Metal Catalysed Intermolecular Hydroacylation

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Abstract

Metal-catalysed hydroacylation is a versatile method for the coupling of aldehydes and alkenes to generate ketones. To date, several systems have been developed, most of which require harsh conditions or are only applicable to a limited range of substrates. This thesis discusses the development of a mild system for the hydroacylation of alkenes with a simple aliphatic aldehyde. A coordinatively unsaturated cationic rhodium catalyst is used, in loadings as low as 1 %. Oxidative addition of the aldehyde C–H bond generates an acyl-rhodium species. A common problem in hydroacylation is decomposition of this complex by decarbonylation, which results in deactivation of the catalyst. The key to the system described is stabilisation of the acyl-rhodium intermediate by chelation of a β-sulfanyl group in the aldehyde. Electron-poor alkenes were found to be the most effective substrates for this system. For example, the hydroacylation of methyl acrylate is complete within 45 minutes at 60 °C. Microwave heating was found to accelerate the reaction, reducing the required time to less than 10 minutes.

Acknowledgements

First, thanks to Mike Willis for his guidance and enthusiasm over the last three years. Paul Beswick at GlaxoSmithKline for invaluable discussions and advice. EPSRC and GlaxoSmithKline for funding. Many thanks also to Andy Weller and Adam Rifat for supplying the carborane catalyst and for practical advice and helpful discussions throughout. The EPSRC Mass Spectrometry Service for prompt and excellent service, and all the technical staff of the University of Bath Chemistry Department.

To everyone in the organic section at Bath: Cheers, I've had a great three years! Thanks to Mike Edwards and Steve Flower for proofreading, and loads of help and advice.

Thanks and lots of love to my Mum and Dad for their continuous support over my countless years in education! Last, but not least, thanks and all my love to Suvi for her support, help and advice, especially over the last few months.

Contents

List of abbreviations

In order to conserve space, the following abbreviations will be used throughout:

acac	–	2,4-pentanedionato
Ac	–	acetyl
BINAP	–	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	–	benzyl
b.p.	–	boiling point
Bu	–	butyl
i-Bu	–	isobutyl
t-Bu	–	tertiary butyl
cod	–	1,5-cyclooctadiene
cot	–	1,3,5-cyclooctatriene
DCE	–	1,2-dichloroethane
DCM	–	dichloromethane
dec.	–	decomposed
DIPMC	–	1,2-bis(diphenylphosphinomethyl)cyclohexane

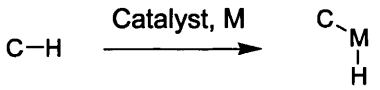
DMSO	–	dimethyl sulfoxide
DMP	–	Dess-Martin periodinane
dppe	–	1,2-bis(diphenylphosphino)ethane
dppf	–	1,1'-bis(diphenylphosphino)ferrocene
d.r.	–	diastereomeric ratio
e.e.	–	enantiomeric excess
Et	–	ethyl
IBX	–	*o*-iodoxybenzoic acid
lit.	–	literature
Me	–	methyl
m.p.	–	melting point
MW	–	microwave
NBD	–	bicyclo[2.2.1]hepta-2,5-diene
NMR	–	nuclear magnetic resonance
PCC	–	pyridinium chlorochromate
Ph	–	phenyl
ppm	–	parts per million
Pr	–	propyl

i-Pr	–	isopropyl
Py	–	pyridyl
r.t.	–	room temperature
THF	–	tetrahydrofuran
Tf	–	trifluoromethane sulfonyl
TMS	–	tetramethylsilane
TPAP	–	tetrapropylammonium perruthenate

Chapter 1 Introduction

1.1 Metal catalysed C–H bond activation

Typical operations across the whole range of synthetic organic chemistry are carried out with the aid of functional groups; most of the carbon-hydrogen bonds in organic compounds are thought of as inert, not as reactive parts of the molecule. In the 1960's it was discovered that certain soluble transition metal complexes were able to undertake cleavage of unactivated C–H bonds, opening up new possibilities in organic synthesis. Metal-catalysed C–H bond activation has now been used in a wide range of synthetic transformations and there are extensive reviews on this subject.[1-3] In its simplest terms, metal catalysed C–H activation can be thought of as the replacement of a strong carbon–hydrogen σ–bond with a weaker, more readily functionalised carbon–metal σ–bond (Scheme 1).

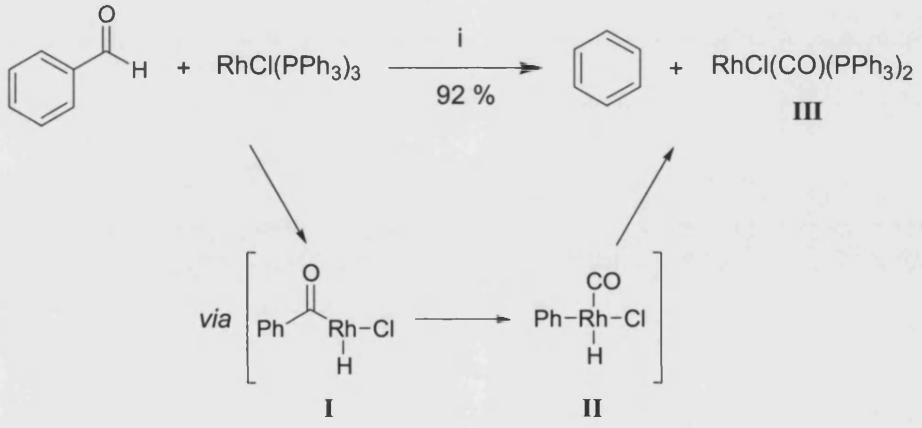


Scheme 1: Metal catalysed C–H bond activation

1.2 Decarbonylation

One important example of C–H bond activation is the decarbonylation of aldehydes. Most reactions of aldehydes involve solely the carbonyl C=O bond; the hydrogen of the aldehyde group is not normally thought of as reactive. However, the aldehyde hydrogen can react with some transition metals. For example, treatment of an

aldehyde with metallic palladium at 200 °C generates the corresponding alkane with evolution of carbon monoxide.[4] Further investigation by Tsuji revealed that $RhCl(PPh_3)_3$ was a more efficient decarbonylating agent, effecting the decarbonylation of aldehydes smoothly at room temperature.[5,6] This has now been developed into a useful synthetic process (e.g. Scheme 2).[7] The key step is the oxidative addition of the aldehyde C–H bond to the metal to give an acyl rhodium hydride (**I**), which undergoes carbonyl migration to give alkyl rhodium hydride (**II**).[8] Reductive elimination then gives the decarbonylated product and a rhodium carbonyl complex (**III**).



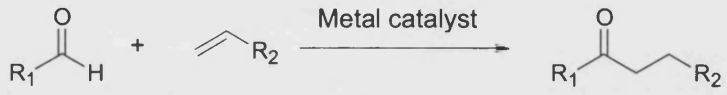
i) toluene, reflux, 1 h.

Scheme 2: Decarbonylation

Under the normal reaction conditions, this is a stoichiometric rather than catalytic process. The active rhodium species is not regenerated, but is converted completely to the carbonyl complex, which is unable to perform the C–H activation. The dissociation of carbon monoxide is very slow at room temperature, effectively rendering this species catalytically inactive.

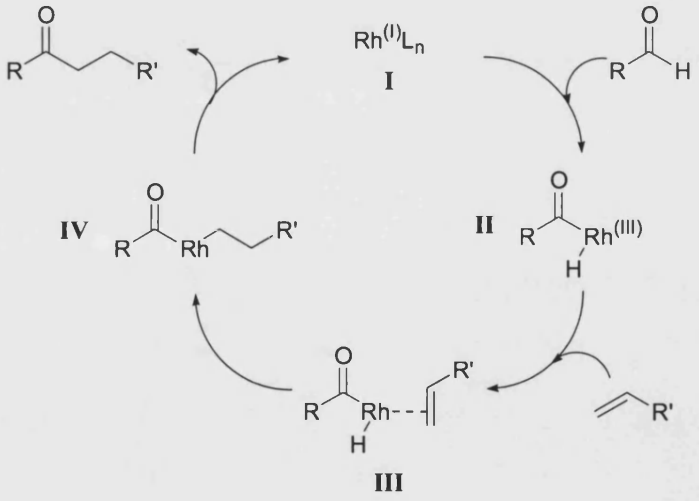
1.3 Hydroacylation

Hydroacylation is the formal addition of a hydrogen atom and an acyl unit across a multiple bond. The most basic example, addition of an aldehyde and alkene, is shown below (Scheme 3).



Scheme 3: Hydroacylation

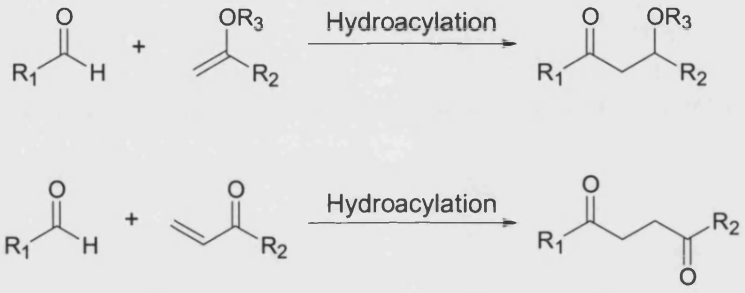
An outline of the currently accepted mechanism is shown in Scheme 4. It is believed the reaction proceeds *via* initial oxidative addition of the aldehyde C–H bond to the metal catalyst (**I**) to form an acyl metal hydride species (**II**), followed by alkene insertion into the metal–hydride bond (**III** to **IV**). Finally, reductive elimination of the ketone product regenerates the catalytic species.



Scheme 4: Mechanism of the hydroacylation reaction

As can be seen from this representative reaction scheme, hydroacylation is an atom-economical process: every atom from the starting materials is incorporated into the

final product. There are no leaving groups, and no by-products. If low catalyst loadings and benign solvents are used, this can be an environmentally friendly process. The hydroacylation of more complex alkene substrates could lead to more functionalised and potentially valuable products. For example the hydroacylation of enol ethers to give β-hydroxyketone derivatives could be a mild, neutral alternative to the aldol reaction; the hydroacylation of α,β-unsaturated ketones or esters would be a direct route to 1,4-dicarbonyl compounds, which are commonly used in the synthesis of furans and other heterocycles.[9,10] (Scheme 5)

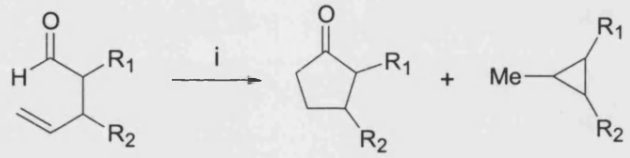


Scheme 5: Hydroacylation to give aldol or 1,4-dicarbonyl products

To date, the direct hydroacylation of simple aldehydes and alkenes such as these has not been realised. The rest of this review describes the advances that have been made to achieving this goal.

1.4 Intramolecular hydroacylation

The first reported example of hydroacylation was in 1972, when a rhodium-promoted cyclisation was used by Sakai during his synthesis of prostanoids (Scheme 6).[11] The reaction used a stoichiometric amount of the rhodium complex $RhCl(PPh_3)_3$ and gave the desired cyclopentanones (**I**) in a maximum of 34 % yield, along with a similar amount of the cyclopropane derivatives (**II**) resulting from decarbonylation.



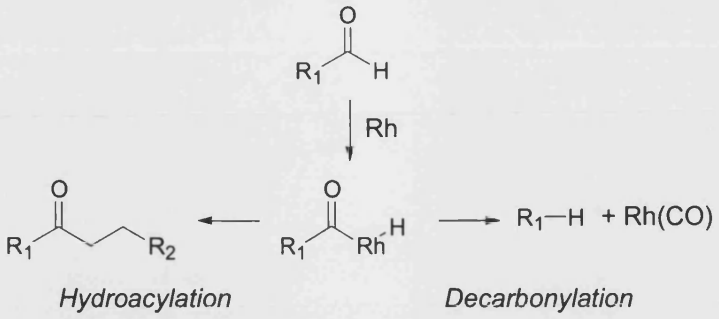
I 17 - 34 %

II 20 - 35 %

i) $RhCl(PPh_3)_3$ (1 equiv.), $CHCl_3$, MeCN or C_6H_6, r.t.

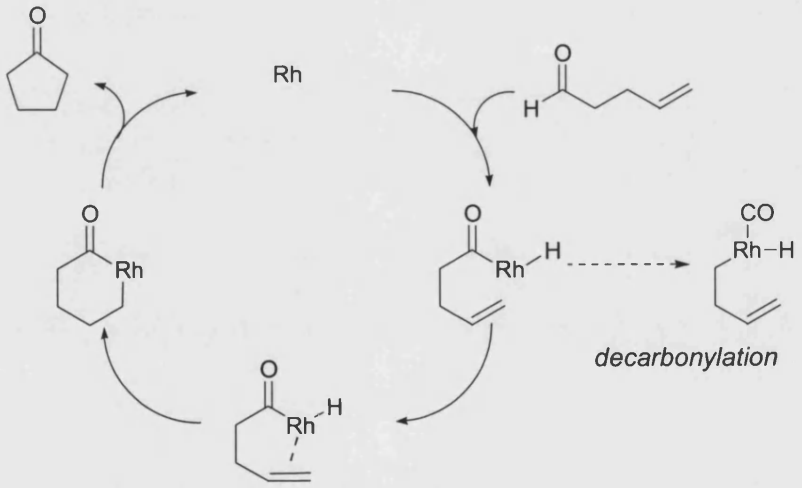
Scheme 6: First example of hydroacylation

The competitive process of decarbonylation is the limiting factor in most simple examples of hydroacylation. This is because it proceeds by a similar C–H activation mechanism to hydroacylation. After oxidative addition of the metal into the aldehyde C–H bond, carbonyl migration followed by reductive elimination of alkane leaves the catalytically inactive rhodium carbonyl complex (Scheme 7).



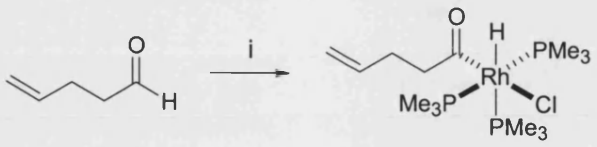
Scheme 7: Decarbonylation

As the previous example demonstrates (Scheme 6), the addition of an acyl unit across an olefin is easy in an intramolecular process. The olefin is in close proximity to the metal centre when oxidative addition occurs and the subsequent cyclisation is fast enough to compete with decarbonylation (Scheme 8).



Scheme 8: Mechanism of intramolecular hydroacylation

The mechanism shown in Scheme 8 is supported by the isolation of an acylrhodium (III) hydride complex (Scheme 9), which is relatively stable due to the very slow rate of trimethylphosphine dissociation.[12]

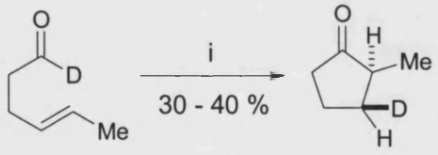


i) $RhCl(PMe_3)_3$, PhMe, r.t.

Scheme 9: Isolation of stable acylrhodium hydride

Upon heating to 50 °C the complex undergoes intramolecular hydroacylation to form cyclopentanone in 72 % yield, along with products resulting from decarbonylation. ^{31}P NMR suggests the ligand geometry shown in Scheme 9, where the acyl unit occupies the site *trans* to the chloride.

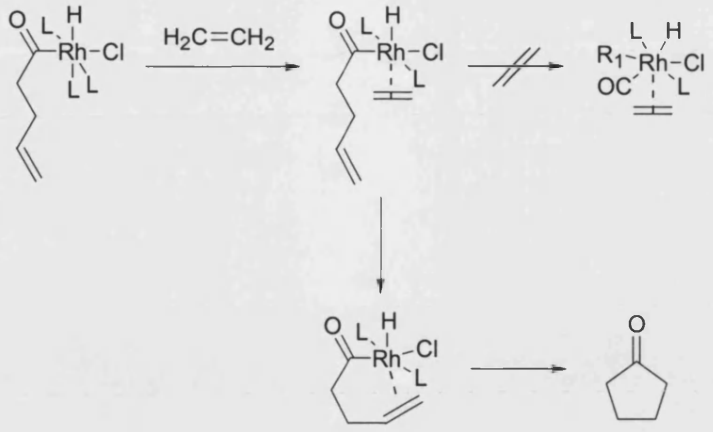
Deuterium labelling studies have shown that the cyclisation proceeds by a *syn* addition of the aldehyde C–H bond across the alkene double bond (Scheme 10).[13]



i) $RhCl(PPh_3)_3$, $CHCl_3$ or C_6H_6, r.t.

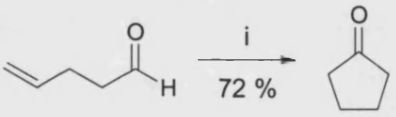
Scheme 10: *Syn*-addition to the alkene

The earliest examples of hydroacylation required stoichiometric quantities of the metal catalyst due to deactivation by decarbonylation. Miller and co-workers demonstrated that the reaction could be performed catalytically by using ethylene-saturated solvent.[14] It is believed that the ethylene ensures coordinative saturation of the rhodium throughout the reaction. This suppresses the decarbonylation process, which requires a vacant coordination site on the metal centre (Scheme 11).



Scheme 11: Suppression of decarbonylation by ethylene

Thus, cyclopentanone was obtained in good yield by treatment of 4-pentenal with 10 mol% catalyst in ethylene-saturated chloroform (Scheme 12).

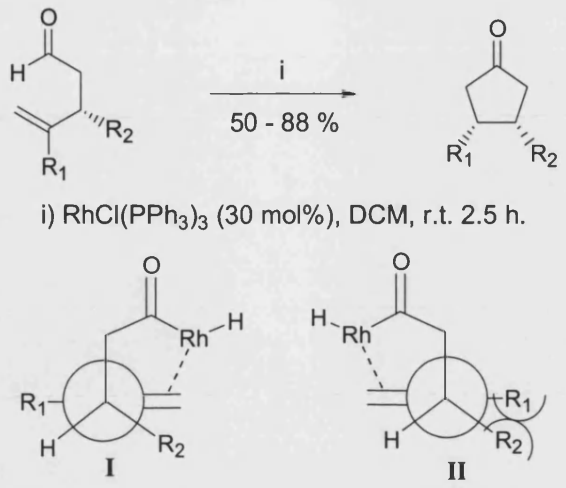


i) $RhCl(PPh_3)_3$ (10 mol%), $CHCl_3$, $CH_2=CH_2$, r.t., 88 h.

Scheme 12: Catalytic cyclisation of 4-pentenal

No other added olefin or acetylene proved as effective. Yields were slightly improved by changes to the nature of the phosphine ligand.[15] It was also reported that adding water had no effect on the yield, but the catalyst was destroyed in the presence of oxygen.

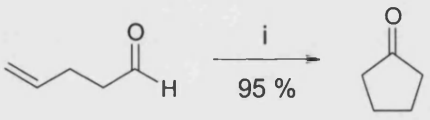
Further work by Sakai expanded the scope of the intramolecular hydroacylation reaction to include the cyclisation of 3,4-disubstituted 4-pentenals, which proceeds in a stereospecific manner to give *cis*-3,4-disubstituted cyclopentanones (Scheme 13).[16] This is explained in terms of steric repulsion between the two vicinal substituents in the olefin-coordinated transition state: arrangement **I** is favoured over **II**.



Scheme 13: Cyclisation to *cis*-3,4-disubstituted cyclopentanones

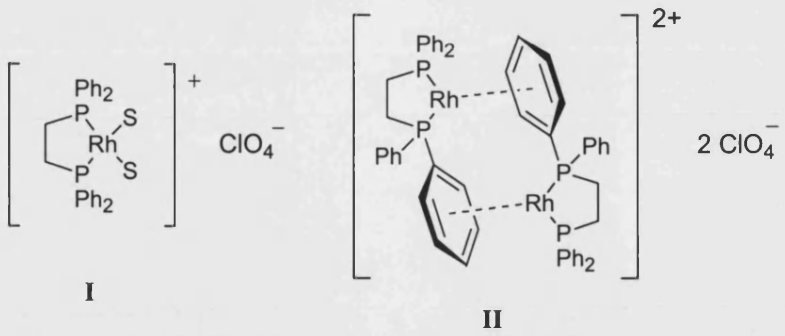
This stereoselective cyclisation has been applied to the enantioselective synthesis of natural products and biologically active compounds such as prostaglandins.[17-22]

In 1988, Bosnich and co-workers showed that the cyclisation of 4-pentenal to cyclopentanone could be carried out efficiently at room temperature with a 1 % loading of a cationic rhodium complex, $[Rh(dppe)]^+ ClO_4^-$ (Scheme 14).[23,24]



Scheme 14: Hydroacylation with cationic catalyst

The catalyst (Figure 1) exists as a disolvento complex (**I**) in coordinating solvents such as acetone or methanol but as a phenyl-bridged dimer (**II**) in the solid state and in weakly coordinating solvents.



S = Coordinating solvent, e.g. acetone or methanol

Figure 1: Cationic rhodium catalyst

Addition of 4-pentenal causes splitting of the dimer or displacement of the solvent, resulting in the coordinated aldehyde species shown in Figure 2.

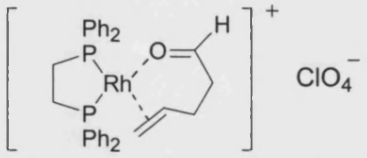
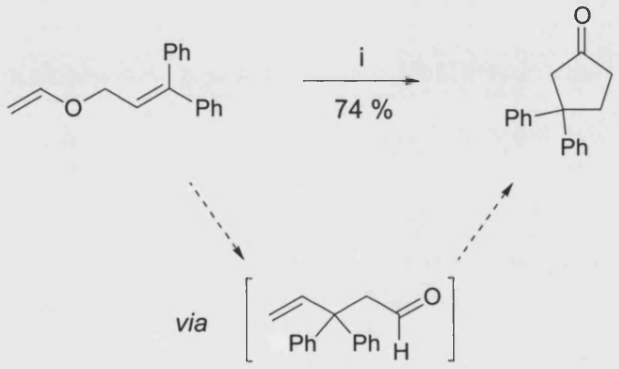


Figure 2: Pentenal rhodium complex

The superiority of this cationic rhodium complex as a hydroacylation catalyst is attributed to the fact that coordination unsaturation of the rhodium (III) complex accelerates the reductive elimination step, although the precise reasons for this are unknown. Coordination unsaturation would also accelerate the decarbonylation of the acyl metal intermediate, but the corresponding metal carbonyl species is expected to be destabilised relative to a neutral species because of the positively charged metal centre.[25]

Direct cyclisation of allyl vinyl ethers

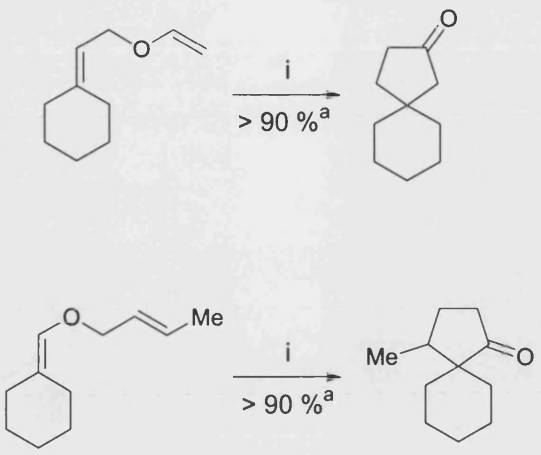
Substituted 4-pentenals, which have been successfully used in the intramolecular hydroacylation reaction, are most conveniently produced by Claisen rearrangement of the corresponding allyl vinyl ethers, which can be promoted by transition metal catalysts.[26,27] With a suitable catalyst, the rearrangement and hydroacylation steps can be performed as a sequential transformation, resulting in a "one-pot" synthesis of cyclopentanones from allyl vinyl ethers (Scheme 15).[28] This avoids the problematic isolation of the sensitive aldehyde intermediates.



i) RhCl(COD)(dppe) (5 mol%), PhCN, 190 °C, 20 h.

Scheme 15: Cyclisation of allyl vinyl ether

This methodology has also been applied to the synthesis of spiro[4.5]decanone products (Scheme 16). [29-31] These products could be valuable as intermediates in the synthesis of terpenoid natural products, some of which are known to contain spirodecane skeletons.[32]



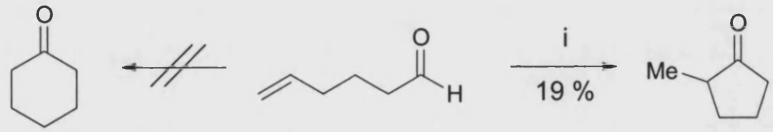
i) RhCl(COD)(dppe) (3 mol%), PhCN, 160 °C

a) Yields by GLC, isolated yields 55-73 %

Scheme 16: Formation of spiro[4.5]decanones

Formation of medium-sized rings

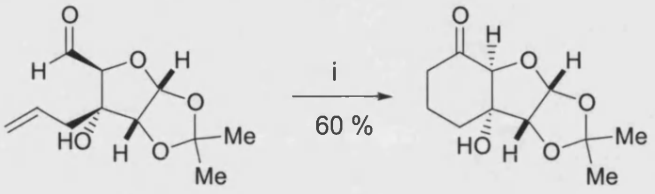
The formation of larger ring systems by hydroacylation is not a trivial matter. This is mainly because the cyclisation of larger ring-sizes is slower, so competition from decarbonylation becomes more of a problem. In addition, if 5-membered ring formation is possible, this will occur in preference. Reaction of 5-hexenal, for example, does not give cyclohexanone but 5-methyl cyclopentanone as the product (Scheme 17).[15]



i) $RhCl(PPh_3)_3$ (50 mol%), DCM, r.t.

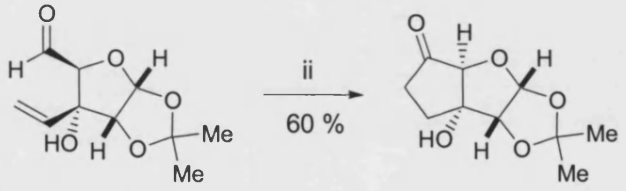
Scheme 17: Cyclisation of 5-hexenal

One example of six-membered ring formation has been shown, using a rigid carbohydrate-based alkene (Scheme 18).[33] In this case formation of a fused 5, 5, 5 tricyclic product may be inhibited by ring strain. This explanation is reinforced by the much slower formation of the cyclopentanone product from a vinyl analogue (**II**). This is not a general process, and is only applicable to a very limited range of substrates.



I

i) $[(Ph_3P)_2RhCl]_2$ (30 mol%), ethylene (1 atm), $CDCl_3$, 70 °C, 6 h.

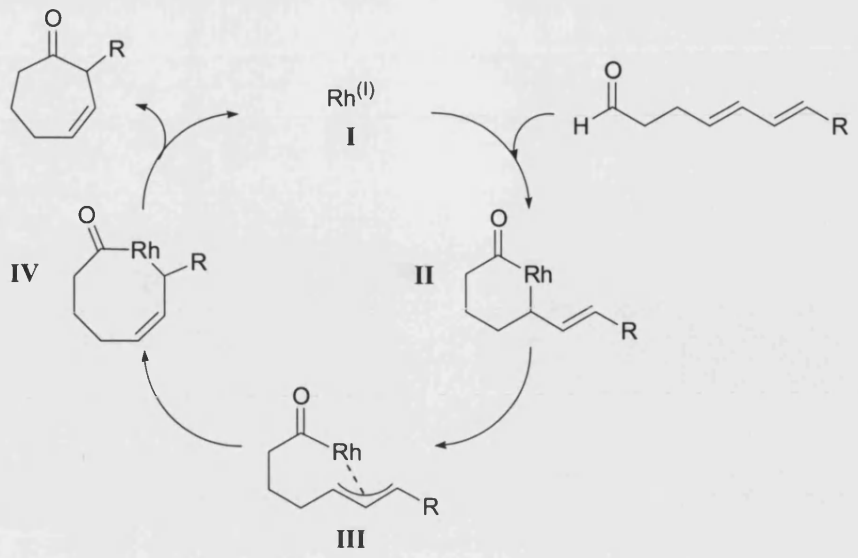


II

ii) $[(Ph_3P)_2RhCl]_2$ (30 mol%), ethylene (1 atm), $CDCl_3$, 75 °C, 15 h.

Scheme 18: Formation of cyclohexanone

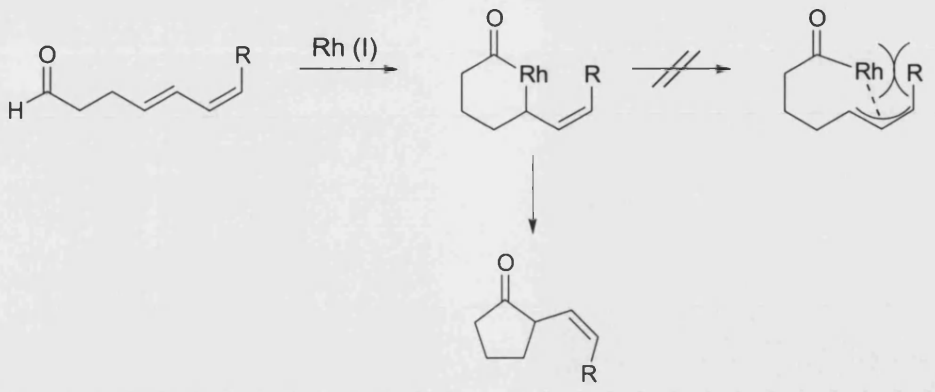
It is possible to build other medium-sized rings by incorporating suitable functionality into the substrates. Mori *et al* reported the cyclisation of 4,6-dienals to give cycloheptenone products (Scheme 19).[34]



Scheme 19: Formation of cycloheptenones

After the normal oxidative addition and olefin insertion, the Rh–C bond of the intermediate is conjugated with the second alkene double bond (**II**), and a ring expansion to give a larger metallacycle (**IV**) can occur *via* a π-allyl rhodium intermediate (**III**).

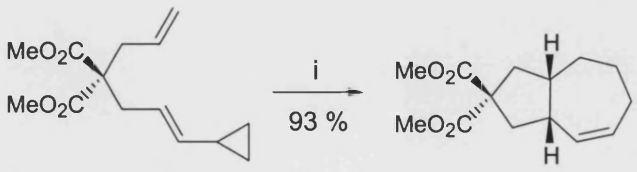
The cycloheptenone products were formed in yields of up to 70 %, along with cyclopentanone products and double-bond isomers. It was found that only dienes with *E*-geometry at the 6-position (4*E*, 6*E*) or (4*Z*, 6*E*) gave cycloheptenone products; (4*E*, 6*Z*) dienes gave only cyclopentanones. This was rationalised by considering the formation of the π-allyl system (**III**), which can only occur with the (*E*)-double bond isomer of the preceding rhodacycle (**II**). The (6*Z*)-alkene would form the corresponding (*Z*)-isomer of the rhodacycle (Scheme 20). In this intermediate, steric repulsion between the substituent R and the metal centre would disfavour formation of the allyl system, resulting in elimination of the cyclopentanone product.



Scheme 20: Cyclisation of (6*Z*)-isomer

A terminal alkyl substituent was also found to be necessary, presumably to stabilise the build-up of positive charge on the terminal carbon atom during formation of the eight-membered rhodacycle intermediate (**IV**).

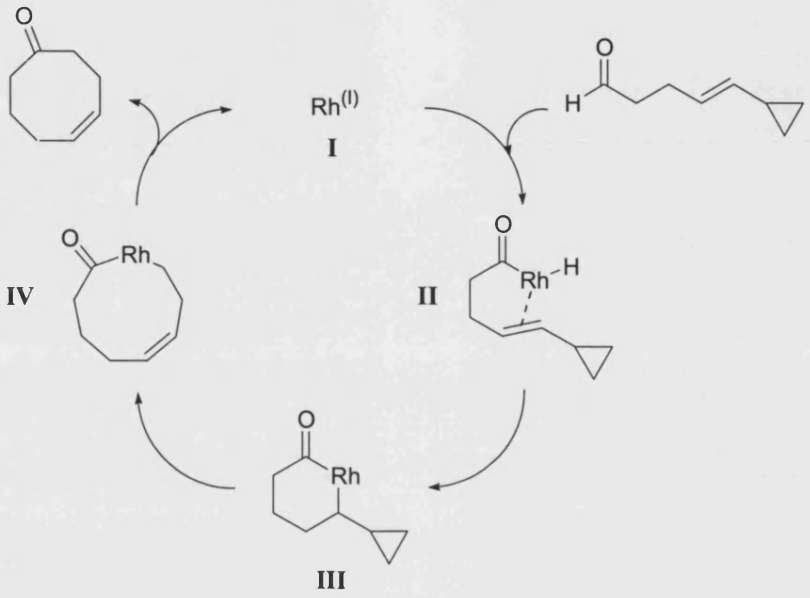
Shair and co-workers have reported an elegant method for the formation of cyclooctenones by intramolecular hydroacylation.[35] Direct cyclisation to eight-membered rings is prohibitively slow under normal hydroacylation conditions. However, this methodology can be extended to eight-membered ring formation by the strategic placement, in the starting material, of a cyclopropane ring capable of fragmentation. A similar strategy was used by Wender[36-39] and Trost[40,41] in rhodium- and ruthenium-catalysed [5+2] cycloadditions affording seven-membered rings (e.g. Scheme 21).[39]



i) $RhCl(PPh_3)_3$ (1 mol%), AgOTf (1 mol%), toluene, 110 °C, 5h.

Scheme 21: [5+2] Cycloadditions of vinylcyclopropanes

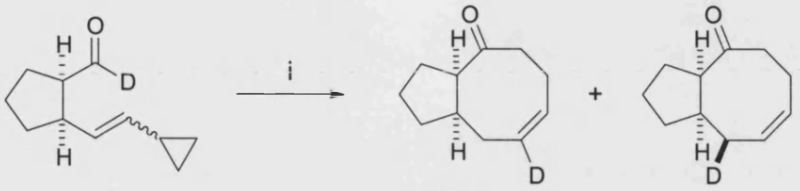
The proposed mechanism of the corresponding rhodium-catalysed hydroacylation is shown in Scheme 22. The key step is the ring fragmentation and isomerisation leading to a nine-membered rhodium metallacycle (**III** to **IV**).



Scheme 22: Formation of eight-membered rings *via* cyclopropane fragmentation

The main concern in this process is whether the rate of the desired ring opening is sufficient to compete with elimination from the six-membered metallacycle (**III**). It was found that treatment with $RhCl(PPh_3)_3$ did not give any hydroacylation products, presumably due to decarbonylation. However, cationic rhodium (I) catalysts of the type favoured by Bosnich allowed the ring fragmentation and subsequent hydroacylation to proceed. In addition, performing the reaction under an ethylene atmosphere reduced the amount of decarbonylation, delivering the cyclooctenone product in 65 % yield. It was observed that coordinating solvents such as tetrahydrofuran drastically inhibited the reaction, presumably due to coordination to the cationic rhodium centre.

During an investigation into the reaction mechanism, it was discovered that alkene geometry had a significant effect (Table 1). Exposing a deuterium-labelled aldehyde to a cationic rhodium catalyst gave a mixture of deuterium-labelled products in a ratio that directly corresponded to the *E*:*Z* ratio of the starting material.



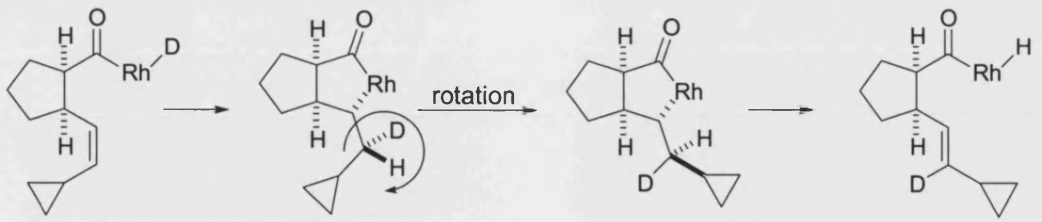
I **II** **III**

i) Rh(dppe)OTf (20 mol%), DCE, 65 °C

E:*Z* ratio of **I**	Product ratio **II**:**III**
78 : 22	78 : 22
95 : 5	94 : 6

Table 1: Deuterium labelled cyclooctenone experiment

This implies that the two isomers are converted into the cyclised product by different routes. It was suggested by Shair that the *E*-isomer is converted directly to cyclooctenone by the mechanism shown in Scheme 22. Because of the rigidity imposed by the cyclic structure, the *Z*-isomer cannot directly form a 6-membered rhodacycle. It undergoes an additional rhodium-catalysed isomerisation to the *E*-alkene (Scheme 23), which is then converted into the cyclooctene product with the deuterium label at the 6-position.

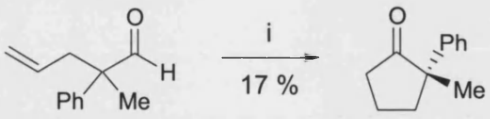


Scheme 23: Isomerisation of *Z*-alkene during cyclooctenone formation

Medium ring heterocyclic products have also been formed in a chelation-assisted hydroacylation process (see next chapter).

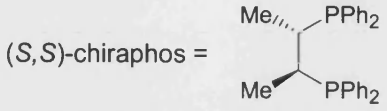
Asymmetric hydroacylation

The intramolecular hydroacylation reaction has also been developed into an asymmetric process. In an early example, James and co-workers demonstrated that racemic 2,2-disubstituted pentenals could be resolved by treatment with rhodium (I) complexes bearing chiral diphosphine ligands at high temperature.[42] Enantiomeric excess of up to 70 % was achieved, but only at low conversion (17 % yield). At high conversion, the e.e. of the product was less than 40 %. One reason for the poor results with this compound is the quaternary α-carbon; 2,2-disubstituted pentenals are known to be poor substrates for hydroacylation.[15,23]



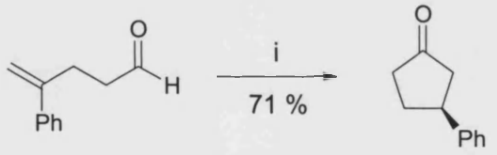
e.e. 69 %

i) [Rh(*S*,*S*-chiraphos)$_2$]Cl, PhCN, 150 °C, 6 h.



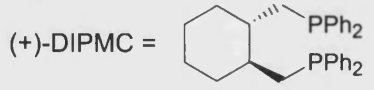
Scheme 24: Resolution of racemic aldehyde

In a more recent example, the cyclisation of 4-substituted pentenals has been carried out stereoselectively by using rhodium complexes with chiral phosphine ligands. 4-Phenyl-4-pentenal was converted into (*S*)-3-phenylcyclopentanone at room temperature. The most effective ligand was found to be (+)-DIPMC (Scheme 25).[43]



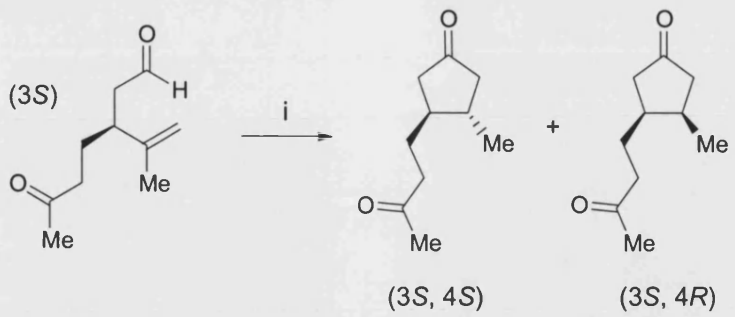
e.e. 76 %

i) Rh(DIPMC)Cl (25 mol%), DCM, r.t. 4 h.



Scheme 25: Asymmetric cyclisation of 4-phenyl-4-pentenal

As discussed earlier, the cyclisation of 3,4-disubstituted aldehydes with $RhCl(PPh_3)_3$ gives exclusively the *cis*-product. However, when chiral rhodium complexes are used, *trans* products can also be obtained. With BINAP ligands, excellent stereoselectivity was obtained (Table 2).[43,44]

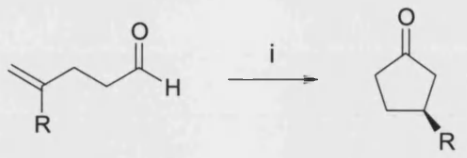


i) $Rh(BINAP)ClO_4$ (5 mol%), DCM, r.t. 2 h.

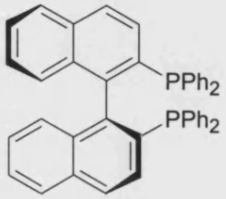
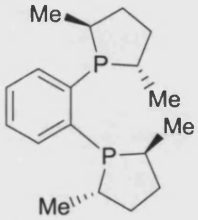
Substrate	Ligand	Yield (%)	*trans* : *cis*	product
(3*S*)	(*R*)-BINAP	86	> 99 : 1	(3*S*, 4*S*)
(3*S*)	(*S*)-BINAP	82	4 : 96	(3*S*, 4*R*)
(3*R*)	(*R*)-BINAP	74	3 : 97	(3*R*, 4*S*)
(3*R*)	(*S*)-BINAP	85	> 99 : 1	(3*R*, 4*R*)

Table 2: Asymmetric cyclisation of 3,4-disubstituted aldehydes

Using chiral diphosphine ligands with cationic rhodium complexes allows the intramolecular hydroacylation to deliver substituted cyclopentanones efficiently and with excellent stereocontrol.[45-48] With 4-substituted pentenals, the appropriate ligand must be selected to maximise the yield. (*S*)-Binap was found to be extremely effective for substrates with a tertiary or ester substituent, but (*S,S*)-Me-Duphos gave better results with primary and secondary alkyl substituents[49,50] (Table 3). Both catalyst systems gave only moderate results with aryl-substituted aldehydes.[45,48,51]



i) [Rh(ligand)] ClO_4 (4 mol%), DCM, r.t.

Entry	Substrate, R =	Ligand	e.e.[a] (%)
1	t-Bu		> 99
2	$SiMe_3$		> 99
3	CO_2Et	(*S*)-BINAP	> 99
4	Me		94
5	Bu		94
6	i-Pr		94
7	cyclohexyl	(*S*,*S*)-MeDuphos	93

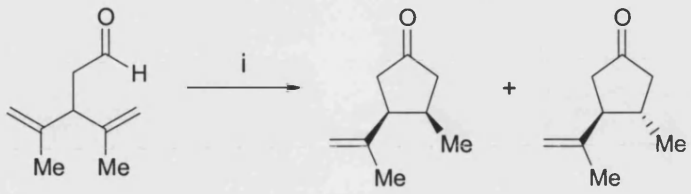
a. e.e. of major product: (*S*)-configuration obtained with both ligands shown.

Table 3: Asymmetric cyclisation of 4-substituted pentenal

The precise mechanism of the asymmetric hydroacylation could not be determined. The enantioselectivity does not appear to be governed by a single step, but arises from a number of reversible steps between reaction intermediates.[52]

Symmetrical disubstituted aldehydes have been desymmetrised by treatment with rhodium (I) BINAP complexes (Table 4).[53] Cationic rhodium perchlorate complexes give *trans* substituted products in good yield and with excellent enantiocontrol (entries 1 and 2). Using the neutral Rh(BINAP)Cl complex as catalyst gives *cis*

products (entries 3 and 4). The yield with the neutral catalyst is low, but the stereoselectivity was still very high. Thus, any of the four stereoisomeric products can be prepared by the choice of the appropriate catalyst complex.



i) Rh (I) catalyst, DCM, r.t.

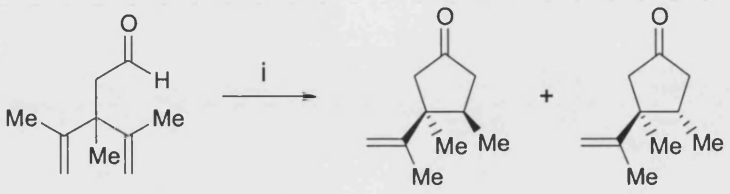
Entry	Catalyst [a]	Yield (%)	*cis/trans*	Config.[b]
1	Rh[*(R)*-BINAP]ClO_4	81	3 / 97	3*S*, 4*S*
2	Rh[*(S)*-BINAP]ClO_4	84	4 / 96	3*R*, 4*R*
3	Rh[*(R)*-BINAP]Cl	25	97 / 3	3*S*, 4*R*
4	Rh[*(S)*-BINAP]Cl	31	97 / 3	3*R*, 4*S*

a. 5 mol% catalyst loading with Rh(BINAP)ClO_4, 50 mol% loading with Rh(BINAP)Cl

b. Absolute configuration of major product: all were obtained with e.e. > 95 %

Table 4: Desymmetrisation of disubstituted aldehyde

Symmetrical 3,3,4-trisubstituted aldehydes have also been used in a desymmetrisation by rhodium BINAP complexes, giving trisubstituted cyclopentanones containing a quaternary carbon atom (Table 5).[53,54] In this case, the neutral rhodium catalyst did not give satisfactory results, but the cationic complex delivered *trans*-cyclopentanones with excellent enantioselectivity.



i) $Rh(BINAP)ClO_4$ (5 mol%), DCM, r.t.

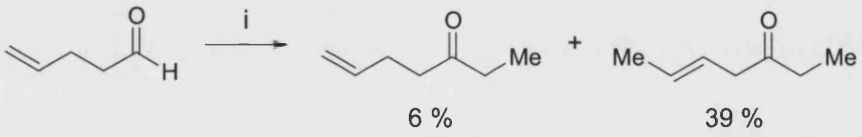
Entry	Ligand	Yield (%)	*cis*/*trans*	Config.[a]
1	*(R)*-BINAP	83	2 / 98	3*S*, 4*S*
2	*(S)*-BINAP	75	2 / 98	3*R*, 4*R*

a. Absolute configuration of major product: all were obtained with e.e. > 95 %

Table 5: Cyclisation of trisubstituted aldehyde

1.5 Intermolecular hydroacylation

Extending the principle of hydroacylation to an intermolecular reaction is an attractive prospect. The products would not be limited to cyclic ketones, and in addition to simple linear ketones, the process could become a mild, neutral route to aldol and dicarbonyl compounds. The isolation of acyl rhodium compounds confirmed that aldehyde C–H bonds can undergo oxidative addition to a metal catalyst and it has been shown that these acyl metal species can be added across an alkene double bond. Miller's early work on the intramolecular reaction showed that performing the reaction in ethylene-saturated solvent suppressed decarbonylation and allowed hydroacylation to proceed in good yield.[14] During their investigation they also discovered that changing the catalyst from $RhCl(PPh_3)_3$ to $Rh(acac)(C_2H_4)_2$ resulted in the generation of heptenones by the intermolecular hydroacylation of ethylene (Scheme 26).[55] Cyclopentanone was detected in only 1 % yield.



6 % 39 %

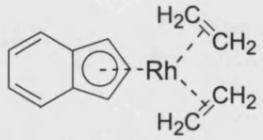
i) $Rh(acac)(C_2H_4)_2$ (10 mol%), $CHCl_3$, C_2H_4, r.t. 16 h.

Scheme 26: Intermolecular hydroacylation of ethylene

The Rh(acac) system requires unsaturation at the aldehyde 4-position, presumably to form a chelated intermediate *via* alkene coordination. The useful range of aldehyde substrates was extended when a rhodium indenyl complex was found to catalyse the addition of aromatic aldehydes to ethylene (Scheme 27).[56] This system requires fairly

harsh reaction conditions: 100°C in a sealed vessel under 70 atm. pressure of ethylene.

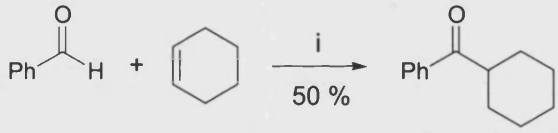
i) **I** (10 mol%), C_6D_6, 100 °C, C_2H_4 (70 atm.)



I

Scheme 27: Hydroacylation with aromatic aldehyde

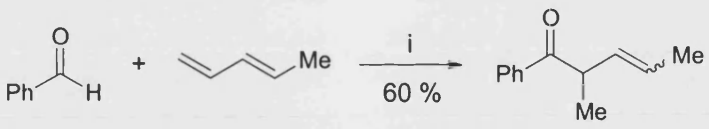
Ruthenium[57-60] and cobalt[61-64] catalysts have also been used. Watanabe and co-workers reported that Ru(0) complexes catalyse the intermolecular hydroacylation of olefins with aldehydes to give ketones.[59] Addition of aromatic and heteroaromatic aldehydes to various alkenes gives the ketone products in moderate yield (Scheme 28).



i) $Ru_3(CO)_{12}$ (1 mol%), CO (20 atm.), 200 °C, 48 h.

Scheme 28: Ruthenium-catalysed hydroacylation

The hydroacylation of 1,3-dienes gives β,γ-unsaturated ketone products *via* η^3-allyl ruthenium species (Scheme 29). Notably, carbon monoxide is not required to prevent aldehyde decarbonylation in this case.

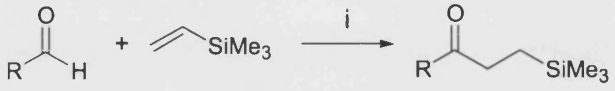


E : *Z* = 61 : 39

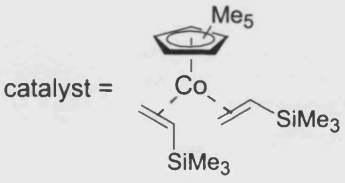
i) Ru(cod)(cot) (4 mol%), PPh_3, 120 °C, 15 h.

Scheme 29: Ruthenium-catalysed hydroacylation of 1,3-diene

Brookhart and co-workers have developed a cobalt complex which efficiently catalyses the addition of aldehydes to vinyl silanes (Table 6).[63-67]



i) Co(I) catalyst, acetone, 25 - 45 °C



Entry	Aldehyde, R =	Conversion[a] (%)
1	Pr	92
2	i-Pr	94
3	i-Bu	99
4	CH_2t-Bu	97
5	cyclohexyl	99

a. Conversion by NMR

Table 6: Hydroacylation of vinyl silane with aliphatic aldehydes

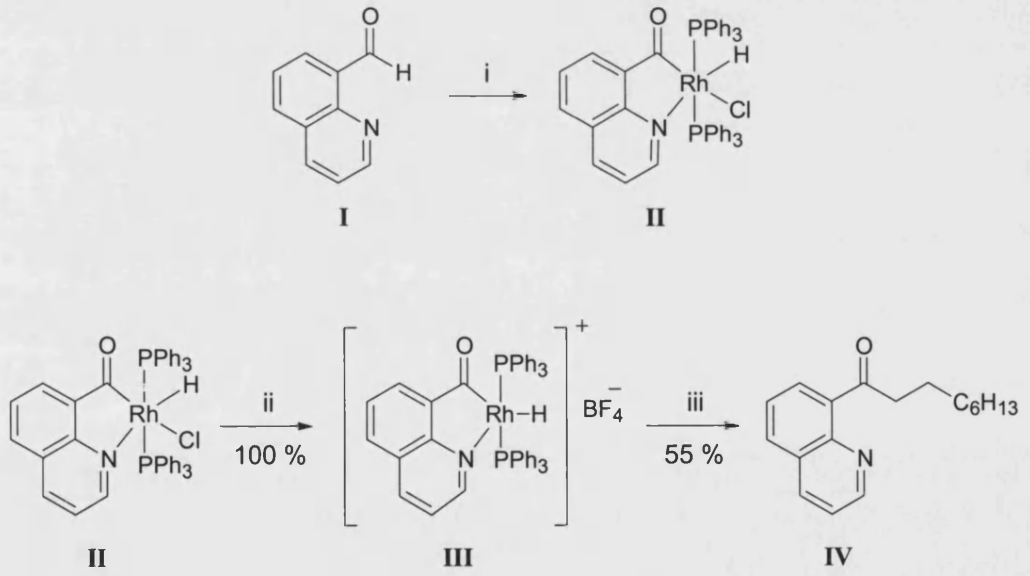
This system is limited to the hydroacylation of vinyl silanes; other alkenes are too strongly coordinating. However, it is compatible with aliphatic aldehydes, which have not been used directly in other systems. In addition, the conditions are considerably milder than most of the other hydroacylation reactions reported.

In most of the examples of intermolecular hydroacylation discussed so far, the reaction needs to be performed under high pressure of carbon monoxide to suppress decarbonylation and prevent decomposition of the catalyst, by maintaining coordinative saturation to stabilise the catalytic species.

1.6 Chelation-assisted hydroacylation

Reactions of quinoline carboxaldehyde

In 1977, while investigating the mechanism of metal-catalysed decarbonylation, Suggs demonstrated that incorporation of a coordinating group close to the reacting site in the aldehyde could lead to a stabilised intermediate: a strategy he termed 'chelate trapping'.[68] An added advantage is that pre-coordination can help position the metal correctly for C–H activation. Thus, treatment of 9-quinoline carboxaldehyde (**I** in Scheme 30)[69] with the rhodium complex $RhCl(PPh_3)_3$ at room temperature did not give the decarbonylation product as might be expected; instead, a stable acyl rhodium hydride species **II** was formed.



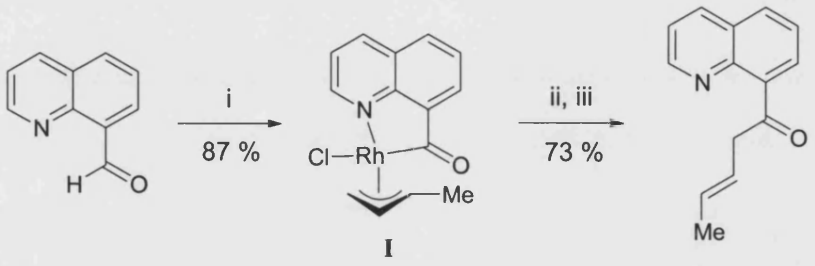
i) $RhCl(PPh_3)_3$, DCM, r.t.;
ii) $AgBF_4$, toluene/DCM, 0 °C; iii) octene, THF, 50 °C, 30 min.

Scheme 30: Isolation of a stable acyl metal hydride

The acyl complex (**II**) is stabilised by chelation *via* the quinoline nitrogen atom, and in the solid state was found to be thermally stable up to its melting point of 175–176

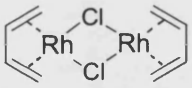
°C. Heating for four hours in refluxing xylene was required to eliminate the decarbonylation product. Treatment with silver tetrafluoroborate gave a coordinatively unsaturated complex (**III**), which was also stable at room temperature. This complex was a suitable reagent for hydroacylation, treatment with octene giving the ketone product (**IV**) in 55 % yield.

Jun and co-workers investigated the hydroacylation of various alkenes with quinoline carboxaldehyde[70-73] and carried out a mechanistic study into the hydroacylation of conjugated dienes (Scheme 31).



i) $[RhCl(diene)]_2$, C_6H_6, r.t. 10 min.; ii) pyridine; iii) $P(OMe)_3$

$[RhCl(diene)]_2$ =



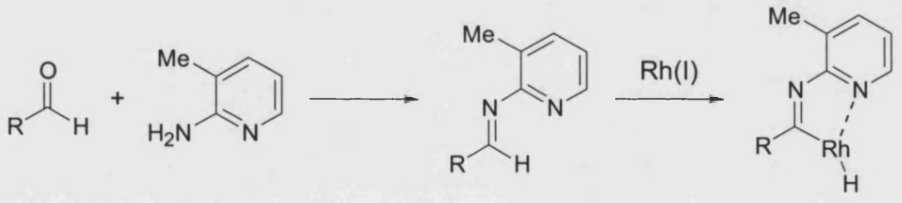
Scheme 31: Hydroacylation of dienes *via* η^3-allyl rhodium

Stoichiometric reaction between the aldehyde and the rhodium diene complex showed that the reaction proceeds *via* an η^3-allyl rhodium species (**I**), which could be isolated and characterised after addition of pyridine to cleave insoluble chlorine-bridged polymeric linkages. Further treatment with a phosphite ligand promoted reductive elimination to yield the β,γ-unsaturated ketone product.[74]

Picolyl aldimines

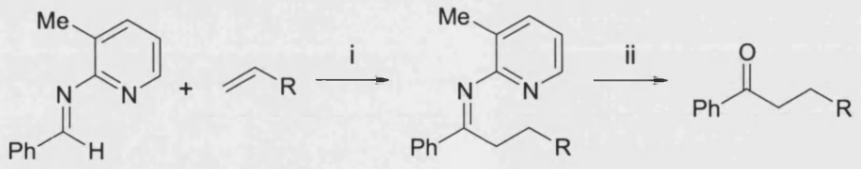
Hydroacylation with quinoline carboxaldehyde cannot give a range of synthetically useful products, as the quinoline group is not easily removed. The imine formed by the reaction of an aldehyde with 2-aminopicoline (Scheme 32) can undergo C–H activation[75] and has the same 1,5-relationship between the coordinating group and the aldimine C–H.[76] This confers the same beneficial features as for quinoline carboxaldehyde:

- Coordination from the pyridine nitrogen holds the rhodium in the correct position for C–H activation.
- After oxidative addition of the C–H bond, a stable five-membered chelated metal species is formed.



Scheme 32: Formation of picolyl imine

As expected, the picolyl imine of benzaldehyde forms a stable chelated intermediate upon oxidative addition to a rhodium (I) catalyst, which can be used for the hydroiminoacylation of various alkenes. This system has the added advantage that the coordinating picolyl group is easily removed by hydrolysis to yield synthetically versatile ketone products (Scheme 33).

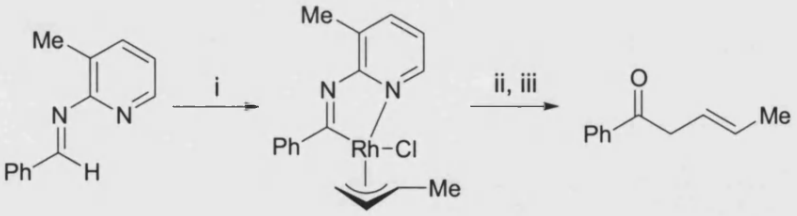


i) Rh(I) catalyst; ii) H^+ / H_2O

Scheme 33: Hydroacylation with picolyl imine

Initial experiments showed that stoichiometric reaction of the aldimine with $RhCl(PPh_3)_3$ under ethylene pressure followed by hydrolysis gave propiophenone in 85 % yield. Suggs also demonstrated in his early work that the reaction can be carried out catalytically: treatment of the aldimine with 5 mol% of catalyst gave propiophenone in 45 % yield. This system has now been greatly developed and has been used for the hydroacylation of various alkenes,[76-79] including polybutadiene[80,81] and has been applied to the synthesis of ^{18}F labelled ketones.[82]

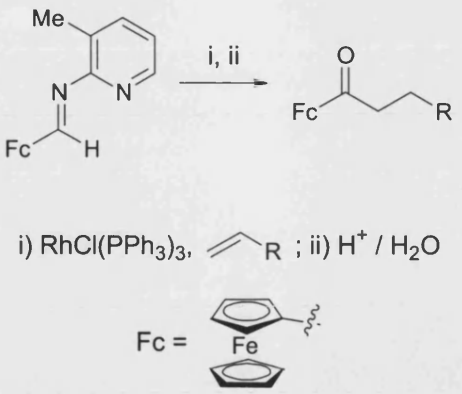
The hydroiminoacylation route has also been used for the formation of β,γ-unsaturated ketones from dienes *via* η^3-allyl rhodium complexes (Scheme 34).[83]



i) $[Rh(diene)Cl]_2$, THF, 55 °C, 10 min.; ii) $P(OMe)_3$, r.t., 30 min.; iii) 1N HCl

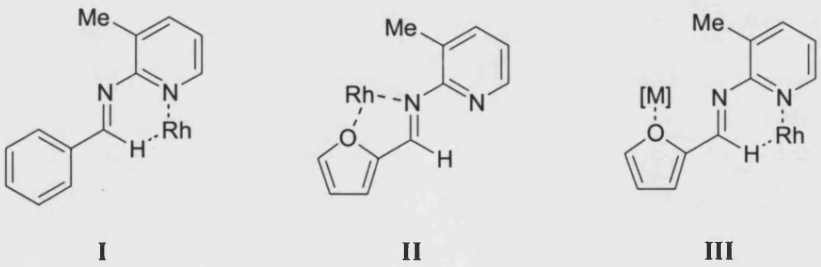
Scheme 34: Hydroiminoacylation of conjugated diene

Aliphatic aldehydes were found to undergo an unfavourable aldol side-reaction, but the picolyl imine system can be applied to other aromatic aldehydes. Jun showed that the imine formed by condensation of ferrocenecarboxaldehyde and aminopicoline could be used for the hydroacylation of alkenes (Scheme 35).[84,85]



Scheme 35: Hydroacylation with ferrocenecarboxaldimine

With heteroaromatic aldehydes, the yield of ketone products was low under the standard conditions, but greatly improved by addition of a catalytic amount of bis(cyclopentadienyl)-zirconium or -titanium dichloride.[86] To undergo C–H activation, the rhodium needs to be held in position near the aldimine C–H bond (Figure 3). This is simple with the benzaldehyde substrate (**I**). With the heteroaromatic substrates such as furaldehyde, the rhodium can be coordinated to the other heteroatom forming a chelated complex with the catalytic rhodium centre held away from the aldimine C–H (**II**). The reason for increased reactivity with the metal additives must be that the early transition metals can coordinate strongly to the oxygen, leaving the rhodium free to undergo C–H activation (**III**).

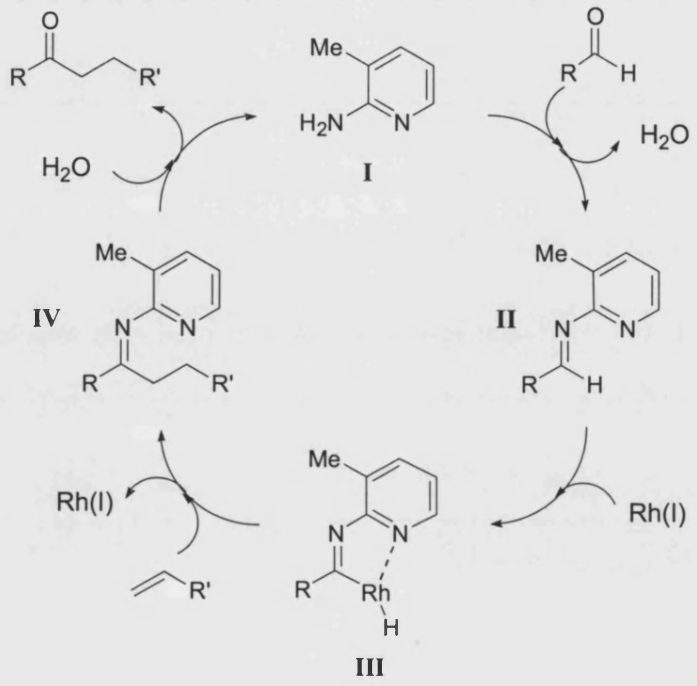


I **II** **III**

Figure 3: Chelation by heteroaromatic aldehydes

A further advantage of this process is that the picolyl imine can be formed *in situ* from the aldehyde and picolyl amine. After hydroiminoacylation of an alkene, the

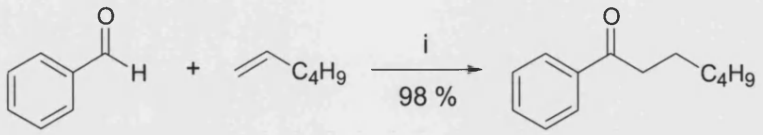
ketimine is hydrolysed to the ketone product, regenerating the picolyl amine.[87] This allows the amine to be used catalytically. The proposed catalytic cycle of the amine is shown in Scheme 36. The water released during condensation of the aldehyde and amine (**I** to **II**) is available for the hydrolysis of ketimine (**IV**) to liberate the ketone product and regenerate the amine.



Scheme 36: Catalytic cycle of picolyl amine

It was found that the addition of a catalytic amount of benzoic acid increases the rate of reaction, suggesting that for this cycle the condensation step is rate-determining.[88] The addition of aniline also helps to accelerate the process.[89] This is attributed to rapid condensation of the aldehyde with aniline, followed by transimination with picolyl amine to give the active imine. The optimised conditions are shown below (Scheme 37). Benzaldehyde is treated with 1-hexene in the presence of 2 mol% $RhCl(PPh_3)_3$, 20 mol% aminopicoline, 6 mol% benzoic acid and 60 mol% aniline.

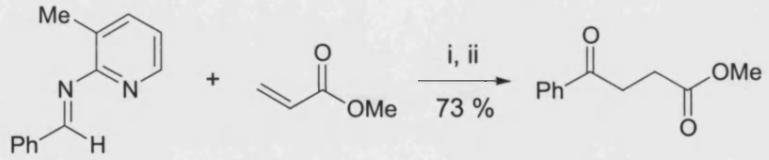
Gas chromatography showed quantitative conversion to the ketone product, with a 98 % isolated yield after chromatographic separation.



i) $RhCl(PPh_3)_3$ (2 mol%), 2-amino-3-picoline (20 mol%), benzoic acid (6 mol%), aniline (60 mol%), toluene, 130 °C

Scheme 37: Hydroiminoacylation of alkenes

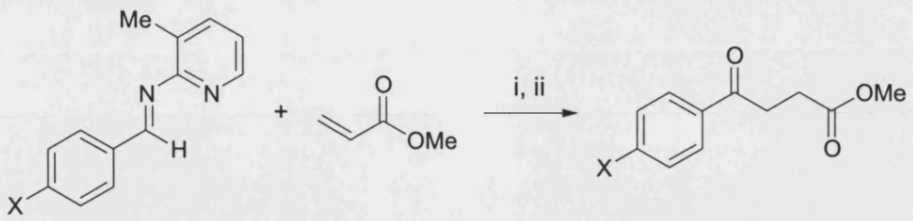
Previous work in our laboratory has shown that the picolyl imine system can also been applied to the synthesis of 1,4-dicarbonyl products by the hydroacylation of acrylate derivatives (Scheme 38).[90,91]



i) $RhCl(PPh_3)_3$ (5 mol%), THF, 135 °C, 8 h; ii) HCl (aq)

Scheme 38: Hydroacylation of acrylate esters

This system works well with unsubstituted acrylates, but further substitution on the alkene reduces the yields of hydroacylation products. In addition, only aromatic aldehydes have so far been used successfully in this system. Electron-withdrawing aryl substituents were found to greatly increase the rate of hydroacylation (Table 7), but this did not increase the yield with disubstituted alkenes.



i) $RhCl(PPh_3)_3$, THF, 135 °C; ii) HCl (aq.)

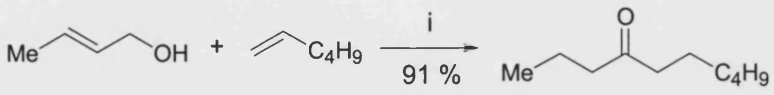
Aldimine, X =	Time	Yield[a] (%)
Me	6 h	98
NO_2	20 min	80

a. Isolated yield after chromatographic purification.

Table 7: Variation in aldimine substituent

Aldimine precursors in tandem reactions

Previous chelation-assisted hydroacylation reactions have been limited to aromatic aldehydes. The effective range of substrates was greatly extended by Jun and co-workers' discovery that allylic alcohols can be converted into aliphatic ketones in a tandem isomerisation-hydroiminoacylation reaction (Scheme 39).



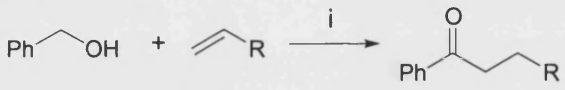
i) $RhCl(PPh_3)_3$ (3 mol%), aminopicoline (40 mol%), benzoic acid (10 mol%), THF, 130 °C, 4 h.

Scheme 39: Tandem isomerisation-hydroacylation of allylic alcohol

Excellent yields of ketone product were obtained with a range of alkyl-substituted allylic alcohols and alkenes.[92] The use of allylic alcohols as aliphatic aldehyde precursors reduces the aldol side-reaction, which was the main problem encountered

during attempts at direct hydroacylation with aliphatic aldehydes. In this system, isomerisation of the alcohol to aldehyde is slower than the condensation of the aldehyde and amine. As the aldehyde is formed, it is converted immediately into imine, maintaining a low concentration of aldehyde and thereby reducing the extent of side-reactions.

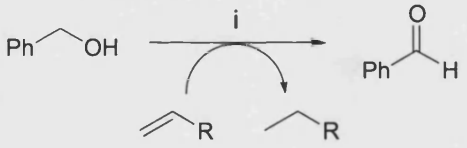
Benzyl alcohol has also been converted directly to ketone by a rhodium catalyst (Scheme 40).[93,94]



i) $RhCl(PPh_3)_3$ (10 mol%), aminopicoline, 130 °C, 72 h.

Scheme 40: Hydroacylation with benzyl alcohol

The alcohol is initially oxidised to aldehyde by a rhodium-catalysed transfer hydrogenation using excess alkene as a hydrogen acceptor (Scheme 41). The aldehyde then undergoes the usual condensation, hydroiminoacylation and hydrolysis steps to give the ketone product.

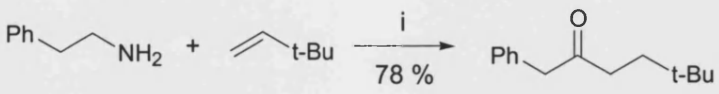


i) $RhCl(PPh_3)_3$

Scheme 41: Rhodium-catalysed dehydrogenation of alcohol

Primary amines can also be used as aldimine precursors in this system (Scheme 42).[95,96] Dehydrogenation and transimination occur under the reaction conditions to

give the picolyl aldimine, which can undergo subsequent C–H activation and hydroacylation.

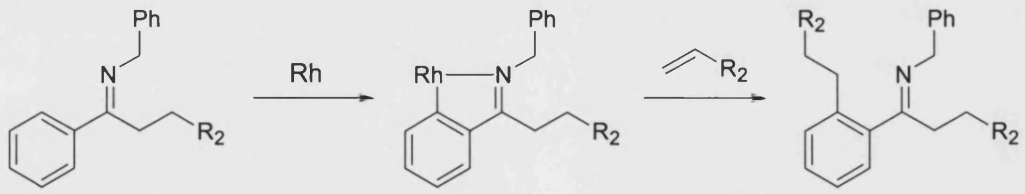


i) $RhCl(PPh_3)_3$ (5 mol%), aminopicoline (50 mol%),
$AlCl_3$ (5 mol%), H_2O (100 mol%), toluene, 170 °C, 24 h.

Scheme 42: Tandem dehydrogenation-hydroacylation of primary amine

As with the previous example, the alkene acts as hydrogen acceptor in the first step and then as the substrate for hydroacylation with the picolyl aldimine. Addition of aluminium chloride and water to the reaction was found to increase the yield of the ketone product, by improving hydrolysis of the initial ketimine hydroiminoacylation product.

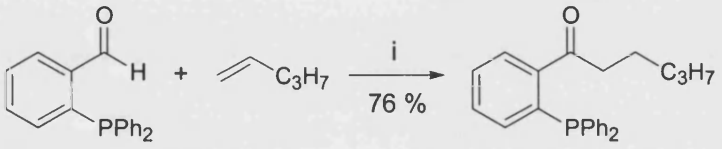
As shown above, phenethylamine gives good yields of the ketone products. When benzylamine is used, *ortho*-alkylation of the aromatic ring also occurs, giving a mixture of products. This is due to activation of the *ortho* C–H bond in the aromatic ketimine intermediate (Scheme 43). The chelation-assisted alkylation of aromatic rings has been developed as a useful synthetic process in its own right.[97-104]



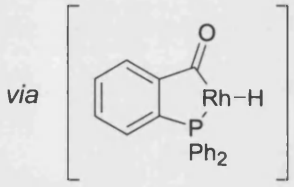
Scheme 43: Rhodium-catalysed *ortho*-alkylation of aromatic ketimine

Other coordinating groups

Acylmetal hydride complexes derived from 2-(diphenylphosphino)benzaldehyde have been reported,[105-110] and this compound has been used for the rhodium-catalysed hydroacylation of alkenes and alkynes.[111,112] Again, oxidative addition of the aldehyde C–H gives a stable five-membered chelated intermediate (Scheme 44).



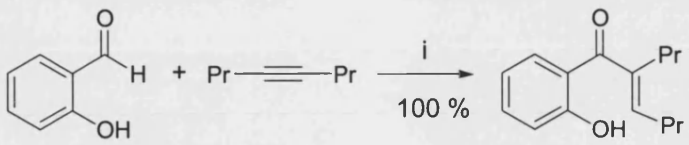
i) $[Rh(COD)Cl]_2$ (5 mol%), THF, 90 °C, 4 h.



Scheme 44: Hydroacylation with 2-(diphenylphosphino)benzaldehyde

One advantage of this substrate is that no external phosphine ligand is required. Normally, a ligand is required to induce reductive elimination of the product, but the phosphine of the aldehyde substrate is sufficient in this case.

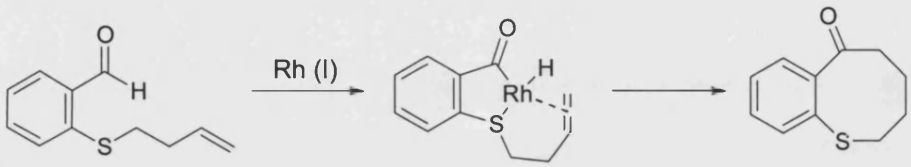
Rhodium catalysed C–H activation and hydroacylation can also be directed by a hydroxy or alkoxy functional group. Addition of salicyl aldehyde to 4-octyne gave the enone product in good yield (Scheme 45).[113,114]



i) $[RhCl(COD)]_2$, dppf, Na_2CO_3, toluene, 110 °C, 30 min.

Scheme 45: Hydroacylation of alkyne with salicyl aldehyde

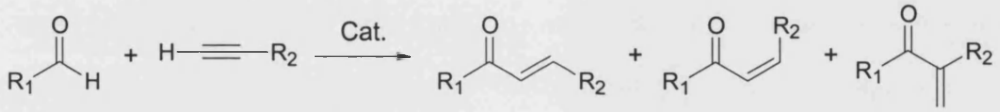
The enhanced stability of a chelated intermediate has been exploited in the intramolecular hydroacylation of ω-alkenals, to give medium-ring sulfur heterocycles *via* a sulfur-chelated intermediate (Scheme 46).[115]



Scheme 46: Intramolecular hydroacylation *via* a sulfur-chelated intermediate

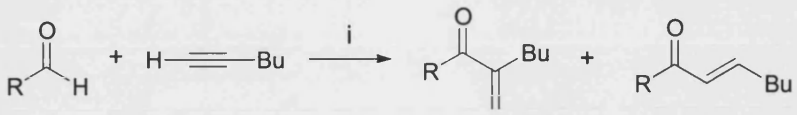
1.7 Hydroacylation of alkynes

Alkynes can be used in most of the hydroacylation reactions outlined in this review. As with alkenes, a variety of transition metal catalysts can be used.[116] The mechanism is the same as for the alkene substrates, proceeding *via* activation of the aldehyde C–H bond by the metal catalyst, then hydrometallation of the alkyne. The hydroacylation of an alkyne can lead to three isomeric enone products: as well as the branched and linear regioisomers, both *E*- and *Z*- stereoisomers of the linear enone are possible (Scheme 47).



Scheme 47: Hydroacylation of alkyne

Jun and co-workers have used alkynes in the chelation-assisted hydroiminoacylation system with picolyl aldimines.[117-119] The addition of aromatic aldehydes to terminal alkynes was found to provide the branched enone products exclusively in good yields (Table 8). Aliphatic aldehydes also gave predominantly branched enones, but with lower selectivity.



I **II**

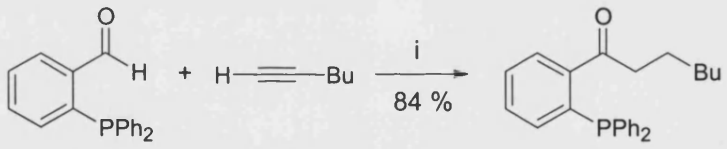
i) $RhCl(PPh_3)_3$ (5 mol%), aminopicoline (40 mol%), benzoic acid (20 mol%), toluene, 80 °C, 12 h.

Entry	Aldehyde, R =	Ratio **I**:**II**	Yield[a] (%)
1	Ph	100 : 0	92 (100)
2	n-C_5H_{11}	78 : 22	85

a. Isolated yields. GC yields are given in parentheses

Table 8: Chelation-assisted hydroacylation of alkyne

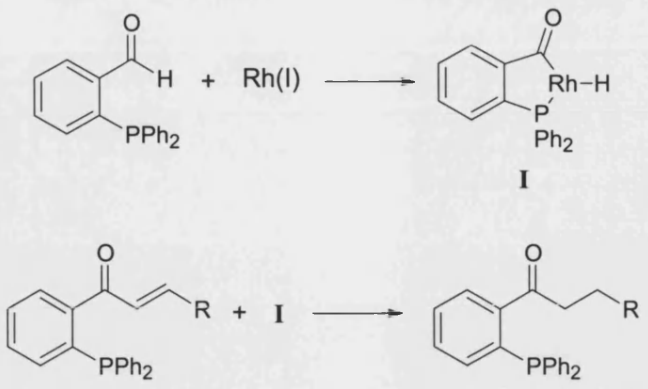
The addition of *o*-(diphenylphosphino)benzaldehyde to primary alkynes gave reduced ketone products rather than the expected enones (Scheme 48).[111]



i) $[RhCl(COE)_2]_2$ (10 mol%), THF, 90 °C, 4 h.

Scheme 48: Hydroacylation of alkyne

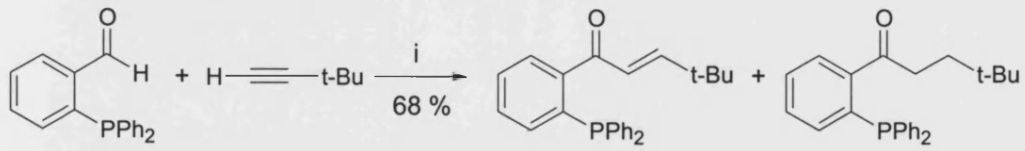
The product enone appears to undergo conjugate reduction with the rhodium hydride species generated by aldehyde C–H bond activation (Scheme 49).



Scheme 49: Conjugate reduction of enone by rhodium hydride

As the hydride for the reduction step is provided by the aldehyde, three equivalents of the aldehyde are consumed in production of the ketone product. One aldehyde unit is used in the hydroacylation, and a further two in the reduction step. High yields were only obtained when an excess of aldehyde, relative to the alkyne, was used. When an excess of the alkyne was used, the maximum yield observed was 30 %.

The use of a bulky alkyne, such as 3,3-dimethyl-1-butyne (R = t-Bu), hindered the reduction step and provided a 7:2 mixture of the enone and ketone products (Scheme 50).



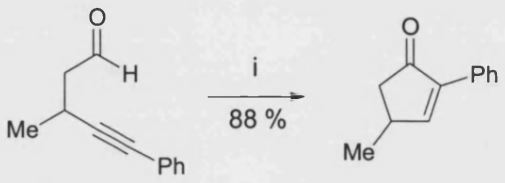
i) $[RhCl(COE)_2]_2$ (10 mol%), THF, 90 °C, 4 h.

Scheme 50: Hydroacylation of hindered alkyne

When the aldehyde was treated with an equimolar mixture of 1-pentene and 1-hexyne, the predominant product was that of addition to the alkyne, the ratio of products being 85:7. This result suggests that 1-alkyne has approximately 12 times

greater reactivity than equivalent 1-alkene in the hydroacylation reaction, presumably because of stronger coordination to the metal.

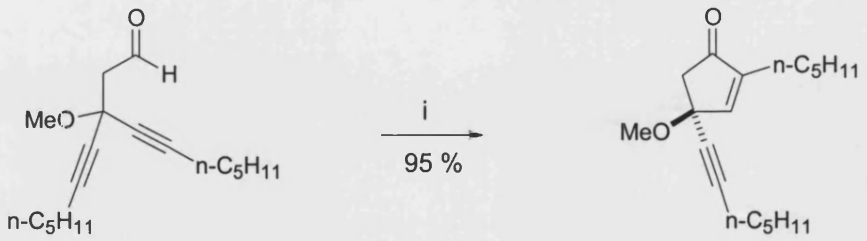
The cyclisation of 4-alkynals in an intramolecular hydroacylation reaction delivers cyclopentenone products (Scheme 51). As with the alkenal cyclisation, the use of a cationic rhodium catalyst allows the reaction to proceed efficiently at room temperature. This proceeds by a similar mechanism to the cyclisation of alkenals: oxidative addition of the aldehyde C–H to the metal, followed by insertion of the alkyne into the metal hydride bond.[120,121]



i) $Rh(dppe)BF_4$ (10 mol%), acetone, r.t.

Scheme 51: Cyclisation of 4-alkynal

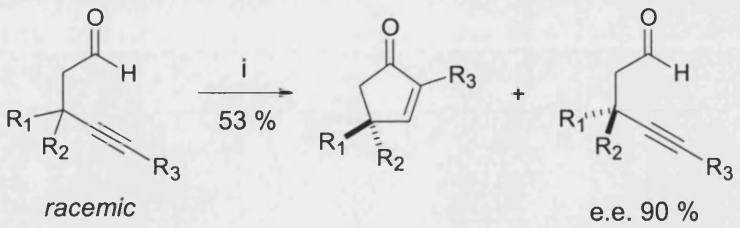
4-Alkynals have also been used in desymmetrisations (Scheme 52) and kinetic resolutions (Scheme 53) with chiral rhodium phosphine complexes.[10,122]



e.e. 92 %

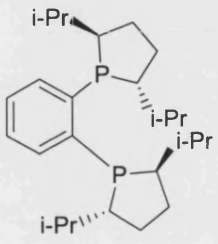
i) $Rh[(R)\text{-Tol-BINAP}]BF_4$ (10 mol%), DCM, 10 °C

Scheme 52: Desymmetrisation of alkynal



i) Rh[(*S*,*S*)-i-Pr-DUPHOS]BF_4 (5 mol%), DCM, 30 °C

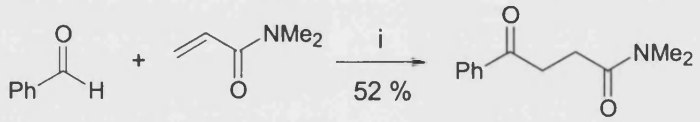
(*S*,*S*)-i-Pr-DUPHOS =



Scheme 53: Kinetic resolution of alkynal

1.8 Alternative methods of hydroacylation

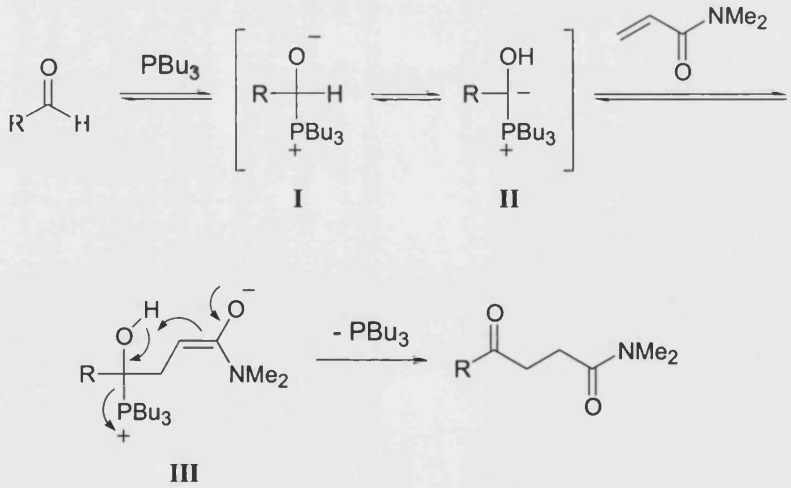
There are relatively few other methods available for the addition of aldehydes to alkenes, and each has severe limitations. The Stetter reaction is a nucleophile-catalysed addition of aldehydes to activated double bonds, which gives hydroacylation products; cyanide[123] and trialkylphosphines[124-127] have been used as catalysts (Scheme 54).



i) PBu_3, THF, reflux

Scheme 54: Stetter reaction

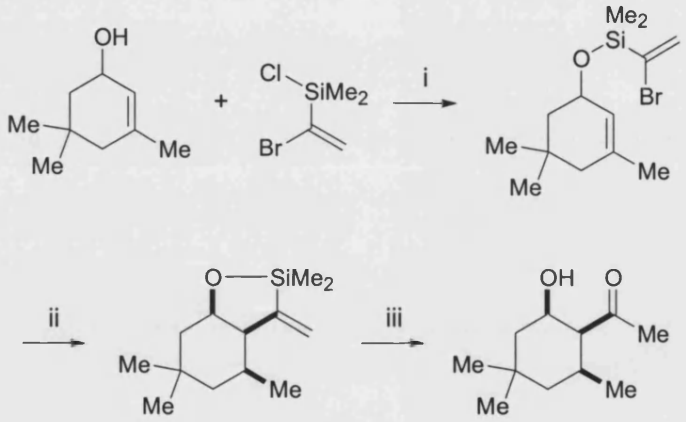
The proposed mechanism is outlined below (Scheme 55).



Scheme 55: Mechanism of the Stetter reaction

It is believed that the reaction proceeds *via* betaine (**I**) and α-oxo ylide (**II**) species, in a similar manner to the benzoin condensation. The α-oxo ylide is then involved in a conjugate addition to the activated alkene.

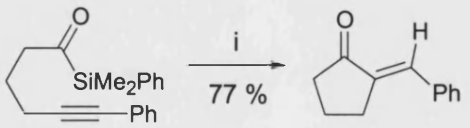
A silicon-mediated hydroacylation of allyl alcohols has been used to generate β-hydroxy ketone products (Scheme 56).[128] A silicon-tethered tethered vinyl bromide is used an acyl equivalent. After a radical cyclisation of the vinyl group onto the double bond of the allyl alcohol, oxidative cleavage releases the aldol product.



i) Et_3N; ii) $^nBu_3SnH$, AIBN (5 mol%), C_6H_6, 80 °C, 8h.; iii) 30 % H_2O_2, KF, $KHCO_3$, MeOH / THF, r.t. 1 day

Scheme 56: Silicon-mediated hydroacylation of allyl alcohols

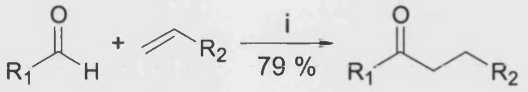
The rhodium catalysed addition of acyl silanes to alkynes gives α,β-unsaturated ketone products (Scheme 57).[129]



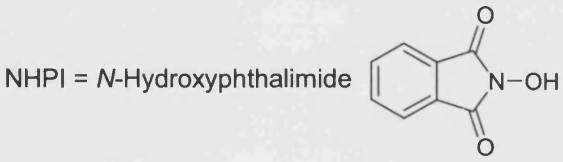
i) $[RhCl(CO)_2]_2$ (5 mol%), AcOH

Scheme 57: Acylation of alkyne with acylsilane

Ketones can also be formed by the radical-chain addition of aldehydes to alkenes.[130] Ishii and co-workers have reported an efficient reaction using *N*-hydroxyphthalimide as a polarity reversal catalyst (Scheme 58).[131] In this example, dibenzoylperoxide was used as the radical initiator.

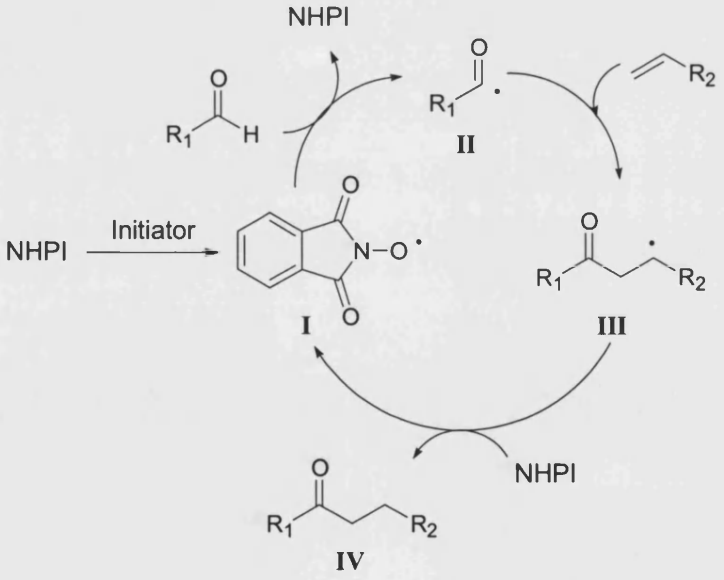


i) NHPI (10 mol%), dibenzoylperoxide (5 mol%), toluene, 80 °C



Scheme 58: Radical addition of aldehydes to alkenes

The proposed mechanism is outlined below (Scheme 59).

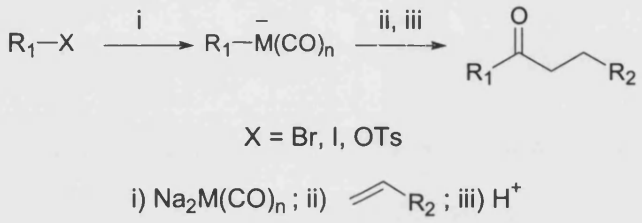


Scheme 59: Mechanism of aldehyde-alkene radical addition

The *N*-oxyl radical (**I**) generated from *N*-hydroxyphthalimide (NHPI) can abstract the hydrogen of the aldehyde group to generate an acyl radical (**II**). This adds to the

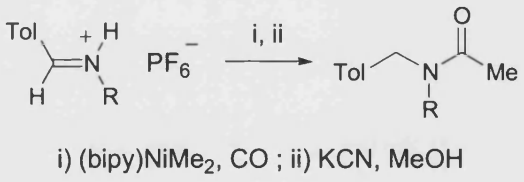
alkene to generate a carbon radical (**III**), which receives a proton from NHPI to give the ketone product (**IV**) and regenerate the *N*-oxyl radical (**I**).

Alkyl metal carbonyl species can also react with alkenes or alkynes to give hydroacylation products. Organocarbonyl-ferrates,[132-134] and -chromates,[135] prepared by alkylation of $Na_2Fe(CO)_4$ or $Na_2Cr(CO)_5$ respectively,[136] readily undergo sequential carbonyl and alkene insertion reactions to give hydroacylation products (Scheme 60).



Scheme 60: Hydroacylation with organotetracarbonylferrates

Dimethylnickel has been reported to undergo sequential imine and carbon monoxide insertions,[137] resulting overall in the hydroacylation of the imine C=N bond (Scheme 61).



Scheme 61: Hydroacylation of imine with dimethylnickel

1.9 Summary

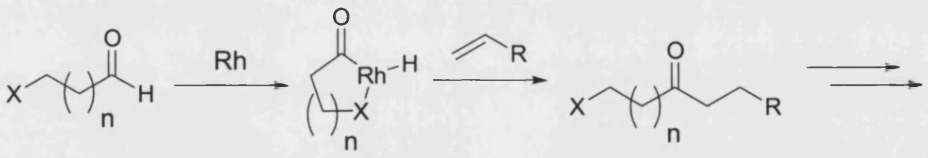
The intramolecular hydroacylation of alkenals has been developed into an extremely powerful tool for the formation of cyclic ketones. The cyclisation can also be performed efficiently in an enantioselective manner by simple modifications to the catalyst. However, most of these systems are limited to the formation of cyclopentanones. Larger ring-sizes can be formed, but this requires more complex, specifically designed substrates.

Many developments have also been made in the intermolecular hydroacylation of aldehydes and alkenes to generate linear ketone products. There are various methods available for the coupling of aldehydes with alkenes to give hydroacylation-type products, either directly or indirectly. Many of these require harsh or inconvenient reaction conditions, such as high temperature or high pressure of carbon monoxide or ethylene. The majority of systems are only applicable to a limited range of aldehyde or alkene substrates. There is no general method for the coupling of simple aliphatic aldehydes with a range of alkenes under mild, convenient conditions.

Chapter 2 Results and Discussion

2.1 Aldehyde design and synthesis

The main objective of the project was to find a valid system for the transition metal-catalysed intermolecular hydroacylation of alkenes with simple aldehydes under mild conditions. The key to this is the formation of a chelation-stabilised acyl rhodium hydride intermediate. This requires the aldehyde component to have a coordinating heteroatom in a suitable position to chelate to the metal catalyst, after oxidative addition has occurred. The coordinating group could also hold the metal in the correct position for oxidative addition. An additional requirement in the design of all substrates was that the chelating group should also act as a handle for further elaboration of the hydroacylation product (Scheme 62).



X = OR, SR, NR_2, PR_2

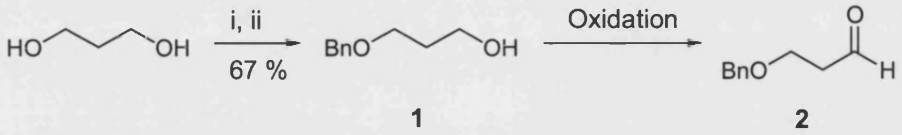
n = 1,2

Scheme 62: Chelating aldehyde strategy

The coordinating groups shown are all known to chelate transition metals effectively. The length of the carbon chain between the aldehyde and coordinating group controls the chelate ring size. A β-substituted aldehyde would form a five-membered ring, which was expected to be the most favourable from previous reports;[68,76,78] γ-

substituted aldehydes, which would give six-membered chelates, were also examined.

Several aldehydes with oxygen-based chelating groups were prepared, each with a different protecting group at the oxygen. The first was 3-(benzyloxy)propanal **2**, which would allow for further elaboration of the product *via* hydrogenolysis of the benzyl group. This aldehyde was readily prepared in two steps from propane-1,3-diol. (Scheme 63)

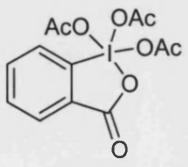


1 **2**

i) Sodium hydride, DMSO, r.t. 30 min.; ii) benzyl chloride, r.t. 2 h.

Scheme 63: Synthesis of 3-(benzyloxy)propanal

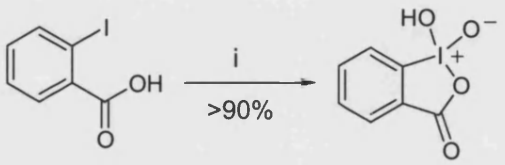
By using an excess of the diol, the mono-benzylation of propane-1,3-diol with benzyl chloride proceeded cleanly to give alcohol **1**. A trial of some standard metal-based oxidising agents such as PCC and TPAP[138] gave only low yields (<20 %) of the desired aldehyde. An attractive alternative was the Dess-Martin periodinane **3** (Figure 4), a mild oxidising agent that can be used to convert primary alcohols to aldehydes.[139]



3

Figure 4: Dess-Martin periodinane

It had been reported that the precursor to this periodinane, 2-iodoxybenzoic acid (IBX) **4** was also an efficient, mild oxidising agent,[140,141] but was less popular because of its insolubility in the majority of organic solvents. However, IBX can be dissolved by stirring in DMSO and is easily prepared by the oxidation of 2-iodobenzoic acid.[140] Whilst the original procedure used potassium bromate in sulfuric acid as the oxidant,[141] a more "user-friendly" approach has been reported recently using potassium monopersulfate triple salt (Oxone®) (Scheme 64).[142] The iodobenzoic acid is stirred in an aqueous solution of Oxone® at 70 °C for 3 hours then cooled in an ice-bath. The precipitate is collected by filtration and washed to give pure IBX in excellent yield.

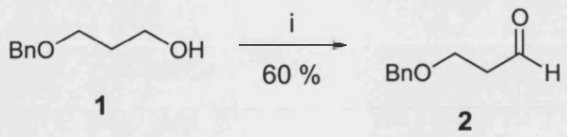


4

i) Oxone, H_2O, 70 °C, 3 h.

Scheme 64: Formation of IBX

Oxidation of alcohol **1** with IBX **4** in DMSO gave aldehyde **2** cleanly and in good yield (Scheme 65). The reaction can be performed at room temperature, but prolonged reaction time is often required. Heating to 40 °C greatly reduces the time needed to dissolve the IBX and increases the rate of reaction: conversion to aldehyde was usually complete within a few hours.

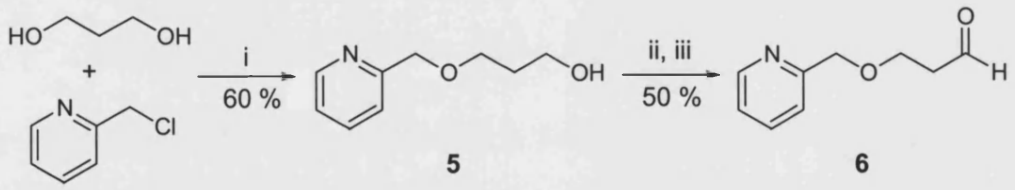


1 **2**

i) **4**, DMSO, 40 °C, 2 h.

Scheme 65: Oxidation of benzyloxypropanol

A similar aldehyde **6**, with the benzyl group replaced by a picolyl group, could be expected to chelate a metal even more effectively through the oxygen of the ether linkage and/or the pyridine nitrogen. It was prepared in a similar manner to aldehyde **2**. The corresponding alcohol **5** was prepared from 1,3-propanediol and picolyl chloride (Scheme 66). In this case, chromatography of the alcohol was difficult due to its polarity. Fortunately, aqueous work-up delivered alcohol **5** cleanly, and it did not require further purification. Swern oxidation delivered aldehyde **6** in moderate yield.

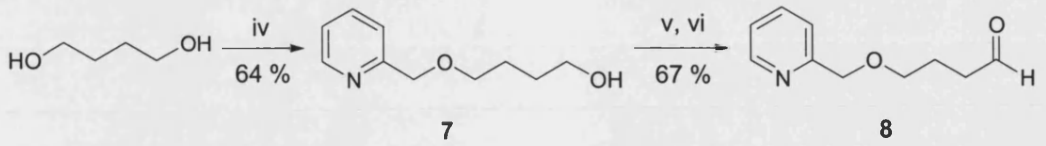


5 **6**

i) NaH, THF, reflux, 24 h.; ii) DMSO, oxalyl chloride,
DCM, -60 °C, 45 min.; iii) Et_3N, 10 min.

Scheme 66: Synthesis of 3-(picolyloxy)propanal

To investigate the effect of chelate ring-size the corresponding butanal **8** was also prepared, by an analogous route from 1,4-butanediol.

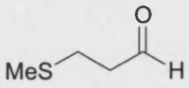


7 **8**

iv) NaH, picolyl chloride, THF, reflux, 24 h.; v) DMSO, oxalyl chloride, DCM, -60 °C, 45 min.; vi) Et_3N, 10 min.

Scheme 67: Preparation of homologous aldehyde

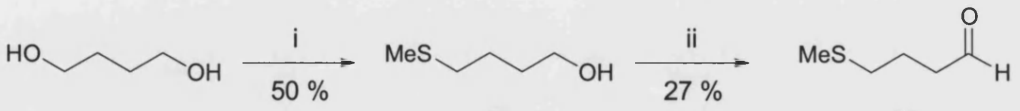
The use of sulfur as a chelating group was also investigated; thioethers have been used previously as chelating ligands for rhodium.[143] Fortunately, 3-methylsulfanyl propanal **9** (Figure 5) is commercially available.



9

Figure 5: 3-Methylsulfanyl propanal

The homologous aldehyde **11** would give a larger 6-membered chelate ring. It was prepared by oxidation of the corresponding alcohol **10**. The sulfide group was introduced by treatment of butane-1,4-diol with dimethyl disulfide and tributylphosphine (Scheme 68).



10 **11**

i) MeSSMe, PBu_3, THF, r.t. 24 h.; ii) DMP (**3**), DCM, r.t. 2 h.

Scheme 68: Synthesis of homologous sulfanyl aldehyde

The nitrogen-containing aldehydes **12** and **13** (Figure 6) were also thought to be promising substrates, based on the previous success of Jun and Suggs with nitrogen-

chelated metal intermediates,[68,72] and other reports of rhodium-amine complexes.[144-146]

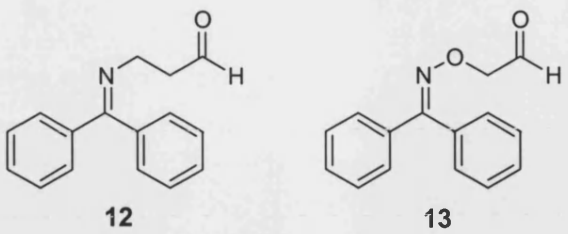
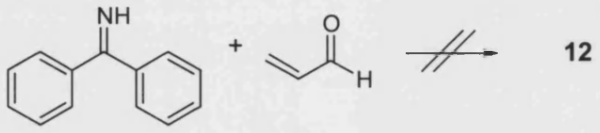


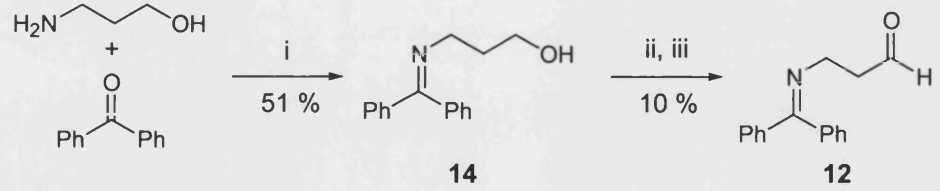
Figure 6: Nitrogen-containing aldehdyes

Direct preparation of aldehyde **12** by addition of benzophenone imine to acrolein was unsuccessful (Scheme 69).



Scheme 69: Addition of benzophenone imine to acrolein

The corresponding alcohol **14** was prepared in moderate yield from the condensation of 3-aminopropanol and benzophenone (Scheme 70).



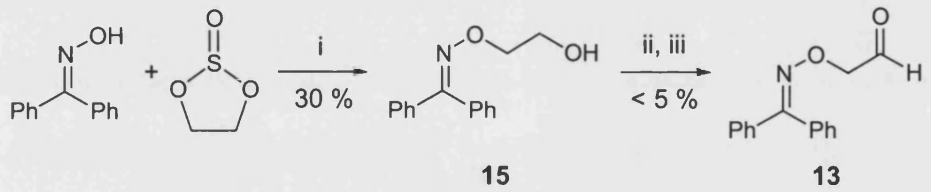
i) 100 °C, 3 days; ii) DMSO, oxalyl chloride, DCM, -60 °C, 1 h; iii) Et_3N, 10 min.

Scheme 70: Preparation of aldehyde 12

Oxidation of alcohol **14** was attempted under various conditions. PCC, TPAP[138] and DMSO with SO_3[147] were unsuitable. Only Swern conditions (DMSO, oxalyl chloride)[148] showed any formation of the desired aldehyde. Crude ^{1}H-NMR analysis

of the reaction showed 60 % conversion to the desired aldehyde, but purification was problematic, with chromatography on silica and Florisil both giving only low yields of the product (5–10 %). In addition, the purity of the isolated aldehyde was unsatisfactory due to contamination with benzophenone from hydrolysis of the imine.

A similar route was used for aldehyde **13**. The corresponding alcohol **15** was prepared by hydroxyethylation of benzophenone oxime with ethylene sulfite (Scheme 71).[149]



15 **13**

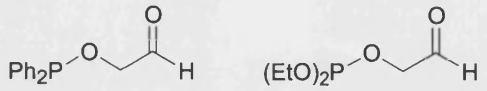
i) Cs_2CO_3, MeCN, reflux, 24 h; ii) DMSO, oxalyl chloride, DCM, -60 °C, 45 min; iii) Et_3N, 10 min.

Scheme 71: Hydroxyethylation of benzophenone oxime

Oxidation of **15** was even less fruitful than for alcohol **14**, and the aldehyde could not be isolated in high yield or purity. Attempts to prepare both of these aldehydes were unsuccessful, mainly due to problematic purification. The decision to abandon work on these substrates was supported by examples in the literature,[150,151] which reported that β-amino aldehydes were unstable and extremely difficult to isolate. Although aldehyde **13**, with an oxime linkage should not be susceptible to β-elimination, it was still difficult to isolate this aldehyde in satisfactory purity for catalytic studies due to rapid hydrolysis, which resulted in contamination with benzophenone.

The desired phosphorus-containing aldehydes were also extremely difficult to prepare and isolate. To simplify elaboration of the hydroacylation product, it was

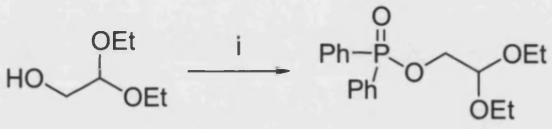
thought preferable to attach the phosphorus through an oxygen linkage rather than a direct carbon–phosphorus bond, as in aldehydes **16** and **17** (Figure 7).



16 **17**

Figure 7: Phosphorus-containing aldehydes

Addition of glycolaldehyde diethyl acetal to chlorodiphenylphosphine gave only the oxidised phosphinic acid **18** (Scheme 72).

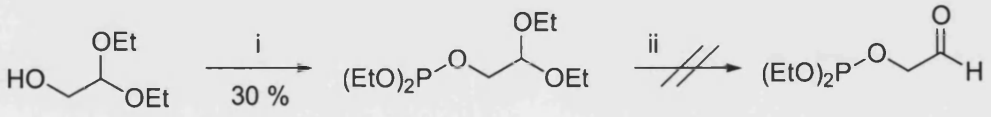


18

i) Ph_2PCl, Et_3N, THF

Scheme 72: Attempted synthesis of phosphorus-containing aldehydes

It was thought that using a phosphite instead of a phosphine could improve the stability of the product and reduce its susceptibility to oxidation. Addition of the glycolaldehyde acetal to diethylchlorophosphite gave the acetal **19** (Scheme 73), but acid hydrolysis caused decomposition and there was no sign of the desired aldehyde **17**.



19 **17**

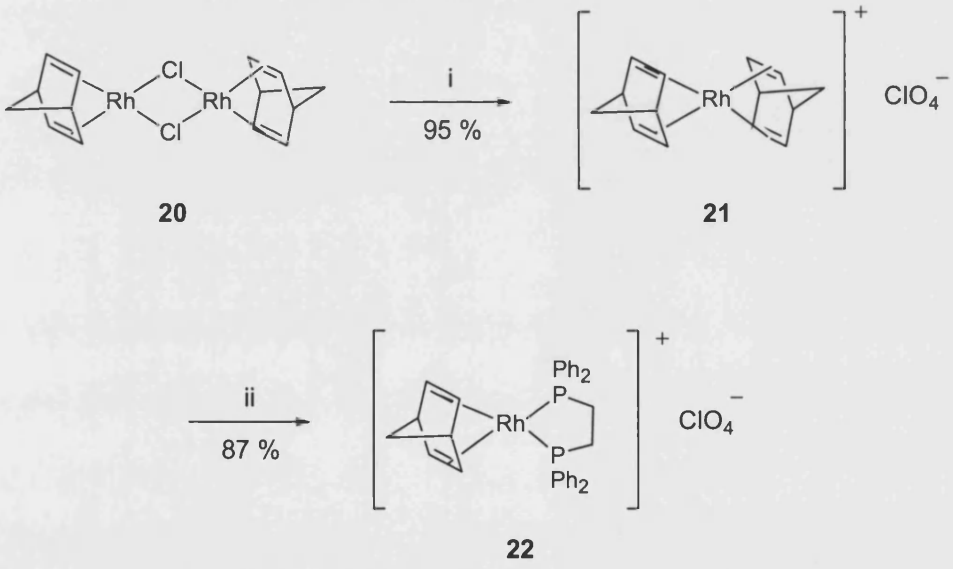
i) $(EtO)_2PCl$, pyridine, THF, r.t. 2 h; ii) HCl (aq.), r.t. 2 min.

Scheme 73: Attempted synthesis of phosphorus-containing aldehydes

Isolation of a phosphorus containing aldehyde without oxidation of the phosphorus group was found to be extremely difficult. Due to the success of hydroacylation trials with the sulfur-containing aldehyde **9** (see later), synthesis of nitrogen- and phosphorus-containing aldehydes was not pursued any further.

2.2 Catalyst synthesis

Previous work with chelation stabilised hydroacylation used Wilkinson's catalyst $RhCl(PPh_3)_3$.[72] This was also taken as the starting point in this investigation. Further catalyst selection was guided by the successful use of the cationic rhodium complex $[Rh(dppe)]^+ ClO_4^-$ in the intramolecular hydroacylation reaction.[23,24] The catalytically active species is generated by hydrogenation of a norbornadiene precursor complex **22**, which is easily prepared from the commercially available dimer $[Rh(NBD)Cl]_2$ **20** in two steps by treatment with silver perchlorate and the appropriate diphosphine (Scheme 74).[152]

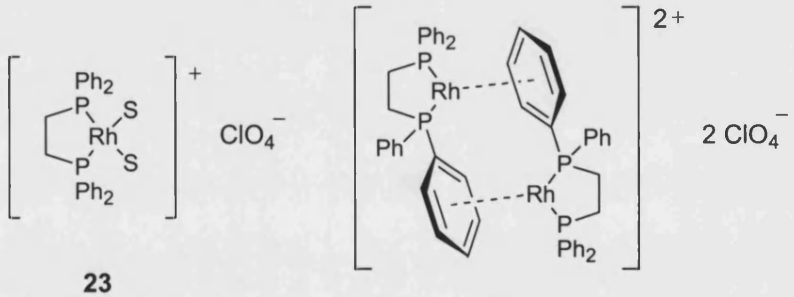


i) $AgClO_4$, NBD, DCM, r.t. 30 mins; ii) dppe, r.t. 3 h.

Scheme 74: Synthesis of cationic rhodium catalyst

The intermediate bis(norbornadiene) rhodium perchlorate **21** can be isolated. Alternatively, the dimer can be converted into the pre-catalyst in a single reaction by stirring with silver perchlorate and excess norbornadiene for about 30 minutes, then

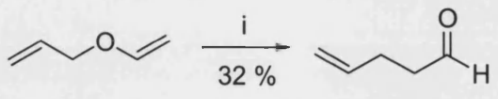
adding the diphosphine. This 'one-pot' reaction gives a slightly lower yield (78 %) than performing the two-step process with the purified intermediate (83 % overall), but it is more convenient and halves the time required for the preparation. The $[Rh(dppe)(NBD)]^+ ClO_4^-$ complex is then converted into the active catalyst $[Rh(dppe)]^+ ClO_4^-$ by hydrogenation to remove norbornadiene. This compound can be isolated as the disolvento complex **23**, in a strongly coordinating solvent such as acetone or methanol. If the hydrogenation is performed in a weakly coordinating solvent such as dichloromethane or nitromethane the compound exists as the η^6-arene bridged dimer **24** (Figure 8). The catalyst can be generated by hydrogenation *in situ*, which avoids any possible complications in isolating the relatively unstable active complex. The norbornadiene precursor is relatively air-stable and is much easier to store and handle.



S = Coordinating solvent, e.g. acetone or methanol

Figure 8: Active cationic rhodium catalyst

A simple example of the cyclisations performed by Bosnich was repeated to ensure formation of the correct catalytic species.[23] 4-Pentenal **25** was prepared by the Claisen rearrangement of allyl vinyl ether (Scheme 75). The ether was heated at 135 °C in a sealed tube for 20 hours, before purifying the aldehyde product by distillation.

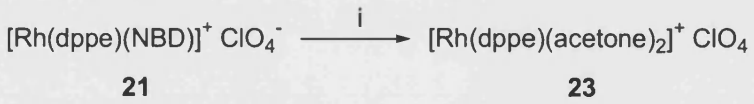


25

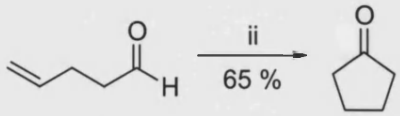
i) 135 °C, 20 h.

Scheme 75: Claisen rearrangement of allyl vinyl ether

The pre-catalyst, rhodium norbornadiene complex **21**, was dissolved in acetone and exposed to pressure of hydrogen gas for approximately 30 minutes. The progress of the hydrogenation was shown by a colour change from red-orange to pale yellow. The solvent and liberated norbornane were then removed under vacuum. The hydrogenated bis(acetone) complex **23** was taken up in dichloromethane and treated with 4-pentenal (Scheme 76). After stirring at room temperature for 15 minutes, the mixture was analysed by gas chromatography. The major peak had the same retention time as an authentic sample of cyclopentanone **26**. The conversion was estimated as approximately 65 %, with 30 % remaining aldehyde and 5 % of an unidentified product, which was probably 3-pentenal formed by isomerisation of the double bond.[23]



21 **23**



25 **26**

i) H_2, acetone, r.t. 15 min.; ii) **23**, DCM, r.t. 10 min.

Scheme 76: Intramolecular hydroacylation of 4-pentenal

The presence of the cyclopentanone product **26** confirmed that the active catalyst had been generated, and further hydroacylation investigations could begin.

2.3 Catalyst and aldehyde evaluation

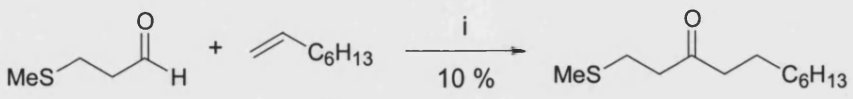
Initial studies showed that both the benzyloxy and picolyloxy substituted aldehydes **2** and **6** underwent rapid decarbonylation in the presence of Wilkinson's catalyst (Scheme 77). The picolyl group slightly reduced the rate of decarbonylation, but still no hydroacylation adducts were observed; presumably the catalyst is deactivated by coordination of the pyridyl nitrogen, suppressing both reaction pathways. The decarbonylation products were not isolated, but the aldehyde was completely consumed and IR analysis revealed the formation of a rhodium carbonyl compound (ν_{max} 1964 cm^{-1}).

R = benzyl (**2**), picolyl (**6**)

i) Octene, DCM, r.t

Scheme 77: Decarbonylation of benzyloxyaldehyde

Aldehyde **9**, with a sulfide as the coordinating group was more promising. Treatment with $RhCl(PPh_3)_3$ and octene gave the hydroacylation product **27**, albeit in low yield (Scheme 78).



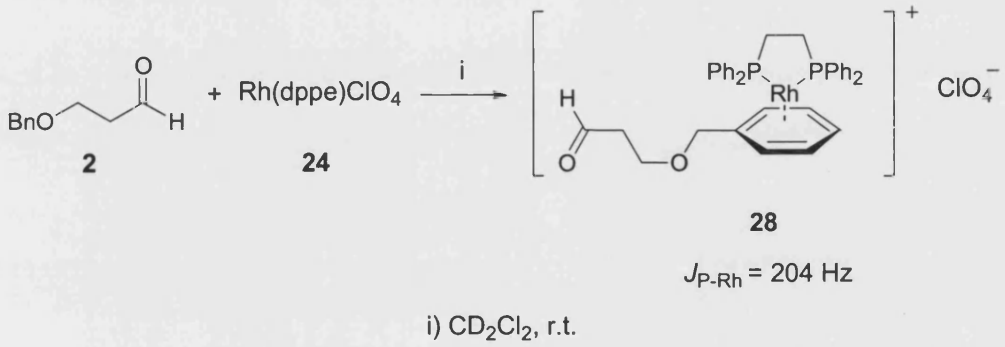
9 **27**

i) $RhCl(PPh_3)_3$, DCM, 60 °C, 16 h.

Scheme 78: Hydroacylation with sulfur-containing aldehyde

The use of cationic rhodium complexes has been shown to give excellent yields of hydroacylation products in the intramolecular reaction.[23,24] This is thought to be due to a decreased rate of decarbonylation. The use of a cationic rhodium complex was therefore investigated with the above oxygen- and sulfur- containing aldehydes, which had been prone to decarbonylation with Wilkinson's complex.

Addition of benzyloxy-substituted aldehyde **2** to cationic rhodium complex **24** gave a stable compound **28**, which showed no signs of decomposition after prolonged heating at 60 °C (Scheme 79).



Scheme 79: Formation of η^6-complex with benzyloxypropanal

An η^6-arene complex was suggested by the P–Rh coupling constant of 204 Hz, in agreement with a η^6-toluene complex in the literature (Figure 9).[153] Unfortunately, the structure of **28** was not confirmed by X-ray diffraction, as a suitable crystal of the compound could not be obtained.

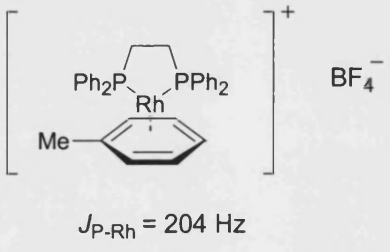
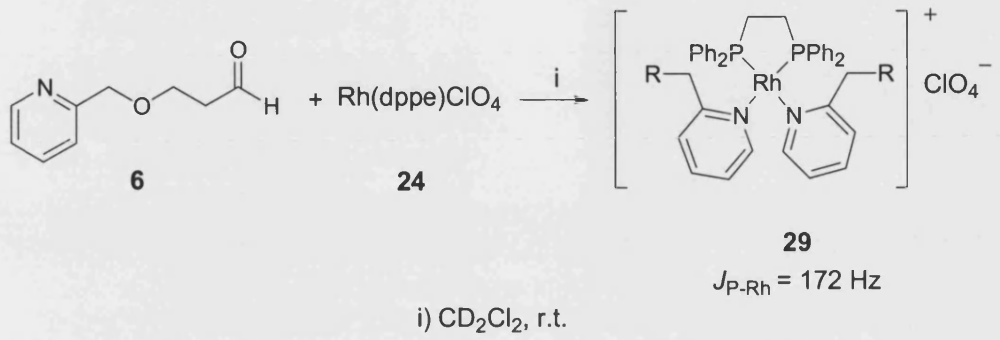


Figure 9: η^6-Arene complex

Pyridyl aldehyde **6** also formed a stable complex **29** with the cationic rhodium catalyst (Scheme 80). Again, no crystal structure was obtained, but a single peak in the ^{31}P NMR spectrum suggests a symmetrical structure.



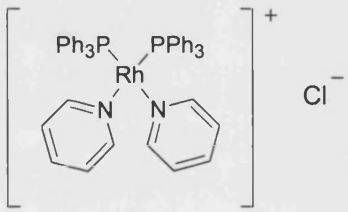
6 **24** **29**

$J_{P\text{-}Rh}$ = 172 Hz

i) CD_2Cl_2, r.t.

Scheme 80: Formation of bis(pyridyl) complex with picolyl aldehyde

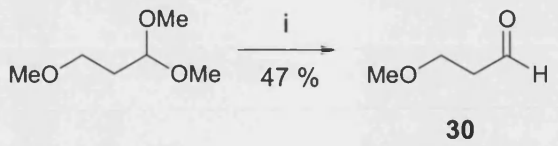
A bis(pyridyl) species can be inferred by the P–Rh coupling constant, which is similar to that of *cis*-[Rh(pyridine)$_2$(PPh$_3$)$_2$]Cl (Figure 10).[154]



$J_{P\text{-}Rh}$ = 168 Hz

Figure 10: Bis(pyridyl) rhodium (I) complex

Changing the benzyl ether of the aldehyde to methyl ether allowed hydroacylation to proceed. Methoxypropanal **30** is readily available by hydrolysis of 1,1,3-trimethoxypropane in aqueous acetic acid (Scheme 81).

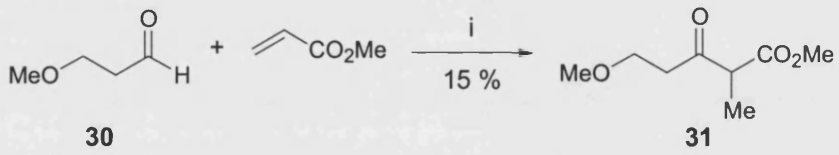


30

i) AcOH / H_2O, 40 °C, 16 h.

Scheme 81: Synthesis of 3-methoxypropanal

Treatment of **30** with methyl acrylate and the cationic rhodium catalyst gave a small amount of the hydroacylation product **31**, but decarbonylation was still the dominant pathway (Scheme 82).



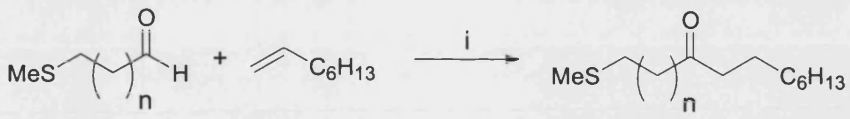
30 **31**

i) $Rh(dppe)ClO_4$, DCM, 60 °C, 16 h.

Scheme 82: Hydroacylation with methoxy aldehyde 30

These initial results revealed that oxygen is a poor chelating group; it does not greatly promote hydroacylation, and is completely ineffective in the presence of other donor groups, even weakly-coordinating aromatic rings.

Sulfur appears to be more effective as a chelating group to stabilise the intermediate and promote hydroacylation. Using the cationic rhodium complex instead of neutral $RhCl(PPh_3)_3$ further increased the yield of hydroacylation products with sulfanyl aldehyde **9**. Thus, treatment of **9** with the cationic rhodium catalyst and octene gave the ketone product **27** in moderate yield. The β-sulfanyl aldehyde, which would form a 5-membered chelated intermediate, appears to be optimal. The longer chain aldehyde **11** underwent decarbonylation, giving no hydroacylation products (Table 9).



i) $Rh(dppe)ClO_4$, DCE, 60 °C, 16 h.

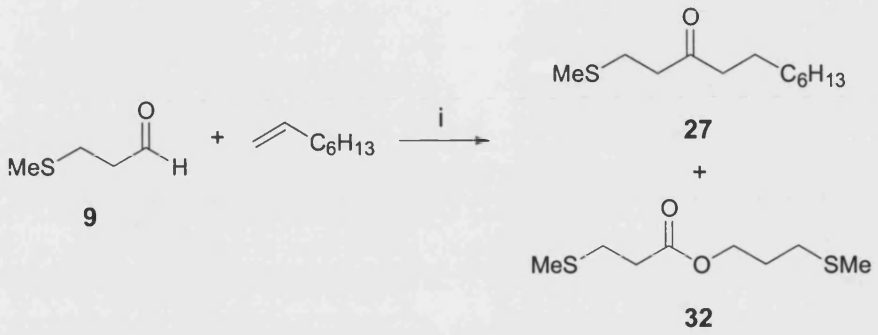
Entry	Aldehyde	n	Product	Yield[a] (%)
1	**9**	1	**27a**	33
2	**11**	2	–	0

a. Isolated yield after chromatographic purification.

Table 9: Effect of aldehyde chain length

Optimisation of conditions

Initial optimisation of reaction conditions was carried out for the addition of 3-methylsulfanyl propanal **9** to octene (Table 10).



i) Rh(I) catalyst, solvent

Entry	Catalyst	Loading	Solvent	Temp.	Yield[a] (%)	
					27	**32**
1	$Rh(dppe)ClO_4$	10 %	DCE	60 °C	33	7
2	$RhCl(PPh_3)_3$	10 %	DCE	60 °C	9	0
3	$Rh(dppe)ClO_4$	10 %	THF	60 °C	0	0
4	$Rh(dppe)ClO_4$	10 %	Benzene	60 °C	0	0
5	$Rh(dppe)ClO_4$	30 %	DCM	25 °C	13	27

a. Isolated yield after chromatographic purification.

Table 10: Optimisation of hydroacylation conditions

The cationic complex **22** (entry 1) is far superior to the neutral $RhCl(PPh_3)_3$, which gave very low yields even under optimised conditions (entry 2). The solvent was found to be critical: tetrahydrofuran and benzene completely inhibit the reaction (entries 3 and 4). Inhibition due to coordination of tetrahydrofuran was expected, but

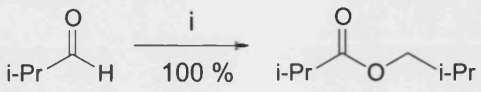
the effect of benzene is not as obvious. Presumably, the catalyst forms a stable 18-electron η^6-benzene complex, similar to the benzyl complex **28** and the arene-bridged dimer **24**. Dichloromethane and 1,2-dichloroethane were suitable solvents, as for the intramolecular reaction reported by Bosnich.[23] Under most conditions a minor side-reaction is also observed, producing ester **32**. At lower temperatures, this reaction predominates over hydroacylation (entry 5). Heating to 60 °C is required to increase the rate of hydroacylation sufficiently to compete with the side-reaction. The ester side-product is derived from the Tischenko-type coupling of two aldehyde units. Ester **32** could be formed in moderate yield by treatment of aldehyde **9** with cationic rhodium catalyst **24** at room temperature in the absence of alkene (Scheme 83).

9 **32**

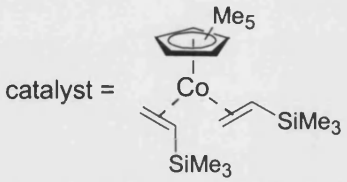
i) $Rh(dppe)ClO_4$, r.t. 24 h.

Scheme 83: Formation of ester by aldehyde disproportionation

This Tischenko-type dimerisation has been reported as a side-reaction during ruthenium- and cobalt-catalysed hydroacylations with aromatic and aliphatic aldehydes.[60,64] Use of excess aldehyde in the absence of added olefin allowed complete conversion to the ester (Scheme 84).

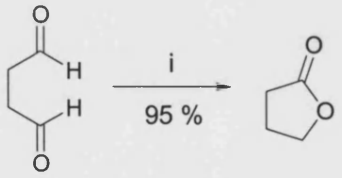


i) Co(I) catalyst, 0 °C, acetone



Scheme 84: Tischenko-type ester formation

This type of reaction has also been observed with the cationic rhodium complex. Bosnich and co-workers demonstrated that 1,4-dialdehydes could be cyclised to lactones (Scheme 85).[155] A ketoaldehyde was also cyclised, but in lower yield due to increased decarbonylation.

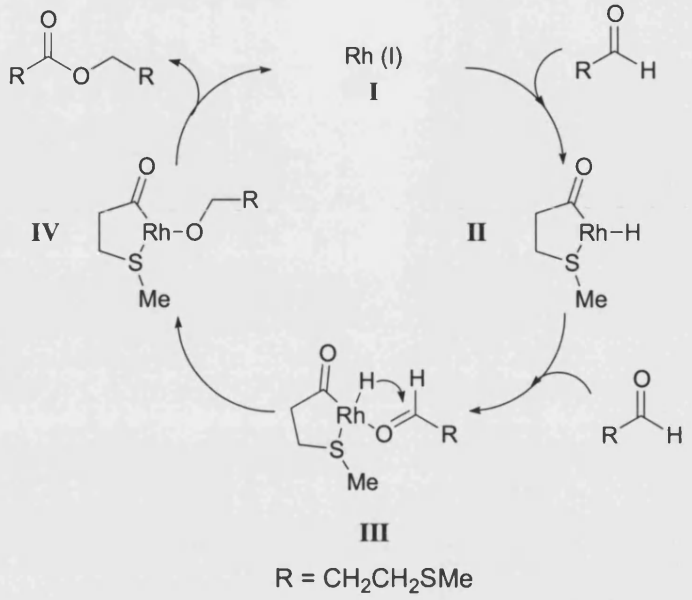


i) $[Rh(dppe)(acetone)_2]ClO_4$, DCM, r.t.

Scheme 85: Tischenko-type cyclisation of dialdehyde

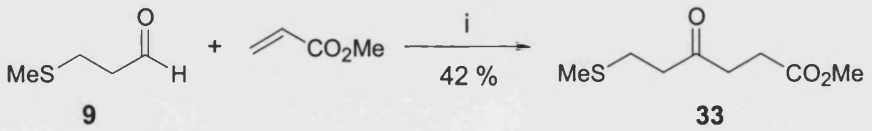
A plausible mechanism for formation of the ester by-product is shown in Scheme 86. Overall, it is effectively the hydroacylation of the aldehyde, and contains many of the same steps as alkene hydroacylation, with the aldehyde C=O behaving in a similar way to the alkene C=C bond. After oxidative addition of the aldehyde C–H bond to the rhodium catalyst (**I** to **II**), a second aldehyde unit can coordinate to the rhodium (**III**). Hydride transfer to the carbonyl gives an acyl rhodium alkoxide species (**IV**). Reductive elimination gives the ester product and regenerates the catalyst. Unlike

decarbonylation, this side-process does not deactivate the catalyst, and can therefore be performed catalytically.



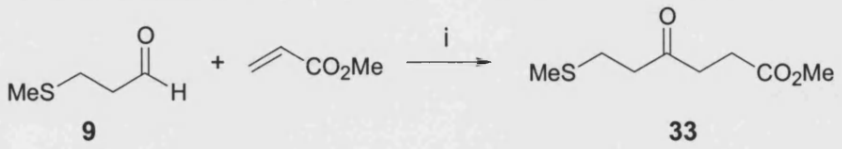
Scheme 86: Plausible mechanism for ester formation

The formation of ester **32** as a side product even under optimised conditions shows that octene is not the most effective substrate for this reaction. Previous work in our laboratory with picolyl aldimines revealed that electron-poor alkenes are excellent substrates for intermolecular hydroacylation.[91] They are also good substrates in this system. Thus, treatment of aldehyde **9** with methyl acrylate and the cationic rhodium complex gave the ketoester hydroacylation product **33** in moderate yield (Scheme 87).



Scheme 87: Hydroacylation of methyl acrylate

It has been shown that changing the counterion of the catalyst can have a significant effect on the rate of some metal-catalysed reactions, particularly those involving cationic metal systems.[156] The reaction between aldehyde **9** and methyl acrylate was used to evaluate the efficiency of rhodium catalysts with different counterions (Table 11).



9 **33**

i) $[Rh(dppe)]^+ X^-$ (20 mol%), DCE, 60 °C, 2 h.

Entry	Catalyst	Counterion, X^-	Yield[a] (%)
1	**22a**	ClO_4^-	42
2	**22b**	BF_4^-	35
3	**22c**	$CF_3SO_3^-$	37

a. Isolated yield after chromatographic purification.

Table 11: Optimisation of hydroacylation catalyst

The results of this study show that these variations to the catalyst counterion have little effect on the yield obtained in the hydroacylation reaction.

Rhodium carborane catalyst

Carborane anions such as [*closo*-$CB_{11}H_6Br_6^-$] (Figure 11) are the least coordinating counterions known to date.

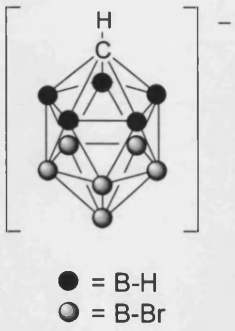


Figure 11: Carborane anion

The introduction of carborane systems has seen significant improvements in various transition metal-catalysed processes, for example hydrogenation (Table 12).[156]

The hydrogenation of cyclohexene by $[Rh(PPh_3)_2(NBD)]BF_4$ is very slow, giving only a 29 % yield of cyclohexane after 2 hours. Changing the counterion to a carborane greatly improves the efficiency of the reaction, delivering quantitative hydrogenation within 30 minutes.

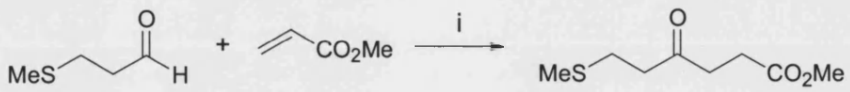
i) $[Rh(PPh_3)_2(NBD)]^+ X^-$ (1 mol%)
H_2 (10 psi), DCM, 20 °C

Entry	Counterion, X =	Time	Yield[a] (%)
1	BF_4^-	2 h.	29
2	$CB_{11}H_6Br_6^-$	30 min.	100

a. Determined by gas chromatography

Table 12: Hydrogenation of cyclohexene with carborane catalyst

The perchlorate and carborane systems were compared over a range of temperatures and catalyst loadings (Table 13).



9 **33**

i) $[Rh(dppe)]^+ X^-$, DCM or DCE

Entry	Counterion	Loading	Temp.	Time	Conversion[a] (%)
1	ClO_4^-	5 %	70 °C	45 min.	>99
2		5 %	40 °C	16 h.	85
3		10 %	20 °C	16 h.	40[b]
4		2 %	70 °C	1 h.	70
5		1 %	60 °C	48 h.	70
7	$CB_{11}H_6Br_6^-$	5 %	40 °C	16 h.	95
8		5 %	20 °C	3 h.	0
9		1 %	40 °C	16 h.	0

a. Conversion of aldehyde to products by ^1H NMR of crude reaction mixture

b. Ester **32** obtained in 30 % yield

Table 13: Comparison of perchlorate and carborane counterions

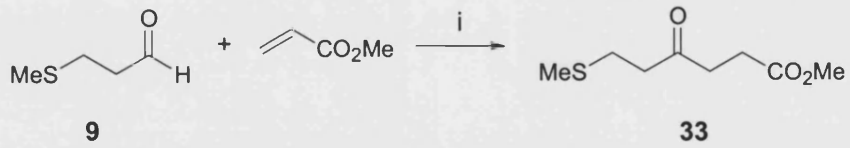
The optimum temperature range is 60–70 °C, where complete conversion of the aldehyde occurred within 45 minutes (entry 1). Unlike the simple alkenes used for initial studies, the more active acrylate substrate delivers good yields of products at lower temperatures, but prolonged reaction times are necessary (entry 2) and competition from the Tischenko-type side-reaction results in low yields at room temperature (entry 3). Good yields are obtained with catalyst loadings down to 1 %, although this also requires prolonged reaction times (entries 4 and 5). Changing the

counterion to hexabromocarborane $[CB_{11}H_6Br_6]^-$ gives a similar yield at 40 °C (entry 7). Unexpectedly, the carborane system shows no sign of conversion at room temperature (entry 8) or with lower catalyst loading (entry 9), even after prolonged reaction times. This could be attributed to the greater sensitivity of the catalyst due to decreased stabilisation of the cationic centre by carborane compared to the perchlorate counterion.

This study shows that under optimised conditions the overall yield of product obtained did not increase upon changing the catalyst counterion from perchlorate to carborane. It appears the rhodium perchlorate catalyst is more robust and can operate efficiently under a wider range of conditions.

Kinetic study

A study was carried out to investigate the relative rates of the reactions with the two counterions. Any kinetic effect due to the counterion would be helpful in further speculation on the reaction mechanism.



9 **33**

i) $[Rh(dppe)]^+ X^-$ (5 mol%), CD_2Cl_2, 40 °C, 24 h.

Scheme 88: Kinetic study

^1H NMR was used to measure the conversion of aldehyde over the course of the reaction. The results are shown below (Figure 12).

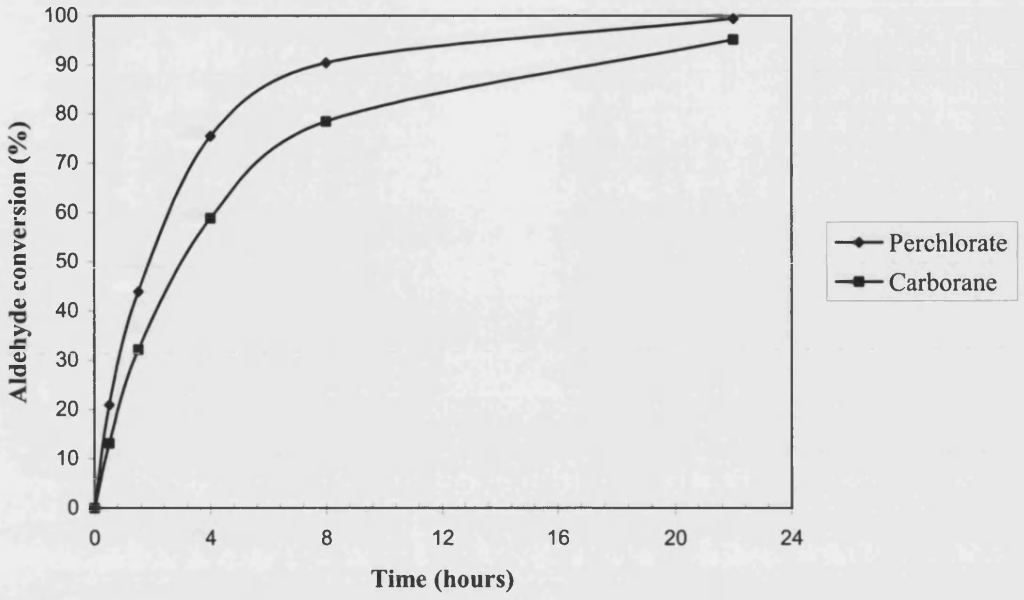


Figure 12: Conversion of aldehyde with carborane and perchlorate catalysts

Overall, there was no significant difference in the rate of reaction with the two catalysts. The slightly lower rate observed with the carborane catalyst is attributed to its sensitivity, and the greater likelihood of decomposition during catalyst preparation. The absence of any counterion effect may still be helpful for determination of the reaction mechanism, as the rate-determining step is apparently not affected by the nature of the counterion.

The reaction profiles with perchlorate and carborane catalysts (Figure 13 and Figure 14 respectively) showed that the reactions proceed in an identical manner, with no difference in regioselectivity.

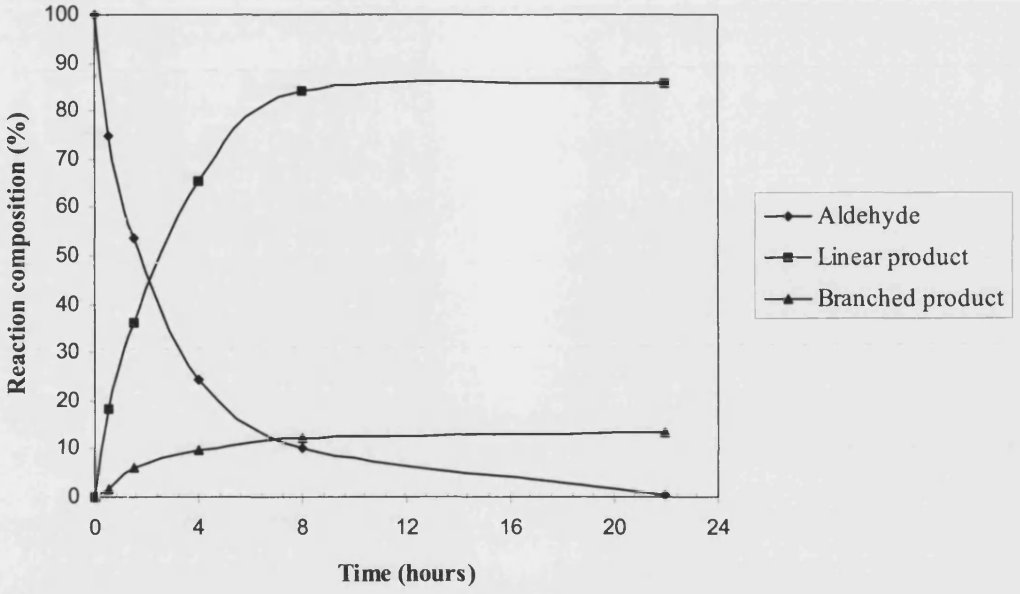


Figure 13: Conversion with perchlorate catalyst

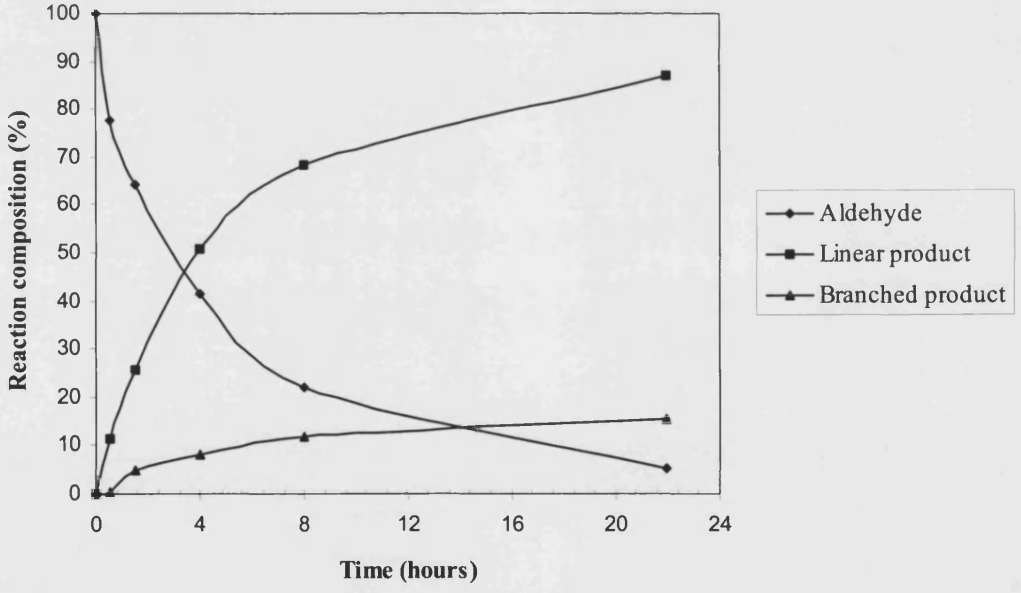
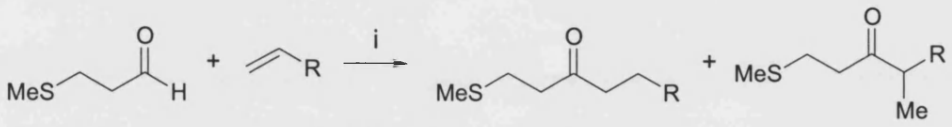


Figure 14: Conversion with carborane catalyst

2.4 Alkene evaluation

With the conditions optimised, the range of applicable alkene substrates was determined. Due to the previous success with methyl acrylate, this investigation began with a selection of electron-poor alkenes (Table 14).



9 **33 a-d** **34 a-d**

i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C, 2 h.

Entry	Alkene, R	Products			
			Yield[a] (%)		Yield[a] (%)
1	CO_2Me	**33a**	60 (80)	**34a**	19 (20)
2	CO_2t-Bu	**33b**	40 (78)	**34b**	6 (17)
3	$C(O)NMe_2$	**33c**	22 (88)	**34c**	0 (<5)
4	SO_2Ph	–	0	**34d**	74 (>98)
5	S(O)Ph	–	0	–	0

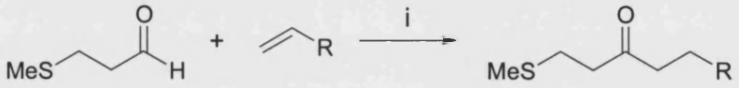
a. Isolated yield after chromatographic purification. Values in parentheses are yields by ^1H NMR of crude reaction mixture, using 2,5-dimethylfuran as a quantitative internal standard.[157]

Table 14: Hydroacylation of electron-poor alkenes

Mono-substituted electron-poor olefins such as the acrylates work very well under these conditions (entries 1 and 2). ^1H NMR analysis of the crude reaction mixture after removal of solvent showed that the aldehyde was converted quantitatively to

products after 45 minutes. The regioselectivity of the addition was approximately 4:1 in favour of the linear regioisomer **33**. *N,N*-Dimethyl acrylamide can also be used, and reacts with higher regioselectivity (entry 3). Hydroacylation of phenyl vinyl sulfone delivers a single product **34d** in good yield, with the opposite regioselectivity (entry 4). The sulfoxide (entry 5) did not give any hydroacylation product.

With more electron-rich alkenes the yields are lower, but the addition is highly regioselective, with the linear isomer obtained exclusively (Table 15).



9 **27 a-e**

i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C

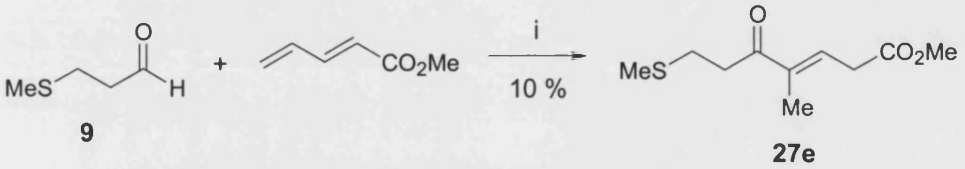
Entry	Alkene, R =	Product	Yield[a] (%)
1	C_6H_{13}	**27a**	33
2	Ph	**27b**	41
3	$(CH_2)_9OMe$	**27c**	31
4	CH_2OAc	**27d**	35
5	OBu	–	0
6	OAc	–	< 2
7	$CH{=}CH_2CO_2Me$	**27e**	10

a. Isolated yield after chromatographic purification.

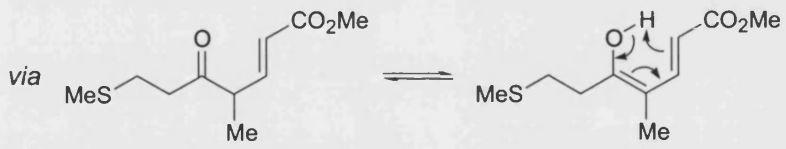
Table 15: Hydroacylation of electron-rich alkenes

Simple alkenes (entries 1–4) give low to moderate yields in the hydroacylation reaction. The main reason for the low yields with these substrates is the reduced rate

of reaction compared to electron-poor olefins. This results in greater competition from the side reactions: decarbonylation and aldehyde disproportionation. The electron-rich butyl vinyl ether showed no sign of hydroacylation (entry 5), but merely gave a complex mixture of decomposition products. The slightly less reactive vinyl acetate (entry 6) did not decompose, but still showed very little sign of hydroacylation. A conjugated diene also underwent hydroacylation, although in low yield. The product appears to have undergone an additional double-bond isomerisation (Scheme 89), probably a 1,5-H shift *via* the enol tautomer to give unsaturated ketone **27e**.



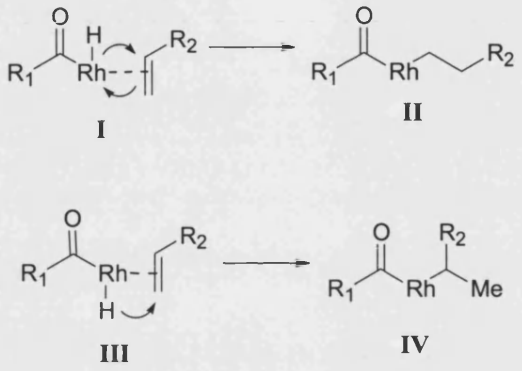
i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C, 16 h.



Scheme 89: Hydroacylation of conjugated diene

Regioselectivity of hydroacylation

The observed variation in regioselectivity of the reaction can be explained by considering the insertion of the olefin into the rhodium-hydride bond, which is the step that defines the regiochemistry of the product (Scheme 90).



Scheme 90: Regiochemistry of olefin rhodium-hydride insertion

With any substrate, steric effects favour insertion, probably by a concerted process (**I**), to give a linear alkyl rhodium species (**II**), leading to linear ketone products. When the alkene substituent (R_2) is electron-withdrawing, polarisation of the double bond may favour addition of the hydride to the terminal carbon atom (**III**) to give a branched alkylrhodium intermediate (**IV**), leading to branched ketone products. With the acrylate esters there is a delicate balance of steric and electronic effects favouring different regioisomers and a mixture of products is obtained. Greater regioselectivity is observed with the acrylamide; the amide group is less electron-withdrawing and the linear product is obtained almost exclusively.

The hydroacylation of phenyl vinyl sulfone also proceeds with a high degree of regioselectivity, and the branched product is formed exclusively. The sulfone group is strongly electron-withdrawing and polarisation of the double bond favours addition of the hydride to the terminal carbon.

The strongly electron withdrawing ketone and nitrile substrates also appear to proceed *via* addition of hydride to the terminal carbon atom, but unusual products are obtained. This is discussed in detail in the next section. Overall, the regioselectivity appears to be defined by the electronic nature of the substituent as shown below (Figure 15).

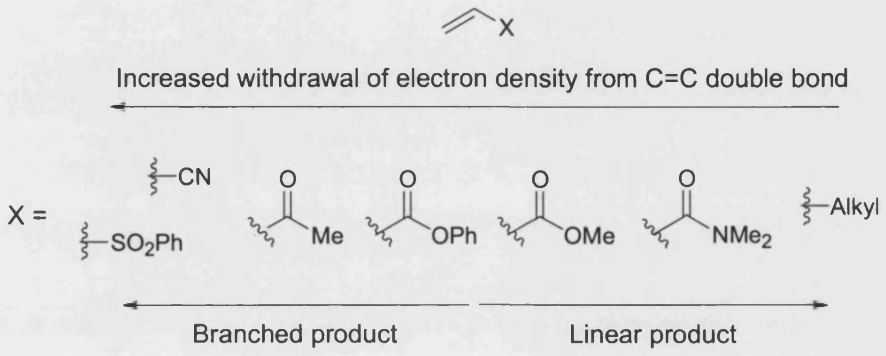
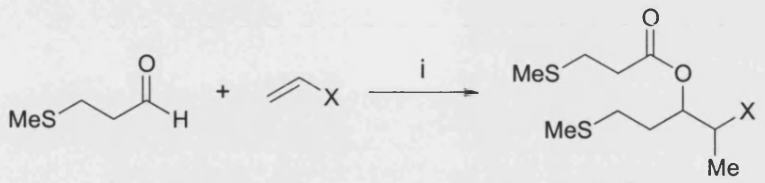


Figure 15: Regioselectivity of hydroacylation

Unusual reactivity of very electron-poor substrates

The hydroacylation of methyl vinyl ketone, acrylonitrile and phenyl acrylate gave different products. Spectroscopic data was consistent with the ester structure shown below (Table 16).



9 **35 a-c**

i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C

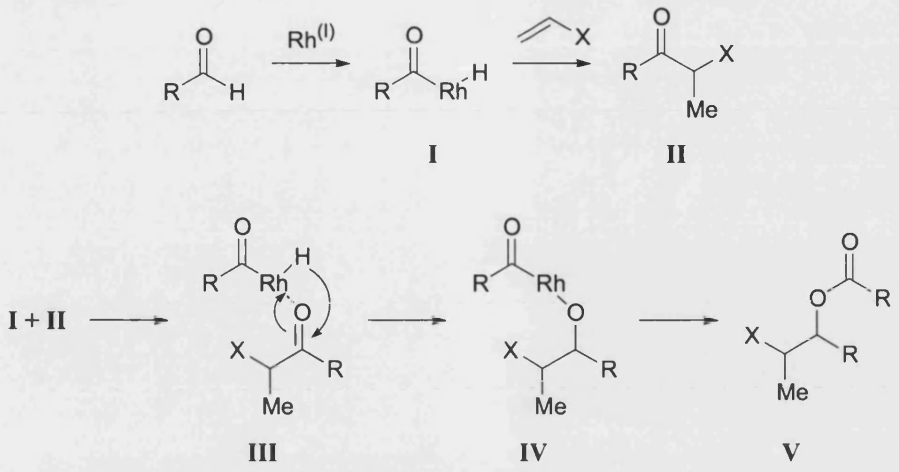
Entry	Alkene, X =	Product	Yield[a] (%)	d.r.[b]
1	C(O)Me	**35a**	72 (>98)	1.2 : 1
2	CN	**35b**	66 (>98)	2.4 : 1
3	CO_2Ph	**35c**	66 (>98)	2 : 1

a. Isolated yield after chromatographic purification. Values in parentheses are yields by ^1H NMR of crude reaction mixture, using 2,5-dimethylfuran as a quantitative internal standard.[157]

b. Determined by ^1H NMR. Each product was obtained as an inseparable mixture of diastereoisomers

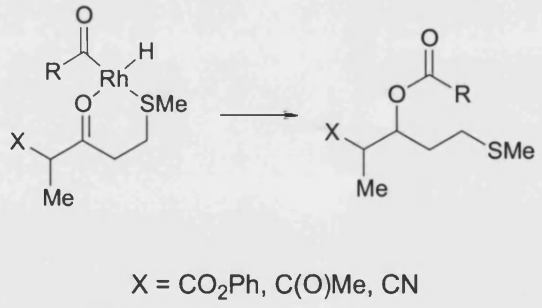
Table 16: Hydroacylation of electron-poor substrates

A plausible route for formation of these products is outlined below (Scheme 91). The electron-poor alkene reacts to give the branched hydroacylation adduct (**II**). The ketone intermediate (**II**), with a strongly electron withdrawing group in the α-position, is prone to undergo a Tischenko-type disproportionation with a second C–H activated aldehyde (**I**) to give the ester product (**V**).



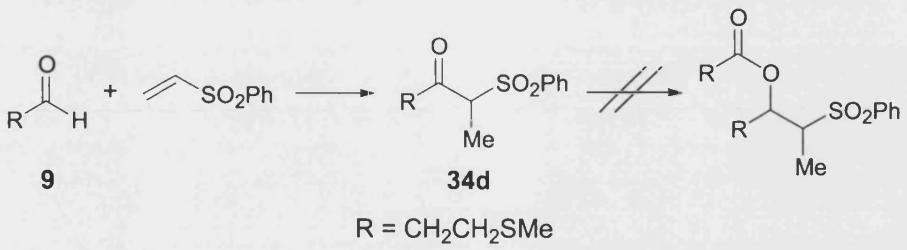
Scheme 91: Possible mechanism for hydroacylation-Tischenko reaction

With the ester and ketone substrates, the initially formed hydroacylation product (**II**) contains two carbonyl groups. Only a single product is observed, suggesting that the hydride addition (**III**) occurs selectively at one of the two carbonyls. It is possible that the sulfide directs the catalyst to the ketone group (Scheme 92).



Scheme 92: Sulfur-directed disproportionation

The vinyl sulfone substrate gives only the hydroacylation product **34d** and does not undergo the disproportionation step (Scheme 93); the reasons for this are not clear.

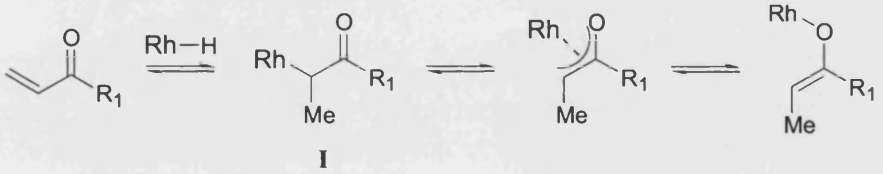


9 **34d**

R = CH_2CH_2SMe

Scheme 93: Hydroacylation of vinyl sulfone

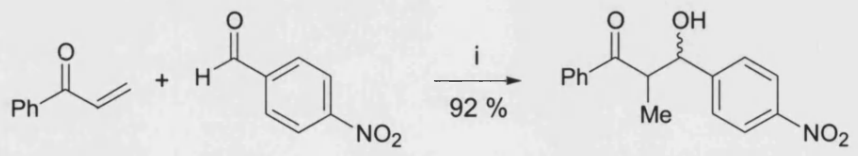
An alternative mechanism for the ester formation is detailed below. It has been reported that treatment of enones with a rhodium hydride can generate rhodium enolates (Scheme 94).[158-160] Presumably, this proceeds *via* the α-metallated intermediate (**I**), where the Rh–C bond is conjugated with the C=O bond of the carbonyl.



I

Scheme 94: Generation of rhodium enolates from enones

Trialkylsilanes and elemental hydrogen have both been used as the hydride donor to generate the metal hydride species.[160] The rhodium enolate can be trapped with an electrophile: for example, treatment with aldehydes gives the corresponding aldol products (Scheme 95).[158]

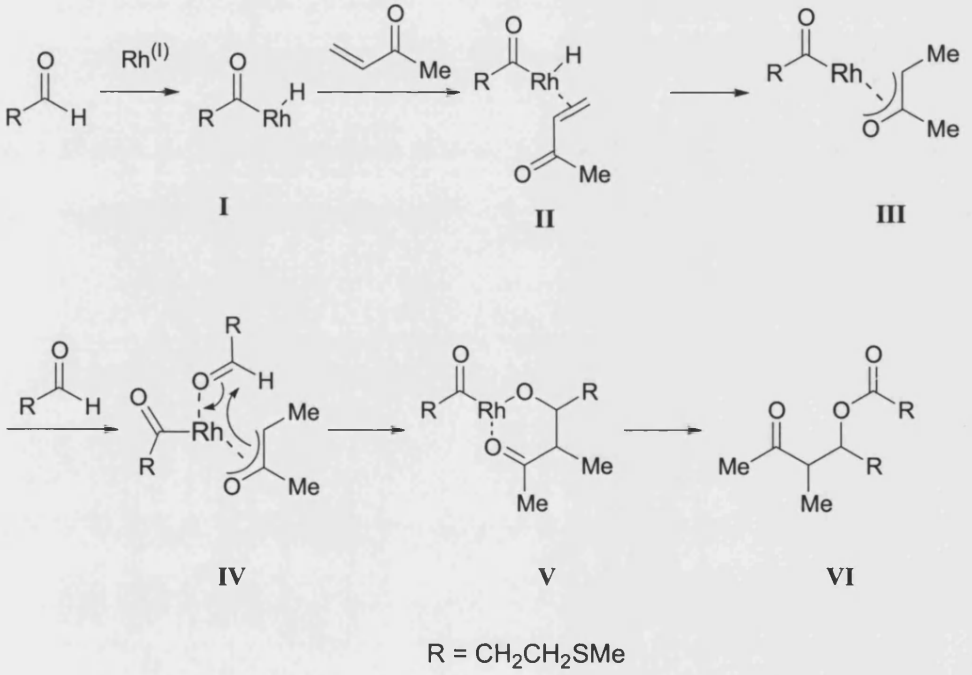


i) $Rh(COD)_2OTf$ (5 mol%), PPh_3, H_2 (1 atm.), KOAc, DCE, 25 °C

Scheme 95: Reductive aldol reaction

Enantioselective variants of the reductive aldol reaction have also been developed.[161]

The generation of ester **32** as a minor product in many of the hydroacylation reactions suggests that an aldehyde can coordinate to the acylrhodium (III) hydride after the initial oxidative addition. Nucleophilic attack by an enolate on such a coordinated aldehyde would result in a rhodium aldolato complex. A possible mechanism for this process involving this rhodium enolate intermediate is outlined below (Scheme 96).



Scheme 96: Possible mechanism for "hydro-aldol-acylation"

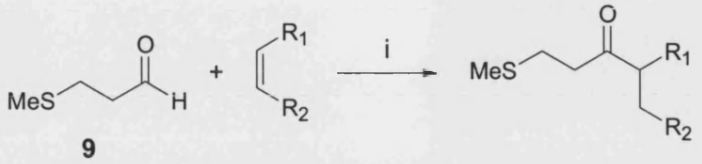
Aldehyde oxidative addition is followed by hydrometallation of alkene. In certain systems, this produces a rhodium enolate complex (**III**). Coordination of a second aldehyde carbonyl group would give a species resembling structure **IV**. As the enolate (**III**) is coordinatively saturated, the second aldehyde would have to displace one of the ligands. It is also possible that the nucleophilic attack by the enolate is an intermolecular process where the second aldehyde is either free or activated by

coordination to a second rhodium centre. Either route would eventually give a rhodium-aldolato complex (**V**). Reductive elimination with carbon–oxygen bond formation yields the substituted ester product (**VI**).

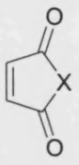
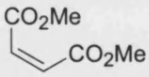
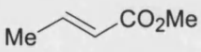
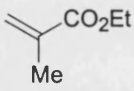
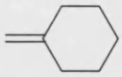
Monitoring of the reaction by IR could be one way to determine which mechanism is operating in this system. The carbonyl groups of the different reaction intermediates may be distinctive and allow further speculation on the mechanism.

Hydroacylation of disubstituted alkenes

Various disubstituted alkene substrates were also tested under hydroacylation conditions. Most of these reactions did not proceed (Table 17).



i) $Rh(dppe)ClO_4$, DCE, 60 °C

Entry	Alkene	Product	Yield[a] (%)
1	 X = NMe	**27f**	52
2	X = O	–	0
3		–	0
4		–	0
5		–	0
6		–	0

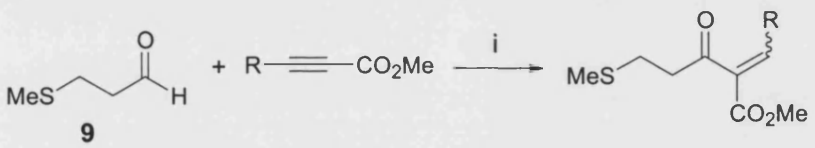
a. Isolated yield after chromatographic purification.

Table 17: Hydroacylation of disubstituted alkenes

The only substrate to undergo hydroacylation under the normal conditions (10 % catalyst, DCE, 60°C) was the cyclic maleimide (entry 1), in which case the double

bond is sufficiently activated to overcome the steric hindrance. The similarly activated maleic anhydride and dimethyl maleate (entries 2 and 3) did not react. It is possible the maleate is isomerised to the more hindered *trans*-fumarate under the reaction conditions. The anhydride decomposed and no reaction was observed. Methyl crotonate, ethyl methacrylate and methylene cyclohexane (entries 4–6) did not give any hydroacylation products under these conditions.

Disubstituted alkyne substrates also failed to give hydroacylation products (Table 18). Dimethyl acetylene dicarboxylate gave a small amount of hydroacylation product (entry 1), but the yield was less than 1 % by NMR of the crude reaction mixture, and the product could not be isolated.



i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C

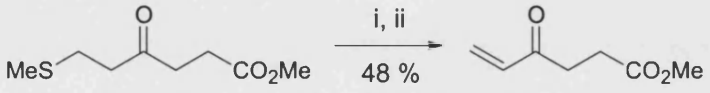
Entry	Alkyne, R =	Yield[a] (%)
1	CO_2Me	0 (<1)
2	Ph	0

a. Isolated yield after chromatographic purification. Values in parentheses are yields by ^1H NMR of crude reaction mixture, using 2,5-dimethylfuran as a quantitative internal standard.[157]

Table 18: Hydroacylation of alkyne substrates

Elimination of sulfide

To allow for further elaboration of the hydroacylation products, it would be beneficial to be able to remove the sulfide group. Sequential treatment of the ketone product **33** with methyl triflate and potassium bicarbonate effected the clean elimination of the sulfide group to produce α,β-unsaturated ketone **36** (Scheme 97).



33 **36**

i) MeOTf, DCM, r.t., 20 min.; ii) $KHCO_3$, r.t. 10 min.

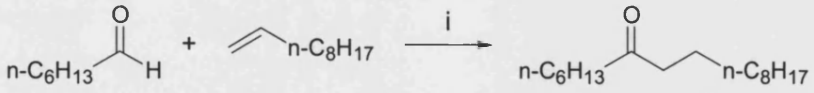
Scheme 97: Elimination of sulfide group

Alternative methods, for example oxidation to the sulfoxide or sulfone, may also be suitable for further functionalisation of the sulfide.

2.5 Microwave-assisted hydroacylation

Microwave heating has been found to increase greatly the efficiency of a wide range of organic transformations, including many homogeneous metal-catalysed reactions. Microwave reactors have several advantages over conventional heating: the reaction medium is heated directly, not through the wall of the reaction vessel; the heating is smooth and homogeneous, resulting in cleaner reactions; and the heating is more controlled, as the power can be turned on or off immediately. There are also drawbacks to microwave heating: the reaction volume is limited, making it difficult to scale up reactions; microwave heating requires very accurate temperature monitoring and power feedback control to maintain reproducibility.

Microwave heating has been used in a variety of metal catalysed processes,[162,163] including rhodium-catalysed hydroacylation.[164,165] In the hydroacylation reaction, microwave heating allowed the use of substrates that had not been suitable under conventional conditions (Table 19).



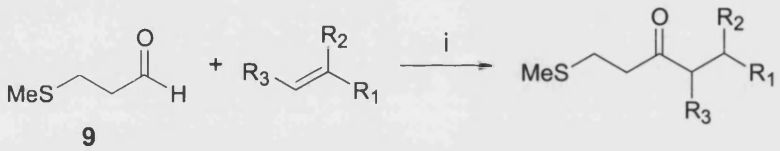
i) $RhCl(PPh_3)_3$ (5 mol%), 2-aminopicoline (40 mol%), benzoic acid (10 mol%), 130 °C

Entry	Solvent	Time	Yield (%)
1	Toluene	4 h.	13
2	None (MW)	10 min.	61

Table 19: Improved rate of hydroacylation with microwave heating

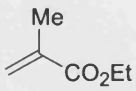
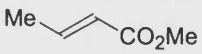
The exact reasons for acceleration of the reaction under microwave heating are not clear. It has been suggested that the induced electric field stabilises dipolar transition states.[164,165]

The efficiency of the hydroacylation with sulfanyl aldehyde **9** was improved by microwave heating (Table 20). The hydroacylation of methyl acrylate was complete within 10 minutes (entry 1). In this case, the previously unreactive methyl methacrylate gave some product (entry 2), but the crotonate substrate did not react (entry 3).



9

i) $Rh(dppe)ClO_4$ (10 mol%), DCE

Entry	Alkene	Temp. (MW)	Time	Yield[a] (%)
1		70 °C	10 min.	82 (>98)
2		90 °C	30 min.	12
3		90 °C	60 min.	0

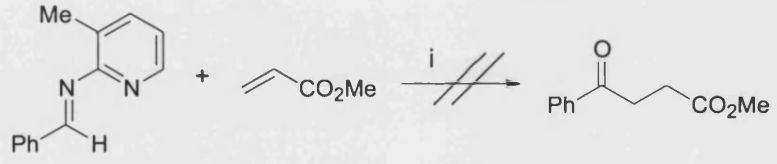
a. Isolated yield after chromatographic purification. Values in parentheses are yields by ^1H NMR of crude reaction mixture, using 2,5-dimethylfuran as a quantitative internal standard.[157]

b. Product not isolated

Table 20: Hydroacylation under microwave irradiation

2.6 Hydroiminoacylation

Previous work in our laboratories has shown that electron-poor alkenes are good substrates for hydroiminoacylation with picolyl aldimine **36** (Scheme 38).[91] The use of electron-poor aldehydes increases the rate of the reaction, but high temperatures are still required. It was thought that the use of a cationic rhodium catalyst could allow the reaction to be performed at lower temperatures. Unfortunately, it appears the picolyl imine is incompatible with the cationic rhodium complex **22**, and no reaction was observed (Scheme 98). This is most likely due to catalyst deactivation by coordination of the pyridyl nitrogen, as was observed with the pyridyl-substituted aldehyde **6** discussed earlier.

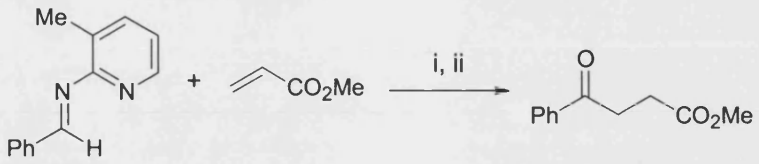


37 **38**

i) $Rh(dppe)ClO_4$ (10 mol%), DCE, 60 °C, 2 h.

Scheme 98: Hydroiminoacylation with cationic rhodium complex

Another possibility for improving the convenience of the hydroiminoacylation reaction was to use microwave heating, which improved the efficiency of hydroacylation with sulfanyl aldehyde **9**. A brief investigation revealed that reaction times could be dramatically reduced and the yields improved over the traditional method of heating in an oil bath (Table 21).



37 **38a**

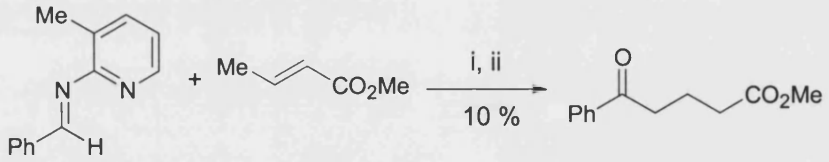
i) $RhCl(PPh_3)_3$, THF, 135 °C; ii) HCl (aq)

Entry	Heating method	Time	Yield[a] (%)
1	Oil bath	8 h.	72
2	Microwave	10 min.	83

a. Isolated yield after chromatographic purification.

Table 21: Hydroiminoacylation under microwave irradiation

The hydroacylation of more hindered methacrylate and cinnamate substrates was not improved, and no products were obtained. Methyl crotonate was isomerised under the reaction conditions and gave a small amount of ketone **38b**.



37 **38b**

i) $RhCl(PPh_3)_3$, THF, 135 °C; ii) HCl (aq)

2.7 Conclusions

The direct intermolecular hydroacylation of simple alkenes has been performed, using a commercially available aldehyde under mild, convenient conditions.

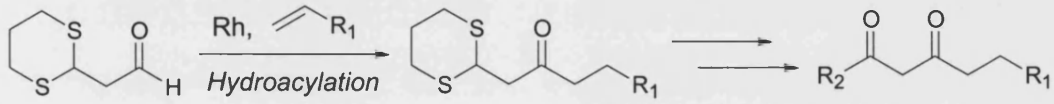
- The chelating sulfide group of the aldehyde, in combination with a cationic rhodium catalyst, prevents decarbonylation and allows low catalyst loadings to be used.

- Electron-poor acrylate esters were found to be excellent substrates for this reaction; normal alkyl substrates can also be used, and deliver moderate yields of products.

- Substrates with a strongly electron-withdrawing group undergo an unexpected reaction, which could possibly be developed into a useful process with further investigation.

2.8 Future Work

- Different chelating groups would allow for more options in the elaboration of hydroacylation products. For example, a dithiane could be used as the chelating group, which would allow for generation of masked 1,3-diketone products.

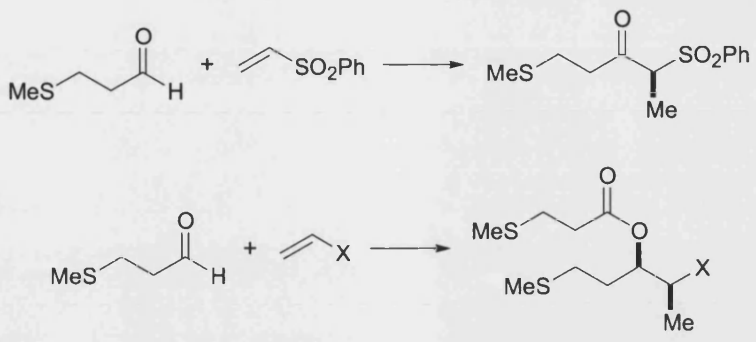


- Our attempts to synthesise phosphorus-containing aldehydes failed, but if suitable synthetic routes could be found, they could be promising substrates due to strong coordination to rhodium.

- Modification of the catalyst may improve the hydroacylation of the simple alkene substrates, which gave only moderate yields. In addition, it may be possible to extend the scope to substituted alkenes. It would also be beneficial to improve the regioselectivity of the reaction with acrylate substrates.

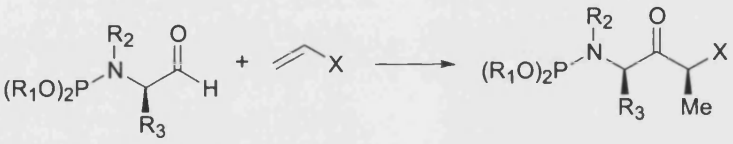
- The hydroacylation of very electron-poor substrates gave unexpected ester products. Further work could identify the mechanism leading to these products. Stereoselective versions could also be developed.

- The branched hydroacylation products contain chiral centres. Modification of the catalyst with chiral phosphine ligands may allow these compounds to be produced enantioselectively.



Rh(I) catalyst, e.g. $Rh(BINAP)ClO_4$

- Alternatively, chiral hydroacylation products could be obtained by using chiral aldehyde substrates. Chiral phosphoramidites could be synthesised from natural α-amino acids.



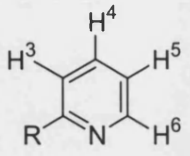
Chapter 3 Experimental Section

3.1 General considerations

Unless otherwise specified, all reactions were performed in anhydrous conditions under a nitrogen atmosphere and commercially available reagents were used as received without further purification. All solvents were freshly distilled from sodium (diethyl ether, toluene and tetrahydrofuran) or calcium hydride (acetonitrile, dichloromethane, 1,2-dichloroethane and dimethyl sulfoxide) and stored over molecular sieves under nitrogen or argon. All reactions involving rhodium complexes were performed using standard Schlenk line techniques under argon; substrates for hydroacylation experiments were purified by distillation or recrystallisation before use. The rhodium pre-catalyst complexes were stored in sealed, argon-filled Schlenk tubes in a refrigerator, but they are relatively moisture- and air-stable, so could be weighed on a normal balance.

NMR analyses were carried out on Bruker 300AM or Varian 400 instruments. ^{1}H and ^{13}C chemical shifts δ are quoted in parts per million, relative to tetramethylsilane. Multiplicities of the signals are recorded as follows: s = singlet, br = broad signal, d = doublet, t = triplet, q = quartet, quint. = quintet and m = unresolved multiplet. Coupling constants J are quoted in Hertz.

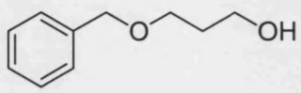
Pyridyl protons are assigned as follows:



Infrared measurements were made as a liquid film in the range 4000–600 cm^{-1}, using a Perkin-Elmer FT-1000 spectrometer; only significant peaks are quoted. The following abbreviations are used: br = broad, w = weak.

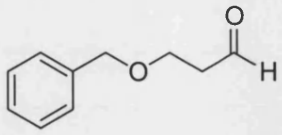
Mass spectrometry measurements were performed at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea; values are quoted as *m/z* with relative intensity in parentheses.

Thin layer chromatographic analyses were performed on plates coated with Kieselgel $60F_{254}$. Visualisation was achieved with a 254 nm ultraviolet lamp, followed by staining with vanillin or potassium permanganate. Column chromatographic separation was carried out using silica gel (35–70 mesh). Petrol refers to light petroleum ether, boiling point range 40–60 °C.



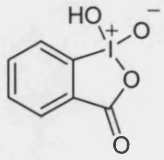
3-Benzyloxypropanol 1[166]

Sodium hydride (1.4 g of 60 % dispersion in mineral oil, 35.0 mmol) was added slowly in small portions to a solution of 1,3-propanediol (5.0 ml, 69.2 mmol) in dimethyl sulfoxide (80 ml). The mixture was stirred at room temperature for 30 minutes. Benzyl chloride (4.0 ml, 34.8 mmol) was added via syringe and the mixture stirred at room temperature for a further 2 hours. The solution was diluted with water (100 ml) and extracted with diethyl ether (3 × 50 ml). The combined organic fractions were washed with brine, dried with sodium sulfate then evaporated. The residue was purified by either distillation (b.p. 52 °C, 4×10^{-2} mmHg) or column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.3) to give *alcohol* **1** as a colourless liquid (3.88 g, 67 %); δ_H (300 MHz; $CDCl_3$) 7.37–7.27 (5H, m, Ph), 4.54 (2H, s, PhC*H*$_2$), 3.80 (2H, t, *J* 6, OC*H*$_2$), 3.68 (2H, t, *J* 6, C*H*$_2$OH), 2.31 (1H, t, *J* 6, OH), 1.88 (2H, quint., *J* 6, $CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 138.0, 128.4, 127.7, 127.6, 73.2, 69.3, 61.8, 32.1; ν_{max} (film) /cm^{-1} 3600–3200 (br, O–H); *m/z* (CI+, NH_3) 184 (100 %, M+NH_4), 167 (16 %, M+H), 108 (12 %, $PhCH_2OH$); found: $[M+H]^+$ 167.1072, $C_{10}H_{15}O_2$ requires 167.1072; data in agreement with literature example.[166]



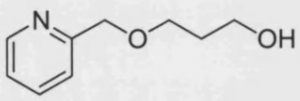
3-Benzyloxypropanal 2

IBX **3** (0.97 g, 3.46 mmol) was dissolved in dimethyl sulfoxide (10 ml) by stirring for 10 minutes at room temperature. Alcohol **1** (0.51 g, 3.07 mmol) was added via syringe. The mixture was stirred at room temperature for 19 hours then diluted with water (150 ml), filtered and extracted with diethyl ether (2 × 100 ml). The combined organic layers were washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (silica, ethyl acetate/petrol, 1:9; R_f 0.26) to give *aldehyde* **2** as a colourless liquid (0.30 g, 60 %). Before use the aldehyde was further purified by distillation (b.p. 36 °C, 4.5 × 10^{-2} mmHg); δ_H (300 MHz; $CDCl_3$) 9.80 (1H, t, *J* 2, CHO), 7.36–7.26 (5H, m, Ph), 4.54 (2H, s, PhCH_2), 3.82 (2H, t, *J* 6, OCH_2), 2.71 (2H, td, *J* 6 and 2, CH_2CHO); δ_C (75MHz, $CDCl_3$) 201.1, 137.8, 128.4, 127.8, 127.7, 73.3, 63.8, 43.9; ν_{max} (film) /cm^{-1} 1722 (C=O); *m/z* (CI+, NH_3) 182 (100 %, M+NH_4), 108 (15 %, $PhCH_2OH$), 91 (9 %, C_7H_7); found $[M+NH_4]^+$ 182.1180, $C_{10}H_{16}NO_2$ requires 182.118; data in agreement with literature example.[166]



1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) 3[140]

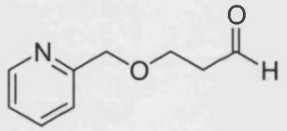
2-Iodobenzoic acid (50 g, 201 mmol) was added to a solution of Oxone® (181 g, 294 mmol) in water (650 ml). The mixture was stirred at 70 °C for 3 hours then cooled in an ice bath. The product was removed by filtration, washed with water (3 × 100 ml) and acetone (2 × 100 ml) and dried in a desiccator to give **3** as a white powder (47.5 g, 84 %); m.p. 230 °C, dec. (lit.[140] m.p. 232–233 °C, dec.); δ_H (400 MHz; d_6-DMSO) 8.14 (1H, d, *J* 8), 8.03 (1H, d, *J* 8), 8.00 (1H, dd, *J* 8 and 7.5), 7.84 (1H, dd, *J* 8 and 7.5); δ_C (75 MHz, d_6-DMSO) 167.5, 146.5, 133.4, 132.9, 131.3, 130.1, 124.9; ν_{max} (Nujol) 3300–3100 (br, OH), 1633 (C=O); data in agreement with literature example. [140]



3-(Pyridin-2-ylmethoxy)propanol 5

Sodium hydride (6.0 g of 60 % dispersion in mineral oil, 150 mmol) was added slowly to a solution of 1,3-propanediol (8.0 ml, 110 mmol) in tetrahydrofuran (75 ml). The mixture was stirred at room temperature for 1 hour then picolyl chloride hydrochloride (10.0 g, 61 mmol) was added in small portions. The mixture was then heated to reflux for 24 hours. Ammonium chloride (75 ml of saturated aqueous solution) was added and the mixture was acidified to pH 4 with hydrochloric acid (2 M aqueous solution). The organic layer was removed and the aqueous layer washed with ethyl acetate (20 ml). The solution was then neutralised to pH 7 with sodium

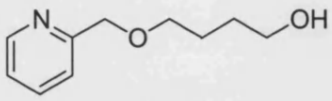
bicarbonate (saturated aqueous solution), before extracting with dichloromethane (3 × 50 ml). The combined dichloromethane fractions were dried with sodium sulfate then evaporated to give *alcohol* **5** as a pale yellow oil (6.7 g, 66 %), which was used without further purification; δ_H (300 MHz; $CDCl_3$) 8.54 (1H, d, *J* 4, py-H^6), 7.72–7.67 (1H, m, py-H^4), 7.40 (1H, d, *J* 8, py-H^3), 7.22–7.18 (1H, m, py-H^5), 4.65 (2H, s, pyCH_2O), 3.81 (2H, t, *J* 5, CH_2OH), 3.75 (2H, t, *J* 6, OCH_2), 3.02 (1H, br s, OH), 1.90 (2H, tt, *J* 6 and 5, $CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 158.3, 149.0, 136.8, 122.5, 121.3, 73.5, 69.4, 60.7, 32.2; ν_{max} (film) /cm^{-1} 3500–3200 (br, O–H); *m/z* (CI+, NH_3) 168 (70 %, M+H), 110 (10 %, $PyCH_2$+NH_4); found $[M+H]^+$ 168.1024, $C_9H_{14}NO_2$ requires 168.1024



3-(Pyridin-2-ylmethoxy)propanal 6

A solution of dimethyl sulfoxide (5.7 ml, 80 mmol) in dichloromethane (20 ml) was added dropwise to a solution of oxalyl chloride (3.5 ml, 40 mmol) in dichloromethane (70 ml) at –78 °C. The rate of addition was adjusted to ensure the temperature did not rise above –60 °C. After stirring for 15 minutes, a solution of alcohol **5** (5.5 g, 33 mmol) in dichloromethane (30 ml) was added dropwise, again keeping the temperature below –60 °C. The mixture was stirred for 1 hour, then triethylamine (25.0 ml, 179 mmol) was added dropwise and the mixture was stirred for a further 15 minutes. Water (75 ml) was added and the mixture was allowed to return to room temperature with stirring. The organic layer was separated and the aqueous layer washed with dichloromethane (3 × 20 ml). The combined organic fractions were dried with sodium sulfate then evaporated. The residue was purified

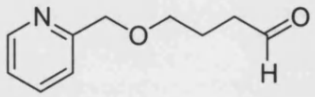
by column chromatography (silica, 1:5 ethyl acetate/petrol; R_f 0.3) to give a dark orange oil (2.7 g, 50 %), which was distilled to give *aldehyde* **6** as a colourless liquid (b.p. 58 °C, 2.8×10^{-2} mmHg); δ_H (300 MHz; $CDCl_3$) 9.86 (1H, d, *J* 2, CHO), 8.60 (1H, br s, py-H^6), 7.73–7.67 (1H, m, py-H^4), 7.40 (1H, d, *J* 8, py-H^3), 7.22–7.18 (1H, m, py-H^5), 4.65 (2H, s, pyCH_2O), 3.94 (2H, t, *J* 6, OCH_2), 2.75 (2H, td, *J* 6 and 2, CH_2CHO); δ_C (75 MHz, $CDCl_3$) 201.0, 158.3, 149.1, 136.7, 122.5, 121.4, 74.0, 64.5, 43.8; ν_{max} (film) /cm^{-1} 2730 (w, CHO), 1726 (C=O); *m/z* (CI+, NH_3) 166 (65 %, M+H), 110 (72 %, pyCH_2+NH_4), 94 (100 %); found $[M+H]^+$ 166.0867, $C_9H_{12}NO_2$ requires 166.0868



4-(Pyridin-2-ylmethoxy)butanol 7

Sodium hydride (6.0 g of 60 % dispersion in mineral oil, 150 mmol) was added portionwise to a solution of 1,4-butanediol (10.0 ml, 113 mmol) in tetrahydrofuran (75 ml). The mixture was stirred at room temperature for 1 hour. Picolyl chloride hydrochloride (10.0 g, 61 mmol) was added portionwise. The mixture was then heated to reflux for 24 hours. Ammonium chloride (75 ml of saturated aqueous solution) was added and the mixture was acidified to pH 4 with 2 M hydrochloric acid solution. The organic layer was separated and the aqueous layer washed with ethyl acetate (20 ml) to remove any organic by-products, which were discarded. The aqueous solution was neutralised with sodium bicarbonate, then extracted with dichloromethane (3 × 50 ml). The combined dichloromethane fractions were dried with sodium sulfate then evaporated to give crude *alcohol* **7** as a pale yellow oil (7.1 g, 64 %), which was used without further purification; δ_H (300 MHz; $CDCl_3$) 8.54

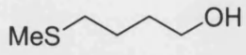
(1H, d, *J* 5, py-H^6), 7.73–7.67 (1H, td, *J* 8 and 2, py-H^4), 7.44 (1H, d, *J* 8, py-H^3), 7.19 (1H, dd, *J* 7 and 5, py-H^5), 4.64 (2H, s, pyCH_2O), 3.66 (2H, br s, *J* 5, CH_2OH), 3.61 (2H, t, *J* 6, OCH_2), 3.44 (1H, br s, OH), 1.8–1.6 (4H, m, 2 × CH_2); δ_C (75 MHz, $CDCl_3$) 158.8, 149.4, 137.1, 122.7, 121.8, 74.0, 71.4, 62.8, 30.3, 26.8; ν_{max} (film) /cm^{-1} 3329 (br, O–H); *m/z* (CI^+, NH_3) 182 (100 %, M+H); found $[M+H]^+$ 182.1180, $C_{10}H_{16}NO_2$ requires 182.1181



4-(Pyridin-2-ylmethoxy)butanal 8

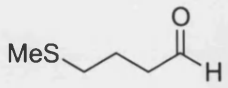
Oxalyl chloride (35.0 ml of a 2 M solution in dichloromethane, 70 mmol) was diluted with dichloromethane (65 ml) and cooled to –78 °C. A solution of dimethyl sulfoxide (7.0 ml, 100 mmol) in dichloromethane (20 ml) was added dropwise ensuring the temperature did not rise above –60 °C. After stirring for 15 minutes, a solution of alcohol **7** (7.1 g, 39 mmol) in dichloromethane (20 ml) was added dropwise, again keeping the temperature below –60 °C. The mixture was stirred for 2 hours, then triethylamine (25.0 ml, 179 mmol) was added dropwise and the mixture was stirred for a further 15 minutes. Water (75 ml) was added and the mixture was allowed to return to room temperature with stirring. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 × 20 ml). The combined organic fractions were washed with brine, dried with sodium sulfate and evaporated. The residue was purified by column chromatography (silica, ethyl acetate; R_f 0.25) to give *aldehyde* **8** as a pale orange oil (3.3 g, 47 %), which was distilled to furnish a colourless liquid (b.p. 68 °C, 9.0×10^{-2} mmHg); δ_H (300 MHz; $CDCl_3$) 9.81 (1H, t, *J* 1.5, CHO), 8.55 (1H, d, *J* 5, py-H^6), 7.70 (1H, td, *J* 8 and 1.5, py-H^4), 7.40 (1H, d, *J*

8, py-H^3), 7.19 (1H, td, *J* 5 and 1.5, py-H^5), 4.62 (2H, s, pyCH_2O), 3.61 (2H, t, *J* 6, OCH_2), 2.59 (2H, td, *J* 7 and 1.5, CH_2CHO), 2.00 (2H, tt, *J* 7 and 6, CH_2); δ_C (75 MHz, $CDCl_3$) 202.6, 158.8, 149.5, 137.1, 122.8, 121.7, 74.2, 70.3, 41.3, 22.9; ν_{max} (film) /cm^{-1} 2731 (CHO), 1723 (C=O); *m/z* (CI^+, NH_3) 180 (100 %, M+H), 92 (50 %, pyCH_2), 78 (20 %, py); found $[M+H]^+$ 180.1027, $C_{10}H_{14}NO_2$ requires 180.1024



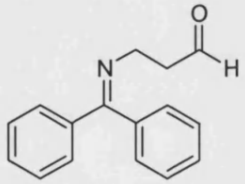
4-Methylsulfanylbutan-1-ol 10

A mixture of 1,4-butanediol (2.0 ml, 23 mmol), dimethyl disulfide (1.3 ml, 15 mmol) and tributylphosphine (3.6 ml, 15 mmol) in tetrahydrofuran (25 ml) was stirred overnight at room temperature. The mixture was diluted with water (50 ml) and extracted with ethyl acetate (3 × 15 ml). The combined organic fractions were washed with brine, dried with sodium sulfate and evaporated. The residue was purified by column chromatography (silica, gradient elution 1:4–1:1 ethyl acetate/petrol) to give *sulfide* **10** as a colourless liquid (0.87 g, 50 %); δ_H (300 MHz; $CDCl_3$) 3.68 (2H, t, *J* 6, CH_2OH), 2.54 (2H, t, *J* 7, SCH_2), 2.11 (3H, s, SMe), 1.72–1.67 (4H, m, CH_2CH_2), 1.44 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 62.8, 34.4, 32.1, 25.8, 15.9; ν_{max} (film) /cm^{-1} 3383 (br, O–H), 1427 (C–S); *m/z* (CI+, NH_3) 138 (70 %, M+NH_4), 121 (100 %, M+H); found $[M+H]^+$ 121.0687, $C_5H_{13}OS$ requires 121.0687; data in agreement with literature example.[167]



4-Methylsulfanylbutanal 11

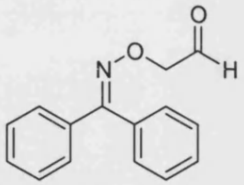
Dess-Martin periodinane **3** (3.0 g of 15 % solution in dichloromethane, 1.06 mmol) was added to a solution of alcohol **10** (0.12 g, 1.00 mmol) in dichloromethane (5 ml) and stirred at room temperature for 2 hours. Sodium hydroxide (5 ml of 1 M solution) was added. The organic layer was washed with sodium hydrogencarbonate, then dried with sodium sulfate and evaporated. The residue was purified by column chromatography (silica, 1:4 ethyl acetate/petrol) to give *aldehyde* **11** as a colourless liquid (32 mg, 27 %), which was used immediately; δ_H (300 MHz; $CDCl_3$) 9.74 (1H, s, CHO), 2.66 (2H, t, *J* 7, SCH_2), 2.54 (2H, t, *J* 7, CH_2CHO), 2.03 (3 H, s, SMe), 1.91 (2H, quint., *J* 7, $CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 201.8, 42.8, 32.0, 22.5, 21.5; data in agreement with literature example.[168]



3-(Diphenylmethylene)aminopropanal 12

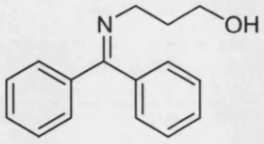
Oxalyl chloride (0.15 ml, 1.7 mmol) was dissolved in dichloromethane (10 ml) and cooled to –78 °C. Dimethyl sulfoxide (0.25 ml, 3.5 mmol) in dichloromethane (5 ml) was added slowly without allowing the temperature to rise above –60 °C, and the mixture was stirred for 15 minutes at –78 °C. Alcohol **14** was added *via* syringe over 10 minutes. The mixture was stirred for 1 hour then triethylamine (1.0 ml, 7.2 mmol) was added dropwise. The cooling bath was removed and water (5 ml) was added. After stirring for 10 minutes the organic layer was separated and the aqueous layer

washed with dichloromethane (5 ml). The combined organic layers were dried with magnesium sulfate and evaporated. The residue was purified by column chromatography (silica, 1:4 ethyl acetate/petrol, R_f 0.24) to give *aldehyde* **12** as a yellow oil (24 mg, 10 %). Performing the chromatography with Florisil® (ethyl acetate/petrol, 1:19) did not improve the isolated yield; δ_H (270 MHz, $CDCl_3$) 9.87 (1H, t, *J* 2, CHO), 7.6-7.1 (10H, m, Ph), 3.71 (2H, t, *J* 7, NCH_2), 2.78 (2H, td, *J* 7 and 2, CH_2CHO); data in agreement with literature example.[169]



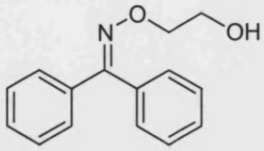
2-(Diphenylmethylene)aminooxyacetaldehyde 13

Oxalyl chloride (0.15 ml, 1.7 mmol) was dissolved in dichloromethane (10 ml) and cooled to –78 °C. Dimethyl sulfoxide (0.25 ml, 3.5 mmol) in dichloromethane (5 ml) was added slowly without allowing the temperature to rise above –60 °C, and the mixture was stirred for 15 minutes at –78 °C. Alcohol **15** was added *via* syringe over 10 minutes. The mixture was stirred for 1 hour then triethylamine (1.0 ml, 7.2 mmol) was added dropwise. The cooling bath was removed and water (5 ml) was added. After stirring for 10 minutes the organic layer was separated and the aqueous layer washed with dichloromethane (5 ml). The combined organic layers were dried with magnesium sulfate and evaporated. ^{1}H NMR of the crude residue showed that the aldehyde was present, but it could not be satisfactorily purified by chromatography (silica, ethyl acetate/petrol, 1:1, R_f 0.4); δ_H (270 MHz; $CDCl_3$) 9.83 (1H, t, *J* 1, CHO), 7.4–7.2 (10H, m, Ph), 4.58 (2H, d, *J* 1, OCH_2)



3-(Diphenylmethylene)aminopropanol 14

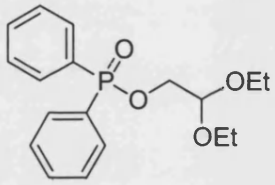
A mixture of benzophenone (1 g, 5.5 mmol) and 3-aminopropanol (1 ml, 12.8 mmol) was stirred without solvent for 3 days at 100 °C. A drop of toluene was added and distilled to azeotropically remove water. Excess propanolamine was removed by distillation at reduced pressure (46 °C, 2 mmHg). The residue was taken up in ether, washed with saturated ammonium chloride solution and water, then dried with magnesium sulphate and evaporated. Recrystallisation from diethyl ether gave *alcohol* **14** as white needles (0.67 g, 51 %); m.p. 57.3–58.0 °C (lit.[170] m.p. 57.5–58.0 °C); δ_H (270 MHz, $CDCl_3$) 7.6–7.3 (10H, m, Ph), 3.90 (2H, t, *J* 6, OCH_2), 3.52 (2H, t, *J* 6, NCH_2), 1.84 (2H, quint., *J* 6, CH_2); δ_C ($CDCl_3$) 130.2, 128.6, 128.3, 128.2, 127.6, 63.8, 53.6, 32.9; ν_{max} (film) /cm^{-1} 1447 (C=N); *m/z* (FAB+) 240 (100 %, M); found [M^+] 240.1387, $C_{16}H_{17}NO$ requires 240.1388; data in agreement with literature example.[170]



2-(Diphenylmethylene)aminooxyethanol 15

Benzophenone oxime (1.0 g, 5.1 mmol) and caesium carbonate (1.6 g, 5.0 mmol) were dried under vacuum (*ca.* 1 mmHg) for 1 hour, then acetonitrile (20 ml) was added. After stirring for 10 minutes, ethylene sulfite (1.0 ml, 13.2 mmol) was added, and the mixture stirred vigorously under reflux for 24 hours. After cooling to room

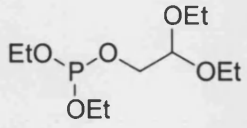
temperature, the mixture was diluted with diethyl ether, filtered through Celite and evaporated. The residue was purified by column chromatography (silica, gradient elution, petrol–3:7 ethyl acetate/petrol; R_f 0.4 at 3:7) to give alcohol **15** as a pale yellow oil (0.37 g, 30 %); δ_H (270 MHz, $CDCl_3$) 7.5–7.3 (10H, m, Ph), 4.30 (2H, t, *J* 4, CH_2OH), 3.92 (2H, t, *J* 4, OCH_2); δ_C (65 MHz, $CDCl_3$) 157.7, 135.9, 132.8, 129.5, 129.0, 128.9, 128.2, 128.1, 127.8, 75.3, 62.9; data in agreement with literature example.[171]



Diphenylphosphinic acid (2,2-diethoxyethyl) ester 18

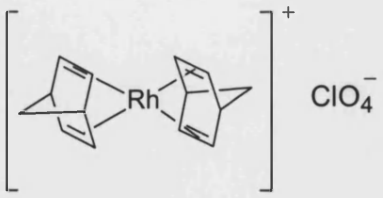
2,2-Diethoxyethanol (1.0 ml, 7.45 mmol) was added to a suspension of sodium hydride (0.45 g of 60 % dispersion in mineral oil, 11.3 mmol) in freeze-thaw degassed tetrahydrofuran (20 ml). Chlorodiphenylphosphine (1.5 ml, 7.70 mmol) was added, and the mixture stirred at room temperature for 30 minutes then at 60 °C for a further 30 minutes. The reaction was quenched by addition of water (50 ml), and the product extracted with diethyl ether (3 × 20 ml). The combined organics were dried with sodium sulfate then evaporated. The residue was purified by column chromatography (silica, 1:1 diethyl ether/petrol then pure diethyl ether, R_f 0.25) to give *acetal* **18** as a yellow oil (0.64 g, 27 %); δ_H (300 MHz; $CDCl_3$) 7.9–7.8 (4H, m, Ph), 7.5–7.4 (6H, m, Ph), 4.75 (1H, t, *J* 8, $CH(OEt)_2$), 4.00 (2H, dd, *J* 8 and 5, $POCH_2$), 3.75–3.49 (4H, m, 2 × OCH_2), 1.20 (6H, t, *J* 7, Me); δ_C (75 MHz, $CDCl_3$) 132.3, 132.2, 131.8, 131.7, 128.6, 128.5, 100.8, 64.2, 62.7, 15.3; δ_P (121.5 MHz,

$CDCl_3$) 33.9 (s); ν_{max} (film) /cm^{-1} 1439 (P–Ph), 1289 (P–O), 1070 (P=O); *m/z* (CI+, NH_3) 335 (95 %, M+H), 289 (100 %, M–EtO), 103 (50 %, $(EtO)_2CH$)



Phosphorus acid diethyl (2,2-diethoxyethyl) ester 19

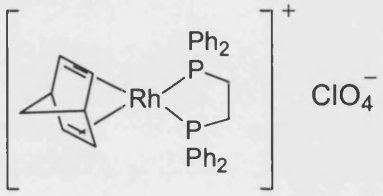
Pyridine (1.0 ml, 12 mmol) was added to a solution of diethylchlorophosphite (1.2 ml, 8.4 mmol) in tetrahydrofuran (10 ml) at 0 °C. Glycolaldehyde diethyl acetal (1.0 ml, 7.8 mmol) in tetrahydrofuran (5 ml) was added and the mixture was allowed to return to room temperature and stirred for 2 hours. After filtration *via* cannula, the solvent was removed. Distillation of the residue gave *phosphite* **19** (b.p. 57 °C, 0.12 mmHg) as a colourless oil (0.6 g, 30 %); δ_H (300 MHz; $CDCl_3$) 4.62 (1H, t, *J* 5, $CH(OEt)_2$, 3.94–3.79 (6H, m, 3 × CH_2OP), 3.75–3.54 (4H, m, 2 × OCH_2), 1.37–1.20 (12H, m, 4 × OCH_2CH_3); δ_P (121.5 MHz, $CDCl_3$) 140.15 (s); *m/z* (CI+, NH_3) 255 (5 %, M+H), 117 (15 %, $CH_2CH(OEt)_2$), 103 (10 %, $CH(OEt)_2$), 44 (100 %, CH_3CHO); found $[M+H]^+$ 255.1364, $C_{10}H_{24}O_5P$ requires 255.1361



Bis(bicyclo[2.2.1]hepta-2,5-diene) rhodium(I) perchlorate 21

Norbornadiene rhodium chloride dimer **20** (470 mg, 1.02 mmol) was dissolved in dichloromethane (20 ml). Norbornadiene (270 mg, 3 mmol) was added, followed by silver perchlorate (620 mg, 3 mmol). The mixture was stirred at room temperature for 16 hours, then filtered and evaporated to leave approximately 1 ml of solvent.

Tetrahydrofuran (1 ml) was added and the solvent was evaporated slowly to induce precipitation. The product was recovered by filtration and dried under vacuum to give *perchlorate* **21** as a fine red powder (750 mg, 95 %); δ_H (300 MHz; $CDCl_3$) 5.18 (8H, d, *J* 2, HC=CH), 4.12 (4H, br s, CH), 1.50 (4H, br s, CH_2); δ_C (75 MHz, $CDCl_3$) 82.1, 66.3, 52.3; data in agreement with literature example.[152]

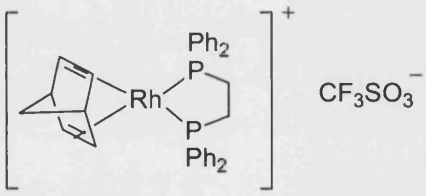


(Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino)ethane) rhodium(I) perchlorate 22a

Bisnorbornadiene rhodium perchlorate **21** (0.75 g, 1.94 mmol) was dissolved in dichloromethane (15 ml), then 1,2-bis(diphenylphosphine)ethane (0.70 g, 1.76 mmol) was added in small portions over 1 minute. The mixture was stirred at room temperature for 15 minutes then filtered *via* cannula. The solution was evaporated to *ca.* 2 ml then an excess of diethyl ether was added to induce precipitation, which was completed by cooling overnight. The product was recovered by filtration, washed with diethyl ether and dried under vacuum to give *perchlorate* **22a** as an orange-red powder (1.2 g, 87 %); δ_H (300 MHz; $CDCl_3$) 7.50–7.58 (20H, m, Ph), 5.36 (4H, br s, HC=CH), 4.27 (2H, br s, CH), 2.40 (4H, d, *J* 20, PCH_2), 1.82 (2H, br s, CH_2); δ_C (75 MHz, $CDCl_3$) 132.5, 131.8, 129.8, 55.9, 12.8; δ_P (121 MHz, $CDCl_3$) 57.4 (d, *J* 157); data in agreement with literature example.[152]

Alternative "one pot" method:

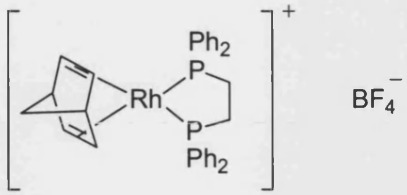
Norbornadiene rhodium chloride dimer **20** (230 mg, 0.49 mmol) was dissolved in dichloromethane (10 ml). 2,5-Norbornadiene (140 μl, 1.3 mmol) was added, followed by silver perchlorate (270 mg, 1.3 mmol). The mixture was stirred at room temperature for 30 minutes, then 1,2-bis(diphenylphosphino)ethane (350 mg, 0.88 mmol) was added in small portions over 1 minute. The mixture was stirred at room temperature for a further 3 hours then filtered *via* cannula. The solution was evaporated to *ca.* 2 ml then an excess of ethanol was added (*ca.* 10 ml). The volume of solvent was carefully reduced further to induce precipitation, which was completed by cooling overnight. The product was recovered by filtration and dried under vacuum to give *perchlorate* **22a** as an orange-red powder (265 mg, 78 %), data as above.



(Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino)ethane) rhodium(I) trifluoromethanesulfonate 22b

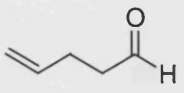
The procedure for perchlorate **22a** was followed, using norbornadiene rhodium chloride dimer (350 mg, 0.76 mmol), norbornadiene (0.26 ml, 2.44 mmol), silver triflate (580 mg, 2.26 mmol) and 1,2-bis(diphenylphosphino)ethane (425 mg, 1.07 mmol). Filtration and crystallisation gave *triflate* **22b** as an orange powder (549 mg, 49 %); δ_H (300 MHz; $CDCl_3$) 7.47–7.42 (20H, m, Ph), 5.27 (4H, d, *J* 2, HC=CH), 4.18 (2H, br s, CH), 2.33 (4H, dd, *J* 20 and 1, PCH_2), 1.76 (2H, s, CH_2); δ_P (121 MHz, $CDCl_3$) 57.3 (d, *J* 157); *m/z* (ES+) 593.2 (100 %, $[Rh(NBD)(dppe)]^+$), 501.1 (2 %, $[Rh(dppe)]^+$); (ES–) 149 (100 %, $CF_3SO_3^-$), 80 (40 %, SO_3); found

$[Rh(NBD)(dppe)]^+$ 593.1034, $C_{33}H_{32}P_2Rh$ requires 593.1033; data in agreement with literature example.[35]



(Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino)ethane) rhodium(I) tetrafluoroborate 22c

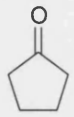
The procedure for perchlorate **22a** was followed, using norbornadiene rhodium chloride dimer (300 mg, 0.65 mmol), norbornadiene (0.18 ml, 1.95 mmol), silver tetrafluoroborate (300 mg, 1.54 mmol) and 1,2-bis(diphenylphosphino)ethane (160 mg, 0.41 mmol). *Tetrafluoroborate* **22c** was obtained as a deep-red powder (194 mg, 22 %); δ_H (300 MHz; $CDCl_3$) 7.54–7.52 (20H, m, Ph), 5.35 (4H, d, *J* 2, HC=CH), 4.25 (2H, br s, CH), 2.38 (4H, d, *J* 20, PCH_2), 1.82 (2H, s, CH_2); δ_P (121 MHz, $CDCl_3$) 58.0 (d, *J* 157); δ_B (96 MHz, $CDCl_3$) 2.30; *m/z* (ES+) 593.2 (100 %, $[Rh(NBD)(dppe)]^+$), 501.1 (15 %, $[Rh(dppe)]^+$); (ES–) 87 (100 %, BF_4^-); data in agreement with literature example.[172]



4-Pentenal 25[23]

Allyl vinyl ether (2.0 g, 24 mmol) was heated in a sealed tube at 135 °C for 22 hours. Distillation at atmospheric pressure gave *pentenal* **25** (b.p. 101 °C) as a colourless liquid (0.6 g, 32 %); δ_H (300 MHz; $CDCl_3$) 9.78 (1H, br s, CHO), 5.88–5.84 (1H, m, C=CH), 5.12–5.07 (1H, m, H_2C=C), 5.06–5.03 (1H, m, H_2C=C), 2.58–2.54 (2H, m

CH_2CO), 2.43–2.39 (2H, m CH_2=CHCH_2); data in agreement with literature example.[23]



Cyclopentanone 26[23]

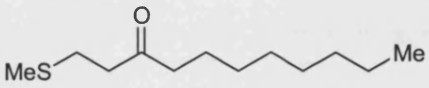
Rhodium complex **22a** (30 mg, 0.043 mmol) was dissolved in acetone (2 ml) and exposed to pressure of hydrogen gas (1.2 atm.) for 20 minutes. The solvent was removed under vacuum, and the residue taken up in dichloromethane (5 ml). Pentenal **25** (70 mg, 0.83 mmol) was added, and the mixture stirred at room temperature for 20 hours. Gas chromatography (, oven temperature 200 °C) showed a peak with the same retention time as an authentic sample of cyclopentanone. The conversion was estimated at approximately 65 %, with 30 % remaining pentenal and 5 % of an unidentified by-product. The products were not isolated.

General procedure for hydroacylation reactions

Pre catalyst **22a** (20 mg, 0.029 mmol) was dissolved in 1,2-dichloroethane (4 ml), and hydrogen gas was bubbled through for 15 minutes to generate the catalytically active species. The solution was degassed and purged with argon then the appropriate alkene (*ca.* 0.7 mmol) was added followed by aldehyde **9** (30 mg, 0.29 mmol). The reaction mixture was stirred at 60 °C for 2 hours then evaporated under reduced pressure. The crude residue was analysed by ^{1}H NMR to measure the approximate conversion of aldehyde to product, using 2,5-dimethylfuran as a quantitative internal standard.[157]

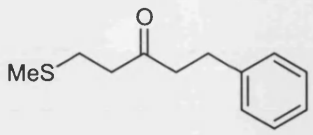
General procedure for microwave-assisted reactions

Pre catalyst **22a** (20 mg, 0.029 mmol) was dissolved in 1,2-dichloroethane (3 ml) in a microwave reaction vial. Hydrogen gas was bubbled through for 15 minutes to generate the catalytically active species. The solution was degassed and purged with argon then alkene (*ca.* 0.7 mmol) was added followed by aldehyde **9** (30 mg, 0.29 mmol). The reaction mixture was heated in the microwave reactor (max. power 200 W) at 60 °C for 10 minutes then evaporated under reduced pressure. The crude residue was analysed by ^{1}H NMR to measure the approximate conversion of aldehyde to products, using 2,5-dimethylfuran as a quantitative internal standard.[157]



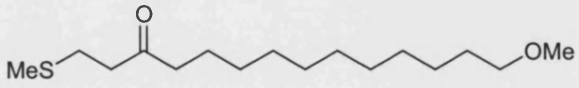
1-Methylsulfanylundecan-3-one 27a

The general procedure was followed using pre-catalyst **22a** (85 mg, 0.12 mmol), octene (0.35 ml, 2.2 mmol) and aldehyde **9** (45 mg, 0.43 mmol). The product was purified by column chromatography (silica, 1:9 diethyl ether/petrol; R_f 0.35) to give *ketone* **27a** as a colourless oil (30 mg, 33 %); δ_H (300 MHz, $CDCl_3$) 2.66 (4H, br s, SCH_2CH_2), 2.35 (2H, t, *J* 7.5, $COCH_2$), 2.05 (3H, s, SMe), 1.52–1.20 (12H, br s, 5 × CH_2), 0.81 (3H, t, *J* 6, Me); δ_C (75 MHz, $CDCl_3$) 209.8, 43.5, 42.7, 32.2, 29.7, 29.6, 29.5, 28.4, 24.1, 23.0, 16.2, 14.5; ν_{max} (film) /cm^{-1} 1711 (C=O); *m/z* (EI+) 216 (15 %, M), 141 (20 %, M–$CH_3SCH_2CH_2$), 103 (42 %, M–C_8H_{17}), 71 (85 %, C_5H_{11}), 61 (85 %, CH_3SCH_2), 57 (65 %, C_4H_9), 43 (65 %, C_3H_7); found M^+ 216.1548, $C_{12}H_{24}OS$ requires 216.1546



1-Methylsulfanyl-5-phenyl-pentan-3-one 27b

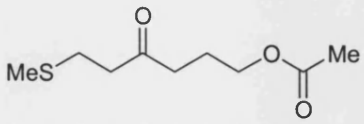
The general procedure was followed using pre-catalyst **22a** (15 mg, 0.022 mmol), styrene (0.13 ml, 1.13 mmol) and aldehyde **9** (40 μl, 0.38 mmol). The product was purified by column chromatography (silica, 1:9 ethyl acetate/petrol; R_f 0.35) to give *ketone* **27b** as a colourless oil (33 mg, 41 %); δ_H (300 MHz, $CDCl_3$) 7.24–7.19 (2H, m, 2 × Ph), 7.14–7.1 (3H, m, 3 × Ph), 2.95–2.75 (2H, m, PhC*H*$_2$), 2.72–2.68 (2H, m, SCH_2), 2.65--2.61 (4H, m, C*H*$_2$COC*H*$_2$), 2.02 (3H, s, MeS); δ_C (75 MHz, $CDCl_3$) 207.2, 139.8, 127.5 (2 × CH), 127.3 (2 × CH), 125.2, 43.5, 41.6, 28.6, 26.9, 14.8; ν_{max} (film) /cm^{-1} 1713 (C=O); *m/z* (CI+, NH_3) 226 (100 %, M+NH_4), 209 (25 %, M); 178 (30 %, M+NH_4–MeS); found $[M+H]^+$ 209.1000, $C_{12}H_{17}OS$ requires 209.1000



1-Methylsulfanyl-14-methoxytetradecan-3-one 27c

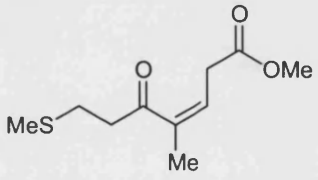
The general procedure was followed using pre-catalyst **22a** (20mg, 0.029 mmol), 1-methoxyundec-10-ene **39** (0.1 ml, 1.1 mmol) and aldehyde **9** (30 μl, 0.29 mmol). The residue was purified by column chromatography (silica, 1:9 diethyl ether/petrol; R_f 0.25) to give *ketone* **27c** as a colourless oil (26 mg, 31 %); δ_H (400 MHz, $CDCl_3$) 3.29 (2H, t, *J* 6.5, OCH_2), 3.26 (3H, s, OCH_3), 2.66–2.63 (4H, m, SCH_2CH_2), 2.35 (2H, t, *J* 7.5, $COCH_2$), 2.05 (3H, s, SMe), 1.52–1.45 (2H, m, C*H*$_2$CH$_2$OMe), 1.21 (10H, br s, 5 × CH_2); ν_{max} (film) /cm^{-1} 1731 (C=O); *m/z* (CI+, NH_3) 306.3 (100 %,

M+NH_4), 289.2 (16 %, M+H); found $[M+H]^+$ 289.2203, $C_{16}H_{33}O_2S$ requires 289.2201



Acetic acid 6-methylsulfanyl-4-oxohexyl ester 27d

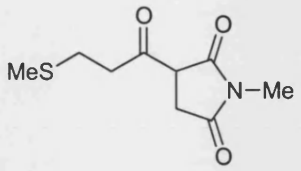
The general procedure was followed using pre-catalyst **22a** (30 mg, 0.043 mmol), aldehyde **9** (20 mg, 0.21 mmol) and allyl acetate (0.12 ml, 1.1 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol) to give *ketone* **27d** as a colourless oil (16 mg, 35 %); δ_H (300 MHz, $CDCl_3$) 4.01 (2H, t, *J* 7, CH_2O), 2.67 (4H, br s, SCH_2CH_2), 2.46 (2H, t, *J* 7, $COCH_2$), 2.05 (3H, s, SMe), 1.98 (3H, s, OCOMe), 1.87 (2H, tt, *J* 7 and 7, CH_2)



4-Methyl-7-methylsulfanyl-5-oxohept-3-enoic acid methyl ester 27e

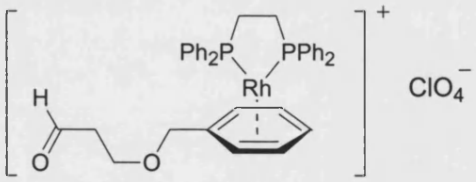
The general procedure was followed using pre-catalyst **22a** (20 mg, 0.029 mmol), methyl penta-2,4-dienoate (0.1 ml, 0.87 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.3) to give *ketoester* **27e** as a colourless oil (6 mg, 10 %); δ_H (300 MHz, $CDCl_3$) 6.75 (1H, tq, *J* 7 and 1.5, C=CH), 3.68 (3H, s, OMe), 3.24 (2H, d, *J* 7, CH_2CO_2Me), 2.96 (2H, t, *J* 7 SCH_2), 2.71 (2H, t, *J* 7, SCH_2CH_2CO), 2.06 (3H, s, SMe), 1.73 (3H, d, *J* 1.5, Me); δ_C (75 MHz, $CDCl_3$) 171.2, 162.0, 139.7, 133.6, 52.6, 37.7, 34.6, 29.2, 16.2, 12.1; *m/z* (CI+, NH_3) 234 (30 %, M+NH_4), 217 (15 %, M+H), 202 (50 %,

M+NH_3–OMe), 186 (100 %, M+NH_3–MeS); found $[M+NH_4]^+$ 234.1157, $C_{10}H_{20}NO_3S$ requires 234.1158; the geometry of the double bond was not confirmed.



1-Methyl-3-(3-methylsulfanylpropionyl)pyrrolidine-2,5-dione 27f

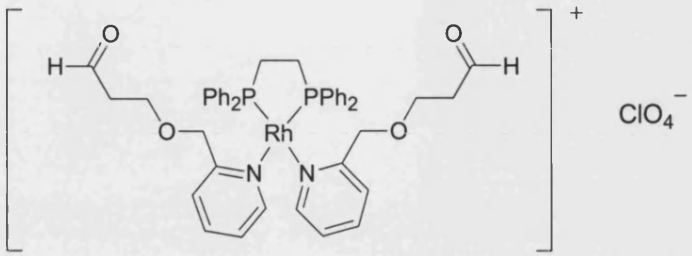
The general procedure was followed using pre-catalyst **22a** (15 mg, 0.022 mmol), *N*-methylmaleimide (85 mg, 0.77 mmol) and aldehyde **9** (40 mg, 0.38 mmol). The product was purified by column chromatography (silica, 3:7 ethyl acetate/petrol; R_f 0.25) to give *ketone* **27f** as a colourless oil (43 mg, 52 %); δ_H (300 MHz, $CDCl_3$) 3.89 (1H, dd, *J* 7 and 3, COCHCO), 2.85 (3H, s, NMe), 2.8–2.4 (6H, m, MeSCH_2CH_2+CH_2CONMe), 2.05 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 200.4, 176.5, 176.2, 52.9, 34.6, 30.8, 30.5, 29.4, 15.8; *m/z* (CI+, NH_3) 233 (60 %, M+NH_4) 97 (100 %); found $[M+H]^+$ 233.0955, $C_9H_{13}O_3NS$ requires 233.0954



η^6-(3-benzyloxypropanal)(1,2-bis(diphenylphosphino)ethane) rhodium(I) perchlorate 28

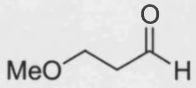
Rhodium perchlorate **22a** (60 mg, 0.087 mmol) and aldehyde **2** (36 mg, 0.22 mmol) were dissolved in dichloromethane (10 ml) and hydrogen gas bubbled through for 10 minutes. The solution was heated to 60 °C for 3 hours. The solvent was removed to leave η^6-benzyl complex **28** as a red oil; δ_H (300 MHz; CD_2Cl_2) 9.67 (1H, t, *J* 2,

CHO) 8.1–6.1 (25H, m, Ph), 4.42 (2H, s, $PhCH_2O$), 3.72 (2H, t, *J* 6, OCH_2), 2.57 (2H, td, *J* 6 and 2, CH_2CHO); δ_C (75 MHz, $CDCl_3$) 202.1, 139.0, 133.0, 132.2, 129.8, 129.1, 128.4, 128.38, 73.8, 64.7, 44.7; δ_P (121 MHz; CD_2Cl_2) 77.9 (d, *J* 204)



Di[3-(pyridin-2-ylmethoxy)propanal](1,2-bis(diphenylphosphino)ethane) rhodium(I) perchlorate 29

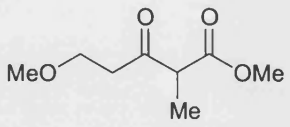
Rhodium perchlorate **22a** (10 mg, 0.014 mmol) was dissolved in CD_2Cl_2 (1 ml) in an NMR tube and exposed to pressure of hydrogen gas. The colour of the solution changed from orange to yellow. Aldehyde **6** (5 μl, 0.03 mmol) was added. ^{31}P NMR analysis showed a single peak; δ_P (121 MHz; CD_2Cl_2) 73 (d, *J* 172). There was no change after heating at 60 °C for 2 hours.



3-Methoxypropanal 30

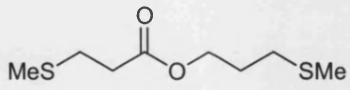
A mixture of 1,1,3-trimethoxy propane (7.0 g, 52 mmol), glacial acetic acid (10.0 ml, 164 mmol) and water (50 ml) was stirred at 40 °C overnight. The solution was neutralised with saturated sodium bicarbonate solution, then extracted with dichloromethane (5 × 10 ml). The combined organic fractions were washed with brine, dried with sodium sulfate and evaporated. The residue was purified by distillation to give *aldehyde* **30** (b.p. 104 °C) as a colourless liquid (3.3 g, 47 %); δ_H

(300 MHz; $CDCl_3$) 9.72 (1H, t, *J* 2, CHO), 6.66 (2H, t, *J* 6, OCH_2), 3.29 (3H, s, OMe), 2.61 (2H, td, *J* 6 and 2, CH_2CHO); δ_C (75 MHz, $CDCl_3$) 201.5, 66.5, 53.8, 44.3; ν_{max} (film) /cm^{-1} 1719 (C=O); *m/z* (CI+, NH_3) 106 (100 %, $M+NH_4$), 88 (45 %, M); found $[M+NH_4]^+$ 106.0861, $C_4H_{12}NO_2$ requires 106.0863; data in agreement with literature example.[173]



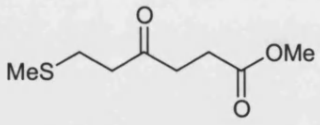
5-Methoxy-2-methyl-3-oxopentanoic acid methyl ester 31

The general procedure was followed, using pre-catalyst **22a** (20 mg, 0.029 mmol), methyl acrylate (80 μl, 0.87 mmol) and aldehyde **9** (25 μl, 0.29 mmol). The reaction mixture was stirred at 60 °C for 20 hours then evaporated under reduced pressure. ^1H NMR analysis of the crude residue (28 mg), using 2,5-dimethylfuran (11.4 mg, 0.119 mmol) as a quantitative internal standard,[157] showed 14 % conversion to the branched hydroacylation product. The residue was purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.25), but the product could not be isolated; δ_H (300 MHz, $CDCl_3$) 3.66 (3H, s, CO_2Me), 3.58 (2H, t, *J* 6, OCH_2), 3.51 (1H, q, *J* 7, C*H*Me), 3.26 (3H, s, OMe), 2.73 (2H, t, *J* 6, CH_2CO_2Me), 1.28 (3H, d, *J* 7, CH*Me*); ν_{max} (film) /cm^{-1} 1735 (br, C=O)

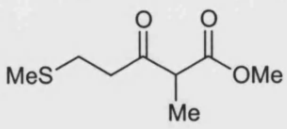


3-Methylsulfanylpropanoic acid 3-methylsulfanylpropyl ester 32

The general hydroacylation procedure was followed using pre-catalyst **22a** (50 mg, 0.072 mmol) and aldehyde **9** (25 mg, 0.26 mmmol) with no alkene added. The reaction was stirred at room temperature overnight. The solvent was removed, and the residue was purified by column chromatography (silica, 1:9 diethyl ether/petrol) to give *ester* **32** (12 mg, 44 %) as a colourless liquid; δ_H (300 MHz; $CDCl_3$) 4.14 (2H, t, *J* 6, OCH_2), 2.70 (2H, td, *J* 7 and 1.5, SCH_2 CH_2CO_2), 2.56 (2H, td, *J* 7 and 1.5, $SCH_2CH_2CO_2$), 2.50 (2H, t, *J* 7, CH_2S), 2.06 (3H, s, SMe), 2.04 (3H, s, SMe), 1.87 (2H, quint., *J* 7, OCH_2CH_2); δ_C (75 MHz, $CDCl_3$) 170.9, 62.3, 33.4, 29.6, 28.1, 27.1, 14.5, 14.49; ν_{max} (film) /cm^{-1} 1732 (C=O), 1244 (C–O); *m/z* (CI+, NH_3) 226 (100 %, $M+NH_4$), 209 (20 %, M+H), 89 (30 %, $(CH_2)_3SMe$); found: $[M+NH_4]^+$ 226.0933, $C_8H_{20}NO_2S_2$ requires 226.0935



33a



34a

6-Methylsulfanyl-4-oxohexanoic acid methyl ester 33a and

2-Methyl-5-methylsulfanyl-3-oxopentanoic acid methyl ester 34a

The general procedure was followed, using pre-catalyst **22a** (15 mg, 0.022 mmol), methyl acrylate (170 µl, 1.9 mmol) and aldehyde **9** (40 µl, 0.38 mmol). The reaction mixture was stirred at 70 °C for 45 minutes then evaporated under reduced pressure. The crude residue (104 mg) was analysed by ^1H NMR to measure the approximate conversion of aldehyde to product, using 2,5-dimethylfuran (23.7 mg, 0.247 mmol)

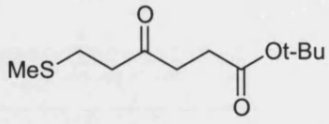
as a quantitative internal standard.[157] The residue was then purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.25) to give *γ-ketoester* **33a** (44 mg, 60 %) and *β-ketoester* **34a** (14 mg, 19 %) as colourless liquids;

γ-ketoester **33a**:

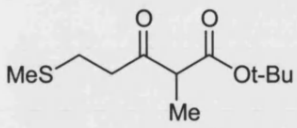
δ_H (300 MHz, $CDCl_3$) 3.68 (3H, s, OMe), 2.78–2.76 (6H, m, $SCH_2CH_2COCH_2$), 2.61 (2H, t, *J* 6.5, CH_2CO_2Me), 2.12 (3H, s, MeS); δ_C (75 MHz, $CDCl_3$) 207.1, 173.2, 51.9, 42.5, 37.3, 27.9, 27.6, 15.8; ν_{max} (film) /cm^{-1} 1738 (C=O); *m/z* (CI+, NH_3) 208 (100 %, M+NH_4), 191 (30 %, M+H), 143 (50 %, M–SCH_3); found $[M+H]^+$ 191.0742, $C_8H_{15}O_3S$ requires 191.0742

β-ketoester **34a**:

δ_H (300 MHz, $CDCl_3$) 3.74 (3H, s, OMe), 3.56 (1H, q, *J* 5, C*H*Me), 2.93–2.81 (2H, m, CH_2CO), 2.78–2.72 (2H, m, SCH_2), 2.12 (3H, s, SMe), 1.36 (3H, d, *J* 5, CH*Me*); δ_C (75 MHz, $CDCl_3$) 204.5, 171.1, 53.2, 52.9, 41.6, 28.2, 16.2, 13.1; ν_{max} (film) /cm^{-1} 1747, 1716 (C=O); *m/z* (EI+) 190 (15 %, M^+), 143 (25 %, M–MeS), 103 (40 %, $MeSCH_2CH_2CO$), 87 (40 %, $CHMeCO_2Me$), 75 (60 %, $MeSCH_2CH_2$), 61 (100 %, $MeSCH_2$), 59 (60 %, CO_2Me); found $[M+H]^+$ 191.0739, $C_8H_{15}O_3S$ requires 191.0742



33b



34b

6-Methylsulfanyl-4-oxohexanoic acid *tert*-butyl ester 33b and 2-methyl-5-methylsulfanyl-3-oxopentanoic acid *tert*-butyl ester 34b

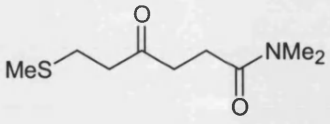
The general procedure was followed, using pre catalyst **22a** (20 mg, 0.029 mmol), *tert*-butyl acrylate (0.1 ml, 0.69 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The crude residue (71.8 mg) was analysed by ^{1}H NMR to measure the approximate conversion of aldehyde to product, using 2,5-dimethylfuran (19.4 mg, 0.202 mmol) as a quantitative internal standard.[157] The residue was then purified by column chromatography (silica, 1:4 ethyl acetate/petrol) to give *γ-ketoester* **33b** (27 mg, 40 %) and *β-ketoester* **34b** (4 mg, 6 %)

γ-ketoester **33b**:

δ_H (300 MHz, $CDCl_3$) 2.69 (4H, br s, SCH_2CH_2), 2.62 (2H, t, *J* 6.5, $COCH_2$), 2.45 (2H, t, *J* 6.5, $CH_2CO_2{}^tBu$), 2.04 (3H, s, MeS), 1.37 (9H, s, t-Bu); δ_C (75 MHz, $CDCl_3$) 207.7, 172.3, 81.0, 42.8, 37.8, 29.5, 28.4 (3 × CH_3), 28.2, 16.1; ν_{max} (film) /cm^{-1} 1719 (br, C=O); *m/z* (CI+, NH_3) 250 (40 %, M+NH_4), 233 (15 %, M+H), 194 (100 %, M–CH_2=C(Me)$_2$ +NH_4); found $[M+H]^+$ 233.1208, $C_{11}H_{21}O_3S$ requires 233.1206

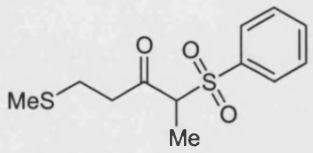
β-ketoester **34b**:

δ_H (300 MHz, $CDCl_3$) 3.37 (1H, q, *J* 7, C*H*Me), 2.8–2.6 (4H, m, SCH_2CH_2), 2.05 (3H, s, SMe), 1.40 (9H, s, t-Bu), 1.23 (3H, d, *J* 7, CH*Me*)



6-Methylsulfanyl-4-oxohexanoic acid dimethylamide 33c

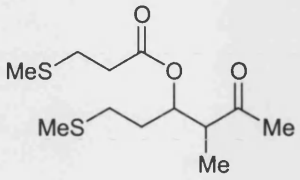
The general procedure was followed using pre-catalyst **22a** (15 mg, 0.022 mmol), *N,N*-dimethyl acrylamide (0.1 ml, 0.95 mmol) and aldehyde **9** (40 mg, 0.38 mmol). The product was purified by column chromatography (silica, 1:1 ethyl acetate/petrol; R_f 0.35) to give *ketoamide* **33c** as a colourless oil (17 mg, 22 %); δ_H (300 MHz, $CDCl_3$) 2.97 (3H, s, NMe), 2.86 (3H, s, NMe), 2.79–2.74 (2H, m, SCH_2CH_2CO), 2.71–2.65 (4H, m, SCH_2+$COCH_2$), 2.57–2.51 (2H, m, CH_2CONMe_2), 2.04 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 208.8, 171.8, 43.1, 37.8, 37.5, 37.4, 28.3, 27.6, 16.1; ν_{max} (film) /cm^{-1} 1714, 1645 (C=O); *m/z* (CI+, NH_3) 204 (100 %, M+H), 156 (40 %, M–MeS); found $[M+H]^+$ 204.1054, $C_9H_{18}NO_2S$ requires 204.1053



4-Benzenesulfonyl-1-methylsulfanylpentan-3-one 34d

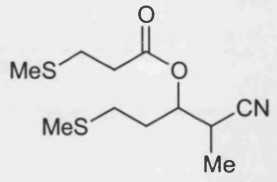
The general procedure was followed using phenyl vinyl sulfone (146 mg, 0.87 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.35) to give *β-ketosulfone* **34d** as a colourless oil (58 mg, 74 %); δ_H (300 MHz, $CDCl_3$) 7.77–7.71 (2H, m, Ph), 7.65–7.60 (1H, m, Ph), 7.59–7.46 (2H, m, Ph), 4.14 (1H, q, *J* 7, COC*H*Me), 3.20 (1H, dt, *J* 18 and 7, 1 × CH_2CO), 2.89 (1H, dt, *J* 18 and 7, 1 × CH_2CO), 2.67 (2H, t, *J* 7, SCH_2), 2.06 (3H, s, MeS), 1.33 (3H, d, *J* 7, Me); δ_C (75 MHz, $CDCl_3$) 201.1, 134.8, 129.8, 129.8, 128.2, 70.4, 43.9, 28.0, 16.1, 12.2; ν_{max} (film) /cm^{-1} 1716 (C=O), 1308,

1148 (S=O); *m/z* (EI+) 272 (10 %, M), 225 (10 %, M–SMe), 141 (20 %, SO_2Ph), 131 (60 %, M–SO_2Ph), 77 (100 %, Ph), 61 (60 %, $MeSCH_2$); found $[M+NH_4]^+$ 290.0881, $C_{12}H_{20}NO_3S_2$ requires 290.0879



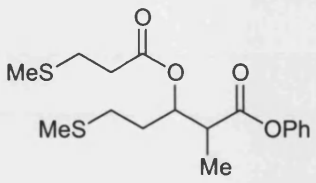
3-Methylsulfanylpropanoic acid 4-methyl-1-methylsulfanyl-5-oxohex-3-yl ester 35a

The general procedure was followed using pre-catalyst **22a** (20 mg, 0.029 mmol), but-3-en-2-one (70μl, 0.84 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.35) to give *ketoester* **35a** as a colourless oil (29 mg, 72 %) as a mixture of diastereoisomers; δ_H (300 MHz, $CDCl_3$) 5.30 (0.4H, ddd, *J* 9, 4.5 and 4.5, OCH), 5.22 (0.6H, ddd, *J* 6, 6 and 6, OCH), 2.84 (0.6H, dq, *J* 7 and 7, C*H*Me), 2.75–2.67 (2.4H, m, C*H*Me+SC*H*$_2$$CH_2CO_2$), 2.58–2.52 (2H, m, SCH_2C*H*$_2$$CO_2$), 2.49–2.35 (2H, m, SCH_2), 2.14 (1.2H, s, COMe), 2.13 (1.8H, s, COMe), 2.05 (3H, s, SMe), 2.03 (1.2H, s, SMe), 2.02 (1.8H, s, SMe), 1.87–1.73 (2H, m, SCH_2C*H*$_2$), 1.05 and 1.04 (3H, d, *J* 7, CH*Me*); δ_C (75 MHz, $CDCl_3$) 209.4, 171.7, 73.9, 50.6, 34.8, 30.6, 30.4, 29.7, 29.5, 15.9, 15.85, 12.0; ν_{max} (film) /cm^{-1} 1735, 1714 (C=O); *m/z* (CI+, NH_3) 296 (100 %, M+NH_4), 279 (25 %, M+H)



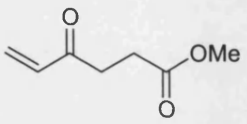
3-Methylsulfanylpropanoic acid 2-cyano-1-(2-methylsulfanylethyl)propyl ester 35b

The general procedure was followed using pre-catalyst **22a** (20 mg, 0.029 mmol), acrylonitrile (60 μl, 0.92 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol; R_f 0.2) to give *nitrile* **35b** as a colourless oil (25 mg, 66 %) as a mixture of diastereoisomers; δ_H (300 MHz, $CDCl_3$) 5.08 (0.7H, ddd, *J* 8, 4 and 4, OCH), 4.96 (0.3H, ddd, *J* 9, 5 and 3, OCH), 2.99 (0.3H, qd, *J* 7 and 5, C*H*Me), 2.90 (0.7H, qd, *J* 7 and 4, C*H*Me), 2.76–2.70 (2H, m, $SCH_2CH_2CO_2$), 2.66–2.61 (2H, m, $SCH_2CH_2CO_2$), 2.50–2.42 (2H, m, SCH_2CH_2), 2.07 (3H, s, SMe), 2.04 (3H, s, SMe), 1.98–1.83 (2H, m, SCH_2CH_2), 1.27 (3H, d, *J* 7, CH*Me*); δ_C (75 MHz, $CDCl_3$) 170.3, 118.8, 70.9, 33.2, 30.6, 29.3, 28.8, 28.0, 14.5, 14.4, 13.5; ν_{max} (film) /cm^{-1} 2244 (C≡N), 1732 (C=O); *m/z* (CI+, NH_3) 279 (100 %, M+NH_4)



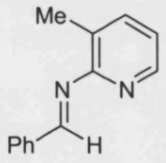
2-Methyl-5-methylsulfanyl-3-(3-methylsulfanylpropionyloxy)pentanoic acid phenyl ester 35c

The general procedure was followed using pre-catalyst **22a** (20 mg, 0.029 mmol), phenyl acrylate (130 μl, 0.87 mmol) and aldehyde **9** (30 mg, 0.29 mmol). The product was purified by column chromatography (silica, 1:4 ethyl acetate/petrol) to give *ester* **35c** as a colourless oil (34 mg, 66 %) as a mixture of diastereoisomers; δ_H (300 MHz, $CDCl_3$) 7.34–7.27 (2H, m, Ph *meta*), 7.19–7.13 (1H, m, Ph *para*), 7.04–6.98 (2H, m, Ph *ortho*), 5.44–5.31 (1H, m, CH–O), 3.00 (0.7H, qd, *J* 7 and 6, C*H*Me), 2.91 (0.3 H, qd, *J* 7 and 5, C*H*Me), 2.73–2.68 (2H, m, $SCH_2CH_2CO_2$), 2.61–2.55 (2H, m, $SCH_2CH_2CO_2$), 2.54–2.42 (2H, m, SCH_2), 2.04 (3H, s, SMe), 2.04 (3H, s, SMe), 2.00–1.89 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 172.4, 172.0, 150.9, 130.0, 129.9, 126.4, 121.8, 121.7, 74.1, 43.6, 34.9, 31.2, 30.4, 29.5, 16.0, 15.9, 13.1; ν_{max} (film) /cm^{-1} 1738 (C=O); *m/z* (CI+, NH_3) 374 (100 %, M+NH_4), 263 (20 %, M–OPh), 254 (M+NH_4–$MeS(CH_2)_2CO_2$); found $[M+NH_4]^+$ 374.1453, $C_{17}H_{28}NO_4S_2$ requires 374.1454



4-Oxohex-5-enoic acid methyl ester 36

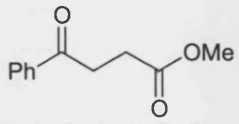
Ketone **33a** (37 mg, 0.19 mmol) was dissolved in dichloromethane (2 ml). Methyl triflate (25 µl, 0.23 mmol) was added *via* syringe, and the mixture stirred at room temperature for 20 minutes. Potassium hydrogen carbonate (40 mg, 0.29 mmol) was added and stirred for a further 10 minutes. The mixture was washed with water and brine, dried with sodium sulfate and evaporated to give *enone* **36** as a colourless oil (13 mg, 48 %); δ_H (300 MHz, $CDCl_3$) 6.32 (1H, dd, *J* 18 and 10, CH=C*H*$_{trans}$), 6.20 (1H, dd, *J* 18 and 2, CH=C*H*$_{cis}$), 5.82 (1H, dd, *J* 10 and 2, C*H*=CH_2), 4.15 (3H, s, OMe), 2.87 (2H, t, *J* 7, COC*H*$_2$), 2.58 (2H, t, *J* 7, C*H*$_2$$CO_2$Me); data in agreement with literature example.[174]



Benzylidene (3-methylpyridin-2-yl) amine 37[83]

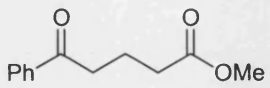
Benzaldehyde (1.9 ml, 18.7 mmol), 3-methyl-2-aminopyridine (1.8 ml, 18.4 mmol) and a catalytic amount of *para*-toluene sulfonic acid (*ca.* 5 mg) were heated in refluxing toluene (25 ml) under Dean-Stark conditions for 24 hours. The product was purified by distillation to give *imine* **37** (b.p. 76 °C, 0.07 mmHg) as a pale yellow liquid (2.4 g, 66 %); δ_H (300 MHz, $CDCl_3$) 9.05 (1H, s, CHN), 8.36–8.33 (1H, m, py-H^6), 8.05–7.98 (2H, m, Ph), 7.57–7.54 (1H, m, py-H^4), 7.51–7.46 (3H, m, Ph), 7.11–7.08 (1H, m, py-H^5), 2.46 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 162.1, 159.9,

146.5, 139.2, 136.6, 132.1, 130.1, 129.8, 129.1, 122.2, 17.8; ν_{max} (film) /cm^{-1} 1734, 1648 (C=N); data in agreement with literature example.[83]



4-Phenyl-4-oxobutanoic acid methyl ester 38a

$RhCl(PPh_3)_3$ (93 mg, 0.10 mmol) was dissolved in degassed tetrahydrofuran (3 ml) in a microwave reaction vial. Imine **37** (200 mg, 1.02 mmol) was added and stirred until the colour of the solution changed from red to yellow. Methyl acrylate (135 µl, 1.51 mmol) was added. The vial was purged with argon and sealed. The mixture was heated in a microwave reactor at 130 °C for 10 minutes, then diluted with ethyl acetate (20 ml), poured into dilute HCl solution (20 ml, 1 M) and stirred for 10 minutes. The product was extracted with ethyl acetate (3 × 10 ml). The combined organic fractions were washed with sodium bicarbonate and brine, dried with sodium sulfate and evaporated. The residue was purified by column chromatography (silica, 1:9 ethyl acetate/petrol), to give *ketone* **38a** as a colourless oil (160 mg, 82 %); δ_H (300 MHz, $CDCl_3$) 7.97–7.93 (2H, m, Ph), 7.57–7.55 (1H, m, Ph), 7.49–7.44 (2H, m, Ph), 3.71 (3H, s, CO_2Me), 3.33 (2H, t, *J* 7, $PhCOCH_2$), 2.77 (2H, t, *J* 7, CH_2CO_2Me); δ_C (75 MHz; $CDCl_3$) 198.0, 173.3, 136.5, 133.2, 128.6, 128.0, 51.8, 33.4, 28.0; ν_{max} (film) /cm^{-1} 1748, 1728 (C=O); data in agreement with literature example.[175]



5-Phenyl-5-oxopentanoic acid methyl ester 38b

$RhCl(PPh_3)_3$ (93 mg, 0.10 mmol) was dissolved in degassed tetrahydrofuran (3 ml) in a microwave reaction vial. Imine **37** (200 mg, 1.02 mmol) was added and stirred until the colour of the solution changed from red to yellow. Methyl crotonate (105 μl, 1.49 mmol) was added. The vial was purged with argon and sealed. The mixture was heated in a microwave reactor at 130 °C for 30 minutes, then diluted with ethyl acetate (20 ml), poured into dilute HCl solution (20 ml, 1 M) and stirred for 10 minutes. The product was extracted with ethyl acetate (3 × 10 ml). The combined organic fractions were washed with sodium bicarbonate and brine, dried with sodium sulfate and evaporated. The residue was purified by column chromatography (silica, 1:9 ethyl acetate/petrol), to give *ketone* **38b** as a colourless oil (22 mg, 10 %); δ_H (300 MHz, $CDCl_3$) 8.43–7.85 (2H, m, Ph), 7.67–7.25 (3H, m, Ph), 3.66 (3H, s, CO_2Me), 3.03 (2H, t, *J* 7, $PhCOCH_2$), 2.45 (2H, t, *J* 7, CH_2CO_2Me), 2.31–1.78 (2H, m, $CH_2CH_2CH_2$); ν_{max} (film) /cm^{-1} 1735, 1718 (C=O); data in agreement with literature example.[176]

1-Methoxyundec-10-ene 39

Undec-10-en-1-ol (4.0 ml, 20 mmol) was dissolved in tetrahydrofuran (20 ml). Sodium hydride (1.2 g of 60 % dispersion in mineral oil, 30 mmol) was added portionwise. Methyl iodide (2.0 ml, 32 mmol) was added in one portion *via* syringe; the exothermic reaction caused gentle reflux, which was maintained by heating for 16 hours. After cooling to room temperature, ammonium chloride (20 ml of saturated

aqueous solution) was added, and the mixture was extracted with diethyl ether (3 × 10 ml). The combined organic fractions were washed with brine, dried with sodium sulfate and evaporated. Column chromatography (silica, 1:9 ethyl acetate/petrol; R_f 0.3) furnished the *methoxy alkene* **39** as a colourless liquid (3.1 g, 85 %), which was further purified before use by distillation under reduced pressure (57 °C, 5 mmHg); δ_H (300 MHz; $CDCl_3$) 5.74 (1H, ddt, *J* 17, 10 and 6.5, C=C*H*), 4.96–4.83 (2H, m, H_2C=C), 3.29 (2H, t, *J* 6.5, OCH_2), 3.26 (3H, s, OCH_3), 1.97 (2H, q, *J* 6.5, C=CHCH_2), 1.49 (2H, quint., *J* 6.5, C$H_2$$CH_2$OMe), 1.32–1.21 (12H, br s, 6 × CH_2); δ_C (75 MHz, $CDCl_3$) 137.96, 112.80, 71.67, 57.25, 32.52, 28.36, 28.24, 28.19, 28.13, 27.82, 27.63, 24.84; ν_{max} (film) /cm^{-1} 1121 (C–O); *m/z* (CI+, NH_3) 202 (100 %, M+NH_4), 45 (50 %, CH_2OMe); found: $[M+NH_4]^+$ 202.2173, $C_{12}H_{28}NO$ requires 202.2171; data in agreement with literature example.[177]

Chapter 4 References

1. Dyker, G. *Angew. Chem. Int. Ed. Engl.* 1999, **38**, 1699-1712.
2. Tonks, L.; Williams, J. M. J. *J. Chem. Soc. Perkin Trans. 1* 1998, 3637-3652.
3. Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* 2002, **102**, 1731-1769.
4. Tsuji, J.; Ohno, K.; Kajimoto, T. *Tetrahedron Lett.* 1965, **6**, 4565-4568.
5. Tsuji, J.; Ohno, K.; Kajimoto, T. *Tetrahedron Lett.* 1965, **6**, 3969-3971.
6. Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* 1968, **90**, 99-107.
7. Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Liable-Sands, L. M.; Rheingold, A. L. *Organometallics* 1999, **18**, 5311-5317, and references therein.
8. Alaimo, P. J.; Arndtsen, B. A.; Bergman, R. G. *Organometallics* 2000, **19**, 2130-2143.
9. Bosshard, P.; Eugster, C. H. *Adv. Heterocycl. Chem.* 1966, **7**, 384-387.
10. Ellison, R. A. *Synthesis* 1973, 397-412.
11. Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* 1972, **13**, 1287-1290.
12. Milstein, D. *J. Chem. Soc. Chem. Commun.* 1982, 1357-1358.
13. Campbell Jr., R. E.; Miller, R. G. *J. Organomet. Chem.* 1980, **186**, C27-C31.
14. Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* 1976, **98**, 1281-1283.
15. Larock, R. C.; Oertle, G. F.; Potter, G. F. *J. Am. Chem. Soc.* 1980, **102**, 190-197.
16. Sakai, K.; Ishiguro, Y.; Funakoshi, K.; Ueno, K.; Suemune, H. *Tetrahedron Lett.* 1984, **25**, 961-964.

17. Takahashi, Y.; Tanaka, M.; Wu, X. M.; Sakai, K. *Nat. Prod. Lett.* 1992, **1**, 217-220.

18. Suemune, H.; Kawahara, T.; Sakai, K. *Chem. Pharm. Bull.* 1986, **34**, 550-557.

19. Suemune, H.; Maruoka, H.; Saeki, S.; Sakai, K. *Chem. Pharm. Bull.* 1986, **34**, 4629-4634.

20. Xie, Z. F.; Ichikawa, Y.; Suemune, H.; Sakai, K. *Chem. Pharm. Bull.* 1987, **35**, 1812-1816.

21. Suemune, H.; Oda, K.; Saeki, S.; Sakai, K. *Chem. Pharm. Bull.* 1988, **36**, 172-177.

22. Sakai, K. *J. Synth. Org. Chem. Jpn.* 1993, **51**, 733-743.

23. Fairlie, D. P.; Bosnich, B. *Organometallics* 1988, **7**, 936-945.

24. Fairlie, D. P.; Bosnich, B. *Organometallics* 1988, **7**, 946-954.

25. Wong, P. K.; Madhavaroa, M.; Marteu, D. F.; Rosenblum, J. J. *J. Am. Chem. Soc.* 1977, **99**, 2828.

26. Overman, L. E. *Angew. Chem. Int. Ed. Engl.* 1984, **23**, 579.

27. Lutz, R. P. *Chem. Rev.* 1984, **84**, 205-247.

28. Eilbracht, P.; Gersmeier, A.; Lennartz, D.; Huber, T. *Synthesis* 1995, 330-334.

29. Sattelkau, T.; Hollmann, C.; Eilbracht, P. *Synlett* 1996, 1221-&.

30. Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* 1998, **39**, 9647-9648.

31. Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* 1998, **39**, 1905-1908.

32. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products*; John Wiley: New York, 1983; Vol. 5.

33. Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* 1991, **32**, 3473-3476.

34. Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem. Int. Ed. Engl.* 2002, **41**, 1218-1221.

35. Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* 2000, **122**, 12610-12611.

36. Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* 1995, **117**, 4720.

37. Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* 1999, **121**, 10442-10443.

38. Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* 1999, **121**, 5348-5349.

39. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* 1998, **120**, 1940-1941.

40. Trost, B. M.; Shen, H. C. *Org. Lett.* 2000, **2**, 2523-2526.

41. Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* 2000, **122**, 2379-2380.

42. James, B. R.; Young, C. G. *J. Organomet. Chem.* 1985, **285**, 321-332.

43. Taura, Y.; Tanaka, M.; Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron* 1991, **47**, 4879-4888.

44. Tanaka, M.; Sakai, K.; Suemune, H. *Curr. Org. Chem.* 2003, **7**, 353-367.

45. Barnhart, R. W.; Wang, X. Q.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *Tetrahedron* 1994, **50**, 4335-4346.

46. Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* 1992, **33**, 6331-6334.

47. Bosnich, B. *Acc. Chem. Res.* 1998, **31**, 667-674.

48. Barnhart, R. W.; Wang, X. Q.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* 1994, **116**, 1821-1830.

49. Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Chem. Commun.* 1997, 589-590.

50. Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *Inorg. Chim. Acta* 1997, **263**, 1-7.

51. Fujio, M.; Tanaka, M.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Chem. Lett.* 1998, 881-882.

52. Barnhart, R. W.; Bosnich, B. *Organometallics* 1995, **14**, 4343-4348.

53. Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* 2000, **65**, 5806-5816.

54. Takahashi, M.; Tanaka, M.; Sakamoto, E.; Imai, M.; Funakoshi, K.; Sakai, K.; Suemune, H. *Chem. Pharm. Bull.* 2000, **48**, 1822-1825.

55. Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* 1980, **192**, 257-264.

56. Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* 1988, **7**, 1451-1453.

57. Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* 1982, **240**, 285-288.

58. Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* 1987, **28**, 6229-6230.

59. Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* 1990, **55**, 1286-1291.

60. Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T. *Organometallics* 1998, **17**, 2131-2134.

61. Vinogradov, M. G.; Tuzikov, A. B.; Nikishin, G. I.; Shelimov, B. N.; Kazansky, V. B. *J. Organomet. Chem.* 1988, **348**, 123-134.

62. Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* 1974, **96**, 4721-4723.

63. Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* 1997, **119**, 3165-3166.

64. Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* 1998, **120**, 6965-6979.

65. Lenges, C. P.; Brookhart, M. *Angew. Chem. Int. Ed. Engl.* 1999, **38**, 3533-3537.

66. Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* 1999, **121**, 6616-6623.

67. Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* 1999, **121**, 4385-4396.

68. Suggs, J. W. *J. Am. Chem. Soc.* 1978, **100**, 640-641.

69. Suggs, J. W. *J. Org. Chem.* 1980, **45**, 1514-1515.

70. Jun, C. H.; Han, J. S.; Kang, J. B.; Kim, S. I. *Bull. Korean Chem. Soc.* 1994, **15**, 204-209.

71. Jun, C. H.; Lim, Y. G.; Kang, J. B. *Bull. Korean Chem. Soc.* 1996, **17**, 1102-1104.

72. Jun, C. H.; Hong, J. B.; Lee, D. Y. *Synlett* 1999, 1-12.

73. Jun, C. H.; Moon, C. W.; Lee, D. Y. *Chem. Eur. J.* 2002, **8**, 2422-2428.

74. Jun, C. H. *Bull. Korean Chem. Soc.* 1989, **10**, 114-116.

75. Ohtaka, A.; Kato, N.; Kurosawa, H. *Organometallics* 2002, **21**, 5464-5466.

76. Suggs, J. W. *J. Am. Chem. Soc.* 1979, **101**, 489.

77. Jun, C. H.; Kang, J. B. *Bull. Korean Chem. Soc.* 1993, **14**, 153-156.

78. Jun, C. H.; Han, J. S.; Kang, J. B.; Kim, S. I. *J. Organomet. Chem.* 1994, **474**, 183-189.

79. Hong, J. B.; Jun, C. H. *Bull. Korean Chem. Soc.* 1995, **16**, 363-369.

80. Kim, J. H.; Jun, C. H. *Bull. Korean Chem. Soc.* 1999, **20**, 27-29.

81. Jun, C. H.; Hwang, D. C. *Polymer* 1998, **39**, 7143-7147.

82. Khan, N. U. H.; Lee, B. C.; Lee, S. Y.; Choe, Y. S.; Jun, C. H.; Chi, D. Y. *J. Label. Compd. Radiopharm.* 2002, **45**, 1045-1053.

83. Jun, C. H. *Bull. Korean Chem. Soc.* 1990, **11**, 187-188.

84. Jun, C. H.; Kang, J. B.; Lim, Y. G. *Bull. Korean Chem. Soc.* 1993, **14**, 287-291.

85. Jun, C. H.; Kang, J. B.; Kim, J. Y. *J. Organomet. Chem.* 1993, **458**, 193-198.

86. Jun, C. H.; Lee, D. Y.; Hong, J. B. *Tetrahedron Lett.* 1997, **38**, 6673-6676.

87. Jun, C. H.; Lee, H.; Hong, J. B. *J. Org. Chem.* 1997, **62**, 1200-1201.

88. Jun, C. H.; Lee, D. Y.; Lee, H.; Hong, J. B. *Angew. Chem. Int. Ed. Engl.* 2000, **39**, 3070-3072.

89. Jun, C. H.; Hong, J. B. *Org. Lett.* 1999, **1**, 887-889.

90. Sapmaz, S. *Intermolecular Hydroacylation*, University of Bath 2003.

91. Willis, M. C.; Sapmaz, S. *Chem. Commun.* 2001, 2558-2559.

92. Lee, D. Y.; Moon, C. W.; Jun, C. H. *J. Org. Chem.* 2002, **67**, 3945-3948.

93. Jun, C. H.; Huh, C. W.; Na, S. J. *Angew. Chem. Int. Ed. Engl.* 1998, **37**, 145-147.

94. Jun, C. H.; Hong, H. S.; Huh, C. W. *Tetrahedron Lett.* 1999, **40**, 8897-8900.

95. Jun, C. H.; Lee, H.; Park, J. B.; Lee, D. Y. *Org. Lett.* 1999, **1**, 2161-2164.

96. Jun, C. H.; Chung, K. Y.; Hong, J. B. *Org. Lett.* 2001, **3**, 785-787.

97. Jun, C. H.; Hwang, D. C.; Na, S. J. *Chem. Commun.* 1998, 1405-1406.

98. Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem. Int. Ed. Engl.* 2000, **39**, 3440-+.

99. Jun, C. H.; Moon, C. W.; Hong, J. B.; Lim, S. G.; Chung, K. Y.; Kim, Y. H. *Chem. Eur. J.* 2002, **8**, 485-492.

100. Jun, C. H.; Moon, C. W.; Kim, Y. M.; Lee, H.; Lee, J. H. *Tetrahedron Lett.* 2002, **43**, 4233-4236.

101. Lim, Y. G.; Kim, Y. H.; Kang, J. B. *J. Chem. Soc. Chem. Commun.* 1994, 2267-2268.

102. Murai, S. *J. Synth. Org. Chem. Jpn.* 1994, **52**, 992-1001.

103. Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* 1997, **69**, 589-594.

104. Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* 2001, **123**, 2685-2686.

105. Rauchfuss, T. B.; Landvatter, E. F. *Organometallics* 1982, **1**, 506.

106. Rauchfuss, T. B. *J. Am. Chem. Soc.* 1979, **101**, 1045-1047.

107. Bianchini, C.; Meli, A.; Peruzzini, M.; Ramirez, J. A.; Vacca, A.; Vizza, F.; Zanobini, F. *Organometallics* 1989, **8**, 337.

108. El Mail, R.; Garralda, M. A.; Hernandez, R.; Ibarlucea, L. *J. Organomet. Chem.* 2002, **648**, 149-154.

109. El Mail, R.; Garralda, M. A.; Hernandez, R.; Ibarlucea, L.; Pinilla, E.; Rosario Torres, M. *Helv. Chim. Acta* 2002, **85**, 1485.

110. Brockaart, G.; El Mail, R.; Garralda, M. A.; Hernandez, R.; Ibarlucea, L.; Santos, J. I. *Inorg. Chim. Acta* 2002, **338**, 249-254.

111. Lee, H.; Jun, C. H. *Bull. Korean Chem. Soc.* 1995, **16**, 1135-1138.

112. Lee, H.; Jun, C. H. *Bull. Korean Chem. Soc.* 1995, **16**, 66-68.

113. Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* 1997, **62**, 4564-4565.

114. Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* 1999, **72**, 303-311.

115. Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* 2002, **43**, 7031-7034.

116. Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* 1990, **55**, 2554-2558.

117. Jun, C. H.; Lee, H.; Hong, J. B.; Kwon, B. I. *Angew. Chem. Int. Ed. Engl.* 2002, **41**, 2146-2147.

118. Jun, C. H.; Lee, H.; Moon, C. W.; Hong, H. S. *J. Am. Chem. Soc.* 2001, **123**, 8600-8601.

119. Lee, D.-Y.; Hong, B.-S.; Cho, E.-G.; Lee, H.; Jun, C.-H. *J. Am. Chem. Soc.* 2003, in press.

120. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* 2001, **123**, 11492-11493.

121. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* 2002, **124**, 1553-1553.

122. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* 2002, **124**, 10296-10297.

123. Stetter, H.; Kuhlmann, H. In *Organic Reactions;* Paquette, L. A. Ed.; Wiley: New York, 1991; Vol. 40; pp. 407-496.

124. Ho, T. L.; Liu, S. H. *Synth. Commun.* 1983, **13**, 1125-1127.

125. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* 1996, **79**, 1899-1902.

126. Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* 2002, **124**, 10298-10299.

127. Gong, J. H.; Im, Y. J.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* 2002, **43**, 1247-1251.

128. Tamao, K.; Maeda, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* 1989, **111**, 4984-4985.

129. Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* 2001, 1210-1211.

130. Dang, H. S.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. 1* 1998, 67-75.

131. Tsujimoto, S.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* 2001, 2352-2353.

132. Yamashita, M.; Tashika, H.; Suemitsu, R. *Chem. Lett.* 1989, 691-692.

133. Yamashita, M.; Tashika, H.; Uchida, M. *Bull. Chem. Soc. Jpn.* 1992, **65**, 1257-1261.

134. Cooke, M. P.; Parlman, R. M. *J. Am. Chem. Soc.* 1977, **99**, 5222-5224.

135. Kang, J.; Kim, J. W.; Kim, Y. W. *Bull. Korean Chem. Soc.* 1994, **15**, 306-310.

136. Baby, A.; Brunet, J. J.; Kindela, F. B.; Neibecker, D. *Synth. Commun.* 1994, **24**, 2827-2834.

137. Davis, J. L.; Arndtsen, B. A. *Organometallics* 2000, **19**, 4657-4659.

138. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* 1994, **640**.

139. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* 1991, **113**, 7277-7287.

140. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* 1994, **35**, 8019-8022.

141. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* 1995, **60**, 7272-7276.

142. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* 1999, **64**, 4537-4538.

143. Valderrama, M.; Contreras, R.; Arancibia, V.; Boys, D. *J. Organomet. Chem.* 2001, **620**, 256–262.

144. Reddy, K. R.; Lin, C.-F.; Lee, G.-H.; Peng, S.-M.; Chen, J.-T.; Liu, S.-T. *J. Chin. Chem. Soc.* 2001, **48**, 997-1002.

145. Dreos, R.; Tauzher, G.; Geremia, S.; Randaccio, L.; Asaro, F.; Pellizer, G.; Tavagnacco, C.; Costa, G. *Inorg. Chem.* 1994, **33**, 5404-5410.

146. Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Muller, T. E.; Zapf, A. *J. Organomet. Chem.* 1998, **566**, 277-285.

147. Epstein, W. W.; Sweat, F. W. *Chem. Rev.* 1967, **67**, 247-260.

148. Omura, K.; Swern, D. *Tetrahedron* 1978, **34**, 1651-1660.

149. Carlson, W. W.; Cretcher, L. H. *J. Am. Chem. Soc.* 1947, **69**, 1952 - 1956.

150. Chesney, A.; Marko, I. E. *Synth. Commun.* 1990, **20**, 3167-3180.

151. Marko, I. E.; Chesney, A. *Synlett* 1992, 275-278.

152. Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* 1971, **93**, 2397-2407.

153. Singewald, E. T.; Slone, C. S.; Stern, C. L.; Mirkin, C. A.; Yap, G. P. A.; Liable-Sands, L. M.; Rheingold, A. L. *J. Am. Chem. Soc.* 1997, **119**, 3048-3056.

154. Heaton, B. T.; Iggo, J. A.; Jacob, C.; Nadarajah, J.; Fontaine, M. A.; Messere, R.; Noels, A. F. *J. Chem. Soc. Dalton. Trans.* 1994, 2875-2880.

155. Bergens, S. H.; Fairlie, D. P.; Bosnich, B. *Organometallics* 1990, **9**, 566-571.

156. Rifat, A.; Patmore, N. J.; Mahon, M. F.; Weller, A. S. *Organometallics* 2002, **21**, 2856-2865.

157. Gerritz, S. W.; Sefler, A. M. *J. Comb. Chem.* 2000, **2**, 39-41.

158. Jang, H. Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* 2002, **124**, 15156-15157.

159. Huddleston, R. R.; Krische, M. J. *Org. Lett.* 2003, in press.

160. Huddleston, R. R.; Krische, M. J. *Synlett* 2003, 12-21.

161. Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* 2000, **122**, 4528-4529.

162. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* 2002, **35**, 717-727.

163. Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* 2003, in press.

164. Jun, C. H.; Chung, J. H.; Lee, D. Y.; Loupy, A.; Chatti, S. *Tetrahedron Lett.* 2001, **42**, 4803-4805.

165. Loupy, A.; Chatti, S.; Delamare, S.; Lee, D. Y.; Chung, J. H.; Jun, C. H. *J. Chem. Soc. Perkin Trans. 1* 2002, 1280-1285.

166. Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* 1989, **54**, 5768-5774.

167. Harpp, D. N.; Vines, S. M.; Montillier, J. P.; Chan, T. H. *J. Org. Chem.* 1976, **41**, 3987-3992.

168. Xu, G.; Micklatcher, M.; Silvestri, M. A.; Hartman, T. L.; Burrier, J.; Osterling, M. C.; Wargo, H.; Turpin, J. A.; Robert W. Buckheit, J.; Cushman, M. *J. Med. Chem.* 2001, **44**, 4092-4113.

169. Wessjohann, L.; McGaffin, G.; Meijere, A. d. *Synthesis* 1989, 359-363.

170. Bergmann; Kaluszyner. *Recl. Trav. Chim. Pays-Bas* 1959, **78**, 289-326.

171. Bachman, G. B.; Hokama, T. *J. Am. Chem. Soc.* 1959, 4223-4226.

172. Schenck, T.; Downes, J. M.; Milne, C. R. C.; Mackenzie, P. B.; Boucher, H.; Whelan, J.; Bosnich, B. *Inorg. Chem.* 1985, **24**, 2334-2337.

173. Lazzaroni, R.; Bertozzi, S.; Pocai, P.; Troiani, F.; Salvadori, P. *J. Organomet. Chem.* 1985, **295**, 371-376.

174. Feldman, K. S.; Berven, H. M.; Romanelli, A. L. *J. Org. Chem.* 1993, **58**, 6851-6856.

175. Sierra, M. A.; del Amo, J. C.; Mancheno, M. J.; Gomez-Gallego, M. *J. Am. Chem. Soc.* 2001, **123**, 851-861.

176. Yasuda, M.; Ohigashi, N.; Shibata, I.; Baba, A. *J. Org. Chem.* 1999, **64**, 2180-2181.

177. Helaja, T.; Hakala, K.; Helaja, J.; Lofgren, B. *J. Organomet. Chem.* 1999, **579**, 167-176.