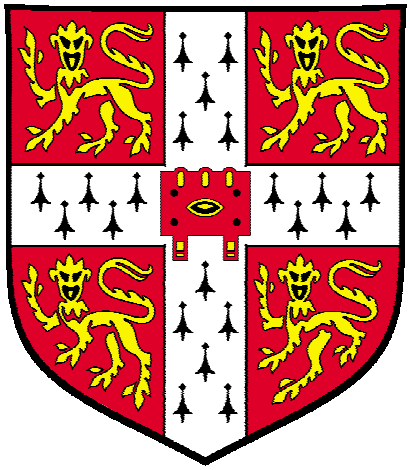
CONTROL OF REGIOSELECTIVITY: OXIDATION AND DEPROTECTION

Joseph A. Wright



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Nemo mortalium omnibus horis sapit

Pliny, Natural History*, VII, xl, 131*

PREFACE

This dissertation is a summary of research work carried out in the Department of Chemistry of the University of Cambridge between October 1999 and December 2002. Unless stated otherwise, the results are those of the author's own work. It has not, either in whole or in part, been submitted for any qualification to any other University.

Joseph A. Wright
December 2002

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ABSTRACT

Palladium is a highly versatile metal, capable of catalysing oxidations, reductions and a myriad of organic transformations. The inorganic chemistry of palladium, and the relation of this to the catalytic activity of the metal, is briefly discussed. A short survey of the range of palladium-catalysed reactions is undertaken.

The Wacker reaction, the palladium(II)-catalysed oxidation of alkenes to carbonyls, is considered in detail. In the absence of heteroatoms, the Wacker reaction of terminal alkenes is known to produce methyl ketones. However, it is shown that the Wacker reaction of styrenes is unusual; under reoxidant-free conditions, the reaction proceeds to give aldehydes as the major products. The scope of this transformation is probed with a series of ring-substituted styrenes: it is found to be general for all substituents studied. The mechanism responsible for this anti-Markovnikov regioselectivity is investigated. Palladium(0) is eliminated as a possible cause of unusual reactivity. NMR studies and reactions of suitable substrates are used to suggest a side-on complex of either an agostic or η^4-type. Kinetic studies show no evidence of an agostic interaction, and thus an η^4-complex is more likely. Attempts at achieving catalytic activity in the formation of aldehydes are unsuccessful with small-molecule reoxidants. However, the use of heteropolyacids is found to lead to a catalytic reaction.

A second source of unexpected regioselectivity in the Wacker reaction is the agostic interaction of hydrogens on the allylic position with the palladium centre. Some new evidence is obtained for this effect in the reaction of 1-phenylbut-1-ene and 1-phenyl-3-methylbut-1-ene. Attempts are made to gain additional insight by seeking a kinetic isotope effect in the Wacker reaction of dec-1-ene and a partially-deuterated analogue. Some evidence of a kinetic isotope effect is found.

The use of benzyl (Bn) groups is one of the most common methods used in synthesis to protect alcohols and amines. The method of choice for the removal of Bn groups is hydrogenolysis over a palladium catalyst. Oxidative deprotection methods are also available, particularly when the MPM (4-methoxybenzyl) group is used in place of Bn. The NAP (2-naphthylmethyl) protective group has recently been introduced and has been shown to be removed by hydrogenolysis more readily than Bn groups. The usefulness of the NAP group is extended: it is demonstrated that NAP is less sensitive to oxidative cleavage with CAN [hexa-amminecerium(IV) nitrate(V)] than MPM. A series of glucose-based substrates are prepared, and used to demonstrate this oxidative selectivity.

CONTENTS

1 ABBREVIATIONS

δ	chemical shift (parts per million)
Δ	heat
Ac	ethanoyl ("acetyl")
acac	pentan-2,4-dionate ("acetylacetonate")
Ad	adamantyl
app	apparent
Ar	aromatic / aryl
BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
Bn	benzyl / phenylmethyl
BQ	1,4-benzoquinone
br	broad
Bu	butyl
calc[d]	calculated
CAN	hexa-ammineceriu(IV) nitrate(V) ("ceric ammonium nitrate")
cat.	catalyst
$CDCl_3$	trichloro(D)methane
chp.	chapter
conv.	conversion
COSY	correlation spectroscopy
d	doublet
dba	(1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	hydridodi(1-methylpropyl)aluminium
DiPAMP	1,2-bis[(2-methoxyphenyl)phenylphospanyl]ethane
dm	doublet of multiplets
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylmethanamide ("*N,N*-dimethylformamide")

DMF-d_7	*N,N*-di(D)methyl(D)methanamide
DMSO	methanesulphinylmethane / dimethylsulphoxide
DMSO-d_6	(D)methanesulphinyl(D)methane / di(D)methylsulphoxide
dppe	1,2-bis(diphenylphosphano)ethane
dt	doublet of triplets
dt	doublet of triplets
$E^{\ominus}$	half potential under standard conditions
edn.	edition
EI	electron ionisation (in MS)
en	ethane-1,2-diamine
eq.	equivalents (mole basis)
ESI	electrospray ionisation (in MS)
Et	ethyl
Et_3SiH	triethylsilane
FT	Fourier transform
G.C.	*see* G.L.C.
G.L.C.	gas liquid chromatography
GmbH	*Gesellschaft mit beschränkter Haftung*
hfac	1,1,1,5,5,5-hexafluoropentan-2,4-dionate
HMQC	heteronuclear multi-quantum correlation
HPA	heteropolyanion / heteropolyacid
hr	hours
Hz	Hertz
IBX	1-hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one
^{i}Pr	1-methylethyl
IR	infra-red / infra-red spectrocopy
J	coupling constant
L	ligand
m	NMR: multiplet *or* IR: medium
M^*	active site on metal surface
M^+	parent ion / molecular ion (in MS)
m/z	mass-to-charge ratio
Me	methyl

MeCN	ethananitrile ("acetonitrile")
MHz	megahertz
min.	minutes
mm Hg	millimetres of mercury
MPM	4-methoxyphenylmethyl / 4-methoxybenzyl
MS	mass spectrometry
NAP	2-naphthylmethyl / naphthalen-2-ylmethyl
NMO	4-methylmorpholin-4-ol
NMR	nuclear magnetic resonance
Np	naphthen-2-yl
Nu	nucleophile
OAc	acetate
p	pentet
p.	page
PCC	pyridinium chlorochromate(VI)
[Pd]	palladium complex with unspecified ligands
PDC	pyridinium dichromate(VI)
PEG	poly(ethane-1,2-diol)
Ph	phenyl
phen	1,10-phenanthroline
pp.	pages
Pr	propyl
py	pyridine
q	quartet
qd	quartet of doublets
qdd	quartet of doublet of doublets
R	generalised organic group (different but unspecified groups referred to as R^1, R^2, *etc.*)
r.t.	room temperature / ambient temperature
R_f	retention factor
s	NMR: singlet *or* IR: strong
s.m.	starting material
t	triplet

T_b	boiling point
^{t}Bu	1,1-dimethylethyl ("*tert*-butyl")
td	triplet of doublets
tdd	triplet of doublet of doublets
TDMPP	tris(2,6-dimethoxyphenyl)phosphane
TEMPO	2,2,6,6-tetramethylpiperidine *N*-oxyl
Tf	4-trifluoromethanesulphonate / 4-trifluoromethanesulphonyl
TfOH	4-trifluoromethanesulphonic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
tm	triplet of multiplets
T_m	melting point
TMS	trimethylsilyl
Ts	(4-methylbenzene)sulphonate / (4-methylbenzene)sulphonyl
TsOH	(4-methylbenzene)sulphonic acid
tt	triplet of triplets
UV	ultra-violet / ultra-violet spectroscopy
V	Volts
v br	very broad
vol.	volume
w	weak
w/w	weight for weight
X	leaving group
xs	excess

2 PALLADIUM – A VERSATILE CATALYTIC METAL

2.1 The discovery and isolation of palladium

The history of palladium can be traced back to the first isolation of the pure element by Wollaston in 1803:[1,2]

> *"Having some time since purified a large quantity of platina by precipitation, I have had an opportunity of observing various circumstances in the solution of this singular material, that have not been noticed by others, and which, I think, cannot fail to be interesting to this Society."* [2]

Having extensively proved that he had indeed discovered a new metallic element, Wollaston named it palladium after the then newly discovered asteroid Pallas, itself named after the Greek god of wisdom παλλάδιου (palladion, of Pallas).[3] The exact timing of Wollaston's discovery is obscure;[4] it appears that he wished to claim credit for the discovery whilst keeping his method for the purification of platinum a secret!

In the original isolation,[2] palladium was obtained by a series of selective precipitations carried out on a solution of crude *platina* in *aqua regia*.[5] Whilst more efficient extraction and ion-exchange methods are now favoured[3], selective precipitation is still used in the isolation of metallic palladium.

Palladium is found in two types of deposit: as the native metal along with the other members of the platinum group (in South America and Russia), and as a trace impurity in nickel and copper deposits (in Russia, Canada and South Africa). Today, the bulk of the world's supply comes from South Africa and Russia; worldwide consumption of palladium in 1997 was approximately 210 metric tonnes.[3]

2.2 Inorganic and co-ordination chemistry

2.2.1 Introduction

The chemistry of the group X metals (Ni, Pd, Pt) shows typical behaviour for a transition metal triad. Thus, nickel is the most reactive of the three, and readily forms compounds with low formal oxidation states; in contrast, platinum is the least reactive, and is the only member of the group to attain oxidation states + 5 and + 6.[6]

Prior to considering the catalytic applications of palladium, it is useful to survey the inorganic and complexation chemistry of the metal. Understanding of catalysis requires a solid grasp of

the inorganic chemistry of the element in question; palladium is no exception to this statement. Useful coverage of the basic inorganic chemistry of palladium has been included in books by Mailtlis,[4] Henry[7] and Hartley;[8] much of the essential information is also found in inorganic textbooks, such as those by Greenwood and Earnshaw,[3] and Cotton *et al.*[9]

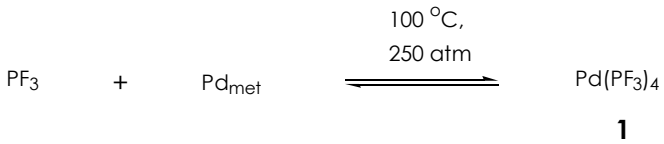
2.2.2 Oxidation states

As explained in the previous section, palladium is intermediate in chemistry between nickel and platinum. Thus, it shares with them three major oxidation states: zero, plus two and plus four. It is the balance between these oxidation states that is vital to the versatility of palladium as a catalyst. There has been, and continues to be, a large amount of scientific effort directed at producing novel complexes of palladium, both from the standpoint of mechanistic study and intrinsic interest in the complexes.

2.2.2.1 Palladium(0)

Bulk palladium is a noble metal, and thus shows the typical low reactivity of the platinum-group metals. However, palladium(0) complexes are reactive species, often used to carry out catalysis or implicated in catalytic cycles. In order to stabilise the metal atoms, ligands are necessary to prevent the formation of bulk palladium.

The zero oxidation state of palladium is somewhat unusual, in that it does not form a simple carbonyl of formula $Pd(CO)_x$; other palladium(0) carbonyl complexes are known, however, such as the mixed triphenylphosphane compounds $Pd(PPh_3)_{4-n}(CO)_n$.[4] Only a small number of palladium(0) complexes can be generated directly from bulk palladium metal; one example is complex **1** (Scheme 1).[4]



Scheme 1 – Direct reaction of Pd metal with PF_3

More usually, palladium(0) complexes are formed by the reduction of a suitable palladium(II) source in the presence of the desired ligand; typical reducing agents for this purpose include sodium tetrahydridoborate(III), hydrazine, copper metal and excess phosphane ligands.

2.2.2.2 Palladium(I)

As is stated by Henry:

> *"this is a rare oxidation state for palladium, but it may be important in the catalytic chemistry of palladium"* [10]

A small number of palladium(I) complexes are known, and usually contain metal-metal bonds.[3,4] As with palladium(III) (section 2.2.2.4), there were conflicting reports as to the true oxidation state of palladium in early work. Genuine palladium(I) complexes are now known, for example complex **2**[11] and $[PdMe(PMe_3)_3][hfac]$.[12]

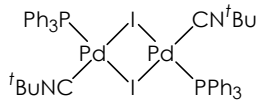


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Figure 1 – Palladium(I) complex

2.2.2.3 Palladium(II)

In contrast to platinum [which tends to form platinum(IV)], the + 2 state is the most common oxidation state for palladium salts. Palladium metal reacts with various strong oxidising agents to give palladium(II) compounds; it reacts directly with oxygen and the elemental halogens at elevated temperatures to give the palladium oxide and binary halides, respectively. In contrast to platinum, palladium will react not only with *aqua regia*, but also with hot concentrated mineral acids, and ethanoic acid containing some nitric acid. From these initial palladium(II) compounds, it is then possible to form other salts and complexes by anion and ligand exchange.

The palladium(II) halides are perhaps the best-known and widest used sources of palladium(II) in catalysis. In common with other palladium compounds, a high degree of covalency is seen throughout the binary halides. Palladium(II) fluoride is one of very few palladium(II) compounds that is not square-planar; instead, it adopts a distorted octahedral structure, and is paramagnetic.[13] In contrast, the other halides all contain approximately square-planar palladium atoms in the solid state. This is seen in both the α- and β-forms[14] of palladium(II) chloride (Figure 2).

3 **4**

Figure 2 – Palladium chloride, α- and β-forms

Palladium(II) fluoride is hydrolysed by water to hydrated palladium(II) oxide (often erroneously called palladium hydroxide); on the other hand, palladium(II) chloride and bromide are slightly water soluble, whilst the iodide is insoluble in and unreactive toward water. The tetrachloro- and tetrabromopalladium(II) ions can be formed by mixing the palladium salts with aqueous solutions of alkali metal chlorides or bromides, respectively. In this way, aqueous organometallic chemistry can be accessed (see section 3.1.3).

The other common source of palladium(II) is the acetate. In the solid state, this is found to be a trimer involving bridging acetate groups **5** (Figure 3),[15] with a Pd-Pd distance of 3.10 – 3.20 Å indicating that no metal-metal bond exists. In solution, the compound can exist as a monomer, dimer or trimer, depending upon the solvent and temperature.[16]

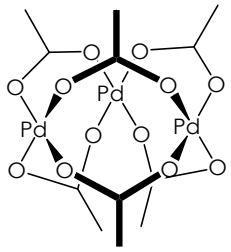

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Figure 3 – Schematic representation of palladium(II) acetate structure

2.2.2.4 Palladium(III)

Palladium(III) is perhaps the most controversial oxidation state of palladium. Early reports of "PdF_3" were believed to offer evidence for the existence of palladium(III). However, later work showed that the compound was actually of the composition $[Pd^{II}(Pd^{IV}F_6)]$.[17] A small number of palladium(III) complexes are now known; for example $[Pd(1,4,7\text{-trithianonane})_2]^{3+}$ **7** has been produced by cyclic voltammetry of the palladium(II) complex (Figure 4).[18] Palladium(III) remains the rarest oxidation state of the metal.

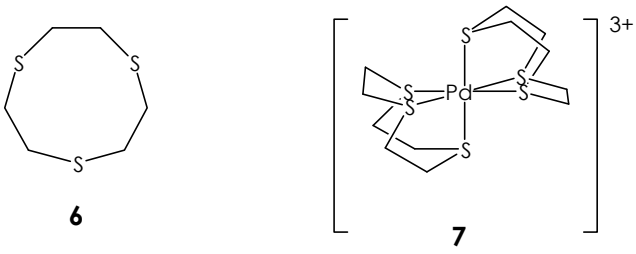


Figure 4 – Ligand and palladium(III) complex

2.2.2.5 Palladium(IV)

Reaction of palladium metal with *aqua regia* initially gives the palladium(IV) species $[PdCl_6]^{2-}$. Analogous hexaholpalladium(IV) ions are also formed with fluorine and bromine. The only tetrapalladium(IV) halide known is PdF_4.[17]

2.2.3 Hard and soft behaviour of palladium(II)

The stability of the simple palladium(II) halides is found to be in the order $I^- \rangle Br^- \rangle Cl^- \gg F^-$; a more quantitative measure of the relative stability of palladium(II) halides can be obtained by studying the half-cell potential for the reaction $Pd \rightleftharpoons Pd^{2+} + 2e^-$ in various different electrolytes (Table 1).[19]

Electrolyte	$E^{\ominus}$ (V)
ClO_4^-	- 0.92
Cl^-	- 0.59
Br^-	- 0.49
I^-	- 0.18

Table 1 – Half-cell potentials for dissolution of palladium

This reactivity pattern is means that palladium(II) is a Chatt[20] class *b* or Pearson[21] soft metal. The soft nature of palladium means that it would be expected to form complexes with carbon ligands, such as alkenes: this behaviour is examined in the next section.

2.2.4 Co-ordination of organic compounds

The key to the catalytic activity of palladium, both in homogeneous and heterogeneous systems, is the ability of the metal centre to form complexes with a range of organic molecules. There are two major types of palladium-organic complexes: σ-bonded systems and π-bonded systems.

Palladium-carbon σ-bonds are formed in two ways. In the same manner as other transition metals, palladium(II) will react with other organometallic compounds, *e.g.* organolithium and

Grignard reagents, to give σ-bonded complexes. Palladium(0) will also insert into carbon-(pseudo)halide bonds, being oxidised to palladium(II). This will be considered in a catalytic context in section 2.3.2.

A vital part to the catalytic of platinum-group metals is the formation of complexes with unsaturated species. Indeed, the first organometallic compound was of this type: Zeise's salts $K[PtCl_3(H_2C{=}CH_2)].H_2O$.[22,23] The nature of the bonding between the alkene and the metal was not understood for well over 100 years;[24,25] the interaction of metals with π-bonds may be explained by σ-donation from the alkene to the metal along with π-back-bonding from the metal to the alkene (Figure 5).

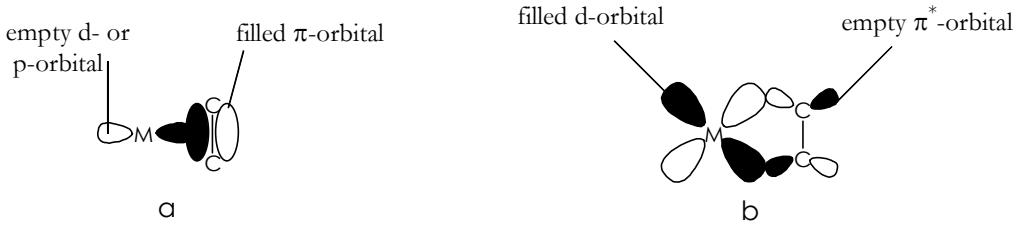
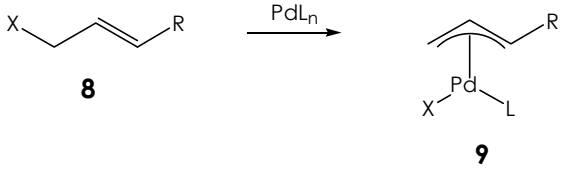


Figure 5 - Chatt-Dewar-Duncanson model of alkene bonding

This bonding model accounts for the activation of alkenes and alkynes to attack by nucleophiles, as the metal co-ordination weakens the carbon-carbon π-bond and removes electron density from the carbon atoms.

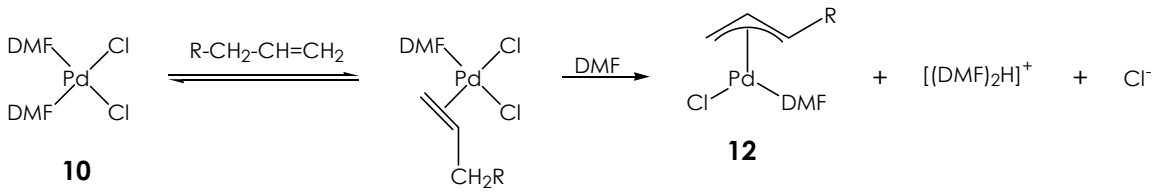
A particularly important type of palladium-carbon complex is the π-allylic system. These may be formed *via* three major routes. The displacement of a leaving group from the allylic position of a double bond by a palladium(0) complex constitutes the most common route (Scheme 2).



8 **9**

Scheme 2 – Formation of π-allylic complex from an allyl halide

The second method for formation is by the action of a base on an alkene co-ordinated to palladium(II). In some cases,[26,27] basic solvents (*e.g.* DMF) are sufficiently strong bases to effect the deprotonation (Scheme 3).



Scheme 3 – π-Allylic complex formation using DMF

The final method for formation of π-allylic complexes is the attack of a nucleophile on a conjugated diene in the presences of a palladium(II) salt.[28]

2.2.5 Co-ordination of hydrogen

Almost all metals will adsorb hydrogen gas;[29] the co-ordination and activation of hydrogen gas can be explained by the Chatt-Dewar-Duncanson model (Figure 6).[29] Palladium is particularly suited to the activation of hydrogen; a plot of the adsorption of hydrogen on metal surfaces *versus* catalytic activity of those metals reveals that palladium fulfils the need for a balance between sufficient adsorption to activate the hydrogen, and formation of a stable metal-hydride.

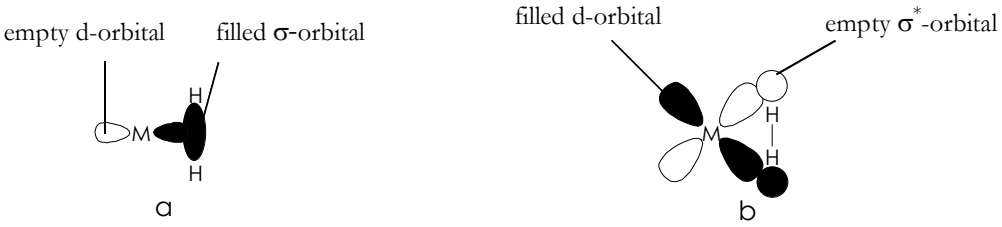


Figure 6 – Metal-hydrogen bonding

2.3 Palladium catalysis – concepts

2.3.1 Homogeneous and heterogeneous catalysis

As was stated earlier, palladium is a highly versatile catalytic metal; it takes part in both homogeneous and heterogeneous catalytic reactions. Many reactions catalysed by palladium occur with both homogeneous and heterogeneous catalysts; industrial research is often concerned with converting homogeneous reactions to efficient heterogeneous processes, thus ensuring retention of the valuable palladium.

In the context of this thesis, however, it is convenient to consider reactions carried out on relatively small scale in research laboratories. Heterogeneous, supported palladium finds its

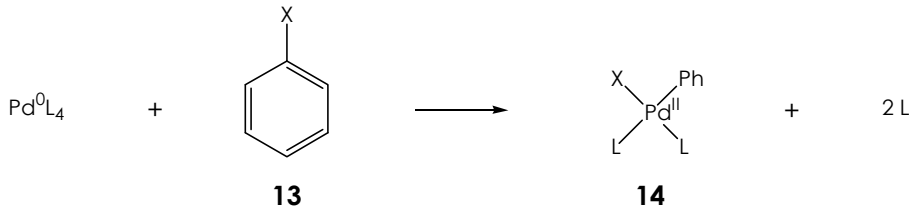
major laboratory application as a hydrogenation and hydrogenolysis catalyst; in contrast, homogeneous catalysis is used in a wide variety of processes.

2.3.2 The elementary reactions of palladium catalysis

There are a series of elemental reactions that are encountered across the spectrum of palladium, and indeed transition-metal catalysed, reactions. These are today well-known by workers in catalysis, and are covered in a large number of texts on the subject;[7,30,31] a brief overview of the key steps will therefore suffice.

Oxidative addition

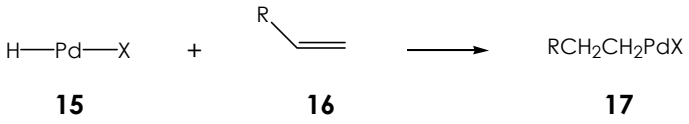
Palladium(0) will add into a variety of bonds, being formally oxidised in the process to palladium(II). The most common substrate for this reaction is a carbon-(pseudo)halide bond, usually involving an sp^2 carbon[32] (Scheme 4); note that the initial product of oxidative addition is the *cis* complex. Oxidative addition can occur with a variety of other bonds, in particular the H-H bond of dihydrogen on metallic palladium.



Scheme 4 – Oxidative addition

Insertion

Unsaturated systems can insert into Pd-X bonds to give σ-bonded carbon ligands; this can occur in a 1,1 or 1,2 sense. A typical example is the addition of a palladium-hydride to an alkene (Scheme 5).



Scheme 5 – Insertion of an alkene into a palladium-hydride

Carbon monoxide undergoes insertion in a 1,1 sense, leading to attachment of both palladium and the X group to the carbon, and generating a carbonyl compound.

Nucleophilic attack

In a similar reaction to insertion, a palladium co-ordinated alkene may be attacked by an external nucleophile; this again gives a σ-bonded palladium species of type **17**.

Reductive elimination

Reductive elimination is the reverse of oxidation addition, with a palladium(II) to palladium(0) transformation occurring concurrently with formation of C–X bond. Reaction must occur from a complex with *cis* orientation of the ligands, in analogy to complex **14**.

β-Hydride elimination

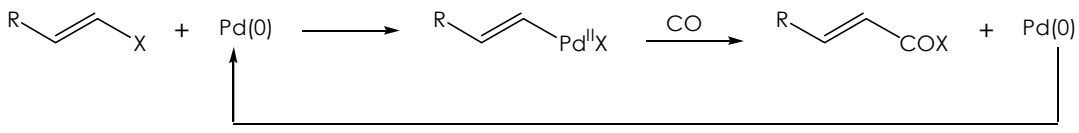
When there are *cis* hydrogens on the atom β to that bearing palladium, it is possible to carry out the reverse of insertion into a Pd-H bond, thus, generating a palladium(II) hydride and an alkene. The palladium hydride generated is usually highly unstable, and will usually break down to HX (where X was the other ligand on palladium) and palladium(0).

2.3.3 Intrinsic and extrinsic catalysis

In his extensive treatise on the use of palladium as both a catalyst and a reagent in organic synthesis, Tsuji defines two types of palladium catalysis.[33]

Intrinsic catalysis

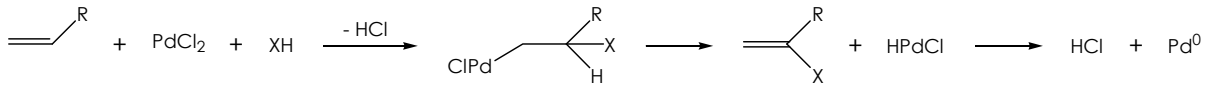
This is seen mainly with palladium(0) complexes; by making use of an "oxidised" starting material (typically alkenyl or aryl halides), it is possible to form an active palladium(II) species by oxidative addition. Reaction, followed by reductive elimination, gives the product and regenerates the palladium(0) catalyst (Scheme 6). This type of catalysis is also seen with heterogeneous hydrogenation; each catalytic cycle regenerates the metallic catalyst.



Scheme 6 – Intrinsic catalysis

Extrinsic catalysis

Palladium(II)-catalysed oxidation reactions demonstrate this form of catalysis; it is also seen in "heterogenised" versions of these reactions. Oxidation of an organic substrate by palladium(II) gives the organic product and a palladium(0) species: thus the reaction is *stoichiometric* in palladium (Scheme 7).



Scheme 7 – Extrinsic catalysis

The crucial aspect to this class of reaction is re-oxidation of the palladium(0) species *in situ* before the formation of bulk palladium metal occurs. This is not always readily achieved; palladium is a noble metal, and so reoxidation would be expected to be non-trivial. This important process will be covered later (see section 3.1.2).

2.4 Palladium(II) catalysed oxidation

2.4.1 Introduction

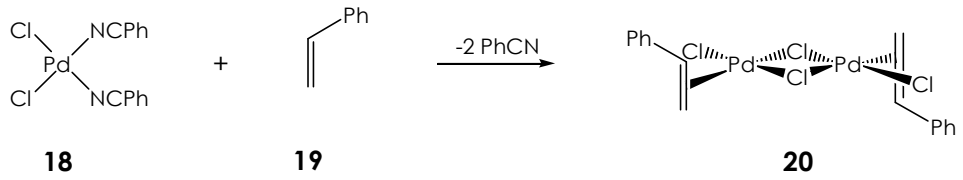
As was explained in the preceding section, palladium(II) oxidation is stoichiometric in palladium; catalysis therefore requires a suitable reoxidation system. This section will be limited to reactions that are amenable to this approach; reactions which have resisted attempts to achieve catalysis are beyond the scope of this work. The area of palladium(II) oxidation has been covered by Tsuji[31], Heck[30] and in great detail by Henry.[7]

2.4.2 The reaction of alkenes

Alkenes are activated toward nucleophilic attack by co-ordination to palladium (and other transition metals) as was explained in section 2.2.4; indeed, the first organometallic complex, Zeise's salt, is a co-ordination complex of an alkene (ethene) and *platinum*. The first reports of the reaction between palladium, an alkene and a nucleophile (water) were made by Phillips;[34,35] the fate of the organic material was not the chief concern in these investigations. Ogburn and Brawstow[36] extended the useful nature of the reaction, demonstrating that stoichiometric reaction of ethene with aqueous palladium salts could be used to precipitate the metal quantitatively from a solution of mixed noble metal salts. The fate of the organic entity was again not commented upon. Note that both Phillips[34,35] and later Smidt *et al.*[37] did see a reaction between other noble metals and ethene, but that palladium reacted most rapidly.

A significant advance in the understanding of the organometallic species involved in this reaction was made by Kharash *et al.*[38] Direct reaction between palladium(II) chloride and alkenes was unsuccessful in forming an isolable entity; however, reaction between the same alkenes and complex **18** (Scheme 8) was able to product a series of Pd-alkene complexes. The analysis of these suggested that they were dimeric, and sensitive to both moisture and alcohols. The

structures of the ethene[39] and styrene[40] complexes were solved by Baenziger and co-workers in the mid-1950s, and are approximately as shown below.



18 **19** **20**

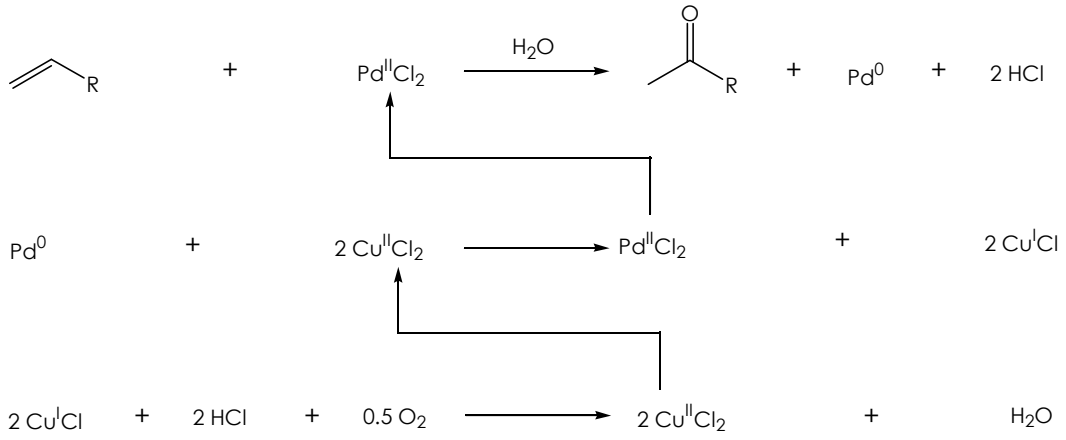
Scheme 8 – Formation of a palladium(II)-alkene complex

The crucial breakthrough in the reactivity of alkenes with palladium(II) was made by Smidt *et al.*,[37,41-43] with the discovery that a catalytic reaction between palladium(II) salts and alkenes could be achieved by using copper(II) chloride and oxygen as a reoxidation system, thus producing carbonyl compounds. Indeed, this discovery was vital to palladium-catalysed reactions in general, as is made clear by Tsuji.

> *"Modern palladium chemistry started in 1960 with the ingenious invention of an industrial process for acetaldehyde production by the air oxidation of ethylene, catalyzed by $PdCl_2$ and $CuCl_2$, which is called the Wacker process."*[44]

2.4.2.1 Reaction with water – The Wacker reaction

As was stated in the previous section, the reaction between palladium(II) salts and water has over one hundred years of history, but it was not until 1959 that Smidt *et al.*[37] were able to apply the reaction to organic synthesis. The general form of the reaction is shown in Scheme 9.

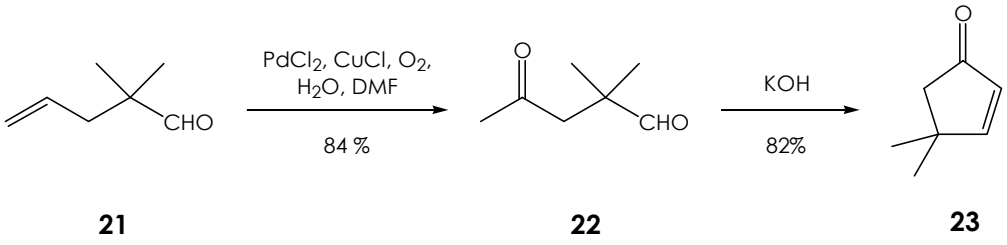


Scheme 9 – Generalised Wacker reaction

As is shown above, a terminal alkene will usually proceed to a methyl ketone, showing Markovnikov regioselectivity. The formation of ketones using the Wacker reaction has been

reviewed a number of times.[30,31,45-49] The Wacker reaction is considered in detail in chapter 3: some general points will be raised here.

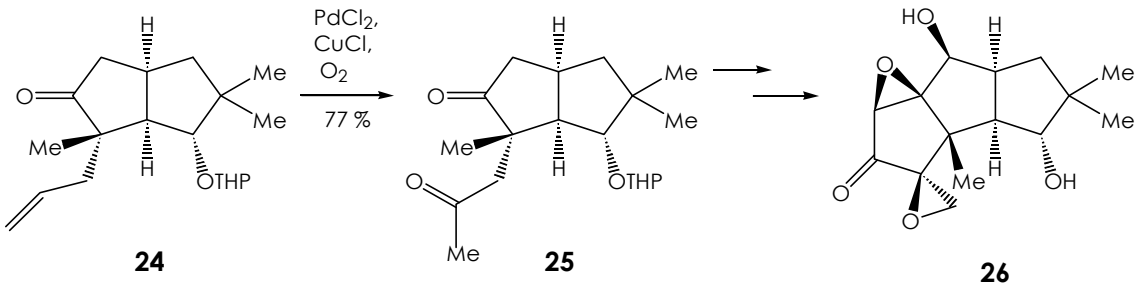
The Wacker reaction has been applied in a wide range of syntheses,[45] allowing terminal alkenes to act as masked methyl ketones. This is possible since the Wacker reaction is tolerant of a range of functional groups: aldehydes, alcohols, ethers, esters, carboxylic acids, acetals, chlorides, bromides, sulphonyl esters and sulphones. While some of these groups react with palladium under Wacker conditions, these side reactions are normally slow compared to the oxidation of alkenes. A simple example of the synthetic utility of the Wacker reaction is shown below (Scheme 10); following oxidation of the terminal alkene, cyclisation gives ready access to the α,β-unsaturated carbonyl system.[50]



21 **22** **23**

Scheme 10 – Wacker reaction followed by cyclisation

A second example is the use of the Wacker reaction in the racemic synthesis of Coriolin **26**; unmasking of the methyl ketone allows access to the third ring of the molecule (Scheme 11).[51]

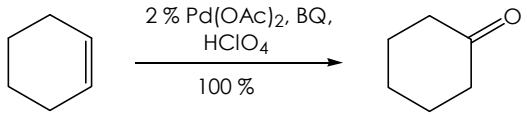


24 **25** **26**

Scheme 11 – Synthesis of Coriolin

Internal double bonds are generally found to be difficult to oxidise in comparison to terminal double bonds. The regioselectivity of the reaction is also poor in the majority of unsymmetrical substrates. Under certain conditions, however, it is possible to carry out the clean oxidation of internal double bonds. Miller and Wayner[52] have reported that it is possible to oxidise symmetrical internal double bonds by using palladium(II) acetate reoxidised by 1,4-benzoquinone. In order for the reaction to be successful, a strong but non-complexing acid had to be added to the reaction medium. Sulphuric, nitric, chloric(VII) or tetrafluoroboric acids were

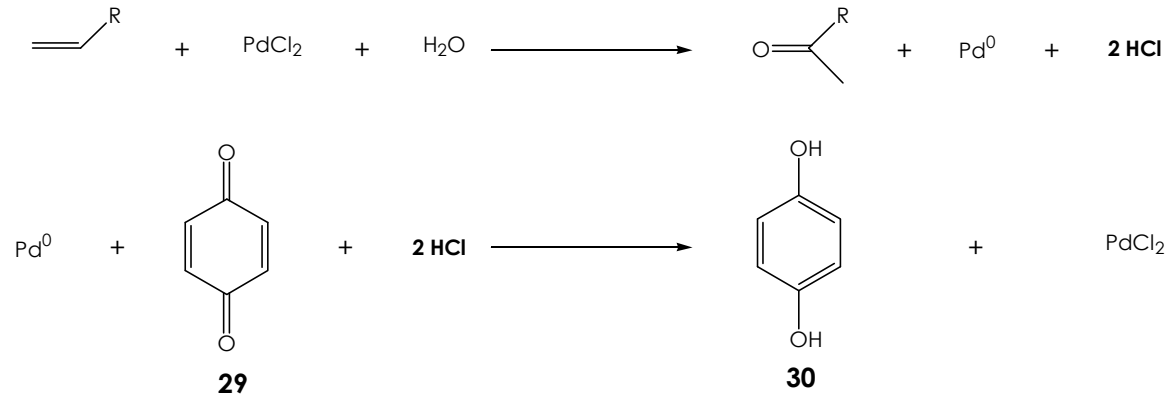
reported to be successful, whereas hydrochloric acid did not lead to the desired product. An example is given below (Scheme 12).



27 **28**

Scheme 12 – Reaction of internal double bond

The reoxidation of palladium(0) to palladium(II) is an issue that concerns all oxidation reactions using palladium(II). As has already been stated, palladium is a noble metal, and so the reoxidation by copper(II) might be expected to be unfavourable. As will be covered in section 3.1.2, this is borne out by half-cell potentials for the reaction. It is only by altering conditions that the reoxidation can be made more facile. However, a number of other reoxidants can also be made use of in the Wacker reaction; one that is particularly useful in the lab is 1,4-benzoquinone **29**. This has the particular advantage of preventing the accumulation of acid (Scheme 13).

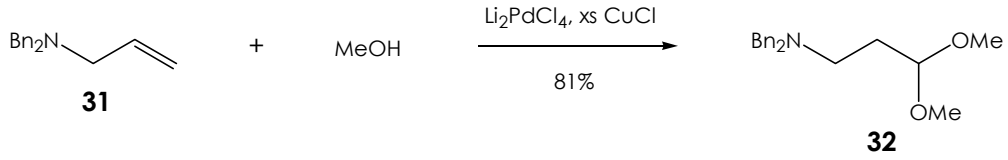


29 **30**

Scheme 13 – Reoxidation using 1,4-benzoquinone (BQ)

2.4.2.2 Reaction with alcohols (and related nucleophiles)

As might be expected from a simple consideration of the reaction, alcohols will readily act in a Wacker-like manner, in place of water. The reaction typically proceeds to produce acetals; reaction of **31** with methanol as the solvent proceeds readily to give the acetal **32** (Scheme 14).[53] The anti-Markovnikov regioselectivity of the reaction is proposed to be due to the presence of a suitably placed heteroatom (see section 3.1.4 for details of regioselectivity in Wacker-type reactions).



31 **32**

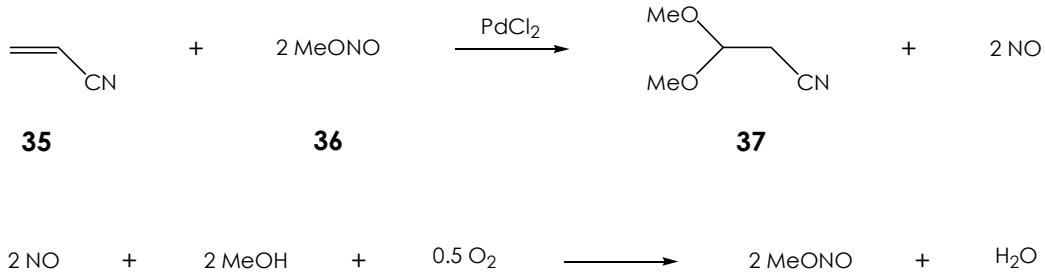
Scheme 14 – Formation of terminal acetal

The reaction with alcohols will also proceed in an intramolecular sense, for example in the synthesis of *endo*-Brevicomin[54] **34** (Scheme 15). Here the reaction proceeds with Markovnikov regioselectivity, although the yield is lower than for the simple case above.

33 **34**

Scheme 15 – Synthesis of *endo*-Brevicomin

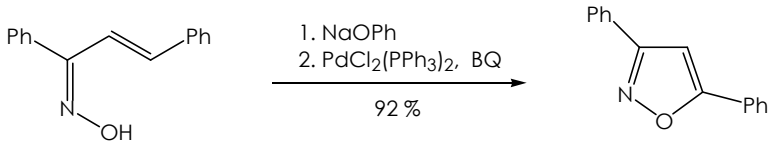
An interesting use of this reaction is the commercial production of 3,3-dimethoxypropanonitrile.[55] This makes use of nitroso-oxymethane **36**, rather than methanol, as the nucleophile, giving a reaction that is catalytic in palladium(II) without the need for a reoxidant (Scheme 16).



35 **36** **37**

Scheme 16 – Formation of 3,3-dimethoxypropanonitrile

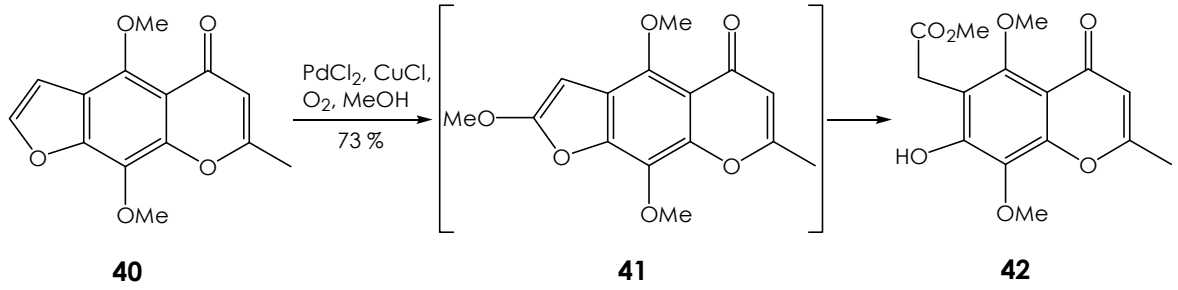
The formation of interesting heterocyclic compounds may be achieved using Wacker-like reactions.[56,57] One example is the formation of isoxazoles from α,β-unsaturated ketoximes, such as the formation of **39** (Scheme 17).



38 **39**

Scheme 17 – Formation of isoxazoles

A final example of the use of a Wacker-like reaction with alcohols is the conversion of cyclic enol ethers to esters by solvolysis of the initially formed product. One example of this type of reaction is shown below (Scheme 18), from an investigation of the reactivity of Khellin **40**.[58] The initial product of the palladium-catalysed reaction is **41**, but this breaks down under the reaction conditions to the ester **42**.

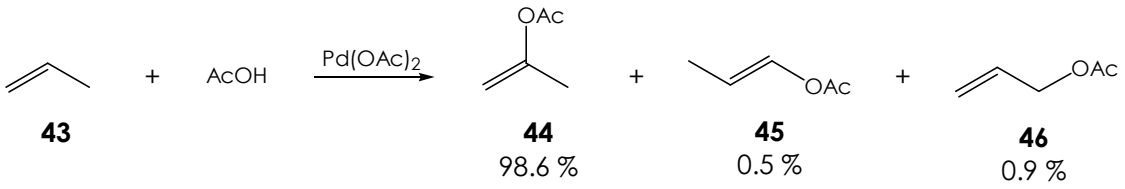


40 **41** **42**

Scheme 18 – Reaction of Khellin with methanol

2.4.2.3 Reaction with carboxylic acids

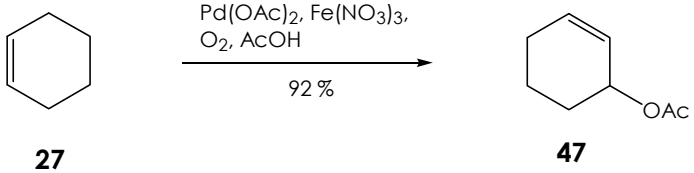
The reaction between alkenes and ethanoic acid was discovered by reacting palladium(II) acetate with ethene in the presence of sodium acetate.[59,60] In general, the reaction can proceed to form either vinyl or allyl esters, although allyl esters are more common.[30] However, addition to the more substituted carbon is favoured, as is shown in the example below (Scheme 19).[61]



43 **44** 98.6 % **45** 0.5 % **46** 0.9 %

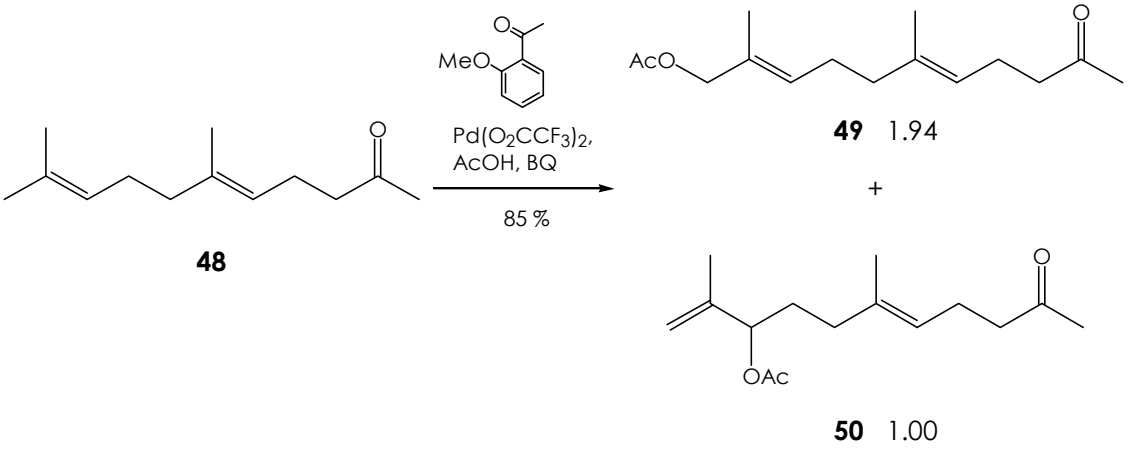
Scheme 19 – Reaction of propene with ethanoic acid

In contrast to the Wacker reaction, internal double bonds will react readily with carboxylic acids, as demonstrated by the reaction of cyclohexene (Scheme 20).[62] However, it is still found that terminal double bonds react more readily than internal double bonds; thus it is possible to carry out the reaction selectively (Scheme 21).[63]



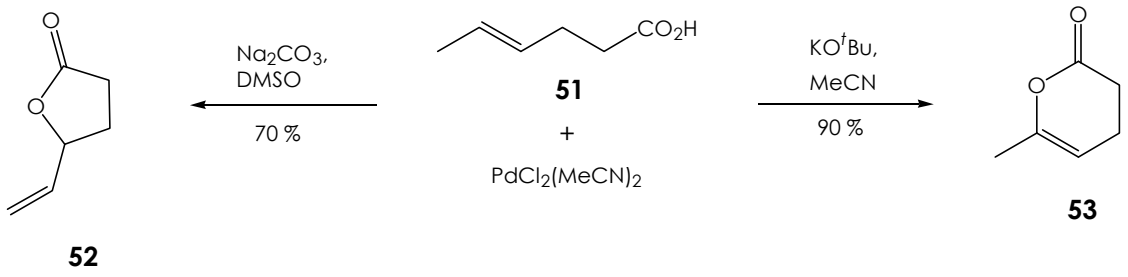
27 **47**

Scheme 20 – Reaction of internal double bond with acetate



Scheme 21 – Selectivity for reaction at terminal double bonds

Once again, the intramolecular reaction has been exploited for the formation of a variety of products. An interesting reaction in this area is that of the ring closure of **51**. In DMSO with sodium carbonate as a base, the reaction proceeds to the five-membered ring **52**; using ethananitrile and potassium 1,1-dimethylethoxide, the six-membered lactone **53** is produced (Scheme 22).[64]

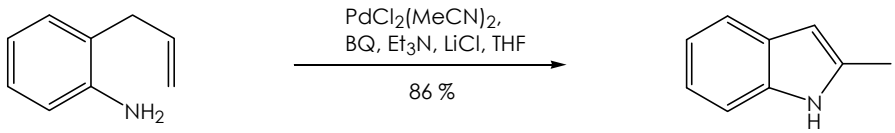


Scheme 22 – Effect of conditions on the acetate reaction

2.4.2.4 Reaction with nitrogen nucleophiles

Unlike alcohols, alkyl amines are usually poor nucleophiles under Wacker-type conditions; this is believed to be due to the ability of the nitrogen to act as a ligand for palladium(II). Reaction of alkyl amines is observed only under intramolecular conditions and is not catalytic, meaning that stoichiometric palladium(II) must be used.[65,66] As might be expected, nitrogen atoms in which the lone pair is delocalised, and which are therefore poor ligands, are successful nucleophiles: reaction takes place with amides or aromatic amines. Even with these nucleophiles, it may be necessary to add a second more powerful complexing agent in order to free the substrate nitrogen of the substrate from the palladium, and thus allow reaction to occur. For example, Hegedus *et al.*[67] have found that the reaction of **54** only proceeds if triethylamine is added to the

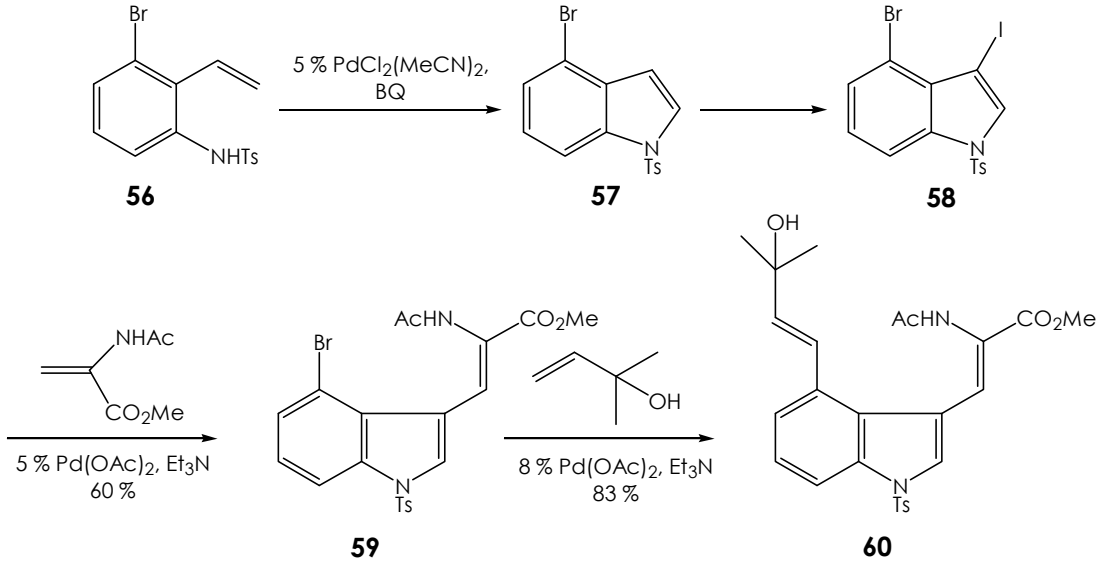
reaction system, releasing the nucleophile from the palladium (Scheme 23). In the absence of triethylamine, a stable complex is formed.



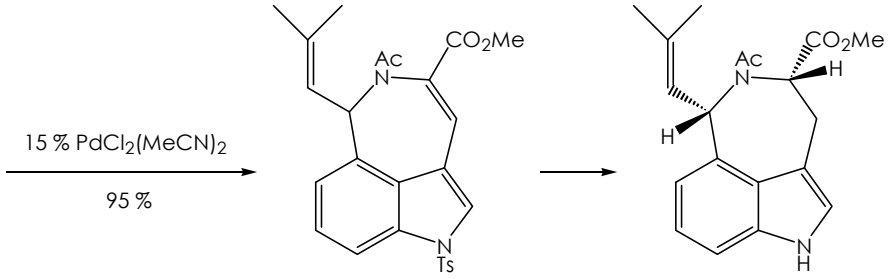
54 **55**

Scheme 23 – Intramolecular reaction of amine

A particularly impressive use of palladium(II) catalysis was reported in a total synthesis of the *N*-ethanoyl methyl ester of racemic Clavicipitic acid **62**.[68] This synthesis involves four palladium(II) catalysed steps, of which two are aminations (Scheme 24). The overall yield of the entire synthesis was around 18 %, which the authors felt compared very favourably to previous syntheses: these had given approximate overall yields of no more than 0.5 %.



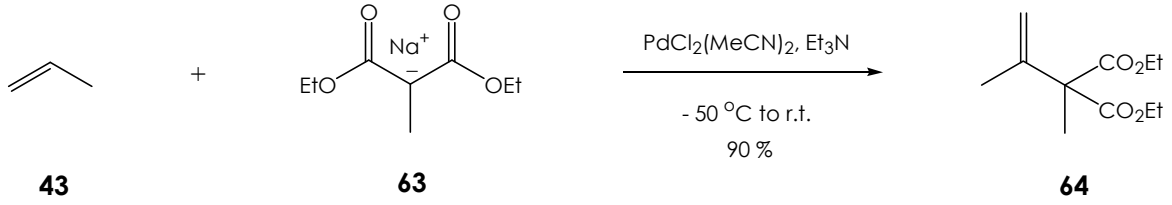
Scheme 24a – Total synthesis of *N*-ethanoyl methyl ester of Clavicipitic acid



Scheme 24b– Total synthesis of N-ethanoyl methyl ester of Clavicipitic acid

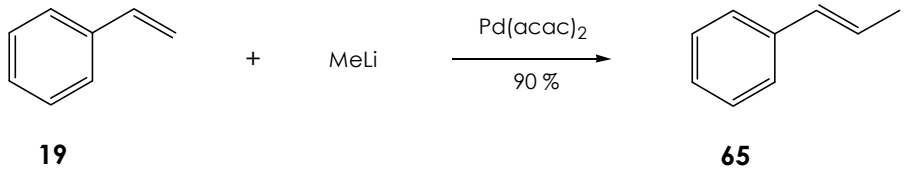
2.4.2.5 Carbon-carbon bond forming reactions

Palladium co-ordinated alkenes are attacked by both hard and soft carbon nucleophiles. The reaction of simple alkenes with soft carbon nucleophiles such as pentan-2,4-dionate (malonate) is not facile, and requires two equivalents of the carbon nucleophile along with the same amount of base (Scheme 25).[69-71] Despite this, the reaction proceeds in high yield, and can be controlled to give saturated or unsaturated products, by choice of appropriate work-up conditions.



Scheme 25 – Attack by a soft carbon nucleophile

Hard nucleophiles, such as Grignard reagents, will also react; methyl lithium reacts with styrene in 90 % yield to give 1-phenylprop-1-ene (Scheme 26)[72].

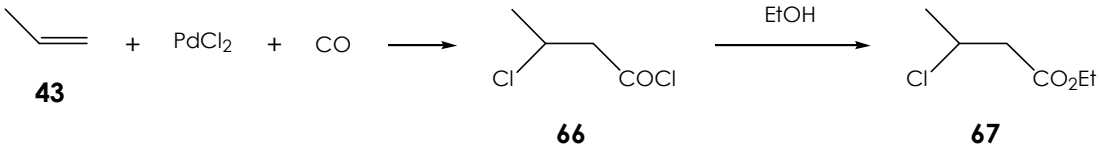


Scheme 26 – Attack by a hard carbon nucleophile

2.4.2.6 Carbonylation

In the presence of carbon monoxide, the reaction of alkenes with alcohols (or amines) may incorporate a carbonyl group between the alkene and the nucleophile. This reaction was first

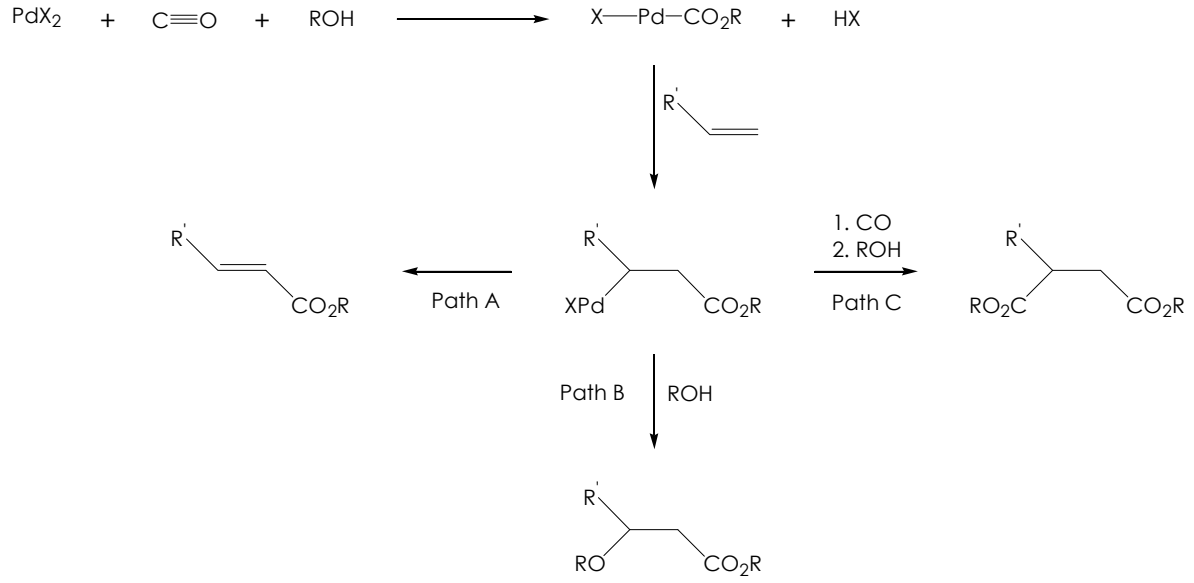
reported by Tsuji *et al.*[73] in 1963. The reaction was carried out in two stages using a stoichiometric amount of palladium(II) chloride (Scheme 27).



43 **66** **67**

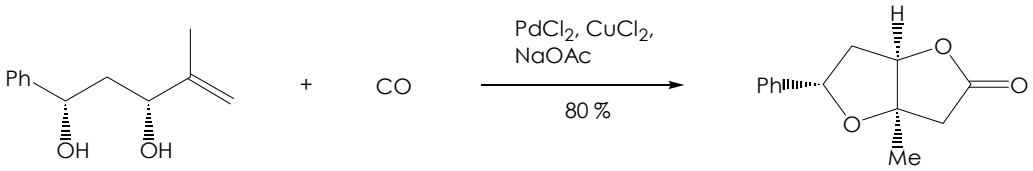
Scheme 27 – First reported oxidative carbonylation

It has been found that the reaction can proceed by one of three pathways (Scheme 28).[74] The first stage of the reaction is believed to be the formation of an alkoxycarbonylpalladium species. This then attacks the double bond to form a σ-bonded palladium species; at this point, the intermediate can break down in one of three different ways. The pathway taken is at least partially determined by the reaction conditions used.



Scheme 28 – Pathways of carbonylation

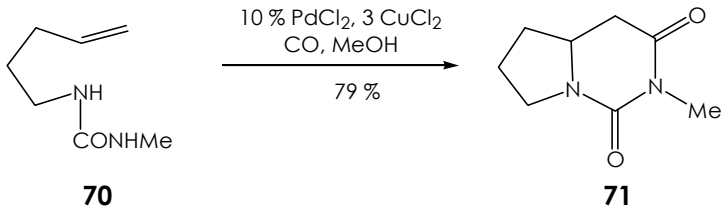
As in other palladium(II) catalysed reactions, the intramolecular reactions have been exploited. An example is given below, in which the intermediate breaks down *via* path B (Scheme 29).



68 **69**

Scheme 29 – Intramolecular oxidative carbonylation

The carbonylation reaction can also be carried out with amides, and again proceeds in a relatively facile manner (Scheme 30).[75]

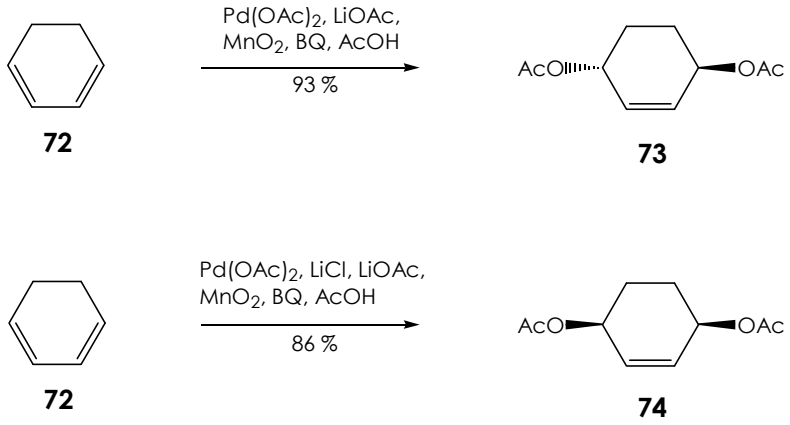


70 **71**

Scheme 30 – Carbonylation of a urea

2.4.3 The reaction of conjugated dienes

It would be expected that conjugated dienes would react in a similar manner to simple alkenes, and indeed this is the case; the main differences being that conjugated dienes undergo 1,4-reaction, and that the reaction intermediates are π-allylic palladium species.[28] Some of the work carried out on dienes has been used to study the modes of addition of nucleophiles to the palladium-bound system. One particularly famous example was published by Bäckvall in 1981 (Scheme 31);[76] it was shown that in the absence of chloride ions, attack on the diene by acetate was *trans*, *i.e. via* co-ordination to the palladium. However, when chloride ions were present in the solution, attack occurred *cis*, as the co-ordination site was blocked by the chloride ion.

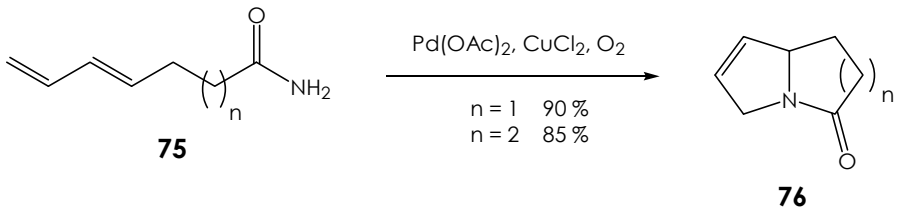


72 **73**

72 **74**

Scheme 31 – 1,4-Addition to dienes: *cis* and *trans*

Closure of two rings simultaneously using dienes has been demonstrated using amides[77] with good yields being obtained for five- and six-membered systems (Scheme 32).



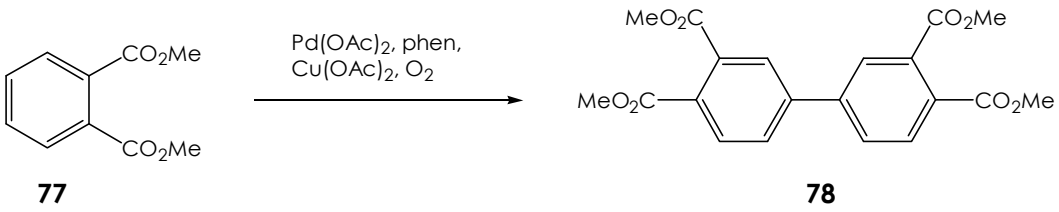
Scheme 32 – Intramolecular ring-closure using a diene

2.4.4 The reaction of aromatic compounds

Unlike other palladium(II) catalysed reactions, the oxidation of aromatic systems is not effective with palladium(II) chloride; only palladium(II) acetate can be used.[78] However, an *in situ* mixture of palladium(II) chloride and sodium acetate is also effective. Two types of reactivity are seen: the coupling of aromatics, and oxidative substitution.

2.4.4.1 Coupling of aromatics

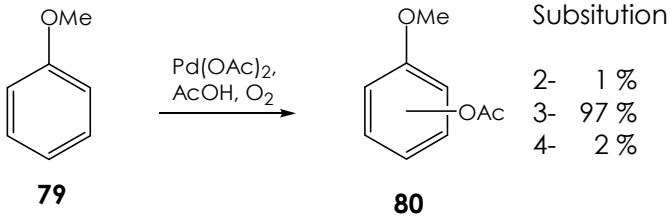
It is possible to couple two aromatic systems by using palladium(II) acetate. This is sometimes, but not always, catalytic. Obviously, this reaction has the potential to form a complex mixture of isomeric products. Control is usually achieved by adjustment of the reaction conditions. An example from the work of Shiotani *et al.*[79,80] is shown below (Scheme 33); selectivity for isomer **78** is achieved by use of the 1,10-phenantholine additive.



Scheme 33 – Aromatic coupling

2.4.4.2 Oxidative substitution onto the ring or benzylic position

The second possible reaction of aromatic systems is to replace hydrogen with a substituent, either on the ring or in the benzylic position. As is shown in the example below (Scheme 34),[81] the major product of substitution on the aromatic ring is found to be the 3- (*meta*) isomer, even with 2- / 4- (*ortho* / *para*) directing substituents such as the methoxy group. The authors suggested that this was because there are two organopalladium intermediates **81** and **82** (Figure 7) for the 3-substituted product, whereas there is only one each for the 2- and 4-substituted products.



Scheme 34 – Aromatic oxidation

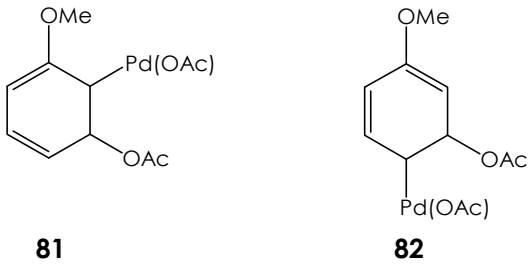
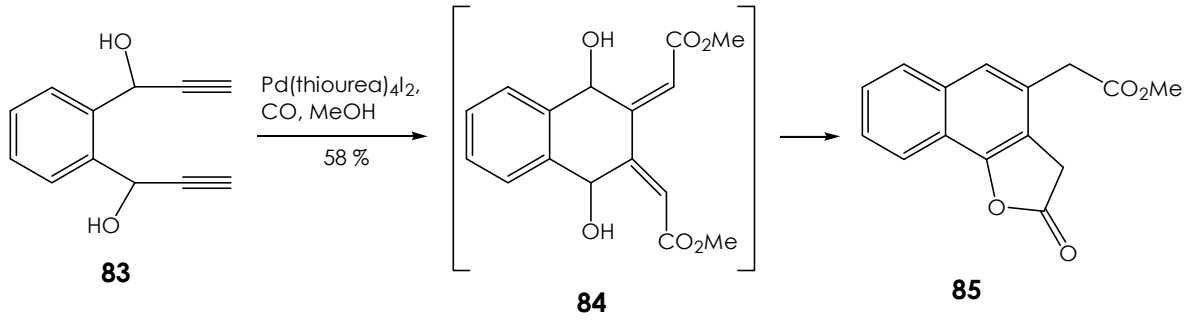


Figure 7 – Possible intermediates

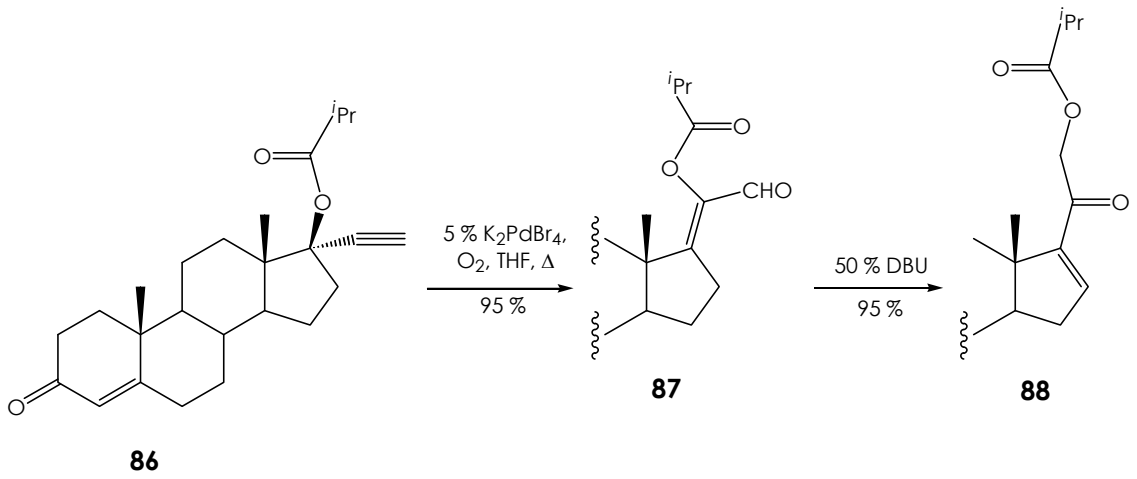
2.4.5 The reaction of alkynes

The reactions of alkynes are again similar to those of alkenes, but in most cases alkyne reactions are carried out under carbonylation conditions. It is possible to carry out either mono-carbonylation or dicarbonylation, dependant upon the reaction conditions. One example, making use of intramolecular attack, was reported by Costa *et al.*:[82] carbonylation of both of the triple bonds of **83** leads initially to **84**, which spontaneously forms to the final product **85** (Scheme 35).



Scheme 35 – Reaction and ring-closure of alkynes

An unusual reaction of alkynes is the rearrangement of propargyl ester **86** to the product **87**, reported by Watanabe *et al.*;[83,84] the reaction requires only palladium(II) and oxygen, with reoxidation occurring without the need for a second re-oxidant (Scheme 36).

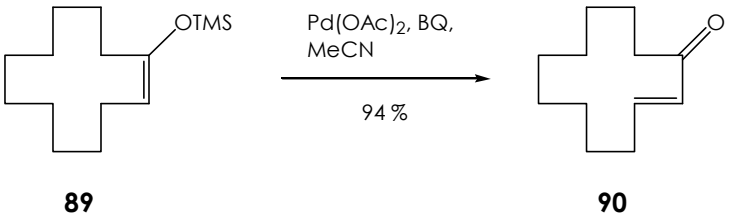


Scheme 36 – Reaction of propargyl ester

2.4.6 Miscellaneous reactions

2.4.6.1 The formation of enones

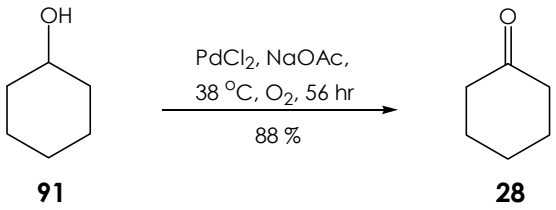
It is possible to form enones directly from ketones using palladium(II), however, yields are very low.[85] Instead, the formation of trimethylsilyl ethers followed by the use of palladium(II) leads to high yields of the desired products (Scheme 37).[86]



Scheme 37 – Formation of an enone

2.4.6.2 Oxidation of alcohols

Oxidation of alcohols is possible using palladium(II); it is not seen under the majority of reaction conditions, as the reaction times are very long. However, the yields reported are high, and so the reaction is not without potential uses (Scheme 38).[87]



Scheme 38 – Oxidation of alcohols

2.5 Palladium catalysed hydrogenation and hydrogenolysis

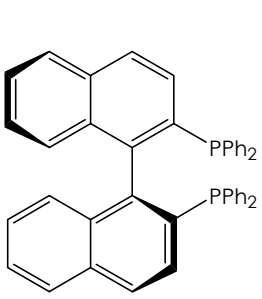
2.5.1 Reductions: an overview

Reduction of multiple bonds, either using dihydrogen gas or an organic hydrogen donor, is a huge field. The range of catalysts and conditions is potentially intimidating, but the power and versatility of hydrogenation means it has been extensively studied. Rylander[88,89] has provided two books which seek to bring much of the available knowledge into an accessible form.

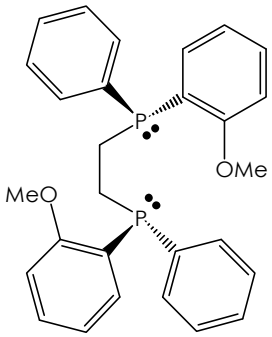
Hydrogenation is catalysed to some extent by all of the precious metals, as well as other systems. Across the range of catalysts, three broad areas may be identified:

1. Heterogeneous reduction by dihydrogen gas, using supported metal catalysts.
2. Homogeneous reduction by dihydrogen gas, using metal-complex catalyst
3. Homogeneous transfer hydrogenation from hydrogen donors, using metal-complex catalysts.

The different methods have advantages and disadvantages. In many reductions, selectivity is a key issue; this is determined by the metal, support and conditions chosen. Homogeneous catalysts are particularly suited to asymmetric hydrogenation, as they are readily amenable to ligand modification. Wilkinson's catalyst[90] and derivatives are perhaps the most successful class of homogeneous hydrogenation catalysts; the presence of readily modified phosphane ligands makes them particularly attractive for use in asymmetric reductions. Indeed, the 2001 Nobel Prize, awarded to Sharpless,[91] Knowles[92] and Noyori,[93] reflects this; two of the three recipients have been involved in the development of ligands for asymmetric reduction. The most famous ligands developed by Noyori and Knowles are BINAP **92** and DiPAMP **93**, respectively; these are illustrated below (Figure 8).



(*S*)-**92**



(*R*,*R*)-**93**

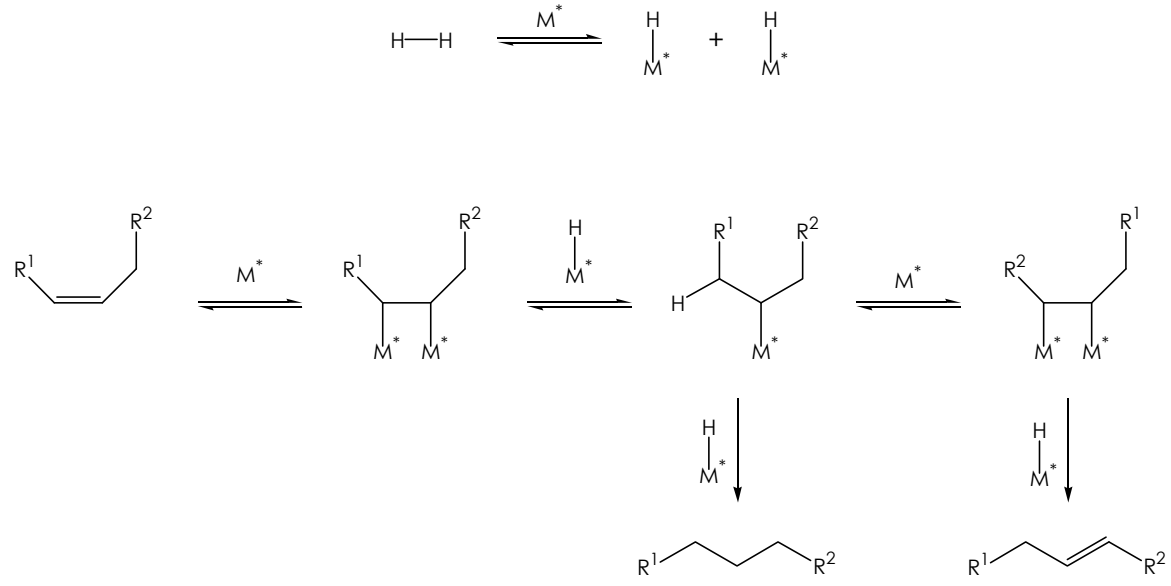
Figure 8 – BINAP and DiPAMP

2.5.2 Choice of metal

The variety of metals and conditions used for catalytic hydrogenation has been commented on above. However, two metals in particular stand out in the field of catalytic reduction. The short discussion of homogeneous reduction above focussed on the rhodium-containing Wilkinson catalyst; rhodium has been by far the most successful metal in homogeneous hydrogenation. In contrast, the first choice metal for heterogeneous hydrogenation (saturation or semi-saturation of multiple bonds) and hydrogenolysis (reductive bond cleavage) is palladium. The key reason for this popularity must be the high degree of selectivity that can be achieved, either by using the supported metal only or by the use of additives (selective poisons).

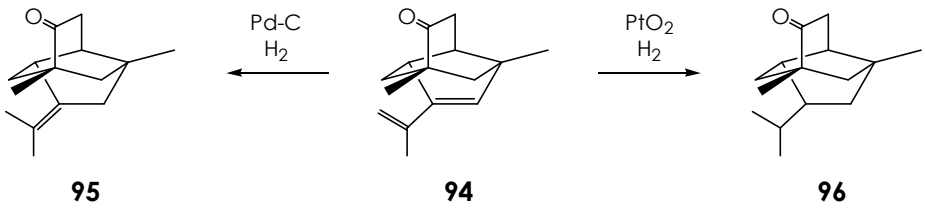
2.5.3 Reduction of alkenes

In many cases, early mechanistic proposals for the paths of transition-metal mediated reaction have been discarded in the face of new evidence; the Horiuti-Polanyi[94] mechanism (Scheme 39) for the reduction of alkenes is therefore one of the longest-surviving mechanistic proposals (despite revisions). Both hydrogen and the alkene become bound to the surface before attack of hydrogen on the alkene. This attack occurs sequentially, leading to an intermediate which is "half-hydrogenated"; only the final reduction step is irreversible, and so isomerisation of the alkene is possible.



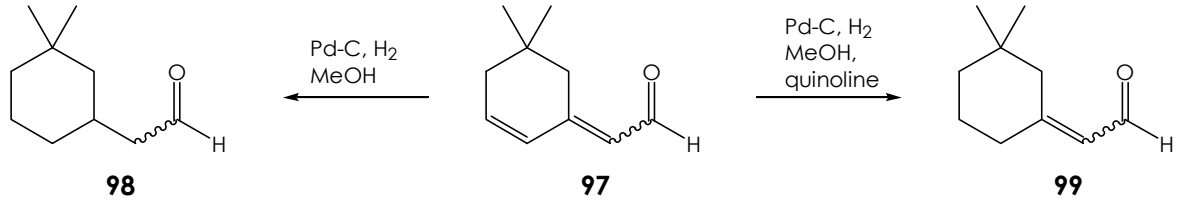
Scheme 39 – The Horiuti-Polanyi mechanism

Palladium has been found to be the most active catalyst for the isomerisation of alkenes under reduction conditions, whilst platinum is the least active.[95] In most cases, isomerisation is not significant: total reduction of the substrate occurs and the double bond is lost. However, isomerisation can sometimes be crucial to reaction outcome (Scheme 40);[96] palladium gives reduction of only one double bond with isomerisation of the second, whilst platinum reduces both (giving a 7 : 3 mixture of **96** and **95**).



Scheme 40 – Effect of isomerisation on reductions

Palladium is a powerful catalyst for the reduction of alkenes; thus, in order to gain selectivity, catalyst poisons are employed. These block the more active sites on the surface, and attenuate reactivity. For example, Pd-C will reduce both C=C bond of **97** unless quinoline is employed as a poison (Scheme 41).[97]

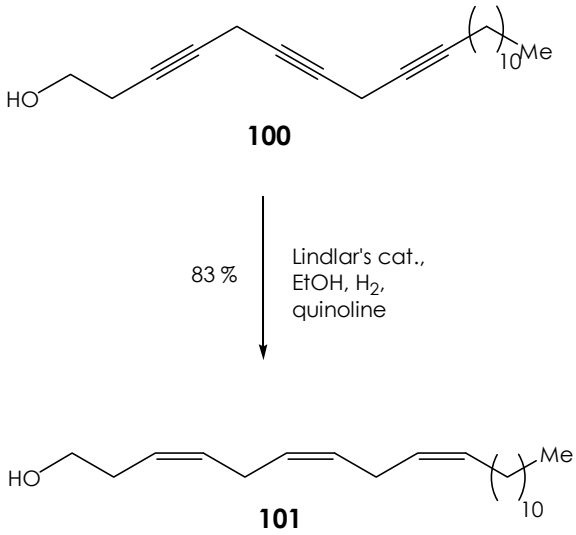


Scheme 41 – Effect of quinoline on reductions

2.5.4 Reduction of alkynes

Although palladium is a highly active catalyst for the reduction of alkenes, moderate to good selectivity for the partial reduction of alkynes to alkenes can be obtained; palladium has been found to be the most selective metal for this reduction.[89] It is believed that this is due to preferential adsorption of alkynes onto the metal surface, compared with the adsorption of alkenes.

Perhaps the most successful system for the reduction of alkynes to alkenes is Lindlar's catalyst:[98,99] palladium supported on calcium carbonate and poisoned with lead, often along with quinoline as a second poison. This can give excellent selectivity, for example in the reduction of **100** to **101** (Scheme 42).[100]

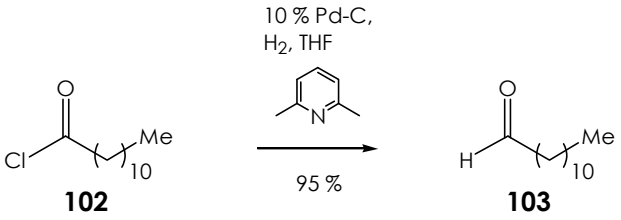


Scheme 42 – Semi-reduction of triple bonds

2.5.5 Dehalogenation of acyl chlorides

Aldehydes are accessible by a variety of methods, most notably oxidation of alcohols. However, some aldehydes are difficult to synthesis by this route. The reduction of acyl chlorides is a useful alternative method for producing aldehydes. A number of methods have been developed for

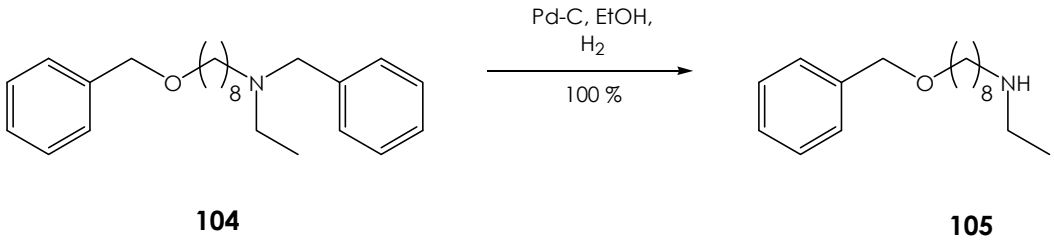
carrying out this conversion; the use of aluminium hydrides was introduced by Brown,[101] and has been improved[102] to be effective in many cases. However, catalytic reduction of acyl chlorides is still attractive, particularly from the atom-economy perspective. This reduction, making use of a poisoned palladium catalyst, was introduced by Rosenmund and Zetzsche[103] in 1921. The original procedure requires careful monitoring of the uptake of hydrogen; improved procedures have been introduced which are more convenient to carry out (Scheme 43).[104]



Scheme 43 – Rosenmund-type reduction

2.5.6 Hydrogenolysis of benzyl groups

The hydrogenolysis of benzyl groups attached to oxygen and nitrogen is particularly important in the field of protective groups; the benzyl group is one of the most widely used groups in organic synthesis, and hydrogenolysis is probably the most common method of removal.[105] Palladium is the catalyst of choice for this type of reaction: it has little tendency to reduce aromatic systems, and so deprotection occurs cleanly.[89] In isolation, benzyl ethers are more rapidly cleaved than similarly situated benzyl amines. If both a benzyl amine and a benzyl ether are present in the same molecule, the amine is preferentially deprotected (Scheme 44).[106]



Scheme 44 – Selective removal of *N*-benzyl group

Hydrogenolysis of benzyl-type groups is considered further in chapter 5.

2.6 Palladium(0) catalysed reactions

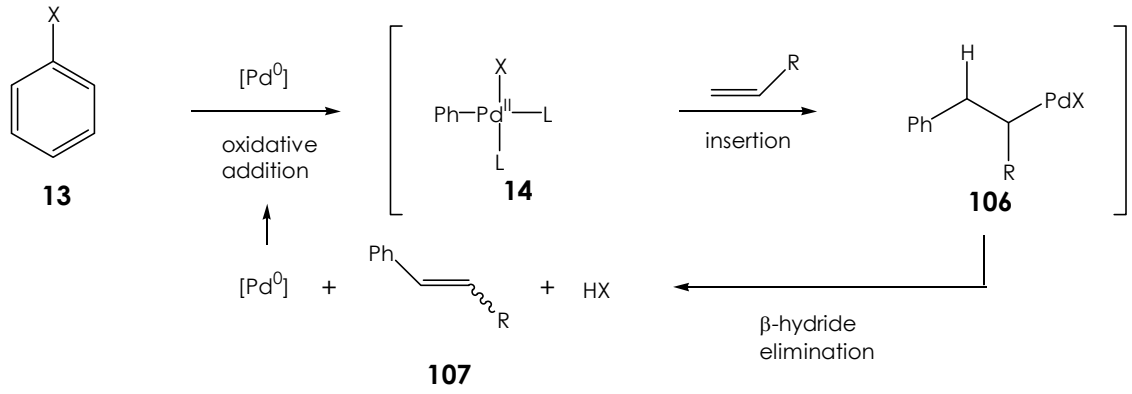
The catalysis of organic transformations by palladium (mainly in the zero oxidation state) has grown over recent decades into a large, diverse field. Indeed, almost three-quarters of Tsuji's treatise[31] on palladium chemistry is taken up by reactions of this type. Palladium(0) catalysed

reactions have become ubiquitous in synthetic chemistry; many have become "name" reactions, such as the Heck (or Mizoroki-Heck)[107,108] and the Tsuji-Trost[109] reactions.

Reactions catalysed by palladium(0) can be viewed in broad classes: those involving "oxidised" sp^2 carbons, and those involving leaving groups allylic to double bonds. A full review of this chemistry is beyond the scope of this report; two examples will be given to illustrate the power of palladium(0) catalysis. Extensive coverage can be found in the books by Heck[30] and Tsuji[31].

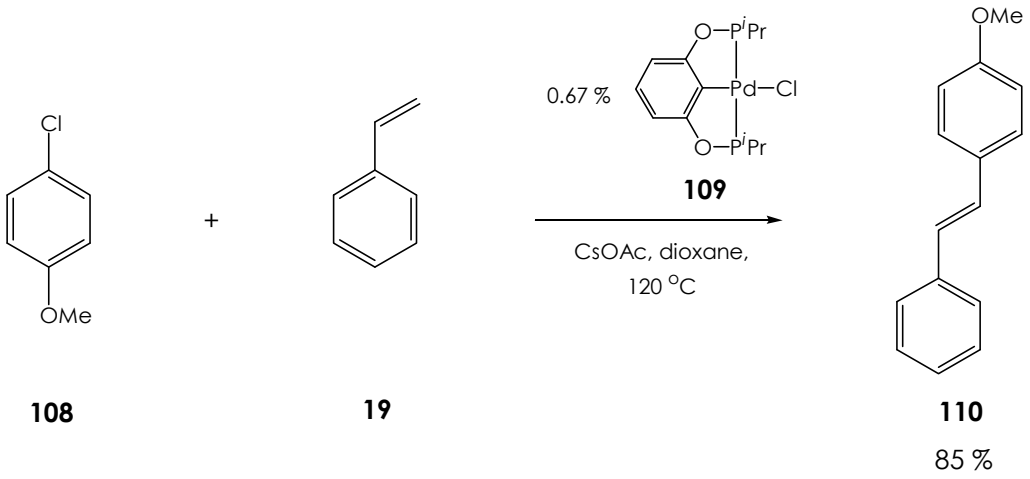
2.6.1 The Heck reaction

The Heck reaction was discovered independently by Mizoroki[107] and Heck[108] in the early 1970s, as an extension of earlier stoichiometric reactivity. The basic process involves the reaction of an aryl halide with an alkene, as is shown below (Scheme 45).



Scheme 45– Generalised Heck reaction

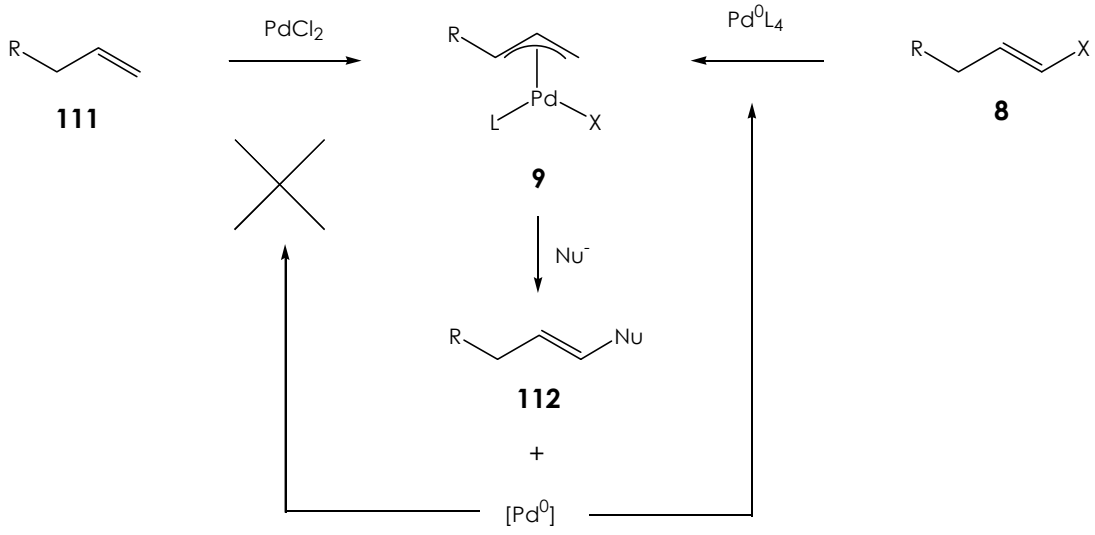
Initially, the reaction was somewhat limited: high temperatures and activated aryl iodides were required. As is made clear in a recent review,[110] much progress has been made recently in the development of ligands and conditions, allowing access to more challenging reactions, such as electron-rich aryl chlorides (Scheme 46).[111]



Scheme 46 – Heck reaction of aryl chloride

2.6.2 The Tsuji-Trost reaction

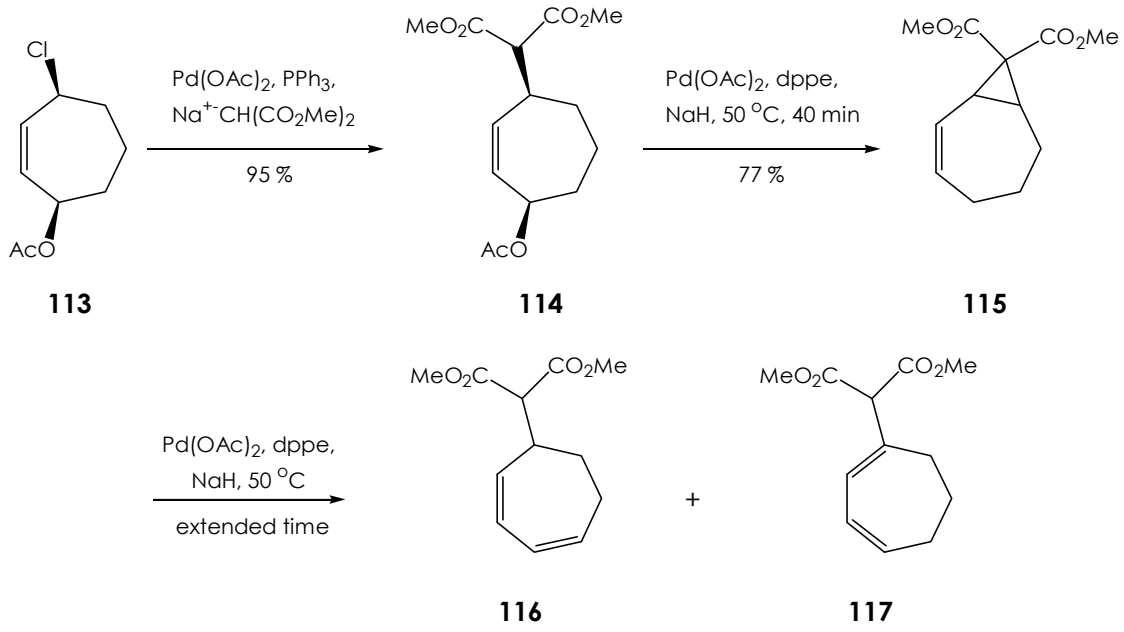
π-Allyl palladium complexes may be formed by two major paths, as is shown below (Scheme 47). Reaction of an alkene with a palladium(II) salt and a base gives an allyl complex in a stoichiometric manner; on the other hand, reaction of palladium(0) with an alkene bearing a leaving group in the allylic position leads to catalysis.



Scheme 47 – Formation and reaction of a π-allylic complex

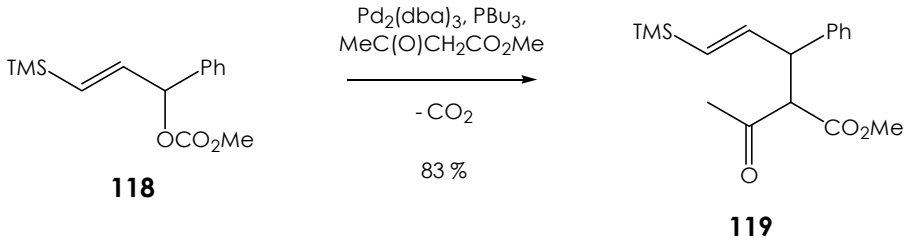
The Tsuji-Trost reaction occurs when an allylic complex is treated with an active methylene compound under basic or neutral conditions; a large number of nucleophiles are suitable for the reaction.[112] An example of a reaction under basic conditions is given below (Scheme 48); control of conditions allows the reaction to be carried out sequentially on **113**, first to give **114**, then to

the cyclopropane-ring containing **115**. Extended reaction converts this kinetic product to a thermodynamic mixture of **116** and **117** in a 2.5 : 1.0 ratio.[113]



Scheme 48 – Tsuji-Trost reaction under basic conditions

Reaction under neutral conditions has obvious advantages; however, there are a limited number of compatible leaving groups. The most reactive substrates are allylic carbonates (Scheme 49),[114] with tributylphosphane as the ligand of choice. In this particular example, triphenylphosphane is not effective, and gives undesired side-reactions.



118 **119**

Scheme 49 – Tsuji-Trost reaction under neutral conditions

3 THE WACKER REACTION OF STYRENES

"Cada piedra es diferente, y no hay que querer hacer de dos una enorme" [115]

A. Gaudí

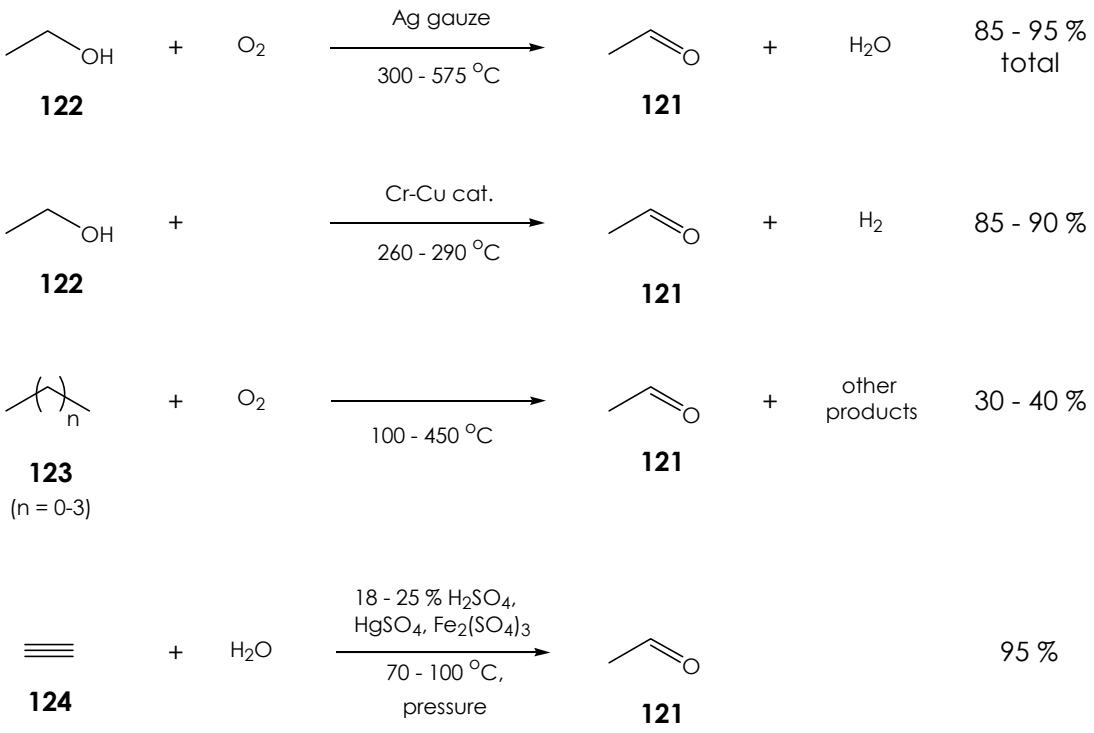
3.1 Introduction

3.1.1 The Wacker Process

The oxidation of alkenes to carbonyl compounds catalysed by palladium(II) salts, usually referred to as the Wacker reaction, was covered briefly in section 2.4.2.1. As was explained, the reaction between palladium(II) and various alkenes had been known for well over one hundred years.[34,35] The key to the development of useful synthetic chemistry from this reaction was the discovery of a system capable of reoxidising palladium(0) to palladium(II). This breakthrough was made by Smidt and co-workers,[37] in the laboratories of the Consortium für elektochemische Industrie, a subsidiary of the München-based Wacker GmbH; the discovery that copper(II) salts could be used to achieve the reoxidation turned the reaction from a curiosity into an industrially useful process.

Scheme 50 – The Wacker Process

The initial success of the reaction was in the conversion of ethene **120** into ethanal **121**, in which context the reaction is usually referred to as the Wacker Process (Scheme 50). The synthesis of ethanal was, and continues to be, a large-scale industrial process; short-chain aldehydes are valuable starting materials in the production of bulk chemicals. Prior to the discovery of the Wacker reaction, four other routes to ethanal were available to industry (Scheme 51).[116] The Wacker Process compared favourably to these, giving approximately 95 % conversion in one pass.



Scheme 51 – Earlier routes to ethanal

Although palladium(II) chloride is usually the catalyst of choice for Wacker reactions, many other palladium(II) salts have been found to be effective, including the sulphate(VI), nitrate(V), acetate and bromide; however, palladium(II) iodide is not effective, presumably due to the high stability of the Pd–I interaction.

3.1.2 Reoxidation of palladium(0) to palladium(II)

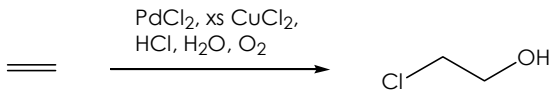
As has already been commented on, the crucial factor in the success of the Wacker reaction [and other palladium(II) catalysed reaction] was the discovery of a method for the *in situ* reoxidation of palladium(0) to palladium(II). As a noble metal, bulk palladium is inert to a large number of reagents: section 2.2 showed the harsh conditions normally needed to attack palladium. The expectation would therefore be that the reoxidation of palladium would be difficult to achieve.

In order to succeed as a reoxidation method, the half-cell potential for the reoxidant must exceed that of the palladium(0) / palladium(II) couple. A key part of the original reoxidation system, using copper(II) chloride, is the presence of excess chloride ions in solution. These have a dramatic effect on the relative stabilities of the two palladium oxidation states.[48] This effect is also enhanced by raising the temperature: heating from 25 °C to 100 °C increases the equilibrium constant by an order of magnitude.

$$Pd_{metal} + 2\,Cu^{2+} \rightleftharpoons Pd^{2+} + 2\,Cu^{+} \qquad K = 10^{-28.2}$$

$$Pd_{metal} + 2\,Cu^{2+} + 8\,Cl^{-} \rightleftharpoons [PdCl_4]^{2-} + 2\,[CuCl_2]^{-} \qquad K = 10^{-5.10}$$

The copper(I) produced in the above reaction can readily be converted to copper(II) by the action of oxygen, thus allowing a reaction which is catalytic in both metals. Indeed, it is not necessary to utilise copper(II) as the copper source: copper(I) salts are found to be effective if allowed to stir under an oxygen atmosphere prior to commencing reaction. This also avoids a common problem with the use of copper(II) chloride: the formation of chlorohydrin by-products (Scheme 52).



120 **125**

Scheme 52 – Chlorohydrin formation

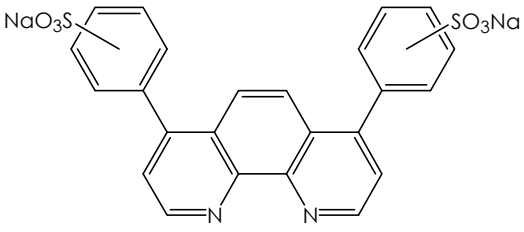
Along with copper salts, a large number of other reoxidants have been used in the Wacker reaction. It is important that the reaction is rapid; atomic palladium is much more readily reoxidised than the bulk metal. As was outlined in section 2.4.2.1, 1,4-benzoquinone (BQ) is often used as a stoichiometric reoxidant (Scheme 13). This reagent is particularly favoured in mechanistic studies; reoxidation with BQ ensures that the concentration of both protons and chloride ions remains constant throughout the reaction. Other reoxidants used in the reaction have included iron(III) chloride, manganese dioxide, organic peroxides, electrochemical methods and vanadium-containing Keggin-type[117] heteropolyanions.

3.1.3 Environmental considerations

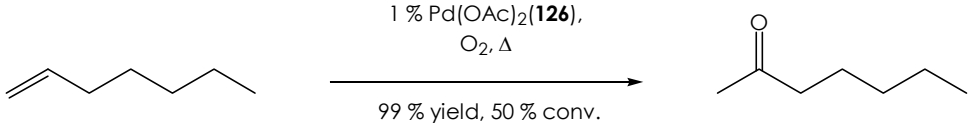
For environmental reasons, there is currently a great deal of interest in carrying out metal-mediated transformations in aqueous media.[118] At first sight, the Wacker reaction is attractive in this context: it is a genuine organometallic reaction taking place readily in water, and uses only the feedstock and oxygen as reagents. Unfortunately, in order to occur effectively, the reaction takes place in hydrochloric acid with large amounts of copper(I) chloride, "a rather nasty situation from environmental aspects".[118] The reaction mixture is also very corrosive, and requires titanium-lined vessels in order to prevent the destruction of the plant.

In order to circumvent some of these problems, various approaches have been adopted. The use of alternative reoxidants has already been mentioned; this does not in itself avoid the use of

chloride ions to stabilise the palladium species, particularly the transient palladium(0). In order to achieve this stabilisation, various water-soluble ligands have been developed, for example **126**, developed by Sheldon *et al.*[119,120] (Scheme 53).



126



127 **128**

Scheme 53 – Chloride-free Wacker reaction

3.1.4 The mechanism of the Wacker reaction

3.1.4.1 Overview

The mechanism of the Wacker reaction has been of interest to chemists since the discovery of the reaction[121]. Many studies have been carried out on the oxidation of ethene in aqueous media, *i.e.* the conditions of the Wacker Process; the amount of work on other substrates and other conditions is noticeably smaller. Henry has provided an overview of the mechanistic understanding as it stood in 1980;[122] many of the key questions had by that time been addressed, as can be seen by comparison to the summaries given by Tsuji in 1995,[123] and Smith and March in 2001.[124] The mechanism of the reaction has been studied theoretically;[125] these studies have focused on the attack of the nucleophile on the double bond.

3.1.4.2 Kinetics

Many important studies have been carried out on the kinetics of the Wacker reaction.[41,126-132] Most of these have been concerned with ethene in aqueous solution, and it is important to bear in mind that these results may not be applicable to other substrates and solvents. With this proviso, the major conclusions of the kinetics are that in the concentration ranges (mol dm^{-3}):

$$0.005 \; < \; [Pd^{II}] \; < \; 0.04$$

$$0.1 \quad < \quad [Cl^-] \quad < \quad 1.0$$

$$0.04 \quad < \quad [H^+] \quad < \quad 1.0$$

The rate equation for the reaction is found to be:

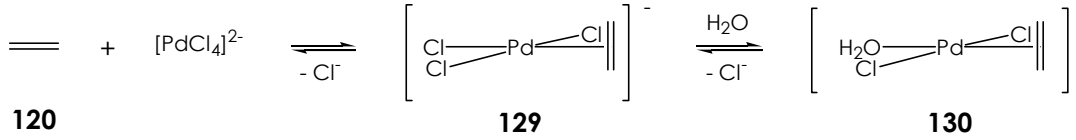
$$\frac{-d(C_2H_4)}{dt} = k\frac{[PdCl_4^{2-}][C_2H_4]}{[Cl^-]^2[H^+]}$$

There are also five key facts which any proposed mechanism has to account for:

1. The rate of reaction rises with μ (total ionic strength) to $\mu \approx 0.4$ mol dm^{-3}, then falls.[126,130]
2. Reaction in heavy water does not lead to the incorporation of deuterium into the product.[42,131]
3. Reaction of C_2D_4 in water gives no loss of deuteriums, and has a k_H/k_D of 1.07.
4. Oxidation of CDH=CDH gives a ratio of CH_2D-CHO to CHD_2CHO of 1.70.[131]
5. The value of k_H/k_D for reaction in D_2O is 4.05.[127]

3.1.4.3 Proposed mechanisms

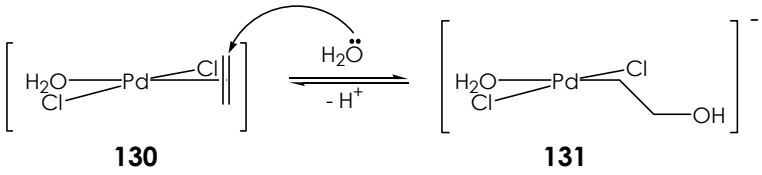
The factors outlined in the previous section can be rationalised by considering the following mechanism. In the first stage (Scheme 54), two equilibria occur to generate the complex **130**. This accounts for the dependence of the rate on the square of [Cl$^-$].



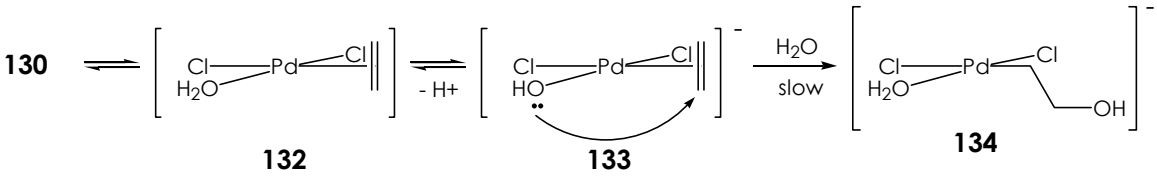
120 **129** **130**

Scheme 54 – Wacker mechanism one

There are then two possible routes open to the reaction for the attack on the double bond (Scheme 55 and Scheme 56). The first is the attack of water from solution on complex **130**, with release of a proton (Scheme 55) (Henry has shown that attack on the co-ordinated bond by a hydroxide ion in solution is impossible[133]). The second is formation of complex **133**, and internal attack by a co-ordinated hydroxyl (Scheme 56). In an unsymmetrical substituted alkene, attack typically occurs in a Markovnikov sense, the OH becoming attached to the more substituted carbon. Two explanations for this can be provided, and are considered in section 3.1.5.

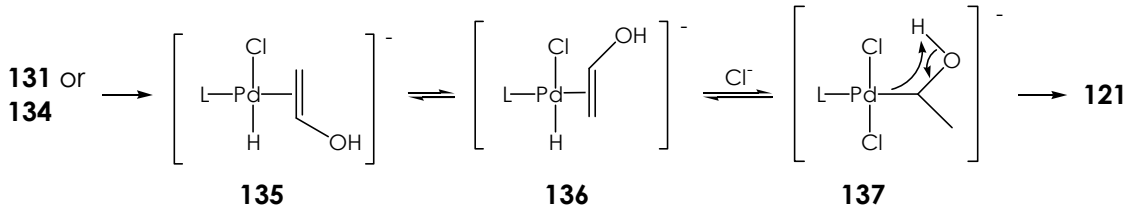


Scheme 55 – Wacker mechanism two



Scheme 56– Wacker mechanism three

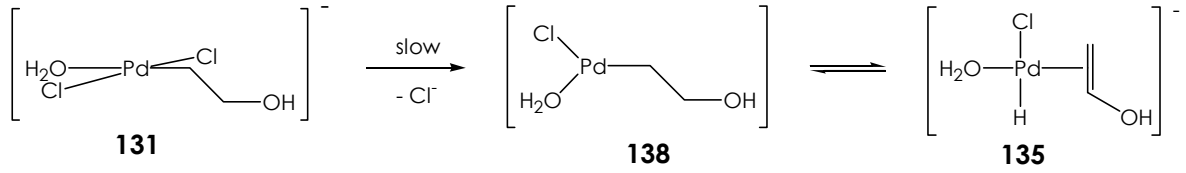
The final stage of the reaction is then the formation of the product (Scheme 57).



Scheme 57 – Wacker mechanism four

The attack of the nucleophile on the double bond has been possibly the most contentious section of the above mechanism. Bäckvall *et al.*[132] showed in 1979 that nucleophilic attack occurs *trans* to palladium, indicating that water attacks from solution. However, Henry *et al.*[134] have recently demonstrated that the sense of attack is different at high (3.0 mol dm^{-3}) and low chloride-ion concentration. The work of Bäckvall was carried out with a high chloride-ion concentration, and Henry has therefore concluded that attack occurs *cis* in systems with lower amounts of chloride, *i.e.* by a palladium-co-ordinated hydroxy group.

Two possibilities have been suggested for the rate-limiting step in the reaction. Henry has shown that ethene-d_4 does not show a significant kinetic isotope effect,[130] and therefore the rate-limiting step must occur before the β-hydride elimination that generates complex **135.**[132] Bäckvall has suggested that hydroxypalladation to **131** is reversible, and that the slow step is therefore formation of complex **138**.[132]



Scheme 58 – Bäckvall's proposal for the rate-limiting step

Henry agrees that this is a possible mechanism, but suggests an alternative.[134b] Nucleophilic attack could also occur *via* a hydroxy ligand co-ordinated to palladium (**133** to **134**, Scheme 56). In this case, it would be possible that the nucleophilic addition is irreversible; the hydroxypalladation would therefore be the rate-determining step.

The copper(II) mediated reoxidation step of the Wacker reaction is perhaps the least well-understood part of the reaction. It is known that copper(II) salts are involved to some extent in the formation of chlorohydrin by-products. François[135] has suggested that copper is directly involved in the palladium-substrate complex (Figure 9).

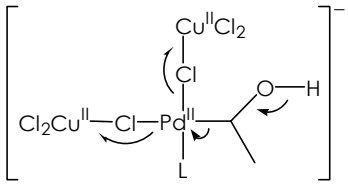
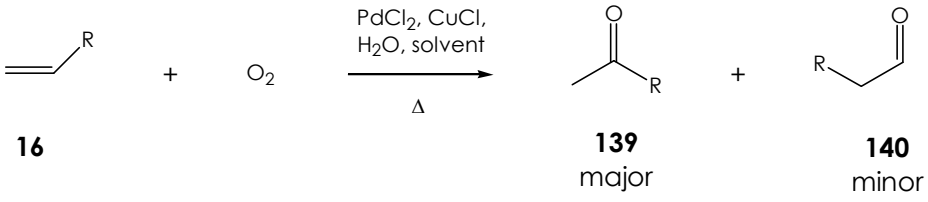


Figure 9 – François' proposal for reoxidation

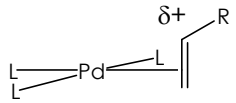
3.1.5 Regioselectivity of the Wacker reaction

The Wacker reaction is most successful with terminal double bonds; internal double bonds usually react more slowly and form mixtures of the two possible ketones. In the case of terminal alkenes, the reaction can proceed to form either aldehydes or ketones. It has been known since the first reports[37,41-43] of the reaction that, in most cases, the reaction proceeds with high regioselectivity to give the methyl ketone (Scheme 59), showing Markovnikov regioselectivity. Indeed, it is often stated that "terminal alkenes may be used as masked methyl ketones".[136]

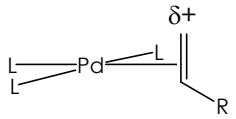


Scheme 59 – Usual regioselectivity in the Wacker reaction

Two reasons have been suggested for the regioselectivity observed substrates not containing heteroatoms. Co-ordination of palladium to the alkene activates the bond to nucleophilic attack: the C=C bond is therefore electron-deficient and carries a partial positive charge (Figure 10). In an unsymmetrical molecule, this charge will not be born evenly by the two carbons, but will be localised at one end of the bond. The complex **141a**, with a secondary partial-positive charge, would be more stable than **141b**, in which the charge is centred on a primary carbon. Attack of the nucleophile (water) would be expected to occur at the more positive end of the alkene, *i.e.* the secondary position. This leads to the Markovnikov product.



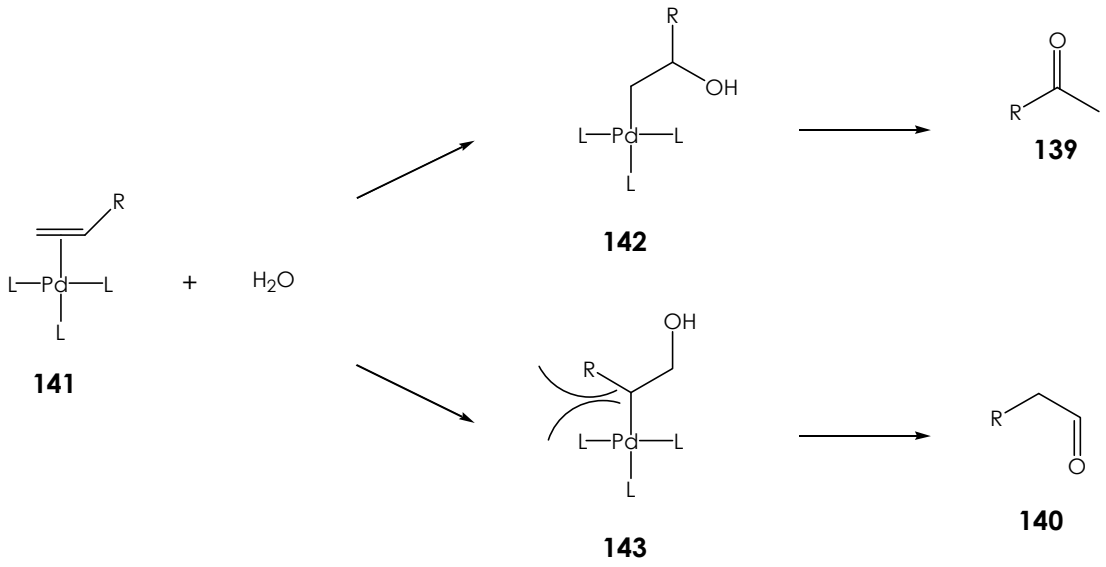
141a



141b

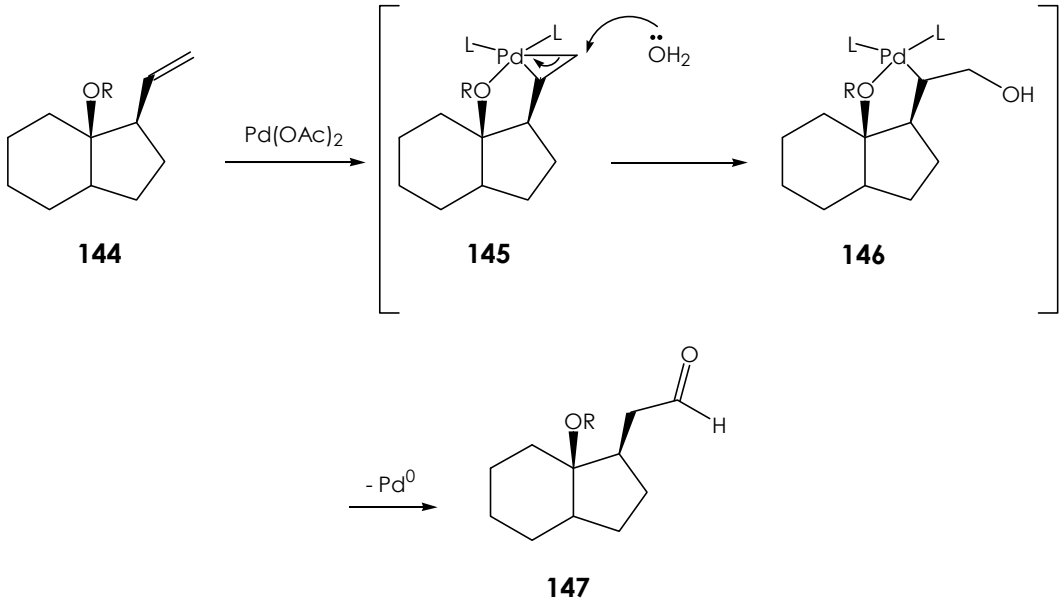
Figure 10 – Electronics in the regioselectivity of the Wacker reaction

Katsuyama *et al.*[137] have shown that variation of the electronics of 4-substituted styrenes alters the regioselectivity of the Wacker reaction. Henry suggests that these results show only "a small degree of carbonium character in the transition state for hydroxypalladation".[138] The rates of oxidation of a variety of terminal and internal alkenes, along with other data, have been used as evidence for a largely steric explanation of the regioselectivity.[139] This can be rationalised by considering the interaction of the palladium centre with the R group of the substrate in the hydroxypalladated intermediates (Scheme 60). Nucleophilic attack on the primary position leads to intermediate **143**, which gives the aldehyde **140**; attack at the internal position gives **142**, and thus the methyl ketone **139**. Steric interactions between the R group and the palladium disfavours the formation of intermediate **143** and reaction therefore proceeds *via* **142**.



Scheme 60 – Sterics in the regioselectivity of the Wacker reaction

Despite the strong preference for Markovnikov selectivity, there are a number of cases in which the reaction of a terminal alkene proceeds to give an aldehyde. In most cases, this effect can be traced to a suitably placed heteroatom in the substrate. For example, Pellisier and co-workers noted this effect during the synthesis of a natural product, and investigated the reasons using a model compound (Scheme 61) and computer modelling.[140-142] These authors found that the Pd–C lengths in **145** are unequal, with the CH_2–Pd bond being longer and weaker than the CHR–Pd bond, thus, favouring terminal attack.



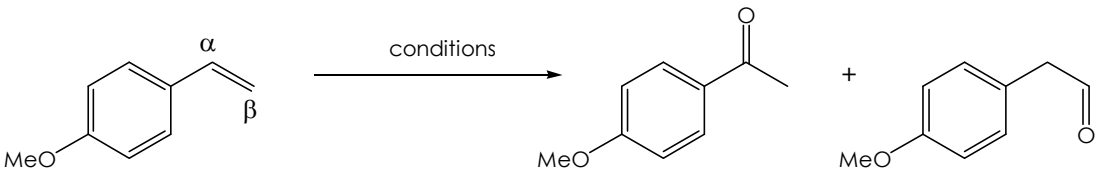
Scheme 61 – Model study for heteroatom binding

There are a limited number of reports of unusual regioselectivity not involving heteroatoms. Some of these involve styrene, and will be discussed in the next section; in other cases, the catalyst used is substantively different from the standard Wacker system. For example, Feringa has reported[143] that a catalyst $(MeCN)_2PdCl(NO_2)$-$CuCl_2$-^{t}BuOH oxidises terminal alkenes to aldehydes: a similar system was reported by Wenzel.[144] It is likely that this reaction proceed *via* non-standard mechanisms; the palladium is proposed to remain as palladium(II) throughout the catalytic cycle, and the copper plays a role different from that in the Wacker reaction.

3.2 The Wacker reaction of styrene

The majority of systematic studies on the mechanism of the Wacker reaction have been carried out on straight-chain alkenes, principally ethene. However, there have been a small number of studies on the reaction of styrene. Katsman *et al.*[128,146-148] and Vojtko *et al.*[149] have studied the kinetics of the oxidation of styrene in aqueous solution, and have found analogies to the reaction of ethene. Okada *et al.*[137,150] have used 4-substituted styrenes to probe the effects of electronic factors on the regioselectivity of the Wacker reaction. Using a limited number of substituents, they found that the ratios of products obtained were dependent upon the electronic effects of the substituent.

As part of an ongoing investigation into palladium(II) chemistry, Spencer *et al.*[145] have briefly studied the regioselectivity of the Wacker reaction 4-ethenyl-1-methoxybenzene **148** (Scheme 62). As was detailed in the preceding section, Markovnikov regioselectivity would be expected for this substrate: a partial-positive charge would be most stable at the conjugated (α) position of the double bond, and the ends of the double bond are highly sterically differentiated. The molecule also contains no heteroatoms capable of co-ordination to the palladium catalyst, and there are no hydrogen atoms allylic to the double bond (see chapter 4). However, the Wacker reaction of **148** did not proceed in the anticipated manner. Whilst under catalytic reaction conditions the major product was indeed the ketone **149**, reaction with a stoichiometric amount of palladium(II) chloride at room temperature gave an predominantly the aldehyde **150** (Scheme 62).



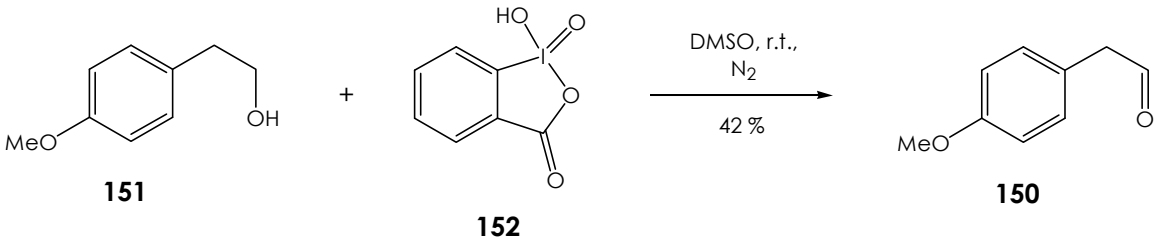
148 **149** **150**

Scheme 62 – Initial reaction

In line with this result, one fact is clear concerning the Wacker reaction of styrene. Unlike most other simple alkenes, the reaction of styrene does not take place in a predominantly Markovnikov sense. This has been briefly commented upon by only three authors, Llyod and Luberoff,[151] Katsman *et al.*,[128] and Vojtko *et al.*,[152] although it has also been observed by Jira *et al.*[41] and others. No rigorous explanation of this phenomenon has been proposed by any of the above authors. It was therefore decided to investigate the scope and mechanism of this transformation.

3.3 Mechanistic investigation of the anti-Markovnikov reaction

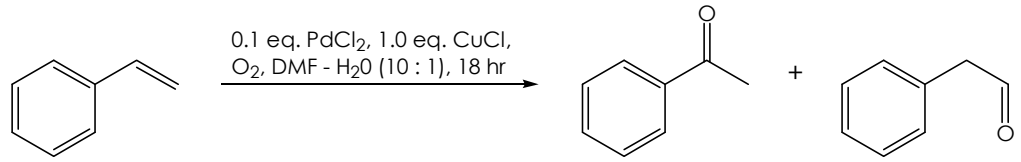
Before moving on to investigate the scope and mechanism of the reaction in depth, it was necessary to establish a basic set of reaction conditions. Initial attempts to carry out the reaction and isolate the products were found to be unreliable. The volatility of the starting material in particular meant that consistent results were not obtained. In order to circumvent this problem, the use of gas-liquid chromatography (G.L.C.) was investigated. To provide certainty in the analysis, an authentic sample of the aldehyde product was required. The alcohol **151** is commercially available; an oxidative route to the aldehyde was therefore the most convenient approach. Although literature precedent is available, oxidations using PDC, PCC,[153] TEMPO[154] and the Swern methodology[155] were all unsuccessful, giving at best low yields of mixtures of products. However, the oxidation procedure of Santagostino *et al.*,[156,157] making use of IBX[158] was partially successful: reaction in the absence of oxygen yielded the required aldehyde in moderate yield (Scheme 63). The same procedure could be utilised to give (4-methylphenyl)-ethanal, in 60 % yield. With standards for G.L.C. analysis in hand, calibration of the volatility of the reaction products, and therefore determination of the product ratio, was possible.



151 **152** **150**

Scheme 63 – Production of aldehyde standard

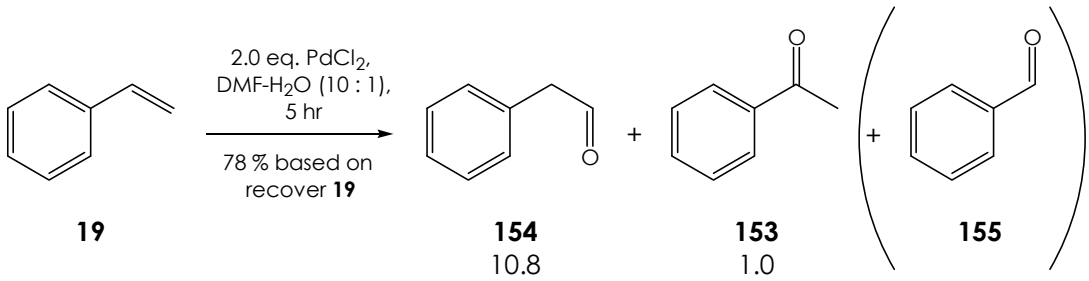
The reaction of styrene under standard Wacker conditions was carried out at room temperature (Scheme 64); as expected, the predominant product was the ketone **153**.



19 **153** 8.4 **154** 1.0

Scheme 64 – Reference reaction under catalytic conditions

The reaction under stoichiometric conditions was initially found to produce, along with **153** and **150**, benzaldehyde **155** (Scheme 65). This was traced to carrying out the reaction in the presence of oxygen (air): when the reaction was performed in degassed solvent no **155** was formed. A reaction reported by Jefford *et al.*[159] may give some indication as to the pathway responsible for formation of the benzaldehyde.[160,161]



19 **154** 10.8 **153** 1.0 **155**

Scheme 65 – Reaction under stoichiometric conditions

It was found that the reaction did not proceed to completion, but instead halted after approximately five hours; the inhibition of the Wacker reaction by both protons and chloride ions could well explain this phenomenon. It was also found that, whilst one equivalent of palladium would give the desired reactivity, the best conversions and yields of aldehyde were obtained with two equivalents of palladium(II) chloride. DMF was the solvent of choice for the reaction; although it has been suggested that DMF may not be stable over long periods in the

presence of palladium(II) and water[162], other solvent used gave inferior results. The effects of solvents on the Wacker reaction of styrene have been studied.[152,163] The ratio of aldehyde to ketone in the reaction was not constant; initially, the ratio was low, but this increased over the period of the reaction.

Analysis of the reaction mixture by G.L.C. was successful in giving reliable results, and good values for mass balance: 87 % recovery. This is in agreement with the data of Katsman *et al.*,[128] who report yields of 75 – 90 % (based on recovered alkene) under aqueous conditions.

3.3.1 The effect of temperature

It is usual to carry out Wacker reactions at elevated temperatures, typically around 50 °C. It was therefore of interest to establish whether heating would be beneficial or detrimental to the unusual reactivity. The reaction was therefore carried out over a range of temperatures between 30 and 50 °C. The results are summarised in Table 2.

Temp. (°C)	Mass recovery (%)	Ratio aldehyde : ketone
r.t.	87	10.8 : 1.0
30	73	6.1 : 1.0
35	69	6.0 : 1.0
40	70	6.0 : 1.0
45	67	5.0 : 1.0
50	55	4.1 : 1.0

Table 2 – Effect of temperature on the reaction of styrene

As can be seen above, heating the reaction is detrimental to both the total mass recovery and the ratio of aldehyde to ketone. Examination of the raw data (see section 6.2.4.19) reveals that this is mainly accounted for by a reduction in the amount of aldehyde recovered, although at 50 °C the starting material also appears to be degraded. This is unsurprising given the reactivity expected of the aldehyde. Further reactions were therefore carried out at ambient temperatures.

3.3.2 The effect of the counter-ion for palladium

Although palladium(II) chloride is the most convenient source of palladium(II) for Wacker reactions, a variety of other palladium(II) may be employed in the reaction; in many cases, the counter-ion is most significant in altering the solubility of the catalyst in the reaction solution. The results obtained with a number of different counter-ions in the reaction of styrene (as Scheme 65) were therefore very surprising; as is shown below (Table 3), replacement of the chloride counter-ion had a significant effect on the regioselectivity of the reaction. As expected,

palladium(II) iodide was unreactive, whilst all other palladium sources strongly favoured the formation of **153**.

Palladium source	Ratio aldehyde : ketone
$PdCl_2$	10.8 : 1.0
$PdBr_2$	1.0 : 1.1
PdI_2	No reaction
$PdCl_2(MeCN)_2$	2.9 : 1.0
$Pd(NO_2)_3$	1.0 : 4.4
$Pd(SO_4)$	1.0 : 11.8

Table 3 – Palladium counter-ions

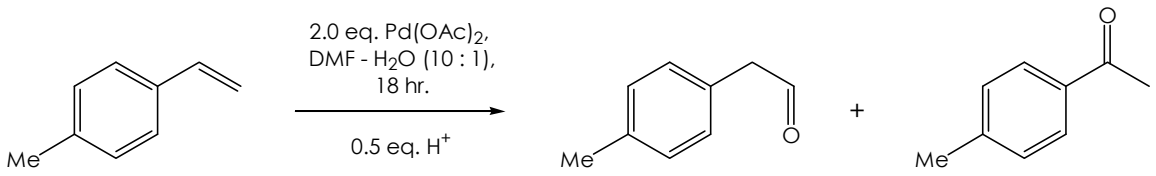
The most striking result was obtained with palladium(II) acetate; a complete elimination of the production of the anti-Markovnikov **150** was observed (Scheme 66). The reaction was notable for the rapid precipitation of palladium metal onto the reaction vessel, which was not seen in reactions that formed the aldehyde.

148 **149**

Scheme 66 – Reaction using palladium(II) acetate

3.3.3 Solution acidity

The reversal of regioselectivity with a change of palladium source had two potential causes: the change of counter-ion and the change of solution acidity. Acid is produced as the reaction progresses, and while hydrochloric acid is fully dissociated, ethanoic acid exists mainly in the undissociated form. In order to eliminate the possibility of a simple acidity effect, the reaction of 4-ethnyl-1-methylbenzene with palladium(II) acetate was carried out in the presence of both hydrochloric and sulphuric acids (Scheme 67). Both strong acids have a limited influence on the reaction outcome: the major product is still the ketone. However, while sulphuric acid does not lead to any aldehyde formation, the presence of chloride ions does give some anti-Markovnikov reaction.



156 **157** **158**

HCl	1.0	3.5
H_2SO_4	0.0	1.0

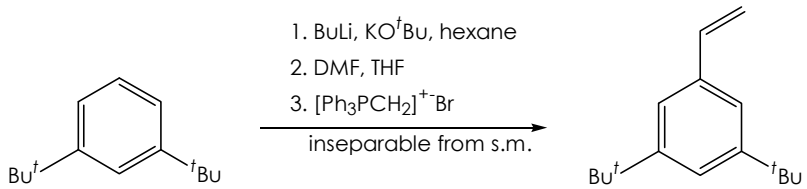
Scheme 67 – Effect of acid

As a confirmation that the acidity of the solution was not responsible for the difference in regioselectivity, the reaction using palladium(II) chloride was carried out in the presence of a number of carbonate bases (see section 6.2.9.4). Although the results were variable, in only one case (sodium carbonate) was the product found to be exclusively the ketone. Most of the bases led to mixtures of the two products. This confirmed that acidity alone could not explain the results.

The complete reversal of regioselectivity of the reaction by changing the counter-ion of the metal strongly indicated that an unusual complex was involved in the anti-Markovnikov reaction, and that further mechanistic study would be valuable.

3.3.4 Electronic effects: substituted styrenes

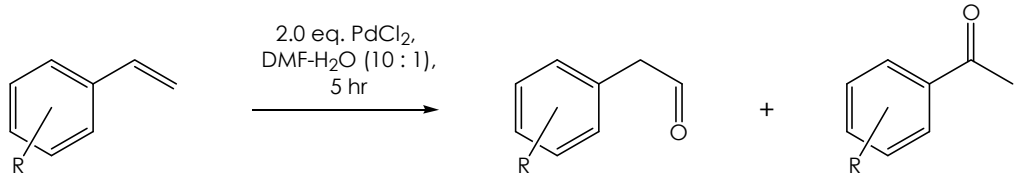
A large range of ring-substituted styrenes is commercially available, allowing access to a variety of steric and electronic variation in the system. Three substrates were not available from commercial sources (although all are known compounds). 1-Ethenylnaphthalene **159** and 2-ethenyl-1-methoxybenzene **160** were synthesised by standard Wittig[164] chemistry, in 75 and 40 % yields, respectively. 1,3-Di-(1,1-dimethylethyl)-5-styrene **162** was available *via* deprotonation of 1,3-di-(1,1-dimethylethyl)benzene **161** with a mixture of butyl lithium and potassium 1,1-dimethylethoxide, followed by reaction with DMF and *in situ* Wittig reaction (Scheme 68).[165]



161 **162**

Scheme 68 – Formation of 162

Wacker reactions were carried out on the available substrates under similar conditions to those used before; in most cases, a reaction time of five hours was found to give the most successful result (Scheme 69, Table 4).



Scheme 69 – Generalised Wacker reaction of styrenes

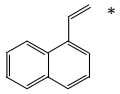
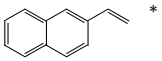
R group	Ratio of aldehyde : ketone	Yield (based on recovered s.m.)
H (**19**)	10.8 : 1.0	78 %
4-OMe (**148**)	9.5 : 1.0	63 %
4-Me (**156**)	7.1 : 1.0	61 %
4-Cl (**163**) *	aldehyde	76 %
4-CF_3 (**164**) *	aldehyde	69 %
4-^{t}Bu (**165**)	8.7 : 1.0	82 %
3-Me (**166**)	5.0 : 1.0	50%
3-Cl (**167**) *	aldehyde	80 %
3-NO_2 (**168**) *	16.2 : 1.0	54 %
3,5-di-^{t}Bu (**162**)	6.4 : 1.0	not available
2-Me (**169**)	aldehyde	89 %
2-OMe (**160**)	17.4 : 1.0	95 %
2-F (**170**)	aldehyde	78 %
2-Br (**171**)	aldehyde	not available
2,4-di-Me (**172**)	aldehyde	82 %
 **159**	aldehyde	60 %
 **173**	13.9 : 1.0	38 %

Table 4 – Wacker reaction of substituted styrenes (* - 18 hr. reaction)

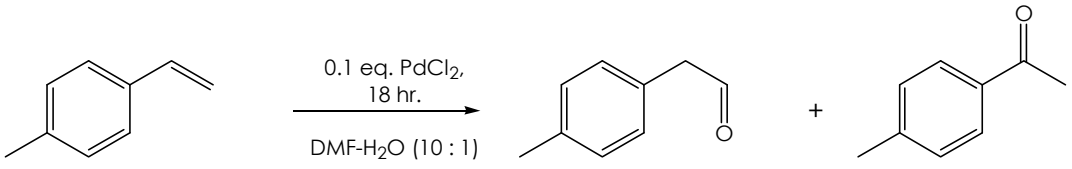
In line with the findings of Katsuyama *et al.*[134], reaction with more electron-withdrawing substituents does indeed give increased selectivity for the formation of aldehydes. However, the reaction proceeds to produce predominantly aldehydes in all cases, even with electron-donating substituents. In general, steric crowding does not appear to affect the course of the reaction; the presence of bulk ^{t}Bu groups does not prevent the reaction proceeding. The presence of a substituent on the 2-position of the aromatic is also significant; substrates containing this motif

give exclusively aldehyde in most cases. This factor will be considered in more detail later (section 3.3.11)

3.3.5 Reaction stoichiometry

Initial investigations of the mechanistic rational for the observed regioselectivity focussed on the stoichiometry of the reaction. The fact that catalytic and stoichiometric reactions gave opposing results could indicate that the ratio of palladium(II) to substrate was a key factor, or that palladium(0) was affecting the reaction pathway.

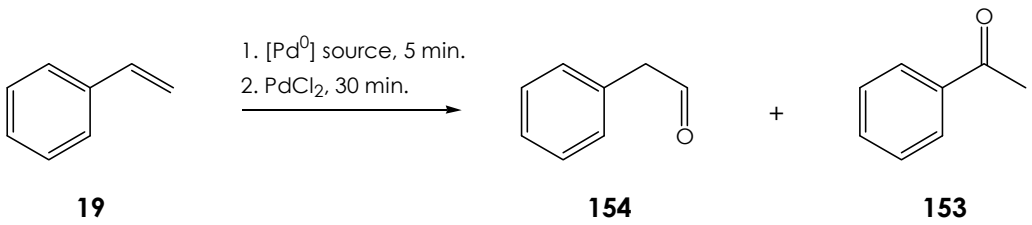
Carrying out the reaction of 4-ethenyl-1-methylbenzene **156** with 0.1 equivalents of palladium(II) chloride gave a ratio of products of 1.2 : 1.0 to the aldehyde (Scheme 70). Whilst this was inferior to the result with a large excess of palladium(II) chloride, it was still favouring the formation of the anti-Markovnikov product. This indicated that the stoichiometry alone was not the determining factor in the formation of the aldehyde.



Scheme 70 – Reaction using 0.1 eq. palladium(II) chloride (substrate molarity as before)

3.3.6 The influence of palladium(0)

The influence of palladium(0) on the reaction was examined by carrying out a period of equilibration with a palladium(0) source, before conducting the reaction over a short period (30 minutes). It was envisaged that if palladium(0) was involved in the regioselectivity, then the ratio of aldehyde to ketone should be raised, in comparison to a reference reaction (Scheme 71, Table 5).



Scheme 71 – Reaction with palladium(0) in reaction

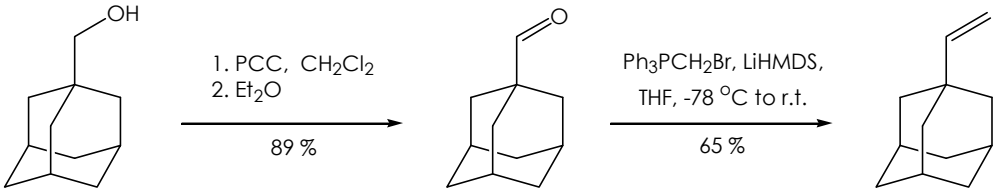
Pd^0 source	Ratio **154** : **153**
None (reference)	2.7 : 1.0
Pd black	2.5 : 1.0
$Pd_2(dba)_3$	2.3 : 1.0
$Pd(PPh_3)_4$	1.7 : 1.0

Table 5 – Reaction in presence of Pd^0

Comparison to the reference reaction shows no significant effect on the reaction in the cases of bulk palladium (Pd black) or the dba complex. The result with triphenylphosphane is slightly **lower** than the reference; in this case, it is likely that the ligand is affecting the reaction pathway. Thus, the regioselectivity cannot be explained by the presence of palladium(0).

3.3.7 Steric factors: Non-aromatic substrates

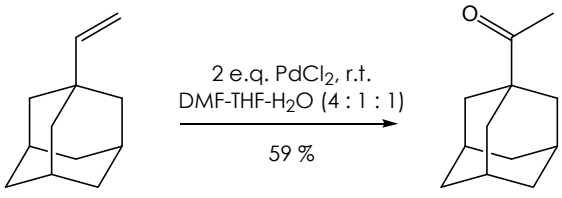
In order to eliminate the involvement of steric factors in the reversal of regioselectivity seen, it was necessary to produce a substrate of similar steric bulk to the styrenes, but lacking aromaticity. The ethenyladamantane system **176** was chosen, as it would be expected to show similar steric bias to styrene. **176** was synthesised in two steps from the commercial alcohol **175**, *via* PCC oxidation followed by Wittig reaction (Scheme 72).



174 **175** **176**

Scheme 72 – Formation of adamantyl substrate

Wacker reaction of **176** proceeded smoothly to form exclusively the ketone **177** (Scheme 73); the starting material showed low solubility in DMF, and therefore a minimal amount of THF was added to effect dissolution.



176 **177**

Scheme 73 – Wacker reaction of adamantyl substrate

It could have been that hindrance of access to the internal position was preventing addition of water at that position. However, this would also have been expected to apply to the non-aromatic system **176**. The result above thus showed that the steric bulk of the aromatic group was very unlikely to explain the reversal of regioselectivity. The control element must therefore be linked to the presence of an aromatic group in the substrates.

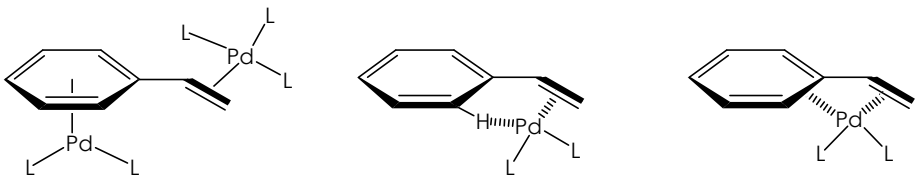
3.3.8 Complex formation

The evidence gained from the studies undertaken to this point seemed to indicate the formation of an unusual complex involving palladium(II) and the substrate, leading to the anti-Markovnikov product. It was envisaged that this postulated complex was responsible for the production of the aldehyde, while the ketone would be formed by reaction of palladium(II) complexed to the alkene in a "classical" manner. It was therefore envisaged that pre-formation of the unusual complex would give enhanced aldehyde production; this would be achieved by mixing the substrate and palladium(II) prior to adding water.

Stirring palladium(II) chloride with styrene in dry DMF resulted in slow formation of a dark-red solution. Over short periods, no significant effect was seen on the product ratio obtained. However, if the complex was allowed to form overnight before addition of water, a product ratio of 6.1 : 1.0 in favour of the aldehyde was obtained after 30 minutes reaction: the reference result was a ratio of 2.7 : 1.0. Pre-complexation therefore showed a significant effect, and provided strong evidence for the existence of a palladium(II)-styrene complex of unusual composition.

3.3.9 NMR studies

Three possible complexes were envisaged, which could explain the anti-Markovnikov reactivity seen in the Wacker reaction of styrenes (Figure 11). The first **178** was a complex involving the interaction of two palladium(II) atoms with the substrate, one with the alkene and a second with the aromatic system. This could reverse the polarity of the double bond, and so favour terminal nucleophilic attack. The second possibility **179** involved an agostic interaction[166] between the palladium and the substrate, whilst the third was an η^4-type complex **180**.



178 **179** **180**

Figure 11 – Possible complexes

To try to distinguish the true nature of the reactive species, variable temperature NMR spectra of the complex were investigated. Following a similar protocol to that used in the previous section, it was possible to form a complex of palladium(II) chloride and 4-ethenyl-1-methylbenzene in DMF-d_7. As a reference system, a similar solution using palladium(II) acetate was prepared. As was shown in section 3.3.2, this system forms only the ketone: only the η^2-alkene-palladium complex is present.

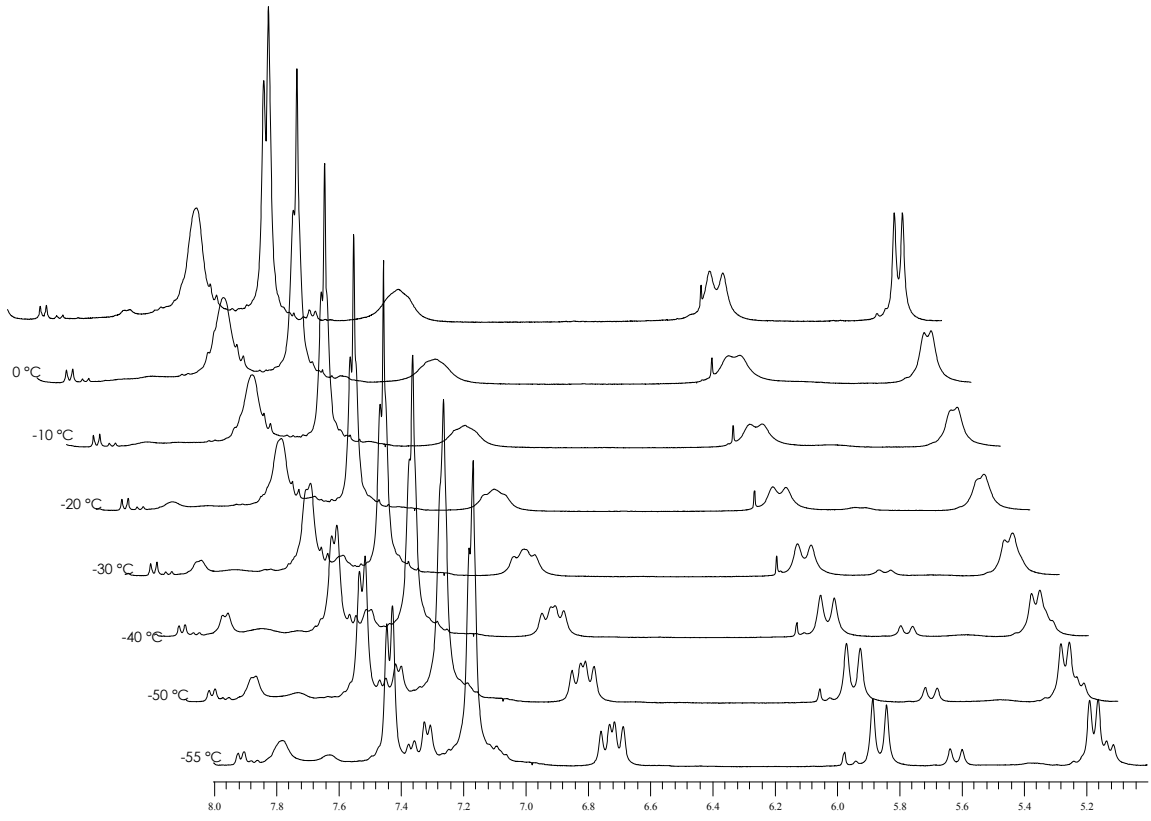


Figure 12 – Variable temperature NMR of $PdCl_2$ complex

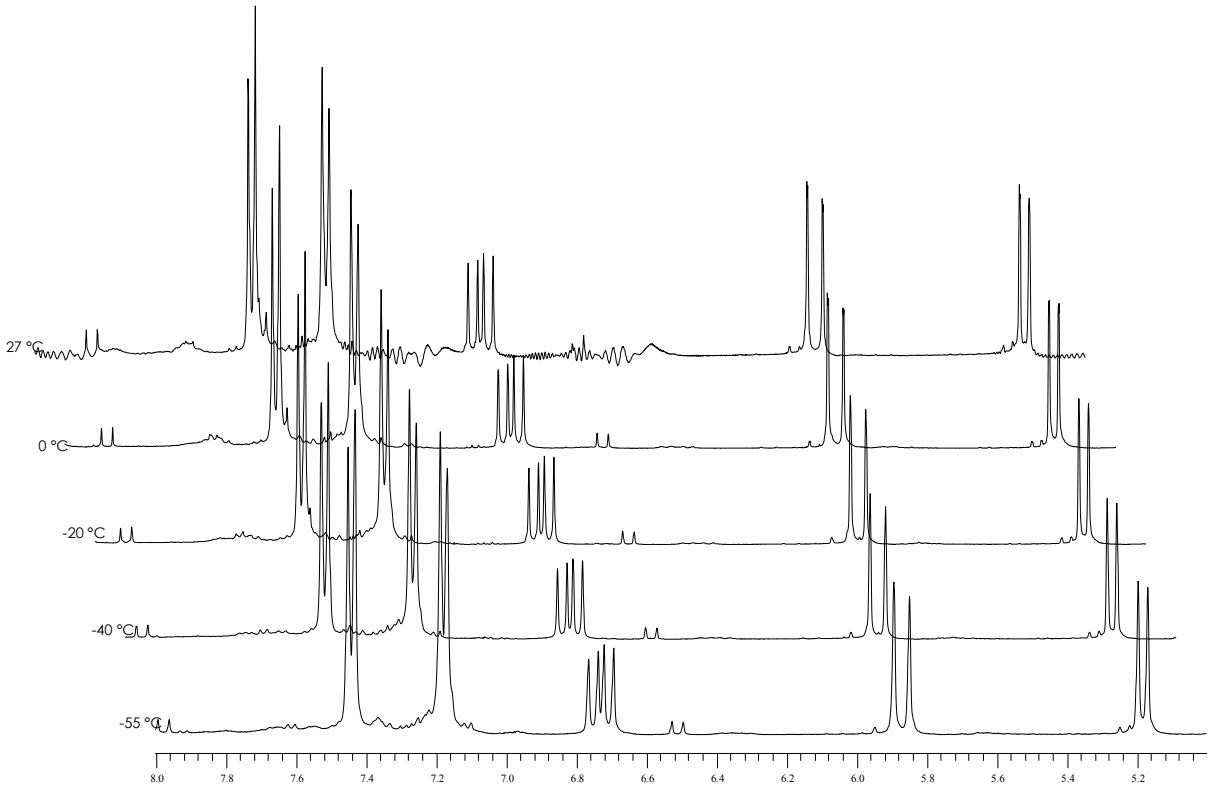


Figure 13 - Variable temperature NMR of $Pd(OAc)_2$ complex

The NMR spectra obtained over the temperature range -55 to 27 °C are shown above (Figure 12, Figure 13);[167] the region covering the alkene and aromatic protons is shown. The spectra for the acetate system show no evidence for a complex; the signals seen are those for the free substrate,[168] the acetate ligand[169] and co-ordinated DMF[170] only. An impurity in the starting material led to the small signal at 7.9 δ. Reaction to give the ketone must therefore occur *via* a complex which is not visible on the NMR timescale, or which only forms in the presence of water. However, the NMR of the chloride-containing system shows a series of extra peaks. At room temperature, the NMR signals are broadened, but become sharper and separate into multiple signals on cooling. This indicates the presence of a complex or complexes in solution. For the alkene protons, two sets of new signals are observed. This is consistent with the formation of a two complexes. It is possible that these are complexes of different stoichiometry, possibly a 1:1 complex and a 2:1 complex of the substrate to palladium(II).

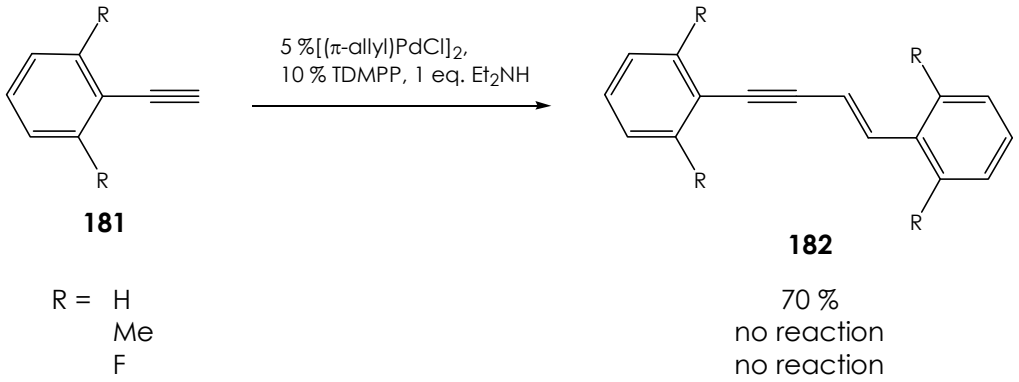
The positions of the alkene signals in the spectrum of the complex were informative. It is clear that the signals for the terminal position of the double bond have been shifted, whilst the effect on the α-position proton is less clear. The signals for the α-proton in the complexes appear between the aromatic peaks of the free substrate. Some information is therefore lost due to overlap of the signals. However, the relative order of the peaks is unchanged; the α-position is

still the most deshielded proton. This implies that attack on the terminal position of the bond is not occurring due to a reversal of the polarity of the bond.

Complexes of palladium(II), alkenes and DMF are known[26,27]: these have only been isolated as amorphous solids. X-Ray quality crystals of styrene-palladium(II) complexes are obtained from apolar solvents such as benzene[39,171]. It is unsurprising, therefore, that attempts to form crystals from the anhydrous solution were unsuccessful.

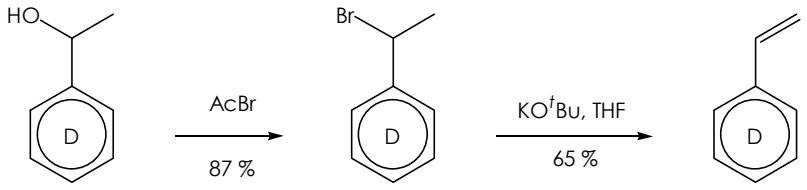
3.3.10 Deuterium labelling studies

The NMR studies indicate that complexes are involved in the reaction, but do not allow the possibilities to be distinguished. Spencer *et al.*[145] have shown that allylic C-H interactions can be involved in the regiochemistry of other Wacker reactions (for more detail, see section 4.1). Recently, Rubina and Gevorgyan[172] have shown that an agostic interaction responsible for unusual regioselectivity in the palladium-catalysed dimerisation of terminal alkynes shows a significant kinetic isotope effect (Scheme 74): the value of k_H/k_D is approximately 3.0 for the ring-deuterated system.



Scheme 74 – Agostic interaction in alkyne dimerisation

As was explained in section 3.1.4.3, the hydroxypalladation step of the reaction may be rate-determining. It was therefore envisaged that if complex **179** was responsible for the reversal of regioselectivity, then 2,2-dideuterated styrene could show a kinetic isotope effect. The synthesis of such a substrate was envisaged to be demanding, and it was felt that a ring-deuterated styrene **185** would provide equally valid data. The synthesis of this substrate is outlined below (Scheme 75).



183 **184** **185**

Scheme 75 – Synthesis of ring-deuterated styrene

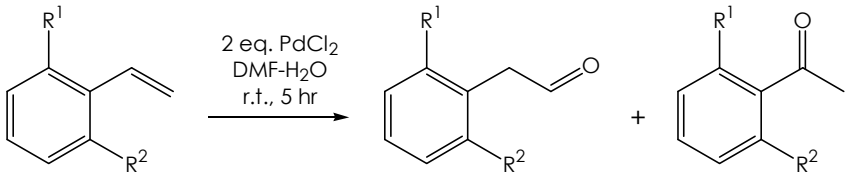
Kinetic data were then obtained over a time range of ½ to 2 hours for this substrate and styrene, under the same conditions as before. The data for these experiments are given below (Table 6). As can be seen, the results for the deuterated and non-deuterated substrate are identical within experimental error. Thus, no additional evidence for an agostic interaction was obtained.

Reaction time (hr)	Conversion	
	19	**185**
0.5	9.3 %	9.8 %
1.0	17.0 %	16.9 %
1.5	20.2 %	20.6 %
2.0	23.8 %	24.0 %

Table 6 – Kinetic investigation into agostic interaction

3.3.11 2-Methyl effect

In order to confirm the involvement of a side-on palladium-substrate interaction, the 2,6-dimethyl substrate **186** was synthesised using standard Wittig chemistry. It was envisaged that the presence of substituents on both sides of the ring would interfere with the formation of a complex of type **180**, and so lead to enhanced ketone production (Scheme 76, Table 7).



Scheme 76 – The effect of 2-position substituents

Substrate	Ratio aldehyde : ketone
R^1, R^2 = H (**19**)	10.8 : 1.0
R^1 = H, R^2 = Me (**169**)	1 : 0
R^1, R^2 = Me (**186**)	1.6 : 1.0

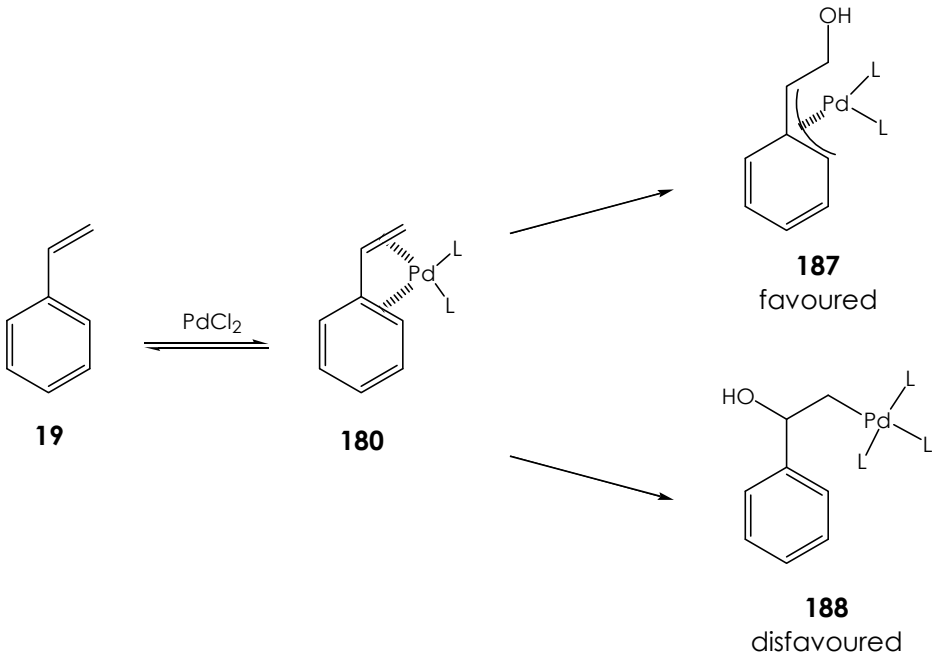
Table 7 – Results for 2-position substituents

As was seen earlier (section 3.3.4), the presence of one substituent in the 2-position enhances the anti-Markovnikov regioselectivity, compared to **19**. On the other hand, substrate **186** gives only a slight excess of the aldehyde over the ketone: as expected, the presence of substituents on both

sides of the alkene interferes with the formation of the reactive complex. This strengthens the case for the presence of a side-on complex of palladium and the aromatic system. The fact that the aldehyde is still the major product indicates the presence of complex **180** rather than **179**; an agostic interaction would be expected to be completely removed by the replacement of both hydrogens, and the Markovnikov product would be expected to dominate.

3.3.12 Mechanistic proposals

The mechanistic insight gained strongly indicates the involvement of an η^4-complex **180** in the anti-Markovnikov regioselectivity of the Wacker reaction of styrenes. Such a complex is highly unusual, but a similar η^4 complex of styrene and rhodium has recently been isolated and studied by X-ray crystallography.[173] The formation of an η^4-complex could be followed in the reaction by conversion to an η^3-system **187**, following attack of the nucleophile. In contrast, attack at the α-position would give the non-delocalised intermediate **188**; this would account for the dominance of the anti-Markovnikov pathway (Scheme 77). This mechanism also accounts for the higher selectivity seen in the naphthyl-type substrates (Table 4). Naphthyl groups are known to act in a diene-like manner,[174] and to form η^3-complexes[175] more readily than phenyl groups: thus, the anti-Markovnikov pathway would be more accessible for the naphthyl substrates.



Scheme 77 – Mechanistic proposal

This mechanism also accounts for the greater regioselectivity of the reaction when a single 2-position substituent is present. The formation of the ketone requires attack to occur

approximately as shown below (Figure 14); the path of the nucleophile would be blocked by a substituent, thus, making attack less likely.

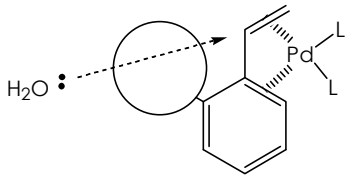


Figure 14 – Effect of a 2-position substituent

3.4 Catalysis

3.4.1 Small molecule reoxidants

Although mechanistically interesting, the anti-Markovnikov reaction elucidated is not synthetically useful; the need for stoichiometric amounts of palladium(II) salts and the fact that the reaction stops after approximately 50 % conversion both make large-scale use unattractive. A number of approaches have been adopted to achieve catalytic cycles with palladium(II) reactions, and so it was hoped that an appropriate reoxidant could be found. It has already been shown that reoxidation using copper(I) was not effective, giving largely the ketone product. The sensitivity of the reaction products to oxygen also precluded this method.

A number of other reoxidants used in the Wacker reaction were examined (Table 8), making use of 0.1 equivalents of palladium(II) chloride as the catalyst, and either **19** or **148** as the substrate. The reoxidants gave variable results: some did lead to catalysis of the Wacker reaction, but gave undesired regioselectivity, whilst others prevented any reaction occurring. For example, 1,4-benzoquinone was a good reoxidant but gave almost exclusively the Markovnikov product.

Reoxidant	Ratio aldehyde : ketone
1,4-benzoquinone	1.0 : 11.1
^{t}BuOOH	1.0 : 3.0
H_2O_2	1.3 : 1.0
$FeCl_3$	no reaction
MnO_2	ketone only
NMO	no reaction

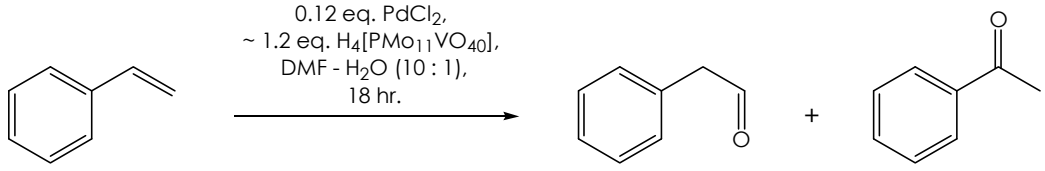
Table 8 – Reoxidation

The results obtained in section 3.3.2 had shown that ions other than chloride appeared to interfere with the desired reaction. It was postulated that a similar effect was occurring with the reoxidants: the active complex was being disrupted by the other species in solution.

3.4.2 Heteropolyanion reoxidation

Heteropolyanions and their conjugated acids, often referred to as HPAs, were first discovered by Berzelius in 1826;[176] the structure of these molecules was not elucidated until over 100 years later.[117] These large cages can be formed with a wide range of elements. HPAs containing molybdenum and vanadium have been used as reoxidants in the Wacker reaction;[177,178] normally, the HPA is used catalytically, with oxygen as the terminal oxidant. It was postulated that, as the ions are large and non-co-ordinating, reoxidation using an HPA could be successful.

The heteropolyacid $H_4[PMo_{11}VO_{40}]$ was synthesised by the literature method[179] and used as an approximately stoichiometric reoxidant for palladium[180] (Scheme 78). Overnight reaction gave approximately ¾ conversion of the starting material; the major product was the anti-Markovnikov aldehyde. The reason for the degradation of the ratio of products is not entirely clear: the acidity of the solution may be involved.



19 | **154** 6.4 | **153** 1.0

Scheme 78 – Reoxidation using HPA

3.5 Summary

In conclusion, unusual anti-Markovnikov regioselectivity in the Wacker reaction of styrenes has been demonstrated. The reaction occurs only with palladium(II) chloride, with other counter-ions interfering with the reaction. Mechanistic studies on the reaction have provided support for the proposal that the reaction proceeds *via* an η^4-complex of palladium(II) and the substrate; formation of an η^3-intermediate is postulated as the reason for the dominance of this pathway. Catalysis of the reaction has been possible using a stoichiometric amount of an HPA; more work is needed to optimise this system.

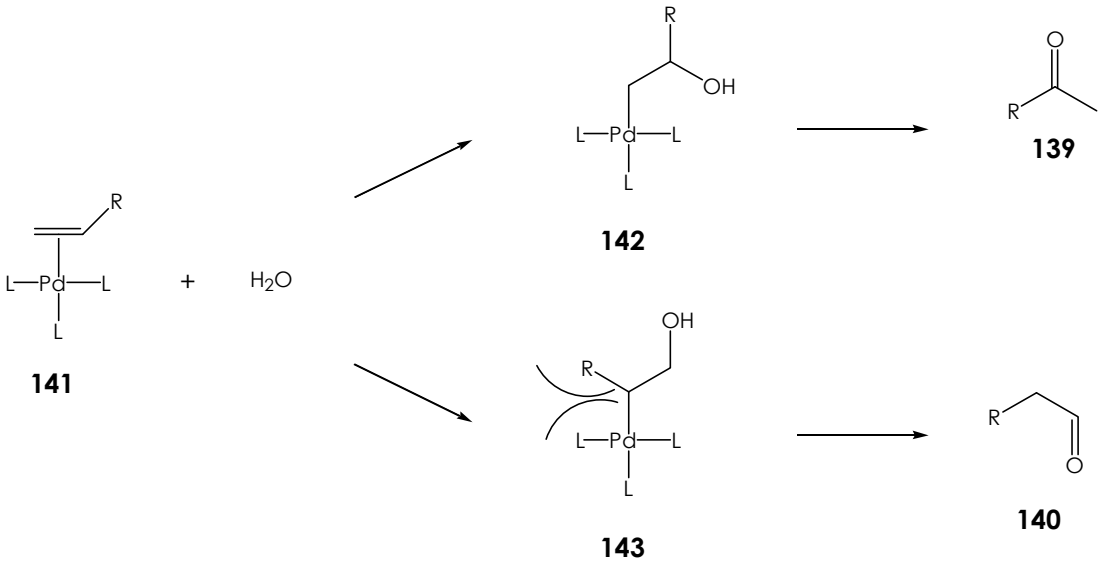
4 THE WACKER REACTION OF ALKENES WITH ALLYLIC HYDROGENS

4.1 Regioselectivity in the Wacker reaction of internal alkenes

The regioselectivity of the Wacker reaction was discussed at length in section 3.1.4. Terminal alkenes typically produce methyl ketones, whilst regioselectivity in the reaction of non-symmetrical internal alkenes is poor. Two explanations have been proposed for the observed regioselectivity: electronic control (Scheme 79) and steric control (Scheme 80).

141a **141b**

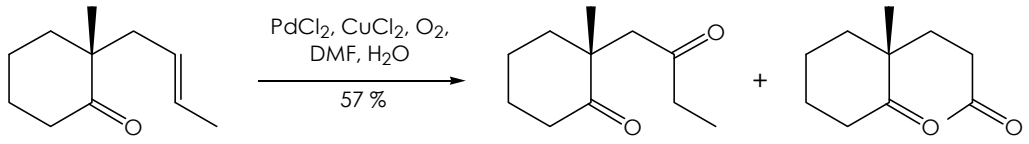
Scheme 79 – Electronic control in the Wacker reaction



141 **142** **139** **143** **140**

Scheme 80 – Steric control in the Wacker reaction

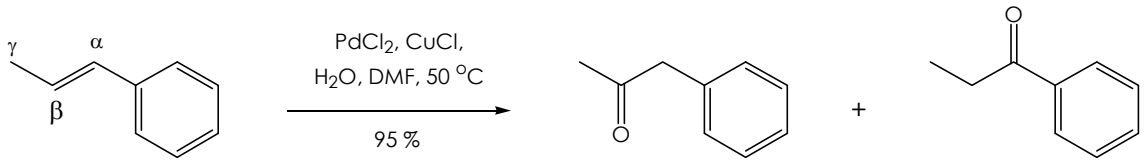
The reaction of internal alkenes is often slow under standard conditions, and modified solvents and catalysts are used to obtain efficient reaction.[181] In order to obtain good regioselectivity in the reaction of unsymmetrical internal alkenes, it is usually necessary for a heteroatom to be present in the substrate. An example is seen in the work of Grattan and Whitehurst, where the presence of a co-ordinating carbonyl gives high selectivity (Scheme 81).[182] This reaction is unusual, as it proceeds under standard Wacker conditions [DMF, water, palladium(II) chloride, copper(II) chloride]: often, specialised conditions are needed.[183]



189 **190** : **191**
91 : 9

Scheme 81 – Regioselective reaction of an internal alkene

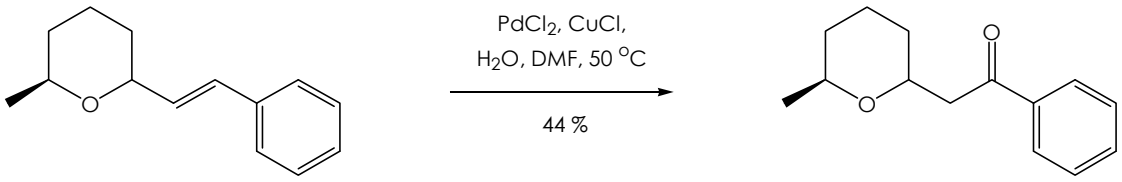
The Wacker reaction of styrenes (styrenes) was described in chapter 3, where it was shown that the reaction proceeds in a largely anti-Markovnikov sense. Unusual regioselectivity has also been observed in the reaction of 1-phenylprop-1-enes (β-methylstyrenes). Keinan *et al.* have shown that 1-phenylprop-1-ene **192** reacts to give mainly the ketone **193** (Scheme 82).[184] As the authors point out, this regioselectivity is unexpected. The electron-donating phenyl group would be expected to stabilise a positive charge on the α-position of the alkene: such an effect might be expected to lead to a predominance of **194**.



192 **193** : **194**
3 : 1

Scheme 82 – Wacker reaction of 1-phenylprop-1-ene

Introduction of a heteroatom completely reverses this regioselectivity (Scheme 83): only **196** is obtained. The authors believed that this demonstrates the powerful effect of heteroatoms on the course of the Wacker reaction; it is possible that the availability of the allylic hydrogens could be a factor.

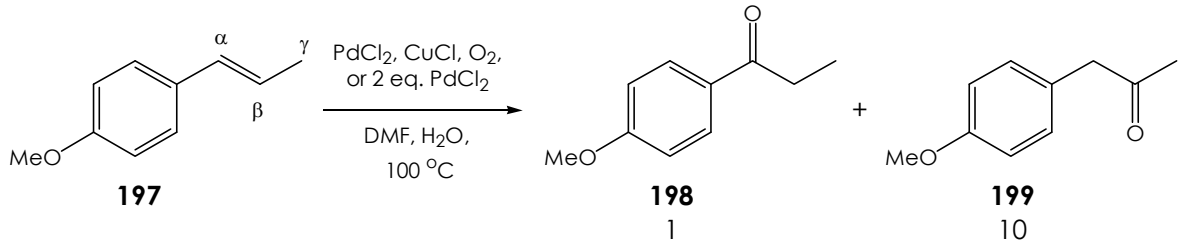


195 **196** only

Scheme 83 – Wacker reaction of 195

The unexpected regioselectivity in the Wacker reaction of **192** is intriguing. Spencer *et al.* have studied the reaction, seeking an understanding of the mechanistic rationale behind the regioselectivity.[145] Unlike the reaction of styrenes discussed in chapter 3, it was found that the

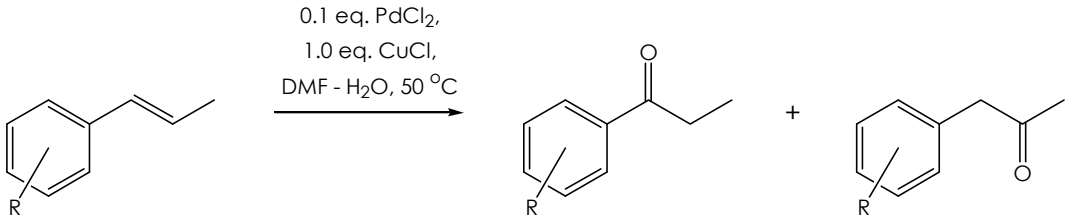
transformation of **197** proceeds identically under both catalytic and stoichiometric conditions (Scheme 84), and therefore the explanation of the unusual regioselectivity must therefore be different.



197 **198** 1 **199** 10

Scheme 84 – Reaction of 197 **under stoichiometric and catalytic conditions**

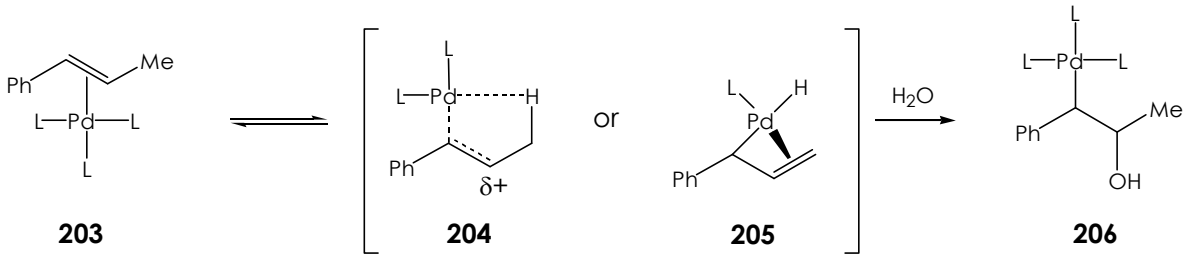
Electronic factors were investigated using a series of substrates of type **200**. When R = CF_3, **200** is formed almost exclusively, while under the same conditions only the presence of three electron-donating OMe groups led to Markovnikov selectivity. This ruled out electronic factors as the main cause of the unusual regioselectivity seen.



	200	**201**	**202**
a	R = 4-CF_3	1.0	> 19
b	R = 4-OMe	1.0	2.0
c	R = 2,4,6-tri-OMe	2.3	1.0

Scheme 85 – The Wacker reaction of 1-phenylprop-1-enes

Spencer *et al.* have therefore proposed that the regioselectivity observed is a consequence of the presence of protons on the allylic (γ) position of the molecule.[145] Two possible intermediates were suggested: an agostic complex **205** and a (σ + π) complex **206** (Scheme 86).

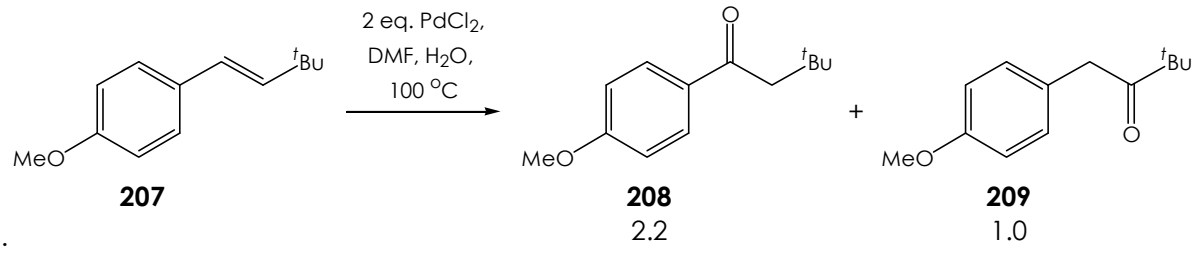


203 **204** **205** **206**

Scheme 86 – Possible mechanism and intermediates

The concept of agostic interactions was introduced by Brookhart and Green;[166] the occupied σ-bond orbital of the C-H bond acts as a donor to the metal, while back-bonding can occur to the empty σ^*-orbital. The presence of such an interaction would lead to the partial carbocation **204**, and thus attack at the β-position. (σ + π)-Complexes have been shown to be involved in unusual regioselectivity;[185] such a structure could also account for attack at the β-position.

Spencer *et al.* were able to gain additional evidence for the involvement of allylic hydrogens by studying the reaction of substrate **207**, which has no allylic hydrogens. Although reaction of this substrate is very slow, and requires forcing conditions, it proceeds mainly in a Markovnikov sense (Scheme 87).



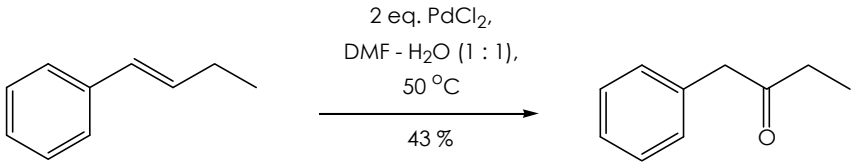
207 **208** 2.2 **209** 1.0

.

Scheme 87 – Reaction with no allylic hydrogens

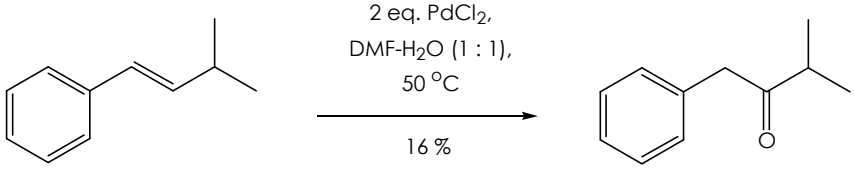
4.2 Investigations into the reaction of 1-phenylprop-1-enes

In order to gain additional evidence for the involvement of allylic hydrogens in the Wacker reaction, an extension of the work of Spencer *et al.*[145] was carried out. The reversal of regioselectivity between substrates **197** and **207** was strong evidence for the involvement of allylic hydrogen in the regioselectivity of the Wacker reaction of internal alkenes. However, the abrupt change in steric bulk could be involved in this effect. It was hoped that, by replacement of one or two of the allylic hydrogens, a sequential alteration of regioselectivity might be seen. Toward this end, the alkenes **210** and **212** were synthesised by standard Wittig methods, in 46 and 44 % yields respectively. The alkenes were then subjected to palladium(II) oxidation (Scheme 88 and Scheme 89).



210 **211**

Scheme 88 – Wacker reactions of substrate with two allylic hydrogens



212 **213**

Scheme 89 – Wacker reaction of substrate with one allylic hydrogen

In both cases, the reaction led to only one isolated product: the β-ketone. Thus, the presence of a single allylic hydrogen was sufficient to give reaction at the non-conjugated position of the alkene. Taken with the result for **207**, this is strong evidence for the involvement of allylic hydrogens in the Wacker reaction of electron-rich internal alkenes.

One possible concern with the above information was the efficiency of the Wacker reaction of substrates **210** and **212**. The reaction proceeds much less readily than that of **192** and **197**. Whilst the less-hindered substrates will react smoothly under catalytic conditions, attempts to use the same protocol with the more-hindered substrates gave very little reaction with **210** and none for **212** (even over extended periods). The use of stoichiometric amounts of palladium(II) chloride was successful in bringing reaction about; however, the isolated yields were low.

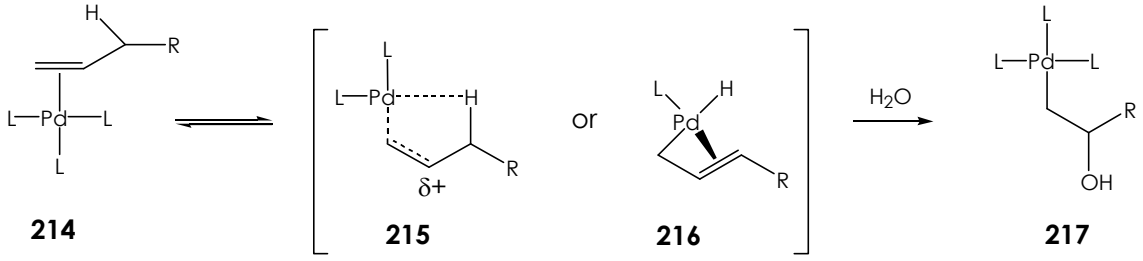
4.3 The reaction of terminal alkenes

4.3.1 Possible involvement of allylic hydrogens

The work of Spencer *et al.* and the results in the preceding section together constitute strong evidence that the regioselectivity of the Wacker reaction is affected by the availability of hydrogen atoms in the allylic position. However, the low reactivity of the internal alkenes **210** and **212** was of concern.

The Wacker reaction is usually employed in the oxidation of terminal alkenes; the poor reactivity of internal double bonds is a general phenomenon in the Wacker oxidation (section 2.4.2.1) and is phenomenon usually attributed to steric hindrance. The regioselectivity of the reaction of

terminal alkenes is normally explained in terms of steric and electronic factors (see section 3.1.5). The possibility of the involvement of allylic hydrogens in the reaction of terminal alkenes was therefore intriguing; it was anticipated that a mechanism similar to that for internal double bonds could be involved (Scheme 90). The higher reactivity of terminal double bonds under Wacker conditions was expected to circumvent the problems experienced with **210** and **212**.



Scheme 90 – Possible involvement of allylic hydrogens

One method for probing the reaction of terminal bonds was a strategy similar to that used in the previous section: the substitution of allylic hydrogens by methyl groups (Figure 15). However, the change of steric environment of the double bond on moving from **218** to **220** was of concern.

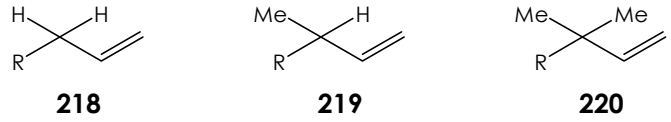
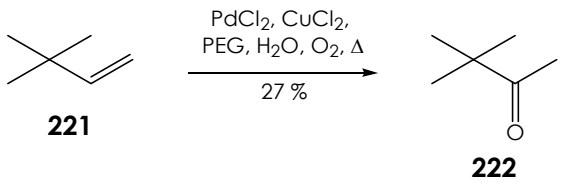
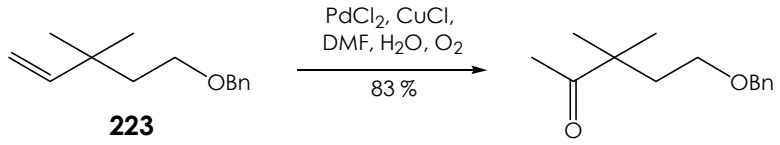


Figure 15 – Potential substrates

The potential for steric interference in the outcome of the reaction and the possibility of low reactivity for **220** both made this strategy unattractive. Indeed, there are only two examples of Wacker reaction of substrate of general structure **220**. In one of these examples, the reaction proceeds in poor yield (Scheme 91);[186] the second substrate **223** contains a potentially significant heteroatom (Scheme 92).[187]



Scheme 91 – Reaction in the absence of allylic hydrogens



223 **224**

Scheme 92 - Reaction in the absence of allylic hydrogens

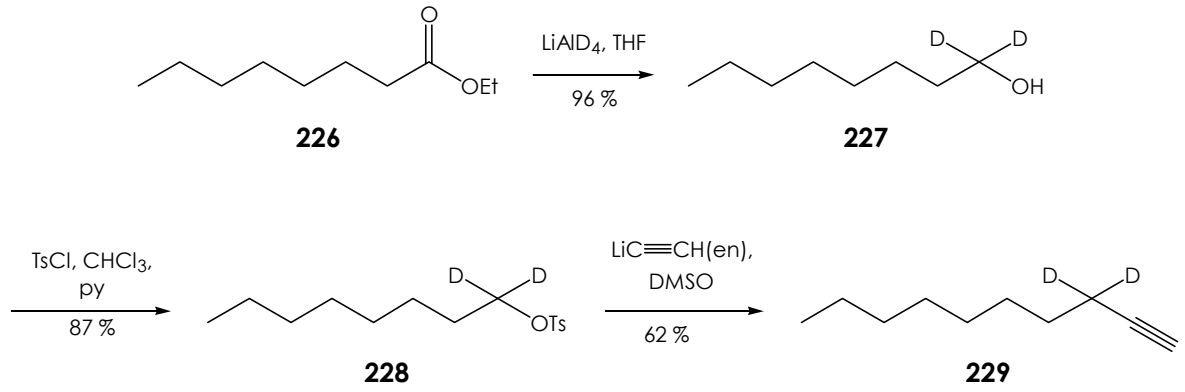
It was decided to use an alternative approach to the problem. The replacement of the allylic hydrogen atoms of a terminal alkene by deuterium would give a substrate sterically and electronically almost identical to the unsubstituted system. It was explained in section 3.1.4.3 that hydroxypalladation may be the rate-limiting step in the Wacker reaction. Thus, it was possible that a kinetic isotope effect could be seen in the Wacker reaction of terminal alkenes.

4.3.2 Kinetic experiments

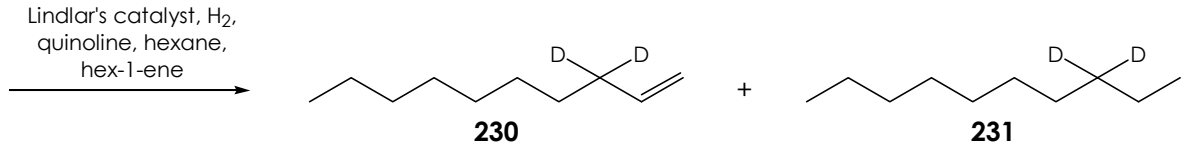
4.3.2.1 Substrate synthesis

Among the most reactive substrates in the Wacker reaction are simple straight-chain alkenes. In principal, therefore, any simple alkene (other than ethene) could have been used as a test substrate. In order to avoid problems of high volatility, both in the synthesis of the deuterated substrate and in subsequent application, it was decided to incorporate a medium-length alkyl chain in the molecule. Dec-1-ene is **225** commercially available and inexpensive, and was chosen as the test substrate.

The synthesis of 3,3-dideuteriodec-1-ene was carried out following the procedure used by Harrod and Chalk in the synthesis of [3,3-D_2]hept-1-ene[188] (Scheme 93). The first two steps, from the commercial ester **226** to the intermediate **228**, proceeded without any incident. Conversion to the alkyne **229** initially proceeded in poor yield; this was found to be due to the volatility of the product. Alteration of the reaction conditions raised the yield to an acceptable level. The final selective semi-reduction was troublesome. Although literature precedent exists for the reduction of dec-1-yne to dec-1-ene,[189] it was found that under all conditions some over-reduction to the fully saturated **231** occurred. The best selectivity was obtained using Lindlar's catalyst,[98,99] quinoline and a solvent mixture consisting of hexane and hex-1-ene.[190] It was not possible to separate the two by distillation, chromatography or chromatography in the presence of silver ions.



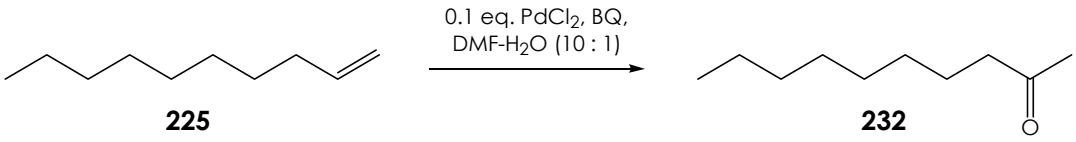
Scheme 93a – Synthesis of [3,3-D_2]dec-1-ene



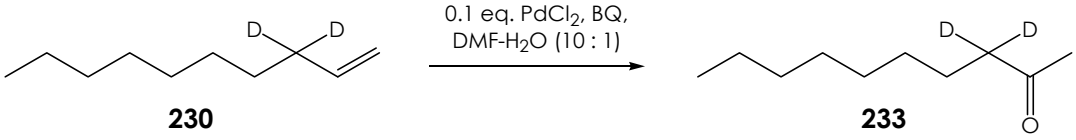
Scheme 92b – Synthesis of [3,3-D_2]dec-1-ene

4.3.2.2 Kinetic experiments

Although it had only been possible to obtain the deuterated substrate contaminated with the fully reduced alkane, it was envisaged that useful information would still be available. As alkanes do not co-ordinate strongly to palladium, the presence of **231** was not expected to interfere with the reaction.



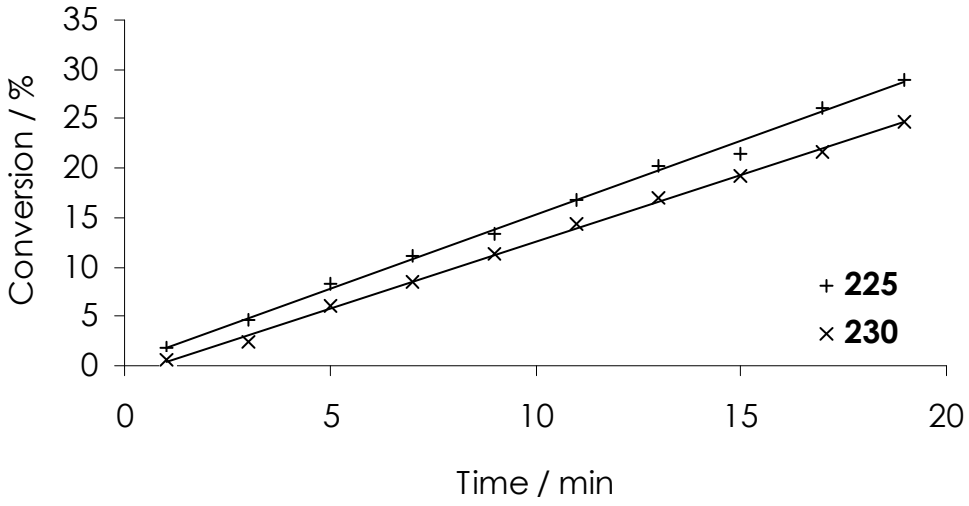
Scheme 94 – Wacker reaction of 225



Scheme 95 – Wacker reaction of 230

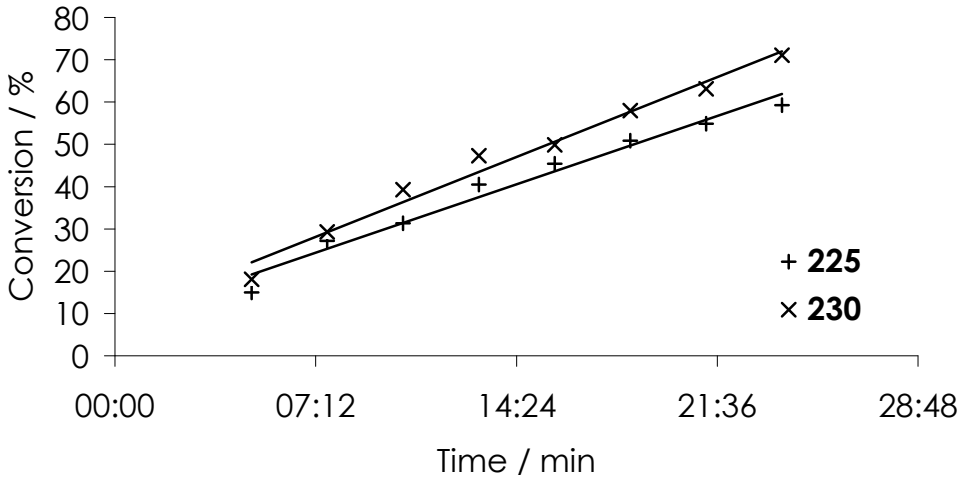
Following preliminary studies, two sets of NMR experiments were designed. In the first set, a catalytic mixture consisting of palladium(II) chloride, 1,4-benzoquinone and water in DMF-d_7 was prepared. Aliquots of this stock solution were then used to carry out the Wacker reactions of **230** and **225** in NMR tubes. The reaction could be conveniently monitored over a period of approximately 30 minutes, with clear separation of signals for starting material, product and

reoxidant. The results are shown below (Graph 1). It is clear that the slopes of the two lines are very similar. More importantly, the rate of reaction is linear to a high conversion of the substrate. This implies that the reaction is zero-order in the substrate. Thus any kinetic evidence for an agostic interaction will not be seen under these conditions.



Graph 1 – Separate kinetics

In light of the previous result, a second experiment was carried out using a mixture of the two alkenes was prepared of known composition (approximately equimolar). This was then used under similar conditions to the first set of experiments;[191] an internal competition reaction would circumvent the independence of reaction rate on substrate concentration. The results are again summarised in graphic form (Graph 2). Details of analysis of the NMR data, with derivations of the equations necessary to obtain the conversion for both substrates, are given in Appendix 1.



Graph 2 – Competition kinetics

Under these conditions, the rates of reaction of the two substrates are different. The deuterated substrate is found to react more rapidly than the non-deuterated **225**. This provides some evidence for the involvement of allylic hydrogens in the regioselectivity of the Wacker reaction.

4.4 Conclusions

The Wacker reaction of 1-phenylprop-1-enes has previously been shown to occur with unusual regioselectivity.[145] This work has been extended, using substrates **210** and **212**. It was demonstrated that a single allylic hydrogen is sufficient to lead to Wacker reaction at the non-conjugated end of the alkene. This is strong evidence that the regioselectivity of the Wacker oxidation of electron-rich internal double bonds is governed by the availability of allylic hydrogens. This could be due either to an agostic interaction or to a ($\sigma+\pi$)-complex.

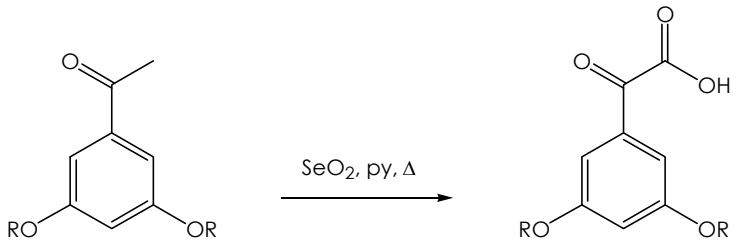
In the reaction of terminal double-bonds, a probe was produced to examine the kinetics of the oxidation. The reaction was found to be zero-order in substrate under the conditions employed. A competition experiment showed some evidence for a kinetic isotope effect in the reaction of a terminal alkene containing deuterium atoms in the allylic position. This requires confirmation, but does provide some evidence for the involvement of allylic hydrogens in the Wacker reaction. The factors governing regioselectivity in the reaction of internal and terminal double-bonds may be different.

5 EXTENSION OF A PROTECTIVE GROUP: REMOVAL OF THE NAP GROUP BY OXIDATION[192]

5.1 Protective groups

5.1.1 The need for protective groups

Protective groups are ubiquitous in organic synthesis; selectivity between potential sites of reaction is crucial in the synthesis of most organic molecules. Without the correct protection in place, the desired reaction will proceed either in poor yield, or not at all. A simple example is given below: oxidation with selenium(IV) oxide proceeds only when the phenolic oxygens are protected (Scheme 96).[193]



234	**235**
R = H	0 %
R = Bn	90 %

Scheme 96 – The need for protective groups

The benzyl group, which will be discussed in section 5.1.2, is perhaps the widest-used protective group for oxygen and nitrogen, although silicon-based protective groups, such as TMS (trimethylsilyl), are also ubiquitous in organic synthesis. A great number of protective groups have been developed for a myriad of functional groups; the latest edition of Greene and Wuts' book[105] includes 848 different protective groups, 348 of which have been added since the second edition (a time-span of only nine years). By far the most common functional groups to be protected are alcohols and amines, the presence of labile protons being the most common problem to be avoided.

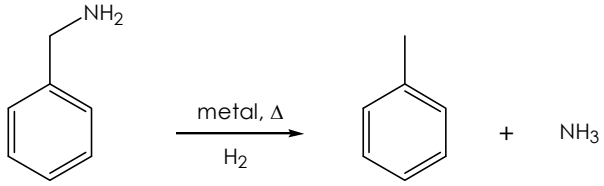
Greene and Wuts define the ideal protective group thus:

> *"It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably non-toxic reagents that do not attack the regenerated functional group. … All things considered no one protective group is the best"* [194]

Two protective-group problems are familiar to most synthetic chemists: failure of deprotection, and interference of a protective group in a synthesis. This continues to drive the innovations in the field of protective groups, with the introduction of novel protection strategies and the extension and improvement of existing methods.

5.1.2 The benzyl group

The hydrogenolysis of benzyl groups, usually over a palladium catalyst, was introduced in section 2.5.6. Indeed, the early history of benzyl protection owes more to studies on hydrogenation than to efforts to discover protective groups. The first reports of cleavage of benzyl amines by hydrogenolysis was made by Sabatier and co-workers, during investigations of hydrogenation (Scheme 97).[195-197]



236 **237**

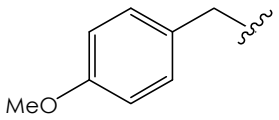
Scheme 97 – The first benzyl amine hydrogenolysis

The practical application of this behaviour was first demonstrated by Rosenmund and Zetzsche,[198] and Krauß and Wolfes.[199,200] However, the use of benzyl protection only became widespread after the benzyl carbamate (Cbz) group was used in peptide synthesis.[201]

Hydrogenolysis is the method of choice for the removal of benzyl protection; the catalyst and cleaved protective group can conveniently be removed by filtration and evaporation. Palladium has been found to be the best metal for achieving deprotection,[202] as it shows little tendency to hydrogenate the aromatic ring.

The major difficultly with hydrogenolysis as a deprotection strategy is the reduction of other functionality in the substrate, such as multiple bonds. Other deprotection strategies have therefore been sought. One common approach has been the application of transfer hydrogenation,[203-205] making use of organic hydrogen sources such as ammonium methanoate. This is often carried out over similar catalysts to hydrogenolysis, *i.e.* supported palladium metal. Although selectivity for deprotection can be improved by this method, the conditions are still reducing. Thus, alternative methods are needed for the removal of benzyl groups from reduction-sensitive molecules.

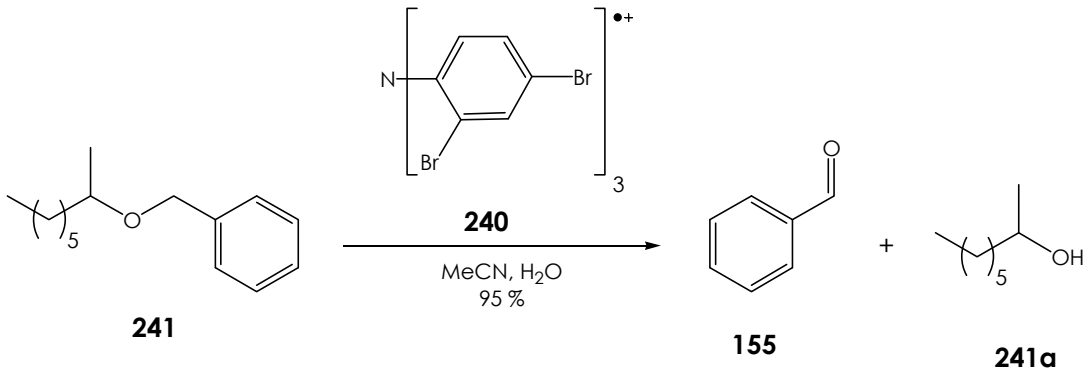
5.1.3 The MPM group: oxidative cleavage



238

Figure 16 – The MPM group

The use of oxidative cleavage for the removal of benzyl-type ethers was first introduced by Steckhan and Schmidt.[206,207] They demonstrated that electron-transfer from amine radical cation **240** brought about deprotection, with oxidation of the benzylic position (Scheme 98).

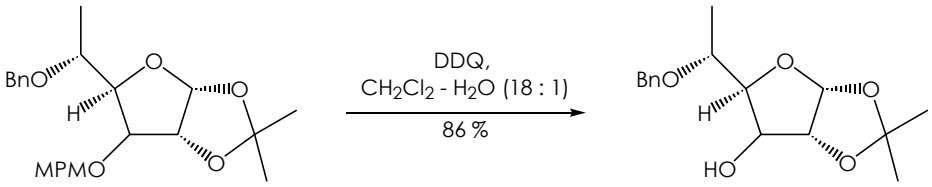


241 **155** **241a**

Scheme 98 – Oxidative cleavage using an amine cation radical

Altering the substituents on the radical cation allowed the redox potential of the system to be altered. By adding substituents to the benzyl group, the redox potential for benzylic oxidation could also be changed. This led to the introduction of the MPM (4-methoxybenzyl, *para*-methoxybenzyl or 4-methoxyphenylmethyl) group **238** as a more readily removed analogue of the benzyl group: the benzylic position of MPM is more readily oxidised than Bn.

Oxidative removal of benzyl-type groups became more accessible when commercial oxidising agents were shown to be effective in the reaction. DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) is known to be effective in the oxidation of benzylic positions.[208] Oikawa *et al.*[209,210] showed that, as they expected, this meant that DDQ was an effective reagent for the deprotection of benzyl ethers, and was very effective for the selective removal of MPM groups, such as in the conversion of **242** to **243** (Scheme 99).[209]



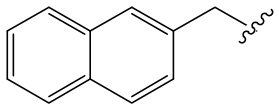
242 **243**

Scheme 99 – Selective removal of the MPM group

By the use of one or more methoxy substituents in different positions on the aromatic ring, Nakajima *et al.*[211] have developed a series of selectively cleavable protective groups.[212] However, only MPM has found widespread use in organic synthesis.[105]

Following the success of DDQ, a number of other oxidative methods have been introduced for the removal of benzyl and MPM groups; deprotection of both oxygen and nitrogen has been achieved by oxidative methods. Along with DDQ, the second common method for oxidative deprotection is the use of CAN [hexa-ammineceriumIV) nitrate(V)].[213] The choice of oxidant is often important for selectivity, although it is not always possible to predict which will be more successful.

5.1.4 The NAP group

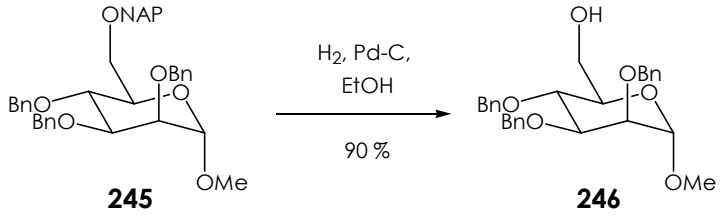


244

Figure 17 – The NAP group

Despite the great success of the benzyl and MPM groups, silicon-based protection and other strategies, the development of novel protective groups continues. Often this is due to the failure of existing methods, and efforts to circumvent the limitations found. However, new protection strategies can also be developed from other perspectives.

The NAP (2-naphthylmethyl) group **244** has been introduced by Spencer *et al.*[214-216] as a novel protective group for oxygen and nitrogen. The NAP group is removed in preference to benzyl groups by hydrogenolysis (Scheme 100); the reason for this was suggested to be the preferential interaction of the more extended aromatic system with the surface of the palladium catalyst.

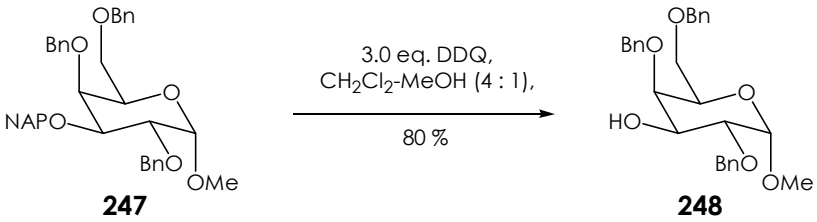


Scheme 100 – Preferential hydrogenolysis of the NAP group

5.2 Oxidative removal of the NAP group

5.2.1 Removal using DDQ

Following the introduction of the NAP group, Matta *et al.* applied the oxidative DDQ deprotection protocol to removal of the NAP group.[217] They demonstrated that the NAP group was removed by DDQ oxidation, in the presence of benzyl groups and other simple protective groups (Scheme 101).

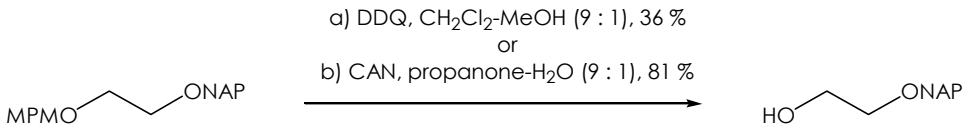


Scheme 101 – Removal of NAP by DDQ oxidation

5.2.2 Selective removal using CAN oxidation

The work of Matta *et al.* had established oxidative discrimination between the NAP and Bn groups; selectivity in the oxidative deprotection of MPM ethers in the presence of Bn ethers is well-established (section 5.1.3). However, the possibility of removal of the MPM group in the presence of the NAP group (or *vice versa*) had not been explored; it was envisaged that this could give a three-step deprotection system: firstly removing MPM, then NAP, and finally Bn.

As an initial probe for the potential of this idea, the linker molecule **245** was synthesised from ethane-1,2-diol (Scheme 102). This was then subjected to deprotection using both DDQ and CAN. DDQ was not selective in the deprotection: allowing reaction to proceed to complete consumption of the starting material led to very poor recovery of the desired product **250**. On the other hand, deprotection using CAN proceeded smoothly, with complete consumption of **245** with good yield of the product.[218] Thus, selectivity for oxidative deprotection of MPM groups in the presence of NAP was promising in a simple system.



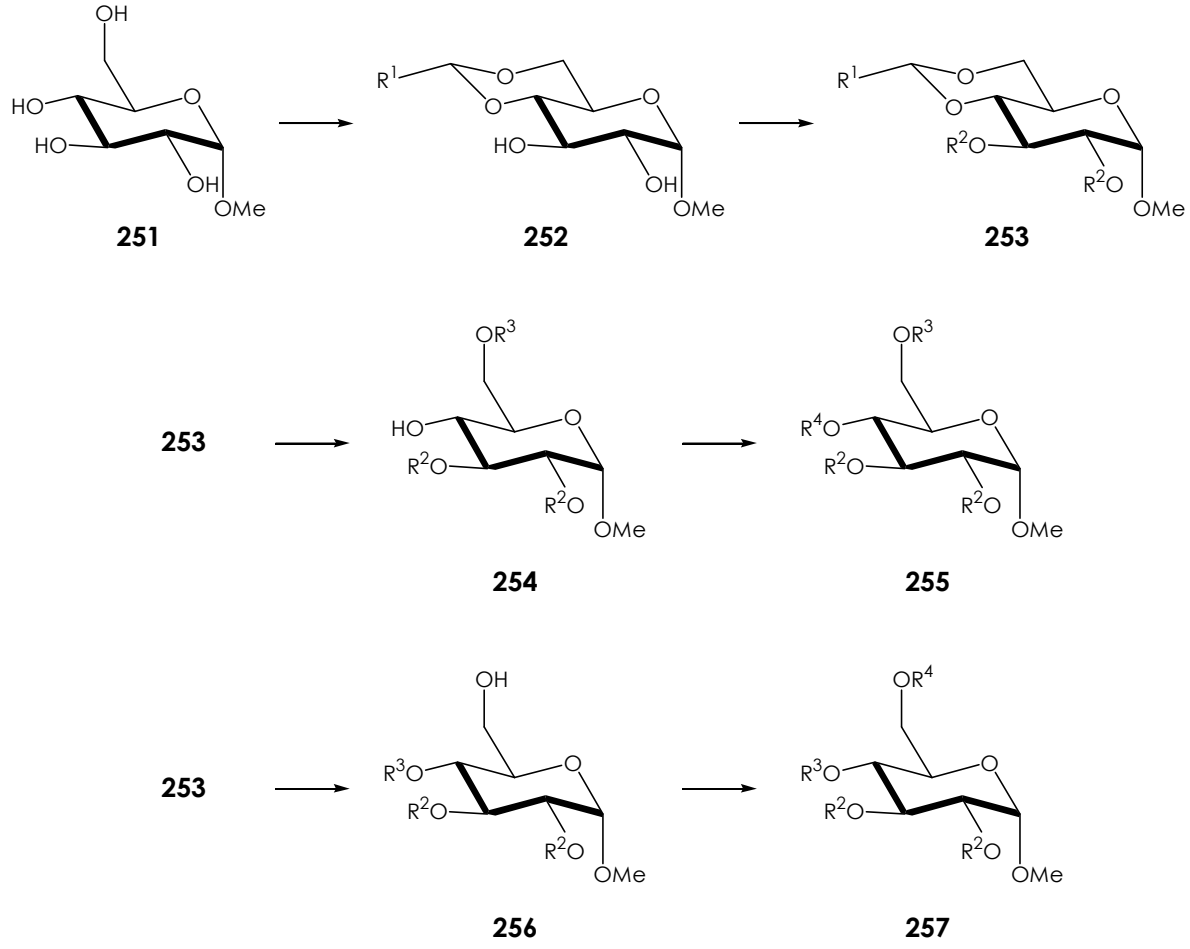
249 **250**

Scheme 102 – Selective deprotection of the linker

5.2.3 Synthesis of glucose-based substrates

5.2.3.1 Strategy

In order to demonstrate the utility of the oxidative selectivity seen with the linker, it was necessary to produce a series of substrates containing Bn, MPM and NAP groups in a variety of positions. Given the commercial availability of sugars and sugar derivatives, it was decided to investigate the use of sugar-based substrates; sugars in which the anomeric position is protected by a methyl group were chosen as the starting materials. Access to a variety of protected sugars was planned as shown below (Scheme 103).



251 **252** **253**

253 **254** **255**

253 **256** **257**

Scheme 103 – Strategy for synthesis of substrates

R^2, R^3 and R^4 represent the three benzyl-type protective groups to be introduced; the R^3 group was to be derived from the acetal methylidene position and the aromatic moiety R^1. It was anticipated that the formation of acetals of type **252**, and protection to give the intermediate **253**, would both occur readily. Selective opening of the acetal was to be carried out to give either **254** or **256**, which could be followed by a final protection step.

Three potential starting materials were considered, the anomeric-position methyl ethers of α-D -glucose (**251**), α-D -galactose (**258**) and α-D-mannose (**259**) (Figure 18). Readily accessible methods exist for the formation of monoacetals of **251** and **258**; on the other hand, **259** readily forms a diacetal[219]. The mannose-based system was therefore avoided, as the difficulty of the synthesis would have been unnecessarily increased. It was decided to carry out two studies, one on a set of substrates based on **251**, and a second based on **258.**[220]

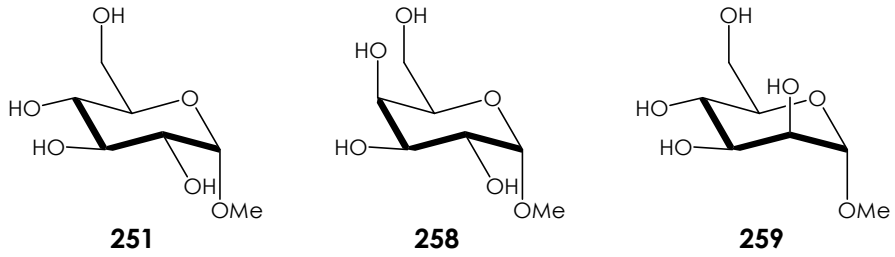
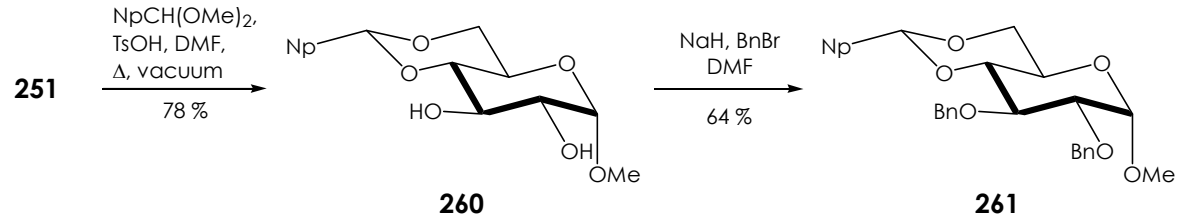


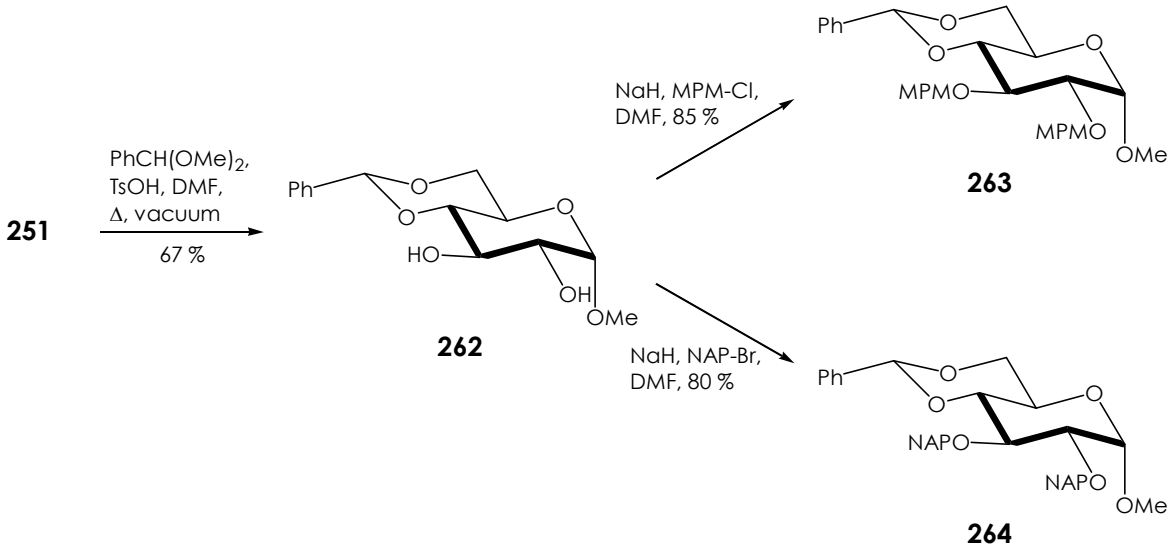
Figure 18 – Potential starting materials

5.2.3.2 Synthesis

It was clear that an exhaustive study of all possible combinations of the three protective groups Bn, NAP and MPM would be without merit: a subset of four substrates was therefore produced. The first two steps of the synthesis proceeded without incident. The acetals **262** and **260** were readily produced on a large scale, following the method of Ferro *et al.*[219]; **262** could also be purchased from commercial sources. Protection of the free hydroxyl groups could then be carried out to introduce a second protective group, again on a large scale (Scheme 104 and Scheme 105).

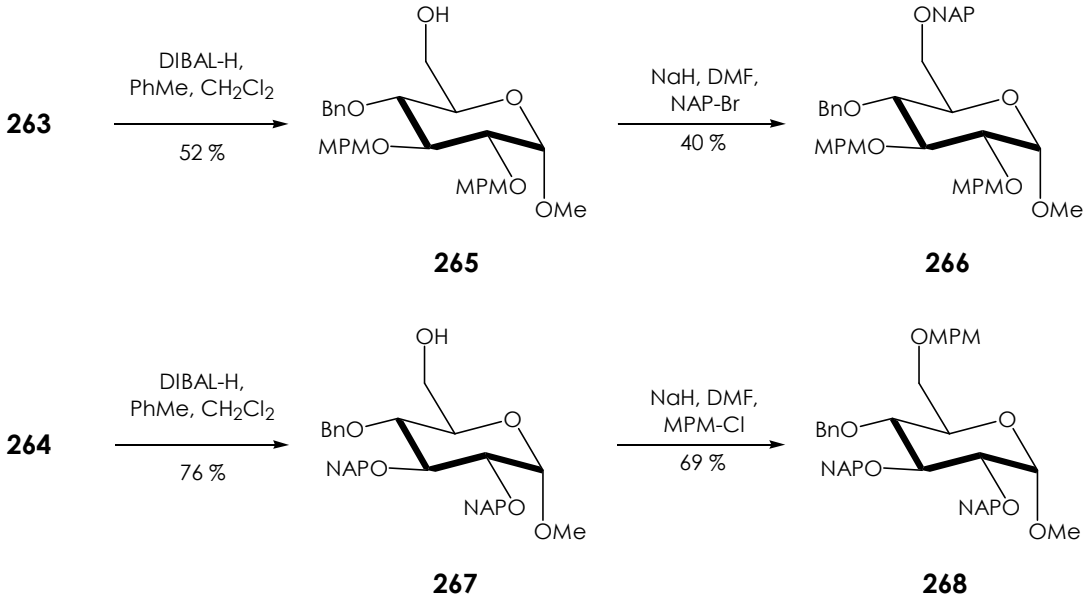


Scheme 104 – Synthesis one

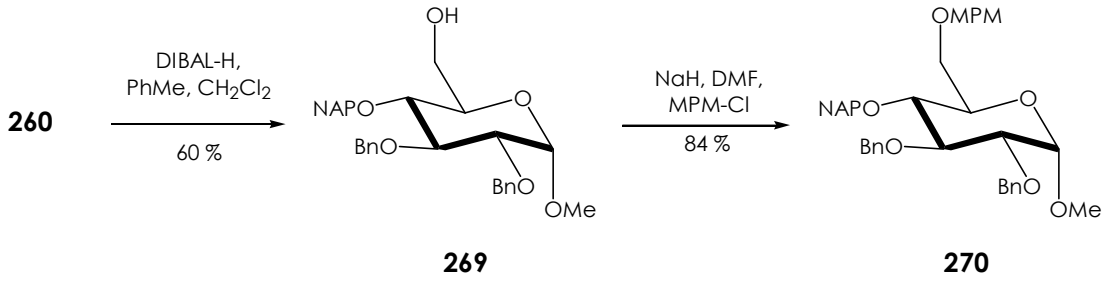


Scheme 105 – Synthesis two

A number of potential methods were available for the opening of the acetals,[221-226] although only two studies of the opening of (2-naphthyl)methylidene acetals have been carried out.[227,228] Methods for selectively opening acetals typically make use of either a Lewis or Brønsted acid to control the regioselectivity of the ring-opening. It is known that DIBAL-H opens acetals derived from glucose selectively to give a free hydroxyl at the 6-position;[225] this method was chosen for selective opening of all three glucose-based acetals (Scheme 107 and Scheme 106). It was found that **263** gave low yields in this transformation; it may be that the MPM group is not completely stable to DIBAL-H. The monoalcohols obtained from these selective openings could then be protected to give the desired substrates.



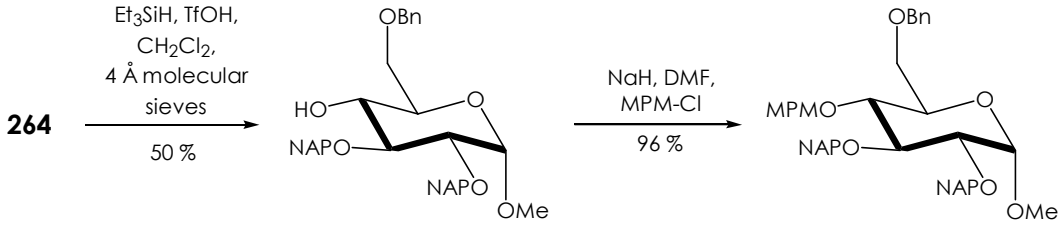
Scheme 106 – Synthesis three



269 **270**

Scheme 107 – Synthesis four

In order to open the benzylidene acetal **264** in the opposite sense, the method of Sakagami and Hamana[226] was used, with TfOH providing regioselectivity in the triethylsilane reduction. This reaction was very sensitive to moisture, proceeding in only moderate yield (Scheme 108). Final protection again gave the desired substrate.



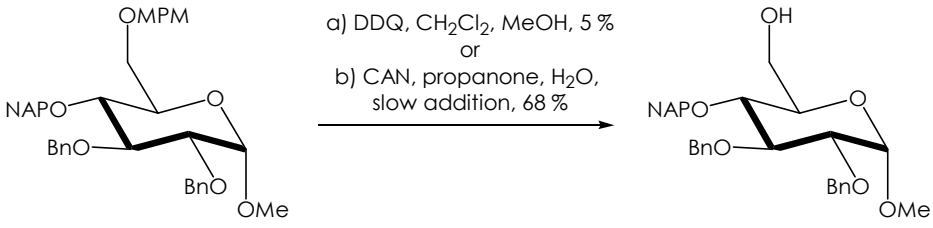
271 **272**

Scheme 108 – Synthesis five

5.2.4 Selective deprotection of challenging substrates

5.2.4.1 Glucose-based substrates

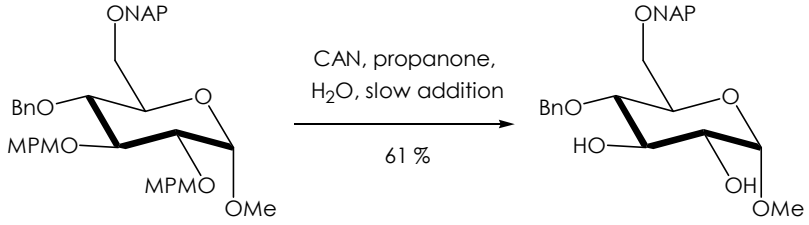
Having obtained the four substrates (each containing the three desired protective groups), it was possible to examine the oxidative cleavage of the protective groups. Initial studies were carried out with substrate **270**. To verify that the linker result also applied to more complex substrates, DDQ deprotection of the substrate was attempted. This reaction proceeded very poorly, with only 5 % recovery of the desired product. CAN oxidative was then carried out under standard literature conditions,[213] using ethananitrile as the solvent. The recovered yields were poor, and this could be attributed to poor solubility of the substrates in the solvent: extended reaction times lowered the selectivity of the deprotection. Changing the solvent to acetone raised the yield, and this could be improved further by adding half of the oxidant in solution over an hour. The reaction then proceeded in acceptable yield (Scheme 109).



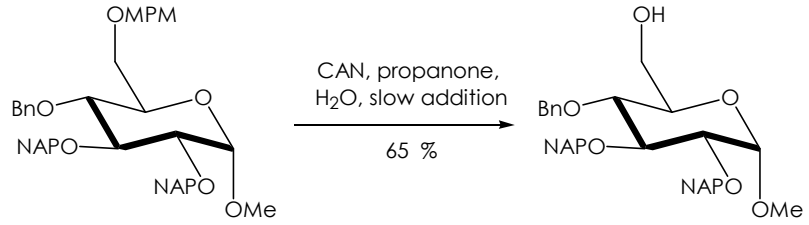
269 **270**

Scheme 109 – Selective deprotection one

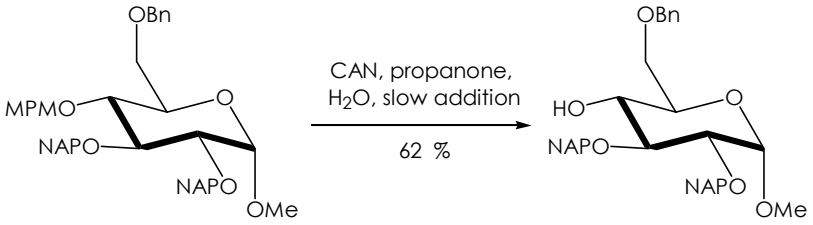
It was then possible to deprotect the other substrates under the same conditions. The yields were again reasonable.



266 **273**



268 **267**



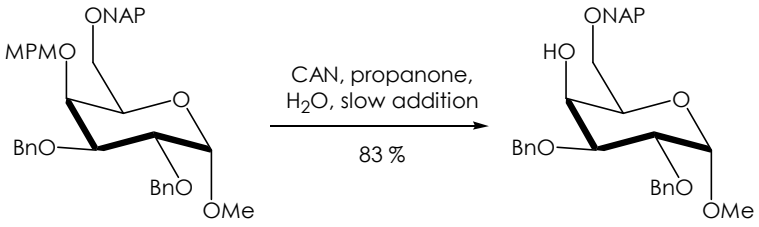
272 **271**

Scheme 110 –Selective deprotection two

5.2.4.2 Galactose-based substrates[229]

A set of four galactose-based substrates were synthesised by Dr. J.-Q. Yu,[230] and were subjected to CAN deprotection under similar conditions to the glucose-based substrates. Selective

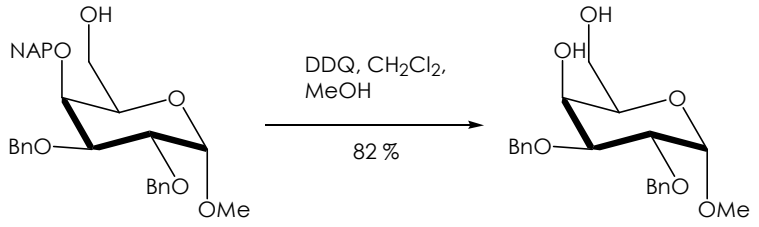
removal of the MPM groups was again achieved. Yields were higher for the galactose-based substrates, in the range 70 – 83 % (Scheme 111).



274 **275**

Scheme 111 – Deprotection of galactose-based substrate

Removal of the NAP group using DDQ oxidation was then demonstrated in the galactose series (Scheme 112).



276 **277**

Scheme 112 – Oxidative removal of NAP using DDQ

5.3 Conclusions

Benzyl groups are ubiquitous in organic synthesis, due to the ease of introduction and removal of the group. The NAP group has been introduced by Spencer *et al.*,[214-216] being removed in preference to the benzyl group by hydrogenolysis. The NAP group has been found to removable under oxidative conditions, using either DDQ or CAN. CAN deprotection will selectively remove MPM groups in the presence of NAP groups. The NAP group thus allows three benzyl-based protective groups to be used in a molecule, which can be removed in a controlled order by the correct choice of deprotection conditions. The utility of MPM *versus* NAP selectivity under oxidative conditions has been demonstrated in a series of sugar-based substrates.

"Me lamento como Leonardo da Vinci; qué cosas tan bellas haná si tuviese los medios."[231]

A. Gaudí

6 EXPERIMENTAL

6.1 General

Chemicals were obtained from Aldrich, Lancaster, Avocado, Fluorochem or Alfa Aesar, and were used as received unless otherwise noted. Dry solvents were obtained from Fluka (stored over molecular sieves) or were dried by standard methods[232] prior to use, and stored under nitrogen over 4 Å molecular sieves. Solvents were degassed by carrying out three freeze-pump degas cycles using an oil pump (vacuum 0.5 mm Hg or better). Degassed solvents were stored over 4 Å molecular sieves, in flame-dried glass ampoules sealed with J. Young taps.[233] All air- or moisture-sensitive reactions were carried out under dry nitrogen using standard Schlenk techniques. Solvents were removed by evaporation on a Büchi rotary evaporator, with vacuum provided either by a water-aspirator pump or by a controlled Teflon-membrane pump. All products were dried at oil-pump vacuum (approximately 0.5 mm Hg or better) for at least one hour before spectroscopic characterization, unless otherwise specified. Thin layer chromatography (TLC) analysis was performed using Merck 60 PF_{254} 0.2 mM plates (glass backed), and were visualized by UV or using potassium manganate(VII),[234] vanillin,[235] 2,4-dintirophenylhydrazine[236] or phosphomolybdic acid[237] dip as appropriate. Flash chromatography[238] was performed using Merck 9385 Kieselgel 60 silica gel, the silica being loaded as a slurry in the elution solvent. Petroleum ethers refers to the fraction with T_b 60 – 80 °C, unless stated otherwise.

NMR (nuclear magnetic resonance) spectra were recorded in trichloro(D)methane ($CDCl_3$) unless otherwise stated. NMR spectra were recorded at 25 °C in 5 mm tubes, at 400.1 MHz (^1H) or 100.6 MHz (^{13}C) on a Bruker Avance 400, unless otherwise stated. Chemical shifts are given in parts per million (δ) and quoted relative to the residual solvent peak (7.24 δ for ^1H and 77.0 δ for ^{13}C in $CDCl_3$); coupling constants (*J*) are given in Hertz. Proton signal multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet), br indicates a broad signal. Assignment of ^1H and ^{13}C spectra was based upon predicted chemical shifts, ^1H-^1H COSY, ^{13}C DEPT-135, ^1H-^{13}C HMQC spectra and tables[239] as needed. For the sugar-based substrates for protective-group studies (section 6.4), assignment of the signals for the pyranose ring is given numbering the pyranose ring anomeric position C^1, and continuing to give the primary oxygen as C^6. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR with ATR Universal Sampling Accessory as neat solids or liquids. Mass spectra were recorded on Kratos 890 spectrometer. G.L.C. analysis was performed on an HP 5890 series II machine,

using an HP-1 25 m column. Melting points were recorded on a Reichert hot-stage melting point apparatus and are corrected. Elemental analysis was carried out on an Exeter Analytical 440.

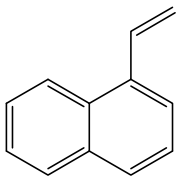
6.2 The Wacker reaction of styrenes (styrenes)

6.2.1 Reference Wacker reaction: styrene, 1 eq. copper(I) chloride, 10 % palladium(II) chloride, room temperature

Palladium(II) chloride (18.5 mg, 0.104 mmol) and copper(I) chloride (101.5 mg, 1.03 mmol) were suspended in a mixture of distilled DMF (4.0 cm^3) and water (0.4 cm^3). The system was stirred under an oxygen atmosphere for one hour, before the addition of styrene (0.115 cm^3, 104 mg, 1.00 mmol). The reaction was stirred for 18 hours, before being poured onto a short silica pad. The products were eluted using ethoxyethane (50 cm^3), and the crude mixture analysed by G.L.C. The ratio of ketone – aldehyde was 8.4 : 1.0.

6.2.2 Preparation of non-commercial alkenes

6.2.2.1 1-Ethenylnaphthalene ***159***

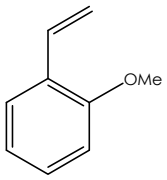


159

The method of Schmidt *et al.*[240] was used. Potassium 1,1-dimethylethoxide (10.78 g, 96.1 mmol) and methyltriphenylphosphonium bromide (34.32 g, 96.1 mmol) were suspended in dry THF (200 cm^3), giving a bright yellow solution containing a suspended solid. A solution of naphthalene-1-carbaldehyde (8.70 cm^3, 10.01 g, 64.1 mmol) dissolved in dry THF (50 cm^3) was added dropwise to the ylide solution, after which the reaction mixture was stirred for one hour. The reaction was then diluted with water (100 cm^3), and extracted with ethoxyethane (150 cm^3, 3 × 50 cm^3). The combined organic extracts were washed with water (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). It was then dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure, giving an oily solid. The solid was extracted with petroleum ethers T_b 40 – 60 ºC (5 × 50 cm^3), the combined extracts evaporated, and the product distilled at reduced pressure. The product was obtained as a colourless oil (7.363 g, 75 %). T_b 75 – 77 ºC / 0.5 mm Hg (Lit.[240] 75 – 76 ºC / 0.1 mbar). ν_{max}/cm^{-1} (film) 3047 (w), 1508 (w), 1418 (w), 1340 (w), 985 (m), 912 (m), 799 (s), 773 (s), 689 (m). Found C 93.49, H 6.51%; $C_{12}H_{10}$ requires C 93.46, H 6.54 %. δ_H ($CDCl_3$, 400.1 MHz) 5.53 (dd, 1H, J = 1.8, 11.2 Hz; terminal CH *trans* to aromatic group), 5.85 (dd, 1H, J = 1.8, 17.2 Hz; terminal CH *cis* to aromatic group), 7.49 – 7.58 (m, 4H), 7.68 (~ d, 1H, J = 7.6 Hz), 7.83 (d, 1H,

J = 8.4 Hz), 7.90 (dd, 1H, J = 1.6, 7.2 Hz), 8.17 (~d, 1H, J = 7.6 Hz). δ_C ($CDCl_3$, 100.6 MHz) 117.0 (CH_2), 123.6 (aromatic CH), 123.7 (aromatic CH), 125.6 (aromatic CH), 125.7 (aromatic CH), 126.2 (aromatic CH), 128.1 (aromatic CH), 128.5 (aromatic CH), 131.5 (aromatic C), 133.6 (aromatic C), 134.3 (alkene CH), 135.6 (aromatic C). m/z (EI) 154.1 (M^+), 126.1; calc[d] for $C_{12}H_{10}$ 154.0783, found 154.0788.

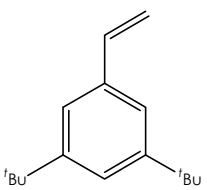
6.2.2.2 2-Ethenyl-1-methoxybenzene ***160***



160

The method of Suschitzky[241] was used. Methyltriphenylphosphonium bromide (8.938 g, 25.0 mmol) was suspended in dry ethoxyethane (100 cm^3) under nitrogen. A solution of butyl lithium in hexane (15 % w/w, 16.5 cm^3, 25.5 mmol) was added dropwise, and the solution stirred for 2¼ hours. A solution of 2-methoxybenzaldehyde (4.692 g, 34.4 mmol) in dry ethoxyethane (40 cm^3) was added dropwise to the reaction, giving a thick solution. This was heated to reflux and stirred overnight, giving a colourless solution and a precipitate. The solution was cooled and filtered, and the solvent removed at reduced pressure. The residue was distilled at reduced pressure to give the product as a colourless oil (1.352 g, 40 %). T_b 38 – 39 °C / 0.05 mm Hg (Lit.[241] 38 – 40 ºC / 0.05 Torr). R_f 0.523 (hexane-ethoxyethane 20:1). ν_{max}/cm^{-1} (film) 3073 (m), 3002 (s), 2957 (s), 2835 (s), 1625 (s), 1598 (s), 1487 (s), 1463 (s), 1437 (s), 1415 (s), 1314 (s), 1291 (s), 1174 (s), 1110 (s), 1036 (s), 997 (s), 909 (s). Found C 80.53, H 7.45 %; $C_9H_{10}O$ requires C 80.56; H 7.51 %. δ_H ($CDCl_3$, 400.1 MHz) 3.87 (s, 3H, MeO), 5.30 (dd, 1H, J = 1.6, 11.2 Hz; alkene CH_2 proton *trans* to ring), 5.78 (dd, 1H, J = 1.6, 17.6 Hz; alkene CH_2 proton *cis* to ring), 6.90 (d, 1H, J = 8.4 Hz, Ph), 6.97 (t, 1H, J = 7.4 Hz, Ph), 7.10 (dd, 1H, J = 11.2, 17.6 Hz; alkene CH), 7.27 (dt, 1H, J = 2.4, 7.8 Hz; Ph), 7.51 (dd, 1H, J = 2.0, 8.4 Hz; Ph). δ_C ($CDCl_3$, 100.6 MHz) 55.4 (MeO), 110.8 (Ph), 114.3 (CH_2), 120.5 (Ph), 126.5 (Ph), 126.7 (Ph quaternary), 128.8 (Ph), 131.6 (alkene CH), 156.7 (Ph quaternary). m/z 68.9, 91.0, 134.1 (M^+), 119.1; calc[d] for $C_9H_{10}O$ (M^+) 134.0732, found 134.0734.

6.2.2.3 1,3-Di-(1,1-dimethylethyl)-5-styrene ***162***

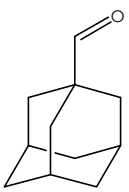


162

The method of Schlosser[165] was used. Potassium 1,1-dimethylethoxide (491 mg, 4.38 mmol) was dissolved in a solution of butyl lithium in hexane (1.6 mol dm^{-3}, 2.8 cm^3, 4.48 mmol). 1,3-Di-(1,1-dimethylethyl)benzene **161** (0.96 cm^3, 825 mg, 4.34 mmol) was added, and the dark-brown solution stirred overnight. The reaction mixture was cooled to 0 °C, and a solution of

DMF (0.34 cm^3, 322 mg, 4.40 mmol) in dry THF (5 cm^3) was added. The reaction was stirred for ten minutes before the addition of methyltriphenylphosphonium bromide (1.568 g, 4.39 mmol). The orange solution was stirred at room temperature for seven hours, before being diluted with water (20 cm^3) and extracted with hexane (3 × 10 cm^3). The organic solution was washed with saturated aqueous sodium chloride solution (20 cm^3), dried over magnesium sulphate(VI) and filtered through a silica pad. The solvent was removed at reduced pressure to give a mixture of the product and 1,3-di-(1,1-dimethylethyl)benzene, which could not be separated by distillation. δ_H ($CDCl_3$, 400.1 MHz) 1.35 (s, 18H, ^{t}Bu × 2), 5.23 (dd, 1H, J = 0.4, 10.8 Hz; alkene CH_2 proton *trans* to ring), 5.75 (dd, 1H, J = 0.4, 17.6 Hz; alkene CH_2 proton *cis* to ring), 6.76 (dd, 1H, J = 11.2, 17.6 Hz; alkene CH), 7.28 (d, 2H, J = 1.2 Hz, Ph), 7.36 (t, 1H, J = 1.2 Hz).

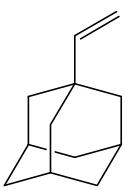
6.2.2.4 Adamantane-1-carbaldehyde ***175***



175

The general procedure of Corey[153] was used, with reference to the methods of Okamoto,[242] Ramsden[243] and Olah[244]. Pyridinium chlorochromate(VI) (PCC) (6.472 g, 20.0 mmol) was suspended in dry dichloromethane (40 cm^3) under nitrogen. Adamantan-1-ylmethanol (3.320 g, 20.0 mmol) dissolved in dry dichloromethane (40 cm^3) was added. The reaction was stirred for seventy minutes, after which time it was diluted with dry ether (~ 400 cm^3) and vigorously stirred. The solution was filtered through a Florisil® pad, the residue being flushed with copious ethoxyethane. The solvent was removed at reduced pressure. The product was obtained as a white, odorous solid (2.933 g, 89 %). Attempts to recrystallise the product failed due to its high solubility in most solvents. R_f 0.402 (hexane-ethoxyethane 4:1). ν_{max}/cm^{-1} (solid) 2901 (s), 2848 (m), 1722 (s, C=O), 1451 (m), 1075 (w), 987 (w). δ_H ($CDCl_3$, 400.1 MHz) 1.70 (d, 6H, J = 2.4 Hz, aliphatic CH_2), 1.66 – 1.77 (m, 6 H), 2.05 (br s, 3H), 9.30 (s, 1H, CHO). δ_C ($CDCl_3$, 100.6 MHz) 27.3 (sp^3), 35.8 (sp^3), 36.4 (sp^3 quaternary), 36.5 (sp^3), 206.0 (CHO). m/z (ESI) calc[d] for $C_{11}H_{16}O$ 187.1099, found 187.1101.

6.2.2.5 1-Ethenyladamantane ***176***

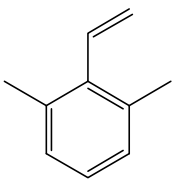


176

Methyltriphenylphosphonium iodide (2.37 g, 5.86 mmol) was dissolved in dry THF (20 cm^3) under nitrogen. The solution was cooled to 0 °C, before dropwise addition of a solution of lithium bis(trimethylsilyl)amide in THF (1.0 mol dm^{-3}, 6.4 cm^3, 6.4 mmol). The reaction was stirred at room temperature for 1 hour, after which

time the solution was clear and yellow. The reaction was cooled to -78 °C, and a solution of **175** (795 mg, 5.30 mmol) in dry THF (8 cm^3) was added dropwise. The reaction was allowed to stir overnight, and was then diluted with ethoxyethane (50 cm^3) and hydrochloric acid (1 mol dm^{-3}, 100 cm^3). The layers were separated, and the aqueous extracted with ethoxyethane (2 × 50 cm^3). The combined organic was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). The solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. Chromatography on silica gel (hexane-ethoxyethane 99:1) gave the product as a clear oil (507 mg, 65 %). R_f 0.800 (hexane-ethoxyethane 50:1). Found C 88.97, H 11.33 %; $C_{12}H_{18}$ requires C 88.82, H 11.18 %. δ_H ($CDCl_3$, 400.1 MHz) 1.57 (d, 6H, J = 2.4 Hz, aliphatic CH_2), 1.63 – 1.75 (m, 6H, aliphatic CH_2), 1.97 (br s, 3H, sp^3 CH), 4.82 (dd, 1H, J = 1.6 Hz, 10.4 Hz; alkene CH_2 proton *trans* to adamantyl), 4.84 (dd, 1H, J = 2.0 Hz, 16.8 Hz; alkene CH_2 proton *cis* to adamantyl), 5.69 (dd, 1H, J = 10.4 Hz, 16.8 Hz; alkene CH). δ_C ($CDCl_3$, 100.6 MHz) 28.5 (sp^3), 36.9 (sp^3), 37.8 (sp^3 quaternary), 41.9 (sp^3), 108.9 (alkene), 150.1 (alkene). m/z (EI) 68.9, 131.0, 162.1 (M^+); calc[d] for $C_{12}H_{18}$ 162.1409, found 162.1416.

6.2.2.6 *1-Ethenyl-2,6-dimethylbenzene* ***186***



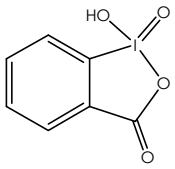
186

The method of Suschitzky[241] was used with modifications. Methyltriphenyl-phosphonium bromide (8.929 g, 25.0 mmol) was suspended in dry ethoxyethane (100 cm^3) under nitrogen. Butyl lithium in hexane (15 % w/w, 16.5 cm^3, 25.5 mmol) was added dropwise, resulting in a strongly yellow-coloured solution. The reaction was stirred for 1½ hours, after which time the entire solid had dissolved. A solution of 2,6-dimethylbenzaldehdye (3.703 g, 27.6 mmol) in dry ethoxyethane (40 cm^3) was added dropwise to the ylide solution, resulting in rapid formation of a precipitate. The solution was then heated to reflux overnight. The cooled reaction solution was filtered, before being washed with hydrochloric acid (1 mol dm^{-3}, 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (50 cm^3) and saturated aqueous sodium chloride solution (50 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The residue was distilled *in vacuo* to give the product as a colourless oil (1.332 g, 40 %). T_b 60 – 61 °C / 5 mbar (Lit.[245] 65 – 66 °C / 10 mm Hg). R_f 0.720 (hexane-ethoxyethane 4:1). ν_{max}/cm^{-1} (film) 3064 (m), 2952 (s), 2861 (m), 1924 (w), 1850 (w), 1632 (s), 1578 (w), 1466 (s), 1443 (m), 1377 (m), 1163 (w), 1097 (w), 993 (s), 922 (s), 767 (s).

Found C 90.98, H 8.89 %; $C_{10}H_{12}$ requires C 90.85, H 9.15 %. δ_H ($CDCl_3$, 400.1 MHz) 2.37 (s, 6H, Me), 5.32 (dd, 1H, J = 2.0, 18.0 Hz; alkene CH_2 *cis* to ring), 5.59 (dd, 1H, J = 2.0, 11.6 Hz; alkene CH_2 *trans* to ring), 6.75 (dd, 1H, J = 11.6, 18.0 Hz; alkene CH), 7.07 – 7.11 (m, 3H, aromatic H). δ_C ($CDCl_3$, 100.1 MHz) 20.8 (Me), 119.3 (CH_2), 126.7 (aromatic CH), 127.7 (aromatic CH), 135.1 (aromatic C), 135.7 (aromatic C), 137.7 (alkene CH). m/z (EI) 68.9, 117.1, 132.1 (M^+); calc[d] for $C_{10}H_{12}$ 132.0939, found 132.0933.

6.2.3 Preparation of aldehyde standards

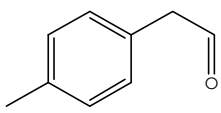
6.2.3.1 1-Hydroxy-1-oxo-1H-1λ5-benzo[d][1,2]iodoxol-3-one (IBX) **152**



152

The method of Santagostino[158] was used. 2-Iodobenzoic acid (92.21 g, 0.150 mol) and potassium monopersulphate triple salt (Oxone®, 24.80 g, 0.100 mol) were heated in water (500 cm^3) to 75 °C for 2¾ hours, with vigorous stirring. Initially, a thick precipitate formed, making stirring difficult. After time, this was converted to a fine suspension. The system was cooled to 0 °C, and stirred slowly for 1¾ hours, before being filtered. The product was washed with copious water, followed by acetone. The product was obtained as a white solid (25.80 g, 92 %). Found C 30.02, H 1.88 %; $C_7H_5IO_4$ requires C 30.03, H 1.80 %. δ_H (DMSO-d_6, 400.1 MHz) 7.84 (dt, 1H, J = 1.2, 7.6 Hz; Ph), 7.97 – 8.04 (m, 2H, Ph), 8.14 (d, 1H, J = 7.2 Hz, Ph). δ_C (DMSO-d_6, 100.6 MHz) 125.0 (aromatic CH), 130.1 (aromatic CH), 131.4 (aromatic C), 132.9 (aromatic CH), 133.4 (aromatic CH), 146.5 (aromatic C), 167.4 (*C*=O).

6.2.3.2 (4-Methylphenyl)ethanal **157**

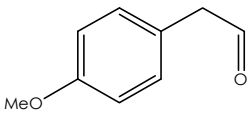


157

The procedure of Santagostino *et al.*[156,157] was used. IBX **152** (15.83 g, 56.5 mmol) was dissolved in DMSO (130 cm^3) and the solution freeze-pump degassed three times. 2-(4-Methylphenyl)ethanol (6.975 g, 51.2 mmol) was dissolved in DMSO (10 cm^3), and the solution freeze-pump degassed three times. The solution of the alcohol was added to the oxidising agent, and the reaction stirred for two hours. It was then diluted with water (200 cm^3), filtered and extracted with ethoxyethane (4 × 50 cm^3). The organic solution was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). It was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was then distilled at reduced pressure, giving a colourless oil (4.128 g, 60 %)[248]. T_b 61 – 62 °C / 6 mm Hg (Lit.[249] 88 – 90 °C /

5 mm Hg). R_f 0.523 (hexane – ethoxyethane 4:1). ν_{max}/cm^{-1} (film) 3427 (w), 3023 (s), 2922 (s), 2821 (s), 2724 (s), 1903 (w), 1729 (s, C=O), 1514 (s), 1452 (m), 1416 (m), 1386 (m), 1311 (w), 1175 (m), 1112 (m), 1041 (s), 932 (m), 809 (s). Found C 79.57, H 7.53 %; $C_9H_{10}O$ requires C 80.56, H 7.51 %. δ_H ($CDCl_3$, 400.1 MHz) 2.46 (s, 3H, Me), 3.75 (d, 2H, *J* = 2.5 Hz, C*H*$_2$CHO), 7.22 (d, 2H, *J* = 8.0 Hz, aromatic H), 7.30 (d, 2H, *J* = 8.0 Hz, aromatic H), 9.83 (t, 1H, *J* = 2.5 Hz, CHO). δ_C ($CDCl_3$, 100.6 MHz) 20.9 (Me), 50.0 (*C*H$_2$CHO), 128.6 (aromatic C), 129.4 (aromatic CH), 129.4 (aromatic CH), 136.9 (aromatic C), 199.4 (*C*HO). m/z (ESI) 158.1 (M^+ + Na); calc[d] for $C_9H_{10}ONa$ 157.0629, found 157.0634.

6.2.3.3 (4-Methoxyphenyl)ethanal ***150***



150

The procedure given in section 6.2.3.2 was followed. Thus, IBX **152** (17.87 g, 63.8 mmol) in DMSO (170 cm^3) and 2-(4-methoxyphenyl)ethanol (8.796 g, 57.8 mmol) in DMSO (20 cm^3) were degassed, before being mixed and stirred for two hours. Aqueous work-up as in section 6.2.3.2, followed by distillation at reduced pressure gave the product as a colourless oil (3.658 g, 42 %)[246]. T_b 76 – 80 ºC / 8 mbar (Lit.[247] 87 ºC / 1 mm Hg). R_f 0.174 (hexane – ethoxyethane 4:1). ν_{max}/cm^{-1} (film) 3426 (w), 2956 (s), 2835 (s), 2725 (s), 2057 (w), 1887 (m), 1715 (s), 1614 (s), 1584 (s), 1514 (s), 1455 (s), 1386 (m), 1300 (s), 1246 (s), 1178 (s), 1111 (s), 1032 (s), 933 (m), 826 (s). Found C 71.68, H 6.73 %; $C_9H_{10}O_2$ requires C 71.98, H 6.71 %. δ_H ($CDCl_3$, 400.1 MHz) 3.61 (d, 2H, *J* = 2.4 Hz, C*H*$_2$CHO), 3.79 (s, 3H, Me), 6.89 (d, 2H, *J* = 8.4 Hz, aromatic H), 7.12 (d, 2H, *J* = 8.4 Hz, aromatic H), 9.71 (t, 1H, *J* = 2.4 Hz, CHO). δ_C ($CDCl_3$, 100.6 MHz) 49.6 (*C*H$_2$CHO), 55.2 (Me), 114.4 (aromatic CH), 120.7 (aromatic C), 130.6 (aromatic CH), 158.9 (aromatic C), 199.6 (*C*HO). m/z (ESI) 158.1, 173.1 (M^+ + Na); calc[d] for $C_9H_{10}O_2Na$ 173.0578, found 173.0586.

6.2.4 The anti-Markovnikov Wacker reaction of a series of substituted styrenes

6.2.4.1 General procedure for the reactions

The following general procedure was adopted for the Wacker reaction of a range of styrenes. The appropriate amount of the substrate was dissolved in a mixture of degassed DMF and degassed water (10 : 1 volume ratio, amounts as given in the following sections). Palladium(II) chloride (2.0 eq.) was added, and the reaction mixture stirred for the time specified at room temperature. The reaction solution was then poured onto a short pad of silica (approximately 10

g), and eluted with ethoxyethane. An appropriate standard was added to the solution, and the ratio of products analysed by G.L.C.

6.2.4.2 *Styrene **19***

The general procedure given in section 6.2.4.1 was followed; styrene **19** (36.5 mg, 0.350 mmol) and palladium(II) chloride (132 mg, 0.746 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (4.6 mg, 0.034 3 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.138 mmol, aldehyde 0.151 mmol, ketone 0.014 mmol.

6.2.4.3 *4-Ethenyl-1-methoxybenzene **148***

The general procedure given in section 6.2.4.1 was followed; 4-ethenyl-1-methoxybenzene **148** (39.6 mg, 0.295 mmol) and palladium(II) chloride (106 mg, 0.599 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (10.3 mg, 0.076 8 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.140 mmol, aldehyde 0.098 mmol, ketone 0.010 mmol.

6.2.4.4 *4-Ethenyl-1-methylbenzene **156***

The general procedure given in section 6.2.4.1 was followed; 4-ethenyl-1-methylbenzene **156** (28.8 mg, 0.244 mmol) and palladium(II) chloride (87.3 mg, 0.492 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of 4-methoxy-1-styrene **148** (19.7 mg, 0.147 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.118 mmol, aldehyde 0.078 mmol, ketone 0.011 mmol.

6.2.4.5 *2-Ethenyl-1-methoxybenzene **160***

The general procedure given in section 6.2.4.1 was followed; 2-ethenyl-1-methoxybenzene **160** (41.9 mg, 0.312 mmol) and palladium(II) chloride (99.2 mg, 0.559 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over an five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanone **158** (18.7 mg, 0.139 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.164 mmol, aldehyde 0.140 mmol, ketone 0.008 mmol.

6.2.4.6 *1,3-Di-(1,1-dimethylethyl)-5-styrene* ***162***

The general procedure given in section 6.2.4.1 was followed; 1,3-Di-(1,1-dimethylethyl)-5-styrene **162** (30.7 mg, 0.232 mmol) and palladium(II) chloride (82.5 mg, 0.465 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over an five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3), G.L.C. analysis of the solution gave an aldehyde : ketone ratio of 1.2 : 1.0.

6.2.4.7 *1-Chloro-4-styrene* ***163***

The general procedure given in section 6.2.4.1 was followed; 1-chloro-4-styrene **163** (76.2 mg, 0.550 mmol) and palladium(II) chloride (183 mg, 1.03 mmol) were reacted in DMF (2.2 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (19.7 mg, 0.147 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.298 mmol, aldehyde 0.192 mmol.

6.2.4.8 *4-Ethenyl-1-trifluoromethylbenzene* ***164***

The general procedure given in section 6.2.4.1 was followed; 4-ethenyl-1-trifluoromethylbenzene **164** (90.4 mg, 0.525 mmol) and palladium(II) chloride (184 mg, 1.04 mmol) were reacted in DMF (2.2 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (13.6 mg, 0.101 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.235 mmol, aldehyde 0.199 mmol.

6.2.4.9 *1-(1,1-Dimethylethyl)-4-styrene* ***165***

The general procedure given in section 6.2.4.1 was followed; 1-(1,1-dimethylethyl)-4-styrene **165** (80.0 mg, 0.499 mmol) and palladium(II) chloride (177 mg, 0.999 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of 4-ethenyl-1-methoxybenzene **148** (67.1 mg, 0.500 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.278 mmol, aldehyde 0.181 mmol, ketone 0.029 mmol.

6.2.4.10 *3-Ethenyl-1-methylbenzene* ***166***

The general procedure given in section 6.2.4.1 was followed; 3-ethenyl-1-methylbenzene **166** (56.3 mg, 0.476 mmol) and palladium(II) chloride (170 mg, 0.958 mmol) were reacted in DMF

(2.0 cm^3) and water (0.2 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of styrene **19** (35.5 mg, 0.341 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.199 mmol, aldehyde 0.140 mmol, ketone 0.028 mmol.

*6.2.4.11 1-Chloro-3-styrene **167***

The general procedure given in section 6.2.4.1 was followed; 1-chloro-3-styrene **167** (74.8 mg, 0.539 mmol) and palladium(II) chloride (179 mg, 1.01 mmol) were reacted in DMF (2.2 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (12.9 mg, 0.096 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.259 mmol, aldehyde 0.226 mmol.

*6.2.4.12 3-Ethenyl-1-nitrobenzene **168***

The general procedure given in section 6.2.4.1 was followed; 3-ethenyl-1-nitrobenzene **168** (78.2 mg, 0.524 mmol) and palladium(II) chloride (183 mg, 1.03 mmol) were reacted in DMF (2.2 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (23.9 mg, 0.178 mol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.227 mmol, aldehyde 0.161 mmol, ketone 0.010 mmol.

*6.2.4.13 2-Ethenyl-1-methylbenzene **169***

The general procedure given in section 6.2.4.1 was followed; 2-ethenyl-1-methylbenzene **169** (58.5 mg, 0.495 mmol) and palladium(II) chloride (176 mg, 0.990 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of 4-ethenyl-1-methoxybenzene **148** (50.4 mg, 0.376 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.257 mmol, aldehyde 0.211 mmol.

*6.2.4.14 2-Ethenyl-1-fluorobenzene **170***

The general procedure given in section 6.2.4.1 was followed; 2-ethenyl-1-fluorobenzene **170** (60.2 mg, 0.493 mmol) and palladium(II) chloride (176 mg, 0.995 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over an five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of 4-ethenyl-1-methoxybenzene **148** (35.8 mg,

0.267 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.206 mmol, aldehyde 0.223 mmol.

6.2.4.15 *1-Bromo-2-styrene* ***171***

The general procedure given in section 6.2.4.1 was followed; 1-bromo-2-styrene **171** (43.4 mg, 0.237 mmol) and palladium(II) chloride (86.2 mg, 0.486 mmol) were reacted in DMF (1.0 cm^3) and water (0.1 cm^3) over an five hour period. After elution of the reaction mixture with ethoxyethane (30 cm^3) and the addition of 4-ethenyl-1-methoxybenzene **148** (26.6 mg, 0.225 mmol) as a standard, G.L.C. analysis of the solution showed only the aldehyde product.

6.2.4.16 *1-Ethenyl-2,4-dimethylbenzene* ***172***

The general procedure given in section 6.2.4.1 was followed; 1-ethenyl-2,4-dimethylbenzene **172** (65.5 mg, 0.495 mmol) and palladium(II) chloride (177 mg, 0.996 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of 4-ethenyl-1-methoxybenzene **148** (71.6 mg, 0.534 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.228 mmol, aldehyde 0.219 mmol.

6.2.4.17 *1-Ethenylnaphthalene* ***159***

The general procedure given in section 6.2.4.1 was followed; 1-ethenylnaphthalene **159** (82.3 mg, 0.534 mmol) and palladium(II) chloride (181 mg, 1.02 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxy-ethane (50 cm^3) and the addition of 2-ethenylnaphthalene **173** (20.9 mg, 0.136 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.164 mmol, aldehyde 0.221 mmol.

6.2.4.18 *2-Ethenylnaphthalene* ***173***

The general procedure given in section 6.2.4.1 was followed; 2-ethenylnaphthalene **173** (77.4 mg, 0.502 mmol) and palladium(II) chloride (188 mg, 1.06 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over an eighteen hour period. After elution of the reaction mixture with ethoxy-ethane (30 cm^3) and the addition of (4-methylphenyl)ethanal **157** (23.7 mg, 0.177 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.097 mmol, aldehyde 0.153 mmol, ketone 0.011 mmol.

6.2.4.19 1-Ethenyl-2,6-dimethylbenzene **186**

The general procedure given in section 6.2.4.1 was followed; 2-ethenyl-1,3-dimethylbenzene **186** (68.3 mg, 0.517 mmol) and palladium(II) chloride (183 mg, 1.03 mmol) were reacted in DMF (2.0 cm^3) and water (0.2 cm^3) over a five hour period. After elution of the reaction mixture with ethoxyethane (50 cm^3) and the addition of 4-methoxy-1-styrene **148** (48.4 mg, 0.361 mmol) as a standard, G.L.C. analysis of the solution gave the following values: alkene 0.348 mmol, aldehyde 0.101 mmol, ketone 0.063 mmol.

6.2.5 Effect of temperature

The general procedure given in section 6.2.4.1 was used. Thus, a mixture of styrene, degassed DMF (2.0 cm^3) and degassed water (0.2 cm^3) was heated to the appropriate temperature prior to addition of palladium(II) chloride. The reactions were stirred for 5 hours following the addition of the metal salt, then poured directly onto a silica pad, eluted with ethoxyethane (50 cm^3), and analysed by G.L.C. *versus* 4-methoxy-styrene. The numerical data are given in Table 9 and Table 10.

Temp.	Substrate		$PdCl_2$		Mass	Standard	
(°C)	Mass (mg)	Moles (mmol)	Mass (mg)	Moles (mmol)	silica (g)	Mass (mg)	Moles (mmol)
30	51.5	0.494	175.2	0.988	9.95	48.6	0.362
35	52.9	0.508	180.2	1.016	9.98	38.0	0.283
40	52.2	0.501	177.4	1.000	9.84	41.4	0.309
45	51.7	0.496	176.1	0.993	9.94	46.6	0.347
50	51.3	0.493	174.7	0.985	9.86	49.7	0.370

Table 9 - Masses and moles for temperature experiments

Temp. (°C)	GC results (mmol)			Ratio aldehyde : ketone
	Alkene	Aldehyde	Ketone	
30	0.169	0.165	0.027	6.1 : 1.0
35	0.156	0.169	0.028	6.0 : 1.0
40	0.163	0.163	0.027	6.0 : 1.0
45	0.151	0.151	0.030	5.0 : 1.0
50	0.100	0.136	0.033	4.1 : 1.0

Table 10 - Results for temperature experiments

6.2.6 Catalyst counter-ions

6.2.6.1 Palladium(II) acetate

Palladium(II) acetate (229 mg, 1.02 mmol) was suspended in dry DMF (0.75 cm^3) and water (0.25 cm^3). 4-Ethenyl-1-methoxybenzene **148** (66.8 mg, 0.498 mmol) was dissolved in DMF (0.35 cm^3) and added to the suspension, which was then stirred under argon. After 90 hours, the

reaction mixture was added to a silica column and eluted using 4:1 hexane-ethyl acetate. (4-Methoxyphenyl)ethanone was obtained as an white solid (53.6 mg, 72 %), identical by NMR to commercial material. δ_H ($CDCl_3$, 400.1 MHz) 2.53 (s, 3H, H_3CCO), 3.85 (s, 3H, MeO), 6.91 (d, 2H, J = 9.2 Hz, Ph), 7.92 (d, 2H, J = 9.2 Hz, Ph).

6.2.6.2 Palladium(II) bromide

The method given in section 6.2.4.1 was followed; palladium(II) bromide (128 mg, 0.481 mmol) and styrene **19** (24.5 mg, 0.235 mmol) were reacted overnight in degassed DMF (1.0 cm^3) and water (0.1 cm^3). After elution from a silica pad with ethoxyethane (30 cm^3) and addition of 4-ethenyl-1-methoxybenzene **148** (21.0 mg, 0.156 mmol), G.L.C. analysis gave the following results: alkene 0.079 mmol, aldehyde 0.062 mmol, ketone 0.066 mmol.

6.2.6.3 Palladium(II) iodide

The method given in section 6.2.4.1 was followed; palladium(II) iodide (157 mg, 0.436 mmol) and styrene **19** (22.7 mg, 0.218 mmol) were reacted overnight in degassed DMF (1.0 cm^3) and water (0.1 cm^3). After elution from a silica pad with ethoxyethane (30 cm^3) and addition of 4-ethenyl-1-methoxybenzene **148** (28.2 mg, 0.210 mmol), G.L.C. analysis showed no products, only the alkene (0.205 mmol).

6.2.6.4 Palladium(II) nitrate

The method given in section 6.2.4.1 was followed; palladium(II) nitrate (152 mg, 0.660 mmol) and styrene **19** (47.6 mg, 0.457 mmol) were reacted overnight in degassed DMF (2.0 cm^3) and water (0.2 cm^3). After elution from a silica pad with ethoxyethane (30 cm^3) and addition of 4-ethenyl-1-methoxybenzene **148** (32.3 mg, 0.240 mmol), G.L.C. analysis gave the following values: alkene 0.029 mmol, aldehyde 0.038 mmol, ketone 0.167 mmol.

6.2.6.5 Palladium(II) sulphate

The method given in section 6.2.4.1 was followed; palladium(II) sulphate (199 mg, 0.982 mmol) and styrene **19** (49.4 mg, 0.473 mmol) were reacted overnight in degassed DMF (2.0 cm^3) and water (0.2 cm^3). After elution from a silica pad with ethoxyethane (30 cm^3) and addition of 4-ethenyl-1-methoxybenzene **148** (26.7 mg, 0.199 mmol), G.L.C. analysis gave the following values: alkene 0333 mmol, aldehyde 0.005 mmol, ketone 0.059 mmol.

6.2.6.6 Dichlorodi(ethananitrile)palladium(II)

The method given in section 6.2.4.1 was followed; dichlorodi(ethananitrile)palladium(II) (140 mg, 0.540 mmol) and styrene **19** (27.8 mg, 0.267 mmol) were reacted overnight in degassed DMF (1.0 cm^3) and water (0.1 cm^3). After elution from a silica pad with ethoxyethane (30 cm^3) and addition of 4-ethenyl-1-methoxybenzene **148** (28.2 mg, 0.210 mmol), G.L.C. analysis gave the following values: alkene 0.055 mmol, aldehyde 0.085 mmol, ketone 0.029 mmol.

6.2.7 Mechanistic investigations

6.2.7.1 Reaction using 10 % palladium(II) chloride only

4-Ethenyl-1-methylbenzene (56.5 mg, 0.478 mmol) was dissolved in DMF (2.2 cm^3) and water (0.2 cm^3). The mixture was freeze-pump degassed three times, and palladium(II) chloride (6.4 mg, 0.036 mmol) was added. The reaction mixture was stirred overnight, poured onto a silica pad and eluted with ethoxyethane (30 cm^3). G.L.C. analysis of the solution gave a ratio of aldehyde : ketone of 1.2 : 1.0.

6.2.7.2 Reaction in the presence of Pd black

Styrene (51.6 mg, 0.495 mmol) was dissolved in a mixture of degassed DMF (2.0 cm^3) and degassed water (0.2 cm^3). Palladium black (5.6 mg, 0.053 mmol) was added, and the reaction mixture stirred for five minutes. After this time, palladium(II) chloride (176 mg, 0.991 mmol) was added, and the reaction mixture stirred for 30 minutes. It was then poured onto a silica pad and eluted with ethoxyethane (30 cm^3). After addition of 4-ethenyl-1-methoxybenzene (48.9 mg, 0.364 mmol), G.L.C. analysis of the mixture gave the following data: alkene 0.362 mmol, aldehyde 0.064 mmol, ketone 0.026 mmol.

6.2.7.3 Reaction in the presence of dipalladium(0) tris[(1E,4E)-1,5-diphenyl-penta-1,4-dien-3-one]

Styrene **19** (52.8 mg, 0.507 mmol) was dissolved in a mixture of degassed DMF (2.0 cm^3) and degassed water (0.2 cm^3). Dipalladium(0) tris[(1*E*,4*E*)-1,5-diphenyl-penta-1,4-dien-3-one] (23.2 mg, 0.025 mmol) was added, and the reaction mixture stirred for five minutes. After this time, palladium(II) chloride (180 mg, 1.014 mmol) was added, and the reaction mixture stirred for 30 minutes. It was then poured onto a silica pad and eluted with ethoxyethane (30 cm^3). After addition of 4-ethenyl-1-methoxybenzene **148** (44.6 mg, 0.332 mmol), G.L.C. analysis of the mixture gave the following data: alkene 0.462 mmol, aldehyde 0.036 mmol, ketone 0.016 mmol.

6.2.7.4 Reaction in the presence of tetrakis(triphenylphosphane)palladium(0)

Styrene **19** (51.1 mg, 0.491 mmol) was dissolved in a mixture of degassed DMF (2.0 cm^3) and degassed water (0.2 cm^3). Tetrakis(triphenylphosphane)palladium(0) (56.8 mg, 0.049 mmol) was added, and the reaction mixture stirred for five minutes. After this time, palladium(II) chloride (175 mg, 0.986 mmol) was added, and the reaction mixture stirred for 30 minutes. It was then poured onto a silica pad and eluted with ethoxyethane (30 cm^3). After addition of 4-ethenyl-1-methoxybenzene **148** (52.4 mg, 0.391 mmol), G.L.C. analysis of the mixture gave the following data: alkene 0.376 mmol, aldehyde 0.030 mmol, ketone 0.018 mmol.

6.2.7.5 Stoichiometric reaction of 1-ethenyladamantane ***176***

Palladium(II) chloride (183 mg, 1.03 mmol) was suspended in DMF (0.75 cm^3) and water (0.25 cm^3). 1-Ethenyladamantane **176** (72.7 mg, 0.490 mmol) was dissolved in DMF (0.25 cm^3) and THF (0.25 cm^3)[250], and was added to the palladium(II) chloride suspension. The reaction mixture was stirred overnight, before being poured onto a silica column and eluted with hexane – ethoxyethane 4:1. 1-(Adamantan-1-yl)ethanone **177** was obtained as a white solid (47.1 mg, 59 %). R_f 0.204 (hexane – ethoxyethane 9:1). δ_H (400.1 MHz, $CDCl_3$) 1.66 (d, 3H, J = 12.0 Hz, one of C^4H_2), 1.73 (d, 3H, J = 12.0 Hz, one of C^4H_2), 1.78 (d, 6H, J = 2.4 Hz, C^2H_2), 2.02 (br s, 3H), 2.07 (s, 3H, Me). δ_C (100.6 MHz, $CDCl_3$) 24.3 (Me), 28.0 (CH of adamantyl), 36.6 (CH_2 of adamantyl), 38.3 (CH_2 of adamantyl); in agreement with literature values[251].

6.2.7.6 Pre-complexation of styrene and palladium(II) chloride

Styrene **19** (52.1 mg, 0.500 mmol) was dissolved in dry DMF (2.0 cm^3), and the solution freeze-pump degassed three times. Palladium(II) chloride (177 mg, 1.00 mmol) was added, and the mixture stirred overnight, giving a dark red-brown solution. Degassed water (0.2 cm^3) was added, and the reaction stirred for thirty minutes. It was then poured onto silica (9.92 g), and eluted with ethoxyethane (50 cm^3). 4-Ethenyl-1-methoxybenzene (41.1 mg, 0.306 mmol) was added, and the solution analysed by G.L.C.: alkene 0.279 mmol, aldehyde 0.135 mmol, ketone 0.022 mmol.

6.2.8 NMR studies

6.2.8.1 Variable-temperature NMR experiments: $PdCl_2$

4-Ethenyl-1-methylbenzene **156** (27.3 mg, 0.230 mmol) was dissolved in DMF-d_7 (1 g) under nitrogen. The system was freeze-pump degassed three times, before the addition of

palladium(II) chloride (84.3 mg, 0.475 mmol). The mixture was stirred overnight to effect complexation, before being filtered through Celite® under nitrogen into a dry NMR tube.

6.2.8.2 Variable-temperature NMR experiments: $Pd(OAc)_2$

The same method was used as for $PdCl_2$, using 4-ethenyl-1-methylbenzene (23.3 mg, 0.197 mmol) and palladium(II) acetate (87.8 mg, 0.391 mmol).

6.2.9 Effects of acids and bases on the Wacker reaction

6.2.9.1 General procedure for the reaction of 4-ethenyl-1-methylbenzene with palladium(II) acetate in the presence of acid

Palladium(II) acetate was suspended in DMF (0.75 cm^3) and the appropriate acid (0.25 cm^3). A solution of 4-ethenyl-1-methylbenzene **156** in DMF (0.35 cm^3) was added, and the reaction stirred overnight. Following this period, the reaction mixture was poured onto a column of silica and eluted with hexane-ethoxyethane 4:1. The product mixture was the examined by ^1H NMR.

6.2.9.2 Reaction in the presence of HCl

The reaction was carried out by the general method given in section 6.2.9.1. Thus, hydrochloric acid (0.25 cm^3, 1.0 mol dm^{-3}, 0.25 mmol), palladium(II) acetate (238 mg, 1.06 mmol) and the substrate (60.9 mg, 0.515 mmol) were allowed to react for 16 hours. The ratio of products (34.8 mg) was found to be ketone : aldehyde 3.5 : 1.0

6.2.9.3 Reaction in the presence of H_2SO_4

The reaction was carried out by the general method given in section 6.2.9.1. Thus, sulphuric acid (0.25 cm^3, 0.5 mol dm^{-3}, 0.125 mmol) palladium(II) acetate (269 mg, 1.20 mmol) and the substrate (59.8 mg, 0.506 mmol) were allowed to react for 16 hours. The product (29.3 mg) was found to be purely ketone.

6.2.9.4 Reactions in the presence of carbonate bases

A method similar to that given in section 6.2.4.1 was used. Thus, styrene **19** was dissolved in a mixture of degassed DMF (1.0 cm^3) and degassed water (0.1 cm^3). The appropriate base was added, followed by palladium(II) chloride, and the reaction stirred overnight. The crude mixture was then poured onto a silica pad and eluted with ethoxyethane (30 cm^3). 4-Ethenyl-1-methoxybenzene **148** was added as a standard, and the reaction mixture was examined by G.L.C. The numerical data is given below in Table 11 and Table 12.

Base	Styrene		$PdCl_2$		Base		Standard	
	Mass (mg)	Moles (mmol)	Mass (mg)	Moles (mmol)	Mass (mg)	Moles (mmol)	Mass (mg)	Moles (mmol)
Li_2CO_3	28.3	0.272	88.6	0.500	22.6	0.306	18.3	0.136
Na_2CO_3	30.7	0.295	89.3	0.504	32.2	0.304	20.9	0.156
K_2CO_3	29.9	0.287	88.9	0.501	41.0	0.297	22.1	0.165
Cs_2CO_3	28.8	0.277	89.3	0.503	91.4	0.281	11.8	0.088
$(NH_4)_2CO_3$	31.4	0.301	89.3	0.504	29.6	0.308	26.9	0.200
$CaCO_3$	28.7	0.276	88.8	0.501	27.3	0.276	20.6	0.154

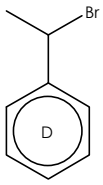
Table 11 – Masses and moles for base experiments

Base	GC results (mmol)			Ratio aldehyde : ketone
	Alkene	Aldehyde	Ketone	
Li_2CO_3	0.093	0.065	0.037	1.7 : 1.0
Na_2CO_3	0.116	0.000	0.043	Ketone
K_2CO_3	0.074	0.014	0.127	1.0 : 9.3
Cs_2CO_3	0.084	0.076	0.042	1.8 : 1.0
$(NH_4)_2CO_3$	0.074	0.063	0.017	3.7 : 1.0
$CaCO_3$	0.066	0.041	0.087	1.0 : 2.1

Table 12 – Results of base experiments

6.2.10 Kinetic studies

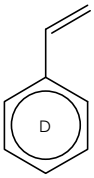
*6.2.10.1 1-(1-Bromoethyl)(D_5)benzene **184***



184

The method of Smith[252] was used. 1-[(D_5)Phenyl]ethanol **183** (5.143 g, 40.4 mmol) was placed in a side-armed flask and flushed with dry nitrogen for five minutes. Ethanoyl bromide (6.00 cm^3 9.98 g, 81.1 mmol) was added dropwise to the reaction mixture, which was cooled with an ice bath as soon as the addition was begun.[253] The reaction was stirred for an addition 10 minutes at 0 °C, followed by 10 minutes at room temperature. The volatile fractions were removed at reduced pressure (100 mbar, water bath 50 °C), and the residue distilled, giving a colourless oil (6.679 g, 87 %). T_b 72 – 74 °C / 7 mbar. R_f 0.582 (hexane – ethoxyethane 20:1). ν_{max}/cm^{-1} (film) 2974 (w), 2921 (w), 1442 (m), 1377 (m), 1186 (s), 1158 (m), 1079 (m), 1039 (m), 967 (m), 954 (m), 841 (s), 825 (m), 735 (m). Found C 50.57, "H" 4.80 %; $C_8H_4BrD_5$ requires C 50.55, "H" 5.07 %. δ_H ($CDCl_3$, 400.1 MHz) 2.08 (d, 3H, *J* = 7.0 Hz, CH_3), 5.25 (q, 1H, *J* = 7.0 Hz, CH). δ_C ($CDCl_3$, 100.6 MHz) 26.7 (CH_3), 49.4 (C*H*Br), 126.3 (t, *J* = 24.1 Hz, Ph), 127.7 (t, *J* = 24.8 Hz, Ph), 128.1 (t, *J* = 24.5 Hz, Ph), 143.0 (Ph quaternary). m/z (EI) 110.1, 68.9, 82.0, 189.0 (M^+); calc[d] for $C_8H_4BrD_5$ (M^+, ^{79}Br) 189.0201, found 189.0194.

6.2.10.2 1-ethenyl(D_5)benzene ***185***



185

Potassium 1,1-dimethylethoxide (11.248 g, 100.0 mmol) was dissolved in dry THF (100 cm^3). 1-(1-Bromoethyl)(D_5)benzene **184** (6.325 g, 33.3 mmol) was added, and the mixture stirred. The solution became yellow, and formation of a precipitate occurred. After 30 minutes, no starting material was visible by TLC. The solution was filtered, diluted with ethoxyethane (100 cm^3), and washed with hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent distilled off *via* a 200 mm Vigreux column. The residue was then distilled at atmospheric pressure, giving a colourless oil (2.360 g, 65 %). T_b 142 – 144 °C. R_f 0.445 (hexane – ether 20:1). ν_{max}/cm^{-1} (film) 3089 (w), 2982 (w), 1629 (m), 1425 (m), 1325 (w), 1154 (w), 988 (m), 906 (s), 841 (m), 780 (m), 679 (m). Found C 88.00, "H" 7.44 %; $C_8H_3D_5$ requires C 88.01, "H" 7.74 %. δ_H ($CDCl_3$, 400.1 MHz) 5.26 (dd, 1H, *J* = 0.8 Hz, 10.4 Hz; alkene CH *trans* to ring), 5.77 (dd, 1H, *J* = 1.2 Hz, 17.6 Hz; alkene CH *cis* to ring), 6.75 (dd, 1H, *J* = 10.4 Hz, 17.6 Hz; alkene CH). δ_C ($CDCl_3$, 100.6 MHz) 113.8 (CH_2) 125.8 (t, *J* = 25.2 Hz, Ph), 127.5 (t, *J* = 25.2 Hz, Ph), 128.0 (t, *J* = 20.0 Hz, Ph), 136.8 (alkene CH), 137.4 (aromatic C). m/z (EI) 109.1 (M^+), 82.0, 68.9; calc[d] for $C_8H_3D_5$ 109.0940 found 109.0941.

6.2.10.3 Kinetic experiments

The general procedure for these was as follows, values are given in Table 13. The substrate (approx. 0.5 mmol) was placed in a side-armed flask, evacuated and filled with nitrogen (three times). The flask was sealed, and the mass of substrate accurately measured (0.5 mmol ± 1 mg). The substrate was then dissolved in degassed DMF (2.0 cm^3) and degassed water (0.2 cm^3) and stirred. Palladium(II) chloride (2.0 eq. ± 1 mg) was then added, and the reaction stirred for the appropriate time. The crude reaction mixture was poured onto a short column of silica of known mass, and eluted with ethoxyethane (50 cm^3). 4-Ethenyl-4-methoxybenzene **148** was added as an internal standard, and the products analyzed by GC (oven conditions 80 °C for 5 minutes, 10 °C per minute ramp, 100 °C for 2 minutes). The results are given in Table 14.

Time (hr)	Substrate	Substrate		$PdCl_2$		Mass silica (g)	Standard	
		Mass (mg)	Moles (mmol)	Mass (mg)	Moles (mmol)		Mass (mg)	Moles (mmol)
0.5	**19**	51.7	0.496	175.8	0.991	9.79	56.6	0.422
0.5	**185**	53.7	0.492	174.5	0.984	9.89	58.3	0.434
1	**19**	51.3	0.493	175.6	0.990	9.86	43.6	0.325
1	**185**	55.3	0.507	180.1	1.016	9.94	49.6	0.370
1.5	**19**	54.5	0.523	186.1	1.049	9.98	56.2	0.419
1.5	**185**	55.1	0.505	178.7	1.008	9.93	50.5	0.376
2	**19**	51.0	0.490	174.7	0.985	9.92	47.8	0.356
2	**185**	55.0	0.504	178.6	1.007	9.87	44.7	0.333

Table 13 - Amounts used for kinetic experiments

Time (hr)	Substrate	GC results (mmol)			% aldehyde (of total s.m.)
		alkene	aldehyde	ketone	
0.5	**19**	0.401	0.046	0.017	9.34 %
0.5	**185**	0.446	0.048	0.018	9.80 %
1	**19**	0.376	0.084	0.025	17.01 %
1	**185**	0.395	0.086	0.018	16.91 %
1.5	**19**	0.360	0.106	0.021	20.19 %
1.5	**185**	0.342	0.104	0.020	20.57 %
2	**19**	0.310	0.116	0.018	23.78 %
2	**185**	0.312	0.121	0.019	23.96 %

Table 14 - Kinetic results

6.2.11 Catalysis of the reaction

6.2.11.1 1,4-Benzoquinone

4-Ethenyl-1-methylbenzene **156** (60.2 mg, 0.509 mmol) was dissolved in DMF (2.25 cm^3) and water (0.25 cm^3), and the mixture freeze-pump degassed three times. 1,4-Benzoquinone (109 mg, 1.01 mmol) and palladium(II) chloride (188 mg, 1.06 mmol) were added, and the reaction stirred overnight. After addition to a silica pad and elution with ethoxyethane (30 cm^3), G.L.C. analysis showed a ratio of ketone : aldehyde of 11.1 : 1.0.

6.2.11.2 2-Methylprop-2-ylhydroperoxide

4-Ethenyl-1-methylbenzene **156** (63.5 mg, 0.537 mmol) was dissolved in DMF (2.5 cm^3) and 2-methylprop-2-ylhydroperoxide solution (70 % in water, 0.15 cm^3, ~ 1.1 mmol), and the mixture freeze-pump degassed three times. Palladium(II) chloride (186 mg, 1.05 mmol) was added, and the reaction stirred for 4 hours. After addition to a silica pad and elution with ethoxyethane (30 cm^3), G.L.C. analysis showed a ratio of ketone : aldehyde of 3.3 : 1.0.

6.2.11.3 Hydrogen peroxide

4-Ethenyl-1-methylbenzene **156** (57.7 mg, 0.488 mmol) was dissolved in DMF (2.2 cm^3) and hydrogen peroxide solution (30 % in water, "100 volumes", 0.10 cm^3, ~ 1.0 mmol), and the mixture freeze-pump degassed three times. Palladium(II) chloride (177 mg, 1.00 mmol) was added, and the reaction stirred overnight. After addition to a silica pad, elution with ethoxyethane (30 cm^3), and addition of (4-methoxyphenyl)ethanone **149** (15.5 mg, 0.103 mol), G.L.C. analysis gave the following data: alkene 0.048 mol, aldehyde 0.101 mmol, ketone 0.077 mmol.

6.2.11.4 Iron(III) chloride

4-Ethenyl-1-methylbenzene **156** (60.3 mg, 0.510 mmol) was dissolved in DMF (2.2 cm^3) and water (0.2 cm^3), and the mixture freeze-pump degassed three times. Iron(III) chloride (161 mg, 0.485 mmol) and palladium(II) chloride (178.5 mg, 1.01 mmol) were added, and the reaction stirred overnight. After addition to a silica pad and elution with ethoxyethane (30 cm^3), G.L.C. analysis showed no reaction had occurred.

6.2.11.5 Manganese(II) oxide

4-Ethenyl-1-methylbenzene **156** (57.3 mg, 0.484 mmol) was dissolved in DMF (2.2 cm^3) and water (0.2 cm^3), and the mixture freeze-pump degassed three times. Manganese(II) oxide (92.7 mg, 1.07 mmol) and palladium(II) chloride (178 mg, 1.00 mmol) were added, and the reaction stirred overnight. After addition to a silica pad and elution with ethoxyethane (30 cm^3), G.L.C. analysis of the solution showed that the product was pure ketone.

6.2.11.6 4-Methylmorpholin-4-ol

Styrene **19** (105 mg, 1.01 mmol) was dissolved in degassed DMF (4.0 cm^3) and degassed water (0.4 cm^3). 4-Methylmorpholin-4-ol (144 mg, 1.06 mmol) and palladium(II) chloride (18.3 mg, 0.103 mmol) were added, and the reaction mixture stirred for five hours. It was then poured onto silica and eluted using ethoxyethane (50 cm^3). G.L.C. analysis showed only the starting material.

6.2.11.7 Formation of 11-molybdo-1-vanadophophoric acid ***278***

The method of Tsigdinos and Hallada was used.[179] Solutions of disodium hydrogen phosphate (7.15 g, 50.4 mmol) in water (100 cm^3) and sodium vanadate(V) (6.13 g, 50.3 mmol) in boiling water (100 cm^3) were prepared, mixed and allowed to cool to room temperature. Concentrated sulphuric acid (5.0 cm^3) was added, giving a dark red solution. A solution of sodium molybdate

decahydrate (133 g, 0.55 mol) in water (200 cm^3) was added, and the mixture stirred vigorously. Concentrate sulphuric acid (85 cm^3) was added cautiously, the reaction mixture cooled to room temperature and diluted with ethoxyethane (400 cm^3). Three layers were formed: an ethoxyethane layer, an aqueous layer, and a bottom layer of deep red liquid. The bottom layer (the product ethoxyethanate) was isolated, and the ethoxyethane evaporated by a stream of nitrogen. The resulting solid was redissolved in water (50 cm^3), which was then concentrated until crystals were formed. The product was obtained as red crystals (54.0 g).

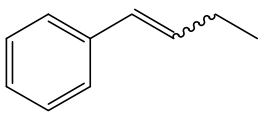
6.2.11.8 11-Molybdo-1-vanadophophoric acid

Styrene **19** (98.0 mg, 0.941 mmol) was dissolved in degassed DMF (4.0 cm^3) and degassed water (0.4 cm^3). The reoxidant **278** (2.02 g, 1.13 mmol) and palladium(II) chloride (19.4 mg, 0.109 mmol) were added, and the reaction mixture stirred overnight. It was then poured onto silica and eluted using ethoxyethane (50 cm^3). G.L.C. analysis gave a ratio of aldehyde : ketone of 6.35 : 1.0, and a ratio of products : starting material of 3.0 : 1.0.

6.3 The agostic interaction in the Wacker reaction

6.3.1 Agostic interaction: synthesis and reactions of aromatic

*6.3.1.1 But-1-enylbenezne **210***

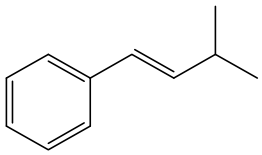


210

1-Propyltriphenylphosphonium bromide (23.116 g, 60.0 mmol) was suspended in dry THF (200 cm^3) and the solution cooled to -78 ºC. A solution of butyl lithium (1.66 mol dm^{-3} in hexane, 40 cm^3, 66.4 mmol) was added dropwise to the solution, which was then allowed to warm to room temperature. The reaction was then cooled to -78 ºC, a solution of benzaldehyde (6.40 cm^3, 6.68 g, 63.0 mmol) in dry THF (100 cm^3) was added dropwise, and the reaction allowed to warm overnight to room temperature. The solution was filtered, the solvent removed *in vacuo* and the residue taken up in ethoxyethane (100 cm^3). The solution was washed with hydrochloric acid (2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). The solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. Distillation at reduced pressure gave the product as a light yellow oil (3.612 g, 46 %), found to be a mixture of *E* and *Z* isomers (*Z*:*E* 1.43:1.00). R_f 0.380 (hexane). T_b 56 – 58 ºC / 9 mbar (Lit.[254] 70 – 71 ºC / 8 mm Hg). ν_{max}/cm^{-1} 2963 (w), 1599 (w), 1493 (w), 1446 (w), 1176 (w), 1075 (m), 964 (s), 743 (s), 694 (s). δ_H ($CDCl_3$, 400.1 MHz) 1.17 (t, 3H, *J* = 7.6 Hz, Me, *Z*), 1.20 (t, 3H, *J* = 7.6 Hz, Me,

E), 2.33 (dp, 2H, *J* = 1.8, 7.6 Hz; CH_2, *E*), 2.45 (dp, 2H, *J* = 1.2, 8.8 Hz; CH_2, *Z*), 5.76 (dt, 1H, *J* = 7.6, 11.6 Hz; C*H*CH_2, *Z*), 6.36 (dt, 1H, *J* = 6.8, 16.0 Hz; C*H*CH_2, *E*), 6.49 (d, 1H, *J* = 16.0 Hz, C*H*Ph, *E*), 6.49 (d, 1H, *J* = 11.6 Hz, C*H*Ph, *Z*), 7.24 – 7.45 (m, 5H, Ph, both isomers). δ_C ($CDCl_3$, 100.6 MHz) 13.6 (Me), 14.4 (Me), 21.9 (*C*H_2Me), 26.0 (*C*H_2Me), 125.9 (CH), 126.4 (CH), 126.7 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 129.8 (CH), 132.5 (CH), 134.6 (CH), 137.7 (aromatic C), 137.9 (aromatic C). m/z (EI) 68.9, 117.1, 132.1 (M^+); calc[d] for $C_{12}H_{12}$ 132.0939, found 132.0934.

6.3.1.2 E-*(3-Methylbut-1-enyl)benzene* ***212***



212

1-Benzyltriphenylphosphonium bromide (6.872 g, 15.8 mmol) was suspended in dry THF (30 cm^3) and the solution cooled to 0 ºC. A solution of lithium bis(trimethylsilyl)amide (1.0 mol dm^{-3} in THF, 15 cm^3, 15.0 mmol) was added dropwise to the solution, which was then allowed to warm to room temperature. The reaction was then cooled to -78 ºC, a solution of 2-methyl-propan-1-al (1.36 cm^3, 1.08 g, 15.0 mmol) in dry THF (15 cm^3) was added dropwise, and the reaction allowed to warm overnight to room temperature. The solution was filtered through Celite®, and poured into saturated aqueous ammonium chloride solution (25 cm^3). The mixture was extracted with ethoxyethane (2 × 15 cm^3), and the combined organic solutions washed with saturated aqueous ammonium chloride solution (2 × 25 cm^3), water (2 × 25 cm^3) and saturated aqueous sodium chloride solution (2 × 25 cm^3). The solution was dried over sodium sulphate(VI), filtered and the solvent removed at reduced pressure. Chromatography on silica gel, eluting with hexane-ethoxyethane 9:1, gave the product as a slightly yellow oil (0.964 g, 44 %). R_f 0.655 (hexane-ethoxyethane 9:1). ν_{max}/cm^{-1} (film) 3025 (s), 2858 (s), 2866 (s), 1729 (m), 1649 (w), 1598 (m), 1493 (m), 1463 (m), 1382 (m), 1072 (m), 966 (s). δ_H ($CDCl_3$, 400.1 MHz) 1.13 (d, 6H, *J* = 6.4 Hz, Me), 2.50 (~ doublet of octets, 1H, *J* = 1.3, 6.4 Hz; C*H*Me_2), 6.23 (dd, 1H, *J* = 7.0, 16.0 Hz; C*H*CH_2). 6.38 (d, 1H, *J* = 16.4 Hz, C*H*Ph), 7.21 (tt, 1H, *J* = 1.2, 7.2 Hz; Ph), 7.32 (~ t, 2H, *J* = 7.6 Hz, Ph), 7.38 (~ d, 2H, *J* = 8.0 Hz, Ph). δ_C ($CDCl_3$, 100.6 MHz) 22.4 (Me), 31.5 [C*H*$(CH_3)_2$], 125.9 (aromatic CH), 126.7 (CH), 126.8 (CH), 128.4 (aromatic CH), 137.9 (*C*HPh). m/z (EI) 131.1, 146.1, 91.1, 68.8; calc[d] for $C_{11}H_{14}$ 146.1096, found 146.1091.

6.3.1.3 Wacker reaction of but-1-enylbenzene **210**

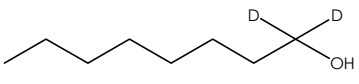
The method of Gaunt was used[225] with modification. The substrate (129 mg, 0.977 mmol) was dissolved in degassed DMF (1.0 cm^3) and degassed water (1.0 cm^3). Palladium(II) chloride (214 mg, 1.21 mmol) was added, the reaction warmed to 50 ºC and stirred overnight. It was then added to a silica column and eluted using 9:1 pentane-ethoxyethane. The product **211** was obtained as a colourless oil (63.6 mg, 43 %). δ_H ($CDCl_3$, 400.1 MHz) 2.14 (s, 3H, Me), 2.38 (s, 2H, CH_2CO), 7.18 – 7.20 (~ d, 2H, J = 8.0 Hz, Ph), 7.26 (~ d, 1H, J = 7.5 Hz, Ph), 7.32 (~ t, 2H, J = 7.0 Hz, Ph). δ_C ($CDCl_3$, 100.6 MHz) 29.1 (Me), 50.9 (*C*H_2Ph), 127.5 (aromatic CH), 128.5 (aromatic CH), 128.7 (aromatic CH), 134.2 (aromatic C), 206.3 (*C*=O) m/z (EI) 80.2, 46.2, 134.1, 60.9; calc[d] for $C_9H_{10}O$ 134.0732, found 134.0736.

6.3.1.4 Wacker reaction of (3-methylbut-1-enyl)benzene **212**

The method given in section 6.3.1.3 was used. Thus, the substrate (145 mg, 0.993 mmol) and palladium(II) chloride (216 mg, 1.22 mmol) were reacted overnight at 50 ºC. Chromatography in 9:1 pentane– ethoxyethane gave the product **213** (26.3, 16 %) as a colourless oil. δ_H ($CDCl_3$, 400.1 MHz) 1.08 (d, 6H, J = 7.0 Hz, 2 × Me), 2.71 (septet, 1H, J = 7.0 Hz, C*H*Me_2), 3.73 (s, 2H, CH_2Ph), 7.18 (~ d, 2H, J = 8.0 Hz, Ph), 7.23 (~ t, 1H, J = 7.0 Hz, Ph), 7.30 (~ t, 2H, J = 7.5 Hz, Ph). δ_C ($CDCl_3$, 100.6 MHz) 7.9 (Me), 35.1 (*C*H_2CH_3), 49.7 (*C*H_2Ph), 126.5 (aromatic CH), 128.5 (aromatic CH), 129.4 (aromatic CH), 134.4 (aromatic C), 208.8 (C=O). m/z (EI) 91.0, 68.9, 119.0, 131.0, 162.1 (M^+), 149.0; calc[d] for $C_{11}H_{14}O$ 162.1045, found 162.1047.

6.3.2 Agostic interaction: synthesis and reactions of [3,3-D_2]dec-1-ene

6.3.2.1 [1,1-D_2]Octan-1-ol **227**

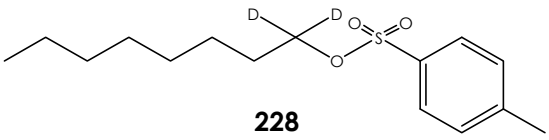


227

The method of Landini *et al.*[255] was used. Lithium tetrahydrido(D)aluminate (6.70 g, 160 mmol) was suspended in freshly distilled THF (~ 200 cm^3). A solution of ethyl octanoate (31.5 cm^3, 27.5 g, 159 mmol) in freshly distilled THF (40 cm^3) was added dropwise to the reaction vessel. Heat was evolved, along with the evolution of gas. After the addition was completed, the reaction was heated to reflux for 2½ hours, before being cooled to 0 ºC. A mixture of THF (30 cm^3) and water (30 cm^3) was cautiously added; initially, a large degree of effervescence occurred, followed by the formation of a solid. The solution was poured into chilled water (100 cm^3), and hydrochloric acid (2.0 mol dm^{-3}, 330 cm^3) was added. The solution

was allowed to cool to room temperature, the layers separated, and the aqueous layer extracted with ethoxyethane (2 × 100 cm^3). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3), dried over magnesium sulphate(VI), filtered and the solvent removed *in vacuo*. The product was obtained as a colourless oil (20.21 g, 96 %), which did not require further purification. R_f 0.422 (petroleum ethers – ethyl acetate 3:2). ν_{max}/cm^{-1} 3326 (br, m, OH), 2957 (m), 2924 (s), 2855 (s), 1466 (m), 1378 (w), 1132 (m), 1092 (m), 967 (s), 723 (w). Found C 72.52, "H" 13.86 %; $C_8H_{16}D_2O$ requires C 72.66, "H" 13.89 %. δ_H ($CDCl_3$, 400.1 MHz) 0.84 (t, 3H, J = 7.0 Hz, Me), 1.25 (br s, 10H, chain), 1.51 (t, 2H, J = 7.0 Hz, CH_2CD_2), 1.72 (s, 1, OH). δ_C ($CDCl_3$, 100.6 MHz) 14.0 (Me), 22.6 (CH_2), 25.6 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 32.4 (CH_2), 61.9 (p, J = 21.4 Hz, CD_2). m/z (EI) 68.9, 114.1 (M^+ - H_2O), 131.0, 119.0; calc[d] for $C_8H_{16}D_2$ (M^+ - H_2O) 114.1376, found 114.1381.

6.3.2.2 *[1,1-D2]Octyl 4-methylbenzenesulphonate* ***228***

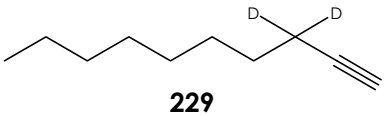


228

The method given in Vogel's for decyl 4-methylbenzenesulphonate was used[256]. Thus, [1,1-D_2]-octan-1-ol **227** (12.270 g, 92.3 mmol) was dissolved in dry trichloromethane (100 cm^3) and the reaction mixture cooled to 0 ºC, before the addition of anhydrous pyridine (15.2 cm^3, 14.7 g, 186 mmol). 4-Methylbenezenesulphonic chloride (26.406 g, 138.5 mmol) was added in portions over 30 minutes, and the reaction allowed to stir at room temperature for two hours. After this time, it was poured into water (100 cm^3) and ethoxyethane (300 cm^3). The layers were separated, and the organic layer washed with hydrochloric acid (1 mol dm^{-3}, 2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. Distillation at reduced pressure gave a low melting solid (T_b 90 ºC / 0.01 mm Hg), which was removed from the apparatus, followed by the product as a clear oil (23.00 g, 87 %). T_b 137 – 143 ºC / 0.01 mm Hg. R_f 0.244 (hexane – ethoxyethane 4 : 1). ν_{max}/cm^{-1} 2926 (m), 2856 (m), 1598 (w), 1457 (w), 1359 (s), 1190 (s), 1176 (s), 1097 (m), 954 (s), 814 (s), 660 (s). $C_8H_{16}D_2O$ requires C 62.90, "H" 8.52 %; found C 62.98, "H" 8.51 %. δ_H ($CDCl_3$, 400.1 MHz) 0.84 (t, 3H, J = 7.0 Hz, CH_3CH_2), 1.18 – 1.26 (m, 10H, alkyl chain), 1.59 (t, 2H, J = 8.0 Hz, CH_2CD_2), 2.42 (s, 3H, Me), 7.31 (~ d, 2H, J = 8.5 Hz, aromatic CH), 7.76 (~ d, 2H, J = 8.0 Hz, aromatic CH). δ_C ($CDCl_3$, 100.6 MHz) 14.0 (CH_3CH_2), 21.6 (Me), 22.5 (CH_2),

25.2 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 70.0 (p, J = 22.4 Hz, CD_2), 127.8 (aromatic CH), 129.7 (aromatic CH), 133.3 (aromatic C), 144.6 (aromatic C). m/z (ESI) 309.1 (M^+ + Na), 205.1; calc[d] for $C_{15}H_{22}D_2O_3SNa$ 309.1469, found 309.1473.

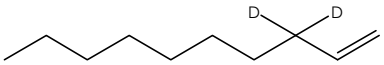
6.3.2.3 *[3,3-D_2]Dec-1-yne* ***229***



229

The methods of Smith and Beumel[257] and of Dear and Pattison[258,259] were used. Lithium ethenylide ethane-1,2-diamine complex (90 %, 14.17 g, 138.5 mmol) was suspended in dry DMSO (60 cm^3). The substrate **228** was added dropwise, the reaction temperature being kept below 30 ºC by means of an ice bath. The reaction left at room temperature for 1½ hours following the addition. It was then cooled to 0 ºC and diluted with hydrochloric acid (1 mol dm^{-3}, 200 cm^3). The mixture was extracted with pentane (4 × 50 cm^3), and the combined organic fractions washed with hydrochloric acid (2 × 50 cm^3, 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). The solution was then dried over magnesium sulphate(VI), filtered and evaporated at room temperature. The product was distilled at 10 mbar, to give a colourless oil (10.99 g, 62 %). R_f 0.575 (hexane-ethoxyethane 50 : 1). T_b 46 – 48 ºC / 10 mbar. ν_{max}/cm^{-1} 3314 (m, alkyne C-H), 2926 (s), 2856 (s), 1457 (m), 1379 (w), 1239 (br, w), 1061 (w), 723 (w). Found C 85.60, "H" 13.05 %; $C_{10}H_{16}D_2$ requires C 85.63, "H" 13.09 %. δ_H ($CDCl_3$, 400.1 MHz) 0.84 (t, 3H, J = 6.6 Hz, Me), 1.24 (br s, 8H, alkyl chain), 1.35 (m, 2H, alkyl chain), 1.47 (~ t, 2H, J = 7.2 Hz, CH_2CD_2), 1.88 (s, 1H, C≡C*H*). δ_C ($CDCl_3$, 100.6 MHz) 14.0 (Me), 17.7 (p, J = 17.7 Hz, CD_2), 22.6 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.8 (CH_2), 68.0 (C≡*C*H), 84.5 (*C*≡CH). m/z 84.0, 98.1, 69.0, 113.1, 140.2 (M^+), 126.1; calc[d] for $C_{10}H_{16}D_2$ 140.1534, found 140.1536.

6.3.2.4 [3,3-D_2]Dec-1-ene ***230***



230

Reference was made to the procedures of Jacobsen *et al.*[190], Lindlar *et al.*[98,99], Bergmann and Becker[260], Savoia *et al.*[189] and Dear and Pattison[259]. The most successful procedure was as follows. The alkyne **229** (5.00 g, 35.7 mmol) was dissolved in hexane (15 cm^3) and hex-1-ene (10 cm^3). Quinoline (0.125 cm^3, 136 mg, 1.06 mmol) and palladium on calcium carbonate (5 %) poisoned with lead (Lindlar's catalyst, 123.7 mg) were then added. The reaction vessel was evacuated and filled with hydrogen, and the suspension stirred vigorously for 3½ hours, after which all of the starting material had been consumed. The crude mixture was filtered through Florisil®, which was washed with pentane. The solution was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 20 cm^3) and saturated aqueous sodium chloride solution (2 × 20 cm^3). It was dried over magnesium sulphate(VI), filtered and the solvent evaporated at room temperature and reduced pressure. The product was distilled at 10 mbar, giving a colourless oil, T_b 38 – 41 °C (2.98 g). This was found to be a mixture of the desired product and the fully saturated compound **231** (approx. ratio 10 : 1). Altering the reaction conditions did not prevent the formation of **231**.

6.3.2.5 NMR kinetics experiments: competition

The catalyst solution was prepared by stirring palladium(II) chloride (18.1 mg, 0.102 mmol) and 1,4-benzoquinone (119.4 mg, 1.10 mmol) in DMF-d_7 (3.0 cm^3) and water (0.040 cm^3) for two hours. After this period, an aliquot of the catalyst solution (0.75 cm^3) was transferred to an NMR tube. A mixture of dec-1-ene (0.047 cm^3) and [3,3-D_2]dec-1-ene (0.052 cm^3) was prepared, and the ratio of alkenes measured by NMR, giving a value mol_D/mol_H of 0.88. The mixture (0.049 cm^3) was added to the catalyst solution, the mixture shaken and the NMR spectra obtained. Analysis as given in section 8 gave the following conversions:

Time (min)	Conversion (%)	
	225	**230**
4'54"	15.0	18.1
7'37"	27.2	29.3
10'20"	31.3	39.3
13'03"	40.5	47.3
15'46"	45.4	49.9
18'29"	50.9	58.0
21'12"	54.9	63.1
23'55"	59.3	71.1

Table 15 - Competition kinetics

6.3.2.6 NMR kinetics experiments: separate reactions

A similar method to that used in section 6.3.2.5 was used. Thus, a stock solution was prepared from palladium(II) chloride 15.0 mg, 0.0845 mmol), 1,4-benzoquinone (83.4 mg, 0.722 mmol), water (0.030 cm^3) and DMF-d_7 (2.25 cm^3); these were stirred together for two hours before the reaction commenced. The reaction was carried out either with dec-1-ene (0.046 cm^3) or [3,3-D_2]-dec-1-ene (0.051 cm^3). The results are given in Table 16.

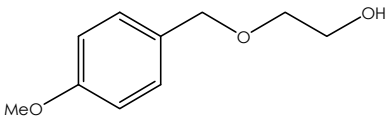
Time (min)	Conversion (%)	
	225	**230**
1	1.8	0.7
3	4.6	2.5
5	8.3	6.0
7	11.2	8.5
9	13.3	11.3
11	16.8	14.4
13	20.3	16.9
15	21.4	19.2
17	26.1	21.6
19	28.9	24.7

Table 16 - Kinetics of dec-1-ene

6.4 Selective oxidative removal of the NAP group

6.4.1 Synthesis and deprotection of linker

6.4.1.1 2-(4-Methoxyphenylmethoxy)ethanol **279**

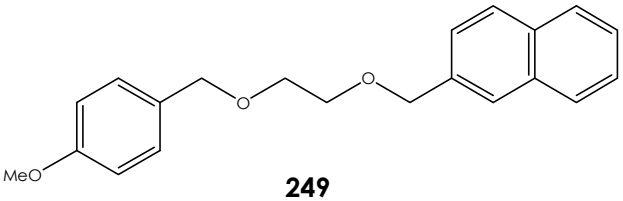


279

The method of Marshall[261] was adapted. Sodium hydride (60 % in mineral oil, 2.99 g, 74.8 mmol) was suspended in dry tetrahydrofuran (150 cm^3) under nitrogen. Ethane-1,2-diol (12.0 cm^3, 13.4 g, 216 mmol) was added over 1½ hours, and the reaction mixture heated to reflux. 1-Chloromethyl-4-methoxybenzene (9.40 cm^3, 10.8 g, 60.0 mmol) was added dropwise over 3 hours, and the reaction left overnight. The reaction mixture was cooled to room temperature and diluted with ethoxyethane (100 cm^3). It was then washed with hydrochloric acid (1 mol dm^{-3}, 2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over sodium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was then distilled at reduced pressure to give a colourless oil (6.38 g, 51 %). T_b 143 °C / 0.5 mm Hg (Lit.[262] 109 °C / 0.5 mm Hg). R_f 0.292 (ethoxyethane). ν_{max}/cm^{-1} (film) 3424 (s, v br, OH), 2861 (s), 1611 (s, aromatic), 1511 (s), 1464 (s), 1356 (s), 1302

(s), 1247 (br), 1174 (s), 1030 (v br), 892 (m), 820 (s br), 757 (m). δ_H ($CDCl_3$, 400.1 MHz) 2.69 (t, 1H, *J* = 6.3 Hz, OH), 3.52 (t, 2H, *J* = 4.6 Hz, CH_2CH$_2$OH), 3.69 (dt, 2H, *J* = 4.6, 6.3 Hz; CH_2OH), 3.77 (s, 3H, MeO), 4.45 (s, 2H, ArCH_2), 6.85 (d, 2H, *J* = 8.4 Hz, aromatic H), 7.24 (d, 2H, *J* = 8.4 Hz, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.1 (*C*H$_2$OH), 61.6 (*C*H$_2$CH$_2$OH), 71.0 (MeO), 72.7 (Ar*C*H$_2$), 113.6 (aromatic CH), 129.3 (aromatic CH), 129.9 (aromatic C), 159.1 (aromatic C-O). m/z (ESI) 205.1 (M^+ + Na); calc[d] for $C_{10}H_{14}O_3$ 205.0841, found 205.0842.

6.4.1.2 2-[2-(4-Methoxybenzyloxy)ethoxymethyl]naphthalene ***249***



249

The method of Chida *et al.*[263] was adapted. Sodium hydride (60 % suspension in mineral oil, 0.565 g, 14.1 mmol) was suspended in dry DMF (20 cm^3) and cooled to 0 °C. 2-(4-Methoxyphenylmethoxy)ethanol **279** (1.985 g, 10.9 mmol) was dissolved in dry DMF (30 cm^3) and added dropwise to the suspension of base. The reaction was stirred for ½ hour at 0 °C following the addition, then allowed to warm to room temperature. 2-(Bromomethyl)naphthalene (2.675 g, 12.1 mmol) was added in portions over one hour, and the reaction allowed to stir overnight. Following this period, TLC of the reaction solution indicated that it had not reached completion. Sodium hydride (60 % suspension in mineral oil, 0.275 g, 8.88 mmol) and 2-(bromomethyl)naphthalene (1.342 g, 6.07 mmol) were added, and the reaction stirred for an additional two hours. The solution was then poured in water (50 cm^3) and extracted with ethoxyethane (2 × 50 cm^3). The combined organic solutions were washed with hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). It was then dried over magnesium sulphate(VI), filtered and the solvent removed *in vacuo*. Chromatography on silica gel, using 4:1 hexane-ethoxyethane as the eluting solvent, gave the product as a yellow oil which solidified on standing (2.773 g, 77 %). T_m < 30 °C. R_f 0.500 (petroleum ethers-ethyl acetate 3:2). ν_{max}/cm^{-1} (solid) 2898 (m), 2861 (w), 1612 (m), 1586 (w), 1512 (m), 1396 (m), 1306 (m), 1248 (m), 1176 (m), 1086 (s), 1033 (s), 970 (m), 815 (s), 750 (s), 732 (m). Found C 78.21, H 6.88 %; $C_{21}H_{22}O_3$ requires C 78.23, H 6.88 %. δ_H ($CDCl_3$, 400.1 MHz) 3.67 (ddd, 2H, *J* = 1.6, 3.6, 5.6 Hz; one pair of OCH_2CH_2O), 3.71 (ddd, 2H, *J* = 1.6, 3.6, 5.6 Hz; one pair of OCH_2CH_2O), 3.81 (s, 3H, MeO), 4.54 (s, 2H, one of ArCH_2O), 4.75 (s, 2H, one of ArCH_2O), 6.88 (d, 2H, *J* = 8.8 Hz, MPM group CH pair), 7.29 (d, 2H, *J* = 8.8 Hz, MPM group CH pair), 7.48 (m, 3H, naphthyl CH), 7.83 (m, 4H, naphthyl CH).

δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 69.2 (CH_2O), 69.5 (CH_2O), 73.9 (CH_2O), 73.3 (CH_2O), 113.7 (aromatic CH), 125.7 (aromatic CH), 126.0 (aromatic CH), 126.4 (aromatic CH), 127.6 (aromatic CH), 127.8 (aromatic CH), 128.1 (aromatic CH), 129.3 (aromatic CH), 130.4 (aromatic C), 132.9 (aromatic C), 133.3 (aromatic C), 135.8 (aromatic C), 159.2 (aromatic C-O). m/z (ESI) 345.1 (M^+ + Na); calc[d] for $C_{21}H_{22}O_3Na$ 345.1467, found 345.1482.

*6.4.1.3 Deprotection of **249** using DDQ*

The methods of Matta[217] and Oikawa[209] were adapted. 2-[2-(4-Methoxybenzyloxy)ethoxymethyl]-naphthalene **249** (252 mg, 0.786 mmol) was dissolved in a mixture of dichloromethane and methanol (9:1, 4 cm^3). 4,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) (533 mg, 2.34 mmol) was added and the reaction mixture stirred for one hour. After this time, the solvent was removed at reduced pressure, and the residue dissolved in dichloromethane (25 cm^3). The solid was washed with saturated aqueous sodium hydrogen carbonate solution (3 × 25 cm^3) and saturated aqueous sodium chloride solution (25 cm^3), before being dried over magnesium sulphate(VI) and filtered. The crude product was purified on silica gel, using hexane-ethoxyethane (4:1) as the elution solvent. The product was obtained as a pale yellow solid (51 mg, 36 %). T_m < 30 °C. R_f 0.118 (ethoxyethane-hexane 3:2). ν_{max}/cm^{-1} (solid) 3338 (br, m, OH), 3054 (w), 2923 (m), 2887 (m), 2849 (m), 597 (m, aromatic), 1506 (m), 1437 (w), 1361 (m), 1340 (m), 1249 (w), 1169 (m), 1120 (m), 1104 (s), 1064 (s), 1035 (s), 993 (m), 969 (w), 951 (m), 894 (s), 862 (s), 822 (s), 747 (s), 725 (m). Found C 77.08, H 6.99 %; $C_{13}H_{14}O_2$ requires C 77.20, H 6.98 %. δ_H ($CDCl_3$, 400.1 MHz) 2.02 (t, 1H, *J* = 6.0 Hz, OH), 3.63 (t, 2H, *J* = 4.0 Hz, C*H*$_2$CH$_2$OH), 3.77 (~ q, 2H, *J* = 4.0 Hz, C*H*$_2$OH), 4.72 (s, 2H, ArC*H*$_2$), 7.45 (m, 3H, aromatic H), 7.70 (br s, 1H, aromatic H), 7.80 – 7.84 (m, 3H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 62.0 (CH_2OH), 71.6 (*C*H$_2$CH$_2$OH), 73.6 (Ar*C*H$_2$), 125.7 (aromatic CH), 126.0 (aromatic CH), 126.2 (aromatic CH), 126.6 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.3 (aromatic CH), 133.1 (aromatic C), 133.3 (aromatic C), 135.5 (aromatic C). m/z (ESI) 225.1 (M^+ + Na); calc[d] for $C_{13}H_{14}O_2Na$ 225.0891, found 225.0898.

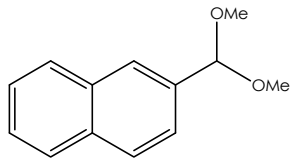
*6.4.1.4 Deprotection of **249** using CAN*

The methods of Davies[264] and Classon[213] were used. 2-[2-(4-Methoxybenzyloxy)ethoxymethyl]-naphthalene **249** (352 mg, 1.09 mmol) was dissolved in ethananitrile-methanol (9:1, 11 cm^3). Hexa-ammineceriumIV) nitrate(V) (CAN) (2.436 g, 4.44 mmol) was dissolved in the same solvent mixture (11 cm^3) and was added to the substrate over one hour using a syringe pump.

The reaction was stirred for 50 minutes, before being partitioned between ethoxyethane (25 cm^3) and hydrochloric acid (1 mol dm^{-3}, 25 cm^3). The layers were separated and the aqueous phase extracted with ethoxyethane (2 × 25 cm^3). The combined organic solutions were washed with hydrochloric acid (1 mol dm^{-3}, 2 × 40 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 40 cm^3) and saturated aqueous sodium chloride solution (2 × 40 cm^3). The solution was dried over magnesium sulphate(VI), filtered and evaporated at reduced pressure. Chromatography on silica gel (petroleum ethers-ethyl acetate 7:3) gave the product as a pale yellow solid (184 mg, 84 %), identical to that obtained *via* DDQ deprotection (section 6.4.1.3).

6.4.2 Synthesis of glucose-based deprotection substrates

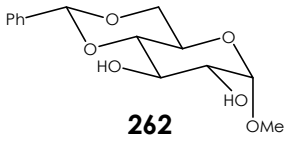
*6.4.2.1 2-(Dimethoxymethyl)naphthalene **280***



280

The method of Gaunt[225] was followed. Naphthalene-2-carbaldehyde (15.30 g, 98.0 mmol) was dissolved in trimethoxymethane (60 cm^3, 59 g, 0.55 mol), and the reaction vessel flushed with a stream of dry nitrogen. Amberlyst-15 ion-exchange resin (2.97 g) was added and the mixture stirred for one hour. The catalyst was removed by filtration and the excess trimethoxymethane removed at reduced pressure. The remaining volatile impurities were removed at 100 °C under vacuum (0.5 mm Hg), leaving the product as a yellow oil (19.09 g, 96 %). The product slowly decomposed upon storage to give the starting aldehyde. T_b 164 – 166 °C / 0.5 mm Hg. R_f 0.455 (petroleum ethers-ethyl acetate 4:1). ν_{max}/cm^{-1} (film) 2937 (w), 2830 (w), 1603 (w), 1510 (w), 1445 (w), 1341 (m), 1191 (m), 1171 (m), 1126 (m), 1100 (m), 1057 (m), 993 (w), 858 (w), 825 (w), 797 (w), 744 (w). Found C 77.49, H 6.95 %; $C_{13}H_{14}O_2$ requires C 77.20, H 6.98 %. δ_H ($CDCl_3$, 400.1 MHz) 3.40 (s, 6H, 2 × MeO), 5.58 (s, 1H, ArC*H*), 7.48 – 7.52 (m, 2H aromatic H), 7.59 (dd, 1H, J = 1.7, 8.4 Hz; aromatic H), 7.85 – 7.90 (m, 3H, aromatic H), 7.98 (br s, 1H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 52.6 (MeO), 103.1 (Ar*C*H), 124.3 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 127.6 (aromatic CH), 128.0 (aromatic CH), 128.2 (aromatic CH), 132.9 (aromatic C), 133.4 (aromatic C), 135.5 (aromatic C). m/z (EI) 171.1, 127.1, 155.1, 202.1 (M^+), 141.1, 186.1; calc[d] for $C_{13}H_{14}O_2$ (M^+) 202.0994, found 202.0997.

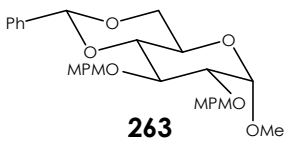
6.4.2.2 *4,6-O-Benzylidene-1-O-methyl-α-D-glucopyranoside or (4aR,6S,7R,8R,8aS)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol* **262**



262

The method of Wong *et al.*[265] was followed. Methyl-α-D-gluco-pyranoside **251** (19.99 g, 103 mmol) was dissolved in dry DMF (80 cm^3) under nitrogen. (Dimethoxymethyl)benzene (16.0 cm^3, 16.3 g, 107 mmol) and 4-methylbenzenesulphonic acid monohydrate (2.06 g, 10.8 mmol) were added, and the flask evacuated with a water-pump. The reaction was refluxed under vacuum at 60 °C for seventy minutes, then cooled and the solvent removed *in vacuo*. The resulting solid was dissolved in saturated aqueous sodium hydrogen carbonate solution (90 cm^3) at 100 °C, giving a yellow solution. The solution was cooled in ice, filtered, and the resulting solid washed with water (8 × 30 cm^3) and hexane (4 × 20 cm^3). The product was dried *in vacuo* over silica gel, giving the title compound as a white solid (19.08 g, 67 %). $[\alpha_D]$ +117.4 º ($CHCl_3$, *c* 1.065) (Lit.[266] 119 º, *c* 1.1). T_m 165 – 166 °C (Lit.[265] 164 – 165 ºC). ν_{max}/cm^{-1} (solid) 3353 (br, OH), 2930 (w), 1451 (w), 1371 (m), 1129 (w), 1075 (s), 1048 (m), 1033 (m), 997 (s), 930 (w), 890 (w), 744 (s), 694 (s). δ_H ($CDCl_3$, 400.1 MHz) 2.18 (d, 1H, *J* = 9.6 Hz, C^2H-O*H*), 2.59 (d, 1H, *J* = 2.0 Hz, C^3H-O*H*), 3.45 (2, 3H, MeO), 3.49 (app t, 1H, *J* = 8.8 Hz, C^4H), 3.62 (dt, 1H, *J* = 3.6, 9.2 Hz; C^2H), 3.73 (dd, 1H, *J* = 9.2, 11.0 Hz; one of C^6H_2), 3.80 (dt, 1H, *J* = 4.4, 10.0 Hz; C^5H), 3.92 (dt, 1H, *J* = 2.4, 10.0 Hz; C^3H), 4.28 (dd, 1H, *J* = 3.6, 9.2 Hz; one of C^6H_2), 4.79 (d, 1H, *J* = 3.6 Hz, C^1H), 5.52 (s, 1H, benzylidene C*H*), 7.33 – 7.37 (m, 3H, Ph), 7.46 – 7.49 (m, 2H, Ph). δ_C ($CDCl_3$, 100.6 MHz) 55.6 (MeO), 62.4 (C^5), 68.9 (C^6), 71.8 (C^3), 72.9 (C^2), 80.9 (C^4), 99.8 (C^1), 101.9 (benzylidene *C*H), 126.3 (aromatic CH), 128.3 (aromatic CH), 129.3 (aromatic CH), 137.0 (aromatic C). m/z (EI) 105.0, 282.1 (M^+), 179.1, 69.0, 119.0, 162.1; calc[d] for $C_{14}H_{18}O_6$ 282.1103, found 282.1105.

6.4.2.3 *4,6-O-Benzylidene-2,3-di-O-(4-methoxybenzyl)-1-O-methyl-α-D-glucopyranoside or (4aR,6S,7R,8S,8aR)-6-methoxy-7,8-bis(4-methoxybenzyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine* **263**

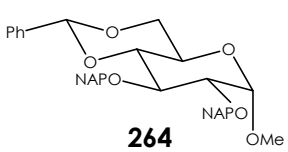


263

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 2.75 g, 68.8 mmol) was suspended in dry DMF (100 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 4,6-*O*-Benzylidene-1-*O*-methyl-α-D-glucopyranoside **262** (7.56 g, 26.8 mmol) was

dissolved in dry DMF (50 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was stirred at 0 °C for 1¼ hours, and then allowed to warm to room temperature, before the addition of 1-chloromethyl-4-methoxybenzene (8.00 cm^3, 9.24 g, 59.0 mmol) dropwise over 30 minutes. The reaction was allowed to stir overnight, before being partitioned between ethyl acetate (450 cm^3) and saturated aqueous sodium hydrogen carbonate solution (450 cm^3). Hydrochloric acid (1 mol dm^{-3}, 200 cm^3) was added, and the layers separated. The organic solution was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The solid product was then recrystallised from ethanol. The product was obtained as an off-white solid (11.84 g, 85 %). $[\alpha_D]$ -33.0 º ($CHCl_3$, *c* 1.50). T_m 98 – 101 ºC. δ_H ($CDCl_3$, 400.1 MHz) 3.38 (s, 3H, MeO), 3.51 (dd, 1H, *J* = 4.4, 9.6 Hz; C^2H), 3.56 (t, 1H, *J* = 9.2 Hz, C^4H), 3.69 (t, 1H, *J* = 10.2 Hz, one of C^6H_2), 3.78 (s, 3H, MeO of MPM), 3.80 (s, 3H, MeO of MPM), 3.82 (m, 1H, C^5H), 4.00 (t, 1H, *J* = 9.2 Hz, C^3H), 4.25 (dd, 1H, *J* = 4.8, 10.2 Hz; one of C^6H_2), 4.52 (d, *J* = 3.6 Hz, C^1H), 4.62 (d, 1H, *J* 12.4 Hz, one of ArCH_2), 4.75(d, 1H, *J* = 10.8 Hz, one of ArCH_2), 4.78 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.82 (d, 1H, *J* = 10.8 Hz, one of ArCH_2), 5.53 (s, 1H, benzylidene CH), 6.86 (d, 2H, *J* = 9.0 Hz, MPM group CH pair), 7.26 (d, 2H, *J* = 6.4 Hz, MPM group CH pair), 7.30 (d, 2H, *J* = 9.0 Hz, MPM group CH pair), 7.35 – 7.39 (m, 3H, Ph), 7.47 – 7.49 (m, 2H, Ph), 8.80 (d, 2H, *J* = 6.4 Hz, MPM group CH pair). δ_C ($CDCl_3$, 100.6 MHz) 55.3 (MeO), 55.3 (MeO), 55.3 (MeO), 62.3 (C^5), 69.1 (C^6), 73.4 (ArCH_2), 75.0 (ArCH_2), 78.3 (C^3H), 78.7 (C^2H), 82.1 (C^4H), 99.3 (C^1), 101.2 (benzylidene CH), 113.7 (aromatic CH), 113.8 (aromatic CH), 126.0 (aromatic CH), 128.2 (aromatic CH), 128.9 (aromatic CH), 129.7 (aromatic CH), 129.7 (aromatic CH), 130.3 (aromatic C), 130.7 (aromatic C), 137.5 (aromatic C), 159.4 (aromatic C-O), 159.2 (aromatic C-O). m/z (EI) 121.0, 401.2, 151.0, 233.0, 265.0, 341.1, 522.2 (M^+); calc[d] for $C_{30}H_{34}O_8$ 522.2254, found 522.2246.

6.4.2.4 *4,6-O-Benzylidene-2,3-di-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (4aR,6S,7R,8S,8aR)-6-methoxy-7,8-bis(naphthalen-2-ylmethoxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine* **264**

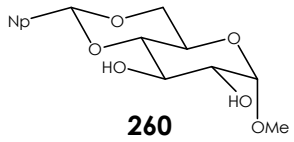


264

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 2.12 g, 52.9 mmol) was suspended in dry

DMF (50 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 4,6-*O*-Benzylidene-1-*O*-methyl-α-D-glucopyranoside **262** (5.94 g, 21.0 mmol) was dissolved in dry DMF (90 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was allowed to warm to room temperature over 50 minutes, before the addition of 2-(bromomethyl)-naphthalene (10.1 g, 45.9 mmol) in portions over 30 minutes. The reaction was allowed to stir overnight, before being poured into hydrochloric acid (1 mol dm^{-3}, 100 cm^3). The mixture was extracted with ethyl acetate (2 × 100 cm^3), and the combined organic solutions washed with hydrochloric acid (1 mol dm^{-3}, 2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The solid product was then recrystallised from ethanol. The product was obtained as a white solid (9.41 g, 80 %). $[\alpha_D]$ -60.8 ° ($CHCl_3$, *c* 0.98). T_m 123 – 126 °C. ν_{max}/cm^{-1} (solid) 2861 (w), 1612 (w), 1512 (w), 1247 (w), 1091 (w), 1035 (w), 816 (w), 751 (w). Found C 76.87, H 6.15 %; $C_{36}H_{34}O_6$ requires C 76.85, H 6.09 %. δ_H ($CDCl_3$, 400.1 MHz) 3.40 (s, 3H, MeO), 3.63 (m, 2H, C^2H and C^4H), 3.69 (d, 1H, *J* = 10.0 Hz, one of C^6H_2), 3.84 (dt, 1H, *J* = 4.5, 10.0 Hz; C^5H), 4.11 (~ t, 1H, *J* = 9.5 Hz, C^3H), 4.24 (dd, 1H, *J* = 4.5, 10.0 Hz; one of C^6H_2), 4.61 (d, *J* = 4.0 Hz, C^1H), 4.87 (d, 1H, *J* = 12.0 Hz, one of $ArCH_2$), 5.00 (d, 1H, *J* = 12.0 Hz, one of $ArCH_2$), 5.00 (d, 1H, *J* = 11.5 Hz, one of $ArCH_2$), 5.07 (d, 1H, *J* = 11.5 Hz, one of $ArCH_2$), 5.55 (s, 1H, benzylidene CH), 7.34 – 7.50 (m, 11H, aromatic H), 7.66 – 7.80 (m, 8H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.3 (MeO), 62.3 (C^5), 69.0 (C^6), 73.8 ($ArCH_2$), 75.4 ($ArCH_2$), 78.6 ($C^2H/C^3H/C^4H$), 79.2 ($C^2H/C^3H/C^4H$), 82.1 ($C^2H/C^3H/C^4H$), 99.2 (C^1), 101.4 (benzylidene CH), 125.7 (aromatic CH), 125.9 (aromatic CH), 126.0 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 126.1 (aromatic CH), 126.2 (aromatic CH), 126.6 (aromatic CH), 127.0 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH), 128.2 (aromatic CH), 128.3 (aromatic CH), 128.9 (aromatic CH), 133.0 (aromatic C), 133.1 (aromatic C), 133.2 (aromatic C), 133.3 (aromatic C), 135.5 (aromatic C), 136.2 (aromatic C), 137.4 (aromatic C). m/z (EI) 141.1, 171.1, 421.2, 562.2 (M^+); calc[d] for $C_{36}H_{34}O_6$ 562.2355, found 562.2360.

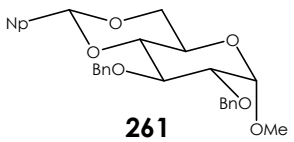
6.4.2.5 4,6-O-(Naphthalene-2-yl)methylene-1-O-methyl-α-D-glucopyranoside or (4aR,6S,7R,8R,8aS)-6-methoxy-2-naphthalen-2-ylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol **260**



260

The method of Wong *et al.*[265] was followed. 2-(Dimethoxymethyl)-naphthalene **280** (10.12 g, 50.0 mmol) was dissolved in dry DMF (40 cm^3) under nitrogen. Methyl-α-D-glucopyranoside **251** (9.71 g, 50.0 mmol) and 4-methylbenzenesulphonic acid monohydrate (0.987 g, 5.20 mmol) were added, and the reaction vessel evacuated with a water-pump. The reaction was refluxed under vacuum at 60 °C for one hour, then cooled to room temperature and the solvent removed at reduced pressure. The residue was dissolved in boiling saturated aqueous sodium hydrogen carbonate solution (50 cm^3). The solution was cooled in ice, filtered, and the resulting solid washed with saturated aqueous sodium hydrogen carbonate solution and hexane. The product was dried *in vacuo* over silica gel, giving the title compound as an off-white solid (13.00 g, 78 %). $[\alpha_D]$ +99.0 ° ($CHCl_3$, *c* 1.01) (Lit.[227] + 99.30 °, *c* 0.50). T_m 189 – 191 °C (Lit.[227] 194 °C). ν_{max}/cm^{-1} (solid) 3440 (br, OH), 2936 (w), 1364 (w), 1127 (m), 1076 (s), 1028 (s), 999 (s), 926 (m), 895 (m), 826 (m), 794 (m), 745 (m), 677 (w). Found C 64.81, H 6.04 %; $C_{18}H_{20}O_6$ requires C 65.05, H 6.07 %. δ_H ($CDCl_3$, 400.1 MHz) 2.44 (br d, 1H, *J* = 8.8 Hz, C^2H-O*H*), 2.98 (br s, 1H, C^3H-O*H*), 3.44 (s, 3H, MeO), 3.51 (app t, 1H, *J* = 9.4 Hz, C^4H), 3.62 (m, 1H, C^2H), 3.78 (app q, 1H, *J* = 10.0 Hz, one of C^6H_2), 3.83 (dt, 1H, *J* = 4.8, 10.0 Hz; C^5H), 3.95 (t, 1H, *J* = 9.4 Hz, C^3H), 4.32 (dd, 1H, *J* = 4.8, 9.6 Hz; one of C^6H_2), 4.78 (d, 1H, *J* = 4.0 Hz, C^1H), 5.67 (s, 1H, benzylidene CH), 7.47 – 7.50 (m, 2H, aromatic H), 7.60 (dd, 1H, *J* = 2.0, 8.8 Hz; aromatic H), 7.82 – 7.87 (m, 3H, aromatic H), 7.90 (s, 1H, aromatic H). δ_C ($CDCl_3$, 100.1 MHz) 55.5 (MeO), 62.4 (C^5), 69.0 (C^6), 71.7 (C^3), 72.9 (C^2), 81.0 (C^4), 99.8 (C^1), 102.0 (benzylidene CH), 123.8 (aromatic CH), 125.9 (aromatic CH), 126.2 (aromatic CH), 126.5 (aromatic CH), 127.7 (aromatic CH), 128.2 (aromatic CH), 128.4 (aromatic CH), 132.9 (aromatic C), 133.8 (aromatic C), 134.4 (aromatic C). m/z (EI) 332.1 (M^+), 131.0, 69.0; calc[d] for $C_{18}H_{20}O_6$ 332.126, found 332.1261.

6.4.2.6 *2,3-Di-O-benzyl-4,6-O-(naphthalene-2-yl)methylene-1-O-methyl-α-D-glucopyranoside or (4aR,6S,7R,8S,8aR)-7,8-bis(benzyloxy)-6-methoxy-2-naphthalen-2-yl-hexahydropyrano[3,2-d][1,3]dioxine* ***261***

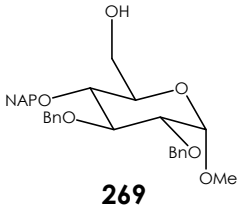


261

The method of Chida *et al.*[263] was used. Sodium hydride (60 % suspension in mineral oil, 1.81 g, 45.3 mmol) was suspended in dry DMF (50 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 4,6-*O*-(Naphthalene-2-yl)methylene-1-*O*-methyl-α-D-glucopyranoside **260** (6.00 g, 18.0 mmol) was dissolved in dry DMF (100 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was allowed to warm to room temperature over one hour, before the addition of (bromomethyl)benzene (4.70 cm^3, 6.77 g, 39.6 mmol) over one hour using a syringe-pump. The reaction was allowed to stir overnight, before being poured into hydrochloric acid (1 mol dm^{-3}, 100 cm^3). The mixture was extracted with ethyl acetate (3 × 100 cm^3), and the combined organic solutions washed with hydrochloric acid (1 mol dm^{-3}, 2 × 100 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed *in vacuo*. The solid product was then recrystallised from ethanol. The product was obtained as an off-white solid (5.87 g, 64 %). $[\alpha_D]$ -44.3 ° ($CHCl_3$, *c* 1.075) (Lit.[228] -54.8 °, $CHCl_3$, *c* 0.33). T_m 105 – 110 °C (Lit.[228] 118 – 119 °C). ν_{max}/cm^{-1} (solid) 2901 (w), 1367 (w), 1342 (w), 1175 (m), 1108 (m), 1078 (s), 1051 (m), 1003 (m), 977 (m), 865 (m), 830 (m), 744 (m), 729 (s), 696 (m). Found C 75.19, H 6.41 %; $C_{32}H_{32}O_6$ requires C 74.98, H 6.29 %. δ_H ($CDCl_3$, 400.1 MHz) 3.43 (s, 3H, MeO), 3.59 (dd, 1H, *J* = 3.6, 13.2 Hz; C^2H), 3.68 (t, 1H, *J* = 9.2 Hz, C^4H), 3.78 (t, 1H, *J* = 10.4 Hz, one of C^6H_2), 3.89 (dt, 1H, *J* = 4.8, 10.0 Hz; C^5H), 4.10 (t, 1H, *J* = 9.2 Hz, C^3H), 4.33 (dd, 1H, *J* = 5.2, 10.0 Hz; one of C^6H_2), 4.62 (d, 1H, *J* = 4.8 Hz, C^1H), 4.73 (d, 1H, *J* = 12.0 Hz, one of benzyl CH_2), 4.88 (d, 1H, *J* = 12.0 Hz, one of benzyl CH_2), 4.88 (d, 1H, *J* = 10.4 Hz, one of benzyl CH_2), 4.93 (d, 1H, *J* = 10.4 Hz, one of benzyl CH_2), 5.70 (s, 1H, methylidene CH), 7.27 – 7.42 (m, 10 H, aromatic H), 7.47 – 7.53 (m, 2H, aromatic H), 7.60 (dd, 1H, *J* = 1.6, 7.2 Hz; aromatic), 7.85 – 7.88 (m, 3H, aromatic H), 7.99 (br s, 1H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.4 (MeO), 62.4 (C^5), 69.2 (C^6), 73.8 (benzyl CH_2), 75.3 (benzyl CH_2), 79.3 (C^3), 79.7 (C^2), 82.3 (C^4), 99.3 (C^1), 101.5 (Np-*C*H), 123.8 (aromatic CH), 125.4 (aromatic CH), 126.1 (aromatic CH), 126.4 (aromatic CH),

127.6 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH), 128.1 (aromatic CH), 128.3 (aromatic CH), 128.4 (aromatic CH), 128.5 (aromatic CH), 128.6 (aromatic CH), 132.9 (aromatic C), 133.6 (aromatic C), 134.8 (aromatic C), 138.2 (aromatic C), 138.8 (aromatic C). m/z (EI) 142.0, 421.2, 248.0, 512.2 (M^+), 91.1; calc[d] for $C_{32}H_{32}O_6$ 512.2199, found 512.2199.

6.4.2.7 2,3-Di-O-benzyl-4-O-(naphthalene-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or [(2R,3R,4S,5R,6S)-4,5-bis(benzyloxy)-6-methoxy-3-(naphthalen-2-ylmethoxy)tetrahydropyran-2-yl]methanol **269**



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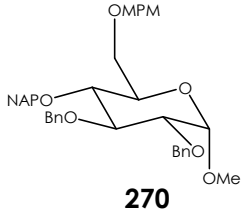
The method of Gaunt[225] was used. 2,3-Di-*O*-benzyl-4,6-*O*-(naphthalene-2-yl)methylene-1-*O*-methyl-α-D-glucopyranoside **261** (2.30 g, 4.49 mmol) was dissolved in dry dichloromethane (20 cm^3) under nitrogen. The solution was cooled to 0 °C, before the dropwise addition of hydridodi(1-methylpropyl)aluminium (1 mol dm^{-3} in methylbenzene, 20 cm^3, 20 mmol) over 30 minutes. The reaction was warmed to room temperature and stirred for 2¾ hours. After this time, a mixture of methanol (10 cm^3) and methylbenzene (10 cm^3) was added dropwise to the reaction[267]. The resulting gelatinous system was mixed with water (50 cm^3) and vigorously stirred for 30 minutes in order to break up the gel. The reaction mixture was extracted with ethyl acetate (100 cm^3), and the organic solution washed with saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI) and filtered. The crude product was purified by chromatography on silica, using petroleum ethers-ethyl acetate 3:2 as the elution solvent. The product was obtained as a white solid (1.39 g, 60 %). $[\alpha_D]$ +0.1 ° ($CHCl_3$, *c* 1.065). T_m range 66 – 74 °C. ν_{max}/cm^{-1} (solid) 3328 (br, w, O-H), 2916 (w), 1497 (w), 1452 (w), 1356 (w), 1326 (w), 1101 (m), 1057 (s), 1026 (s), 996 (s), 910 (m), 852 (m), 812 (m), 731 (s), 695 (s). Found C 74.47, H 6.69 %; $C_{32}H_{34}O_6$ requires C 74.69, H 6.66 %. δ_H ($CDCl_3$, 400.1 MHz) 1.70 (br s, 1H, OH), 3.36 (s, 3H, MeO), 3.51 (dd, 1H, *J* = 3.2, 9.6 Hz; C^2H), 3.57 (dd, 1H, *J* = 9.2, 9.2 Hz; C^4H), 3.66 – 3.74 (m, 2H, C^5H and one of C^6H_2), 3.78 – 3.81 (m 1H, one of C^6H_2), 4.03 (dd, 1H, *J* = 9.2, 9.6 Hz; C^3H), 4.57 (d, 1H, *J* = 3.2 Hz, C^1H), 4.66 (d, 1H, *J* = 11.6 Hz, one of $ArCH_2$), 4.80 (d, 1H, *J* = 11.6 Hz, one of $ArCH_2$), 4.80 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 4.85 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 5.00 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 5.02 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 7.27 – 7.40 (m, 11H, aromatic H), 7.44 – 7.46 (m, 2H, aromatic H), 7.70 (br s, 1H, aromatic H), 7.76 – 7.80 (m, 3H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 62.0 (C^6),

70.7 (C^5), 73.4 (one of Ar*C*H_2), 75.1 (one of Ar*C*H_2), 75.7 (one of Ar*C*H_2), 77.5 (C^4), 80.0 (C^2), 82.0 (C^3), 98.2 (C^1), 125.9 (aromatic CH), 125.9 (aromatic CH), 126.1 (aromatic CH), 126.7 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.1 (aromatic CH), 128.2 (aromatic CH), 128.4 (aromatic CH), 128.5 (aromatic CH), 133.0 (aromatic C), 133.3 (aromatic C), 135.6 (aromatic C), 138.1 (aromatic C), 138.8 (aromatic C). m/z (EI) 91.0, 141.0, 423.2, 175.1, 247.1, 482.2, 514.2 (M^+), 303.1; calc[d] for $C_{32}H_{34}O_6$ 514.2355, found 514.2378.

6.4.2.8 *2,3-Di-O-benzyl-6-O-(4-methoxybenzyl)-4-O-(naphthalene-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (2S,3R,4S,5R,6R)-3,4-Bis(benzyloxy)-2-methoxy-6-(4-methoxybenzyloxymethyl)-5-(naphthalen-2-ylmethoxy)tetrahydropyran* ***270***

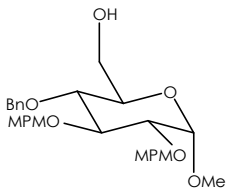


270

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 218 mg, 5.44 mmol) was suspended in dry DMF (15 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 2,3-Di-*O*-benzyl-4-*O*-(naphthalene-2-yl)methyl-1-*O*-methyl-α-D-gluco-pyranoside **269** (2.20 g, 4.28 mmol) was dissolved in dry DMF (30 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was stirred for one hour at 0 °C, then allowed to warm to room temperature, before the addition of 1-chloromethyl-4-methoxybenzene (0.640 cm^3, 0.737 g, 4.70 mmol) over one hour using a syringe-pump. The reaction was allowed to stir overnight, after which time TLC analysis (petroleum ethers-ethyl acetate 3:2) showed that the reaction had not reached completion. Sodium hydride (60 % suspension in mineral oil, 100 mg, 2.5 mmol) and 1-chloromethyl-4-methoxybenzene (0.320 cm^3, 368 mg, 2.35 mmol) were added, and the reaction was allowed to stir overnight. The reaction mixture was diluted with ethyl acetate (50 cm^3), and washed with hydrochloric acid (1 mol dm^{-3}, 2 × 25 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 25 cm^3) and saturated aqueous sodium chloride solution (2 × 25 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel, using petroleum ethers-ethyl acetate 3:2 as the elution solvent. The title compound was obtained as an off-white solid (2.23 g, 82 %). $[\alpha_D]$ +5.1 ° ($CHCl_3$, *c* 2.020). ν_{max}/cm^{-1} (solid) 2814 (w), 1609 (w), 1511 (m), 1454 (m), 1356 (m), 1246 (s), 1110 (s), 1067 (s), 1046 (s), 1028 (s), 950 (m), 828 (s), 730 (s), 696 (s). δ_H ($CDCl_3$, 400.1 MHz) 3.37 (s, 3H, OMe), 3.56 (dd, 1H, *J* = 3.6, 9.6 Hz; C^2H), 3.60 (dd, 1H, *J* = 9.4, 10.0 Hz; C^4H), 3.67 – 3.72 (m, 2H, C^6H_2), 3.72 - 3.76 (m, 1H, C^5H), 3.67 (s, 3H, MPM

OMe), 3.98 (dd, 1H, *J* = 9.2, 9.2 Hz; C^3H), 4.35 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.55 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.55 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.62 (d, 1H, *J* = 3.6 Hz, C^1H), 4.65 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.78 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.81 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.93 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.98 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 6.77 (d, 2H, *J* = 8.4 Hz, aromatic H), 7.20 (d, 2H, *J* = 8.4 Hz, aromatic H), 7.24 – 7.35 (m, 11H, aromatic H), 7.44 (m, 2H, aromatic H), 7.51 (br s, 1H, aromatic H), 7.71 (d, 2H, *J* = 7.6 Hz, aromatic H), 7.78 (t, 1H, *J* = 5.0 Hz, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.5 (MeO), 55.2 (MeO), 67.9 (C^6), 70.1 (C^5), 73.1 (one of ArCH_2), 73.4 (one of ArCH_2), 75.0 (one of ArCH_2), 75.7 (one of ArCH_2), 77.6 (C^4), 79.8 (C^2), 82.2 (C^3), 98.3 (C^1) , 113.7 (aromatic CH), 125.8 (aromatic CH), 126.0 (aromatic CH), 126.4 (aromatic CH), 127.5 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH), 128.1(aromatic CH), 128.4 (aromatic CH), 128.4 (aromatic CH), 129.6 (aromatic CH), 129.9 (aromatic C), 132.9 (aromatic C), 133.2 (aromatic C), 135.8 (aromatic C), 138.2 (aromatic C), 138.9 (aromatic C), 159.2 (aromatic *C*-O). m/z (EI) calc[d] for $C_{40}H_{42}O_7Na$ (M^+ + Na) 657.2828, found 657.2850.

6.4.2.9 *4-O-Benzyl-2,3-di-O-(4-methoxybenzyl)-1-O-methyl-α-D-glucopyranoside or [(2R,3R,4S,5R,6S)-3-benzyloxy-6-methoxy-4,5-bis(4-methoxybenzyloxy)tetrahydropyran-2-yl]methanol* ***265***

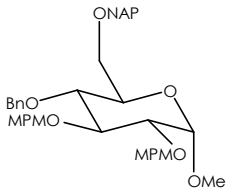


265

The method of Gaunt[225] was used. 4,6-*O*-Benzylidene-2,3-di-*O*-(4-methoxybenzyl)-1-*O*-methyl-α-D-glucopyranoside **263** (2.10 g, 4.01 mmol) was dissolved in dry dichloromethane (20 cm^3). The solution was cooled to 0 °C, before the dropwise addition of di(1-methylpropyl)aluminium hydride (1 mol dm^{-3} in methylbenzene, 20 cm^3, 20 mmol) over 30 minutes. The reaction was warmed to room temperature and stirred for 3 hours 20 minutes. After this time, a mixture of methanol (10 cm^3) and methylbenzene (10 cm^3) was added dropwise. The resulting gelatinous system was mixed with water (50 cm^3) and vigorously stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate (100 cm^3), and the organic solution washed with saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI) and filtered. The crude product was purified by chromatography on silica gel, using petroleum ethers-ethyl acetate 3:2, giving **265** as a white solid (1.09 g, 52 %). R_f 0.260 (petroleum ethers-ethyl acetate 3:2). δ_H ($CDCl_3$, 400.1 MHz) 1.68 (t, 1H, *J* = 6.5 Hz, OH), 3.34 (s, 3H, MeO), 3.45 (dd, 1H, *J* = 3.5, 9.5 Hz; C^2H), 3.74 (dd, 1H, *J* = 9.5, 9.5 Hz; C^4H), 3.58 – 3.64 (m, 1H, C^5H),

3.58 – 3.76 (m, 2H, C^6H_2), 3.78 (d, 3H, MeO), 3.79 (s, 3H, MeO), 3.96 (dd, 1H, *J* = 9.0, 9.0 Hz; C^3H), 4.51 (d, 1H, *J* = 3.5 Hz, C^1H), 4.58 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.62 (d, 1H, *J* = 11.0 Hz, one of ArCH_2), 4.73 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.74 (d, 1H, *J* = 10.5 Hz, one of ArCH_2), 4.87 (d, 1H, *J* = 11.0 Hz, one of ArCH_2), 4.89 (d, 1H, *J* = 10.5 Hz, one of ArCH_2), 6.84 (~ d, 2H, *J* = 8.8 Hz, aromatic CH), 6.85 (~ d, 2H, *J* = 8.8 Hz, aromatic CH), 7.24 – 7.32 (m, 9H, aromatic CH). δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 55.3 (MeO), 55.3 (MeO), 61.9 (C^6), 70.7 (C^5), 73.1 (one of ArCH_2), 75.0 (one of ArCH_2), 75.4 (one of ArCH_2), 77.5 (C^2), 79.7 (C^4), 81.7 (C^3), 98.3 (C^1), 113.8 (aromatic CH), 113.9 (aromatic CH), 127.8 (aromatic CH), 128.0 (aromatic CH), 128.5 (aromatic CH), 129.6 (aromatic CH), 129.7 (aromatic CH), 130.3 (aromatic C), 131.0 (aromatic C), 138.2 (aromatic C), 159.2 (aromatic C), 159.4 (aromatic C). m/z (ESI) 547.2 (M^+ + Na), 425.2; calc[d] for $C_{30}H_{36}O_8Na$ 547.2308, found 547.2316.

6.4.2.10 4-O-Benzyl-2,3-di-O-(4-methoxybenzyl)-6-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (2R,3R,4S,5R,6S)-3-Benzyloxy-6-methoxy-4,5-bis(4-methoxybenzyloxy)-2-(naphthalen-2-ylmethoxymethyl)tetrahydropyran **266**

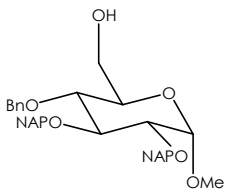


266

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 160 mg, 3.99 mmol) was suspended in dry DMF (10 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 4-*O*-Benzyl-2,3-di-*O*-(4-methoxybenzyl)-1-*O*-methyl-α-D-glucopyranoside **265** (1.65 g, 3.16 mmol) was dissolved in dry DMF (20 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was stirred for 1½ hours at 0 °C, then allowed to warm to room temperature, before the addition of 2-(bromomethyl)naphthalene (702 mg, 3.18 mmol). The reaction was allowed to stir overnight, before being diluted with ethyl acetate (50 cm^3). The reaction solution was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 20 cm^3) and saturated aqueous sodium chloride solution (2 × 20 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel, using methylbenzene-ethyl acetate 9:1 as the elution solvent. The title compound was obtained as a yellow oil (845 mg, 40 %). T_m 69 – 72 °C. R_f 0.350 (methylbenzene-ethyl acetate 9:1). $[\alpha_D]$ -1.4 (*c* 1.555, $CHCl_3$). δ_H ($CDCl_3$, 400.1 MHz) 3.37 (s, 3H, MeO), 3.53 (dd, 1H, *J* = 3.6, 10.0 Hz; C^2H), 3.60 (app t, 1H, *J* = 9.2 Hz, C^4H), 3.65 – 3.68 (m, 1H, one of C^6H_2), 3.72 – 3.75 (m, 1H, one of C^6H_2), 3.72 – 3.75 (m, 1H, C^5H),

3.79 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.95 (dd, 1H, *J* = 9.2, 10.0 Hz; C^3H), 4.42 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.58 (d, 1H, *J* = 3.2 Hz, C^1H), 4.60 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.62 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.73 (d, 1H, *J* = 10.8 Hz, one of ArCH_2), 4.74 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.76 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.81 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.89 (d, 1H, *J* = 10.8 Hz, one of ArCH_2), 6.84 (d, 2H, *J* = 8.4 Hz, MPM CH), 6.87 (d, 2H, *J* = 8.4 Hz, MPM CH), 7.01 (m, 2H, aromatic CH), 7.13 – 7.19 (m, 3H, aromatic CH), 7.25 (d, 2H, *J* = 8.4 Hz, MPM CH), 7.29 (d, 2H, *J* = 8.4 Hz, MPM CH), 7.43 – 7.47 (m, 3H, aromatic CH), 7.75 – 7.83 (m, 4H, aromatic CH). δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 55.3 (MeO), 68.5 (C^6), 70.1 (C^5), 73.0 (benzyl CH_2), 73.6 (benzyl CH_2), 75.0 (benzyl CH_2), 75.4 (benzyl CH_2), 77.7 (C^4), 79.6 (C^2), 81.9 (C^3), 98.3 (C^1), 113.8 (aromatic CH), 113.9 (aromatic CH), 125.9 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 126.7 (aromatic CH), 127.4 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.4 (aromatic CH), 129.0 (aromatic CH), 129.6 (aromatic CH), 129.7 (aromatic CH), 130.4 (aromatic C), 131.1 (aromatic C), 133.0 (aromatic C), 133.2 (aromatic C), 135.4 (aromatic C), 138.2 (aromatic C), 159.2 (aromatic C-O), 159.4 (aromatic C-O). m/z (EI+) calc[d] for $C_{41}H_{44}O_8Na$ (M^+ + Na) 687.2934, found 687.2929.

6.4.2.11 *4-O-Benzyl-2,3-di-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or [(2R,3R,4S,5R,6S)-3-benzyloxy-6-methoxy-4,5-bis(naphthalen-2-ylmethoxy)tetrahydropyran-2-yl]methanol* **267**

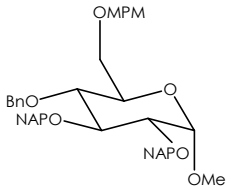


267

The method of Gaunt[225] was used. 4,6-*O*-Benzylidene-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-glucopyranoside **264** (2.25 g, 4.00 mmol) dissolved in dry dichloromethane (20 cm^3). The solution was cooled to 0 °C, before the dropwise addition of di(1-methylpropyl)aluminium hydride (1 mol dm^{-3} in methylbenzene, 20 cm^3, 20 mmol) over 30 minutes. The reaction was warmed to room temperature and stirred for 5 hours. After this time, a mixture of methanol (10 cm^3) and methylbenzene (10 cm^3) was added dropwise. The resulting gelatinous system was mixed with water (50 cm^3) and vigorously stirred for 30 minutes. The reaction mixture was extracted with ethyl acetate (100 cm^3), and the organic solution washed with saturated aqueous sodium hydrogen carbonate solution (2 × 100 cm^3) and saturated aqueous sodium chloride solution (2 × 100 cm^3). The organic solution was dried over magnesium sulphate(VI) and filtered. The crude product was purified by chromatography on silica gel, using petroleum ethers-ethyl acetate 3:2, giving **267** as a sticky and viscous oil (1.54 g, 68 %). $[\alpha_D]$ -10.7 ° ($CHCl_3$, *c* 1.075). T_m 75 – 78 °C. R_f 0.180 (petroleum ethers-ethyl acetate 3:2). ν_{max}/cm^{-1}

(solid) 3370 (br, w), 2919 (w), 1509 (w), 1454 (w), 1362 (w), 1159 (m), 1048 (s), 815 (s), 743 (s), 695 (s). δ_H ($CDCl_3$, 400.1 MHz) 1.71 (br s, 1H, OH), 3.40 (s, 3H, MeO), 3.58 (dd, 1H, *J* = 9.4, 9.4 Hz; C^4H), 3.60 (dd, 1H, *J* = 3.6, 9.2 Hz; C^2H), 3.68 – 3.73 (m, 2H, C^5H and one of C^6H), 3.78 – 3.80 (m, 1H, one of C^6H), 4.11 (dd, 1H, *J* = 9.4, 9.4 Hz; C^3H), 4.63 (d, 1H, *J* = 3.6 Hz, C^1H), 4.68 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 4.87 (d, 1H, *J* = 12.0 Hz, one of $ArCH_2$), 4.93 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 4.97 (d, 1H, *J* = 12.0 Hz, one of $ArCH_2$), 5.03 (d, 1H, *J* = 11.0 Hz, one of $ArCH_2$), 5.19 (d, 1H, *J* = 11.0 Hz, one of $ArCH_2$), 7.29 (br s, 5H, Ph), 7.45 – 7.53 (m, 6H, aromatic CH), 7.73 – 7.84 (m, 8H, aromatic CH). δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 61.8 (C^6), 70.7 (C^5), 73.5 (one of $ArCH_2$), 75.0 (one of $ArCH_2$), 75.7 (one of $ArCH_2$), 77.4 (C^2), 79.9 (C^4), 82.0 (C^3), 98.1 (C^1), 125.8 (aromatic CH), 126.0 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 126.5 (aromatic CH), 127.0 (aromatic CH), 127.6 (aromatic CH), 127.8 (aromatic CH), 127.9 (aromatic CH), 128.1 (aromatic CH), 128.3 (aromatic CH), 128.4 (aromatic CH), 132.9 (aromatic C), 133.1 (aromatic C), 133.3 (aromatic C), 135.5 (aromatic C), 136.3 (aromatic C), 137.1 (aromatic C). m/z (ESI) 547.2 (M^+ + Na), 425.2, 522.4 (M^+); calc[d] for $C_{30}H_{36}O_8$ 547.2308, found 547.2316.

6.4.2.12 *4-O-Benzyl-6-O-(4-methoxybenzyl)-2,3-di-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (2R,3R,4S,5R,6S)-3-benzyloxy-6-methoxy-2-(4-methoxybenzyloxymethyl)-4,5-bis(naphthalen-2-ylmethoxy)tetrahydropyran* **268**

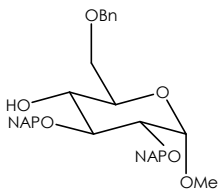


268

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 140 mg, 3.49 mmol) was suspended in dry DMF (10 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 4-*O*-Benzyl-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-gluco-pyranoside **267** (1.51 g, 2.68 mmol) was dissolved in dry DMF (35 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was stirred for 1 hour at 0 °C, then allowed to warm to room temperature, before the addition of 1-chloromethyl-4-methoxybenzene (0.400 cm^3, 0.462 mg, 2.95 mmol). The reaction was allowed to stir overnight, after which time TLC analysis (petroleum ethers-ethyl acetate 3:2) showed that the reaction had not reached completion. Sodium hydride (60 % suspension in mineral oil, 68.6 mg, 1.72 mmol) was added, and the reaction stirred for 30 minutes before the addition of 1-chloromethyl-4-methoxybenzene (0.200 cm^3, 232 mg, 1.48 mmol). The reaction was allowed to stir overnight, before being diluted with ethyl acetate (100 cm^3). The reaction solution was washed with

hydrochloric acid (1 mol dm^{-3}, 2 × 50 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 50 cm^3) and saturated aqueous sodium chloride solution (2 × 50 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel, using petroleum ethers-ethyl acetate 3:2 as the elution solvent. The title compound was obtained as a yellow oil (1.26 g, 69 %). $[\alpha_D]$ – 14.5 º ($CHCl_3$, *c* 1.05). R_f 0.500 (petroleum ethers-ethyl acetate 3:2). ν_{max}/cm^{-1} (solid) 2903 (w), 1510 (w), 1049 (s), 816 (s), 745 (s), 696 (s). δ_H ($CDCl_3$, 400.1 MHz) 3.40 (s, 3H, MeO), 3.60 (dd, 1H, *J* = 2.0, 10.4 Hz; one of C^6H_2), 3.65 (dd, 1H, *J* = 3.6, 9.2 Hz; C^2H), 3.65 (dd, 1H, *J* = 0.0, 9.4 Hz; C^4H), 3.70 (dd, 1H, *J* = 3.6, 10.4 Hz; one of C^6H_2), 3.74 (s, 3H, MeO), 3.76 – 3.81 (m, 1H, C^5H), 4.06 (dd, 1H, *J* = 9.4, 9.4 Hz; C^3H), 4.39 (d, 1H, *J* = 11.6 Hz, one of ArCH_2), 4.45 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.55 (d, 1H, *J* = 11.6 Hz, one of ArCH_2), 4.67 (d, 1H, *J* = 3.6 Hz, C^1H), 4.83 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.86 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.95 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.99 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 5.16 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 6.82 (d, 2H, *J* = 8.4 Hz, MPM CH), 7.09 – 7.11 (m, 2H, aromatic CH), 7.22 – 7.25 (m 5H, aromatic CH), 7.44 – 7.51 (m, 6H, aromatic CH), 7.71 – 7.83 (m, 8H, aromatic CH). δ_C ($CDCl_3$, 100.6 MHz) 55.2 (MeO), 65.9 (C^6), 70.1 (C^5), 73.1 (one of ArCH_2), 73.4 (one of ArCH_2), 75.0 (one of ArCH_2), 75.7 (one of ArCH_2), 77.7 (C^2 or C^4), 79.8 (C^2 or C^4), 82.1 (C^3), 98.2 (C^1), 113.7 (MPM CH), 125.7 (aromatic CH), 125.9 (aromatic CH), 125.9 (aromatic CH), 126.0 (aromatic CH), 126.4 (aromatic CH), 127.0 (aromatic CH), 127.6 (aromatic CH), 127.6 (aromatic CH), 125.7 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH),129.4 (aromatic CH), 129.6 (aromatic CH), 129.9 (aromatic CH), 132.9 (aromatic C),133.1 (aromatic C),133.2 (aromatic C),133.3 (aromatic C), 135.6 (aromatic C), 136.4 (aromatic C), 138.3 (aromatic C), 159.2 (aromatic C-O). m/z (ESI) 598.4, 707.3 (M^+ + Na), 698.6 (M^+); calc[d] for $C_{44}H_{44}O_7Na$ 707.2985, found 707.3014.

6.4.2.13 *6-O-Benzyl-2,3-di-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (2R,3R,4S,5R,6S)-2-benzyloxymethyl-6-methoxy-4,5-bis(naphthalen-2-ylmethoxy)tetrahydropyran-3-ol* ***271***

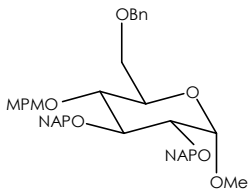


271

The method of Sakagami[226] was used . Molecular sieves (4 Å, pellets, 6.32 g) were dried under vacuum at 170 ºC for 90 minutes[268]. These were cooled to room temperature, before dry dichloromethane (30 cm^3) and 4,6-*O*-benzylidene-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-gluco-pyranoside **264** (1.61 g, 2.86 mmol) were added under nitrogen. The

solution was stirred at room temperature to dry the system completely, then cooled to -78 ºC and stirred for a further 15 minutes. Triethylsilane (0.960 cm_3, 0.699 g, 6.01 mmol) was added, followed immediately by trifluoromethanesulphonic acid[269] (0.520 cm^3, 0.888 g, 5.92 mmol). The reaction was stirred at -78 ºC for a further 15 minutes, before the addition of triethylamine (10 cm^3) and methanol (10 cm^3). The reaction was diluted with trichloromethane (30 cm^3) and allowed to warm to room temperature. The molecular sieves were removed by filtration, and the reaction solution washed with saturated aqueous sodium hydrogen carbonate solution (2 × 40 cm^3) and saturated aqueous sodium chloride solution (2 × 40 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel, using 1% methanol in dichloromethane as the elution solvent. The product was obtained as a white solid (704 mg, 50 %[270]) along with unchanged starting material (196 mg). $[\alpha_D]$ +1.5 ° (*c* 1.185, $CHCl_3$). T_m 61 – 65 ºC. ν_{max}/cm^{-1} 2903 (w), 1510 (m), 1360 (m), 1246 (m), 1041 (s), 820 (m). δ_H ($CDCl_3$, 400.1 MHz) 2.44 (br s, 1H, OH), 3.40 (s, 3H, MeO), 3.63 (dd, 1H, *J* = 3.6, 9.6 Hz; C^2H), 3.65 (dd, 1H, *J* = 9.6, 10.0 Hz; C^4H), 3.66 (d, 2H, *J* = 4.0 Hz, C^6H_2), 3.73 (dt, 1H, *J* = 4.0, 10.0 Hz; C^5H), 3.89 (dd, 1H, *J* = 9.6, 9.6 Hz; C^3H), 4.53 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.58 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.68 (d, 1H, *J* = 3.6 Hz, C^1H), 4.85 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.93 (d, 1H, *J* = 12.4 Hz, one of ArCH_2), 4.95 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 5.19 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 7.25 - 7.31 (m, 5H, Ph), 7.46 – 7.52 (m, 6H, naphthyl CH), 7.74 – 7.83 (m, 8H, naphthyl CH). δ_C ($CDCl_3$, 100.6 MHz) 55.3 (MeO), 69.6 (C^6), 79.9 (C^5), 70.9 (C^4), 73.3 (one of ArCH_2), 73.6 (one of ArCH_2), 75.5 (one of ArCH_2), 79.7 (C^2), 81.4 (C^3), 98.2 (C^1) , 125.9 (aromatic CH), 126.0 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 126.2 (aromatic CH), 126.7 (aromatic CH), 127.0 (aromatic CH), 127.6 (aromatic CH), 127.7 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH), 128.4 (aromatic CH), 133.0 (aromatic C), 133.1 (aromatic C), 133.2 (aromatic C), 133.4 (aromatic C), 133.5 (aromatic C), 136.3 (aromatic C), 138.0 (aromatic C). m/z (EI) 423.2, 447.2, 231.0, 517.0, 567.3 (M^+); calc[d] for $C_{36}H_{36}O_6$ 564.2512, found 564.2468.

6.4.2.14 *6-O-Benzyl-4-O-(4-methoxybenzyl)-2,3-di-O-(naphthalen-2-yl)methyl-1-O-methyl-α-D-glucopyranoside or (2R,3R,4S,5R,6S)-2-benzyloxymethyl-6-methoxy-3-(4-methoxy-benzyloxy)-4,5-bis(naphthalen-2-ylmethoxy)tetrahydropyran* **272**



272

The method of Chida *et al.*[263] was followed. Sodium hydride (60 % suspension in mineral oil, 89.2 mg, 2.23 mmol) was suspended in dry

DMF (5 cm^3) under nitrogen, and the system stirred and cooled to 0 °C. 6-*O*-Benzyl-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-glucopyranoside **271** (0.932 g, 1.65 mmol) was dissolved in dry DMF (10 cm^3) under nitrogen, and was added dropwise to the suspension of hydride. The reaction mixture was stirred for one hour twenty minutes at 0 °C, and then allowed to warm to room temperature, before the addition of 1-chloromethyl-4-methoxybenzene (0.250 cm^3, 289 mg, 1.84 mmol) over twenty-five minutes. The reaction was allowed to stir overnight, before being diluted with ethyl acetate (40 cm^3). The reaction solution was washed with hydrochloric acid (1 mol dm^{-3}, 2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 × 20 cm^3) and saturated aqueous sodium chloride solution (2 × 20 cm^3). The organic solution was dried over magnesium sulphate(VI), filtered and the solvent removed at reduced pressure. The product was purified by chromatography on silica gel, using methylbenzene-ethyl acetate 9:1 as the elution solvent. The title compound was obtained as a yellow oil (1.08 g, 96 %). R_f 0.340 (methylbenzene-ethyl acetate 9:1). $[\alpha_D]$ -34.0 ° (*c* 0.65, $CHCl_3$). T_m 94 – 96 °C. ν_{max}/cm^{-1} (solid) 2903 (w), 1510 (m), 146 (m), 1081 (s), 1041 (s), 821 (s), 749 (s). δ_H ($CDCl_3$, 400.1 MHz) 3.39 (s, 1H, MeO), 3.61 – 3.66 (m, 3H, three of $C^2H/C^4H/C^5H/C^6H_2$), 3.69 – 3.72 (m, 1H, one of $C^2H/C^4H/C^5H/C^6H_2$), 3.72 – 3.76 (m, 1H, one of $C^2H/C^4H/C^5H/C^6H_2$), 3.74 (s, 3H, MeO), 4.05 (dd, 1H, *J* = 9.4, 9.4 Hz; C^3H), 4.42 (d, 1H, *J* = 10.4 Hz, one of $ArCH_2$), 4.47 (d, 1H, *J* = 12.2 Hz, one of $ArCH_2$), 4.60 (d, 1H, *J* = 12.2 Hz, one of $ArCH_2$), 4.70 (d, 1H, *J* = 3.2 Hz, C^1H), 4.76 (d, 1H, *J* = 10.4 Hz, one of $ArCH_2$), 4.85 (d, 1H, *J* = 12.0 Hz, one of $ArCH_2$), 4.94 (d, 1H, *J* = 10.4 Hz, one of $ArCH_2$), 5.00 (d, 1H, *J* = 11.2 Hz, one of $ArCH_2$), 5.16 (d,1H, *J* = 11.2 Hz, one of $ArCH_2$), 6.74 (d, 2H, *J* = 8.4 Hz, MPM group CH pair), 7.01 (d, 2H, *J* = 8.4 Hz, MPM group CH pair), 7.30 – 7.31 (m, 5H, aromatic CH), 7.46 – 7.50 (m, 6H, aromatic H), 7.73 – 7.84 (m, 8H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.1 (MeO), 55.2 (MeO), 68.5 (C^6), 70.1 ($C^2/C^4/C^5$), 73.4 (one of $ArCH_2$), 74.6 (one of $ArCH_2$), 75.8 (one of $ArCH_2$), 77.4 ($C^2/C^4/C^5$), 79.9 ($C^2/C^4/C^5$), 82.1(C^3), 98.1 (C^1), 113.8 (aromatic CH), 125.8 (aromatic CH), 125.9 (aromatic CH), 126.0 (aromatic CH), 126.1 (aromatic CH), 126.3 (aromatic CH), 127.0 (aromatic CH), 127.6 (aromatic CH), 127.9 (aromatic CH), 127.9 (aromatic CH), 128.0 (aromatic CH), 128.2 (aromatic CH), 128.3 (aromatic CH), 129.4 (aromatic CH), 130.4 (aromatic C), 132.9 (aromatic C), 133.0 (aromatic C), 133.2 (aromatic C), 133.3 (aromatic C), 135.5 (aromatic C), 136.4 (aromatic C), 137.9 (aromatic C), 159.1 (aromatic C-O). m/z (ESI) 707.3 (M^+ + Na); calc[d] for $C_{44}H_{44}O_7Na$ 707.2985, found 707.2014.

6.4.3 Deprotection of glucose-based substrates

6.4.3.1 DDQ deprotection of **270**

2,3-Di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-4-*O*-(naphthalene-2-yl)methyl-1-*O*-methyl-α-D-gluco-pyranoside **270** (122 mg, 0.192 mmol) was dissolved in dichloromethane-methanol (9:1, 2 cm^3), and DDQ (203 mg, 0.370 mmol) was added. The reaction was stirred for 70 minutes, after which time the solvent was removed at reduced pressure. The residue was dissolved in trichloromethane (50 cm^3), and washed with saturated aqueous sodium hydrogen carbonate solution (3 × 25 cm^3) and saturated aqueous sodium chloride solution (25 cm^3). The solution was dried over sodium sulphate(VI), filtered, and the solvent removed at reduced pressure. Flash chromatography in petroleum ethers-ethyl acetate 7:3 followed by 3:2 gave the **269** (3.8 mg, 4 %) identical to that obtained in section 6.4.2.7.

6.4.3.2 CAN deprotection of **270**

2,3-Di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-4-*O*-(naphthalene-2-yl)methyl-1-*O*-methyl-α-D-gluco-pyranoside **270** (200 mg, 0.315 mmol) was dissolved in a mixture of acetone and water (9:1, 4 cm^3). CAN (350 mg, 0.638 mmol) was added as a solid, and the reaction stirred for 35 minutes. After this time, a solution of CAN (345 mg, 0.630 mmol) in the solvent mixture (0.5 cm^3) was added over 70 minutes using a syringe pump. The reaction was stirred for an additional one hour twenty minutes, before being poured in saturated aqueous sodium hydrogen carbonate solution (50 cm^3). This was extracted with dichloromethane (4 × 50 cm^3), and the combined organic extracts washed with saturated aqueous sodium chloride solution (50 cm^3). This was extracted with dichloromethane (2 × 25 cm^3), and the combine organic solutions dried over sodium sulphate(VI). Following filtration and removal of the solvent at reduced pressure, the crude product was purified by flash chromatography (elution solvent petroleum ethers-ethyl acetate 3:2). This gave the product as a white solid (110 mg, 68 %), identical in all respects to **269**.

6.4.3.3 CAN deprotection of **272**

An analogous method to section 6.4.3.2 was followed. 6-*O*-Benzyl-4-*O*-(4-methoxybenzyl)-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-glucopyranoside **272** (130 mg, 0.190 mmol) was dissolved in a mixture of acetone and water (9:1, 2.2 cm^3). CAN (196 mg, 0.357 mmol) was added as a solid, and a solution of CAN (202 mg, 0.369 mmol) in the solvent mixture (1.0 cm^3) was added over one hour using a syringe pump. The reaction was stirred for an additional forty

minutes, before being poured in saturated aqueous sodium hydrogen carbonate solution (25 cm^3). This was extracted with trichloromethane (3 × 25 cm^3), and the combined organic extracts washed with saturated aqueous sodium chloride solution (25 cm^3). This was extracted with trichloromethane (2 × 10 cm^3), and the combine organic solutions dried over sodium sulphate(VI). Following filtration and removal of the solvent at reduced pressure, the crude product was purified by flash chromatography (elution solvent hexane-ethyl acetate 4:1 followed by 7:3). This gave the product as a white solid (67 mg, 62 %), identical in all respects to **271**, along with starting material (11 mg[271]).

6.4.3.4 CAN deprotection of ***268***

An analogous method to section 6.4.3.2 was followed. 4-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-2,3-di-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-glucopyranoside **268** (127 mg, 0.185 mmol) was dissolved in a mixture of acetone and water (9:1, 1.4 cm^3). CAN (204 mg, 0.373 mmol) was added as a solid, and a solution of CAN (204 mg, 0.373 mmol) in the solvent mixture (1 cm^3) was added over one hour using a syringe pump. The reaction was stirred for an additional three hours, before being poured in saturated aqueous sodium hydrogen carbonate solution (25 cm^3). This was extracted with trichloromethane (3 × 25 cm^3), and the combined organic extracts washed with saturated aqueous sodium chloride solution (25 cm^3). This was extracted with trichloromethane (2 × 10 cm^3), and the combine organic solutions dried over sodium sulphate(VI). The drying agent was removed by filtration, and the solvent reduced pressure. The product was purified by chromatography on silica gel, using hexane-ethyl acetate 7:3 followed by 3:2 as the elution solvent. This gave the product as a white solid (61 mg, 59 %). The product was identical to **267** by ^{1}H NMR.

6.4.3.5 CAN deprotection of ***266***

An analogous method to section 6.4.3.2 was followed. 4-*O*-Benzyl-2,3-di-*O*-(4-methoxybenzyl)-6-*O*-(naphthalen-2-yl)methyl-1-*O*-methyl-α-D-glucopyranoside **266** (361 mg, 0.543 mmol) was dissolved in a mixture of acetone and water (9:1, 8 cm^3). CAN (1.14 g, 2.08 mmol) was added as a solid, and a solution of CAN (1.16 g, 2.12 mmol) in the solvent mixture (2 cm^3) was added over one hour using a syringe pump. The reaction was stirred for an additional forty minutes, before being poured in saturated aqueous sodium hydrogen carbonate solution (150 cm^3). This was extracted with dichloromethane (4 × 100 cm^3), and the combined organic extracts washed with saturated aqueous sodium chloride solution (100 cm^3). This was extracted with dichloromethane

(2 × 50 cm^3), and the combine organic solutions dried over sodium sulphate(VI). The drying agent was removed by filtration, and the solvent reduced pressure. The product was purified by chromatography on silica gel, using ethyl acetate-petroleum ethers 4:1 as the elution solvent. This gave the product **273** as an oil (140 mg, 61 %). $[\alpha_D]$ +119.0 (*c* 0.504, $CHCl_3$). δ_H ($CDCl_3$, 400.1 MHz) 2.54 (s, 1H, C^3-O*H*), 3.13 (d, 1H, *J* = 9.2 Hz, C^2-O*H*), 3.41 (s, 3H, MeO), 3.52 – 3.57 (m, 2H, C^2*H* and C^4*H*), 3.71 – 3.79 (m, 3H, C^5*H* and C^6H_2), 3.83 (dd, 1H, *J* = 9.0, 9.0 Hz; C^3H), 4.53 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.78 (d, 1H, *J* = 11.2 Hz, one of ArCH_2), 4.67 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.80 (d, 1H, *J* = 12.0 Hz, one of ArCH_2), 4.80 (d, 1H, *J* = 3.6 Hz, C^1H), 7.11 – 7.17 (m, 2H, aromatic H), 7.17 – 7.20 (m, 3H, aromatic H), 7.46 – 7.49 (m, 3H, aromatic H), 7.78 – 7.82 (m, 4H, aromatic H). δ_C ($CDCl_3$, 100.6 MHz) 55.3 (MeO), 68.5 (C^6), 70.2 (C^2/C^4/C^5), 72.6 (Ar*C*H_2), 73.7 (Ar*C*H_2), 74.6 (C^3), 75.3 (C2/C4/C5), 77.4 (C^2/C^4/C^5), 99.1 (C^1), 126.0 (aromatic CH), 126.6 (aromatic CH), 126.8 (aromatic CH), 127.7 (aromatic CH), 127.8 (aromatic CH), 127.9 (aromatic CH), 128.2 (aromatic CH), 128.4 (aromatic CH), 133.1 (aromatic C), 133.2 (aromatic C), 135.4 (aromatic C), 138.2 (aromatic C). m/z (ESI) 447.2 (M^+ + Na), 316.2; calc[d] for $C_{25}H_{28}O_6Na$ 447.1784, found 447.1799.

7 REFERENCES

1. W.H. Wollaston, *Phil. Trans. Roy. Soc. London*, 1804, **94**, 419-430.
2. W.H. Wollaston, *Phil. Trans. Roy. Soc. London*, 1805, **95**, 316-220.
3. N.N. Greenwood and A. Earnshaw, *Chemistry of the Elements*, Butterworth-Heinemann, Oxford, 2nd edn., 1997.
4. P.M. Maitlis, *The Organic Chemistry of Palladium. Metal Complexes*, Academic Press, New York, 1971, vol. 1.
5. A three to one mixture of concentrated hydrochloric and concentrated nitric acids.
6. Perhaps the most famous example of the reactivity of platinum(VI) is the reaction of PtF_6 with xenon to give $Xe[PtF_6]$; see N. Bartlett, *Proc. Chem. Soc.*, 1962, 218.
7. P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980.
8. F.R. Hartley, *The Chemistry of Platinum and Palladium*, Applied Science Publishing, London, 1973.
9. F.A. Cotton, G. Wilkinson, C.A. Murillo, and M. Bochmann, *Advanced Inorganic Chemistry*, Wiley Interscience, New York, 6th edn., 1999.
10. P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980, p. 5.
11. S. Otsuka, Y. Tatsuno, and K. Ataka, *J. Am. Chem. Soc.*, 1971, **93**, 6705-6706.
12. W.B. Lin, S.R. Wilson, and G.S. Girolami, *Inorg. Chem.*, 1994, **33**, 2265-2272.
13. N. Bartlett and R. Maitland, *Acta Crystallogr.*, 1958, **11**, 747-748.
14. H. Schaëfer, U. Weise, K. Rinke, and K. Brendel, *Angew. Chem.*, 1966, **79**, 244; *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 253-254.
15. A.C. Skapski and M.L. Smart, *J. Chem. Soc., Chem. Commun.*, 1970, 658-659.
16. M. Tamura and T. Yasui, *Kogyo Kagaku Zasshi (J. Chem. Soc. Jpn., Ind. Chem. Sect.)*, 1968, **71**, 1855-1859; English abstract p. A116.
17. N. Bartlett and P.R. Rao, *Proc. Chem. Soc.*, 1964, 394.
18. A.J. Blake, A.J. Holder, T.I. Hyde, and M. Schröder, *J. Chem. Soc., Chem. Commun.*, 1987, 987-988.
19. P.M. Henry, Palladium *Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980, p. 6.
20. S. Ahrland, J. Chatt, and N.R. Davies, *Q. Rev. (Chem. Soc. London)*, 1958, **12**, 265-276.
21. R.G. Pearson, *J. Am. Chem. Soc.*, 1963, **85**, 3533-3539.

22. W.C. Zeise, *Ann. Phys. Chem.*, 1827, **9**, 632.
23. W.C. Zeise, *Ann. Phys. Chem.*, 1831, **21**, 497-541.
24. J.S. Dewar, *Bull. Soc. Chim. Fr.*, 1951, **18**, C71-C79.
25. J. Chatt and A.L. Duncanson, *J. Chem. Soc.*, 1953, 2939-2947.
26. M. Donati, D. Morelli, F. Conti, and R. Ugo, *Chim. Ind. (Milan)*, 1968, **50**, 231-235.
27. F. Conti, M. Donati, and G.F. Pregaglia, *J. Organomet. Chem.*, 1971, **30**, 421-429.
28. B.L. Shaw, *Chem. Ind. (London)*, 1962, 1190.
29. R.L. Augustine, *Heterogeneous Catalysis for the Organic Chemist*, Marcel Dekker, New York, 1995.
30. R.F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, 1985.
31. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995.
32. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. 15.
33. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, chp. 2, pp. 13-18.
34. F.C. Phillips, *Am. Chem. J.*, 1894, **16**, 255-277.
35. F.C. Phillips, *Z. Anorg. Chem.*, 1894, **6**, 213-228.
36. S.G. Ogburn, Jr. and W.C. Brawston, *J. Am. Chem. Soc.*, 1933, **55**, 1307-1310.
37. J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, and H. Kojer, *Angew. Chem.*, 1959, **71**, 176-182.
38. M.S. Kharasch and F.R. Mayo, *J. Am. Chem. Soc.*, 1938, **60**, 882-884.
39. N.C. Baenziger and J.N. Dempsey, *J. Am. Chem. Soc.*, 1955, **77**, 4984-4987.
40. J.R. Holden and N.C. Baenziger, *J. Am. Chem. Soc.*, 1955, 4987-4990.
41. W. Hafner, R. Jira, J. Sedlmeier, and J. Smidt, *Chem. Ber.*, 1962, **95**, 1575-1581.
42. J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, and A. Sabel, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 80-88.
43. R. Jira, J. Sedlmeier, and J. Smidt, *Liebigs Ann. Chem.*, 1966, **693**, 99-108.
44. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. xi.
45. J. Tsuji, *Synthesis*, 1984, 369-284.
46. H.-J. Kabbe and R. Jira, *Ketone Durch Oxidation Unter Erhalt Des Kohlenstoffgerüstes. C) Ketone Aus Olefinen*, chp. III, pp. 781-790 in *Houben-Weyl. Methoden der organischen Chemie. Ketone. Teil 1,* Georg Thieme, Stuttgart, 4th edn., 1973, vol. VII/2a.

47. B. Wistuba, *Kobalt-, Nickel-, Ruthenium-, Rhodium-, Palladium-, Osmium- Und Platin-Verbindungen Als Oxidationsmittel. D. Palladium(II)-Chlorid.*, pp. 856-860 in *Houben-Weyl. Methoden der organischen Chemie. Oxidation II: metallische und organische Oxidationsmittel, elekrochemische Oxidation, oxidationshemmung,* Georg Thieme, Stuttgart, 4th edn., 1975, vol. IV/1b.
48. R. Jira and W. Freieleben, *Olefin Oxidation and Related Reactions With Group VIII Noble Metal Compounds*, chp. 1, *Organometallic Reactions,* Wiley Interscience, New York, 1972, vol. 3.
49. R. Jira, *A. Herstellung. 2. Durch Oxidation. 2.3. Von Methylen-Gruppen in 1-Alkenen*, chp. 2.3, pp. 340-349 in *Houben-Weyl. Methoden der organischen Chemie. Aldehdye,* Georg Thieme, Stuttgart, 4th edn., 1983, vol. E3.
50. P.D. Magnus and M.S. Nobbs, *Synth. Commun.*, 1980, **10**, 273-278.
51. K. Iseki, M. Yamazaki, M. Shibasaki, and S. Ikegami, *Tetrahedron*, 1981, **37**, 4411-4418.
52. D.G. Miller and D.D.M. Wayner, *J. Org. Chem.*, 1990, **55**, 2924-2927.
53. J. Lai, X. Shi, and L. Dai, *J. Org. Chem.*, 1992, **57**, 3485-3487.
54. K. Mori and Y.-B. Seu, *Tetrahedron Lett.*, 1985, **41**, 3429-3431.
55. K. Matsui, S. Uchimumi, A. Iwayama, and T. Umeza, Eur. Pat. Appl. EP55,108; Jpn. Pat. Appl. 80/181,332; *Chem. Abs.*, 1982, **97**, 162364b.
56. L.S. Hegedus, *Angew. Chem.,* 1988, **100**, 1147; *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1113-1126.
57. T. Hosokawa and S.-I. Murshashi, *Heterocycles*, 1992, **33**, 1079-1100.
58. R.B. Gammill and S.A. Nash, *J. Org. Chem.*, 1986, **51**, 3116-3123.
59. I.I. Moiseev, M. N. Vargaftik and Ya. K. Syrkin, *Dokl. Akad. Nauk SSSR*, 1960, **133**, 377-380; *Chem. Abs.*, 1960, **54**, 24350g.
60. E.W. Stern and M.L. Spector, *Proc. Chem. Soc.*, 1961, 370.
61. W. Kitching, Z. Rappoport, S. Winstein, and W.G. Young, *J. Am. Chem. Soc.*, 1966, **88**, 2054-2055.
62. E.M. Larsson and B. Åkermark, *Tetrahedron Lett.*, 1993, **34**, 2523-2526.
63. J.E. McMurry and P. Kočovský, *Tetrahedron Lett.*, 1984, **25,** 4187-4190.
64. U. Annby, M. Stenkula, and P.G. Andersson, *Tetrahedron Lett.*, 1993, **34**, 8545-8548.
65. J.-E. Bäckvall, *Tetrahedron Lett.*, 1975, **17**, 2225-2228.
66. J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1977, 413-414.
67. L.S. Hegedus, G.F. Allen, J.J. Bozell, and E.L. Waterman, *J. Am. Chem. Soc.*, 1978, **100**, 5800-5807.

68. P.J. Harrington, L.S. Hegedus, and K.F. McDaniel, *J. Am. Chem. Soc.*, 1987, **109**, 4335-4338.
69. T. Hayashi and L.S. Hegedus, *J. Am. Chem. Soc.*, 1977, **99**, 7093-7094.
70. L.S. Hegedus, T. Hayashi, and W.H. Darlington, *J. Am. Chem. Soc.*, 1978, **100**, 7747-7748.
71. L.S. Hegedus, R.E. Williams, M.A. McGuire, and T. Hayashi, *J. Am. Chem. Soc.*, 1980, **102**, 4973-4979.
72. S.I. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, 1977, **42**, 2870-2874.
73. J. Tsuji, M. Morikawa, and J. Kiji, *Tetrahedron Lett.*, 1963, 1061-1064.
74. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. 51.
75. H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, and Y. Tamaru, *J. Org. Chem.*, 1997, **62**, 2113-2122.
76. J.-E. Bäckvall and R.E. Nordberg, *J. Am. Chem. Soc.*, 1981, **103**, 4959-4960.
77. P.G. Andersson and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 1992, **114**, 8696-8698.
78. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, pp. 55-59.
79. A. Shiotani, M. Yoshikiyo, and H. Itatani, *J. Mol. Catal.*, 1983, **18**, 23-31.
80. A. Shiotani, H. Itatani, and T. Inagaki, *J. Mol. Catal.*, 1986, **34**, 57-66.
81. L. Eberson and L. Gomez-Gonzales, *J. Chem. Soc., Chem. Commun.*, 1971, 263-264.
82. M. Costa, L.D. Santos, G.P. Chiusoli, B. Gabriele, and G. Salerno, *J. Mol. Catal.*, 1993, **78**, 151-158.
83. H. Kataoka, K. Watanabe, and K. Goto, *Tetrahedron Lett.*, 1990, **31**, 4181-4184.
84. H. Kataoka, K. Watanabe, K. Miyazaki, S. Tahara, K. Ogu, R. Matsuoka, and K. Goto, *Chem. Lett.*, 1990, 1705-1708.
85. R.J. Theissen, *J. Org. Chem.*, 1971, **36**, 752-757.
86. Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011-1013.
87. T.F. Blackburn and J. Schwartz, *J. Chem. Soc., Chem. Commun.*, 1977, 157-158. Very recent examples, applying the oxidation to kinetic resolution a) D. R. Jensen and M. S. Sigman, *Org. Lett.*, 2003, **5**, 63-65; b) J. T. Bagdanoff, E. M. Ferreira and B. M. Stoltz, *Org. Lett.*, 2003, **5**, 835-837.
88. P.N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, 1979.
89. P.N. Rylander, *Hydrogenation Methods*, Academic Press, New York, 1985.

90. J.A. Osburn, F.H. Jardine, J.F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1966, 1711-1732.
91. K.B. Sharpless, *Angew. Chem.*, 2002, **114**, 2116-2145; *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2024-2032.
92. W.S. Knowles, *Angew. Chem.*, 2002, 114, 2096-2107; *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 1999-2007.
93. R. Noyori, *Angew. Chem.*, 2002, **114**, 2108-2123; *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 2008-2022.
94. I. Horiuti and M. Polanyi, *Trans. Faraday Soc.*, 1934, **30**, 1164-1172.
95. I.V. Gostunskaya, V.S. Petrova, A.I. Leonava, V.A. Mironava, M. Abubaker, and B.A. Kazanski, *Neftekhimiya*, 1967, **7**, 3-8; *Chem. Abs.*, 1967, **67**, 21276t.
96. G.A. Schiehser and J.D. White, *J. Org. Chem.*, 1980, **45**, 1864-1868.
97. P.C. Traas, H. Boelens, and H.J. Takken, *Synth. Commun.*, 1976, **6**, 489-493.
98. H. Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446-450.
99. H. Lindlar and R. Dubuis, *Org. Syn., Coll. Vol.*, 1973, **5**, 880-883.
100. W. Huang, S.P. Pulaski, and J. Meinwald, *J. Org. Chem.*, 1983, **48**, 2270-2274.
101. H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, 1958, **80**, 5377-5380.
102. J.S. Cha and H.C. Brown, *J. Org. Chem.*, 1993, **58**, 4732-4734.
103. K.W. Rosenmund and F. Zetzche, *Ber. Dtsch. Chem. Ges.*, 1921, **54**, 425-440.
104. A.W. Burgstahler, L.O. Weigel, and C.G. Shaefer, *Synthesis*, 1976, 767-768.
105. T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 3rd edn., 1999.
106. B.P. Czech and R.A. Bartsch, *J. Org. Chem.*, 1984, **49**, 4076-4078.
107. T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581.
108. R.F. Heck and J.P. Nolley, Jr., *J. Org. Chem.*, 1972, **37**, 2320-2322.
109. See J. Tsuji*, Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. 297.
110. N.J. Whitcombe, K.K. Hii, and S.E. Gibson, *Tetrahedron*, 2001, **57**, 7449-7476.
111. D. Morales-Morales, R. Rédon, C. Yung, and C.M. Jensen, *J. Chem. Soc., Chem. Commun.*, 2000, 1619-1620.
112. See J. Tsuji*, Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. 298.
113. J.-E. Bäckvall, J.O. Vagberg, C. Zercher, J.P. Genet, and A. Denis, *J. Org. Chem.*, 1987, **52**, 5430-5435.

114. J. Tsuji, M. Yuhara, M. Minato, H. Yamada, F. Sato, and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 343-346.
115. "Every stone is different, do not try to make from two one enormous one".
116. G. Szonyi, *Adv. Chem. Ser.*, 1968, **70**, 53-96.
117. J.F. Keggin, *Proc. Roy. Soc. London, A*, 1934, **144**, 75-100.
118. F. Joó, *Aqueous Organometallic Chemistry*, Kluwer Academic Press, Dordrecht, 2001.
119. G.-J. ten Brink, I.W.C.E. Arends, G. Papadogianakis, and R.A. Sheldon, *J. Chem. Soc., Chem. Commun.*, 1998, 2359-2360.
120. G.-J. ten Brink, I.W.C.E. Arends, G. Papadogianakis, and R.A. Sheldon, *Appl. Catal. A*, 2000, **194-195**, 435-442.
121. See for example: a) R. Jira, J. Sedlmeier, and J. Smidt, *Liebigs Ann. Chem.*, 1966, **693**, 99-108; b) I.I. Moiseev, O.G. Levanda, and M.N. Vargaftik, *J. Am. Chem. Soc.*, 1974, **96**, 1003-1007; c) P.M. Henry, *J. Org. Chem.,* 1973, **38**, 2415-2416; d) J.-E. Bäckvall, B. Åkermark, and S.O. Ljunggern, *J. Am. Chem. Soc.*, 1979, **109**, 2411-2416.
122. P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980, pp. 52-84.
123. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, p. 22.
124. M.B. Smith and J. March, *March's Advanced Organic Chemistry*, John Wiley & Sons, New York, 5th edn., 2001, pp. 1537-1538.
125. A. Dedieu, *Wacker Reaction* in *Theoretical Aspects of Homogeneous Catalysis,* Kluwer Academic Press, Dordrecht, 1995.
126. M.N. Vargaftik, I.I. Moiseev and Ya. K. Syrkin, *Dokl. Akad. Nauk SSSR*, 1961, **139**, 1396-1399; *Chem. Abs.*, 1962, **56**, 14976h.
127. I.I. Moiseev, M.N. Vargaftik, and Ya.K. Syrkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963, 1144-1145; *Chem. Abs.*, 1963, **59**, 5837g.
128. L.M. Zakharova, M.N. Vargaftik, I.I. Moiseev, and L.A. Katsman, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1970, 700-702; *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1970, 656-658.
129. I.I. Moiseev, O.G. Levanda, and M.N. Vargaftik, *J. Am. Chem. Soc.*, 1974, **96**, 1003-1007.
130. P.M. Henry, *J. Am. Chem. Soc.*, 1964, **86**, 3246-3250.
131. P.M. Henry, *J. Org. Chem.*, 1973, **38**, 2415-2416.
132. J.-E. Bäckvall, B. Åkermark, and S.O. Ljunggern, *J. Am. Chem. Soc.*, 1979, **109**, 2411-2416.
133. P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980, p. 65.

134. a) O. Hamed, P.M. Henry, and C. Thompson, *J. Org. Chem.*, 1999, **64**, 7745-7750; b) For further discussion, see: P.M. Henry, *The Wacker Oxidation and Related Asymmetric Syntheses*, chp. V.3.1.1, pp. 2119-2140, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, Wiley Interscience, New York, 2002, vol. 2.
135. P. François, *Ann. Chim. (Paris)*, 1969, **4**, 371-289.
136. J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 1976, **18**, 2975-2976.
137. H. Okada, T. Noma, Y. Ketsuyama, and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 1395-1400.
138. P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980, p. 74.
139. See P.M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Riedel Pub. Co., Dordrecht (Netherlands), 1980 pp. 72-74 and references therein.
140. H. Pellissier, P.-Y. Michellys, and M. Santelli, *Tetrahedron Lett.*, 1994, **35**, 6481-6484.
141. H. Pellissier, P.-Y. Michellys, and M. Santelli, *Tetrahedron*, 1997, **53**, 7577-7586.
142. H. Pellissier, P.-Y. Michellys, and M. Santelli, *Tetrahedron*, 1997, **53**, 10733-10742.
143. B.L. Feringa, *J. Chem. Soc., Chem. Commun.*, 1986, 909-910.
144. T.T. Wenzel, *J. Chem. Soc., Chem. Commun.*, 1993, 862-864.
145. M.J. Gaunt, J. Yu, and J.B. Spencer, *J. Chem. Soc., Chem. Commun.*, 2001, 1844-1845.
146. L.M. Zakharova, M.N. Vargaftik, I.I. Moiseev, and L.A. Katsman, *Kinet. Katal.*, 1969, **10**, 901-903; *Kinet. Catal.*, 1969, **10**, 4, 736-744.
147. L.M. Martynova and L.A. Katsman, *Kinet. Katal.*, 1988, **30**, 1489-1491; *Kinet. Catal.*, 1989, **30**, 6, 1298-1299.
148. L.M. Martynova and L.A. Katsman, *Kinet. Katal.*, 1990, **31**, 844-849; K*inet. Catal.*, 1990, **31**, 4, 739-744.
149. J. Vojtko, A. Kaszonyi, M. Cihová, and M. Hrušovský, *Collect. Czech. Chem. Commun.*, 1981, **46**, 573-583.
150. H. Okada and H. Hashimoto, *Kogyo Kagaku Zasshi (J. Chem. Soc. Jpn., Ind. Chem. Sect.)*, 1966, **69**, 2137-2141; English trans. P. A120.
151. W.G. Llyod and B.J. Luberoff, *J. Org. Chem.*, 1969, **34**, 3949-3952.
152. J. Vojtko, M. Hrušovský, and M. Cihová, *Zb. Pr. Chemickotechnol. Fak. SVŠT*, 1973, 195-200; *Chem. Abs.*, 1978, **89**, 146285f.
153. E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 1975, **17**, 2647-2650.
154. R. Siedlecka, J. Skazewski, and J. Mlochowski, *Tetrahedron Lett.*, 1990, **31**, 2177-280.
155. K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651-1660.

156. M. Frigerio, M. Santagostino, S. Sputore, and G. Palmisano, *J. Org. Chem.*, 1995, **60**, 7272-7276.
157. M. Frigerio and M. Santagostino, *Tetrahedron Lett.*, 1994, **35**, 8019-8022.
158. M. Frigerio, M. Santagostino, and S. Sputore, *J. Org. Chem.*, 1999, **64**, 4537-4538.
159. C.W. Jefford, S. Kohomoto, J. Boukouvalas, and U. Burger, *J. Am. Chem. Soc.*, 1983, **105**, 6498-6499.
160. Other authors have also noted some benzaldehyde formation. No explanation was given as to any possible source.
161. It was established that benzaldehyde was formed from the product aldehyde only, and not from the ketone. This reaction was accelerated by the presence of palladium(II) salts.
162. D.R. Fahey and E.A. Zuech, *J. Org. Chem.*, 1974, **39**, 3276-3277.
163. A. Kaszonyi, J. Vojtko, and M. Hrušovský, *Collect. Czech. Chem. Commun.*, 1982, **47**, 2128-2139.
164. G. Wittig and M. Schlosser, *Chem. Ber.*, 1961, **94**, 1373-1378.
165. Q. Wang, H.-X. Wei, and M. Schlosser, *Eur. J. Org. Chem.*, 1999, 3263-3268.
166. M. Brookhart and M.L.H. Green, *J. Organomet. Chem.*, 1983, **250**, 395-408.
167. The solvent beings to freeze below this limit.
168. This was confirmed by NMR of pure 4-ethenyl-1-methylbenzene in DMF-d_7.
169. Confirmed by NMR of palladium(II) acetate allowed to dissolve overnight in DMF-d_7.
170. DMF is known to co-ordinate to palladium(II) to give complexes, see: a) M. Donati, D. Morelli, F. Conti, and R. Ugo, *Chim. Ind. (Milan)*, 1968, *50*, 231-235; b) F. Conti, M. Donati, and G.F. Pregaglia, *J. Organomet. Chem.*, 1971, *30*, 421-429.
171. Dr. J.-Q. Yu, personal communication.
172. M. Rubina and V. Gevorgyan, *J. Am. Chem. Soc.*, 2001, **123**, 11107-11108.
173. H. Wadepohl, A. Metz, and H. Pritzkowl, *Chem. Eur. J.*, 2002, **8**, 1591-1602.
174. a) J. March *Advanced Organic Chemistry*, John Wiley and Sons, Chicester, 4th edn., 1992, pp. 42-44. b) J.-Y. Legros, M. Toffano and J.-C. Fiaud, *Tetrahedron* 1995, **51**, 3235-3246.
175. J.-E. Bäckvall, S.E. Byström, and R.E. Nordberg, *J. Org. Chem.*, 1984, **49**, 4619-4631.
176. J.J. Berzelius, *Ann. Phys. Chem.*, 1826, **6**, 369-392.
177. S.F. Davison, B.E. Mann, and P.M. Maitlis, *J. Chem. Soc., Dalton Trans.*, 1984, 1223-1228.
178. B. El Ali, J.-M. Brégeault, and J. Martin, *J. Organomet. Chem.*, 1987, **317**, C9-C14.
179. G.A. Tsigdinos and C.J. Hallada, *Inorg. Chem.*, 1968, **7**, 437-441.
180. The unknown quantity of water in the HPA makes exact stoichiometry difficult to assess.

181. See for example: a) D.G. Miller and D.D.M. Wayner, *J. Org. Chem.*, 1990, **55**, 2924-2927; b) H. Alper, K. Januszkiewicz, and D.J.H. Smith, *Tetrahedron Lett.*, 1985, **26**, 2263-2264.
182. T.J. Grattan and J.S. Whitehurst, *J. Chem. Soc., Chem. Commun.*, 1988, 43-44.
183. J. Tsuji, *Palladium Reagents and Catalysts. Applications in Organic Synthesis*, Wiley, New York, 1995, pp. 28-29.
184. E. Keinan, K.K. Seth, and R. Lamed, *J. Am. Chem. Soc.*, 1986, **108**, 3474-3480.
185. P.A. Evans and J.D. Nelson, *J. Am. Chem. Soc.*, 1998, **120**, 5581-5582.
186. H. Alper, K. Januszkiewicz, and D.J.H. Smith, *Tetrahedron Lett.*, 1985, **26**, 2263-2264.
187. C.Q. Wei, X.R. Jiang, and Y. Ding, *Tetrahedron*, 1998, **54**, 12623-12630.
188. J.F. Harrod and A.J. Chalk, *J. Am. Chem. Soc.*, 1966, **88**, 3491-3497.
189. D. Savoia, C. Tombini, A. Umani-Ronchi, and G. Verardo, *J. Chem. Soc., Chem. Commun.*, 1981, 540-541.
190. E.N. Jacobsen, L. Deng, Y. Furukawa, and L.E. Martinez, *Tetrahedron*, 1994, **50**, 4323-4334.
191. The rates are different between the two sets of reactions due to differences in the mixing protocol employed.
192. The work in this section has been reported: J.A. Wright, J.-Q. Yu and J.B. Spencer, *Tetrahedron Lett.*, 2002, **42**, 4033-4036.
193. J.A. Wright and C.E.T. Mitchell, unpublished results.
194. T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 3rd edn., 1999, p. 1.
195. P. Sabatier and J.-B. Senderens, *Ann. Chim. Phys.*, 1905, **4**, 319-488.
196. P. Sabatier and A. Mailhe, *C. R. Hedb. Séances Acad. Sci.*, 1911, **153**, 160-162.
197. P. Sabatier and M. Murat, *C. R. Hedb. Séances Acad. Sci.*, 1913, **156**, 424-427.
198. K.W. Rosenmund and F. Zetzche, *Ber. Dtsch. Chem. Ges.*, 1921, **54**, 2038-2042.
199. O. Wolfes and W. Krauß, Ger. Pat. 407487.
200. W. Krauß, Ger. Pat. 417916.
201. M. Bergmann and L. Zervas, *Ber. Dtsch. Chem. Ges.*, 1932, **65**, 1192-1201.
202. W. Hartung and R. Simonoff, *Org. React. (N. Y.)*, 1953, **7**, 263-326.
203. T. Bieg and W. Szeja, *Synthesis*, 1985, 76-77.
204. S. Ram and L.D. Spicer, *Synth. Commun.*, 1987, **17**, 415-418.
205. S. Ram and L.D. Spicer, *Tetrahedron Lett.*, 1987, **28**, 515-516.
206. W. Schmidt and E. Steckhan, *Angew. Chem.*, 1979, **91**, 850; *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 801-802.

207. W. Schmidt and E. Steckhan, *Angew. Chem.*, 1979, **91**, 717; *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 802-803.
208. See Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, 1982, 23, 885-888 and references therein.
209. Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885-888.
210. Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, 1984, **25**, 5393-5396.
211. N. Nakajima, R. Abe, and O. Yonemitsu, *Chem. Pharm. Bull. Jpn.*, 1988, **36**, 4244-4247.
212. The approximate order of reactivity is 3,4-di-OMe › 4-OMe › 2,3,4-tri-OMe › 3,4,5-tri-OMe › 2,5-di-OMe › 2,3-di-OMe › 3-OMe › 2,6-di-OMe.
213. B. Classon, P.J. Garegg, and B. Samuelsson, *Acta Chem. Scand. B*, 1984, **38**, 419-422.
214. M.J. Gaunt, J.-Q. Yu, and J.B. Spencer, *J. Org. Chem.*, 1998, **63**, 4172-4173.
215. M.J. Gaunt, C. Boschetti, J. Yu, and J.B. Spencer, *Tetrahedron Lett.*, 1999, **40**, 1803-1806.
216. E.A. Papageorgiou, M.J. Gaunt, J. Yu, and J.B. Spencer, *Org. Lett.*, 2000, **2**, 1049-1051.
217. J. Xia, S.A. Abbas, R.S. Locke, C.F. Piskorz, J.L. Alderfer, and K.L. Matta, *Tetrahedron Lett.*, 2000, **41**, 169-173.
218. The use of acetone as a solvent for the deprotection was found to be beneficial for the sugar substrates. In the case of the linker, deprotection using ethananitrile as the solvent gave a very similar result.
219. V. Ferro, M. Mocerino, R.V. Stick, and D.M.G. Tilbrook, *Aust. J. Chem.*, 1988, **41**, 813-815.
220. This work was carried out by Dr. J.-Q. Yu.
221. S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, *Chem. Lett.*, 1983, 1593-1596.
222. R. Johansson and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2371-2374.
223. S. Hanessian, *Regioselective Cleavage of O-Benzylidene Acetals to Benzyl Ethers*, chp. 3 in *Preparative Carbohydrate Chemistry,* Marcel Dekker, New York, 1997.
224. L. Jiang and T.-H. Chan, *Tetrahedron Lett.*, 1998, **39**, 355-358.
225. M.J. Gaunt, Ph.D. thesis, University of Cambridge, 1999.
226. M. Sakagami and H. Hamana, *Tetrahedron Lett.*, 2000, **41**, 5547-5551.
227. A. Lipták, A. Borbás, L. Jánossy, and L. Szilágyi, *Tetrahedron Lett.*, 2000, **41**, 4949-4953.
228. A. Borbás, Z. Szarbó, L. Szilágyi, A. Bényei, and A. Lipták, *Tetrahedron*, 2002, **58**, 5723-5732.
229. This work was carried out by Dr. J.-Q. Yu.
230. J.A. Wright, J.-Q. Yu, and J.B. Spencer, *Tetrahedron Lett.*, 2001, **42**, 4033-4036.

231. "I weep like Leonardo da Vinci; such things I could make if only I had the materials"
232. W.L.F. Armarego and D.D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 4th edn., 2000.
233. Ampoules were manufactured by Soham Scientific Glassware, to the authors design.
234. Made up using potassium manganate(VII) (5.5 g), potassium carbonate (33.8 g), sodium hydroxide solution (1 mol dm^{-3}, 82 cm^3) and water (500 cm^3).
235. Vanillin (25 g) dissolved in a mixture of methanol (425 cm^3), ethanoic acid (60 cm^3) and concentrated sulphuric acid (15 cm^3).
236. 2,4-Dinitrophenylhydrazine (0.5 g) dissolved in hydrochloric acid (1 mol dm^{-3}, 200 cm^3).
237. Phosphomolybdic acid (12 $MoO_3.H_3PO_4.xH_2O$, 8 g) dissolved in ethanol (250 cm^3).
238. W.C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923-2925.
239. M. Hesse, H. Meier, and B. Zeeh, *Spectroscopic Methods in Organic Chemistry*, Georg Thieme Verlag, Stuttgart, 5th edn., 1997.
240. A.H. Schmidt, G. Kircher, J. Zylla, and S. Veit, *J. Chem. Soc., Perkin Trans. 1*, 1999, 409-414.
241. F. Hollywood, H. Suschitzky, and R. Hull, *Synthesis*, 1982, 662-665.
242. K. Takeuchi, I. Kitagawa, F. Akiyama, T. Shibata, M. Kato, and K. Okamoto, *Synthesis*, 1987, 612-615.
243. P. Nongkunsarn and C.A. Ramsden, *Tetrahedron*, 1997, **53**, 3805-3830.
244. O. Farooq, M. Marcelli, G.K.S. Prakash, and G.A. Olah, *J. Am. Chem. Soc.*, 1988, **110**, 864-867.
245. L.H. Schwartzman and B.B. Corson, *J. Am. Chem. Soc.*, 1954, **76**, 781-785.
246. The product was found to be air-sensitive, and was stored under nitrogen at -30 ºC. Exposure to air led to the slow formation an unidentified solid.
247. C. Lemini, M. Ordoñez, J. Pérez-Flores, and R. Cruz-Almanza, *Synth. Commun.*, 1995, **25**, 2695-2702.
248. The product was found to be air-sensitive, and was stored under nitrogen at -30 ºC. Exposure to air led to the slow formation an unidentified solid.
249. J.B. Lambert, H.W. Mark, and E. Stedman Magyar, *J. Am. Chem. Soc.*, 1977, **99**, 3059-3061.
250. THF was needed in order to dissolve the substrate.
251. V.V. Krishnamurthy, P.S. Iyer, and G.A. Olah, *J. Org. Chem.*, 1983, **48**, 3373-3378.
252. P.J. Smith and M. Amin, *Can. J. Chem.*, 1989, **67**, 1457-1467.
253. Cooling the neat alcohol in ice led to the liquid freezing.

254. F. Kunckell and K. Siecke, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 774-775.
255. D. Landini, A. Maia, F. Montanari, and F. Rolla, *J. Org. Chem.*, 1983, **48**, 3774-3777.
256. B.S. Furniss, A.J. Hannaford, P.W.G. Smith, and A.R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Pearson Education, Harlow, 5th edn. (rev.), 1989.
257. W.N. Smith and O.F. Beumel, Jr., *Synthesis*, 1974, 441-442.
258. R.E.A. Dear and F.L.M. Pattison, *J. Am. Chem. Soc.*, 1963, **85**, 622-626.
259. F.L.M. Pattison and R.E.A. Dear, *Can. J. Chem.*, 1963, **41**, 2600-2606.
260. E.D. Bergmann and A. Becker, *J. Am. Chem. Soc.*, 1959, **81**, 221-225.
261. J.A. Marshall, J.D. Trometer, B.E. Blough, and T.D. Crute, *J. Org. Chem.*, 1988, **53**, 4274-4282.
262. H.A. Davis and R.K. Brown, *Can. J. Chem.*, 1971, **49**, 2563-2577.
263. S. Amano, N. Ogawa, M. Ohtsuka, and N. Chida, *Tetrahedron*, 1999, **55**, 2205-2224.
264. S.D. Bull, S.G. Davies, G. Fenton, A.W. Mulvaney, R.S. Prasad, and A.D. Smith, *J. Chem. Soc., Chem. Commun.*, 2000, 337-338.
265. W.M. Ho, H.N.C. Wong, L. Navailles, C. Destrade, H.T. Nguyen, and N. Isaert, *Tetrahedron*, 1995, **51**, 7373-7388.
266. I. Kitagawa, M. Yoshokawa, K. Kobayashi, Y. Imakura, K.S. Im, and Y. Ikenishi, *Chem. Pharm. Bull.*, 1980, **28**, 296-300.
267. **Caution**. This process was found to be very vigorous.
268. Drying the molecular sieves to this degree was essential for the success of the reaction.
269. Exercise **caution** with this reagent. It was found to damage plastic syringes, and on one occasion was able to escape from such a syringe sideways, posing a risk to the user. Glass equipment is strongly recommended.
270. Based on recovered starting material.
271. Yield based on recovered starting material 68 %.

8 APPENDIX: ANALYSIS OF KINETIC NMR DATA FOR DEC-1-ENE

The use of dec-1-ene and 3,3-dideuteriodec-1-ene to probe the regioselectivity of the Wacker reaction was described in section 4.3.2.2.. Analysis of the NMR data for the competition kinetics experiments was carried out as follows.

The Wacker reaction of dec-1-ene with water in DMF, using palladium(II) chloride as the catalyst and 1,4-benzoquinone as the reoxidant, proceeds cleanly: the only reaction product is decan-2-one. In the competition experiment there are, therefore, four species of interest: the two starting materials and the two products (Figure 19).

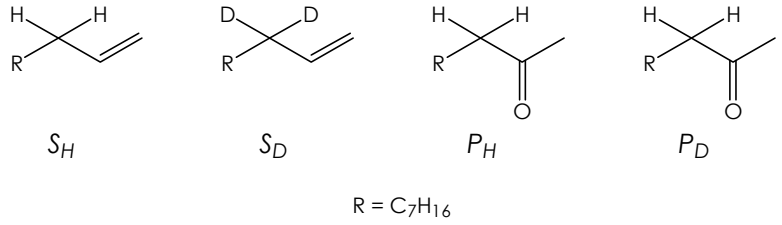


Figure 19 – Structures

It has been established by separate NMR experiments that deuterium scrambling does not occur; thus, the total amount of deuterated material is constant throughout the reaction. This is also true for the non-deuterated material. The ratio of the two is measured before the reaction begins by NMR of the starting-material mixture. Thus:

$$r = \frac{S_D^0}{S_H^0} = \frac{S_D + P_D}{S_H + P_H} \qquad \textbf{(A1)}$$

In order to establish the rates of the two reactions, it is necessary to analyse the conversion of the reagents as a function of time. The two target values are therefore C_H and C_D, the conversions for the reactions of S_H and S_D, respectively.

$$C_H = \frac{P_H}{P_H + S_H} \qquad \textbf{(A2)}$$

$$C_D = \frac{P_D}{P_D + S_D} \qquad \textbf{(A3)}$$

The reaction mixture gives an NMR spectrum, which can be represented by the following cartoon (Figure 20).

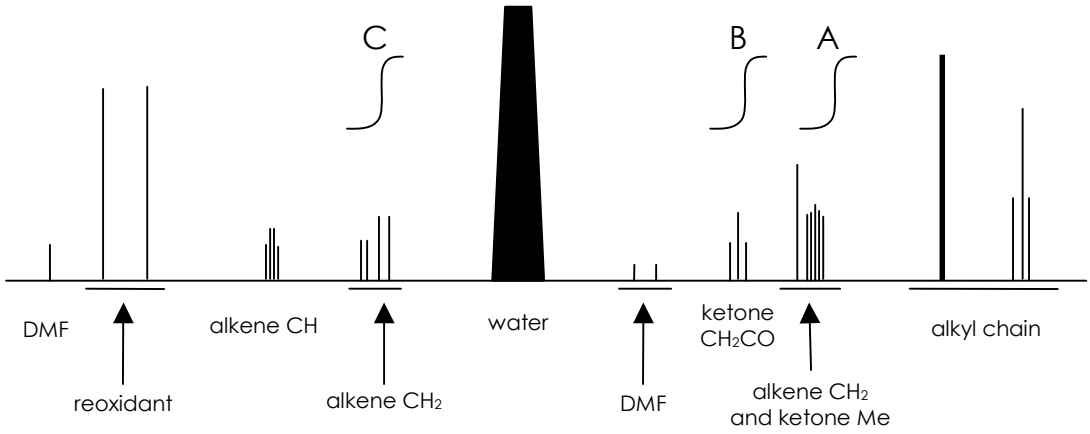


Figure 20 – Carton of NMR spectrum

There are three regions of interest in the NMR:

- Region A, consisting of the allylic CH_2 of the product and the methyl group adjacent to the ketone of the product. The region has an integration given by $2S_H+3P_H+3P_D$.
- Region B, the CH_2 adjacent to the ketone; integration proportional to $2P_H$.
- Region C, the terminal position of the alkene of the starting material. This region has integration proportional to $2S_H+2S_D$.

As it is only necessary to calculate the *relative* amounts of the materials, it is possible to use the integrations directly, giving:

$$A = 2S_H + 3P_H + 3P_D \quad \textbf{(A4)}$$

$$B = 2P_H \quad \textbf{(A5)}$$

$$C = 2S_H + 2S_D \quad \textbf{(A6)}$$

By inspection, it is possible to arrive directly at a value for P_H. Now, the linear sum of the three integrals:

$$A + B + C = 2S_H + 3P_H + 3P_D + 2P_H + 2S_D + 2S_H$$

Using **A1** and **A5**:

$$A + B + C = 4S_H + 5P_H + P_D + 2r(S_H + P_H)$$
$$\Rightarrow A + B + C = (4 + 2r)S_H + \frac{(5 + r)B}{2} + P_D$$

And so:

$$S_H = \frac{A - (\tfrac{3}{2} + r)B + C - P_D}{4 + 2\alpha}$$

It is possible to rearrange **A4** to give:

$$S_H = \frac{A - \tfrac{3}{2}B - 3P_D}{2}$$

And so:

$$\frac{A - (\tfrac{3}{2} + r)B + C - P_D}{4 + 2r} = \frac{A - \tfrac{3}{2}B - 3P_D}{2}$$

$$\therefore P_D = \frac{(1 + r)A - \tfrac{1}{2}(3 + r)B - C}{5 + 3r}$$

Substitution into **A4** gives:

$$S_H = \frac{2A - 3(1 + \alpha)B + 3C}{2(5 + 3\alpha)}$$

And therefore from **A6**:

$$S_D = \frac{3(1 + r)B + (2 + r)C - 2A}{2(5 + 3r)}$$

Substitution of these values into **A2** and **A3** will give the desired conversion values:

$$C_H = \frac{(5 + 3r)B}{2A + 2B + 3C} \qquad \textbf{(A7)}$$

$$C_D = \frac{2(1 + r)A - (3 + r)B - 2C}{(2A + 2B + 3C)r} \qquad \textbf{(A8)}$$

Ich bin mit meinem Latein am Ende

German expression