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Professor K. J. Cavell
Head, School of Chemistry

Novel Selenium Catalysis

A thesis submitted for the degree of Doctor in Philosophy at University of Cardiff

By

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April 2008

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Thanks to the Wirth Group for all the help they have given me especially Dr. Rob Richardson and Sabine Altermann.

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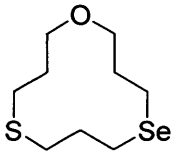
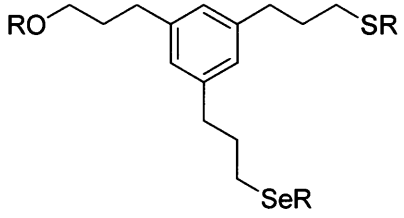
Contents

Abstract

This thesis describes work carried out on catalytic selenium reagents in a range of organic transformations. Four different areas have been investigated and are reported herein.

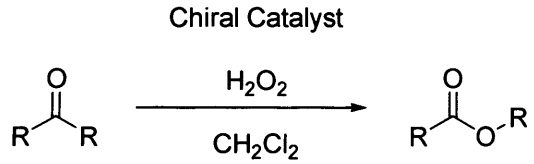
Chapter 2 reports the unsuccessful development into prochiral ligands, where three different chalcogen atoms are incorporated into either a trisubstituted structure or into a crown ether ring. Then reports how these structures could attach to a metal atom and become chiral.

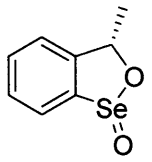




Chapter 3 describes a range of selenium-based ligands, which has been used in the palladium allylic substitution reaction to see if there is good co-ordination between selenium and palladium and if good enantioselectivities can be achieved.

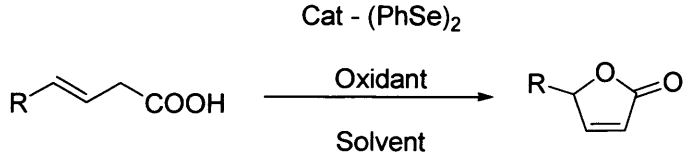
Chapter 4 describes the use of seleninic acids as catalysts in a range of reactions where the most successful is used in asymmetric Baeyer-Villiger oxidations using a range of ketones with enantiotopic migrating groups. The enantioselectivities were investigated.





Chiral Catalyst

Chapter 5 describes the successful work on catalytic selenium reagents used to convert β,γ-alkenoic acids into their corresponding butenolides. The work describes the optimum conditions investigated, asymmetric version of the reaction and also investigates mechanistic aspects of the catalytic cycle.



Abbreviations

°C	degree(s) Celsius
Δ	reflux
τ_R	retention time
Ac	acetyl
Ar	aryl group
br	broad
BSA	*N,O*-bis(trimethylsilyl)acetamide
Bu	butyl
calc.	calculated
conv	conversion
d	doublet
DIP-Cl	*B*-chlorodiisopinocampheylborane
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
dr	diastereomeric ratio
E	electrophile
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI+	electron impact (mass spectrometry)
eq	equatorial
equiv.	equivalents
ESI	electrospray ionisation (mass spectrometry)
Et	ethyl
Et_3N	triethylamine
HPLC	high pressure liquid chromatography
hr	hour(s)
^{i} or i-	*iso*
IR	infrared
J	coupling constant
Lig or L	ligand
LDA	lithium diisopropylamide
LTMP	lithium tetramethylpiperide

LRMS	low resolution mass spectrometry
M	metal
m	multiplet
m-	*meta*
m/z	mass to charge ratio
Me	methyl
min	minute(s)
mol	mole
*m*CPBA	*meta*-chloroperbenzoic acid
mp	melting point
Ms	methanesulfonyl
N	normal (molar acid / base concentration in aqueous solution)
n or *n-*	normal (linear alkyl group)
nbd	norbornadiene
ND	not determined
NMR	nuclear magnetic resonance (spectroscopy)
Np	naphthyl
Nu	nucleophile
o-	*ortho*
p-	*para*
Ph	phenyl
Pr	propyl
prim	primary
p-Tol	4-methylphenyl
q	quartet
qn	quintet
R	general (alkyl) group
rt	room temperature
sec	secondary
t	triplet
tert- or t-	*tertiary*
TBDMSCl	*tert*-butylchlorodimethylsilane
THF	tetrahydrofuran
THP	tetrahydropyran(yl)
TLC	thin layer chromatography

TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TOF	time of flight (mass spectrometry)
Ts	4-methylbenzenesulfonyl
TS	transition state
w/v	weight per unit volume concentration
Z or EWG	electron withdrawing group

Chapter 1

Introduction

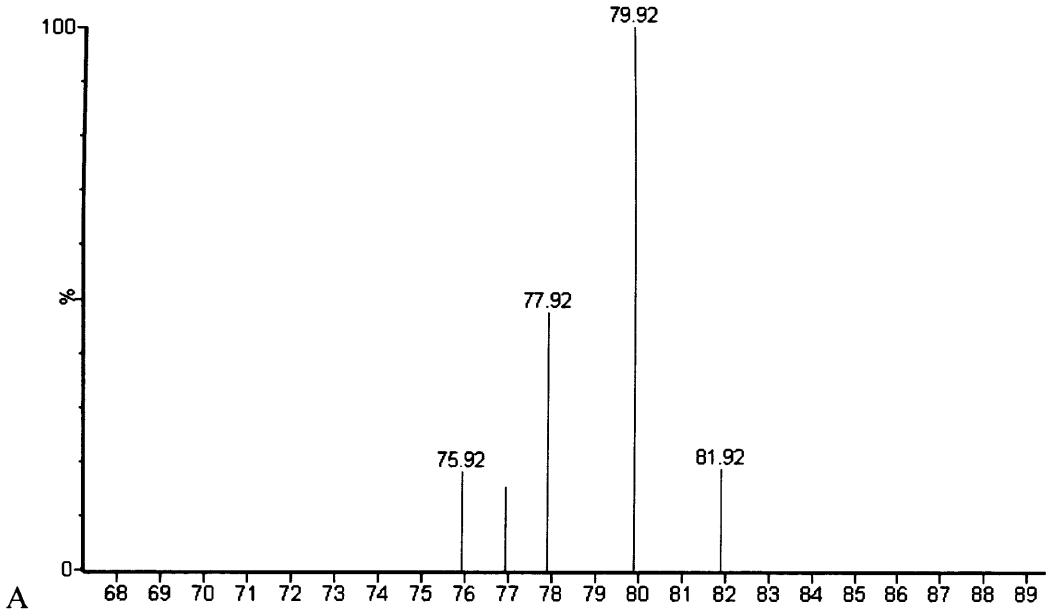
General Introduction on Selenium

History of Selenium

Jöns Jacob Berzelius, a Swedish chemist, discovered selenium in 1817 after analysing an impurity that was contaminating the sulphuric acid being produced at a particular factory in Sweden. Originally believing the material was tellurium, Berzelius eventually realised that it was actually a previously unknown element.[1] Selenium is derived from "Selene", the Greek meaning "Moon".

Properties of Selenium

Selenium is a non-metallic element in group 16 of the periodic table. It exists in several allotropic forms, of which three are generally known. Selenium can be prepared with either an amorphous or crystalline structure. The colour of amorphous selenium is either red, in powder form, or black, in vitreous form. Crystalline monoclinic selenium is deep red and crystalline hexagonal selenium, the most stable form, is grey. Naturally occurring selenium contains six stable isotopes: ^{74}Se (0.89%), ^{76}Se (9.37%), ^{77}Se (7.63%), ^{78}Se (23.77%), ^{80}Se (49.61%) and ^{82}Se (8.73%). 23 other unstable isotopes have also been characterised.



A

B

A: Diagram shows different isotopes of selenium.

B: Diagram shows black, grey and red selenium in its different forms.[2]

Sources of Selenium

Selenium is most commonly found in many sulphur ores, such as copper, silver or lead. It is obtained as a by-product of processing these ores from the anode mud of copper refineries and the mud from lead chambers of sulphuric acid plants. These muds can be processed by a number of means to obtain the rare free selenium.[1]

Uses of Selenium

Selenium has good photovoltaic and photoconductive properties and is extensively used in electronics, photocells, light meters and solar cells. It also used in the glass industry where it is used to remove colour from glass and also to give a red colour to glass and enamels.[1]

Health Effects

Elemental selenium is known to be practically non-toxic. However, hydrogen selenide and other organoselenium reagents are extremely toxic. H_2Se in a concentration of 1.5 ppm in the body would be enough to kill a human being. The exposure to selenium mainly takes place through food, as selenium is naturally present in grains, cereals and meat. Adults need to absorb 55 μg of selenium daily in order to maintain good health and is proven to be an essential trace element. However over exposure to selenium may cause fluid on the lungs, garlic breath, bronchitis, nausea, headaches, sore throat and many more health problems including death.[1]

Organoselenium Chemistry

Organoselenium compounds have been known since the 19th century, early examples include alkyl selenols, selenides, diselenides and selenoxides. In the early 1970s only selenium dioxide and elemental selenium were in general use in laboratories. The *syn*-selenoxide elimination reaction, which was also discovered in the 1970s, was found to be a powerful and effective olefin forming method.[3] The required selenoxides were readily available from the oxidation of the corresponding selenides, which were in turn prepared by the reaction of nucleophilic or electrophilic selenium species.

The chemistry of selenium compounds bears resemblance to that of sulphur and tellurium analogues. Reactions of sulphur compounds have been well studied, but those of tellurium are less well known and are undergoing more in-depth research.

Certain features make selenium compounds particularly valuable, for example the C–Se bond is weaker than C–S bond and the Se=O bond in the selenoxide functionality is more strongly polarised than the sulfoxide counterpart. Therefore, the selenoxide elimination can occur rapidly below room temperature whereas the sulphur analogues require heating to over 100 °C. The poor π overlap in C=Se bonds makes them more reactive than C=S bonds, e.g. in cycloadditions. It is found that the seleninate ($RSeO_2^-$) group functions as an excellent leaving group where as sulfinates are poor leaving groups. Selenium compounds display useful redox chemistry, where seleninic acids, anhydrides and the well known selenium dioxide are useful oxidants for a variety of functional groups. Selenols and certain selenium anions are valuable reducing agents. These compounds can also be used catalytically, together with stoichiometric use of more common oxidants.[4]

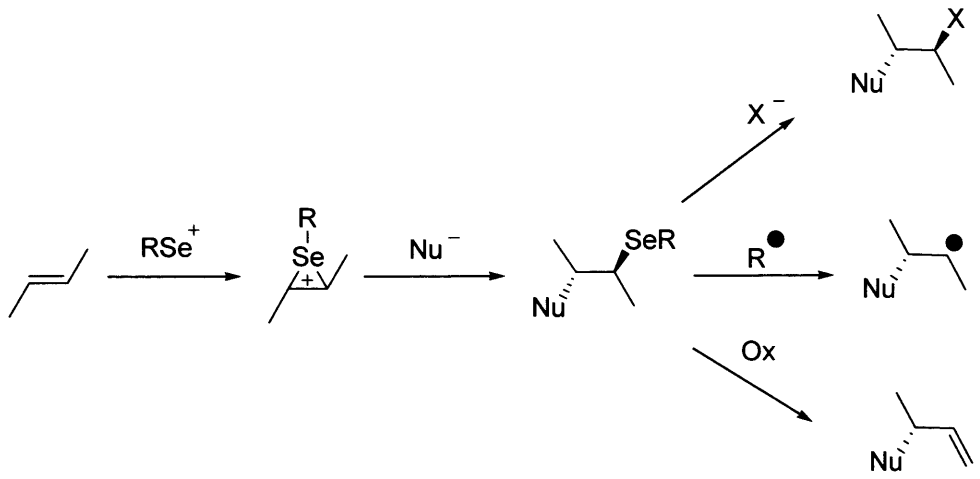


Fig 1. Reactions of organoselenium compounds.

Selenium can be introduced, modified and removed in a variety of methods under mild conditions and in good yields. Selenides can be attacked by nucleophiles, converted into radicals by homolytic cleavage of the carbon-selenium bond and then undergo further radical reactions as shown in Figure 1.[5] Oxidation to the selenoxide and subsequent *β*-elimination allows the stereospecific introduction of double bonds as shown in Figure 2.

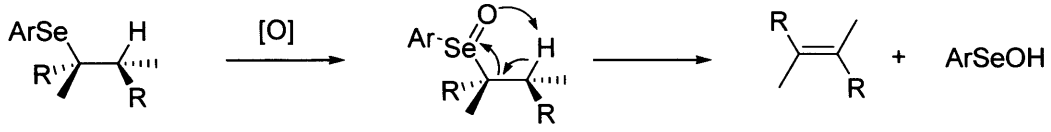


Fig 2. Selenoxide *syn*-elimination reaction

Selenium reagents are more expensive than sulphur reagents and therefore there is more of an interest in recycling these compounds as well as using them as catalysts.

Synthesis of enantiopure organoselenium compounds and their application in asymmetric synthesis are of current interest in many research groups. Wirth *et al.* have developed a range of chiral selenium reagents, which are accessible in high yields in only a few steps[6] where previously only long and tedious routes were known. It has been found that having a heteroatom-containing functional group in the *ortho*-position is essential for the stereoselectivity as intramolecular co-ordination of this heteroatom lone pair to the positively charged selenium results in a fixed conformation as shown in Figure 3. This then draws the chiral centre closer to the reaction centre and therefore the transfer of chirality is greater.

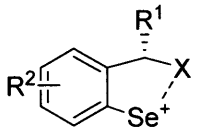
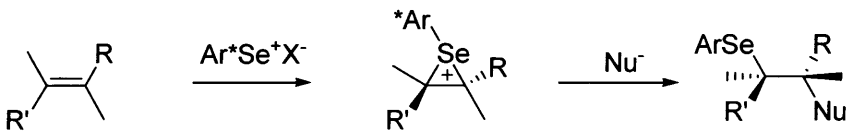


Fig 3. Chelation of Se cation by γ heteroatoms.

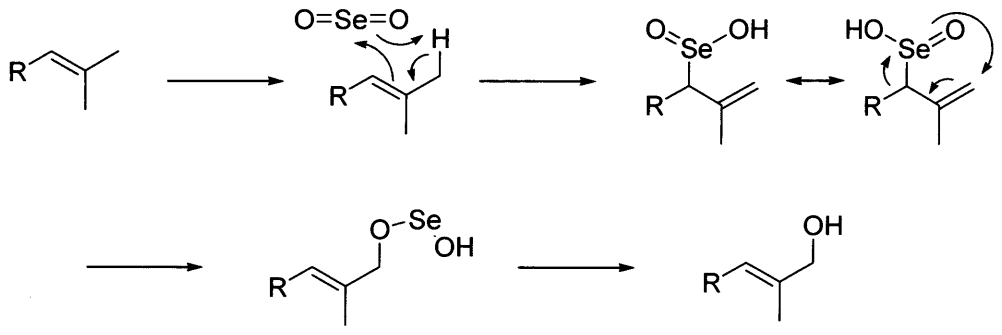
Another area of organoselenium chemistry, which has been well developed by the Wirth group, is the electrophilic selenylation reactions of alkenes using chiral and achiral selenium electrophiles. The selenenylation reaction is initiated by the selenium electrophile to form the seleniranium ion. The nucleophile then attacks the substrate from the backside, leading to the *anti* addition product. The attack of the nucleophile occurs on carbon atom that has the more stable positive charge, therefore the most substituted carbon atom.



Scheme 1. Electrophilic selenenylation reaction of alkenes.

Allylic Oxidation using Selenium Dioxide

Selenium dioxide is a well known and traditionally used oxidising agent for alkenes. It was found that only catalytic amounts of selenium dioxide in the prescence of a stoichiometric oxidant could be used to help enhance the rate of oxidation of olefins. Selenium dioxide reacts with an alkene, similar to an ene reaction. Firstly an allylic seleninic acid is formed, which undergoes allylic rearrangement to give an unstable compound that rapidly decomposes to an allylic alcohol.



Chapter 2

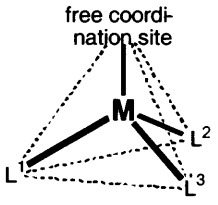
Prochiral Ligands for Metals

Prochiral Ligands – Aims

The use of chiral ligands in enantioselective transition metal catalysed reactions has been widely studied. The use of selenium based chiral ligands in transition metal catalysed reactions has also already been investigated.[7] Much less explored is the concept of prochiral ligands, which after coordination to a metal atom can form chiral complexes. The reason these types of complexes have not been explored yet is that transition metal complexes are often configurationally labile and will be hard to resolve.

In enantioselective catalysis, a prochiral substrate is converted into an optically product, using an enantiopure catalyst.[7a] Asymmetric catalysis incorporates a small amount of chiral compound into a chemical reaction where the activation energy of a single diastereomeric transition state will be lower, leading to a more favoured reaction pathway and therefore a predominance of one enantiomer being produced. The difference between the racemic reaction and the enantioselective reaction therefore lies in the difference in transition states leading to the production of *R* or *S* enantiomers. In a racemic reaction the transition states are of equal energy and therefore produce *R* and *S* in equal amounts. In an enantioselective reaction, the chiral catalyst interacts with the substrate and lowers the transition state of the reaction pathway leading to *R* for example, whereas the transition state leading to *S* remains unaffected. It has been found that a change in free energy by approximately 3.0k cal/mol can result in enantioselectivities of 98-100%.[7b]

Based on the tetrahedral complex **A**, which is chiral at the metal centre, syntheses of tridentate ligands **B** and **C** will be tested and evaluated. Complexes involving these tridentate ligands should avoid problems of configurational lability, as they are less likely to dissociate. These metal complexes will still have a free coordination site, which is necessary for catalytic activity.



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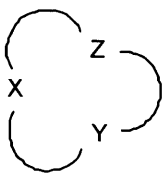

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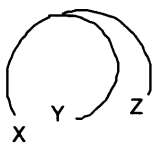
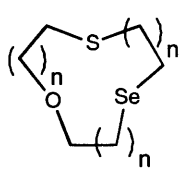


C

Examples of the tridentate ligands proposed are prochiral crown ethers **D** and tridentate ligand of type **E**. Not only chalcogen atoms will be used but also group 15 elements such as nitrogen, phosphorus and arsenic as shown in ligand **F**.



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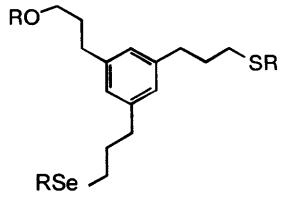
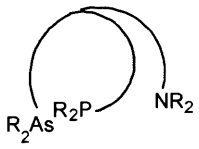


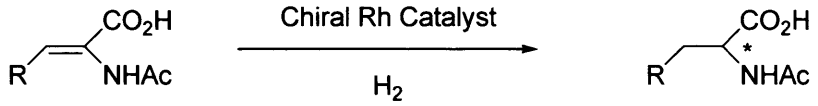
E



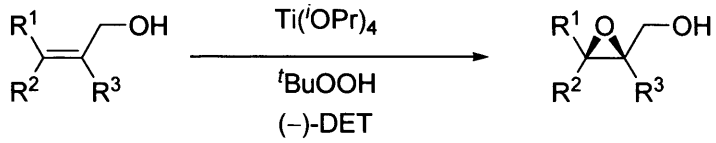
F

The stable complexes formed will be identified and the optical resolution will be carried out by including chiral ligands on the free coordination site. Finally the complexes, which are chiral at the metal centre, will be used in stereoselective catalytic reactions where the resolving agent is removed, for example.

- Ruthenium catalysed reactions, e.g. hydrogenations



- Epoxidation e.g. Sharpless epoxidation



Prochiral Ligands – Background

Inorganic chemists have synthesised organometallic half-sandwich complexes of three and four-legged piano-stool structure whose metal atom is stereogenic ("chiral transition metal atom"), where optically active transition metal M is surrounded by four different ligands L^1, L^2, L^3, L^4 as shown in Figure 4.

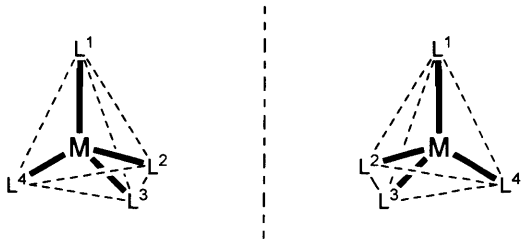


Fig 4. Image and mirror image of a transition metal complex with 4 different ligands.

A simple chiral anion derived from tetrahedral $[NiCl_4]^{2-}$ would be $[NiFClBrI]^{2-}$, this type of compound would be impossible to resolve due to rapid ligand exchange. The organometallic compounds are kinetically inert because the ligands are bound strongly to the metal atom by a combination of σ–donor and π–acceptor bonds where the ligand exchange is slow.

Chiral isomerism of the asymmetric carbon atom has dominated stereochemistry since its discovery by van't Hoff and LeBel in 1874.[8] Other compounds, including silicon compounds, have also been obtained in optically active form. Now chiral compounds have been formed using group 14 and 16 elements. Other examples of chiral compounds include the ammonia derivatives $NR^1R^2R^3$ which use its lone pair as a fourth substituent, however this compound is labile due to the inversion at the nitrogen atom through the plane of its substituents, more stable substituents of this type are phosphines $PR^1R^2R^3$ and sulfoxides $S(O)\ R^1R^2$ due to pyramidal inversion being slow.[9]

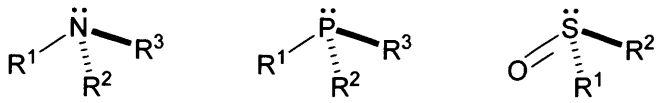
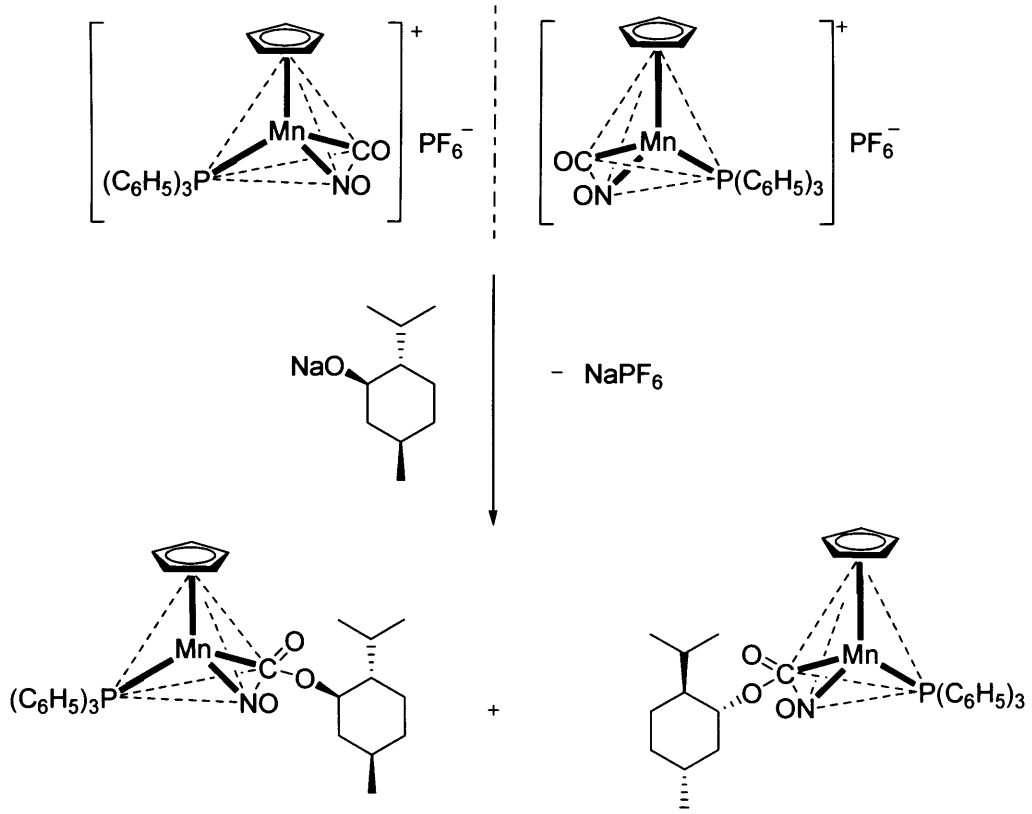


Fig 5. Compound showing lone pair occupying the fourth space in chiral compound.

The first transition metal complex with four different substituent was made 30 years ago using manganese as shown in Scheme 2. The resolution of the compound used the sodium derivative of the optically active alcohol (1*R*,3*R*,4*S*)-menthol to convert the enantiomers into diastereomers by addition of the mentholate ion to the carbonyl group. These diastereoisomers can then be separated on the basis of their solubility difference. Once separated the mentholate ion can then be removed leaving the products as single enantiomers. Other methods used to separate diasteromers are chromatography and fractional distillation.



Scheme 2. The first chiral-at-metal centre complex.

Theory of Chirality Transfer

In enantioselective catalysis the distance between the inductor and substrate plays an important role. The smaller the distance the better the chirality transfer and, therefore, the optical induction. For example, transition metal compounds with optically active ligands where the chirality is in the ligand itself can be too far away from the metal atom. However, special mechanisms of chirality transfer have ensured that these reactions occurred with high enantioselectivities. If the metal atom was to be the chiral centre this

would be the shortest possible distance and therefore chirality transfer should be at its best as catalytic reactions occur at the metal centre. Although the theory has been tested, the compounds that have been used to date have either been too stable or use unsuitable catalysts for the reactions tried; so far there has been no solution to this problem.[10]

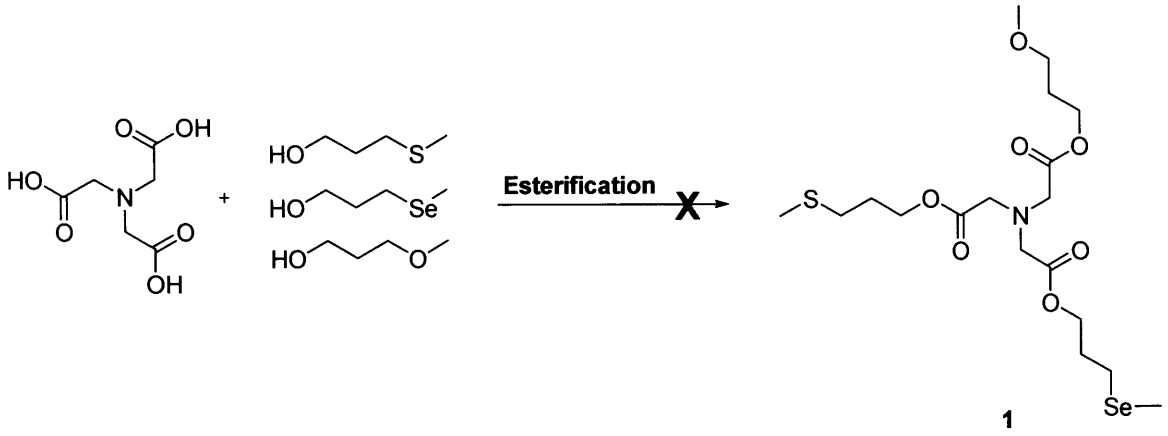
Concept and Design of Prochiral Ligands.

The design of the prochiral ligands is based on three different heteroatoms in the molecule showing different electronic properties, therefore creating chiral space around the molecule. Once this compound has attached to the metal atom it then allows the relay of chiral information by having these three different substituents in for example the crown ether ring. When choosing a metal to co-ordinate to these prochiral ligands a careful choice needs to be made as metals can adopt a range of shapes. A good metal would be a titanium as this likes a tetrahedral arrangement, whereas palladium would be a bad choice as this metal prefers to be square planar which would not be chiral as this type of compound would always have a plane of symmetry. However if for example nickel was the metal of choice this can adopt tetrahedral and square planar complexes depending on the ligands attached. However if the nickel is tetrahedral this could easily interconvert between the square planar arrangement causing racemisation of the original chiral complex. The prochiral ligands proposed would help stop this racemisation as the ligands are chelated to each other and would therefore have to detach from the metal all together in order to racemise. Once the prochiral ligands are attached to the metal of choice there is a free coordination site, which is necessary for catalytic activity and is produced by a labile group that was originally attached to the metal atom. Octahedral metals such, as cobalt would also be a good choice, as this would produce a *fac* isomer.

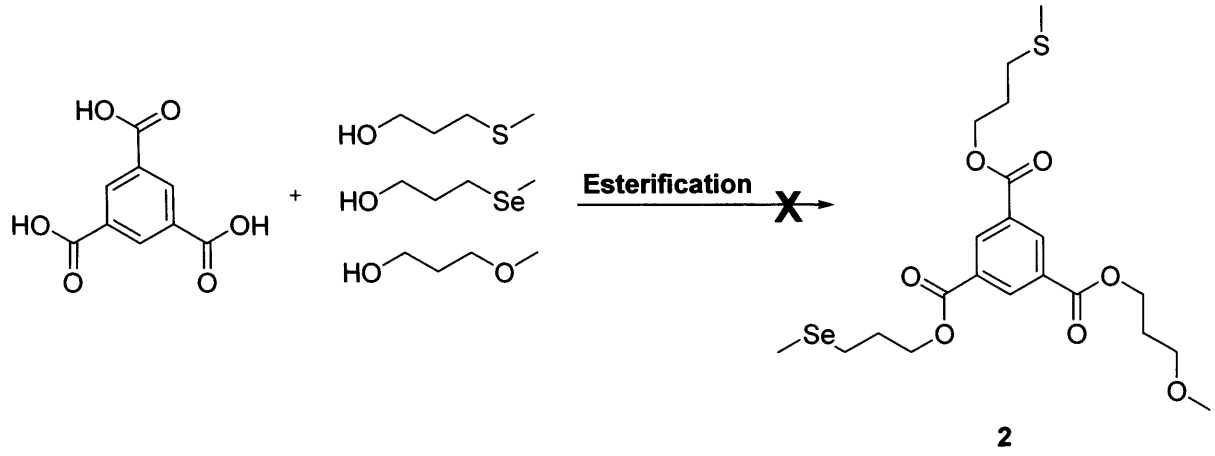
Results and Discussion

Synthesis of Prochiral Tridentate Ligands

Proposal of Prochiral Tridentate Ligands



Scheme 3. Design of prochiral ligand from nitrilotriacetic acid.



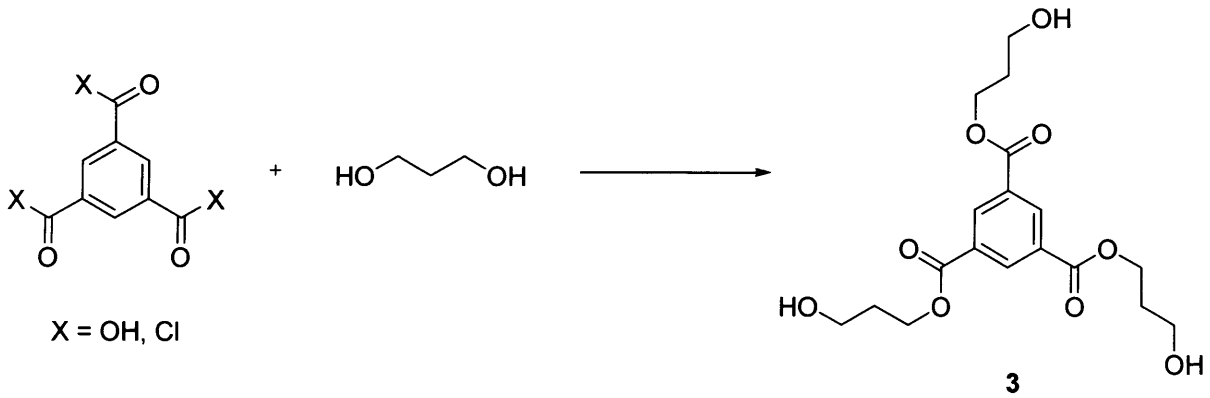
Scheme 4. Design of prochiral ligand from trimesic acid

Esters are readily prepared from carboxylic acids and alcohols in the presence of an acid catalyst such as sulphuric acid. Many different tricarboxylic acid compounds can be bought from many suppliers and the two obtained are nitrilotriacetic acid as shown in Scheme 3 and trimesic acid as shown in Scheme 4. The idea is to introduce the chalcogen containing atoms by using the alcohols containing these atoms. 3-Methylthiopropanol can be bought and 3-methylselanylpropanol is easily synthesised. Therefore a way to introduce these compounds is by esterification as shown in Scheme 3 and Scheme 4. The

reaction is reversible and water is produced. Also many carboxylic acids are insoluble in organic solvents.

Many of the traditional methods for esterification were tried on both starting materials using 3-methylthiopropanol to monosubstitute one of the acid moieties. Unfortunately, these were unsuccessful and resulted in only starting materials.

Using similar esterification procedures on trimesic acid and trimesoyl chloride with 1,3-propandiol resulted in the formation of the required product **3** by ^{1}H NMR along with other unidentifiable products.



Scheme 5. Attempted synthesis of compound **3**

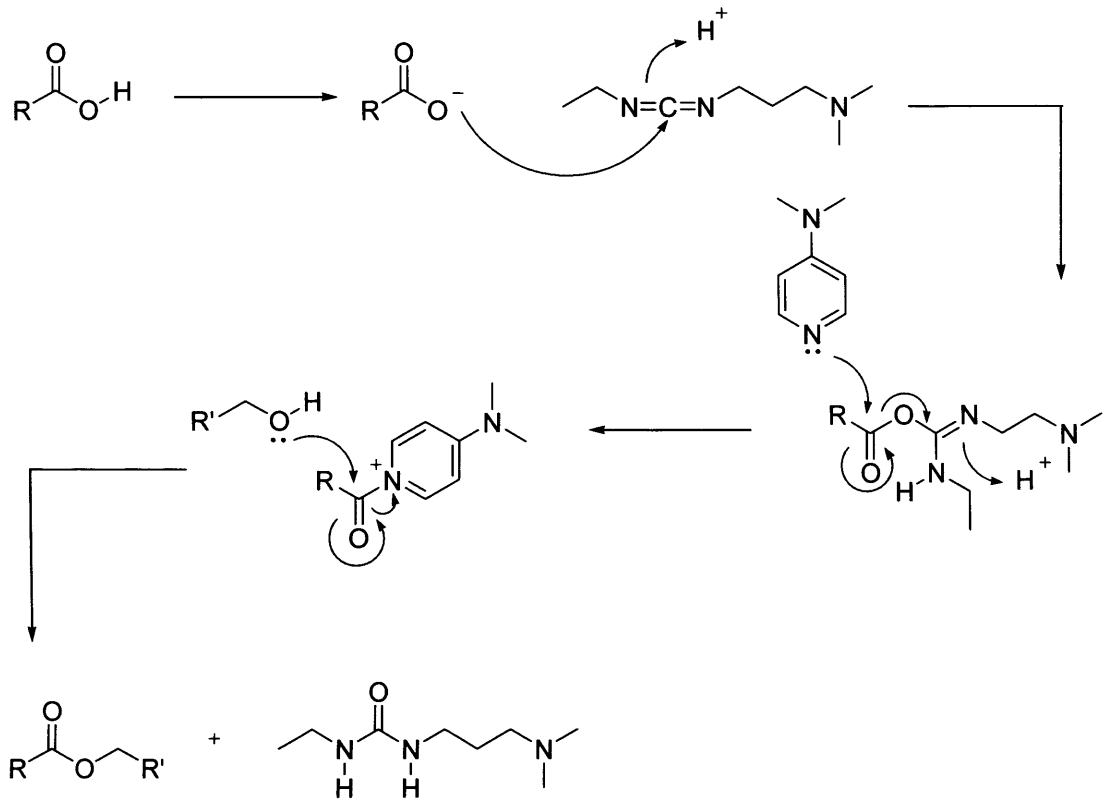
The results are summarised in **Table 1**.

Starting Materials	Reagents	Solvent	Temperature	Comments/ Observations
Trimesoyl chloride	10 equiv. Et_3N, 0.1 equiv. DMAP	CH_2Cl_2	0 °C → rt	Many spots on TLC, inseparable
Trimesoyl chloride	15 equiv. DMAP	THF	0 °C → rt	Many spots on TLC, inseparable, Too much DMAP in spectra.
Trimesoyl chloride	1 equiv. Et_3N	THF	rt	Many spots on TLC, inseparable,
Trimesoyl chloride	0.1 equiv. DMAP	Pyridine	rt	Many spots on TLC, inseparable
Trimesic acid	3.3 equiv. DMAP, 3.3 equiv. EDCI	CH_2Cl_2	rt	Many spots on TLC, inseparable

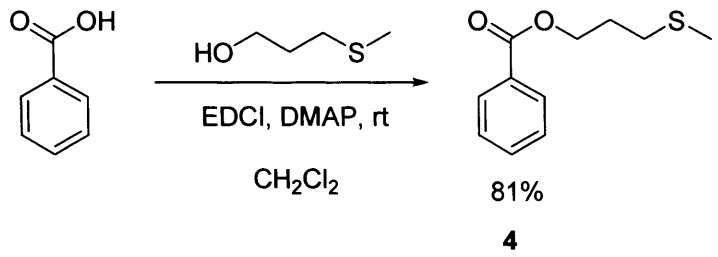
Table 1. Shows a range of conditions used to synthesis compound **3**

This molecule was synthesised to then incorporate the different chalcogen atoms by displacing two of the oxygen moieties with a selenium and a sulphur but due to the difficulty in purifying compound **3**, this route was not continued.

Another esterification procedure, which is less recognised than other traditional routes, uses EDCI. This would help circumvent some of the problems that have been encountered, as this reaction is not reversible as shown in Scheme 6. To test the reaction conditions, benzoic acid, DMAP, EDCI and 3-methylthiopropanol were added together and formed 3-(methylthio)propyl benzoate **4** in 81% yield. The driving force for this reaction to occur is the formation of the urea derivative. More traditional routes produce water or HCl as a by-product which can then allows the reaction to reverse back to the starting materials.

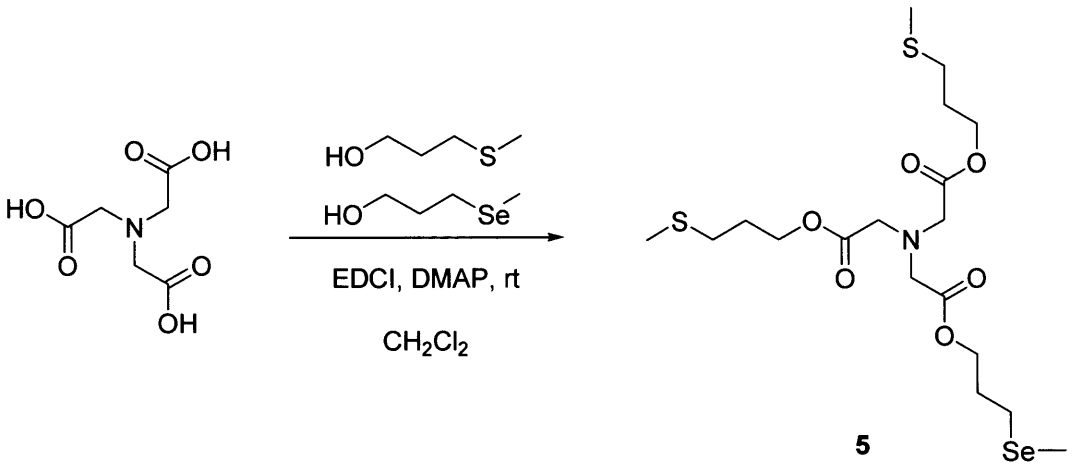


Scheme 6. EDCI irreversible reaction.



Scheme 7. Benzoic acid converted to ester

As these conditions gave good yields they were applied to both nitrilotricetic acid and trimesic acid. Unfortunately, the trimesic acid resulted in starting materials but nitrilotriacetic acid formed **5** in 25% yield.



25%

Synthesis of Prochiral Crown Ethers

It has been well established that crown ethers bind strongly to metal cations in which the ionic radii best match the radius of the cavity formed by the macrocyclic ring.[11] There has been a growing interest in chalcogen macrocycles in terms of their structure and bonding of metal-chalcogen complexes.[12] The recent interest in mixed macrocycles is due to the highly selective nature for complexation with ions. Macrocycles incorporating donor atoms such as oxa, thia, and selenacrown ethers have been well studied and also mixed donor atoms, which incorporate only two out of the three chalcogen for example oxa-thia-crown ethers.[13] Incorporating the large selenium atom would lead to a change in size of the cavity and therefore would allow some interesting co-ordination behaviour. The lower electronegativity and the σ-donating properties of the selenium over sulphur suggest that incorporating the selenium atom in a mixed macrocycle should yield ligands capable of rich co-or dination chemistry.

General Approaches used to Prepare Crown Ethers

Previous synthesis to crown ethers normally use high dilutions techniques with DMF or THF. The reaction involves the co-condensation of for example a *bis*-thiol with a dialkyl halide. Common bases used in the reaction are Cs_2CO_3, K_2CO_3 and Na_2CO_3. These types of conditions are applied to oxygen, sulphur and nitrogen-containing crown ethers. When synthesising selenium-containing crown ethers a similar method is used.[13a] However, normally diselenides are used as the starting material and are converted into a nucleophile with $NaBH_4$ *in situ*, which then reacts with the alkyl dihalide in a solvent under high

dilution techniques, with long reaction times.[13b] Many of these crown ethers contain either one or two heteroatoms, if crown ethers containing three heteroatoms were easy to prepare they would have already been synthesised.

Proposal for the Synthesis of Prochiral Crown Ethers

The prochiral ligands that are to be synthesised involve a two-carbon bridge and a three-carbon bridge, and a mix of both two-carbon bridge and three-carbon bridge crown ether, all of which are shown in Figure 6.

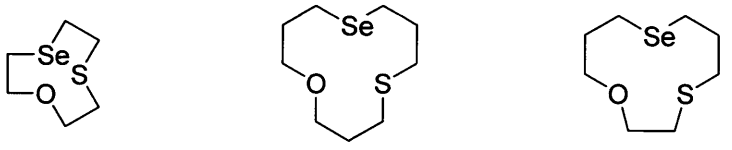
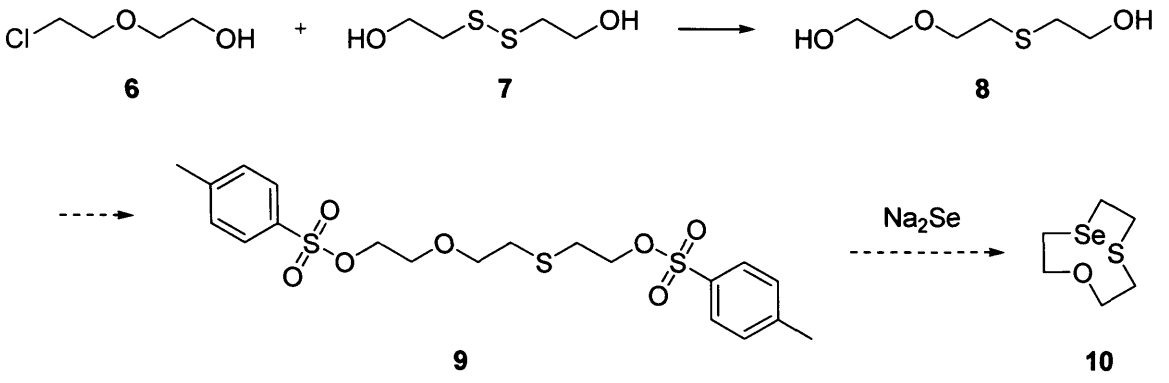


Fig 6. Shows 2, 3 and mix of 2,3-carbon bridge prochiral crown ethers

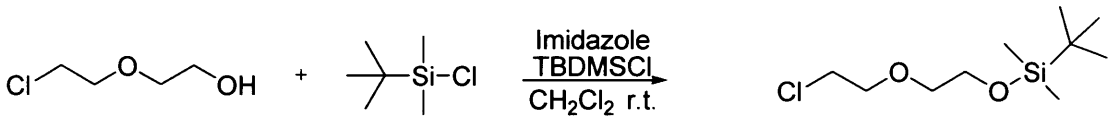
2-Carbon Bridged Crown Ether



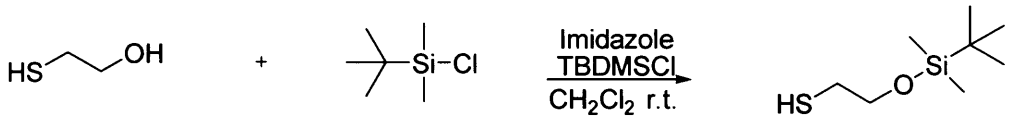
Scheme 7. Proposed synthesis of 2-carbon bridged crown ether, where bold arrows show reactions achieved and dotted arrows show next planned reaction step.

The commercially available starting materials 2-(2-chloroethoxy)ethanol **6** and bis(2-hydroxyethyl)disulfide **7**, were used in an S_N2 reaction under a variety of conditions via the breaking of the disulphide bond to produce the required nucleophile. The compound **8** was synthesised using sodium borohydride in ethanol at room temperature in 48% yield. Although all characterisation show that this compound has been made, high-resolution mass spectroscopy was not able to finally characterise this compound due to the fragmentation of the compound. When the same procedure was attempted again to go to

the next step of converting the hydroxy groups into the tosylate, the reaction procedure resulted in starting materials. Other procedures were attempted but again were unsuccessful, by the addition of sodium hydroxide to the original reaction procedure and also using **6** and **7** with sodium borohydride in methanol instead of ethanol. If the reaction were to be successful the hydroxy groups would have been converted into tosylates **9** and then cyclised using sodium selenide. One of the problems thought to be associated with this is that the hydroxy moieties do not allow the reaction to proceed in the alcohols used as the alcohol may be acting as a competing nucleophile. To circumvent this problem the starting materials were protected and instead of using bis(2-hydroxyethyl) disulfide, mercaptoethanol was used as an alternative. These were obtained in good yields.



80% **11**

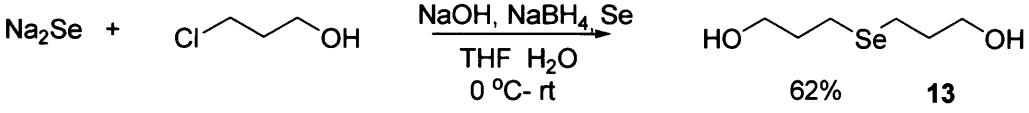


70% **12**

Scheme 8. Protection of alcohols.

However due to time constraints a follow up to this procedure was not possible.

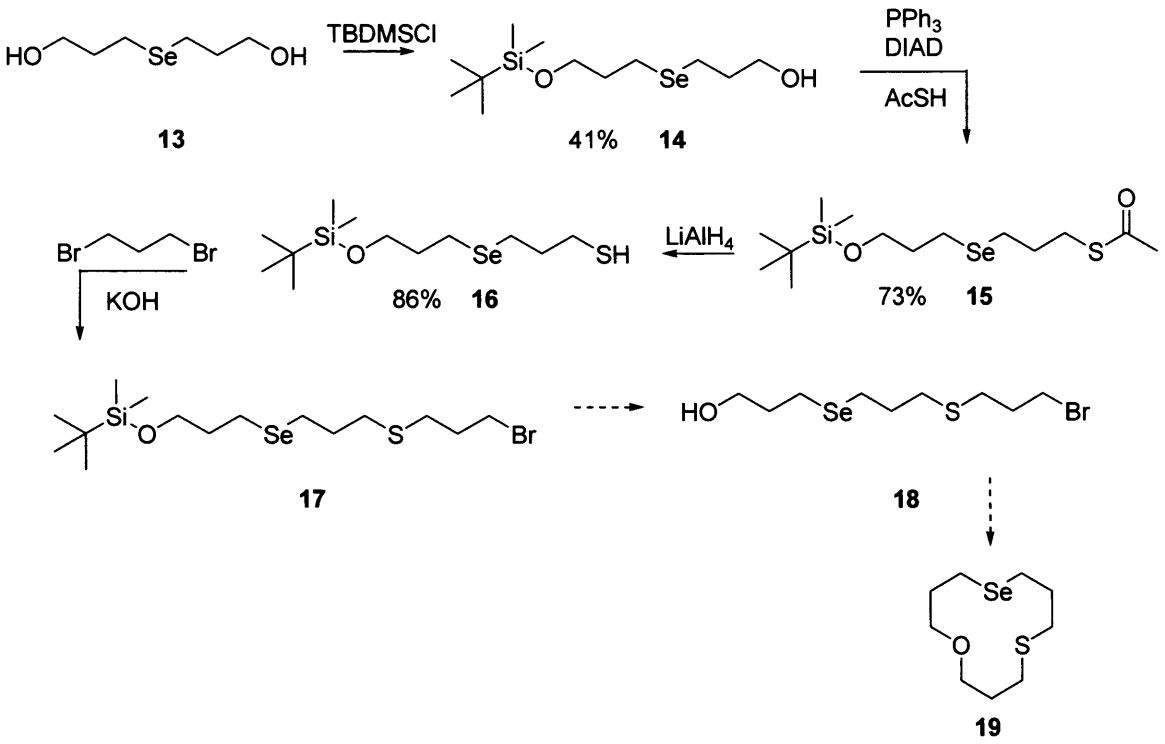
3-Carbon Bridged Crown Ether



62% **13**

Scheme 9. Synthesis of bis(3-hydroxypropyl)selenide

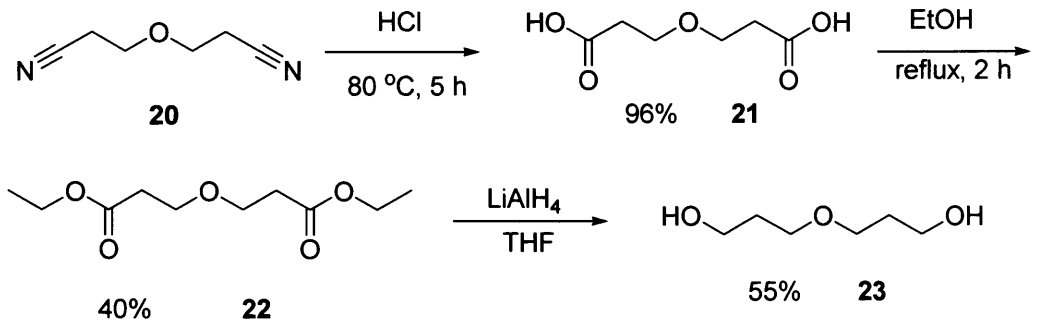
Bis(3-hydroxypropyl)selenide **13** can be prepared by treatment of 3-chloropropan-1-ol with sodium selenide (prepared *in situ* from Se, NaOH, $NaBH_4$) and is used as a starting material in many of the attempted prochiral crown ether syntheses.



Scheme 10. Synthetic route to 3-carbon bridged crown ether

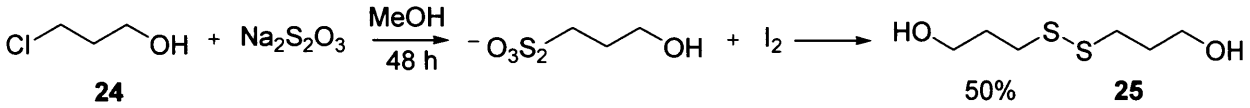
Starting from bis(3-hydroxypropyl)selenide **13**, one of the hydroxy groups were protected with *tert*-butyldimethylchlorosilane TBDMSCl in 41% yield **14** to allow functionalisation at one end of the molecule. The other hydroxy group was then converted into a thioester **15** under Mitsunobu-type conditions in 73% yield using PPh_3, diisopropyl azodicarboxylate and thioacetic acid in THF at 0 °C. The thioester was then reduced to the thiol **16** in 86% yield using $LiAlH_4$ in THF. The substitution reaction with 1,3-dibromopropane and potassium hydroxide in methanol yielded the product **17**. The crude reaction mixture shows that the product **17** was observed by LRMS, however this compound could not be isolated due to the mixture of products observed on the TLC and the amount of compound that was left at this point after a long synthetic route.

Another attempt to make the 3-carbon bridged crown ether was based on the synthetic route of the 2-carbon bridged structure. However, the starting materials were commercially available for the 2-carbon bridged structure, but had to be synthesised for the 3-carbon bridged crown ether.



Scheme 11. Synthetic route to diol for 3-carbon bridged crown ether synthesis

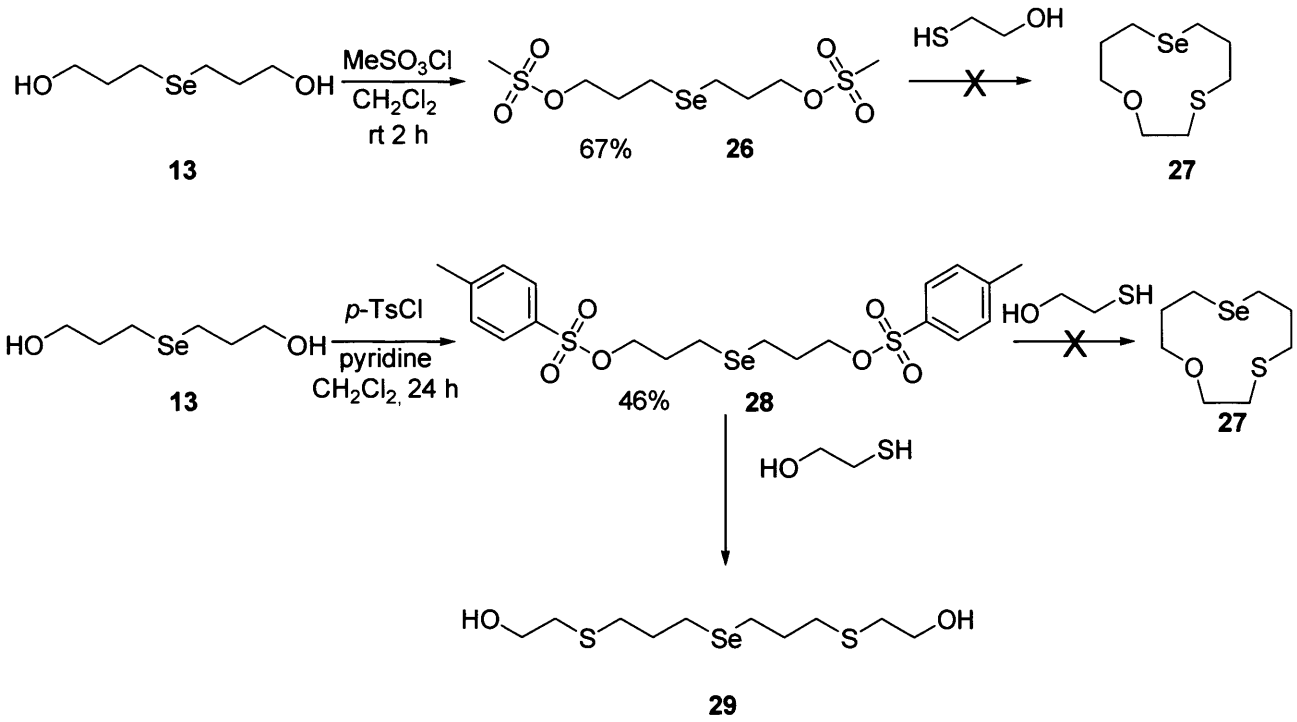
2-Cyanoethyl ether **20** was refluxed in 37% aqueous HCl to obtain the diacid **21** after recrystallisation in 96% yield. Esterification of the diacid was accomplished by refluxing the compound in ethanol with concentrated H_2SO_4 as the catalyst and the pure compound was formed without any further purification in 40% yield. The diol **23** was the obtained in 55% yield from the reduction of the ester with $LiAlH_4$ in THF. Then one end of the diol would be converted into a leaving group for example a mesylate or a tosylate, to then undergo the same reactions in the 2-carbon bridged crown ether synthesis.



Scheme 12. Synthetic route to the disulphide for 3-carbon bridged crown ether synthesis

The disulphide **25** was synthesised from 3-chloro-1-propanol **24** and sodium thiosulphate in aqueous methanol 50% v/v. After 2 days, iodine was added to the refluxing solution and the disulphide **25** was obtained in 50% yield. However, the subsequent reaction was not followed as the conditions that were to be used were not successful when applied to the 2-carbon bridged crown ether.

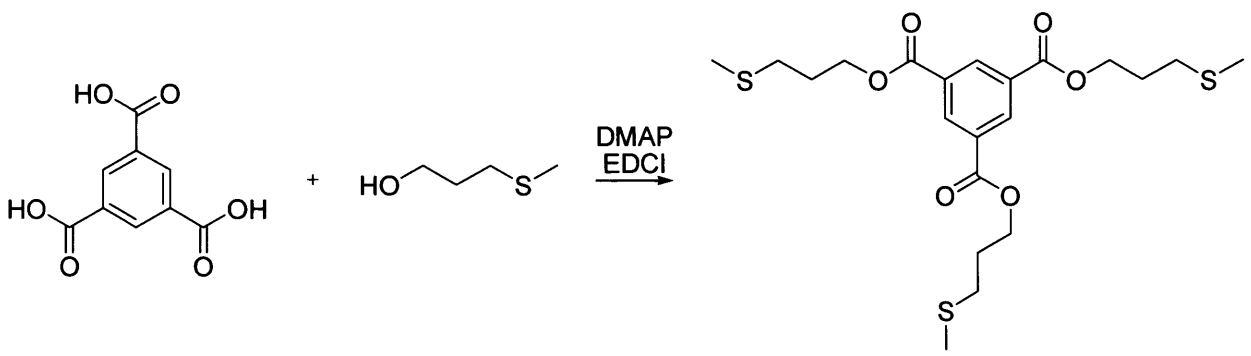
Mixed Carbon Bridged Crown Ether



Scheme 13. Synthetic route to mixed carbon prochiral crown ether

The plan to synthesise the crown ether **27** was to convert the diol **13** in to either the mesylate **26** (67%) or the tosylate[14] **28** (46%) then, using mercaptoethanol, which contains the oxygen and sulphur moieties to cyclise the compound. Treatment of the dimesylate with mercaptoethanol, potassium carbonate in DMF failed to produce any identifiable products. Using the tosylate and $NaBH_4$ in THF appeared to give **29** along with a range of by-products. It is known that S_N2 reactions of oxygen nucleophiles are difficult and closing rings of medium size are difficult so a combination of these two factors will not allow the reaction to proceed smoothly.

Metal Complexation

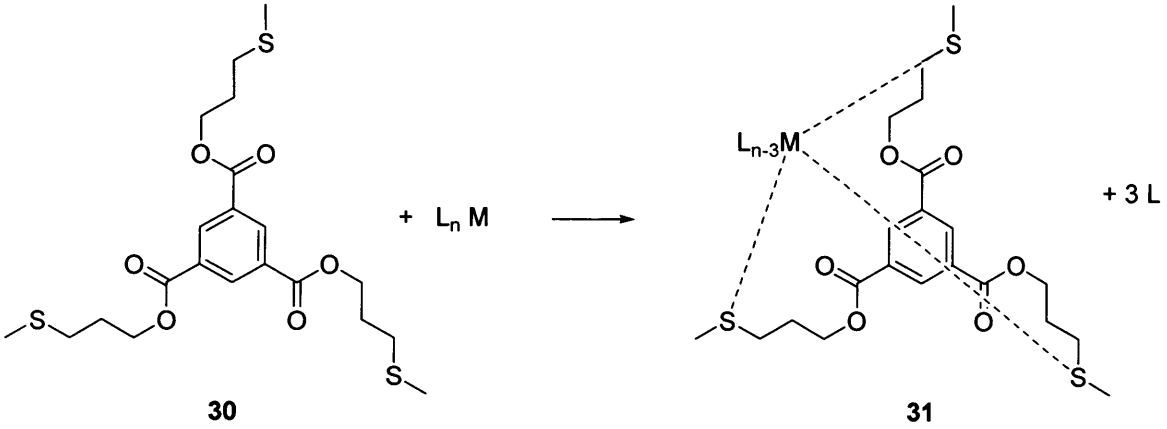


85% **30**

Scheme 14. Synthesis of tris(3-(methylthio)propyl)benzene-1,3,5-tricarboxylate

Using 3.3 equivalents of 3-methylthiopropanol, 1 equivalent of trimesic acid, 3.3 equivalents of DMAP and EDCI the tri-substituted product **30** was formed in 85% yield using traditional stirring methods and formed in 30% yield when microwave conditions (100 W, 25 °C, 1 h) were applied. The same reaction conditions were attempted with nitrilotriacetic acid but unfortunately no reaction occurred and only starting materials were recovered.

This sulphur-containing ligand was then allowed to react with a range of metal complexes in $CDCl_3$ at room temperature, to see if metal complexation occurs.

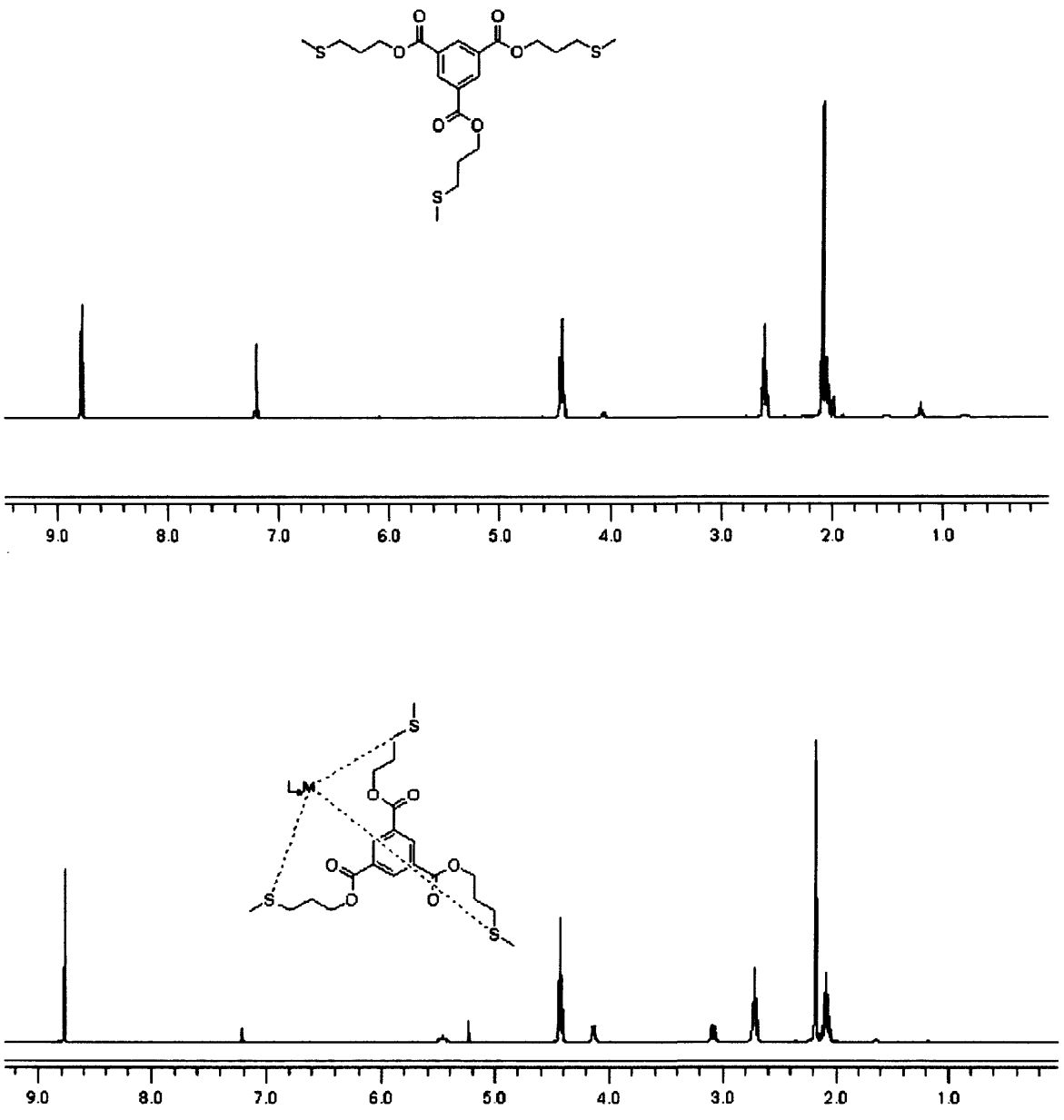


30 **31**

ML_n = $Pd_2(dba)_3$ $PdCl_2(CH_3CN)_2$ $Ti(O^iPr)_4$ $Rh(PPh_3)_3Cl$ $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$

Scheme 15. Range of metals tried in metal ligand complexation reaction

The reactions were monitored by ^1H NMR every hour, but the only metal that formed a metal-ligand complex was the allyl palladium dimer. This was observed in the proton NMR by a downfield shift of the 9H-singlet of the protons attached to the carbon next to the sulphur. The NMR shows a clear shift in the peak from 2.09 ppm to 2.19 ppm. From the spectra it is believed that all three sulphur atoms have coordinated due to there being only being one strong 9H-singlet peak. If all three sulphurs had not coordinated this would be evidenced in the spectra by having a mixture of peaks at different intergrals.



Spectra 1. Shows the methyl singlet has shifted from 2.09 to 2.19 ppm, where M is Pd.

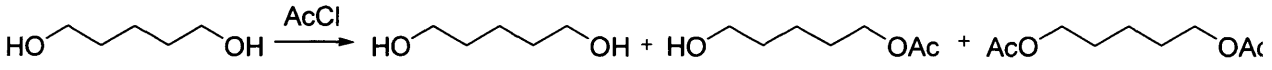
Even though compound **35** shows a shift of 0.1 ppm, it can be questioned if the palladium has actually attached at all. When compared to a similar compound containing the Pd-S-Me skeleton it was found that the 3H singlet in the molecule comes at 2.53 ppm, that's a difference of 0.41 ppm compared to un coordinated complex which comes at 2.12 ppm.[14a] It can be seen from the NMR that compound **35** maintains its symmetry and therefore this small shift could be due to all sulphur binding or a fluxional process occurring.

Conclusion

Having attempted lots of methods to prepare prochiral ligands of this type, the level and standard of chemistry was very difficult and I believe more background and pratical work is needed in order to successfully achieve this. As an excellent idea, if this were to be successful a whole new area of organic chemistry could be developed.

One of the major problems is trying to monofunctionalise the acid moieties, as a mixture of products is often observed. Even if a protecting group strategy was incorporated this would still leave a mixture of products resulting in low overall yields. The table below shows a theoretical outlook at statistical mixtures of reagents used and the resulting outcomes where all alcohols in the system are of equal reactivity.[15]

$(A + B \rightarrow A + AB + AB_2)$



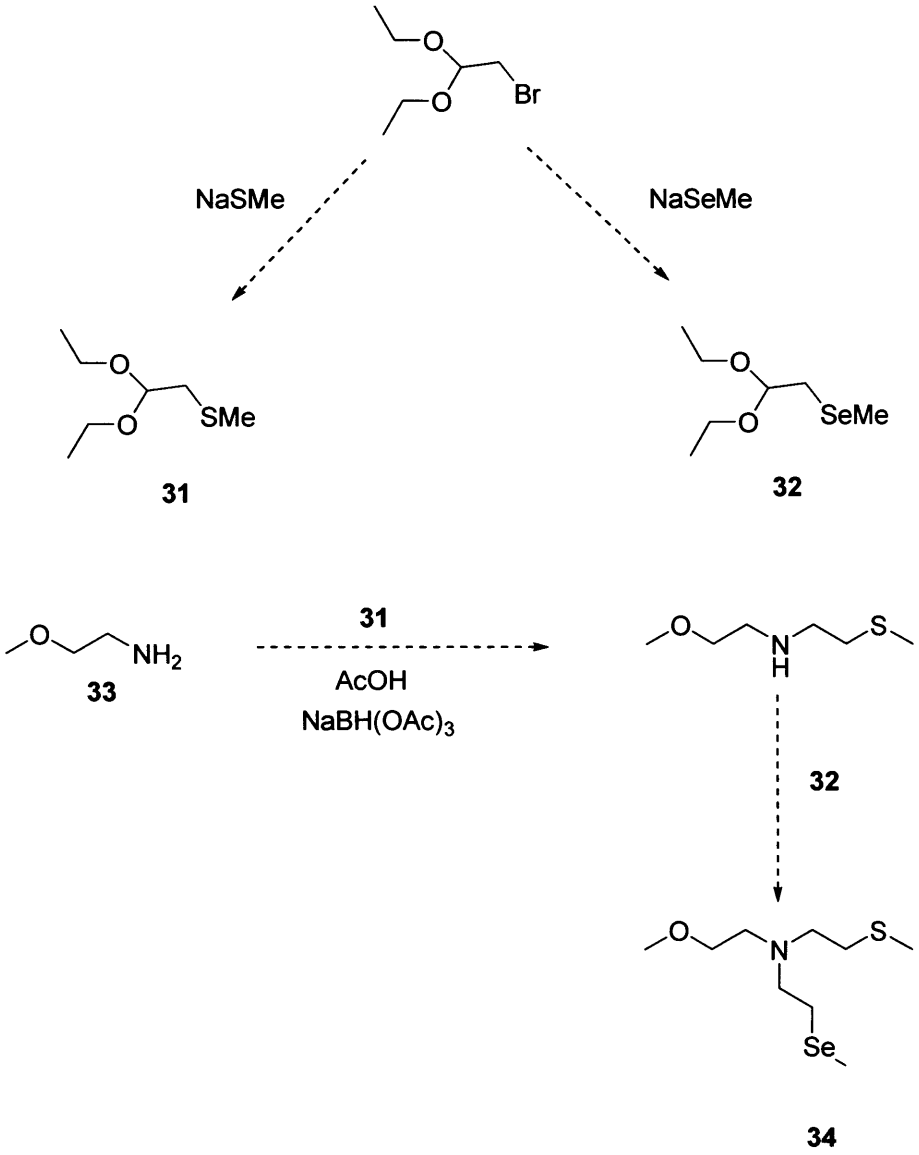
SM	Products		
A/B	A	AB	AB_2
1 : 2	0%	0%	100%
1 : 1.5	6%	38%	56%
1 : 1	25%	50%	25%
1.5 : 1	44%	44%	11%
2 : 1	56%	38%	6%
4 : 1	76.5%	22%	1.5%

Table 2. Theoretical product ratios of difunctional reagent A with monofunctionalisation reagent B.

As can be seen from the theoretical yields, a high yield of AB or the monofuntionalised products **1** and **2** can never be obtained.

Further Work

The starting materials for the reactions tried are reasonably cheap, so for this project to succeed maybe an unsymmetrical starting material could be used and for example using a reductive amination procedure to incorporate the different moieties separately.



Scheme 16. Shows example of a series of reductive aminations reactions.

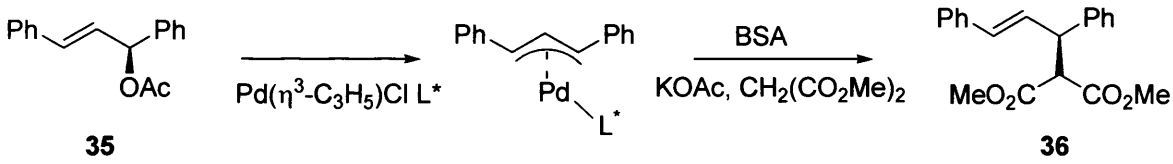
The bromine containing acetal can be reacted with sodium thiomethoxide to obtain **31** and with sodium selenamethoxide to obtain **32**. These can in turn react with 2-methoxyethanamine **33** to produce compound **34**.

Chapter 3

Selenium Compounds as Ligands

Palladium Allylic Substitution Reaction

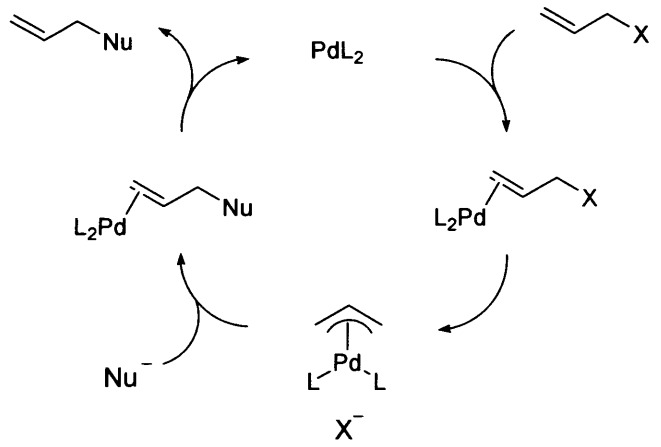
Palladium catalysed reactions can be carried out without protection of most functional groups. Although the reactions should be carried out carefully, palladium is not sensitive to oxygen, moisture or even acid. It is a noble metal and even though it is expensive it is cheaper than most other noble metals.[16] Dimethyl malonate with racemic 1,3 diphenylprop-2-enyl acetate **35**[17] in Pd(0)–catalysed allylic substitution reaction was used to evaluate chiral selenium ligands and ligands which have already been used in palladium allylic substitution reactions in order to test the reaction conditions used. The palladium complex below is an attractive candidate as a variety of established asymmetric catalytic reactions have been carried out. The catalytic palladium allylic substitution reaction will serve as a good test for the new catalysts.



35 **36**

Scheme 17. Palladium allylic substitution reaction.[18]

Palladium allylic substitution reaction – Background



The catalytic cycle begins with the association of a unsaturated Pd(0) complex with an allylic substrate. The formed olefin complex undergoes oxidative addition to form a π-allyl complex. In this process Pd(0) is oxidised to Pd(II). The nucleophile attacks the Pd(II) complex to form the product associated to a Pd(0) complex. The cycle is completed by product dissociation from the Pd(0) complex.

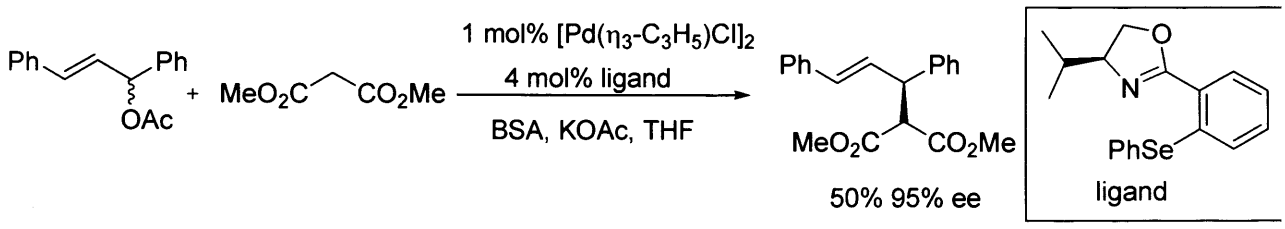
A good chiral ligand for the palladium allylic substitution reaction involves using different levels of electronic effects. It was found that that using hard nitrogen and soft phosphorus, selenium or sulphur donor atoms has helped increase the enantioselectivity greatly, where ligands using these atoms are mainly used in palladium allylic substitution reaction.[18a]

Exo (W) isomer Endo (M) isomer

It has been deduced that the nucleophile preferentially attacks *trans* to the phosphorus, known as the *trans* effect. The *trans* effect is defined as to what extent an atom can influence the dissociation of a ligand co-ordinated *trans* to it. Based on the larger *trans* influence of the phosphorus over that of the nitrogen ligand the stereochemical outcome can be explained by nucleophilic attack on the allylic carbon *trans* to the phosphorus. The [(1,3-diphenyl)allyl]Pd complex undergoes rapid equilibration between endo (W) and exo (M) π allyl Pd complexes. The nucleophile attacks at the less sterically hindered part of the π allyl Pd complexe. Due to a combination of these effects high enantioselectivities can be achieved.[18b] The present thesis uses ligands based on this design.

The development of new structurally diverse chiral ligands for the palladium allylic substitution reaction have attracted much attention in the last few years, where chiral organoselenium compounds have been reported as an important class of catalysts for the induction in this reaction.

The first chiral selenium ligand used in the palladium catalysed asymmetric allylic substitution reaction contains an oxazoline moiety and was first prepared by Helmchen *et al.*[19]



Scheme 18. Example of ligand that achieves high ee.

In 2007 Skarzewski[20] *et al.* showed that selenium and nitrogen containing ligands are good ligands in the palladium allylic substitution reaction, where it is found that the properties of the softer donating selenium increases the enantioselectivity of the compound compared to the sulphur analogues.[20]

Many reactions used mixed donor ligands, which mainly include N or P donor atoms and it is believed this has a strong influence over the donating properties of the selenium atom. Also the steric properties on the selenium might influence the pathway of the incoming nucleophile.[20]

Ferrocene-based ligands have attracted much scientific interest over the last few decades, due to a range of modifications can be made on the cyclopentadienyl rings. It has also shown some interesting complexing behaviour with Pd(II) and excellent selectivity for the palladium-catalysed asymmetric allylic substitution reaction.

Interestingly it has been found that ruthenocene ligands actually performed better with similar enantioselectivities.

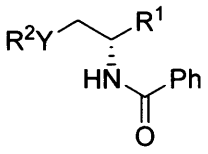
37 **38**

Fig 7. Iron and ruthenium based ligands

Last year Zhang *et al.* found that ruthenocene complex **38** was more air stable than **37** making the use and preparation of **38** easier. It has also been found that it can be stored in atmosphere for more than 10 months without change to its properties. When **38** was used as a ligand, enantioselectivities up to 98% were achieved in 30 minutes compared to the ferrocene derivative, which takes 6 hours to give the same conversion with the same selectivity.[21]

The most recent work in this area shows remarkable results using chiral selenium, sulphur and tellurium amides **39** in the palladium allylic substitution reaction. Good yields of the

alkylated product were achieved with excellent enantioselectivities of up to 98%. Firstly ligands of type **39** were used and found to give good results in terms of both yields and enantioselectives.



R^1, R^2 = aryl, alkyl
Y = S, Se, Te

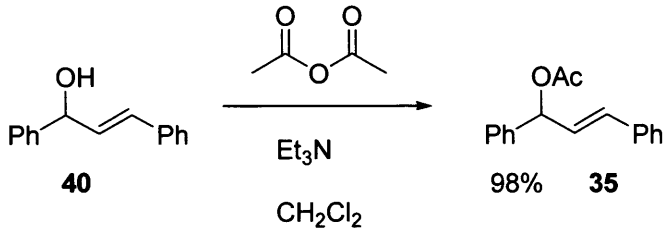
39

Fig 8. Ligand containing S, Se or Te

The catalytic process shows that, with the selenium compounds different alkyl and aryl groups can be tolerated in the reaction showing that variation in the steric and electronic properties does not affect the ability of the selenium to coordinate to the palladium atom. They found that selenium containing chiral compounds gave better yields and enantiomeric excess over the sulphur and tellurium analogues. Therefore, beta selenium amides are more efficient catalysts.[22]

Results and Discussion

Racemic 1,3–diphenylprop-2-enyl acetate **35** was synthesised from commercially available (*E*)-1,3-diphenylprop-2-en-1-ol **40** using acetic anhydride and triethylamine in 98% yield.



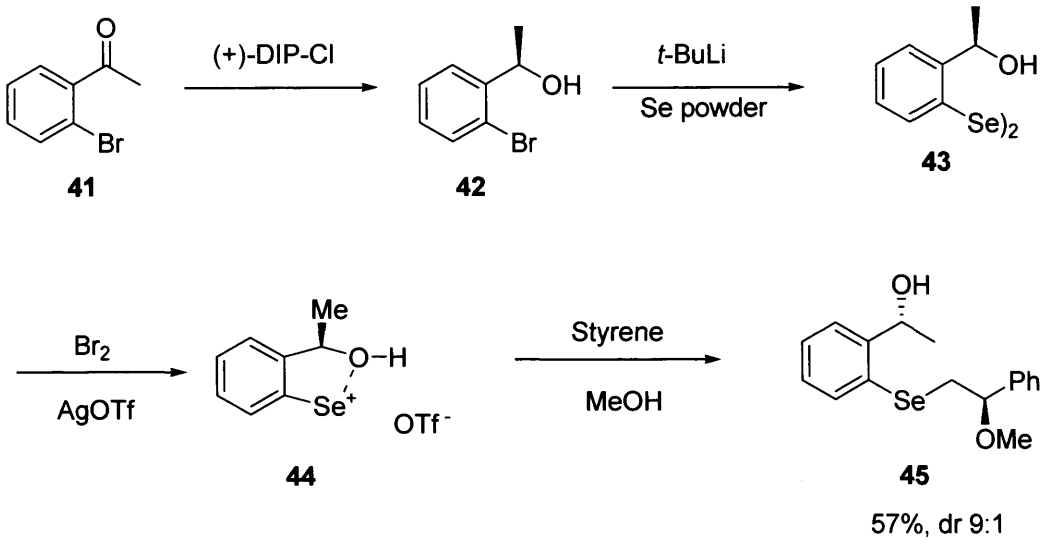
Scheme 19. Synthesis of 1,3–diphenylprop-2-enyl acetate

A range of conditions has been reported for the palladium catalysed allylic substitution reaction. It was found that the optimum conditions were using 1 equiv. of the starting material **40**, 2 mol% of the precatalyst (palladium allyl chloride dimer), 5 mol% of the ligand, 3 equiv. of *N,O*-bis(trimethylsilyl)acetamide (BSA), 3 equiv. of dimethyl malonate and 0.1 equiv. of potassium acetate.

The ligands tested in this reaction were either synthesised or prepared by a previous student.

Synthesis of Ligands

Previous research by Wirth *et al.* showed that a good organoselenium compound in the electrophilic selenenylation reaction of alkenes is (*S,S*)-bis[2-(1-hydroxyethyl)phenyl] diselenide **43**. It was found that the intramolecular oxygen-selenium interaction is necessary for high diastereoselectivity. It is better to have a small R group on the oxygen, as this will bind the oxygen and selenium closer to each other, hence the chiral centre is brought closer to the reaction centre and therefore the transfer of chirality is greater as shown in compound **44**.[23]

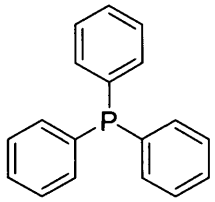
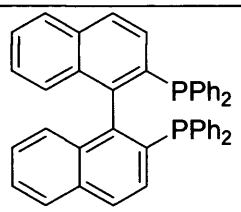
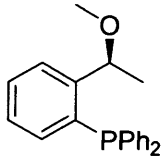
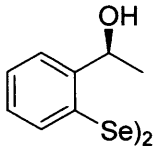
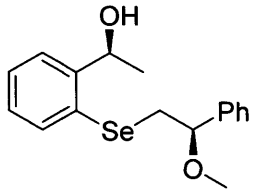
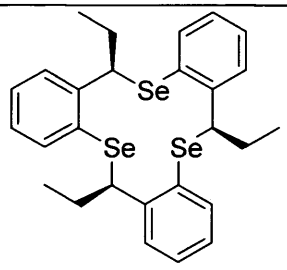


Scheme 20. Synthetic route to diselenide and addition product by methoxy selenylation reaction.

The conversion from **42** to **43** involves a lithium-halogen exchange using *t*-BuLi. The lithiated species is then converted to the diselenide by addition of elemental selenium, followed by mild oxidative work up. The optically active diselenide **43** is then converted to the corresponding selenium electrophile by cleavage of the selenium-selenium bond. The selenium electrophile then adds to the double bond of styrene in the presence of a nucleophile, methanol. The seleniranium cation is then attacked from the *anti*-side, leading to the *trans* addition product **45**.

Testing Ligands in Palladium Allylic Substitution Reaction

The table below shows the ligands that have been tested in the palladium allylic substitution reaction and the yields obtained. Some enantioselectivities have been incorporated when chiral reagents have been used. To test the reaction conditions for the use of selenium based ligands, ligands that have given good yields previously have been tested and also chiral, non-selenium containing ligands.

Entry	Catalyst	Yield %	% ee[a]
a		80	-
b	 rac	94	-
c		13	37
d		NR	NR
e		25	38
f[24]		16	0

[a]The ee values were determined by chiral HPLC (chiracel AD column) (90/10 hexane/isopropanal), NR = No reaction

Table 3. Range of ligands tested in palladium allylic substitution reaction

Conclusion

After finding a method that gave good yields for both triphenylphosphine and BINAP a range of chiral selenium based reagents were tested without either good yields or good enantioselectivities. The theory behind bringing the chiral centre closer to the reaction centre did not become useful in this type of reaction due to the addition product having a weaker interaction between the selenium and oxygen as the selenium is now no longer electrophilic due to an addition reaction taking place. However there are many different types of selenium based ligands that have proved successful and therefore the need to screen more chiral selenium based ligands in this type of reaction is only useful to test the effectiveness of the ligand.

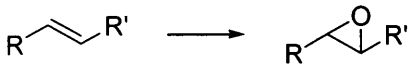
Chapter 4

Seleninic Acids as Catalysts

Cyclic Seleninate Esters – Aims

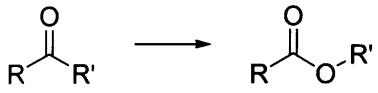
Benzeneseleninic acids are valuable oxidising agents, which have found diverse application in a range of organic transformations. Some examples include:

Epoxidation[25]



Sulfides to Sulfoxides[26]

Baeyer-Villiger Oxidation[27]



Aldehydes to Carboxylic acids[28]

There are a range of other organic transformations, which have not been mentioned here but will be mentioned later in the chapter.

The use of cyclic seleninate esters is a relatively new concept and the idea is to try a range of chiral cyclic seleninate esters, which are prepared *in situ* from the corresponding diselenide and excess hydrogen peroxide in a range of reactions. Once a suitable procedure is found this will then be tested with more than one chiral seleninate ester to see if the induction of chirality is greater than when other known methods are used. It has been found that these cyclic seleninate esters work at their best in Baeyer-Villiger oxidations and this will be the main discussion of this chapter.

Background

Seleninic Acids

Elemental selenium and, more often, its compounds have been successfully used as stoichiometric reagents and catalysts for oxidation of different organic substrates. The oxidation mechanisms depend on the substrate and oxidant or catalyst used.

Oxidation is one of the fundamental processes in contemporary organic synthesis in both research and industry. Particularly important among the oxidants are hydrogen peroxide and *tert*-butyl hydroperoxide (TBHP) as commercially available and cheap reagents of low molecular weight. They contain a high proportion of active oxygen and are environmentally friendly, because their reduction products are water or *tert*-butanol. Some are only moderately active toward most organic substrates so promoters are used; among them are selenium compounds. In most reactions these function as catalysts, transferring oxygen atoms from stoichiometric donor to the oxidised substrate.

Hydrogen peroxide oxidation catalysed by selenium reagents is, in most cases high yielding. The method is attractive because other oxidising agents such as potassium permanganate, chromic acid, bromine, fuming nitric acid and Jones's reagent do not meet environmental restrictions.

In the 1970s and 1980s Barton, Ley and Back[29] recognised the synthetic utility of benzeneseleninic acid **46** and anhydride **47** as oxidants or as catalysts of hydrogen peroxide oxidation. These acids and anhydrides are easily prepared by oxidation of the corresponding diselenide with ozone, *tert*-butyl hydroperoxide or hydrogen peroxide. They show some similarity to selenium(IV) oxide in their behaviour, but often react more cleanly making isolation of the product less troublesome, the bad smelling by-products are minimised and formation of red selenium is generally avoided.[30]

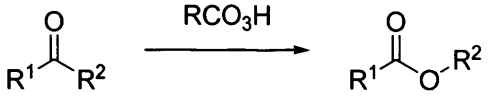
46 **47**

Fig 10. Seleninic acid and seleninic anhydride

Within the family of organic chalcogen-containing compounds, seleninic acids have been efficient catalysts for the activation of hydrogen peroxide. A range of reactions has used catalytic amounts of benzeneseleninic acid and stoichiometric amounts of peracid. Examples include epoxidation reactions of alkenes, oxidation of sulfides to sulfoxides and sulfones, Baeyer-Villiger oxidations, oxidation of aldehydes to carboxylic acids and oxidation of thiols to disulfides.[31]

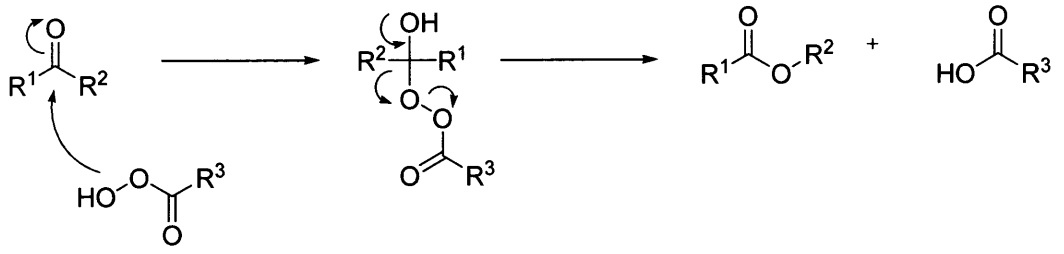
Baeyer-Villiger Oxidation

The reaction is named after German chemist A. Baeyer (1835 – 1917) and Swiss chemist V. Villiger (1868 – 1917).[32] They found that treating a ketone with a peroxyacid (RCO_3H) could produce an ester, where an oxygen atom inserts next to the carbonyl group.[33]



Scheme 21. Baeyer-Villiger Oxidation.

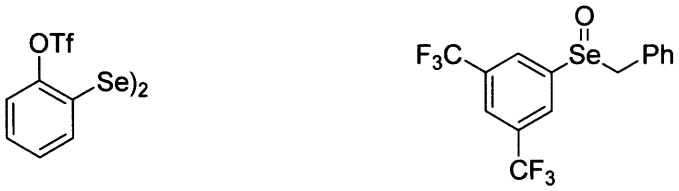
Key features of the Baeyer-Villiger oxidation reaction are its stereospecifity and predictable regioselective chemistry. The regiospecificity of the reaction depends on the relative migratory ability of the substituents attached to the carbonyl. Substituents which are able to stabilise a positive charge migrate more readily, hence the order of preference is *t*-alkyl > cyclohexyl > sec-alkyl > phenyl > prim-alkyl > methyl. Therefore the product forms preferentially from the more substituted carbon. In some cases stereoelectronic and ring strain factors also affect the regiochemical outcome.[34]



Scheme 22. Mechanism of Baeyer-Villiger Reaction.

Selenium Reagents as Oxidants

There is great ease in transforming cyclic ketones into lactones by Baeyer-Villiger oxidation, which makes it an important method for the total synthesis of natural products. Several selenium compounds are efficient reagents for the oxidation of organic compound. Ichikawa and co-workers showed that non-chiral selenium reagent **48** with 30% hydrogen peroxide gives high yields of Baeyer-Villiger product. They found, after trying a range of catalysts, that a triflate moiety in the *ortho* position was very important factor allowing the catalyst to work effectively.[35]



48 **49**

Fig 11. Structure of effective catalyst for Baeyer-Villiger oxidation and selenoxide catalyst

Many reactions involving hydrogen peroxide are slow and require the use of a catalyst to give useful rates of reaction. Two reactions where hydrogen peroxide is a useful oxidant are epoxidation of alkenes and the Baeyer-Villiger oxidation of aldehydes and ketones. It has been found that selenium(IV) oxide and arylseleninic acids have been used to catalyse of the Baeyer-Villiger reaction where arylseleninic acids have been the most efficent. Detty and Goodman reported the use of selenoxides as good catalysts for epoxidation and Baeyer-Villiger reactions.[36] They found that the fluorinated selenoxide **49** was the kinetically most active catalyst in this class. There seemed to be no obvious trend in the catalysts tested, which had different electronic

properties. Catalyst **49** was then used in a range of epoxidation and Baeyer-Villiger reactions giving high yields of products.[36]

Asymmetric Baeyer-Villiger oxidation

A hundred years after the discovery of the Baeyer-Villiger oxidation, its modification into an asymmetric variant is still a challenging task in modern chemistry. Until recently, enzyme catalysis was the sole way of achieving enantioselective Baeyer-Villiger oxidation with a single report of an abiotic equivalent.[37] Bolm and Beckmann reported the use of zirconium-mediated asymmetric Baeyer-Villiger oxidation. Although reasonable enantioselectivities were achieved, stoichiometric amounts of the zirconium reagent were needed making this an unfavourable route.[38] However, Uemera *et al.* found that using peroxyseleninic acids ($RSeO_3H$) and seleninic acids ($RSeO_2H$) in catalytic amounts gave moderate yields and low enantioselectivities based on a chiral diselenide having an chiral oxazoline moiety. Even when a Lewis acid was added there was very little improvement on yield and enantioselectivity. Therefore, the search continues for chiral diselenides that give higher yields and better enantioselectivities.

Desymmetrisation of meso Compounds

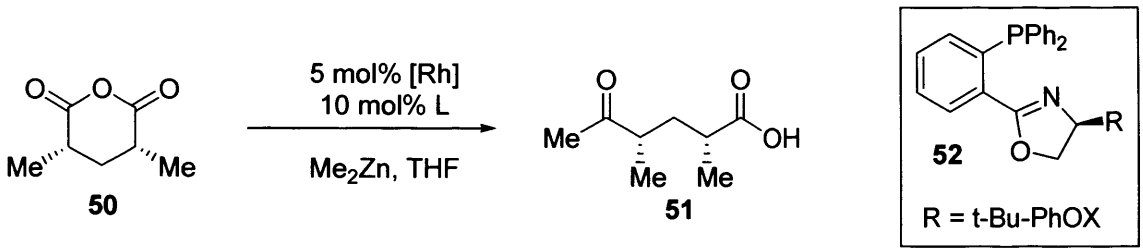
The production of enantiomerically pure materials is usually achieved in one of two ways either by using enantiomerically pure starting materials derived from sources called the 'chiral pool' and the resolution of racemic mixtures. However these methods have some drawbacks. The chiral pool is limited to compounds only found in nature. The resolution of racemates, which require the use of a resolving agent and can often be inconvenient and time consuming. Further more, resolution often means that the undesired enantiomer is discarded resulting decreased efficiency and wasting half of the material.[39]

Recently the desymmetrisation of meso-substrates has become a powerful method in asymmetric synthesis. The advantage of desymmetrisation over conventional kinetic resolution is the ability to achieve high enantioselectivities at high conversion, with a theoretical yield of 100% whereas classical kinetic resolution only allows a maximum yield of 50%. The ability to selectively transform a meso compound to an

enantiomerically pure chiral compound has broad application, especially in the agricultural, pharmaceutical and polymer industries. In the latter part of studies the catalytic use of chiral diselenides is used in preliminary studies for the catalytic asymmetric desymmetrisation of meso compounds.[40]

Successful Desymmetrisations

Examples of previously successful desymmetrisation of meso compounds include work from Rovis and co workers.[41]

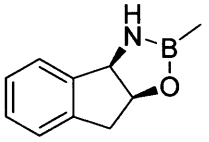


Scheme 23. Example of effective desymmetrisation procedure

They found that the use of commercially available dimethyl and diethyl zinc reagents together with $[Rh(nbd)Cl]_2$ allows the desymmetrisation of compound **50** to proceed with excellent yields (90-97%) and excellent ee's (80-86%) to yield compound **51**. Under these conditions it was found that a range of 3,5-substituted meso-glutaric anhydrides give rapid access to substituted *syn*-deoxypoly propionate fragments in a single transformation.[41]

Desymmetrisation of meso compounds is a powerful and versatile strategy in asymmetric synthesis as the differentiation of two-enantiotopic groups faciliate the formation of multiple stereocentres in a single transformation.[42]

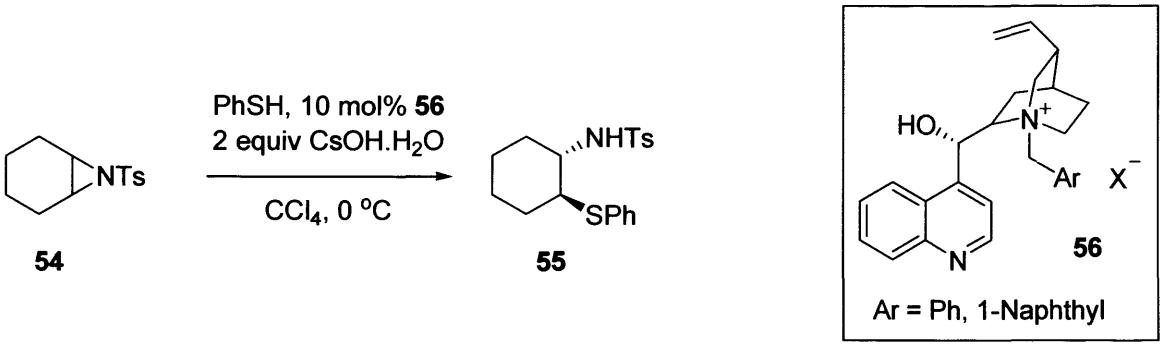
In 2002, Jones and Dixon showed that good yields and enantioselectivities would be achieved by using only 1 mol% of the catalyst oxazaborolidine **53** in the reaction of the enantioselective reduction of a meso amide.[43] Previously it has been reported that high catalytic loading of 20-50% was often required to successfully achieve this reaction.



53

Fig 12. Oxazaborolidine catalyst

The synthesis of optically organic compounds using a desymmetrisation strategy has attracted much attention because it offers the opportunity to generate two stereogenic centres in a single step. More recently it was reported that chiral quaternary ammonium salts could help to desymmetrise meso-*N*-sulfonylaziridines.[44]

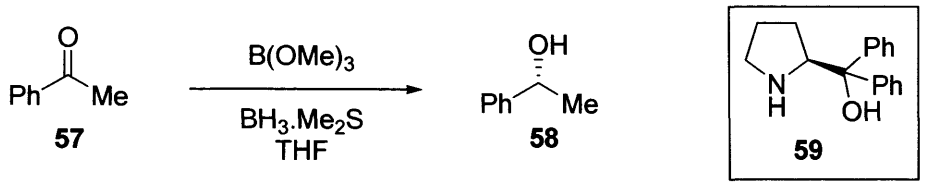


Scheme 24. Effective catalyst used in the desymmetrization of meso aziridines

Hou and Li-Xin found a simple method for the desymmetrization of meso aziridines by arylthiols using cinchonine derivative **56** giving thioamine **55** in high yields (85-99%) and low to moderate enantioselectivites (3-73%).[44]

An example where excellent results were achieved of asymmetric reduction was by Masui in 1996.[45] He found that prochiral ketones are reduced to the corresponding secondary alcohols by the reaction of chiral amine alcohols and trimethyl borate, which generates the active catalyst *in situ*.

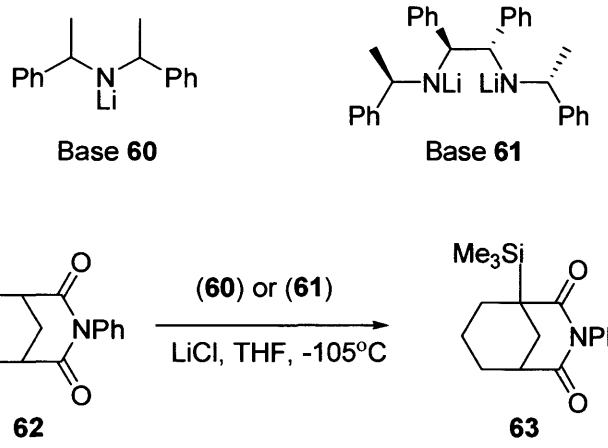
Initial studies began using acetophenone as the starting material, they found that using 1 equiv. of the amine **59**, 0.12 equiv. trimethyl borate and 1 equiv. of borane dimethyl sulfide complex gave excellent yields and enantioselectivities.



Scheme 25. Reduction of acetophenone

Enantioselective excess of up to 98% was achieved with quick reaction times, using temperatures ranging from 0 °C to 30 °C. They found under these conditions a range of nitrogen containing alcohols also gave high enantioselectivities.[46] This work is a classic example of the CBS reduction.

Simpkins and coworkers have found that meso compounds can be desymmetrised in very high enantioselectivities by asymmetric bridgehead metalation.



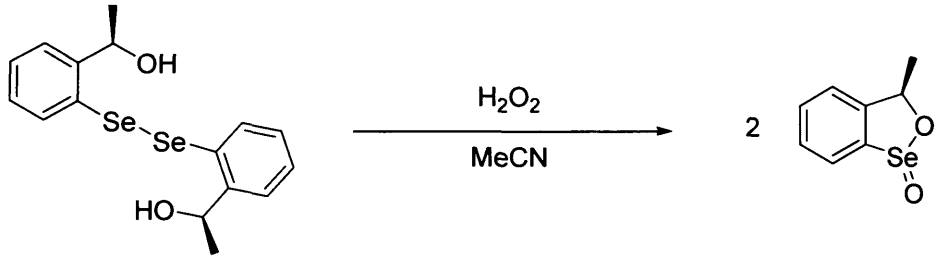
Scheme 26. Desymmetrisation by asymmetric bridgehead metalation.

Amide base **60** and amide base **61** was found to be able to asymmetrically desymmetrise meso-imide **62** as shown in Scheme 26 in high yields and enantiomeric excess, showing more efficient behaviour than LDA or LTMP. They have shown that a variety of electrophiles can be added to these substrates with ees ranging from 95-98% can be achieved. This shows examples of how desymmetrisation of meso compounds can be used without the usual time consuming techniques of resolution.[47]

Desymmetrisation of meso compounds is one of the most attractive methods for the production of asymmetric materials. Enzymatic techniques are mostly used but more chemical techniques are being investigated for the analagous transformation.

Results and Discussion

Benezeneseleninic acid has been a successful oxidant in many organic transformations; the use of cyclic chiral seleninic esters is a relatively new theme. The idea is that the cyclic seleninic acid is in a locked conformation and therefore the chirality is closer to the selenium centre and therefore transfer of chirality to the reaction products would be greater. (*S,S*)-bis[2-(1-hydroxyethyl)phenyl] diselenide **43** was reacted with excess hydrogen peroxide in acetonitrile to obtain the cyclic seleninate ester **64** in 73% yield. This product was used in a range of organic transformations to see if the theory can be made to work in practice.



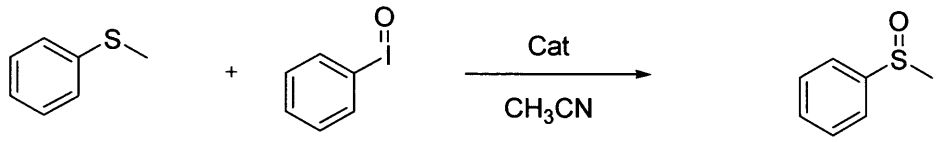
43 **64**

Scheme 27. Shows cyclic seleninic ester prepared from the corresponding diselenide.

As most of the reactions use hydrogen peroxide in stoichiometric quantities this active catalyst is then prepared *in situ* from the corresponding diselenide.

Sulfides to Sulfoxides

It has previously been reported[26] that benzeneseleninic acid is an efficient catalyst to convert sulfides to sulfoxides in excellent yields without over-oxidising to the sulfone. Previous oxidation conditions which use, for example, hydrogen peroxide, *m*-chloroperbenzoic acid, sodium metaperiodate, bromine have all resulted in the over-oxidation to the sulfone. So this convenient method was adapted to use the cyclic chiral seleninic ester catalytically with iodosobenzene as a stoichiometric oxidant in acetonitrile.[26]



65 **66** **67**

Scheme 28. Model reaction to test conditions of catalyst

Methyl(phenyl)sulfane **65** was used a model substrate to test the chosen catalyst. Firstly the same reactions were carried out as the original procedure[26] to check the validity of the method and it was found that the reaction proceeded smoothly in 96% yield to give the sulfoxide as a single product. However when (*R*)-[2-(1-hydroxyethyl)phenyl] seleninate ester **64** was used as a catalyst the yield was only 54% and there was no induced chirality in the sulfoxide: the results yielded a racemate. When benzeneseleninic acid was tested on another substrate, 3-methylthiopropanol **68**, the corresponding sulfoxide **69** was obtained in only 35% yield. In the absense of a catalyst, no reaction occurred after 24 hours indicating that a catalyst is required in order to obtain the oxidation product.

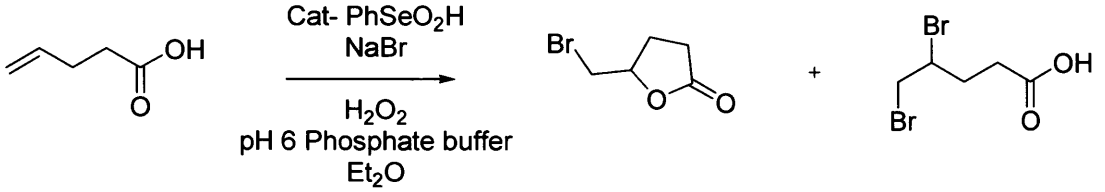
68 **69**

Scheme 29. Conversion of 3-methylthiopropanol to the corresponding sulfoxide

Due to the low yields and no selectivity this research was stopped at this point.

Bromolactonisation

Detty and co-workers[48] claimed to have found that using arylseleninic acids, where benzeneseleninic acid is one of the best catalysts, is useful for the bromination of organic substrates with sodium bromide and hydrogen peroxide in a two-phase system of diethyl ether and pH 6 phosphate buffer.

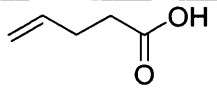
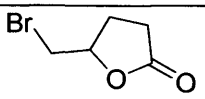
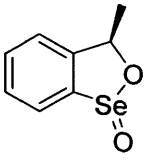
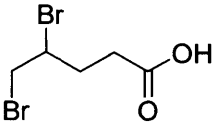
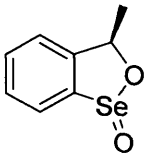


70 **71** **72**

Scheme 30. Model reaction for the bromolactonisation.

This seemed to be a good model for investigation of the cyclic seleninate esters.

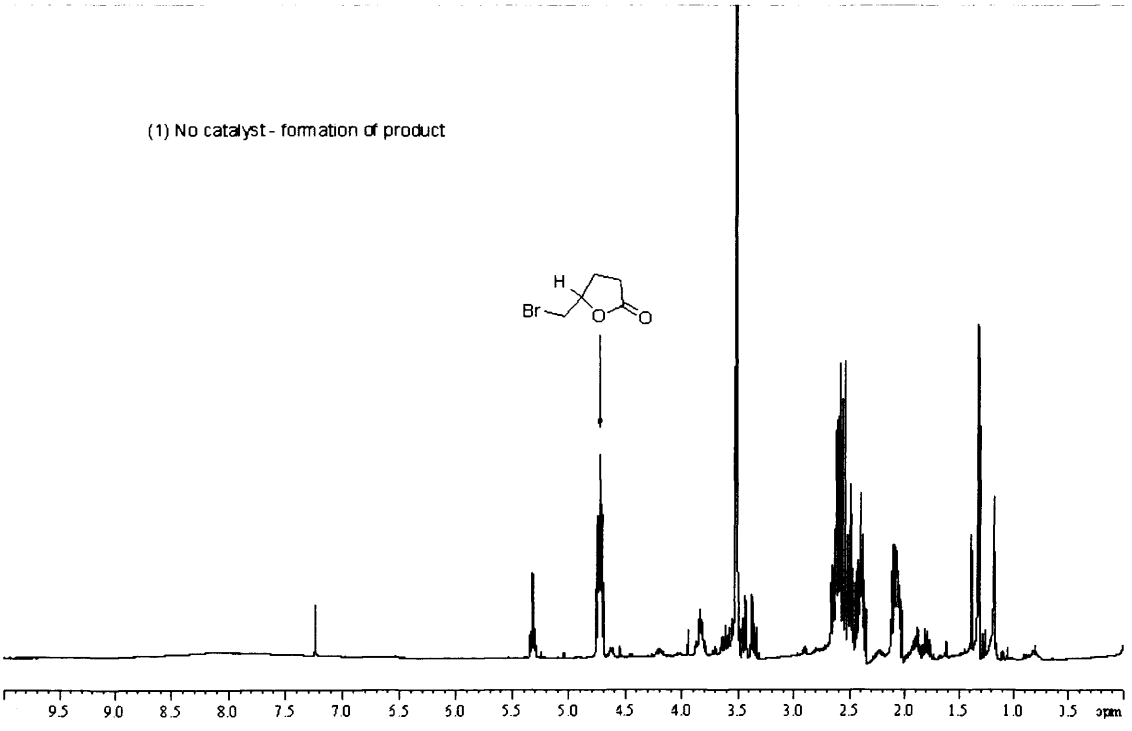
Firstly benzeneseleninic acid was tested in this reaction sequence but a mixture of products was observed by NMR, including the starting material **70**, the product **71**, and a side product identified as 4,5-dibromopropanoic acid **72**. This was stated in the original literature which was also comparable to work achieved in this thesis. However when no catalyst was used in the reaction the product **71** was still formed contradicting the paper these conditions came from.[48] The peaks from the three different products were identifiable by ^{1}H NMR as shown in Spectrum 2. It was only when the reaction was allowed to stir overnight that the starting material disappeared. When cyclic seleninate ester **64** was used, the crude yield of the reaction mixture was only 29%. Due to the fact that this reaction allows the formation of the desired product **71** without the use of catalyst and the mixture of products observed, combined with low crude yields, there is no need to achieve this catalytically. The background reaction is as fast as the catalytic reaction and therefore enantiomeric excess will be low. Due to the mixture of products formed in this reaction this would never be a high yielding procedure and therefore new routes would be required in order to do this enantioselectively as even though the yield is high this was probably due to the catalyst being inactive. The spectra of these compounds show a mixture of products and therefore an undersirable method for enantioselective work to be carried out. Included is Table 4 to show the original results compared to the findings here. Three different spectra are included for observation, which include (**1**) no catalyst, which clearly shows the formation of the product **71** (**2**) $PhSeO_2H$, which shows the formation of **71** and **72** (**3**) cyclic seleninate ester **64**, which shows formation of **71** and undesired side reactions taking place. Due to these results these investigations were stopped at this point.

Substrate	Products	Catalyst	Lit %[a]	Actual %[a]
	 **71**	No Cat	< 6	85
		$PhSeO_2H$	84	84
			-	83
	 **72**	No Cat	< 6	< 6
		$PhSeO_2H$	16	16
			-	13

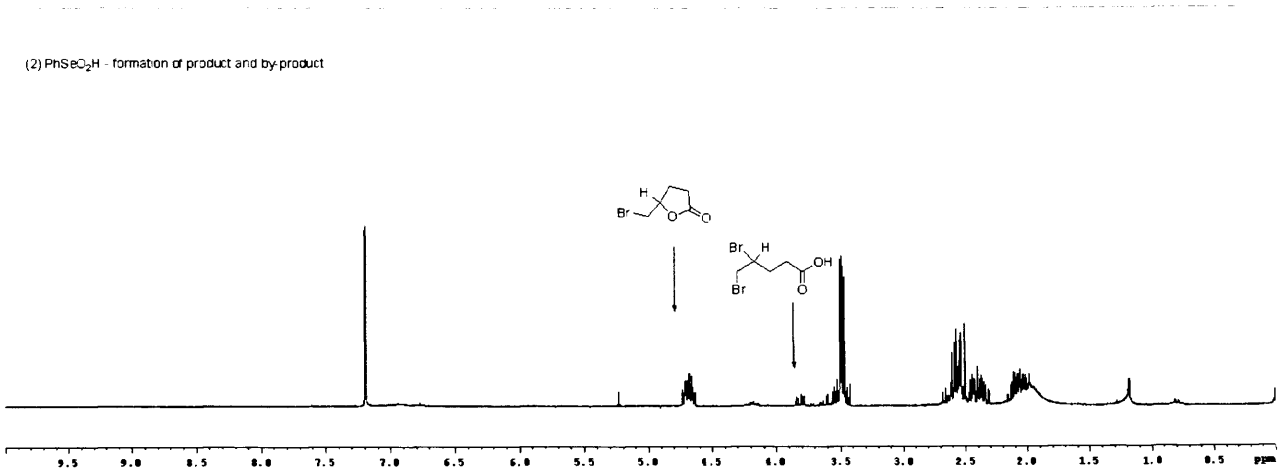
[a] Conversion by ^{1}H NMR

Table 4. Comparison of literature data to actual work achieved in this thesis

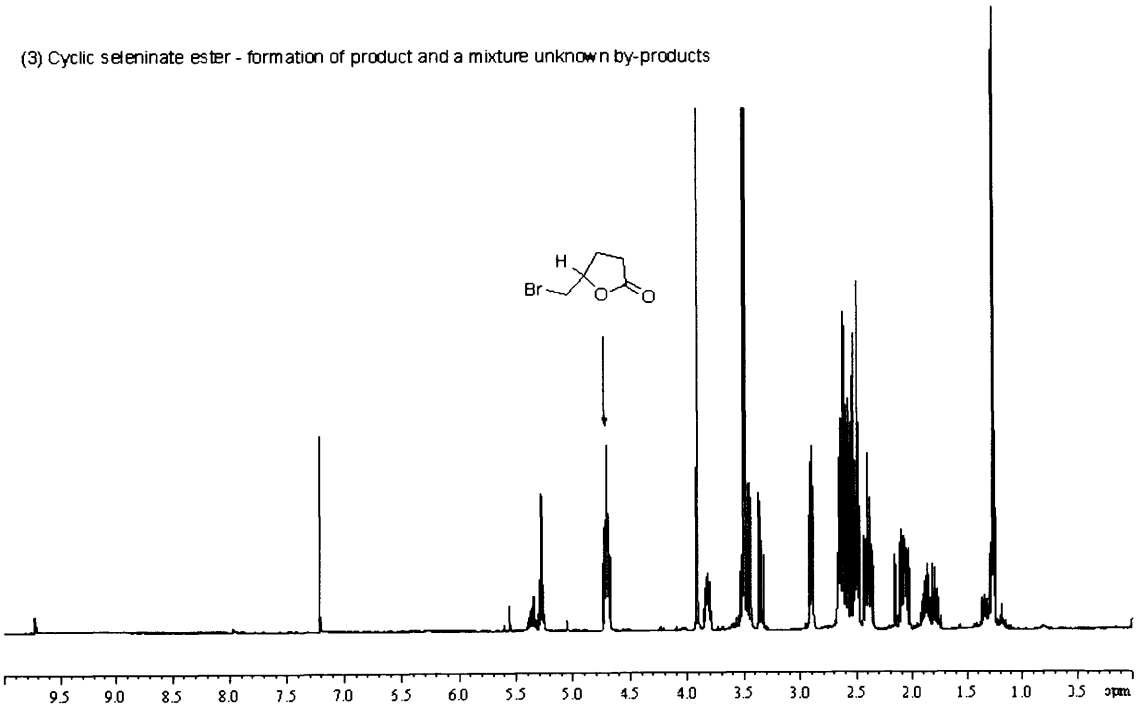
^{1}H NMR - 400MHz



^{1}H NMR - 250MHz



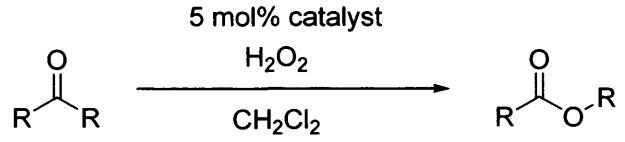
^{1}H NMR - 400MHz



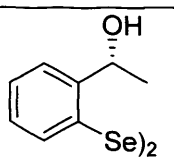
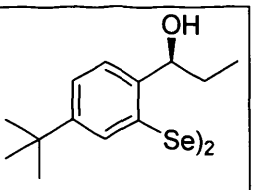
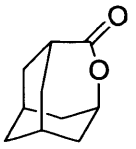
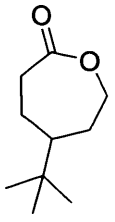
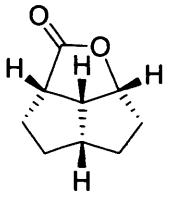
Spectra 2. Show the difference spectra using (**1**) no catalyst, (**2**) $PhSeO_2H$, (**3**) cyclic seleninic ester **64**

Epoxidation and Baeyer-Villiger Oxidations

Benzeneseleninic acid was then tested using cyclohexene and 2-adamantanone on a first trial basis, it was found that no reaction took place with cyclohexene but 2-adamantanone was converted into the corresponding oxidation product **73** in 75% yield. To check the conditions of the epoxidation reaction, styrene and stilbene were also tested but again no reaction occurred so the focus remained on Baeyer-Villiger oxidations. 2-Adamantanone was then tested without the use of the catalyst, which resulted in only starting materials showing that the selenium-containing catalyst is an important factor in allowing this oxidation procedure to take place. Although the 2-adamantanone is not prochiral, (*R*)-[2-(1-hydroxyethyl)phenyl]seleninate ester **64** was also tested as previous work showed the use of this catalyst often leads to a significantly lower yield. However, this was quite the opposite and a higher yield of 84% was obtained. These conditions were then subjected to a range of prochiral ketones in order to obtain high yields and enantioselectivities.



Scheme 31. Baeyer-Villiger Reaction

Catalyst → Product ↓	No Cat	$(PhSe)_2$[a]		
 **73**	0	75%	84%	-
 **74**	0	91%	54% racemate[b]	81% racemate[b]
 **75**	0	58%	79% racemate[b]	99% racemate[b]

[a] $(PhSe)_2$ was used to prepare racemates for the comparison of products by GC.[b]ees were determined by Alpha dex 120 – fused silica capillary column- 30 m x 0.25 mm x 0.25 μm or Beta dex 120 – fused silica capillary column- 30 m x 0.25 mm x 0.25 μm.

Table 5. Show the different catalysts used in the Baeyer Villiger reaction.

From the results it can be seen that high yields were obtained using 5 mol% of catalyst with excess hydrogen peroxide. As the cyclic seleninate ester is formed *in situ* from the use of excess hydrogen peroxide these studies were not carried using independently prepared cyclic seleninate esters. Also the catalyst for these reactions was not re-isolated at the end of the procedure. The ketone leading to **75** was thought to be a good choice due to the control it has over the facial attack of the peroxide, however this gave a disappointing result.

Conclusion

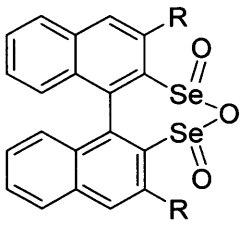
It has been found that the chiral seleninate ester did not work well in the oxidation of sulfides to sulfoxides. The yields were poor and there was no induced enantioselectivity. When benzeneseleninic acid was used the outcome was a clean reaction product therefore, if a range of chiral seleninate esters were tested on this procedure, I believe that this could be an area of interest for further research.

The bromolactonisation of organic substrates would have been a good research project if my results didn't contradict the literature. However, the product was formed even without catalyst, therefore it would be difficult to obtain an accurate yield, as it will not be known if the catalyst helped produce the product or if it was the background reaction.

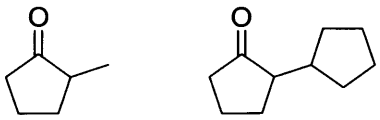
The Baeyer-Villiger reaction was very successful and high yields were obtained for this preliminary investigation, however the products are formed, as racemates and again a wider range of diselenides need to be screened.

Further Work

An example of another seleninate ester that could be used is shown be below. This structure is a modified version of the well known BINAP, which has proved to be successful in a range of reactions. Also the R groups could be substituted with a wide range of functional groups.

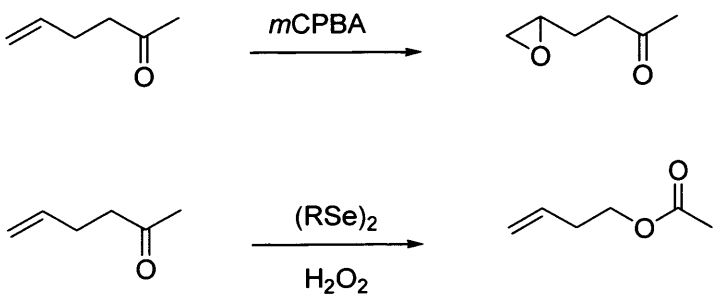


Also these conditions could be used to test the kinetic resolution of racemates; some examples of cheap commercially available starting materials are:



where the reaction will run to approximately 50% and the enantioseletivities of the starting materials and products would be investigated.

As the oxidation did not work for the epoxidation of alkenes but worked effectively in the Baeyer-Villiger reaction, it would be interesting to see what would happen if an alkene and a ketone functional group were in the same molecule. Epoxidation is normally found to be faster than the Baeyer-Villiger oxidation and therefore this could possibly offer an alternative route when a peracid is used with the diselenide catalyst.



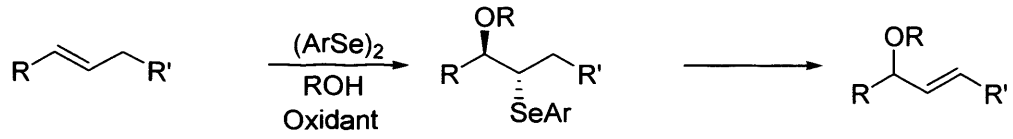
Chapter 5

Catalytic use of Selenium Electrophiles in Cyclisations

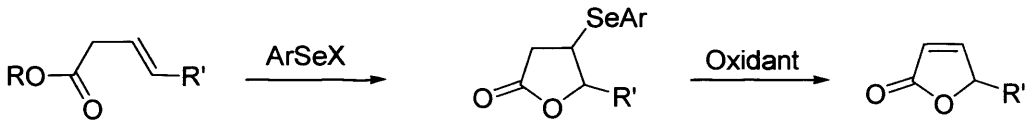
Catalytic use of Selenium Electrophiles in Cyclisations – Aims

Organoselenium reagents are largely used in organic synthesis to introduce new functional groups into organic substrates under mild reaction conditions. Over the years many research groups have described the synthesis of non-chiral and chiral diselenides, which can be transformed *in situ* into electrophilic selenenylating reagents. The reactions of these intermediates with alkenes in the presence of an external or internal nucleophile result in diasteroselective addition or cyclisation reactions.[49]

Diastereoselective addition with external nucleophiles (ROH)



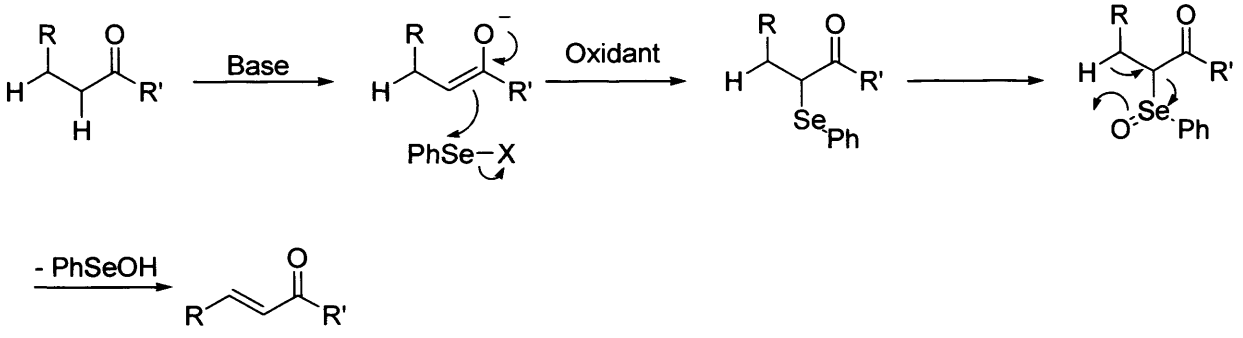
Cyclisation reaction with internal nucleophiles



The oxyselenenylation-deselenylation reaction allows double bond transposed allylic alcohols and ethers to be prepared from a variety of olefins using an external nucleophile where diastereoselective addition takes place.[50] The intramolecular selenenylation-deselenenylation reaction allows a range of butenolides to be formed using the carboxylic acid as an internal nucleophile. The process can occur due to the acid moiety in the α-position of the starting material and the presence of a β-hydrogen atom. Once the selenium electrophile has added to the alkene, an excess of oxidant allows the selenide to convert to a selenoxide, which undergoes an elimination process called selenoxide elimination.[51]

Selenoxide elimination

In presence of a β-proton, a selenide will give an elimination reaction after oxidation to the selenoxide leading to an alkene and leaving a selenenic acid. However when benzeneselenenic acid is produced as in Scheme 32 this causes many difficulties, as benzeneselenenic acid is unreactive and therefore unable to re-enter the catalytic cycle. This means other methods for elimination need to operate. Later in this chapter it is shown that a catalytic cycle can be constructed, as benzeneselenenic acid is not produced in the reaction. Oxidising agents that have been used previously are hydrogen peroxide, ozone or mCPBA.[51] Previously this type of reaction has been achieved with stoichiometric amounts of the selenium reagent. The purpose of this section of work involves optimising conditions in order to achieve these using only catalytic amounts of selenium reagents.



Scheme 32. Shows the selenoxide elimination reaction

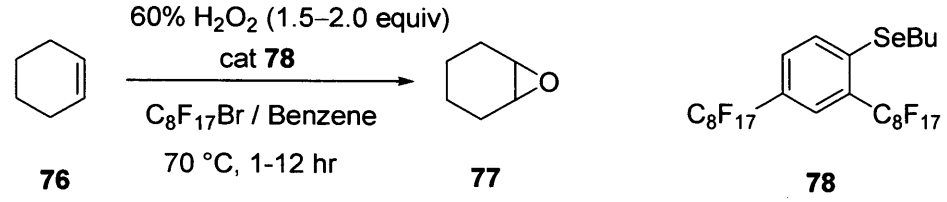
Catalytic use of Selenium Electrophiles in Cyclisations – Background

In recent years, selenium reagents have attracted much interest for their application in organic synthesis.[4,52] Selenium dioxide is a well known and traditionally used oxidising agent for alkenes, ketones and other substrates, but it wasn't until 1977 that Umbriet and Sharpless found that only catalytic amounts of selenium dioxide could be used to help enhance the rate of oxididation of olefins.[53] Firstly, it was found that hydrogen peroxide in the presence of catalytic selenium dioxide oxidised the highly reactive β-pinene smoothly *via* selenenic allylic oxidation, but less reactive olefins gave either epoxide or a complex mixture of products. They anticipated that using an alkyl hydroperoxide would avoid the peracid behaviour associated with hydrogen peroxide in this system. They found that *t*BuOOH in the presence of catalytic amounts (1.5 – 2.0 mol%) of SeO_2, oxidised even the less reactive olefins to the corresponding allylic alcohols in comparable or better yields than those observed with stoichiometric amounts of SeO_2.[53]

Phenylseleninic acid has been used as a catalyst for the epoxidation of olefins and Baeyer-Villiger reactions of ketones. It was found in 1983 that polystyrene bound phenylseleninic acid can be used in catalytic amounts in the oxidation of olefins, ketones and aromatic systems, which has helped avoid the toxicity of selenium compounds and contamination of reaction products.[54] It was found that the catalyst is stable to the reaction conditions and can be recycled with no apparent loss of activity.

In 1999 Knochel and co-workers found that using organoselenium reagents containing perfluoroalkyl substituents in fluorous solvents helps avoid contamination of the reaction products with selenium compounds. Fluorous biphasic catalysis introduced by Rábai allows efficient separation of the catalyst from the reaction mixture. The organoselenium catalyst bears perfluoroalkyl substituents shown in Scheme 31, which are necessary for selective solubilisation in perfluorinated solvents. It was found that the catalyst could be reused more than ten times without decrease in yields or increase in reaction times. The toxic selenium catalyst can be exclusively dissolved in

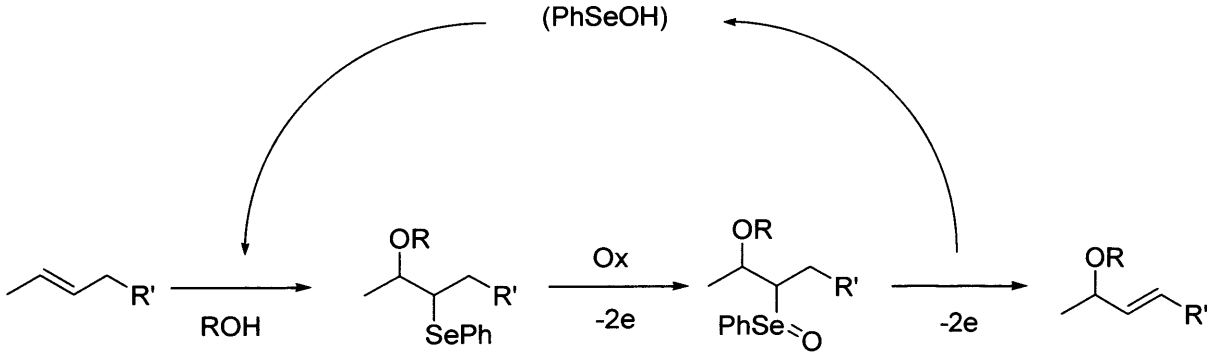
perfluorinated solvents, which allows the facile separation from the reaction mixture and its reuse for further reactions.[55]



76 **77** **78**

Scheme 33. Fluorinated selenium catalyst in epoxidation reaction.

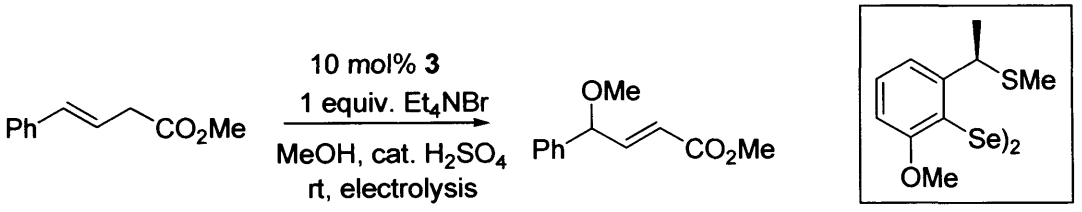
Oxyselenenylation–oxidative deselenenylation provides double bond transposed allylic alcohols and ethers from olefins. The method involves two steps: selenenylation with PhSeX (X = Cl, OR, NR_2) followed by oxidation with O_3, $NaIO_4$, and peroxides (H_2O_2, *t*-BuOOH, *m*CPBA). Stoichiometric amounts of PhSeX and large excess of oxidant are normally required. It was found by Torii *et al.* that this could be achieved in one step by electrochemical generation of and recycled use of selenium reagents from catalytic amounts of diphenyl diselenide, without the formation of phenylseleninic acid and in the absence of peroxides. Forming phenylseleninic acid would break the catalytic cycle. It was found that electrooxidatively generated phenylselenenyl electrophiles react regioselectively with olefins producing the oxyselenide, followed by the electrochemical oxidation to provide the corresponding selenoxide. The selenoxide is formed due to water being one of the solvents in the solvent system used, which instantly undergoes *syn* elimination to give the desired product.



Scheme 34. Electrochemical oxidation of alkenes to allylic alcohols or ethers

It was found that the selenenylation reagent (PhSeOH) is generated *in situ* and the transformation is promoted by adding a metal salt e.g. $MgSO_4$.[56]

Further development in 2006 by Wirth *et al.*[57] for the electrochemical oxyselenenylation-deselenenylation conversion of alkenes into allylic compounds was successfully achieved using catalytic amounts of diphenyl diselenide (10 mol%) and enantiomerically pure diselenides where the alkene has an acid or an ester moiety such as compound **79**. Tetraethylammonium bromide was employed in the reaction to act as both as a redox catalyst and as an electrolyte in dry methanol. The reaction is initiated by the anodic oxidation of bromide to bromine, which then reacts with diphenyl diselenide to form arylselenenyl bromide. The arylselenenyl bromide then reacts with an alkene to form a seleniranium cation, which subsequently reacts with a nucleophile to form a selenide. When the next equivalent of bromine is generated, this forms an unstable tetravalent selenenyl bromide intermediate which acts as a good leaving group thus forming the elimination product **80**. In previous work, ammonium peroxidisulfate was used but this was only advantageous over the electrochemical method when acetic acid was used as the nucleophile.



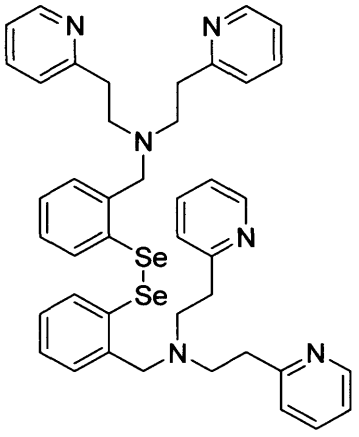
79 **80** **81**

Scheme 35. Electrochemical oxidation of organic substrate and chiral diselenide used in reaction.

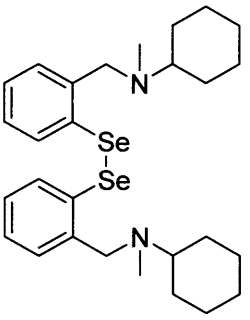
When using chiral diselenides in place of diphenyl diselenide moderate yields and good enantioselectivities were observed in the formation of the allylic compounds where diselenide **81** gave the highest enantioselectivity of 66% in product **80**. Previously, sulfuric acid has been reported to stop the elimination occurring so isolation of the selenide could be achieved. It has now been found that sulfuric acid does not help stop the elimination but does enhance the rate and yield of the reaction. Also much work in this area uses metal salts to improve reaction yields but under

these reaction conditions the metal salts have no effect on the yield but do increase reaction times.[57]

The reaction sequence developed by Tomoda *et al.* uses organoselenium reagents such as 2,2-diselenidebis{*N,N*-di[2-(2-pyridyl)ethyl]benzylamine}**82** or 2,2-diselenobis(*N*-cyclohexyl-*N*-methylbenzylamide) **83** in Figure 13 as a catalyst in the presence of copper(II) nitrate for the catalytic conversion of alkenes into the allylic compounds. After screening a range of oxidising agents it was found that sodium persulfate was best for the catalytic reaction. The most efficient conversion was observed in the presence of 3Å molecular sieves, showing that removal of water is essential for the reaction to proceed. They state that the reaction is sluggish and turnover numbers are low.[58]



82



83

Fig 13. 2,2-diselenidebis{*N,N*-di[2-(2-pyridyl)ethyl]benzylamine}**82** and 2,2-diselenobis(*N*-cyclohexyl-*N*-methyl benzylamide) **83**

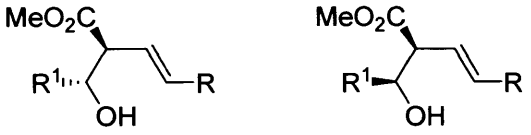
This prompted work by Tiecco and Testaferri on the conversion of *β,γ*-unsaturated esters, amides and nitriles into *γ*-alkoxy or *γ*-hydroxy derivatives. They developed a multistep one-pot synthesis using excess ammonium persulfate and catalytic amounts of diphenyl diselenide, which was obtained in low to excellent yields (23-90%) in just a few hours.

They found that having an electron-withdrawing group in the α-position in the molecule is essential for the success of the reaction as simple unsubstituted alkenes

gave rise to a mixture of products. The increasing work in this area contributes to a better understanding of organoselenium chemistry.[59]

They also carried out an intramolecular version of this catalytic oxidation to produce butenolides, which are obtained from the reaction of the easily available β,γ-unsaturated acids with catalytic amounts of diphenyl diselenide and an excess of ammounium persulfate in acetonitrile. The carboxy group is found to act as an internal nucleophile and again produces good yields in relatively short reaction times compared to previous work. It was also observed in some cases that better yields were obtained with the catalytic reaction compared to using stoichiometric amounts of diphenyl diselenide.[60]

Tiecco and co-workers have taken this one step further and utilised the previous reaction conditions to convert alkenols to the corresponding 2,5-dihydrofurans. Excellent yields were obtained (90-96%) with traces of a side product. The cyclisation-elimination process gave rise to two stereoisomers of the 2,5-dihydrofurans in good yields, where observed selectivity reflects the steric demands in the approach of the electrophile to the π-bond. It was found that *erythro*-unsaturated alcohol gave *trans*-2,5-dihydrofurans and the *threo*-unsaturated alcohol gave the *cis*-product.

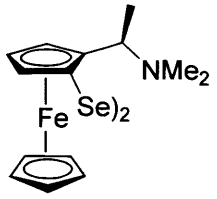


Erythro *Threo*

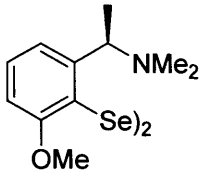
Fig 14. Shows the two different isomers *Erythro* and *Threo*.

The observed stereoselecitvity of the process implies that only the major isomer of the intermediate undergoes elimination to afford the corresponding 2,5-dihydrofurans. When ammonium persulfate was reacted with the major isomer of the intermediate the desired product was quantitatively transformed, whereas the minor isomer gave unidentified products, showing the *cis* relationship between the phenylselenyl and the methoxycarbonyl groups renders the approach of the persulfate anion to the selenium atom more difficult.[61]

Tomoda *et al.* reported the first catalytic asymmetric conversion of *trans* β-methyl styrene into optically active allylic ethers using diaryl diselenides having a chiral pyrrolidine ring at the *ortho* position.[62] Yields of 24% and enantioselectivities of 32% ee were observed using previous literature methods and copper(II) nitrate. The moderate asymmetric induction is believed to be due the strong Se–N interaction between electrophilic selenium and *tertiary* amine of the chiral pyrolidine ring during the addition to the olefin.[62]



84



85

Fig 15. Chiral ferrocene-containing diselenide **84** and chiral amine containing-diselenide **85**.

The highest diastereoselectivity (96% de) of asymmetric methoxyselenenylation of alkenes was achieved using the ferrocenyl selenium triflates in excellent chemical yields (99%). The use of **84** gave this result and, when applied to a range of alkenes, all resulted in high yields (96–99 %) and moderate to high diastereoselectivities (15–96%). It was observed that sterically large groups in the alkene are necessary to achieve high facial selectivity.[63]

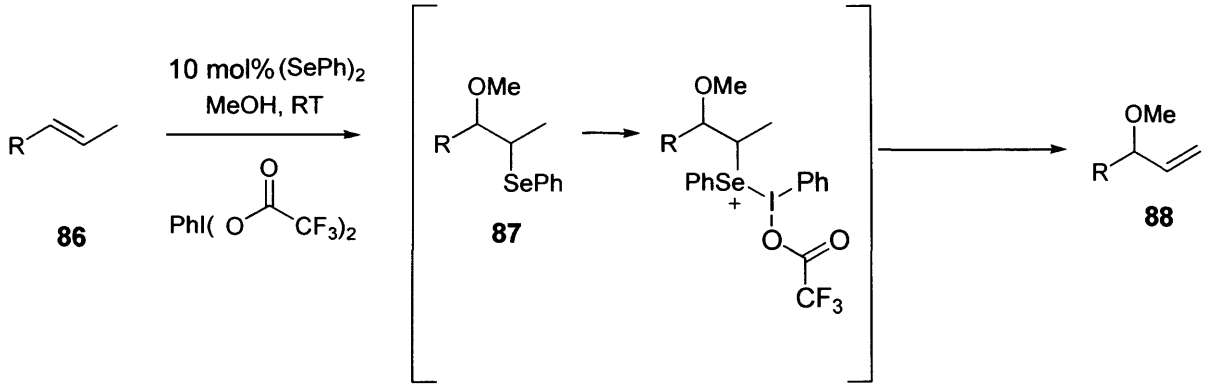
In 1998 Wirth and co-workers used peroxydisulfates for the generation of the nitrogen containing selenium electrophile for the catalytic oxyselenenylation-elimination reaction with *trans*-β-methylstyrene. It is known that metal ions can accelerate the decomposition of peroxydisulfates and varying the metal salts was found to have a strong influence on the stereoselectivity with $Ni(NO_3)_2.6H_2O$ being the most effective salt with ee's up to 71% and when diselenide **85** was used ees up to 75% were observed. These are the highest enantioselecitivities obtained for the catalytic oxyselenenylation-elimination reaction so far obtained, but the drawback is that the turnover number is low.[64]

Results and Discussion

Methoxyselenenylation-dehydroselenenylation reaction

Selenium containing reagents can be used as catalysts or as ligands in various stereoselective reactions. It has been attempted to perform methoxyselenylation-deselenylation reactions with only catalytic amounts of selenium species.

The starting alkene is transformed into allylic ethers when methanol is used.[65]



Scheme 35. Methoxyselenylation-dehydroselenylation sequence with catalytic amounts of diphenyl diselenide.

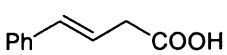
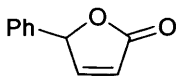
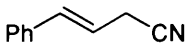
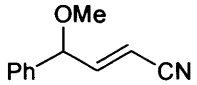
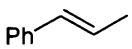
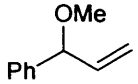
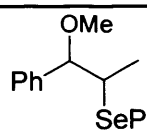
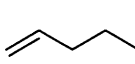
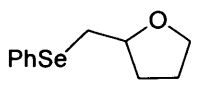
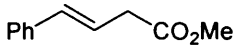
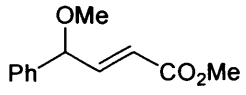
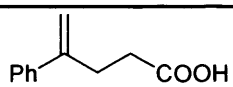
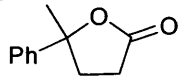
The initial addition to the alkene **86** involves the electrophilic addition of the selenenyl cation and nucleophilic addition of methanol. The resulting selenide **87** is oxidised by excess [bis(trifluoroacetoxy)iodo]benzene, allowing elimination to allyl ethers **88**.[66]

A range of alkenes has been employed in these reactions resulting in different allylic compounds being formed. Unfortunately the results were poor with the use of methanol. Without the use of methanol, and when the R group contains a carboxylic acid function, phenylselenolactonisation occurs with high yields and short reaction times.

Phenylselenolactonisation is known as a means of functionalising unsaturated carboxylic acids, which undergo cyclisation when treated with the electrophile produced from diphenyl diselenide. When (*E*)-4-phenylbut-3-enoic acid was treated with 5 mol% diphenyldiselenide and stoichiometric

[bis(trifluoroacetoxy)iodo]benzene in acetonitrile the yields varied with varying temperature. As the temperature is decreased from room temperature to 0 °C and –30 °C, reaction times were longer and decreased yields were observed. Times ranged from 70 min at room temperature to 165 min at –30 °C.

When adding methanol as the nucleophile in the methoxyselenylation-deselenenylation reaction the results were poor, yielding either inseparable complex mixtures or stopping at the selenide intermediate **87**. A range of alkenes was used to test the reaction conditions. It was found to be critical to add [bis(trifluoroacetoxy)iodo]benzene last to ensure good oxidation and elimination.

Starting Alkene	Product	Diphenyl Diselenide (mol%)[c]	Temp	Addition MeOH 10 equiv.	Time (h)	Yield (%)
	 **89a**	5	0°C	×	1.50	65[a]
		5	-30°C	×	2.75	35[a]
		5	RT	×	1.16	70[a]
		5	0°C	✓	3	0
		5	RT	✓	2	0
		5	RT	✓	1.5	0
	 **90**	50	RT	✓	2.75	30[b]
		50	RT	✓	48	0
	 **91**	5	RT	✓	3	30[b]
		5	RT	×	24	7[b]
		50	RT	✓	24	44[b]
		5	RT	✓	48	0
		5	RT	×	24	0

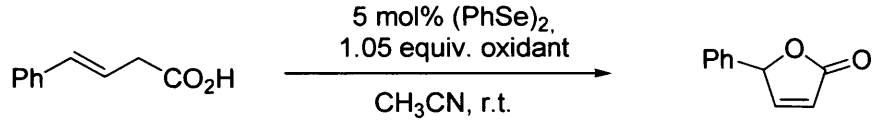
[a]Isolated yields; [b]Conversion by ^{1}H NMR; RT: room temperature, [c]Oxidant used in all reactions is 1.05 equiv. $PhI(OCOCF_3)_2$.

Table 6. Methoxyselenenylation-deselenenylation reactions

Having found that the selenolactonisation occurs in good reaction times and high yields using a selenium reagent as catalyst, acetonitrile as solvent and [bis(trifluoroacetoxy)iodo]benzene as the oxidant. The optimisation of this reaction procedure was carried out.

Optimisation of Oxidant

All optimisation studies was carried out on (*E*)-4-phenylbut-3-enoic acid **92a**, which is then converted to 5-phenylfuran-2(*5H*)-one **89a**. Tiecco *et al.* have described a similar sequence using 10 mol% diphenyl diselenide and 3 equiv. of peroxydisulfate as oxidant leading to the corresponding lactone in good yields.[67] They also found that using 2 equivalents of (diacetoxyiodo)benzene with diphenyl diselenide in acetonitrile cleanly gave the reaction product.[68] Recently Denmark has also investigated this transformation in great detail.[69] Therefore the reaction with acid **92a** and 1.05 equiv. of hypervalent iodine reagents as oxidants in the presence of 5 mol% diphenyl diselenide in acetonitrile was conducted.



92a **89a**

Scheme 36. Catalytic cyclisation of (*E*)-4-phenylbut-3-enoic acid

Entry	Hypervalent iodine oxidant	**89a**, yield (%)
1	$PhI(OAc)_2$	27
2	$PhI(OCOCF_3)_2$	70
3	$C_6F_5I(OCOCF_3)_2$	59
4	IBA[a]	Traces
5	FIBA[b]	50
6	IBX[c]	0

[a]1-hydroxy-1,2-benziodoxol-3-(*1H*)-one. [b]5,6,7,8-tetrafluoro-1-hydroxy-1,2-benziodoxol-3-(*1H*)-one, [c]1-hydroxy-1,2-benziodoxol-3-(*1H*)-one 1-oxide.

Table 7. Catalytic cyclisation of (*E*)-4-phenylbut-3-enoic acid using a range of hypervalent iodine reagents as oxidants.

It was found that [bis(trifluoroacetoxy)iodo]benzene produces butenolide **89a** in 70% yield. The previously used oxidant (diacetoxyiodo)benzene only gave a yield of 27%. The more soluble fluorinated reagent [bis(trifluoroacetoxy)iodo]pentafluorobenzene[60] resulted in 59% yield believing that the having fluorine in the molecule enhanced the rate of reaction. The cyclic derivative IBA as well as the iodine(V) reagent IBX[71] did not activate the diselenide and therefore resulted mainly in starting material. Only the reactive cyclic FIBA[72] led to a 50% yield of the desired product.

Optimisation of Solvents

Previously Tiecco has used acetonitrile as solvent in a similar reaction and therefore this solvent was used as a first choice, however for full optimisation of the reaction conditions a range of solvents was tested on compound **89a** which is shown in Table 8.

Entry	Solvent	**89a**, yield (%)
1	CH_3CN	70
2	toluene	68
3	CH_2Cl_2	66
4	Et_2O	64
5	MeOH	20[a]
6	THF	15[a]

[a]Conversion by NMR

Table 8. Optimisation of Solvents

There was complete conversion with acetonitrile, toluene and dichloromethane after 3 hours. In the rest of the solvents tested starting material remained with hardly any conversion at all in methanol and tetrahydrofuran.

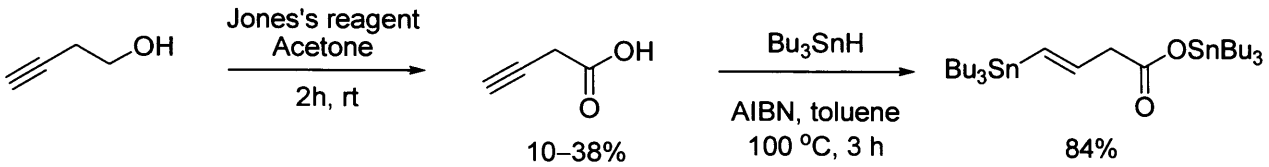
Scope of Catalytic Reaction

The scope of the reaction was investigated further by using a range of different substituted β,γ-unsaturated carboxylic acids in the catalytic cycle. The starting

materials for the reaction were either obtained by Stille cross-coupling reaction with a stannane[73] and an aryl halide or by modified Knoevenagel condensation[74] using a range of aldehydes and malonic acid. The syntheses are shown below.

Starting Materials for Cyclisation Reaction

Stille Cross coupling reaction

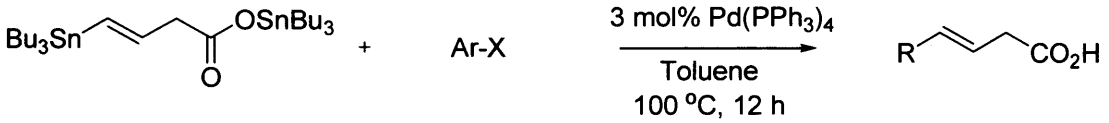


93 **94** **95**

10–38% 84%

Scheme 38. Synthesis of vinyl stannane **95**

In order to obtain the vinyl stannane (*E*)-tributylstannyl-4-(tributylstannyl)but-3-enoate **95** required for the Stille cross coupling reaction the commercially available but-3-yn-1-ol **93** was reacted with Jones's reagent to oxidise the alcohol to the required carboxylic acid **94**. The yield ranges between 10–38%, where higher yields were obtained using an overhead stirrer[75] compared to the standard magnetic stirrer.[76] The acid **93** was then reacted with tributyltin hydride, 0.1 equiv. AIBN in toluene and stirred for 3 h to obtain the vinyl stannane **95** in 84% yield with an *E/Z* selectivity of 85:15.



95 **92**

Scheme 38. Synthesis of butenoic acids *via* Stille cross coupling reaction

The vinyl stannane **95** was then reacted with various aryl halides in order to obtain a range of (*E*)-*β,γ*-unsaturated carboxylic acids **92** using 3 mol% tetrakis(triphenylphosphine) palladium as the catalyst in toluene at 100 °C stirring overnight.

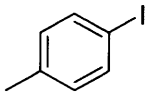
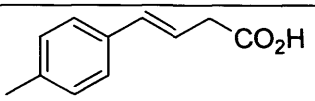
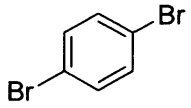
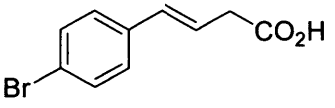
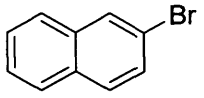
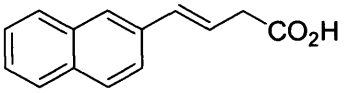
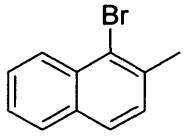
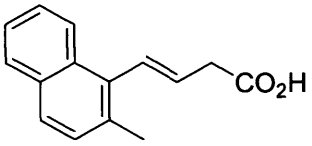
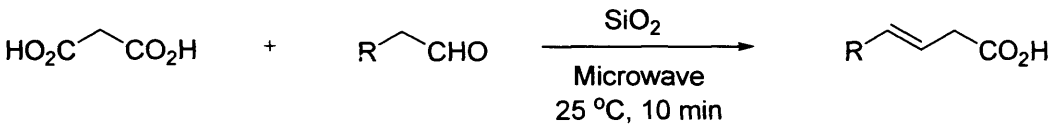
Entry	Aryl Halide	Product	**92**, yield (%)
1		 **92c**	55
2		 **92d**	55
3		 **92e**	63
4		 **92f**	54

Table 9. Results of Stille cross coupling reaction

Modified Knoevenagel Condensation Reaction



96 **92**

Scheme 39. Synthesis of butenoic acids *via* Knoevenagel condensation reaction

The rest of the starting materials were made from a modified version of the Knoevenagel condensation reaction, using malonic acid and a range of aldehydes. The reaction was catalysed by laboratory grade silica and was subjected to microwave radiation at 25 °C for 10 min. The results are shown in Table 10.

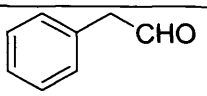
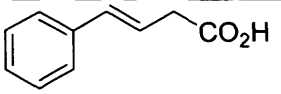
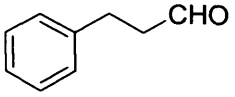
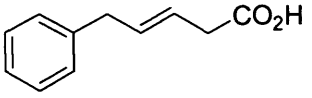
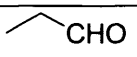
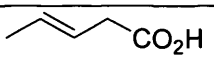
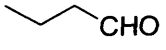
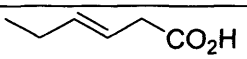
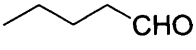
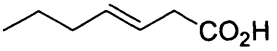
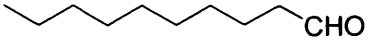
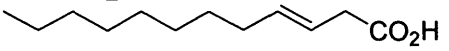
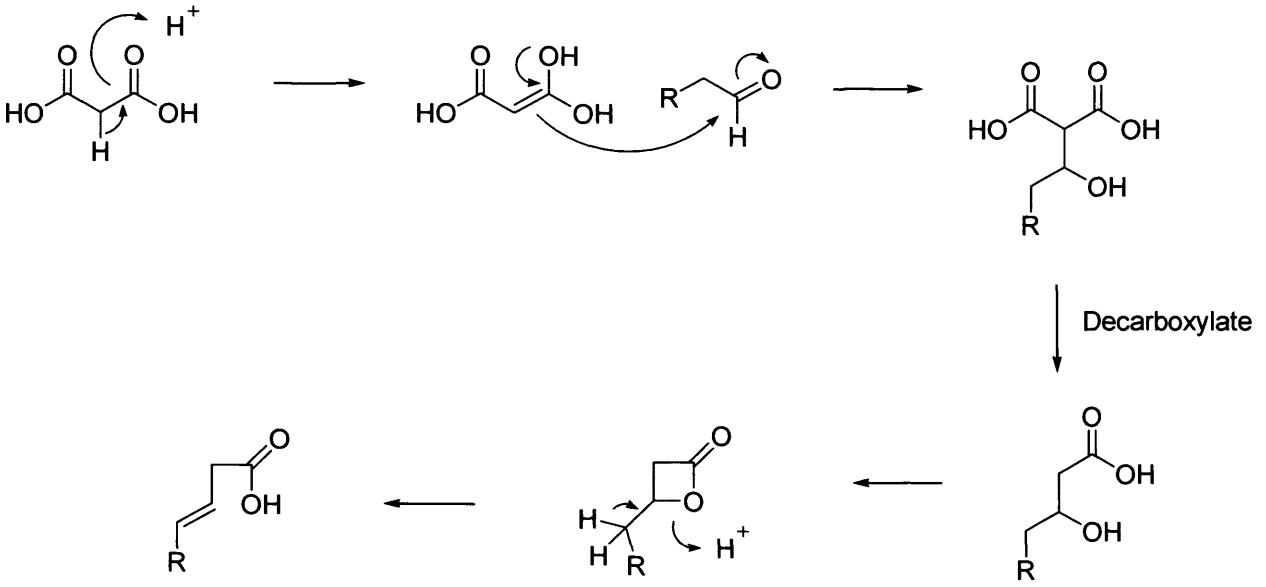
Entry	Aldehyde	Product	**92**, yield (%)
1		 **92a**	58
2		 **92b**	31
3		 **92g**	21
4		 **92h**	28
5		 **92i**	66
6		 **92j**	35

Table 10. Results of modified Knoevenagel condensation reaction

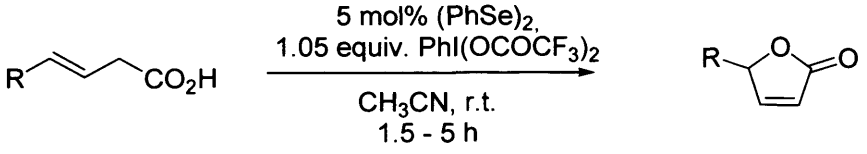
As can be seen from the table of results the yields are quite low as the literature procedure used a standard cooking microwave. For the procedure used here a CEM microwave was used. However these were satisfactory enough to go and try out the cyclisation reaction. Under these conditions only β,γ-unsaturated carboxylic acids were observed along with starting materials. When longer reaction times were used there seemed to be a mixture of products including the α,β-unsaturated carboxylic acids. The β,γ-unsaturated carboxylic acids are the kinetic product and therefore need to be isolated before the α,β-unsaturated carboxylic acids which are the thermodynamic product. Also the *Z* isomer could not be detected based on coupling constants observed in the ^{1}H NMR spectra.

General Mechanism for Knoevenagel Condensation Reaction



A simple mechanism for the condensation elimination reaction would normally proceed to give the α,β-unsaturated product which the thermodynamic product and most stable. Therefore special mechanisms need to operate in which the β,γ-unsaturated acid is isolated. It can either be obtained under kinetic control where it is isolated before the thermodynamic is produced or it can go through the β-lactone, which can only eliminate to give the β,γ-unsaturated acid as shown above. The other protons in the molecule are now unable to eliminate, as there is an incorrect alignment of molecular orbitals.

As the highest yields have been observed using [bis(trifluoroacetoxy)iodo]benzene in acetonitrile these conditions were used in all experiments.



92 **89**

Scheme 39. Catalytic cyclistaion of (*E*)- β,γ-unsaturated carboxylic acids **92** into butenolides **89**.

Entry	R	**89**, yield (%)
1	**92a**, Ph	70
2	**92b**, CH_2Ph	59
3	**92c**, 4-MeC_6H_4	57
4	**92d**, 4-BrC_6H_4	54
5	**92e**, 2-naphthyl	60
6	**92f**, 1-(2-methylnaphthyl)	65
7	**92g**, *n*-C_3H_7	65
8	**92h**, *n*-C_4H_9	65
9	**92i**, *n*-C_5H_{11}	49
10	**92j**, *n*-$C_{10}H_{21}$	96

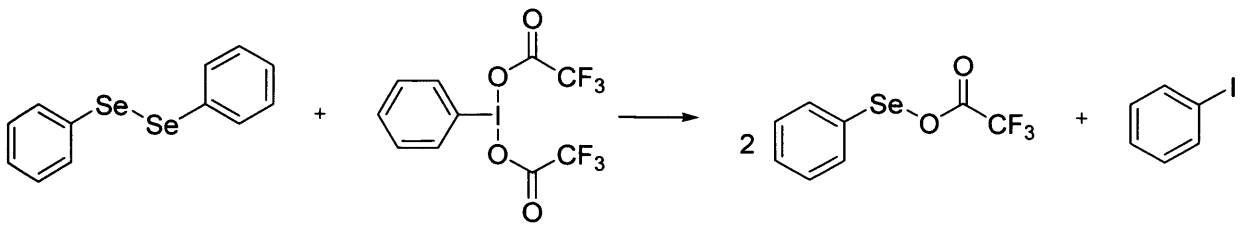
Table 11 Catalytic cyclistaion of (*E*)-β,γ-unsaturated carboxylic acids **92** into butenolides **89**.

As can be seen from the table of results, the reaction conditions work well on a range of (*E*)-*β,γ*-unsaturated carboxylic acids. It can be seen from table 11 that the acids containing an aryl moiety gave yields ranging from (54–70%) and acids containing a linear alkyl chain gave yields ranging from (49–96%).

Mechanistic Studies

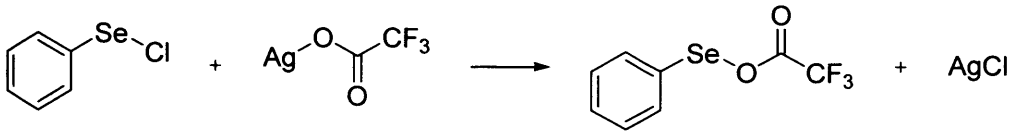
The successful conversion of these butenoic acids into the corresponding butenolides prompted experiments to identify the active catalytic species responsible for their formation. 1 equiv. of diphenyl diselenide **97** and 1 equiv. of [bis(trifluoroacetoxy)iodo]benzene **98** were added to a NMR tube in $CDCl_3$ shown in Scheme 40. The ^1H, ^{13}C and ^{19}F NMR spectra of this adduct were recorded at room temperature. Interestingly, the ^1H and ^{13}C NMR showed a clear formation of iodobenzene **100** suggesting a reduction had taken place and therefore an oxidation has also occured. Furthermore, the ^{19}F NMR shows a typical value for a trifluoroacetate group at –75ppm. In order to confirm the formation phenylselenyl trifluoroacetate **99**, phenylselenenyl chloride **101** and silver trifluoroacetate **102** were added to a NMR tube in $CDCl_3$ shown in Scheme 39 and was also subjected to ^1H, ^{13}C and ^{19}F NMR experiments. It was found that phenylselenenyl trifluoroacetate **99**

was formed and also gave –75 ppm in the ^{19}F NMR spectra. These results confirm that phenylselenenyl trifluoroacetate **100** was the active catalytic species for this reaction to take place.



97 **98** **99** **100**

Scheme 40. Diphenyl diselenide and [bis(trifluoroacetoxy)iodo]benzene in $CDCl_3$

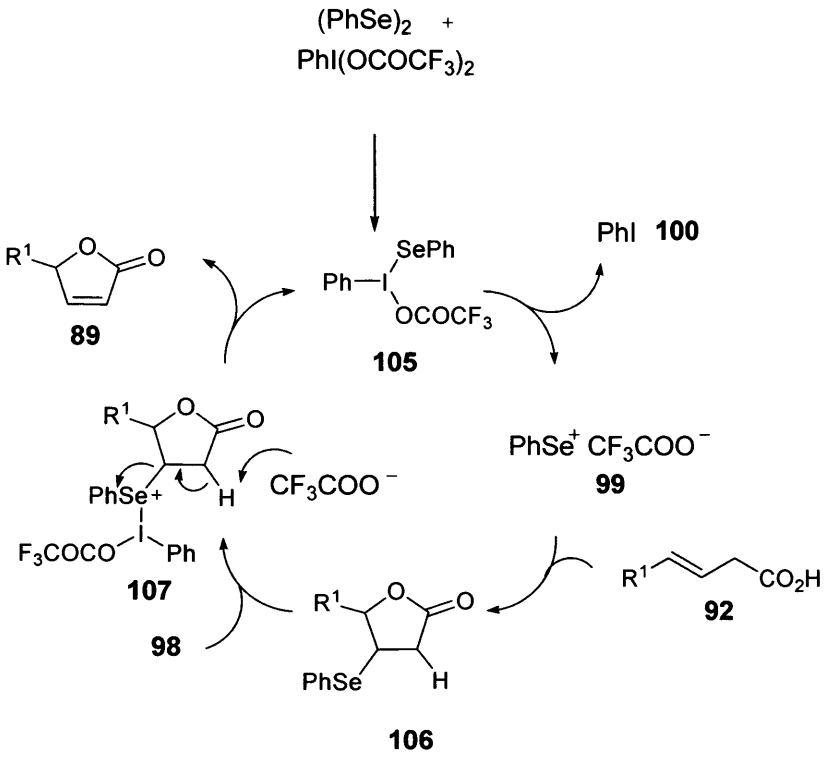


101 **102** **99** **103**

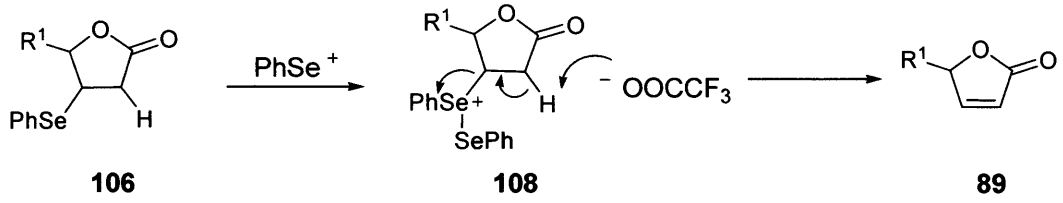
Scheme 41. Phenylselenenyl chloride and silver trifluoroacetate in $CDCl_3$

On the basis of the experiments undertaken the following mechanistic pathway for the selenocyclisation reaction of 3-butenoic acids with catalytic amounts of diphenyl diselenide and [bis(trifluoroacetoxy)iodo]benzene as the oxidant a catalytic cycle can be constructed as shown in Scheme 42.

The reaction is initiated by the oxidation of diphenyl diselenide by the hypervalent iodine compound **98** to form phenylselenenyl trifluoroacetate **99** and iodobenzene **100**. Reagent **99** then reacts with the β,γ-unsaturated carboxylic acids **92** in a cyclisation reaction to yield compound **106**. The selenide in lactone **106** can then be activated for elimination either by [bis(trifluoroacetoxy)iodo]benzene **98** or by phenylselenenyl trifluoroacetate **99** as shown in Scheme 42 and Scheme 43.



Scheme 42. Proposed catalytic cycle

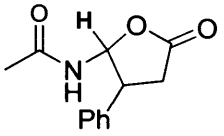


Scheme 43. Alternative mechanism for the elimination of selenide **106**

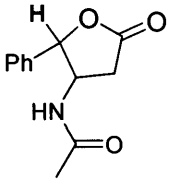
Treatment of independently synthesised **106** (R = Ph) with **98** and **99** revealed that a fast elimination proceeded only with [bis(trifluoroacetoxy)iodo]benzene **98**, although some elimination product **89** was also found in the stoichiometric reaction of **106** and **99**. When oxidant [bis(trifluoroacetoxy)iodo]benzene **98** was used the product was formed in 1.5 h, whereas the starting material was still observed after 5 h using phenylselenyl trifluoroacetate **99** as the oxidant. Therefore it is believed that the catalytic cycle proceeds mainly *via* the intermediate **107** to butenolide **89** as well as regenerating the selenium electrophile **99** as shown in Scheme 42 and Scheme 43.

Catalytic Loading

When only 2 mol% of the diselenide was used in this reaction it was found that only 32% product **89a** was formed together with a side product **109**. When the reaction was performed without the use of diphenyl diselenide as the catalyst the yield of **109** increased to 43%. It is believed that the hypervalent iodine compound reacted as an electrophile and after cyclisation a phenyl migration took place and the resulting carbocation was captured by acetonitrile in a Ritter like reaction.[77] These phenyl migrations have also been observed with cyclisation reactions with substituted styrene and hypervalent iodine reagents.[78]



109

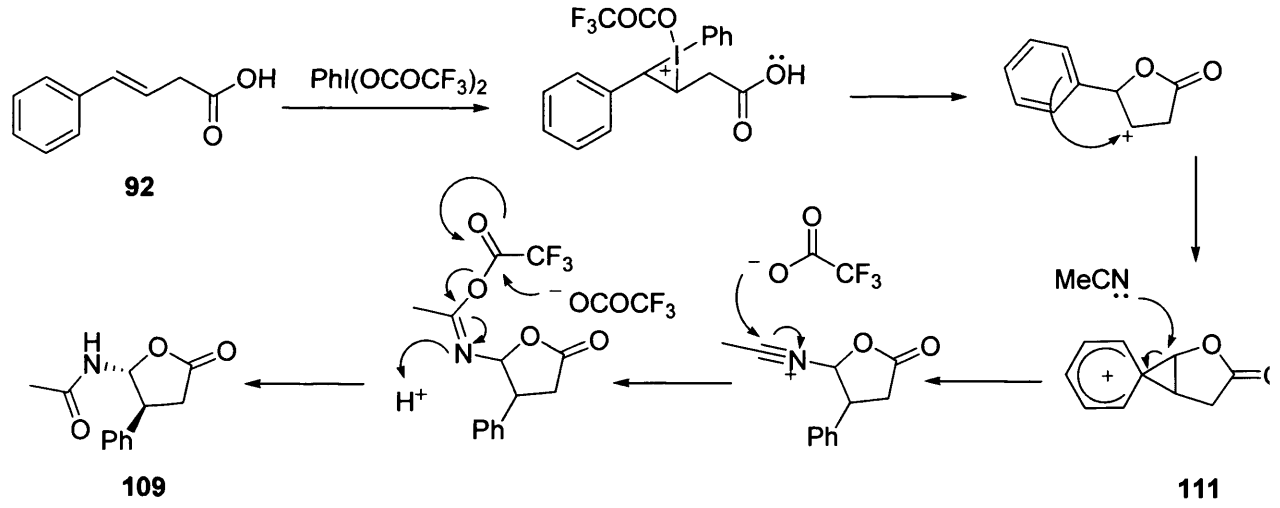


110

Fig 16. Side product **109** obtained without catalyst and the excluded product **110**

The product **109** was elucidated from the coupling pattern by ^{1}H NMR spectrosocopy. The proton shown in **109** shows a coupling pattern of a triplet due to the proton coupling to the hydrogen in the amide moiety, whereas in the product that was excluded **110** the coupling pattern would have been completely different showing a doublet.

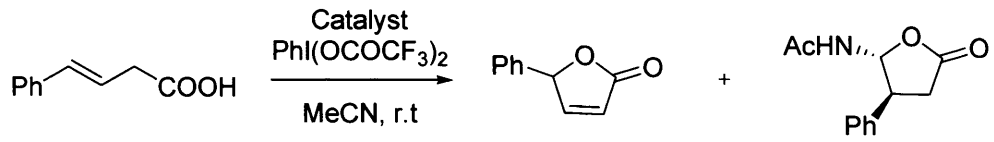
The phenyl migration takes place due to the intermediate in this reaction being very unstable, thus forming **109** as shown in Scheme 44. This mechanism is similar to the known Ritter reaction, a trifluoroacetate anion acts as a nucleophile and intercepts the nitrilium cation, the trifluoroacetate group is then attacked by a second trifluoroacetate anion to afford the amide and trifluoroacetic anhydride.



Scheme 44. Mechanism for formation of **109**

Optimisation of Catalyst

A range of different dichalcogen compounds was used to test the efficiency of the catalyst used and to see if diphenyl diselenide is the best catalyst for the reaction.



92a **89a** **109**

Scheme 45. Cyclisation products

Entry	Catalyst	ratio[a] **89a:109**	Yield% **89a**
1	$(PhSe)_2$	100:0	70
2	$(MeSe)_2$	100:0	56
3	$(PhS)_2$	25:75[a]	–
4	$(MeS)_2$	25:75[a]	–
5	$(PhTe)_2$	28:72[a]	–

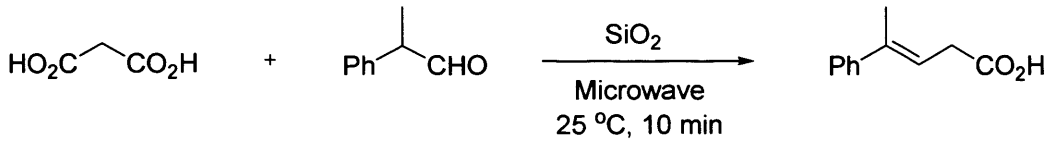
[a]Ratio given from NMR spectra, – No isolated yield obtained

Table 12. Range of catalysts used in cyclisation reaction.

Full conversion to the products was only observed with the diselenides, where diphenyl diselenide gave the highest isolated yield. The disulphides showed less reactivity than the diselenides and diphenyl ditelluride only slightly better than the disulphides. This lower reactivity is then reflected in the amount of by-product observed in the ^{1}H NMR spectra, which results in the direct reaction of alkene **92a** with hypervalent iodine oxidant. When performed in acetonitrile, the capture of the intermediate phenonium ion by acetonitrile and subsequent hydrolysis led to the formation of the by-product **109**.

Trisubstituted alkenes

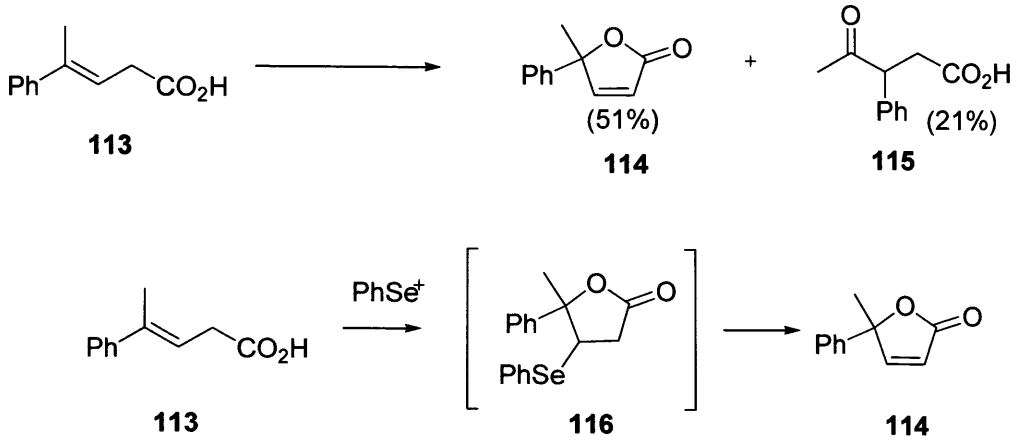
For further investigation of trisubstituted alkenes in such cyclisation reactions, (*E*)-4-phenylpent-3-enoic acid **113** was synthesised by the previous reported Knovenagel condensation reaction of 2-phenylpropanal **112** and malonic acid **96** using silica as the catalyst under microwave conditions as shown in Scheme 46.



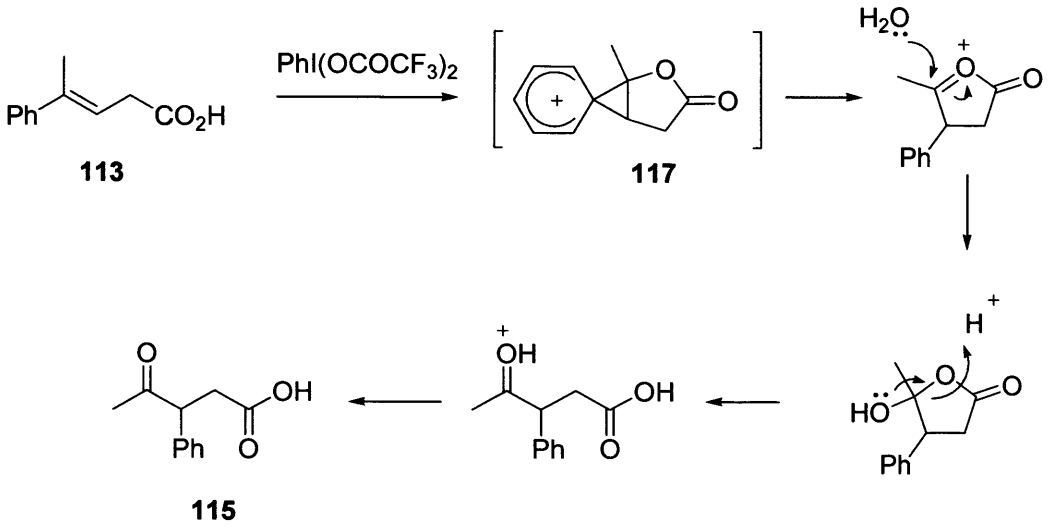
96 **112** **113**

Scheme 46. Synthesis of (*E*)-4-phenylpent-3-enoic acid **113**.

The cyclisation of **113** resulted in a mixture of products and compounds **114** and **115** were observed.



Scheme 47. Cyclisation products of (*E*)-4-phenylpent-3-enoic acid

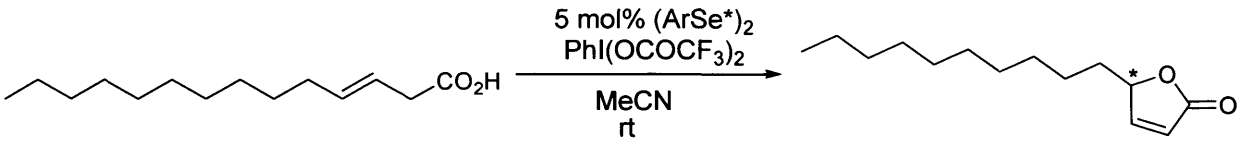


Scheme 48. Mechanism of formation of side product

It was found that the trisubstituted alkenes reacted similarly to disubstituted alkenes. After the initial selenolactonisation to **116** the elimination to **114** occured, however 4-oxo-3-phenylpentanoic acid **115** was found as a by-product. When the reaction was performed without the catalyst, **115** was the only product formed in 55% yield. The reaction of [bis(trifluoroacetoxy)iodo]benzene with **113** leads a to a phenyl migration *via* phenonium ion **117** and reaction with trifluoroacetate or acetonitrile and subsequent ring opening of the hemi ketal results in the formation of **115**. In order to investigate this further, compound **116** was independently synthesised and oxidised with the hypervalent iodine compound. It was found that only the elimination product **114** was formed in 86% yield. Therefore it is believed that the rearrangement only occurs with direct reaction of **113** with [bis(triflouroactoxy)iodo]benzene.

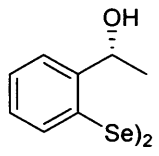
Asymmetric synthesis

The development of organoselenium reagents for asymmetric synthesis has produced a range of chiral diselenides which are efficient in the transfer of chiral information. Catalytic quantities of several enantiomerically enriched diselenides as shown in Figure 17 were used in place of diphenyl diselenide.

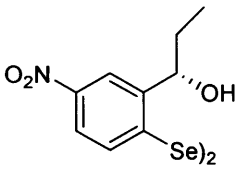


92j **89j**

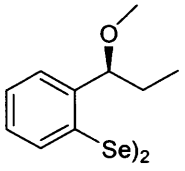
Scheme 49. Chiral diselenides used in place of diphenyldiselenide.



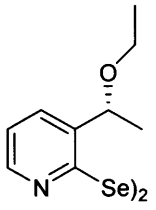
118a
12 h, 84%, 13% ee



118b
24 h, 88%, 3% ee



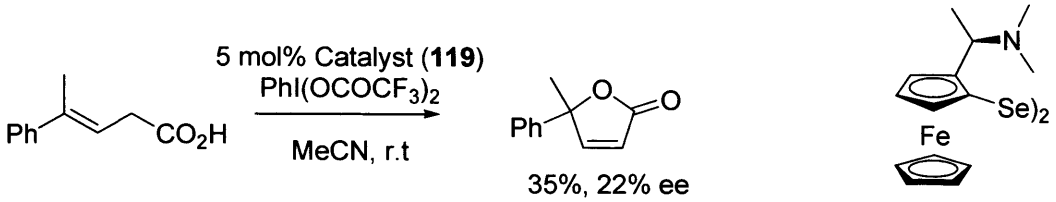
118c
36 h, 64%, 3% ee



118d
96 h, 46%, 22% ee

Fig 17. Range of enantiopure diselenides used in catalytic reaction.

This substrate was chosen as it gave the highest isolated yield in the range of examples chosen. It was found that longer reaction times were required and lower yields were observed and also the enantioselectivity was low. The use of diselenides **118b** and **118c** resulted in almost racemic product **89j**, whereas with **118a** butenolide **89j** was obtained with an enantiomeric excess of 13% (84% yield). Diselenide **118d** led to 22% *ee* (46% yield) of **89j** in the catalytic reaction.[23]



113 **114** **119**

Scheme 50. Cyclisation of (*E*)-4-phenylpent-3-enoic acid using [*R,S; R,S*]-Bisferrocenyl diselenide[80] as catalyst.

Previously it has been found that [*R,S;R,S*]-bisferrocenyl diselenide **119** has been a good catalyst where high enantioselectivites have been achieved. So this catalyst was reacted under the usual reaction conditions with compound **113**. It was found again that low enantioselectivities were observed 22% ee, 35% yield. However better enantioselectivities may occur at lower reaction temperatures. Further work is required to scan a broader range of diselenides and substrates for the asymmetric catalytic reaction.

Conclusion

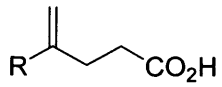
We have developed a novel method for the synthesis of γ-butenolides from butenoic acids using catalytic amounts of diphenyl diselenide. It was found that using [bis(trifluoroacetoxy)iodo]benzene as a stoichiometric oxidant in acetonitrile gave the highest yields and that using 5 mol% of the catalyst was the critical amount as lower catalytic loadings resulted in an undesired side product. Further work is required to achieve higher enantioselectivites in the reaction.

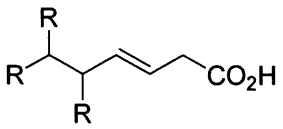
We have developed a novel method for the synthesis of butenolides from butenoic acids using only catalytic amounts of diphenyl diselenide. It was found that the best oxidant for the reaction was [bis(trifluoroacetoxy)iodo]benzene. Acetonitrile, dichloromethane and toluene gave clean reaction products and high yields showing the diversity of the reaction conditions. A range of starting materials including aryl moieties and linear alkyl chain moieties smoothly transform into these butenolides. It was found that two mechanistic pathways are possible, where the oxidant is the hypervalent iodine complex or the selenium electrophile, however the rates between these reactions show that the hypervalent iodine as the oxidant predominates. A new reaction sequence has also been found when no catalyst was used in this reaction and could lead to another area of research to be conducted. A range of catalysts from the chalcogen group has been tested in this reaction even the less used diphenyl ditelluride. However it was shown that the selenium based catalysts were the most efficient. When substituted alkenes are used yields are still fair, however a different side reaction took place showing the methyl substituents affects the reaction pathway, showing another way of forming 4-oxo-3-phenylpentanoic acid in a quick reaction time. The asymmetric version of this reaction was less successful with longer reaction times and lower yields obtained together with low enantioselectivities.

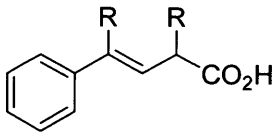
However a new reaction sequence has been achieved to form butenolides from butenoic acids.

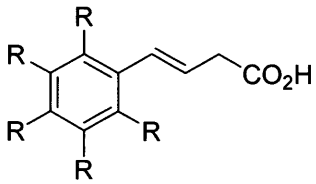
Further Work

Further work in this area could involve trying a wider range of starting materials for example some of the molecules shown below.

A 

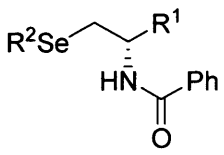
B 

C 

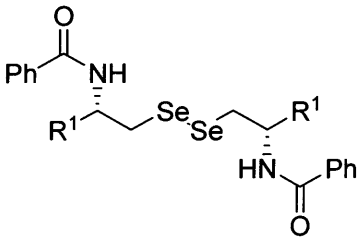
D 

The double bond could be in a different position as in example A, or different substituents along either the alkyl chain or alkene functionality as in examples B and C could be tested. A range of electron withdrawing and electron donating substituents in the *ortho*, *meta* and *para* position could be tested in order to see if this affects the rate of the reaction and reaction yield.

There is lots of scope to change the diselenide that is used as the catalyst in order to achieve this reaction enantioselectively. For example a range of catalysts that have already given high enantioselectivities previously could be tested. In chapter 3 it was shown that compound **40** gave high yields and enantioselectivities. The diselenide version of this molecule **120** could prove to give interesting results shown below. Lower reaction temperatures could also help increase the enantioselectivities.



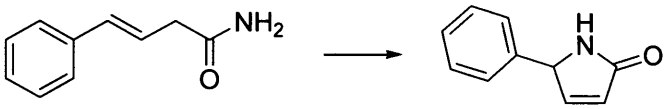
40



120

It would be interesting to see what would happen if all the starting materials were applied under the same reaction conditions but without the use of catalyst, to follow up the hypervalent iodine aryl migration where mechanistic studies are carried out.

Finally the acid moiety could be changed to an amide functionality to see if cyclisation also occurs to give pyrrol-2(*5H*)-one.



As can be seen this work has opened the doors to a whole range of interesting chemistry to be researched.

Chapter 6

Experimental

General Methods

Most reactions were carried out using standard laboratory equipment. Inert reactions conditions are applied by vacuum dried or oven dried (120 °C) apparatus under argon atmosphere. Non-sensitive reactions were performed open to air or in loosely stoppered vessels. All reactions were continually agitated with magnetic stirring unless otherwise stated. Reactions requiring constant temperature were performed using hotplates with temperature probe control in silicon oil or dry heating blocks. The solvent evaporation was performed with Bűchi B-461, B-481, B-490 rotary evaporator (vacuum down to ca. 15 mbar). Further drying was obtained under high vacuum at ca. 0.05 mbar. Kugelrohr distillation was performed in a Bűchi GKR-50 Kugelrohr distillation apparatus. Anhydrous solvents were freshly distilled: THF and diethyl ether were distilled over sodium and benzophenone under inert atmosphere. Toluene was distilled over sodium. Acetonitrile and dichloromethane were distilled over calcium hydride. All other high purity solvents employed in reactions were purchased from Aldrich, Alfa Aeser, Fluka or Acros in septum bottles and handled under argon. The temperature –78 °C for certain reaction was achieved by preparing a cooling bath with dry ice and acetone, while 0 °C was achieved by ice and water. All other temperatures below 0 °C were achieved using a cooling machine RK 8 LP Lauda with methanol as the coolant.

Physical data

^{1}H NMR-spectroscopy

Bruker DPX 500 (500 MHz), Bruker DPX 400 (100 MHz) or Bruker DPX 250 (250 MHz).

The chemical shifts δ are given in ppm downfield of tetramethylsilane. The compounds are dissolved in deuterated chloroform ($CDCl_3$) unless otherwise stated. All coupling constants *J* are reported in Hertz. The multiplicity of a signal is designated: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd, = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, Ar = aromatic ring protons which could not be assigned.

^{13}C NMR-spectroscopy

*Bruker UltraShield 500 (*125 MHz*)*, Bruker DPX 400 (100 MHz) *or Bruker DPX 250 (63 MHz).*

The chemical shift δ is given in ppm downfield of tetramethylsilane. The peak at (δ 77.0 t) is assigned to the solvent $CDCl_3$.

^{77}Se NMR and ^{19}F NMR spectroscopy

Jeol Eclipse 300

^{77}Se NMR – 57.3 MHz. The chemical shifts are referenced to the solvent used, ^{19}F NMR – 282 MHz. The chemical shifts are referenced to the solvent used.

Mass Spectroscopy

Waters LCT Premier XE – tof

Rob Jenkins, Robin Hicks or Dave Walker performed the analyses at the mass spectrometry laboratory at Cardiff University. Ions were generated by the atmospheric pressure ionisation techniques voltage applied corana discharge pin (APCI), voltage on a tip (ES) or electronical ionisation (EI). In all cases the mass fragments are given in atomic mass units per elementary charge (m/z). The intensity relative to the strongest signal is quoted in brackets using percentages. High-resolution mass spectrometry of the compounds was carried out either at Cardiff University or EPSRC NMSSC Swansea. All molecular formulae are values quoted for either molecular ions ($M^{\bullet+}$), molecular + hydrogen ($M + H^+$), molecular + ammonium ion ($M + NH_4^+$), molecular + sodium ($M + Na^+$) or molecular + potassium ($M + K^+$).

Gas Chromatography Mass Spectroscopy

Waters GCT Premier – EI Source

DB 5-MS, 30 m, column 0.32 mm inner diameter and helium at 12 psi used as the carrier gas. Injector set at 230 °C, ions were generated by Electron Ionisation and ions separated in a Time of Flight analyser, detected using a MCP detector multi channel plate. column conditions varied between experiments.

High Pressure Liquid Chromatography

Shimadzu Class VP

A Merck-Hitachi L6200 gradient pump with Merck-Hitachi L4200 UV/Vis detector Merck-Hitachi L2500 intergrator was used. The solvent delivery system used a Shimadzu LC-AT-VP, the detector Shimadzu SPD-M10A-VP DAD. Analytical columns used for separations were Chiracel (OB, OB-H, OD, OD-H, AD) from the Diacel Chemical Industries column length 25 cm, diamter 0.46 mm, Solvent flow was fixed at 0.5 mL/min for all separations.

IR-Spectroscopy

Perkin Elmer 1600 FTIR spectrometer

Wave numbers quoted in cm^{-1}. Samples were measured either neat or as a solution in $CDCl_3$.

Chromatography

Flash column chromatography was performed using Merck Kieselgel 60 silica (230–400 mesh). Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with ceric ammonium molybdate, aqueous basic potassium permanganate or vanillin.

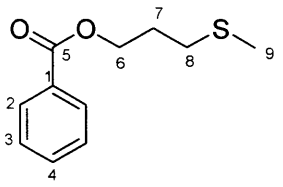
Melting Point

Electrothermal melting apparatus

Melting points of all compounds were measured in open capillary tubes and values are uncorrected.

Experimental for Chapter 2

3-(Methylthio)propyl-2-benzoate 4[81]



Benzoic acid (300 mg, 2.46 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and 3-methylthiopropanol (0.25 mL, 2.46 mmol), DMAP (331 mg, 2.706 mmol) and EDCI (519 mg, 2.706 mmol) were added. The mixture was stirred overnight at room temperature. Water was added and the mixture extracted with CH_2Cl_2 (5 × 10 mL). The organic solution was washed with 1 M NaOH (10 mL), 1 M HCl (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure and purified by flash chromatography diethyl ether : light petroleum (2 : 8) to yield 3-(methylthio)propyl-2-phenylacetate **4** (419 mg, 81% yield).

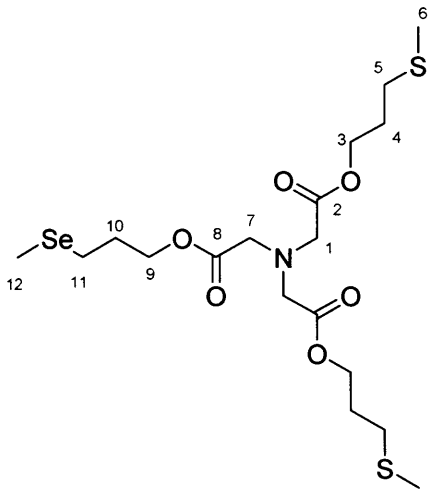
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (2H, d, J = 7.0 Hz, H-2), 7.60 (1H, t, J = 7.3 Hz, H-4), 7.48 (2H, t, J = 7.8 Hz, H-3), 4.48 (2H, t, J = 6.3 Hz, H-6), 2.70 (2H, t, J = 7.1 Hz, H-8), 2.17 (3H, s, H-9), 2.09–2.08 (2H, m, H-7) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 166.5 (C-5), 132.9 (C-1), 129.5 (2C, C-2), 128.4 (2C, C-3), 63.5 (C-6), 30.7 (C-8), 28.3 (C-7), 15.6 (C-9) ppm.

MS *m/z* (EI^+) (%): 224 (M^+, 1), 105 (100), 77 (32), 406 (3)

HRMS found: m/z (EI^+) = 224.0863, $C_{12}H_{16}O_2S^+$ calcd 224.0871.

Nitriloacetic acid bis(3-[methylthio]propyl) 3-(methylselanyl)propyl triester 5[81]



Nitrilotriacetic acid (100 mg, 0.52 mmol) was dissolved in dry dichloromethane (10 mL) and 3-methylthio-1-propanol (58 μL, 0.52 mmol), DMAP (72 mg, 0.59 mmol) and EDCI (113 mg, 0.59 mmol) were added. The mixture was stirred for 24 h and then 3-(methylselanyl)propanol (77 mg, 0.5 mmol) in dry dichloromethane (2.5 mL) was added. The mixture was allowed stir for a further 24 h. Water was added and the mixture extracted with dichloromethane (5 × 10 mL). The organic solution was washed with 1 M NaOH (5 mL) and 1 M HCl (5 mL), dried with $MgSO_4$, concentrated under reduced pressure and product purified by column chromatography eluting *iso*-propanol : chloroform (1 : 4) to yield a colourless oil (54mg, 25%).

IR (film): ν_{max} = 2917, 1730, 1426, 1260, 1195, 1015, 794, 729, 650 cm^{-1}

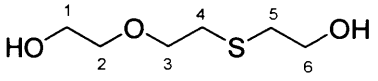
^1H NMR (400 MHz, $CDCl_3$) δ: 4.15 (2H, t, *J* 6.0 Hz, H-9), 4.14 (4H, t, *J* 6.0 Hz, H-3), 3.60 (6H, s, H-1,7), 2.50 (4H, t, *J* 7.2 Hz, H-5), 2.47 (2H, t, *J* 7.3 Hz, H-11), 2.05 (6H, s, H-6,12), 1.95 (4H, m, H-4), 1.87 (2H, m, H-10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 170.8 (3C, C-2,8), 64.1 (C-9), 63.2 (2C, C-3), 55.0 (3C, C-1,7), 30.5 (2C, C-4,10), 29.0 (C-11), 28.1 (C-5), 14.2 (C-6, C-12) ppm.

MS *m/z* (EI^+) (%): 504 (M^+, 38), 478 (78), 456 (100), 406 (3), 322 (12), 256 (4), 251 (2)

HRMS found: m/z (EI^+) = 504.0974, $C_{18}H_{34}NO_6S_2{}^{80}Se^+$ calcd 504.0993.

2-Oxa-4-thiahexane diol 8



Bis(2-hydroxyethyl) disulfide (740 mg, 4.8 mmol) was dissolved in ethanol (10 mL) and cooled to 0 °C. Sodium borohydride (242 mg, 0.4 mmol) was then added followed by 2-(2-chloroethoxy)ethanol (1000 mg, 8 mmol) and the reaction was monitored by TLC. Water was added and the mixture extracted with dichloromethane (5 × 10 mL) dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by column chromatography eluting ethyl acetate : methanol (9.5 : 0.5) to yield a colourless oil (635 mg, 48%).

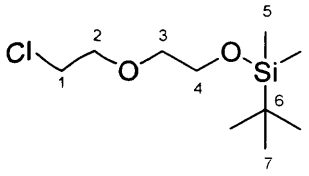
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20–4.14 (2H, m, H-6), 4.02 (4H, q, *J* 5.7 Hz, H-1, 3), 3.92–3.87 (2H, m, H-2), 3.14 (4H, m, H-4,5) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 72.3 (C-3), 71.2 (C-2), 61.4 (C-1), 60.3 (C-6), 43.0 (C-5), 41.2 (C-4) ppm.

General Procedure for the protection of alcohols using *t*butylchloro dimethylsilane.

The alcohol (1 equiv.), imidazole (1.4 equiv.) and TBDMSCl (1 equiv.) were dissolved in dichloromethane (10 mL) and allowed to stir until TLC showed no remaining starting material. Water was added and the mixture extracted with dichloromethane (3 × 5 mL). The organic layers were washed with brine and purified by flash chromatography eluting with ethyl acetate : petroleum ether (3 : 7).

(2-(2-Chloroethoxy)ethoxy)(*t*butyl)dimethylsilane 11



(3.062 g, 80%) as a colourless oil

IR (film): ν_{max} = 2856, 2829, 2858, 1463, 1360, 1298, 1255, 1144, 940, cm^{-1}

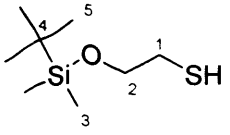
^1H NMR (400 MHz, $CDCl_3$) δ: 3.70 (4H, m, H-2,4), 3.53 (4H, m, H-1,3), 0.75 (9H, s, H-7), 0.00 (6H, s, H-5) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 72.8 (C-3), 71.5 (C-2), 62.8 (C-4), 42.8 (C-1), 25.9 (3C, C-7), 18.4 (C-6), -5.2 (2C, C-5) ppm.

MS *m/z* (EI^+) (%): 239 (M^+, 100), 223 (29), 156 (74)

HRMS found: m/z (EI^+) = 239.1227, $C_{10}H_{24}O_2SiCl^+$ calcd 239.1234

2-Mercaptoethoxy(*t*butyl)dimethylsilane 12



(3.474 g, 70%) as a colourless oil

IR (film): ν_{max} = 2096, 1471, 1380, 1361, 1298, 1256, 1205, 1100, 1042, 1006, 953cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ: 3.67 (2H, t, *J* 6.4 Hz, H-2), 2.55 (2H, t, *J* 6.4 Hz, H-1), 0.81 (9H, s, H-5), 0.00 (6H, s, H-3) ppm.

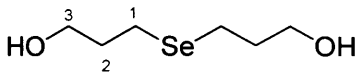
^{13}C NMR (63 MHz, $CDCl_3$) δ: 65.1 (C-2), 27.3 (C-1), 25.9 (3C, C-5), 18.3 (, C-4),

-5.2 (2C, C-3) ppm.

MS *m/z* (EI^+) (%): 177 (M^+, 4), 135 (80), 91 (22), 75 (100)

HRMS found: m/z (EI^+) = 177.0771, $C_7H_{17}OSiS^+$ calcd 177.0769

Bis(3-hydroxypropyl)selenide 13[82]



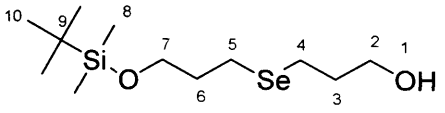
Method 1 Sodium selenide was generated by reaction of grey elemental selenium (3000 mg, 38.0 mmol), sodium hydroxide (3344 mg, 83.6 mmol) and sodium borohydride (3162 mg, 83.6 mmol) (exothermic) in aqueous THF (50 mL + 0.5 mL H_2O) under argon. The colourless sodium selenide solution obtained was allowed to warm to room temperature over 0.5 h then treated with a solution of 3-bromopropanol (7185 mg, 6.9 mL, 76 mmol) in THF (20 mL) under argon. The reaction mixture was stirred for 24 h at room temperature and concentrated under reduced pressure. The residue was diluted with deionised water and extracted with chloroform (3 × 50 mL). The combined organic fractions were collected, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and product purified by flash chromatography eluting with ethyl acetate : light petroleum (7 : 3) yielding a colourless viscous liquid (4660 mg, 62%).

Method 2 Sodium (184 mg, 8 mmol), selenium (316 mg, 4 mmol) and naphthalene (51 mg, 0.4 mmol) was stirred under reflux for 2 h in THF (10 mL) under argon. 3-bromopropan-1-ol (1390 mg, 0.9 mL, 10 mmol) was added and the reaction was allowed to stir overnight at room temperature. Water was added and extracted with dichloromethane (3 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The reaction was purified by flash chromatography eluting with ethyl acetate : petroleum eher (8 : 2) to yield a colourless oil in (374 mg, 47 %).

^1H NMR (400 MHz, $CDCl_3$) δ: 3.73 (4H, t, *J* 7.0 Hz, H-3), 2.67 (4H, t, *J* 6.0 Hz, H-1), 2.46 (2H, s, OH), 1.95–1.90 (4H, m, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 61.1 (C-3), 32.1 (C-1), 19.5 (C-2) ppm.

tButyldimethyl(propoxy) propan-1-ol selenide 14



Bis(3-hydroxypropyl)selenide (220 mg, 1.1 mmol), imidazole (124 mg, 1.815 mmol) and TBDMSCl (165 mg, 1.1 mmol) was dissolved in dichloromethane (10 mL) and allowed to stir until TLC showed no remaining starting material. Water was added and the mixture extracted with dichloromethane (3 × 5 mL). The organic layers were washed with brine to yield *t*butyldimethyl(propoxy) propan-1-ol selenide as colourless oil in (140 mg, 41%) yield.

IR (film): ν_{max} = 3372, 1098 cm^{-1}

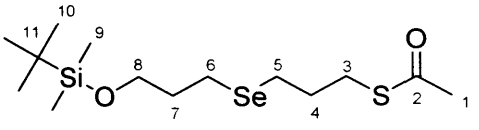
^1H NMR (400 MHz, $CDCl_3$) δ: 3.71 (2H, t, *J* 6.0 Hz, H-7). 3.62 (2H, t, *J* 6.0 Hz, H-2), 2.60 (4H, q, *J* 7.5, Hz, H-4,5), 1.80–1.72 (2H, m, H-6), 1.95–1.81 (2H, m, H-3), 0.87 (9H, s, H-10), 0.00 (6H, s, H-8) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 62.6 (C-7). 62.4 (C-2), 33.5 (C-4, 5), 32.9 (2C, C-3,6), 26.0 (3C, C-10), 20.2 (C-9), -5.3 (C-8) ppm.

MS *m/z* (EI^+) (%): 311 (M^+, 100), 290 (90), 251 (50), 179 (4).

HRMS found *m/z* (EI^+) = 311.0940, $C_{12}H_{27}O_2{}^{28}Si^{80}Se^+$ calcd 311.0946.

tButyldimethyl(propoxy) propyl ethanethioate selenide 15



Diisopropyl azodicarboxylate (1617 mg, 1.6 mL, 8.0 mmol), was added to a well stirred solution of triphenylphosphine (2077 mg, 7.9 mmol) in dry THF (20 mL) at 0 °C. The reaction mixture was allowed to stir for 30 min. The protected alcohol (1270 mg, 4 mmol) and thioacetic acid (731 mg, 0.9 mL, 9.6 mmol) were premixed in THF (10 mL) and added over 5 min. The reaction was allowed to warm to room temperature and monitored by TLC. Once complete the mixture was concentrated

under reduced pressure and purified by flash chromatography eluting with hexane : ethyl acetate (9 : 1) to yield the thioester (1077 mg, 73%).

IR (film): ν_{max} = 2930, 2856, 1694, 1472, 1255, 1098 cm^{-1}

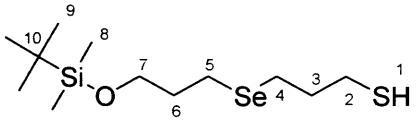
^1H NMR (400 MHz, $CDCl_3$) δ: 3.62 (2H, t, *J* 6.0 Hz, H-8), 2.91 (2H, t, *J* 7.2 Hz, H-3), 2.51–2.59 (4H, m, H-5,6), 2.28 (3H, s, H-1), 1.88 (2H, qn, *J* 7.2 Hz, H-4), 1.79 (2H, qn, *J* 7.1 Hz, H-7), 0.82 (9H, s, H-10), 0.00 (6H, s, H-9) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.7 (C-2), 72.3 (C-8), 33.6 (C-3), 30.3 (C-1), 29.1 (C-5), 26.0 (C-7), 25.0 (C-6), 22.4 (C-4), 21.7 (3C, C-10), 20.3 (C-11), -5.3 (2C, C-9) ppm.

MS *m/z* (EI^+) (%): 327 (M^+, 19), 313 (37), 196 (11), 181 (18), 173 (14), 117 (100), 75 (69).

HRMS found *m/z* (EI^+) = 370.0901, $C_{14}H_{30}O_2{}^{28}SiS^{80}Se^+$ calcd 370.0901.

_t_Butyldimethyl(propoxy) propane-1-thiol selenide 16[83]



The thioester (1000 mg, 2.71 mmol) in dry THF (25 mL) was added to a stirred suspension of $LiAlH_4$ (367 mg, 10.8 mmol) at 0 °C in dry THF (12 mL). The reaction was stirred at room temperature until TLC showed no remaining starting material. The resulting mixture was quenched at 0 °C by careful addition of water (0.2 mL), aqueous NaOH (15% w/w 0.1 mL) and water 6 mL. The resulting mixture was filtered through a pad of celite and the white solid residue washed with THF (10 mL). The organic layer dried with $MgSO_4$ and purified by flash chromatography eluting with ethyl acetate : petroleum ether (3 : 7) to yield *t*butyldimethyl(propoxy) propane-1-thiol selenide in (760 mg, 86%).

IR (film): ν_{max} = 2929, 2851, 1478, 1097, 717 cm^{-1}

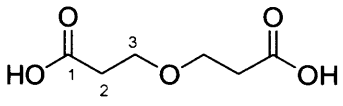
^1H NMR (400 MHz, $CDCl_3$) δ: 3.62 (2H, t, *J* 6.0 Hz, H-7), 2.72 (2H, t, *J* 7.1 Hz, H-2), 2.55–2.64 (4H, m, H-4,5), 1.99 (2H, qn, *J* 7.2 Hz, H-6), 1.80 (2H, m, H-3) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: ppm. 62.4 (C-7), 38.4 (C-2), 33.6 (C-5), 30.3 (C-4), 26.0 (3C, C-9), 24.5 (C-3), 22.0 (C-6), 18.3 (C-10), -5.8 (2C, C-8) ppm.

MS *m/z* (EI^+) (%): 328 (M^+, 1), 271 (11), 205 (12), 149 (4), 115 (6), 75 (100).

HRMS found *m/z* (EI^+) = 328.0808, $C_{12}H_{28}OSiS^{80}Se^+$ calcd 328.0795.

Bis(2-carboxyethyl) ether 21[83a]

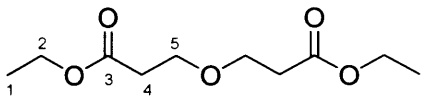


2-Cyanoethyl ether (1 g, 8.06 mmol) was dissolved in conc HCl (3.2 mL) and heated to 80 °C. The reaction became quickly exothermic, at which point the heating source was removed. After boiling ceased (15 min) heating was resumed for 5 h. The resulting mixture was concentrated by rotary evaporation at 65 °C and the residue treated with hot acetone and filtered. The resulting oil was fully recrystalised after cooling overnight in the freezer to yield bis(2-carboxyethyl) ether in (1.258g, 96%).

^1H NMR (400 MHz, $CDCl_3$) δ: 3.68 (4H, t, *J* 5.5 Hz, H-3), 3.64 (4H, t, *J* 5.5 Hz, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 178.2 (2C, C-1), 65.8 (2C, C-3), 35.0 (2C, C-2) ppm.

Diethyl 4-oxa-1,7-heptane dioate 22[83a]



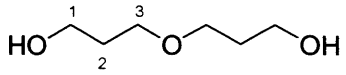
The diacid (1.258 g, 7.76 mmol) was refluxed for 2 h in absolute ethanol (14 mL) containing 1.6 g of conc sulphuric acid. The solution was cooled and neutralised with 5% ethanolic potassium hydroxide. Subsequently the mixture was poured into a seperating funnel containing chloroform (25 mL) and water (25 mL), the organic layer was drawn off and the aqueous phase was extracted with chloroform (2 × 20 mL). The combined organic extracts were concentrated to a volume of 20 mL by rotary evaporation, washed with brine (20 mL) and dried over anhydrous Na_2SO_4.

Filtration and solvent evaporation gave the diester as colourless oil without purification (3.609 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.0 (4H, q, *J* 7.1 Hz, H-2), 3.68 (4H, t, *J* 6.5 Hz, H-5), 2.49 (4H, t, *J* 6.4 Hz, H-4), 1.19 (6H, t, *J* 7.1 Hz, H-1) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.5 (2C, C-3), 66.4 (2C, C-5), 60.5 (2C, C-2), 35.1 (2C, C-4), 14.2 (2C, C-1) ppm.

(Propane-1,7-diol) ether 23[83a]

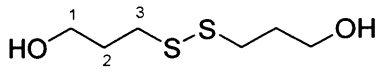


Lithium aluminium hydride (839 mg, 0.0221 mol) was dissolved in THF (30 mL) at 0 °C under argon. The ester was dissolved in THF (17 mL) and added to the mixture over 90 mins. Cooling was removed and the reaction mixture was stirred for an additional 45 mins, subsequently 20% H_2SO_4 (10 mL) was added whilst stirring. Following filtration and drying over Na_2SO_4, the solvent was removed under reduced pressure at 50 °C and purified by flash chromatography eluting with ethyl acetate : petroleum ether (7 : 3) to yield the diol as a colourless oil (1.268 g, mol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (4H, t, *J* 5.7 Hz, H-1), 3.58 (4H, t, *J* 5.8 Hz, H-3), 1.80 (4H, m, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 69.9 (2C, C-3), 61.5 (2C, C-1), 32.1 (2C, C-3) ppm.

3,3'-Dithiodipropanol 25[84]



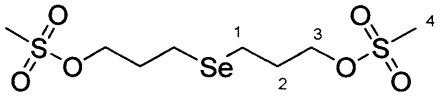
3-Chloropropanol (2000 mg, 21.16 mmol) was refluxed in a solution of sodium thiosulphate (5778 mg, 23.28 mmol) in 25 mL of a 50% v/v aqueous methanol with stirring for 1.8 days. A solution of iodine (2954 mg, 11.6 mmol) in methanol (30 mL) was added dropwise over a period of 2 h to the refluxing solution. The resulting solution was filtered and the filtrate was evaporated under vacuum to remove most of the methanol. The aqueous solution was extracted with diethyl ether and the ether

layer was decolourised with 0.6 M aqueous sodium thiosulphate and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 3,3'-dithiodipropanol 1945 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (4H, t, *J* 6.2 Hz, H-1), 2.76 (4H, t, *J* 7.1 Hz, H-3), 1.90 (4H, qn, *J* 6.5 Hz, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 61.0 (2C, C-1), 35.8 (2C, C-3), 31.8 (2C, C-2) ppm.

4-Selenaheptan-1,7-dimethanesulfonate 26[85]



4-Selanaheptan-1,7-diol (100 mg, 0.51 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (303 mg, 3 mmol) and methanesulfonyl chloride (163 mg, 1.43 mmol) were added and the reaction was allowed to stir for 2 h. Water (5 mL) was then added and the extraction made with dichloromethane (3 × 5 mL). The organic layer was then washed with 1 M HCl (5 mL), sat $NaHCO_3$ (5 mL), brine (5 mL) and dried with $MgSO_4$. The reaction was purified by flash chromatography eluting with ethyl acetate : light petroleum (7 : 3) yielding a colourless liquid (59 mg, 67%).

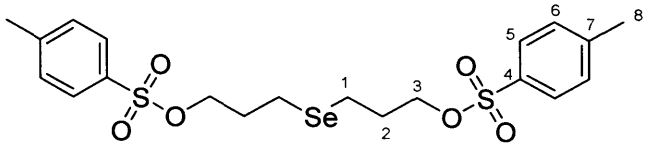
^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.28 (4H, t, *J* 6.0 Hz, H-3), 2.99 (6H, s, H-4), 2.62 (4H, t, *J* 7.1 Hz, H-1), 2.05 (4H, qn, *J* 6.1 Hz, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 69.0 (2C, C-3). 40.0 (2C, C-4), 37.4 (2C, C-1), 19.3 (2C, C-2) ppm.

MS *m/z* (ESI-K^+) (%) 393 (M^+, 10), 258 (100), 137 (15);

HRMS found m/z (ESI-K^+) = 392.9366 $C_8H_{18}O_6S_2K^{80}Se^+$ calcd 392.9347.

4-Selenaheptan-1,7-di-*p*-tolulenesulfonate 28[14]

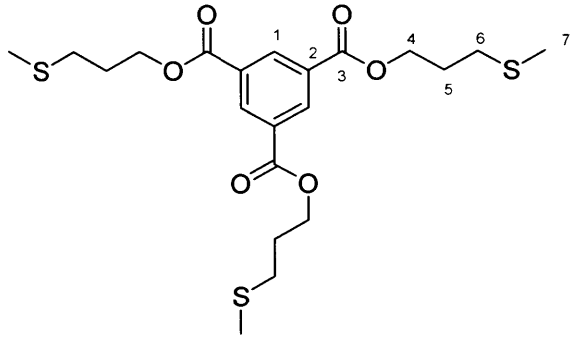


Pyridine (0.3 mL, 3.6 mmol) and *p*-toluenesulfonyl chloride (214 mg, 1.12 mmol) were dissolved in dichloromethane (8 mL) and added dropwise to 4-selenaheptan-1,7-diol (100 mg, 0.51 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature overnight. The mixture was extracted with dichloromethane (30 mL) and the organic layer washed with 1 M HCl (3 × 20 mL), sat aq $NaHCO_3$ (3 × 20 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a light yellow oil which was purified by flash chromatography eluting with ethyl acetate : hexane (2 : 5) to give a colourless oil (118 mg, 46 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (4H, d, *J* 8.1 Hz, H-5), 7.20 (4H, d, *J* 8.2 Hz, H-6), 4.01 (4H, t, *J* 7.0 Hz, H-3), 2.41 (4H, t, *J* 7.3, H-1), 2.33 (6H, s, H-8), 2.00–1.83 (4H, m, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ: 144.9 (2C, C-4), 132.8 (C-7), 129.9 (C-5), 127.9 (4C, C-6), 69.5 (2C, C-3), 29.6 (2C, C-1), 21.6 (2C, C-8), 19.2 (2C, C-2) ppm.

Tris(3-(methylthio)propyl)benzene-1,3,5-tricarboxylate 30



Trimesic acid (50 mg, 0.24 mmol) was dissolved in dry dichloromethane (2 mL) and 3-methylthio-1-propanol (74 μL, 0.072 mmol), DMAP (97 mg, 0.79 mmol) and EDCI (151 mg, 0.79 mmol) were added. The reaction was heated under microwave conditions (100 W, 25 °C, 1 h). Water was added and the mixture extracted with

chloroform (5 × 2 mL). The organic solution was washed with 1 M NaOH (5 mL), 1 M HCl, (5 mL) dried with $MgSO_4$ and concentrated under reduced pressure and purified by flash chromatography ethyl acetate : light petroleum (7 : 3) to give a colourless oil (34 mg, 30%).

IR (film): ν_{max} = 2944, 2952. 1724, 1240, 650 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (3H, s, H-1), 4.41 (6H, t, *J* 6.3 Hz, H-4), 2.61 (6H, t, *J* 7.1 Hz, H-6), 2.09 (9H, s, H-7), 2.03–1.98 (6H, m, H-5) ppm.

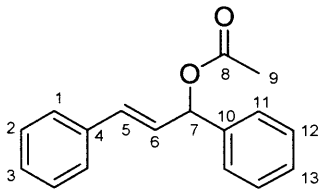
^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.9 (3C, C-3), 134.5 (3C, C-2), 131.3 (3C, C-1), 64.3 (3C, C-4), 30.7 (3C, C-5), 28.2 (3C, C-7), 15.6 (3C, C-6) ppm.

MS *m/z* (EI^+) (%): 475 (M^+, 21), 459 (2), 369 (4.5), 305 (4), 123 (18)

HRMS found *m/z* (EI^+) = 475.1293, $C_{21}H_{31}O_6S_3^+$ calcd 475.1283.

Experimental for Chapter 3

Acetic acid 1, 3-diphenylallyl ester 35[86]

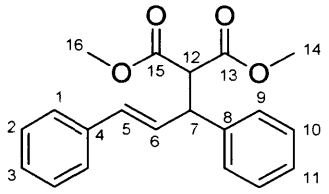


(*E*)-1,3-Diphenylprop-2-enyl alcohol (2000 mg, 9.5 mmol) was dissolved dichloromethane (20 mL). Triethylamine (2.8 mL, 19 mmol) and acetic anhydride (1.940 g, 19 mmol) were then added slowly at 0 °C to the reaction mixture. The reaction was allowed to stir overnight at room temperature until TLC showed that there was no alcohol remaining. The organic layers were washed with sat $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), dried with $MgSO_4$, the solvent was removed under reduced pressure and purified by flash chromatography eluting with hexane : ethyl acetate (9 : 1) to afford a clear yellow oil (2349 mg, 98%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.10 (10H, m, H-1,2,3,11,12,13), 6.60 (1H, d, *J* 15.7 Hz, H-5), 6.35 (1H, d, *J* 7.0 Hz, H-7), 6.25 (1H, dd, *J* 15.8, 6.8, Hz, H-6), 2.15 (3H, s, H-9) ppm.

^{13}C NMR ($CDCl_3$, 500 MHz) δ: 170.2 (C-8), 139.4 (C-10), 136.3 (C-4), 132.7 (C-5), 128.8 (C-12), 128.7 (C-2), 128.3 (C-3), 128.2 (C-13), 127.6 (C-11), 127.2 (C-1), 126.8 (C-6), 76.3, (C-7), 21.4 (C-9) ppm.

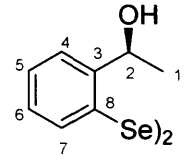
2-(1,3-Diphenylallyl)malonic acid dimethyl ester 36[87]



The ligand (0.05 mmol, 5 mol%) and $[Pd(\eta 3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 2 mol%) were dissolved in dichloromethane (2 mL) in a Schlenk tube and allowed to stir at room temperature for 1 h. Subsequently, (*E*)-1,3-diphenylprop-2-ene-1-yl acetate (252 mg, 1 mmol) in dichloromethane (2 mL) was added followed by dimethyl malonate (390 mg, 0.34 mL, 3 mmol), *N,O*-Bis(trimethylsilyl)acetamide (BSA) (610 mg, 0.74 mL, 3 mmol) and potassium acetate (9.8 mg, 0.1 mmol). The reaction was carried out under argon. When the reaction was complete (TLC monitoring). Diethyl ether (15 mL) was added and the organic layer washed with sat NH_4Cl (2 × 10 mL) and dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography on silica gel to afford 2-(1,3-diphenylallyl)malonic acid dimethyl ester.

^1H NMR ($CDCl_3$, 400 MHz) δ: 7.24–7.17 (10, m, H-1,2,3,9,10,11), 6.48 (1H, d, *J* 15.8 Hz, H-5), 6.34 (1H, dd, *J* 15.5, 8.5 Hz, H-6), 4.27 (1H, dd, *J* 11.0, 8.5 Hz, H-7), 3.97 (1H, d, *J* 11.0 Hz, H-12), 3.69 (3H, s, H-16), 3.52 (3H, s, H-14) ppm.

(*S,S*)-Bis[2-(1-hydroxyethyl)phenyl] diselenide 43[7]



The aryl bromide (1980 mg, 9.80 mmol) was dissolved in dry THF (50 mL) under argon, cooled to –78 °C and treated slowly with *tert*-butyllithium in hexane (1.5 M, 19.5 mL, 29.4 mmol). After warming and stirring for 30 mins at 0 °C, selenium powder was added (851 mg, 10.8 mmol). The mixture was allowed to stir at room temperature for a further 3 h and then 1 M HCl (50 mL) was added. After extraction of the mixture with diethyl ether (3 × 30 mL), the combined organic layers were dried with $MgSO_4$ and powdered potassium hydroxide (500 mg) was added and stirred for 15 min. The residue was then purified by flash chromatography on silica gel eluting

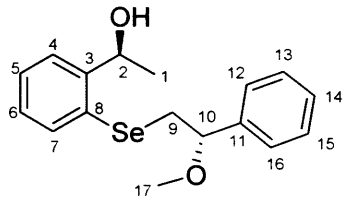
with diethyl ether : petroleum ether (1 : 1) to afford the diselenide as a yellow solid in 53% yield, (1055 mg, 2.63 mmol) .

Mp = 82–83 °C

^{1}H NMR ($CDCl_3$, 400MHz) δ: 7.74 (2H, d, *J* 7.5 Hz, H-7), 7.50 (2H, d, *J* 7.5, H-4), 7.34 (2H, t, *J* 7.5 Hz, H-6), 7.20 (2H, t, *J* 7.5 Hz, H-5) 5.04 (2H, q, *J* 6.4 Hz, H-2), 2.19 (2H, s, OH), 1.38 (6H, d, *J* 6.4 Hz, H-1) ppm.

^{13}C NMR ($CDCl_3$, 63 MHz) δ: 147.3 (C-3), 135.2 (C-7), 129.3 (C-5), 129.1 (C-4), 128.4 (C-8), 125.8 (C-6), 69.4 (C-2), 24.4 (C-1) ppm.

(*S*,*S*)-1-[2-(2-Methoxy-2-phenylethylselanyl)phenyl]ethanol 45[7]



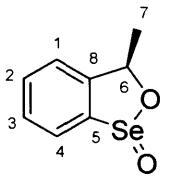
The diselenide (100 mg, 0.250 mmol) was dissolved in dry diethyl ether (10 mL) under argon, cooled to –78 °C and treated with bromine (0.275 mmol, 0.275 mL of a 1 M solution of 1,1,2-trichlorotrifluoroethane). After 10 min a solution of silver triflate (0.25 mL, 0.7 mmol) in methanol (0.1 mL) was added and the reaction mixture was stirred for 10 min at –78 °C. The reaction mixture was then cooled to –100 °C and treated with styrene (0.112 mL, 1.0 mmol). After 4 h of stirring at –100 °C, *sym*-collidine (0.099 mL, 0.75 mmol) was added followed by water (10 mL). The reaction was extracted with diethyl ether (3 × 10 mL), the combined layers were dried with $MgSO_4$ and solvent removed under reduced pressure. The residue was then purified by flash chromatography on silica gel eluting with diethyl ether : petroleum ether (1 : 1) to afford (*S*,*S*)-1-[2-(2-methoxy-2-phenylethylselanyl)phenyl]ethanol in (48 mg, 57%, dr = 9:1 determined by ^{1}H NMR).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (2H, m, H-Ar), 7.35–7.22 (8H, m, H-Ar), 7.14 (1H, td, *J* 7.5, 1.5 Hz, H-14), 5.28 (1H, q, *J* 6.5 Hz, H-2), 4.34(1H, dd, *J* 8.6, 4.8 Hz, H-10), 3.24 (1H, dd, *J* 12.2, 8.6 Hz, H-9A), 3.22 (3H, s, H-17), 3.10 (1H, dd, *J* 12.2, 4.8 Hz, H-9B), 2.56 (1H, s, OH), 1.47 (3H, d, *J* 6.5 Hz, H-1) ppm.

^{13}C NMR ($CDCl_3$, 63 MHz) δ: 147.0 (C-3), 140.7 (C-11), 133.8 (C-7), 128.6 (C-8), 128.5 (C-5), 128.2 (2C, C-13,15), 127.8 (C-4), 126.7 (2C, C-12,16), 126.6 (C-4, 6), 125.7 (C-6), 83.0 (C-2), 69.3 (C-10), 57.0 (C-17), 36.1 (C-9), 24.0 (C-1) ppm.

Experimental for Chapter 4

(*R*)-[2-(1-hydroxyethyl)phenyl] seleninate ester 64



(*S,S*)-bis[2-(1-hydroxyethyl)phenyl] diselenide (100 mg, 0.24 mmol) was dissolved in acetonitrile (6 mL). Hydrogen peroxide (30%, 24.5 mg, 72 μL, 0.72 mmol) was then added and the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into water (10 mL), extracted with dichloromethane (3 × 5 mL) and the products purified by column chromatography eluting with ethyl acetate : methanol (9 : 1) to afford (*R*)-[2-(1-hydroxyethyl)phenyl] seleninate ester as a colourless oil (50 mg, 96%).

IR (film): ν_{max} = 2357, 1595, 1438, 1041, 853, 787 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (1H, d, *J* 7.6 Hz, H-4), 7.77 (1H, dt, *J* 7.8, 0.9, H-2), 7.65 (1H, t, *J* 7.6 Hz, H-3), 7.48 (1H, d, J 7.8 Hz, H-1), 5.75 (1H, q, *J* 6.5 Hz, H-6), 1.71 (3H, d, *J* 6.5 Hz, H-7) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 142.0 (C-8), 135.3 (C-2), 133.8 (C-5), 130.9 (C-4), 124 9 (C-3), 123.9 (C-1), 78.9 (C-6), 22.9 (C-7) ppm.

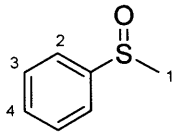
MS *m/z* (ES^+) (%) = 217 (M^+, 100), 215 (44), 213 (16), 204 (6), 196 (2), 102 (1).

HRMS found *m/z* (ES^+) = 216.9759, $C_8H_9O_2{}^{80}Se^+$ calcd. 216.9768.

General procedure for the oxidation of sulfides to sulfoxides

Iodosobenzene (184.8 mg, 0.84 mmol) and catalyst $(ArSe)_2$ (15.8 mg, 0.084 mmol, 5 mol%) were added to sulfide (0.8 mmol) in acetonitrile (10 mL) at room temperature. The reaction was monitored by TLC. Upon completion, the reaction mixture was poured into water (10 mL), extracted with dichloromethane (3 × 10 mL) and the products purified by column chromatography.

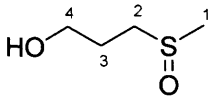
1-(Methylsulfinyl)benzene 67[88]



(108 mg, 96%) as a colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.54 (2H, m, H-2), 7.45–7.41 (3H, m, H-3,4), 2.63 (3H, s, H-1) ppm.

3-(Methylsulfinyl)propanol 69



(34 mg, 35%) as a colourless oil

IR (film): ν_{max} = 3435, 2923, 2847, 1734, 1633, 1425, 1374, 1216, 1052, 1030 cm^{-1}.

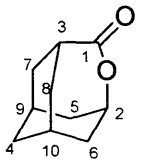
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (2H, t, *J* 6.1 Hz, H-4), 2.74 (2H, t, *J* 7.1 Hz, H-2), 2.05 (3H, s, H-1), 1.85 (2H, qn, *J* 6.1 Hz, H-3) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 66.7 (C-4), 61.1 (C-2), 32.4 (C-3), 28.9 (C-1) ppm.

General Procedure for the Baeyer-Villiger Oxidation[36]

Catalyst (0.05 mmol), carbonyl compound (2 mmol) and H_2O_2 (8.8 M in water, 0.4 mL, 4 mmol) were stirred in dichloromethane (2 mL) at room temperature. The progress of the reaction was followed by TLC. Upon completion, the reaction mixture was poured into water (10 mL), extracted with dichloromethane (3 × 10 mL) and the products purified by column chromatography.

Tricyclo[3.3.1.1(3,7)]decane-2-ate 73[36]

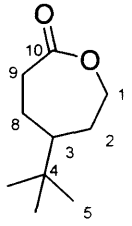


(279 mg, 84%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (1H, t, *J* 2.3 Hz, H-2), 2.99 (1H, t, *J* 5.8 Hz, H-3), 2.03–1.65 (12H, m, H-4,5,6,7,8,9,10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.0 (C-1), 73.2 (C-2), 41.2 (C-3), 35.8 (2C, C-5,6), 33.8 (C-4), 31.0 (2C, C-7,8), 25.9 (2C, C-9,10) ppm.

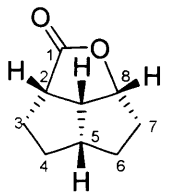
5-*t*butyloxepan-2-one 74[89]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (1H, ddd, *J* 12.9, 5.9, 1.8 Hz, H-1A), 4.10 (1H, dd, *J* 12.8, 10.4 Hz, H-1B), 2.65 (1H, dd, *J* 7.1, 0.9 Hz, H-9A), 2.55–2.47 (1H, m, H-9B), 2.40–1.93 (2H, m, H-8A,2A), 1.30–1.12 (3H, m, H-8B,2B,3), 0.80 (9H, s, H-5,6,7) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 176.7 (C-10), 68.8 (C-1), 50.8 (C-3), 33.5 (C-9), 32.3 (C-4), 30.1 (C-2), 27.6 (3C, C-5), 23.5 (C-8) ppm.

2-Oxatricyclo[5.2.1.0]decan-3-one 75[37]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (1H, t, *J* 5.3 Hz, H-8), 3.11 (1H, td, J Hz, H-2), 2.99 (1H, ddd, J Hz, H-9), 2.62–2.50 (1H, m, H-5), 2.11–2.01 (3H, m, H-3, 7B), 1.86–1.77 (3H, m, H-4B,6B,7A), 1.49–1.40 (1H, m, H-6A), 1.40–1.32 (1H, m, H-4A) ppm

^{13}C NMR (63 MHz, $CDCl_3$): δ = 181.2 (C-1), 84.8 (C-8), 50.8 (C-2), 46.3 (C-9), 45.4 (C-5), 34.6 (C-3), 31.9 (C-7), 28.9 (C-6) ppm.

Experimental for Chapter 5

GP 1. General procedure for the catalytic reaction 89a–89j, 114

Diphenyl diselenide (5 mol%, 3.4 mg, 0.01 mmol) was dissolved in acetonitrile (3 mL) and the β,γ-unsaturated acid **92** (0.22 mmol) was added, followed by [bis(trifluoroacetoxy)iodo]benzene (100 mg, 0.23 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate : petroleum ether (2 : 8) to yield the cyclisation products

GP 2. General Procedure for the synthesis of 4-alkylbut-3-enoic acids 92a, 92b, 92g–92j, 113

The aldehyde (10 mmol) and malonic acid (10 mmol, 1.04 g) was mixed thoroughly with chromatography grade silica (200 mesh, 1 g) and the resulting powder was packed into a microwave tube and subjected to microwave irradiation (300 W, 50 °C, 10 min). The reaction mixture was allowed to cool to room temperature and water was added (10 mL) and extracted with dichloromethane (30 mL). The solvent was removed under reduced pressure and the compound was purified by flash chromatography eluting with petroleum ether : ethyl acetate : acetic acid (90 : 8 : 2).[90]

GP 3. General procedure for the synthesis of 4-arylbut-3-enoic acids 92c–92f

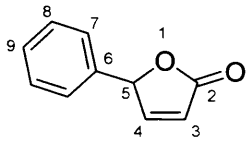
(*E*)-Tributylstannyl 4-tributylstannyl-but-3-enoate (1.5 g, 2.26 mmol), aryl bromide (0.8 equiv.) and tetrakis(triphenylphosphine) palladium(0) (3 mol%, 78 mg, 0.068 mmol) were dissolved in toluene (20 mL). The mixture was degassed under vacuum and stirred for 10 h at 100 °C. After cooling, the stannyl ester was hydrolysed with 1 M HCl solution (10 mL). After extraction with diethyl ether (3 × 20 mL), the combined organic layers were treated with aq. 1 M NaOH (20 mL). The aqueous phase was washed with diethyl ether and reacidified with aq. 1 M HCl (40 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and, after removal of the solvent under reduced pressure, the compound

was purified by flash chromatography eluting with petroleum ether : ethyl acetate : acetic acid (90 : 8 : 2).[73]

GP. 4. General procedure for the stoichiometric addition of selenium reagents 106a, 106b, 116

The diselenide (0.6 mmol) was dissolved in acetonitrile (10 mL) and (*E*)-4-phenylbut-3-enoic acid (1.2 mmol) was added, followed by [bis(trifluoroacetoxy)iodo]benzene (0.6 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate : light petroleum (1 : 4) to yield the addition products.

5-Phenylfuran-2(5*H*)-one 89a[91]



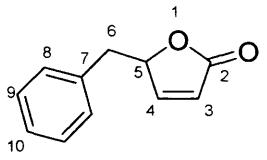
Synthesied according to GP 1.

(24 mg, 70%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (1H, dd, *J* 5.5, 1.6 Hz, H-4), 7.40–7.35 (3H, m, H-7,9), 7.30–7.25 (2H, m, H-8), 6.23 (1H, dd, *J* 5.5, 2.0 Hz, H-5), 6.01 (1H, dd, *J* 2.0, 1.6 Hz, H-3) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.1 (C-2), 155.9 (C-4), 134.3 (C-6), 129.4 (C-9), 129.2 (2C, C-8), 126.5 (2C, C-7), 120.1 (C-3), 84.4 (C-5) ppm.

5-Benzylfuran-2(*5H*)-one 89b[92]



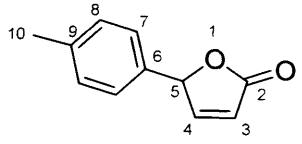
Synthesied according to GP 1.

(20 mg, 59%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (1H, dd, *J* 5.7, 1.4 Hz, H-4), 7.29–7.22 (2H, m, H-9), 7.21–7.18 (2H, m, H-10), 7.14 (1H, d, *J* 8.3 Hz, H-8), 6.00 (1H, dd, *J* 5.7, 2.0, H-3), 5.15 (1H, m, H-5), 3.07 (1H, dd, *J* 13.8, 6.4 Hz, H-6A), 2.89 (1H, dd, *J* 13.9, 7.0 Hz, H-6B) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.8 (C-2), 155.6 (C-4), 134.8 (C-7), 129.4 (2C, C-9), 128.7 (2C, C-8), 127.3 (C-10), 122.1 (C-3), 83.4 (C-5), 36.6 (C-6) ppm.

5-(*p*-Tolyl)furan-2-(*5H*)-one 89c[93]



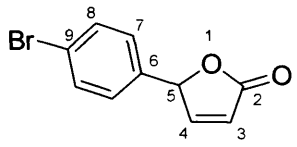
Synthesied according to GP 1.

(16 mg, 57%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (1H, dd, *J* 5.6, 1.6 Hz, H-4), 7.13 (2H, d, *J* 8.1 Hz, H-8), 7.01 (2H, d, *J* 7.9 Hz, H-7), 6.16 (1H, ddd, *J* 6.7, 5.7, 2.1 Hz, H-5), 5.92 (1H, td, *J* 17.9, 1.8 Hz, H-3), 2.29 (3H, s, H-10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$) δ 172.0 (C-2), 154.8 (C-4), 138.4 (C-6), 133.3 (C-9), 128.7 (2C, C-8) 128.1 (2C, C-7), 125.5 (C-3), 83.4 (C-5), 20.2 (C-10) ppm.

5-(4-Bromophenyl)furan-2(*5H*)-one 89d[93]



Synthesied according to GP 1.

(19 mg, 54%) as a colourless oil.

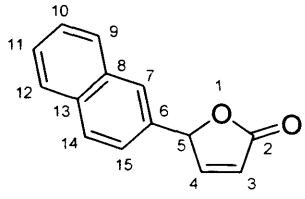
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (1H, d, *J* 8.1 Hz, H-8), 7.51 (2H, d, *J* 5.5 Hz, H-4), 7.10 (2H, t, *J* 7.8 Hz, H-7), 6.22 (1H, dd, *J* 5.6, 2.1 Hz, H-5), 5.97 (1H, d, *J* 2.1 Hz, H-3) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.1 (C-2), 155.8 (C-4), 131.6 (2C, C-8), 129.1 (2C, C-7), 126.2 (C-3), 121.1 (C-9), 84.6 (C-5) ppm.

MS *m/z* (EI^+) (%): 240 (M^+, 50), 185 (100), 159 (50), 131 (35).

HRMS found *m/z* (EI^+) = 237.9625, $C_{10}H_7O_2{}^{79}Br^+$ calcd. 236.9629.

5-(Naphthalen-2-yl)furan-2(*5H*)-one 89e[92]



Synthesied according to GP 1.

(25 mg, 60%) as a colourless oil

IR (film): ν_{max} = 1754, 1158, 1087, 1026, 901, 818, 749 cm^{-1}.

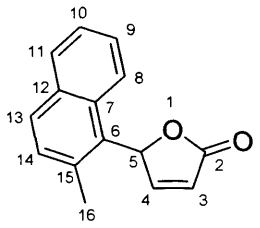
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.76 (3H, m, H-Ar), 7.70 (1H, s, H-7), 7.54 (1H, dd, *J* 5.6, 1.7 Hz, H-4), 7.50–7.44 (2H, m, H-Ar), 7.23 (1H, dd, *J* 8.5, 1.7 Hz, H-15), 6.25 (1H, dd, *J* 5.7, 2.1 Hz, H-5), 6.12 (1H, s, H-3) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.1 (C-2), 155.9 (C-4), 133.6 (C-6), 133.2 (C-8), 131.6 (C-13), 129.1 (C-15), 128.2 (C-12), 127.8 (C-9), 126.9 (C-14), 126.8 (C-7), 126.2 (C-10), 123.3 (C-3), 121.1 (C-11), 84.5 (C-5) ppm.

MS *m/z* (EI^+) (%): 210 (M^+, 88), 155 (100), 127 (49).

HRMS found *m/z* (EI^+) = 210.0679, $C_{14}H_{10}O_2^+$ calcd. 210.0681.

5-(2-Methylnaphthalen-1-yl)furan-2(*5H*)-one 89f



Synthesied according to GP 1.

(32 mg, 65%) as a colourless oil.

IR (film): ν_{max} = 1759, 1157, 1099, 816 cm^{-1}.

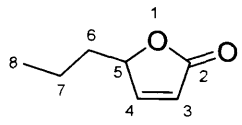
^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (1H, t, *J* 7.9 Hz, H-4), 7.71 (1H, d, *J* 8.4 Hz, H-8), 7.62–7.55 (1H, m, H-11) 7.43 –7.34 (1H, m, H-13), 7.41–7.32 (1H, m, H-9), 7.23–7.12 (1H, m, H-10), 6.82–6.78 (1H, m, H-3), 6.30 (1H, dd, *J* 5.6, 2.5 Hz, H-5), 2.41 (3H, s, H-16) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.5 (C-2), 156.4 (C-4), 136.2 (C-6), 132.9 (C-15), 131.9 (C-12), 130.2 (C-7), 130.0 (C-11), 129.0 (C-13), 127.0 (C-9), 125.2 (C-14), 124.8 (C-3), 122.4 (C-10), 121.9 (C-8), 82.0 (C-5), 20.8 (C-16) ppm.

MS *m/z* (EI^+) (%): 224 (M^+, 100), 195 (75), 165 (68), 141 (25), 115 (18).

HRMS found *m/z* (EI^+) = 224.0837, $C_{15}H_{12}O_2^+$ calcd. 224.0837.

5-Propylfuran-2(*5H*)-one 89g[94]



Synthesied according to GP 1.

(32 mg, 65%) as a colourless oil.

IR (film): ν_{max} = 2963, 1748, 1165, 1114, 818 cm^{-1}.

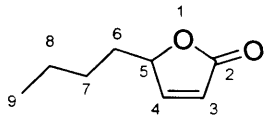
^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (1H, dd, *J* 5.7, 1.4 Hz, H-4), 6.03 (1H, dd, *J* 5.7, 1.9 Hz, H-5), 5.02–4.96 (1H, m, H-3), 1.69 (1H, m, H-6A), 1.59 (1H, m, H-6B), 1.40 (2H, m, H-7), 0.90 (3H, t, *J* 7.4 Hz, H-8) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.2 (C-2), 156.4 (C-4), 121.5 (C-3), 83.2 (C-5), 35.2 (C-6), 18.4 (C-7), 13.8 (C-8) ppm.

MS *m/z* (EI^+) (%): 126.1 (M^+, 11), 97.1 (100), 84.0 (78)

HRMS found *m/z* (EI^+) = 126.0681, $C_7H_{10}O_2^+$ calcd. 126.0681.

5-Butylfuran-2(*5H*)-one 89h



Synthesied according to GP 1.

(32 mg, 65%) as a colourless oil.

IR (film): ν_{max} = 2925, 1753, 1465, 1164, 820 cm^{-1}.

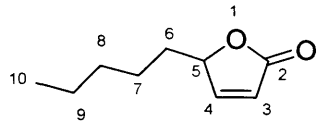
^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (1H, dd, *J* 5.8, 1.5 Hz, H-4), 6.05 (1H, dd, *J* 5.8, 2.0 Hz, H-5), 5.02–4.98 (1H, m, H-3), 1.75–1.65 (1H, m, H-6A), 1.65–1.55 (1H, m, H-6B), 1.40–1.23 (4H, m, H-7,8), 0.85 (3H, t, *J* 7.1, H-9) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.2 (C-2), 156.4 (C-4), 121.5 (C-3), 83.5 (C-5), 32.9 (C-6), 27.0 (C-7), 22.4 (C-8), 13.8 (C-9) ppm.

MS *m/z* (EI^+) (%): 140.1 (M^+, 9), 111.1 (88), 84.0 (100).

HRMS found *m/z* (EI^+) = 140.0840, $C_8H_{12}O_2^+$ calcd. 140.0837.

5-Pentylfuran-2(*5H*)-one 89i



Synthesied according to GP 1.

(22 mg, 49 %) as a colourless oil.

IR (film): ν_{max} = 2931, 1753, 1163, 817 cm^{-1}.

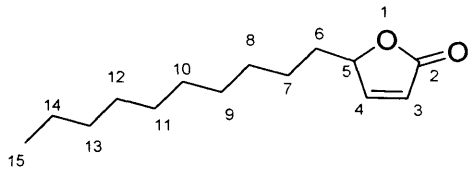
^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (1H, dd, *J* 5.7, 1.4 Hz, H-4), 6.02 (1H, dd, *J* 5.7, 2.0 Hz, H-5) 5.02–4.94 (1H, m, H-3), 1.75–1.65 (1H, m, H-6A), 1.55–1.65 (1H, m, H-6B), 1.42–1.32 (2H, m, H-9) 1.30–1.20 (4H, m, H-7,8), 0.85 (3H, t, *J* 7.1 Hz, H-10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.2 (C-2), 156.3 (C-4), 121.5 (C-3), 83.4 (C-5), 33.2 (C-6), 31.5 (C-7), 24.6 (C-8), 22.4 (C-9), 13.9 (C-10) ppm.

MS *m/z* (EI^+) (%): 154 (M^+, 4), 125 (70), 84 (100), 83 (20), 55 (15).

HRMS found *m/z* (EI^+) = 154.0988, $C_9H_{14}O_2^+$ calcd. 154.0994.

5-Decylfuran-2(*5H*)-one 89j



Synthesied according to GP 1.

(48 mg, 96 %) as a white solid.

mp = 120–122 °C

IR (CDl_3 deposit): ν_{max} = 2920, 2851, 2360, 1693, 1467, 965 cm^{-1}.

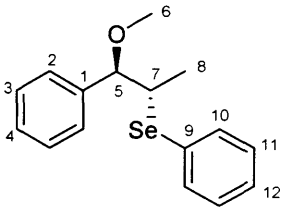
^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (1H, dd, *J* 5.7, 1.4 Hz, H-4), 6.05 (1H, dd, *J* 5.7, 2.0 Hz, H-5), 5.02–4.98 (1H, m, H-3), 1.75–1.65 (1H, m, H-6A), 1.55–1.65 (1H, m, H-6B), 1.45–1.35 (2H, m, H-7), 1.22–1.18 (14H, m, H-8,9,10,11,12,13,14) 0.82 (3H, t, *J* 6.7 Hz, H-15) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.4 (C-2), 157.0 (C-4), 121.4 (C-3), 84.2 (C-5), 33.0 (C-6), 32.6 (C-13), 29.6 (C-12), 29.5 (C-11), 29.4 (C-10), 29.3 (C-9), 29.1 (C-8), 24.6 (C-7), 22.1 (C-14), 14.1 (C-15) ppm.

MS *m/z* (EI^+) (%): 224 (M^+, 18), 164 (38), 97 (100), 84 (39), 69 (31).

HRMS found *m/z* (EI^+) = 224.1778, $C_{14}H_{24}O_2^+$ calcd. 224.1776.

(1-Methoxy-1-phenylpropan-2-yl)(phenyl)selane 90[95]

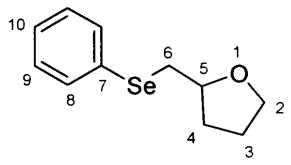


Methanol (95 mg, 2.96 mmol), (*E*)-β-methylstyrene (35 mg, 0.296 mmol), diphenyl diselenide (46 mg, 0.148 mmol) were dissolved in acetonitrile (3 mL) followed by [bis(trifluoroacetoxy)]iodobenzene (134 mg, 0.3108 mmol) and and the reaction mixture stirred under argon at room temperature for 3 h. Water (3 mL) was added and

the mixture extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield (1-methoxy-1-phenylpropan-2-yl)(phenyl)selane (30% conversion by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) 7.60–7.40 (2H, m, H-Ar), 7.30–7.10 (8H, m, H-Ar) 5.10 (1H, d, *J* 3.7 Hz, H-5), 4.11 (1H, d, *J* 4.7 Hz, H-7), 3.33 (3H, s, H-6), 1.78 (1H, dd, *J* 6.5, 1.6 Hz, H-7) 1.36 (3H, d, *J* 7.2 Hz, H-8) ppm.

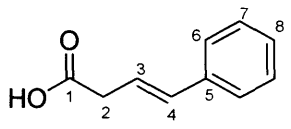
Tetrahydro-2-[(phenylselanyl)methyl]furan 91[96]



Methanol (131 mg, 4.1 mmol), pent-4-en-1-ol (35 mg, 0.41 mmol) and diphenyl diselenide (6.4 mg, 0.0205 mmol, 5 mol%) were dissolved in acetonitrile (3 mL) and followed by [bis(trifluoroacetoxy)iodo]benzene (185 mg, 0.431 mmol) and the reaction mixture stirred under argon at room temperature for 4.5 hr. Water (3 mL) was added and the mixture extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield tetrahydro-2-[(phenylselanyl)methyl]furan (44% conversion by ^1H NMR).

^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, dd, *J* 7.9, 2.2 Hz, H-8), 7.25–7.15 (3H, m, H-9, H-10), 4.02 (1H, qn, *J* 6.7 Hz, H-5), 3.85 (1H, q, *J* 6.7 Hz, H-2A), 3.70 (1H, q, *J* 7.6 Hz, H-2B), 3.05 (1H, dd, *J* 11.9, 5.7 Hz, H-6A), 2.92 (1H, dd, *J* 12.1, 6.8 Hz, 6-H-6B), 2.05–1.95 (2H, m, H-4), 1.90-1.80 (2H, m, H-3) ppm.

(*E*)-4-Phenylbut-3-enoic acid 92a[73]



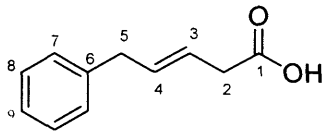
Synthesised according to GP 2.

(2.084g, 68%) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.12 (5H, m, H-6,7,8), 6.45 (1H, d, *J* 15.9 Hz, H-4), 6.20 (1H, dt, *J* 15.9, 7.0 Hz, H-3), 3.20 (2H, d, *J* 7.0 Hz, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.8 (C-1), 136.7 (C-5), 134.0 (C-4), 128.6 (2C, C-7), 127.7 (C-8), 126.4 (2C, C-6), 120.8 (C-3), 38.0 (C-2) ppm.

(*E*)-5-Phenylpent-3-enoic acid 92b[73]



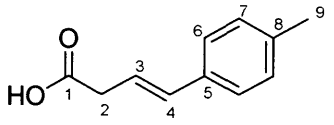
Synthesised according to GP 2.

(406 mg, 31%) as colourless oil

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35–7.15 (5H, m, H-7,8,9), 5.75 (1H, q, *J* 6.9 Hz, H-4), 5.62 (1H, q, *J* 7.0 Hz, H-3), 3.40 (1H, d, *J* 6.09 Hz, H-5A), 3.10 (1H, d, *J* 6.30 Hz, H-5B) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.8 (C-1), 151.4 (C-6), 140.0 (C-3), 128.6 (2C, C-7), 128.4 (2C, C-8), 126.3 (C-4), 122.5 (C-9), 40.0 (C-5), 37.8 (C-2) ppm.

(*E*)-4-(*p*-Tolyl)but-3-enoic acid 92c



Synthesised according to GP 3.

(220 mg, 55%) as a colourless oil.

IR (film): ν_{max} = 3425, 2958, 2927, 2871, 1709, 1514, 1413, 1180, 967 cm^{-1}.

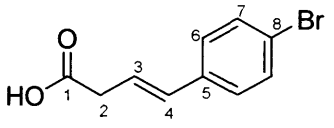
^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (2H, d, *J* 7.6 Hz, H-6), 7.05 (2H, d, *J* 7.8 Hz, H-7), 6.41 (1H, d, *J* 15.2, H-4), 6.14 (1H, m, H-3), 3.24 (2H, t, *J* 7.3 Hz, H-2), 2.26 (3H, s, H-9) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.2 (C-1), 137.5 (C-8), 133.9 (C-5), 129.3 (C-4), 129.1 (2C, C-7), 126.3 (2C, C-6), 119.8 (C-3), 38.0 (C-2), 21.2 (C-9) ppm.

MS *m/z* (EI^+) (%):176 (M^+, 48), 131 (94), 115 (100), 91 (57).

HRMS found *m/z* (EI^+) = 176.0839, $C_{11}H_{12}O_2^+$ calcd. 176.0837.

***(E)*-4-(4-Bromophenyl)but-3-enoic acid 92d**[73]



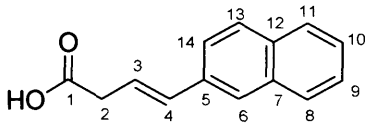
Synthesised according to GP 3.

(298 mg, 55%) as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.70 (2H, m, H-7), 7.40–7.35 (2H, m, H-6), 6.62 (1H, d, *J* 15.9 Hz, H-4), 6.37 (1H, dt, *J* 15.9, 7.1 Hz, H-3), 3.31 (2H, d, *J* 7.1 Hz, H-2) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.9 (C-1), 135.6 (C-5), 132.8 (C-4), 131.7 (2C, C-7), 127.7 (2C, C-6), 121.5 (C-3), 120.8 (C-8), 37.9 (C-2) ppm.

(*E*)-4-(Naphthalen-3-yl)but-3-enoic acid 92e[97]



Synthesised according to GP 3.

(297 mg, 63%) as a colourless oil.

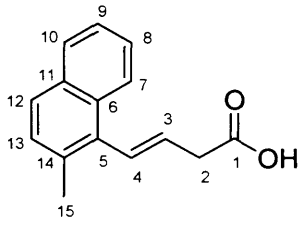
IR (film): ν_{max} = 3434, 2359, 1642 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (3H, d, *J* 8.5 Hz, H-9,10,14), 7.20 –7.15 (4H, m, H-6,8,11,13), 6.39 (1H, d, *J* 15.9 Hz, H-4), 6.21–6.18 (1H, m, H-3), 3.23 (2H, d, *J* 7.0 Hz, H-2) ppm.

MS *m/z* (EI^+) (%): 212 (M^+, 82), 167 (100), 152 (61), 115 (15).

HRMS found *m/z* (EI^+) =212.0835, $C_{14}H_{12}O_2^+$ calcd. 212.0837.

(*E*)-5-(2-Methylnaphthalen-1-yl)but-3-enoic acid 92f



Synthesised according to GP 3.

(276 mg, 54%) as a white solid.

m.p. = 76–78 °C

IR (film): ν_{max} = 2926, 2851, 2356, 1705, 1461, 1373, 1292, 1223, 1079 cm^{-1}.

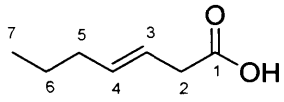
^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (1H, d, *J* 8.3 Hz, H-7), 7.72 (1H, d, *J* 7.7 Hz, H-10), 7.61 (1H, d, *J* 8.4 Hz, H-12), 7.42–7.32 (2H, m, H-8,9), 7.26 (1H, d, *J* 8.4 Hz, H-13), 6.78 (1H, d, *J* 16.1 Hz, H-4), 5.88 (1H, dt, *J* 16.0, 7.1 Hz, H-3), 3.40 (2H, d, *J* 7.1 Hz, H-2), 2.41 (3H, s, H-15) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.7 (C-1), 133.1 (C-4), 131.0 (2C, C-5,14), 130.3 (C-11), 128.8 (C-6), 128.2 (C-10), 128.1 (C-8), 127.3 (C-12), 127.1 (C-13), 126.1 (C-9), 125.1 (C-7), 124.8 (C-3), 38.4 (C-2), 20.8 (C-15) ppm.

MS *m/z* (EI^+) (%): 226 (M^+, 60), 181 (18), 166 (100), 152 (22), 115 (11).

HRMS found *m/z* (EI^+) = 226.0997, $C_{15}H_{14}O_2^+$ calcd. 226.0994.

(*E*)-Hept-3-enoic acid 92g[98]



Synthesised according to GP 2.

(313 mg, 21%) as a colourless oil.

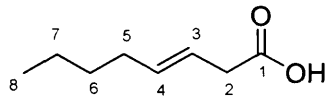
IR (film): ν_{max} = 2926, 2876, 1712, 1411, 1292, 1224, 1174, 1123, 967, 936 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.58–5.40 (2H, m, H-3,4), 3.00 (2H, d, *J* 7.2 Hz, H-2), 1.95 (2H, q, *J* 6.8 Hz, H-5), 1.39–1.27 (2H, m, H-6), 0.82 (3H, t, *J* 7.4 Hz, H-7) ppm.

MS *m/z* (EI^+) (%): 128 (M^+, 13), 110 (69), 68 (100).

HRMS found *m/z* (EI^+) = 128.0833, $C_7H_{12}O_2^+$ calcd. 128.0837.

(*E*)-Oct-3-enoic acid 92h[98]



Synthesised according to GP 2.

(391 mg, 28%) as a colourless oil.

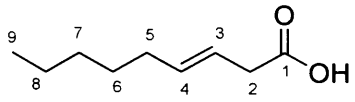
^1H NMR (400 MHz, $CDCl_3$): δ = 5.58–5.40 (2H, m, H-3,4), 3.02 (2H, d, *J* 6.7 Hz, H-2), 1.95 (2H, q, *J* 7.0 Hz, H-5), 1.32–1.18 (4H, m, H-6,7), 0.82 (3H, t, *J* 7.0 Hz, H-8) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.0 (C-1), 135.5 (C-4), 120.7 (C-3), 37.9 (C-2), 32.1 (C-5), 31.2 (C-6), 22.2 (C-7), 13.9 (C-8) ppm.

MS *m/z* (EI^+) (%): 142 (M^+, 10), 124 (86), 96 (22), 82 (100).

HRMS found *m/z* (EI^+) =142.0995, $C_9H_{16}O_2^+$ calcd. 142.0994.

(*E*)-Non-3-enoic acid 92i[99]



Synthesised according to GP 2.

(908 mg, 66%) as a colourless oil.

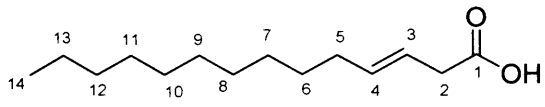
^1H NMR (400 MHz, $CDCl_3$) δ = 5.58–5.40 (2H, m, H-3,4), 3.02 (2H, d, *J* 6.7 Hz, H-2), 1.95 (2H, q, *J* 6.2 Hz, H-5), 1.28–1.14 (6H, m, H-6,7,8), 0.82 (3H, t, *J* 6.7 Hz, H-9) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.7 (C-1), 135.6 (C-4), 120.6 (C-3), 37.8 (C-2), 32.4 (C-5), 31.4 (C-7), 28.8 (C-6), 22.5 (C-8), 14.0 (C-9) ppm.

MS *m/z* (EI^+) (%): 156 (M^+, 8), 138 (65), 101 (23), 96 (49), 87 (51), 73 (81), 60 (100).

HRMS found *m/z* (EI^+) = 156.1150, $C_9H_{16}O_2^+$ calcd. 156.1150.

(*E*)-Tetradec-3-enoic acid 92j



Synthesised according to GP 2.

(373 mg, 35%) as a white solid.

m.p. = 37–39 °C

IR ($CDCl_3$ deposit): ν_{max} = 3432, 1642 cm^{-1}.

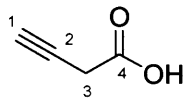
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.69–5.49 (2H, m, H-3,4), 3.09 (2H, d, *J* 6.6 Hz, H-2), 2.10–2.03 (2H, m, H-5), 1.35–1.25 (16H, m, H-6,7,8,9,10,11,12,13), 0.92 (3H, t, H-14) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.9 (C-1), 135.5 (C-4), 120.2 (C-3), 37.9 (C-2), 34.5 (C-5), 32.5 (C-6), 31.9 (C-7), 29.6 (C-8), 29.5 (C-9), 29.4 (C-10), 29.3 (C-11), 29.1 (C-12), 22.7 (C-13), 14.1 (C-14) ppm.

MS *m/z* (EI^+) (%): 226 (M^+, 20), 208 (94), 190 (41), 166 (70), 123 (56), 100 (62), 83 (68), 69 (100).

HRMS found *m/z* (EI^+) = 226.1941, $C_{14}H_{26}O_2^+$ calcd. 226.1933.

But-3-ynoic acid 94[76]

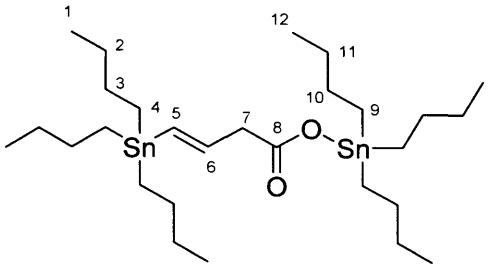


3-Butyn-1-ol (1g, 0.014 mmol) in acetone (10 mL) was added dropwise to a stirred solution of chromic acid solution (CrO_3 1.8 g, conc. H_2SO_4 1.6 mL, H_2O 7.6 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for a further 2 h. The liquid was then poured into a mixture of ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (5 x 20 mL). The extracts were combined and washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaported under reduced pressure to yield but-3-ynoic acid (441 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (2H, d, *J* 2.7 Hz, H-3), 2.20 (1H, t, *J* 2.7 Hz, H-1) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 166.4 (C-4), 74.8 (C-2), 72.4 (C-1), 25.5 (C-3) ppm.

(*E*)-tributylstannyl 4-(tributylstannyl)but-3-enoate 95[73]

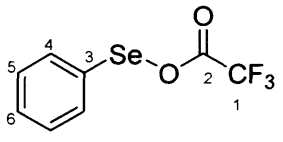


But-3-ynoic acid (1 g, 0.012 mol), tributyltin hydride (8.6 g, 0.029 mol) and azobis(isobutyronitrile) (10 mg) was stirred at 100 °C in toluene (20 mL). After 3 h, toluene was removed under reduced pressure and carbon tetrachloride (15 mL) added to react with the excess tributyltin hydride. The solution was allowed to stir for 1 h then potassium fluoride (0.5 M, 15 mL) and acetone (15 mL) were added. The solution was extracted with diethyl ether (5 × 20 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure to yield (*E*)-tributylstannyl 4-(tributylstannyl)but-3-enoate as a off yellow viscous liquid in an 85/15 mixture of *E* and *Z* isomers, (6.69g, 84% yield). *E* isomer isolated.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (1H, dt, *J* 18.9, 5.9 Hz, H-6), 6.05 (1H, d, *J* 18.9 Hz, H-5), 3.19 (2H, d, *J* 5.7 Hz, H-7), 1.65–0.80 (54H, m, H-1,2,3,4,9,10,11,12) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 176.2 (C-8), 141.9 (C-5), 131.2 (C-6), 44.1 (C-7), 29.1 (3C, C-3), 28.4 (3C, C-2), 28.0 (3C, C-11), 27.8 (3C, C-10), 16.4 (3C, C-9), 15.0 (6C, C-1,12), 11.3 (3C, C-4)

Phenylselenenyl trifluoroacetate 99



Method 1. Phenylselenenylchloride (50 mg, 0.2 mmol) and silver trifluoroacetate (58 mg, 0.26 mmol) were stirred in $CDCl_3$. The silver chloride precipitate was removed by filtration and the remaining solution was subjected to NMR experiments.

Method 2. Diphenyl diselenide (100 mg, 0.32 mmol) and [bis(trifluoroacetoxy)iodo]benzene (138 mg, 0.32 mmol) were dissolved in $CDCl_3$ and subjected to NMR experiments which gave 100% conversion.

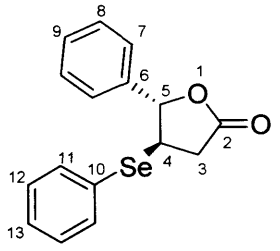
IR ($CDCl_3$ deposit): ν_{max} = 3056, 2360, 1700, 1667, 1474, 1437, 1177, 1065, 1020, 833 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (2H, d, *J* 7.6 Hz, H-4), 7.71 (1H, t, *J* 7.2 Hz, H-6), 7.53 (2H, t, *J* 7.3 Hz, H-5) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 159.9 ($^2J_{CF}$ 40 Hz, C-2), 137.5 (C-4), 135.1 (C-6), 130.2 (C-5), 127.5 (C-3), 114.3 ($^1J_{CF}$, 286 Hz, C-1) ppm.

^{19}F NMR δ = – 75.7339 ppm.

(4*RS*, 5*SR*)-Dihydro-5-phenyl-4(phenylselanyl)furan-2(*3H*)-one 106a



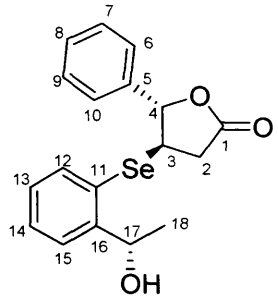
Synthesised according to GP 4.

(223 mg, 58%) as a pink oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.51 (2H, dd, *J* 8.3, 1.2 Hz, H-Ar), 7.40–7.15 (8H, m, H-Ar), 5.40 (1H, d, *J* 6.9 Hz, H-5), 3.75 (1H, td, *J* 8.4, 6.9 Hz, H-4), 3.05 (1H, dd, *J* 18.0, 8.3 Hz, H-3A), 2.68 (1H, dd, *J* 18.0, 8.4 Hz, H-3B) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.6 (C-2), 137.3 (C-6), 136.2 (2C, C-11), 129.6 (C-10), 129.1(3C, C-12, 13), 128.9 (2C, C-8), 128.8 (2C, C-7), 125.8 (C-9), 86.1 (C-5), 42.3 (C-3), 36.0 (C-4) ppm.

(4*RS*,5*SR*)-Dihydro-4-((2-((*S*)-1-hydroxyethyl)phenyl)selanyl)-5-phenylfuran-2(3*H*)-one 106b



Synthesised according to GP 4.

(89 mg, 79%) as a colourless oil.

IR (film): ν_{max} = 3429, 1782, 1456, 1201, 1088, 755, 699, cm^{-1}.

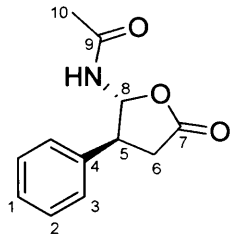
^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.00 (9H, m, H-Ar), 5.35 (1H, dd, *J* 5.4, 2.6 Hz, H-4), 5.15 (1H, q, *J* 6.4 Hz, H-17), 3.75 (1H, qn, *J* 7.7 Hz, H-3), 2.95 (1H, dt, *J* 18.1, 5.6, H-2A), 2.60 (1H, dd, *J* 18.0, 7.7 Hz, H-2B), 2.20 (1H, s, OH), 1.31 (3H, d, *J* 6.4 Hz, H-18) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.8 (C-1), 148.7 (C-16), 137.3 (C-5), 136.3 (C-12), 129.7 (C-11), 129.0 (C-14), 128.9 (C-6,10), 128.3 (C-13), 126.3 (C-8), 125.8 (C-7,9), 86.2 (C-4), 69.5 (C-17), 42.8 (C-2), 36.2 (C-3), 24.8 (C-18) ppm.

MS *m/z* ($M+H^+$) (%): 363 (M^+, 16), 345 (100), 317 (11), 299 (18), 211 (18), 183 (26), 159 (48)

HRMS found *m/z* ($M+H^+$) = 363.0485, $C_{18}H_{19}O_3{}^{80}Se^+$ calcd. 363.0499.

_N_-(5*RS*,8*SR*)-(5-Oxo-3-phenyltetrahydrofuran-2-yl)ethanamide 109



(29 mg, 28%) as a colourless oil.

IR (film): ν_{max} = 3299, 1782, 1678, 1541, 1372, 1260, 1166, 943, 826, 732, 698 cm^{-1}.

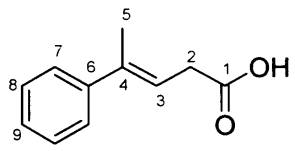
^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.12 (5H, m, H-1,2,3), 6.15 (1H, t, *J* 8.8 Hz, H-8), 3.55 (1H, q, *J* 9.1 Hz, H-5), 3.00 (1H, dd, *J* 17.6, 8.8 Hz, H-6A), 2.70 (1H, dd, *J* 17.6, 10.7 Hz, H-6B), 1.95 (3H, s, H-10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.3 (C-7), 171.4 (C-9), 136.9 (C-4), 129.3 (2C, C-2), 128.2 (C-1), 127.1 (2C, C-3), 86.1 (C-8), 46.9 (C-5), 37.2 (C-6), 23.2 (C-10) ppm.

MS *m/z* (EI^+) (%): 160 (M^+, 100), 178 (58), 201 (70), 220 (18).

HRMS found *m/z* (EI^+) = 220.0979, $C_{12}H_{14}NO_3^+$ calcd. 220.0974.

(*E*)-4-phenylpent-3-enoic acid 113



Synthesised according to GP 2.

(689 mg, 41%) as a white solid.

m.p. = 56–58 °C

IR ($CDCl_3$ deposit): ν_{max} = 3583, 3055, 2360, 2341, 1699, 1444, 1392, 1287, 939, 818, 748, 696, 666 cm^{-1}.

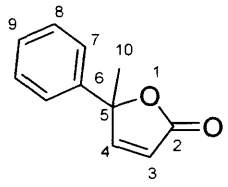
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.41 (2H, m, H-7), 7.37–7.32 (2H, m, H-8), 7.29–7.26 (1H, m, H-9), 5.96 (1H, td, *J* 7.0, 1.4 Hz, H-3), 3.34 (2H, d, J 7.2 Hz, H-2), 2.13 (3H, s, H-5) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.2 (C-1), 142.9 (C-6), 138.7 (C-4), 128.8 (C-8), 128.3 (C-9), 125.8 (C-7), 118.4 (C-3), 34.2 (C-2), 16.3 (C-5) ppm.

MS *m/z* (EI^+) (%): 176 (M^+, 44), 131 (100), 91 (38)

HRMS found *m/z* (EI^+) = 176.0830, $C_{11}H_{12}O_2^+$ calcd. 176.0837.

5-methyl-5-phenylfuran-2(5*H*)-one 114[100]



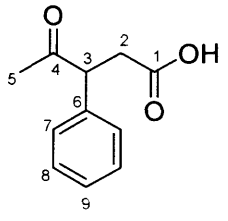
Synthesised according to GP 1

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (1H, d, *J* 5.5 Hz, H-4), 7.40–7.20 (5H, m, H-7,8,9), 5.98 (1H, d, *J* 5.5 Hz, H-3), 1.78 (3H, s, H-10) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.4 (C-1), 160.4 (C-3), 139.3 (C-5), 128.9 (2C, C7), 128.4 (C-8), 124.8 (2C, C6), 119.4 (C-2), 88.9 (C-4), 26.4 (C-11) ppm.

The ee values of **89j** was determined by HPLC analysis with a Diacel Chiracel OD-H coloumn (eluent: hexane/isopropanol = 90/10, flow rate.5 mL/min, column temperature 10°C, retention time: 28.1 min and 24.4 min).

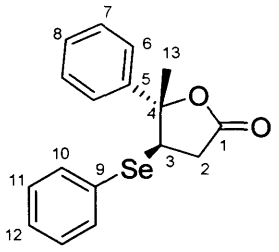
4-Oxo-3-phenylpentanoic acid 115[101]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (5H, m, H-7,8,9), 4.10 (1H, dd, *J* 9.8, 4.7 Hz, H-3), 3.20 (1H, dd, *J* 17.4, 9.9 Hz, H-2A), 2.50 (1H, dd, *J* 17.4, 4.7 Hz, H-2B), 2.05 (3H, s, H-5) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 206.8 (C-4), 177.8 (C-1), 142.9 (C-6), 128.9 (2C, C-7), 127.9 (2C, C-8), 127.3 (C-9), 54.6 (C-3), 36.7 (C-5), 28.8 (C-2) ppm.

(4*RS*,5*SR*)-Dihydro-5-methyl-5-phenyl-4-(phenylselenyl)furan-2(*3H*)-one 116



Synthesised according to GP 4.

(71 mg, 38%)

IR (film): ν_{max} = 3016, 2918, 2860, 1608, 1472, 1375, 1037, 835, 687 cm^{-1}.

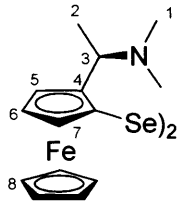
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.37 (4H, m, H-Ar), 7.30–7.15 (6H, m, H-Ar), 3.95 (1H, t, *J* 7.5 Hz, H-3), 2.85 (1H, dd, *J* 18.0, 7.8 Hz, H-2A), 2.70 (1H, dd, *J* 18.0, 7.3 Hz, H-2B) ppm.

^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.2 (C-1), 143.2 (C-5), 134.9 (2C, C-10), 129.5 (2C, C-11), 128.7 (2C, C-7), 128.5 (C-12), 128.1 (C-8), 124.3 (2C, C-6), 89.0 (C-4), 48.2 (C-3), 37.8 (C-2), 25.7 (C-2), 14.2 (C-13) ppm.

MS *m/z* (EI^+) (%): 332 (M^+, 8), 314 (20), 234 (10), 184 (26), 159 (56), 131 (100), 103 (35), 91 (9), 77 (70).

HRMS found *m/z* (EI^+) = 332.0314 $C_{17}H_{16}O_2{}^{80}Se^+$ calcd. 332.0316

(*RS; RS*)-Bisferrocenyl diselenide [(Fc*Se)$_2$] 119[80]



(*R*)-(+)-*N,N*-dimethyl(1-ferrocenylethyl)amine (1030 mg, 4.13 mmol) was treated with *s*-BuLi (4.5 mL, 4.51 mmol) in dry diethyl ether (10 mL) at 0 °C under argon. After 2 h selenium powder (388 mg, 4.10 mmol) was added portionwise, and the resulting mixture was stirred for 3 h at 0 °C. The mixture was poured into water and air bubbled through the solution for 5 h at room temperature. The diselenide was isolated by column chromatography with ethyl acetate as the eluent to yield bisferrocenyl diselenide [(Fc*Se)$_2$] (518 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51–4.27 (6H, m, H-5), 4.08 (10H, s, H-6), 3.85 (2H, q, *J* 6.9 Hz, H-3), 2.19 (12H, s, H-1), 1.44 (6H, d, *J* 6.9 Hz, H-2) ppm.

Chapter 7

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Chapter 8

Publications

New Developments with Chiral Electrophilic Selenium Reagents

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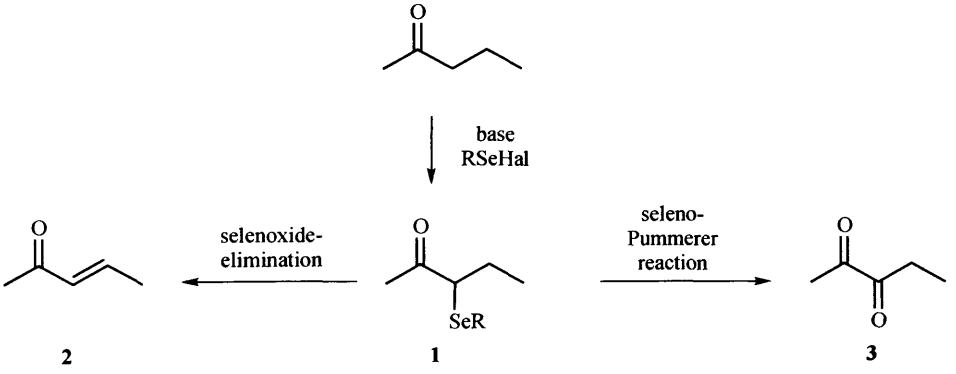
Abstract: This review describes the development of enantiomerically pure selenium reagents as electrophiles in stereoselective synthesis. It outlines the addition of selenium electrophiles to alkenes, which can be used as part of key reactions in various transformations. Different nucleophiles can be employed in the addition reactions including oxygen, nitrogen and carbon nucleophiles. Furthermore, it has been shown that selenocyclisations can been performed using similar nucleophiles for the formation of different heterocycles. It has been established that the structure of the selenium electrophile, its counterion and the solvent all influence the course of these reactions. Most transformations use stoichiometric amounts of selenium containing reagents. Recently, selenenylation - deselenenylation reactions were discovered where only catalytic amounts of reagents are necessary.

1. INTRODUCTION

Selenium-based methods in organic chemistry have developed rapidly over the past years and organoselenium chemistry is now a very useful tool in the hands of synthetic chemists. A major breakthrough for the development of organoselenium chemistry was the discovery of the selenoxide elimination in the early seventies [1]. But before organoselenium reagents became important reagents it was discovered that electrophilic selenium compounds can add stereospecifically to alkenes [2]. Since that time this reaction has been an important tool in the portfolio of organic chemists and is now routinely used even for the synthesis of complex target compounds. Comprehensive reviews on this chemistry have appeared [3-8] and in recent times the synthesis of chiral selenium electrophiles and their application in asymmetric synthesis has emerged. This review will highlight new developments using chiral electrophilic selenium compounds as versatile reagents in stereoselective synthesis.

2. GENERAL CONSIDERATIONS ON ELECTROPHILIC SELENIUM REAGENTS

Versatile precursors for the synthesis of different electrophilic selenium reagents are the corresponding diselenides, as they can be easily transferred into selenenyl halides or into selenenyl compounds with non-halide counterions. These electrophilic reagents can react with a variety of carbon or heteroatom nucleophiles to produce a wide range of different selenenylated compounds. For example, they can be used for the α-selenenylation of carbonyl compounds. The resulting addition product **1** can either be used in a selenoxide-elimination for the synthesis of α,β-unsaturated carbonyl compounds **2** [9] or the selenenylation can be followed by a seleno-Pummerer reaction to yield bisketones of type **3** [10, 11]. The selenenylation of silyl enolethers is possible as well [12] and products of type **1** have also been employed in diastereoselective reductions [13].



Scheme 1.

The reaction of selenium electrophiles with alkenes is a stereospecific *anti* addition. It involves the initial formation of seleniranium ion intermediates **4**, which are immediately opened in the presence of nucleophiles. External nucleophiles lead to the formation of addition products **5** while internal nucleophiles will lead to the corresponding cyclized products as described later. The addition to un-

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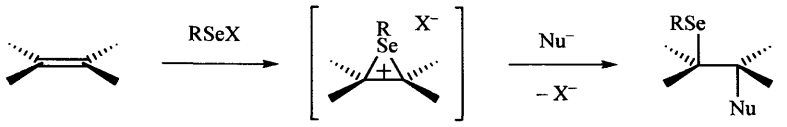
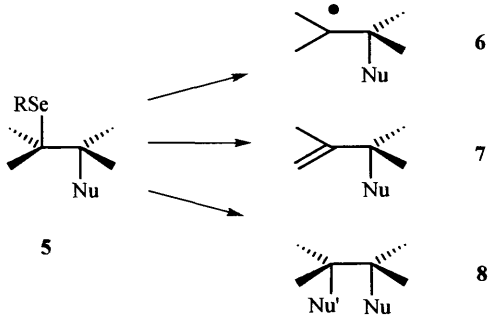


4 5

Scheme 2.

symmetrically substituted alkenes follows the thermodynamically favored Markovnikov orientation. Depending on the reaction conditions, the formation of the seleniranium ions can be reversible. The addition reaction can also be dependent on the counterion X of these electrophilic selenium reagents and different methods have been developed to exchange the counterions.

The reaction products **5** are very versatile building blocks in organic synthesis because of the various reactions they can undergo. Additions of selenium electrophiles to double bonds are most frequently used as part of a synthetic sequence, and the addition products **5** can be used for the generation of radicals **6**, in the above mentioned selenoxide-elimination to synthesize compounds **7** or, after oxidation of the selenide to the selenone, as a leaving group in a substitution reaction to generate compounds **8**.



Scheme 3.

Diselenides are very versatile precursors for selenium electrophiles as they can be cleaved readily into two equivalents of selenium electrophiles. For addition reactions the use of selenenyl halides can lead to complications because the halide can act as a nucleophile. Therefore, an exchange to less nucleophilic counterions is often necessary. A range of different counterions to the selenium electrophiles such as phthalimide [14, 15], tetrafluoroborate, hexafluoroantimonate [16], hexafluorophosphate [16], triflate [17, 18, 19], sulfate [20, 21], and tosylate [22, 23], have been employed successfully in addition reactions. The choice of the reagent is dependent on the requirements of the particular transformation. Mostly used are triflates and sulfates, although the latter have very low reactivity at temperatures below –30 °C. Diselenides can also be used together with oxidizing reagents to generate selenium electrophiles. Several oxidants like potassium nitrate [20, 21, 24], copper sulfate [20, 21], cerium ammonium nitrate (CAN) [20, 21, 25], manganese(III)acetate [26], nitrogen dioxide [27], 2-nitro-benzenesulfonyl peroxide [28, 29], (diacetoxy)iodobenzene [30], and bis(trifluoroacetoxy) iodobenzene [31, have been used to generate selenenylating reagents. Furthermore, the phenylselenyl cation can also be generated by photo-sensitized single electron transfer [32-34].

3. CHIRAL ELECTROPHILIC SELENIUM REAGENTS

The synthesis of chiral, non-racemic selenium electrophiles has been investigated by several research groups. Some examples of optically active diselenides as precursors for selenium electrophiles are shown in Fig. (**1**).

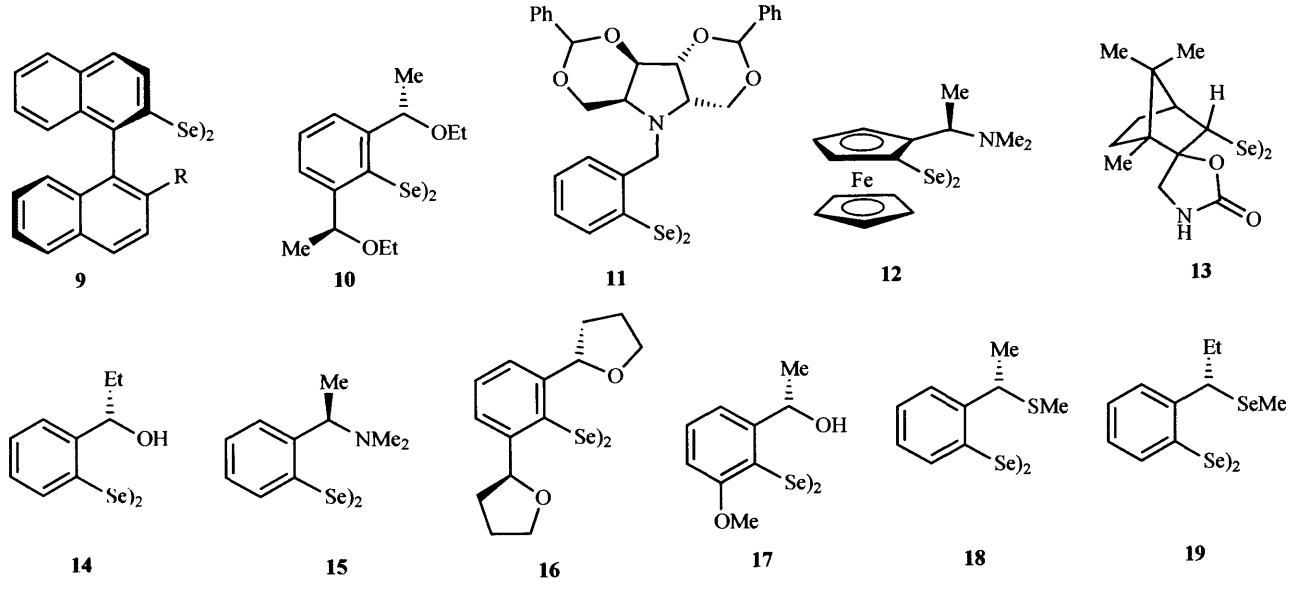


Fig. (1).

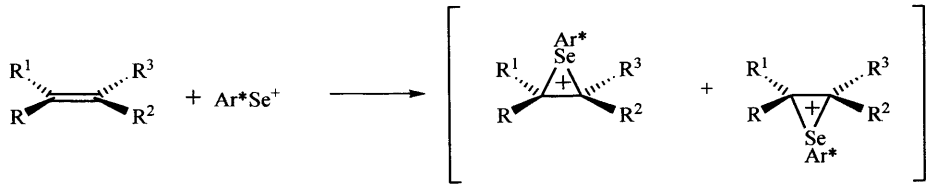
One of the first stereoselective selenenylation reactions were reported using the selenium electrophile generated from the binaphthyl diselenide **9** [35-40]. After this initial observation, that stereoselective reactions are indeed possible using chiral selenium electrophiles, several other diselenides have been prepared, initial attempts used quite long syntheses to obtain these compounds, for example the C_2 symmetrical diselenides **10** [41-43] and **16** [44] and the mannose-derived diselenide **11** [45-48]. The ferrocenyl-based diselenide **12** [49-53] is using expensive starting materials and in 1995 more simple and easy accessible diselenides like **14** and **15** have been described in literature [54-57]. Camphor-based diselenides such as **13** [58-62] have been prepared as well. Based on the success of diselenides **14** and **15**, structural variants **17** [63, 64] and diselenides with different coordinating heteroatoms such as sulfur **18** [65-72] and selenium **19** [73] have been described recently.

3.1. Oxygen Nucleophiles

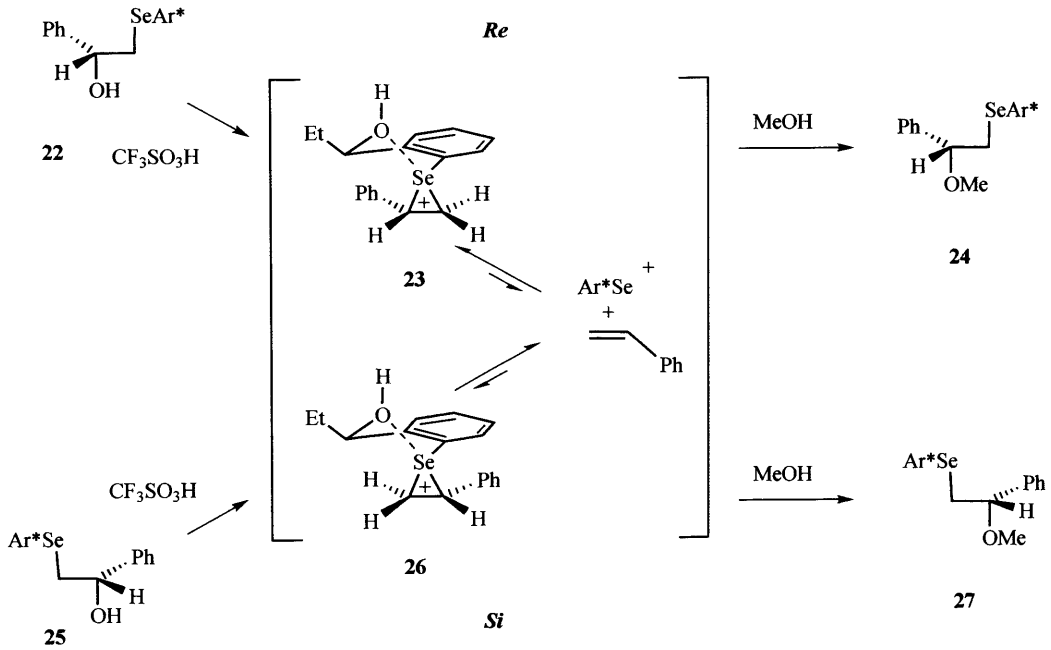
Different nucleophiles can be used in the addition reactions sketched out in Scheme **2**. Most prominent are oxygen nucleophiles and the stereospecific *anti*-addition of an organoselenium moiety and nucleophiles such as OH, OR, OCOR is very useful. There are many examples of such reactions including the synthesis of cyclitols [74, 75]. Carbon nucleophiles have been used with limited success, but very recently there have been several examples of successful reactions reported in the literature.

The first step in such selenenylation reactions is the formation of the seleniranium ions. The selenium electrophile can attack the double-bond from both sides. These seleniranium ions are then ring-opened resulting in an *anti* addition of the selenium moiety and the nucleophile. The formation of the seleniranium ions is reversible, but at low temperatures the reaction is under kinetic control. The mechanistic course of the oxyselenenylation reaction with some chiral reagents has been investigated in great detail [76, 77, 78]. The presence of a chiral moiety in these reagents results in a differentiation between the two faces of un-symmetrically substituted alkenes. Therefore, the attack of the alkene double bond from either the Re- or the Si-side is different from the steric and electronic point of view and the resulting seleniranium ions **20** and **21** are diastereomers as shown in Scheme **4**.

Experimentally this was verified by the independent synthesis of the diastereomeric seleniranium ions **23** and **26**. The corresponding β-hydroxyselenides **22** and **25** were obtained by reaction of the selenium anion with enantiomerically pure (*R*)- and (*S*)-styrene epoxide. These β-hydroxyselenides **22** and **25** were then treated with trifluoromethane sulfonic acid to selectively generate the corresponding seleniranium ions *via* an intramolecular S_N2 displacement. In case of β-hydroxyselenide **22**, it forms the more stable seleniranium ion **23** corresponding to a *Re*-attack of the selenium electrophile to the styrene double-bond. The subsequent reaction with methanol gave almost exclusively



Scheme 4.



Scheme 5.

the addition product **24**. Using the β-hydroxyselenide **25** under identical reaction conditions, the less stable seleniranium ion **26** is formed initially. *Via* a decomplexation – complexation mechanism as indicated in Scheme **5** the more stable seleniranium ion **23** is formed and the ring-opened products **24** and **27** are obtained in a ratio of about 1:3. This decomplexation – complexation mechanism could be further verfied as it was possible to trap the selenium electrophile (Ar^*Se^+) by the addition of a different substituted alkene to the reaction mixture. Calculation of the seleniranium intermediates have been performed and the computational results on different *ab-initio* levels are supporting the experimental findings [76, 77].

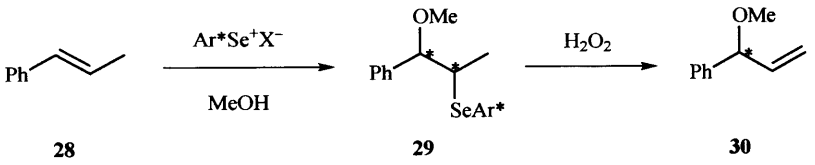
Most of the selenium electrophiles generated from the diselenides shown in Figure 1 have been used in a variety of addition reactions to double bonds. For example, the addition reactions to styrene derivatives such as (*E*)-1-phenylpropene **28** is leading to products **29**, this reaction is shown as a representative example in Scheme **6**. After oxidative elimination the ether **30** can be obtained. Diastereomeric ratios of up to 99:1 in **29** have been obtained with the electrophile generated from diselenide **16**, but also other enantiomerically pure selenium electrophiles gave selectivities of 95:5 or above. A detailed comparison of different selenium electrophiles in such addition reactions is given in reference [6].

The counterion X of the selenium electrophile plays an important, but not yet completely clear role in the selenenylations. A decreased nucleophilicity of the counterion X can lead to an increased electrophilicity of the selenium electrophile and hence to an increased selectivity which is reflected in higher diasteromeric ratios [48]. Similar observations were also made by other researchers [79] and recently, counterion effects together with coordinating additives have been investigated in cyclization reactions [80, 81].

The high selectivities obtained in selenenylation reactions have been used in different natural product syntheses. Even functionalized nucleophiles can be used in these reactions allowing a subsequent radical cyclization. This reaction sequence was applied to the synthesis of furofuran lignans as shown in Scheme **7**. The stereoselective selenenylation of the functionalised alkene **31** with the selenium electrophile generated from diselenide **14** and an allenylic alcohol **32** as nucleophile led to addition products of type **33** in good yields and diastereoselectivities. The favored 5-*exo-trig* radical cyclization of the major isomer yielded the cyclized product **34**. The vinylic side chain of the tetrahydrofuran derivative **34** was oxidatively cleaved and after deprotection of the hydroxy-moiety the hemiacetal **35** was formed, which, in the case of R,R = CH_2 is (+)-Samin [82], but can also serve as a versatile building block for the synthesis of other lignans [83].

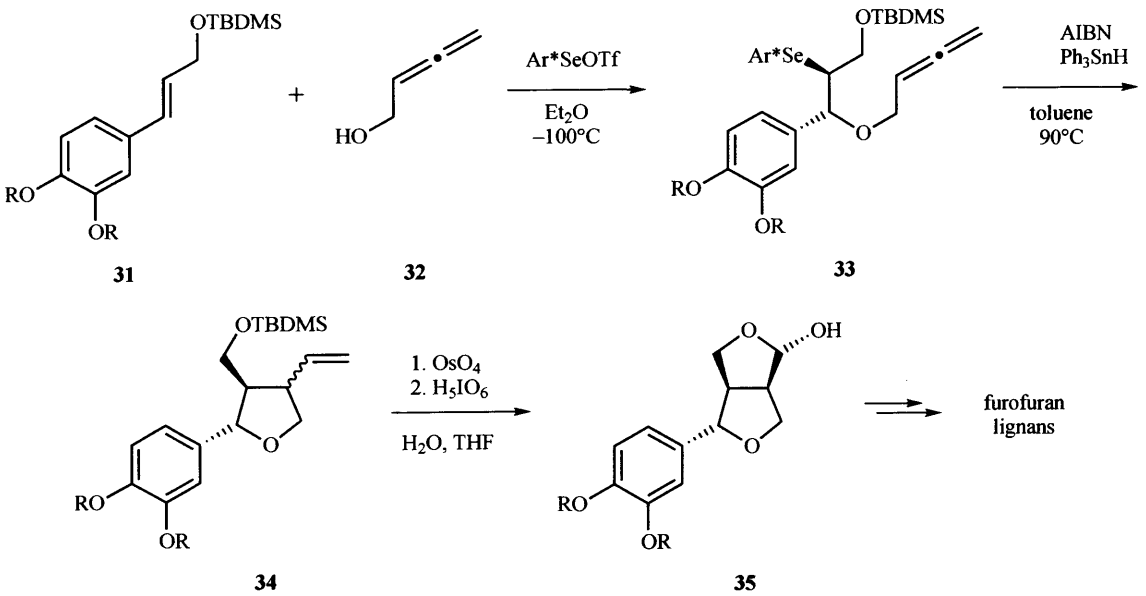
3.2. Selenocyclizations with Oxygen Nucleophiles

The potential of electrophilic reagents for cyclization reactions is enormous [84]. The great importance of heterocyclic compounds as final products or as reaction intermediates and their occurence in many natural products and in biologically active compounds has led to intensive research in this area. Depending on ring-size and reaction conditions, compounds of type **36** can undergo either *endo*-cyclization to products **37** or *exo*-cyclizations yielding heterocyclic



28 **29** **30**

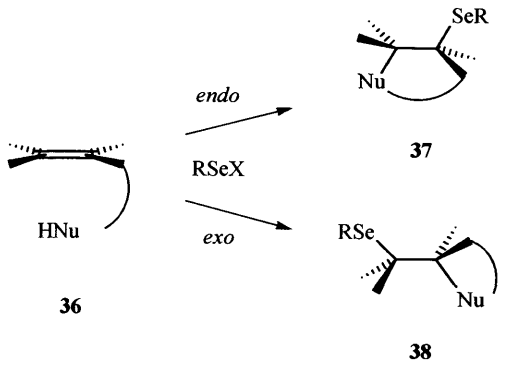
Scheme 6.



31 **32** **33** **34** **35**

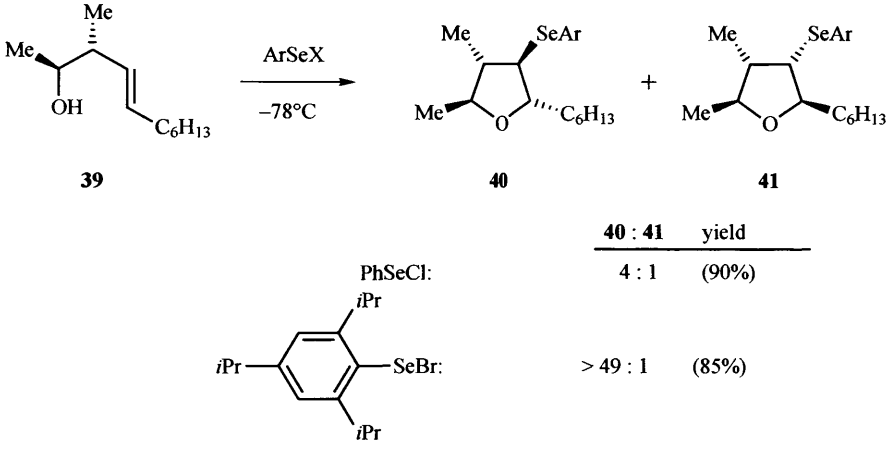
Scheme 7.

derivatives **38**. The selenium moiety in the products **37** and **38** can be used for subsequent manipulations making this a very versatile approach for the synthesis of heterocyclic compounds having various ring-sizes.



Scheme 8.

The size of the selenium electrophile has a large influence on the selectivity obtained in selenocyclizations of unsaturated alcohols **39**. The diastereomeric ratio for the isomers **40** and **41** ranges from from 4:1 [85] using phenylselenenyl chloride as an electrophile to >49:1 using the triisoproyl phenylselenenyl bromide as shown in Scheme **9** [86].



Scheme 9.

Almost all enantiomerically pure selenium electrophiles, generated from the diselenides **9** – **19**, have been employed in cyclization reactions. Different heterocycles with new stereogenic centers have been synthesized. Again, oxygen nucleophiles are widely used and some selected examples of selenolactonizations of unsaturated acids **42** [44] and **48** [87] and selenoetherifications of unsaturated alcohols **44** [48] and **46** [62] (stereochemistry unknown) are shown in Scheme **10**. Unsaturated oximes such as **50** can also be used for cyclization reactions. In the case of the oxime **50** with (*E*)-configuration, the oxygen is acting as the nucleophile generating 1,2-oxazine **51** (stereochemistry unknown). The (*Z*)-isomer, however, cyclizes *via* the oxime nitrogen atom to a cyclic nitrone [68].

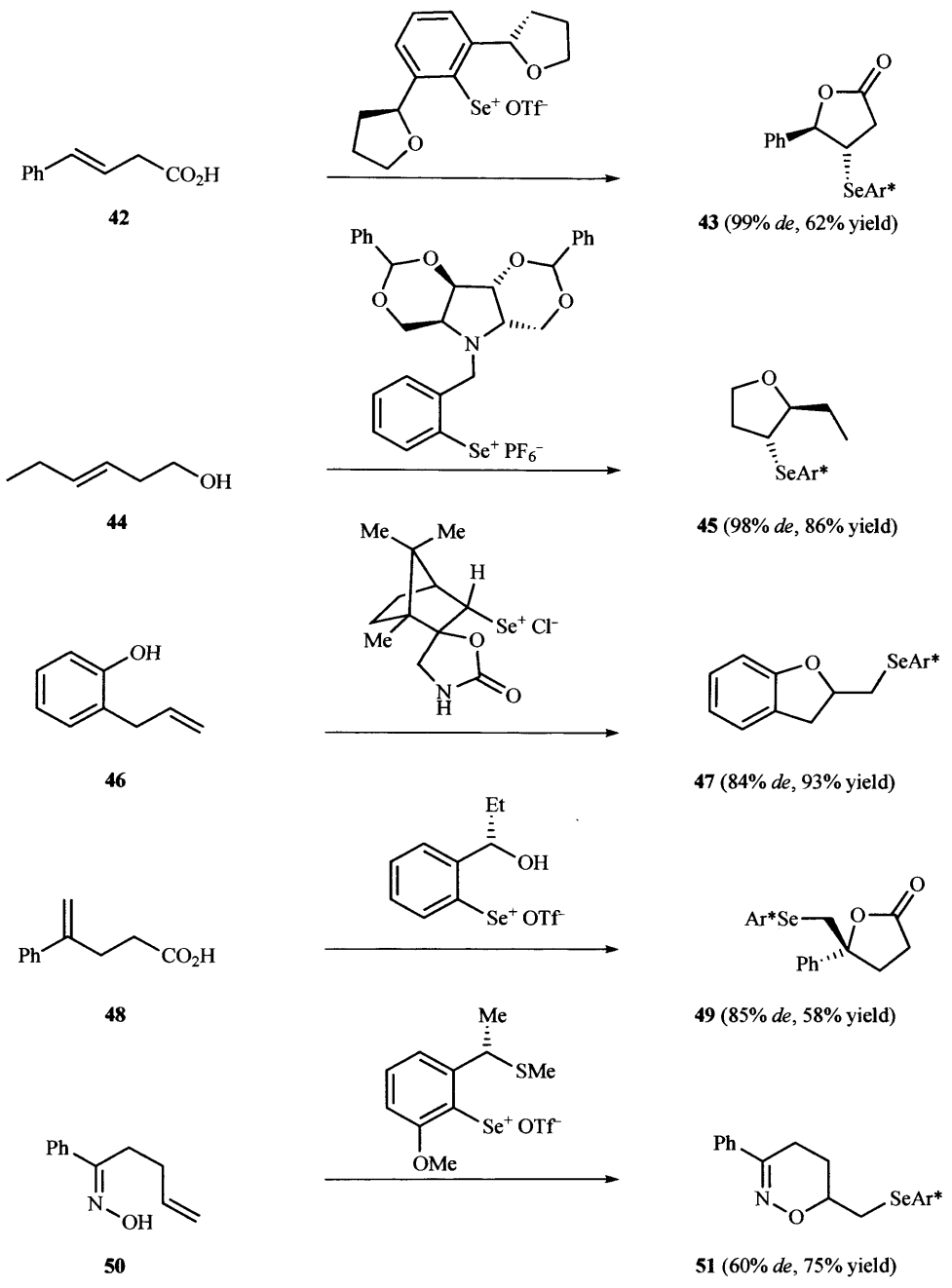
The structure of the selenium electrophile, its counter ion, solvents and external additives coordinating to the electrophilic species are influencing the course of such cyclizations. They can also be used to control such processes with high degrees of efficiency. This has recently been demonstrated by the selective cyclization of substrate **52**, which contains a hydroxy and a carboxylic acid functionality as internal nucleophiles. 5-*exo*-Cyclizations of alkene **52** can lead, depending on the cyclizing nucleophile to two different heterocycles: tetrahydrofurans **53** or lactones **54**. We have reported how different interactions with selenium electrophiles can be used to influence the cyclization of **52** either towards tetrahydrofurans **53** or towards lactones **54** [80, 81]. For example, phenylselenenyl triflate (X = OTf) with 10 equivalents of acetic acid leads exclusively to the formation of compounds **53**, whereas with phenylselenenyl hexafluorophosphate (X = PF_6) and 10 equivalents of methanol as external additive only lactones **54** are formed. Enantiomerically pure selenium electrophiles have also been employed in this cyclization reaction and selectivities similar to the ones reported in Scheme **10** have been obtained.

3.3. Nitrogen Nucleophiles

The addition of selenium electrophiles to alkenes using nitrogen nucleophiles are also synthetically relevant processes. Nitriles have been used as versatile nucleophiles in this reaction which can be converted into the corresponding amides [88, 89, 90]. But also other nitrogen-containing nucleophiles such as carbamates [91] or tosylamides [92] can be employed. Azidoselenenylations have been investigated as well, with the azide ion serving as a nitrogen nucleophile [93, 94, 95]. Under certain reaction conditions, however, a radical reaction pathway is possible leading to non-stereospecific addition products [96]. Recently, Tiecco reported an efficient azidoselenenylation using the electrophile **55**. Using styrene as alkene, the product **56** is obtained in a diastereomeric ratio of 97:3 and can be converted into oxazoline **57** [97].

3.4. Selenocyclizations with Nitrogen Nucleophiles

A wide range of nitrogen heterocycles is accessible by aminoselenenylations. Some selected examples are shown in Scheme **13**. Pyrrolidine derivative have been cyclized to pyrrolizidines [6], whereas homoallylamines can be either

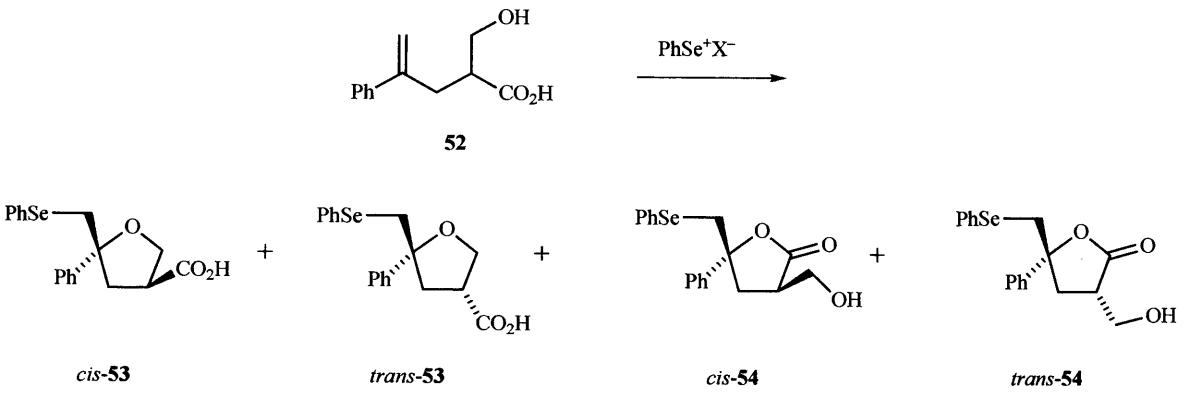


Scheme 10.

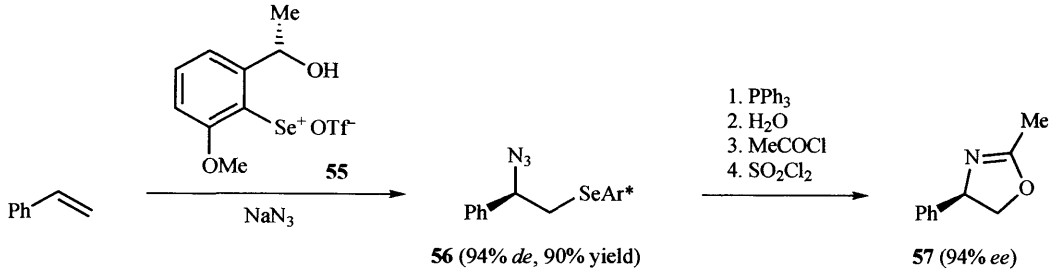
cyclized to afford azetidines *via* a *4-exo-trig* cyclization or to pyrrolidines by a *5-endo-trig* pathway [98]. An amino-cyclization was used as the key reaction for the synthesis of isoquinoline alkaloids. Cyclization of the compound **58** with different chiral selenium electrophiles yielded the cyclized product **59** in up to 85% *de*. After deselenylation and cleavage of the Boc-protecting group salsolidine **60** was synthesized [99]. Also *O*-allyl oximes such as **61** can be cyclized using phenylselenenyl bromide, after an aqueous work-up isoxazolidines **62** can be obtained [100, 101]. Recently, also chiral selenium electrophiles generated from **18** have been employed in this reaction to yield enantiomerically enriched isoxazolidines **62** with up to 88% *de* [67]. Those compounds can be used as versatile building blocks for various syntheses. The reaction products in the cyclization of oximes depend on their configuration as already described with compound **50**. In this case, the two isomeric oximes **63** interconvert under the reaction conditions and the nitrone **64** is the only reaction product [68]. A subsequent dipolar cycloaddition reaction can be used for the synthesis of bicyclic molecules such as **65**. Cyclizations of compounds with two different nitrogen atoms and their competition in cyclization reactions has been studied as well [102, 103].

3.5. Carbon Nucleophiles

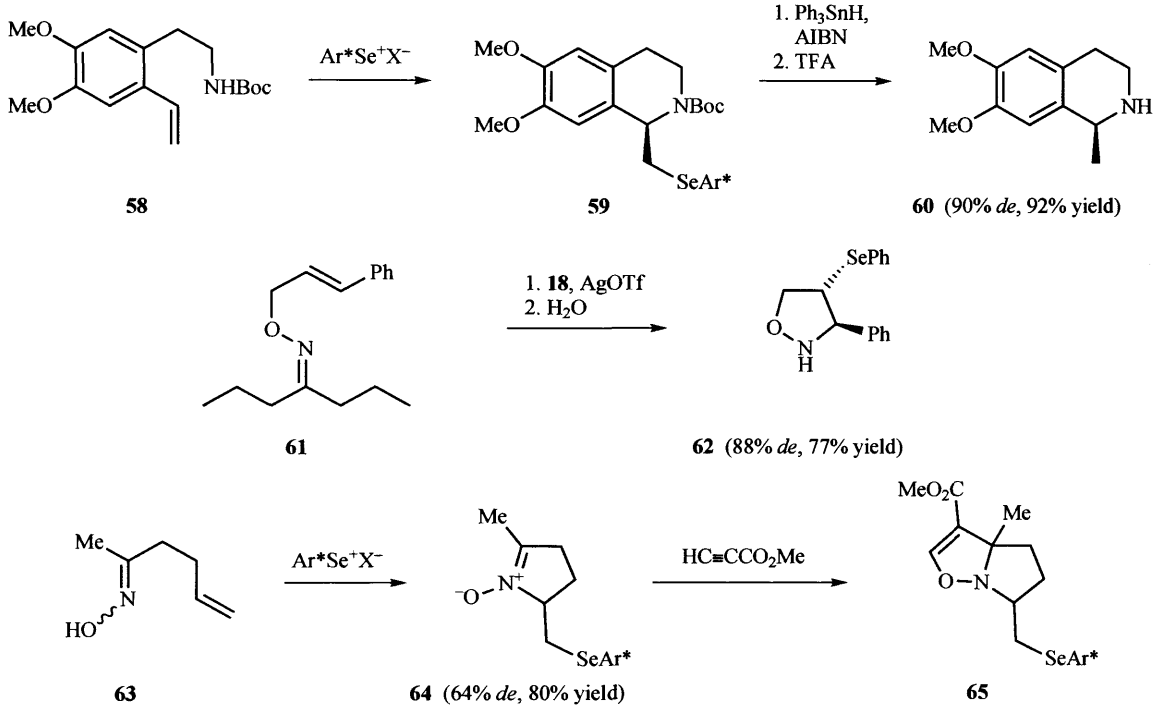
Carbon nucleophiles can also be employed in seleno-cyclization reactions. Starting with optically active β-hydroxyselenides **66**, available by ring-opening reactions of



Scheme 11.



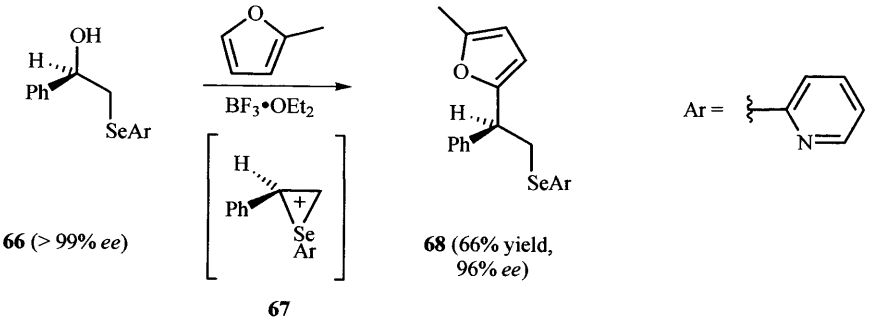
Scheme 12.



Scheme 13.

enantiomerically pure epoxides with selenium nucleophiles, addition products **68** can be obtained *via* the selective generation of seleniranium ions of type **67**. In order to obtain high stereoselectivities in the addition reactions, coordinating aryl moieties such as 2-pyridyl or bulky aryl moieties such as 2,4,6-tris-*tert*-butylphenyl must be employed in these reactions. Their use is essential to prevent racemisation during the reaction. The stereospecificity of these reactions has been found to also depend to a large extent on the aromatic nucleophiles involved [104, 105]. The aromatic nucleophile attacks selectively on the most substituted carbon atom of the seleniranium ion (Markovnikov addition product).

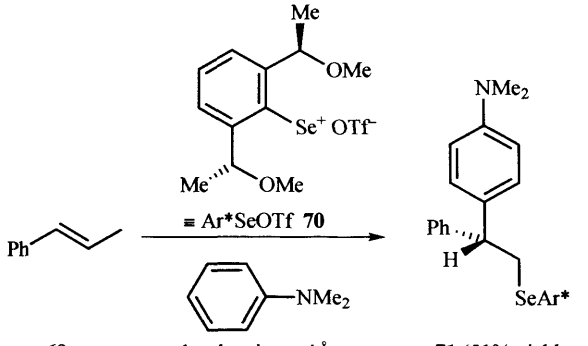
Good yields and high diastereoselectivities can also be obtained by carboselenenylation of β-methyl styrene **69** using the optically active reagent **70** as chiral selenium



66 (> 99% *ee*) **67** **68** (66% yield, 96% *ee*)

Scheme 14.

electrophile employing a range of aromatic compounds as nucleophiles. The structure of this electrophile is quite similar to diselenide **10**, but the selectivities obtained with **70** are much higher. The presence of 4Å molecular sieves is essential to obtain these products in high yields although the exact reason is still unknown. This method is convenient for the preparation of chiral hydrocarbons, which contain an aryl moiety at the stereogenic carbon atom. Not only hetero-aromatic compounds, but also electron-rich benzene derivatives such as *N,N*-dimethylaniline can be used as shown in Scheme **15**. Selectivities of up to 90% *de* have been obtained. The reaction is comparable to an asymmetric Friedel-Crafts alkylation of aromatic compounds with alkenes [106].

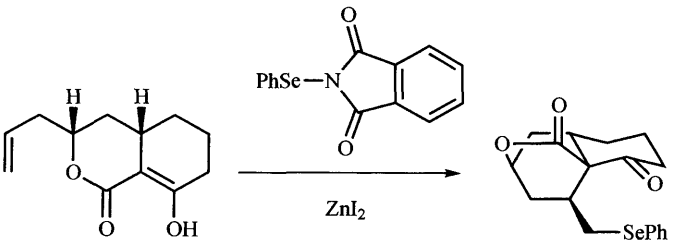


69 molecular sieves 4Å **71** (51% yield, 80% *de*)

Scheme 15.

3.6. Selenocyclizations with Carbon Nucleophiles

Cyclizations of β-dicarbonyl compounds have been investigated earlier [107, 108, 109, 110], recently it was shown that this reaction can be used for the preparation of tricyclic compounds such as **73** from precursor **72** [111].



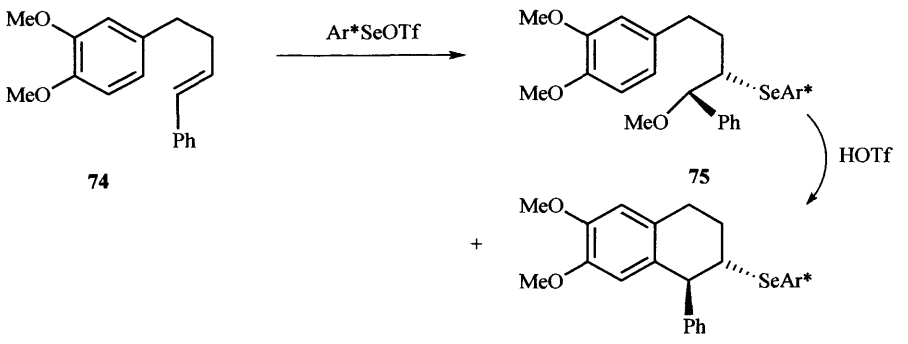
72 **73**

Scheme 16.

Even aromatic carbon atoms of electron-rich benzene derivatives can be used for such cyclizations. In cyclizations carried out by Déziel and coworkers the arene containing alkene **74** was reacted with the chiral selenium electrophile prepared from diselenide **16** in the presence of methanol. Firstly, the product of a methoxyselenenylation **75** was obtained with 98% *de* in a 1:1 ratio with the cyclized product **76**. Further treatment of **75** with triflic acid resulted in a complete conversion to **76**. It has been observed that a small amount of methanol is essential for obtaining a high selectivity, however, there is a competing reaction between the methoxylated and the cyclized product. Without methanol, the cyclization product **76** is obtained in low yields and with low diastereoselecitvites [112].

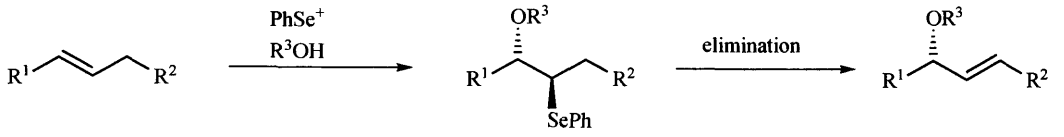
3.7. Catalytic Reactions

All the transformations described above need stoichiometric amounts of selenium-containing reagents. The addition or cyclization products are usually intermediates in



74 **75** **76**

Scheme 17.



Scheme 18.

synthetic sequences. Most target compounds do not contain a selenium moiety and there is the need for deselenenylation at some stage. Often this can be combined with a subsequent functionalization like substitution or elimination. Combinations of addition and deselenenylation reactions with only catalytic amounts of a selenium reagent are described now, whereas the use of chiral, selenium-containing compounds as ligands in catalysis is reviewed elsewhere [113].

It is possible to perform selenenylation – deselenenylation sequences with only catalytic amounts of selenium reagents. Such a reaction sequence will provide allylic ethers **79** as reaction products from the corresponding alkenes **77**. This sequence can be performed electrochemically, and the selenium electrophile is generated from catalytic amounts of diphenyl diselenide [114, 115]. It has been shown that the electrophilic selenium species can also be generated using diselenides and peroxosulfates together with copper (II) nitrate. Moderate yields of the allylic ethers or esters **79** have been obtained [116, 117].

Other reactions rely on the formation of the selenenyl sulfates with peroxodisulfates from the corresponding diselenides as electrophilic reagents for the initial addition reaction to alkenes. The addition products are then oxidized by an excess peroxodisulfate and the subsequent elimination reaction yields allylic compounds [20]. The first stereoselective example of such a reaction has been reported by Tomoda *et al.* using the enantiomerically pure diselenide **11** [45]. Good yields are obtained in cases when R^2 is an electron-acceptor substituent leading to α,β-unsaturated compounds of type **79**. Under similar experimental conditions, intramolecular versions of such catalytic transformations can lead to butenolides in good yields [118, 119]. Different chiral diselenides have been employed in this reaction and after careful optimization of the reaction conditions, enantioselectivities up to 75% (R^1 = Ph, R^2 = H, R^3 = Me in **79**) have been obtained [45, 52, 79, 120]. However, the turnover numbers are still small and further work is needed to improve the catalytic oxyselenenylation – elimination sequence.

In this review, we decribe the developments using enantiomerically pure selenium reagents as electrophiles in stereoselective synthesis. Various aspects of these reagents are summarized. Although high selectivities can now be obtained for some of these reactions, improved and novel selenium electrophiles will surely be developed in future to improve low or modest selectivities in selenenylation reactions.

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Catalytic Use of Selenium Electrophiles in Cyclizations

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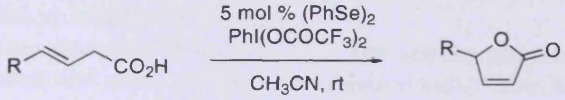
ABSTRACT



A new and convenient one-pot method for a catalytic addition–elimination reaction using selenium electrophiles has been developed. In the presence of 5 mol % diphenyl diselenide, [bis(trifluoroacetoxy)iodo]benzene in acetonitrile converted a range of (*E*)-3-butenoic acids into the corresponding butenolides in good yields.

Organic selenium compounds are frequently used as convenient reagents for introducing various functional groups to carbon−carbon double bonds and for constructing heterocyclic compounds via ring-closure processes. The mild reaction conditions usually associated with these reagents led to frequent use in organic chemistry. Some of these reactions suffer the drawback that the selenium reagent must be used in stoichiometric quantities and that the preparation of more advanced reagents requires several synthetic steps.[1]

We[2] and other research groups have reported the use of peroxydisulfates as oxidants in addition − elimination sequences,[3] but the turnover numbers are still small and the amount of catalyst is relatively high. Recently, we reported on an electrochemically induced selenenylation−deselenenylation sequence.[4] The use of hypervalent iodine compounds as oxidants to form selenium electrophiles from diselenides has been reported previously but has not yet been applied to catalytic reaction conditions.[5] Herein, we describe a convenient way to cyclize a range of β,γ-butenoic acids to the corresponding butenolides with catalytic amounts of selenium reagents. As butenolides are a class of biologically active compounds, different methodologies for their synthesis have been developed.[6]

Initial studies have been carried out using (*E*)-4-phenylbut-3-enoic acid **1a**, which is converted to 5-phenylfuran-2(5*H*)-one **2a**. A similar sequence has been described by Tiecco et al. using 10 mol % of diselenide and 3 equiv of peroxydisulfate as oxidant leading to the corresponding lactones in good yields.[3b] Tiecco also found that using 2 equiv of (diacetoxyiodo)benzene with diphenyl diselenide in acetonitrile gave cleanly the corresponding lactone.[7] The same transformation has been investigated recently by Denmark in great detail.[8] Thus, the reaction of acid **1a** with 1.05 equiv of different hypervalent iodine reagents in the presence of 5 mol % of diphenyl diselenide in acetonitrile was performed. The results are shown in Table 1. It was found that [bis-

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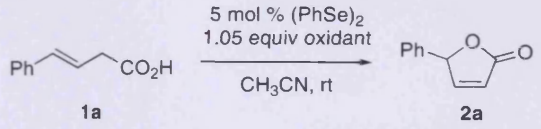
Table 1. Catalytic Cyclization of (*E*)-4-Phenylbut-3-enoic Acid **1a**



1a **2a**

entry	hypervalent iodine oxidant	**2a**, yield (%)
1	$PhI(OAc)_2$	27
2	$PhI(OCOCF_3)_2$	70
3	$C_6F_5I(OCOCF_3)_2$	59
4	IBA[a]	traces
5	FIBA[b]	50
6	IBX[c]	0

[a] 1-Hydroxy-1,2-benziodoxol-3-(*1H*)-one. [b] 5,6,7,8-Tetrafluoro-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide. [c] 1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide.

(trifluoroacetoxy)iodo]benzene produced butenolide **2a** in 70% yield, while the less reactive (diacetoxyiodo)benzene only gave 27% yield. The fluorinated and more soluble reagent [bis(trifluoroacetoxy)iodo]pentafluorobenzene[9] resulted in only 59% yield, whereas the cyclic derivative IBA as well as the iodine(v) reagent IBX[10] did not activate the diselenide sufficiently, and starting material was recovered. Only the more reactive cyclic FIBA[11] led to a 50% yield of **2a**.

The optimization of the solvent used in the catalytic reaction is summarized in Table 2. Complete conversion was

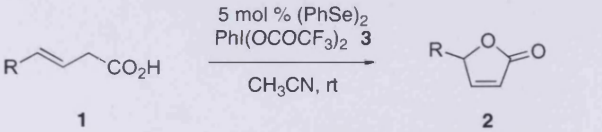
Table 2. Optimization of Solvents

entry	solvent	**2a**, yield (%)
1	CH_3CN	70
2	toluene	68
3	CH_2Cl_2	66
4	Et_2O	64
5	MeOH	20[a]
6	THF	15[a]

[a] Conversion by ^1H NMR.

observed in acetonitrile, toluene, and dichloromethane after a reaction time of 3 h; in the other solvents, starting material **1a** remained after the same reaction time. The scope was further investigated by using different substituted β,γ-unsaturated carboxylic acids in this catalytic reaction (Table 3).

Table 3. Catalytic Cyclization of (*E*)-β,γ-Unsaturated Carboxylic Acids **1** to Butenolides **2**



1 **2**

entry	R	**2**, yield (%)
1	**1a**, Ph	70
2	**1b**, CH_2Ph	59
3	**1c**, 4-MeC_6H_4	57
4	**1d**, 4-BrC_6H_4	54
5	**1e**, 2-naphthyl	60
6	**1f**, 1-(2-methylnaphthyl)	65
7	**1g**, *n*-C_3H_7	65
8	**1h**, *n*-C_4H_9	65
9	**1i**, *n*-C_5H_{11}	49
10	**1j**, *n*-$C_{10}H_{21}$	96

The starting materials required for these reactions were obtained either from a Stille cross-coupling reaction with a stannyl ester[12] and an aryl halide or by a modified Knoevenagel condensation[13] using a range of aldehydes and malonic acid. As highest yields have been observed using [bis(trifluoroacetoxy)iodo]benzene **3** in acetonitrile, these conditions were used in all experiments.

The successful conversion of these butenoic acids into the corresponding butenolides prompted experiments to identify the active catalytic species responsible for their formation. The ^1H, ^{13}C, and ^{19}F NMR spectra of a mixture of diphenyl diselenide and [bis(trifluoroacetoxy)iodo]benzene **3** (1:1, in $CDCl_3$) were recorded. The ^1H and ^{13}C NMR indicated a clear formation of iodobenzene. The ^{19}F NMR showed a chemical shift of $\delta = -75$ ppm, which can be assigned to phenylselenenyl trifluoroacetate **4**. Compound **4** was independently prepared from phenylselenenyl chloride and silver trifluoroacetate, and NMR experiments confirmed the results suggesting that phenylselenenyl trifluoroacetate **4** is the active catalytic selenenylating species in this reaction.

The reaction is initiated by the oxidation of diphenyl diselenide by the hypervalent iodine reagent **3** to form phenylselenenyl trifluoroacetate **4** (Scheme 1). Reagent **4** then reacts with the β,γ-unsaturated carboxylic acid **1** in a cyclization reaction to yield compound **5**. The selenide in lactone **5** can then be activated for elimination either by [bis(trifluoroacetoxy)iodo]benzene **3** or by phenylselenenyl trifluoroacetate **4**. Treatment of independently synthesized **5** (R = Ph)[14] with **3** and **4** revealed that a fast elimination proceeded only with [bis(trifluoroacetoxy)iodo]benzene **3**, although some elimination product **2** was found also in the stoichiomeric reaction of **5** and **4**. We propose that the

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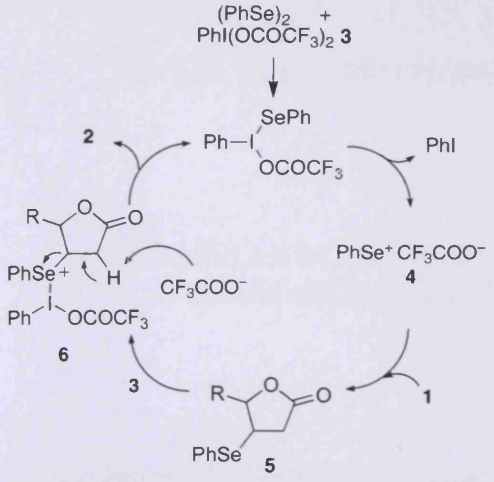
Scheme 1. Proposed Catalytic Cycle



catalytic cycle proceeds mainly via the intermediate **6** to the butenolide **2** in an elimination process while regenerating the selenium electrophile **4**.

When only 2 mol % of the catalyst was used in this reaction, the yield of **2a** was reduced to 32% together with a side product **7** (Figure 1). The formation of **7** was increased

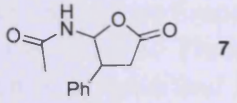


Figure 1. Side product **7** obtained without catalyst.

to 43% when the reaction was performed without diphenyl diselenide as catalyst. It seems that the hypervalent iodine compound reacted as an electrophile, and after cyclization, a phenyl migration took place and the resulting carbocation was captured by acetonitrile. Such phenyl migrations in cyclization reactions of substituted styrene derivatives with hypervalent iodine reagents have already been observed.[15]

The development of organoselenium reagents for asymmetric synthesis has produced a range of chiral diselenides, which are efficient in the transfer of chiral information.[1a,c]

Catalytic quantities of several enantiomerically pure diselenides were used in place of diphenyl diselenide with identical reaction conditions (Scheme 2). Substrate **1j** was chosen as it gave the highest yields in the range of examples.

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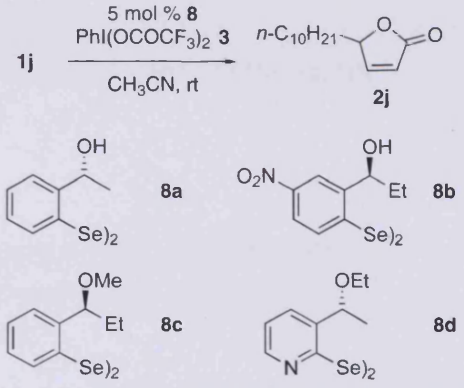
Scheme 2. Use of Enantiomerically Pure Diselenides **8**



It was found that longer reaction times were required, lower yields were observed, and the enantioselectivity was low. The use of diselenides **8b** and **8c** resulted in almost racemic product **2j**, whereas with **8a** the butenolide **2j** was obtained with an enantiomeric ratio (er) of 57:43 (84% yield). Diselenide **8d** led to 61:39 er (46% yield) of **2j** in the catalytic reaction.[16] In a stoichiometric reaction, performed at −100 °C, the lactone **2a** was obtained in a enantiomeric ratio of 86:14,[17] this ratio changed to 63:37 when the reaction was performed at room temperature. Further work is required to scan a broader range of diselenides and substrates for the asymmetric catalytic reaction. Sulfur-containing diselenides[3h] and a camphor-based compound[18] have been used for the peroxydisulfate-promoted reaction to butenolides and up to 78:22 er have been obtained.

We have developed a novel method for the synthesis of butenolides **2** from butenoic acids **1** using catalytic amounts of diphenyl diselenide. [Bis(trifluoroacetoxy)iodo]benzene **3** as stoichiometric oxidant in acetonitrile gave the highest yields. Using 5 mol % of the catalyst is critical since lower catalytic loadings resulted in a side product. Further work is required to achieve higher enantioselectivities in this reaction.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071223Y

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CATALYTIC ADDITION-ELIMINATION REACTIONS TOWARDS BUTENOLIDES

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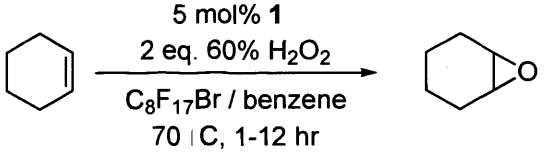
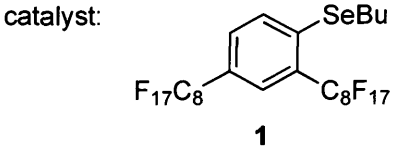
A wide range of selenium-containing reagents are known to undergo addition – elimination reactions under different reaction conditions. We report on selenium electrophiles which are regenerated under the reaction conditions employed and therefore only catalytic amounts of these reagents are necessary.

Keywords: butenolides, diselenides, selenium electrophiles, stereoselective synthesis

For several decades now, selenium reagents have attracted growing interest for their application in organic synthesis.[1,2] Selenium dioxide is a well known and traditionally used oxidising agent for alkenes, ketones and other substrates, but it wasn't until 1977 that Umbreit and Sharpless found that only catalytic amounts of selenium dioxide could be used to functionalize alkenes.[3] Phenylseleninic acid (Ph-SeO_2H) has been used as a catalyst for the epoxidation of alkenes and Baeyer-Villiger oxidations. Also polystyrene bound arylseleninic acid can be used in catalytic amounts in the oxidation of alkenes, ketones and aromatic systems, which has avoided the contamination of reaction products. It was found that the catalyst is stable to the reaction conditions and can be recycled with no apparent loss of activity.[4] Knochel and coworkers reported the use of organoselenium reagents containing perfluoroalkyl substituents in flourous solvents in similar transformations.[5] The butylselenide pre-catalyst **1** is oxidized to the corresponding selenenic acid under the reaction conditions while the fluorous biphasic catalysis allowed efficient separation of the catalyst from the reaction mixture. The catalyst could be recycled more than ten times without either decrease in yields or increase in reaction times. A typical epoxidation is shown below.

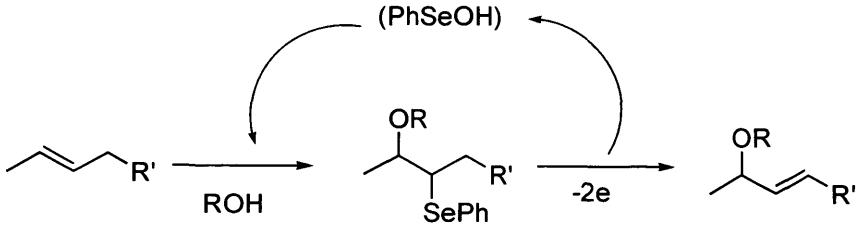




1

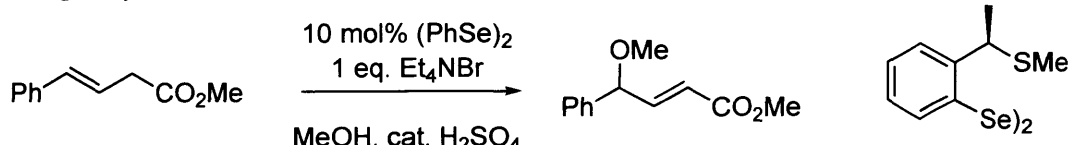
Selenenylation – deselenenylation sequences provides double bond transpositioned allylic alcohols and ethers from alkenes. The sequence involves two steps: Selenenylation with PhSeX (X = Cl, OR, NR_2) followed by oxidation with O_3, $NaIO_4$, or peroxides (H_2O_2, *t*-BuOOH, *m*CPBA) where stoichiometric amounts of PhSeX and large excess of oxidant are normally required. It was found by Torii et al. that this could be achieved in a single step by electrochemical generation of selenium electrophiles from catalytic amounts of diphenyl diselenide.[6] This was achieved without the formation of phenylseleninic acid and selenamide and in the absence of peroxides. Electrochemically generated phenylselenenyl electrophiles

react regioselectively with alkenes producing the selenide, followed by electrochemical oxidation to provide the corresponding selenoxide which instantly undergoes *syn*-elimination to give the desired product.



The selenenylation reagent is regenerated *in situ* and the transformation is enhanced by the addition of metal salts such as magnesium sulfate. This is increasing the yields of the corresponding products by preventing the reaction to phenylselenenic acid and phenylseleninic acid both by disproportionaton and electrooxidation.

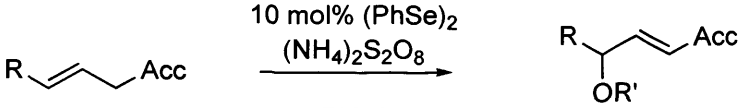
Further developments by Wirth et al. showed that the electrochemical oxyselenenylation-deselenenylation conversion of alkenes into allylic compounds can be successfully achieved with catalytic amounts of diphenyl diselenide (10 mol%) or other enantiomerically pure diselenides using acceptor substituted alkenes such as **2** as substrates.[7] Tetraethylammonium bromide was employed in the reaction to act as both, a redox catalyst and an electrolyte. The reaction is initiated by the anodic oxidation of bromide to bromine which reacts with the diselenide to form the corresponding arylselenenyl bromide. After addition to the alkene and formation of the selenide, a second equivalent of bromine forms an unstable tetravalent selenium derivative which acts as a good leaving group thus generating the elimination product **3**. Compound **3** has been obtained with up to 66% *ee* with 10 mol% of diselenide **4** in place of diphenyl diselenide in this reaction.



2 **3** **4**

The reaction sequence developed by Tomada et al. employs nitrogen-containing enantiomerically pure selenium reagents as catalysts in the presence of copper(II) nitrate for the conversion of alkenes into the allylic compounds.[8] After screeing a range of oxidising agents it was found that sodium persulfate was best for the catalytic reaction. Higher conversions were observed using 3Å molecular sieves, showing that the removal of water is essential for the reaction to proceed. But still the reaction is sluggish and turnover numbers are low.

This prompted work by Tiecco et al. to convert α,β-unsaturated esters, amides and nitriles into α-alkoxy or α-hydroxy derivatives.[9] They developed a multistep one-pot synthesis using excess ammonium persulfate and using only catalytic amounts of diphenyl diselenide. They have shown that the intermediate alkylphenyl selenides reacts with the persulfates regioselectively towards the elimination products **5**, which were obtained in good yields (23-90%) in just a few hours. An electron-withdrawing group in the allylic position is essential for the success of the reaction as simple unsubstitued alkenes gave rise to product mixtures.



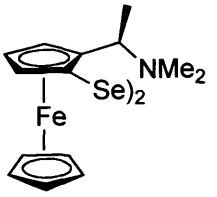
5 (Acc: CO_2Me, CN, $CONMe_2$)
(R: H, Me, Et, Ph, R': H, Me)

Tiecco et al. also carried out intermolecular versions of this catalytic oxidation to produce butenolides, which are obtained from the reaction the reaction of the easily available β,γ-unsaturated acids with catalytic amounts of diphenyl diselenide and an excess of ammounium persulfate in acetonitrile.[10] The carboxy group is found to act as both an internal nucleophile and as an electron withdrawing group in the γ position and again produces good yields in relatively short reaction times. It was also observed in some cases that better yields were obtained with the catalytic reaction compared to using stoichiometric amounts of diphenyl diselenide.

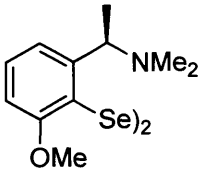
Tiecco and coworkers has taken this one step further and utilises the previous reaction conditions to convert alkenols to the corresponding 2,5-dihydrofurans.[11] Excellent yields were obtained (90-96%) with traces of a side product. The cyclisation - elimination process gives rise to two stereoisomeric of the 2,5-dihydrofurans in good yields, where the selectivity reflects the steric demands in the approach of the electrophile to the π-bond. *Erythro*-unsaturated alcohols yield *trans*-2,5-dihydrofurans whereas the *threo*-unsaturated alcohols gave the *cis*-products. The observed stereoselecitvities of the process imply that only the major isomer of the intermediate undergoes elimination to afford the corresponding 2,5-dihydrofurans. When ammonium persulfate was reacted with the major isomer of the intermediate the desired product was quantitatively transformed, where as the minor isomer gave unidentified products, showing the *cis* relationship renders the approach of the persulfate anion to the selenium atom more difficult.

Tomoda et al. reported the first catalytic asymmetric conversion of *trans*-β-methyl styrene into optically active allylic ethers using diaryl diselenides with a chiral pyrrolidine moiety in the *ortho*-position.[12] Yields of 24% and enantioselectivities of up to 32% *ee* were observed using previous literature methods and with copper(II) nitrate. The moderate asymmetric induction is believed to be due the strong interaction between the electrophilic selenium atom and the tertiary nitrogen of the chiral pyrrolidine moiety.

The highest diastereoselectivities (96% *de*) of asymmetric methoxyselenenylation of alkenes together with excellent chemical yields (99 %) were achieved using ferrocenyl selenium triflates.[13] Diselenide **6** is the precursor for the electrophile and when applied to a range of alkenes all resulted in high yields (96-99 %) and moderate to high diastereoselectivities (15-96 %). It was observed that sterically large groups in the alkene are necessary to achieve high facial selectivity.



6

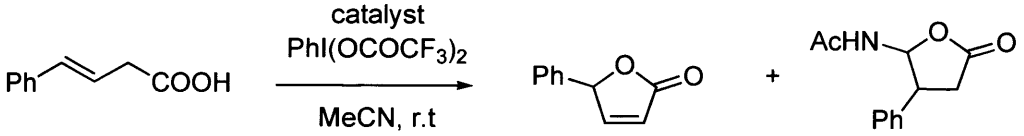


7

In 1998 Wirth and coworkers used peroxydisulfates for the generation of the nitrogen containing selenium electrophile for the catalytic oxyselenenylation-elimination reaction with

trans-β methylstyrene.[14] It is known that metal ions can accelerate the decomposition of peroxo disulfates and varying the metal salts was found to have a strong influence on the stereoselectivity with nickel nitrate being the most effective salt with ee's of up to 71% and when diselenide **7** was used enantioselectivities of up to 75% was observed. These are the highest enantioselecitivities obtained for the catalytic oxyselenenylation-elimination reaction so far obtained, but a major drawback was again the low turnover number.

In recent work on the cyclisation of alkenoic acids **8** into the corresponding butenolides **9** we found that acetonitrile, 5 mol% diphenyl diselenide as a catalyst and bis(trifluoroacetoxy)-iodobenzene as the oxidant were the optimum conditions for this reaction procedure.[15] Lower catalytic loading resulted in the rearranged products **10** because the hypervalent iodine reagent then directly reacts with the substrate.



8 **9** **10**

Full conversion to the products was observed only with diphenyl diselenide. Diphenyl disulfide showed less reactivity and also diphenyl ditelluride did react even slower. This lower reactivity is then reflected in the increased amount of rearranged product **10** which results from the direct reaction of alkene **8** with the hypervalent iodine oxidant. If performed in acetonitrile, the capture of the intermediate phenonium ion by acetonitrile and subsequent hydrolysis led to the formation of the by-product **10**. A range of other dichalcogen catalysts was also tested and the results are summarised in Table I.

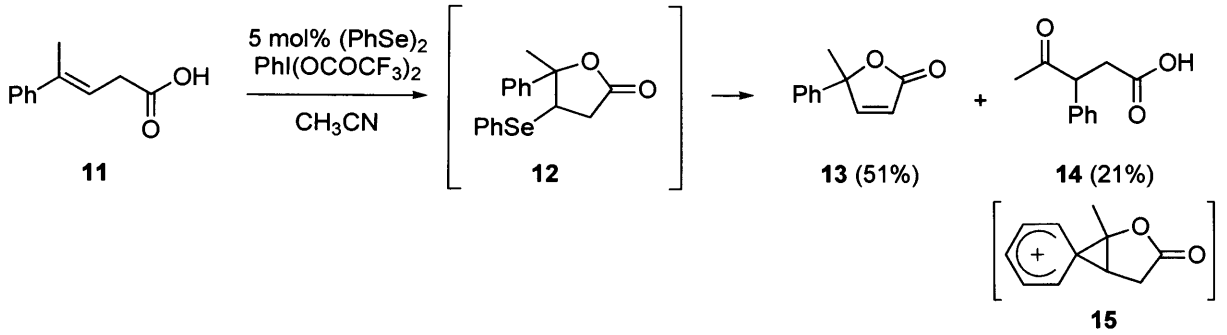
TABLE I Different Dichalcogen Catalysts for the Addition / Elimination Sequence

Catalyst	**13** : **14** (Ratio)	Yield
$(PhSe)_2$	100:0	70%
$(MeSe)_2$	100:0	56%
$(PhS)_2$	25:75 [a]	-
$(MeS)_2$	25:75 [a]	-
$(PhTe)_2$	28:72 [a]	-

[a] determined by NMR

From these results it can be clearly seen that diselenides are the better catalysts where diphenyl diselenide having superior yields to dimethyl diselenide. The other results indicate that the other catalysts are not as active as the diselenides and give mainly the rearranged product that correlate with the results of using lower catalytic loadings with diphenyl diselenide or no catalyst at all.

For the investigation of trisubstituted alkenes in such cyclisation reactions, (*E*)-4-phenylpent-3-enoic acid **11** was synthesised. The cyclisation resulted in a mixture of products and compounds **13** and **14** were observed.

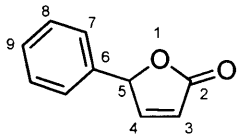


After the initial selenolactonisation to **12** the elimination to **13** occurred similar to disubstituted alkene substrates. 4-Oxo-3-phenylpentanoic acid **14** was found as a by-product, but without the diselenide catalyst, **14** was the only product being formed. The reaction of bis(trifluoroacetoxy)iodobenzene with **11** leads, after cyclisation, to a phenyl migration via phenonium ion **15** and reaction with trifluoroacetate or water and subsequent ring-opening of the ketal results in the formation of **14**. Compound **12** was also synthesised independently to investigate its further oxidation. The elimination product **13** (86% yield) was the only product observed and no rearranged product **14** was detected. The rearrangement to **14** therefore occurs only via the direct reaction of **11** with bis(trifluoroacetoxy)iodobenzene.

Acknowledgement
We are thankful for the high-resolution mass spectrometric data obtained from the EPSRC National Mass Spectrometry Service Centre, Swansea, UK. We thank EPSRC for support.

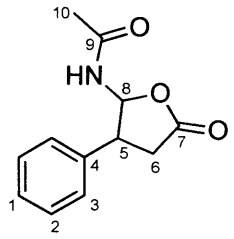
Experimental
General: ^{1}H and ^{13}C NMR experiments were carried out on a Bruker 400-DPX spectrometer. IR measurements were taken using a Perkin-Elmer 1600FTIR spectrometer as a liquid film. Low resolution mass spectrometry was carried out using a Varian Saturn 2 GC-MS. Flash chromatography was carried out using Fisher Silica Gel (35-70 mesh). Preparative thin layer chromatography was carried out using Merck silica gel 60 F254 on glass plates. All solvents used were dried and purified by standard methods. Reactions requiring the exclusion of air were carried out under an atmosphere of argon in oven dried glassware.

5-Phenylfuran-2(5*H*)-one (9)[16]



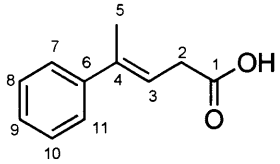
Colorless oil, (24 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (1H, dd, *J* 5.5, 1.6 Hz, H-4), 7.40–7.35 (3H, m, H-7,9), 7.30–7.25 (2H, m, H-8), 6.23 (1H, dd, *J* 5.5, 2.0 Hz, H-5), 6.01 (1H, dd, *J* 2.0, 1.6 Hz, H-3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.1 (C-2), 155.9 (C-4), 134.3 (C-6), 129.4 (C-9), 129.2 (2C, C-8), 126.5 (2C, C-7), 120.1 (C-3), 84.4 (C-5) ppm.

***N*-(5-Oxo-3-phenyltetrahydrofuran-2-yl)ethanamide (10)**



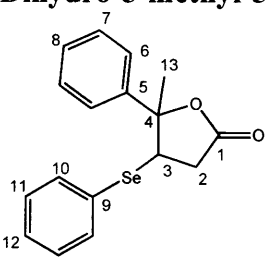
Colorless oil, (29 mg, 28%); IR (film): ν_{max} = 3299, 1782, 1678, 1541, 1372, 1260, 1166, 943, 826, 732, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.12–7. 38 (5H, m, H-1,2,3), 6.15 (1H, t, *J* 8.8 Hz, H-8), 3.55 (1H, q, *J* 9.1 Hz, H-5), 3.00 (1H, dd, *J* 8.8, 17.6 Hz, H-6a), 2.70 (1H, dd, *J* 10.7, 17.6 Hz, H-6b), 1.95 (3H, s, H-10) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.3 (C-7), 171.4 (C-9), 136.9 (C-4), 129.3 (2C, C-2), 128.2 (C-1), 127.1 (2C, C-3), 86.1 (C-8), 46.9 (C-5), 37.2 (C-6), 23.2 (C-10) ppm; MS: *m/z* (%): 160 (100), 178 (58), 201 (70), 220 (18); HRMS $C_{12}H_{14}NO_3$: found 220.0979, calcd. 220.0974.

(*E*)-4-Phenylpent-3-enoic acid (11):[17]



2-Phenylpropanal (10 mmol, 1.34 g) and malonic acid (10 mmol, 1.04 g) was mixed thoroughly with chromatography grade silica (200 mesh, 1 g) and the resulting powder in a microwave tube was subjected to microwave irradiation (300 W, 50 °C, 10 min). The reaction mixture was allowed to cool to room temperature and extracted with dichloromethane (30 mL). The solvent was removed under reduced pressure the compound was purified by flash chromatography eluting with petroleum ether:ethyl acetate:acetic acid (90:8:2).[18]
White solid (689 mg, 41 %); m.p. = 56–58 °C; IR (film): ν_{max} = 3583, 3055, 2360, 2341, 1699, 1444, 1392, 1287, 939, 818, 748, 696, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.45 (2H, m, H-7,11), 7.32-7.37 (2H, m, H-8, 10), 7.26-7.29 (1H, m, H-9), 5.96 (1H, td, *J* 7.0, 1.4 Hz, H-3), 3.34 (2H, d, J 7.2 Hz, H-2), 2.13 (3H, s, H-5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 178.2 (C-1), 142.9 (C-6), 138.7 (C-4), 128.8 (C-8, 10), 128.3 (C-9), 125.8 (C-7, 11), 118.4 (C-3), 34.2 (C-2), 16.3 (C-5) ppm; MS: *m/z* (%): 176 (44), 131 (100), 91 (38); HRMS $C_{11}H_{12}O_2$: found 176.0830, calcd. 176.0837.

Dihydro-5-methyl-5-phenyl-4-(phenylselenyl)furan-2(*3H*)-one (12)



To a solution of diselenide (0.6 mmol) in acetonitrile (10 mL) (*E*)-4-phenylbut-3-enoic acid (1.2 mmol) was added, followed by bis(trifluoroacetoxy)iodobenzene (0.6 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was

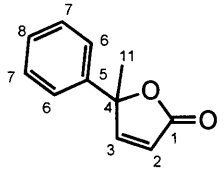
purified immediately by flash column chromatography eluting with ethyl acetate : light petroleum (2 : 8) to yield the addition products.

IR (film): ν_{max} = 3016, 2918, 2860, 1608, 1472, 1375, 1037, 835, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.43 (4H, m, H-Ar), 7.15-7.30 (6H, m, H-Ar), 3.95 (1H, t, *J* 7.5 Hz, H-3), 2.85 (1H, dd, *J* 18.0, 7.8 Hz, H-2a), 2.70 (1H, dd, *J* 18.0, 7.3 Hz, H-2b) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 174.2 (C-1), 143.2 (C-5), 134.9 (2C, C-10), 129.5 (2C, C-11), 128.7 (2C, C-7), 128.5 (C-12), 128.1 (C-8), 127.7 (C-9) 124.3 (2C, C-6), 89.0 (C-4), 48.2 (C-3), 37.8 (C-2), 25.7 (C-13) ppm; MS: *m/z* (%): 332 (M^+, 8), 314 (20), 234 (10), 184 (26), 159 (56), 131 (100), 103 (35), 91 (9), 77 (70); HRMS $C_{17}H_{16}O_2Se$: found 332.0314, calcd. 332.0316.

General procedure for the catalytic reaction:

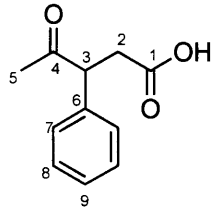
To a solution of diphenyl diselenide (5 mol%, 3.4 mg, 0.01 mmol) in acetonitrile (3 mL) was added the β,γ-unsaturated acid (0.22 mmol), followed by bis(trifluoroacetoxy)iodobenzene (100 mg, 0.23 mmol) and the mixture stirred under argon at room temperature until TLC showed no remaining starting material. The solvent was then evaporated under reduced pressure and the residue was purified immediately by flash column chromatography eluting with ethyl acetate : light petroleum (2 : 8) to yield the cyclisation products.

5-Methyl-5-phenylfuran-2(5*H*)-one (13):[19]



^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (1H, d, *J* 5.5 Hz, H-3), 7.20-7.40 (5H, m, H-6,7,8), 5.98 (1H, d, *J* 5.5 Hz, H-2), 1.78 (3H, s, H-11) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.4 (C-1), 160.4 (C-3), 139.3 (C-5), 128.9 (2C, C-7), 128.4 (C-8), 124.8 (2C, C-6), 119.4 (C-2), 88.9 (C-4), 26.4 (C-11) ppm.

4-Oxo-3-phenylpentanoic acid (14):[20]



^1H NMR (400 MHz, $CDCl_3$): δ = 7.20-7.40 (5H, m, H-7,8,9), 4.10 (1H, dd, *J* 9.8, 4.7 Hz, H-3), 3.20 (1H, dd, *J* 17.4, 9.9 Hz, H-2a), 2.50 (1H, dd, *J* 17.4, 4.7 Hz, H-2b), 2.05 (3H, s, H-5) ppm; ^{13}C NMR (63 MHz, $CDCl_3$): δ = 206.8 (C-4), 177.8 (C-1), 142.9 (C-6), 128.9 (2C, C-7), 127.9 (2C, C-8), 127.3 (C-9), 54.6 (C-3), 36.7 (C-5), 28.8 (C-2) ppm.

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