes use either a mixture of carbon monoxide and hydrogen gas,[3] or introduce a hydride source such as sodium formate.[34] Carbonylative Suzuki reactions have been investigated, for example reaction of benzyl bromide with boronic acid **15** in the presence of a

palladium catalyst and carbon monoxide results in ketone **16**, which can be used in the synthesis of flavone **17** (Scheme 8).[33] Reactions where alkenes are subjected to hydroboration followed by Suzuki coupling have also been reported.[35] Simple trialkyl boranes are able to perform transmetallation as well in the presence of zinc salts, resulting in the aliphatic ketones.[36]



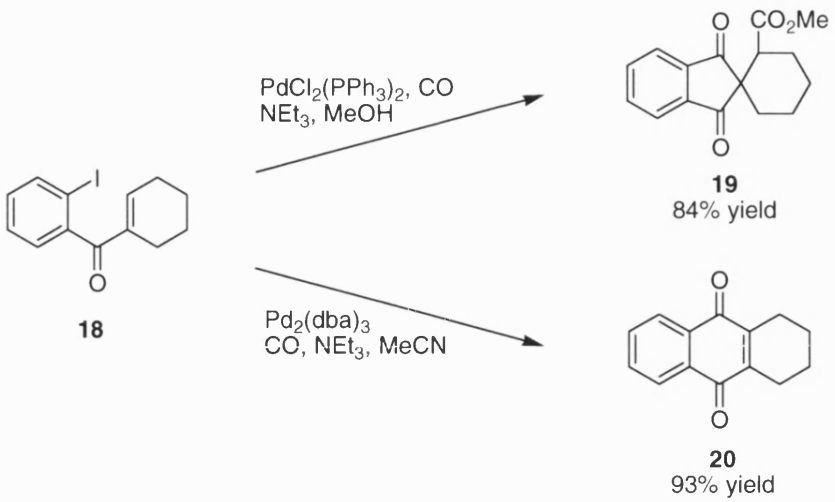
15 **16** 78% yield **17**

Scheme 8: example of a carbonylative Suzuki coupling

Negishi-type couplings to produce ketones are also applicable to carbonylation, where treatment of an alkyl halide with zinc and copper produces a organozinc reagent that is able to perform transmetallation.[37] Alternatively dialkyl- and diarylzinc reagents can be reacted directly with diaryliodonium salts in the presence of palladium catalysts.[38] Organoaluminium compounds can also be used for ketone synthesis[39] as well as there being reports of arylfluorosilanes being able to react in a similar manner in the synthesis of unsymmetrical ketones.[40, 41]

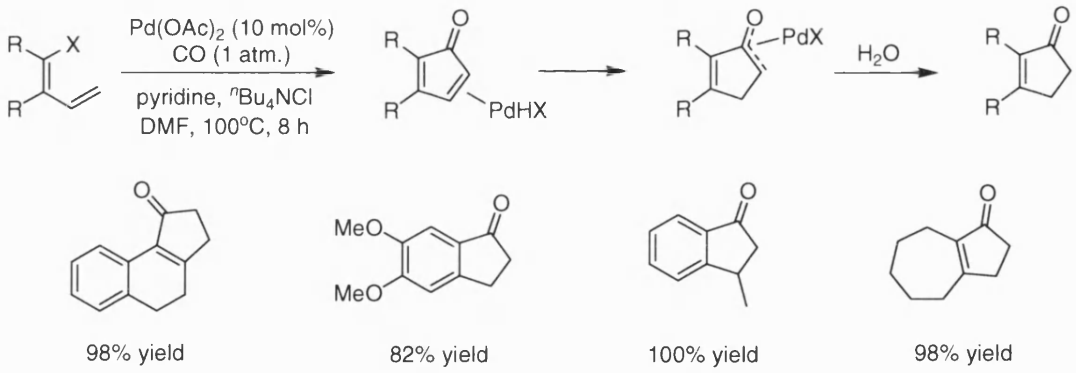
1.4 - Carbonylative reactions of alkenes and alkynes

The carbonylative Heck reaction has also been a topic of considerable interest in this methodology. Reactions between activated aryl- or alkenyl- substrates with alkenes in the presence of carbon monoxide provides the possibility to form unsaturated carbonyl compounds, as can be seen in the intramolecular carbonylative coupling of aryl iodide **18**. Interestingly in this example, variation of the catalyst system lead to two different cyclic ketone products with **19** and **20** selectively available in high yields (Scheme 9).[42, 43]



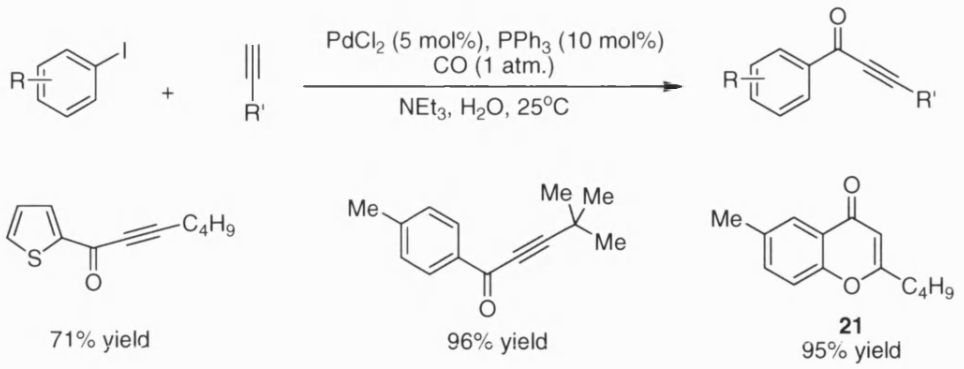
Scheme 9: selective product formation in an intramolecular Heck carbonylation

Larock has performed phosphine free reductive Heck reactions that also incorporate carbon monoxide in indanone and cyclopentenone syntheses.[44] Reaction of aryl- and vinylhalides to form indenones had been performed by Negishi, however unexpected traces of water in the reaction were able to act on the species formed by the addition of a hydrido-palladium species to the α,β-unsaturated ketones, with hydrolysis leading to the observed indanones (Scheme 10).



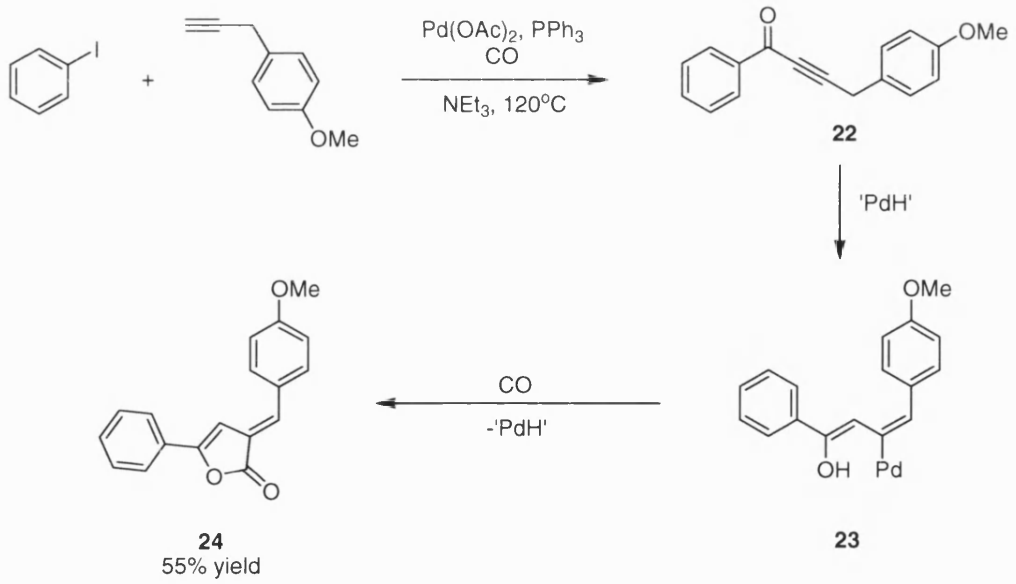
Scheme 10: indanone synthesis by palladium-catalysed carbonylation

Alkynes are also able to react under catalytic carbonylation conditions in Sonogashira-type processes. There has recently been the development of a copper-free carbonylative Sonogashira reaction using water as the solvent.[45] Varying aryl iodides could be coupled with terminal acetylenes to give the expected products in good yields. Use of 2-hydroxy aryliodides afforded flavones such as **21**, *via* intramolecular cyclisation (Scheme 11).



Scheme 11: carbonylative Sonogashira reactions of aryl iodides

Alper has reported a novel synthesis of butenolides from the addition of two equivalents of carbon monoxide in the Sonogashira coupling of iodobenzene and *para*-methoxybenzyl acetylene.[46] The initial coupling produces yields **22**, which then undergoes hydropalladation and enolisation to form **23**. A second carbonyl insertion into the alkenyl-palladium species followed by trapping with the enol produces *E*-3-arylidenebutenolide **24** (Scheme 12). Negishi has performed similar studies into the synthesis of related compounds.[47]

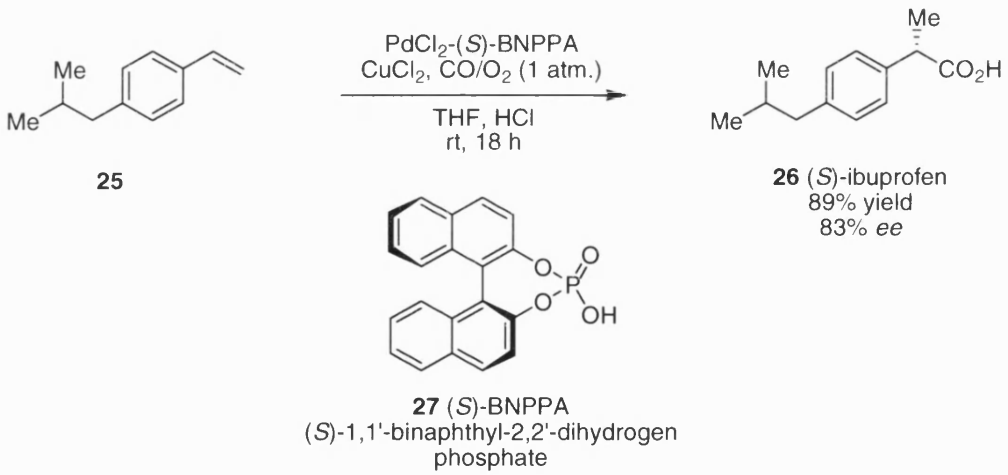


Scheme 12: Sonogashira coupling followed by carbonylative cyclisation

Reactions of benzynes with allyl-palladium species have been investigated by Chatani *et al.* with some success, producing bicyclic ketones bearing *exo*-alkenes.[48]

1.5 - Enantioselective palladium-catalysed carbonylations

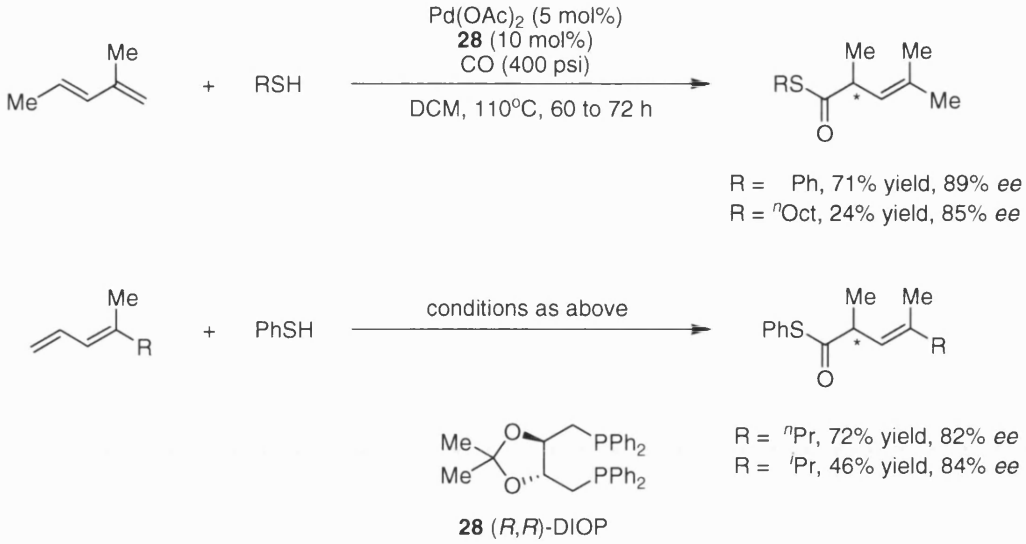
Many of the carbonylation processes described above can be applied to systems that involve the creation of new stereocentres.[1] The ease in which reaction conditions can be adapted simply by addition of chiral ligands makes this an attractive proposition. One simple but effective example of this is illustrated by the synthesis of the anti-inflammatory agent (*S*)-ibuprofen **26**.[49] Palladium-catalysed hydrocarboxylation of styrene **25** with phosphate ligand **27** leads to production of the desired carboxylic acid in good yield and *ee* (Scheme 13).



Scheme 13: enantioselective carbonylation in the synthesis of (*S*)-ibuprofen

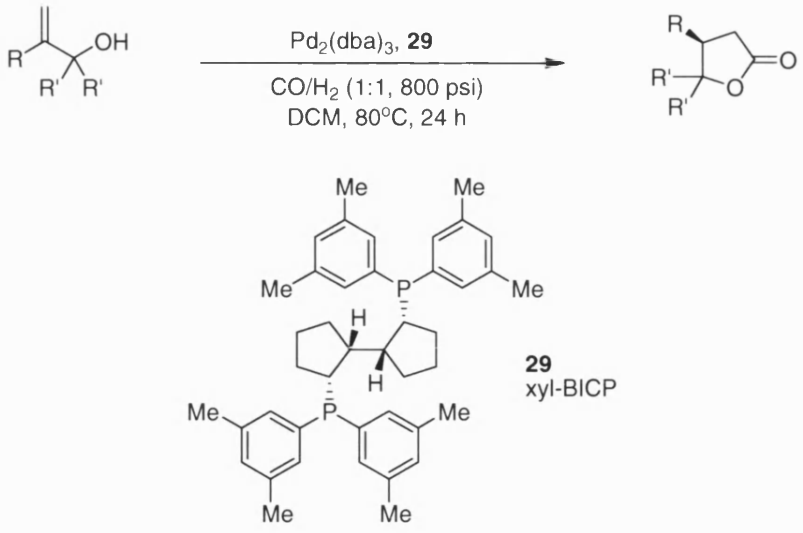
A *bis*-alkoxycarbonylation reaction of styrenes has also been reported by Consiglio *et al.*[50] Alper has discovered the enantioselective thiocarbonylation of prochiral alkenes.[51] Reaction of simple alkenes with carbon monoxide and a thiol in the presence of a palladium catalyst and the chiral ligand (*R*,*R*)-DIOP **28** provided the thioester products in good yields and enantioselectivities (Scheme 14). The reaction was applied to both terminal and *trans*-substituted alkenes, as

well as cyclic systems, however high pressures of carbon monoxide were required to effect the transformation.



Scheme 14: enantioselective thiocarbonylation of prochiral alkenes

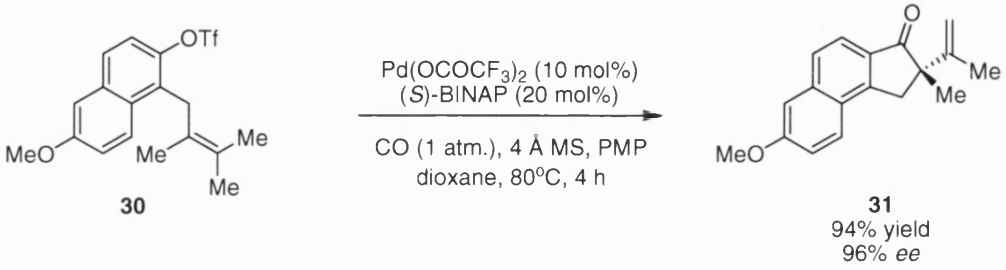
A selection of β-allylic alcohols have been used in cyclocarbonylation reactions to form alkylated lactones with excellent yields and enantioselectivities by Zhang *et al.*[52] (Table 1). The reactions used chiral xyl-BICP ligand **29** but again required high pressures of carbon monoxide as a 1:1 mixture with hydrogen. The methodology was also extended to the synthesis of *trans*-α,β-disubstituted chiral lactones with equal success, whilst a similar lactam forming reaction has been investigated by Alper.[53]



R	R'	Yield (%)	*ee* (%)
Ph	Me	87	95
para-FC_6H_4	Me	91	96
ortho-MeC_6H_4	Me	91	82
Me	Ph	91	74

Table 1: synthesis of small ring lactones

More recently, Hayashi has reported the enantioselective synthesis of indanones and related compounds by intramolecular carbonylation.[54] The allyl-aryltriflate **30** could be cyclised in the presence of a palladium-BINAP catalyst system to yield the indanone **31** in excellent yield and *ee* (Scheme 15). What is especially impressive is that the product also contains a stereodefined quaternary carbon centre and the reaction required only atmospheric carbon monoxide pressure.

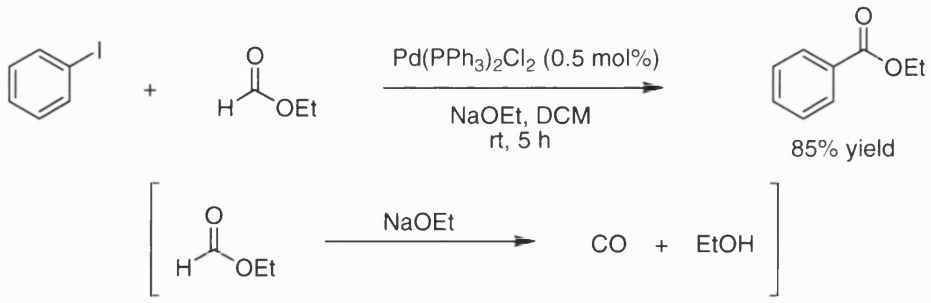


Scheme 15: enantioselective indanone synthesis by palladium-catalysed carbonylation

Enantioselective copolymerisation has also been shown to be possible using chiral palladium catalysts and carbon monoxide, with efficient systems developed by Lu,[55] Consiglio,[56] Sen[57] and Nozaki.[58]

1.6 - Carbonylations in the absence of gaseous carbon monoxide

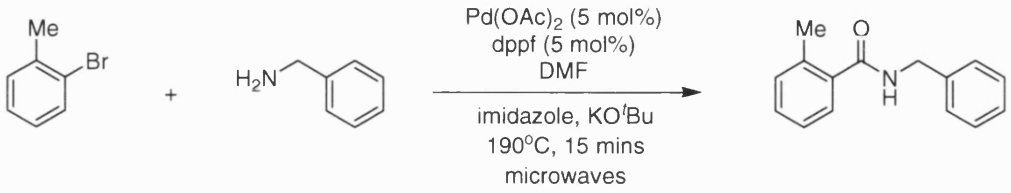
Despite the apparent synthetic utility of carbonylation chemistry there remains the drawback that carbon monoxide is a toxic gas. In addition to this, high pressures are sometimes required to facilitate the desired transformations which can make certain procedures less attractive to the synthetic chemist due to the need for specialist equipment to perform the reactions in. Due to these problems, the development of solid and liquid reagents that form carbon monoxide *in situ* has received considerable attention.[59] The use of alkyl formates and their corresponding alkoxides has been reported by Petit *et al.* in the carbonylation of iodobenzene and similar simple aryl iodides.[60] The action of the alkoxide on the formate ester causes decarbonylation to form carbon monoxide and an alcohol, which is then able to participate in the carbonylation process (Scheme 16). Reactions with ethyl formate/sodium ethoxide were able to be performed at room temperature, however the analogous methyl combination required elevated temperatures to effect decarbonylation. Potassium *tert*-butoxide proved too strong a base and violent decarbonylation of the formate occurred even at 0°C.



Scheme 16: carbonylation using formate esters

It has also been shown that *N,N*-dimethylformamide can be used as a source on carbon monoxide in work by Alterman.[61] Action of potassium *tert*-butoxide

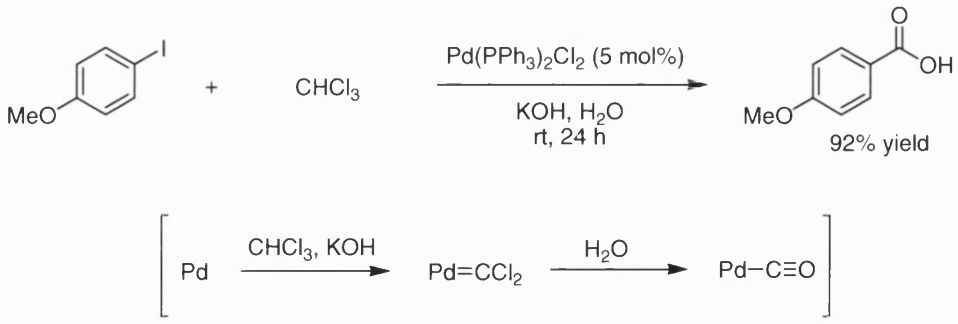
on *N,N*-dimethylformamide under microwave irradiation forms carbon monoxide and dimethylamine. This enables the coupling of a range of aryl bromides with amines (Scheme 17). An excess of the amine had to be used in the reactions to ensure it acted as the nucleophile in preference to either the dimethylamine produced by decarbonylation or the imidazole used as base for catalyst regeneration.



Scheme 17: *N,N*-dimethylformamide as a source of carbon monoxide

Cacchi *et al.* have also shown that a mixture of a formate salt and acetic anhydride can achieve similar results by formation of a mixed anhydride which decomposes to acetic acid and carbon monoxide upon heating.[62]

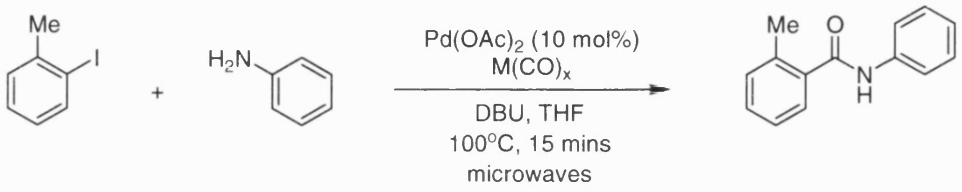
One surprising method for performing carbonylation reactions in the absence of gaseous carbon monoxide involves the use of chloroform.[63] Reaction with aqueous alkali and palladium forms a palladium-bound dichlorocarbene, which hydrolyses to produce ligated carbon monoxide for insertion reactions (Scheme 18). It has been used in the hydroxycarbonylation of aryl halides to form the acid products in good yields.



Scheme 18: chloroform as a carbon monoxide equivalent

Metal carbonyl reagents have also found use in this methodology. Liberation of a ligated carbon monoxide from one metal reagent is clearly a more favourable

process in terms of bond-dissociation energy than liberation of the gas from organic molecules. Corey reported a simple and efficient procedure for the alkoxylcarbonylation of aromatic and vinyl iodides using alkoxide and nickel tetracarbonyl,[64] and similar reports exist for iron pentacarbonyl.[65] The use of these reagents usually relies on the metal complex being both a functional reagent and source of carbon monoxide, however they have been shown to display reactivity solely as sources of carbon monoxide in the palladium-catalysed carbonylation of aryliodides by Larhed.[66] Reaction of an aryliodide with aniline in the presence of a palladium catalyst and substoichiometric quantities of metal carbonyls was able to produce the amide products in good yields (Table 2). In addition to this work, molybdenum hexacarbonyl has been employed as a carbon monoxide source in couplings of aryl bromides with both amines[67] and sulfonamides.[68]



Entry	$M(CO)_x$	Yield (%)
1	$Cr(CO)_6$	80
2	$Mo(CO)_6$	84
3	$W(CO)_6$	77
4	$Fe(CO)_5$	0
5	$Fe_3(CO)_{12}$	0
6	$Co_2(CO)_8$	28

Table 2: metal carbonyl carbon monoxide sources in palladium-catalysed carbonylation

In conclusion, palladium-catalysed carbonylation chemistry has been shown to be diverse methodology. It allows for a range of transformations to form products such as esters, amides, carboxylic acids, aldehydes and ketones in very efficient reactions and without the need for stoichiometric quantities of the harsh reagents often used in the synthesis of these functional groups. Addition of chiral ligands to the catalyst system is an effective way of generating new

stereocentres. Alternatives to carbon monoxide have also been discovered that can produce the reagent *in situ* and avoid the use of gaseous reagents.

Chapter 2: Catalytic Enantioselective Desymmetrisation

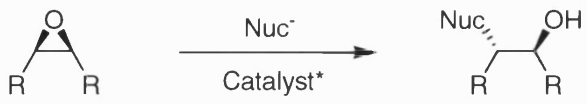
2.1 - Introduction and principle

The aim of this chapter is to provide an overview on the highlights achieved in the area of enantioselective desymmetrisation. Whilst the major contributions and pioneering work in each substrate and reaction class will be mentioned, the main focus will be on those examples that manage to achieve their goal *via* a catalytic process.

Enantioselective desymmetrisation is becoming an effective method of generating highly enantiopure products from achiral or *meso*- molecules.[69] It requires that the substrate to be desymmetrised contains a plane of symmetry which, upon reaction with a chiral reagent, is destroyed either by direct reaction at this centre, or at a reactive group that appears on both sides of this plane. This is a process that has the ability to create a molecule containing multiple stereo-defined centres by a single reaction. Until recent years, enzymes were widely used as very effective tools for this process,[70] however the desire to be able to effect a wider range of transformations had led to great interest in developing specific systems that can be tailored to fit the needs of the substrate.

The method of desymmetrisation is highly dependent on the nature of the substrate, two examples of which are illustrated below:

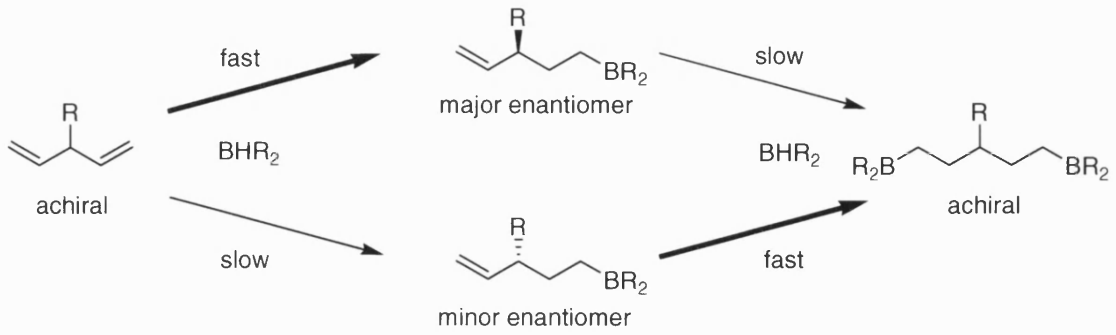
(i) single reaction of a compound which can then react no further e.g. attack of a nucleophile on a *cis*-epoxide (Scheme 19)



Scheme 19: desymmetrisation *via* epoxide opening

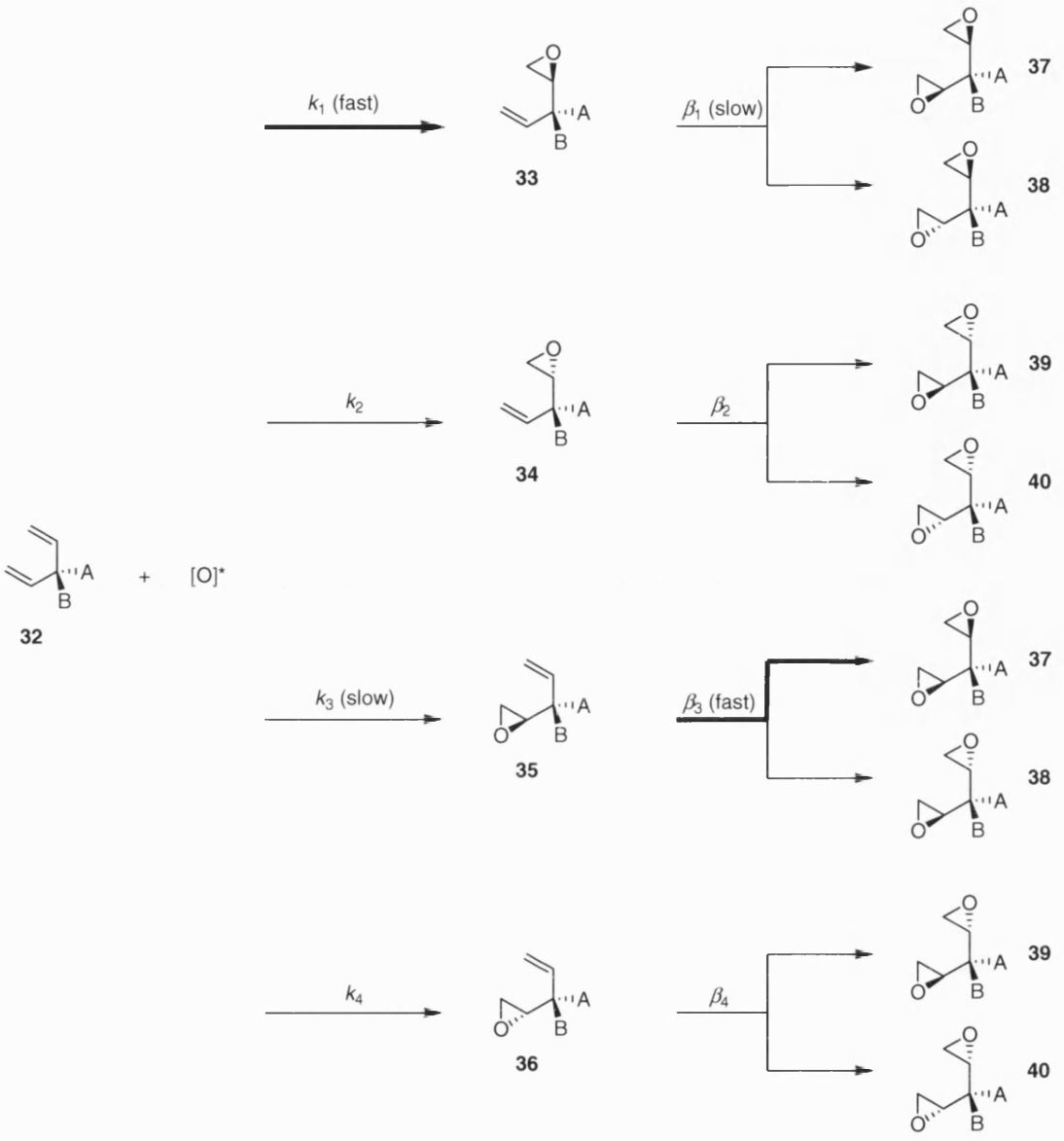
In this system, once the desymmetrising step has been performed, the active group that the functionalisation was performed on is altered, and no further reaction can happen.

(ii) discrimination between two groups of a *bis*-functional compound where further reaction is possible e.g. hydroboration of an achiral diene (Scheme 20)



Scheme 20: hydroboration of an achiral diene

After desymmetrisation, both the major and minor enantiomer can react further to produce a *bis*-functionalised achiral product. The potential double reaction of substrates of this type can often lead to an *in situ* kinetic resolution, illustrated by the desymmetrisation of an achiral diene by enantioselective epoxidation (Scheme 21).

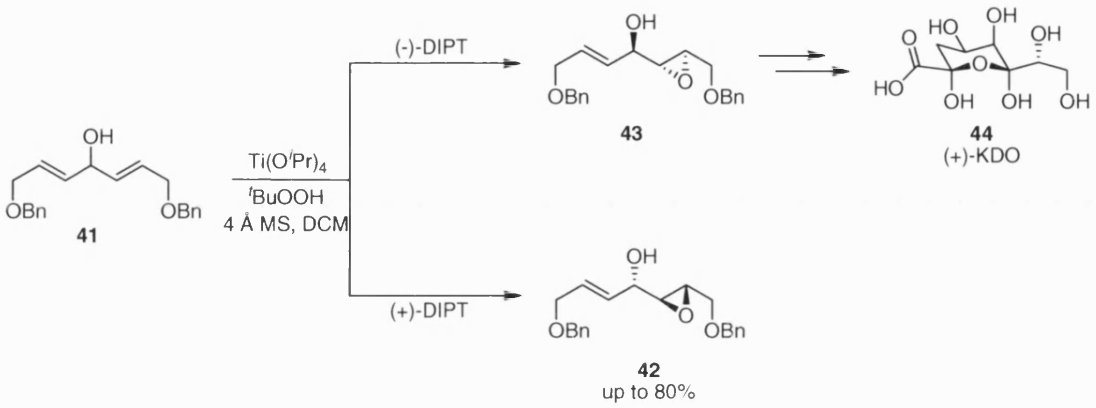


Scheme 21: hypothetical enantioselective desymmetrisation of an achiral diene

Action of a chiral epoxidising reagent ([O]*) upon diene **32** can form one of four stereoisomers **33**-**36**, where **33** and **35** are enantiomers (as are **34** and **36**). The nature of the chiral reagent will mean that formation of two of these products (**33** and **35**) will be favourable, and within these two products the difference between the enantiotopic faces of the substrate will result in preferential formation of **33**, where $k_1 > k_3$. This double stereoselective process will then act again on epoxide enantiomers **33** and **35** to form *meso*-epoxide **37**, however in this reaction the process β_3 is performing the same action as k_1 (as are k_3 and β_1), and can be considered approximately equivalent. As such $\beta_3 > \beta_1$, which selectively removes the minor enantiomer **35** from the reaction

mixture, and increases the enantiopurity of epoxide **33**. The longer the reaction is left for, the more of the minor enantiomer **35** is consumed, and hence a kinetic resolution is observed.

A good example of this sequence of events was observed by Schreiber *et al.* in the enantioselective epoxidation of *E,E*-divinylcarbinol **41** with titanium *iso*-propoxide and di-*iso*-propyltartrate (Table 3).[71]



Entry	Time (h)	*ee* of 42 (%)	*de* of 42 (%)
1	1	93	>97
2	3	95	>97
3	44	>97	>97

Reaction conditions: ^{t}BuOOH (2.60 eq.), Ti(O^{i}Pr)$_4$ (1.15 eq.), (+)-DIPT (1.50 eq.), DCM, -25°C

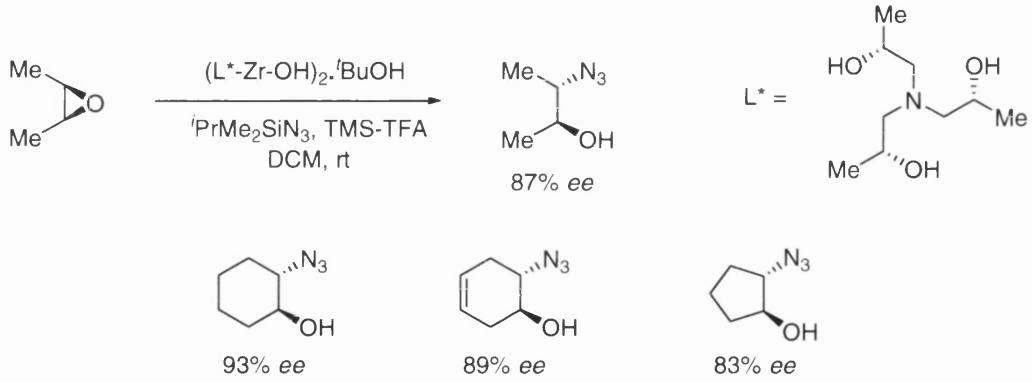
Table 3: kinetic resolution in the desymmetrisation of *E,E*-divinylcarbinol

Desymmetrisation with (+)-DIPT proceeded in good yield, and excellent enantioselectivity (93%). A kinetic resolution was observed in this epoxidation, with longer reaction times providing the product **42** in up to 97% *ee*. Alternatively, when this reaction was performed with (-)-DIPT the product could be further elaborated to provide an enantioselective synthesis of 3-deoxy-*D-manno*-2-octulosonic acid ((+)-KDO) **44**.[72] This type of desymmetrisation is further complicated as the epoxidation adds new stereogenic centres, as well as exploiting the prochiral or *meso*- nature of the substrate. Mathematical

models have been established to account for the observations seen in this type of reaction. [71]

2.2 - Epoxide and aziridine substrates

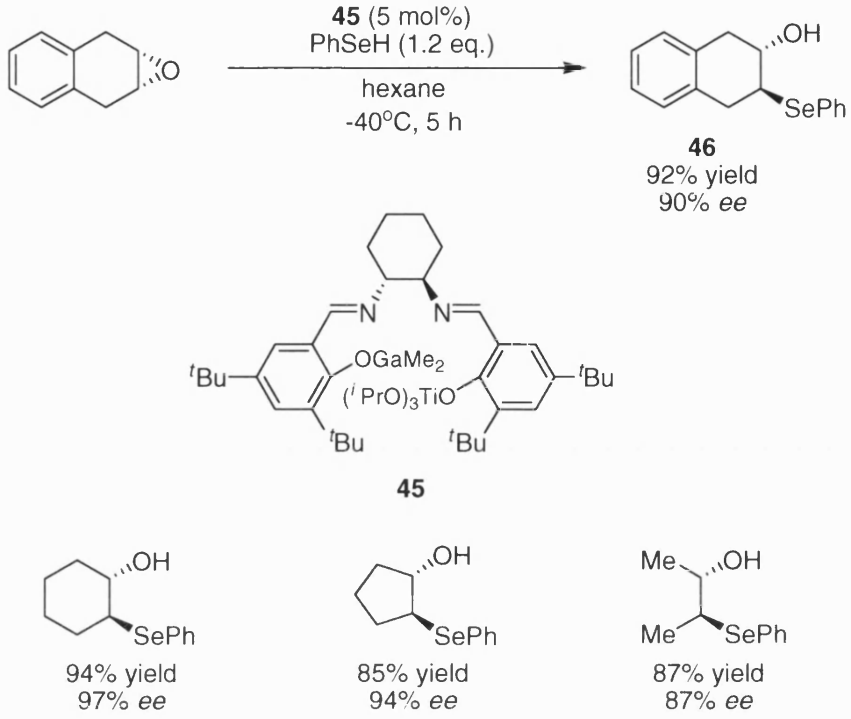
Perhaps the most simple and common of type desymmetrisation is the opening of a *meso*-epoxide by a nucleophile. This is largely down to both their commercial availability and ease of preparation. The first desymmetrisations of *meso*-epoxides of note were carried out independently by Hayashi *et al.* and Yamashita.[73, 74] Although an enantioselective addition of an azide was developed using a combination of transition-metals with tartrate ligands, their results were improved upon by Nugent who used a chiral zirconium complex to effect the transformation in high *ee* for a range of acyclic and cyclic substrates (Scheme 22).[75]



Scheme 22: enantioselective desymmetrisation of a *meso*-epoxide by an azide

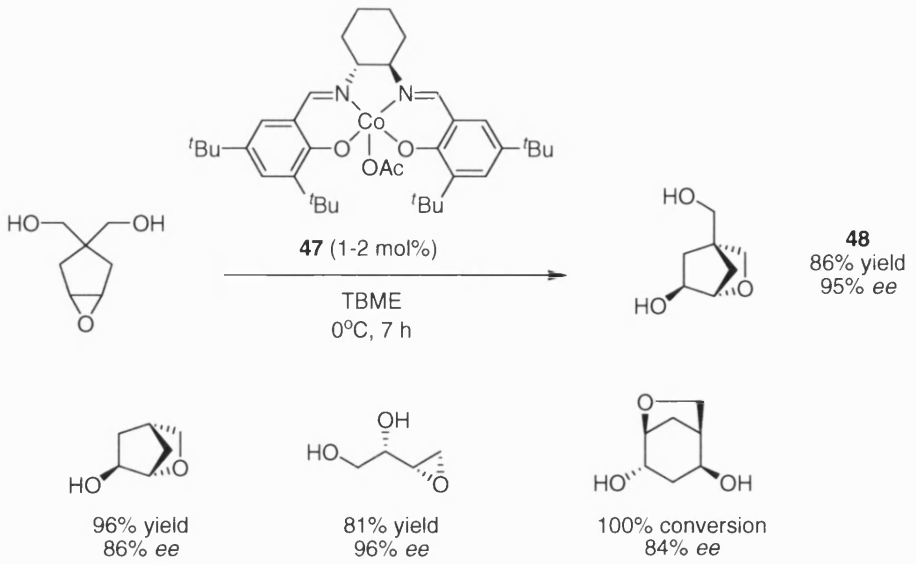
A small modification in the above conditions and addition of allyl bromide to the reaction allowed the direct preparation of the TMS-protected *β*-bromohydrins.[76] The addition of azides to epoxides in this manner has also been investigated by Jacobsen who, among others, has used both chromium and cobalt complexes to achieve excellent enantioselectivity in this process.[77, 78] These catalysts have also been used in the addition of sulfur nucleophiles such as thiols to produce the corresponding *β*–hydroxy sulfides. Zhu *et al.* have performed the addition of aryl selenols to *meso*-epoxides using an interesting heterometallic titanium-gallium Salen catalyst complex **45**.[79] This was able to deliver the *β*-arylseleno alcohols (e.g. **46**) in excellent yield and enantioselectivity (Scheme 23). An

alternative synthesis of seleno alcohols involves the use of chiral selenium nucleophiles.[80]



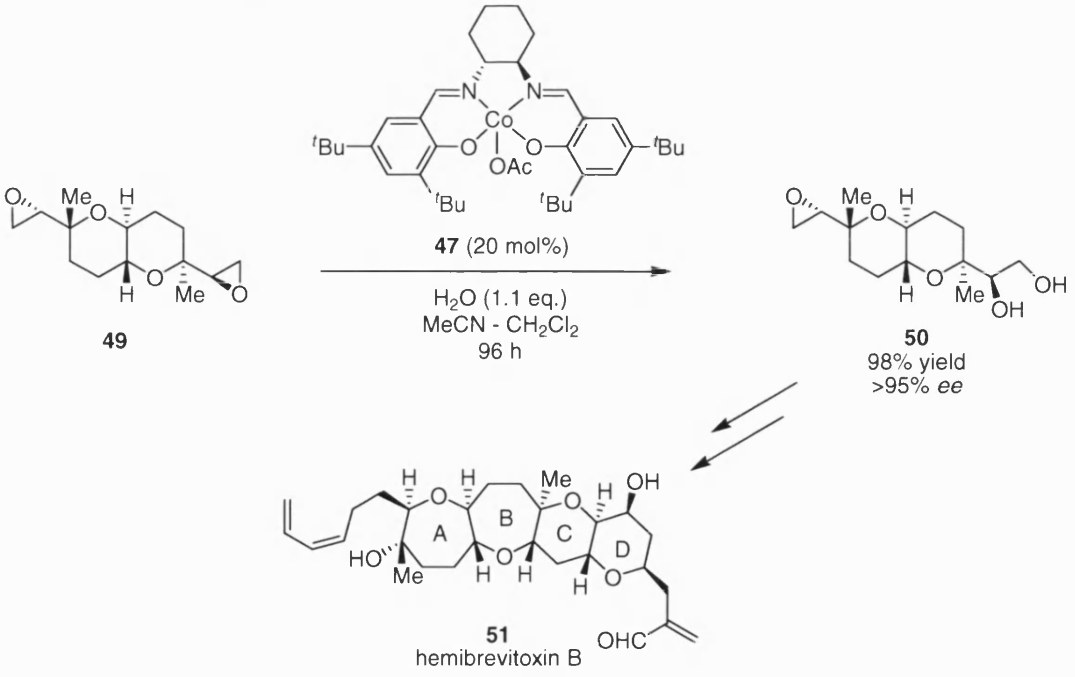
Scheme 23: desymmetrisation of a *meso*-epoxide with a selenium nucleophile

A similar Salen-type catalyst **47** has been used by Jacobsen for intramolecular desymmetrisations of epoxides to form bicyclic ethers (e.g. **48**) with impressive enantioselectivities (Scheme 24).[81] They also provided evidence that the catalyst may be bimetallic in nature, with the cobalt (III) complexes acting as Lewis acids to activate both the epoxide and alcohol. The same catalyst has also been used by Ganem in desymmetrisations of highly functionalised epoxides by azide addition as a key step in the synthesis of (-)-allosamidin,[82] and also in the addition of carboxylic acid nucleophiles.[78]



Scheme 24: intramolecular cobalt-catalysed desymmetrisation of an epoxide

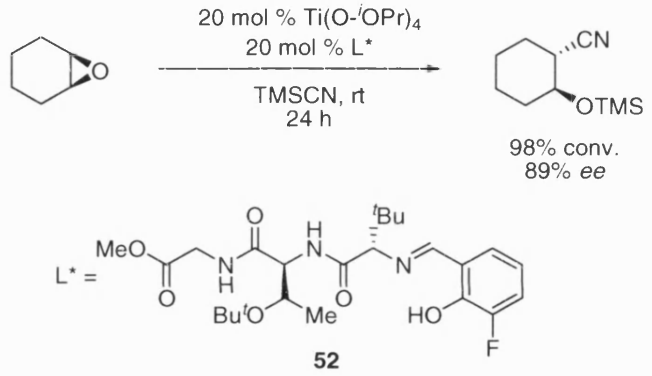
This cobalt (III) Salen catalyst has also found use in the extremely elegant desymmetrisation of a centrosymmetric *bis*-epoxide by hydrolysis. This lead to the formation of a key intermediate in the total synthesis of hemibrevitoxin B. Mono-hydrolysis of **49** provided **50** in 98% yield and >95% *ee* (Scheme 25).[83-85] This AB ring fragment has then been taken forward to hemibrevitoxin B **51** *via* a double tetrahydropyran-oxepane ring expansion in 32 steps.[86]



Scheme 25: synthesis of the AB rings of hemibrevitoxin B *via* desymmetrisation

Shibasaki has used a gallium-binaphthoxide catalyst in the formation of β-hydroxy sulfides in a very effective manner, using simple thiols to generate acyclic and cyclic products.[87] More recently this methodology has been extended to allow the addition of simple amines, as demonstrated in the key step in his total synthesis of 4-demethoxyduanomycin.[88] Incorporation of alternative heteroatoms from nucleophiles such as alcohols (to form the mono-protected *trans*-diols)[89] have also been shown to be useful protocols.[90-92]

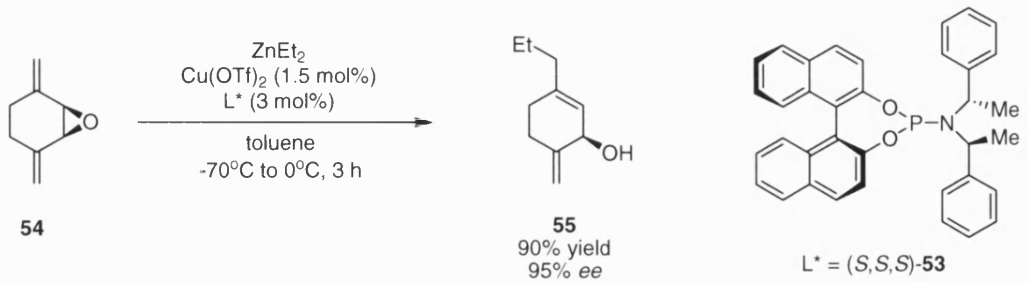
The addition of carbon nucleophiles has been achieved by Hoveyda, who employed a titanium catalyst with a highly-tunable series of peptide ligands (e.g. **52**) in the addition of cyano groups to epoxides (Scheme 26). [93]



Scheme 26: catalytic addition of carbon nucleophiles to a *meso*-epoxide

Further work in this field has now allowed selective preparation of the corresponding isocyano derivatives in up to 95% *ee* by using softer Lewis acid gallium catalysts with BINOL-monoether ligands.[94]

More recently, Feringa *et al.* reported the addition of dialkyl zinc reagents to methylidene cycloalkene oxides.[95] A copper catalyst and BINOL-derived phosphoroamidite ligand **53** were able to effect the enantioselective addition of diethyl zinc to cyclohexene oxide **54** to give the desymmetrised allylic alcohol **55** in 90% yield and 97% *ee* (Scheme 27).



54

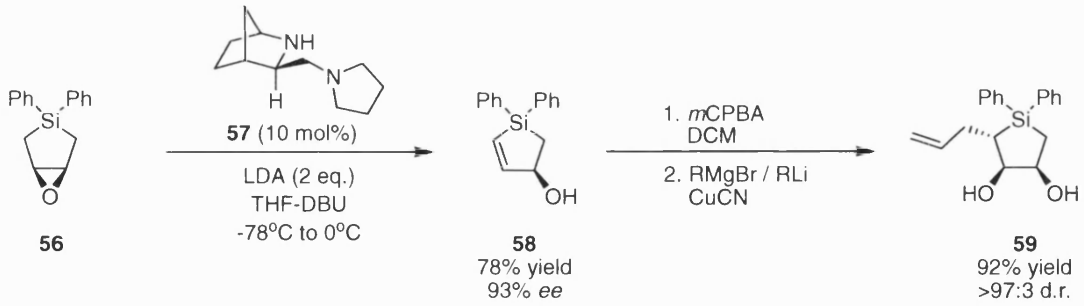
55
90% yield
95% *ee*

L* = (*S*,*S*,*S*)-**53**

Scheme 27: desymmetrising alkyl zinc additions to methylidene cycloalkene oxides

The same catalyst system has been applied to dialkyl zinc reagents to cyclooctatriene monoepoxide by Pineschi.[96, 97]

A recent report by Kozmin *et al.* details the desymmetrising isomerisation of silacyclopentene oxides.[98] Treatment of *meso*-epoxide **56** with catalytic amounts of chiral amine **57** and LDA (2 eq.) provided desymmetrised **58** in good yield and excellent enantioselectivity. The allylic alcohol could readily be elaborated to yield the alkylated polyol **59** with good stereocontrol (Scheme 28).



56

58
78% yield
93% *ee*

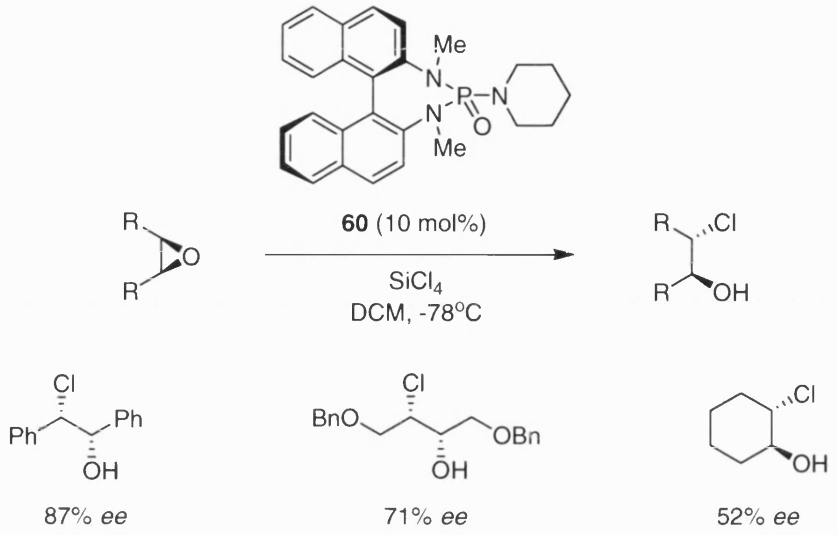
59
92% yield
>97:3 d.r.

Scheme 28: synthesis of cyclopentane polyols *via* desymmetrisation

Hodgson has published numerous papers on similar desymmetrising processes using the chiral amine (-)-sparteine or a sparteine analogue, however these generally require stoichiometric quantities of the chiral amine.[99-104] Chiral tridentate ether ligands have also been used in the alkylative desymmetrisation of epoxides, with the reaction also applicable to oxetanes, however a stoichiometric amount of the chiral reagent is again required.[105]

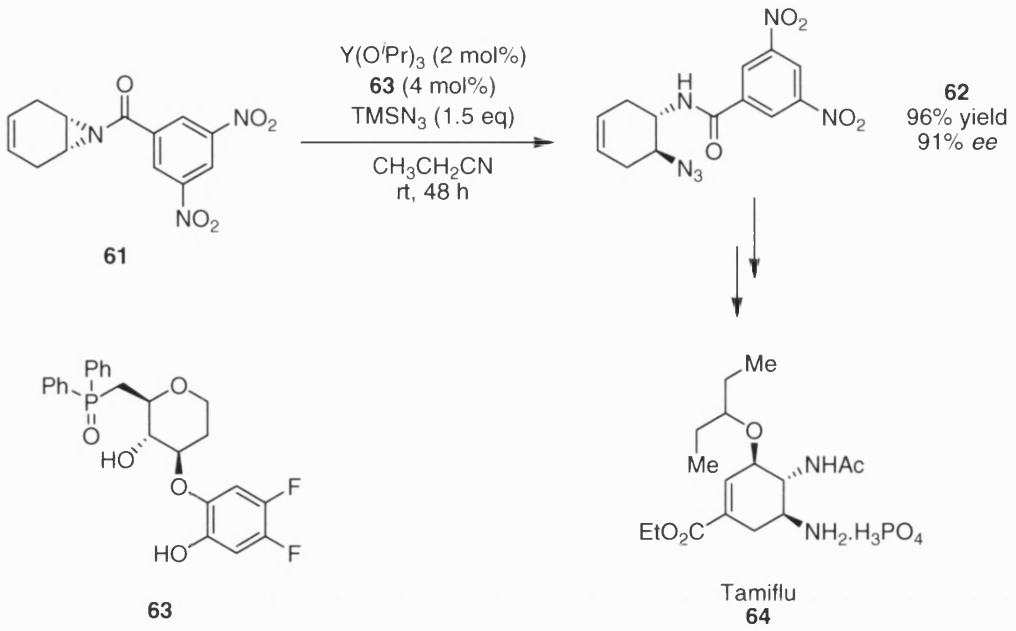
The majority of examples discussed so far involve the use of a Lewis acid to activate the epoxide. Denmark has developed the enantioselective addition of a

chloride ion to an epoxide catalysed by a formal Lewis base, the phosphoramide **60**.[106] The acyclic chlorohydrin products were obtained with good levels of enantioselectivity, in contrast to cyclic epoxides of which cyclohexene oxide was the only substrate to react with moderate selectivity (Scheme 29).



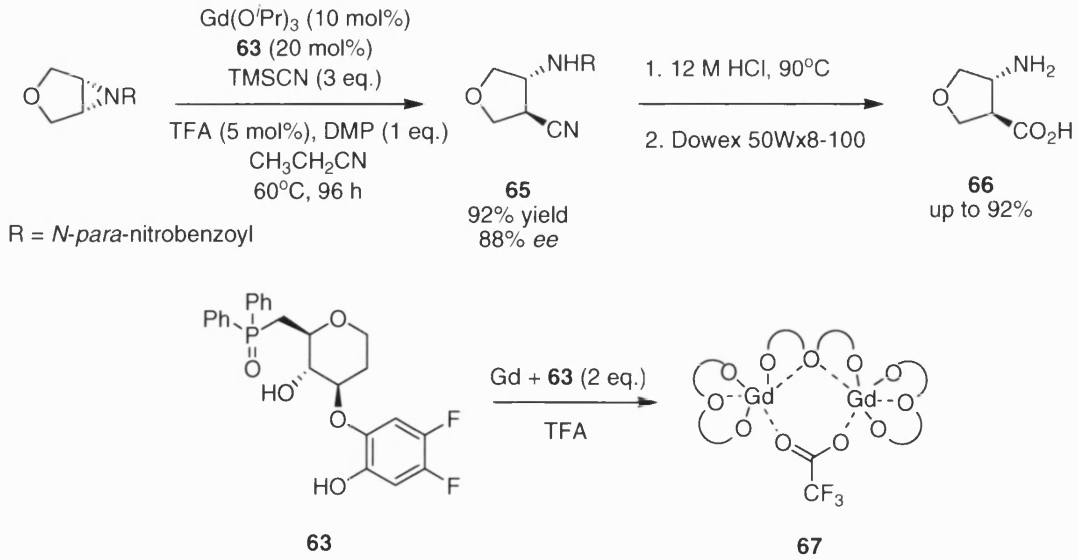
Scheme 29: Lewis base catalysed formation of chlorohydrins

The desymmetrisation of aziridines is less common, however the stoichiometric zinc-promoted desymmetrisation of cyclic aziridines with thiols was reported in 1994 by Oguni and co-workers, delivering the amino-sulfides in up to 93% *ee*.[107] An efficient catalytic desymmetrisation of these substrates was used by Shibasaki *et al.* as the key step in their synthesis of the anti-influenza drug Tamiflu **64**.[108] The use of yttrium tri-*iso*-propoxide with tridentate ligand **63** was able to effect the enantioselective attack of an azide on **61** to produce the azido-amine product **62** in excellent yield and enantioselectivity (Scheme 30).



Scheme 30: desymmetrisation of an aziridine in the synthesis of Tamiflu

The reaction is thought to proceed through a bimetallic catalyst in a similar fashion to the gadolinium-catalyst **67** used for the desymmetrisation of these aziridines with TMSCN. Catalytic amounts of trifluoroacetic acid aided in the production of the *β*-amino cyanides such as **65** in excellent yields and good enantioselectivities, which can then be hydrolysed to produce their respective *β*-amino acids **66** (Scheme 31).[109]

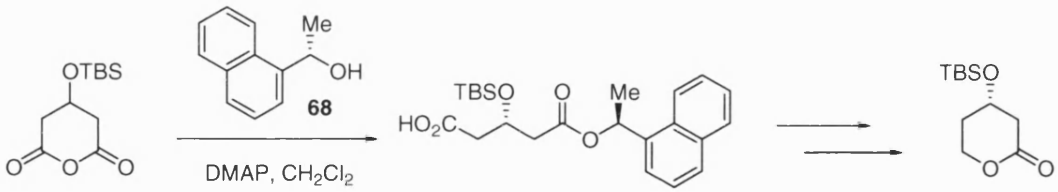


Scheme 31: desymmetrisation of aziridines with TMSCN

Jacobsen has also developed enantioselective catalytic aziridine desymmetrisation with nitrogen nucleophiles using chromium (III) Schiff base complexes.[110] The copper-catalysed ring opening of aziridines by alkyl-Grignard reagents has been achieved by Muller, using both phosphoroamidite and Schiff base ligands.[111] The same group has also reported other desymmetrisation strategies for these substrates,[112, 113] whilst Singh *et al.* have synthesised 1,2-diamines by aziridine opening with aliphatic amines.[114]

2.3 - Anhydride Substrates

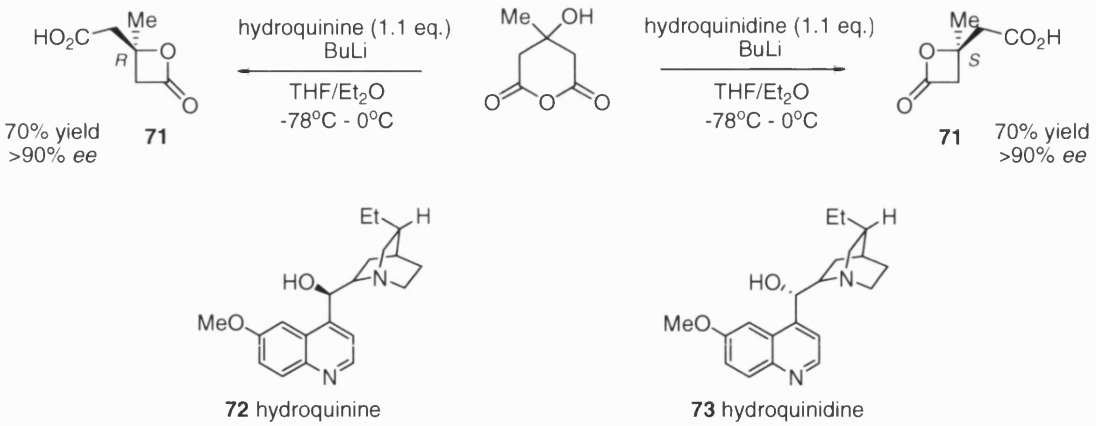
Anhydrides, both cyclic and acyclic, have also received considerable attention. In particular there are numerous examples of their asymmetric alcoholysis.[115, 116] Chiral alcohols have been successfully used with cyclic substrates to produce esters containing two stereocentres (e.g. **69**), as shown in the reaction of 3-substituted glutaric anhydrides with 1-(1'-naphthyl)ethanol **68** (Scheme 32). This provided an efficient route to the chiral δ–lactones **70** in excellent enantiopurity.[117, 118]



69 50:1 dr, 92% yield **70**

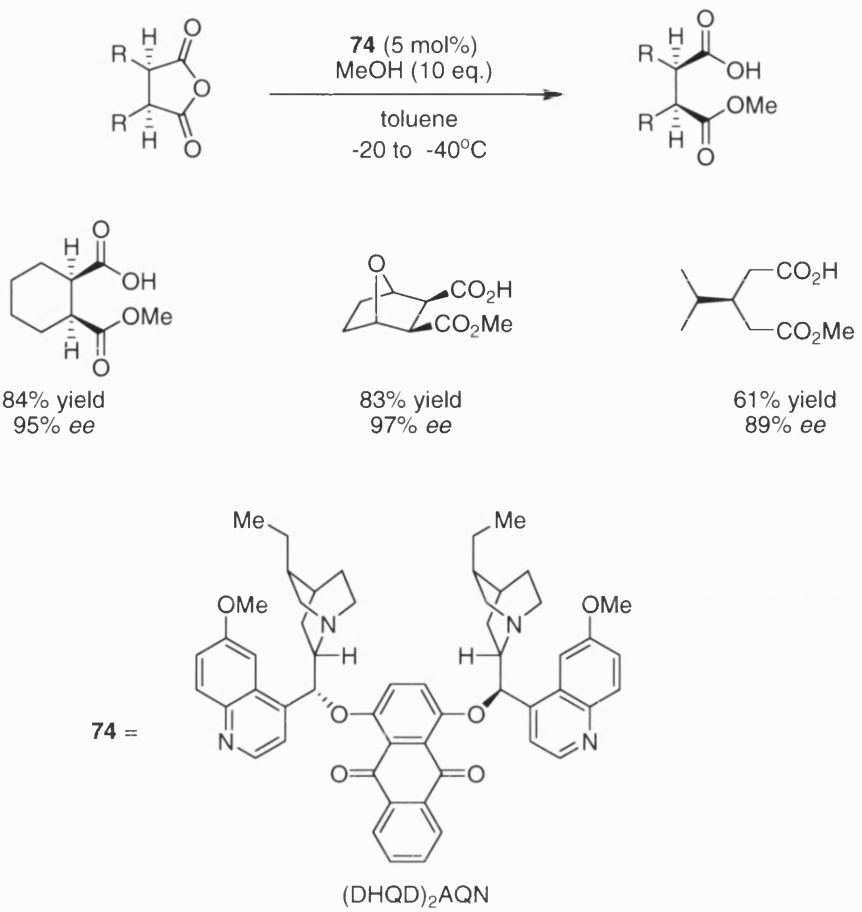
Scheme 32: desymmetrisation of a cyclic anhydride with a chiral nucleophile

A similar reaction has also been described with methyl (*S*)-prolinate by North *et al.* in various studies including their total synthesis of idrapril analogues.[119, 120] Desymmetrisation of an anhydride by intramolecular nucleophilic attack has been shown by Shirihama *et al.* to be an efficient method of generating a β–lactone **71**, the desired enantiomer of which could be readily obtained in excellent *ee* by switching between hydroquinine **72** and hydroquinidine **73** (Scheme 33).[121]



Scheme 33: alkaloid-catalysed intramolecular desymmetrisation

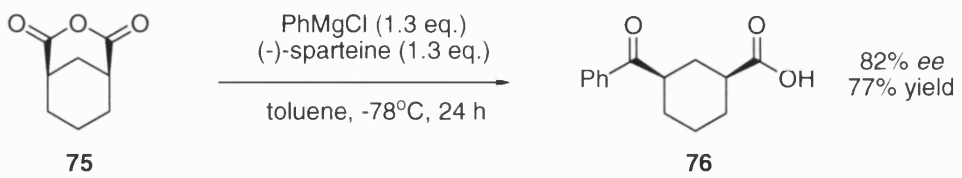
This methodology has been explored by Bolm employing quinine and quinidine for the synthesis of β-amino acids.[122] Similar cinchona alkaloids have been used as catalysts by Deng *et al.* in the methanolysis of cyclic anhydrides. Treatment with just 5 mol% of the modified alkaloid $(DHQD)_2AQN$ **74** and methanol in toluene was able to effect the mono-functionalisation in high yield and selectivity (Scheme 34).[123] The catalyst could be easily recovered and gave identical results, even when used in large scale reactions.



Scheme 34: modified cinchona alkaloid desymmetrisation by methanolysis

Similar catalysts supported on silica gel have also been prepared for asymmetric alcoholysis reactions by Han *et al.*,[124, 125] whereas Nagai has used imidazolones for the same reaction.[126] Both cyclic anhydrides[127] and dicarboximides[128] have been desymmetrised by Seebach with stoichiometric amounts of di-*iso*-propyloxytitanium TADDOLates with excellent results, however the dicarboximides did exhibit generally lower selectivities.

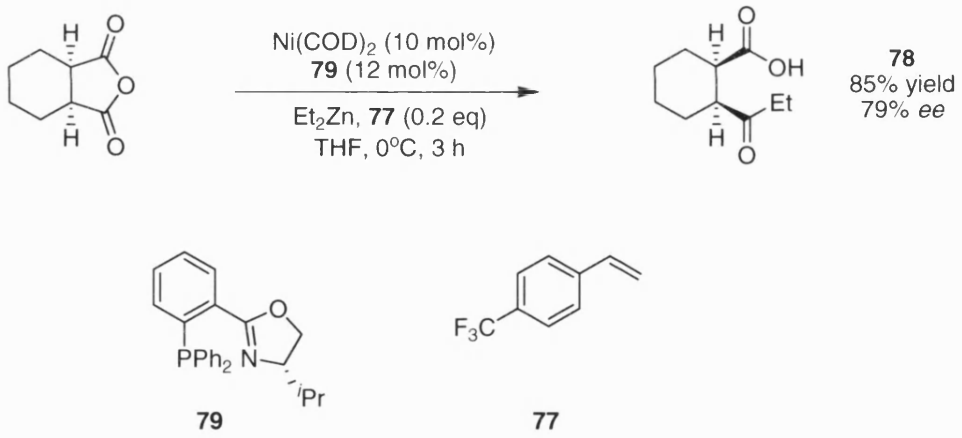
More recently, Fu has desymmetrised cyclic anhydrides with Grignard reagents in the presence of (-)-sparteine. Again, a range of 3-substitued glutaric anhydrides were investigated with various aryl-magnesium reagents, all giving excellent yields and *ee*'s.[129] One example involved the desymmetrisation of bicyclic anhydride **75** with phenylmagnesium chloride, to give the 1,3-disubstituted cyclohexane product **76** with high enantioselectivity (Scheme 35).



75 76

Scheme 35: sparteine-mediated desymmetrisation with Grignard reagents

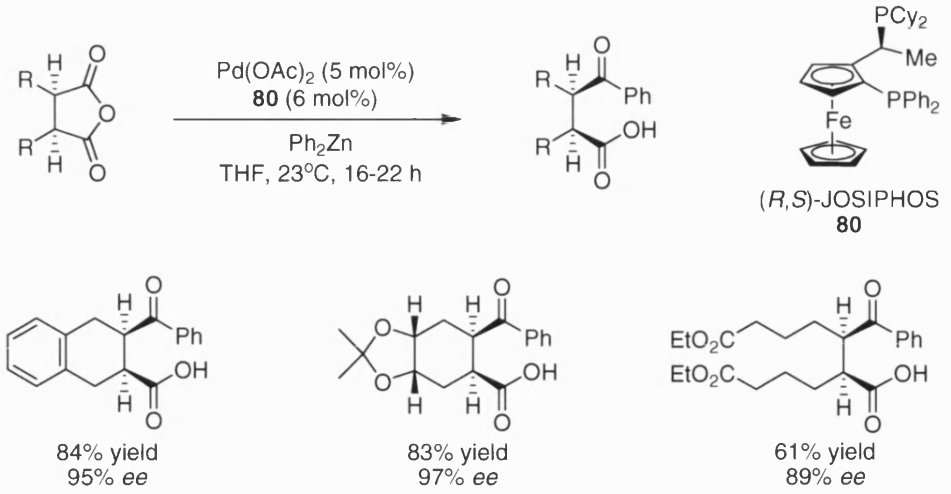
Rovis has also had success in the alkylative desymmetrisation of cyclic anhydrides, employing a nickel (II) catalyst in combination with alkylzinc reagents and a styrene additive **77.** [130] The styrene aided in promoting reductive elimination over β-hydride elimination from the presumed acyl ethyl nickel intermediate. Initial studies into an analogous enantioselective method proved effective, with the phosphine-oxazoline ligand **79** able to produce the desymmetrised ketone **78** in 85% yield and 79% *ee* (Scheme 36). More recent studies into this nickel-based system have enabled selective alkyl transfer from mixed zinc reagents, however the enantioselectivities of these reactions are moderate.[131]



79 77

Scheme 36: nickel-catalysed alkylative desymmetrisation of an anhydride

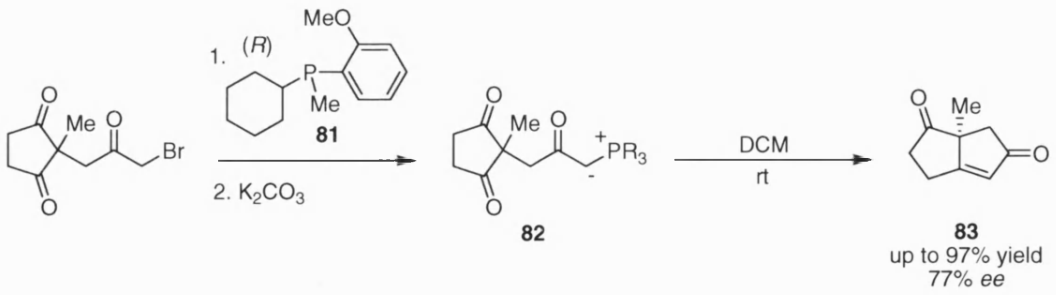
A complimentary palladium-catalysed process has also been investigated, providing more promising results. Reaction of a cyclic anhydride with diphenyl zinc in the presence of palladium acetate and (*R*, *S*)-JOSIPHOS **80** was able to provide the mono-alkylated products in good yields and excellent enantioselectivities (Scheme 37).[132]



Scheme 37: palladium-catalysed desymmetrisation of anhydrides

2.4 - Ketone and aldehyde substrates

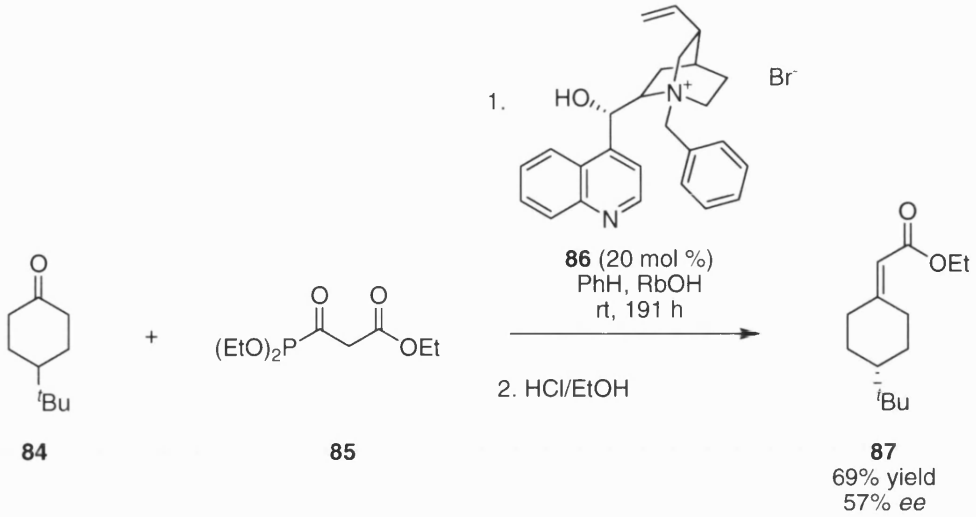
There exist many examples of the desymmetrisation of ketone substrates with chiral Wittig-type reagents, such as the synthesis of Wieland-Miescher ketone **83** by Trost and Curran.[133] Reaction of an *α*-bromoketone with chiral phosphine **81** and treatment with base resulted in the chiral ylide **82**. Stirring in DCM at room temperature afforded the cyclised product **83** *via* intramolecular attack in good yield and respectable enantioselectivity (based on 88% *ee* of the chiral phosphine) (Scheme 38).



Scheme 38: intramolecular desymmetrisation by Wittig reaction

A catalytic asymmetric Horner-Wadsworth-Emmons reaction has been developed by Arai under phase-transfer conditions using phosphonate **85**, rubidium hydroxide and the chiral quaternary ammonium salt **86**, derived from cinchonine.[134] This system was able to effect the desymmetrisation of 4-*tert*-

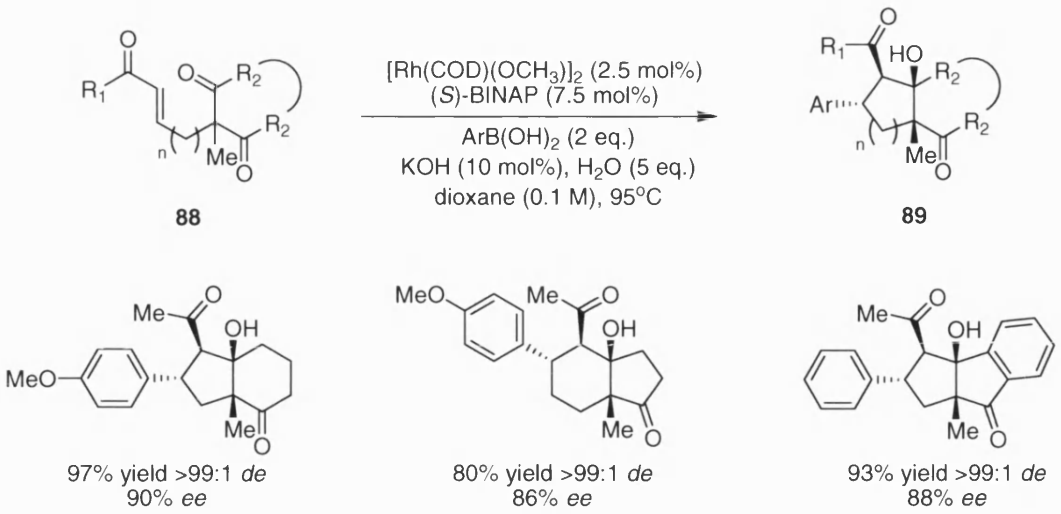
butylcyclohexanone **84**, to provide the α,β-unsaturated ester **87** in 69% yield and 57% *ee* (Scheme 39).



Scheme 39: catalytic desymmetrisation by Horner-Wadsworth-Emmons reaction

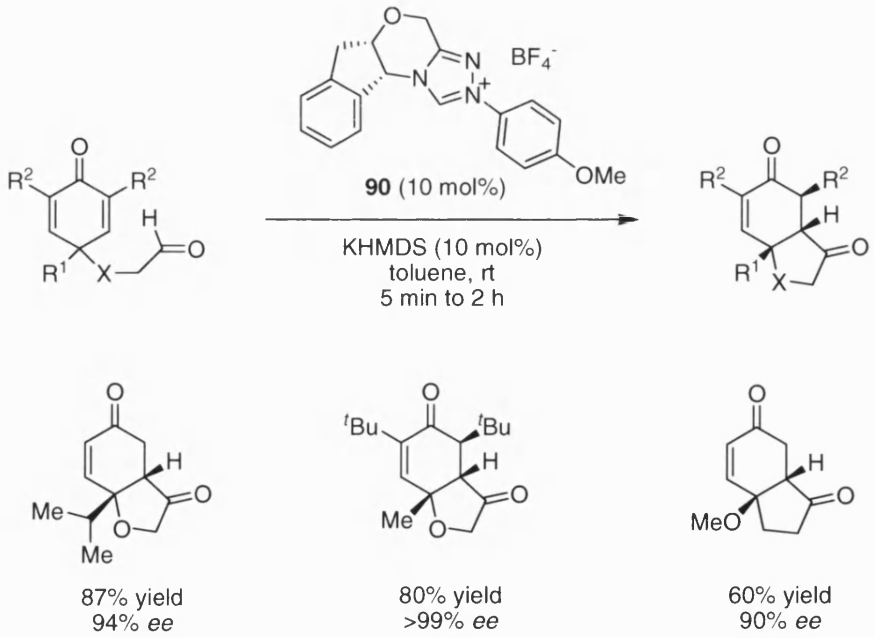
Similar examples using stoichiometric amounts of chiral reagents have been used in comparable manners by Hanessian[135, 136] and Masamune,[137] often giving excellent enantioselectivities of the desymmetrised products. The desymmetrisation of a dialdehyde with a chiral Wittig-type reagent derived from menthol has also been reported by Rein.[138, 139]

Krische has shown that a chiral rhodium-BINAP complex is able to catalyse the intramolecular desymmetrisation of enone diones, whilst also incorporating a new stereocentre formed with an external reagent.[140] Rhodium-catalysed carbometallation of enone **88** with an aryl boronic acid, followed by subsequent diastereoselective electrophilic trapping of the rhodium-enolate by one of the ketones generates complex products (e.g. **89**) containing four contiguous stereocentres, including two adjacent quaternary centres (Scheme 40).



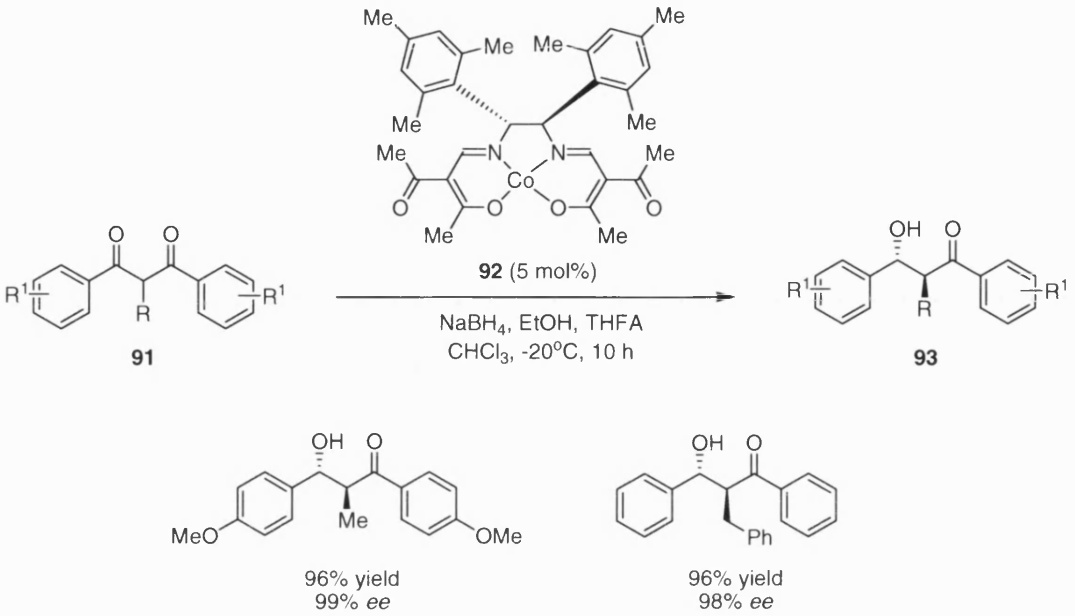
Scheme 40: rhodium-catalysed desymmetrisation of enone-diones

Catalytic desymmetrisation of enones has also been investigated by Rovis in his work on the intramolecular Stetter reaction.[141] When subjected to a small amount of the chiral triazolium salt **90** with catalytic KHMDS the cyclic products could be isolated in up to 99% ee as a single diastereomer, to form both heterocycles and carbocycles (Scheme 41).



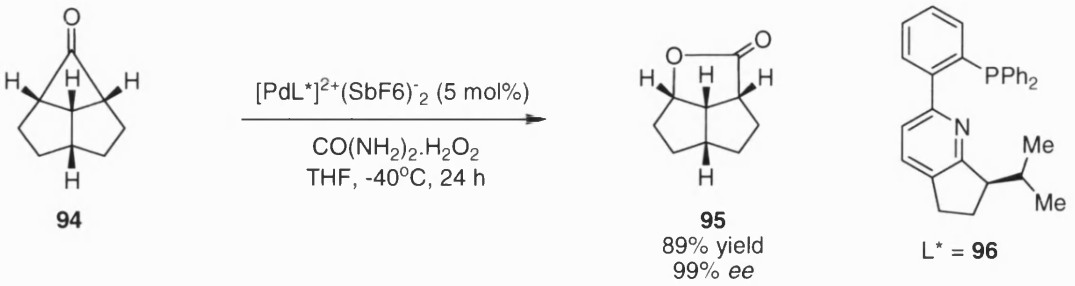
Scheme 41: intramolecular desymmetrisation of dienones by Stetter reaction

The reductive desymmetrisation of a 2-alkyl-1,3-diketone **91**, reported by Yamada *et al.*, has been shown to be a highly enantioselective method to generate the mono-alcohol product **93** as a single diastereomer through the use of a chiral β-ketoiminato cobalt complex **92** in tandem with stoichiometric sodium borohydride (Scheme 42).[142]



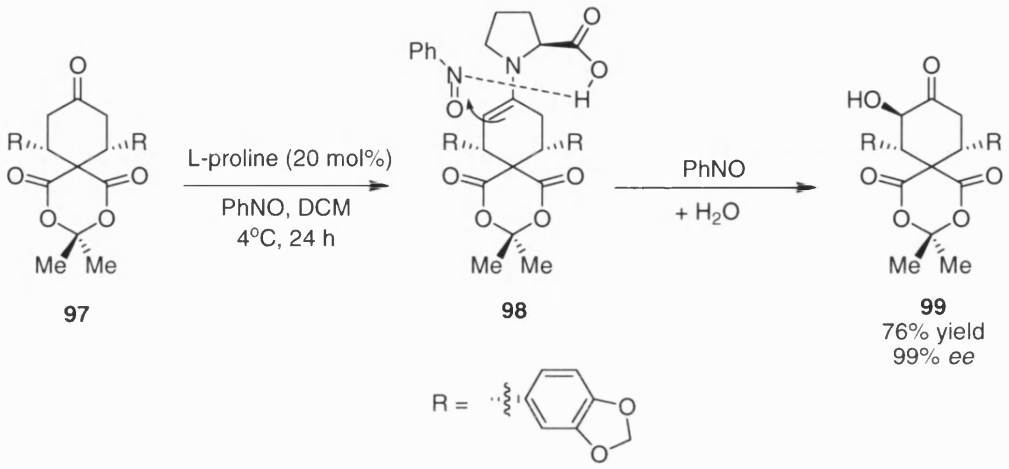
Scheme 42: desymmetrisation by selective ketone reduction

An asymmetric palladium-catalysed Baeyer-Villiger reaction on achiral and *meso*-cyclobutanones has also been investigated by Katsuki *et al.*[143] A palladium complex with chiral phosphine ligand **96** was able to perform selective oxidation on tricyclic ketone **94** to furnish the lactone product **95** in excellent yield and enantioselectivity (Scheme 43).



Scheme 43: desymmetrisation by enantioselective Baeyer-Villiger reaction

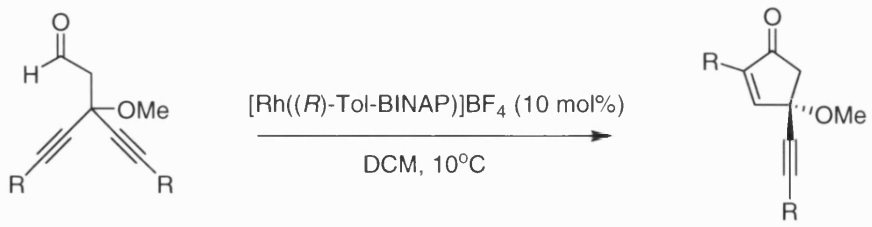
The emergence of proline as an organocatalyst in a range of enantioselective reactions has lead to the development of mild conditions to accompany the existing metal-catalysed processes. Barbas has used this to good effect in the desymmetrising α-oxidation of cyclic ketones *via* tandem aminoxylation/*O-N* bond heterolysis.[144] Addition of L-proline to spirotrione **97** forms the enamine **98**, which is then able to direct the nitrosobenzene electrophile, followed by iminium hydrolysis and *O-N* bond heterolysis to form the α-hydroxy-ketone product **99** in good yield as essentially a single enantiomer (Scheme 44).



Scheme 44: organocatalytic oxidative desymmetrisation of **97**

Proline has also been used as an organocatalyst in other desymmetrisation reactions including similar work by Ramachary *et al.*,[145] and in Pearson's total synthesis of (+)-cocaine.[146]

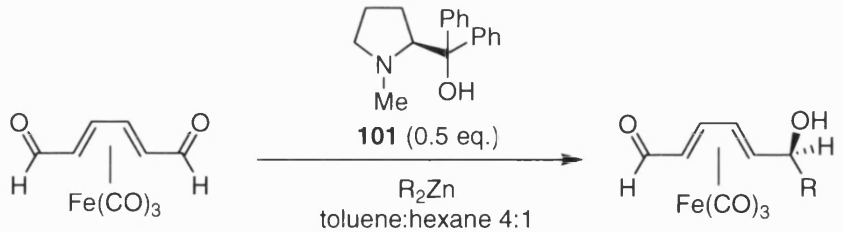
Fu has reported the desymmetrisation of prochiral diynes *via* an intramolecular rhodium-catalysed hydroacylation.[147] Reaction of a range of aldehydes in the presence of a chiral rhodium catalyst afforded the cyclopentenone products in excellent yields and enantioselectivities (Table 4). The desymmetrisation conditions were also applicable to the kinetic resolution of racemic 4-alkynals.



R	Yield (%)	*ee* (%)
$^{n}C_5H_{11}$	95	92
Cy	94	95
$(CH_2)_3Cl$	91	91
CH_2OMe	93	82

Table 4: desymmetrisation by intramolecular hydroacylation

The asymmetric desymmetrising allylation of dialdehydes is well known, with chiral allyl boranes[148, 149] and allyl titanium tartrate complexes[150] providing the chiral products in excellent enantioselectivity, however stoichiometric quantities of the allylating reagent are always required. Methodology has been developed by Takemoto that allows the addition of alkylzinc reagents to dialdehydes in (diene)$Fe(CO)_3$ complex **100**, using 0.5 equivalents of diphenylprolinol **101**.[151, 152] The mono-addition product **102** from diethyl zinc could be isolated in 98% *ee*, with the corresponding methyl derivative being formed in 86% *ee* (Scheme 45).



100

102
R = Et, >98% *ee*
R = Me, 86% *ee*

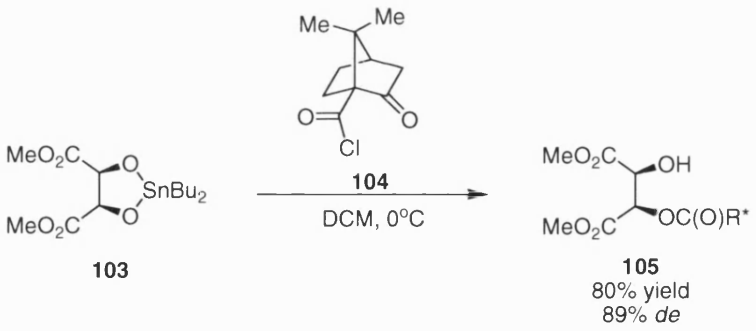
Scheme 45: the desymmetrisation of dialdehyde **100**

Chiral auxiliaries have also been shown to effectively desymmetrise aldehyde substrates in work by Oppolzer,[153] and Fox has experimented with dicarboxylic acids,[154] whereas Bosch has incorporated chiral amino alcohols in the

synthesis of bicyclic lactams from prochiral δ-oxoacid derivatives.[155] The enantioselective reduction of a cyclic *meso*-imide has been performed by Nishiyama using BINAL-H to provide the hydroxylactam product in 83% *ee*[156] with a similar reaction by Jones using catalytic amounts of chiral oxazaborilidines giving the reduced products in up to 86% *ee*,[157] and a desymmetrising Beckmann rearrangement of prochiral ketones using chiral azides has been reported by Aubé.[158]

2.5 - Diol, polyol and diamine substrates

The ease of preparation of *meso*-diols by *cis*-hydroxylation of suitable alkenes has lead to much interest in the enantioselective desymmetrisation of the resultant substrates. Early work by Mukaiyama made use of a chiral bicyclic acid chloride **104** in the desymmetrisation of *meso*-tin acetals (e.g. **103**) at 0°C to produce the mono-acylated **105** in good yield and diastereoselectivity (Scheme 46).[159] The reaction proved to be extremely substrate dependent with varying degrees of diastereoselectivity.



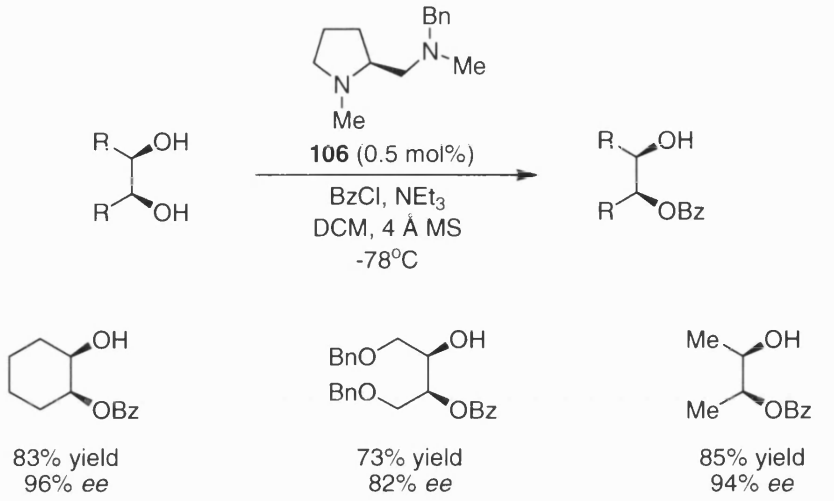
103

105
80% yield
89% *de*

Scheme 46: desymmetrisation of a *meso*-tin acetal

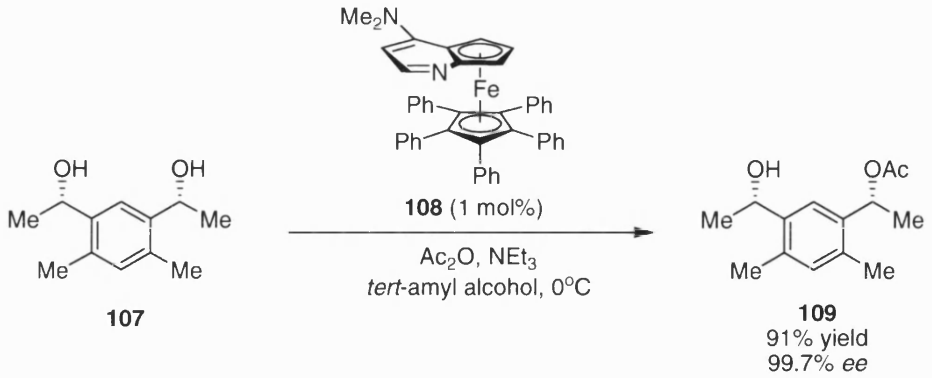
The absolute asymmetric induction of one specific desymmetrisation has been shown to be temperature dependent in the enantioselective synthesis of a carbamate from an achiral 1,3-diol.[160] Glycerol and more complicated polyols have also been desymmetrised by treatment with a C_2-symmetric *bis*-dihydropyran derivative.[161, 162] Many other chiral reagents have been used in stoichiometric quantities[163, 164] such as menthone,[165, 166] a methylnorbornene aldehyde,[167, 168] and chiral *bis*-sulfoxides.[169, 170] Oriyama has reported a catalytic acylation procedure, using low loadings of chiral diamine **106** with benzoyl chloride, triethylamine and 4 Å molecular sieves.[171] The mono-acylated

products are formed in good yield and excellent *ee*, and the reaction was applicable to a wide range of substrates with even the simplest *meso*-diols performing well (Scheme 47).



Scheme 47: catalytic desymmetrisation of *meso*-diols by chiral amine **106**

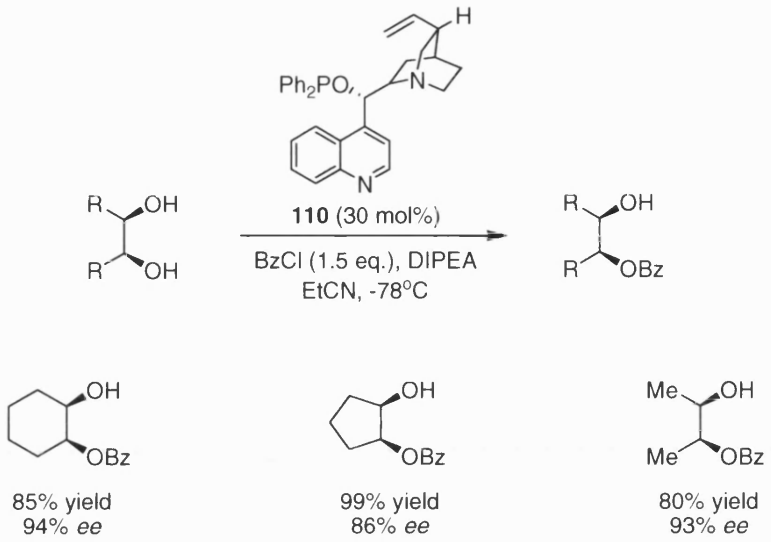
Desymmetrising acylation of *meso*-diols has also been performed by Fu. He has developed a planar-chiral DMAP catalyst **108** by coordination to a metal centre as a ferrocene.[172] This catalyst is able to effect the mono-acylation of *meso*-diol **107** in excellent yield and enantioselectivity to provide the ester product **109** (Scheme 48).



Scheme 48: chiral DMAP derivative **108** in the desymmetrisation of a *meso*-diol

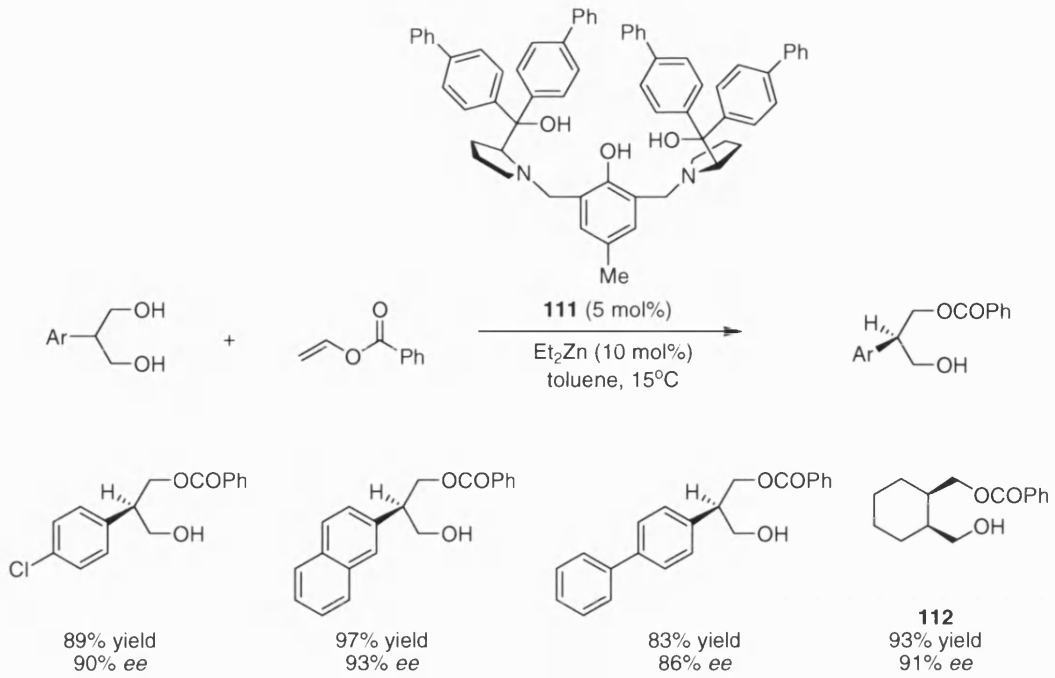
Similar results have been achieved by Fujimoto *et al.* in the acylation of *meso*-diols using phosphinite derivatives of cinchona alkaloids such as **110** (Scheme

49).[173] The reaction has also been shown to be effective in desymmetrising bicyclic systems with subtle modifications to the quinidine backbone.[174]



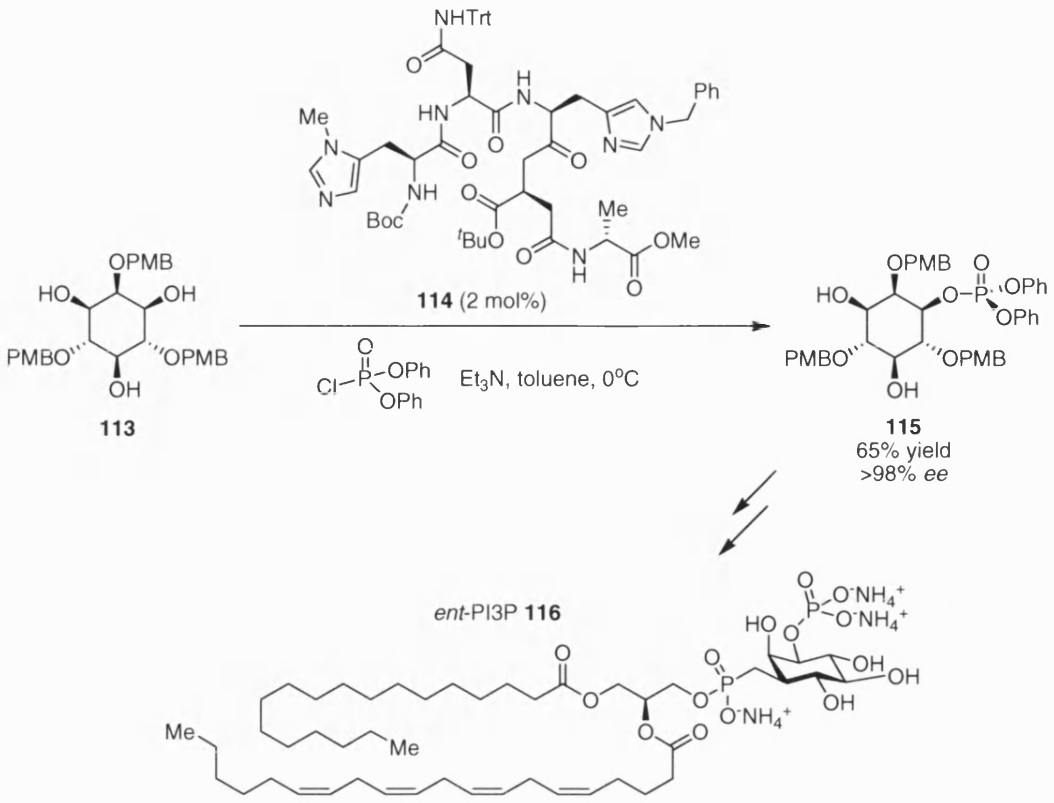
Scheme 49: cinchona alkaloid-catalysed desymmetrisation

Prochiral 1,3- and 1,4-diols have been desymmetrised by Trost using a dinuclear zinc catalyst in efforts towards mimicking an enzyme.[175] Reaction of a diol in the presence of multidentate ligand **111** and catalytic diethyl zinc with vinyl benzoate as the acyl-transfer reagent yielded the desymmetrised products in good yield and enantioselectivity (Scheme 50). None of the dibenzoate products were detected, and the reaction could also be applied to the desymmetrisation of a *meso*-diol in the formation of **112**.



Scheme 50: zinc-catalysed desymmetrisation of prochiral diols

Miller has also performed desymmetrisations on prochiral and *meso*-1,3-diols using a peptide based acylation catalyst,[176] however it was found to be more effective when used on the protected polyol substrate **113** in the total synthesis of phosphatidylinositol-3-phosphate (PI3P) and related compounds.[177] Treatment of **113** with catalyst **114** and diphenyl phosphochloridate was able to provide the mono-phosphate product **115** in 65% isolated yield and >98% *ee* (Scheme 51). This desymmetrised product could then be taken through to form *ent*-PI3P **116**. The other enantiomer was also readily available in >98% *ee* and slightly decreased 55% yield with an alternative peptide catalyst, and could be carried through the sequence to produce PI3P.

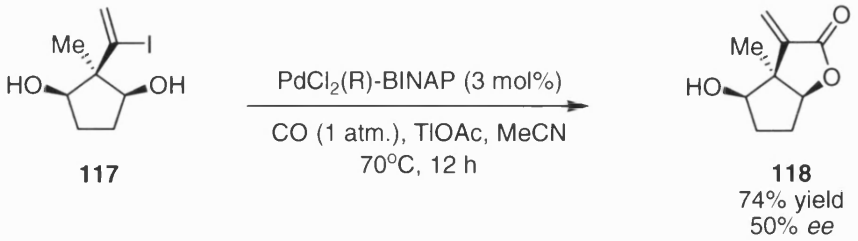


Scheme 51: desymmetrisation as the key step in the synthesis of *ent*-PI3P

Other notable catalysts for desymmetrising acylation of diols include Spivey's biaryl DMAP derivatives,[178] diamines used by Kündig for desymmetrising chromium-complexed diols,[179] Vedejs chiral phosphine nucleophiles,[180] the chiral auxiliary bearing pyridines studied by Yamada,[181] and the pyrrolidinopyridines synthesised by Kawabata.[182] Harada has also performed desymmetrisation studies on *meso*-diols first by conversion to the acetals, followed by enantioselective Lewis acid mediated ring cleavage by a chiral oxazaborolidinone, however stoichiometric quantities of this reagent are required.[183, 184]

Shibasaki *et al.* have used *meso*-diols in the generation of stereodefined quaternary carbon centres *via* a desymmetrisation strategy.[185] An intramolecular palladium-catalysed carbonylation of diol **117** on to the pendant vinyliodide produced bicyclic lactone **118** in 74% yield and 50% *ee* (Scheme 52). Use of simple inorganic bases such as potassium carbonate resulted in significantly reduced enantioselectivities, due to the hypothesis that this was

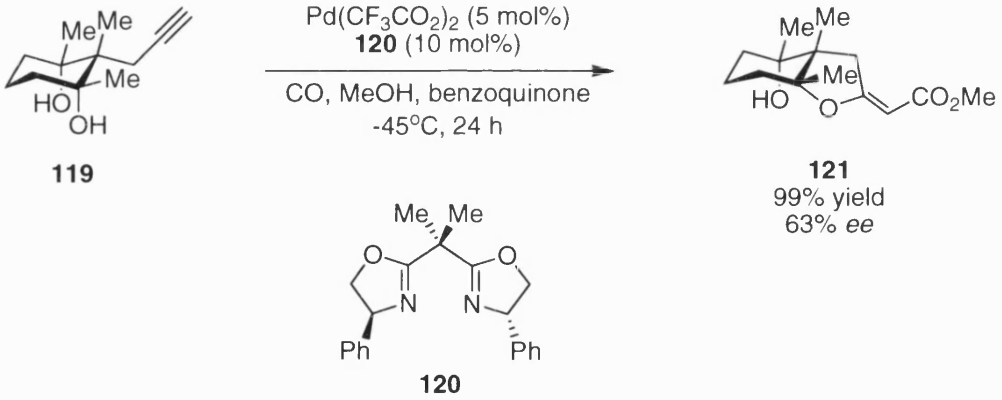
deprotonating the hydroxyl group of the substrate which was subsequently coordinating to the palladium catalyst and causing partial ligand dissociation.



117 **118**
74% yield
50% *ee*

Scheme 52: intramolecular desymmetrisation of a *meso*-diol by carbonylation

Kato has also published the enantioselective desymmetrisation of *meso*-diols in palladium-catalysed carbonylation of alkynes.[186] Intramolecular cyclisation of diol **119** in the presence of carbon monoxide, a palladium catalyst and chiral *bis*-oxazoline ligand **120** afforded the ester product **121** in quantitative yield and reasonable *ee* (Scheme 53).



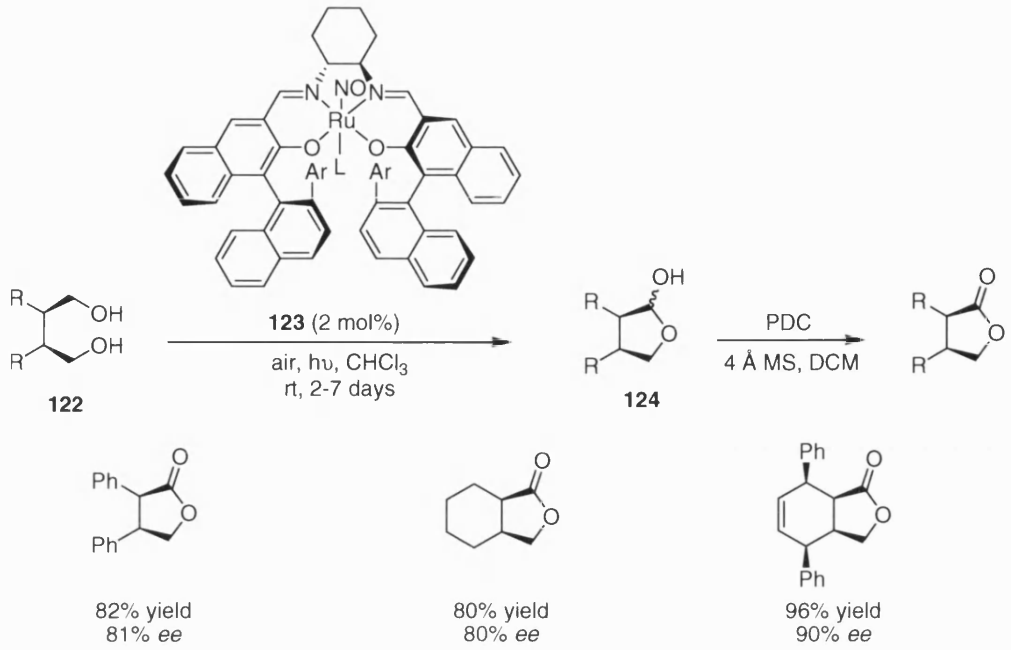
119 **121**
99% yield
63% *ee*

120

Scheme 53: carbonylative desymmetrisation of a *meso*-diol

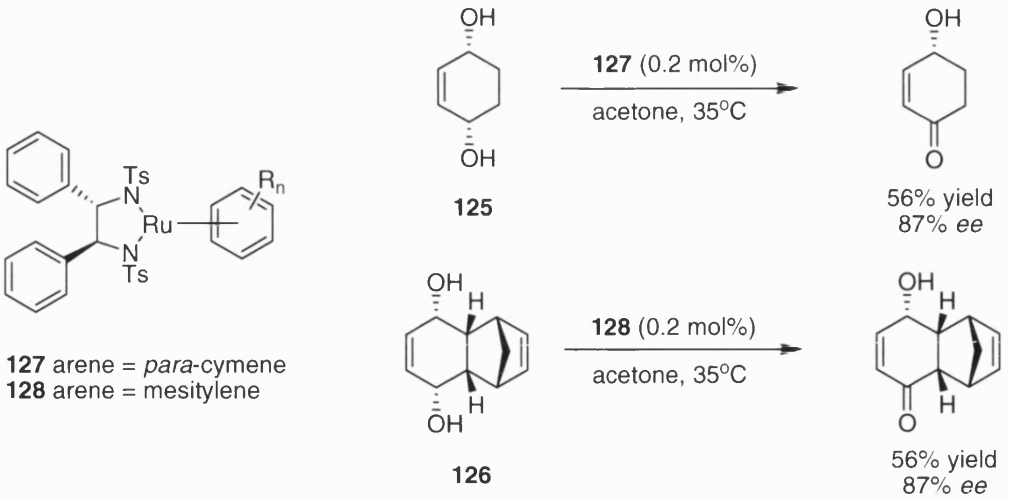
Another popular method of desymmetrising *meso*-diols is by selective oxidation, as detailed in the extensive investigations of Katsuki *et al.*[187] Enantioselective mono-oxidation of *meso*-diol **122** with a ruthenium Salen complex **123** under aerobic conditions, followed by lactol formation gave the product **124** in good yield and *ee*. These lactols could then readily be oxidised to the corresponding lactones with pyridinium dichromate (Scheme 54). It was discovered that irradiation of the reaction mixture was essential in order to both facilitate dissociation of the nitrosyl ligand, and enable single electron transfer from the alcohol-bound ruthenium ion to dioxygen. The catalyst was however found to

be extremely substrate-specific, with variation of the ligand and aryl group (L and Ar respectively, Scheme 54) necessary to achieve good results.



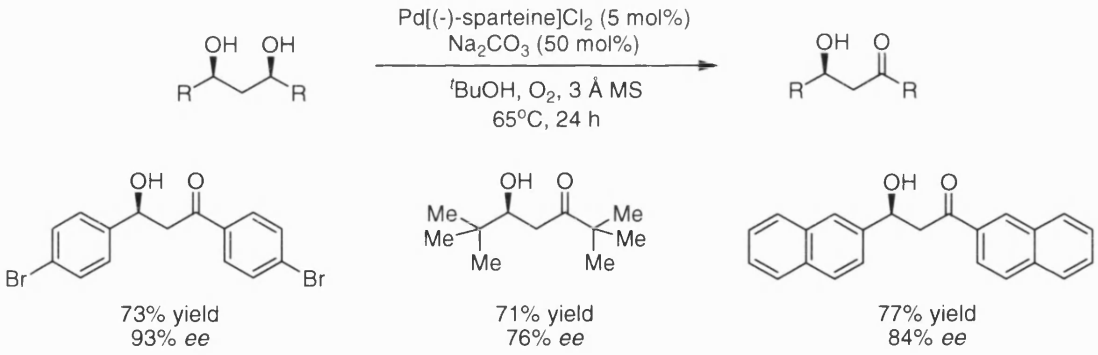
Scheme 54: ruthenium-catalysed aerobic oxidation of *meso*-diols

A chiral ruthenium complex has also been shown to effect the desymmetrisation of *meso*-diols by selective oxidation in work by Noyori.[188] Both simple (**125**) and complex (**126**) substrates were efficiently desymmetrised using just 0.2 mol% of the ruthenium catalyst to deliver the mono-oxidised products in good yields and enantioselectivities (Scheme 55).



Scheme 55: selective oxidation with ruthenium complexes

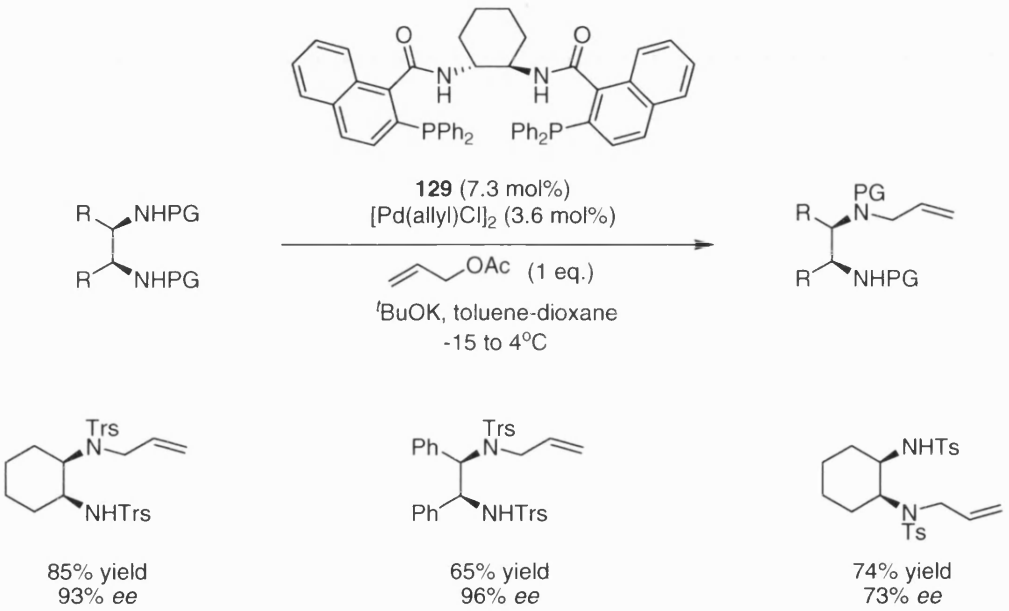
Sigman has reported the aerobic oxidative desymmetrisation of *meso*-diols, employing a palladium-sparteine catalyst (Scheme 56).[189, 190] The ketone products were formed in good yield and enantioselectivity, with either (-)-sparteine (20 mol%) or sodium carbonate (50 mol%) used as base.



Scheme 56: palladium-sparteine catalysed desymmetrisation of *meso*-diols

Murahashi has also used selective oxidation as a means of desymmetrisation in reactions of silylated *meso*-diols with catalytic amounts of manganese-Salen complexes.[191, 192] Recently, Kishi has developed NMR databases for the assignment of relative and absolute stereochemistry of *meso*-compounds, through observing the chemical shifts in carbon spectra of *meso*-diols in chiral solvents.[193]

Desymmetrisation of *meso*-diamines is much less common than that of diols, however Taguchi *et al.* have achieved this *via* palladium-catalysed *N*-allylation.[194] Sulfonyl-protected diamines were subjected to an enantioselective allylic substitution using allyl palladium chloride dimer and Trost ligand **129** (Scheme 57). The mono-allylated products could be isolated in good yield and enantioselectivity, however 1,2-diamines were the only substrates to show substantial enantiocontrol, with cyclic and acyclic 1,3-diamines giving poor results. It was also later noted that changing the *N*-sulfonyl group from trisyl-(2,4,6-tri-*iso*-propylbenzenesulfonyl) to tosyl- resulted in production of the opposite enantiomer of the desymmetrised products, albeit in reduced *ee*.[195]



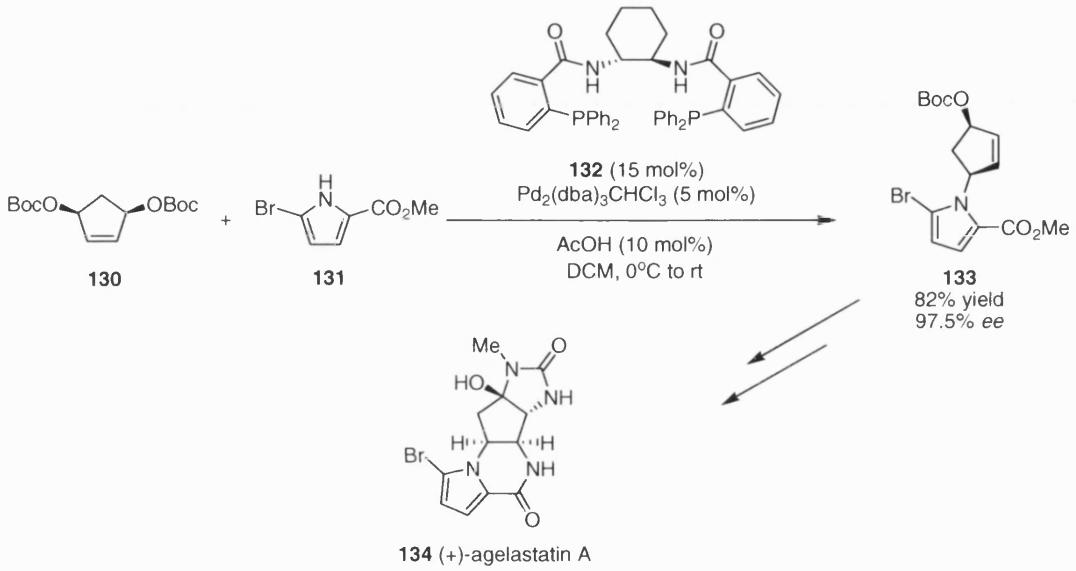
Scheme 57: palladium-catalysed desymmetrisation of *meso*-diamines

2.6 - Alkene and diene substrates

2.6.1 - Desymmetrisation by asymmetric allylic alkylation

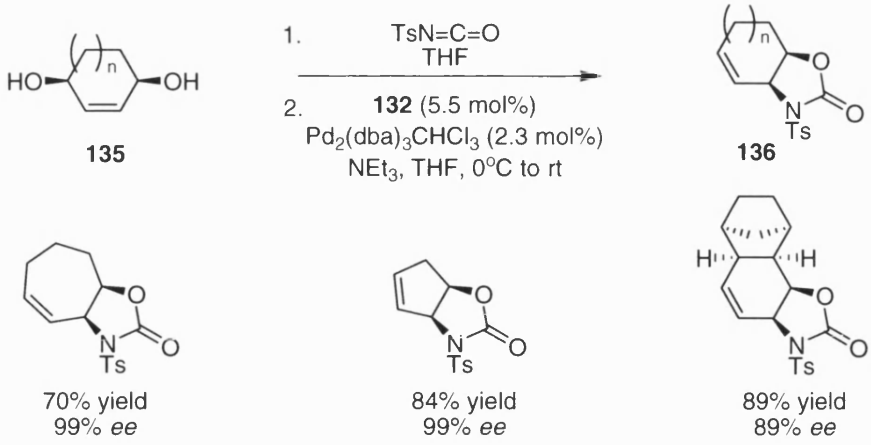
Whilst it has been shown that the desymmetrisation of *meso*-diamines can be performed using an allylic substitution reaction, there also exist a number of alternative *meso*-substrates that can be desymmetrised by this method. [196] The pioneering work in the application of palladium-catalysed asymmetric allylic alkylation (AAA) has been published by Trost. He has used *meso*-2-ene-1,4-

diol derivatives as desymmetrisation substrates in the total synthesis of (-)-epibatidine,[197] (-)-neplanocin,[198] and more recently (-)-swainsonine[199] and L-showdowmycin.[200] He has also used this methodology to synthesise (+)-agelastatin A **134**, with (-)-agelastatin A readily available through the opposite enantiomer of ligand **132**.[201] Reaction of Boc-activated cyclopentene-1,4-diol **130** with bromo-pyrrole **131** under palladium-catalysed AAA conditions was able to provide the coupled product **133** in excellent yield and enantioselectivity. Further derivatisation provided (+)-agelastatin A in just eight steps (Scheme 58).



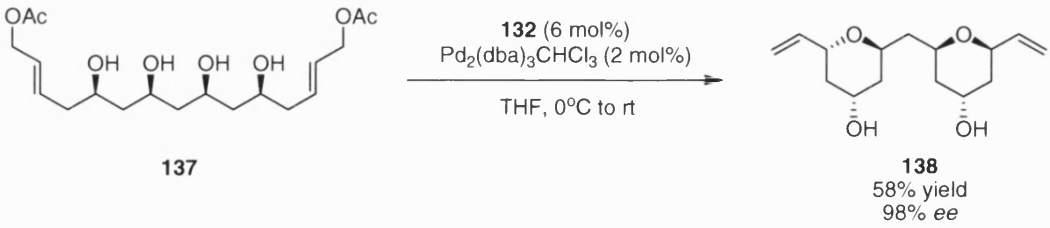
Scheme 58: asymmetric allylic alkylation in the total synthesis of (+)-agelastatin A

A complimentary intramolecular procedure has been developed, whereby *bis*-carbamates **135** are cyclised under palladium-catalysed AAA conditions to provide the oxazolidin-2-one products **136** in excellent yield and with exceptional enantioselectivity. A two step reaction could be performed from the parent *meso*-diol, with *bis*-carbamate formation and cyclisation occurring in one pot (Scheme 59).[202]



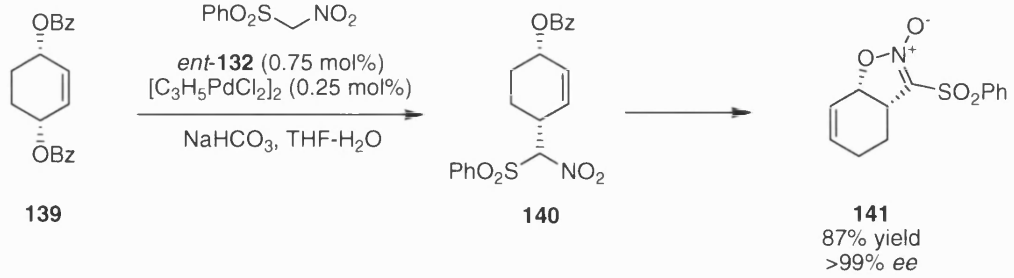
Scheme 59: intramolecular desymmetrisation by AAA

This methodology has been used by Blechert *et al.* in the total synthesis of (-)-swainsonine.[203] A series of peptide ligands have also been developed for this transformation by Gilbertson, however the selectivities achieved by Trost could not be bettered.[204] Another intramolecular desymmetrisation has been shown by Burke to be an efficient way of generating tetrahydropyran cores of high enantiopurity in studies towards the synthesis of phorboxazoles A and B (Scheme 60). When polyol **137** was subjected to Trost's AAA catalyst system (ligand **132**, see above) the *bis*-cyclised product **138** could be isolated in 58% yield and 98% *ee*.[205]



Scheme 60: desymmetrisation of a polyol by intramolecular AAA

Trost has also shown that this methodology can be used for *C-C* bond construction using reagents such as (phenylsulfonyl)nitromethane. Allylic substitution of dibenzoate **139** with *ent*-**132** provides mono-benzoate **140**. This is then cyclised to form isoxazoline *N*-oxide **141** in excellent yield and *ee*, which is a key intermediate in the synthesis of (+)-valienamine (Scheme 61).[206] Malonates have also been used as carbon nucleophiles in these reactions.[207]

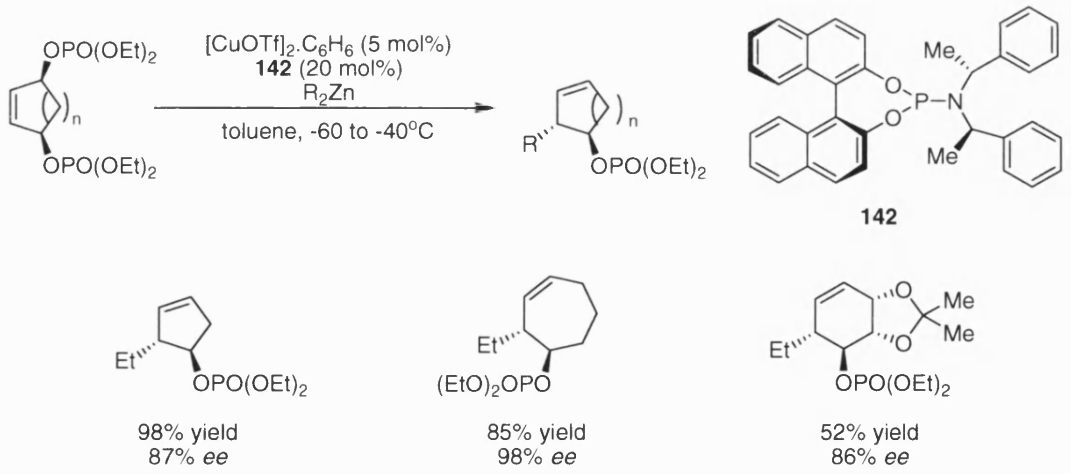


139 **140** **141**
87% yield
>99% *ee*

Scheme 61: carbon nucieophiles in desymmetrising AAA

The enantioselective ring opening of *meso*-bicyclic hydrazines has also been reported by Micouin *et al.*,[208] whilst many groups have focussed on the preparation of new ligands for the AAA-desymmetrisation process.[209-211]

Gennari *et al.* have developed a copper-catalysed alkylative desymmetrisation of cyclic allylic *bis*-diethylphosphates with organo-zinc reagents. The reactions use either chiral Schiff base ligands or phosphoroamidites (e.g. **142**) to produce the alkylated mono-phosphate products in good yields and enantioselectivities, often as a single diastereomer (Scheme 62).[212-214]



142

98% yield
87% *ee*

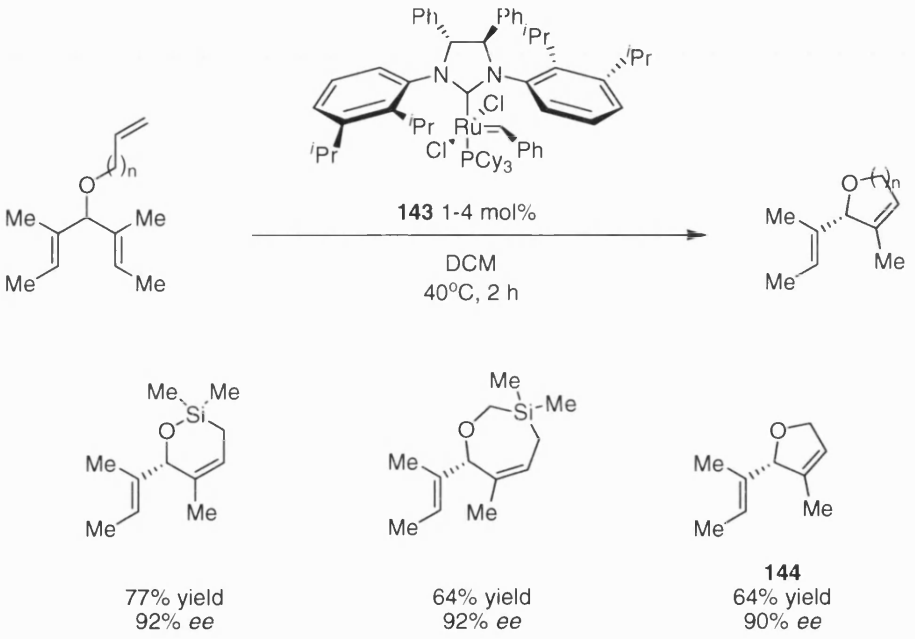
85% yield
98% *ee*

52% yield
86% *ee*

Scheme 62: alkylzinc additions to *meso-bis*-phosphonates

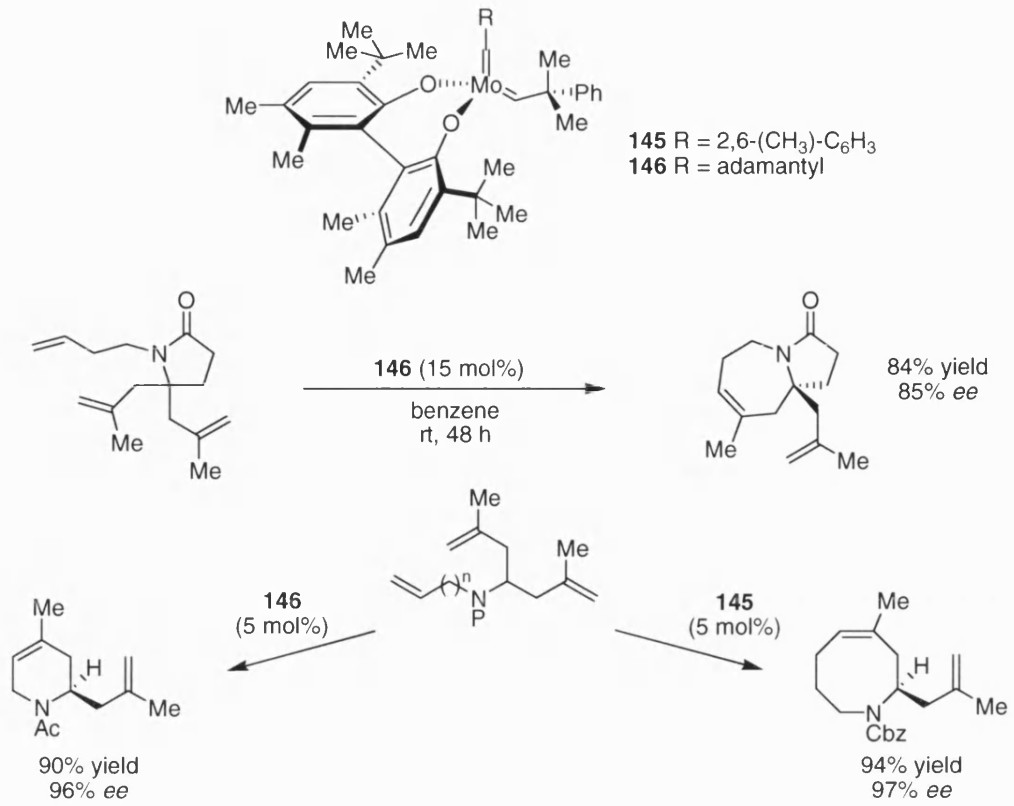
2.6.2 - Desymmetrisation by metathesis reactions

Schrock, Hoveyda and Grubbs have published a considerable body of work on the desymmetrisation of diene substrates, using ruthenium and molybdenum catalysts in olefin metathesis reactions.[215, 216] The chiral ruthenium complex **143** has been shown to catalyse the enantioselective cyclisation of a series of dienes, to provide the desymmetrised products in good yield and enantioselectivity (Scheme 63).[217, 218] Subtle modifications of the aryl groups of the *N*-heterocyclic carbene ligand and halide substituents allowed the catalyst to act effectively on smaller substrates (e.g. **144**).



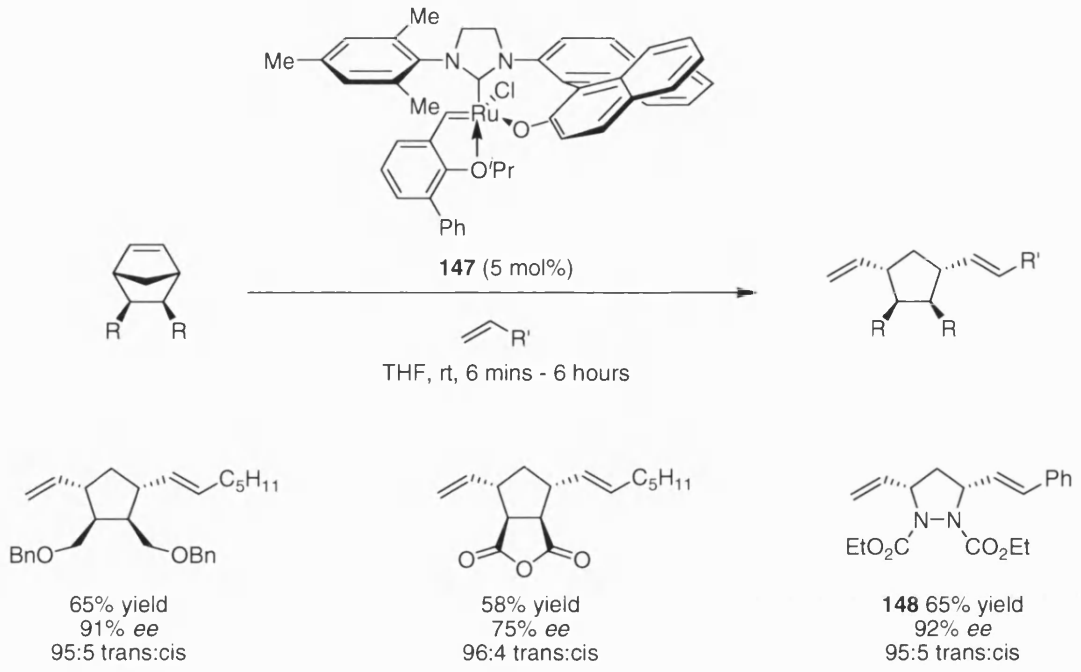
Scheme 63: RCM desymmetrisation of achiral dienes

Schrock and Hoveyda have made use of chiral molybdenum alkylidene complexes to synthesise amines and bicyclic amides.[219] Treatment of an achiral diene with **145**, **146** or analogous catalysts produced the desymmetrised products in high yield and with good to excellent selectivity (Scheme 64). A range of substrates were examined, however no single catalyst was effective for all the transformations, with alternative catalysts bearing adamantyl and binaphthyl groups required. These catalysts have also been used in the synthesis of cyclic allylboronates.[220]



Scheme 64: synthesis of cyclic amines and amides *via* desymmetrising RCM

Desymmetrising ring-opening metathesis has also been shown to be possible by Hoveyda *et al.* whereby *meso*-bicyclic substrates were reacted with ruthenium complex **147** and an olefin.[221] Reactions were performed at room temperature with a catalyst loading of 5 mol%, and afforded the products in good selectivity (Scheme 65). The diamide **148** could also be reduced to provide a new enantioselective route to 1,3-diamines.

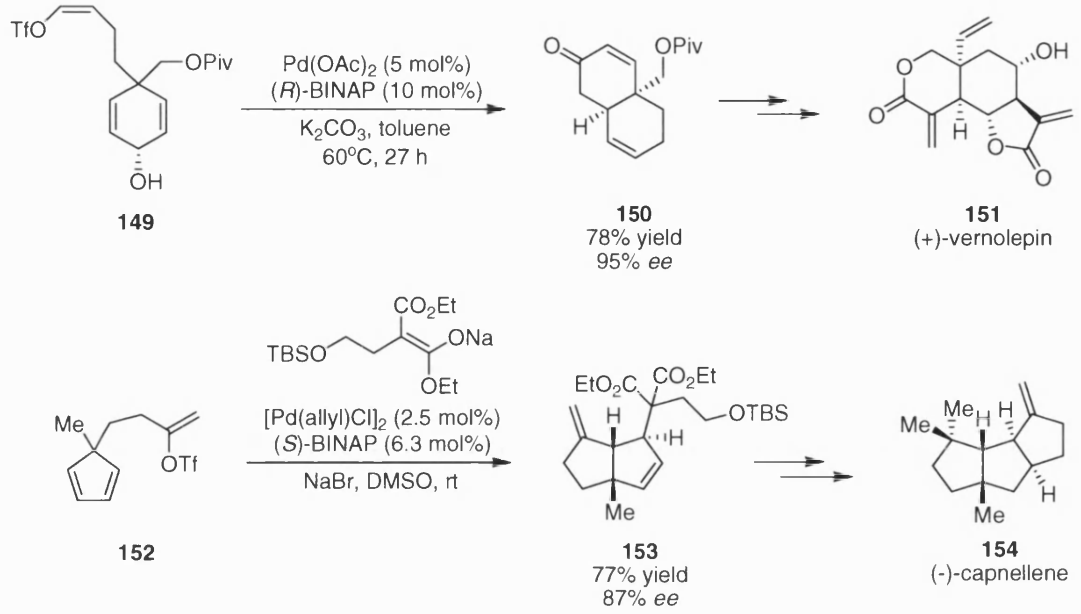


Scheme 65: desymmetrisation by ring-opening metathesis

2.6.3 - Cyclohexadiene substrates

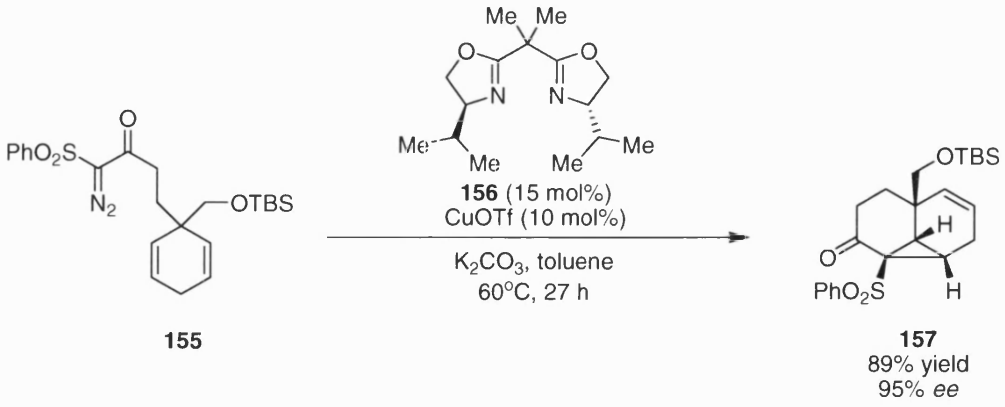
Desymmetrisations of 1,4-cyclohexadienes are well known,[222] however the majority involve the use of stoichiometric amounts of chiral compounds. Epoxidations,[223] dihydroxylations and aminohydroxylations,[224, 225] and metallation with chiral titanium complexes[226, 227] are common examples. Shi *et al.* have developed an epoxidation reaction using oxone and a fructose derivative, however the reaction gives mixed results when sub-stoichiometric quantities of the chiral reagent are used.[228] Far fewer examples exist of catalytic processes, however Shibasaki has reported a intramolecular desymmetrising Heck reaction of alkenyltriflate **149**.[229] A palladium-BINAP catalyst was able to effect the transformation to produce the bicyclic **150** which contains a chiral quaternary carbon centre in good yield and excellent *ee* (Scheme 66). This could be further elaborated to provide a route to the natural product (+)-vernolepin **151**.[230, 231] In similar fashion, cyclohexadiene **152** could be cyclised, followed by trapping with a malonate equivalent to provide **153**, which lead to an efficient synthesis of (-)-capnellene **154**,[232-234] whilst other key intermediates have also been synthesised with this methodology.[235] Initial

studies had focussed on the corresponding vinyliodides, however these substrates were less successful and displayed significantly lower selectivity.



Scheme 66: desymmetrisation *via* intramolecular Heck reaction

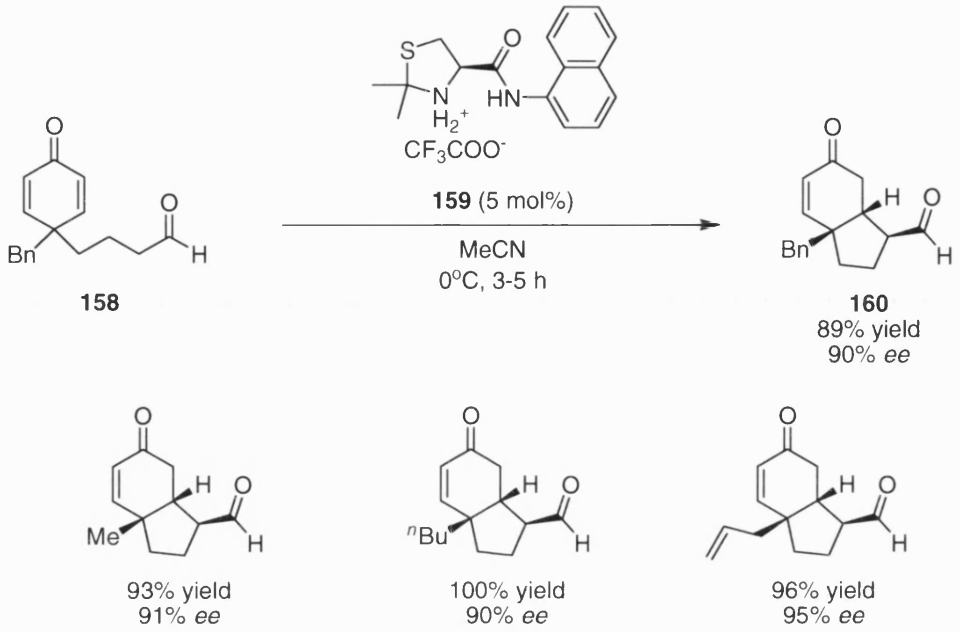
Nakada and Honma have also studied an intramolecular desymmetrisation process involving cyclohexadiene **155**.[236] Copper-catalysed asymmetric cyclopropanation using chiral *bis*-oxazoline ligand **156** afforded the highly functionalised **157** in 89% yield and 95% *ee* (Scheme 67). The reaction was also applied to a range of acyclic compounds, however the yields did not match that of cyclohexadiene **155**.



Scheme 67: copper-catalysed cyclopropanation applied to desymmetrisation

An organocatalytic intramolecular Michael addition has been reported by Hayahsi *et al.*[237] Well-established organocatalysts such as proline and those

pioneered by MacMillan provided unsatisfactory results, however action of cysteine-derived **159** on aldehyde **158** gave the Michael addition product **160** in excellent yield, *ee* and diastereoselectivity (Scheme 68). The reaction was applied to a number of other substrates to form products containing quaternary stereodefined carbon centres.

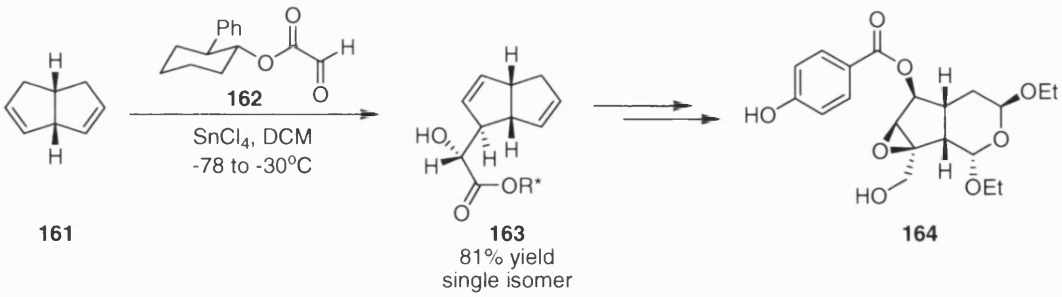


Scheme 68: organocatalytic desymmetrisation of Michael acceptors

Mori has also published work on desymmetrising cyclohexadienes, using a chiral zirconium complex to form bicyclic products with good enantioselectivity, however yields are generally 40% or lower.[238]

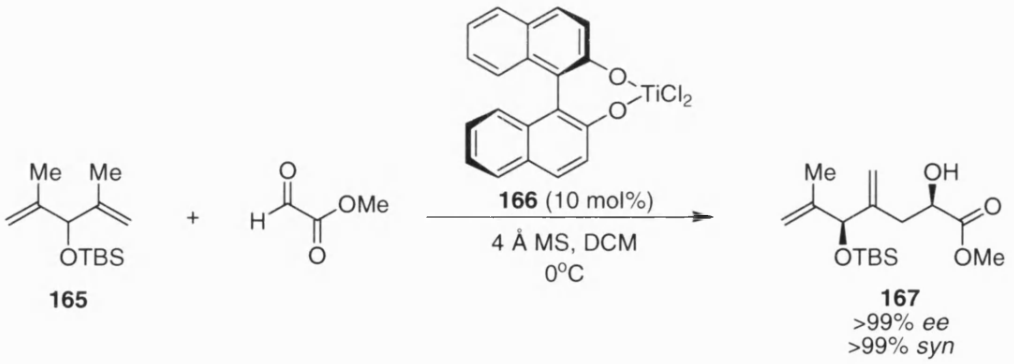
2.6.4 - Miscellaneous alkene substrates and reactions

Some very early work in desymmetrisation methodology was performed by Whitesell in his synthesis of (-)-specionin.[239, 240] He used chiral gloxylate esters such as **162** as enophiles in an intermolecular ene reaction with diene **161** and stoichiometric tin tetrachloride (Scheme 69). The desymmetrised product could **163** be isolated in 81% yield as a single isomer. The final target (-)-specionin **164** could then be prepared in an 11 step sequence.



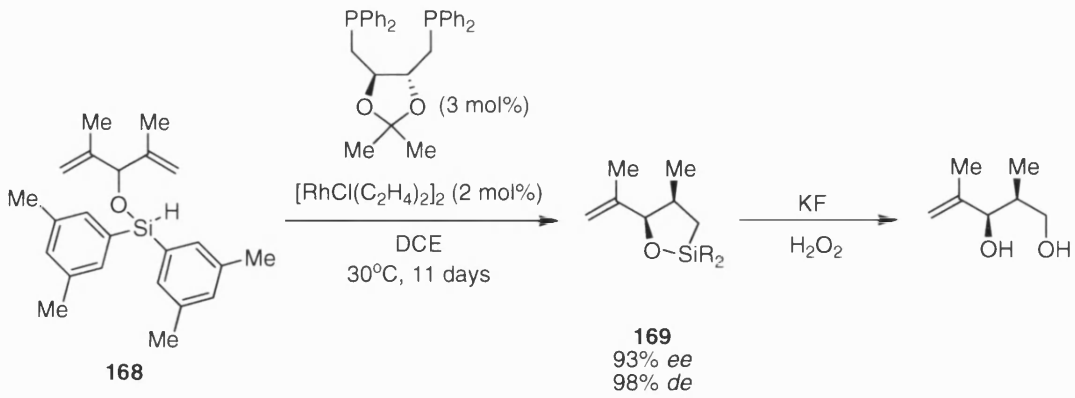
Scheme 69: desymmetrisation of **161** by intermolecular ene reaction

A catalytic ene reaction of an achiral diene with a glyoxylate has also been reported by Mikami.[241] A titanium-BINOL catalyst **166** was used to facilitate reaction between *bis*-allylic silyl ether **165** and methyl glyoxylate, affording the ene product **167** as essentially a single enantiomer and diastereomer (Scheme 70). This methodology was extended to incorporate the use of vinylogous glyoxylate esters in the synthesis of isocarbacyclin,[242] and a related reaction has been used by Daniewski in the desymmetrisation of 1-alkyl-4-methylenecyclohexanes in the first total synthesis of pravastatin.[243]



Scheme 70: a catalytic ene reaction in the desymmetrisation of **165**

A similar substrate has been desymmetrised *via* intramolecular hydrosilylation by Ito and co-workers.[244] When stirred for extended time periods with a chiral rhodium-DIOP catalyst, diene **168** was able to undergo cyclisation to yield silane **169** in 93% *ee* and 98% *de*. Simple oxidative workup with potassium fluoride and hydrogen peroxide then gave access to enantiomerically enriched diols (Scheme 71). Less bulky silanes were shown to give diminished enantioselectivities.

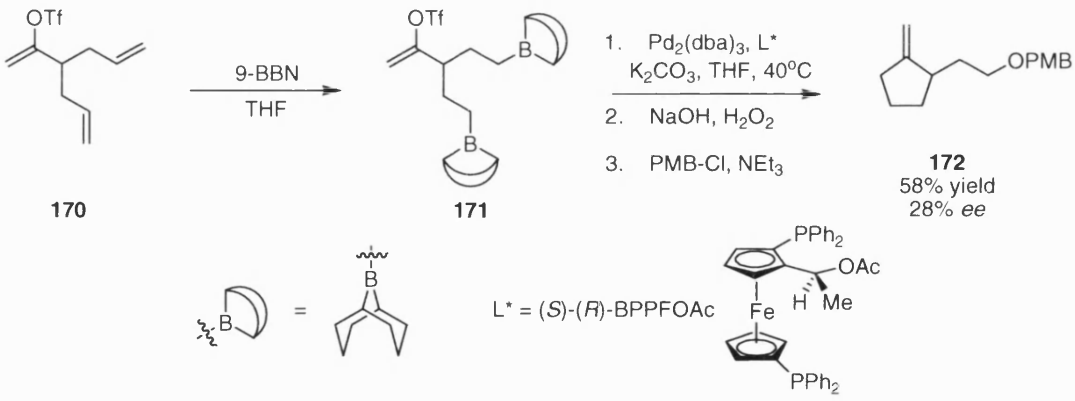


168

169
93% *ee*
98% *de*

Scheme 71: desymmetrisation via intramolecular rhodium-catalysed hydrosilylation

Palladium-catalysed desymmetrisation of diene substrates has been performed by Shibasaki *via* a one-pot hydroboration-Suzuki procedure.[245] Treatment of dienes such as **170** with 9-BBN produces the dialkylborane **171**, which is not isolated and is directly subjected to Suzuki reaction conditions in an intramolecular cyclisation (Scheme 72). The resultant *exo*-alkene **172** could be isolated in good yield, however the enantioselectivity of the process could not be increased above 28% *ee*.



170

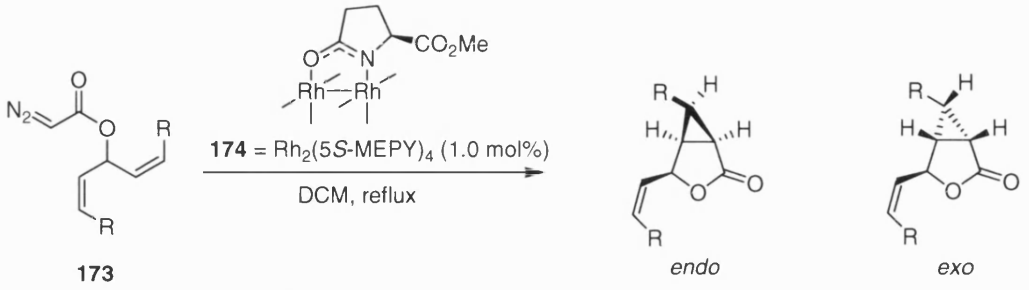
171

172
58% yield
28% *ee*

Scheme 72: desymmetrisation of diene **170** by hydroboration-Suzuki process

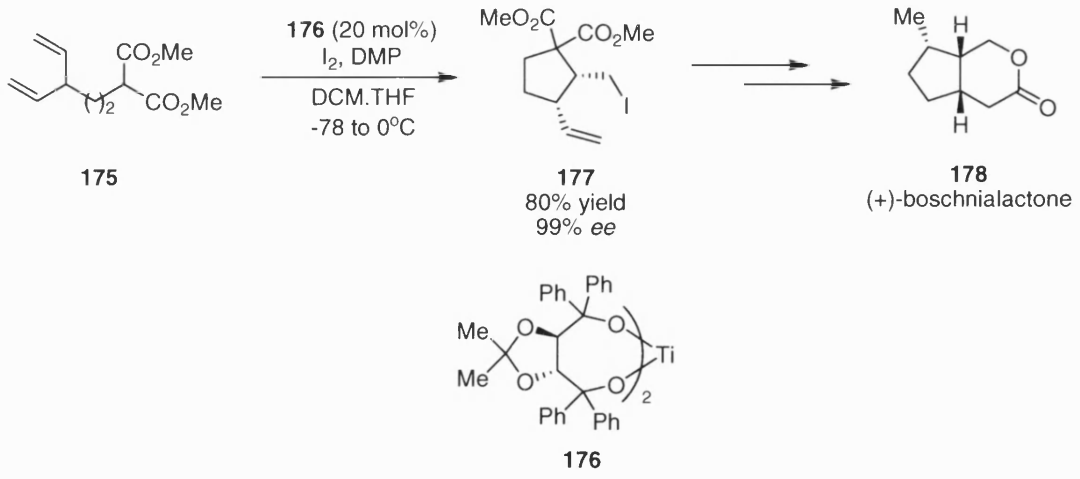
Oestreich has studied similar systems, focussing on the Heck cyclisation of the dienes, rather than the Suzuki substrates, in which coordinating groups within the substrate were shown to play a key role in the enantioselectivities observed.[246] More recently, Bräse *et al.* have reported an efficient desymmetrising intramolecular Heck reaction using the ferrocene ligand JOSIPHOS.[247] One other successful process involves a rhodium-catalysed cyclopropanation, in which Martin has desymmetrised diazo-diene **173**.[248] The

rhodium (II) carboximide catalyst **174** was found to be the most successful, delivering the fused cyclopropane-δ-lactone adducts in good yield and enantioselectivity (Scheme 73). The diastereoselectivity of the reaction was however very substrate dependent, and sometimes delivered poor ratios of *endo* and *exo* products.



Scheme 73: intramolecular cyclopropanation of diene **173**

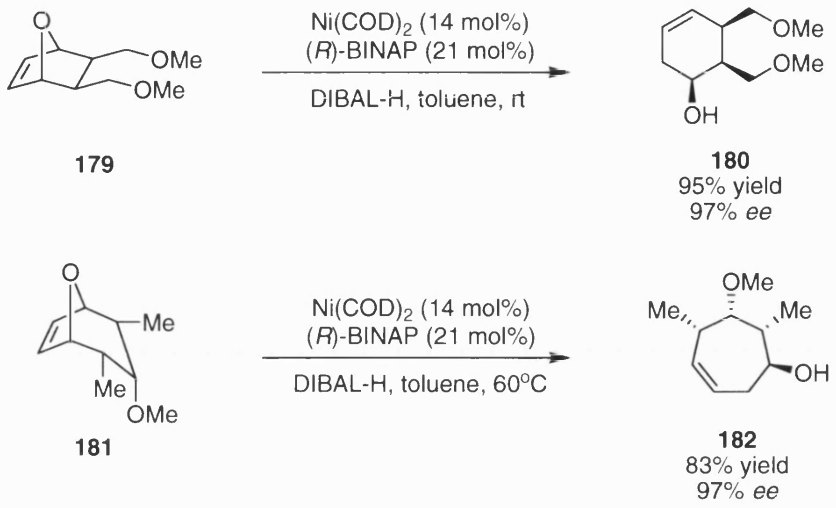
A desymmetrising iodocarbocyclisation has been used by Taguchi and co-workers in the synthesis of (+)-boschnialactone **178**.[249] The malonate diene **175** was reacted with iodine in the presence of catalytic amounts of chiral titanium-TADDOL complex **176** to give cyclopentane **177** in good yield and an excellent 99% *ee* (Scheme 74). A few short steps then resulted in (+)-boschnialactone.



Scheme 74: catalytic desymmetrisation by iodocarbocyclisation

Lautens has developed the ring-opening reduction of oxabicyclic alkenes with DIBAL-H and chiral nickel catalysts.[250] When subjected to these conditions

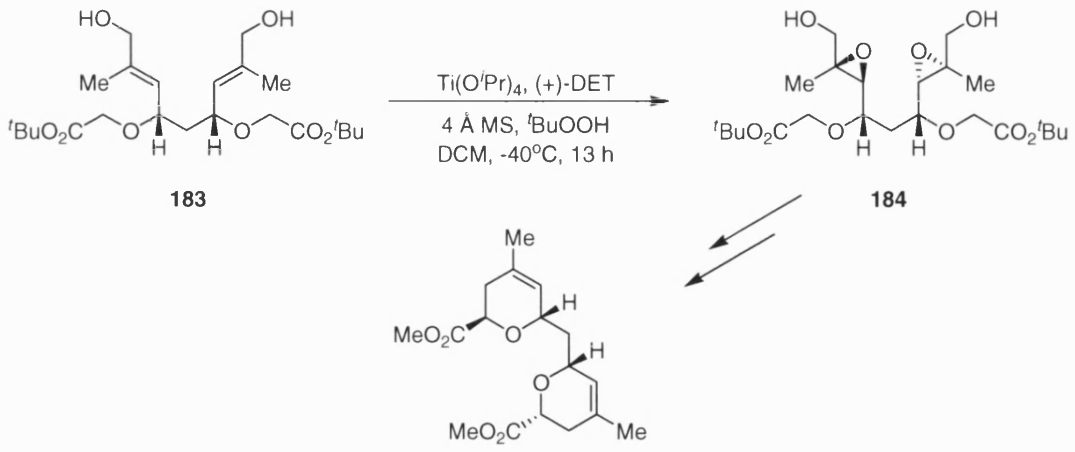
meso-bicyclic alkene **179** undergoes reductive ring-opening to provide the cyclohexene product **180** which now contains three defined stereocentres. In similar fashion, *meso*-substrate **181** ring-opens to form cycloheptene **182** containing four contiguous stereocentres in excellent *ee* (Scheme 75).



Scheme 75: nickel-catalysed reduction of bicyclic olefins

There are several more examples of the catalytic desymmetrisation of alkene and diene substrates, such as the Pauson-Khand reactions performed by Jeong *et al.*,[251] and the rhodium-catalysed hydroformylations of Breit.[252] Moberg has also reported a palladium-catalysed oxidative cyclisation reaction, which incorporates a chiral alcohol into the desymmetrisation process.[253, 254]

The asymmetric desymmetrising epoxidation of alkenes and dienes can be an extremely complex process.[71] Much of the pioneering work in this field has been performed by Schreiber, including studies into the kinetic resolutions observed in cases where a diene can undergo two consecutive epoxidation reactions.[72] Burke has shown that this can be beneficial in a case where the double epoxidation product was in fact the desired result.[255] Reaction of diene **183** under Sharpless asymmetric epoxidation (SAE) conditions yielded *bis*-epoxide **184** in 81% yield and "high diastereo- and enantiomeric purity". This could then be further elaborated to form the C(22)-C(34) fragment of halichondrin (**185**) (Scheme 76).



185 C(22)-C(34) fragment of halichondrin

Scheme 76: double epoxidation in the desymmetrisation of **183**

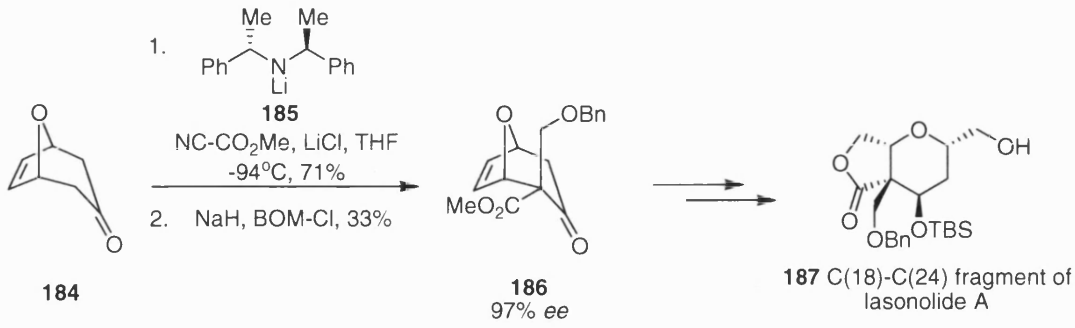
This oxidative desymmetrisation methodology has also been explored by Nelson, using stoichiometric chiral epoxidation reagents in the desymmetrisation of *meso*-difuryl alcohol derivatives,[256, 257] and by Spivey with a zirconium-based SAE process.[258] Numerous groups have also made use of chiral boranes in desymmetrising hydroboration-oxidation reactions on tropinones[259] and bicyclic hydrazines,[260] and their practicality is also observed in studies toward the syntheses of (+)-discodermolide[261] and phorboxazoles A and B.[262]

2.7 - Desymmetrisation by enantioselective deprotonation

Enantioselective deprotonation by chiral bases is a popular research area in desymmetrisation studies, and as such has been comprehensively reviewed by O'Brien,[263] Beak,[264] and Hoppe.[265] These reviews are significantly more detailed than the summary of work presented here, and should be referred to for studies in this methodology.

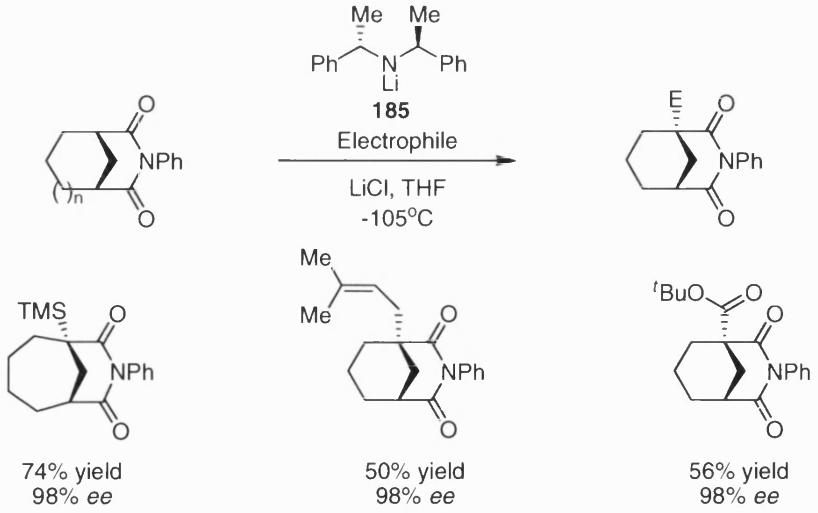
One of the most common reagents for enantioselective deprotonations is Simpkin's base **185** ((+)-*bis*(α-methylbenzyl)amine).[266] It has found great use in the desymmetrisation of carbonyl compounds by α-deprotonation followed by either enolate trapping or α-functionalisation. Hoffman has used this to good effect in studies towards the synthesis of lasonolide A **187**.[267] Enantioselective deprotonation of bridged ketone **184** with Simpkin's base **185** and quenching

with methyl cyanoformate was then followed by further deprotonation, this time quenching with benzyloxymethyl chloride (BOM-Cl) to deliver the desymmetrised ketone **186** in 97% *ee* (Scheme 77).



Scheme 77: desymmetrising enantioselective deprotonation in the synthesis of **187**

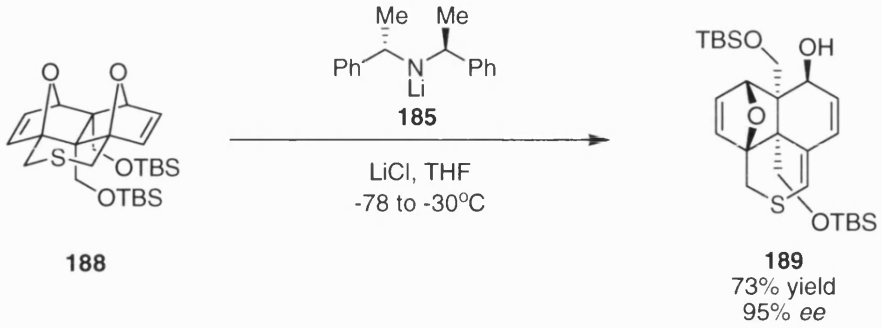
A more recent example of enantioselective desymmetrisation by this base has also been demonstrated in the α-functionalisation of bridged bicyclic imides.[268] Treatment with **185**, followed by electrophile addition produced a range of desymmetrised products in reasonable yield and excellent enantioselectivity (Scheme 78). Yields were affected by formation of the undesired *bis*-alkylation products.



Scheme 78: bicyclic imide desymmetrisation by enantioselective deprotonation

Lautens has also used this base in the ring-opening desymmetrisation of a dioxacyclic alkene. Enantioselective deprotonation by **185** of the methylene adjacent to the sulfur atom of **188**, followed by ring opening resulted in decalin

189 in good yield and excellent *ee* (Scheme 79). The system was prone to over-reaction, and without strict control of the reaction conditions the doubly ring-opened *meso*-product was often observed.

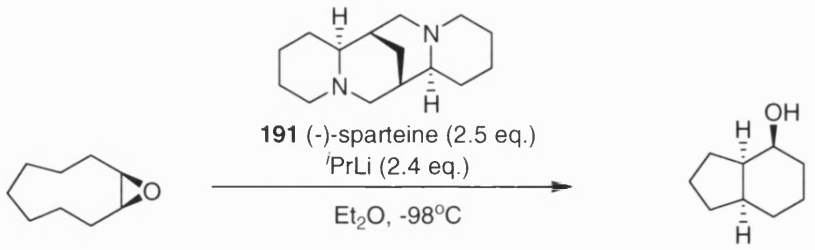


188 **189** 73% yield 95% *ee*

Scheme 79: desymmetrisation by deprotonation/ring-opening

Simpkin's base has been widely applied to desymmetrisations, as can be seen in the recent synthesis of (-)-epibatidine by Aggarwal.[269] It has also been employed by Magnus *et al.* in the synthesis of lycorane amaryllidaceae alkaloids,[270] and by Ferezou in the C(1)-C(11) fragment of bafilomycin A[271] among others. Simpkins has applied this chemistry to desymmetrising phospholanes[272] and in synthesising several natural products,[273-277] whilst he has also studied chiral bases of similar structure.[278]

Several alternative chiral bases have been investigated,[279-283] however considerable success has been achieved with sparteine.[284-286] Hodgson has utilised this base to perform a desymmetrisation on epoxide **190**.[287] Deprotonation by an alkyllithium in the presence of stoichiometric (-)-sparteine **191** yielded bicyclic alcohol **192** in 77% yield and 83% *ee* (Scheme 80). The proposed mechanism for this transformation involves formation of a carbenoid intermediate which facilitates transannular *C-H* insertion.



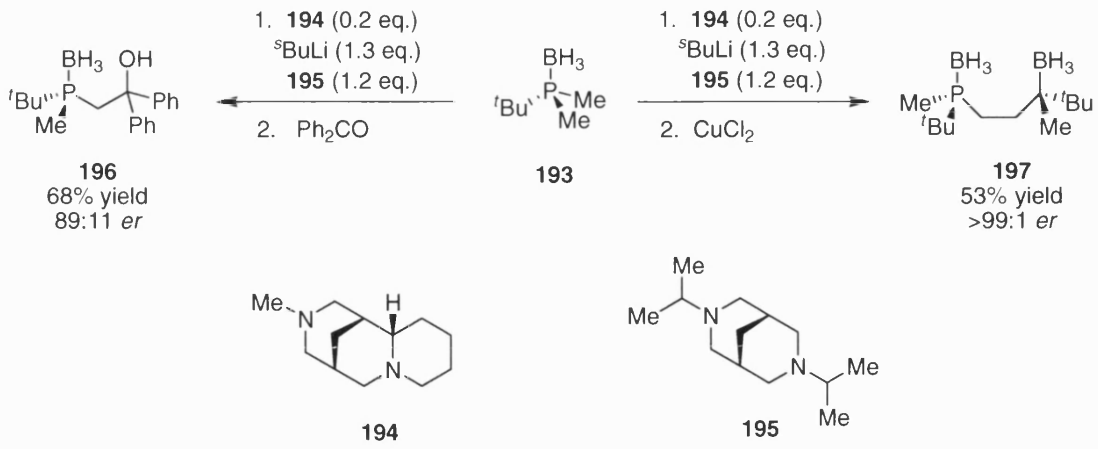
190

192
77% yield
83% *ee*

Scheme 80: (-)-sparteine as a chiral base for desymmetrisations

The same base has been used for enantioselective deprotonations in numerous other desymmetrisation processes, such as the enolboration of ketones with chiral boron reagents.[288]

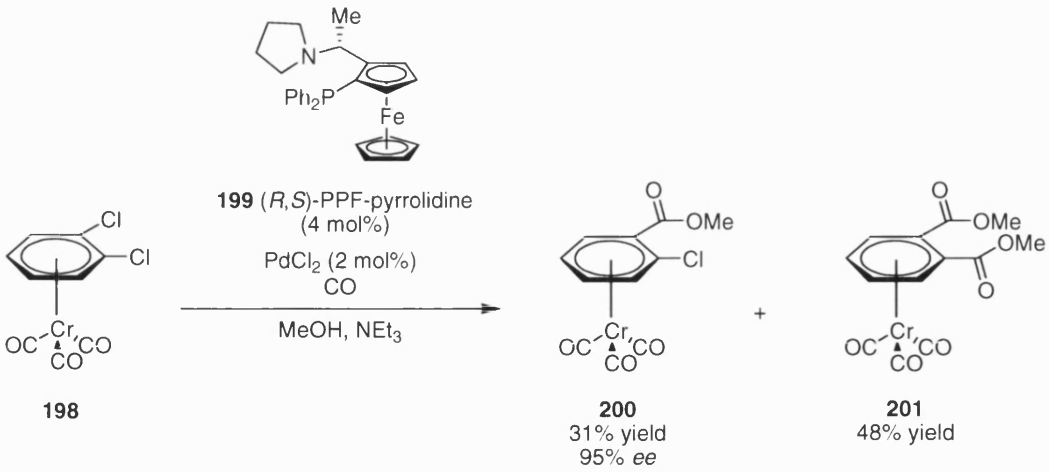
All the above examples of enantioselective deprotonations require stoichiometric amounts of the chiral amine, however recently O'Brien has reported methodology that only requires catalytic amounts.[289] A ligand exchange approach is utilised, whereby catalytic (-)-sparteine is combined with stoichiometric amounts of an achiral analogous base. Once the chiral (-)-sparteine lithium complex has coordinated to the substrate, the achiral mimic base replaces (-)-sparteine. The geometry of the lithiated substrate has however now been set, and deprotonation proceeds, followed by trapping with a suitable electrophile. This reaction was applied to functionalisation of *N*-Boc pyrrolidines, but also to the desymmetrisation of prochiral phosphine boranes. The chiral sparteine surrogate **194** was found to produce better enantioselectivities with certain substrates, and this in combination with achiral mimic bispidine **195** was able to effect the desymmetrisation of **193** *via* either quenching with benzophenone to form alcohol **196**, or copper (II) promoted dimerisation to **197** in good yields and enantioselectivities (Scheme 81).



Scheme 81: catalytic enantioselective deprotonation using sparteine analogues

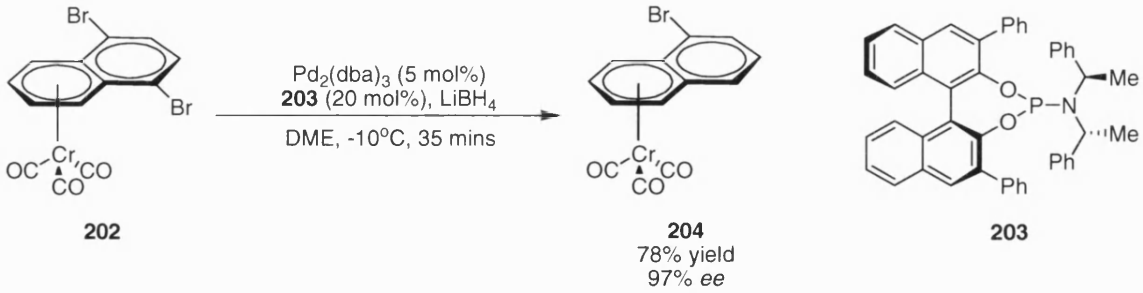
2.8 - Miscellaneous substrates and reactions

Schmalz has reported the desymmetrisation of the 1,2-dichloroarene chromium (0) tricarbonyl complex **198** using palladium-catalysed methoxycarbonylation.[290, 291] Using the chiral ligand **199**, the desymmetrised planar-chiral mono-ester product **200** could be formed in up to 95% *ee*, however significant amounts of the achiral diester product **201** were also isolated (Scheme 82). A kinetic resolution was observed in this reaction and was responsible for the high enantioselectivities seen, as at lower conversions the selectivity decreased. Although oxidative addition to palladium species of aryl chlorides is less favourable than that of aryl iodides and bromies, complexation to the chromium withdraws electron density from the *C-Cl* bonds and facilitates this process.



Scheme 82: desymmetrisation of planar chiral chromium complexes

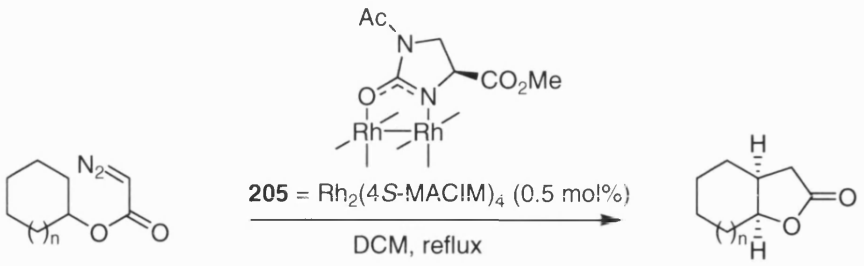
Similar methodology has been developed by Hayashi for analogous Suzuki reactions of this dichloroarene, however the reactions provided generally lower enantioselectivities.[292] Kündig has also performed enantioselective desymmetrisation reactions on aryl-chromium complexes.[293] The palladium-catalysed reduction of dibromo-naphthyl complex **202** proceeded well in the presence of phosphoroamidite ligand **203** to give the mono-bromo-naphthalene complex **204** in good yield and *ee*, with only small amounts of the achiral debromominated product isolated (Scheme 83).



Scheme 83: enantioselective desymmetrisation by palladium-catalysed reduction

Rhodium-catalysed *C-H* insertions have been performed in a desymmetrising manner by Doyle *et al.*[294] Treatment of cycloalkanes of varying ring sizes bearing α-diazo esters with chiral rhodium (II) catalyst **205** in dichloromethane yielded the lactone products with excellent selectivity (Table 5). The reaction could also incorporate substituted cycloalkanes, however the

diastereoselectivity of the reaction was heavily dependent on the nature of the substituent.

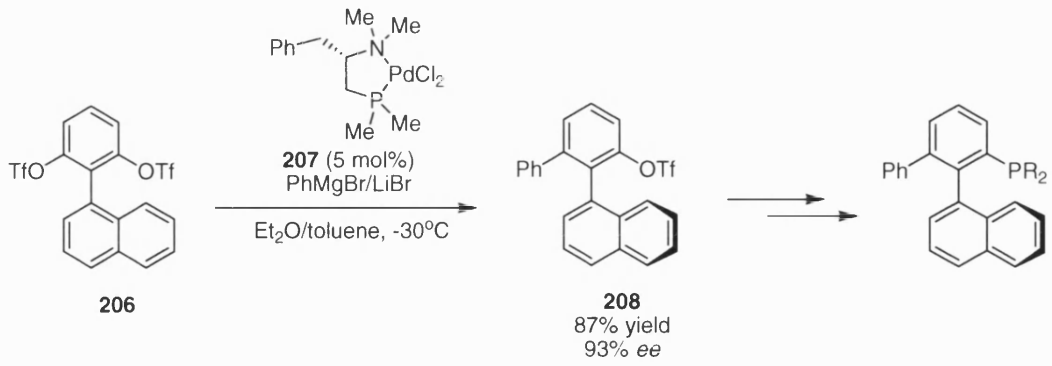


n	Yield (%)	*dr* (%)	*ee* (%)
1	70	99:1	97
2	75	99:1	96
3	62	99:1	97

Table 5: desymmetrisation by intramolecular *C-H* activation

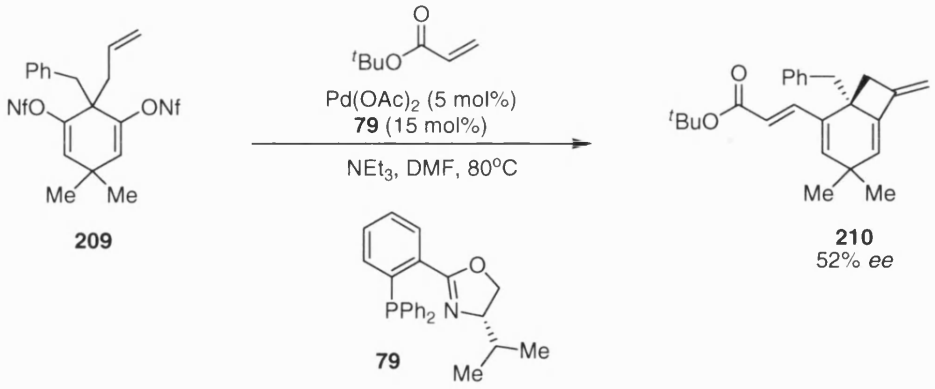
This methodology has also been applied to the desymmetrisation of *meso*-oxabicyclic compounds by Chiu *et al.*, however the enantioselectivities achieved by Doyle could not be matched.[295]

The synthesis of axially chiral biaryls is essential for developing new ligands for asymmetric catalysis, however many syntheses use resolutions to isolate the enantiomerically pure compounds. Hayashi has developed a desymmetrising Kumada coupling of biaryl *bis*-triflate **206** using a chiral palladium catalyst **207** and phenylmagnesium bromide.[296, 297] The mono-coupled biaryl product **208** could be isolated in 87% yield and 93% *ee* (Scheme 84). The product was especially useful as a wide range of functionalisations could be performed on the remaining aryltriflate, giving an efficient route to a new class of ligands. Synthesis of these ligands was also attempted by complexation to chromium, however the results were not as impressive.[292]



Scheme 84: synthesis of biaryl ligands by enantioselective desymmetrisation

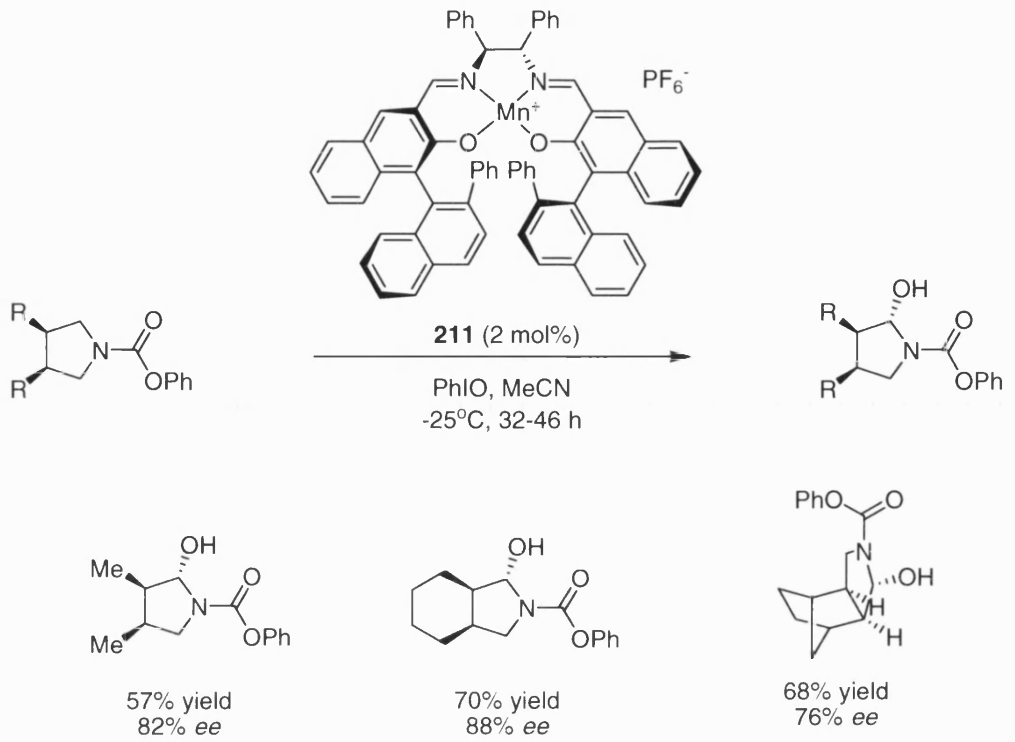
Another palladium-catalysed desymmetrisation has been reported by Bräse, whereby *bis*-alkenylnonaflate **209** was subjected to two sequential Heck reactions, one intramolecular with the pendant allyl group, and the other an intermolecular reaction with an acrylate (Scheme 85).[298] This produced the cyclobutane product **210** which is surprising, as a Cope rearrangement of 1,5-hexadienes is sometimes favoured,[299] as well as this kind of *exo-trig*-cyclisation being a rare occurrence in Heck chemistry.[300, 301] Whilst some ligands provided enantioselectivities up to 52% ((*S*)-^{i}Pr-PHOX **79**), and others yields up to 57% ((*R*)-BINAP) a ligand could not be found that was suitable for both factors.



Scheme 85: consecutive Heck reactions in the desymmetrisation of **209**

As well as the desymmetrisation of *meso*-diols by oxidation, Katsuki has also studied selective oxidations of *meso*-pyrrolidine derivatives.[302] The asymmetric catalytic *C-H* oxidation of these *meso*- substrates with manganese Salen complex **211** provided the hydroxypyrrolidine derivatives in reasonable yields and good enantioselectivities (Scheme 86). These could then be further

oxidised to provide the corresponding lactams. The same complex was also effective in the desymmetrisation of *meso*-cyclic ethers of similar structure.[303, 304]



Scheme 86: manganese oxidative desymmetrisation

A copper-catalysed desymmetrisation of *gem*-diazides has been investigated by Finn *et al.* using chiral pybox ligands.[305] Many other substrates have also been used in desymmetrisation studies, such as the CBS reduction of a centrosymmetric molecule by Spivey[306] and the desulfurization of *meso*-cyclic disulfides by Uemura,[307] however these all require stoichiometric quantities of the chiral reagent. The enantioselective ring-opening of *meso*-cyclopropanes has also been studied by Müller,[308] whilst Cossu has made use of enantiomerically pure 1,2-diols in the desymmetrisation of *bis*-(phenylsulfonyl)alkenes.[309]

2.9 - Conclusions

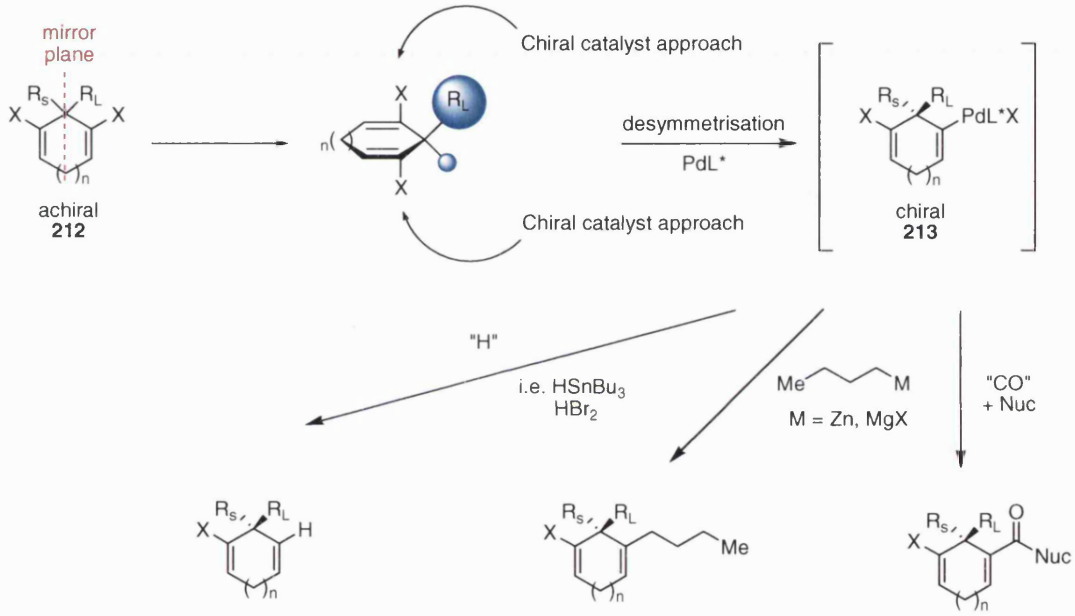
Since its inception, desymmetrisation methodology has shown to be a useful way of generating enantio- and diastereomerically pure compounds from achiral or *meso*- starting materials. Unlike many modern transformations, they also have the ability to create multiple stereodefined centres in one step, resulting in highly functionalised and useful products. In early reports, stoichiometric quantities of chiral compounds were generally used to effect these transformations, however it is increasingly desirable to perform these reactions with catalytic amounts of chiral reagents in order to minimise the costs of the process. Both metal-catalysed and organocatalytic systems have been developed, and with the ever increasing range of chiral ligands available to the user these appear to be the future of this field of study. Whilst much of the work performed has made use of carbon-heteroatom bond formation, the number of carbon-carbon bond forming reactions is increasing and will continue to do so. The art of creating stereodefined all-carbon quaternary centres has been explored, however there still remains a lot of work to be done in this area before it can be said to be even close to perfection.

2.10 – Generating stereogenic carbon centres through enantioselective desymmetrisation

As can be seen in the above review, desymmetrisation has become a powerful method of generating enantiomerically enriched products, although this methodology has not been widely exploited as a synthetic tool. Palladium catalysts have been shown to be effective in this chemistry as they can perform a range of functionalisations. The wealth of chiral ligands known to be able to achieve high enantioselectivities in these palladium-catalysed transformations makes this route particularly favourable to the synthetic chemist.

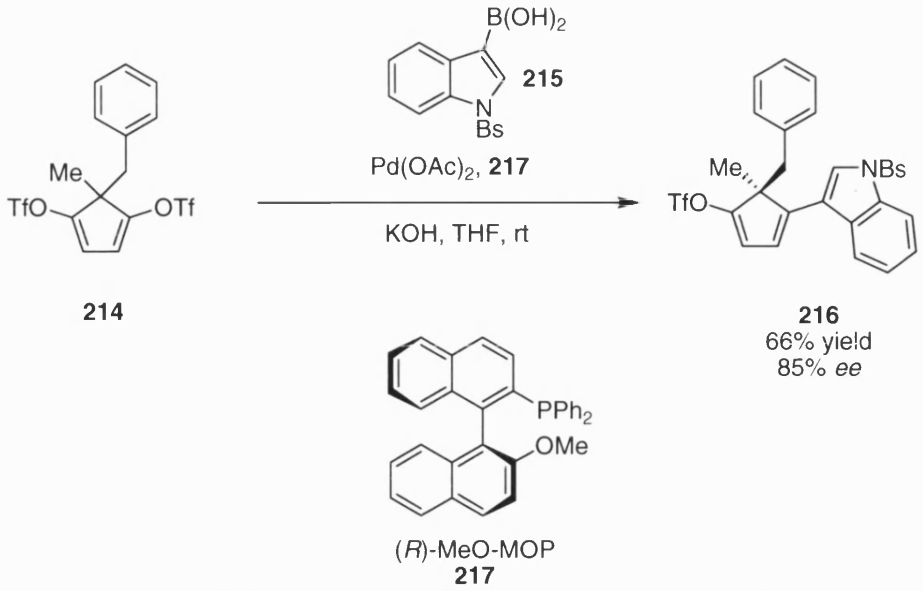
We envisaged a system for desymmetrisation using an achiral cyclic substrate that contained a mirror plane (**212**). This substrate would have an activated group on either side of this mirror plane that could undergo a palladium-catalysed transformation, and a group within the molecule that upon desymmetrisation is made chiral. This prochiral group enables selective oxidative addition of a chiral palladium catalyst *via* discrimination between the

two enantiotopic activating groups of the substrate. Once this oxidative addition has occurred the symmetry of the molecule is destroyed and a chiral alkenyl-palladium species **213** is produced. This intermediate is then able to undergo a range of palladium-catalysed coupling reactions to produce a variety of final products (Scheme 87). One added advantage of this desymmetrisation reaction is that the newly formed enantiomerically enriched substrates have a remaining activating group, and as such can undergo further functionalisation by numerous palladium-catalysed processes to generate a large range of interesting substrates. Alternatively, the alkene moieties could be exploited *via* reactions such as hydroboration, epoxidation or ozonolysis.



Scheme 87: the proposed desymmetrisation strategy

Previous work in the group has focussed on the desymmetrisation of *bis*-alkenyltriflates by enantioselective Suzuki reaction.[310] This is illustrated below, whereby *bis*-alkenyltriflate **214** undergoes enantioselective palladium-catalysed coupling with a boronic acid **215**, to produce the mono- functionalised product **216** in good yield and enantioselectivity (Scheme 88). The hemi-labile ligand (*R*)-MeO-MOP **217** was found to be a suitable ligand for this transformation. This reaction is especially note-worthy as it results in the formation of a new chiral quaternary carbon centre.



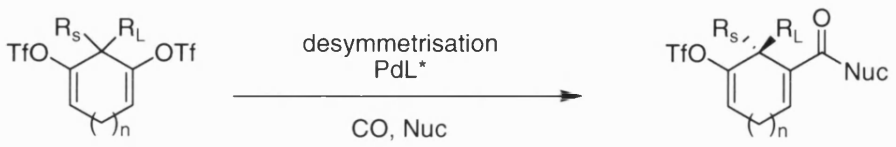
214

216
66% yield
85% *ee*

(*R*)-MeO-MOP
217

Scheme 88: desymmetrisation of *bis*-alkenyltriflate by enantioselective Suzuki coupling

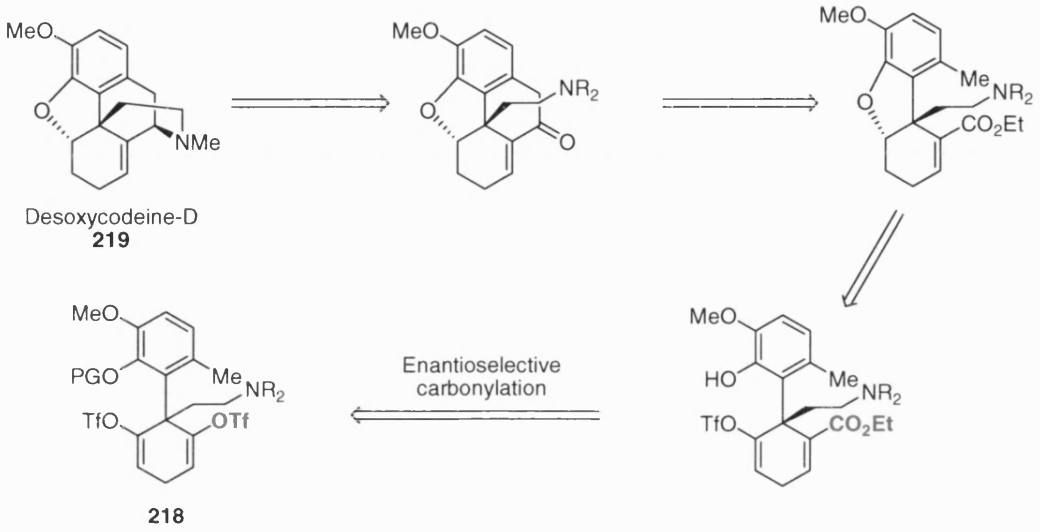
The reaction was shown to be applicable to a range of boronic acids, with little detriment to the enantioselectivity of the process. The reactions occasionally suffered from problems in their purification due to boronic acid by-products. For this reason we sought to make use of palladium-catalysed carbonylation chemistry in a similar manner to produce esters and related products (Scheme 89). These reactions have the benefit of the coupling partners being a gas (carbon monoxide), and a nucleophile (often a simple alcohol) which leads to exceptionally clean reactions where minimal purification is required to remove the catalyst. The majority of palladium-catalysed reactions also involve a catalytic cycle in which transmetallation is the *rate-determining step*, however this is not the case in carbonylation reactions. As carbon monoxide insertion into *Pd-C* bonds is a facile process, the rate determining step is often oxidative addition, meaning that in these desymmetrisation reactions this could be both the *enantio-* and *rate-determining step*.



Scheme 89: desymmetrisation of a *bis*-alkenyltriflate by enantioselective carbonylation

Variation of the nature of the substituents R_S and R_L (Scheme X), as well as ring size (n) and core structure may provide an insight into the mechanistic aspects of this desymmetrisation process, whilst also generating new compounds bearing quaternary carbon centres.

It was then hoped that this methodology could be adapted as the key step in studies towards target syntheses, such as the proposed route to desoxycodeine-D **219** (Scheme 90).



Scheme 90: proposed retrosynthesis of desoxycodeine-D *via* desymmetrisation

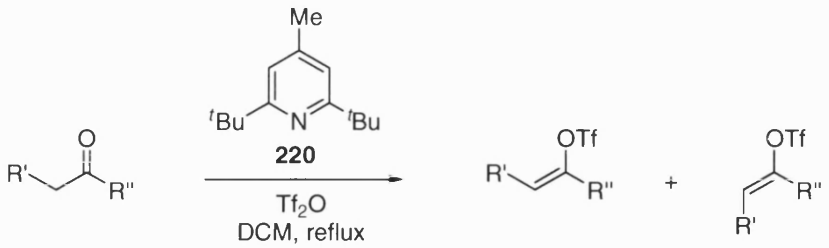
This synthesis would involve desymmetrisation of *bis*-alkenyltriflate **218** to form an ester product with the required stereodefined quaternary carbon centre, which may occur *via* a combination of steric effects and participation of the amine as a directing group. Following this, a palladium-catalysed *O*-arylation could yield a tricyclic intermediate which could be further advanced using standard chemistry. This proposed synthesis provides a highly convergent and concise route to the codeine core structure, and could enable preparation of analogous target molecules.

Chapter 3: Results and Discussion

3.1 - Preparation of a simple *bis*-alkenyltriflate

The presence of triflate groups is common in organic chemistry, and although they have been used regularly in the past as leaving groups, their greatest synthetic utility arises from their ability to undergo oxidative insertion with transition metals. This opens up an enormous range of potential transformations that can then be applied, many of which are palladium-catalysed processes and employ both aryl- and alkenyltriflates. Major examples include Heck, Suzuki, Negishi and Stille couplings among others.[311] The fact that triflates can be readily synthesised from alcohols and ketones makes them particularly attractive to the synthetic chemist, as the range of commercially available or easily synthesisable compounds is vast, much more so than the aryl/vinyl halides that are also used in palladium chemistry.[9]

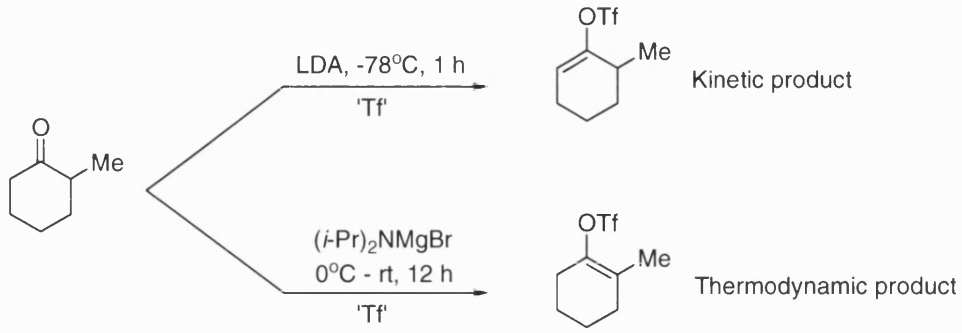
Aryl triflates can be simply formed from the reaction of a phenol with pyridine and triflic anhydride, and the reaction is very general in terms of its application. Synthesis of alkenyltriflates from ketones can be performed by a number of methods, one of which utilises the non-nucleophilic hindered base 2,6-di-*tert*-butyl-4-methylpyridine **220** and triflic anhydride (Scheme 91), however this method usually gives rise to mixtures of both *E*- and *Z*-alkenyltriflates in acyclic compounds, with the more thermodynamically stable *E*-vinyltriflate predominating.



Scheme 91: The synthesis of an alkenyltriflate with 2,6-di-*tert*-butyl-4-methylpyridine

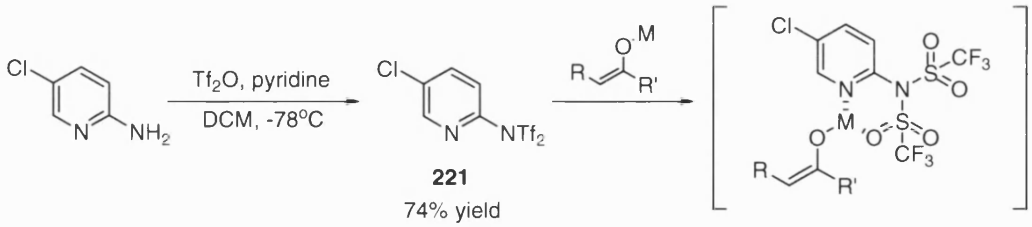
Geometric and regio-control over the nature of the alkenyltriflate can be achieved by α-deprotonation of a ketone with a strong base (e.g. LDA, NaHMDS) to form a stereo/regio-defined enolate, followed by trapping with an electrophilic triflate source (Scheme 92).[312] Both the thermodynamic and kinetic

alkenyltriflates can be produced by this method, as with standard enolate chemistry.



Scheme 92: Regio-control of alkenyltriflate formation

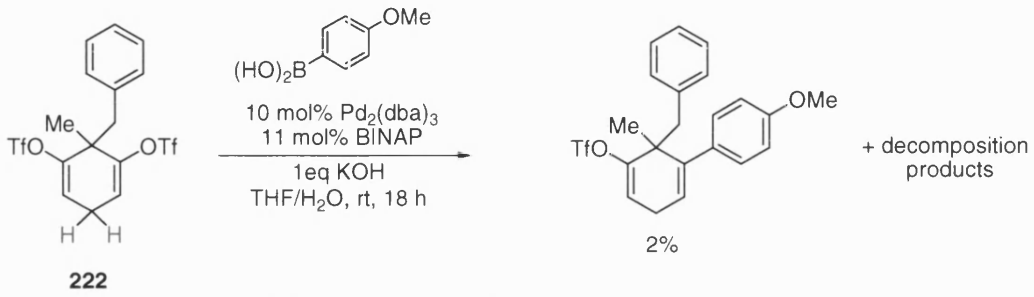
One such electrophilic triflate source is *N*-phenyltriflimide, which is common in the preparation of alkenyltriflates.[313] A more reactive derivative was introduced by Comins *et al.* who synthesised *N*-(5-chloro-2-pyridyl)triflimide **221** from reaction of the corresponding commercially available aminopyridine by triflation with triflic anhydride (Scheme 93).[314] The electron poor pyridine ring makes the triflate groups even more electrophilic, and hence more reactive towards enolates. It has also been postulated that the pyridyl nitrogen can chelate the metallo-enolate, which unmasks its anionic character, and also increases the reagents electrophilicity.



Scheme 93: enhanced reactivity of *N*-(5-chloro-2-pyridyl)triflimide

To continue our studies in this area, we desired to construct a cyclic *bis*-alkenyltriflate with a quaternary carbon centre suitable for desymmetrisation studies. Previous work in the group had used the pyridyl triflimide **221** to generate *bis*-alkenyltriflate **214** for use in Suzuki couplings.[315] These couplings proved unsuccessful, which was thought to be due to the acidity of the doubly-vinylic protons (highlighted, Scheme 94). The Suzuki chemistry performed on this *bis*-alkenyltriflate required strong bases such as potassium hydroxide, or

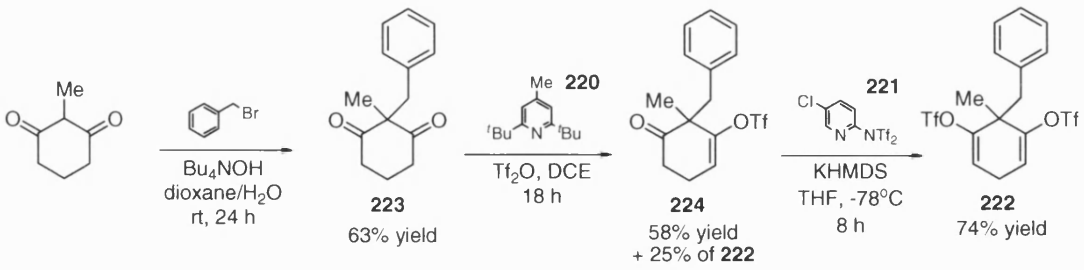
cesium fluoride to achieve the desired reactivity with similar substrates, however these bases proved to be problematic when used in conjunction with *bis*-alkenyltriflate **222** (Scheme 94). It was thought that the generally milder conditions used in palladium-catalysed carbonylations might be more tolerant of this substrate.



222

Scheme 94: Unsuccessful Suzuki chemistry of *bis*-alkenyltriflate **222**

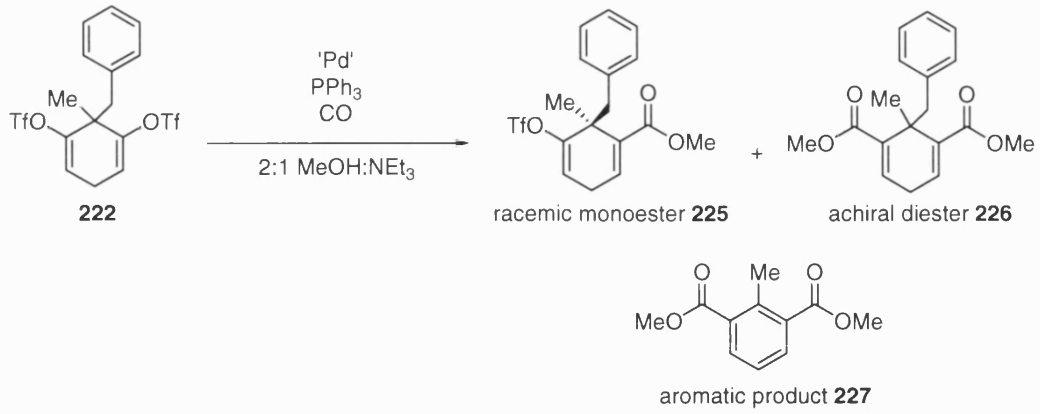
Synthesis of the *bis*-alkenyltriflate began with alkylation of 2-methyl-1,3-cyclohexanedione by benzyl bromide, to provide diketone **223** containing the key quaternary carbon centre that would later be stereodefined *via* desymmetrisation. The reaction proceeded well using the method published by Shibasaki *et al.* to give the product in 63% yield.[316] It was then attempted to convert this directly to the *bis*-alkenyltriflate in one step using 2.2 equivalents of KHMDS and 2.2 equivalents of pyridyl triflimide **221**, however the product was obtained in only 18% yield, and there were problems in purification due to the large quantities of remaining pyridyl triflimide **221** left in the crude mixture. To avoid this, the *bis*-alkenyltriflate was synthesised over two steps, firstly by conversion to mono-alkenyltriflate **224** with 2,6-di-*tert*-butyl-4-methylpyridine **220** and triflic anhydride to give the desired product in 58% yield, as well as *bis*-alkenyltriflate **222** in 25% yield. Mono-alkenyltriflate **224** was then reacted with pyridyl triflimide **221** and KHMDS in the same manner as before, this time giving the desired *bis*-alkenyltriflate in a more favourable 74% yield (Scheme 95). This two-step process proved to be significantly higher yielding overall than the attempted one-step method.



Scheme 95: The synthesis of *bis*-alkenyltriflate **222**

3.2 - Desymmetrising palladium-catalysed methoxycarbonylation of *bis*-alkenyltriflate 222

After *bis*-alkenyltriflate **222** had been produced in significant quantity (the procedure was reproducible on up to 3 g scale), it was tested in achiral reactions to determine the feasibility of the process. From the carbonylation work performed on aryl tricarbonylchromium complexes by Schmalz *et al.*[290] it was decided to begin with a similar basic system, comprising of a palladium (II) or palladium (0) precatalyst, triphenylphosphine as a ligand and a 2:1 mixture of anhydrous MeOH:NEt_3 as a solvent and base (Table 6). A balloon of carbon monoxide was used to simulate a pressure of 1 atm. It was imperative that high pressures of gas were not required for this reaction, to make the methodology more amenable to the user.



222 racemic monoester **225** achiral diester **226**

aromatic product **227**

Entry	Pd source	Time (h)	Mono-ester 225 yield (%)	Diester 226 yield (%)	Aromatised 227 yield (%)
1	$PdCl_2$	1	31	36	-
2	$PdCl_2$	2	41	19	13
3	$PdCl_2$	4	15	31	38
4	$PdCl_2$	6	-	-	86
5[a]	$PdCl_2$	2	34	6	-
6	$Pd(OAc)_2$	2	-	97	-
7	$Pd_2(dba)_3$	2	-	95	-

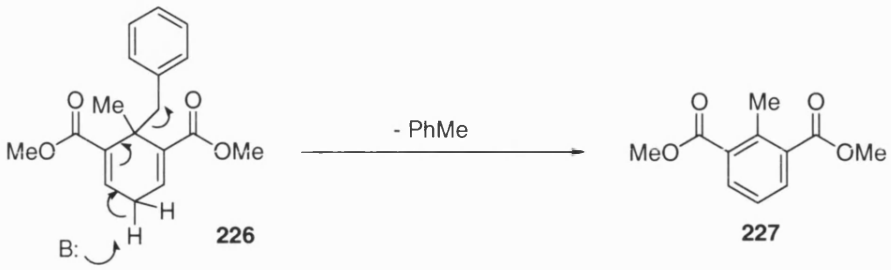
Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), Pd (10 mol% w.r.t Pd), PPh_3 (5.5 mg, 20 mol%), CO (1 atm balloon), 2:1 MeOH:NEt_3 (1 mL), 60°C

[a] Reaction performed with 1 atm CO volume of Schlenk tube – no balloon

Table 6: First achiral desymmetrisations of *bis*-alkenyltriflate **222**

The reactions were encouragingly successful, producing the racemic, desymmetrised mono-ester **225**. Also observed was the expected achiral diester **226**, produced by double reaction of the *bis*-alkenyltriflate. Unsurprisingly, the longer the reaction was left, the more diester was formed, with the best result being a 41% yield of mono-ester **225** after just one hour (Table 6, Entry 2). When the carbon monoxide balloon was shut off from the reaction, leaving only the volume of the Schlenk tube of gas available for consumption, the system performed considerably more slowly, giving an overall conversion of just 40% (Table 6, Entry 5). When the reactions were left for too long, an unexpected compound, dimethyl-2-methylisophthalate **227**, was seen

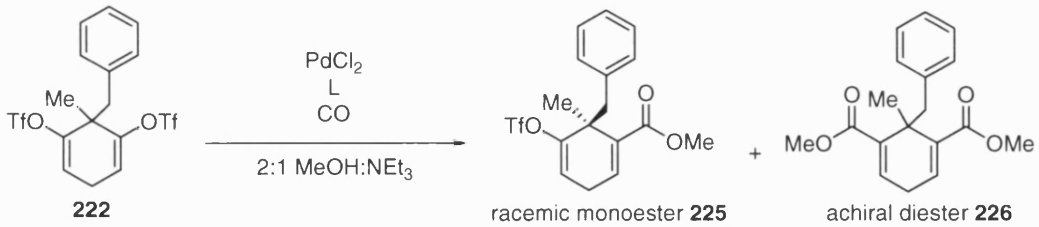
in high yield. This is presumably formed from deprotonation of one of the aforementioned doubly-vinylic protons, and subsequent expulsion of the benzyl moiety of the diester **226**, driven by aromatisation (Scheme 96).



Scheme 96: formation of the aromatic diester **227**.

Interestingly, this product was only seen when palladium (II) chloride was used as the precatalyst, intimating that it could be a specific palladium species formed only by palladium (II) chloride that gives rise to this product. This theory was however disproven when isolated diester was stirred for six hours in a 2:1 methanol:triethylamine mixture at 60°C, and produced a 60% yield of the aromatised material. Both palladium (II) acetate and $Pd_2(dba)_3$ were considerably more active catalysts in this reaction (Table 6, Entries 6 & 7), giving quantitative conversion to the undesired diester in just two hours, however conversion to the aromatised **227** did not occur with either. Saturation of the solvent with carbon monoxide by slowly bubbling gas through the reaction mixture for 10 minutes proved to make little difference to the results obtained above, and was therefore deemed to be an unnecessary hazard for this work.

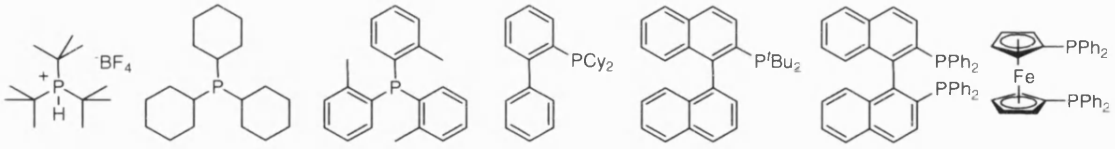
Although the results from this system were not outstanding, they were promising, and proved that *bis*-alkenyltriflate **222** was able to react well under general palladium-catalysed carbonylation conditions, in contrast to its reactivity problems seen in the Suzuki chemistry. A further screen of achiral ligands was performed to gauge the efficiency of various phosphines of differing electronic nature in the reaction (Table 7).



222 racemic monoester **225** achiral diester **226**

Entry	Ligand	Mono-ester 225 yield (%)	Diester 226 yield (%)
1	20 mol% **228**	34	46
2	20 mol% **229**	31	7
3	20 mol% **230**	35	12
4	20 mol% **231**	-	84
5	20 mol% (*rac*)-**232**	trace	-
6	10 mol% (*rac*)-**233**	trace	-
7	10 mol% **234**	trace	-

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $PdCl_2$ (1.8 mg, 10 mol%), CO (1 atm balloon), 2:1 MeOH:NEt_3 (1 mL), 60°C, 2 h

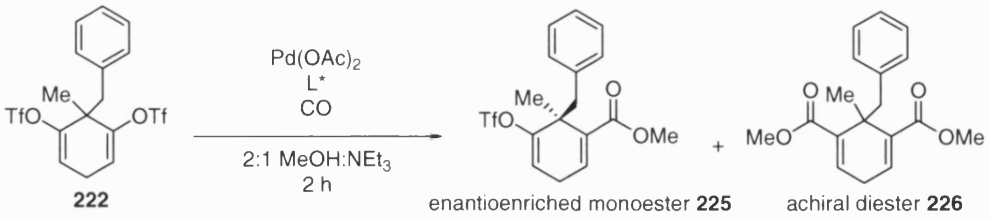


228 **229** **230** **231** **232** **233** **234**

Table 7: Achiral ligand screen for desymmetrisation of *bis*-alkenyltriflate **222**

Electron-rich mono-dentate phosphines **228**, **229** and **230** all behaved in a similar manner to triphenylphosphine, providing a mixture of both mono- and diester with slight variation in ratio. Biaryl dicyclohexylphosphine **231** resulted in near quantitative conversion to the undesired diester **226** in the same time-frame, whilst binaphthyl di-*tert*-butylphosphine **232** gave little reaction, potentially due to the repulsions involved in coordinating the large ligand and sterically encumbered *bis*-alkenyltriflate to the palladium centre. Disappointingly, the bidentate ligands (*rac*)-BINAP **233** and DPPF **234** showed little reactivity, and led to palladium black deposits within an hour. Many chiral derivatives of these ligands exist and they have been shown to provide excellent enantioselectivities in a range of palladium-catalysed processes.

With the knowledge that the carbonylation reaction worked with a variety of ligands, it was decided to explore the desymmetrisation in an enantioselective process. Some of the common chiral ligands were screened, as well as (*R*)-MeO-MOP **217** which had worked well in the corresponding Suzuki reactions of 5-membered ring *bis*-alkenyltriflate **214**[310] and a chiral amino ferrocene analogue of the PPF-pyrrolidine **235** that had resulted in high enantioselectivities in Schmalz's desymmetrisation studies (Table 8).[290]



Entry	Ligand	Temp. (°C)	Mono-ester 225 yield (%)	Diester 226 yield (%)	Mono-ester *ee* (%)
1	**79**	60	21	-	21
2	**217**	60	41	13	65
3	**217**	45	34	9	74
4	**235**	45	40	18	2
5	**236**	45	25	7	17
6	**132**	45	13	-	11
7	**80**	45	22	17	16
8	**237**	45	4	88	3
9	**28**	45	21	66	26

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (10 mol%), CO (1 atm balloon), 2:1 MeOH:NEt_3 (1 mL), 2 h

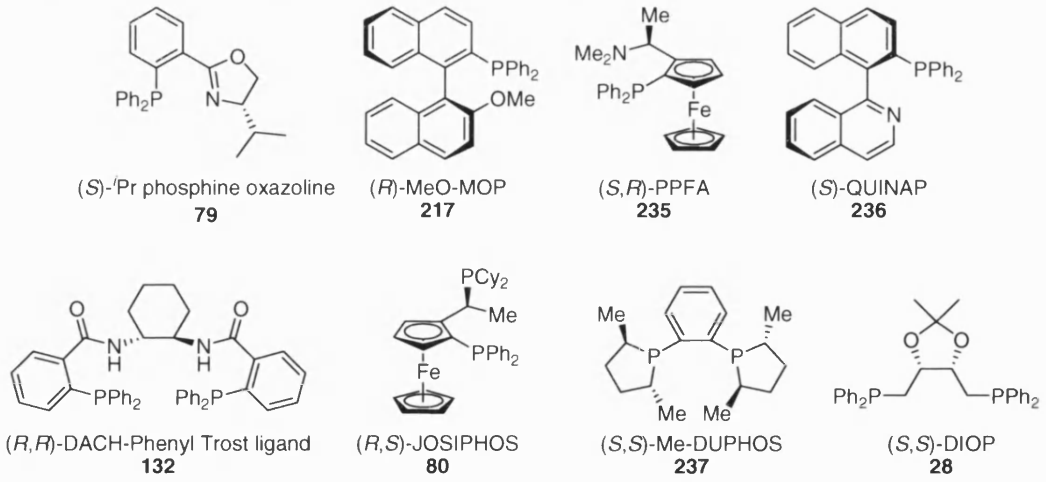


Table 8: First enantioselective desymmetrisations of *bis*-alkenyltriflate **222**

All reactions were performed with both palladium (II) chloride and palladium (II) acetate, the latter providing slightly higher yields and enantioselectivities, potentially due to its greater solubility in the reaction mixture. For this reason, the palladium (II) acetate results are displayed above. The phosphine oxazoline

79 [317] gave both poor yield and enantioselectivity, however a 21% *ee* meant that this substrate could undergo an enantioselective desymmetrisation, and proof of concept was established. A much improved 65% *ee* was obtained by use of the bidentate, hemi-labile (*R*)-MeO-MOP **217**. This intriguing ligand, first synthesised by Hayashi *et al.*,[318] has been shown in enantioselective allylic alkylation studies to bind to cationic palladium centres *via* both the diphenyl phosphine and in an η^2- manner through the *C1'-C2' C=C* bond of the binaphthyl backbone (Figure 1).[319]

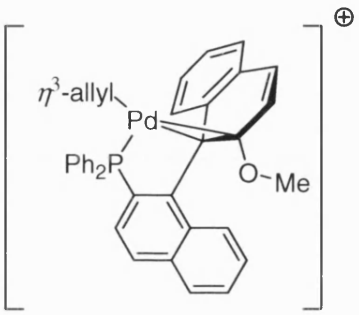


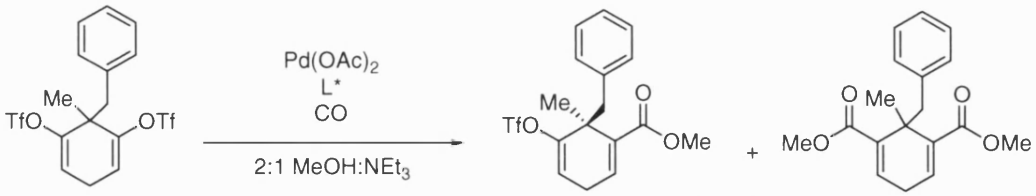
Figure 1: the η^2- binding of the chiral ligand MOP

Reduction of the reaction temperature from 60 to 45°C increased the enantioselectivity to give mono-ester **225** in 74% *ee*. After this observation, all reactions with the other chiral ligands were also performed at 45°C in the hope that the same effect would be seen. Reactions run at temperatures lower than 45°C proved sluggish, a topic that will be discussed in more detail later in this chapter. Diphenylphosphino ferrocenes that also carried stereodefined amines (both primary and tertiary) had resulted in high enantioselectivities when applied to the desymmetrisation of aryl tricarbonylchromium complexes by Schmalz *et al.*,[290] however the asymmetric control of **235** was diminished in our system. Although the yields were among the best seen for this reaction, it was essentially a racemic process giving only 2% *ee*. Two chiral ligands well known to be effective in a range of palladium-catalysed reactions, (*S*)-QUINAP **236** [320] and the phenyl Trost ligand **132** [321, 322] performed poorly in comparison, giving both low conversions and enantioselectivities (17 and 11% *ee* respectively). The incompatibility of (*S*)-QUINAP in this reaction was unexpected, due to its apparent similarity in structure and coordination mode to MOP. The ferrocenyl (*R,S*)-JOSIPHOS **80** [323] also gave low yield and selectivity, whereas both (*S,S*)-Me-DUPHOS **237** [324] and (*S,S*)-DIOP **28** [325] showed considerable overreaction

to form large quantities of the diester. The small amounts of chiral mono-ester yielded by this reaction were also low in enantiomeric purity.

From this data, it was chosen to perform further reactions with (*R*)-MeO-MOP in order to optimise the process. With a total conversion of only around 45% (of both mono- and diester) it was expected that if the reaction time was increased then more of the desired mono-ester could be obtained, and there was the possibility of observing a kinetic resolution of the type explained in Chapter 2.1. Longer reaction times of 3, 4 and 6 hours did not result in higher conversion of starting material. Very similar yields of mono-ester (~40%) and diester (~10%) were produced in all reactions, as well as considerable palladium black deposits in the reaction vessel. These results point to an unsuitable ligand-catalyst combination where the palladium could not be supported for a long enough period of time to effect the full transformation. This is potentially due to the coordination mode of the MOP ligand. When triphenylphosphine was used as a ligand, it was likely that two molecules of ligand coordinated to the palladium throughout the catalytic cycle. The η^2-coordination mode of MOP described above may not be sufficiently electron-donating to sustain the active catalyst species for long, before the catalyst is converted to palladium black and dies. The use of potassium bromide and lithium chloride as additives resulted in decreased yields of the ester products, despite their common use in palladium chemistry to both stabilise the catalyst and improve reactivity by increase in the cationic character of the catalyst complex.[326]

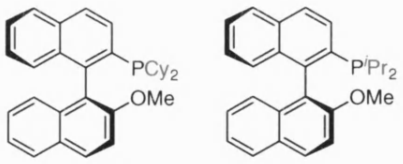
Electron-donation properties of the ligand were thought to be the key to increased catalyst reactivity. From the screen of achiral catalysts it was thought that more electron-rich alkyl phosphines may be better ligands for this system, as demonstrated by the near quantitative yield of diester **226** provided by the biaryl dicyclohexylphosphine **231** (Table 8, Entry 4). The enantioselectivities produced by (*R*)-MeO-MOP were very promising, so it was decided that variation of the diphenylphosphine of this ligand to a complimentary dialkylphosphine may result in prolonged catalyst life, and hence higher yields. After synthesis of both the dicyclohexylphosphine and di-*iso*-propylphosphine analogues of MOP, as published by Hayashi *et al.*,[318] they were introduced into the same reaction, the results of which are displayed below (Table 9).



enantioenriched monoester **225** achiral diester **226**

Entry	Ligand	Time (h)	Temp (°C)	Mono-ester 225 yield (%)	Diester 226 yield (%)	Mono-ester *ee* (%)
1	**238**	0.5	45	31	15	-
2	**238**	1	45	38	45	89
3	**238**	2	45	40	55	95
4	**238**	4	45	34	57	95
5	**238**	17	rt	33	8	78
6	**238**	1	35	25	14	-
7	**238**	1	40	32	27	-
8	**239**	2	45	27	57	96

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (10 mol%), CO (1 atm balloon), 2:1 MeOH:NEt_3 (1 mL)



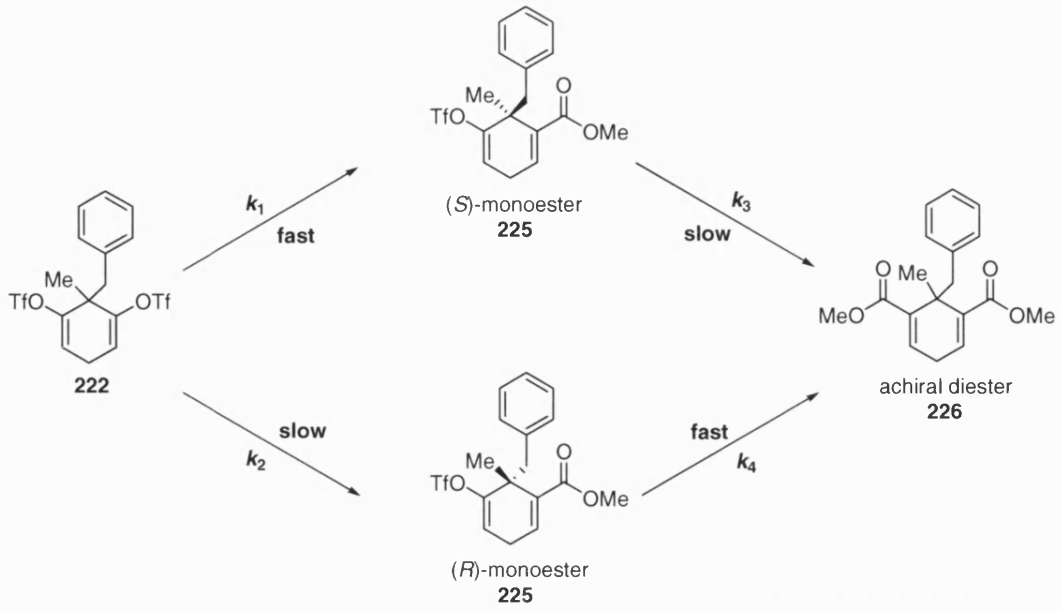
(*R*)-PCy_2MOP **238** (*R*)-P^iPr_2MOP **239**

Table 9: Alkylphosphine analogues in desymmetrisations of *bis*-alkenyltriflate **222**

The dicyclohexylphosphine **238** produced an instant increase in catalyst turnover, giving a near quantitative conversion of starting material to a mixture of mono- and diester in just one hour. The desymmetrised mono-ester **225** was produced in 38% yield with an 89% *ee*. Running the reaction for two hours now saw the yield rise to 40%, and also a gain in enantioselectivity to an excellent 95% *ee*. Both of these reactions also gave high yields of the undesired achiral diester **226**, so in changing the phosphine from diaryl to dialkyl we had gone from poor reactivity to over-reaction. Decreasing the reaction temperature to room temperature in an attempt to slow the rate of the reaction did so, but to too great an extent. The results were poor in yield giving an overall conversion

of approximately 40%, and an erosion of *ee* was seen. After seventeen hours palladium black was again seen in the reaction vessel, and leaving the reaction for longer time periods did not increase the yields. The drop in *ee* was attributed to the low diester yield, and hence limited expected kinetic resolution, whereby the undesired minor enantiomer of mono-ester **225** reacts preferentially in the second coupling to make diester **226**. As the minor enantiomer is consumed, the enantiopurity of the remaining mono-ester increases, explaining the much higher enantioselectivities seen when the reaction is heated at 45°C and the diester yield is considerably greater (Scheme 97). In the first carbonylation reaction $k_1 > k_2$, leading to greater amounts of the (*S*)-mono-ester. However in the second carbonylation reaction, $k_4 > k_3$, so the minor (*R*)-enantiomer is consumed more quickly in making the achiral diester.

Running the reaction at 35 and 40°C also led to decreased yields implying that either the active catalyst is formed at 45°C, or that this temperature is required to accelerate the oxidative addition of the alkenyltriflate to the palladium. When the reaction was heated for 5 minutes at 45°C, followed by a further two hours at room temperature a mono-ester yield of 35% with 80% *ee*, and a diester yield of 11% were observed. This result indicates that it is indeed the oxidative addition that requires the higher temperature, as residual heat in the reaction vessel could lead to this similar yield in a much shorter time to that seen for a reaction performed at room temperature for seventeen hours. When the heat-source is removed the catalytic activity is not maintained and the reaction slows down.

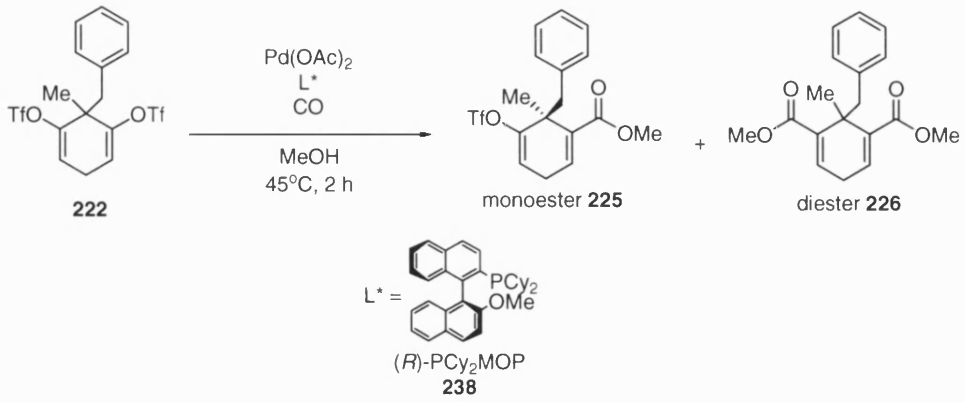


Scheme 97: representative mechanism of kinetic resolution in the carbonylation system (stereochemical assignments are not determined)

The corresponding di-*iso*-propylphosphine ligand **239** gave similar results, however this system resulted in even higher yields of diester, and just 27% of the mono-ester, albeit in 96% *ee*. For this reason it was decided to attempt to further optimise the reaction using PCy_2MOP **238**, as it had given the best compromise between yield and enantioselectivity.

Dilution can often play an important role in reaction inhibition, generally in intramolecular processes, however its effects have been seen in other circumstances. For this reason, the reaction was performed with a dilution factor of ten with the aim of decreasing the amount of diester formed, to give a greater mono-ester yield. After three hours this gave a 30% yield of mono-ester **225** and 18% yield of diester **226**, with approximately 50% of the *bis*-alkenyltriflate starting material remaining, indicating that this was not a viable process to improve the ratio of the two products in a favourable manner.

Up to this point, variation of reaction conditions had only involved the ligand catalyst combination, and temperature and time. For this reason a range of both organic and inorganic bases were screened in the hope that their differing properties may affect the reaction to increase mono-ester yield (Table 10).



Entry	Base	Mono-ester 225 yield (%)	Diester 226 yield (%)
1	**N^nBu_3**	32	38
2	**DIPEA**	36	24
3	**Cy_2NMe**	21	-
4	**$^iPr_2NH$**	34	18
5	**TMG**	Hydrolysed mono-ester	-
6	**K_3PO_4**	Hydrolysed mono-ester	-
7	**KF**	32	19
8	**Cs_2CO_3**	Hydrolysed mono-ester	-

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), base (0.416 mmol), MeOH (1 mL), 45°C, 2 h

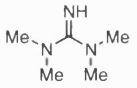
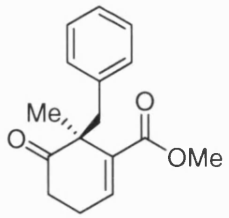
TMG = 1,1,3,3-tetramethylguanidine 

Table 10: Base screen in desymmetrisation of *bis*-alkenyltriflate **222**

None of the bases tested proved to be any better in increasing mono-ester:diester ratio, and most gave overall decreased conversions in comparison with triethylamine. Although 0.33 mL (44 eq.) of triethylamine had been used in previous reactions and only four equivalents of each base were employed the above, triethylamine had proven that it worked equally well when only four equivalents were added as to when it was in large excess. Three of the bases tested produced a previously unseen product **240** (Table 10, Entries 5, 6 and 8) which upon characterisation was assigned to be a result of a mono-ester of which the remaining alkenyltriflate had been hydrolysed to the ketone (Figure 2).



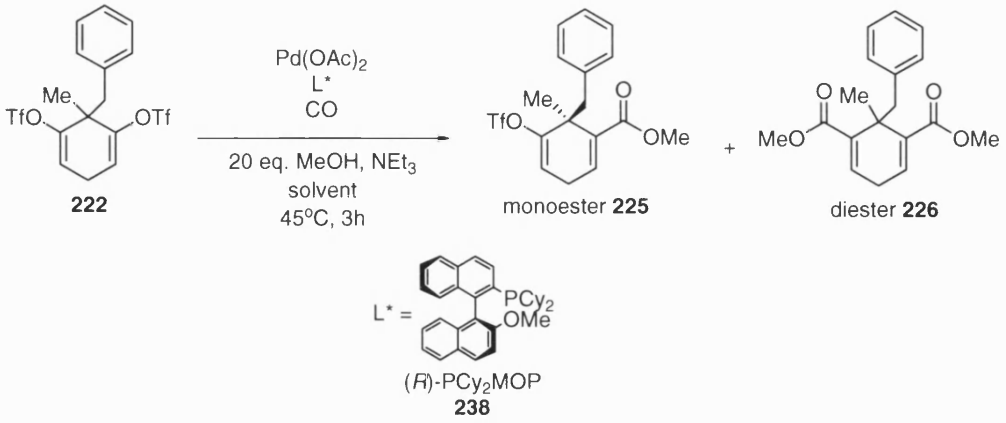
ketoester **240**

Figure 2: the coupled/hydrolysed product afforded by tetramethylguanidine, potassium phosphate and cesium carbonate.

This was produced in up to 55% yield, however when isolated from the reaction that used cesium carbonate as base the ketoester **240** was shown to be racemic. This result will be discussed in more detail later on (Chapter 3.3). Formation of this ketone may well have been due to the presence of small amounts of water in the corresponding bases, as both cesium carbonate and potassium phosphate are known to require rigorous drying to obtain sufficient reagent quality for some reactions. It was not thought to be a palladium-catalysed process as a sample of mono-ester **225** left stirring overnight in methanol with two equivalents of potassium phosphate also gave rise to ketoester **240**.

Currently in the reaction mixture there was no limiting reagent other than the *bis*-alkenyltriflate. Both carbon monoxide and methanol (the two coupling partners) were present in large excess. Limitation of the number of moles of carbon monoxide delivered into the system could potentially be over come by the use of gas-liberating reagents, such as nickel tetracarbonyl and iron pentacarbonyl which produce free carbon monoxide upon heating and have been shown to be useful for such processes.[64, 73, 327-329] This method would however introduce a new complex factor into the reaction, and could also make purification more complex. The reactions carried out under a carbon monoxide atmosphere were exceptionally clean, producing a mixture of starting material, and esters which were easily separated after concentration of reaction mixture under reduced pressure and simple flash chromatography. For this reason, the complexity of adding such a gas-liberating reagent was not deemed to be a useful process. An alternative solution was to limit the amount of the nucleophile (methanol) so that complete conversion to the diester was either a slower (e.g. 10 eq. methanol) or impossible process (e.g. 1 eq. methanol). For this to be done a new solvent in which to perform the reactions was required.

This solvent needed to be non-nucleophilic in order that it should not replace methanol in direct participation in the carbonylation reaction (Table 11).



Entry	Solvent	Mono-ester 225 yield (%)	Diester 226 yield (%)	Mono-ester *ee* (%)
1	Dioxane	40	19	83
2	THF	34	15	-
3	**MeCN**	**36**	**43**	**93**
4	Acetone	17	7	-
5	DCE	12	2	-
6	Toluene	11	2	-
7	DMF	10	-	-
8	DCM	27	31	88
9	TCE	trace	-	-

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (58 µL, 0.416 mmol), MeOH (42 µL, 1.04 mmol), solvent (1 mL), 45°C, 3 h

Table 11: Effects of non-nucleophilic solvent on the reaction

Most solvents were unsuitable for the reaction, with very little of either mono- or diester produced. DMF is one of the more common solvents used in palladium chemistry, however in this study it was ineffective. Improved results were seen when dioxane was used as solvent, yielding 40% of the mono-ester **225** with an 83% *ee*, however acetonitrile bettered this with 36% yield (~80% overall conversion) and an excellent 93% *ee* (Table 11, Entry 3), comparable to the

reactions performed in neat methanol. This is unusual as acetonitrile is known to coordination to palladium catalysts quite effectively, and it was thought that this may obstruct ligand coordination and result in a diminished enantioselectivity. Both the yields and enantioselectivities attained with this solvent were promising enough to prompt further investigation.

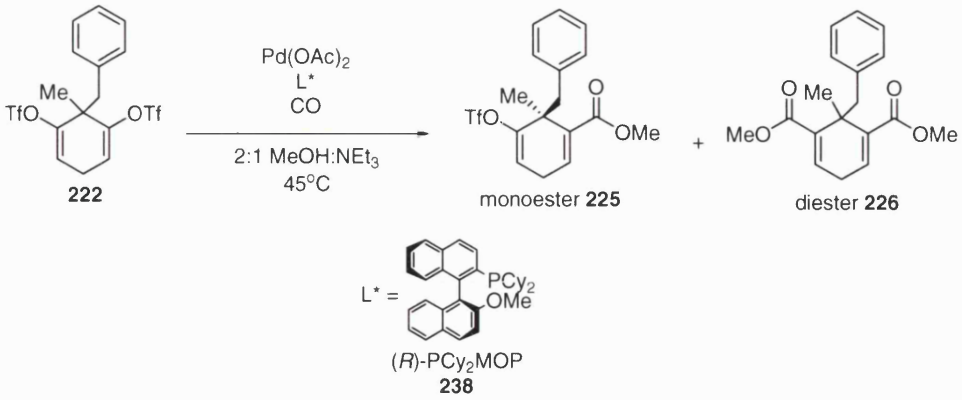
A reaction performed in acetonitrile, using 1.5 equivalents of methanol could only give a maximum theoretical yield of 50% mono-ester, and 50% diester. After four hours the reaction yielded 26% mono-ester, and 28% diester, a disappointing result which could not be further improved by longer reaction times. It was also possible that with such a small amount of methanol in the reaction mixture (6.3 μL) that the reaction temperature (45°C) was resulting in a portion of this existing as a gas in the Schlenk tube. When this was replaced with 1.5 equivalents of the solid sodium methoxide the reaction failed. Petit *et al.* have described a method for palladium-catalysed alkoxycarbonylation that requires no gaseous carbon monoxide.[60] Alternatively, this system generates carbon monoxide from decarbonylation of a formate ester by its corresponding alkoxide base, which is also able to act as a nucleophile in the reaction. Application of this to our desymmetrisation system using ethanol/sodium ethoxide with the aim of introducing a known molar amount of carbon monoxide failed, with decomposition and hydrolysis products isolated after 4 hours.

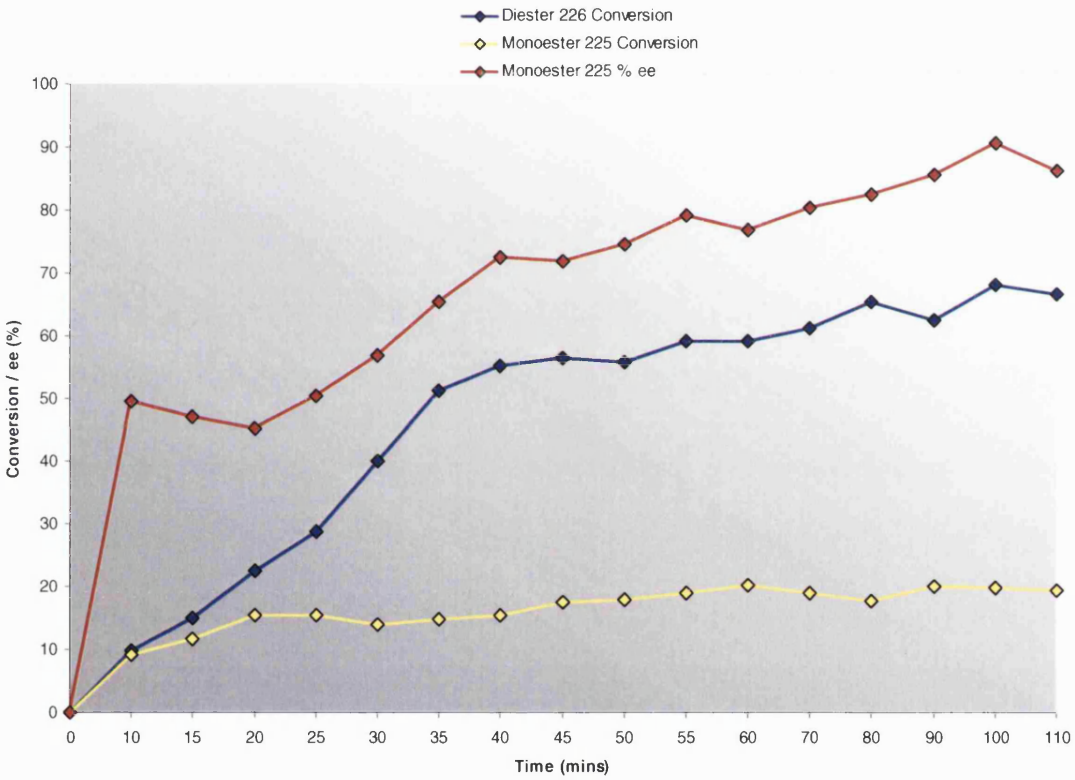
In conclusion, the desymmetrisation of *bis*-alkenyltriflate **222** had been successfully achieved in reasonable yield with excellent enantioselectivities. Of all ligands examined, those hemi-labile bidentate in nature and based around a binaphthyl backbone proved most effective, in particular dicyclohexylphosphine **238**. The reaction could be performed in a number of non-nucleophilic solvents (acetonitrile being the optimum) with limited equivalents of methanol added as a nucleophile, with little change in yield or selectivity.

3.3 - Kinetic studies – modeling the reaction

From most desymmetrisation reactions performed so far, there was a considerable amount of the unwanted achiral diester **226** formed. Although this was thought to be contributing to the high enantioselectivities through kinetic resolution of the mono-ester, its production was also removing the mono-ester from the reaction nearly as quickly as it was being produced i.e. rate of diester formation ≥ rate of mono-ester formation. To learn more about the mechanistic aspects of this complex, two-stage reaction it was decided to isolate each step and investigate the enantioselectivities and rates of each one.

The first step was to study the overall reaction and determine how mono-ester formation, diester formation and the enantioselectivity of the total process changed with time (Figure 3). A reaction where aliquots were taken from the reaction at regular time intervals, quenched on silica and then analysed was performed to monitor these steps.





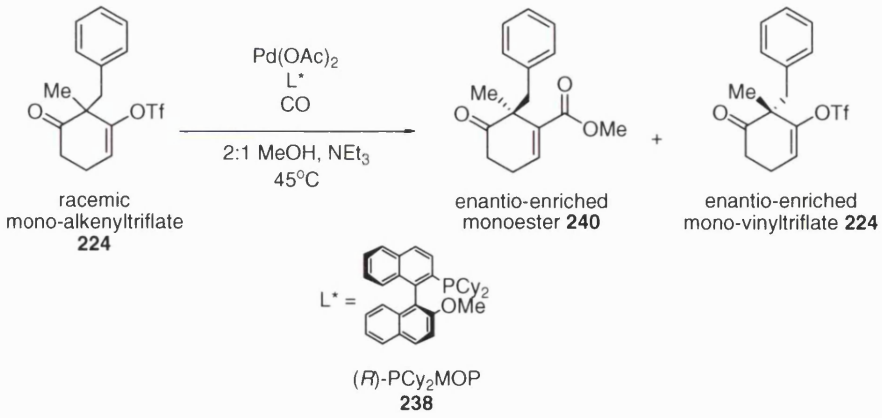
Reaction conditions: *bis*-alkenyltriflate **222** (100 mg, 0.208 mmol), $Pd(OAc)_2$ (4.6 mg, 10 mol%), L* (10.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (1 mL), MeOH (2 mL), 45°C

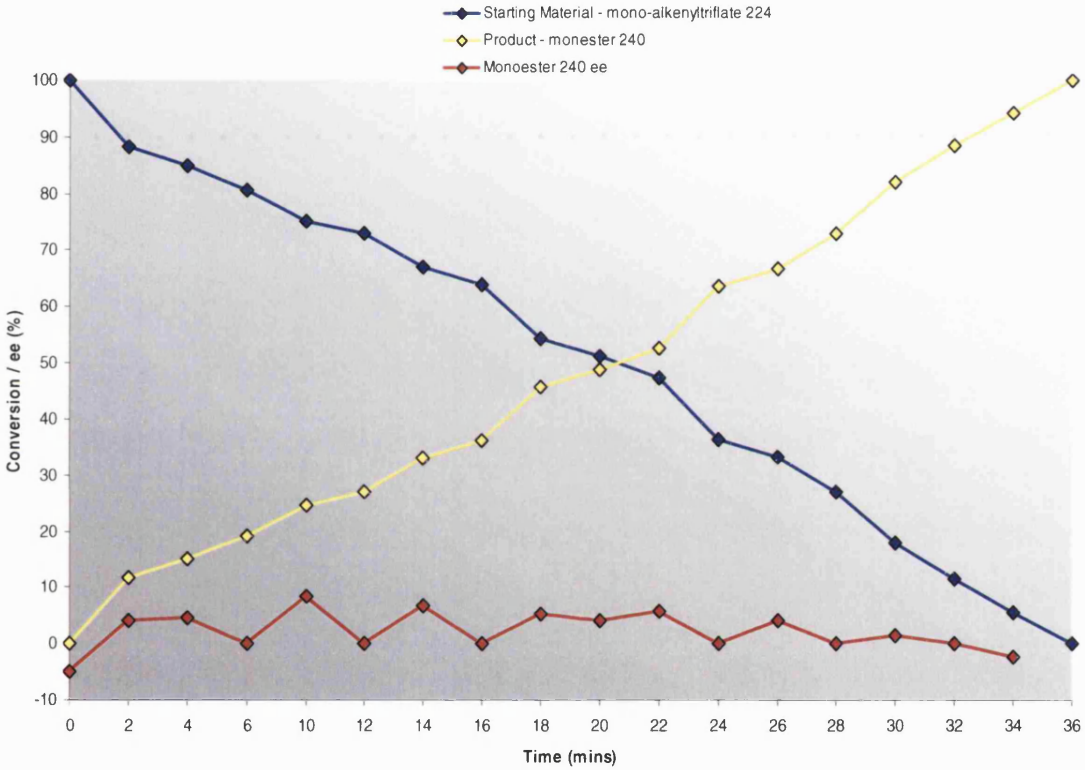
Figure 3: a kinetic profile of the reaction

The results from this reaction were surprising, as after just ten minutes there was an equal amount of mono-ester **225** and diester **226** in the reaction mixture. This was contrary to previous reactions where significant diester formation did not happen for a much greater time period and mono-ester yield was approximately 40%. In these studies the mono-ester yield could never be

increased above 20%, despite repeat reactions being performed. This is possibly due to the sampling process which involves insertion of a needle into the carbon monoxide reaction environment through a rubber septum. Every time a needle was inserted it may have been introducing oxygen or water into the reaction mixture, despite attempts to eliminate this. Even so, it is clear from this graph that diester formation is a significantly faster process than mono-ester formation, even though mono-ester **225** must first be formed before it can react further to form the diester. As expected, the enantioselectivity of the reaction steadily increases with time, indicating that a kinetic resolution is indeed taking place. As diester conversion increases so does the enantiopurity of the mono-ester (up to 90% *ee*), whilst it's conversion stays approximately constant throughout this reaction. After just ten minutes mono-ester **225** was found to have a 50% *ee* with the reaction mixture containing a 1:1 mono-ester:diester ratio. This enantioselectivity could be due to either the formation of mono-ester **225** being an enantioselective step, or that of diester **226** formation being the enantioselective step. Investigation of these separate processes was required to determine which of these was responsible for the enantioselectivities achieved in the reaction.

Kinetic resolutions have been shown to be useful tools to take racemic starting materials, and selectively react one enantiomer to produce an enantio-enriched derivative, whilst also increasing the enantio-purity of the remaining starting material.[330] The drawback of this process is that if high *ee*'s of both product and starting material are required then the maximum yield for the reaction can only reach 50% (unless the reaction is a dynamic-kinetic resolution[331]). Formation of mono-ester **225** from the achiral *bis*-alkenyltriflate **222** could not be effectively studied in this reaction due to the problems of diester production, therefore it was decided that the process of the first coupling could be modelled with a kinetic resolution of racemic mono-alkenyltriflate **224** in a palladium-catalysed methoxycarbonylation (Figure 4).





Reaction conditions: mono-alkenyltriflate **224** (72 mg, 0.208 mmol), $Pd(OAc)_2$ (4.6 mg, 10 mol%), L* (10.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (1 mL), MeOH (2 mL), 45°C

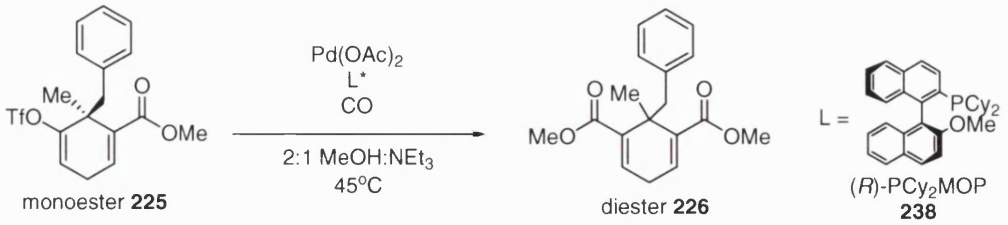
Figure 4: kinetic resolution of mono-alkenyltriflate **224**

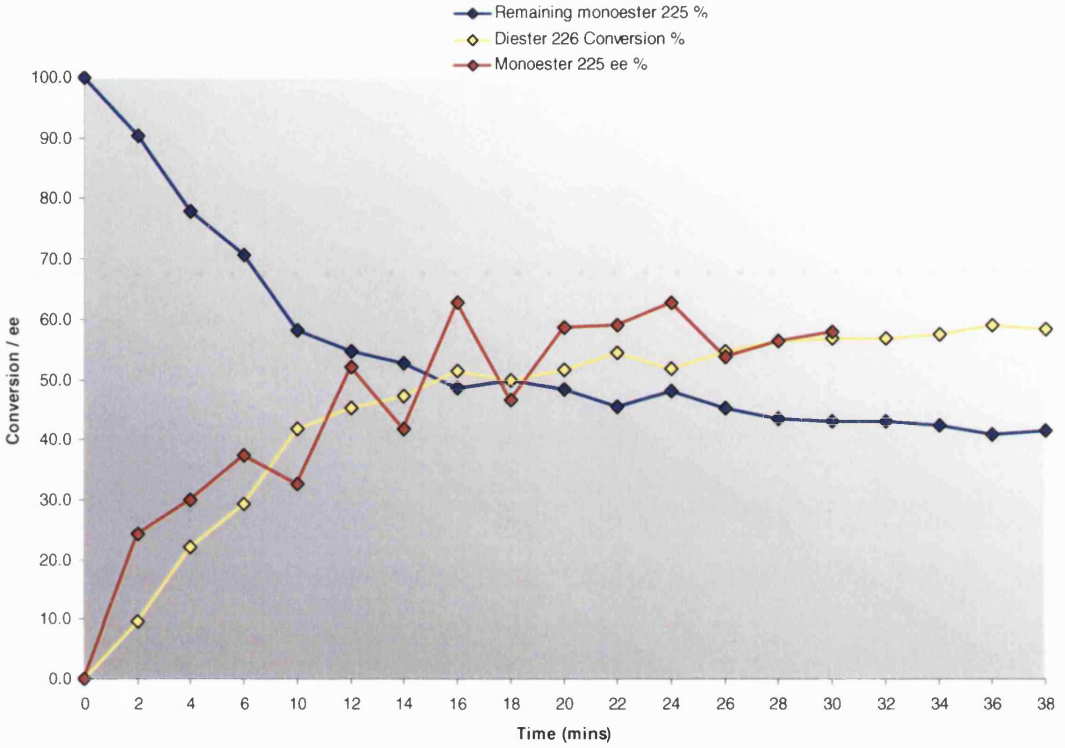
As can be seen from the graph, carbonylation of the mono-alkenyltriflate proceeded smoothly, giving complete conversion to the ester in less than forty minutes with the reaction followed by NMR. The reaction suffered poor enantio-control as the chiral ligand failed to impart any selectivity on the substrate and produced essentially racemic ester, also leaving the remaining starting material as a racemic compound (not shown) at all points throughout the forty minute

time-course. This was especially surprising, given the excellent enantioselectivities observed in the desymmetrisation of *bis*-alkenyltriflate **222**. The only logical reason for this obscure discovery is that the dicyclohexylphosphine ligand **238** is not suitable for use with this mono-triflate substrate, which is in contrast to its effectiveness when combined with the structurally similar *bis*-alkenyltriflate. This implied that this reaction was not an effective model for the desymmetrising first carbonylation of *bis*-alkenyltriflate **222**. This data was in accordance with the finding that the ketoester **240** produced by the attempted desymmetrisation reaction of *bis*-alkenyltriflate **222** with a cesium carbonate base was also racemic (Table 10, Entry 8). This leads to the theory that hydrolysis of *bis*-alkenyltriflate **222** is performed to form mono-alkenyltriflate **224** before that substrate is consumed in the palladium-catalysed carbonylation. As the first desymmetrising carbonylation of *bis*-alkenyltriflate **222** is thought to be an enantioselective process, and that of mono-alkenyltriflate **224** is not, this is the order in which the sequence of reactions produces the racemic ketoester **240** when insufficiently pure hygroscopic bases are used.

It seemed doubtful that it was solely the proposed kinetic resolution of the mono-ester **225** to diester **226** that was responsible for the high enantioselectivities seen, as even at low conversions and diester yields the reaction still produced a high *ee* of mono-ester. To test this theory it was necessary to now perform a kinetic resolution of racemic mono-ester **225** in it's reaction to form diester **226**. If the reaction proceeded with exceptionally high enantioselectivity then this would imply that it was solely the kinetic resolution involved in the second carbonylation that was causing the high enantioselectivities obtained.

A sample of racemic mono-ester **225** was isolated from carbonylation of *bis*-alkenyltriflate **222** with the achiral catalyst system palladium (II) acetate/ triphenylphosphine and subjected to a kinetic resolution under the enantioselective carbonylation conditions to form achiral diester **226**, and hopefully leave evidence of enantiomerically enriched mono-ester **225** (Figure 5).





Reaction conditions: mono-ester **225** (81 mg, 0.208 mmol), $Pd(OAc)_2$ (4.6 mg, 10 mol%), L* (10.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (1 mL), MeOH (2 mL), 45°C

Figure 5: kinetic resolution of mono-ester **225**

Unlike the previous kinetic resolution studies this reaction showed the expected trends. Mono-ester **225** was converted into achiral diester **226**, with the reaction slowing as it neared 50% conversion and the faster reacting mono-ester enantiomer is almost completely consumed. This leaves the reaction involving the disfavoured enantiomer of mono-ester **225**, and as a consequence the reaction rate drops. Pleasingly, the enantiopurity of the remaining starting material also increased as one enantiomer was preferentially converted to achiral diester, providing the mono-ester **225** in up to 60% *ee*. This proves that the process of diester formation is enantioselective, however the enantioselectivity of this process is moderate in comparison to that shown by

bis-alkenyltriflate **222** in desymmetrisations to form both mono-ester **225** (up to 95% *ee*) and diester **226**. This data indicates that both mono-ester formation and diester formation are enantioselective processes, and their combined actions result in the high enantioselectivities achieved in the desymmetrisation. It remains unknown as to why the second carbonylation reaction to form the undesired diester is a quicker process than mono-ester formation. One possible reason is the nature of added ester group, and its effect on the desymmetrised substrate. When one carbonylation reaction has taken place an electron-withdrawing group has been added to one side of the molecule. Even though the system is not in conjugation, this may have the ability to pull electron density out of the cyclohexadiene ring and weaken the *C-O* bond of the remaining alkenyltriflate, aiding a second oxidative addition of the palladium catalyst (Figure 6).

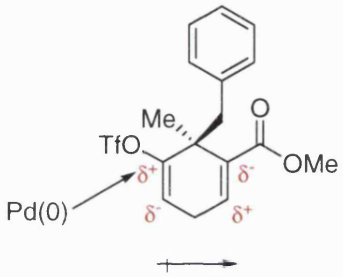


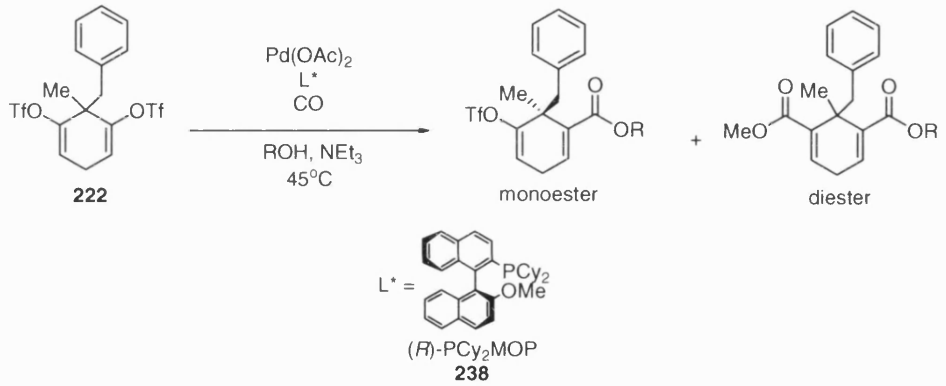
Figure 6: electron-withdrawing ester aiding the second oxidative addition

One other possible reason is that the cyclohexadiene ring of the *bis*-alkenyltriflate can act as a ligand for the palladium catalyst, and actually slightly inhibits the reaction. In contrast to this the more electron-poor diene of the mono-ester does not ligate as well, therefore the overall reaction speeds up as more ester is formed, or this reacts preferentially to the *bis*-alkenyltriflate as diene interaction is diminished. Alternatively, the transformation of an alkenyltriflate to a methyl ester in the first carbonylation could bring about a conformational change in the substrate which results in an easier, accelerated second oxidative addition.

These studies proved that a kinetic resolution is in effect in this reaction and contributes to the high enantioselectivities seen in the desymmetrisation of *bis*-alkenyltriflate **222**. The formation of both mono-ester **225** and diester **226** appear to be enantioselective steps, however the rate of diester formation is faster than that of the mono-ester.

3.4 - Alternative nucleophiles

All reactions to date had been performed using the same nucleophile (methanol) as the quenching reagent for the acyl-palladium intermediate of the carbonylative catalytic cycle. It was thought that the small relative size of methanol could be partially responsible for the over-reaction seen in the formation of diester **226**. Variation of this factor to form esters bearing larger alkoxy groups could create a substrate that may no longer fit into the catalysts' specific steric environment, and therefore decrease the feasibility of this undesired second carbonylation. When used as solvent as well as nucleophile, the varying viscosities and the solubility of both the solid and gaseous reagents in said solvent may also have profound effects on the reaction's result. To test this, a series of alcohols were employed in the reaction using the same catalytic-system as those performed in methanol (Table 12).



Entry	ROH	Time (h)	Mono-ester yield (%)	Diester yield (%)	Mono-ester *ee* (%)
1	EtOH	2	38 (**241**)	47 (**242**)	94
2	^{i}PrOH	3	48 (**243**)	18 (**244**)	90
3	^{t}BuOH	3	24[a]	9[a]	-
4[b]	*p*-hydroxyanisole (10 eq in MeCN)	3	37 (**245**)	Trace	76

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), ROH (0.66 mL), 45°C; [a] conversions from crude NMR spectra – products could not be isolated; [b] *p*-hydroxyanisole (129 mg, 1.04 mmol), NEt_3 (58 µL, 0.416 mmol), MeCN (1 mL)

Table 12: alcohol variation to inhibit diester formation.

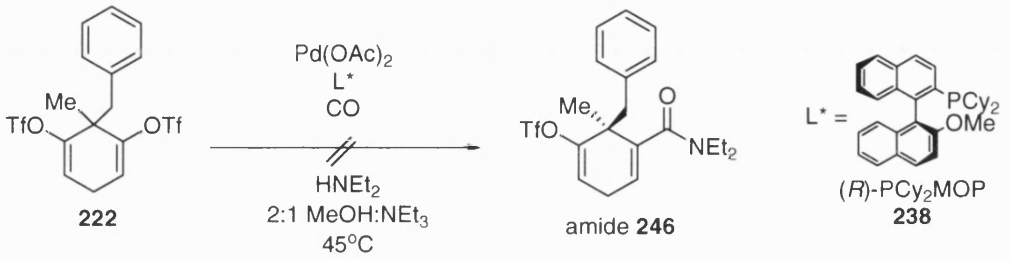
The reactivity of ethanol was similar to that seen for methanol, giving a mono-ester **241** yield of 38% after two hours, with a 94% *ee* (Table 12, Entry 1). This result was not surprising as although ethanol is greater in steric bulk than methanol, the terminal -CH_3 of the ethyl group could easily orientate itself in a manner that did not compromise the oxidative addition to the chiral catalyst. Increasing the size further to *iso*-propanol gave the highest mono-ester yield seen thus far, 48%, with a 90% *ee* (**243**). The diester (**244**) yield in this reaction was also limited to 18%, indicating that increasing the ester bulk did indeed aid in prevention of diester formation. Attempts to push this reaction further towards completion and hopefully greater mono-ester yield were unsuccessful, as at longer reaction times (4 h & 6 h) the mono-ester **243** was seemingly converted into diester **244** more efficiently than it was formed from the *bis*-alkenyltriflate starting material, as seen in the methanol system.

Reactions in *tert*-butanol proved sluggish, and gave only low yields of the ester products. Even after 6 hours the yields did not increase, as palladium black deposits were formed before the reaction ran to higher conversion, indicating that the catalyst was not well-enough supported by the ligand to survive. The yields of reactions performed in *tert*-butanol were erratic when the reaction was repeated the products were not able to be isolated as clean compounds, hence the enantioselectivity was not established. The aromatic alcohol *para*-methoxyanisole was also coupled successfully to form **245**, with the reaction being performed in acetonitrile due to the nucleophile being a solid at room temperature (Table 12, Entry 4). Whilst overall consumption of starting material did not pass 40%, the high mono-ester:diester ratio was intriguing even though the lower enantioselectivity (76% *ee*) was indicative of similar selectivity observed with methanol, where the kinetic resolution involved in the so-far minimal diester formation has not had as profound an effect due to low conversion. Attempts to optimise this reaction to produce larger amounts of the mono-ester failed due to catalyst decomposition at prolonged reaction times and increased temperatures. Even though it proved the reaction to be applicable to all alcohols shown (with the exception of *tert*-butanol), variation of the alcohol had not given any definite indication that exploration of steric variation of the ester was a feasible method of enhancing mono-ester yields.

Aside from alcohols, the most common nucleophiles used in palladium-catalysed carbonylation reactions are amines. Using amines in this

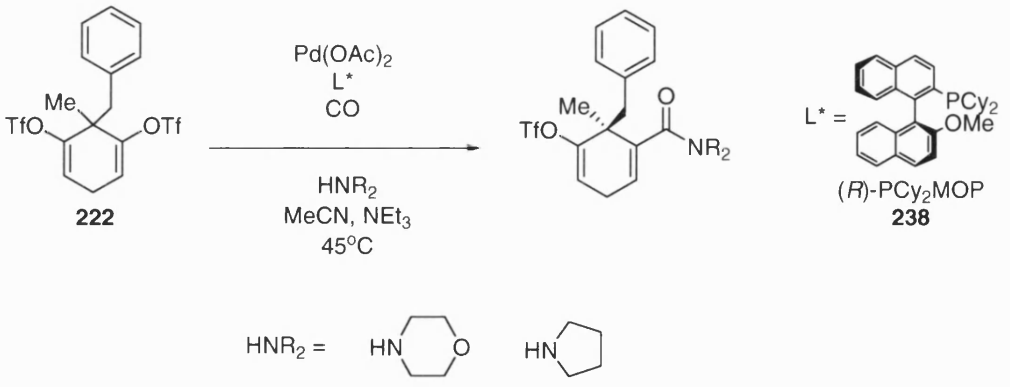
desymmetrisation reaction may lead to mono-coupled amide substrates differing in electronic and steric nature to their ester counterparts.

Attempted reaction of diethylamine in this system was unsuccessful. The reaction was performed with 20 equivalents in the same methanol/triethylamine mixture as other desymmetrisations. Despite the secondary amine being a better nucleophile than methanol, the only products isolated from this reaction were mono-ester **225** and diester **226**, with none of the amide **246** formed (Scheme 98). This is likely due to the large excess of methanol present in comparison to diethylamine, so it reacts preferentially.



Scheme 98: unsuccessful coupling of diethylamine

It was clear that amine nucleophiles could not compete with methanol when it was used as the reaction solvent, so several reactions were examined using secondary amines as nucleophiles in acetonitrile, which had worked effectively as a non-nucleophilic solvent when used in conjunction with alcohols (Scheme 99).



Scheme 99: attempted coupling of cyclic amines

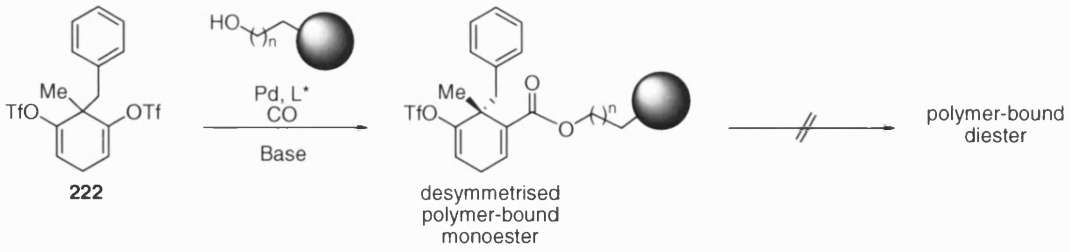
From crude NMR examination it was clear to see that both morpholine and pyrrolidine were able to couple to form the amide products, although the

conversions were less than reactions using alcoholic nucleophiles and the mono-coupled:di-coupled ratios were not of significant difference. Isolation of the coupled amides proved to be taxing, with apparent decomposition when purified by flash chromatography.

In summary, the variation of the nucleophile among alcohols has some effect on the overall rate of reaction with extremely bulky alcohols slowing down and, as seen with *tert*-butanol, exhibiting decreased reactivity. When alcohols were successfully coupled there was little difference observed in either mono-ester yield or enantioselectivity. Coupling amines may have yielded the expected amides, however purification could not provide the products for analysis.

3.5 - Polymer supported nucleophiles

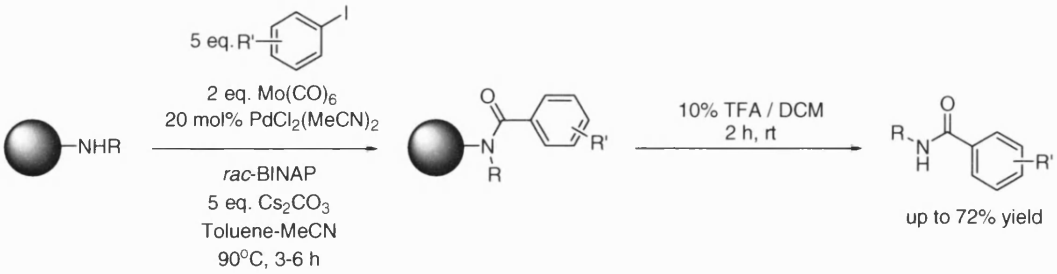
In recent years, the discovery and advancement of combinatorial chemistry has resulted in not only numerous publications, but also somewhat of a shift in the way that chemistry is conducted in industrial laboratories to produce large libraries of structurally similar compounds for screening as potential pharmaceutical targets. This surge in combinatorial research has lead to the development of scavenger reagents, compounds that remove often-unwanted reagents and by-products from the reaction mixture. This methodology differs from most polymer chemistry whereby a compound is immobilised on a solid support, a transformation is performed on the polymer-bound substrate and the product remains attached to the polymer for ease of purification. We sought to utilise the idea of a scavenger reagent in the desymmetrisation reaction by use of a polymer-supported alcohol. It was anticipated that this alcohol could behave as a nucleophile in the reaction, to furnish the desymmetrised mono-ester, which would then be unable to react further seeing as it would now be directly attached to the polymer-scaffold (Scheme 100).



Scheme 100: proposed use of a polymer-supported alcohol

This idea had the potential to be extremely effective, as purification of polymer-bound compounds is often simple, with unwanted reagents and by-products simply being washed away whilst the desired product remains insoluble. Cleavage of the mono-functionalised product from the polymer is well known for ester linkages, and methylation of the resultant acid could provide the same desymmetrised mono-ester as seen before. There is little literature precedence for such a reaction, with the majority of publications performing carbonylative chemistry on polymer-bound vinyl or aryl halides. There exist however two examples where the polymer reagent is used as a trapping or scavenger reagent in palladium-catalysed carbonylations.

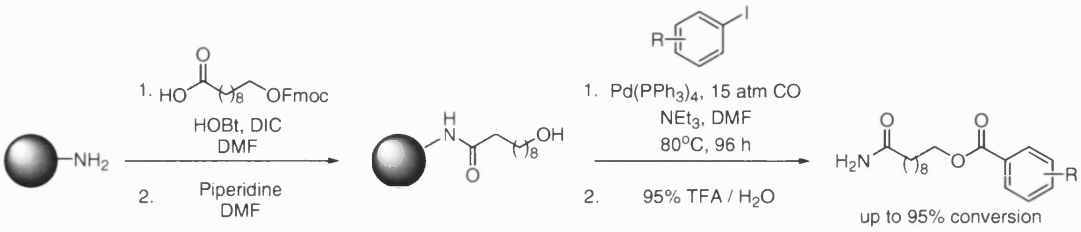
Yamazaki has used a polymer-bound amine as a nucleophile to trap carbonylated aryl halides.[332] A number of resins such as Rink, PAL and FMPE were successfully coupled at high temperature, using molybdenum hexacarbonyl as a source of carbon monoxide. After cleavage from the resin using trifluoroacetic acid the aryl amides were isolated in good to moderate yields and in high purity (Scheme 101).



Scheme 101: The use of polymer-bound amines as nucleophiles in carbonylation

Takahashi *et al.* have also reported the use of a polymer-supported nucleophile in the carbonylation of aryl iodides.[333] The Fmoc-protected alcohol 10-

hydroxydecanoic acid was coupled to Rink resin with DIC/HOBt and the Fmoc group cleaved using piperidine/DMF. This provided a free alcohol which could be used in a palladium-catalysed carbonylation. Action of trifluoroacetic acid on the resultant compound cleaved the substrate from the polymer at the amide position, rather than the newly formed aryl-ester to give the products in good conversion, albeit with long reaction times and a carbon monoxide pressure of 15 atm required (Scheme 102). This methodology was also applied to form new amide bonds, starting from the corresponding Fmoc-protected amines and amino acids to produce a large library of derivatives.



Scheme 102: The carbonylation of aryl iodides using a polymer-bound alcohol

It was decided to use a polymer supported alcohol as the nucleophile in the proposed desymmetrisation reactions as so far they had shown greater reactivity and ease of purification. After cleavage from the resin, the possibility to methylate the resultant acid to give identical products to those produced so far was more attractive than making the amides that had proved so difficult to purify in previous reactions. For these reasons, Wang resin was thought to be suitable as it is well established in combinatorial chemistry and product cleavage is usually achieved by simply stirring in trifluoroacetic acid. The polymer end-group has a simplistic structure, comprised of a benzyl ether with a terminal *para*-benzylic alcohol, which would hopefully avoid any unwanted reactivity further down the linker (Figure 7).

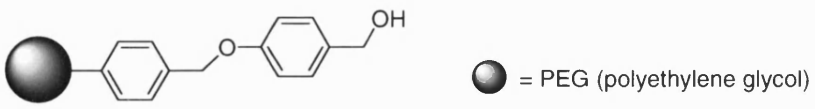
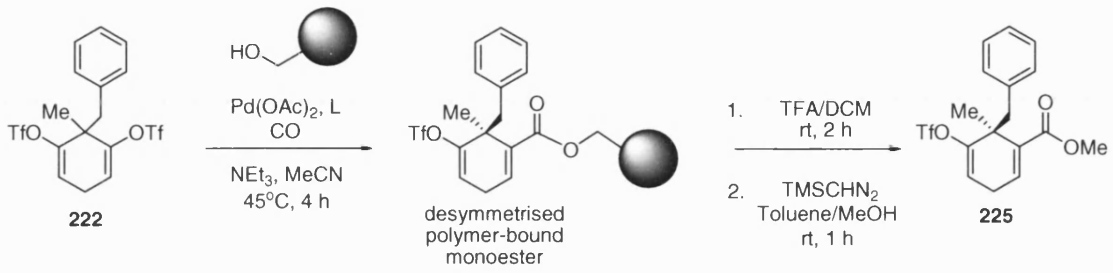


Figure 7: the structure of Wang resin

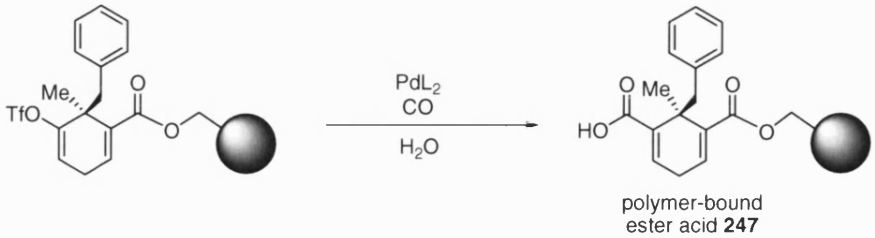
Incorporation of the Wang resin into the reaction meant that again a non-nucleophilic solvent was required, so the reaction was performed in acetonitrile.

Two equivalents of the resin (1.20 mmol/g OH-loading) were also added, and the reaction stirred at 45°C. Within four hours, reactions using triphenylphosphine as a ligand, and those where dicyclohexylphosphine **238** was employed, showed complete consumption of starting material by TLC. The resin was filtered and washed with DMF, DCM and water. Cleavage was then performed by stirring the polymer-bound product in a 1:1 mixture of trifluoroacetic acid and DCM followed by filtration of the polymer. The resultant compound was then treated with trimethylsilyldiazomethane to afford an oily product (Scheme 103).



Scheme 103: the incorporation of Wang resin as a nucleophile

Unfortunately, on examination of the oil using ^{1}H NMR spectroscopy, it was found to be the undesired achiral diester **226** in 72% yield, seen in so many previous reactions, with no trace of the mono-ester. This result was confusing, as it seemed unlikely that the diester could be formed by reaction with two equivalents of the polymer functionality due to structural constraints. It was hypothesised that the polymer or solvent may be contaminated with water, which could form ester-acid **247**, first by action of the Wang resin as a nucleophile, then by carbonylation and quenching with water of the remaining free alkenyltriflate (Scheme 104). This free acid could then also potentially be converted to the diester via methylation with trimethylsilyldiazomethane.

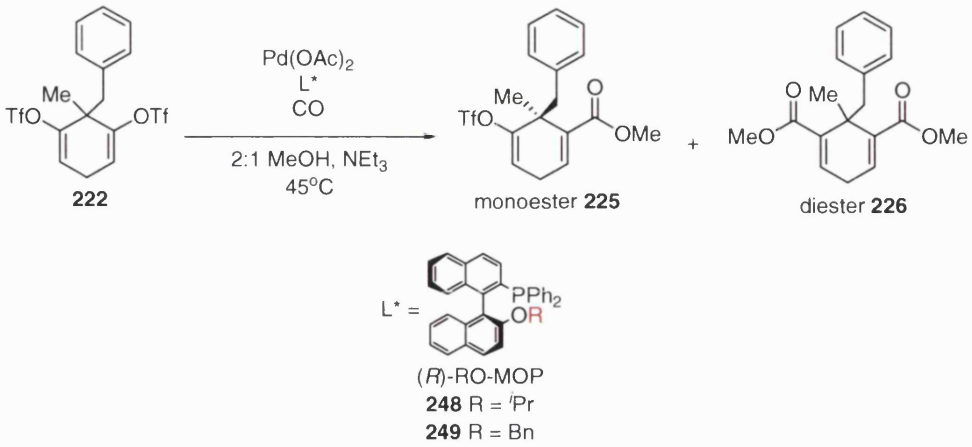


Scheme 104: potential acid formation of polymer-bound mono-ester

To eliminate this possibility the solid reagents were added to a Schlenk tube and dried under vacuum overnight, then freshly distilled solvents were added and the reaction was run. A similar result was observed, with a 64% yield of diester isolated, indicating that formation of the acid was not responsible for the eventual diester product. A test reaction performed in a 1:1 mixture of acetonitrile:water in a direct attempt to form this diester failed to react at all, with almost complete recovery of the starting *bis*-alkenyltriflate possible, further pointing to the fact that this pathway involving water as a nucleophile was unlikely. The unexpected over-reactivity of these couplings meant that further work to optimise the process was not undertaken. It is probable that diester formation was indeed due to double reaction of the polymer-bound alcohol. In general, because polymers are described as beads they are pictured as a solid sphere with functional groups extending from it, however the actual structure is comprised of a cross-linked mesh of polymer fibres which is easily penetrated by solvents and substrates alike. The relatively high functionality loading of the Wang resin used for these carbonylation reactions may mean that the proximity of the hydroxyl groups is such that the linking of two of these polymer chains by each one reacting with the *bis*-alkenyltriflate substrate is possible.

3.6 - Revisiting the ligands' structural properties

With variation of solvent, base and nucleophile proving to be unfruitful in increasing mono-ester yields, it was decided to reinvestigate the ligand. Although a range of chiral ligands had been screened and an excellent 95% *ee* had been obtained with dicyclohexylphosphine **238**, it was thought that if this ligand could be optimised further then results could be improved. If a highly enantioselective system was discovered that could produce the mono-ester as a single enantiomer then the second carbonylation reaction to form the diester should theoretically be extremely unfavourable, and therefore the reaction would stop, or become significantly slower when the conversion to the mono-ester was complete. Several structural analogues of the MOP family are known, some of which have been synthesised by Hayashi, and Kocovsky.[318, 334] Simple positions of variation are the alkoxy group and the phosphine (-methoxy and -diphenylphosphine respectively in MOP). Two alkoxy-MOP derivatives were synthesised, and tested in the basic reaction to examine the effects of this change in steric environment (Table 13).



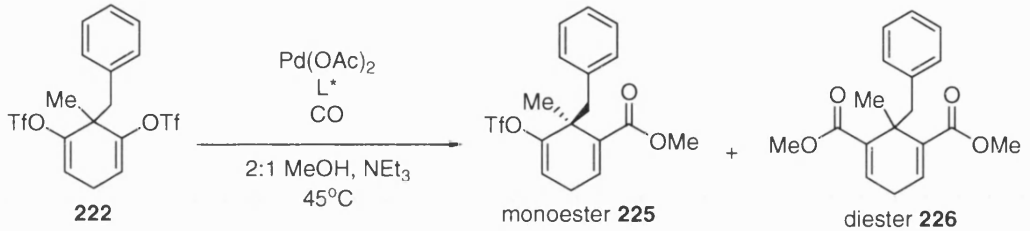
Entry	(*R*)-RO-MOP R =	Time (h)	Mono-ester 225 yield (%)	Diester 226 yield (%)	Mono-ester *ee* (%)
1	^{i}Pr	2	42	9	73
2	^{i}Pr	6	47	8	75
3	Bn	2	35	12	72
4	Bn	6	37	7	74

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL), 45°C

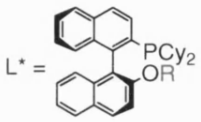
Table 13: Effects of differing ligand alkoxy groups

Of particular interest from these reactions was the effect of increasing the steric bulk of the alkoxy group from methoxy to *iso*-propoxy (Table 13, Entry 2). Although some diester was still produced from this reaction using ligand **248**, the mono-ester:diester ratio was the highest produced from any reaction so far at approximately 6:1 with a 75% *ee*, directly comparable with the enantioselectivity observed with (*R*)-MeO-MOP. The corresponding benzyloxy ligand **249** gave slightly improved results again, with a more favourable mono-ester:diester ratio, and equivalent enantioselectivity. The same catalyst lifetime issues seen with (*R*)-MeO-MOP plagued these reactions, whereby there was little difference in yields between reactions heated for two hours and six hours. After this time palladium-black deposits were seen in the reaction vessel, and the conversion could not be increased. It was known that the more electron-rich alkylphosphines such as dicyclohexylphosphine **238** provided much improved

reactivity, so it was hypothesised that the nature of the phosphine was responsible for catalyst activity, and the alkoxy group could control the formation of unwanted diester **226**. With this in mind ligands bearing differing alkoxy groups and electron-rich alkylphosphines were synthesised according to Hayashi *et al.*[318] in efforts to combine the properties of the groups and increase mono-ester yields, whilst maintaining catalyst turnover and selectivity (Table 14).



222 monoester **225** diester **226**



(*R*)-RO-MOP
250 R = ^{i}Pr
251 R = Bn

Entry	(*R*)-RO-MOP R =	Time (h)	Mono-ester 225 yield (%)	Diester 226 yield (%)	Mono-ester *ee* (%)
1	^{i}Pr	1	34	26	-
2	^{i}Pr	2	27	58	97
3	Bn	1	37	19	-
4	Bn	2	19	77	95

Reaction conditions: *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL), 45°C

Table 14: Effects of differing ligand alkoxy groups combined with alkylphosphines

Much to our chagrin, the results were not what were hoped for. Whilst enantioselectivities were excellent and similar to those seen with dicyclohexylphosphine **238**, the mono-ester yields retrieved were disappointing, producing large quantities of the achiral diester and not following the expected trend seen in alkoxy variation of (*R*)-MOP. These ligands, synthesised in

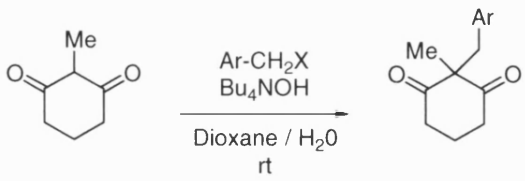
considerably lower yields than dicyclohexylphosphine **238**, showed no benefits in their further use as over-reactivity was still an issue.

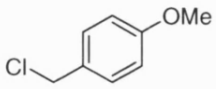
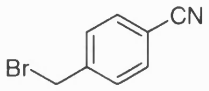
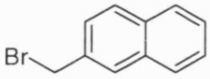
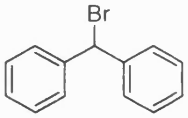
3.7 - Developing new substrates

Despite the kinetic studies and other investigations into the mechanistic aspects of this desymmetrisation system, there remained a number of unknown factors that may dramatically adjust the reactivity seen with *bis*-alkenyltriflate **222**. It had been thought that the presence of the benzyl group used to provide contrast to the size of the methyl group at the quaternary centre may be contributing to the reactivity of this substrate, or increasing its propensity to undergo the reaction *via* coordination to the palladium catalyst. The steric difference between these two groups is not large, as the phenyl ring of the -CH_2Ph group can orient away from the approaching catalyst; this is evident upon inspection of the relevant *A* values (*A* values; CH_3 = 1.74; CH_2Ph ~ 1.76). If it did indeed act in this coordinating manner then it is possible that it was directing the catalyst to one face of the planar substrate through means other than by steric hindrance, whilst also potentially altering the electronic nature of the palladium centre. It may also be that the model substrate (*bis*-alkenyltriflate **222**) was not the ideal molecule for this desymmetrisation process, and changing to a structurally or electronically different *bis*-alkenyltriflate may result in the higher mono-ester yields desired.

The first substrates synthesised aimed to explore the nature of any aryl-palladium interaction that may be affecting the nature of this reaction. Variation of the aryl group to ones of differing electronic and steric properties may lead to some trend in reactivity that would provide a valuable insight into the unknown mechanistic aspects discussed above. The four target substrates incorporated aryl groups bearing electron-rich (*para*-methoxy) and electron-poor (*para*-cyano) substituents, as well as the increased bulk provided by replacing the phenyl ring with a naphthyl or benzyhydryl group. It was thought that either increased or decreased electron density of the phenyl ring would bring about a corresponding alteration in aryl-palladium interactions, and hence lead to a change in either yield or enantioselectivity. Synthesis of the precursory diketones was performed by the same method used to prepare diketone **223**, whereby 2-methyl-1,3-cyclohexanedione was alkylated by a benzylic halide to

yield the respective 2,2-dialkyl-1,3-cyclohexanedione in comparable yields, with traces of what was thought to be the *O*-alkylated products also seen (Table 15).



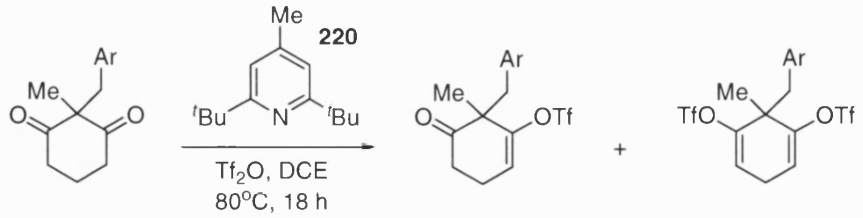
Entry	Ar-CH_2X	Time (h)	Yield (%)
1		72	54 (**252**)
2		48	61 (**253**)
3		48	53 (**254**)
4		72	24 (**255**)

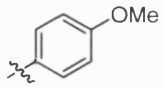
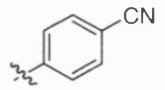
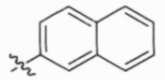
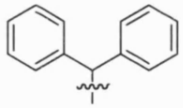
Reaction conditions: 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol), benzyl halide (60.3 mmol), tetrabutyl ammonium hydroxide (40%w/w in water, 27.0 mL, 41.6 mmol), dioxane (30 mL), rt

Table 15: alkylation of 2-methyl-1,3-cyclohexanedione with benzylic bromides

The incorporation of *para*-methoxybenzyl chloride and benzhydryl bromide required longer reaction times than those using primary benzyl bromides, however in all cases the only product seen in significant quantities was the *C*-alkylated diketone when the weak base tetrabutyl ammonium hydroxide was used. Slightly lower yields could also be achieved without this phase-transfer base when the reactions were performed in a 1 M solution of potassium hydroxide, however yields were generally less reproducible and required even longer reaction times.

These 2,2-alkylated diketones were then subjected to the triflation reaction to give mixtures of both mono- and *bis*-alkenyltriflates (Table 16).



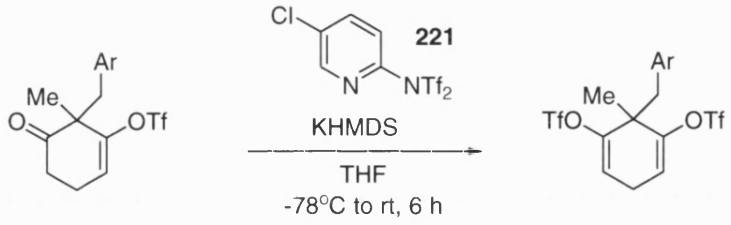
Entry	Ar	Mono-alkenyltriflate yield (%)	*bis*-alkenyltriflate yield (%)
1	 **252**	48 (**256**)	25 (**257**)
2	 **253**	63 (**258**)	9 (**259**)
3	 **254**	54 (**260**)	22 (**261**)
4	 **255**	-	-

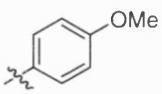
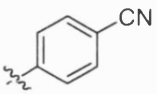
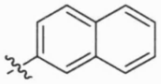
Reaction conditions: 2,2-dialkyl-1,3-cyclohexanedione (4.07 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (2.08 g, 10.16 mmol), triflic anhydride (1.71 mL, 10.16 mmol), DCE (25 mL), 80°C, 18 h

Table 16: triflation of 2,2-dialkylcyclohexane diones

The triflation of these diketones proceeded much as expected with the mono-alkenyltriflate the predominant product, however in some cases up to 25% of the final *bis*-alkenyltriflate could also be isolated. The one exception to this was benzhydryl diketone **255** which failed to produce any of either the mono- or *bis*-alkenyltriflate derivatives. Both the *para*-methoxy **252** and 2-naphthyl **253**

substrates (Table 16, Entries 1 and 3 respectively) gave similar yields to those seen in synthesis of *bis*-alkenyltriflate **222**. The *para*-cyano compound **253** (Table 17, Entry 2) produced less of the *bis*-alkenyltriflate, but a greater yield of the mono-alkenyltriflate. Combined yields for all three substrates were reasonable, and the mono-alkenyltriflates were then treated under the KHMDS triflation conditions to afford the corresponding *bis*-alkenyltriflates, ready to be subjected to the palladium-catalysed desymmetrisation (Table 18).



Entry	Ar	*bis*-alkenyltriflate yield (%)
1	 (**257**)	65
2	 (**259**)	15
3	 (**261**)	59

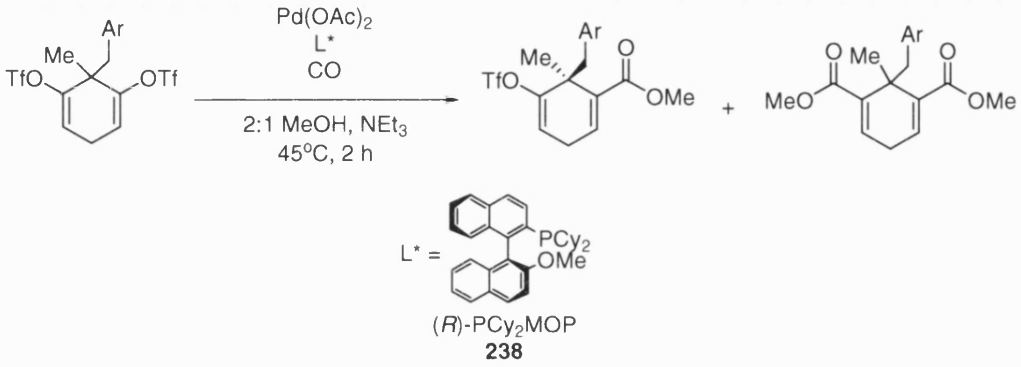
Reaction conditions: mono-alkenyltriflate (0.64 mmol), 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino] -5-chloropyridine (0.30 g, 0.77 mmol), KHMDS (0.5M in toluene, 1.53 mL, 0.77 mmol), THF (10 mL), -78°C (2 h), rt (4 h)

Table 18: triflation of 2,2-dialkyl-mono-alkenyltriflates

Triflation of the *para*-methoxy **256** and 2-naphthyl **260** mono-alkenyltriflates again proceeded smoothly to produce the respective *bis*-alkenyltriflates in adequate yields. However, for the second time the *para*-cyano **258** proved difficult to convert to the *bis*-alkenyltriflate as had been seen in the low yield of this product in Table 17. Approximately 30% of the starting material could be

recovered from this reaction, with the rest forming a mixture of unidentifiable products. This low yield could be due to reaction of the nucleophilic cyano group, which may also attack the pyridyl triflating reagent and could form, among other things, an amide upon aqueous work-up.

The carbonylative-desymmetrisation of these three new substrates was then reviewed to examine the effects of varied aryl substitution in the hope that it would indicate if any role was played in the catalysis by an aryl-palladium coordination species (Table 19). The reactions were performed in the same conditions that had given optimum yields of mono-ester **225** in the desymmetrisation of *bis*-alkenyltriflate **222**.



Entry	Ar	Mono-ester yield (%)	Diester yield (%)	Mono-ester *ee* (%)
1	*para*-$C_6H_4OCH_3$	44 (**262**)	32 (**263**)	89
2	*para*-C_6H_4CN	37 (**264**)	42 (**265**)	90
3	2-Napthyl	44 (**266**)	33 (**267**)	93

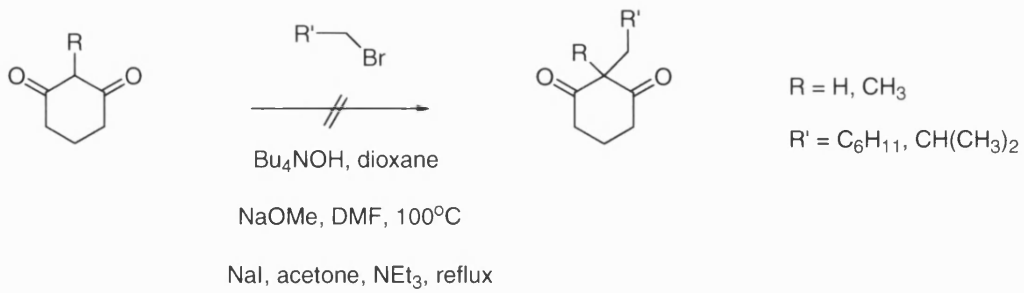
Reaction conditions: *bis*-alkenyltriflate (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL), 45°C, 2 h

Table 19: the effects of aryl groups of varying electronic and steric nature

All the *bis*-alkenyltriflates subjected to the desymmetrisation produced their respective mono-esters in high enantioselectivity. Both mono- and diester yields were similar to those seen in the reaction of *bis*-alkenyltriflate **222**, however there were slightly improved yields of the desired mono-esters. Although the

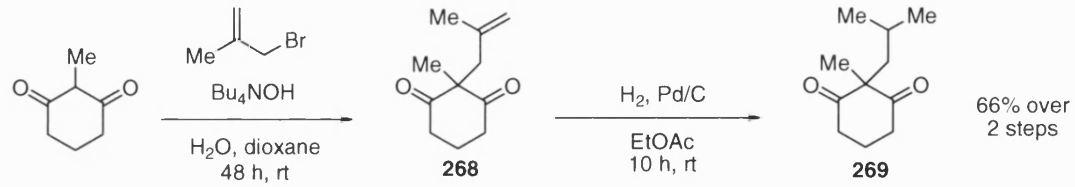
enantioselectivities are approximately 5% lower than those seen in previous studies on the test-substrate **222**, the diester yields are also lower. Presumably, if desired, the reaction could be run for a longer time to form more diester and improve the mono-ester enantiopurity to the 95% *ee* seen for mono-ester **225**. This variation in substitution did not bring about the expected changes seen in either enantioselectivity or yield, and with results so similar to those observed in the simpler phenyl system indicated that any electronic interaction of the aryl unit with the palladium catalyst was not the likely cause of either the over-reaction or high enantioselectivity.

In further efforts to determine the presence of an aryl-palladium coordinate species it was decided to synthesise a range of *bis*-alkenyltriflates bearing two aliphatic groups at the quaternary centre. Hopefully these substrates would react in a considerably different manner to those 2-aryl-*bis*-alkenyltriflates previously studied to give a notable change in either yield or enantioselectivity. Aliphatic groups of similar steric bulk to a phenyl ring were required to provide a relatively accurate comparison, so a methylcyclohexyl- and *iso*-butyl- group were chosen. Alkylation of 2-methyl-1,3-cyclohexane dione with the corresponding alkylbromides and tetrabutylammonium hydroxide proved to be a difficult process, presumably down to the poor nucleophilicity of the diketone and the steric encumbrance of the 2-methyl group. The compound also exists as a mixture or tautomers with both the 1,3-diketone and enol stable forms, and is known to exhibit poor reactivity in comparison to a number of other 1,3-dicarbonyl substrates such as malonates. This is thought to be due to its *W*-geometry, which can also often lead to preferential *O*-alkylation.[335, 336] Attempted *in situ* Finkelstein reactions to form the more reactive alkyliodides also failed to give the desired products.[337] It was thought that reverse addition of the alkyl groups to the cyclic dione to install the larger alkyl group first, then perform a *C*-2 methylation would be a simple way to synthesise the 2,2-dialkyl substrates, however every alkylation reaction attempted on this system also failed (Scheme 105).



Scheme 105: attempted alkylation of cyclic diones

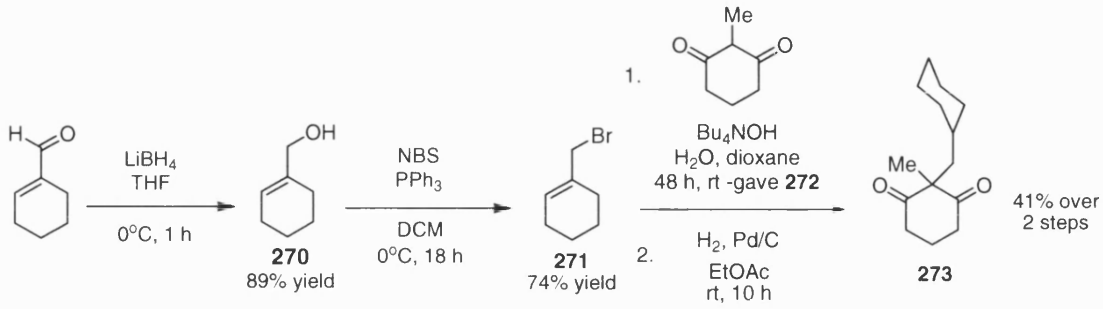
Alkylation of these 2-methyl-1,3-diones is known to be difficult with alkyl halides, and as such alkylation is generally performed with *α,β*–unsaturated carbonyl compounds,[338] *α,β*-unsaturated nitriles[339] or *α*–halo carbonyls.[340] Benzylic bromides had been shown to alkyate 2-methyl-1,3-cyclohexanedione effectively, and alkylation of this compound was also known by allylic bromides. To synthesise the desired diketones it was proposed that alkylation by an allylic bromide of similar structure followed by reduction of the *C=C* bond would be an effective manner in which to subvert the problems associated with the alkyl bromides previously investigated. The allylic bromide 2-bromo-3-methylpropene is commercially available and was able to alkylate 2-methyl-1,3-cyclohexanedione to give **268** under the phase transfer conditions. This reaction, followed by quantitative reduction of the remaining *C=C* bond with hydrogen and palladium/charcoal gave *iso*-butyldiketone **269** in 66% yield (Scheme 106).



Scheme 106: synthesis of 2-*iso*-butyldiketone 269

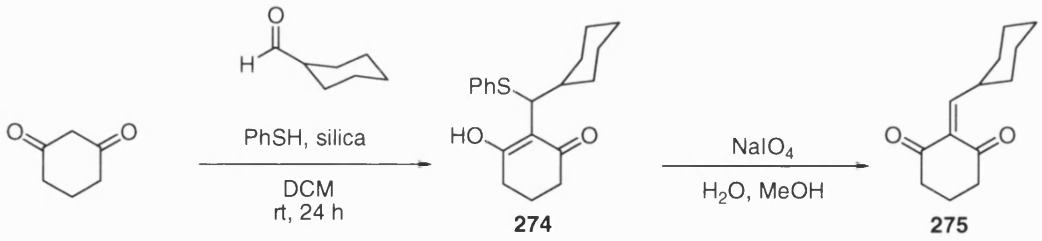
Unfortunately, the allylic bromide required to synthesise the 2-methylcyclohexyl diketone by the same methodology was not available, however it was readily available in two steps from 1-cyclohexenecarboxaldehyde.[341, 342] Reduction of this aldehyde with lithium borohydride gave allylic alcohol **270**, which could then be converted to the allylic bromide **271** by reaction with triphenylphosphine and

N-bromosuccinimide. The crude allylic bromide was subjected to only minimal purification, passing it through a silica plug to remove triphenylphosphine oxide and succinimide by-products, after which alkylation to form 1-cyclohexenyl diketone **272** and reduction gave the desired 2-methylcyclohexyl diketone **273** in 41% yield (Scheme 107).



Scheme 107: synthesis of 2-methylcyclohexyl diketone **273**

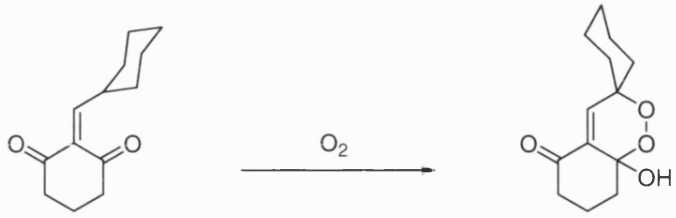
An alternative synthesis of this diketone was also explored using methodology developed by Paquette *et al.* whereby 1,3-cyclohexanedione undergoes a Knoevenagel reaction with cyclohexanecarboxaldehyde.[343] The product can then be trapped with a thiol to form enol-sulfide **274** and prevent reaction with remaining starting material of the extremely active Michael acceptor formed. This affords a product which upon oxidation to the sulfoxide and elimination can yield the α,β-unsaturated diketone **275** (Scheme 108).



Scheme 108: synthesis of diketone precursor

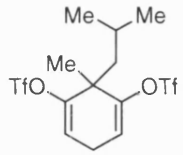
It was hoped that this procedure, could produce a powerful reagent that could rapidly lead to several derivatives via manipulation of the *C=C* double bond, including reduction and methylation to give the target diketone. This method failed to produce any of the enol-sulfide intermediate **274**, giving a mixture of unidentifiable products with some starting material remaining. It was decided not to use this methodology further to make other diketone precursors, despite

the good results reported by Paquette for other substrates, due to the known problems with product stablility, as they are prone to oxidise readily in air to cyclic peroxides (Scheme 109).

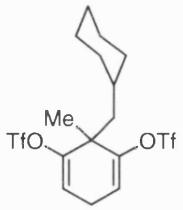


Scheme 109: oxidation of unsaturated cyclic diketones

Aliphatic diketone substrates **269** and **273** were then converted to the mono-alkenyltriflates using 2,6-di-*tert*-butyl-4-methylpyridine and triflic anhydride in satisfactory yield (61%-**276** and 54%-**277** respectively with traces of *bis*-alkenyltriflate), and then to the *bis*-alkenyltriflates **278** and **279** in lower yields than previously given by 2-aryl-*bis*-alkenyltriflate **222** (Figure 8).



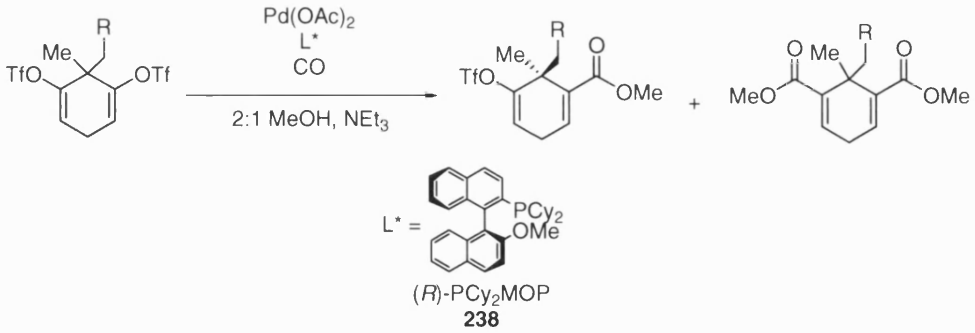
278
29%
(2 steps)



279
16%
(2 steps)

Figure 8: *iso*-butyl and methylcyclohexyl *bis*-alkenyltriflates

These new aliphatic substrates were then employed in the carbonylative desymmetrisation to examine the effects of the absence of an aryl substituent (Table 20).



Entry	R	Time (h)	Temp. (°C)	Mono-ester yield (%)	Diester yield (%)	Mono-ester *ee* (%)
1	-$CH(CH_3)_2$	2	45	9 (**280**)	-	69[a]
2	-$CH(CH_3)_2$	6	45	Trace	-	-
3	-$CH(CH_3)_2$	6	60	Trace	-	-
4	-C_6H_{11}	2	45	5	-	-
5	-C_6H_{11}	6	45	Trace	-	-

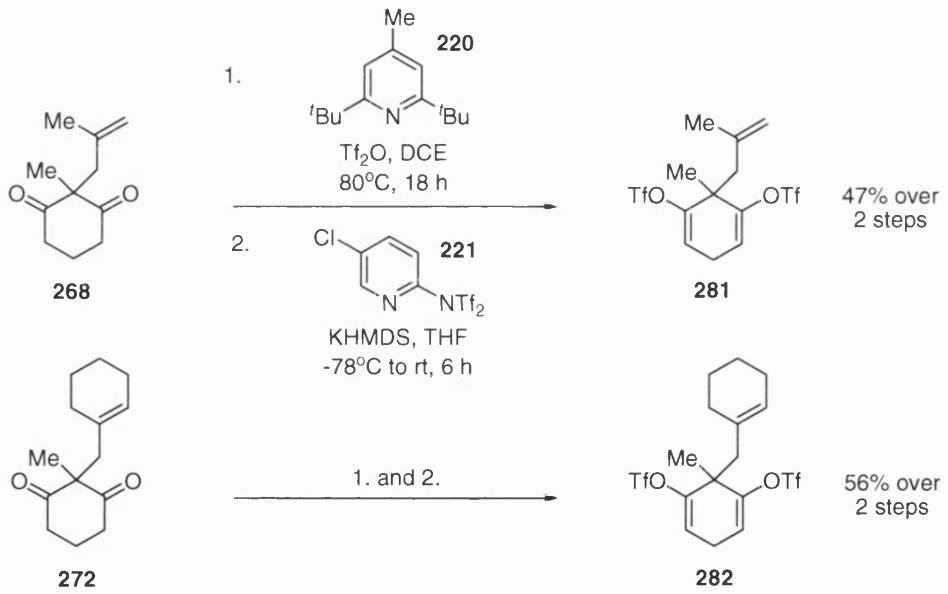
Reaction conditions: *bis*-alkenyltriflate (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL); [a] Baseline separation of enantiomers not achieved, result is approximate

Table 20: the effects of aliphatic groups on the desymmetrisation reaction

Both these *bis*-alkenyltriflates performed extremely poorly in the desymmetrisation, giving almost none of the mono- or diester products. They produced very low yields of the desymmetrised mono-ester, purification of which was difficult due to the small scale of the reaction. Approximately 9% yield of the *iso*-butylmono-ester **280** was isolated, however this product could not be purified to an acceptable standard for analysis, and baseline separation of the enantiomers *via* HPLC was not possible meaning that the 69% *ee* may not be an accurate representation. Attempts to increase the yields by prolonged reaction times and increased temperature failed to effect the transformation. These substrates were also inactive to methoxycarbonylation when the racemic and highly active palladium (II) acetate / triphenylphosphine catalyst system was used. This evidence pointed to the suspected role of an electron enriched aryl-palladium system whereby increased electron density via η_x donation was helping to stabilise the catalyst, or direct it to one of the

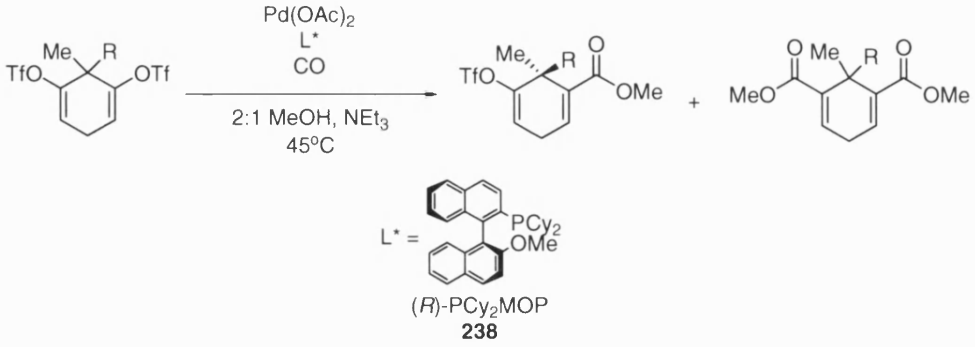
molecules enantiotopic triflates, in contrast to the results obtained by variation of the aryl group.

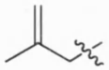
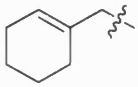
These results led to the examination of two related substrates. If indeed there was some electronic interaction from the quaternary substituents towards palladium then this effect might be replicated by an alkenyl group, the *C=C* bond of which may also be able to act as a ligand for the palladium catalyst. As both the above aliphatic substrates **278** and **279** were prepared from reduction of parent compounds containing *C=C* bonds, synthesis of unsaturated analogues of these compounds was straight-forward. Alkylation proceeded in the same manner to form diketones **268** and **272**, which were then converted to the mono- and *bis*-alkenyltriflates by the same methods (Scheme 110).



Scheme 110: synthesis of alkenyl *bis*-alkenyltriflates **281** and **282**

The two-step synthesis of these *bis*-alkenyltriflates proceeded in higher yield than their respective aliphatic counterparts, giving *iso*-butenyl *bis*-alkenyltriflate **281** in 47% yield, and methyl-1-cyclohexenyl *bis*-alkenyltriflate **282** in 56% yield over two steps. Desymmetrisation of these substrates afforded interesting results (Table 21).



Entry	R	Time (h)	Mono-ester yield (%)	Diester yield (%)	Mono-ester *ee* (%)
1		2	Unidentifiable Products		-
2		4	41 (**283**)	20 (**284**)	74

Reaction conditions: *bis*-alkenyltriflate (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL)

Table 21: the effects of unsaturated alkyl groups on the desymmetrisation reaction

The desymmetrisation of *iso*-butenyl substrate **281** did not proceed as expected and resulted in several products after complete consumption of starting material within two hours, none of which were the expected mono- or diesters (Table 21, Entry 1). This ambiguous reactivity may well arise from the presence of the terminal *C=C* double bond of the *iso*-butenyl side chain, which may have the ability to be a Heck coupling partner. This gives the substrate a number of potential products, whereby methoxycarbonylation, Heck reaction, and carbonylative Heck reaction are all viable reaction pathways. Migration of the *C=C* double bond to facilitate *syn*-elimination from any potential Heck reaction is also possible.

The methyl-1-cyclohexenyl *bis*-alkenyltriflate **282** was considerably more well behaved, with Heck reaction of the tri-substituted internal *C=C* double bond less of an issue. In stark contrast to the poor reactivity of cyclohexyl *bis*-

alkenyltriflate **279**, it readily underwent methoxycarbonylation to produce the mono-ester **283** in 41% yield and 74% *ee*. When the reaction time was extended with the aim of increasing either mono-ester yield or *ee*, the results varied only slightly and the overall conversion could not be increased. This result was particularly intriguing, as it indicated that steric hindrance was unlikely to be the cause of the aliphatic substrates' extremely limited reactivity due to the large size of the methyl-1-cyclohexenyl substituent. It also pointed towards the predicted η_x coordination of the *C=C* double bond to the palladium centre that was aiding the reaction either by electron donation to form a more active/stable catalyst or by directing the catalyst to a specific face of the substrate (Figure 9).

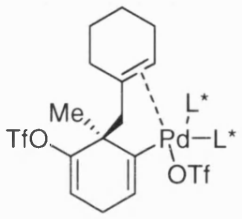
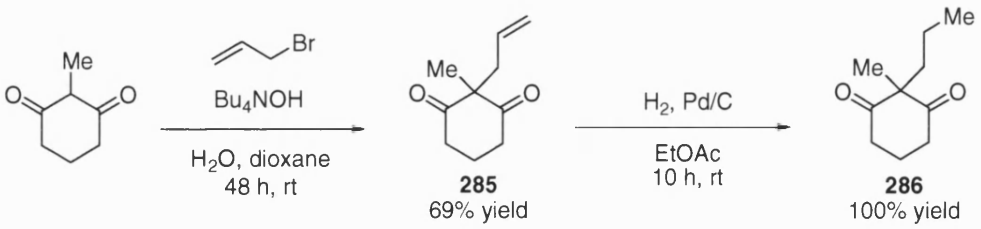


Figure 9: potential coordination of alkenyl substrate to palladium

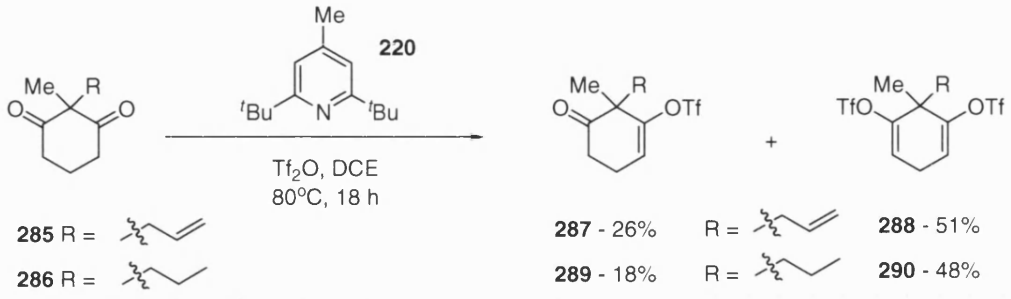
In an effort to further demonstrate this principle more alternative substrates were synthesised. Allylation of 2-methyl-1,3-cyclohexane dione with allyl bromide and the phase transfer conditions produced allyl diketone **285** in good yield, and reduction of the terminal *C=C* double bond with hydrogen and a palladium/charcoal catalyst afforded quantitative *n*-propyl diketone **286** (Scheme 111).



Scheme 111: preparation of allyl diketone **285** and *n*-propyl diketone **286**

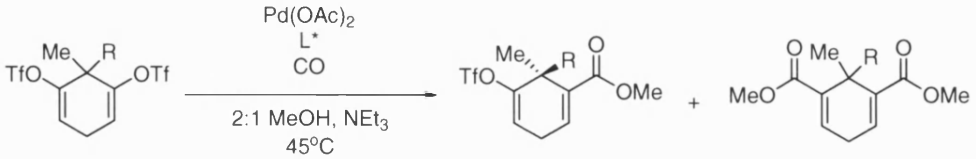
Transformation of these substrates into their respective mono- and *bis*-alkenyltriflates only required one reaction due to the high yields of *bis*-

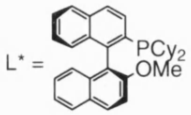
alkenyltriflate produced by action of 2,6-di-*tert*-butyl-4-methylpyridine and triflic anhydride (Scheme 112). These significantly higher yields may well be attainable because of the relatively small steric hindrance of the two substituents at the quaternary centre which can orientate themselves away from any reaction at proximal functional groups.



Scheme 112: preparation of allyl- and *n*-propyl *bis*-alkenyltriflates

Again, desymmetrisation of these *bis*-alkenyltriflates gave conflicting results with the allyl *bis*-alkenyltriflate **288** giving a myriad of products and *n*-propyl *bis*-alkenyltriflate **290** undergoing the desymmetrisation reaction smoothly (Table 22).





(*R*)-PCy$_2$MOP
238

Entry	R	Time (h)	Mono-ester yield (%)	Diester yield (%)	Mono-ester *ee* (%)
1	allyl	2	Unidentifiable Products		-
2	*n*-propyl	2	32 (**291**)	38 (**292**)	87

Reaction conditions: *bis*-alkenyltriflate (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL)

Table 22: the effects of unsaturated alkyl groups on the desymmetrisation reaction

As seen with *iso*-butenyl *bis*-alkenyltriflate **281**, the allyl substituted *bis*-alkenyltriflate **288** produced a number of products due to potential Heck cyclisation and methoxycarbonylation. Surprisingly, desymmetrisation of *n*-propyl *bis*-alkenyltriflate **290** occurred, producing the desired mono-ester **291** in 32% yield and 87% *ee*, regardless of the absence of a potential alkenyl or aryl group for the proposed catalyst coordination. The high enantioselectivity of this process was especially unexpected with the *n*-propyl substituent offering only marginally larger steric hindrance than the methyl substituent. This result may mean that the key to substrate reactivity involves a relatively unhindered centre at the *C*-2 position on the carbon chain extending from the quaternary centre, and as such cannot be a tertiary aliphatic centre (Figure 10).

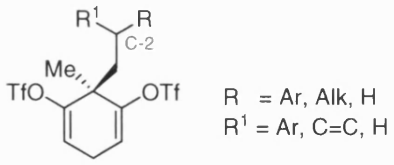
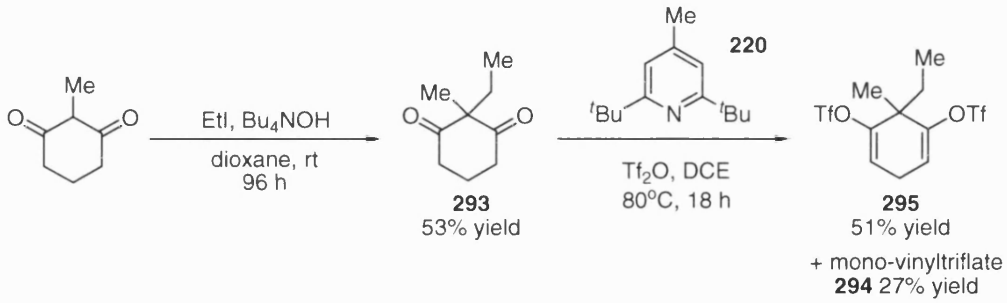


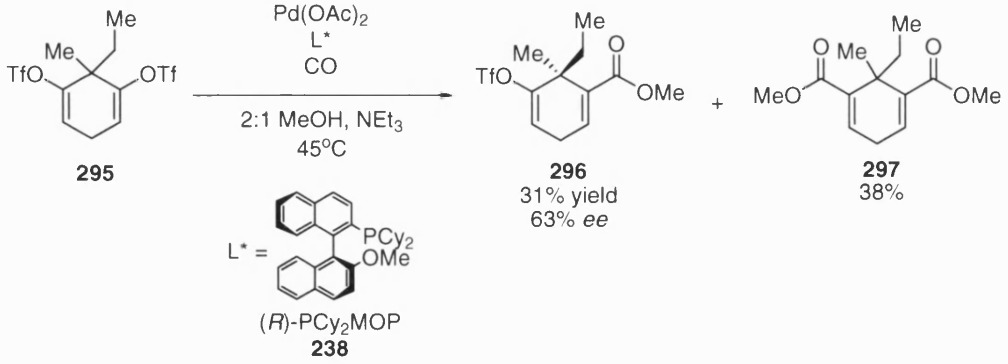
Figure 10: the need for a secondary or sp^2 centre at *C*-2

To test whether an even simpler substrate could also be desymmetrised in this manner without the need for an unsaturated or aryl substituent, it was decided to investigate a 2-ethyl-2-methyl *bis*-alkenyltriflate. Synthesis of this substrate was straight forward, with alkylation of 2-methyl-1,3-cyclohexane dione by ethyl iodide to form diketone **293** occurring in 53%, albeit with a considerably extended reaction time of 96 hours. The diketone was then converted to the mono-alkenyltriflate **294** and *bis*-alkenyltriflate **295** in one step, in similarly high yields that were seen for the allyl and *n*-propyl substrates (Scheme 113).



Scheme 113: preparation of *bis*-alkenyltriflate **295**

The *bis*-alkenyltriflate **295** was then subjected to the methoxycarbonylation desymmetrisation reaction under the standard conditions (Scheme 114).

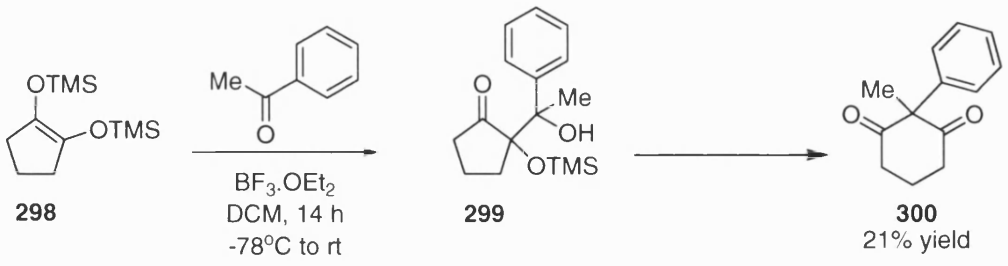


Reaction conditions: *bis*-alkenyltriflate **295** (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL)

Scheme 114: desymmetrisation of *bis*-alkenyltriflate **295**

Desymmetrisation of this substrate was facile, producing mono-ester **296** in 31% yield and diester **297** in 38% yield. Whilst the ratio of these two products was not drastically different from any other experiment performed, the enantioselectivity of the reaction was surprisingly high. Although a 63% *ee* of **296** is low in comparison to those afforded by other substrates, considering the size difference between the two enantiotopic groups (methyl and ethyl) this seemed to still be an effective desymmetrisation with the chiral catalyst able to efficiently discriminate between two such small groups.

As a model for a precursor substrate in the proposed synthesis of desoxycodeine-D (Chapter 2.10) we sought to develop the desymmetrisation of a *bis*-alkenyltriflate bearing a phenyl substituent directly on the cyclohexadiene frame, which could then undergo palladium-catalysed *O*-arylation to form a tricyclic core. Such a substrate was not trivial to synthesise, as alkylation in this position directly onto an aryl ring was not possible. An alternative method was proposed, using methodology developed by Burnell *et al.* whereby both the aryl and methyl groups could be installed in one step.[344] The reagent 1,2-*bis*-(trimethylsiloxy)cyclopentene **298** was prepared according to Fraenkel *et al.* in a much improved 91% yield after distillation of all liquid reagents and extending the reaction time to 18 hours.[345] Reaction of this compound with acetophenone and excess boron trifluoride etherate resulted in aldol product **299**, which undergoes a Pinacol rearrangement. Aqueous workup then affords 2-methyl-2-phenyl cyclohexanedione **300** (Scheme 115).



Scheme 115: synthesis of diketone **300**

This reaction produced only 21% of the desired diketone. The corresponding *para*-cyanophenyl diketone **301** could only be synthesised in 4% yield from *para*-cyanoacetophenone, however *para*-methoxyacetophenone afforded diketone **302** in slightly improved 34% yield (Figure 11).

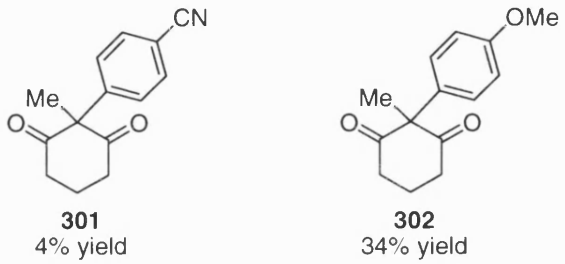
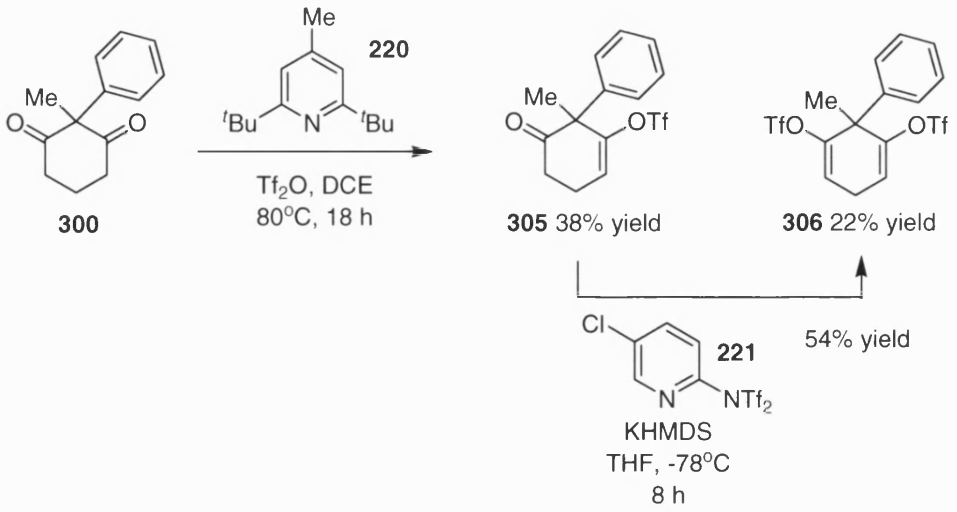


Figure 11: 2-aryl diketones prepared from 1,2-*bis*-(trimethylsiloxy)cyclopentene

The yields of 2-methyl-2-phenylcyclohexane dione **300** and it's *para*-cyano analogue **301** were increased by use of the aryl dioxalanes (**303** and **304** – experimental), prepared from reaction of the acetophenones with ethylene glycol under Dean-Stark conditions. When utilised in the aldol-Pinacol reaction under slightly modified conditions they provided 2-phenyl cyclohexanedione **300** in an improved 57% yield, whilst 2-*para*-cyanophenyl cyclohexanedione **301** was isolated in 11% yield.

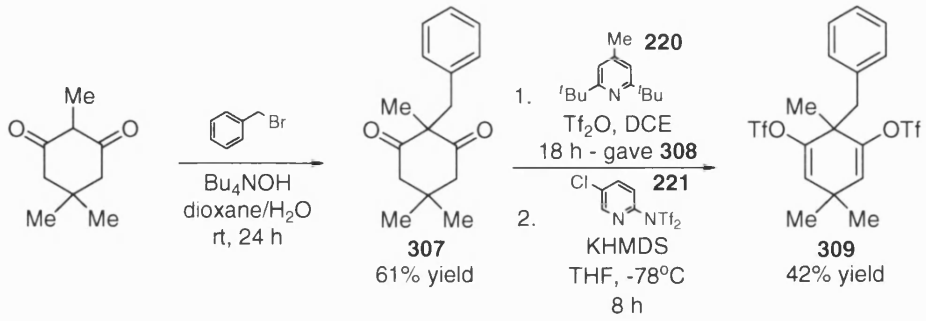
Attempted synthesis of the *bis*-alkenyltriflates from these diketones proved difficult, with only the simple 2-phenyl diketone **300** being successful. Reaction with 2,6-di-*tert*-butyl-4-methylpyridine and triflic anhydride produced mixtures of unidentifiable products for both **301** and **302**, however 2-phenyl diketone **300** yielded mono-alkenyltriflate **305** and *bis*-alkenyltriflate **306** in 38% yield and 22% yield respectively. The mono-alkenyltriflate could then be converted to *bis*-alkenyltriflate **306** via the usual procedure in 54% yield (Scheme 116).



Scheme 116: synthesis of *bis*-alkenyltriflate **306**

It was hoped that the increased steric hindrance offered by the size of phenyl ring attached directly to the quaternary centre would increase the enantioselectivity of the reaction, to produce the mono-ester in greater than the 95% *ee* achieved with *bis*-alkenyltriflate **222**. Disappointingly the phenyl substituted *bis*-alkenyltriflate **306** failed to undergo methoxycarbonylation, with near quantitative starting material again recoverable from the reaction mixture. Increases in both reaction time and temperature had no effect on this poor reactivity, only resulting in catalyst decomposition. This result may well be caused by the increased sterics around each of the alkenyltriflate moieties that is provided by direct attachment of the aryl unit to the cyclohexadiene core.

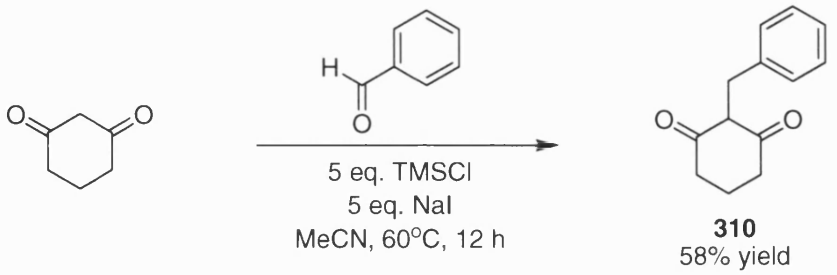
All *bis*-alkenyltriflates thus far had been based around a simple cyclohexadiene frame, with a quaternary centre bearing a methyl group, and another group of differing size or electronic nature. Further substrate variation was desired to extend the scope of the reaction. In the previous desymmetrising Suzuki chemistry performed within the group, the dimedone derived *bis*-alkenyltriflate **309** had been used to mimic this cyclohexadiene system, as complications occurred when substrates of the type investigated above were used (Chapter 3.1). This *bis*-alkenyltriflate had performed well in the Suzuki chemistry, so was synthesised for use in the carbonylative desymmetrisation. Alkylation of dimedone with benzyl bromide yielded diketone **307** in 61%, after which the two-step triflation process gave *bis*-alkenyltriflate **309** in 42% overall yield (Scheme 117).[315]



Scheme 117: preparation of *bis*-alkenyltriflate **309**

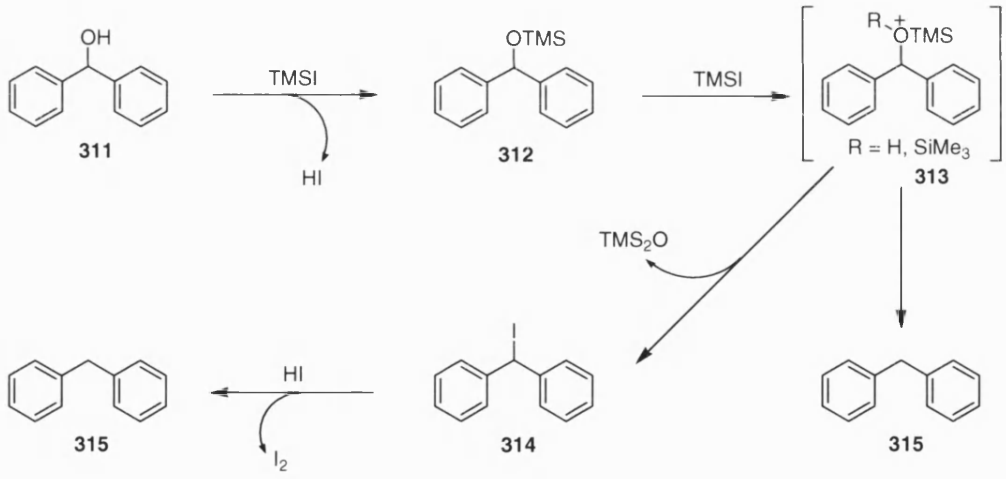
Frustratingly, as with phenyl-substituted *bis*-alkenyltriflate **306**, the dimedone derived *bis*-alkenyltriflate **309** failed to react at all when tested in the desymmetrisation reactions. Extended reaction times (up to 6 hours) and increased reaction temperatures (60°C) failed to promote the reaction, with almost complete recovery of starting material possible. As the only difference between this substrate and *bis*-alkenyltriflate **222** is the presence of the *gem*-dimethyl substituents on the cyclohexadiene frame it is logical to assume that these are responsible for the inability of *bis*-alkenyltriflate **309** to undergo the desymmetrising methoxycarbonylation reaction. These may add extra shielding to both of the enantiotopic faces of the molecule, to hinder approach of the bulky chiral catalyst.

To further probe this reaction, we aimed to explore the effects of replacing the methyl group at the quaternary centre with an alternative group, whilst retaining the benzyl group. Alkylation of 1,3-cyclohexanedione is known to often be a troublesome procedure, displaying surprisingly poor reactivity[346-348] or being prone to over-reaction with benzaldehyde to form a dimeric product.[349] This reaction was however made possible via methodology reported by Sakai *et al.*[350, 351] Reaction of 1,3-cyclohexane dione with benzaldehyde, TMSCl and sodium iodide yielded 2-benzyl diketone **310** in 58% yield (Scheme 118).



Scheme 118: preparation of 2-benzyl diketone **310**

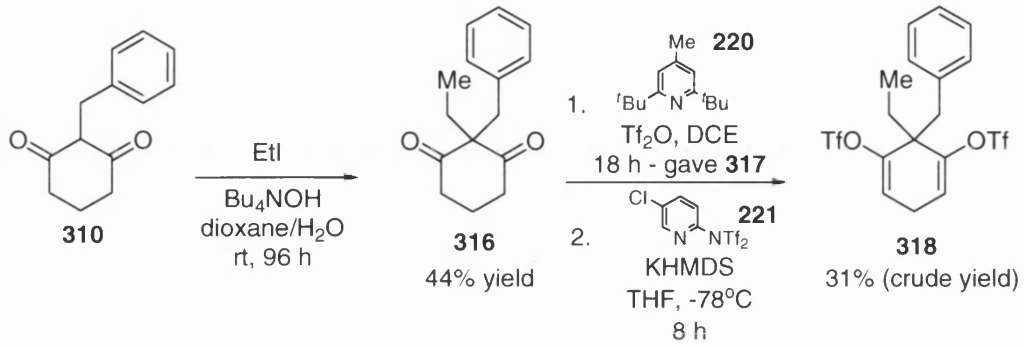
The exact mechanism of this process is not known, however there have been a number of possible explanations put forward by Sakai and Sako.[350-352] The most comprehensive investigation into this process has been proposed by Stoner *et al.* in his studies of benzhydrol.[353] After formation of a benzylic alcohol by either radical or aldol-type reaction, it was necessary to reduce this to the aliphatic compound. This was thought to proceed by *in situ* generation of TMSI, which could then react with **311** to form a silylated benzhydrol **312**. This may then undergo direct reduction, or form benzhydryl iodide **314**, which is in turn reduced by hydroiodic acid to give the desired product **315** (Scheme 119).



Scheme 119: proposed mechanism for TMSI reduction

It was also suggested through NMR studies that, as proposed by Sakai *et al.* the reaction appears to proceed *via* a carbonium cation intermediate at the reduction site, and TMSI reduction is facilitated by Lewis acid activation of the silyl intermediate, as suggested by transition state **313**.

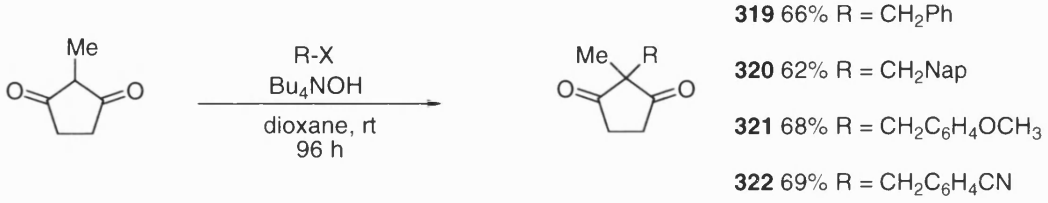
With diketone **310** in hand, alkylation was performed with ethyl iodide to form diketone **316** in 44% yield. Again, this reaction required a longer reaction time (96 hours) than those of allylic or benzylic bromides. Transformation to the *bis*-alkenyltriflate was problematic, and although the mono-alkenyltriflate **317** could be isolated cleanly, the *bis*-alkenyltriflate **318** was inseparable from two minor unknown products which could not be removed, even when mono-alkenyltriflate was converted to *bis*-alkenyltriflate **318** under pyridyl triflimide conditions (Scheme 120).



Scheme 120: synthesis of *bis*-alkenyltriflate **318**

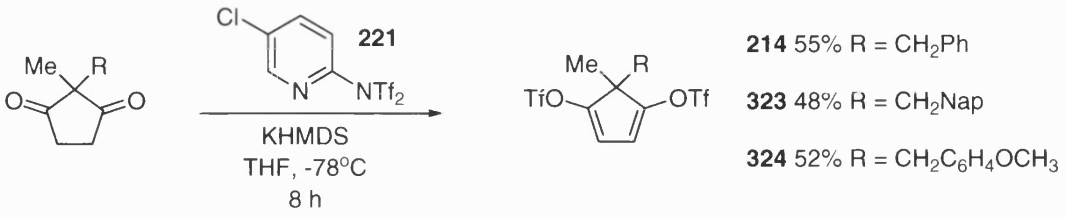
When desymmetrisation of *bis*-alkenyltriflate **318** was attempted, the crude mixture produced no identifiable products, other than a small amount of clean starting material recovered.

With these new substrates not showing the desired reactivity, it was decided to trial the cyclopentadiene *bis*-alkenyltriflates that had shown good reactivity in the Suzuki reactions performed on them. Their one-step preparation from the diketones rather than the sometimes-troublesome two-step sequence used for the cyclohexadiene *bis*-alkenyltriflates was also attractive. Alkylation of 2-methyl-1,3-cyclopentanedione with a range of benzylic halides produced the desired diketones in consistent yields of approximately 60% (Scheme 121).[310]



Scheme 121: synthesis of 2,2-dialkylcyclopentane diones

The diketones **319**, **320** and **321** were then converted in one step to their respective *bis*-alkenyltriflates with *N*-(5-chloro-2-pyridyl)triflimide **221** and KHMDS in good yields (Scheme 122).



Scheme 122: synthesis of cyclopentadiene *bis*-alkenyltriflates

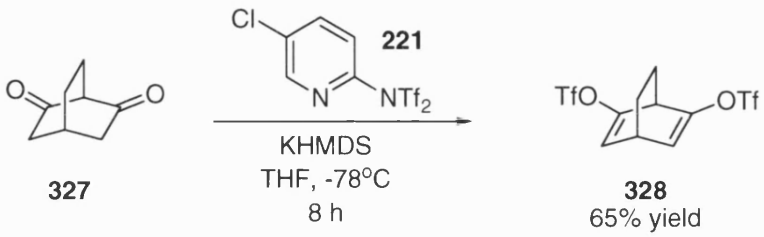
The electron-neutral *bis*-alkenyltriflate **214** was the first to be evaluated in the desymmetrisation reaction, however it produced none of the expected mono- or diester products. Instead, after two hours it gave a mixture of starting material and another compound, the NMR of which showed a similar vinylic-proton signal. Upon analysis of this unknown substance it was shown to be α,β–unsaturated diketone **325**, isolated in 41% yield (Figure 12). This compound was known from Suzuki reactions performed on this substrate, where it was occasionally formed in trace amounts, and had been shown be produced when *bis*-alkenyltriflate **214** was stirred in 1 M aqueous sodium hydroxide for extended time periods. It's appearance in this chemistry in such considerable yield was however unanticipated due to the mild conditions and short reaction time. When naphthyl *bis*-alkenyltriflate **323** was employed in the reaction, the analogous α,β–unsaturated diketone **326** was observed (Figure 12).

325
41% yield

326
33% yield

Figure 12: α,β–unsaturated diketones produced by *bis*-alkenyltriflates **214** and **323**

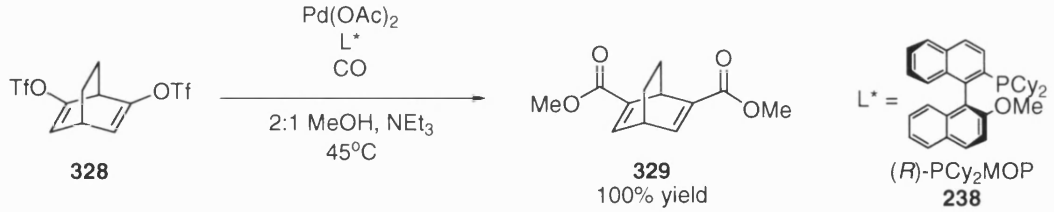
After it appeared that desymmetrisation of these cyclopentadiene *bis*-alkenyltriflates was not viable, attention switched to two substantially different targets. The bridged bicylic diketone **327** was prepared according to Frejd *et al.*[354] and then transformed into *bis*-alkenyltriflate **328** in 65% yield with the one-step triflation procedure used on the cyclopentadione substrates (Scheme 123).



327 **328**
65% yield

Scheme 123: synthesis of *bis*-alkenyltriflate **328**

The carbonylative desymmetrisation of *bis*-alkenyltriflate under standard conditions provided quantitative conversion to the diester **329** in two hours (Scheme 124). Reduction of the reaction time to 45 minutes again provided quantitative diester, and even after five minutes, a reaction which was quenched by plunging into an ice bath and removal of the carbon monoxide atmosphere contained an approximate 50:50 mixture of *bis*-alkenyltriflate:diester, with only trace amounts of what was believed to be the desired mono-ester visible. The extraordinary reactivity of this substrate could not however be repeated when the reaction was run at room temperature, producing small amounts of diester **329** with the majority of starting material recoverable. It may be that the bicyclic structure exposes the alkenyltriflates and has minimal steric clash with the approaching catalyst. The lack of a quaternary carbon centre may also be responsible for the exceptional reactivity of this substrate as there is minimal hindrance around the alkenyltriflates.

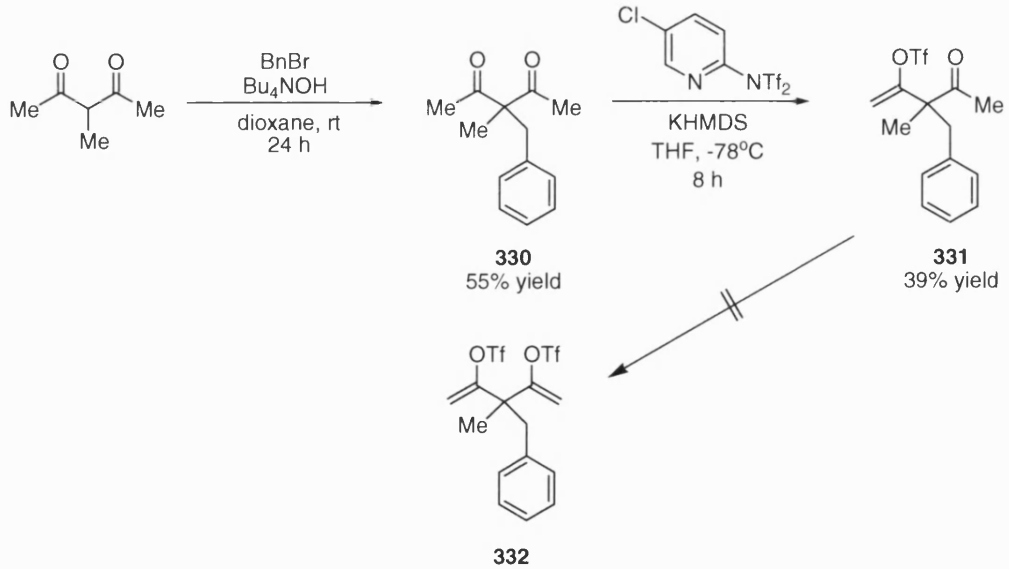


328 **329** 100% yield (*R*)-PCy_2MOP **238**

Reaction conditions: *bis*-alkenyltriflate **328** (0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL)

Scheme 124: the rapid reaction of *bis*-alkenyltriflate **328**

One further structurally different substrate undertaken was acyclic *bis*-alkenyltriflate **332**. After alkylation of 3-methyl-2,4-pentanedione with benzyl bromide to form **330**, attempted triflation with 2,6-di-*tert*-butyl-4-methylpyridine and triflic anhydride resulted in polymerisation of the reaction mixture. It was possible to synthesise mono-alkenyltriflate **331** in 39% yield *via* reaction with the pyridyl triflimide and KHMDS, however none of the desired *bis*-alkenyltriflate was isolated from this reaction, despite using 2.2 equivalents of both reagents. Once isolated, mono-alkenyltriflate **331** was re-subjected to these triflation conditions but with no success and starting material recovered every time (Scheme 125).



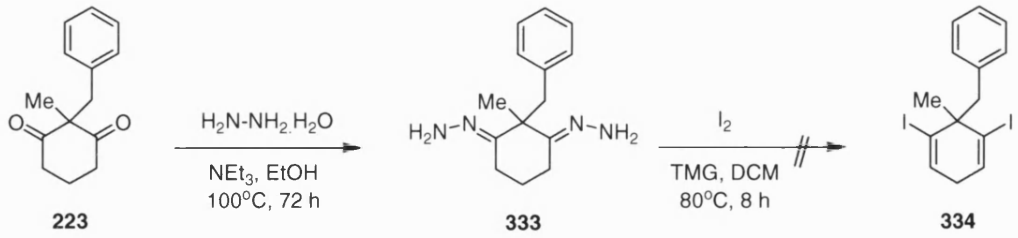
330 55% yield **331** 39% yield **332**

Scheme 125: attempted synthesis of *bis*-alkenyltriflate **332**

In conclusion, a number of substrates based around a cyclohexadiene core were synthesised. Those that were able to undergo methoxycarbonylation did so in reasonable yield and generally excellent *ee*. Aryl and alkenyl substituted diketones were significantly more reactive than those with bulky aliphatic substituents, however smaller aliphatic groups (*n*-propyl, ethyl) allowed the desymmetrisation to take place and performed well. None of the substrates investigated had a profound effect on the ratio of the ester products. Those substrates with different ring size or varied core-structure gave widely varied results, some failing to react at all.

3.8 - Alternative activating groups

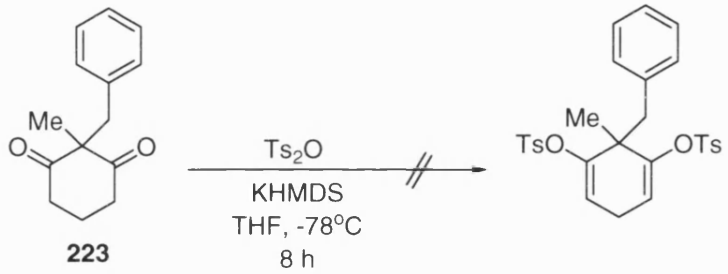
Throughout the study so far alkenyltriflates had been the focus of attention, however many other groups have the ability to undergo oxidative addition of the *C-X* bond with palladium catalysts. The most common of these are vinylhalides, with both vinyliodides and bromides being ubiquitous in palladium chemistry. It was thought that the use of a different activating group may lead to altered reactivity and give valuable information for improving the efficiency of the reaction. The simple 2-benzyl-2-methyl cyclohexane dione **223** was chosen for investigation, as alternative substrates had not displayed beneficiary effects. Refluxing with hydrazine hydrate in ethanol for 72 hours in a Shapiro-type reaction yielded crude dihydrazone **333**, to which was added iodine and tetramethylguanidine in the hope of synthesising *bis*-vinyliodide **334**. However none of the expected product was isolated, with a mixture of what was thought to be *gem*-diiodinated products predominating (Scheme 126).



Scheme 126: attempted synthesis of *bis*-vinyliodide **334**

In more recent times, aryl- and alkenyltosylates have been receiving more attention as activating groups in palladium chemistry.[355-357] This sulfonate group

offers many benefits including general low toxicity, ease of synthesis and low manufacturing costs in comparison to their respective aryl- and alkenyltriflates. Whilst the ability of tosylates to undergo oxidative addition to palladium is thought to be less than triflates, it was thought this may indeed benefit this study, as the majority of substrates were prone to over-reaction and already required short reaction times and mild conditions. Previous work in the group had focussed on the synthesis and application of alkenyltosylates in palladium catalysed processes, with these compounds being readily available through reaction of a ketone with KHMDS and tosylic anhydride. This had been used to synthesise a range of simple alkenyltosylates, however when this methodology was used diketone **223** failed to react at all, producing none of the desired mono- or *bis*-alkenyltosylate (Scheme 127).

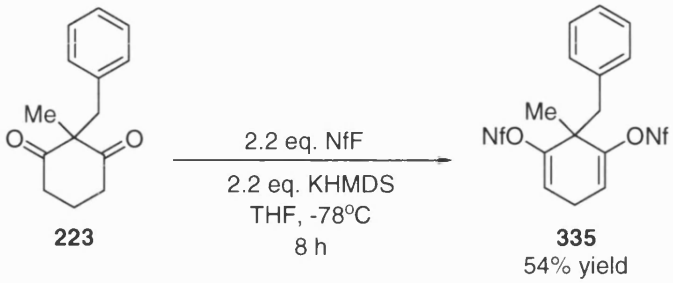


Scheme 127: attempted synthesis of an alkenyltosylate

Even when the mono-alkenyltosylate was targeted, with α-deprotonation of diketone **223** performed first by KHMDS, followed by slow addition of either tosylic anhydride or tosyl chloride no product was seen. When tosylic anhydride was employed in conjunction with 2,6-di-*tert*-butyl-4-methylpyridine in a similar manner to the original triflation conditions the reaction was again unsuccessful. The problems in alkenyltosylate production were thought to be heavily affected by the proximity of the quaternary carbon centre, as previous studies had used more simple, unsubstitued ketones.

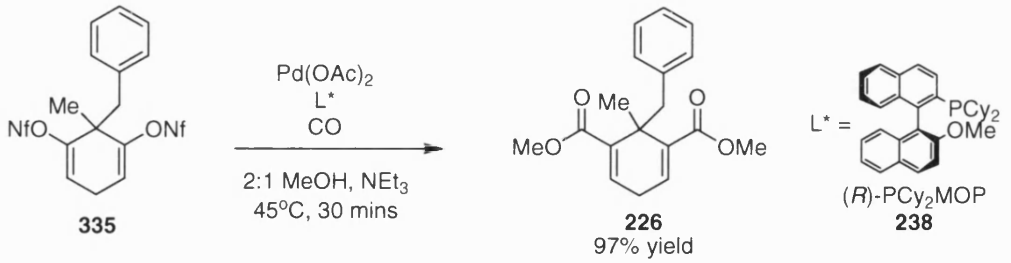
Other than triflates, nonaflates (nonafluorobutanesulfonates) are another common activating group based on a sulfonate bearing a fluorinated carbon chain. Synthesis of aryl nonaflates of phenols is easily achieved by stirring with nonaflyl fluoride and a weak base (e.g. triethylamine), and they have been found to perform well in various palladium-catalysed coupling reactions.[358, 359] In order to synthesise the desired *bis*-alkenylnonaflate a stronger base than

triethylamine would be required, as this would not be sufficient to form the enolate of cyclic dione **223**. Pleasingly, on first attempt, reaction of diketone **223** with nonaflyl fluoride in the presence of KHMDS yielded *bis*-alkenylnonaflate **335** in reasonable yield (Scheme 128). None of the mono-alkenylnonaflate could be isolated from this reaction.



Scheme 128: synthesis of *bis*-alkenylnonaflate **335**

When subjected to the palladium-catalysed desymmetrisation reaction *bis*-alkenylnonaflate **335** was extremely active, providing quantitative conversion to diester **226** in just one hour (Scheme 129). Reduction of the reaction time to just thirty minutes again provided quantitative diester, and when run at room temperature the reaction became extremely sluggish and resulted in catalyst decomposition prior to any significant conversion.

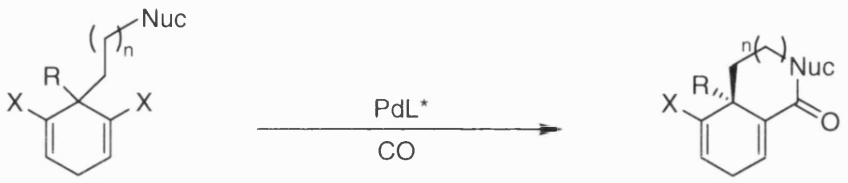


Reaction conditions: *bis*-alkenylnonaflate **335** (81 mg, 0.104 mmol), $Pd(OAc)_2$ (2.3 mg, 10 mol%), L* (5.0 mg, 10 mol%), CO (1 atm balloon), NEt_3 (0.33 mL), MeOH (0.66 mL)

Scheme 129: the carbonylation of *bis*-alkenylnonaflate **335**

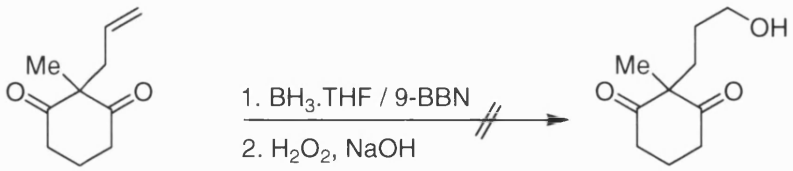
3.9 - Steps towards an intramolecular reaction

In order to remove all possibility of the unwanted achiral *bis*-coupled products being formed in this reaction one potential solution would be to only have one equivalent of nucleophile available to couple. Whilst this principle had failed to produce satisfactory results in intermolecular reactions using an alcohol (i.e. methanol) it was hoped that development of an intramolecular process could curb this over-reactivity. A *bis*-activated substrate bearing a nucleophilic group could potentially solve this problem, as once the coupling reaction had occurred the nucleophilic species would have been consumed, and barring intermolecular reaction with another molecule no further reaction could occur (Scheme 130). It was hoped that this reaction could then be driven to completion to afford high yields of the cyclic product.



Scheme 130: a proposed intramolecular reaction

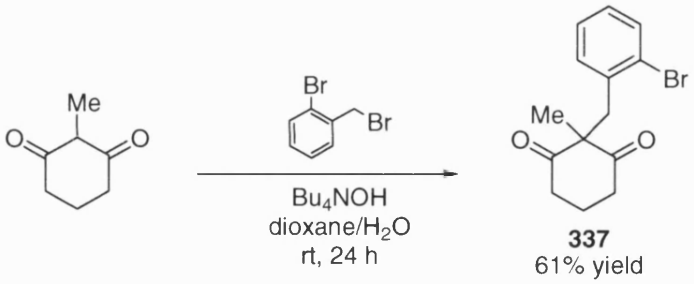
As *n*-propyl *bis*-alkenyltriflate had shown good reactivity and enantioselectivity it was chosen as the model substrate for initial investigations. Installing a free hydroxyl functionality in this system was thought to encounter problems, as protection/deprotection of said group at some point was probably necessary. Hydroboration-oxidation of allyl *bis*-alkenyltriflate **288** with both borane-THF complex and 9-BBN produced a number of unidentifiable compounds, presumably through poor selectivity and multiple reactions taking place at the alkenyltriflate groups as well as the terminal allyl functionality. Similar problems were encountered in functionalisation of it's parent diketone **285**, where attempted hydroboration-oxidation did not provide the desired terminal alcohol **336** (Scheme 131).



285 **336**

Scheme 131: failed hydroboration-oxidation of allyl diketone **285** and *bis*-alkenyltriflate **288**

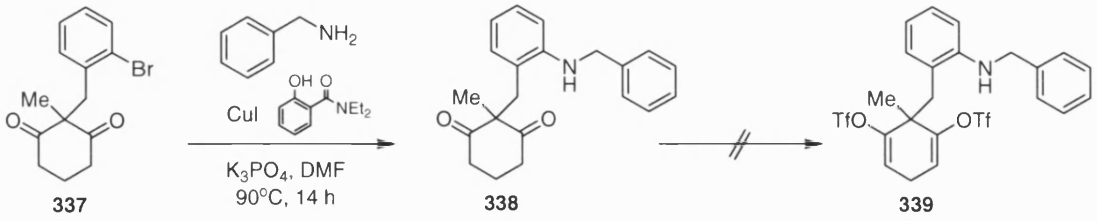
An alternative pathway was required to install a free hydroxyl group on the *bis*-alkenyltriflate frame. It was decided to try to synthesise a 2-hydroxy/amino benzyl unit to mimic simple *bis*-alkenyltriflate **222**, the phenol/aniline of which could cyclise to form the corresponding lactone/lactam. Alkylation of 2-methyl-1,3-cyclohexanedione with 2-bromobenzyl bromide afforded bromo diketone **337** in 61% yield, with the aim of the arylbromide providing a handle for further reactions (Scheme 132).



337
61% yield

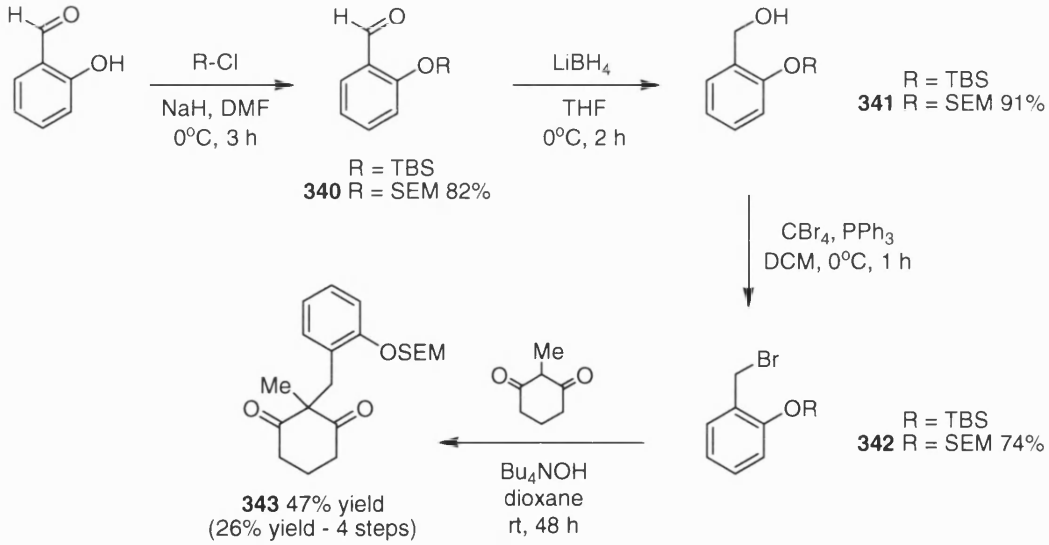
Scheme 132: synthesis of bromo diketone **337**

Functionalisation of this 2-bromophenyl unit to install a free hydroxyl group by reaction with *tert*-butyllithium and either camphoroxaziridine or Davis' oxaziridine failed.[360] A copper-catalysed amination developed by Buchwald produced benzyl amine **338** in good yield however it was inseparable from a small amount of a byproduct and attempted conversion to the *bis*-alkenyltriflate **339** resulted in decomposition of the starting material (Scheme 133).



Scheme 133: attempted synthesis of a lactam-forming substrate

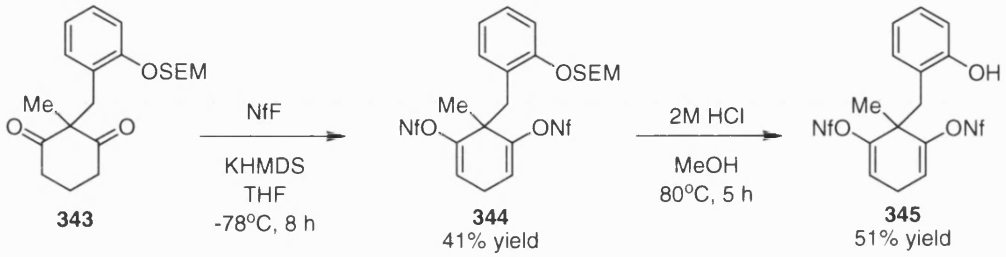
With the difficulties encountered so far, it was decided to incorporate a protected phenol into the alkylation process, which could later be unmasked in the final stages of substrate synthesis. The phenol salicylaldehyde was first protected with one of two silyl groups (TBS and SEM), followed by reduction of the aldehyde with lithium borohydride and transformation to the benzyl bromide.[361] When the alkylation reaction was performed on 2-methyl-1,3-cyclohexanedione the TBS protected benzyl bromide produced almost exclusively the unwanted *O*-alkylated product, presumably due to steric hindrance of the TBS group making attack at the methyl-substituted *C*-2 position of the diketone less favourable. In contrast to this, the SEM protected benzyl bromide was able to perform *C*-alkylation to yield diketone **343** in 47% yield, 26% overall yield based on salicylaldehyde (Scheme 134).



Scheme 134: synthesis of SEM-protected diketone **343**

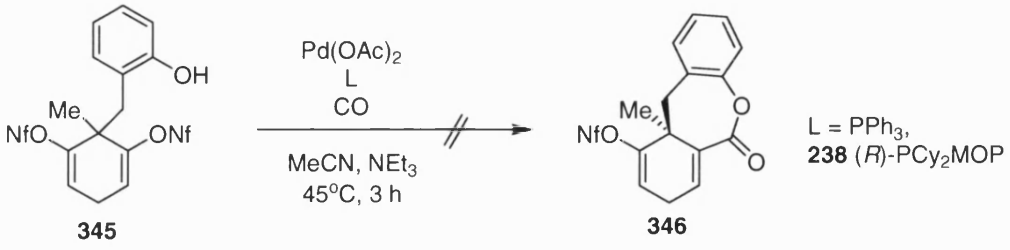
Triflation of this SEM-protected diketone unfortunately resulted in none of the alkenyltriflate products, with degradation of starting material and nothing

recoverable. Given that synthesis of *bis*-alkenylnonaflate **335** had been so facile, and it had shown even greater reactivity than its' analogous *bis*-alkenyltriflate, synthesis of the *bis*-alkenylnonaflate of SEM-protected diketone **343** was undertaken. Under the same conditions applied to diketone **223**, the SEM-protected *bis*-alkenylnonaflate **344** was formed in 41% yield. Deprotection of the SEM group was unsuccessful with TBAF, cesium fluoride and lithium tetrafluoroborate, however the free phenol was eventually attained by 2 $M_{(aq)}$ hydrochloric acid in methanol, after heating at 80°C for five hours to yield *bis*-alkenylnonaflate **345** in 51% (Scheme 135).



Scheme 135: synthesis of *bis*-alkenylnonaflate **344** followed by SEM deprotection

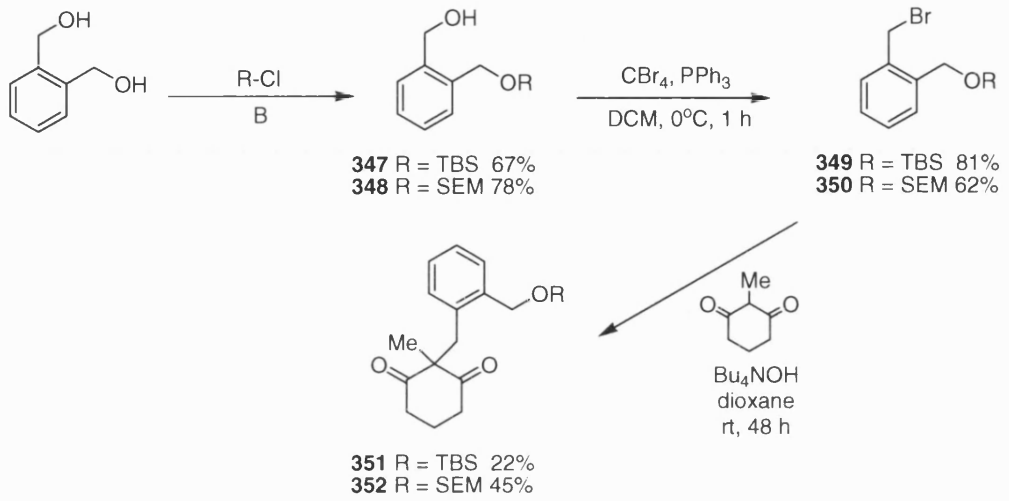
Once deprotected, *bis*-alkenylnonaflate **345** was subjected to the desymmetrisation conditions. The non-nucleophilic solvent acetonitrile was used in place of methanol to avoid any methoxycarbonylation, and whilst complete consumption of starting material was observed after 3 hours in both racemic and enantioselective reactions, none of the products isolated after flash chromatography could be identified as the expected lactone **346** (Scheme 136).



Scheme 136: unsuccessful lactonisation reaction of *bis*-alkenylnonaflate **346**

One possible reason thought to be hindering the formation of lactone **346** was the presence in the ring of a number of sp^2 carbon centres (aryl, vinyl and

carbonyl), which may give the system a rigid structure that could not accommodate the 7-membered ring motif. It was postulated that extension of this ring by cyclisation of a benzylic alcohol rather than a phenol may allow more structural flexibility and lead to an effective intramolecular variant. Mono-protection of 1,2-benzenedimethanol with both TBS-Cl and SEM-Cl was followed by bromination of the remaining benzylic alcohol. Alkylation of 2-methyl-1,3-cyclohexanedione followed, to give the respective benzyl alcohol protected derivatives **351** and **352** (Scheme 137).



Scheme 137: synthesis of silyl-protected diketones **351** and **352**

Unfortunately, SEM-protected diketone **352** could not be elaborated to its *bis*-alkenylnonaflate, as the reaction conditions resulted in apparent desilylation and decomposition products. Surprisingly, the TBS-protected diketone **351** proved more robust when the same reaction was performed, providing a 42% yield of its *bis*-alkenylnonaflate **353**. Deprotection of the TBS group was less efficacious than before, with all the conditions (TBAF, CsF, HCl/MeOH) either having no effect or destroying the starting material. As a result of this, the intramolecular reaction of a benzylic alcohol could not be evaluated.

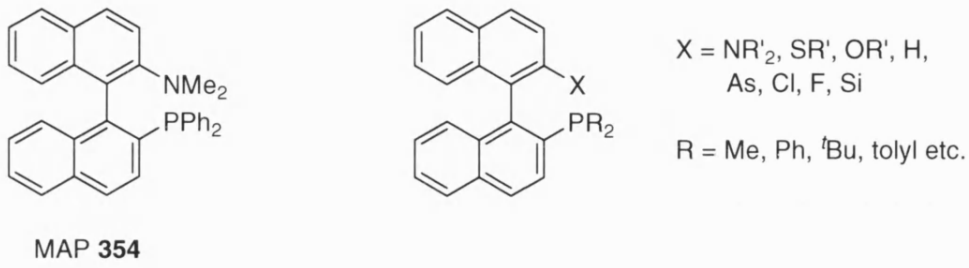
Chapter 4: Conclusions

The catalytic enantioselective desymmetrisation of *bis*-alkenyltriflate **222** has been achieved by palladium-catalysed carbonylation. This provided the mono-ester product in excellent *ee* (up to 97%), and reasonable yield (approx. 40%). The reaction was also applicable to a range of alcohol coupling partners, showing little or no detriment to either yield or enantioselectivity, however coupling of amines proved problematic. The high enantioselectivities seen in this reaction were partly due to the presence of a kinetic resolution, which preferentially removed the minor enantiomer of the mono-ester *via* a second coupling reaction to form an achiral diester. Formation of this undesired diester was prevalent in a number of reactions performed, with its formation being more favourable than that of the desymmetrised mono-ester, confirmed by investigation of the mechanistic aspects and rate of the reaction. Variation of the substrate structure was also performed at the quaternary carbon centre, with enantiotopic groups of different size and electronic nature explored including aryl, alkenyl and aliphatic substituents. Several substrates of different core-structure were also evaluated, providing mixed results of unexpected products, limited reactivity or pronounced over-reactivity.

In order to stem the production of the undesired diester products a number of avenues were explored such as the use of polymer-supported alcohols, however this methodology only resulted in diester formation. Studies into developing an intramolecular process to combat this problem of diester formation produced interesting compounds that unfortunately could not be reacted in the expected manner, due to either problems in their synthesis or unidentifiable coupled products.

Although attempts to effect an intramolecular desymmetrisation failed, I believe this may still be the key to achieving high mono-ester yields. With the reactivity demonstrated by the majority of these *bis*-alkenyltriflate substrates it is obvious that intermolecular reactions are very fast. In theory, this should make the intramolecular cyclisation an extremely feasible process which, with the right ligand, could provide the bicyclic products in near quantitative yield. Further derivatisation of both the remaining alkenyltriflate moiety and lactone could readily yield large libraries of compounds that may provide access to short routes to codeine-based natural products. Ligand variation may yet provide the

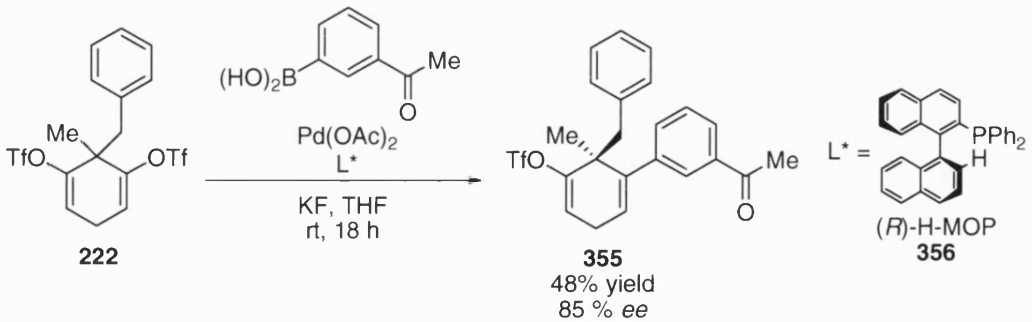
key to a truly enantioselective process in which the chiral catalyst is so substrate specific that the mono-coupled products can no longer react to form the achiral diesters. The most successful ligands tested so far were hemi-labile bidentate in nature, and based around a binaphthyl backbone. Exploration of both the phosphine and heteroatom to form ligands such as the dimethylamino phosphine MAP **354** may be the ligands that enable this desymmetrisation process to be more efficient (Figure 13).[334]



MAP **354**

Figure 13: possible ligands for desymmetrisation

Future work in this area should be aimed at investigating the *bis*-alkenyltriflates synthesised in this study in the desymmetrising Suzuki reactions. Recently Fu has reported mild conditions for a number of Suzuki reactions of aryl- and alkenyltriflates, using potassium fluoride as a base and THF as solvent.[362, 363] An enantioselective test reaction performed under these conditions on *bis*-alkenyltriflate **222** gave the mono-coupled product **355** in 48% yield and 85% *ee* with ligand **356** (Scheme 138), whereas previous attempts to react this substrate had given extremely poor results.



222

355
48% yield
85 % *ee*

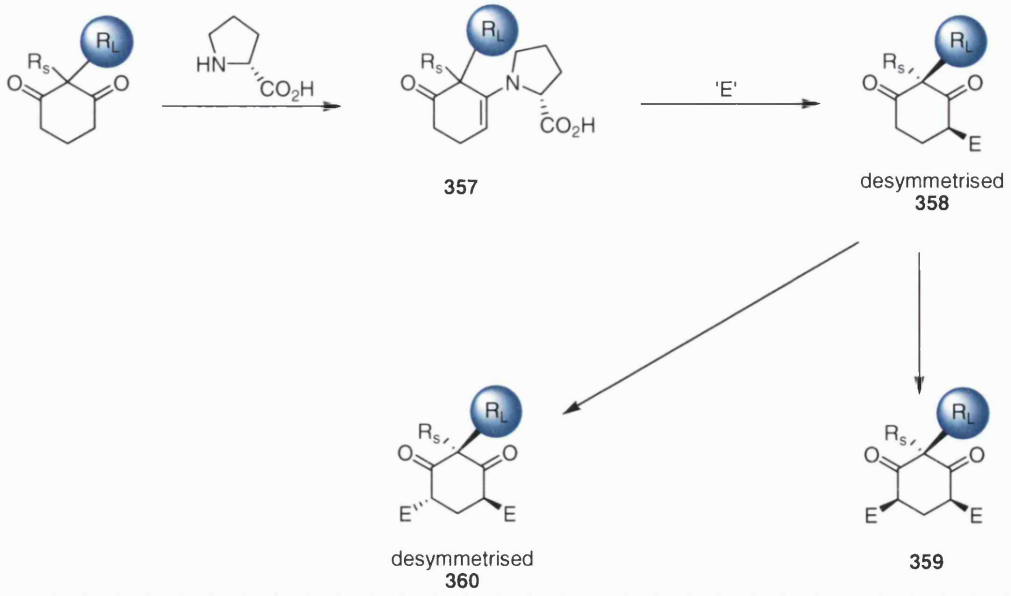
(*R*)-H-MOP
356

Reaction conditions: *bis*-alkenyltriflate **222** (100 mg, 0.208 mmol), 3-acetyl phenylboronic acid (51 mg, 0.312 mmol), $Pd(OAc)_2$ (4.6 mg, 10 mol%), L* (9.1 mg, 10 mol%), KF (36 mg, 0.624 mmol), THF (2 mL), rt, 18 h

Scheme 138: improved Suzuki reaction of *bis*-alkenyltriflate **222**

Both starting material and boronic acid remained at the end of this reaction and only trace amounts of *bis*-coupled product were seen, indicating that by moderate variation of reaction conditions the mono-coupled product could be attained in increased yield. This *bis*-alkenyltriflate methodology may be more suited to Suzuki chemistry, where the possibility exists to add more electron-rich groups to the cyclohexadiene core which may result in the second undesired oxidative addition becoming less favourable, as opposed to the carbonylative chemistry which, by nature, adds electron-withdrawing fragments.

One final area of research may involve applying this desymmetrisation methodology to the *bis*-alkenyltriflate precursors, the cyclic 1,3-diones. These substrates still contain the mirror plane feature, essential for the enantioselective desymmetrisation principle, but are easier to synthesise as they do not require the often-messy triflation procedures used to create the *bis*-alkenyltriflate compounds. Although processes such as α-deprotonation by a chiral base, followed by electrophile addition could be successful in desymmetrising these cyclic diones, a potentially more interesting procedure could make use of organocatalysts such as proline or the imidazolidinones developed by MacMillan.[364-366] The steric or electronic differences between the enantiotopic faces of these cyclic diones may aid a chiral organocatalyst in performing the α–functionalisation *via* either an enamine or iminium intermediate **357** with high enantioselectivity to produce diastereomeric products **358** and essentially create two chiral centres in one step. As the desymmetrisation step could create a new chiral centre, over-reaction of these cyclic diones to produce *bis*-α-functionalised products could result in the creation of another chiral centre that would either have achieved the formation of three chiral centres in one step (**360**), or a molecule containing a mirror plane but with two stereodefined centres (**359**) (Scheme 139).



Scheme 139: the organocatalytic desymmetrisation of a cyclic 1,3-dione

This organocatalytic methodology may provide the opportunity to create small, highly functionalised compounds with multiple stereocentres in very few steps, extending this theory to non-metal based enantioselective desymmetrisations.

Experimental

General Considerations

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, using the residual solvent or tetramethylsilane (δ_H = 0 ppm) as an internal standard. *J* values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 75 MHz, unless otherwise noted, using the residual solvent as an internal standard. Signals in these spectra for C_4F_9 groups of nonaflates were not observed. Mass spectroscopy measurements were performed at the EPSRC National Spectrometry Service Centre, University of Wales, Swansea, or at the Mass Spectrometry Service, University of Bath. All accurate mass measurements are reported for the lighter isotopes. Elemental analyses were performed at the microanalysis service, University of Bath, using an Exeter Analytical Inc. CE-440 elemental analyser.

Anhydrous acetonitrile, Et_2O, DCM, hexane, THF, toluene and methanol were obtained by passing through anhydrous alumina columns[367] using an Innovative Technology Inc. PS-400-7 solvent purification system. Dioxane, DME, DIPEA, triethylamine, pyridine and DCE were distilled over calcium hydride and stored over 4Å moleculer sieves. DMF was distilled under reduced pressure over 4Å molecular sieves and stored over 4Å molecular sieves. *tert*-Butanol, *iso*-propanol and ethanol were distilled over $MgSO_4$ and stored over 4Å molecular sieves. Acetone was distilled over Drierite™ and stored over 4Å molecular sieves. Nitrogen was passed through a Drierite™ filled drying tube before use. Petroleum ether refers to the fraction obtained between 40-60°C.

All glassware was dried in an oven at 180°C and allowed to cool under a constant stream of nitrogen prior to use. All commercial reagents were used as obtained.

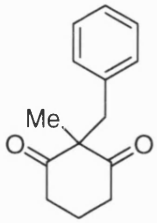
The phosphine ligands were purchased from Aldrich chemical company or Strem chemicals, with the exception of those synthesised according to Hayashi [318, 368] and Buchwald.[369]

Flash column chromatography was conducted under medium pressure, using Merck Kieselgel 60H silica. HPLC was performed on either an Agilent 1100 Series or Dionex P680 HPLC with detection at 254 nm, using OD-H and OJ-H columns and with a flow rate of 0.50-1.00 mL/min of hexane/*iso*-propanol (approx 99.8:2) after 30 minutes equilibration time.

General procedure A: The preparation of 2,2-dialkyl-1,3-cyclic diketones

To a stirred solution of 2-methyl-1,3-cyclic diketone (39.7 mmol) and tetrabutyl ammonium hydroxide (40% w/w in water, 27.0 mL, 41.6 mmol) in dioxane (30 mL) was added alkyl bromide (60.3 mmol). The reaction was stirred at room temperature for 24 h, then 1M $HCl_{(aq)}$ (200 mL) and ethyl acetate (100 mL) were added. The layers were partitioned and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The organic portions were combined and washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce an orange oil which was purified by flash chromatography (solvents as stated).

2-Benzyl-2-methyl-cyclohexane-1,3-dione (223)



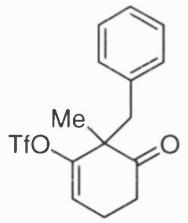
Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and benzyl bromide (8.39 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **223** (5.30 g, 62%) as white crystalline needles; δ_H (300 MHz, $CDCl_3$) 7.28-7.16 (3H, m, 2 × Ar-*H*), 7.04-6.99 (2H, m, 2 × Ar-*H*), 3.11 (2H, s, CCH_2Ar), 2.60-2.48 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.35-2.23 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.80-1.67 (1H, m, $CH_AH_BCH_2CO$), 1.55-1.42 (1H, m, $CH_AH_BCH_2CO$), 1.28 (3H, s, CH_3CCO); δ_C

(75 MHz, $CDCl_3$) 211.8, 137.1, 130.3, 128.8, 127.4, 65.7, 44.3, 39.7, 22.5, 17.0. Data consistent with literature.[370]

General procedure B: The preparation of 2,2-dialkyl-1-alkenyltriflate-3-cyclohexanones

A stirred solution of 2,2-dialkyl-1,3-cyclohexanedione (0.93 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (418 mg, 2.04 mmol) in anhydrous DCE (5 mL) was cooled to 0°C. To this was added trifluoromethanesulfonic anhydride (0.33 mL, 1.94 mmol), dropwise. The reaction was then heated at 80°C for 18 h, after which it was allowed to cool to room temperature. Diethyl ether (40 mL) was added, and the white pyridinium triflate salt was removed by filtration, washing with diethyl ether. The filtrate was concentrated under reduced pressure to produce a dark oil which was purified by flash chromatography (solvents as stated).

Trifluoro-methanesulfonic acid 6-benzyl-6-methyl-5-oxo-cyclohex-1-enyl ester (224)

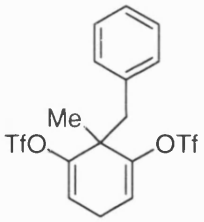


Prepared using general procedure **B** from diketone **223** (201 mg, 0.93 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **224** (188 mg, 58%) as a yellow oil. ν_{max} (film)/cm^{-1} 3065 (C-H), 2936 (C-H), 1722 (C=O), 1680 (C=C), 1416 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.28-7.20 (3H, m, 2 × Ar-*H*), 7.08-7.02 (2H, m, 2 × Ar-*H*), 5.97 (1H, dd (app. t), *J* 4.7 and 4.7, $CH_2CHCOSO_2$), 3.17 (1H, d, *J* 13.5, CCH_AH_BAr), 2.83 (1H, d, *J* 13.5, CCH_AH_BAr), 2.40-2.32 (1H, m, $CH_2CH_AH_BCO$), 2.21-2.12 (1H, m, $CH_2CH_AH_BCO$), 1.98-1.90 (1H, m, $CH_AH_BCH_2CO$), 1.74-1.65 (1H, m, $CH_AH_BCH_2CO$), 1.43 (3H, s, CH_3CCO); δ_C (100 MHz, $CDCl_3$) 209.4, 149.6, 136.3, 130.1, 128.5, 128.2, 118.8, 117.9, 54.8, 43.1, 37.1, 23.4, 19.6. Data consistent with literature.[315]

General procedure C: The preparation of 2,2-dialkyl-1,3-cyclohexadienyl *bis*-alkenyltriflates

A stirred solution of 2,2-dialkyl-1-alkenyltriflate-3-cyclohexanone (0.64 mmol) and 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine **221** (0.30 g, 0.77 mmol) in anhydrous THF (10 ml) was cooled to -78°C. To this was added potassium hexamethyldisilazide (0.5M in toluene, 1.53 mL, 0.77 mmol), dropwise over 15 minutes. The reaction was stirred at -78°C for 2 h, then warmed to room temperature and stirred for a further 4 h. The mixture was then diluted with hexane (30 mL), and washed with water (20 mL), 10% $NaOH_{(aq)}$ (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce a dark oil which was purified by flash chromatography (solvents as stated).

Trifluoro-methanesulfonic acid 6-benzyl-6-methyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (222)

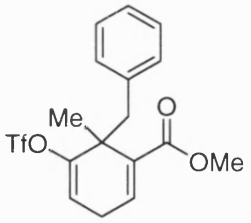


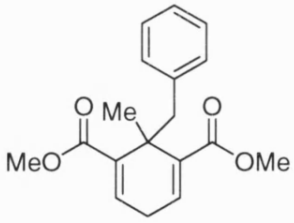
Prepared using general procedure **C** from mono-alkenyltriflate **224** (223 mg, 0.64 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **222** (227 g, 74%) as white needles. mp 89-91°C (hexane) ν_{max} (film)/cm^{-1} 3054 (C-H), 2987 (C-H), 1673 (C=C), 1418 (O-SO_2), 1141 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.29-7.21 (3H, m, 3 × Ar-*H*), 7.10-7.06 (2H, m, 2 × Ar-*H*), 5.69 (2H, dd (app.t), *J* 3.9 and 3.5, 2 × $CH_2CHCOSO_2$), 2.87 (2H, s, CCH_2Ar), 2.76 (1H, dt, *J* 22.8 and 3.9, CH_AH_BCHCO), 2.33 (1H, dt, *J* 22.8 and 3.5, CH_AH_BCHCO), 1.55 (3H, s, CH_3CCOSO_2); δ_C (100 MHz, $CDCl_3$) 147.7, 135.0, 130.1, 128.5, 127.4, 118.7, 114.2, 45.9, 42.1, 24.5, 23.1. Data consistent with literature.[315]

General procedure D: The enantioselective methoxycarbonylation of *bis*-alkenyltriflates

An oven dried Schlenk tube was charged with *bis*-alkenyltriflate (0.104 mmol), palladium (II) acetate (2.3 mg, 0.0104 mmol) and PCy_2-MOP **238** (5.0 mg, 0.0104 mmol). To this was added anhydrous methanol (0.66 mL) and anhydrous triethylamine (0.33 mL). The Schlenk tube was purged with nitrogen, and then fitted with a balloon of carbon monoxide (previously back-filled with N_2 and purged three times) with a glass tap attachment. The vessel was purged under vacuum, and filled with carbon monoxide using the balloon. This process was repeated three times. The reaction was then left open to the balloon, and heated at 45°C in a pre-heated oil bath for 2 h. The reaction was then cooled to room temperature, diluted with diethyl ether (5 mL) and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (solvents as stated).

6-Benzyl-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid methyl ester (225) and 2-benzyl-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (226)

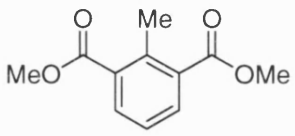




Prepared using general procedure **D** from *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **225** (15.4 mg, 38%, 95% *ee*) as a colourless oil. $[\alpha]_D^{20}$ = +5.4 (c. 0.021 in DCM) ν_{max} (neat)/cm^{-1} 3063, 3030, 2952 (CH sat.), 2884 (CH sat.), 1719 (C=O), 1696 (C=C), 1416 (O-SO_2), 1213 (O-SO_2), 1142 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.20-7.15 (3H, m, 3 × Ar-*H*), 7.02-6.99 (2H, m, 2 × Ar-*H*), 6.76 (1H, dd (app. t), *J* 3.5 and 3.5, CH_2CHCCO_2), 5.67 (1H, dd (app. t), *J* 3.5 and 3.5, $CH_2CHCOSO_2$), 3.81 (3H, s, CH_3OCO), 3.51 (1H, d, *J* 13.4, $ArCH_AH_BCCH_3$), 2.85 (1H, d, *J* 13.4, $ArCH_AH_BCCH_3$), 2.74 (1H, ddd (app. dt), *J* 24.0, 4.1 and 4.1, $CH_AH_BCHCOSO_2$), 2.28 (1H, ddd (app. dt), *J* 24.0, 3.3 and 3.3, $CH_AH_BCHCOSO_2$), 1.63 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 166.5, 151.1,

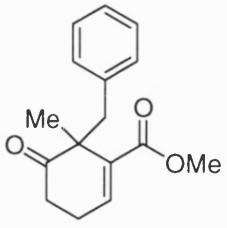
138.0, 137.2, 132.9, 130.2, 128.1, 126.7, 118.8, 113.5, 52.2, 43.9, 42.2, 26.9, 24.3; *m/z* (FAB$^+$) 390.9 ([M+H]$^+$, 20%); HRMS calc. for $C_{17}H_{18}F_3O_5S$: 390.0749 [M+H]$^+$; found: 390.0732 [M+H]$^+$ and diester **226** (14 mg, 45%) as a colourless oil. ν_{max} (Nujol)/cm^{-1} 3061, 3028, 2988 (CH sat.), 2950 (CH sat.), 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 7.13-7.11 (3H, m, 3 × Ar-*H*), 6.98-6.95 (2H, m, 2 × Ar-*H*), 6.69 (2H, overlapping dd, *J* 4.4 and 3.0, 2 × CH_2CHCCO_2), 3.80 (6H, s, 2 × CH_3OCOC), 3.50 (2H, s, $ArCH_2CCO$), 2.58 (1H, dt, *J* 24.9 and 4.5 CH_AH_BCHCCO), 2.00 (1H, dt, *J* 24.9 and 3.0, CH_AH_BCHCCO), 1.68 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 167.8, 139.8, 136.1, 135.4, 130.6, 127.7, 126.1, 52.0, 43.1, 42.2, 27.5, 25.8; *m/z* (FAB$^+$) 301.0 ([M+H]$^+$, 25%); HRMS calc. for $C_{18}H_{21}O_4$: 301.1440 [M+H]$^+$; found: 301.1440 [M+H]$^+$.

2-Methyl-isophthalic acid dimethyl ester (227)



Prepared using general procedure **D** from *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield diester **227** (18.6 mg, 86%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 7.8, 2 × Ar-*H*), 7.28 (1H, t, *J* 7.8, Ar-*H*), 3.91 (6H, s, 2 × CO_2CH_3), 2.69 (3H, s, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 168.3, 139.6, 132.8, 132.7, 125.4, 52.2, 18.0. Data consistent with literature.[371]

6-Benzyl-6-methyl-5-oxo-cyclohex-1-enecarboxylic acid methyl ester (240)



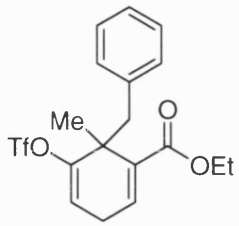
Prepared according to general procedure **D** using mono-alkenyltriflate **224** (36.0 mg, 0.104 mmol) and purified by flash chromatography (hexane:EtOAc

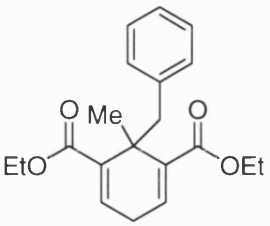
5:1) to yield keto-ester **240** (25.2 mg, 94%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3029 (C-H), 2934 (C-H), 1713 (C=O), 1496, 1436, 1360, 1302, 1246, 1188, 1075, 1044; δ_H (300 MHz, $CDCl_3$) 7.20-7.13 (3H, m, 3 x Ar-*H*), 7.09-7.06 (1H, m, $CH_2CHCCO_2CH_3$), 6.96-6.93 (2H, m, 2 x Ar-*H*), 3.82 (3H, s, CH_3OCO), 3.40 (1H, d, *J* 13.1, $ArCH_AH_BCCO$), 3.28 (1H, d, *J* 13.1, $ArCH_AH_BCCO$), 2.41-2.19 (2H, m, CH_2CH_2CO), 2.04-1.95 (1H, m, $CH_AH_BCH_2CO$), 1.86-1.74 (1H, m, $CH_AH_BCH_2CO$), 1.51 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 213.3, 166.7, 140.7, 138.3, 134.8, 129.8, 128.0, 126.4, 52.7, 51.7, 43.0, 36.7, 24.9, 23.1; *m/z* LRMS (EI^+) 258.1 (4%), 115.0 (8%), 91.0 (100%), 76.9 (23%), 65.0 (22%), 42.1 (21%); (CI^+) 276 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{16}H_{22}NO_3$: 276.1594 $[M+NH_4]^+$; found: 276.1595 $[M+NH_4]^+$.

General procedure E: The enantioselective alkoxycarbonylation of *bis*-alkenyltriflates

An oven dried Schlenk tube was charged with *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol), palladium (II) acetate (2.3 mg, 0.0104 mmol) and PCy_2-MOP **238** (5.0 mg, 0.0104 mmol). To this was added anhydrous alcohol (0.66 mL) and anhydrous triethylamine (0.33 mL). Where *para*-hydroxyanisole (129 mg, 1.04 mmol) was used as the alcohol the reaction was performed in acetonitrile (1 mL). The Schlenk tube was purged with nitrogen, and then fitted with a balloon of carbon monoxide (previously back-filled with N_2 and purged three times) with a glass tap attachment. The vessel was purged under vacuum, and filled with carbon monoxide using the balloon. This process was repeated three times. The reaction was then left open to the balloon, and heated at 45°C in a pre-heated oil bath for the time stated. The reaction was then cooled to room temperature, diluted with diethyl ether (5 mL) and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (solvents as stated).

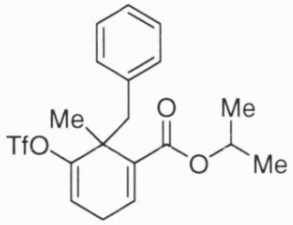
6-Benzyl-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid ethyl ester (241) and 2-benzyl-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid diethyl ester (242)

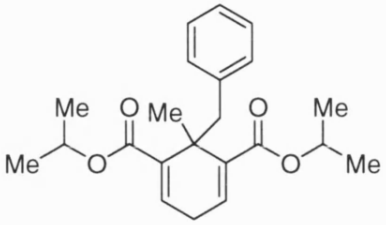




Prepared using general procedure **E** from *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **241** (16.0 mg, 38%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.21-7.15 (3H, m, 3 × Ar-*H*), 7.03-7.00 (2H, m, 2 × Ar-*H*), 6.77-6.74 (1H, m, CH_2CHCCO_2), 5.69-5.66 (1H, m, $CH_2CHCOSO_2$), 4.35-4.20 (2H, m, $CO_2CH_2CH_3$), 3.52 (1H, d, *J* 13.7, $ArCH_AH_BCCH_3$), 2.85 (1H, d, J 13.7, $ArCH_AH_BCCH_3$), 2.74 (1H, ddd (app. dt), *J* 24.0, 4.1 and 4.1, $CH_AH_BCHCOSO_2$), 2.28 (1H, ddd (app. dt), *J* 24.0, 3.3 and 3.3, $CH_AH_BCHCOSO_2$), 1.63 (3H, s, CH_3CCH_2Ar), 1.35 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 165.7, 150.9, 137.7, 136.4, 132.8, 129.9, 127.8, 126.4, 113.1, 60.7, 43.6, 41.9, 26.5, 23.9, 14.3 (CF_3 not seen); *m/z* LRMS (EI^+) 285.0 (30%), 241.1 (30%), 209.1 (35%), 165.0 (40%), 151.0 (40%), 135.1 (50%), 128.1 (60%), 91.1 ($[C_6H_5CH_2]^+$, 100%); (CI^+) 422 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{18}H_{23}F_3NO_5S$: 422.1244 $[M+NH_4]^+$; found: 422.1244 $[M+NH_4]^+$ and diester **242** (16.0 mg, 47%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.14-7.10 (3H, m, 3 × Ar-*H*), 7.00-6.97 (2H, m, 2 × Ar-*H*), 6.68 (2H, dd, *J* 4.4 and 3.0, 2 × CH_2CHCCO_2), 4.32-4.22 (4H, m, 2 × $CO_2CH_2CH_3$), 3.51 (2H, s, $ArCH_2CCO$), 2.58 (1H, dt, *J* 24.9 and 4.4 CH_AH_BCHCCO), 1.99 (1H, dt, *J* 24.9 and 3.0, CH_AH_BCHCCO), 1.69 (3H, s, CH_3CCH_2Ar), 1.35 (6H, t, *J* 7.1, 2 × $CO_2CH_2CH_3$); δ_C (75 MHz, $CDCl_3$) 167.1, 139.6, 135.4, 135.3, 130.3, 127.3, 125.7, 60.4, 42.8, 41.9, 27.1, 25.4, 14.3; *m/z* LRMS (EI^+) 237.1 (10%), 92.2 (45%), 91.0 ($[C_6H_5CH_2]^+$, 100%), 77.1 ($[C_6H_5]^+$, 15%), 65.1 (25%); (CI^+) 346 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{20}H_{28}NO_4$: 346.2013 $[M+NH_4]^+$; found: 346.2016 $[M+NH_4]^+$.

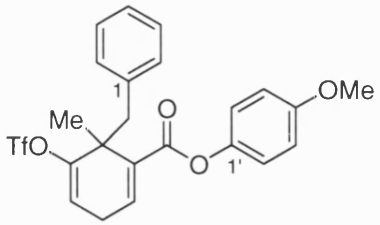
6-Benzyl-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid *iso*-propyl ester (243) and 2-benzyl-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid di-*iso*-propyl ester (244)





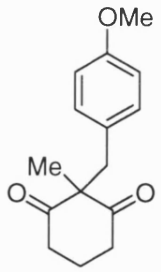
Prepared using general procedure **E** from *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) *iso*-propyl mono-ester **243** (21.0 mg, 48%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.20-7.15 (3H, m, 3 × Ar-*H*), 7.04-7.01 (2H, m, 2 × Ar-*H*), 6.74-6.71 (1H, m, CH_2CHCCO_2), 5.70-5.66 (1H, m, $CH_2CHCOSO_2$), 5.16 (1H, septet, *J* 6.2, $(CH_3)_2CHOCO$), 3.52 (1H, d, *J* 13.5, $ArCH_AH_BCCO$), 2.85 (1H, d, *J* 13.5, $ArCH_AH_BCCO$), 2.74 (1H, dt, *J* 24.0 and 4.1 CH_AH_BCHCCO), 2.27 (1H, dt, *J* 24.0 and 3.3, CH_AH_BCHCCO), 1.64 (3H, s, CH_3CCH_2Ar), 1.34 (3H, d, *J* 2.1, $CH_3(CH_3)CHO$), 1.32 (3H, d, *J* 2.1, $CH_3(CH_3)CHO$); δ_C (75 MHz, $CDCl_3$) 165.3, 150.9, 137.7, 136.1, 133.1, 129.9, 127.7, 126.3, 113.1, 68.2, 43.6, 41.9, 26.5, 23.9, 21.9 (2 × C) (CF_3 not seen); *m/z* LRMS (EI^+) 327.1 ($[M-C_6H_6CH_2]^+$, 10%), 285.1 (100%), 151.0 (40%), 135.1 (38%), 91.0 ($[C_6H_6CH_2]^+$, 100%); (CI^+) 436 (100%) $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{19}H_{22}F_3O_5S$: 419.1135 $[M+H]^+$; found: 419.1136 $[M+H]^+$ and *iso*-propyl diester **244** (6.7 mg, 18%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.14-7.10 (3H, m, 3 × Ar-*H*), 7.02-6.98 (2H, m, 2 × Ar-*H*), 6.65 (2H, overlapping dd, *J* 4.4 and 3.0, 2 × CH_2CHCCO_2), 5.17 (2H, septet, *J* 6.2, 2 × $CO_2CH(CH_3)_2$), 3.51 (2H, s, $ArCH_2CCO$), 2.57 (1H, dt, *J* 24.8 and 4.4 CH_AH_BCHCCO), 1.98 (1H, dt, *J* 24.8 and 3.0, CH_AH_BCHCCO), 1.69 (3H, s, CH_3CCH_2Ar), 1.35 (6H, d, *J* 2.6, 2 × $CH_3CH(CH_3)CO_2$), 1.33 (6H, d, *J* 2.6, 2 × $CH_3CH(CH_3)CO_2$); δ_C (75 MHz, $CDCl_3$) 166.7, 139.6, 135.6, 135.1, 130.3, 127.3, 125.6, 67.7, 42.8, 42.0, 27.0, 25.4, 21.9 (2 × C); *m/z* LRMS (EI^+) 265.1 ($[M-C_6H_6CH_2]^+$, 100%), 255.1 (50%), 91.1 ($[C_6H_6CH_2]^+$, 100%), 43.1 ($[C_3H_7]^+$, 71%); (CI^+) 374 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{22}H_{32}NO_4$: 374.2326 $[M+NH_4]^+$; found: 374.2327 $[M+NH_4]^+$.

6-Benzyl-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-diene carboxylic acid 4-methoxy-phenyl ester (245)



Prepared using general procedure **E** from *bis*-alkenyltriflate **222** (50 mg, 0.104 mmol) and purified by flash chromatography (hexane:diethyl ether 10:1) to yield mono-ester **245** (18.5 mg, 37%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3030 (C-H), 2935 (C-H), 2838 (C-H), 1733 (C=O), 1699, 1639, 1505, 1415 (O-SO_2), 1193 (O-SO_2), 1142 (SO_2), 1034, 991, 942, 868, 743, 704, 600; δ_H (300 MHz, $CDCl_3$) 7.27-7.19 (3H, m, 3 × Ar-*H*), 7.09-7.02 (5H, m, CH_2CHCCO_2, 2 × Ar-*H* and 2 × Ar'-*H*), 6.97-6.92 (2H, m, 2 × Ar'-*H*), 5.76-5.73 (1H, m, $CH_2CHCOSO_2$), 3.83 (3H, s, CH_3OAr), 3.50 (1H, d, *J* 13.8, $ArCH_AH_BCCH_3$), 2.93-2.80 (2H, m, $ArCH_AH_BCCH_3$ and $CH_AH_BCHCOSO_2$), 2.42 (1H, dt, *J* 24.3 and 3.3, $CH_AH_BCHCOSO_2$), 1.70 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 164.4, 157.4, 150.8, 144.0, 138.5, 137.7, 132.2, 129.8, 127.9, 126.5, 122.4, 120.5, 114.6, 112.9, 55.7, 43.7, 41.7, 26.7, 24.0; *m/z* LRMS (EI$^+$) 482.1 ([M+H]$^+$, 100%), 267.0 (20%), 91.1 ([$C_6H_6CH_2$]$^+$, 100%), 69.1 ([CF_3]$^+$, 18%); (CI$^+$) 500 (20%) [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{23}H_{25}F_3NO_6S$: 500.1349 [M+NH_4]$^+$; found: 500.1345 [M+NH_4]$^+$.

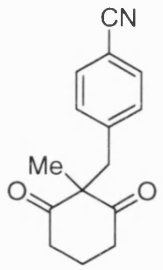
2-(4-Methoxy-benzyl)-2-methyl-cyclohexane-1,3-dione (252)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and *p*-methoxybenzylchloride (8.39 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **252** (5.27 g,

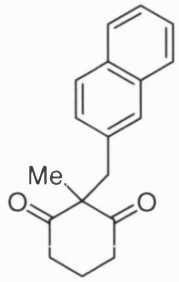
54%) as white crystalline needles. mp 87-89°C (EtOAc/hexane) ν_{max} (film)/cm^{-1} 2951 (C-H), 2839 (O-CH_3), 1691, 1610 (Ar), 1511 (Ar), 1457 (Ar), 1247, 1185, 1027, 868 (Ar); δ_H (300 MHz, $CDCl_3$) 6.97-6.92 (2H, m, 2 × Ar-*H*), 6.78-6.73 (2H, m, 2 × Ar-*H*), 3.76 (3H, s, C*H*$_3$OAr), 3.07 (2H, s, CC*H*$_2$Ar), 2.59-2.49 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.39-2.26 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.82-1.68 (1H, m, $CH_AH_BCH_2CO$), 1.60-1.47 (1H, m, $CH_AH_BCH_2CO$), 1.27 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 211.7, 158.6, 130.9, 128.6, 113.8, 65.4, 55.2, 43.3, 39.4, 22.0, 16.6; *m/z* LRMS (EI$^+$) 246.1 ([M]$^+$, 100%), 203.1 (30%), 175.0 (90%), 159.1 (45%), 121.1 ([$CH_3OC_6H_4CH_2$]$^+$, 100%); (CI$^+$) 264 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{15}H_{22}NO_3$: 264.1594 [M+NH_4]$^+$; found: 264.1597 [M+NH_4]$^+$; Anal. Calc. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.37; N, 0.00. Found: C, 73.2; H, 7.42; N, 0.00 %.

4-(1-Methyl-2,6-dioxo-cyclohexylmethyl)-benzonitrile (253)



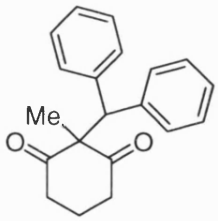
Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and *p*-cyano benzylbromide (11.8 g, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 1:1) to yield diketone **253** (5.90 g, 61%) as white crystalline needles: mp 94-103°C (DCM/hexane) ν_{max} (film)/cm^{-1} 2967 (C-H), 2227 (CN), 1694 (C=O), 1607, 1506, 1418, 1320, 1029, 821 (Ar); δ_H (300 MHz, $CDCl_3$) 7.53-7.50 (2H, m, 2 × Ar-*H*), 7.21-7.18 (2H, m, 2 × Ar-*H*), 3.21 (2H, s, CC*H*$_2$Ar), 2.69-2.59 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.38-2.29 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.94-1.82 (1H, m, $CH_AH_BCH_2CO$), 1.59-1.45 (1H, m, $CH_AH_BCH_2CO$), 1.35 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 210.5, 142.9, 132.0, 131.1, 118.7, 110.7, 65.4, 41.3, 38.9, 24.1, 16.6; *m/z* LRMS (EI$^+$) 241.2 ([M]$^+$, 30%), 198.1 (35%), 185.1 ([M-$CH_2C_6H_4CN$]$^+$, 10%), 170.1 (30%), 116.1 (85%), 97.1 (45%), 89.1 (60%), 55.1 (100%); (CI$^+$) 259 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{15}H_{19}N_2O_2$: 259.1441 [M+NH_4]$^+$; found: 259.1442 [M+NH_4]$^+$; Anal. Calc. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.27; N, 5.81. Found: C, 74.5; H, 6.30; N, 5.85%.

2-Methyl-2-naphthalen-2-ylmethyl-cyclohexane-1,3-dione (254)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and 2-bromomethylnapthalene (13.3 g, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **254** (8.51 g, 53%) as yellow crystalline needles: mp 86-93°C. ν_{max} (film)/cm^{-1} 2982 (C-H), 2938 (C-H), 1693 (C=O), 1461 (Ar), 1320, 1223, 1028, 827, 769; δ_H (300 MHz, $CDCl_3$) 7.79-7.69 (3H, m, 3 × Ar-*H*), 7.50-7.40 (3H, m, 3 × Ar-*H*), 7.16 (1H, dd, *J* 8.5 and 1.8, Ar-*H*), 3.30 (2H, s, ArCH_2CCH_3), 2.59-2.49 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.31-2.20 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.79-1.65 (1H, m, $CH_AH_BCH_2CO$), 1.51-1.38 (1H, m, $CH_AH_BCH_2CO$), 1.36 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 211.5, 134.3, 133.3, 132.3, 128.7, 128.1, 128.0, 127.8, 127.6, 126.1, 125.8, 65.3, 43.9, 39.4, 22.7, 16.6; *m/z* LRMS (EI$^+$) 141.1 ([$C_{10}H_7CH_2$]$^+$, 100%), 115.0 (20%); (CI$^+$) 284 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{18}H_{22}NO_2$: 284.1645 [M+NH_4]$^+$; found: 284.1641 [M+NH_4]$^+$.

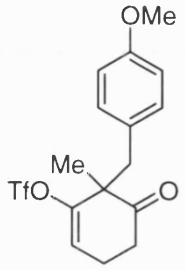
2-Benzhydryl-2-methyl-cyclohexane-1,3-dione (255)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and benzhydryl bromide (14.8 g, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **255** (2.8 g, 24%) as a white powder: mp 115-120°C. ν_{max} (film)/cm^{-1} 3027 (C-H), 2966 (C-H), 1693 (C=O), 1495, 1450 (Ar), 1316, 1089, 1022, 701 (Ar); δ_H (300 MHz, $CDCl_3$) 7.37-

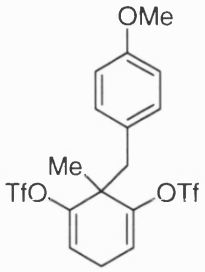
7.20 (10H, m, 10 × Ar-*H*), 4.84 (1H, s, Ar_2CHC), 2.61-2.55 (4H, m, 2 × CH_2CH_2CO), 1.82-1.64 (2H, m, CH_2CH_2CO), 1.24 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 210.0, 139.5, 129.9, 128.4, 127.1, 69.7, 57.4, 39.1, 19.0, 17.3; *m/z* LRMS (EI^+) 292.2 (6%), 221.1 (10%), 167.1 (100%), 152.0 (30%), 115.1 (34%), 91.1 (19%), 77.2 (18%), 55.1 (18%), 42.2 (20%); (CI^+) 310.3 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{20}H_{24}NO_2$: 310.1802 $[M+NH_4]^+$; found: 310.1799 $[M+NH_4]^+$; Anal. Calc. for $C_{20}H_{20}O_2$: C, 82.2; H, 6.89; N, 0.00. Found: C, 82.1; H, 6.87; N, 0.00 %.

Trifluoro-methanesulfonic acid 6-(4-methoxy-benzyl)-6-methyl-5-oxo-cyclohex-1-enyl ester (256)



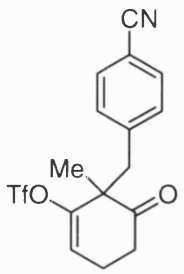
Prepared using general procedure **B** from diketone **252** (250 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **256** (185 mg, 48%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 3424 (C-H), 2938 (C-H), 2838 (C-H), 1716 (C=O), 1614, 1516, 1418 (O-SO_2), 1246 (SO_2), 1143, 1015, 937, 874, 812, 756, 679; δ_H (300 MHz, $CDCl_3$) 6.98-6.95 (2H, m, 2 × Ar-*H*), 6.78-6.75 (2H, m, 2 × Ar-*H*), 5.97 (1H, dd (app. t), *J* 4.5 and 4.5, $CH_2CHCOSO_2$), 3.77 (3H, s, CH_3OAr), 3.10 (1H, d, *J* 13.5, CCH_AH_BAr), 2.78 (1H, d, *J* 13.5, CCH_AH_BAr), 2.41-2.32 (1H, m, $CH_2CH_AH_BCO$), 2.24-2.12 (1H, m, $CH_2CH_AH_BCO$), 2.01-1.92 (1H, m, $CH_AH_BCH_2CO$), 1.80-1.68 (1H, m, $CH_AH_BCH_2CO$), 1.39 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 209.6, 158.5, 149.6, 130.9, 128.2, 118.4 (q, *J* 319.3, CF_3), 117.7, 113.6, 55.2, 54.5, 41.9, 36.8, 22.8, 19.2; *m/z* LRMS (ES^+) 149 $[M-CF_3SO_3]^+$ (100%), 121 $[M-C_8H_9O]^+$ (100%); (ES^+) 396 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{16}H_{21}F_3NO_5S$: 396.1087 $[M+NH_4]^+$; found: 396.1086 $[M+NH_4]^+$.

Trifluoro-methanesulfonic acid 6-(4-methoxy-benzyl)-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienyl ester (257)



Prepared using general procedure **C** from mono-alkenyltriflate **256** (274 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **257** (240 mg, 65%) as a white powder: mp 57-60°C. ν_{max} (film)/cm^{-1} 1514, 1417 (O-SO_2), 1211 (SO_2), 1142, 995, 874; δ_H (300 MHz, $CDCl_3$) 7.01-6.99 (2H, m, 2 × Ar-*H*), 6.80-6.77 (2H, m, 2 × Ar-*H*), 5.69 (2H, dd (app.t), *J* 3.8 and 3.8, 2 × $CH_2CHCOSO_2$), 3.78 (3H, s, CH_3OAr), 2.83-2.73 (3H, m, $ArCH_2CCO$ and CH_AH_BCHCO), 2.37 (1H, dt, *J* 22.7 and 3.5, CH_AH_BCHCO), 1.52 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 158.6, 147.5, 130.7, 127.7, 118.4 (q, *J* 320.1, CF_3), 113.9, 113.5, 55.2, 45.7, 41.0, 24.2, 22.5; *m/z* LRMS (EI$^+$) 388.0 (53%), 255.1 (78%), 241.1 (53%), 211.1 (56%), 199.1 (100%), 121.0 (100%), 77.0 (27%), 69.0 (58%); (CI$^+$) 528.2 $[M+NH_4]^+$; HRMS (ES$^+$) calc. for $C_{17}H_{20}F_6NO_7S_2$: 528.0580 $[M+NH_4]^+$; found: 528.0587 $[M+NH_4]^+$; Anal. Calc. for $C_{17}H_{16}F_6O_7S_2$: C, 40.0; H, 3.16; N, 0.00. Found: C, 40.5; H, 3.30; N, 0.15 %.

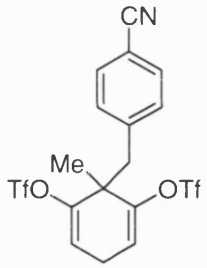
Trifluoro-methanesulfonic acid 6-(4-cyano-benzyl)-6-methyl-5-oxo-cyclohex-1-enyl ester (258)



Prepared using general procedure **B** from diketone **253** (246 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 5:1) to yield mono-

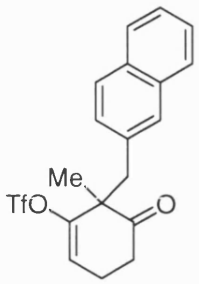
alkenyltriflate **258** (240 mg, 63%) as a white powder. mp 54-58°C ν_{max} (film)/cm^{-1} 2981 (C-H), 2939 (C-H), 2230 (CN), 1272 (C=O), 1609, 1415 (O-SO_2), 1215 (SO_2), 1142, 1019, 875; δ_H (300 MHz, $CDCl_3$) 7.55-7.52 (2H, m, 2 × Ar-*H*), 7.19-7.16 (2H, m, 2 × Ar-*H*), 6.00 (1H, dd, *J* 3.6 and 2.0, $CH_2CHCOSO_2$), 3.32 (1H, d, *J* 13.3, CCH_AH_BAr), 2.84 (1H, d, *J* 13.3, CCH_AH_BAr), 2.53-2.43 (1H, m, $CH_2CH_AH_BCO$), 2.32-2.21 (1H, m, $CH_2CH_AH_BCO$), 2.15-2.05 (1H, m, $CH_AH_BCH_2CO$), 1.80-1.68 (1H, m, $CH_AH_BCH_2CO$), 1.44 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 208.5, 148.8, 141.9, 132.1, 130.8, 118.6, 118.2, 111.1, 54.5, 41.7, 36.3, 23.7, 19.3 (CF_3 not seen); *m/z* LRMS (EI$^+$) 373.2 [M]$^+$ (100%), 116.0 (100%), 107.1 (19%), 89.0 (31%), 79.1 (27%), 69.0 (68%), 55.1 (55%); (CI$^+$) 391 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{16}H_{14}F_3NO_4S$: 373.0590 [M]$^+$; found: 373.0590 [M]$^+$; Anal. Calc. for $C_{16}H_{14}NO_4SF_3$: C, 51.5; H, 3.78; N, 3.75. Found: C, 57.5; H, 3.83; N, 3.79 %.

Trifluoro-methanesulfonic acid 6-(4-cyano-benzyl)-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienyl ester (259)



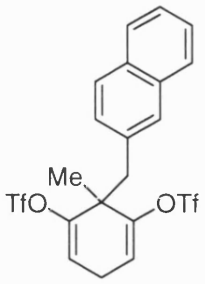
Prepared using general procedure **C** from mono-alkenyltriflate **258** (270 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **259** (55 mg, 15%) as a cream solid: mp 62-65°C. ν_{max} (film)/cm^{-1} 2991 (C-H), 2944 (C-H), 2230 (CN), 1705, 1410 (O-SO_2), 1221 (SO_2), 1140, 1068, 1002, 945, 873, 803, 756, 659; δ_H (300 MHz, $CDCl_3$) 7.59-7.56 (2H, m, 2 × Ar-*H*), 7.21-7.19 (2H, m, 2 × Ar-*H*), 5.73 (2H, dd (app.t), *J* 3.7 and 3.7, 2 × $CH_2CHCOSO_2$), 2.94 (2H, s, $ArCH_2CCO$), 2.85 (1H, dt, *J* 23.0 and 4.0 CH_AH_BCHCO), 2.40 (1H, dt, *J* 23.0 and 3.6, CH_AH_BCHCO), 1.57 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 146.7, 141.1, 132.0, 130.4, 116.0, 114.4, 111.2, 45.4, 41.5, 24.2, 22.9 (CF_3 not seen); *m/z* LRMS (EI$^+$) 506.0 (9%), 389.1 (26%), 255.0 (100%), 239.0 (36%), 206.1 (51%), 117.1 (100%), 89.1 (30%), 69.0 (82%); (CI$^+$) 523.1 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{17}H_{17}F_6N_2O_6S_2$: 523.0427 [M+NH_4]$^+$; found: 523.0423 [M+NH_4]$^+$.

Trifluoro-methanesulfonic acid 6-methyl-6-naphthalen-2-ylmethyl-5-oxo-cyclohex-1-enyl ester (260)



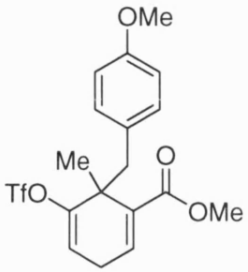
Prepared using general procedure **B** from diketone **254** (271 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **260** (219 mg, 54%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 3057 (C-H), 2979 (C-H), 2936 (C-H), 1722 (C=O), 1682, 1601, 1418 (O-SO_2), 1216 (SO_2), 1141, 1017, 871, 817, 754; δ_H (300 MHz, $CDCl_3$) 7.80-7.70 (3H, m, 3 × Ar-*H*), 7.52-7.44 (3H, m, 3 × Ar-*H*), 7.18 (1H, dd, *J* 8.4 and 1.8, Ar-*H*), 5.94 (1H, dd (app. t), *J* 4.6 and 4.6, $CH_2CHCOSO_2$), 3.36 (1H, d, *J* 13.4, CCH_AH_BAr), 3.00 (1H, d, *J* 13.4, CCH_AH_BAr), 2.42-2.32 (1H, m, $CH_2CH_AH_BCO$), 2.18-2.06 (1H, m, $CH_2CH_AH_BCO$), 1.99-1.90 (1H, m, $CH_AH_BCH_2CO$), 1.67-1.54 (1H, m, $CH_AH_BCH_2CO$), 1.47 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 209.4, 149.5, 133.8, 133.2, 132.3, 128.8, 127.9 (2 × C), 127.8, 127.6, 126.1, 125.8, 118.4 (q, *J* 324.6, CF_3), 117.7, 54.6, 42.7, 36.7, 23.2, 19.2; *m/z* LRMS (ES$^+$) 149.0 [M-F_3CSO_3]$^+$ (100%), 141.1 [M-$C_{11}H_9O$]$^+$ (90%), 191.1 (65%), 115.1 (100%) 80.0 (100%); (ES$^+$) 416 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{19}H_{21}F_3NO_4S$: 416.1138 [M+NH_4]$^+$; found: 416.1139 [M+NH_4]$^+$.

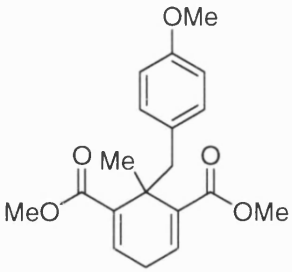
Trifluoro-methanesulfonic acid 6-methyl-6-naphthalen-2-ylmethyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienyl ester (261)



Prepared using general procedure **C** from mono-alkenyltriflate **260** (288 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **261** (227 mg, 59%) as a yellow oil. ν_{max} (film)/cm^{-1} 3058 (C-H), 2991 (C-H), 2940 (C-H), 1704, 1602, 1510, 1420 (O-SO_2), 1216 (SO_2), 1141, 1001, 946, 892, 743; δ_H (300 MHz, $CDCl_3$) 7.81-7.44 (6H, m, 6 × Ar-*H*), 7.23-7.20 (1H, dd, *J* 8.6 and 1.7, Ar-*H*), 5.64 (2H, dd (app.t), *J* 3.8 and 3.8, 2 × $CH_2CHCOSO_2$), 3.04 (2H, s, $ArCH_2CCO$), 2.62 (1H, dt, *J* 22.8 and 4.0, CH_AH_BCHCO), 2.22 (1H, dt, *J* 22.8 and 3.5, CH_AH_BCHCO), 1.59 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 147.4, 133.2 (2 × C), 132.4, 128.8, 127.8, 127.7, 127.6, 126.1, 125.9, 118.4 (q, *J* 323.1, CF_3), 113.9, 45.7, 41.8, 24.2, 22.9 (CF_3 not seen); *m/z* LRMS (EI^+) 530.1 ([M]$^+$, 42%), 397.1 (100%), 388.0 (83%), 142.1 (41%), 140.9 (100%), 115.0 (42%), 69.0 (77%); (CI^+) 548.1 [M+NH_4]$^+$; HRMS (ES^+) calc. for $C_{20}H_{20}F_6NO_6S_2$: 548.0631 [M+NH_4]$^+$; found: 548.0631 [M+NH_4]$^+$.

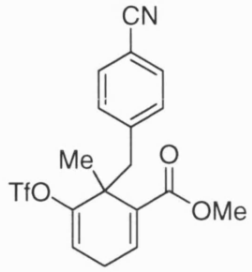
6-(4-Methoxy-benzyl)-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid methyl ester (262) and 2-(4-methoxy-benzyl)-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (263)

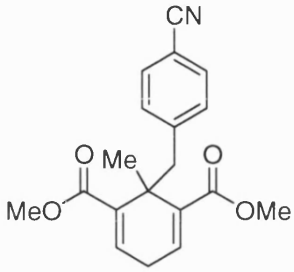




Prepared using general procedure **D** from *bis*-alkenyltriflate **257** (53 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **262** (19 mg, 44%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.95-6.90 (2H, m, 2 × Ar-*H*), 6.77-6.70 (3H, m, 2 × Ar-*H* and CH_2CHCCO_2), 5.69-5.66 (1H, m, $CH_2CHCOSO_2$), 3.81 (3H, s, CH_3OCO), 3.76 (3H, s, CH_3OAr), 3.44 (1H, d, *J* 13.9, $ArCH_AH_BCCH_3$), 2.82 (2H, m, $ArCH_AH_BCCH_3$ and CH_AH_BCHCCO), 2.34 (1H, dt, *J* 24.1 and 3.3, CH_AH_BCHCCO), 1.60 (3H, s, CH_3CCCH_2Ar); δ_C (75 MHz, $CDCl_3$) 166.1, 158.1, 150.9, 136.7, 132.6, 130.8, 129.8, 116.3, 113.2, 113.0, 55.1, 51.8, 43.6, 41.0, 26.6, 23.8 (CF_3 not seen); *m/z* LRMS (EI^+) 239.2 (30%), 213.1 (30%), 165.0 (55%), 141.1 (55%), 135.1 (100%), 121.1 (100%); (CI^+) 438 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{18}H_{23}F_3NO_6S$: 438.1193 $[M+NH_4]^+$; found: 438.1194 $[M+NH_4]^+$ and diester **263** (11 mg, 32%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.89-6.87 (2H, m, 2 × Ar-*H*), 6.70-6.66 (4H, m, 2 × Ar-*H* and 2 × CH_2CHCCO_2), 3.80 (6H, s, 2 × CH_3OCO), 3.74 (3H, s, CH_3OAr), 3.43 (2H, s, $ArCH_2CCH_3$), 2.59 (1H, dt, *J* 24.9 and 4.4 CH_AH_BCHCCO), 2.06 (1H, dt, *J* 24.9 and 3.0, CH_AH_BCHCCO), 1.65 (3H, s, CH_3CCCH_2Ar); δ_C (75 MHz, $CDCl_3$) 167.5, 157.7, 135.6, 135.2, 131.6, 131.1, 112.7, 55.1, 51.6, 41.9 (2 × C), 27.2, 25.3; *m/z* LRMS (EI^+) 330.2 ($[M]^+$, 20%), 300.3 (20%), 299.2 (100%), 121.1 (100%), 91.1 ($[C_6H_5CH_2]^+$, 30%), 77.1 ($[C_6H_5]^+$, 20%); (CI^+) 348 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{19}H_{26}NO_5$: 348.1805 $[M+NH_4]^+$; found: 348.1802 $[M+NH_4]^+$.

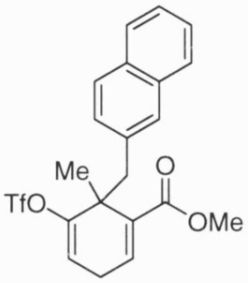
6-(4-Cyano-benzyl)-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid methyl ester (264) and 2-(4-cyano-benzyl)-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (265)

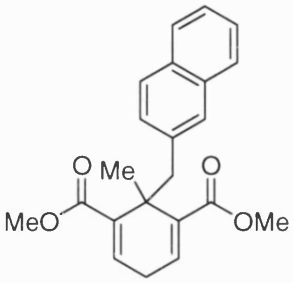




Prepared using general procedure **D** from *bis*-alkenyltriflate **259** (53 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **264** (16.0 mg, 37%) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.0, 2 × Ar-*H*), 7.11 (2H, d, *J* 8.0, 2 × Ar-*H*), 6.76 (1H, dd (app. t), *J* 3.0 and 3.0, $CH_2CH_AH_BCCO_2$), 5.69 (1H, dd (app. t), *J* 3.0 and 3.0, $CH_2CH_AH_BCCO_2$), 3.79 (3H, s, CH_3OCO), 3.60 (1H, d, *J* 13.0, $ArCH_AH_BCCH_3$), 2.89 (1H, d, *J* 13.0, $ArCH_AH_BCCH_3$), 2.79 (1H, dt, *J* 24.0 and 4.0 CH_AH_BCHCCO), 2.33 (1H, dt, *J* 24.0 and 3.0, CH_AH_BCHCCO), 1.53 (3H, s, CH_3CCCH_2Ar); δ_C (125 MHz, $CDCl_3$) 165.9, 150.1, 143.4, 136.9, 132.0, 131.6, 130.5, 118.9, 118.4 (q, *J* 319.4, CF_3), 113.4, 110.4, 52.0, 43.4, 41.7, 26.5, 24.1; HRMS (ES^+) calc. for $C_{18}H_{17}F_3NO_5S$: 416.0774 $[M+H]^+$; found: 416.0773 $[M+H]^+$ and diester **265** (14.2 mg, 42%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.45-7.42 (2H, m, 2 × Ar-*H*), 7.10-7.07 (2H, m, 2 × Ar-*H*), 6.71 (2H, dd, J 4.4 and 3.0, 2 × CH_2CHCCO_2), 3.81 (6H, s, 2 × CH_3OCO), 3.61 (2H, s, $ArCH_2CCH_3$), 2.65 (1H, dt, *J* 25.2 and 4.4 CH_AH_BCHCCO), 2.06 (1H, dt, *J* 25.2 and 3.0, CH_AH_BCHCCO), 1.67 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 167.2, 145.4, 135.8, 134.5, 131.2, 130.9, 115.3, 111.2, 51.8, 42.7, 41.8, 27.1, 25.6; *m/z* LRMS (EI^+) 209.0 (100%), 177.1 (90%), 117.1 ($[NCC_6H_4CH_2]^+$, 60%), 91.1 ($[C_6H_5CH_2]^+$, 80%), 59.1 (90%); (CI^+) 343.3 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{19}H_{23}N_2O_4$: 343.1652 $[M+NH_4]^+$; found: 343.1652 $[M+NH_4]^+$.

6-Methyl-6-naphthalen-2-ylmethyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-dienecarboxylic acid methyl ester (266) and 2-methyl-2-naphthalen-2-ylmethyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (267)

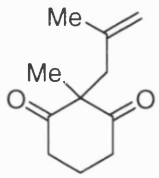




Prepared using general procedure **D** from *bis*-alkenyltriflate **261** (55 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **266** (20.0 mg, 44%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3057 (C-H), 2951 (C-H), 1717 (C=O), 1418 (O-SO_2), 1244, 1215 (O-SO_2), 1142, 1011, 892, 867, 761, 608; δ_H (300 MHz, $CDCl_3$) 7.78-7.71 (2H, m, 2 × Ar-*H*), 7.67-7.65 (1H, m, Ar-*H*), 7.48-7.40 (3H, m, 3 × Ar-*H*), 7.16 (1H, dd, *J* 8.4 and 1.7, Ar-*H*), 6.73-6.70 (1H, m, CH_2CHCCO_2), 5.67-5.65 (1H, m, $CH_2CHCOSO_2$), 3.84 (3H, s, CH_3OCO), 3.69 (1H, d, *J* 13.7, $ArCH_AH_BCCH_3$), 3.04 (1H, d, *J* 13.7, $ArCH_AH_BCCH_3$), 2.70 (1H, ddd (app. dt), *J* 24.1, 4.1 and 4.1, $CH_AH_BCHCOSO_2$), 2.22 (1H, ddd (app. dt), *J* 24.1, 3.3 and 3.3, $CH_AH_BCHCOSO_2$), 1.68 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 166.1, 150.9, 136.8, 135.4, 133.2, 132.5, 132.1, 128.6, 128.1, 127.7, 127.5, 127.2, 125.7, 125.4, 118.4 (q, *J* 319.3, CF_3), 113.0, 51.9, 43.7, 41.9, 26.5, 24.2; *m/z* LRMS (EI$^+$) 440.2 (18%), 231.1 (18%), 215.1 (32%), 202.1 (52%), 189.0 (40%), 178.1 (53%), 165.2 (100%), 141.0 (100%), 115.0 (40%), 69.0 (37%); (CI$^+$) 458 $[M+NH_4]^+$; HRMS (ES$^+$) calc. for $C_{21}H_{23}F_3NO_5S$: 458.1244 $[M+NH_4]^+$; found: 458.1246 $[M+NH_4]^+$ and diester **267** (11.9 mg, 33%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.76-7.68 (2H, m, 2 × Ar-*H*), 7.59 (1H, d, *J* 8.4, Ar-*H*), 7.41-7.37 (3H, m, 3 × Ar-*H*), 7.15 (1H, d, *J* 8.4, Ar-*H*), 6.70 (2H, dd (app.t), *J* 3.1 and 3.1, 2 × CH_2CHCCO), 3.83 (6H, s, 2 × CH_3OCOC), 3.69 (2H, s, $ArCH_2CCH_3$), 2.53 (1H, dt, *J* 25.0 and 4.4 CH_AH_BCHCCO), 1.93 (1H, dt, *J* 25.0 and 3.0, CH_AH_BCHCCO), 1.73 (3H, s, CH_3CCH_2Ar); δ_C (75 MHz, $CDCl_3$) 167.4, 137.0, 135.6, 135.1, 133.1, 131.9, 128.8, 128.6, 127.6, 127.5, 126.6, 125.4, 125.0,

51.6, 42.8, 41.9, 27.2, 25.7; *m/z* LRMS (EI^+) 350.2 (9%), 319.2 (10%), 259.2 (12%), 215.1 (53%), 177.1 (40%), 142.1 (100%), 115.0 (63%), 91.1 (32%), 59.1 (33%); (CI^+) 368.3 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{22}H_{26}NO_4$: 368.1856 $[M+NH_4]^+$; found: 368.1860 $[M+NH_4]^+$.

2-Methyl-2-(2-methyl-allyl)-cyclohexane-1,3-dione (268)

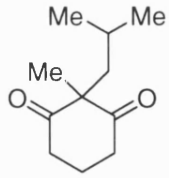


Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and 3-bromo-2-methylpropene (6.0 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **268** (4.7 g, 66%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3079 (C-H), 2968 (C-H), 1694 (C=O), 1644 (C=C), 1455 (C=C), 1376, 1320, 1026, 900; δ_H (300 MHz, $CDCl_3$) 4.82-4.80 (1H, m, $CH_AH_BCCH_2$), 4.52-4.40 (1H, m, $CH_AH_BC(CH)_3CH_2$), 2.79-2.61 (4H, m, 2 × CH_2CH_2CO), 2.58 (2H, d, *J* 0.7 Hz, $CH_2C(CH)_3CH_2CCO$), 2.12-1.84 (2H, m, CH_2CH_2CO), 1.65 (3H, s, CH_3CCH_2), 1.26 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 210.4, 141.1, 114.7, 64.8, 44.7, 38.3, 24.0, 21.2, 17.6; *m/z* LRMS (EI^+) 149.0 (8%), 137.0 (13%), 124.1 (36%), 109.0 (51%), 67.0 (45%), 55.0 (86%); (CI^+) 181.1 $[M+H]^+$; HRMS (ES^+) calc. for $C_{11}H_{17}O_2$: 181.1223 $[M+H]^+$; found: 181.1225 $[M+H]^+$.

General procedure F: The reduction of 2-alkenyl-2methyl-1,3-cyclohexanediones

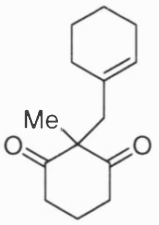
To a stirred solution of palladium on activated carbon (10% wt. loading, 100 mg, 0.094 mmol) in anhydrous ethanol (10 mL) was added 2-alkenyl-1,3-cyclohexanedione (0.94 mmol) as a solution in anhydrous ethanol (20 mL). The reaction was fitted with a balloon of hydrogen to simulate a pressure of 1 atmosphere, and stirred at room temperature for 24 hours. The reaction was diluted with ethyl acetate and filtered through a celite plug. The filtrate was then concentrated under reduced pressure to yield the aliphatic diketone.

2-*iso*-Butyl-2-methyl-cyclohexane-1,3-dione (269)



Prepared using general procedure **F** from diketone **268** (170 mg, 0.94 mmol) to yield diketone **269** (170 mg, 100%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 2958 (C-H), 2872 (C-H), 1725, 1692 (C=O), 1467, 1370, 1315, 1137, 1024, 910, 861; δ_H (300 MHz, $CDCl_3$) 2.84-2.73 (2H, m, 2 × $COCH_AH_BCH_2$), 2.66-2.57 (2H, m, 2 × $COCH_AH_BCH_2$), 2.14-2.01 (1H, m, $COCH_2CH_AH_BCH_2$), 1.92-1.80 (1H, m, $COCH_2CH_AH_BCH_2$), 1.79 (2H, d, *J* 6.2, $(CH_3)_2CHCH_2$), 1.72-1.59 (1H, m, $(CH_3)_2CHCH_2$), 1.24 (3H, s, CH_3CCO), 0.83 (6H, d, *J* 6.6, $(CH_3)_2CHCH_2$); δ_C (75 MHz, $CDCl_3$) 210.7, 65.5, 46.4, 38.0, 25.2, 23.8, 19.9, 18.0; *m/z* LRMS (EI^+) 182.1 (7%), 139.1 (39%), 126.0 (58%), 111.0 (100%), 97.9 (56%), 69.0 (67%), 55.0 (52%), 41.2 (85%); (CI^+) 200 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{11}H_{22}NO_2$: 200.1645 $[M+NH_4]^+$; found: 200.1646 $[M+NH_4]^+$; Anal. Calc. for $C_{11}H_{18}O_2$: C, 72.5; H, 9.95; N, 0.00. Found: C, 71.1; H, 9.90; N, 0.00 %.

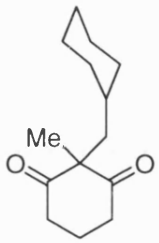
2-Cyclohex-1-enylmethyl-2-methyl-cyclohexane-1,3-dione (272)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and 1-(bromomethyl)cyclohex-1-ene (10.5 g, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **272** (3.6 g, 41%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3395 (C-H), 2932 (C-H), 1698 (C=O), 1455, 1318, 1025, 909; δ_H (300 MHz, $CDCl_3$) 5.35-5.30 (1H, m, $CCHCH_2CH_2$), 2.80-2.70 (2H, m, 2 × $COCH_AH_BCH_2$), 2.65-2.56 (2H, m, 2 × $COCH_AH_BCH_2$), 2.48 (2H, s, $CHCCH_2CCO$), 2.14-1.93 (3H, m, $COCH_2CH_AH_BCH_2$ and 2 × Cy-*H*), 1.91-1.77 (3H, m, $COCH_2CH_AH_BCH_2$ and 2 ×

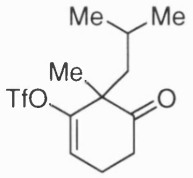
Cy-*H*), 1.60-1.44 (4H, m, 4 × Cy-*H*), 1.21 (3H, s, CH_3CO); δ_C (75 MHz, $CDCl_3$) 210.7, 133.0, 126.7, 65.4, 46.7, 38.5, 29.8, 25.3, 21.9, 19.6, 17.7, 14.2; *m/z* LRMS (EI^+) 220.1 (20%), 177.0 (22%), 164.1 (43%), 149.0 (42%), 127.0 (73%), 91.0 (66%), 78.9 (93%), 67.1 (70%), 54.8 (100%); (CI^+) 221.1 $[M+H]^+$; HRMS (ES^+) calc. for $C_{14}H_{21}O_2$: 221.1536 $[M+H]^+$; found: 221.1536 $[M+H]^+$.

2-Cyclohexylmethyl-2-methyl-cyclohexane-1,3-dione (273)



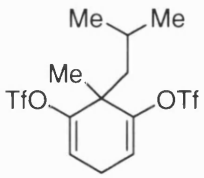
Prepared using general procedure **F** from diketone **272** (208 mg, 0.94 mmol) to yield diketone **273** (208 g, 99%) as white crystalline needles: mp 47-50°C. ν_{max} (film)/cm^{-1} 2922 (C-H), 2847 (C-H), 1691 (C=O), 1449, 1425, 1311, 1027, 899; δ_H (300 MHz, $CDCl_3$) 2.84-2.73 (2H, m, 2 × COC$H_A$$H_B$$CH_2$), 2.65-2.56 (2H, m, 2 × COC$H_A$$H_B$$CH_2$), 2.13-1.98 (1H, m, COC$H_2CH_A$$H_B$$CH_2$), 1.91-1.78 (1H, m, COC$H_2CH_A$$H_B$$CH_2$), 1.76 (2H, d, *J* 6.1, CC$H_2$$C_6H_{11}$), 1.66-1.49 (5H, m, 5 × Cy-*H*), 1.37-0.99 (4H, m, 4 × Cy-*H*), 1.23 (3H, s, CH_3CO), 0.93-0.81 (2H, m, 2 × Cy-*H*); δ_C (75 MHz, $CDCl_3$) 210.8, 65.3, 45.3, 38.0, 34.4, 26.2, 26.0, 19.9, 18.0, peak coincidence – one cyclohexyl carbon cannot be seen; *m/z* LRMS (EI^+) 222.1 (9%), 139.0 (57%), 127.1 (97%), 111.0 (85%), 98.1 (62%), 81.1 (36%), 69.1 (75%), 55.1 (98%), 41.1 (100%); (CI^+) 240 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{14}H_{26}O_2N$: 240.1958 $[M+NH_4]^+$; found: 240.1957 $[M+NH_4]^+$; Anal. Calc. for $C_{14}H_{22}O_2$: C, 75.6; H, 9.97; N, 0.00. Found: C, 75.6; H, 10.0; N, 0.00 %.

Trifluoro-methanesulfonic acid 6-*iso*-butyl-6-methyl-5-oxo-cyclohex-1-enyl ester (276)



Prepared using general procedure **B** from diketone **269** (186 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **276** (195 mg, 61%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 2961 (C-H), 2874 (C-H), 1722 (C=O), 1418 (O-SO_2), 1214 (SO_2), 1142, 1018, 932, 873, 689; δ_H (300 MHz, $CDCl_3$) 6.05 (1H, dd (app. t), *J* 4.4 and 4.4, $CH_2CHCOSO_2$), 2.69-2.54 (2H, m, CH_2CH_2CO), 2.53-2.44 (2H, m, CH_2CH_2CO), 1.99-1.90 (1H, m, $(CH_3)_2CHCH_2$), 1.55-1.48 (2H, m, $(CH_3)_2CHCH_2C$), 1.27 (3H, s, CH_3CCO), 0.89 (3H, d, *J* 6.4, $CH_3C(CH_3)CH_2$), 0.74 (3H, d, *J* 6.5, $CH_3C(CH_3)CH_2$); δ_C (75 MHz, $CDCl_3$) 209.1, 151.1, 118.4 (q, *J* 319.3, CF_3), 115.9, 52.1, 44.4, 35.8, 25.6, 24.8, 23.9, 23.7, 20.2; HRMS (ES^+) calc. for $C_{12}H_{18}F_3O_4S$: 315.0872 $[M+H]^+$; found: 315.0869 $[M+H]^+$.

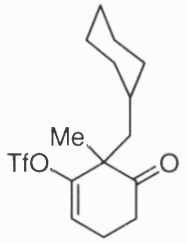
Trifluoro-methanesulfonic acid 6-*iso*-butyl-6-methyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (278)



Prepared using general procedure **C** from mono-alkenyltriflate **276** (227 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **278** (155 g, 48%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 2962 (C-H), 2938 (C-H), 2875 (C-H), 1705, 1419 (O-SO_2), 1141 (SO_2), 1001, 917, 862, 744, 590; δ_H (300 MHz, $CDCl_3$) 5.85 (2H, dt (app. t), *J* 3.7 and 3.7, 2 × $CH_2CHCOSO_2$), 3.09-3.05 (2H, m, $CH_2CHCOSO_2$), 1.73-1.57 (1H, m, $(CH_3)_2CHCH_2$), 1.53 (2H, d, *J* 4.8, $(CH_3)_2CHCH_2$), 1.36 (3H, s, CH_3CCOSO_2), 0.91 (6H, d, *J* 6.5, $(CH_3)_2CHCH_2$); δ_C (75 MHz, $CDCl_3$) 149.1, 118.3 (q, *J* 319.3,

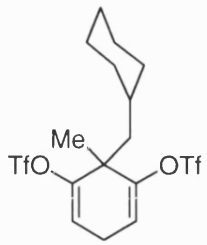
CF_3)112.5, 43.5, 43.3, 25.3, 24.6, 24.5, 23.6 (peak coincidence, one carbon cannot be seen).

Trifluoro-methanesulfonic acid 6-cyclohexylmethyl-6-methyl-5-oxo-cyclohex-1-enyl ester (277)



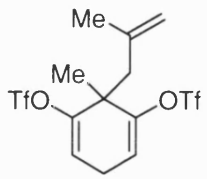
Prepared using general procedure **B** from diketone **273** (226 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **277** (195 mg, 54%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 2927 (C-H), 2854 (C-H), 1722 (C=O), 1450, 1417 (O-SO_2), 1214 (SO_2), 1143, 1017, 883, 601; δ_H (300 MHz, $CDCl_3$) 6.05 (1H, dd (app. t), *J* 4.4 and 4.4, $CH_2CHCOSO_2$), 2.67-2.54 (2H, m, CH_2CH_2CO), 2.49-2.43 (2H, m, CH_2CH_2CO), 1.96-1.89 (1H, overlapping dd, *J* 7.4 and 4.8, $CyCH_AH_BC$), 1.66-1.55 (4H, m, 4 × Cy-*H*), 1.47 (1H, dd, *J* 14.2 and 4.8, $CyCH_AH_BC$), 136-0.77 (7H, m, 7 × Cy-*H*), 1.26 (3H, s, CH_3CO); δ_C (75 MHz, $CDCl_3$) 209.1, 151.2, 118.4 (q, *J* 320.1, CF_3), 115.8, 51.9, 43.4, 35.9, 34.9, 34.6, 34.1, 26.2, 26.1, 24.6, 20.2; *m/z* LRMS (EI^+) 312.2 (100%), 297.2 (17%), 271.1 (17%), 258.0 (28%), 95.0 (16%), 82.9 (49%), 68.9 (93%), 55.0 (100%); (CI^+) 372.2 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{15}H_{25}F_3NO_4S$: 372.1451 $[M+NH_4]^+$; found: 372.1455 $[M+NH_4]^+$.

Trifluoro-methanesulfonic acid 6-cyclohexylmethyl-6-methyl-5-trifluoro-methanesulfonyloxy-cyclohexa-1,4-dienyl ester (279)



Prepared using general procedure **C** from mono-alkenyltriflate **277** (257 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **279** (105 mg, 30%) as an yellow oil. ν_{max} (liquid film)/cm^{-1} 2928 (C-H), 2855 (C-H), 1704, 1419 (O-SO_2), 1214 (SO_2), 1142, 1001, 947, 889, 840, 742, 612, 590; δ_H (300 MHz, $CDCl_3$) 5.84 (2H, dd (app. t), 2 × $CH_2CHCOSO_2$), 3.08-3.05 (2H, overlapping dt, *J* 3.8 and 1.9, $CH_2CHCOSO_2$), 1.78-1.49 (8H, m, 6 × Cy-*H* and CCH_2Cy), 1.35 (3H, s, CH_3CCOSO_2), 1.32-0.87 (5H, m, 5 × Cy-*H*); δ_C (75 MHz, $CDCl_3$) 149.2, 118.3 (q, *J* 319.3, CF_3), 112.4, 43.2, 42.2, 34.5, 34.1, 26.3, 26.1, 24.5 (peak coincidence – one cyclohexyl carbon cannot be seen); *m/z* LRMS (ESI$^-$) 824.3 (45%), 823.4 ([M]$^+$, 100%), 477.1 (60%).; HRMS (ES$^+$) calc. for [2M-OTf]$^+$: 823.1688; found: 823.1696 [2M-OTf]$^+$.

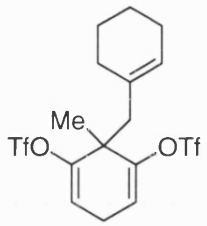
Trifluoro-methanesulfonic acid 6-methyl-6-(2-methyl-allyl)-5-trifluoro-methanesulfonyloxy-cyclohexa-1,4-dienyl ester (281)



Prepared using general procedures **B** and **C** from diketone **268** (226 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **281** (151 mg, 47%) as a yellow oil. ν_{max} (film)/cm^{-1} 2975 (C-H), 2939 (C-H), 1704, 1418 (O-SO_2), 1247, 1213 (SO_2), 1139, 1036, 1003, 908, 876, 802, 754, 610; δ_H (300 MHz, $CDCl_3$) 5.67 (2H, dd (app. t), *J* 3.8 and 3.8, 2 × $CH_2CHCOSO_2$), 4.73-4.72 (1H, m, $CH_AH_BCCH_2C$), 4.57-4.56 (1H, m,

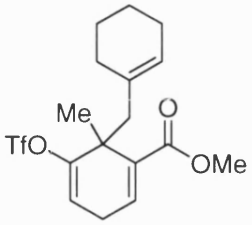
$CH_AH_BCCH_2C$), 2.95-2.75 (2H, m, $CH_2CHCOSO_2$), 2.16 (2H, s, CH_2CHCH_2CCO), 1.39 (3H, s, CH_3CCOSO_2), 1.25 (3H, s, $CH_3C(CH_2)CH_2$); δ_C (75 MHz, $CDCl_3$) 148.9, 140.6, 116.1, 113.2, 44.4, 43.2, 25.0, 24.3, 23.8 (CF_3 not seen).

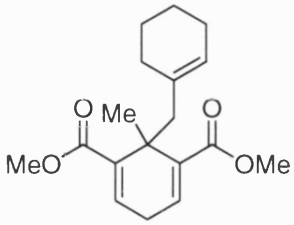
Trifluoro-methanesulfonic acid 6-cyclohex-1-enylmethyl-6-methyl-5-trifluoro-methanesulfonyloxy-cyclohexa-1,4-dienyl ester (282)



Prepared using general procedures **B** and **C** from diketone **272** (255 mg, 0.725 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **282** (197 mg, 56%) as white needles: mp 52-54 (hexane). ν_{max} (film)/cm^{-1} 2936 (C-H), 1699, 1410 (O-SO_2), 1246, 1206 (SO_2), 1139, 1069, 1101, 957, 852, 745; δ_H (300 MHz, $CDCl_3$) 5.81 (2H, dd (app. t), *J* 3.7 and 3.7, 2 × $CH_2CHCOSO_2$), 5.46 (1H, br s, $CH_2CH_2CHCCH_2$), 3.10-2.89 (2H, m, $CH_2CHCOSO_2$), 2.24 (2H, s, $CyCH_2CCO$), 1.93 (4H, br d, *J* 20.7, 4 × Cy-*H*), 1.56-1.45 (4H, m, 4 × Cy-*H*), 1.39 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 148.9, 132.5, 127.0, 112.5, 44.1, 43.8, 29.3, 25.4, 24.6, 23.6, 23.1, 22.1 (CF_3 not seen); *m/z* LRMS (EI^+) 484.0 (100%), 443.1 (75%), 419.0 (36%), 401.0 (31%), 95.1 (100%), 69.0 (61%); (CI^+) 502.1 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{16}H_{18}O_6F_6S_2$: 484.0444 $[M+NH_4]^+$; found: 484.0447 $[M+NH_4]^+$.

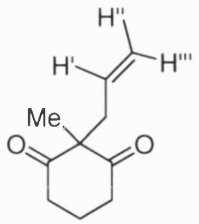
6-Cyclohex-1-enylmethyl-6-methyl-5-trifluoromethanesulfonyloxy – cyclohexa -1,4-dienecarboxylic acid methyl ester (283) and 2-cyclohex-1-enylmethyl-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (284)





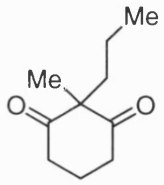
Prepared using general procedure **D** from *bis*-alkenyltriflate **282** (53 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **283** (16.8 mg, 41%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3445, 2939 (C-H), 2863 (C-H), 1716 (C=O), 1418 (O-SO_2), 1219 (SO_2), 1141, 1037, 1001, 962, 905, 799, 613; δ_H (300 MHz, $CDCl_3$) 6.93 (1H, td, *J* 3.6 and 1.2, CH_2CHCCO_2), 5.75 (1H, td, *J* 3.6 and 1.2, $CH_2CHCOSO_2$), 5.32 (1H, br s, $CH_2CH_2CHCCH_2$), 3.75 (3H, s, CH_3OCO), 3.10-2.89 (2H, m, $CH_2CHCOSO_2$), 2.80 (1H, d, *J* 14.1, $CyCH_AH_BCCH_3$), 2.27 (1H, d, *J* 14.0, $CyCH_AH_BCCH_3$), 1.87 (4H, br d, *J* 14.0, 4 × Cy-*H*), 1.51-1.43 (7H, m, CH_3CCH_2Cy and 4 × Cy-*H*); δ_C (75 MHz, $CDCl_3$) 166.0, 152.6, 135.4, 134.3, 134.0, 125.8, 111.3, 51.7, 43.9, 42.2, 29.3, 26.9, 25.5, 25.2, 23.2, 22.2 (CF_3 not seen); *m/z* LRMS (EI$^+$) 394 (10%), 299.1 ([M-$C_6H_9CH_2$]$^+$, 100%), 107.1 (32%), 95.0 ([$C_6H_9CH_2$]$^+$, 90%), 81.0 ([C_6H_9]$^+$, 100%), 69.0 ([CF_3]$^+$, 82%), 55.1 (45%); (CI$^+$) 412 (20%) [M+NH_4]$^+$; HRMS (EI) calc. for $C_{17}H_{21}F_3O_5S$: 394.1056 [M]$^+$; found: 394.1057 [M]$^+$ and diester **284** (6.3 mg, 20%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.84 (2H, dd (app.t), *J* 3.7 and 3.7, 2 × CH_2CHCCO), 5.21 (1H, br s, $CH_2CH_2CHCCH_2$), 3.73 (6H, s, 2 × CH_3OCOC), 2.92 (2H, dd, *J* 6.9 and 3.7, CH_2CHCCO_2), 2.83 (2H, s, $CyCH_2CCH_3$), 1.88-1.75 (4H, m, 4 × Cy-*H*), 1.61 (3H, s, CH_3CCH_2Cy), 1.48-1.41 (4H, m, 4 × Cy-*H*); δ_C (75 MHz, $CDCl_3$) 167.2, 136.7, 136.0, 134.1, 124.7, 51.5, 44.6, 40.5, 31.6, 29.4, 27.3, 25.5, 23.2, 22.3; *m/z* LRMS (EI$^+$) 209.1 (23%), 119.0 (51%), 91.0 (82%), 81.1 ([C_6H_9]$^+$, 100%), 67.1 (60%), 59.1 ([CH_3OCO]$^+$, 75%); (CI$^+$) 322.3 (10%) [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{18}H_{25}O_4$: 305.1747 [M+H]$^+$; found: 305.1751 [M+H]$^+$.

2-Allyl-2-methyl-cyclohexane-1,3-dione (285)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and allylbromide (5.15 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **285** (4.55 g, 69%) as a colourless oil: ν_{max} (liquid film)/cm^{-1} 3079 (C-H), 2978 (C-H), 2875 (C-H), 1699 (C=O), 1455, 1427, 1373, 1320, 1026, 921; δ_H (300 MHz, $CDCl_3$) 5.65-5.51 (1H, m, *H'*), 5.10-5.03 (2H, m, *H''* and *H'''*), 2.68-2.63 (4H, m, 2 × CH_2CH_2CO), 2.53 (2H, dt, *J* 7.3 and 1.1, CH_2CHCH_2C), 2.08-1.81 (2H, m, CH_2CH_2CO), 1.24 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 209.9, 132.2, 119.2, 65.2, 41.3, 38.2, 19.5, 17.5; *m/z* LRMS (EI$^+$) 110.1 (10%), 95.0 (12%), 67.1 (18%), 55.0 (25%); (CI$^+$) 184.1 [M+NH$_4$]$^+$; HRMS (EI$^+$) calc. for $C_{10}H_{14}O_2$: 166.0988 [M]$^+$; found: 166.0986 [M]$^+$; Anal. Calc. for $C_{10}H_{14}O_2$: C, 72.3; H, 8.49; N, 0.00. Found: C, 70.3; H, 8.41; N, 0.00 %.

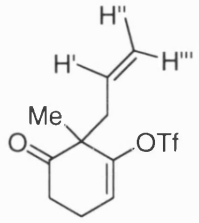
2-Methyl-2-propyl-cyclohexane-1,3-dione (286)



Prepared using general procedure **F** from diketone **285** (158 mg, 0.94 mmol) to yield diketone **286** (160 mg, 100%) as a colourless oil: ν_{max} (liquid film)/cm^{-1} 2962 (C-H), 2874 (C-H), 1688 (C=O), 1456, 1426, 1373, 1331, 1131, 1025, 934, 841; δ_H (300 MHz, $CDCl_3$) 2.77-2.56 (4H, m, 2 × CH_2CH_2CO), 2.10-1.97 (1H, m, $CH_AH_BCH_2CO$), 1.92-1.80 (1H, m, $CH_AH_BCH_2CO$), 1.78-1.73 (2H, m, $CH_3CH_2CH_2C$), 1.22-1.09 (5H, m, CH_3CCO and $CH_3CH_2CH_2C$), 0.87 (3H, t, *J* 7.2, $CH_3CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 210.4, 65.9, 40.0, 38.0, 18.7, 18.1, 17.8, 14.4; *m/z* LRMS (EI$^+$) 168.1 ([M]$^+$, 10%), 139.1 (13%), 126.1 (20%), 111.1 (35%), 69.1 (43%), 55.0 (36%), 41.2 (100%); (CI$^+$) 186.2 [M+NH$_4$]$^+$; HRMS

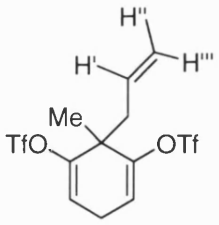
(ES$^+$) calc. for $C_{10}H_{20}NO_2$: 186.1489 $[M+NH_4]^+$; found: 186.1491 $[M+NH_4]^+$; Anal. Calc. for $C_{10}H_{16}O_2$: C, 71.4; H, 9.59; N, 0.00. Found: C, 69.5; H, 9.31; N, 0.00 %.

Trifluoro-methanesulfonic acid 6-allyl-6-methyl-5-oxo-cyclohex-1-enyl ester (287)



Prepared using general procedure **B** from diketone **285** (1.69 g, 10.2 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **287** (790 mg, 26%) as a yellow oil: ν_{max} (liquid film)/cm^{-1} 3083 (C-H), 2982 (C-H), 2840 (C-H), 1725 (C=O), 1680, 1418 (O-SO_2), 1213 (SO_2), 1142, 1018, 935, 874, 599; δ_H (300 MHz, $CDCl_3$) 6.08 (1H, dd (app. t), *J* 4.5 and 4.5, $CH_2CHCOSO_2$), 5.66-5.52 (1H, m, *H'*), 5.10-5.09 (1H, m, *H''*), 5.05-5.04 (1H, m, *H'''*), 2.64-2.49 (3H, m, CH_2CH_2CO and $CH_AH_BCH_2CO$), 2.46-2.38 (2H, m, $CH_AH_BCH_2CO$ and $CH_2CHCH_AH_BC$), 2.35-2.28 (1H, m, $CH_2CHCH_AH_BC$) 1.31 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 208.4, 150.1, 132.2, 118.4 (q, *J* 319.3, CF_3), 119.4, 116.8, 52.8, 40.6, 36.2, 24.2, 20.0; HRMS (ES$^+$) calc. for $C_{11}H_{14}F_3O_4S$: 299.0559 $[M+H]^+$; found: 299.0569 $[M+H]^+$.

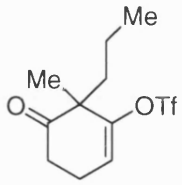
Trifluoro-methanesulfonic acid 6-allyl-6-methyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (288)



Prepared using general procedure **B** from diketone **285** (206 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **288** (2.24 g, 21%) as a white powder: mp 48-53°C (hexane) ν_{max}

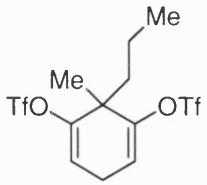
(film)/cm^{-1} 1414 (O-SO_2), 1211 (SO_2), 1144, 994, 926, 860, 746, 598; δ_H (300 MHz, $CDCl_3$) 5.86 (2H, dd (app.t), *J* 4.8 and 4.8, 2 x $CH_2CHCOSO_2$), 5.72-5.58 (1H, m, *H'*), 5.16-5.15 (1H, m, *H''*), 5.11-5.09 (1H, m, *H'*), 3.10-2.92 (2H, m, $CH_2CHCOSO_2$), 2.35 (2H, d, J 7.3, CH_2CHCH_2C), 1.41 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 148.1, 131.6, 119.6, 118.3 (q, *J* 319.3, CF_3), 113.3, 44.0, 39.5, 24.5, 22.7; Anal. Calc. for $C_{12}H_{12}O_6S_2F_6$: C, 33.5; H, 2.81; N, 0.00. Found: C, 33.4; H, 2.82; N, 0.30 %.

Trifluoro-methanesulfonic acid 6-methyl-5-oxo-6-propyl-cyclohex-1-enyl ester (289)



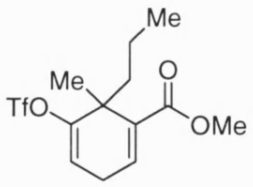
Prepared according to general procedure **B** using diketone **286** (1.71 g, 10.2 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-alkenyltriflate **289** (550 mg, 18%) as a yellow oil: ν_{max} (liquid film)/cm^{-1} 2964 (C-H), 2938 (C-H), 2877 (C-H), 1723 (C=O), 1679, 1415 (O-SO_2), 1215 (SO_2), 1141, 1017, 932, 870, 786, 603; δ_H (300 MHz, $CDCl_3$) 6.07 (1H, dd (app. t), *J* 4.2 and 4.2, $CH_2CHCOSO_2$), 2.65-2.39 (4H, m, CH_2CH_2CO and $CH_3CH_2CH_2C$), 1.94-1.83 (1H, m, $CH_AH_BCHCOSO_2$), 1.55-1.45 (1H, m, $CH_AH_BCHCOSO_2$), 1.28 (3H, s, CH_3CCO), 1.27-0.99 (2H, m, $CH_3CH_2CH_2C$), 0.87 (3H, t, *J* 7.2, $CH_3CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 209.2, 150.9, 118.4 (q, *J* 319.3, CF_3), 116.5, 52.7, 38.5, 36.2, 23.1, 20.0, 18.37, 14.2; HRMS (ES^+) calc. for $C_{11}H_{16}F_3O_4S$: 301.0716 $[M+H]^+$; found: 301.0728 $[M+H]^+$.

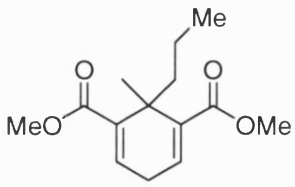
Trifluoro-methanesulfonic acid 6-methyl-6-propyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (290)



Prepared using general procedure **B** from diketone **286** (1.71 g, 10.2 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **290** (2.12 g, 48%) as a yellow oil: ν_{max} (liquid film)/cm^{-1} 2966 (C-H), 2941 (C-H), 2879 (C-H), 1705, 1418 (O-SO_2), 1213 (SO_2), 1142, 1063, 1000, 912, 862, 809, 612; δ_H (300 MHz, $CDCl_3$) 5.85 (2H, dd (app.t), *J* 3.8 and 3.8, 2 × $CH_2CHCOSO_2$), 3.03 (2H, td, *J* 3.8 and 1.1, $CH_2CHCOSO_2$), 1.58-1.53 (2H, m, $CH_3CH_2CH_2C$), 1.37 (3H, s, CH_3CCOSO_2), 1.33-1.20 (2H, m, $CH_3CH_2CH_2C$), 0.92 (3H, t, *J* 7.2, $CH_3CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 148.7, 118.4 (q, *J* 319.3, CF_3), 113.2, 43.9, 37.3, 24.5, 23.3, 18.0, 13.7; *m/z* LRMS (EI$^+$) 432.1 ([M]$^+$, 10%), 389.1 ([M-C_3H_7]$^+$, 100%), 105.0 (40%), 69.0 ([CF_3]$^+$, 100%); HRMS (EI) calc. for $C_{12}H_{14}F_6O_6S_2$: 432.0131 [M]$^+$; found: 432.0127 [M]$^+$.

6-Methyl-6-propyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-diene carboxylic acid methyl ester (291) and 2-Methyl-2-propyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (292)

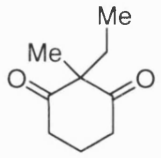




Prepared using general procedure **D** from *bis*-alkenyltriflate **290** (47 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **291** (11.4 mg, 32%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.95 (1H, td, *J* 3.6 and 1.1, CH_2CHCCO_2), 5.80 (1H, td, *J* 3.6 and 1.1, $CH_2CHCOSO_2$), 3.75 (3H, s, CH_3OCO), 3.03 (2H dd (app. t), *J* 3.6 and 3.6, $CH_2CHCOSO_2$), 2.13 (1H, overlapping ddd, *J* 14.0, 12.4 and 4.8, $CH_3CH_2CH_AH_BC$), 1.57-1.48 (1H, m, $CH_3CH_2CH_AH_BC$), 1.46 (3H, s, CH_3CCOSO_2), 1.28-0.99 (2H, m, $CH_3CH_2CH_2$),

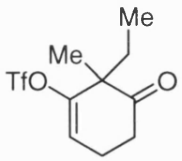
0.87 (3H, t, *J* 7.2, C*H*$_3$CH$_2$CH$_2$); δ_C (75 MHz, $CDCl_3$) 165.8, 152.1, 135.6, 133.5, 118.4 (q, *J* 317.8, CF_3), 112.0, 51.7, 42.0, 37.7, 26.9, 24.6, 18.7, 14.0; *m/z* LRMS (EI^+) 299.1 ([M-C_3H_7]$^+$, 73%), 298.1 (100%), 107.0 (40%), 91.1 (50%), 69.0 ([CF_3]$^+$, 100%), 40.1 (70%); (CI^+) 360 (100%) [M+NH_4]$^+$; HRMS (ES^+) calc. for $C_{13}H_{21}F_3NO_5S$: 360.1087 [M+NH_4]$^+$; found: 360.1087 [M+NH_4]$^+$ and diester **292** (10.0 mg, 38%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.85 (2H, dd (app. t), *J* 4.6 and 4.6, 2 × CH_2CHCCO), 3.73 (6H, s, 2 × C*H*$_3$OCOC), 2.94 (2H, dd (app. t), *J* 4.6 and 4.6, C*H*$_2$CHCCO$_2$), 2.09-2.04 (2H, m, $CH_3CH_2CH_2C$), 1.55 (3H, s, C*H*$_3$CCCO$_2$), 1.09-0.96 (2H, m, $CH_3CH_2CH_2C$), 0.83 (3H, t, *J* 7.2, C*H*$_3$CH$_2$CH$_2$C); δ_C (75 MHz, $CDCl_3$) 167.2, 136.1, 134.1, 51.5, 40.3, 39.0, 27.6, 26.4, 19.3, 14.4; *m/z* LRMS (EI^+) 252.2 ([M]$^+$, 100%), 235.1 (85%), 193.1 ([M-CO_2CH_3]$^+$, 40%), 165.1 (100%), 119.0 (35%), 91.0 (36%), 59.1 ([CH_3OCO]$^+$, 40%), 43.2 ([C_3H_7]$^+$, 43%); (CI^+) 270 (100%) [M+NH_4]$^+$; HRMS (ES^+) calc. for $C_{14}H_{24}NO_4$: 270.1700 [M+NH_4]$^+$; found: 270.1700 [M+NH_4]$^+$.

2-Ethyl-2-methyl-cyclohexane-1,3-dione (293)



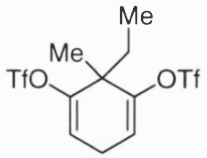
Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and ethyl iodide (4.76 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 2:1) to yield diketone **293** (3.24 g, 53%) as a colourless oil: ν_{max} (liquid film)/cm^{-1} 2969 (C-H), 2939 (C-H), 2879 (C-H), 1699 (C=O), 1373, 1325, 1265, 1129, 1026, 829; δ_H (300 MHz, $CDCl_3$) 2.77-2.58 (4H, m, 2 × CH_2CH_2CO), 2.10-1.97 (1H, m, CH_AH$_B$CH$_2$CO), 1.92-1.77 (3H, m, CH$_A$H$_B$CH$_2$CO and CH_3CH_2CCO), 1.21 (3H, s, C*H*$_3$CCO), 0.80 (3H, t, *J* 7.5, C*H*$_3$CH$_2$CCO); δ_C (75 MHz, $CDCl_3$) 210.4, 66.2, 38.0, 30.8, 18.1, 17.8, 9.1; *m/z* LRMS (EI^+) 154.1 ([M]+, 42%), 111.1 (61%), 97.1 (45%), 69.0 (53%), 55.0 (58%), 42.2 (100%); (CI^+) 172.2 [M+NH_4]$^+$; HRMS (EI^+) calc. for $C_9H_{14}O_2$: 154.0988 [M]$^+$; found: 154.0987 [M]$^+$.

Trifluoro-methanesulfonic acid 6-ethyl-6-methyl-5-oxo-cyclohex-1-enyl ester (294)



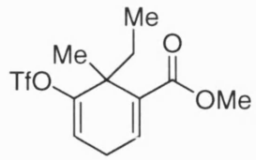
Prepared using general procedure **B** from diketone **293** (1.00 g, 6.49 mmol) and purified by flash chromatography (hexane:EtOAC 10:1) to yield mono-alkenyltriflate **294** (501 mg, 27%) as an orange oil: ν_{max} (liquid film)/cm^{-1} 2975 (C-H), 2941 (C-H), 1723 (C=O), 1679, 1460, 1416 (O-SO_2), 1214 (SO_2), 1142, 1017, 932, 886, 832, 677, 609; δ_H (300 MHz, $CDCl_3$) 6.11 (1H, dd (app. t), *J* 4.1 and 4.1, $CH_2CHCOSO_2$), 2.66-2.51 (2H, m, $CH_2CH_AH_BCO$ and $CH_3CH_AH_BCCO$), 2.48-2.40 (2H, m, $CH_2CH_AH_BCO$ and $CH_3CH_AH_BCCO$), 2.02-1.90 (1H, m, $CH_AH_BCHCOSO_2$), 1.64-1.49 (1H, m, $CH_AH_BCHCOSO_2$), 1.28 (3H, s, CH_3CCO), 0.78 (3H, dd (app. t), *J* 7.4 and 7.4, $CH_3CH_AH_BCCO$); δ_C (75 MHz, $CDCl_3$) 209.15, 150.6, 118.4 (q, *J* 320.1, CF_3), 116.9, 53.2, 36.2, 29.2, 22.7, 20.0, 9.32.

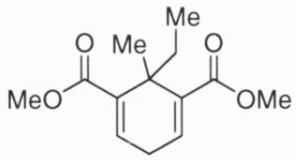
Trifluoro-methanesulfonic acid 6-ethyl-6-methyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (295)



Prepared using general procedure **B** from diketone **293** (1.00 g, 6.49 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **295** (1.36 g, 51%) as an orange oil: ν_{max} (liquid film)/cm^{-1} 2977 (C-H), 2944 (C-H), 2885 (C-H), 1705, 1418 (O-SO_2), 1213 (SO_2), 1140, 998, 895, 803, 737, 611; δ_H (300 MHz, $CDCl_3$) 5.89 (2H, dd (app. t), *J* 3.7 and 3.7, 2 × $CH_2CHCOSO_2$), 3.05 (2H, td, *J* 3.8 and 0.7 $CH_AH_BCHCOSO_2$), 1.63 (2H, q, *J* 7.4, CH_3CH_2CCO), 1.38 (3H, s, CH_3CCO), 0.87 (3H, t, *J* 7.4, CH_3CH_2CCO); δ_C (75 MHz, $CDCl_3$) 148.3, 118.3 (q, *J* 319.3, CF_3), 113.5, 44.4, 28.0, 24.5, 23.0, 8.8.

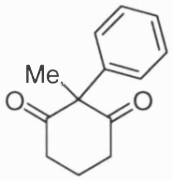
6-Ethyl-6-methyl-5-trifluoromethanesulfonyloxy-cyclohexa-1,4-diene carboxylic acid methyl ester (296) and 2-ethyl-2-methyl-cyclohexa-3,6-diene-1,3-dicarboxylic acid dimethyl ester (297)





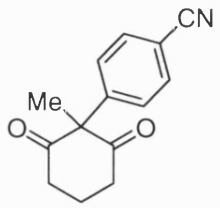
Prepared using general procedure **D** from *bis*-alkenyltriflate **295** (44 mg, 0.104 mmol) to yield in order of elution (hexane:diethyl ether 10:1) mono-ester **296** (10.6 mg, 31%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.00 (1H, td, *J* 3.6 and 1.2, CH_2CHCCO_2), 5.83 (1H, td, *J* 3.6 and 1.2, $CH_2CHCOSO_2$), 3.75 (3H, s, CH_3OCO), 3.04 (2H dd (app. t), *J* 3.7 and 3.7, $CH_2CHCOSO_2$), 2.17 (1H, dt (app. septet), *J* 7.4 and 7.0, $CH_3CH_AH_BCO$), 1.61 (1H, dt (app. septet), *J* 7.4 and 7.0, $CH_3CH_AH_BCO$), 1.47 (3H, s, CH_3CCOSO_2), 0.74 (3H, t, *J* 7.5, CH_3CH_2C); δ_C (75 MHz, $CDCl_3$) 165.8, 151.7, 136.1, 133.1, 118.3 (q, *J* 320.1, CF_3), 112.4, 51.7, 42.5, 28.3, 26.9, 24.3, 9.5; *m/z* LRMS (EI^+) 299.1 ($[M-C_2H_5]^+$, 45%), 107.0 (50%), 91.1 (50%), 69.1 ($[CF_3]^+$, 100%), 59.1 (40%); (CI^+) 346 (15%) $[M+NH_4]^+$; HRMS (EI^+) calc. for $C_{12}H_{15}F_3O_5S$: 328.0587 $[M]^+$; found: 325.0585 $[M]^+$ and diester **297** (9.4 mg, 38%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 6.89 (2H, dd (app. t), *J* 3.6 and 3.6, 2 × CH_2CHCCO), 3.73 (6H, s, 2 × CH_3OCOC), 2.95 (2H, dd (app. t), *J* 3.6 and 3.6, CH_2CHCCO_2), 1.56 (3H, s, CH_3CCCO_2), 0.65 (3H, t, *J* 7.5, CH_3CH_2C); δ_C (75 MHz, $CDCl_3$) 167.2, 135.6, 134.6, 51.5, 40.9, 29.4, 27.6, 26.2, 10.1; *m/z* LRMS (EI^+) 209.2 (20%), 165.1 (25%), 119.0 (30%), 91.1 (100%), 69.1 (25%), 59.1 (45%); (CI^+) 256 (100%) $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{13}H_{22}NO_4$: 256.1543 $[M+NH_4]^+$; found: 256.1543 $[M+NH_4]^+$.

2-Methyl-2-phenyl-cyclohexane-1,3-dione (300)



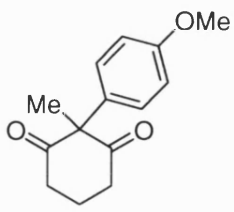
A solution of 2-methyl-2-phenyl-[1,3]dioxolane **303** (1.64 g, 10.0 mmol) in dry DCM (40 mL) was cooled to -78°C under N_2. Boron trifluoride etherate (19.4 mL, 152.6 mmol) was added, followed by the dropwise addition of 1,2-*bis*-(trimethylsiloxy)cyclopentene (3.66 g, 15 mmol) as a solution in DCM (10 mL). The mixture was stirred overnight, during which time the mixture reached room temperature. Water (50 mL) was added, then the aqueous layer was extracted with DCM (3 × 50 mL). The organic portions were combined, and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The dark residue was purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **300** (1.15 g, 57%) as a colourless oil: ν_{max} (liquid film)/cm^{-1} 3059 (C-H), 2936 (C-H), 1698 (C=O), 1598, 1493, 1445, 1371, 1272, 1080, 1024, 892, 762, 701; δ_H (300 MHz, $CDCl_3$) 7.39-7.26 (3H, m, 3 × Ar-*H*), 7.02-6.98 (2H, m, 2 × Ar-*H*), 2.85-2.74 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.61-2.51 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.98-1.84 (1H, m, $CH_AH_BCH_2CO$), 1.78-1.63 (1H, m, $CH_AH_BCH_2CO$), 1.43 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 207.8, 140.4, 129.7, 127.7, 126.0, 72.5, 38.6, 20.9, 17.9; *m/z* LRMS (EI$^+$) 202.1 (71%), 129.1 (39%), 104.1 (63%), 77.1 (58%), 51.1 (37%), 42.2 (100%); (CI$^+$) 220 $[M+NH_4]^+$; HRMS (ES$^+$) calc. for $C_{13}H_{18}NO_2$: 220.1332 $[M+NH_4]^+$; found: 220.1332 $[M+NH_4]^+$; Anal. Calc. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.98; N, 0.00. Found: C, 75.5; H, 7.08; N, 0.00 %.

4-(1-Methyl-2,6-dioxo-cyclohexyl)-benzonitrile (302)



A solution of 4-(2-methyl-[1,3]dioxolan-2-yl)-benzonitrile **304** (1.89 g, 10.0 mmol) in dry DCM (40 mL) was cooled to -78°C under N_2. Boron trifluoride etherate (19.4 mL, 152.6 mmol) was added, followed by the dropwise addition of 1,2-*bis*-(trimethylsiloxy)cyclopentene (3.66 g, 15 mmol) as a solution in DCM (10 mL). The mixture was stirred overnight, during which time the mixture reached room temperature. Water (50 mL) was added, then the aqueous layer was extracted with DCM (3 × 50 mL). The organic portions were combined, and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The dark residue was purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **302** (250 mg, 11%) as a cream solid: mp 58-62°C. ν_{max} (film)/cm^{-1} 2963 (C-H), 2937 (C-H), 2229 (CN), 1732, 1699 (C=O), 1605, 1502, 1404, 1273, 1098, 1023, 841; δ_H (300 MHz, $CDCl_3$) 7.69-7.65 (2H, m, 2 × Ar-*H*), 7.17-7.13 (2H, m, 2 × Ar-*H*), 2.78-2.59 (4H, m, 2 × CH_2CH_2CO), 1.97-1.72 (2H, m, CH_2CH_2CO), 1.46 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 206.7, 145.2, 133.3, 127.0, 118.0, 112.0, 72.0, 38.7, 21.1, 17.7; *m/z* LRMS (EI$^+$) 227.1 (18%), 157.0 (20%), 129.1 (26%), 102.0 (25%), 55.1 (52%), 42.2 (100%); (CI$^+$) 245 $[M+NH_4]^+$; HRMS (CI$^+$) calc. for $C_{14}H_{17}N_2O_2$: 245.1285 $[M+NH_4]^+$; found: 245.1283 $[M+NH_4]^+$.

2-(4-Methoxy-phenyl)-2-methyl-cyclohexane-1,3-dione (301)



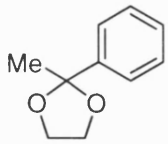
To a stirred solution of *para*-methoxyacetophenone (1.25 g, 8.33 mmol) in anhydrous DCM (40 mL) was added boron trifluoride etherate (1.27 mL, 10.00 mmol), followed by a solution of 1,2-*bis*-(trimethysilyl)cyclopentene (3.05 g,

12.49 mmol) in anhydrous DCM (10 mL), at room temperature. After 2.5 h water (1.30 mL, 72.40 mmol) was added, and after a further 10 minutes boron trifluoride etherate (15.80 mL, 125.00 mmol) was added. The reaction mixture was stirred for an additional 1 h, then washed with water (2 × 30 mL). The combined aqueous washings were then re-extracted with DCM (2 × 30 mL), the organic layers combined, and washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a dark oil. The crude mixture was then redissolved in diethyl ether (50 mL), and decolourising charcoal (3 g) was added. This suspension was then filtered through a plug containing more charcoal (6 g), and florisil (18 g), eluting with diethyl ether (150 mL). The filtrate was then concentrated under reduced pressure to produce yellow needles, which upon recrystallisation (DCM/hexane) produced diketone **301** (657 mg, 34%) as colourless needles: mp 78-80°C (DCM/hexane). ν_{max} (film)/cm^{-1} 3011 (C-H), 2937 (C-H), 2839 (O-CH_3), 1699 (C=O), 1606 (Ar), 1364, 1294, 1246, 1187, 1029, 836, 807; δ_H (300 MHz, $CDCl_3$) 6.93-6.86 (4H, m, 4 × Ar-*H*), 3.80 (3H, s, CH_3OAr), 2.85-2.74 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.59-2.49 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.97-1.84 (1H, m, $CH_AH_BCH_2CO$), 1.77-1.63 (1H, m, $CH_AH_BCH_2CO$), 1.41 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 208.1, 159.0, 132.2, 127.2, 115.0, 71.8, 55.3, 38.5, 20.9, 17.9; *m/z* LRMS (EI^+) 232.0 (42%), 161.1 (22%), 148.1 (100%), 133.1 (25%), 91.1 (29%), 65.1 (22%); (CI^+) 250.3 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{14}H_{20}NO_3$: 250.1438 $[M+NH_4]^+$; found: 250.1438 $[M+NH_4]^+$; Anal. Calc. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.94; N, 0.00. Found: C, 72.4; H, 6.96; N, 0.00 %.

General procedure G: The preparation of aryl dioxolanes

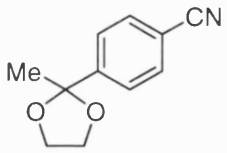
To a stirred solution of *para*-toluenesulfonic acid monohydrate (0.95 g, 5.00 mmol) and ethylene glycol (13.94 mL, 249.9 mmol) in toluene (50 mL) was added the corresponding acetophenone (24.99 mmol). The flask was fitted with Dean-Stark apparatus, and the reaction for heated at 130°C for 24 h. The reaction was then cooled to room temperature, diluted with ethyl acetate (200 mL), and washed with water (50 mL) and brine (50 mL). The organic portion was dried over $MgSO_4$, and the concentrated under reduced pressure. The crude mixtures were then purified by flash chromatography (hexane:EtOAc, 3:1) to yield the desired products.

2-Methyl-2-phenyl-[1,3]dioxolane (303)



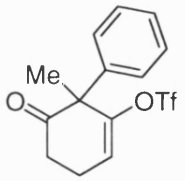
Prepared using general procedure **G** to provide dioxolane **303** (3.10 g, 76%) as white needles: mp 50-56°C. ν_{max} (film)/cm^{-1} 2989 (C-H), 2895 (C-H), 1438, 1372, 1202, 1030, 870, 767, 702, 597; δ_H (300 MHz, $CDCl_3$) 7.50-7.46 (2H, m, 2 × Ar-*H*), 7.38-7.27 (3H, m, 3 × Ar-*H*), 4.07-3.99 (2H, m, $OCH_AH_BCH_AH_BO$), 3.84-3.75 (2H, m, $OCH_AH_BCH_AH_BO$), 1.66 (3H, s, CH_3CAr); δ_C (75 MHz, $CDCl_3$) 143.3, 128.2, 127.8, 125.2, 108.8, 64.4, 27.6. Data consistent with literature.[372]

4-(2-Methyl-[1,3]dioxolan-2-yl)-benzonitrile (304)



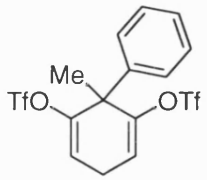
Prepared using general procedure **G** to provide dioxolane **304** (3.71 g, 79%) as white needles: mp 61-64°C. ν_{max} (film)/cm^{-1} 2993 (C-H), 2888 (C-H), 2233 (CN), 1375, 1244, 1203, 1096, 1039, 888, 838, 738, 611, 558; δ_H (300 MHz, $CDCl_3$) 7.67-7.59 (4H, m, 4 × Ar-*H*), 4.09-4.05 (2H, m, $OCH_AH_BCH_AH_BO$), 3.78-3.73 (2H, m, $OCH_AH_BCH_AH_BO$), 1.64 (3H, s, CH_3CAr); δ_C (75 MHz, $CDCl_3$) 148.7, 132.2, 126.2, 118.8, 111.8, 108.2, 64.7, 27.4; *m/z* LRMS (EI$^+$) 174.1 (100%), 158.1 (15%), 130.0 (80%), 102.0 (66%), 87.1 (52%), 75.1 (35%); (CI$^+$) 207 $[M+NH_4]^+$; HRMS (CI$^+$) calc. for $C_{11}H_{15}N_2O_2$: 207.1128 $[M+NH_4]^+$; found: 207.1129 $[M+NH_4]^+$.

Trifluoro-methanesulfonic acid 6-methyl-5-oxo-6-phenylcyclohex-1-enyl ester (305)



Prepared using general procedure **B** from diketone **300** (246 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 5:1) to yield mono-alkenyltriflate **305** (129 mg, 38%) as a yellow oil: ν_{max} (liquid film)/cm^{-1} 3062 (C-H), 2987 (C-H), 2944 (C-H), 1728 (C=O), 1681, 1494, 1418 (O-SO_2), 1376, 1214 (SO_2), 1140, 1014, 930, 891, 811, 699, 611; δ_H (300 MHz, $CDCl_3$) 7.37-7.27 (5H, m, 5 × Ar-*H*), 6.28-6.26 (1H, m, CH_2CHCO), 2.68-2.39 (4H, m, 4 × CH_2CH_2CO), 1.73 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 205.0, 149.2, 138.7, 129.0, 127.9, 126.6, 120.4, 117.5, 57.2, 34.1, 20.9, 20.2; *m/z* LRMS (EI$^+$) 334.1 ([M+H]$^+$, 4%), 292.1 (10%), 159.1 (18%), 131.1 (13%), 91.1 ([$C_6H_6CH_2$]$^+$, 12%), 77.1 ([C_6H_6]$^+$, 10%), 69.1 ([CF_3]$^+$, 100%), 55.1 (27%), 43.2 (42%); (CI$^+$) 352 [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{14}H_{17}NO_4SF_3$: 352.0825 [M+NH_4]$^+$; found: 352.0826 [M+NH_4]$^+$.

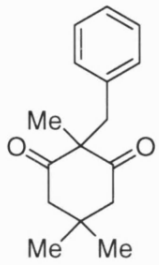
Trifluoro-methanesulfonic acid 6-methyl-6-phenyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (306)



Prepared using general procedure **C** from mono-alkenyltriflate **305** (129 mg, 0.388 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **306** (98 mg, 54%) as a yellow oil: ν_{max} (liquid film)/cm^{-1} 3094 (C-H), 2993 (C-H), 2950 (C-H), 1703, 1418 (O-SO_2), 1214 (SO_2), 1140, 1002, 923, 897, 790,699, 606; δ_H (300 MHz, $CDCl_3$) 7.42-7.31 (5H, m, 5 × Ar-*H*), 5.90 (2H, dd (app. t), *J* 3.7 and 3.7, 2 × CH_2CHCO), 3.33-3.13 (2H, m, CH_2CHCO), 1.84 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 149.6, 137.5, 128.7, 128.4, 127.5, 118.1 (q, *J* 320.1, CF_3), 111.8, 46.8, 24.6, 20.3; *m/z* LRMS (EI$^+$)

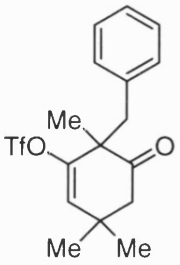
466.1 (8%), 183.1 (54%), 167.1 (68%), 155.1 (100%), 129.1 (51%), 91.1 ($[C_6H_6CH_2]^+$, 25%), 69.1 ($[CF_3]^+$, 100%); (CI^+) 484 $[M+NH_4]^+$; HRMS (EI^+) calc. for $C_{15}H_{12}O_6F_6S_2$: 465.9974 $[M+H]^+$; found: 465.9974 $[M+H]^+$.

2-Benzyl-2,5,5-trimethyl-cyclohexane-1,3-dione (307)



Prepared using general procedure **A** from 2,5,5-trimethyl-1,3-cyclohexanedione (6.12 g, 39.7 mmol) and benzylbromide (8.39 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 4:1) to yield diketone **307** (5.91 g, 61%) as white needles; mp 52-53°C (EtOAc/hexane). ν_{max} (film)/cm^{-1} 3030 (C-H), 2955 (C-H), 2871 (C-H), 1726 (C=O), 1496 (Ar); δ_H (400 MHz, $CDCl_3$) 7.21-7.18 (3H, m, 3 × Ar-*H*), 7.17-7.03 (2H, m, 2 × Ar-*H*), 3.07 (2H, s, CCH_2Ar), 2.47 (2H, d, *J* 15.0, 2 × $C(CH_3)_2CH_AH_BCO$), 2.35 (2H, d, *J* 15.0, 2 × $C(CH_3)_2CH_AH_BCO$), 1.26 (3H, s, CH_3CCO), 0.87 (3H, s, $(CH_3)C(CH_3)CH_2CO$), 0.79 (3H, s, $(CH_3)C(CH_3)CH_2CO$); δ_C (100 MHz, $CDCl_3$) 210.4, 135.9, 130.1, 128.2, 126.9, 64.7, 52.8, 44.2, 30.2, 29.2, 28.2, 20.8. Data consistent with literature.[373]

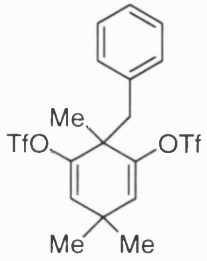
Trifluoro-methanesulfonic acid 6-benzyl-3,3,6-trimethyl-5-oxo-cyclohex-1-enyl ester (308)



Prepared using general procedure **B** from diketone **307** (992 mg, 4.07 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield mono-

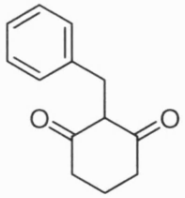
alkenyltriflate **308** (1.09 g, 71%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 3033 (C-H), 2963 (C-H), 2933 (C-H), 1724 (C=O), 1675 (C=C), 1416 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.27-7.20 (3H, m, 3 × Ar-*H*), 7.19-7.05 (2H, m, 2 × Ar-*H*), 5.81 (1H, s, CC*H*$COSO_2$), 3.09 (1H, d, *J* 13.4, CCH_AH_BAr), 2.87 (1H, d, *J* 13.4, CCH_AH_BAr), 2.26 (1H, d, *J* 14.7, $C(CH_3)_2CH_AH_BCO$), 1.69 (1H, d, *J* 14.7, $C(CH_3)_2CH_AH_BCO$), 1.41 (3H, s, CH_3CCO), 1.02 (3H, s, $(CH_3)C(CH_3)CH_2CO$), 0.47 (3H, s, $(CH_3)C(CH_3)CH_2CO$); δ_C (100 MHz, $CDCl_3$) 208.2, 147.8, 135.9, 130.1, 128.1, 127.4, 126.9, 118.3, 53.7, 51.4, 41.8, 32.5, 29.5, 28.5, 23.6. Data consistent with literature.[315]

Trifluoro-methanesulfonic acid 6-benzyl-3,3,6-trimethyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (309)



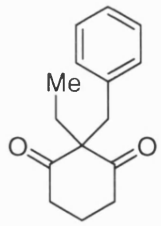
Prepared using general procedure **C** from mono-alkenyltriflate **308** (500 mg, 1.33 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **309** (283 mg, 42%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3034 (C-H), 2968 (C-H), 2942 (C-H), 1602 (C=C), 1422 (O-SO_2), 1213 (SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.29-7.18 (3H, m, 3 × Ar-*H*), 7.06-7.03 (2H, m, 2 × Ar-*H*), 5.48 (2H, s, 2 × CC*H*$COSO_2$), 2.85 (2H, s, CCH_2Ar), 1.52 (3H, s, CH_3CCO), 1.09 (3H, s, $(CH_3)C(CH_3)CHCO$), 0.34 (3H, s, $(CH_3)C(CH_3)CHCO$); δ_C (100 MHz, $CDCl_3$) 145.6, 135.7, 130.1, 128.3, 127.3, 124.3, 118.8, 46.1, 41.8, 35.5, 30.2, 28.7, 23.2. Data consistent with literature.[315]

2-Benzyl-cyclohexane-1,3-dione (310)



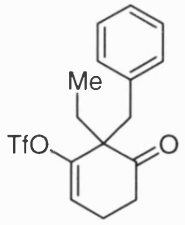
A stirred solution of trimethylsilylchloride (6.35 mL, 50.0 mmol), sodium iodide (7.49 g, 50.0 mmol) and 1,3-cyclohexanedione (1.24 g, 10.0 mmol) in acetonitrile was cooled to 0°C. Benzaldehyde (1.02 mL, 10.0 mmol) was then added and the reaction mixture was allowed to warm to room temperature, and stirred for 6 h. The reaction was then heated at 60°C for 10 h and then cooled to room temperature, water (25 mL) was added, and the mixture was extracted with diethyl ether (50 mL). The organic layer was then washed with aqueous saturated sodium thiosulfate (15 mL) to remove liberated iodine, hydrochloric acid (10 mL, 2M), and brine (30 mL). Aqueous washings were then re-extracted with diethyl ether (50 mL). The organic washings were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to produce a viscous orange oil. This crude diketone was purified by flash chromatography (EtOAc) to yield diketone **310** (1.17 g, 58%) as white needles: mp 184-186°C (EtOAc/hexane). ν_{max} (film)/cm^{-1} 1557 (C=O), 1495, 1357, 1271, 1176, 1141, 1080, 1004, 704; δ_H (300 MHz, CD_3OD) 7.22-7.14 (4H, m, 4 × Ar-*H*), 7.10-7.05 (1H, m, Ar-*H*), 3.58 (2H, s, ArCH_2CHCO), 2.45 (4H, t, *J* 6.2, 2 × CH_2CH_2CO), 1.96 (2H, quintet, *J* 6.4, CH_2CH_2CO); δ_C (75 MHz, CD_3OD) 143.4, 129.9, 129.3, 126.7, 117.0, 28.8, 22.4; *m/z* LRMS (EI$^+$) 202.1 ([M]$^+$, 4%), 145.1 (70%), 131.1 (100%), 91.1 ([$C_6H_5CH_2$]$^+$, 100%), 77.1 ([C_6H_5]$^+$, 70%), 55.2 (65%), 51.2 (75%), 42.2 (100%); (CI$^+$) 220 [M+NH_4]$^+$; HRMS (CI$^+$) calc. for $C_{13}H_{15}O_2$: 203.1067 [M+NH_4]$^+$; found: 203.1067 [M+NH_4]$^+$; Anal. Calc. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; N, 0.00. Found: C, 76.5; H, 6.95; N, 0.00 %.

2-Benzyl-2-ethyl-cyclohexane-1,3-dione (316)



Prepared using general procedure **A** from 2-benzyl-1,3-cyclohexanedione **310** (1.50 g, 7.43 mmol) and ethyl iodide (1.78 mL, 22.28 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **316** (752 mg, 44%) as white needles: mp 54-56°C ν_{max} (film)/cm^{-1} 2967 (C-H), 2881 (C-H), 1685 (C=O), 1454, 1348, 1087, 1031, 861, 756, 703; δ_H (300 MHz, $CDCl_3$) 7.25-7.16 (3H, m, 3 × Ar-*H*), 7.02-6.98 (2H, m, 2 × Ar-*H*), 3.07 (2H, s, ArCH_2CCO), 2.45-2.34 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.16-2.05 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.96 (2H, q, *J* 7.5, CH_3CH_2CCO), 1.73-1.60 (1H, m, $CH_AH_BCH_2CO$), 1.30-1.16 (1H, m, $CH_AH_BCH_2CO$), 0.76 (3H, t, *J* 7.5, CH_3CH_2CCO); δ_C (75 MHz, $CDCl_3$) 212.8, 136.8, 129.9, 128.5, 127.0, 70.0, 44.9, 41.2, 31.8, 15.6, 10.0 (CF_3 not seen); *m/z* LRMS (EI^+) 230.2 ([M]$^+$, 100%), 173.1 (45%), 145.1 (40%), 115.1 (25%), 91.1 ([$C_6H_5CH_2$]$^+$, 100%); (CI^+) 248 ([M+NH_4]$^+$, 100%); HRMS (ES^+) calc. for $C_{15}H_{22}NO_3$: 231.1380 [M+H]$^+$; found: 231.1379 [M+H]$^+$; Anal. Calc. for $C_{15}H_{18}O_2$: C, 78.2; H, 7.88; N, 0.00. Found: C, 78.1; H, 7.85; N, 0.00 %.

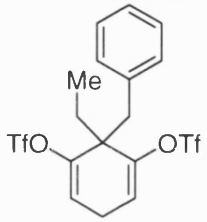
Trifluoro-methanesulfonic acid 6-benzyl-6-ethyl-5-oxo-cyclohex-1-enyl ester (317)



Prepared using general procedure **B** from diketone **316** (1.40 g, 6.14 mmol) and purified by flash chromatography (10:1 hexane:ethyl acetate) to yield mono-alkenyltriflate **317** (1.09 g, 49%) as a yellow oil. ν_{max} (liquid film)/cm^{-1} 3031 (C-H), 2971 (C-H), 2939 (C-H), 1719 (C=O),1679, 1456, 1415 (O-SO_2), 1215 (SO_2), 1143, 1033, 966, 877, 746, 703; δ_H (300 MHz, $CDCl_3$) 7.26-7.20

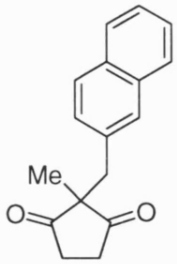
(3H, m, 3 × Ar-*H*), 7.06-7.02 (2H, m, 2 × Ar-*H*), 6.10 (1H, dd (app. t), *J* 4.5 and 4.5, C*H*CH_2CH_2CO), 3.08 (1H, d, *J* 13.2, ArCH_AH_BCCO), 2.85 (1H, d, *J* 13.2, ArCH_AH_BCCO), 2.27-2.02 (3H, m, CH_2CH_2CO and $CH_3CH_AH_BCCO$), 1.85-1.66 (3H, m, CH_2CH_2CO and $CH_3CH_AH_BCCO$), 0.83 (3H, dd (app. t), *J* 7.4 and 7.4, $CH_3CH_AH_BCCO$); δ_C (75 MHz, $CDCl_3$) 209.9, 148.1, 135.9, 129.9, 128.4, 127.0, 120.1, 118.5, 59.6, 43.0, 38.6, 29.7, 18.9, 9.3; *m/z* LRMS (EI^+) 362 ($[M]^+$, 5%), 91.1 ($[C_6H_5CH_2]^+$,100%), 69.1 (38%); (CI^+) 380 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{16}H_{21}NO_4SF_3$: 380.1138 $[M+NH_4]^+$; found: 380.1142 $[M+NH_4]^+$.

Trifluoro-methanesulfonic acid 6-benzyl-6-ethyl-5-trifluoromethane sulfonyloxy-cyclohexa-1,4-dienyl ester (318)



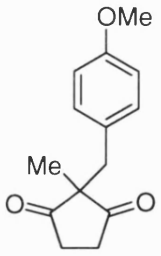
Prepared using general procedure **C** from mono-alkenyltriflate **317** (800 mg, 2.21 mmol) and purified by flash chromatography (10:1 hexane:EtOAc) to yield crude *bis*-alkenyltriflate **318** (338 mg, 31%) as a colourless oil. ν_{max} (film)/cm^{-1} 2977 (C-H), 2944 (C-H), 2886 (C-H), 1703, 1423 (O-SO_2), 1216 (SO_2), 1140, 1031, 959, 875, 804, 736; δ_H (300 MHz, $CDCl_3$) 7.21-7.14 (3H, m, 3 × Ar-*H*), 7.05-7.02 (2H, m, 2 × Ar-*H*), 5.70 (2H, dd (app.t), *J* 3.8 and 3.8, 2 × $CH_2CHCOSO_2$), 2.80-2.69 (3H, m, CCH_2Ar and CH_AH_BCHCO), 2.37 (1H, dt, *J* 22.7 and 3.7, CH_AH_BCHCO), 1.73 (2H, q, *J* 7.5, $CH_3CH_2CCOSO_2$), 0.90 (3H, t, *J* 7.5, $CH_3CH_2COSO_2$); δ_C (75 MHz, $CDCl_3$) 146.2, 135.9, 130.0, 128.5, 127.4, 118.7 (q, *J* 319.3, CF_3), 114.8, 51.1, 41.7, 28.1, 24.6, 9.0.

2-Methyl-2-naphthalen-2-ylmethyl-cyclopentane-1,3-dione (320)



Prepared using general procedure **A** from 2-methyl-1,3-cyclopentanedione (1.00 g, 8.92 mmol) and 2-bromomethylnapthalene (2.94 g, 13.38 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **320** (1.40 g, 62%) as yellow needles: mp 64-66°C. ν_{max} (film)/cm^{-1} 3055 (C-H), 2971 (C-H), 2920 (C-H), 1722 (C=O), 1600, 1508, 1451, 1415, 1370, 1322, 1071, 825, 751; δ_H (300 MHz, $CDCl_3$) 7.79-7.70 (3H, m, 3 × Ar-*H*), 7.51-7.42 (3H, m, 3 × Ar-*H*), 7.18-7.15 (1H, dd, *J* 7.4 and 1.8, Ar-*H*), 3.14 (2H, s, ArCH_2CCO), 2.63-2.44 (2H, m, 2 × CH_AH$_B$COCCH$_3$), 2.11-1.92 (2H, m, 2 × CH$_A$$H_B$COCCH$_3$), 1.26 (3H, s, C$H_3$CCO); δ_C (75 MHz, $CDCl_3$) 217.5, 133.3, 133.2, 132.4, 128.4, 128.2, 127.8, 127.7, 127.6, 126.2, 126.0, 58.5, 43.1, 35.9, 20.3; *m/z* LRMS (EI$^+$) 252.1 [M]$^+$ (31%), 164.9 (36%), 152.0 (33%), 141.2 (100%), 115.0 (42%); (CI$^+$) 270.1 [M+NH$_4$]$^+$; HRMS (CI$^+$) calc. for $C_{17}H_{20}NO_2$: 270.1489 [M+NH$_4$]$^+$; found: 270.1490 [M+NH$_4$]$^+$.

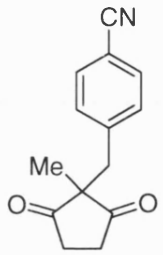
2-(4-Methoxy-benzyl)-2-methyl-cyclopentane-1,3-dione (321)



Prepared using general procedure **A** from 2-methyl-1,3-cyclopentanedione (1.0 g, 8.92 mmol) and *para*-methoxybenzyl chloride (1.86 mL, 13.38 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **321** (1.41 g, 68%) as white needles: mp 79-81°C. ν_{max} (film)/cm^{-1} 2951 (C-H), 2923 (C-H), 2838 (O-CH$_3$), 1722 (C=O), 1611, 1512 (Ar), 1444, 1242, 1181, 1073, 1033, 845, 824, 755; δ_H (300 MHz, $CDCl_3$) 6.98-6.95 (2H, m, 2 × Ar-*H*), 6.77-

6.74 (2H, m, 2 × Ar-*H*), 3.76 (3H, s, C*H*$_3$OAr), 2.91 (2H, s, ArC*H*$_2$CCO), 2.60-2.45 (2H, m, 2 × C*H*$_A$H$_B$COCCH$_3$), 2.18-2.04 (2H, m, 2 × CH$_A$*H*$_B$COCCH$_3$), 1.18 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 217.8, 158.7, 130.6, 127.7, 113.9, 58.5, 55.2, 42.4, 35.9, 19.8; *m/z* LRMS (EI^+) 232 $[M]^+$ (70%), 189.0 (68%), 175.2 (63%), 161.1 (100%), 121.1 (100%), 77.0 (25%), 55.1 (39%), 41.2 (48%); (CI^+) 250.2 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{14}H_{20}NO_3$: 250.1438 $[M+NH_4]^+$; found: 250.1440 $[M+NH_4]^+$.

4-(1-Methyl-2,5-dioxo-cyclopentylmethyl)-benzonitrile (322)



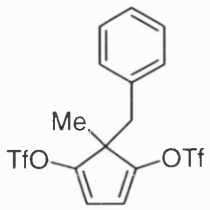
Prepared using general procedure **A** from 2-methyl-1,3-cyclopentanedione (1.00 g, 8.92 mmol) and *para*-bromotolubenzonitrile (2.62 g, 13.38 mmol) and purified by flash chromatography (hexane:EtOAc 2:1) to yield diketone **322** (1.40 g, 69%) as white needles: mp 84-88°C. ν_{max} (film)/cm^{-1} 222.9 (CN), 1720 (C=O), 1604, 1505, 1335, 1317, 1194, 1031, 998, 832, 811; δ_H (300 MHz, $CDCl_3$) 7.54-7.52 (2H, m, 2 × Ar-*H*), 7.20-7.17 (2H, m, 2 × Ar-*H*), 3.03 (2H, s, ArC*H*$_2$CCO), 2.75-2.66 (2H, m, 2 × C*H*$_A$H$_B$COCCH$_3$), 2.22-2.14 (2H, m, 2 × CH$_A$*H*$_B$COCCH$_3$), 1.24 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 216.1, 141.6, 132.2, 130.2, 127.4, 111.2, 58.2, 41.0, 35.5, 21.2; Anal. Calc. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77; N, 6.16. Found: C, 73.7; H, 5.74; N, 6.30 %.

General procedure H: The preparation of 2,2-dialkyl-1,3-cyclopentadienyl *bis*-alkenyltriflates

A stirred solution of 2,2-dialkyl-1,3-cyclopentanedione (4.6 mmol) and 2-[*N,N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (3.97g, 10.1 mmol) in anhydrous THF (40 ml) was cooled to -78°C. To this was added potassium hexamethyldisilazide (0.5M in toluene, 20.2 mL, 10.1 mmol), dropwise over 15 minutes. The reaction was stirred at -78°C for 2 hours, then warmed to room temperature and stirred for a further 4 h. The mixture was then diluted with

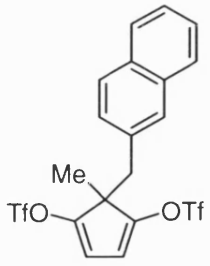
hexane (100 mL), and washed with water (50 mL), 10% $NaOH_{(aq)}$ (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce a dark oil which was purified by flash chromatography (solvents as stated).

Trifluoro-methanesulfonic acid 5-benzyl-5-methyl-4-trifluoromethane sulfonyloxy-cyclopenta-1,3-dienyl ester (214)



Prepared using general procedure **H** from diketone **319** (400 mg, 1.98 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **214** (507 mg, 55%) as a white solid: mp 37-38°C. ν_{max} (film)/cm^{-1} 3034 (C-H), 2982 (C-H), 2938 (C-H), 1631 (C=C), 1497 (Ar), 1429 (O-SO_2), 1140 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.25-7.20 (3H, m, 3 × Ar-*H*), 7.07-7.06 (2H, m, 2 × Ar-*H*), 5.81 (2H, s, 2 × C*H*$COSO_2$), 2.97 (2H, s, ArCH_2C), 1.41 (3H, s, CH_3CO); δ_C (100 MHz, $CDCl_3$) 151.9, 134.0, 128.9, 128.0, 127.2, 118.3, 111.9, 54.2, 3.7, 18.5; Data consistent with literature.[310]

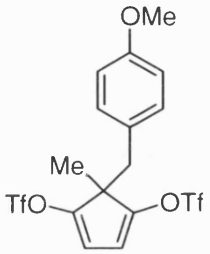
Trifluoro-methanesulfonic acid 5-methyl-5-naphthalen-2-ylmethyl-4-trifluoro methanesulfonyloxy-cyclopenta-1,3-dienyl ester (323)



Prepared using general procedure **H** from diketone **320** (500 mg, 1.98 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **323** (490 mg, 48%) as yellow needles: mp 56-58°C. ν_{max} (film)/cm^{-1} 3060 (C-H), 2981 (C-H), 2939 (C-H), 1631, 1429 (O-SO_2), 1214 (SO_2), 1139, 1067, 892, 859, 764, 607; δ_H (300 MHz, $CDCl_3$) 7.80-7.70 (3H, m, 3 × Ar-*H*), 7.53-7.42 (3H, m, 3 × Ar-*H*), 7.20-7.17 (1H, dd, *J* 8.3 and 1.8, Ar-*H*),

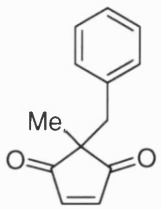
5.76 (2H, s, 2 × C*H*COSO$_2$), 3.14 (2H, s, ArC*H*$_2$CCO), 1.47 (3H, s, C*H*$_3$CCOSO$_2$); δ_C (75 MHz, $CDCl_3$) 151.9, 133.0, 132.5, 131.7, 127.9, 127.7, 127.6, 127.1, 126.1, 125.9, 124.4, 112.1, 54.4, 39.8, 18.6 (CF_3 not seen); *m/z* LRMS (EI$^+$) 516 [M]$^+$ (100%), 383.1 (56%), 366.1 (42%), 141.0 (100%); (CI$^+$) 534.0 [M+NH$_4$]$^+$; HRMS (CI$^+$) calc. for $C_{19}H_{18}F_6NO_6S_2$: 534.0474 [M+NH$_4$]$^+$; found: 534.0476 [M+NH$_4$]$^+$.

Trifluoro-methanesulfonic acid 5-(4-methoxy-benzyl)-5-methyl-4-trifluoro methanesulfonyloxy-cyclopenta-1,3-dienyl ester (324)



Prepared using general procedure **H** from diketone **321** (460 mg, 1.98 mmol) and purified by flash chromatography (hexane:EtOAc 10:1) to yield *bis*-alkenyltriflate **324** (511 mg, 52%) as white needles: mp 56-58°C. ν_{max} (film)/cm^{-1} 3134 (C-H), 2939 (C-H), 2840 (C-H), 1630, 1615, 1568, 1516, 1429 (O-SO$_2$), 1251, 1217 (SO$_2$), 1139, 1066, 948, 788, 764; δ_H (300 MHz, $CDCl_3$) 7.00-6.97 (2H, m, 2 × Ar-*H*), 6.77-6.74 (2H, m, 2 × Ar-*H*), 5.82 (2H, s, 2 × C*H*COSO$_2$), 3.76 (3H, s, C*H*$_3$OAr), 2.91 (2H, s, ArC*H*$_2$CCO), 1.39 (3H, s, C*H*$_3$CCOSO$_2$); δ_C (75 MHz, $CDCl_3$) 158.7, 152.1, 130.1, 126.2, 118.5 (q, *J* 320.1, CF_3), 113.5, 112.0, 155.2, 54.4, 38.9, 18.3; *m/z* LRMS (EI$^+$) 496.0 [M]$^+$ (100%), 362.1 (8%), 122.2 (18%), 121.1 (100%); (CI$^+$) 514.0 [M+NH$_4$]$^+$; HRMS (CI$^+$) calc. for $C_{16}H_{18}F_6NO_7S_2$: 514.0423 [M+NH$_4$]$^+$; found: 514.0422 [M+NH$_4$]$^+$.

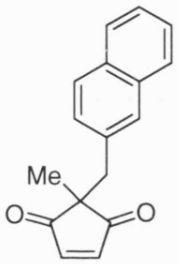
2-Benzyl-2-methyl-cyclopent-4-ene-1,3-dione (325)



Prepared using general procedure **D** from *bis*-alkenyltriflate **214** (48 mg, 0.104 mmol) and purified by flash chromatography (hexane:EtOAc 6:1) to yield

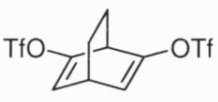
diketone **325** (8.5 mg, 41%) as yellow plates. mp 115-116°C; ν_{max} (film)/cm^{-1} 3055 (C-H), 2985 (C-H), 2931 (C-H), 1746 (C=O), 1604 (C=C), 1496 (Ar); δ_H (300 MHz, $CDCl_3$) 7.19-7.13 (3H, m, 3 × Ar-*H*), 6.99 (2H, s, 2 × C*H*COCCH$_3$), 6.94-6.91 (2H, m, 2 × Ar-*H*), 3.00 (2H, s, ArC*H*$_2$CCO), 1.26 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 207.3, 148.7, 129.7, 128.4, 127.0, 52.5, 40.9, 19.3, peak coincidence – one Ar-C cannot be seen; *m/z* LRMS (EI$^+$) 200 ([M]$^+$, 38%); HRMS (ES$^+$) calc. for $C_{13}H_{12}O_2$: 200.0827 [M]$^+$; found: 200.0837 [M]$^+$.

2-Methyl-2-naphthalen-2-ylmethyl-cyclopent-4-ene-1,3-dione (326)



Prepared using general procedure **D** from *bis*-alkenyltriflate **323** (51 mg, 0.104 mmol) and purified by flash chromatography (hexane:EtOAc 6:1) to yield diketone **326** (8.6 mg, 33%) as yellow plates: mp 102-106°C. δ_H (300 MHz, $CDCl_3$) 7.73 (2H, dd, *J* 4.8 and 4.1, 2 × Ar-*H*), 7.64 (1H, d, *J* 8.4, Ar-*H*), 7.46-7.39 (3H, m, 3 × Ar-*H*), 7.04 (1H, dd, *J* 8.4 and 1.8, Ar-*H*), 6.93 (2H, s, 2 × C*H*COCCH$_3$), 3.16 (2H, s, ArC*H*$_2$CCO), 1.31 (3H, s, C*H*$_3$CCO); δ_C (75 MHz, $CDCl_3$) 207.3, 148.8, 133.1 (2 × C), 132.3, 128.5, 128.0, 127.8 (2 × C), 127.5, 126.1, 125.8, 52.7, 41.0, 19.4; *m/z* LRMS (EI$^+$) 250.1 (25%), 141.1 ([$C_{10}H_7CH_2$]$^+$, 100%), 115.0 (25%), 82.0 (10%); (CI$^+$) 268 [M+NH_4]$^+$; HRMS (CI$^+$) calc. for $C_{17}H_{18}NO_2$: 268.1332 [M+NH_4]$^+$; found: 268.1329 [M+NH_4]$^+$.

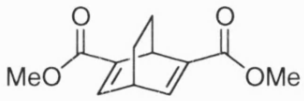
Preparation of trifluoro-methanesulfonic acid 6-trifluoromethanesulfonyl-oxy-bicyclo[2.2.2]octa-2,5-dien-2-yl ester (328)



A stirred solution of diketone **327** (0.50 g, 3.62 mmol) and 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (3.12 g, 7.97 mmol) in anhydrous THF (50 ml) was cooled to -78°C. To this was added potassium

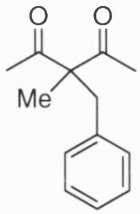
hexamethyldisilazide (15.9 mL, 7.97 mmol, 0.5M in toluene), dropwise over 15 minutes. The reaction was stirred at -78°C for 2 hours, then warmed to room temperature and stirred for a further 4 hours. The mixture was then diluted with hexane (100 mL), and washed with water (50 mL), 10% $NaOH_{(aq)}$ (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to produce an orange oil which was purified by flash chromatography (hexane:EtOAc 6:1) to yield *bis*-alkenyltriflate **328** (0.95 g, 65%) as a colourless oil: ν_{max} (liquid film)/cm^{-1} 2957 (C-H), 2885 (C-H), 1662, 1639, 1427 (O-SO_2), 1337, 1210 (SO_2), 1136, 1081, 1060, 943, 895, 823, 755, 607; δ_H (300 MHz, $CDCl_3$) 6.13 (2H, dd, *J* 7.0 and 2.5, 2 × CHC*H*$COSO_2$), 3.81-3.75 (1H, m, C*H*$COSO_2$), 3.67 (1H, quintet, *J* 2.5, C*H*$CHCOSO_2$), 1.87-1.82 (2H, m, CH_2CH_2CHCO), 1.63-1.58 (2H, m, CH_2CH_2CHCO); δ_C (75 MHz, $CDCl_3$) 153.3, 121.5, 118.9 (q, *J* 320.8, CF_3), 43.9, 36.3, 25.7, 24.5; *m/z* LRMS (EI^+) 402.0 (5%), 374.0 (100%), 268.9 (17%), 91.0 (13%), 69.0 (100%); (CI^+) 420 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{10}H_{12}F_6NO_6S_2$: 420.0005 $[M+NH_4]^+$; found: 420.0003 $[M+NH_4]^+$.

Bicyclo[2.2.2]octa-2,5-diene-2,6-dicarboxylic acid dimethyl ester (329)



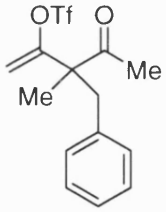
Prepared according to general procedure **D** using *bis*-alkenyltriflate **328** (42 mg, 0.104 mmol) and purified by flash chromatography (hexane:EtOAc 6:1) to yield bicyclic diester **329** (21 mg, 92%) as a white powder: mp 59-62°C. ν_{max} (film)/cm^{-1} 3005 (C-H), 2956 (C-H), 2876 (C-H), 1713 (C=O), 1600, 1439, 1254, 1213, 1068, 762; δ_H (300 MHz, $CDCl_3$) 7.25 (2H, dd, *J* 6.2 and 1.8, 2 × CHC*H*CCO_2CH_3), 4.77 (1H, t, *J* 2.0, C*H*CCO_2CH_3), 3.94-3.89 (1H, m, C*H*$CHCCO_2CH_3$), 3.75 (6H, s, 2 × CCO_2CH_3), 1.46-1.36 (4H, m, $CHCH_2CH_2CH$); δ_C (75 MHz, $CDCl_3$) 163.9, 143.2, 138.1, 50.7, 37.6, 35.3, 23.4, 22.9; *m/z* LRMS (EI^+) 222.1 (100%), 207.1 (30%), 193.9 (17%), 162.9 (100%), 135.0 (16%); (CI^+) 240 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{12}H_{18}NO_4$: 240.1230 $[M+NH_4]^+$; found: 240.1229 $[M+NH_4]^+$; Anal. Calc. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.35; N, 0.00. Found: C, 64.0; H, 6.41; N, 0.00 %.

3-Benzyl-3-methyl-pentane-2,4-dione (330)



Prepared using general procedure **A** from 3-methyl-2,4-pentanedione (8.3 mL, 39.7 mmol) and benzyl bromide (7.2 mL, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 2:1) to yield diketone **330** (4.5 g, 55%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3029 (C-H), 2984 (C-H), 2933 (C-H), 1699 (C=O), 1495, 1454, 1356, 1202, 1091, 961, 756 (Ar), 703 (Ar); δ_H (300 MHz, $CDCl_3$) 7.29-7.21 (3H, m, 3 × Ar-*H*), 7.08-7.05 (2H, m, 2 × Ar-*H*), 3.18 (2H, s, Ar*CH*$_2$CCO), 2.12 (6H, s, 2 × *CH*$_3$COCCO), 1.29 (3H, s, *CH*$_3$CCH$_2$Ar); δ_C (75 MHz, $CDCl_3$) 207.1, 136.4, 130.1, 128.3, 126.8, 67.3, 40.3, 27.3, 18.2; Anal. Calc. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.90; N, 0.00. Found: C, 75.3; H, 7.79; N, 0.00 %.

Trifluoro-methanesulfonic acid 2-benzyl-2-methyl-1-methylene-3-oxo-butyl ester (331)

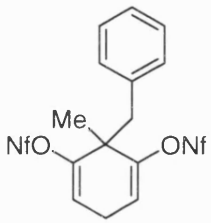


Prepared using general procedure **H** from diketone **330** (206 mg, 1.02 mmol) and purified by flash chromatography (hexane:EtOAc 8:1) to yield mono-alkenyltriflate **331** (134 mg, 39%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.30-7.24 (3H, m, 3 × Ar-*H*), 7.11-7.08 (2H, m, 2 × Ar-*H*), 5.36 (1H, d, *J* 5.0, *CH*$_A$H$_B$COSO$_2$), 4.96 (1H, d, *J* 5.0, CH$_A$*H*$_B$COSO$_2$), 3.06 (2H, d, *J* 8.5, Ar*CH*$_2$CCO), 2.23 (3H, s, *CH*$_3$CO), 1.23 (3H, s, *CH*$_3$CCH$_2$Ar); δ_C (75 MHz, $CDCl_3$) 205.9, 156.7, 135.7, 130.5, 128.2, 127.0, 116.0, 104.1, 57.6, 39.4, 25.6, 19.6; *m/z* LRMS (EI$^+$) 203.1 (100%), 186.1 (18%), 171.0 (24%), 129.1 (39%), 91.1 (100%), 69.0 (20%), 43.1 (82%); (CI$^+$) 354.1 [M+NH$_4$]$^+$; HRMS (CI$^+$) calc. for $C_{14}H_{19}F_3NO_4S$: 354.0981 [M+NH$_4$]$^+$; found: 354.0978 [M+NH$_4$]$^+$.

General procedure I: The preparation of *bis*-alkenylnonaflates

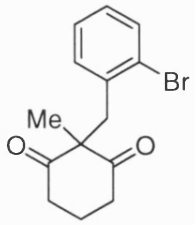
A solution of 2,2-dialkylcyclohexane-1,3-dione (2.07 mmol) in THF (25 mL) was cooled to -78°C under N_2. To this, KHMDS (12.4 mL, 6.22 mmol, 0.5M solution in toluene) was added dropwise. This mixture was stirred for 15 minutes, before dropwise addition of perfluoro-1-butanesulfonyl fluoride (1.12 mL, 6.22 mmol). The reaction was allowed to warm to room temperature overnight, and then diluted with ethyl acetate (70 mL). The solution was washed with 1M sodium hydroxide (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The orange oil was purified by flash chromatography (solvents as noted).

Nonafluoro-butane-1-sulfonic acid 6-benzyl-6-methyl-5-(nonafluorobutane-1-sulfonyloxy)-cyclohexa-1,4-dienyl ester (335)



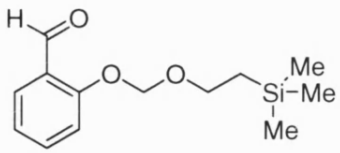
Prepared according to general procedure **I** using 2-benzyl-2-methylcyclohexane-1,3-dione **223** (0.447 g) and purified by flash chromatography (hexane:EtOAc 20:1) to yield *bis*-alkenylnonaflate **335** (0.890 g, 54%) as a white solid. mp 69-74°C; δ_H (300 MHz, $CDCl_3$) 7.26-7.23 (3H, m, 3 × Ar-*H*), 7.08-7.05 (2H, m, 2 × Ar-*H*), 5.71-5.68 (2H, t, *J* 3.7, 2 × SO_3CCHCH_2), 2.86 (2H, s, $ArCH_2C$), 2.82 (1H, dt, *J* 22.8 and 4.1, $SO_3CCHCH_ACH_B$), 2.33 (1H, dt, *J* 22.8 and 3.5, $SO_3CCHCH_ACH_B$), 1.56 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 147.5, 135.6, 129.7, 128.1, 127.1, 114.2, 45.7, 41.7, 24.3, 22.8, carbons of nonaflate cannot be seen; *m/z* LRMS (EI^+) 780.1 (18%), 689.1 (100%), 497.5 (79%), 480.5 (20%), 219.4 (22%), 181.4 (28%), 131.3 (61%), 115.4 (38%), 105.3 (100%); (CI^+) 798 $[M+NH_4]^+$; HRMS (EI^+) calc. for $C_{22}H_{14}O_6F_{18}S_2$: 779.9939 $[M]^+$; found: 779.9940 $[M]^+$.

2-(2-Bromo-benzyl)-2-methyl-cyclohexane-1,3-dione (337)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (5.0 g, 39.7 mmol) and 2-bromobenzylbromide (15.0 g, 60.3 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **337** (7.1 g, 61%) as a white powder: mp 68-71°C. ν_{max} (film)/cm^{-1} 2963 (C-H), 2939 (C-H), 1693 (C=O), 1471 (Ar), 1439 (Ar), 1321, 1279, 1024, 759 (C-Br); δ_H (300 MHz, $CDCl_3$) 7.53 (1H, d, *J* 7.9, Ar-*H*), 7.20 (1H, t, *J* 7.5, Ar-*H*), 7.11-7.00 (2H, m, 2 × Ar-*H*), 3.31 (2H, s, CC*H*$_2$Ar), 2.70-2.65 (4H, m, 2 × CH_2CH_2CO), 2.04-1.75 (2H, m, CH_2CH_2CO), 1.29 (3H, s, CH_3CCO); δ_C (75 MHz, $CDCl_3$) 210.0, 135.9, 133.3, 131.4, 128.6, 127.3, 125.6, 65.2, 41.9, 38.8, 20.0, 17.3; Anal. Calc. for $C_{14}H_{15}O_2Br$: C, 57.0; H, 5.12; N, 0.00 Found: C, 56.8; H, 5.10; N, 0.00 %. Data consistent with literature.[316]

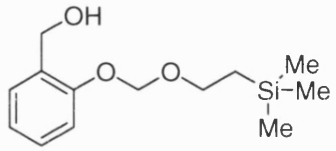
2-(2-Trimethylsilanyl-ethoxymethoxy)-benzaldehyde (340)



To a flask charged with sodium hydride (60% in mineral oil, 0.488 g, 20.35 mmol) was added anhydrous hexane (15 mL). The mixture was stirred for 10 minutes, then left to settle for a further 10 minutes. The hexane was removed *via* syringe, anhydrous DMF (10 mL) was added, and the mixture was cooled to 0°C. Salicylaldehyde (1.23 mL, 11.56 mmol) was added dropwise as a solution in anhydrous DMF (10 mL), and the mixture was stirred at 0°C for 30 mins. SEM-Cl (2.46 mL, 13.87 mmol) was then added dropwise and the reaction warmed to room temperature and allowed to stir for 2 h. The reaction was quenched by careful addition of a saturated solution of ammonium chloride (50 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The organic

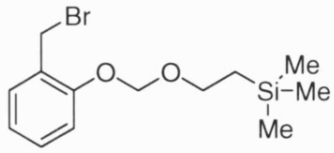
portions were combined and washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The colourless oil was purified by flash chromatography (hexane:EtOAc 20:1) to yield benzaldehyde **340** (2.39 g, 82%) as a colourless oil. ν_{max} (Nujol)/cm^{-1} 2923 (C-H), 2849 (C-H), 1754, 1668, 1460, 1378, 1248, 1092, 859, 837, 755; δ_H (300 MHz, $CDCl_3$) 10.50 (1H, d, *J* 0.8, C*H*OAr), 7.85 (1H, dd, *J* 7.7 and 1.8, Ar-*H*), 7.56-7.50 (1H, m, Ar-*H*), 7.25 (1H, dd, *J* 8.5 and 0.5, Ar-*H*), 7.10-7.05 (1H, m, Ar-*H*), 5.35 (2H, s, OCH_2OAr), 3.83-3.77 (2H, m, OCH_2CH_2Si), 2H (2H, m, OCH_2CH_2Si), 0.00 (9H, s, $(CH_3)_3Si$); δ_C (75 MHz, $CDCl_3$) 191.3, 161.4, 137.3, 129.7, 126.8, 123.1, 116.5, 94.5, 68.3, 19.5, 1.4.

[2-(2-Trimethylsilanyl-ethoxymethoxy)-phenyl]-methanol (341)



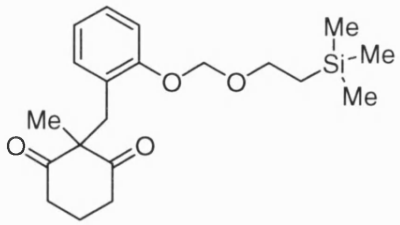
A solution of benzaldehyde **340** (2.91 g, 11.6 mmol) in THF (30 mL) was cooled to 0°C. To this was carefully added lithium borohydride (0.30 g, 13.9 mmol). The reaction was allowed to reach room temperature over 3 hours, the quenched by careful addition of 10% citric acid (100 mL). The mixture was extracted with ethyl acetate (3 × 50 mL), and the organic portions combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The colourless oil was purified by flash chromatography (hexane:EtOAc 6:1) to yield benzyl alcohol **341** (2.68 g, 91%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3399 (O-H), 2953 (C-H), 2985 (C-H), 1603, 1490 (O-H), 1456, 1411, 1381, 1249, 1227 ($SiMe_3$), 1152, 1089, 1002, 919, 835 ($SiMe_3$), 754, 694; δ_H (300 MHz, $CDCl_3$) 7.32-7.23 (2H, m, Ar-*H*), 7.13 (1H, dd, *J* 8.2 and 0.9, Ar-*H*), 7.00 (1H, td, *J* 7.4 and 0.9, Ar-*H*), 5.28 (2H, s, OCH_2OAr), 4.69 (2H, s, $OHCH_2Ar$), 3.79-3.73 (2H, m, OCH_2CH_2Si), 2.37 (1H, br s, $HOCH_2Ar$), 0.99-0.94 (2H, m, OCH_2CH_2Si), 0.00 (9H, s, $(CH_3)_3Si$); δ_C (75 MHz, $CDCl_3$) 156.8, 131.4, 130.3 (2 × C), 123.3, 115.7, 94.6, 68.0, 63.4, 19.5, 1.4.

[2-(2-Bromomethyl-phenoxymethoxy)-ethyl]-trimethyl-silane (342)



A stirred solution of SEM-benzyl alcohol **341** (2.50 g, 9.84 mmol) and triphenylphosphine (2.84 g, 10.8 mmol) in anhydrous DCM (40 mL) was cooled to 0°C, and carbon tetrabromide (3.58 g, 10.8 mmol) as a solution in DCM (10 mL) was added dropwise. The reaction was warmed to room temperature over 2 h, then neutralised with brine (60 mL). The aqueous layer was re-extracted with DCM (2 × 50 mL), then the combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane:EtOAc 20:1) to yield benzyl bromide **342** (2.30 g, 74%) as a colourless oil. ν_{max} (Nujol)/cm^{-1} 2723, 1603, 1490, 1452, 1378, 1248, 1231, 1088, 997, 859, 833, 746; δ_H (300 MHz, $CDCl_3$) 7.35-7.24 (2H, m, 2 × Ar-*H*), 7.11 (1H, dd, *J* 8.3 and 0.8, Ar-*H*), 6.97 (1H, td, *J* 7.4 and 1.1, Ar-*H*), 5.32 (2H, s, BrCH_2Ar), 4.58 (2H, s, ArOCH_2OCH_2), 3.84-3.77 (2H, m, OCH_2CH_2Si), 1.00-0.92 (2H, m, OCH_2CH_2Si), 0.00 (9H, s, $CH_2Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 156.7, 132.3, 131.6, 128.1, 123.0, 115.7, 93.9, 69.7, 30.5, 19.5, 1.4.

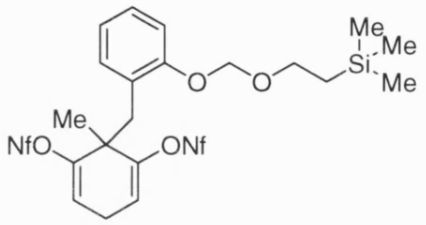
2-Methyl-2-[2-(2-trimethylsilanyl-ethoxymethoxy)-benzyl]-cyclohexane-1,3-dione (343)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (1.19 g, 9.41 mmol) and SEM-benzylbromide **342** (2.70 g, 9.41 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **343** (1.60 g, 47%) as a colourless oil. ν_{max} (Nujol)/cm^{-1} 2853 (C-H), 2728 (C-H), 1724, 1698 (C=O), 1495, 1460, 1378, 1248 ($SiMe_3$), 1231, 1088, 859, 837, 751; δ_H (300 MHz,

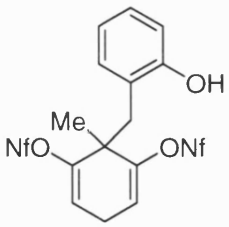
$CDCl_3$) 7.17 (1H, td, *J* 7.0 and 1.8, Ar-*H*), 7.10 (1H, dd, *J* 8.2 and 1.2, Ar-*H*), 6.97 (1H, dd, *J* 7.5 and 1.8, Ar-*H*), 6.88 (1H, td, *J* 7.2 and 1.2, Ar-*H*), 5.11 (2H, s, ArOCH_2O), 3.75-3.69 (2H, m, OCH_2CH$_2$Si), 3.08 (2H, s, ArCH_2CCO), 2.80-2.69 (2H, m, 2 × COCH_AH$_B$CH$_2$), 2.58-2.49 (2H, m, 2 × COCH$_A$$H_BCH_2$), 2.02-1.90 (1H, m, COCH$_2$CH_AH$_B$), 1.78-1.64 (1H, m, COCH$_2$CH$_A$$H_B$), 1.14 (3H, s, C$H_3$CCO), 0.97-0.91 (2H, m, OCH$_2$CH_2Si), 0.00 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 211.4, 157.2, 133.6, 130.2, 125.8, 122.7, 115.5, 94.6, 67.8, 67.2, 40.9, 40.0, 19.5, 19.0 (2 × C), 1.4.

Nonafluoro-butane-1-sulfonic acid 6-methyl-5-(nonafluorobutane-1-sulfonyloxy)-6-[2-(2-trimethylsilanyl-ethoxymethoxy)-benzyl]-cyclohexa-1,4-dienyl ester (344)



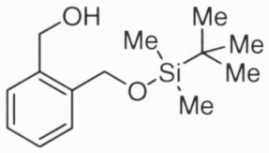
Prepared according to general procedure **I** using 2-methyl-2-[2-(2-trimethylsilanyl-ethoxymethoxy)-benzyl]-cyclohexane-1,3-dione **343** (0.750 g) and purified by flash chromatography (hexane:EtOAc 20:1) to yield *bis*-alkenylnonaflate **344** (0.828 g, 41%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3565, 3338, 2956 (C-H), 1706, 1412 (O-SO_2), 1353, 1239 ($SiMe_3$), 1202 (SO_2), 1145, 999, 945, 837, 753, 739, 585; δ_H (300 MHz, $CDCl_3$) 7.22-7.14 (2H, m, 2 × Ar-*H*), 7.05-7.03 (1H, m, Ar-*H*), 6.92-6.85 (1H, m, Ar-*H*), 5.71 (2H, dd (app. t), *J* 4.2 and 4.2, 2 × SO_3CC*H*CH$_2$), 5.15 (2H, s, ArOCH_2OCH$_2$), 3.74-3.69 (2H, m, OCH_2CH$_2$Si), 2.97 (2H, s, ArCH_2C), 2.76 (1H, dt, *J* 22.7 and 4.4, SO_3CCHCH_ACH$_B$), 2.31 (1H, dt, J 22.7 and 3.2, SO_3CCHCH$_A$CH_B), 1.56 (3H, s, CH_3CCOSO_2), 0.98-0.92 (2H, m, OCH$_2$CH_2Si), 0.00 (9H, s, (CH_3)$_3$Si); δ_C (75 MHz, $CDCl_3$) 158.0, 149.7, 133.3, 130.1, 126.2, 122.6, 115.9, 115.0, 94.8, 67.6, 46.8, 37.9, 25.8, 24.0, 19.6, 1.5; *m/z* LRMS (EI$^+$) 688.1 (50%), 496.2 (42%), 341.2 (100%), 219.1 ([C_4F_9]$^+$, 7%), 107.1 (100%), 69.1 ([CF_3]$^+$, 42%); (CI$^+$) 944 (90%) [M+NH_4]$^+$; HRMS (ES$^+$) calc. for $C_{28}H_{32}F_{18}NO_8S_2Si$: 944.1046 [M+$NH_4$]$^+$; found: 944.1058 [M+$NH_4$]$^+$.

Nonafluoro-butane-1-sulfonic acid 6-methyl-5-(nonafluorobutane-1-sulfonyl oxy)-6-[2-hydroxybenzyl]-cyclohexa-1,4-dienyl ester (345)



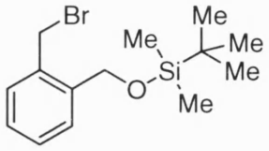
To a stirred solution of *bis*-alkenylnonaflate **344** (0.30 g, 0.324 mmol) in methanol (7 mL) was added 2M $HCl_{(aq)}$ (0.48 mL, 0.972 mmol).The mixture was brought to reflux under N_2, and heated for 5 h, then cooled to room temperature and diluted with ethyl acetate (20 mL). The mixture was washed with water (10 mL), and sat. $NaHCO_{3(aq)}$ (5 mL). The organic washings were then re-acidified to pH 1 with 1M HCl (20 mL), and re-extracted with ethyl acetate (3 × 10 mL). The organic portions were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The yellow oil was purified by flash chromatography (hexane:EtOAc 3:1) to yield *bis*-alkenylnonaflate **345** (0.131 g, 51%) as white needles: mp 55-58°C. ν_{max} (film)/cm^{-1} 3565 (O-H), 3041 (C-H), 2993 (C-H), 2937 (C-H), 1705, 1418 (O-SO_2), 1354, 1239, 1201 (SO_2), 1144, 998, 946, 877, 754, 733, 594; δ_H (300 MHz, $CDCl_3$) 7.09 (1H, td, *J* 7.5 and 1.6, Ar-*H*), 7.00 (1H, dd, *J* 7.5 and 1.6, Ar-*H*), 6.83 (1H, t, *J* 7.4, Ar-*H*), 6.69 (1H, d, *J* 8.1, Ar-*H*), 5.73 (2H, dd (app. t), J 3.7 and 3.7, 2 × $CH_2CHCOSO_2$), 4.65 (1H, br s, Ar-O*H*), 2.97 (2H, s, CCH_2Ar), 2.77 (1H, dt, J 22.7 and 4.3, $SO_3CCHCH_ACH_B$), 2.34 (1H, dt, J 22.7 and 3.2, $SO_3CCHCH_ACH_B$), 1.56 (3H, s, CH_3CCOSO_2); δ_C (75 MHz, $CDCl_3$) 154.4, 148.2, 132.1, 128.4, 122.1, 120.2, 115.1, 113.3, 45.2, 35.9, 24.3, 22.4, carbons of nonaflate cannot be seen; *m/z* LRMS (EI^+) 688.1 (100%), 514.4 (33%), 405.5 (79%), 341.6 (92%), 325.5 (31%), 107.4 (100%), 69.3 (28%); (CI^+) 340 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{22}H_{18}F_{18}NO_7S_2$: 814.0232 $[M+NH_4]^+$; found: 814.0229 $[M+NH_4]^+$.

[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-phenyl]-methanol (347)



To a stirred solution of 1,2-benzenedimethanol (2.00 g, 14.47 mmol) and imidazole (1.18 g, 17.37 mmol) in anhydrous DCM (20 mL), was added TBSCl (2.29 g, 15.20 mmol) as a solution in DCM (10 mL). The reaction was stirred at room temperature for 24 h, then quenched with brine (30 mL). The aqueous layer was re-extracted with DCM (50 mL), then the combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane:EtOAc 5:1) to yield benzyl alcohol **347** (2.44 g, 67%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.39-7.28 (4H, m, 4 × Ar-*H*), 4.81 (2H, s, ArCH_2OH), 4.68 (2H, s, ArCH_2OSi), 3.26 (1H, br s, ArCH_2OH), 0.92 (9H, s, Si$C(CH_3)_3$), 0.13 (6H, s, Si$(CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 139.9, 138.7, 129.5, 128.7, 128.3, 128.0, 64.8, 64.0, 25.9, 18.3, -5.2; *m/z* LRMS (EI^+) 195.2 (22%), 119.1 (24%), 91.1 (27%), 75.1 (100%), 57.2 (17%), 41.2 (13%); (CI^+) 270.3 $[M+NH_4]^+$; HRMS (CI^+) calc. for $C_{14}H_{25}O_2$: 253.1618 $[M+H]^+$; found: 253.1620 $[M+H]^+$.

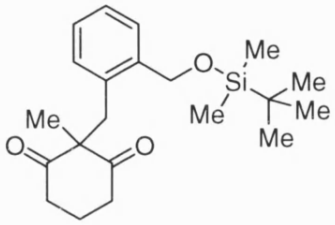
(2-Bromomethyl-benzyloxy)-*tert*-butyl-dimethyl-silane (349)



A stirred solution of TBS-benzyl alcohol **347** (1.90 g, 7.42 mmol) and triphenylphosphine (2.34 g, 8.91 mmol) in anhydrous DCM (40 mL) was cooled to 0°C, and carbon tetrabromide (2.95 g, 8.91 mmol) as a solution in DCM (10 mL) was added dropwise. The reaction was warmed to room temperature over 2 h, then quenched with brine (60 mL). The aqueous layer was re-extracted with DCM (2 × 50 mL), then the combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane:EtOAc 20:1) to yield benzyl bromide **349** (1.89 g, 81%) as a colourless oil. δ_H (300 MHz,

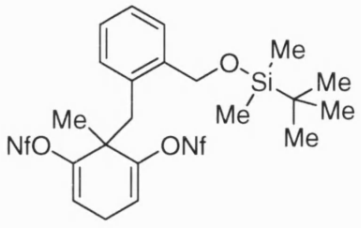
$CDCl_3$) 7.46-7.43 (1H, m, Ar-*H*), 7.35-7.21 (3H, m, 3 × Ar-*H*), 4.87 (2H, s, ArCH_2Br), 4.58 (2H, s, ArCH_2OSi), 0.95 (9H, s, SiC(CH_3)$_3$), 0.12 (6H, s, Si(CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 139.9, 134.8, 130.3, 128.9, 127.7, 127.6, 62.5, 31.0, 25.9, 18.4, -5.3.

2-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-benzyl]-2-methyl-cyclohexane-1,3-dione (351)



Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (381 mg, 3.03 mmol) and TBS-benzyl bromide **349** (1.50 g, 4.55 mmol) to yield diketone **351** (240 mg, 22%) as a colourless oil: δ_H (300 MHz, $CDCl_3$) 7.41 (1H, dd, *J* 7.5 and 0.8, Ar-*H*), 7.20 (1H, td, *J* 7.5 and 1.3, Ar-*H*), 7.11 (1H, td, *J* 7.5 and 1.5, Ar-*H*), 6.89 (1H, dd, *J* 7.5 and 1.2, Ar-*H*), 4.69 (2H, s, ArCH_2OSi), 3.18 (2H, s, ArCH_2CCO), 2.63-2.53 (2H, m, 2 × $CH_2CH_AH_BCO$), 2.45-2.34 (2H, m, 2 × $CH_2CH_AH_BCO$), 1.86-1.63 (2H, m, CH_2CH_2CO), 1.29 (3H, s, CH_3CCO), 0.94 (9H, s, (CH_3)$_3$CSi), 0.10 (6H, s, (CH_3)$_2$SiO); δ_C (75 MHz, $CDCl_3$) 211.5, 139.8, 134.0, 129.5, 127.7, 127.1, 126.9, 65.1, 62.9, 39.2, 39.0, 26.0, 25.7, 22.1, 18.4, -5.3.

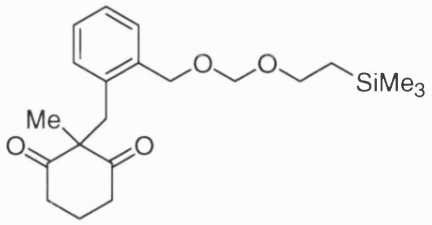
Nonafluoro-butane-1-sulfonic acid 6-[2-(*tert*-butyl-dimethyl-silanyloxy methyl)-benzyl]-6-methyl-5-(nonafluorobutane-1-sulfonyloxy)-cyclohexa-1,4-dienyl ester (353)



Prepared using general procedure **I** from diketone **351** (200 mg, 0.532 mmol) and purified by flash chromatography (hexane:EtOAc 20:1) to yield *bis*-alkenylnonaflate **353** (206 mg, 42%) as a colourless oil: δ_H (300 MHz, $CDCl_3$) 7.40 (1H, d, *J* 7.6, Ar-*H*), 7.25-7.07 (3H, m, 3 × Ar-*H*), 6.75 (2H, dd, *J* 3.3 and

1.0, 2 × $CH_2CHCOSO_2$), 4.70 (2H, s, $ArCH_2OSi$), 2.97 (2H, s, $ArCH_2CCO$), 2.82 (1H, dt, *J* 22.8 and 3.2, $CH_AH_BCHCOSO_2$), 2.41 (1H, dt, *J* 22.8 and 3.2, $CH_AH_BCHCOSO_2$), 1.57 (3H, s, CH_3CCO), 0.91 (9H, s, $(CH_3)_3CSi$), 0.02 (6H, s, $(CH_3)_2SiO$); δ_C (75 MHz, $CDCl_3$) 148.1, 140.3, 132.9, 130.1, 127.7, 127.1, 126.6, 114.8, 62.5, 45.2, 37.7, 25.8, 24.4, 23.1, 18.3, -5.5. *m/z* LRMS (ES^+) 942.2 ($[M+NH_4)^+$], 40%), 828.1 (100%), 628.2 (10%), 546.3 (20%), 493.2 (20%).

2-Methyl-2-[2-(2-trimethylsilanyl-ethoxymethoxymethyl)-benzyl]-cyclohexane -1,3-dione (352)



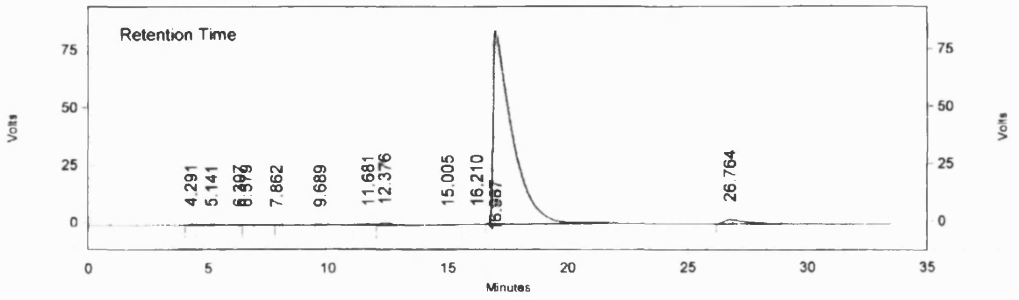
Prepared using general procedure **A** from 2-methyl-1,3-cyclohexanedione (381 mg, 3.03 mmol) and SEM-benzyl bromide **350** (1.50 g, 4.55 mmol) and purified by flash chromatography (hexane:EtOAc 3:1) to yield diketone **352** (513 mg, 45%) as a colourless oil. ν_{max} (liquid film)/cm^{-1} 3403, 2952 (C-H), 2892 (C-H), 1695 (C=O), 1456, 1373, 1321, 1249 ($SiMe_3$), 1101, 1029, 937, 860, 837 ($SiMe_3$), 760; δ_H (300 MHz, $CDCl_3$) 7.33-7.30 (1H, m, Ar-*H*), 7.20-7.11 (2H, m, 2 × Ar-*H*), 6.93-6.90 (1H, m, Ar-*H*), 4.68 (2H, s, $ArCH_2OCH_2O$), 4.56 (2H, s, $ArCH_2OCH_2O$), 3.68-3.59 (2H, m, OCH_2CH_2Si), 3.24 (2H, s, $ArCH_2CCO$), 2.61-2.51 (2H, m, 2 × $COCH_AH_BCH_2$), 2.43-2.30 (2H, m, 2 × $COCH_AH_BCH_2$), 1.85-1.62 (2H, m, $COCH_2CH_2$), 1.27 (3H, s, CH_3CCO), 0.97-0.91 (2H, m, OCH_2CH_2Si), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 212.3, 138.0, 136.9, 131.5, 131.2, 129.2, 128.5, 95.4, 68.5, 66.7, 66.6, 40.5, 40.3, 23.6, 19.5, 18.2, 1.3; *m/z* LRMS (EI^+) 300.2 (55%), 257.2 (100%), 199.1 (35%), 115.1 (40%), 104.1 (40%), 91.0 (50%), 73.1 (100%); (CI^+) 394 $[M+NH_4]^+$; HRMS (ES^+) calc. for $C_{21}H_{36}NO_4Si$: 394.2408 $[M+NH_4]^+$; found: 394.2410 $[M+NH_4]^+$.

Appendix

HPLC traces of racemic and enantiopure monoester **225**

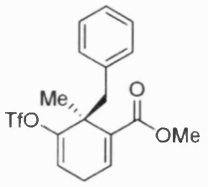
Area % Report

Data File: C:\EZChrom Elite\Projects\Default\Data\SJB 274
Method: C:\EZChrom Elite\Projects\Default\Methods\sy3-(99.7 - 0.3).met
Acquired: 5/23/2005 3:51:56 PM
Printed: 5/23/2005 6:30:08 PM



VWD 1 Results

Retention Time	Area	Area %	Height	Height %
4.291	6319	0.13	561	0.63
5.141	7691	0.16	130	0.15
6.307	243	0.01	31	0.03
6.579	1539	0.03	91	0.10
7.862	274	0.01	31	0.03
9.689	785	0.02	44	0.05
11.681	9741	0.20	380	0.43
12.376	27035	0.56	1081	1.22
15.005	4707	0.10	170	0.19
16.210	4169	0.09	174	0.20
* 16.987	4612297	96.38	84161	94.85
* 26.764	110952	2.32	1872	2.11
Totals	4785752	100.00	88726	100.00

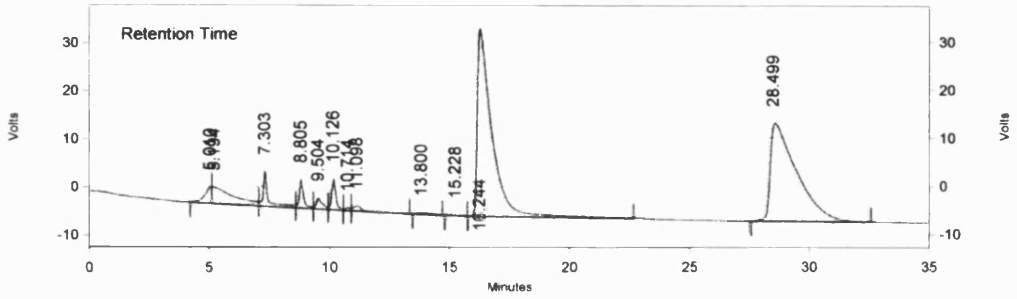


95% *ee*

n.b. absolute stereochemistry not determined

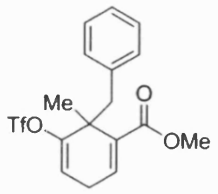
Area % Report

Data File: C:\EZChrom Elite\Projects\Default\Data\SJB 282
Method: C:\EZChrom Elite\Projects\Default\Methods\sy3-(99.7 - 0.3).met
Acquired: 6/8/2005 11:30:26 AM
Printed: 6/8/2005 12:50:15 PM



VWD 1 Results

Retention Time	Area	Area %	Height	Height %
5.010	66733	1.76	3328	3.73
5.194	209486	5.51	3320	3.72
7.303	109805	2.89	7199	8.06
8.805	71262	1.88	5864	6.56
9.504	39987	1.05	2230	2.50
10.126	76954	2.03	6340	7.10
10.714	8210	0.22	496	0.56
11.098	26897	0.71	1026	1.15
13.800	12252	0.32	318	0.36
15.228	3700	0.10	122	0.14
* 16.244	1610738	42.40	38790	43.42
* 28.499	1562736	41.14	20296	22.72
Totals	3798760	100.00	89329	100.00



racemic

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