PALLADIUM-CATALYZED [1,3] O→C REARRANGEMENT OF PYRANS TOWARDS FUNCTIONALIZED CYCLOHEXANONES

The University Of Sheffield.

A thesis submitted in partial fulfilment of the degree of Doctor of Philosophy

THOMAS

ANDREW

BARKER

Department of Chemistry

May 2012

"Time spent wishing is time wasted"

"When you do things right, people won't be sure you've done anything at all"

"Nothing in this world that’s worth having comes easy"

I ABSTRACT

Functionalised cyclohexanones are prepared from cyclic enol ethers *via* a Pd-catalysed [1,3] O→C rearrangement reaction. A variety of α-arylketones are generated with excellent diastereocontrol and yield when basic phosphine ligands are used. In contrast, a Lewis acid is required to promote rearrangement of alkyl-substituted enol ether systems. These reactions proceed in excellent yield, but exhibit poor diastereocontrol.

Attempts towards an asymmetric [1,3] O→C rearrangement reaction through the use of chiral phosphine ligands are also described. After screening a wide range of ligands only ^{t}Bu-Phox has provided reasonable levels of enantiocontrol (84% yield, 49% *ee*).

The preparation of enantiomerically enriched enol ethers is also described. Unfortunately, when applied to the rearrangement chemistry, two enantiopure enol ethers have each provided racemic cyclic ketones.

Aspects of the reaction mechanism are described, which resulted in the development of a kinetic resolution protocol. This led to the preparation of enantiopure enol ethers (>95% *ee*) and cyclic ketones.

Finally, initial chemistry into the development of a new rearrangement paradigm utilizing a cyclobutadieneiron tricarbonyl mofit is discussed. Although late stage intermediates are prepared, the desired enol ethers could not be prepared, potentially due to the lability of the substrates.

II CONTENTS

III ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor Prof. Joe Harrity for accepting me into his research group. I know I have not been the easiest person to work with, but I thank you for believing in me and giving me the support and encouragement to achieve my best throughout. I would also like to thank Mike Barker and the other members of GSK during my short period at Stevenage for the support and help you have provided me, and especially for the Phox ligands!!

Additionally, my thanks go out to all the technicians of the department for providing help with NMR, mass spec, chromatography, chemicals and equipment.

Lastly, I would like to say thanks all the people I have worked with over the years: Julien for helping me settle into the group and getting my chemistry started; Claire, Duncan, Nicole and Jianhui for the advice you have given me; Calum for all the terrible music you like to play, although you did manage to find some songs I did like!; Jerome for all the French you have taught me… we are all missing you; Danny for all the extremely weird and wonderful conversations we have had; James for keeping the lab upbeat and your… not so beautiful singing!; Anne-Laure for all the craziness you have brought to the lab; Rob for random sport conversations and the cakes :D; Kat for all the food I secretly steal… hehe; Jean-Olivier for carrying on with my chemistry and the great results; Julong and Anne-Chloe good luck with the rest of the PhD; Matt and Wes for the enjoyable conversations and wacky chemistry you have introduced me to; the MChem and summer students I have worked with, especially “Little” James and Owen; and also the Jones and Chen members of E26 for all the banter and the great times over the last 3.5 years…I cannot believe we never broke anything!!

IV ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
Aq.	Aqueous
BBN	Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
Boc	Di-*tert*-butyl dicarbonate
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat	Catalyst
CBS	Corey-Bakshi-Shibata
Cbz	Carboxybenzyl
CSA	Camphorsulfonic acid
d	Day
DACH	1,2-Diaminocyclohexane-*N*,*N*'-bis(2-diphenylphosphinobenzoyl)
DavePhos	2-Dicyclohexylphosphino-2'-(*N*,*N*'-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
de	Diastereomeric excess
DIBAL	Diisobutylaluminium hydride
DIOP	2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DiPhos	1,2-Bis(methylphenylphosphino)benzene
DMAP	4-Dimethylaminopyridine
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
DMS	Dimethylsulfide

DMSO	Dimethylsulfoxide
DMF	*N*,*N*-Dimethylformamide
dppe	1,2-Bis(diphenylphosphino)ethane
dr	Diastereomeric ratio
DuPhos	1,2-Bis[2,5-dimethylphospholano]benzene
Δ	Heat
ee	Enantiomeric excess
eq	Equivalents
Et	Ethyl
g	Gram
GC	Gas chromatography
h	hour
Hex	Hexyl
HKR	Hydrolytic Kinetic Resolution
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
Hz	Hertz
i	*Iso*
JosiPhos	1-[2-(Dicyclohexylphosphino)ferrocenylethyl]diphenylphosphine
L	Ligand/Litre
LA	Lewis acid
LDA	Lithium diisopropylamide
m	milli/metre
M	Metal or Mega or Molar
μ	Micro
m-cpba	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Min	Minutes
mol	Moles
MS	Molecular Sieves

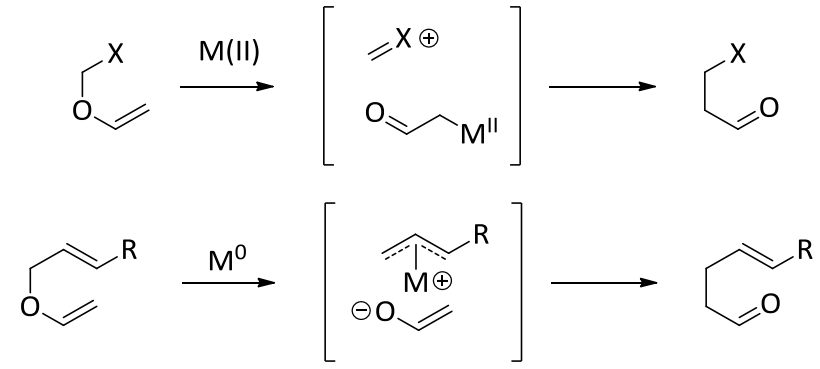
Ms	Mesyl
n	*Normal*/Nano
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
p	Para
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PPTS	Pyridinium toluene-4-sulfonate
Pr	Propyl
psi	Pounds per square inch
PTSA	*p*-Toluenesulfonic acid monohydrate
"R"-Phox	2-[2-(Diphenylphosphino)phenyl]-4-"R"-2-oxazoline
rt	Room temperature
s/*sec*	*Secondary*
T/Temp	Temperature
t/*tert*	*Tertiary*
TBAF	Tetrabutylammonium fluoride
TBAT	Tetrabutylammonium triphenyldifluorosilicate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethyl-ethane-1,2-diamine
TMS	Trimethylsilyl
Tf	Triflyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMAO	Trimethylamine *N*-oxide
Ts	Tosyl
uv	Ultraviolet

1 INTRODUCTION

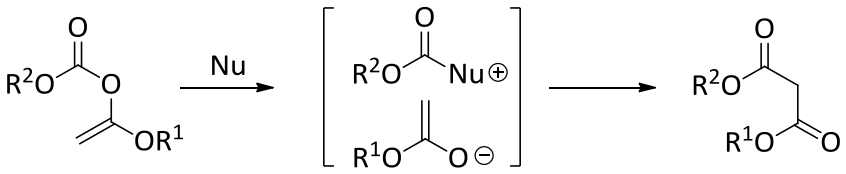
1.1 OVERVIEW

O→C rearrangements, whether [1,3] or [3,3], have been widely studied.[1,2] In particular, the rearrangement of vinyl ethers to carbonyl containing compounds has received worldwide interest. In recent years, there has been a significant effort to accomplish such transformations catalytically and stereoselectively. **Scheme 1** summarises three main general methods by which O→C rearrangements have been employed in organic chemistry.

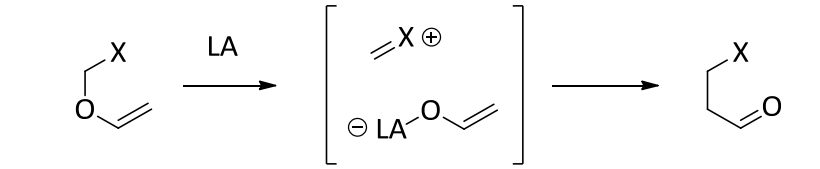
Transition Metal Catalysis



Nucleophilic Catalysis



Lewis Acid Catalysis

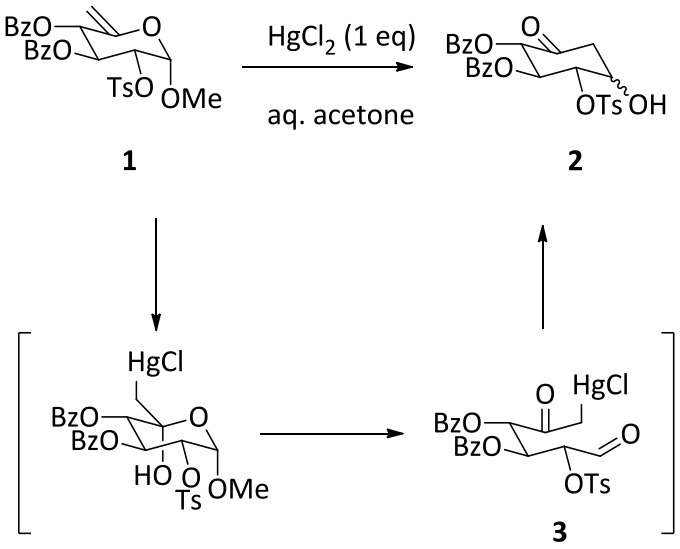


Scheme 1

1.2 TRANSITION METAL CATALYSIS

1.2.1 FERRIER TYPE II REARRANGEMENTS

The Ferrier type II rearrangement reaction was first reported by Ferrier in 1979.[3] It is a mercury-mediated synthetic route to carbocycles or carbosugars **2** using a common sugar enol ether **1** as the starting material (**Scheme 2**).

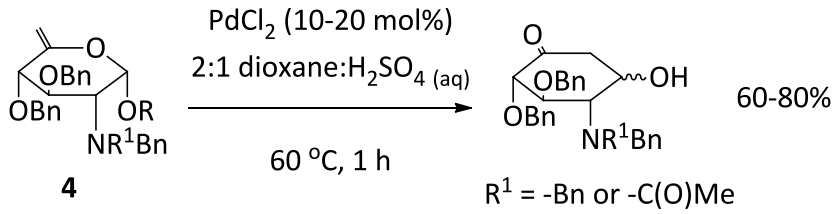


Scheme 2

The mechanism that is proposed involves oxymercuration followed by ring closure on to the *in situ* generated aldehyde **3**.

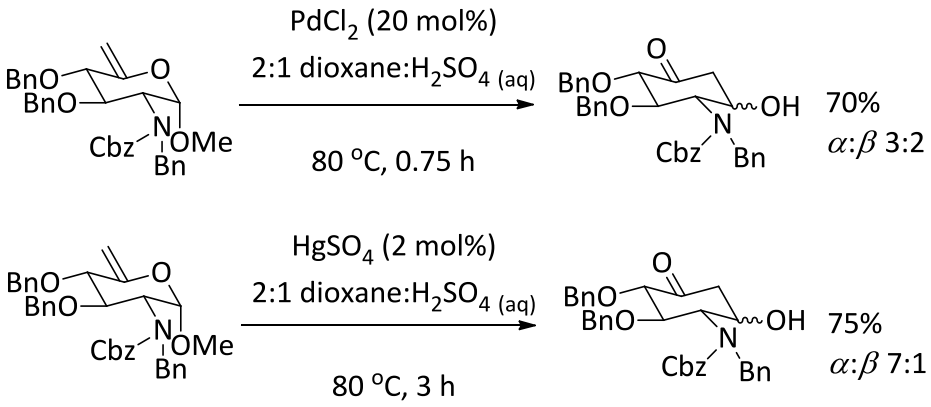
Aside from mercury(II) chloride, other mercury salts have been used in such transformations. Studies have shown that one equivalent of mercury(II) trifluoroacetate at room temperature proved more effective.[4] Catalytic transformations have also been developed including the use of mercury(II) sulphate in dioxane with aqueous sulphuric acid at 50-60 ^{o}C.[5]

Similar to Ferrier's chemistry, Adam reported that palladium(II) chloride and palladium(II) acetate salts also led to the rearrangement of enol ether containing carbohydrates **4** (**Scheme 3**).[6]



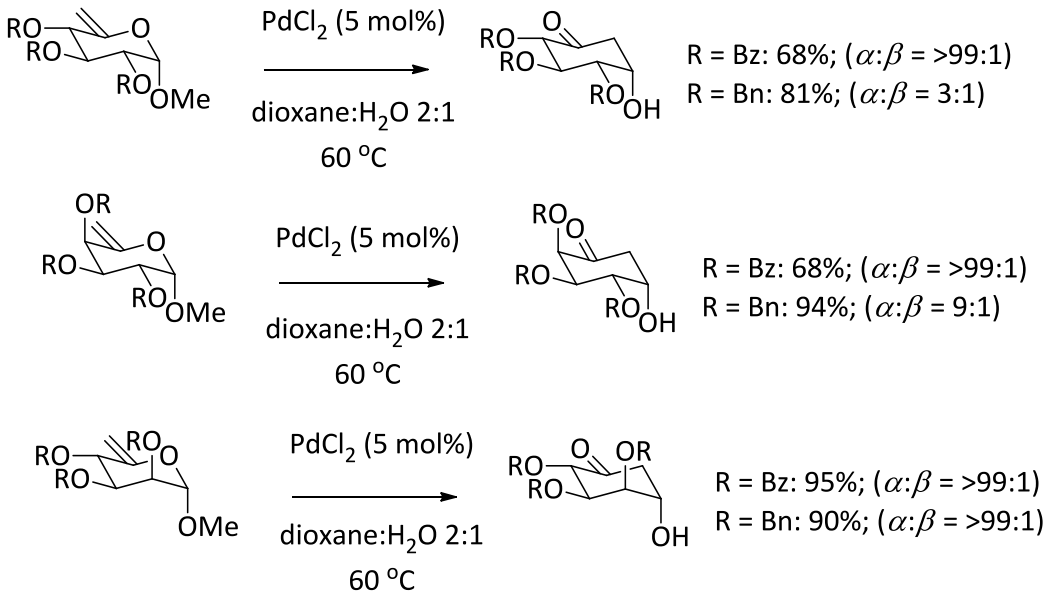
Scheme 3

Applying the above chemistry with the use of mercury(II) salts (2 mol%) led to similar results, albeit, over a longer reaction time. The main difference is in the stereochemistry of the isolated products. The palladium(II) system gives a diastereomeric ratio of 3 : 2 whilst the mercury(II) system gave a 7 : 1 mixture of diastereomers (**Scheme 4**).[7,8]



Scheme 4

Further development of the palladium(II) rearrangement was undertaken by Ikegami, where several sugar units underwent transformation to the corresponding ketone in high yields and with excellent stereoselectivities (**Scheme 5**).[9]



Scheme 5

The use of palladium(II) acetate and palladium(II) sulfate salts produced significantly lower yields (<10%). A rationale for the observed stereocontrol is highlighted in **Figure 1** (OR groups omitted for clarity).

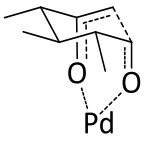
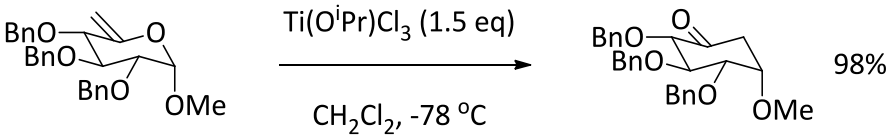


Figure 1

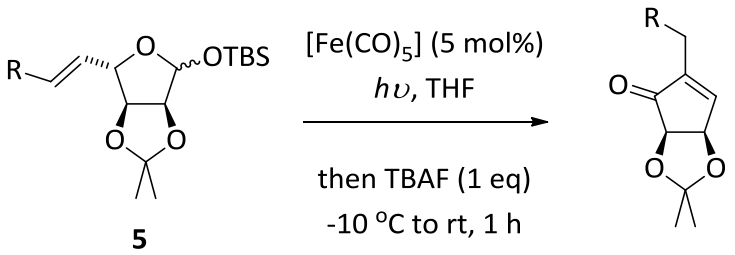
In a similar fashion, sugar units can also undergo rearrangements with the use of a titanium(IV) complex as shown in **Scheme 6**.[10]



Scheme 6

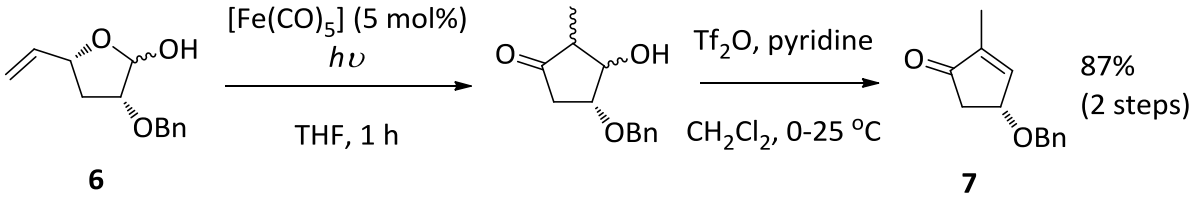
Titanium(IV) chloride, a stronger Lewis acid than $Ti(O^iPr)Cl_3$, was initially used in this transformation however this gave a poorer yield of ~50%. Several similar sugar units can undergo this rearrangement, all with yields >80% and which exhibit a high degree of stereoselectivity. Stereocontrol is proposed to originate from an analogous intermediate to that in **Figure 1**.

Chemistry of a similar manner has been used to obtain cyclopentenones. Grée has demonstrated that vinylic furanoses **5** undergo skeletal rearrangement with the use of an iron catalyst under *uv* irradiation (**Scheme 7**).[11] The reaction appears to involve isomerisation of the allylic acetal to the corresponding enol ether.



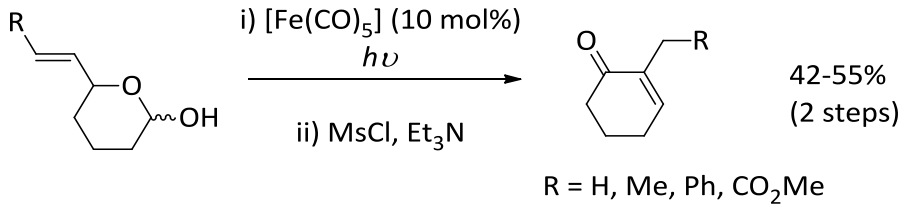
Scheme 7

Aside from the 5-vinyl furan derivatives (R = H), various functional groups have been shown to undergo this transformation under identical conditions including aryls (R = Ph, 42% yield) and esters (R = CO_2Me, 52%). Further examples expanded to 3-alkoxy-substituted derivatives, precursors to prostaglandins. These rearrangements on vinyl sugars **6** gave aldol products from which cyclopentenone **7** can be accessed *via* elimination (**Scheme 8**).



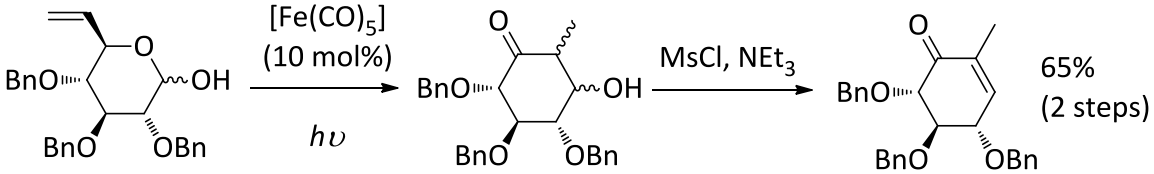
Scheme 8

Further examples have been recently reported where cyclohexenones can be obtained from vinyl lactols, again using the $[Fe(CO)_5]$ catalyst (**Scheme 9**).[12]



Scheme 9

Compared to the cyclopentenone examples, the yields are lower. However, when applied to a vinyl pyranose **8**, an excellent yield was obtained (**Scheme 10**).

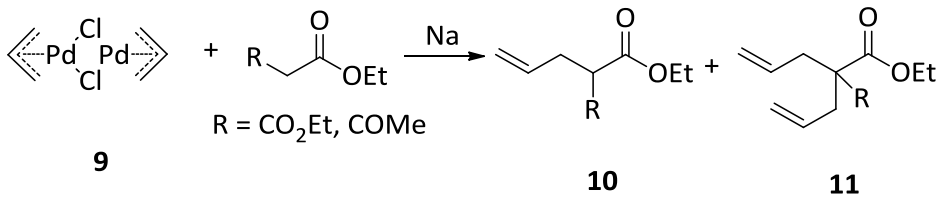


8

Scheme 10

1.2.2 TSUJI-TROST REARRANGEMENT

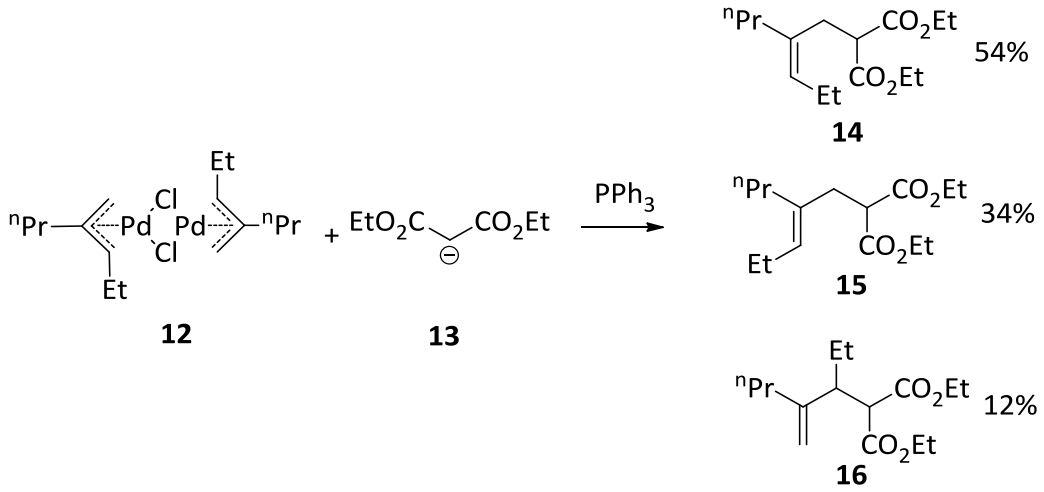
The Tsuji-Trost reaction is the widely used palladium catalysed substitution of allylic- or propargylic-compounds with carbon nucleophiles such as enolates. In the first example reported by Tsuji, the reaction of allylpalladium chloride dimer **9** with diethyl malonate and ethyl acetoacetate with sodium at room temperature provided mono- and di-allylated products **10** and **11** (**Scheme 11**).[13]



9 **10** **11**

Scheme 11

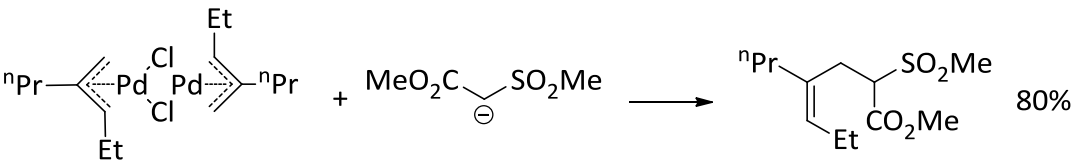
Trost's initial investigations also concentrated on the use of allylpalladium complexes,[14] which were made directly from olefins with palladium(II) chloride and a base. Using such complexes (**12**) in the presence of the anion derived from diethyl malonate **13**, and triphenylphosphine, led to immediate allylation at room temperature (**Scheme 12**).



12 **13** **14** **15** **16**

Scheme 12

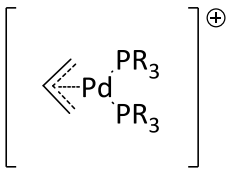
This reaction provides a mixture of three isomers; the major products were derived from nucleophilic addition at the least hindered position (**14** and **15**; 88%; ~3 : 2; *Z* : *E*). Further studies with dimethylsulfonylacetate **17** using the same catalyst yielded a single product **18** (**Scheme 13**). In this case, the reaction proceeds with high regio- and stereoselectively. From this investigation, Trost made the surprising conclusion that the alkylating species can affect the regio- and stereo-selectivity.



12 **17** **18**

Scheme 13

Although the exact mechanisms of these transformations were unknown at the time, Trost proposed the intermediacy of an ionic complex **19**, as shown in **Figure 2**. This proposal was based on the observation that four equivalents of phosphine per dimer were required in order for the reaction to proceed.

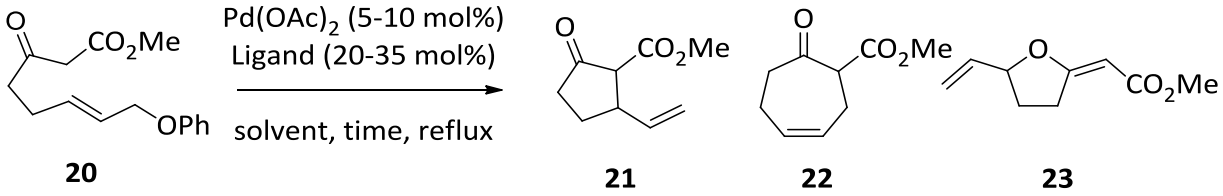


19

Figure 2

1.2.3 O→C MIGRATIONS

Attempts to promote intramolecular trapping of π-allyl palladium complexes by Tsuji and co-workers showed that octenoates **20** can undergo various reactions to give a variety of products with the use a palladium catalyst, as shown in **Table 1**.[15]

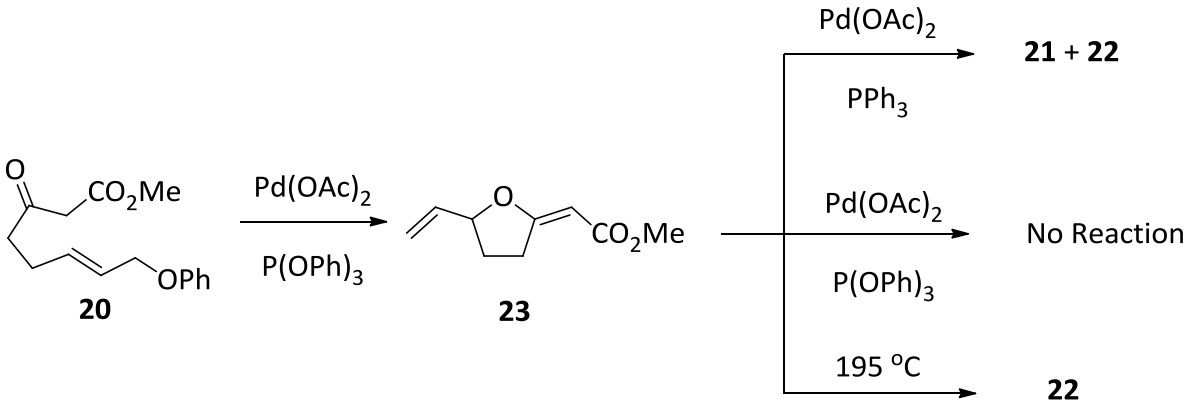


20 **21** **22** **23**

Ligand	Solvent	Time / h	% 21	% 22	% 23
$P(OPh)_3$	MeCN	8	0	0	100
PBu_3	MeCN	1	85	15	0
PPh_3	MeCN	1	87	13	0
PPh_3	THF	8	37	57	0

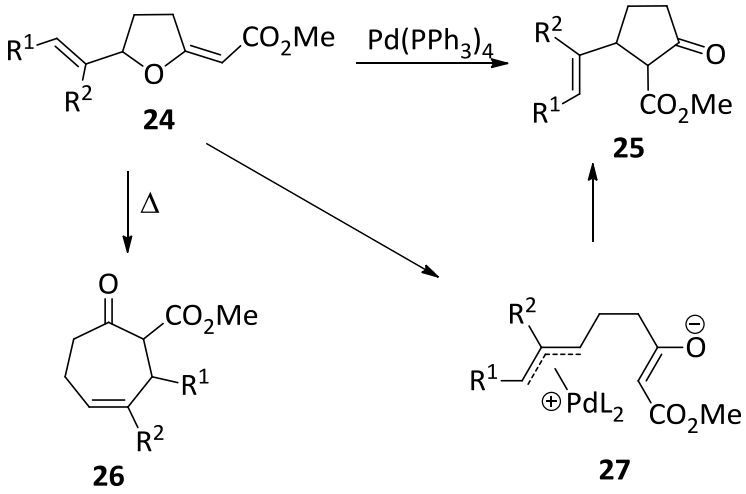
Table 1

When the allyl enol ether **23** was subjected to the $Pd(OAc)_2/PPh_3$ conditions in acetonitrile, the same ratio of cyclopentanone **21** and cycloheptanone **22** was obtained (87 : 13). This showed that the phosphite ligand could not catalyse the O→C rearrangement of the enol ether **23** whilst triphenyl- and tributylphosphine could. From the results obtained, Tsuji proposed that the vinyl allyl ether **23** was an intermediate, leading onto various rearranged products. **Scheme 14** summarises these findings.



Scheme 14

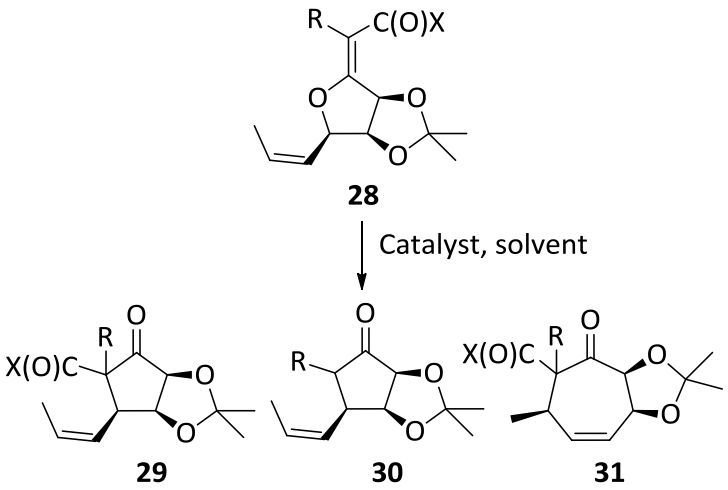
Trost has further developed methodology for the catalytic rearrangement of alkylidenetetrahydrofuran derivatives **24** to form carbocycles **25**, as shown in **Scheme 15**.[16]



Scheme 15

When alkylidenetetrahydrofuran **24** is exposed to heat only, the cycloheptanone **26** product is formed (*cf* Claisen rearrangement).[17] In all cases, the cyclopentanone **25** was the sole product when a palladium catalyst was employed, with no trace of cycloheptanone **26** observed. At the same time, Tsuji found that the terminal alkene **23** would undergo rearrangements to the cyclopentanone **21** and cycloheptanone **22** when palladium(II) acetate/triphenylphosphine was utilised.[15]

In principle, the zwitterionic intermediate **27** could undergo competing cyclisation reactions. The influence of catalyst system, solvent and additives on the regio- and stereochemistry of the rearrangements has been studied by Trost. A summary of these investigations is shown in **Table 2**.[18]



X	R	Catalyst	Solvent	Yield / %	% 29	% 30	% 31
O^tBu	H	$Pd(PPh_3)_4$	DMSO	85	0	59	41
O^tBu	H	$Pd(dppe)_2$	DMSO	64	0	0	100
O^tBu	H	Pd(polymer)[a]	PhMe	100	98	0	2
$N(Et)_2$	Me	$Pd(dppe)_2$	DMSO	62	56	0	44
$N(Et)_2$	Me	$Pd(dppe)_2$	Dioxane	93	100	0	0

Table 2

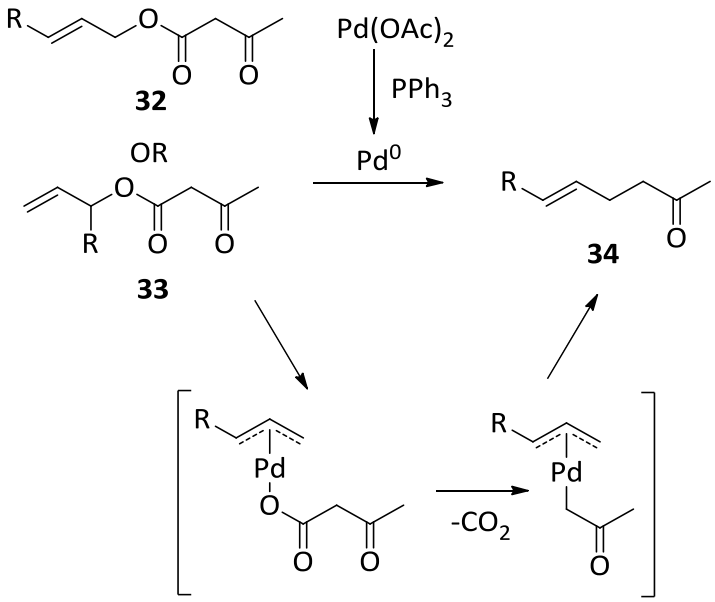
[a] Pd(polymer): derived from phosphinylated polystyrene[19]

Using tetrakis(triphenylphosphine)palladium, a mixture of cycloheptanone **31** and decarboxylated cyclopentanone **30** was obtained. This was the first time that cycloheptanones had been observed in a palladium catalysed rearrangement reaction (**Table 1**, *vide supra*). The use of a less sterically demanding catalyst, $Pd(dppe)_2$, yielded cycloheptanone **31** only. However, a polymer-bound catalyst (which can be viewed as been sterically hindered) gave mainly cyclopentanone **29**. Replacing the ester group with an amide, using the dppe system, gave approximately equal ratios of cyclopentanone **29** and cycloheptanone **31**. Changing the solvent to dioxane yielded cyclopentanone **29** exclusively.

With respect to the intermediate palladium-π-allyl complex, the use of dimethyl sulfoxide[20] and pyridine[21] are known to favour *syn-anti* interconversion. Therefore a wide range of solvents were screened in this reaction, however there was not a significant change in the product *E* : *Z* ratios.

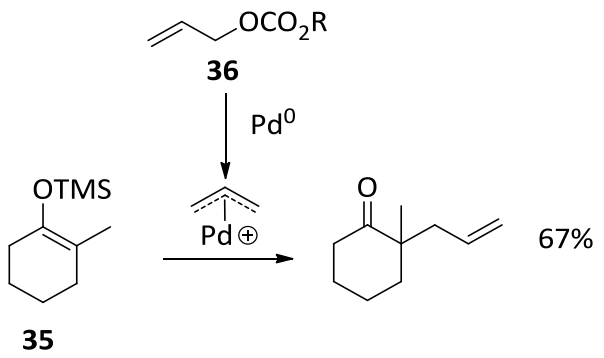
The structural dependence of the starting alkylidenetetrahydrofuran **24** on the stereochemistry of the resulting cyclopentanone was next studied.[22] Specifically, both *E* and *Z* isomers of the starting material were subjected to O→C rearrangements, using similar conditions. The use of a sterically unhindered palladium catalyst, such as $Pd(dppe)_2$, yielded little of the desired cyclopentanone **25**, instead the Claisen product was obtained. However, the use of a polymer bound palladium catalyst gave ratios in excess of 17 : 1 in favour of the cyclopentanone **25**.

Tsuji undertook related studies on the palladium-catalysed reaction of allyl acetoactates **32** and **33**. In the presence of palladium, these substrates undergo a rearrangement to give allyl ketones **34**, with the loss of carbon dioxide. Regardless of stereochemistry of the starting allyl ester, only one product was obtained, as outlined in **Scheme 16**.[23]



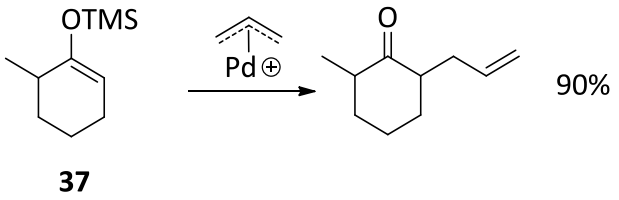
Scheme 16

A key step in the Tsuji-Trost chemistry is the C-C bond forming alkylation step. This type of reaction is quite general. For example, silyl enol ethers **35** can undergo allylation with a π-allyl palladium complex. Here, the π-allyl palladium complex was accessed from an allyl carbonate **36**, as shown in **Scheme 17**.[23]



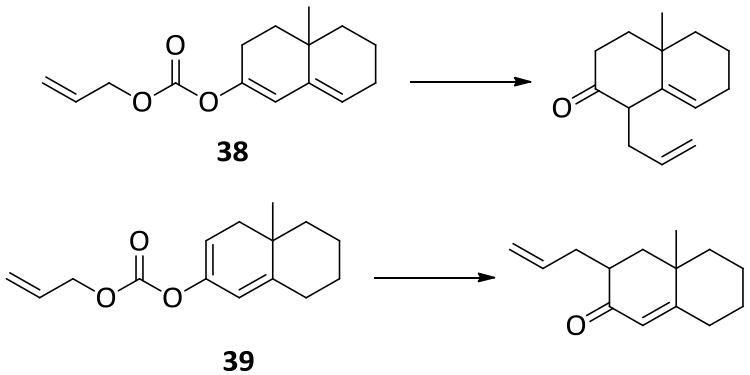
Scheme 17

These allylations occur regiospecifically, and are dependent on the regiochemistry of the starting silyl enol ether **37** (**Scheme 18**).



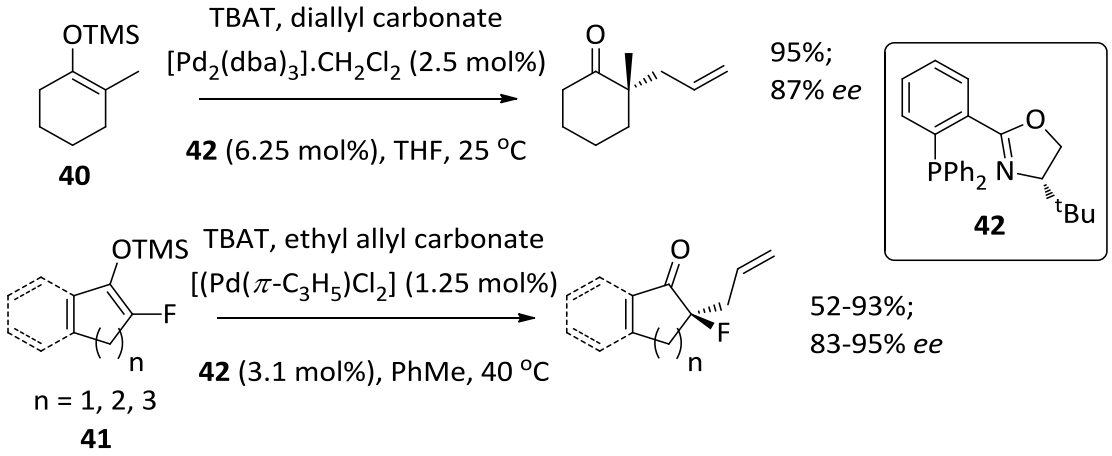
Scheme 18

In a similar fashion, intramolecular allylations have been performed with vinyl allyl carbonates **38** and **39**, and have been shown to proceed regioselectively (**Scheme 19**).



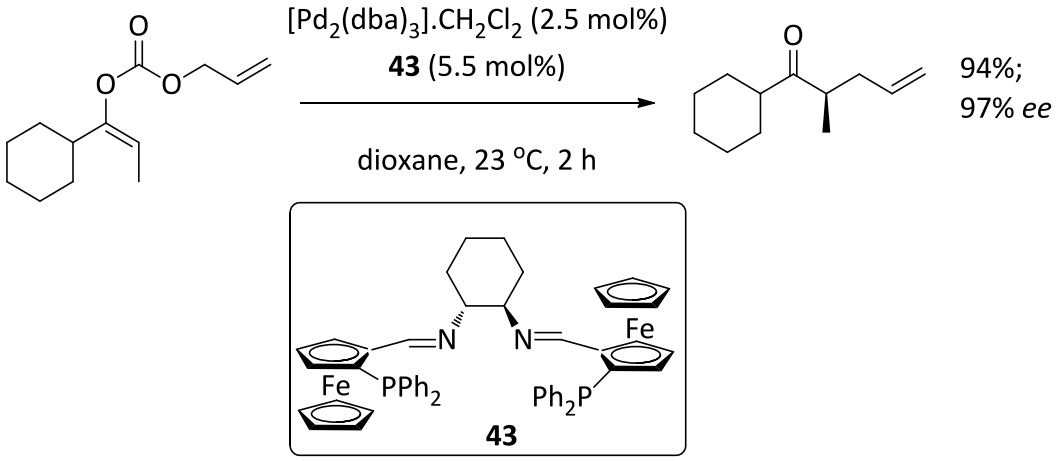
Scheme 19

Recently, asymmetric allylation reactions have been developed by analogy to Tsuji's chemistry. Firstly, a phoshinooxazoline ligand **42** has been found to allylate enol silyl ethers **40** and **41** enantioselectively, as shown by Stoltz and Paquin respectively (**Scheme 20**).[24,25]



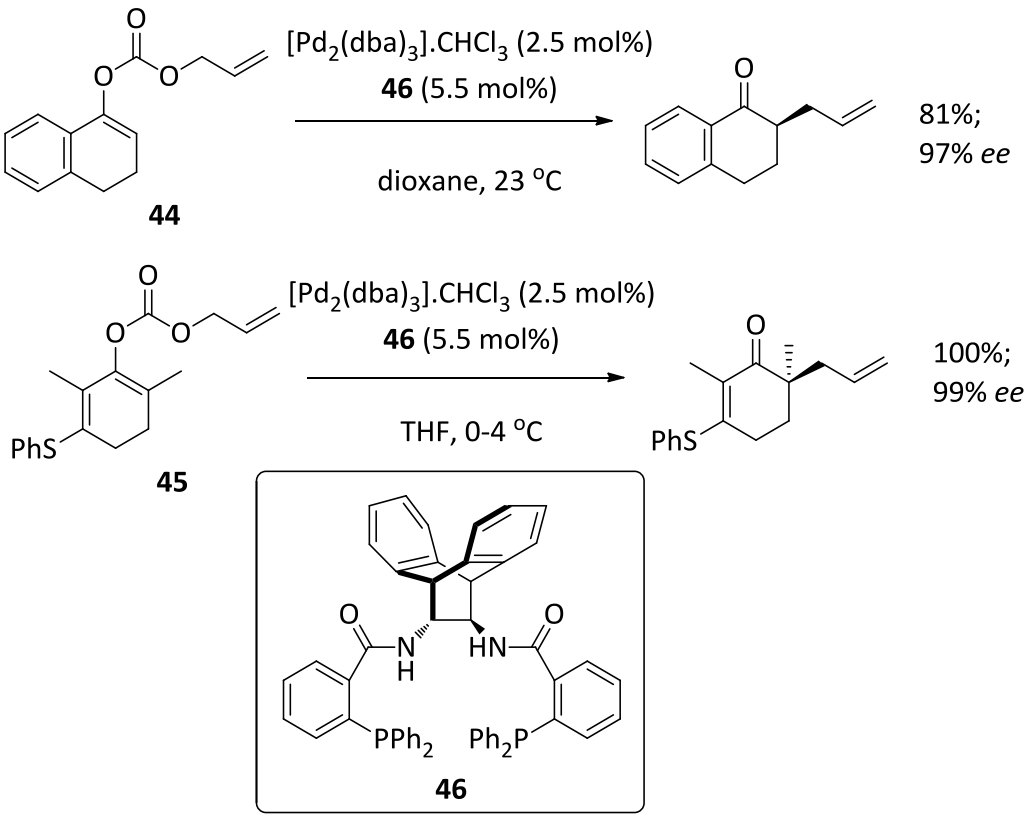
Scheme 20

Likewise, the vinyl allyl carbonate decarboxylative alkylations can be performed enantioselectively. Trost has shown that the use of a bisiminoferrocene ligand **43** affords the rearranged product in excellent yields and enantioselectivity, an example is shown in **Scheme 21**.[26]



Scheme 21

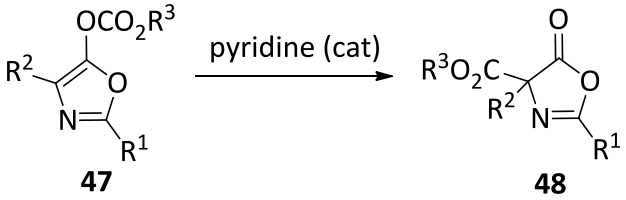
Yields are somewhat lower with carbonates **44**. However, when applied to dienyl carbonates **45**, quantitative yields and excellent enantioselectivities can be obtained (**Scheme 22**).[27]



Scheme 22

1.3 NUCLEOPHILIC CATALYSTS

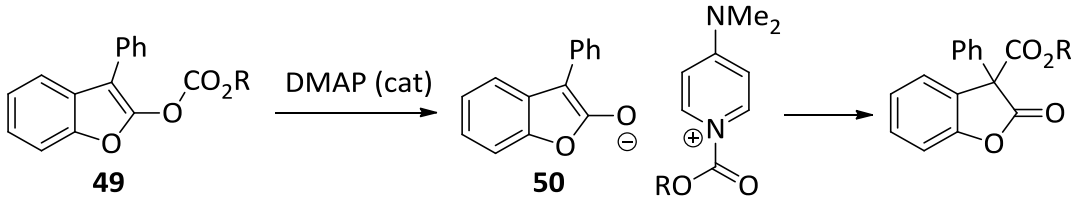
The rearrangement of vinyl ethers can also be accomplished by the use of a nucleophilic molecule or organocatalyst as described by Steglich and Höfle. Their examples involve the rearrangement of oxazoles **47** with pyridine to obtain oxazolinones **48** (**Scheme 23**).[28,29]



47 **48**

Scheme 23

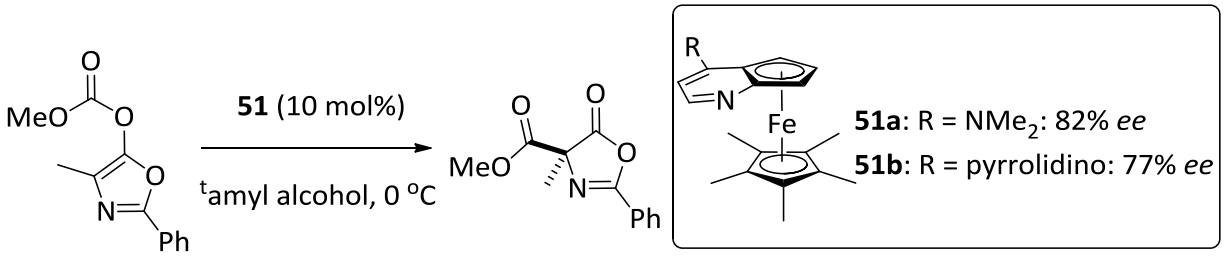
Black also reported similar chemistry where 4-dimethylaminopyridine was used in the rearrangement of enol carbonates **49**, *via* a proposed enolate intermediate **50** (**Scheme 24**).[30]



49 **50**

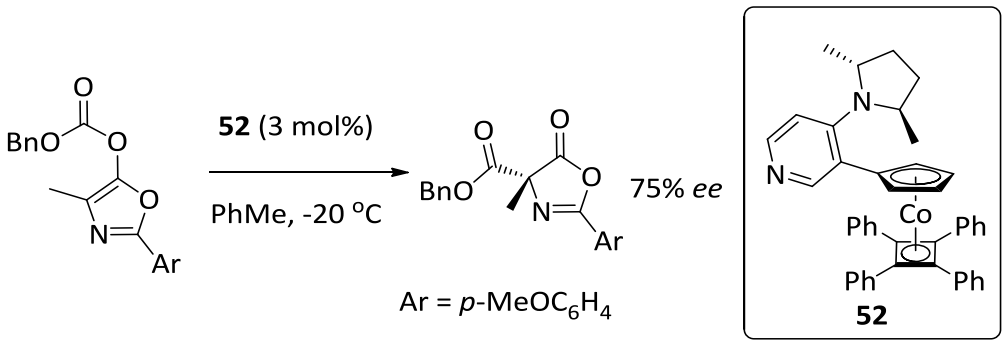
Scheme 24

Further development of this type of rearrangement has been described by Fu where a chiral nucleophilic catalyst can be used to promote an enantioselective rearrangement (**Scheme 25**).[31]



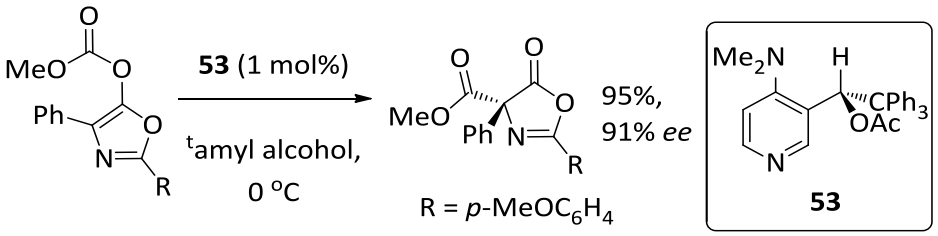
Scheme 25

A similar system has also been developed by Richards, using a cobalt metallocene rather than iron. This catalyst can be used at lower loadings but gives similar enantioselectivities (**Scheme 26**).[32]



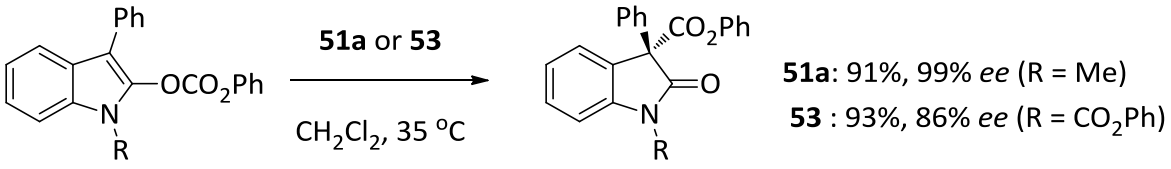
Scheme 26

Other 4-dimethylaminopyridine based metal free catalysts have been used for rearrangements of similar substrates, such as in the examples by Vedejs (**Scheme 27**).[33]



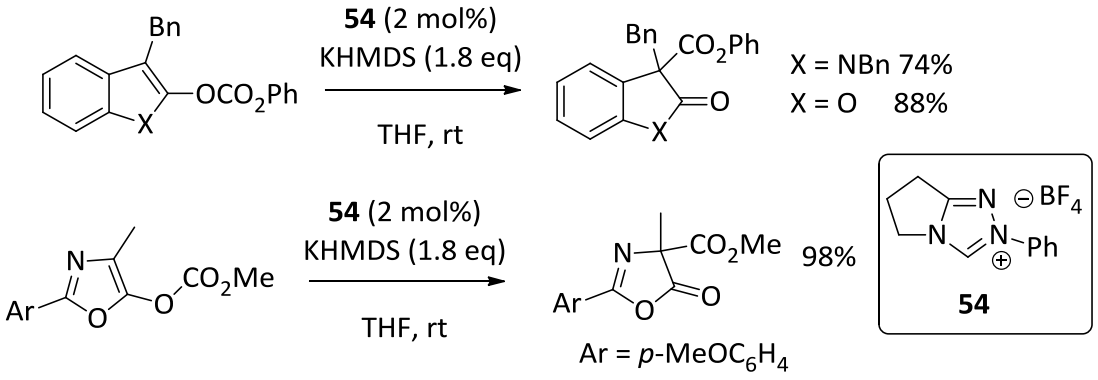
Scheme 27

Similar catalyst can also be used in rearrangements in other systems, such as indoles to oxindoles (**Scheme 28**).[34,35]



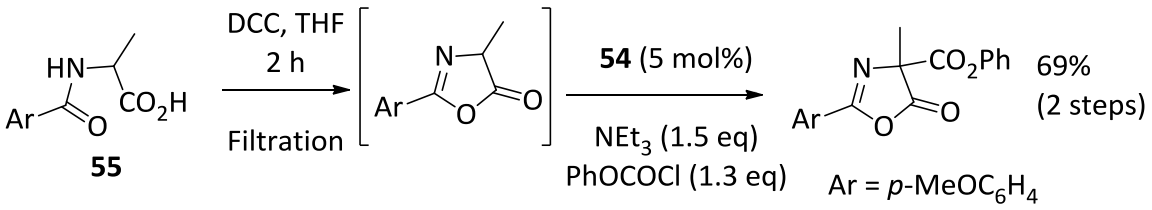
Scheme 28

Carbene ligands have also been utilised not only in the rearrangements of oxazoles and indoles, but also in the case of benzofurans. The examples in **Scheme 29** show how these heterocycles can be rearranged using the same NHC catalyst **54** generated *in situ* from a triazolium salt.[36,37]



Scheme 29

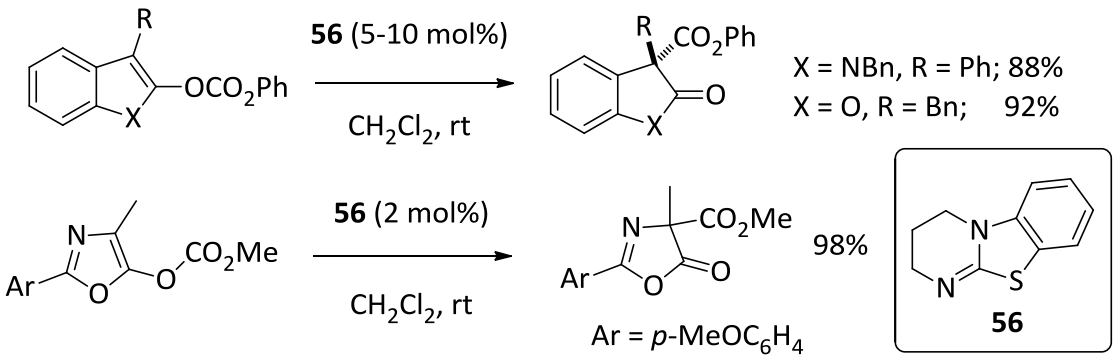
Recently, a cascade reaction has been developed whereby oxazolinones can be obtained from amino acid derivatives **55** *via* *N*,*N*'-dicyclohexylcarbodiimide coupling, carbonate formation, followed by O→C rearrangement, as shown in **Scheme 30**.[38]



Scheme 30

Aside from *N*-*p*-anisoyl alanine, other amino acid derivatives that have undergone this chemistry include phenylalanine (71%), leucine (70%), norleucine (73%) and tyrosine (84%).

Furthermore, Smith has shown that the exact same transformations can be performed with amidines (for example **56**), as illustrated in **Scheme 31**.[39] Other amidines are able to catalyse the oxazole rearrangement, albeit in lower yields.

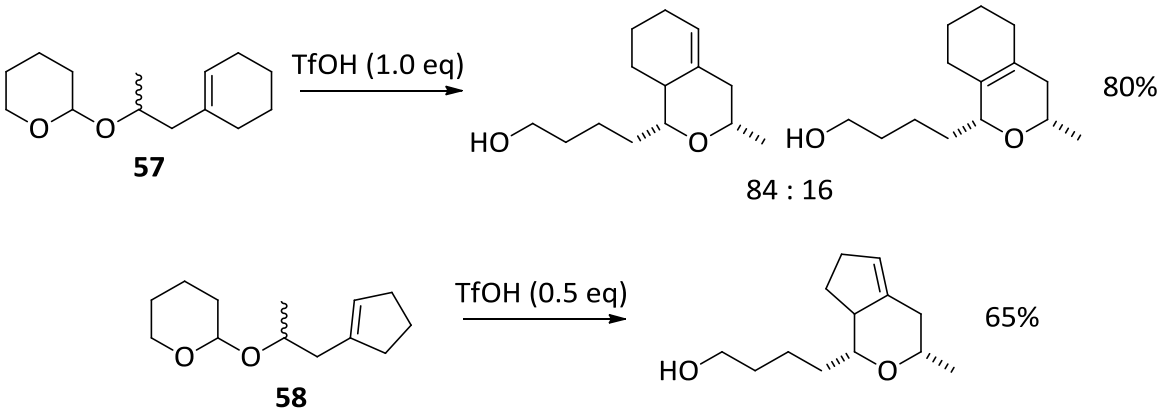


Scheme 31

1.4 ACID CATALYSTS

1.4.1 BRØNSTED ACIDS

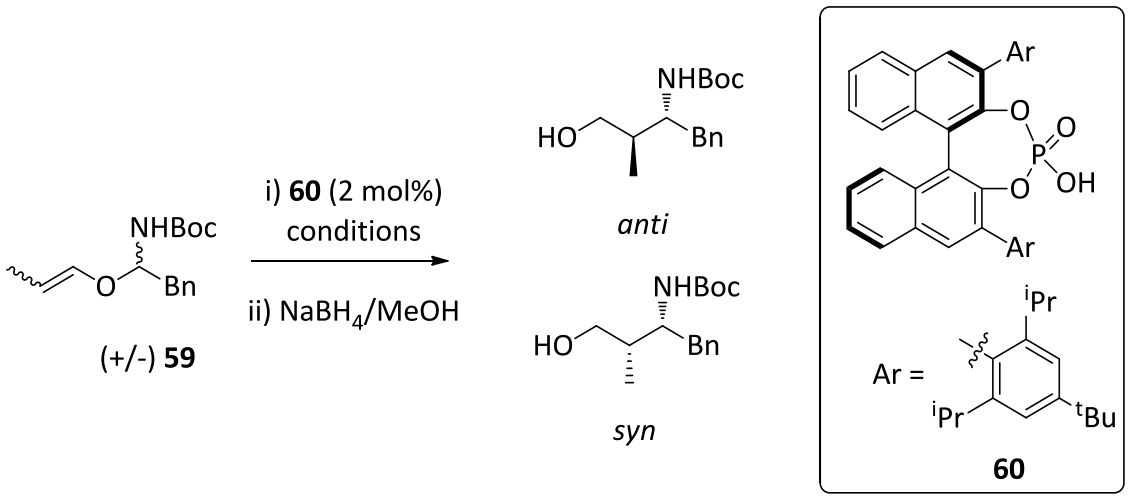
Ring opening of pyranyl ethers followed by cyclisation can be accomplished with Brønsted acids as reported by Ley and co-workers. Examples reported utilise triflic acid for these rearrangements, which can either be used in stoichiometric or substoichiometric amounts (**Scheme 32**).[40]



Scheme 32

With the cyclohexenyl ether **57**, stoichiometric triflic acid was required and gave an excellent yield of rearranged product with excellent stereocontrol, although two alkene isomers were formed. However, only one product was obtained with the cyclopentenyl ether **58**, which used 0.5 equivalents of acid, albeit with a lower yield.

A recent report by Terada described the synthesis of β-amino aldehydes from a hemiaminal vinyl ether **59** *via* a Petasis-Ferrier rearrangement.[41] To accomplish these transformations, a chiral phosphoric acid catalyst **60** is utilised, as outlined in **Table 3**.



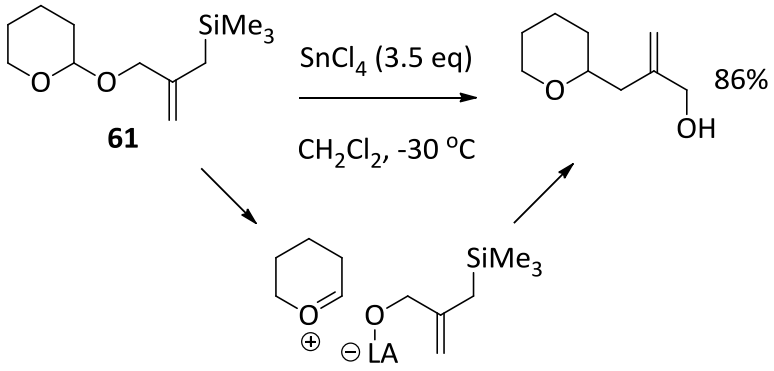
E/Z	Solvent	Temp / °C	Time / h	Yield / % (*anti* : *syn*)	*ee* / % (*anti* /*syn*)
Z	AcOEt	0	18	89 (99 : 1)	89 / 65
Z	AcOEt	40	1.5	93 (97 : 3)	95 / 6
Z	Acetone	40	6	82 (99 : 1)	95 / 13
E	AcOEt	40	1.5	94 (23 : 77)	17 / 88
E	Acetone	40	6	69 (8 : 92)	38 / 88

Table 3

As results in the table show, higher temperatures gave better enantioselectivities. This chemistry has also been used in the synthesis of aliphatic β-amino aldehydes. Examples include replacing the benzyl group with methyl, pentyl or hexyl groups under the same conditions to give up to 86% yield of the *anti*-product with *ee*'s greater than 97%.

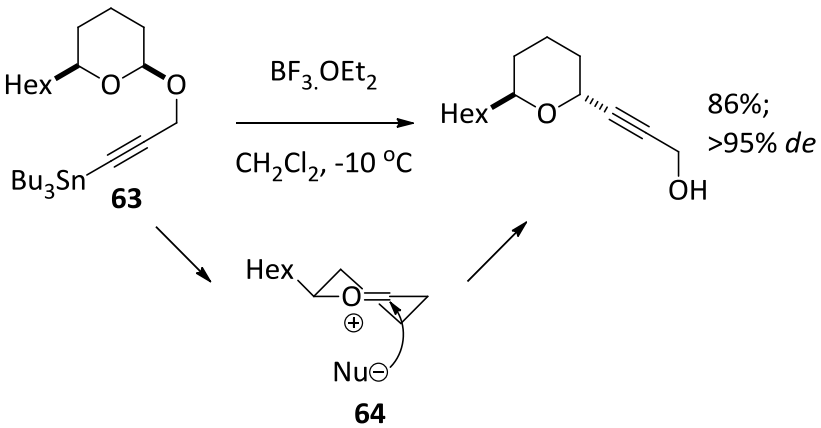
1.4.2 LEWIS ACIDS

Ley and co-workers have shown that pyranyl vinyl acetals with an attached nucleophilic component on the anomeric oxygen (for example **61**) can undergo O→C rearrangements by the use of a Lewis acid. These processes are postulated to proceed *via* an oxocarbenium intermediate **62** (**Scheme 33**).[42]



Scheme 33

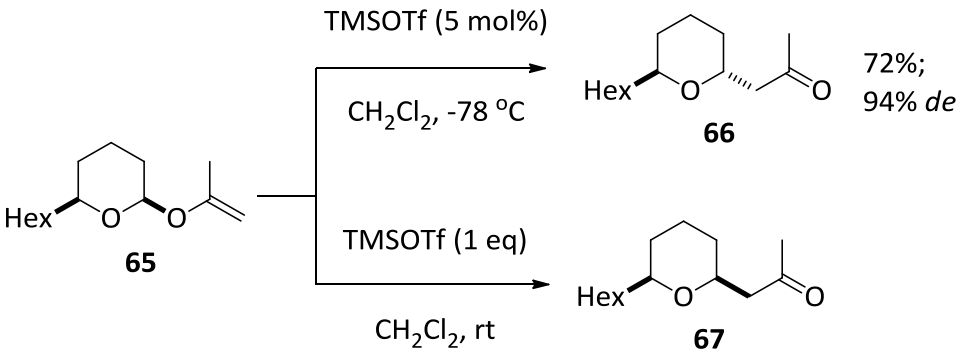
2,6-Di-substituted pyrans **63** can undergo diastereoselective transformations in the presence of a Lewis acid. The stereochemistry is rationalised by a half-chair, oxocarbenium intermediate **64** (**Scheme 34**).[43]



Scheme 34

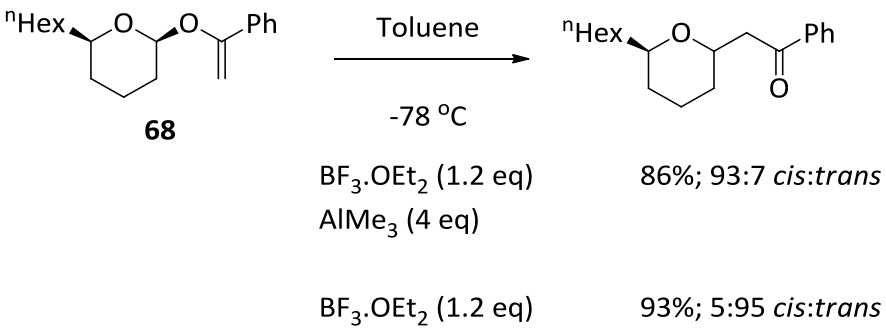
Aside from pyran formation, substituted tetrahydrofurans can also be accessed and this approach has been employed in the synthesis of muricatetrocin C.[44]

Further development has led to a catalytic Lewis acid system for the rearrangement of the vinyl acetals **65** to obtain *trans*-pyrans **66**. However, using a stoichiometric amount of Lewis acid at a higher temperature leads to the *cis*-pyran **67** (**Scheme 35**).[45]



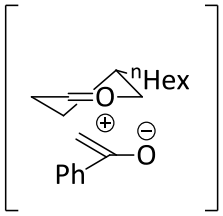
Scheme 35

Lewis acid catalysed stereoretentive rearrangements of pyranyl vinyl acetal **68** has also been developed recently by Rovis. The use of a mixture of Lewis acids influences the product diastereomeric ratio, as shown in **Scheme 36**.[46]



Scheme 36

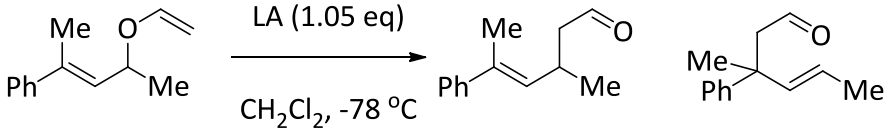
The use of boron trifluoride and trimethylaluminium provides the *cis* product *via* a tight ion pair. The use of boron trifluoride only gives the *trans* product. From this, it was deduced that two ionic species were involved. In the case of boron trifluoride, the solvent-equilibrated ion pair equates to an intermolecular nucleophilic addition to an oxocarbenium intermediate **69** (**Figure 3**).



69

Figure 3

Rovis has also utilised a Lewis acid in the [1,3] rearrangement of allyl vinyl ethers **70**.[47] Although stoichiometric quantities of the Lewis acids are generally required in such rearrangements, a small number are effective at lower loadings (**Table 4**).

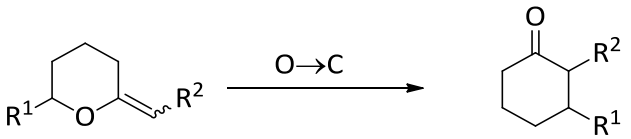


70 **[1,3]** **[3,3]**

Lewis Acid	Yield / %	Ratio [1,3] : [3,3]
$SnCl_4$	40	80 : 20
$TiCl_4$	44	>95 : 5
$EtAlCl_2$	55	>95 : 5
Me_2AlCl	73	>95 : 5
$Cu(OTf)_2$ (10 mol%)	81	>95 : 5

Table 4

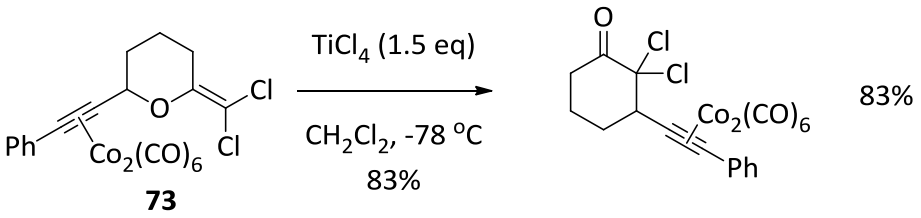
Recent chemistry in the Harrity group on O⟶C rearrangements have focused on the synthesis of cyclohexanones **72** from enol ethers **71**, as shown in **Scheme 37**.[48]



71 **72**

Scheme 37

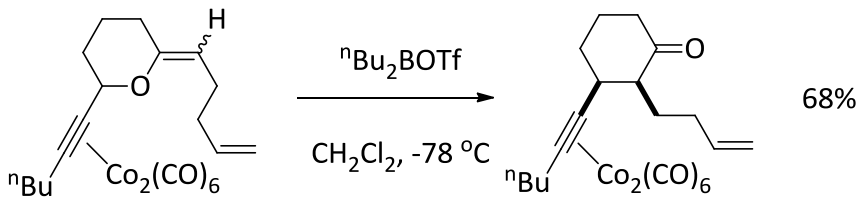
Initial chemistry focused on a Lewis acid mediated rearrangement reaction of a pyran bearing a cobalt-alkyne cluster **73** with titanium(IV) chloride (**Scheme 38**).[49]



73

Scheme 38

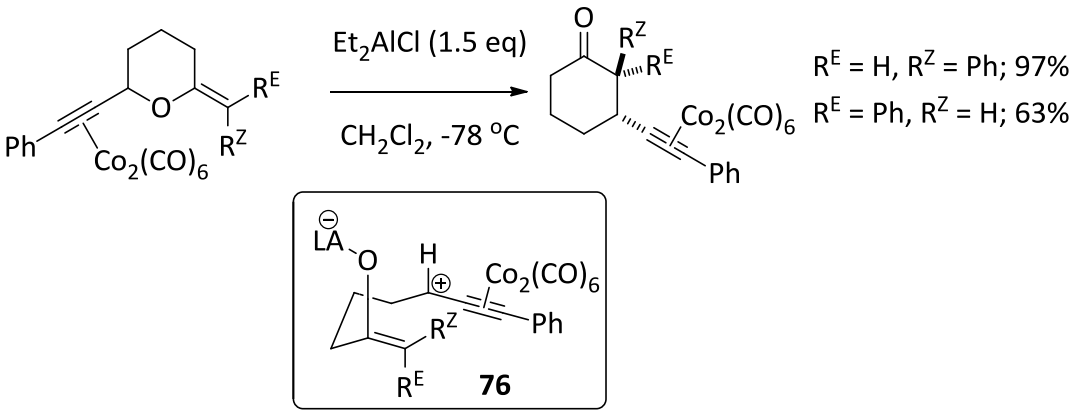
Aside from titanium(IV) chloride, boron trifluoride can also be used to perform such transformations in yields varying from 86-98%. Moreover, $^{n}Bu_2BOTf$ can be used in the rearrangement of pyrans **74** with a tri-substituted enol ether bearing a butenyl moiety to give a single diastereomer of cyclohexanone **75** (**Scheme 39**).[50]



74 **75**

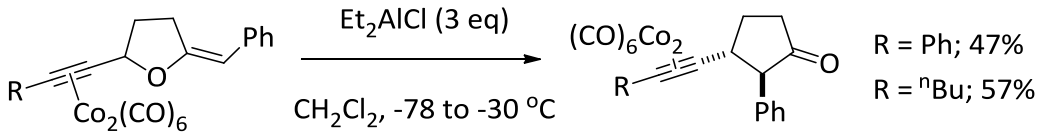
Scheme 39

The use of diethylaluminium chloride promoted rearrangements of enol ethers not only gives the desired cyclohexanone, but proceeds with high degrees of stereochemical control. The diastereoselectivity of these rearrangements was rationalised by invoking a chair-like transition state **76** (**Scheme 40**).



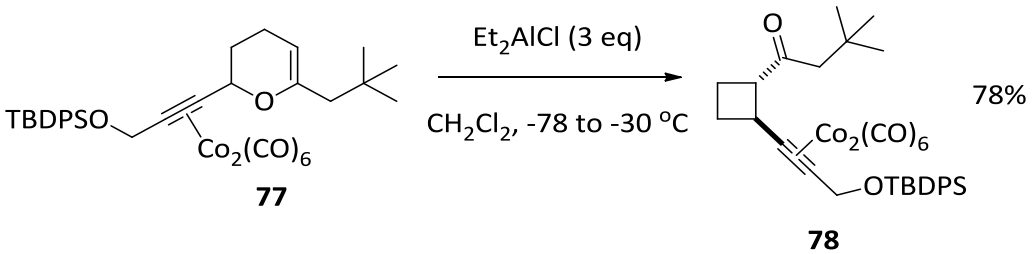
Scheme 40

Aside from cyclohexanones, similar conditions can be used in the synthesis of cyclopentanones and cycloheptanones. However, the former transformation requires three equivalents of Lewis acid and results in poorer yields (**Scheme 41**).[51]



Scheme 41

This chemistry can also be applied to the rearrangement of *endo* enol ethers **77** to gain disubstituted cyclobutanes **78** in high yields (**Scheme 42**).[52]



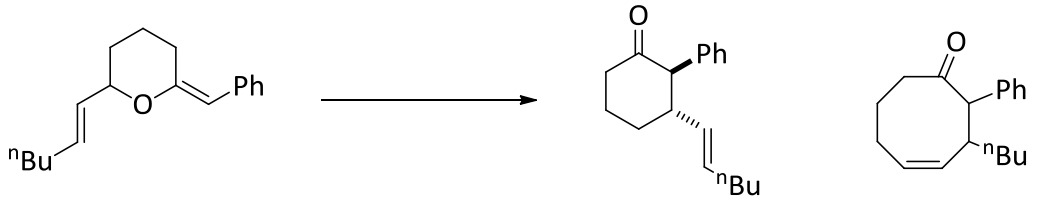
Scheme 42

2 PROJECT PLAN

2.1 BACKGROUND

Although the Lewis acid mediated O→C rearrangement chemistry of pyran-based enol ethers bearing cobalt-alkyne clusters is a very robust and an excellent method to access functionalised cyclic ketones, the fact that stoichiometric quantities of a cobalt carbonyl are required for these transformations limits its appeal.

As discussed earlier in **Scheme 15**, Trost has shown that vinyl allyl ethers can undergo rearrangement in the presence of a palladium catalyst to provide cyclic ketones. This chemistry seemed limited in scope as the only examples involved 5-membered ring systems in which the enolate intermediate **27** is stabilised by an electron withdrawing functional group. However using this chemistry as a basis, similar substrates to those employed in the cobalt-mediated rearrangement were subject to conditions analogous to those reports by Trost (**Table 5**).[53]



79 **80** **81**

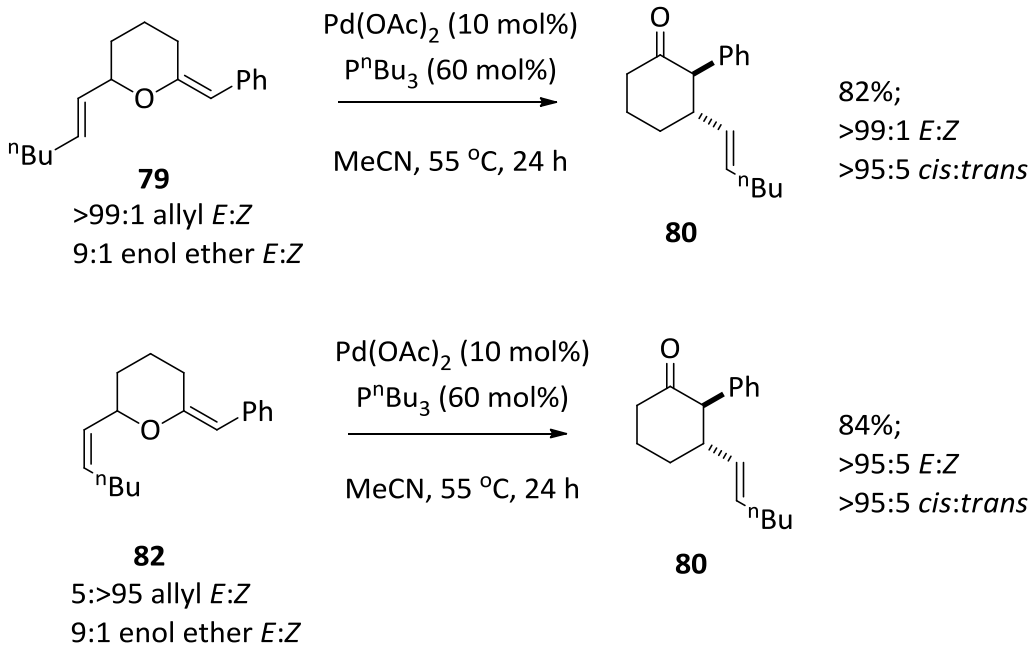
Entry	Conditions	% 80	% 81
1	$Pd(PPh_3)_4$ (15%), Et_2AlCl, PhMe, 50 ^oC	40	<5
2	Et_2AlCl, PhMe, 50 ^oC	<5	50
3	$PhNO_2$, 185 ^oC	<5	80
4	$Pd(PPh_3)_4$ (10%), MeCN, 55 ^oC, 48 h	70	<5
5	$Pd(OAc)_2$ (10%), P^nBu_3 (60%), MeCN, 55 ^oC, 24 h	82	<5

Table 5

Subjecting enol ether **79** to palladium catalysis in the presence of a Lewis acid provided the desired cyclic ketone **80** in moderate yield (**Table 5**, Entry 1). Subjecting **79** to the Lewis acid alone did not generate **80**, however cyclooctenone **81** was isolated (Entry 2), the result of a Claisen rearrangement of **79**. This showed that Lewis

acid alone could not lead to an O→C rearrangement as reported by Rovis (**Scheme 36**). In a similar vein, just refluxing **79** in nitrobenzene gave **81** in excellent yields (Entry 3). Removal of the Lewis acid and using a polar solvent solely provided **80** in good yield (Entry 4). Replacing $Pd(PPh_3)_4$ with a more electron-rich palladium-phosphine system gave an excellent yield of **80** (Entry 5).

With a suitable catalyst system in hand, various aspects of the rearrangement were investigated. Firstly, the effect of *E*- and *Z*-allyl ether moieties on the stereoselectivity of the rearrangement was studied (**Scheme 43**).

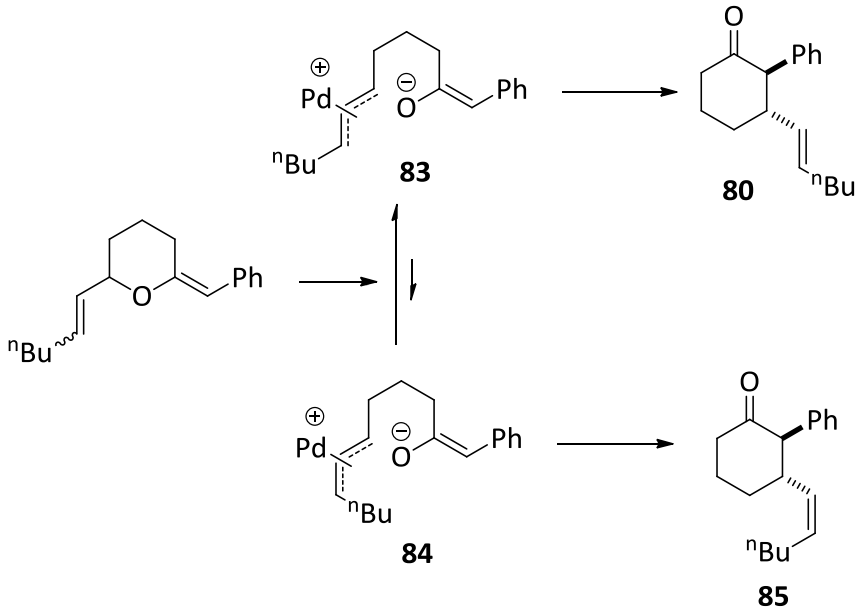


Scheme 43

Regardless of the alkene configuration of the enol ethers, the product was generated bearing an *E*-alkene exclusively in both cases. A rationale for this observation can be invoked upon examination of the intermediate palladium-π-allyl complex (**Scheme 44**).

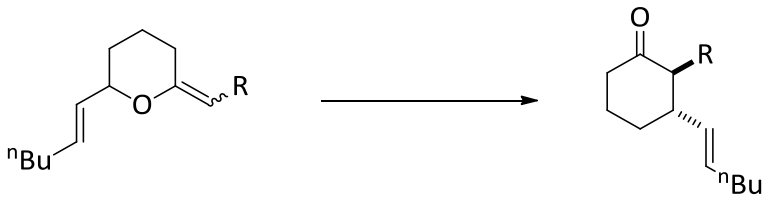
When either enol ether **79** or **82** is exposed to palladium, intermediates **83** and **84** can be formed in both cases. These isomers can interconvert *via* π-σ-π process such that both are in equilibrium. The so-called *syn-syn* isomer **83** is favoured over **84** as an unfavourable $A^{1,3}$ interaction is present in the latter intermediate. Assuming that the

enolate collapse is irreversible, this equilibrium must be faster than cyclisation of **84** as only trace amounts of the *Z*-cyclic ketone **85** are observed over **80**.



Scheme 44

Secondly, the effect of the enol ether substituent was examined. As summarised in **Table 6**, the catalyst system provided different results for aryl and alkyl substituents.



Entry	R[a]	Conditions	Yield	*cis* : *trans*
1	Ph **79**	$Pd(OAc)_2$ (10%), P^nBu_3 (60%), MeCN, 55 °C	**80**; 82%	>5 : 95
2	Et **86**	$Pd(OAc)_2$ (10%), P^nBu_3 (40%), MeCN, 70 °C	0	-
3	Et **86**	$Pd(OAc)_2$ (10%), DavePhos[b] (40%), Et_2AlCl (50%), PhMe, 55 °C	**87**; 71%	1 : 1.5

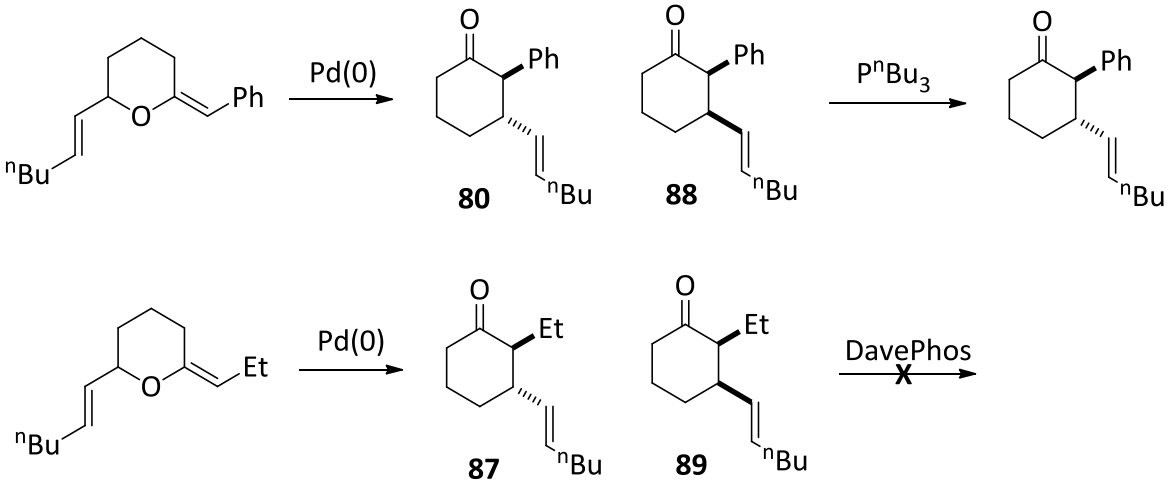
Table 6

[a] 9 : 1 *E* : *Z* enol ratio in all cases

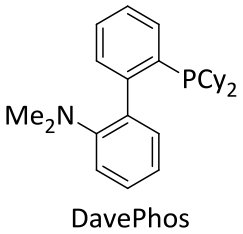
[b] DavePhos: 2-Dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl. See **Figure 4** for structure

Using the phenyl enol ether **79**, the cyclic ketone **80** was isolated in an 82% yield, with a *cis* : *trans* ratio of <5 : 95 (**Table 6**, Entry 1). When identical conditions were applied to the ethyl enol ether **86**, none of the desired product was observed (Entry 2). However, varying the catalyst conditions, **87** was obtained in a 71% yield, with a *cis* : *trans* ratio of 1 : 1.5 (Entry 3). In this case, the addition of a Lewis acid presumably promotes ionisation and the formation of the enolate intermediate.

The observed differences in the product diastereoselectivities could be explained by a combination of the pK_a of the α-proton and the basicity of the phosphine. As outlined in **Scheme 45**, the O→C rearrangement can give either *cis* or *trans* cyclic ketones. In the case of the phenyl derivatives (**80** and **88**) the α-protons are relatively acidic (pK_a ~ 17), whereas in the ethyl-substituted product **87** and **89,** the acidity is less pronounced (pK_a ~ 25).[54] Since *n*-tributylphosphine is more electron rich than DavePhos (**Figure 4**), it is more basic, hence more likely to deprotonate the product. Upon reprotonation, the more stable configuration of the cyclic ketones will be formed.



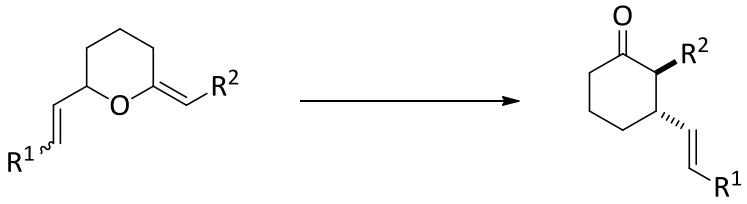
Scheme 45



DavePhos

Figure 4

Table 7 summarises the rearrangement chemistry of the various enol ethers that have previously been studied. Electron donating and withdrawing enol ethers can undergo rearrangement in good yields (**Table 7**, Entries 1 and 2). Additionally, the terminal alkene rearranges smoothly in an excellent yield (Entry 3). In line with results highlighted earlier, *Z*-alkene gave *E*-alkene cyclic ketone **93** in an 87% yield (Entry 4). Alkyl enol ether bearing a terminal alkene also gave a good yield under DavePhos conditions (Entry 5). Lastly, the ethyl enol ether with a *Z*-alkene substituent provides the *E*-alkene cyclic ketone **95** in a high yield (Entry 6).



Entry	R^1	R^2	Method[a]	Yield (*cis* : *trans*)
1	*E*-^{n}Bu	*p*-$MeOC_6H_4$	A	**90**; 66% (>5 : 95)
2	*E*-^{n}Bu	*p*-$NO_2C_6H_4$	A	**91**; 73% (>5 : 95)
3	H	Ph	A	**92**; 84% (>5 : 95)
4	*Z*-(CH_2)OTBDPS	Ph	A	**93**; 87% (>5 : 95)
5	H	CH_2OBn	B	**94**; 64% (1 : 2.5)
6	*Z*-^{n}Bu	Et	B	**95**; 74% (-)[b]

Table 7

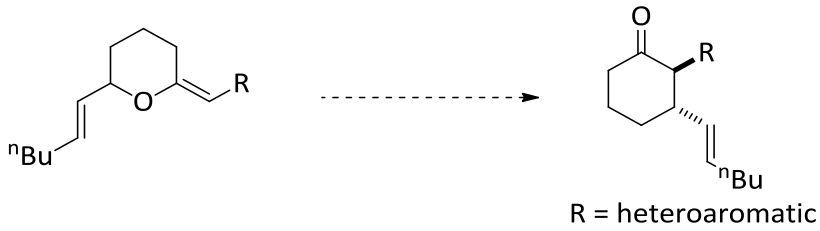
[a] Method A: $Pd(OAc)_2$ (10%), P^nBu_3 (60%), MeCN, 55 °C, 24 h

Method B: $Pd(OAc)_2$ (10%), DavePhos (40%), Et_2AlCl (50%), PhMe, 55 °C, 24 h

[b] Ratio not determined

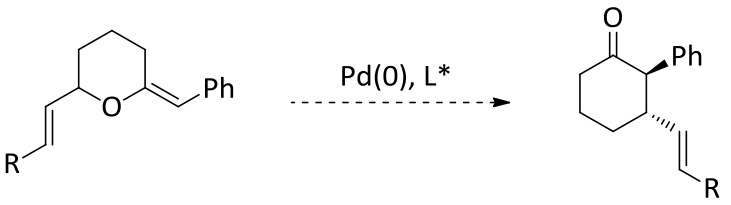
2.2 AIMS

The palladium catalyzed O→C rearrangement reactions of aryl enol ethers studied to-date have all been carbocyclic. To expand to scope of this chemistry, we wished to extend this process to include heteroaromatic substituents (**Scheme 46**).



Scheme 46

Additionally, the development of an asymmetric catalyst system would have the exciting potential to generate enantioenriched cyclic ketones, which could have an important impact in the enantioselective synthesis of functionalised carbocycles (**Scheme 47**).

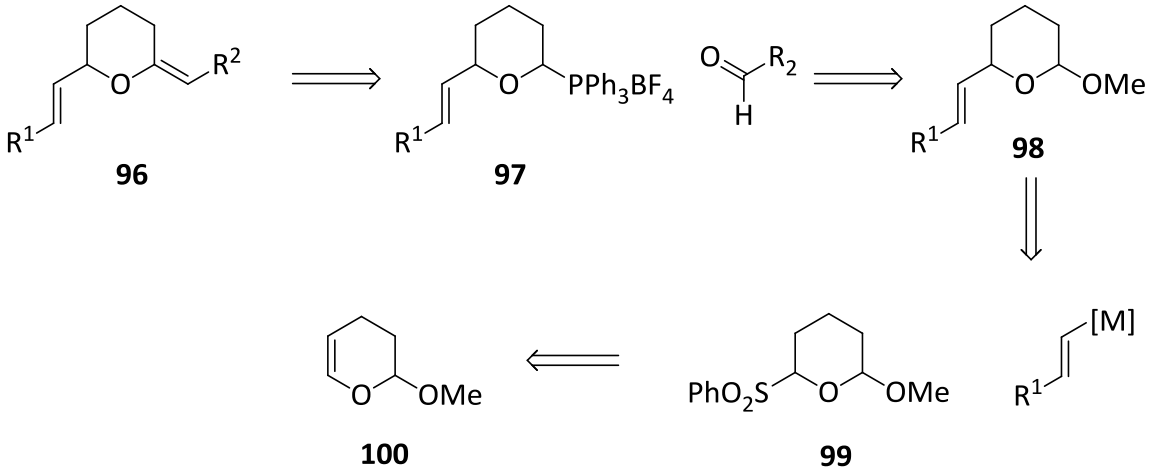


Scheme 47

3 RESULTS AND DISCUSSION

3.1 STUDIES TOWARDS α-HETEROAROMATIC CYCLOHEXANONES

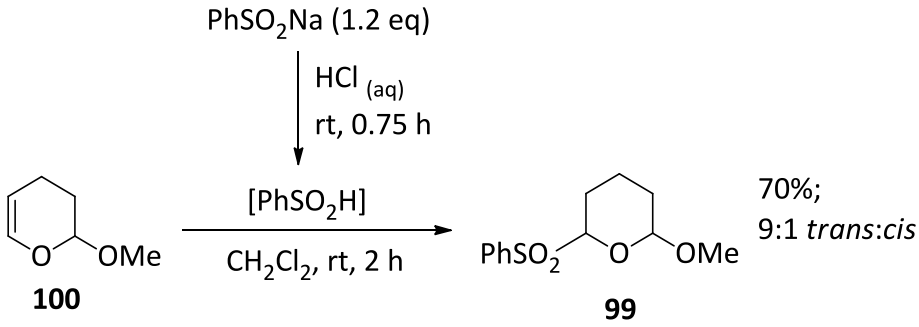
Before any rearrangement chemistry could be attempted, the necessary enol ethers had to be prepared. The synthesis of the requisite enol ethers had previously been optimised within the group,[50,53] and this method provided significant flexibility with respect to incorporation of the substituents at the allyl and enol ether moieties. The retrosynthetic analysis is highlighted in **Scheme 49**.



Scheme 49

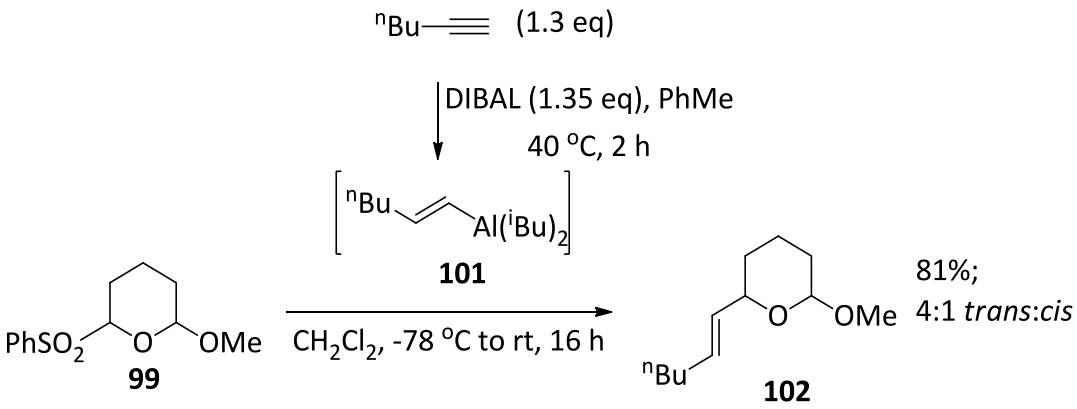
The enol ether substituents were to be installed by a Wittig olefination from phosphonium salt **97**. The insertion of various R^2 groups late in the synthesis is appealing, provided that the required aldehyde is readily available. The phosphonium salts would be obtained by treating pyranyl ethers **98** with triphenylphosphine tetrafluoroborate. Compound **98** would be prepared by the addition of vinyl metal reagents to cyclic sulfone **99**.[55]

The synthesis started by preparing cyclic sulfone **99** following the method of Ley and co-workers.[56] Specifically, benzenesulfinic acid was added to 3,4-dihydro-2-methoxy-2*H*-pyran **100** to generate the desired product in 70% yield. The cyclic sulfone **99** can be synthesised on a 40 gram scale in good yield. Although the two diastereoisomers of **99** could be separated *via* column chromatography, the mixture was carried on through subsequent transformations as they ultimately converge to a single compound during enol ether formation (**Scheme 50**).



Scheme 50

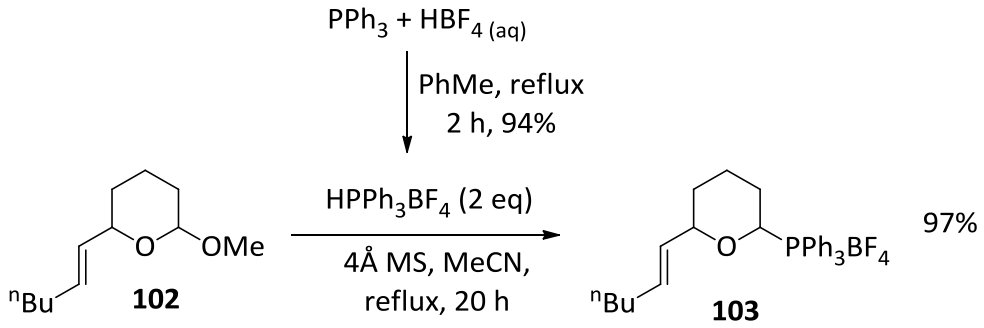
Cyclic sulfone **99** is a very versatile intermediate as various aryl and vinyl zinc reagents can be used to substitute the sulfone group. Although Ley's studies focused on aryl and vinyl zinc reagents (some *via* the Grignard reagent), it was hoped that vinyl aluminium reagents would perform equally well. The reason for choosing the aluminium reagent was the relative ease of accessing the required organometallic intermediate **101** from terminal alkynes (**Scheme 51**).[57]



Scheme 51

In the event, alkenyl aluminium **101** was prepared *via* the diisobutylaluminium hydride reduction of 1-hexyne, and employed directly *in situ*. Pleasingly, **101** displaced the sulfone of **99** to give pyranyl ether **102** in excellent yield. Notably, **102** can be synthesised on a reasonably large scale (>5 grams).

Using chemistry that had already been developed within the laboratory, phosphonium salt **103** was readily synthesised from pyranyl ether **102** and hydrogen triphenylphosphonium tetrafluoroborate.[58] Hydrogen triphenylphosphonium tetrafluoroborate itself can be easily made by heating triphenylphosphine at reflux with aqueous tetrafluoroboric acid, and is accessible on a multigram scale (**Scheme 52**).[59]



Scheme 52

The Wittig olefination to provide the target enol ethers was also optimised within the group. The use of potassium bis(trimethylsilyl)amide was found to be the most suitable base for this transformation. It was found that the enol ethers are sensitive to both extremely basic and acid environments where isomerisation could occur to give **104** (**Figure 5**). Additionally, the use potassium *tert*-butoxide leads to the oxidation of the phosphonium salt to give **105**.

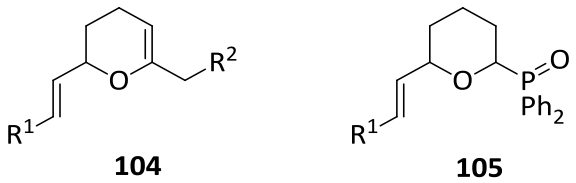
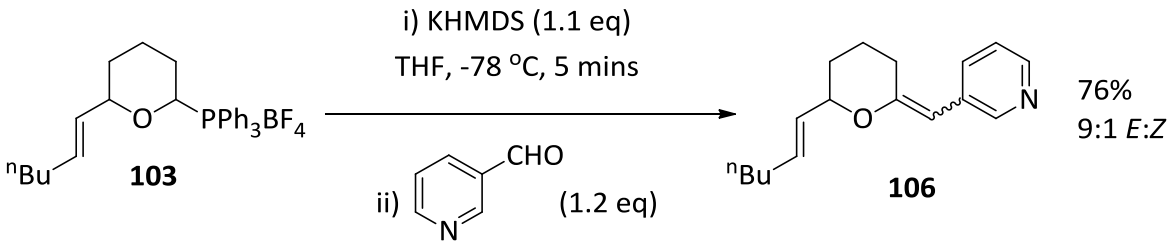


Figure 5

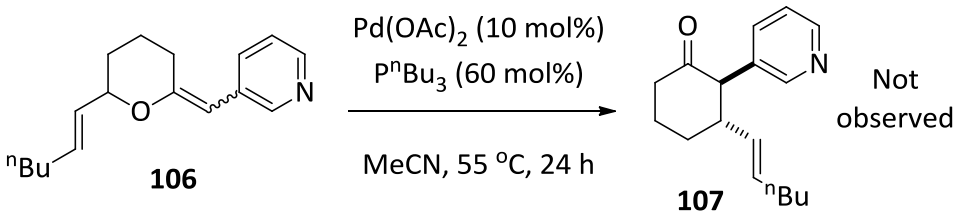
With regard to the olefin isomerisation problem, the best method of purification of the enol ethers was found to be flash chromatography on Florisil®, which minimised isomerisation but provided the products with small traces of triphenylphosphine oxide still present. Nonetheless, using the optimised conditions, analytically pure enol ether **106** was obtained by reaction with pyridine-3-carboxaldehyde in a good yield of 76%

(**Scheme 53**). The yield of this reaction is dependent on the age of the potassium bis(trimethylsilyl)amide solution; if this was stored for more than one week, the olefination yields dropped significantly (~40%).



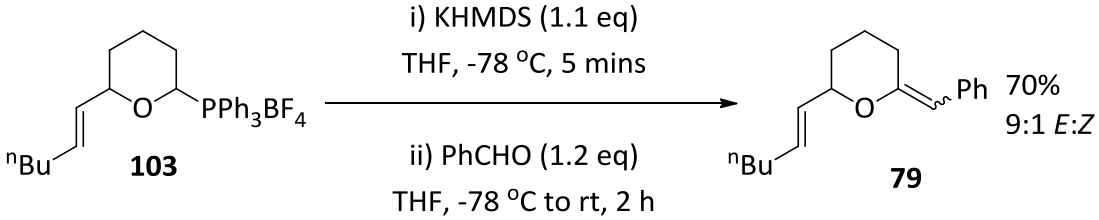
Scheme 53

With the enol ether **106** in hand, the rearrangement chemistry was attempted. Unfortunately, using the standard conditions, no cyclohexanone **107** was observed after numerous attempts (**Scheme 54**).



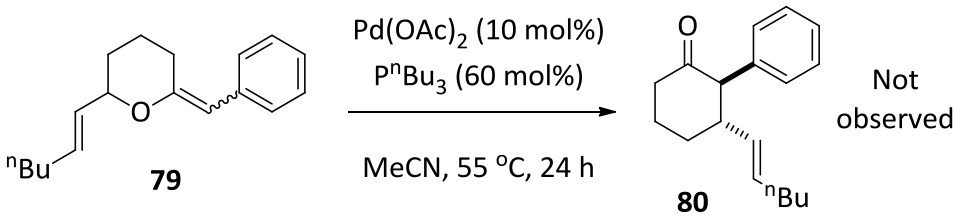
Scheme 54

Due to the disappointment of enol ether **106** not undergoing successful rearrangement, it was decided to attempt to replicate the conditions with enol ether **79**. This was synthesised using the optimised Wittig olefination conditions in good yield (**Scheme 55**).



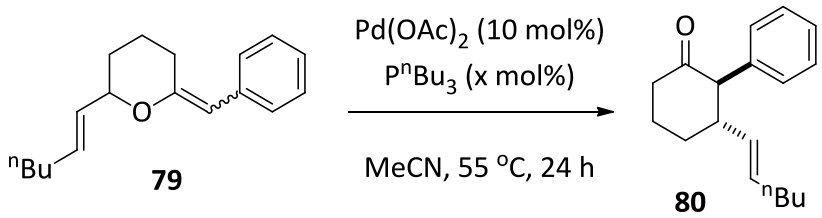
Scheme 55

The exact conditions that had provided cyclic ketone **80** in good yield previously (**Scheme 43**), failed to afford **80** after numerous attempts (**Scheme 56**).



Scheme 56

At this point, attempts were made to find conditions that would promote the rearrangement of **79**. This included varying the solvent, palladium and phosphine ligand aspects. The findings are summarised in **Table 8**.



Entry	P^nBu_3 loading / x mol%[a]	Yield / %
1	60[b]	<5[c]
2	60[d]	<5[c]
3	60[e]	<5[c]
4	60[f]	<5[c]
5	40[f]	<5[c]
6	80[f]	<30
7	100[f]	78

Table 8

[a] $Pd(OAc)_2$ and P^nBu_3 are pre-treated at 80 °C for 20 minutes prior to cooling to 55 °C then the addition of substrate **79**

[b] Using freshly distilled MeCN

[c] Starting material recovered (>80%)

[d] Using degassed MeCN (Freeze-Pump-Thaw)

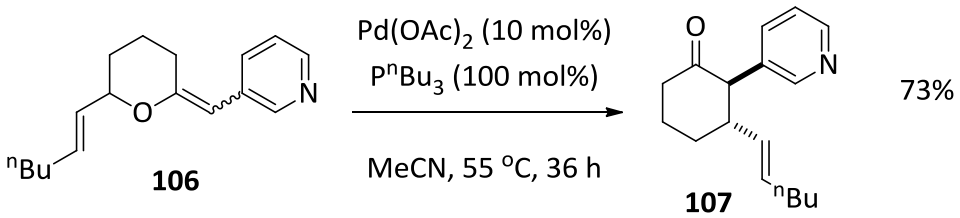
[e] Using an alternate $Pd(OAc)_2$ batch

[f] Using freshly distilled P^nBu_3

Unfortunately, additional purification of the solvent failed to provide cyclic ketone **80**. Using freshly distilled acetonitrile (**Table 8**, Entry 1) and thoroughly degassed acetonitrile, *via* the Freeze-Pump-Thaw method (Entry 2) returned starting material in both cases. An alternate batch of palladium(II) acetate was also used, an attempt to rule out the possibility of batch contamination. The rearrangement was unsuccessful in this case (Entry 3).

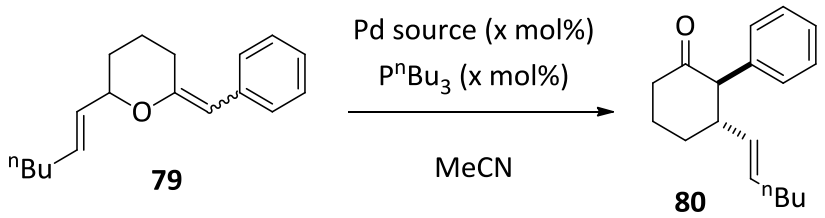
Our attention was then turned to the quality of the phosphine sample. ^{31}P NMR analysis showed that phosphine contained a considerably amount of phosphine oxide. When present in the reaction, this could inhibit the catalyst, leading to low conversion. Although the phosphine was successfully purified *via* vacuum distillation, applying this in the rearrangement was ineffective (Entry 4). Changing the loading of the phospine ligand was next examined; a lower loading was found to be inadequate (Entry 5), however, increasing the loading was more promising. Indeed, using 80 mol% of the phosphine gave a 30% yield (Entry 6), whilst 100 mol% gave an excellent yield of 78% after an extended reaction time (Entry 7).

Applying these conditions to enol ether **106** smoothly provided cyclic ketone **107** in an excellent yield of 73%, albeit after an extended reaction time (**Scheme 57**).



Scheme 57

It appears that phosphine loading is critical for the rearrangements to proceed. To examine this observation further, a detailed survey of catalyst conditions were undertaken, including varying the palladium and phosphine loading, temperature and time of both the catalyst synthesis and rearrangement. Under the optimal conditions, the palladium and phosphine were heated at reflux for 20 minutes, before cooling and then adding the enol ether. **Table 9** summarises the major findings.



Entry	Pd source, (x mol%)	P^{n}Bu$_3$ / x mol%	Catalyst preparation temperature, time	Rearrangement temperature, time	Yield / %
1	Pd(OAc)$_2$ (20)	80	rt, 64 h	rt, 48 h	<5
2	Pd(OAc)$_2$ (20)	120	rt, 64 h	rt, 48 h	<5
3	Pd(OAc)$_2$ (20)	160	rt, 64 h	rt, 48 h	87
4	Pd(OAc)$_2$ (20)	160	40 ^{o}C, 1.5 h	40 ^{o}C, 16 h	93
5	Pd(OAc)$_2$ (10)	40	40 ^{o}C, 1.5 h	40 ^{o}C, 16 h	<5
6	Pd(OAc)$_2$ (10)	60	40 ^{o}C, 1.5 h	40 ^{o}C, 16 h	<5
7	Pd(OAc)$_2$ (10)	80	40 ^{o}C, 1.5 h	40 ^{o}C, 16 h	59
8	[(allyl)PdCl]$_2$ (5)	40	rt, 16 h	40 ^{o}C, 16 h	<5
9	[(allyl)PdCl]$_2$ (10)	80	rt, 16 h	40 ^{o}C, 16 h	70
10	None	160	-	rt, 5 days	0
11	None	160	-	40 ^{o}C, 16 h	0

Table 9

Adjusting the phosphine loading had a significant effect on the rearrangement. Using 20 mol% of palladium with both 80 and 120 mol% of phosphine failed to promote the rearrangement (**Table 9**, Entries 1 and 2). Pleasingly, a loading of 160 mol% provided cyclic ketone **80** in an excellent yield of 87%. This was however conducted at room temperature and required extensive reaction times; 64 hours for catalyst preparation and 48 hours for the rearrangement to reach completion. Increasing the temperature dramatically reduced reaction times. At 40 ^{o}C, the catalyst was prepared in 90 minutes and, after addition of the enol ether, the rearrangement was complete within 16 hours with an excellent yield of 93% (Entry 4).

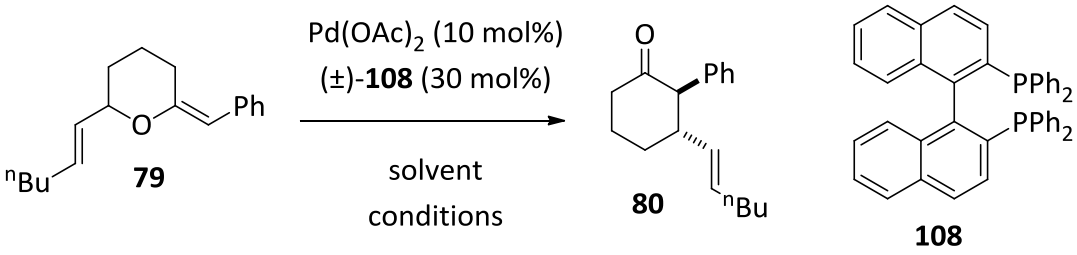
The effect of the palladium loading was next examined. Using 10 mol% of the catalyst, 40 and 60 mol% of the phosphine failed to mediate the rearrangement (Entries 5 and 6). However, using 80 mol% (the same palladium-phosphine ratio as entry 4) gave the cyclic ketone in a modest 59% yield (Entry 7). When a dipalladium catalyst source was employed at 5 mol% with 40 mol% phosphine, the same palladium-phosphine ratio to entries 1 and 5, only starting material was returned (Entry 8). However, using 10 mol% dipalladium and 80 mol% phosphine afford ketone **80** in a good yield of 70% (Entry 9).

It appears that having a high phosphine loading is key for the rearrangement to proceed, and this raised the possibility that the phosphine might be promoting the rearrangement itself. To test this hypothesis, the rearrangements were conducted in the absence of palladium. Using 160 mol% of phosphine, under thermal conditions and extended reaction times, no trace of the cyclic ketone was observed (Entries 10 and 11). This confirmed that the rearrangements are palladium catalysed.

Based on these studies, the scope of the palladium catalyzed O→C rearrangement reactions have been expanded to include a heteroaromatic substituent. Although unsuccessful using previously optimised conditions, the rearrangement occurs smoothly with a higher phosphine loading. Consistent results are obtained using this method provided that the phosphine is free of major impurities.

3.2 STUDIES TOWARDS AN ENANTIOSELECTIVE REARRANGEMENT REACTION

The palladium-catalysed rearrangement with an electron rich phosphine provides the ketone product as a single diastereomer, favouring *trans* stereochemistry. We envisaged that a chiral phosphine ligand would provide the opportunity for enantiocontrol, and decided to explore a series of chiral phosphines towards this end. The first ligand screened was BINAP **108**. Initial chemistry was conducted with the racemic form of the ligand due to the high expense of the enantiopure sample. If suitable conditions could be uncovered, enantiopure ligands would then be used in the rearrangement (**Table 10**).



Entry	Conditions	Yield / %[a]	Comment
1	MeCN, 55 ^{o}C, 48 h	<5	Heterogeneous
2	PhMe, 55 ^{o}C, 48 h	<5	Homogeneous
3	PhMe, Et_2AlCl (0.5 eq), 55 ^{o}C, 48 h	<5	72% **81** (page 27)
4	MeCN:PhMe (1:1), 55 ^{o}C, 16 h	<5	Homogeneous
5	MeCN:PhMe (2:1), 55 ^{o}C, 16 h	<5	Homogeneous

Table 10

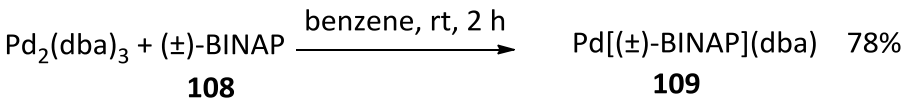
[a] Starting material (>80%) recovered in all cases

Disappointingly, replacing *n*-tributylphosphine directly with BINAP under the optimised conditions, failed to afford the cyclic ketone **80** (**Table 10**, Entry 1). A possible reason for this catalyst system's apparent inactivity likely lies in the fact that BINAP is insoluble in acetonitrile, therefore the active catalyst may not have formed. Unfortunately, using the same conditions but with toluene as the solvent also returned starting material (Entry 2). Although a homogeneous solution was present throughout, the low polarity of the solvent may have prevented the formation of the enolate intermediate **83** (**Scheme 44**, page 29).

Upon addition of a Lewis acid, which promotes rearrangements in toluene, full conversion of the enol ether was obtained. Unfortunately, the material isolated was not that of cyclic ketone **80**, but cyclooctanone **81** (**Table 5**, page 27). The use of Lewis acids has already been shown to promote this Claisen rearrangement (Entry 3).

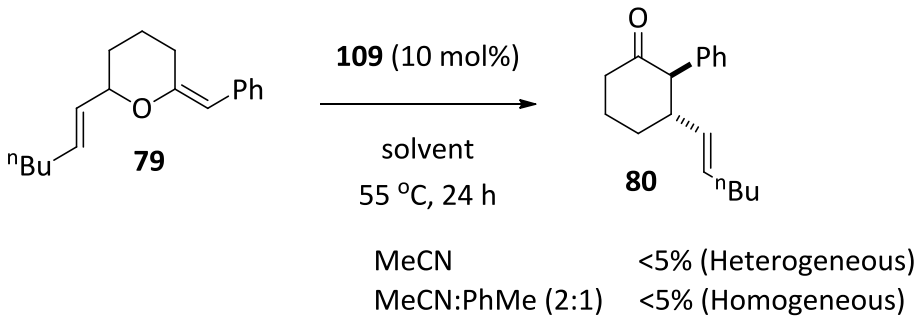
The use of a mixed toluene-acetonitrile solvent system was also attempted. It was hoped that toluene would aid in the solubility of the BINAP ligand and acetonitrile would promote the rearrangement. Unfortunately, using both a 1 : 1 mixture (Entry 4) and 2 : 1 ratio (acetonitrile/toluene, Entry 5) failed to afford cyclic ketone **80**, although both solutions were homogeneous throughout.

The fact that BINAP had failed to provide the cyclic ketone was surprising and we speculated that this may be due to a slow complexation with the palladium source. We therefore decided to synthesise and isolate a palladium-BINAP complex **109** according to a known procedure (**Scheme 58**).[60]



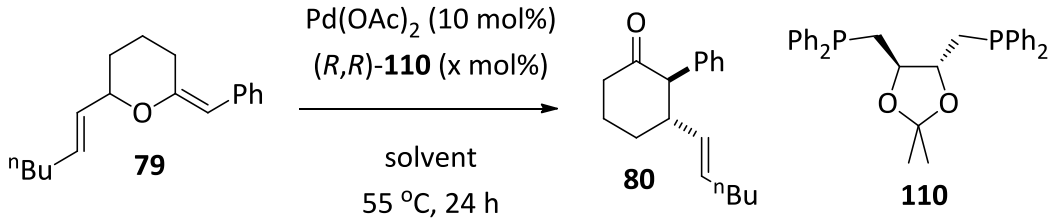
Scheme 58

Pleasingly, the complex **109** was isolated in an excellent yield of 78% and showed identical spectroscopic data to that previously reported. With a palladium(0)/phosphine catalyst in hand, its effect on the rearrangement was assessed. Unfortunately, no rearrangement was observed in either acetonitrile or acetonitrile/toluene mixtures (**Scheme 59**).



Scheme 59

We next decided to study a more electron rich chiral ligand and turned our attention to commercially available (*R*,*R*)-DIOP **110**. Once again, under identical conditions to the BINAP mediated reactions, the rearrangement was found to be unsuccessful (**Table 11**, Entry 1).



Entry	x mol%	Solvent	Yield / % (*ee* / %)
1	30	MeCN	<5 (-)[a]
2	60	MeCN	<5 (-)[a]
3	100	MeCN	49 (-)[b]
4	60	PhMe/Et_2AlCl (0.5 eq)	<5 (-)[a]
5	60	THF	<5 (-)[a]
6	60	DMF	<5 (-)[a]
7	60	DMSO[c]	36 (<5)[d]

Table 11

[a] Starting material recovered (>80%)

[b] *ee* not determined

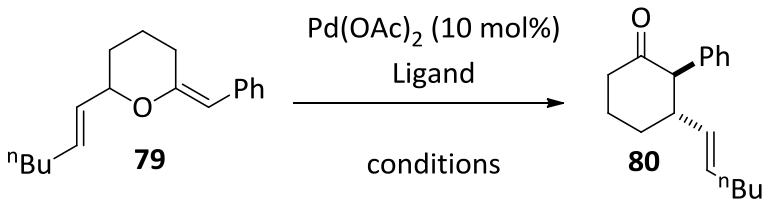
[c] Heated for 36 hours

[d] *ee* determined *via* chiral GC with purified material

Increasing the loading of the ligand initially proved fruitless (Entry 2), however when one equivalent was used, a modest 49% yield of the cyclic ketone **80** was isolated (Entry 3). It should be noted that in acetonitrile, the precipitation of elemental palladium black was observed in all cases. To minimise this formation, a solvent screen was undertaken. Using a variety of solvents initially did not solve the problem. Toluene (Entry 4) failed to mediate the rearrangement. Using more polar solvents, tetrahydrofuran and *N*,*N*-dimethylformamide (Entries 5 and 6) also failed, each were accompanied by formation of palladium black. Pleasingly, when dimethyl sulfoxide was utilised, no precipitation was observed. Disappointingly however, cyclic ketone

was isolated in a poor 36% yield and was determined to be essentially racemic by chiral stationary phase gas chromatography.

Other ligands screened included (*R*,*S*)-JosiPhos **111** (**Table 12**, Entries 1 and 2), (*R*,*R*)-DiPhos **112** (Entry 3) and (*S*,*S*)-Me-DuPhos **113** (Entries 4 and 5). Use of these ligands gave **80** in moderate yields (40-48%) and in all cases, **80** was determined to be racemic. Pleasingly, when (*R*)-^{i}PrPhox **114** (Entry 6) was used, cyclohexanone **80** was obtained in a 25% *ee*, albeit in a moderate yield of 45%.



Entry	L (mol%)[a]	Conditions	Yield / % (*ee* / %)
1	(*R*,*S*)-**111** (40)	MeCN, 40 °C, 48 h	0 (-)[b]
2	(*R*,*S*)-**111** (40)	PhMe/Et_2AlCl (0.5 eq), 40 °C, 48 h	40 (<5)[c]
3	(*R*,*R*)-**112** (40)	MeCN, 40 °C, 48 h	48 (<5)[c]
4	(*S*,*S*)-**113** (20)	MeCN, 40 °C, 48 h	0 (-)[b]
5	(*S*,*S*)-**113** (20)	PhMe/Et_2AlCl (0.5 eq), 40 °C, 48 h	40 (<5)[c]
6	(*R*)-**114** (60)	MeCN, 40 °C, 48 h	45 (25)[c]

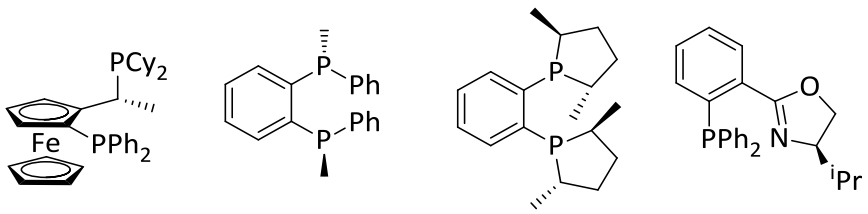
Table 12

[a] See **Figure 6** for ligand structure

[b] Starting material recovered (>80%)

[c] *ee* determined *via* chiral-GC with purified material

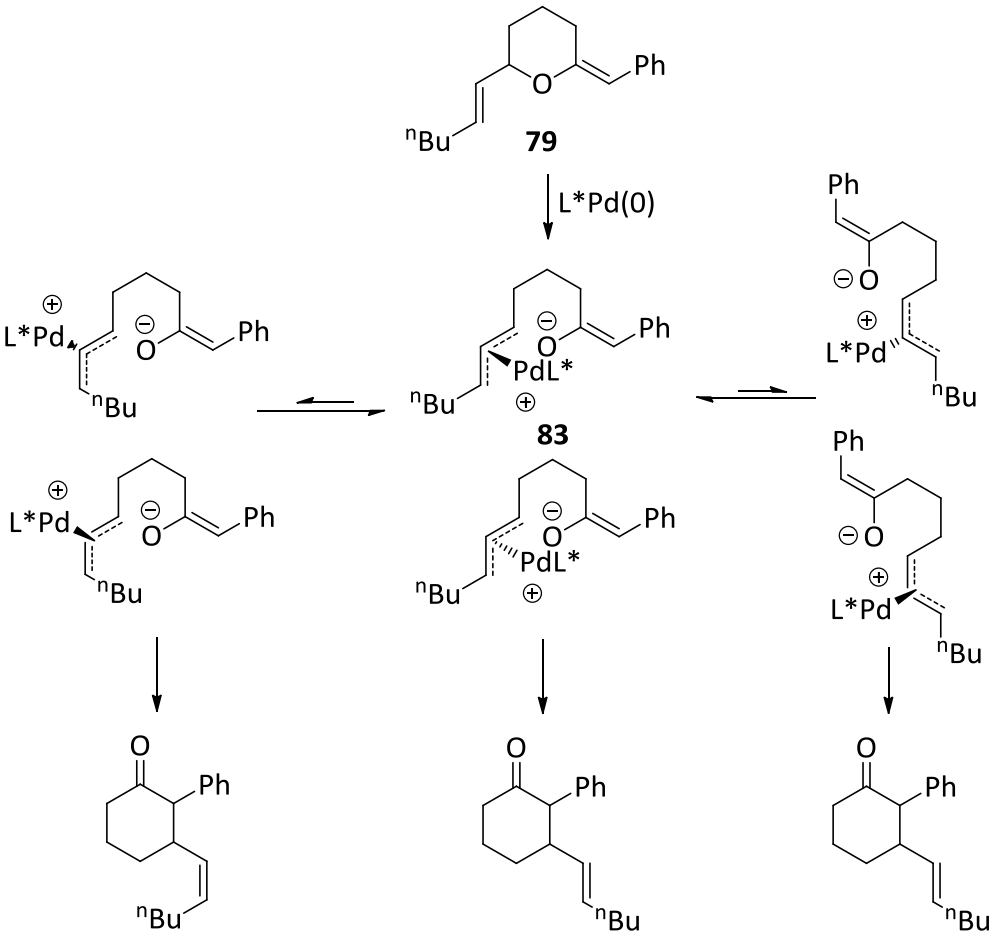
Of all the ligands used in this transformation, none of them were able to provide excellent yields of cyclohexanone **80** (the highest being **112** with 48%). Additionally, only (*R*)-**114** gave any reasonable levels of enantioselectivity.



111 **112** **113** **114**

Figure 6

To explore potential reasons for the consistently low levels of enantioselectivity observed in the palladium-catalysed rearrangement, we considered the potential intermediates in this process (**Scheme 60**). For the chiral catalyst system to give high enantioselectivity, two scenarios can be envisaged: (1) a single stereoisomer of the π-allyl complex intermediate **83** is generated that is reactive. (2) a rapidly equilibrating mixture of diastereomeric complexes are formed that have different reactivities.

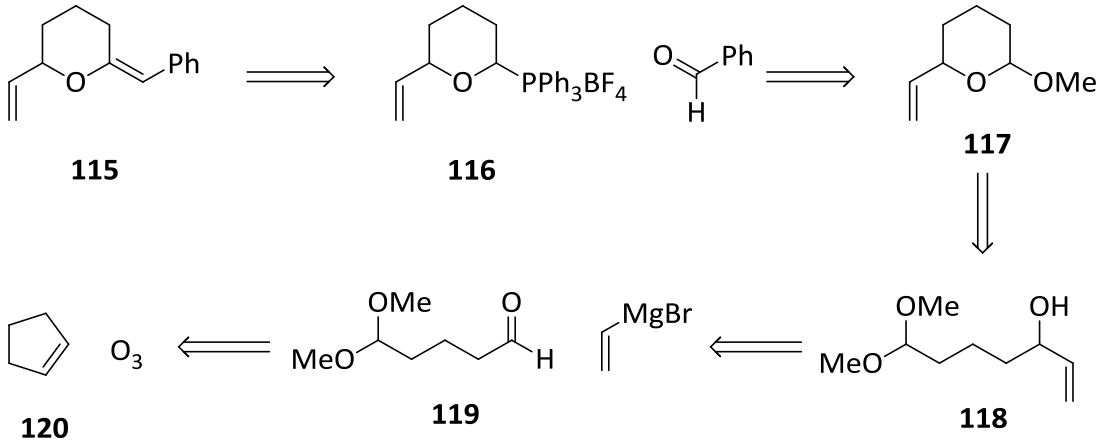


Scheme 60

One mechanism of isomerisation is *via* π-facial migration of the palladium-complex,[61] this should be controllable by modulating reaction concentration. An alternative sequence would be *via* π-σ-π interconversion, however, this process would lead to a *syn-anti* complex that would be unfavourable due to $A^{1,3}$ strain. Therefore, in the case of substrate **79**, it may be that inhibition of the π-facial isomerisation results in essentially enantiospecific rearrangement of each enantiomer of the racemic substrate, thereby providing the product in low *ee*.

However, if π-σ-π interconversion is in operation, it appears that the cyclisation occurs through only two of the three possible equilibrium pairs, as no *Z*-olefin is observed in these reactions (indeed, as outlined earlier *Z*-substrates are cleanly isomerised to *E*-products). In order to further clarify this important issue, we opted to prepare enantioenriched substrates in an effort to explore the potential for these reactions to proceed enantiospecifically. This will be described in a later section.

This analysis highlighted that the π-σ-π interconversion could well be promoted by the use of a terminal olefin containing substrate, as it would eliminate the unfavourable $A^{1,3}$ interactions, which occur in the π-σ-π isomerisation process at the terminal π-allyl moiety. Such rapid isomerisation may help establish chiral ligand control in the key C-C bond forming step. A proposed route for the synthesis of terminal alkene enol ether **115** is described is **Scheme 61**.

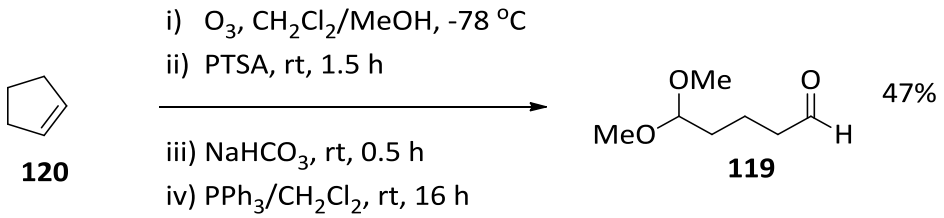


115 **116** **117** **118** **119** **120**

Scheme 61

Using chemistry developed by Maier,[62] pyranyl ether **117** can be obtained by cyclising alcohol **118**. This alcohol can be obtained by Grignard addition to monoprotected dialdehyde **119**, accessed *via* the ozonolysis of cyclopentene in the presence of methanol.

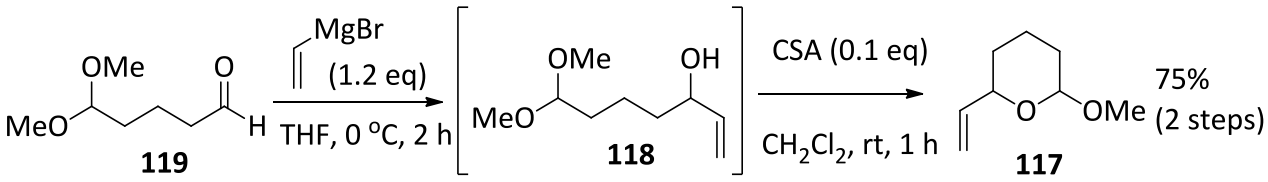
Indeed, ozonolysis of cyclopentene in the presence of methanol, allowed access to monoprotected aldehyde **119** in a moderate 47% yield (**Scheme 62**).[63] Although not ideal, ozonolysis can be carried out on a large scale and the obtained aldehyde was found to be stable towards degradation over time.



120 **119**

Scheme 62

The addition of the vinyl Grignard reagent to the aldehyde **119** occurred smoothly (**Scheme 63**), yielding alcohol **118** which was of sufficient purity to be used directly in subsequent reactions.

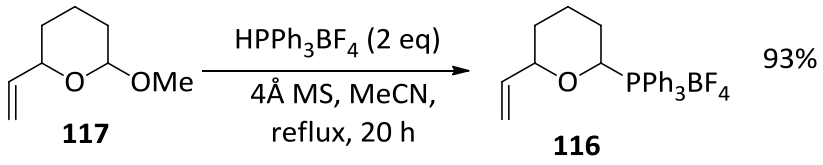


119 **118** **117**

Scheme 63

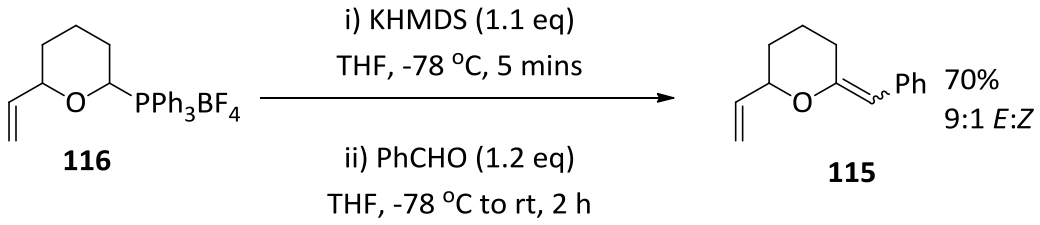
Immediate cyclisation of alcohol **118** in the presence in sub-stoichiometric amounts of camphorsulfonic acid yielded pyranyl acetal **117** in an excellent 75% yield over the two steps. Importantly, it was found that **117** is a volatile intermediate and care had to be taken during work up and purification stages. Although excellent yields were recorded on a gram scale, yields did diminish when milligram amounts of material were used.

From here on, the synthesis of enol ether **115** followed the procedure developed for the other enol ether substrate synthesis. Therefore, heating pyranyl ether **117** in the presence of triphenylphosphine tetrafluoroborate gave phosphonium salt **116** in excellent yield (**Scheme 64**).



Scheme 64

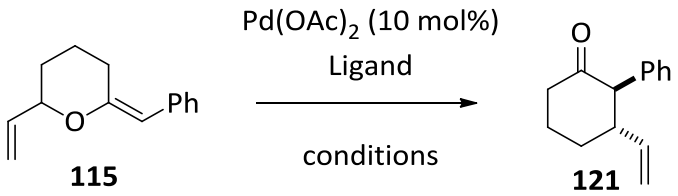
Phosphonium salt **116** was then subjected to the optimised Wittig conditions (**Scheme 65**) to give the desired enol ether **115** in good yield.



Scheme 65

With enol ether **115** in hand, we carried out a screen of the same chiral ligands employed with the ^{n}butyl substrate **79**. Standard rearrangement conditions were used in order to obtain a racemic sample of **121** (**Table 13**, Entry 1). The first chiral ligand used was (*R*,*R*)-DIOP **110** (Entry 2). Pleasingly, a good yield of 62% was obtained, the first time any rearrangement using a chiral ligand had proceeded further than 50%. Additionally, the cyclic ketone **121** was formed in 13% *ee*. Compared to the ^{n}butyl substrate, the terminal alkene appeared not only to be more reactive, but also provided product with higher *ee* values.

Building upon the success of the DIOP ligand, other chiral ligands that were used included (*R*,*S*)-JosiPhos **111** (Entry 3), (*R*,*R*)-DiPhos **112** (Entry 4) and (*S*,*S*)-Me-DuPhos **113** (Entries 5-6). Except for DuPhos, the rearrangement progressed in very good yields, but unfortunately in all cases, **121** was found to be racemic.



115 121

Entry	L (mol%)[a]	Conditions	Yield / % (*ee* / %)
1	P^nBu_3 (60)	MeCN, 55 °C, 24 h	84 (-)
2	(*R*,*R*)-**110** (30)	MeCN, 40 °C, 18 h	62 (13)[b]
3	(*R*,*S*)-**111** (30)	MeCN, 40 °C, 36 h	71 (<5)[b]
4	(*R*,*R*)-**112** (40)	MeCN, 40 °C, 36 h	65 (<5)[b]
5	(*S*,*S*)-**113** (40)	MeCN, 40 °C, 36 h	0 (-)[c]
6	(*S*,*S*)-**113** (40)	PhMe/Et_2AlCl (0.5 eq), 40 °C, 36 h	0 (-)[c]
7	(*R,R*)-**122** (40)	MeCN, 40 °C, 36 h	0 (-)[c]
8	(*R,R*)-**122** (40)	PhMe/Et_2AlCl (0.5 eq), 40 °C, 36 h	0 (-)[c]
9	(*R,R*)-**122** (40)	1,4-dioxane, 40 °C, 36 h	0 (-)[c]
10	(*S*)-**114** (60)	MeCN, 40 °C, 18 h	93 (33)[b]
11	(*S*)-**42** (60)	MeCN, 40 °C, 18 h	84 (49)[b]

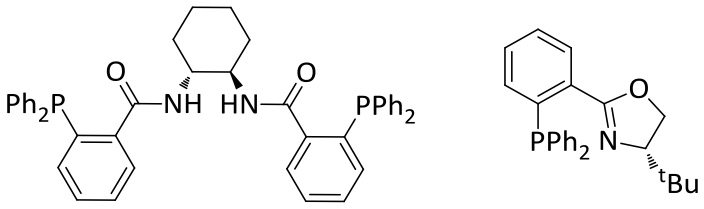
Table 13

[a] See **Figures 6** and **7** for ligand structure

[b] *ee* determined *via* chiral GC with purified material

[c] Starting material recovered (>80%)

At this point, we decided to use chiral ligands that had been successful for asymmetric addition to palladium-π-allyl complexes in particular those reactions which closely related to our rearrangement reaction.[64] Firstly, the ligand developed by Trost, (*R*,*R*)-DACH **122** (**Figure 7**), was used. Unfortunately, using acetonitrile, 1,4-dioxane and toluene as solvent only starting enol ether was returned (Entries 7-9).

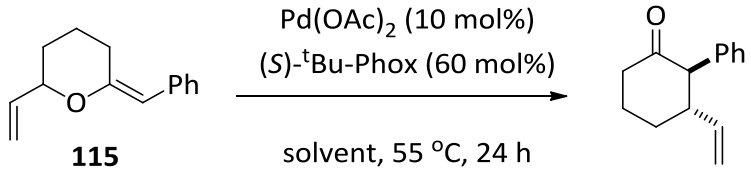


122 **42**

Figure 7

Finally, we returned to the (*S*)-^{i}PrPhox ligand **114**, the only ligand to give a promising *ee* in the ^{n}butyl system. Pleasingly, after only 18 hours, cyclohexanone **121** was isolated in a 93% yield, and had an *ee* of 33% (Entry 10). Using a bulkier analogue, the (*S*)-^{t}BuPhox **42** also gave a high yield of the rearrangement product but in 49% *ee* (Entry 11).

In an effort to improve the *ee*, several solvents were screened. These included solvents which have been previous reported for similar palladium/ligand systems. The results are summarized in **Table 14**.



115 **121**

Entry	Solvent	Yield / %	ee / %[a]
1	MeCN	84	49
2	DMF	78	37
3	DMSO	0[b]	0
4	CH_2Cl_2	0[b]	0
5	1,4-dioxane	75	43

Table 14

[a] *ee* determined *via* chiral GC with purified material

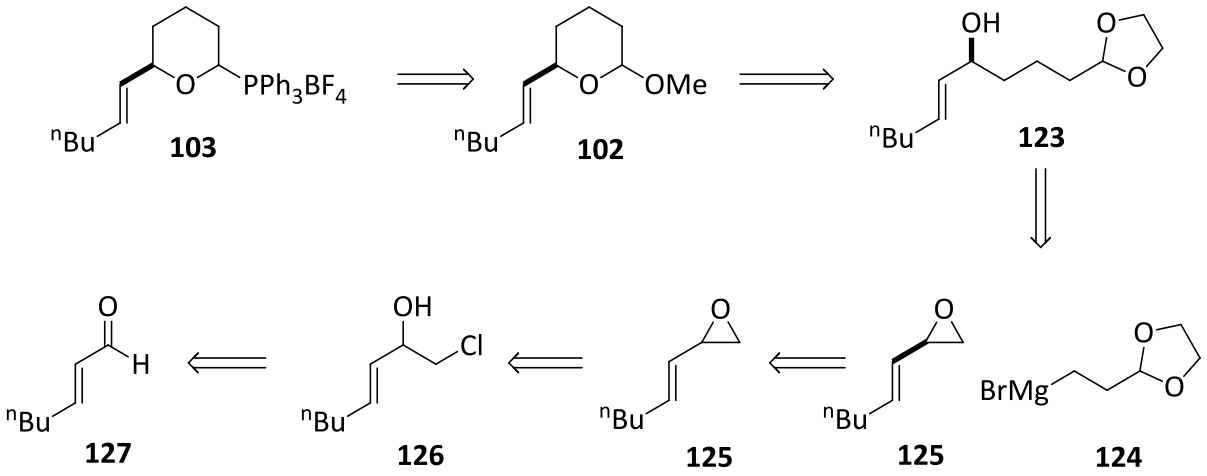
[b] Starting material recovered (>80%)

Unfortunately, none of the additional solvents screened were able to improve the yield or *ee* of the reaction. Of the seven chiral ligands examined, only the Phox-class of ligands afforded cyclic ketones with moderate degree of enantiopurity. In addition, the chiral catalyst system was more effective for the terminal alkene **115** than the ^{n}butyl analogue **79**.

3.3 CHEMISTRY TOWARDS THE SYNTHESIS OF ENANTIOPURE ENOL ETHERS

3.3.1 ^{n}BUTYL ENOL ETHER

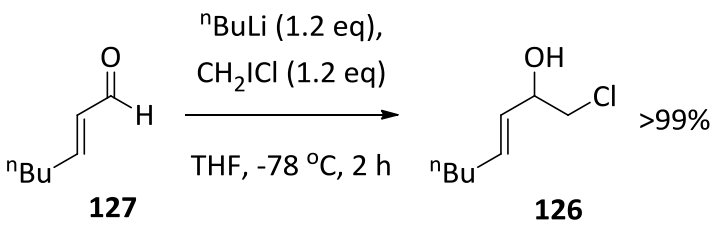
As highlighted earlier, in an effort to explore some critical stereochemical aspects of the rearrangement reaction, we identified the synthesis of enantioenriched substrates as being of potential value. However, the synthesis of enantiopure enol ethers was a task that did not look easy. Several possible routes were considered, but many were lengthy and the insertion of the required stereocentre did not appear optimal. The route that initially appeared to be the most promising is highlighted in **Scheme 66**.



Scheme 66

To access the required enol ether, phosphonium salt **103** should be generated *via* pyranyl ether **102**, as in the racemic route. We further envisaged that **102** could be accessed *via* cyclisation of alcohol **123**. This itself could be assembled from the addition of Grignard **124** to chiral epoxide **125**, making use of Jacobsen hydrolytic kinetic resolution (HKR) of racemic epoxide **125**. Aldehyde **127** could be used to synthesis epoxide **125** *via* chloro-alcohol **126**.

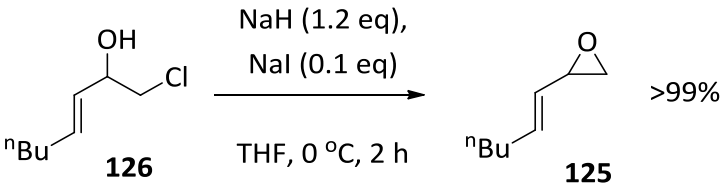
The synthesis began by preparing chloro-alcohol **126** using methodology developed by Lautens.[65] Accordingly, aldehyde **127** was treated with chloromethyllithium, itself generated *in situ* by lithium-halogen exchange of chloroiodomethane with *n*-butyllithium (**Scheme 67**).



Scheme 67

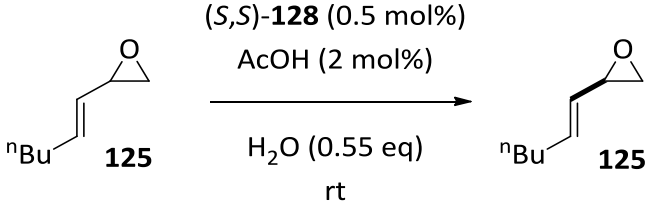
This transformation proceeded smoothly, however, problems were encounted because of the volatility of chloro-alcohol **126**. Nonetheless, by simply avoiding prolonged exposure to low vacuum, **126** was obtained in quantitative yield with no purification required.

Chloro-alcohol **126** was transformed to the epoxide **125** by a substitution reaction, promoted *via in situ* Finkelstein substitution of the chloride with sodium iodide (**Scheme 68**).



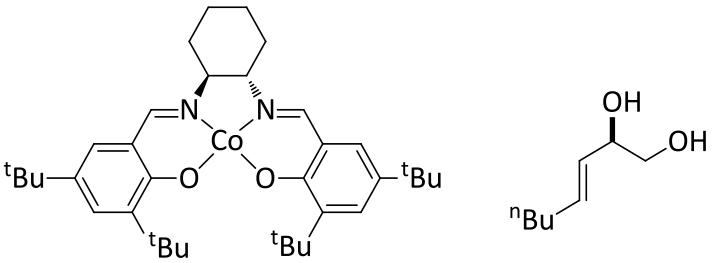
Scheme 68

Not surprisingly, epoxide **125** was also found to be very volatile, so care was required to minimise losses. In spite of this, epoxide **125** was obtained in quantitative yield. Notably, attempts to further purify this material by column chromatography on silica gel resulted in significant decomposition. With epoxide **125** in hand, HKR was then attempted in order to obtain enantiopure epoxide **125**, as shown in **Scheme 69**.[66]



Scheme 69

The catalyst was prepared *in situ* from its precursor (*S*,*S*)-**128** (**Figure 8**), by treatment with acetic acid, the epoxide **125** and water. Monitoring the reaction proved troublesome as TLC analysis was impractical. In the event, the reaction was conveniently monitored by ^{1}H NMR spectroscopy, where the olefin signals for the epoxide and the diol side product **129** were used to judge conversion. The time that was required for a ~50% conversion varied, depending on the room temperature and the quantities of residual solvent still present with the epoxide **125**. Determination of the *ee* of the epoxide at this stage proved difficult. The epoxide was too volatile for chiral-GC analysis and HPLC failed to provide any separation. Therefore, the *ee* of the substrate was to be determined at a later stage.

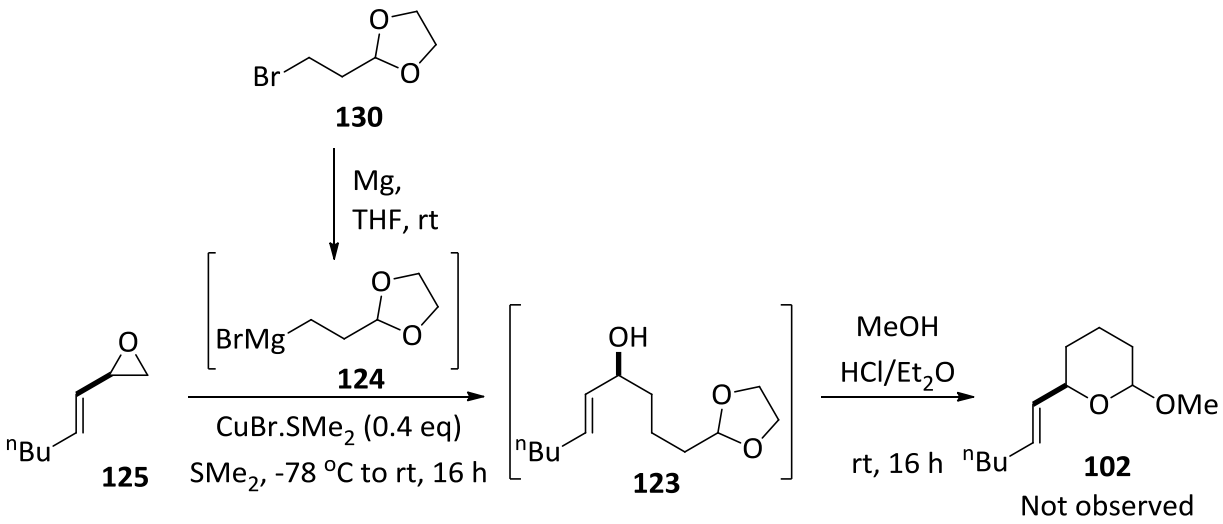


128 **129**

Figure 8

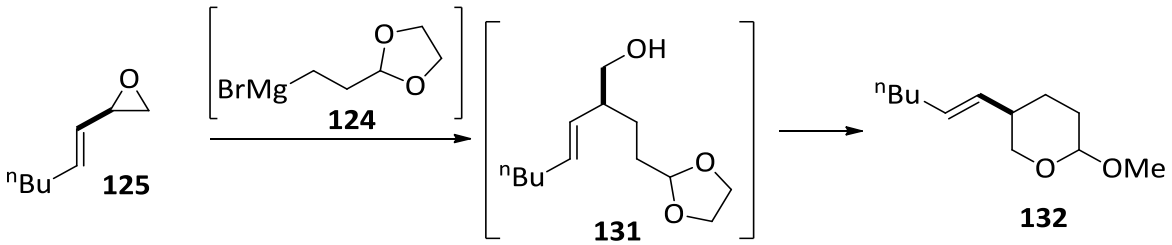
Ring opening of the epoxide was attempted next. We expected that this reaction would occur regioselectively at the methylene of the epoxide, rather than at the allylic methine, or *via* conjugate addition. The Grignard **124** (Büchi Grignard) was generated *in situ* from the bromide acetal **130**. This was added to epoxide **125** in the presence of a copper catalyst (**Scheme 70**).

Due to difficulties encountered in purification of this product, the crude alcohol **123** was carried on to the cyclisation stage. This occurred smoothly, where cyclisation proceeded in the presence of methanol and dry hydrochloric acid.



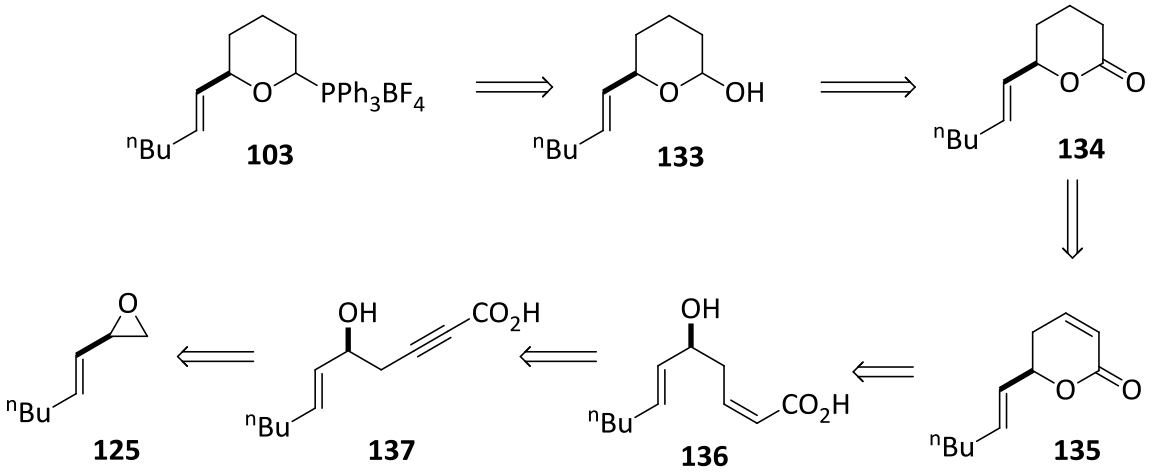
Scheme 70

Unfortunately, the desired pyranyl ether **102** was not observed by ^{1}H NMR spectroscopy. What was found however was the product that resulted from Grignard **124** opening at the allylic methine to give alcohol **131**. This in turn cyclised to give presumably acetal **132** (**Scheme 71**).



Scheme 71

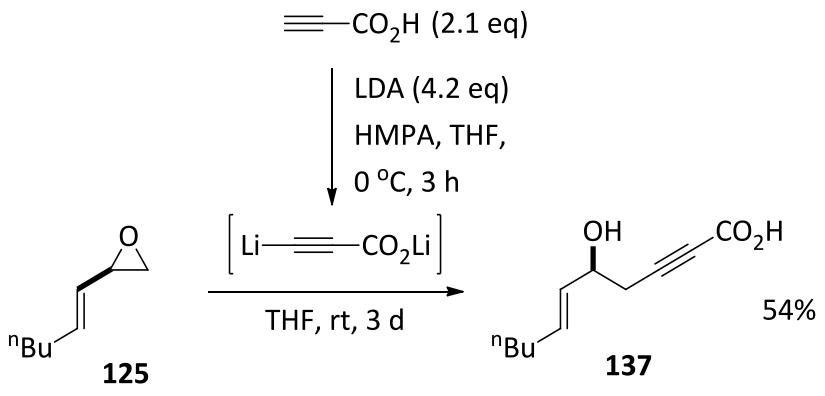
The structure of **132** is proposed by comparing the ^{1}H NMR spectra with those of similar substrates (δ 3.20 (dd, *J* = 11.5, 9.5 Hz, alkene-CHC*H*$_2$O)).[67] As this route was not successful, an alternative sequence was required. As the synthesis of epoxide **125** was an attractive method for installing the allylic C-O bond enantioselectively, we devised a route that made use of this material (**Scheme 72**).



Scheme 72

Phosphonium salt **103** can be accessed from hemi-acetal **133** by an analogous method to other phosphonium salt syntheses. The hemi-acetal can be obtained from reduction of lactone **134**, which itself is the result of a reduction of the α,β-unsaturated lactone **135**. This can be acquired from the cyclisation of α,β-unsaturated carboxylic acid **136**, *via* reduction of the alkyne **137**.[68] Finally, this alkyne is the result of ring opening of epoxide **125** with propiolic acid.

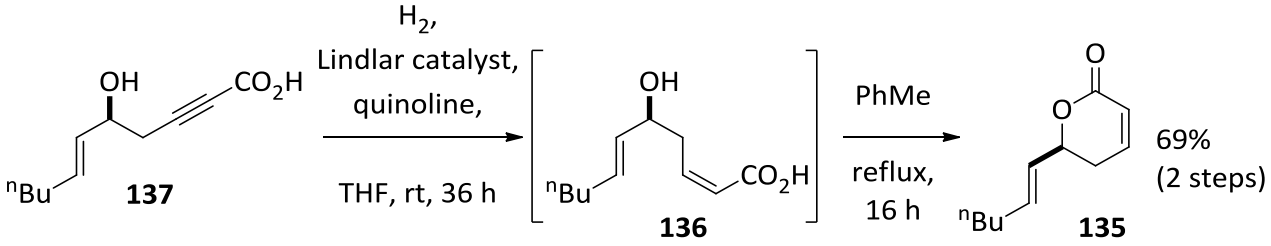
Using chemistry that had been developed by Carlson, terminal epoxides can be ring opened at the methylene position with the dianion of propiolic acid.[69] This is generated *in situ* from the acid upon addition of four equivalents of lithium diisopropylamide, as shown in **Scheme 73**.



Scheme 73

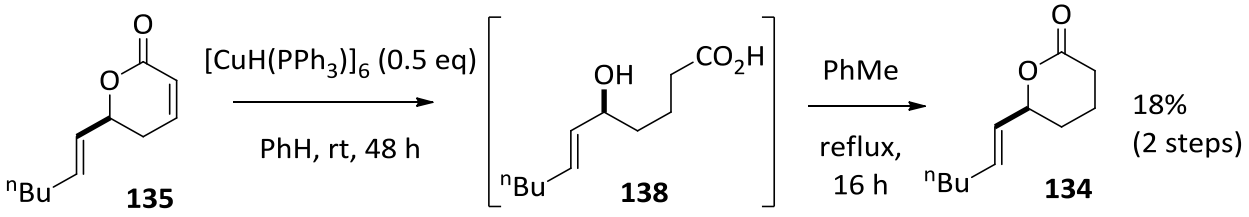
This reaction was found to be very sluggish, with only a 54% yield of the desired product **137** after 3 days. The material obtained was also very difficult to handle, being a thick oil which was fairly insoluble in most common solvents, hence any attempts to purify this material returned poor yields.

Therefore, the crude material was processed to the hydrogenation stage. This was carried out using Lindlar's catalyst at room temperature. Pleasingly, **137** was fully soluble in tetrahydrofuran and extended stirring in the presence quinoline under a balloon of hydrogen at atmospheric pressure yielded the desired alkene **136** (**Scheme 74**).



Scheme 74

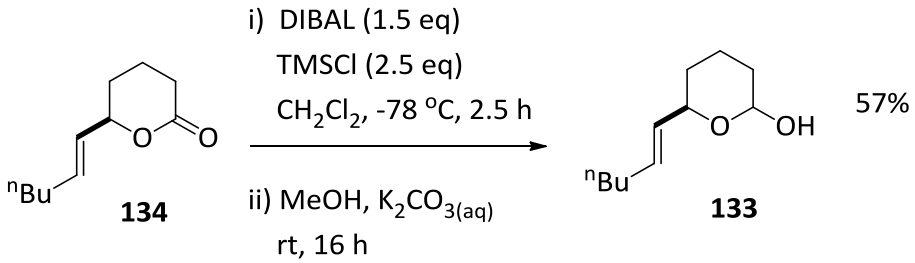
We found alkene **136** to be equally difficult to handle so this material was taken on to the cyclisation step without purification. This was a simple process of refluxing **136** in toluene to give the desired α,β-unsaturated lactone **135** in 69% yield over the two steps.[70] Finally, **135** was subject to reduction to lactone **134** *via* 1,4-conjugate addition with Stryker's reagent.[71] The reaction appeared to occur smoothly, however only a trace amount of the desired lactone **134** was isolated. Extraction of the acidified aqueous phase after work-up (saturated with sodium chloride), gave a reasonable amount of reduced, ring opened material **138** (**Scheme 75**).



Scheme 75

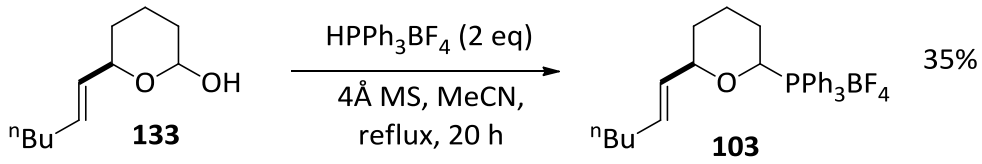
Applying the crude alcohol **138** to cyclisation conditions as with the α,β-unsaturated lactone **135** gave, after column chromatography, lactone **134** is a modest 18% yield. The major loss of material is presumed to occur in the work-up from the Stryker reduction. Several attempts were made at this point to improve the isolation yields of lactone **134** or alcohol **138**. This included extracting the aqueous phase with more polar solvents, not employing a basic workup and simply removing the copper salts by filtration and cyclising the crude material. All of these attempts proved fruitless and 18% was the optimal yield recorded for the two steps.

From here on in, the chemistry performed towards enantiopure enol ether **79** had already been developed within the group.[50] Accordingly, the lactone **134** was reduced with diisobutylaluminium hydride in the presence of chlorotrimethylsilane (**Scheme 76**).



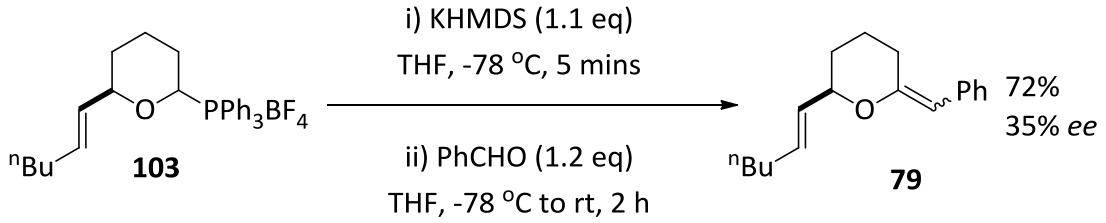
Scheme 76

The hemi-acetal **133** was isolated cleanly, by filtering the reaction mixture through Celite®, so no further purification as attempted. As discussed in **Scheme 52**, pyranyl ether **133** was heated at reflux with triphenylphosphonium tetrafluoroborate to obtain the phosphonium salt **103** (**Scheme 77**).



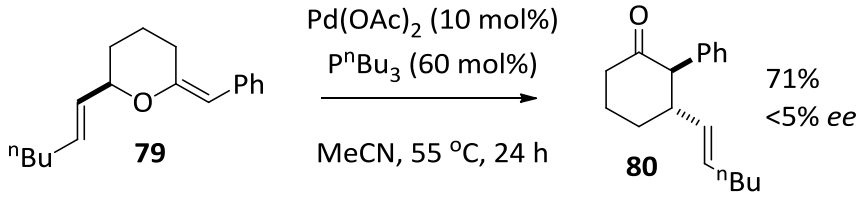
Scheme 77

As previously described, the Wittig salt **103** was isolated cleanly after several triturations. Application of the previously described Wittig conditions (**Scheme 55**), gave non-racemic enol ether **79** after column chromatography on Florisil® (**Scheme 78**).



Scheme 78

Although a good yield of **79** was obtained, the *ee* (determined *via* chiral-GC) was found to be very low. There are a number of possible reasons for this. Either the HKR did not go to completion or that at some point in synthesis, a degree of epimerisation had occurred. Nonetheless, the rearrangement chemistry was attempted on this material. The O→C rearrangement conditions used were identical to those previously described. Pleasingly, cyclic ketone **80** was isolated in a good yield of 71% (**Scheme 79**).

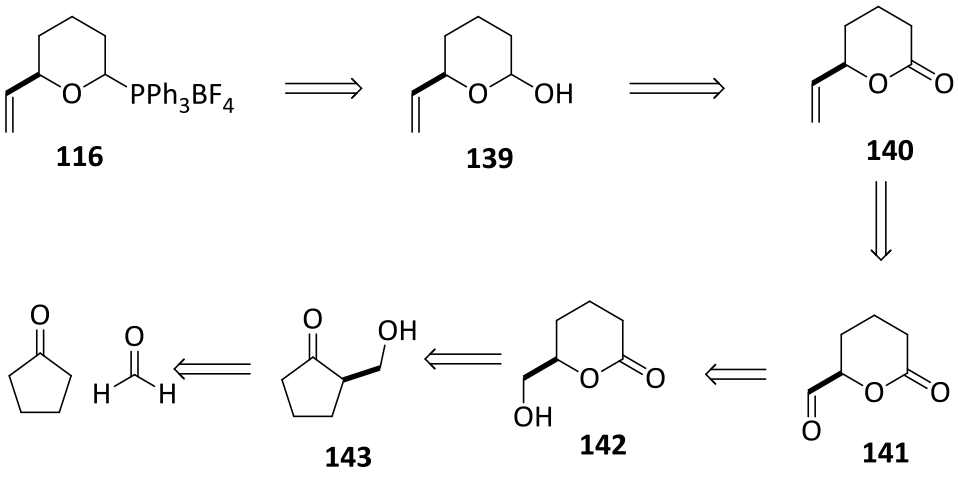


Scheme 79

Disappointingly however, the product *ee* was found to be <5%. Considering that the starting enol ether had an *ee* of 35%, this shows that the rearrangement process is not stereospecific, under these conditions. The inefficiency of the enantioselective substrate synthesis meant that we were unable to carry out the rearrangement under a selection of conditions that would demonstrate whether some level of stereochemical retention was possible. We therefore sought a more efficient route to non-racemic rearrangement substrates, in particular, one that would provide higher levels of enantiomeric purity.

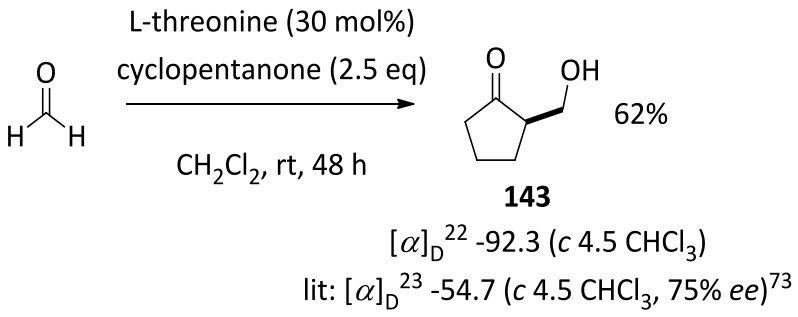
3.3.2 TERMINAL ALKENE ENOL ETHER

The route towards enantiopure terminal alkene phosphonium salt **116** follows a similar route in which lactone **140** is a key intermediate (**Scheme 80**). This lactone can be obtained *via* a Wittig olefination of the corresponding aldehyde **141**, resulting from the oxidation of the alcohol **142**. The route to alcohol **142** follows a known procedure, involving an asymmetric aldol, followed by Baeyer-Villiger oxidation.



Scheme 80

The asymmetric aldol reaction between cyclopentanone and formaldehyde was achieved using organocatalysis. The best catalyst for this transformation was found to be L-threonine (**Figure 9**).[72] The reaction occurs smoothly over 48 hours and alcohol **143** was isolated in a reasonable yield of 62% after chromatography (**Scheme 81**).



Scheme 81

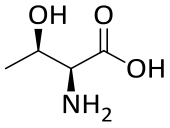
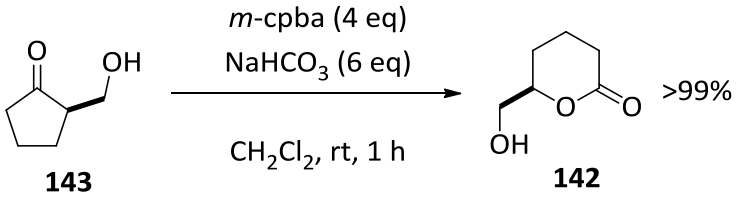


Figure 9

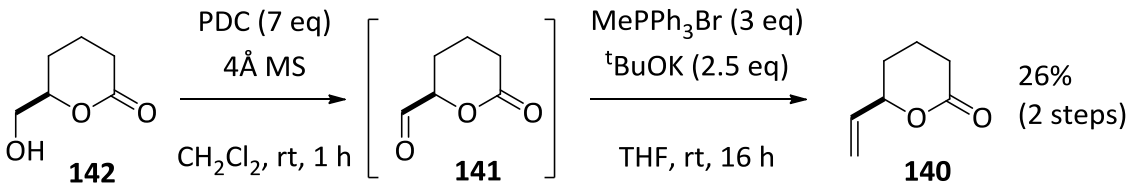
The organocatalysed aldol reaction can be performed on a large scale, and around 6 grams of **143** could be synthesised in a single operation. This compound can be stored in the freezer over an extended period of time with no significant decomposition. The Baeyer-Villiger oxidation also occurred smoothly, additionally on a reasonable scale, to give alcohol **142** in quantitative yield (**Scheme 82**).



Scheme 82

Although excellent yields of the alcohol were obtained in this process, some optimisation was required. The reaction itself appeared to proceed to 100% conversion, however, after work-up, only 20% of the desired alcohol was isolated. It was found that a significant amount of the alcohol was soluble in aqueous media (saturated sodium thiosulfate and sodium bicarbonate are typically used upon work-up). Accordingly, aqueous work-up was avoided and the crude reaction was filtered through Celite® and purified directly by chromatography.

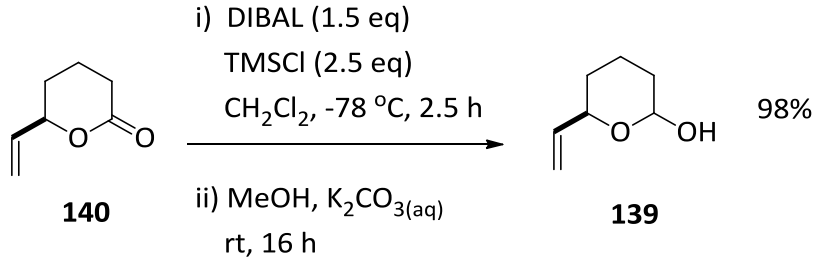
Unlike its precursor, alcohol **142** was found to decompose over time in the freezer, so it had to be used almost immediately. Oxidation to aldehyde **141** followed a known procedure, with pyridinium dichromate (**Scheme 83**).[74] This aldehyde is reported to degrade very rapidly, therefore no attempts were made to purify and isolate it (only filtration to remove insoluble chromium salts). Instead, all the solvent was removed and the crude material was used directly in the next stage. This involved forming the terminal alkene lactone *via* Wittig olefination with methyl triphenylphosphonium bromide.[75]



Scheme 83

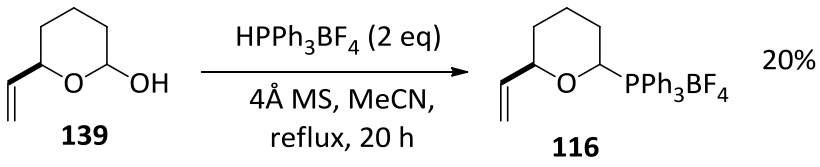
Lactone **140** was isolated in a reasonable 26% yield over the 2 steps after purification. This yield obtained is on a par with those reported for oxidations and Wittig reactions on similar systems. The low yield may possibly be due to the volatility of the lactone and aldehyde, as well as the ability of aldehyde **141** to degrade and the fact that the crude oxidation product was used in the Wittig olefination.

With lactone **140** in hand, the route towards the enol ether employed chemistry previous described. Accordingly, reduction of the lactone to hemi-acetal **139** occurred smoothly in excellent yield (**Scheme 84**).



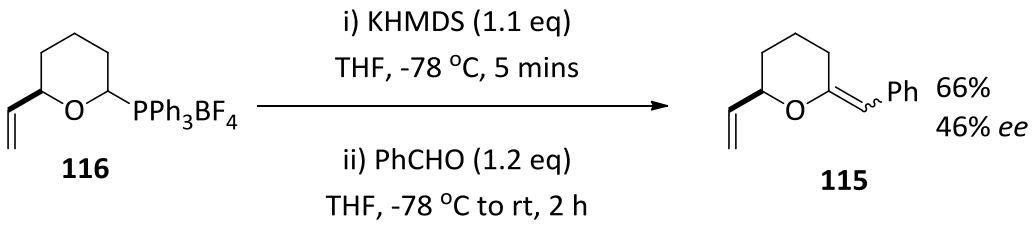
Scheme 84

Formation of the phosphonium salt **116** occurred in a disappointing yield of 20% (**Scheme 85**). The reason behind this is unknown, although the extreme volatility of hemi-acetal **139** may be factor.



Scheme 85

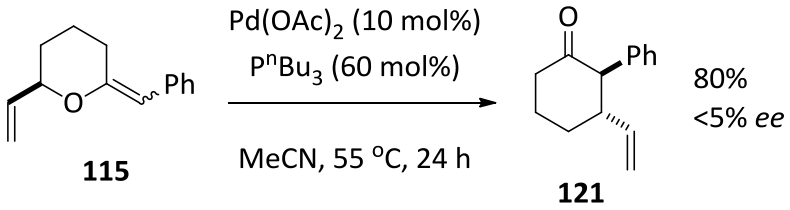
Pleasingly when **116** was subjected to the Wittig reaction, enol ether **115** was obtained in a good yield of 66% (**Scheme 86**). Furthermore, **115** was found to have an *ee* of 46%, as determined by chiral-gas chromatography.



116 **115**

Scheme 86

When enol ether **115** was subjected to the rearrangement conditions, this substrate efficiently afforded cyclohexanone **121** in an excellent 80% yield (**Scheme 87**). Unfortunately however, the cyclohexanone was found to be racemic.



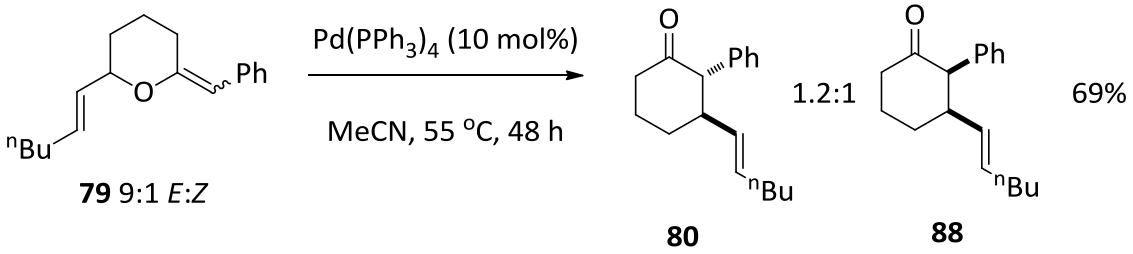
115 **121**

Scheme 87

3.4 MECHANISTIC STUDIES

Despite the setback from the results of the rearrangement of enantioenriched enol ether substrates, we set out to establish a plausible mechanism of the rearrangement. In particular, some stereochemical factors that we wanted to better understand included: (1) is the isolation of a single diastereomer of the cyclic ketone the result of kinetic diastereoselectivity, or product epimerisation at the α-centre? (2) why does the *ee* of the cyclic ketones not proceed past 50%?

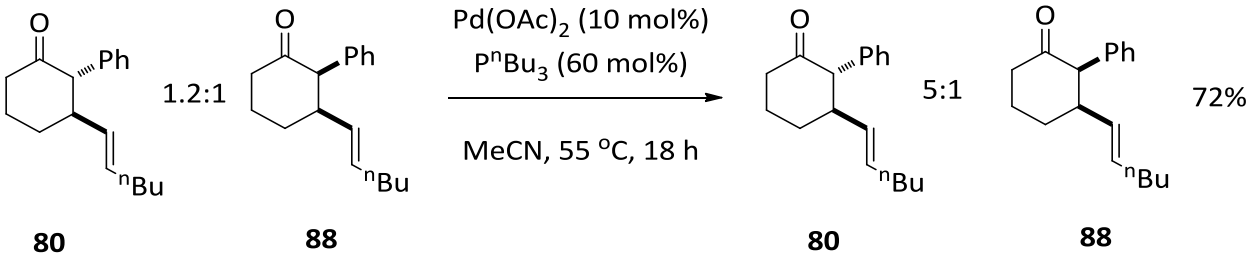
With respect to addressing the first question, previous studies within the laboratory showed that conducting the rearrangement with a catalyst system consisting of an electron poor phosphine/palladium source led to formation of cyclic ketone diastereoisomers **80** and **88** (**Scheme 88**).[53]



79 9:1 *E*:*Z* **80** **88**

Scheme 88

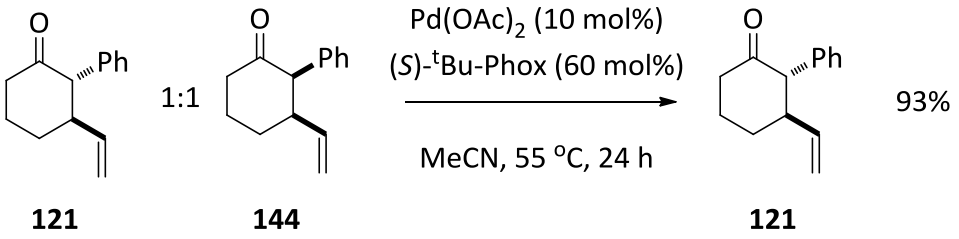
The mixture of diastereomers was subsequently subjected to the optimal rearrangement conditions (electron rich phosphine *cf* **Scheme 57**). In the event, an increase in the *trans*-diastereomer **80** was observed (**Scheme 89**).



80 **88** **80** **88**

Scheme 89

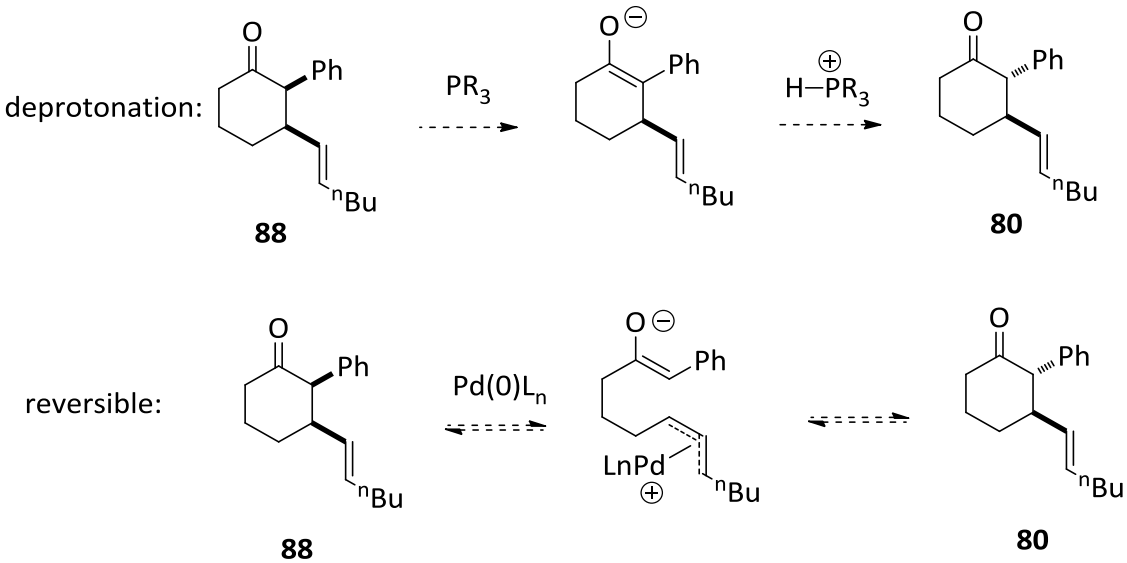
However, using the (*S*)-^{t}Bu-Phox ligand **42** in place of *n*-tributylphosphine resulted in the total epimerisation of **144** albeit over a slightly extended reaction time (**Scheme 90**).



121 **144** **121**

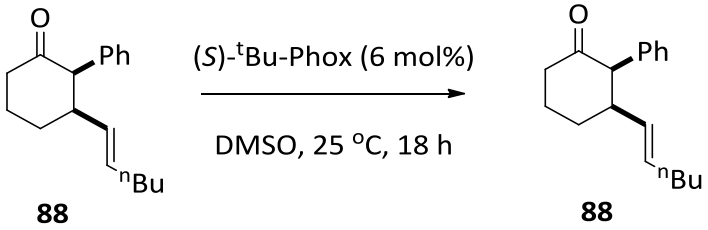
Scheme 90

The use of an electron rich phosphine/palladium catalyst appears to lead to epimerisation of the *cis*-cyclic ketone to the *trans*-isomer. However, the process as to how this happens remains unclear. It is postulated that the phosphine is basic enough to promote deprotonation of the α-proton followed by reprotonation to obtain the *trans*-cyclic ketone. Another possible process is that the ring closure reaction is reversible (**Scheme 91**).



Scheme 91

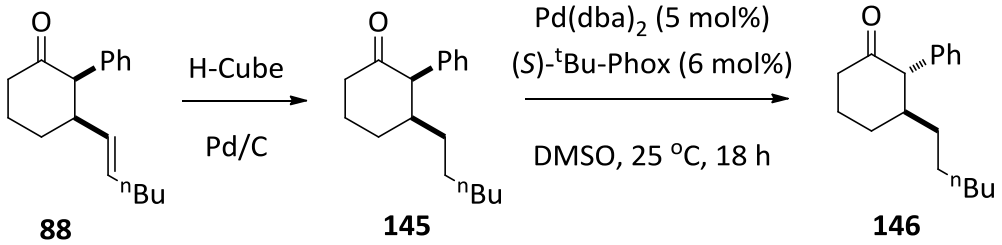
Studies to further determine the origin of the epimerisation were carried out by J.-O. Zirimwabagabo,[76] the outcomes of which are highlighted below. Exposure of **88** to (*S*)-^{t}Bu-Phox, in the absence of a palladium source, resulted in no detectable epimerization. This result excludes the protonation/reprotonation proposal (**Scheme 92**).



88 **88**

Scheme 92

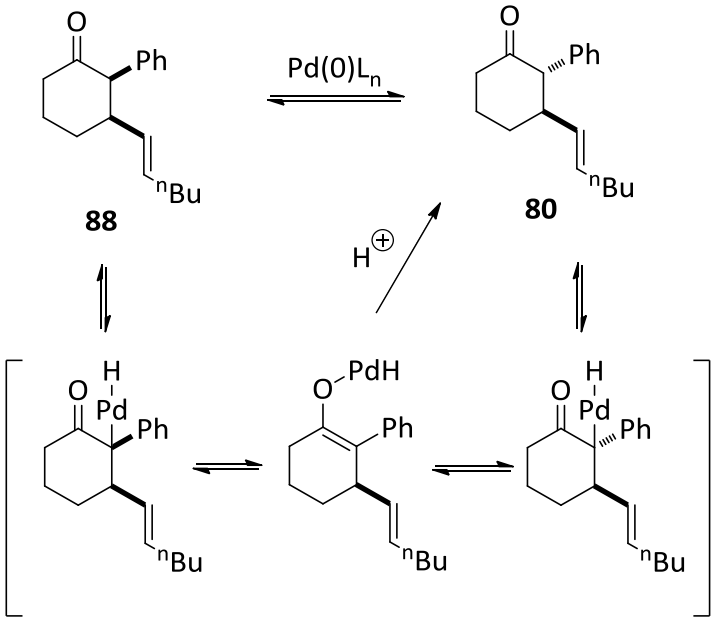
With regard to gathering evidence for the ring opening of the cyclic ketone, the alkene of **88** was reduced under H-Cube® flow conditions to give the cyclic ketone **145**. Subjection of this to a palladium/phosphine catalyst resulted in total epimerisation to **146** suggesting that epimerization *via* π-allyl complex formation is not in operation (**Scheme 93**).



88 **145** **146**

Scheme 93

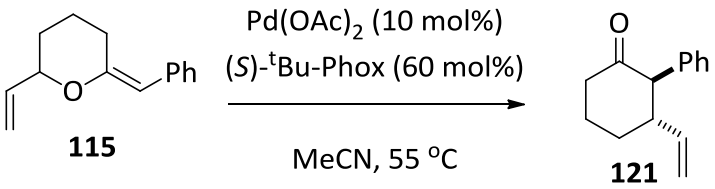
From these experiments, it has been postulated that a palladium-enolate intermediate is formed during the process of the rearrangement, potentially *via* C-H insertion (**Scheme 94**).



Scheme 94

Even though this reaction mode is plausible, further experiments are required to further support this mechanism.

The focus of attention was next switched to the use of chiral ligands in the rearrangement process. The maximum *ee* obtain thus far was 49% utilizing the (*S*)-^{t}Bu-Phox **42** ligand with enol ether **115** (**Table 14**, page 50). To try to understand the processes taking place, the *ee* of the cyclic ketone was monitored *via* gas chromatography by carefully taking aliquots of the reaction mixtures. The collated results of two independent reactions are highlighted in **Table 15**. Additionally, the *ee* of the enol ether **115** could also be determined under identical gas chromatography condition and thus a conversion could be calculated.



115 **121**

Entry	Time / h	Conversion / %[a]	cyclic ketone *ee* / %[b]	enol ether *ee* / %[b]
1[c]	30 secs	27	5	6
2[c]	1	54	24	6
3[d]	2	62	28	5
4[c]	2	63	34	13
5[c]	3	79	33	20
6[d]	3	80	32	18
7[d]	4	86	35	32
8[c]	4	87	33	33
9[c]	5	92	34	50
10[d]	5	93	35	54
11[c]	6	94	34	57
12[d]	6	95	36	63
13[c]	7	96	36	71
14[c]	18	100	40	-

Table 15

[a] conversion determined *via* chiral GC with crude reaction material

[b] *ee* determined *via* chiral GC with crude reaction material

[c] Run 1

[d] Run 2

These results are presented in graphical form in **Figure 10**.

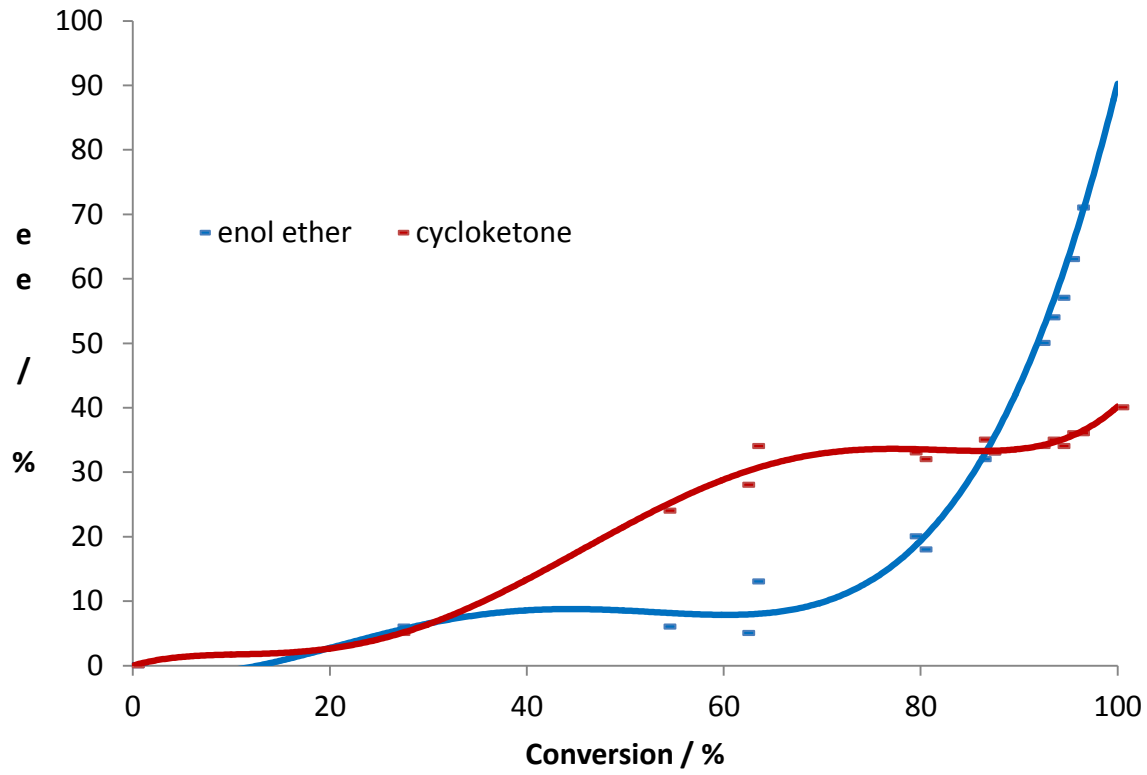


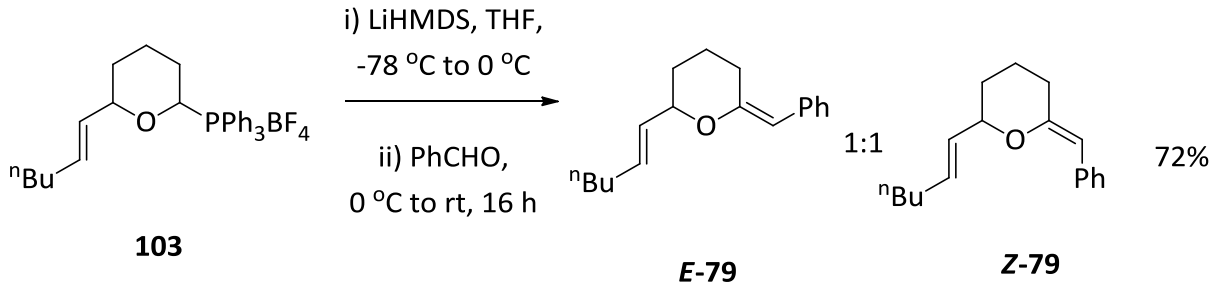
Figure 10

These studies showed that the chiral catalyst itself appears to be very active. After just 30 seconds, the reaction had already reached 27% conversion (**Table 15**, Entry 1) and was almost complete after 7 hours (Entry 13). As the reactions progressed, the *ee* of the cyclic ketone slowly increased (Entries 2 to 6), albeit after proceeding without any *ee* initially (Entry 1). This could explain why the *ee* of the cyclic ketone is low after complete conversion. However, at high conversion, the *ee* stalls (Entries 7-13), and essentially remains the same until complete conversion. However, the most surprising aspect of the reaction is in regard of the enol ether enantioselectivity. Although the *ee* remains low during the initial stages of the reaction, the *ee* starts to climb once the *ee* of the cyclic ketone has reached its maximum value.

Although these results gave little insight into how the enol ether and the active catalyst are interacting, it does show that one particular enantiomer is significantly more "matched" to the system. This opens the prospect of developing a kinetic resolution protocol to obtain enantioenriched enol ethers.

3.5 DEVELOPMENT OF A KINETIC RESOLUTION PROTOCOL

To simplify the establishment of a kinetic resolution protocol, we conducted our development studies using single enol ether isomers. To do this, a procedure was required to obtain both enol ether diastereoisomers in significant amounts. This was done simply by changing the base used in the Wittig olefination. The use of potassium bis(trimethylsilyl)amide could only provide a 9 : 1 ratio of the enol ether in favour of the *E*-isomer. Exchanging with lithium bis(trimethylsilyl)amide improved the ratio significantly to 1 : 1 (**Scheme 95**).

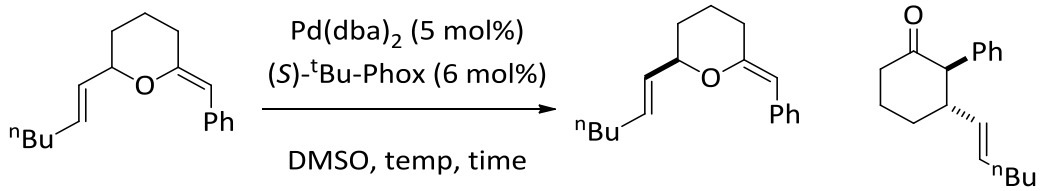


103 ***E*-79** ***Z*-79**

Scheme 95

Although the individual isomers could be isolated *via* careful column chromatography on silica gel, significant amounts of decomposition occurred. However, separation with no appreciable decomposition could be achieved *via* preparative HPLC using a C18 column.

Optimisation of the kinetic resolution protocol was performed by J.-O. Zirimwabagabo utilizing (*S*)-^{t}Bu-Phox **42**;[76] the results of which are highlighted in **Table 16**. Carefully adjusting the reaction temperature and time, racemic ***Z*-79** enol ether could be isolated in enantiopure form (up to 99% *ee*), and in recovered yields ranging from 33-38%. Unfortunately, the cyclic ketone **80**, could not be isolated enantiopure, instead generally between -25 and -10% *ee*.



***Z*-79** ***Z*-79** **80**

Entry	Temperature / °C	Time / h	Unreacted enol ether / % (*ee* / %)[ab]	Cyclic ketone conv / % (*ee* / %)[ab]
1	60	1	38 (+66)	62 (-48)
2	60	4	33 (+96)	67 (-29)
3	60	16	15 (+99)	85 (-10)
4	60	40	10 (+99)	90 (-5)
5	40	1	-[c] (+47)	-[c] (-48)
6	40	3.25	-[c] (+92)	-[c] (-29)
7	40	5	-[c] (+98)	-[c] (-10)
8	40	6.5	36 (+99)	63 (-5)

Table 16

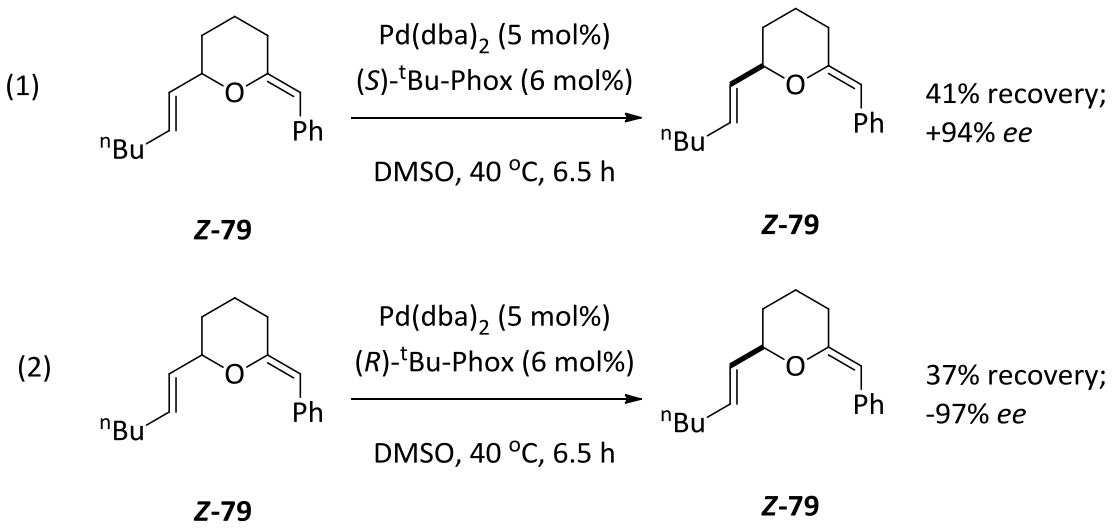
[a] conversion and *ee* measure *via* HPLC with crude reaction material

[b] "+" *ee* refers to the first enantiomer observed on HPLC is the major. The reverse applies to "-" *ee*.

[c] conversion not calculated

Indeed, entry 8 highlights an excellent kinetic resolution protocol, providing ideal yield and *ee* in a consistent manner. The chemistry was found to be reproducible in my hand, utilizing both enantiomers of the ^{t}Bu-Phox ligand, providing both enantiomers of enol ether ***Z*-79** in essentially enantiopure form (**Scheme 96**).

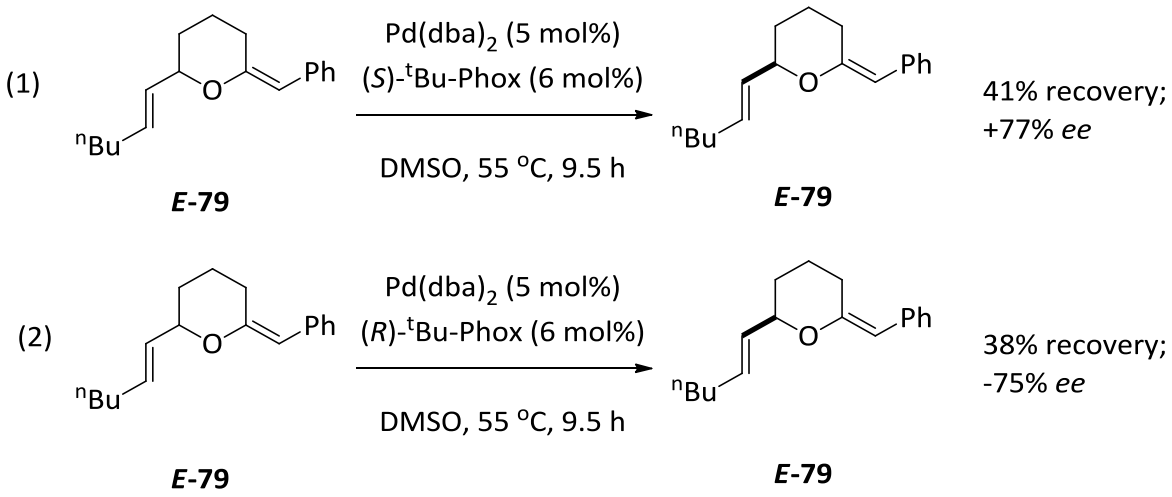
Although the chemistry is reproducible, several measures needed to be taken in order to achieve this. The enol ether substrate was required to be as dry as possible as the presence of other solvents inhibited the yield significantly. The reaction vessel needed to be free of all molecular oxygen. This was achieved by placing the reaction vessel under high vacuum for a continuous two minute period before back filling with argon. This method also served to degas the dimethyl sulfoxide.



Scheme 96

Finally, to achieve reproducible results, the reaction vessels needed to remain at the same temperature throughout. Any fluctuations resulted in poor conversion and *ee*. If all the measures were adhered to, the kinetic resolution worked reliably up to scales of 500 milligrams.

Unfortunately, applying the same reaction conditions to enol ether ***E*-79** resulted in poor conversion and *ee*. The reason behind this observation was unclear, however with a subtle change in reaction conditions, the kinetic resolution proceeded with acceptable results (**Scheme 97**).



Scheme 97

Again, all the measures outlined for the kinetic resolution of the *Z*-enol ether substrate apply in this case. Compared to the *Z*-enol ether, the *E*-enol ether required more forcing conditions, an increase in temperature and time. The slower reaction time implies that the *E*-enol ether is not as well matched to the catalyst system as the *Z*-enol ether.

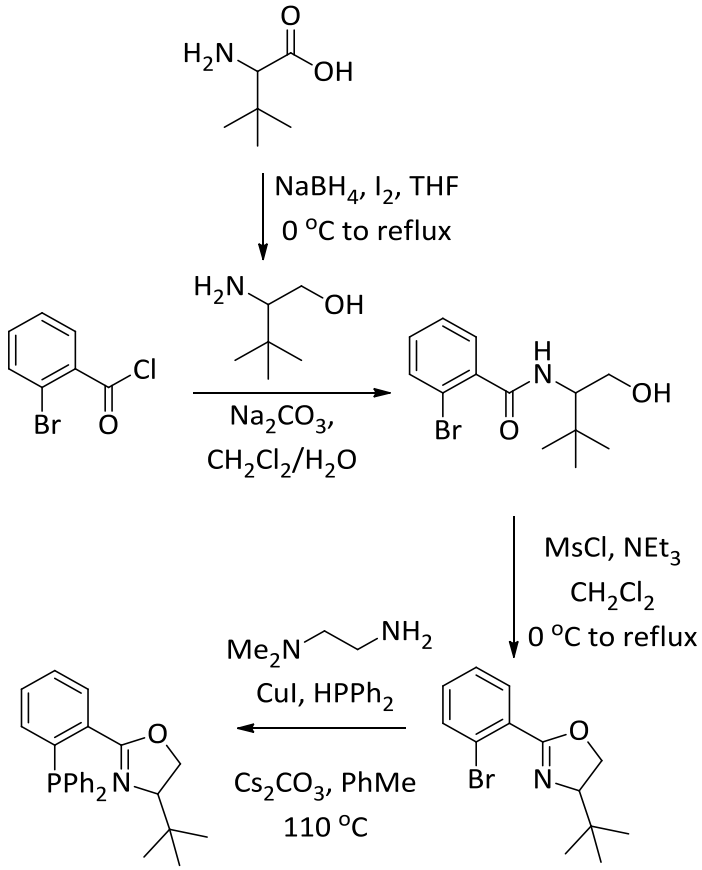
These results can be compared quantitatively by calculating the selectivity factor (s-factor) for both kinetic resolutions. The s-factors are calculated using the following formulae:[77]

$$s = \frac{\ln[(1 - c).(1 - ee)]}{\ln[(1 - c).(1 + ee)]}$$

where s is the selectivity factor, c is the conversion decimalised and *ee* is the enantioexcess of the recovered enol ether decimalised. Generally, accepted s-factors for kinetic resolutions are 15.0 and above. Applying the formula to the results of the kinetic resolution, we see that the *Z*-enol ether has s-factors of 16.1 (**Scheme 96**, equation (1)) and 14.2 (**Scheme 96**, equation (2)). However, the *E*-enol ether has s-factors of 7.4 (**Scheme 96**, equation (1)) and 5.7 (**Scheme 96**, equation (2)).

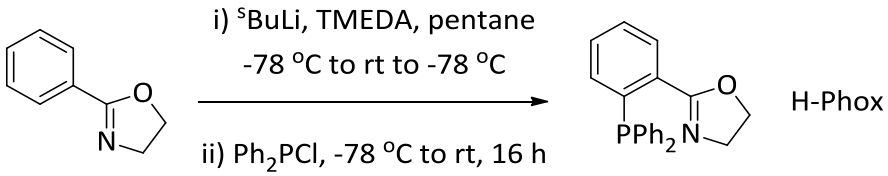
With highly enantioenriched enol ethers in hand, we decided to re-examine the stereospecificity of the rearrangement. This is an extension of the chemistry discussed in chapter 3.3.1. However, rather than exclusively utilising none enantiopure phosphine ligands (such as P^nBu_3), both enantiomers of the ^{t}Bu-Phox, as well as the racemic form and an achiral analogue were used. All ligands used were prepared in house on a multigram scale.

The ^{t}Bu-Phox analogues were prepared using the protocol developed by Stoltz, as illustrated in **Scheme 98**.[78]



Scheme 98

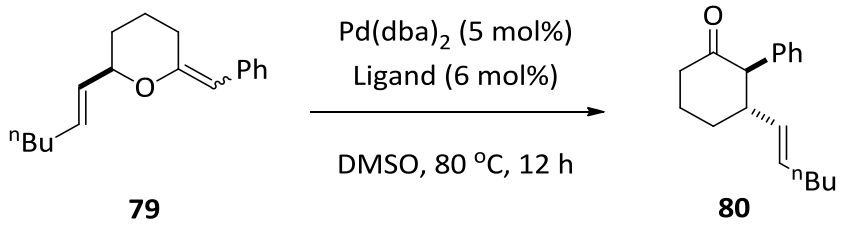
An achiral analogue, 2-[2-(diphenylphosphino)phenyl]-4,5-dihydro-oxazole (H-Phox), was prepared according to the procedure by Pfaltz (**Scheme 99**).[79]



Scheme 99

All syntheses used cheap, commercially available reagents and could be handled without the need for oxygen-free conditions.

The rearrangements were carried out using a procedure optimised elsewhere,[76] the results of which are highlighted in **Table 17**.



79 **80**

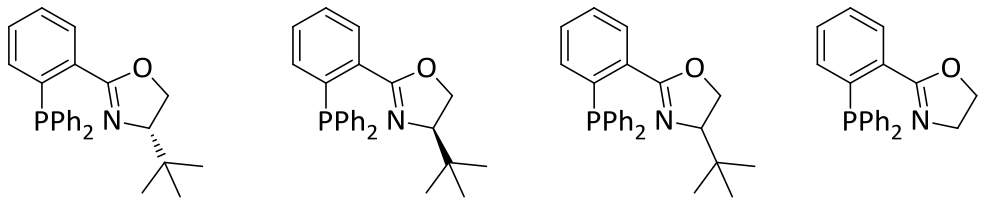
Entry	Ligand[a]	enol ether	Yield / %[b]	ee / %[c]
1	(*S*)-^{t}Bu-Phox	*Z*; +99% *ee*	84	+98
2	(*R*)-^{t}Bu-Phox	*Z*; +99% *ee*	86	+99
3	(±)-^{t}Bu-Phox	*Z*; +94% *ee*	83	+92
4	H-Phox	*Z*; +96% *ee*	80	+90
5	(*R*)-^{t}Bu-Phox	*E*; +77% *ee*	74	+73
6	(±)-^{t}Bu-Phox	*E*; +71% *ee*	85	+68

Table 17

[a] See **Figure 11** for ligand structures

[b] yields adjusted to account for dba contamination

[c] *ee*'s measured *via* HPLC with isolated materials



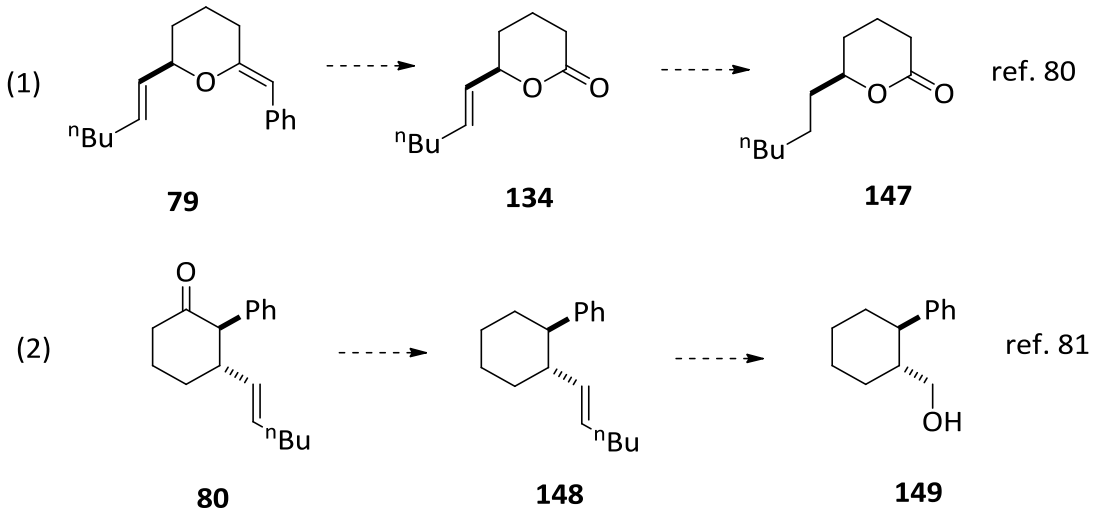
(*S*)-^{t}Bu-Phox (*R*)-^{t}Bu-Phox (±)-^{t}Bu-Phox H-Phox

Figure 11

Pleasingly, when enantiopure enol ether ***Z*-79** was subject to rearrangement with (*S*)-^{t}Bu-Phox, very little erosion of the *ee* was observed. Indeed, additionally utilising (*R*)-^{t}Bu-Phox and (±)-^{t}Bu-Phox gave identical results. Even using an achiral variant of the Phox ligand (H-Phox), resulted in no significant *ee* loss. Likewise, enantioenriched *E*-enol ether rearrangement proceeded with good levels of stereoretention.

3.6 DETERMINATION OF A STEREOCHEMICAL MODEL

In order to establish a stereochemical model for the kinetic resolution, and to determine if the rearrangement of enantiopure enol ether occurred with retention of configuration, the absolute stereochemical assignments of enantiopure enol ethers and cyclic ketones had to be determined. To accomplish this, derivatisation of the enol ether and cyclic ketone to molecules with known absolute stereochemistry was required. Our proposed routes to accomplish this are outlined in **Scheme 100**.

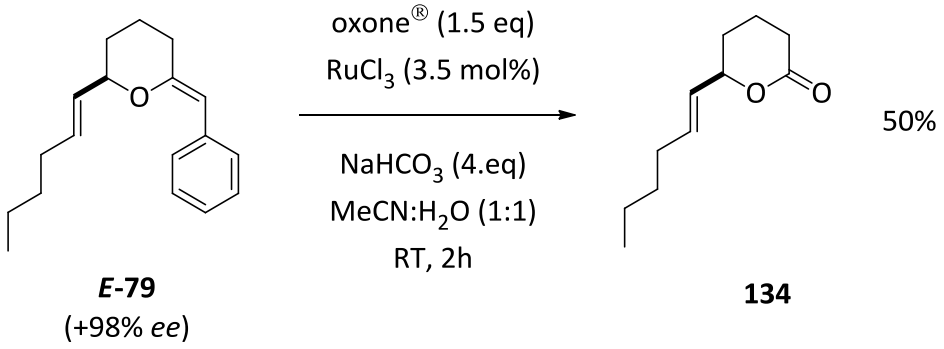


Scheme 100

With regard to the enol ether, selective oxidative cleavage of the enol ether-alkene would yield lactone **134**. Hydrogenation of the alkene would then provide known lactone **147** (equation (1)). The cyclic ketone would undergo carbonyl reduction to cyclohexane **148**, followed by oxidative cleavage/reduction to furnish alcohol **149** (equation (2)).

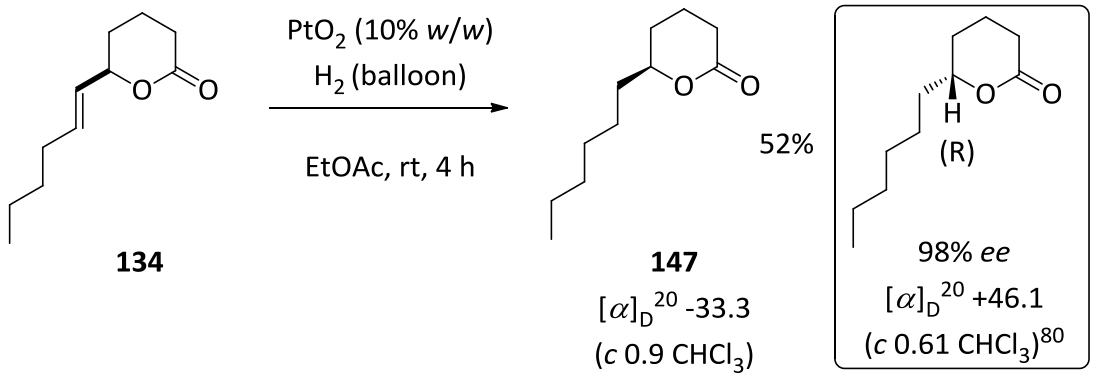
Our initial efforts to oxidatively cleave the enol ether employed ozonolysis. However, in this case, no enol ether or lactone based material was isolated. This is possibly due to the acidic nature of the ozone/dichloromethane combination (although the addition of small amounts of sodium hydrogen carbonate also failed to provide the desired material) and/or ozonolysis of the allylic ether olefin leading to unstable or volatile intermediates.

Instead, a milder oxidation system was utilised. The use of ruthenium(III) chloride and oxone® in the presence water/acetonitrile proved to be the most consistent method of oxidation to the lactone intermediate (**Scheme 101**).[82] Other *in situ* oxidations, such as sodium metaperiodate and alternative solvent mixtures gave poor yields. This reaction was carried out on enantioenriched material derived from kinetic resolution with (*S*)-Phox (+99% *ee*).



Scheme 101

With lactone **134** in hand, attention turned to the hydrogenation. Unfortunately, standard palladium/carbon catalysed hydrogenation under a balloon of hydrogen gas failed to reduce the alkene to any extent. Gratifyingly, stirring the lactone in the presence of Adam's catalyst for an extended period under a hydrogen atmosphere led to complete consumption (**Scheme 102**). Although only a 52% yield of lactone **147** was isolated, it was free from contaminants.



Scheme 102

A rotation value was recorded for the purified lactone and compared with the literature value. From this we concluded that the lactone **147** isolated has (*S*)-stereochemistry. This lactone must then have been derived from the (*R*)-enol ether (Note: the assignment switch is due to the different priority values in applying the Cahn-Ingold-Prelog rules and is not meant to imply a switch in configuration).

On this basis, we have established that the *Z*-enol ether isolated from the kinetic resolution with (*S*)-^{t}Bu-Phox is enantiopure (*R*)-*Z*-enol ether. Therefore, (*S*)-*Z*-enol ether is the enantiomer that is matched to the (*S*)-^{t}Bu-Phox/palladium system.

With data from the stereochemical proof in hand, we decided to formulate a proposal for the enantiocontrol observed in the kinetic resolution. The chemistry of π-allyl palladium complexes bearing Phox-ligands has been studied in detail with respect to the nucleophilic addition step. Specifically, nucleophiles tend to add to the carbon atom *trans* to the phosphine group, as this is a better π-acceptor than the imine-moiety. This has the effect of rendering the carbon atom *trans* to the phosphine ligand more electrophilic than the carbon *trans* to the nitrogen atom, which is not a π-acceptor.[83] Additional evidence for this effect has been provided by Helmchen, where the two carbon-palladium bond lengths have been determined to be distinct *via* X-ray crystallography, as illustrated in **Figure 12**.[84,85]

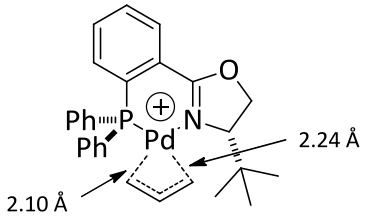
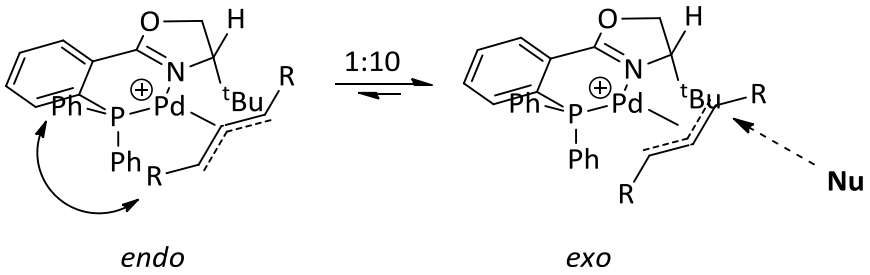


Figure 12

As such, the carbon-palladium bond *trans* to the phosphorus is weaker than the carbon-palladium bond *trans* to the nitrogen, making it more susceptible to nucleophilic attack.

In addition and with regard to stereochemical control, the *exo*-diastereomer of the π-allyl palladium complex is subject to less steric strain and predominates over the corresponding *endo*-isomer (**Scheme 103**).[83]

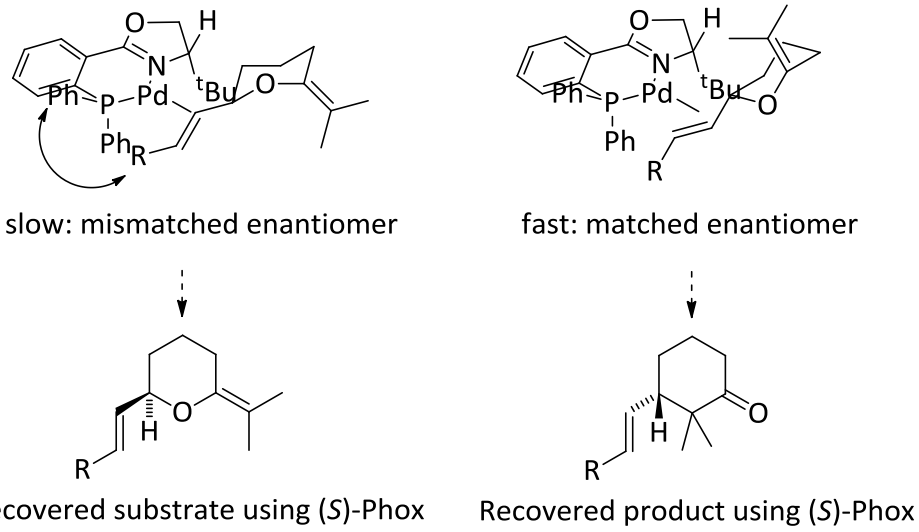


Scheme 103

Taken together, these arguments have been used by several research groups to explain the stereochemical outcome of such reactions.[83,86]

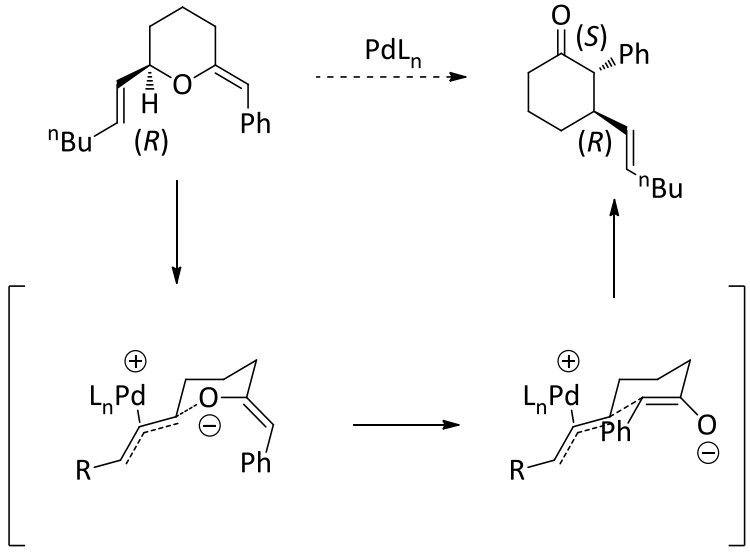
In the context of our kinetic resolution and based on the assumption that the oxidative insertion event follows a similar pathway to the nucleophilic addition described above (*i.e.* it is the reverse process), a model for the kinetic resolution of enol ethers by palladium-Phox catalysts can be put forward (**Scheme 104**). We propose that two modes of insertion are possible, each with the allylic ether in an equatorial orientation, and the phosphorus atom *trans* to the breaking C-O bond.

Coordination of the palladium-Phox in an *endo* like mode should be subject to steric interactions with the phosphine-phenyl group resulting in a slow ionisation step. In contrast, the other enantiomer can ionise to form the more favoured *exo* mode, and should therefore undergo rearrangement more easily. Assuming the rearrangement proceeds with double inversion, the product should contain epimeric stereogenicity at C-3 relative to the recovered starting material.



Scheme 104

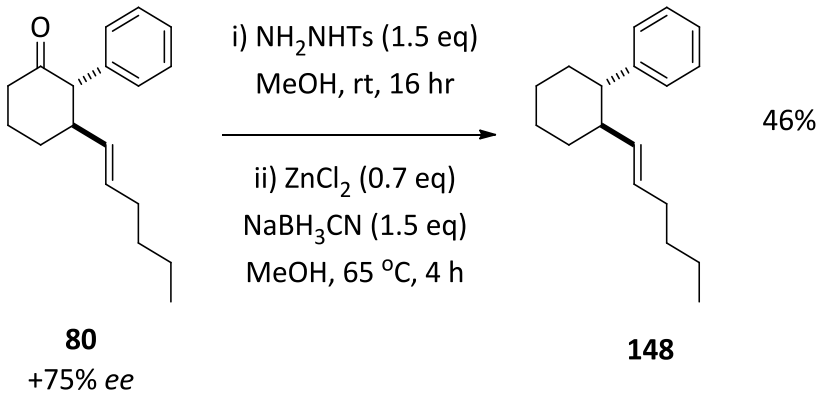
To ascertain further evidence for this proposal, we set about determining the absolute stereochemistry of the cyclic ketone. If the rearrangement of (*R*)-enol ether does indeed proceed with retention of configuration, the cyclic ketone should have (2*S*,3*R*) stereochemistry, as outlined in **Scheme 105**.



Scheme 105

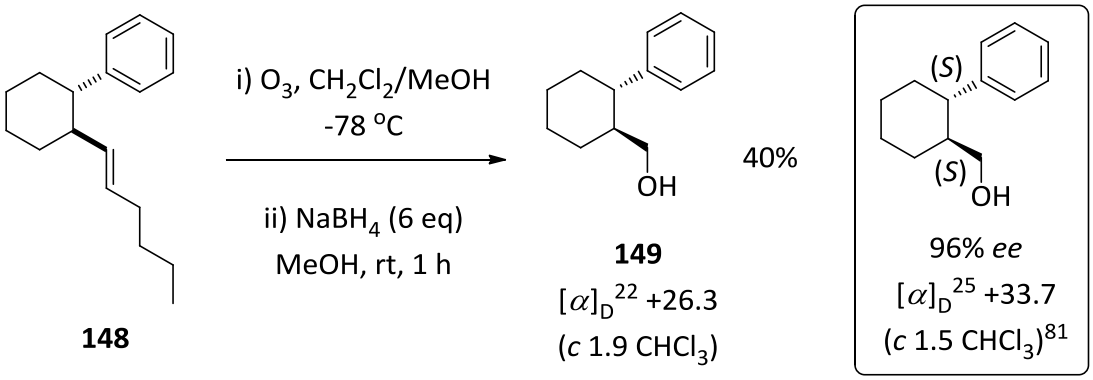
In the event, we carried out a rearrangement of (*R*)-*Z*-enol ether under standard conditions but using racemic Phox catalyst (**Table 17**). Using enol ether of +77% *ee* gave cyclic ketone **80** in 82% yield with +75% *ee* utilising (±)-^{t}Bu-Phox.

With enantioenriched cyclic ketone in hand, derivatisation to known compound **149** was undertaken as highlighted earlier in **Scheme 100**. Attempts to reduce the carbonyl group under Clemmensen conditions failed to furnish the desired cyclohexane. However, using a modification of the Wolff-Kishner reduction developed by Charette[87] gave *trans*-cyclohexane **148** in an overall yield of 46% (**Scheme 106**). Yields of up to 80% were achieved on the racemic substrate. This drop in yield may be due to the presence of dibenzylideneacetone impurity in the cyclic ketone sample, which co-elutes with the cyclic ketone.



Scheme 106

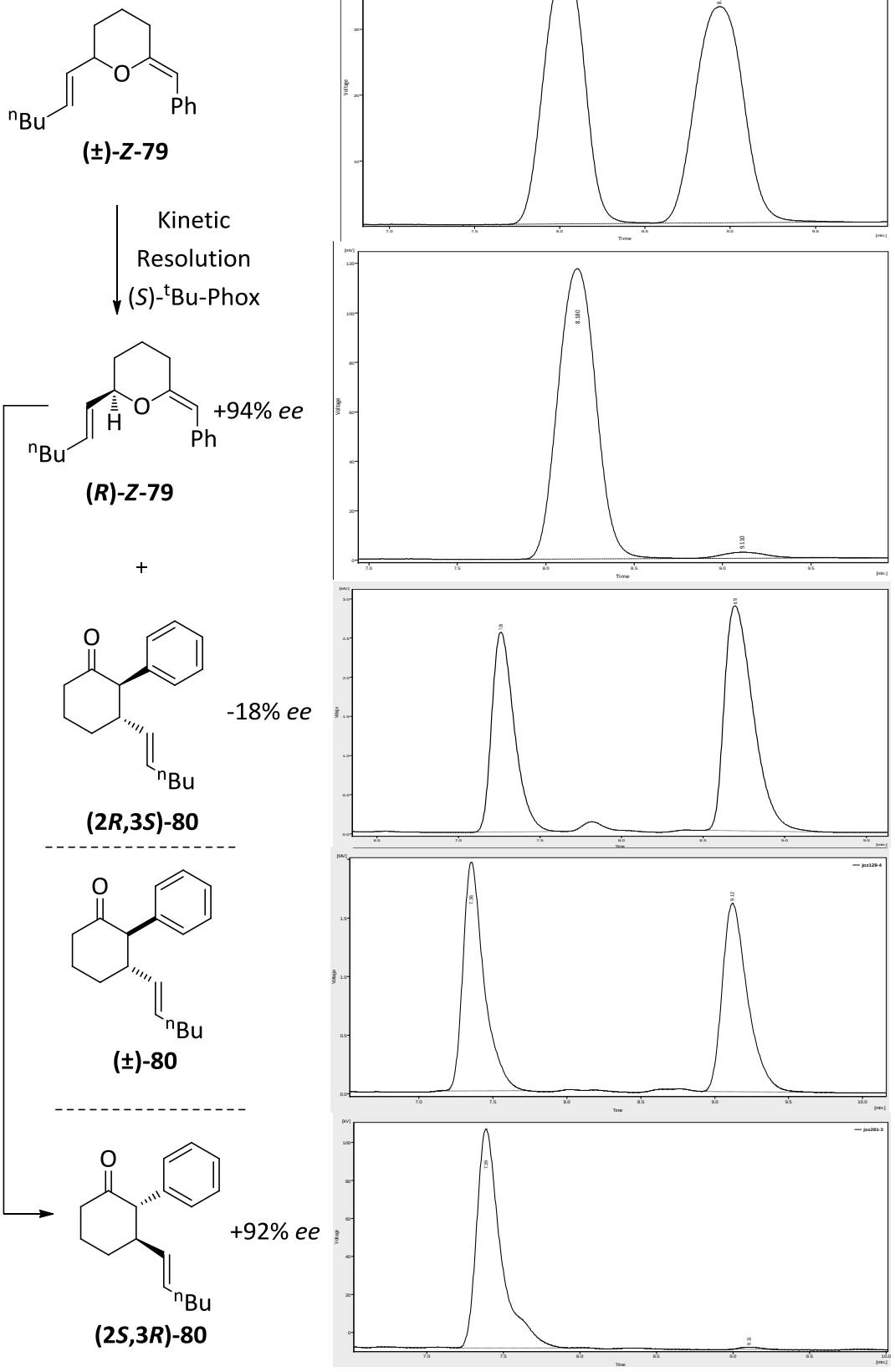
With cyclohexane **148** in hand, oxidative cleavage was accomplished by ozonolysis followed by a reductive quench with excess sodium borohydride to yield *trans*-cyclohexane **149** in an overall yield of 40% (**Scheme 107**).



Scheme 107

With derivatisation complete, the cyclohexane **149** isolated had the (1*S*,2*S*) stereochemistry. By inference therefore, the parent cyclic ketone **80** has the required (2*S*,3*R*) stereochemistry. This stereochemical proof therefore provided strong evidence that the rearrangement of the enol ethers occurs with retention of stereochemistry. A summary of the kinetic resolution/rearrangement chemistry is highlighted in **Scheme 108**.

Racemic enol ether ***Z*-79** can undergo a kinetic resolution in the presence of (*S*)-^{t}Bu-Phox. The recovered materials are enantiopure (*R*)-enol ether and enantioenriched (2*R*,3*S*) cyclic ketone. Subjection of enantiopure (*R*)-enol ether to a palladium/Phox ligand system leads to a rearrangement with retention of the stereocentre to yield enantiopure cyclic ketone **(2*S*,3*R*)-80**. This cyclic ketone is the opposite enantiomer to that isolated from the kinetic resolution, where (*S*)-enol ether undergoes rearrangement.


O
nBu
Ph
(±)-Z-79
Kinetic
Resolution
(S)-tBu-Phox
H
+94% ee
(R)-Z-79
+
-18% ee
(2R,3S)-80
O→C
(±)-80
+92% ee
(2S,3R)-80

Scheme 108

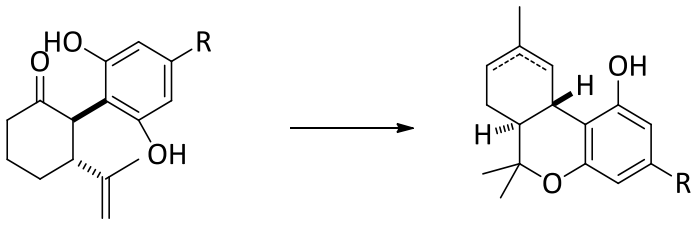
3.7 CONCLUSIONS AND FUTURE WORK

The scope of the palladium catalysed O→C rearrangement chemistry has been expanded to show that heteroaromatics can participate in this process. We can now conclude that the rearrangement chemistry is viable for a range of alkyl and various aryl enol ethers.

The development of a chiral palladium/ligand system showed promise. Although cyclic ketones have been formed with a modest degree of enantiopurity (~50% *ee*) we hoped that screening alternative ligands (especially those based on Phox) will result in an effective enantioselective process. Attempts to study the rearrangement of enantiopure enol ethers had been thwarted by challenging substrate synthesis using classical approaches.

Whilst trying to understand mechanistic details of the reaction, it became apparent that a kinetic resolution was occurring between the enol ethers and the palladium/Phox system. After extensive experimentation, an excellent kinetic resolution protocol has been developed. This led to the prospect of obtaining enol ethers with high levels of enantiopurity and recovery. Additionally, enantiopure cyclic ketones can be accessed *via* rearrangement of enantiopure enol ethers.

This kinetic resolution protocol is to be developed further, which will give access to enantiopure alkyl, aromatic and terminal alkene enol ether and cyclic ketones. It is hoped that these substrates can be utilised in the asymmetric total synthesis of natural products. For example, various analogues of the cannabinoid family can be obtained from enantiopure cyclic ketones (**Scheme 109**)



Tetrahydrocannabinol (THC) core

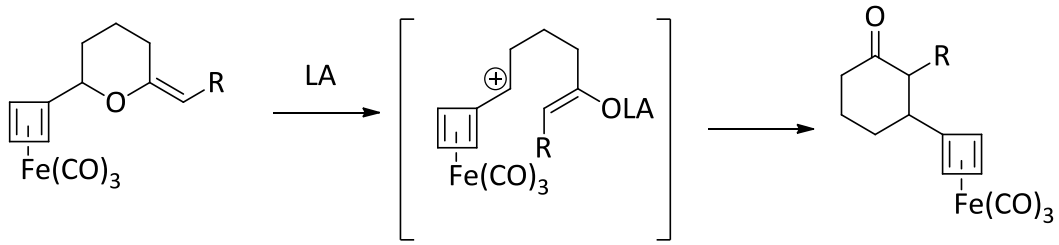
Scheme 109

4 DEVELOPMENT OF AN IRON MEDIATED REARRANGEMENT SYSTEM

With the successful development of a palladium-catalysed method for the formation of functionalised cyclic ketones to complement the cobalt/Lewis acid-mediated rearrangement chemistry, attention turned further generalising this strategy. Although high degrees of success were noted with the colbalt and palladium promoted methods, there are drawbacks associated with each of the methods developed.

The propargyl enol ether rearrangement required the use of stoichiometric amounts of cobalt hexacarbonyl; cobalt compounds are listed as potential carcinogens and can impair fertility. In addition, the palladium mediated O→C rearrangement, although used in substoichiometric amounts, required the use of an expensive transition metal. Despite their high success, these drawbacks have an adverse impact on their appeal.

The new paradigm would make use of the cation stabilising potential of cyclobutadieneiron tricarbonyl complex (see chapter 4.1.2 for discussion on this effect), as illustrated in **Scheme 110**.



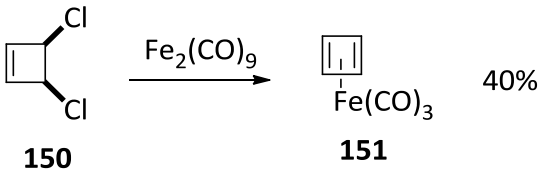
Scheme 110

Cyclobutadieneiron tricarbonyl was chosen based on the ease of preparation on multigram scale, the diversity of chemistry that the complex can undergo (chapter 4.1.2), and the use of relatively cheap and benign starting materials.

4.1 BACKGROUND

4.1.1 CYCLOBUTADIENEIRON TRICARBONYL[88]

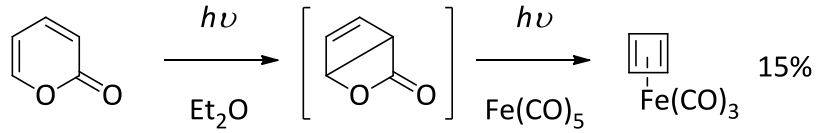
The preparation of cyclobutadieneiron tricarbonyl **151** was first described by Pettit in 1965. This was achieved by exposing *cis*-3,4-dichlorocyclobutene **150** to diiron nonacarbonyl (**Scheme 111**).[89]



150 **151**

Scheme 111

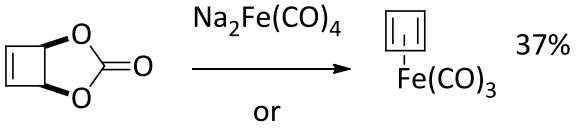
Several other methods have been developed to access cyclobutadieneiron tricarbonyl **151**. Rosenblum utilised photolysis of α-pyrone **152** to give photoproduct **153** which, following the addition of iron pentacarbonyl gave complex **151**, albeit in a poor 15% yield (**Scheme 112**).[90]



152 **153** **151**

Scheme 112

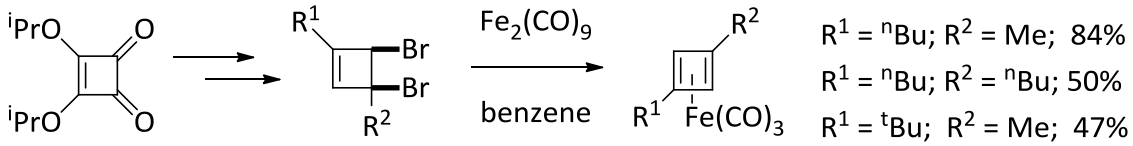
Another common method was developed by Grubbs, where *cis*-3,4-carbonyldioxycyclobutene **154** was treated with either disodium iron tetracarbonyl or diiron nonacarbonyl to give complex **151** in a yield of 37% (**Scheme 113**).[91]



154 **151**

Scheme 113

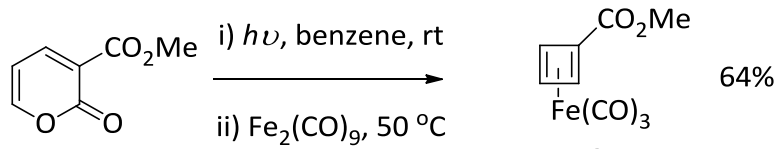
Aside from the parent complex, the above methods have been utilised in the preparation of simple substituted cyclobutadieneiron tricarbonyls. Indeed, Adams prepared a variety of cyclobutenes **156**, in 7 steps from diisopropyl squarate **155**, which underwent complexation with diiron nonacarbonyl to yield cyclobutadieneiron tricarbonyls **157** in moderate to excellent yields (**Scheme 114**).[92]



155 **156** **157**

Scheme 114

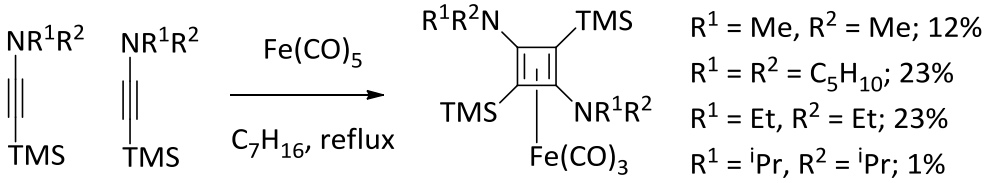
Snapper has utilised the photolysis method to prepare a methyl ester iron complex **159** in a good yield from pyrone **158**. This proved to be a useful handle to further derivatise cyclobutadienes (**Scheme 115**).[93]



158 **159**

Scheme 115

King and Davis prepared highly functionalised iron complex **161** *via* thermal dimerisation of silyl ynamides **160**. Despite the poor yields, numerous amines could be prepared which can lead to further functionalization (**Scheme 116**).[94]



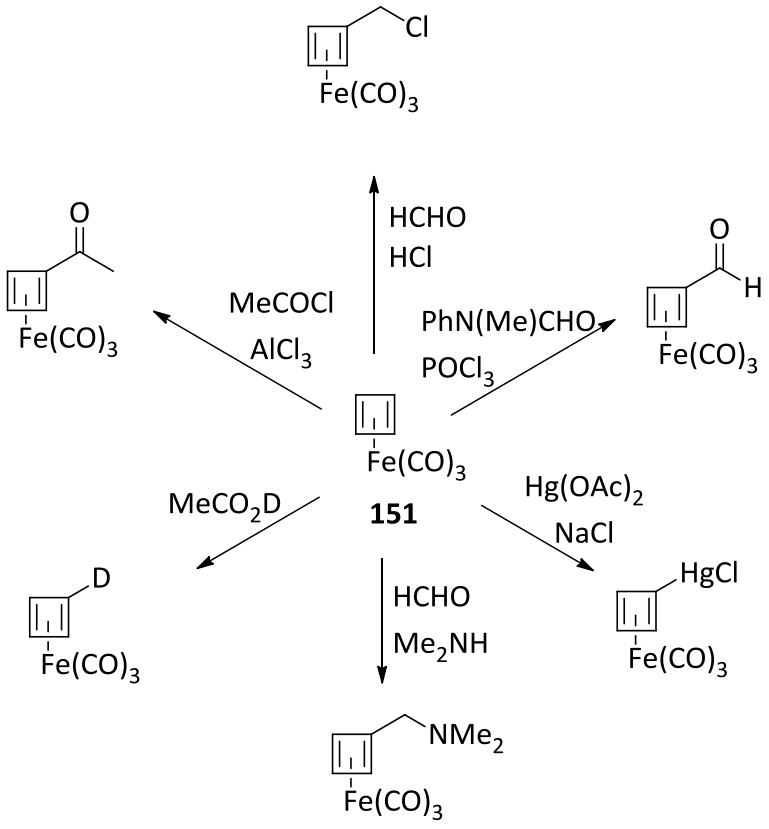
160 **161**

Scheme 116

4.1.2 DERIVATISATION CYCLOBUTADIENEIRON TRICARBONYL

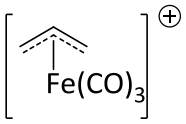
Subsequent to his seminal work on the formation of cyclobutadieneiron tricarbonyl, Pettit showed how the complex behaves like an aromatic system. This is despite the fact that the organic ligand is a cyclic, 4 π electron compound that would otherwise be classified as anti-aromatic. However, X-ray crystallography of cyclobutadieneiron tricarbonyl shows that the cyclobutadiene is not a perfect square. There are two different C-C bond lengths (1.420 Å and 1.430 Å respectively).[95] As such, the cyclobutadiene could be potentially be viewed as two individual double bonds.

Nonetheless, **Scheme 117** highlights the various electrophilic aromatic substitution reactions iron complex **151** can undergo.[96]



Scheme 117

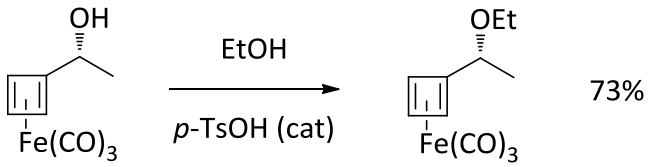
Although no yields or experimental procedures were reported, iron complex **151** was documented to readily undergo Friedel-Crafts, chloromethylation, Vilsmeier-Haack formylation, mercuration, aminomethylation and deuterium exchange. The driving force behind these reactions was proposed to be the formation of a stable π-allyl-iron tricarbonyl cation **162** (**Figure 13**). Indeed, prior to reporting the formation of cyclobutadieneiron tricarbonyl, Pettit prepared examples of iron tricarbonyl allyl-salts.[97]



162

Figure 13

Schmalz has extended the π-allyl-iron tricarbonyl cation to include side chain cation stability.[98] Based on experimental observations, alcohol **163** readily afforded ether **164** in the presence of ethanol and catalytic acid (**Scheme 118**). This substitution proceeded with retention of stereochemistry.



163

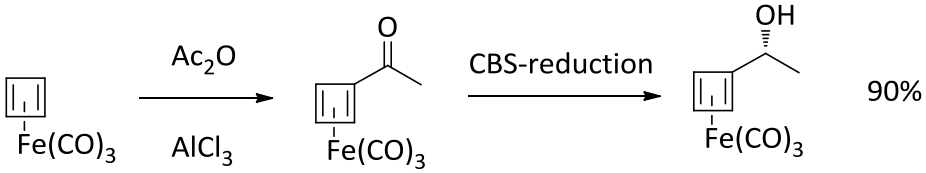
92% *ee*

164

92% *ee*

Scheme 118

Alcohol **163** was prepared from Corey-Bakshi-Shibata reduction of ketone **165**, a result of Friedel-Crafts acylation of cyclobutadieneiron tricarbonyl **151** (**Scheme 119**).



151

165

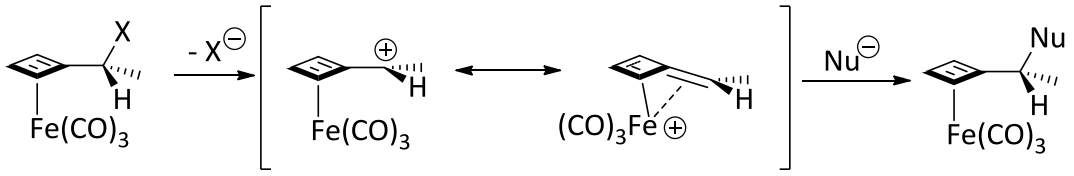
54%

163

92% *ee*

Scheme 119

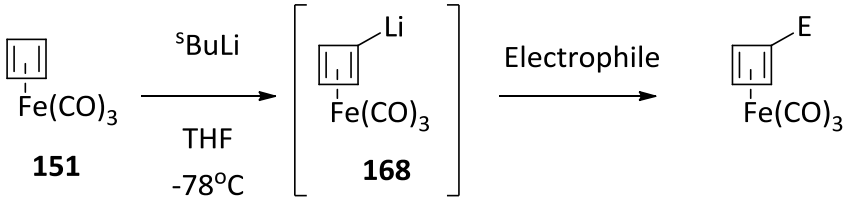
The retention of stereochemistry lead to Schmalz to propose the reaction intermediates as highlighted in **Scheme 120**. Loss of the leaving group X would leave cation intermediate **166**, which is in resonance with **167**. This leaves a π-allyl-iron tricarbonyl cation and an alkene, in coordination with the iron tricarbonyl. Therefore, subsequent nucleophilic attack would result in retention of stereochemistry.



166 **167**

Scheme 120

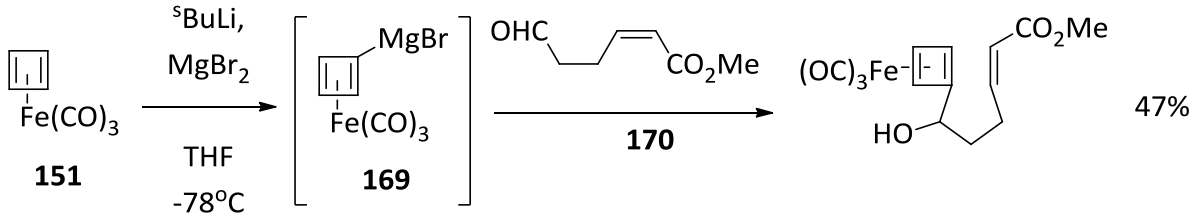
In addition to undergoing electrophilic aromatic substitution, cyclobutadieneiron tricarbonyl can be readily deprotonated with *sec*-butyllithium, forming organolithium complex **168**. Bunz has shown that the lithium species **168** can be quenched with a variety of electrophiles in good yields (**Scheme 121**).[99]



$SiMe_3Cl$	E = $SiMe_3$	59%
ICH_2CH_2I	E = I	67%
SMe_2	E = SMe	61%
$SnMe_3Cl$	E = $SnMe_3$	60%
PPh_2Cl	E = PPh_2	58%
Cl_3CCCl_3	E = Cl	26%
MeI	E = Me	58%

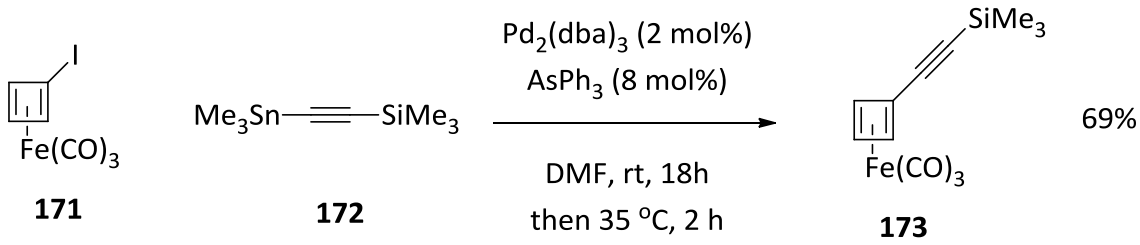
Scheme 121

Snapper has expanded this protocol to include the preparation of organomagnesium complex **169**, which was used for the addition to aldehyde **170** (**Scheme 122**).[100]



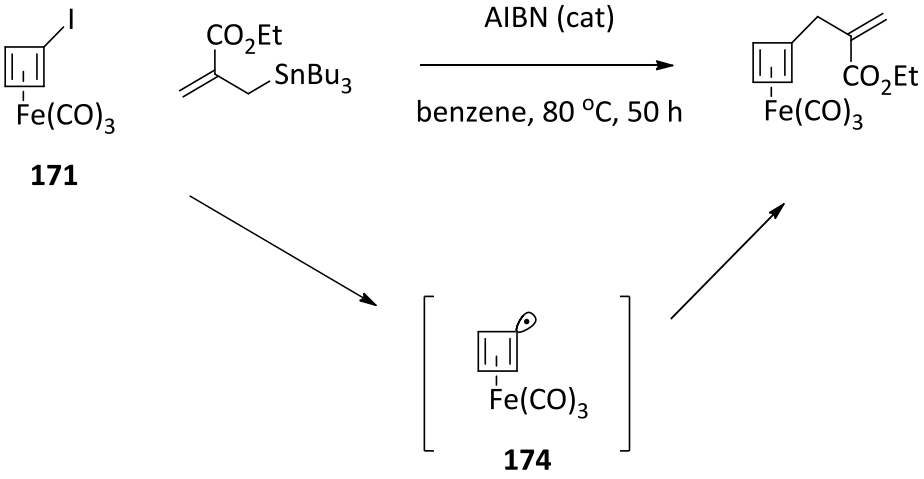
Scheme 122

Bunz has also demonstrated that iodo-cyclobutadieneiron tricarbonyl **171** can readily undergo a palladium catalysed cross coupling reaction with stannane **172** to afford acetylene complex **173** in good yield (**Scheme 123**).[101]



Scheme 123

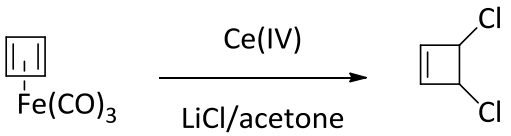
Additionally, stannanes can undergo reaction with iodo complex **171** promoted by a radical initiator.[102] Indeed, in the presence of azobisisobutyronitrile, coupling occurred presumably *via* radical complex **174** (**Scheme 124**).



Scheme 124

4.1.3 CLEAVAGE OF IRON TRICARBONYL

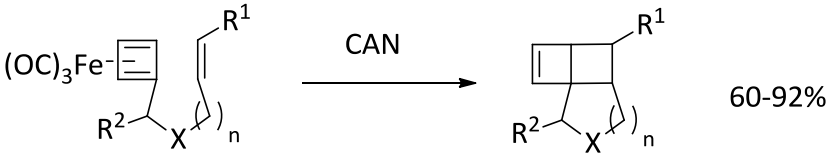
The most common process for the removal of the iron tricarbonyl motif involves oxidative methods. Indeed, in the seminal publication relating to the preparation of cyclobutadieneiron tricarbonyl, Pettit showed that the iron tricarbonyl can be removed in the presence of ceric ammonium nitrate (**Scheme 125**).[89]



151 **150**

Scheme 125

A saturated lithium chloride solution was required to trap cyclobutadiene and to prevent polymerisation. Ceric ammonium nitrate has been used widely for the removal of iron tricarbonyl. Once removed, the resulting reactive cyclobutadiene has been trapped with a variety of alkenes in a [4+2] cycloaddition reaction. Indeed, Snapper has demonstrated that internal alkenes can readily undergo cycloadditions in the preparation of numerous natural products (**Scheme 126**).[103]



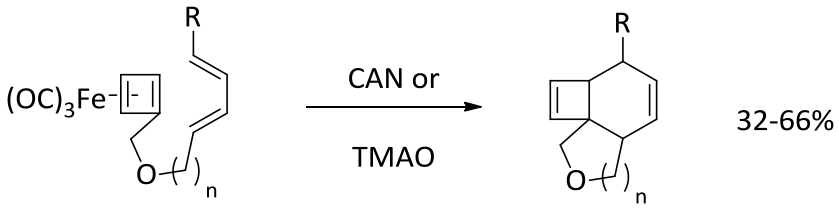
R^2 = H, OR^3

X = CH_2, NTs, O

Scheme 126

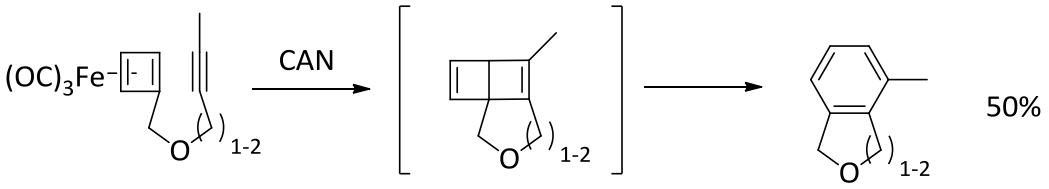
Additionally, trimethylamine *N*-oxide can be used in the removal of the iron tricarbonyl group. Snapper has shown that this proceeds in a similar system to those depicted in **Scheme 126** with 63% yield.[93] Notably, Paquette showed that trimethylamine *N*-oxide can promote [4+2] cycloadditions with external alkenes.[104]

Expanding on the cycloadditions chemistry, Snapper has demonstrated that dienes can also under cycloadditions in a [4+2] fashion where the cyclobutadiene acts as the dienophile. In this way, fused cyclohexenes are generated in the presence of either ceric ammonium nitrate or trimethylamine *N*-oxide.[105] These reactions generally proceed in low yield due to competing cycloadditions whereby cyclobutadiene acts as the diene component (**Scheme 127**).



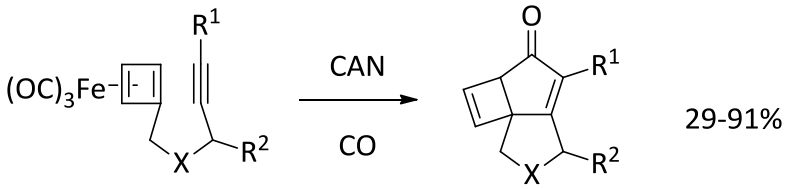
Scheme 127

Aromatic motifs can also be prepared. This is accomplished by [4+2] cycloadditions between cyclobutadiene and tethered alkynes followed by thermolysis. Grubbs prepared two examples in yields of around 50% (**Scheme 128**).[106]



Scheme 128

However, if the oxidation/thermolysis is performed in the presence of carbon monoxide, a formal [2+2+1] reaction takes place to provide cyclopentenones. Snapper has prepared several examples highlighted in **Scheme 129**.[107]



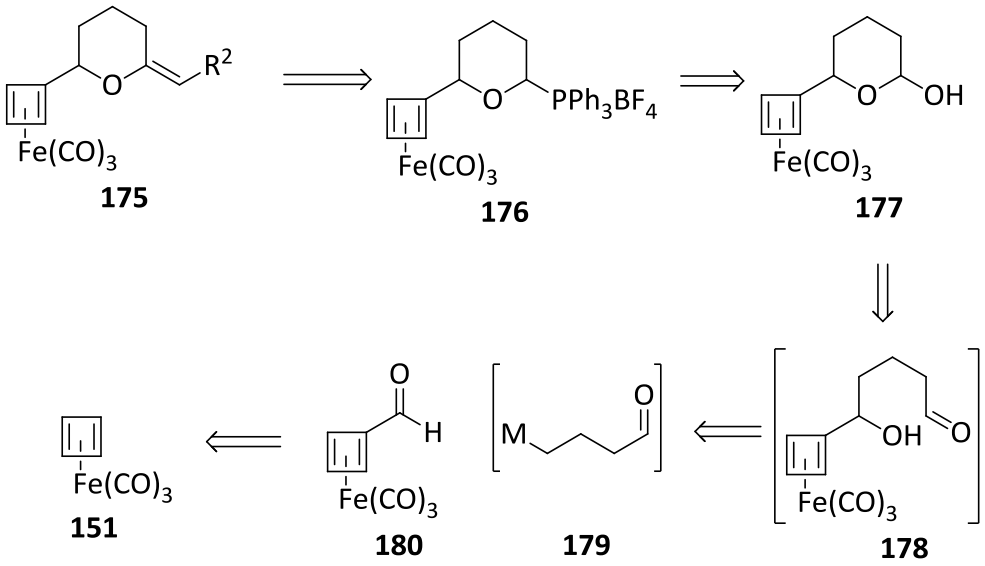
X = O, CMe_2, NTs

R^2 = H, OR^3

Scheme 129

4.2 PREPARATION OF ENOL ETHER IRON COMPLEX

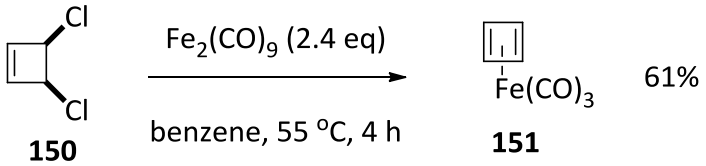
We hoped to exploit the rich chemistry of the cyclobutadiene iron complexes to expand the scope of our metal promoted rearrangement chemistry. We envisaged that the desired enol ether substrates **175** could be prepared *via* an appropriate phosphonium salt in an identical fashion to the palladium chemistry. **Scheme 130** highlights the route sought to achieve this.



Scheme 130

The phosphonium salt **176** would be installed using chemistry already described (**Scheme 77**, page 57) from lactol **177**. This can be accessed from the intermediate **178**, from addition to aldehyde **180** with a protected aldehyde organometallic **179**. Aldehyde **180** can be prepared using known chemistry from parent iron complex **151**.

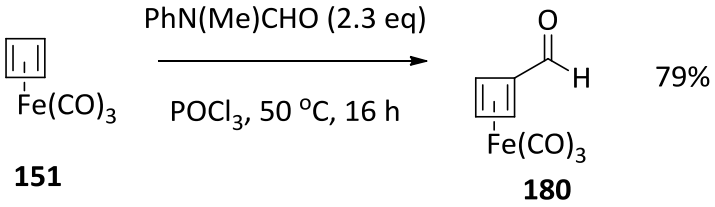
Cyclobutadieneiron tricarbonyl **151** can be prepared on a large scale in accordance to the procedure developed by Pettit.[89,108] In the event, complexation of iron to cyclobutadiene occurred smoothly in a useful 61% yield (**Scheme 131**).



Scheme 131

Complex **151** was stable enough to be purified *via* Kugelrohr distillation under vacuum and not exceeding 100 ^{o}C. This had to be performed carefully to avoid contamination with triiron dodecacarbonyl. However, iron carbonyl impurities could be readily removed if necessary *via* silica gel chromatography with no significant decomposition. Complex **151** could be stored in the freezer under nitrogen without degradation for a significant period of time.

With iron complex **151** in hand, addition turned to the formation of aldehyde **180**. This was to be accomplished *via* a Vilsmeier-Haack formylation. Attempts to achieve this using *N*,*N*-dimethylformamide proved fruitless, with starting material returned in all cases. Pleasingly, utilising *N*-methylformanilide in excess phosphorus oxychloride gave the desired aldehyde in a 79% yield (**Scheme 132**).[109]

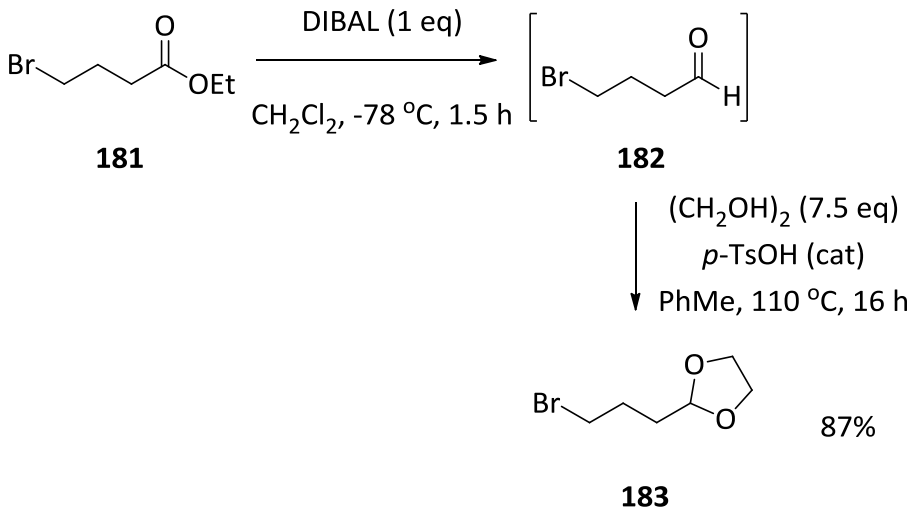


Scheme 132

Like the parent complex, aldehyde **180** was stable to silica gel chromatography and prolonged freezer storage.

Installation of the methylene backbone of the pyran can be achieved utilizing acetal **183**. This was prepared on a 16 gram scale starting with ethyl 4-bromobutanoate using a known procedure (**Scheme 133**).[110]

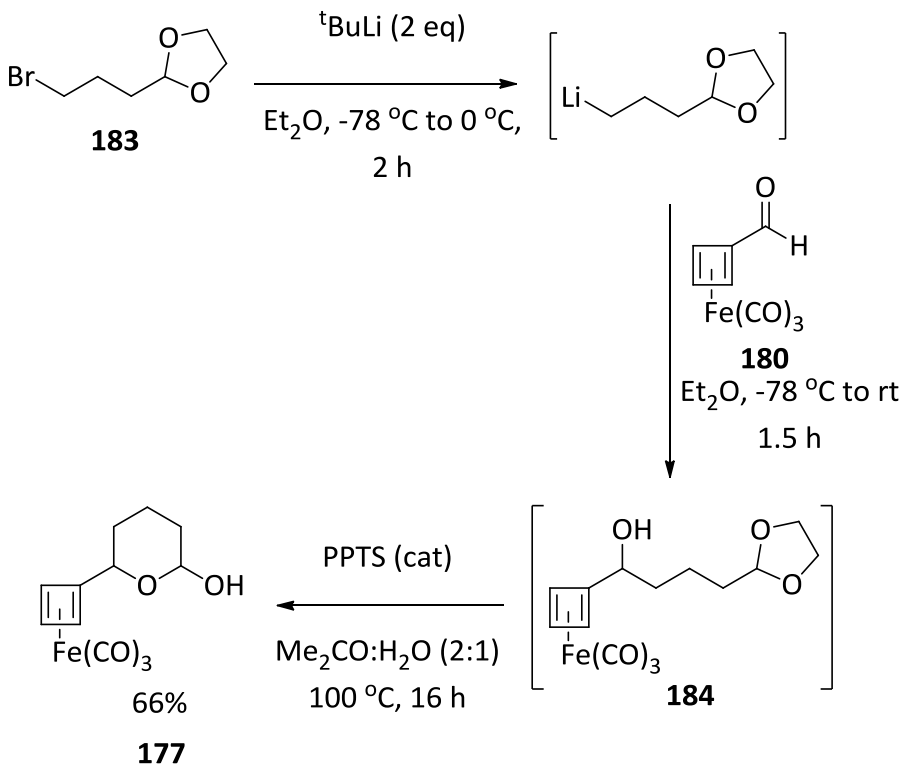
Ester **181** was reduced with diisobutylaluminium hydride at low temperature to give aldehyde **182**. The crude aldehyde was subsequently protected with ethylene glycol performed under Dean-Stark conditions to give acetal **183** in an excellent 87% yield over 2 steps.



Scheme 133

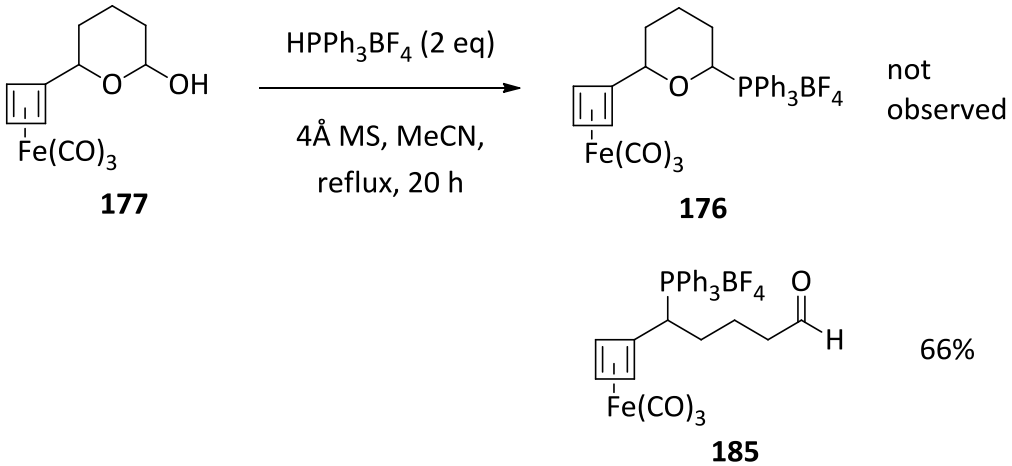
Several organometallic reagents derived from acetal **183** were prepared, namely organozinc, magnesium and lithium, and reacted with aldehyde **180**. Using zinc, with the aid of a Lewis acid resulted in a complex mixture of unidentifiable products. Generating the Grignard reagent prior to addition of aldehyde **180** gave the desired alcohol **184** in a moderate yield of 62%. However, this product was difficult to purify and was contaminated with a diacetal complex, a result of homo-Wurtz coupling with compound **183**.

Pleasingly, utilising the organolithium reagent, derived from *tert*-butyllithium, smoothly gave alcohol **184**. Due to the instability of this alcohol, the crude reaction mixture was taken on to the subsequent cyclisation step. Refluxing in an acetone/water mixture in the presence of acid gave lactol **177** in 66% yield over 2 steps (**Scheme 134**).[103(b)]



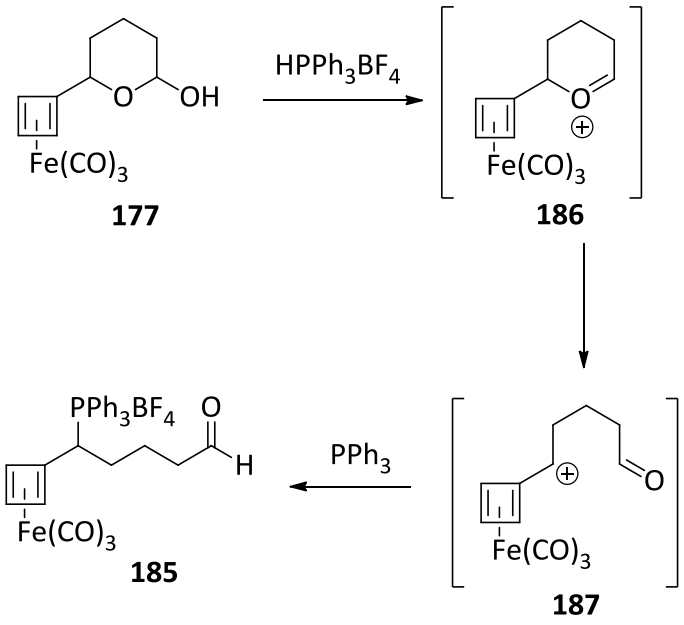
Scheme 134

Subjecting lactol **177** to the standard phosphonium salt forming conditions (**Scheme 77**, page 57) appeared to progress well, providing a solid with an overall yield of 70%. Unfortunately, the desired phosphonium salt **176** was not isolated. What was isolated however was aldehyde **185** (**Scheme 135**).



Scheme 135

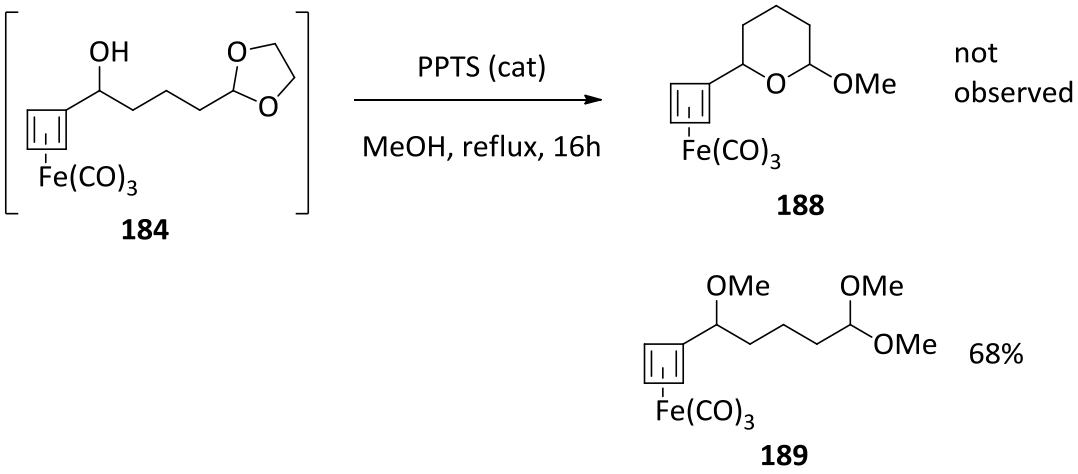
A plausible mechanism for the formation of aldehyde **185** is outlined in **Scheme 136**. The formed oxocarbenium **186** can break open to give an aldehyde and a cation **187** stabilised by the cyclobutadieneiron motif. This cation was quenched with triphenylphosphine to give phosphonium salt **185**.



Scheme 136

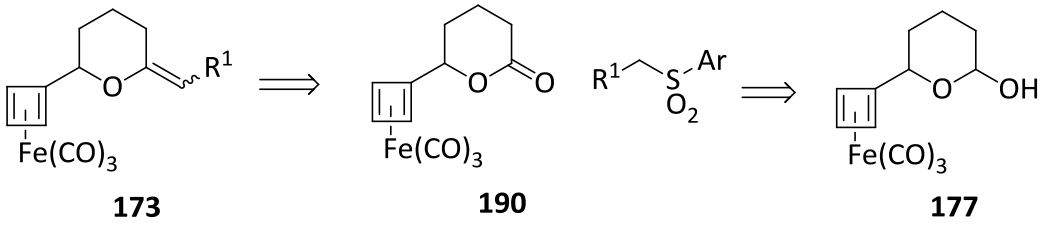
Despite this set back, the potential presence of an iron stabilised cation gave promise that the proposed O→C chemistry is viable. In one further attempt to form phosphonium salt **176**, it was sought to form acetal **188**. This acetal is known to form phosphonium salts (**Scheme 52**, page 35). Unfortunately, acetal **188** was not formed (**Scheme 137**).

Formation of acetal **189** presumably proceeds *via* a similar route to that in **Scheme 136**. Again, this gave further proof of the formation of a stabilised cation and further impetus that O→C chemistry would work.



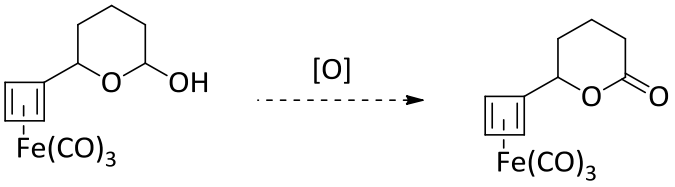
Scheme 137

Despite the setback, another route to the desired enol ether substrates was next examined. Installation of the double bond could be achieved *via* a Julia olefination. To achieve this, lactone **190** would be required, possibly accessible *via* oxidation of lactol **177** (**Scheme 138**).



Scheme 138

In the event however, although several methods were attempted to perform this oxidation, in all cases, no lactone **190** was observed (**Table 18**). Starting material was returned in all cases. It should be noted that only mild conditions were used for the oxidations as it has been shown that manganese(IV) oxide and pyridinium chlorochromate can remove the iron tricarbonyl group in diene systems.[111,112] It was feared that using harsh oxidising conditions could lead to oxidative cleavage of the iron tricarbonyl.

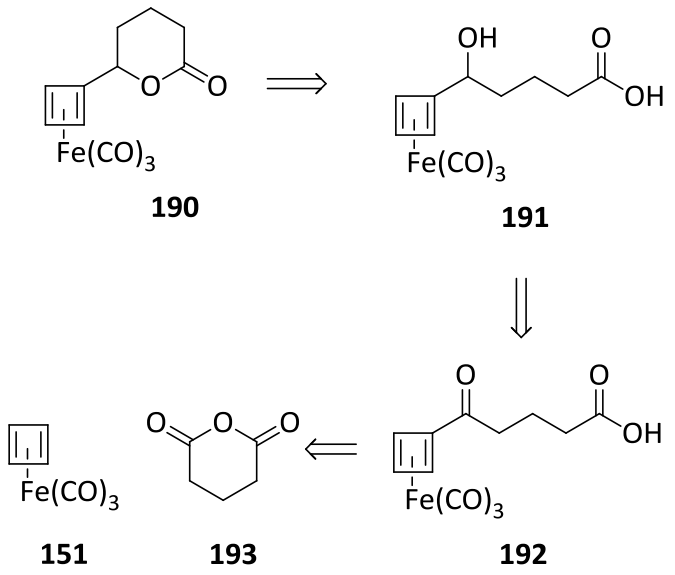


177 **190**

Entry	[O]	Yield / %	Comment
1	MnO_2	0	Starting Material Returned
2	PDC	0	Starting Material Returned
3	Ag_2CO_3/Celite®	0	Starting Material Returned
4	DMSO/$COCl_2$/NEt_3	0	Starting Material Returned
5	PCC	0	Starting Material Returned

Table 18

In light of these results, an alternative route to lactone **190** was sought. We envisaged that this compound could be accessed in a similar manner to before, but employing a carboxylic acid (**Scheme 139**).

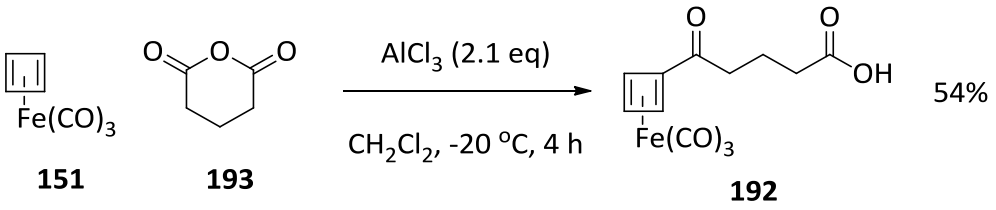


190 **191** **192** **193** **151**

Scheme 139

As discussed in chapter 4.1.2, the parent cyclobutadieneiron tricarbonyl complex can undergo Friedel-Crafts acylation with acid anhydrides.[98] We therefore hoped that by using glutaric anhydride (**193**) followed by reduction we could access alcohol **191**.

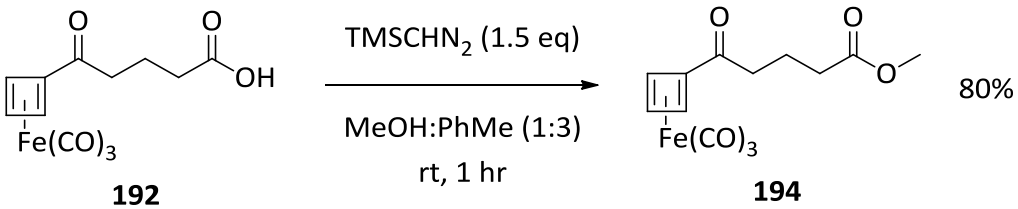
In the event, the Friedel-Crafts reacton between cyclobutadieneiron tricarbonyl and glutaric anhydride occurred smoothly in the presence of aluminium trichloride (**Scheme 140**).



Scheme 140

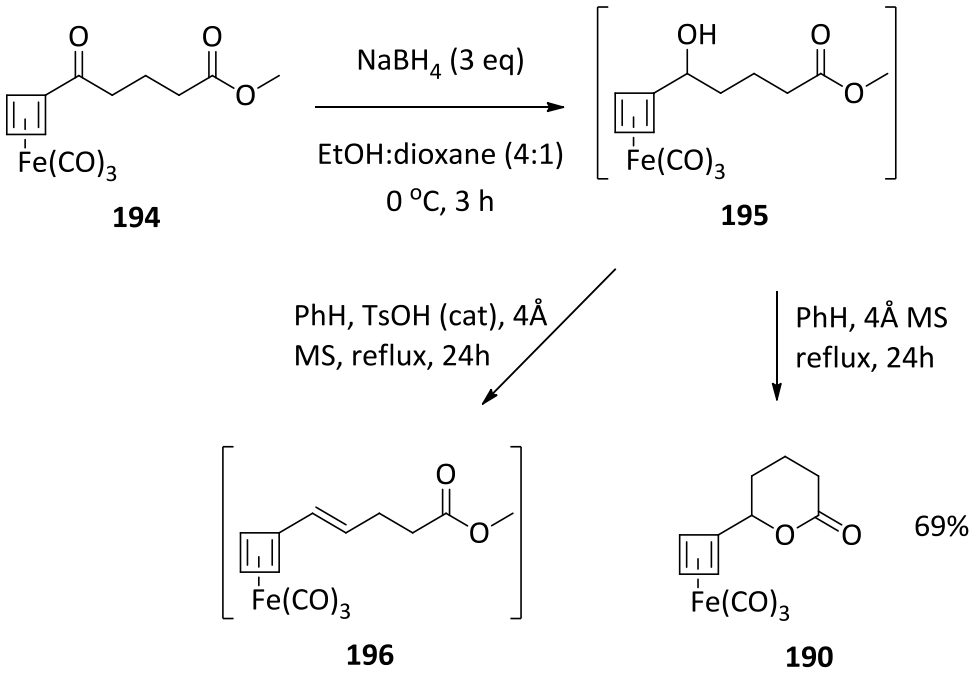
Although acid **192** was prepared in a reasonable yield, there were issues with isolation. Firstly, removal of the aluminium salts upon quenching with water proved extremely troublesome. This was ultimately achieved by extracting the reaction mixture with sodium hydrogen carbonate solution. Acidification followed by further extraction gave the crude acid **192**. This acid was extremely difficult to handle and streaked during purification by silica gel chromatography, even after buffering with acetic acid.

In view of this, the crude acid **192** was transformed to the ester **194** using (trimethylsilyl)diazomethane (**Scheme 141**). This readily improved handling and purification.



Scheme 141

Reduction of the carbonyl with excess sodium borohydride also occurred smoothly. However, this material was unstable to chromatography and so was subjected to cyclisation conditions as the crude mixture. Unfortunately, lactone **190** formation proved difficult (**Scheme 142**).

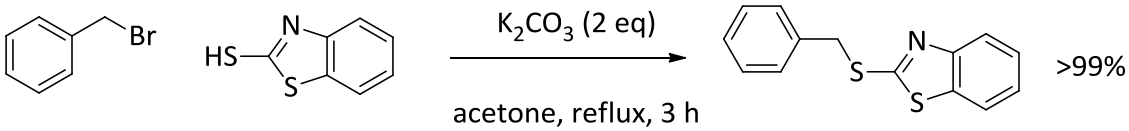


Scheme 142

Refluxing alcohol **195** in the presence of catalytic acid failed to furnish lactone **190**. Instead, what was presumed to be alkene **196** was observed by crude NMR spectroscopy. This could potentially have formed *via* the loss of water leaving a stabilised cation. Pleasingly, refluxing in the absence of acid cleanly gave lactone **190** in a 69% yield over 2 steps.

With lactone **190** in hand, attention turned to forming the necessary sulfones to explore the Julia olefination.[113]

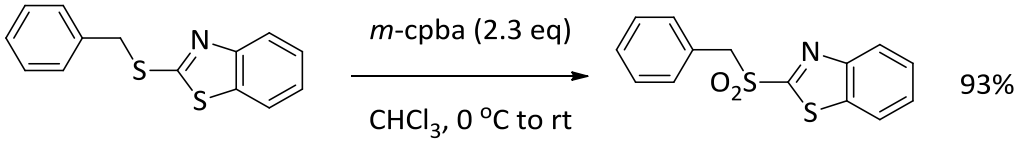
To trial this chemistry, only one sulfone was prepared. This was one that could be readily prepared on large scale. Using a known procedure, commercially available 2-mercaptobenzothiazole **197** was alkylated with benzyl bromide to give sulfide **198** in quantitative yield (**Scheme 143**).[114]



197 **198**

Scheme 143

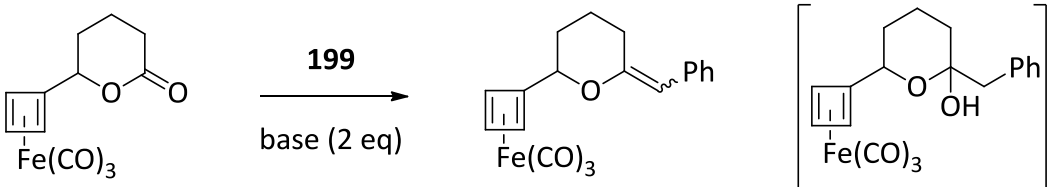
Numerous methods are reported for the oxidation of sulfides to sulfones. In the event, *m*-chloroperbenzoic acid readily performed the oxidation in excellent yield and sulfone **199** was isolated without the need for chromatography (**Scheme 144**).[115]



198 **199**

Scheme 144

Unfortunately however, attempts to perform Julia olefinations with lactone **190** and sulfone **199** to give enol ether **200** proved fruitless. Results of this study are highlighted in **Table 19**.



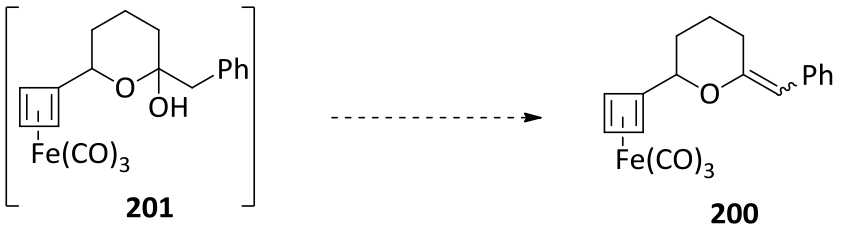
190 **200** **201**

Entry	Base	Comment	Outcome
1	LiHMDS	One Pot	Return of Starting Materials
2	LiHMDS	Sulfone/base premix	Return of Starting Materials
3	^{n}BuLi	One Pot	Observation of **201**

Table 19

The use of lithium bis(trimethylsilyl)amide failed to promote a reaction. Starting lactone was isolated in both cases, even pre-treatment of sulfone **199** with lithium bis(trimethylsilyl)amide (which resulted in a colour change of colourless to orange) failed. Switching to a more powerful base, *n*-butyllithium looked promising as no lactone or sulfone was recovered. Unfortunately, hemi-acetal **201** was isolated rather than enol ether **200**.

Attempts to dehydrate hemi-acetal **201** to enol ether **200** using several conditions are highlighted in **Scheme 145**.



A: DBU/NaOH rt: Starting Material
Δ: Decomposition

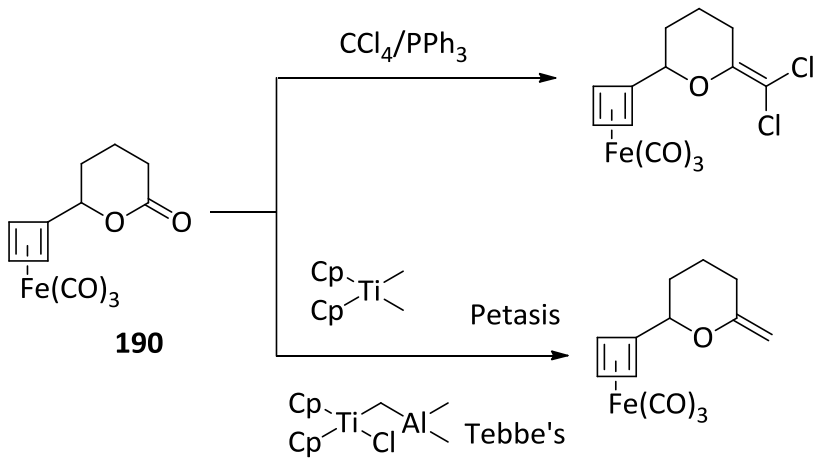
B: TsOH/MS rt: Starting Material
Δ: Decomposition

C: H_2SO_4 rt: Starting Material
Δ: Decomposition

Scheme 145

Utilising acid, base or molecular sieves to promote dehydration did not give enol ether **200**. Under room temperature conditions, starting material was returned; whereas with heating, decomposition occurred. It is possible that the enol ether was formed in all cases, but is extremely sensitive to the reaction conditions.

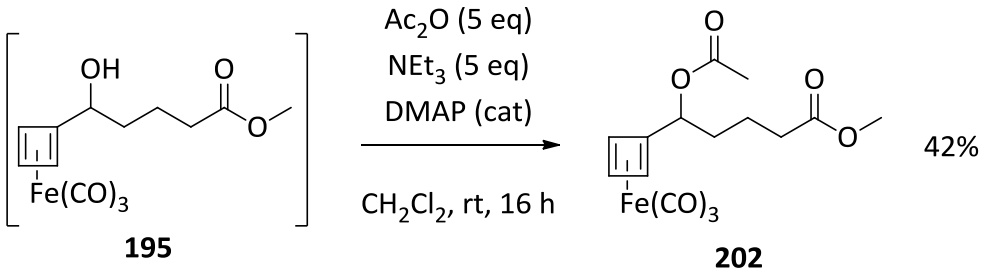
As access to substituted enol ethers *via* Wittig and Julia olefinations had proved fruitless thus far, attention turned to accessing the enol ether core by mild methods of olefination of lactone **190**. Three methods were envisaged to achieve this, using known procedures for olefination of lactones.[48,116,117] These included using a carbon tetrachloride/triphenylphosphine protocol previously employed within the group, as well as utilising Petasis and Tebbe's reagents (**Scheme 146**).



Scheme 146

Unfortunately in all cases, none of the desired enol ether was produced when each of these transformations was attempted. In the case of the carbon tetrachloride/triphenylphosphine conditions, only what appeared to be alkene **196** was observed. Using freshly prepared Petasis reagent, from titanocene dichloride and methylmagnesium bromide,[118] failed to promote a reaction; lactone **190** was isolated with >90% recovery. Employing commercially available Tebbe's reagent led to complete decomposition of starting material and/or products.

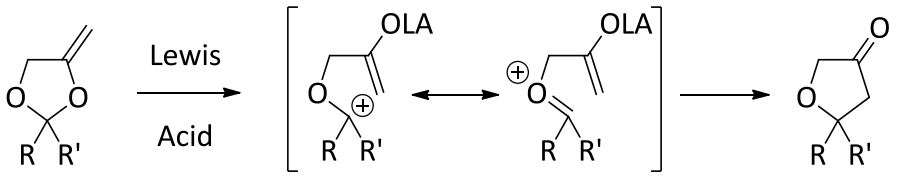
In a final attempt, a non-cyclic enol ether complex was targeted as it was felt that this substrate would be easier to access and would allow confirmation of the proposed O→C rearrangement. To achieve this, crude alcohol **195** was acylated with acetic anhydride to give acetate **202** (**Scheme 147**).



Scheme 147

Unfortunately, attempts to form the corresponding enol ether using Petasis and Tebbe's reagents led to total decomposition. This further highlights the potential instability of enol ether substrate bearing an iron tricarbonyl mofit.

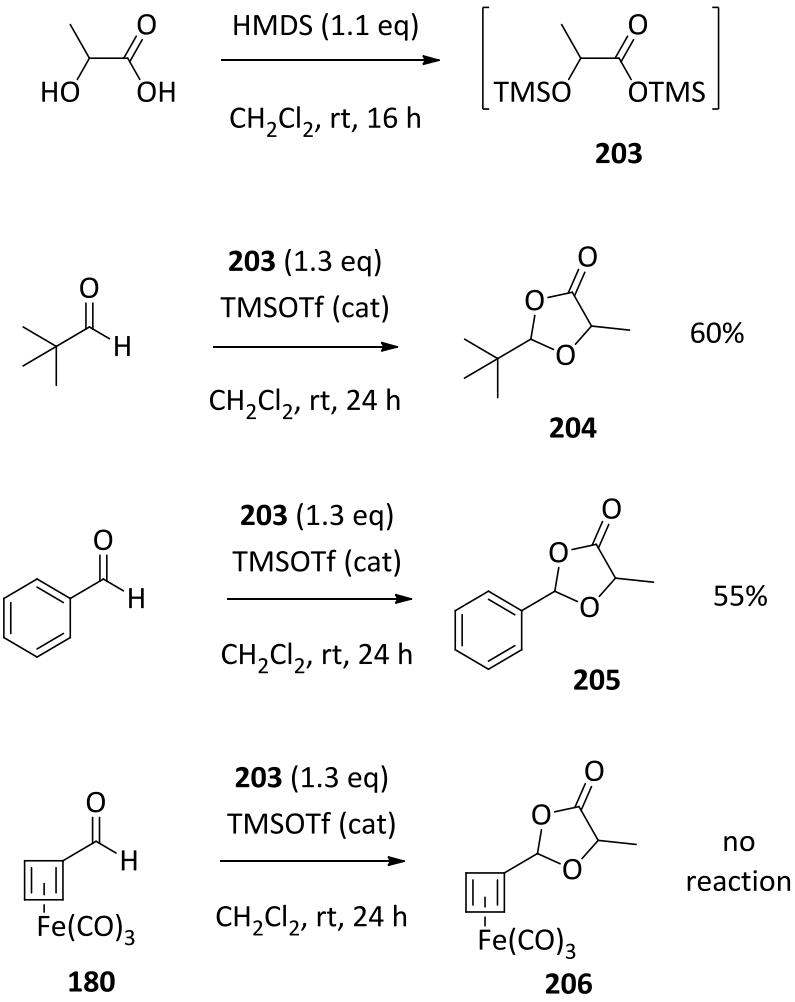
With the goal of designing substrates that could more easily incorporate the iron-diene complex, a new strategy was sought in which an O→C rearrangement would take place with a further stabilisation from an adjacent heteroatom. Inspiration for this comes from work by Scharf where methylene dioxolanes were found to undergo rearrangement in the presence of acid catalysis (**Scheme 148**).[119]



Scheme 148

Preparation of the desired methylene dioxolane would be derived from the necessary dioxolanone. These dioxolanones were prepared *via* a known condensation reaction between an aldehyde and a α-hydroxy acid.[120] To test the suitability of this chemistry, trial runs were performed on known substrates before using aldehyde **180** (**Scheme 149**).

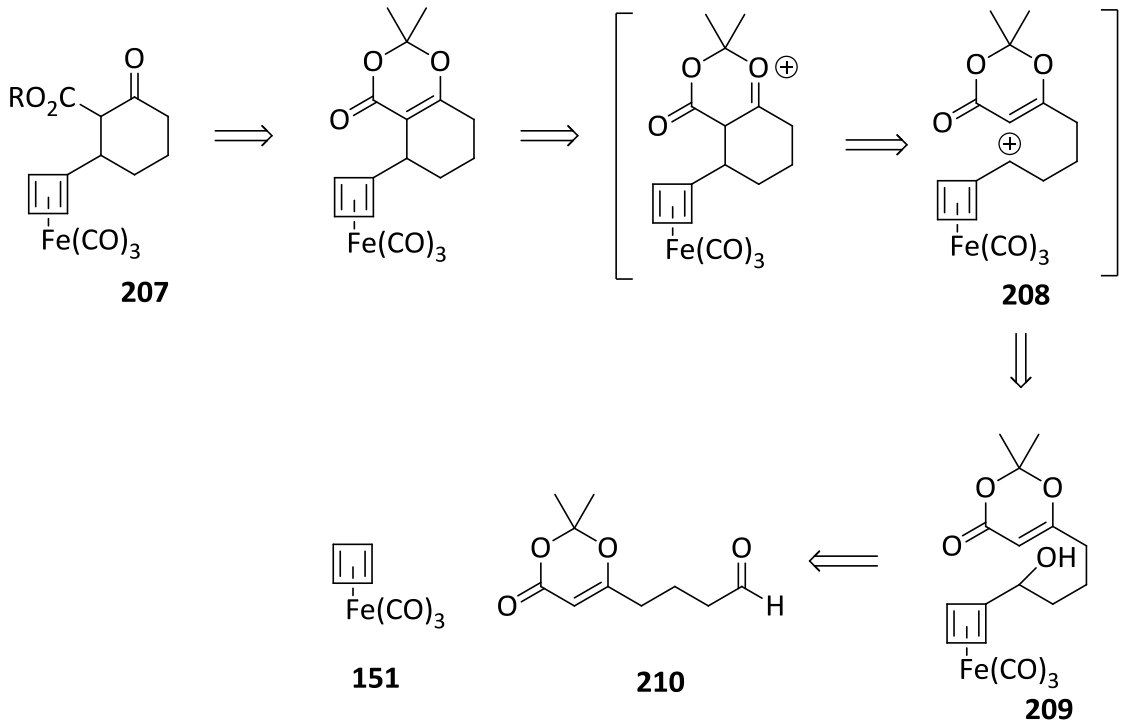
Attempts to prepare dioxolanones direct from the lactic acid failed. However, using the bis-trimethylsilyl protected lactic acid **203** gave promising results.[121] Purification of **203** proved troublesome, however, when used crude in the condensation reaction with simple aldehydes, reactions were found to be successful. In the event, pivalaldehyde and benzaldehyde formed dioxolanones **204** and **205** with 60 and 55% yield respectively. Unfortunately, using aldehyde **180** with the same batch of **203** failed to provide dioxolanone **206** after several attempts; starting aldehyde was returned in all cases.



Scheme 149

Finally, an alternative route to provide functionalised cyclohexanones taking advantage of the stabilised cation chemistry was sought. To this end, the route presented in **Scheme 150** was explored.

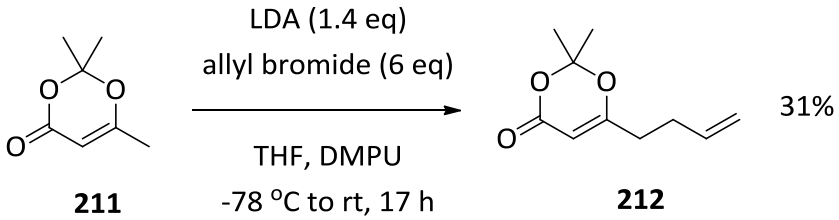
The key to formation of functionalised cyclohexanones **207** is the creation of cation complex **208**. Schmalz (see chapter 4.1.2, page 88) has shown that alcohols adjacent to the iron tricarbonyl complex, such as in **209**, can give access to the required cation **208**.[98] These intermediate can be trapped with a variety of nucleophiles, in our case, we hoped to exploit an enol ether.



Scheme 150

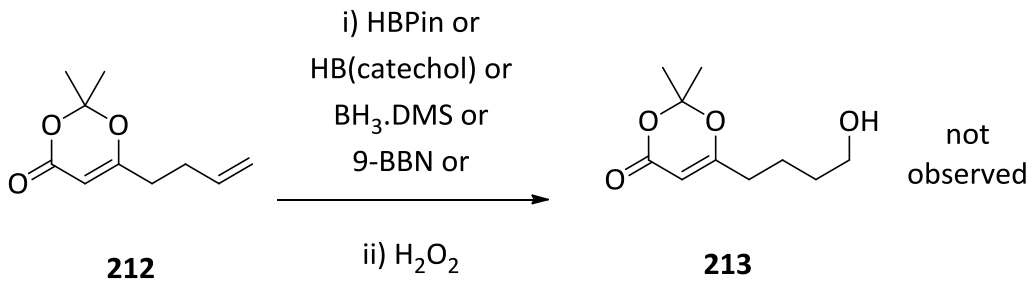
A significant component of this route was gaining access to aldehyde **210**. In this respect, it has been shown that dioxinone **211** can undergo conjugate addition and alkylation *via* the extended enolate.[122,123] The route of choice involved alkylation with allyl bromide followed by hydroboration/oxidation and a further oxidation stage.

In the event, alkylation of dioxinone **211** proved to be extremely poor yielding. After several attempts, 31% was the highest yield recorded using excess allyl bromide (**Scheme 151**).



Scheme 151

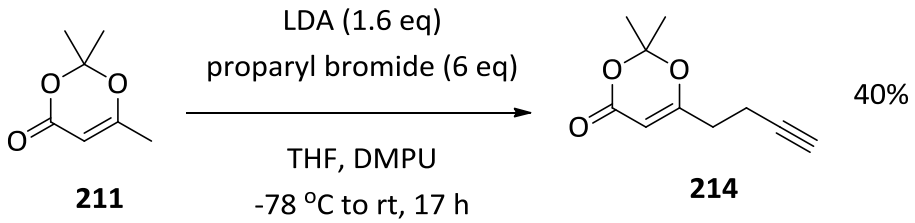
Unfortunately, hydroboration of alkene **212** proved to be rather troublesome. After utilising several borane species, as highlighted in **Scheme 152**, none of the desired alcohol **213** was observed. Despite the observation of complete consumption of alkene **212** by TLC analysis, it was isolated after workup in greater than 80% recovery in all cases.



212 **213**

Scheme 152

We next decided to access aldehyde **210** without proceeding *via* alcohol **213**. The initial approach to achieve this used propargyl bromide in place of allyl bromide, followed by hydroboration/oxidation. Using identical conditions to those in **Scheme 151**, alkylation of dioxinone **211** proceeded in a similar yield of 40% (**Scheme 153**).

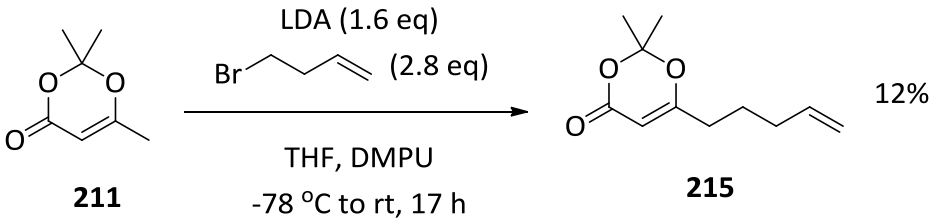


211 **214**

Scheme 153

Unfortunately, hydroboration/oxidation again failed. Using the same reagents as shown in **Scheme 152** only led to the recovery of alkyne **214**. This is despite conducting control reactions that confirmed that the borane reagents would undergo successful hydroboration/oxidation on simple linear alkenes and alkynes.

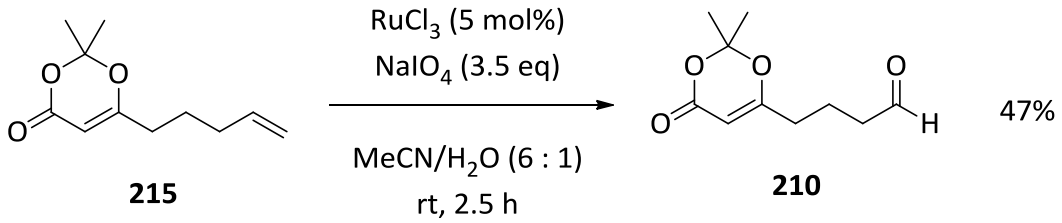
In a final attempt to access aldehyde **210**, an oxidative cleavage protocol was used. To achieve this, 4-bromo-1-butene was used in the alkylation, under identical conditions to those previously presented (**Scheme 154**).



211 **215**

Scheme 154

Although isolated in a poor yield, alkene **215** was successful oxidised to aldehyde **210** in moderate yield using the ruthenium(III) chloride/sodium periodate protocol (**Scheme 155**).

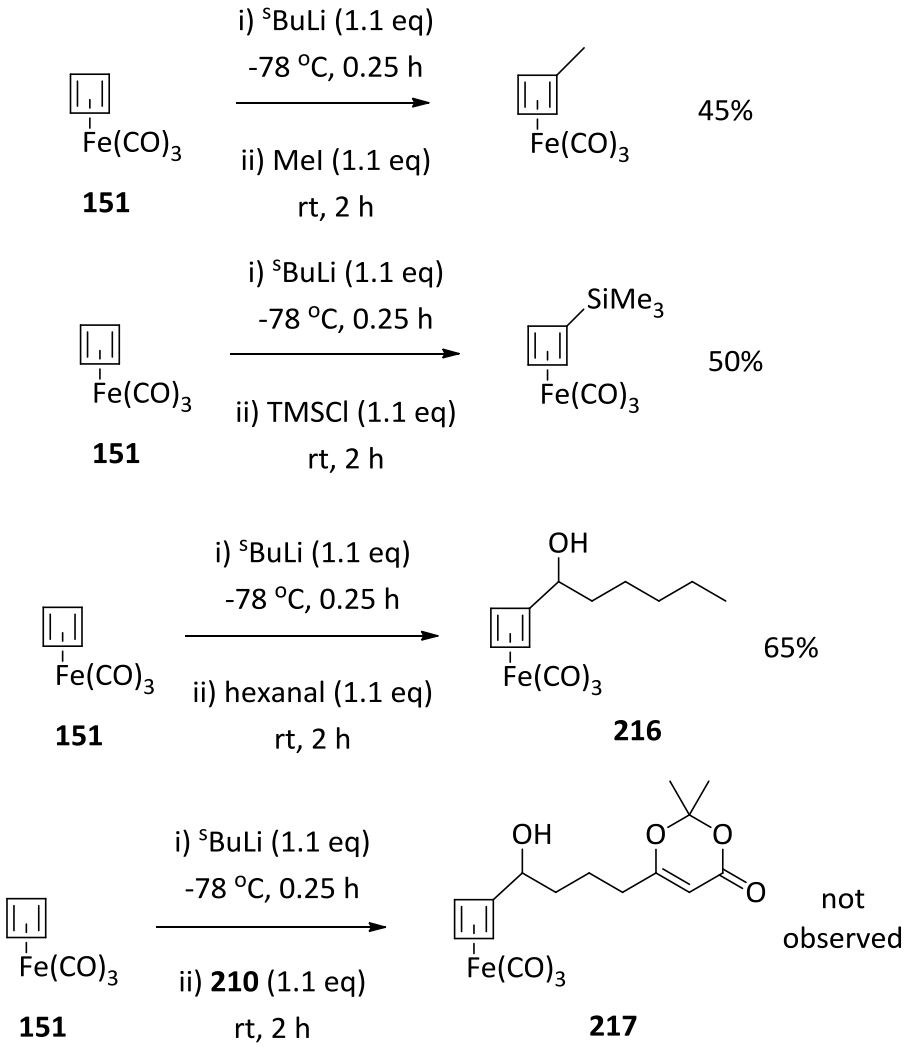


215 **210**

Scheme 155

With aldehyde **210** in hand, attention turned to the alkylation of the cyclobutadieneiron tricarbonyl complex **151**. It has been shown by Bunz, that the iron complex **151** can undergo deprotonation with *sec*-butyllithium.[99] The resulting organolithium can then react with a variety of electrophiles (chapter 4.1.2). Literature chemistry was repeated beforehand to ensure reproducibility.

In the event, iron complex **151** was successfully deprotonated with *sec*-butyllithium and trapped with methyl iodide and chlorotrimethylsilane with yields of 45% and 50% respectively (**Scheme 156**). Additionally, hexanal was effectively reacted to give **216** in a good yield of 65%; this was performed in an attempt to mimic the chemistry of aldehyde **210**. Unfortunately, aldehyde **210** did not undergo addition with the iron complex **151**. After two attempts, none of the desired product **217** was observed and only the iron complex **151** was isolated. Aldehyde **210** was not recovered in both cases, presumably this decomposed under the reaction conditions.



Scheme 156

4.3 CONCLUSIONS AND FUTURE WORK

The development of a Lewis acid mediated rearrangement utilising the cation stabilising effects of iron tricarbonyl has thus far proved fruitless. Although late stage intermediates were prepared, the synthesis of key intermediates was unsuccessful. This is presumably due to the instability of these intermediates. Specifically the preparation of enol ether substrates failed in part due to the requirement to prepare them in media to which they were susceptible to decomposition.

All steps in the preparation of the intermediates required substantial effort to improve yield and aid isolation due to the sensitive nature of handling the iron complex, especially in case where the stabilised cation could be formed (*e.g.* in preparation of the phosphonium salts). Despite these draw backs, the potential presence for the desired stabilised cation gave impetus to pursue chemistry to take advantage of this.

In spite of these failures, development of a rearrangement protocol still remains a possibility. This would require a different route to prepare the desired substrates. As complexes involving the iron tricarbonyl motif are unstable, the installation of the cyclobutadieneiron tricarbonyl should occur as late as possible in the synthesis. This should improve handling of intermediates and reduce potential side reactions occurring due to the presence of the iron moiety.

5 EXPERIMENTAL

5.1 GENERAL CONSIDERATIONS

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of dry nitrogen. Flash chromatography was performed on silica gel (Davisil). Thin layer chromatography was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) which were developed using standard visualizing agents: Ultra Violet light or potassium permanganate.

^{1}H NMR spectra were recorded on a Bruker AC-250 (250 MHz) or AMX-400 (400 MHz) or AV1-250 instruments or AMX-400 or AV1-400 instruments supported by an Aspect 3000 data system, unless otherwise stated. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) in Hz, and assignment.

^{13}C NMR spectra were recorded on a Bruker AC-250 (63 MHz) or AMX-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ77.0 ppm).

Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, υ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films from a CH_2Cl_2 solution using sodium chloride plates.

Low resolution mass spectra were recorded on Micromass Autospec, operating in E.I., C.I. or FAB mode; or a Perkin-Elmer Turbomass Benchtop GC-MS operating in either E.I. or C.I mode. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in either FAB (FAB^+), EI (EI^+) or CI (CI^+) mode.

Melting points, performed on recrystallised solids, were recorded on a Gallenkamp melting point apparatus and are uncorrected.

All solvents and reagents were purified using standard laboratory techniques according to methods published in “Purification of Laboratory Chemicals” by Perrin, Armarego, and Perrin (Pergamon Press, 1996), where necessary.

Determination of enantiomeric excess by GC analysis was performed using PerkinElmerArnel Autosystem XL Gas Chromatography with a β-cyclodextrin / permethyl (ASTEC, 30 m) GC column.

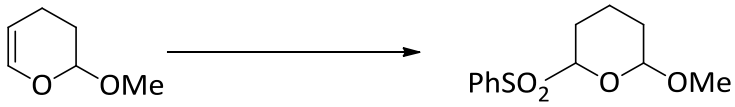
Determination of enantiomeric excess by HPLC analysis was performed using Gilson HPLC with a Phenomenex “Lux 3u Cellulose-1” or “Lux 3u Cellulose-2” column (250 mm x 4.6 mm).

GRUBBS’ SOLVENT SYSTEM

The departmental dry solvent system is a Grubbs type one manufactured by Innovative Technology. In an individual solvent line the untreated solvent is contained within a lined metal reservoir and, using nitrogen gas pressure, forced through a pair of metal columns each containing either activated alumina or molecular sieve. If oxygen removal is also required one of the cylinders contains a catalyst instead. The water and oxygen removal occurs as the solvent passes over the drying agents. The dried solvent is then dispensed to a suitable collection vessel under vacuum *via* a Schlenk line system.

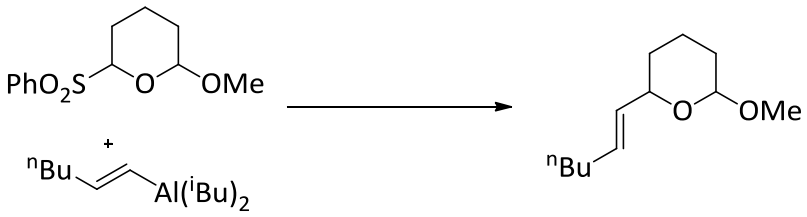
5.2 PREPARATION OF SUBSTRATES

PREPARATION OF 2-(BENZENESULPHONYL)TETRAHYDRO-6-METHOXY-2*H*-PYRAN **99**[55]



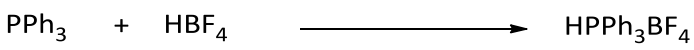
A suspension of sodium benzenesulphinate (40 g, 242.0 mmol) in hydrochloric acid (1 M in water, 300 mL) was stirred for 45 minutes at room temperature. The reaction mixture was extracted with dichloromethane (2 x 250 mL). The combined extracts were washed with brine, dried with magnesium sulfate and concentrated to afford benzene sulphinic acid (31.1 g, 21.9 mmol). The formed benzenesulphinic acid was dissolved in dichloromethane (500 mL). 3,4-Dihydro-2-methoxy-2*H*-pyran **100** (24.8 g, 217.6 mmol) was added and resulting solution stirred for 2 hours at room temperature. The reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over magnesium sulfate, filtered through Celite® and concentrated. The crude residue was purified by flash chromatography on silica gel (70 : 30 petroleum ether/ethyl acetate) to give **99** as a white crystalline solid (39.0 g, 152.3 mmol, 70%) containing a 9 : 1 mixture of diastereoisomers; M.p. = 75-77 ^{o}C (Lit. 77-78 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.90 (2H, m, Ar-*H*), 7.72-7.50 (3H, m, Ar-*H*), 4.75 (0.9H, t, *J* = 2.5 Hz, OC*H*SO_2Ph), 4.65 (0.9H, dd, *J* = 10.5, 2.5 Hz, OC*H*OMe), 4.40 (0.1H, dd, *J* = 10.5, 2.5 Hz, OC*H*SO_2Ph), 4.24 (0.1H, dd, *J* = 9.0, 2.0 Hz, OC*H*OMe), 3.23 (0.3H, s, CH_3), 2.93 (2.7H, s, OCH_3), 2.24-2.07 (1H, m, C*H*), 1.92-1.55 (5H, m, 5 x C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 136.4, 133.9, 129.4, 128.8, 99.8, 84.8, 54.7, 28.7, 22.7, 17.1.

PREPARATION OF (*E*)-2-(HEX-1-ENYL)-6-METHOXYTETRAHYDRO-2H-PYRAN **102**[53]



To a solution of 1-hexyne (5.7 mL, 50.6 mmol) in toluene (50 mL) at 0 °C was added diisobutylaluminium hydride (1 M in toluene, 52.5 mL, 52.5 mmol) dropwise. The resulting solution was stirred at 40 °C for 2 hours, cooled to -78 °C and a solution of cyclic sulphone **99** (10 g, 39.0 mmol) in dichloromethane (15 mL) was added *via* cannula. The resulting solution was stirred at -78 °C for 2 hours, then at room temperature for a further 16 hours. The reaction was quenched with water (50 mL), filtered through Celite® and washed with ethyl acetate and the filtrate was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (92 : 2 petroleum ether/ethyl acetate) to give **102** as a yellow oil (6.3 g, 31.8 mmol, 81%) as a 4 : 1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (1H, dtd, *J* = 15.0, 6.5, 1.0 Hz, CH_2-alkene-*H*), 5.54-5.40 (0.8H, ddt, *J* = 15.0, 7.0, 1.5 Hz, CH-alkene-*H* and 0.2H, m, CH-alkene-*H*), 4.73 (0.8H, m, OC*H*OMe), 4.34 (0.2H, d, *J* = 9.0, 2.0 Hz, OC*H*OMe), 4.17-4.08 (0.8H, m, pyran-OC*H*), 3.88-3.82 (0.2H, m, pyran-OC*H*), 3.49 (0.6H, s, OCH_3), 3.37 (2.4H, s, OCH_3), 2.08-1.97 (2H, m, CH_2), 1.91-1.24 (10H, m, 5 x CH_2), 0.88 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 132.5, 130.9, 98.6, 69.4, 54.5, 32.0, 31.4, 31.2, 29.4, 22.3, 18.0, 14.0; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 2933 (s), 2873 (s), 1458 (m), 1439 (m), 1195 (m), 1125 (s), 1062 (s), 1022 (s), 968 (m), 948 (s); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{12}H_{22}O_2$: 198.1620, found 198.1624.

SYNTHESIS OF HYDROGENTRIPHENYLPHOSPHONIUM TETRAFLUORBORATE[124]

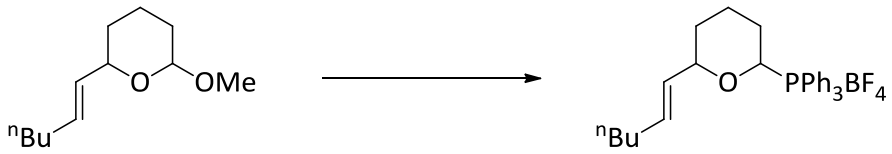


To a solution of triphenylphosphine (38.5 g, 0.145 mol) in toluene (110 mL) was added tetrafluoroboric acid solution (48% in water, 19.8 mL, 0.145 mol). The resulting suspension was stirred at room temperature for 2 hours. The water was azeotropically removed using a Dean-Stark trap. The white suspension was concentrated *in vacuo*. The resulting white solid was dissolved in chloroform (500 mL), dried over magnesium sulfate, concentrated *in vacuo*, washed with hexane/diethyl ether (1 : 1, 300 mL) to give $HPPh_3BF_4$ as a white solid (48 g, 94%); M.p. = 157-159 ^{o}C (Lit. 160-164 ^{o}C); ^{1}H NMR (250 MHz, $CDCl_3$): δ7.80-7.54 (15H, m, Ar-*H*); ^{31}P NMR (63 MHz, $CDCl_3$): δ2.6.

PREPARATION OF A KHMDS SOLUTION IN THF[125]

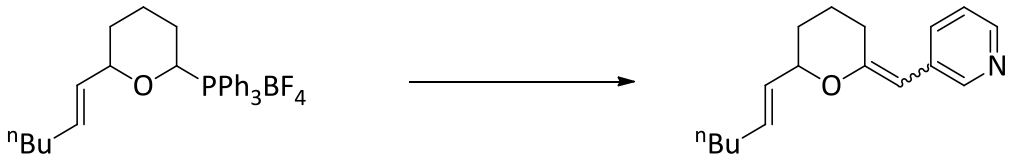
To a suspension of potassium hydride (washed with tetrahydrofuran, 300 mg, 7.48 mmol) in tetrahydrofuran (6.0 mL) was added dropwise freshly distilled hexamethyldisilazane (1.00 mL, 4.79 mmol) at room temperature. The suspension was stirred for 1 hour at room temperature. After this time, the solution was stored at -20 °C under inert atmosphere and was left to settle for 12 hours before use. The molarity was assumed at 0.68 M, based on the quantity of hexamethyldisilazane used.

PREPARATION OF (*E*)-(6-(HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-YL)TRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE **103**[53]



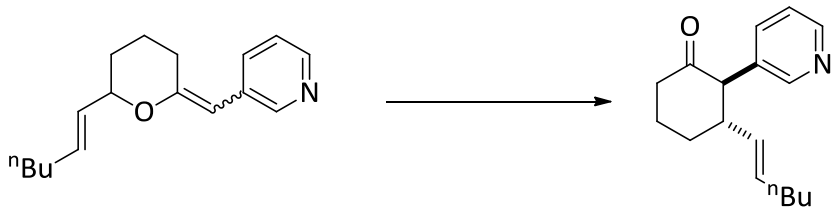
To a suspension of 4 Å molecular sieves (20 g) and a solution of $HPPh_3BF_4$ (22.2 g, 63.4 mmol) in acetonitrile (80 mL) was added a solution of pyranyl ether **102** (6.3 g, 31.8 mmol) in acetonitrile (80 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a thick pale yellow oil. To this was added dichloromethane (2 mL) then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated *in vacuo* to give **103** as a white solid (15.97 g, 97%) as a 5 : 1 mixture of diastereoisomers; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88-7.56 (15H, m, Ar-*H*), 5.99-5.45 (2H, m, C*H*P, CH_2-alkene-*H*), 5.39-5.20 (1H, m, CH-alkene-*H*), 4.57-4.46 (0.2H, m, pyran-OC*H*), 4.38-4.15 (0.8H, m, pyran-OC*H*), 2.24-1.49 (7H, m, 7 x C*H*), 1.44-1.09 (5H, m, 5 x C*H*), 0.87 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 135.2, 134.4 (J_{CP} = 8.5 Hz), 133.4, 130.4 (J_{CP} = 12.5 Hz), 129.4, 116.4 (J_{CP} = 84.5 Hz), 81.0 (J_{CP} = 11.5 Hz), 73.0 (J_{CP} = 70.0 Hz), 31.8, 31.1, 25.4, 22.6, 22.4, 22.0, 13.9; ^{31}P NMR (250 MHz, $CDCl_3$): δ 19.9.

PREPARATION OF (*E*/*Z*)-3-((6-((*E*)-HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-YLIDENE)MERTHYL PYRIDINE **106**



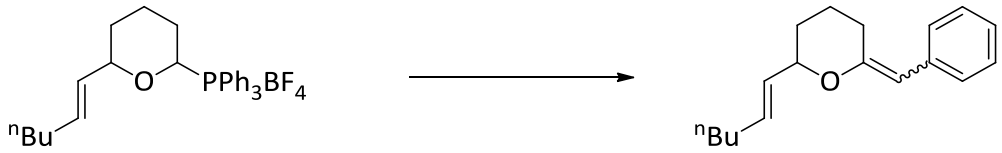
To a solution of phosphonium salt **103** (250 mg, 0.483 mmol) in tetrahydrofuran (5 mL) at -78 ^{o}C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 0.80 mL, 0.544 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 ^{o}C for 5 minutes then 3-pyridinecarboxaldehyde (63 mg, 0.581 mmol) was added at -78 ^{o}C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/ water/methanol, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on Florisil® (3 : 1 petroleum ether/ethyl acetate) to give **106** as a colourless oil (95 mg, 76%) as a 9 : 1 mixture of diastereoisomers; ^{1}H NMR (250 MHz, CD_3OD): δ 8.40-8.11 (2H, m, Ar-*H*), 7.64-7.53 (1H, m, Ar-*H*), 7.34-7.25 (1H, m, Ar-*H*), 5.92 (0.9H, m, O-alkene-*H*), 5.78-5.63 (1H, m, CH_2-alkene-*H*), 5.57-5.42 (1H, m, CH-alkene-*H*), 5.34 (0.1H, m, O-alkene-*H*), 4.33-4.23 (0.1H, m, pyran-OC*H*), 4.18-4.06 (0.9H, m, pyran-OC*H*), 2.67-2.53 (1H, m, C*H*), 2.31-1.91 (3H, m, 3 x C*H*), 1.87-1.46 (4H, m, 2 x CH_2), 1.39-1.24 (4H, m, 2 x CH_2), 0.94-0.80 (3H, m, CH_3); ^{13}C NMR (63 MHz, CD_3OD) major diastereoisomer: δ 178.8, 159.2, 149.9, 146.7, 137.8, 133.8, 131.5, 124.9, 106.1, 81.2, 33.1, 32.5, 32.0, 25.9, 23.3, 22.6, 14.4; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 3086 (w), 3063 (w), 3029 (m), 2828 (s), 2857 (s), 1714 (s), 1674 (m), 1496 (m), 1454 (m), 969 (m); HRMS (EI) *m/z* $[M]^+$ calcd for $C_{17}H_{24}NO$: 258.1858, found 258.1848.

PREPARATION OF 3-((*E*)-HEX-1-ENYL)-2-(PYRIDIN-3-YL)CYCLOHEXANONE **107**



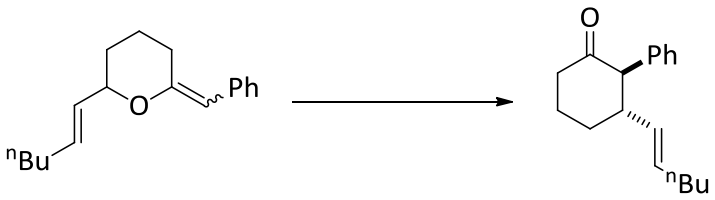
To a solution of palladium(II) acetate (3.4 mg, 10 mol%) in acetonitrile (1 mL) was added tri-*n*-butylphosphine (38 μL, 0.15 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether **106** (39 mg, 0.15 mmol) in acetonitrile (1.0 mL) was added. The resulting yellow solution was heated at 55 ^{o}C for 36 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (1 : 1 / petroleum ether/diethyl acetate) to give **107** as a colourless oil (29 mg, 73%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.46 (1H, m, Ar-*H*), 8.25 (1H, m, Ar-*H*), 7.39 (1H, m, Ar-*H*), 7.29-7.17 (1H, m, Ar-*H*), 5.20-4.99 (2H, m, alkene-*H*), 3.41 (1H, d, *J* = 12.0 Hz, (CO)C*H*), 2.67-2.42 (3H, m, alkene-C*H*, CH_2), 2.26-1.60 (6H, m, 3 x CH_2), 1.13-0.82 (4H, m, 2 x CH_2), 0.74 (3H, t, *J* = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 150.6, 147.7, 137.4, 133.1, 132.5, 131.3, 123.1, 60.7, 49.6, 41.8, 32.8, 31.8, 31.2, 25.9, 21.6, 13.8; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 3026 (w), 2946 (s), 2922 (s), 2858 (m), 1711 (s), 1575 (w), 1458 (w), 1422 (m), 1166 (m), 1021 (w), 965 (m), 797 (w); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{17}H_{24}NO$: 258.1858, found 258.1848.

PREPARATION OF (*E*/*Z*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN **79**[53]



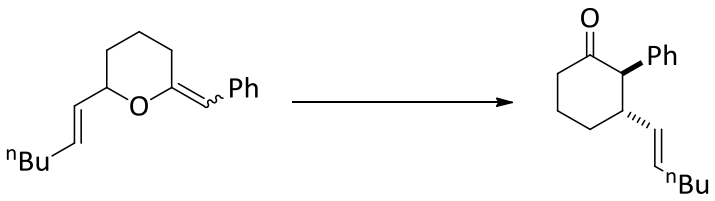
To a solution of Wittig salt **103** (380 mg, 0.736 mmol) in tetrahydrofuran (8 mL) at -78 ^{o}C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 1.14 mL, 0.773 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 ^{o}C for 5 minutes then benzaldehyde (93 μL, 0.883 mmol) was added at -78 ^{o}C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give **79** as a colourless oil (132 mg, 70%) as a 9 : 1 mixture of diastereoisomers; ^{1}H NMR (250 MHz, CD_3OD): δ 7.32-7.01 (5H, m, Ar-*H*), 6.02 (0.9H, m, O-alkene-*H*), 5.85-5.68 (1H, m, CH_2-alkene-*H*), 5.65-5.46 (1H, m, CH-alkene-*H*), 5.38 (0.1H, m, O-alkene-*H*), 4.31-4.21 (0.1H, m, pyran-OC*H*), 4.19-4.08 (0.9H, m, pyran-OC*H*), 2.80-2.64 (1H, m, C*H*), 2.37-1.99 (3H, m, 3 x C*H*), 1.92-1.49 (4H, m, 2 x CH_2), 1.47-1.25 (4H, m, 2 x CH_2), 1.01-0.82 (3H, m, CH_3); ^{13}C NMR (100 MHz, CD_3OD) major diastereoisomer: δ 156.7, 137.9, 133.6, 131.7, 129.8, 129.1, 126.7, 110.8, 81.3, 33.0, 32.5, 32.4, 26.0, 23.2, 23.1, 14.3.

PREPARATION OF 3-((*E*)-HEX-1-ENYL)-2-PHENYLCYCLOHEXANONE **80**[53]



To a solution of palladium(II) acetate (10 mg, 10 mol%) in acetonitrile (4 mL) was added tri-*n*-butylphosphine (75 μL, 0.28 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether **79** (119 mg, 0.46 mmol) in acetonitrile (4.5 mL) was added. The resulting yellow solution was heated at 55 ^{o}C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **80** as a white solid (98 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.20 (3H, m, Ar-*H*), 7.05-6.98 (2H, m, Ar-*H*), 5.18 (1H, dt, *J* = 15.5, 6.0 Hz, CH_2-alkene-*H*), 5.11 (1H, dd, *J* = 15.5, 7.0 Hz, CH-alkene-*H*), 3.36 (1H, d, *J* = 11.5 Hz, (CO)C*H*), 2.70-2.60 (1H, m, alkene-C*H*), 2.58-2.40 (2H, m, CH_2), 2.20-2.11 (1H, m, C*H*), 2.07-1.98 (1H, m, C*H*), 1.91-1.67 (4H, m, 2 x CH_2), 1.14-0.92 (4H, m, 2 x CH_2), 0.77 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 209.7, 137.3, 132.1, 131.5, 129.6, 128.1, 126.7, 63.4, 49.1, 42.0, 32.7, 32.0, 31.4, 25.9, 21.7, 13.9.

GENERAL PROCEDURE FOR THE CHIRAL LIGAND PROMOTED REARRANGEMENT FOR THE SYNTHESIS OF CYCLOHEXANONE **80**



To a solution of palladium(II) acetate (10 mol%) in acetonitrile and/or toluene (0.05 M) was added ligand (30-100 mol%). The solution was heated at reflux for 20 minutes. The resulting solution was cooled to 55 °C and enol ether **79** (1 eq) in acetonitrile and/or toluene (0.05 M) was added. The resulting solution was heated at 55 ^{o}C. Upon cooling to room temperature, the solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **80** as a white solid. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 150 °C isothermal, H_2 carrier gas at 14 psi.

DIOP **110** (**Table 11**, Entry 7): First component: 26.427 min; Second component: 27.040 min; <5% *ee*;

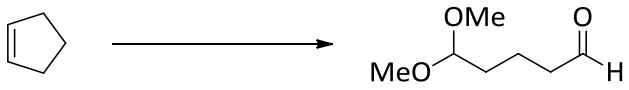
JosiPhos **111** (**Table 12**, Entry 2): First component: 26.349 min; Second component: 27.158 min; <5% *ee*;

DiPhos **112** (**Table 12**, Entry 3): First component: 26.507 min; Second component: 27.103 min; <5% *ee*;

Me-DuPhos **113** (**Table 12**, Entry 5): First component: 26.910 min; Second component: 27.525 min; <5% *ee*;

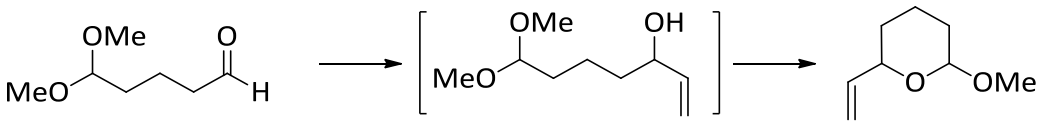
^{i}Pr-Phox **114** (**Table 12**, Entry 6): First component: 26.312 min; Second component: 26.928 min; 25% *ee*.

PREPARATION OF 5,5-DIMETHOXYPENTANAL **119**[126]



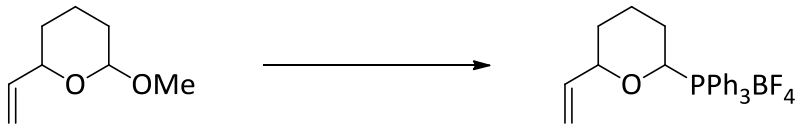
Ozone was bubbled through a stirring -78 °C solution of cyclopentene (4.0 mL, 45 mmol) in dichloromethane (250 mL) and methanol (50 mL) until a blue colour remained. Nitrogen was bubbled through the reaction mixture until the blue colour disappeared. The cold bath was removed, *p*-toluenesulfonic acid monohydrate (1.1 g) was added and the reaction was stirred at room temperature for 90 minutes. After this time, sodium hydrogen carbonate (2.0 g) was added and the reaction mixture was stirred for 30 minutes after which time a solution of triphenylphosphine (17.5 g) in dichloromethane (50 mL) was added dropwise. After stirring for 12 hours, the reaction mixture was concentrated to approximately 50 mL by rotary evaporation. Dichloromethane (100 mL) was added and the mixture was washed with water. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (60 : 40 petroleum ether/ethyl acetate) to give **119** as a colourless oil (3.1 g, 47%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.77 (1H, t, *J* = 1.5 Hz, C*H*O), 4.36 (1H, t, *J* = 5.5 Hz, C*H*$(OMe)_2$), 3.31 (6H, s, CH$(OCH_3)_2$), 2.52-2.44 (2H, m, CH_2), 1.78-1.56 (4H, m, 2 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 104.3, 53.0, 43.6, 31.9, 17.4.

PREPARATION OF 2-METHOXY-6-VINYLTETRAHYDRO-2*H*-PYRAN **117**[62]



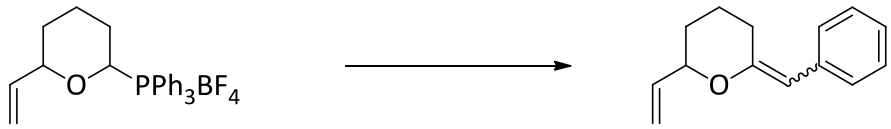
To a stirred solution of aldehyde **119** (1.5 g, 10.26 mmol) in tetrahydrofuran (140 mL) at 0 °C was added dropwise vinylmagnesium bromide (1 M in tetrahydrofuran, 11.3 mL, 11.30 mmol). The orange reaction solution was stirred for 90 minutes. The reaction was quenched with water, extracted with diethyl ether and the combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue (1.8 g) was dissolved in dichloromethane (170 mL), and camphorsulfonic acid (240 mg, 1.03 mmol) was added. The reaction was stirred at room temperature for 1 hour. Sodium hydrogen carbonate (4.3 g, 51.3 mmol) was added and the reaction was stirred for another 30 minutes. The mixture was filtered and the filtrate was carefully concentrated *in vacuo* (**care:** the compound is volatile). The crude residue was purified by flash chromatography on silica gel (90 : 10 pentane/diethyl ether) to give **117** as an colourless oil (1.1 g, 75% over two steps) as a 1 : 2 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94-5.79 (1H, m, alkene-*H*), 5.29-5.21 (1H, m, alkene-H_2), 5.12-5.07 (1H, m, alkene-H_2), 4.75 (0.33H, m, OC*H*OMe), 4.36 (0.66H, dd, *J* = 9.0, 2.0 Hz, OC*H*OMe), 4.22-4.15 (0.33H, m, pyran-OC*H*), 3.94-3.86 (0.66H, m, pyran-OC*H*), 3.50 (2H, s, OCH_3), 3.36 (1H, s, OCH_3), 1.92-1.23 (6H, m, 3 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereoisomer: δ 138.7, 114.7, 103.2, 76.6, 56.1, 31.0, 22.1, 18.0.

PREPARATION OF TRIPHENYL(6-VINYLTETRAHYDRO-2*H*-PYRAN-2-YL)PHOSPHONIUM TETRAFLUOROBORATE **116**[53]



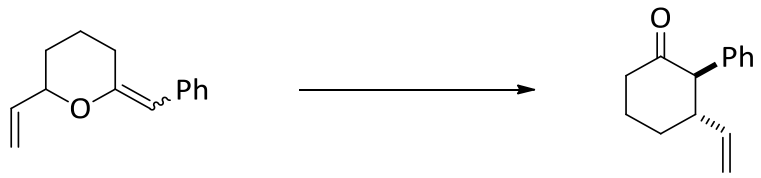
To a suspension of 4 Å molecular sieves (4.5 g) and a solution of $HPPh_3BF_4$ (4.9 g, 14.0 mmol) in acetonitrile (35 mL) was added a solution of pyranyl ether **117** (1.0 g, 7.0 mmol) in acetonitrile (35 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a thick pale yellow oil. To this was added dichloromethane (2 mL) then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated *in vacuo* to give **116** as a white solid (3.0 g, 93%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.87-7.59 (15H, m, Ar-*H*), 5.91-5.57 (2H, m, C*H*P, alkene-*H*), 5.16-4.93 (2H, m, alkene-H_2), 4.39 (1H, m, pyran-OC*H*), 2.19-1.52 (5H, m, 5 x C*H*), 1.45-1.21 (1H, m C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 135.3, 134.5 (J_{CP} = 9.0 Hz), 130.5 (J_{CP} = 12.0 Hz), 116.5 (J_{CP} = 84.0 Hz), 80.6 (J_{CP} = 10.5), 72.8 (J_{CP} = 44.5 Hz), 30.9, 25.6, 22.4, 22.3; ^{31}P NMR (250 MHz, $CDCl_3$): δ 20.5.

PREPARATION OF 2-BENZYLIDENE-6-VINYLTETRAHYDRO-2*H*-PYRAN **115**[53]



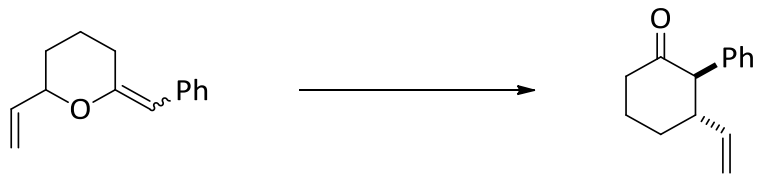
To a solution of phosphonium salt **116** (250 mg, 0.543 mmol) in tetrahydrofuran (5 mL) at -78 ^{o}C was added potassium hexamethyldisilazide dropwise at -78 °C (0.68 M, 0.84 mL, 0.570 mmol). The resulting red solution was stirred at -78 ^{o}C for 5 minutes then benzaldehyde (70 μL, 0.650 mmol) was added at -78 ^{o}C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give **115** as a colourless oil (76 mg, 70%) as a 9 : 1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, CD_3OD): δ 7.31-7.11 (5H, m, Ar-*H*), 6.05 (0.9H, m, O-alkene-*H*), 6.04-5.90 (0.1H, m, alkene-*H*), 5.95 (0.9H, ddd, *J* = 17.0, 10.5, 5.5 Hz, alkene-*H*) 5.42 (0.1H, m, O-alkene-*H*), 5.39-5.35 (0.1H, m, alkene-H_2), 5.33 (0.9H, dt, *J* = 17.0, 1.5 Hz, alkene-H_2), 5.21-5.13 (0.9H, dt, *J* = 10.5, 1.5 Hz, alkene-H_2 and 0.1H, m, alkene-H_2), 4.33-4.27 (0.1H, m, pyran-OC*H*), 4.21-4.14 (0.9H, m, pyran-OC*H*), 2.78-2.70 (1H, m, C*H*), 2.41-2.16 (1H, m, C*H*), 1.96-1.54 (4H, m, 2 x CH_2); ^{13}C NMR (100 MHz, CD_3OD) major diastereoisomer: δ 156.5, 140.0, 137.9, 129.8, 129.2, 126.7, 115.5, 110.9, 81.2, 32.0, 26.0, 23.1.

PREPARATION OF 2-PHENYL-3-VINYLCYCLOHEXANONE **121**[53]



To a solution of palladium(II) acetate (5.6 mg, 10 mol%) in acetonitrile (2 mL) was added *n*-tributylphosphine (40 μL, 0.15 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether **115** (50 mg, 0.25 mmol) in acetonitrile (3 mL) was added. The resulting yellow solution was heated at 55 ^{o}C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **121** as a white solid (42 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (3H, m, Ar-*H*), 7.11-7.06 (2H, m, Ar-*H*), 5.56 (1H, ddd, *J* = 17.5, 10.0, 7.5 Hz, alkene-*H*), 4.90-4.82 (2H, m, alkene-H_2), 3.43 (1H, d, *J* = 11.5 Hz, (CO)C*H*), 2.82-2.71 (1H, m, alkene-*CH*), 2.63-2.44 (2H, m, CH_2), 2.27-2.17 (1H, m, C*H*), 2.14-2.05 (1H, m, C*H*), 1.97-1.75 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 140.4, 137.1, 129.6, 128.3, 127.0, 115.1, 62.9, 49.5, 41.9, 31.9, 25.8.

GENERAL PROCEDURE FOR THE CHIRAL LIGAND PROMOTED REARRANGEMENT FOR THE SYNTHESIS OF CYCLOHEXANONE **121**



To a solution of palladium(II) acetate (10 mol%) in acetonitrile and/or toluene (0.05 M) was added ligand (30-60 mol%). The solution was heated at reflux for 20 minutes. The resulting solution was cooled to 55 °C and enol ether **115** (1 eq) in acetonitrile and/or toluene (0.05 M) was added. The resulting solution was heated at 55 ^{o}C. Upon cooling to room temperature, the solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **121** as a white solid. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H_2 carrier gas at 14 psi.

DIOP **110** (**Table 13**, Entry 2): First component: 26.715 min; Second component: 27.658 min; 13% *ee*;

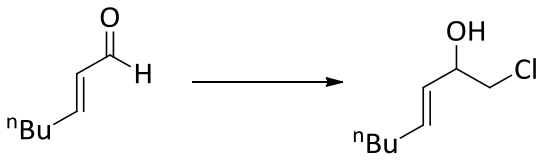
JosiPhos **111** (**Table 13**, Entry 3): First component: 26.853 min; Second component: 27.859 min; <5% *ee*;

DiPhos **112** (**Table 13**, Entry 4): First component: 26.368 min; Second component: 27.221 min; <5% *ee*;

^{i}Pr-Phox **114** (**Table 13**, Entry 10): First component: 26.605 min; Second component: 27.523 min; 25% *ee*;

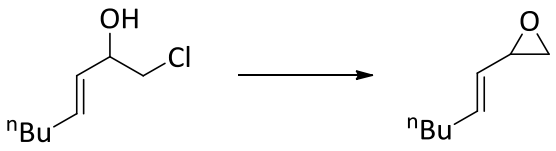
^{t}Bu-Phox **42** (**Table 13**, Entry 11): First component: 26.536 min; Second component: 27.448 min; 49% *ee*.

PREPARATION OF (3*E*)-1-CHLOROOCT-3-EN-2-OL **126**[127]



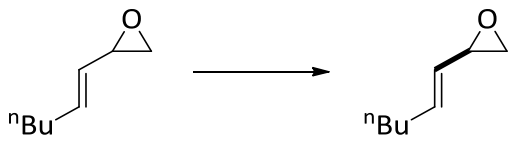
To a stirred solution of aldehyde **127** (1.31 mL, 9.89 mmol) in tetrahydrofuran (20 mL) at -78 ^{o}C was added chloroiodomethane (1.10 mL, 14.83 mmol) followed by the slow addition of *n*-butyllithium (1.1 M in hexanes, 13.4 mL, 14.83 mmol). The resulting cloudy solution was stirred at -78 ^{o}C for 2 hours. The reaction was quenched by the addition of ammonium chloride solution and extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried over sodium sulfate and carefully concentrated *in vacuo* to give **126** as a pale yellow oil (1.85 g, 100%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (1H, dtd, *J* = 15.5, 7.0, 1.0 Hz, CH_2-alkene-*H*), 5.48 (1H, ddt, *J* = 15.5, 6.5, 1.5 Hz, CH-alkene-*H*), 4.34-4.28 (1H, m, C*H*), 3.62 (1H, dd, *J* = 11.0, 4.0 Hz, CH_AH$_B$), 3.51 (1H, dd, *J* = 11.0, 7.5 Hz, CH$_A$$H_B$), 2.36 (1H, ddd, *J* = 15.0, 7.0, 1.5 Hz, O*H*), 2.07 (2H, q, *J* = 6.5 Hz, CH_2), 1.44-1.25 (4H, m, 2 x CH_2), 0.93-0.89 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 128.2, 72.3, 49.7, 31.9, 31.1, 22.6, 14.0.

PREPARATION OF 2-[(1*E*)-HEX-1-ENYL]OXIRANE **125**[127]



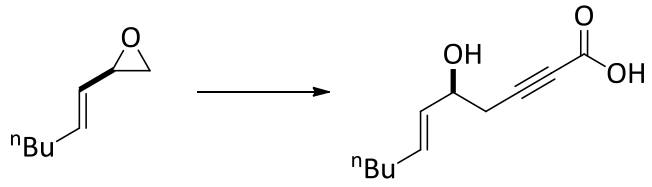
A suspension of sodium hydride (60% suspension in mineral oil, 1.075 g, 16.12 mmol) and sodium iodide (220 mg, 1.46 mmol) in tetrahydrofuran (35 mL) at 0 ^{o}C was stirred for 10 minutes. Alcohol **126** (1.85 g, 14.65 mmol) in tetrahydrofuran (10 mL) was added *via* cannula at 0 ^{o}C over 30 minutes and the resulting suspension was stirred at 0 ^{o}C for 2 hours. The reaction was quenched by the addition of ammonium chloride solution and extracted with diethyl ether. The aqueous layer was further extracted with diethyl ether and the combined organic layers were dried over sodium sulfate and carefully concentrated *in vacuo* to give **125** as a pale yellow oil (1.44 g, 100%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (1H, dt, *J* = 15.5, 7.0 Hz, CH_2-alkene-*H*), 5.14 (1H ddt, *J* = 15.5, 8.5, 1.5 Hz, CH-alkene-*H*), 3.36-3.31 (1H, m, C*H*), 2.96 (1H, dd, *J* = 5.0, 4.0 Hz, CH_AH$_B$), 2.67 (1H, dd, *J* = 5.0, 3.0 Hz, CH$_A$$H_B$), 2.13-2.06 (2H, m, C$H_2$), 1.44-1.20 (4H, m, 2 x CH_2), 0.91 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 137.2, 127.4, 52.4, 48.7, 32.0, 31.0, 25.6, 14.0.

HYDROLYTIC KINETIC RESOLUTION OF 2-[(1*E*)-HEX-1-ENYL]OXIRANE **125**[66]



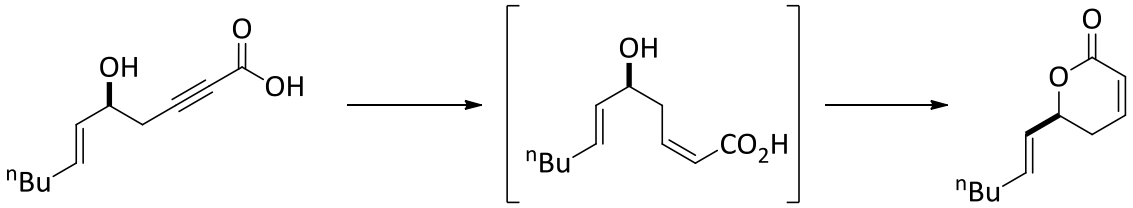
To a solution (*S*,*S*)-**128** (34 mg, 0.057 mmol), epoxide **125** (1.44 g, 11.41 mmol) and acetic acid (12 μL, 0.02 mmol) at 0 ^{o}C was added water (113 μL, 6.27 mmol) and the resulting dark red solution stirred at room temperature until crude NMR analysis showed 1 : 1 epoxide **125** to diol **129**. The resulting red solution was purified chromatography on Florisil® (100 : 0 to 0 : 100 petroleum ether/diethyl ether) to give enantioenriched **125** as a colourless oil (720 mg, ~50%). The compound showed identical NMR spectroscopic data to racemic **125**.

PREPARATION OF (*E*)-5-HYDROXYUNDEC-6-EN-3-YNOIC ACID **137**[68]



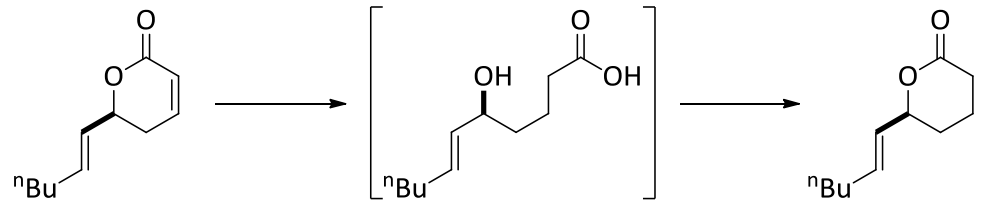
To a stirred solution of diisopropylamine (3.76 mL, 26.68 mmol) in tetrahydrofuran (15 mL) at -78 ^{o}C was added *n*-butyllithium (2.0 M in hexanes, 13.4 mL, 26.68 mmol). After 15 minutes, hexamethylphosphoramide (2.25 mL) was added followed by propiolic acid (750 μL, 12.15 mmol) in tetrahydrofuran (5 mL). The resulting grey solution was stirred at 0 ^{o}C for 3 hours before the addition of enantioenriched epoxide **125** (750 mg, 5.95 mmol). The resulting thick red/brown solution was stirred at room temperature for 3 days. The reaction mixture was concentrated *in vacuo* to give a deep red residue which was dissolved in water and extracted with dichloromethane. The aqueous solution was treated with concentrated hydrochloric acid to pH 1, saturated with sodium chloride and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give **137** as a dark red oil (620 mg, 54%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.78 (1H, dt, *J* = 15.5, 7.0 Hz, CH_2-alkene-*H*), 5.53 (1H ddt, *J* = 15.5, 7.0, 1.5 Hz, CH-alkene-*H*), 4.37 (1H, q, *J* = 6.5 Hz, C*H*), 2.13-2.02 (2H, m, alkyne-CH_2), 1.42-1.27 (6H, m, 3 x CH_2), 0.91 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 180.2, 132.4, 128.6, 92.2, 73.3, 69.2, 33.3, 32.5, 24.8, 23.2, 14.1.

PREPARATION OF (*E*)-6(HEX-1-ENYL)-5,6-DIHYDRO-2*H*-PYRAN-2-ONE **135**[128]



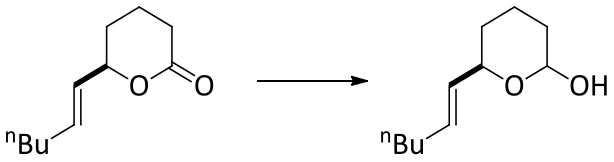
A suspension of alcohol **137** (620 mg, 3.21 mmol), Lindlar's catalyst (110 mg) and quinoline (1.0 mL) in tetrahydrofuran (10 mL) was stirred under an atmosphere of hydrogen (*via* balloon at atmospheric pressure) at room temperature for 36 hours. The resulting black suspension was concentrated *in vacuo* and partitioned between ethyl acetate and 1M hydrochloric acid. The organic layer was extracted a further 3 times with hydrochloric acid, passed through Celite®, dried over sodium sulfate and concentrated to give a dark oil. The crude material was dissolved in toluene and heated at reflux for 16 hours. The water was azeotropically removed using a Dean-Stark trap. The resulting solution was concentrated *in vacuo* to give **135** as a dark solid (400 mg, 69%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.89 (1H, dt, *J* = 9.5, 4.0 Hz, C(O)-alkene-*H*), 6.06 (1H dt, *J* = 9.5, 2.0 Hz, CH_2-alkene-*H*), 5.84 (1H, dtd, *J* = 15.5, 7.0, 0.5 Hz, CH_2-alkene-*H*), 5.59 (1H, ddt, *J* = 15.5, 7.0, 1.0 Hz, CH-alkene-*H*), 4.89 (1H, q, *J* = 7.0 Hz, pyran-OC*H*), 2.48-2.40 (2H, m, CH_2), 2.14-2.03 (2H, m, CH_2), 1.47-1.25 (4H, m, 2 x CH_2), 0.98-0.85 (3H, m, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.4, 150.8, 134.8, 124.4, 121.9, 81.5, 34.9, 32.7, 32.0, 22.9, 14.1.

PREPARATION OF (*E*)-6-(HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-ONE **134**[129]



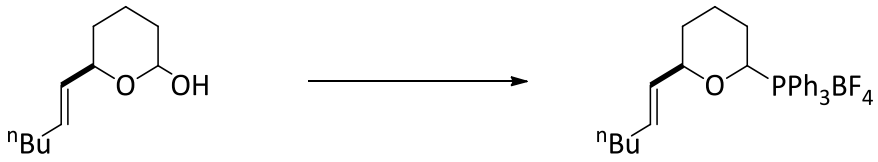
To a solution of lactone **135** (400 mg, 2.22 mmol) in degassed benzene (5 mL) was added (triphenylphosphine)copper hydride (Stryker's reagent, 2.00 g, 1.02 mmol). The resulting red solution was stirred at room temperature for 48 hours then exposed to air for 1 hour. Saturated sodium hydrogencarbonate was added and the reaction mixture extracted with diethyl ether. The aqueous layer was treated with concentrated hydrochloric acid to pH 1, saturated with sodium chloride and extracted with ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give a thick, dark oil. The crude material was dissolved in toluene and heated at reflux for 16 hours. The water was azeotropically removed using a Dean-Stark trap. The resulting solution was concentrated *in vacuo* to give a dark solid which was purified by flash chromatography on silica gel (75 : 25 to 0 : 100 petroleum ether/ethyl acetate) to give **134** as a colourless oil (35 mg, 18%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (1H, dtd, *J* = 15.5, 7.0, 1.0 Hz, alkene-*H*), 5.48 (1H, ddt, *J* = 15.5, 6.5, 1.5 Hz, alkene-*H*), 5.78-5.71 (1H, m, OC*H*), 2.61-2.52 (1H, m, C(O)CH_AH$_B$), 2.50-2.40 (1H, m, C(O)CH$_A$$H_B$), 2.08-2.00 (2H, m, C$H_2$), 1.98-1.82 (2H, m, C$H_2$), 1.67-1.59 (1H, m, C*H*), 1.40-1.26 (5H, m, 5 x C*H*), 0.88 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 134.6, 127.9, 80.7, 31.8, 31.0, 29.5, 28.4, 22.1, 18.2, 13.9.

PREPARATION OF (*E*)-6-(HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-OL **133**



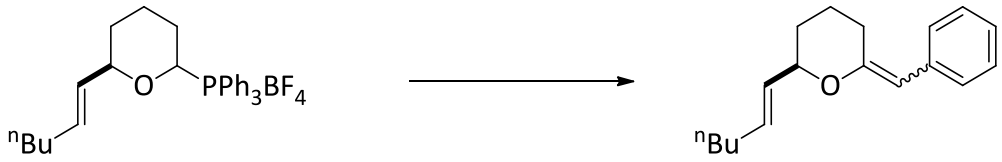
To a stirred solution of lactone **134** (35 mg, 0.19 mmol) in dichloromethane (1 mL) at -78 ^{o}C was added diisobutylaluminium hydride (1 M in hexanes, 190 μL, 0.28 mmol) followed by chlorotrimethylsilane (60 μL, 0.47 mmol). The resulting reaction mixture was stirred at -78 ^{o}C for 2.5 hours. After this period, methanol (0.5 mL) and potassium carbonate (500 mg in 0.5 mL of water) was added to the reaction mixture which was stirred at room temperature for a further 16 hours at room temperature. Afterwards, sodium sulfate was added, and the reaction mixture stirred for 15 minutes, filtered through Celite®, washed with dichloromethane and concentrated *in vacuo* to give **133** as a colourless oil (20 mg, 57%) as a 1 : 1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76-5.66 (1H, m, CH_2-alkene-*H*), 5.55-5.42 (1H, m, CH-alkene-*H*), 5.37-5.33 (0.5H, m, C*H*OH), 4.81-4.74 (0.5H, m, C*H*OH), 4.47-4.40 (0.5H, m, pyran-OC*H*), 3.96-3.90 (0.5H, m, pyran-OC*H*), 3.30-3.23 (0.5H, m, O*H*), 2.85-2.79 (0.5H, m, O*H*), 2.10-1.99 (2H, m, CH_2), 1.93-1.84 (2H, m, CH_2), 1.76-1.50 (4H, m, 2 x CH_2), 1.42-1.24 (4H, m, 2 x CH_2), 0.90 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 131.7, 130.6, 124.8, 123.5, 95.3, 94.7, 71.5, 71.0, 35.7, 35.6, 33.3, 33.2, 32.7, 32.6, 32.5, 32.4, 23.2, 23.2, 16.6, 16.5, 14.2, 14.1.

PREPARATION OF (*E*)-(6-(HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-YL)TRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE **103**



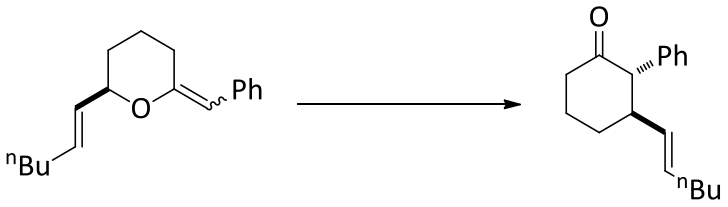
To a suspension of 4 Å molecular sieves (1.0 g) and a solution of $HPPh_3BF_4$ (200 mg, 0.57 mmol) in acetonitrile (2.5 mL) was added a solution of hemi-acetal **133** (20 mg, 0.11 mmol) in acetonitrile (2.5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a thick pale yellow oil. To this was added dichloromethane (1 mL) then diethyl ether/petroleum ether (1 : 1, 40 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated *in vacuo* to give **103** as a white solid (20 mg, 35%). The compound showed identical NMR spectroscopic data to racemic **103**.

PREPARATION OF (*E*/*Z*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN **79**



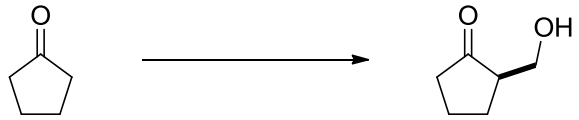
To a solution of phosphonium salt **103** (20 mg, 0.038 mmol) in tetrahydrofuran (500 μL) at -78 ^{o}C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 80 μL, 0.054 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 ^{o}C for 5 minutes then benzaldehyde (6.7 μL, 0.066 mmol) was added at -78 ^{o}C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give **79** as a colourless oil (7 mg, 72%) as a 5 : 1 mixture of diastereoisomers. The compound showed identical NMR spectroscopic data to racemic **79**. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 150 °C isothermal, H_2 carrier gas at 14 psi. First component: 23.954 min; Second component: 24.558 min; 35% *ee*.

PREPARATION OF 3-((*E*)-HEX-1-ENYL)-2-PHENYLCYCLOHEXANONE **80**



To a solution of palladium(II) acetate (1 mg, 10 mol%) in acetonitrile (0.5 mL) was added *n*-tributylphosphine (7 μL, 0.028 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether **79** (7 mg, 0.046 mmol) in acetonitrile (0.5 mL) was added. The resulting yellow solution was heated at 40 ^{o}C for 24 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **80** as a white solid (5 mg, 71%). The compound showed identical NMR spectroscopic data to racemic **80**. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 150 °C isothermal, H_2 carrier gas at 14 psi. First component: 27.123 min; Second component: 27.637 min; <5% *ee*.

PREPARATION OF 2-(HYDROMETHYL)CYCLOPENTANONE **143**[71]

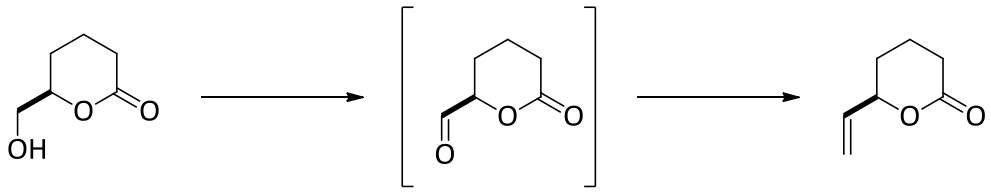


A suspension of cyclopentanone (35.0 g, 416 mmol) and L-threonine (6.0 g, 50.4 mmol) in dichloromethane (200 mL) was stirred at room temperature for 1 hour. Formaldehyde solution (37% in water, 5.0 mL, 166.5 mmol) was added and the mixture was stirred vigorously for 48 hours. The organic phase was separated and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (50 : 50 to 0 : 100 petroleum ether/ethyl acetate) to give **143** as a colourless oil (6.0 g, 62%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.89-3.68 (2H, m, CH_2OH), 2.58 (1H dd, *J* = 8.0, 4.0 Hz, C*H*), 2.45-2.30 (2H, m, C(O)CH_2), 2.25-2.03 (3H, m CH_2 and O*H*), 1.89-1.67 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 222.3, 62.1, 50.6, 38.5, 26.1, 20.9; $[\alpha]_D^{22}$ -92.3 (*c* 4.5 $CHCl_3$), $[\alpha]_D^{23}$ -54.7 (*c* 4.5 $CHCl_3$) reported for (*S*)-2-(hydromethyl)cyclopentanone with 75% *ee*.[72]

PREPARATION OF 6-(HYDROXYMETHYL)TETRAHYDRO-2*H*-PYRAN-2-ONE **142**[130,131]

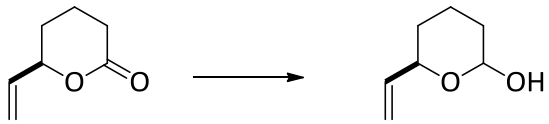
A suspension of alcohol **143** (1.00 g, 8.77 mmol), sodium hydrogen carbonate (4.5 g, 55.56 mmol) and 3-chloroperbenzoic acid (>77% *w*/*w*, 8.0 g, 35.70 mmol) in dichloromethane (100 mL) was stirred at room temperature for 1 hour. The reaction was quenched by the addition of sodium thiosulphate and sodium hydrogen carbonate, dried over sodium sulfate, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (100 : 0 to 90 : 10 dichloromethane/methanol) to give **142** as a colourless oil (1.2 g, 100%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.38-4.27 (1H, m, C(O)OC*H*), 3.68 (1H dd, *J* = 12.0, 3.5 Hz, CH_AH$_B$), 3.58 (1H dd, *J* = 12.0, 5.5 Hz, CH$_A$$H_B$), 2.57-2.27 (2H, m, C(O)CH_2), 1.89-1.56 (4H, m, 2 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 80.6, 64.9, 31.4, 24.4, 18.3.

PREPARATION OF 6-VINYLTETRAHYDRO-2*H*-PYRAN-2-ONE **140**[12]



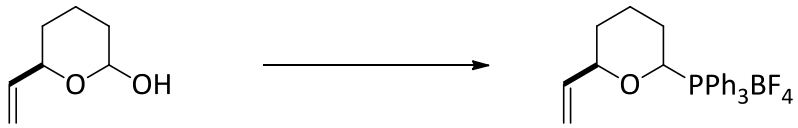
The reaction was conducted in duplicate and the reaction mixtures combined upon workup. A suspension of alcohol **142** (100 mg, 0.76 mmol), pyridinium dichromate (2.25 g, 5.98 mmol) and activated 4 Å molecular sieves (1.0 g) in dichloromethane (7.5 mL) was stirred vigorously at room temperature for 1 hour. The reaction mixtures were combined, diluted with pentane, filtered through Celite®, washed with pentane and carefully concentrated *in vacuo* to give a dark oil. A suspension of methyltriphenylphosphonium bromide (825 mg, 2.31 mmol) and potassium *t*-butoxide (225 mg, 2.01 mmol) in tetrahydrofuran (15 mL) was stirred at 0 ^{o}C for 15 minutes. The crude dark oil was dissolved in tetrahydrofuran (10 mL) and added to the resulting bright yellow solution at 0 ^{o}C *via* cannula. The resulting dark solution was stirred at room temperature for 16 hours. After this, the reaction mixture was diluted in pentane, carefully concentrated *in vacuo*, washed with pentane and the filtrate carefully concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (90 : 10 to 0 : 100 pentane/diethyl ether) to give **140** as a colourless oil (50 mg, 26% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (1H, ddd, *J* = 17.5, 10.5, 5.5 Hz, alkene-*H*), 5.37 (1H, dt, *J* = 17.5, 1.5 Hz, alkene-H_2), 5.26 (1H, dt, *J* = 10.5, 1.5 Hz, alkene-H_2), 4.88-4.82 (1H, m, pyran-OC*H*) 2.67-2.46 (2H, m, CH_2), 2.07-1.84 (3H, m, 3 x C*H*), 1.75-1.64 (1H, m, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 138.9, 115.6, 80.4, 29.5, 27.8, 18.0.

PREPARATION OF 6-VINYLTETRAHYDRO-2*H*-PYRAN-2-OL **139**[12]



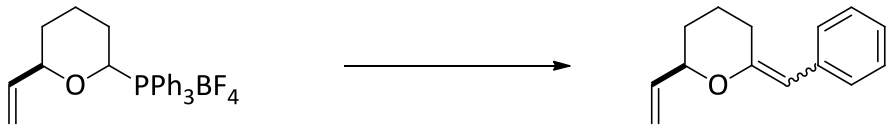
To a stirred solution of lactone **140** (50 mg, 0.40 mmol) in dichloromethane (2 mL) at -78 ^{o}C was added diisobutylaluminium hydride (1 M in hexanes, 555 μL, 0.55 mmol) followed by chlorotrimethylsilane (126 μL, 0.99 mmol). The resulting reaction mixture was stirred at -78 ^{o}C for 2.5 hours. After this period, methanol (0.2 mL) and potassium carbonate (500 mg in 0.4 mL of water) was added to the reaction mixture which was stirred at room temperature for a further 16 hours. Afterwards, sodium sulfate was added, the reaction mixture stirred for 15 minutes, filtered through Celite®, washed with dichloromethane and concentrated *in vacuo* to give **139** as a colourless oil (50 mg, 98%) as a 1 : 1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ5.96-5.81 (1H, m, alkene-*H*), 5.39-5.34 (0.5H, m, C*H*OH), 5.31-5.21 (1H, m, alkene-H_2), 5.14-5.08 (1H, m, alkene-H_2), 4.79-4.82 (0.5H, m, C*H*OH), 4.53-4.46 (0.5H, m, pyran-OC*H*), 4.02-3.95 (0.5H, m, pyran-OC*H*), 3.71-3.64 (0.5H, m, O*H*), 3.05-2.98 (0.5H, m, O*H*), 1.94-1.22 (6H, m, 3 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.2, 115.2, 115.0, 96.5, 91.9, 69.7, 68.9, 32.4, 31.2, 30.4, 29.5, 21.9, 17.2.

PREPARATION OF TRIPHENYL(6-VINYLTETRAHYDRO-2*H*-PYRAN-2-YL)PHOSPHONIUM TETRAFLUOROBORATE **116**



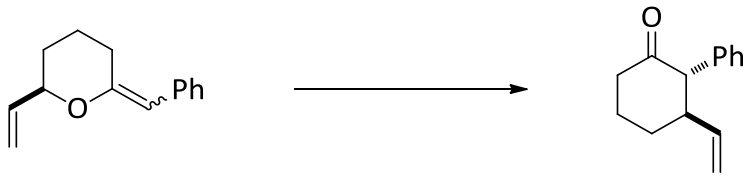
To a suspension of 4 Å molecular sieves (400 mg) and a solution of $HPPh_3BF_4$ (373 mg, 0.78 mmol) in acetonitrile (5 mL) was added a solution of hemi-acetal **139** (50 mg, 0.39 mmol) in acetonitrile (5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a thick pale yellow oil. To this was added dichloromethane (1 ml) then diethyl ether / petroleum ether (1 : 1, 40 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated five times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated *in vacuo* to give **116** as a white solid (35 mg, 20%). The compound showed identical NMR spectroscopic data to racemic **116**.

PREPARATION OF 2-BENZYLIDENE-6-VINYLTETRAHYDRO-2*H*-PYRAN **115**



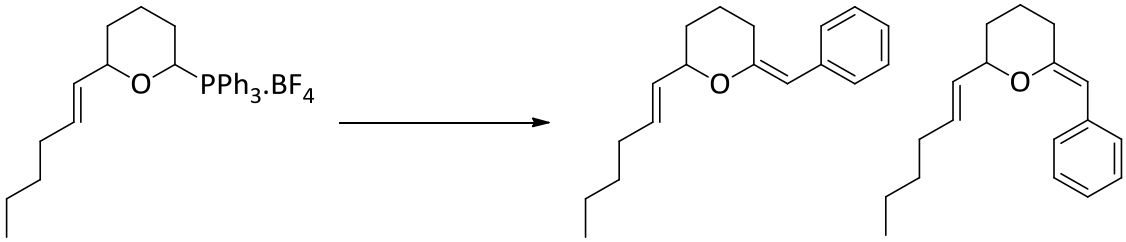
To a solution of phosphonium salt **116** (35 mg, 0.076 mmol) in tetrahydrofuran (1 mL) at -78 ^{o}C was added potassium hexamethyldisilazide (0.68 M in tetrahydrofuran, 0.60 mL, 0.41 mmol) dropwise at -78 °C. The resulting red solution was stirred at -78 ^{o}C for 5 minutes then benzaldehyde (40 μL, 0.36 mmol) was added at -78 ^{o}C. The resulting yellow solution was stirred at -78 °C for 45 minutes, then at room temperature for a further 60 minutes. The resulting yellow solution was quenched with water and extracted with diethyl ether. The organic layer was washed three times with a mixture of 3 : 3 : 1 brine/water/methanol, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give **115** as a colourless oil (10 mg, 66%). The compound showed identical NMR spectroscopic data to racemic **115**. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H_2 carrier gas at 14 psi. First component: 23.029 min; Second component: 24.565 min; 46% *ee*.

PREPARATION OF 2-PHENYL-3-VINYLCYCLOHEXANONE **121**



To a solution of palladium(II) acetate (1.1 mg, 10 mol%) in acetonitrile (1 mL) was added *n*-tributylphosphine (7.5 μL, 0.03 mmol). The solution was heated at reflux for 20 minutes. The resulting yellow solution was cooled to 55 °C and enol ether **115** (10 mg, 0.05 mmol) in acetonitrile (1 mL) was added. The resulting yellow solution was heated at 55 ^{o}C for 48 hours. Upon cooling to room temperature, the yellow solution was diluted with diethyl ether, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (95 : 5 petroleum ether/ethyl acetate) to give **121** as a white solid (8 mg, 80%). The compound showed identical NMR spectroscopic data to racemic **121**. Resolution between the enantiomers was determined using chiral stationary phase gas chromatography with a Chiracel-bonded column (30 m × 0.25 m, β-cyclodextrin / permethyl); T = 120 °C isothermal, H_2 carrier gas at 14 psi. First component: 27.120 min; Second component: 28.160 min; <5% *ee*.

PREPARATION OF (*E*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN ***E*-79** and (*Z*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN ***Z*-79**

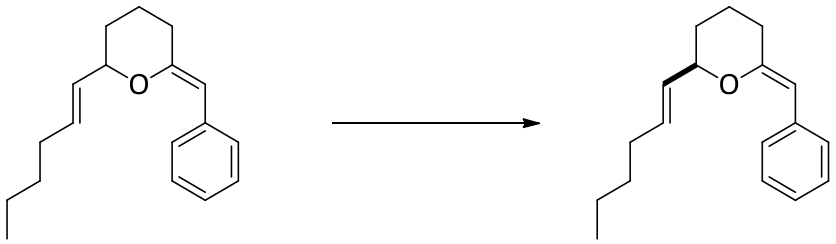


To a stirred solution of phosphonium salt **103** (1.00 g, 1.938 mmol) in tetrahydrofuran (20 mL) at -78 ^{o}C was added dropwise lithium hexamethyldisilazide (1.0 M in tetrahydrofuran, 2.3 mL, 2.33 mmol, 1.2 eq). The resulting red solution was stirred at -78 ^{o}C for 10 minutes, then the dry-ice bath was removed and stirred for 10 minutes further. Benzaldehyde (250 mg, 2.33 mmol, 1.2 eq) was added *via* syringe and the resulting yellow solution was stirred at room temperature for 16 hours. Water (5 mL) then hydrogen peroxide (1 mL) was added and stirred at room temperature for 1 hour. The reaction mixture was quenched with water and extracted with diethyl ether. The ether layer was washed with a 3 : 3 : 1 brine/water/methanol mixture (3 x 25 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on Florisil® (99 : 1 petroleum ether/ethyl acetate) to give enol ethers ***E*-79** and ***Z*-79** as colourless oil (357 mg, 1.395 mmol, 72% yield) containing a 1 : 1 *E*/*Z* mixture of diastereoisomers. Separation of the diasteroisomers was accomplished *via* preparative HPLC using an Alltech “Alltima HP C18 5u” column (150 mm x 22 mm) to give (*E*)-enol ether (150 mg, 0.586 mmol, 30%) and (*Z*)-enol ether (130 mg, 0.508 mmol, 26%); conditions: 15 : 85 / water : methanol/ammonium hydroxide (1%), 20.0 mL/min, 254 nm.

(***E*-79**): ^{1}H NMR (250 MHz, CD_3OD): δ 7.33-7.22 (2H, m, Ar-*H*) 7.20-7.09 (3H, m, Ar-*H*), 6.02 (1H, s, O-alkene-*H*), 5.85-5.69 (1H, m, CH_2-alkene-*H*), 5.54 (1H, dd, *J* = 15.5, 6.5 Hz, CH-alkene-*H*), 4.20-4.05 (1H, m, pyran-OC*H*), 2.81-2.64 (1H, m, C*H*), 2.28-2.04 (3H, m, 3 x C*H*), 1.90-1.75 (2H, m, CH_2), 1.67-1.54 (2H, m, CH_2), 1.46-1.33 (4H, m, 2 x CH_2), 0.92 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, CD_3OD): δ 156.6, 137.9, 133.6, 131.7, 129.8, 129.1, 126.7, 110.8, 81.3, 33.0, 32.4, 32.3, 26.0, 23.2, 23.1, 14.3; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 2955 (s), 2929 (s), 2860 (m), 1652 (s), 1234 (s), 1138 (s) 1035 (s), 969 (m) 922 (m); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{18}H_{25}O$: 257.1905, found 257.1895.

(***Z*-79**): ^{1}H NMR (250 MHz, CD_3OD): δ 7.67-7.45 (2H, m, Ar-*H*), 7.22-7.13 (2H, m, Ar-*H*), 7.10-6.98 (1H, m, Ar-*H*), 5.90-5.69 (1H, m, CH_2-alkene-*H*), 5.60 (1H, ddt, *J* = 15.5, 6.0, 1.5 Hz, CH-alkene-*H*), 5.38 (1H, m, O-alkene-*H*), 4.35-4.09 (1H, m, pyran-OC*H*), 2.37-2.21 (2H, m, CH_2), 2.15-2.03 (2H, m, CH_2), 1.91-1.56 (4H, m, 2 x CH_2), 1.44-1.38 (4H, m, 2 x CH_2), 0.94 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, CD_3OD): δ 155.8, 137.9, 133.7, 131.5, 129.2, 128.9, 126.2, 108.1, 80.4, 33.0, 32.5, 32.1, 31.1, 23.5, 23.1, 14.3; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 2928 (s), 2859 (m), 1655 (m), 1166 (m), 1030 (s), 968 (m), 928 (m), 1496 (m), 1454 (m), 969 (m); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{18}H_{25}O$: 257.1905, found 257.1899.

REPRESENTATIVE PROCEDURE FOR THE KINETIC RESOLUTION OF (*Z*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN ***Z*-79**

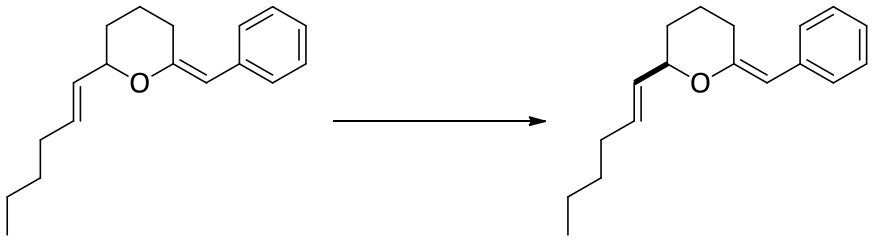


To a reaction vial was added racemic enol ether ***Z*-79** (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and ^{t}Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for *ca.* 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 40 ^{o}C for 6.5 hours. The reaction vial was cooled to room temperature, and directly purified *via* column chromatography on Florisil® (99 : 1 to 90 : 10 petroleum ether/ethyl acetate) to give enantioenriched enol ethers ***Z*-79** as colourless oils. The compounds showed identical NMR spectroscopic data to racemic enol ether ***Z*-79**. The *ee*'s were determined by HPLC analysis using a Phenomenex "Lux 3u Cellulose-2" column (250 mm x 4.6 mm); conditions: *n*-hexane (100%), 1.0 mL/min, 254 nm.

(*S*)-^{t}Bu-Phox (**Scheme 96**, equation (1)): First component: 8.180 min; Second component: 9.110 min; +94% *ee*; $[\alpha]_D^{23}$ -20.0 (*c* 1.0 MeOH).

(*R*)-^{t}Bu-Phox (**Scheme 96**, equation (2)): First component: 10.210 min; Second component: 10.983 min; -97% *ee*; $[\alpha]_D^{20}$ +20.0 (*c* 1.0 MeOH).

REPRESENTATIVE PROCEDURE FOR THE KINETIC RESOLUTION OF (*E*)-2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRAN ***E*-79**

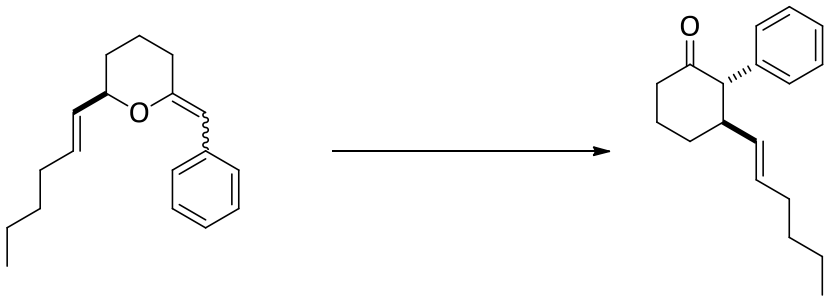


To a reaction vial was added racemic enol ether ***E*-79** (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and ^{t}Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for *ca.* 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 55 ^{o}C for 9.5 hours. The reaction vial was cooled to room temperature, and directly purified *via* column chromatography on Florisil® (99 : 1 to 90 : 10 petroleum ether/ethyl acetate) to give enantioenriched enol ethers ***E*-79** as colourless oils. The compounds showed identical NMR spectroscopic data to racemic enol ether ***E*-79**. The *ee* of the enol ethers were determined by HPLC analysis using a Phenomenex "Lux 3u Cellulose-2" column (250 mm x 4.6 mm); conditions: *n*-hexane (100%), 1.0 mL/min, 254 nm.

(*S*)-^{t}Bu-Phox (**Scheme 97**, equation (1)): First component: 9.170 min; Second component: 12.610 min; +77% *ee*; $[\alpha]_D^{22}$ -50.0 (*c* 1.0 MeOH).

(*R*)-^{t}Bu-Phox (**Scheme 97**, equation (2)): First component: 13.720 min; Second component: 19.967 min; -75% *ee*.

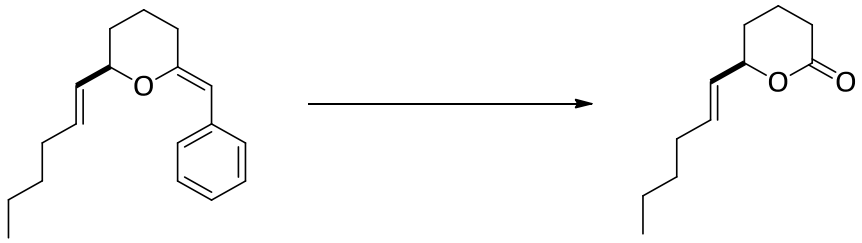
GERNERAL PROCEDURE FOR THE O→C REARRANGEMENT OF ENANTIOPURE 2-BENZYLIDENE-6-((*E*)-PENT-1-ENYL)TETRAHYDRO-2*H*-PYRANS



To a reaction vial was added enantioenriched enol ether **79** (1 eq), bis(dibenzylideneacetone)palladium(0) (5 mol%) and ^{t}Bu-Phox (6 mol%). The vial was sealed with a rubber septum, evacuated under reduced pressure and back filled with argon. Dimethyl sulfoxide (0.4 M) was added under argon, and the vial evacuated for *ca.* 2 minutes. The vial was back filled with argon and stirred in a preheated heating block at 80 ^{o}C for 12 hours. The reaction vial was cooled to room temperature, and directly purified *via* column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give enantioenriched cyclic ketones **80** as solids contaminated with dibenzylideneacetone. The compounds showed identical NMR spectroscopic data to racemic cyclic ketone **80**. The *ee*'s of the cyclic ketones were determined by HPLC analysis using a Phenomenex "Lux 3u Cellulose-1" column (250 mm x 4.6 mm); conditions: 95 : 5 *n*-Hexane/*iso*-propanol, 1.0 mL/min, 220 nm.

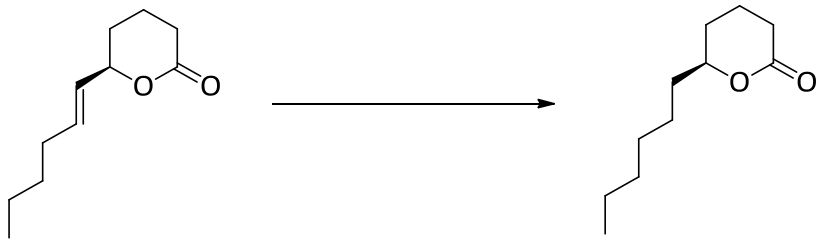
Example (**Table 17**, Entry 1): First component: 7.390 min; Second component: 9.107 min; +98% *ee*; $[\alpha]_D^{22}$ -30.0 (*c* 1.0 CH_3Cl).

PREPARATION OF (*E*)-6-(HEX-1-ENYL)TETRAHYDRO-2*H*-PYRAN-2-ONE **134**



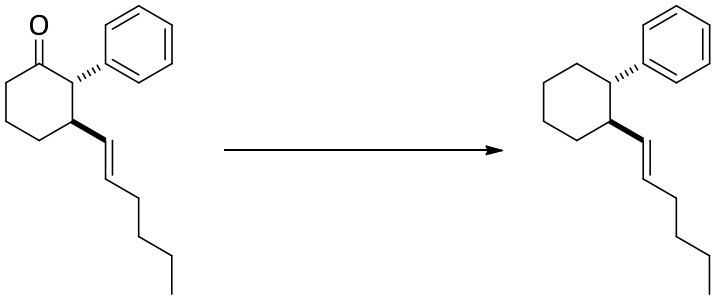
To a stirred solution of enantiopure enol ether ***Z*-79** (37 mg, 0.145 mmol, +98% *ee*) and ruthenium(III) chloride (1.1 mg, 0.005 mmol, 3.5 mol%) in acetonitrile/water (1 : 1, 0.5 mL) at room temperature was added portionwise a mixture of oxone® (133 mg, 0.217 mmol) and sodium hydrogen carbonate (56 mg, 0.664 mmol) over 10 minutes. The reaction mixture was stirred for 2 hours and the dark suspension quenched with saturated sodium thiosulfate solution and extracted with dichloromethane. The organic layer was washed twice with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give lactone **134** as a colourless oil (13.3 mg, 0.073 mmol, 50% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (1H, dtd, *J* = 15.5, 7.0, 1.0 Hz, alkene-*H*), 5.48 (1H, ddt, *J* = 15.5, 6.5, 1.5 Hz, alkene-*H*), 5.78-5.71 (1H, m, OC*H*), 2.61-2.52 (1H, m, C(O)CH_AH$_B$), 2.50-2.40 (1H, m, C(O)CH$_A$$H_B$), 2.08-2.00 (2H, m, C$H_2$), 1.98-1.82 (2H, m, C$H_2$), 1.67-1.59 (1H, m, C*H*), 1.40-1.26 (5H, m, 5 x C*H*), 0.88 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 134.6, 127.9, 80.7, 31.8, 31.0, 29.5, 28.4, 22.1, 18.2, 13.9; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 2956 (m), 2928 (m), 2876 (w), 1735 (s), 1237 (m), 1037 (m), 970 (w); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{11}H_{19}O_2$: 183.1385, found 183.1392.

PREPARATION OF 6-HEXYLTETRAHYDRO-2*H*-PYRAN-2-ONE **147**



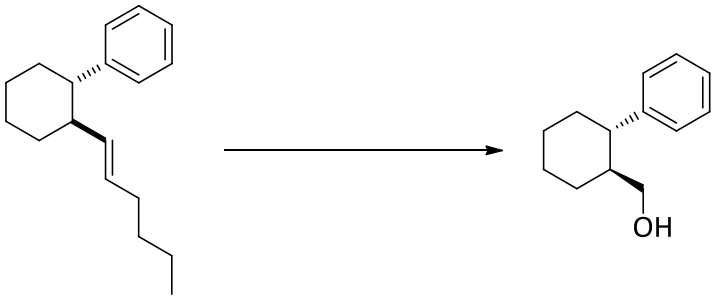
A solution of lactone **134** (13.3 mg, 0.073 mmol) and platinum(IV) oxide (Adam's catalyst, 1.3 mg, 10% w/w) in ethyl acetate (5 mL) was stirred at room temperature under an atmosphere of hydrogen (balloon) for 4 hours. Upon completion, the atmosphere was replaced with nitrogen, and the dark solution filtered through Celite®, washed with ethyl acetate and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica gel (80 : 20 petroleum ether/ethyl acetate) to give lactone **147** as a colourless oil (7.0 mg, 0.038 mmol, 52% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.32-4.22 (1H, m, OC*H*), 2.63-2.52 (1H, m, C(O)CH_AH$_B$), 2.50-2.38 (1H, m, C(O)CH$_A$$H_B$), 1.96-1.84 (3H, m, 3 x C*H*), 1.74-1.65 (1H, m, C*H*), 1.60-1.45 (3H, m, 3 x C*H*), 1.32-1.25 (7H, m, 7 x C*H*), 0.91-0.85 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 80.6, 35.9, 31.7, 29.5, 29.1, 27.8, 24.9, 22.6, 18.5, 14.0; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 1735 (s), 1465 (w), 1342 (w), 1242 (s); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{11}H_{21}O_2$: 185.1542, found 185.1541; $[\alpha]_D^{20}$ -33.3 (*c* 0.9 $CHCl_3$), $[\alpha]_D^{20}$ +46.1 (*c* 0.61 $CHCl_3$) reported for (*R*)-6-hexyltetrahydro-2*H*-pyran-2-one with 98% *ee*.[80]

PREPARATION OF [2-(1-HEXEN-1-YL)CYCLOHEXYL]-BENZENE **148**



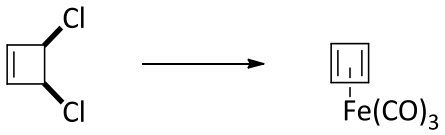
A solution of enantioenriched cyclic ketone **80** (73 mg, 0.285 mmol, +75% *ee*) and *p*-toluenesulfonyl hydrazine (80 mg, 0.428 mmol) in methanol (1.5 mL) was stirred at room temperature for 16 hours. To this was added a solution of zinc chloride (27 mg, 0.199 mmol) and sodium cyanoborohydride (27 mg, 0.428 mmol) in methanol (0.75 mL) *via* cannula. The reaction mixture was heated at 65 ^{o}C for 4 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate, washed with 1M hydrochloric acid, sodium hydrogen carbonate, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica gel (100% petroleum ether) to give *trans*-cyclohexane **148** as a colourless oil (32 mg, 0.132 mmol, 46% yield); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30-7.19 (2H, m, Ar-*H*) 7.18-7.07 (3H, m, Ar-*H*), 5.18-4.93 (2H, m, 2 x alkene-*H*), 2.33-2.06 (2H, m, CH_2), 1.92-1.64 (6H, m, 3 x CH_2), 1.49-1.22 (4H, m, 2 x CH_2), 1.13-0.94 (4H, m, 2 x CH_2), 0.74 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 146.5, 134.3, 129.7, 128.0, 127.8, 125.6, 50.7, 46.4, 35.4, 33.7, 32.1, 31.6, 26.8, 26.2, 21.7, 13.8; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 2956 (s), 2924 (s), 2852 (s), 1446 (w), 965 (w), 754 (w), 698 (w); HRMS (EI) *m/z* [M] calcd for $C_{18}H_{26}$: 242.2034, found 242.2024.

PREPARATION OF *TRANS*-2-PHENYL-CYCLOHEXANEMETHANOL **149**



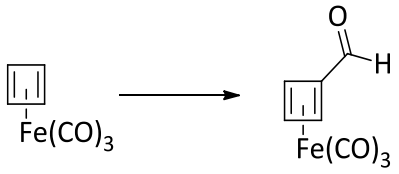
A stirred solution of cyclohexane **148** (30 mg, 0.124 mmol) in methanol/dichloromethane (1 : 1, 5.0 mL) containing a small amount of sodium hydrogen carbonate at -78 ^{o}C was bubbled with ozone until a blue colour persisted. At this point, nitrogen was bubbled through the solution until disappearance of the blue colour. Sodium borohydride (28 mg, 0.744 mmol) was added and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture quenched with ethyl acetate and washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica gel (90 : 10 petroleum ether/ethyl acetate) to give *trans*-cyclohexane **149** as a colourless oil (9.5 mg, 0.050 mmol, 40% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.26 (2H, m, Ar-*H*), 7.24-7.16 (3H, m, Ar-*H*), 3.37 (1H, dd, *J* = 11.0, 4.0 Hz, CH_AH$_B$OH), 3.23 (1H, dd, J = 11.0, 4.0 Hz, CH$_A$$H_B$OH), 2.33 (1H, td, J = 11.5, 3.5 Hz, C*H*), 2.00-1.93 (1H, m, C*H*), 1.90-1.77 (3H, m, 3 x C*H*), 1.54-1.44 (2H, m, CH_2), 1.41-1.35 (2H, m, CH_2), 1.23-1.20 (1H, m, C*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 145.8, 128.6, 127.4, 126.3, 66.6, 47.4, 45.3, 35.5, 29.9, 26.7, 26.1; FTIR (CH_2Cl_2, υ_{max} cm^{-1}): 3368 (br), 2923 (s), 2851 (m), 1452 (m), 1029 (m), 757 (m), 700 (s); HRMS (EI) *m/z* [M] calcd for $C_{13}H_{18}O$: 190.1358, found 190.1352; $[\alpha]_D^{22}$ +26.3 (*c* 1.9 $CHCl_3$), $[\alpha]_D^{25}$ +33.7 (*c* 1.5 $CHCl_3$) reported for (1*S*,2*S*)-2-phenyl-cyclohexanemethanol with 96% *ee*.[81]

PREPARATION OF CYCLOBUTADIENEIRON TRICARBONYL **151**[108]



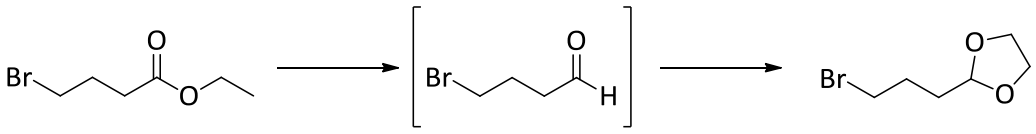
To a stirred solution of *cis*-3,4-dichlorocyclobutene (2.00 g, 16.26 mmol) in anhydrous benzene (12.5 mL) at room temperature was added diironnonacarbonyl (2.00 g). The resulting dark solution was heated to 55 ^{o}C where the evolution of carbon monoxide commenced. Once stopped, further portions of diironnonacarbonyl were added over 3 hours, governed by carbon monoxide evolution (total amount of diironnonacarbonyl used was 14.0 g, 38.48 mmol). Upon addition of the last portion, the dark reaction solution was stirred at 50 ^{o}C for 1 hour. The reaction mixture was cooled to room temperature, diluted with pentane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a dark green oil. Kugelrohr distillation at 75-100 ^{o}C under 40 mmHg gave cyclobutadieneiron tricarbonyl **151** as a pale yellow oil (1.9 g, 9.89 mmol, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (4H, s, 4 x C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.5, 63.8; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2923 (m), 2852 (m), 2049 (s), 1965 (s); HRMS (EI) *m/z* [M] calcd for $C_7H_4{}^{56}FeO_3$: 191.9510, found 191.9517.

PREPARATION OF CYCLOBUTA-1,3-DIENECARBALDEHYDEIRON TRICARBONYL **180**



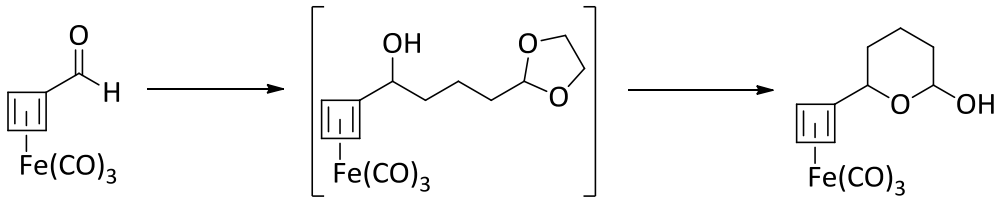
To *N*-methylformanilide (520 mg, 3.84 mmol) at 0 ^{o}C was added phosphorus oxychloride (4.0 mL) and the resulting solution stirred at 0 ^{o}C for 30 minutes. Cyclobutadieneiron tricarbonyl **151** (330 mg, 1.72 mmol) was added and the resulting yellow solution stirred at 50 ^{o}C for 16 hours. The red reaction mixture was poured onto ice/water and extracted twice with dichloromethane. The combined dichloromethane washings were washed with water (3 x 10 mL), hydrochloric acid (1 M in water, 3 x 10 mL), saturated sodium hydrogen carbonate solution (2 x 10 mL), brine (10 mL), dried with sodium sulphate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give **180** as a dark red oil (300 mg, 1.36 mmol, 79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (1H, s, C*H*O), 4.67 (2H, s, 2 x C*H*), 4.53 (1H, s, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2, 187.6, 71.6, 69.6, 65.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2924 (s), 2852 (s), 2061 (s), 1989 (s), 1671 (m), 1561 (w), 1432 (w); HRMS (EI) *m/z* [M] calcd for $C_8H_4{}^{56}FeO_4$: 219.9459, found 219.9452.

PREPARATION OF 2-(3-BROMOPROPYL)-1,3-DIOXOLANE **183**[110]



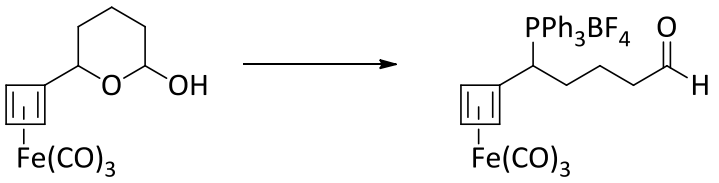
To a stirred solution of ethyl 4-bromobutanoate **181** (19.5 g, 0.10 mol) in dichloromethane (180 mL) at -78 °C was added diisobutylaluminium hydride (1.0 M in hexanes, 100 mL, 0.1 mol) dropwise. The reaction mixture was stirred at -78 °C for 90 minutes. The reaction mixture was quenched by pouring into ice-cold hydrochloric acid (4 M in water) and stirred at 0 °C for 1 hour. The organic phase was separated, and the aqueous extracted with dichloromethane. The combined organic extracted were washed subsequently with water, and brine then dried over sodium sulphate and concentrated *in vacuo*, to give crude aldehyde **182** as yellow oil (17.0 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (1H, s, C*H*O), 3.45 (2H, t, *J* = 6.5 Hz, -C*H*$_2$Br), 2.67 (2H, dt, *J* = 7.0, 0.5 Hz, C*H*$_2$), 2.17 (2H, quin, *J* = 6.5 Hz, C*H*$_2$). The residue was dissolved in toluene (350 mL), then ethylene glycol (46.0 g, 0.75 mol) and *p*-toluenesulfonic acid (0.68 g, 4.0 mmol) was added followed by refluxing of the reaction mixture with a Dean-Stark trap. Once all the water was removed, the reaction mixture was allowed to cool to room temperature, and sodium hydrogen carbonate (3 g) was added. After stirring for 10 minutes, the reaction mixture was washed with saturated sodium hydrogen carbonate solution, dried with potassium carbonate and concentrated *in vacuo*. The crude residue was purified by Kugelrohr distillation at 94-96 °C under 10 mmHg to give acetal bromide **183** as a pale yellow oil (16.8 g, 0.09 mol, 87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86 (1H, t, *J* = 4.5 Hz, C*H*), 3.95-3.90 (2H, m, -OC*H*$_2$CH$_2$O-), 3.83-3.78 (2H, m, -OCH$_2$C*H*$_2$O-), 3.42 (2H, t, *J* = 7.0 Hz, -C*H*$_2$Br), 1.99-1.92 (2H, m, C*H*$_2$), 1.81-1.74 (2H, m, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.7, 64.9, 33.5, 32.3, 27.2; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2958 (s), 2884 (s), 2765 (w), 1735 (s), 1440 (s), 1410 (s), 1252 (s), 1131 (s), 943 (s).

PREPARATION OF 6-(CYCLOBUTA-1,3-DIENYL)TETRAHYDRO-2*H*-PYRAN-2H-OLIRON TRICARBONYL **177**



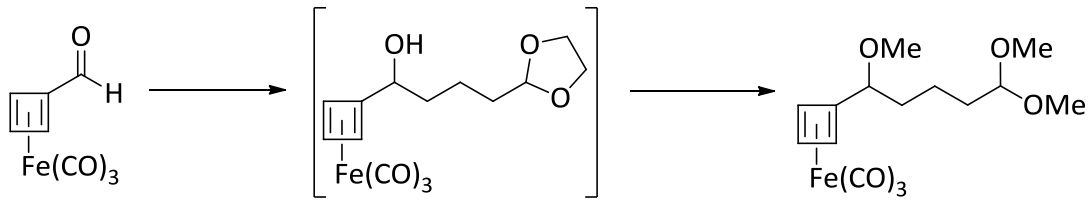
To a stirred solution of acetal-bromide **183** (800 mg, 4.145 mmol) in diethyl ether (9.0 mL) at -78 ^{o}C was added *tert*-butyllithium (1.5 M in pentane, 5.4 mL, 8.290 mmol) dropwise over 5 minutes. The cloudy reaction mixture was stirred at -78 ^{o}C for 1 hour, then at 0 ^{o}C for 1 hour before cooling back to -78 ^{o}C. To the reaction mixture was added a solution of aldehyde **180** (200 mg, 1.04 mmol) in diethyl ether (2.5 mL) slowly *via* cannula. The red reaction mixture was stirred at -78 ^{o}C for 45 minutes, then at 0 ^{o}C for 45 minutes. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether (x3). The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*, to give crude alcohol **184** as yellow oil. To a stirred solution of the crude residue in acetone/water (2 : 1, 20 mL) was added pyridinium toluene-4-sulfonate (200 mg, 0.800 mmol) and the reaction mixture heated at reflux for 16 hours. The reaction mixture was diluted with diethyl ether, the aqueous separated and extracted with further diethyl ether. The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give lactol **177** as a yellow oil (200 mg, 0.685 mmol, 66%) as a 1 : 1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 (0.5H, s, C*H*OH), 4.72 (0.5H, br t, *J* = 6.5 Hz, C*H*OH), 4.37 (0.5H, d, *J* = 11 Hz, pyran-OC*H*), 4.18-4.00 (3H, m, 3 x C*H*), 3.86 (0.5H, d, *J* = 11 Hz, pyran-OC*H*), 3.37 (0.5H, d, *J* = 5.5 Hz, O*H*), 2.85 (0.5H, s, O*H*), 1.78-1.15 (6H, m, 3 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 214.4, 96.6, 92.0, 86.9, 84.7, 71.9, 64.4, 62.9, 62.5, 62.3, 61.9, 32.2, 30.6, 29.6, 29.4, 21.8, 17.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 3446 (br), 2956 (s), 2924 (s), 2853 (s), 2046 (s), 1969 (s); HRMS (EI) *m/z* [M] calcd for $C_{12}H_{12}{}^{56}FeO_5$: 292.0034, found 292.0036.

PREPARATION OF (1-(CYCLOBUTA-1,3-DIENYL)-5-OXOPENTYL)TRIPHENYLPHOSPHONIUM TETRAFLUOROBORONATEIRON TRICARBONYL **185**



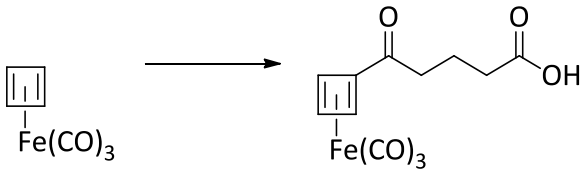
To a suspension of 4 Å molecular sieves (400 mg) and a solution of $HPPh_3BF_4$ (400 mg, 1.00 mmol) in acetonitrile (2.5 mL) was added a solution of lactol **177** (160 mg, 0.57 mmol) in acetonitrile (2.5 mL). The resulting suspension was heated at reflux for 20 hours. Upon cooling to room temperature, the suspension was diluted with dichloromethane, filtered through Celite® and the filtrate concentrated *in vacuo* to give a thick pale yellow oil. To this was added 2 mL of dichloromethane, then diethyl ether/petroleum ether (1 : 1, 100 mL) followed by vigorous stirring for 15 minutes. The clear solution was decanted and the process repeated four times to the remaining pale yellow gum. Upon final decantation, the yellow gum was concentrated *in vacuo* to give **185** as a yellow solid (250 mg, 0.40 mmol, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (1H, s, C*H*O), 7.87-7.72 (15H, m, Ar*H*), 4.23-4.13 (1H, m, C*H*P), 4.11 (1H, s, C*H*), 3.92 (1H, d, *J* = 9.0 Hz, C*H*), 3.43 (1H, d, *J* = 9.0 Hz, C*H*), 2.56-2.43 (2H, m, CH_2), 2.14-2.00 (1H, m, C*H*), 1.96-1.82 (2H, m, CH_2), 1.31-1.21 (1H, m, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.5, 201.4, 135.2, 133.9 (J_{CP} = 10.0 Hz), 130.5 (J_{CP} = 12.0 Hz), 116.9 (J_{CP} = 82.0 Hz), 75.2, 65.3, 64.3, 62.8, 42.4, 34.6 (J_{CP} = 43.0 Hz), 27.6, 20.6 (J_{CP} = 10.0 Hz); ^{31}P NMR (100 MHz, $CDCl_3$): δ 27.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2925 (w), 2050 (s), 1981 (s), 1721 (w), 1440 (m), 1110 (m), 1059 (s), 725 (m); HRMS (EI) *m/z* $[M\text{-}BF_4]^+$ calcd for $C_{30}H_{26}{}^{56}FeO_4P$: 537.0918, found 537.0921.

PREPARATION OF 1-(1,5,5-TRIMETHOXYPENTYL)CYCLOBUTA-1,3-DIENEIRON TRICARBONYL **189**



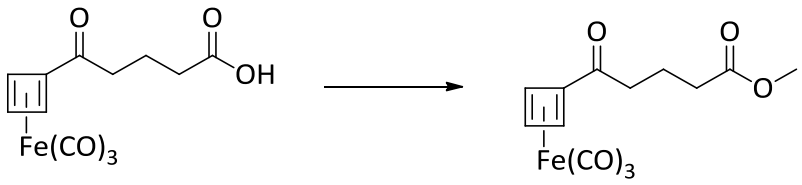
To a stirred solution of acetal-bromide **183** (1.20 g, 6.218 mmol) in diethyl ether (15.0 mL) at -78 ^{o}C was added *tert*-butyllithium (1.7 M in pentane, 7.2 mL, 12.240 mmol) dropwise over 5 minutes. The cloudy reaction mixture was stirred at -78 ^{o}C for 1 hour, then at 0 ^{o}C for 1 hour before cooling back to -78 ^{o}C. To the reaction mixture was added a solution of aldehyde **180** (400 mg, 2.08 mmol) in diethyl ether (5.0 mL) slowly *via* cannula. The red reaction mixture was stirred at -78 ^{o}C for 45 minutes, then at 0 ^{o}C for 45 minutes. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The organic extracts dried over sodium sulphate and concentrated *in vacuo*, to give crude alcohol **184** as yellow oil. To a stirred solution of the crude residue in methanol (20 mL) was added pyridinium toluene-4-sulfonate (200 mg, 0.800 mmol) and the reaction mixture heated at reflux for 16 hours. The reaction mixture was diluted with diethyl ether, the aqueous separated and extracted with further diethyl ether. The combined organic extracts were dried over sodium sulphate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (4 : 1 petroleum ether/diethyl ether) to give acetal **189** as a yellow oil (500 mg, 1.420 mmol, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (1H, t, *J* = 5.0 Hz, C*H*$(OMe)_2CH_2$), 4.13 (1H, s, C*H*), 4.06 (2H, s, 2 x C*H*), 3.53-3.45 (1H, m, CC*H*$(OMe)CH_2$), 3.37 (3H, s, OCH_3), 3.31 (6H, s, 2 x OCH_3), 1.67-1.40 (6H, m, 3 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.5, 104.4, 85.6, 76.5, 63.2, 62.9, 62.6, 57.1, 52.7, 34.1, 32.2, 20.7; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2919 (s), 2045 (s), 1970 (s), 1737, (w), 1467 (w), 1126 (m); HRMS (EI) *m/z* [M] calcd for $C_{15}H_{20}{}^{56}FeO_6$: 352.0609, found 352.0614.

PREPARATION OF 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOIC ACIDIRON TRICARBONYL **192**



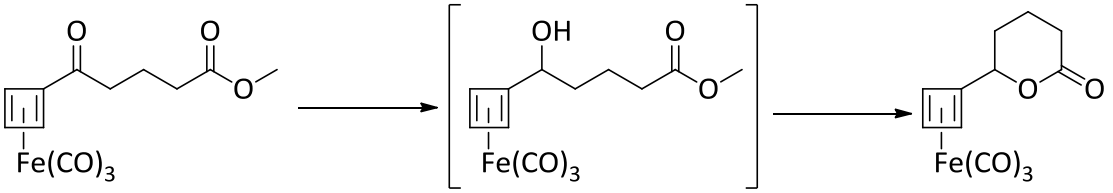
To a stirred solution of cyclobutadieneiron tricarbonyl **151** (200 mg, 1.04 mmol) and glutaric anhydride (125 mg, 1.10 mmol) in dichloromethane (1.0 mL) at -20 ^{o}C was added aluminium(III) chloride (300 mg, 2.19 mmol) portionwise over 15 minutes. After 4 hours at -20 ^{o}C, the reaction mixture was poured onto saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The aqueous layer was adjusted to pH 1 with concentrated HCl and extracted with ethyl acetate, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate with 1% acetic acid) to give acid **192** as a brown oil (167 mg, 0.54 mmol, 54%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.61 (1H, br, CO_2H), 4.56 (2H, s, 2 x C*H*), 4.43 (1H, s, C*H*), 2.40 (2H, t, *J* = 7.0 Hz, CH_2), 2.32 (2H, t, *J* = 7.0 Hz, CH_2), 1.92 (2H, quin, *J* = 7.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 199.2, 179.1, 69.7, 69.6, 64.6, 36.5, 32.9, 19.1; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 3360 (br), 2924 (s), 2853 (m), 2059 (m), 1988 (m), 1710 (m), 1591 (s), 1439 (s); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{12}H_{11}{}^{56}FeO_6$: 306.9905, found 306.9902.

PREPARATION OF METHYL 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOATEIRON TRICARBONYL **194**



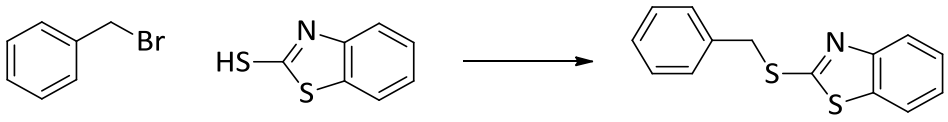
To a stirred solution of acid **192** (240 mg, 0.781 mmol) in methanol/toluene (1 : 3, 6 mL) at room temperature was added (trimethylsilyl)diazomethane solution (2.0 M in hexanes, 0.6 mL, 1.171 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 hour and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give ester **194** as a yellow oil (200 mg, 0.625 mmol, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (2H, s, 2 x C*H*), 4.42 (1H, s, C*H*), 3.67 (3H, s, CH_3), 2.37-2.25 (4H, m, 2 x CH_2), 1.97-1.85 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.8, 199.1, 173.4, 69.5, 64.7, 51.6, 36.7, 32.8, 29.7, 19.3; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2056 (s), 1980 (s), 1736 (m), 1668 (w), 1436 (w), 1201 (w); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{13}H_{13}{}^{56}FeO_6$: 321.0062, found 321.0059.

PREPARATION OF METHYL 5-(CYCLOBUTA-1,3-DIEN-1-YL)-5-OXOPENTANOATEIRON TRICARBONYL **190**



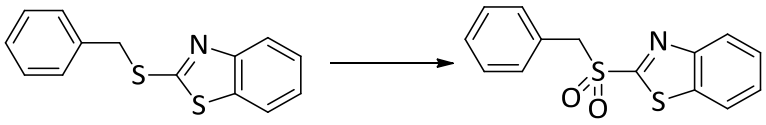
To a stirred solution of ester **194** (160 mg, 0.500 mmol) in ethanol/1,4-dioxane (4 : 1 , 10 mL) at 0 ^{o}C was added sodium borohydride (57 mg, 1.500 mmol). After stirring at 0 ^{o}C for 3 hours, the reaction was quenched with water and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude residue was dissolved in benzene (10 mL). Activated 4 Å molecular sieves (200 mg) were added and the resulting suspension heated at reflux for 24 hours and cooled to room temperature. The reaction mixture was filtered through Celite®, washed with ethyl acetate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (2 : 1 petroleum ether/ethyl acetate) to give lactone **190** as a yellow oil (100 mg, 0.345 mmol, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (1H, dd, *J* = 11.0, 3.5 Hz, >C*H*OC(O)), 4.24-4.13 (3H, m, 3 x C*H*), 2.64-2.54 (1H, m, C(O)CH_AH$_B$), 2.50-2.39 (1H, m, C(O)CH$_A$$H_B$), 2.02-1.94 (3H, m, 3 x C*H*), 1.57-1.46 (1H, m, C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 170.9, 92.9, 63.6, 62.9, 60.4, 31.5, 29.4, 18.9; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2928 (w), 2855 (w), 2046 (s), 1966 (s), 1737 (m), 1234 (w), 613 (m), 590 (m); HRMS (EI) *m/z* [M]$^{+}$ calcd for $C_{12}H_{10}{}^{56}FeO_5$: 289.9878, found 289.9882.

PREPARATION OF 2-(BENZYLTHIO)BENZO[D]THIAZOLE **198**[114]



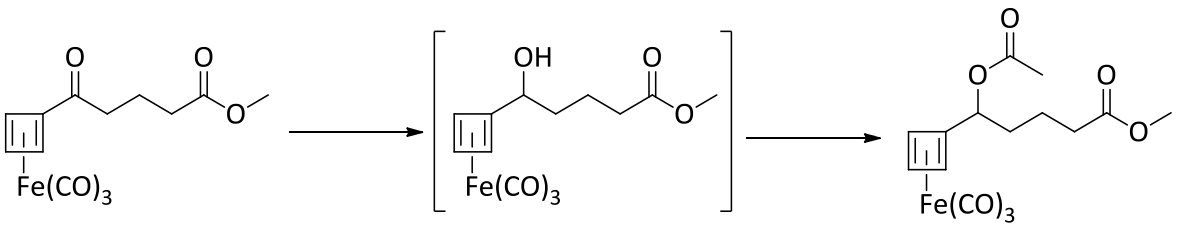
A stirred suspension of benzyl bromide (1.00 g, 5.84 mmol), 2-mercaptobenzothiazole **197** (980 mg, 5.84 mmol) and potassium carbonate (1.62 g, 11.69 mmol) in acetone (10 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*, to give sulfide **198** as a yellow solid (1.53 g, 5.95 mmol, >99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.76 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.50-7.41 (3H, m, Ar-*H*), 7.38-7.28 (4H, m, Ar-*H*), 4.62 (2H, s, C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 153.1, 136.1, 135.3, 129.1, 128.7, 127.7, 126.0, 124.3, 121.5, 121.0, 37.7; HRMS (EI) *m/z* $[M]^+$ calcd for $C_{14}H_{12}NS_2$: 258.0411, found 258.0407.

PREPARATION OF 2-(BENZYLSULFONYL)BENZO[D]THIAZOLE **199**[115]



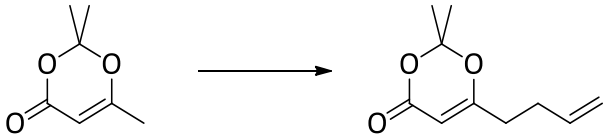
To a stirred solution of sulfide **198** (1.53 g, 5.95 mmol) in chloroform (15 mL) at 0 ^{o}C was added a solution of *m*-chloroperbenzoic acid (70%, 3.375 g, 13.69 mmol) in chloroform (35 mL) dropwise over 45 minutes. Upon addition, the reaction mixture was stirred at 0 ^{o}C for 30 minutes then at room temperature overnight. The reaction mixture was poured into saturated sodium hydrogen carbonate solution and stirred for 15 minutes. The layers were separated and the aqueous extracted further with chloroform. The combined organic extracted were washed subsequently with saturated sodium hydrogen carbonate solution, saturated sodium thiosulfate solution and water then dried and concentrated *in vacuo*, to give sulfone **199** as a white solid (1.50 g, 5.53 mmol, 93%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.95 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.66 (1H, td, *J* = 7.5, 1.0 Hz, Ar-*H*), 7.59 (1H, td, *J* = 7.5, 1.0 Hz, Ar-*H*), 7.36-7.27 (5H, m, Ar-*H*), 4.77 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 152.6, 137.1, 131.1, 129.2, 128.9, 128.0, 127.6, 126.3, 125.5, 122.3, 61.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2924 (m), 2853 (w), 1471 (m), 1457 (m), 1333 (s), 1154 (s), 1126 (m), 763 (s) 730 (w); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{14}H_{12}NO_2S_2$: 290.0309, found 290.0304.

PREPARATION OF METHYL 5-(ACETYLOXY)-5-(CYCLOBUTA-1,3-DIEN-1-YL)PENTANOATEIRON TRICARBONYL **202**



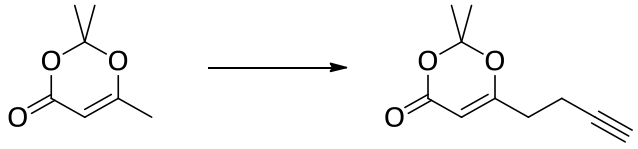
To a stirred solution of ester **194** (100 mg, 0.31 mmol) in ethanol (10 mL) at 0 ^{o}C was added sodium borohydride (35 mg, 0.93 mmol). After stirring at 0 ^{o}C for 3 hours, the reaction was quenched with water and extracted with ethyl acetate, dried over sodium sulfate and concentrated *in vacuo*. To crude residue dissolved in dichloromethane (10 mL) was added 4-dimethylaminopyridine (2 mg, 0.016 mmol), acetic anhydride (150 μL, 1.55 mmol), triethylamine (216 μL, 1.55 mmol) and the reaction mixture stirred at room temperature for 16 hours. To the reaction mixture was poured onto saturated potassium carbonate solution and extracted with ethyl acetate. The aqueous layer was washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give diester **202** as a brown oil (50 mg, 0.13 mmol, 42%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27-5.10 (1H, m, $CH_3C(O)OCH<$), 4.16 (1H, s, C*H*), 4.04 (2H, s, 2 x C*H*), 3.66 (3H, s, C(O)OCH_3), 2.38-2.26 (2H, m, CH_2), 2.05 (3H, s, C(O)CH_3), 1.71-1.52 (4H, m, 2 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.1, 173.5, 170.3, 68.2, 63.6, 63.2, 62.9, 60.4, 51.6, 33.3, 32.9, 20.8; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2982 (w), 2961 (w), 2046 (s), 1965 (s), 1736 (m), 1234 (m), 592 (m).

PREPARATION OF 6-(BUT-3-EN-1-YL)-2,2-DIMETHYL-4*H*-1,3-DIOXIN-4-ONE **212**



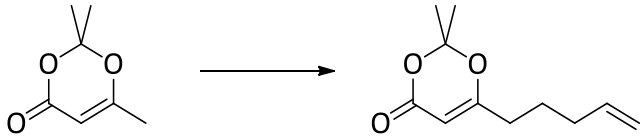
To a stirred solution of diisopropylamine (485 μL, 3.47 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (3 mL) in tetrahydrofuran (20 mL) at -78 ^{o}C was added *n*-butyllithium (2.4 M in hexanes, 1.25 mL, 3.00 mmol) dropwise. After stirring at -78 ^{o}C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 ^{o}C. Dioxinone **211** (278 μL, 2.10 mmol) was added dropwise at -78 ^{o}C and stirred for 30 minutes. After this time, allyl bromide (1100 μL, 12.82 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give alkene **212** as a yellow oil (116 mg, 0.67 mmol, 31%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76-5.63 (1H, m, C*H*CH_2), 5.16 (1H, s, C*H*), 5.04-4.90 (2H, m, CHC*H*$_2$), 2.29-2.19 (4H, m, 2 x C*H*$_2$), 1.60 (6H, s, 2 x C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 161.2, 135.9, 116.1, 106.3, 93.4, 32.8, 29.6, 25.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2998 (w), 2923 (w), 1732 (s), 1635 (m), 1391 (m), 1273 (m), 1205 (m), 1015 (m); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{10}H_{15}O_3$: 183.1021, found 183.1014.

PREPARATION OF 6-(BUT-3-YN-1-YL)-2,2-DIMETHYL-4*H*-1,3-DIOXIN-4-ONE **214**



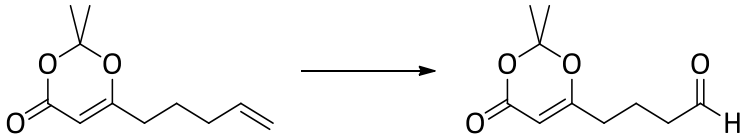
To a stirred solution of diisopropylamine (1000 μL, 6.94 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (6 mL) in tetrahydrofuran (40 mL) at -78 ^{o}C was added *n*-butyllithium (2.4 M in hexanes, 2.50 mL, 6.00 mmol) dropwise. After stirring at -78 ^{o}C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 ^{o}C. Dioxinone **211** (500 μL, 4.20 mmol) was added dropwise at -78 ^{o}C and stirred for 30 minutes. After this time, propargyl bromide (2000 μL, 25.64 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/ethyl acetate) to give alkyne **214** as a yellow oil (300 mg, 1.67 mmol, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (1H, s, C*H*), 2.28-2.24 (4H, m, 2 x CH_2), 1.80 (1H, s, CC*H*), 1.50 (6H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 160.7, 106.5, 94.2, 93.6, 70.1, 32.3, 24.8, 15.0; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 3290 (w), 3000 (w), 1728 (s). 1638 (m), 1393 (m), 1378 (m), 1274 (m), 1254 (m), 1204 (m); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{10}H_{13}O_3$: 181.0865, found 181.0857.

PREPARATION OF 6-(BUT-3-EN-1-YL)-2,2-DIMETHYL-4*H*-1,3-DIOXIN-4-ONE **215**



To a stirred solution of diisopropylamine (812 μL, 5.81 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (6 mL) in tetrahydrofuran (30 mL) at -78 ^{o}C was added *n*-butyllithium (2.0 M in hexanes, 2.50 mL, 5.00 mmol) dropwise. After stirring at -78 ^{o}C for 20 minutes, the reaction mixture was stirred at room temperature for 5 minutes, and then cooled back to -78 ^{o}C. Dioxinone **211** (467 μL, 3.52 mmol) was added dropwise at -78 ^{o}C and stirred for 30 minutes. After this time, 4-bromo-1-butene (1000 μL, 9.85 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 17 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (3 : 1 petroleum ether/diethyl ether) to give alkene **215** as a yellow oil (84 mg, 0.43 mmol, 12%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.68 (1H, m, C*H*CH_2), 5.21 (1H, s, C*H*), 5.06-4.96 (2H, m, CHCH_2), 2.24-2.17 (2H, m, CH_2), 2.11-2.04 (2H, m, CH_2), 1.66 (6H, s, 2 x CH_3), 1.65-1.60 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 161.3, 137.3, 115.7, 106.3, 93.3, 32.8 (x2), 25.0, 24.8; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2999 (w), 2940 (w), 1731 (s), 1636 (m), 1377 (m), 1273 (m), 1205 (m), 1013 (w), 903 (w), 807 (w); HRMS (EI) *m/z* $[MH]^+$ calcd for $C_{11}H_{17}O_3$: 197.1178, found 197.1170.

PREPARATION OF 4-(2,2-DIMETHYL-4-OXO-4*H*-1,3-DIOXIN-6-YL)BUTANAL **210**



To a stirred solution of alkene **215** (66 mg, 0.33 mmol) and ruthenium(III) chloride (4 mg, 0.02 mmol, 5.0 mol%) in acetonitrile/water (6 : 1, 3.5 mL) at room temperature was added sodium periodate (252 mg, 1.18 mmol) and the mixture stirred for 2.5 hours. The dark suspension was quenched with saturated sodium thiosulfate solution and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude mixture was purified *via* column chromatography on silica gel (2 : 1 petroleum ether/ethyl acetate) to give aldehyde **210** as a yellow oil (31 mg, 0.16 mmol, 47% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (1H, t, *J* = 1.0 Hz, C*H*O), 5.24 (1H, s, C*H*), 2.53 (2H, td, *J* = 7.0, 1.0 Hz, CH_2CHO), 2.26 (2H, t, *J* = 7.5, CH_2CH$_2$CH$_2$CHO), 1.87 (2H, tt, *J* = 7.5, 7.0 Hz, CH$_2$CH_2CH$_2$), 1.67 (6H, s, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 170.6, 161.1, 106.5, 93.7, 42.6, 32.7, 25.0, 18.2; FTIR ($CDCl_3$, υ_{max} cm^{-1}): 2933 (w), 2855(w), 1724 (s), 1633 (m), 1392 (m), 1274 (m), 1204 (m), 1014 (m); HRMS (EI) *m/z* [MH]$^+$ calcd for $C_{10}H_{15}O_4$: 199.0970, found 199.0961.

6 REFERNECES

1 Meek, S. J.; Harrity, J. P. A. *Tetrahedron* **2007**, *63*, 3081

2 Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939

3 Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455

4 Chretien, F.; Chapleur Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1268

5 Machado, A. S.; Olesker, A.; Lukacs, G. *Carbohydr. Res.* **1985**, *135*, 231

6 Adam, S. *Tetrahedron Lett.* **1988**, *29*, 6589

7 (a) Barton, D. H.; Camara, J.; Dalko, P.; Gero, S. D.; Quiclet-Sire, B.; Stutz, P. *J. Org. Chem.* **1989**, *54*, 3764
(b) Barton, D. H.; Augy-Dorey, S.; Camara, J.; Dalko, P.; Delaumeny, J. M.; Gero, S. D.; Quiclet-Sire, B.; Stutz, P. *Tetrahedron* **1990**, *46*, 215

8 László, P.; Dudon, A. *J. Carbohydr. Chem.* **1992**, *11*, 587

9 Iimori, T.; Takahaski, H.; Ikagami, S. *Tetrahedron Lett.* **1996**, *37*, 649

10 Sollogoub. M.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1998**, *39*, 3471

11 Petrignet, J.; Prathap, I.; Chandrasekhar, S.; Yadav, J. S.; Greé, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6297

12 Mac, D. H.; Samineni, R.; Petrignet, J.; Srihari, P.; Chandrasekhar, S.; Yadav, J. S.; Greé, R. *Chem. Commun.* **2009**, 4717

13 Tsuji, J.; Takahaski, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387

14 Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292

15 Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahaski, T. *Tetrahedron Lett.* **1980**, *21*, 1475

16 Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840

17 (a) Rhoads, S. J.; Watson, J. M. *J. Am. Chem. Soc.* **1971**, *93*, 5813
(b) Demole, E.; Enggish, P. *J. Chem. Soc., Chem. Comm.* **1969**, 264

18 Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2485

19 Card, R. J.; Neckers, D. C. *J. Org. Chem.* **1978**, *43*, 2958

20 Cotton, F. A.; Faller, J. W.; Musco, A. *Inorg. Chem.* **1967**, *6*, 179

21 Faller, J. W.; Thomson, M. E.; Mattina, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 2642

22 Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559

23 Shimizu, S.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199

24 Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem.* **2005**, *117*, 7084; *Angew. Chem., Int. Ed.* **2005**, *44*, 6924

25 Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034

26 Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846

27 Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180

28 Steglich, W.; Höfle G. *Tetrahedron Lett.* **1970**, *11*, 4727

29 Höfle G.; Steglich, W.; Vorbrügglin, H. *Angew. Chem., Int. Ed.* **1978**, *17*, 569

30 Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425
31 Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532
32 Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769
33 Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368
34 Hills I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921
35 Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925
36 Thomson, J. E.; Kyle, A. F.; Concellón, C.; Gallagher, K. A.; Lenden, P.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, 2805
37 Thomson, J. E.; Campbell, C. D.; Concellón, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784
38 Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A; Smith, A. D. *Chem. Commun.* **2008**, 3528
39 Joannesse, C.; Simal, C.; Concellón, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900
40 Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1829
41 Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354
42 Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *Synlett* **1997**, 1055
43 Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1091
44 Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622
45 Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2665
46 Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720
47 Nasvesckuk, C. G.; Rovis, T. *Org. Lett.* **2005**, *7*, 2173
48 Carbery, D. R.; Reignier, S.; Myatt, J. W.; Miller, N. D.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2584
49 Carbery, D. R.; Miller, N. D.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1546
50 Carbery, D. R.; Reignier, S.; Miller, N. D.; Adams, H.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4392
51 Meek, S. J.; Pradaux, F.; Carbery, D. R.; Demont, E. H.; Harrity, J. P. A. *J. Org. Chem*. **2005**, *70*, 10046
52 Meek, S. J.; Pradaux, F.; Demont, E. H.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 5597
53 Brioche, J. C. R., Unpublished observations
54 Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456
55 Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293
56 Brown, D. S.; Ley, S. V. *Tetrahedron Lett.* **1988**, *29*, 4869
57 Elzner, S.; Maas, S.; Engel, S.; Kunz, H. *Synthesis* **2004**, 2153

58 Dunkel, R.; Treu, J.; Hoffmann, H. M. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1539
59 Lieberknecht, A.; Griesser, H.; Krämer, B.; Bravo, R. D.; Colinas, P. A.; Grigera, R. J. *Tetrahedron* **1999**, *55*, 6475
60 Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215
61 (a) Ogasaqara, M.; Takizawa, K-i; Hayashi, T. *Organometallics* **2002**, *21*, 4853
(b) Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464
(c) Krämer, K.; Kazmaier, U. *J. Org. Chem.* **2006**, *71*, 8950
62 Sasmal, K. P.; Maier, M. E. *Org. Lett.* **2002**, *4*, 1271
63 Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867
64 Trost, B. M.; Xu. J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343
65 Lautens, M.; Maddess, M. L. *Org. Lett.* **2004**, *6*, 1883
66 Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307
67 Vanheusden, V.; Busson, R.; Herdewijn, P.; Van Calenbergh, S. *J. Org. Chem.* **2004**, *69*, 4446
68 Chen, J.; Lin, G.-Q.; Wang, Z.-M.; Liu, H.-Q. *Synlett* **2002**, 1265
69 Carlson, R. M.; Oyler, A. R. *Tetrahedron Lett.* **1974**, *30*, 2615
70 Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539
71 Ishikawa, T.; Shimizu, K.; Ishii, H.; Ikeda, S.; Saito, S. *J. Org. Chem.* **2001**, *66*, 3834
72 Mase, N.; Inoue, A.; Nishio, M.; Takabe, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3955
73 Walton, A. Z.; Conerly, W. C.; Pompeu, Y.; Sullivan, B.; Stewart, J. D. *ACS Catal.* **2011**, *1*, 989
74 (a) Coutrot, P.; Grison, C.; Bômont, C. *J. Organomet. Chem.* **1999**, *586*, 208
(b) Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett.* **1983**, *24*, 4883
75 Coutrot, P.; Grison, C.; Bômont, C. *Tetrahedron Lett.* **1994**, *35*, 8381
76 Zirimwabagabo, J.-O., Unpublished observations
77 Goodman, J. M.; Köhler, A.-K.; Alderton, S. C. M. *Tetrahedron Lett.* **1999**, *40*, 8715
78 Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181
79 Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174
80 Goergens, U.; Schneider, M. P *Tetrahedron: Asymmetry* **1992**, *3*, 831
81 Hong, B.-C.; Nimje, R. Y.; Sadani, A. A.; Liao, J.-H. *Org. Lett.* **2008**, *10*, 2345
82 Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814
83 Williams, J. M. J. *Synlett* **1996**, 705
84 Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523
85 Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336

86 Behenna, D. C.; Mohr, J. T.; Sherden, N. H; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist Jr., J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199

87 Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873

88 (a) Pettit, R. *J. Organomet. Chem.* **1975**, *100*, 205
(b) Seyferth, D. *Organometallics* **2003**, *22*, 2

89 Emerson, G. F.; Watts, L.; Pettit, R. *J. Am. Chem. Soc.* **1965**, *87*, 131

90 Rosenblum, M.; Gatsonis, C. *J. Am. Chem. Soc.* **1967**, *89*, 5074

91 Grubbs, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 6693

92 Adams, C. M.; Joslin, S. A.; Crawford, E. S.; Schemenaur, J. E. *Organometallics* **1993**, *12*, 656

93 Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071

94 King, R. B.; Murray, R. M.; Davis, R. E.; Ross, P. K. *J. Organomet. Chem.* **1987**, *330*, 115

95 Harvey, P. D.; Schaefer, W. P.; Gray, H. B.; Gilson, D. F. R.; Butler, I. S. *Inorg. Chem.* **1988**, *27*, 57

96 Fitzpatrick, J. D.; Watts, L.; Emerson, G. F.; Pettit, R. *J. Am. Chem. Soc.* **1965**, *87*, 3254

97 Emerson, G. F.; Pettit, R. *J. Am. Chem. Soc.* **1962**, *84*, 4591

98 Pfletschinger, A.; Schneider, U.; Lex, J.; Schmalz, H.-G. *Eur. J. Org. Chem.* **2007**, 3991

99 Bunz, U. *Organometallics* **1993**, *12*, 3594

100 Limanto, J.; Tallarico, J. A.; Porter, J. R.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 14748

101 Wiegelmann, J. E. C.; Bunz, U. H. F. *Organometallics* **1993**, *12*, 3792

102 Byers, J. H.; Sontum, S. F.; Dimitrova, T. S.; Huque, S.; Zegarelli, B. M.; Zhang, Y.; Jasinski, J. P.; Butcher, R. J. *Organometallics* **2006**, *25*, 3787

103 (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196
(b) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478
(c) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152
(d) Williams, M. J.; Deak, H. L.; Snapper, M. L. *J. Am. Chem. Soc.* **2007**, *129*, 486

104 Paquette, L. A.; Gugelchuk, M.; Hsu, Y.-L. *J. Org. Chem.* **1986**, *51*, 3864

105 Limanto, J.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 16310

106 Grubbs, R. H.; Pancoast, T. A.; Grey, R. A. *Tetrahedron Lett.* **1974**, *28*, 2425

107 Seigal, B. A.; An, M. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4929

108 Pettit, R. Henery, J. *Org. Synth.* **1970**, *50*, 21

109 Adams, C. M.; Holt, E. M. *Organometallics* **1990**, *9*, 980
110 Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881
111 Knölker, H.-J.; Fröhner, W.; Reddy, K. R. *Eur. J. Org. Chem.* **2003**, 740
112 Knox, G. R.; Thom, I. G. *J. Chem. Soc., Chem. Comm.* **1981**, 373
113 (a) Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjian, P. G. *Tetrahedron Lett.* **2008**, *49*, 750
(b) Gueyrard, D.; Haddoub, R.; Salem, A.; Said Bacar, N.; Goekjian, P. G. *Synlett*, **2005**, 520
114 Vinod Kumar, R.; Seshu Kumar, K. V. S. R.; Raja Gopal, K. *J. Heterocyclic Chem.* **2005**, *42*, 153
115 Ghosh, A. K.; Zajc, B. *Org. Lett.* **2006**, *8*, 1553
116 Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392
117 Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212
118 Payack, J. F.; Hughes, D. L.; Cali, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19
119 Meister, C.; Scharf, H.-D. *Synthesis* **1981**, 733
120 Stayshich, R. M.; Meyer, T. Y. *J. Am. Chem. Soc.* **2010**, *132*, 10920
121 (a) Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351
(b) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1987**, *52*, 1353
122 Petasis, N. A.; Patane, M. A. *Res. Chem. Intermed.* **1996**, *22*, 781
123 Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274
124 Clark, D. A.; Fuchs, P. L. *Synthesis* **1977**, 628
125 Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913
126 Aggarwal, V.K; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227
127 Lautens, M.; Maddess, M. L.; Sauer, E. L. O.; Ouellet, S. G. *Org. Lett.* **2002**, *4*, 83
128 Virolleaud, M.-A.; Piva, O. *Tetrahedron Lett.* **2007**, *48*, 1417
129 Larock, R. C.; Leuck, D. J.; Harrison, L. W. *Tetrahedron Lett.* **1988**, *29*, 6399
130 Alcundia, A.; Arrayás, R. G.; Liebeskind, L. S. *J. Org. Chem.* **2002**, *67*, 5773
131 Lees, W. J.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 1887