Rhodium (I) catalysed intermolecular hydroacylation

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RHODIUM (I) CATALYSED INTERMOLECULAR HYDROACYLATION

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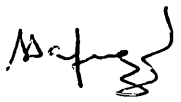

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Anneme ve Babama

Hayatım boyunca gösterdiğiniz sonsuz ilgiye, sevgiye ve inançа.

Abstract

The first chapter reviews the literature of transition metal catalysed sp^3 C-H bond activation and the concept of chelation assisted C-H activation processes.

Chapter II reviews hydroformylation. Particularly the chelation-assisted hydroformylation will be discussed towards the development of a regio and stereocontrolled process.

Chapters III and IV review an example of transition metal catalysed sp^2 C-H bond activation: hydroacylation. Chapter III will introduce the concept of intramolecular hydroacylation and show its application to total synthesis, whereas Chapter IV will deal with the concept and challenges of intermolecular hydroacylation and discuss how the previously introduced chelation assisted methodology can be used towards a better understanding of the hydroacylation process.

Chapter V will relate how the chelation assisted intermolecular hydroacylation has been used successfully to prepare 1,4-dicarbonyl compounds in good to high yields from benzaldehyde derivatives. Our progress towards the study and the delivery of more heavily functionalised compounds *via* chelation assisted intermolecular hydroacylation is also discussed.

Chapter VI provides detailed experimental procedures.

Acknowledgements

I would like to thank Dr. Mike Willis for giving me the opportunity to work on a challenging project in a great city. I express all my gratitude to him for his guidance and support throughout these three years of work. Particularly for the patience, help and rigour during the writing up process.

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Abbreviations

Ac	acetate
Ar	aromatic
BINAP	2,2'-bis(diphenylphosphino)-3,3'-binaphthyl
Bn	benzyl
(S,S)-CHIRAPHOS	*(2S,3S)*-bis(diphenylphosphino)butane
conc	concentrated
conv	conversion
d	doublet
DCM	dichloromethane
de	diastereoisomeric excess
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron Impact
eq	equivalent
Et	ethyl
FAB	fast atom bombardment
g	gram
h	hours
HPLC	high pressure liquid chromatography
^{i}Pr	*iso*-propyl
IR	infra red
L	ligand
L*	chiral ligand
LDA	lithium diisopropylamide

m	multiplet
Me	methyl
mg	milligram
min	minute
mL	millilitre
mp	melting point
MS	molecular sieves
N	normal
*n*BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
nr	no reaction
o-	*ortho*-
p-	*para*-
Ph	phenyl
q	quartet
p-TSA	*para*-toluenesulfonic acid
py	pyridine
RSM	recovered starting material
RT	room temperature
t	triplet
TBDMS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
TEA	triethylamine
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
Tol	tolyl
Rt	retention time

Contents

CHAPTER I

Chapter I

Transition metal catalysed chelation assisted C-H activation

This chapter reviews the literature covering unreactive C-H bond activation by transition metal complexes. Whereas historical investigations concentrated upon the use of stoichiometric reagents to achieve C-H activation, the major interest is now focused on the development of procedures for the selective catalytic activation of sp^3 C-H bond, which cannot be cleaved easily under classical reaction conditions. The new concept of chelation-assisted C-H activation will be introduced and in particular the application of this approach towards the synthesis of complex amines will be discussed.

1-1 Introduction

Hydrocarbons are the main constituents of oil and gas, the feedstock for the chemical industry. Therefore transformations of hydrocarbons (both saturated and unsaturated) constitute an extremely important field of contemporary chemistry.[1] Development of this area is necessary in order to discover new routes from hydrocarbons to more valuable products, such as alcohols, ketones, acids, and peroxides. Contrary to the widespread opinion that only particularly inert alkanes require activation, C-H acidic substrates can also benefit from the new reaction pathways opened by transition metal catalysis. Consequently, transition metal activation can be considered as a replacement of a strong C-H bond with a weaker, more readily functionalised M-C bond.

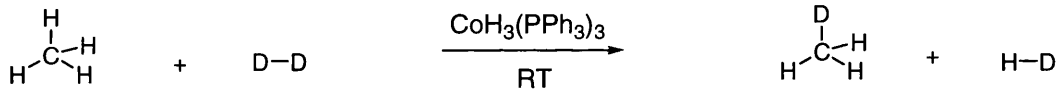
The last 30 years have seen considerable development in transition metal catalysis. In particular this progress has expanded our knowledge of olefin transformations and is beginning to explore alkane transformations. Such transformations are a very

promising area particularly when the transition metals can be used in catalytic amounts.[2,3,1]

1-2 Transition metal catalysed activation of sp^3 C-H bond

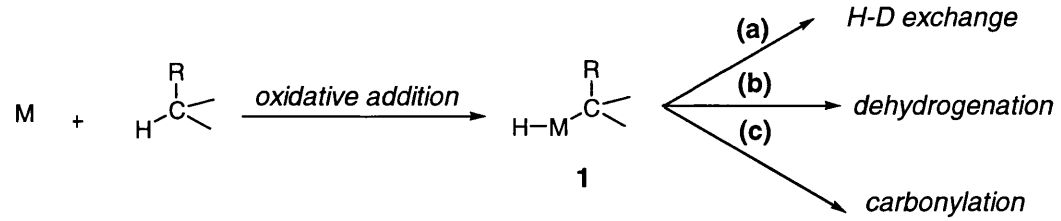
The activation of alkane sp^3 C-H bonds remains a considerable challenge. Despite this, metal containing systems that are capable of undergoing reaction with hydrocarbons have been known since the 19th century. Mercury salts for direct mercuration of olefins is representative of this heterogeneous activation through the metal surface.[1] In 1969 the first sp^3 C-H bond activation by a transition metal was reported. It was found that Pt and Co catalysed the activation of C-H bonds in methane molecules with D_2O or D_2 at room temperature (H-D exchange) (Scheme **1**).[1]

Scheme 1



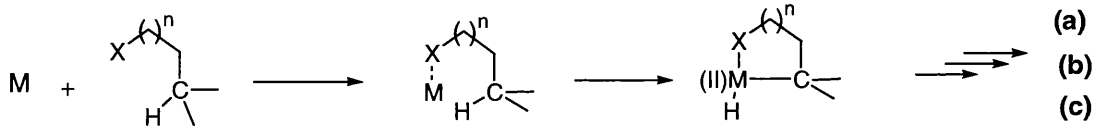
In the last two decades numerous examples of C-H activation by low-valent metal complexes have been reported.[3,4,1] In general the mechanism of C-H bond activation proceeds *via* an oxidative addition of the metal into the C-H bond leading to a σ M-C intermediate before further modification leading to C-C coupling adducts (Scheme **2**). In some cases, the metal-hydride intermediate **1** cannot be isolated, although evidence of their formation can be obtained.[1] The oxidative addition can occur in solution at room temperature, although in the majority of cases heating or irradiation is necessary. Light or heat has been shown to be essential to generate coordinatively unsaturated complexes capable of oxidatively adding into C-H bonds.[1]

Scheme 2



It has been demonstrated that an intramolecular delivery of the metal to the C-H bond facilitates the oxidative addition. Such processes occur more readily than the intermolecular activation and lead to the formation of more stable σ M-C cyclometallated intermediates **2** (Scheme **3**).[1]

Scheme 3

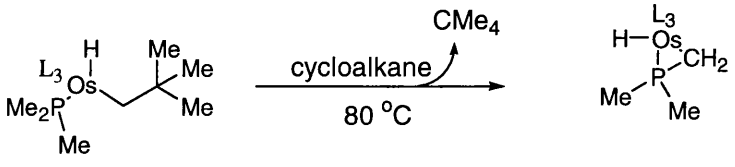


X= coordinating group or atom

2

The cases where X represents an heteroatom which can coordinate to the metal, *eg* nitrogen *N*[5] or phosphorus *P*[6] have been reported. An example of a phosphorus directed reaction is given in Scheme **4**.[7]

Scheme 4



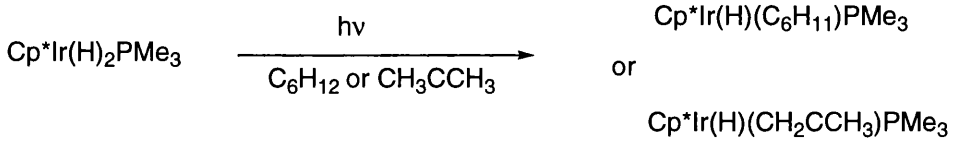
L= PMe_3

3 *stable*

1.3 The intermolecular oxidative addition of C-H bonds: Stoichiometric studies

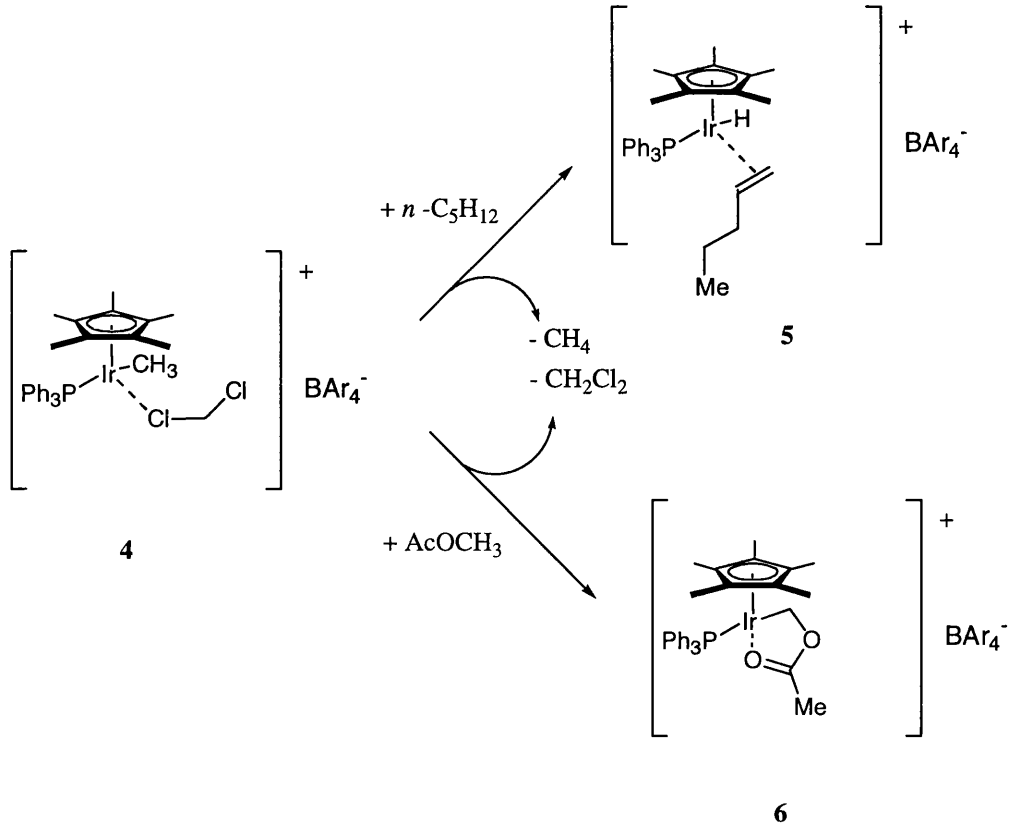
In many cases the alkyl metal hydride resulting from oxidative addition is a stable species.[8] Such a complex was isolated for the first time by Bergman *et al* in studies using iridium complexes; the iridium-dihydride derivative $Cp^*Ir(H)_2PMe_3$ (Cp^*: pentamethylcyclopentadienyl) was irradiated in a cyclohexane or neopentane solution to give the complexes $Cp^*(PMe_3)Ir(H)(C_6H_{11})$ and $Cp^*(PMe_3)Ir(H)CH_2CMe_3$ in good yield (Scheme **5**).[8]

Scheme 5



Significant progress was achieved by irradiating alkanes with an analogous rhodium complex[9] or by changing to a cationic iridium complex **4** (Scheme **6**). Complex **4** proved to be particularly reactive; the C-H activation occurs with *n*-pentane within a few minutes at room temperature, leading to the alkene complex **5**. The selectivity of the C-H activation becomes especially significant during the reaction with methyl acetate; the activation occurs exclusively at the methoxy group and leads to the cyclometallated complex **6**. The more acidic acetyl methyl group is not attacked.[10] This process will be discuss in greater detail, *vide infra.*

Scheme 6



4 5 6

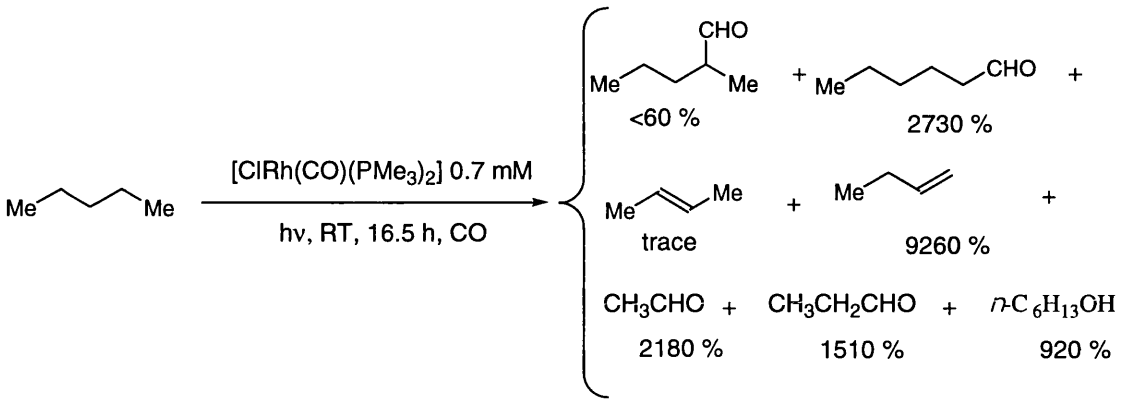
Ar= 3,5-bistrifluoromethylphenyl

1.4 Application to C-C bond synthesis

A small number of metal catalysed activations of aliphatic hydrocarbons have been reported. These consist mainly of carbonylation reactions.[4,1] The carbonylation of aliphatic hydrocarbons with carbon monoxide under nonoxidising conditions is of particular industrial interest since such processes might potentially compete with hydroformylation.[4,11]

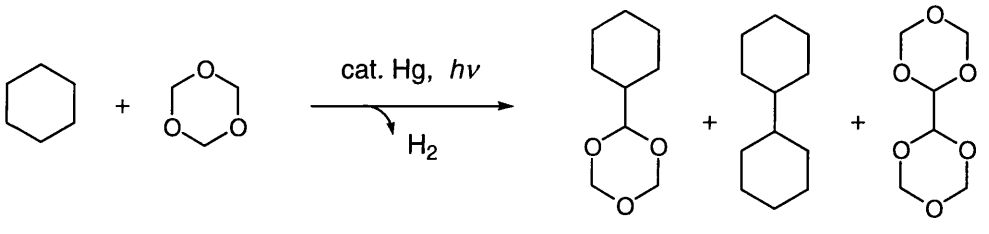
The rhodium complex, $RhCl(CO)(PMe_3)_2$, was successfully used as an efficient co-catalyst for the photochemical introduction of a CO group into alkanes. Scheme **7** below illustrates the products obtained using this catalyst in the carbonylation of *n*-pentane (yields are given based on the Rh complex).[12,13]

Scheme 7



Recent results have shown that polytungstenates can also be used as alternatives to rhodium systems for the photochemical cyanation of alkanes with cyanoformate.[14] Although these examples of C-C coupling reactions with alkanes are promising, they are far from being industrially viable. One exception is the Mercat process, developed mainly by Crabtree *et al.* This unique process combines photochemistry with heterogeneous transition metal catalysis in the gas phase, as illustrated by the coupling reaction of cyclohexane **7** with trioxane (Scheme **8**). A mixture of the organic substrates and a drop of mercury are heated under reflux and irradiated by UV light; mercury atoms in the excited triplet state effect the homolysis of the C-H bond. The resulting alkyl radical can dimerise and the higher boiling coupling products **8, 9** and **10** accumulate in the condensed phase in which they are protected from multiple reactions.[15,16]

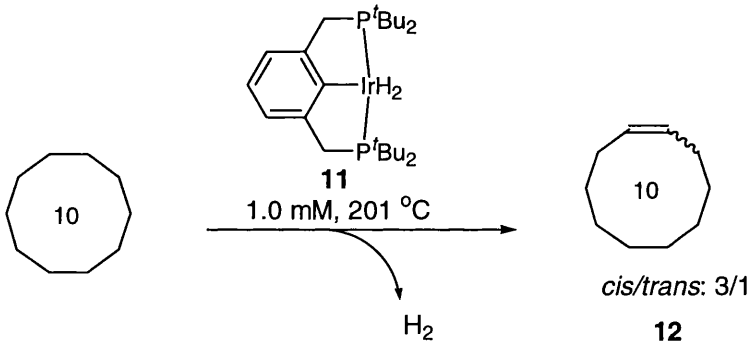
Scheme 8



7 **8** **9** **10**

Finally, the transition metal catalysed dehydrogenation of alkanes as a special case of C-C coupling under C-H activation conditions is discussed. A detailed discussion can be found in the literature.[17] A large number of different transition metal complexes have proved to be active for this dehydrogenation process including iridium, rhenium, rhodium, ruthenium and tungsten in addition to heterogeneous catalysts such as palladium on carbon. Since the dehydrogenation reaction is usually an equilibrium with the reverse hydrogenation reaction, an excess of alkane is often added in order to prevent the reverse reaction. The decomposition of ligands at the high reaction temperatures also represents a problem. Recently several research groups have reported that the cyclometallated iridium complex **11** is sufficiently stable under the required reaction conditions for the dehydrogenation of cyclodecane to give **12** (Scheme **9**).[17]

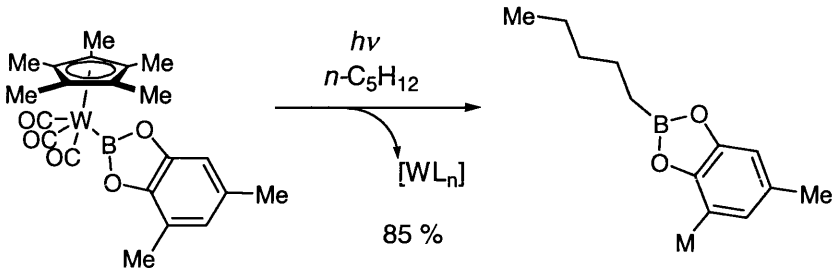
Scheme 9



In the search for more active transition metal complexes Hartwig *et al* turned their attention to compounds containing a bond between a transition metal and boron. With alkanes, such boryl complexes **13** are capable of forming photochemically induced alkylboronates such as **14** (Scheme **10**). In this reaction the boryl group is selectively incorporated in the terminal position. So far, the best results have been achieved with the tungsten complex **13**, however, similar iron and ruthenium complexes are also

active. The driving force of these reactions is the formation of the relatively stable C-B bonds **13**, which makes the development of a catalytic variant look promising.[18]

Scheme 10



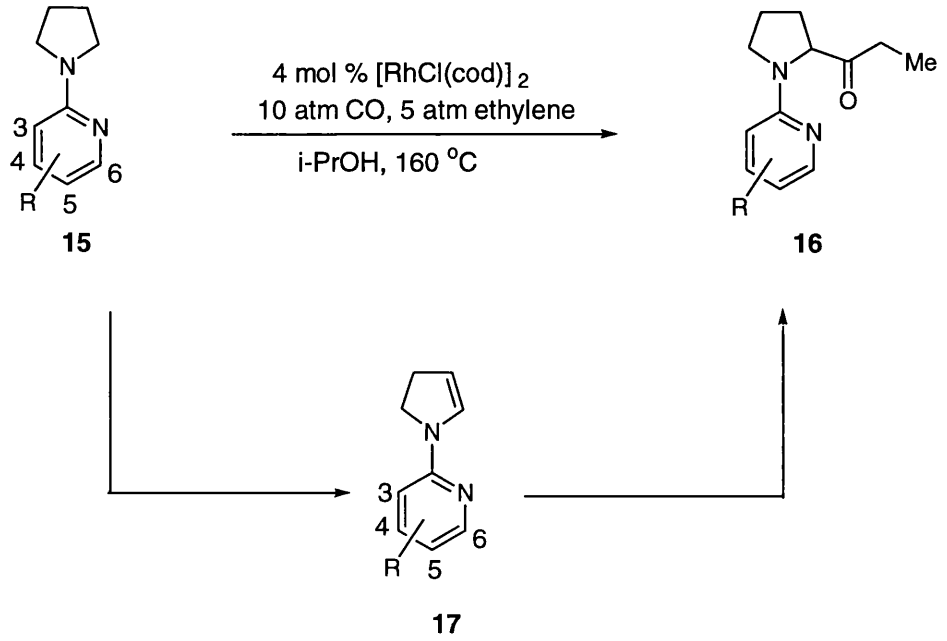
13 **14**

1.5 Catalytic sp^3 C-H bond activation: C-H bond α- to a nitrogen atom

1.5.1) Examples

Recently two new and promising catalytic procedures for the activation of sp^3 C-H bonds adjacent to a nitrogen atom have been published by Murai *et al*[3,19] and Ishii *et al.*[20] The procedure developed by Murai is a regioselective example of $[RhCl(cod)]_2$ catalysed carbonylation of several tertiary amines **15** in the α-position to the nitrogen atom. Although the optimised reaction conditions appear forcing (160 °C, 10 atm CO, 5 atm ethylene, 4 mol % $[RhCl(cod)]_2$, 2-propanol, 40-60 h), the process leads to the formation of valuable α-amino ketones **16** (Table **1**).[19]

Table 1



Entry	R	Yield
1	H	68 %
2	5-Me	84 %
3	6-Me	12 %
4	5-CF_3	15 %

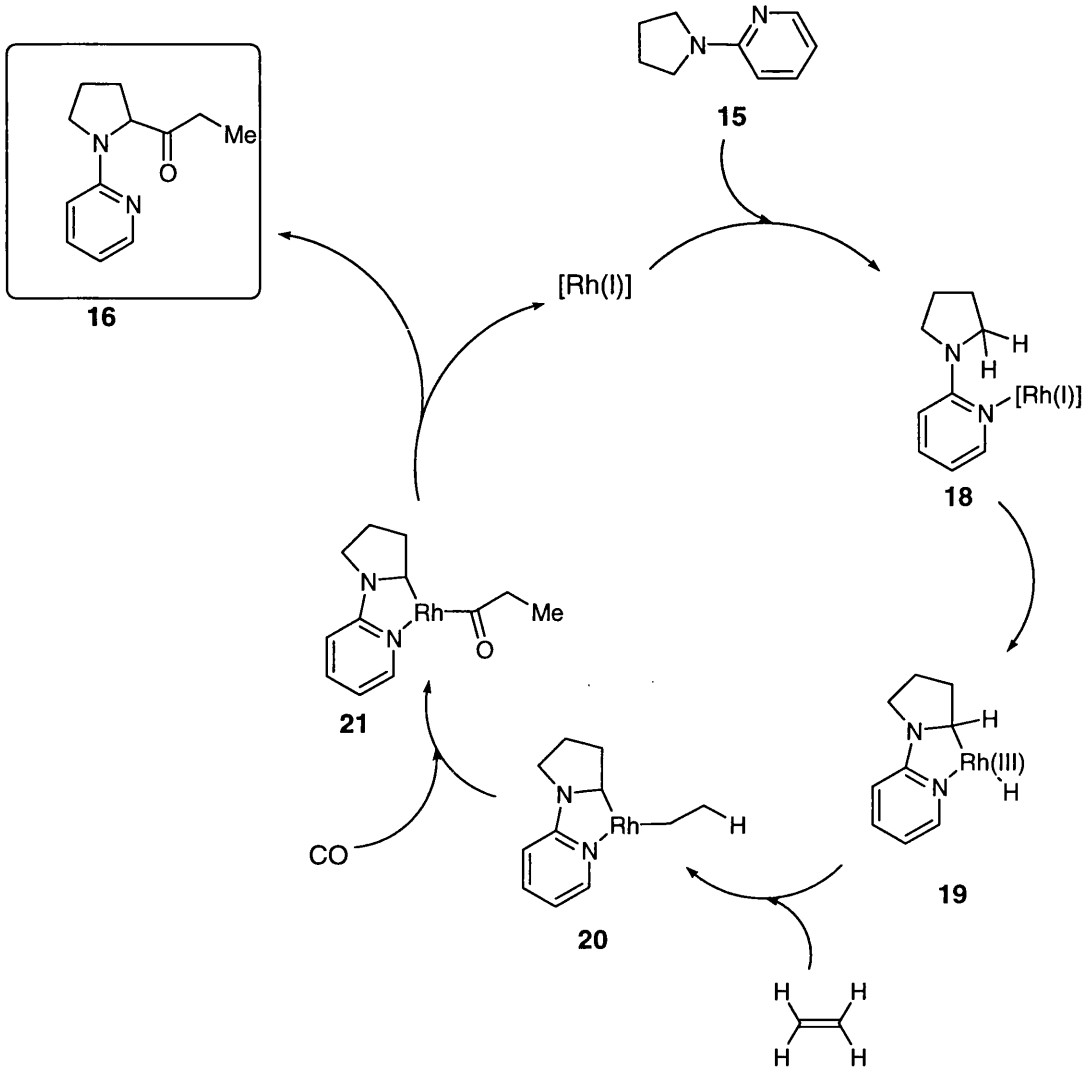
For a successful reaction the authors found that it is important to match the correct rhodium complex with the appropriate solvent (2-propanol). In a previous study Murai showed that under comparable reaction conditions the carbonylation of piperazine derivatives proceeded with a catalytic amount of $[Rh_4(CO)_{12}]$ and toluene as solvent. Such a process takes place *via* an initial dehydrogenation of the starting material. The activation of the resulting sp^2 hybridised C-H bond followed by carbonylation yields the tetrahydropyrazine products.[21] The presence of the *pyridine group* in the tertiary amine substrates **15** is crucial to the success of the reaction. The related complex $[Ru(CO)_{12}]$ can catalyse similar carbonylation reactions. The pyridine functionality is again acting as a directing group, *i.e.* delivering the catalyst to the reaction site.[22,23]

1.5.2) Mechanistic aspects

A detailed investigation of the behaviour of several pyrrolidine derivatives **15** under the reaction conditions indicated that the electronic and steric properties of the directing substituent had a significant influence on the reactivity of the substrate (Table **1**). The reaction of **15** (entry **2**, Table **1**), which bears a relatively electron-rich (5-methylpyridine) substituent affords a much higher yield than reactions of substrates possessing a sterically more hindered (entry **3**) or an electron deficient substituent (entry **4**). This finding combined with the regioselectivity of the reaction (the carbonylation takes place at a C-H bond located next to the pyridine substituent) lead to the assumption that a coordination of the active rhodium species to the nitrogen atom of the pyridine ring (cyclometalation) is an essential step in the catalytic cycle. The mechanism proposed by the authors is shown below (Scheme **11**).[19]

In this mechanism, the catalytically active rhodium species is initially coordinated to the pyridine nitrogen atom to give complex **18** (Scheme **11**). The rhodium centre in **18** can insert into the C-H bond in the α-position to the amine nitrogen, leading to metallacyclopentane species **19**. The insertion of ethylene into the Rh-H bond gives **20**, CO insertion provides the acyl-rhodium complex **21**. Reductive elimination then provides carbonylation product **16** with concomitant regeneration of the active catalyst.[19]

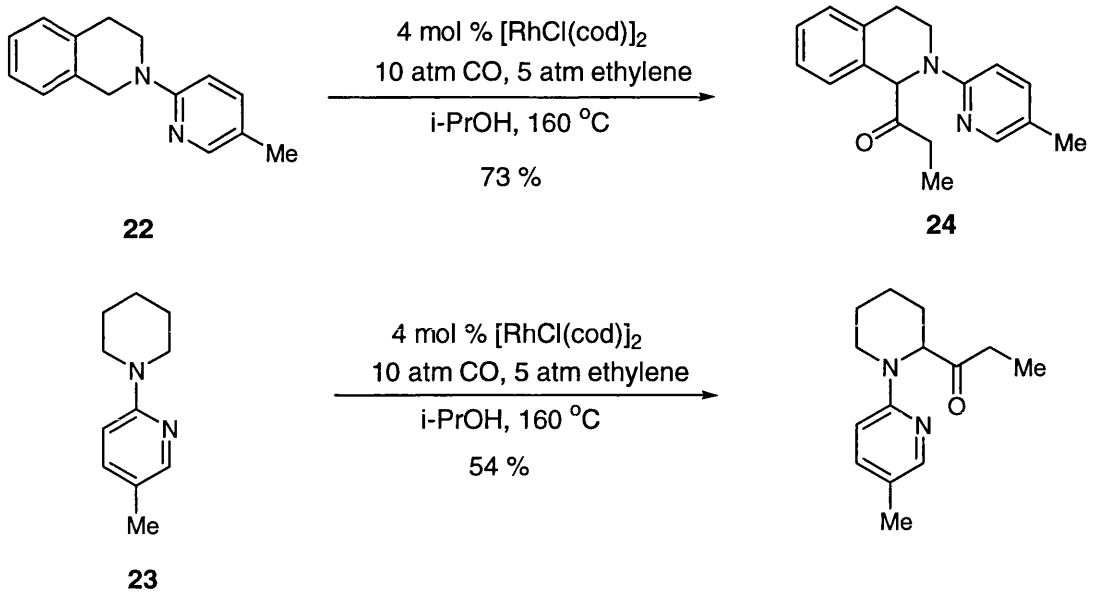
Scheme 11: Proposed mechanism for the $[RhCl(cod)]_2$ catalysed carbonylation of amines



1.5.3) C-H bond α- to a nitrogen atom: Cyclic amines

Further studies to probe the structural requirements of the cyclic amine were performed. To date the only successful candidates are **22** and **23**, both of which feature a pyridine substituent (Scheme **12**). Interestingly, in the case of unsymmetrical amine **22**, the carbonylation takes place selectively at the benzylic position to give **24**.

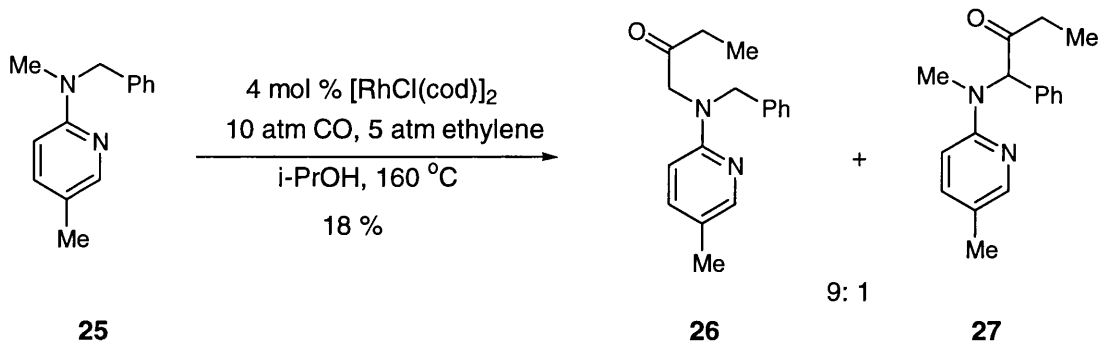
Scheme 12



1.5.4) C-H bond α- to a nitrogen atom: Acyclic amines

Such an approach has also been applied to acyclic substrates. However, in contrast to the cyclic systems the acyclic amine **25** is converted into a mixture of two regioisomers **26** and **27**; activation of the benzylic position gave the minor product **27** (Scheme **13**). Furthermore, the yield obtained (18 %) is lower than that for reactions of cyclic amines.

Scheme 13



These studies represent the first successful example of the carbonylation of acyclic amines.[19] However, this newly developed process still requires significant

optimisation before it can be considered as a widely applicable synthetic method for the synthesis of α-functionalised amines.

1.6 Three component coupling reaction involving sp^3 C-H bond activation

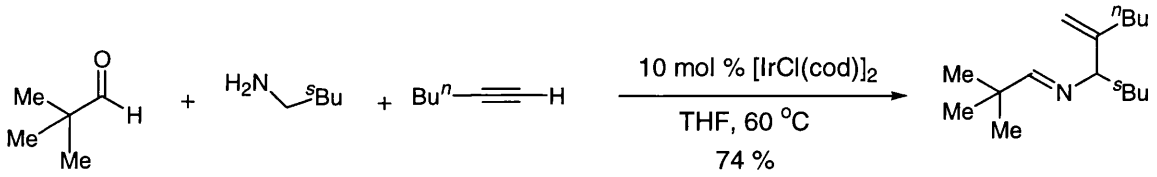
The second promising procedure for the catalytic activation of sp^3 C-H bonds has been recently reported by Ishii *et al.*[20] The study involves a three-component coupling reaction of aldehydes, primary amines and terminal alkynes in the presence of an iridium catalyst to give allylic imines under mild reaction conditions (Scheme **14**).

Scheme 14

1.6.1) Example

The reaction system has already shown some impressive results. Sterically hindered aldehydes such as 2,2-dimethylpropanal **28** are well tolerated and can be coupled with alkylamines **29** and terminal alkynes **30** in good yield (Scheme **15**).[20]

Scheme 15

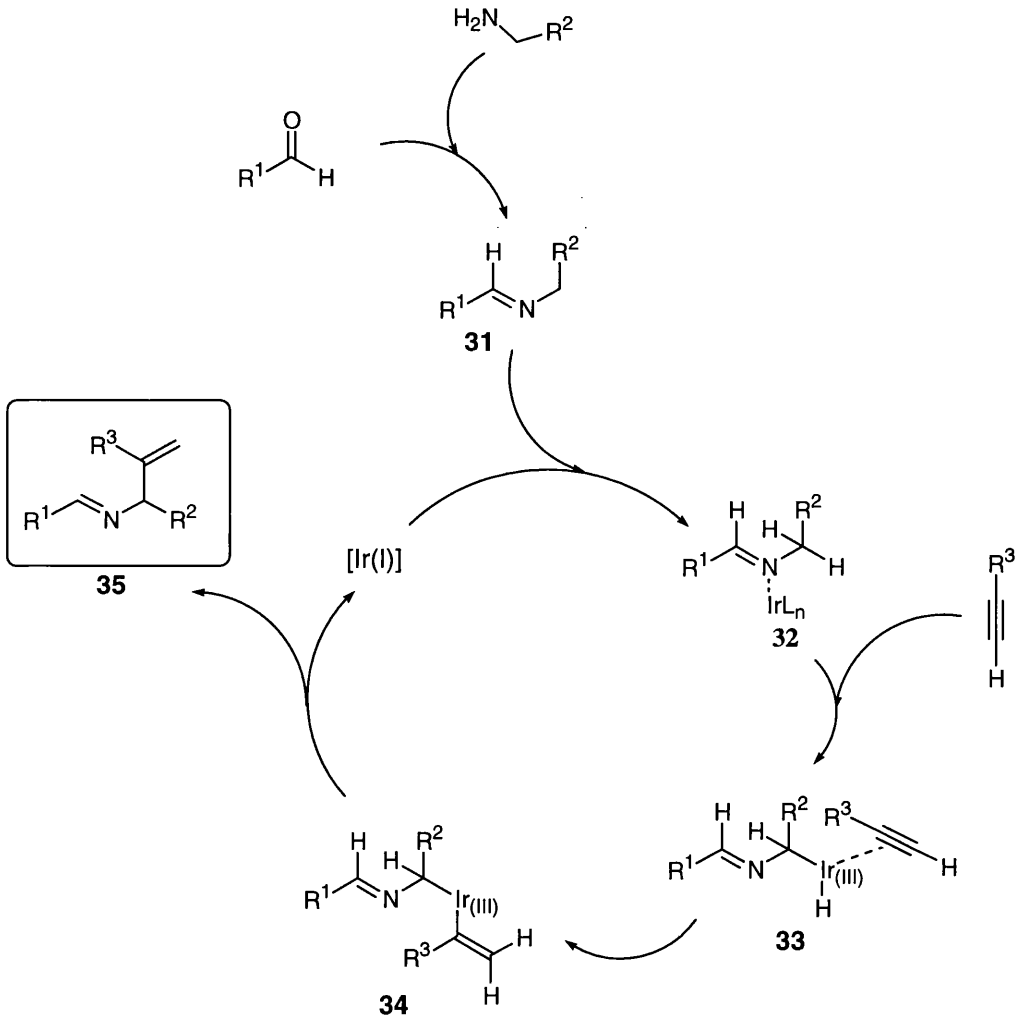


28 **29** **30**

1.6.2) Mechanism

The reaction is initiated by the condensation of the aldehyde with the amine to give the corresponding imine **31** (Scheme **16**). Such functionality can coordinate the Ir(I) species *via* the nitrogen atom. The coordinated species **32** undergoes oxidative addition of Ir(I) into the C-H bond adjacent to the nitrogen atom to give an Ir(III)-H complex **33**, which subsequently inserts into the terminal alkyne. The reductive elimination of **34** regenerates the catalyst and the product **35**.

Scheme 16



Although alkylamines **29** are employed successfully, *tert*-butyl substituted alkylamine was found to be a poor substrate as were internal alkynes, which do not react at all.[20]

1.7 Conclusion

The development, since 1997, of the use of *substrate directed sp^3 C-H bond activation* has allowed sp^3 C-H bond activation to begin to be used to selectively form C-C bonds. In particular catalytic systems using both rhodium and iridium complexes can now be employed.[3] However future studies are necessary in order to establish whether these new procedures can be sufficiently optimised for broad application in research.

The following chapter gives a brief review of hydroformylation reactions and discusses the use of substrate directed processes.

CHAPTER II

Chapter II

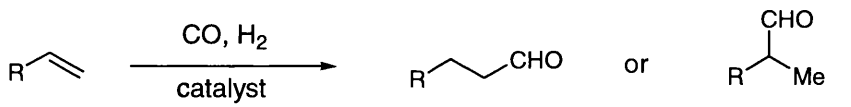
Transition metal catalysed hydroformylation reaction

Chapter I focused on the use of substrate chelation to allow sp^3 C-H bond activation. In this chapter the literature on transition metal catalysed hydroformylation of olefins is reviewed. The concept of chelation-assisted hydroformylation is discussed particularly towards the development of a regio- and stereocontrolled hydroformylation process.

2.1 Introduction

Under transition metal catalysis olefin **36** undergoes formal addition of one equivalent of carbon monoxide and dihydrogen to give aldehydes **37** and **38** (Scheme **17**).

Scheme 17



36 *linear* **37** *branched* **38**

The hydroformylation reaction is one of the most versatile methods for the functionalisation of olefins and represents a very powerful synthetic tool for the preparation of fine chemicals.[24,11,25] Such a reaction can be considered as a prototype of an atom economical transformation as defined by Trost, where all the atoms of the starting materials are incorporated into the product.[26] The aldehyde function is introduced under neutral conditions with low catalyst loadings and a wide range of functional groups are well tolerated during the course of the reaction (among these are

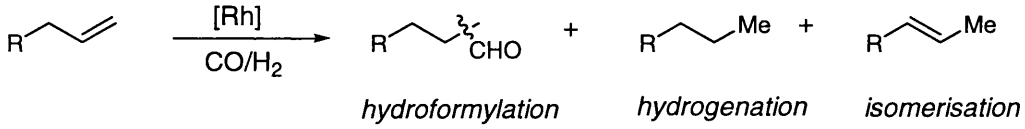
sensitive and reactive functional groups such as aldehydes, free alcohols, carboxylic acids, alkyl halides and tosylates)[27,28,29,30]

It has been shown that it is possible to introduce these simple carbon units in an asymmetric manner; chiral aldehydes arising from such an asymmetric hydroformylation serve as synthetic intermediates for the production of sophisticated pharmacologically active molecules and are produced on an industrial scale.[31,32]

2.2 Rhodium: Catalyst of choice

The challenge of asymmetric hydroformylation lies in controlling not only the regioselectivity and enantioselectivity but also the chemoselectivity; hydrogenation and olefin isomerisation are both competing reaction processes (Scheme **18**).

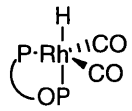
Scheme 18



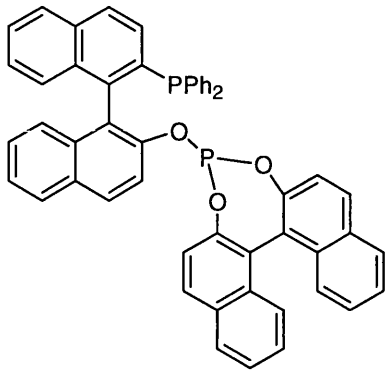
A wide range of transition metals can be used as catalysts: cobalt, rhodium, platinum-tin combinations, ruthenium, iridium, and palladium. However, in the field of asymmetric hydroformylation the rhodium- and platinum- based systems have proved to be superior.[11]

The development of new chiral rhodium phosphine-phosphite catalysts (with BINAPHOS **39**[33] or BIPHEMPHOS **40**) and the possibility of substrate control *via* a directing group on the alkene have established the supremacy of rhodium-based systems **41** (Figure **1**).[34] This will be discussed in more detail *(vide infra).*

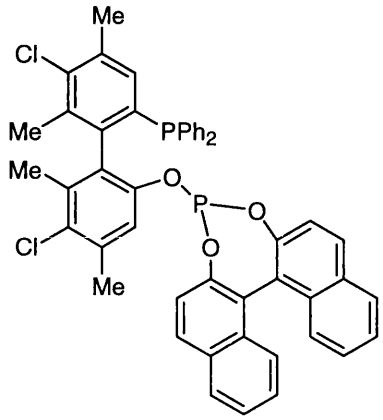
Figure 1



41



39-BINAPHOS

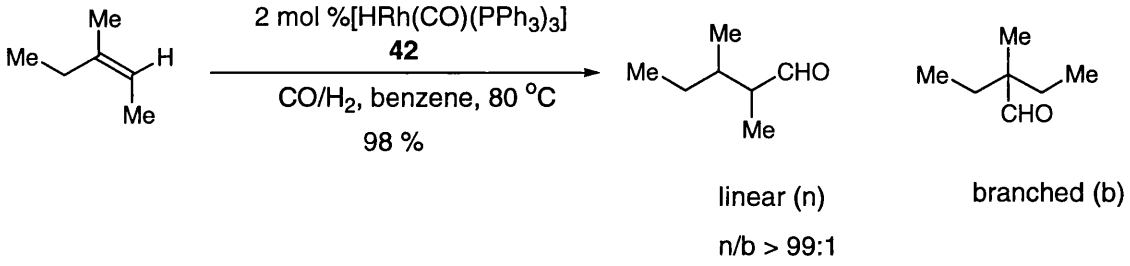


40-BIPHEMPHOS

Such rhodium/phosphine-phosphite based systems tolerate a wide range of substrates without competitive hydrogenation while still delivering excellent asymmetric inductions.[24,35] In the following we will mainly discuss the substrate-based selectivity.

Modern hydroformylation research expanded upon Wilkinson and co-workers' investigations into the effect of ligands upon the reactivity of rhodium carbonyl catalysts.[24] The use of triarylphosphines, as in complex **42** (Scheme **19**), allowed reactions to proceed under more moderate temperatures and pressures (5-100 bar). Furthermore, improved isomer ratios were observed and no isomerisation was detectable.[36]

Scheme 19

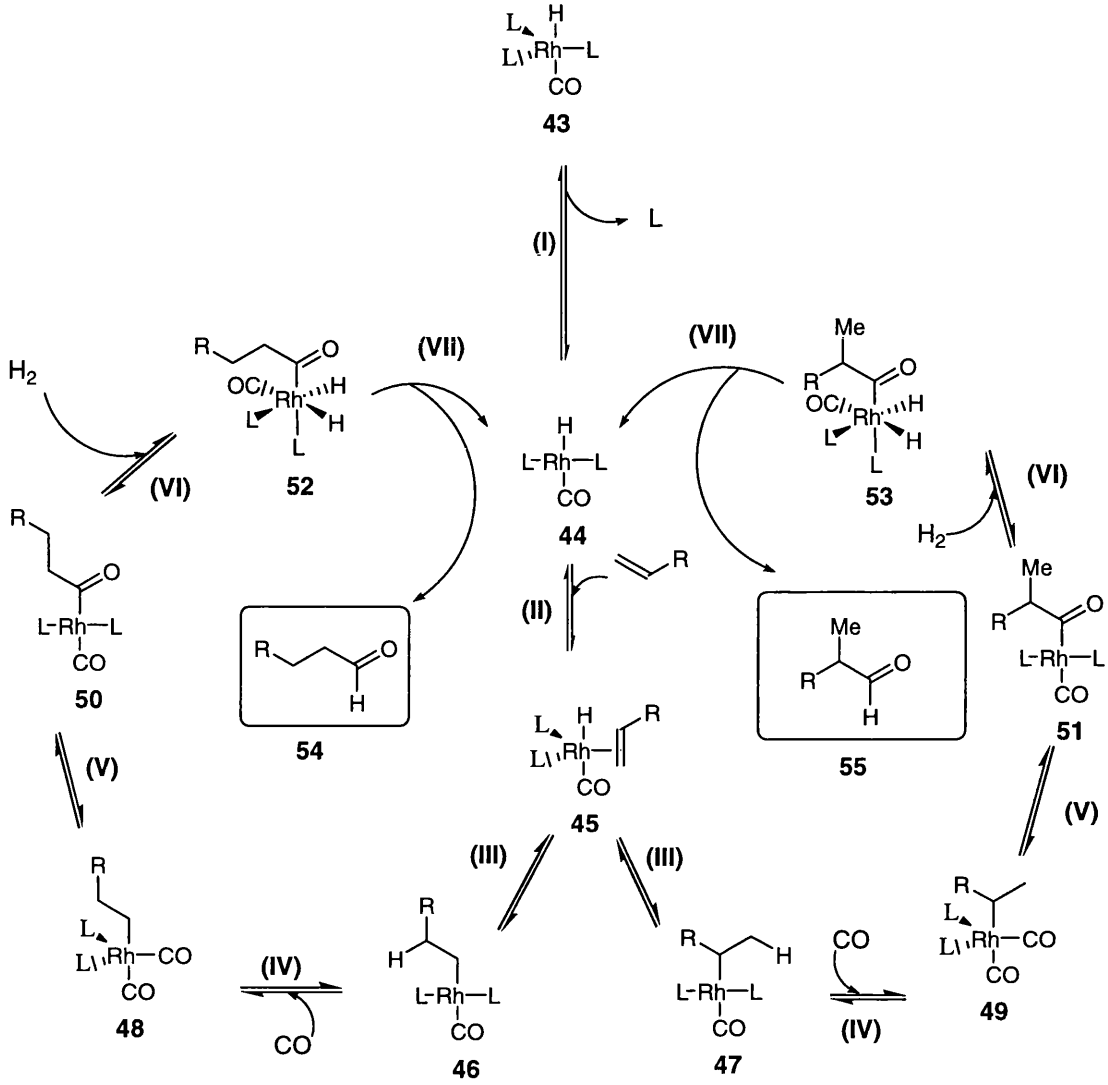


2.2.1) Mechanism

The current mechanistic explanation for the rhodium-catalysed hydroformylation is described below (Scheme **20**).[37] This mechanism is based upon the widely accepted *dissociative mechanism* proposed by Breslow and Heck for the cobalt catalysed hydroformylation reaction.[38]

Starting from a Rh(I) species under carbon monoxide pressure in the presence of ligands L (phosphines, phosphites, carbon monoxide) the complex **43** is formed (18 electron, trigonal bipyramid geometry). Ligand dissociation from **43** gives the catalytically active 16-electron species **44** [step **I**]. Alkene coordination, in the equatorial position affords trigonal bipyramidal hydrido olefin complex **45** [step **II**]. Insertion of the olefin into the Rh-H bond ([step **III**], *hydrometallation*) gives isomeric tetragonal alkyl rhodium complexes **46** and **47**. Subsequent coordination of carbon monoxide [step **IV**] yields trigonal bipyramidal species **48** and **49**. Migratory insertion of the alkyl group to one of the coordinated carbon monoxide ligands [step **V**] generates tetragonal acyl complexes **50** and **51**. Molecular hydrogen [step **VI**] undergoes oxidative addition to form tetragonal bipyramidal rhodium(II) complexes **52** and **53**. The cycle is completed by subsequent reductive elimination [step **VII**], generating the isomeric aldehydes **54** and **55** and the catalytically actives Rh(I) species **43** (Scheme **20**).

Scheme 20: **Currently accepted mechanistic description for the rhodium-catalysed hydroformylation of alkenes**



Kinetic studies and *ab initio* calculations for $[HRh(CO)_2(PPh_3)_2]$ suggest that for linear alkenes the rate-determining step is the oxidative addition of dihydrogen [Step **VI**]. However, kinetic studies of the triphenylphosphine modified rhodium catalyst indicate that even for sterically less demanding olefins such as ethylene or propene the rate determining step is early in the catalytic cycle and thus may be either the olefin addition [step **III**] or insertion step [step **IV**].[39]

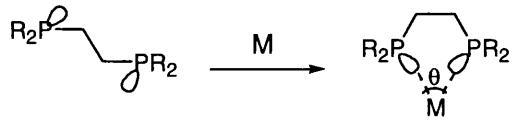
The deuteroformylation of 1-hexene by chiral phosphine-phosphite-Rh(I) complexes demonstrated the reversibility of the hydrometallation [step **III**]. It was found that in most cases the hydrometallation step determines the regio- diastereo- and enantioselectivity of the reaction. The overall stereochemistry of the hydroformylation reaction exhibits *syn* addition of the hydride and the formyl group.[40,36]

2.2.2) Catalyst based regio- and enantioselectivity

Much of the work on rhodium-catalysed hydroformylation of olefins has focused on the development of methods enabling a mechanistic understanding of the selective production of the linear aldehyde regioisomers **54**. This is now a well-developed process for alkyl substituted terminal olefins. The different stability and reactivity of the hydrometallation intermediates **46** and **47** (Scheme **20**) governs the regioselectivity. Thus, inherent substrate preference due to steric and/or electronic factors has to be taken in account. Furthermore, directing effects exerted by functional groups have to be considered as they may overrule these intrinsic substrate preferences. Finally the effects induced by the catalyst have a great impact on the regioselectivity as the nature of the ligand shape determines the accessible space at the catalytic centre.[24]

However, the development of methods for the production of branched aldehyde regioisomers **55** is receiving increasing attention as the efficient synthesis of chiral aldehydes in diastereo- and enantiomerically pure form is of fundamental importance in organic chemistry.[35] A major breakthrough in catalyst-based regiocontrol came with the use of bidentate ligands (Figure **1**).

Figure 1



bidentate ligand θ = natural bite angle

Casey has demonstrated that the bite angle of the chelating ligand to the metal centre plays a crucial role on the properties of the metal catalyst since it dictates the type of coordination mode at the metal centre (*eg*: one axial and one equatorial (**ea**) **56** or both equatorial (**ee**) **57**) (Figure **2**).[41]

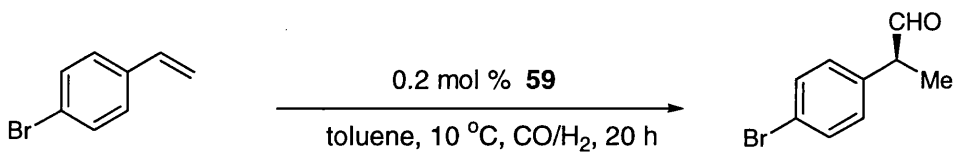
Figure 2

equatorial-axial **(ea)** **56**

bis-equatorial **(ee)** **57**

Once the coordination mode of the ligand as well as the complex geometry and conformation are defined, efficient differentiation of the possible coordination sites of the substrate to the metal centre is possible. Thus, hydroformylation of vinylarene substrate **58** was achieved with high *b*-type (branched) selectivity and reasonable enantioselectivity under Rh(I)-aminophosphine phosphite (AMPP) complex **59** catalysis (Scheme **21**) and (Figure **3**).[42]

Scheme 21



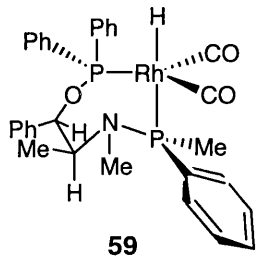
58

b:n = 98:2

ee = 71 %

In situ ^{1}H and ^{31}P NMR studies revealed that AMMP (aminophosphine phosphite) ligand in complex **59** follows an **(ea)** coordination mode (Figure **3**). The chiral phosphorus atom bearing one relatively small and a larger group gives rise to differentiation of the two possible coordination sites **(ea)** (phosphite coordinating in an equatorial *versus* axial fashion).[42]

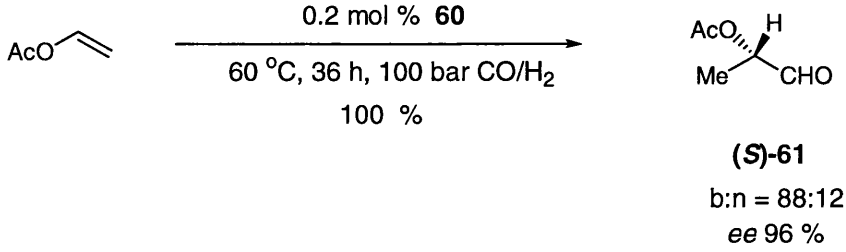
Figure 3: Aminophosphine phosphite (AMPP)-Rh complex 59



59

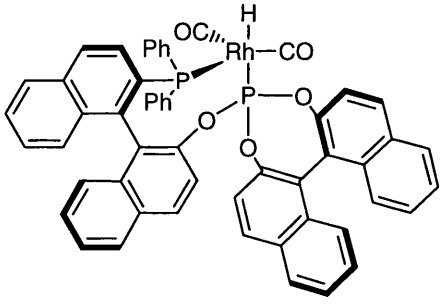
Asymmetric hydroformylation has been studied extensively on vinylarene substrates, particularly styrene, due to their high reactivity and the good regioisomer ratios they deliver. Furthermore, one may speculate that the formation of a more rigid π-arene rhodium intermediate in the course of the hydroformylation reaction allows higher levels of asymmetric induction compared to other alkene classes.[43,24] High levels of enantioselectivity have been achieved with bidentate ligands. Amongst the various Rh-based systems attempted to date Takaya and Nozaki's phosphine-phosphite, Rh-*(R,S)*-BINAPHOS, complex **60** has provided the most impressive enantioselective hydroformylation. An example is reported below; (*S*)-aldehyde **61** was obtained in 96 % *ee* combined with a reasonable isomer ratio (b:n) > 88:12 under Rh-*(R,S)*-BINAPHOS **60** catalysis (Scheme **22**) and (Figure **4**).[33,44]

Scheme 22



As with AMPP ligands, NMR spectroscopy studies demonstrated that the success of the asymmetric hydroformylation relies on the exclusive formation of a single catalytically active species **60** (Figure **4**). In this case it is the fixed *(S)*-binaphthalenyl part of the phosphite, which efficiently shields the axial coordination site. The ligand coordination mode is efficiently controlled by the chelation bite angle; the phosphine part forms an eight-membered ring chelate with a flexible ligand backbone with a bite angle of about 90 °C hence the ligand adopts (**ea**) coordination mode with the phosphite trans to the hydride (Figure **4**).[34]

Figure 4: Structure of the catalytic species Rh-(*R,S*)-BINAPHOS 60

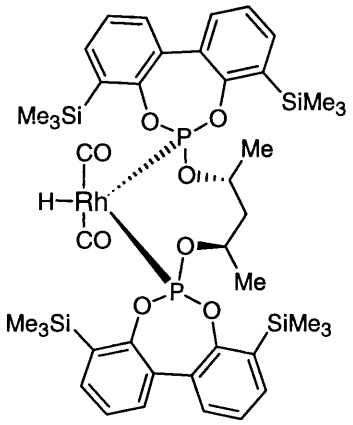


60

Changing the electronic nature of the ligands substituent results in different coordination behaviour.[42] Newly developed C_2 symmetric *bis*-phosphite ligands based on a chiral 2,4-pentanediol backbone coordinates rhodium in a *bis* equatorial

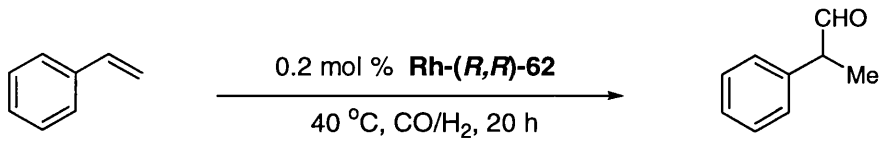
(**ee**) fashion **62** (Figure **5**).[42] Although Rh- based system **62** has shown excellent regioselectivity (b/n = 95:5) in styrene hydroformylation with enantioselectivity up to 67 % *ee*, such a system suffers from instability at elevated temperatures (Scheme **23**).[45]

Figure 5



Rh-(*R,R*)62

Scheme 23



63

b:n = 95:5

ee= 67 %

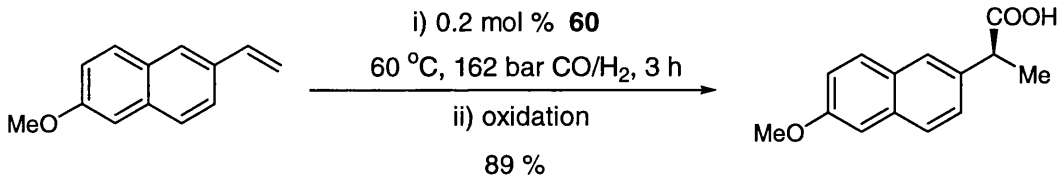
The reaction rate decreases with substrate substitution; this system is applicable to only a limited number of substrates in comparison with Rh-BINAPHOS **60** systems.[45]

2.2.2.1 Applications to total synthesis

The hydroformylation reaction has attracted particular attention since it provides a straightforward method for the preparation of arylpropionic acids, an

important class of non-steroidal anti-inflammatory agents. The synthesis of *(S)*-Naproxen **64** using Rh-*(R,S)*-BINAPHOS **60** catalyst is shown in Scheme **24**.[11]

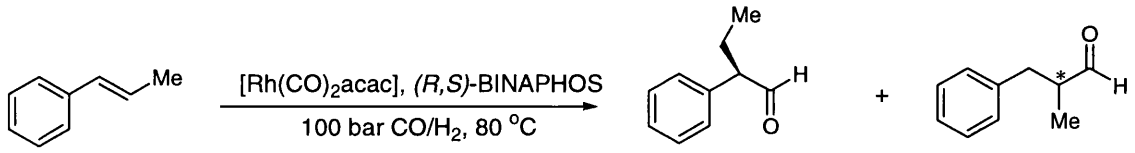
Scheme 24



64-(*S*)-Naproxen
b:n = 94:6
ee = 96 %

The Rh-*(R,S)*-BINAPHOS **60** catalyst system remains efficient for the hydroformylation of 1,2-disubstituted alkene **65** (Scheme **25**). The resulting hydroformylation product *(R)*-2-phenylbutanal **66** has been used as an intermediate in the synthesis of spasmolytic butetamate.[46]

Scheme 26



65

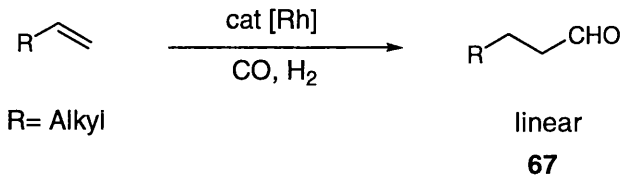
66
ee = 80 %

2.2.3) Substrate based regio- and stereocontrol

The nature of the olefin substituent itself is also important in the selectivity of the hydroformylation reaction as intrinsic substrate preferences may be overruled by directing effects, such as repulsive steric interactions, electronic effects or positive coordinating interactions with the approaching catalyst. In the latter case, an intramolecular delivery of the catalyst to the olefin occurs.[35]

Whereas good solutions now exist for the synthesis of linear aldehydes **67** from terminal olefins (Scheme **26**),[11] the selective formation of the branched aldehyde (in particular from alkyl substituted olefins) is an unsolved problem.

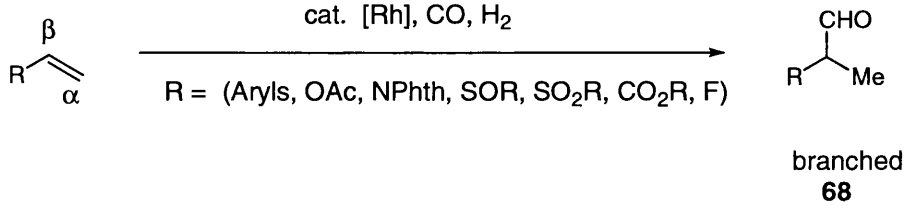
Scheme 26



67

Likewise, olefins possessing an electronegative or electron withdrawing vinylic substituent such as vinyl acetate and vinyl phthalimide,[47] acrylic esters,[48] vinyl sulfones and sulfoxides[49] as well as fluorine-substituted derivatives[47] show in general a selectivity toward the branched aldehyde isomer (Scheme **27**).

Scheme 27



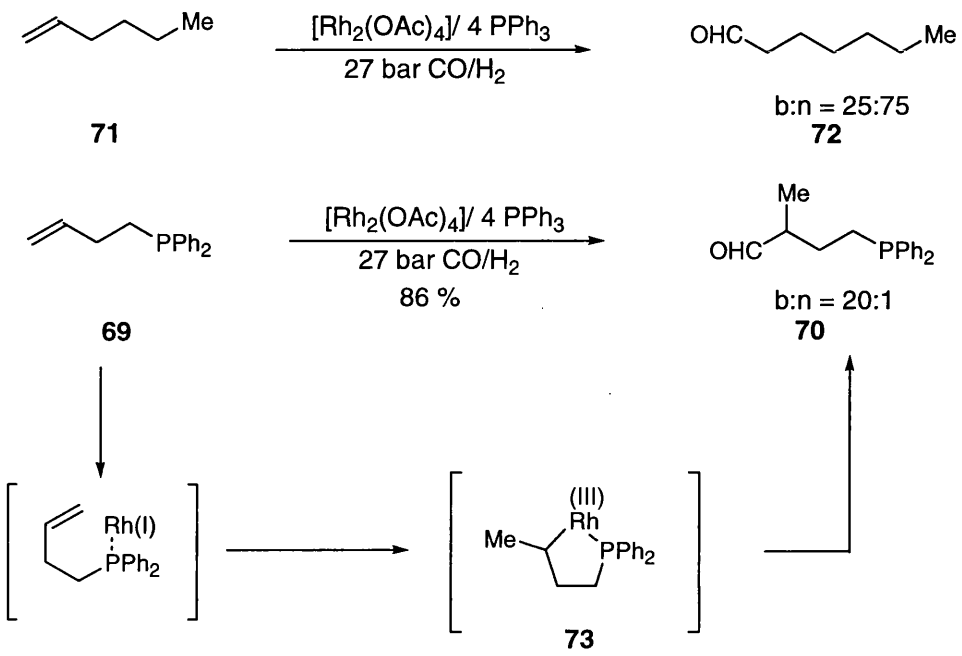
68

It was suggested that this may be due to the higher stability of the C_α-M bond formed upon olefin insertion compared to the alternative C_β-M bond because of substantial stabilisation of the formal negative charge developing at C_α.[24,47]

To overrule an inherent substrate selectivity preference one may rely on substrate direction, where a formal intramolecular process takes place *via* precoordination of the catalyst to the coordinating group (see chapter I).[50,24]

An impressive early example of coordination controlling regioselectivity is given below. Reaction of 4-(diphenylphosphino)1-butene **69** affords the branched hydroformylation adduct **70** (Scheme **28**). Using the corresponding phosphine oxide or 1-hexene **71** yields preferentially the linear aldehyde **72**. The reaction proceeds *via* a 5-membered chelated intermediate **73**.[51]

Scheme 28

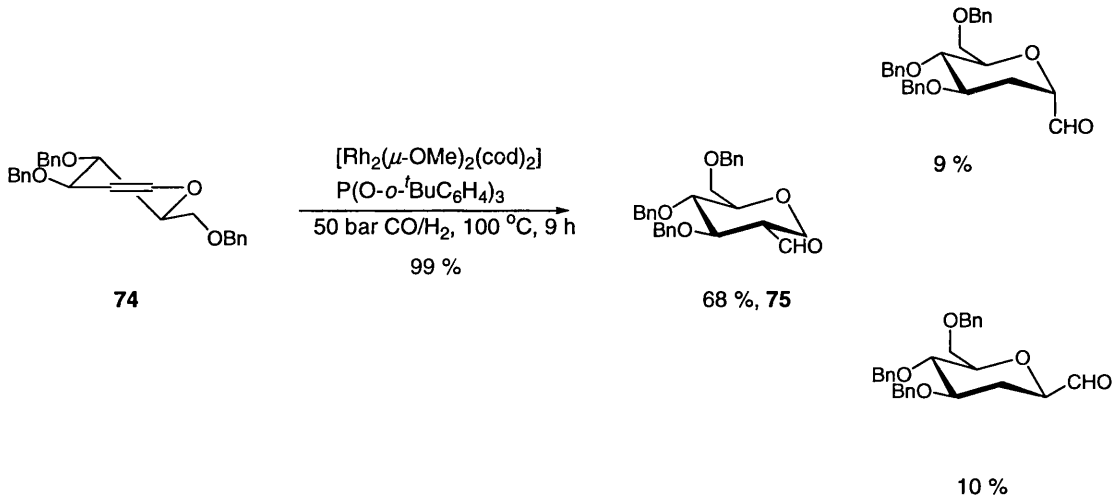


Phosphites, amines[52] and even amide functionalities[53] are well tolerated under rhodium catalysed hydroformylation conditions. All three functional groups can direct the hydroformylation of alkenes, with a modest to high preference for the branched adduct in the case of amides. The problem with amines is that stoichiometric amounts of metal catalyst are required, whereas the phosphite systems are catalytic. Simultaneous control of regio- and diastereoselectivity was achieved in the hydroformylation of cyclohexene derivatives relying on similar substrate directing effects.[35]

2.2.3.1) Passive substrate control regio- and stereoselectivy

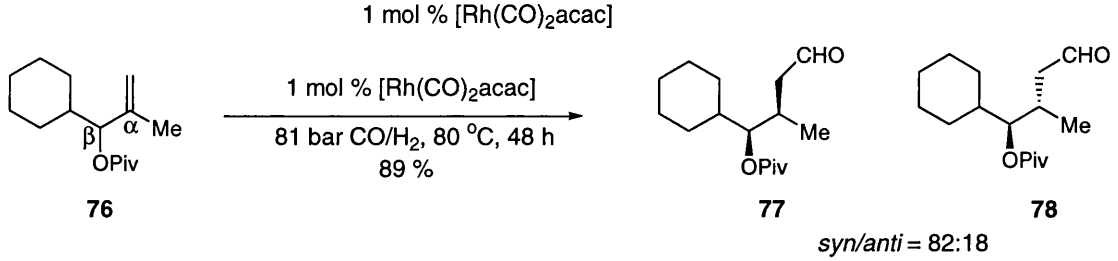
Hydroformylation of glucal derivative **74** afforded 2-formyl product **75**, a potentially interesting substrate in *C*-glucoside chemistry, with good regio- and stereoselectivity (Scheme **29**). The observed diastereoselectivity is controlled by 1,2 induction from the three benzylic ether substituents.[54]

Scheme 29



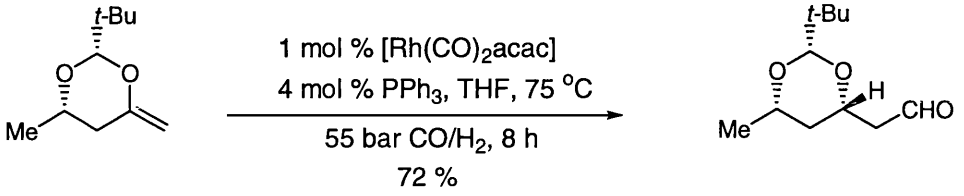
1,2 induction in the hydroformylation of acyclic methallylic pivalate protected alcohol **76** was reported by Yamamoto *et al* (Scheme **30**).[55] Under rhodium catalysis, hydroformylation occurs exclusively at the terminal position providing protected homoaldol products **77** and **78** with a reasonable level of *syn* selectivity.

Scheme 30



The hydroformylation of substituted 4-methylene-1,3-dioxane **79** with a rhodium/ triphenylphosphine catalyst proceeds with good regioselectivity and high diastereoselectivity to give protected *syn*-3,5-dihydroxyaldehyde **80** (Scheme **31**).[56]

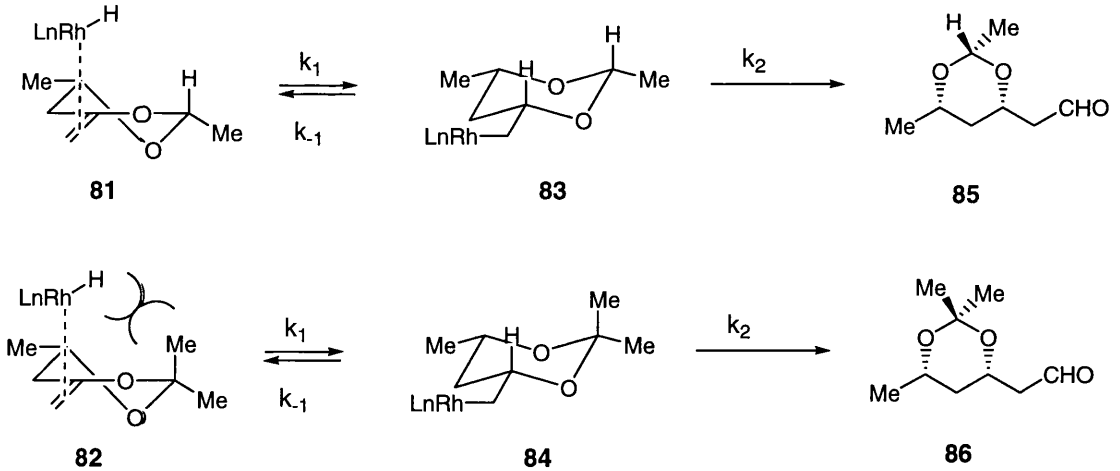
Scheme 31



79 *syn*-**80**
b:n = 1:13

To determine whether the observed *syn*-selectivity is thermodynamic or kinetic in origin, a competition experiment was performed with substrates **81** and **82** (Table **2**). The results suggest that the axial methyl group of **82** has a significant effect on the reaction rate. This is consistent with rate determining olefin insertion to give intermediates **83** and **84** prior to CO insertion ($k_2 >> k_{-1}$).[56]

Table 2



	Conversion (after 2 h)
85	59 %
86	9 %

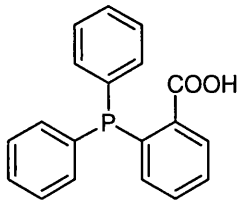
To summarise, it is evident that high and predictable diastereo- and regioselectivity can be achieved with specific substrates. However, such substrate-directable reactions rely upon the nature of the coordinating functionality present in a particular substrate. This places limitations upon the set of reagents directable by a specific functional group.

To overcome such intrinsic limitations of directed-reactions by only specific substrates, an ideal system would be where a catalyst specific-directing group could:
(a) be specifically introduced, function as a good ligand under the reaction conditions
(b) provide reversible coordination with the catalyst to allow turn-over
(c) allow a highly ordered cyclic transition state for the step definining the stereochemistry, and
(d) be easily cleaved from the product once the reaction finishes.

2.2.4) The concept of substrate directed reactions

Breit has recently reported a general and effective method using the concept of substrate-directed reactions in which the reacting substrate is appropriately equipped with functionality designed to allow precoordination of the reagent followed by intramolecular catalyst delivery.[57] The recent progress in diastereoselective hydroformylation of acyclic substrates led to the design of *o*-(diphenylphosphanyl)benzoic acid derivatives (*o*-DPPB) **87** as a *catalyst directing group* (Figure **6**).[58]

Figure 6: ***o*-(diphenylphosphanyl)benzoic acid (*o*-DPPB) 87**

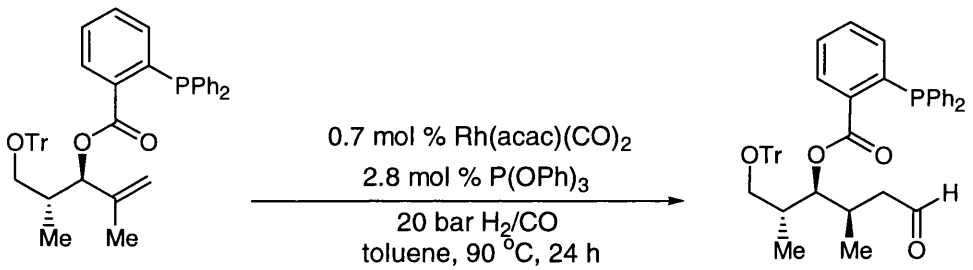


87

2.2.4.1) Examples

An illustrative example of 1,2 asymmetric induction is given below. The Rh(I) catalysed hydroformylation of the methallylic (*o*-DPPB) ester **88** gives the aldehyde **89** in good yield and with excellent *syn* diastereoselectivity (Scheme **32**). Compound **89** was successfully applied to the construction of stereotriad building blocks for the polyketide class of natural product.[59]

Scheme 32



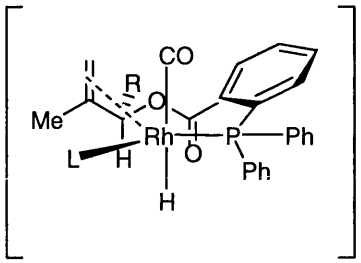
88
Tr = trityl, CPh_3

stereotriad-**89**
syn/anti= 96:4

Substrate control occurs, as observed in the chelation assisted sp^3 hybridised C-H bond activation, *via* precoordination of the metal catalyst to the suitably positioned functionality in the substrate (see chapter I). The coordinating properties of the phosphorus atom combined with the structure of (*o*-DPPB) control the regio- and diastereoselectivity of the hydroformylation process. The high selectivity is a result of

the ester linkage to the α–substituted methallylic alcohol **88** inducing an energetically preferred well-defined cyclic transition state **90** (Figure **7**).[59]

Figure 7

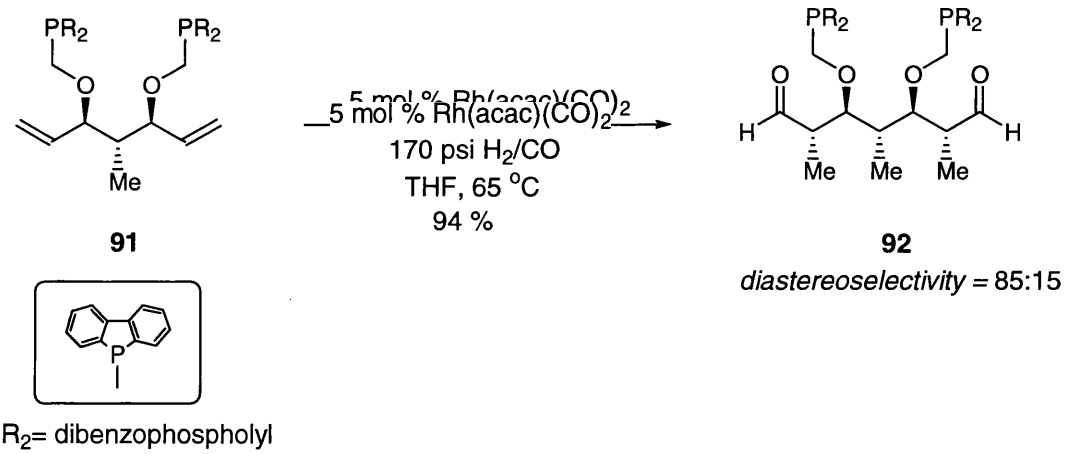


90

This concept was successfully applied to 1,3 asymmetric induction with homomethallylic *o*-DPPB esters with similarly high diastereoselectivities.[60]

Leighton *et al* have reported an effective directing group strategy for the branched-selective hydroformylation of dibenzophosphol-5-ylmethyl ethers of allylic alcohols **91** (Scheme **33**).[61] Hydroformylation of symmetrical substrate **91** proceeded smoothly to give dialdehyde **92** in 94 % yield and with 85:15 diastereoselectivity for the establishment of two new stereocenters (Scheme **33**).

Scheme 33



91

92

diastereoselectivity = 85:15

2.3 Conclusion

The advent of powerful substrate-bound directing groups has provided new directions in the field of diastereoselective hydroformylation. Although there has been tremendous progress achieved in controlling the regio-, chemo-, and stereoselectivity of Rh(I) catalysed hydroformylation reactions, synthetic applications to total syntheses are still rare. One reason for this is that the reaction introduces only one carbon atom and in the case of substrate-directed methodology two additional steps are required: the introduction and removal of the directing group which in certain cases may require the development of new cleavage methods.

A closely related rhodium catalysed C-C bond forming transformation capable of introducing units longer than 1 carbon unit is the hydroacylation reaction. This allows a carbon chain to be appended, rather than the one carbon extension resulting from hydroformylation. The next chapter will examine the intramolecular hydroacylation.

CHAPTER III

Chapter III

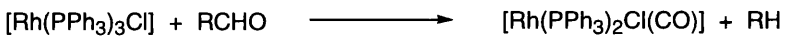
Rhodium catalysed intramolecular hydroacylation

In chapter I the activation of sp^3 hybridised systems was studied. The following chapters III and IV describe an example of sp^2 C-H activation: the hydroacylation reaction. Hydroacylation in chapters III and IV will be considered in relation to the work described in chapters I and II. This chapter will mainly discuss the intramolecular hydroacylation of 4-pentenals.

3.1 Introduction

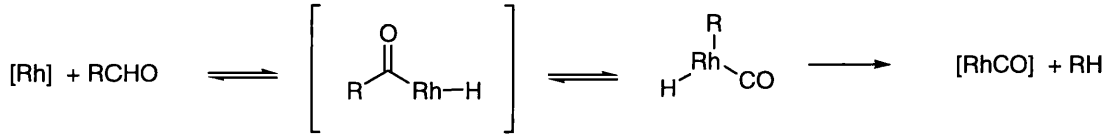
Reactions that involve insertion of transition metal-based catalysts into C-H bond and subsequent C-C bond creation represent an underdeveloped area of organic synthesis. One exception is the hydroacylation reaction. Tsuji *et al* reported that Wilkinson's catalyst, $[Rh(PPh_3)_3Cl]$, reacted with aldehydes to give decarbonylated products as illustrated in Scheme **34**.[62]

Scheme 34



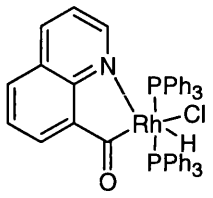
The mechanism of this process is believed to involve the steps outlined in Scheme **35**, where oxidative addition across the formyl hydrogen bond occurs. Carbonyl deinsertion followed by alkyl-hydride reductive elimination provides the decarbonylated products together with an inactive Rh-carbonyl complex.[63]

Scheme 35



Subsequently, the hydrido-acyl intermediate **93** resulting from the oxidative addition of 8-quinoline-carboxaldehyde to $[Rh(PPh_3)_3Cl]$ was isolated and characterised by Suggs (Figure **8**).[64]

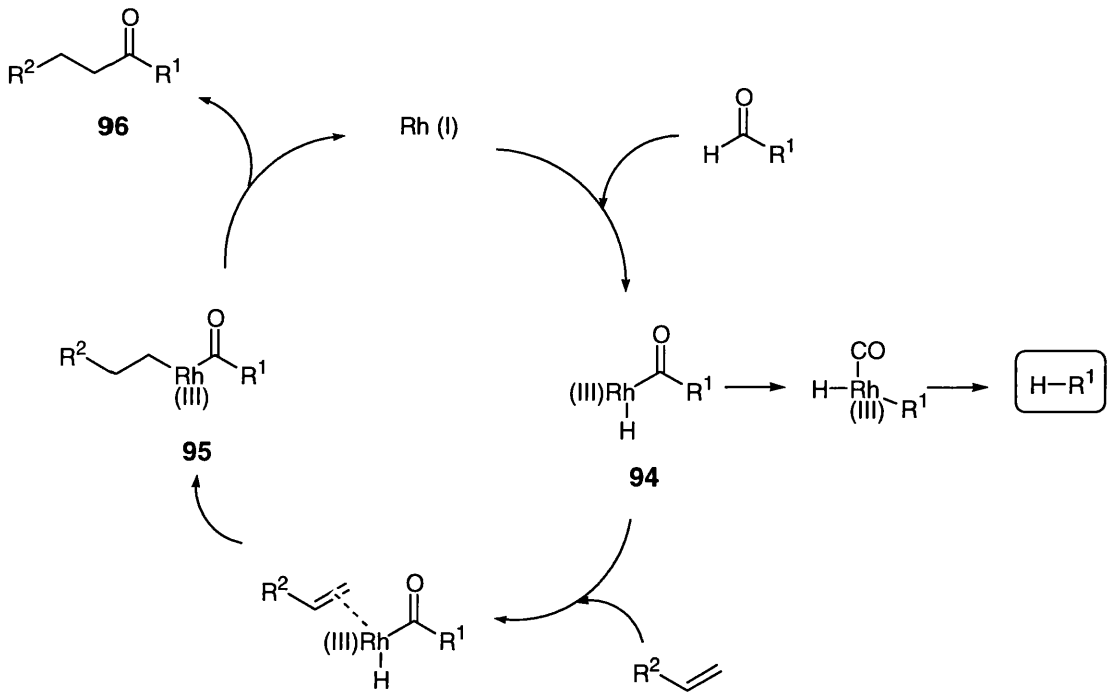
Figure 8



93

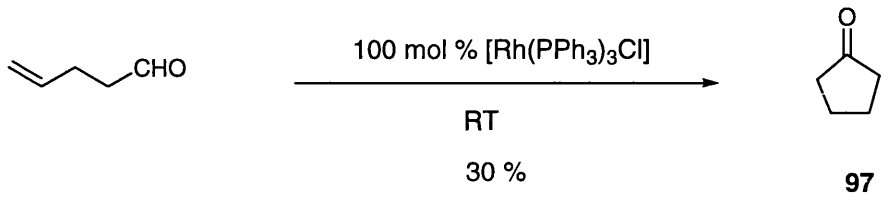
The formation of the hydrido-acyl intermediate **94** suggests that, in the presence of an olefin, it might be possible to obtain hydride-olefin insertion to form the alkyl-acyl intermediate **95**, which in turn, may undergo reductive elimination to yield the ketone **96** (Scheme **36**).

Scheme 36



First reported in 1972, the Rh(I)-catalysed cyclisation of 4-pentenal into cyclopentanone **97**, an intramolecular hydroacylation, is an example of such a reaction (Scheme **37**).[65,66]

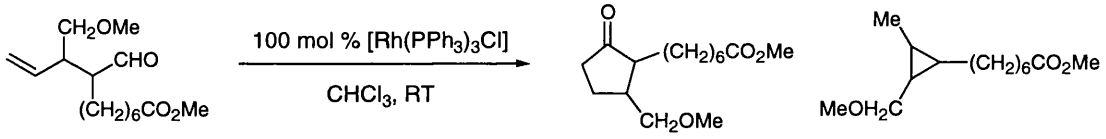
Scheme 37



97

In addition to the formation of cyclopentanone derivatives, unexpected cyclopropane derivatives resulting from decarbonylation were also produced. The treatment of 2,3-disubstituted 4-pentenal **98** with a stoichiometric amount of Wilkinson's complex, $[Rh(PPh_3)_3Cl]$, in $CHCl_3$ afforded the cyclopentanone **99** in 17 % yield and cyclopropane **100** in 35 % yield together with the catalytically inactive complex $[Rh(PPh_3)_2Cl(CO)]$ (Scheme **38**).

Scheme 38



98 | **99** 17 % | **100** 35 %

3.2 Ethylene pressure and decarbonylation

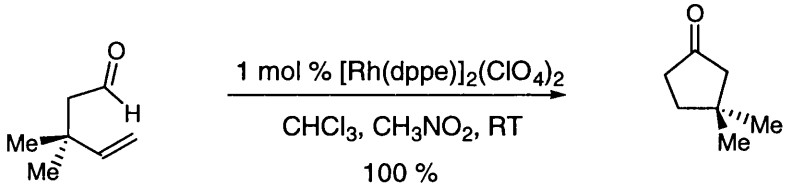
Following this discovery, Miller *et al* reported catalytic examples of intramolecular hydroacylation with the same reaction conditions depicted in Scheme **37** above, where the key feature is the use of $[Rh(PPh_3)_3Cl]$ under ethylene pressure in the reaction mixture to suppress the decarbonylation. Indeed, higher yields (increased

from 30 % to 69 %) of cyclopentanone **97** were obtained when ethylene saturated chloroform was employed.[67]

3.3 Neutral *versus* cationic Rh complexes and decarbonylation

The major breakthrough in intramolecular hydroacylation came with the use of cationic Rh-complexes. Bosnich *et al* demonstrated the effectiveness of cationic rhodium with diphosphine ligands $[Rh(diphosphine)]^+$; using 1 mol % of rhodium(I) complexes containing (dppe), converts 4-pentenal **101** to cyclopentanone **102** at room temperature (Scheme **39**).

Scheme 39



101 **102**

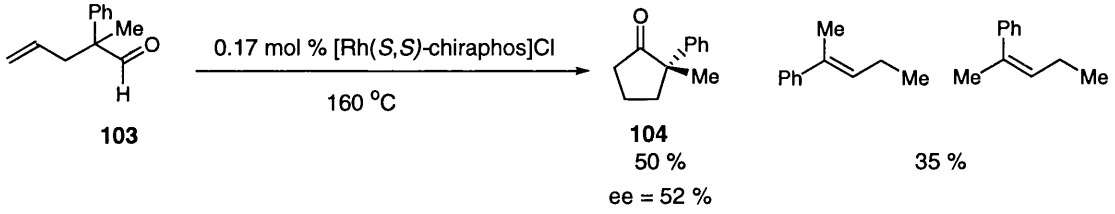
These catalysts tolerate substitution at the 3-, 4- and in rare examples 2- positions of the aldehyde partner; no catalysis was observed with the terminal 5-position substituted. Disubstitution at the 2-position slows the reaction rate dramatically, although disubstitution at the 3-position is well tolerated. Unlike the case of hydroacylation with Wilkinson's catalyst no cyclopropane derivatives were isolated. Double bond migration was observed as a competing reaction dependent upon the reaction conditions.[68,69]

Given the efficiency of the $[Rh(diphosphine)]^+$ catalysts and the synthetic importance of cyclopentanones, investigations on an asymmetric intramolecular hydroacylation process focused on the use of cationic rhodium catalysts bearing a chiral diphosphine ligand.

3.4 Asymmetric catalysis

In the first reported example, [Rh(*S,S*-CHIRAPHOS)]Cl was used for the kinetic resolution of neat racemic mixture of chiral 2,2-disubstituted-pent-4-enals **103** (Scheme **40** and Figure **9**). Despite the elevated temperatures employed a fairly good enantioselectivity for cyclopentanone **104** was observed.[70]

Scheme 40



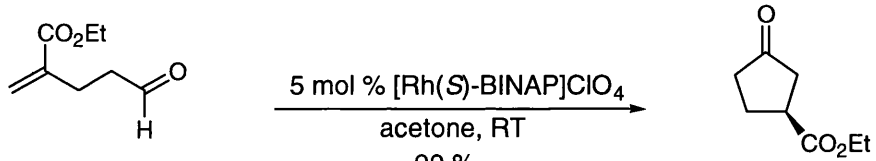
103

104
50 %
ee = 52 %

35 %

Recent studies with BINAP and DUPHOS as chiral bisphosphine ligands gave even better results; indeed [Rh(*S*)-BINAP]ClO_4 complex rapidly and efficiently converts 4-substituted 4-pentenal bearing an ester group **105** into the corresponding 3-substituted cyclopentanone **106** with an impressive enantioselectivity (> 99 % ee) at room temperature (Scheme **41** and Figure **9**).[71,72]

Scheme 41

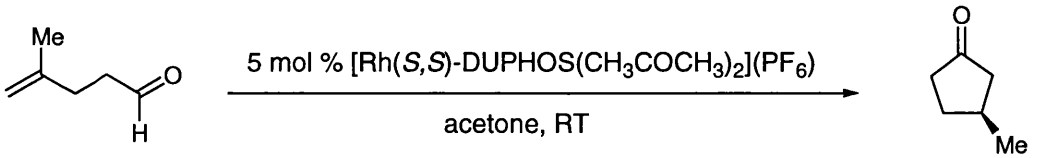


105

106
ee > 99 %

Similarly, in the presence of 5 mol % of [Rh(*S,S*)-DUPHOS(CH_3COCH_3)$_2$](PF_6) complex, 4-substituted-4-pentenal with a primary group (Me) **107** was converted into the corresponding cyclopentanone **108** with 95 % ee (Scheme **42**).[72,63]

Scheme 42



107 **108**

ee > 95%

As impressive as these results are it was demonstrated that a match between the substrate substitution and the chiral ligand was necessary to achieve high enantioselectivity. Results indicated that:

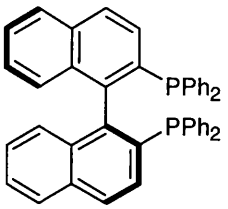
- The *(S)*-BINAP catalyst gives essentially enantiomerically pure products with tertiary alkyl, ester or acyl substituents at the 4-position.

- The *(S,S)*-CHIRAPHOS catalyst affords hydroacylation products of opposite enantiomeric configuration to the *(S)*-BINAP catalyst with the same substrates.

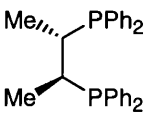
- The *(S,S)*-DUPHOS catalyst provides excellent enantioselectivity with *n*-alkyl and *iso*-alkyl substitutents at the 4-position.

One limitation of the system is that moderate to poor enantioselectivy is observed with 4-aryl substitutents despite the various catalyst systems.[63,73]

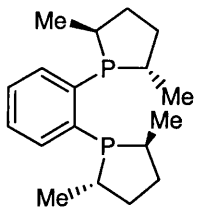
Figure 9: Bidentate phosphines used in the asymmetric intramolecular hydroacylation



***(S)*-BINAP**



***(S,S)*-CHIRAPHOS**



***(S,S)*-DUPHOS**

The diastereoselectivity of the intramolecular hydroacylation has been investigated with 3, 4-disubstituted and 3,3,4-trisubstituted 4-pentenals **109** (Table **3**).

The cyclisation of symmetrical 4-pentenal (Table **3**, entry 1) by a neutral [ClRh(*S*)-BINAP] catalyst afforded *cis*-3,4-disusbtituted (3*R*,4*S*)-cyclopentanone. Conversely, the cyclisation promoted by a cationic complex [Rh(*S*)-BINAP]$^+ClO_4^-$ (entry 2) afforded *trans*-3,4-disubstituted (3*R*,4*R*)-cyclopentanone. Consequently all stereoisomers of cyclopentanones bearing a chiral quaternary carbon centre could be obtained stereoselectively by judicious choice of rhodium catalyst (entry 3 and 4). However, in the case of neutral complexes, competitive decarbonylation occurs decreasing the yield in cyclopentanone.[66]

Table 3

109

Entry	R	[Rh]	Reaction time(h)	*cis/trans*	*ee* (%)	Yield	Abs. config.
1	H	[ClRh(*S*)-BINAP]	72	97/3	95	31 %	3*R*,4*S*
2	H	[Rh(*S*)-BINAP]$^+ClO_4^-$	1	4/96	>95	84 %	3*R*,4*R*
3	Me	[ClRh(*R*)-BINAP]	72	95/5	88	5 %	3*S*,4*R*
4	Me	[Rh(*R*)-BINAP]$^+ClO_4^-$	0.5	2/98	>95	83 %	3*S*,4*S*

3.4.1) Mechanistic studies

In order to explain the stereochemical outcome of the products, Sakai *et al* assumed that after oxidative addition of Rh(I) catalyst **114** into aldehyde **110**, the hydride was positioned *cis* to the BINAP ligand **111** (Scheme **43** and Figure **10**). On this assumption the carbon-carbon double bond of the olefin would coordinate *cis* to

the hydride ligand **112**; this would allow hydride-olefin insertion to give **113**. The carbon atom at the C(4)-position of pentenal **110** would locate *syn* to the hydride for the formation of the six-membered metallacycle **113** (Scheme **43**).[70]

Scheme 43

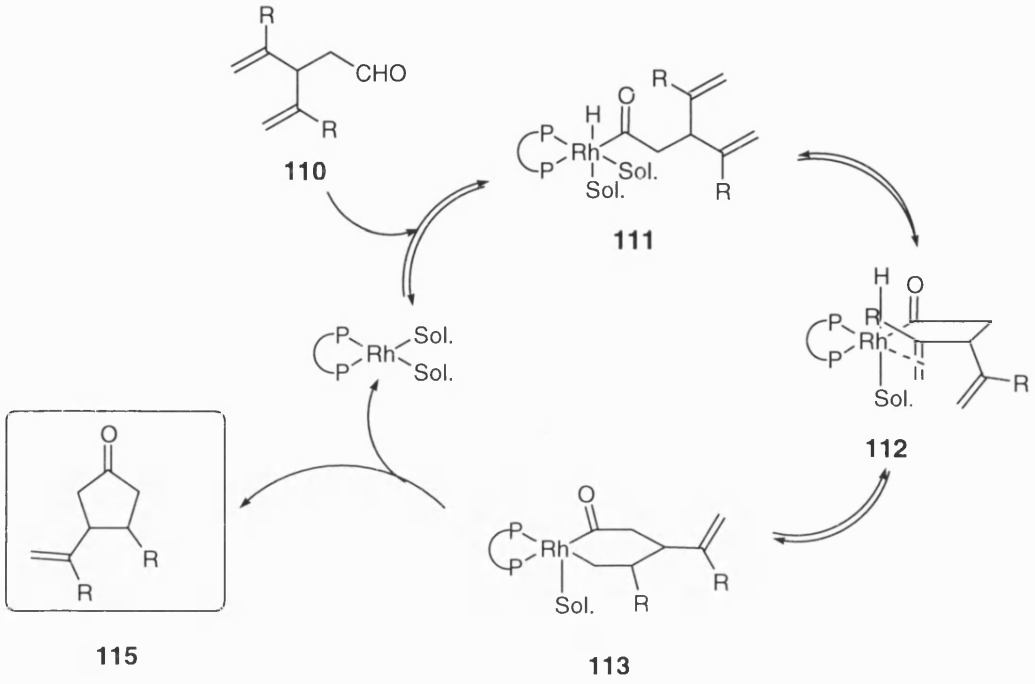
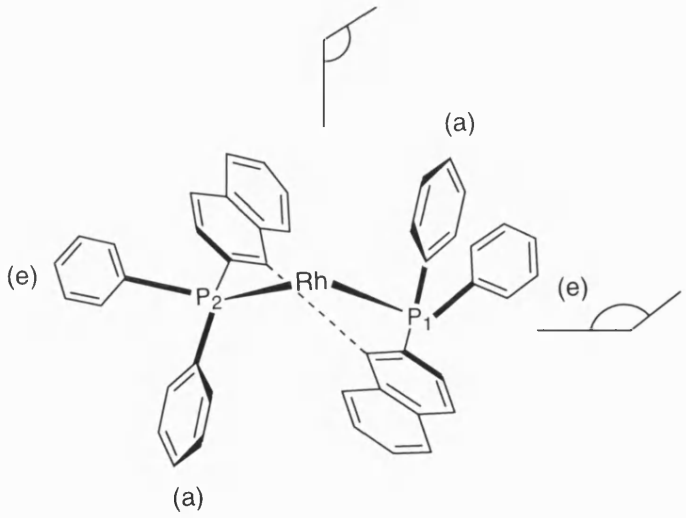


Figure 10



[Rh(*R*)-BINAP] 114

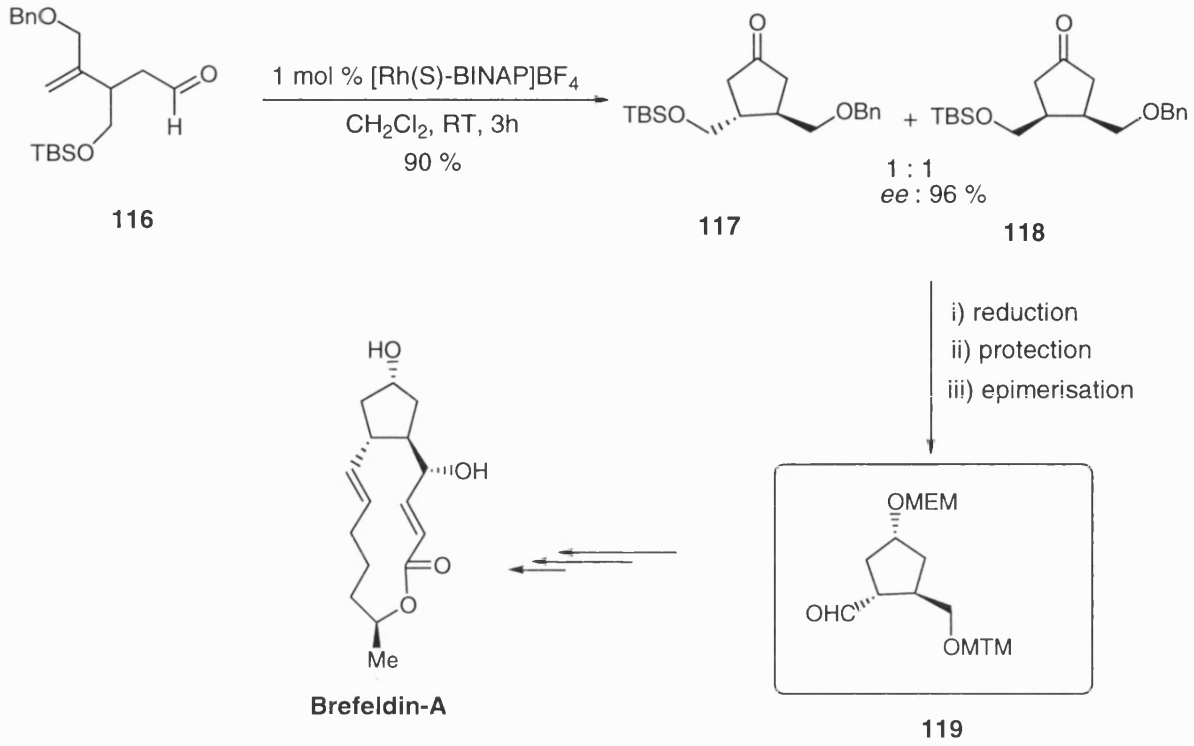
Steric factors favour the intermediates, which possess fewer repulsive interactions in the case of neutral Rh-complexes (thermodynamically preferred). In the case of cationic Rh-complexes, the cyclisation proceeds *via* the least stable intermediate. The rate of reductive elimination governs the enantioselectivity in this case.[66]

The proposed mechanisms of cyclisation were supported by Bosnich's deuterium labelling experiments, which showed numerous equilibrating intermediates that precede the final step to form cyclopentanone product. The enantioselectivity depends upon the relative rates of formation of the diastereomeric six-membered metallacyclic intermediates **113** and on their rates of reductive elimination to the cyclopentanone **115**; there might be no single enantioselective step (Scheme **43**). Therefore, a complex mixture of rates determines the enantiomeric excess obtained.[63,66]

3.4.2) Application

The stereoselective intramolecular hydroacylation reaction has recently been applied to the enantioselective synthesis of natural products and biologically active compounds.[74] Starting from racemic pentenal **116**, the intramolecular hydroacylation proceeded smoothly with only 1 mol % of cationic [Rh*(S)*-BINAP]$^{+}BF_4^{-}$ to afford a 1:1 mixture of *trans*-(3*R*,4*R*)-cyclopentanone **117** and *cis*-(3*R*,4*S*)-cyclopentanone **118** in high yield (90 %) and *ee*. Further elaboration lead to the key aldehyde synthon **119** of brefeldin-A (BFA). Brefeldin-A was found to have interesting biological activities including antitumor, antifungal and antiviral effects (Scheme **44**).[75]

Scheme 44

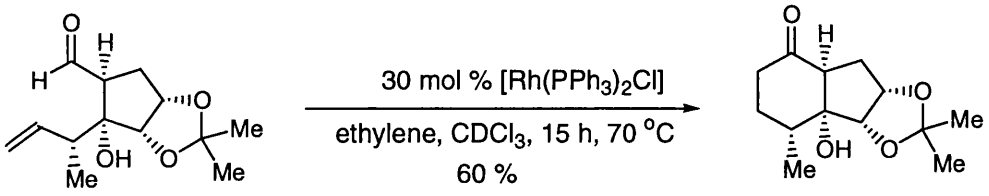


Although cyclopentanones are formed most readily using this hydroacylation strategy, application of this reaction to the synthesis of larger ring sizes would be a useful transformation.

3.5 Synthesis of 6-membered rings

Carbohydrates are important synthetic precursors to enantiomerically pure compounds because of their well-defined stereochemistry and availability. Gable *et al* reported that intramolecular hydroacylation of suitable derivatives can lead to new 6-membered carbocycles whose stereochemistry is derived from chiral sugar-based substrates like D-glucose. Allyl derivative **120** reacted with the indicated Rh(I) catalyst under 1 atm ethylene pressure to give cyclohexanone **121** in good yield (Scheme **45**).[76] The tolerance of Lewis basic sites is also noteworthy.

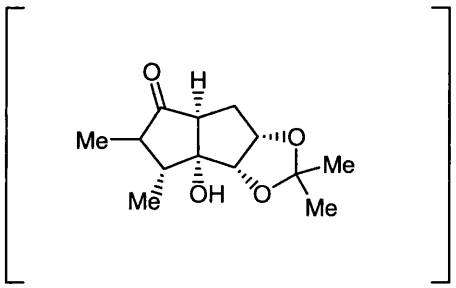
Scheme 45



120 **121**

However, this remains a rare example of a 6-membered ring formation.[77] Substitution of the vinyl group leads to competitive reactions, such as rearrangement and the *ene* reaction. A possible explanation for the formation of the cyclohexanone product **121** is the ring strain, which may inhibit the formation of the fused 5,5,5-tricyclic product **122** (Figure **11**).[76]

Figure 11



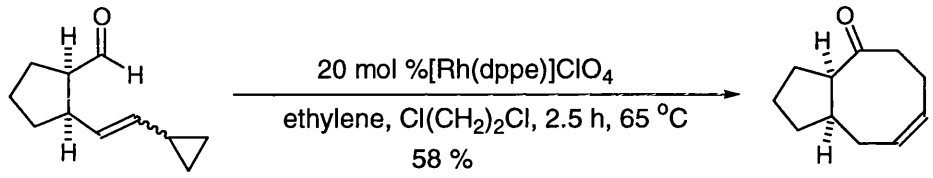
122

3.6 Synthesis of 8-membered rings

Application of the intramolecular hydroacylation reaction to the synthesis of medium-sized rings remains unexplored due to competitive decarbonylation as the ring size increases and to the prohibitively slow cyclisation rates for eight-membered rings. Recently, inspired by Wender[78] and Trost's[79] work on transition metal catalysed [5+2] cycloadditions towards seven-membered rings, Shair *et al* developed a strategy leading to cyclooctenones *via* intramolecular hydroacylation incorporating

cyclopropane ring fragmentation. Compound **123** in the presence of 20 mol % $[Rh(dppe)]^+ClO_4^-$ under an atmosphere of ethylene afforded the 5,8 fused ring system **124** in 58 % yield (Scheme **46**).[80]

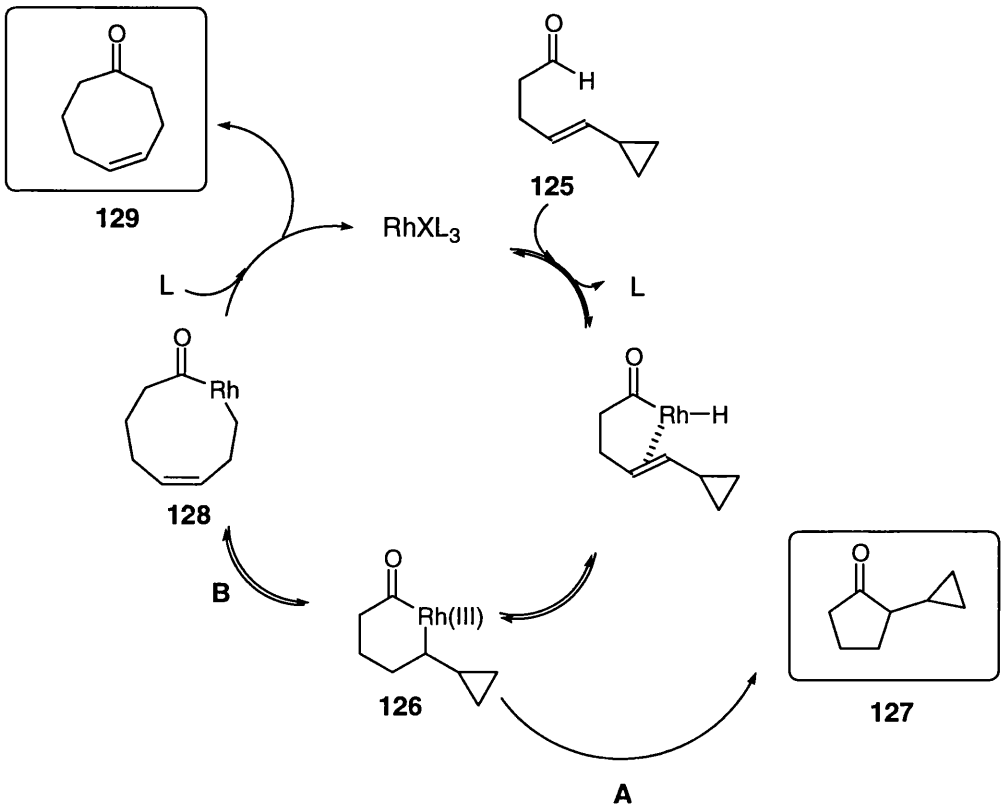
Scheme 46



123 **124**

A proposed catalytic cycle is depicted in Scheme **47**. The strategy relies on the presence of a cyclopropane ring capable of fragmentation **125**. From the six-membered Rh-metallacycle **126**, two pathways are possible. Reductive elimination (pathway **A**) is usually observed delivering cyclopentanone **127**. The presence of a cyclopropane ring adjacent to Rh(III) in **126** provides access to pathway **B**, leading to ring fragmentation and isomerisation affording nine-membered Rh-metallacycle **128**. Reductive elimination gives 4-cycloocten-1-one **129**. The relative rates of pathway **A** *versus* pathway **B** are influenced by the catalyst structure. Cationic Rh(I) catalysts were found to be superior to neutral catalysts for facilitating cyclopropane ring fragmentation (Scheme **47**).[80]

Scheme 47



3.7 Conclusion

Impressive levels of enantio- and diastereocontrol can be obtained in the cationic and/or neutral Rh(I) catalysed intramolecular hydroacylation of γ-δ,unsaturated aldehydes to provide cyclopentanones. Enantiomeric excess of up to 99 % can be readily achieved and it is now a well-established method of producing cyclopentanones. The scope of the cyclisation is limited to 3,4-substituted 4-pentenals only. With alternative substrates competitive decarbonylation becomes the major pathway. The intramolecular hydroacylation of 4-pentenals can also be achieved by using other transition metal complexes like cobalt[81] and ruthenium complexes,[82] although they still remain rare.

The intermolecular variants of hydroacylation remain an under-developed area due to the difficulty in overcoming the competitive decarbonylation process.

CHAPTER IV

Chapter IV

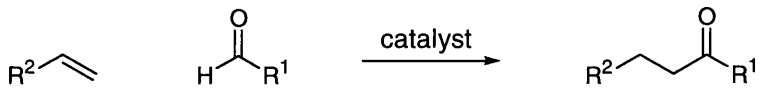
Chelation assisted Rh(I) catalysed intermolecular hydroacylation

This chapter reviews the literature on the intermolecular hydroacylation reaction of aldehydes and the chelation assisted process with aldimines, followed by our work toward 1-4,dicarbonyl-product synthesis via intermolecular hydroacylation of aldimines

4.1 Introduction

The selective activation of a C-H bond by a transition metal complex followed by the functionalisation of the activated substrate has been an area of intensive research (see chapter I). Hydroformylation, studied in chapter II, is one of the most useful applications of transition metal organometallics to organic synthesis. However, no corresponding process exists for hydroacylation; the addition of a generalised aldehyde to an olefin yielding ketone adducts **130** (Scheme **48**).

Scheme 48: Hydroacylation



130

As discussed in the previous chapter, hydroacylation is a useful synthetic method for obtaining ketones from aldehydes.

The most thoroughly studied examples of this reaction have been the intramolecular hydroacylations of 4-pentenals to generate cyclopentanones using a cationic Rh(I)

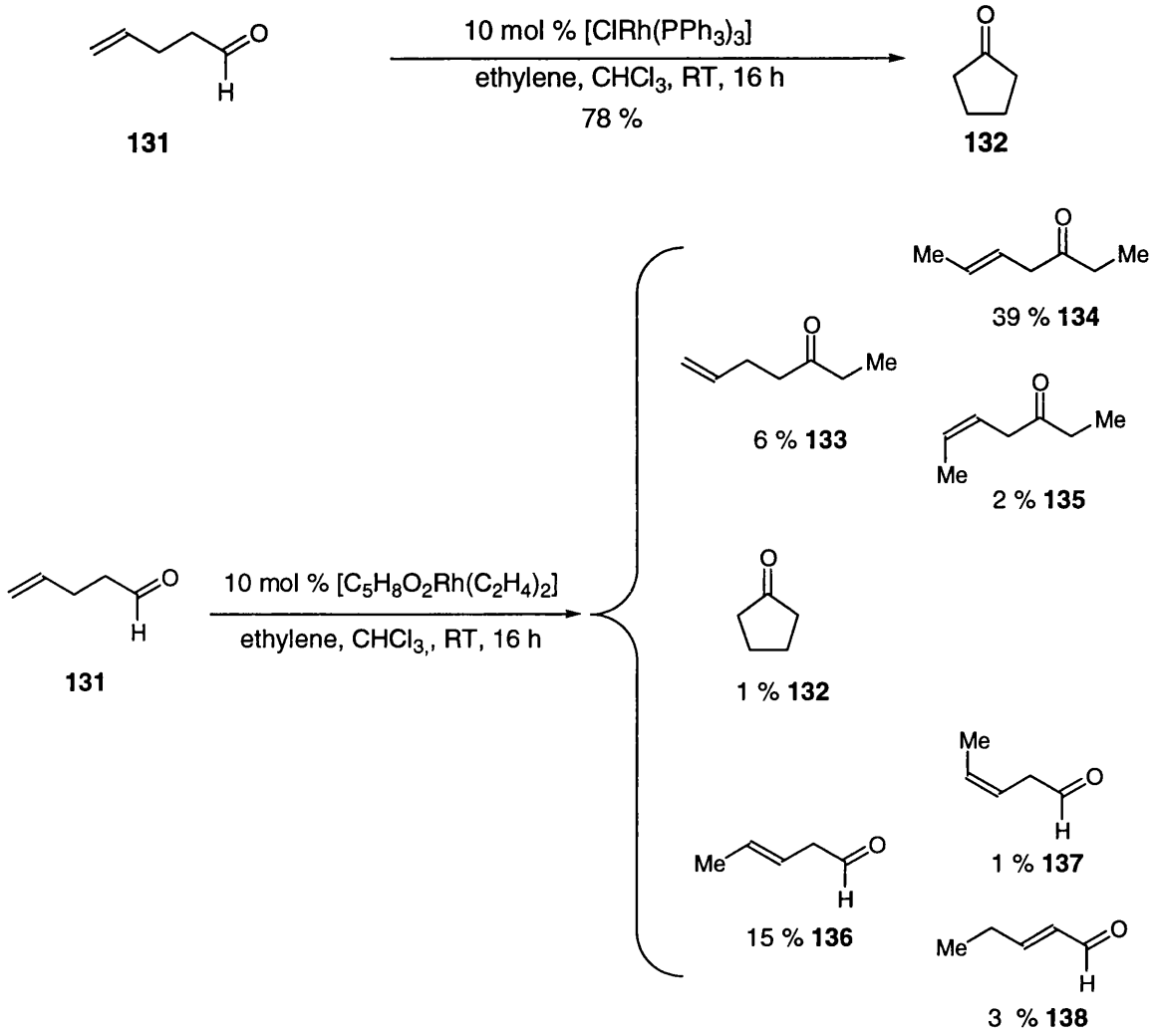
catalyst. To date this cationic catalyst system has proved to be specific for intramolecular hydroacylation (see chapter III).

4.2 Intermolecular hydroacylation: Precedents

The intermolecular process of hydroacylation has received little attention and only a few examples have been reported.[83,84,85,86] An early example of intramolecular *versus* intermolecular hydroacylation is shown below (Scheme **49**).[67]

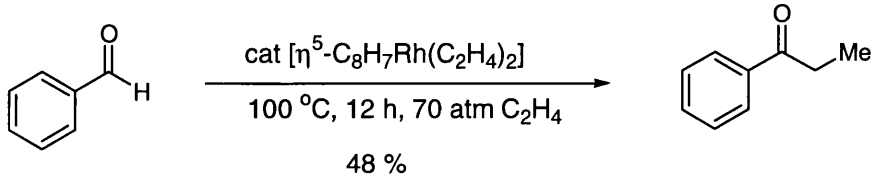
Treatment of 4-pentenal **131** with Wilkinson's catalyst in chloroform yields the cyclopentanone **132** *(intramolecular hydroacylation)*, whereas the reaction of **131** in the presence of $[C_5H_8O_2Rh(C_2H_4)_2]$ resulted in the catalytic generation of three heptenones, **133**, **134** and **135** *(intermolecular hydroacylation with double bond isomerisation)* together with three *double bond isomerisation* products **136**, **137** and **138**. An excess of ethylene gas was used in both cases to prevent catalyst deactivation by the competing decarbonylation reaction (Scheme **49**).[67]

Scheme 49



More recently Milstein *et al* reported the addition of benzaldehyde to ethylene with an indenylrhodium ethylene complex, $[\eta^5\text{-}C_8H_7Rh(C_2H_4)_2]$, under forcing reaction conditions (Scheme **50**).[86]

Scheme 50

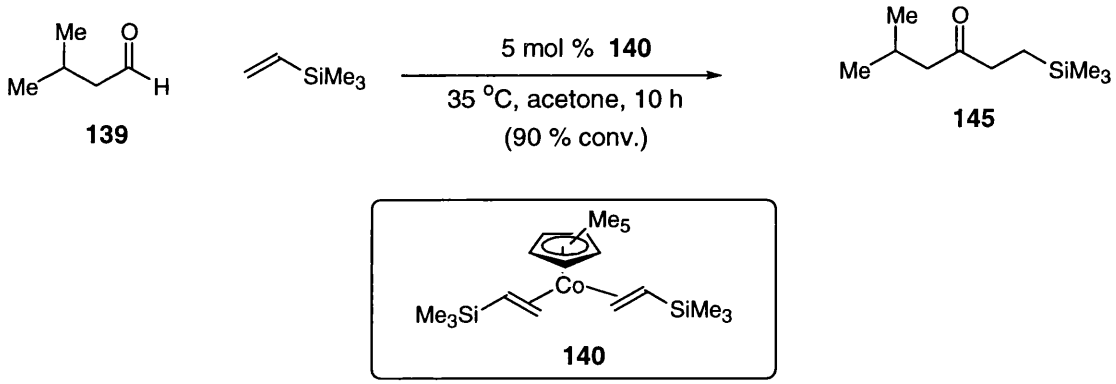


Beside rhodium complexes, intermolecular hydroacylations with other transition metals such as cobalt,[87,88] palladium,[89] ruthenium,[90] and nickel,[91] have been reported.

4.3 Cobalt-catalysed intermolecular hydroacylation

Although an impressive conversion as monitored by ^{1}H NMR was obtained in the cobalt-catalysed intermolecular hydroacylation of isovaleraldehyde **139** with vinyltrimethylsilane under mild conditions, the use of cobalt complex **140** is limited (Scheme **51**). The intermolecular hydroacylation using this catalyst is restricted mainly to electron rich aromatic aldehydes in combination with vinylsilanes.[88]

Scheme 51

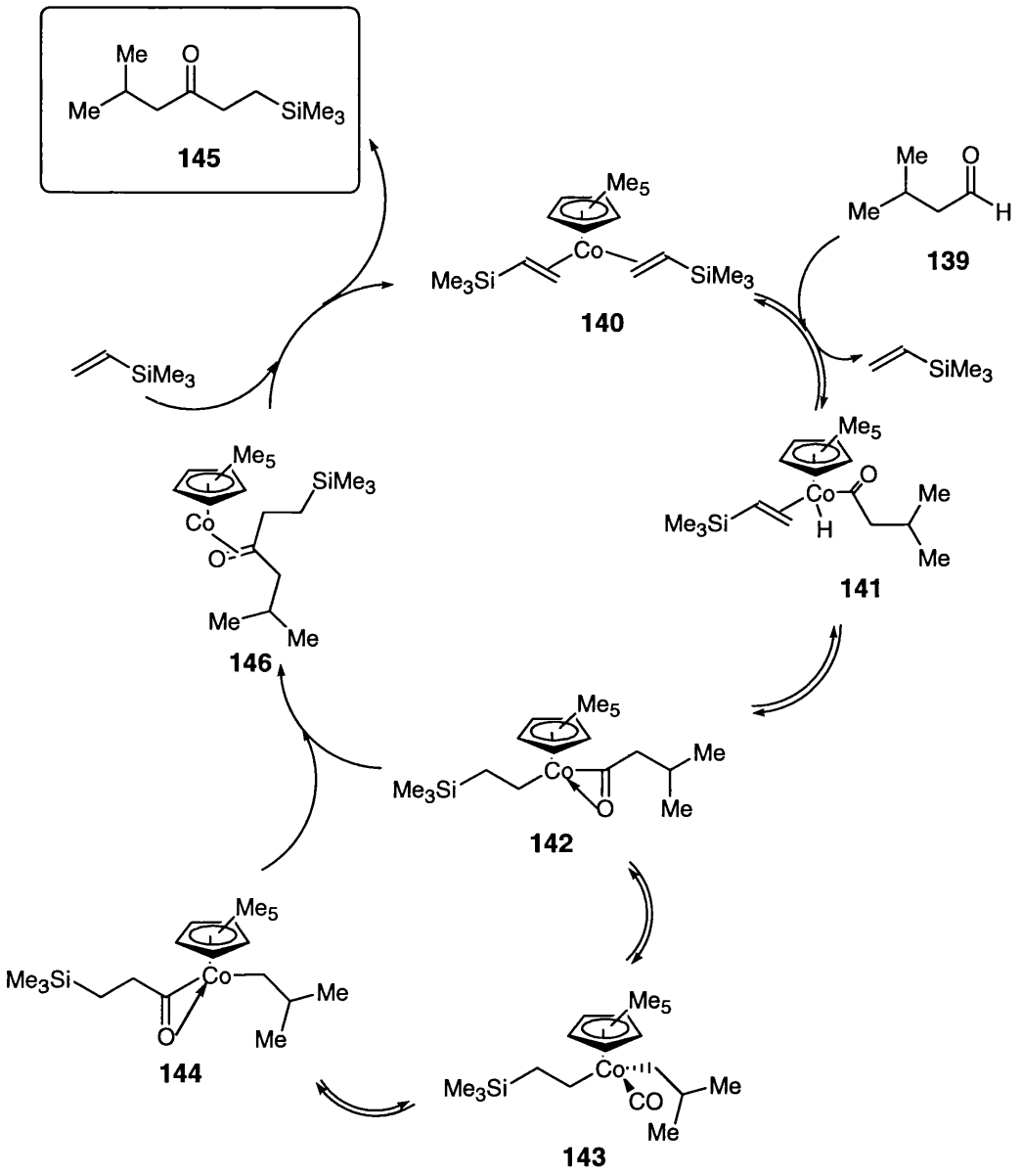


4.3.1) Mechanism

Kinetic investigations into the turnover process of the cobalt-catalysed system have been carried out with isovaleraldehyde **139**. The authors proposed the following mechanism for intermolecular hydroacylation of trimethylvinylsilane with isovaleraldehyde **139** catalysed by **140** (Scheme **52**).[87] Oxidative addition of **139** to cobalt(I) complex **140** gives the acyl hydride intermediate **141**. Hydride migration gives intermediate **142**, which is in equilibrium with the bisalkyl carbonyl cobalt(III) complex **143**. Insertion of CO into either Co-C bond generates alkyl acyl

intermediates **142** and **144** which can undergo reductive elimination to form the corresponding ketone **145**. The results showed that reductive elimination is not assisted by the olefin and occurs under these conditions from a 16-electron, possibly solvated intermediate **146**, or from an 18-electron η^2-acyl intermediate **142** or **144**.[87]

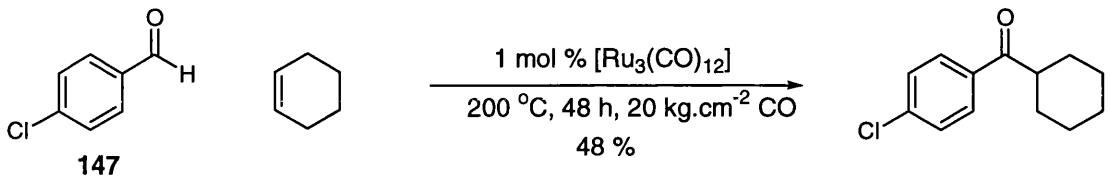
Scheme 52



In the cases of Ru, Pd and Ni-catalysed intermolecular hydroacylation the reaction conditions are required to be forcing. A high pressure of CO or ethylene is necessary

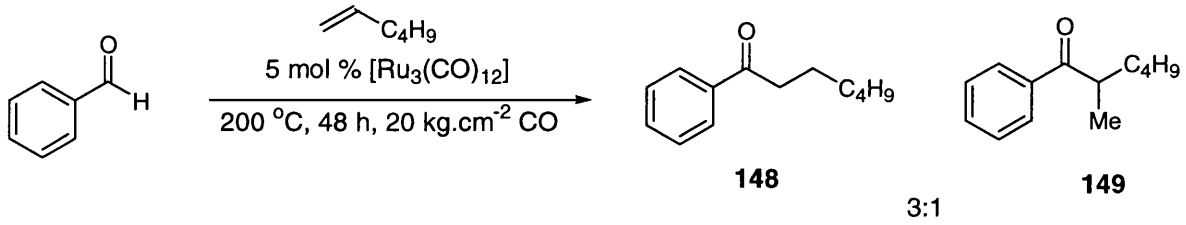
in order to prevent the competitive decarbonylation reaction resulting in poor to moderate yields. The addition of cyclohexene to *p*-chlorobenzaldehyde, Scheme **53** below, is a representative example of such a procedure.[92]

Scheme 53



Under such forcing conditions, acyclic olefins such as 1-hexene, react with benzaldehyde under Ru-catalysis to give rise to a mixture of regioisomers **148** and **149** in a 3:1 ratio (Scheme **54**).[93]

Scheme 54

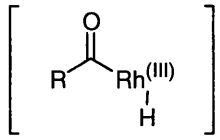


4.4 Intermolecular hydroacylation: Limitations

The ketone products obtained from intermolecular hydroacylation of sp^2-hybridised centres continue to represent a challenge. Rhodium is the metal of choice for such a process as the use of Ru, Pd or Ni is limited by the need for harsh reaction conditions (high pressure of CO or ethylene).[86] The main limitation of the Rh reaction is the instability of the proposed hydrido-acyl metal intermediate **150** which favours the competitive decarbonylation (Figure **150**).[62]

The challenge of intermolecular hydroacylation lies in the stabilisation of this intermediate **150** to allow hydrometallation of olefins to take place (Figure **12**).

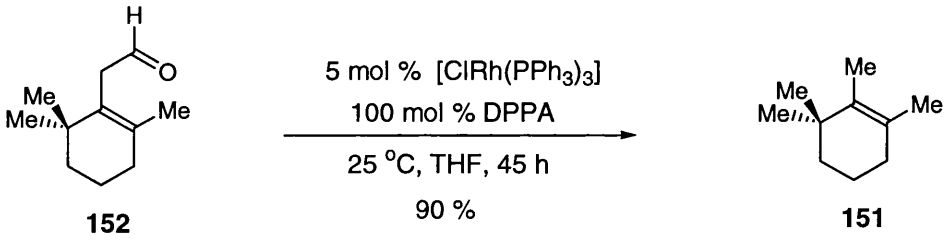
Figure 12



150

This is a considerable challenge as the Rh catalysed decarbonylation has been developed as a synthetic procedure.[94] Scheme **55** gives an example of the synthesis of cyclohexene **151** from primary aldehyde **152** *via* decarbonylation catalysed by Wilkinson's system and diphenylphosphoryl azide.[94]

Scheme 55



152 **151**

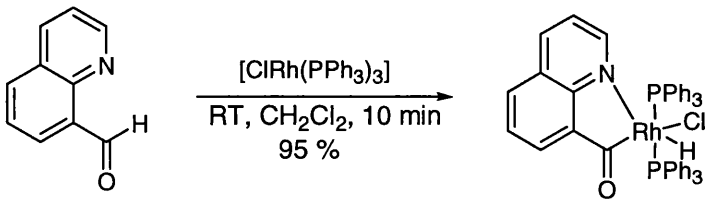
DPPA = diphenylphosphoryl azide

4.5 Chelation assisted intermolecular hydroacylation

4.5.1 Stoichiometric studies

The hydrido-acyl intermediate **153** was isolated for the first time in 1978, after oxidative addition of Wilkinson's catalyst to 8-quinolinecarboxaldehyde **154** (Scheme **56**).[64]

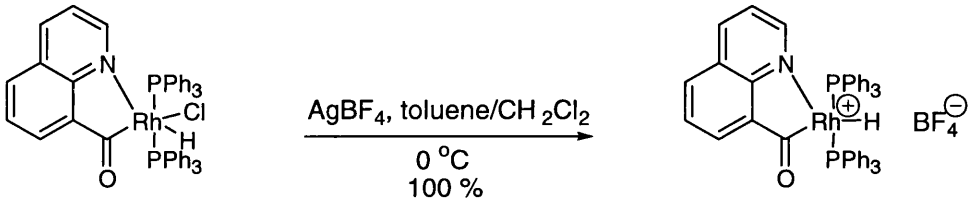
Scheme 56



154 **153**

Treatment of **153** with $AgBF_4$ gave rise to coordinatively unsaturated rhodium salt **155** (Scheme **57**); although a vacant site is available, the complex is stable at room temperature. However, decarbonylation was observed at elevated temperatures.[64]

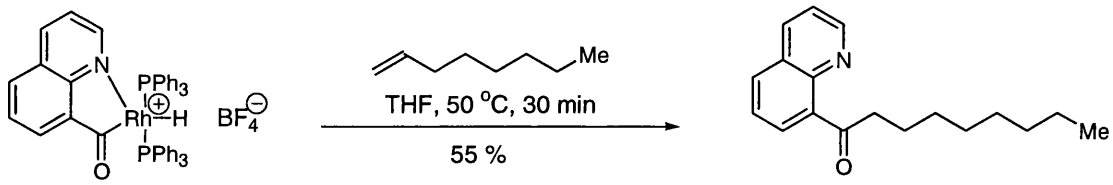
Scheme 57



153 **155**

Treatment of a THF suspension of cationic complex **155** with excess 1-octene gave hydroacylation product **156** in reasonable yield in a mixture with isomerised 3- and 4-octenes (Scheme **58**).

Scheme 58

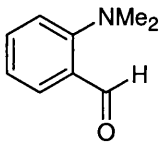


155 **156**

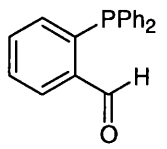
The reaction is regioselective with solely the anti-Markovnikov product **156** being isolated. The stability of intermediates **153** and **155** is explained by *cyclometalation.* The presence of a nitrogen atom in the side chain of the aldehyde substrate gives a five-membered metallacyclopentane (Scheme **56** and **57**). Thus extra coordination to the metal centre led to a coordinatively saturated, 18-electron complex, retarding acyl to alkyl rearrangement as well as reductive elimination to the starting aldehyde. Such a cyclometalated complex has also been observed with palladium.[95]

A similar type of chelation-assisted aldehyde C-H activation has been reported in the case of 2-dimethylaminobenzaldehyde **157** and 2-diphenylphosphinobenzaldehyde **158** using Ir(I) and Pd(II) complex precursors (Figure **13**).[96] The utility of these coordinating groups has already been discussed in detail (see Chapters I, II and III). Such aldehydes have been used successfully in hydroacylation reactions; the metal can be placed in the correct position prior to C-H activation *via* coordination. The resulting five membered metallacycles **159** and **160** are stable and can undergo olefin hydrometallation followed by reductive elimination to give the ketone products (see Chapters I, II and III).

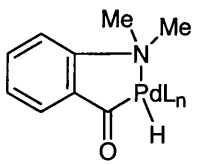
Figure 13



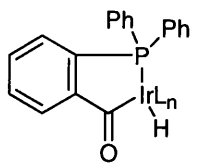
157



158



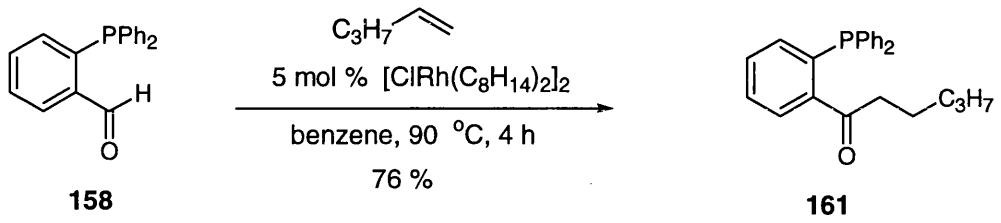
159



160

An example of this type of process is shown below; 1-pentene reacted with 2-diphenylphosphinobenzaldehyde **158** using a catalytic amount of Rh(I) complex to give the corresponding ketone **161** as a single regioisomer in good yield (Scheme **59**).[97]

Scheme 59



158 **161**

The limitations of such substrates include complex methods for their syntheses and associated handling difficulties. In the case of 2-diphenylphosphinobenzaldehyde **158** the phosphorus atom is easily oxidised leading to a complex mixture of hydroacylation adducts. **157** and **158** are not useful candidates for use in the development of a synthetically viable hydroacylation reaction.[97]

4.5.2) Conclusion

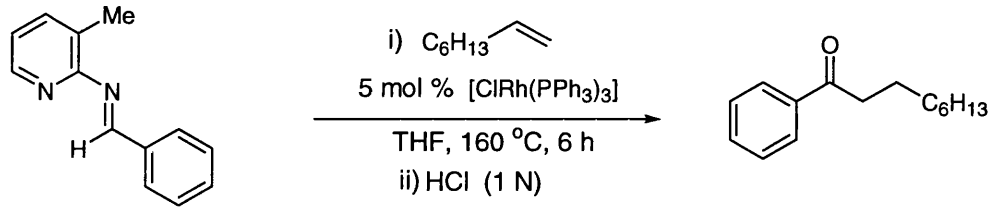
From these results it appears that either of two conditions must be met for successful reaction. Either forcing reaction conditions with high-pressure ethylene and/or CO are needed or a 1,5-relationship between a potential coordinating group and the aldehyde C-H bond is necessary. Direct intermolecular hydroacylation *via* cyclometalation could be applied to specific substrates only. An indirect but related method for the synthesis of ketones from aldehydes has also been investigated with aldimines.[98] This process allows the concept of intermolecular hydroacylation to be applied to a generalised aldehyde once it is converted into a suitably substituted

aldimine derivative where a 1,5-coordinating relationship exists between the C-H bond to be activated and the coordinating group *(chelation assisted process).*[98]

4.6 Intermolecular hydroacylation with imines: Catalytic studies

Suggs demonstrated the potential of such an approach in 1979. Aldimine **162** is used as an activated aldehyde equivalent. Intermolecular hydroacylation with 1-octene using Wilkinson's complex, followed by acid hydrolysis of the resulting ketimine intermediate gives ketone **163** (Scheme **60**).[98]

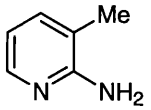
Scheme 60



162 **163**

Although the conversion is low, (only 10 % of product **163** was isolated after hydrolysis) the use of aldimines bearing a chelating group, such as those originating from 2-aminopicoline derivatives **164** (Figure **14**), has broadened the scope of chelation-assisted hydroacylation to general aldehydes rather than simply 8-quinolinecarboxaldehyde **154**.

Figure 14: **2-amino-3-picoline 164**

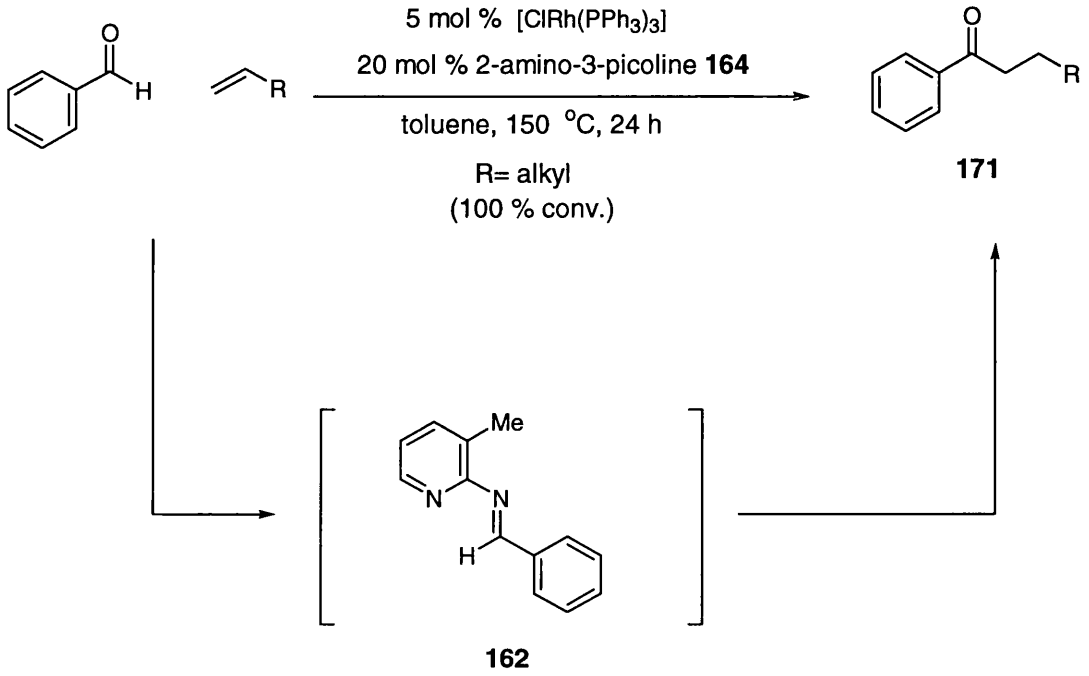


164

Until recently no practical direct intermolecular hydroacylation had been reported. Jun *et al* have described the use of a reaction system employing Wilkinson's complex

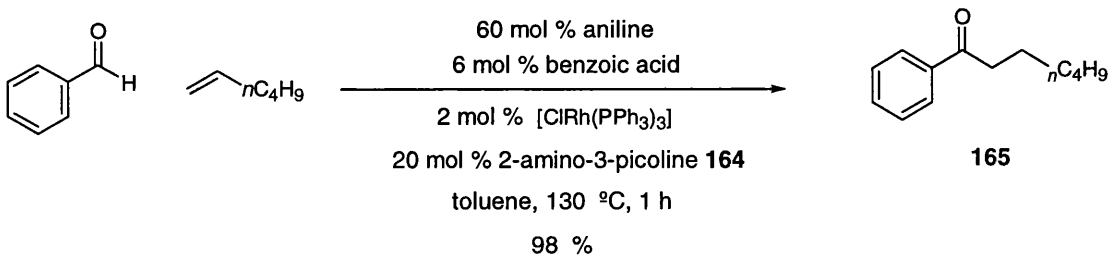
and 2-aminopicoline **164** as cocatalysts that allows hydroacylation of 1-alkenes to proceed (Scheme **61**).[99,100] The key feature is the *in situ* formation of Suggs' aldimine **162**, an intermediate that suppresses decarbonylation.[101]

Scheme 61



Amongst various catalyst systems tested, Rh(I) complexes containing electron-rich phosphine ligands like Wilkinson's catalyst were the most efficient. It was found that the reactivity in the hydroacylation reaction depicted in Scheme **61**, is improved when the starting benzaldehyde is contaminated with benzoic acid. The benzoic acid is assumed to catalyse the condensation of benzaldehyde with amine **164** to generate the imine **162**. When 60 mol % of aniline is used as an additive a further enhancement of the reaction rate was observed (Scheme **62**). 1-alkyl-substituted olefins are well tolerated under the reaction conditions depicted in Scheme **62** and gave rise to hydroacylation product **165** in good yield.[100]

Scheme 62

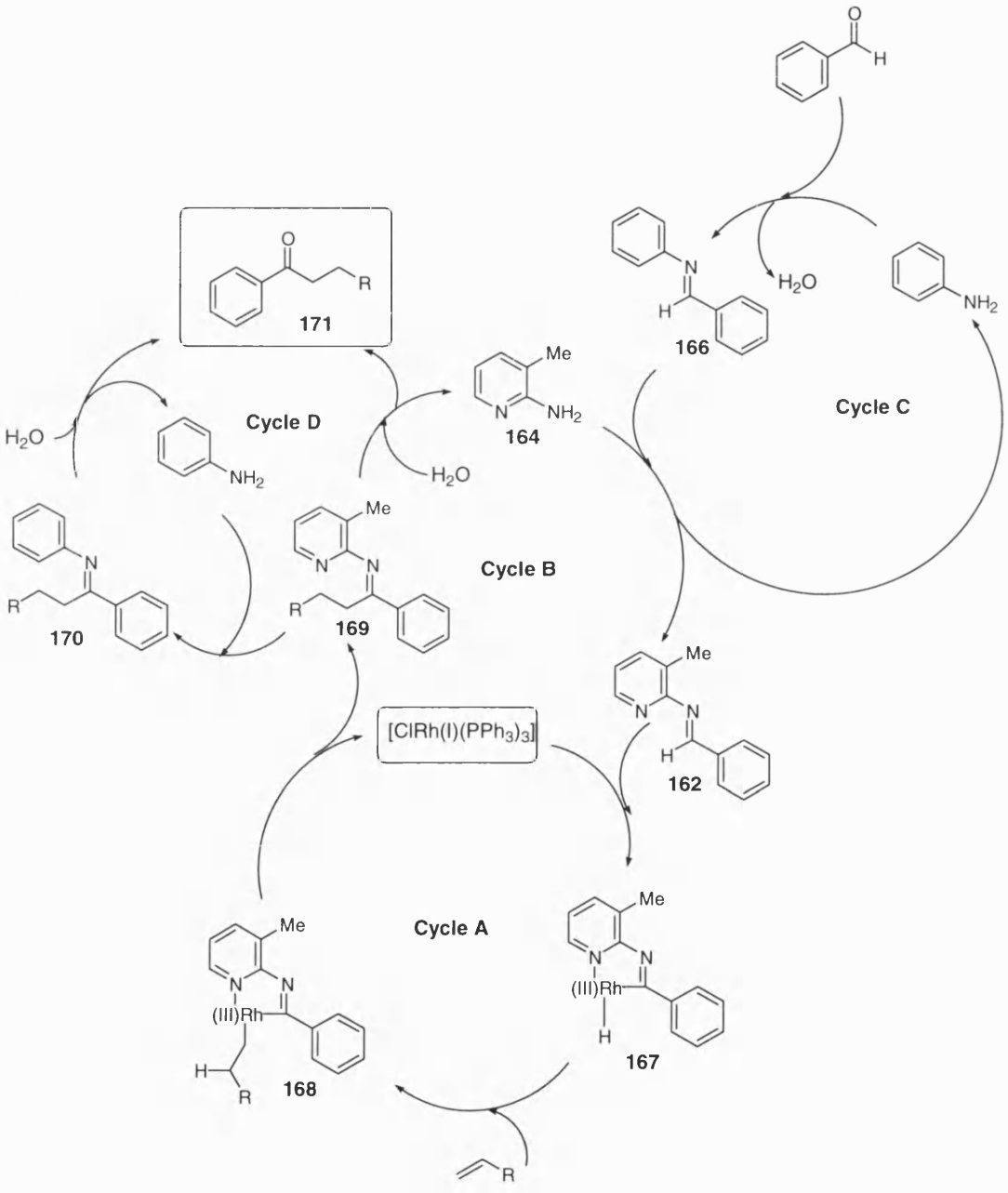


4.6.1) Mechanism

A postulated mechanism for the above transformation is given Scheme **63**.[100] Cycle **A** represents the mechanism for the catalyst system consisting of imine **162** and Wilkinson's catalyst. Cycle **B** represents the catalytic system regenerating cocatalyst 2-amino-3-picoline **164**. Cycles **C** and **D** represent the catalytic systems using aniline. Condensation of benzaldehyde with aniline catalysed by benzoic acid gives imine **166**, followed by transimination with picoline **164** to give **162**. Imine **162** coordinates *via* the nitrogen atom to the rhodium complex followed by oxidative addition to give metallacycle **167**. Olefin coordination and hydrometallation gives alkyl-acyl Rh(III) intermediate **168.** Reductive elimination regenerates Wilkinson's catalyst along with ketimine **169**. Two pathways are considered for **169**; transimination into ketimine **170** and/or direct hydrolysis to ketone product **171**. Ketimine **170** is also hydrolysed into **171**. Kinetic studies have demonstrated that benzaldehyde condensation with aniline **(Cycle C)** is faster than the direct reaction of picoline **164** with benzaldehyde in presence of benzoic acid. Benzoic acid was also found to catalyse the transimination processes. A similar reaction namely semicarbazone formation from carbonyl compounds catalysed by aniline in acidic media was previously reported.[102] This process, known as nucleophilic catalysis, consists of the initial formation of the imine compound and consecutive transimination with semicarbazide to form the semicarbazone.[102] Transimination of imine **166** with picoline **164** is more facile than

the direct condensation of benzaldehyde with **164**.[100] It was found that under similar reaction conditions without the aniline and benzoic acid additives the reaction is very slow. For example, after a 1-hour reaction time only 6 % of product **171** is observed in GC. Internal olefins such as 2-pentene or cyclohexene failed to undergo hydroacylation.[100]

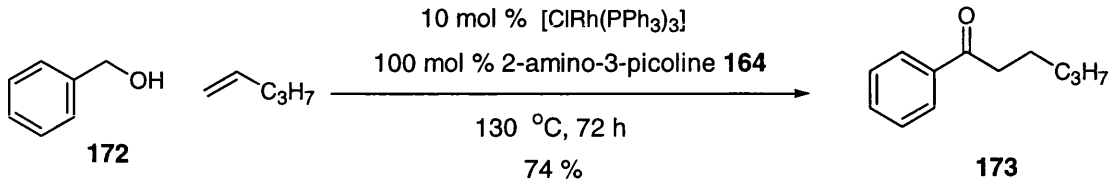
Scheme 63



4.6.2) Application to direct synthesis of ketones from primary alcohols

Recent results from the Jun laboratory have investigated the direct reaction of primary alcohol **172** giving ketone **173** in a one-pot reaction in excellent yield (Scheme **64**).[101,103]

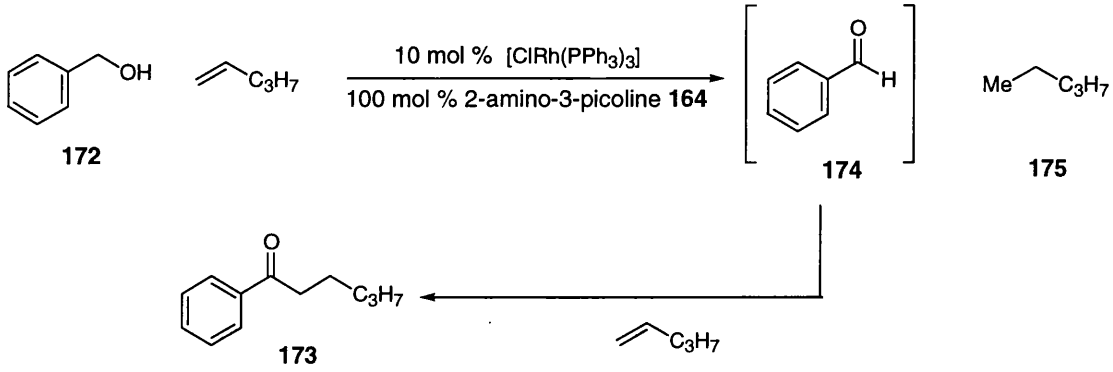
Scheme 64



172 **173**

This is the first example of direct ketone synthesis from a primary alcohol and 1-alkene under Rh(I) catalysis. The reaction proceeds without the need of solvent. A possible explanation for such a reaction is given below: The first step involves oxidation of benzyl alcohol **172** to benzaldehyde **174** *via* hydrogen transfer to 1-pentene to give pentane **175** (Scheme **65**). *In situ* trapping of the formed aldehyde **174** by 2-amino-3-picoline **164** gave condensation product aldimine **169** and water. Subsequent *chelation assisted hydroacylation* with 1-pentene as described in the previous section and *in situ* hydrolysis by H_2O formed during the reaction affords regioselectively the linear ketone **173** as the final product (Scheme **65**).[103]

Scheme 65

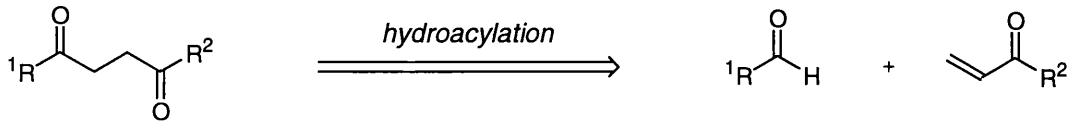


172 **174** **175** **173**

4.7 Perspectives

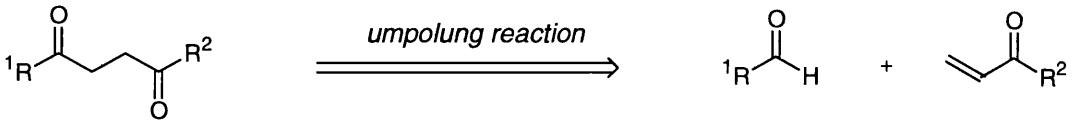
The majority of intermolecular hydroacylation reactions reported to date utilise unfunctionalised olefins as substrates thus generating simple ketones as products. We speculated that the use of alkenes substituted directly with either an ester or ketone group would provide direct access to the synthetically challenging 1,4-dicarbonyl arrays (Scheme **66**).

Scheme 66



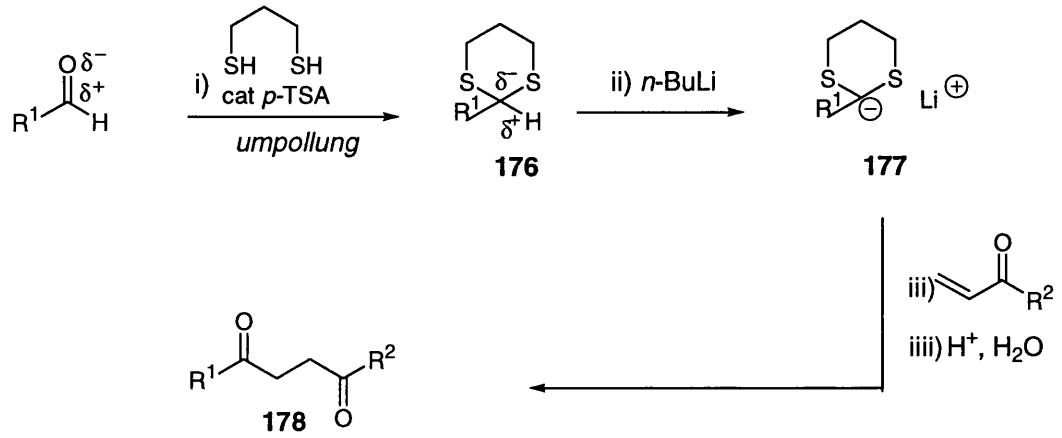
These 1,4-difunctionalised motifs are synthetically useful intermediates for the preparation of substituted furans,[104] butyrolactones[105] and succinate derivatives.[106] Such 1,4-dicarbonyl systems are traditionally obtained from a multistep umpolung approach (Scheme **67**).

Scheme 67



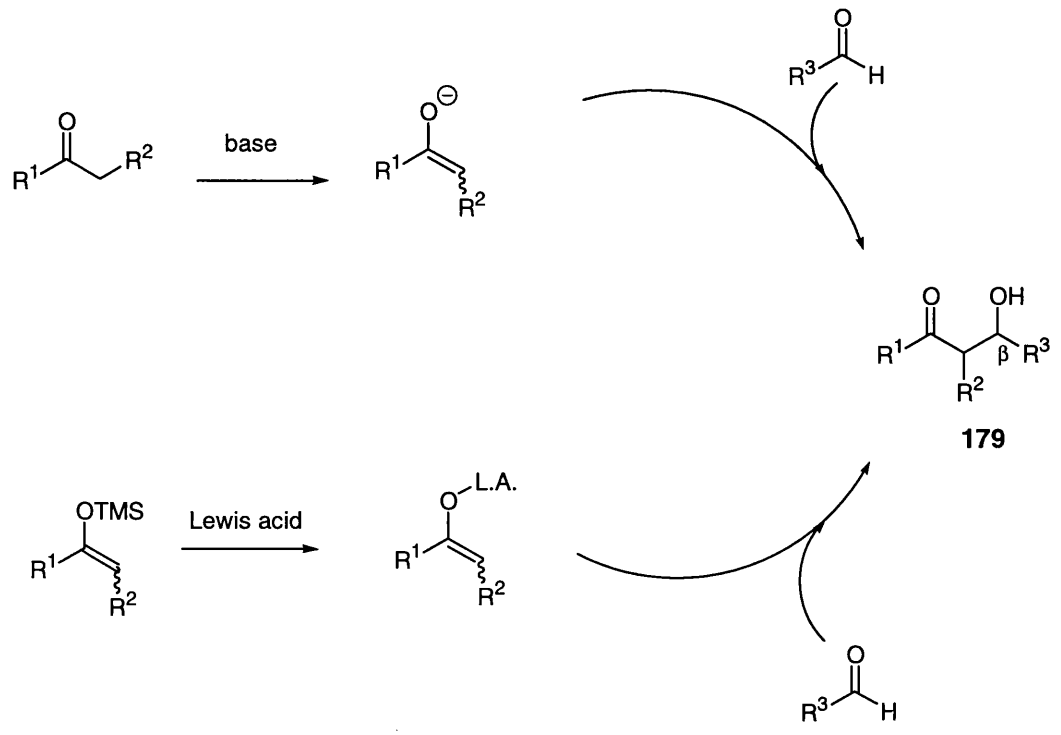
As reported previously 1,4- dicarbonyl systems are not straightforward to prepare; the approach presented here can be considered as the equivalent of an acyl-anion addition to an enoate (Scheme **68**).[107,108] An example of such an umpolung reaction is given below (Scheme **68**). The condensation of aldehydes with dithiols under acid catalysis gives thioacetals **176**. The acyl-anion equivalent **177** generated by treatment with *n*-butyllithium reacts with α-β-unsaturated ketone by a [1,4] Michael addition to give after hydrolysis the corresponding 1,4-dicarbonyl adduct **178**.

Scheme 68



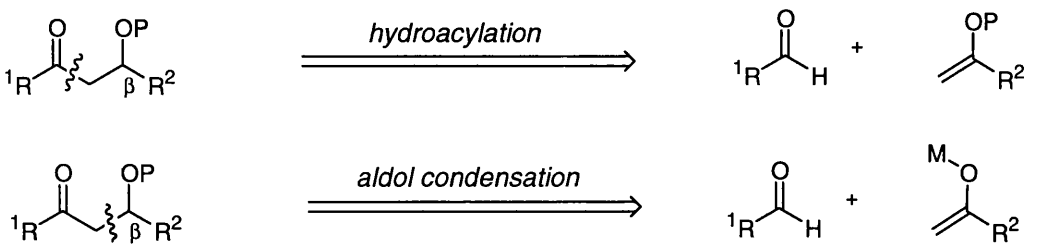
α,β-Unsaturated ketones and esters are examples of electron poor alkenes. We also considered that it would be interesting to investigate the use of electron rich olefins. The use of enol ethers as electron rich olefins would provide direct access to the aldol moiety **179** (Scheme **69**). The numerous examples of the use of the aldol addition reaction in complex synthesis are testament to its general utility and practicability.[109,110] However there are cases in which it is not feasible to use a traditional aldol reaction, particularly if one of the reaction substrates is labile to basic conditions. The advent of the Lewis acid catalysed addition of enol silanes to aldehydes by Mukaiyama went someway to solving this problem, although in this system the reaction is now conducted in formally acidic conditions.[111]

Scheme 69



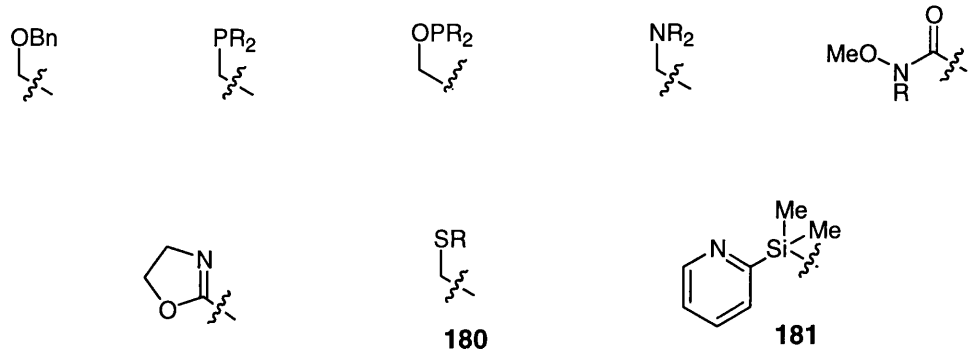
It would be desirable to achieve an aldol type bond construction under truly neutral conditions. In recent years there has been considerable effort devoted to developing catalytic enantioselective versions of both types of aldol reaction and there have been some impressive successes,[112] particularly with the Mukaiyama systems that employ chiral Lewis acids.[113] One limitation of such systems is the relatively high catalyst loadings (typically 10 mol %) that are generally employed. An attractive alternative to the aldol addition reaction is the metal catalysed hydroacylation of enol ethers (Scheme **70**). Such a system would be performed under neutral conditions. The aldol unit, *i.e.* a β-hydroxyketone, would be formed by construction of the alternative C-C bond to that formed in a traditional aldol reaction, this necessitates the joining of the reversed coupling partners and as such will be beneficial if an enolate (or enol silane) of a certain compound is not readily accessible (for example if it was base sensitive).

Scheme 70



We proposed to study the hydroacylation of both electron poor and electron rich alkenes and to employ chelation-assisted hydroacylation methodology in order to prevent the competitive decarbonylation reaction. Thus a heteroatom group present in the side chain of the aldehyde substrate would direct the catalyst to the site of C-H insertion and stabilise *via* cyclometalation the acyl-metal intermediate as previously reported. The possibility also exists for this directing group to act as a control element for further diastereo- and enantioselection. This chelating group might also serve as a synthetically useful handle for further elaboration. The functional groups shown below all effectively coordinate late transition metals.[35,114] Thioether **180**[115,116] and 2-pyridyldimethylsilyl **181** group[117] have recently been reported as effective directing groups in the platinum catalysed hydrosilylation of olefins (Figure **15**).

Figure 15



180 **181**

CHAPTER V

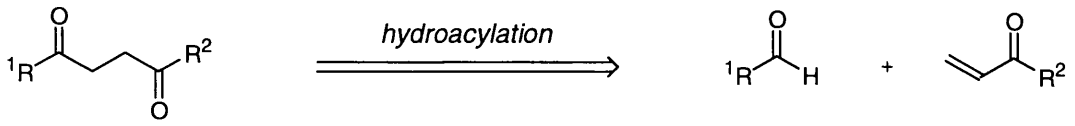
Chapter V

Results and Discussion

5.1 Introduction

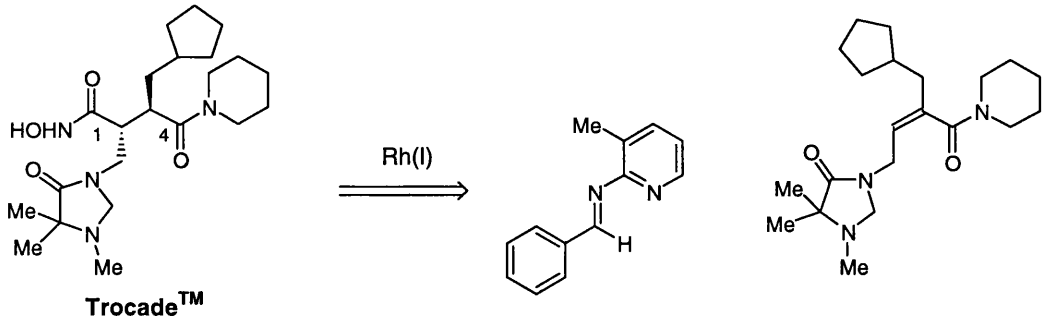
To assess the feasibility of intermolecular hydroacylation reactions with functionalised alkenes, we elected to study the reaction of imine **162** as an aldehyde equivalent and thus limit decarbonylation. In order to avoid the *in situ* imine formation which has been shown to be the rate determining step in the Jun hydroacylation system, hydroacylation reactions were studied on isolated imine substrates.[101] Thus the reaction of imine **162** with a suitably substituted electron-poor alkene under Rh(I) catalysed hydroacylation conditions followed by aqueous work-up would afford 1,4-dicarbonyl moieties (Scheme **71**).

Scheme 71



Such a 1,4-dicarbonyl moiety is present in numerous natural products.[108] An example is given below with the synthesis of Trocade™ **182** (Scheme **72**), a selective inhibitor of matrix metalloproteases (MMPs) currently undergoing Phase III clinical trials for the treatment of rheumatoid arthritis.[118] A synthetic route to such a 1,4-dicarbonyl synthon could be envisaged *via* an intermolecular hydroacylation of imine **162** with a suitably substituted olefin partner **183** (Scheme **72**).

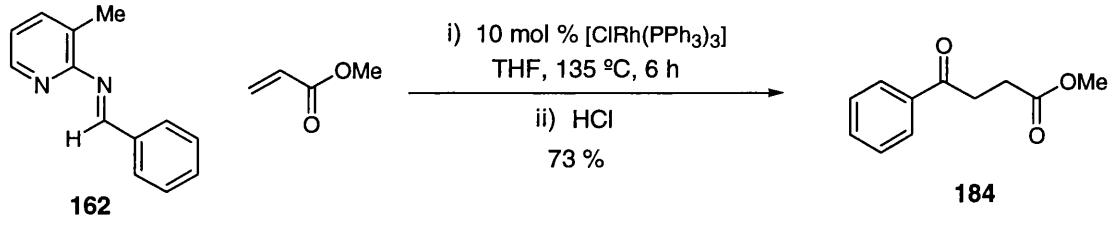
Scheme 72



5.2 Intermolecular hydroacylation with electron poor olefins

Our early investigations focused on the use of imine **162** and simple electron poor alkenes. Initially, imine **162** was reacted with methyl acrylate in presence of 10 mol % of Wilkinson's catalyst in THF at 135 °C in a sealed tube. Pleasingly, after hydrolysis using aqueous 1 N hydrochloric acid, the desired hydroiminoacylation adduct **184** was obtained in good yield (Scheme **73**). To our knowledge this is the first example of intermolecular hydroacylation with electron-poor olefins.

Scheme 73

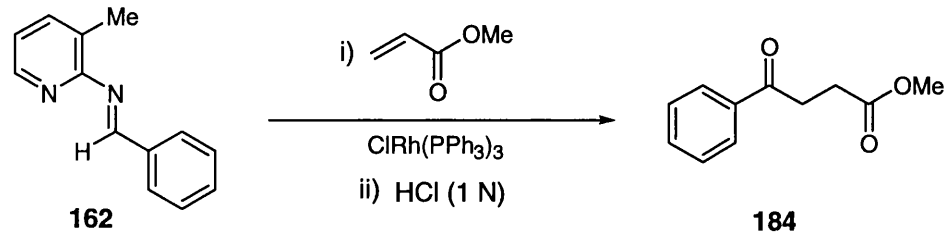


5.2.1) Reaction conditions: Studies

To investigate the optimum conditions for the Rh(I) catalysed intermolecular hydroacylation with electron poor olefins, the reaction of imine **162** with methyl acrylate was performed under a variety of conditions, which included the use of

different solvents, catalyst loadings, reaction temperatures and reaction times (Table **4**).

Table 4: **Intermolecular hydroacylation of 162 with methyl acrylate, reaction conditions studies**



162 **184**

Entry	Solvent	Catalyst loading	Reaction time	T ºC	Yield
1	THF	10 mol %	6 h	135	73 %
2	THF	10 mol %	4 h	135	59 %
3	THF	10 mol %	7h	70	38 %
4	THF	5 mol %	6 h	135	47 %
5	Toluene	10 mol %	6 h	135	56 %
6	Cl-Benzene	10 mol %	6 h	135	9 %
7	Dioxane	10 mol %	2 h 45	135	74 %

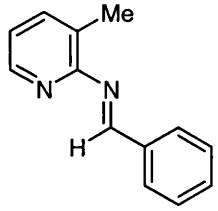
All the conditions outlined in Table **4** provided the 1,4-dicarbonyl adduct **184**. Using apolar solvents such as toluene, the reaction was not complete after 6 hours, with 56 % of the desired hydrolysed product **184** obtained (Table **4**, entry 5). The reaction efficiency decreases more dramatically with chlorobenzene with only 9 % of **184** being isolated (entry 6). When THF was used the reaction occurred much faster. A 4 hours reaction time with THF gave similar conversion compared to toluene after 6 hours (Table **4**, entry 2 and 5). The ^{1}H NMR spectrum of the crude compound obtained from the reaction using THF was cleaner than the one obtained from toluene, in which a more complex reaction mixture is produced. Lowering the reaction temperature to 70 °C with THF as solvent resulted in a less efficient process; after 7 hours reaction time, less than half of the starting material imine **162** was consumed

(entry 3). Similarly, lowering the catalyst loading to 5 mol % gave poorer conversion (entry 4). The use of dioxane was found to increase the reaction rate; the reaction is complete within less than 3 hours and 74 % of product **184** was isolated.

5.2.2) Enoates and alkyl substituted olefins as coupling partner

In order to test the generality of the process with regard to functional group tolerance, a range of substituted enoates and alkyl-substituted olefins were evaluated in the reaction with imine **162** under the conditions described above, involving heating a THF solution of the substrates at 135 °C for 6 hours with 10 mol % catalyst (Table **5**). Under these conditions it was found that a variation in the ester group is tolerated well, with Me and ^{t}Bu esters both delivering the expected adducts in good yields (Table **5**, entry 1 and 3). In addition entry 4 demonstrates the tolerance towards amides with *N,N*-dimethyl acrylamide generating the corresponding product in 74 % yield. Surprisingly, phenyl acrylate was found to be less effective to react under these reactions conditions delivering the required product in 27 % yield (entry 2). Alkyl substituted terminal olefins are also well tolerated delivering the required products in good yield (entry 5 and 6). All these olefins reacted with high regioselectivity to give the anti-Markovnikov adducts as described in the literature.[119] The reason for the low reactivity of the phenyl acrylate is as yet unclear and may be due to catalyst poisoning from decomposition of the phenyl ester.

Table 5: Intermolecular hydroacylation with enoates and alkyl substituted olefins

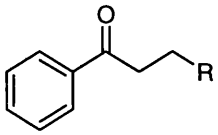


162

i) 10 mol % $[ClRh(PPh_3)_3]$
THF, 135ºC, 6h

R

ii) HCl (1 N)

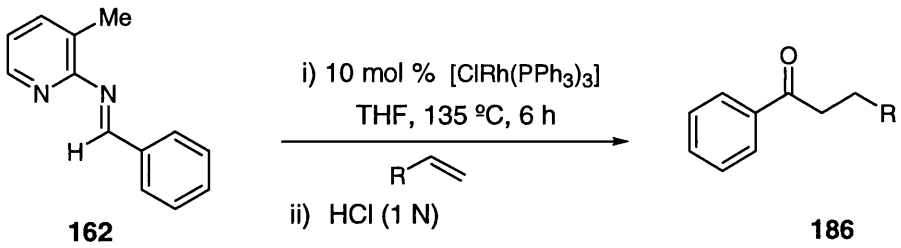


185

Entry	R	Yield
1	CO_2Me	73 %
2	CO_2Ph	27 %
3	$CO_2{}^tBu$	71 %
4	$CON(Me)_2$	70 %
5	C_4H_9	72 %
6	CH_2OCOMe	79 %

To study the electronic effects of the olefin substrate a variety of electron poor olefins were tested (Table **6**). Methyl vinyl ketone was found to be an unsuitable substrate for intermolecular hydroacylation of imine **162** under the conditions previously outlined with polymerisation occurring (entry 2). Phenyl vinyl sulfoxide and phenyl vinyl sulfone (entry 3 and 4) respectively were also submitted to hydroacylation conditions with imine **162**. Although these electron poor olefins are regarded as highly activated, after a 6 hours reaction time and hydrolysis, a complex reaction mixture was obtained where no desired product formation could be observed by crude ^1H NMR. These final two reactions could be complicated by the substrates coordinating with the catalyst.

Table 6: Intermolecular hydroacylation with electron-poor olefins



162 **186**

Entry	R	Yield
1	CO_2Me	73 %
2	COMe	nr
3	SOPh	nr
4	SO_2Ph	nr

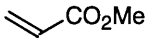
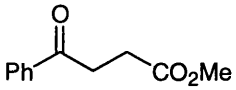
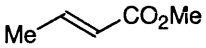
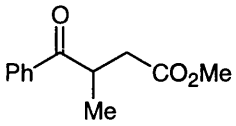
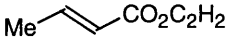
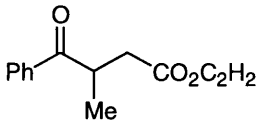
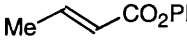
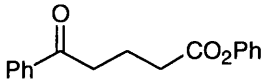
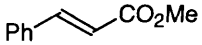
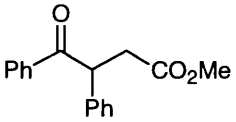
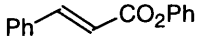
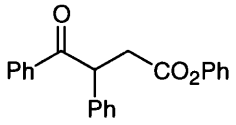
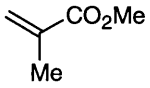
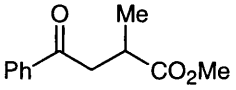
(nr: No reaction)

5.2.3) Substituted electron poor olefins

To be a useful process, the hydroacylation reaction needs to tolerate substituted alkenes. Attention was focused primarily on β-*trans*-substituted electron poor olefins; the results are reported in Table **7**. Such substitution dramatically reduces the reaction efficiency; indeed reaction of imine **162** with methyl crotonate in THF at 135 °C for 18 hours gave 24 % of the coupled product after hydrolysis, (entry 2) and no by-product formation was observed. Methyl cinnamate gave 7 % of the required product after 12 hours reaction time and hydrolysis (entry 5), whereas with benzyl cinnamate no conversion was observed after 6 hours (entry 6). Substitution at the α-position has a similar effect on the reaction efficiency with methyl methacrylate yielding only 16 % of the requisite product (Table **7**, entry 7). Vinyl crotonate did not react with imine **162**, after 6 hours reaction time (entry 3). The reason for this low reactivity remains unclear. With phenyl crotonate, 14 % of **187**, the product arising from alkene isomerisation was observed (Table **7**, entry 4 and Scheme **74**). In this

case hydroacylation take place with the *in situ* isomerised terminal olefin, no product resulting of the reaction of phenyl crotonate itself was observed.

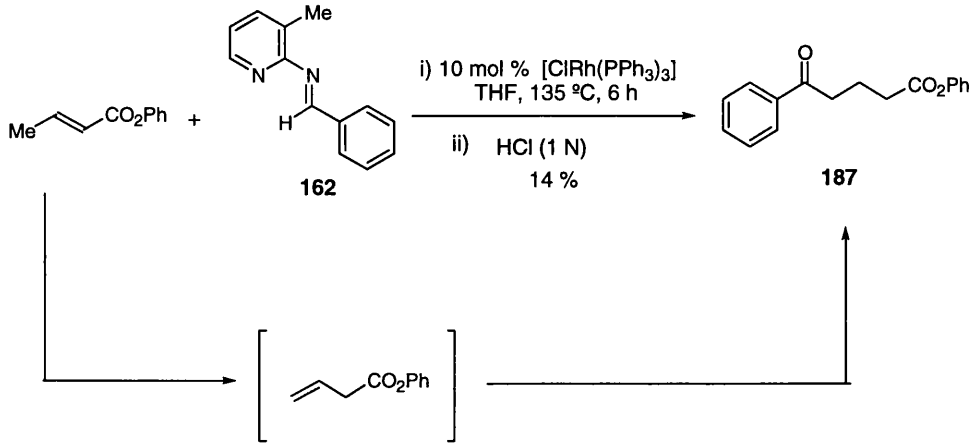
Table 7: Substitution effects of electron poor olefins in the intermolecular hydroacylation.

Entry	Olefin	Reaction time	Product	Yield
1		6 h		73 %
2[a]		18 h		24 %
3		6 h		nr
4		6 h		14 %
5		12 h		7 %
6		6 h		nr
7		12 h		16 %

Conditions: 10 mol % [ClRh(PPh$_3$)$_3$], olefin, THF, 135 °C, sealed tube, followed by HCl (1 N).

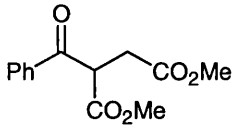
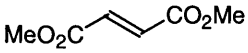
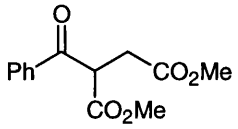
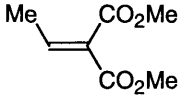
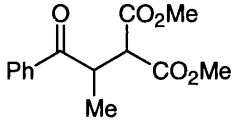
[a]methyl crotonate was also reacted with imine **162** in presence of 1 mol % [ClRh(PPh$_3$)$_3$],THF, 80 °C 48 h, atmospheric pressure, only 5 % of product was isolated

Scheme 74



To investigate the possible factors responsible for such a low conversion attention was turned to *cis*-olefins. Thus dimethyl maleate was reacted with imine **162** in the presence of 10 mol % of Wilkinson's catalyst in THF for 6 hours at 135 °C (Table **8**, entry 1). No hydroacylation product was isolated after hydrolysis of the reaction mixture. When the unreacted starting material was recovered, it was found that isomerisation of the maleate to the fumarate had occurred, probably following a mechanism catalysed by PPh_3. Reaction with dimethyl fumarate as starting material under the conditions outline in Table **8** gave no hydroacylation product (entry 2). A doubly activated olefin gave a complex reaction mixture after 6 hours reaction time followed by hydrolysis, where no product formation was observed by ^1H NMR (entry 3).

Table 8

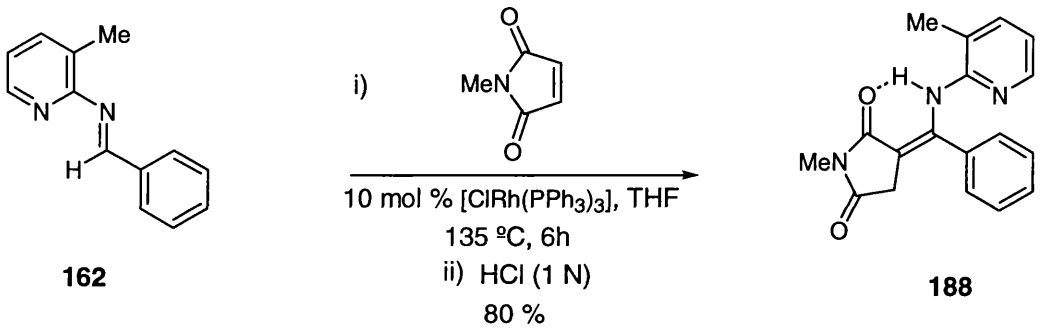
Entry	Olefin	Reaction time	Product	Yield
1		6 h		nr
2		6 h		nr
3		6 h		complex reaction mixture

Conditions: imine **162**, 10 mol % [ClRh(PPh$_3$)$_3$], olefin, THF, 135 °C, sealed tube, followed by hydrolysis HCl (1 N)

5.2.4) Cyclic electron poor olefins

In order to avoid isomerisation of the olefins occurring during the reaction, cyclic olefins were submitted to hydroacylation conditions. A β-substituent could be successfully introduced if it was sufficiently activating; the use of *N*-methyl maleimide as the alkene component generated the hydroacylation product followed by tautomerisation *in situ* to the *enamine* **188**. An 80 % yield of the non hydrolysed enamine was recovered (Scheme **75**).

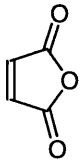
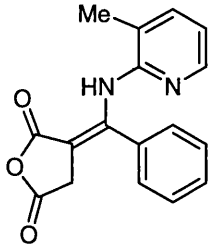
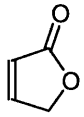
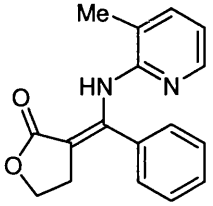
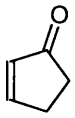
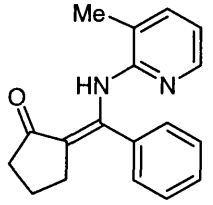
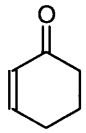
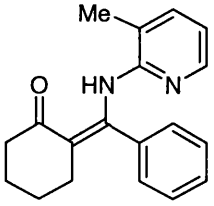
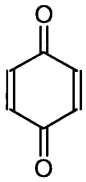
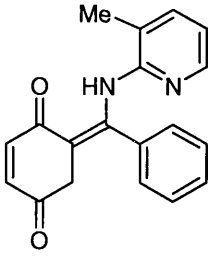
Scheme 75



162 **188**

The main difficulty was then to find olefin candidates sufficiently activated to undergo hydroacylation. A selection of cyclic electron-poor alkenes was evaluated (Table **9**). Hydroacylation of imine **162** with oxygenated electron poor olefins such as maleic anhydride led to a complex mixture with no hydroacylation adduct being isolated (Table **9**, entry 1). Cyclopentenone and 2-furanone reacted similarly yielding a complex reaction mixture with no hydroacylation product isolated (entry 2 and 3). Similarly alkenes in the cyclohexene series were tested under the same reaction conditions. Neither cyclohexenone nor hydroquinone reacted with imine **162**, only hydrolysed starting material was isolated (Table **9**, entry 4 and 5).

Table 9: Intermolecular hydroacylation with cyclic electron-poor olefins

Entry	Olefin	Reaction time	Product	Yield
1		6 h		nr
2		6 h		nr
3		6 h		nr
4		6 h		nr
5		6 h		nr

Conditions: imine **162**, 10 mol % $[ClRh(PPh_3)_3]$, olefin, THF, 135 °C, sealed tube, followed by hydrolysis HCl (1 N)

It appears so far that fine-tuning between the substrate and the catalyst is necessary to achieve intermolecular hydroacylation with electron-poor olefins, as subtle changes in the structure of the substrate can completely inhibit the reaction. Only unsubstituted

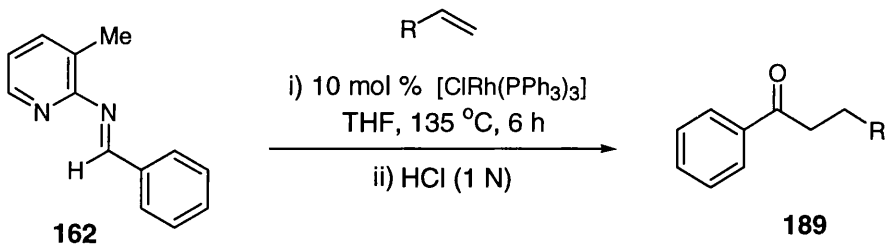
enoates are sufficiently activated for this reaction process, with even an α- or β-substituent dramatically slowing the reaction. The use of polar solvents such as THF and dioxane has a beneficial effect on the reaction rate.

5.3 Intermolecular hydroacylation with electron rich olefins

5.3.1) Cyclic and acyclic electron rich olefin substrates

After these encouraging initial results, the challenge was to test the scope of the intermolecular hydroacylation with regard to electron enriched olefins. In this case the olefin moiety is less activated compared to the enoates in some ways, which are known to readily undergo Michael additions.[120] Submitted to the hydroacylation conditions outlined in Table **9** above, enol ethers such as butyl vinyl ether and ethyl vinyl ether did not react with aldimine **162** (Table **10**, entry 3 and 4). Less electron-rich olefins such as vinyl benzoate and vinyl propionate were also found to be unsuitable substrates for intermolecular hydroacylation as no product **189** was isolated under these conditions (entry 1 and 2). To date no example of electron rich olefin substrates has been reported in the intermolecular hydroacylation.[119]

Table 10: Intermolecular hydroacylation with electron-rich olefins

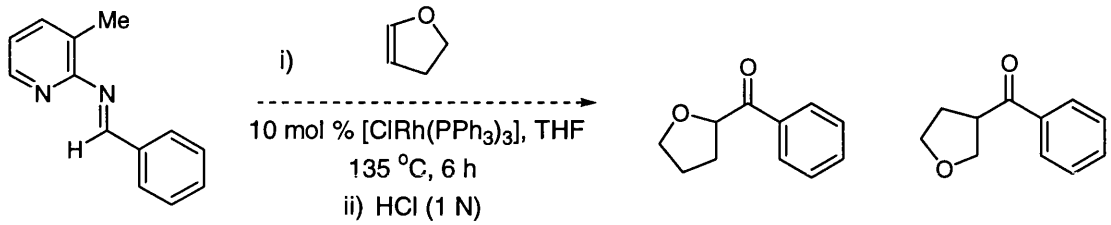


162 **189**

Entry	R	Yield
1	OCOEt	nr
2	OCOPh	nr
3	OBu	nr
4	OEt	nr

The reaction of imine **162** with dihydrofuran gave a complex reaction mixture where no hydroacylation product **190** nor **191** was isolated (Scheme **76**).

Scheme 76



162 **190** **191**

5.3.2) Limitations and discussion

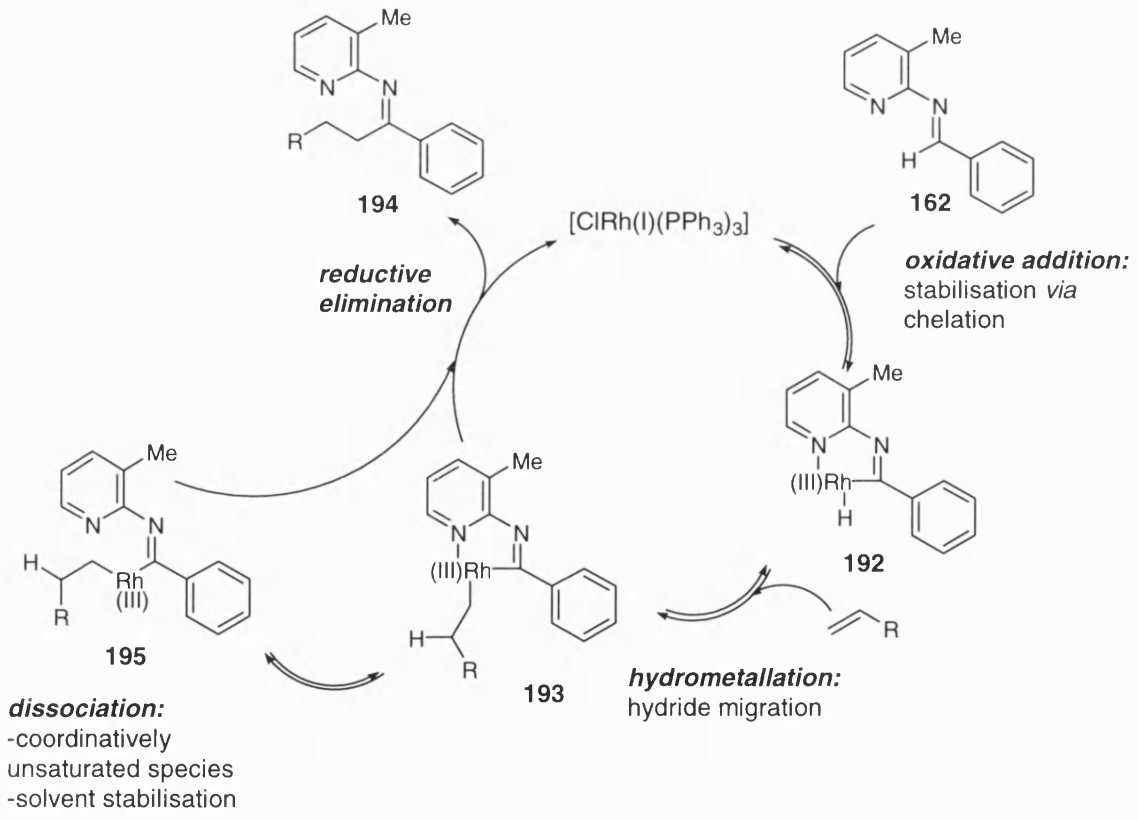
It was speculated that the lack of reactivity of such electron enriched olefin substrates with imine **162**, might be due to the stability of the cyclometalated Rh-imine intermediate **192** formed after coordination of an olefin and that the insertion of the olefin could occur to give hydrometalated intermediate **193** reversibly. Subsequently, oxidative addition and reductive elimination might be competing processes giving back starting materials or hydroacylation product **194** (Scheme **77**). This raises questions as to the nature of the active species, the nature of the catalyst precursors that can be used and what constitutes the essential rate-determining step of the catalytic system (Scheme **77**):

1) Wilkinson's catalyst was found to be the best catalyst for intermolecular hydroacylations of imine **162**.[101]
2) The 2-amino-picoline **164** moiety has been demonstrated to stabilise the hydrido-acyl intermediate **192** toward decarbonylation (Chapter IV).[121]
3) As suggested above, a possible explanation of the lack of reactivity of imine **162** with olefin might be the strength of the chelation in the cyclometalated

Rh-imine intermediate **192**, inhibiting hydride migration. The olefin coordinates to the Rh centre but the hydride migration step leading to **193** is inhibited *(hydrometallation)*.

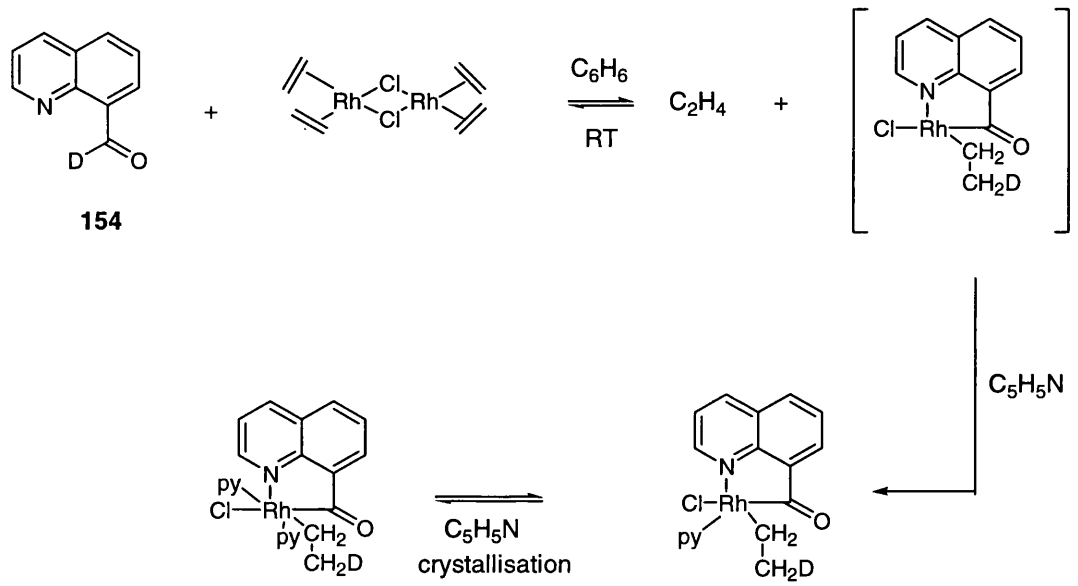
4) Another possible explanation could be that the nature of the olefin substrate determines the rate of reductive elimination. The chelated intermediate **193** is in equilibrium with a coordinatively unsaturated complex **195** (where the chelating *N*- group is dissociated), which may give rise to lower activation energy barriers for reductive elimination to occur. Such an intermediate **195** might be stabilised by solvent serving as a weakly coordinating ligand. The increase in reaction rate, obtained with dioxane would support this hypothesis (Scheme **77**).

Scheme 77



Similar catalytic cycles have been postulated for rhodium- and ruthenium-catalysed hydroarylation reactions involving substrates with a nitrogen-directing group.[119] The strong influence of ether additives in the chelation-assisted hydroarylation process has also been discussed[122,119] as well as in the case of intermolecular hydroacylation (See Chapter IV): a few years later Suggs confirmed that acylrhodium (III) hydrides are intermediates in the hydroacylation of terminal olefins and the synthesis and structure of stable acylrhodium(III) ethyl complexes derived from 8-quinolinecarboxaldehyde **154** and $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ were described (Scheme **78**).[123]

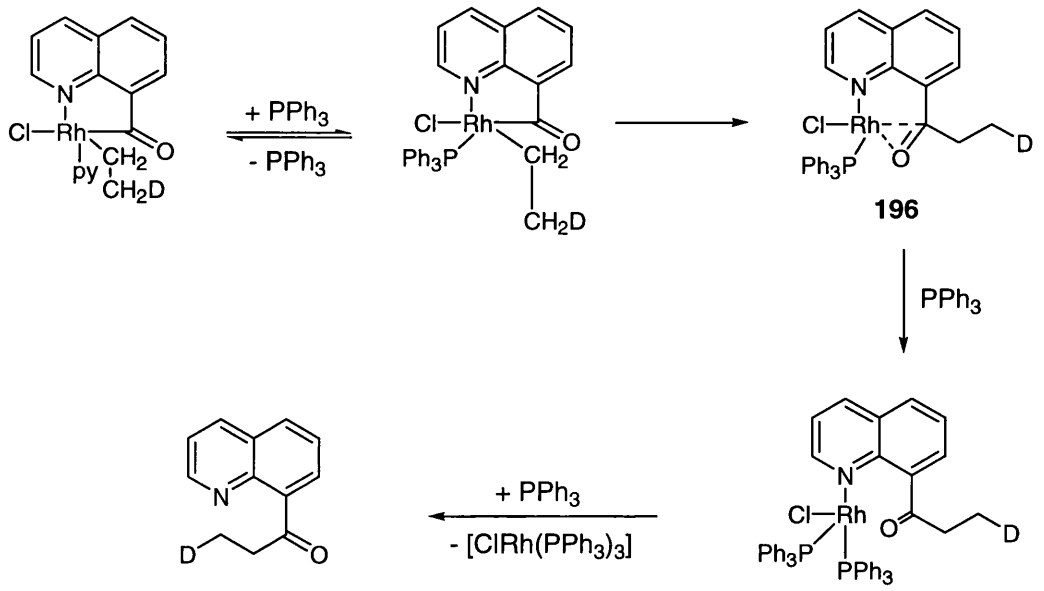
Scheme 78



The acyl alkyl intermediate involves displacing ethylene or splitting the chlorine bridge in $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ followed by oxidative addition to the rhodium centre. The remaining ethylene would then insert into the Rh-H bond. In agreement with this mechanism, a deuterated aldehyde reacted with $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$ to give the deuterated complex in which all the molecules contain one deuterium in the methyl group. Substitution of the pyridine ligand by an excess of PPh_3 induced reductive elimination of 8-quinolinyl ethyl ketone and the formation of $[ClRh(PPh_3)_3]$. Using

^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, the authors were able to follow the course of this ligand-promoted reductive elimination at –40 °C and identify the intermediates shown in Scheme **79** below. According to the authors, the formation of an η^2–ketone complex **196** is a specific example of reductive elimination reactions with groups containing π-bonds or lone pairs of electrons. Whenever the reductive elimination step of the process generates a potential ligand, there is no reason why the ligand should remain coordinated to the reduced metal centre thus regenerating the catalytic species, unless there are steric or conformational factors that could interfere (Scheme **79**).[123] The use of external strong π-acceptor ligands like pyridine or phosphites has been reported in the literature as inducing reductive elimination.[124]

Scheme 79

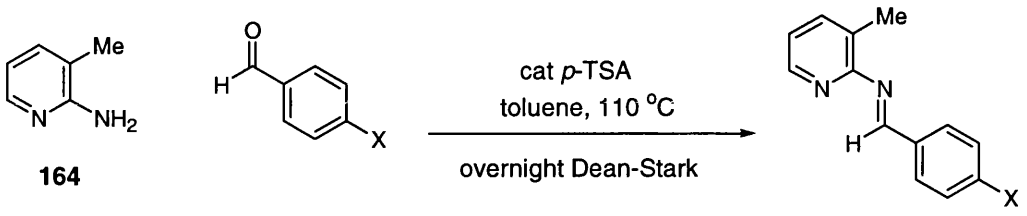


5.4 Intermolecular hydroacylation with substituted imines

An alternative way to destabilise the cyclometalated intermediate might be to weaken the cyclometalated Rh-*N* interaction by changing the electron-density on the imine substrate.

In order to explore this hypothesis, a selection of 2-amino-3-methyl pyridyl imines bearing a range of substituents were readily prepared from 2-amino-3-picoline **164** and substituted benzaldehyde substrates (Table **11**).

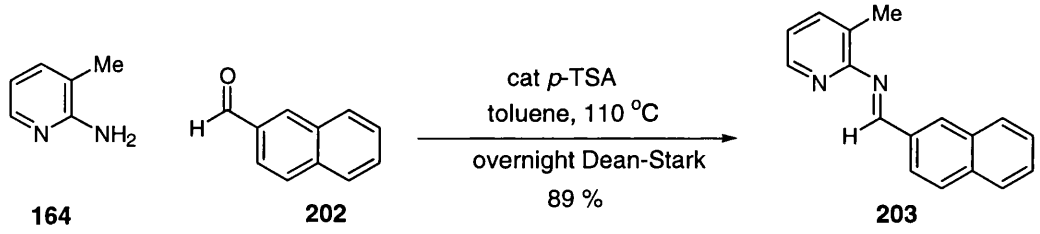
Table 11: Substituted imine synthesis



X	Yield	Product
NO_2	84 %	**197**
CN	69 %	**198**
Br	91 %	**199**
Me	82 %	**200**
OMe	89 %	**201**

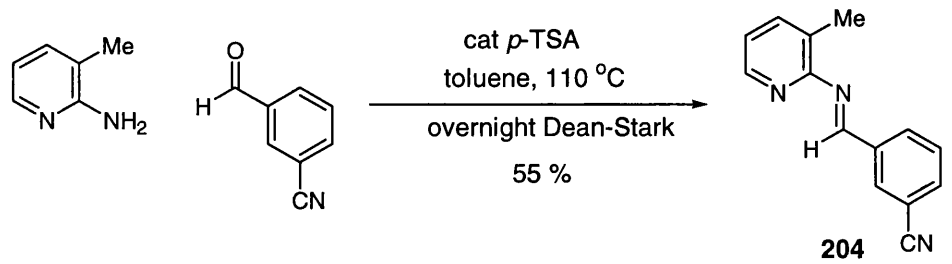
The acid catalysed condensation of naphthaldehyde with 2-amino-3-picoline gave imine **203** after distillation in good yield (Scheme **80**).

Scheme 80



Similarly *m*-cyano-substituted 2-amino-3-methyl pyridyl imine **204** was synthesised, although a lower yield was obtained due to recrystallisation difficulties (Scheme **81**).

Scheme 81

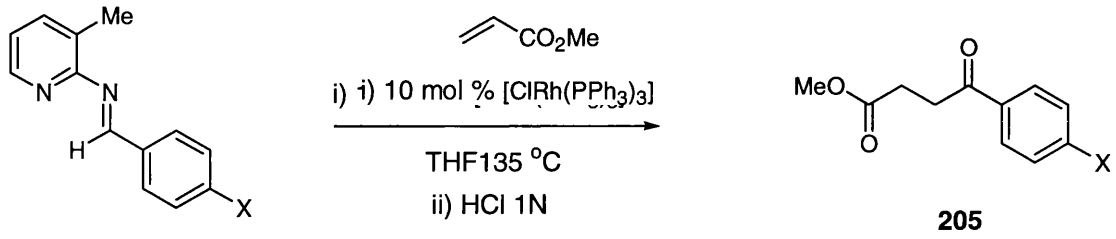


204

5.4.1) Electron poor olefins as coupling partner

These substituted imines were evaluated in hydroacylation reactions with methyl acrylate (Table **12**). Electron withdrawing groups such as $-NO_2$ and –CN had a beneficial effect on the rate of the reaction with good yields of the desired products **205** being obtained in only 20 mins and 80 mins respectively (Table **12**, entry 1 and 2). Electron donating substituents had a smaller influence on the rate of reaction, a –OMe substituent had minimal effect compared to the parent phenyl system with an 83 % yield achieved after 6 h with 12 % of hydrolysed starting material being recovered (entry 5). *p*-Methyl and *p*-bromo groups are also well tolerated delivering the corresponding1,4-dicarbonyls in 98 % and 85 % yield respectively (entries 4 and 3).

Table 12: Effect of imine *p*-substitutions on the reaction rate

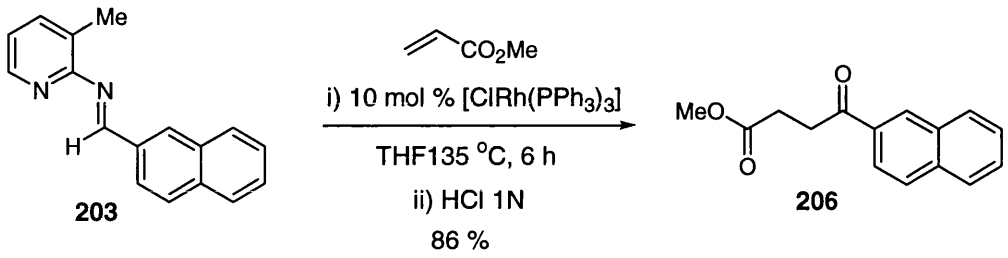


205

Entry	X	Reaction time	Yield
1	NO_2	20 min	80 %
2	CN	80 min	79 %
3	Br	6 h	85 %
4	Me	6 h	98 %
5	OMe	6 h	83 %

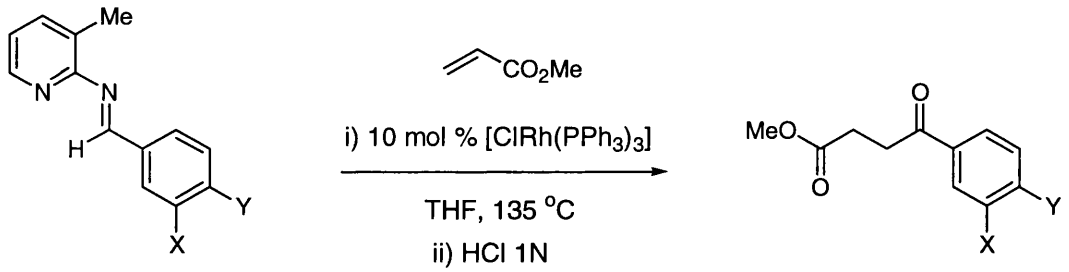
Exchange of a phenyl for the more electron-rich naphthyl derived imine **203** again showed little difference, with the naphthyl derived adduct **206** being obtained in 86 % yield after 6 hours reaction (Scheme **82**).

Scheme 82



A change from *para-* to *meta*-CN substitution on the phenyl ring induces a significant drop in the reaction rate; after 8 hours reaction 35 % of hydrolysed starting material was recovered (Table **13**, entry 2 and 3).

Table 13: Effect of -CN substitutions on hydroacylation



Entry	X	Y	Time	Yield
1	H	H	6 h	73 %
2	H	CN	80 min	79 %
3	CN	H	8 h	48 % (35 %RSM)

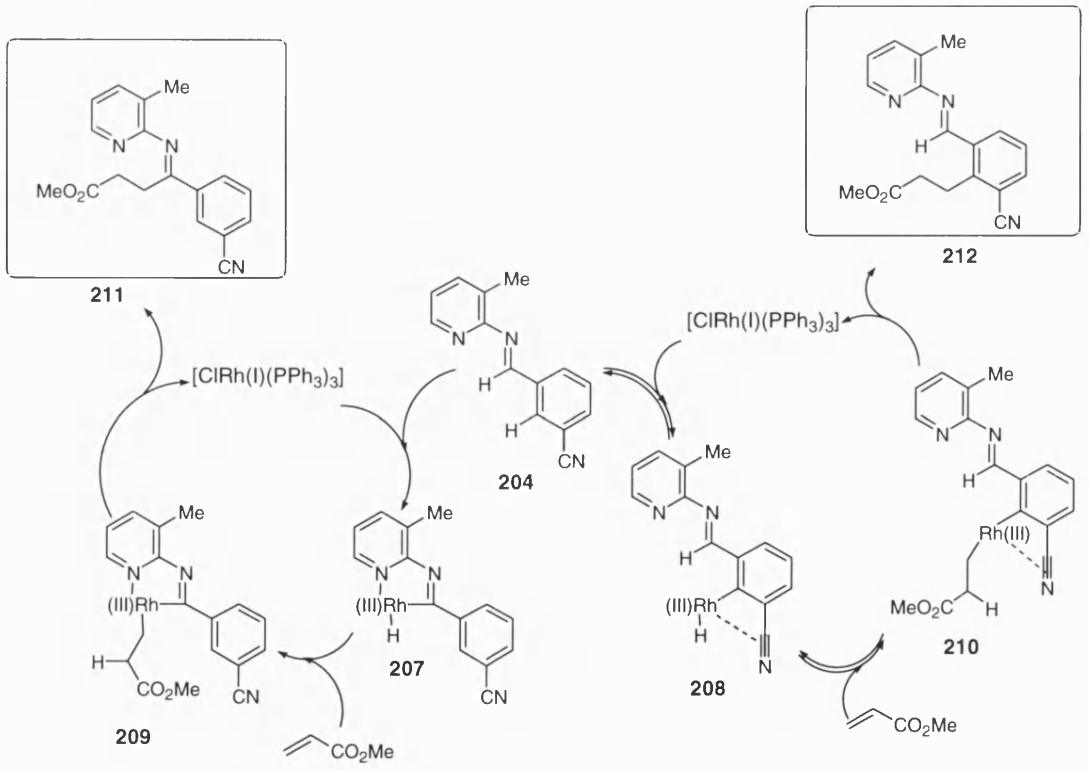
5.4.2) Discussion

The reasons for the rate deceleration observed with *m*-cyano-substituted imine **204** are unclear (Table **13**, entry 3). There are several postulated explanations:

1) the loss of conjugation compared with benzaldimine **162** and the subsequent reduction in the electron withdrawing effect,

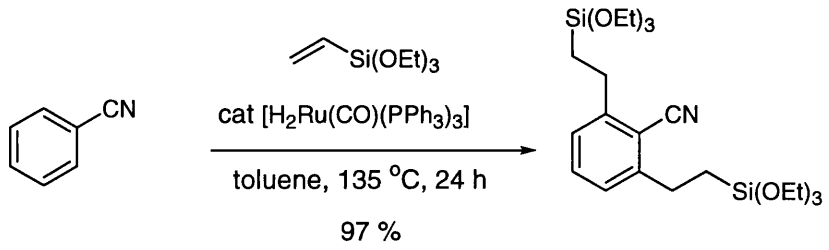
2) the cyano group reinforces the activation of the *ortho*- and *para*- C-H aromatic bonds at the same time as the imine C-H bond. Thus a competition between imine C-H activation and aromatic C-H activation **204** may occur. These processes lead reversibly in both cases to metallacyclopentanes **207** and **208**, followed by hydrometallation **209** and **210**. Reductive elimination gives hydroacylation adduct **211** and *ortho*-alkylation product **212** and its regioisomer (Scheme **83**). However, in our case, beside the hydroacylation product **211** no ortho-alkylated by-product **212** was observed after 8 hours.

Scheme 83



An example where a -CN group serves as a directing functionality for the aromatic C-H/olefin coupling is reported below (Scheme **84**). The reaction of benzonitrile with vinylsilanes using a Ru-based catalyst gave the corresponding double coupling product **213** in 97 % yield. The exclusive *ortho* selectivity implies that the -CN group is able to direct the Ru to the *ortho* sp^2 C-H bond.[125]

Scheme 84

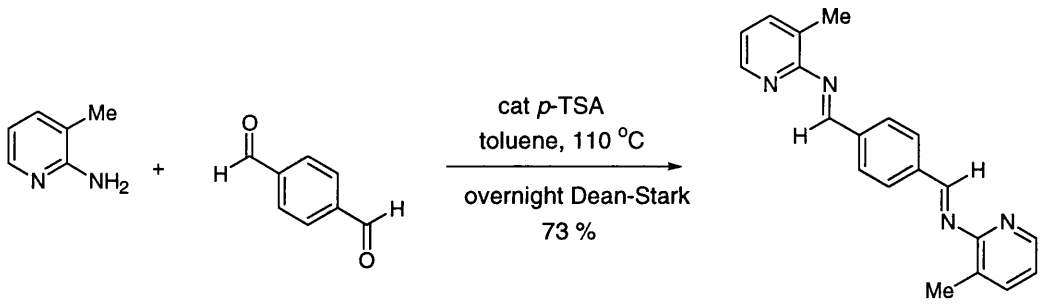


213

The aromatic activation by a -CN group added to the activation directed *via* coordination of the pyridyl group and *N* of the imine functionality have both been reported in the literature [126] and discussed in chapter I.

Given the rate accelerations observed with the *p*-NO_2 and *p*-CN substituted imines, the diimine **214**, prepared in good yield from benzene-1,4-dicarboxaldehyde offers a potential starting point for two directional synthesis (Scheme **85**).[127]

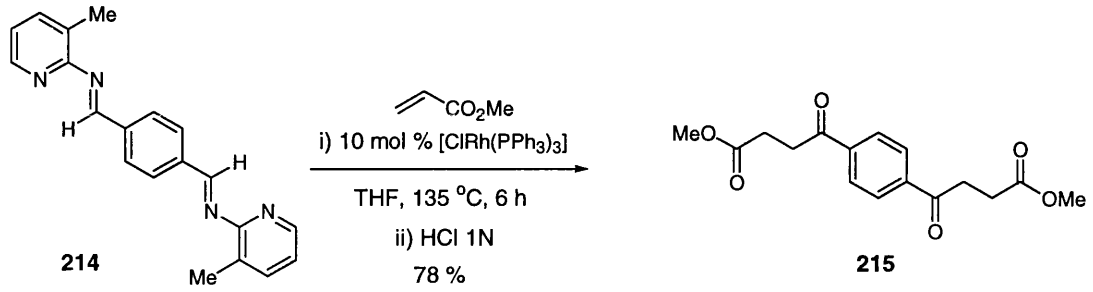
Scheme 85



214

A double hydroacylation was successfully attempted on diimine **214** (Scheme **86**). Although **214** can be regarded as an electron deficient imine, the reaction is not complete after 6 hours, with 78 % of product **215** being isolated and 9 % of the hydrolysed benzene-1,4-dicarboxaldehyde being recovered.

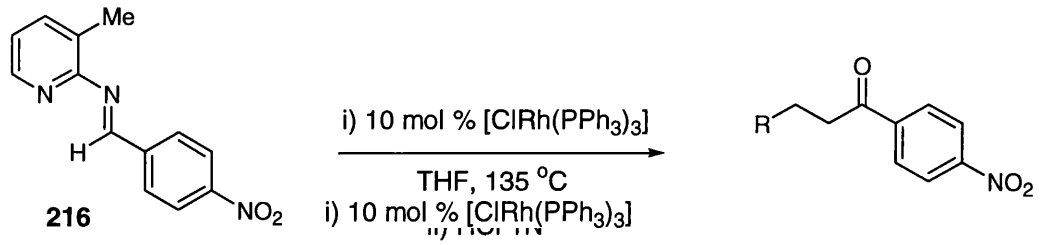
Scheme 86



5.4.3) Hydroacylation with p-NO_2 substituted imine and olefins: Discussion

The effect of the -NO_2 group on the reaction with substituted alkenes was next investigated. As reported in the case of imine **162**, *N,N*-dimethyl acrylamide is a sufficiently activated substrate in the reaction conditions outlined in Table **14** (entry 2), but again electron rich olefins like butylvinylether failed to react in intermolecular hydroacylation, although the *p*-NO_2 substitution was shown to enhance the reaction rate with methyl acrylate (Table **14**, entry 3 and 1).

Table 14: Effect of imine *p*-NO_2 substitution with alkenes substitution.

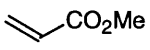
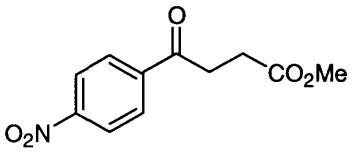
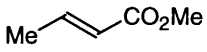
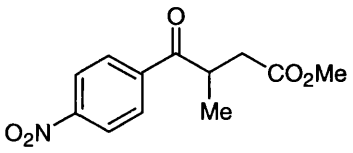
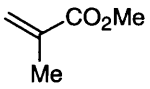
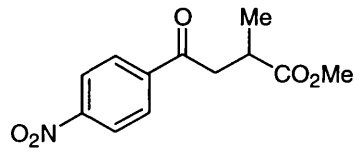


Entry	R	Time	Yield
1	CO_2Me	20 min	80 %
2[a]	$CONMe_2$	5 h 45	70 %
3	OBu	7 h	nr

[a]lower reaction time was not studied

Reactions using α- and β-substituted alkenes were also undertaken using 10 mol % of $[ClRh(PPh_3)_3]$ in THF (Table **15**). After 16 hours reaction time with methyl crotonate no hydroacylation adduct was isolated, whereas 20 % of hydroacylation adduct is formed after a 6 hour reaction time with imine **216** (Table **15**, entry 1 and 2).

Table 15: Effect of imine *p*-NO_2 substitution with α- and β-substituted alkenes

Entry	Olefin	Reaction time[a]	Product	Yield
1		6 h		80 %
2		16 h		nr
3		6 h		20 %[b]

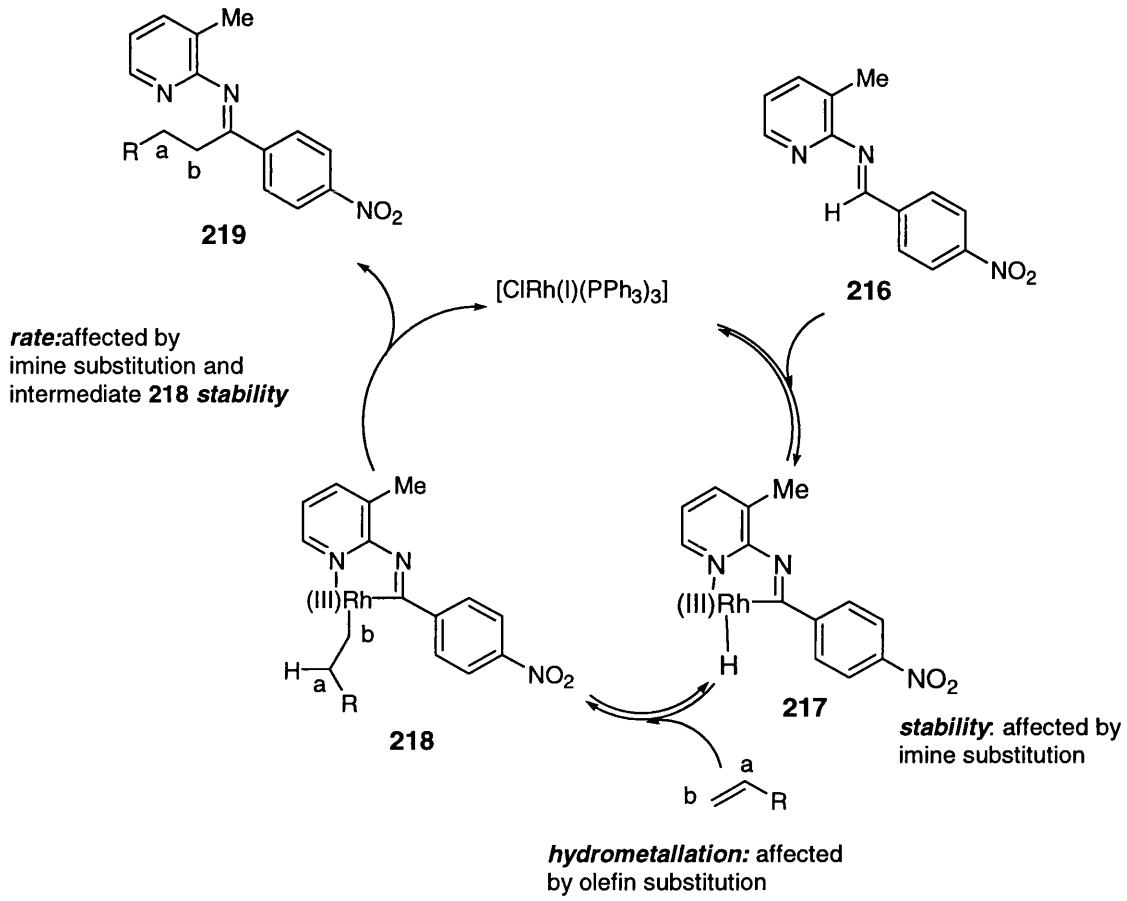
[a]reaction with *p*-NO_2Ph-imine **216**, 10 mol % $[ClRh(PPh_3)_3]$, THF, 135 °C, sealed tube, followed by hydrolysis HCl 1 N

[b] ^1H NMR conversion

The low reactivity is similar to the benzaldimine **162** suggesting that simple steric effects may be responsible leading to a decrease in the hydride migration rate (the hydrometalation step) (Scheme **87**). As discussed earlier *p*–NO_2 substitution enhances the reactivity of the imine substrate: a destabilisation of cyclometalated intermediate **217** might occur. This destabilisation favours the ability of **217** to undergo hydrometalation and increases the reductive elimination rate to give **219**. The rate of

olefin insertion (hydride migration) leading to **218** is dependent on the olefin substitution (Scheme **87**).

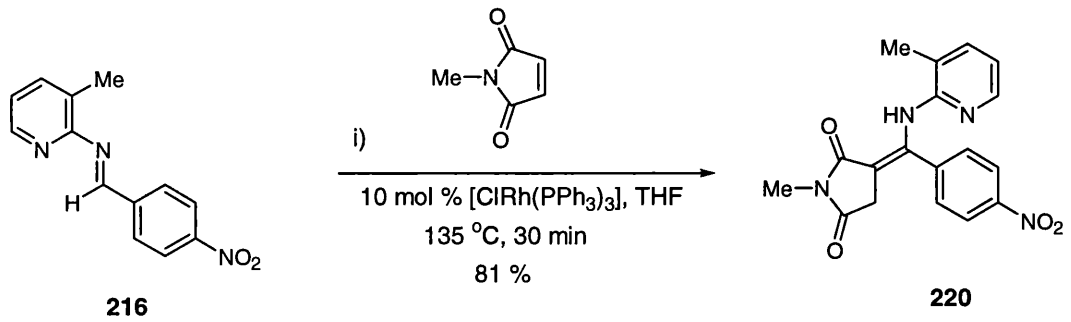
Scheme 87



This hypothesis is supported by the insertion of methyl methacrylate into the cyclometalated intermediate of *p*-NO_2 imine **216** being faster than methyl crotonate. This is likely due to the cooperative effect of steric hindrance at the β-position of the olefin and the destabilisation of the cyclometalated intermediate **217** (Table **15** above, entry 2 and 3).

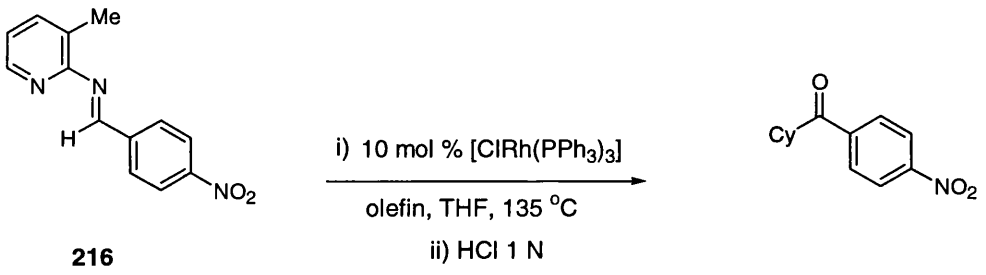
In order to investigate this further, the reaction of imine **216** with *N*-methyl maleimide was studied (Scheme **88**). Enamine **220** was obtained in good yield and the increase in the reaction rate is in accordance with the increase observed with linear olefins.

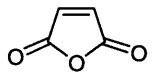
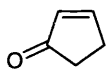
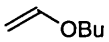
Scheme 88



However neither maleic anhydride nor cyclopentene-2-one delivered any of the expected intermolecular hydroacylation products. Similarly under these conditions butyl vinyl ether still did not react with imine **216**. The reason for this is unclear (Table **16,** entry 1,2 and 3).

Table 16



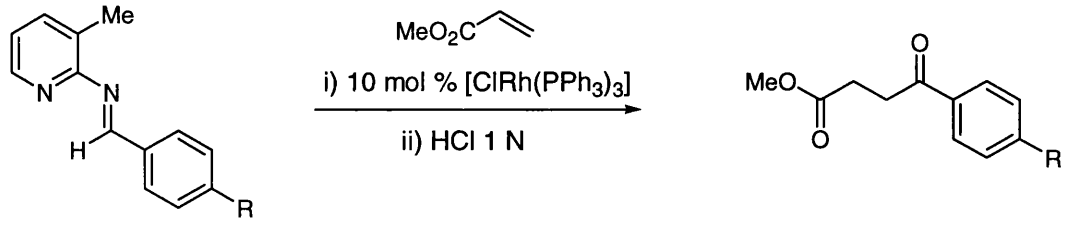
Entry	Olefin	Time	Yield
1		6 h	nr
2		8 h	nr
3		6 h	nr

Cy =cyclic substituent for entry 1 and 2,
$(CH_2)_2OBu$ for entry 3

In order to investigate the possible destabilisation of the cyclometalated intermediate **217** and **218** by solvent and the generation of a coordinatively unsaturated complex

intermediate, the *p*-NO_2 imine **216** was reacted with methyl acrylate using dioxane as solvent instead of THF. An increase of the reaction rate from 20 min to 5 min at 135 °C was observed by ^1H NMR (Table **17,** entry 3 and 4). The increase is more significant in the case of a less activated benzaldehyde-derived imine **162** (entry 1 and 2).

Table 17

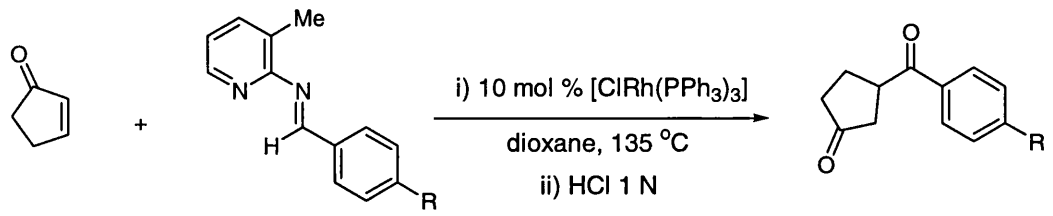


Entry	R	Solvent	Temp	Time	Yield
1	H	THF	135 °C	6 h	72 %
2	H	Dioxane	135 °C	2 h 45	74 %
3	NO_2	THF	135 °C	20 min	80 %
4	NO_2	Dioxane	135 °C	5 min	70 %
5	NO_2	THF	RT	3h	nr
6	NO_2	THF	50 °C	1h	nr

conditions: imine, 10 mol % [$ClRh(PPh_3)_3$], followed by hydrolysis HCl 1 N

These new conditions were next investigated with more challenging alkenes. However neither the change of the solvent or the substitution of the imine activated the cyclopentene-2-one to undergo hydroacylation (Table **18**).

Table 18

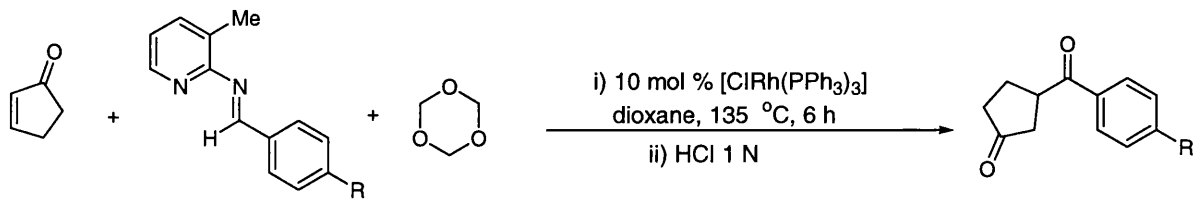


R	Time	Yield
NO_2	8 h	nr
H	7 h	nr

It was further speculated that dioxane might activate the metallacyclopentanes **217** and **218** by competing in the coordination process with the nitrogen of the pyridyl unit. It was decided to investigate the use of even better coordinating molecule such as trioxane as an additive.

The addition of trioxane to the previously studied unsuccessful reaction with cyclopentenone as alkene partner did not affect the reaction course using either imine **162** or **216** (Table **19**). However this result cannot be considered as a proof of the proposed hypothesis because the effect of trioxane has not been studied on the reaction using methyl acrylate.

Table 19



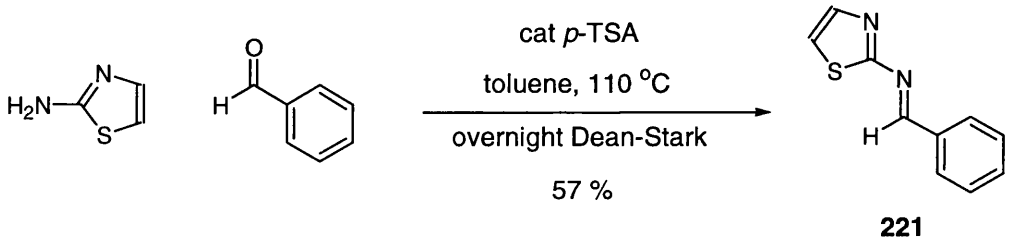
R	Yield
H	nr
NO_2	nr

Another method for activating the metallacyclopentane intermediate would be the destabilisation of the intermediate by increasing the ring size of the chelate (such as a six-membered ring size instead of five), or changing the nature of the coordinating group.[116,115, 128,129]

5.5 Sulfur containing group as chelating agent

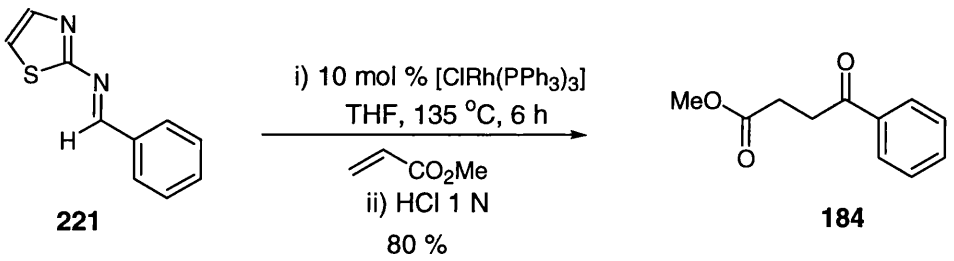
In order to study the effect of the chelating group, the thiazole derivative imine **221** was synthesised by condensation of 2-aminothiazole with benzaldehyde. Beside *N*, a second coordination site *via* the *S* unit was introduced (Scheme **89**).

Scheme 89



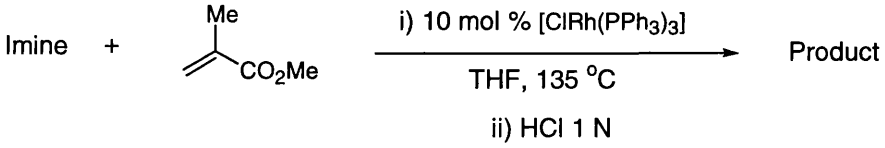
Submitted to hydroacylation conditions with methyl acrylate, imine **221** gave after hydrolysis the desired product in 80 % yield in accordance with the result obtained with imine **162** (Scheme **90**).

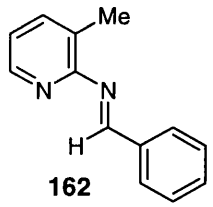
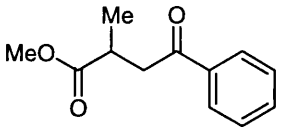
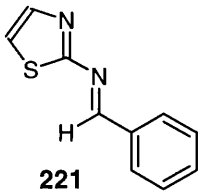
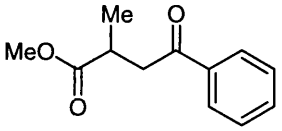
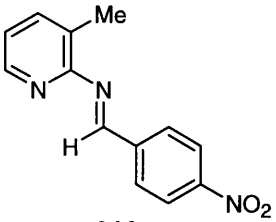
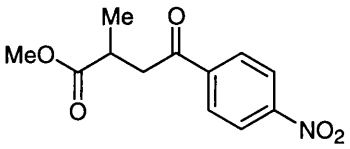
Scheme 90



The substitution of the olefin component was next studied. Methyl methacrylate was reacted with imine **221** to give the corresponding product in 16 % yield with 38 % of hydrolysed starting material being recovered (Table **20**, entry 2). Thiazole imine **221** is more reactive than benzaldehyde imine **162** toward hydroacylation with methyl methacrylate (entry 1). Such a conversion is similar to that obtained with *p*-NO_2 imine **216** (entry 3).

Table 20: Hydroacylation of imines with methyl methacrylate

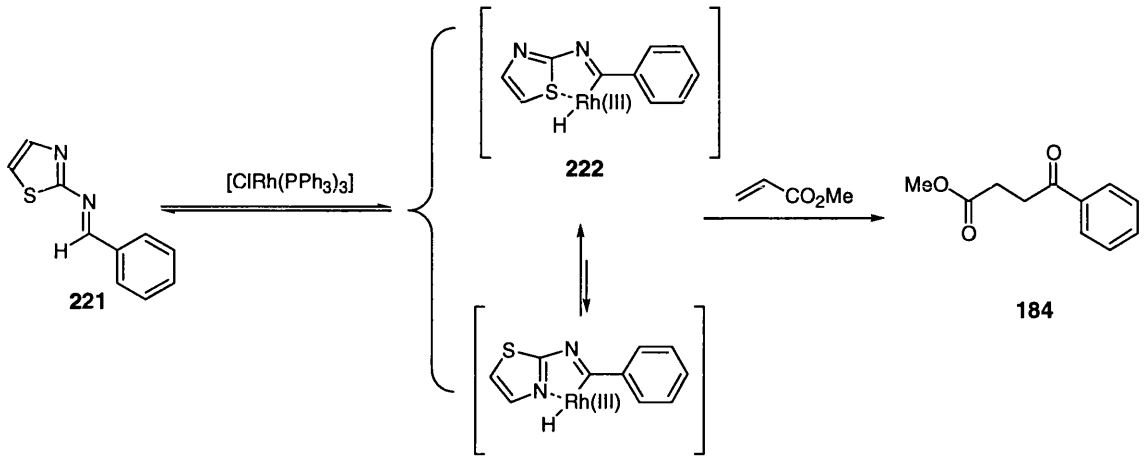


Entry	Imine	Time	Product	Yield
1	 **162**	12 h		12 %
2	 **221**	6 h		16 % (38 % RSM)
3	 **216**	6 h		20 %

Conditions: Imine, 10 mol % [$ClRh(PPh_3)_3$], THF, 135 °C, followed by hydrolysis HCl 1 N

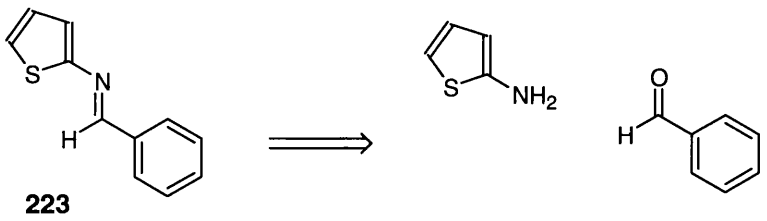
It was envisaged that the possible formation of metallacyclopentane **222** *via S* chelation activates the substrate, although this has yet to be demonstrated by using an imine bearing no coordinating group (Scheme **91**).

Scheme 91



To verify this hypothesis the reaction of thiophene imine **223** under identical conditions would be a desirable system to study, however aminothiophene is not a readily available substrate (Scheme **92**).

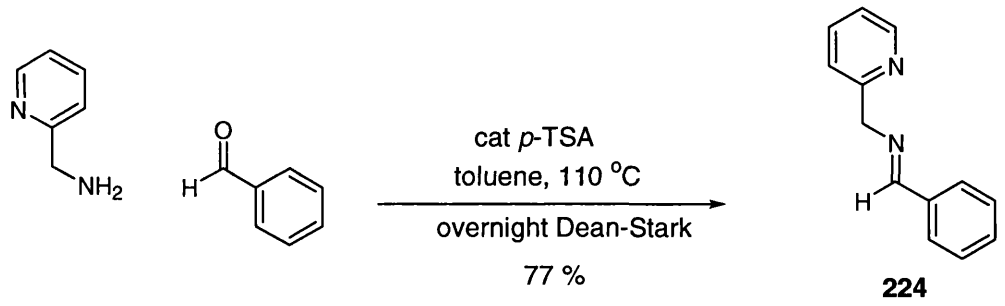
Scheme 92



5.6 Chelating tether length: studies

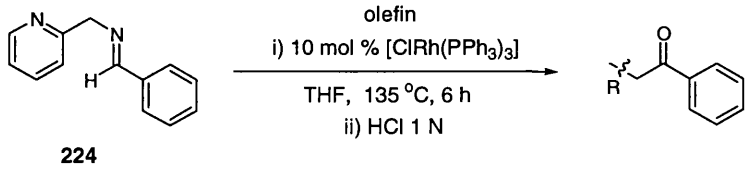
Attention was next turned to the synthesis of imine **224** with a longer tether length while retaining *N* as the coordinating group (Scheme **93**).

Scheme 93



The newly synthesised imine **224** was submitted to a standard hydroacylation reaction with methyl acrylate. A strong change in colour of the reaction mixture from orange to green-blue occurred. Attempts to isolate any intermediate during the reaction process failed; in contact with air the solution changed colour from green-blue to brown. No hydroacylation product was isolated and starting material was detected by ^{1}H NMR (Table **21**). The reaction solvent was changed to dioxane and imine **224** was reacted with the olefins previously studied. After 6 hours, the strong green-blue coloration occurred and no product formation was observed.

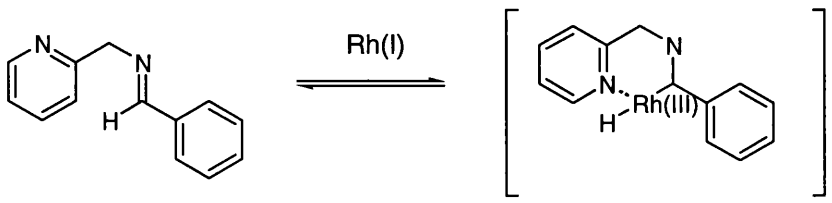
Table 21



Olefin	OBu	C_4H_9	CO_2Me	Me, CO_2Me	Me, CO_2Me
Yield	nr	nr	nr	nr	nr

A possible explanation of the lack of reactivity of imine substrate **224** may be a strong 6 membered metallacyclohexane **224-a** resulting from the oxidative addition (Scheme **94**). Alternatively the strong *N* donor may be too far away from the reaction C-H functionality.

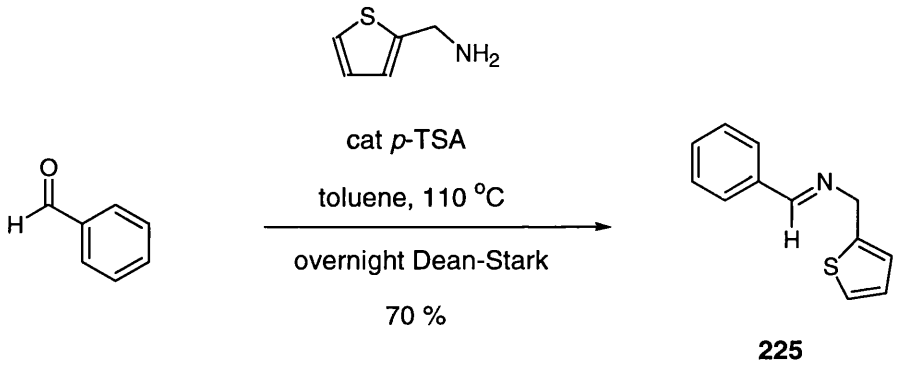
Scheme 94



224 **224-a**

To investigate the role of the ring chelate further, imine **225** was synthesised in good yield (Scheme **95**).

Scheme 95

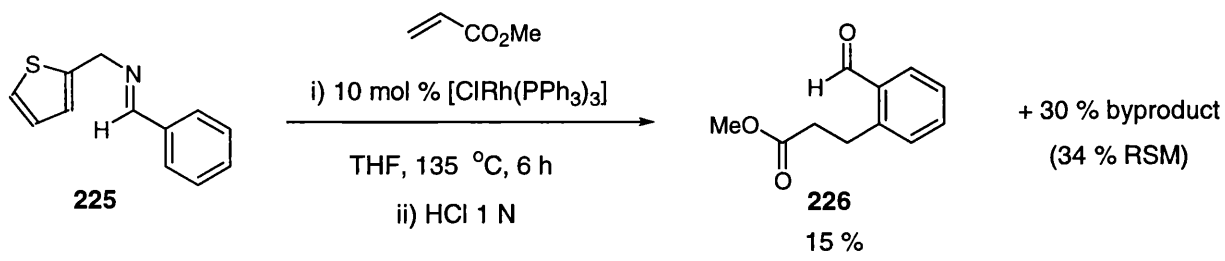


225

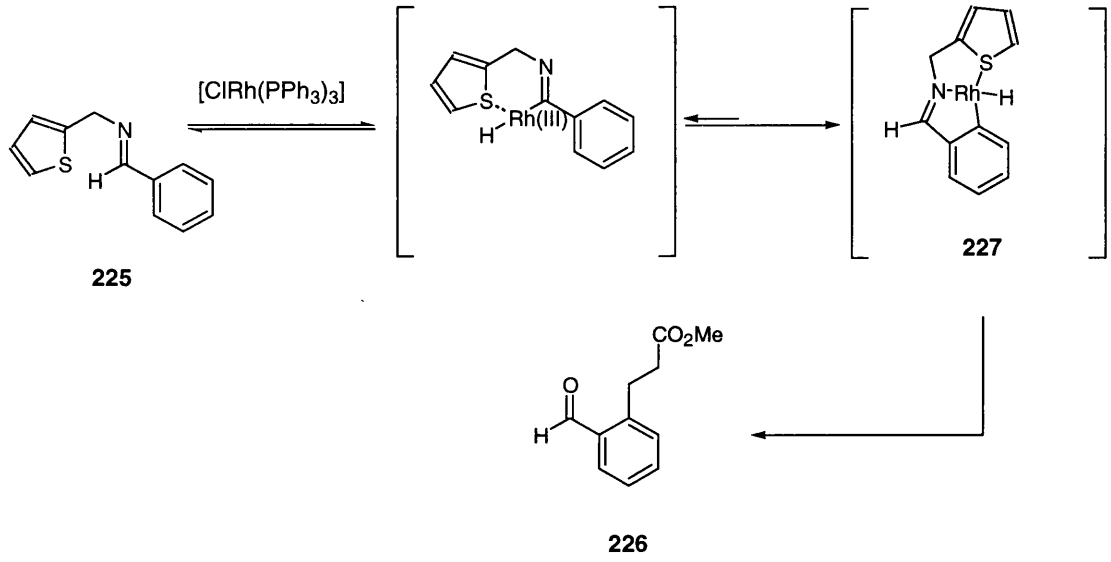
5.7 Hydroacylation *versus ortho*-alkylation

Imine **225** was reacted under standard hydroacylation conditions with methyl acrylate followed by hydrolysis. No hydroacylation product was isolated; however 15 % of *ortho*-alkylation product **226** was isolated with 35 % aldehyde starting material and an as-yet unidentified mixture of compounds (Scheme **96-a**). *Ortho*-alkylation product **226** is believed to result from the addition of methyl acrylate to cyclometalated intermediate **227** (Scheme **96-b**).

Scheme 96-a

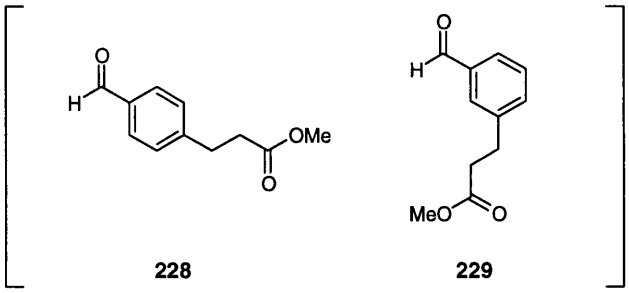


Scheme 96-b



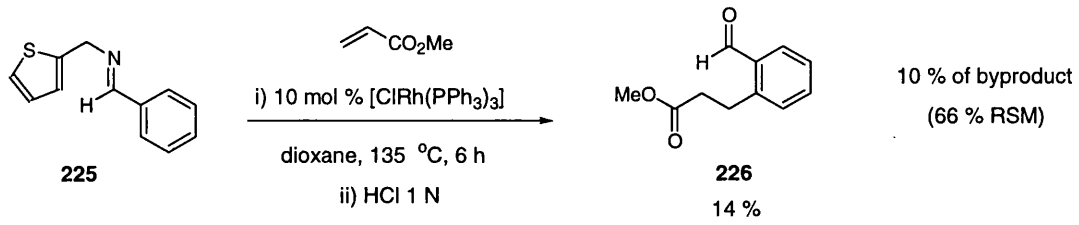
The by-product is tentatively assigned as alkylation products **228** and **229** (Figure **16**). Using dioxane instead of THF as solvent after 6 hours reaction time, followed by hydrolysis, yielded 14 % of ortho-alkylated aldehyde **226** (Scheme **97**). 30 mg of a complex reaction mixture was also isolated however separation difficulties prevented these compounds from being fully characterised. From ^{1}H NMR the presence of a singlet and 2 doublets in the aromatic region amongst other peaks might be due to a *meta*- alkylation process (**229**, Figure **16**).

Figure 16



228 **229**

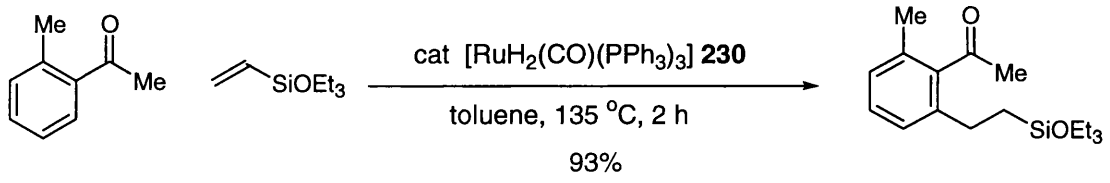
Scheme 97



225 **226**
14 %

Examples of *ortho*-alkylation are reported in the literature, mainly between olefins and aromatic ketones or esters under the action of a directed process. Such examples use highly reactive triethoxyvinylsilane as the olefin partner and a Ru catalyst (4 mol % **230**) (Scheme **98**).[130,131]

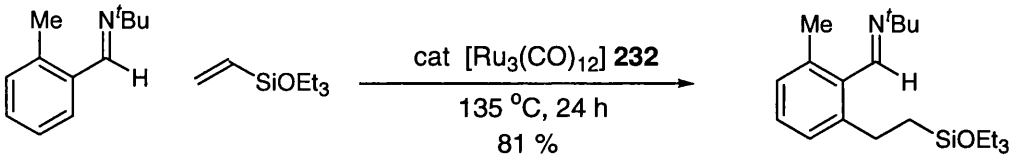
Scheme 98



Examples using aromatic imines with olefins are more scarce, although recent reports by the three groups of Murai *et al,*[132] Jun *et al*[133,134] and Brookhart *et al*[135] have appeared:

Murai's system consists of using imine **231** mainly with triethoxyvinylsilane and terminal alkyl-substituted olefins with a non-phosphine Ru catalyst **232** (Scheme **99**). The system is limited to this very activated olefins.

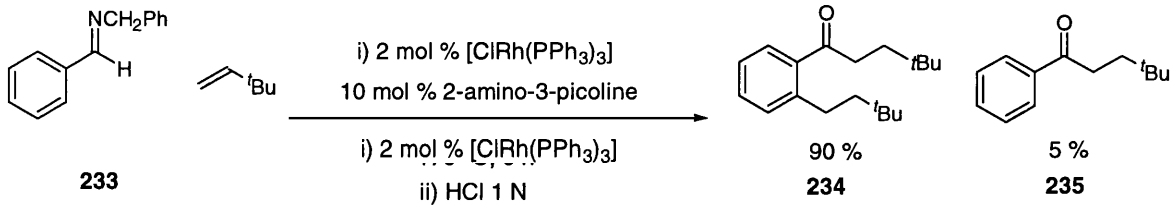
Scheme 99



231

Jun *et al* reported a similar unexpected alkylation reaction of aromatic ketimines with olefins using Wilkinson's catalyst.[134] Treatment of aldimine **233** and 3,3-dimethylbut-1-ene with 2-amino-3-picoline **164** and [ClRh(PPh$_3$)$_3$] as cocatalysts gave after 6 h at 170 °C followed by hydrolysis, *ortho*-alkylated ketone **234** in 90 % yield along with 5 % of hydroacylated keto-compound **235** (Scheme **100**). The authors suggested that hydroacylation is necessary for *ortho*-alkylation to proceed. However, the results found earlier demonstrated that it is possible for *ortho*-alkylation to proceed without hydroacylation (see Scheme **96** and **97**). Both systems use identical imine **162** as intermediates. To date neither *meta*- nor *para*-alkylation has been reported with reaction systems using Wilkinson's catalyst.

Scheme 100



233 **234** **235**

Interestingly Brookhart *et al* reported a preliminary work, where the rhodium *bis*-olefin complex [C$_5$Me$_5$Rh(C$_2$H$_3$SiMe$_3$)$_2$] was shown to be a catalyst for the selective addition of olefins to the *ortho*- position of aromatic ketones. According to H/D exchange experiments, this rhodium complex activated all *ortho*-, *meta*-, *para*-positions of the substrates.[136]

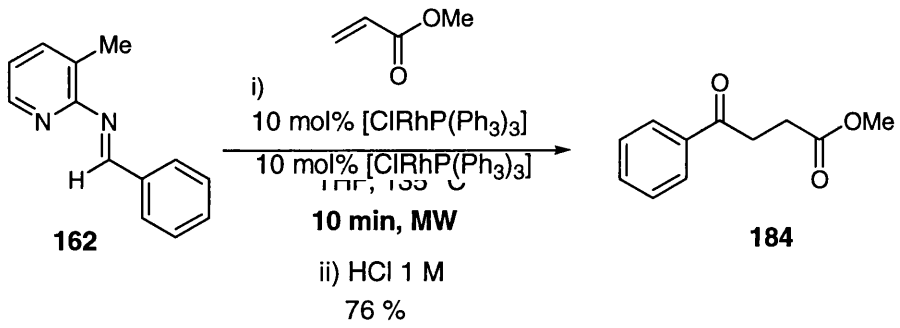
5.8 Limitations

The 1,4-dicarbonyl moiety obtained from intermolecular hydroacylation of a generalised aldehyde continues to represent a challenge. Wilkinson's catalyst is an efficient catalyst for the reaction using electron-poor olefins such as enoates, however its use is limited with subtle changes to enones rendering the reaction very slow. There is a lack of reactivity towards electron-enriched olefins. α- and β-Substituted olefins gave low conversion rates which do not facilitate their study. Once a longer tether length and *S* chelation was considered, aromatic C-H activation occurs.

To become a generalised process, the system needs to be investigated in more detail. Long reaction times are not an ideal reaction property. In order to accelerate the overall rate of the chelation-assisted hydroacylation and as a green alternative towards solvent free reactions, the use of microwave irradiation instead of conventional heating was considered.[137]

Pleasingly, the reaction of imine **162** under the standard hydroacylation conditions with Wilkinson's catalyst led after 10 minutes heating under microwave irradiation and hydrolysis to the expected product **184** in comparable yield to conventional heating (Scheme **101**).[138]

Scheme 101



162 **184**

5.9 Future work

Several challenges remain. The first is the poor reactivity of substituted olefin substrates. Possible areas to explore include:

a. A catalyst and ligand screening: in order to study the effect of other phosphorus ligands such as phosphites, bidentate phosphines or phosphine-phosphites on the reductive elimination step. Similarly other catalysts such as $[Rh(\eta^2\text{-}C_2H_4)_2Cl]_2$, cationic Rh catalysts[68] could be studied. In particular the change of metal centre from Rh to Ru (*eg* Ru(phosphines)$_n$, Ru(non-phosphines)$_n$[126] to cobalt,[136] Pd and Ni[139] should be investigated.

The use of bidentate ligands would be an interesting case to study as the geometry of the catalyst should be more rigid and the influence on the reactivity should be studied.[119]

b. To study in more detail the effect of additives containing π-bonds and lone pairs of electrons, such as pyridine or phosphites and ethers, on the reaction kinetics.[119,140]

c. Microwave reaction conditions should be investigated.[141]

Secondly, to determine whether the hydrometallation step does not occur due to steric effects on the catalyst, a Rh catalyst such as $[Rh(olefin)_2Cl_2]_2$ could be synthesised and stoichiometric reactions should be first studied.[142] ^{1}H NMR experiments could be useful to determine any migration of hydrogen by using deuterium labelled substrates.[69,136,10]

A change from *N* to other heteroatoms as coordinating group such as: *P*, *S* and *O* will be important in determining the reactivity of imine substrates with olefins.[117,115,129] As *S* chelation and longer tether length favours competitive aromatic C-H activation, this process should be investigated further and the by-products obtained with *ortho*-alkylated compounds characterised. A change in the olefin regioselectivity might also be observed with electron rich olefins.

Larger chelate-ring sizes should be further investigated particularly with *N* and *S*. The use of additives such as $ZrCl_2$ should be studied to see if these added functionalities affect the catalyst reactivity towards hydrometalation.[101]

The generalisation of the reaction to non-aromatic aldehydes should be investigated under chelation-assisted processes as cyclohexane carboxaldehyde was reported to undergo condensation with 2-amino-3-picoline without proton migration.[98]

Substituted alkynes should be studied as they offer possible further elaboration of the obtained products.[119]

Once a solution to the low conversions is found, the development of an asymmetric version can be envisaged using chiral bidentate ligands[72] already investigated in the asymmetric hydroformylation process (see Chapter II).[24] The use of chiral sulfoxides and sulfonimines can be envisaged as well as chiral or bulky substituents on the picoline ring.[143]

CHAPTER VI

EXPERIMENTAL SECTION

Chapter VI

General Experimental

^{1}H NMR spectra were recorded on JEOL 270 EX, JEOL 400 EX or Bruker AM-300 spectrometers at 270 MHz, 400 MHz and 300 MHz respectively. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or TMS (δ_H = 0 ppm) were used as internal references. Coupling constants were measured in Hz. ^{13}C spectra were recorded in $CDCl_3$, unless otherwise stated, at 100 MHz, 75 MHz or 67.5 MHz on JEOL 400 EX, Bruker AM-300 and JEOL 270 EX spectrometers respectively, using the resonance of $CDCl_3$ (δ_C = t, 77 ppm) as the internal reference. Infra red spectra were recorded in the range of 4000-600 cm^{-1} on a Perkin Elmer FT 1000 spectrometer with internal calibration. Mass spectra were carried out either at the University of Bath (Finnigan MAT 8340 instrument) or at the University of Wales, Swansea (Finnigan MAT 900 XLT instrument). Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected.

Analytical thin layer chromatography was carried out using glass-backed plates coated with Merck Kieselgel 60 GF_{254} or aluminium-backed plates coated with Merck G/UV_{254}. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, vanillin, cerium ammonium molybdate or *p*-anisaldehyde followed by heating. Flash chromatography was carried out using Merck 60 H silica or Merck Florisil®. Samples were pre-absorbed on silica or used as saturated solutions in an appropriate solvent.

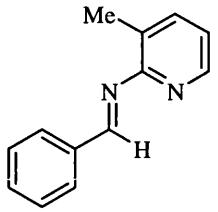
Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, toluene from sodium and dichloromethane from CaH_2 all under nitrogen. Dry 1,4

dioxane 99.9 % was purchased from Aldrich in a Sure Seal Bottle ™. Petrol refers to light petroleum, bp 40-60 °C, ether refers to diethyl ether.

Unless otherwise stated, commercially available starting materials were used throughout without any further purification. Wilkinson's catalyst was supplied by Johnson Matthey PLC. Reactions requiring anhydrous conditions were performed under nitrogen or argon in oven or flame dried apparatus.

6.1 Imines Synthesis

Preparation of Benzylidene-(3-methyl-pyridin-2-yl)-imine 162[144]

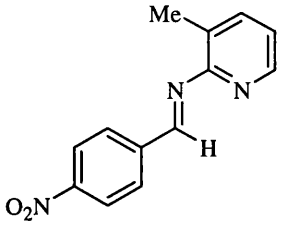


162

*The preparation of **162** is a representative procedure:*

Benzaldehyde (1.87 mL, 18.35 mmol) was added to a stirred solution of *p*-TSA (2 mg, 0.01 mmol) in toluene (15 mL) at room temperature. 2-Amino-3-picoline **164** (1.85 mL, 18.35 mmol) was added and the reaction mixture was refluxed overnight in a Dean-Stark apparatus. When no more evolution of water was observed the reaction mixture was concentrated *in vacuo* and the residue was purified by distillation under reduced pressure to give the imine **162** (2.91 g, 81 %) as a yellow oil, bp 155-157 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 3010, 2962, 2874, 1734, 1648, 680; δ_H (300 MHz; $CDCl_3$) 9.01 (1 H, s, H imine), 8.32 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 8.03-7.98 (2 H, m, 2 × phenyl), 7.55 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.49-7.46 (3 H, m, 3 × phenyl), 7.09 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.49 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 162.1, 159.9, 146.5, 139.2, 136.6, 132.1, 130.1 (2 CH), 129.8, 129.1, 122.2 (2 CH) , 17.8. Data consistent with that reported in the literature[144]

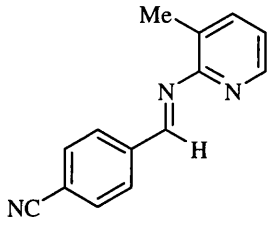
Preparation of 4-Nitrobenzylidene-(pyridin-2-yl)-imine 197[145]



197

The general procedure for the preparation of picolyl-imines was followed employing: 4-Nitrobenzaldehyde (2.12 g, 14.00 mmol), 2-amino-3-picoline **164** (1.48 mL, 14.00 mmol), *p*-TSA (2 mg, 0.01 mmol) and toluene (15 mL). Recrystallisation (from $CHCl_3$-hexane) gave the imine ***197*** (2.83 g, 84 %) as bright yellow crystals; mp 93-94 °C; ν_{max} (film)/cm^{-1} 3090, 2979, 2874, 1730, 1682, 1610, 1537, 1356, 850; δ_H (300 MHz; $CDCl_3$) 9.21 (1 H, s, H imine), 8.34-8.25 (3 H, m, 1 × picoline and 2 × phenyl), 8.17 (2 H, d, *J* 8.2, 2 × phenyl), 7.60 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.15 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline) 2.49 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 159.2, 158.6, 149.8, 146.6, 142.0, 139.6, 130.3 (2 CH), 130.1, 124.3 (2 CH), 123.3, 17.7. Data consistent with that reported in the literature.[145]

Preparation of 4-Cyanobenzylidene-(3-methyl-pyridin-2-yl)-imine 198

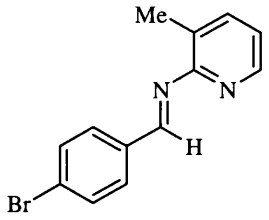


198

The general procedure for the preparation of picolyl-imines was followed employing: 4-Cyanobenzaldehyde (0.37 g, 2.86 mmol), *p*-TSA (2 mg, 0.01 mmol), toluene (15

mL), 2-amino-3-picoline (0.31 g, 2.86 mmol). Recrystallisation from $CHCl_3$-hexane gave *imine* ***198*** (0.44 g, 68 %) as a pale yellow solid, mp 83- 84 °C; ν_{max} (film)/cm^{-1} 2973, 2925, 2865, 1734, 1636, 1539, 1470, 900; δ_H (300 MHz; $CDCl_3$) 9.09 (1 H, s, H imine), 8.28 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 8.05 (2 H, d, *J* 8.2, 2 × phenyl), 7.72 (2 H, d, *J* 8.2, 2 × phenyl), 7.55 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.10 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.41 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 159.1, 158.1, 146.0, 139.0, 138.9, 134.2, 132.3 (2 CH), 129.4 (2 CH), 122.6, 118.3, 114.5, 17.4; *m/z* (EI) 220 (M^+-H, 25 %), 193 (10 %), 93 (100 %), 65 (40 %); (Found (ES) MH^+ 222.1028 $C_{14}H_{11}N_3H^+$ requires 222.1031).

Preparation of 4-Bromobenzylidene-(3-methyl-pyridin-2-yl)-imine 199

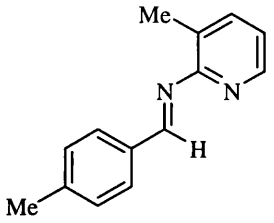


199

The general procedure for the preparation of picolyl-imines was followed employing: *p*-Bromo benzaldehyde (2.89 g, 15.63 mmol), *p*-TSA (3 mg, 0.016 mmol), toluene (15 mL), 2-amino-3-picoline (1.77 g, 15.63 mmol). The residue was purified by distillation under reduced pressure to give the *imine* ***199*** (3.87 g, 91%) as a pale green oil which crystallised as needles on standing, mp 26-27 °C; bp 170-172 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 2972, 2864, 1734, 1645, 1367, 850; δ_H (300 MHz; $CDCl_3$) 9.01(1 H, s, H imine), 8.29 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 7.82 (2 H, d, *J* 8.2, 2 × phenyl), 7.56 (2 H, d, *J* 8.2, 2 × phenyl), 7.49 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline),

7.03 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.41 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 159.1, 157.9, 145.1, 137.9, 134.1, 130.9 (2 CH), 129.6 (2 CH), 127.9, 125.2, 121.0, 16.0; *m/z* (CI, NH_3) 231 MH^+(100%) (Found: C, 56.4 %; H, 3.89 %; N, 10.1 % $C_{13}H_{11}N_2Br$ requires C, 56.7 %; H, 4.02 %; N, 10.2 %).

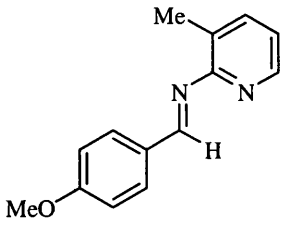
Preparation of 4-Methylbenzylidene-(3-methyl-pyridin-2-yl)-imine 200



200

The general procedure for the preparation of picolyl-imines was followed employing: 4-Methylbenzaldehyde (1.73 g, 14.00 mmol), *p*-TSA (2 mg, 0.01 mmol), toluene (15 mL), 2-amino-3-picoline **164** (1.51 g, 14.00 mmol). Distillation under reduced pressure gave the *imine **200*** (2.40 g, 82 %) as a pale green oil, bp 170-172 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 2972, 2860, 1738, 1646, 1598, 1452, 1366, 896, 816; δ_H (300 MHz; C_6D_6) 9.46 (1 H, s, H imine), 8.39 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 7.92 (2 H, d, *J* 8.2, 2 × phenyl), 7.19 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.05 (2 H, d, *J* 8.2, 2 × phenyl), 6.80 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.47 (3 H, s, CH_3), 2.11 (3 H, s, CH_3); δ_C (75 MHz; C_6D_6) 162.0, 160.1, 146.9, 142.4, 139.1 (2 CH), 134.9, 130.7 (2 CH), 129.5 (2 CH), 122.3, 21.9, 17.9; *m/z* (EI) 209 (M^+-H, 65 %), 93 (100 %), 65 (60 %); (Found (ES) MH^+ 211.1235 $C_{14}H_{14}N_2H^+$ requires 211.1235).

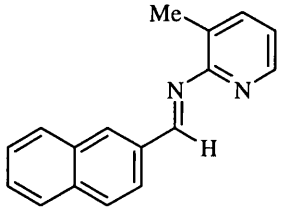
Preparation of 4-Methoxybenzylidene-(3-methyl-pyridin-2-yl)-imine 201



201

The general procedure for the preparation of picolyl-imines was followed employing: 4-Methoxybenzaldehyde (1.90 g, 14.00 mmol), *p*-TSA (2 mg. 0.01 mmol), toluene (15 mL), 2-amino-3-picoline **164** (1.51 g, 14.00 mmol). Distillation under reduced pressure gave the *imine* ***201*** (2.51 g, 89 %) as a pale green oil, bp 170-172 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 2910, 2842, 2721, 1681, 1620, 1579, 1460, 1150, 1025, 822, 774; δ_H (300 MHz; $CDCl_3$) 9.01(1 H, s, H imine), 8.29 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 7.96 (2 H, d, *J* 8.2, 2 × phenyl), 7.52 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.10 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 6.99 (2 H, d, *J* 8.2, 2 × phenyl), 3.87 (3 H, s, OCH_3), 2.46 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 162.9, 161.1, 160.2, 146.4, 139.1, 131.5 (2 CH), 129.7, 128.9, 121.8, 114.9 (2 CH), 55.9, 17.8; *m/z* (EI) 226 (M^+, 60 %), 93 (100 %), 77 (25 %), 65 (62 %); (Found (ES) MH^+ 227.1182 $C_{14}H_{14}N_2OH^+$ 227.1184).

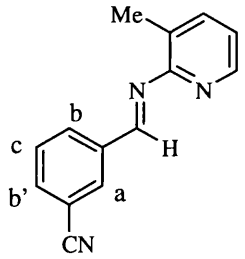
Preparation of (3-Methyl-pyridin-2-yl)-naphthalen-2-ylmethylene)-imine 203



203

The general procedure for the preparation of picolyl-imines was followed employing: 2-Naphtaldehyde (1.40 g, 8.97 mmol), *p*-TSA (2 mg, 0.01 mmol), toluene (15 mL), 2-amino-3-picoline (1.01 g, 8.97 mmol). Distillation under reduced pressure gave the *imine* ***203*** (1.96 g, 89 %) as a pale yellow oil which crystallised as needles on standing, mp 65- 66 °C; bp 170-172 °C/1 mm Hg, ν_{max} (film)/cm^{-1} 3067, 3026, 2824, 1684, 1614, 1592, 1574, 1456, 820, 748; δ_H (300 MHz; C_6D_6) 9.11 (1 H, s, H imine), 8.22 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 8.15 (2 H, d, *J* 8.2, 2 × arom.), 7.85-7.72 (3 H, m, 2 × arom. and 1 × picoline), 7.47-7.36 (3H, m, 3 × arom.), 6.95 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.39 (3 H, s, CH_3); δ_C (75 MHz; C_6D_6) 162.2, 160.1, 146.8, 139.5, 135.9, 134.7, 133.7, 133.0, 129.6 (2 CH), 129.5, 129.2, 128.5 (2 CH), 124.8, 122.5, 18.1; *m/z* (CI^+, NH_3) 247 (MH^+, 100 %), 109 (20 %); (Found (ES) MH^+ 247.1237 $C_{17}H_{14}N_2H^+$ requires 247.1235).

Preparation of 3-Cyanobenzylidene-(3-methyl-pyridin-2-yl)-imine 204

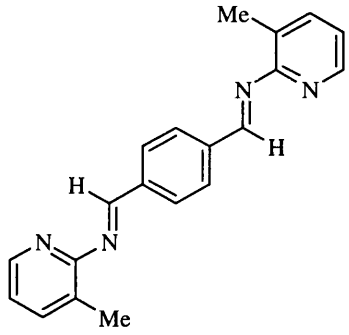


204

The general procedure for the preparation of picolyl-imines was followed employing: 3-Cyanobenzaldehyde (0.42 g, 3.14 mmol), *p*-TSA (2 mg, 0.01 mmol), toluene (15 mL), 2-amino-3-picoline (0.34 g, 3.14 mmol). Recrystallisation from $CHCl_3$-hexane gave *imine* ***204*** (0.38 g, 55 %) as a pale yellow solid, mp 85-86°C; ν_{max} (film)/cm^{-1} 2980, 2865, 1734, 1636, 1542, 1470, 844, 720; δ_H (300 MHz; $CDCl_3$) 9.11 (1 H, s, H

imine), 8.32-8.30 (2 H, m, 2 × phenyl (a & c)), 8.17 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 7.76 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 7.61-7.57 (2 H, m, 2 × phenyl (b & b')), 7.14 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.09 (3 H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 158.6, 158.0, 146.0, 139.0, 137.2, 134.2, 133.3, 132.2, 129.4, 129.3, 122.5, 118.2, 113.0, 17.4; *m/z* (CI, NH_3) 222 (MH^+, 100 %), 108 (35 %), (Found (ES) MH^+ 222.1026 $C_{14}H_{11}N_3H^+$ requires 222.1031).

Preparation of (3-Methyl-pyridin-2-yl)-4[4-(3'-methyl-pyridin-2'-yl)iminomethylbenzylidene]-imine 214

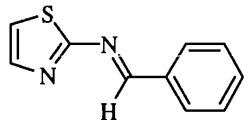


214

The general procedure for the preparation of picolyl-imines was followed employing: Benzene-1,4-dicarboxaldehyde (1.07 g, 8.04 mmol), *p*-TSA (4 mg, 0.02 mmol), toluene (15 mL), 2-amino-3-picoline **164** (1.74, 16.08 mmol). Recrystallisation from $CHCl_3$-hexane gave *imine **214*** (1.83g, 73 %) as bright yellow needles; mp 141-142 °C; ν_{max} (film)/cm^{-1} 2972, 1738, 1646, 1598, 1366, 896; δ_H (300 MHz; $CDCl_3$) 9.15 (2 H, s, *2* × H imine), 8.32 (2 H, dd, *J* 4.6 and 1.1, 2 × picoline), 8.11 (4 H, s, 4 × phenyl), 7.55 (2 H, dd, *J* 7.4 and 1.1, 2 × picoline), 7.11 (2 H, dd, *J* 7.4 and 4.6, 2 × picoline), 2.49 (6H, s, 2 × CH_3); δ_C (75 MHz; $CDCl_3$) 161.1 (2 C),159.5 (2 C), 146.6 (2 C), 139.4 (2 C), 139.3 (2 C), 130.0 (4 C), 129.5 (2 C), 122.5 (2 C), 17.8 (2 C);

(Found: C, 76.0 %; H, 5.84 %; N, 17.9 % $C_{20}H_{18}N_4$ requires C, 76.4 %; H, 5.77 %; N, 17.8 %); *m/z* (CI^+, NH_3) 315 (MH^+, 70 %), 109 (100 %); (Found (ES) MH^+ 315.1610 $C_{20}H_{18}N_4H^+$ requires 315.1609).

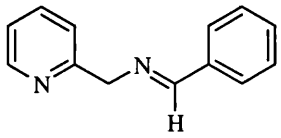
Preparation of Benzylidene-thiazol-2-yl-imine 221[146]



221

Benzaldehyde (1.04 mL, 10.23 mmol) was added to a stirred solution of *p*-TSA (2 mg, 0.01 mmol) in toluene (15 mL) at room temperature. 2-Aminothiazole (1.03 g, 10.23 mmol) was added and the mixture was refluxed overnight in a Dean-Stark apparatus. When no more evolution of water was observed the reaction mixture was concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give the imine ***221***(1.09 g, 57 %) as a yellow-green oil which crystallised on standing, mp 98-99 °C (from $CHCl_3$-hexane), bp 170-173 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 3150, 3062, 3026, 2871, 2837, 1700, 1645, 1550, 1450, 1318, 1050, 849 , 757; δ_H (300 MHz; $CDCl_3$) 9.22 (1 H, s, H imine), 7.88-7.82 (2 H, m, 2 × phenyl), 7.55 (1 H, d, *J* 4.3, 1 × thiazole), 7.12-7.08 (3H, m, 3 × phenyl), 6.68 (1 H, d, *J* 4.3, 1× thiazole); δ_C (75 MHz; $CDCl_3$) 174.6, 161.0, 140.0, 134.0, 130.6, 128.2 (2 CH), 127.8 (2 CH), 117.1; m/z (EI): 189 MH^+ (5 %), 188 M^+ (15 %), 187 (50 %), 121 (95 %), 58 (100 %), (Found (ES) MH^+, 189.0488. $C_{10}H_8N_2SH^+$ requires 189.0486). Data consistent with that reported in the literature.[146]

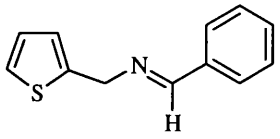
Preparation of Benzylidene-pyridin-2-ylmethyl-imine 224



224

Benzaldehyde (1.43 mL, 14.06 mmol) was added to a stirred solution of *p*-TSA (2 mg, 0.01 mmol) in toluene (15 mL) at room temperature. 2-Aminomethylpyridine (1.45 mL, 14.00 mmol) was added and the mixture was refluxed overnight in a Dean-Stark apparatus. When no more evolution of water was observed the reaction mixture was concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give the *imine **224*** (2.10 g, 77 %) as a bright yellow oil, bp 155-157 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 3055, 3010, 2882, 2842, 1645, 1589, 1495, 1484, 1435, 1310, 1220, 1147, 1049, 756, 686; δ_H (300 MHz; acetone-d_6) 8.57-8.40 (2 H, broad s, H imine and 1 × pyridine), 7.88-7.75 (2 H, m, 2 × pyridine), 7.73-7.65 (1 H, m, 1 × phenyl), 7.47-7.28 (4 H, m, 4 × phenyl), 7.24-7.11 (1 H, m, 1 × pyridine), 4.85 (2 H, broad s, CH_2); δ_C (75 MHz; $CDCl_3$) 163.8, 160.9, 150.5, 137.7, 137.6, 132.0, 129.8 (2 CH), 129.4 (3 CH), 123.3, 67.7; *m/z* (EI) 197 MH^+ (15 %), 180 (20 %), 93 (100 %); (Found (ES) MH^+, 197.1085 $C_{13}H_{12}N_2H^+$ requires 197.1079).

Preparation of Benzylidene-thiophen-2-ylmethyl-imine 225[147]

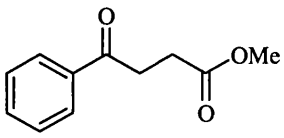


225

Benzaldehyde (1.43 mL, 14.06 mmol) was added to a stirred solution of *p*-TSA (2 mg, 0.01 mmol) in toluene (15 mL) at room temperature. 2-Thiophenemethylamine (1.43 mL, 13.00 mmol) was added and the mixture was refluxed overnight in a Dean-Stark apparatus. When no more evolution of water was observed the reaction mixture was concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give the imine ***225*** (1.82 g, 70 %) as a pale green oil, bp 150-153 °C/1 mm Hg; ν_{max} (film)/cm^{-1} 3271, 3082, 3062, 3026, 2871, 2837, 1700, 1643, 1579, 1450, 1318, 1025, 849, 758, 693; δ_H (300 MHz; $CDCl_3$) 8.39 (1 H, s, H imine), 7.82 (2 H, dd, *J* 4.1 and 3.5, 2 × thiophene), 7.46-7.42 (3 H, m, 3 × phenyl), 7.27-7.25 (1 H, m, 1 × thiophene), 7.02-7.01 (2 H, m, 2 × phenyl), 5.01 (2 H, s, CH_2); δ_C (75 MHz; $CDCl_3$) 162.6, 142.4, 136.3, 131.3, 129.0 (2 CH), 128.9(2 CH), 127.2, 125.3, 125.1, 59.7; (Found: C, 71.5 %; H, 5.56 %; N, 7.1 % $C_{12}H_{11}N_1S$ requires C, 71.6 %; H, 5.51 %; N, 7.0 %). Data consistent with that reported in the literature.[147]

6.2 Hydroacylation Reactions

Preparation of Methyl 4-oxo-4-phenylbutanoate 184[148]



184

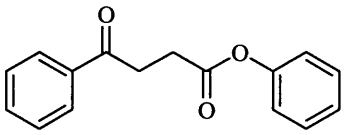
Method a:

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (60 mg, 0.33 mmol,) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (31 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow-orange was observed. Methyl acrylate (36 μL, 0.40 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give the dicarbonyl compound ***184*** (46 mg, 73 %) as a yellow oil; ν_{max} (film)/cm^{-1} 2949, 1748, 1728, 1685, 1595, 1447, 1356, 1168, 1068, 755; δ_H (300 MHz; $CDCl_3$) 7.97-7.93 (2 H, m, 2 × phenyl), 7.57-7.55 (1H, m, 1 × phenyl), 7.49-7.44 (2 H, m, 2 × phenyl), 3.71 (3 H, s, OMe), 3.33 (2 H, t, *J* 6.7, CH_2), 2.77 (2 H, t, *J* 6.7, CH_2); δ_C (75 MHz; $CDCl_3$) 198.0, 173.3, 136.4, 133.2, 128.5 (2 C), 128.0 (2 C), 51.8, 33.3, 27.9. Data consistent with that reported in the literature.[148]

Method b:

A solution of benzylidene-thiazol-2-yl-imine ***162*** (45 mg, 0.24 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (22 mg, 10 mol %,) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (64 μL, 0.72 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give the dicarbonyl compound ***184*** (36 mg, 80 %).

Preparation of Phenyl 4-(4'-phenyl)-4-oxobutanoate (Table 5, entry 2)

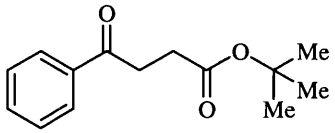


(Table 5, entry 2)

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (125 mg, 0.68 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (63 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Phenyl acrylate (163 mg, 1.02 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at

135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give *dicarbonyl compound* ***(Table 5, entry 2)*** (43 mg, 27 %) as a yellow oil which crystallised on standing as a yellow solid, mp 38-39 °C; ν_{max} (film)/cm^{-1} 2952, 1740, 1679, 1620, 1475, 1150, 0890, 655; δ_H (400 MHz; $CDCl_3$) 8.07-8.01 (2 H, m, 2 × phenyl), 7.58-7.54 (1 H, m,1 × phenyl), 7.52-7.45 (2H, m, 2 × phenyl), 7.42-7.35 (2 H, m, 2 × phenyl), 7.22-7.19 (1 H, m, 1 × phenyl), 7.14-7.09 (2 H, m, 2 × phenyl), 3.43 (2 H, t, *J* 6.6, CH_2), 3.02 (2 H, t, *J* 6.6, CH_2); δ_C (75 MHz; $CDCl_3$) 197.8, 171.6, 150.8, 136.6, 133.5, 129.5 (2 C), 128.8 (2 C), 128.2 (2 C), 125.9, 121.7 (2 C), 33.8, 22.8; *m/z* (CI^+, NH_3) 272 (MNH_4^+,100 %), 255 (MH^+, 50 %); (Found (ES) MH^+ 255.1020 $C_{16}H_{14}O_3H^+$ requires 255.1021).

Preparation of *tert*-Butyl 4-oxo-4-phenylbutanoate 185 (Table 5, entry 3)[149]

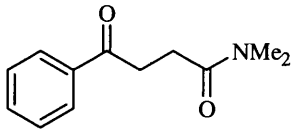


185 (Table 5, entry3)

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (127 mg, 0.70 mmol,) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (64 mg, 10 mol %,) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. ^{ter}Butyl acrylate (307 μL, 2.10 mmol) in THF (2 mL) was added *via* cannula and the

reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give the dicarbonyl compound ***185 (Table 5, entry 3)*** (136 mg, 83 %) as a brown oil; ν_{max} (film)/cm^{-1} 2932, 2888, 1748, 1723, 1645, 1595, 1447, 1356, 1168, 1068, 725, 680; δ_H (300 MHz; $CDCl_3$) 7.91-7.88 (2 H, m, 2 × phenyl), 7.47-7.44 (1H, m, 1 × phenyl), 7.36-7.32 (2 H, m, 2 × phenyl), 3.17 (2 H, t, *J* 6.9, CH_2), 2.59 (2 H, t, *J* 6.9, CH_2), 1.36 (9 H, s, ^{t}Bu); δ_C (75 MHz; $CDCl_3$) 198.2, 172.0, 136.6, 133.0, 128.4 (2 C), 127.9 (2 C), 80.4, 33.3, 29.3, 27.9 (3 CH_3). Data consistent with that reported in the literature.[149]

Preparation of *N,N*-Dimethyl 4-oxo-4-phenylbutyramide (Table 5, entry 4)[150]

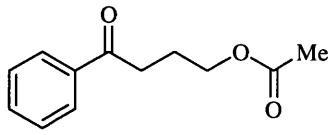


(Table 5, entry 4)

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (122 mg, 0.63 mmol,) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (58 mg, 10 mol %,) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Dimethyl acrylamide (195 μL, 1.89 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then

heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 30 % EtOAc-petrol) to give dicarbonyl compound ***(Table 5, entry 4)*** (85 mg, 70 %) as a brown oil; ν_{max} (film)/cm^{-1} 3040, 2926,1697, 1640, 1603, 1528, 1403, 1346, 730, 680; δ_H (300 MHz; C_6D_6) 8.02-7.88 (2 H, m, 2 × phenyl), 7.28-7.12 (3 H, m, 3 × phenyl), 3.21 (2 H, t, *J* 6.6, CH_2), 2.71 (3 H, s, NMe), 2.49 (2 H, t, *J* 6.6, CH_2), 2.36 (3 H, s, NMe); δ_C (75 MHz; C_6D_6) 199.0, 171.2, 138.0 (2 CH), 132.8 (2 CH), 132.6, 132.0, 36.5, 35.3, 34.7, 27.8; Data consistent with that reported in the literature.[150]

Preparation of Methyl 4-phenyl-4-oxo-butanoate (Table 5, entry 6)[151]

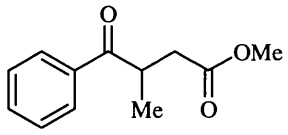


(Table 5, entry 6)

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (127 mg, 0.70 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (64 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Allyl acetate (302 μL, 2.80 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and

poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give ***(Table 5, entry 6)*** (175 mg, 81 %) as a yellow oil; ν_{max} (film)/cm^{-1} 3123, 2968, 2920, 2865, 1735, 1672, 1648, 1448,1355, 1255, 1138, 1072, 732, 680; δ_H (300 MHz; $CDCl_3$) 7.95-7.89 (2 H, m, 2 × phenyl), 7.56-7.52 (1 H, m, 1 × phenyl), 7.46-7.41 (2 H, m, 2 × phenyl), 4.16 (2 H, t, J 6.4, OCH_2), 3.07 (2 H, t, J 6.4, CH_2), 2.09 (2 H, q^t, J 6.4, $CH_2CH_2CH_2$), 2.03 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 198.0, 173.4, 136.5, 133.4, 128.6 (2 CH), 128.0 (2 CH), 61.0, 35.3, 23.4, 19.9; m/z (CI^+, NH_3) 224 (MNH_4^+, 100 %), 207 (MH^+, 5 %); (Found (EI^+) MH^+ 207.2486 $C_{12}H_{14}O_3H^+$ requires 207.2487). Data consistent with that reported in the literature.[151]

Preparation of Methyl 2-methyl-4-oxo-4-phenylbutanoate (Table 7, entry 2)[152]



(Table 7, entry 2)

Method a

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (381 mg, 2.10 mmol) in THF (4 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (22 mg, 01 mol %) in THF (4 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl crotonate (890 μL, 6.30 mmol) in THF (4 mL) was added *via* cannula and the reaction vessel was flushed with argon and then heated to THF reflux for 24 h at

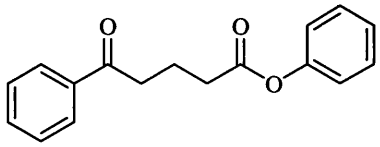
atmospheric pressure. The reaction was cooled to room temperature concentrated *in vaccuo*, then diluted with EtOAc (30 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, gradient EtOAc-petrol) to give dicarbonyl compound ***(Table7, entry 2)*** (13 mg, 5 %) as a yellow oil; ν_{max} (film)/cm^{-1} 3092, 2958, 2920, 2860, 1735, 1685, 1638, 1470,1355, 1265, 1168, 1076, 732, 691; δ_H (270 MHz; $CDCl_3$) 8.06-7.95 (2 H, m, 2 × phenyl), 7.45-7.18 (3 H, m, 3 × phenyl), 4.06-3.92 (1 H, m, CH), 3.65 (3 H, s, OMe), 2.97 (1 H, dd, *J* 16.6 and 8.2, 1 × C*H*CO_2Me), 2.43 (1 H, dd, *J* 16.6 and 5.8, 1 × C*H*CO_2Me), 1.24 (3 H, d, *J* 7.4, CH_3); δ_C (75 MHz; $CDCl_3$) 196.1, 174.4, 132.1, 131.2 (2 CH), 127.0 (2 CH), 126.1, 55.0, 34.7, 30.4, 27.2. Data consistent with that reported in the literature.[152]

Method b

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (127 mg, 0.70 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (64 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl crotonate (223 μL, 2.10 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon and then heated to THF reflux for 18 h at atmospheric pressure. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, gradient EtOAc-petrol) to give dicarbonyl compound ***(Table 7, entry 2)*** (35 mg, 24 %). Data consistent with that reported in the literature.[152]

Preparation of Phenyl 5-phenyl-2-oxo-5-phenylpentanoate 187 (Table 7, entry 4)[153]

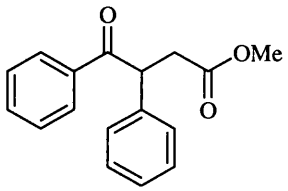


187 (Table 7, entry 4)

A solution of 4-methylbenzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (123 mg, 0.70 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (58 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Phenyl crotonate (prepared from a literature procedure)[154] (176 mg, 1.10 mmol), in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound ***187 (Table 7, entry 4)*** as white crystals (24 mg, 14 %), mp 74-75 °C (from $CHCl_3$-hexane); ν_{max} (film)/cm^{-1} 3060, 2942, 1753, 1684, 1595, 1440, 1449, 1265, 1195, 1134, 910, 734; δ_H (300 MHz; $CDCl_3$) 7.92-7.88 (2 H, m, 2 × phenyl), 7.52-

7.49 (1 H, m, 1 × phenyl), 7.41-7.36 (2 H, m, 2 × phenyl), 7.30-7.27 (2 H, m, 2 × phenyl), 7.15-7.08 (1 H, m, 1 × phenyl), 6.97-6.91 (2 H, m, 2 × phenyl), 3.08 (2 H, t, *J* 7.1, 2 × CH_2), 2.64 (2 H, t, *J* 7.1, 2 × CH_2), 2.13 (2 H, quintuplet, *J* 7.1, 2 × CH_2); δ_C (75 MHz; $CDCl_3$) 201.0, 173.5, 152.3, 138.4, 134.8, 131.1 (2 CH), 130.3 (2 CH), 129.7 (2 CH), 126.0, 123.2 (2 CH), 38.9, 35.0, 20.9; *m/z* (CI^+, NH_3) 269 (MH^+, 65 %), 286 (MNH_4^+, 100 %); (Found (ES) MH^+ 269.1187 $C_{17}H_{16}O_3H^+$ requires 269.1177). Data consistent with that reported in the literature.[153]

Preparation of Methyl 3-phenyl-4-oxo-4-phenylbutanoate (Table 7, entry 5)[155]

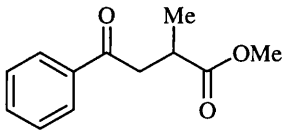


(Table 7, entry 5)

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (127 mg, 0.70 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (64 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl cinnamate (340 mg, 2.10 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 12 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2,

gradient EtOAc-petrol) to give dicarbonyl compound ***(Table 7, entry 5)*** (13 mg, 7 %) as a yellow solid, mp 89-90 °C; ν_{max} (film)/cm^{-1} 3032, 2810, 1735, 1670, 1648, 1448, 1346, 1150, 1076, 770, 738; δ_H (270 MHz; $CDCl_3$) 8.01-7.96 (2 H, m, 2 × phenyl), 7.49-7.44 (1 H, m, 1 × phenyl), 7.41-7.33 (2 H, m, 2 × phenyl), 7.29-7.18 (5 H, m, 5 × phenyl), 5.09 (1 H, dd, *J* 17.1 and 5.1, CH), 3.64 (3 H, s, OMe), 3.39 (1 H, dd, *J* 17.1 and 9.8, 1 × CH_2), 2.72 (1 H, dd, *J* 9.8 and 5.1, 1 × CH_2); δ_C (75 MHz; $CDCl_3$) 198.5, 172.5, 138.1 (2 CH), 136.1, 133.0 (2 CH), 129.2 (2 CH), 128.9, 128.5 (2 CH), 128.1, 127.5, 51.8, 49.5, 38.4. Data consistent with that reported in the literature.[155]

Preparation of Methyl 3-methyl-4-oxo-4-phenylbutanoate (Table 7, entry 7)[156]



(Table 7, entry 7)

Method a

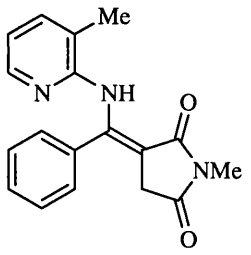
A solution of benzylidene-thiazol-2-yl-imine ***221*** (155 mg, 0.83 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (70 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl methacrylate (266 μL, 2.49 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*.

The residue was purified by flash chromatography (SiO_2, 10 % EtOAc-petrol) to give dicarbonyl compound ***(Table 7, entry 7)*** (27 mg, 16 %) as a brown oil; ν_{max}(film)/cm^{-1} 3060, 3028, 2951, 2879, 1735, 1685, 1636,1597, 1448, 1346, 1265, 1168, 1076, 756, 691; δ_H (300 MHz; $CDCl_3$) 7.91-7.86 (2 H, m, 2 × phenyl), 7.48-7.43 (1 H, m, 1 × phenyl), 7.45-7.41 (2 H, m, 2 × phenyl), 3.66 (3 H, s, OMe), 3.42 (1 H, dd, *J* 17.6 and 8.2, 1 × CH_2), 3.10-3.04 (1 H, m, CH), 2.95 (1 H, dd, *J* 17.6 and 5.1, 1 × CH_2), 1.12 (3 H, d, *J* 7.2, Me); δ_C (75 MHz; $CDCl_3$) 193.1, 173.4, 134.1, 134.0 (2 CH), 125.0 (2 CH), 125.0, 52.0, 35.7, 28.4, 27.3. Data consistent with that reported in the literature.[156]

Method b

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (127 mg, 0.70 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (64 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl methacrylate (225 μL, 2.1 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 12 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 10 % EtOAc-petrol) to give dicarbonyl compound ***(Table 7, entry 7)*** (21 mg, 15 %) as a brown oil. Data consistent with that reported in the literature.[156]

Preparation of *N*-methyl-3-[(3-methyl-pyridin-2-amino)-phenyl-methylene]-pyrrolidine-2,5-dione 188

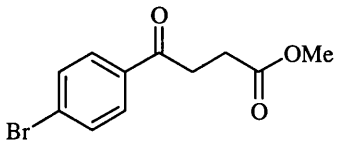


188

A solution of benzylidene-(3-methyl-pyridin-2-yl)-imine ***162*** (134 mg, 0.73 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (66 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl maleimide (272 mg, 2.19 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give *enamine* compound ***188*** (175 mg, 81 %) as a yellow solid, mp 118-119 °C (from $CHCl_3$-hexane); ν_{max} (film)/cm^{-1} 2994, 2930, 2876, 2838,1654, 1616, 1564, 1549, 1452, 720; δ_H (300 MHz; C_6D_6) 10.92 (1 H, s, H enamine), 7.62 (1 H, dd, *J* 4.6 and 1.1, 1 × picoline), 7.11-7.05 (5 H, d, m, 5 × phenyl), 6.75 (1 H, dd, *J* 7.4 and 1.1, 1 × picoline), 6.19 (1 H, dd, *J* 7.4 and 4.6, 1 × picoline), 2.75 (3 H, s, N-Me), 2.68 (2 H, s, CH_2), 2.13(3 H, s, CH_3); δ_C (75 MHz; C_6D_6) 173.8, 173.2, 152.7, 151.2, 145.8 (2 C), 143.1, 138.4, 137.1 (2 C), 128.0 (2 C), 121.9, 117.9, 99.8, 34.0, 24.2, 17.6; *m/z* (EI^+)

307 (MH^+, 20 %), 222 (100 %), 92 (25 %), (Found (ES) MH^+308.1292 $C_{17}H_{17}N_3O_2H^+$ requires 308.1399).

Preparation of Methyl 4-(4'-bromophenyl)-4-oxobutanoate (Table 12, entry 3)[157]

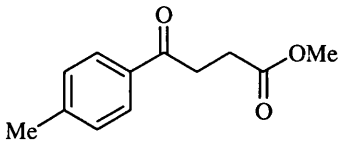


(Table 12, entry 3)

A solution of 4-bromobenzylidene-(3-methyl-pyridin-2-yl)-imine ***199*** (221 mg, 0.80 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (69 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (217 μL, 2.40 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound **(Table 12, entry 3)** (184 mg, 85 %) as a yellow oil; ν_{max} (film)/cm^{-1} 3019, 2953, 1735, 1686, 1576, 1438, 1400, 1356, 1323, 1218, 1171, 1070, 817, 756; δ_H (300 MHz; $CDCl_3$) 7.76 (2 H, d, *J* 8.6, 2 × phenyl), 7.53 (2 H, d, *J* 8.6, 2 × phenyl), 3.65 (3 H, s, OMe), 3.21 (2 H, t, *J* 6.5, CH_2), 2.68 (2 H, t, *J* 6.5, CH_2); δ_C (75 MHz; $CDCl_3$) 197.0, 173.1, 135.2, 131.8 (2 CH), 129.5 (2

CH), 128.3, 51.8, 33.2, 27.8; *m/z* (EI) 272 (MH^+, 10 %), 239 (10 %), 183 (100 %), 155 (30 %), 76 (45 %); (Found (ES^+) ^{79}Br, MNH_4^+ 288.0231 $C_{11}H_{11}O_3{}^{79}BrNH_4^+$ requires 288.0235); Data consistent with that reported in the literature.[157]

Preparation of Methyl 4-(4'-methylphenyl)-4-oxobutanoate (Table 12, entry 4)[158]

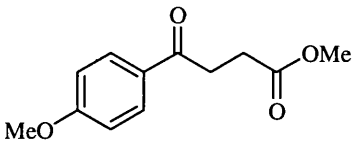


(Table 12, entry 4)

A solution of 4-methylbenzylidene-(3-methyl-pyridin-2-yl)-imine ***200*** (246 mg, 1.17 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (81 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (316 μL, 3.51 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound **(Table 12, entry 4)** (236 mg, 98 %) as a yellow oil; ν_{max} (film)/cm^{-1} 3030, 2951, 2920, 2850, 1732, 1673, 1610, 1570, 1433, 1404, 1324, 1215, 1169, 998, 809, 734; δ_H (300 MHz; $CDCl_3$) 7.82 (2 H, d, *J* 8.2, 2 × phenyl), 7.16 (2 H, d, *J* 8.2, 2 × phenyl), 3.61 (3 H, s, OMe), 3.22 (2 H, t, *J* 6.4, CH_2),

2.67 (2 H, t, *J* 6.4, CH_2), 2.29 (3 H, s, Me); δ_C (75 MHz; $CDCl_3$) 197.9, 173.7, 144.3, 134.4, 129.6 (2 CH), 128.4 (2 CH), 52.1, 33.6, 28.4, 21.9; *m/z* (EI) 206 (M^+, 10 %), 175 (7 %), 119 (100 %), 91 (65 %); (Found (EI) MH^+ 207.1020 $C_{12}H_{14}O_3H^+$ requires 207.1021). Data consistent with that reported in the literature.[158]

Preparation of Methyl 4-(4'-methoxyphenyl)-4-oxobutanoate (Table 12, entry 5)[159]

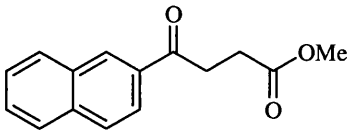


(Table 12, entry 5)

A solution of 4-methoxybenzylidene-(3-methyl-pyridin-2-yl)-imine ***201*** (160 mg, 0.79 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (70 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (240 μL, 2.37 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, gradient EtOAc-petrol) to give dicarbonyl compound ***(Table 12, entry 5)*** (144 mg, 83 %) as a brown oil; ν_{max} (film)/cm^{-1} 2950, 2928, 2888, 1749, 1723, 1645, 1447, 1356, 1250,1117, 1068, 820; δ_H (300 MHz; $CDCl_3$) 7.88 (2 H, d, *J* 8.2, 2 × phenyl), 6.86 (2

H, d, *J* 8.2, 2 × phenyl), 3.82 (3 H, s, OMe), 3.62(3 H, s, OMe), 3.23 (2 H, t, *J* 6.6, CH_2), 2.71 (2 H, t, *J* 6.6, CH_2); δ_C (75 MHz; $CDCl_3$) 196.9, 173.8, 163.9, 130.2 (2 CH), 130, 114.1 (2 CH), 55.8, 52.1, 33.3, 28.4; *m/z* (EI^+): 222 (M^+, 25 %), 191 (25%), 135 (100 %), 107 (35 %), 92 (45 %), 77 (55 %); (Found (ES) MH^+ 223.0969 $C_{12}H_{14}O_4H^+$ requires 223.0970). Data consistent with that reported in the literature.[159]

Preparation of 4-Methyl 4-naphthalen-2-yl-4-oxo-butanoate 206[160]

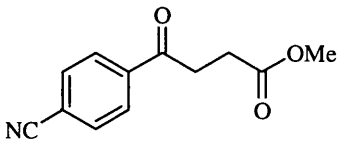


206

A solution of (3-methyl-pyridin-2-yl)-naphthalen-2-ylmethylene)-imine ***203*** (198 mg, 0.80 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (74 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (217 μL, 2.40 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound ***206*** (138 mg, 71 %) as a yellow solid, mp 68-69 °C (from $CHCl_3$-hexane); ν_{max} (film)/cm^{-1} 2952, 2843, 1736, 1679, 1622, 1463, 1377, 1307, 1149, 980, 796, 765, 745; δ_H (300 MHz; $CDCl_3$) 8.35 (1 H, s, 1 x

arom), 7.93 (1 H, dd, *J* 8.6 and 1.6, 1 × arom), 7.85-7.72 (3 H, m, 3 × arom), 7.52-7.39 (2 H, m, 2 × arom), 3.62 (3 H, s, OMe), 3.33 (2 H, t, *J* 6.6, CH_2), 2.7 (2 H, t, *J* 6.6, CH_2); δ_C (75 MHz; $CDCl_3$) 196.1, 171.5, 133.7, 132.8, 131.9, 127.9, 126.6, 126.2, 125.9 (2 C), 124.9, 121.8 (2 C), 50.0, 31.6, 26.2; *m/z* (EI^+) 242 (M^+, 25 %), 155 (100 %), 127 (90 %), 77 (20 %); (Found (ES) MH^+ 243.1026 $C_{15}H_{14}O_3H^+$ requires 243.1021). Data consistent with that reported in the literature.[160]

Preparation of Methyl 4-(4'-cyanophenyl)-4-oxobutanoate (Table 13, entry 2)[161]

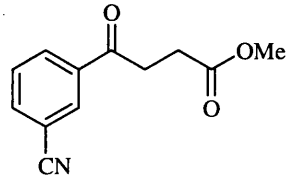


(Table 13, entry 2)

A solution of 4-cyanobenzylidene-(3-methyl-pyridin-2-yl)-imine ***(Table 12, entry 2)*** (28 mg, 0.10 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (17 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (30 μL, 0.30 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 2 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound ***(Table 13, entry 2)*** (18 mg, 80 %) as a

pale yellow solid; mp 83-84 °C; ν_{max} (film)/cm^{-1} 3032, 2960, 2925, 2854, 1735, 1695, 1648, 1435, 1360, 1119, 820; δ_H(400 MHz; $CDCl_3$) 7.99 (2 H, d , *J* 8.1, 2 × phenyl), 7.72 (2 H, d, *J* 8.1, 2 × phenyl), 3.64 (3 H, s, OMe), 3.24 (2 H, t, *J* 6.6, CH_2), 2.73 (2 H, t, *J* 6.6, CH_2); δ_C (75 MHz; $CDCl_3$) 196.8, 173.1, 139.5, 134.2, 132.7 (2 CH),128.6 (2 CH), 118.1, 52.3, 28.2, 14.6. Data consistent with that reported in the literature.[161]

Preparation of Methyl 4-(3-cyano phenyl)-4-oxo-butanoate (Table 13, entry 3)

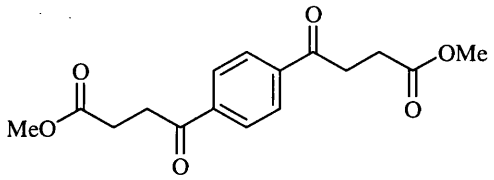


(Table 13, entry 3)

A solution of 3-cyanobenzylidene-(3-methyl-pyridin-2-yl)-imine ***204*** (34 mg, 0.15 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (16 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (42 μL, 0.45 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 8 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give ***(Table 13, entry 3)*** as a thick yellow oil (16mg, 48 %); ν_{max} (film)/cm^{-1} 3022, 2953, 2925, 2854, 1735, 1695, 1599, 1435, 1360, 1222, 1157, 992,

758; δ_H (400 MHz; $CDCl_3$) 8.20 (1 H, s, 1 × phenyl), 8.14 (1 H, d, *J* 7.8, 1 × phenyl), 7.78 (1 H, d, *J* 7.8, 1 × phenyl), 7.55 (1 H, t, *J* 7.8, 1 × phenyl), 3.64 (3 H, s, OCH_3), 3.23 (2 H, t, *J* 6.3, CH_2), 2.73 (2 H, t, *J* 6.3, CH_2); δ_C (75 MHz; $CDCl_3$) 196.1, 173.1, 148.0, 137.4, 136.3, 132.1, 131.9, 129.9, 113.4, 52.3, 28.2, 17.6; *m/z* (EI) 217 (M^+, 5 %), 186 (60 %), 158 (10 %), 130 (100 %), 102 (65 %), 75 (18 %); (Found MH^+ (ES) 218.0826 $C_{12}H_{11}NO_3H^+$ requires 218.0817) together with the hydrolysed starting material as aldehyde (7 mg, 35 %).

Preparation of Methyl 4-[4-(3-methoxycarbonyl-propionyl)-phenyl]-4-oxobutanoate 215

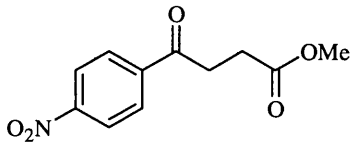


215

A solution of (3-methyl-pyridin-2-yl)-4[4-(3'-methyl-pyridin-2'-yl)iminomethyl-benzylidene]-imine **214** (282 mg, 1.79 mmol) in THF (1 mL) was added dropwise via cannula to a solution of $[ClRh(PPh_3)_3]$ (167 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (484 μL, 5.36 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and then heated at 135 °C for 6 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted

with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 25 % EtOAc-petrol) to give the tetracarbonyl compound ***215*** (212 mg, 78 %) as pale yellow plates, mp 95-96 °C (from $CHCl_3$-hexane); ν_{max} (film)/cm^{-1} 3061, 3030, 2997, 2918, 2842, 2727, 1756, 1718, 1672, 1622, 1580, 1462, 1216, 759; δ_H (300 MHz; $CDCl_3$) 8.01 (4 H, s, 4 × phenyl), 3.65 (6H, s, 2 × OMe), 3.29 (4 H, t, J 6.8, 2 × CH_2), 2.70 (4 H, t, J 6.8, 2 × CH_2CO_2Me); δ_C (75 MHz; $CDCl_3$) 197.9 (2 C), 173.5 (2 C), 140.1 (2 C), 128.6 (4 C), 52.2 (2 C), 34.1 (2 C), 28.2 (2 C); m/z (EI) 306 (M^+, 3 %), 277 (40 %), 219 (100 %), 104 (30 %), 77 (30 %); (Found (ES) MH^+ 307.1176 $C_{16}H_{18}O_6H^+$ requires 307.1182).

Preparation of Methyl 4-(4'-nitrophenyl)-4-oxobutanoate (Table 14, entry 1)[162]

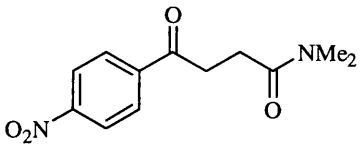


(Table 14, entry 1)

A solution of 4-nitrobenzylidene-(3-methyl-pyridin-2-yl)-imine ***216*** (164 mg, 0.68 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$] (63 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (130 μL, 2.04 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 20 minutes. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases

were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give dicarbonyl compound ***(Table 14, entry 1)*** (129 mg, 80 %) as a yellow solid, mp 86-87 °C; ν_{max} (film)/cm^{-1} 2954, 1736, 1680, 1602, 1526, 1437, 1343, 1319, 1216, 1167, 998, 854, 754; δ_H (400 MHz; $CDCl_3$) 8.24 (2 H, d , *J* 8.7, 2 × phenyl), 8.18 (2 H, d, *J* 8.7, 2 × phenyl), 3.64 (3 H, s, OMe), 3.31 (2 H, t, *J* 6.4, CH_2), 2.72 (2 H, t, *J* 6.4, CH_2); δ_C (75 MHz; $CDCl_3$) 197.0, 173.3, 150.7, 141.3, 129.9 (2 CH), 124.2 (2 CH), 52.3, 34.2, 28.2; *m/z*, (EI) 237 (M^+, 5 %), 206 (10 %), 150 (70 %), 104 (70 %), 76 (100 %), (Found ES) MNH_4^+ 255.0977; $C_{11}H_{11}NO_5NH_4^+$ requires 255.0981). Data consistent with that reported in the literature.[162]

Preparation of *N,N*-Dimethyl 4-(4-nitrophenyl)-4-oxo-butyramide (Table 14, entry 2)

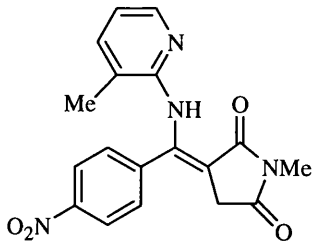


(Table 14, entry 2)

A solution of 4-nitrobenzylidene-(pyridin-2-yl)-imine ***216*** (119 mg, 0.49 mmol) in dioxane (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (46 mg, 10 mol %) in dioxane (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Dimethyl acrylamide (103 μL, 1.48 mmol) in dioxane (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was

sealed and heated at 135 °C for 6 h. The reaction was cooled to room temperature, concentrated in *vaccuo*, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by flash chromatography (SiO_2, 10 % EtOAc-petrol) to give *amide* compound ***(Table 14, entry 2)*** in mixture with triphenylphosphine oxide. Successive recrystallisation from diethyl ether and hexane gave amide ***(Table 14, entry 2)*** as pale yellow crystals (90 mg, 77 %), mp 153-154 °C; ν_{max} (film)/cm^{-1} 2938, 1694, 1639, 1604, 1528, 1403, 1346, 908, 734, 650; δ_H (400 MHz; $CDCl_3$) 8.31 (2 H, d , *J* 8.9, 2 × phenyl), 8.18 (2 H, d, *J* 8.9, 2 × phenyl), 3.33 (2 H, t, *J* 6.2, CH_2CONMe_2), 3.09 (3 H, s, NMe_2), 2.95 (3 H, s, NMe_2), 2.83 (2 H, t, *J* 6.2, CH_2Ph); δ_C ($CDCl_3$) 198.2, 171.0, 150.0, 141.0, 129.5 (2 C), 124.1 (2 C), 37.5, 35.9, 34.4, 27.9; *m/z* (CI, NH_3) 251(*M*H^+, 100 %), 221 (90%); (Found (ES) *M*H^+ 251.1032 $C_{12}H_{14}N_2O_4H^+$ requires 251.1031).

Preparation of 1-Methyl-3-[(3-methyl-pyridin-2-ylamino)-(4-nitrophenyl)-methylene]-pyrrolidine-2,5-dione 220

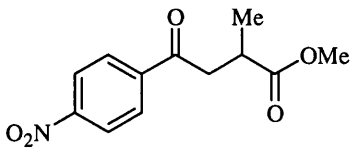


220

A solution of 4-nitrobenzylidene-(3-methyl-pyridin-2-yl)-imine ***216*** (23 mg, 0.10 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of [$ClRh(PPh_3)_3$]

(09 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl maleimide (16 mg, 0.15 mmol), in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 30 minutes. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 20 % EtOAc-petrol) to give the ***enamine 220*** as a yellow solid (28 mg, 81 %), mp 48-49 °C (from $CHCl_3$-hexane); ν_{max} (film)/cm^{-1} 3055, 2966, 2926, 2856, 1735, 1707, 1670, 1638, 1589, 1524, 1438, 1347, 1268, 1117, 1046, 858, 738; δ_H (300 MHz; $CDCl_3$) 10.65 (1 H, s, H enamine), 8.21 (2 H, d, *J* 6.9, 2 × phenyl), 7.72-7.38 (4 H, m, 2 × phenyl and 2 × picoline), 6.73 (1 H, t, *J* 6.9, 1 × picoline), 3.17 (2 H, s, CH_2), 3.09 (3 H, s, NMe), 2.41 (3 H, s, CH_3 picoline); δ_C (75 MHz; $CDCl_3$) 174.4, 172.0, 152.0, 151.3, 149.3, 147.9, 145.3, 143.1, 132.4 (2 CH), 129.0 (2 CH), 122.1, 118.6, 99.2, 33.7, 28.6, 17.6; *m/z*(EI^+) 353 (MH^+, 2 %), 352 (M^+, 5 %), 277 (89%), 278 (30 %), 267 (50 %), 77 (90 %), 51 (100 %) (Found M^+ (ES) 352.1176. $C_{18}H_{16}N_4O_4$ requires 352.1176).

Preparation of Methyl 2-methyl(4'-nitrophenyl)-4-oxobutanoate (Table 20, entry 3)[163]



(Table 20, entry 3)

A solution of 4-nitrobenzylidene-(3-methyl-pyridin-2-yl)-imine ***216*** (127 mg, 0.53 mmol) in dioxane (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (60 mg, 10 mol %) in dioxane (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl methacrylate (300 μL, 2.12 mmol) in dioxane (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 135 °C for 21 h (50 % conversion from ^1H NMR). The reaction was cooled to room temperature concentrated *in vaccuo*, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, gradient EtOAc-petrol) to give *linear* compound ***(Table 20, entry 3)*** (40 mg, 30 %) as a brown oil; ν_{max} (film)/cm^{-1} 2920, 2849, 1730, 1692, 1602, 1524, 1461, 1343, 1208, 1169, 1008, 854; δ_H (300 MHz; $CDCl_3$) 8.23 (2 H, d, *J* 8.7, 2 × phenyl), 8.04 (2 H, d, *J* 8.7, 2 × phenyl), 3.62 (3 H, s, OMe), 3.47 (1 H, dd, *J* 17.8 and 8.3, 1 × CH_2), 3.12-3.07 (1 H, m, $CHCH_3$), 2.95 (1 H, dd, *J* 17.8 and 5.0, 1 × CH_2), 1.24 (3 H, d, *J* 7.2, CH_3); δ_C(75 MHz; $CDCl_3$) 196.3, 175.8, 140.8, 128.9 (2 CH), 123.7 (2 CH), 93.3, 52.1, 42.4, 35.2,

21.4; *m/z* (CI^+, NH_3) 252 (MH^+, 100 %); (Found (ES) MH^+ 252.2442. $C_{12}H_{13}N_1O_5H^+$ requires 252.2463). Data consistent with that reported in the literature.[163]

Preparation of methyl 4-(2'-formylphenyl)-4-butanoate 226[164]

225 **226**

A solution of benzylidene-thiophen-2-ylmethyl-imine ***225*** (143 mg, 0.71 mmol) in THF (1 mL) was added dropwise *via* cannula to a solution of $[ClRh(PPh_3)_3]$ (61 mg, 10 mol %) in THF (1 mL) at room temperature and the mixture was stirred under a positive pressure of argon until a colour change to yellow orange was observed. Methyl acrylate (193 μL, 2.13 mmol) in THF (2 mL) was added *via* cannula and the reaction vessel was flushed with argon. The reaction tube was sealed and heated at 152 °C for 8 h. The reaction was cooled to room temperature, diluted with EtOAc (20 mL) and poured into aqueous HCl (1 M, 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The organic portions were collected and washed with brine (20 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 10 % EtOAc-petrol) to give *ortho*-alkylated aldehyde ***226*** (20 mg, 15 %) as a yellow oil, ν_{max} (film)/cm^{-1} 3048, 2950, 2844, 2744, 1735, 1684, 1599, 1574, 1440, 1364, 1291, 1255, 1196, 1023, 831, 760; δ_H (300 MHz; $CDCl_3$) 10.12 (1 H, s, H aldehyde), 7.74 (1 H, dd, *J* 7.6 and 1.3, 1 × phenyl), 7.45 (1 H, dt, *J* 7.6 and 1.3, 1 × phenyl), 7.35 (1 H, dt, *J* 7.6 and 1.3, 1 × phenyl), 7.24 (1 H, d, *J* 7.6, 1 × phenyl), 3.58 (3 H, s, OMe), 3.29 (2 H, t, *J* 7.6, CH_2),

2.58 (2 H, t, *J* 7.6, CH_2); δ_C (75 MHz; $CDCl_3$) 193.1, 173.5, 143.1, 134.2 (2 CH), 134.0, 131.6 (2 C), 127.4, 52.5, 35.7, 28.5; *m/z* (CI^+, NH_3) 210 (MNH_4^+, 100 %), 193 (MH^+, 30 %); (Found (EI^+) M^+ 192.0786 $C_{11}H_{12}O_3$ requires 192.0786).[164] (Hydrolysed starting material (25 mg, 33 %) as well as a complex mixture of compounds yet not identified were also isolated)

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