New Reactions of Cyclic Oxygen, Nitrogen and Sulfur Acetal Derivatives

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I, Samuel Edward Mann confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

This thesis describes the development of new reactions of cyclic oxygen, nitrogen and sulfur acetal derivatives and their applications in a diverse range of synthetic organic and organometallic chemistry. Detailed herein are advances in three main areas of acetal chemistry, namely: studies towards a new methodology for the synthesis of medium ring heterocycles; the use of thioacetals as directing groups for the palladium-mediated oxidation of olefins; and multi-component reactions for the synthesis of drug-like heterocyclic compounds. A brief overview of the chemistry of cyclic acetal derivatives is given in the first chapter, followed by a chapter on each of the three areas investigated. Relevant introductory literature is reviewed at the beginning of each chapter.

Firstly, the ring expansion chemistry of unsaturated cyclic oxygen, nitrogen and sulfur acetal derivatives was explored for the development of a new methodology for the synthesis of medium ring heterocycles. This methodology has thus far proved unsuccessful in the synthesis of medium rings, although several interesting and unusual transformations were observed, such as the unexpected formation of an intriguing bicyclic enaminium salt.

The use of thioacetals as directing groups for the palladium-mediated oxidation of terminal olefins was also explored, leading to the evolution of a new methodology for the catalytic, regioselective formation of either vinyl or allylic acetates. Dithianes were shown to stabilise intermediates in the allylic oxidation pathway, allowing their structure elucidation and characterisation by low-temperature NMR spectroscopy and in one case X-ray crystallography. This enabled a detailed mechanistic study leading to the observation of two finely balanced, divergent reaction mechanisms.

Finally, building upon previously unpublished results, a number of three and four-component reactions were investigated, giving drug-like α-aminoamides; this methodology was applied to the synthesis of some medium ring heterocycles.

Contents

Ac	Acetyl
acac	Acetylacetonyl
Ar	Aryl
Boc	*tert*-Butyl carbamate
Bu	Butyl
Bn	Benzyl
bpy	2,2'-Bipyridyl
p-BQ	*p*-Benzoquinone
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat.	Catalytic
coll	2,4,6-Trimethylpyridyl
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
dec.	Decomposition
DET	Diethyltartrate
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DIEA	Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	*N*,*N*-Dimethylaminopyridine
DMBQ	Dimethylbenzoquinone
DMF	*N*,*N*-Dimethylformamide
DMM	Dimethoxymethane
dmphen	2,9-Dimethyl-1,10-phenanthroline
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphoryl azide
E	Electrophile
ee	Enantiomeric excess
EDMS	Ethyldimethylsilyl
EPHP	1-Ethylpiperidine hypophosphite
Et	Ethyl
eq	Equivalents
Grubbs I	Benzylidene-*bis*(tricyclohexylphosphine)dichlororuthenium
HMBC	Heteronuclear multi bond coherence
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
^{i}Pr	Isopropyl
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
KHMDS	Potassium hexamethyldisilazide
Me	Methyl
MNBA	2-Methyl-6-nitrobenzoic anhydride
m.p.	Melting point

Ms	Mesyl
MW	Microwaves
n	Integer number
NBS	*N*-Bromosuccinimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser enhancement
Nu	Nucleophile
o-	Ortho
p-	Para
Ph	Phenyl
PMA	Phosphomolybdic acid
PhBQ	Phenylbenzoquinone
ppm	Parts per million
RCM	Ring-closing metathesis
rt	Room temperature (19-22 °C)
t or *tert*	Tertiary
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
UCL	University College London
UV	Ultraviolet

First of all, I would like to thank my supervisor Dr. Tom Sheppard for giving me the opportunity to work on this project. As well as the motivation and continued support he has given me throughout my time in the group, his knowledge and enthusiasm have been a source of inspiration from the start.

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For my parents

1. Introduction to the Chemistry of Cyclic Acetals

Derived from the condensation of two molecules of an alcohol with either an aldehyde or a ketone, the acetal moiety is composed of a *gem*-diether at an sp^3 hybridised carbon atom.[1] The terms acetal and ketal describe *gem*-diethers derived from aldehydes and ketones respectively, although both are often grouped under the former term. In the context of this thesis, the term oxygen, nitrogen or sulfur acetal derivative will serve to describe any *gem*-*O, N*- or *S*-disubstituted sp^3 carbon atom. Some examples of naturally occurring and biologically important *O, N*- and *S*-acetal and hemiacetal derivatives are shown below in figure **1.1**.[2-10]

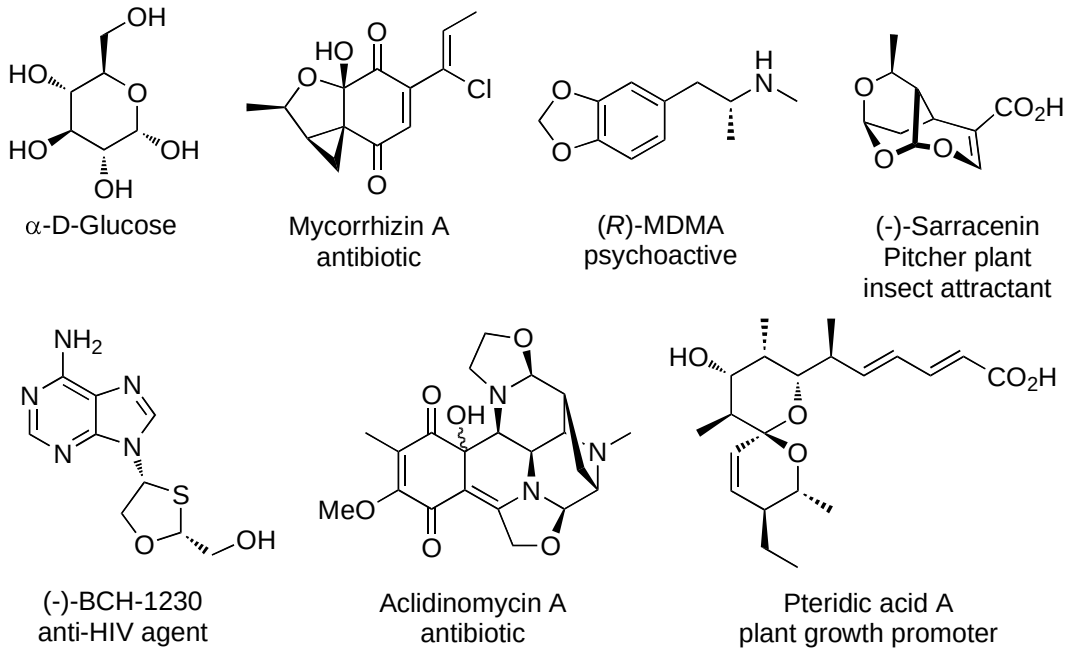


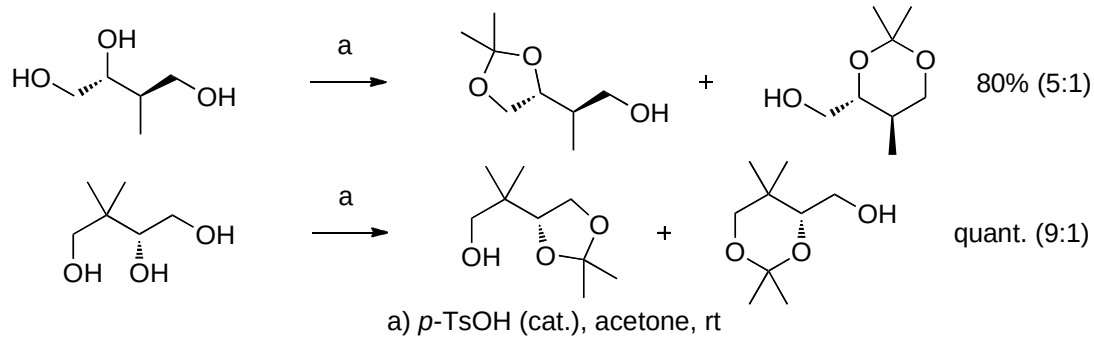
Figure 1.1

1.1 Cyclic Acetals as Protecting Groups

Due to their greater stability to a range of basic, nucleophilic and redox conditions, cyclic acetals are most commonly used as protecting groups for their parent diols and carbonyl compounds.[11]

Formed by acid-catalysed condensation with acetone, acetonides are among the most common protecting groups for 1,2- and 1,3-diols.[12] They are both easily prepared and readily cleaved under mildly acidic conditions, making them excellent protecting groups in the multi-step syntheses of molecules with sensitive functional groups. The

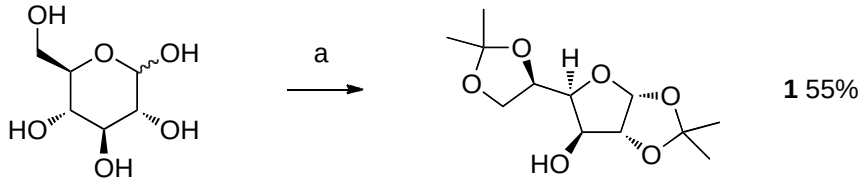
preparation of acetonides derived from triols usually results in the 1,2-acetonide being favoured over the 1,3-derivative (scheme **1.1**).[13,14]



a) *p*-TsOH (cat.), acetone, rt

Scheme 1.1

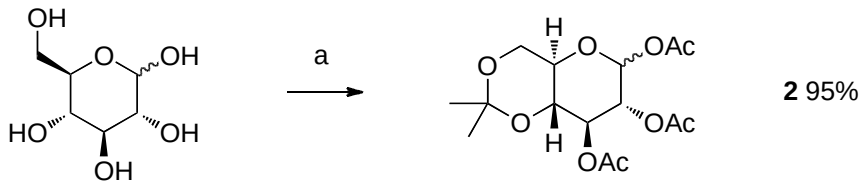
The selective protection of 1,2- and 1,3-diols is central to carbohydrate chemistry and a number of elegant methods have therefore been developed for this purpose.[15] For example, as with the linear triols discussed above, D-glucose undergoes selective 1,2-acetonation with acidified acetone to give the thermodynamically favoured diisopropylidene diacetal **1** (scheme **1.2**).[16]



a) H_2SO_4 (cat.), acetone, reflux

Scheme 1.2

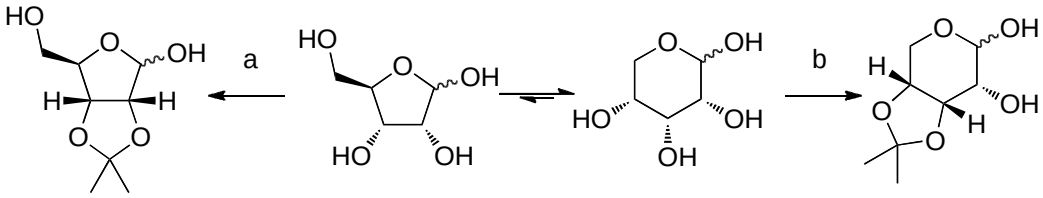
Under kinetic control however, the same monosaccharide selectively undergoes acetonation at the primary alcohol to give 1,3-acetonide **2** (scheme **1.3**).[17] Formation of acetonides by this method is often favoured over the use of acidified acetone as it is generally higher yielding and employs much milder reaction conditions.[18]



a) 2-Methoxypropene (2 eq), *p*-TsOH (cat.), DMF, 0 ^{o}C, then Ac_2O

Scheme 1.3

The difference between kinetic and thermodynamic control in sugar protection is nicely demonstrated by the selective acetonation of D-ribose (scheme **1.4**). In solution, this pentose exists mainly as its pyranose isomer, resulting in the formation of **4** upon acetonation under kinetic control.[19] Conversely, under more forcing conditions, the thermodynamically favoured product **3** predominates.[20]

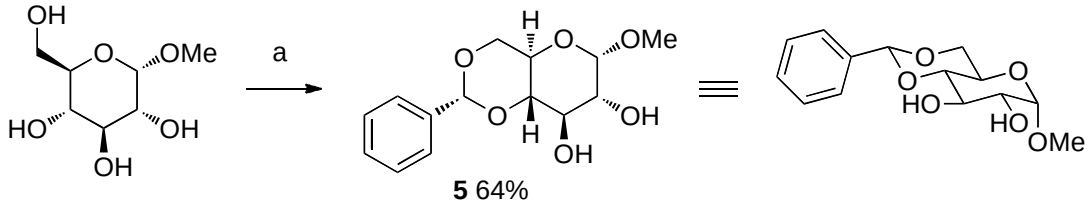


3 70% **4** 50%

a) *p*-TsOH, acetone, reflux; b) 2-MeO-C_3H_5 (2 eq), *p*-TsOH (cat.), DMF, 0 °C

Scheme 1.4

Benzylidene acetals can be used to selectively protect 1,3-diols in the presence of other hydroxyl groups (scheme **1.5**). For example, treatment of methyl-α-D-glucopyranoside with benzaldehyde dimethyl acetal in the presence of an acid catalyst gives the 1,3-benzylidene acetal **5** selectively.[21] Formation of the six-membered acetal allows the phenyl group to sit in an equatorial position of the resultant 6,6-fused ring system, minimising steric interactions in this low energy conformation.

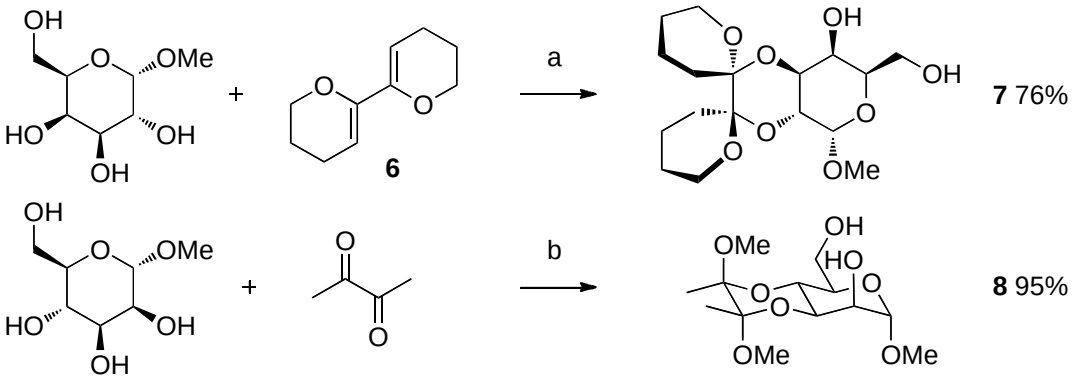


5 64%

a) *p*-TsOH (cat.), benzaldehyde dimethyl acetal, DMF, 1 h, 65 °C

Scheme 1.5

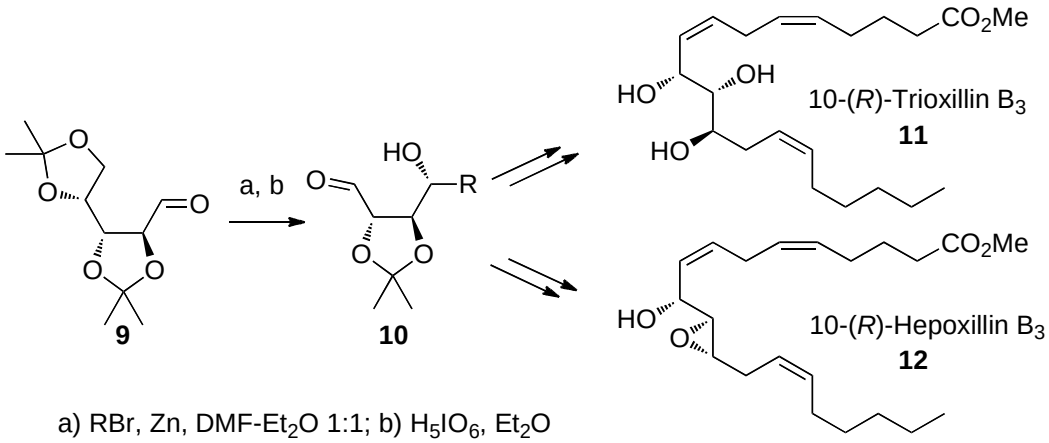
A selective protection strategy for *trans*-1,2-diols was developed by Ley and co-workers that employs the formation of dispiroketal **7** from *bis*-dihydropyran **6** (scheme **1.6**).[22] This diacetal species benefits from the stabilisation of multiple anomeric effects, which explains its ready formation even in the presence of other hydroxyl groups. This strategy was later expanded to the use of butanedione as the protecting agent to give butane diacetal **8**, with two molecules of methanol providing the added anomeric stabilisation.[23,24]



a) CSA (cat.), $CHCl_3$, 1.5 h, reflux, then ethylene glycol, 0.5 h, reflux;
b) CSA (cat.), $CH(OMe)_3$ (3 eq), MeOH, 17 h, rt

Scheme 1.6

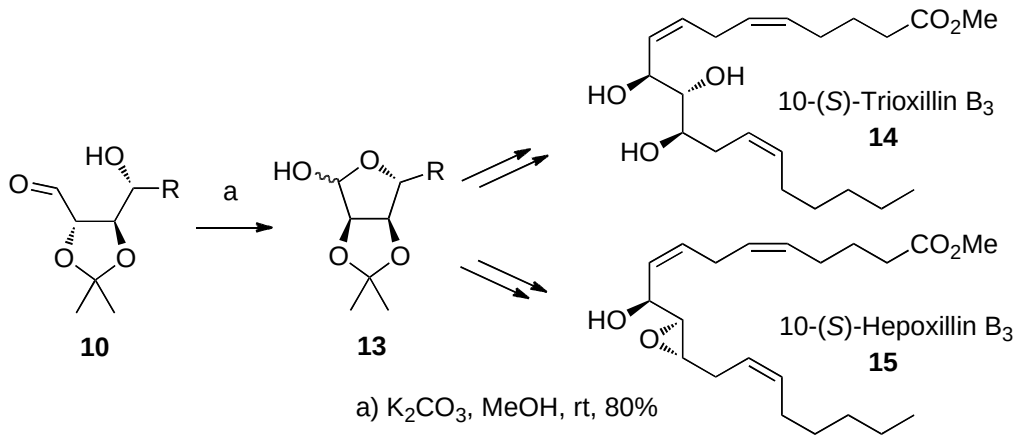
Cyclic acetals are used as protecting groups for 1,2- and 1,3- diols in a wide range of natural product syntheses. Wu and co-workers demonstrated the manipulation of acetonides in the total synthesis of trioxillin and hepoxillin **11** and **12**.[25,26] They found that two diastereoisomers of each natural product could be synthesised from the same chiral aldehyde **10**, derived from δ-gluconolactone **9**.[27] Organozinc addition to **9**, followed by selective hydrolysis and oxidative cleavage of the less hindered terminal acetonide gave aldehyde **10**, which was further elaborated to give 10-(*R*)-trioxillin and 10-(*R*)-hepoxillin **11** and **12** respectively (scheme **1.7**).



a) RBr, Zn, DMF-Et_2O 1:1; b) H_5IO_6, Et_2O

Scheme 1.7

Aldehyde **10** was found to epimerise in the presence of a base, giving the *cis*-fused acetonide **13** (scheme **1.8**). Upon further transformation, this intermediate was elaborated to give the opposite diastereoisomers 10-(*S*)-trioxillin and 10-(*S*)-hepoxillin **14** and **15** respectively, demonstrating that all four isomers of the natural products could be synthesised from the same chiral building block.[28,29]



Scheme 1.8

As mentioned above, cyclic acetals are also used to protect aldehydes and ketones, which are often very sensitive to basic conditions as well as being reactive towards a range of nucleophiles.[30] Formed by condensation of the corresponding carbonyl compound with either ethylene or propylene glycol in the presence of an acid catalyst, the preparation of these cyclic acetals often requires elevated temperatures under Dean-Stark conditions.[31] Alternatively, the Noyori method also affords dioxolanes in excellent yield, under somewhat milder conditions.[32]

Generally speaking, dioxolanes are more readily prepared than dioxanes,[33] although *gem*-dialkyl groups on the diol increase the rates of dioxane formation due to the Thorpe-Ingold effect.[34,35] This general trend in the ease of cyclic acetal formation is depicted in figure **1.2** below.

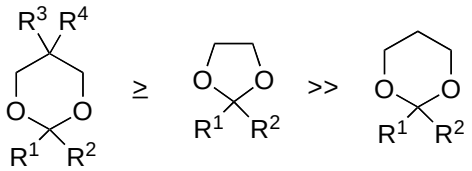
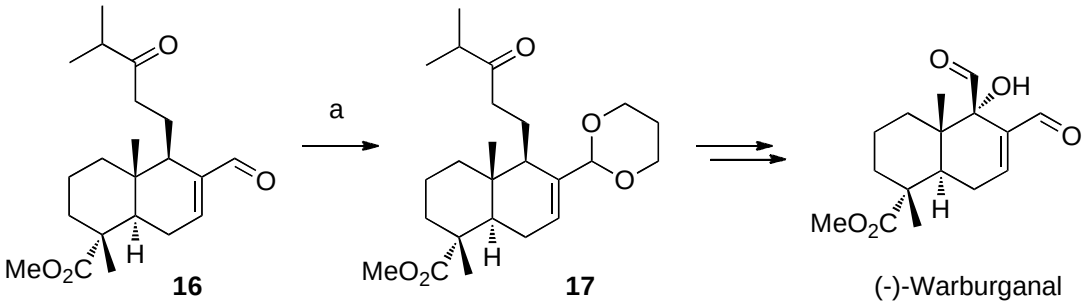


Figure 1.2

Cyclic acetals are more readily prepared than the analogous ketal derivatives, as demonstrated by Ohno in the total synthesis of (-)-warburganal (scheme **1.9**).[36] Selective protection of the aldehyde moiety in **16** gives dioxane **17**, whilst leaving the ketone intact.

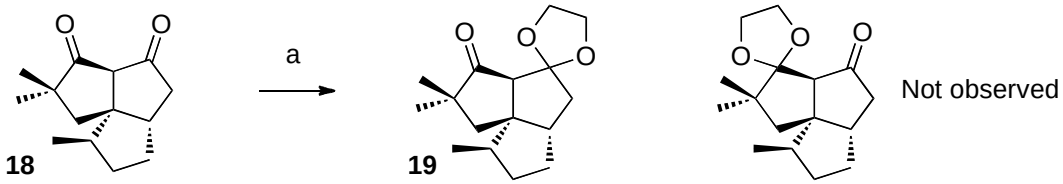


16 **17** (-)-Warburganal

a) $HO(CH_2)_3OH$, *p*-TsOH, PhH, 83%

Scheme 1.9

If a molecule contains two or more of the same carbonyl moiety, the cyclic acetal will usually form at the least hindered position. Crimmins demonstrated this in the differentiation of carbonyl groups in dione **18** by selective ketalisation at the least hindered position (scheme **1.10**).[37] The selectivity in this reaction was remarkable, with dioxolane **19** being the only observed product, even in the presence of an excess of ethylene glycol.

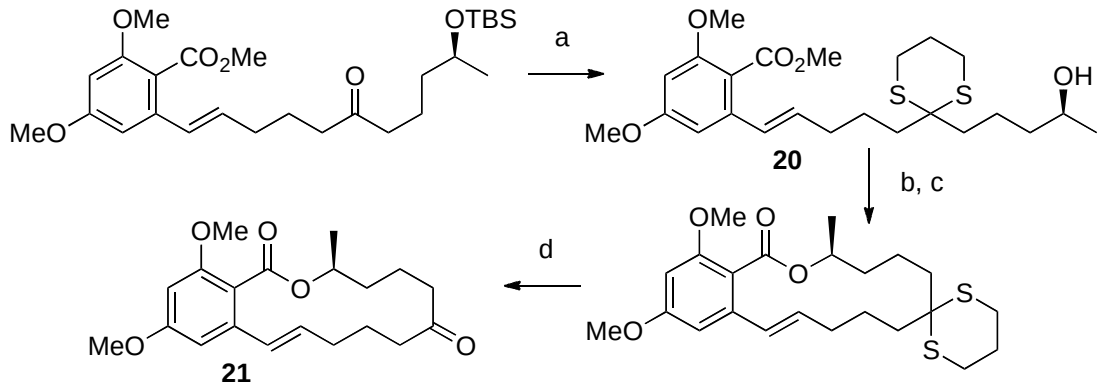


18 **19**

a) Ethylene glycol, *p*-TsOH, PhH, 80 ^{o}C, 81%

Scheme 1.10

Thioacetals such as 1,3-dithiolanes and 1,3-dithianes can also be used as protecting groups for carbonyl compounds, due to their facile, high yielding synthesis and stability to both acidic and basic conditions.[38] For example, Solladié used a 1,3-dithiane to protect a ketone in the late-stage macrocyclisation of **20** in the synthesis of (*S*)-zearalenone dimethyl ether **21** (scheme **1.11**).[39]



a) $HS(CH_2)_3SH$, $BF_3.OEt_2$, DCM, rt, 78%; b) KOH, $HO(CH_2)_2OH$, 140 ^oC, 84%; c) $(PhO)_2POCl$, DMAP, NEt_3, THF, 60%; d) MeI, $CaCO_3$, MeCN, H_2O, 84%

Scheme 1.11

1.2 Asymmetric Induction with Cyclic Acetal Derivatives

Dioxolanes are used in a wide range of stereoselective transformations as chiral auxiliaries, chiral ligands and as chiral catalysts; some examples are given in figure **1.3** below.[40-42]

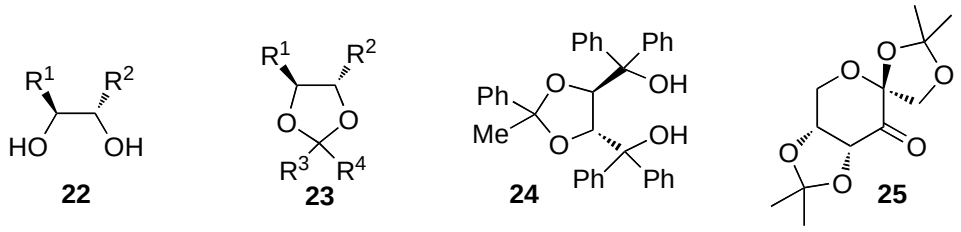
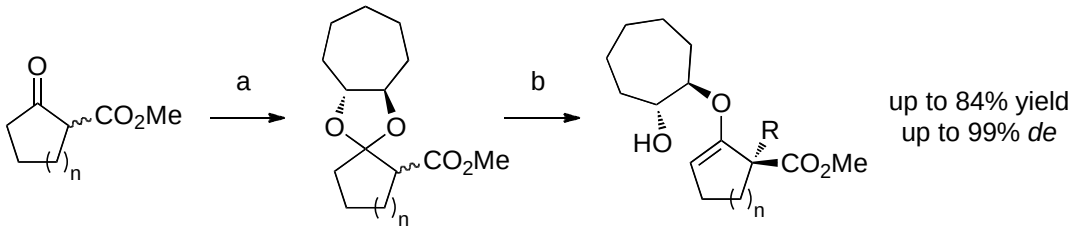


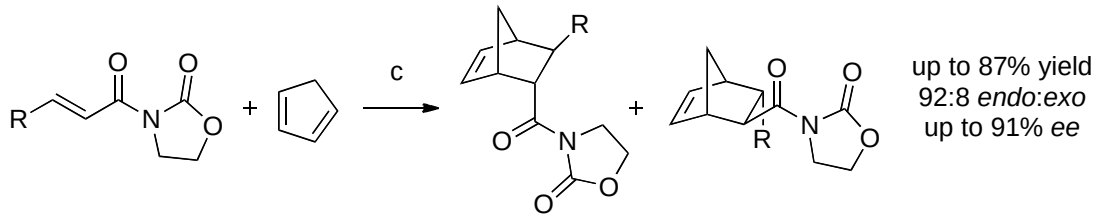
Figure 1.3

C_2-Symmetric diols **22** can be condensed with carbonyl compounds to give dioxolane chiral auxiliaries of the general form **23**, which are used in a variety of asymmetric aldol reactions[43] and Michael additions.[44] Dioxolanes of the form **24** have been employed extensively as asymmetric ligands in a variety of titanium-mediated reactions,[45] whilst fructose-derived ketone **25** acts as a chiral catalyst in the asymmetric epoxidation protocol developed by Shi and co-workers.[46]

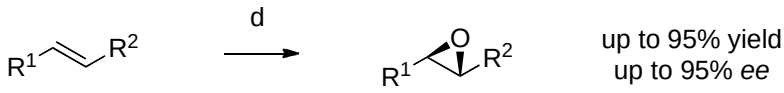
Examples of this chemistry are numerous, with many elegant uses of asymmetric induction with cyclic acetals such as **23**, **24** and **25** being reported; a representative example of each is given below in scheme **1.12**.[47-52]



a) (*R,R*)-Cycloheptane-1,2-diol, *p*-TsOH (cat.), benzene, reflux, 98%;
b) LDA, HMPA, THF, -78 ^{o}C, then RX; n = 1, 2



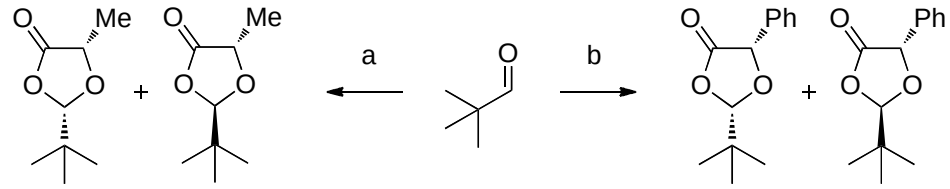
c) **24**.$TiCl_2$ (10 mol%), toluene, 0 ^{o}C



d) **25** (30 mol%), Oxone (1.4 eq), MeCN-DMM 1:2, buffer pH 10, 0 ^{o}C

Scheme 1.12

Seebach first reported the use of cyclic acetals as chiral enolate precursors in 1981, providing the first examples of successful building blocks for the asymmetric synthesis of α-hydroxy acids.[53,54] Condensation of pivalaldehyde with commercially available lactic or mandelic acids gave chiral enolate precursor dioxolanones **26** and **27** respectively (scheme **1.13**).

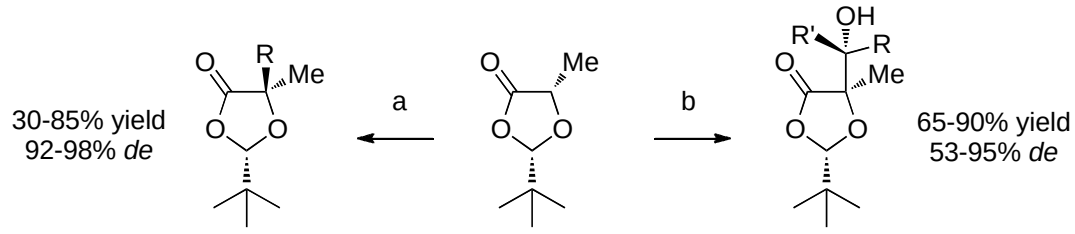


26 93% (4:1) **27** 82% 20:1

a) (*S*)-Lactic acid, *p*-TsOH, pentane, reflux; b) (*S*)-Mandelic acid, *p*-TsOH, pentane, reflux

Scheme 1.13

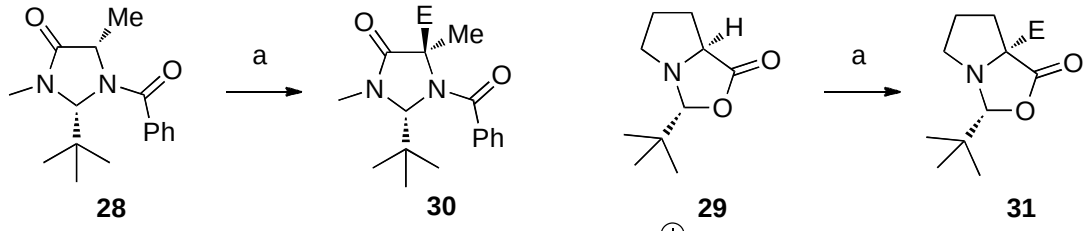
The enolates of **26** and **27** react readily with a range of electrophiles to give the corresponding α-substituted glycolates in good yield and excellent diastereoselectivity (scheme **1.14**).[55]



a) LDA, THF, -78 °C, then RX; b) LDA, THF, -78 °C, then RCOR'

Scheme 1.14

Seebach later extended this concept to the use of imidazolidines[56] **28** and proline-derived oxazolidines[57] **29**, which also undergo asymmetric alkylations and aldol reactions to give high yields of diastereomerically pure α-substituted products **30** and **31** (scheme **1.15**).

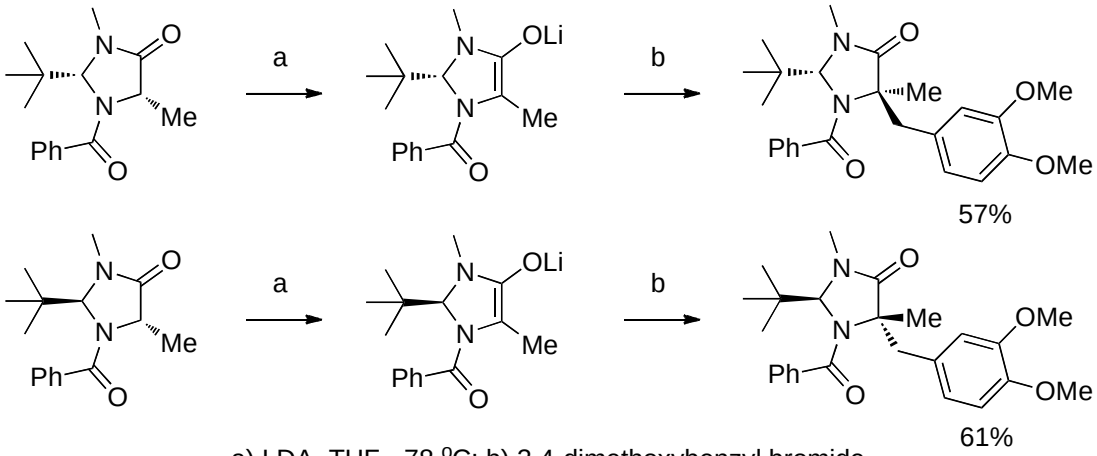


28 **30** **29** **31**

a) LDA, THF, -78 °C, then E⊕

Scheme 1.15

This methodology was used in the asymmetric synthesis of (*R*)- and (*S*)-α-methyldopa from *cis* and *trans*-imidazolidine **28** respectively (scheme **1.16**).[58]

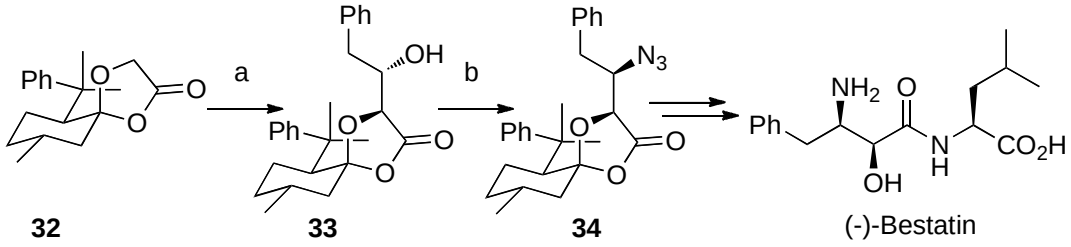


a) LDA, THF, -78 °C; b) 3,4-dimethoxybenzyl bromide

Scheme 1.16

Because of the high levels of enantiopurity that can be obtained in the absence of an external chiral auxiliary, Seebach named this concept the self-reproduction of chirality.[59] Many other groups have since reported advances in this area, though the sheer volume of examples makes it impossible to review all relevant reports in this thesis. Two representative examples of natural product syntheses that utilise this self-reproduction of chirality are given below.

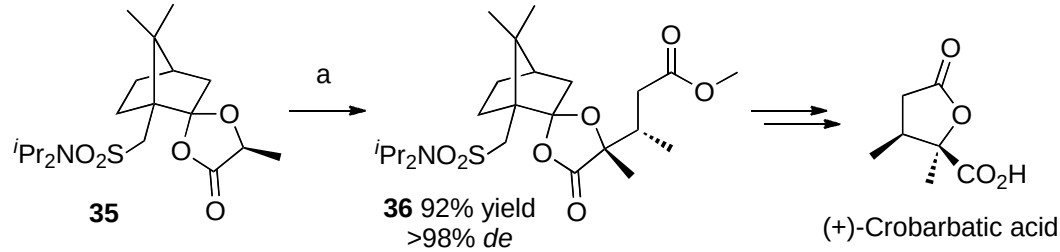
Firstly, Pearson used spiroketal **32** as a chiral enolate precursor in the synthesis of (-)-bestatin (scheme **1.17**).[60,61] Aldol reaction of **32** with phenylacetaldehyde gave protected *anti*-diol **33**, which was then subjected to a Mitsunobu reaction, inverting the stereochemistry to give *syn*-α-hydroxyazide **34**.



a) LHMDS, THF, -78 °C, then phenylacetaldehyde, 56% (6:1 *anti*:*syn*);
b) PPh_3, DEAD, DPPA, THF, 0 °C to rt, 79%

Scheme 1.17

Some years later, Uang reported the use of chiral camphorsulfonamide **35** in the enantioselective synthesis of (+)-crobarbatic acid (scheme **1.18**).[62,63] Michael addition of the chiral enolate derived from **35** to methyl crotonate gave **36**, which upon deprotection and cyclisation furnished the natural product in excellent yield.

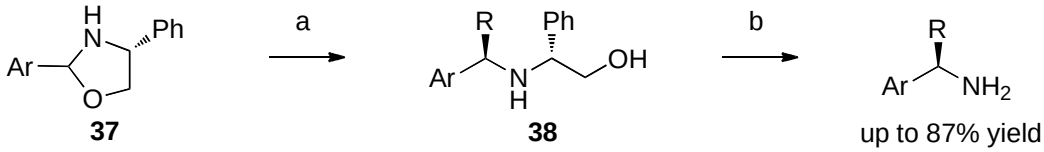


a) LDA, THF, -100 °C, then methyl crotonate, -78 °C

Scheme 1.18

Pridgen and co-workers demonstrated the use of oxazolidines as templates for the asymmetric synthesis of chiral amines.[64,65] Addition of a Grignard or organocerium

reagent to chiral amino alcohol-derived oxazolidine **37** gives **38** in good yield and high diastereoselectivity (scheme **1.19**). Oxidative cleavage of this second amino alcohol then furnishes the chiral amine.

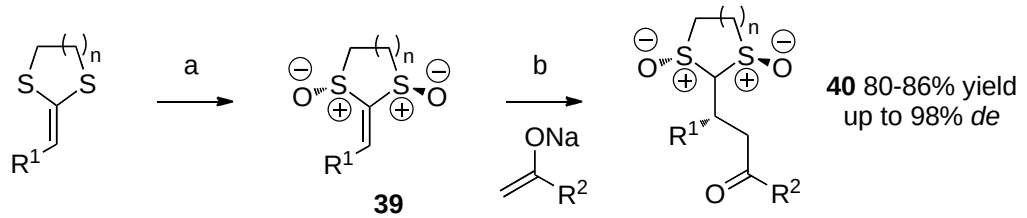


37 **38** up to 87% yield 99% *de*

a) RMgX or $RCeCl_2$ (3 eq), THF, 2 h, -78 ^oC; b) $Pb(OAc)_4$

Scheme 1.19

More recently, Podlech reported the asymmetric conjugate addition of enolates to alkylidene thioacetal *bis*-sulfoxides[66] **39** (scheme **1.20**).[67,68] These reactions proceed rapidly at low temperatures to give masked 1,4-dicarbonyl species **40** in good yield and high diastereoselectivity.



39 **40** 80-86% yield up to 98% *de*

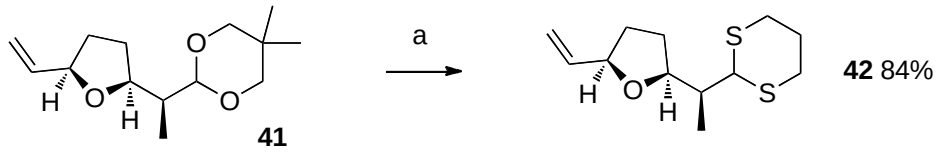
a) $PhC(Me)_2OOH$, (+)-DET, $Ti(O^iPr)_4$, DCM, rt, 55-67%; b) THF, -78 ^oC, 20 min; n = 1,2

Scheme 1.20

1.3 Reactions of Cyclic Acetals with Nucleophiles

As described above for oxazolidines, the *gem*-diether carbon of an acetal is electrophilic and is susceptible to attack by a number of nucleophiles. A simple example of this is the acidic hydrolysis of an acetal, in which water acts as a nucleophile, cleaving the *gem*-diether to reveal its parent carbonyl species.

Dioxolanes and dioxanes readily undergo transacetalation with dithiols in the presence of a Lewis acid to give the corresponding cyclic thioacetals.[69,70] This reaction was used by Honda in the direct conversion of dioxane **41** into dithiane **42**, which was then used as a carbanion stabilising group (discussed later) in a subsequent carbon-carbon bond forming alkylation (scheme **1.21**).[71]

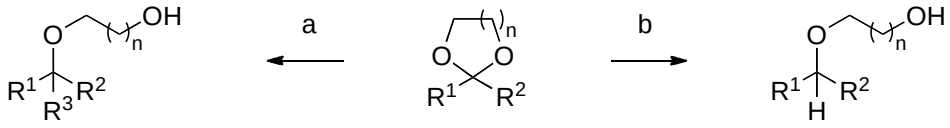


41 **42** 84%

a) $HS(CH_2)_3SH$, $BF_3.OEt_2$, DCM, rt

Scheme 1.21

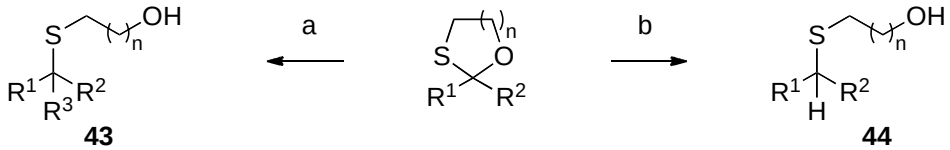
Cyclic *O,O'*-acetals undergo nucleophilic ring-opening with Grignard reagents[72,73] and reduction with $LiAlH_4$[74-76] in the presence of a Lewis acid, as reported by Eliel and co-workers (scheme **1.22**).[77]



a) R^3MgX, benzene, reflux; b) $AlCl_3$, $LiAlH_4$, Et_2O, rt; n = 1,2

Scheme 1.22

Eliel also demonstrated that oxathiolanes reacted in a similar fashion to the cyclic *O,O'*-acetals under these conditions, giving rise to the ring opened hydroxythioethers **43** and **44** (scheme **1.23**).[78]

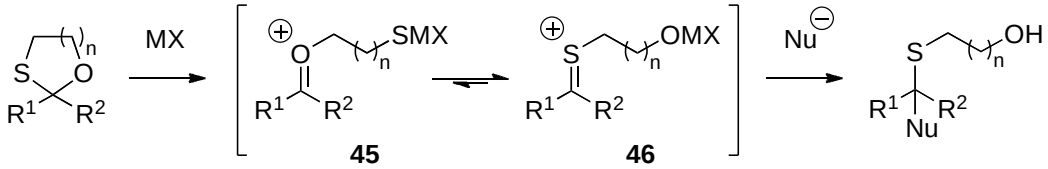


43 **44**

a) R^3MgX, benzene, reflux; b) $AlCl_3$, $LiAlH_4$, Et_2O, rt; n = 1,2

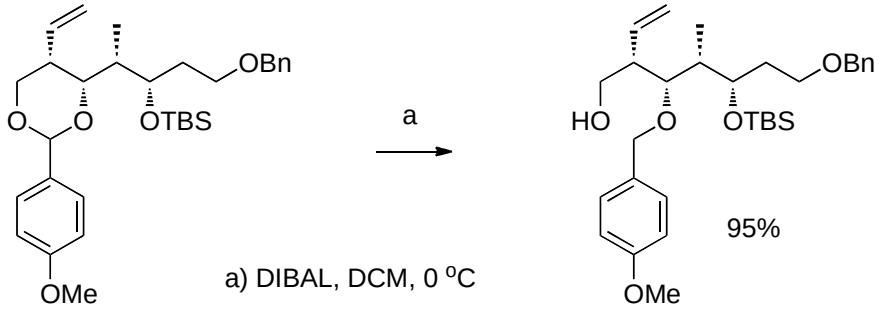
Scheme 1.23

Interestingly, none of the corresponding mercaptoethers were observed, demonstrating that oxathiolanes exclusively undergo C-O bond cleavage under these conditions. This phenomenon was attributed to the oxophilicity of the metal species resulting in the ring-opened thiocarbenium species **46** being favoured over the analogous oxocarbenium species **45** (scheme **1.24**). Trapping of this ring-opened thiocarbenium ion with the nucleophilic species then gives the observed products **43** and **44**.[79]



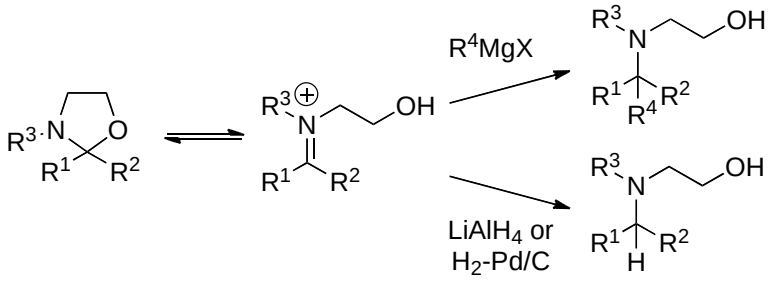
Scheme 1.24

Benzylidene acetals also react with reducing agents such as DIBAL to unmask one of the hydroxyl groups selectively whilst keeping the other protected as a benzyl ether.[80] This protocol was used by Iqbal and co-workers in a late-stage functional group manipulation in the synthesis of the C(8)-C(17) fragment of tedanolide (scheme **1.25**).[81]



Scheme 1.25

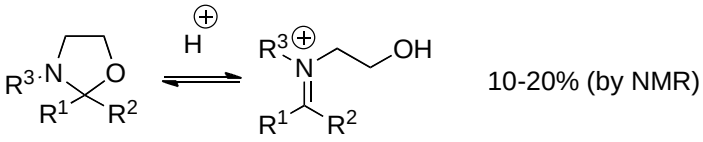
As mentioned above, oxazolidines also undergo rapid nucleophilic attack with Grignard reagents (scheme **1.19**). Senkus first demonstrated that oxazolidines readily tautomerise to give highly electrophilic iminium species, which can then be trapped by Grignard reagents or a reducing agent to give substituted aminoalcohols (scheme **1.26**).[82,83]



Scheme 1.26

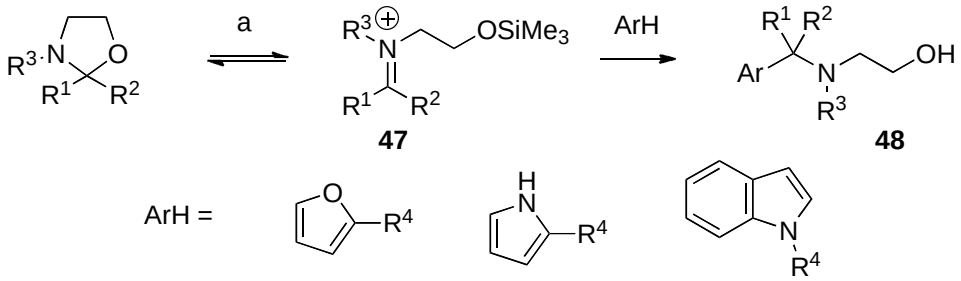
The ring-chain tautomerism of oxazolidines is accelerated in the presence of mineral or Lewis acids, as demonstrated by Lambert (scheme **1.27**).[84] In an NMR

experiment, Lambert observed that the open-chain iminium tautomer constituted 10-20% of the equilibrium mixture in the presence of CF_3CO_2H.[85]



Scheme 1.27

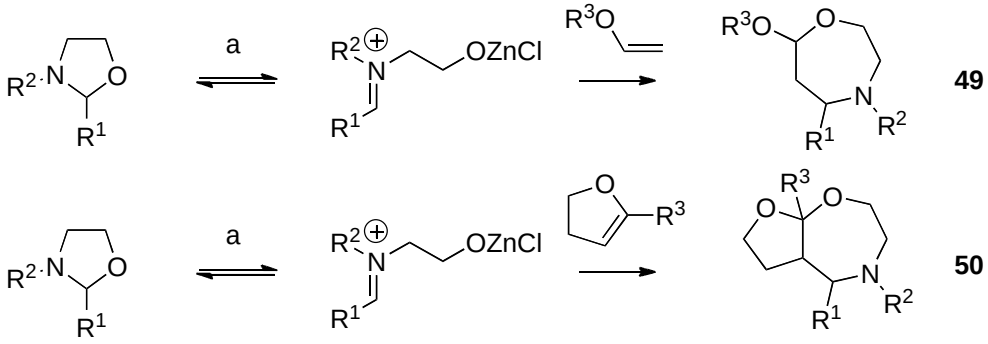
This chemistry was exploited by Heaney, who demonstrated that when oxazolidines were treated with trimethylchlorosilane, the resultant iminium ions **47** could be trapped with a range of electron-rich aromatic species to give *N*-arylmethylene compounds **48** (scheme **1.28**).[86,87]



a) Me_3SiCl (1.1 eq), ArH (1.1 eq), MeCN, 48 h, rt, up to 90% yield

Scheme 1.28

Griengl was also able to exploit the Lewis acid-mediated ring opening of oxazolidines, using the resultant iminium species in a formal cycloaddition to give seven-membered heterocycles **49** and **50** (scheme **1.29**).[88-90]



a) $ZnCl_2$ (1.2 eq), olefin (1.2 eq), DMSO, 20 h, 40 ^oC, up to 85%

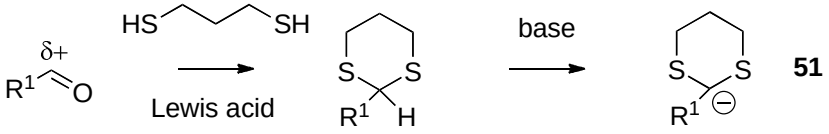
Scheme 1.29

Despite the apparent synthetic utility of this oxazolidine chemistry, it has received little attention in the literature and could be an interesting avenue for future investigations into the chemistry of acetal derivatives.[91]

1.4 Reactions of Cyclic Acetals with Electrophiles

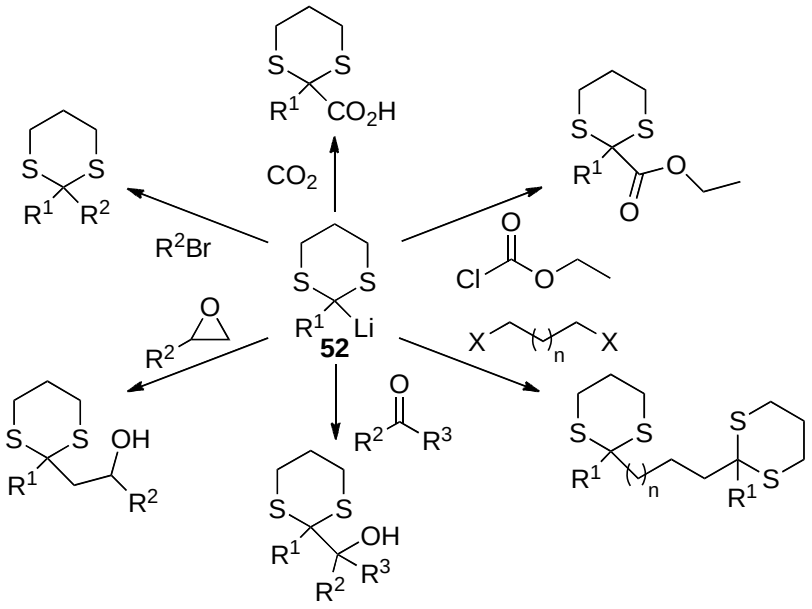
Besides being useful protecting groups, dithianes are used in a wide range of chemical syntheses due to their ability to mediate the umpolung chemistry of aldehydes.[92] First introduced by Wittig in 1951, the German term umpolung describes the inversion of polarity at a carbon atom by temporary modification of its substituents, resulting in the reversal of its nucleophilic or electrophilic nature.[93]

Corey and Seebach applied this idea to the chemistry of aldehydes by temporary modification of the carbonyl functionality.[94] Thioacetalisation of an aldehyde followed by deprotonation with a strong base gives dithiane-stabilised carbanion **51**, rendering the masked carbonyl highly nucleophilic (scheme **1.30**).



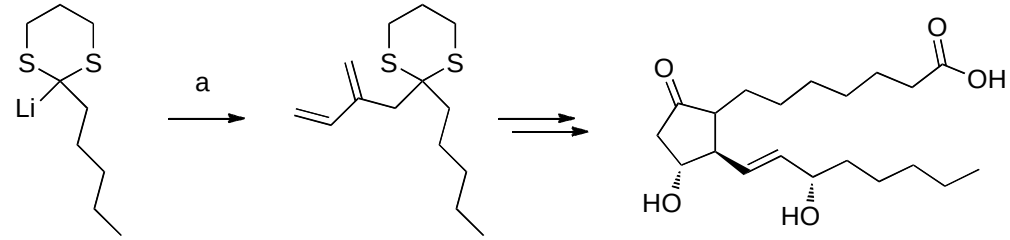
Scheme 1.30

Lithiated dithianes **52** react with a variety of different electrophiles to give a wide range of asymmetric ketones and 1,n-dicarbonyl species (scheme **1.31**).[95] This approach has led to dithianes becoming some of the most widely used precursors in the synthesis of highly oxygenated polyketide natural products.[96,97]



Scheme 1.31

Corey later used this protocol in the first step of the total synthesis of prostaglandin E_1; alkylation of 2-lithio-2-^{n}pentyl dithiane **53** gave the early stage precursor dialkyl dithiane **54** in good yield (scheme **1.32**).[98]

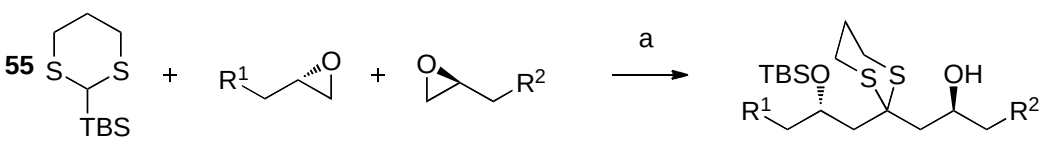


53 **54** Prostaglandin E_1

a) 2-Bromomethylbutadiene, THF-pentane, -25 ^{o}C, 70%

Scheme 1.32

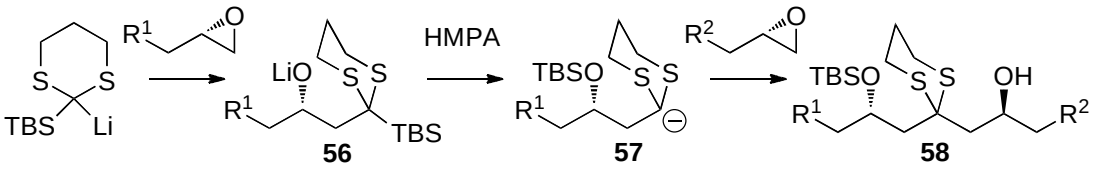
Some years later, Smith and co-workers extended this methodology to the multi-component, sequential dialkylation of silyl dithianes (scheme **1.33**).[99,100]



a) ^{t}BuLi (2.6 eq), HMPA (30 mol%), Et_2O, -78 ^{o}C to rt, 56-74%

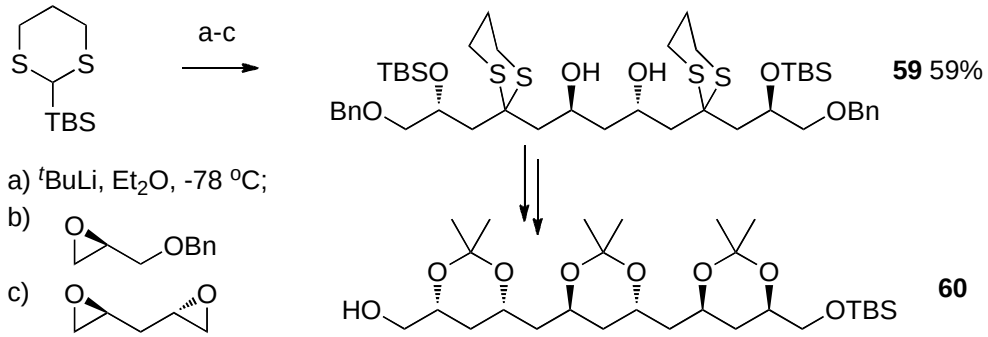
Scheme 1.33

This so-called linchpin coupling proceeds via lithiation-alkylation of 2-TBS dithiane **55** to give intermediate **56** (scheme **1.34**). Addition of a catalytic amount of HMPA then induces a 1,4-Brook rearrangement[101] to give a second carbanion **57**, which upon alkylation with a second electrophile gives the product as its mono-TBS-protected diol **58**.



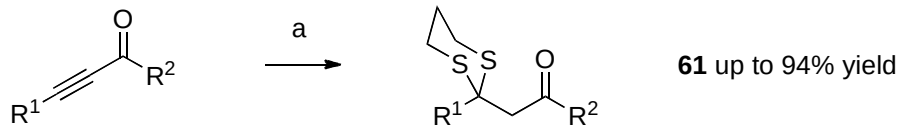
Scheme 1.34

Smith later used this linchpin approach in a one-pot 5-component coupling to give diol **59**,[102] which was then elaborated to *tris*-acetonide **60**, an advanced intermediate in Schreiber's total synthesis of mycoticins A and B[103] (scheme **1.35**).



Scheme 1.35

The Ley group recently reported the formation of 1,3-dithianes by double conjugate addition of propane dithiol to propargylic carbonyl compounds to generate protected 1,3-dicarbonyl compounds **61** (scheme **1.36**).[104,105]

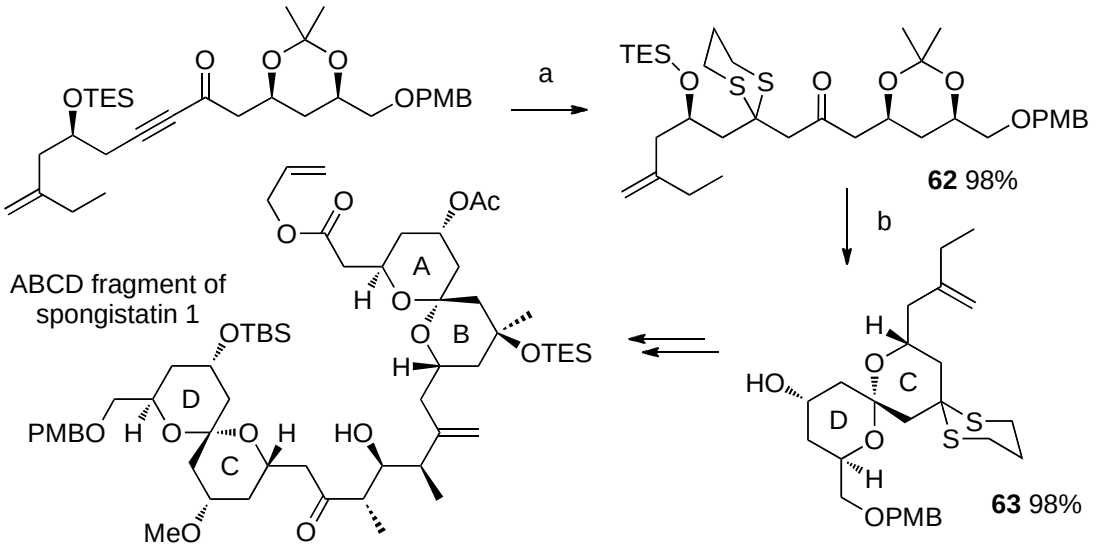


a) $HS(CH_2)_3SH$ (1.1-1.3 eq), NaOMe (1.3 eq), MeOH-DCM 4:1, -10 to 0 °C

Scheme 1.36

This chemistry was then applied to the synthesis of the ABCD fragment of spongistatin 1, employing the dithiane first to generate the desired protected 1,3-

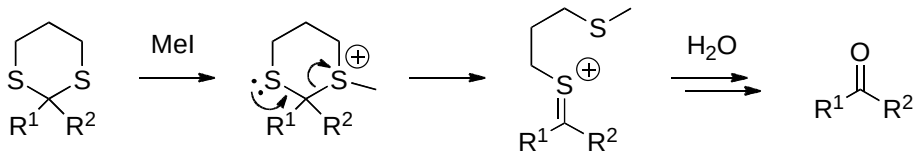
dicarbonyl derivative **62** and then as a protecting group in the following spiroketalisation to give key intermediate **63** (scheme **1.37**).[106,107]



a) $HS(CH_2)_3SH$ (1.3 eq), NaOMe (1.3 eq), MeOH-DCM 4:1, 16 h, -10 to 0 °C;
b) 10% $HClO_4$ (aq), MeCN-DCM, 30 min, rt

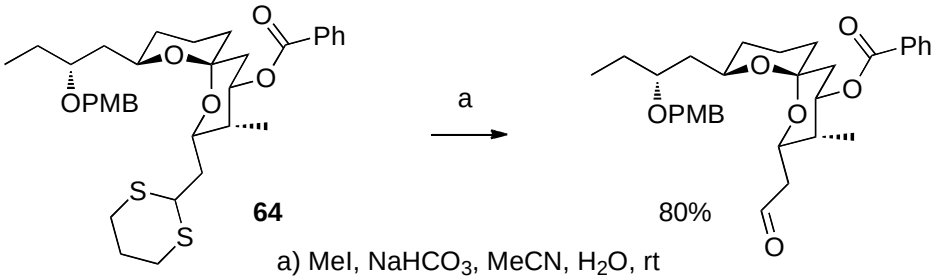
Scheme 1.37

As with many cyclic ethers, amines and sulfides, *O,N*- and *S*-acetal derivatives are able to act as nucleophiles via a lone pair on one of the heteroatoms. A simple example of this is the cleavage of dithianes with methyl iodide by alkylation of one of the sulfur atoms (scheme **1.38**).[108]



Scheme 1.38

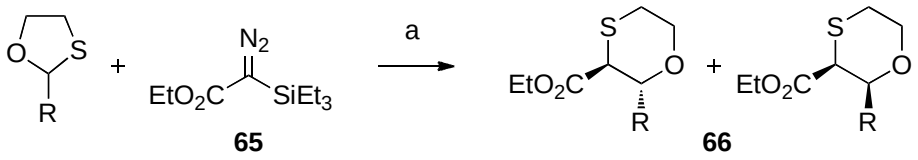
This technique was used recently by Trost as a mild deprotection of aldehyde **64** in the total synthesis of ushikulide A (scheme **1.39**).[109]



a) MeI, $NaHCO_3$, MeCN, H_2O, rt

Scheme 1.39

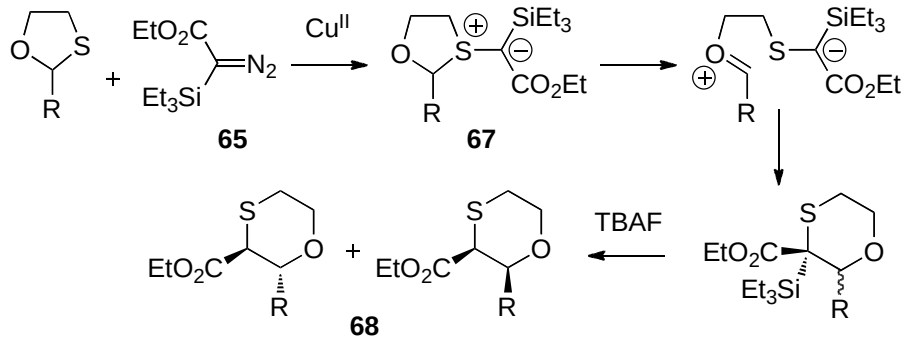
Porter and co-workers recently exploited the nucleophilicity of 1,3-oxathiolanes towards copper carbenes in the synthesis of 1,4-oxathianes **66** (scheme **1.40**).[110]



a) $Cu(acac)_2$ (cat.), benzene, 16 h, reflux, then TBAF, THF; 2:1 *cis*:*trans*

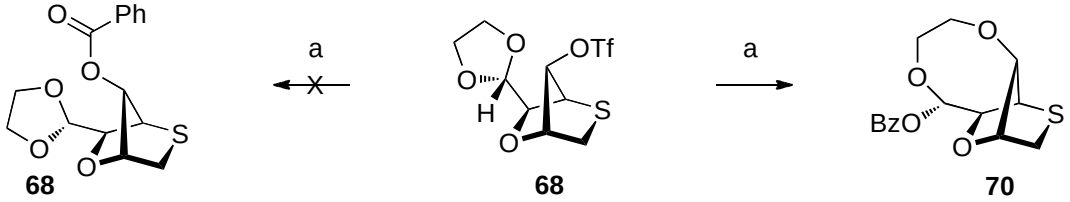
Scheme 1.40

Treatment of the oxathiolane with silylated diazoester[111] **65** in the presence of a Cu^{II} catalyst gives sulfonium ylide **67** (scheme **1.41**). Cleavage of the benzylic C-S bond either heterolytically (as shown) or via a Stevens-type radical mechanism, followed by ring closure gives the desired 1,4-oxathiane. *In situ* desilylation then affords the final product as a 2:1 mixture of *cis* and *trans* isomers **68**.



Scheme 1.41

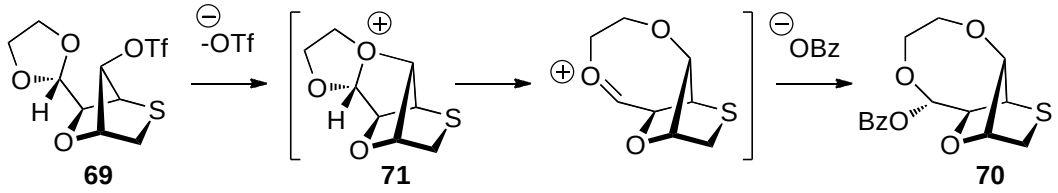
If the electrophilic species reacting with the cyclic acetal is contained within the same molecule, an intramolecular nucleophilic attack can occur, as reported by Popsavin and co-workers.[112] In an attempt to displace the triflate from sugar derivative **69**, Popsavin observed the formation of 9-crown-3-ether **70**, rather than the desired product **68** (scheme **1.42**).



a) LiOBz, DMF, 24 h, reflux

Scheme 1.42

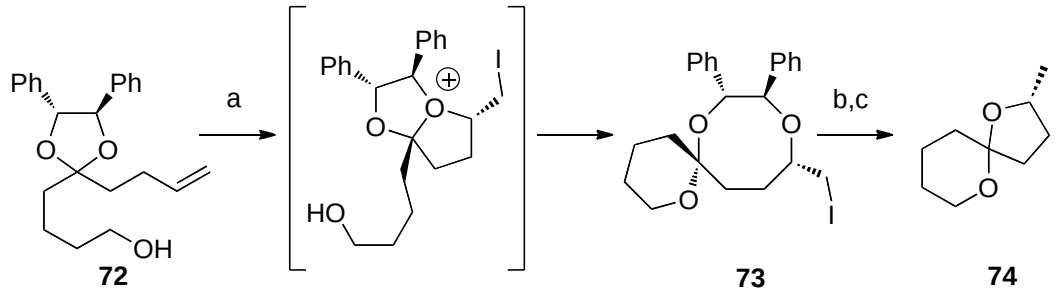
The proposed mechanism for this transformation is an intramolecular displacement of triflate by the dioxolane, to give charged bicyclic intermediate **71** (scheme **1.43**). Ring expansion and trapping by lithium benzoate at the least hindered face of the oxocarbenium species then furnishes the product.



69 **71** **70**

Scheme 1.43

Using a similar transformation, Fujioka recently employed the intramolecular iodoetherification of dioxolane **72** in the synthesis of eight-membered diether **73** (scheme **1.44**).[113] Radical reduction of the iodide[114] followed by CAN oxidation[115] furnished spiroketal **74**, a *Paravespula Vulgaris* wasp pheremone in excellent yield.



72 **73** **74**

a) $I(coll)_2PF_6$ (1.5 eq), MeCN, -40 ^oC to rt, 90%;
b) VA-061, EPHP, $NaHCO_3$, ^iPrOH-H_2O, 75 ^oC, 83%; c) CAN, MeCN-H_2O, rt, 70%

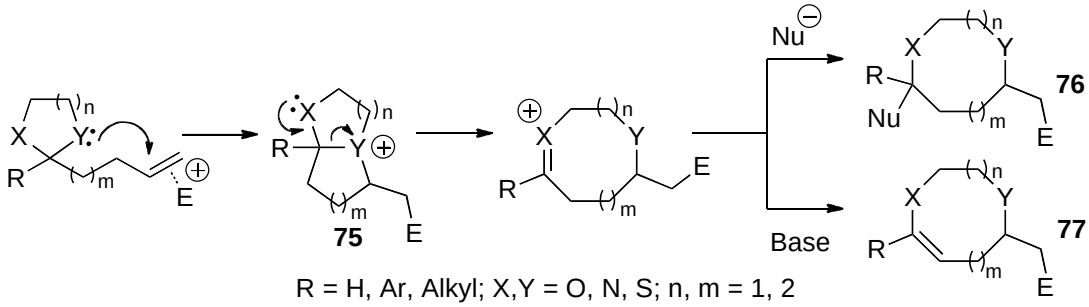
Scheme 1.44

1.5 Conclusions

A brief overview of the chemistry of cyclic acetal derivatives has been given in this chapter, demonstrating their wide range of applications in chemical synthesis. The aim of this project was to explore new reactions of cyclic oxygen, nitrogen and sulfur acetal derivatives and their application to a variety of new methodologies.

Firstly, the ring expansion chemistry of some unsaturated *O, N*- and *S*-acetal derivatives was explored, with the aim of developing a new methodology for the synthesis of medium ring heterocycles (chapter 2). The proposed methodology is outlined below in scheme **1.45**. Intramolecular nucleophilic addition of the acetal to

an unsaturated carbon-carbon bond should give a charged bicyclic species **75**, which upon ring expansion and trapping with a suitable nucleophile or base should furnish medium ring heterocycles **76** or **77**.



Scheme 1.45

Leading on from observations made in the development of this methodology, chapter three then describes the use of thioacetals as directing groups for the palladium-mediated oxidation of olefins. Finally, builing upon previous research in the Sheppard group, the development of isocyanide-based multi-component reactions of oxazolidines is discussed in chapter four.

2. Development of Ring Expansion Reactions of Cyclic Acetals for Medium Ring Synthesis

2.1 Introduction

Medium rings are interesting and extremely challenging targets for the synthetic organic chemist. Generally considered to be carbocycles or heterocycles containing 8 to 12 atoms, medium rings are found in a structurally diverse range of natural products.[116-118] Oxygen and nitrogen containing heterocycles are the most common examples of medium ring structures in Nature, with many natural products containing 8-, 9- or 10-membered ether, lactone or lactam scaffolds (figure **2.1**).[119-124]

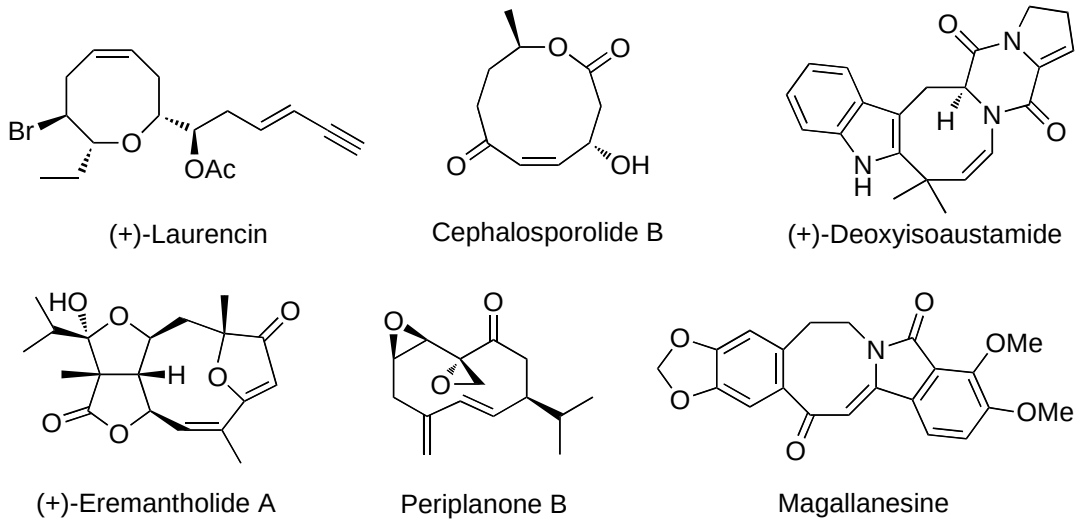
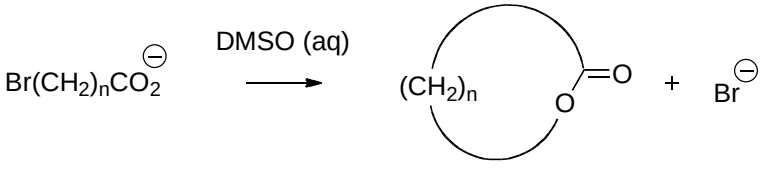


Figure 2.1

Generally speaking, medium rings are highly strained molecules and their synthesis is made difficult by a combination of physical factors. Ruzicka's pioneering work on macrolactonisation identified medium ring lactones as being more difficult to synthesise than their small ring (3 to 7-membered) and macrocyclic (13-membered and larger) counterparts.[125] Mandolini expanded upon this, studying the end-to-end lactonisation of ω-bromoalkanoic acids in DMSO (scheme **2.1**).[126]



Scheme 2.1

Plotting the rate of the intramolecular reaction as a function of ring size, Mandolini demonstrated that 8- to 12-membered rings are the slowest to form (figure **2.2**). Macrocyclic rings (13-membered and larger) have similar rate constants of formation to that of the 3-membered lactone, with the 4- to 7-membered examples showing by far the most reactivity. The slow formation of the 3-membered lactone can be attributed to an increased deformation of bond angles due to the presence of an sp^2 carbon atom. Formation of 3-membered rings in which all three atoms are sp^3 hybridised is typically much faster.

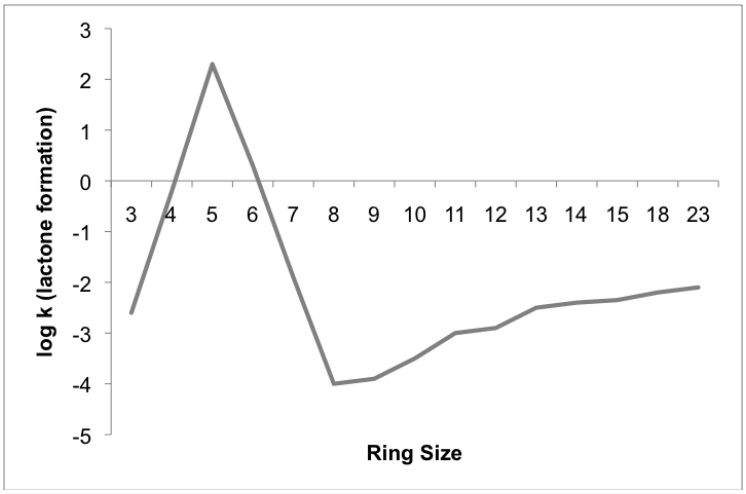
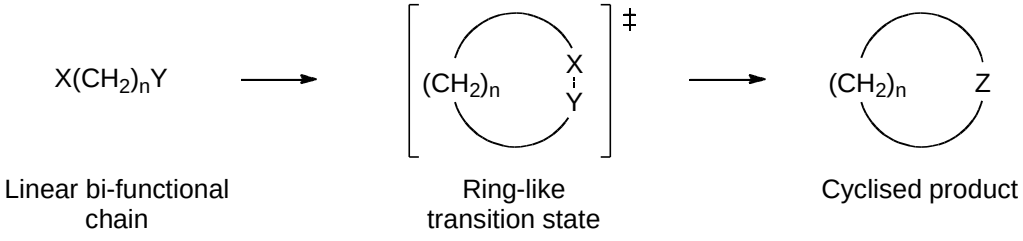


Figure 2.2

A generic end-to-end cyclisation of a bi-functional chain molecule is outlined below (scheme **2.2**). Entropically, the probability of a reaction occurring between the two functional groups decreases as the length of the chain increases. Torsional degrees of freedom are restricted upon formation of a ring-like transition state, which is also entropically unfavourable.[127]



Scheme 2.2

The activation energy of cyclisation reflects the ring strain in the cyclic transition state and product. This ring strain can be attributed to three main factors, namely; Baeyer strain, Pitzer strain and unfavourable transannular interactions.

Baeyer strain arises as a result of the deformation of bond angles from their optimal values (109.5° for an sp^3 hybridised centre). Pitzer strain occurs due to bond opposition forces arising from the imperfect staggering of a molecule. This phenomenon is illustrated in figure **2.3** by the eclipsing of bonds in the chair conformation of an 8-membered ring.

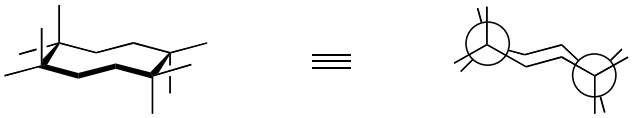


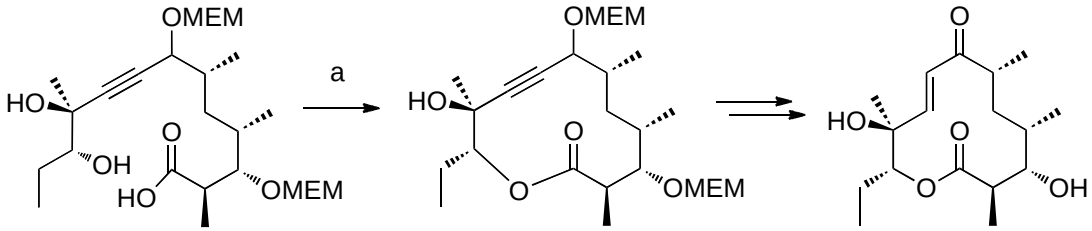
Figure 2.3

Transannular strain arises from unfavourable steric interactions between atoms across the ring being forced into close spatial proximity with one another. Both Pitzer strain and transannular interactions have been shown to be particularly severe for medium rings; comprising a large portion of the heightened ring strain in these molecules.[128]

The kinetic result of these factors is to create very strained, high-energy transition states, which require large activation energies to achieve. This combination of factors makes the synthesis of medium rings extremely challenging.

To date there are few generally applicable methods for the synthesis of medium rings.[129] However, the available literature on medium ring synthesis provides a range of diverse and elegant methods for their formation.[130]

Many natural products contain a medium ring lactone moiety; as a result of this, lactonisation is a common approach to their construction.[131] The majority of such techniques involve the activation of the carboxylic acid terminus by formation of mixed anhydrides, which will undergo lactonisation much more readily. Yamaguchi applied this technique to the total synthesis of methynolide, forming the key 12-membered lactone **78** via a mixed 2,4,6-trichlorobenzoic anhydride in the presence of DMAP (scheme **2.3**).[132]

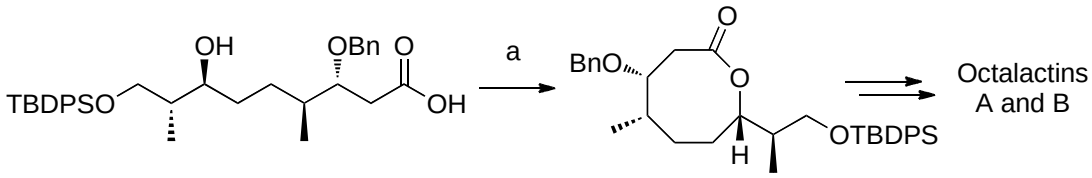


78 Methynolide

a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, benzene, 42%

Scheme 2.3

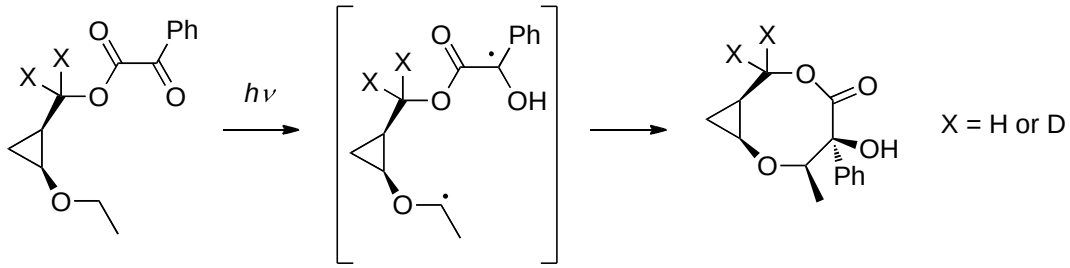
Shiina's synthesis of octalactins A and B employs a similar lactonisation, using 2-methyl-6-nitrobenzoic anhydride (MNBA) as the acid-activating group (scheme **2.4**).[133] Other lactonisation techniques involving activation of the alcohol terminus have been applied to the synthesis of medium rings, though they are less common.[134]



a) MNBA, DMAP, NEt_3, DCM, 89%

Scheme 2.4

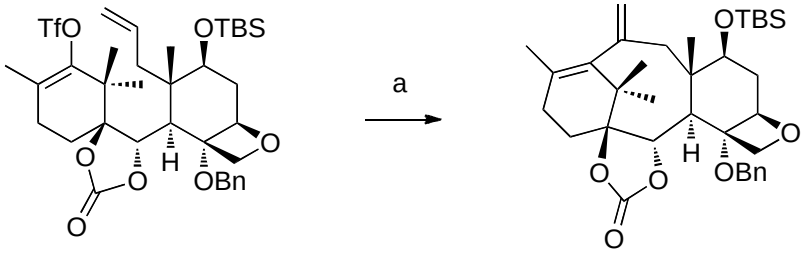
Radical cyclisation reactions have also played an important role in medium ring syntheses in the literature.[135] For example, Kraus demonstrated that photochemical excitation of α-keto ester **79** led to formation of eight-membered lactone **81** (scheme **2.5**).[136] Photolysis of **79** promotes a rare 1,9-hydrogen atom abstraction to give biradical species **80**, which then cyclises to give the medium ring product. A deuterium-labeling study confirmed that the reaction proceeded via a 1,9-hydrogen atom abstraction, rather than a sequential 1,5-abstraction/hydrogen atom transfer.



79 **80** **81** 51%

Scheme 2.5

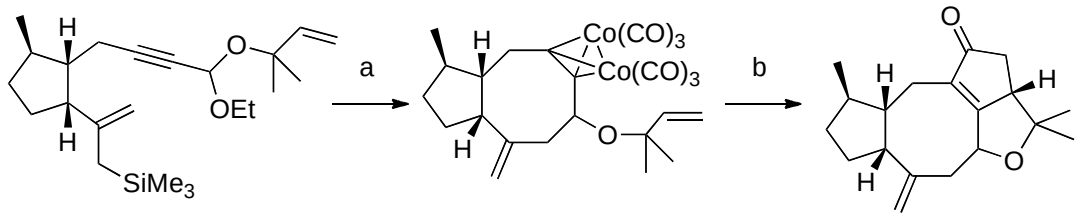
Transition metal-mediated reactions play an important role in organic chemistry; accordingly, many elegant medium ring syntheses employ these valuable methodologies.[137] Danishefsky's synthesis of taxol famously employs a key intramolecular Heck reaction to form the central 8-membered ring (scheme **2.6**).[138]



a) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 49%

Scheme 2.6

Another example of transition metal-mediated medium ring formation can be found in Schreiber's total synthesis of (+)-epoxydictymene.[139] Lewis acid-mediated Nicholas reaction of enyne **82** gave the 8-membered cobalt-alkyne complex **83** in good yield (scheme **2.7**). This stable complex could then undergo an intramolecular Pauson-Khand reaction to give the tetracyclic core of the natural product **84**.

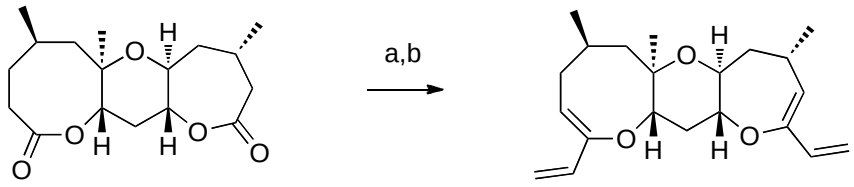


82 **83** **84**

a) $Co_2(CO)_8$, Et_2O then TMSOTf, THF, 82%; b) MeCN, reflux, 85%

Scheme 2.7

Functional group conversions can be employed to change the nature of medium ring scaffolds. For example, Nicolaou used a ketene-acetal formation/Stille[140] coupling sequence to convert medium ring lactone **85** into ether **86**, a key intermediate in the synthesis of brevetoxin A (scheme **2.8**).[141]

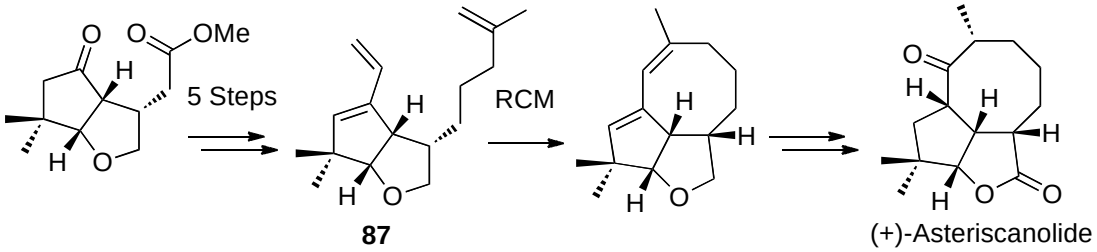


85 **86**

a) KHMDS, HMPA, $(PhO)_2POCl$, THF; b) Vinyltributyltin, $Pd(PPh_3)_4$, LiCl, THF, 78% overall

Scheme 2.8

Perhaps the most important metal-mediated route to medium ring scaffolds is the Nobel prize-winning ring closing metathesis reaction (RCM).[142,143] Olefin metathesis is an extremely powerful tool in the organic chemist's arsenal and can be successfully applied to the synthesis of a range of ring sizes. [144] The RCM reaction exploits the entropic gain of producing a molecule of ethene, facilitating an otherwise disfavoured ring closure. As with other methods of cyclisation, the RCM of eight to twelve-membered rings is by far the most difficult, with competing dimerisation reactions often being favoured over the desired transformation.[145] A number of conformational constraints can facilitate the RCM reaction however, resulting in high yields of the desired medium ring alkenes.[146] For example, attachment of olefinic side chains to a pre-existing cyclic structure can increase the rate of the RCM reaction by restricting the rotational degrees of freedom of the precursor.[147,148] Paquette's synthesis of (+)-asteriscanolide involved the RCM of **87**, in which the reacting olefinic side chains are attached to a fused bicyclic ring system (scheme **2.9**).[149]

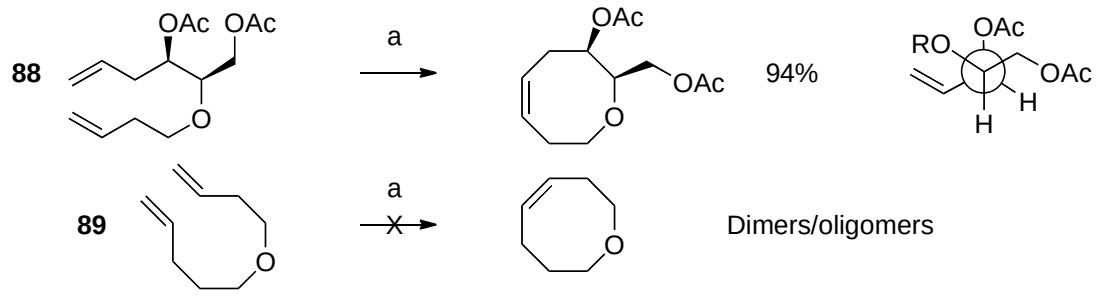


87 (+)-Asteriscanolide

Scheme 2.9

Crimmins demonstrated that the *gauche* effect could be used to facilitate the RCM reaction of ether **88** in the synthesis of (+)-laurencin (scheme **2.10**).[150] The RCM of **88** is greatly enhanced by the favourable *gauche* effect in the 1,2-dioxygenated

chain, whereas exposure of the analogous monoether **89** to the same conditions results in the formation of oligomers.

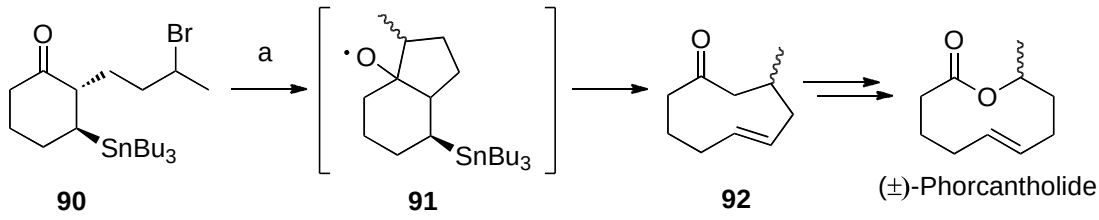


a) Grubbs 1 (cat.), DCM, 2 h, 40 °C

Scheme 2.10

Ring expansions and rearrangements constitute another key approach to the synthesis of medium rings. The justification of this approach relies on the fact that smaller rings (5- to 7-membered) are far more easily accessible than their medium ring counterparts. Fragmentation and/or rearrangement of 5- and 6-membered species can facilitate the formation of medium rings in bypassing the need for end-to-end reactions of bifunctional chain molecules.[151]

For example, Baldwin employed a radical cyclisation/ring expansion cascade in the synthesis of (±)-phorcantholide (scheme **2.11**).[152] Bromoketone **90** underwent radical cyclisation to give bicyclic alkoxy radical **91**, which, upon ring expansion and loss of a tributylstannyl radical gave medium ring ketone **92** in 62% yield. This reaction sequence is comparable to the Grob fragmentation,[153] which is also a common method for the synthesis of medium ring scaffolds.[154] Catalytic hydrogenation of **92** followed by Baeyer-Villiger oxidation[155,156] furnished the natural product in just 5 steps from cyclohexenone.

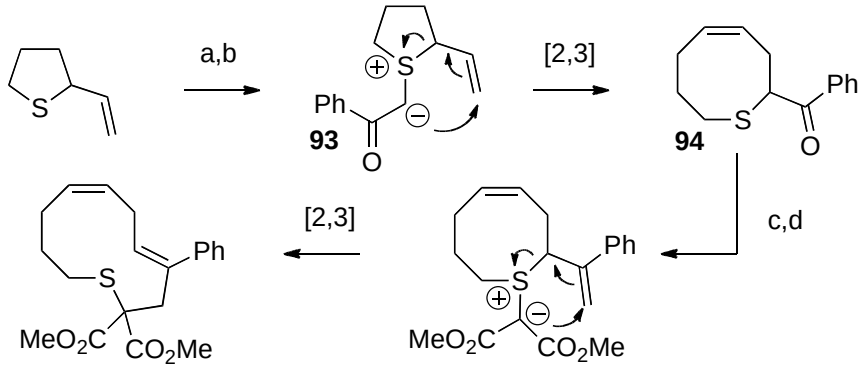


90 **91** **92**

a) Bu_3SnH, AIBN, benzene, 62%

Scheme 2.11

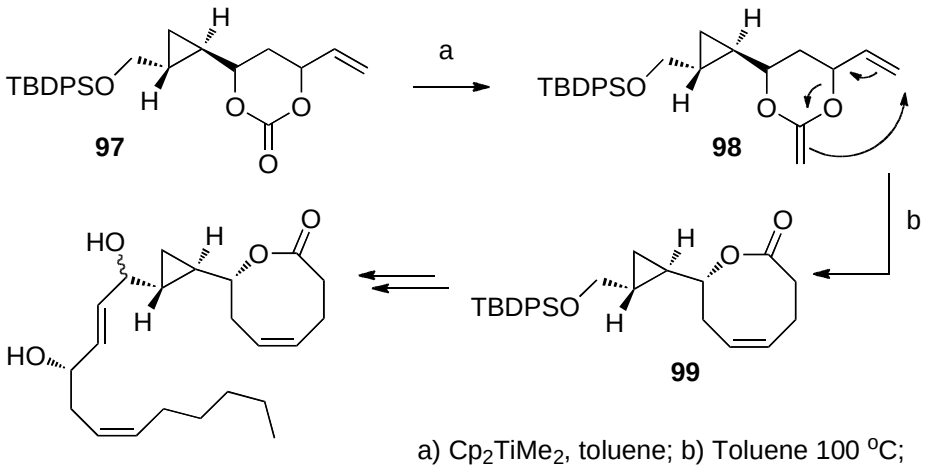
Vedejs used this approach in the synthesis of 8- and 11-membered cyclic sulfides by a series of [2,3] sigmatropic rearrangements.[157] Sulfonium ylide **93** underwent a [2,3] sigmatropic rearrangement to give 8-membered sulfide **94** (scheme **2.12**). This species was then further elaborated to a second sulfonium ylide **95**, which upon a further [2,3] sigmatropic rearrangement gave 11-membered cyclic sulfide **96**.



a) $PhCOCHN_2$, $HClO_4$, MeCN; b) DBU, PhMe; c) Ph_3PCH_2;
d) $(MeO_2C)_2CN_2$, copper bronze

Scheme 2.12

Another important sigmatropic rearrangement for the synthesis of medium rings is the intramolecular Claisen rearrangement[158] developed by Holmes,[159-161] and used by White in the synthesis of solandelactones E and F.[162] Treatment of cyclic carbonate **97** with Petasis's reagent[163] gave ketene acetal **98**, which underwent [3,3] sigmatropic rearrangement to give 8-membered lactone **99**, a key intermediate in the synthesis of the diastereomeric natural products (scheme **2.13**).

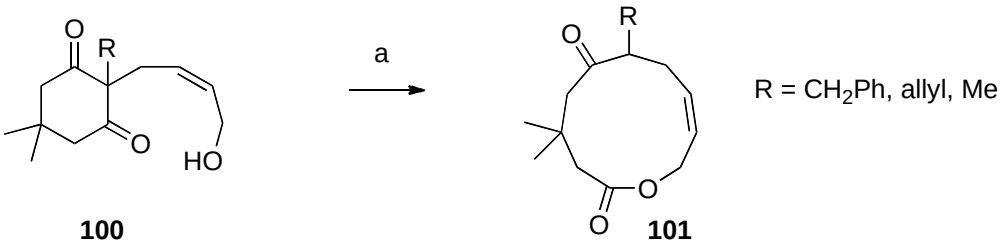


a) Cp_2TiMe_2, toluene; b) Toluene 100 ^oC;
64% over 2 steps

Solandelactones E and F

Scheme 2.13

Mahajan used a cyclisation/fragmentation approach in the synthesis of some medium ring ketolactones via an intramolecular reverse Dieckmann reaction.[164] Treatment of diones **100** with sodium hydride in refluxing benzene gave 11-membered ketolactones **101** (scheme **2.14**).

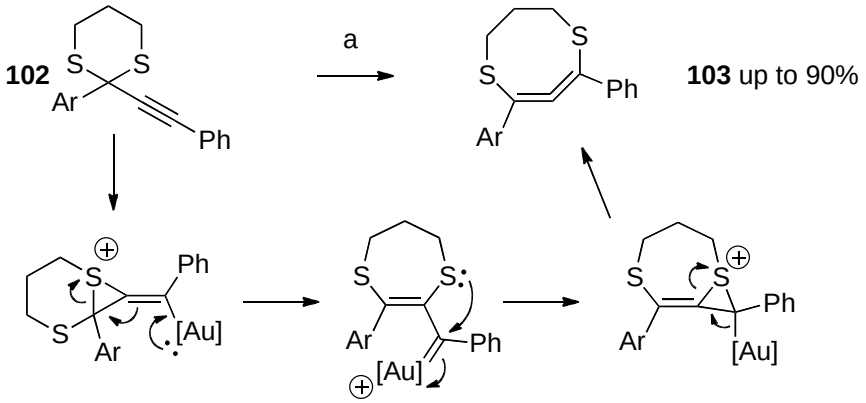


100 **101**

a) NaH, benzene, reflux, 60-72%

Scheme 2.14

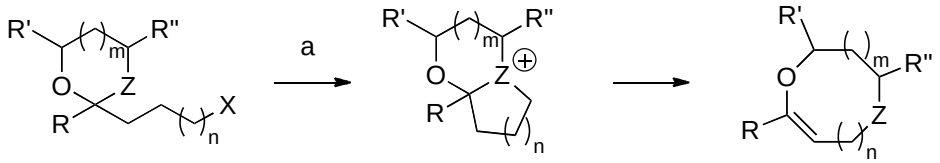
Recently, Wang employed the gold-catalysed ring expansion of propargylic dithianes **102** in the synthesis of eight-membered allenes **103** (scheme **2.15**).[165] The proposed mechanism for this transformation is a series of 1,2-sulfur shifts via a gold carbene intermediate, furnishing the medium ring disulfide in excellent yield.



a) $Au(PPh_3)Cl/AgSbF_6$ (cat.), DCE, 30 min, 80 °C

Scheme 2.15

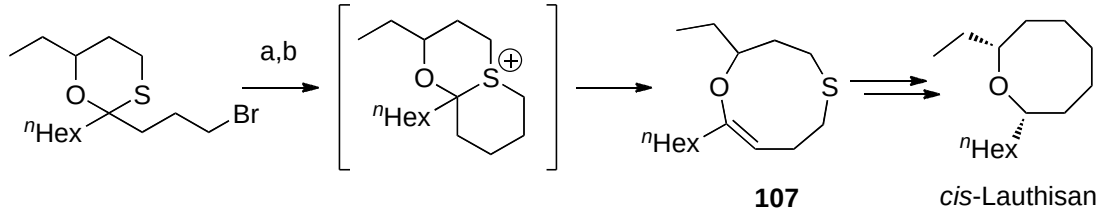
Finally, De Voss and Sui developed a series of acetal ring expansion reactions for the synthesis of medium ring heterocycles (scheme **2.16**).[166,167] Intramolecular S_N2-like displacement of a halide by oxygen and sulfur acetal derivatives **104** afforded charged bicyclic species **105**, which upon ring expansion and trapping with a base furnished medium ring heterocycles **106**.



a) DMF, $^{i}Pr_2NEt$, reflux, 37-86%; m, n = 0-2; R, R', R" = H, Me, Ph; X = Cl, Br; Z = O, S

Scheme 2.16

De Voss later expanded this methodology to the synthesis of *cis*-lauthisan, forming the key 8-membered ether via Ramberg-Backlund ring contraction of 9-membered cyclic sulfide **107** (scheme **2.17**).[168]



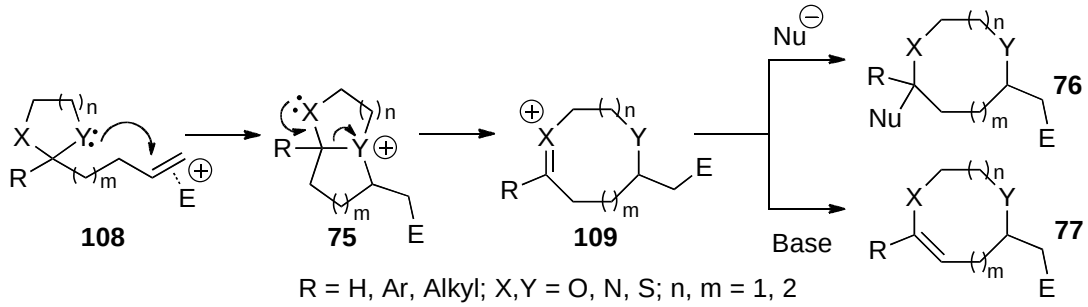
a) NEt_3, DCM; b) $NaCNBH_3$, TFA, THF, 49 % over 2 steps

Scheme 2.17

Many other useful cyclisation and ring expansion methods are also available for the synthesis of medium ring scaffolds; the Thorpe-Ziegler, Acyloin,[169] Tiffeneau-Demjanov[170] and Beckmann[171,172] reactions are to name but a few. Given these elegant examples and the vast number of diverse medium ring syntheses in the literature, the expansion of methodologies for the formation of such structures is both challenging and worthwhile. A generally applicable method for the synthesis of a variety of medium ring heterocycles would be a very valuable resource for the organic chemist.

2.2 Design of Methodology

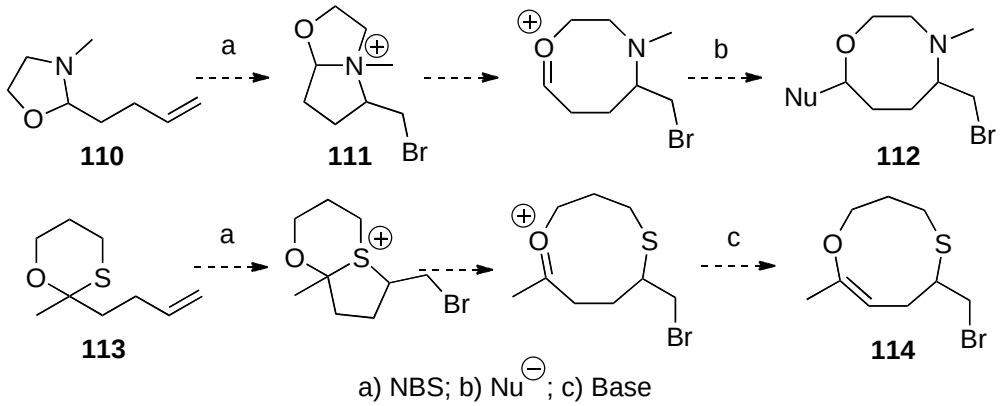
Building on the work of Fujioka, De Voss and co-workers, the aim of this project was to explore the ring expansion chemistry of unsaturated oxygen, nitrogen and sulfur acetal derivatives. One major goal was the development of a new methodology for the synthesis of medium rings, which would facilitate the synthesis of a range of 8- to 11-membered heterocycles. The proposed methodology is outlined below (scheme **2.18**).



Scheme 2.18

Activation of the double bond in **108** with a suitable electrophile should facilitate formation of charged bicyclic species **75** by intramolecular nucleophilic addition. This bicyclic species could then undergo ring expansion to give charged intermediate **109**, which could in turn be trapped by addition of a nucleophile or base to give medium ring heterocycles **76** and **77** respectively.

Variation of the tether length and size of cyclic acetal in the substrate should enable the formation of 8-, 9-, 10- and 11-membered rings, depending on the *endo*- or *exo*-nature of the initial cyclisation. Two representative examples are given in scheme **2.19**, where an electrophilic halogen is used to activate the double bond to nucleophilic attack by the acetal.



Scheme 2.19

A 5-*exo* cyclisation of oxazolidine **110** with NBS would give bicyclic species **111**, which upon ring opening and trapping with a nucleophile would furnish oxazocine **112**. Similarly, cyclisation of oxathiane **113** would give dehydrooxathionine **114** upon ring expansion and trapping with a suitable base. Variation of the electrophile

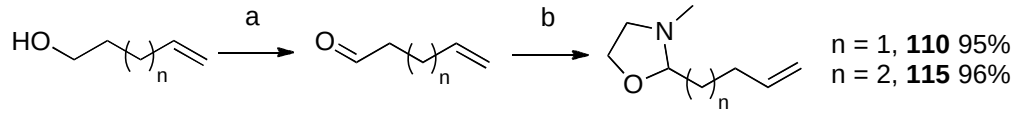
should result in products with a range of groups in place for further functionalisation of the molecule.

Development of this methodology should therefore facilitate the rapid synthesis of a variety of functionalised medium ring heterocycles.

2.3 Synthesis of Unsaturated *O, N*- and *S*-Acetal Derivatives

Work in this area began with the synthesis of a number of oxygen, nitrogen and sulfur acetal derivatives for use in the proposed methodology.

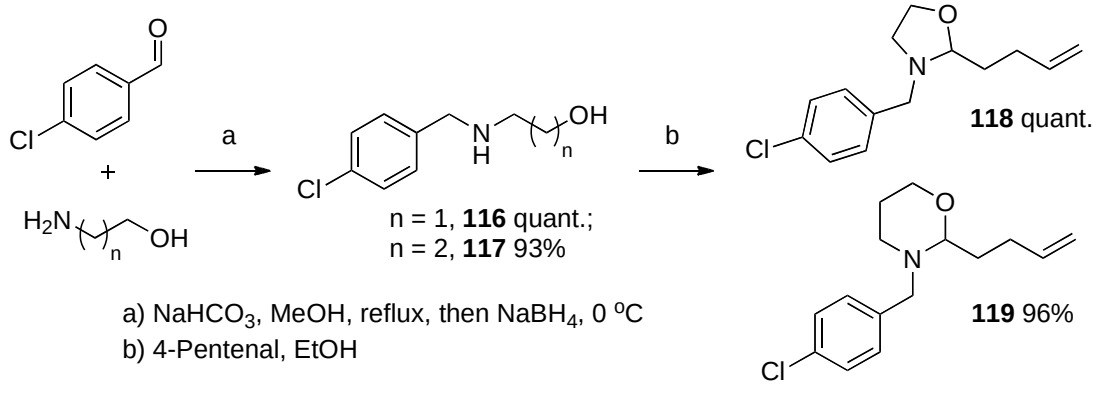
Oxazolidines **110** and **115** were synthesised in good yield by condensation of *N*-methylaminoethanol and the corresponding aldehyde (scheme **2.20**).[173,174]



a) $(COCl)_2$, DMSO, NEt_3, DCM; b) *N*-Methylaminoethanol, EtOH

Scheme 2.20

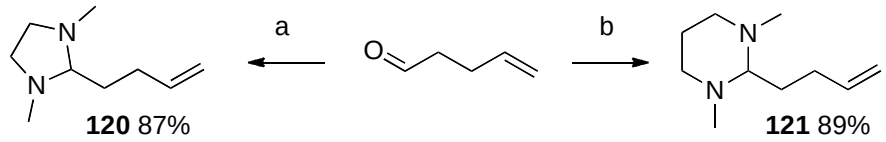
N-(*p*-Chlorobenzyl)aminoalcohols **116** and **117** were prepared by reductive amination of *p*-chlorobenzaldehyde with either 2-aminoethanol or 3-aminopropanol. These were then used to furnish oxazolidine **118** and 1,3-oxazinane **119** by the above procedure (scheme **2.21**).[175]



a) $NaHCO_3$, MeOH, reflux, then $NaBH_4$, 0 ^oC
b) 4-Pentenal, EtOH

Scheme 2.21

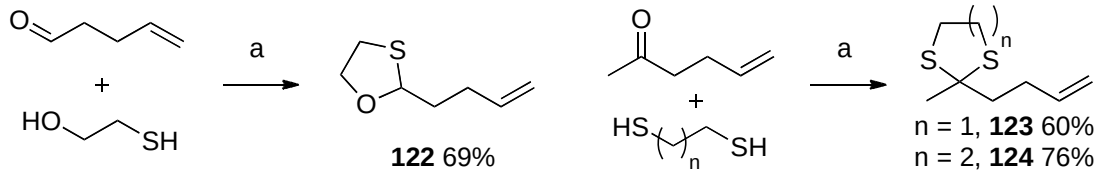
Using *N,N'*-dimethyldiamines in place of the aminoalcohol, imidazolidine **120** and hexahydropyrimidine **121** were prepared using the same condensation technique (scheme **2.22**).



a) *N,N'*-Dimethylethanediamine, EtOH; b) *N,N'*-Dimethylpropanediamine, EtOH

Scheme 2.22

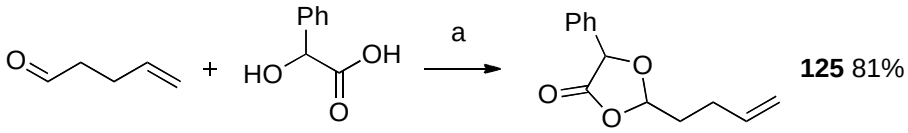
More forcing conditions were required for the synthesis of *S,O*- and *S,S*-acetal derivatives **122**, **123** and **124** and boron trifluoride diethyletherate was used as a Lewis acid to facilitate the transformation (scheme **2.23**).[176]



a) $BF_3.OEt_2$, DCM, 0 ^oC to rt

Scheme 2.23

Finally, dioxolanone **125** was prepared by treatment of 4-pentenal with mandelic acid under microwave irradiation in the presence of anhydrous copper sulfate[177] (scheme **2.24**).



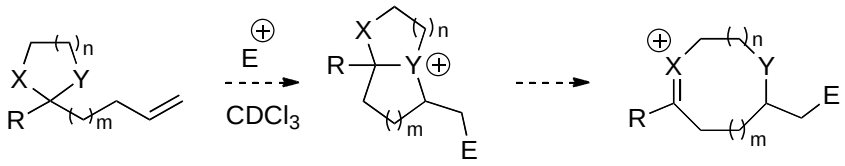
a) $CuSO_4$, MW, 100 ^oC

Scheme 2.24

With these substrates in hand, it was then possible to begin the screening of suitable electrophiles for activation of the double bond.

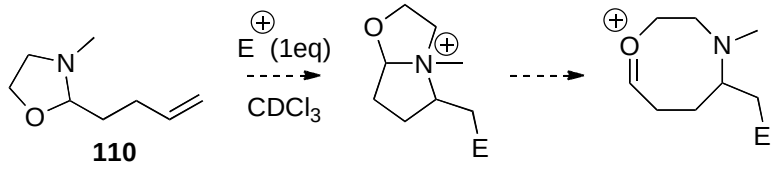
2.4 Results and Discussion

Initially, each of the new substrates was subjected to a screen of a stoichiometric amount of seven different electrophiles in $CDCl_3$ and the reactions were monitored by TLC and ^1H NMR (scheme **2.25**).



Scheme 2.25

Results of the screen of oxazolidine **110** with the 7 electrophiles are summarised below in table **2.1**.



110

E = NBS, I_2, $Pd(OAc)_2$, $PdCl_2$, $PtCl_2$, $Au(PPh_3)Cl/AgOTf$, $AgNO_3$/silica

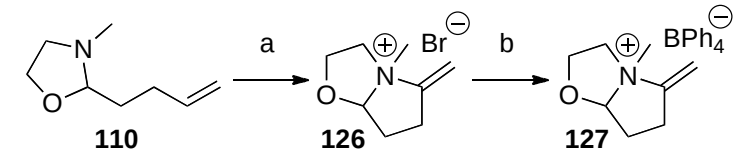
Entry	Electrophile	Time/h	Temp/°C	Observation
1	NBS	1	25	Conversion to new product
2	I_2	0.5	25	Complex mixture
3	$Pd(OAc)_2$	0.5	25	Complex mixture
4	$PdCl_2$	24	25	No reaction
5	$PdCl_2$	24	60	No reaction
6	$PtCl_2$	24	25	No reaction
7	$PtCl_2$	24	60	No reaction
8	$AuPPh_3$/AgOTf	24	25	No reaction
9	$AuPPh_3$/AgOTf	24	60	No reaction
10	$AgNO_3$/silica	24	25	No reaction
11	$AgNO_3$/silica	24	60	No reaction

Table 2.1

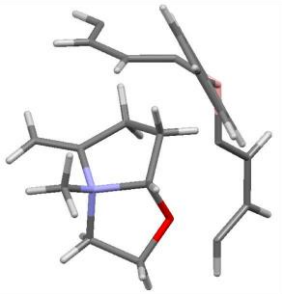
Surprisingly there was no observable reaction with $PdCl_2$, $PtCl_2$, $AuPPh_3Cl$ or $AgNO_3$ even upon heating the reaction mixtures for several hours (entries 4-11). Oxazolidine **110** reacted rapidly with both I_2 and $Pd(OAc)_2$, although the product mixtures obtained were complex and inseparable by conventional purification techniques (entries 2 and 3).

However, reaction of oxazolidine **110** with NBS (entry 1) proceeded smoothly and after 1 h at room temperature the NMR spectrum showed complete conversion to a

new product, which was believed to be bicyclic enaminium species **126** (scheme **2.26**). A similar species was observed in the crude NMR of entry 2, although isolation from the complex reaction mixture was not possible.



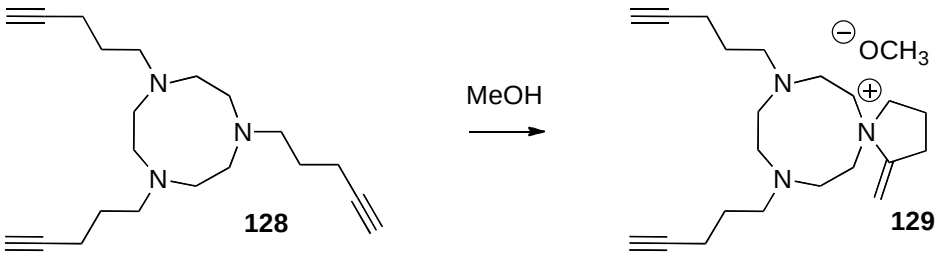
a) NBS (1 eq), $CDCl_3$, 1 h, rt; b) $NaBPh_4$ (1 eq), MeOH, 1 min, rt



Scheme 2.26

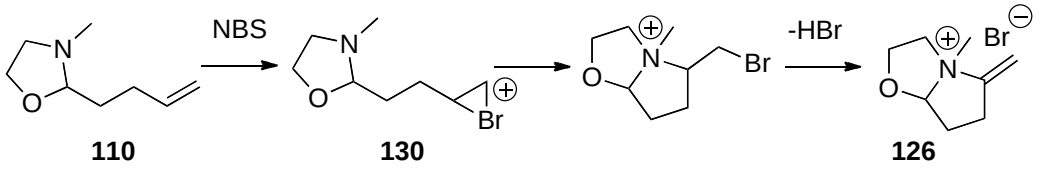
Upon addition of $NaBPh_4$ to a solution of **126** in methanol, tetraphenylborate salt **127** precipitated in quantitative yield. Slow recrystallisation of **127** by vapour diffusion (DMSO-water) produced a single crystal, which was submitted for X-ray analysis, confirming the structure of this intriguing enaminium salt. Pleasingly, formation of **126** also proceeded rapidly in DCM, which was therefore used in place of $CDCl_3$ for repeat preparations.

Formation of cyclic enaminium species has been reported for the intramolecular hydroamination of alkynes by tertiary amines.[178] For example, Baker *et al* observed that triazacyclononane species **128** underwent intramolecular hydroamination to form azoniaspiro[4.8]tridecane **129** in methanol solution (scheme **2.27**).[179] Formation of such a species by amination of an alkene has yet to be reported.



Scheme 2.27

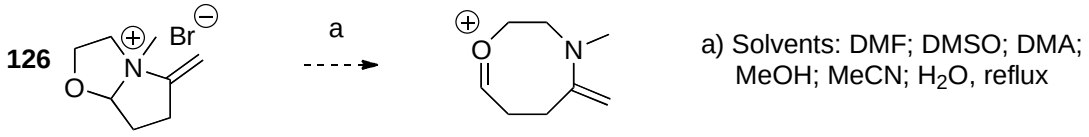
The formation of **126** was initially thought to proceed via 5-*exo* cyclisation of bromonium species **130**, followed by loss of HBr (scheme **2.28**).



Scheme 2.28

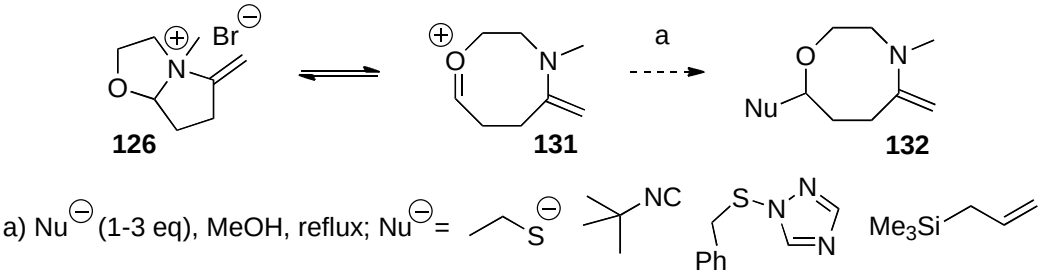
With this surprisingly stable new species in hand, several attempts were then made to open the bicyclic structure to give the desired 8-membered ring. Frustratingly, all attempts to do so were unsuccessful and the enaminium salt remained intact after several hours under forcing conditions.

Firstly, the enaminium salt was heated in polar solvents in an attempt to promote ring expansion. However, **126** was left intact even after several hours in refluxing solvents such as DMF and DMSO (scheme **2.29**).



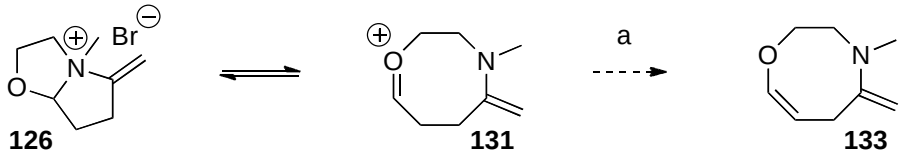
Scheme 2.29

Nucleophiles such as thiolates, isocyanides and triazoles were then used in an attempt to trap the charged ring-opened species **131** to give functionalised oxazocines **132** (scheme **2.30**). Again, the bicyclic structure was resistant to these conditions and was the only species isolated from the reaction mixtures.



Scheme 2.30

Several attempts were made to trap the charged ring-opened species **131** by deprotonation to give dehydrooxazocine derivative **133**, although none proved successful (scheme **2.31**).

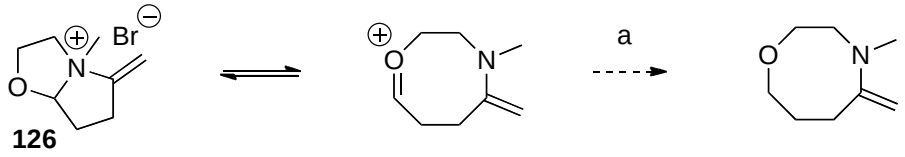


126 **131** **133**

a) Base (1-3 eq), solvent, reflux; Bases = NEt_3, DIEA, DBU, KO^tBu, NaO^tBu, NaOMe, KHMDS; Solvents = DMSO, MeOH or THF

Scheme 2.31

The enaminium salt was even stable to a range of strong reducing agents such as $LiAlH_4$ and $NaBH_4$ (scheme **2.32**).

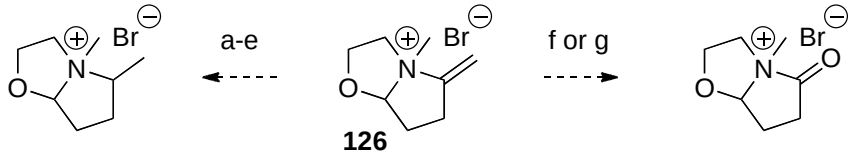


126

a) [H] (1-5 eq), MeOH/THF, rt; [H] = $LiAlH_4$, $LiBH_4$, $NaBH_4$, $NaCNBH_3$, Et_3SiH, Et_3SiH/TFA

Scheme 2.32

Finally, attempts were made to react the exocyclic double bond in **126**, firstly by hydrogenation and then by oxidative cleavage (scheme **2.33**). Once more the bicycle remained untouched in both cases.



126

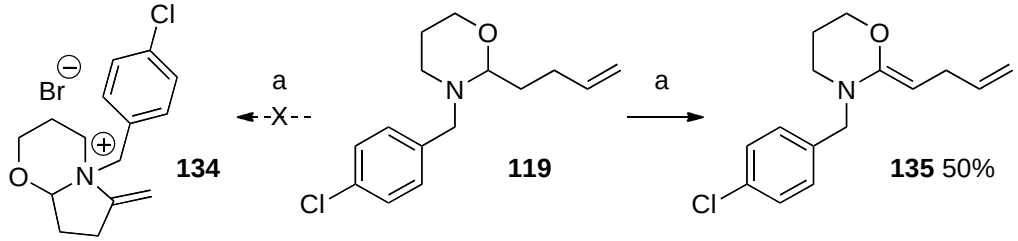
a) H_2 (1 atm), Pd/C (10 mol%), MeOH; b) H_2 (1 atm), Pd/C (10 mol%), MeOH, H_2O, HCl; c) H_2 (1 atm), $Pd(OH)_2$ (10 mol%), MeOH; d) H_2 (1 atm), PtO_2 (10 mol%), MeOH; e) H_2 (1 atm), Pt/Kaowool (5 mol%), MeOH; f) O_3, DCM; g) RuO_2 (2.5 mol%), $NaIO_4$ (4 eq), $NaHCO_3$ (1.5 eq), EtOAc/H_2O

Scheme 2.33

The 5,5-ring system in **126** may be too rigid to allow orientation of the oxygen lone pair at 180° to the central bond, making elimination of the amine extremely difficult. Synthesis of an analogous 6,5-ring system may therefore allow sufficient flexibility in the bicyclic salt for successful ring opening (figure **2.2**).

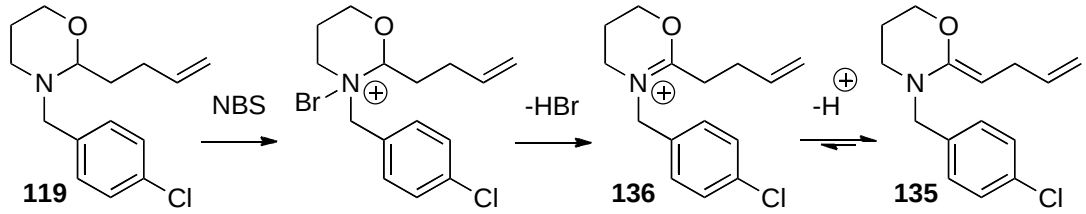
Figure 2.2

Unsaturated oxazinane derivative **119** was therefore expected to undergo a similar 5-*exo* cyclisation upon treatment with NBS to give the corresponding 6,5-bicyclic enaminium salt **134** (scheme **2.34**). However, *N,O*-ketene acetal **135** was the only product isolated from this reaction, with no observation of cyclisation to form the enaminium species.



Scheme 2.34

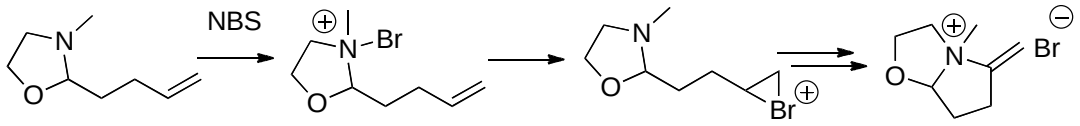
One plausible mechanism for the formation of this *N,O*-ketene acetal is outlined below (scheme **2.35**). *N*-Bromination of the oxazinane followed by loss of HBr forms cyclic amidium species **136**, which can then lose a proton to give the *N,O*-ketene acetal.



Scheme 2.35

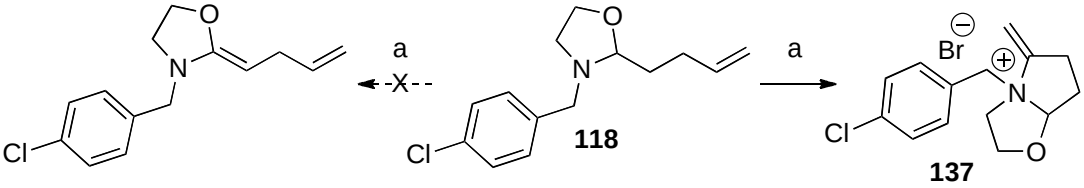
This observation suggests that the formation of bicyclic enaminium species **126** may proceed via a similar *N*-bromination prior to bromonium ion formation (scheme **2.36**). If this is the case, then loss of HBr occurs at a slower rate than the cyclisation

and the bicyclic species is the only product observed. Alternatively, a Hofmann-Löffler-Freytag-type radical mechanism can also be envisaged.[180,181]



Scheme 2.36

At this point it was unclear whether it was the nature of the heterocycle or the substituent on nitrogen that was hindering the cyclisation in this case. To investigate this, *N*-(*p*-chlorobenzyl)oxazolidine **118** was subjected to the same reaction conditions (scheme **2.37**).

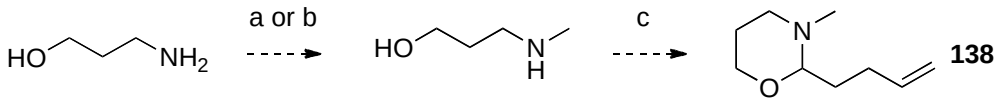


a) NBS (1 eq), DCM, 1 h, rt

Scheme 2.37

As with oxazolidine **110**, **118** rapidly reacted with NBS to give the corresponding 5,5-bicyclic enaminium species **137**, proving that the larger *p*-chlorobenzyl substituent on nitrogen has no effect on the outcome of the reaction.

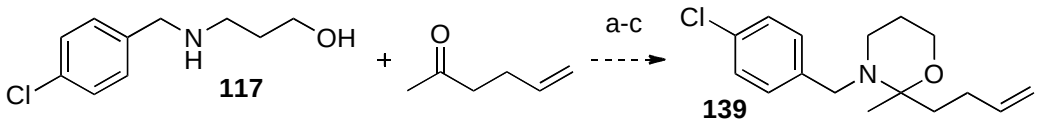
Attempts were made to make *N*-methylaminopropanol by reductive amination of formaldehyde in order to prepare the analogous *N*-methyloxazinane derivative **138** (scheme **2.38**). Unfortunately preparation of the aminoalcohol proved to be difficult, resulting in complex, insoluble reaction mixtures and efforts to form the oxazinane derivative were abandoned.



a) CH_2O (aq), $NaHCO_3$, MeOH then $NaBH_4$; b) $(CH_2O)_n$, $NaHCO_3$, MeOH then $NaBH_4$; c) 4-Pentenal, EtOH

Scheme 2.38

In order to avoid the formation of *N,O*-ketene acetals such as **135**, it was decided that synthesis of a ketal derivative with no α-hydrogen was necessary. Focus therefore turned to the synthesis of *N,O*-ketal derivative **139** (scheme **2.39**).

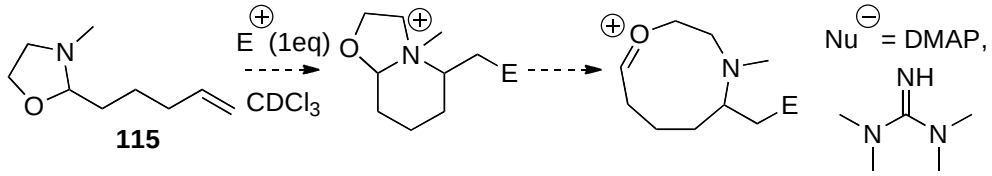


a) EtOH, reflux; b) $CuSO_4$, MW, 100 ^oC; c) Amberlyst resin, toluene, Dean-Stark

Scheme 2.39

Frustratingly, all attempts at the synthesis of **139** were unsuccessful. No condensation was observed between aminoalcohol **117** and hexen-2-one under standard *N,O*-acetal formation conditions. Treatment of the reaction mixture with copper sulfate under microwave conditions resulted in an insoluble complex mixture, presumably due to polymerisation. This was also the case when the reagents were subjected to Dean-Stark conditions in the presence of Amberlyst resin.

Longer chain oxazolidine derivative **115** showed no signs of reaction with any of the seven electrophiles screened (scheme **2.40**). No cyclisation was observed with NBS even in the presence of nucleophilic catalysts such as DMAP or tetramethylguanidine.

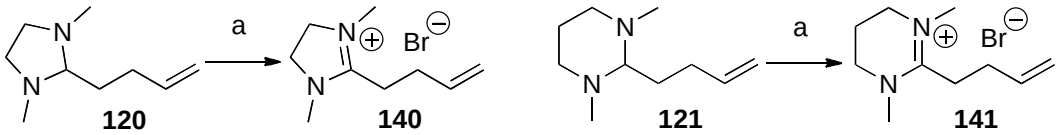


$E^{\oplus}$ = NBS, I_2, $Pd(OAc)_2$, $PdCl_2$, $PtCl_2$, $Au(PPh_3)Cl/AgOTf$, $AgNO_3$/silica, NBS/$Nu^{\ominus}$

Scheme 2.40

N,N-Acetal derivatives **120** and **121** also appeared to undergo *N*-bromination when treated with NBS; giving rapid, clean conversion to new species **140** and **141**. The NMR spectra of these new species showed that the terminal double bond remained intact in both cases. Quaternary carbon resonances at 168 and 164 ppm in **140** and **141** respectively had HMBC correlations with the two sets of diastereotopic protons next to nitrogen. These observations are consistent with cyclic amidinium species

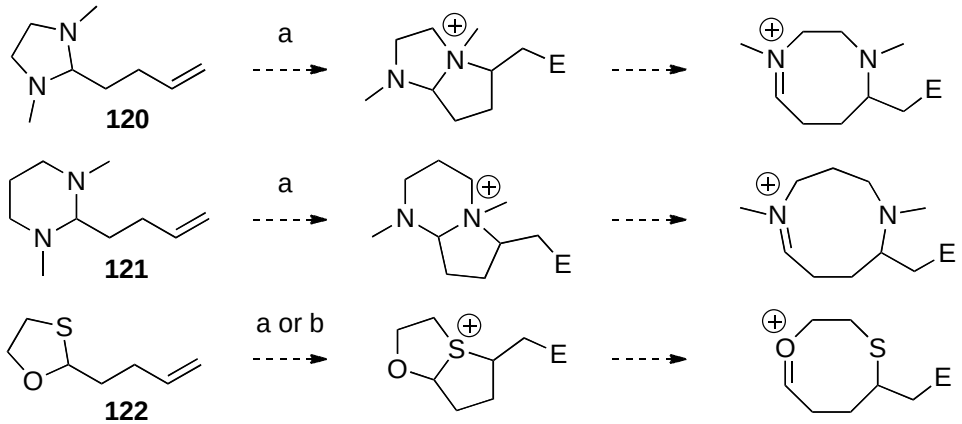
140 and **141** (scheme **2.41**).[182] Isolation of the products proved difficult however and the salts could not be fully characterised.



a) NBS (1 eq), $CDCl_3$, 1 h, rt

Scheme 2.41

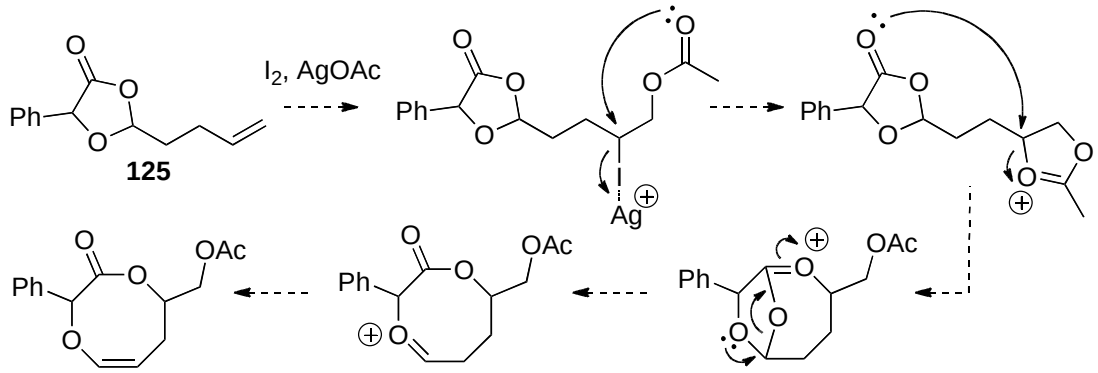
As with oxazolidine **110**, **120** and **121** gave complex, inseparable mixtures on treatment with iodine. Screens of **120** and **121** with the other 5 electrophiles proved fruitless, with little to no reactivity observed in each instance. This was also the case with oxathiolane **122**, which reacted with none of the electrophiles screened (scheme **2.42**).



a) $E^{\oplus}$ = I_2; $Pd(OAc)_2$; $PdCl_2$; $PtCl_2$; $Au(PPh_3)Cl/AgOTf$; $AgNO_3$/silica, $CDCl_3$;
b) NBS, $CDCl_3$

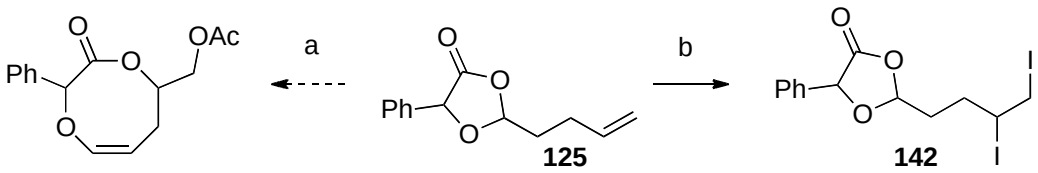
Scheme 2.42

Dioxolanone **125** was also screened against the standard seven electrophiles, but was observed to be unreactive in all cases. It was therefore decided to attempt a Woodward-Prevost type reaction as outlined in scheme **2.43** by treating **125** with iodine in the presence of a silver (I) salt.[183]



Scheme 2.43

Firstly, **125** was treated with iodine in the presence of an excess of silver acetate[184] in $CDCl_3$. Extremely slow formation of a new product was observed by crude NMR, although this species could not be isolated. Screening of a range of silver salts (table **2.2**) identified AgCl as the most efficacious and this reaction was allowed to reach completion over a period of 72 h. The NMR spectra of the new species showed consumption of the double bond, but no cyclisation and appeared to be consistent with iodination of the double bond to form **142** (scheme **2.44**).[185] Acceleration of the iodination in the presence of AgCl could be due to the formation of the more reactive electrophile ICl *in situ*. All attempts to isolate this new species were unsuccessful, presumably due to decomposition on silica gel.



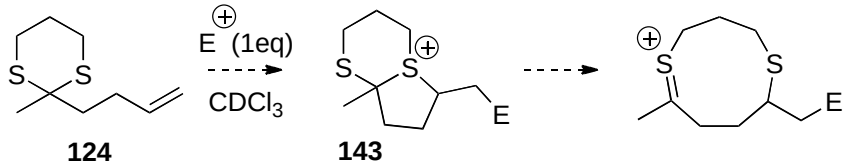
I_2, AgX, AcOH, $CDCl_3$; a) AgX = AgOAc, $AgPF_6$, AgOTf, $AgNO_3$, AgOTs, $AgBF_4$; b) AgX = AgCl

Scheme 2.44

Entry	AgX	Time/h	Observation
1	AgOAc	24	Extremely slow formation of **142**
2	AgOTf	24	Complex mixture
3	AgCl	72	Slow formation of **142**
4	AgOTs	72	Complex mixture
5	$AgNO_3$	24	Complex mixture
6	$AgPF_6$	72	No reaction
7	$AgBF_4$	72	No reaction

Table 2.2

The final substrate screened against the standard seven electrophiles was dithiane derivative **124**. Frustratingly, no reaction was observed with NBS, iodine or the gold and silver salts and there was no formation of the desired bicyclic species **143** (scheme **2.45**).

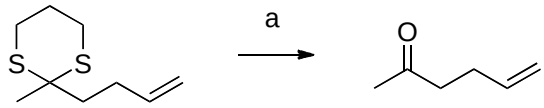


124 **143**

E = NBS, I_2, $Au(PPh_3)Cl/AgOTf$, $AgNO_3$/silica

Scheme 2.45

However, treatment of **124** with stoichiometric $PdCl_2$ resulted in slow conversion to a new species by TLC and crude NMR. Upon completion, the reaction mixture appeared to contain only ketone **144**, suggesting that the $PdCl_2$ acts as a Lewis acid in this case, facilitating the cleavage of the dithiane (scheme **2.46**). A brown precipitate formed during the course of the reaction, which was presumably an insoluble complex between the palladium and propanedithiol.

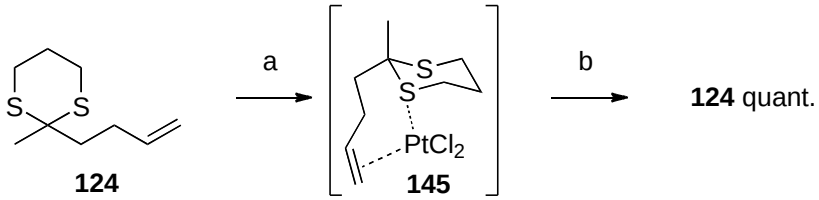


124 **144**

a) $PdCl_2$ (1 eq), $CDCl_3$, 5 d, rt

Scheme 2.46

In contrast to the slow reactivity with $PdCl_2$, dithiane **124** reacted rapidly with $PtCl_2$ to give what appeared to be a sulfur-platinum complex of the form **145** (scheme **2.47**). Addition of one equivalent of triphenylphosphine to this complex resulted in rapid dissociation to give the starting dithiane in quantitative conversion by NMR.

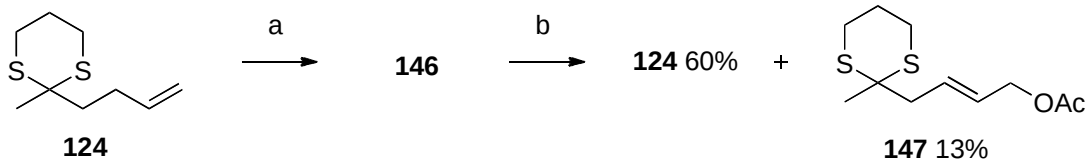


124 **145**

a) $PtCl_2$ (1 eq), $CDCl_3$, 5 min, rt; b) PPh_3 (1 eq), 1 min, rt

Scheme 2.47

Similarly, **124** reacted with $Pd(OAc)_2$ to give a new species **146** by crude NMR, which also dissociated rapidly upon addition of triphenylphosphine (scheme **2.48**). However, whilst starting dithiane **124** was the major component of the reaction mixture, trace amounts of other species were visible in the crude NMR spectrum. Purification of the reaction mixture on silica gel confirmed the formation of a new species; allylic acetate **147**, which was isolated in 13% yield.



a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 5 min, rt; b) PPh_3 (1 eq), 1 min, rt

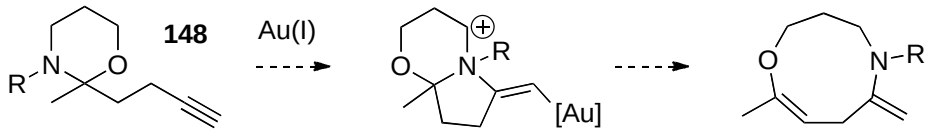
Scheme 2.48

The isolation of **147** was the first, perhaps serendipitous step towards an investigation into the use of thioacetals as directing groups in the palladium-mediated oxidation of olefins. Details of this new project and elucidation of the structure of **146** will be discussed in the next chapter.

2.5 Conclusions and Future Work

A number of unsaturated acetal derivatives have been made for use in the proposed methodology and subjected to a screen of electrophiles with varying outcomes. Although no medium rings have been successfully created thus far, some interesting observations were made. These observations have given insight into the factors affecting the formation of the desired charged bicyclic precursors to ring expansion and the likelihood of future success for this methodology.

Firstly, formation of bicyclic enaminium species **126** was an encouraging start; demonstrating that the double bond in **110** could be activated towards nucleophilic attack from the acetal. However, in the majority of cases, the double bond was resistant to activation by the electrophiles screened and no cyclisation was observed. Acetal derivatives **148** bearing a more reactive pendant alkyne may be more susceptible to activation by soft metal π-acids such as gold (I) species (scheme **2.49**). This will be one area of exploration in the future development of this methodology.

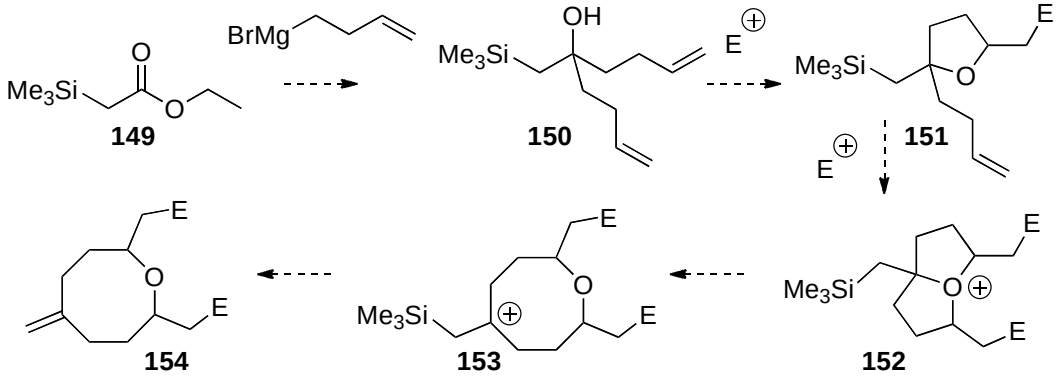


Scheme 2.49

The surprising stability of **126** to standard ring opening and trapping conditions suggested that the 5,5-bicyclic system was too rigid for ring-expansion and that an analogous 6,5-system may be more likely to ring-open. Conversely, synthesis of an analogous 6-membered *N,O*-acetal **119** resulted in the formation of *N,O*-ketene acetal **135** via loss of the α-proton upon *N*-bromination and no cyclisation was observed. Similar observations were made with *N,N*-acetals **120** and **121**, suggesting a requirement for the formation of ketal derivatives that possess no α-hydrogens.

Future work on this methodology will therefore focus on the synthesis of ketone-derived *N*-,*O*- and *S*-acetals bearing both alkene and alkyne tethers for activation by a range of metal π-acids and electrophilic halogens.

Another interesting route to explore is the use of silicon as a cation-stabilizing group in some similar bicycle fragmentation reactions. For example, double butenyl Grignard addition to ethyl trimethylsilylacetate **149** should give tertiary alcohol **150** (scheme **2.50**).

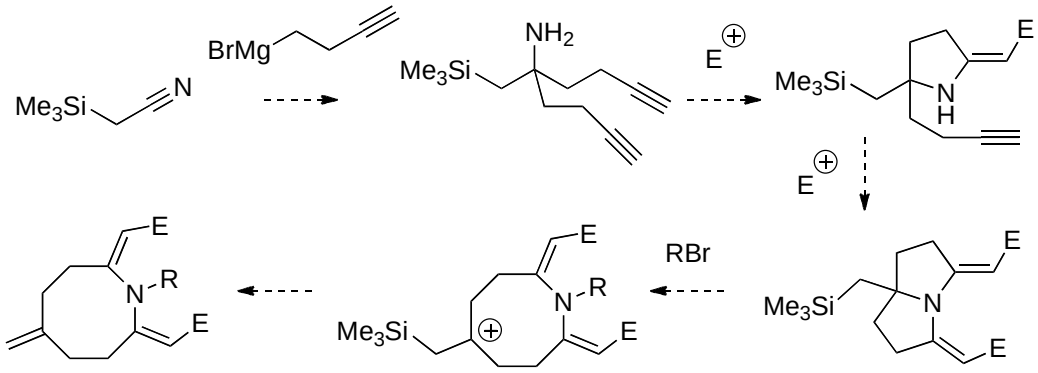


Scheme 2.50

Successive activation of the double bonds in **150** should furnish charged bicyclic species **152** via tetrahydrofuran **151**. Ring opening would lead to stabilized carbocation **153**, which could then be quenched upon work-up to give medium ring

ether **154**. This approach is comparable to that used by Fujioka (discussed earlier) although with the absence of a tethered nucleophile. Efforts have already begun to synthesise the tertiary alcohol **150**, although its isolation has proved difficult thus far.

A nitrogen analogue is feasible, simply by replacing the ethyl trimethylsilylacetate with trimethylsilylacetonitrile. This route is also expected to be compatible with the use of alkynes in place of alkenes (scheme **2.51**).

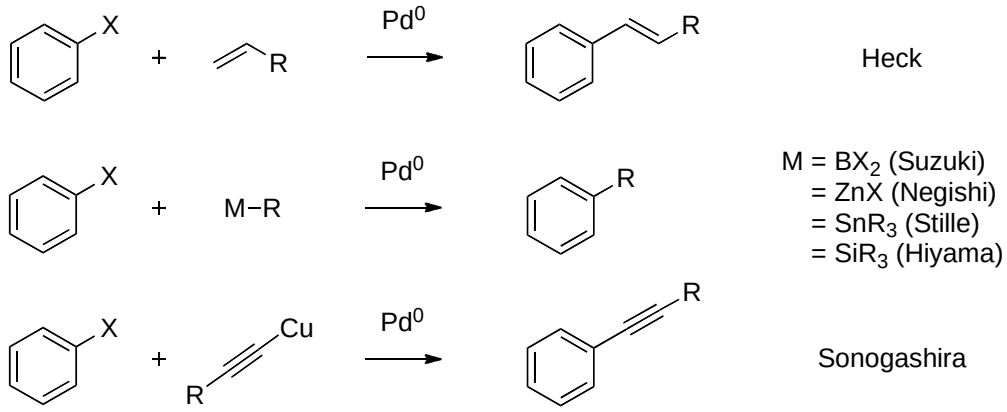


Scheme 2.51

3. Thioacetals as Directing Groups in the Palladium-Mediated Oxidation of Olefins

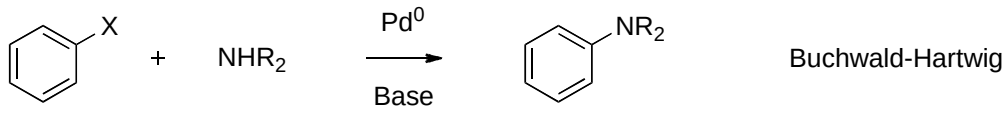
3.1 Introduction

Palladium is commonly regarded to be one of the most important transition metals used in organic synthesis.[186] Its versatility and wide range of applications make organopalladium chemistry an extremely powerful synthetic tool.[187] The palladium-catalysed cross-coupling alone is one of the most powerful and widely used reactions in modern organic chemistry.[188,189] Many elegant Pd^0-mediated cross-coupling procedures for the formation of carbon-carbon bonds have been developed and studied in great detail; the Mizoroki-Heck,[190,191] Negishi,[192] Suzuki-Miyaura,[193] Kosugi-Migita-Stille,[194,195] Hiyama[196] and Sonogashira[197] reactions are to name but a few (scheme **3.1**).



Scheme 3.1

The Buchwald-Hartwig C-X amination is an extremely powerful variant of this theme, building upon the traditional cross-coupling procedures mentioned above (scheme **3.2**).[198,199]

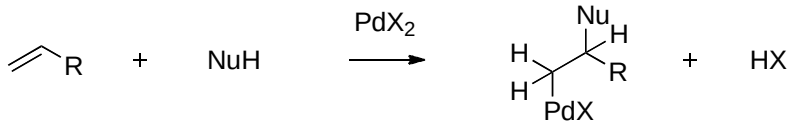


Scheme 3.2

The wealth and breadth of research in this area is remarkable, proving the palladium-mediated cross-coupling to be an indispensible tool in modern organic synthesis. For

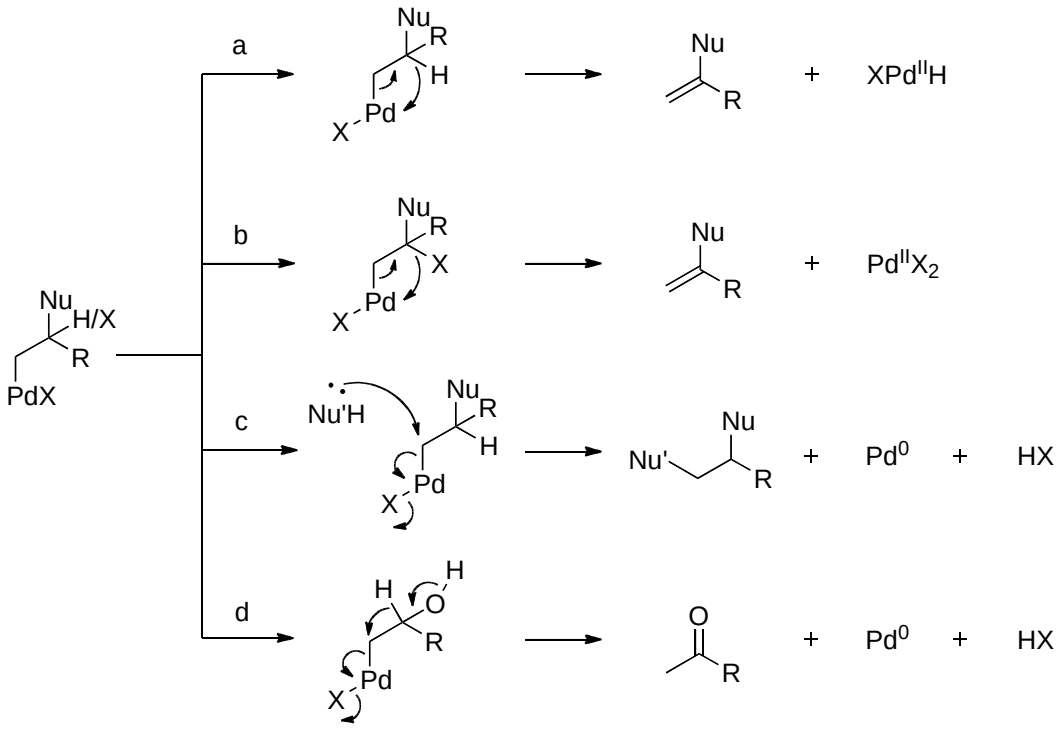
their respective contributions to this chemistry, Professors Heck, Negishi and Suzuki were awarded the joint Nobel Prize for Chemistry in 2010.

The chemistry of Pd^{II} species is very different and, whilst extremely useful and powerful in its own right, has received somewhat less attention.[200] Pd^{II} salts such as $PdCl_2$ and $Pd(OAc)_2$ are unique oxidising agents with a remarkable affinity for alkenes. Alkenes bind to electrophilic Pd^{II} salts, reducing their electron density and rendering them susceptible to nucleophilic attack. Many olefins undergo palladation to form Pd-C σ-complexes in the presence of a nucleophile (scheme **3.3**).



Scheme 3.3

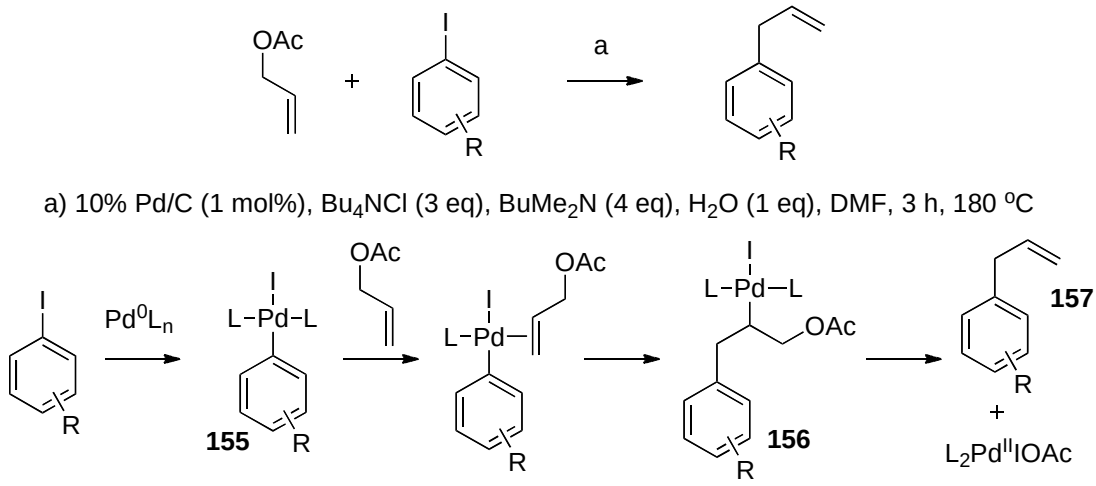
These Pd-C species are generally short-lived and readily undergo further transformations to give oxidised products, with reduction of the Pd^{II} to generate Pd^0. Four main pathways for the decomposition of such palladated alkenes are detailed below in scheme **3.4**.



X = Hal, OAc; NuH = H_2O, RNH_2, ROH, RCO_2H

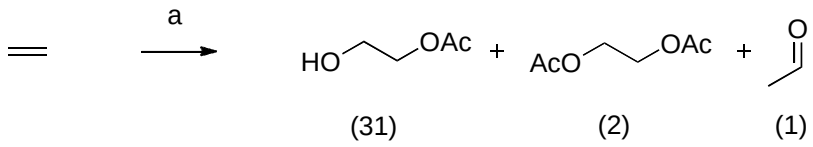
Scheme 3.4

The hydrogen atom β-to the palladium is readily eliminated to give an alkene and a palladium hydride, which in turn eliminates H-X to give Pd^0 (path a). This is also a common route for the decomposition of Pd-C σ-complexes containing a β-heteroatom, whereby the eliminated species (typically a halide or acetate) takes the place of the hydride, resulting in a β-chloride or β-acetoxy elimination (path b). Lautens recently published an intermolecular Heck-type coupling of aryl iodides and allylic acetates, which involves a β-acetoxy elimination of this kind.[201] The allylic acetate undergoes carbopalladation with aryl palladium species **155** to give Pd-C σ-complex **156** (scheme **3.5**). A β-acetoxy elimination then gives the allyl aromatic product **157** and a Pd^{II} species, which upon reduction regenerates Pd^0 and completes the catalytic cycle. Whilst formally catalysed by Pd^0, this example neatly demonstrates the β-heteroatom elimination decomposition pathway for Pd^{II}-C σ-complexes.



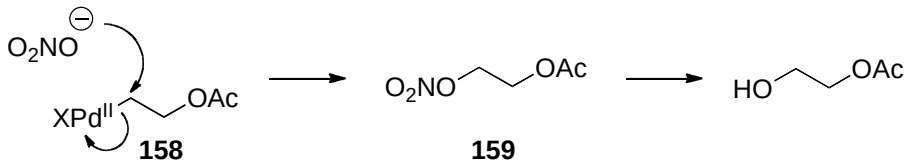
Scheme 3.5

Pd-X can be substituted by an appropriate nucleophile to give a trisubstituted alkane (path c); this route also reduces the palladium to Pd^0. Tamura and Yasui demonstrated the utility of this transformation in the synthesis of ethylene glycol monoacetate from ethylene in the presence of catalytic $PdCl_2$ and $LiNO_3$ (scheme **3.6**).[202] The authors propose an acetoxypalladation of ethylene to give Pd-C σ-species **158**, which then undergoes nucleophilic attack by nitrate to give **159**. This organic nitrate is then hydrolysed *in situ* to give the glycol monoacetate as the major product, with traces of the diacetate and acetaldehyde.



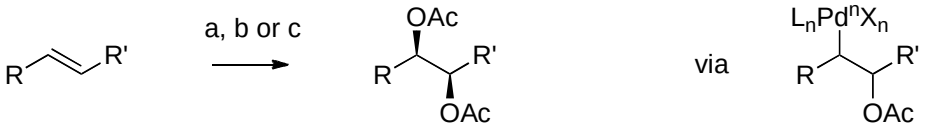
(31) (2) (1)

a) $PdCl_2$ (cat.), $LiNO_3$ (1 eq), AcOH, 2 h, 50 ^oC; product ratios in parentheses



Scheme 3.6

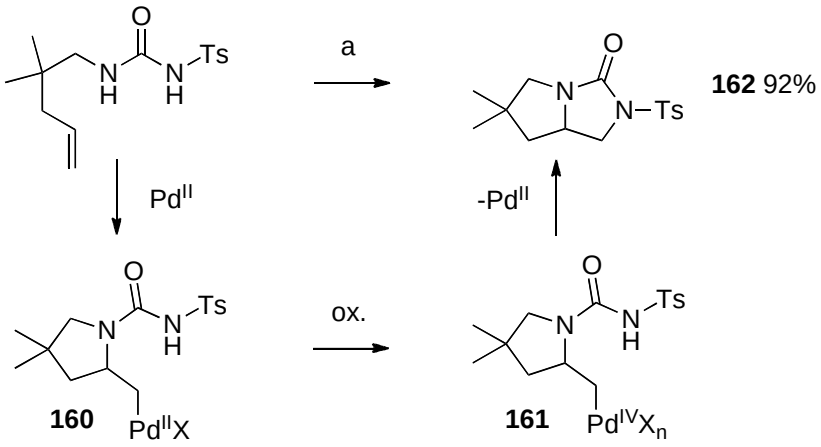
More recently, there has been much interest in the Pd^{II}-catalysed diacetoxylation of olefins, as reported by Dong,[203] Jiang[204] and Jung[205] (scheme **3.7**).



a) $Pd(bpy)OAc_2$ (2 mol%), $PhI(OAc)_2$ (1.1 eq), H_2O (3 eq), AcOH; then Ac_2O, rt (Dong);
b) $Pd(OAc)_2$ (2 mol%), KI (20 mol%), AcOH, O_2 (8 atm), 24 h, 100 ^oC (Jiang);
c) $Pd(OAc)_2$ (2 mol%), CH_3CO_3H (1.2 eq), Ac_2O, AcOH, 60 min, rt (Jung)

Scheme 3.7

The exact mechanism of this transformation is the subject of much debate, although many reports propose a Pd^{II}/Pd^{IV} catalytic pathway under these oxidising conditions. For example, Muñiz reported the intramolecular diamination of olefins under similar conditions to those described above for diacetoxylation (scheme **3.8**).[206] An initial intramolecular aminopalladation of the olefin gives Pd-C σ-species **160**, which then undergoes nucleophilic substitution by the other amine to give the diaminated product **162**. Muñiz proposes that **160** is oxidised to Pd^{IV} species **161** under these highly oxidising conditions prior to substitution by the second amine. This suggestion is supported by the observation that no diaminated product was observed in a stoichiometric example in the absence of $PhI(OAc)_2$.



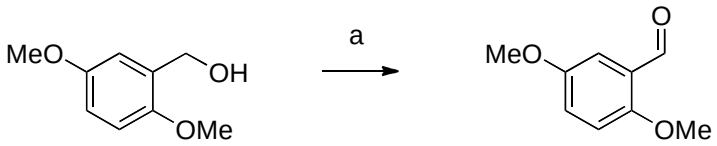
a) $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2.2 eq), NaOAc (1 eq), DCM, 12 h, rt

Scheme 3.8

The fourth main pathway for decomposition of Pd-C σ-complexes is a hydride shift such as the one depicted in path d (scheme **3.4**). If the initial nucleophilic species is hydroxide, a hydride shift can take place, forming a carbonyl with loss of Pd^0 to give a methyl ketone. This latter process is proposed as the mechanism for the formation of acetaldehyde in the Wacker oxidation (discussed later).

All of the processes described above result in the formation of Pd^0, which is inactive as an oxidising agent and unable to react with a second equivalent of alkene as a result. Consequently, it is necessary to re-oxidise the Pd^0 to Pd^{II} if an efficient catalytic cycle is to be established.[207-209] Species such as Cu^{II} salts, *p*-BQ, MnO_2 and peroxides are often used as stoichiometric co-oxidants and many well established catalytic methods operate efficiently under these conditions. However, more recently there have been significant advances in the use of dioxygen as an environmentally benign co-oxidant for metal-mediated processes such as Pd^{II} catalysis.[210]

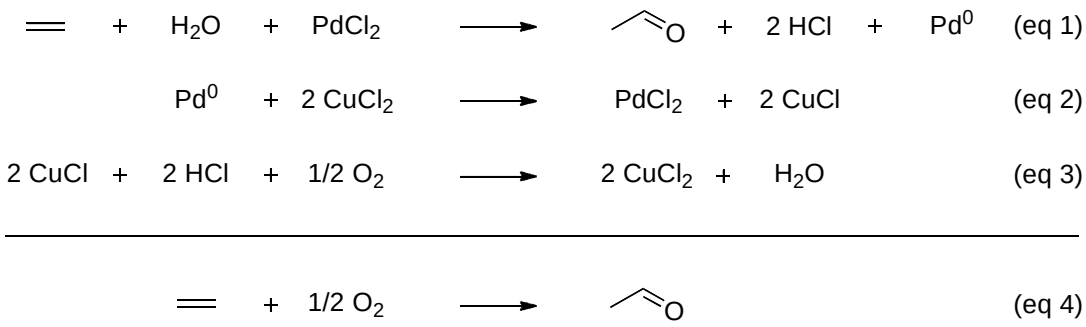
For example, Larock reported the catalytic oxidation of benzylic alcohols to aldehydes in the presence of $Pd(OAc)_2$ and a $DMSO/O_2$ co-oxidant system (scheme **3.9**).[211] The catalytic turnover was relatively slow, although yields were high; this was confirmed by Stahl, who demonstrated that oxidation of Pd^0 by dioxygen was the rate-limiting step in this catalytic cycle.[212]



a) $Pd(OAc)_2$ (5 mol%), DMSO, O_2, 80 ^oC, 95%

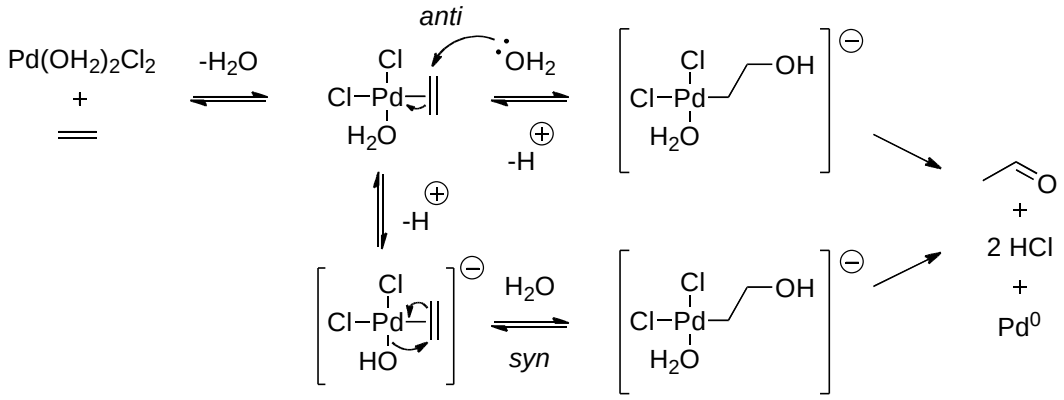
Scheme 3.9

As mentioned above, perhaps the most important example of palladium-mediated alkene oxidation is that of the Wacker process.[213] The traditional Wacker oxidation involves the catalytic conversion of ethylene into acetaldehyde in the presence of $PdCl_2$, $CuCl_2$ and dioxygen (scheme **3.10**). The active catalyst $PdCl_2$ is regenerated *in situ* by co-oxidation of Pd^0 with $CuCl_2$ (eq 2), which is itself re-oxidised by dioxygen (eq 3). The three half equations in scheme **3.10** can be combined to give the overall catalytic transformation (eq 4).[214]



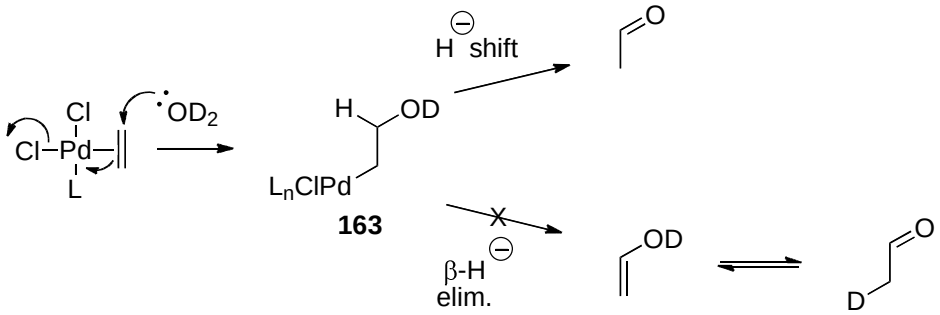
Scheme 3.10

The mechanism of the Wacker oxidation has been the subject of some debate, but is generally considered to proceed via a hydroxypalladation such as the one shown in scheme **3.11**.[215] The *syn*- or *anti*-nature of the hydroxypalladation has been shown to be highly dependent upon the reaction conditions (concentrations of $CuCl_2$ and Cl^- in particular).[216]



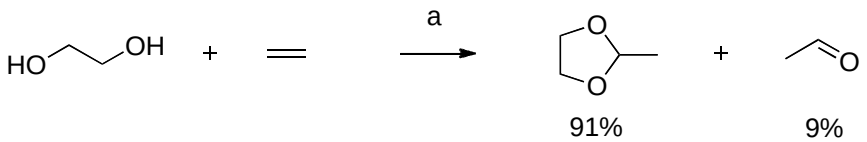
Scheme 3.11

Smidt demonstrated that all four hydrogen atoms were retained in the product and no deuterium was incorporated upon performing the oxidation in D_2O. This suggests that the decomposition of Pd-C σ-complex **163** proceeds via a hydride shift, rather than a β-hydride elimination (scheme **3.12**).[217]



Scheme 3.12

When carried out in alcoholic media, the Wacker oxidation of ethylene gives the corresponding acetal, as demonstrated by the formation of 2-methyl[1,3]dioxolane by Lloyd (scheme **3.13**).[218]

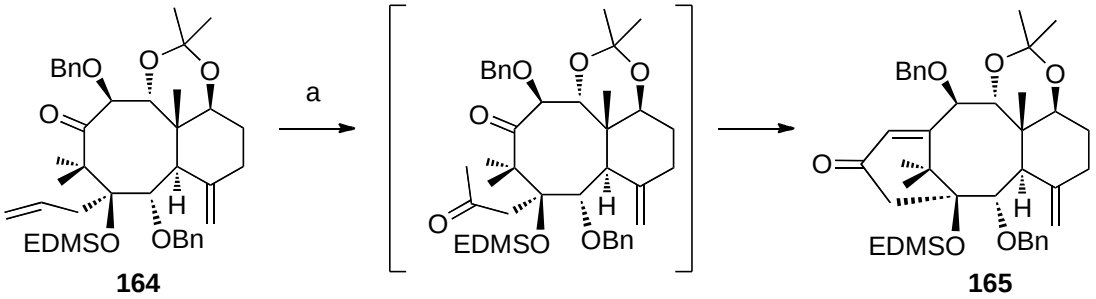


a) $PdCl_2$ (cat.), $CuCl_2$ (cat.), O_2, 50 °C

Scheme 3.13

Higher alkenes give the corresponding methyl ketones upon subjection to these reaction conditions.[219] This transformation was put to good use by Shiina in the

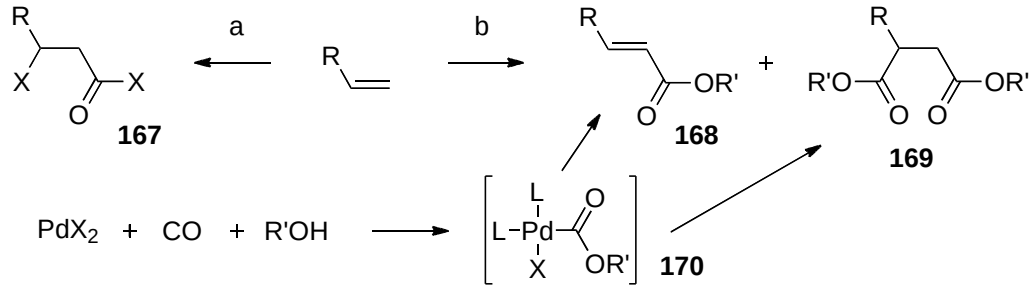
synthesis of Taxoid **165** (scheme **3.14**); Wacker oxidation of alkene **164** followed by *in situ* aldol condensation gave the cyclohexenone in excellent yield.[220]



a) $PdCl_2$ (1 eq), O_2, DMF, 45 ^oC, 60%

Scheme 3.14

Other unique Pd^{II} promoted oxidation reactions include the oxidative carbonylation of alkenes.[221,222] Reaction of a Pd^{II} salt with an alkene in the presence of carbon monoxide gives carbonylated products **167**, **168** and **169** depending upon the reaction conditions used (scheme **3.15**).

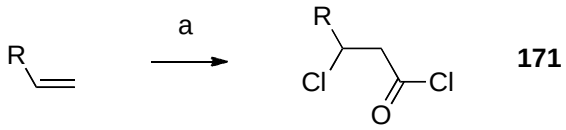


a) PdX_2, CO, aprotic solvent; b) PdX_2, CO, R'OH

Scheme 3.15

Reaction in aprotic media results in the palladation of the alkene, followed by insertion of CO into the Pd-C bond to give β-substituted carbonyl compounds **167**. When the reaction is carried out in alcoholic media, esters **168** and succinates **169** are obtained via formation of an alkoxycarbonyl palladium species **170**, followed by palladation of the alkene.

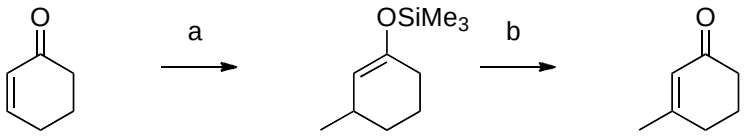
Tsuji reported the synthesis of β-chloroacyl chlorides **171** via this method by treatment of alkenes with $PdCl_2$ in benzene under a CO atmosphere (scheme **3.16**).[223]



a) $PdCl_2$, CO, benzene; R = H, alkyl, Hal

Scheme 3.16

Another important Pd^{II} mediated oxidation is the formation of enones from silyl enol ethers reported by Saegusa.[224] Treatment of trimethylsilyl ether **172** with substoichiometric $Pd(OAc)_2$ in the presence of *p*-BQ gave enone **173** in 91% yield (scheme **3.17**).

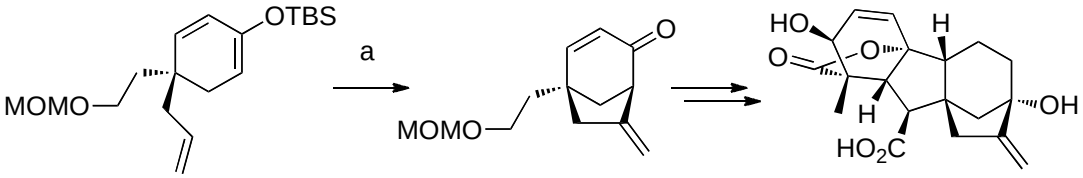


172 **173** 91%

a) $(Me)_2CuLi$ then Me_3SiCl; b) $Pd(OAc)_2$ (0.5 eq), *p*-BQ (0.5 eq), MeCN, rt

Scheme 3.17

This methodology was used by Toyota in the total synthesis of gibberellic acid, whereby a tandem Saegusa oxidation-Heck cyclisation was used to make key intermediate **175** (scheme **3.18**).[225] Treatment of silyl enol ether **174** with catalytic $Pd(OAc)_2$ gave bicyclic enone **175** in excellent yield, furnishing the right hand 5,6-fused ring system of the natural product.[226]



174 **175** 87% gibberellic acid

a) $Pd(OAc)_2$ (10 mol%), O_2, DMSO, 45 ^oC

Scheme 3.18

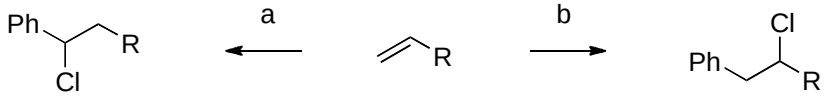
In recent years, much attention has been focussed on the development of efficient, catalytic Pd^{II} mediated Heck reactions.[227,228] These so called oxidative Heck reactions differ from the traditional format in the fact that the Pd^{II} species is the active catalyst. Internal co-oxidants are generally required in order to create an efficient catalytic cycle for the smooth re-oxidation of Pd^0 to the active Pd^{II} species.

Larhed demonstrated the utility of such processes in the open-air oxidative Heck reaction of arylboronic acids with butyl acrylate (scheme **3.19**).[229] An initial transmetallation is postulated as the first step in the catalytic cycle, giving the active arylpalladium species, which is then able to undergo a Heck reaction with the double bond. This highly efficient procedure is carried out at room temperature, with air as the only added oxidant; use of a dimethylphenanthroline ligand facilitates the oxidation of Pd^0 by dioxygen allowing a smooth Pd^0-Pd^{II} redox cycle in air.[230]

a) $Pd(OAc)_2$ (1 mol%), dmphen (1 mol%), NMM (1 eq), MeCN, rt ; > 35 examples

Scheme 3.19

More recently, Sanford has been exploring the oxidative interception of Pd-C σ-bonded Heck intermediates to give 1,1- or 1,2-disubstituted alkanes, depending on the conditions used (scheme **3.20**).[231,232] Oxidation with $PhICl_2$ gives predominantly the 1,2-arylchlorinated product **176**, whereas the 1,1-disubstituted product **177** is observed upon oxidation with $CuCl_2$.

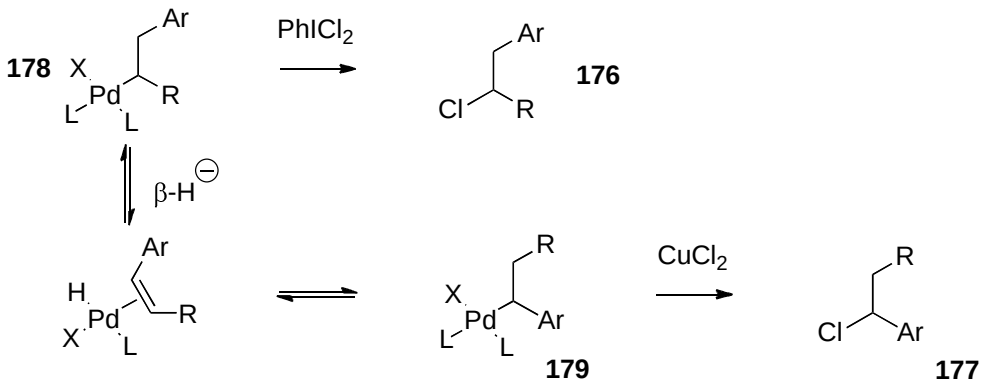


176 **177**

a) $Pd(MeCN)_2$ (10 mol%), $PhSnBu_3$ (2.6 eq), $CuCl_2$ (4 eq), Et_2O, -78 °C to rt
b) $Pd(MeCN)_2$ (10 mol%), $PhSnBu_3$ (2.6 eq), $PhICl_2$ (4 eq), DCM, -78 °C to rt

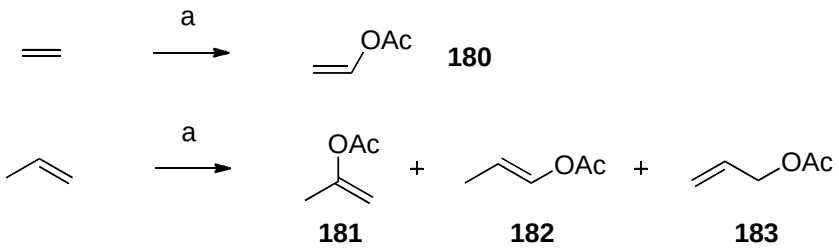
Scheme 3.20

The difference in selectivity observed in these reactions is attributed to the respective electrophilicity of the chlorinating reagents used. Therefore, with the highly reactive $PhICl_2$, rapid Pd-C bond chlorination of **178** occurs and the 1,2-arylchlorinated product **177** predominates (scheme **3.21**). Conversely, the less electrophilic $CuCl_2$ reacts more slowly with **178**, allowing a rapid β-hydride elimination/isomerisation to give Pd-C intermediate **179**, which is stabilised by a π-benzyl interaction.[233] Slow chlorination of the Pd-C bond in **179** then gives the 1,1-arylchlorinated product **176** as the predominant isomer.



Scheme 3.21

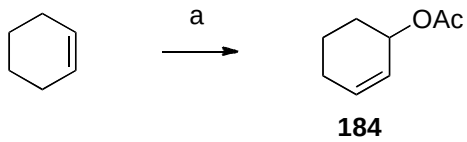
The first example of the palladium-mediated oxidative esterification of alkenes was reported by Mosieev in 1960, whereby ethylene underwent an acetoxypalladation followed by a β-hydride elimination to give vinyl acetate **180** (scheme **3.22**).[234,235] Propene was also oxidised under these conditions to give isopropenyl acetate **181**, as well as trace amounts of the corresponding linear vinyl acetate **182** and allyl acetate **183**. The mechanism of this palladium-mediated acetoxylation of olefins will be discussed in detail towards the end of this chapter.



a) $PdCl_2$, NaOAc, AcOH

Scheme 3.22

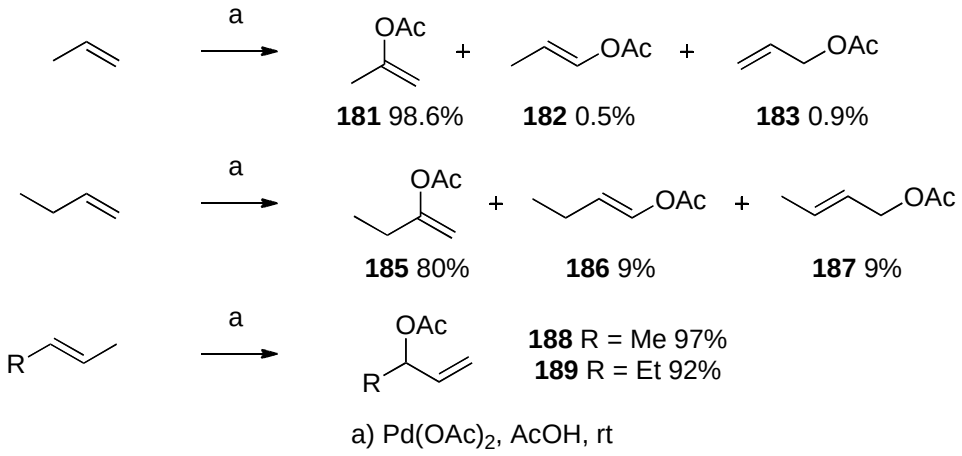
Winstein later reported the oxidation of cyclohexene in the presence of $Pd(OAc)_2$ to give allylic acetate **184** as the major product (scheme **3.23**).[236]



a) $Pd(OAc)_2$, AcOH, rt

Scheme 3.23

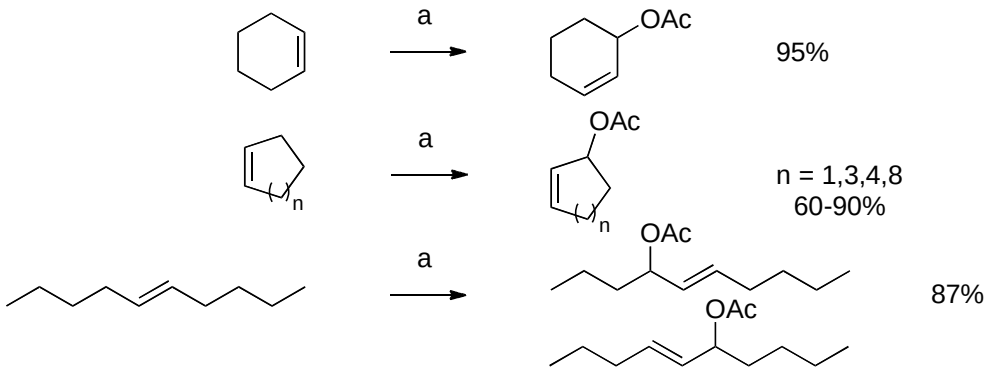
In a more comprehensive study, Winstein investigated the oxidation of a number of different alkenes under these conditions. For example, as in Mosieev's example, propene gave almost exclusive oxidation to isopropenyl acetate **181**, with trace amounts of linear vinyl and allyl acetates **182** and **183** respectively (scheme **3.24**).[237]



Scheme 3.24

But-1-ene also gave the internal vinyl acetate **185** as the major product, but with somewhat more of the linear vinyl and allylic acetates **186** and **187** respectively. In contrast, internal alkenes but-2-ene and pent-2-ene gave the corresponding branched allylic acetates **188** and **189** almost exclusively. These are the first examples of the selective formation of allylic acetates from alkenes in the presence of Pd^{II} salts.

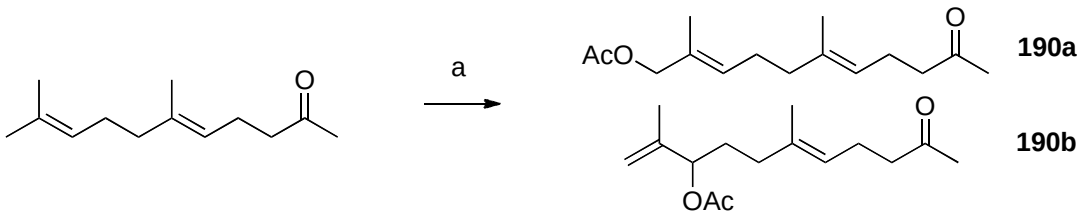
Whilst early non-Pd-mediated catalytic allylic oxidations are known,[238-240] it was not until much later that the first palladium-catalysed examples were reported.[241] These initial reports focussed on internal and cyclic olefins; for example, Heumann reported the catalytic allylic oxidation of cyclohexene in excellent yield (scheme **3.25**).[242-244] Other cyclic and internal olefins were also found to undergo allylic oxidation under these conditions, albeit in lower yield.



a) $Pd(OAc)_2$ (5 mol%), *p*-BQ (40 mol%), MnO_2 (1 eq), AcOH, 60 ^oC

Scheme 3.25

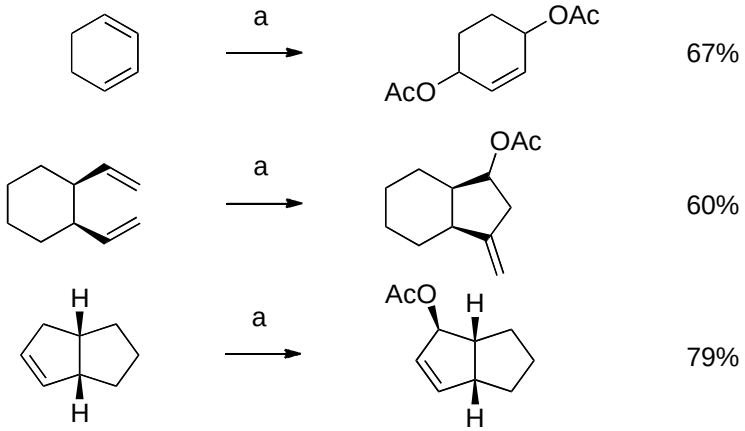
In the same year, McMurry reported the allylic oxidation of geranylacetone with $Pd(CF_3CO_2)_2$ in the presence of an *o*-methoxyacetophenone ligand to give the corresponding allylic acetate as a mixture of branched and linear regioisomers **190** (scheme **3.26**).[245]



a) $Pd(CF_3CO_2)_2$ (5 mol%), *o*-methoxyacetophenone (20 mol%), *p*-BQ (2 eq), AcOH, rt; 87% **190a**:**190b** 2:1

Scheme 3.26

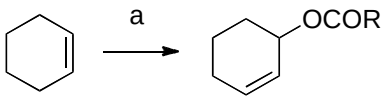
Further advances in the catalytic allylic oxidation of olefins saw the use of a highly efficient *p*-BQ/*tert*-butylhydroperoxide co-oxidant system by Åkermark in the synthesis of allylic acetates with ever increasing structural diversity (scheme **3.27**).[246]



a) $Pd(OAc)_2$ (5 mol%), *p*-BQ (10 mol%), ^{t}BuOOH (1.5 eq), AcOH, rt

Scheme 3.27

This system also proved applicable to the formation of a number of different allylic esters by addition of an excess of the corresponding carboxylic acid (scheme **3.28**).

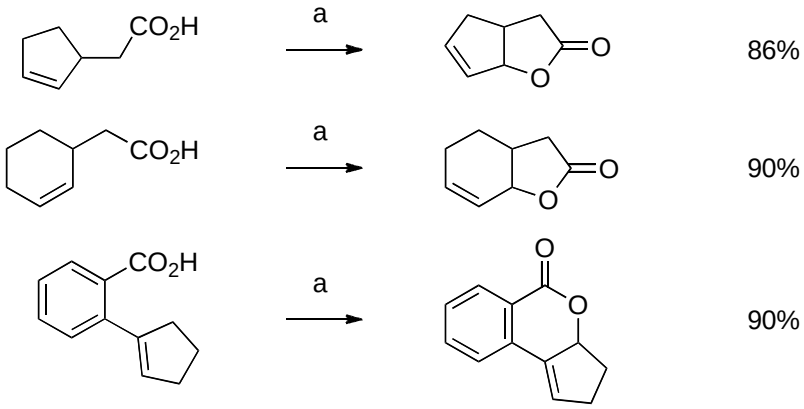


R = Ph (77%), *p*-$NO_2C_6H_4$ (82%), *p*-$MeOC_6H_4$ (85%), PhCH=CH (89%), ^{t}Bu (65%)

a) $Pd(OAc)_2$ (5 mol%), *p*-BQ (10 mol%), ^{t}BuOOH (1.5 eq), RCO_2H (200 eq), DCM, rt

Scheme 3.28

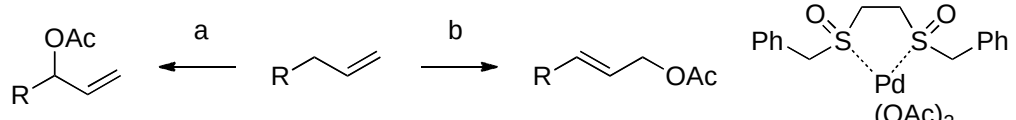
Larock demonstrated the utility of this increasingly popular catalytic reaction in the synthesis of a number of lactones by intramolecular allylic oxidation of alkenoic acids (scheme **3.29**).[247]



a) $Pd(OAc)_2$ (5 mol%), NaOAc (2 eq), DMSO, O_2, rt

Scheme 3.29

Perhaps the most important recent advance in palladium-mediated allylic oxidation chemistry was the development of a method for the selective oxidation of terminal olefins by White and co-workers in 2004.[248] White demonstrated that *bis*-sulfoxide complex **193** could be used to control the regiochemistry in the oxidation of monosubstituted olefins (scheme **3.30**).



191 up to 72% yield, up to 22:1 branched:linear

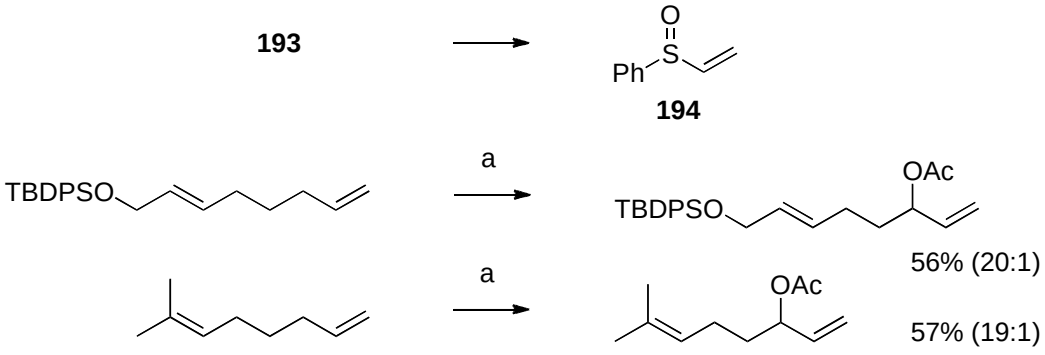
192 up to 65% yield, up up to 20:1 linear:branched

193

a) **193** (10 mol%), *p*-BQ (2 eq), DCM/AcOH 1:1, 48 h, 40 ^{o}C; b) $Pd(OAc)_2$ (10 mol%), *p*-BQ (2 eq), DMSO/AcOH 1:1, 48 h, 40 ^{o}C; >20 examples

Scheme 3.30

Oxidation of a number of terminal olefins with catalytic $Pd(OAc)_2$ in the presence of *p*-BQ as a co-oxidant in a mixture of DMSO and acetic acid gave predominantly the linear allylic acetates **192**. On the contrary, the corresponding branched allylic acetates **191** were observed almost exclusively upon oxidation of monosubstituted olefins in the presence of complex **193** and *p*-BQ in a mixture of DCM and acetic acid. *bis*-Sulfoxide complex **193** was found to partially decompose to give vinylsulfoxide **194** under these reaction conditions; commercially available **194** was also found to be an active ligand for the allylic transformation (scheme **3.31**).[249,250]

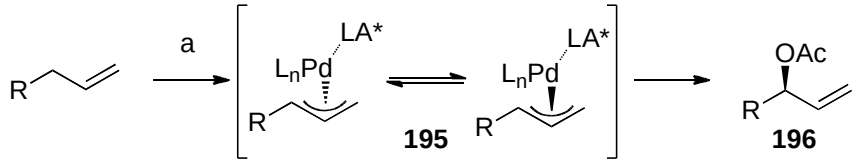


a) **194** (10 mol%), $Pd(OAc)_2$ (10 mol%), *p*-BQ (2 eq), AcOH (4 eq), dioxane, 72 h, 43 ^{o}C; branched:linear ratios in parentheses

Scheme 3.31

This is not only the first example of a regioselective formation of allylic acetates, but it is also the first chemoselective allylic oxidation of terminal olefins over internal disubstituted alkenes. This is demonstrated by the selective formation of branched allylic acetates over the corresponding internal isomers, which were observed in previous reports (scheme **3.25**).

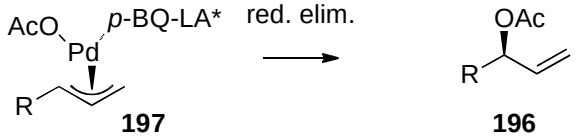
White later developed an asymmetric version of this transformation by addition of a chiral Lewis acid catalyst to give the enantioenriched branched allylic acetates **196** (scheme **3.32**).[251] Cleavage of an allylic C-H bond in the presence of chiral Lewis acid (*R*,*R*)-[(salen)Cr^{III}F] gives a mixture of chiral π-allyl species **195**. Upon formation of the C-O bond, the chiral information is transferred to the resulting allylic acetate product **196**, in good yield and reasonable levels of enantioselectivity.



a) **193** (10 mol%), (*R,R*)-[(salen)CrF] (10 mol%), AcOH (1.1 eq), *p*-BQ (2 eq), EtOAc, 48 h, rt; up to 90% yield; up to 63% *ee*

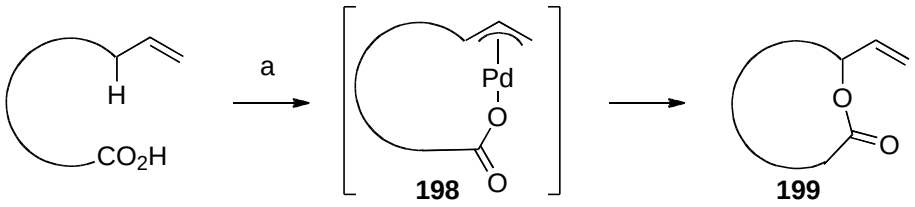
Scheme 3.32

The formation of the enantioenriched product is postulated to proceed via a facially controlled reductive elimination of an acetate from π-allyl complex **197**, in which the oxophilic chromium species is bound to the carbonyl moiety of *p*-BQ (scheme **3.33**).



Scheme 3.33

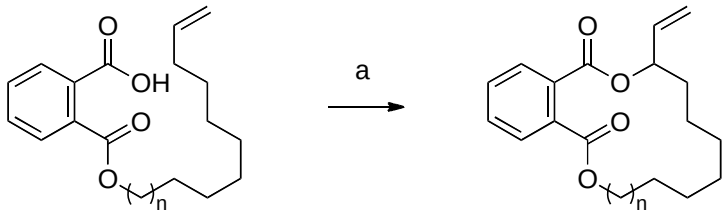
The White group were also able to develop an intramolecular version of this allylic oxidation, based upon a hypothesis that Pd-π-allyl chelation to a pendant carboxylate **198** would give the lactonised products **199** (scheme **3.34**).[252]



a) **193** (cat.), *p*-BQ, DCM, 45 °C

Scheme 3.34

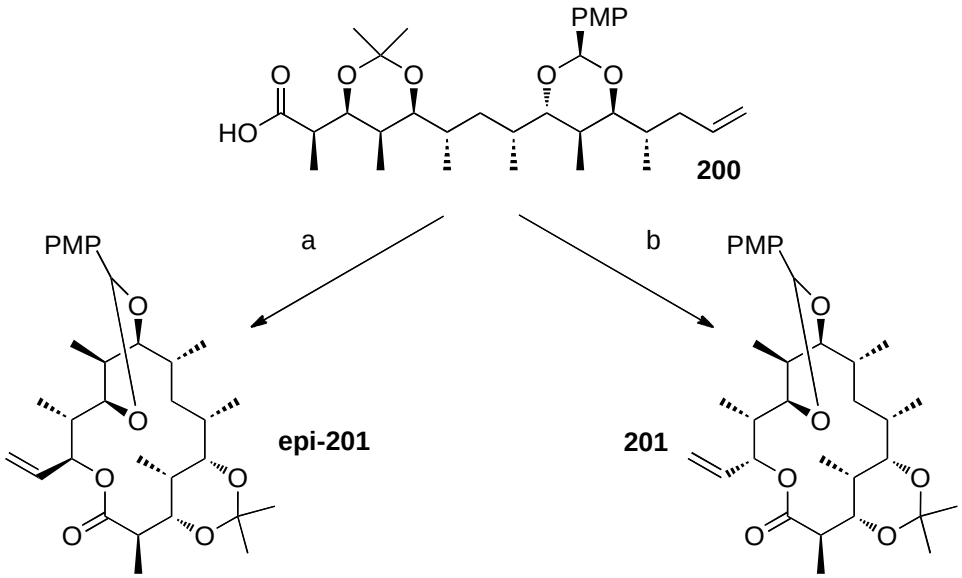
Several macrolactones were successfully synthesised by this method, without the need for the high dilutions typically required for transformations of this type, clearly proving its synthetic utility (scheme **3.35**).



a) **193** (10-20 mol%), *p*-BQ (2 eq), DCM, 72 h, 45 ^{o}C, up up to 63%; n = 1-4

Scheme 3.35

This macrolactonisation technique was later employed in the impressive total synthesis of 6-deoxyerythronolide B by a late stage allylic oxidation of linear precursor **200** to give key intermediate **201** (scheme **3.36**).[253]

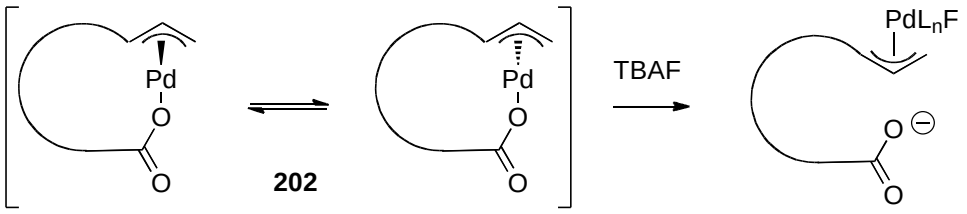


a) **193** (30 mol%), TBAF (30 mol%), *p*-BQ (2 eq), 45 ^{o}C, 44% 1:1.3 **201**:***epi*-201**;
b) **193** (30 mol%), *p*-BQ (2 eq), 45 ^{o}C, 56%, 40:1 **201**:***epi*-201**

Scheme 3.36

The C-13 epimer of **201** was also successfully synthesised by a modification of the standard reaction conditions, giving the natural and unnatural intermediates as a 1.3:1 mixture of separable diastereomers. Unfortunately, ***epi*-201** could not be elaborated further to give the C-13 epimer of the natural product, although this example clearly demonstrates the power of this chemistry.

The stereoselectivity for the natural isomer is a result of the interconverting π-allyl-Pd-carboxylate chelates **202** favouring the less hindered natural diastereomer **201** (scheme **3.37**).

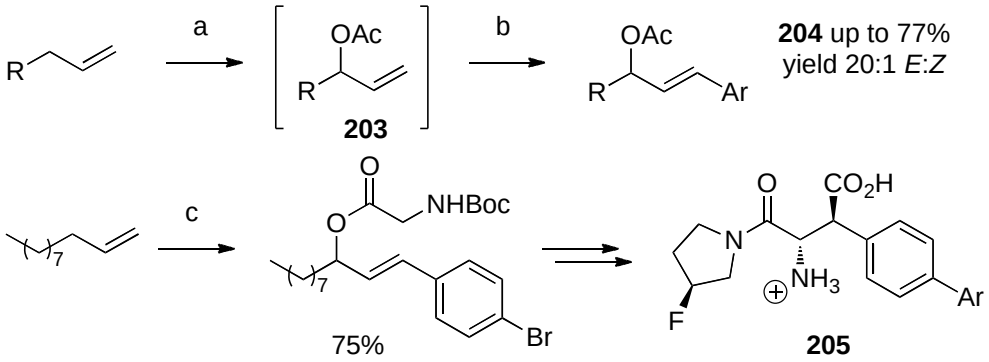


Scheme 3.37

The addition of fluorides to π-allyl Pd-complexes is known to increase the rate of π-σ-π interconversion, by occupation of a coordination site on the palladium.[254] The TBAF added to the reaction mixture is therefore able to interfere with the π-allyl-Pd-carboxylate chelation, disrupting the stereoselectivity for the natural isomer and resulting in a mixture of the natural and unnatural diastereomers.

Several other elegant allylic functionalisation procedures have also been reported by the White group, including a tandem allylic oxidation/vinyl C-H arylation[255] (scheme **3.38**), allylic amination[256,257] (scheme **3.39**) and allylic alkylation[258] (scheme **3.40**).

The one-pot allylic oxidation/vinyl C-H arylation proceeds via allylic oxidation, followed by an *in situ* oxidative Heck reaction of the resultant allylic acetate **203** (scheme **3.38**). This method was employed in the formal synthesis of biologically active dipeptidyl peptidase IV inhibitors **205**.[259]

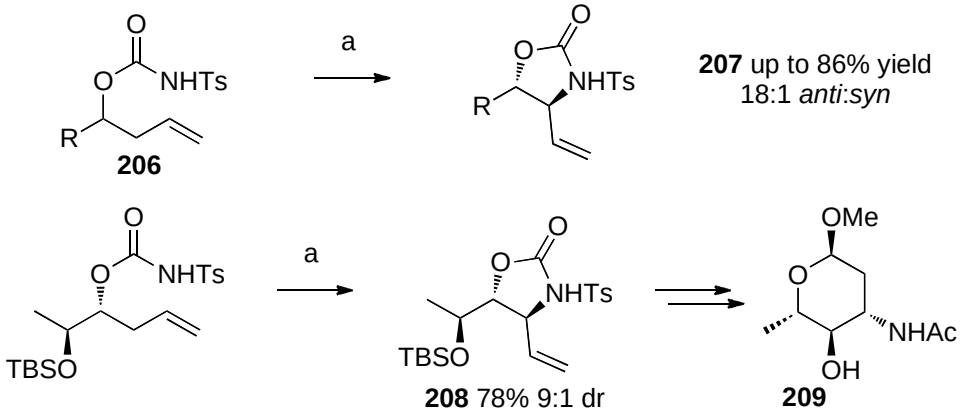


a) **193** (10 mol%), *p*-BQ (2 eq), AcOH (4 eq), dioxane, 48 h, 45 °C;
b) $ArB(OH)_2$ (1.5 eq), 5 h, 45 °C;
c) **193** (10 mol%), *p*-BQ (2 eq), Boc-Gly (4 eq), dioxane, 48 h, 45 °C, then $ArB(OH)_2$

Scheme 3.38

Palladium-catalysed allylic amination of unsaturated *N*-tosylcarbamates **206** also proceeded smoothly and with high levels of diastereoselectivity to furnish *anti*-

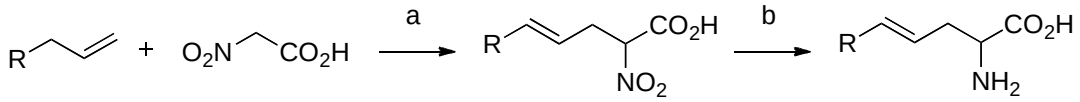
oxazolidinone derivatives **207** in good yield (scheme **3.39**).[260] This approach was used in the synthesis of *anti*-oxazolidinone **208**, a key precursor to aminosugar (-)-*N*-acetyl-*O*-methyl acosamine **209**.[261,262]



a) **193** (10 mol%), PhBQ (2 eq), THF, 72 h, 45 ^{o}C

Scheme 3.39

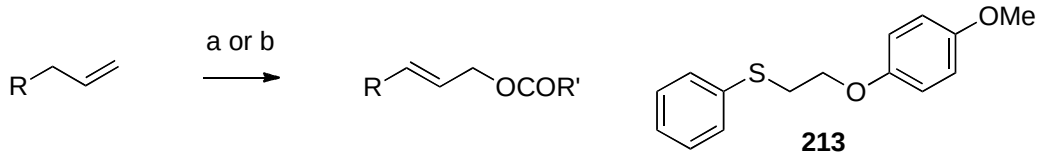
Finally, treatment of terminal olefins with an excess of carbon nucleophile **210** in the presence of catalyst **193** gives allylic alkylation to furnish *trans*-alkenes **211** in excellent yield. These nucleophilic species are readily elaborated to highly valuable α-amino acids **212** by reduction of the nitro group with zinc dust (scheme **3.40**).



a) **193** (10 mol%), DMBQ (1.5 eq), AcOH (0.5 eq), dioxane/DMSO 4:1, 72 h, 45 ^{o}C;
b) Zn, AcOH

Scheme 3.40

Many other groups have since reported efficient catalytic protocols for the selective oxidation of terminal olefins to linear allylic acetates, using a range of conditions. For example, Stambuli demonstrated the use of thioether ligand **213** to give linear allylic acetates in the absence of DMSO (scheme **3.41**).[263] Le Bras also reported the selective formation of linear allylic acetates in the presence of a base and absence of an added ligand.[264]

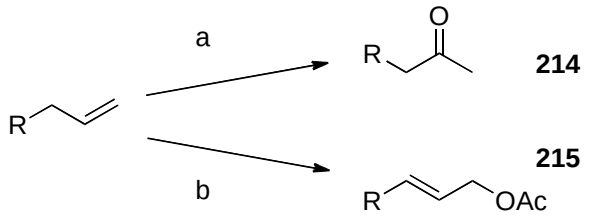


213

a) $Pd(OAc)_2$ (5 mol%), **213** (5 mol%), *p*-BQ (2 eq), AcOH, 12-20 h, 40 ^oC, up to 78% yield, 20:1 *E*:*Z*, 12 examples; b) $Pd(OAc)_2$ (10 mol%), *p*-BQ (2 eq), LiOH (2 eq), $R'CO_2H$, 24 h, 40 ^oC, up to 80% yield, *E* only, >20 examples

Scheme 3.41

Kaneda reported the selective C-1 or C-2 oxygenation of terminal olefins to give either Wacker products **214** or terminal allylic acetates **215** under extremely efficient catalytic conditions.[265] In this respect, Kaneda found that addition of water to the catalytic oxidation of monosubstituted alkenes by $PdCl_2$ gave exclusive oxidation to the corresponding methyl ketones **214**, as expected to form via a Wacker-type mechanism (scheme **3.42**). On the other hand, addition of acetic acid and sodium acetate gave almost quantitative conversion to terminal allylic acetates **215** under very similar conditions. This powerful example uses dioxygen as the sole reoxidant, eliminating the requirement for added ligands or co-oxidants such as *p*-BQ.



214

215

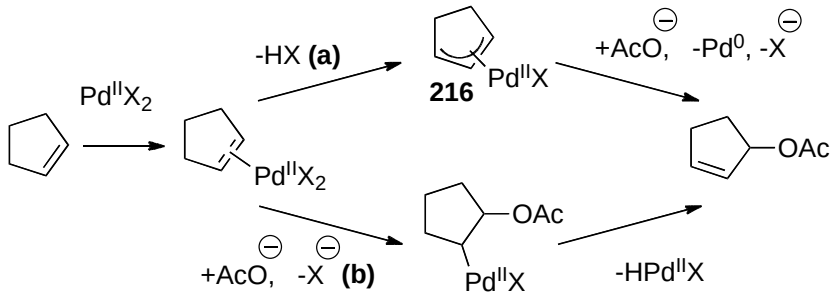
a) $PdCl_2$ (0.5 mol%), DMA/H_2O 6:1, O_2 (6 atm), 40 h, 80 ^oC, up to 92% yield, 13 examples
b) $PdCl_2$ (1 mol%), DMA/AcOH 25:1, O_2 (6 atm), 40 h, 80 ^oC, up to 85% yield, 8 examples

Scheme 3.42

Since its discovery, the mechanism of the palladium-mediated allylic oxidation of olefins has been the subject of some debate.[266-268] Several detailed reports have given valuable insight into the different reaction pathways of this unique transformation, although the exact nature of the mechanism still proves elusive.[269,270]

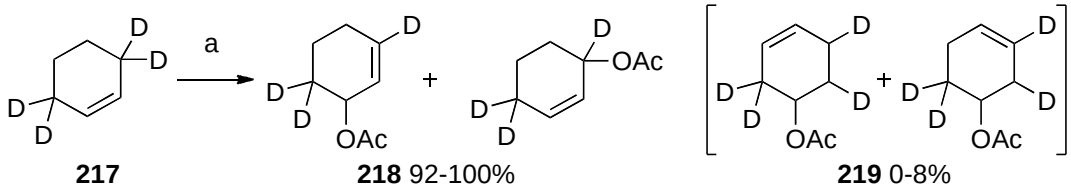
The two main pathways that have been postulated for the allylic oxidation of alkenes are depicted in scheme **3.43**. Path **a** involves the abstraction of an allylic hydrogen to give a π-allyl intermediate **216**, with nucleophilic attack by an acetate and loss of Pd^0

furnishing the oxidised product; path **b** on the other hand proceeds via a direct acetoxypalladation of the double bond followed by a β-hydride elimination.[271]



Scheme 3.43

Early attempts to determine the mechanism of this transformation were inconclusive, with different groups reporting seemingly conflicting results. For example, Wolfe demonstrated that subjection of 3,3,6,6-tetradeuteriocyclohexene **217** to oxidising conditions in the presence of a Pd^{II} salt gave the expected mixture of allylic acetates **218** as well as a trace of homoallylic acetates **219** (scheme **3.44**).[272,273]

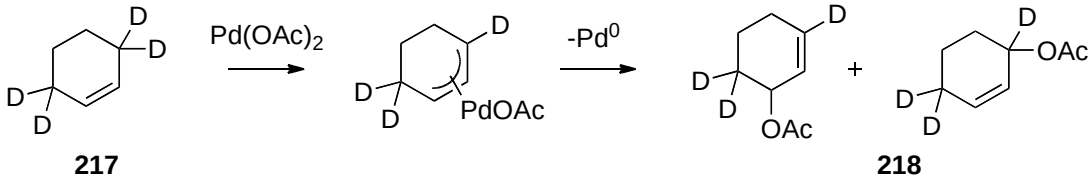


217 **218** 92-100% **219** 0-8%

a) $[Pd(OAc)_2]_3.NO_2$ (0.9 eq), HNO_3 (30 mol %), AcOH, rt

Scheme 3.44

Formation of a Pd-π-allyl species by abstraction of an allylic deuteride from **217** would furnish the expected allylic acetates **218**, as shown below in scheme **3.45**.

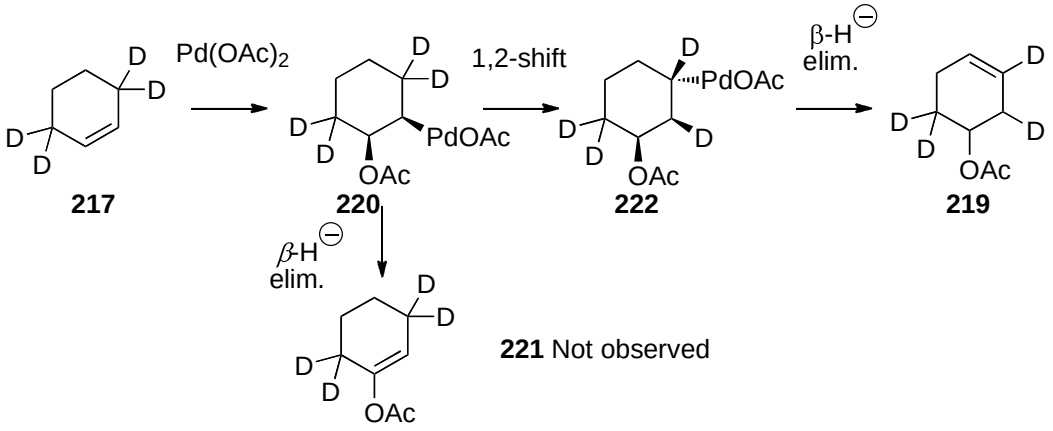


217 **218**

Scheme 3.45

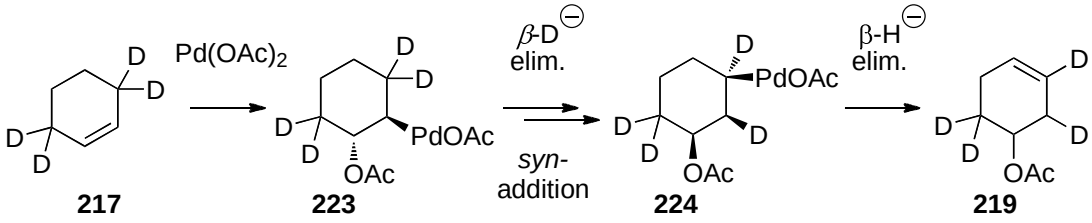
However, this mechanism does not account for the formation of homoallylic acetates **219**, as all four deuterium atoms remain present in the products. In this case, a direct acetoxypalladation of the double bond can be envisaged, giving a Pd-C σ-species, which could then undergo a rearrangement to give homoallylic acetates **219** (scheme

3.46). A *syn*-addition would furnish Pd-C σ-complex **220**, which could then either undergo a *β*-hydride elimination to give vinyl acetate **221** (which is not observed) or a 1,2-shift to give a second Pd-C σ-species **222**. A *β*-hydride elimination from this second species would then give the observed homoallylic acetate **219**.



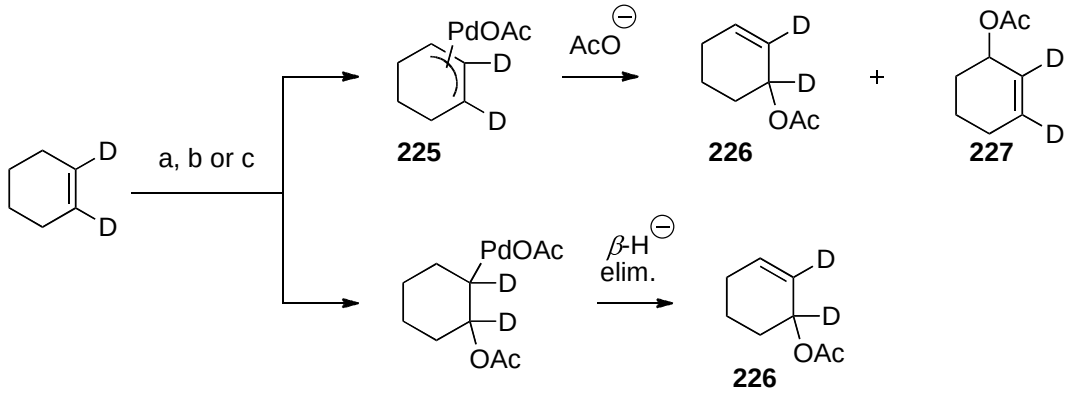
Scheme 3.46

An *anti*-addition would give the *trans*-adduct **223**, which could undergo a *β*-deuteride elimination and *syn*-readdition sequence to give Pd-C σ-species **224** (scheme **3.47**). A *β*-hydride elimination from this species would then give the observed homoallylic acetate **219**.



Scheme 3.47

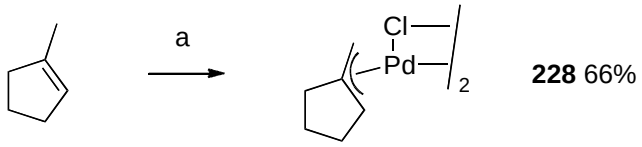
Bäckvall later conducted a similar experiment on 1,2-dideuteriocyclohexene, subjecting it to both stoichiometric and catalytic reaction conditions.[274] Formation of a π-allyl intermediate by hydride abstraction from 1,2-dideuteriocyclohexene to give **225** would result in a 1:1 ratio of allylic acetates **226** and **227** (scheme **3.48**). Conversely, only **226** would be observed from the corresponding acetoxypalladation/*β*-hydride elimination mechanism. Under each set of reaction conditions examined, the ratio of allylic acetates **226** and **227** was precisely 1:1, suggesting that the π-allyl mechanism predominates, with little to no evidence of an acetoxypalladation taking place.



a) $Pd(OAc)_2$ (1 eq), AcOH; b) $Pd(OAc)_2$ (cat.), *p*-BQ (2 eq), AcOH;
c) $Pd(OAc)_2$ (cat.), MnO_2 (2 eq), AcOH

Scheme 3.48

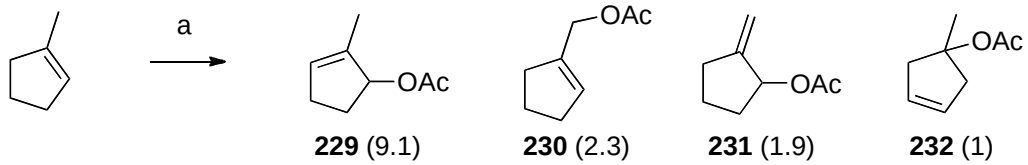
Mechanistic studies on systems such as these have often been thwarted by the observation of different outcomes from stoichiometric and catalytic reactions.[263] For example, Trost reported that treatment of 1-methylcyclopentene with stoichiometric quantities of Pd^{II} salts resulted in the exclusive formation of π-allyl species **228** (scheme **3.49**).[275]



a) $PdCl_2$, NaCl, NaOAc, $CuCl_2$, AcOH, 95 °C

Scheme 3.49

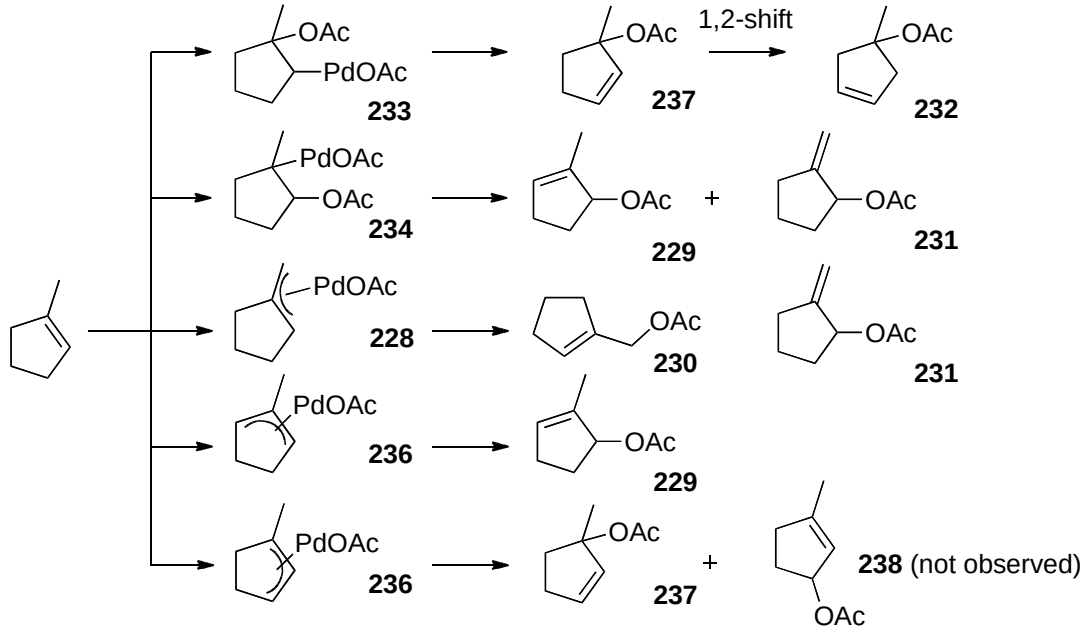
In contrast, Åkermark reported that exposure of the same substrate to catalytic oxidation conditions resulted in the formation of several unexpected products (scheme **3.50**).[276] Allylic acetates **230** and **231**, which are the expected products from a π-allyl type mechanism are only observed in relatively small quantities.



a) $Pd(OAc)_2$ (5 mol%), *p*-BQ (20 mol%), MnO_2 (2 eq), AcOH, 48 h, 40 °C,
95% conversion, 25% isolated; product ratios given in parentheses

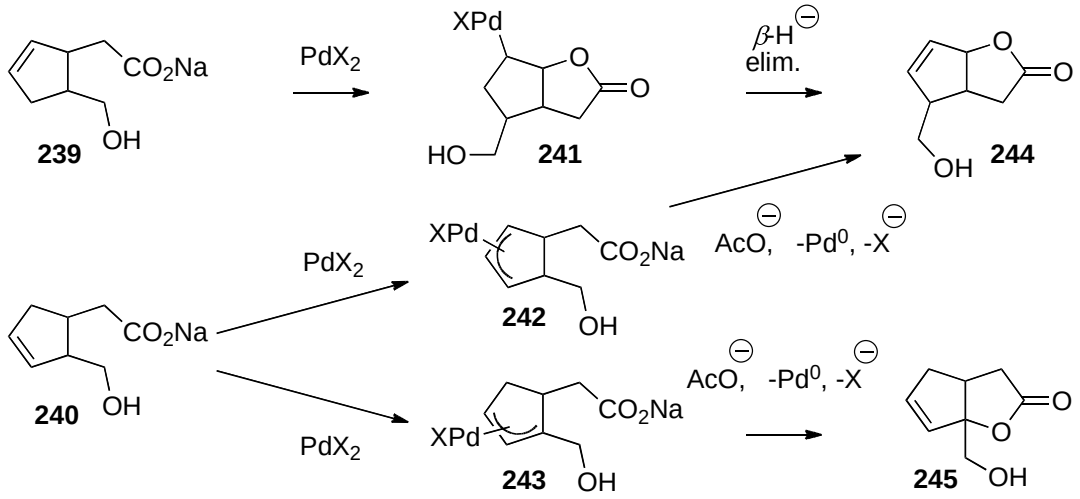
Scheme 3.50

Whilst the product distribution is surprising, the formation of **229-232** can be rationalised by a number of different reaction mechanisms. As well as the formation of **230** and **231** from π-allyl species **228**, the observed products can be expected via either π-allyl intermediates **235** and **236**, or Pd-C σ-species **233** and **234** (scheme **3.51**). Homoallylic acetate **232** is presumably a result of a Pd^{II}-mediated isomerisation of allylic acetate **237**, which is itself not observed.



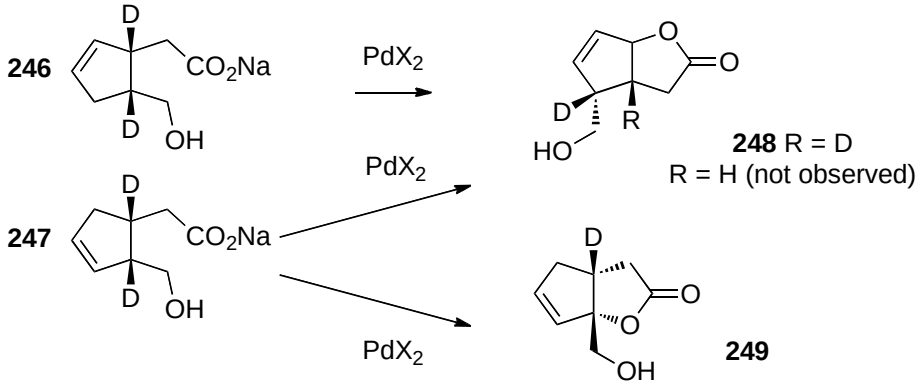
Scheme 3.51

More recently, Vidari reported the Pd^{II}-mediated intramolecular allylic oxidation of cyclopentenoic acids **239** and **240**, giving bicyclic lactones **244** and **245** (scheme **3.52**).[277] Interestingly, lactone **245** is formed only from **240**, whereas isomeric lactone **244** is isolated from the oxidation of both alkenes. This suggests that two different mechanisms are in operation under these conditions; lactone **244** can be reached via either π-allyl intermediate **242**, or Pd-C σ-species **241**, whereas **245** can only be accessed from π-allyl complex **243**.



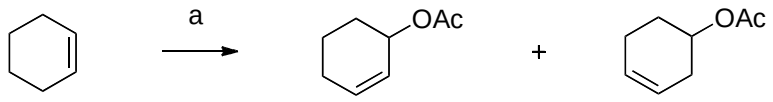
Scheme 3.52

Vidari rules out the intermediacy of a π-allyl species in the transformation of **239** into **244** based on two observations; firstly, when an equimolar mixture of olefins **239** and **240** were subjected to the Pd^{II}-mediated oxidation conditions, **239** was found to react three times faster than **240**, suggesting a difference in reaction mechanisms. Secondly, no scrambling or loss of deuterium content was observed upon oxidation of *bis*-deuterated olefins **246** and **247**, giving lactones **248** and **249** (scheme **3.53**).



Scheme 3.53

As described above for the formation of homoallylic acetates, Pd^{II} salts are known to promote isomerisation reactions of alkenes.[278] Åkermark, Bäckvall and Heumann conducted a study to ascertain the effect of strong acids upon the allylic oxidation of cyclohexene and the ratio of products observed therein.[279] Their findings are summarised below in table **3.1**.



250 **251**

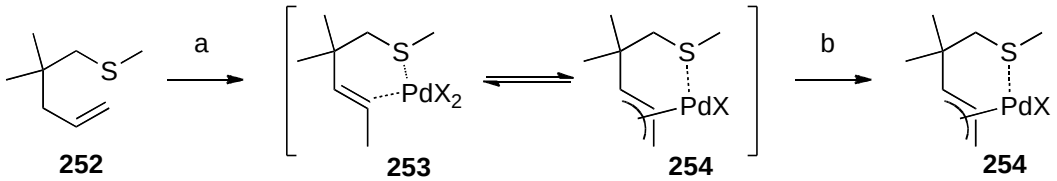
a) $Pd(OAc)_2$ (5 mol%), *p*-BQ (2 eq), AcOH, $H^{\oplus}$

Entry	Acid	Quantity (mol%)	Temp/ °C	Time/h	Yield %	250:251
1	-	-	25	47	86	98:2
2	CF_3CO_2H	500	25	5	60	96:4
3	CH_3SO_3H	50	25	4.5	62	21:79
4	CH_3SO_3H	110	50	1.25	50	2:98

Table 3.1

The results clearly demonstrate that the acidity of the reaction media has a profound effect on the selectivity and product distribution. Strong acids and longer reaction times appear to increase the extent of double bond isomerisation, with addition of methanesulfonic acid effectively reversing the selectivity of the reaction from allylic acetate **250** to homoallylic acetate **251** (entries 3, 4 and 1 respectively).

Another noteworthy double bond isomerisation in the context of this thesis is the Pd^{II}-mediated bond migration of unsaturated sulfide **252** (scheme **3.54**).[280] McCrindle observed the isomerisation of the terminal double bond in **252** to give the Pd^{II}-bound internal olefin **253** in $CDCl_3$ solution, which is presumably in equilibrium with π-allyl species **254**. Upon addition of an equivalent of triethylamine to a solution of **252** and $Pd(PhCN)_2Cl_2$ in acetone, π-allyl complex **254** was isolated in good yield.



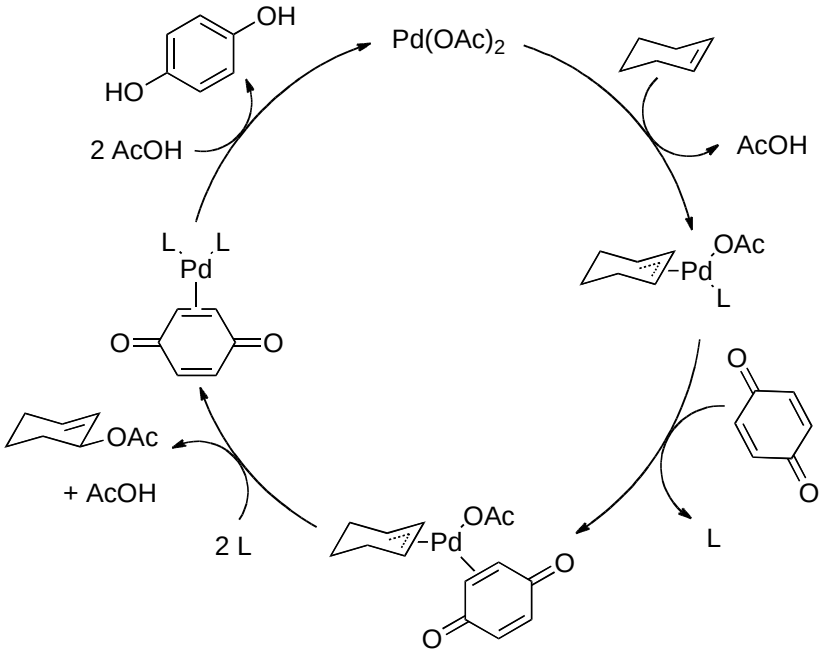
252 **253** **254** **254**

a) $Pd(MeCN)_2Cl_2$ (1 eq), $CDCl_3$; b) NEt_3 (1 eq), acetone

Scheme 3.54

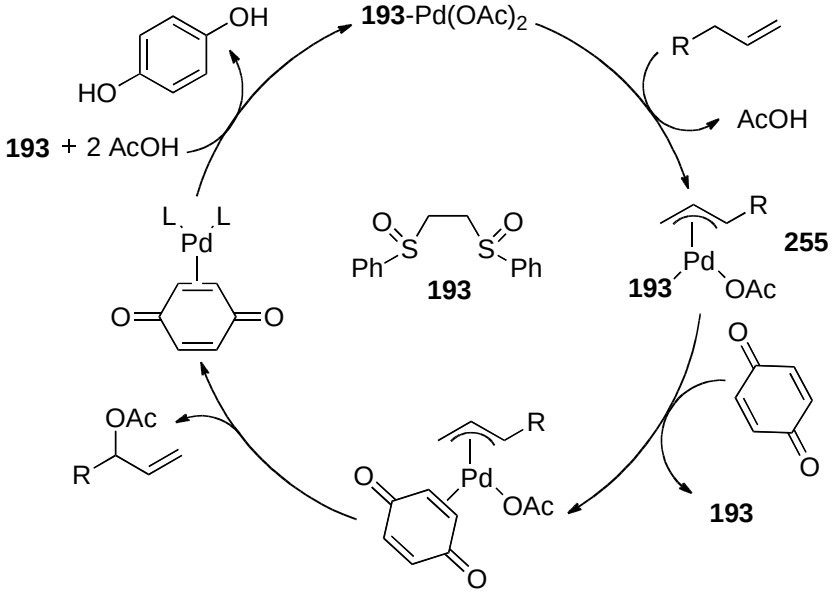
Finally, *p*-BQ has been demonstrated to have an integral role in the Pd^{II}-mediated oxidation of olefins.[281,282] This unique reagent is believed to play a more important part in allylic oxidation reactions than simply acting as a reoxidant for Pd^0.[283] For

example, it has been postulated that *p*-BQ activates Pd-π-allyl complexes to nucleophilic attack by acetate (scheme **3.55**).



Scheme 3.55

The White group hypothesise that *bis*-sulfoxide ligand **193** facilitates allylic C-H cleavage to give π-allyl species **255**, which upon addition of *p*-BQ undergoes nucleophilic attack by acetate to give the oxidised products. The resulting *p*-BQ-bound Pd^0 is then reoxidised, generating hydroquinone and completing the catalytic cycle (scheme **3.56**).[249]

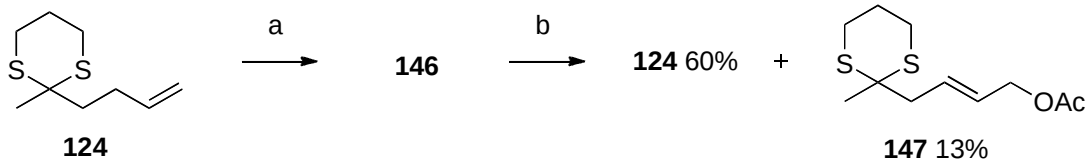


Scheme 3.56

In conclusion, there are several elegant and unique methods available for the palladium-mediated allylic oxidation of olefins, with an impressive array of challenging molecular architectures achieved by this transformation. The precise nature of the mechanism of this reaction still remains unclear, despite much effort having been invested into its exploration.

3.2 Catalytic Oxidation of Olefins

Observation of the allylic oxidation of unsaturated dithiane **124** upon treatment with stoichiometric $Pd(OAc)_2$ (scheme **3.57**) was described in the previous chapter.

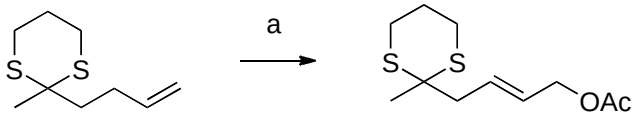


124 **147** 13%

a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 5 min, rt; b) PPh_3 (1 eq), 1 min, rt

Scheme 3.57

In early attempts to develop a catalytic version of this transformation, $Cu(OAc)_2$ was initially identified as a suitable co-oxidant, giving moderate conversions to the allylic acetate upon heating for several days in DMSO (scheme **3.58**).

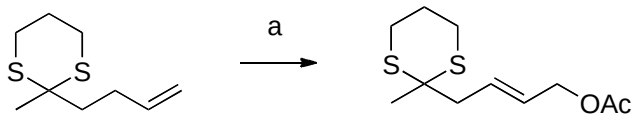


124 **147** 48% conv. (NMR)

a) $Pd(OAc)_2$ (0.1 eq), $Cu(OAc)_2$ (1 eq), $(CD_3)_2SO$, 3d, 80 ^oC

Scheme 3.58

Using $Cu(OAc)_2$ as a co-oxidant, a range of different solvents were then screened for the reaction (scheme **3.59**, table **3.2**).



124 **147** % conv. (NMR)

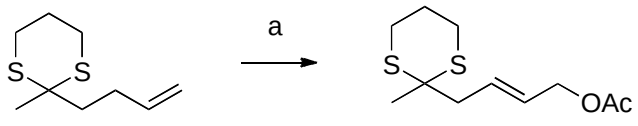
a) $Pd(OAc)_2$ (0.1 eq), $Cu(OAc)_2$ (1 eq), solvent, 24 h, 80 ^oC

Scheme 3.59

Entry	Solvent	Temp/°C	% Conversion (NMR)
1	$CDCl_3$	25	<5
2	$CDCl_3$	70	<5
3	DCM	25	0
4	DMSO	25	<5
5	DMSO	70	40
6	DMSO	80	48
7	DMSO	120	39
8	DMA	80	35
9	THF	70	10
10	MeCN	70	14
11	AcOH	25	<5
12	AcOH	80	dec.
13	DCE	80	12

Table 3.2

High boiling, polar solvents such as DMSO and DMA gave the best results, with up to 48% conversion in DMSO at 80 °C (entry 6). Higher temperatures did not seem to improve the conversion, with 80 °C proving optimal. Interestingly, little to no conversion was observed in acetic acid, which is commonly used as a solvent for this type of transformation (entries 11 and 12).[276,248] DMSO was therefore selected as the solvent for a more comprehensive screen of co-oxidants (scheme **3.60**, table **3.3**).



124 **147** % conv. (NMR)

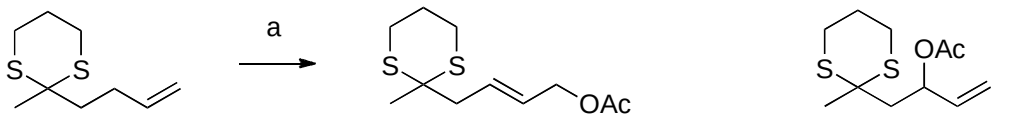
a) $Pd(OAc)_2$ (0.1 eq), oxidant (1 eq), AcOH (2 eq), DMSO, 24 h, 80 ^oC

Scheme 3.60

Entry	Co-oxidant	% Conversion (NMR)
1	$Cu(OAc)_2$	48
2	$Cu(OAc)_2/O_2$	25
3	$CuCl_2$[a]	<5
4	$PhI(OAc)_2$	0
5	MnO_2[a]	10
6	*p*-BQ[a]	<5
7	O_2[a]	10
8	$Mn(OAc)_3$	45
9	*p*-BQ/MnO_2[a]	>95

Table 3.3 - [a]AcOH (2 eq) added

Again, common co-oxidants such as $PhI(OAc)_2$, $CuCl_2$ and *p*-BQ showed little efficacy in this reaction and gave low conversions to the desired allylic acetate (entries 3, 4 and 6). $Mn(OAc)_3$ proved to be a promising co-oxidant, although there was still no improvement in conversion over $Cu(OAc)_2$ (entries 8 and 1 respectively). Finally, Heumann's conditions[243] were applied to this reaction, requiring 40 mol% of *p*-BQ and stoichiometric MnO_2 to give by far the best conversion to the allylic acetate (entry 9). Addition of an oxygen balloon was found to reduce reaction times, although this had no effect on the overall conversion. The fully optimised reaction conditions are given below in scheme **3.61**; the allylic acetate **147** being isolated in 68% yield after chromatographic purification.



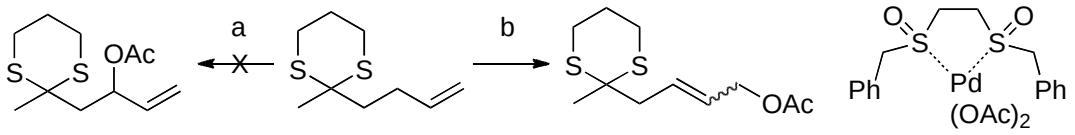
124 **147** 68% (isolated) **256** (not observed)

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC

Scheme 3.61

Interestingly, the terminal allylic acetate **147** was the only product isolated; the corresponding branched allylic acetate **256**, which might be expected to form under these reaction conditions was not observed. This suggests that the thioacetal moiety is controlling the regiochemistry of the oxidation in favour of the terminal allylic acetate.

To verify this, dithiane **124** was treated with *bis*-sulfoxide-palladium complex **193** in an attempt to form the branched allylic acetate **256** selectively over the linear (scheme **3.62**). Under the conditions reported by White,[249] dithiane **124** proved unreactive and neither the branched or linear allylic acetate was observed. Using the *bis*-sulfoxide complex in place of palladium acetate under the standard reaction conditions resulted in a high conversion to the expected linear allylic acetate. This suggests that the dithiane is a better ligand for the palladium than the *bis*-sulfoxide and that upon treatment of dithiane **124** with **193**, the *bis*-sulfoxide ligand is replaced by the dithiane. No formation of the branched or linear allylic acetate is observed under White's conditions, whereas the linear allylic acetate is the only product isolated in the presence of either ligand in DMSO. Little to no oxidation of dithiane **124** was observed in either acetic acid or DCM (table **3.2**), which presumably accounts for the fact that no oxidation was observed under White's conditions.

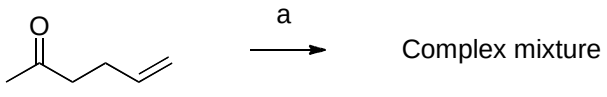


256 **124** **147** Full conversion (NMR) **193**

a) **193** (0.1 eq), *p*-BQ (2 eq), DCM:AcOH (1:1), 48 h, 40 °C;
b) **193** (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 °C

Scheme 3.62

The parent ketone **144** gave a complex mixture of inseparable products when subjected to the standard reaction conditions (scheme **3.63**).

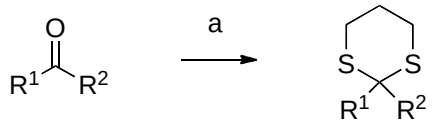


144

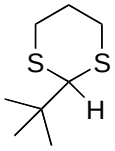
a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 °C

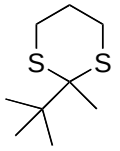
Scheme 3.63

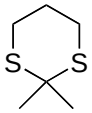
To evaluate the scope of this catalytic reaction, a number of analogous dithiane substrates were prepared and subjected to the optimised reaction conditions. A general approach to the synthesis of dithiane derivatives is outlined in scheme **3.64** below.

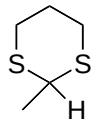


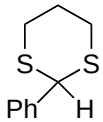
a) 1,3-Propanedithiol (1 eq), BF_3OEt_2 (1.5 eq), DCM, -78 ^oC to rt; R^1 = H, alkyl; R^2 = alkyl

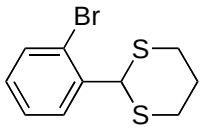

256 78%

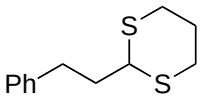

257 77%


258 93%


259 55%


260 87%


261 89%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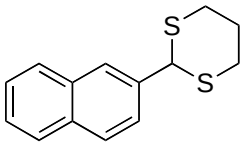
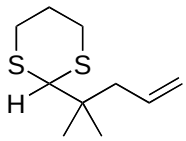
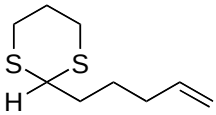
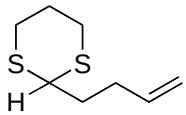
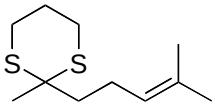
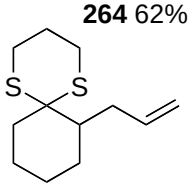

263 92%


264 62%


265 51%

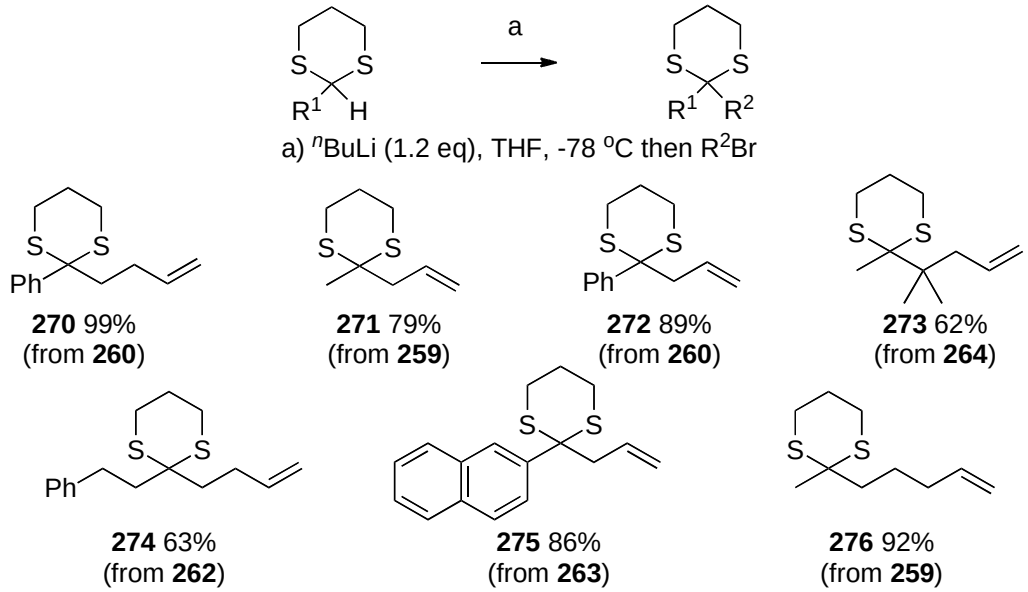

266 59%


267 21%


268 61%

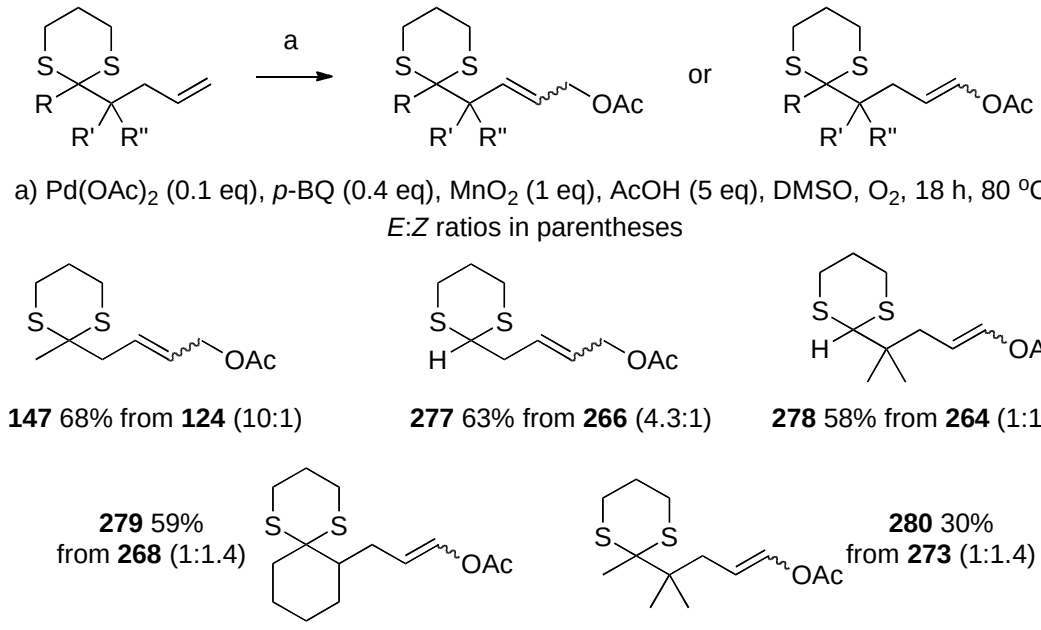
Scheme 3.64

In the majority of cases, the new substrates could be prepared simply by Lewis acid-mediated condensation of 1,3-propanedithiol and the corresponding carbonyl compound.[38] Other derivatives were prepared by lithiation-alkylation of their corresponding monosubstituted dithiane precursors (scheme **3.65**).



Scheme 3.65

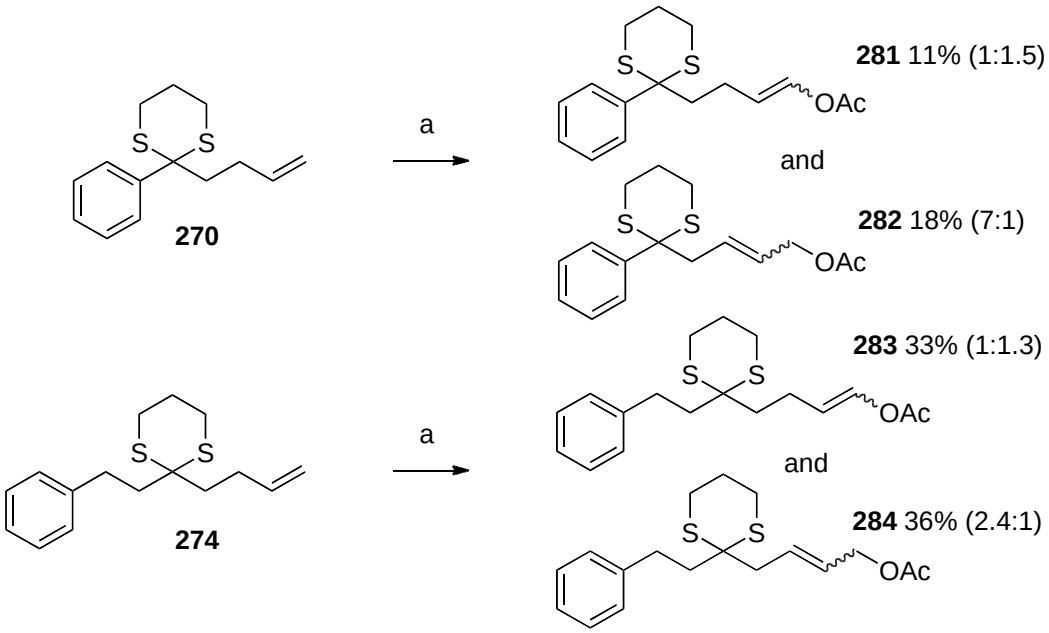
Each of the new substrates was then subjected to the optimised reaction conditions to determine the scope and synthetic utility of this reaction. Pleasingly, a number of the new substrates reacted smoothly under these conditions and full conversion to new species was observed by TLC and crude NMR. However, upon isolation of these new products, some unexpected observations were made. Firstly, as well as the expected allylic acetates, many of the substrates underwent selective oxidation to the corresponding vinyl acetates (scheme **3.66**).



Scheme 3.66

Formation of vinyl acetates under these conditions is extremely rare,[284,285] which makes the selectivity of these reactions remarkable. In fact, only substrates **124** and **266** were selectively oxidised to allylic acetates. The implication from this first set of results is that the nature of the oxidation is dependent upon the substituents at the homoallylic position of the unsaturated dithiane. Substrates **124** and **266**, which contain no substituents at the homoallylic position (R' = R" = H) gave only the expected allylic acetates under the reaction conditions. However, dithianes **278**, **279** and **280**, which all contain at least one substituent in the homoallylic position (R' ≠ H) were all oxidised to the corresponding vinyl acetates with no observation of the analogous allylic oxidation products. In all cases the substrates underwent oxidation at the terminal position and no branched allylic or internal vinyl acetates were observed.

Interestingly, unsaturated dithiane derivatives **270** and **274**, which contain no substituents at the homoallylic position gave a mixture of both allylic and vinyl acetates when subjected to the standard reaction conditions (scheme **3.67**).



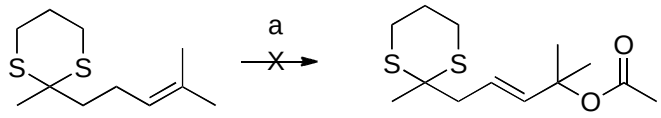
a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC; *E*:*Z* ratios in parentheses

Scheme 3.67

Although poor yielding, phenyldithiane derivative **270** gave a roughly 2:1 mixture of allylic and vinyl oxidation products **281** and **282**. This low yield could be due to the

palladium interacting with the phenyl ring rather than the double bond, although no other oxidation products were isolated from the reaction mixture. Phenylethyldithiane **274** was more readily oxidised under the reaction conditions, giving a roughly 1:1 mixture of allylic and vinyl acetates **283** and **284**. These results suggest that the nature of the oxidation is also dependent upon the second substituent in the 2-position of the dithiane ring and not solely on those in the homoallylic position.

Dithiane **267**, which contains a trisubstituted double bond was not oxidised under the reaction conditions, with the reaction mixture consisting exclusively of starting materials even after several days of heating (scheme **3.68**).

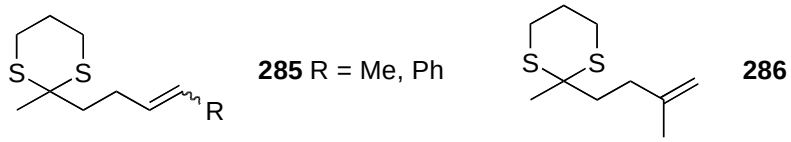


267

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 3 d, 80 ^oC;

Scheme 3.68

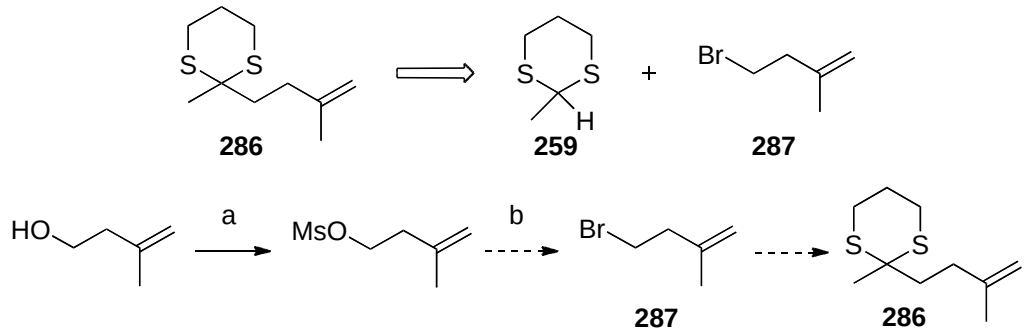
To investigate the effects of other substituents on the double bond, attempts were made to form dithianes **285** and **286** (figure **3.69**).



285 R = Me, Ph **286**

Scheme 3.69

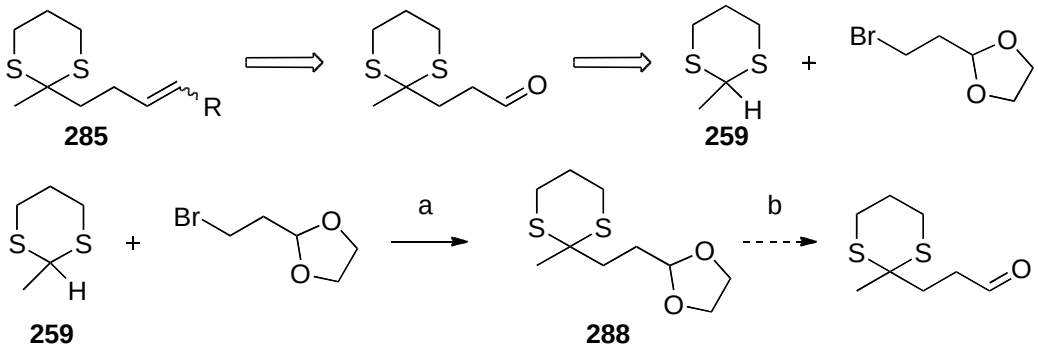
Firstly, retrosynthesis of the 1,1-disubstituted alkene **286** led to a forward synthesis involving lithiation-alkylation of methyldithiane **259** with alkyl bromide **287** (scheme **3.70**). Frustratingly, isolation of the volatile alkyl bromide **287** proved difficult and the attempt to form dithiane **286** was abandoned.



a) MsCl, NEt_3, DCM, 1 h, 0 ^oC, 99%; b) LiBr, acetone, reflux

Scheme 3.70

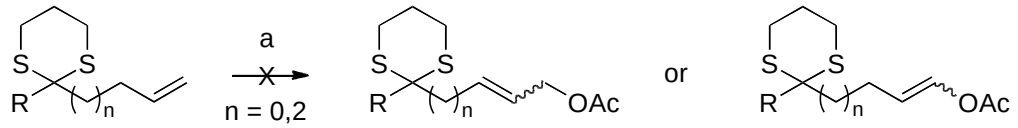
Retrosynthetic analysis of 1,2-disubstituted alkene **285** gave the forward synthesis outlined in scheme **3.71**. Lithiation-alkylation of methyldithiane **259** proceeded smoothly, furnishing protected aldehyde **288** in 55% yield. Unfortunately, all attempts to cleave the dioxolane protecting group in **288** were unsuccessful, with a maximum of 20-30% conversion to the aldehyde. Use of a dimethylacetal protecting group might have proved a more successful route, although this approach was not attempted.



a) ^nBuLi, THF, 4 h, -78 ^oC, 55%; b) Amberlyst resin, acetone, rt

Scheme 3.71

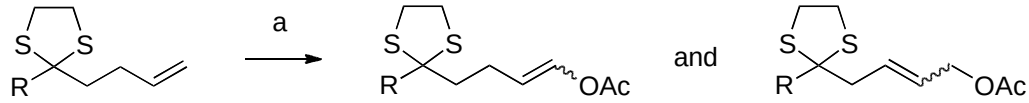
The effect of increasing or decreasing the length of the tether between the dithiane and the alkene was to stop the reaction altogether. For example, none of the substrates with one more or one less methylene unit in the tether were oxidised under these conditions (scheme **3.72**).



a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC;

Scheme 3.72

Unsaturated dithiolane derivative **123** also underwent regioselective oxidation at the terminal position when subjected to the reaction conditions (scheme **3.73**). This thioacetal substrate gave a mixture of allylic and vinyl acetates in excellent yield, with the allylic regioisomer as the major product. This is an interesting observation considering that the analogous dithiane derivative **124** gave solely the allylic acetate, suggesting that the nature of the thioacetal moiety may also be affecting the outcome of the reaction.

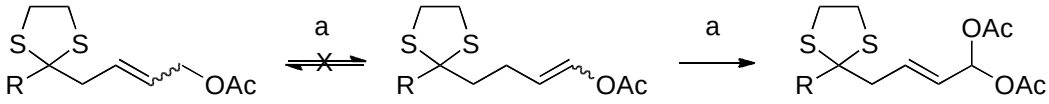


123 **289** 21% (1:1.3) **290** 72% (8:1)

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC;
E:*Z* ratios in parentheses

Scheme 3.73

Isolated samples of **289** and **290** were re-subjected to the reaction conditions to determine whether or not their formation was due to palladium-mediated isomerisation processes (scheme **3.74**).[280] Allylic acetate **290** was stable to prolonged heating under the standard conditions and remained unchanged after several days at 80 °C. Conversely, vinyl acetate **289** slowly underwent a further oxidation to furnish geminal diacetate **291**, with no observation of isomerisation to the allylic species. This suggests that the two regioisomers are the result of two different and competing reaction mechanisms.

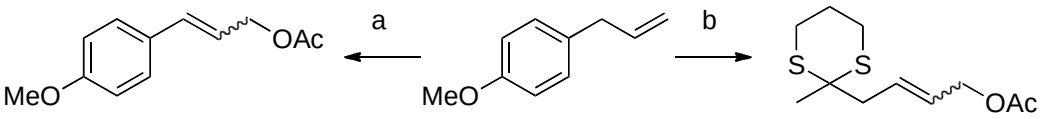


290 **289** **291** 40%
with 40% **289** recovered

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 36 h, 80 ^oC;
E:*Z* ratios in parentheses

Scheme 3.74

In an attempt to determine whether or not this reaction could be carried out chemoselectively, dithiane **124** was subjected to the standard reaction conditions in the presence of another alkene (scheme **3.75**).



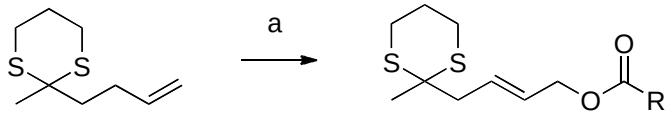
293 93% (10:1) **292** **147** 70% + **292** 86% + **293** 0.6%

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC;
b) Same conditions with 1 eq **124** added; *E*:*Z* ratios in parentheses

Scheme 3.75

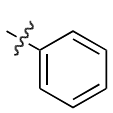
In the absence of dithiane **124**, allyl anisole **292** was readily oxidised to its corresponding allylic acetate **293** in 93% yield. However, when equimolar equivalents of **124** and allyl anisole **292** were subjected to the reaction conditions, only the unsaturated dithiane was oxidised to any significant extent. A trace of **293** was observed, although the majority of the allyl anisole was recovered unreacted, demonstrating that the transformation could be carried out chemoselectively in the presence of a second readily oxidisable alkene. It is interesting to note that the formation of **293** under these conditions (in the absence of an added ligand) is higher yielding than in previous reports, whilst being just as selective for the linear allylic acetate.[263]

Finally, it was found that a number of different allylic esters could be prepared by this method by simply replacing the acetic acid with two equivalents of the corresponding carboxylic acid (scheme **3.76**).

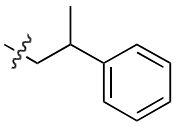


a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), RCO_2H (2 eq), DMSO, O_2, 18 h, 80 °C; *E*:*Z* ratios in parentheses

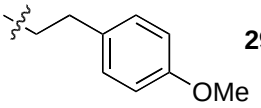
R =



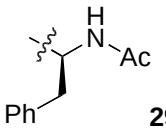
294 85% (10:1)



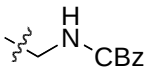
295 33% (6:1)



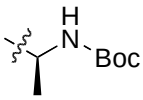
296 37% (6:1)



297 27% (*E*)



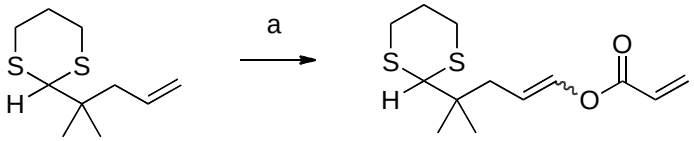
298 49% (*E*)



299 79% (6:1)

Scheme 3.76

In this manner, several allylic esters were prepared in moderate to excellent yield; the procedure even proving compatible with *N*-protected amino acid derivatives **297**, **298** and **299**. One example of a vinyl ester was prepared using an analogous procedure with *gem*-dimethyl dithiane **164** (scheme **3.77**).

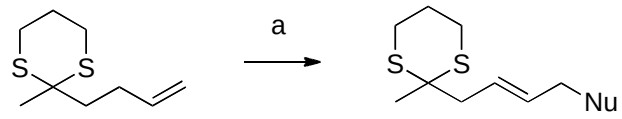


264 **300** 40% (1:1.4)

a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), $CH_2{=}CHCO_2H$ (2 eq), DMSO, O_2, 18 h, 80 °C; *E*:*Z* ratio in parentheses

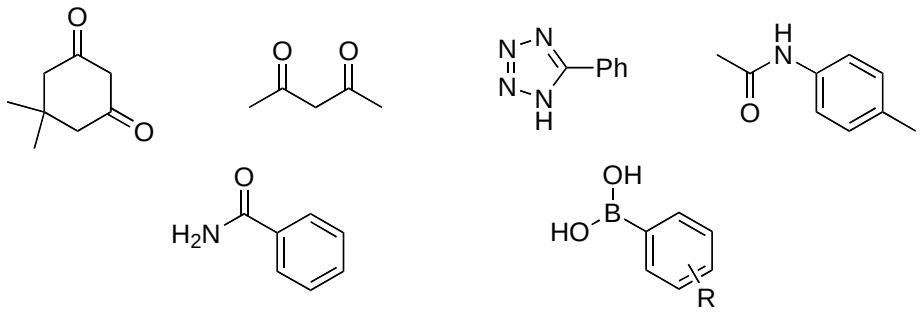
Scheme 3.77

Frustratingly, all attempts to introduce other nucleophilic species in place of the carboxylic acid were unsuccessful (scheme **3.78**).



a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), NuH (2 eq), DMSO, O_2, 18 h, 80 ^oC;

NuH =

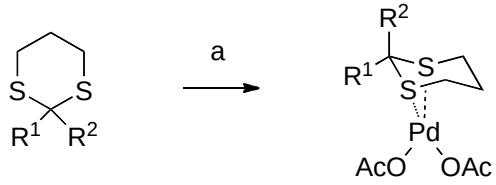


Scheme 3.78

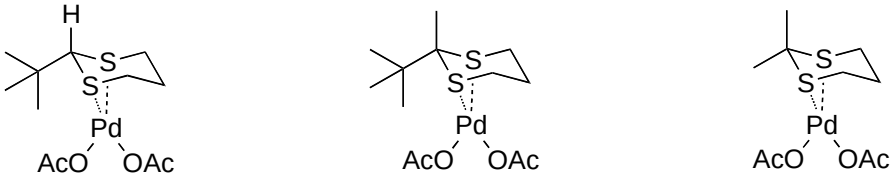
3.3 Mechanistic Study

The observation of a sulfur-palladium complex by NMR in the initial stoichiometric reaction (chapter 2) suggests that the sulfur may be acting as a stabilising group for one or more of the reaction intermediates. This result led to a mechanistic investigation into the role played by the dithiane in the oxidation reaction.

A number of 1,3-dithianes were found to be good bidentate ligands for palladium. For example, several dithiane-palladium complexes were prepared simply by mixing equimolar amounts of the appropriate dithiane and palladium acetate in DCM (scheme **3.79**).



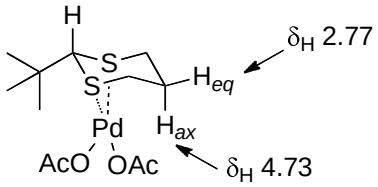
a) $Pd(OAc)_2$ (1 eq), DCM, 1 min, rt, quantitative



301 **302** **303**

Scheme 3.79

Large ^3J couplings for *trans*-diaxial protons and an unusually high chemical shift difference for the axial and equatorial protons at C-7 suggest that the ring adopts a chair conformation in chloroform solution (figure **3.1**).



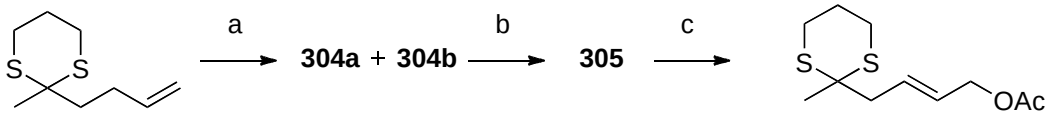
301

Figure 3.1

This affinity for palladium suggested that the dithiane moiety might stabilise reactive intermediates in the allylic oxidation pathway, allowing their structure elucidation and giving insight into the mechanism of the transformation.

Mechanistic studies on palladium-mediated allylic oxidation pathways have often been thwarted by discrepancies between stoichiometric and catalytic reaction products.[269] Co-oxidants such as *p*-BQ and copper salts are known to have an important role in catalytic cycles, often playing an integral role in the mechanism of the transformation of starting material into products.[283,209] In the case of dithiane **124**, the same oxidised product is obtained in both the catalytic and stoichiometric reactions, which suggests that this system might give valuable mechanistic information.[286]

In order to observe any reaction intermediates, dithiane **124** was once again treated with an equivalent of $Pd(OAc)_2$ in $CDCl_3$ and then immediately cooled to 269 K inside a 600 MHz NMR spectrometer (scheme **3.80**). The work in this section was carried out in collaboration with Dr. Abil Aliev (UCL Chemistry Department).



124 **147** 78% isolated

a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 10 min, 269 K; b) 10 min, 322 K; c) 16 h, 298 K

Scheme 3.80

With careful monitoring of the ^{1}H and ^{13}C NMR spectra, immediate formation of an approximately 1:1 mixture of two isomeric complexes **304** was observed. Upon warming to 298 K for 30 min (or 322 K for 10 min), this mixture underwent clean conversion to a single species **305**. No further intermediates were observed in this pathway and complex **305** slowly converted to the expected allylic acetate **147**, which was isolated in good yield.

Isomeric complexes **304** both exhibited an unusually high chemical shift for the axial proton in the 7-position, which is characteristic of the palladium-dithiane complexes observed previously. The symmetrical nature of the dithiane and large ^{3}J values for *trans*-diaxial protons suggest that the ring adopts a chair conformation, with the palladium coordinated to both sulfur atoms. The isomeric relationship between these two complexes appears to be due to the palladium coordinating to either face of the dithiane ring, in an approximately 1:1 ratio. NOEs were observed between the 6- and 8-axial protons and the 4-methylene unit (**304a**) or methyl group (**304b**), supporting this assumption. There was no significant change in the ^{1}H or ^{13}C NMR signals for the double bond in either isomer, suggesting that there is little to no interaction between the palladium and the alkene (figure **3.2**).

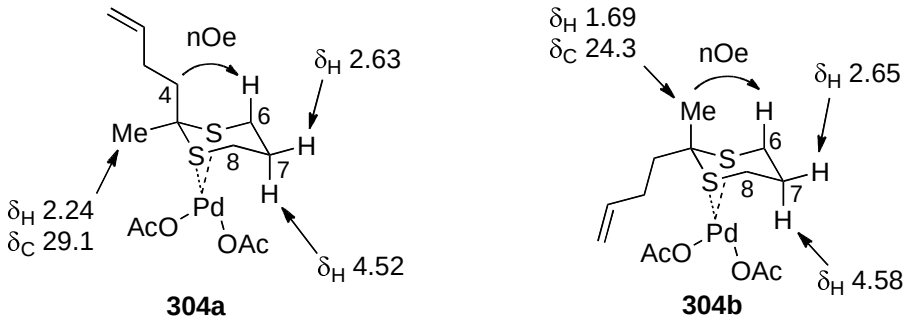
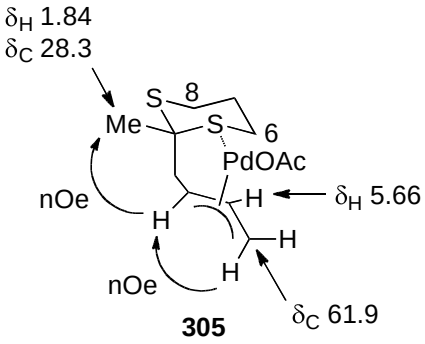


Figure 3.2

Intermediate **305** had an NMR spectrum consistent with a π-allyl palladium species such as the one shown in figure **3.3**.[287,276,288] Again, large ^{3}J couplings were observed for *trans*-diaxial protons, suggesting a chair conformation of the dithiane ring. Deshielding of the protons on C-6, but not C-8 indicates that the palladium is coordinated to only one of the sulfur atoms.

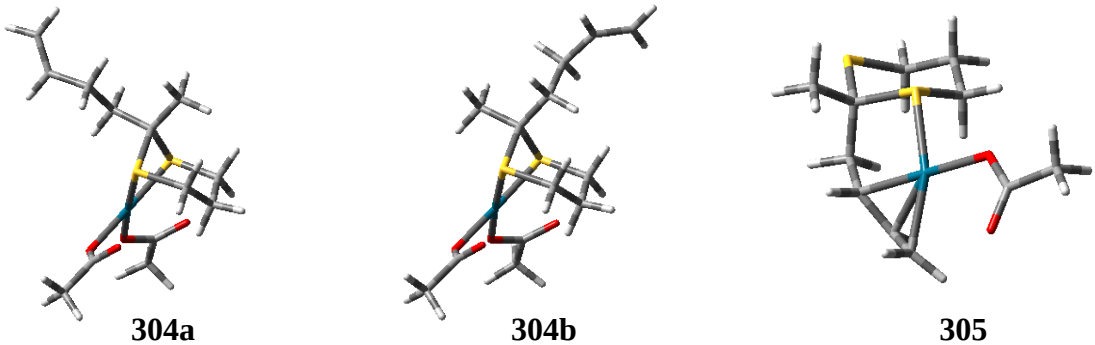


305

Figure 3.3

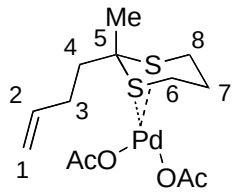
The structures of **304a**, **304b** and **X** were ascertained using a combined application of NMR, semi-empirical (PM6) and quantum mechanical methods. Initially, provisional molecular models were built, satisfying the experimentally measured NOEs and vicinal *J*-couplings. The geometries of these structures were then optimised by Dr. Aliev, using PM6 followed by quantum mechanical DFT calculations; NMR chemical shifts were then calculated for comparison to the experimentally obtained values.

All semi-empirical and quantum mechanical calculations were carried out by Dr. Aliev, using *Gaussian 09*.[289] Optimisation of molecular geometries was performed with DFT PBEPBE[290] calculations, with chloroform solvent effects accounted for by the reaction field method IEFPCM.[291] A basis set of 6-311+G(2d,p) was used for H, C, O and S, whilst for palladium, a quasi-relativistic pseudopotential ECP28MWB was used in conjunction with the ECP28MWB basis set.[292] This same level of theory was then used in calculating the NMR chemical shifts by the GIAO method.[293] The fully optimised structures determined in this fashion are given below in figure **3.4**; calculated and experimentally measured NMR chemical shifts are given in table **3.4**.

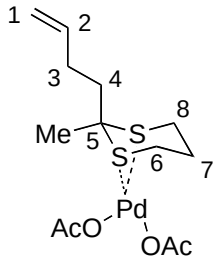


304a **304b** **305**

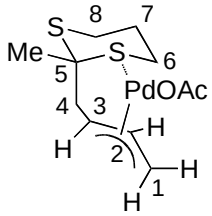
Figure 3.4



304a



304b



305

Proton	**304a** δ_{exp} **/ppm**	**304a** δ_{calc}**/ppm**	**304b** δ_{exp}**/ppm**	**304b** δ_{calc}**/ppm**	**305** δ_{exp}**/ppm**	**305** δ_{calc}**/ppm**
1*cis*	5.10	5.23	5.08	5.21	4.12	3.24
1*trans*	5.13	5.34	5.09	5.29	3.13	2.79
2	5.80	6.10	5.74	6.23	5.66	5.64
3	2.06	2.06	2.20	2.17	3.70	3.36
3´	2.06	2.06	2.20	2.17	-	-
4	2.06	2.01	2.69	2.47	2.67	3.01
4´	2.06	2.01	2.69	2.47	1.92	2.39
5-Me	2.24	1.94	1.69	1.60	1.84	1.72
6*ax*	2.88	3.12	2.91	3.14	3.15	3.28
6*eq*	3.59	3.63	3.64	3.65	3.37	3.01
7*ax*	4.52	3.93	4.58	4.01	1.90	1.68
7*eq*	2.63	2.58	2.65	2.64	2.19	2.17
8*ax*	2.88	3.12	2.91	3.14	3.09	3.21
8*eq*	3.59	3.58	3.64	3.65	2.81	2.60
Me (Ac)	2.00	1.86	2.00	1.87	2.03	1.82

Carbon	**304a** δ_{exp}**/ppm**	**304a** δ_{calc}**/ppm**	**304b** δ_{exp}**/ppm**	**304b** δ_{calc}**/ppm**	**305** δ_{exp}**/ppm**	**305** δ_{calc}**/ppm**
1	117.8	119.6	117.3	119.1	61.9	62.7
2	134.5	144.4	135.1	145.3	115.2	109.7
3	25.3	31.7	28.2	34.8	77.5	80.2
4	36.4	41.1	43.1	48.9	43.7	45.5
5	69.7	93.4	70.5	95.0	64.8	85.9
5-Me	29.1	29.2	24.3	23.4	28.3	27.4
6	31.9	41.1	32.19	41.6	31.2	43.2
7	30.4	34.1	31.1	35.1	24.6	28.1
8	31.9	41.1	32.2	41.6	27.5	34.4
CO (Ac)	178.7	179.2	178.6	179.2	176.5	181.4
Me (Ac)	23.0	22.6	23.1	22.5	22.2	22.0

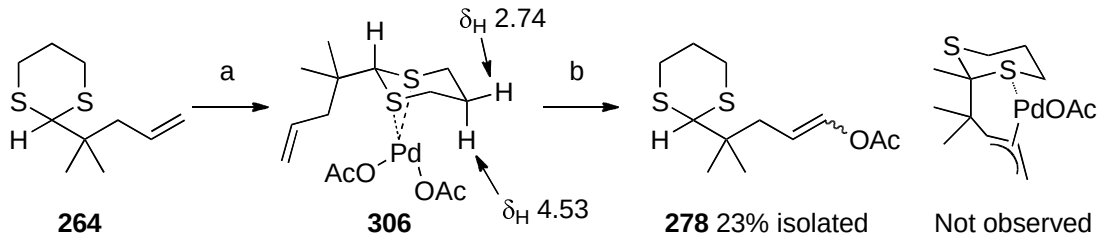
Table 3.4

The experimentally measured ^{1}H and ^{13}C chemical shifts compare well with those calculated computationally, including the unusually high frequency shift for H-7*ax* in complexes **304a** and **304b**. This observation can be attributed to the close spatial proximity of these protons to the neighbouring oxygen atoms of the palladium-bound acetates (3.4 Å in the structures shown). Deshielding of the equatorial protons on C-6, but not C-8 in complex **305** confirms the asymmetric nature of this species, with the palladium being bound to an equatorial lone pair of a single sulfur atom.

Discrepancies between the calculated and experimentally observed ^{13}C chemical shifts for C-6, C-8 and the quaternary C-5 can be attributed to relativistic effects associated with these carbons being bonded to heavy sulfur atoms. In order to accommodate for these effects and achieve a more realistic approximation of these values, a higher level of theory would be required.

Whilst it is unclear whether this π-allyl species undergoes intra- or intermolecular acetate addition, the close proximity of the acetate carbonyl to the terminal position of the π-allyl system suggests that an intramolecular addition is plausible.

Catalytic oxidation of closely related *gem*-dimethyldithiane derivative **264** gave selective formation of the corresponding vinyl acetate **278**, with no observation of any allylic oxidation products. **264** was therefore selected for a similar low-temperature NMR study in order to observe any intermediates in its formation. As with **124**, **264** initially formed a complex when treated with an equivalent of $Pd(OAc)_2$ in $CDCl_3$ (scheme **3.81**). This complex however existed as a single isomer **306**, with the palladium coordinated to the more hindered face of the conformationally locked dithiane. Again, a characteristically high chemical shift was observed for the 7-H_{ax}.

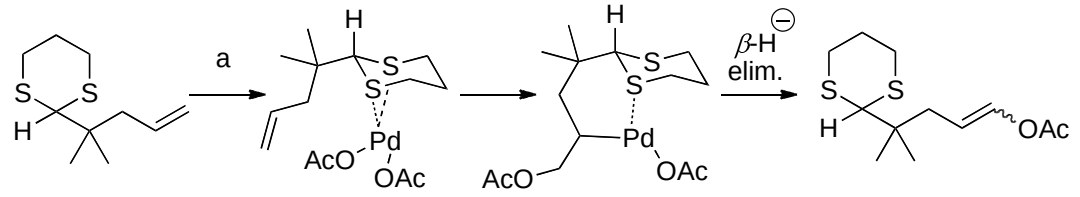


a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 5 min, 298 K; b) 18 h, 298 K

Scheme 3.81

Upon warming this complex to 298 K, there was no indication of the formation of a π-allyl species; instead, slow conversion to vinyl acetate **278** was observed. This suggests that **278** is the result of a direct acetoxypalladation, followed by a regioselective *β*-hydride elimination (scheme **3.82**). This addition of palladium acetate across the double bond is likely to be the rate-determining step, as formation of the initial complex **306** occurs rapidly. The fact that Pd-C σ-bonded species **307** is

not observed suggests that *β*-hydride elimination is also fast, giving rapid decomposition to the vinyl acetate.

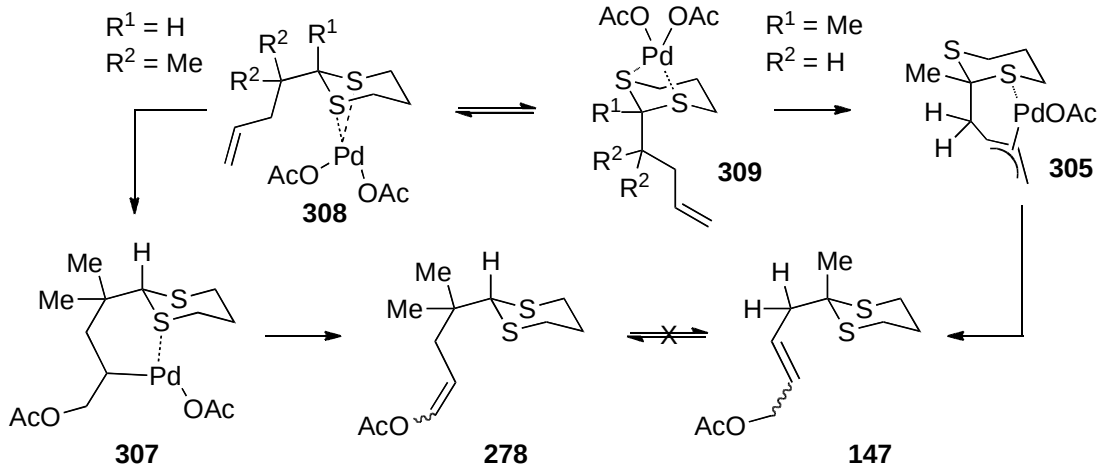


264 **306** **307** - Not observed **278**

a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, rt

Scheme 3.82

Considering the information obtained from these low-temperature NMR experiments, it appears that two divergent reaction mechanisms are at work in the oxidation of these unsaturated dithiane derivatives (scheme **3.83**).

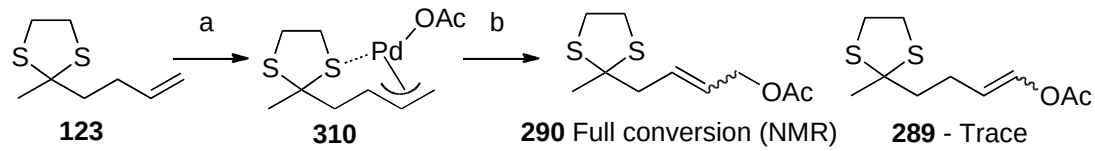


Scheme 3.83

In both cases, formation of an initial dithiane-palladium complex is observed, with the palladium coordinated to one or both faces of the dithiane. Reaction can then proceed via one of two pathways: either a) abstraction of an allylic hydride to form a π-allyl intermediate, followed by attack of acetate on the terminal position and elimination of palladium (0) to give allylic acetate **147**; or b) direct acetoxypalladation, followed by rapid *β*-hydride elimination to give vinyl acetate **278**. The rate of this second pathway is presumably increased by the presence of substituents at the homoallylic position because; firstly, a) abstraction of an allylic hydrogen atom is made more difficult and formation of a π-allyl species is

unfavourable; and b) access to an axial π-allyl species is prevented by the bulky nature of the alkyl chain, favouring complex **308** over **309**.

Treatment of dithiolane **123** with stoichiometric $Pd(OAc)_2$ led to the formation of π-allyl species **310**, with a small trace of vinyl acetate **289** (scheme **3.84**). **310** very gradually reacted to give allylic acetate **290**, although the π-allyl species was surprisingly stable at room temperature. Unfortunately, this stability could not be utilised to grow a single crystal for X-ray analysis, with all attempts resulting in an amorphous black solid.

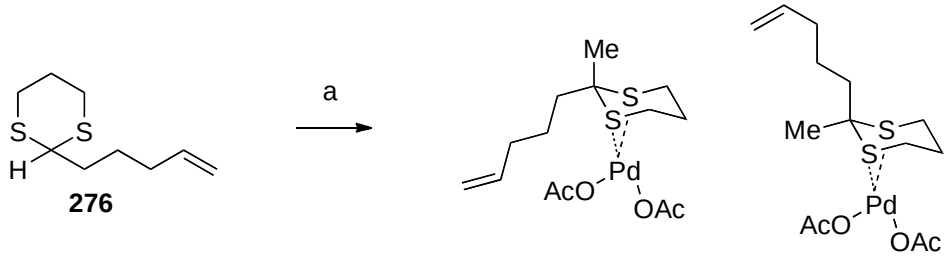


123 **310** **290** Full conversion (NMR) **289** - Trace

a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 25 min, rt; b) 5 d, rt

Scheme 3.84

When treated with one equivalent of $Pd(OAc)_2$ in $CDCl_3$, longer chain dithiane derivative **276** also formed a 1:1 mixture of isomeric complexes **311** (scheme **3.85**). These complexes proved to be relatively stable however and no oxidation products were observed, even on heating the mixture.



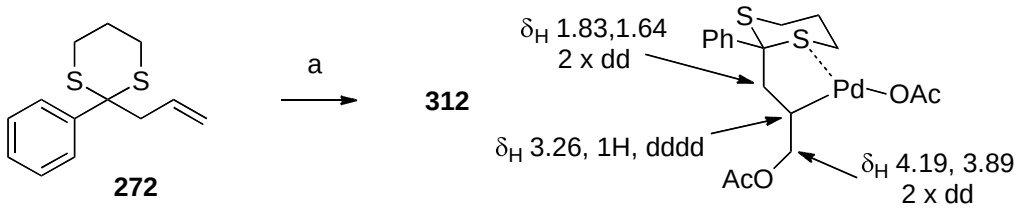
276 a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 5 min, rt **311a** **311b**

Scheme 3.85

3.4 Pd-C σ-Complexes

Allyl dithiane derivative **272** behaved very differently when treated with $Pd(OAc)_2$, forming a stable new complex **312** as a single isomer. The ^1H NMR of this complex contained a sharp dddd at 3.26 ppm, which integrated as a single proton. Four sets of dds showed COSY cross peaks to this single proton, suggesting the formation of a dithiane-stabilised Pd-C σ-complex, such as the one shown in scheme **3.86**. This

unusual new complex was an interesting discovery, which led to the formation of a number of similar Pd-C σ-bonded species.



a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 25 min, rt

Scheme 3.86

Stable Pd-C σ-complexes that contain *β*-hydrogen atoms are extremely rare, as they often readily undergo *β*-hydride elimination.[294] The formation of complex **312** and its subsequent stability towards *β*-hydride elimination is remarkable bearing in mind it has no fewer than four *β*-hydrogen atoms.

Another surprise was the unexpected clarity of the ^{1}H NMR spectrum of this complex; the one *α*- and four *β*-protons all having very sharp, well-defined peaks (figure **3.5**).

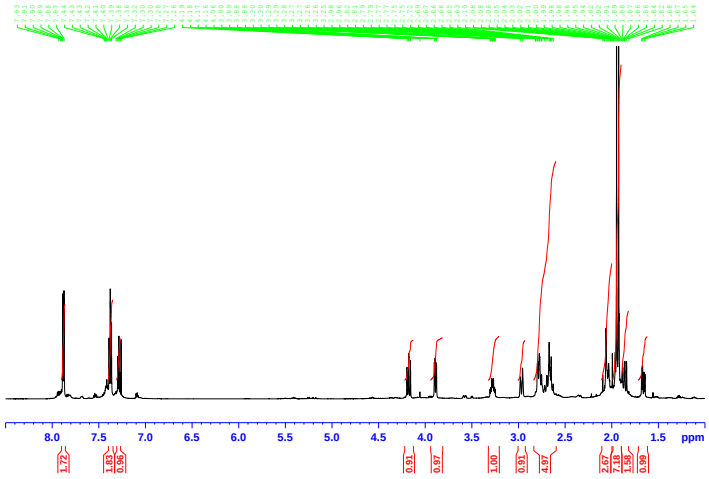


Figure 3.5

The ^{13}C NMR spectrum of **312** was also extremely well defined, with the resonance assigned to the carbon atom bonded to palladium at 32.2 ppm (figure **3.6**).

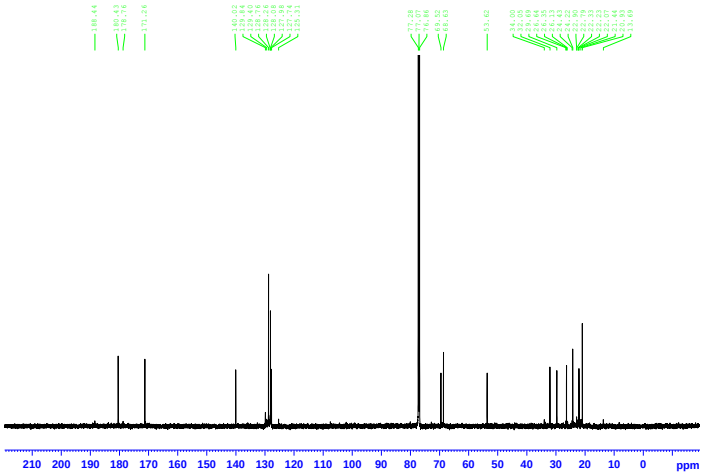


Figure 3.6

This structural rigidity greatly facilitated the elucidation of the nature of the complex. An unexplained NOE was observed between the 6-H_{ax} proton and the 2-methylene unit, suggesting that the complex may be dimeric (figure **3.7**). Close proximity of the 6-H_{ax} proton of one monomeric unit and the 2'-methylene unit of another in a dimeric structure such as **313** could explain the observation of this NOE. Unfortunately, all attempts to recrystallise this complex were unsuccessful, resulting in an amorphous resinous substance.

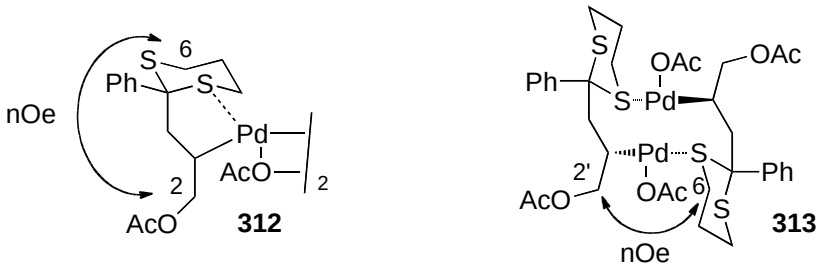
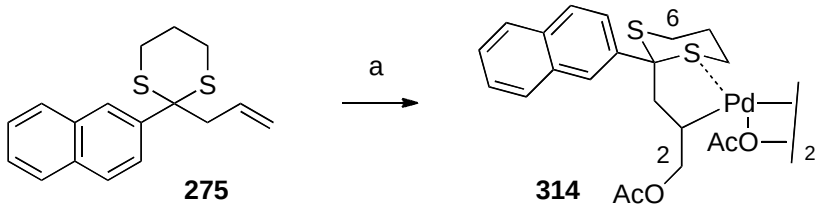


Figure 3.7

2-naphthyl dithiane derivative **275** gave an analogous dimeric complex **314** upon treatment with $Pd(OAc)_2$ (scheme **3.87**).



a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 25 min, rt

Scheme 3.87

Again, the NOE between the 6-H_{ax} proton and 2'-methylene unit was observed, as well as the distinctive resonance for the Pd-C-H unit (a dddd coupled to four β-hydrogens). The NMR spectra of **314** are given below in figure **3.8**.

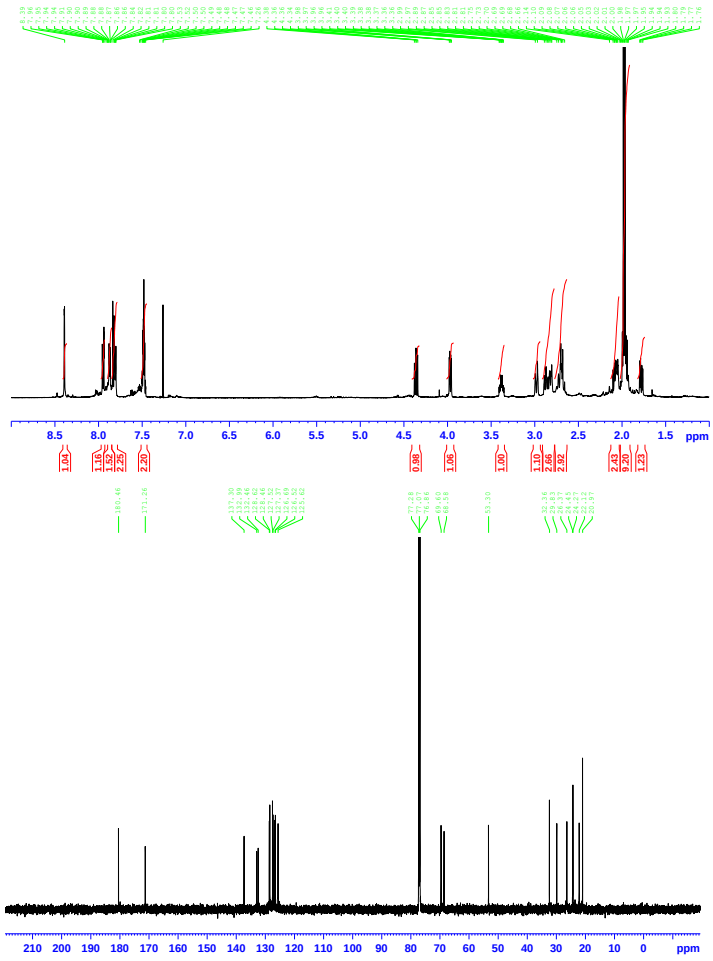


Figure 3.8

Pleasingly, this complex proved amenable to crystallisation; slow recrystallisation via vapour diffusion ($CHCl_3$-Et_2O/petrol 1:1) gave a single crystal, which was submitted for X-ray analysis, confirming the dimeric structure of the complex (figure **3.9**).

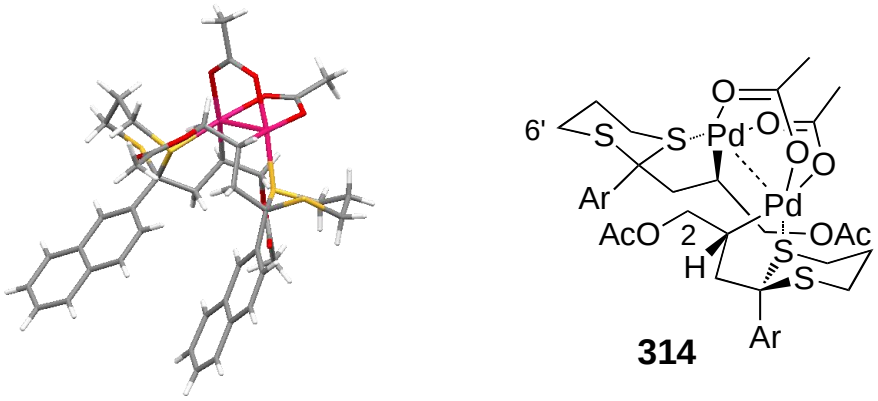
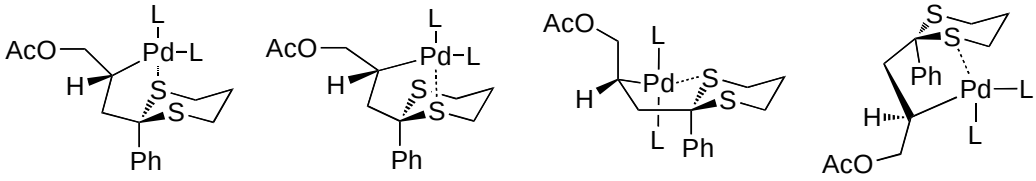


Figure 3.9

314 is dimeric, with two bridging acetate ligands; the palladium atoms having an internuclear distance of just 2.959 Å. The palladium atoms sit in an axial position on the dithiane ring, adopting a square-planar geometry. This X-ray structure confirms that the palladium atoms are coordinated to just one sulfur atom each, as well as showing the close spatial proximity of the 2-methylene unit and 6'-H_{ax} proton observed by NOE. The rigid nature of this dimeric structure may account for the fact that **314** is surprisingly stable towards β-hydride elimination.

The complex was isolated as a single diastereoisomer, which is interesting, considering that three stereocentres are generated upon formation of **314** and **312**. There are four possible diastereomers for **312**; each of which is shown below in figure **3.10**.

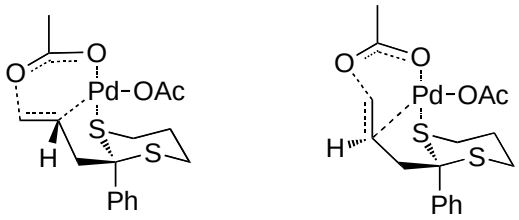


312a **312b** **312c** **312d**

Figure 3.10

Of the four possible diastereomers, **312a** and **312b** are *cis*-fused 6,5-bicyclic systems, with the palladium atom occupying an axial position on the dithiane ring. **312c** and **312d**, which have the palladium coordinated to an equatorial lone pair are the more strained *trans*-fused isomers and are presumably less favourable as a result.

Orientation of the acetoxymethylene unit *exo*- to the concave 6,5-fused system rather than *endo*- is a likely explanation for the observation of **312a**, but not **312b**. Possible transition states for the formation of **312a** and **312b** are given below in figure **3.11**.

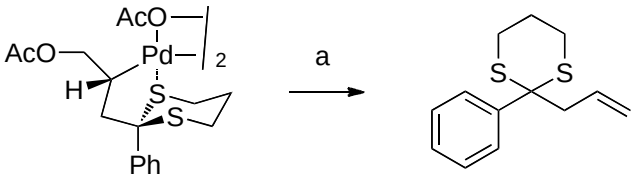


Exo - **312a** *Endo* - **312b**

Figure 3.11

These transition states assume *syn*-acetoxypalladation of the double bond, although an *anti*-addition cannot be ruled out. However, the same stereochemistry would be observed in either case, regardless of the *syn*- or *anti*-nature of the acetoxypalladation.

Treatment of **312** with an equivalent of pyridine resulted in an immediate β-acetoxy elimination to regenerate starting dithiane **272**, which was recovered in 81% yield after chromatography (scheme **3.38**).

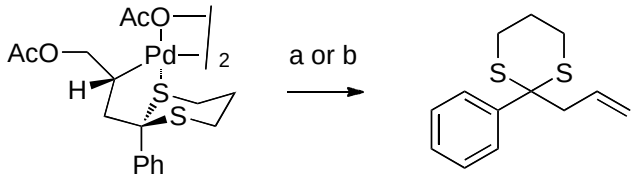


312 **272** 81% isolated

a) Pyridine (1 eq), $CDCl_3$, 1 min, rt

Scheme 3.88

The same result was obtained upon treatment of **312** with either PPh_3 or a Grignard reagent, with full conversion to the starting material observed by crude NMR (scheme **3.89**).

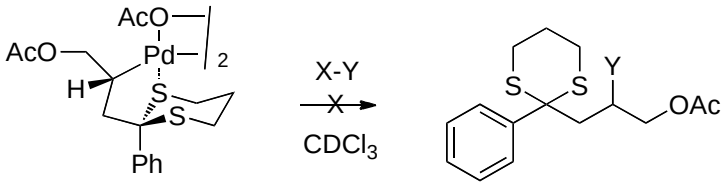


312 **272** Full conversion (NMR)

a) PPh_3 (1 eq), $CDCl_3$, 1 min, rt; b) PhMgBr (1-2 eq), $CDCl_3$, 1 min, rt

Scheme 3.89

A number of different reagents that were used in attempts to induce further transformations of this complex are given in table **3.5**. Frustratingly, no isolable products were observed in any of these reactions.



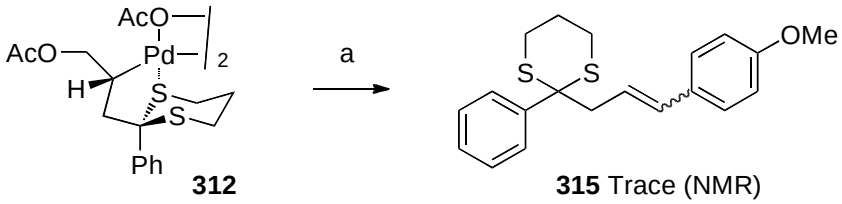
312

Entry	Reagent	Temp/°C	Time	Observation
1	$NaBH_4$/MeOD	25	<1 min	Complex mixture
2	NBS	25	<1 min	Complex mixture
3	Ph_2IOTf/MeOD	25	<1 min	Complex mixture
4	LiCl/MeOD	25	<1 min	Complex mixture
5	Bu_3SnPh	60	2 d	No reaction
6	Ethyl acrylate	60	2 d	No reaction

Table 3.5

Attempts at reduction (entry 1), oxidation (entry 2), and ligand exchange (entries 3 and 4) all resulted in immediate formation of palladium black and inseparable complex mixtures. Surprisingly, complex **312** was unreactive to both transmetallation with an organostannane (entry 5) and Heck reaction with another alkene (entry 6), even upon heating for several days.

Treatment of **312** with an aryl boronic acid in the presence of CsF also resulted in rapid β-acetoxy elimination, with the starting dithiane **272** as the major product (scheme **3.90**). A trace of 1,2-disubstituted alkene **315** was also observed in the crude NMR, but this species could not be isolated.

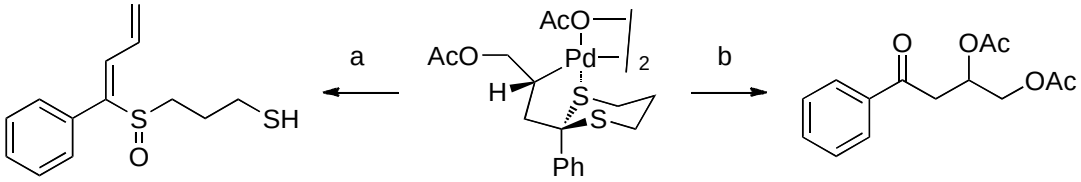


312 **315** Trace (NMR)

a) *p*-$MeOC_6H_4B(OH)_2$ (1 eq), CsF (1.5 eq), $CDCl_3$, 5 min, rt

Scheme 3.90

Two additional attempts were made to induce a further transformation of complex **312** by oxidation (scheme **3.91**).



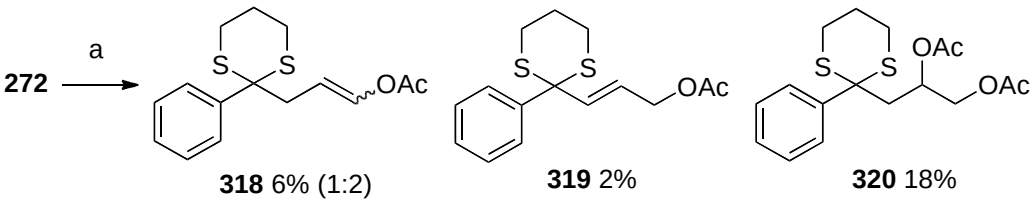
316 40% Isolated **312** **317** 22% Isolated

a) $CuCl_2$ (2 eq), $CDCl_3$, 1 h, rt; b) $PhI(OAc)_2$ (2 eq), $CDCl_3$, 1 h, rt

Scheme 3.91

Upon treatment with $CuCl_2$, **312** dissociated with concurrent oxidative cleavage of the dithiane to give diene **316**, which was isolated in 40 % yield. $PhI(OAc)_2$ also induced cleavage of the dithiane, although there was some evidence for the oxidation of the carbon-palladium bond; vicinal diacetate **317** being the only product isolated from the reaction mixture. This result was encouraging, suggesting that the Pd-C bond is oxidisable and that further transformations should therefore be possible.

A catalytic version of this oxidation reaction was attempted, by dropwise addition of a solution of $PhI(OAc)_2$ to dithiane **272** in the presence of catalytic palladium acetate (scheme **3.92**).



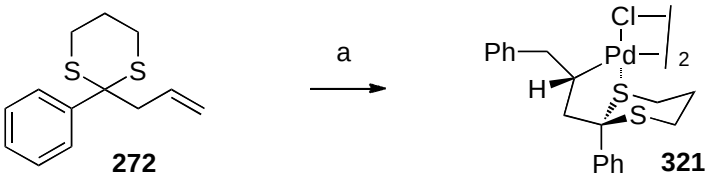
318 6% (1:2) **319** 2% **320** 18%

a) $Pd(OAc)_2$ (0.1 eq), $PhI(OAc)_2$ (3 eq), 18 h, rt

Scheme 3.92

Several variations of this reaction were attempted, though none were particularly successful. The best results were obtained by slow addition of three equivalents of the oxidising agent to a DCM solution of the dithiane and 10 mol% $Pd(OAc)_2$, yielding oxidised products **318**, **319** and **320** in poor yield.

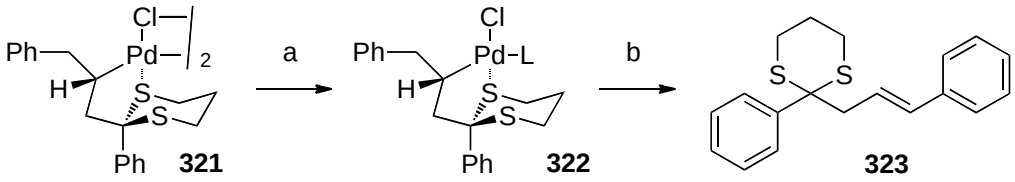
Treatment of allyl dithiane **272** with an equivalent of phenyltributyltin in the presence of $Pd(MeCN)_2Cl_2$ furnished the analogous chloride dimer **321** by carbopalladation of the double bond (scheme **3.93**).[231]



a) $Pd(MeCN)_2Cl_2$ (1 eq), $PhSnBu_3$ (1 eq), $CDCl_3$, 1h, rt

Scheme 3.93

The NMR spectrum of this complex was extremely broad, perhaps due to monomer-dimer exchange. However, addition of an equivalent of a coordinating ligand such as pyridine or isocyanide was sufficient to cleave the dimer, to form monomeric species **322** (scheme **3.94**), which were much more readily characterised by NMR. These monomeric species were relatively stable towards β-hydride elimination, only giving very slow conversion to alkene **323** over several days in solution. ^{1}H NMR spectra of **321** and **322** are given below in figures **3.12** and **3.13** respectively.



a) L (1 eq), $CDCl_3$, 1 min, rt; L = ^{t}BuNC, pyridine; b) several days, rt

Scheme 3.94

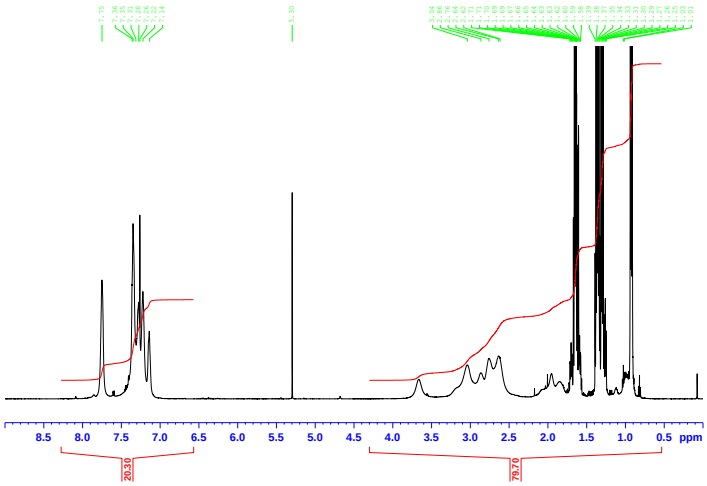


Figure 3.12

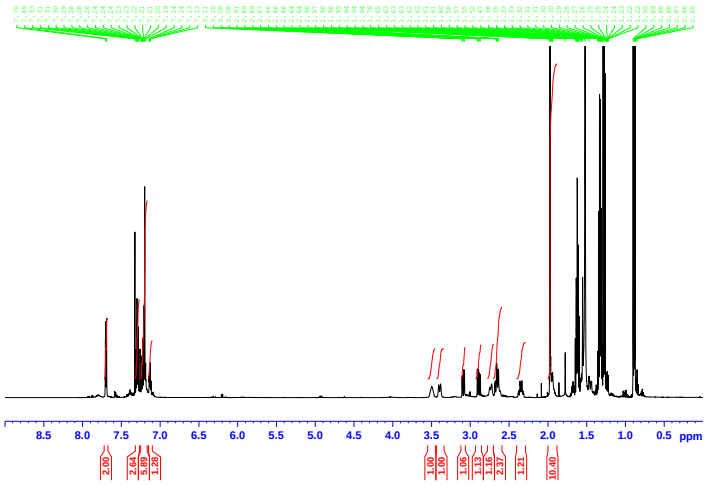
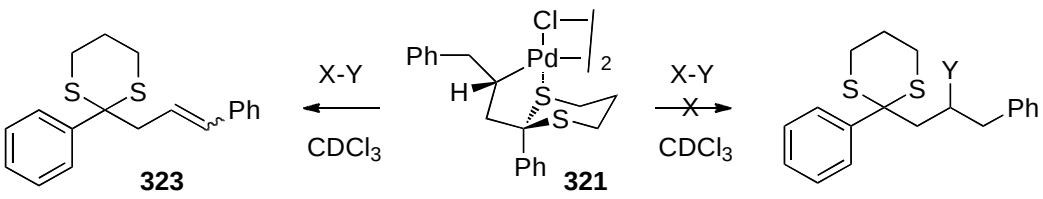


Figure 3.13

Carbopalladated species **321** was also subjected to a number of different conditions in attempts to induce further transformations of this complex (table **3.6**).

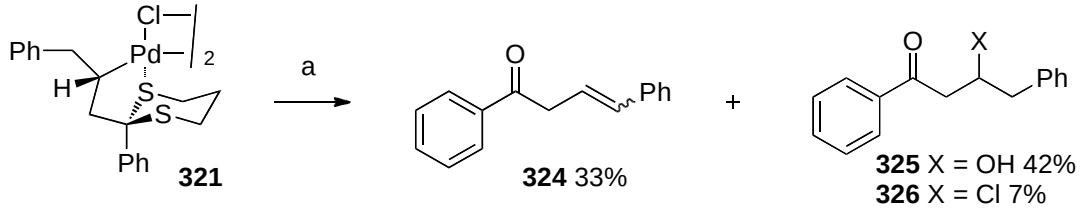


Entry	Reagent	Temp/°C	Time	Observation
1	$NaBH_4$/MeOD	25	<1 min	Unidentified product
2	NBS	25	<1 min	Complex mixture
3	Ph_2IOTf/MeOD	25	<1 min	Complex mixture
4	PPh_3	25	5 min	β-Hydride elimination to give **323**
5	PhMgBr	25	<1 min	β-Hydride elimination to give **323**
6	$CuCl_2$	25	1 h	β-Hydride elimination to give **323**
7	Ethyl acrylate	60	2 d	No reaction

Table 3.6

Attempts to reduce **321** with $NaBH_4$ resulted in a complex mixture, which gave trace amounts of an unidentifiable product after aqueous work-up and chromatography on silica gel (entry 1). Extremely low yields and difficulties in reproduction of this result meant that elucidation of the structure of the new species was not possible. As with complex **312**, oxidation of **321** with NBS (entry 2) and diphenyliodonium salts (entry 3) gave complex, inseparable mixtures. Treatment of **321** with PPh_3, PhMgBr and $CuCl_2$ all resulted in rapid β-hydride elimination to give alkene **323** (entries 4-6). Complex **321** was also unreactive to Heck acceptor ethyl acrylate (entry 7).

One final attempt was made to oxidise this chloropalladium dimer in the presence of Oxone.[295-297] Pleasingly, **321** reacted smoothly to give a mixture of three oxidised products in excellent yield (scheme **3.95**). Oxidation of the carbon-palladium bond proceeded rapidly, with concomitant cleavage of the dithiane to give β-hydroxyketone **325** and β-chloroketone **326**, with alkene **324** being the only other product isolated from the reaction mixture.

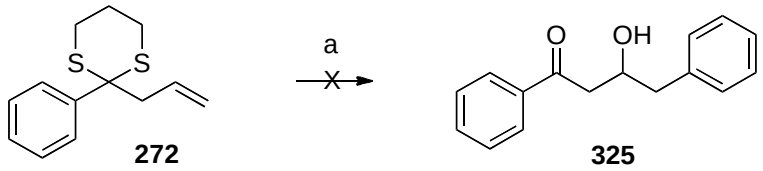


321 **324** 33% **325** X = OH 42% **326** X = Cl 7%

a) Oxone (2 eq), DCM/MeCN/H_2O 1:1:1, 1 h, rt

Scheme 3.95

Unfortunately, all attempts at developing a catalytic version of this reaction were unsuccessful, resulting in cleavage of the starting dithiane and incomplete oxidation (scheme **3.96**).

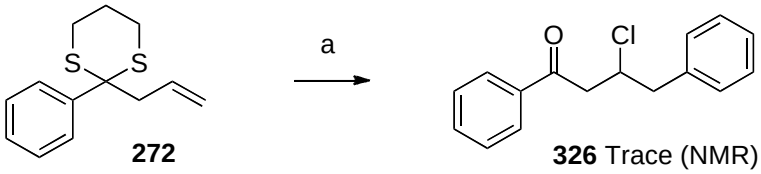


272 **325**

a) $Pd(MeCN)_2Cl_2$ (0.1 eq), $PhSnBu_3$ (1 eq), Oxone (2 eq), DCM/MeCN/H_2O 1:1:1, rt

Scheme 3.96

Attempts at a catalytic oxidative Heck reaction of dithiane **272** in the presence of phenyltributyltin and $CuCl_2$ resulted in the observation of trace amounts of chloride **326** (scheme **3.97**). Isolation of this product proved difficult however, and the reaction conditions could not be optimised in favour of the chloride product.

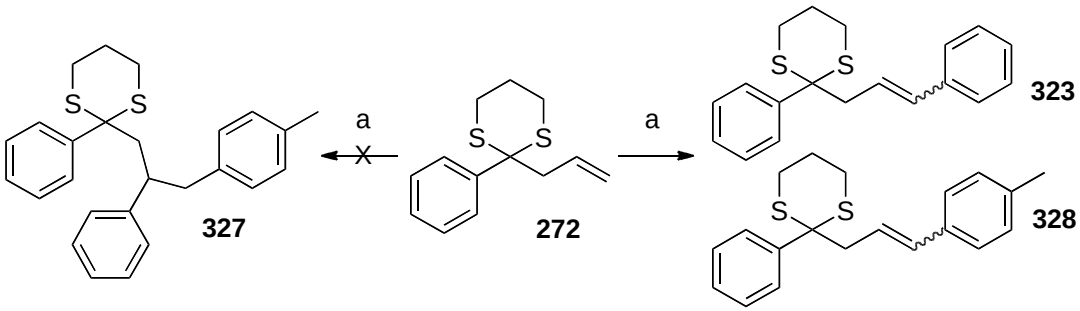


272 **326** Trace (NMR)

a) $Pd(MeCN)_2Cl_2$ (0.1 eq), $PhSnBu_3$ (1 eq), $CuCl_2$ (4 eq), Et_2O, rt

Scheme 3.97

Finally, dithiane **272** was treated with phenyltributyltin in the presence of $Pd(MeCN)_2Cl_2$ and an aryl iodide (scheme **3.98**). Interestingly, none of the desired diarylated product **327** was observed; a 1:1 mixture of 1,2-disubstituted alkenes **323** and **328** being the only products isolated from the reaction mixture.

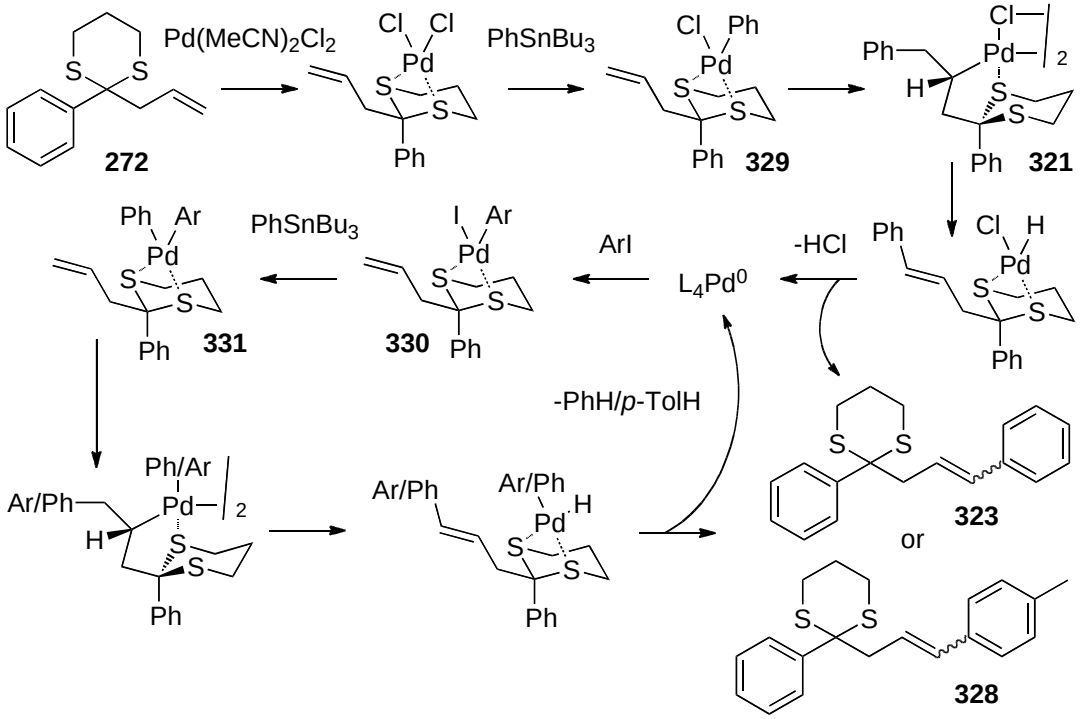


327 **272**

a) $Pd(MeCN)_2Cl_2$ (0.1 eq), $PhSnBu_3$ (1 eq), *p*-Tol-I (1 eq), toluene, 24 h, 80 ^oC, 50% 1:1 **323**:**328**

Scheme 3.98

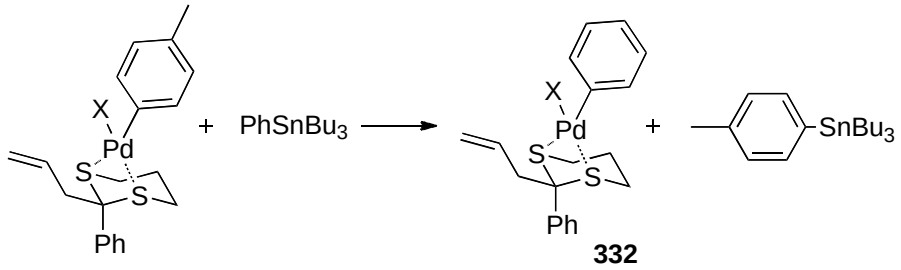
The mechanism of this transformation is unclear, although one plausible pathway is shown below in scheme **3.99**. Firstly, palladium-dithiane complex formation, followed by a transmetallation could give aryl palladium species **329**. This could then undergo carbopalladation of the double bond to give dithiane-bound Pd-C σ-complex **321**, which upon *β*-hydride elimination would give alkene **323** and a palladium hydride species. The resulting Pd^0 could undergo oxidative insertion into the aryl iodide to give Pd^{II} species **330**. Another transmetallation would give diarylpalladium species **331**, which would presumably give a mixture of phenyl- and tolyl-Heck products **323** and **328**. Reductive elimination of either toluene or benzene would then regenerate the Pd^0, completing the catalytic cycle.



Scheme 3.99

To further investigate this, it would be interesting to vary the stoichiometry of the reaction to discern the effect of having an excess of either the aryl iodide or the organostannane. The catalytic turnover is presumably dependent on there being a stoichiometric amount of the aryl iodide, in which case a reduction of the amount of organostannane would presumably result in a greater proportion of *p*-tolyl alkene **328**.

Another plausible pathway for the formation of this intriguing mixture of products is scrambling of the aryl groups to give a mixture of *p*-tolyltributylstannane and phenylpalladium species **322**, which cannot be ruled out in this case (scheme **3.100**).[298]

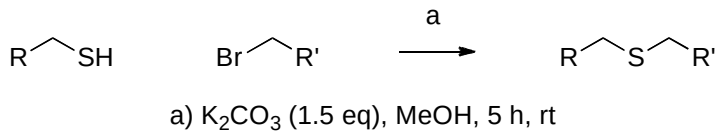


332

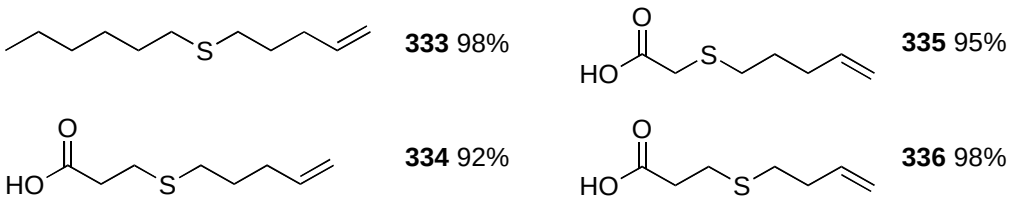
Scheme 3.100

3.5 Oxidation of Unsaturated Linear Thioethers

Given the success of the palladium-mediated oxidation of unsaturated dithiane derivatives, a number of unsaturated linear thioethers were also made and subjected to the catalytic conditions. Each was made in excellent yield by simply stirring the appropriate thiol with an alkyl bromide in the presence of an excess of K_2CO_3 in methanol (scheme **3.101**).



a) K_2CO_3 (1.5 eq), MeOH, 5 h, rt



333 98%

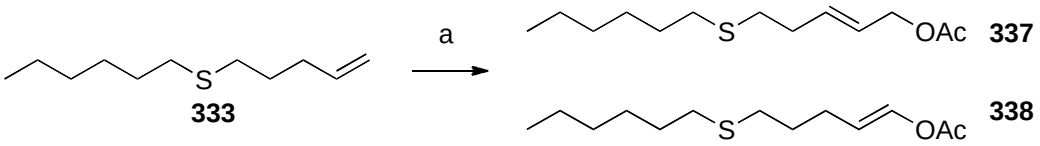
335 95%

334 92%

336 98%

Scheme 3.101

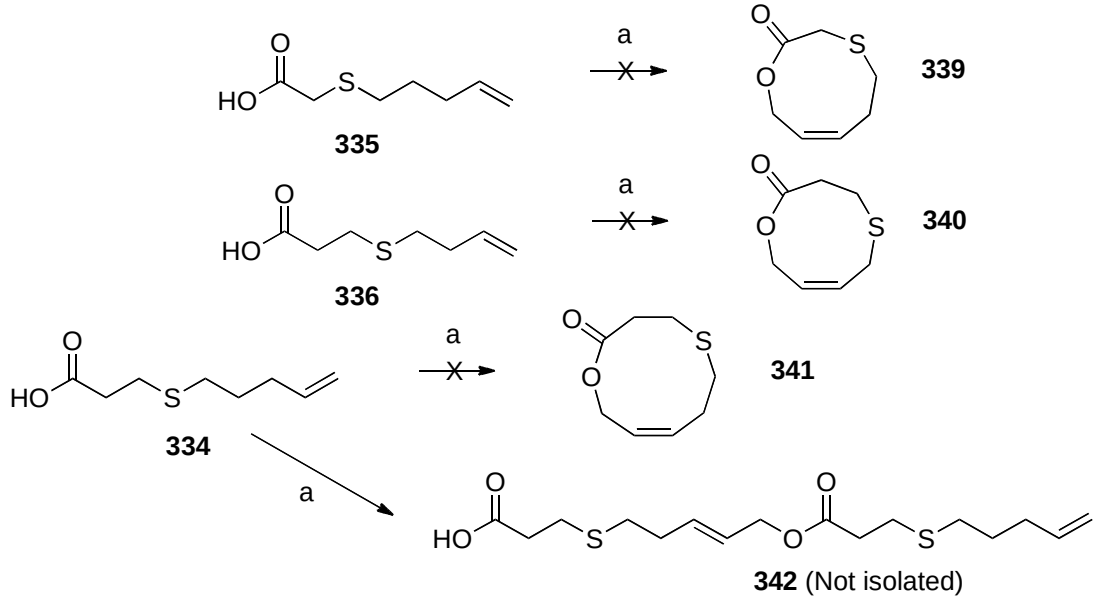
^{n}Hexylsulfide derivative **333** appeared to undergo relatively smooth oxidation to a mixture of the corresponding allylic and vinyl acetates **337** and **338** by crude NMR (scheme **3.102**). However, these species were not particularly stable and repeated attempts at isolation by column chromatography resulted in degradation of the products.



a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), AcOH (5 eq), DMSO, O_2, 18 h, 80 ^oC; **337**:**338** 2:1 (not isolated)

Scheme 3.102

Carboxylic acid derivatives **334**, **335** and **336** were subjected to the same catalytic conditions in the absence of acetic acid, in the hope that they might cyclise to form medium ring lactones **339**, **340** and **341** (scheme **3.103**).

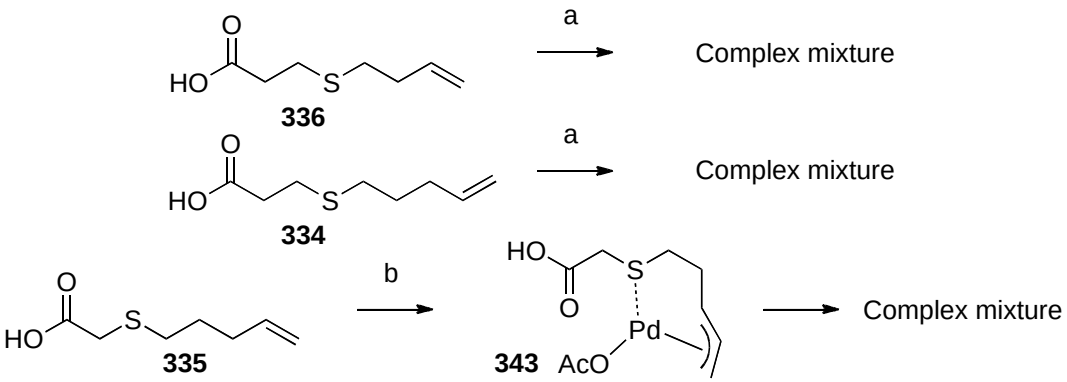


a) $Pd(OAc)_2$ (0.1 eq), *p*-BQ (0.4 eq), MnO_2 (1 eq), DMSO, 18 h, 80 ^oC

Scheme 3.103

No reaction was observed for **335** or **336**, with the starting materials remaining intact after several hours at 80 °C. **334** did undergo oxidation to a new species, although the crude NMR spectrum of this new product appeared to be consistent with an intermolecular allylic ester formation to give **342**, rather than the desired intramolecular lactonisation. This suggests that the concentration was too high, favouring the intermolecular reaction; perhaps repeating this reaction under a higher dilution might favour the lactonisation. Again, this product was unstable to silica gel chromatography and could not be isolated from the reaction mixture.

The three carboxylic acid derivatives were also subjected to the stoichiometric reaction conditions and monitored by NMR (scheme **3.104**). **334** and **336** reacted quickly with $Pd(OAc)_2$ to give very broad ^1H NMR spectra, which were almost impossible to interpret; no oxidised products could be isolated from these complex reaction mixtures. Acid **335** on the other hand reacted more slowly, undergoing smooth transformation to a new species **343**, which had ^1H and ^{13}C NMR spectra consistent with a π-allyl palladium complex.



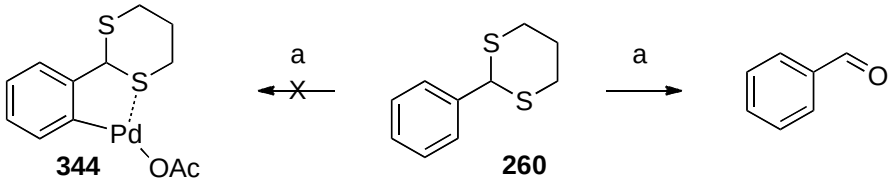
a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 5 min, rt; b) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 24 h, rt

Scheme 3.104

Unfortunately, this π-allyl species did not go on to form the desired medium ring lactone, but gradually gave a complex reaction mixture similar to those obtained from **334** and **336**. No further transformations were clearly discernible and no products could be isolated from the reaction mixture.

3.6 Aryl C-H Activation

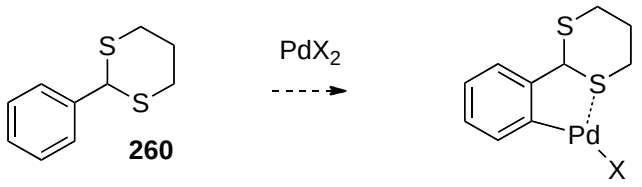
Several attempts were made to induce aryl C-H activation using a thioacetal as a removable directing group. For example, phenyldithiane **260** was treated with $Pd(OAc)_2$ in $CDCl_3$ and the reaction was monitored by NMR (scheme **3.105**).



a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 6 h, rt

Scheme 3.105

Rather than the desired C-H activation taking place, the palladium acted as a Lewis acid, cleaving the dithiane to give benzaldehyde as the only observed product. Other more common cyclopalladating conditions were therefore attempted; the results of which are given in table **3.7**.



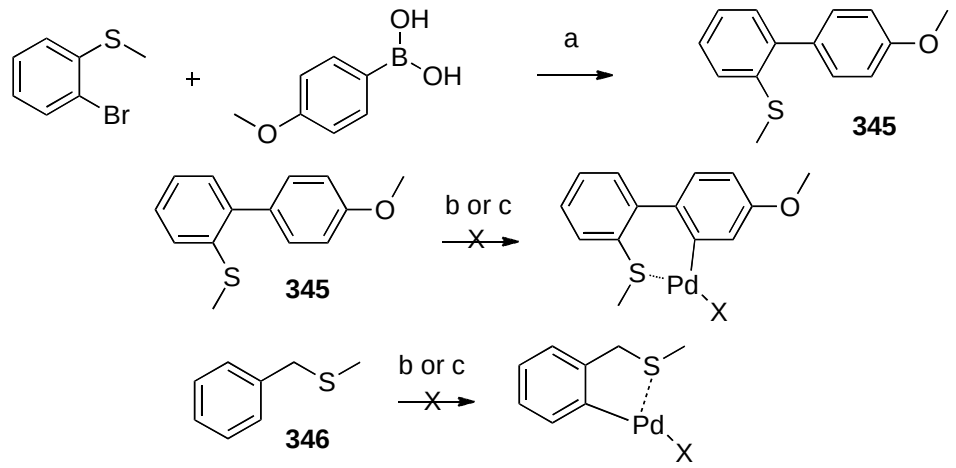
260

Entry	PdX_2	Additive	Solvent	Temp/°C	Observation
1	$Pd(OAc)_2$	-	MeOH	60	Insoluble orange solid
2	$Pd(OAc)_2$	NaOAc	MeOH	60	Insoluble orange solid
3	$Pd(OAc)_2$	NaOAc	AcOH	80	Dithiane cleavage
4	$Pd(OAc)_2$	LiCl	MeOH	60	Insoluble brown solid
5	$PdCl_2$	-	MeOH	60	Dithiane cleavage
6	$PdCl_2$	-	AcOH	80	Dithiane cleavage

Table 3.7

Heating **260** in acetic acid in the presence of a Pd^{II} salt resulted in cleavage of the dithiane (entries 3 and 6). This cleavage was also observed upon refluxing **260** in methanol in the presence of $PdCl_2$ (entry 5). Refluxing **260** in methanol with $Pd(OAc)_2$ resulted in insoluble orange-brown powders, irrespective of the additive used (entries 1, 2 and 4).

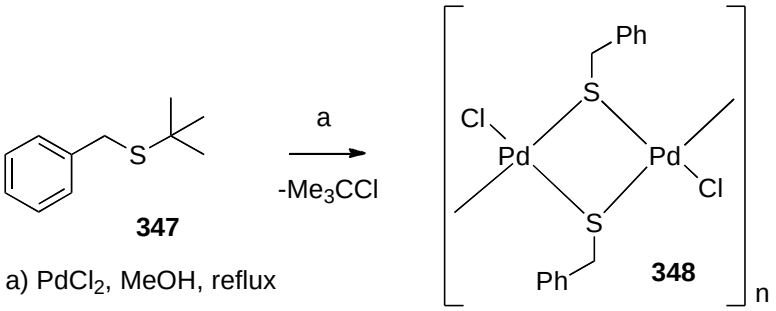
Biaryl sulfide species **345** was prepared in good yield by Suzuki coupling of *S*-methyl-2-bromothiophenol and *p*-methoxyphenylboronic acid (scheme **3.106**). Frustratingly, both **345** and *S*-methylbenzylthiol **346** behaved similarly to dithiane **260**, giving insoluble complex mixtures under cyclometallating conditions.



a) $Pd(PPh_3)_2Cl_2$ (3 mol%), K_2CO_3 (1.5 eq), MeCN, H_2O, MW, 120 ^oC, 10 min, 81%;
b) $Pd(OAc)_2$, $CDCl_3$; c) $Pd(OAc)_2$, MeOH, reflux, insoluble complex mixture

Scheme 3.106

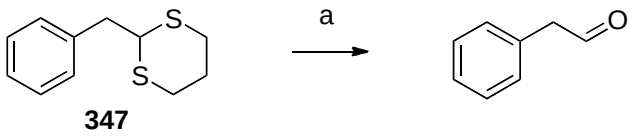
Insoluble polymeric materials such as those obtained in the above experiments have been reported for aryl sulfides in the presence of Pd^{II} salts. For example, Hiraki observed that *tert*-butylbenzylsulfide **347** underwent an unusual C-S bond cleavage to form insoluble polymer **348** upon treatment with $PdCl_2$ in methanol (scheme **3.107**).[299]



a) $PdCl_2$, MeOH, reflux

Scheme 3.107

Other aryl C-H activations were also attempted, though all attempts ultimately met with failure. Firstly, phenylacetaldehyde-derived dithiane **349** was cleaved in the presence of $Pd(OAc)_2$ to give phenylacetaldehyde and no C-H insertion was observed (scheme **3.108**).

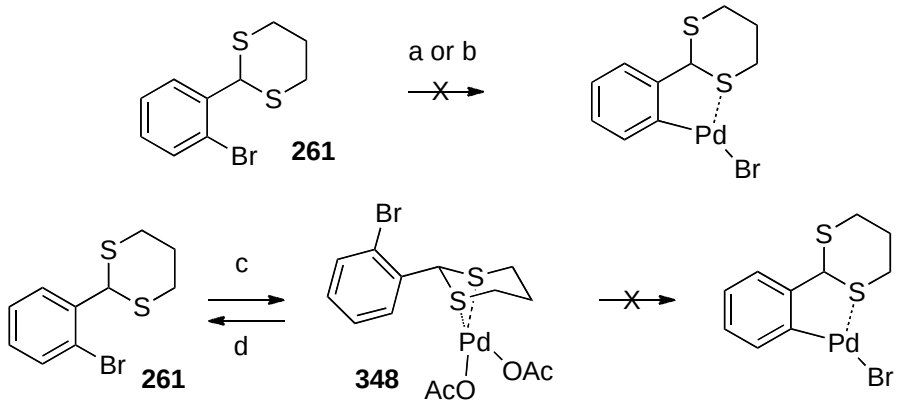


347

a) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 12 h, rt

Scheme 3.108

2-Bromobenzyldithiane **261** was expected to undergo oxidative insertion in the presence of a Pd^0 species, although none was observed, even upon heating for several hours (scheme **3.109**). Formation of a complex between dithiane **261** and $Pd(OAc)_2$ **348** was observed in $CDCl_3$, although addition of PPh_3 in an attempt to reduce the palladium and induce oxidative insertion merely resulted in cleavage of the complex to give the starting dithiane.



a) $Pd(PPh_3)_4$ (1 eq), $CDCl_3$, reflux; b) $Pd_2(dba)_3$ (1 eq), $CDCl_3$, reflux;
c) $Pd(OAc)_2$ (1 eq), $CDCl_3$, 20 min, rt; d) PPh_3 (1 eq), 1 min, rt

Scheme 3.109

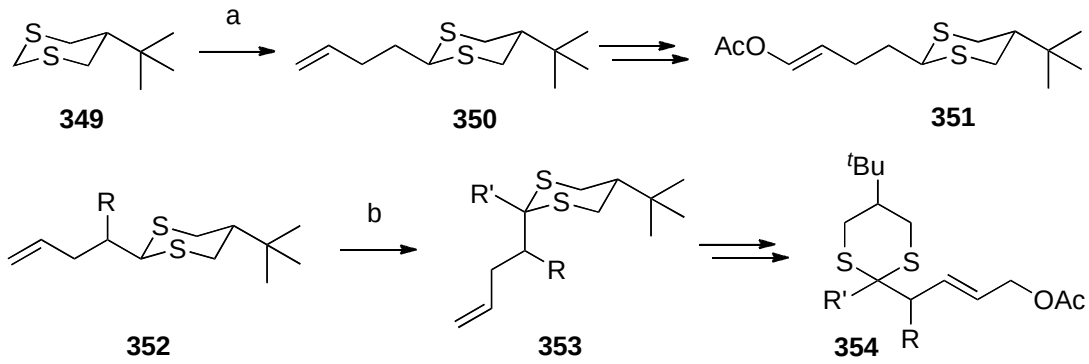
3.7 Conclusions and Future Work

A new methodology for the oxidation of unsaturated thioacetals was developed, using the dithiane moiety as a directing group to control the regiochemistry in favour of oxidation at the terminal carbon atom. A number of linear allylic and vinyl acetates were synthesised in moderate to good yield using this procedure.

A detailed mechanistic study was carried out in collaboration with Dr. Abil Aliev, resulting in the proposal of two divergent reaction mechanisms in the oxidation of unsaturated thioacetals, leading to either allylic or vinyl acetates.

One interesting area for future work on this project would be the development of a similar methodology that could generate allylic or vinyl acetates selectively. For example, synthesis of 5-*tert*-butyl dithiane **349** and alkylation with 4-bromobutene should give dithiane **350** (scheme **3.110**). Access to an equatorial π-allyl intermediate should therefore be limited due to the *tert*-butyl group being forced into an axial position, hence favouring the vinyl acetates **351**.

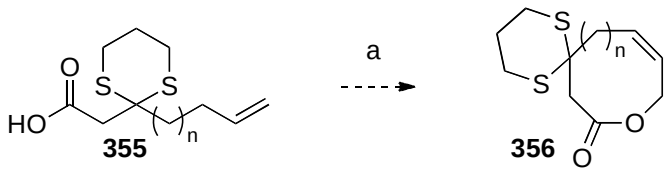
Likewise, synthesis of 2-alkyl-5-*tert*-butyl dithianes **352** and alkylation with a suitable alkyl bromide should furnish 2,2-dialkyl dithianes **353**, in which the double bond tether is forced into the axial position. With the double bond tether in the axial position, access to the π-allyl intermediate would be facilitated, favouring the formation of allylic acetates **354**.[300]



a) ^{n}BuLi, 4-bromobutene, THF; b) ^{n}BuLi, R'Br, THF

Scheme 3.110

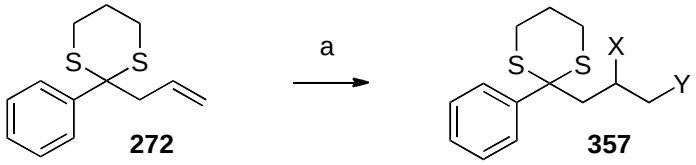
Another area to explore is the formation of medium ring lactones using an intramolecular dithiane-directed allylic oxidation. Dithiane substrates **355** might undergo intramolecular allylic oxidation to give medium ring lactones **356** under appropriate conditions (scheme **3.111**).



a) $Pd(OAc)_2$, *p*-BQ, MnO_2, DMSO, O_2, 80 ^oC, dilute

Scheme 3.111

Formation of the unusual Pd-C σ-complexes **312** and **321** was observed, with the resulting species being surprisingly stable to β-hydride elimination. Further investigation into the reactivity of these complexes would be another interesting avenue to explore. In particular, the development of a catalytic procedure for the 1,2-functionalisation of the double bond in allyldithiane **272** is a very attractive goal (scheme **3.112**).

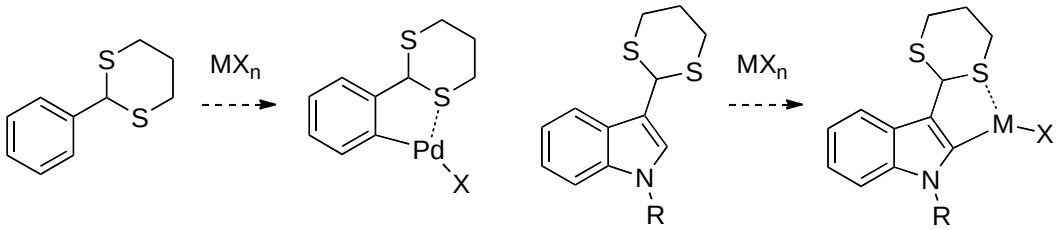


272 **357**

a) Pd (cat.), X-Y

Scheme 3.112

Finally, attempts were made at cyclopalladation reactions with aryl dithianes, although no progress has been made thus far. The thioacetal-directed insertion of palladium into an aryl C-H bond is another key goal for this project. In this respect, the scope is not limited to the use of palladium; a range of different transition metal ions are known to undergo cyclometallation reactions of this type and could therefore potentially be used in this context (scheme **3.113**). *N*-Alkylindoles are known to readily undergo metal-mediated C-H activation reactions of this type;[301] a removable moiety such as a dithiane, which could potentially be used as a C-2 or C-3 directing group would therefore be a very useful synthetic tool. Future work on this project will explore this possibility as well as the other C-H activation chemistry described above.



M = Pd, Pt, Rh, Ru, Au etc.

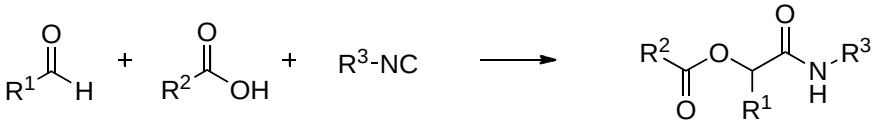
Scheme 3.113

4. Isocyanide-Based Multi-Component Reactions of *N*, *O*-Acetal Derivatives

4.1 Introduction

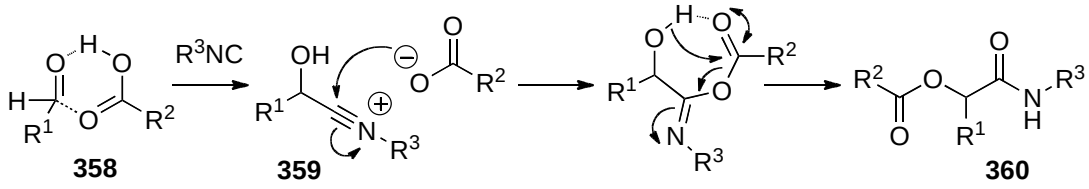
Defined as reactions in which three or more components combine to give a single product, multi-component reactions are highly atom efficient, convergent methods for the rapid synthesis of complex molecular architectures. Despite having received much attention over the last few decades,[302] isocyanide-based multi-component reactions have a long history,[303] which dates back to the publication of the Passerini three-component reaction (P-3CR) in 1921.[304,305] More recently, several advances have been made in the field, with a range of methods now available for the rapid entry into libraries of compounds for drug discovery.[306]

The Passerini reaction involves the condensation of an aldehyde, an isocycanide and a carboxylic acid to give highly functionalised α-carboxyamides (scheme **4.1**).



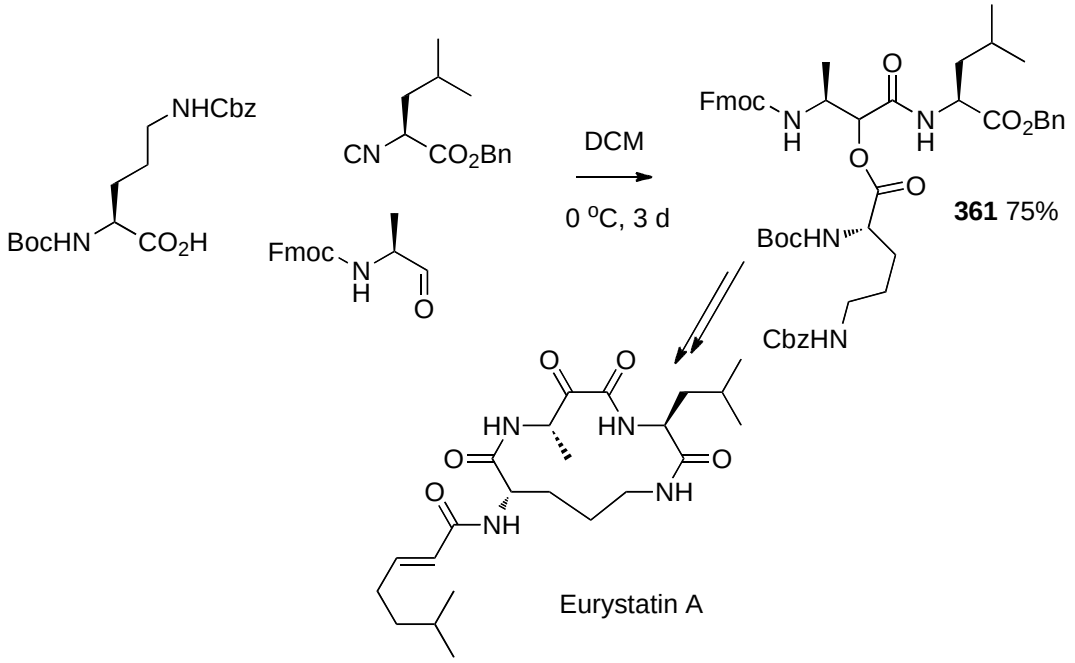
Scheme 4.1

This reaction exploits the ambiphilic nature of the isocyanide moiety, which is able to act as both a nucleophile and an electrophile sequentially at the same carbon atom. The isocyanide inserts into the acid-activated aldehyde **358** to give nitrilium ion **359**, which is in turn attacked by the resultant carboxylate (scheme **4.2**). An *O*-*O*'-acyl transfer then takes place, with concomitant formation of the amide to give the product **360**. The atom-efficiency[307,308] of this transformation is remarkable, with all atoms present in the starting materials being retained in the product.



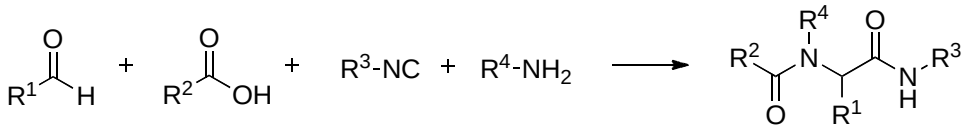
Scheme 4.2

Semple recently put this reaction to excellent use in the concise total synthesis of eurystatin A (scheme **4.3**). A Passerini three-component reaction furnished key intermediate **361** in good yield, which was then elaborated in just six steps to give the natural product.[309]



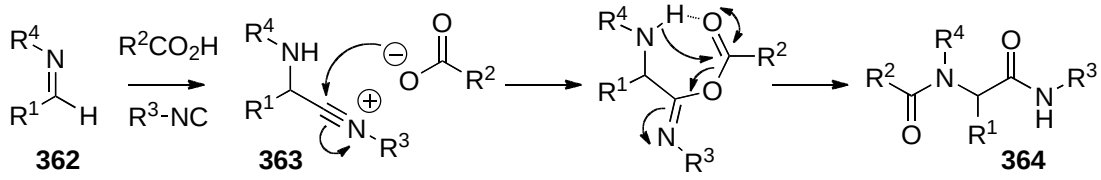
Scheme 4.3

Since its discovery in the late 1950s,[310,311] the Ugi four-component reaction (U-4CR) has become one of the most celebrated and widely used of all multi-component reactions.[312,313] As with the Passerini reaction, the Ugi four-component reaction also employs the unique reactivity of isocyanides in their condensation with an aldehyde, a primary amine and a carboxylic acid (scheme **4.4**).



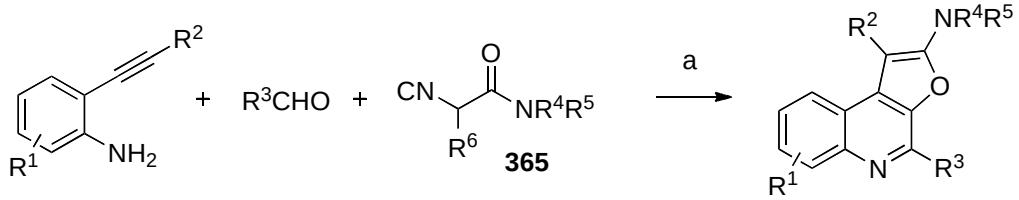
Scheme 4.4

The imine **362**, formed upon condensation of the primary amine and aldehyde is protonated by the carboxylic acid and attacked by the isocyanide to give nitrilium ion **363** (scheme **4.5**). Attack by the carboxylate followed by a Mumm rearrangement[314] (*O-N* acyl transfer) then gives the highly functionalised α-amidoamide product **364**.



Scheme 4.5

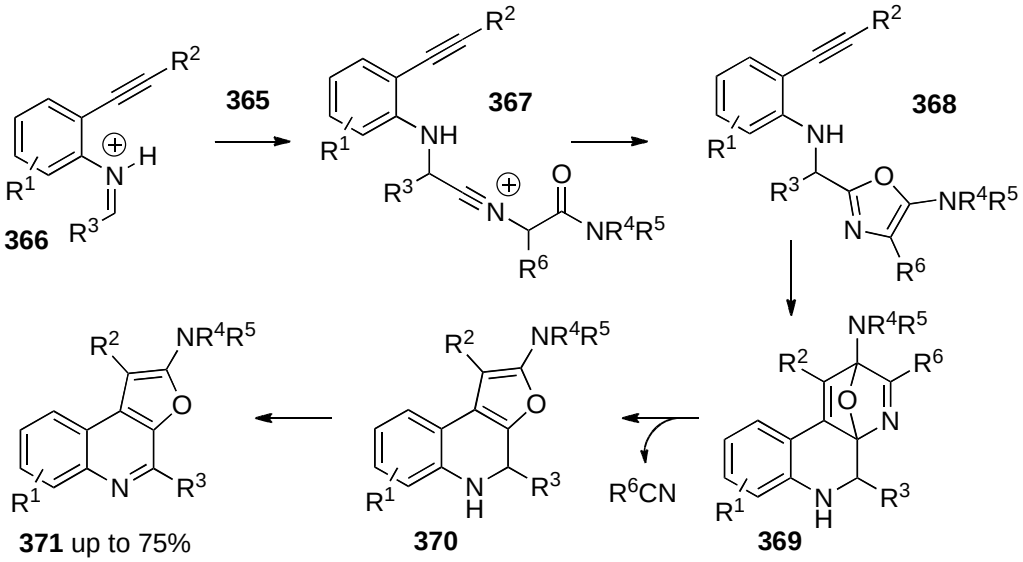
One recent example of the use of this multi-component approach to the construction of complex, highly functionalised molecular architectures is the three-component/domino sequence reported by Zhu for the synthesis of furoquinolines (scheme **4.6**).[315]



a) NH_4Cl (1 eq), toluene, 15 h, reflux; 10 examples, up to 75%

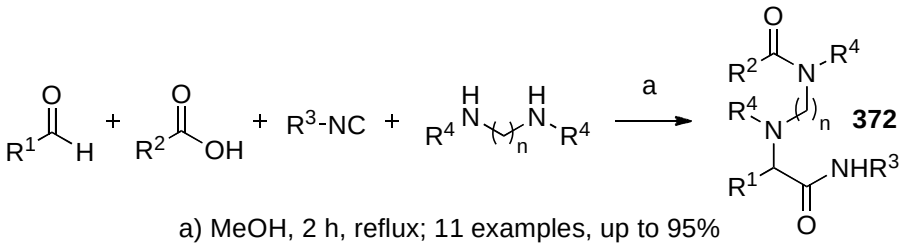
Scheme 4.6

Condensation of the aldehyde and aniline gives iminium ion **366**, which is attacked by isocyanide **365** to give nitrilium ion **367** (scheme **4.7**). Oxazole **368** is then formed *in situ*, followed by an intramolecular Diels-Alder reaction to give bridged adduct **369**, which in turn undergoes a retro-Diels-Alder fragmentation to give **370**. Aromatisation of **370** finally furnishes the furoquinoline product **371** in excellent yield.



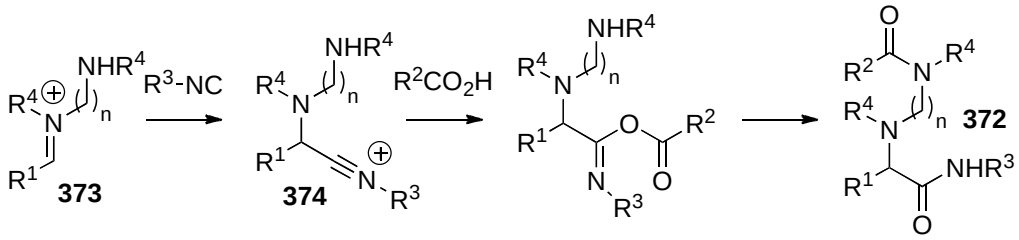
Scheme 4.7

Giovenzana recently reported a modified Ugi four-component reaction,[316] which involves the use of *bis*-secondary diamines as mimics for the primary amine. The *bis*-diamine splits the *N*-alkylation and *N*-acylation steps between two different nitrogen atoms in this so-called *N*-split U-4CR, giving even more highly functionalised products in excellent yield (scheme **4.8**).



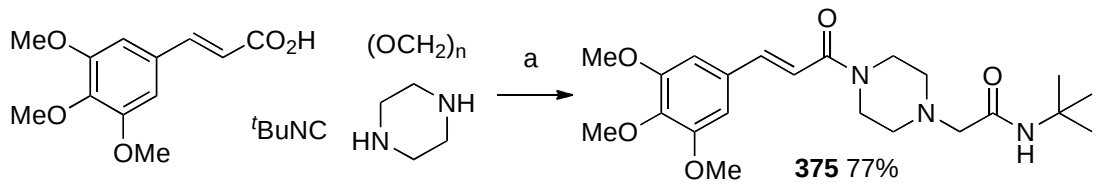
Scheme 4.8

The mechanism of this transformation is similar to that of the Ugi reaction, although the initial condensation between the secondary amine and the aldehyde gives iminium ion **373**, rather than an imine. This iminium species is then attacked by the isocyanide to give the analogous nitrilium species **374**, which reacts with the carboxylic acid as in the conventional Ugi reaction. Finally, an *O*-*N*-acyl transfer onto the other secondary amine gives the product **372**, as the first has already become a tertiary amine and cannot accept the acyl group (scheme **4.9**).



Scheme 4.9

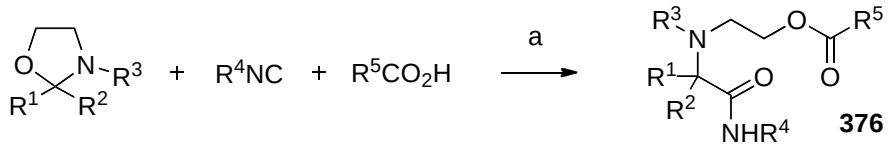
The synthetic utility of this reaction was elegantly demonstrated in the one step synthesis of vasodilator **375** from piperazine (scheme **4.10**). This route is both higher yielding than the previous synthesis, as well as being far more atom efficient, clearly proving this to be a powerful synthetic transformation.



a) MeOH, 2 h, reflux

Scheme 4.10

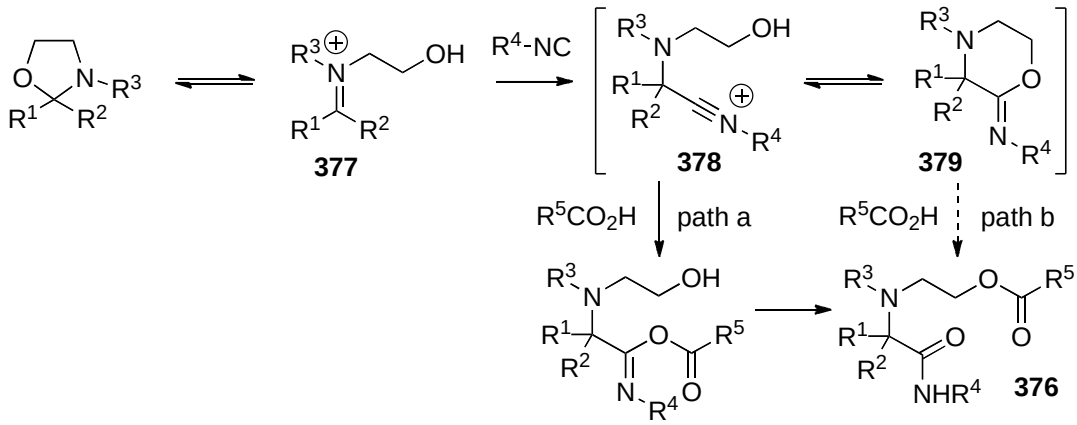
In the same year, Motherwell reported the isocyanide-based multi-component reaction of oxazolidines with carboxylic acids to give ethanolamine derivatives **376** (scheme **4.11**).[173]



a) TsOH (10 mol%), MeCN, 18-24 h, reflux; >20 examples, up to 80%

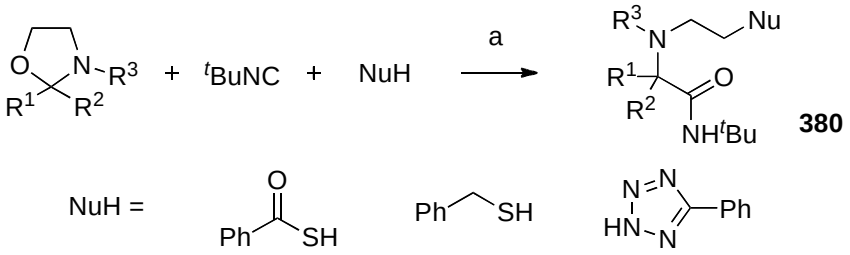
Scheme 4.11

The acid-catalysed ring opening of the oxazolidine gives iminium species **377**, which is subsequently attacked by the isocyanide to give nitrilium ion **378** (scheme **4.12**). This nitrilium species can then be trapped by the carboxylic acid to give the multi-component product **376** following an *N-O* acyl transfer (path a). Nitrilium species **378** is presumably in equilibrium with cyclic iminoether **379** and an alternative mechanism involving nucleophilic ring opening of **379** by the carboxylate can also be envisaged (path b). An isotopic labelling experiment using ^{18}O-labelled acetic acid later confirmed that the reaction does indeed proceed via path a.[174]



Scheme 4.12

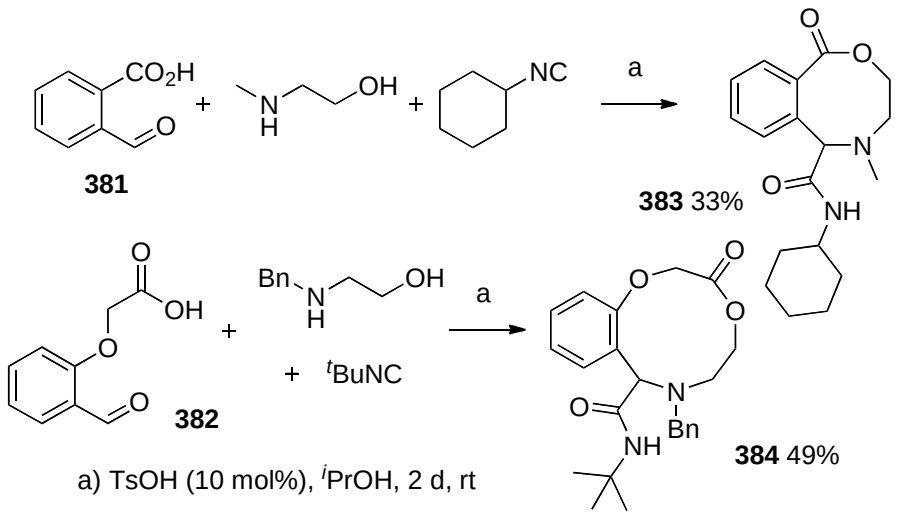
This methodology was later extended to the use of other nucleophiles, which take the place of the carboxylic acid to give a range of substituted α-aminoamides **380** (scheme **4.13**).



a) NuH (1 eq), TsOH (10 mol%), MeCN, 18-24 h, reflux; 6 examples, up to 71%

Scheme 4.13

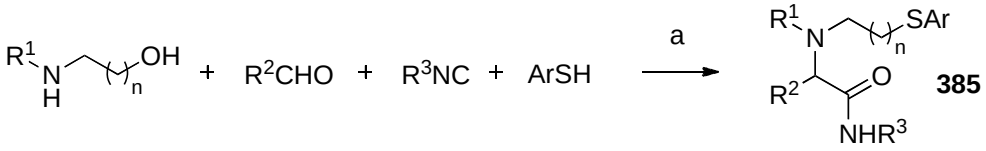
Combining the aldehyde and carboxylic acid components in bifunctional substrates **381** and **382** allowed the synthesis of medium ring heterocycles **383** and **384** by the same procedure (scheme **4.14**).



a) TsOH (10 mol%), *i*PrOH, 2 d, rt

Scheme 4.14

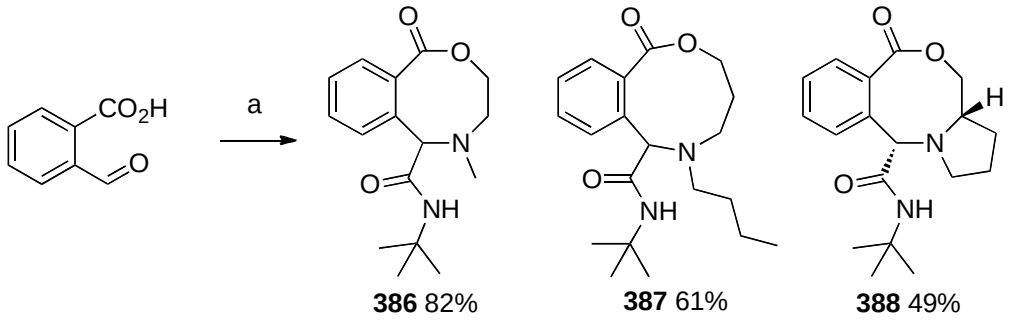
More recently, a co-worker in the Sheppard group has extended the scope of this methodology, optimising reaction conditions for a microwave-assisted four-component reaction between amino alcohols, aldehydes, isocyanides and thiols (scheme **4.15**).[317]



a) MeOH, 20-30 min, 60 °C, MW; >20 examples, up to 88%

Scheme 4.15

Reaction times are much shorter than previously reported, with improved yields and greater product diversity; this procedure was also applied to the synthesis of a number of medium ring heterocycles (scheme **4.16**).



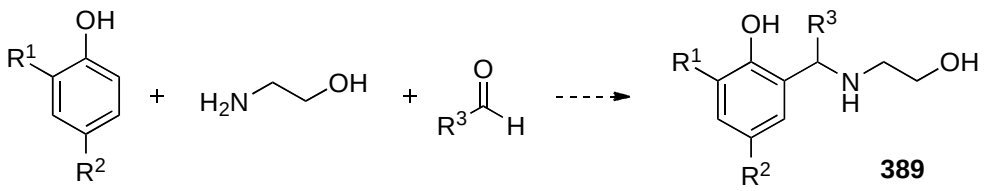
a) Aminoalcohol (1 eq), ^{t}BuNC (1 eq), MeOH, 20-30 min, 60 °C, MW

Scheme 4.16

4.2 Objectives and Synthetic Rationale

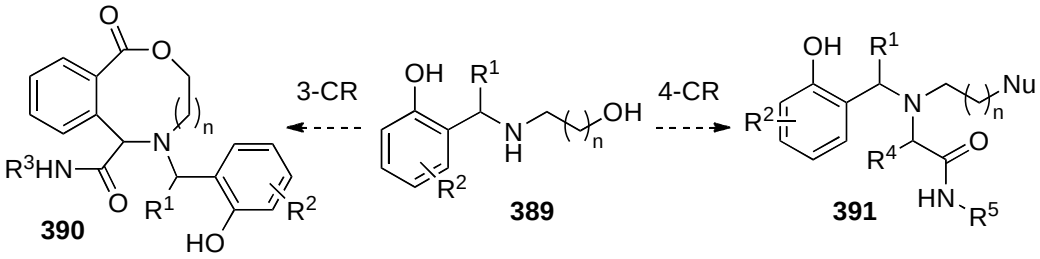
In an attempt to expand upon the methodologies being developed in the Sheppard group, the aim of this project was to synthesise a number of amino alcohols for use in new multi-component reactions.[318] In particular, the synthesis of new amino alcohols via a multi-component approach would lead to consecutive multi-component reactions, allowing the synthesis of highly functionalised products in just two steps from commercially available starting materials.

For this purpose two multi-component approaches to amino alcohols were envisaged. Firstly, a three-component reaction between an aldehyde, ethanolamine and a phenol would give rise to 2-hydroxybenzylamino alcohols **389** (scheme **4.17**).[319]



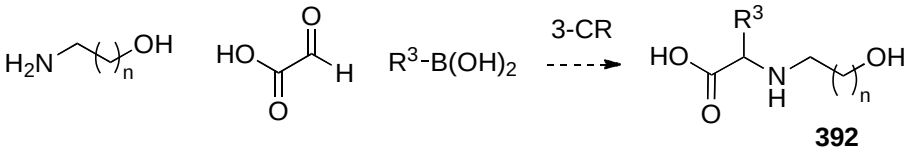
Scheme 4.17

These new amino alcohols could then be used sequentially in either a three or four-component reaction to give diversely substituted medium ring heterocycles **390**, or densely functionalised α-amino amides **391** (scheme **4.18**).



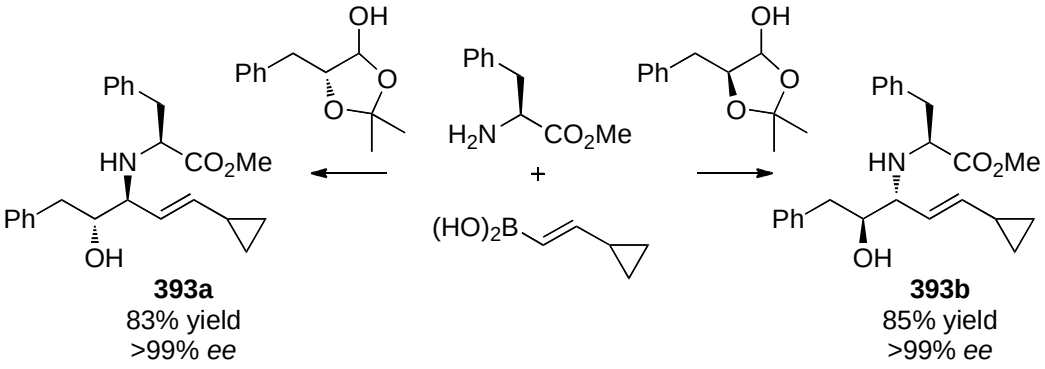
Scheme 4.18

Secondly, a three-component Petasis borono-Mannich reaction between ethanolamine, glyoxylic acid and a boronic acid would give α-substituted amino acid derivatives **392** (scheme **4.19**).[320-322]



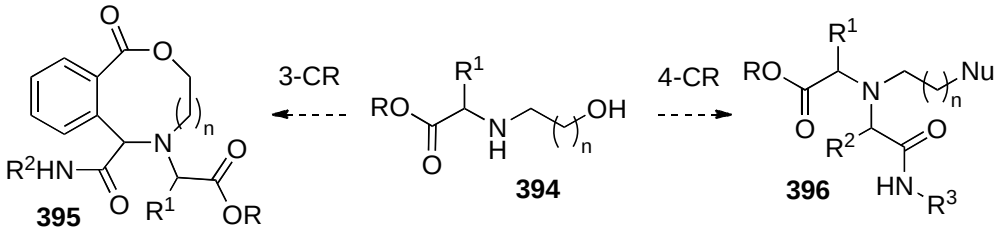
Scheme 4.19

This reaction has seen many advances in the years since its discovery, with many groups reporting advances in the scope and diversity of this synthetically useful reaction.[323] For example, Schreiber recently reported the synthesis of large and varied libraries of stereochemically diverse compounds for drug discovery assays, starting from just two diastereomers **393** derived from the same Petasis three-component reaction (scheme **4.20**).[324]



Scheme 4.20

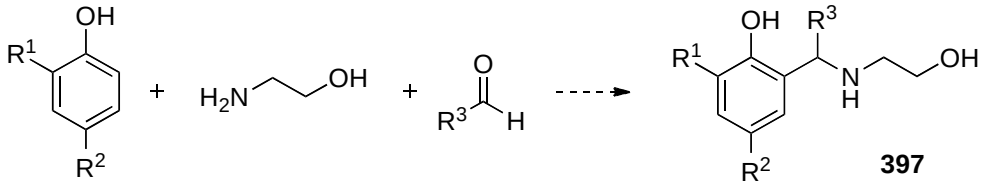
Ester-protection of these α-amino acids would give amino alcohols **394**, which could be subjected to further multi-component reaction conditions to give similarly densely functionalised products **395** and **396** (scheme **4.21**).[325]



Scheme 4.21

4.3 Results and Discussion

Attempts began with the three-component reaction between ethanolamine, aldehydes and phenols, the results of which are summarised below in table **4.1**.



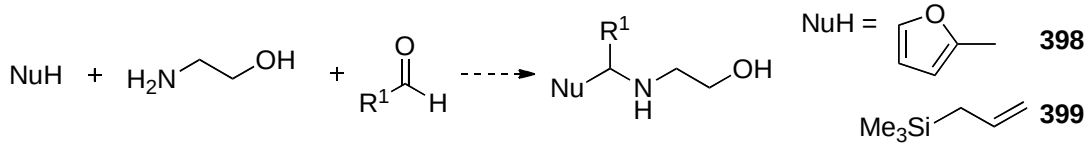
Entry	R^1	R^2	R^3	Additive	Solvent	Temp/ °C	t/h	Observation
1	H	NO_2	H	-	-	25	48	No reaction
2	H	NO_2	H	-	-	60	24	Insoluble resin
3	H	NO_2	H	-	EtOH	reflux	48	No reaction
4	Me	Cl	H	-	-	60	24	Insoluble resin
5	Me	Cl	H	-	EtOH	reflux/MW	48	No reaction
6	Me	Cl	H	cat. HCl	EtOH	reflux	48	No reaction
7	Me	Cl	^{n}Bu	-	-	60	24	Insoluble resin
8	Me	Cl	^{n}Bu	-	EtOH	reflux/MW	48	No reaction
9	Me	Cl	^{n}Bu	cat. HCl	EtOH	reflux	48	No reaction

Table 4.1

Frustratingly, all attempts to trap the imine formed upon adding ethanolamine to the aldehyde with phenols were unsuccessful. When performed neat, the reactions invariably resulted in complex mixtures of insoluble resinous substances (entries 2, 4 and 7), except when carried out at room temperature (entry 1). Heating the reaction mixtures at reflux and in the microwave in ethanol proved ineffective, as did the addition of catalytic amounts of HCl (entries 3, 5, 6, 8 and 9).

The addition of a primary amine to an aldehyde at room temperature to form an imine proceeds rapidly; many of the above examples being strongly exothermic, suggesting reaction was taking place. The trapping of the resultant imine by a phenol is presumably the rate-limiting step in this process, with the phenols used proving insufficiently nucleophilic to give the desired products.

2-Methylfuran **398** and allyltrimethylsilane **399** were also used in attempts to trap the imine, although all efforts were frustratingly ineffectual (table **4.2**).[326,327]

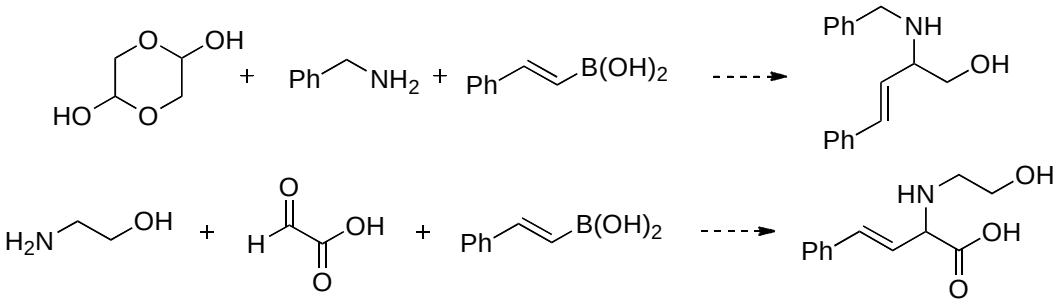


Entry	R^1	NuH	Solvent	Temp/ °C	t/h	Observation
1	H	**398**	-	25	48	No reaction
2	H	**398**	-	60	24	Insoluble resin
3	H	**399**	MeOH	reflux	48	No reaction
4	^{n}Bu	**398**	-	60	24	Insoluble resin
5	^{n}Bu	**398**	MeOH	reflux/MW	48	No reaction
6	^{n}Bu	**399**	-	60	48	No reaction
7	^{n}Bu	**399**	MeOH	reflux/MW	48	No reaction

Table 4.2

As was the case with the phenols, conducting the reactions neat at room temperature resulted in no product formation (entry 1). Heating the neat reaction mixtures with **398** gave insoluble, resinous materials, which were presumably the result of polymerisation (entries 2 and 4). Heating the reaction mixtures to reflux and in the microwave in methanol was similarly ineffectual (entries 3, 5 and 7).

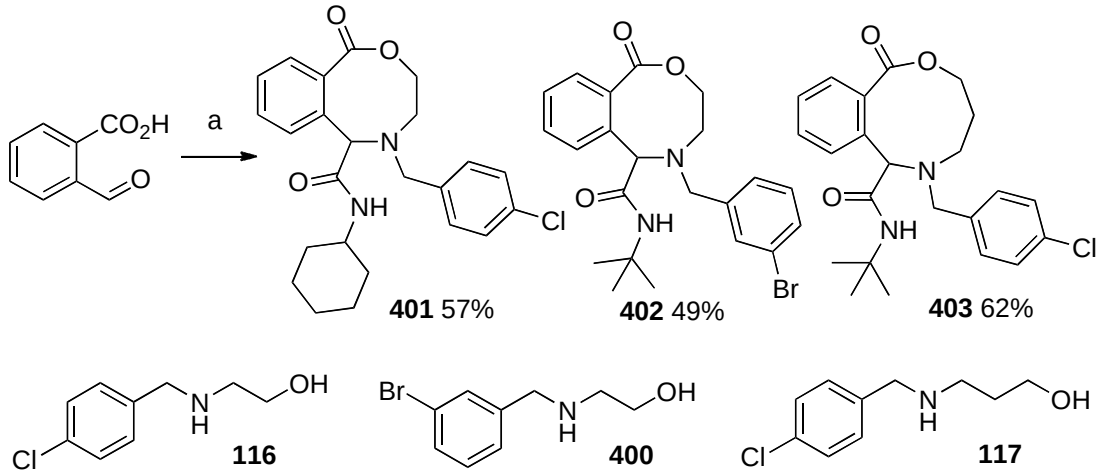
Attempts were then made to effect the Petasis three-component borono-Mannich reaction between an aldehyde, an amine and a boronic acid (scheme **4.22**).



Scheme 4.22

Little to no reaction was observed upon stirring the reaction mixtures at room temperature in ethanol, methanol, water or mixtures thereof. Heating the reaction mixtures only resulted in the formation of thick, brown insoluble resins and none of the desired products were observed in any of the reaction mixtures.

Finally, a number of three-component reactions were carried out using previously prepared amino alcohols **116** and **117**, as well as newly prepared **400** (scheme **4.23**). Pleasingly, the three-component condensations of each of these amino alcohols with 2-carboxybenzaldehyde and an isocyanide proceeded smoothly, giving medium ring heterocycles **401**, **402** and **403** respectively in good yield.



a) Amino alcohol (1 eq), RNC (1 eq), MeOH, 20 min, 60 ^{o}C, MW

Scheme 4.23

Eight-membered *N,O*-heterocycle **402** was sufficiently crystalline to allow its X-ray structure to be determined after slow recrystallisation from a diethyl ether-petrol mixture (figure **4.1**).

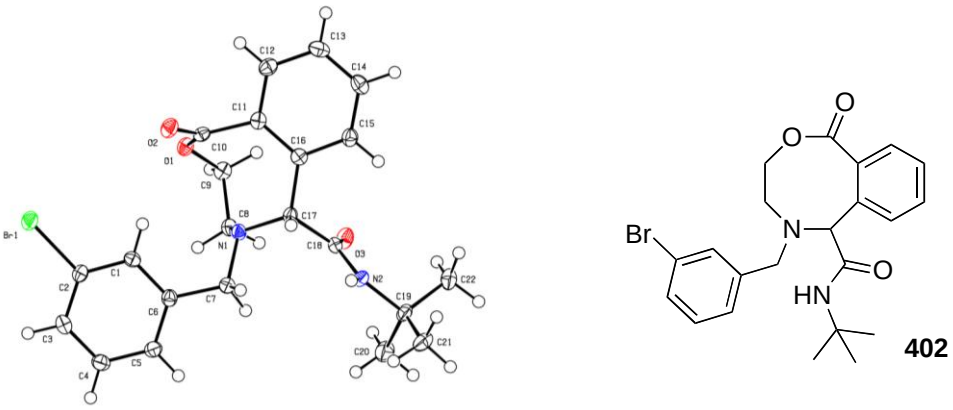
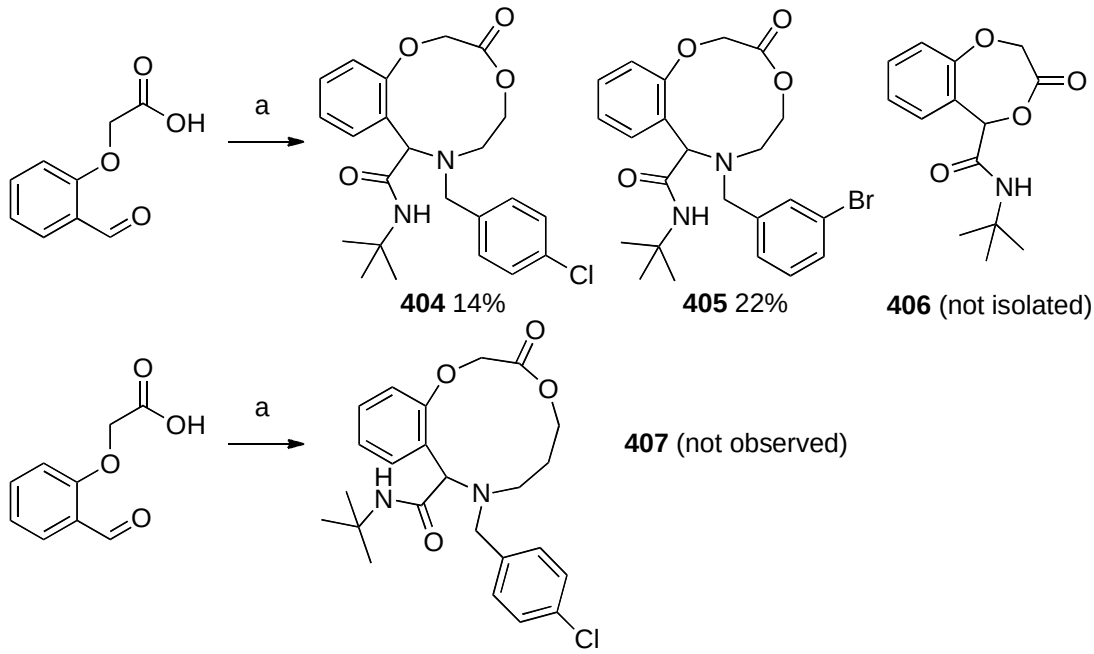


Figure 4.1

The same amino alcohols were also used in a three-component reaction with 2-formylphenoxyacetic acid, giving ten-membered heterocycles **404** and **405** (scheme **4.24**).

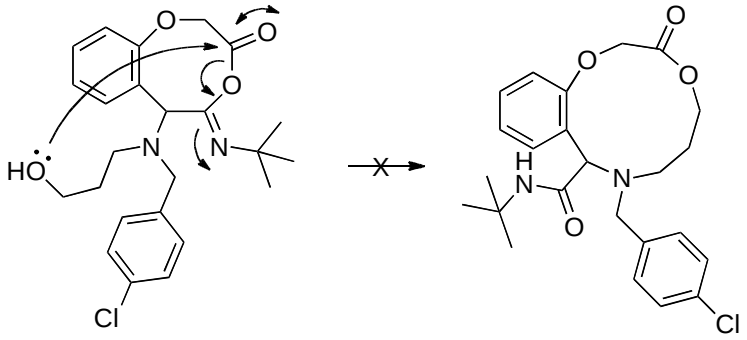


a) Amino alcohol (1 eq), ^{t}BuNC (1 eq), MeOH, 20 min, 60 ^{o}C, MW

Scheme 4.24

Although un-optimised, the yields of these ten-membered heterocycles are low, perhaps due to the inherent difficulties in the formation of rings of this size. In order to form the eleven-membered heterocycle, the reaction of **117** with 2-formylphenoxyacetic acid and ^{t}BuNC would have to proceed via a nine-membered ring-closing transition state such as the one depicted in scheme **4.25**. Substantial quantities of a second product were also observed by crude NMR, although this

compound could not be isolated in pure form. The seven-membered Passerini-type product **406** is the most likely structure of this side product based on its NMR spectra.



Scheme 4.25

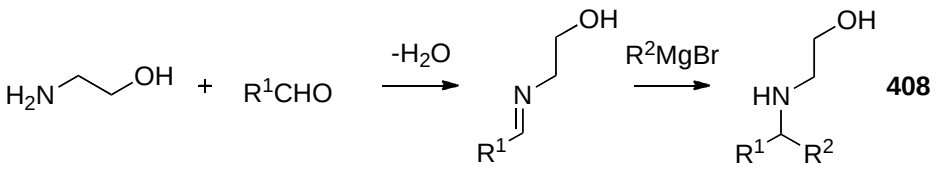
4.3 Conclusions and Future Work

Attempts towards the three-component synthesis of a range of amino alcohols were made, employing two different methods. Firstly, phenols were used as nucleophiles in an attempt to trap imines in a one-pot, three-component reaction. Secondly, the Petasis borono-Mannich three-component reaction was attempted for the one-pot synthesis of α-amino acid-derived amino alcohols. Unfortunately all attempts have thus far proved unsuccessful.

The three-component condensations of 2-carboxybenzaldehyde and 2-formylphenoxyacetic acid with amino alcohols and isocyanides was explored, resulting in the synthesis of a range of eight to ten-membered heterocycles. Attempts were made to expand the scope of this reaction to the synthesis of an eleven-membered heterocycle, although all efforts have so far been unproductive.

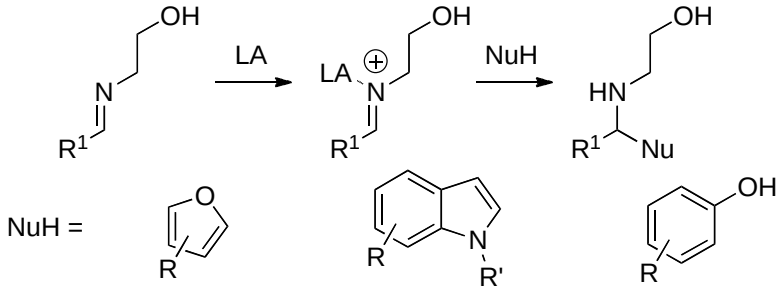
Future work on this project will focus on the optimisation of reaction conditions to improve the yields of ten and eleven-membered heterocycles, as well as the synthesis of a more diverse range of amino alcohols for use in new multi-component reactions.

Finally, a number of new methods for the one-pot, three-component synthesis of amino alcohols will be explored. For example, the use of Grignard reagents as nucleophiles for imines derived from the condensation of ethanolamine and an aldehyde should lead to the formation of amino alcohols **408** (scheme **4.26**).



Scheme 4.26

Another interesting avenue to explore would be the use of Lewis-acids as activating agents for the imine,[328,329] facilitating the addition of nucleophiles such as phenols, furans and possibly even nitrogen heterocycles such as indoles (scheme **4.27**).



Scheme 4.27

If successful, the resulting amino alcohol products will be employed in the newly developed three and four-component reactions to give densely functionalised α-amino acids and medium ring heterocycles.

5. Experimental Section

5.1 General Methods

All reactions were carried out at atmospheric pressure with stirring unless otherwise stated. All reagents and solvents were purchased from suppliers and used without further purification unless otherwise stated. Anhydrous THF was obtained from an Anhydrous Engineering (USA) solvent system after drying over alumina granules or pellets. NBS was recrystallised from water prior to use.

Reactions were monitored by TLC or ^{1}H NMR as stated. TLC plates pre-coated with silica gel 60 F_{254} on aluminium (Merck KGaA) were used, being visualised by UV (254 or 365 nm) or chemical stain ($KMnO_4$ or PMA). Normal phase silica gel (BDH) was used for flash column chromatography.

NMR spectra were recorded on Bruker Avance 400 and AMX600 instruments operating at 400 and 600 MHz for ^{1}H and at 100 and 150 MHz for ^{13}C measurements respectively. All spectra were recorded at 298 K unless otherwise stated. Chemical shifts were measured in ppm and are quoted as δ, relative to TMS. Multiplicities are quoted as s (singlet), d (doublet), t (triplet), q (quartet), quintet and m (multiplet) with coupling constants defined as *J* given in Hz. All peaks should be taken as sharp unless otherwise stated. NMR spectra of palladium complexes **304-322** were assigned with assistance from Dr. Abil Aliev (UCL Chemistry Department).

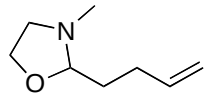
High and low resolution mass spectra were recorded by Dr. Lisa Haigh using a VG70 SE instrument operating in modes CI, EI, ES and FAB.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FTIR instrument operating in ATR mode. Melting points were determined using Gallenkamp apparatus and are uncorrected.

X-ray crystallographic structure analyses were carried out by Dr. Graham Tizzard at the EPSRC National Crystallography Service, Southampton.

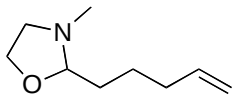
5.2 Experimental Procedures

2-(But-3-enyl)-*N*-methyl-1,3-oxazolidine (110)



A solution of 4-pentenal (764 μl, 7.74 mmol) and 2-(methylamino)ethanol (622 μl, 7.74 mmol) in ether (50 ml) and DCM (50 ml) was stirred at rt for 1 h. The solvent was removed *in vacuo*; EtOH (3 × 50 ml) was added, then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *oxazolidine* (1.04 g, 7.35 mmol, 95%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 2946, 1455, 1366, 1217, 1033, 910; δ_H (600 MHz, $CDCl_3$) 1.58 (1 H, dddd, *J* 13.6, 9.8, 6.9 and 5.6, OCHCH*H*), 1.72 (1 H, dddd, *J* 13.6, 9.8, 6.0 and 3.4, OCHCH*H*), 2.13-2.28 (2 H, m, CH_2=CHCH_2), 2.37 (3 H, s, Me), 2.60-2.64 (1 H, m, NCH*H*), 3.21 (1 H, ddd, *J* 9.9, 6.0 and 4.1, NCH*H*), 3.85-3.90 (3 H, m, OCH and OCH_2), 4.98 (1 H, app. dq, *J* 10.2 and 1.7, CH=CH*H*), 5.06 (1 H, app. dq, *J* 16.9 and 1.7, CH=CH*H*), 5.87 (1 H, ddt, *J* 16.9, 10.2 and 6.6, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 29.2, 32.5, 39.1, 54.7, 64.1, 96.8, 114.6, 138.4; *m/z* (CI) 142.1234 (M+H, $C_8H_{16}NO$ requires 142.1232), 112 (82%), 110 (54), 88 (100), 87 (68), 84 (28).

N-Methyl-2-(pent-4-enyl)-1,3-oxazolidine (115)



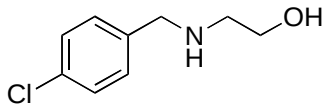
A solution of 5-hexenal (768 μl, 6.66 mmol) and 2-(methylamino)ethanol (535 μl, 6.66 mmol) in ether (50 ml) and DCM (50 ml) was stirred at rt for 1 h. The solvent was removed *in vacuo*; EtOH (3 × 50 ml) was added, then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *oxazolidine* (1.24 g, 6.39 mmol, 96%) as a yellow oil; ν_{max}(film)/cm^{-1} 2945, 1456, 1366, 1217, 1090, 1016, 908; δ_H (600 MHz, $CDCl_3$) 1.47-1.67 (4 H, m, OCHCH_2 and OCHCH_2CH_2), 2.11 (2 H, dtd, *J* 7.1, 6.7 and 1.2, CH_2=CHCH_2), 2.36 (3 H, s, Me), 2.59-2.64 (1 H, m, NCH*H*), 3.21 (1 H, ddd, *J* 9.9, 6.4 and 3.8, NCH*H*), 3.85-3.90 (3 H, m, OCH and OCH_2), 4.96 (1 H, ddt, *J* 10.2, 1.8 and 1.2, CH=CH*H*), 5.03 (1 H, app. dq, *J* 16.9 and

1.8, CH=CH*H*), 5.83 (1 H, ddt, *J* 16.9, 10.2 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 24.2, 32.7, 33.8, 39.0, 54.8, 64.1, 97.2, 114.6, 138.7; *m/z* (CI) 156.1387 (M^+, $C_9H_{18}NO$ requires 156.1388), 112 (46%), 104 (16), 86 (100), 84 (39).

General Procedure for Reductive Amination (Procedure A)

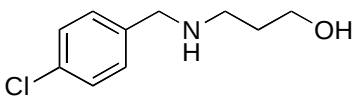
A mixture of aldehyde (12.50 mmol), primary amine (15.00 mmol) and sodium bicarbonate (1.60 g, 19 mmol) in MeOH (15 ml) was heated at reflux for 4 h. The solution was then cooled to 0 °C; sodium borohydride (567 mg, 15 mmol) was added portionwise and the mixture was allowed to warm to rt over 3 h. The solvent was removed *in vacuo* and water (30 ml) and DCM (30 ml) were added. The organic phase was washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the *secondary amine*.

2-(4-Chlorobenzylamino)ethanol[330] (116)



From procedure A: Quant. yield as a colourless oil; ν_{max}(film)/cm^{-1} 3301, 2842, 1491, 1458, 1088, 1050, 1015, 804; δ_H (600 MHz, $CDCl_3$) 2.06 (2 H, br s, NH and OH), 2.78 (2 H, t, *J* 5.2, C*H*$_2$CH$_2$OH), 3.65 (2 H, t, *J* 5.2, C*H*$_2$OH), 3.77 (2 H, s, C*H*$_2$Ar), 7.25 (2 H, d, *J* 8.3, Ar), 7.29 (2 H, d, *J* 8.3, Ar); δ_C (150 MHz, $CDCl_3$) 50.6, 52.9, 61.1, 128.7, 129.6, 132.9, 138.6; *m/z* (CI) 186.0684 (M+H, $C_9H_{13}NOCl$ requires 186.0686).

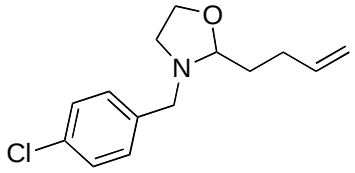
3-(4-Chlorobenzylamino)propanol[330] (117)



From procedure A: 93% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2931, 2845, 1490, 1366, 1088, 1014, 802; δ_H (600 MHz, $CDCl_3$) 1.74 (2 H, tt, *J* 6.1 and 5.2, HOCH$_2$C*H*$_2$), 2.89 (2 H, br s, NH and OH), 2.90 (2 H, t, *J* 6.1, HOCH$_2$CH$_2$C*H*$_2$), 3.78 (2 H, s, CC*H*$_2$NH), 3.82 (2 H, t, *J* 5.2, HOC*H*$_2$), 7.25 (2 H, d, *J* 8.4, Ar), 7.31 (2 H, d, *J* 8.4, Ar); δ_C (150 MHz, $CDCl_3$) 30.7, 49.4, 53.2, 64.3, 128.7, 129.5, 133.0,

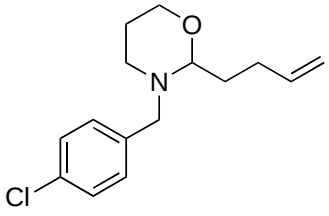
137.9; *m/z* (EI) 199.0759 (M^+, $C_{10}H_{14}NOCl$ requires 199.0758), 154 (40%), 140 (34), 125 (100), 89 (13).

2-(But-3-enyl)-*N*-(4-chlorobenzyl)-1,3-oxazolidine (118)



A solution of 4-pentenal (400 μl, 3.86 mmol) and 2-(4-chlorobenzyl)aminoethanol **116** (652 mg, 3.51 mmol) in ether (10 ml) and DCM (10 ml) was stirred at rt for 1 h. The solvent was removed *in vacuo*; EtOH (3 × 50 ml) was added, then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *oxazolidine* (969 mg, 3.85 mmol, quant.) as a pale yellow oil; ν_{max}(film)/cm^{-1} 2942, 1491, 1168, 1086, 1015, 910, 804; δ_H (600 MHz, $CDCl_3$) 1.61 (1 H, dddd, *J* 13.9, 12.2, 9.6 and 6.1, OCHCH*H*), 1.68 (1 H, dddd, *J* 13.9, 10.0, 6.1 and 4.1, OCHCH*H*), 2.11-2.23 (2 H, m, CH_2=CHCH_2), 2.60 (1 H, app. dt, *J* 10.3 and 7.2, OCH_2CH*H*), 3.07 (1 H, ddd, *J* 10.3, 6.7 and 5.2, OCH_2CH*H*), 3.43 (1 H, d, *J* 13.2, ArCH*H*), 3.80 (1 H, d, *J* 13.2, ArCH*H*), 3.82-3.87 (2 H, m, OCH_2), 4.22 (1 H, dd, *J* 6.1 and 4.1, OCH), 4.95 (1 H, app. dq, *J* 10.3 and 1.6, CH=CH*H*), 5.01 (1 H, app. dq, *J* 17.0 and 1.6, CH=CH*H*), 5.82 (1 H, ddt, *J* 17.0, 10.3 and 6.1, CH_2=C*H*), 7.29 (4 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 29.2, 33.2, 51.9, 56.9, 64.2, 95.9, 114.7, 128.6, 130.1, 132.9, 137.7, 138.5; *m/z* (CI) 252.1151 (M^+, $C_{14}H_{18}NOCl$ requires 252.1155), 198 (33%), 196 (100), 125 (12).

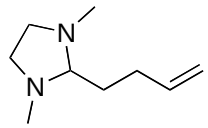
2-(But-3-enyl)-*N*-(4-chlorobenzyl)-1,3-oxazinane (119)



A solution of 4-pentenal (956 μl, 9.68 mmol) and 3-(4-chlorobenzyl)aminopropanol **117** (1.93 g, 9.68 mmol) in ether (100 ml) and DCM (100 ml) was stirred at rt for 16

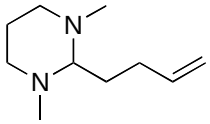
h. The solvent was removed *in vacuo*; EtOH (3 × 100 ml) was added, then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *oxazinane* (2.56 g, 9.58 mmol, 99%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 2947, 2846, 1490, 1365, 1230, 1156, 1089, 1014, 910, 830, 798; δ_H (600 MHz, $CDCl_3$) 1.16 (1 H, app. dquintet, *J* 13.6 and 2.5, $OCH_2CH\mathit{H}$), 1.67-1.78 (2 H, m, $OCHC\mathit{H}_2$), 1.98-2.21 (3 H, m, $OCH_2CH\mathit{H}$ and CH_2=$CHC\mathit{H}_2$), 2.78 (1 H, ddd, *J* 13.7, 12.3 and 3.2, NCH*H*), 2.89 (1 H, app. dquintet, *J* 13.7 and 2.0, NCH*H*), 3.72 (1 H, dt, *J* 11.3 and 3.0, OCH*H*), 3.78 (2 H, d, *J* 2.6, $NC\mathit{H}_2C$), 4.09 (1 H, ddd, *J* 11.3, 4.9 and 2.0, OCH*H*), 4.25 (1 H, dd, *J* 7.0 and 5.1, OCH), 4.95 (1 H, app. dq, *J* 10.2 and 1.7, CH=CH*H*), 5.01 (1 H, app. dq, *J* 17.1 and 1.7, CH=CH*H*), 5.81 (1 H, ddt, *J* 17.1, 10.2 and 6.7, CH_2=C*H*), 7.25-7.29 (4 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 20.7, 29.8, 32.5, 48.7, 49.2, 67.9, 92.2, 114.9, 128.6, 129.9, 132.5, 138.3, 138.5; *m/z* (FAB) 266.1306 (M^+, $C_{15}H_{21}NOCl$ requires 266.1312), 210 (76%), 200 (20), 176 (100).

2-(But-3-enyl)-*N*,*N'*-dimethyl-1,3-imidazolidine (120)



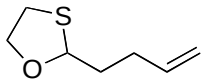
A solution of 4-pentenal (117 μl, 1.19 mmol) and *N,N'*-dimethylethane-1,2-diamine (127 μl, 1.19 mmol) in ether (5 ml) and DCM (5 ml) was stirred for 16 h at rt. The solution was concentrated *in vacuo*; EtOH (2 × 50 ml) was added and then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *imidazolidine* (160 mg, 1.04 mmol, 87%) as a colourless oil; ν_{max}(film)/cm^{-1} 2943, 2779, 1640, 1453, 1357, 1247, 906; δ_H (600 MHz, $CDCl_3$) 1.62-1.65 (2 H, m, $NCHC\mathit{H}_2$), 2.17-2.21 (2 H, m, CH_2=$CHC\mathit{H}_2$), 2.36 (6 H, s, 2 × Me), 2.48 (2 H, br ddd, *J* 9.7, 6.0 and 3.7, 2 × NCH*H*), 2.64 (1 H, t, *J* 4.3, NCH), 3.14 (2 H, br ddd, *J* 9.7, 6.0 and 3.7, 2 × NCH*H*), 4.95 (1 H, app. dq, *J* 10.3 and 1.6, CH=CH*H*), 5.04 (1 H, app. dq, *J* 17.0 and 1.6, CH=CH*H*), 5.87 (1 H, ddt, *J* 17.0, 10.3 and 6.6, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 28.4, 30.6, 40.9, 53.1, 88.0, 114.2, 139.1; *m/z* (CI) 155.1549 (M+H, $C_9H_{19}N_2$ requires 155.1548), 153 (32%), 125 (18), 99 (100), 98 (26).

2-(But-3-enyl)-*N,N'*-dimethylhexahydropyrimidine (121)



A solution of 4-pentenal (100 μl, 0.97 mmol) and *N,N'*-dimethylpropane-1,3-diamine (121 μl, 0.97 mmol) in ether (5 ml) and DCM (5 ml) was stirred for 16 h at rt. The solution was concentrated *in vacuo*; EtOH (2 × 50 ml) was added and then removed *in vacuo* repeatedly. The product was dried under high vacuum to give the *hexahydropyrimidine* (145 mg, 0.86 mmol, 89%) as a colourless oil; ν_{max}(film)/cm^{-1} 2940, 2778, 1447, 1372, 1218, 1044, 906; δ_H (600 MHz, $CDCl_3$) 1.35 (1 H, br dt, *J* 13.3 and 3.7, $NCH_2CH\mathit{H}$), 1.52-1.57 (2 H, m, $NCHC\mathit{H}_2$), 1.84-1.87 (1 H, m, $NCH_2CH\mathit{H}$), 1.99-2.04 (2 H, m, CH_2=$CHC\mathit{H}_2$), 2.20 (6 H, s, 2 × Me), 2.32 (2 H, br t, *J* 12.0, 2 × $NCH\mathit{H}$), 2.72 (1 H, t, *J* 6.1, NCH), 2.84 (2 H, app. dt, *J* 12.7 and 3.4, 2 × $NCH\mathit{H}$), 4.88 (1 H, app. dq, *J* 10.1 and 1.5, CH=$CH\mathit{H}$), 4.97 (1 H, app. dq, *J* 16.9 and 1.5, CH=$CH\mathit{H}$), 5.79 (1 H, ddt, *J* 16.9, 10.1 and 6.6, CH_2=$C\mathit{H}$); δ_C (150 MHz, $CDCl_3$) 21.9, 28.0, 29.1, 39.5, 54.4, 82.6, 114.2, 138.8; *m/z* (EI) 167.1540 (M-H, $C_{10}H_{19}N_2$ requires 167.1548) 127 (11), 114 (11), 113 (100).

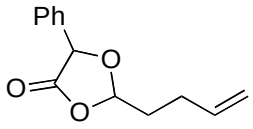
2-(But-3-enyl)-1,3-oxathiolane (122)



Boron trifluoride diethyl etherate (53 μl, 0.45 mmol) was added to a solution of 4-pentenal (31 μl, 0.30 mmol) and 2-mercaptoethanol (21 μl, 0.30 mmol) in DCM (1 ml). The mixture was stirred at rt for 16 h, then water (1 ml) was added and the layers separated. The aqueous phase was washed with DCM (1 ml) and the combined organics were washed with brine (2 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the product (30 mg, 0.31 mmol, 69%) as a colourless oil; ν_{max}(film)/cm^{-1} 2925, 1455, 1217, 990, 911; δ_H (600 MHz, $CDCl_3$) 2.00 (1 H, dtd, *J* 13.5, 6.3 and 6.1, $OCHCH\mathit{H}$), 1.84 (1 H, dtd, *J* 13.5, 7.5 and 6.1, $OCHCH\mathit{H}$), 2.14-2.24 (2 H, m, CH_2=$CHC\mathit{H}_2$), 3.00-3.02 (2 H, m, SCH_2), 3.77 (1 H, ddd, *J* 9.1, 8.1 and 6.5, $OCH\mathit{H}$), 4.32 (1 H, ddd, *J* 9.1, 5.3 and 3.8, $OCH\mathit{H}$), 4.97 (1 H, app. dq, *J* 10.2 and 1.7,

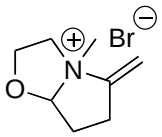
CH=CH*H*), 5.04 (1 H, app. dq, *J* 17.1 and 1.7, CH=CH*H*), 5.07 (1 H, t, *J* 6.1, OCH), 5.81 (1 H, ddt, *J* 17.1, 10.2 and 6.5, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 30.5, 32.7, 35.6, 71.2, 86.3, 115.2, 137.4; *m/z* (CI) 144.0599 (M^+, $C_7H_{12}SO$ requires 144.0609), 77 (100%).

2-(But-3-enyl)-5-phenyl-1,3-dioxolan-4-one (125)



A mixture of 4-pentenal (207 μl, 2.00 mmol), mandelic acid (200 mg, 1.30 mmol) and copper sulfate (200 mg, 1.30 mmol) was heated to 100 °C for 10 min under microwave irradiation. The mixture was cooled to rt, diluted with EtOAc (15 ml) and filtered through a plug of celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (EtOAc-petrol 1:9) to give the product as a colourless oil (230 mg, 1.62 mmol, 81%); ν_{max}(film)/cm^{-1} 2971, 1792, 1738, 1365, 1206, 1187, 916; δ_H (600 MHz, $CDCl_3$) 2.08 (2 H, m, OCHCH_2), 2.35 (2 H, m, CH_2=CHCH_2), 5.07 (1 H, app. dq, *J* 10.3 and 1.6, CH=CH*H*), 5.13 (1 H, app. dq, *J* 17.1 and 1.6, CH=CH*H*), 5.26 (1 H, s, COC*H*Ph), 5.75 (1 H, t, *J* 4.9, OCH), 5.89 (1 H, ddt, *J* 17.1, 10.3 and 6.6, CH_2C*H*), 7.40-7.48 (5 H, m Ar); δ_C (150 MHz, $CDCl_3$) 27.1, 33.3, 76.8, 103.9, 116.0, 126.9, 128.8, 129.3, 133.5, 136.5, 171.6; *m/z* (FAB) 241.0840 ($[MNa]^+$, $C_{13}H_{14}O_3Na$ requires 241.0841), 221 (24%), 207 (18), 195 (19), 167 (26), 157 (100).

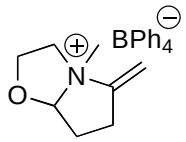
***N*-Methyl-5-methylenehexahydro-2*H*-pyrrolo[2,1-*b*]oxazol-4-ium bromide (126)**



NBS (64 mg, 0.36 mmol) was added to a stirred solution of *N*-methyl-2-(but-3-enyl)oxazolidine **110** (51 mg, 0.36 mmol) in DCM (1 ml). The mixture was stirred at rt for 90 min, then filtered through a plug of sand and the solvent was removed *in vacuo* to give the *enaminium salt* (79 mg, 0.36 mmol, 100%) as an amorphous yellow solid; ν_{max}(film)/cm^{-1} 3054, 1581, 1479, 1427, 1098, 745, 733, 705; δ_H (600

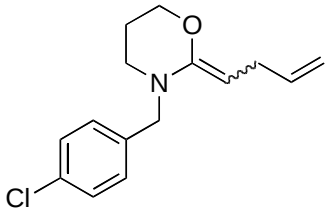
MHz, $CDCl_3$) 2.23 (1 H, app. ddd, *J* 10.7, 7.9 and 2.9, OCHCH*H*), 2.41 (1 H, dddd, *J* 13.5, 10.7, 9.1 and 4.4, OCHCH*H*), 2.88-2.92 (2 H, m, NC(=CH_2)CH_2)), 3.65 (3 H, s, Me), 4.09 (1 H, app. dt, *J* 11.8 and 7.6, NCH*H*), 4.29 (1 H, ddd, *J* 11.8, 7.4 and 4.3, OCH*H*), 4.48-4.52 (1 H, m, OCH*H*), 4.59 (1 H, ddd, *J* 11.8, 7.4 and 4.5, NCH*H*), 5.41 (1 H, br s, C=CH*H*), 5.80 (1 H, br d, *J* 4.4, OCH), 6.03 (1 H, br s, C=CH*H*); δ_C (150 MHz, $CDCl_3$) 25.3, 27.4, 50.9, 64.9, 67.1, 108.0, 109.4, 154.9.

_N_-Methyl-5-methylenehexahydro-2*H*-pyrrolo[2,1-*b*]oxazol-4-ium tetraphenylborate (127)



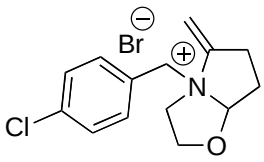
Sodium tetraphenylborate (1.49 g, 4.36 mmol) in MeOH (10 ml) was added to a solution of *N*-methyl-5-methylenehexahydro-2*H*-pyrrolo[2,1-*b*]oxazol-4-ium bromide **126** (960 mg, 4.36 mmol) in DCM (10 ml). The precipitate was filtered and washed with MeOH (2 × 10 ml). Recrystallisation from DMSO-water gave the *tetraphenylborate salt* (2.00 g, 4.36 mmol, 100%) as an off-white solid, decomp. > 210 °C; ν_{max}(film)/cm^{-1} 3054, 1581, 1479, 1427, 1098, 745, 733, 705; δ_H (600 MHz, DMSO-d_6) 2.15-2.19 (1 H, m, OCHCH*H*), 2.33 (1 H, dddd, *J* 14.2, 10.2, 9.2 and 4.4, OCHCH*H*), 2.83-2.87 (2 H, m, NC(=CH_2)CH_2)), 3.36 (3 H, s, Me), 3.96 (1 H, app. dt, *J* 11.4 and 7.5, NCH*H*), 4.06 (1 H, ddd, *J* 11.5, 6.9 and 4.4, OCH*H*), 4.19-4.23 (1 H, m, OCH*H*), 4.31 (1 H, ddd, *J* 11.4, 7.1 and 4.4, NCH*H*), 5.44 (1 H, d, *J* 4.5, OCH), 5.53 (1 H, br s, C=CH*H*), 6.85 (1 H, br s, C=CH*H*), 6.79 (4 H, t, *J* 7.2, Ar), 6.93 (8 H, t, *J* 7.5, Ar), 7.16-7.19 (8 H, m, Ar); δ_C (150 MHz, DMSO-d_6) 25.3, 27.5, 49.9, 64.8, 67.1, 108.3, 108.4, 121.2, 125.8, 136.0, 155.4, 163.8 (q, *J* 49.0).

2-(But-3-enylidene)-*N*-(*p*-chlorobenzyl)-1,3-oxazinane (135a and 135b)



NBS (15 mg, 0.083 mmol) was added to a solution of 2-(but-3-enyl)-*N*-(4-chlorobenzyl)-1,3-oxazinane **119** (22 mg, 0.083 mmol) in DCM (0.75 ml) and the mixture was stirred at rt for 24 h. The mixture was filtered through a plug of celite and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc-petrol 1:4) to give the *diene* (11 mg, 0.042 mmol, 50%) as a pale yellow oil (**135a**:**135b** 1:1.2); ν_{max}(film)/cm^{-1} 1648, 1492, 1407, 1245, 1091, 1015, 925, 803; δ_H (600 MHz, $CDCl_3$) **135a**: 2.02-2.23 (2 H, m, OCH_2CH_2), 2.69 (1 H, ddd, *J* 14.6, 7.0 and 6.5, CH_2=CHCH*H*), 2.96 (1 H, ddd, *J* 14.6, 8.1 and 7.0, CH_2=CHCH*H*), 3.19 (1 H, ddd, *J* 13.7, 7.4 and 6.1, OCH*H*), 3.36-3.38 (2 H, m, NCH_2CH_2), 3.81 (1 H, ddd, *J* 13.7, 8.1 and 5.8, OCH*H*), 4.21 (1 H, dd, *J* 8.1 and 6.5, NC=CH), 4.28 (1 H, d, *J* 15.1, NCH*H*Ar), 4.90 (1 H, d, *J* 15.1, NCH*H*Ar), 5.10 (1 H, dd, *J* 10.1 and 1.4, CH=CH*H*), 5.11 (1 H, dd, *H* 17.3 and 1.4, CH=CH*H*), 5.66 (1 H, app. dtt, *J* 17.3, 10.1 and 7.0, CH_2=C*H*), 7.11 (2 H, d, *J* 8.6, Ar), 7.35 (2 H, d, *J* 8.6, Ar); **135b**: 2.02-2.23 (2 H, m, OCH_2CH_2), 2.97 (1 H, ddd, *J* 14.4, 7.1 and 6.9, CH_2=CHCH*H*), 3.03 (1 H, ddd, *J* 14.4, 8.0 and 7.1, CH_2=CHCH*H*), 3.27 (1 H, ddd, *J* 15.3, 9.1 and 5.1, OCH*H*), 3.41-3.44 (2 H, m, NCH_2CH_2), 3.64 (1 H, ddd, *J* 15.3, 9.0 and 6.3, OCH*H*), 4.47 (1 H, d, *J* 17.3, NCH*H*Ar), 4.52 (1 H, dd, *J* 8.0 and 6.7, NC=CH), 4.77 (1 H, d, *J* 17.3, NCH*H*Ar), 5.17 (1 H, dd, *J* 10.2 and 1.5, CH=CH*H*), 5.22 (1 H, dd, *H* 17.2 and 1.5, CH=CH*H*), 5.78 (1 H, app. dtt, *J* 17.2, 10.2 and 7.1, CH_2=C*H*), 7.19 (2 H, d, *J* 8.5, Ar), 7.30 (2 H, d, *J* 8.5, Ar); δ_C (150 MHz, $CDCl_3$) **135a**: 30.0, 31.6, 38.9, 42.2, 46.0, 48.6, 119.4, 127.8, 129.4, 133.7, 134.0, 135.5, 169.0; **135b**: 30.3, 30.8, 39.2, 42.0, 45.6, 51.5, 119.5, 129.1, 129.4, 133.6, 133.8, 134.8, 169.2; *m/z* (ES) 262.1005 (M-H, $C_{15}H_{17}ClNO$ requires 262.0999), 168 (30%), 166 (100), 125 (70).

_N_-(4-Chlorobenzyl)-5-methylenehexahydro-2_H_-pyrrolo[2,1-_b_]oxazol-4-ium bromide (137)

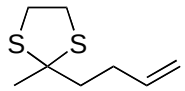


NBS (30 mg, 0.17 mmol) was added to a stirred solution of 2-(but-3-enyl)-*N*-(4-chlorobenzyl)oxazolidine **118** (42 mg, 0.17 mmol) in DCM (1 ml). The mixture was stirred at rt for 45 min, then filtered through a plug of sand and the solvent was removed *in vacuo* to give the *enaminium salt* (56 mg, 0.17 mmol, quant.) as an amorphous yellow solid; ν_{max}(film)/cm^{-1} 3210, 1698, 1492, 1347, 1293, 1175, 1090, 815, 715; δ_H (600 MHz, $CDCl_3$) 1.71 (1 H, app. ddd, *J* 14.4, 9.9 and 4.4, OCHCH*H*), 2.04 (1 H, app. ddd, *J* 14.4, 9.1 and 2.2, OCHCH*H*), 2.63-2.68 (1 H, m, CH_2=CCH*H*), 2.83 (1 H, ddtd, *J* 17.5, 8.1, 2.2 and 1.5, CH_2=CCH*H*), 3.92 (1 H, ddd, *J* 11.9, 7.6 and 7.4, OCH_2CH*H*), 4.20 (1 H, ddd, *J* 9.0, 7.4 and 5.0, OCH*H*), 4.66 (1 H, app. dt, *J* 9.0 and 7.6, OCH*H*), 4.90 (1 H, ddd, *J* 11.9, 7.8 and 5.0, OCH_2CH*H*), 5.47-5.56 (3 H, m, ArCH_2 and C=CH*H*), 5.81 (1 H, m, C=CH*H*), 6.06 (1 H, br d, *J* 4.4, OCH), 7.25 (2 H, d, *J* 8.5, Ar), 7.62 (2 H, d, *J* 8.5, Ar); δ_C (150 MHz, $CDCl_3$) 25.4, 27.9, 63.4, 64.3, 66.8, 106.6, 111.6, 126.8, 129.4, 134.4, 137.2, 152.4; *m/z* 250.0993 (M-Br, $C_{14}H_{17}NOCl$ requires 250.0999).

General Procedure for Dithiane Formation (Procedure B)

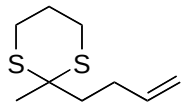
A stirred solution of 1,3-propanedithiol (1.30 ml, 15.00 mmol) and aldehyde or ketone (15.00 mmol) in DCM (30 ml) was cooled to −78 °C under an argon atmosphere. Boron trifluoride diethyl etherate (2.66 ml, 22.50 mmol) was added dropwise and the mixture was allowed to warm slowly to rt overnight. Triethylamine (1.20 ml, 8.00 mmol) was added, followed by water (30 ml) and the aqueous layer was extracted with DCM (30 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 3:10).

2-But-3-enyl-2-methyl-1,3-dithiolane[331] (123)



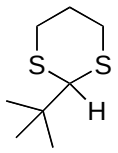
From procedure B (ethane-1,2-dithiol used in place of propane-1-3-dithiol): 60% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2901, 1423, 1274, 1217, 906; δ_H (600 MHz, $CDCl_3$) 1.78 (3 H, s, Me), 2.01-2.04 (2 H, m, MeCC*H*$_2$), 2.28-2.33 (2 H, m, CH_2=CHC*H*$_2$), 3.35 (4 H, m, 2 × SCH_2), 4.98 (1 H, dq, *J* 10.3 and 1.3, CH=CH*H*), 5.07 (1 H, dq, *J* 17.0 and 1.7, CH=CH*H*), 5.85 (1 H, ddt, *J* 17.0, 10.3 and 6.6, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 31.6, 32.4, 40.4, 44.9, 66.5, 114.8, 138.0; *m/z* (CI) 175 (M^+, 8%), 120 (100), 88 (59), 86 (98), 71 (55), 51 (97).

2-But-3-enyl-2-methyl-1,3-dithiane[332] (124)



From procedure B: 76% yield as a pale yellow oil; ν_{max}(film)/cm^{-1} 2899, 1423, 1277, 990, 908; δ_H (600 MHz, $CDCl_3$) 1.60 (3 H, s, Me), 1.88-2.01 (4 H, m, SCH_2CH_2 and MeCC*H*$_2$), 2.26 (2 H, dtt, *J* 7.6, 6.5 and 1.3, CH_2=CHC*H*$_2$), 2.81 (2 H, ddd, *J* 14.4, 6.9 and 3.6, 2 × SCH*H*), 2.86 (2 H, ddd, *J* 14.4, 8.2 and 3.6, 2 × SCH*H*), 4.97 (1 H, ddt, *J* 10.3, 1.8 and 1.3, CH=CH*H*), 5.05 (1 H, dq, *J* 17.1 and 1.8, CH=CH*H*), 5.83 (1 H, ddt, *J* 17.1, 10.3 and 6.5, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 25.3, 26.5, 27.8, 29.0, 40.5, 48.9, 114.9, 138.0; *m/z* (EI) 188 (M^+, 30%), 133 (100), 113 (60), 99 (65), 81 (88), 73 (53).

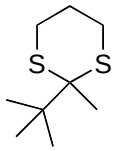
2-*tert*-Butyl-1,3-dithiane[176] (256)



From procedure B: 78% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2958, 2903, 1422, 1364, 1246, 904, 778; δ_H (600 MHz, $CDCl_3$) 1.07 (9 H, s, 3 × Me), 1.72-1.79 (1 H, m, SCH_2CH*H*), 2.03 (1 H, app. dquintet, *J* 14.0 and 3.4, SCH_2CH*H*), 2.84-2.86 (4 H,

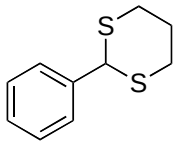
m, 2 × SCH_2), 3.95 (1 H, s, SCH); δ_C (150 MHz, $CDCl_3$) 26.0, 27.9, 31.3, 35.7, 62.0; *m/z* (CI) 177.0741 (M+H, $C_8H_{17}S_2$ requires 177.0772), 163 (17%), 119 (88), 107 (80), 71 (100).

2-*tert*-Butyl-2-methyl-1,3-dithiane[176] (257)



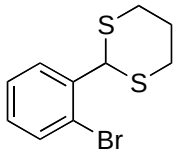
From procedure B: 77% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2971, 1422, 1372, 1217, 1097, 1067, 910; δ_H (600 MHz, $CDCl_3$) 1.17 (9 H, s, 3 × CMe), 1.72-1.79 (1 H, m, SCH_2CH*H*), 1.82 (3 H, s, SCMe), 2.06 (1 H, dtt, *J* 13.7, 4.1 and 3.2, SCH_2CH*H*), 2.71 (2 H, app. dt, *J* 14.8 and 4.1, 2 × SCH*H*), 3.03 (2 H, ddd, *J* 14.8, 12.2 and 3.2, 2 × SCH*H*); δ_C (150 MHz, $CDCl_3$) 23.4, 25.4, 25.8, 26.5, 39.4, 59.5; *m/z* (CI) 191.0930 (M+H, $C_9H_{19}S_2$ requires 191.0928), 133 (100%), 107 (32), 106 (59), 85 (38).

2-Phenyl-1,3-dithiane[333] (260)



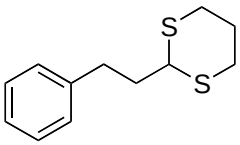
From procedure B: 87% yield as a white solid, m.p. 70-72 °C (lit. 71-72 °C); ν_{max}(film)/cm^{-1} 2891, 1451, 1411, 1275, 1171, 882, 723, 695; δ_H (600 MHz, $CDCl_3$) 1.95 (1 H, dtt, *J* 14.2, 12.4 and 3.1, SCH_2CH*H*), 2.19 (1 H, dtt, *J* 14.2, 4.4 and 2.5, SCH_2CH*H*), 2.93 (2 H, ddd, *J* 14.7, 4.4 and 3.1, 2 × SCH*H*), 3.08 (2 H, ddd, *J* 14.7, 12.4 and 2.5, 2 × SCH*H*), 5.19 (1 H, s, SCH), 7.32 (1 H, br tt, *J* 7.3 and 1.3, Ar), 7.34-7.37 (2 H, m, Ar), 7.48-7.50 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 25.1, 32.1, 51.5, 127.8, 128.5, 128.8, 139.1; *m/z* (EI) 196.0376 (M^+, $C_{10}H_{12}S_2$ requires 196.0375), 153 (19%), 131 (24), 121 (76), 91 (22).

2-(2-Bromophenyl)-1,3-dithiane[334] (261)



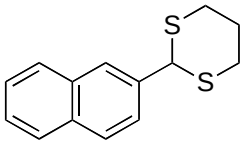
From procedure B: 89% yield as a white powder, m.p. 78-80 °C; ν_{max}(film)/cm^{-1} 2897, 1467, 1421, 1275, 1021, 746; δ_H (600 MHz, $CDCl_3$) 1.94 (1 H, dtt, *J* 14.2, 12.6 and 3.0, $SCH_2CH\mathit{H}$), 2.19 (1 H, dtt, *J* 14.2, 4.3 and 2.4, $SCH_2CH\mathit{H}$), 2.93 (2 H, ddd, *J* 14.5, 4.3 and 3.0, 2 × $SCH\mathit{H}$), 3.13 (2 H, ddd, *J* 14.5, 12.6 and 2.4, 2 × $SCH\mathit{H}$), 5.63 (1 H, s, SCH), 7.15 (1 H, ddd, *J* 8.2, 7.4 and 1.5, Ar), 7.32 (1 H, dd, *J* 7.8 and 7.4, Ar), 7.54 (1 H, d, *J* 8.2, Ar), 7.67 (1 H, dd, *J* 7.8 and 1.5, Ar); δ_C (150 MHz, $CDCl_3$) 25.2, 32.4, 50.8, 123.1, 128.3, 2 × 129.9, 133.1, 138.3; *m/z* (CI) 274.9559 (M+H, $C_{10}H_{12}S_2Br$ requires 274.9564), 215 (16%), 86 (14), 84 (23).

2-(2-Phenylethyl)-1,3-dithiane[335] (262)



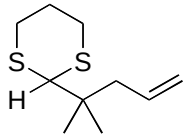
From procedure B: 63% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2898, 1453, 1421, 1274, 1217, 1204, 906, 749, 698; δ_H (600 MHz, $CDCl_3$) 1.90 (1 H, ddd, *J* 14.6, 9.5 and 5.4, $SCH_2CH\mathit{H}$), 2.09 (2 H, dt, *J* 13.4 and 7.0, $PhCH_2C\mathit{H}_2$), 2.12-2.16 (1 H, m, $SCH_2CH\mathit{H}$), 2.84-2.88 (6 H, m, 2 × SCH_2 and $PhC\mathit{H}_2$), 4.01 (1 H, t, *J* 7.0, SCH), 7.21-7.24 (3 H, m, Ar), 7.30-7.33 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 26.0, 30.3, 32.5, 36.9, 46.6, 126.1, 128.46, 128.54, 140.9; *m/z* (EI) 224.0690 (M^+, $C_{12}H_{24}S_2$ requires 224.0688), 133 (29%), 119 (90), 106 (27), 91 (50).

2-Naphthalen-2-yl-1,3-dithiane[336] (263)



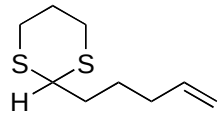
From procedure B: 92% yield as an off-white powder, m.p. 114-116 °C (lit. 115 °C); ν_{max}(film)/cm^{-1} 2897, 1599, 1508, 1421, 1275, 815, 776, 763; δ_H (600 MHz, $CDCl_3$) 1.98 (1 H, dtt, *J* 14.3, 12.5 and 3.0, $SCH_2CH\mathit{H}$), 2.21 (1 H, dtt, *J* 14.3, 4.3 and 2.4, $SCH_2CH\mathit{H}$), 2.96 (2 H, ddd, *J* 14.5, 4.3 and 3.0, 2 × $SCH\mathit{H}$), 3.11 (2 H, ddd, *J* 14.5, 12.5 and 2.4, 2 × $SCH\mathit{H}$), 5.34 (1 H, s, SCH), 7.45-7.49 (2 H, m, Ar), 7.58 (1 H, dd, *J* 8.5 and 1.8, Ar), 7.80-7.84 (3 H, m, Ar), 7.96 (1 H, s, Ar); δ_C (150 MHz, $CDCl_3$) 25.3, 32.3, 51.7, 125.8, 126.41, 126.43, 127.0, 127.8, 128.2, 128.6, 133.36, 133.42, 136.6; *m/z* (EI) 246.0529 (M^+, $C_{14}H_{14}S_2$ requires 246.0531), 181 (15%), 172 (100), 167 (13), 128 (21).

2-(1,1-Dimethylbut-3-enyl)-1,3-dithiane (264)



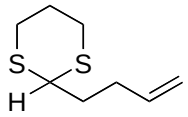
From procedure B: 62% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2970, 1367, 1217; δ_H (600 MHz, $CDCl_3$) 1.09 (6 H, s, 2 × Me), 1.82 (1 H, dtt, *J* 14.0, 8.4 and 6.9, $SCH_2CH\mathit{H}$), 2.09 (1 H, dtt, *J* 14.0, 3.7 and 3.0, $SCH_2CH\mathit{H}$), 2.24 (2 H, app. dt, *J* 7.4 and 1.0, CCH_2), 2.89-2.91 (4 H, m, 2 × SCH_2), 4.01 (1 H, s, CCH), 5.11 (1 H, ddt, *J* 10.4, 2.4 and 0.9, CH=$CH\mathit{H}$), 5.12 (1 H, ddt, *J* 16.8, 2.4 and 1.2, CH=$CH\mathit{H}$), 5.84 (1 H, ddt, *J* 16.8, 10.4 and 7.4, CH_2=$C\mathit{H}$); δ_C (150 MHz, $CDCl_3$) 25.2, 26.2, 31.4, 38.5, 44.5, 60.5, 118.2, 134.3 ; *m/z* (EI) 202.0840 (M^+, $C_{10}H_{18}S_2$ requires 202.0844), 161 (10%), 119 (100).

2-Pent-4-enyl-1,3-dithiane[337] (265)



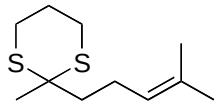
From procedure B: 51% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2933, 2899, 1422, 1275, 991, 907; δ_H (600 MHz, $CDCl_3$) 1.58-1.63 (2 H, m, $SCHCH_2CH_2$), 1.75 (2 H, app. td, *J* 7.1 and 6.7, $SCHCH_2$), 1.85 (1 H, dtt, *J* 14.0, 11.6 and 3.3, SCH_2CHH), 2.07 (2 H, td, *J* 7.2 and 7.0, CH_2=$CHCH_2$), 2.11 (1 H, dtt, *J* 14.0, 4.6 and 2.8, SCH_2CHH), 2.79-2.90 (4 H, m, 2 × SCH_2), 4.04 (1 H, t, *J* 7.0, SCH), 4.96 (1 H, app. dq, *J* 10.3 and 1.9, CH=CH*H*), 5.01 (1 H, app. dq, *J* 17.0 and 1.9, CH=CH*H*), 5.78 (1 H, ddt, *J* 17.0, 10.3 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 25.9, 26.1, 30.6, 33.4, 35.0, 47.6, 115.1, 138.2; *m/z* (CI) 189.0775 (M+H, $C_9H_{17}S_2$ requires 189.0772), 107 (59%), 81 (22).

2-But-3-enyl-1,3-dithiane[338] (266)



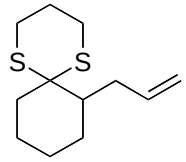
From procedure B: 59% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2898, 1422, 1278, 991; δ_H (600 MHz, $CDCl_3$) 1.81-1.85 (2 H, m, $SCHCH_2$), 1.86 (1 H, dtt, *J* 14.2, 11.3 and 3.6, SCH_2CHH), 2.11 (1 H, dtt, 14.3, 4.5 and 2.7, SCH_2CHH), 2.26 (2 H, tdt, *J* 7.5, 6.6 and 1.3, CH_2=$CHCH_2$), 2.82 (2 H, ddd, *J* 14.4, 4.5 and 3.6, 2 × $SCHH$), 2.86 (2 H, ddd, *J* 14.4, 11.3 and 2.7, 2 × $SCHH$), 4.03 (1 H, t, *J* 7.0, SCH), 5.00 (1 H, ddt, *J* 10.3, 1.8 and 1.3, CH=CH*H*), 5.06 (1 H, dq, *J* 17.1 and 1.8, CH=CH*H*), 5.78 (1 H, ddt, *J* 17.1, 10.3 and 6.6, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 26.0, 30.3, 30.5, 34.5, 46.7, 115.6, 137.1; *m/z* (CI) 175 (M^+, 63%), 119 (100), 107 (80).

2-Methyl-2-(4-methylpent-3-enyl)-1,3-dithiane[332] (267)



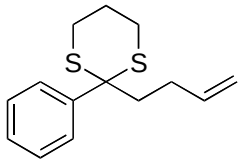
From procedure B: 21% yield as a colourless oil; ν_{max}(film)/cm^{-1} 2970, 2926, 1447, 1371, 1317, 1071, 909; δ_H (600 MHz, $CDCl_3$) 1.61 (3 H, s, SCMe), 1.62 (3 H, br s, CH=C*Me*), 1.68 (3 H, br d, *J* 1.5, CH=C*Me*), 1.90-1.99 (4 H, m, SCH_2CH_2 and $SCCH_2$), 2.14 (2 H, dt, *J* 8.8 and 7.1, CH_2=CHCH_2), 2.81 (2 H, ddd, *J* 14.5, 7.0 and 3.8, 2 × SC*H*H), 2.86 (2 H, ddd, *J* 14.5, 8.0 and 3.8, 2 × SC*H*H), 5.12 (1 H, tt, *J* 7.1 and 1.5, C=C*H*); δ_C (150 MHz, $CDCl_3$) 17.7, 23.5, 25.3, 25.7, 26.5, 27.7, 41.4, 49.1, 123.4, 132.3; *m/z* (EI) 216.1.008 (M^+, $C_{11}H_{20}S_2$ requires 216.1001), 147 (22%), 133 (45), 109 (100), 107 (29), 84 (31).

7-Allyl-1,5-dithiaspiro[5.5]undecane (268)



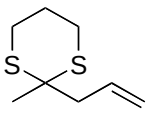
From procedure B: 61% as a colourless oil; ν_{max}(film)/cm^{-1} 2930, 1445, 1366, 1217, 908, 760; δ_H (600 MHz, $CDCl_3$) 1.22-1.32 (1 H, m, CCHCH*H*), 1.35-1.44 (1 H, m, $CCHCH_2CH$*H*), 1.55-1.78 (6 H, m, CCH, CCHCH*H*, $CCHCH_2CH$*H*, CCH*H*, and 2 × CCH_2CH_2), 1.84 (1 H, ddt, *J* 14.0, 11.7 and 3.5, SCH_2CH*H*), 1.96-2.09 (2 H, m, CH_2=CHCH*H* and SCH_2CH*H*), 2.60-2.73 (3 H, m, CCH*H* and 2 × SC*H*H), 2.88 (1 H, ddd, *J* 14.0, 11.7 and 3.0, SC*H*H), 2.89-2.96 (1 H, m, CH_2=CHCH*H*), 3.10 (1 H, ddd, 14.0, 11.7 and 3.0, SC*H*H), 4.98-5.06 (2 H, m, CH=CH_2), 5.75 (1 H, dddd, *J* 17.0, 10.1, 8.5 and 5.6, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 22.7, 24.9, 25.0, 25.88, 25.93, 26.0, 35.6, 37.1, 46.5, 56.3, 115.9, 137.8; *m/z* (EI) 228.1011 (M^+, $C_{12}H_{20}S_2$ requires 228.1001), 187 (46%), 153 (100), 145 (76), 121 (51), 79 (89).

2-(But-3-enyl)-2-phenyl-1,3-dithiane[332] (270)



n-Butyllithium (2.54 ml of a 1.6 M solution in hexane, 6.36 mmol) was added dropwise to a solution of 2-phenyl-1,3-dithiane **260** (1.00 g, 5.09 mmol) in ether (25 ml) at –40 °C. The solution was stirred at –40 °C for 2 h, then 4-bromobut-1-ene (568 μl, 5.60 mmol) was added dropwise. After warming to rt and stirring for a further 4 h, sat. ammonium chloride (10 ml) was added, followed by water (10 ml) and the mixture was extracted with ether (2 × 20 ml). The combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (1.29 g, 5.04 mmol, 99%) as a colourless oil; ν_{max}(film)/cm^{-1} 2904, 1442, 1217, 906, 762, 699; δ_H (600 MHz, $CDCl_3$) 1.94-2.04 (4 H, m, SCH_2CH_2 and $SCCH_2$), 2.11 (2 H, tdd, *J* 7.4, 6.5 and 1.8, CH_2=CHCH_2), 2.70 (2 H, ddd, *J* 14.3, 9.2 and 4.3, 2 × SC*H*H), 2.71-2.75 (2 H, m, 2 × SC*H*H), 4.90 (1 H, app. dq, *J* 10.2 and 1.5, CH=C*H*H), 4.94 (1 H, app. dq, *J* 17.1 and 1.5, CH=C*H*H), 5.69 (1 H, ddt, *J* 17.1, 10.2 and 6.5, CH_2=C*H*), 7.28 (1 H, tt, *J* 7.3 and 1.2, Ar), 7.40 (2 H, dd, *J* 8.3 and 7.3, Ar), 7.93 (2 H, dd, *J* 8.3 and 1.2, Ar); δ_C (150 MHz, $CDCl_3$) 25.3, 27.6, 28.2, 44.1, 58.7, 114.9, 127.0, 128.5, 128.8, 137.6, 141.6; *m/z* (EI) 250.0844 (M^+, $C_{14}H_{18}S_2$ requires 250.0844), 195 (48%), 175 (100), 143 (44), 121 (55), 103 (60).

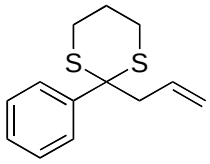
2-Allyl-2-methyl-1,3-dithiane[339] (271)



n-Butyllithium (2.54 ml of a 1.6 M solution in hexane, 6.36 mmol) was added dropwise to a solution of 2-methyl-1,3-dithiane **259**[38] (683 mg, 5.09 mmol) in ether (25 ml) at –40 °C. The solution was stirred at –40 °C for 2 h, then allyl bromide (484 μl, 5.60 mmol) was added dropwise. After warming to rt and stirring for a further 4 h, sat. ammonium chloride (10 ml) was added, followed by water (10 ml) and the

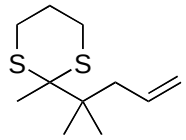
mixture was extracted with ether (2 × 20 ml). The combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (701 mg, 4.02 mmol, 79%) as a colourless oil; ν_{max}(film)/cm^{-1} 2908, 1422, 1037, 992, 909; δ_H (600 MHz, $CDCl_3$) 1.58 (3 H, s, Me), 1.92-2.01 (2 H, m, SCH_2CH_2), 2.69 (2 H, d, *J* 7.1, $SCCH_2$), 2.82 (2 H, ddd, *J* 14.4, 7.0 and 3.7, 2 × SCH*H*), 2.89 (2 H, ddd, *J* 14.4, 8.3 and 3.6, 2 × SCH*H*), 5.12-5.16 (2 H, m, $CH=CH_2$), 5.89 (1 H, ddt, *J* 17.1, 10.3 and 7.1, $CH_2=CH$); δ_C (150 MHz, $CDCl_3$) 25.3, 26.6, 27.8, 45.6, 48.3, 118.6, 133.2; *m/z* (EI) 174.0539 (M^+, $C_8H_{14}S_2$ requires 174.0531), 135 (11%), 133 (100), 85 (14).

2-Allyl-2-phenyl-1,3-dithiane[340] (272)



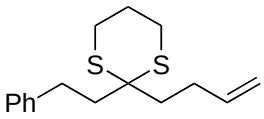
n-Butyllithium (2.02 ml of a 1.6 M solution in hexane, 5.05 mmol) was added dropwise to a solution of 2-phenyl-1,3-dithiane (793 mg, 4.04 mmol) in ether (20 ml) at –40 °C. The solution was stirred at –40 °C for 2 h, then allyl bromide (385 μl, 4.44 mmol) was added dropwise. After warming to rt and stirring for a further 4 h, sat. ammonium chloride (10 ml) was added, followed by water (10 ml) and the mixture was extracted with ether (2 × 20 ml). The combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (850 mg, 3.60 mmol, 89%) as a colourless oil; ν_{max}(film)/cm^{-1} 2906, 1442, 1366, 1265, 1217, 918, 734, 700; δ_H (600 MHz, $CDCl_3$) 1.90-1.99 (2 H, m, SCH_2CH_2), 2.67-2.74 (4 H, m, 2 × SCH_2), 2.76 (2 H, d, *J* 7.1, $SCCH_2$), 5.04-5.07 (2 H, m, $CH=CH_2$), 5.62 (1 H, ddt, *J* 16.2, 11.0 and 7.1, $CH_2=CH$), 7.28 (1 H, tt, *J* 8.2 and 1.4, Ar), 7.40 (2 H, dd, *J* 8.2 and 7.1, Ar), 7.94 (2 H, dd, *J* 7.1 and 1.4, Ar); δ_C (150 MHz, $CDCl_3$) 25.0, 27.5, 49.5, 58.2, 118.8, 127.0, 128.5, 128.8, 131.9, 141.6; *m/z* (EI) 236.0687 (M^+, $C_{13}H_{16}S_2$ requires 236.0688), 195 (100%), 161 (52), 121 (31).

2-(1,1-Dimethylbut-3-enyl)-2-methyl-1,3-dithiane (273)



n-Butyllithium (2.20 ml of a 1.6 M solution in hexane, 3.55 mmol) was added dropwise to a solution of 2-(1,1-dimethylbut-3-enyl)-1,3-dithiane (600 mg, 2.96 mmol) in THF (20 ml) at −78 °C. The solution was warmed to 0 °C for 30 min and methyl iodide (203 μl, 3.26 mmol) was added dropwise. After warming to rt and stirring for a further 6 h, sat. ammonium chloride (10 ml) was added, followed by water (10 ml) and the mixture was extracted with ether (2 × 20 ml). The combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (397 mg, 1.84 mmol, 62%) as a colourless oil; ν_{max}(film)/cm^{-1} 2962, 1422, 1367, 1274, 997, 911, 776; δ_H (600 MHz, $CDCl_3$) 1.12 (6 H, s, 2 × CH_2C*Me*), 1.79 (1 H, dtt, *J* 13.6, 12.0 and 3.8, SCH_2CH*H*), 1.85 (3 H, s, SCMe), 2.07 (1 H, dtt, *J* 13.6, 4.2 and 3.3, SCH_2CH*H*), 2.43 (2 H, d, *J* 7.4, CCH_2), 2.73 (2 H, dt, *J* 14.7 and 4.2, 2 × SCH*H*), 3.05 (2 H, ddd, *J* 14.7, 12.0 and 3.3, 2 × SCH*H*), 5.03-5.08 (2 H, m, CH=CH_2), 5.83 (1 H, ddt, *J* 16.7, 10.3 and 7.4, CH); δ_C (150 MHz, $CDCl_3$) 21.9, 23.4, 25.6, 26.6, 41.3, 42.3, 60.4, 117.9, 135.6; *m/z* (EI) 216.0996 (M^+, $C_{11}H_{20}S_2$ requires 216.1001), 175 (14%), 133 (100).

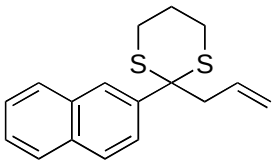
2-(But-3-enyl)-2-(2-phenylethyl)-1,3-dithiane (274)



n-Butyllithium (2 ml of a 1.6 M solution in hexane, 3.25 mmol) was added dropwise to a solution of 2-(2-phenylethyl)-1,3-dithiane (331 mg, 1.48 mmol) in THF (10 ml) at −78 °C. The solution was warmed to 0 °C for 30 min and 4-bromobutene (165 μl, 1.63 mmol) was added dropwise. After warming to rt and stirring for a further 6 h, sat. ammonium chloride (5 ml) was added, followed by water (5 ml) and the mixture was extracted with ether (2 × 15 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue

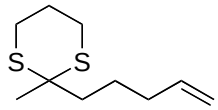
was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (258 mg, 0.93 mmol, 63%) as a colourless oil; ν_{max}(film)/cm^{-1} 2970, 1366, 1229, 1217; δ_H (600 MHz, $CDCl_3$) 1.96-2.00 (2 H, m, SCH_2CH_2), 2.02-2.05 (2 H, m, $CHCH_2CH_2$), 2.17-2.19 (2 H, m, $PhCH_2CH_2$), 2.26 (2 H, tdt, *J* 7.6, 6.4 and 1.4, $CHCH_2$), 2.75-2.78 (2 H, m, $PhCH_2$), 2.83-2.85 (4 H, m, 2 × SCH_2), 5.00 (1 H, app. dq, *J* 10.2 and 1.4, CH=CH*H*), 5.08 (1 H, app. dq, *J* 17.1 and 1.6, CH=CH*H*), 5.85 (1 H, ddt, *J* 17.1, 10.2 and 6.5, CH_2CH), 7.17-7.21 (3 H, m, Ar), 7.28-7.30 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 25.5, 26.1, 28.7, 30.9, 37.7, 40.4, 52.9, 115.2, 126.1, 128.57, 128.61, 137.9, 141.9; *m/z* (EI) 278.1157 (M^+, $C_{16}H_{22}S_2$ requires 278.1157), 223 (22%), 173 (16), 129 (32), 91 (100), 84 (63).

2-Allyl-2-naphthalen-2-yl-1,3-dithiane (275)



n-Butyllithium (4.61 ml of a 1.6 M solution in hexane, 7.37 mmol) was added dropwise to a solution of 2-naphthalen-2-yl-1,3-dithiane (1.51 g, 6.14 mmol) in THF (40 ml) at –78 °C. The solution was stirred at –78 °C for 1 h, then allyl bromide (685 μl, 6.75 mmol) was added dropwise. After warming to RT and stirring for a further 30 min, sat. ammonium chloride (10 ml) was added, followed by water (30 ml) and the mixture was extracted with ether (2 × 40 ml). The combined organic layers were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:5) to give the *alkene* (1.51 g, 5.27 mmol, 86%) as a colourless oil; ν_{max}(film)/cm^{-1} 2904, 1423, 1275, 913, 819, 747; δ_H (600 MHz, $CDCl_3$) 1.92-1.96 (2 H, m, SCH_2CH_2), 2.69 (2 H, ddd, *J* 14.6, 4.1 and 3.8, 2 × SCH*H*), 2.73-2.77 (2 H, m, 2 × SCH*H*), 2.83 (2 H, d, *J* 7.1, $SCCH_2$), 5.03 (1 H, app. dq, *J* 10.0 and 1.6, CH=CH*H*), 5.05 (1 H, app. dq, *J* 17.1 and 1.6, CH=CH*H*), 5.61 (1 H, ddt, *J* 17.1, 10.0 and 7.1, CH_2=C*H*), 7.48-7.52 (2 H, m, Ar), 7.83-7.90 (3 H, m, Ar), 8.02 (1 H, dd, *J* 8.8 and 1.7, Ar), 8.38 (1 H, d, *J* 1.7, Ar); δ_C (150 MHz, $CDCl_3$) 25.1, 27.8, 49.4, 58.3, 119.1, 126.2, 126.37, 126.41, 127.5, 128.4, 128.5, 128.7, 131.6, 132.4, 133.3, 139.0; *m/z* (EI) 286.0841 (M^+, $C_{17}H_{18}S_2$ requires 286.0844), 245 (100%), 178 (21), 171 (65), 127 (15), 84 (15).

2-Methyl-2-pent-4-enyl-1,3-dithiane[341] (276)

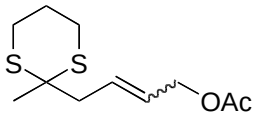


n-Butyllithium (2.54 ml of a 1.6 M solution in hexane, 6.36 mmol) was added dropwise to a solution of 2-methyl-1,3-dithiane **259**[38] (683 mg, 5.09 mmol) in ether (25 ml) at −40 °C. The solution was stirred at −40 °C for 2 h, then 5-bromopent-1-ene (662 μl, 5.60 mmol) was added dropwise. After warming to rt and stirring for a further 4 h, sat. ammonium chloride (10 ml) was added, followed by water (10 ml) and the mixture was extracted with ether (2 × 20 ml). The combined organic layers were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:4) to give the *alkene* (948 mg, 4.68 mmol, 92%) as a colourless oil; ν_{max}(film)/cm^{-1} 2940, 1422, 1275, 993, 907; δ_H (600 MHz, $CDCl_3$) 1.55-1.60 (2 H, m, CH_2=CHCH$_2$C*H*$_2$), 1.61 (3 H, s, Me), 1.90-1.97 (4 H, m, SCH$_2$C*H*$_2$ and SCCH$_2$), 2.09 (2 H, td, *J* 7.1 and 6.7, CH_2=CHC*H*$_2$), 2.83-2.85 (4 H, m, 2 × SCH$_2$), 4.97 (1 H, app. dq, *J* 10.3 and 1.7, CH=CH*H*), 5.03 (1 H, app. dq, *J* 17.0 and 1.7, CH=CH*H*), 5.81 (1 H, ddt, *J* 17.0, 10.3 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 23.9, 25.5, 26.6, 27.9, 33.8, 41.1, 49.3, 115.1, 138.5; *m/z* (EI) 202.0853 (M^+, $C_{10}H_{18}S_2$ requires 202.0844), 133 (24%), 86 (86), 84 (100).

General Procedure for Olefin Oxidation (Procedure C)

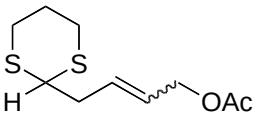
A 10 ml carousel tube was charged with olefin (0.15 mmol), palladium acetate (4 mg, 0.015 mmol), *p*-benzoquinone (7 mg, 0.06 mmol), manganese dioxide (13 mg, 0.15 mmol), acetic acid (43 μl, 0.75 mmol), DMSO (1 ml) and a magnetic stirrer. The reaction mixture was then heated to 80 °C for 24 h under an oxygen atmosphere (balloon). After cooling to rt, water (5 ml) was added and the solution was extracted with ether (2 × 10 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 4:1).

4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl acetate (147)



From procedure C: 68% yield as a pale yellow oil (*E:Z* 4.5:1); ν_{max}(film)/cm^{-1} 2899, 1735, 1367, 1227, 1172, 1025, 967, 907; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.58 (3 H, s, CMe), 1.93-2.04 (2 H, m, SCH_2CH_2), 2.09 (3 H, s, COMe), 2.72 (2 H, d, *J* 7.0, CCH_2), 2.84 (2 H, ddd, *J* 14.6, 7.1 and 3.5, 2 × SCH*H*), 2.90 (2 H, ddd, *J* 14.6, 8.8 and 3.4, 2 × SCH*H*), 4.57 (2 H, dd, *J* 6.3 and 1.0, OCH_2), 5.70 (1 H, dtt, *J* 15.3, 6.3 and 1.3, OCH_2CH), 5.87 (1 H, dtt, *J* 15.3, 7.0 and 1.0, CCH_2CH); *Z*-isomer: 1.58 (3 H, s, CMe), 1.93-2.04 (2 H, m, SCH_2CH_2), 2.08 (3 H, s, COMe), 2.78 (2 H, d, *J* 7.3, CCH_2), 2.84 (2 H, ddd, *J* 14.6, 7.1 and 3.5, 2 × SCH*H*), 2.90 (2 H, ddd, *J* 14.6, 8.8 and 3.4, 2 × SCH*H*), 4.67 (2 H, d, *J* 6.8, OCH_2), 5.75 (1 H, dtt, *J* 11.1, 6.8 and 1.4, OCH_2CH), 5.82 (1 H, dtt, *J* 11.1, 7.3 and 1.3, CCH_2CH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.0, 25.1, 26.5, 27.7, 44.0, 48.2, 64.8, 127.8, 130.2, 170.9; *Z*-isomer: 21.0, 25.2, 26.6, 27.8, 44.0, 48.2, 64.8, 127.8, 130.2, 170.9; *m/z* (EI) 246.0748 (M^+, $C_{11}H_{18}S_2O_2$ requires 246.0743), 202 (25%), 133 (100), 111 (32), 99 (21).

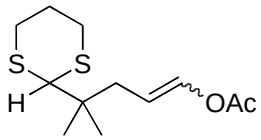
4-(-1,3-Dithian-2-yl)pent-2-en-1-yl acetate (277)



From procedure C: 63% yield as a pale yellow oil (*E:Z* 3.8:1); ν_{max}(film)/cm^{-1} 2900, 1735, 1423, 1365, 1226, 1172, 1023, 967, 907; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.84 (1 H, dtt, *J* 14.3, 11.5 and 3.5, SCH_2CHH), 2.06 (3 H, s, Me), 2.09-2.14 (1 H, m, SCH_2CHH), 2.51 (2 H, app. td, *J* 6.9 and 0.8, $SCHCH_2$), 2.83 (2 H, ddd, *J* 14.4, 8.1 and 3.5, 2 × SCH*H*), 2.88 (2 H, ddd, *J* 14.4, 11.5 and 2.7, 2 × SCH*H*), 4.08 (1 H, t, *J* 6.8, SCH), 4.53 (2 H, dd, *J* 6.1 and 0.8, OCH_2), 5.70 (1 H, dtt *J* 15.5, 6.1 and 1.2, OCH_2CH), 5.80 (1 H, dtt, *J* 15.5, 7.0 and 1.1, $SCHCH_2CH$); *Z*-isomer: 1.84 (1 H, dtt, *J* 14.0, 11.3 and 3.5, SCH_2CHH), 2.06 (3 H, s, Me), 2.09-2.14 (1 H, m, SCH_2CHH), 2.58 (2 H, app. t, *J* 6.9, $SCHCH_2$), 2.83 (2 H, ddd, *J* 14.4, 8.1 and 3.5, 2 × SCH*H*), 2.88 (2 H, ddd, *J* 14.4, 11.5 and 2.7, 2 × SCH*H*), 4.09 (1 H, t, *J* 6.8, SCH), 4.63 (2 H,

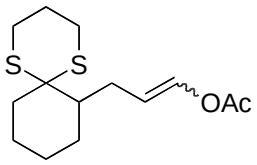
d, *J* 6.6, OCH_2), 5.70 (1 H, dtt *J* 11.0, 6.1 and 1.2, OCH_2CH), 5.74 (1 H, dtt, *J* 11.0, 6.6 and 1.2, $SCHCH_2CH$); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.0, 25.7, 30.4, 38.2, 46.9, 64.6, 127.3, 130.5, 170.8; *Z*-isomer: 21.0, 25.6, 30.4, 33.4, 47.0, 60.2, 126.4, 129.8, 170.9; *m/z* (EI) 232.0598 (M^+, $C_{10}H_{16}S_2O_2$ requires 232.0592), 173 (48%), 119 (89), 106 (100).

4-(1,3-Dithian-2-yl)-4-methylpent-1-en-1-yl acetate (278)



From procedure C: 58% yield as a pale yellow oil (*E:Z* 1:1); ν_{max}(film)/cm^{-1} 2970, 1751, 1367, 1217, 1101, 1073, 1029; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.07 (6 H, s, 2 × CMe), 1.76-1.84 (1 H, m, SCH_2CH), 2.05-2.10 (1 H, m, SCH_2CH), 2.12 (3 H, s, COMe), 2.15 (2 H, dd, *J* 8.3 and 1.0, CCH_2), 2.87-2.89 (4 H, m, 2 × SCH_2), 4.00 (1 H, s, SCH), 5.42 (1 H, dt, *J* 12.3 and 8.3, CH_2CH), 7.11 (1 H, dt, *J* 12.3 and 1.0, OCH); *Z*-isomer: 1.09 (6 H, s, 2 × CMe), 1.76-1.84 (1 H, m, SCH_2CH), 2.05-2.10 (1 H, m, SCH_2CH), 2.14 (3 H, s, COMe), 2.32 (2 H, dd, *J* 7.9 and 1.2, CCH_2), 2.87-2.89 (4 H, m, 2 × SCH_2), 4.02 (1 H, s, SCH), 4.94 (1 H, td, *J* 7.9 and 6.4, CH_2CH), 7.09 (1 H, dt, *J* 6.4 and 1.2, OCH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 20.9, 25.2, 26.2, 31.5, 38.0, 38.6, 60.5, 110.3, 137.7, 168.4; *Z*-isomer: 20.9, 25.2, 26.2, 31.4, 35.1, 39.1, 60.2, 109.9, 136.2, 168.3; *m/z* (EI) 260.0902 (M^+, $C_{12}H_{20}S_2O_2$ requires 260.0899), 218 (22%), 200 (11), 161 (24), 119 (100).

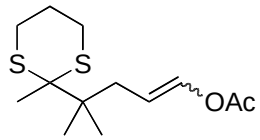
3-(1,5-Dithiaspiro[5.5]undecan-7-yl)prop-1-en-1-yl acetate (279)



From procedure C: 59% yield as a pale yellow oil (*E:Z* 1:1.4); ν_{max}(film)/cm^{-1} 2931, 1751, 1446, 1367, 1217, 1100; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.23-1.29 (1 H, m, $CCHCH$), 1.34-1.44 (1 H, m, $CCHCH_2CH$), 1.57-1.73 (6 H, m, CCH, $CCHCH$, $CCHCH_2CH$, CCH and 2 × CCH_2CH_2), 1.79-1.88 (1 H, m, SCH_2CH), 1.94 (1

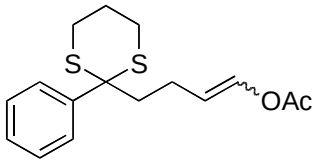
H, dtd, *J* 14.4, 10.1 and 1.0, CCHCH*H*), 2.03-2.08 (1 H, m, SCH_2CH*H*), 2.14 (3 H, s, Me), 2.60-2.70 (3 H, m, CCH*H* and 2 × SCH*H*), 2.83 (2 H, m, SCH*H* and CCHCH*H*), 3.08-3.13 (1 H, m, SCH*H*), 5.35 (1 H, ddd, *J* 12.5, 9.4 and 6.6, OCH=C*H*), 7.07 (1 H, app. dq, *J* 12.5 and 1.0, OCH); *Z*-isomer: 1.23-1.29 (1 H, m, CCHCH*H*), 1.34-1.44 (1 H, m, $CCHCH_2CH$*H*), 1.57-1.73 (6 H, m, CCH, CCHCH*H*, $CCHCH_2CH$*H*, CCH*H* and 2 × CCH_2C*H*$_2$), 1.79-1.88 (1 H, m, SCH_2CH*H*), 2.03-2.08 (1 H, m, SCH_2CH*H*), 2.10 (3 H, s, Me), 2.24 (1 H, dtd, *J* 14.0, 10.4 and 0.8, CCHCH*H*), 2.60-2.70 (3 H, m, CCH*H* and 2 × SCH*H*), 2.83 (2 H, m, SCH*H* and CCHCH*H*), 3.08-3.13 (1 H, m, SCH*H*), 4.85 (1 H, dt, *J* 9.9 and 6.2, OCH=C*H*), 7.05 (1 H, app. dq, *J* 9.9 and 0.8, OCH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 22.7, 25.07, 25.13, 26.0, 26.1, 26.3, 29.1, 37.2, 47.2, 56.3, 113.8, 136.4, 168.3; *Z*-isomer: 22.8, 25.1, 25.2, 26.0, 26.1, 26.4, 29.1, 37.1, 47.2, 56.3, 113.2, 135.2, 168.4; *m/z* (EI) 286.1046 (M^+, $C_{14}H_{22}S_2O_2$ requires 286.1046), 187 (63%), 151 (45), 137 (100), 119 (37), 106 (44), 84 (45).

4-(2-Methyl-1,3-dithian-2-yl)-4-methylpent-1-en-1-yl acetate (280)



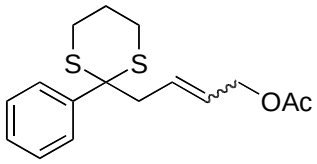
From procedure C: 30% yield as a pale yellow oil (*E*:*Z* 1:1.4); ν_{max}(film)/cm^{-1} 2972, 1752, 1368, 1217, 1079; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.10 (6 H, s, 2 × CH_2C*Me*), 1.75-1.83 (1 H, m, SCH_2CH*H*), 1.84 (3 H, s, SCMe), 2.05-2.10 (1 H, m, SCH_2CH*H*), 2.12 (3 H, s, COMe), 2.38 (2 H, d, *J* 8.0, CCH_2), 2.71-2.76 (2 H, m, 2 × SCH*H*), 3.02-3.09 (2 H, m, 2 × SCH*H*), 5.44 (1 H, dt, *J* 12.2 and 8.0, OCH=C*H*), 7.07 (1 H, dt, *J* 12.2 and 1.4, OCH); *Z*-isomer: 1.12 (6 H, s, 2 × CH_2C*Me*), 1.75-1.83 (1 H, m, SCH_2CH*H*), 1.87 (3 H, s, SCMe), 2.05-2.10 (1 H, m, SCH_2CH*H*), 2.15 (3 H, s, COMe), 2.54 (2 H, d, *J* 7.9, CCH_2), 2.71-2.76 (2 H, m, 2 × SCH*H*), 3.02-3.09 (2 H, m, 2 × SCH*H*), 4.94 (1 H, td, *J* 7.9 and 6.4, OCH=C*H*), 7.12 (1 H, dt, *J* 6.4 and 1.2, OCH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 20.9, 21.9, 23.4, 25.5, 26.6, 34.7, 42.5, 60.2, 111.5, 137.1, 168.4; *Z*-isomer: 20.9, 21.9, 23.4, 25.6, 26.2, 31.6, 42.8, 60.3, 110.8, 135.9, 168.2; *m/z* (CI) 275.1138 (M^+, $C_{13}H_{23}S_2O_2$ requires 275.1140), 175 (11%), 135 (10), 133 (100), 69 (14).

4-(2-Phenyl-1,3-dithian-2-yl)but-1-en-1-yl acetate (281)



From procedure C: 11% yield as a pale yellow oil (*E:Z* 1:1.5); ν_{max}(film)/cm^{-1} 2971, 1738, 1366, 1230, 1217, 1029; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.92-1.97 (4 H, m, SCH_2CH_2 and $SCCH_2$), 2.06-2.10 (5 H, m, $OCH{=}CHCH_2$ and OAc), 2.67-2.74 (4 H, m, 2 × SCH_2), 5.26 (1 H, dt, *J* 12.5 and 7.6, $OCH{=}CH$), 6.96 (1 H, dt, *J* 12.5 and 1.5, OCH), 7.27 (1 H, dd, *J* 7.4 and 1.1, Ar), 7.37-7.41 (2 H, m, Ar), 7.89 (2 H, dd, *J* 8.6 and 1.1, Ar); *Z*-isomer: 1.92-1.97 (4 H, m, SCH_2CH_2 and $SCCH_2$), 2.06-2.10 (5 H, m, $OCH{=}CHCH_2$ and OAc), 2.67-2.74 (4 H, m, 2 × SCH_2), 4.72 (1 H, td, *J* 6.9 and 6.3, $OCH{=}CH$), 6.91 (1 H, dt, *J* 6.3 and 1.3, OCH), 7.27 (1 H, dd, *J* 7.4 and 1.2, Ar), 7.37-7.41 (2 H, m, Ar), 7.92 (2 H, dd, *J* 8.6 and 1.2, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 19.6, 20.8, 22.3, 25.3, 44.8, 58.6, 113.8, 127.2, 128.7, 128.9, 135.9, 141.4, 168.3; *Z*-isomer: 19.6, 20.8, 22.3, 27.7, 44.3, 58.8, 112.8, 127.3, 128.7, 128.9, 134.6, 141.6, 168.1; *m/z* (EI) 308.0910 (M^+, $C_{16}H_{20}S_2O_2$ requires 308.0899), 191 (14%), 103 (17), 86 (64), 84 (100).

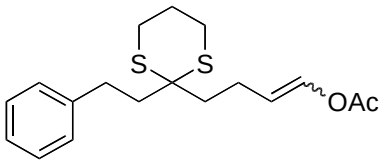
4-(2-Phenyl-1,3-dithian-2-yl)but-2-en-1-yl acetate (282)



From procedure C: 18% yield as a pale yellow oil (*E:Z* 7:1); ν_{max}(film)/cm^{-1} 2961, 1739, 1366, 1228, 1217, 909; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.89-1.96 (2 H, m, SCH_2CH_2), 2.02 (3 H, s, OAc), 2.64-2.71 (4 H, m, 2 × SCH_2), 2.73 (2 H, d, *J* 5.9, $SCCH_2$), 4.44 (2 H, d, *J* 5.0, OCH_2), 5.49-5.54 (2 H, m, $OCH_2CH{=}CH$ and OCH_2CH), 7.26 (1 H, tt, *J* 7.3 and 1.1, Ar), 7.37 (2 H, dd, *J* 8.5 and 7.3, Ar), 7.89 (2 H, dd, *J* 8.5 and 1.1, Ar); *Z*-isomer: 1.89-1.96 (2 H, m, SCH_2CH_2), 2.01 (3 H, s, OAc), 2.64-2.71 (4 H, m, 2 × SCH_2), 2.80 (2 H, d, *J* 7.7, $SCCH_2$), 4.39 (2 H, d, *J* 6.3, OCH_2), 5.55-5.59 (2 H, m, $OCH_2CH{=}CH$ and OCH_2CH), 7.26 (1 H, tt, *J* 7.3 and 1.2,

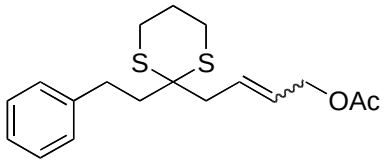
Ar), 7.37 (2 H, dd, *J* 8.6 and 7.3, Ar), 7.91 (2 H, dd, *J* 8.6 and 1.2, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.1, 25.0, 27.6, 47.9, 58.4, 64.7, 127.2, 128.2, 128.6, 128.8, 128.9, 141.4, 170.9; *Z*-isomer: 21.1, 25.0, 27.6, 42.9, 58.7, 60.3, 127.2, 127.3, 127.8, 128.7, 129.7, 141.2, 171.0; *m/z* (EI) 308.0891 (M^+, $C_{16}H_{20}S_2O_2$ requires 308.0899), 195 (100%), 121 (26), 84 (29).

4-[2-(2Phenylethyl)-1,3-dithian-2-yl]but-1-en-1-yl acetate (282)



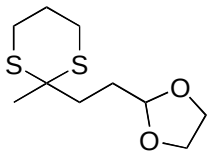
33% yield as a pale yellow oil (*E:Z* 1:1.3); ν_{max}(film)/cm^{-1} 2971, 1739, 1435, 1366, 1229, 1217; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.95-2.04 (4 H, m, SCH_2CH_2 and $PhCH_2CH_2CCH_2$), 2.12 (3 H, s, Me), 2.15-2.23 (4 H, m, $CH{=}CHCH_2$ and $PhCH_2CH_2$), 2.74-2.79 (2 H, m, $PhCH_2$), 2.82-2.86 (4 H, m, 2 × SCH_2), 5.43 (1 H, dt, *J* 12.4 and 7.4, $OCH{=}CH$), 7.13 (1 H, dt, *J* 12.4 and 1.5, OCH), 7.17-7.22 (3 H, m, Ar), 7.28-7.31 (2 H, m, Ar); *Z*-isomer: 1.95-2.04 (4 H, m, SCH_2CH_2 and $PhCH_2CH_2CCH_2$), 2.14 (3 H, s, Me), 2.15-2.23 (2 H, m, $PhCH_2CH_2$), 2.32-2.39 (2 H, m, $CH{=}CHCH_2$), 2.74-2.79 (2 H, m, $PhCH_2$), 2.82-2.86 (4 H, m, 2 × SCH_2), 4.92 (1 H, dt, *J* 7.5 and 6.4, $OCH{=}CH$), 7.05 (1 H, dt, *J* 6.4 and 1.5, OCH), 7.17-7.22 (3 H, m, Ar), 7.28-7.31 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 20.9, 22.6, 25.4, 26.1, 30.9, 37.8, 40.5, 53.6, 114.0, 126.1, 128.4, 128.6, 136.0, 141.8, 168.3; *Z*-isomer: 19.8, 20.9, 25.5, 26.1, 30.8, 38.4, 40.4, 52.8, 112.9, 126.1, 128.5, 128.6, 134.8, 141.9, 168.1; *m/z* (EI) 336.1201 (M^+, $C_{18}H_{24}S_2O_2$ requires 336.1212), 223 (46%), 169 (15), 91 (77), 84 (100).

4-[2-(2Phenylethyl)-1,3-dithian-2-yl]but-2-en-1-yl acetate (284)



36% yield as a pale yellow oil (*E:Z* 2.4:1); ν_{max}(film)/cm^{-1} 2970, 1738, 1365, 1230, 1217, 1028, 908; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.96-2.01 (2 H, m, SCH_2CH_2), 2.08 (3 H, s, Me), 2.11-2.17 (2 H, m, $PhCH_2CH_2$), 2.75-2.80 (4 H, m, $PhCH_2CH_2CCH_2$ and $PhCH_2$), 2.84-2.86 (4 H, m, 2 × SCH_2), 4.57 (2 H, dd, *J* 6.4 and 0.8, OCH_2), 5.75 (1 H, dtt, *J* 15.6, 6.4 and 1.1, CCH_2CH), 5.90 (1 H, dtt, *J* 15.6, 7.0 and 0.8, OCH_2CH), 7.18-7.21 (3 H, m, Ar), 7.27-7.29 (2 H, m, Ar); *Z*-isomer: 1.96-2.03 (2 H, m, SCH_2CH_2), 2.08 (3 H, s, Me), 2.11-2.17 (2 H, m, $PhCH_2CH_2$), 2.75-2.80 (4 H, m, $PhCH_2CH_2CCH_2$ and $PhCH_2$), 2.84-2.86 (4 H, m, 2 × SCH_2), 4.67 (2 H, d, *J* 7.3, OCH_2), 5.74-5.77 (1 H, m, CCH_2CH), 5.84 (1 H, dtt, *J* 11.2, 7.3 and 1.1, OCH_2CH), 7.18-7.21 (3 H, m, Ar), 7.27-7.29 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.1, 25.3, 26.2, 30.7, 40.6, 41.4, 52.2, 64.9, 126.1, 127.9, 128.58, 128.59, 130.2, 141.8, 171.0; *Z*-isomer: 21.1, 25.3, 26.2, 30.9, 36.5, 40.9, 52.6, 60.5, 126.1, 127.9, 128.58, 128.59, 130.2, 141.8, 171.1; *m/z* (EI) 336.1223 (M^+, $C_{18}H_{24}S_2O_2$ requires 336.1212), 149 (7%), 91 (96), 84 (100).

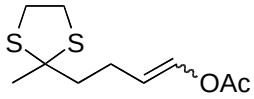
[3-(1,3-Dioxolan-2-yl)propyl]-2-methyl-1,3-dithiane (288)



n-Butyllithium (5.60 ml of a 1.6 M solution in hexane, 8.94 mmol) was added dropwise to a solution of 2-methyl-1,3-dithiane **259**[38] (1.09 g, 8.13 mmol) in THF (40 ml) at −78 °C. The solution was stirred at −78 °C for 2 h, then 1-bromo-3-(1,3-dioxolan-2-yl)propane (950 μl, 8.13 mmol) was added dropwise. After warming to rt and stirring for a further 4 h, sat. ammonium chloride (10 ml) was added, followed by water (30 ml) and the mixture was extracted with ether (2 × 40 ml). The combined organic layers were washed with water (60 ml), brine (60 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column

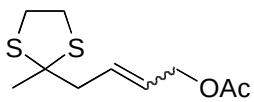
chromatography (EtOAc-petrol 1:9) to give the *acetal* (1.05 g, 4.47 mmol, 55%) as a colourless oil; ν_{max}(film)/cm^{-1} 2889, 1417, 1142, 1036, 906; δ_H (600 MHz, $CDCl_3$) 1.51 (3 H, s, Me), 1.84-1.87 (2 H, m, OCHC*H*$_2$), 1.91 (1 H, dtt, *J* 13.9, 9.6 and 3.2, SCH$_2$CH*H*), 1.99 (1 H, dtt, *J* 13.9, 7.0 and 2.9, SCH$_2$CH*H*), 2.06-2.09 (2 H, m, SCCH$_2$), 2.77 (2 H, ddd, *J* 14.5, 7.0 and 3.2, 2 × SCH*H*), 2.90 (2 H, ddd, *J* 14.5, 9.6 and 2.9, 2 × SCH*H*), 3.85-3.89 (2 H, m, 2 × OCH*H*), 3.77-3.79 (2 H, m, 2 × OCH*H*), 4.92 (1 H, t, *J* 4.9, OCH); δ_C (150 MHz, $CDCl_3$) 25.3, 26.5, 27.8, 29.3, 34.9, 48.7, 65.1, 104.3; *m/z* (EI) 234.0743 (M^+, $C_{10}H_{18}O_2S_2$ requires 234.0743), 133 (50%), 99 (21), 86 (100).

4-(2-Mehtyl-1,3-dithiolan-2-yl)but-1-en-1-yl acetate (289)



From procedure C: 21% yield as a pale yellow oil (*E:Z* 1:1.1); ν_{max}(film)/cm^{-1} 2971, 1740, 1366, 1228, 1217, 1102, 913, 733; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.79 (3 H, s, CMe), 2.00-2.03 (2 H, m, CCH$_2$), 2.13 (3 H, s, COMe), 2.25-2.29 (2 H, m, CHC*H*$_2$), 3.30-3.40 (4 H, m, 2 × SCH$_2$), 5.45 (1 H, dt, *J* 12.5 and 7.4, CH$_2$C*H*), 7.13 (1 H, dt, *J* 12.5 and 1.4, OCH); *Z*-isomer: 1.81 (3 H, s, CMe), 2.00-2.03 (2 H, m, CCH$_2$), 2.18 (3 H, s, COMe), 2.38-2.42 (2 H, m, CHC*H*$_2$), 3.30-3.40 (4 H, m, 2 × SCH$_2$), 4.90 (1 H, td, *J* 7.3 and 6.5, CH$_2$C*H*), 7.03 (1 H, dt, *J* 6.5 and 1.5, OCH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 20.9, 25.3, 32.5, 40.1, 45.5, 66.6, 113.2, 135.9, 168.2; *Z*-isomer: 20.9, 22.6, 32.4, 40.1, 45.0, 66.3, 114.2, 134.5, 168.4; *m/z* (FAB) 255.0478 ([MNa]$^+$, $C_{10}H_{16}S_2O_2Na$ requires 255.0489), 199 (33%), 176 (100), 173 (41), 167 (11).

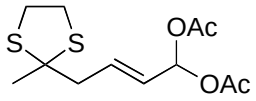
4-(2-Mehtyl-1,3-dithiolan-2-yl)but-2-en-1-yl acetate (290)



From procedure C: 72% yield as a pale yellow oil (*E:Z* 10:1); ν_{max}(film)/cm^{-1} 2971, 1738, 1365, 1230, 1218, 1026, 971; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.75 (3 H, s, CMe), 2.09 (3 H, s, COMe), 2.70 (2 H, d, *J* 7.0, CCH$_2$), 3.31-3.40 (4 H, m, 2 ×

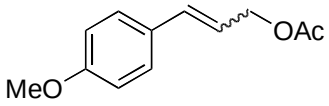
SCH_2), 4.57 (2 H, dd, *J* 6.3 and 1.0, OCH_2), 5.70 (1 H, dtt, *J* 15.4, 6.3 and 1.3, OCH_2CH), 5.88 (1 H, dtt, *J* 15.4, 7.0 and 1.0, CCH_2CH); *Z*-isomer: 1.77 (3 H, s, CMe), 2.08 (3 H, s, COMe), 2.76 (2 H, d, *J* 7.5, CCH_2), 3.31-3.40 (4 H, m, 2 × SCH_2), 4.67 (2 H, d, *J* 6.8, OCH_2), 5.74 (1 H, dtt, *J* 11.1, 6.8 and 1.5, OCH_2CH), 5.82 (1 H, dtt, *J* 11.1, 7.5 and 1.5, CCH_2CH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.1, 31.9, 40.0, 48.7, 64.9, 65.7, 127.9, 132.0, 171.0; *Z*-isomer: 21.1, 32.1, 40.2, 43.4, 60.6, 66.0, 126.6, 131.1, 171.0; *m/z* (FAB) 255.0484 ($[MNa]^+$, $C_{10}H_{16}S_2O_2Na$ requires 255.0489), 199 (59%), 176 (100), 173 (89).

4-(2-Mehtyl-1,3-dithiolan-2-yl)but-2-en-1,1-diyl diacetate (291)



From procedure C: 40% yield as a pale yellow oil; ν_{max}(film)/cm^{-1} 2921, 1759, 1372, 1237, 1203, 958; δ_H (600 MHz, $CDCl_3$) 1.73 (3 H, s, SC*Me*), 2.09 (6 H, s, 2 × COMe), 2.69 (2 H, dd, *J* 7.3 and 1.5, CCH_2), 3.29-3.37 (4 H, m, 2 × SCH_2), 5.65 (1 H, ddt, *J* 15.4, 6.3 and 1.5, OCHC*H*), 6.12 (1 H, dtd, *J* 15.4, 7.3 and 0.7, OCHCH=C*H*), 7.12 (1 H, d, *J* 6.3, OCH); δ_C (150 MHz, $CDCl_3$) 21.0, 32.0, 40.2, 48.5, 65.4, 89.4, 127.0, 134.1, 168.8; *m/z* (FAB) 313.0533 ($[MNa]^+$, $C_{12}H_{18}S_2O_4Na$ requires 313.0544), 199 (28%), 176 (100), 173 (50).

3-(4-Methoxyphenyl)prop-2-en-1-yl acetate[269] (293)



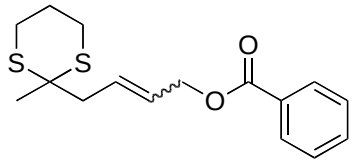
From procedure C: 93% yield as a pale yellow oil (*E:Z* 10:1); δ_H (600 MHz, $CDCl_3$) *E*-isomer: 2.09 (3 H, s, OAc), 3.81 (3 H, s, OMe), 4.70 (2 H, dd, *J* 6.5 and 1.1, CH_2), 6.15 (1 H, dt, *J* 15.9 and 6.5, PhCH=C*H*), 6.60 (1 H, d, *J* 15.9, PhC*H*), 6.85 (2 H, d, *J* 8.7, Ar), 7.33 (2 H, d, *J* 8.7, Ar); *Z*-isomer: 2.09 (3 H, s, OAc), 3.82 (3 H, s, OMe), 4.84 (2 H, dd, *J* 6.6 and 1.5, CH_2), 5.72 (1 H, dt, *J* 11.7 and 6.6, PhCH=C*H*), 6.61 (1 H, d, *J* 11.7, PhC*H*), 6.89 (2 H, d, *J* 8.6, Ar), 7.17 (2 H, d, *J* 8.6, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 21.2, 55.4, 65.5, 114.1, 120.9, 128.0, 129.0, 134.2, 159.7, 171.1; *Z*-isomer: 21.1, 55.7, 61.7, 113.9, 124.1, 128.8, 130.3, 132.7, 159.1, 171.1; *m/z* (EI)

206.0945 (M^+, $C_{12}H_{14}O_3$ requires 206.0938), 163 (66%), 147 (100), 135 (72), 103 (84), 91 (51).

General Procedure for Olefin Oxidation with Carboxylic Acids (Procedure D)

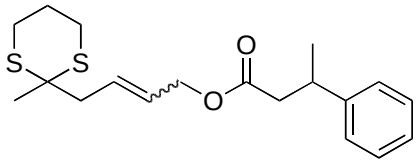
A 10 ml carousel tube was charged with olefin (0.15 mmol), palladium acetate (4 mg, 0.015 mmol), *p*-benzoquinone (7 mg, 0.06 mmol), manganese dioxide (13 mg, 0.15 mmol), carboxylic acid (0.30 mmol), DMSO (1 ml) and a magnetic stirrer. The reaction mixture was then heated to 80 °C for 24 h under an oxygen atmosphere (balloon). After cooling to rt, water (5 ml) was added and the solution was extracted with ether (2 × 10 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 4:1).

4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl benzoate (294)



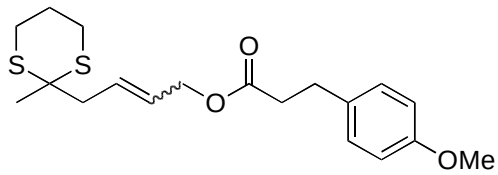
From procedure D: 85% yield as a pale yellow oil (*E:Z* 10:1); ν_{max}(film)/cm^{-1} 2970, 1441, 1717, 1371, 1268, 1218, 1106, 907, 728, 712; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.59 (3 H, s, Me), 1.90-2.06 (2 H, m, SCH_2CH_2), 2.74 (2 H, d, *J* 7.1, CCH_2), 2.83 (2 H, ddd, *J* 14.5, 6.8 and 3.7, 2 × SC*H*H), 2.90 (2 H, ddd, *J* 14.5, 8.3 and 3.7, 2 × SCH*H*), 4.82 (2 H, dd, *J* 6.2 and 0.9, OCH_2), 5.82 (1 H, dtt, *J* 15.3, 6.2 and 1.1, OCH_2CH), 5.97 (1 H, dtt, *J* 15.3, 7.1 and 0.9, OCH_2CH=C*H*), 7.44 (2 H, br t, *J* 7.5, Ar), 7.56 (1 H, tt, *J* 7.5, 1.5, Ar), 8.06 (2 H, dd, *J* 8.2, 1.5, Ar); *Z*-isomer: 1.62 (3 H, s, Me), 1.90-2.06 (2 H, m, SCH_2CH_2), 2.74 (2 H, d, *J* 7.1, CCH_2), 2.83 (2 H, ddd, *J* 14.5, 6.8 and 3.7, 2 × SC*H*H), 2.90 (2 H, ddd, *J* 14.5, 8.3 and 3.7, 2 × SCH*H*), 4.92 (2 H, d, *J* 5.4, OCH_2), 5.84-5.91 (2 H, m, OCH_2CH and OCH_2CH=C*H*), 7.44 (2 H, br t, *J* 7.5, Ar), 7.56 (1 H, tt, *J* 7.5, 1.5, Ar), 8.06 (2 H, dd, *J* 8.2, 1.5, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 25.1, 26.5, 27.7, 44.0, 48.2, 65.3, 127.9, 128.4, 129.6, 130.2, 130.4, 132.9, 166.4; *Z*-isomer: 25.1, 26.6, 27.8, 44.0, 48.2, 65.3, 127.9, 128.4, 129.5, 130.2, 130.4, 133.0, 166.4; *m/z* (FAB) 331.0809 ($[MNa]^+$, $C_{16}H_{20}S_2O_2Na$ requires 331.0802), 199 (13%), 187 (48), 176 (90).

4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl 3-phenylbutyrate (295)



From procedure D: 33% yield as a pale yellow oil (*E:Z* 5.9:1); ν_{max}(film)/cm^{-1} 2920, 1733, 1371, 1217, 1162, 971, 700; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.30 (3 H, d, *J* 7.2, CH*Me*), 1.55 (3 H, s, SCMe), 1.90-2.02 (2 H, m, SCH_2CH_2), 2.56 (1 H, dd, *J* 15.3 and 8.3, COCH*H*), 2.63 (1 H, dd, *J* 15.3 and 7.0, COCH*H*), 2.67 (2 H, d, *J* 7.2, $SCCH_2$), 2.82 (2 H, ddd, *J* 14.5, 10.7 and 3.4, 2 × SCH*H*), 2.88 (2 H, ddd, *J* 14.5, 8.6 and 3.4, 2 × SCH*H*), 3.28 (1 H, app. sextet, *J* 7.2, PhC*H*), 4.51 (2 H, d, *J* 6.3, OCH_2), 5.59 (1 H, ddt, *J* 15.5, 6.3 and 1.2, OCH_2CH), 5.81 (1 H, ddt, *J* 15.5, 7.1 and 1.0, OCH_2CH=C*H*), 7.18-7.22 (3 H, m, Ar), 7.28-7.30 (2 H, m, Ar); *Z*-isomer: 1.30 (3 H, d, *J* 7.2, CH*Me*), 1.56 (3 H, s, SCMe), 1.90-2.02 (2 H, m, SCH_2CH_2), 2.55 (1 H, dd, *J* 15.1 and 8.2, COCH*H*), 2.63 (1 H, dd, *J* 15.1 and 7.1, COCH*H*), 2.72 (2 H, d, *J* 7.3, $SCCH_2$), 2.82 (2 H, ddd, *J* 14.5, 10.7 and 3.4, 2 × SCH*H*), 2.88 (2 H, ddd, *J* 14.5, 8.6 and 3.4, 2 × SCH*H*), 3.28 (1 H, app. sextet, *J* 7.2, PhC*H*), 4.60 (2 H, dd, *J* 6.8 and 2.8, OCH_2), 5.64 (1 H, ddt, *J* 11.1, 6.8 and 1.5, OCH_2CH), 5.76 (1 H, ddt, *J* 11.1, 7.3 and 1.3, OCH_2CH=C*H*), 7.18-7.22 (3 H, m, Ar), 7.28-7.30 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 22.0, 25.2, 26.6, 27.8, 36.6, 43.0, 44.1, 48.3, 64.7, 126.5, 126.9, 127.9, 128.6, 130.2, 145.8, 172.2; *Z*-isomer: 25.2, 26.7, 27.9, 31.1, 36.6, 39.0, 44.1, 48.6, 60.3, 126.5, 126.9, 127.9, 128.6, 129.3, 145.7, 172.3; *m/z* (EI) 350.1373 (M^+, $C_{19}H_{26}S_2O_2$ requires 350.1369), 187 (5%), 135 (48), 133 (100), 111 (19), 105 (71).

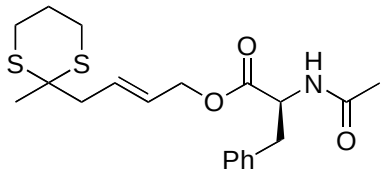
4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl 3-(4-methoxyphenyl)propionate (296)



From procedure D: 37% yield as a pale yellow oil (*E:Z* 6.3:1); ν_{max}(film)/cm^{-1} 2920, 1732, 1513, 1245, 1176, 1153, 1035, 971, 827; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.55

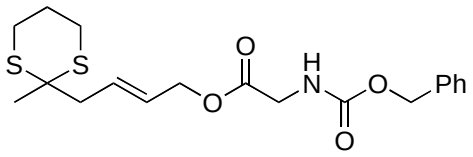
(3 H, CMe), 1.91-2.01 (2 H, m, SCH_2CH_2), 2.61 (2 H, t, *J* 8.1, $COCH_2$), 2.69 (2 H, d, *J* 7.1, $SCCH_2$), 2.80-2.90 (6 H, m, 2 × SCH_2 and $PhCH_2$), 3.78 (3 H, s, OMe), 4.55 (2 H, d, *J* 6.4, OCH_2), 5.65 (1 H, ddt, *J* 15.3, 6.4 and 1.2, OCH_2CH=C*H*), 5.83 (1 H, ddt, *J* 15.3, 7.1 and 1.0, OCH_2CH), 6.82 (2 H, d, *J* 8.6, Ar), 7.11 (2 H, d, *J* 8.6, Ar); *Z*-isomer: 1.60 (3 H, CMe), 1.91-2.01 (2 H, m, SCH_2CH_2), 2.60 (2 H, t, *J* 8.0, $COCH_2$), 2.75 (2 H, d, *J* 7.3, $SCCH_2$), 2.80-2.90 (6 H, m, 2 × SCH_2 and $PhCH_2$), 3.78 (3 H, s, OMe), 4.65 (2 H, d, *J* 6.9, OCH_2), 5.70 (1 H, ddt, *J* 11.1, 6.9 and 1.5, OCH_2CH=C*H*), 5.78 (1 H, ddt, *J* 11.1, 7.3 and 1.2, OCH_2CH), 6.82 (2 H, d, *J* 8.6, Ar), 7.11 (2 H, d, *J* 8.6, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 25.2, 26.6, 27.8, 30.2, 36.3, 44.1, 48.3, 55.4, 64.8, 114.0, 127.9, 129.4, 130.2, 132.7, 158.1, 172.8; *Z*-isomer: 21.2, 25.2, 26.7, 27.9, 29.8, 39.0, 48.6, 60.4, 64.9, 114.0, 127.9, 129.4, 130.3, 132.6, 158.2, 172.9; *m/z* (EI) 366.1311 (M^+, $C_{19}H_{26}S_2O_3$ requires 366.1318), 179 (5%), 135 (25), 133 (100), 121 (28).

(*E*,*S*)-4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl 2-*N*-acylamino-3-phenylpropionate (297)



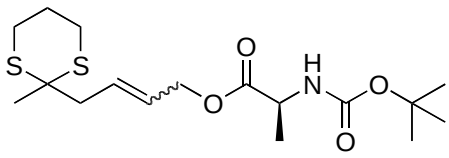
From procedure D: 27% yield as a pale yellow oil; $[\alpha]_D^{20}$ + 3.5 (c 1.0 g dm^{-3}, $CHCl_3$); ν_{max}(film)/cm^{-1} 3272, 2924, 1740, 1656, 1544, 1372, 1179, 1029, 701; δ_H (600 MHz, $CDCl_3$) 1.56 (3 H, s, SCMe), 1.91-2.01 (5 H, m, COMe and SCH_2CH_2), 2.70 (2 H, d, *J* 7.2, $SCCH_2$), 2.82 (2 H, ddd, *J* 14.4, 7.2 and 3.6, 2 × SCH*H*), 2.88 (2 H, ddd, *J* 14.4, 8.4 and 3.4, 2 × SCCH*H*), 3.10 (1 H, dd, *J* 13.9 and 5.7, PhCH*H*), 3.14 (1 H, dd, *J* 13.9 and 5.9, PhCH*H*), 4.56-4.62 (2 H, m, OCH_2), 4.89 (1 H, dt, *J* 7.9 and 5.7, COCH), 5.63 (1 H, dt, *J* 15.3 and 6.4, OCH_2CH), 5.87 (1 H, dt, *J* 15.3 and 7.2, OCH_2CH=C*H*), 5.93 (1 H, br d, *J* 7.7, NH), 7.09 (2 H, d, *J* 6.9, Ar), 7.23-7.29 (3 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 23.3, 25.2, 26.6, 27.9, 38.0, 44.1, 48.3, 53.2, 65.9, 127.0, 127.2, 128.7, 129.5, 131.4, 135.9, 169.7, 171.5; *m/z* (CI) 394.1528 (M^+, $C_{20}H_{28}NO_3S_2$ requires 394.1511), 305 (15%), 220 (22), 188 (26), 187 (82), 178 (12), 86 (68), 84 (100).

(*E*)-4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl *N*-benzyloxycarbonylaminoacetate (298)



From procedure D: 49% yield as a pale yellow oil; ν_{max}(film)/cm^{-1} 3350, 2933, 1722, 1523, 1191, 1053,975; δ_H (600 MHz, $CDCl_3$) 1.55 (3 H, s, Me), 1.90-2.02 (2 H, m, SCH_2CH_2), 2.69 (2 H, d, *J* 7.1, $SCCH_2$), 2.82 (2 H, ddd, *J* 14.5, 10.8 and 3.6, 2 × SCH*H*), 2.87 (2 H, ddd, *J* 14.5, 8.5 and 3.5, 2 × SCH*H*), 4.00 (2 H, d, *J* 5.6, $COCH_2$), 4.64 (2 H, d, *J* 6.4, OCH_2), 5.13 (2 H, br s, $PhCH_2$), 5.26 (1 H, br s, NH), 5.67 (1 H, ddt, *J* 15.4, 6.4 and 1.2, OCH_2CH), 5.88 (1 H, ddt, *J* 15.4, 7.1 and 1.0, $OCH_2CH=CH$), 7.30-7.36 (5 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 25.2, 26.6, 27.9, 42.9, 44.0, 48.3, 65.8, 67.2, 127.1, 128.25, 128.34, 128.7, 131.3, 136.3, 156.3, 169.9; *m/z* (FAB) 418.1109 ($[MNa]^+$, $C_{19}H_{25}NO_4S_2Na$ requires 418.1123), 292 (11%), 246 (20), 199 (14), 176 (19), 178 (12).

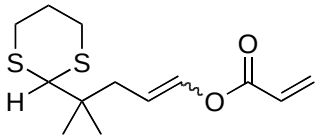
(*S*)-4-(2-Methyl-1,3-dithian-2-yl)but-2-en-1-yl 2-*N*-(*tert*-butyloxycarbonyl)aminopropionate (299)



From procedure D: 82% yield as a pale yellow oil; $[\alpha]_D^{20}$ – 20.1 (c 1.0 g dm^{-3}, $CHCl_3$); ν_{max}(film)/cm^{-1} 3374, 2977, 1714, 1367, 1164, 1069; δ_H (600 MHz, $CDCl_3$) 1.37 (3 H, s, COCH*Me*), 1.43 (9 H, s, 3 × OCMe), 1.54 (3 H, s, SCMe), 1.91-2.00 (2 H, m, SCH_2CH_2), 2.69 (2 H, d, *J* 7.2, $SCCH_2$), 2.81 (2 H, ddd, *J* 14.4, 7.1 and 3.3, 2 × SCH*H*), 2.87 (2 H, ddd, *J* 14.4, 8.7 and 3.1, 2 × SCH*H*), 4.31 (1 H, app. quintet, *J* 7.2, COCH), 4.59 (1 H, dd, *J* 12.8 and 6.3, OCH*H*), 4.62 (1 H, dd, *J* 12.8 and 6.3, OCH*H*), 5.04 (1 H, br d, *J* 6.6, NH), 5.66 (1 H, dt, *J* 15.3 and 6.3, OCH_2CH), 5.85 (1 H, dt, *J* 15.3 and 7.2, $OCH_2CH=CH$); δ_C (150 MHz, $CDCl_3$) 18.9, 25.2, 26.6, 27.8, 28.4, 44.1, 49.3, 65.6, 79.9, 127.3, 130.9, 155.2, 173.2; *m/z* (FAB) 398.1421

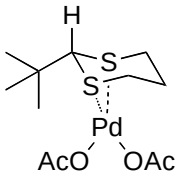
([MNa]$^+$, $C_{17}H_{29}NO_4S_2Na$ requires 398.1436), 375 (9%), 349 (14), 323 (30), 199 (42), 175 (89), 173 (100).

4-(2-Methyl-1,3-dithian-2-yl)but-1-en-1-yl propenoate (300)



From procedure D: 40% yield as a pale yellow oil (*E:Z* 1:1.4); ν_{max}(film)/cm^{-1} 2962, 1735, 1405, 1255, 1168, 1079; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.08 (6 H, s, 2 × Me), 1.77-1.84 (1 H, m, $SCH_2CH\mathit{H}$), 2.08 (1 H, dtt, *J* 14.2, 3.4 and 3.2, $SCH_2CH\mathit{H}$), 2.19 (2 H, dd, *J* 8.2 and 1.2, CCH_2), 2.87-2.90 (4 H, m, 2 × SCH_2), 3.98 (1 H, s, SCCH), 5.50 (1 H, dt, *J* 12.2 and 8.2, OCH=C*H*), 5.93 (1 H, dd, *J* 10.5 and 1.2, COCH=CH*H*), 6.15 (1 H, dd, *J* 17.3 and 10.5, COCH), 6.51 (1 H, dd, *J* 17.3 and 1.2, COCH=CH*H*), 7.22 (1 H, dt, *J* 12.2 and 1.2, OCH); *Z*-isomer: 1.10 (6 H, s, 2 × Me), 1.77-1.84 (1 H, m, $SCH_2CH\mathit{H}$), 2.08 (1 H, dtt, *J* 14.2, 3.4 and 3.2, $SCH_2CH\mathit{H}$), 2.37 (2 H, dd, *J* 7.9 and 1.2, CCH_2), 2.87-2.90 (4 H, m, 2 × SCH_2), 4.03 (1 H, s, SCCH), 5.00 (1 H, td, *J* 7.9 and 6.4, OCH=C*H*), 5.93 (1 H, dd, *J* 10.4 and 1.2, COCH=CH*H*), 6.17 (1 H, dd, *J* 17.4 and 10.4, COCH), 6.53 (1 H, dd, *J* 17.4 and 1.2, COCH=CH*H*), 7.20 (1 H, dt, *J* 6.4 and 1.2, OCH); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 25.2, 26.2, 31.4, 38.0, 38.7, 60.2, 110.9, 127.7, 132.4, 137.6, 163.3; *Z*-isomer: 25.2, 26.2, 31.5, 35.1, 39.1, 60.5, 110.4, 127.8, 132.4, 136.0, 163.3; *m/z* (EI) 272.0903 (M^+, $C_{13}H_{20}S_2O_2$ requires 272.0899), 217 (11%), 200 (12), 161 (30), 121 (27), 119 (100).

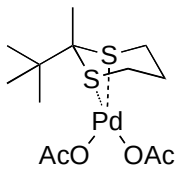
***S,S'*-(2-*tert*-Butyl-1,3-dithianyl)palladium acetate (301)**



Palladium acetate (320 mg, 1.31 mmol) was added to a solution of 2-*tert*-butyl-1,3-dithiane **256**[176] (231 mg, 1.31 mmol) in DCM (3 ml) and the mixture was stirred at rt for 90 min. The solvent was removed *in vacuo* to give the product (520 mg, 1.31 mmol, quant.) as dark orange needles, dec. > 125 °C; ν_{max}(film)/cm^{-1} 2970, 1739,

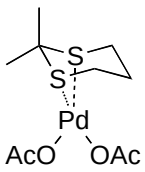
1618, 1366, 1307, 1217; δ_H (600 MHz, $CDCl_3$) 1.31 (9 H, s, 3 × CMe), 1.96 (6 H, s, 2 × OAc), 2.77 (1 H, app. dquintet, *J* 15.1 and 2.4, $SCH_2CH\mathit{H}$), 2.90 (2 H, br td, *J* 13.4 and 3.3, 2 × SC$H\mathit{H}$), 3.82 (2 H, ddd *J* 13.4, 4.8 and 2.0, 2 × SC$H\mathit{H}$), 4.71-4.75 (2 H, m, $SCH_2CH\mathit{H}$ and SCH); δ_C (150 MHz, $CDCl_3$) 22.9, 27.9, 33.9, 35.0, 40.4, 85.4, 178.5.

_S,S'_-(2-*tert*-Butyl-2-methyl-1,3-dithianyl)palladium acetate (302)



Palladium acetate (252 mg, 1.03 mmol) was added to a solution of 2-*tert*-butyl-2-methyl-1,3-dithiane **257**[176] (196 mg, 1.03 mmol) in DCM (3 ml) and the mixture was stirred at rt for 90 min. The solvent was removed *in vacuo* to give the product (427 mg, 1.03 mmol, quant.) as dark orange needles, dec. > 120 °C; ν_{max}(film)/cm^{-1} 2970, 1739, 1366, 1217, 1108; δ_H (600 MHz, $CDCl_3$) 1.57 (9 H, s, 3 × CMe), 1.71 (3 H, s, SCMe), 2.03 (6 H, s, 2 × OAc), 2.67 (1 H, dtt, *J* 15.3, 6.0 and 2.0, $SCH_2CH\mathit{H}$), 2.97 (2 H, br td, *J* 13.4, and 4.1, 2 × SC$H\mathit{H}$), 3.87 (2 H, ddd *J* 14.4, 6.2 and 2.0, 2 × SC$H\mathit{H}$), 4.68 (1 H, dtt, *J* 15.3, 8.9 and 6.2, $SCH_2CH\mathit{H}$); δ_C (150 MHz, $CDCl_3$) 22.0, 22.8, 27.9, 30.2, 32.8, 38.9, 80.1, 178.5.

_S,S'_-(2,2-Dimethyl-1,3-dithianyl)palladium acetate (303)



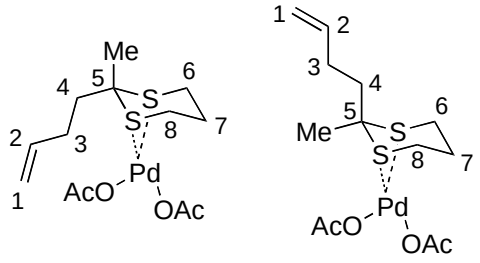
Palladium acetate (236 mg, 1.05 mmol) was added to a solution of 2,2-dimethyl-1,3-dithiane **258**[38] (155 mg, 1.05 mmol) in DCM (3 ml) and the mixture was stirred at rt for 90 min. The solvent was removed *in vacuo* to give the product (391 mg, 1.03 mmol, quant.) as dark orange needles, dec. > 120 °C; ν_{max}(film)/cm^{-1} 2968, 1738, 1366, 1219, 1105; δ_H (600 MHz, $CDCl_3$) 1.70 (3 H, s, SCMe), 1.98 (6 H, s, 2 × OAc), 2.25 (3 H, s, SCMe), 2.62 (1 H, dtt, *J* 15.1, 3.7 and 1.6, $SCH_2CH\mathit{H}$), 2.91 (2

H, ddd, *J* 14.3, 13.2 and 3.7, 2 × SCH*H*), 3.63 (2 H, ddd *J* 14.3, 5.3 and 1.6, 2 × SCH*H*), 4.56 (1 H, dtt, *J* 15.1, 13.2 and 5.3, SCH_2CH*H*); δ_C (150 MHz, $CDCl_3$) 22.7, 27.3, 30.5, 32.1, 32.6, 66.1, 178.5.

NMR Experiments with Pd-Dithiane Complexes

Palladium acetate (25 mg, 0.10 mmol) was added to a solution of dithiane (0.10 mmol) in $CDCl_3$ (1 ml) in an NMR tube and the mixture was immediately cooled to 269 K inside a Bruker 600 MHz spectrometer. Spectra were recorded as a function of time to observe the different intermediates formed.

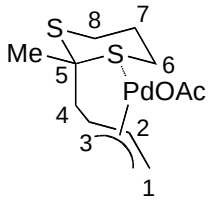
***S,S'*-(2-methyl-2-but-3-enyl-1,3-dithianyl)palladium acetate (304)**



304a **304b**

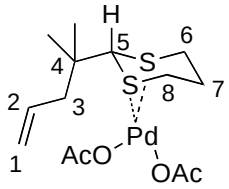
Spectra recorded after 10 min at 269 K; (**304a**:**304b** 52:48); δ_H (600 MHz, $CDCl_3$) **304a**: 2.00 (6H, s, OAc), 2.06 (4 H, br s, H-3 and H-4), 2.24 (3 H, s, 5*Me*), 2.63 (1 H, br d, *J* 13.3, H-7*eq*), 2.88 (2 H, ddd, *J* 14.2, 13.3 and 3.8, H-6*ax* and H-8*ax*), 3.59 (2 H, ddd, *J* 14.2, 5.4 and 2.0, H-6*eq* and H-8*eq*), 4.52 (1 H, app. qt, *J* 13.3 and 5.4, H-7*ax*), 5.10 (1 H, app. dq, *J* 10.4 and 1.3, H-1*cis*), 5.13 (1 H, dq, *J* 17.2 and 1.4, H-1*trans*), 5.80 (1 H, ddt, *J* 17.2, 10.4 and 6.2, H-2); **304b**: 1.69 (3 H, s, 5*Me*), 2.00 (6 H, s, OAc), 2.20 (2 H, m, H-3), 2.65 (1 H, br d, *J* 13.3, H-7*eq*), 2.69 (2 H, m, H-4), 2.91 (2 H, ddd, *J* 14.2, 13.2 and 3.8, H-6*ax* and H-8*ax*), 3.64 (2 H, ddd, *J* 14.2, 5.5 and 2.0, H-6*eq* and H-8*eq*), 4.58 (1 H, app. qt, *J* 13.3 and 5.5, H-7*ax*), 5.08 (1 H, app. dq, *J* 10.1 and 1.0, H-1*cis*), 5.09 (1 H, dq, *J* 17.0 and 1.1, H-1*trans*), 5.74 (1 H, ddt, *J* 17.0, 10.1 and 5.8, H-2); δ_C (150 MHz, $CDCl_3$) **304a**: 2 × 23.0 (2 × CO*Me*), 25.3 (C-3), 29.1 (C-5Me), 30.4 (C-7), 2 × 31.9 (C-6 and C-8), 36.5 (C-4), 69.7 (C-5*q*), 117.8 (C-1), 134.5 (C-2), 2 × 178.7 (2 × C=O); **304b**: 2 × 23.1 (2 × CO*Me*), 24.3 (C-5Me), 28.2 (C-3), 31.1 (C-7), 2 × 32.2 (C-6 and C-8), 43.1 (C-4), 70.5 (C-5*q*), 117.3 (C-1), 135.1 (C-2), 2 × 178.6 (2 × C=O).

_S_-(1,2,3-η)-4-(2-Methyl-1,3-dithian-2-yl)butanyl palladium acetate (305)



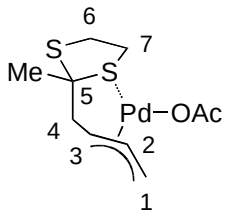
Spectra recorded after 10 min at 322 K; δ_H (600 MHz, $CDCl_3$) 1.85 (3 H, s, 5-Me), 1.93 (1 H, m, H-7*ax*), 1.94 (1 H, m, H-4), 2.06 (3 H, br s, OAc), 2.19 (1 H, m, H-7*eq*), 2.63 (1 H, dd, *J* 13.7 and 11.5, H-4), 2.83 (1 H, ddd, *J* 14.5, 6.7 and 2.9, H-8*eq*), 3.10 (1 H, ddd, *J* 14.5, 10.5 and 2.7, H-8*ax*), 3.14 (1 H, app. dt, *J* 12.2 and 1.1, H-1*trans*), 3.16 (1 H, ddd, *J* 14.1, 11.2 and 2.6, H-6*ax*), 3.35 (1 H, ddd, *J* 14.1, 6.0 and 2.4, H-6*eq*), 3.71 (1 H, td, *J* 11.0 and 3.2, H-3), 4.13 (1 H, dd, *J* 6.8 and 1.1, H-1*cis*), 5.66 (1 H, ddd, *J* 12.2, 11.0 and 6.8, H-2); δ_C (150 MHz, $CDCl_3$) 21.5 (br, CO*Me*), 24.4 (C-7), 27.6 (C-8), 28.5 (C-5Me), 30.9 (br, C-6), 44.0 (C-4), 61.8 (C-1), 65.1 (br C-5*q*), 78 (v. br C-3), 115.0 (C-2), 176.2 (br, C=O).

_S,S'_-(2-(1,1-dimethylbut-3-enyl)-1,3-dithianyl)palladium acetate (306)



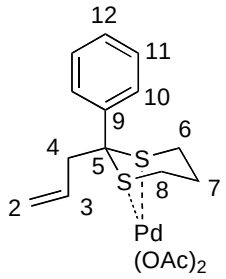
Spectra recorded after 10 min at 269 K; δ_H (400 MHz, $CDCl_3$) 1.33 (6 H, s, 4*Me*$_2$), 1.94 (6 H, s, OAc), 2.13 (2 H, br d, *J* 7.5, H-3), 2.74 (1 H, br d, *J* ~14, H-7*eq*), 2.79 (2 H, br t, *J* ~13, H-6*ax* and H-8*ax*), 3.71 (2 H, br d, *J* ~13, H-6*eq* and H-8*eq*), 4.53 (1 H, br q, *J* ~13.5, H-7*ax*), 4.69 (1 H, s, H-5), 5.05 (1 H, dd, *J* 16.9 and 2.0, H-1*trans*), 5.08 (1 H, br dd, *J* 10.2 and 2.0, H-1*cis*), 5.65 (1 H, ddt, *J* 16.9, 10.2 and 7.5, H-2); δ_C (100 MHz, $CDCl_3$) 23.2 (CO*Me*), 25.6 (2 × 4*Me*), 34.0 (C-7), 37.4 (C-4q), 39.9 (C-6 and C-8), 43.9 (C-3), 83.1 (C-5), 120.1 (C-1), 132.2 (C-2), 178.7 (2 × C=O).

_S_-(1,2,3-η)-4-(2-Methyl-1,3-dithiolan-2-yl)butanyl palladium acetate (310)



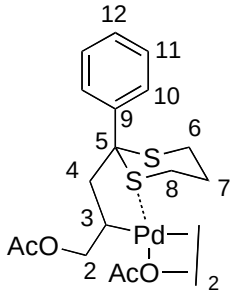
Spectra recorded after 120 min at 298 K; δ_H (600 MHz, $CDCl_3$) 1.87 (3 H, s, 5-Me), 2.01 (3 H, s, OAc), 2.18 (1 H, dd, *J* 14.4 and 3.5, H-4*cis*), 2.33 (1 H, dd, *J* 14.4 and 11.4, H-4*trans*), 3.19 (1 H, d, *J* 12.4, H-1*trans*), 3.52 (1 H, ddd, *J* 11.8, 9.5 and 4.5, H-6*cis*), 3.60 (1 H, dt, *J* 11.8 and 4.1, H-7*trans*), 3.97 (1 H, ddd, *J* 11.8, 9.5 and 4.5, H-7*cis*), 4.02 (1 H, m, H-6*trans*), 4.12 (1 H, m, H-3), 4.13 (1 H, d, *J* 7.0, H-1*cis*), 5.73 (1 H, ddd, *J* 12.4, 10.4 and 7.0, H-2); δ_C (150 MHz, $CDCl_3$) 22.0 (CO*Me*), 34.2 (C-5Me), 43.9 (C-7), 45.3 (C-6), 47.5 (C-4), 63.1 (C-1), 80.7 (C-3), 83.9 (C-5*q*), 116.3 (C-2), 176.5 (C=O).

_S,S'_-(2-Allyl-2-phenyl-1,3-dithianyl)palladium acetate (312-1)



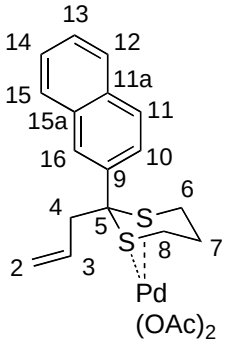
Spectra recorded after 1 min at 298 K; δ_H (600 MHz, $CDCl_3$) 1.98 (6 H, s, OAc), 2.36 (1 H, dtt, *J* 15.2, 3.6 and 2.4, H-7*eq*), 2.73 (2 H, ddd, *J* 14.0, 13.0 and 3.6, H-8*ax* and H-6*ax*), 3.47 (2 H, app. dt, *J* 7.2 and 1.1, 2 × H-4), 3.52 (2 H, ddd, *J* 14.0, 4.9 and 2.4, H-6*eq* and H-8*eq*), 4.52 (1 H, m, H-7*ax*), 5.16 (1 H, ddt, *J* 10.0, 1.3 and 0.9, H-2*cis*), 5.22 (1 H, ddt, *J* 17.0, 10.0 and 7.3, H-3), 5.45 (1 H, ddt, *J* 17.0, 1.3 and 1.1, H-2*trans*), 7.05 (2 H, m, 2 × H-10), 7.40 (1 H, m, H-12), 7.52 (2 H, m, 2 × H-11); δ_C (150 MHz, $CDCl_3$) 2 × 22.9 (2 × CO*Me*), 31.8 (C-7), 2 × 33.7 (C-6 and C-8), 50.9 (C-4), 79.4 (C-5), 119.0 (C-2), 123.3 (C-3), 125.3 (2 × C-10), 129.8 (C-12), 129.9 (2 × C-11), 131.9 (C-9), 2 × 178.6 (2 × C=O).

_C,S_-{1-Acetoxy-3-(2-phenyl-1,3-dithian-2-yl)}propan-2-ylpalladium acetate dimer (312)



Spectra recorded after 90 min at 298 K; δ_H (600 MHz, $CDCl_3$) 1.66 (1 H, dd, *J* 15.1 and 6.2, H-4*cis*), 1.86 (1 H, dd, *J* 15.1 and 11.1, H-4*trans*), 1.93 (3 H, s, CH_2OCOMe), 1.95 (3 H, s, PdO*Ac*), 2.04 (1 H, m, H-7*eq*), 2.67 (1 H, m, H-8*ax*), 2.68 (1 H, m, H-7*ax*), 2.77 (1 H, m, H-6*ax*), 2.78 (1 H, m, H-8*eq*), 2.97 (1 H, m, H-6*eq*), 3.28 (1 H, dddd, *J* 12.0, 11.1, 6.2 and 4.1, H-3), 3.89 (1 H, dd, *J* 10.3 and 4.1, H-2*cis*), 4.18 (1 H, dd, *J* 12.0 and 10.3, H-2*trans*), 7.28 (1 H, m, H-12), 7.38 (2 H, m, 2 × H-11), 7.88 (2 H, m, 2 × H-10); δ_C (150 MHz, $CDCl_3$) 21.0 (PdOCO*Me*), 22.2 (C-7), 24.3 (CH_2OCOMe), 26.5 (C-8), 29.8 (C-6), 32.2 (C-3), 53.7 (C-4), 68.7 (C-5), 69.6 (C-2), 127.9 (C-12), 128.2 (2 × C-10), 128.9 (2 × C-11), 140.1 (C-9), 171.4 (CH_2OCOMe), 180.5 (PdO*C*OMe); *m*/*z* (EI) 474.9884 ($[MCH_3]^+$, $[C_{18}H_{25}O_4PdS_2]^+$ requires 475.0224).

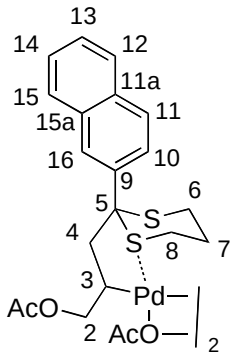
_S,S'_-(2-Allyl-2-naphth-2-yl-1,3-dithianyl)palladium acetate (314-1)



Spectra recorded after 3 min at 278 K; δ_H (600 MHz, $CDCl_3$) 2.08 (6 H, s, OAc), 2.32 (1 H, br dtt, *J* 15.2, ~5 and ~3, H-7*eq*), 2.69 (1 H, v. br, H-8*ax*), 2.91 (1 H, v. br, H-6*ax*), 3.53 (1 H, v. br, H-4), 3.57 (2 H, v. br, H-6*eq* and H-8*eq*), 3.63 (1 H, v. br, H-4), 4.55 (1 H, br tt, *J* ~14 and ~5, H-7*ax*), 5.18 (1 H, dq, *J* 17.0 and 1.2, H-2*trans*),

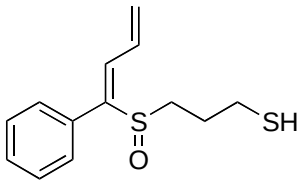
5.23 (1 H, ddt, *J* 10.0, 1.2 and 0.7, H-2*cis*), 5.50 (1 H, ddt, *J* 17.0, 1.0.0 and 7.3, H-3), 7.16 (1 H, dd, *J* 8.6 and 2.0, H-10), 7.51 (1 H, br d, *J* 2.0, H-16), 7.61 (2 H, m, H-13 and H-14), 7.86 (1 H, m, H-15), 7.90 (1 H, m, H-12), 8.01 (1 H, d, *J* 8.6, H-11); δ_C (150 MHz, $CDCl_3$) 2 × 23.0 (2 × CO*Me*), 31.8 (C-7), 2 × 33.9 (C-6 and C-8), 50.8 (C-4), 79.6 (C-5), 121.3 (C-10), 123.4, (C-2), 125.6 (C-16), 127.6 (C-3), 127.9 (C-13), 2 × 128.0 (C-12 and C-14), 128.1 (C-15), 130.3 (C-11), 132.1 (C-9), 132.7 (C-15a), 133.2 (C-11a), 2 × 178.7 (2 × C=O).

_C,S_-{1-Acetoxy-3-(2-(2-naphthalen-2-yl)-1,3-dithian-2-yl)}propan-2-ylpalladium acetate dimer (314)



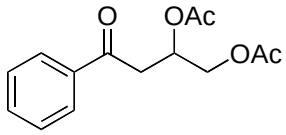
Spectra recorded after 160 min at 298 K; δ_H (600 MHz, $CDCl_3$) 1.78 (1 H, dd, *J* 15.2 and 6.2, H-4*cis*), 1.96 (3 H, s, CH_2OAc), 1.97 (1 H, dd, *J* 15.2 and 11.4, H-4*trans*), 1.99 (3 H, s, PdO*Ac*), 2.06 (1 H, m, H-7*eq*), 2.69 (1 H, m, H-8*ax*), 2.71 (1 H, m, H-7*ax*), 2.86 (1 H, m, H-8*eq*), 2.87 (1 H, app. dd, *J* 14.6 and 12.1, H-6*ax*), 2.98 (1 H, dt, *J* 14.6 and ~3.5, H-6*eq*), 3.38 (1 H, dddd, *J* 12.1, 11.4, 6.2 and 4.2, H-3), 3.97 (1 H, dd, *J* 10.5 and 4.2, H-2*cis*), 4.36 (1 H, dd, *J* 12.1 and 10.5, H-2*trans*), 7.47 (1 H, m, H-14), 7.48 (1 H, m, H-13), 7.81 (1 H, m, H-15), 7.83 (1 H, d, *J* 8.7, H-11), 7.87 (1 H, m, H-12), 7.95 (1 H, dd, *J* 8.7 and 2.1, H-10), 8.39 (1 H, d, *J* 2.1, H-16); δ_C (150 MHz, $CDCl_3$) 21.1 (PdOCO*Me*), 22.2 (C-7), 24.4 (CH_2OCOMe), 26.5 (C8), 29.9 (C-6), 32.5 (C-3), 53.4 (C-4), 68.7 (C-5), 69.7 (C-2), 125.7 (C-10), 126.6 (C-13), 126.8 (C-14), 127.5 (C-15), 127.6 (C-16), 128.6 (C-11), 128.7 (C-12), 132.6 (C-11a), 133.1 (C-15a), 137.4 (C-9), 171.4 (CH_2OCOMe), 180.6 (PdO*C*OMe); *m*/*z* (EI) 511.0087 (M+H, $C_{21}H_{23}O_4PdS_2$ requires 511.0070).

1-(3-Mercaptopropyl)sulfinyl-1-phenylbutadiene (316)



A mixture of 2-allyl-2-phenyl-1,3-dithiane **272** (14 mg, 0.06 mmol) and palladium acetate (13 mg, 0.06 mmol) in $CDCl_3$ (1 ml) was stirred at rt for 90 min. Copper (II) chloride (32 mg, 0.24 mmol) was added; the mixture was stirred for a further 3 h at rt, then filtered through a plug of celite and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc-petrol 1:9) to give the *sulfoxide* (6 mg, 0.024 mmol, 40%) as a colourless oil; ν_{max}(film)/cm^{-1} 2925, 1443, 1421, 915, 724, 699; δ_H (600 MHz, $CDCl_3$) 1.99-2.21 (2 H, m, $HSCH_2CH_2$), 2.43 (1 H, ddd, *J* 14.1, 7.0 and 2.4, HSCH*H*), 2.50 (1 H, ddd, *J* 14.1, 9.6 and 2.1, HSCH*H*), 2.57 (1 H, ddd, *J* 14.1, 7.1 and 2.1, SOCH*H*), 2.91 (1 H, ddd, *J* 14.1, 10.9 and 1.6, SOCH*H*), 5.34 (1 H, d, *J* 10.3, CH=CH*H*), 5.65 (1 H, d, *J* 17.0, CH=CH*H*), 6.28 (1 H, ddd, *J* 17.0, 10.9 and 10.3, CH_2=C*H*), 7.38-7.46 (5 H, m, Ar), 7.89 (1 H, d, *J* 10.9, CH_2=CHC*H*); δ_C (150 MHz, $CDCl_3$) 28.1, 29.2, 31.7, 123.9, 129.1, 129.4, 130.1, 131.4, 132.5, 134.3, 141.8.

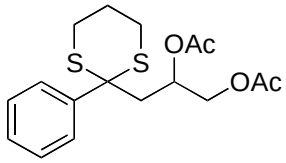
4-Oxo-4-phenylbutane-1-2-diyl diacetate (317)



Iodosobenzene diacetate (122 mg, 0.38 mmol) in $CDCl_3$ (1 ml) was added dropwise to a solution of 2-allyl-2-phenyl-1,3-dithiane **272** (44 mg, 0.19 mmol) and palladium acetate (9 mg, 0.037 mg) in $CDCl_3$ (1 ml). The mixture was stirred at rt for 18 h, then concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc–petrol 1:4) to give the *diacetate* (11 mg, 0.042 mmol, 22%) as a yellow oil; ν_{max}(film)/cm^{-1} 1742, 1687, 1370, 1227, 1044; δ_H (600 MHz, $CDCl_3$) 2.04 (3 H, s, OAc), 2.07 (3 H, s, OAc), 3.23 (1 H, dd, *J* 17.1 and 6.6, COCH*H*), 3.40 (1 H, dd, *J* 17.1 and 6.7, COCH*H*), 4.22 (1 H, dd, *J* 11.9 and 5.4, OCH*H*), 4.39 (1 H, dd, *J* 11.9 and 3.6, OCH*H*), 5.63 (1 H, dddd, *J* 6.7, 6.6, 5.4 and 3.6, OCH), 7.48 (2 H, dd, *J* 8.1

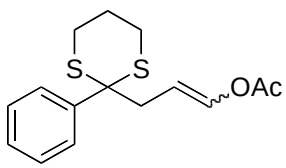
and 7.5, Ar), 7.59 (2 H, tt, *J* 7.5 and 1.1, Ar), 7.95 (1 H, dd, *J* 8.1 and 1.1, Ar); δ_C (150 MHz, $CDCl_3$) 20.9, 21.1, 39.4, 64.7, 68.2, 128.2, 128.9, 133.7, 136.6, 170.3, 170.8, 196.1; *m/z* (CI) 265.1074 (M+H, $C_{14}H_{17}O_5$ requires 265.1076), 205 (11%), 146 (10), 145 (100).

3-(2-Phenyl-1,3-dithian-2-yl)propane-1,2-diyl diacetate (320) (Procedure E)



Procedure E: A solution of 2-allyl-2-phenyl-1,3-dithiane **272** (50 mg, 0.21 mmol), palladium acetate (5 mg, 0.021 mmol) and iodosobenzene diacetate (68 mg, 0.21 mmol) was stirred at rt for 48 h. Water (2 ml) was added and the organic layer was washed with brine (2 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified to give the *diacetate* (13 mg, 0.037 mmol, 18%) as a yellow oil; ν_{max}(film)/cm^{-1} 2919, 1738, 1370, 1219, 1046, 702; δ_H (600 MHz, $CDCl_3$) 1.76 (3 H, s, OAc), 1.91-1.95 (2 H, m, SCH_2CH_2), 2.01 (3 H, s, OAc), 2.27 (1 H, dd, *J* 15.2 and 2.5, SCCH*H*), 2.46 (1 H, dd, *J* 15.2 and 8.2, SCCH*H*), 2.67-2.74 (4 H, m, 2 × SCH_2), 3.84 (1 H, dd, *J* 11.4 and 5.2, OCH*H*), 4.03 (1 H, dd, *J* 11.7 and 4.1, OCH*H*), 5.15 (1 H, dddd, *J* 8.2, 5.2, 4.1 and 2.5, OCH), 7.27 (1 H, d, *J* 7.2, Ar), 7.39 (2 H, dd, *J* 7.8 and 7.2, Ar), 7.89 (2 H, d, *J* 7.8, Ar); δ_C (150 MHz, $CDCl_3$) 20.9, 21.0, 24.9, 27.6, 27.7, 45.7, 56.9, 65.5, 67.6, 127.4, 128.8, 128.9, 140.8, 170.0, 170.7; *m/z* (EI) 354.0963 (M^+, $C_{17}H_{22}O_4S_2$ requires 354.0954), 195 (27%), 177 (36), 105 (24), 86 (59), 84 (100).

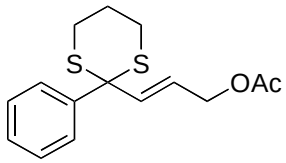
3-(2-Phenyl-1,3-dithian-2-yl)prop-1-en-1-yl acetate (318)



Isolated from procedure E: (4 mg, 0.014 mmol, 6%) as a yellow oil (*E:Z* 1:2); ν_{max}(film)/cm^{-1} 2905, 1755, 1214, 1093, 702; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.92-1.96 (2 H, m, SCH_2CH_2), 2.07 (3 H, s, OAc), 2.65-2.71 (4 H, m, 2 × SCH_2), 2.87 (2

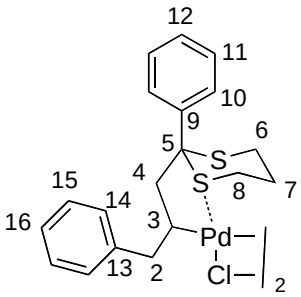
H, d, *J* 7.5, $SCCH_2$), 5.21 (1 H, dt, *J* 12.5 and 7.5, OCH=C*H*), 7.04 (1 H, d, *J* 12.5, OCH), 7.26 (1 H, t, *J* 7.2, Ar), 7.39 (2 H, dd, *J* 8.5 and 7.2, Ar), 7.90 (2 H, d, *J* 8.5, Ar); *Z*-isomer: 1.92-1.96 (2 H, m, SCH_2CH_2), 2.06 (3 H, s, OAc), 2.65-2.71 (4 H, m, 2 × SCH_2), 2.87 (2 H, d, *J* 7.5, $SCCH_2$), 4.79 (1 H, td, *J* 7.5 and 6.7, OCH=C*H*), 7.03 (1 H, d, *J* 6.7, OCH), 7.28 (1 H, t, *J* 7.3, Ar), 7.38 (2 H, dd, *J* 8.4 and 7.3, Ar), 7.92 (2 H, d, *J* 8.4, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 20.8, 24.9, 27.6, 27.7, 43.3, 58.6, 108.3, 127.2, 128.8, 129.2, 137.8, 141.4, 168.0; *Z*-isomer: 20.8, 25.0, 27.6, 27.7, 39.8, 58.5, 107.1, 127.3, 128.7, 128.9, 136.4, 141.3, 167.8; *m/z* (CI) 295.0819 (M+H, $C_{15}H_{19}O_2S_2$ requires 295.0827), 235 (30%), 195 (21), 161 (11), 84 (10).

(*E*)-3-(2-Phenyl-1,3-dithian-2-yl)prop-2-en-1-yl acetate (319)



Isolated from procedure E: (1 mg, 0.007 mmol, 2%) as a yellow oil; ν_{max}(film)/cm^{-1} 2925, 1741, 1445, 1365, 1227, 1031; δ_H (600 MHz, $CDCl_3$) 1.95 (1 H, dtt, *J* 14.1, 9.3 and 3.0, SCH_2CH*H*), 2.02-2.12 (4 H, m, SCH_2CH*H* and OAc), 2.73 (2 H, ddd, *J* 14.2, 7.4 and 3.0, 2 × SCH*H*), 2.90 (2 H, ddd, *J* 14.2, 9.3 and 2.8, 2 × SCH*H*), 4.69 (2 H, d, *J* 6.0, OCH_2), 5.86 (1 H, dt, *J* 15.8 and 6.0, OCH_2CH), 6.02 (1 H, d, *J* 15.8, SCCH), 7.29 (1 H, t, *J* 7.3, Ar), 7.37 (2 H, dd, *J* 8.3 and 7.3, Ar), 7.77 (2 H, d, *J* 8.3, Ar); δ_C (150 MHz, $CDCl_3$) 21.1, 24.6, 28.6, 58.1, 64.0, 128.1, 128.6, 128.7, 128.8, 136.4, 140.9, 170.9; *m/z* (EI) 294.0745 (M^+, $C_{15}H_{18}O_2S_2$ requires 294.0745), 178 (47%), 160 (21), 86 (58), 84 (100).

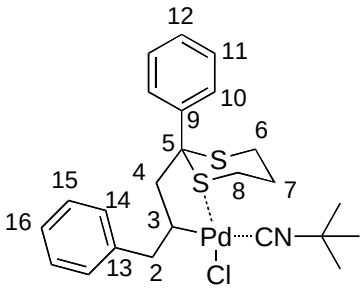
_C,S_-{1-Phenyl-3-(2-phenyl-1,3-dithian-2-yl)propan-2-ylpalladium chloride dimer (321)



Phenyltributylstannane (0.085 mmol) and *bis*(acetonitrile)dichloropalladium (22 mg, 0.085 mmol) were added to a solution of 2-allyl-2-phenyl-1,3-dithiane (0.085 mmol) in $CDCl_3$ (1 ml) in an NMR tube and the mixture was immediately cooled to 269 K inside a Bruker 600 MHz spectrometer. Spectra were recorded as a function of time to observe the different intermediates formed.

Spectra recorded after 2 h at 298 K; δ_H (600 MHz, $CDCl_3$) 0.99 (1 H, br m, H-4*cis*), 1.83 (1 H, br m, H-4*trans*), 1.95 (2 H, br m, 2 × H-7), 2.62 (1 H, br m, H-6*ax*), 2.67 (1 H, br m, H-8*ax*), 2.76 (1 H, br, m, H-8*eq*), 2.85 (1 H, br m, H-2*trans*), 3.03 (1 H, br, m, H-2*cis*), 3.04 (1 H, br m, H-6*eq*), 3.66 (1 H, br m, H-3), 7.14 (1 H, br m, H-16), 7.22 (2 H, br m, 2 × H-14), 7.28 (2 H, br m, 2 × H-15), 7.35 (3 H, br m, 2 × H-11 and H-12), 7.74 (2 H, br m, 2 × H-10); δ_C (150 MHz, $CDCl_3$) 22.7 (C-7), 26.4 (C-8), 30.5 (C-6), 45.4 (C-3), 45.6 (C-2), 54.3 (C-4), 67.7 (C-5), 125.6 (C-16), 127.9 (C-12), 128.1 (2 × C-10), 128.3 (2 × C-14), 128.8 (2 × C-15), 129.5 (2 × C-11), 139.7 (C-9), 140.3 (C-13); *m*/*z* (EI) 490.9487 (M+Cl, $C_{19}H_{21}Cl_2PdS_2$ requires 490.9481).

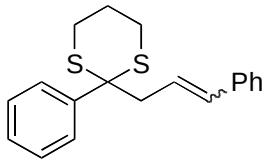
(*tert*-Butylisocyano)-*C,S*-{1-phenyl-3-(2-phenyl-1,3-dithian-2-yl)propan-2-ylpalladium chloride (322)



tert-Butylisocyanide (10 µl, 0.085 mmol) was added to a solution of *C,S*-{1-phenyl-3-(2-phenyl-1,3-dithian-2-yl)propan-2-ylpalladium chloride dimmer **321** (0.085 mmol) in $CDCl_3$ (1 ml) in an NMR tube and the mixture was immediately cooled to 269 K inside a Bruker 600 MHz spectrometer. Spectra were recorded as a function of time to observe the different intermediates formed.

Spectra recorded after 1 min at 298 K; δ_H (600 MHz, $CDCl_3$) 1.45 (1 H, dd, *J* 15.1 and 5.4, H-4*cis*), 1.52 (9 H, s, ^{t}Bu), 1.95 (1 H, m, H-4*trans*), 1.96 (1 H, m, H-7*eq*), 2.35 (1 H, ddt, *J* 14.4, 11.7 and 3.0, H-7*ax*), 2.65 (1 H, br m, H-8*ax*), 2.66 (1 H, ddd, *J* 14.0, 11.7 and 3.0, H-6*ax*), 2.74 (1 H, br m, H-8*eq*), 2.89 (1 H, dd, *J* 14.4 and 9.8, H-2*trans*), 3.09 (1 H, dd, *J* 14.4 and 4.1, H-2*cis*), 3.40 (1 H, br dt, *J* 14.0, 3.0, H-6*eq*), 3.50 (1 H, m, H-3), 7.13 (1 H, m, H-16), 7.20 (2 H, m, 2 × H-14), 7.21 (2 H, m, 2 × H-15), 7.23 (1 H, m, H-12), 7.30 (2 H, m, 2 × H-11), 7.70 (2 H, m, 2 × H-10); δ_C (150 MHz, $CDCl_3$) 2.05 (3 × Me), 22.9 (C-7), 26.9 (C-8), 29.1 (C-6), 40.4 (C-3), 47.4 (C-2), 53.7 (br, C-4), 66.0 (C-5), 116.6 (*C*Me$_3$), 126.0 (C-16), 127.9 (C-12), 128.0 (2 × C-10), 128.5 (2 × C-14), 128.8 (2 × C-11), 128.9 (2 × C-15), 135.4 (PdCN), 139.7 (C-9), 141.2 (C-13).

1Phenyl-3-(2-phenyl-1,3-dithian-2-yl)prop-1-ene (323)

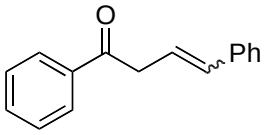


A mixture of 2-allyl-2-phenyl-1,3-dithiane (27 mg, 0.11 mmol), *bis*-(benzonitrile)palladium dichloride (44 mg, 0.11 mmol) and phenyltributylstannane (37 μl, 0.11 mmol) in benzene (1 ml) was stirred at rt for 4 h. Phenylmagnesium bromide (74 μl, 0.22 mmol) was added; the mixture was stirred for a further 30 min at rt, then filtered through a plug of celite and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc-petrol 1:9) to give the *alkene* (6 mg, 0.019 mmol, 17%) as a colourless oil (*E*:*Z* 1:1.9); ν_{max}(film)/cm^{-1} 1483, 1442, 1277, 959, 743, 699; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 1.96-1.88 (2 H, m, SCH_2CH_2), 2.63-2.74 (4 H, m, 2 × SCH_2), 2.88 (2 H, dd, *J* 7.3 and 1.2, $SCCH_2$), 5.96 (1 H, dt, *J* 15.9 and 7.3, PhCH=C*H*), 6.33 (1 H, dt, *J* 15.9 and 1.2, PhC*H*), 7.14-7.30 (6 H, m, Ar), 7.35-7.41 (2 H, m, Ar), 7.87-7.96 (2 H, m, Ar); *Z*-isomer: 1.96-1.88 (2 H, m, SCH_2CH_2), 2.63-2.74 (4 H, m, 2 × SCH_2), 3.05 (2 H, dd, *J* 7.0 and 1.8, $SCCH_2$), 5.66 (1 H, dt, *J* 11.8 and 7.0, PhCH=C*H*), 6.50 (1 H, dt, *J* 11.8 and 1.8, PhC*H*), 7.14-7.30 (6 H, m, Ar), 7.35-7.41 (2 H, m, Ar), 7.87-7.96 (2 H, m, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 25.1, 27.6, 48.9, 59.0, 123.7, 128.3, 128.4, 128.6, 128.7, 128.9, 129.0, 133.8, 137.2, 141.8; *Z*-isomer: 24.9, 27.7, 43.3, 58.8, 125.6, 128.3, 128.4, 128.5, 128.7, 128.8, 129.0, 131.7, 137.1, 141.7; *m/z* (CI) 313.1090 (M+H, $C_{19}H_{21}S_2$ requires 313.1085), 239 (13%), 195 (100), 86 (25), 84 (39).

Oxidation of Chloride Dimer 321 (Procedure F)

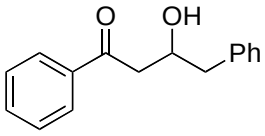
A mixture of 2-allyl-2-phenyl-1,3-dithiane **272** (27 mg, 0.11 mmol), *bis*-(acetonitrile)palladium dichloride (30 mg, 0.11 mmol) and phenyltributylstannane (37 μl, 0.11 mmol) in DCM (1 ml) was stirred at rt for 2 h. The solution was diluted with acetonitrile (1 ml); oxone (135 mg, 0.22 mmol) in water (1 ml) was added in one portion and the biphasic mixture was stirred vigorously for 18 h at rt. The crude reaction mixture was partitioned between water (5 ml) and DCM (5 ml); the organics were washed with water (10 ml), brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc-petrol 1:9).

1,4-Diphenylbut-3-en-1-one[342] (324)



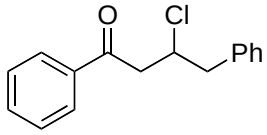
From procedure F: (8 mg, 0.036 mmol, 33 %) as a white solid (*E*:*Z* 13:1), m.p. 91-92 °C (lit. 92-93 °C); ν_{max}(film)/cm^{-1} 1684, 1448, 1208, 983, 750, 732, 688; δ_H (600 MHz, $CDCl_3$) *E*-isomer: 3.92 (2 H, dd, *J* 6.5 and 1.2, CH_2), 6.48 (1 H, dt, *J* 16.0 and 6.5, PhCH=C*H*), 6.55 (1 H, dt, *J* 16.0 and 1.2, PhC*H*), 7.22 (1 H, tt, *J* 7.4 and 1.7, Ar), 7.30 (2 H, dd, *J* 7.9 and 7.4, Ar), 7.39 (2 H, dd, *J* 8.5 and 1.3, Ar), 7.49 (2 H, dd, *J* 7.9 and 7.5, Ar), 7.58 (1 H, tt, *J* 7.3 and 1.3, Ar), 8.01 (2 H, dd, *J* 8.2 and 1.1, Ar); *Z*-isomer: 4.00 (2 H, dd, *J* 7.1 and 1.9, CH_2), 6.06 (1 H, dt, *J* 11.6 and 7.1, PhCH=C*H*), 6.73 (1 H, dt, *J* 11.6 and 1.9, PhC*H*), 7.22 (1 H, tt, *J* 7.4 and 1.7, Ar), 7.30 (2 H, dd, *J* 7.9 and 7.4, Ar), 7.39 (2 H, dd, *J* 8.5 and 1.3, Ar), 7.49 (2 H, dd, *J* 7.9 and 7.5, Ar), 7.58 (1 H, tt, *J* 7.3 and 1.3, Ar), 8.01 (2 H, dd, *J* 8.2 and 1.1, Ar); δ_C (150 MHz, $CDCl_3$) *E*-isomer: 42.8, 122.7, 127.6, 128.5, 128.6, 128.8, 133.4, 133.6, 133.7, 136.7, 137.1, 198.1; *Z*-isomer: 38.4, 124.0, 127.6, 128.5, 128.6, 128.8, 132.3, 133.4, 133.6, 136.7, 137.1, 198.0; *m/z* (CI) 223.1116 (M+H, $C_{16}H_{15}O$ requires 223.1123), 117 (51%), 105 (100), 91 (58), 77 (72).

1,4-Diphenyl-3-hydroxybutan-1-one (325)



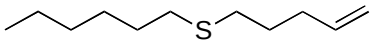
From procedure F: (12 mg, 0.50 mmol, 45 %) as a colourless oil; ν_{max}(film)/cm^{-1} 3462, 1679, 1449, 1213, 1083, 745, 701; δ_H (600 MHz, $CDCl_3$) 2.85 (1 H, dd, *J* 13.5 and 6.4, PhCH*H*), 2.98 (1 H, dd, *J* 13.5 and 7.1, PhCH*H*), 3.09 (1 H, dd, *J* 17.6 and 8.6, COCH*H*), 3.16 (1 H, dd, *J* 17.6 and 3.1, COCH*H*), 3.22 (1 H, d, *J* 3.4, OH), 4.49 (1 H, ddddd, *J* 8.6, 7.1, 6.4, 3.4 and 3.1, C*H*OH), 7.23-7.27 (3 H, m, Ar), 7.33 (2 H, app. t, *J* 7.3, Ar), 7.45 (2 H, app. t, *J* 7.8, Ar), 7.57 (1 H, tt, *J* 7.4 and 1.2, Ar), 7.91 (2 H, d, *J* 8.2, Ar); δ_C (150 MHz, $CDCl_3$) 43.0, 44.2, 69.0, 126.7, 128.2, 128.7, 128.8, 129.6, 133.7, 136.8, 138.1, 200.7; *m/z* (CI) 241.1232 (M+H, $C_{16}H_{17}O_2$ requires 241.1229), 223 (100%), 149 (52), 121 (99), 105 (99), 91 (55).

3-Chloro-1,4-diphenylbutan-1-one (326)



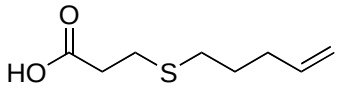
From procedure F: (2 mg, 0.0077 mmol, 7 %) as a colourless oil; ν_{max}(film)/cm^{-1} 2926, 1686, 1449, 1261, 1023, 799, 756, 700; δ_H (600 MHz, $CDCl_3$) 3.38 (1 H, dd, *J* 17.2 and 6.1, COCH*H*), 3.48 (1 H, dd, *J* 17.2 and 7.5, COCH*H*), 3.62 (1 H, app. quintet, *J* 6.6, CHCl), 3.81-3.89 (2 H, m, PhCH_2), 7.24 (1 H, tt, *J* 7.2 and 1.5, Ar), 7.29 (2 H, dd, *J* 8.3 and 1.7, Ar), 7.33 (2 H, dd, *J* 7.9 and 7.1, Ar), 7.45 (2 H, dd, *J* 8.3 and 7.6, Ar), 7.56 (1 H, tt, *J* 7.4 and 1.3, Ar), 7.95 (2 H, dd, *J* 8.3 and 1.1, Ar); δ_C (150 MHz, $CDCl_3$) 41.5, 43.5, 67.2, 127.1, 128.0, 128.2, 128.7, 128.9, 133.3, 137.0, 141.9, 199.3; *m/z* (EI) 222 (M-Cl, 19%), 210 (24), 149 (29), 120 (17), 105 (100).

6-Thiadodec-1-ene (333)



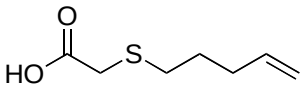
5-Bromopent-1-ene (840 μl, 7.10 mmol) was added to a stirred suspension of potassium carbonate (1.47 g, 10.65 mmol) and hexanethiol (1.00 ml, 7.10 mmol) in MeOH (50 ml). The reaction mixture was stirred at rt for 6 h then concentrated *in vacuo*. DCM (50 ml) and water (50 ml) were added and the organic layer was washed with 1 M NaOH solution (25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (DCM-petrol 1:9) to give the *sulfide* as a colourless oil (1.30 g, 6.98 mmol, 98%); ν_{max}(film)/cm^{-1} 2925, 1455, 1217, 990, 911; δ_H (600 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.0, Me), 1.32-1.24 (4 H, m, MeCH_2 and MeCH_2CH_2), 1.37 (2 H, app. quintet, *J* 7.5, MeCH_2CH_2CH_2), 1.57 (2 H, app. quintet, *J* 7.5, MeCH_2CH_2CH_2CH_2), 1.67 (2 H, app. quintet, *J* 7.4, CHCH_2CH_2), 2.15 (2 H, ddt, *J* 6.9, 6.8 and 1.1, CHCH_2), 2.50 (2 H, t, *J* 6.8, MeCH_2CH_2CH_2CH_2CH_2), 2.51 (2 H, t, *J* 6.7, CHCH_2CH_2CH_2), 4.97 (1 H, ddt, *J* 10.3, 1.9 and 1.1, CH=CH*H*), 5.03 (1 H, app. dq, *J* 17.1 and 1.9, CH=CH*H*), 5.79 (1 H, ddt, *J* 17.1, 10.3 and 6.9, CH); δ_C (150 MHz, $CDCl_3$) 14.2, 22.7, 28.7, 28.9, 29.8, 2 × 31.6, 32.2, 33.0, 115.2, 138.0; *m/z* (CI) 187.1514 (M+H, $C_{11}H_{23}S$ requires 187.1520), 187 (100%), 185 (9), 131 (13).

4-Thianon-8-enoic acid (334)



5-Bromopent-1-ene (1.36 ml, 11.49 mmol) was added to a stirred suspension of potassium carbonate (4.76 g, 34.47 mmol) and 3-mercaptopropionic acid (1.00 ml, 11.49 mmol) in methanol (60 ml). The reaction mixture was stirred at rt for 6 h then concentrated *in vacuo*. DCM (60 ml) and water (60 ml) were added; the aqueous phase was acidified to pH 4 with 2 M HCl, extracted with DCM (2 × 60 ml) and the combined organics were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the *acid* as a colourless oil (1.85 g, 10.62 mmol, 92%); ν_{max}(film)/cm^{-1} 2930, 1710, 1417, 1262, 914; δ_H (600 MHz, $CDCl_3$) 1.68 (2 H, tt, *J* 7.6 and 7.3, CH_2=CHCH$_2$C*H*$_2$), 2.16 (2 H, td, *J* 7.3 and 6.7, CH_2=CHC*H*$_2$), 2.54 (2 H, t, *J* 7.6, CH_2=CHCH$_2$CH$_2$C*H*$_2$), 2.66 (2 H, t, *J* 7.6, COCH$_2$), 2.78 (2 H, t, *J* 7.6, COCH$_2$C*H*$_2$), 4.98 (1 H, app. dq, *J* 10.3 and 1.6, CH=CH*H*), 5.03 (1 H, app. dq, *J* 17.1 and 1.6, CH=CH*H*), 5.78 (1 H, ddt, *J* 17.1, 10.3 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 26.6, 28.7, 31.6, 32.8, 34.7, 115.5, 137.8, 177.9; *m/z* (CI) 175.0785 (M+H, $C_8H_{15}SO_2$ requires 175.0793), 157 (81%), 119 (15), 84 (24).

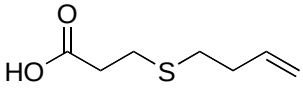
3-Thiaoct-7-enoic acid[343] (335)



5-Bromopent-1-ene (1.69 ml, 14.30 mmol) was added to a stirred suspension of potassium carbonate (5.90 g, 43.00 mmol) and mercaptoacetic acid (1.00 ml, 14.30 mmol) in MeOH (80 ml). The reaction mixture was stirred at rt for 6 h then concentrated *in vacuo*. DCM (60 ml) and water (60 ml) were added; the aqueous phase was acidified to pH 4 with 2 M HCl, extracted with DCM (2 × 60 ml) and the combined organics were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the *acid* as a colourless oil (2.17 g, 13.50 mmol, 95%); ν_{max}(film)/cm^{-1} 2927, 1706, 1419, 1294, 1134, 913; δ_H (600 MHz, $CDCl_3$) 1.71 (2 H, tt, *J* 7.5 and 7.4, SCH$_2$C*H*$_2$), 2.16 (2 H, dt, *J* 7.5 and 6.7, CH_2=CHC*H*$_2$), 2.67 (2 H, t, *J* 7.4, CH_2=CHCH$_2$CH$_2$C*H*$_2$), 3.25 (2 H, s, COCH$_2$), 4.99 (1 H, app. dq, *J* 10.2 and

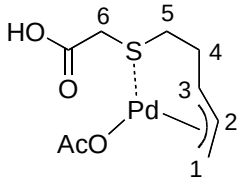
1.7, CH=CH*H*), 5.04 (1 H, app. dq, *J* 17.0 and 1.7, CH=CH*H*), 5.78 (1 H, ddt, *J* 17.0, 10.2 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 28.1, 32.2, 32.7, 33.5, 115.6, 137.5, 176.5; *m/z* (EI) 160.0546 (M^+, $C_7H_{12}SO_2$ requires 160.0553), 105 (48%), 101 (100), 86 (70), 84 (99).

4-Thiaoct-7-enoic acid (336)



4-Bromobut-1-ene (1.17 ml, 11.49 mmol) was added to a stirred suspension of potassium carbonate (4.76 g, 34.47 mmol) and 3-mercaptopropionic acid (1.00 ml, 11.49 mmol) in MeOH (60 ml). The reaction mixture was stirred at rt for 16 h then concentrated *in vacuo*. DCM (60 ml) and water (60 ml) were added; the aqueous phase was acidified to pH 4 with 2 M HCl, extracted with DCM (2 × 60 ml) and the combined organics were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the *acid* as a colourless oil (1.80 g, 11.23 mmol, 98%); ν_{max}(film)/cm^{-1} 2920, 1708, 1416, 1263, 916; δ_H (600 MHz, $CDCl_3$) 2.35 (2 H, td, *J* 7.7 and 6.7, CH_2=CHCH_2), 2.61 (2 H, t, *J* 7.7, CH_2=CHCH_2CH_2), 2.67 (2 H, t, *J* 7.1, $COCH_2$), 2.80 (2 H, t, *J* 7.1, $COCH_2CH_2$), 5.04 (1 H, app. dq, *J* 10.2 and 1.7, CH=CH*H*), 5.09 (1 H, app. dq, *J* 17.0 and 1.7, CH=CH*H*), 5.82 (1 H, ddt, *J* 17.0, 10.2 and 6.7, CH_2=C*H*); δ_C (150 MHz, $CDCl_3$) 26.7, 31.6, 33.9, 34.7, 116.3, 136.6, 177.9; *m/z* (CI) 161.0634 (M+H, $C_7H_{13}SO_2$ requires 161.0636), 143 (30%), 119 (48), 89 (29), 88 (28).

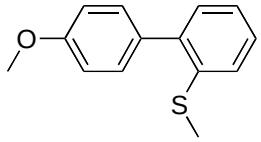
***S*-(6,7,8-*η*)-3-Thiaoctanoic acid palladium acetate (343)**



Palladium acetate (35 mg, 0.16 mmol) was added to a solution of 3-thiaoct-7-enoic acid (25 mg, 0.16 mmol) **335** in $CDCl_3$ (1 ml) in an NMR tube. The reaction was monitored over 18 h by ^1H and ^{13}C NMR.

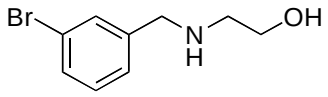
Spectra recorded after 18 h at rt: δ_H (600 MHz, $CDCl_3$) 1.66-1.69 (2 H, m, 2 × H-4), 2.07 (3 H, s, OAc), 2.74 (1 H, ddd, *J* 14.7, 7.6 and 2.3, H-5), 2.88 (1 H, ddd, *J* 14.7, 6.8 and 2.4, H-5), 3.18 (1 H, d, *J* 17.3, H-6), 3.86 (1 H, d, *J* 17.3, H-6), 3.88 (1 H, dd, *J* 12.9 and 1.6, H-1*trans*), 4.29 (1 H, dd, *J* 7.3 and 1.6, H-1*cis*), 4.76 (1 H, ddd, *J* 10.6, 6.9 and 5.4, H-3), 5.68 (1 H, ddd, *J* 12.9 10.6 and 7.3, H-2); δ_C (150 MHz, $CDCl_3$) 21.0 (CO*Me*), 27.6 (C-4), 37.5 (C-6), 37.9 (C-5), 59.5 (C-1), 75.7 (C-3), 109.2 (C-2), 177.1 (*C*OMe), 179.8 (COOH).

2-(4-Methoxyphenyl)-*S*-methylthiophenol (345)



A 10 ml microwave vial was charged with 2-bromo-*S*-methylthiophenol (67 μl, 0.51 mmol), 4-methoxyphenylboronic acid (93 mg, 0.61 mmol), bis-(triphenylphosphine) palladium dichloride (11 mg, 0.015 mmol), potassium carbonate (106 mg, 0.77 mmol), MeCN (1.2 ml) and water (0.8 ml). The mixture was heated to 120 °C for 10 min under microwave irradiation, cooled to rt and diluted with ether (5 ml). The organic phase was washed with water (5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc-petrol 1:9) to give the product (95 mg, 0.41 mmol, 81%) as a white solid, m.p. 71-73 °C; ν_{max}(film)/cm^{-1} 2918, 1511, 1460, 1239, 1172, 1033, 832, 760; δ_H (600 MHz, $CDCl_3$) 2.38 (3 H, s, SMe), 3.86 (3 H, s, OMe), 6.97 (2 H, d, *J* 8.6, Ar), 7.17-7.21 (2 H, m, Ar), 7.26 (1 H, br d, *J* 7.7, Ar), 7.32 (1 H, ddd, *J* 8.3, 6.9 and 2.0, Ar), 7.35 (2 H, d, *J* 8.6, Ar); δ_C (150 MHz, $CDCl_3$) 16.1, 55.4, 113.6, 124.8, 125.1, 127.8, 130.2, 130.6, 133.0, 137.4, 140.6, 159.1; *m/z* (CI) 231.0836 (M+H, $C_{14}H_{15}SO$ requires 231.0836).

2-(3-Bromobenzylamino)ethanol (400)

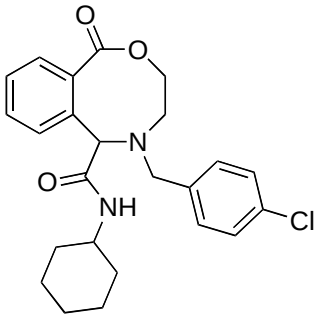


From procedure A: 89% yield as a colourless oil; ν_{max}(film)/cm^{-1} 3016, 2971, 1366, 1217, 1092, 903, 782; δ_H (600 MHz, $CDCl_3$) 2.80 (2 H, t, *J* 5.2, C*H*$_2$CH$_2$OH), 3.66 (2 H, t, *J* 5.2, CH$_2$O*H*), 3.79 (2 H, s, C*H*$_2$Ar), 7.19 (1 H, dd, *J* 8.0 and 7.7, Ar), 7.24 (1 H, d, *J* 8.0, Ar), 7.38 (1 H, d, *J* 7.7, Ar), 7.48 (1 H, s, Ar); δ_C (150 MHz, $CDCl_3$) 50.6, 53.0, 61.1, 122.7, 126.8, 130.2, 130.3, 131.2, 142.6; *m/z* (FAB) 230.0175 (M+H, $C_9H_{13}NOBr$ requires 230.0181), 199 (10%), 176 (100), 154 (48).

General Procedure for 3-Component Reactions of Amino Alcohols, Isocyanides and 2-Carboxybenzaldehyde (Procedure G)

A solution of 2-carboxybenzaldehyde (150 mg, 1.00 mmol), amino alcohol (1.00 mmol) and isocyanide (1.00 mmol) in methanol (1 ml) was stirred under microwave irradiation at 60 °C for 20 min. The solvent was removed *in vacuo* and the residue purified by column chromatography EtOAc-petroleum ether (1:9) to afford the *amide*.

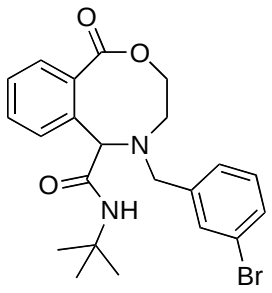
4-(4-Chlorobenzyl)-*N*-cyclohexyl-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]oxazocine-5-carboxamide (401)



From procedure G: 57% as a pale yellow solid, m.p. 117-119 °C; ν_{max}(film)/cm^{-1} 3307, 2929, 1703, 1665, 1540, 1297, 1094, 1015, 829, 773, 743; δ_H (600 MHz, $CDCl_3$) 1.06-1.18 (3 H, m, cyclohexyl), 1.26-1.35 (2 H, m, cyclohexyl), 1.55-1.57 (1 H, br m, cyclohexyl), 1.63-1.66 (2 H, m, cyclohexyl), 1.73 (1 H, m, cyclohexyl), 1.83 (1 H, m, cyclohexyl), 2.75 (1 H, ddd, *J* 13.9, 10.3 and 5.6, OCH$_2$CH*H*), 3.13 (1

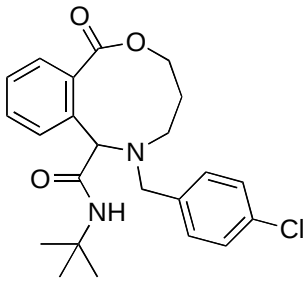
H, ddd, *J* 13.9, 7.2 and 5.6, $OCH_2CH\mathit{H}$), 3.68-3.81 (3 H, m, $ArC\mathit{H}_2$ and NHC*H*), 3.85 (1 H, ddd, *J* 12.4, 7.2 and 5.6 OCH*H*), 4.08 (1 H, ddd, *J* 12.4, 10.3 and 5.6, OCH*H*), 4.45 (1 H, s, COCH), 6.28 (1 H, br d, *J* 7.2, NH), 7.28-7.30 (3 H, m, Ar), 7.35 (2 H, d, *J* 8.5, Ar), 7.40-7.43 (3 H, m, Ar); δ_C (150 MHz, $CDCl_3$) 24.7, 25.5, 32.8, 48.5, 51.6, 58.6, 65.1, 71.5, 128.0, 128.8, 128.9, 129.2, 129.9, 130.4, 130.6, 133.6, 135.5, 135.9, 168.8, 174.1; *m/z* (EI) 426.1703 (M^+, $C_{24}H_{27}O_3N_2Cl$ requires 426.1705), 302 (32%), 300 (100).

4-(3-Bromobenzyl)-*N*-(*tert*-butyl)-8-oxo-2,3,5-trihydrobenzo[*f*][1,4]oxazocine-5-carboxamide (402)



From procedure G: 49% as a pale yellow solid, m.p. 135-136 °C; ν_{max}(film)/cm^{-1} 3344, 2966, 1706, 1674, 1538, 1283, 1096, 779, 733; δ_H (600 MHz, $CDCl_3$) 1.30 (9 H, s, ^{t}Bu), 2.80 (1 H, ddd, *J* 14.2, 6.9 and 4.4, $OCH_2CH\mathit{H}$), 3.15 (1 H, ddd, *J* 14.2, 6.0 and 4.5, $OCH_2CH\mathit{H}$), 3.64 (1 H, br d, *J* 14.4, ArCH*H*), 3.72 (1 H, d, *J* 14.4, ArCH*H*), 3.84 (1 H, ddd, *J* 12.7, 6.0 and 4.5, OCH*H*), 4.07 (1 H, ddd, *J* 12.7, 6.9 and 4.4, OCH*H*), 4.40 (1 H, s, COCH), 6.57 (1 H, br s, NH), 7.20-7.21 (1 H, m, Ar), 7.22 (1 H, t, *J* 7.7, Ar), 7.27 (1 H, ddd, *J* 7.7, 1.6 and 1.3, Ar), 7.35-7.36 (3 H, m, Ar), 7.39 (1 H, ddd, *J* 7.8, 2.0 and 1.2, Ar), 7.44 (1 H, t, *J* 1.9, Ar); δ_C (150 MHz, $CDCl_3$) 28.7, 51.1, 51.7, 58.2, 65.0, 71.1 (br), 122.9, 127.0, 128.2, 128.67, 128.74, 130.4, 130.7, 130.8, 130.9, 131.5, 135.5, 140.1, 168.9, 173.8 (br); *m/z* (CI) 445.1116 (M+H, $C_{22}H_{26}O_3N_2Br$ requires 445.1127), 429 (16%), 346 (34), 84 (38).

***N*-(*tert*-Butyl)-5-(4-chlorobenzyl)-9-oxo-2,3,4,6-tetrahydrobenzo[*g*][1,5]oxazonine-6-carboxamide (403)**

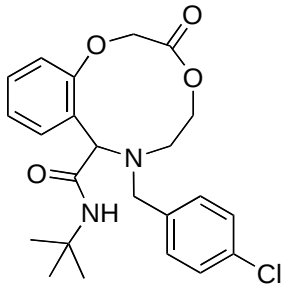


From procedure G: 62% as a pale yellow foam, m.p. 68-70 °C; ν_{max}(film)/cm^{-1} 3335, 2970, 1737, 1723, 1660, 1365, 1226, 1218, 1087, 731; δ_H (600 MHz, $CDCl_3$) 1.42 (9 H, s, ^{t}Bu), 1.47-1.54 (1 H, m, $OCH_2CH\mathit{H}$) 1.74-1.84 (1 H, m, $OCH_2CH\mathit{H}$), 2.85 (1 H, ddd, *J* 14.2, 6.2 and 3.3, $OCH_2CH_2CH\mathit{H}$), 3.00 (1 H, ddd, *J* 14.2, 9.1 and 3.4, $OCH_2CH_2CH\mathit{H}$), 3.66 (1 H, d, *J* 13.8, ArCH*H*), 3.85 (1 H, d, *J* 13.8, ArCH*H*), 4.26 (1 H, ddd, *J* 14.8, 6.1 and 3.4, OCH*H*), 4.47 (1 H, ddd, *J* 14.8, 8.4 and 2.4, OCH*H*), 4.79 (1 H, s, COCH), 6.05 (1 H, br s, NH), 7.23 (2 H, d, *J* 8.4, Ar), 7.27 (2 H, d, *J* 8.4, Ar), 7.32-7.42 (3 H, m, Ar), 7.55 (1 H, dt, *J* 6.6 and 1.7, Ar); δ_C (150 MHz, $CDCl_3$) 25.6, 28.8, 50.9, 51.8, 55.8, 68.1, 69.4 (br), 127.8, 128.3, 128.4, 128.6, 130.2, 131.1, 133.0, 133.1, 136.8, 139.2, 169.0, 171.6; *m/z* (CI) 415.1792 (M+H, $C_{23}H_{28}O_3N_2Cl$ requires 415.1789), 316 (7%), 314 (21), 273 (18), 125 (10).

General Procedure for 3-Component Reactions of Amino Alcohols, Isocyanides and 2-Formylphenoxyacetic Acid (Procedure H)

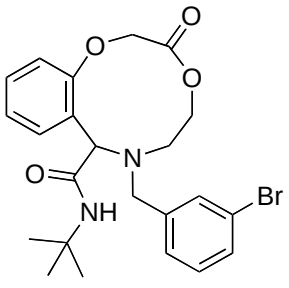
A solution of 2-formylphenoxyacetic acid (180 mg, 1.00 mmol), amino alcohol (1.00 mmol) and isocyanide (1.00 mmol) in methanol (1 ml) was stirred under microwave irradiation at 60 °C for 20 min. The solvent was removed *in vacuo* and the residue purified by column chromatography EtOAc-petroleum ether (1:9) to afford the *amide*.

_N_-(_tert_-Butyl)-7-(2-chlorobenzyl)-3-oxo-2,3,5,6,7,8-hexahydrobenzo[_i_][1,4,7]dioxazecine-8-carboxamide (404)



From procedure H: 14% as a white solid, m.p. 138-140 °C; ν_{max}(film)/cm^{-1} 3378, 2965, 1741, 1673, 1489, 1284, 1015, 909, 729; δ_H (600 MHz, $CDCl_3$) 1.32 (9 H, s, ^{t}Bu), 2.54-2.60 (1 H, m, $OCH_2CH\mathit{H}$), 2.75 (1 H, ddd, *J* 15.0, 11.6 and 3.1, $OCH_2CH\mathit{H}$), 3.85 (1 H, d, *J* 13.9, NCH*H*Ar), 3.98 (1 H, d, *J* 13.9, NCH*H*Ar), 4.16 (1 H, ddd, *J* 11.6, 3.6 and 2.0, $CO_2CH\mathit{H}$), 4.30-4.33 (1 H, m, $CO_2CH\mathit{H}$), 4.54 (1 H, d, *J* 13.4, ArOCH*H*), 4.73 (1 H, d, *J* 13.4, ArOCH*H*), 5.08 (1 H, s, ArC*H*), 6.56 (1 H, s, NH), 7.11 (1 H, ddd, *J* 7.9, 7.3 and 1.1, Ar), 7.17 (1 H, dd, *J* 8.3 and 1.1, Ar), 7.31 (1 H, ddd, *J* 8.3, 7.3 and 1.7, Ar), 7.34 (2 H, d, *J* 8.5, Ar), 7.37 (2 H, d, *J* 8.5, Ar), 7.42 (1 H, d, *J* 7.9, Ar); δ_C (150 MHz, $CDCl_3$) 28.8, 45.7, 51.1, 53.9, 60.8, 65.5, 72.9, 121.4, 124.8, 128.9, 129.0, 129.8, 129.9, 130.7, 133.3, 136.6, 157.0, 168.5, 171.3; *m/z* (ES+) 431.1730 (M+H, $C_{23}H_{28}O_4N_2Cl$ requires 431.1738), 403 (12%), 330 (10), 224 (15), 208 (11).

7-(3-Bromobenzyl)-_N_-(_tert_-butyl)-3-oxo-2,3,5,6,7,8-hexahydrobenzo[_i_][1,4,7]dioxazecine-8-carboxamide (405)



From procedure H: 22% as a white solid, m.p. 135-136 °C; ν_{max}(film)/cm^{-1} 3373, 2965, 1742, 1675, 1506, 1453, 1285, 1224, 1039, 775, 735; δ_H (600 MHz, $CDCl_3$) 1.33 (9 H, s, ^{t}Bu), 2.56-2.59 (1 H, m, $OCH_2CH\mathit{H}$), 2.78 (1 H, ddd, *J* 15.4, 11.8 and 3.2, $OCH_2CH\mathit{H}$), 3.84 (1 H, d, *J* 14.0, NCH*H*Ar), 3.98 (1 H, d, *J* 14.0, NCH*H*Ar), 4.17 (1 H, ddd, *J* 11.8, 4.0 and 1.9, $CO_2CH\mathit{H}$), 4.32-4.37 (1 H, m, $CO_2CH\mathit{H}$), 4.55 (1

H, d, *J* 13.4, ArOCH*H*), 4.73 (1 H, d, *J* 13.4, ArOCH*H*), 5.06 (1 H, s, ArC*H*), 6.58 (1 H, s, NH), 7.12 (1 H, ddd, *J* 8.3, 7.5 and 0.9, Ar), 7.17 (1 H, dd, *J* 8.2 and 0.9, Ar), 7.23-7.26 (1 H, m, Ar), 7.31 (1 H, ddd, *J* 8.2, 7.5 and 1.7, Ar), 7.37 (1 H, d, *J* 7.7, Ar), 7.41 (2 H, m, Ar), 7.59 (1 H, s, Ar); δ_C (150 MHz, $CDCl_3$) 28.8, 45.9, 51.3, 54.1 60.8, 65.5, 73.1, 121.4, 123.0, 124.8, 127.2, 128.9, 130.0, 130.4, 130.6, 130.8, 131.5, 140.5, 157.1, 168.5, 171.3; *m/z* (EI) 474.1149 (M^+, $C_{23}H_{27}O_4N_2Br$ requires 474.1149), 218 (24%), 162 (45), 64 (12).

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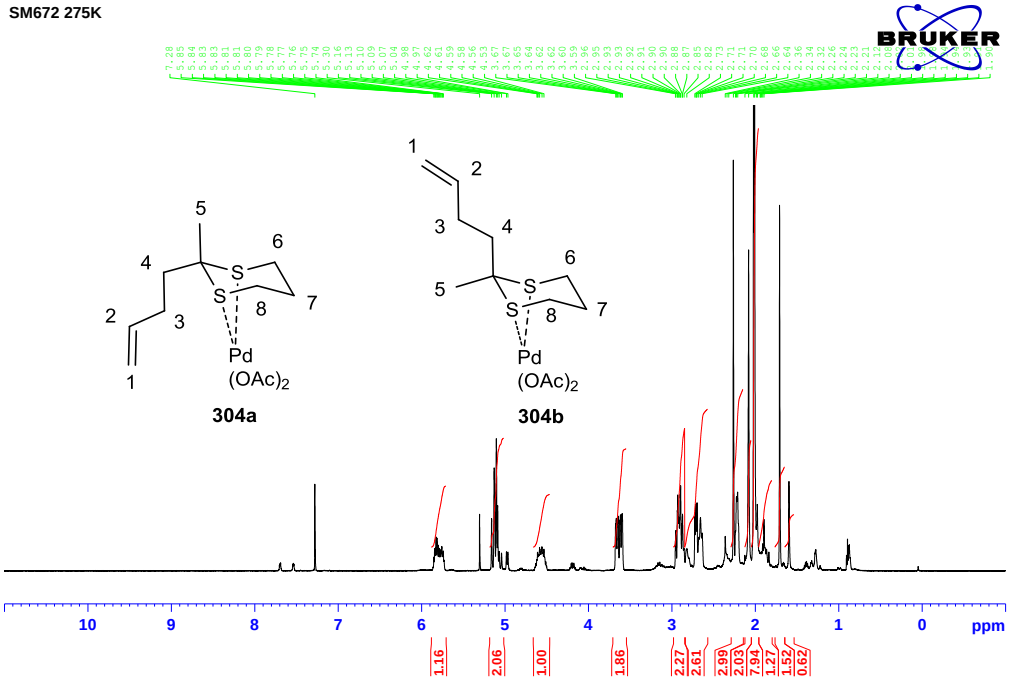
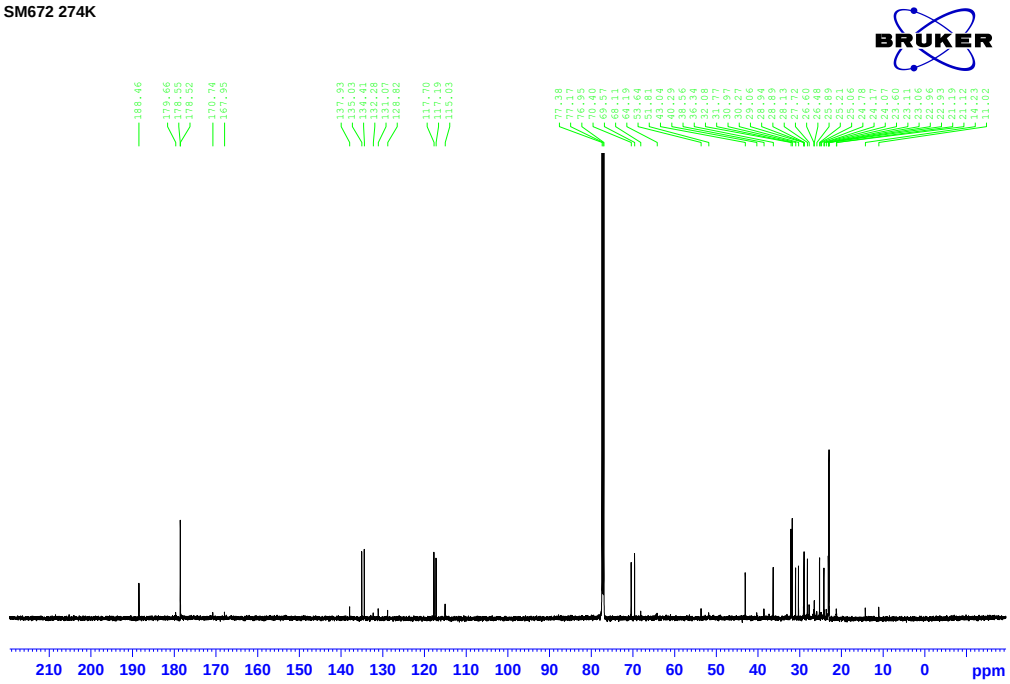
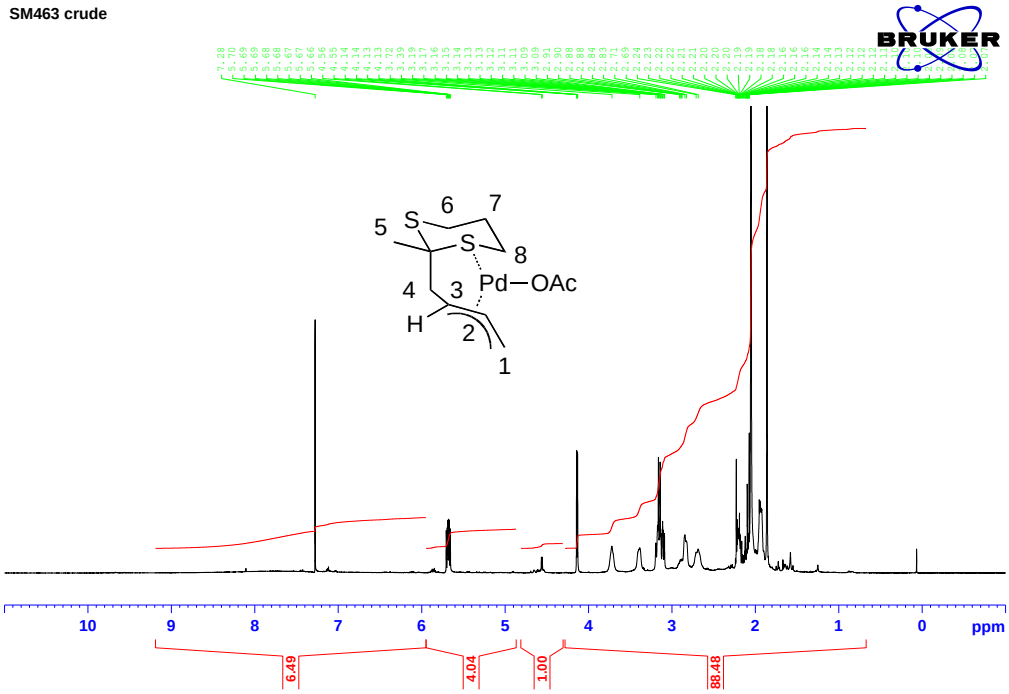


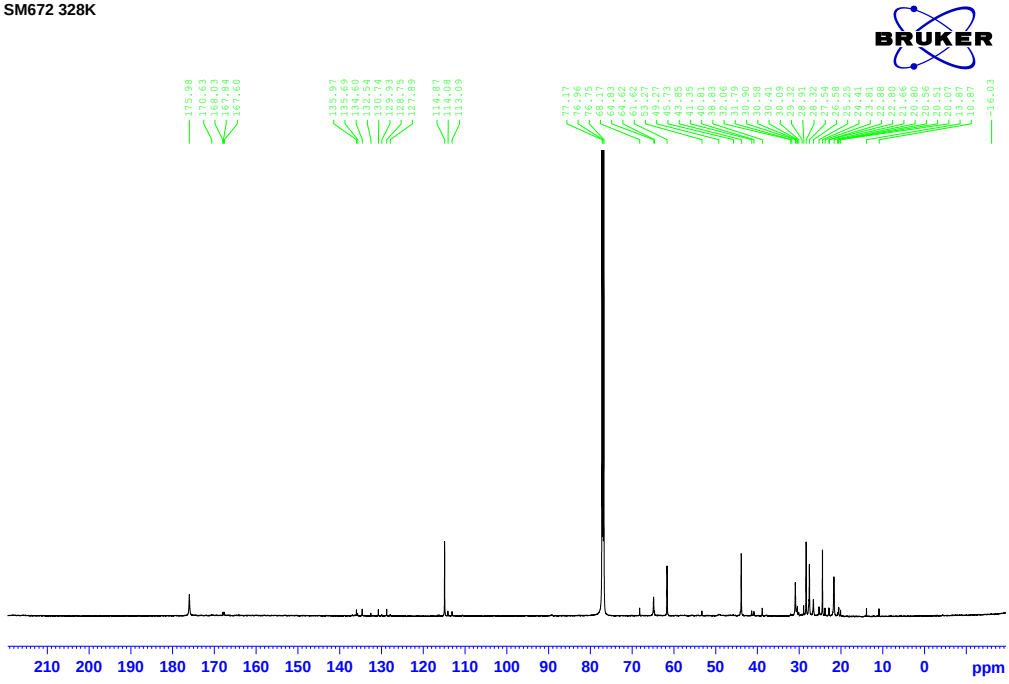
SM672 274K

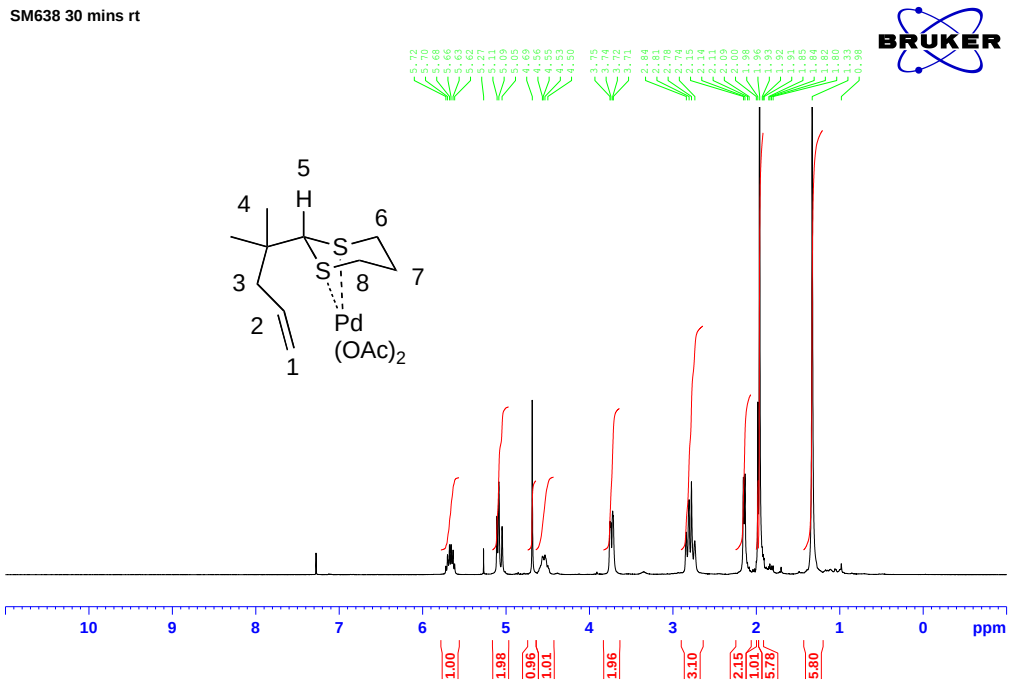


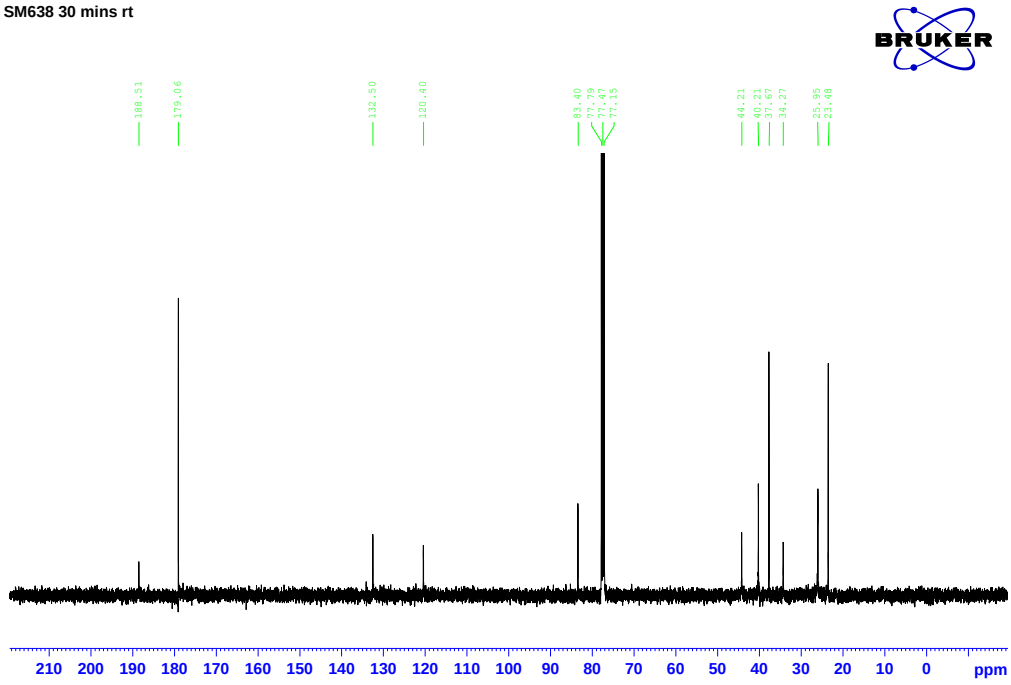
SM463 crude



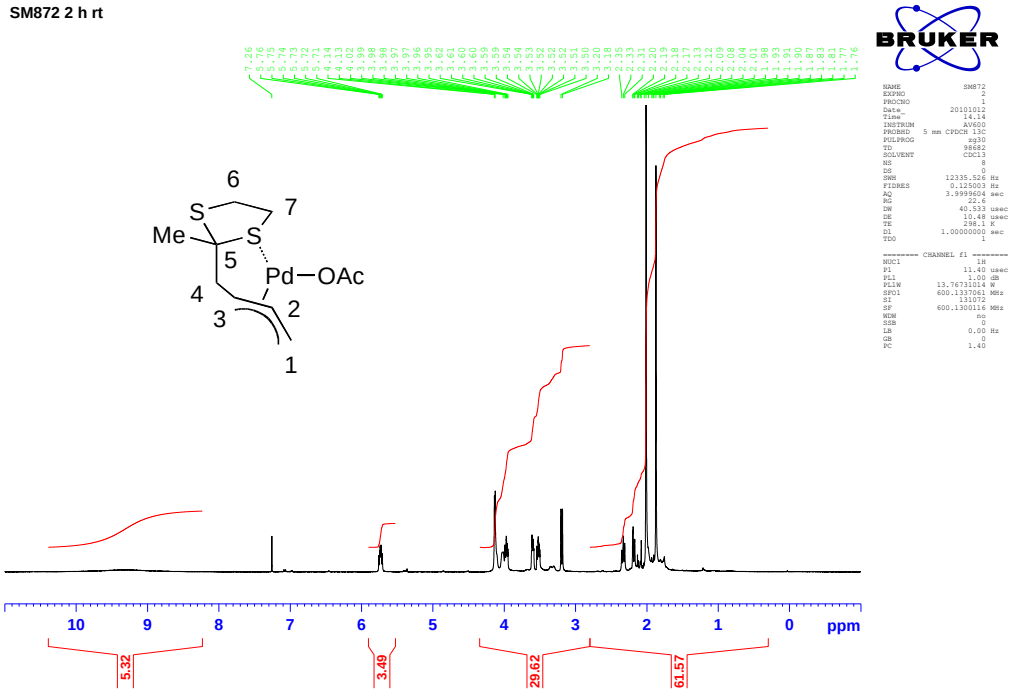
SM672 328K




SM638 30 mins rt
BRUKER
5
H
4
6
S
S
3
8
7
2
Pd
(OAc)2
1
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.98 0.96 1.01 1.96 3.10 2.15 1.01 5.78 5.80


SM638 30 mins rt
BRUKER
188.51
179.06
132.50
120.40
83.40
77.79
77.47
77.15
44.21
40.21
37.67
34.27
25.95
23.48
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SM872 2 h rt



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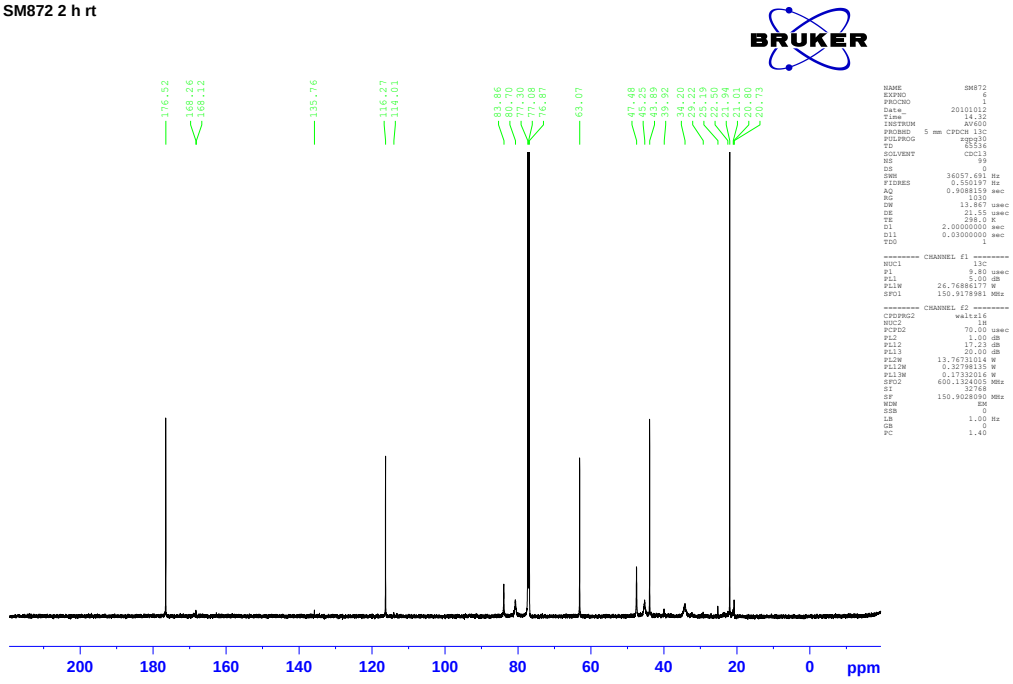

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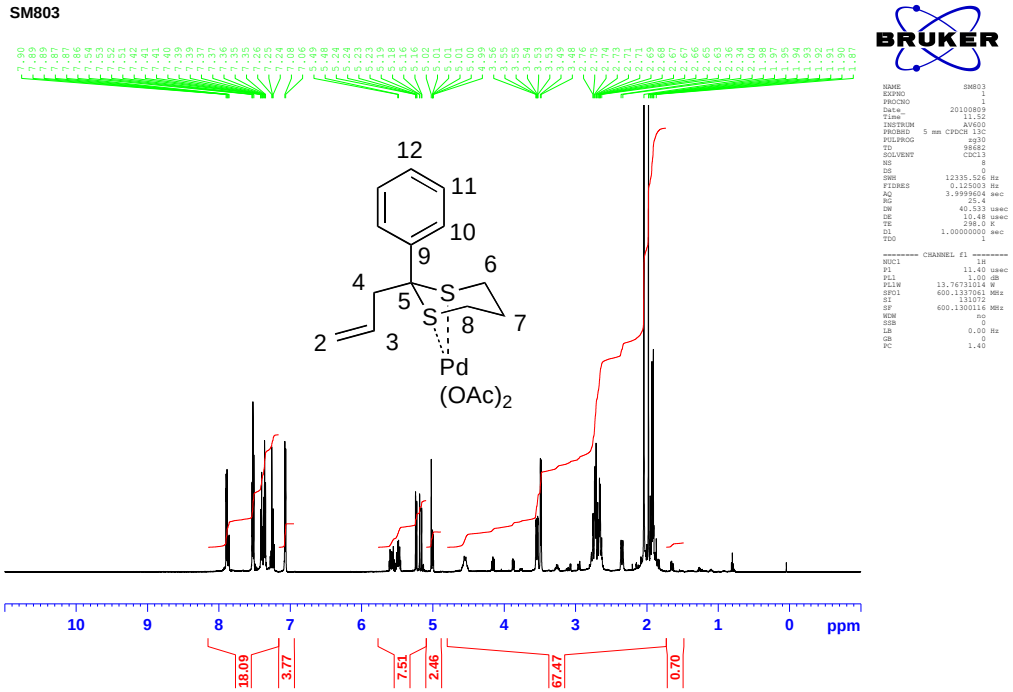
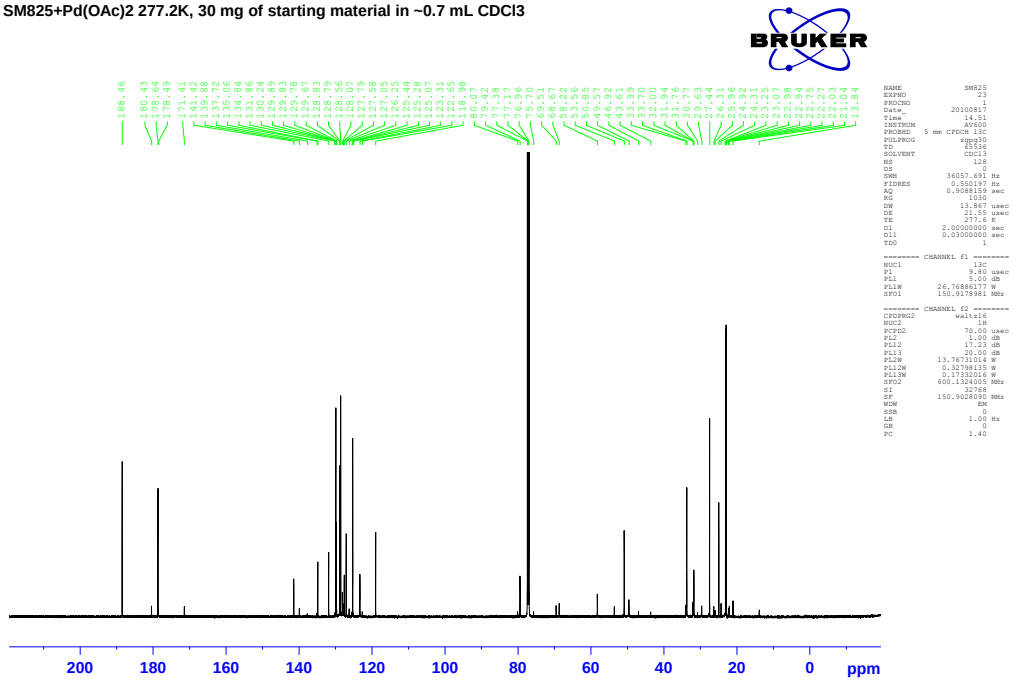
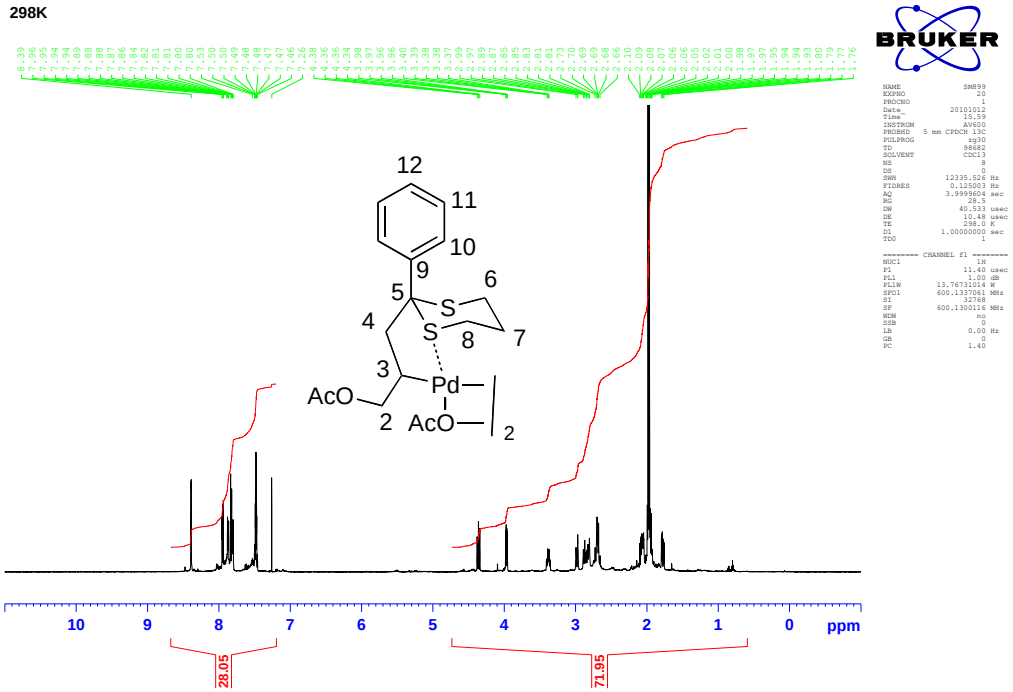
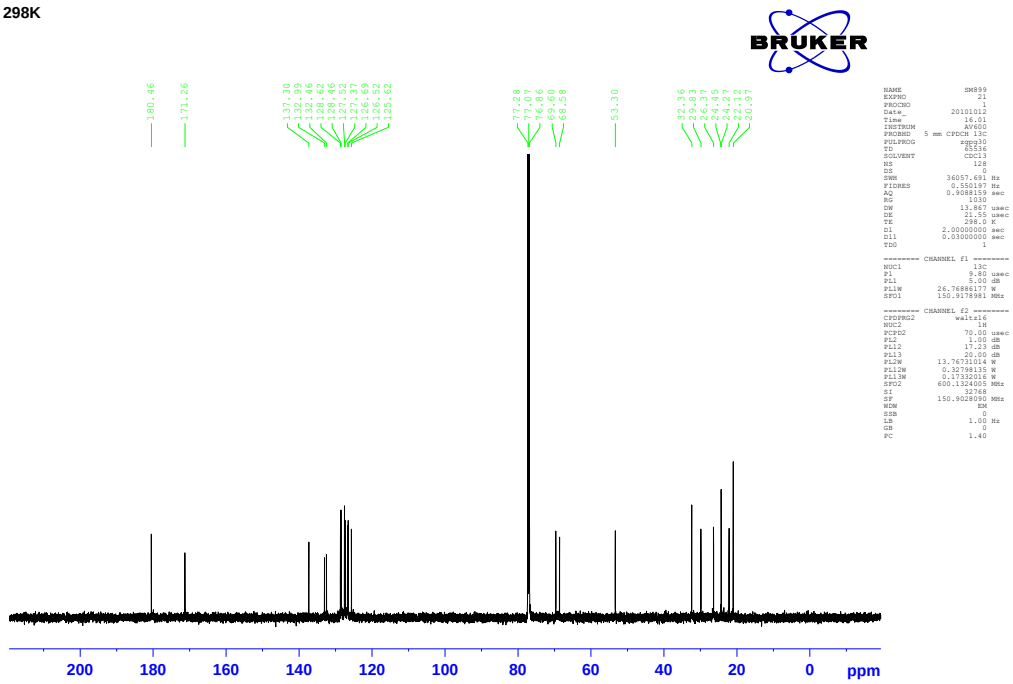


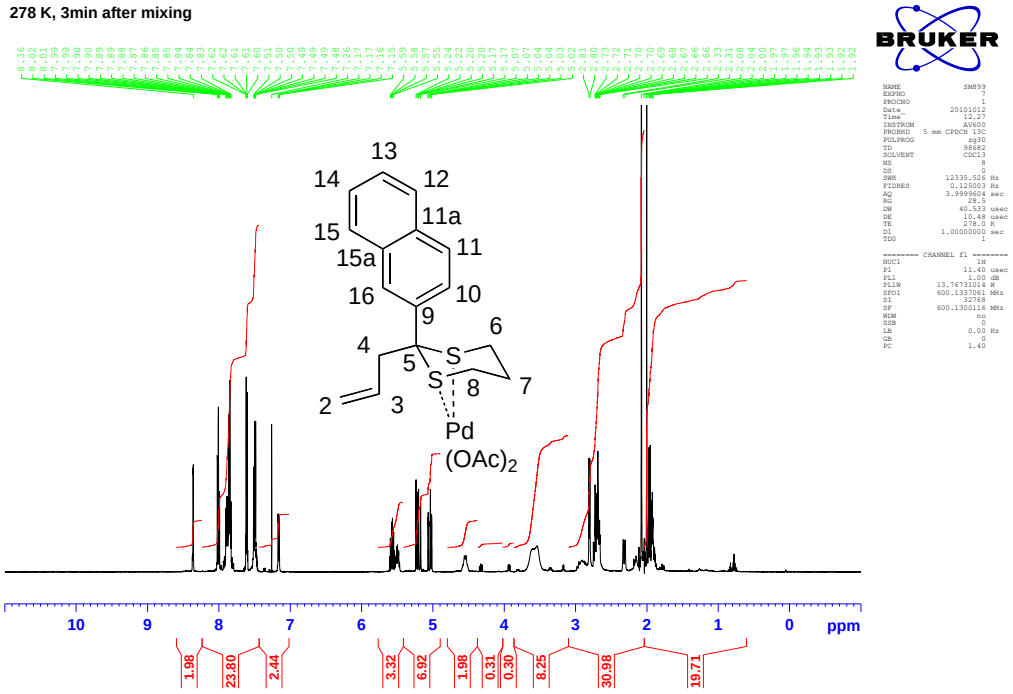
SM825+Pd(OAc)2 277.2K, 30 mg of starting material in ~0.7 mL CDCl3



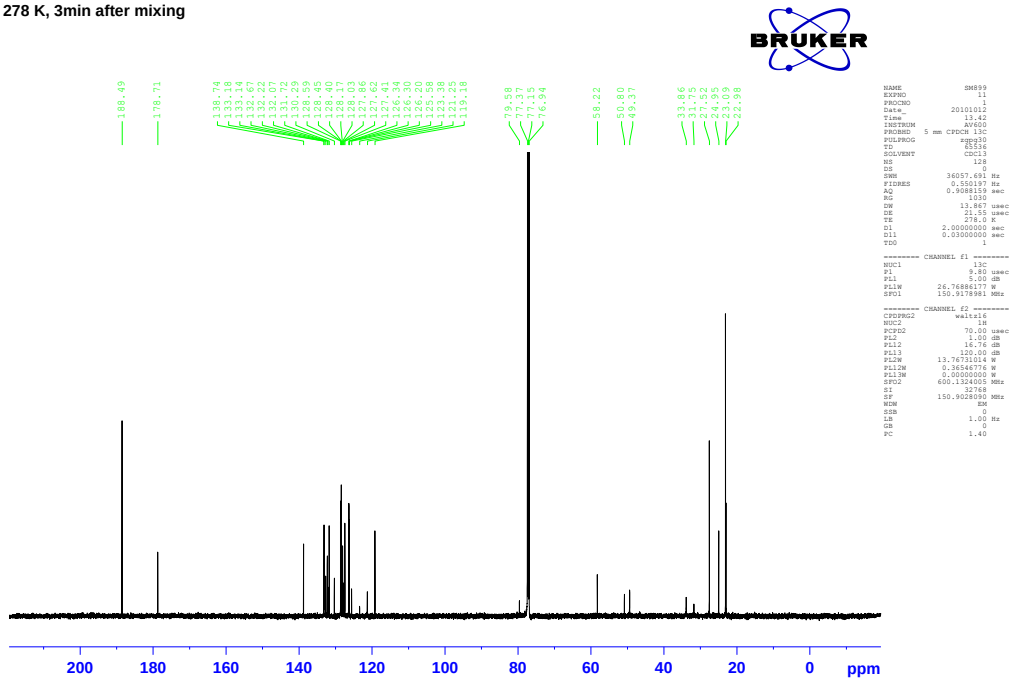

298K
BRUKER
12
11
10
9
6
5
S
4
S
8
7
3
Pd
AcO
2
AcO
2
10
9
8
7
6
5
4
3
2
1
0
ppm
28.05
71.95

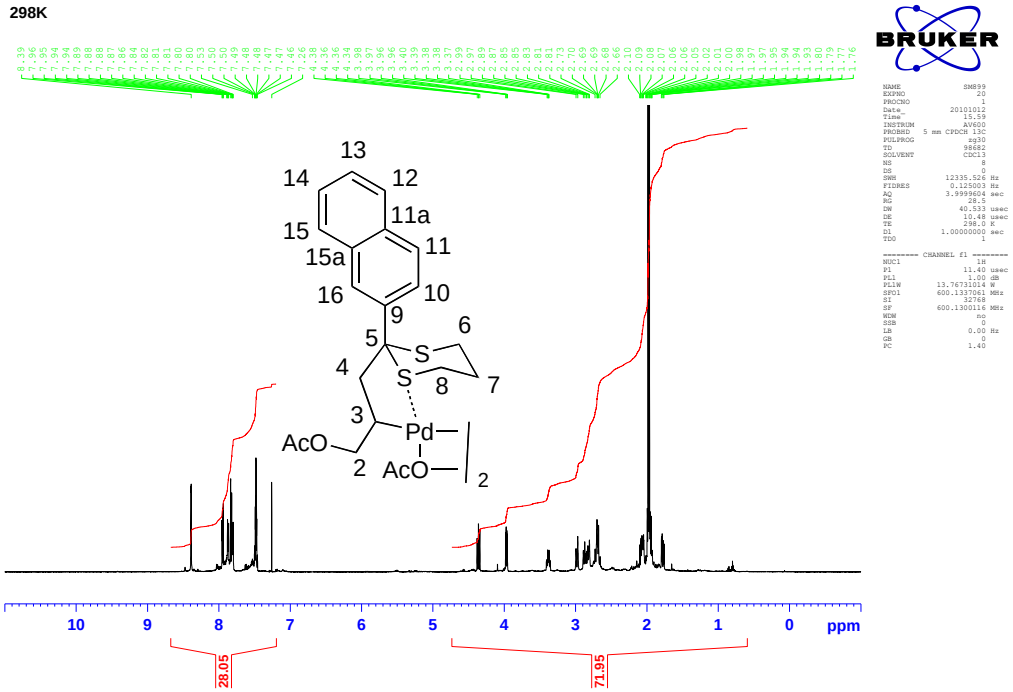

298K
BRUKER
200
180
160
140
120
100
80
60
40
20
0
ppm

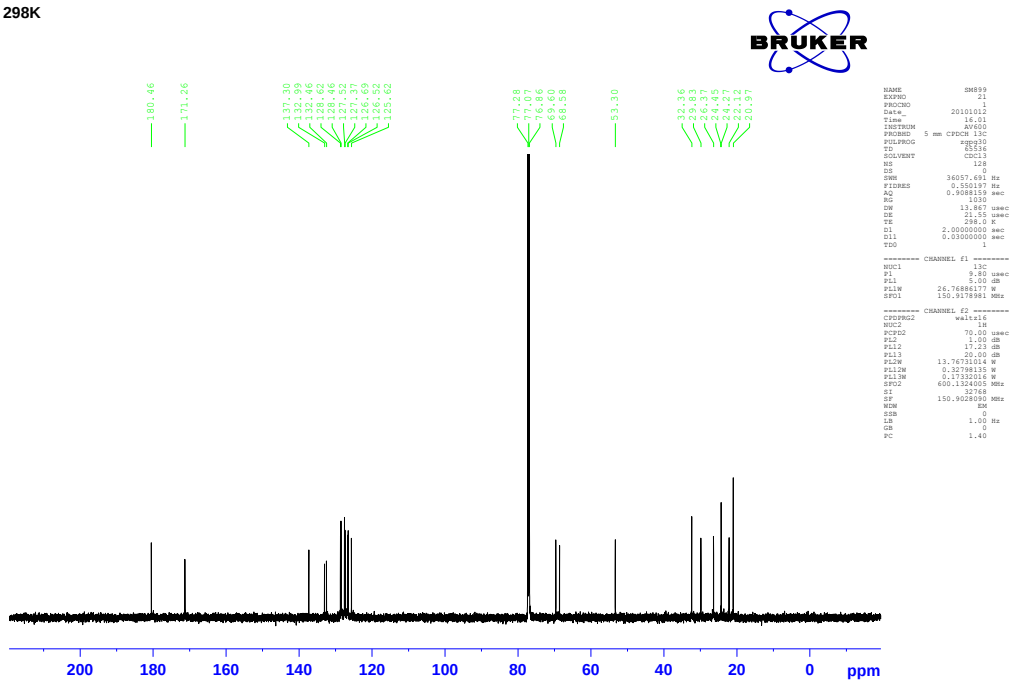
278 K, 3min after mixing

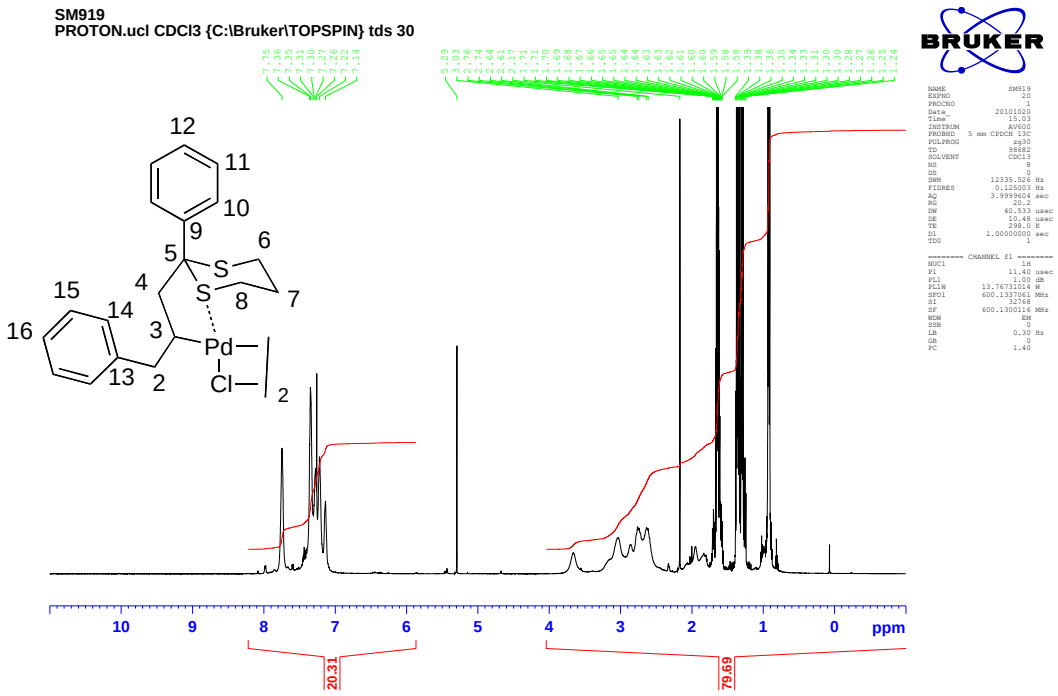


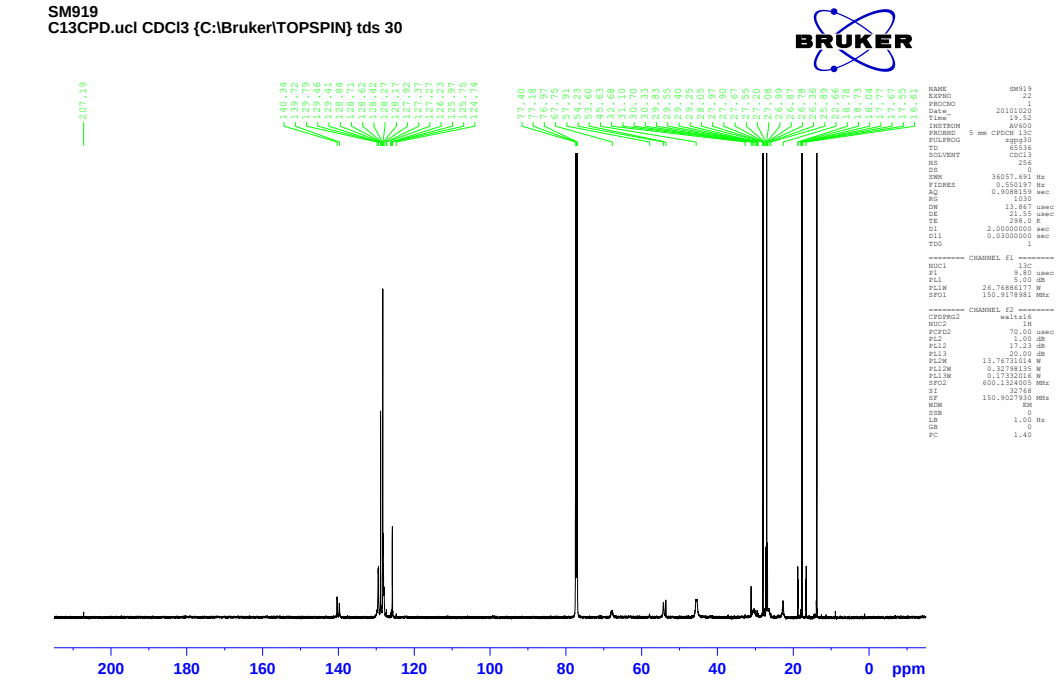
278 K, 3min after mixing

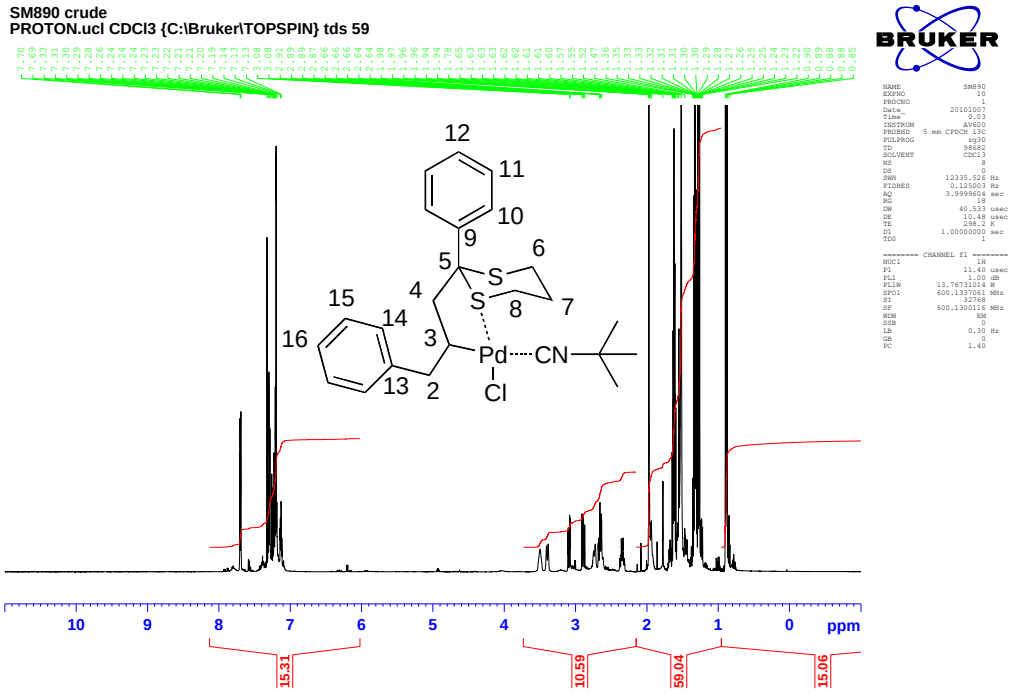


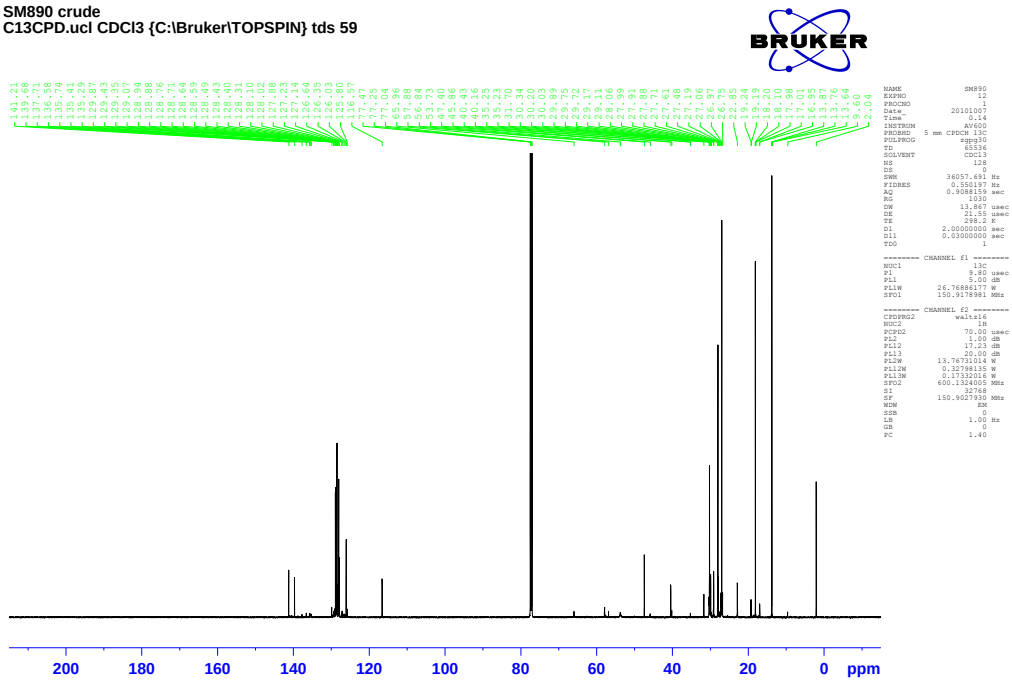

298K
BRUKER
13
14
12
11a
15
11
15a
16
10
9
5
6
S
4
S
8
7
3
Pd
AcO
2
AcO
2
10
9
8
7
6
5
4
3
2
1
0
ppm
28.05
71.95

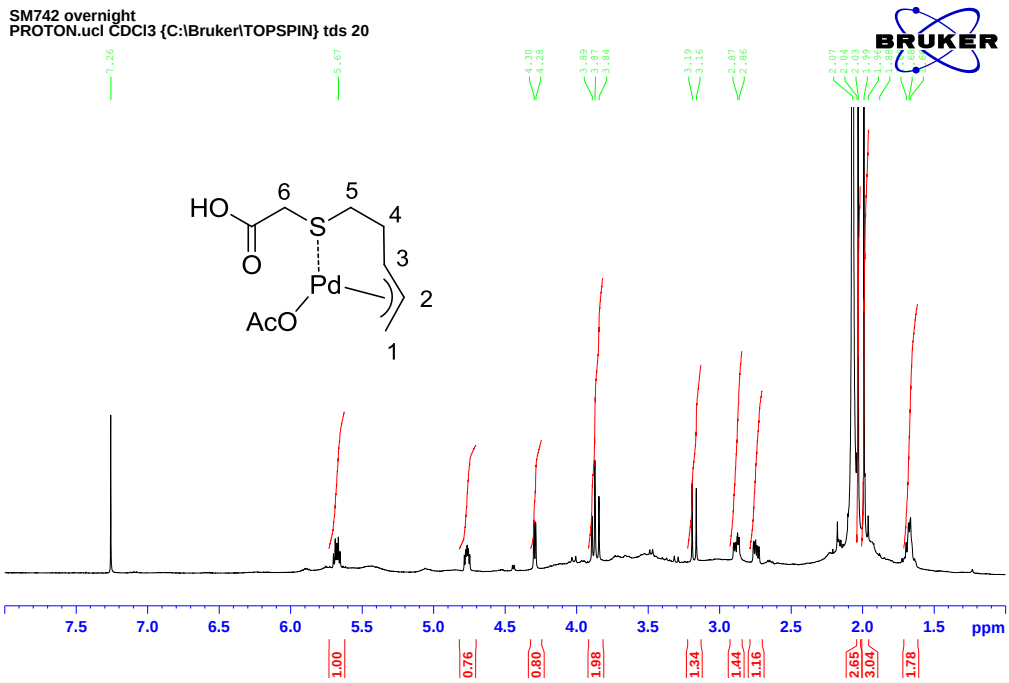

298K
BRUKER
180.46
171.26
137.30
133.39
132.46
128.62
128.46
127.52
127.35
126.69
126.52
125.62
77.28
77.07
76.86
69.60
68.58
53.30
32.36
29.83
25.87
24.45
24.27
22.12
20.97
200
180
160
140
120
100
80
60
40
20
0
ppm

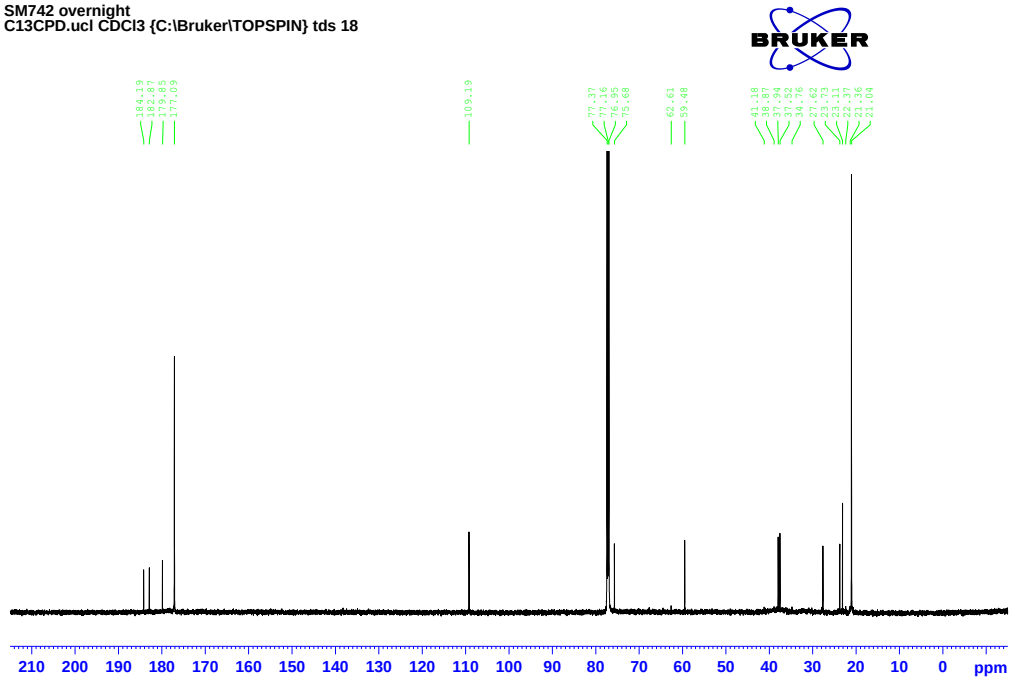

SM919
PROTON.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 30
BRUKER
12
11
10
9
6
5
S
4
S
8
7
15
14
3
16
Pd
13
2
Cl
2
10
9
8
7
6
5
4
3
2
1
0
ppm
20.31
79.69


SM919
C13CPD.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 30
BRUKER
200
180
160
140
120
100
80
60
40
20
0
ppm


SM890 crude
PROTON.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 59
BRUKER
12
11
10
9
6
5
S
4
S
8
7
15
14
16
3
Pd
CN
Cl
13
2
10
9
8
7
6
5
4
3
2
1
0
ppm
15.31
10.59
59.04
15.06


SM890 crude
C13CPD.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 59
BRUKER
200
180
160
140
120
100
80
60
40
20
0
ppm

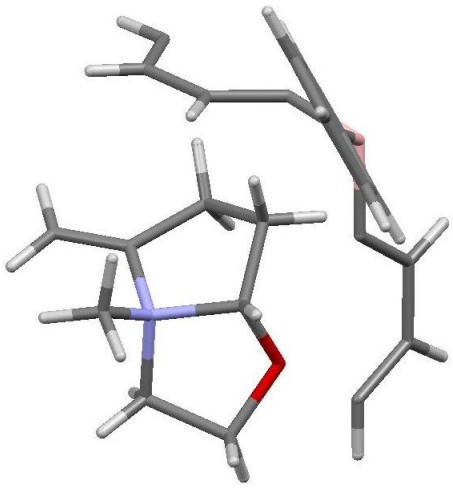

SM742 overnight
PROTON.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 20
BRUKER
HO
O
6
5
4
S
3
Pd
2
AcO
1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


SM742 overnight
C13CPD.ucl CDCl3 {C:\Bruker\TOPSPIN} tds 18
BRUKER
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Appendix B: X-Ray Crystal Data

X-ray crystal data (.cif files) for compounds **127**, **314** and **402**.

N-Methyl-5-methylenehexahydro-2*H*-pyrrolo[2,1-*b*]oxazol-4-ium Tetraphenylborate (127)



data_2009src0893c

_audit_creation_method SHELXL-97

_chemical_name_systematic

;

?

;

_chemical_name_common ?

_chemical_melting_point ?

_chemical_formula_moiety

'C24 H20 B, C8 H14 N O'

_chemical_formula_sum

'C32 H34 B N O'

_chemical_formula_weight 459.41

loop_

_atom_type_symbol

_atom_type_description

_atom_type_scat_dispersion_real

_atom_type_scat_dispersion_imag

_atom_type_scat_source

'C' 'C' 0.0033 0.0016

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

'H' 'H' 0.0000 0.0000

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

'B' 'B' 0.0013 0.0007

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

'N' 'N' 0.0061 0.0033

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

'O' 'O' 0.0106 0.0060

'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_cell_setting orthorhombic

_symmetry_space_group_name_H-M 'P n m a'

```
_symmetry_space_group_name_Hall   '-P 2ac 2n'


loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x+1/2, -y, z+1/2'
 'x+1/2, -y+1/2, -z+1/2'
 '-x, y+1/2, -z'
 '-x, -y, -z'
 'x-1/2, y, -z-1/2'
 '-x-1/2, y-1/2, z-1/2'
 'x, -y-1/2, z'


_cell_length_a                19.3041(7)
_cell_length_b                13.1353(5)
_cell_length_c                10.1462(3)
_cell_angle_alpha             90.00
_cell_angle_beta              90.00
_cell_angle_gamma             90.00
_cell_volume                  2572.72(16)
_cell_formula_units_Z         4
_cell_measurement_temperature 120(2)
_cell_measurement_reflns_used 33465
_cell_measurement_theta_min   2.91
_cell_measurement_theta_max   27.48


_exptl_crystal_description    'cut block'
_exptl_crystal_colour         colourless
_exptl_crystal_size_max       0.48
_exptl_crystal_size_mid       0.34
_exptl_crystal_size_min       0.16
_exptl_crystal_density_meas   ?
_exptl_crystal_density_diffrn 1.186
_exptl_crystal_density_method 'not measured'
_exptl_crystal_F_000          984
_exptl_absorpt_coefficient_mu 0.070
_exptl_absorpt_correction_type multi-scan
_exptl_absorpt_correction_T_min 0.9673
_exptl_absorpt_correction_T_max 0.9889
_exptl_absorpt_process_details 'SADABS 2007/2
(Sheldrick, G.M., 2007)'


_exptl_special_details
;
SADABS was used to perform the Absorption correction
Estimated minimum and maximum transmission: 0.6502
0.7456
The given Tmin and Tmax were generated using the
SHELX SIZE command
;


_diffrn_ambient_temperature   120(2)
_diffrn_radiation_wavelength  0.71073
_diffrn_radiation_type        MoK\a
_diffrn_radiation_source      'Bruker-Nonius FR591
rotating anode'
_diffrn_radiation_monochromator 'graphite'
_diffrn_measurement_device_type
'Bruker-Nonius Roper CCD camera on \k-goniostat'
_diffrn_measurement_method    '\f & \w scans'
_diffrn_detector_area_resol_mean '9.091'
_diffrn_standards_number      ?
_diffrn_standards_interval_count ?
_diffrn_standards_interval_time ?
_diffrn_standards_decay_%     ?
_diffrn_reflns_number         18899
_diffrn_reflns_av_R_equivalents 0.0416
_diffrn_reflns_av_sigmaI/netI 0.0254
_diffrn_reflns_limit_h_min    -22
_diffrn_reflns_limit_h_max    22
_diffrn_reflns_limit_k_min    -15
_diffrn_reflns_limit_k_max    14
_diffrn_reflns_limit_l_min    -12
_diffrn_reflns_limit_l_max    10
_diffrn_reflns_theta_min      3.30
_diffrn_reflns_theta_max      25.00
_reflns_number_total          2360
```

_reflns_number_gt 2101

_reflns_threshold_expression >2\s(I)

_computing_data_collection

'COLLECT (Hooft, R.W.W., 1998)'

_computing_cell_refinement

'DENZO (Otwinowski & Minor, 1997) & COLLECT (Hooft, R.W.W., 1998)'

#Although determined using DirAx, the cell is refined in the HKL

#package during data reduction

_computing_data_reduction

'DENZO (Otwinowski & Minor, 1997) & COLLECT (Hooft, R.W.W., 1998)'

_computing_structure_solution 'SHELXS-97 (Sheldrick, 2008)'

_computing_structure_refinement 'SHELXL-97 (Sheldrick, 2008)'

_computing_molecular_graphics 'CAMERON (Watkin, et al., 1993)'

_computing_publication_material 'WINGX (Farrugia, 1998)'

_refine_special_details

;

Refinement of F^2^ against ALL reflections. The weighted R-factor wR and

goodness of fit S are based on F^2^, conventional R-factors R are based

on F, with F set to zero for negative F^2^. The threshold expression of

F^2^ > 2\s(F^2^) is used only for calculating R-factors(gt) etc. and is

not relevant to the choice of reflections for refinement. R-factors based

on F^2^ are statistically about twice as large as those based on F, and R-

factors based on ALL data will be even larger.

;

_refine_ls_structure_factor_coef Fsqd

_refine_ls_matrix_type full

_refine_ls_weighting_scheme calc

_refine_ls_weighting_details

'calc w=1/[\s^2^(Fo^2^)+(0.0501P)^2^+1.8892P] where P=(Fo^2^+2Fc^2^)/3'

_atom_sites_solution_primary direct

_atom_sites_solution_secondary difmap

_atom_sites_solution_hydrogens geom

_refine_ls_hydrogen_treatment constr

_refine_ls_extinction_method none

_refine_ls_extinction_coef ?

_refine_ls_number_reflns 2360

_refine_ls_number_parameters 212

_refine_ls_number_restraints 0

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_refine_ls_R_factor_gt 0.0559

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_refine_ls_wR_factor_gt 0.1326

_refine_ls_goodness_of_fit_ref 1.106

_refine_ls_restrained_S_all 1.106

_refine_ls_shift/su_max 0.000

_refine_ls_shift/su_mean 0.000

loop_

_atom_site_label

_atom_site_type_symbol

_atom_site_fract_x

_atom_site_fract_y

_atom_site_fract_z

_atom_site_U_iso_or_equiv

_atom_site_adp_type

_atom_site_occupancy

_atom_site_symmetry_multiplicity

_atom_site_calc_flag

_atom_site_refinement_flags

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C1 C -0.22565(18) -0.7838(3) -0.0824(4) 0.0336(10) Uani 0.50 1 d P A -1

H1A H -0.2298 -0.7334 -0.0103 0.040 Uiso 0.50 1 calc PR A -1

H1B H -0.2702 -0.8200 -0.0934 0.040 Uiso 0.50 1 calc PR A -1

C2 C -0.20175(17) -0.7343(11) -0.2110(4) 0.037(3) Uani 0.50 1 d P A -1

H2A H -0.2148 -0.7765 -0.2879 0.045 Uiso 0.50 1 calc PR A -1

H2B H -0.2222 -0.6657 -0.2214 0.045 Uiso 0.50 1 calc PR A -1

C3 C -0.10837(18) -0.7964(3) -0.0741(3) 0.0279(8) Uani 0.50 1 d P A -1

H3 H -0.0985 -0.7549 0.0064 0.033 Uiso 0.50 1 calc PR A -1

C4 C -0.04797(19) -0.8607(3) -0.1121(4) 0.0303(9) Uani 0.50 1 d P A -1

H4A H -0.0488 -0.9265 -0.0645 0.036 Uiso 0.50 1 calc PR A -1

H4B H -0.0038 -0.8254 -0.0924 0.036 Uiso 0.50 1 calc PR A -1

C5 C -0.0563(2) -0.8771(3) -0.2599(4) 0.0316(8) Uani 0.50 1 d P A -1

H5A H -0.0111 -0.8917 -0.3019 0.038 Uiso 0.50 1 calc PR A -1

H5B H -0.0884 -0.9341 -0.2782 0.038 Uiso 0.50 1 calc PR A -1

C6 C -0.08552(18) -0.7785(2) -0.3086(3) 0.0279(10) Uani 0.50 1 d P A -1

C7 C -0.0984(2) -0.6215(3) -0.1721(4) 0.0332(9) Uani 0.50 1 d P A -1

H7A H -0.0484 -0.6225 -0.1549 0.050 Uiso 0.50 1 calc PR A -1

H7B H -0.1226 -0.5933 -0.0956 0.050 Uiso 0.50 1 calc PR A -1

H7C H -0.1078 -0.5793 -0.2497 0.050 Uiso 0.50 1 calc PR A -1

N1 N -0.12326(14) -0.7280(2) -0.1970(3) 0.0243(11) Uani 0.50 1 d P A -1

O1 O -0.16880(13) -0.8538(2) -0.0602(3) 0.0339(6) Uani 0.50 1 d P A -1

C8 C -0.0829(2) -0.7362(16) -0.4253(3) 0.041(3) Uani 0.50 1 d P A -1

H8A H -0.0594 -0.7695 -0.4954 0.049 Uiso 0.50 1 calc PR A -1

H8B H -0.1046 -0.6722 -0.4400 0.049 Uiso 0.50 1 calc PR A -1

C9 C 0.00788(13) -0.7500 0.2393(2) 0.0208(5) Uani 1 2 d S . .

C10 C -0.03140(9) -0.84010(13) 0.23822(16) 0.0253(4) Uani 1 1 d . . .

H9 H -0.0077 -0.9035 0.2359 0.030 Uiso 1 1 calc R . .

C11 C -0.10349(10) -0.84062(15) 0.24043(17) 0.0308(5) Uani 1 1 d . . .

H10 H -0.1277 -0.9036 0.2402 0.037 Uiso 1 1 calc R . .

C12 C -0.14016(14) -0.7500 0.2429(3) 0.0316(6) Uani 1 2 d S . .

H11 H -0.1893 -0.7500 0.2462 0.038 Uiso 1 2 calc SR . .

C13 C 0.11020(12) -0.7500 0.0727(2) 0.0227(5) Uani 1 2 d S . .

C14 C 0.11449(14) -0.66178(16) -0.0013(2) 0.0517(7) Uani 1 1 d . . .

H13 H 0.1140 -0.5983 0.0435 0.062 Uiso 1 1 calc R . .

C15 C 0.11957(16) -0.6615(2) -0.1384(2) 0.0614(8) Uani 1 1 d . . .

H14 H 0.1219 -0.5984 -0.1840 0.074 Uiso 1 1 calc R . .

C16 C 0.12125(14) -0.7500 -0.2080(3) 0.0377(7) Uani 1 2 d S . .

H15 H 0.1235 -0.7500 -0.3015 0.045 Uiso 1 2 calc SR . .

C17 C 0.12664(9) -0.65208(13) 0.31056(17) 0.0235(4) Uani 1 1 d . . .

C18 C 0.18980(9) -0.60740(14) 0.2756(2) 0.0319(5) Uani 1 1 d . . .

H17 H 0.2121 -0.6293 0.1970 0.038 Uiso 1 1 calc R . .

C19 C 0.22139(11) -0.53207(16) 0.3513(2) 0.0443(6) Uani 1 1 d . . .

H18 H 0.2645 -0.5041 0.3241 0.053 Uiso 1 1 calc R . .

C20 C 0.19041(12) -0.49771(16) 0.4659(2) 0.0446(6) Uani 1 1 d . . .

H19 H 0.2118 -0.4462 0.5176 0.054 Uiso 1 1 calc R . .

C21 C 0.12781(12) -0.53968(15) 0.5040(2) 0.0413(5) Uani 1 1 d . . .

H20 H 0.1056 -0.5165 0.5820 0.050 Uiso 1 1 calc R . .

C22 C 0.09734(11) -0.61537(14) 0.42858(17) 0.0328(5) Uani 1 1 d . . .

H21 H 0.0548 -0.6438 0.4577 0.039 Uiso 1 1 calc R . .

B1 B 0.09310(15) -0.7500 0.2320(3) 0.0223(6) Uani 1 2 d S . .

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C1 0.0259(17) 0.042(2) 0.0326(19) 0.0063(15) -0.0057(15) 0.0048(14)

C2 0.0263(15) 0.050(9) 0.0358(17) 0.008(3) -0.0010(13) 0.001(2)

C3 0.0341(19) 0.0275(16) 0.0220(18) 0.0036(14) -0.0028(15) -0.0013(15)

C4 0.0252(18) 0.034(2) 0.031(2) 0.0056(17) -0.0056(16) 0.0040(16)

C5 0.034(2) 0.029(2) 0.032(2) -0.0054(16) -0.0009(17) 0.0060(16)

C6 0.0298(17) 0.028(3) 0.0258(18) -0.0049(13) -0.0033(14) 0.0001(13)

C7 0.043(2) 0.0237(19) 0.033(2) -0.0028(16) -0.0026(19) -0.0026(17)

N1 0.0286(13) 0.022(3) 0.0226(13) 0.0015(11) -0.0011(10) -0.0001(11)

O1 0.0278(13) 0.0372(15) 0.0368(14) 0.0093(12) 0.0000(11) -0.0052(11)

C8 0.053(2) 0.045(10) 0.0248(17) 0.003(3) 0.0047(14) 0.012(4)

C9 0.0299(13) 0.0201(11) 0.0123(11) 0.000 0.0012(9) 0.000

C10 0.0331(9) 0.0208(9) 0.0219(8) 0.0028(7) -0.0004(7) -0.0010(7)

C11 0.0346(10) 0.0330(10) 0.0249(9) 0.0070(8) -0.0014(8) -0.0092(8)

C12 0.0280(14) 0.0445(16) 0.0224(13) 0.000 0.0018(11) 0.000

C13 0.0201(12) 0.0266(13) 0.0213(12) 0.000 0.0000(10) 0.000

C14 0.102(2) 0.0278(11) 0.0248(10) 0.0018(9) -0.0054(11) -0.0086(12)

C15 0.106(2) 0.0516(15) 0.0262(11) 0.0150(11) -0.0061(12) -0.0288(15)

C16 0.0269(14) 0.067(2) 0.0191(13) 0.000 0.0039(11) 0.000

C17 0.0306(9) 0.0179(8) 0.0220(8) 0.0030(7) -0.0048(7) 0.0012(7)

C18 0.0296(9) 0.0266(9) 0.0396(11) -0.0008(8) -0.0038(8) -0.0001(8)

C19 0.0346(11) 0.0345(11) 0.0637(15) 0.0023(11) -0.0147(10) -0.0079(9)

C20 0.0604(14) 0.0305(11) 0.0429(13) -0.0036(10) -0.0267(11) -0.0083(10)

C21 0.0661(15) 0.0320(11) 0.0258(10) -0.0035(8) -0.0089(9) -0.0084(10)

C22 0.0467(11) 0.0281(10) 0.0235(9) -0.0020(8) -0.0013(8) -0.0084(9)

B1 0.0283(14) 0.0197(13) 0.0190(13) 0.000 -0.0002(11) 0.000

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All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes)

are estimated using the full covariance matrix. The cell s.u.'s are taken

into account individually in the estimation of s.u.'s in distances, angles

and torsion angles; correlations between s.u.'s in cell parameters are only

used when they are defined by crystal symmetry. An approximate (isotropic)

treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.

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C1 C2 1.529(8) . ?

C1 H1A 0.9900 . ?

C1 H1B 0.9900 . ?

C2 N1 1.524(4) . ?

C2 H2A 0.9900 . ?

C2 H2B 0.9900 . ?

C3 O1 1.396(4) . ?

C3 C4 1.490(5) . ?

C3 N1 1.564(4) . ?

C3 H3 1.0000 . ?

C4 C5 1.524(5) . ?

C4 H4A 0.9900 . ?

C4 H4B 0.9900 . ?

C5 C6 1.496(5) . ?

C5 H5A 0.9900 . ?

C5 H5B 0.9900 . ?

C6 C8 1.309(10) . ?

C6 N1 1.501(4) . ?

C7 N1 1.500(4) . ?

C7 H7A 0.9800 . ?

C7 H7B 0.9800 . ?

C7 H7C 0.9800 . ?

C8 H8A 0.9500 . ?

C8 H8B 0.9500 . ?

C9 C10 1.406(2) . ?

C9 C10 1.406(2) 8_545 ?

C9 B1 1.647(4) . ?

C10 C11 1.392(3) . ?

C10 H9 0.9500 . ?

C11 C12 1.385(2) . ?

C11 H10 0.9500 . ?

C12 C11 1.385(2) 8_545 ?

C12 H11 0.9500 . ?

C13 C14 1.383(2) . ?

C13 C14 1.383(2) 8_545 ?

C13 B1 1.650(3) . ?

C14 C15 1.395(3) . ?

C14 H13 0.9500 . ?

C15 C16 1.360(3) . ?

C15 H14 0.9500 . ?

C16 C15 1.360(3) 8_545 ?

C16 H15 0.9500 . ?

C17 C18 1.399(3) . ?

C17 C22 1.409(3) . ?

C17 B1 1.646(2) . ?

C18 C19 1.393(3) . ?

C18 H17 0.9500 . ?

C19 C20 1.383(3) . ?

C19 H18 0.9500 . ?

C20 C21 1.383(3) . ?

C20 H19 0.9500 . ?

C21 C22 1.386(3) . ?

C21 H20 0.9500 . ?

C22 H21 0.9500 . ?

B1 C17 1.646(2) 8_545 ?

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O1 C1 C2 100.0(4) . . ?

O1 C1 H1A 111.8 . . ?

C2 C1 H1A 111.8 . . ?

O1 C1 H1B 111.8 . . ?

C2 C1 H1B 111.8 . . ?

H1A C1 H1B 109.5 . . ?

N1 C2 C1 104.1(4) . . ?

N1 C2 H2A 110.9 . . ?

C1 C2 H2A 110.9 . . ?

N1 C2 H2B 110.9 . . ?

C1 C2 H2B 110.9 . . ?

H2A C2 H2B 109.0 . . ?

O1 C3 C4 112.0(3) . . ?

O1 C3 N1 103.7(3) . . ?

C4 C3 N1 105.2(3) . . ?

O1 C3 H3 111.8 . . ?

C4 C3 H3 111.8 . . ?

N1 C3 H3 111.8 . . ?

C3 C4 C5 104.6(3) . . ?

C3 C4 H4A 110.8 . . ?

C5 C4 H4A 110.8 . . ?

C3 C4 H4B 110.8 . . ?

C5 C4 H4B 110.8 . . ?

H4A C4 H4B 108.9 . . ?

C6 C5 C4 104.0(3) . . ?

C6 C5 H5A 110.9 . . ?

C4 C5 H5A 110.9 . . ?

C6 C5 H5B 110.9 . . ?

C4 C5 H5B 110.9 . . ?

H5A C5 H5B 109.0 . . ?

C8 C6 C5 130.7(8) . . ?

C8 C6 N1 120.9(8) . . ?

C5 C6 N1 108.4(3) . . ?

C7 N1 C6 112.5(3) . . ?

C7 N1 C2 112.6(6) . . ?

C6 N1 C2 112.8(4) . . ?

C7 N1 C3 110.1(3) . . ?

C6 N1 C3 105.0(2) . . ?

C2 N1 C3 103.1(4) . . ?

C3 O1 C1 106.0(3) . . ?

C6 C8 H8A 120.0 . . ?

C6 C8 H8B 120.0 . . ?

H8A C8 H8B 120.0 . . ?

C10 C9 C10 114.7(2) . 8_545 ?

C10 C9 B1 122.58(11) . . ?

C10 C9 B1 122.58(11) 8_545 . ?

C11 C10 C9 122.91(17) . . ?

C11 C10 H9 118.5 . . ?

C9 C10 H9 118.5 . . ?

C12 C11 C10 120.47(18) . . ?

C12 C11 H10 119.8 . . ?

C10 C11 H10 119.8 . . ?

C11 C12 C11 118.5(2) 8_545 . ?

C11 C12 H11 120.8 8_545 . ?

C11 C12 H11 120.8 . . ?

C14 C13 C14 113.8(2) . 8_545 ?

C14 C13 B1 122.93(12) . . ?

C14 C13 B1 122.93(12) 8_545 . ?

C13 C14 C15 123.2(2) . . ?

C13 C14 H13 118.4 . . ?

C15 C14 H13 118.4 . . ?

C16 C15 C14 121.1(2) . . ?

C16 C15 H14 119.4 . . ?

C14 C15 H14 119.4 . . ?

C15 C16 C15 117.5(3) . 8_545 ?

C15 C16 H15 121.3 . . ?

C15 C16 H15 121.3 8_545 . ?

C18 C17 C22 114.95(16) . . ?

C18 C17 B1 123.22(17) . . ?

C22 C17 B1 121.39(17) . . ?

C19 C18 C17 122.64(19) . . ?

C19 C18 H17 118.7 . . ?

C17 C18 H17 118.7 . . ?

C20 C19 C18 120.4(2) . . ?

C20 C19 H18 119.8 . . ?

C18 C19 H18 119.8 . . ?

C21 C20 C19 118.82(19) . . ?

C21 C20 H19 120.6 . . ?

C19 C20 H19 120.6 . . ?

C20 C21 C22 120.2(2) . . ?

C20 C21 H20 119.9 . . ?

C22 C21 H20 119.9 . . ?

C21 C22 C17 122.97(19) . . ?

C21 C22 H21 118.5 . . ?

C17 C22 H21 118.5 . . ?

C17 B1 C17 102.80(19) . 8_545 ?

C17 B1 C9 111.78(14) . . ?

C17 B1 C9 111.78(14) 8_545 . ?

C17 B1 C13 113.32(14) . . ?

C17 B1 C13 113.32(14) 8_545 . ?

C9 B1 C13 104.13(19) . . ?

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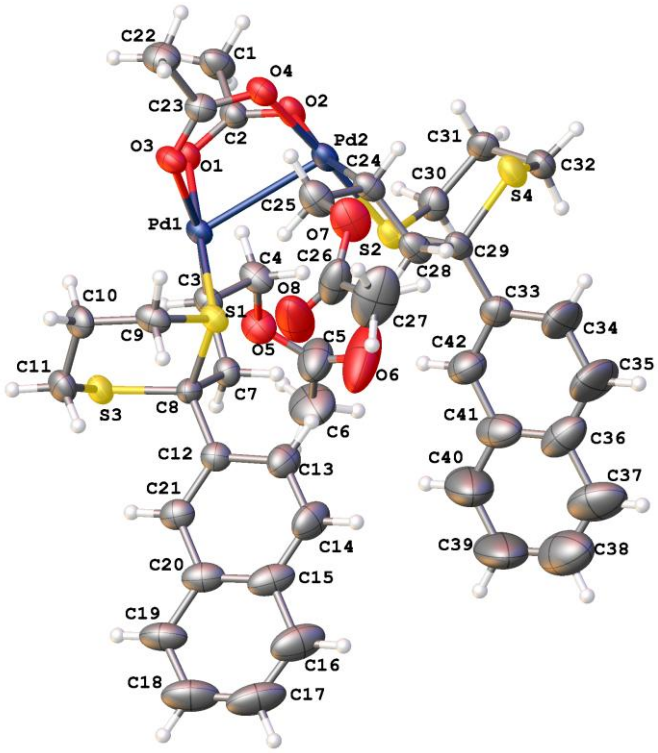
C,S-{1-Acetoxy-4-([1,3]dithian-2-yl)-4-napthalen-2-yl}butan-2-ylpalladium acetate dimer (314)



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'-x, -y, -z'

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_cell_angle_alpha 66.5690(10)
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_cell_angle_gamma 71.0010(10)
_cell_volume 2508.42(9)
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_exptl_crystal_colour yellow
_exptl_crystal_size_max 0.12
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SADABS was used to perform the Absorption correction
Parameter refinement on 31163 reflections reduced R(int) from 0.0761 to 0.0502
Ratio of minimum to maximum apparent transmission: 0.773364
The given Tmin and Tmax were generated using the SHELX SIZE command
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#Although determined using DirAx, the cell is refined in the HKL
#package during data reduction
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'OLEX2 (Dolomanov, Bourhis, Gildea, Howard & Puschmann, 2009)'
_computing_publication_material 'WINGX (Farrugia, 1998)'

_refine_special_details
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Refinement of F^2^ against ALL reflections. The weighted R-factor wR and
goodness of fit S are based on F^2^, conventional R-factors R are based
on F, with F set to zero for negative F^2^. The threshold expression of
F^2^ > 2\s(F^2^) is used only for calculating R-factors(gt) etc. and is
not relevant to the choice of reflections for refinement. R-factors based

on F^2^ are statistically about twice as large as those based on F, and R-
factors based on ALL data will be even larger.
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_atom_site_symmetry_multiplicity
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_atom_site_disorder_assembly
_atom_site_disorder_group
C1 C -0.3571(5) 0.0750(4) 0.2672(3) 0.0479(13) Uani 1 1 d . . .
H1A H -0.3658 0.0381 0.3266 0.072 Uiso 1 1 calc R . .
H1B H -0.3930 0.0512 0.2319 0.072 Uiso 1 1 calc R . .
H1C H -0.4078 0.1442 0.2513 0.072 Uiso 1 1 calc R . .
C2 C -0.2107(5) 0.0619(3) 0.2546(3) 0.0342(10) Uani 1 1 d . . .
C3 C -0.0453(5) 0.2023(3) 0.0794(3) 0.0346(10) Uani 1 1 d U . .
H3 H -0.1054 0.2158 0.0300 0.042 Uiso 1 1 calc R . .
C4 C -0.1292(5) 0.2571(3) 0.1280(3) 0.0414(11) Uani 1 1 d U . .
H4A H -0.2056 0.2332 0.1478 0.050 Uiso 1 1 calc R . .
H4B H -0.0736 0.2452 0.1781 0.050 Uiso 1 1 calc R . .
C5 C -0.1329(8) 0.4182(5) 0.0950(5) 0.0725(19) Uani 1 1 d U . .
C6 C -0.1999(10) 0.5241(5) 0.0386(5) 0.087(2) Uani 1 1 d U . .
H6A H -0.2002 0.5640 0.0695 0.131 Uiso 1 1 calc R . .
H6B H -0.2929 0.5351 0.0208 0.131 Uiso 1 1 calc R . .
H6C H -0.1502 0.5420 -0.0111 0.131 Uiso 1 1 calc R . .
C7 C 0.0706(5) 0.2404(3) 0.0439(3) 0.0336(10) Uani 1 1 d . . .
H7A H 0.1151 0.2482 0.0884 0.040 Uiso 1 1 calc R . .
H7B H 0.0333 0.3054 -0.0031 0.040 Uiso 1 1 calc R . .
C8 C 0.1760(4) 0.1722(3) 0.0117(3) 0.0307(9) Uani 1 1 d . . .
C9 C 0.3009(5) -0.0377(4) 0.0711(3) 0.0395(11) Uani 1 1 d . . .
H9A H 0.3906 -0.0337 0.0545 0.047 Uiso 1 1 calc R . .
H9B H 0.3155 -0.1016 0.1187 0.047 Uiso 1 1 calc R . .
C10 C 0.2244(5) -0.0340(4) -0.0021(3) 0.0408(11) Uani 1 1 d . . .
H10A H 0.1346 -0.0384 0.0141 0.049 Uiso 1 1 calc R . .
H10B H 0.2735 -0.0912 -0.0147 0.049 Uiso 1 1 calc R . .
C11 C 0.2058(5) 0.0580(4) -0.0811(3) 0.0419(11) Uani 1 1 d . . .
H11A H 0.1721 0.0505 -0.1294 0.050 Uiso 1 1 calc R . .
H11B H 0.2945 0.0670 -0.0929 0.050 Uiso 1 1 calc R . .
C12 C 0.3000(5) 0.2032(3) -0.0115(3) 0.0358(10) Uani 1 1 d U . .
C13 C 0.3817(5) 0.2027(4) 0.0511(4) 0.0467(12) Uani 1 1 d U . .
H13 H 0.3628 0.1778 0.1083 0.056 Uiso 1 1 calc R . .
C14 C 0.4874(6) 0.2371(4) 0.0313(4) 0.0578(14) Uani 1 1 d U . .
H14 H 0.5409 0.2356 0.0747 0.069 Uiso 1 1 calc R . .
C15 C 0.5173(6) 0.2745(4) -0.0527(4) 0.0579(14) Uani 1 1 d U . .
C16 C 0.6273(7) 0.3105(5) -0.0753(6) 0.081(2) Uani 1 1 d U . .
H16 H 0.6814 0.3112 -0.0334 0.097 Uiso 1 1 calc R . .
C17 C 0.6545(7) 0.3442(6) -0.1586(6) 0.087(2) Uani 1 1 d U . .
H17 H 0.7282 0.3678 -0.1734 0.104 Uiso 1 1 calc R . .
C18 C 0.5780(8) 0.3445(6) -0.2200(6) 0.083(2) Uani 1 1 d U . .

H18 H 0.5993 0.3681 -0.2768 0.100 Uiso 1 1 calc R . .
C19 C 0.4711(7) 0.3115(4) -0.2011(4) 0.0620(16) Uani 1 1 d U . .
H19 H 0.4181 0.3129 -0.2447 0.074 Uiso 1 1 calc R . .
C20 C 0.4394(6) 0.2752(4) -0.1168(4) 0.0508(13) Uani 1 1 d U . .
C21 C 0.3308(5) 0.2388(4) -0.0936(3) 0.0420(11) Uani 1 1 d U . .
H21 H 0.2773 0.2390 -0.1363 0.050 Uiso 1 1 calc R . .
C22 C 0.0793(6) -0.2595(4) 0.2958(4) 0.0497(13) Uani 1 1 d . . .
H22A H 0.0267 -0.2581 0.2499 0.075 Uiso 1 1 calc R . .
H22B H 0.0412 -0.2859 0.3491 0.075 Uiso 1 1 calc R . .
H22C H 0.1731 -0.3008 0.2996 0.075 Uiso 1 1 calc R . .
C23 C 0.0744(5) -0.1579(3) 0.2784(3) 0.0360(10) Uani 1 1 d . . .
C24 C 0.2830(5) -0.0653(4) 0.3689(3) 0.0367(10) Uani 1 1 d U . .
H24 H 0.2930 -0.1066 0.4308 0.044 Uiso 1 1 calc R . .
C25 C 0.3546(5) -0.1320(4) 0.3267(3) 0.0489(13) Uani 1 1 d U . .
H25A H 0.3165 -0.1851 0.3408 0.059 Uiso 1 1 calc R . .
H25B H 0.3418 -0.0951 0.2647 0.059 Uiso 1 1 calc R . .
C26 C 0.5850(6) -0.1517(6) 0.2965(5) 0.0683(18) Uani 1 1 d U . .
C27 C 0.7272(7) -0.1956(8) 0.3361(7) 0.108(3) Uani 1 1 d U . .
H27A H 0.7581 -0.2662 0.3526 0.162 Uiso 1 1 calc R . .
H27B H 0.7314 -0.1822 0.3862 0.162 Uiso 1 1 calc R . .
H27C H 0.7854 -0.1673 0.2956 0.162 Uiso 1 1 calc R . .
C28 C 0.3482(5) 0.0110(4) 0.3572(3) 0.0410(11) Uani 1 1 d . . .
H28A H 0.3666 0.0387 0.2975 0.049 Uiso 1 1 calc R . .
H28B H 0.4359 -0.0213 0.3921 0.049 Uiso 1 1 calc R . .
C29 C 0.2628(5) 0.0943(4) 0.3807(3) 0.0368(10) Uani 1 1 d . . .
C30 C -0.0256(5) 0.2060(4) 0.3570(3) 0.0436(12) Uani 1 1 d . . .
H30A H -0.0132 0.2697 0.3415 0.052 Uiso 1 1 calc R . .
H30B H -0.1144 0.2186 0.3299 0.052 Uiso 1 1 calc R . .
C31 C -0.0290(5) 0.1607(4) 0.4513(3) 0.0433(12) Uani 1 1 d . . .
H31A H -0.0469 0.0988 0.4669 0.052 Uiso 1 1 calc R . .
H31B H -0.1044 0.2048 0.4677 0.052 Uiso 1 1 calc R . .
C32 C 0.1017(5) 0.1403(4) 0.5007(3) 0.0426(12) Uani 1 1 d . . .
H32A H 0.0865 0.1241 0.5608 0.051 Uiso 1 1 calc R . .
H32B H 0.1275 0.1997 0.4791 0.051 Uiso 1 1 calc R . .
C33 C 0.3247(5) 0.1735(4) 0.3572(3) 0.0454(12) Uani 1 1 d U . .
C34 C 0.4151(8) 0.1710(7) 0.4157(5) 0.088(2) Uani 1 1 d U . .
H34 H 0.4253 0.1252 0.4726 0.106 Uiso 1 1 calc R . .
C35 C 0.4885(9) 0.2322(8) 0.3937(7) 0.112(3) Uani 1 1 d U . .
H35 H 0.5472 0.2288 0.4356 0.134 Uiso 1 1 calc R . .
C36 C 0.4797(7) 0.2968(6) 0.3143(6) 0.0780(19) Uani 1 1 d U . .
C37 C 0.5626(10) 0.3588(8) 0.2909(8) 0.108(3) Uani 1 1 d U . .
H37 H 0.6205 0.3569 0.3324 0.129 Uiso 1 1 calc R . .
C38 C 0.5566(14) 0.4144(8) 0.2157(8) 0.126(3) Uani 1 1 d U . .
H38 H 0.6165 0.4508 0.2002 0.151 Uiso 1 1 calc R . .
C39 C 0.4649(17) 0.4264(10) 0.1518(8) 0.163(5) Uani 1 1 d U . .
H39 H 0.4607 0.4716 0.0953 0.195 Uiso 1 1 calc R . .
C40 C 0.3797(15) 0.3688(9) 0.1747(7) 0.138(4) Uani 1 1 d U . .
H40 H 0.3161 0.3763 0.1334 0.166 Uiso 1 1 calc R . .
C41 C 0.3885(8) 0.3042(5) 0.2540(5) 0.0737(18) Uani 1 1 d U . .
C42 C 0.3116(7) 0.2414(5) 0.2780(4) 0.0608(15) Uani 1 1 d U . .
H42 H 0.2487 0.2472 0.2371 0.073 Uiso 1 1 calc R . .
O1 O -0.1773(3) 0.0671(2) 0.18222(19) 0.0341(7) Uani 1 1 d . . .
O2 O -0.1361(3) 0.0492(3) 0.3146(2) 0.0385(8) Uani 1 1 d . . .
O3 O 0.0700(3) -0.1009(2) 0.20375(19) 0.0372(7) Uani 1 1 d . . .
O4 O 0.0757(3) -0.1395(2) 0.3432(2) 0.0392(8) Uani 1 1 d . . .
O5 O -0.1813(4) 0.3625(3) 0.0749(2) 0.0470(9) Uani 1 1 d U . .
O6 O -0.0402(8) 0.3861(4) 0.1490(5) 0.134(3) Uani 1 1 d U . .
O7 O 0.4986(4) -0.1729(3) 0.3555(3) 0.0622(11) Uani 1 1 d U . .
O8 O 0.5489(6) -0.1025(6) 0.2229(4) 0.103(2) Uani 1 1 d U . .
S1 S 0.21990(11) 0.05738(8) 0.10813(7) 0.0319(2) Uani 1 1 d . . .
S2 S 0.10490(12) 0.13437(9) 0.31375(7) 0.0355(3) Uani 1 1 d . . .
S3 S 0.08955(12) 0.16537(9) -0.07189(7) 0.0355(3) Uani 1 1 d . . .
S4 S 0.23817(13) 0.04089(10) 0.49199(8) 0.0431(3) Uani 1 1 d . . .

Pd1 Pd 0.01652(3) 0.05619(2) 0.14884(2) 0.02980(10) Uani 1 1 d . . .
Pd2 Pd 0.08125(3) -0.00579(3) 0.33138(2) 0.03300(10) Uani 1 1 d . . .

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_atom_site_aniso_U_33
_atom_site_aniso_U_23
_atom_site_aniso_U_13
_atom_site_aniso_U_12
C1 0.034(3) 0.064(4) 0.040(3) -0.018(3) 0.010(2) -0.015(2)
C2 0.037(2) 0.036(2) 0.032(2) -0.0158(19) 0.0081(19) -0.012(2)
C3 0.035(2) 0.035(2) 0.031(2) -0.0141(19) 0.0049(18) -0.0069(19)
C4 0.045(3) 0.030(2) 0.036(2) -0.011(2) 0.006(2) -0.001(2)
C5 0.097(5) 0.052(3) 0.071(4) -0.024(3) -0.012(4) -0.026(4)
C6 0.125(7) 0.042(3) 0.090(5) -0.022(3) 0.007(5) -0.028(4)
C7 0.035(2) 0.032(2) 0.033(2) -0.0159(19) 0.0033(18) -0.0075(19)
C8 0.032(2) 0.032(2) 0.028(2) -0.0107(18) 0.0024(17) -0.0136(19)
C9 0.038(3) 0.034(3) 0.039(3) -0.014(2) 0.013(2) -0.005(2)
C10 0.050(3) 0.040(3) 0.040(3) -0.026(2) 0.012(2) -0.013(2)
C11 0.047(3) 0.050(3) 0.036(2) -0.025(2) 0.011(2) -0.016(2)
C12 0.033(2) 0.031(2) 0.038(2) -0.013(2) 0.0037(18) -0.0070(19)
C13 0.044(3) 0.041(3) 0.048(3) -0.011(2) -0.007(2) -0.012(2)
C14 0.041(3) 0.053(3) 0.072(4) -0.017(3) -0.013(3) -0.015(3)
C15 0.036(3) 0.038(3) 0.085(4) -0.010(3) 0.006(3) -0.011(2)
C16 0.043(3) 0.061(4) 0.114(5) -0.010(4) -0.001(3) -0.020(3)
C17 0.050(4) 0.066(5) 0.126(6) -0.013(5) 0.022(4) -0.029(3)
C18 0.059(4) 0.070(5) 0.100(5) -0.014(4) 0.036(4) -0.024(4)
C19 0.059(4) 0.049(3) 0.071(4) -0.017(3) 0.032(3) -0.022(3)
C20 0.041(3) 0.036(3) 0.064(3) -0.013(2) 0.016(2) -0.010(2)
C21 0.038(3) 0.036(3) 0.050(3) -0.019(2) 0.011(2) -0.010(2)
C22 0.058(3) 0.035(3) 0.051(3) -0.013(2) 0.010(3) -0.014(3)
C23 0.033(2) 0.031(2) 0.038(2) -0.012(2) 0.0054(19) -0.0063(19)
C24 0.029(2) 0.042(3) 0.030(2) -0.011(2) 0.0051(18) -0.005(2)
C25 0.037(3) 0.057(3) 0.044(3) -0.021(3) 0.004(2) -0.003(2)
C26 0.043(3) 0.104(6) 0.094(5) -0.073(4) 0.019(3) -0.030(3)
C27 0.042(4) 0.138(8) 0.172(9) -0.106(7) 0.013(4) -0.011(4)
C28 0.027(2) 0.053(3) 0.036(2) -0.016(2) 0.0050(19) -0.007(2)
C29 0.030(2) 0.052(3) 0.029(2) -0.016(2) 0.0052(18) -0.016(2)
C30 0.037(3) 0.051(3) 0.048(3) -0.029(3) 0.009(2) -0.011(2)
C31 0.037(3) 0.058(3) 0.048(3) -0.030(3) 0.020(2) -0.023(2)
C32 0.049(3) 0.054(3) 0.035(2) -0.023(2) 0.014(2) -0.024(3)
C33 0.038(3) 0.058(3) 0.050(3) -0.028(3) 0.016(2) -0.021(2)
C34 0.078(5) 0.127(7) 0.083(5) -0.034(5) 0.002(4) -0.073(5)
C35 0.091(6) 0.151(9) 0.121(6) -0.043(6) 0.003(5) -0.089(6)
C36 0.060(4) 0.077(5) 0.124(5) -0.060(4) 0.029(4) -0.036(4)
C37 0.088(6) 0.107(7) 0.145(7) -0.055(6) 0.058(5) -0.054(5)
C38 0.164(10) 0.110(8) 0.145(8) -0.072(7) 0.066(7) -0.079(8)
C39 0.289(15) 0.157(10) 0.097(7) -0.037(7) 0.063(7) -0.167(10)
C40 0.239(12) 0.132(8) 0.083(5) -0.032(5) 0.037(6) -0.128(9)
C41 0.095(5) 0.054(4) 0.083(4) -0.034(3) 0.039(4) -0.036(4)
C42 0.065(4) 0.058(4) 0.069(4) -0.028(3) 0.015(3) -0.031(3)
O1 0.0321(16) 0.0435(19) 0.0325(16) -0.0212(14) 0.0088(13) -0.0133(14)

O2 0.0307(17) 0.057(2) 0.0316(16) -0.0236(16) 0.0089(13) -0.0138(15)
O3 0.0461(19) 0.0342(18) 0.0293(16) -0.0127(14) 0.0111(14) -0.0123(15)
O4 0.0422(19) 0.0424(19) 0.0323(17) -0.0158(15) 0.0098(14) -0.0135(16)
O5 0.049(2) 0.0358(18) 0.047(2) -0.0158(16) 0.0027(16) -0.0043(16)
O6 0.176(7) 0.077(4) 0.147(6) -0.050(4) -0.076(5) -0.024(4)
O7 0.0318(19) 0.075(3) 0.068(3) -0.033(2) 0.0016(18) 0.0025(19)
O8 0.078(4) 0.197(7) 0.080(3) -0.082(4) 0.037(3) -0.076(4)
S1 0.0325(6) 0.0335(6) 0.0271(5) -0.0131(4) 0.0061(4) -0.0073(5)
S2 0.0315(6) 0.0453(7) 0.0285(5) -0.0161(5) 0.0046(4) -0.0104(5)
S3 0.0378(6) 0.0423(7) 0.0280(5) -0.0157(5) 0.0048(4) -0.0137(5)
S4 0.0427(7) 0.0567(8) 0.0295(6) -0.0176(6) 0.0035(5) -0.0161(6)
Pd1 0.03201(19) 0.03216(19) 0.02507(17) -0.01378(14) 0.00764(13) -0.00844(14)
Pd2 0.02839(18) 0.0439(2) 0.02667(18) -0.01652(15) 0.00677(13) -0.00984(15)

_geom_special_details
;
All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell s.u.'s are taken
into account individually in the estimation of s.u.'s in distances, angles
and torsion angles; correlations between s.u.'s in cell parameters are only
used when they are defined by crystal symmetry. An approximate (isotropic)
treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.
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C1 C2 1.505(7) . ?
C1 H1A 0.9800 . ?
C1 H1B 0.9800 . ?
C1 H1C 0.9800 . ?
C2 O2 1.244(5) . ?
C2 O1 1.267(5) . ?
C3 C4 1.504(6) . ?
C3 C7 1.534(7) . ?
C3 Pd1 2.032(5) . ?
C3 H3 1.0000 . ?
C4 O5 1.475(6) . ?
C4 H4A 0.9900 . ?
C4 H4B 0.9900 . ?
C5 O6 1.214(9) . ?
C5 O5 1.312(8) . ?
C5 C6 1.506(10) . ?
C6 H6A 0.9800 . ?
C6 H6B 0.9800 . ?
C6 H6C 0.9800 . ?
C7 C8 1.535(6) . ?
C7 H7A 0.9900 . ?
C7 H7B 0.9900 . ?
C8 C12 1.523(6) . ?
C8 S3 1.806(4) . ?
C8 S1 1.854(4) . ?
C9 C10 1.509(7) . ?
C9 S1 1.817(5) . ?
C9 H9A 0.9900 . ?
C9 H9B 0.9900 . ?
C10 C11 1.517(7) . ?
C10 H10A 0.9900 . ?
C10 H10B 0.9900 . ?
C11 S3 1.809(5) . ?
C11 H11A 0.9900 . ?
C11 H11B 0.9900 . ?
C12 C21 1.375(7) . ?
C12 C13 1.413(7) . ?
C13 C14 1.366(8) . ?
C13 H13 0.9500 . ?
C14 C15 1.404(9) . ?
C14 H14 0.9500 . ?
C15 C20 1.408(9) . ?
C15 C16 1.426(9) . ?
C16 C17 1.380(12) . ?
C16 H16 0.9500 . ?
C17 C18 1.364(12) . ?
C17 H17 0.9500 . ?
C18 C19 1.365(9) . ?
C18 H18 0.9500 . ?
C19 C20 1.412(8) . ?
C19 H19 0.9500 . ?

C20 C21 1.416(7) . ?
C21 H21 0.9500 . ?
C22 C23 1.503(7) . ?
C22 H22A 0.9800 . ?
C22 H22B 0.9800 . ?
C22 H22C 0.9800 . ?
C23 O3 1.243(5) . ?
C23 O4 1.271(6) . ?
C24 C25 1.508(7) . ?
C24 C28 1.522(7) . ?
C24 Pd2 2.041(5) . ?
C24 H24 1.0000 . ?
C25 O7 1.464(6) . ?
C25 H25A 0.9900 . ?
C25 H25B 0.9900 . ?
C26 O8 1.202(9) . ?
C26 O7 1.352(8) . ?
C26 C27 1.497(10) . ?
C27 H27A 0.9800 . ?
C27 H27B 0.9800 . ?
C27 H27C 0.9800 . ?
C28 C29 1.532(7) . ?
C28 H28A 0.9900 . ?
C28 H28B 0.9900 . ?
C29 C33 1.509(7) . ?
C29 S4 1.820(5) . ?
C29 S2 1.851(5) . ?
C30 C31 1.506(7) . ?
C30 S2 1.821(5) . ?
C30 H30A 0.9900 . ?
C30 H30B 0.9900 . ?
C31 C32 1.528(7) . ?
C31 H31A 0.9900 . ?
C31 H31B 0.9900 . ?
C32 S4 1.809(5) . ?
C32 H32A 0.9900 . ?
C32 H32B 0.9900 . ?
C33 C42 1.346(8) . ?
C33 C34 1.405(9) . ?
C34 C35 1.362(10) . ?
C34 H34 0.9500 . ?
C35 C36 1.337(13) . ?
C35 H35 0.9500 . ?
C36 C41 1.398(11) . ?
C36 C37 1.451(11) . ?
C37 C38 1.241(14) . ?
C37 H37 0.9500 . ?
C38 C39 1.419(17) . ?
C38 H38 0.9500 . ?
C39 C40 1.419(15) . ?
C39 H39 0.9500 . ?
C40 C41 1.335(12) . ?
C40 H40 0.9500 . ?
C41 C42 1.411(9) . ?
C42 H42 0.9500 . ?
O1 Pd1 2.067(3) . ?
O2 Pd2 2.156(3) . ?
O3 Pd1 2.167(3) . ?
O4 Pd2 2.071(3) . ?
S1 Pd1 2.2281(12) . ?
S2 Pd2 2.2195(13) . ?
Pd1 Pd2 2.9591(5) . ?

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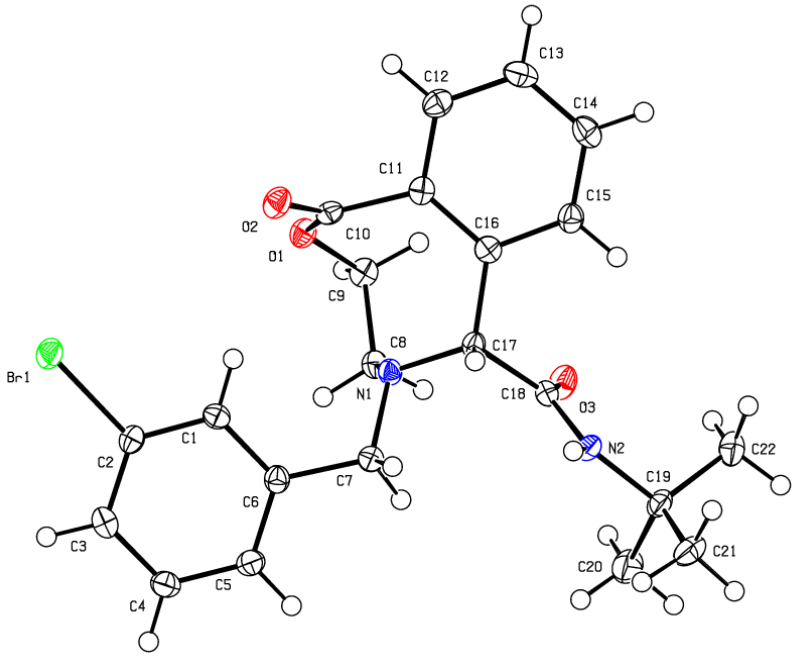


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F^2^ > 2\s(F^2^) is used only for calculating R-factors(gt) etc. and is
not relevant to the choice of reflections for refinement. R-factors based
on F^2^ are statistically about twice as large as those based on F, and R-
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C2 0.0192(9) 0.0139(9) 0.0200(9) 0.0001(7) 0.0073(7) 0.0000(7)
C3 0.0247(10) 0.0202(10) 0.0161(9) 0.0011(7) 0.0052(8) 0.0035(8)
C4 0.0203(10) 0.0236(10) 0.0197(9) -0.0011(8) 0.0012(8) -0.0016(8)
C5 0.0169(9) 0.0198(10) 0.0223(9) 0.0007(7) 0.0038(7) -0.0014(7)
C6 0.0184(9) 0.0176(9) 0.0181(9) 0.0019(7) 0.0053(7) 0.0017(7)
C7 0.0167(9) 0.0229(10) 0.0183(9) 0.0033(7) 0.0031(7) -0.0011(8)
C8 0.0203(9) 0.0180(9) 0.0176(9) 0.0000(7) 0.0057(7) 0.0004(7)
C9 0.0195(9) 0.0173(9) 0.0222(9) -0.0003(7) 0.0068(8) 0.0025(7)
C10 0.0117(8) 0.0216(10) 0.0200(9) -0.0001(7) 0.0038(7) -0.0008(7)
C11 0.0177(9) 0.0152(9) 0.0189(9) 0.0002(7) 0.0067(7) 0.0032(7)
C12 0.0185(10) 0.0217(10) 0.0251(10) -0.0021(8) 0.0075(8) -0.0002(8)
C13 0.0188(10) 0.0308(11) 0.0216(9) -0.0050(8) -0.0003(8) 0.0012(8)
C14 0.0268(11) 0.0270(10) 0.0168(9) -0.0012(8) 0.0047(8) 0.0036(8)
C15 0.0202(9) 0.0211(10) 0.0193(9) 0.0012(7) 0.0076(7) 0.0014(8)
C16 0.0166(9) 0.0170(9) 0.0181(9) -0.0006(7) 0.0050(7) 0.0032(7)
C17 0.0153(9) 0.0159(9) 0.0170(8) 0.0022(7) 0.0060(7) 0.0015(7)
C18 0.0175(9) 0.0192(9) 0.0132(8) 0.0014(7) 0.0033(7) -0.0001(7)
C19 0.0205(10) 0.0185(9) 0.0216(9) 0.0001(7) 0.0084(8) -0.0056(7)
C20 0.0392(13) 0.0297(12) 0.0256(10) -0.0086(9) 0.0127(9) -0.0151(10)
C21 0.0195(10) 0.0308(12) 0.0338(11) -0.0004(9) 0.0108(9) -0.0056(8)
C22 0.0304(11) 0.0243(11) 0.0232(10) 0.0048(8) 0.0105(9) -0.0018(9)
N1 0.0151(8) 0.0190(8) 0.0154(7) 0.0026(6) 0.0044(6) 0.0023(6)
N2 0.0148(7) 0.0151(8) 0.0204(8) 0.0018(6) 0.0059(6) -0.0008(6)
O1 0.0192(7) 0.0222(7) 0.0207(7) -0.0006(5) 0.0092(5) 0.0005(5)
O2 0.0238(7) 0.0189(7) 0.0275(7) 0.0044(6) 0.0085(6) -0.0015(6)
O3 0.0236(7) 0.0198(7) 0.0298(7) 0.0069(6) 0.0111(6) 0.0046(6)
Br1 0.02953(12) 0.02282(11) 0.02206(11) 0.00035(8) 0.00824(8) -0.00864(8)

_geom_special_details
;
 All s.u.'s (except the s.u. in the dihedral angle between two l.s. planes)
 are estimated using the full covariance matrix. The cell s.u.'s are taken
 into account individually in the estimation of s.u.'s in distances, angles
 and torsion angles; correlations between s.u.'s in cell parameters are only
 used when they are defined by crystal symmetry. An approximate (isotropic)
 treatment of cell s.u.'s is used for estimating s.u.'s involving l.s. planes.
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C5 C6 1.392(3) . ?
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C8 N1 1.474(2) . ?
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C8 H8A 0.9900 . ?
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C9 O1 1.443(2) . ?
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C10 O1 1.348(2) . ?
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C6 C7 H7B 108.9 . . ?
H7A C7 H7B 107.7 . . ?
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N1 C8 H8A 109.4 . . ?
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N1 C8 H8B 109.4 . . ?
C9 C8 H8B 109.4 . . ?
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O2 C10 O1 118.52(17) . . ?
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H22B C22 H22C 109.5 . . ?
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C7 N1 C17 110.21(14) . . ?
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