The Preparation of Enolates Via Metal Catalysed Allylic Isomerisation

The Transition Metal Catalysed Isomerisation Of Allylic Alkoxides

A Thesis Presented By

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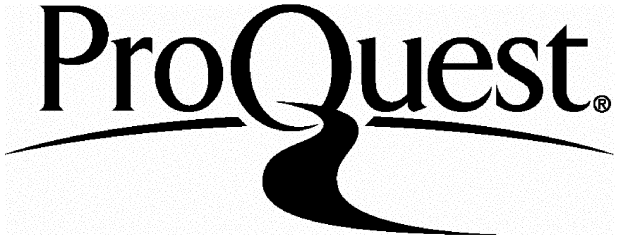


Abstract

This thesis is divided into three chapters. As an introduction to this work, Chapter One presents an overview of current stereoselective enolate syntheses. In Chapter Two a new approach to enolate chemistry is described, involving the transition metal catalysed isomerisation of allylic alkoxides. The regio- and stereochemical consequences are investigated, and the mechanism discussed. Chapter Three details the experimental procedures employed.

It is shown that treatment of 1-phenyl-2-propen-1-ol with catalytic quantities of chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in tetrahydrofuran at reflux effects allylic isomerisation to give exclusively the (Z)-enolate stereoisomer in good yield, as evidenced by aldol reaction or trapping as the enol acetate. Schlenk-line techniques were adopted as standard. Related substrates with increasing substitution around the double bond require longer reaction times but are effectively isomerised. Highly substituted substrates show little or no reactivity—the catalyst is deactivated by extended reflux times and starting material is isolated.

It is found that with substrates for which it is possible, mixtures of enolate regioisomers are produced. Also, in the production of tetra-substituted enolates the several possible starting alcohols lead to identical ratios of enolate stereoisomers. This apparent equilibration of reaction products is thought not to be directly metal-mediated but caused by protic reaction by-products. Discussion and evidence are presented.

It is found that catalysts formed *in situ* from bis(cyclooctadiene)nickel (0) and monophosphines are efficient catalysts, and affect the isomerisation of substrates unreactive towards the rhodium catalyst. However chiral chelating diphosphines give inactive species and this approach to asymmetric induction is therefore unfruitful. Instead it is shown that complexes with chelating nitrogenous ligands are far more active. A number of chiral ligands are synthesised and compared with the aim of generating homochiral enolate derivatives from achiral precursors.

Contents

Abbreviations

acac.....Acetylacetonate (2,4-Pentanedione anion)

Ar.....Undefined aromatic group

atm .....Atmospheres (pressure)

(9-BBN)OTf.....9-Borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate

(*S,S*)-BDPP.....(2*S*,4*S*)-2,4-Bis(diphenylphosphino)pentane

(*R*)-BINAP.....(*R*)-2,2'-Bis(diphenylphosphino)-1,1'-binapthyl

Bis(oxazoline) .....4,4'-Dialkyl-4,4',5,5'-tetrahydro-2,2'-bi(oxazole)

b.p.....Boiling point

cat .....Catalyst

(*S*,*S*)-CHIRAPHOS .....(2*S*,3*S*)-2,3-Bis(diphenylphosphino)butane

cod 1,5-Cyclooctadiene

Cy .....Cyclohexyl

DAD.....1,4-Diaza-1,3-diene

DCE.....1,2-Dichloroethane

DCM .....Dichloromethane

DHP.....2,3-Dihydropyran

(-)-DIOP.....(4*R*,5*R*)-O-Isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino)butane

DME 1,2-Dimethoxyethane

DMSO .....Dimethyl sulfoxide

dppe.....1,2-Bis(diphenylphosphino)ethane

(*R*,*R*)-Me-DUPHOS.....1,2-Bis(2*R*,5*R*-2,5-dimethyl-1-phospholano)benzene

equiv .....Molar equivalents

ETSA .....Ethyl (trimethylsilyl)acetate

fod.....6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyloctane-3,5-dione anion

GC .....Gas Chromatography

h.....Hour(s)

Hex.....*n*-Hexyl

HMPA.....Hexamethylphosphoric triamide

HOMO.....Highest Occupied Molecular Orbital

HRMS.....High Resolution Mass Stectrometry

IR.....Infrared spectroscopy

L.....Undefined ligand

LCPA.....Lithium cyclohexylisopropylamide

LDA.....Lithium diisopropylamide

LHMDS.....Lithium hexamethyldisilazide

lit.....Literature Value

LOBA.....Lithium isooctyl-*tert*-butylamide [Lithium (1,1,3,3-Tetramethylbutyl)-*tert* -butylamide]

LTMP.....Lithium 2,2,6,6-tetramethylpiperidide

LUMO.....Lowest Unoccupied Molecular Orbital

M.....Undefined metallic element

Mes.....Mesityl (2,4,6-Trimethylphenyl)

min.....Minute(s)

m.p.....Melting Point

MS.....Mass Stectrometry

NMR.....Nuclear Magnetic Resonance Spectroscopy

nOe.....Nuclear Overhauser Effect

PCC.....Pyridinium chlorochromate

PPEI.....(–)-2-Pyridinalphenylethylimine

PTSA.....*para*-Toluenesulfonyl chloride (4-Methylbenzenesulfonyl chloride)

Py.....Pyridine

r.t.....Ambient (room) Temperature

s.....Second(s)

tfc.....(+)-Trifluoroacetylcamphorate

THF.....Tetrahydrofuran

THP.....2-Tetrahydropyranyl

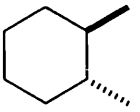
TLC.....Thin Layer Chromatography

TMPH.....2,2,6,6-Tetramethylpiperidine

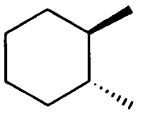
TMS.....Trimethylsilyl

Stereochemical Conventions

The stereochemistry of compounds is illustrated graphically following the conventions of Maehr.[1] Thus bold type is used to represent bonds towards the observer relative to the page, and dashed type to represent bonds away from the observer. Diastereomeric compounds are represented using bold and dashed lines when racemic, and bold and dashed wedges when homochiral.

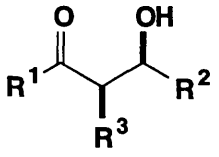


Racemic

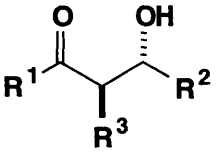


Homochiral

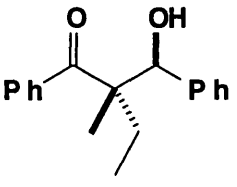
Aldol products are described following the standard *syn*- and *anti*- nomenclature proposed by Masamune,[2] as illustrated. In describing the 2,2-disubstituted aldol products **43** and **44**, for which Masamune's nomenclature is inadequate, the *erythro*- and *threo*- conventions of Noyori were adopted.[3]



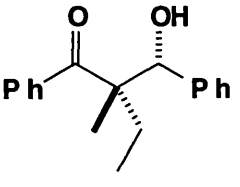
syn



anti



43 (*threo*)



44 (*erythro*)

Acknowledgements

Above all I must thank Professor Willie Motherwell for his help and inspiration. His incredible knowledge and friendly disposition have made it a pleasure to work for him. I also owe a huge debt of gratitude to Dr. David Sandham, who in working on this project before me was a leading light.

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To all the members of the Barton, Whiffen and Southside labs at Imperial, and everyone I know at UCL, cheers everyone, you made it fun to be there, especially Donogh, Caroline, Ian, Lisa, Dave and Lee. And thanks for putting up with me, Simon, and for not breaking the vac-line. Simon again, Ade, Ashley, Rod, Martin and Kit, thanks for the proof reading, I didn't leave you too much.

Finally, and nothing to do with chemistry, I owe more than words can say to Jenny, and to my parents.

One last note: 'Nickel' was the name of the mischievous goblin fabled to inhabit mines in Germany. That might explain a few things.

Chapter 1

Stereoselectivity In The Preparation Of Enolate Anions

1.1 Introduction

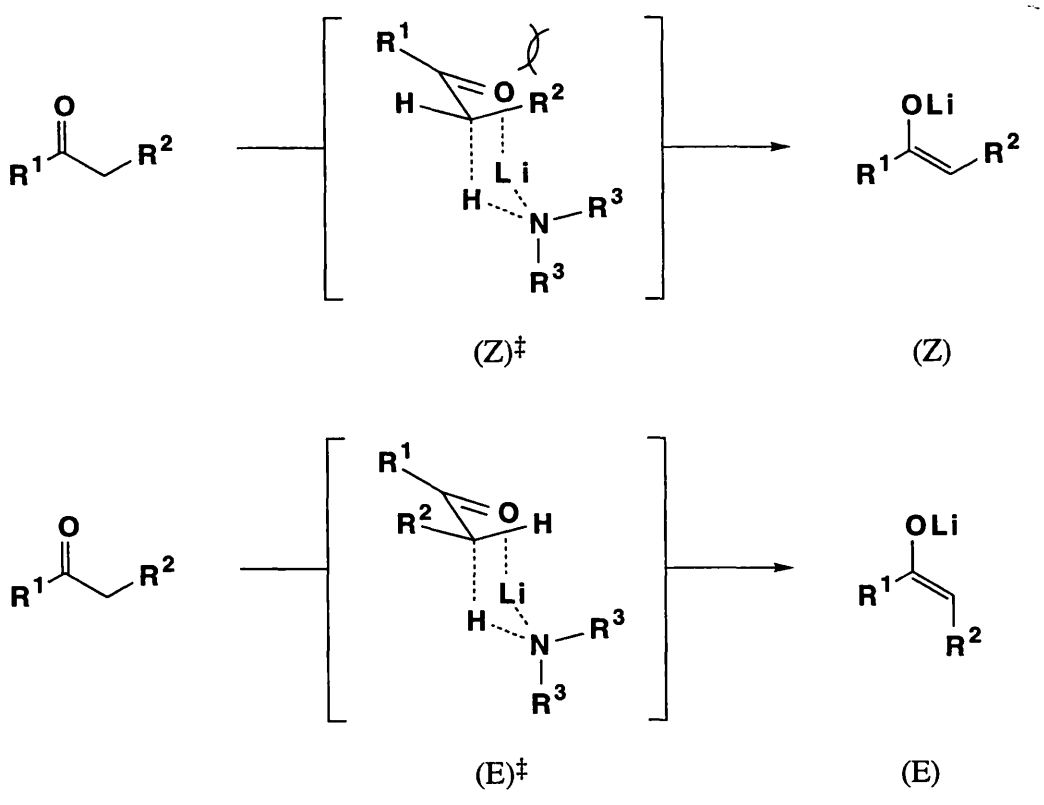
The chemistry described in this thesis involves a novel approach to enolate anion chemistry, *via* the transition metal catalysed isomerisation of allylic alkoxides. To put this work into perspective, a survey of the current methods of stereoselective enolate preparation is presented. The survey is restricted to enolates of simple, unactivated ketones and aldehydes that are reactive without catalysis. The regioselective preparation of enolates has been reviewed.[4]

The most common preparation of enolates involves basic enolisation of the parent ketones,[5] particularly deprotonation under kinetic control with lithium dialkylamide bases. Kinetic deprotonation has been discussed in several reviews largely concerned with the aldol reaction,[6-9] but the origins of kinetic stereoselectivity were only briefly considered. In the first section, a broadly chronological review of mechanistic hypotheses is presented, and the second section compares stereoselective deprotonation techniques. The third and final sections survey the preparation of enolates by conjugate addition and reduction, and by miscellaneous routes. Although many methods have been reported, the stereoselectivity of these processes has not always been of prime importance and is in many cases unknown.

For the following discussions it must be noted that the (Z)-stereoisomer of simple alkali metal enolates is always the more thermodynamically stable, and so can result from equilibrating conditions.[7] This is usually also true of other enolate species.

1.2 The Mechanism Of Kinetic Deprotonation

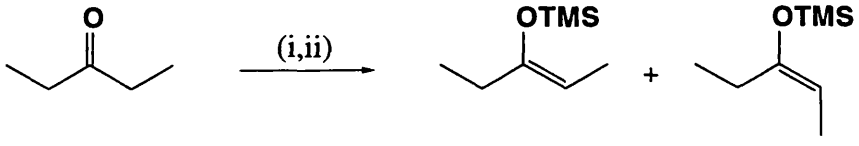
A cyclic, six-membered chair transition state was first proposed by Ireland to explain the stereochemical outcome of kinetic deprotonations with lithium dialkylamide bases.[10] Although these studies were primarily concerned with esters, it was found that deprotonation of 3-pentanone with lithium diisopropylamide (LDA) in THF yielded the (E)-enolate stereoisomer with moderate selectivity (E:Z=77:23). Prior coordination of lithium to the carbonyl group served to stabilise the developing negative charge on oxygen and provide order for the process. Enolate stereoselectivity was then rationalised as being a sterically-based competition between the two diastereomeric transition states leading to each enolate isomer. The (E)-selectivity observed was proposed to result from a destabilising steric interaction in the transition state (Z)‡ between the carbonyl group, with which the lithium dialkylamide is associated, and the carbonyl α-substituent R^2 (scheme 1.1).



Scheme 1.1 – The Ireland Model

Ireland also discovered that deprotonation in a mixture of THF and hexamethylphosphoric triamide (HMPA) was, in contrast, highly (Z)-selective. It was proposed that solvation of the lithium ion with HMPA, a co-solvent of high cation-solvating ability, lessened the importance of carbonyl-lithium bonding and decreased the effective steric bulk of the carbonyl group. In this case, the transition state $(Z)^{\ddagger}$ would be preferred, with the group R^2 avoiding a steric interaction with the carbonyl substituent R^1 (scheme 1.1).

Ireland's claim of kinetic (Z)-stereoselectivity in the presence of HMPA was subsequently placed in doubt when Rathke and co-workers investigated the effect of HMPA on kinetic deprotonation with lithium 2,2,6,6,-tetramethylpiperidide (LTMP).[11] Using higher base to ketone ratios low (E)-selectivity was observed, and the (Z)-selectivity obtained by Ireland was concluded to be a result of rapid product equilibration in the presence of HMPA (table 1.1). Comparison of entries (3) and (4) indicate that the absolute quantity of (E)-enolate falls as more ketone is added.



(Z) (E)

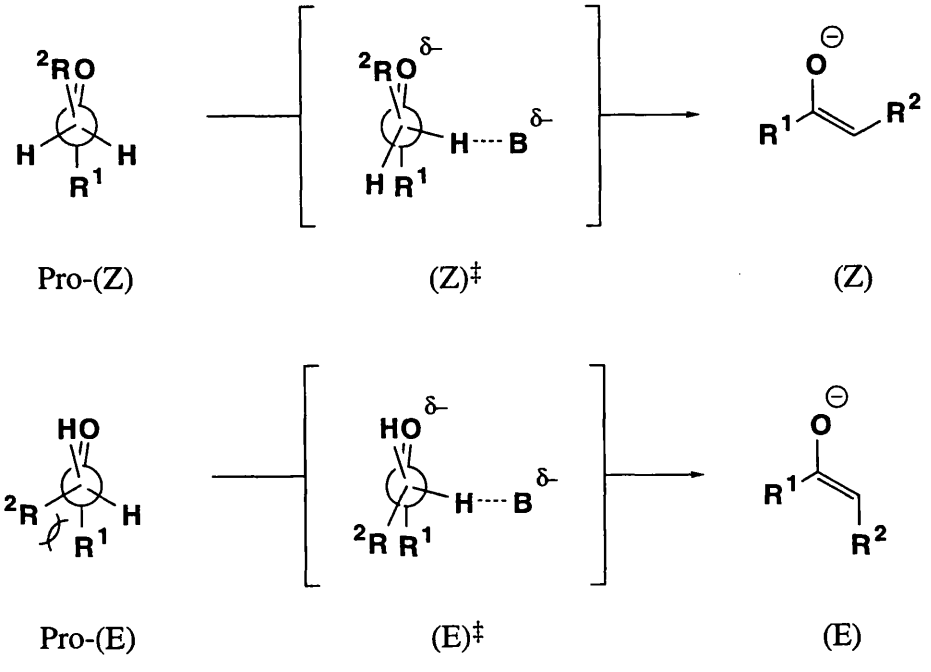
Reagents: (i) Add to LTMP (1.0 equiv), THF, HMPA (equiv), 0°C; (ii) TMSCl.

Entry	3-Pentanone (equiv)	HMPA (equiv)	Ratio (Z : E)
1)	0.9	–	14 : 86
2)	0.45	–	14 : 86
3)	0.9	1.0	92 : 8
4)	0.45	1.0	35 : 65

Table 1.1 – The Effect Of HMPA On Kinetic Deprotonation

An aldol/retro-aldol sequence was proposed as the mechanism of enolate equilibration. Further evidence for the equilibrating influence of HMPA was provided by the studies of Corey and Gross, which investigated deprotonation in the presence of trimethylsilyl chloride as an "internal quench".[12] The greater (E)-selectivity obtained was attributed to trapping of the kinetically formed enolate before significant equilibration could occur.

In their seminal study, Heathcock and co-workers surveyed the deprotonation of a number of ethyl ketones with several lithium dialkylamide bases in THF solution, and it was established that when the group R^1 is large a reversal of the usual stereoselectivity occurs and the (Z)-isomer is favoured.[13] Stereochemical control was discussed in terms of steric effects determining the reacting conformation of the ketone. It has been established that the most stable conformer of a ketone is that with the α-substituent R^2 eclipsing the carbonyl group (the pro-(Z) conformer).[14] In the pro-(E) conformer the group R^2 suffers a gauche interaction with the carbonyl substituent R^1, and this interaction is exacerbated in proceeding to the pseudo-planar transition state (scheme 1.2).



Scheme 1.2 – The Heathcock Model

Kuwajima and co-workers had first observed higher (E)-selectivity using the more hindered base LTMP, and had concurred with the Ireland model.[15] However, it was concluded that a steric interaction of the group R^2 with the amide substituent R^3, rather than with the carbonyl group as Ireland suggested, provided a better explanation for this stereoselectivity. Heathcock demonstrated that increasing (E)-selectivity as the size of the base (ie. the group R^3) increased was a general phenomenon, and in agreement with Kuwajima, invoked an interaction between the group R^2 and the amide group R^3.[13] As the basis of (E)-selectivity, this destabilising effect had to be greater for the transition state $(Z)^{\ddagger}$, with the group R^2 *cis* to the carbonyl, and implied close association of lithium with the carbonyl oxygen. A cyclic transition state very similar to Ireland's was therefore proposed. Thus, stereoselectivity in kinetic deprotonation is commonly viewed as a balance between these two destabilising interactions (figure 1.1).

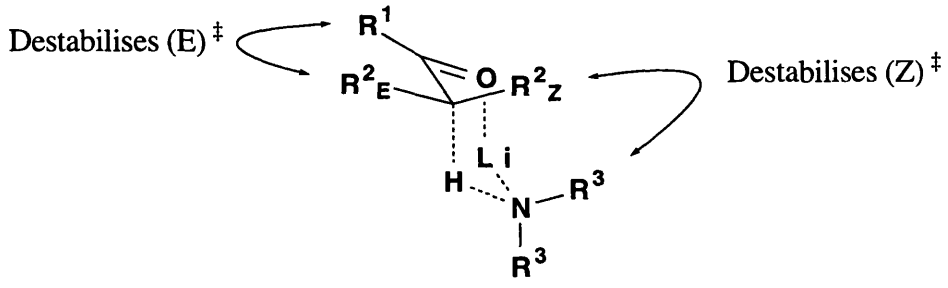


Figure 1.1

Narula criticised Ireland's model as being incompatible with stereoelectronic requirements.[16] It was suggested that the ketone must adopt a conformation in which the breaking C-H bond is perpendicular to the carbonyl plane so as to maximise orbital overlap and stabilisation of the developing carbanion (figure 1.2).[17] In an idealised chair arrangement, the dihedral angle between the carbonyl and the C-H bond is 60°, and the distortion created by incorporation of the carbonyl double bond into the ring decreases it further.

Pro-(Z) Pro-(E)

Figure 1.2 – Stereoelectronically Ideal Conformers

(Normal) (Narula)

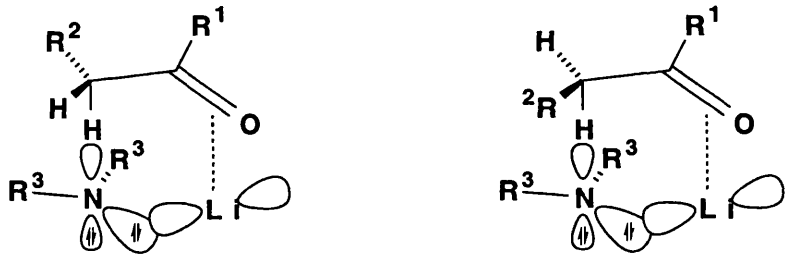
Figure 1.3

Secondly, Narula suggested that in a transition state with chair geometry an increase in the size of the dialkylamide base should have a more pronounced effect on stereoselectivity than had been observed by Heathcock.

Narula's model involves two alternative transition state geometries, and is based on a unusual description of the carbonyl molecular orbitals (figure 1.3). Instead of the more normal sp^2 hybridisation, the non-bonding electrons on oxygen are considered to be situated in an *sp* orbital and a second *p*-type orbital (the HOMO), and thus are electronically and spatially non-equivalent.[18] When R^1 is not sterically demanding, it is proposed that oxygen coordinates to lithium through the *p*-type orbital, perpendicular to the C-O bond in the carbonyl plane. In order to minimise 1,3-allylic strain between R^2 and lithium,[19] deprotonation proceeds *via* the σ-pro-(E) transition state (figure 1.4). Alternatively, when R^1 is large, carbonyl π-coordination is preferred and so as to minimise the steric interaction between R^1 and R^2 the π-pro-(Z) transition state operates (figure 1.4). Notable features are the linear C–H–N arrangement, and the more similar interactions of R^2 with the group R^3 in both the pro-(E) and pro-(Z) transition states.

σ-Pro-(E) σ-Pro-(Z)

(Small R^1)



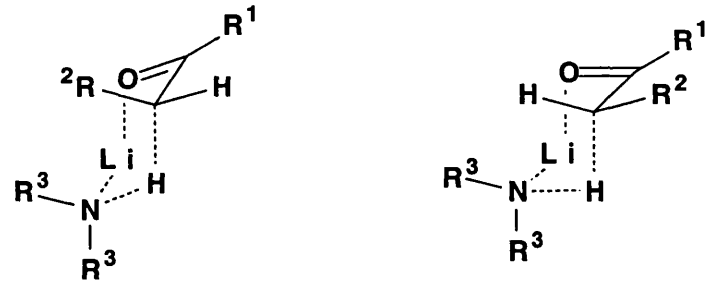
π-Pro-(E) π-Pro-(Z)

(Large R^1)

Figure 1.4 – The Narula Model

In view of Rathke's equilibration experiments,[11] the influence of HMPA on these transition states was not discussed.

Narula's arguments were originally discounted by Evans,[7] and this model has received little attention. In particular, it is unclear why an increase in the size of the carbonyl substituent R^1 would cause a change in the manner of coordination. Although the poor stereochemical alignment of the Ireland model has been generally acknowledged, it does at least explain the observed trends in stereoselectivity more clearly. Consequently, a distorted Ireland model has often been invoked[12] with an exaggerated (and probably unrealistic) puckering of the chair geometry so as to incorporate the ideal 90° dihedral angle between the carbonyl and the C-H bond (figure 1.5).

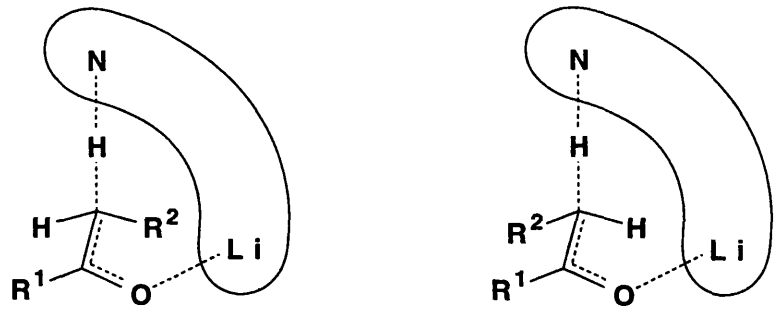


Normal Distorted

Figure 1.5 – Representations Of The Ireland Model

Moreland and Dauben used molecular mechanics modelling to examine the transition state of kinetic deprotonation with lithium dialkylamides, comparing observed product ratios with those calculated from the relative stabilities of the reacting ketone conformers and the corresponding enol stereoisomers.[20] Clear evidence was obtained for an early or reactant-like transition state, supporting the approach of the Heathcock model.[13] For a given base and solvent, the enolate ratios indicated a direct correlation between stereoselectivity and the steric requirements of the groups R^1 and R^2. Evidence also supported a steric interaction between R^2 and the amide group R^3 as the basis of (E)-selectivity; this seems to contradict Narula's supposition[16] that such a direct interaction would have a more marked effect than had been observed. Although close association of lithium and oxygen was implicated, the nature of the reacting lithium amide species could not be elucidated. However, the ketone conformers with the ideal 90° dihedral angle between the carbonyl and the reacting C-H bond provided the best correlations, and it was proposed that reaction with the amide base in the form of an undefined aggregate could allow a larger 'ring' and so accommodate this larger angle (figure 1.6). The carbonyl oxygen need not coordinate to the same lithium atom as the reacting dialkylamide.

Moreland and Dauben also studied deprotonation conducted in the presence of HMPA. In agreement with Ireland's original suggestion,[10] a cyclic transition state was again proposed which was expanded, or in some way loosened, relative to that in THF alone.



Pro-(Z) Pro-(E)

Figure 1.6 – The Moreland-Dauben 'Aggregate Model'

Contrary to the conclusions of Rathke however, a more advanced, more product-like transition state was suggested to explain the greater preference for the thermodynamically favoured (Z)-enolate. This was rationalised as diminished Lewis-acidic activation of the carbonyl group by lithium when coordinated by HMPA. The possibility of product equilibration was not considered.

The proposition of an oligomeric reactive dialkylamide species was also used to explain the increased (Z)-stereoselectivity observed when using lithium hexamethyldisilazide (LHMDS), as it is has been shown to be entirely monomeric in THF solution.[21] LDA exists exclusively as a cyclic dimer in THF (figure 1.7),[22] and similar structures are reported for a number of lithium dialkylamides including LTMP.[23] Heathcock has previously explained the greater (Z)-selectivity as being a result of the lower basicity of LHMDS relative to dialkylamides, and consequently a more product-like transition state.[13]

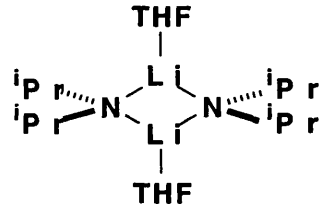
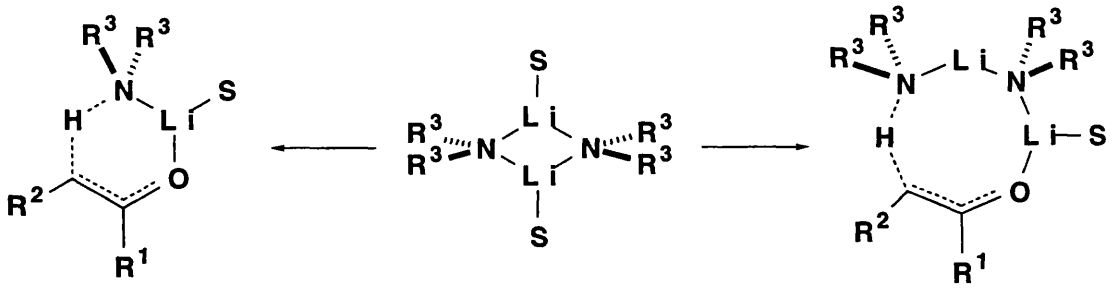


Figure 1.7

Saunders and co-workers have studied deuterium isotope effects in lithium dialkylamide-mediated deprotonation, with high base to ketone ratios to ensure the process was kinetically-controlled.[24,25] A reactant-like transition state was indicated. Evidence also suggested that stereoselectivity was largely controlled by activation enthalpy differences, and that regioselectivity, in contrast, was controlled by activation *entropy* differences and so by different factors. Similar steric interactions between the base and substrate are commonly used to explain both regio- and stereoselectivities, but a better explanation could not be provided with the limited data. It was concluded that none of the models previously discussed were fully adequate. Importantly, abnormal isotope effects observed in THF solution indicated that two or more basic species were responsible for the observed selectivities. However, the normal isotope effects observed in the presence of HMPA indicated a single, probably monomeric species.

The work of Moreland and Dauben, and of Saunders and co-workers, has suggested that the greater understanding of the deprotonation process would most likely result from more detailed investigation into the nature of the basic species, particularly in the presence of HMPA. A number of lithium dialkylamide solid state structures have been published,[26] and much recent work has involved the study of the solution structure of the lithium dialkylamides.[26a] As with LDA in the solid state (figure 1.7), cyclic dimers are the most common structures in ethereal solvents, usually with one solvent molecule per lithium due to steric constraints. The more hindered base LTMP exists largely as a cyclic dimer in THF.[23] It is notable, however, that these spectroscopically observable dimers are not necessarily the reactive species.[22]

Collum and co-workers have recently applied computer modelling techniques to analyse possible transition states which are implied by the dimeric nature of the base, with some startling results.[27] Comparisons were primarily made between deprotonations with monomeric and ring-opened dimeric lithium dialkylamide species (scheme 1.3), and a range of representative chemical components were considered. McKee had earlier applied more sophisticated *ab initio* methods to elucidate the likely geometry of the Ireland-type transition state.[28]



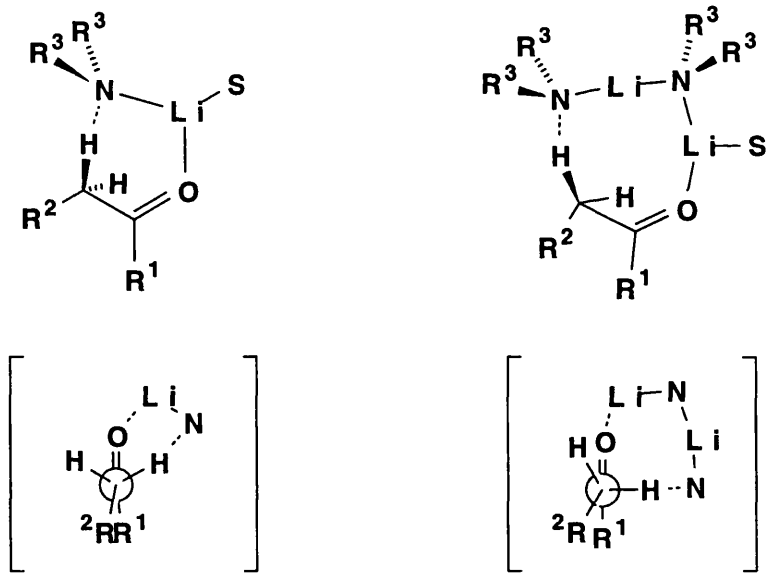
(Monomer) (Opened Dimer)

[S = H_2O, Me_2O, THF, NMe_3 or HMPA]

Scheme 1.3

McKee used the reaction of acetaldehyde with lithium amide as a model, and good agreement was found with comparable systems analysed by Collum. The monomer transition states had little in common with the idealised cyclohexane chair geometry, being considerably flatter, and surprisingly varied little between the different systems. The dihedral angle between the carbonyl and breaking C-H bond varied from 52° to 63°, confirming Narula's prime objection to the Ireland model.[16] Remarkably, and contrary to Narula's supposition, the minimum energy six-membered transition state could accommodate an almost linear C-H-N arrangement (the C-H-N angles being ≈160°). The eight-membered, open-dimer transition states were similarly quite unlike the idealised carbocyclic geometry. The C-H-N angles again consistently large (163-165°), and N-Li-N angles were also approximately linear (≈155°) as favoured in acyclic lithium dialkylamide dimers.[29] Notably, HC-CO dihedral angles were in all cases very close to perpendicular (84-95°), and indicated that the more conformationally flexible open-dimer transition states were more able to achieve the ideal stereoelectronic alignments.[17] The transition states are thus better represented as shown below (figure 1.8).

Most striking is comparison of the two mechanistic pathways. The calculated activation enthalpies for the open-dimer transition states are generally lower, and predict dominance of this route. Only in the model systems involving a sterically undemanding solvent (S = H_2O) was the monomer pathway favoured.[28]



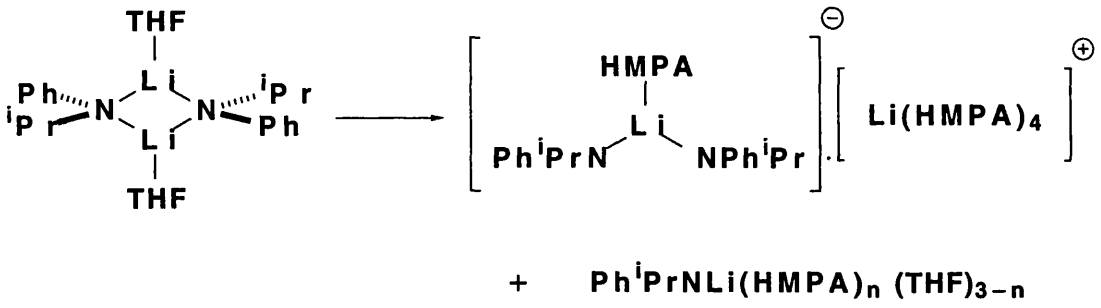
(Monomer) (Opened Dimer)

Figure 1.8 – The Collum Models

Increasing the steric requirements of any of the various components, and thus creating more chemically realistic models, increases the dominance of the open-dimer pathway. In summary, the Ireland model of the monomer transition state finds no support, in terms of either its geometry or its applicability as the dominant route.

The Collum open-dimer model was therefore presented as a new description of the kinetic deprotonation process. It is notable that the studies of Collum and co-workers are consistent with the largely theoretical studies of Moreland and Dauben, and of the experimentally-based conclusions of Saunders and co-workers (in particular the competition of two basic species in THF). However, both pathways predict the observed (E)-selective deprotonation of 3-pentanone equally successfully.[27]

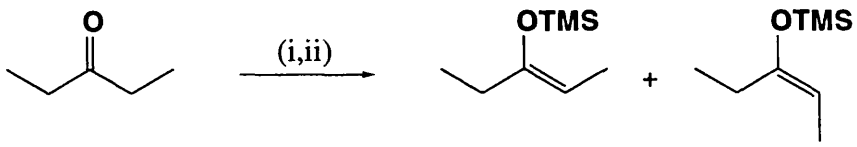
The effect of HMPA is commonly attributed to deaggregation of the reactive amide species, but recent studies contradict this long-held belief. Jackman used ^{6}Li, ^{15}N and ^{31}P NMR in the first detailed studies of lithium amide-HMPA solutions.[30] Lithium *N*-isopropylanilide is dimeric in ethereal solution, but in the presence of 4.1 equivalents of HMPA was transformed into a 'triple ion' salt, with a minor quantity of solvated monomer (in the ratio 6:1) (scheme 1.4).



Scheme 1.4

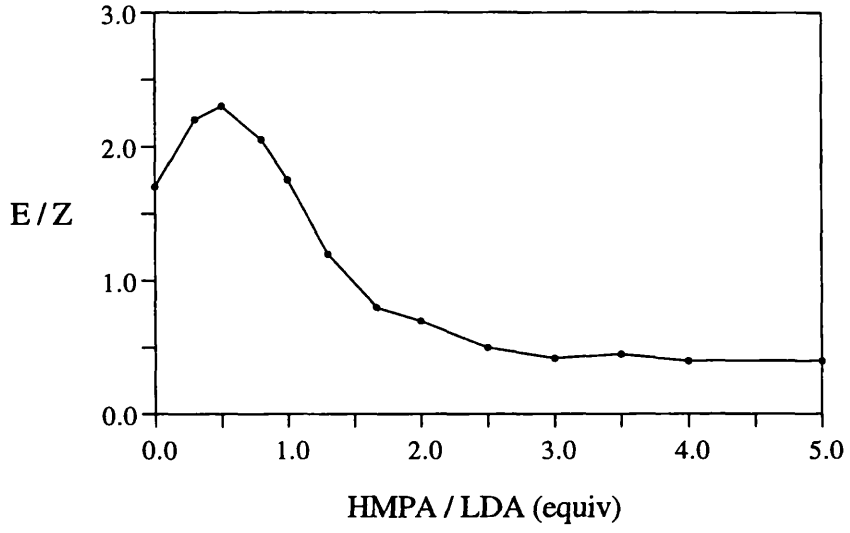
The more hindered base LTMP exists as a 9:1 mixture of cyclic dimer and solvated monomer in THF,[23] but in THF/HMPA has been shown to form variously solvated monomers and cyclic dimers, an open dimer and triple ions.[31] In contrast, LDA retains the cyclic structure on addition of excess HMPA (figure 1.7), instead undergoing stepwise displacement of the two coordinated solvent molecules to give $[(LDA)(HMPA)]_2$ as the only detectable species even at high HMPA concentrations.[31] The nature of the dialkylamide base in the presence of HMPA is therefore complex and structure dependant.

Both the cyclic models studied by Collum and co-workers predict (E)-selective kinetic deprotonation of 3-pentanone with LDA in the presence of HMPA.[27] This is in agreement with the studies of Rathke and co-workers with LTMP, who have attributed the (Z)-selectivity originally observed by Ireland to product equilibration.[11] However, the stereochemical consequences of deprotonation in the presence of HMPA must once more be revised. More recent studies have led both Saunders[24] and Collum[27] to report kinetic (Z)-selectivity in this reaction, and Saunders has also reported often considerable kinetic (Z)-selectivity with a number of related lithium dialkylamide deprotonations.[25] No evidence to support product equilibration could be found. Rathke employed considerable quantities of HMPA (23% by volume in THF), whereas Saunders has used only three molar equivalents with respect to the base. Furthermore, LDA-mediated deprotonation of 3-pentanone is reportedly highly dependant on the exact quantity of HMPA employed (scheme 1.5).[31]



(Z) (E)

Reagents: (i) Add to LDA (1.0 equiv), THF, HMPA (equiv), –78°C; (ii) TMSCl.



Scheme 1.5

Saunders has also observed a dependence of kinetic stereoselectivity on HMPA concentration.[25] Deprotonation of 2-pentanone with LDA was found to be three times as (Z)-selective on ten-fold dilution with THF, the relative quantities of base and HMPA remaining unchanged. The seemingly contradictory effects of HMPA and the confusion that has resulted are likely a result of concentration differences.

Due to the failure of cyclic models to explain kinetic (Z)-selectivity in the presence of HMPA, Collum and co-workers have also considered acyclic transition states.[27] Monomeric and dimeric deprotonation models both predicted (Z)-selectivity, but do not benefit from stabilisation of the developing negative charge on oxygen and unsurprisingly have higher activation barriers than cyclic models. When the dialkylamide is ionised, in the form of a triple-ion and non-coordinating counter cation, deprotonation is by nature acyclic and is also predicted to be (Z)-selective (figure 1.9). In this case the position of the counter cation has no significant effect.

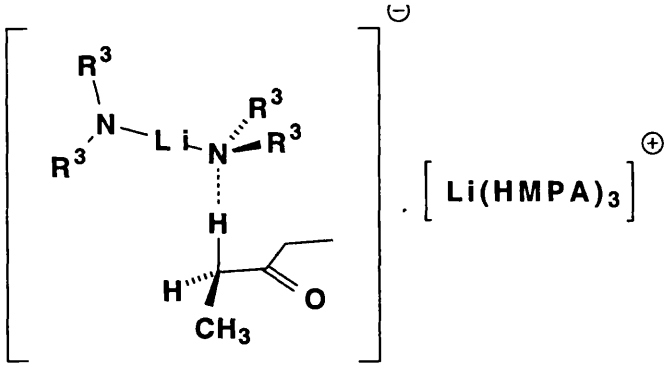
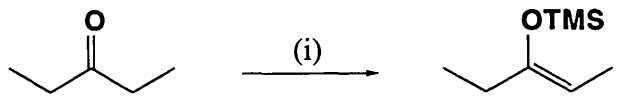


Figure 1.9 – Acyclic Triple-Ion Transition State

Triple-ions are thought to be reactive species, and conditions which promote their formation are predicted to promote (Z)-selectivity. Formation of triple-ions in significant quantities has been demonstrated in the presence of HMPA.[30,31] Collum's model is again calculated to have a higher activation energy than the alternative cyclic models, but the computational methods used are thought to underestimate the stability these triple-ions.[27]

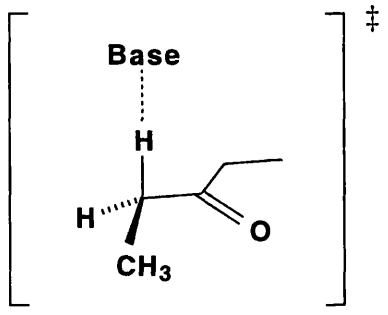
The hypothesis of an acyclic transition state in the presence of HMPA was opposed by the theoretical work of Moreland and Dauben.[20] However, acyclic kinetic deprotonation was proposed by Kuwajima to account for the (Z)-specific silylation of ketones with ethyl (trimethylsilyl)acetate (ETSA) and catalytic tetrabutylammonium fluoride (TBAF) (scheme 1.6).[15] Equilibration of the silyl enol ether products with further catalytic TBAF (Z:E=87:13) indicated that thermodynamic control was not operating. It was suggested that (Z)-stereoselectivity resulted from the conformational preference of the ketone, as proposed in the Heathcock model,[13] and rapid trapping of the enolate before proton exchange could equilibrate the enolate stereoisomers.

The final consideration is that of mixed aggregation. The aforementioned studies have viewed the deprotonation process in terms of the initial reaction components, and often used high base to ketone ratios to roughly maintain this state. This is a gross approximation, since practical synthetic applications commonly use only a very small excess of base, and the ratio of reaction components changes drastically.



(Z:E) = 200:1

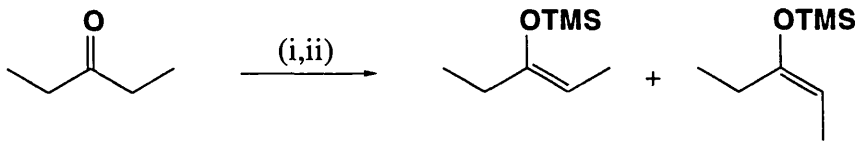
Reagents: (i) ETSA (1.2), TBAF (1 mol%), THF, –78°C.



Scheme 1.6

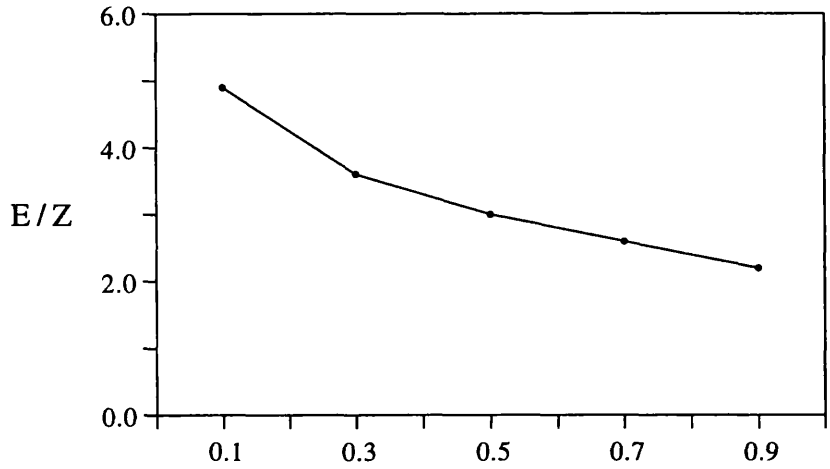
Early in the reaction the base certainly is in excess, but when nearing completion it is a minor component in comparison to the enolate product. Also, the increasingly popular use of trimethylsilyl chloride as an *in situ* trapping agent produces significant quantities of lithium chloride.[32] Discussion of more synthetically realistic systems requires consideration of mixed aggregates formed from amide, amine, enolate, lithium halides etc. It is notable that Rathke's studies of the effect of HMPA on stereoselectivity used varying excesses of base but did not consider that the predominant basic species might change.[11]

The issue of mixed aggregates was primarily raised by Seebach.[33] The study of these species in solution, and the possible consequences arising, has been minimal.[34] However, Collum and co-workers have recently reported a number of spectroscopic[35-38] and computational studies[29,39] of lithium dialkylamide-enolate and lithium dialkylamide-lithium halide mixed aggregates. Two particular observations in deprotonation of the standard test substrate 3-pentanone illustrate the importance of these species. The degree of (E)-stereoselectivity with LDA drops with the quantity of ketone added (scheme 1.7),[36] but no equilibration can be detected (in the absence of HMPA). This has been attributed to the changing nature of the reacting basic species.



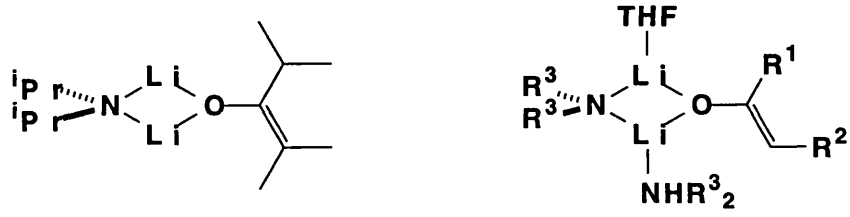
(Z) (E)

Reagents: (i) Add to LDA (1.0 equiv), THF, –78°C; (ii) TMSCl.



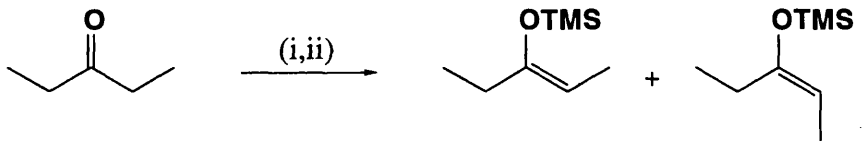
Scheme 1.7

A number of lithium dialkylamide-lithium enolate mixed aggregates have been characterised. For example, the lithium enolate of 2,4-dimethyl-3-pentanone reacts with LDA quantitatively to form a 1:1 aggregate (figure 1.10.A, solvation unknown).[38] It is notable that reaction of a lithium dialkylamide in dimeric form as proposed by Collum implies direct formation of a three component mixed-aggregate (figure 1.10.B).



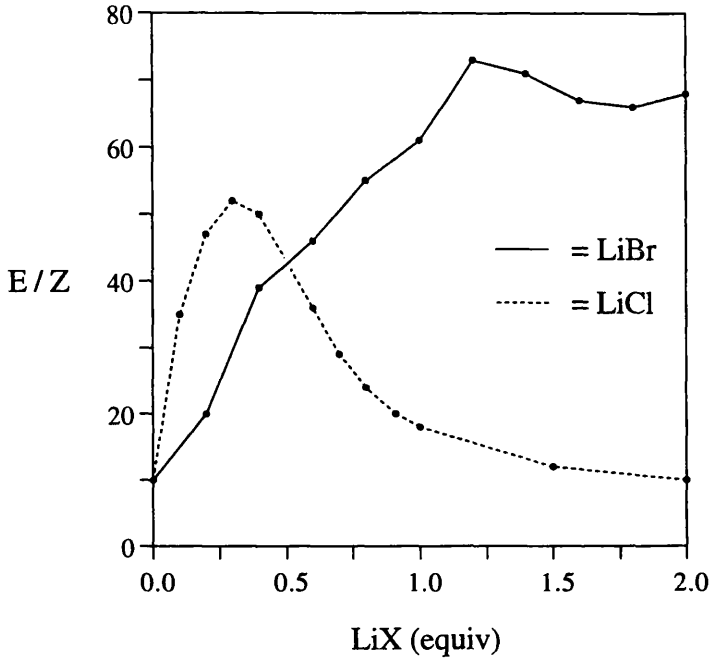
A B

Figure 1.10



(Z) (E)

Reagents: (i) Add to LTMP , LiCl or LiBr (equiv), THF, –78°C; (ii) TMSCl.



Scheme 1.8

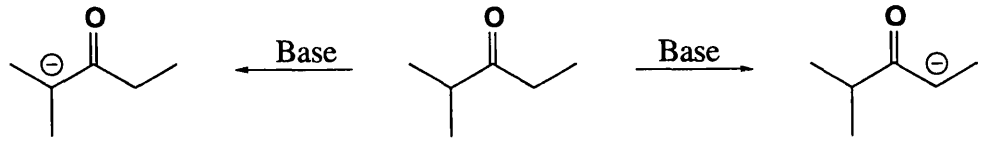
A **B**

Figure 1.11

Secondly, it has been discovered that deprotonation of 3-pentanone with lithium dialkylamide-lithium halide mixtures greatly increases (E)-selectivity (scheme 1.8).[36] At low concentrations of lithium bromide a 2:1-LTMP:LiBr species has been demonstrated (figure 1.11.A), with conversion to exclusively a 1:1 species with greater

than one equivalent of lithium bromide (figure 1.11.B).[37] It has therefore been proposed that a mixed aggregate base is responsible.

In summary, the traditional view of kinetic deprotonations proceeding via a cyclic, chair-like transition state serves as a useful pneumonic for the prediction of stereochemistry, but is probably unrealistic. The aggregation state of the base, and the possible involvement of mixed aggregation, are important considerations. It has also been proposed that discussion of stereoselectivity purely in terms of steric interactions is over simplistic. Heathcock has discussed stereoselectivity in terms of the ground state conformational preferences of the ketone.[13] That these preferences might also apply to the transition state is supported by the evidence obtained for an early transition state. Saunders and Xie have suggested the importance of both electronic effects and the remnants of ground-state conformational preferences.[25] With an early transition state, rehybridisation of the α-carbon might lag behind electronic reorganisation; the preference for the less-substituted enolate regioisomer could then be rationalised as destabilisation of the essentially carbon-based anion by the electron-donating alkyl group (figure 1.12). It is also suggested that electrostatic repulsion (rather than steric) between the alkyl group R^2 and the highly polar base might be promoting formation of the (E)-stereoisomer. Electrostatic effects operate at longer ranges than steric effects. These ideas have not as yet been tested experimentally.



More destabilised, Disfavoured

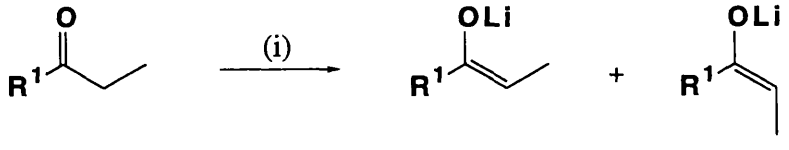
Less destabilised Favoured

Figure 1.12

1.3 Deprotonation Techniques

The (Z)-enolate stereoisomer is always the more thermodynamically stable, to a degree dependant upon a number of factors.[6,7,40] Kinetic deprotonation with lithium dialkylamide bases is generally (E)-selective and so contra-thermodynamic. The 'kinetic' alkali-metal bases give enolates with stereoselectivities that are variable, but the trends can be rationalised in terms of the degree to which true kinetic control is maintained. Control of enolate geometry is therefore dependent upon the promotion of kinetic or thermodynamic control.[7,40]

The most commonly used 'kinetic bases' are the lithium dialkylamides, being more reactive and considerably more soluble in organic media than the simple alkali-metal amides derived from ammonia. For a given base, the size of R^1 is again the most important factor in determining stereoselectivity (table 1.2).[13] The inherent kinetic (E)-selectivity is diminished drastically in ketones branched at the α'-position.

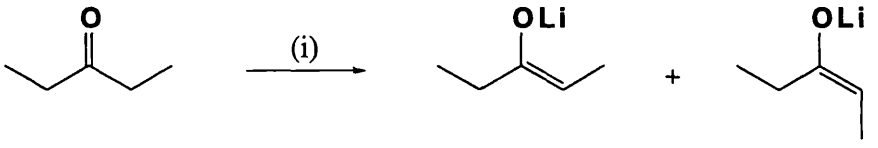


(Z) (E)

Reagents: (i) Add to LDA, THF, –70°C.

Entry	R^1	Product Ratio (Z:E)
1)	Et	30 : 70
2)	^{i}Pr	60 : 40
3)	^{t}Bu	>98 : 2
4)	Ph	>98 : 2

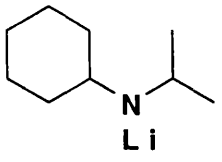
Table 1.2



(Z) (E)

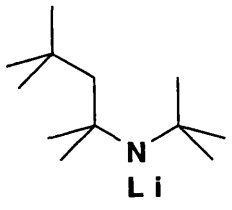
Reagents: (i) Add to $LiNR^3_2$, (Additive), THF, –70°C.

Entry	Base	Product Ratio (Z:E)
1)	LDA	30 : 70
2)	LCPA	35 : 65
3)	LTMP	20 : 80
4)	LHMDS	66 : 34
5)	LTMP/LiBr	<2 : 98
6)	LOBA/TMSCl	2 : 98



LCPA

(Lithium cyclohexylisopropylamide)



LOBA

(Lithium isooctyl-*tert*-butylamide)

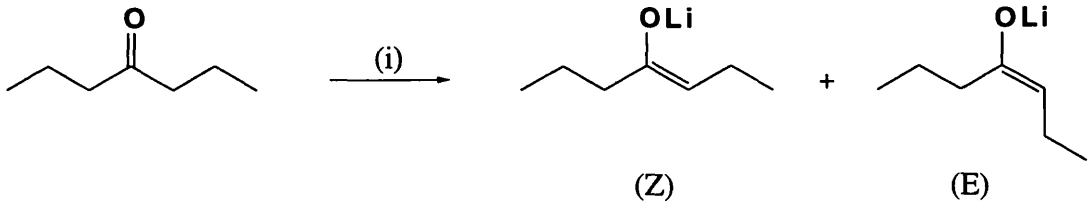
Table 1.3

For a given substrate, the degree of (E)-selectivity is increased with a larger amide substituent (R^3), but the effect is not as significant (table 1.3, entries 1-3).[6,7] However, the use of the less reactive disilylamide bases (entry 4) promotes formation of the (Z)-isomer, and this is most probably true kinetic (Z)-selectivity rather than the result of enolate equilibration.[13] Excellent (E)-selectivity can be obtained using LTMP in conjunction with lithium halides (entry 5); the basic species is best generated from

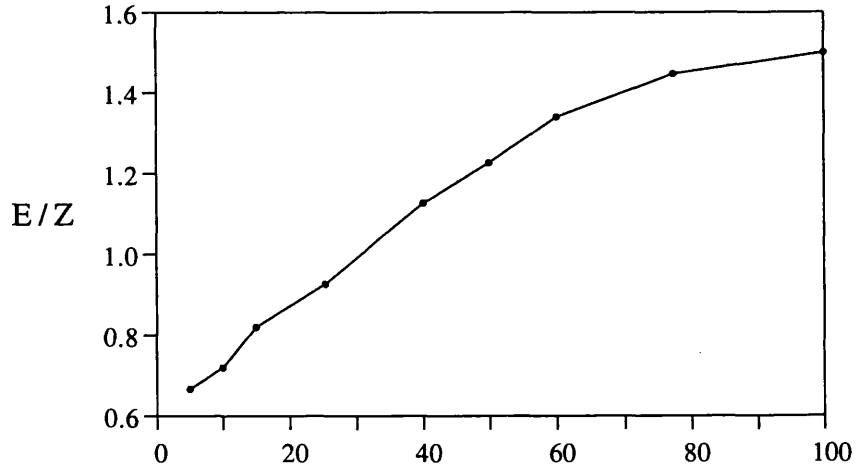
the non-hygroscopic hydrobromide salt and two equivalents of alkyllithium.[36] This general method represents the most efficient formation of (E)-enolates currently known.

The *in situ* trapping protocol of Corey and Gross, involving deprotonation with LOBA in the presence of trimethylsilyl chloride, is notable for producing similar (E)-selectivities to the lithium halide method (table 1.3, entry 6).[12] Deprotonation with LOBA is very slow, allowing equilibration of enolate regioisomers (and so undoubtedly stereoisomers) in the absence of the trapping agent. Although trimethylsilyl enol ethers are produced, enolate species can be regenerated and this method provides an indirect route to a variety of (E)-metal enolates (*vide infra*).

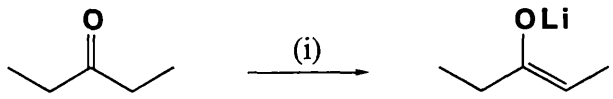
It has also been demonstrated that the stereoselectivity of deprotonation with LDA in THF-hexane mixtures varies with the relative proportions of solvent (scheme 1.9).[41] Deprotonation is increasingly (E)-selective as the proportion of THF increases.



Reagents: (i) Add to LDA, THF, –78°C.



Scheme 1.9



(Z:E) = 95:5

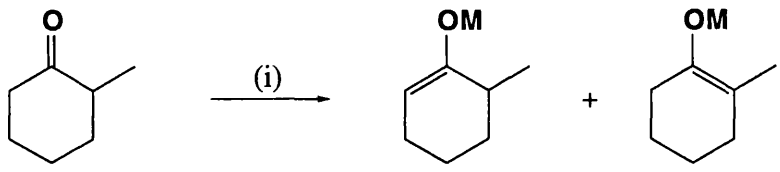
Reagents: (i) Add to LDA, THF:HMPA 3:1, –78°C.

Scheme 1.10

Obtaining (Z)-stereoselectivity from ketones with no α'-branching, such as 3-pentanone, is commonly achieved using HMPA as a co-solvent to promote equilibration (scheme 1.10).[10] Use of only a few molar equivalents of HMPA (or TMEDA) is far less efficient (table 1.1).[11] Equilibration is also promoted by addition of the base to the ketone, or the use of a slightly less the one equivalent of the base.

Increasing the ionic character of the metal-oxygen bond, as in sodium and potassium enolates, increases the reactivity of the enolates and so the propensity for proton exchange.[6] Equilibration is illustrated in the deprotonation regioselectivity with trityllithium and tritylpotassium, traditional 'kinetic' bases that are now rarely used (table 1.4, entries 2, 3).[40,42] The regio- and stereochemical compositions of enolate mixtures under equilibrium conditions are also cation dependant, with larger cations tending to give less selective mixtures (entries 4–6).[6] Potassium and sodium silylamide bases are available, but show broadly similar (Z)-stereoselectivities to the lithium counterparts, implying true kinetic control.[43] These are primarily of use when potassium or sodium enolates are specifically required. Magnesium dialkylamides are commonly used under equilibrating conditions.[44]

Metal hydride reagents operate under poor kinetic control, even when using a large excess.[45] The heterogeneous nature of the base would slow deprotonation and thus promote equilibration. However, the active basic species are generally considered to be traces of hydroxide and alkoxide, acting to relay protons from the ketone to the metal hydride surface.[46] These are weak bases, making deprotonation reversible and further promoting equilibration. Hydride reduction of the ketone has been shown to be a minor side reaction, producing alkoxide *in situ*.[47]



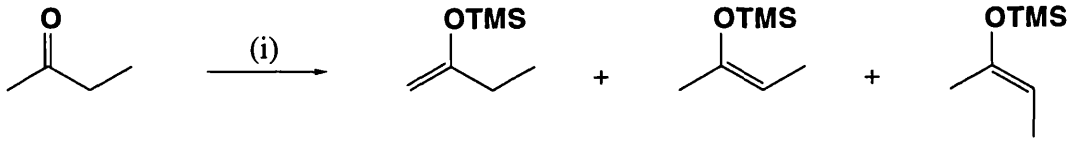
Methylene Methine

Reagents: (i) Base, THF, –78°C (Kinetic) or 0°C (Equilibrium).

Entry	Base	Control	Product Ratio (Methylene : Methyl)
1)	LDA	Kinetic	99 : 1
2)	Ph_3CLi	Kinetic	90 : 10
3)	Ph_3CK	Kinetic	67 : 33
4)	Ph_3CLi	Equilibrium	10 : 90
5)	NaH	Equilibrium	26 : 74
6)	Ph_3CK	Equilibrium	38 : 62

Table 1.4

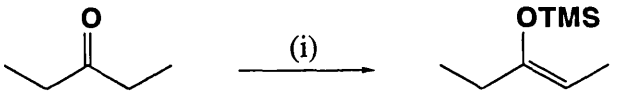
The kinetic products can be promoted by using trimethylsilylchloride as a trapping agent, but selectivity is not significantly improved (scheme 1.11).[47] Metal hydrides are therefore of use only when regio- and stereochemistry are unambiguous or irrelevant. Lithium hydride is not sufficiently reactive to be a practical base.[47]



53 : 33 : 14

Reagents: (i) KH (2), TMSCl (2.0), Dioxane, reflux.

Scheme 1.11



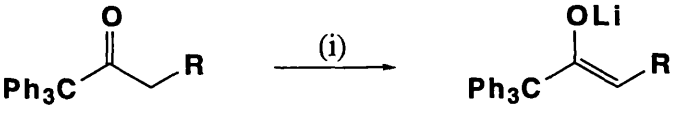
(Z:E) = 200:1

Reagents: (i) $(TMS)CH_2CO_2Et$ (1.2), TBAF (1 mol%), THF, –78°C.

Scheme 1.12

(Z)-Specific enolisation is achieved using the kinetic silylation methodology of Kuwajima and co-workers (scheme 1.12)[15]; kinetic (Z)-selectivity is explained by an acyclic deprotonation mechanism. Enolate species can then be regenerated without loss of stereochemical integrity, providing the most efficient if indirect route to (Z)-enolates.

With extremely hindered ketones nucleophilic addition is suppressed and direct deprotonation with organolithium reagents is possible. Trityl ketones react with *n*-butyllithium to give (Z)-enolates stereospecifically (scheme 1.13).[48] Reaction of ethyl trityl ketone with trimethylaluminium gives aluminium enolates but the stereochemistry is not known.[49]

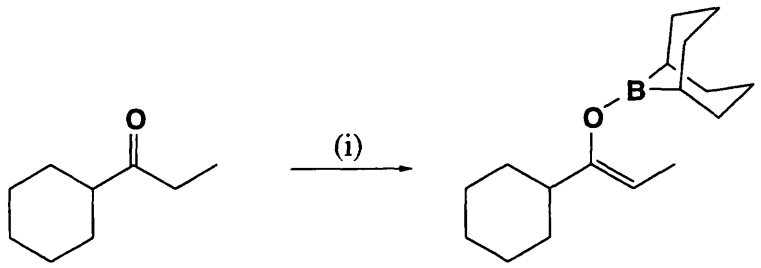


(Z)

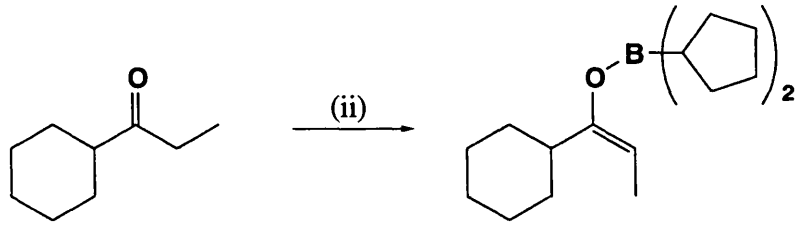
Reagents: (i) ^nBuLi (1.1), THF, –78°C.

Scheme 1.13

Enolates of more covalently bound metals are far less basic than those of the alkali metals and so can be form under milder conditions. Dialkylboron enolates are readily prepared by reaction of ketones with dialkylboron triflates and a hindered amine base at low temperature.[7] The nature of the boron ligands are important; dibutylboron triflate usually favours the (Z)-isomer, but other reagents can provide the alternative (E)-isomer (scheme 1.14).[50] Deprotonation occurs under kinetic control.[7]



(Z:E) > 95:5

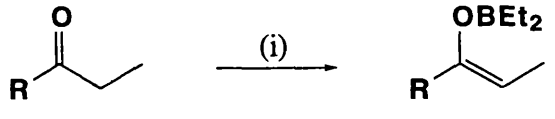


(Z:E) = 12:88

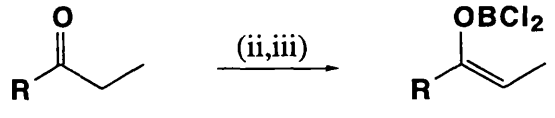
Reagents: (i) (9-BBN)OTf, EtN^iPr_2, –78 to 0°C; (ii) Dicyclopentylboron triflate, EtN^iPr_2, –78 to 0°C.

Scheme 1.14

Diethylboron enolates are formed (Z)-selectively under more forcing conditions by reaction of triethylboron and catalytic diethylboron ester (scheme 1.15).[51] (Z)-Dichloroboron enolates are formed by deprotonation of ketone-boron trichloride complexes with an amine base; a one step reaction is precluded by formation of an unreactive boron-amine complex (scheme 1.15).[52]



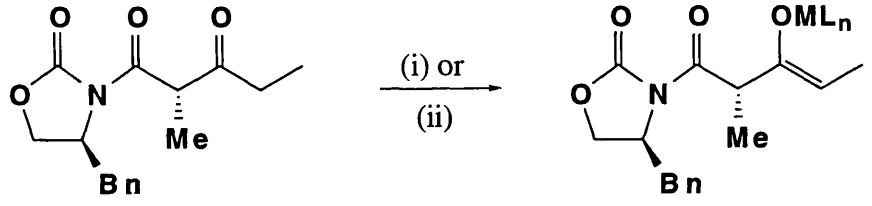
(Z:E) > 90:10



(Z)

Reagents: (i) BEt_3, $^tBuCO_2BEt_2$ (cat.), 85-100°C; (ii) BCl_3 (2.0); (iii) EtN^iPr_2 (2.0).

Scheme 1.15



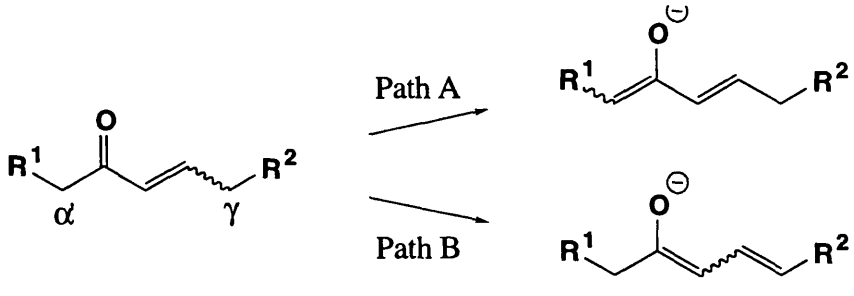
(Z)

Reagents: (i) $Sn(OTf)_2$, NEt_3, DCM, –20°C; (ii) $TiCl_4$, EtN^iPr_2, DCM, –10°C.

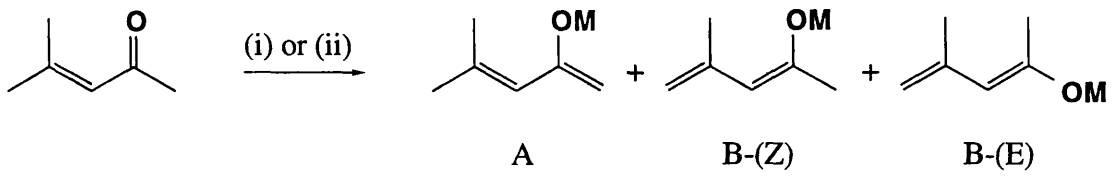
Scheme 1.16

Ketones react at low temperature with tin (II) triflate and a tertiary amine, usually ethylpiperidine, to give tin (II) enolates.[53] Less hindered amine bases form unreactive tin complexes. Similarly, titanium (IV) chloride and various amines react with ketones to form trichlorotitanium enolates.[54] The products of aldol reaction indicate predominant (Z)-stereochemistry, and on the rare occasions when enolate stereochemistry has been directly studied the (Z)-isomer is formed specifically. Deprotonation occurs under kinetic control, giving the less substituted enolate and preserving stereochemistry at the carbonyl α'-position (scheme 1.16).[55]

The regiochemistry of deprotonations of α,β-unsaturated ketones has often been reported.[4,7] Deprotonation at the α'-position is favoured, giving a cross-conjugated product under kinetic control (path A), with the fully-conjugated product corresponding to γ-deprotonation under equilibrating conditions (path B) (scheme 1.17). Kinetic deprotonation (A) follows the usual trends, but the stereochemistry in the thermodynamically-controlled process (B) has rarely been investigated.



Scheme 1.17



A B-(Z) B-(E)

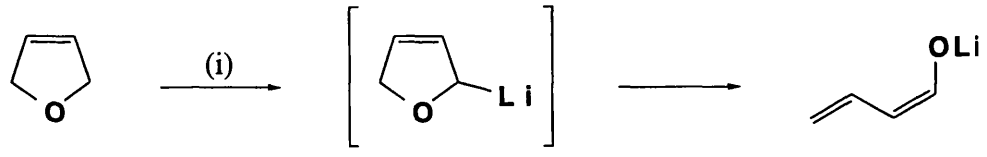
Reagents: (i) Add to MNR_2, THF:Et_2O 1:1, –70°C; (ii) As before, then 20°C, 20 h.

Entry	MNR_2	Conditions	Product Ratio A : B-(Z) : B-(E)
1)	LDA	(i)	85 : 15 : 0
2)	NaHMDS	(i)	65 : 35 : 0
3)	LDA	(ii)	10 : 55 : 35
4)	NaHMDS	(ii)	0 : 95 : 5

Table 1.5

However, the deprotonation of mesityl oxide with LDA or sodium hexamethyldisilylazide (NaHMDS) gives only the (Z)-isomer under kinetic control (table 1.5).[56]

Lithiation of tetrahydrofuran with alkyllithium reagents and subsequent decomposition provides a route to the lithium enolate of acetaldehyde. In an analogous reaction the (Z)-enolate of crotonaldehyde can be obtained stereospecifically by the decomposition of 2-lithio-2,5-dihydrofuran (scheme 1.18).[57]



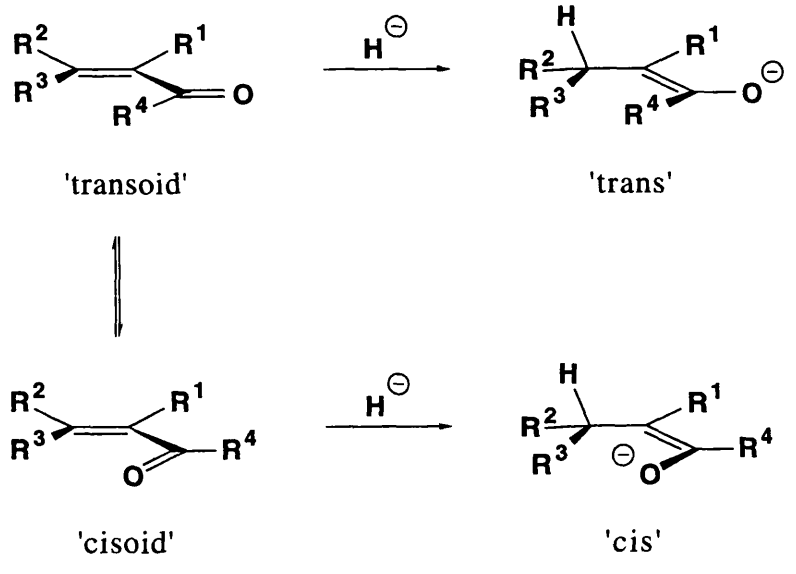
(Z)

Reagents: (i) ^{n}BuLi, neat, –78°C.

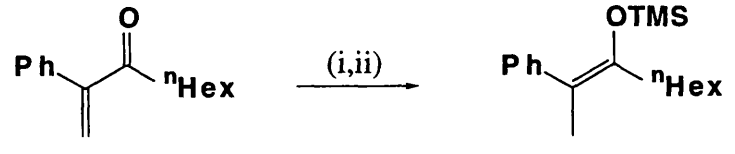
Scheme 1.18

1.4 Conjugate Addition And Reduction Methods

Conjugate additions to α,β-unsaturated ketones offer a useful approach to regio-defined enolates.[5] Two quite different methods for the preparation of lithium enolates are hydride reduction with 'L-selectride' (lithium tri-*sec*-butylborohydride, method A),[58] and electron-transfer reduction with lithium in ammonia (method B).[59] Both methods result in a transformation equivalent to conjugate addition of hydride. Chamberlin and Reich have reported correlation of the product enolate geometry with the conformational preference of the enone in both reactions (schemes 1.19, 1.20).[60]



Scheme 1.19



(transoid:cisoid>20:1) (Z:E) = 170:1

(96%)

Reagents: (i) L-selectride, THF, –78°C; (ii) TMSCl, NEt_3, –78°C.

Scheme 1.20

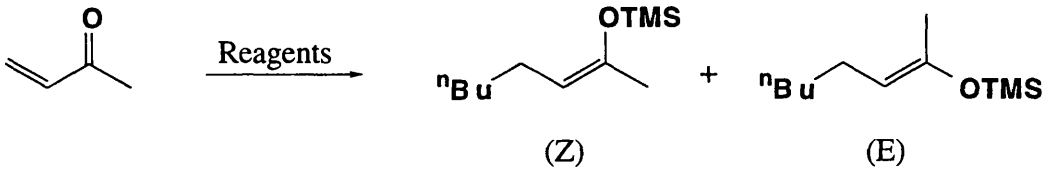
Entry	Enone				Method	Conformer	Enolate Ratio
	R^1	R^2	R^3	R^4		(transoid:cisoid)	(trans:cis)
1)	^{i}Pr	H	H	^{n}Hex	A	>20:1	170:1
2)	H	^{n}Bu	H	^{n}Hex	B	3:1	2:1
3)	H	^{n}Bu	H	^{t}Bu	B	<1:100	<1:300
4)	H	H	^{n}Bu	^{n}Hex	B	1:20	1:30

Method A = Li/NH_3, –78°C; Method B = L-selectride, THF, –78°C

Table 1.6

Enone conformation is controlled by steric effects and dependant upon the specific substitution pattern, and so increasing the steric bulk of any substituent increases this preference. In general, a large group at the α-position (R^1) favours the 'transoid' conformer (entry 1, table 1.6), and a large carbonyl substituent (R^4) or group at the *cis*-β-position (R^3) favours the 'cisoid' conformer (entries 3,4). The size of substituent R^2 has the least effect (entry 2). The conformer ratio is locked early in the reaction coordinate by introduction of electron density into the enone π^* orbital, whether by hydride or electron transfer. Reduction of α,β-unsaturated amides with L-selectride is reported to proceed exclusively via the 'cisoid' conformation.[61]

Catalytic and stoichiometric organocuprate reagents provide the most significant methods of carbanionic conjugate addition to α,β-unsaturated aldehydes and ketones,[62] but are generally unselective in terms of the stereochemistry of the enolate product.[63] However, in the presence of trimethylsilyl chloride and HMPA reactions are accelerated, and are more regio- and stereoselective.[63] Ketones give silyl enol ethers with generally low (Z)-selectivity (table 1.7). In the absence of the trapping agent, aldehydes give approximately equal mixtures of enolate stereoisomers, and often poor yields.[64] In the presence of TMSCl and HMPA however, high (E)-stereoselectivity (E:Z>10:1) and excellent yields can be obtained.

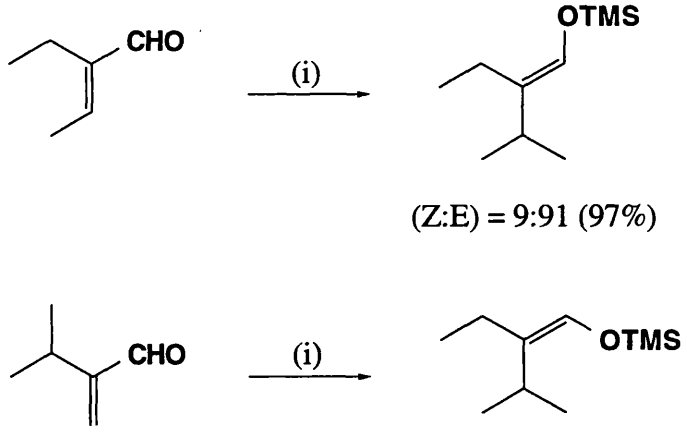


(Z) (E)

Entry	Reagents	Ratio (Z:E)	Yield (%)
1)	(i) $^{n}Bu_2CuLi$; (ii) TMSCl.	33 : 67	–
2)	$^{n}Bu_2CuLi$, TMSCl, HMPA.	72 : 28	84
3)	$^{n}BuCu$, TMSCl, HMPA.	85 : 15	82
4)	$^{n}BuMgBr$, 5% CuBr, TMSCl, HMPA.	72 : 28	96

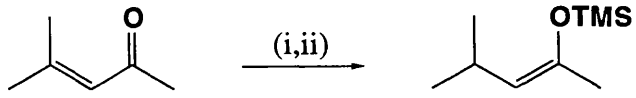
Table 1.7

A ground-state conformational preference was again invoked to explain this selectivity, with the 'transoid' conformer greatly favoured in aldehydes. This procedure allows the preparation of either stereoisomer by judicious choice of substrate (scheme 1.21), and is thus an important route to stereo-defined enolate precursors.[63,65]

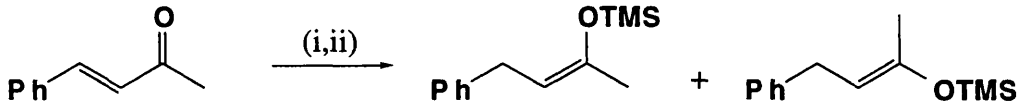


Reagents: (i) MeMgBr (2), CuBr.SMe_2 (0.05), TMSCl (2), HMPA (3), THF, –70°C.

Scheme 1.21



(Z) (95% GC)



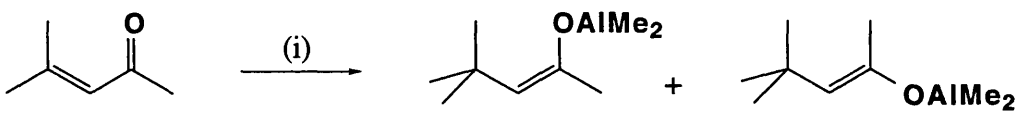
(Z:E) = 2.6:1 (89% GC)

Reagents: (i) DIBAL (1.1), CuI/MeLi (0.05), HMPA (1.7), THF, –50°C; (ii) TMSCl.

Scheme 1.22

Copper (I) has been employed to catalyse conjugate reductions with diisobutylaluminium hydride (DIBAL).[66] A copper (I) hydride species is thought to be active. The resulting dialkylaluminium enolates are reactive towards aldol condensation and silylation, and undergo alkylation once converted to an 'ate complex' by reaction with methyllithium. The thermodynamically more stable products are favoured; aldehydes gave exclusively (E)-silyl enol ethers, and ketones favoured the (Z)-isomer to varying degrees (scheme 1.22).[66b]

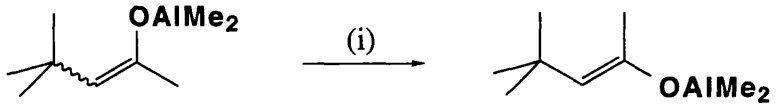
Trimethylaluminium undergoes nickel-catalysed 1,4-addition to mesityl oxide to give the dimethylaluminium enolates stereoselectively (Z:E=4:1) (scheme 1.23).[67] The (Z)-enolate has been isolated as a dimer and characterised. Upon heating the (Z)-isomer to 150°C in toluene, isomerisation occurs to give the (E)-enolate as a dimer; upon heating a neat mixture of the enolates to 110°C the trimeric (E)-enolate is recovered (scheme 1.24).



(Z:E) = 4:1 (*ca.* 80%)

Reagents: (i) $AlMe_3$ (1.2), $Ni(acac)_2$ (0.03), Et_2O, –50°C to r.t.

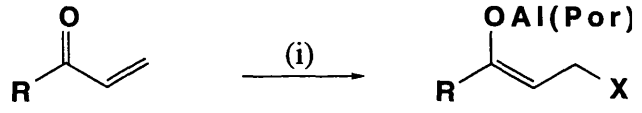
Scheme 1.23



(E)

Reagents: (i) 110–150°C, toluene or neat, 64 h.

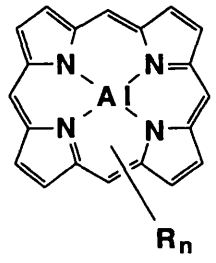
Scheme 1.24



(Z)

Reagents: (i) (Por)AlX, $CDCl_3$, hν. [X = Et, SR']

(Por)Al =

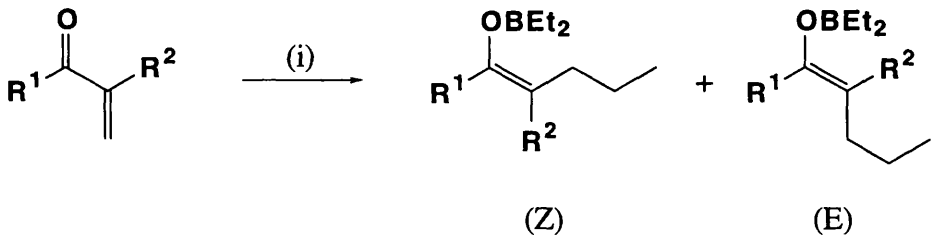


Scheme 1.25

(Porphinato)aluminium ethyl and thiolate complexes undergo conjugate addition to enones under ultraviolet irradiation to give exclusively (Z) aluminium enolates (scheme 1.25).[68]

Trialkylboranes undergo rapid, uncatalysed conjugate additions to α,β-unsaturated aldehydes and ketones at ambient temperature.[69] The stereoselectivity of the addition of triethylborane to ketones has been studied, and varies depending upon the substitution pattern and the reaction temperature (table 1.8).[69b] Once again it was proposed that the conformational preference of the aldehyde or ketone defined stereoselectivity.

Enones also undergo conjugate reduction with a variety of dialkylboranes to give (Z)-boron enolates usually stereospecifically (scheme 1.26).[70,71]

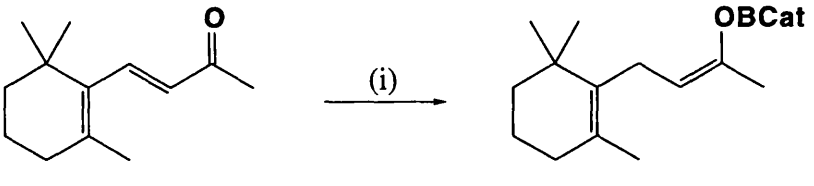


(Z) (E)

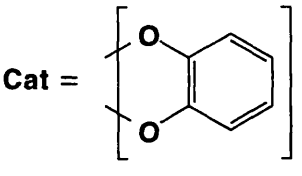
Reagents: (i) BEt_3, THF, r.t.

Entry	Enone		Ratio	Yield
	R^1	R^2	(Z:E)	(%)
1)	H	Me	(E)	85
2)	Me	H	*ca.* 50:50	50
3)	Me	Me	15:85	75
4)	Ph	H	(Z)	66
5)	Ph	Me	50:50	100

Table 1.8

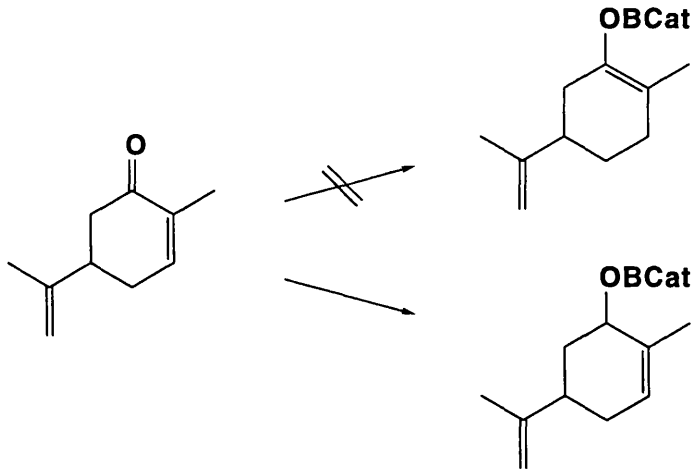


(Z) (82%)



Reagents: (i) CatBH (1.5), THF, 25°C, 30 min.

Scheme 1.26



Scheme 1.27

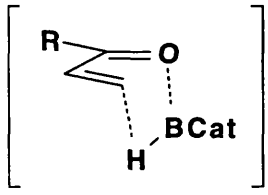


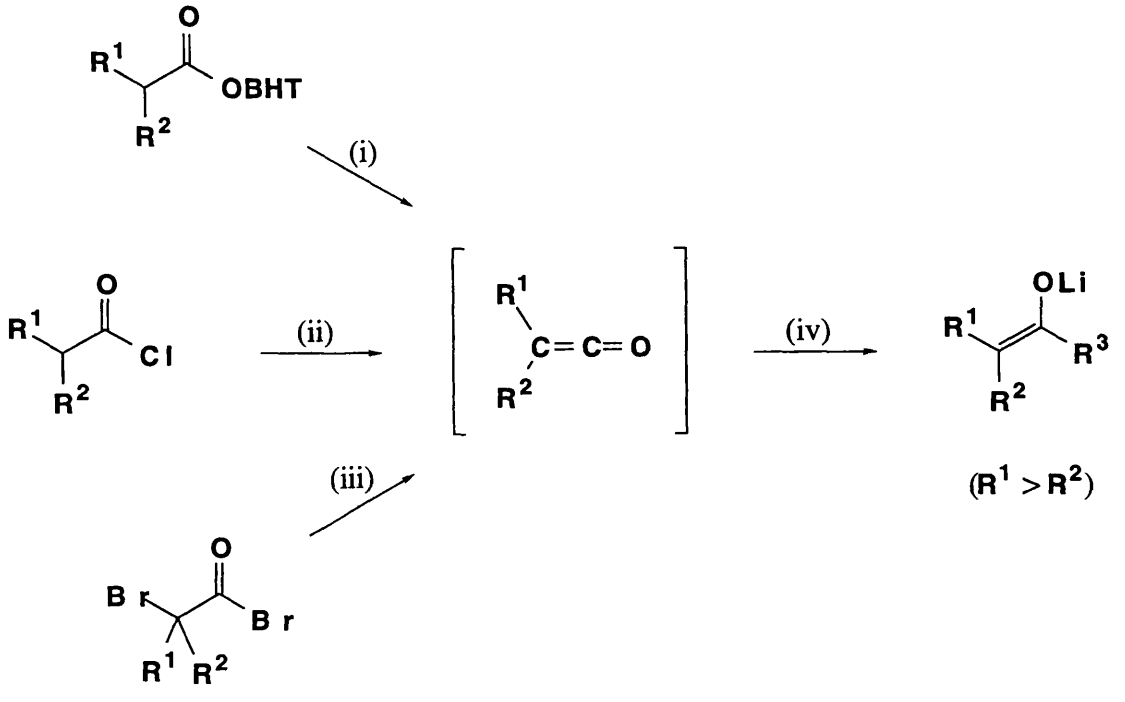
Figure 1.13

Substrates which cannot access this arrangement are instead slowly reduced in a 1,2-fashion (scheme 1.27), and the stereospecificity is consequently explained by reaction exclusively *via* the cisoid conformer in a [4π+2σ] process (figure 1.13).[70] An alternative rationale, involving competing 1,2-hydroboration of the carbon-carbon double bond and subsequent migration of boron, has been proposed to explain occasional poor stereoselectivities.[71]

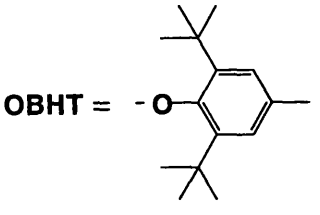
Carboxylic acid derivatives are reduced only in the presence of Wilkinson's catalyst, but with ketones this procedure erodes the 1,4-regioselectivity.[70] The rhodium-catalysed conjugate reduction of enones with trialkylsilanes is an important preparation of silyl enol ethers, but displays comparatively poor stereoselectivity.[72]

1.5 Miscellaneous Methods

The preparation of lithium enolates by the addition of organolithium reagents to ketenes is notable as being a frequently stereospecific approach to tetrasubstituted enolates.[73,74] The ketene intermediates have been prepared by the facile thermal decomposition of highly hindered 2,6-di-*tert*-butyl-4-methylphenyl (BHT) esters (method A),[73] by the basic elimination of acyl chlorides (method B)[74] and by reductive elimination of α-bromo acyl bromides (method C)[74] (scheme 1.28).



Reagents: (i) ^{n}BuLi (1.05), THF, –78°C to r.t.; (ii) NEt_3, THF, reflux (then filter); (iii) Zn (1.0), THF, 0°C; (iv) R^3Li (1.0), THF, –78°C.



Scheme 1.28

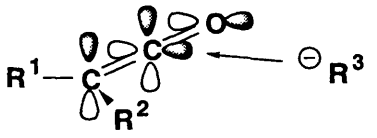
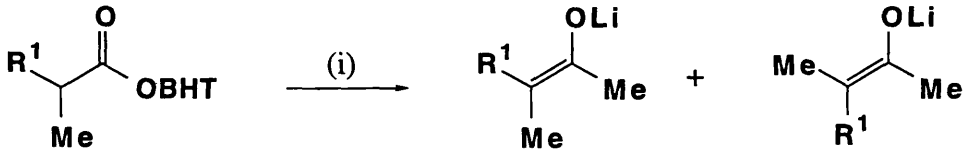


Figure 1.14

Stereoselection results from steric hindrance to the approach of the organolithium nucleophile in the plane of the substituents (figure 1.14), and depends on the relative sizes of the groups R^1 and R^2 (table 1.9).[73] High selectivity is only possible when there is a significant difference in size, but a larger nucleophile (R^3) increases the selectivity. The enolate stereochemistry can be complementary to that obtained by other means (scheme 1.29). Kinetic deprotonation is rarely selective with α-branched ketones.

Alkylboron reagents react with α-halo ketones,[75] α-diazo ketones[76] and sulfur ylids[77] to displace the leaving group and give boron enolates regiospecifically.

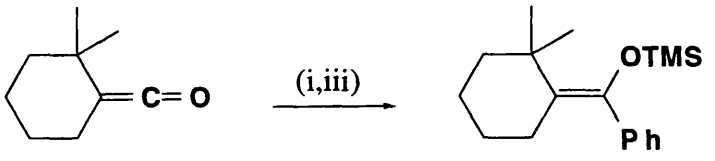


(Z) (E)

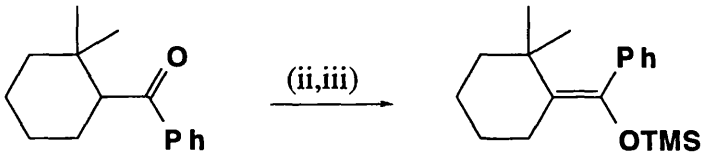
Reagents: (i) ^{n}BuLi (1.05), THF, –78°C; (ii) MeLi (1.0), THF, –78°C to r.t.

Entry	R^1	Ratio (Z:E)
1)	Et	1.7:1
2)	^{i}Pr	7.0:1
3)	^{t}Bu	>99:1

Table 1.9



(Z) (63%)

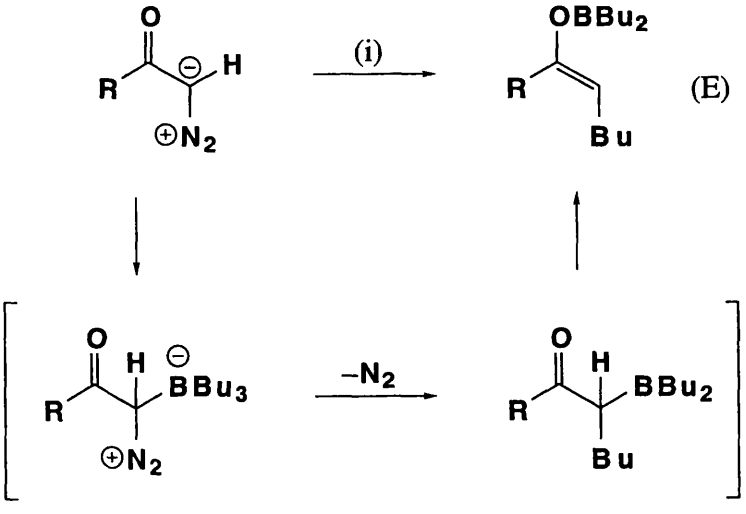


(E) (81%)

Reagents: (i) PhLi (4), THF, –78°C; (ii) LDA, THF, –78°C; (iii) TMSCl, –78°C.

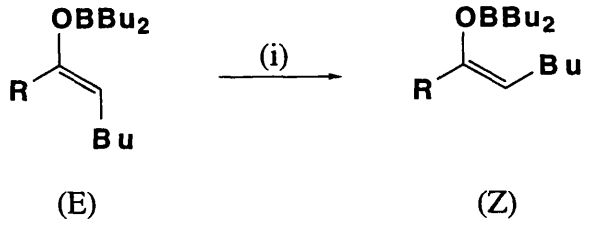
Scheme 1.29

Tri-*n*-butylborane reacts with diazomethyl ketones to give *n*-pentyl ketone (E)-boron enolates stereospecifically (scheme 1.30).[78] Initial formation of a boron 'ate complex' is followed by alkyl migration with displacement of dinitrogen, and the β-keto borane then rearranges to the enolate. Treatment of the (E)-enolate product with a mild base results in conversion to the (Z)-isomer (scheme 1.31).[78]



Reagents: (i) BBu_3, Et_2O, reflux.

Scheme 1.30

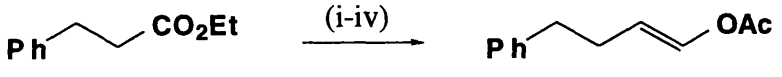


(E) (Z)

Reagents: (i) LiOPh (cat.) or Py (cat.), benzene, r.t.

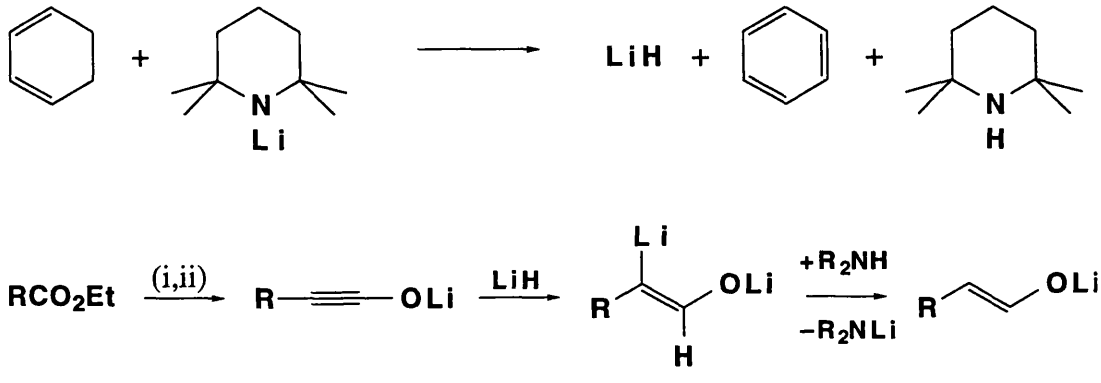
Scheme 1.31

Kowalski has reported an ester homologation reaction, involving rearrangement of an α-bromo-α-lithio ketone enolate to an ynolate intermediate.[79] Treatment of the ynolate with 'active lithium hydride', instead of an alcohol quench, yields (E)-aldehyde enolates stereospecifically (scheme 1.32).[80] The lithium hydride is generated by deprotonation of 1,3-cyclohexadiene to give a pentadienyl anion, and subsequent aromatisation by expulsion of hydride.



(E)

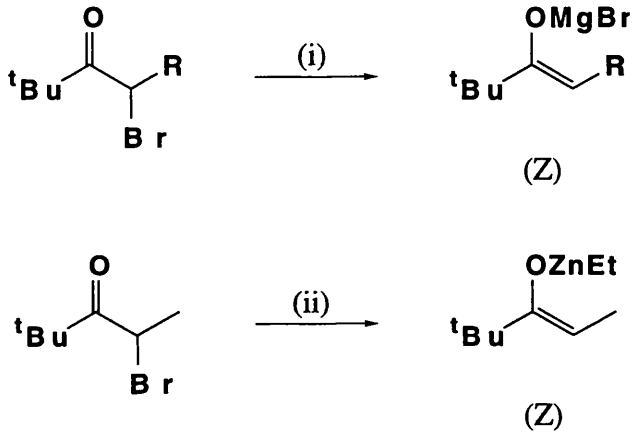
Reagents: (i) ^{n}BuLi (2.2), TMPH (2.4), CH_2Br_2 (2.2), THF, –90°C; (ii) ^{n}BuLi (5), THF, –90°C to r.t., 30 min; (iii) 1,3-cyclohexadiene (10), 0°C; (iv) Ac_2O (excess), 0°C.



Scheme 1.32

The extremely basic conditions limit the utility of the reaction, but reasonable yields are obtainable and this is one of the few ways to prepare lithium aldehyde enolates.

Reduction of α-halo ketones is another regio-defined route to enolate species, but stereoselectivity has not often been investigated. Treatment of α-bromo ketones with magnesium gives the more thermodynamically stable (Z)-enolate stereospecifically (scheme 1.33).[81] Similarly, reaction of an α-bromo ketone with diethylzinc has been shown to give exclusively the (Z)-isomer.[82]



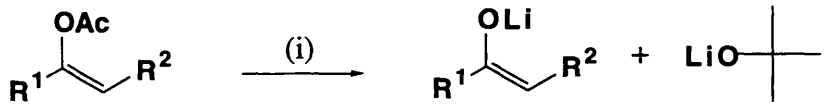
Reagents: (i) Mg, Et_2O, reflux; (ii) Et_2Zn, THF, reflux.

Scheme 1.33

The most common route to enolates of non-alkali metals is *via* transmetallation of the readily prepared alkali metal enolates.[5] Enolates prepared by this route suffer from the presence of metal salt by-products, which can effect reactivity, and from ambiguity in the exact nature of the counter cations. Enolates commonly prepared by this route include those of halomagnesium, dialkylboron and dialkylborate, tin (II) and trialkyltin, titanium (IV), zirconium (IV), halozinc, and transistion metal enolate complexes.[5]

A particularly useful method involves generation of enolates from stable enol derivatives. An efficient, stereoselective route to these precursors is obviously required, but being stable and easily handled these compounds can also be purified and

separated into the individual stereoisomers. This method is of most importance in the preparation of stereochemically pure tetrasubstituted enolates, which are otherwise inaccessible. Lithium enolates may be generated by treatment of enol acetates with two equivalents of methyllithium, without loss of stereochemical integrity (scheme 1.34).[83] However, an equal quantity of lithium *tert*-butoxide is also produced. A more general method involves cleavage of trimethylsilyl enol ethers. Reaction with one equivalent of methyllithium produces only tetramethylsilane as an inert by-product.[84] Other stereochemically-defined metal enolates have also been prepared from silyl enol ethers (table 1.10).



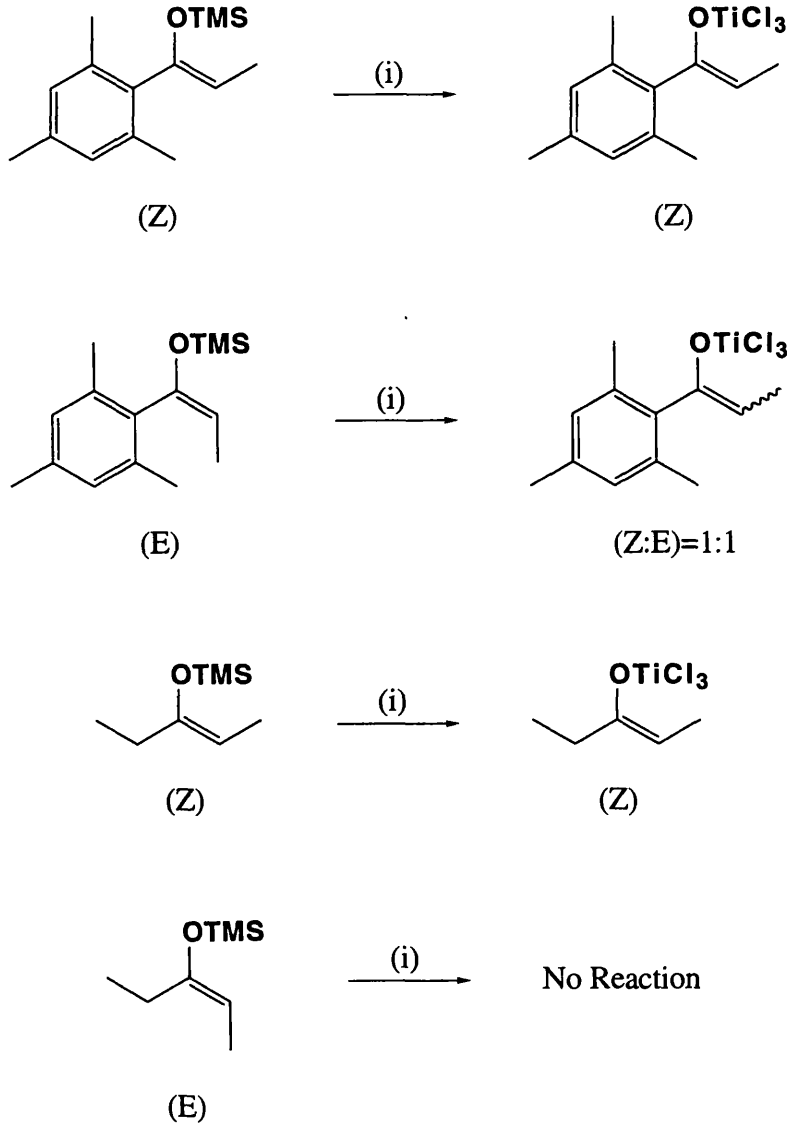
Reagents: (i) MeLi (2), DME, 0°C.

Scheme 1.34

Entry	ML_n	Reagent, conditions
1)[84]	Li	MeLi, THF, 0°C
2)[84]	MgX	MeMgX, glyme, reflux
3)[85]	B^nBu_2	$^nBu_2BOTf$, Et_2O, –78°C
4)[86]	NR_4^+	$NR_4^+.F^-$, THF, –78°C

Table 1.10

The use of anhydrous fluoride (table 1.10, entry 4) is notable for producing highly reactive, 'free' enolates with a non-coordinating, ion-paired tetraalkylammonium cation.[86] However, the formation of trichlorotitanium enolates by treatment of trimethylsilyl enol ethers with titanium tetrachloride is prone to loss of stereochemical integrity. (Z)-Enol ethers usually react cleanly, but the (E)-isomers often give mixtures of (E)- and (Z)-products. While the (Z)-trimethylsilyl enol ether derived from 3-pentanone is converted readily, the (E)-isomer is unreactive (scheme 1.35).[87] The synthesis of enol ether and carboxylate derivatives has been reviewed.[88]



Reagents: (i) $TiCl_4$, DCM, 20°C.

Scheme 1.35

1.6 Conclusions

The direct preparation of either enolate stereoisomer as required is not yet generally possible. For ketones with a small carbonyl substituent R^1, such as 3-pentanone, kinetic deprotonation with lithium dialkylamides can be (E)-specific in the presence of a lithium halide, and highly (Z)-selective in the presence of HMPA. However, kinetic deprotonation of ketones with a large carbonyl substituent provides the (Z)-enolate, which is the thermodynamically more stable and so also formed under equilibrating conditions. The formation of enolates of the less electropositive metals is usually also (Z)-selective. Direct access to (E)-metal enolates in general is not currently possible.

Tetra-substituted enolates provide a particular problem, and deprotonation of α,α-disubstituted ketones is unselective. Although the ketene methodology can be very effective, stereoselectivity relies upon a considerable difference in steric bulk between the two α-substituents, and can only provide the enolate with the larger group and oxygen *cis*-disposed. The stability of the ketene intermediate may also present problems.

Another consideration is the role of preparation by-products in subsequent enolate reactions. There are few methods which allow the generation of enolates free of amines, metal or amine salts, alkoxides or other by-products. The most notable method is the generation of stereo-defined lithium enolates from silyl enol ethers, but this route is indirect, and similar problems of stereochemical control exist in preparation of the precursor. Separation of silyl enol ether stereoisomers is possible, but inconvenient.

In summary, new direct methods of stereoselective enolate synthesis are required. These methods will ideally be direct, clean, and specific in either stereochemical sense as desired for any pattern of substitution.

Chapter 2

Results And Discussion

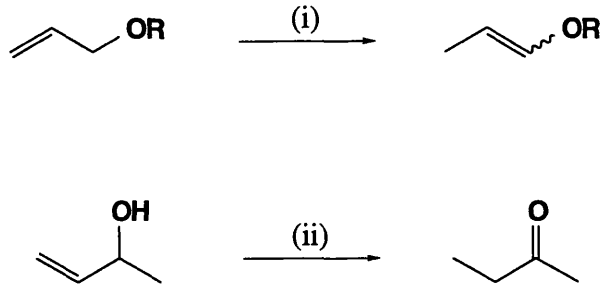
2.1

Introduction

2.1.1 A New Approach To Enolate Chemistry

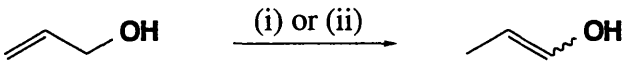
The enolate anion is undoubtedly the most important reactive intermediate in synthetic organic chemistry, being the most accessible and versatile of all reactive species and historically providing many of the most reliable methods of carbon-carbon bond formation.[4-9,89] The ever increasing number of enolate-based transformations are constantly demonstrated in the synthetic literature, and yet new approaches to the enolates themselves are rare and inevitably based upon the reactivity of the carbonyl group. Within our group however, it was envisaged that transition metal catalysed isomerisation of a pre-formed alkoxide of an allylic alcohol would provide access to enolate anions from an entirely new direction.

The well known isomerisation of allylic compounds to their enolic counterparts is thermodynamically favoured due to the stabilisation gained by conjugation of the double-bond with the oxygen functionality. This transformation has been widely reported for allylic alcohols and ethers,[90] and a wide variety of catalytic systems have been employed (scheme 2.1.1).[91] With allylic alcohols a rapid tautomerisation from the first-formed enol to the corresponding carbonyl compound usually occurs under the reaction conditions. Recently, suitably mild catalytic systems have been developed to prepare solutions of simple enols themselves, with sufficient kinetic stability to be observed for several hours (scheme 2.1.2).[92,93]



Reagents: (i) Pd/C, H_2, 180°C or KO^{t}Bu; (ii) $Fe(CO)_5$ or $[Ir(cod)(PPh_2Me)_2]^+PF_6^-$.

Scheme 2.1.1



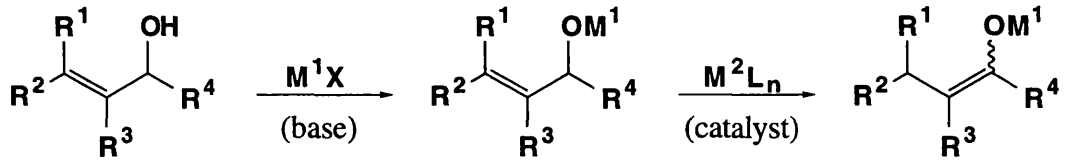
Reagents: (i) $[Rh(dppe)]_2(ClO_4)_2$ (0.5 mol%), acetone-d_6, 25°C, 15 min., 90%;

(ii) $[Ir(cod)(PhCN)(PPh_3)]ClO_4$ (0.5 mol%), acetone-d_6, 5°C, 1 hr, 60%.

Scheme 2.1.2

However the expected transformation to carbonyl products still occurs slowly and the synthetic utility of enols remains low.

Enolate anions are, in contrast, stable and synthetically useful species. It was therefore proposed that treatment of an allylic alcohol with base (M^1X) would yield a metal alkoxide, which when further treated with a suitable transition metal catalyst (M^2L_n) would isomerise to the more stable metal enolate, and could then undergo reaction with a suitable electrophile in the usual way (scheme 2.1.3). It was also envisaged that the presence of a formal negative charge on oxygen would further activate the migrating hydrogen relative to the corresponding free alcohol.



Scheme 2.1.3

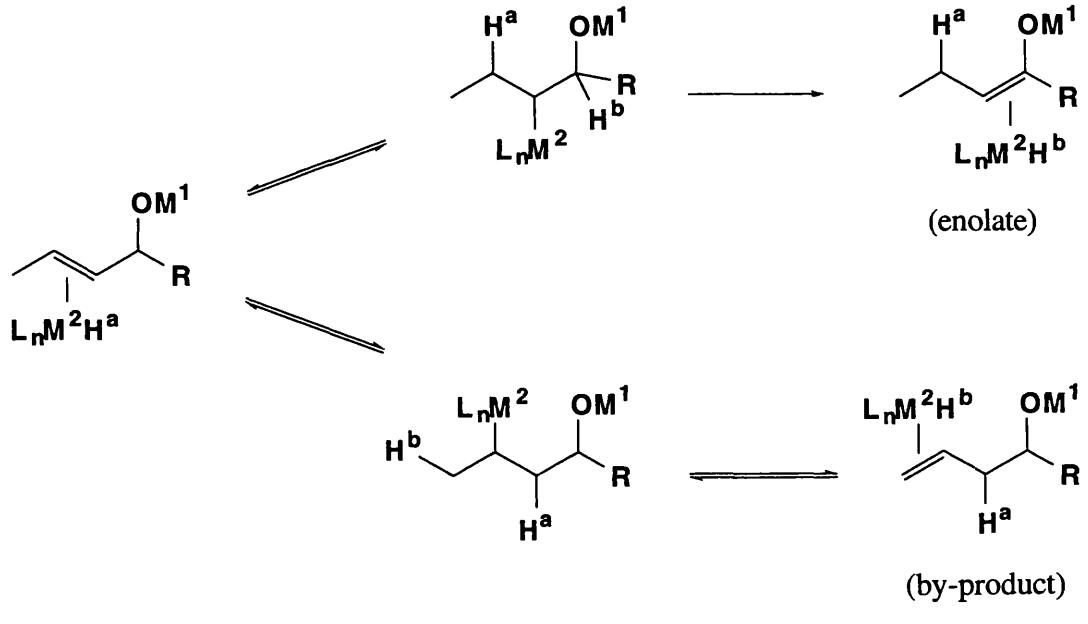
In the choice of base and catalyst there are a number of criteria to consider. The base (M^1X) must be far stronger than the alkoxide or the enolate product so that deprotonation is irreversible. Also, the conjugate acid (HX) must not deactivate the catalyst by reaction or competition with the alkoxide as a ligand. Ideally the alkoxide will be a much better ligand for the catalyst than the enolate, so that a high turnover rate can be achieved even as the isomerisation nears completion and the enolate is present in

far greater quantity. Clearly, neither conjugate acid nor catalyst should interfere with any subsequent reaction of the enolate.

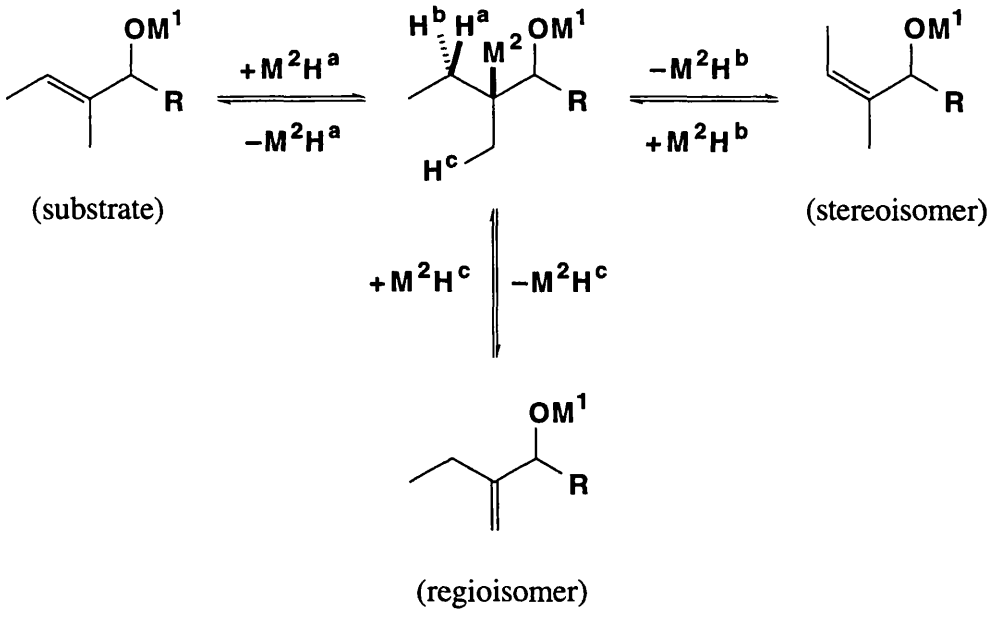
2.1.2 Mechanisms Of Metal-Catalysed Allylic Isomerisation

Allylic isomerisations catalysed by transition metal complexes have been broadly divided between two alternative mechanistic pathways,[94] the 'metal hydride addition-elimination' sequence (A) and the 'π-allyl hydride' mechanism (B), and the important features of each will now be discussed in turn.

Mechanism A requires a metal hydride catalytic species. Coordination of the alkene and insertion into the metal hydride bond gives one of two alkylmetallic intermediates, with the possibility of reversion by β-hydride transfer to either the starting complex or an isomer corresponding to double-bond migration (scheme 2.1.4).[95] In one sense the isomerised product is the desired enolate and in the other a homoallylic alkoxide, but the reversibility of the process leads to an accumulation of the lower energy enolate. An important implication of this reversibility is the possible unwanted interconversion of substrate stereo- and regioisomers (scheme 2.1.5). Clearly this scrambling can be minimised if transfer of the carbinolic hydride is activated and by far the more rapid.



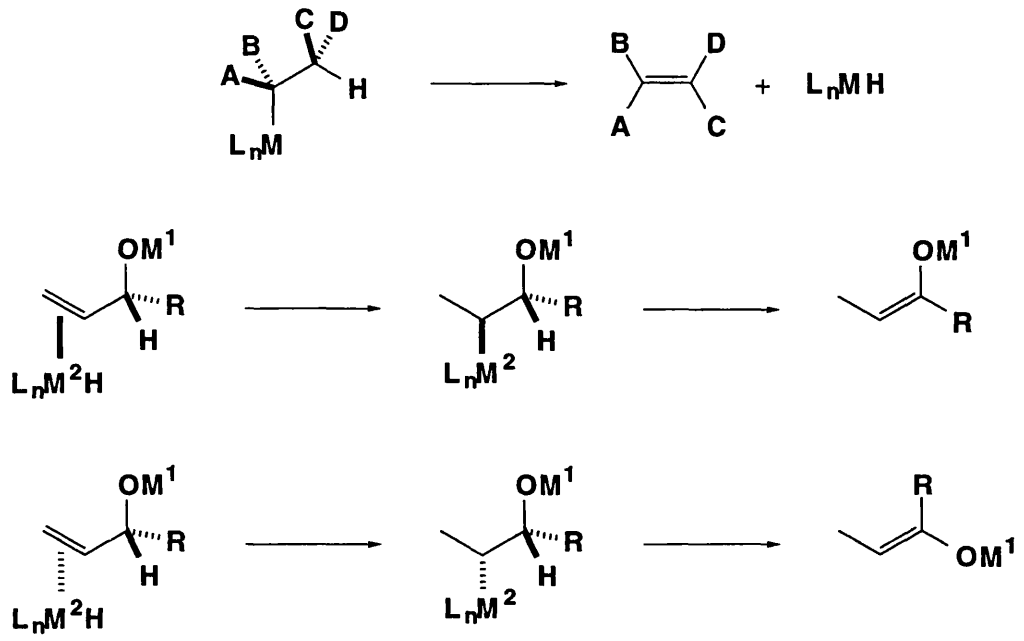
Scheme 2.1.4 – Mechanism A



Scheme 2.1.5 – Interconversion Of Substrate Isomers

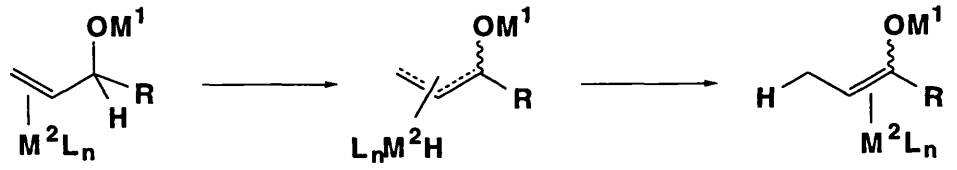
The β-hydrogen has been shown to be transferred more nearly as a hydride than as a proton,[96] and a donor atom should therefore stabilise the developing positive charge.

A further consequence of mechanism A is the requirement of a *cis*-coplanar relationship between the metal-carbon and carbon-hydrogen bonds for β-hydride transfer.[97] For secondary alcohols, with only one carbinolic hydrogen, elimination to the enolate is stereospecific once hydrometallation has occurred (scheme 2.1.6). Stereoselectivity may therefore be dependant upon the facial selectivity of hydrometallation, and is likely to be high only if bonding interactions with oxygen can direct catalyst coordination. Stereoselectivity might also arise from a disparity in the rates of metal hydride elimination between the two diastereomeric complexes. If elimination to the enolate of only one diastereomer is sufficiently slow for reversion to the starting material to compete, isomerisation *via* the other diastereomer to give the alternative enolate will be favoured. It must be emphasised that these arguments only apply to 'kinetic' product ratios. It is possible that enolates might themselves undergo metal-hydride addition and a kinetic ratio may be transformed into a thermodynamically controlled mixture. This has been reported with related allylic isomerisations.[93]

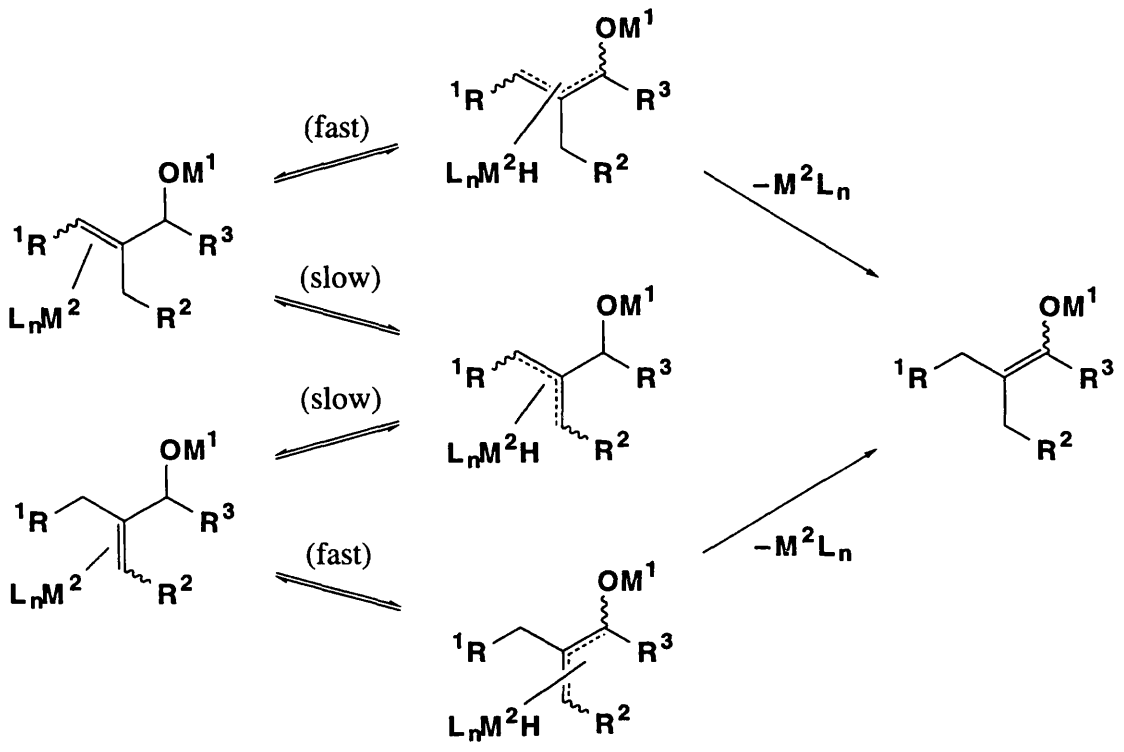


Scheme 2.1.6 – Stereospecific β-Hydride Elimination

The alternative 'π-allyl hydride' mechanism (B)[98] does not require a hydridic catalytic species. Coordination of the alkene is followed by oxidative addition of the proximate carbinolic carbon-hydrogen bond to the metal centre to give the η^3-allyl (or 'π-allyl') metal hydride complex. The isomerisation is completed by a subsequent reductive elimination, delivering the hydrogen atom to the alternative allylic position (scheme 2.1.7). The catalyst must again have a free coordination site, but also access to a second site, at least once the alkene has become ligated. A comparatively low oxidation state is required with a higher state, corresponding to a formal two-electron oxidation, readily available.



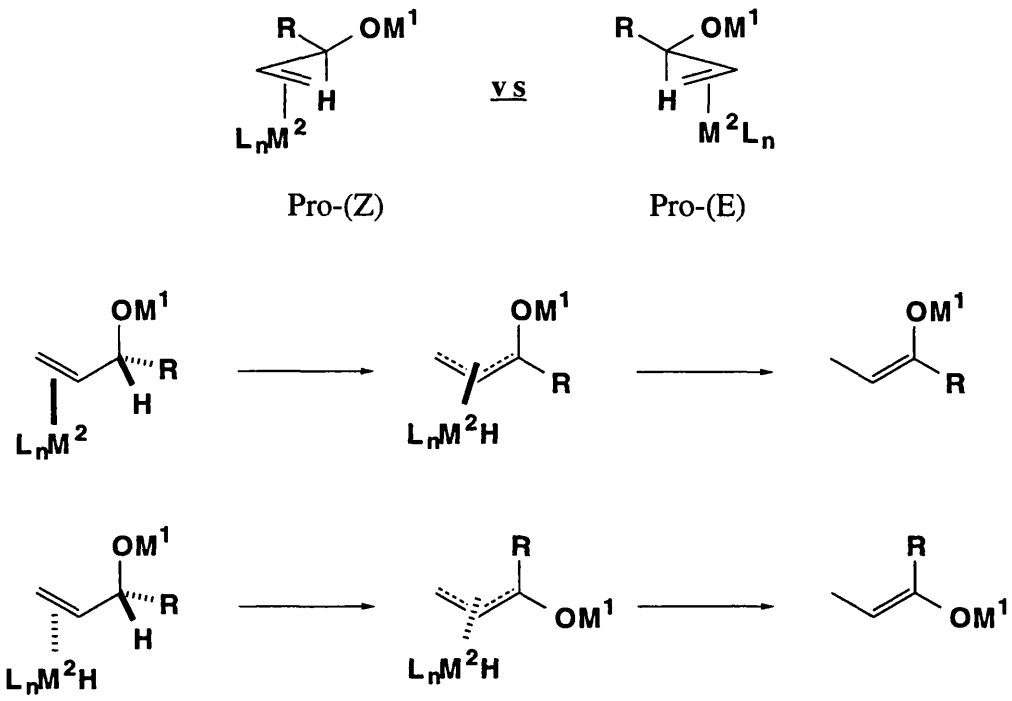
Scheme 2.1.7 – Mechanism B



Scheme 2.1.8 – Predicted Relative Reaction Rates

In this case scrambling of substrate regiochemistry is unlikely. Whereas metal hydride elimination (mechanism A) would most probably be rapid and unselective, here the oxidative addition step is expected to be rate-determining and highly selective for the hydrogen aided by donation from the oxygen (scheme 2.1.8). Reversion of the enolate product to a regioisomeric substrate would also be unactivated and consequently extremely slow.

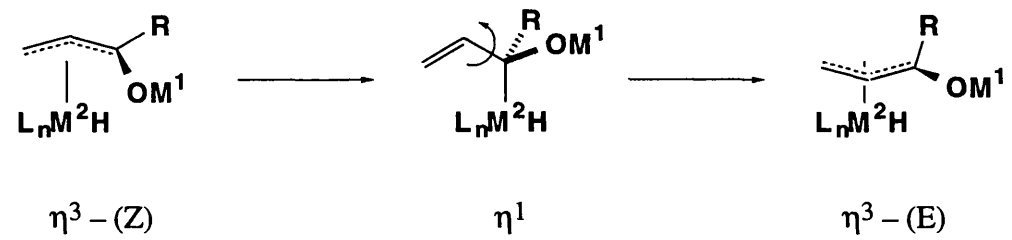
In the π-allyl hydride mechanism, enolate stereochemistry can be related to the conformational preference of the catalyst-substrate complex when oxidative addition occurs. The carbinolic carbon-hydrogen bond must lie perpendicular to the alkene plane in an endo sense for hydride transfer to occur, determining enolate geometry even before subsequent reductive elimination. For secondary alcohols, having only one carbinolic hydrogen, the pro-(E) and pro-(Z) complexes leading to the alternative enolate stereoisomers are not conformers but coordinative facial isomers and must dissociate to interchange (scheme 2.1.9).



Scheme 2.1.9

The ratio of these two complexes will depend most crucially on the degree of bonding interactions (if any) between oxygen and the catalyst. Importantly, and in contrast to mechanism A, the probable rate-determining step is also the stereo-defining step, and a higher selectivity might be inferred.

A final consideration is the possible interconversion of π-allyl hydride intermediates via the well-known 'π-σ-π' fluxionality of transition metal allyl complexes (scheme 2.1.10).[99] The usually favoured η^3-form may be in equilibrium with the η^1-forms, allowing bond rotation and scrambling of stereochemistry.



Scheme 2.1.10 – 'π-σ-π' Fluxionality

There are therefore several important differences between the two mechanisms. Consideration of these various features of each approach leads us to the conclusion that the 'π-allyl hydride' mechanism (B), and consequently non-hydridic catalysts, should prove to be the more suitable.

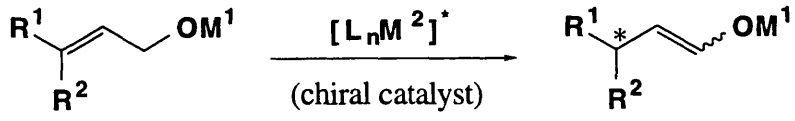
2.1.3 The Aims Of This Project

This project forms a conceptually unique approach to enolate chemistry, and as such is in itself of interest. Most notably the fundamental link with the chemistry of the carbonyl group is severed. To be synthetically useful there are several basic aims to be met, but the methodology also has a number of additional prospective advantages.

The most fundamental goal is the control of regiochemistry, and the use of a regiochemically defined starting material is by design expected to translate into a regiochemically pure product—the enolate is pre-defined by the position of the allylic double bond in the alcohol substrate. The second goal is the control of enolate stereochemistry but success here is harder to predict, and the geometry around the double bond of the starting material is expected to have an effect. Ideally, by a logical choice of catalyst and substrate, either enolate stereoisomer could be selectively prepared with any substitution pattern. In many cases this is not currently possible.

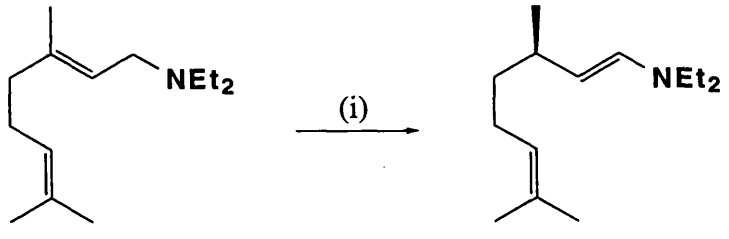
The susceptibility of carbonyl compounds to nucleophilic addition and reduction has required the use of metal amide bases for irreversible deprotonation, giving rise to amine by-products which have been shown to interact with enolate oligomers and effect reactivity.[33] The preparation of more unusual metal enolates by transmetallation of pre-formed group (I) enolates similarly produces metal salt by-products.[5] In contrast alkoxides are readily prepared cleanly, using organometallic reagents, metal hydrides or even a reactive metal itself. This approach should allow the study of not only pure enolates, but enolates of metals or complexes not previously prepared.

Transition metal catalysis is of a generally mild nature and well suited to a broad functional group compatibility. Catalysis is also the most powerful and economical of methods for the introduction of asymmetry into an achiral substrate. The isomerisation with a chiral catalyst of an allylic alcohol bearing two different substituents at the C-3 double bond terminus can in theory generate the new asymmetric centre in an enantioselective manner (scheme 2.1.11).



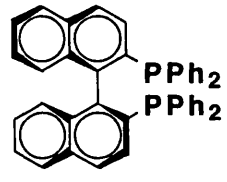
Scheme 2.1.11

Enantioselective isomerisation is the most ambitious of our goals and potentially the most synthetically useful. The process is dramatically illustrated by the related rhodium-catalysed isomerisation of diethylgeranylamine, in 99% chemical yield and 96% enantiomeric excess (scheme 2.1.12).[100] This procedure, developed by Noyori and co-workers, is currently being used as the key step in a multi-tonne scale commercial synthesis of homochiral menthol. This route presently accounts for approximately 25% of world production and is a striking testimony to the power of enantioselective transition metal catalysis.



(E) (99%, 96% ee)

Reagents: (i) [Rh{(*S*)-BINAP}]$^+$ (1.0 mol%), THF, 60°C.

(*S*)-BINAP = 

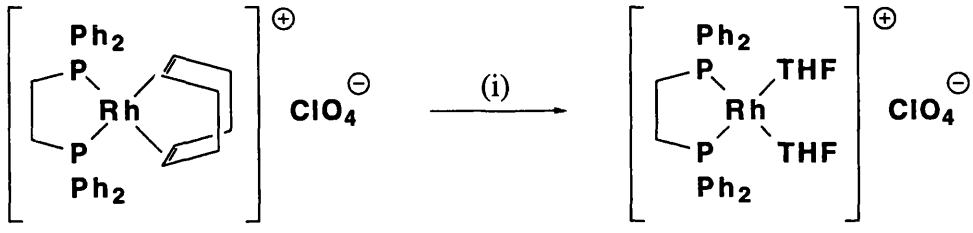
Scheme 2.1.12

2.2

Wilkinson's Catalyst Mediated Isomerisation

2.2.1 Introduction

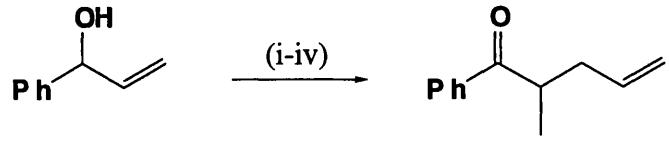
The initial choice of catalyst was $[Rh(dppe)(THF)_2]^+$, an air-sensitive cationic rhodium species generated *in situ* by hydrogenation of the more stable precursor $[Rh(cod)(dppe)]^+ClO_4^-$ in THF solution (scheme 2.2.1).[101] As mentioned earlier, this catalyst was subsequently employed for the generation of enols in a very closely related process (scheme 2.1.2).[92]



Reagents: (i) H_2, THF, r.t.

Scheme 2.2.1

The activity of this catalyst in the isomerisation of allylic alkoxides was earlier established by other workers in our group.[102] Thus, the lithium alkoxide of 1-phenyl-2-propen-1-ol (**1**) was isomerised to the corresponding enolate by 2 mol% of $[Rh(dppe)(THF)_2]^+$ in THF at reflux in 6.5 hours. Quench with allyl bromide afforded the alkylation product **2** of propiophenone enolate in 77% yield (scheme 2.2.2).



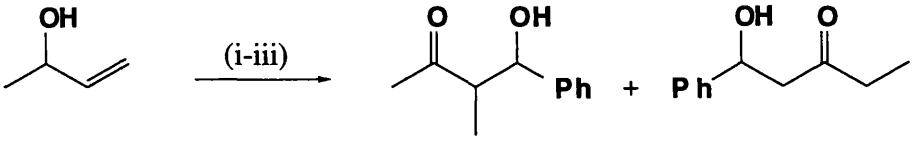
1 **2** (77%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $[Rh(cod)(dppe)]^+ClO_4^-/H_2$ (2.2 mol%), THF, then reflux 6.5 h; (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.2

From the evidence of many isomerisation experiments, and with literature precedent including the isomerisation of free allylic alcohols,[92] a π-allyl hydride mechanism was proposed. Several important general points were noted:

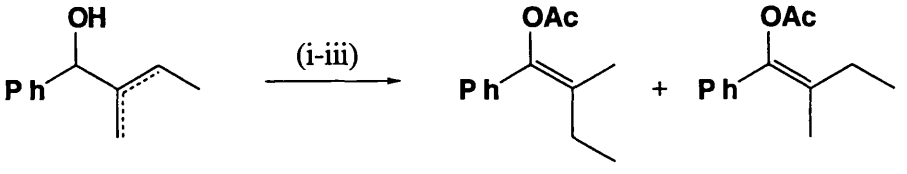
- Isomerisation is slow in comparison to the reported reaction of similar free alcohols with the same catalyst;
- The isolation of a small quantity of unalkylated ketone was often observed;
- A drop in activity of the catalyst occurred with increasing double-bond substitution, tending towards a total loss of activity particularly with terminally disubstituted substrates;
- The regiochemical integrity of the substrate is lost in conversion to the enolate (scheme 2.2.3);
- Different alcohols giving enolates corresponding to the same ketone gave similar products regardless of the regio- and stereochemistry of the starting material (scheme 2.2.4).



6:1

Reagents: (i) ^{n}BuLi; (ii) $[Rh(dppe)]^{+}$, reflux; (iii) PhCHO, –78°C.

Scheme 2.2.3



3:1

Reagents: (i) ^{n}BuLi; (ii) $[Rh(dppe)]^{+}$, reflux; (iii) Ac_2O, –78°C.

Scheme 2.2.4

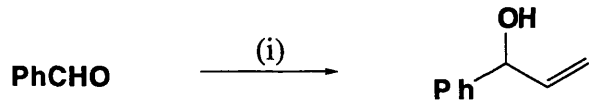
Chlorotris(triphenylphosphine)rhodium (I),[103] or Wilkinson's catalyst, has found wide utility in organic chemistry, including several allylic isomerisation processes.[104] Allylic alcohols have been isomerised to the corresponding carbonyl compounds in good yields.[105] Corey has used the complex for the conversion of allylic ethers to 1-propenyl ethers prior to acid hydrolysis, establishing the allylic ether as a method of protecting hydroxyl groups under a variety of conditions.[106] Wilkinson's catalyst has similarly been found to isomerise allyl 2,6-dimethylphenyl ether in a highly (Z)-selective manner.[107] However, unactivated carbon-carbon double bonds are resistant to isomerisation.

A parallel study of Wilkinson's catalyst was therefore undertaken for comparison with the cationic rhodium catalyst, and to hopefully overcome some of the difficulties encountered with this work. Wilkinson's catalyst requires no prior activation procedure such as hydrogenation, and was expected to be more easily handled than the cationic catalyst. From the outset, while it was expected (and desirable) that a π-allyl hydride mechanism would operate, we were always aware of the possibility of metal hydride formation *in situ*.

The isomerisation of allylic alkoxides with the catalyst $[Rh(cod)(dppe)]^+ClO_4^-$ has been reported in the literature by our group.[108]

2.2.2 The Test Substrate — 1-Phenyl-2-propen-1-ol

Our initial aim was to show the activity of Wilkinson's catalyst in this chemistry. As a test substrate, 1-phenyl-2-propen-1-ol (**1**) was prepared in 83% yield by Grignard reaction with benzaldehyde (scheme 2.2.5).



1 (83%)

Reagents: (i) Vinylmagnesium bromide, THF, 0°C.

Scheme 2.2.5

Alcohol **1** was chosen as a substrate which would offer the minimum substitution and a single possible enolate regioisomer. It was also envisaged that isomerisation might be further promoted by benzylic activation of the carbinolic hydrogen, and by the resulting styryl-type conjugation. It is our intention to produce enolates of wide general utility, and as lithium enolates are the most well known and are synthetically useful in many transformations, lithium was chosen as the standard counter-cation. For similar reasons of literature precedence THF was chosen as the standard solvent. Lithium alkoxides are also readily available free of amine or metal salt by-products from the reaction of organolithiums with the free alcohols.

While Wilkinson's catalyst is itself quite stable to oxidation in air, at least in the solid state, it was expected that organorhodium intermediates would be formed in the reaction mixture which would be extremely oxidatively labile. Consequently all isomerisations were performed using Schlenk-type glassware and standard vacuum-line handling techniques,[109] and under an atmosphere of argon which was dried and deoxygenated by passage through silica gel impregnated with chromium (II). All solutions were degassed repeatedly prior to mixing.

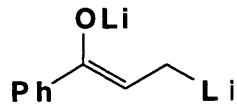
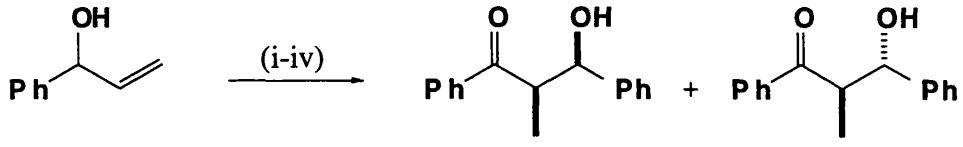


Figure 2.1



8.3:1

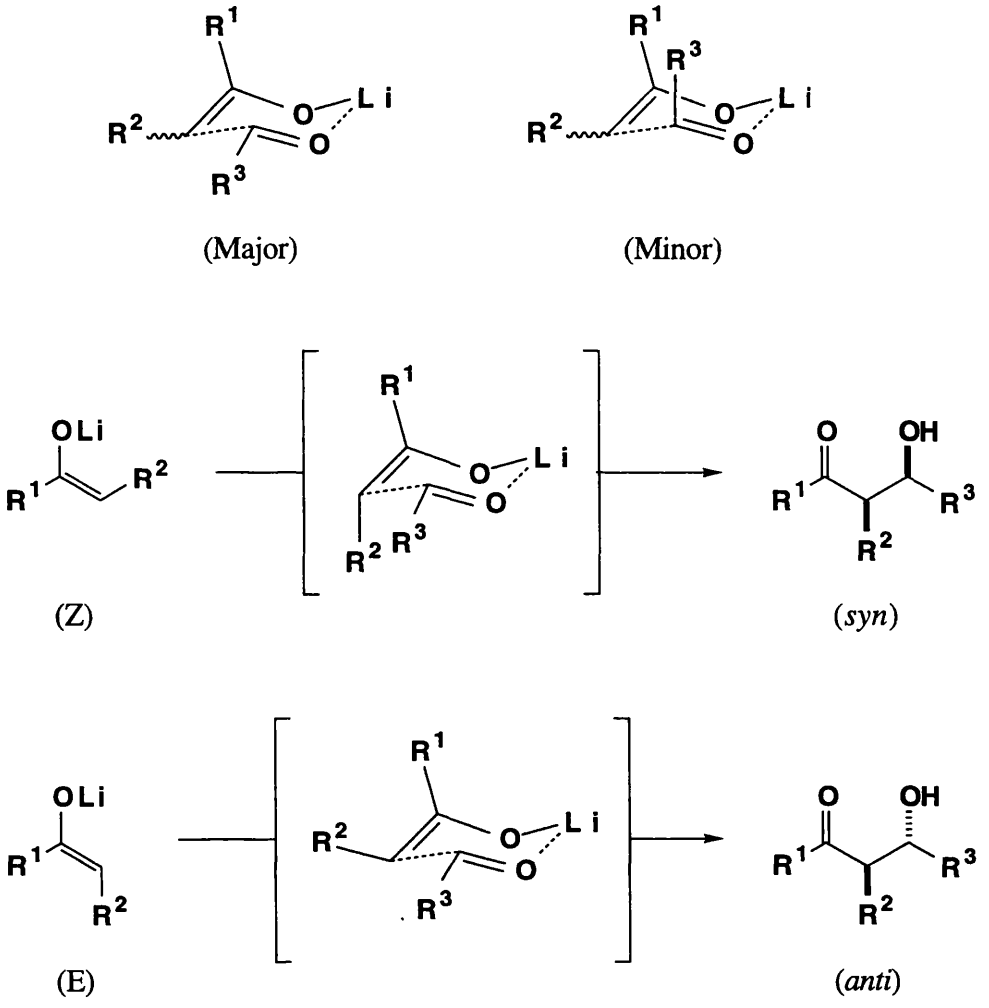
1 **3** (70%) **4**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 1.5 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.6

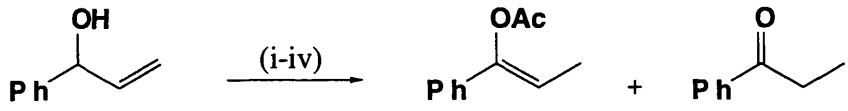
Thus alcohol **1** was treated with a slight excess of n-butyllithium in THF, the resulting solution degassed and treated with a THF solution of 2.0 mol% of Wilkinson's catalyst, and the mixture heated to reflux for 1.5 hours. Complete deprotonation of **1** is indicated by a temporary faint red colour due to dianion formation (figure 2.1).[110] The resulting enolate solution was quenched with benzaldehyde following the procedure developed by Heathcock and co-workers for kinetic aldol reaction.[13] Benzaldehyde (1.1 equivalents) was added as rapidly as possible at –78°C, followed by saturated aqueous ammonium chloride after exactly five seconds, providing aldols **3** and **4** in 70% combined yield and in the ratio **3**:**4**=8.3:1 (scheme 2.2.6). The major isomer was identified as *syn* by having the smaller C2-H to C3-H ^{1}H NMR coupling constant, a trend established in the literature.[111]

Heathcock and others have established the dependency of aldol stereochemistry on the geometry of the enolate under conditions of kinetic control.[13] For simple lithium enolates the (Z)-stereoisomer shows a strong preference for *syn*-aldol products while the (E)-isomer selectively gives *anti* products. This selectivity is commonly rationalised by the 'pericyclic' Zimmerman-Traxler transition state model (scheme 2.2.7).[112]



Scheme 2.2.7 — The Zimmerman-Traxler Transition State Model

Prior coordination of the aldehyde serves to order the transition state, lowering the activation entropy and minimising charge separation. The selectivity arises from the tendency of aldehyde substituent R^3 to occupy a pseudo-equatorial position in the chair-like arrangement rather than suffer a 1,3-non-bonded interaction with enolate substituent R^1. A similar transition state applies to either enolate isomer, with the boat conformer thought to be insignificant while the substituent R^2 remains relatively small.[113] Aldol reactions therefore provide useful qualitative information about enolate stereochemistry, and by comparison with reported ratios allow estimations to be made in a quantitative sense. Recourse to the literature gives the kinetic ratio **3**:**4**=4.9–7.3:1 for reaction of the (Z)-lithium enolate of 1-phenyl-1-propanone with benzaldehyde.[13]



1 **5** (56%) **6** (*ca.* 1%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 1.5 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.8

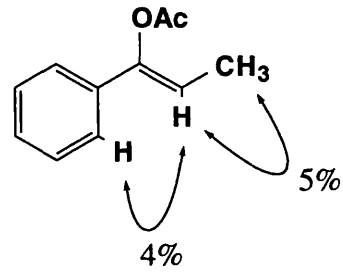


Figure 2.2 — nOe Experiments

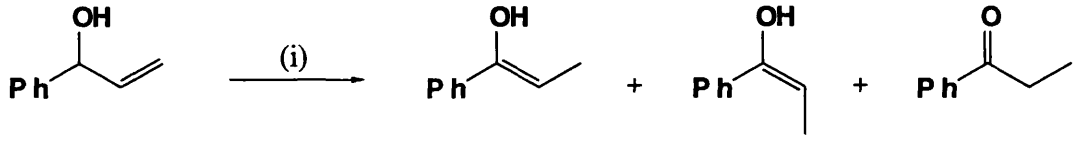
This range of ratios is a result of the aldol reactions being conducted in the presence of an amine, derived from the lithium dialkylamide base used to prepare the enolates, and ratios vary with the amine involved. Although the observed ratio (**3**:**4**=8.3:1) suggests a (Z)-specific isomerisation, a more accurate measurement was needed.

Isomerisation of **1** as before and quench with ten equivalents of acetic anhydride at –78°C resulted in apparently instant formation of enol acetate **5**, in 56% isolated yield (scheme 2.2.8). The expected (Z)-stereochemistry of this product was confirmed by nOe experiments (figure 2.2). No trace of the (E)-isomer was detected, nor the C-acylated product, however a very minor quantity of 1-phenyl-1-propanone (**6**) was isolated (*ca.* 1%).

Several points were noted from these experiments which later proved to be of general value. The enol acetates are easily prepared and isolated, and give an accurate measure of stereoselectivity, but free ketone is also isolated as a by-product despite the use of a slight excess of butyllithium and rigorously de-acidified acylating agent. Even

taking this free ketone into account the aldol reaction gives considerably higher yields, and so is a more accurate measure of the enolate yield. The aldol reaction also allows a more direct spectroscopic determination of stereochemistry.

In summary, test substrate **1** gave solely the (Z)-enolate stereoisomer in good yield; the same stereospecificity is seen in the kinetic deprotonation of ketone **6** with lithium amide bases.[13] Bergens and Bosnich have demonstrated that the isomerisation of alcohol **1** may be readily achieved using catalysts of the type [Rh(diphosphine)]$^+$, giving the corresponding enols in very closely related process (scheme 2.2.9).[92] The initial (kinetic) stereoselectivity again favoured the (Z)-isomer, in the ratio (Z:E)=11:1.



Initial (kinetic) ratio: (Z) 11:1 (E)

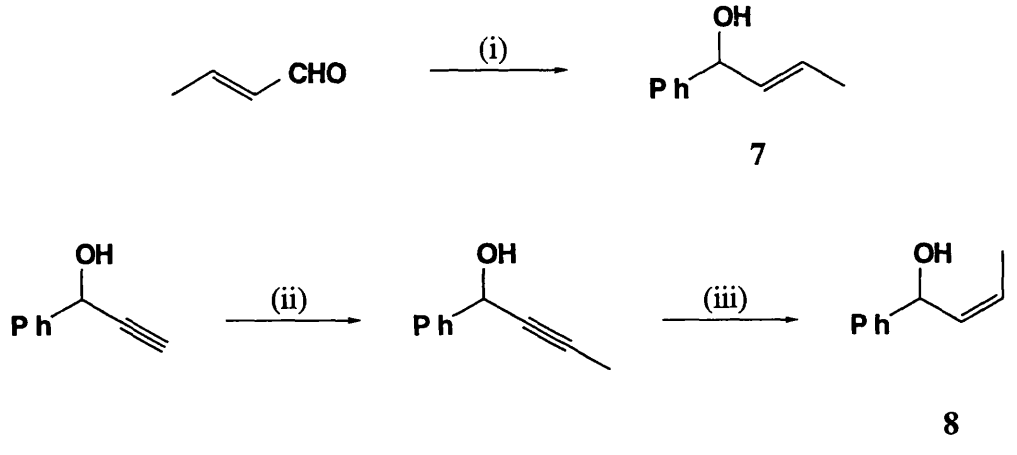
Reagents: (i) $[Rh(dppe)]_2(ClO_4)_2$ (2 mol%, 1 mol% cat.), acetone-d_6, 25°C, 2 h.

Scheme 2.2.9

The reaction time was also notable, full conversion being achieved in just 2 hours at 25°C using 1 mol% of the catalyst. It was envisaged that when using an alkoxide, the presence of a full formal negative charge on oxygen might accelerate the reaction relative to that of the free alcohol or comparable allyl ethers. However isomerisation with Wilkinson's catalyst, or with the [(diphosphine)Rh]$^+$ catalyst used by Bergens and Bosnich,[102] was not as facile as initially hoped. With these results in hand, our attention then turned to potentially more challenging substrates.

2.2.3 More Challenging Substrates

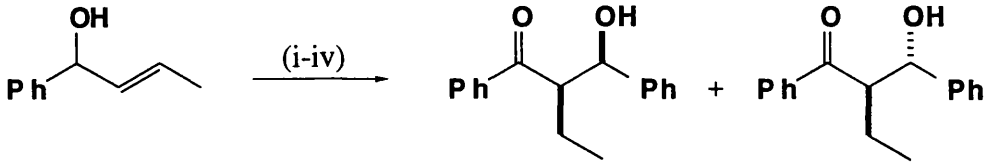
In order to study the effects of increasing double-bond substitution the isomeric substrates **7** and **8** were prepared as shown (scheme 2.2.10).[102] We envisaged that both would be less reactive than **1** as a consequence of the increasing steric effects hindering coordination to the catalyst, a well-documented trend in hydrogenation and related chemistry involving alkenes and transition metal catalysis.[114]



Reagents: (i) PhMgBr, THF, 0°C; (ii) Li/NH_3, –78°C, then MeI; (iii) H_2, $Pd/CaCO_3$, quinoline, hexane, 0°C.

Scheme 2.2.10

Isomerisation of (E)-1-phenyl-2-buten-1-ol (**7**) with 2 mol% of Wilkinson's catalyst under our standard conditions proceeded smoothly in 5.5 hours to give aldols **9** and **10** in an excellent 92% combined yield and relative ratio **9**:**10**=3.0:1 (scheme 2.2.11). The degree of *syn*-selectivity is low but identical to that observed when 1-phenyl-1-butanone is deprotonated under kinetic control with LDA[102]; this is an established method for the (Z)-specific generation of enolates and implies that isomerisation is again strongly (Z)-selective. It was also encouraging to find the increase in reaction time relative to **1** was comparatively small. Attempts to prepare the enol acetates, however, were met with limited success.



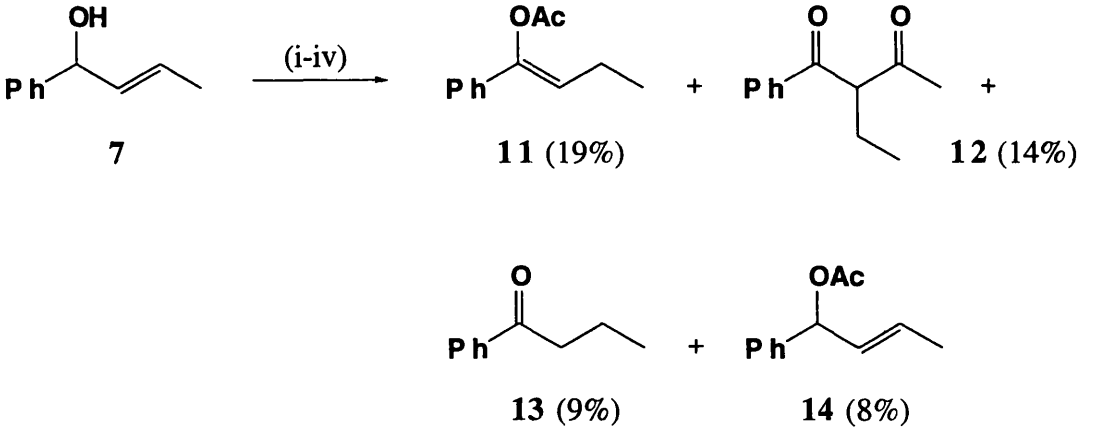
3.0:1

7 **9** (92%) **10**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 5.5 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.11

Isomerisation as before and quench at –78°C with ten equivalents of acetyl chloride gave three isomerisation products: the (Z)-enol acetate **11** (19%), the C-acylated product **12** (14%), and the parent ketone **13** (9%) in a poor combined yield of 42%. Acetylated starting material **14** (8%) was also recovered (scheme 2.2.12). The (Z)-geometry of **11** had previously been confirmed by nOe experiments,[102] and it is emphasised that no trace of the (E)-enol acetate was detected. As lithium enolates usually react with acetyl chloride to give solely O-acyl products, in contrast to other carboxylic acid chlorides,[115] the observed selectivity in this case (O-acylation:C-acylation = 1.4:1) is particularly low.

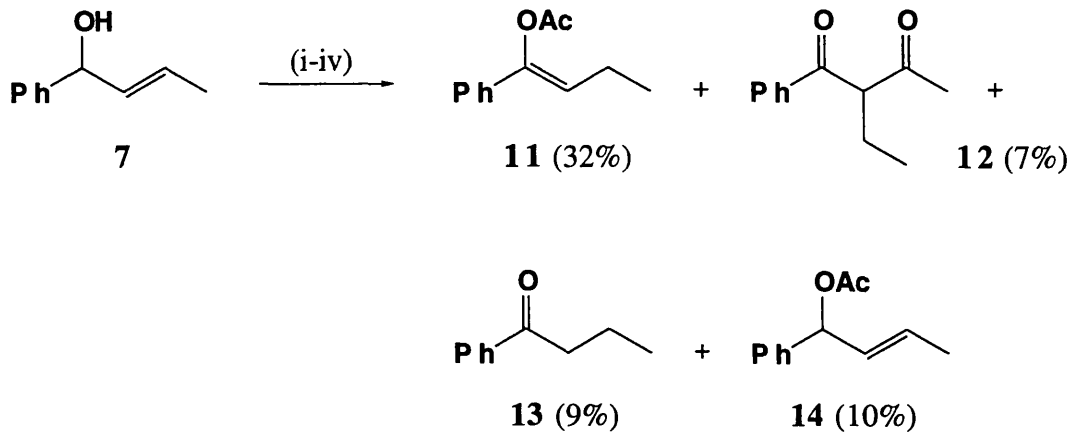


7 **11** (19%) **12** (14%)

13 (9%) **14** (8%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 6 h; (iii) AcCl (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.12



7 **11** (32%) **12** (7%)

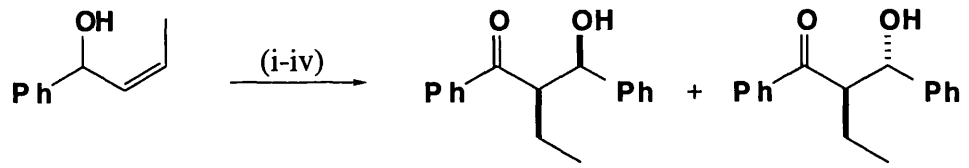
13 (9%) **14** (10%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 8 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.13

Repeating the isomerisation and trapping with acetic anhydride under similar conditions proved more fruitful giving considerably more of the desired (Z)-enol acetate **11** (32%) (scheme 2.2.13, other yields shown). This improved ratio (O-acylation:C-acylation = 4.6:1) and higher combined yield of isomerised products (49%) allowed us to more confidently assign to the enolate pure (Z)-geometry, and later prompted us to adopt acetic anhydride as the standard reagent. A large quantity of ketone **13** (9%) was again isolated, and a degree of capriciousness in isomerisation rates is evident from the isolation of a large quantity of acetylated starting material **14** (10%). It is notable that no trace of starting material isomerised to the (Z)-geometry, or of homoallylic by-product could be found. Such products would be indicative of a metal hydride addition-elimination mechanism promoting simple alkene isomerisation prior to enolate formation (scheme 2.1.5).

Our attention then turned to the isomerisation of (Z)-1-phenyl-2-buten-1-ol (**8**), which was achieved in 6.5 hours under standard conditions. Reaction with benzaldehyde under conditions of kinetic control gave aldols **9** and **10** in a good, but lower 75% combined yield and in an identical ratio **9**:**10**=3.0:1 (scheme 2.2.14). No other identifiable products were isolated.

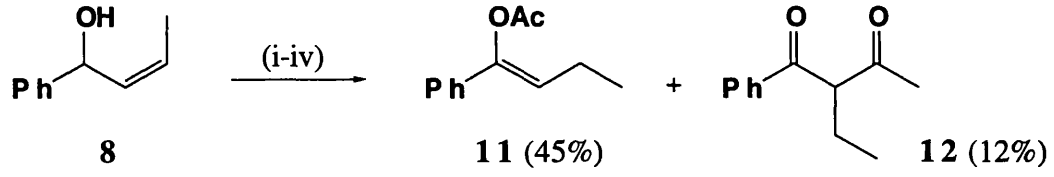


3.0:1

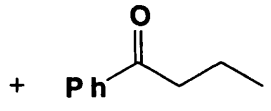
8 **9** (75%) **10**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 6.5 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.14



8 **11** (45%) **12** (12%)



13 (14%)

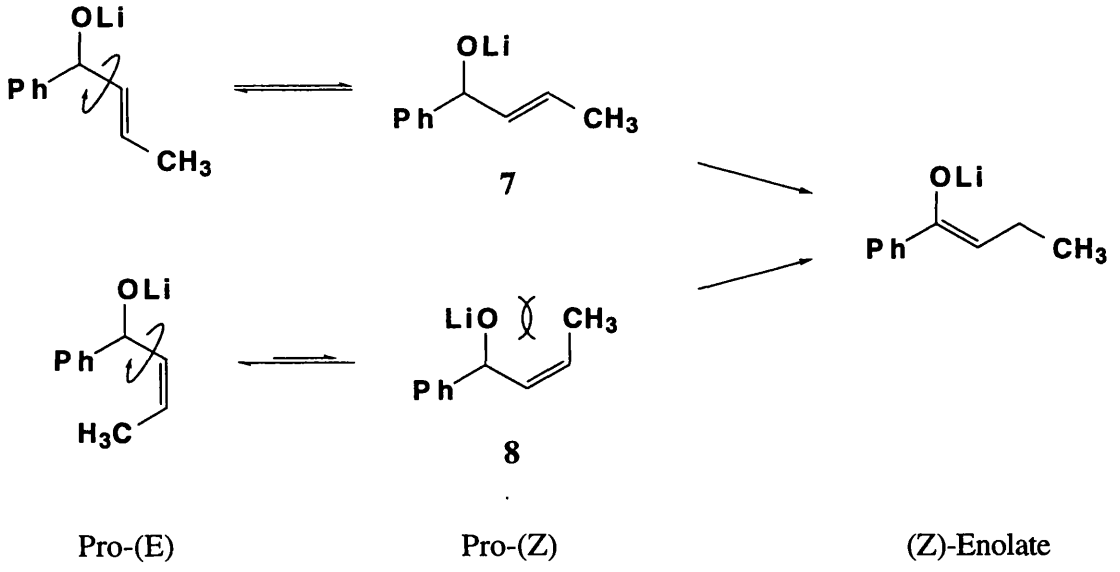
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 7 h; (iii) AcCl (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.15

Isomerisation for 7 hours and acetylation was in this case more successful giving a moderate 45% yield of (Z)-enol acetate **11** with no trace of the (E)-isomer (scheme 2.2.15). Diketone **12** (12%) and 1-phenyl-1-butanone **13** (14%) were also isolated giving a 71% total yield of isomerised material, in good agreement with the aldol reaction, and no starting material was recovered.

The substrates **7** and **8** are therefore precursors for the same enolate, and both substrates show similar results, although the (E)-geometry substrate **7** is the more favoured. This may be a result of less steric crowding in the conformation leading to the favoured (Z)-enolate (the pro-(Z) conformation) than with the (Z)-substrate **8**

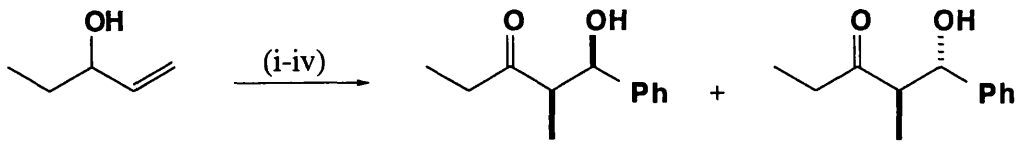
(scheme 2.2.16). It is expected that the lithium alkoxides would aggregate in THF solution, increasing the effective size of the -OLi group and accentuating this preference.[116] The position of the methyl substituent has no great effect on the rate of isomerisation, but both isomerisations are slower than that of the unsubstituted alcohol **1**, taking approximately four times as long.



Scheme 2.2.16

It was then of interest to examine 1-penten-3-ol (**15**), an aliphatic alcohol of equivalent substitution to our test substrate, but lacking in any benzylic assistance. Isomerisation proceeded smoothly under standard conditions but with a considerably longer reaction time of 10 hours to give the enolate of the symmetrical ketone 3-pentanone. Kinetic aldol reaction with benzaldehyde as before gave aldol products **16**:**17** in the relative ratio **16**:**17**=3.5:1 and in 80% yield (scheme 2.2.17). Once again the *syn*-aldol predominated indicating (Z)-selectivity.

3-Pentanone shows a poor stereoselectivity when deprotonated with lithium amide bases due to the small size of the ethyl group.[13] An enolate mixture (Z:E)=2:1, prepared using lithium cyclohexylisopropylamide (LCPA), has been shown to yield the ratio of aldols **16**:**17**=3.3:1.



3.5:1

15 **16** (80%) **17**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 10 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.17

The ratio of aldol products is therefore higher than the ratio of the enolates, a result of the commonly high *syn*-selectivity of the (Z)-enolate and very poor *anti*-selectivity of the (E)-enolate.[117] This effect has been explained as skewing of the Zimmerman-Traxler transition state model to increase the idealised 60° dihedral angle between the reacting carbonyl and the enolate double bond towards 90° (figure 2.3).[9,118] Whereas the aldehyde substituent (a phenyl group in this case) suffers steric interactions in both transition states of the (E)-enolate, the (Z)-enolate is hindered only in the (Z)-*anti* transition state. Thus we have (Z:E)=2:1 as a crude estimation of the product enolate stereochemistry.

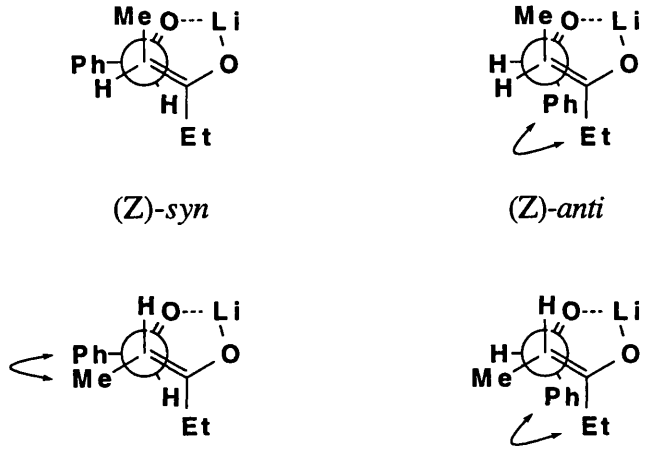
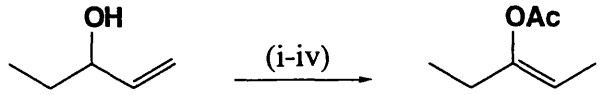


Figure 2.3 – 'Skewed' Zimmerman-Traxler TS Model



15 **18** (27%)

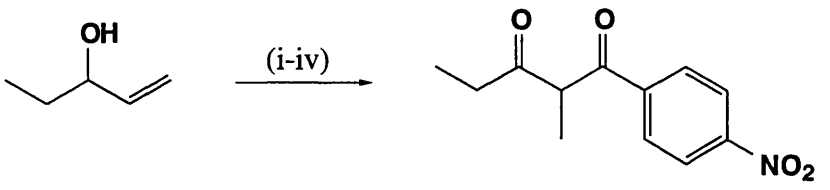
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 11 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.18

However, in congruity with earlier examples, acetylation with acetic anhydride gave the known, pure (Z)-enol acetate **18** in 27% yield (scheme 2.2.18). This poor isolated yield is undoubtedly a result of product volatility. Since it seems most unlikely that the undetected (E)-enolate could be totally unreactive towards acetylation, or that a significant quantity of (E)-enol acetate could be preferentially lost during evaporation, we consider the acetylation to be the more trustworthy indicator of enolate geometry.

The noted ratio of aldol products is reproducible and has also been obtained by colleagues in the group, but the reasons for this discrepancy between observed and literature results are unclear. It is possible that subtle changes (such as concentration) have surprisingly significant effects on the stereoselectivity of this reaction, but the most significant difference is the absence here of the stoichiometric quantities of amine produced when the enolates are prepared by lithium dialkylamide deprotonation of the ketone. Heathcock has reported different aldol ratios using the same ratio of enolates, depending on the amide base used.[13] It is therefore probable that the formation of mixed amine-lithium enolate oligomers is influencing the reported results.[33,65]

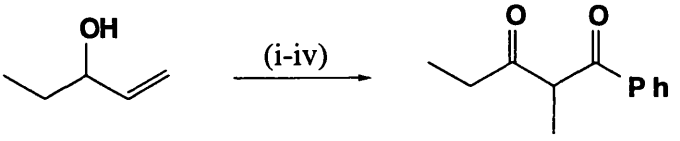
Attempts to trap isomerisation products as non-volatile O-acyl derivatives were unsuccessful, giving instead 1,3-diketones. Reaction with excess 4-nitrobenzoyl chloride yielded the crystalline diketone **19** (63%) (scheme 2.2.19), and reaction with benzoic anhydride gave the diketone **20** (39%) (scheme 2.2.20). The use of benzoic anhydride was prompted by the greater O-selectivity of acetic anhydride versus acetyl chloride observed in this work, but the extremely low reactivity of this reagent resulted in a very poor yield.



15 **19** (63%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 10 h; (iii) 4-NO_2-C_6H_4COCl (10), 3.0M in THF, –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.19



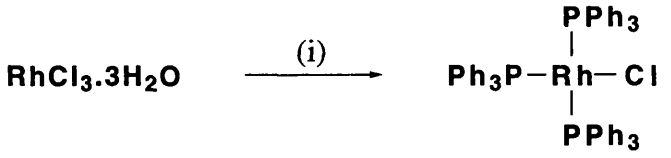
15 **20** (39%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 10 h; (iii) $(PhCO)_2O$ (5.0), 1.2M in THF, –78°C; (iv) $NaHCO_{3(aq)}$, then LiOH (15), 0.74M in 4:1 THF:H_2O.

Scheme 2.2.20

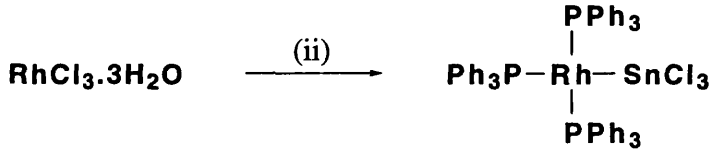
An interesting effect was discovered when 1-penten-3-ol (**15**) was isomerised in the presence of tin (II) chloride under otherwise standard conditions. Treatment of the lithium alkoxide with 2.0 mol% of an equimolar mixture of Wilkinson's catalyst and anhydrous tin (II) chloride in THF solution caused complete isomerisation in just 3 hours, less than one third the reaction time with Wilkinson's catalyst alone.

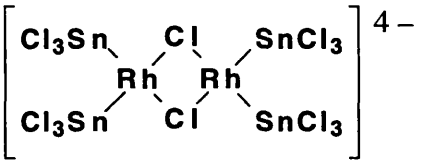
The addition of tin (II) chloride to Wilkinson's catalyst was prompted by the expectation that (trichlorostannato)tris(triphenylphosphine)rhodium (I) would be formed. The preparation of Wilkinson's catalyst involves reduction of rhodium (III) chloride trihydrate in refluxing ethanolic solution with excess triphenylphosphine; triphenylphosphine oxide is a by-product (scheme 2.2.21).[103] A similar reaction in the presence of tin (II) chloride gives the orange-brown trichlorostannate complex.



Reagents: (i) PPh_3 (6.0), EtOH, reflux, 30 min.

Scheme 2.2.21



via 

Reagents: (i) PPh_3 (30), $SnCl_2$ (10), EtOH, reflux, 1 h.

Scheme 2.2.22

In this case it is an initially formed rhodium (III) salt $(Ph_3PH)_4[Rh_2Cl_2(SnCl_3)_4]$ that is reduced (scheme 2.2.22).[119] The large excess of phosphine was required to give a clean, crystalline product. Similarly, the formation of trichlorostannate complexes by the insertion of tin (II) chloride into the metal-chlorine bonds of a variety of platinum metal phosphine complexes is also well precedented.[120]

The dissociation of a phosphine is a requirement for catalytic activity in this chemistry. Wilkinson's catalyst dissociates a phosphine ligand only to a small extent in the absence of other ligands ($K = 2.3 \times 10^{-7}$ M at 25°C in benzene solution) (scheme 2.2.23).[121] In a donor solvent such as THF a solvent molecule can replace the phosphine and dissociation is slightly more favoured. When an alkene is introduced, a ligand with a high trans effect, exchange with a phosphine occurs much more readily.

$$Rh(PPh_3)_3Cl \underset{(K = 2.3 \times 10^{-7}\ M)}{\rightleftharpoons} Rh(PPh_3)_2Cl + PPh_3$$

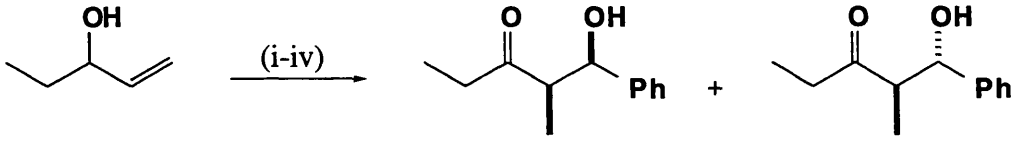
Scheme 2.2.23

$$Rh(PPh_3)_3Cl + C_2H_4 \underset{(K = 0.4)}{\rightleftharpoons} (C_2H_4)Rh(PPh_3)_2Cl + PPh_3$$

Scheme 2.2.24

With ethene, exchange with a phosphine via a five-coordinate intermediate is favourable (K=0.4) (scheme 2.2.24),[121] but more highly substituted alkenes promote the displacement far less effectively. The behaviour of the trichlorostannate complex in hydrogenation chemistry is very similar to that of Wilkinson's catalyst, and more so than the other rhodium halide analogues.[122] However, the trichlorostannate ligand has been shown to exhibit a far stronger trans effect than the chloro ligand,[123] and consequently it was expected that the trichlorostannate complex would more readily dissociate a phosphine ligand and might be a more effective catalyst.

Thus, isomerisation of alcohol **15** in 3 hours gave after kinetic aldol reaction the aldols **16** and **17** in 74% combined yield, slightly lower than when using Wilkinson's catalyst alone, and in an identical ratio **16**:**17**=3.3:1 (scheme 2.2.25).

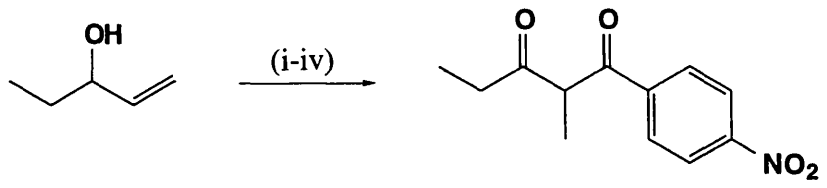


3.3:1

15 **16** (74%) **17**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl/SnCl_2$ (2.0 mol%), THF, then reflux 3 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.25



15 **19** (65%)

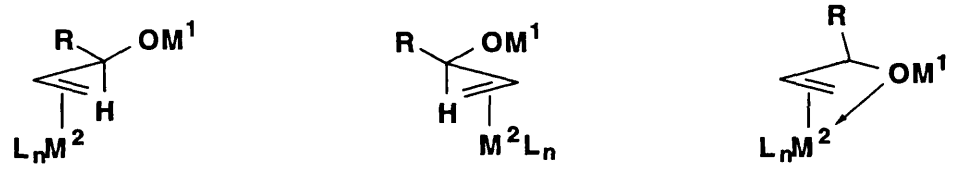
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), $SnCl_2$ (2.1 mol%), THF, then reflux 3.25 h; (iii) 4-NO_2-C_6H_4COCl (10), 2.8M in THF, –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.26

This observed ratio indicates that isomerisation was again (Z)-specific. Isomerisation and reaction with 4-nitrobenzoyl chloride yielded diketone **19** in a similar 65% yield (scheme 2.2.26). Apart from the rate enhancement, results when using the rhodium-tin system are comparable to the standard methodology and suggest that the mechanism is unchanged. This is consistent with simply an increased tendency for the catalyst to dissociate.

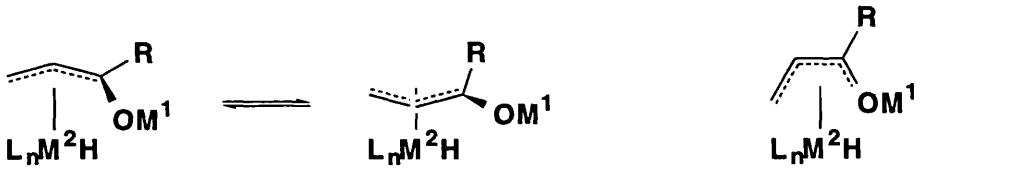
2.2.4 Initial Mechanistic Discussion

The substrates so far investigated have shown a considerable preference for the (Z)-enolate isomer, and it is appropriate to consider how this might arise. If we first make the assumption that the catalytic species is essentially unaltered, ie. non-hydridic, then this requires a π-allyl hydride mechanism to be operating. Making the second assumption that enolate geometry is not altered after the isomerisation has taken place, either oxidative addition of the pro-(Z) complex must be strongly favoured (scheme 2.2.27), or interconversion of η^3-allyl intermediates must strongly favour a 'cisoid' arrangement of the double bond and oxygen (scheme 2.2.28).



a) Pro-(Z) (MAJOR) b) Pro-(E) (MINOR) c) Oxygen coordination

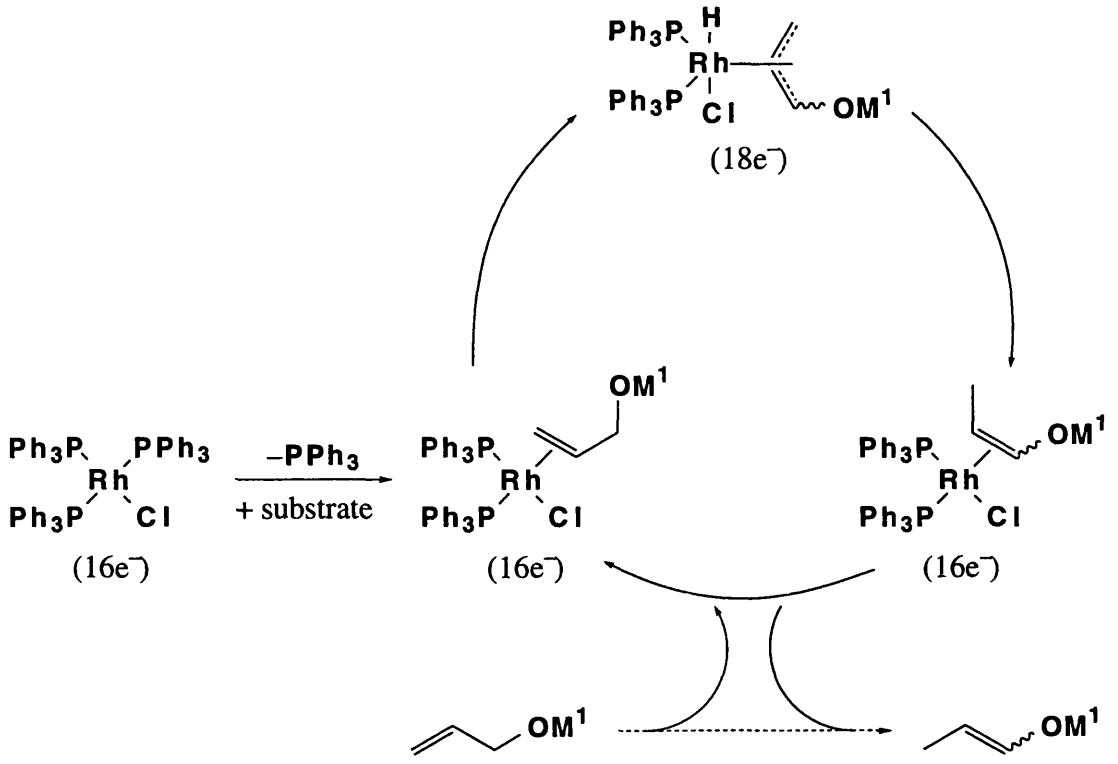
Scheme 2.2.27



a) 'Cisoid' (MAJOR) b) 'Transoid' (MINOR) c) Oxa-butadiene complex

Scheme 2.2.28

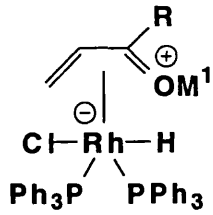
In either case it is tempting to invoke a bonding interaction between the alkoxide oxygen and rhodium. However, coordination of oxygen prior to oxidative addition (scheme 2.2.27.c) requires the successive loss of two phosphine ligands from the catalyst. Wilkinson's catalyst and the complex derived by coordination of the substrate and subsequent loss of one phosphine are both sixteen-electron ($16e^-$) complexes.



Scheme 2.2.29 – Simple Catalytic Cycle

Oxidative addition formally increases the oxidation state of rhodium by two units and introduces two two-electron donor ligands, giving an electronically saturated eighteen-electron π-allyl hydride intermediate (scheme 2.2.29). Prior coordination of oxygen would contribute a further two electrons, requiring dissociation of a second phosphine in order to regain the sixteen-electron state and permit oxidative addition, and this is unlikely.

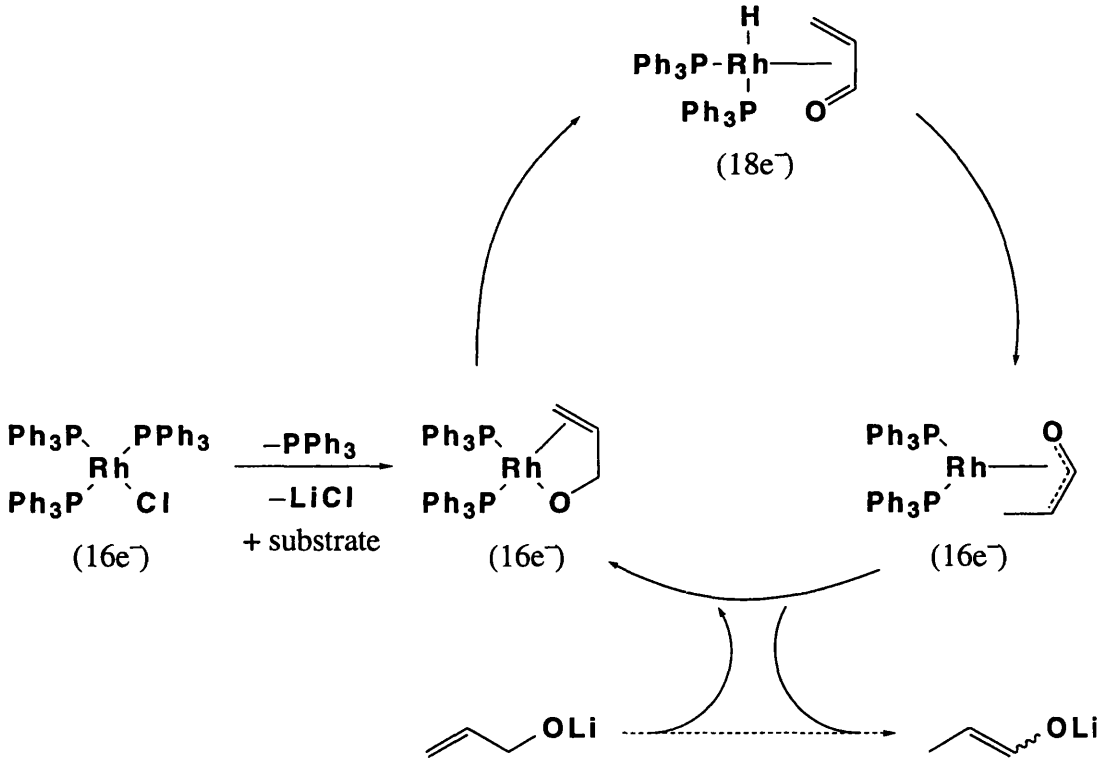
With the alternative theory involving fluxional π-allyl hydride intermediates, involvement of a rhodium-oxygen bonding interaction to give an η^4-1-oxabutadiene type complex (scheme 2.2.28.c) might similarly be used to explain the preference for (Z)-stereochemistry. The higher stability of cisoid butadiene complexes over the more linear transoid equivalents is general, and explained as providing a closer and tighter contact with the metal.[124] However this intermediate suffers a charge separation and again requires the improbable dissociation of a second phosphine ligand to avoid a twenty-electron complex (figure 2.4).



Rh (I), 20e⁻

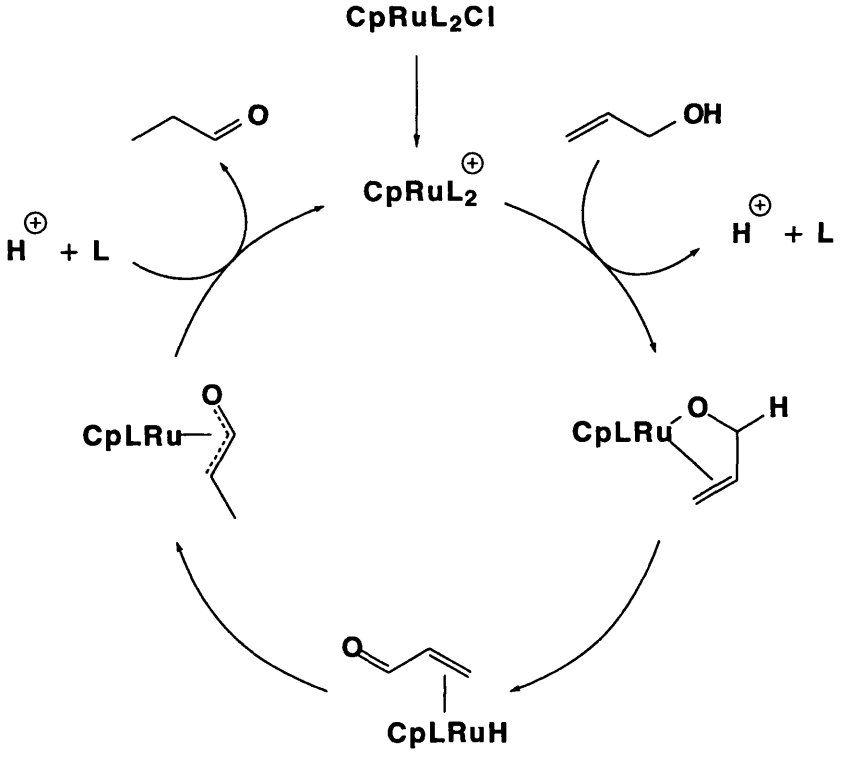
Figure 2.4

Alternatively, there is a different bonding scheme which would allow a rhodium-oxygen interaction. It is possible that the alkoxide can displace chloride anion from the complex, forming a rhodium alkoxide, and one phosphine ligand to give a four-coordinate chelate (scheme 2.2.30). Isomerisation can then occur as normal, and the resulting rhodium enolate transmetallate with a further molecule of lithium alkoxide to give the product lithium enolate and a rhodium alkoxide once more.



Scheme 2.2.30 – Modified Catalytic Cycle

An alkoxide-based mechanism has been proposed previously for the isomerisation of allylic alcohols. Bäckvall demonstrated more than fifty-fold rate enhancements in the presence of potassium carbonate using ruthenium catalysts, including the related $Ru(PPh_3)_3Cl_2$, and concluded that a ruthenium alkoxide was the primary intermediate.[125] The basic conditions were considered to be promoting formation of the alkoxide. The complex $CpRu(PPh_3)_2Cl$, in conjunction with Et_3NHPF_6, was studied by both Trost[126] and Bäckvall[125] and a similar alkoxide-centred mechanism proposed (scheme 2.2.31). In this case the catalyst is readily ionised, and a mild acid was used to promote protonation and dissociation of the organic product. The alcohol dehydrogenation–double bond reduction process was evidenced by the isolation of saturated alcohol and unsaturated ketone by-products. This scheme is very similar in concept to our proposed rhodium alkoxide pathway.

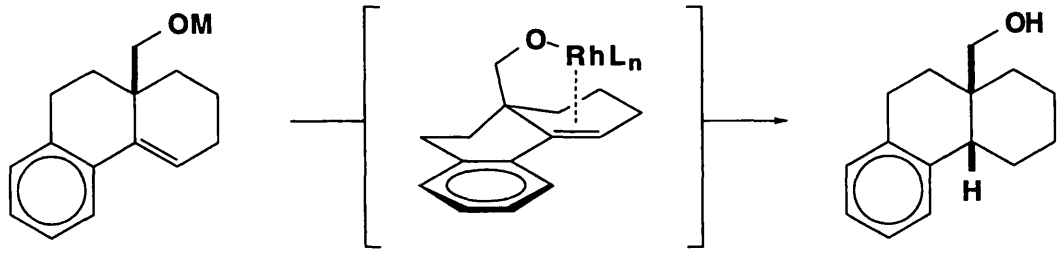


Isomerisation With $CpRu(PPh_3)_2Cl$ / Et_3NHPF_6 (L = PPh_3)

Scheme 2.2.31

The intermediacy of transition metal alkoxides has been postulated in other related chemistry. These ruthenium catalysts are active in transfer hydrogenation and alcohol oxidation (dehydrogenation), and in these reactions the addition of potassium carbonate is also beneficial.[127] Transfer hydrogenations have commonly been achieved using rhodium complexes including Wilkinson's catalyst and an alcohol hydrogen source, and again addition of a weak base increases the rate of reaction.[128]

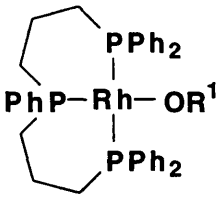
Thompson reported the stereospecific hydrogenation of alkali metal salts of a homoallylic alcohol mediated by Wilkinson's catalyst (scheme 2.2.32).[129] The free alcohol was totally unreactive under the same conditions. The potassium salt gave the best results with conversions of up to 68%, but the lithium salt was also far more reactive, and consequently a rhodium alkoxide intermediate was proposed. Prior coordination of oxygen not only forced the reduction but defined the stereochemistry of the product.



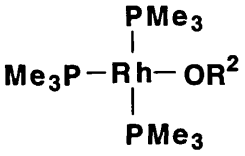
Reagents: (i) $(PPh_3)_3RhCl$ (3.6 mol%), H_2 (7 atm.), benzene, 50°C.

Scheme 2.2.32

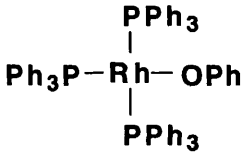
There is clearly precedence for the postulated alkoxide mechanism. Alkoxides of rhodium phosphine complexes have been little studied, but Meek has demonstrated that alkoxides of type A (figure 2.5) react only with acids with $pK_a<4.2$ to give the equivalent carboxylate, and concluded that the rhodium-oxygen bond is comparatively strong and covalent.[130] However alkoxides of type B (figure 2.5) form uncommonly strong hydrogen bonds with free alcohol, and undergo slow alkoxide group exchange.



A



B



C

R^1 = H, Ph, CH_2CF_3; R^2 = 4-(CH_3)-C_6H_4, 4-(CF_3)-C_6H_4, CH_2CF_3, $CH(CF_3)_2$.

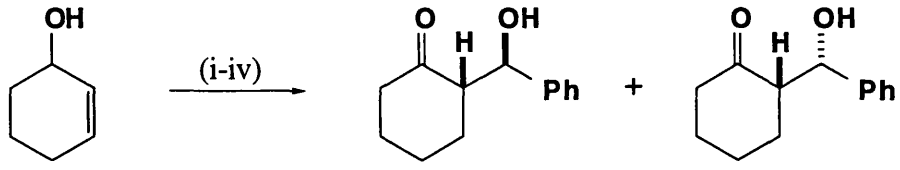
Figure 2.5

These observations led Bergman to declare "the oxygen atom in the rhodium-bound alkoxide [is] a site of unusually high electron density...the rhodium-oxygen bond is strongly polarised, having excess negative charge at oxygen and excess positive charge at the rhodium atom".[131] Keim reported the phenoxide complex C (figure 2.5), which is most closely related to the proposed mechanism.[132] It was observed to very readily lose a triphenylphosphine ligand so as to increase the hapticity of phenoxide.

Formation of an alkoxide would have another benefit. The oligomeric nature of lithium alkoxides in relatively poor donor solvents such as THF renders the -OLi group extremely bulky and far more sterically demanding than a hydroxyl function.[116] Approach of the catalyst to an allylic lithium alkoxide might therefore be impeded, and an extended solvent sphere would accentuate the effect. By invoking a simple, monomeric rhodium alkoxide the steric problems of aggregation expected with lithium alkoxides are removed. Isomerisation is made an intramolecular process and a rationale for the (Z)-stereospecificity provided.

In light of this proposed mechanism an obvious question arises: is the availability of a pro-(Z) conformation a necessity for isomerisation to occur? This was tested with a cyclic substrate locked in the pro-(E) geometry, which would at best form a very poor rhodium alkoxide chelate. It should be noted that the allyl alcohol nucleus of 2-cyclohexenol is of approximately equivalent substitution to the successful substrates **7** and **8**. Treatment of 2-cyclohexenol (**21**) with 2.0 mol% or 5.0 mol% of Wilkinson's catalyst caused very slow conversion to a number of products, and

reaction with benzaldehyde after 48 hours gave a complex mixture. Using 5.0 mol% of catalyst the aldols **22** and **23** were isolated in a very low yield (*ca.* 7%) and in the ratio **22**:**23**=4.2:1 (scheme 2.2.33). This ratio lies within the broad range reported[13,133] and is in any case unimportant as enolate geometry is unambiguous. Since only the (E)-enolate can be formed and isomerisation is, presumably as a result, extremely sluggish, this suggests that access to the pro-(Z) conformer is extremely important.



4.2:1

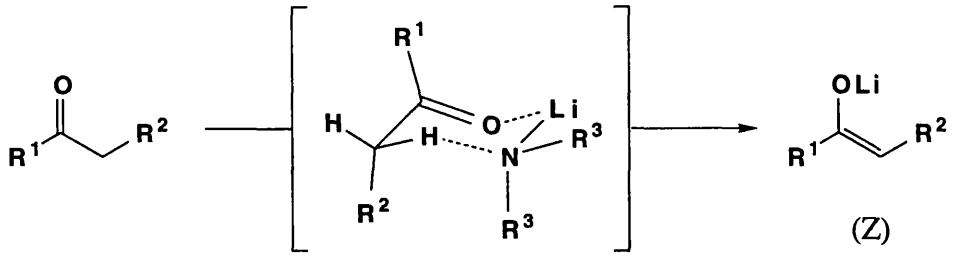
21 **22** (*ca.* 7%) **23**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (5.0 mol%), THF, then reflux 48 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.33

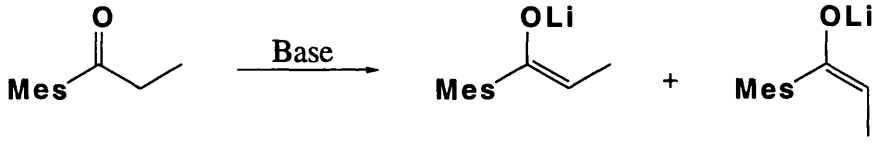
The ruthenium-based methodologies of Bäckvall[125] and Trost[126] (scheme 2.2.31) exhibited a similar retardation in the isomerisation of cyclic substrates, including 2-cyclohexenol (**21**), but still produced good yields. These catalyst systems have been used for dehydrogenation of non-allylic alcohols and so do not require double bond coordination for the carbinolic hydride transfer step. With Wilkinson's catalyst a chelated alkoxide is more important. Isomerisation of 2-cyclohexenol can occur only slowly, either via a rhodium alkoxide (with hydride transfer 'unactivated' by coordination of the allylic double bond) or via the alternative, classical 'π-allyl hydride' route (scheme 2.2.29). In the latter case alkoxide formation would serve only to divert the catalyst from the intended task.

With the benzylic alcohols so far discussed the (Z)-enolate can be obtained with high selectivity by lithium dialkylamide deprotonation of the corresponding carbonyl compound.[13,102]



Scheme 2.2.34

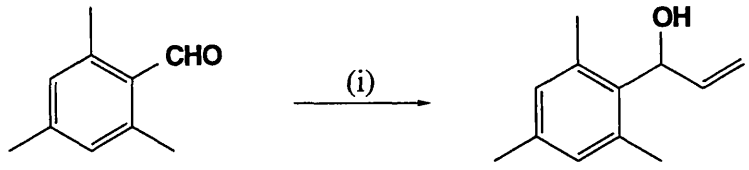
In the Ireland transition state model this observation is explained as the group R^2 preferring a pseudo-axial position to avoid a *syn*-coplanar steric interaction with the group R^1 (scheme 2.2.34).[10] Heathcock has shown that kinetic deprotonation of 1-(2,4,6-trimethylphenyl)-1-propanone (**24**) is anomalous, giving varying results depending upon the base used but generally favouring the (E)-enolate (table 2.1).[13] It is suggested that with the seemingly large mesityl group the aromatic plane is twisted perpendicular to the carbonyl, presenting a sterically undemanding face towards the group R^2. It was therefore interesting to see if the usual (Z)-specificity would be maintained in generating these enolates by the isomerisation route.



24 (Z) (E)

Entry	Base	(Z : E)
1)	LDA	5 : 95
2)	LCPA	4 : 96
3)	LHMDS	87 : 13

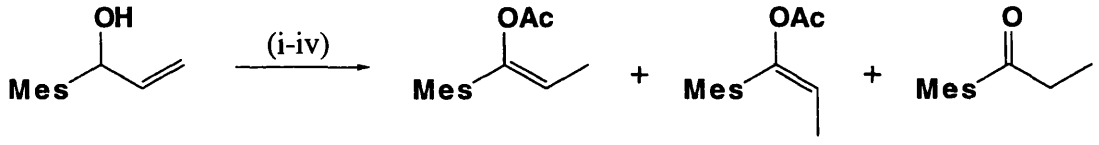
Table 2.1



25 (88%)

Reagents: (i) Vinylmagnesium bromide, THF, 0°C.

Scheme 2.2.35



1:1.69

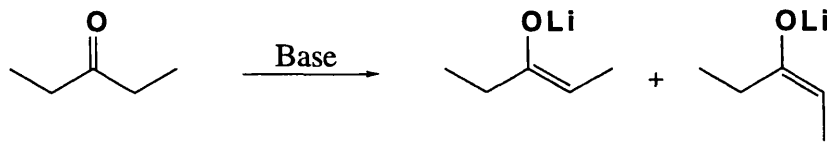
25 **26** (52%) **27** **24** (12%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 5.5 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.36

The required substrate was prepared by reaction of vinylmagnesium bromide with 2,4,6-trimethylbenzaldehyde, providing crystalline alcohol **25** in 88% yield (scheme 2.2.35). Isomerisation under standard conditions took 5.5 hours, notably longer than the 1.5 hours for 1-phenyl-2-propen-1-ol (**1**). Acetylation gave an inseparable mixture of (Z)-enol acetate **26** and (E)-enol acetate **27**, in 52% combined yield and in the ratio **26**:**27**=1:1.69, with the parent ketone **24** in 12% yield (scheme 2.2.36). The enol acetate stereochemistry was assigned by analogy with the corresponding trimethylsilyl enol ethers.[13]

For the first time a mixture of enolate stereoisomers was observed, and with the (E)-isomer predominating. Clearly this is incompatible with the requirement of 'cisoid' oxygen to rhodium bonding in the stereo-defining step, so either the proposed mechanism is not operating or the ratio is the result of product equilibration. The (Z)-isomer of lithium enolates is the more thermodynamically stable,[6,7,40] as with other enol derivatives,[134] and evidence suggests this to be true of the enolates prepared here.



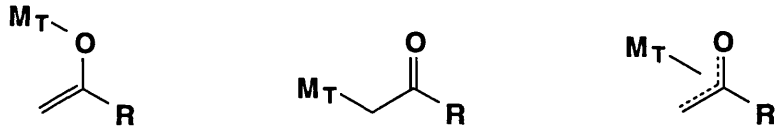
(Z) (E)

Entry	Base	(Z : E)
1)	LDA	30 : 70
2)	LHMDS	66 : 34

Table 2.2

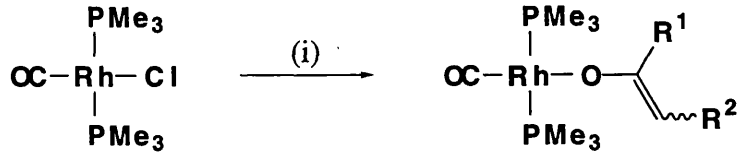
Deprotonation of the ketone **24** with lithium hexamethyldisilazide is (Z)-selective (table 2.1). This reaction reportedly proceeds through a product-like or 'late' transition state; ratios are largely determined by the relative thermodynamic stabilities of the developing products.[13] Similarly, deprotonation of 3-pentanone with LHMDS gives a ratio of enolates close to the thermodynamic mixture (Z:E=84:16)[11] (table 2.2), so equilibration of the lithium enolates would seem to be inconsistent with the observed result.

A further consequence of the proposed alkoxide mechanism is that prior to transmetallation with another molecule of substrate to give the lithium enolate product, a rhodium enolate is formed. Transition metal enolates can exist in three forms: an η^1-oxygen bound isomer (A, figure 2.6), an η^1-carbon bound isomer (B), or an η^3-1-oxaallyl complex (C).

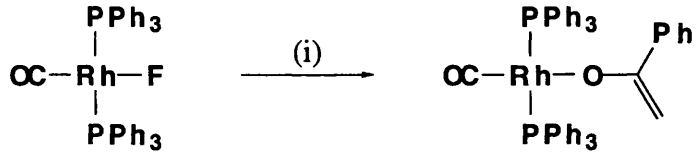


A (η^1-O) B (η^1-C) C (η^3)

Figure 2.6



[R^1 = Ph; R^2 = H]
[R^1 = Ph, Mes, ^{t}Bu; R^2 = Me]

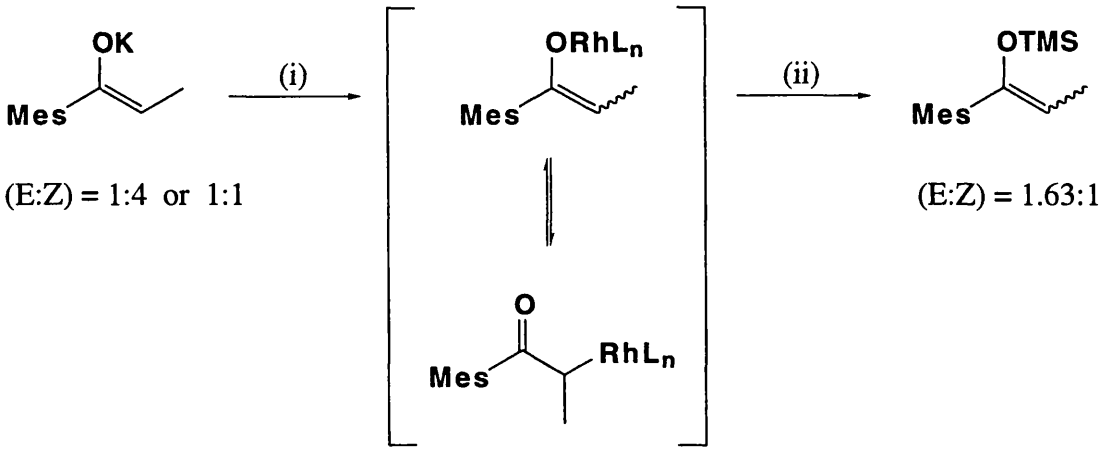


Reagents: (i) K^+(enolate)$^-$, THF or Et_2O, –40°C.

Scheme 2.2.37

All three forms have been attributed to rhodium (I) phosphine enolates. Heathcock has prepared type-A carbonylbis(trialkylphosphine)rhodium (I) enolates by transmetallation of rhodium halides with potassium enolates in nearly quantitative yield (scheme 2.2.37).[135] The most closely related enolate prepared, the carbonylbis-(triphenylphosphine)rhodium (I) enolate of acetophenone, exhibited a coalescence of the methylene proton signals in the ^{1}H NMR spectrum, and this was explained as a rapid interconversion between the two positions. Although these enolates undoubtedly exist primarily in the η^1-O form a dynamic equilibrium with a small quantity of the η^1-C-bound form (B) was proposed, with an activation free energy barrier for the process calculated as $\Delta G^{\ddagger} \approx 10$ kcal.mol^{-1} (scheme 2.2.38).

Scheme 2.2.38

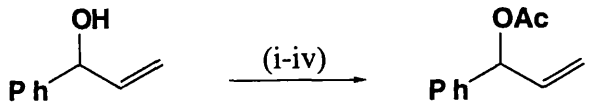


Reagents: (i) $(CO)(PMe_3)_2RhCl$, Et_2O, –40°C; (ii) TMSCl, toluene-d_8, r.t. [L_nRh = $(CO)(PMe_3)_2Rh$]

Scheme 2.2.39

The consequences of this equilibrium were well illustrated by the preparation of the rhodium enolate of 1-(2',4',6'-trimethylphenyl)-1-propanone (**24**) (scheme 2.2.39). When a mixture of potassium enolates of largely the (Z)-stereoisomer (E:Z=1:4) was treated with carbonylchlorobis(trimethylphosphine)rhodium (I) the resulting rhodium enolates were isolated in a different ratio, instead favouring the (E)-isomer (E:Z=1.63:1). An identical ratio was obtained using an equal mixture of potassium enolate stereoisomers (E:Z=1:1). Equilibrium formation of an η^1-C-enolate (B) results in loss of all stereochemical information by random bond rotation, and the generation of a thermodynamically controlled mixture of enolate isomers. It would seem that with rhodium enolates this mixture is controlled by factors which are different from their lithium counterparts. It is interesting that the ratio recorded by Heathcock (E:Z=1.63:1) is very similar to that recorded in this work for the same enolates (E:Z=1.69:1).

An attempt to isomerise the test substrate 1-phenyl-2-propen-1-ol (**1**) with carbonylchlorobis(triphenylphosphine)rhodium (I)[136] under otherwise standard conditions was unsuccessful. Reflux for 9 hours and treatment with acetyl chloride gave a complex mixture from which only starting material (**1**) (16%) and acetylated starting material (**28**) (32%) could be isolated (scheme 2.2.40).



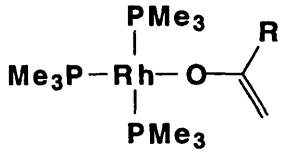
1 28

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(CO)(PPh_3)_2RhCl$ (2.0 mol%), THF, then reflux 9 h; (iii) AcCl (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.40

No trace of isomerised materials could be detected. The lesser tendency of these rhodium enolate complexes to dissociate a phosphine ligand, and instead to increase the coordination number, may be responsible for this inactivity.

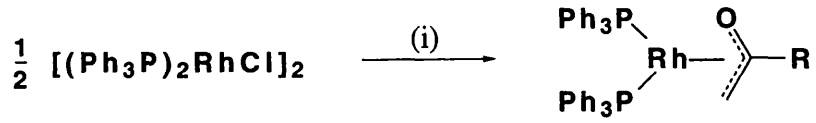
Rhodium enolates more directly related to the proposed alkoxide mechanism have also been prepared. Tulip has reported the tris(trimethylphosphine)rhodium (I) enolates of several methyl ketones to be exclusively of the η^1-O-type (A) below –30°C (figure 2.7), but to sample both forms B and C at higher temperatures.[137] It is unclear whether phosphine displacement had occurred in the η^3-form (C), but probable.



R = Me, ^{t}Bu, Ph.

Figure 2.7

Slough has prepared enolates of the exact type thought to be generated from Wilkinson's catalyst. Cleavage of chlorobis(triphenylphosphine)rhodium (I) dimer with potassium enolates produces the bis(triphenylphosphine)rhodium (I) enolates as pseudo-square-planar η^3-1-oxaallyl complexes (scheme 2.2.41).[138] These complexes were shown to undergo rapid addition of ligands (carbonyl or isonitrile) to give variously η^1-O (type A) and η^1-C (type B) rhodium enolates.

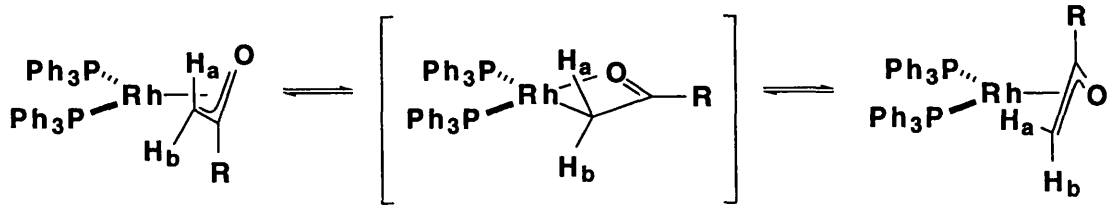


[R = Ph, ^{t}Bu]

Reagents: (i) K^+(enolate)$^-$, THF, r.t.

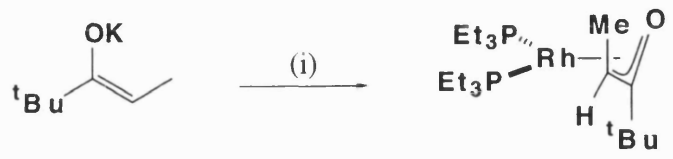
Scheme 2.2.41

As with the η^1-O-bound enolates studied by Heathcock,[135] spectroscopic studies indicated that a rapid equilibration of the methylene hydrogens was occurring. For the rhodium enolates of acetophenone (R=Ph) and 3,3-dimethyl-2-butanone (R=^{t}Bu) activation free energy barriers were calculated as $\Delta G^{\ddagger}$ = 13.9 and 14.4 kcal.mol^{-1} respectively; these are of the same order as the η^1-O-enolates. From ^{1}H, ^{31}P and ^{13}C NMR studies it was concluded that an intermediate interceded in the equilibration which maintained the square-planar geometry of the complex, and a four-membered metallacycle was proposed (scheme 2.2.42).



Scheme 2.2.42

Spectroscopic data indicated that the analogous triethylphosphine complexes did not exhibit similar fluxional behaviour at ambient temperature. This was further evidenced by preparation of the stereochemically pure rhodium (Z)-η^3-enolate of 2,2-dimethyl-3-pentanone from the pure potassium (Z)-enolate (scheme 2.2.43), although no alternative mixture of potassium enolates was studied to prove that the pure (Z)-stereochemistry of the product was not simply the favoured equilibrium position.



(Z) (Z)

Reagents: (i) $[(cod)RhCl]_2/4PEt_3$ (0.5), THF, r.t., 40 min.

Scheme 2.2.43

The η^3-1-oxaallyl complexes exhibit the bonding patterns typical of the isoelectronic η^3-allyl complexes.[124a] The lowest energy molecular orbital of the simple allyl fragment (Ψ_1) involves a roughly equal bonding interaction with all three carbons (figure 2.8). However the frontier orbital is the Ψ_2 molecular orbital, in which electron density is concentrated at the terminal carbons C1 and C3, with a nodal plane at C2. In order to maximise overlap with the appropriate metal orbital a tilting occurs, with the allyl plane canted at an angle θ from perpendicular to the metal-ligand axis (figure 2.9.a). This moves the allyl termini closer to the metal centre than would be expected were the metal-ligand axis at an idealised 90° to the allyl plane. For bis(phosphine)rhodium (I) η^3-allyl complexes θ is often larger than the usual 5-10° (eg. bis(dicyclohexylphosphine)rhodium (I) η^3-methallyl: θ = 17.6°).[139]

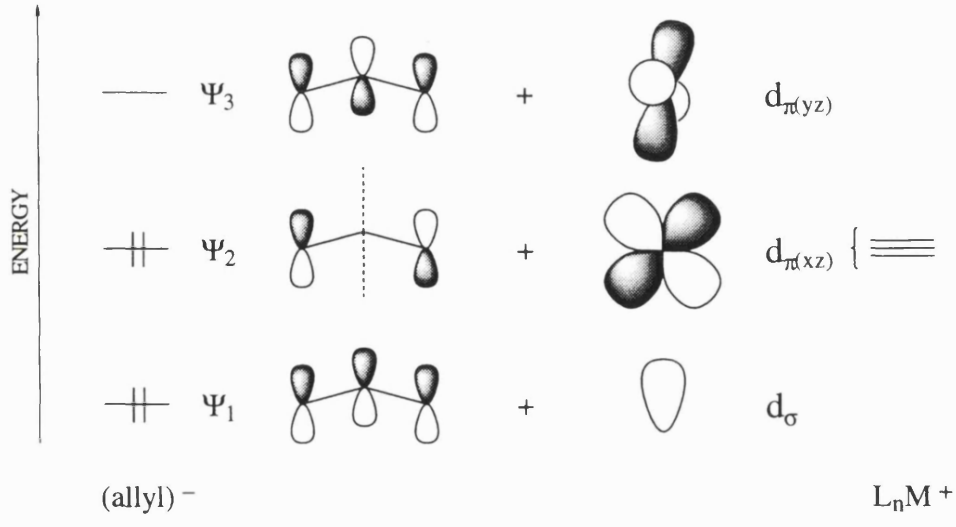
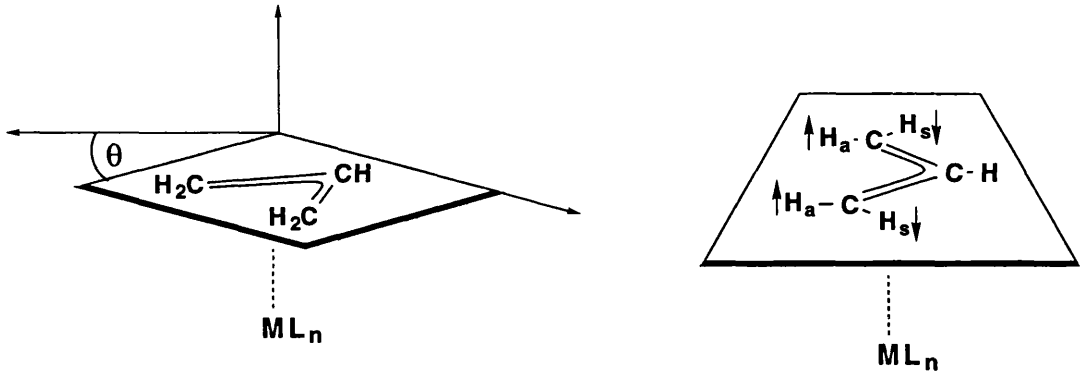


Figure 2.8



(a) (b)

Figure 2.9

This distortion is accompanied by twisting of the terminal carbon trigonal planes relative to the allyl framework in a sense roughly opposite to the tilting of the ligand plane (figure 2.9.b). This acts to bend the terminal substituents *anti-* to the central carbon-hydrogen bond (H_a) away from the metal, and the *syn*-substituents (H_s) towards the metal. Both these distortions could be predicted by description of the η^3-allyl ligand in terms of a resonance hybrid (figure 2.10).

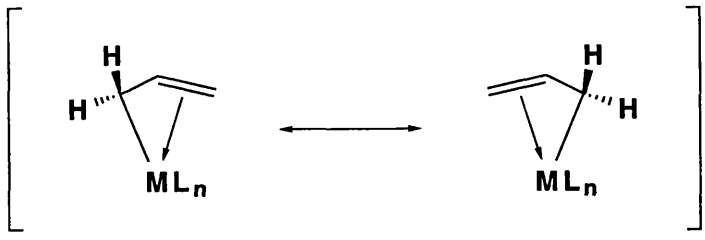
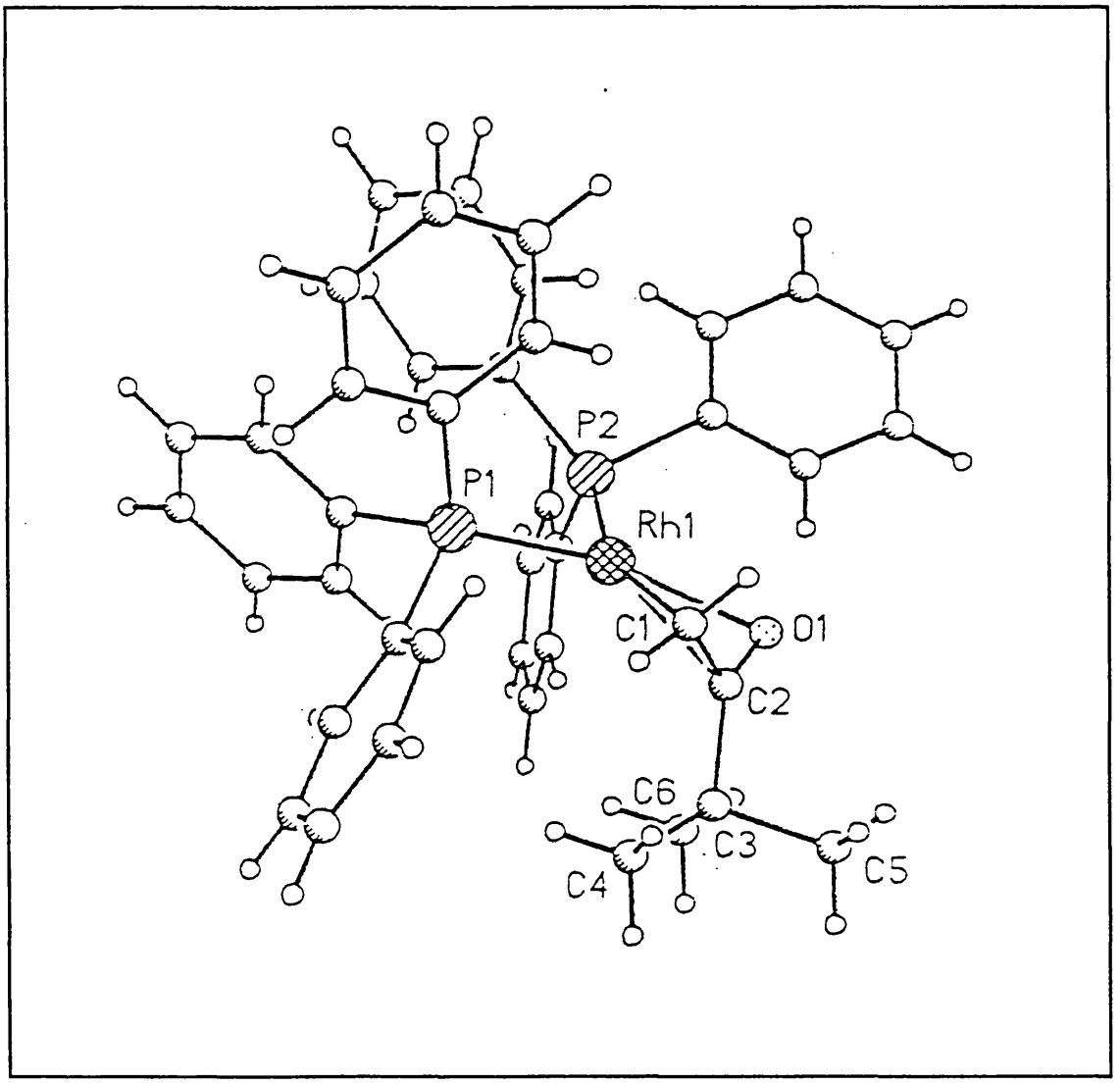
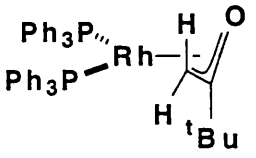


Figure 2.10

Slough and co-workers have obtained X-ray crystallographic data for the bis(triphenylphosphine)rhodium (I) η^3-enolate of 3,3-dimethyl-2-butanone (figure 2.11).[138] The structure displays pseudo-square-planar geometry. The rhodium, the two phosphorous and the enolate oxygen atoms are coplanar, with the enolate double bond occupying the fourth position; the two carbon atoms of the enolate allyl group are displaced equally above and below this plane.





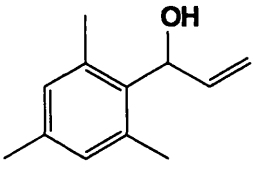
X-Ray Crystal Structure Of

(η^3-3,3-Dimethyl-2-oxo-1-butenyl)bis(triphenylphosphine)rhodium (I)

Figure 2.11[138]

As expected the complex exhibits allyl-type distortion as described above, with a very large tilting angle θ = 28.9°. From close study of the X-ray structure it appears that the C1-substituent *anti-* to oxygen is placed closer to the phosphine, and suffers increased steric repulsion in the ligand plane (figure 2.11). In contrast, the *syn*-substituent at C1, which is already less sterically congested for being out of the ligand plane, is moved away from the metal centre into essentially free space. A rhodium enolate bearing a single C1-substituent would thus be expected to strongly favour (Z)-geometry.

The continued importance of relieving a steric interaction with the C2-substituent is suggested by the poorly (E)-selective isomerisation of 1-(2,4,6-trimethylphenyl)-2-propen-1-ol (**25**). As noted previously, coplanarity of the mesityl group with the enolate π-system is precluded by the steric requirements of the *ortho*-methyl groups, and the *syn*-substituent is presented a sterically undemanding face of the aryl ring. However isomerisation of 1-penten-3-ol (**15**), also with a small C2-substituent (Et), is still (Z)-specific. It is possible that the extremely demanding edge-on interaction between the mesityl group and the phosphine ligands is further tilting the allyl plane, and redressing the skew of the allylic termini. The η^3-enolate becomes more like the metallacyclic fluxional intermediate (figure 2.12), in which the C1-substituents are symmetrical about the ligand plane.



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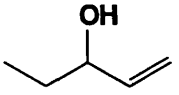

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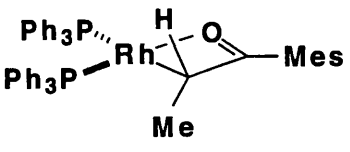
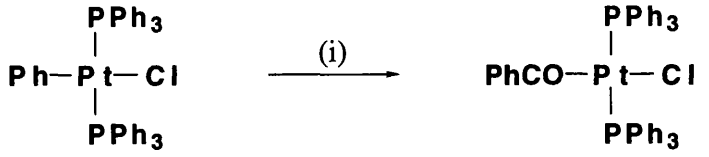


Figure 2.12

Thus by invoking an η^3-rhodium enolate the usually (Z)-specific nature of the isomerisation can be explained, and the proposed alkoxide mechanism leads directly to such an intermediate. The fluxional behaviour of rhodium enolates is well precedented, and equilibration results in accumulation of the generally less sterically crowded (Z)-enolate isomer.

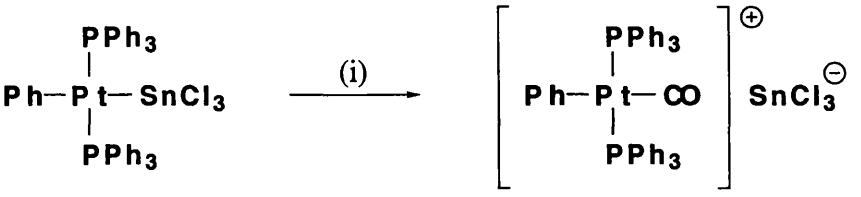
A final consideration is the rate enhancing effect of catalytic quantities of tin (II) chloride, and the proposition that trichlorostannate-rhodium species are produced. Similar experimental results to those obtained with Wilkinson's catalyst alone suggest that no fundamental change in mechanism occurs. A variety of unusual properties have been invoked to explain the curious effects in trichlorostannate complexes, including a high trans effect and trans influence,[123] an ability to stabilise five coordinate species relative to the four coordinate square-planar complexes,[120c,140] and a low tendency to form bridged species.[120c] The expectation that greater trans effect of the trichlorostannato ligand would increase the lability of the phosphines was the impetus for these experiments with tin (II) chloride. With a classical π-allyl hydride mechanism any of these properties could conceivably aid the isomerisation and represent a reasonable explanation for the rate enhancements, but the trichlorostannato ligand must be present in the catalytic species. With an alkoxide route however, the trichlorostannato ligand must be lost in forming the catalytic intermediates and can have no further influence in the catalytic cycle.

Clark has reported mechanistic studies[141] of the promotion of carbonylation reactions of phenylplatinum (II) complexes in the presence of tin (II) chloride.[142] When the chloro complex chlorophenylbis(triphenylphosphine) platinum (II) was treated with carbon monoxide in chloroform at ambient temperature, only a 15% conversion to the corresponding benzoyl complex was achieved after one hour (scheme 2.2.44). The equivalent trichlorostannate complex phenyl(trichlorostannato)bis-(triphenylphosphine)platinum (II) was completely transformed under the same conditions in just one minute to give instead the ionic compound carbonylphenylbis-(triphenylphosphine) platinum (II) trichlorostannate (scheme 2.2.45).



Reagents: (i) $CO_{(g)}$ (1 atm.), $CHCl_3$, r.t., 1 h, 15%.

Scheme 2.2.44



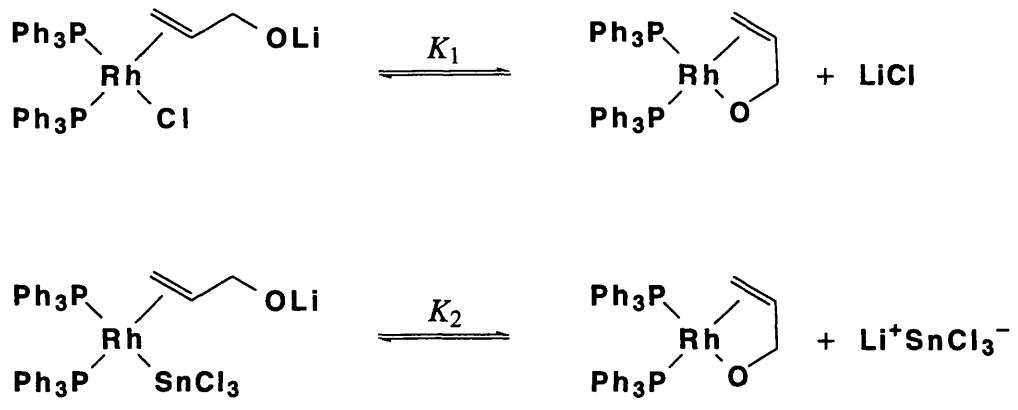
Reagents: (i) $CO_{(g)}$ (1 atm.), $CHCl_3$, r.t., 1 min, 100%.

Scheme 2.2.45

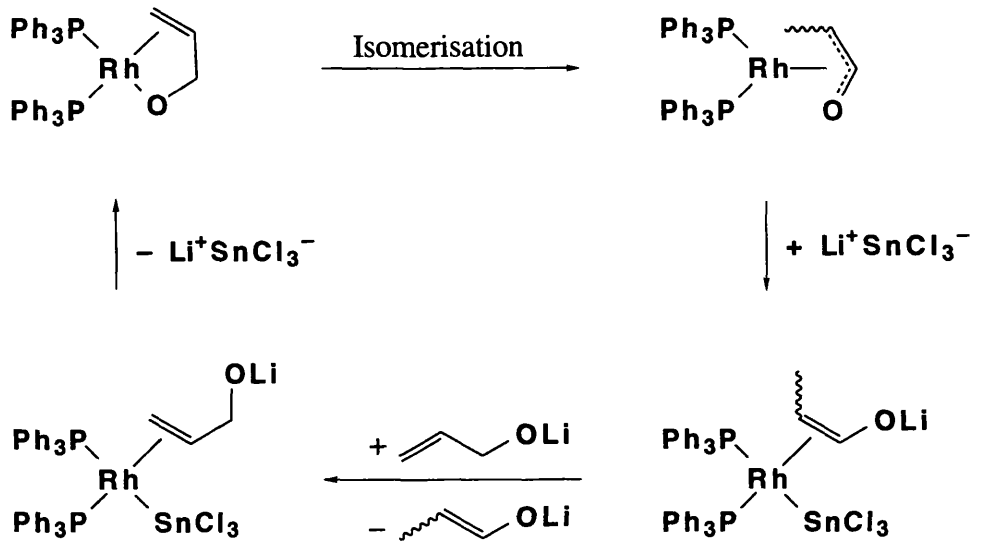
With continued exposure to carbon monoxide his latter compound is transformed into the equivalent benzoyl-trichlorostannate complex with 50% conversion after one hour.

In both cases the reaction follows an associative mechanism, but while the square-planar geometry is regained by aryl migration in the chloro complex, the trichlorostannate complex readily dissociates the $SnCl_3^-$ ligand. The ionic product is not ion-paired to any significant degree even in chloroform solution. Furthermore, it was shown that no equilibrium exists between this ionic complex and a neutral platinum trichlorostannate. It was also shown that the $SnCl_3^-$ anion remained intact in solution rather than dissociating into chloride anion and $SnCl_2$.

Thus, tin (II) chloride is promoting the reaction not as a ligand, but as a halide acceptor. Insertion into the metal-chlorine bond generates a labile ligand, the displacement of which is promoted by stabilisation of chloride as a complex ion. A carbonyl ligand can then coordinate, and subsequent migration is promoted by reattachment of trichlorostannate to stabilise the otherwise three-coordinate complex.



Scheme 2.2.46

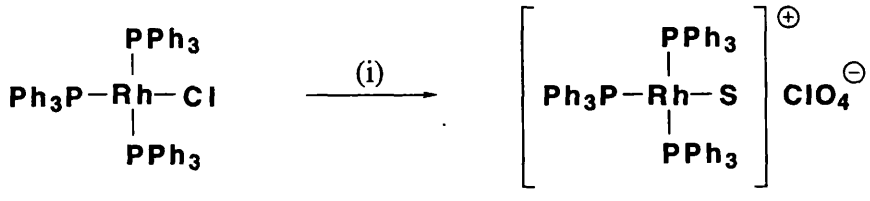


Scheme 2.2.47

Clearly an equivalent effect in this isomerisation chemistry could be beneficial in the formation of the proposed rhodium alkoxide intermediates. An increased tendency of the anionic ligand to act as a leaving group could drive an equilibrium between Wilkinson's catalyst and the rhodium alkoxide ($K_2 > K_1$) (scheme 2.2.46). If isomerisation is rapid in comparison to alkoxide formation, then a similar argument applies to the relative reaction rates. Isomerisation can then proceed to give the rhodium enolate, and subsequent transmetallation with a molecule of lithium alkoxide

completes the catalytic cycle. Again, coordination of the trichlorostannate ligand may be involved in promoting transmetallation (scheme 2.2.47). True ionisation of Wilkinson's catalyst can be achieved using thallium perchlorate as a halide acceptor, giving tris(triphenylphosphine)rhodium (I) cation (scheme 2.2.48),[143] but addition of tin (II) chloride to Wilkinson's catalyst produces the covalent trichlorostannate analogue and alkoxide formation may be assumed to be associative.

Thus, the tin (II) chloride experiments are consistent with the proposed alkoxide mechanism. It is suggested that the tendency of the trichlorostannate intermediates to readily dissociate and recombine are responsible for the observed rate enhancements. In order not to broaden these studies, and because of the slightly lower yields, few further experiments were conducted with this rhodium-tin system.

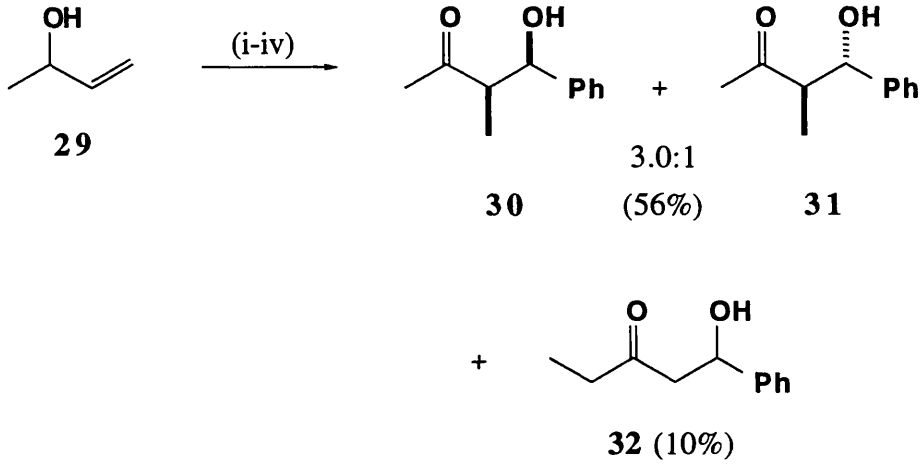


Reagents: (i) $Tl(ClO_4)_3$, acetone or DCM, r.t. [S = solvent]

Scheme 2.2.48

2.2.5 Equilibration Of Enolate Regioisomers

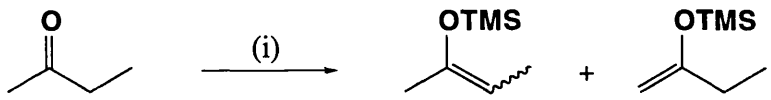
The most fundamental requirement in any preparation of enolates is that it is regioselective. However, in the isomerisation of 1-buten-3-ol (**29**), producing enolates corresponding to the unsymmetrical ketone 2-butanone, a disastrous problem was highlighted. Isomerisation of **29** with 2 mol% Wilkinson's catalyst under standard conditions was complete in 3 hours. This was slower than 1-phenyl-2-propen-1-ol (**1**) but much faster than the more comparable substrate 1-penten-3-ol (**16**). Subsequent kinetic aldol reaction with benzaldehyde gave three aldol products (scheme 2.2.49).



Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 3 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.49

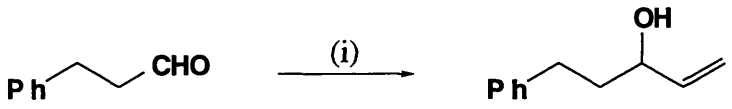
The expected aldol diastereomers **30** and **31** were isolated in 56% combined yield and in the ratio **30**:**31**=3.0:1, a *syn*-selective aldol reaction again indicating (Z)-selective isomerisation. However the regioisomeric aldol **32** was also isolated in 10% yield. Clearly the first-formed enolate is being partially converted into the alternative regioisomer. More seriously, although the observed ratio of 5.6:1 favours the desired product, this is comparable to the ratio of thermodynamic enolisation of 2-butanone[46b] and suggests that the enolate regioisomers are in equilibrium (scheme 2.2.50).



7.3:1

Reagents: (i) TMSCl, NEt_3, DMF.

Scheme 2.2.50



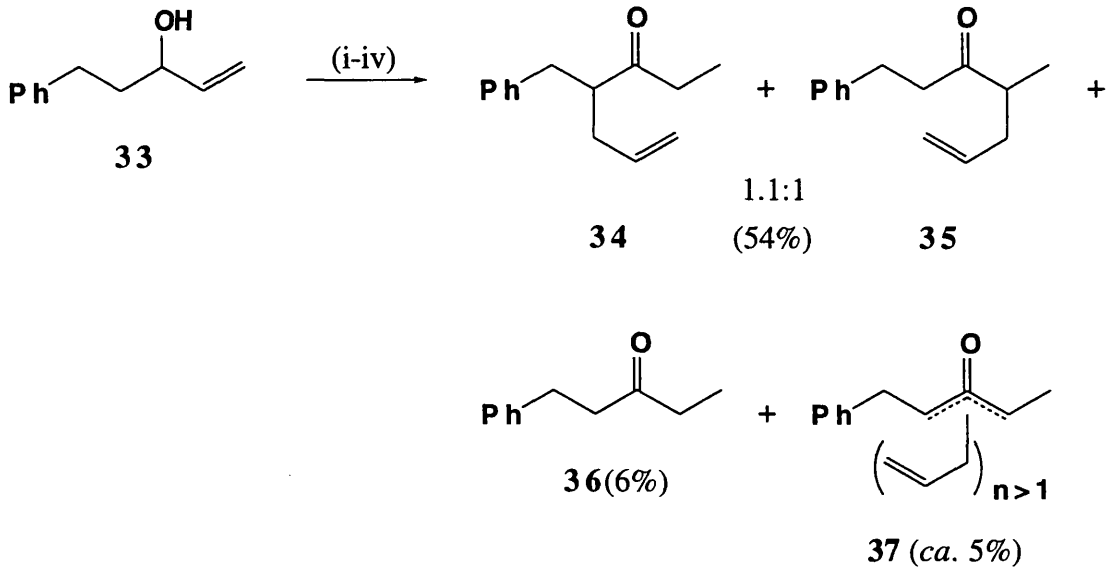
33 (67%)

Reagents: (i) Vinylmagnesium bromide, THF, 0°C.

Scheme 2.2.51

To further study this phenomenon a less biased substrate was required which would also be more easily handled. Reaction of vinylmagnesium bromide with 3-phenylpropanal at 0°C in THF yielded alcohol **33** in 67% yield (scheme 2.2.51). As the primary objective at this stage was the study of regiochemistry, reaction mixtures were quenched with the reactive alkylating agent allyl bromide to avoid the complication of generating diastereomers.

Isomerisation proceeded to completion in 3 hours, and ten molar equivalents of allyl bromide were added instantly at 0°C. Work-up and chromatography yielded a mixture of monoalkylated ketones in 54% yield and in the ratio **34**:**35**=1.1:1 (scheme 2.2.52). The free ketone **36** (6%) and an intractable mixture of polyalkylated ketones **37** (*ca.* 5%) were also isolated, with no trace of starting material. The yield of polyalkylated products can only be estimated from the relative proportions of dialkylated and trialkylated components but compares well with the yield of free ketone. These products undoubtedly arise from competing proton exchange during the alkylation step, and are minimised by the use of a large excess of allyl bromide. The rate of this proton exchange is too low to explain the total loss of regioselectivity.[89]

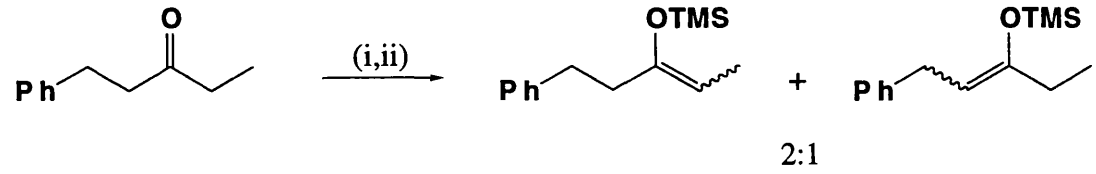


Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 3 h; (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.52

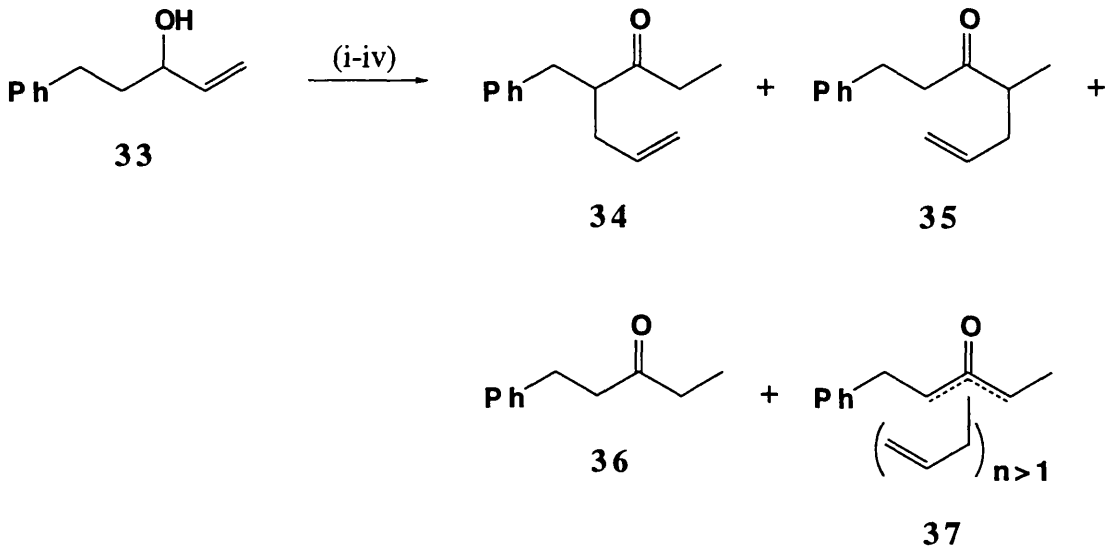
With this substrate the equilibration is even more obvious, as there is actually slightly more of the unwanted regioisomer **34**. A roughly equal thermodynamic mixture is expected as both enolates have a similar pattern of substitution and even kinetic deprotonation shows poor selectivity (scheme 2.2.53).[144]

It is possible that the first formed enolate is converted to the equilibrium mixture only slowly by prolonged exposure to the reaction mixture. To discover if the enolate ratio varies with time the isomerisation was repeated with several different reaction times (table 2.3). It is clear that the ratio remains constant throughout the reaction and equilibration is occurring at a similar rate to isomerisation.



Reagents: (i) LDA, THF, –78°C; (ii) TMSCl.

Scheme 2.2.53



Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux (time); (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

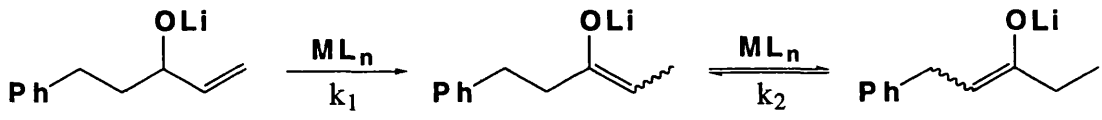
Entry	Time (hours)	Isolated Yields (%) 34+35	(34:35)	36	37	Total
1)	0.5	18	(1.1:1)	11	2	31
2)	1.5	50	(1.3:1)	14	3	67
3)	3	54	(1.1:1)	6	5	65
4)	6	33	(1.4:1)	12	4	49

Table 2.3 – Time Dependence Of Isomerisation

Examination of the table reveals several other interesting points about the reaction. One third of the isolated product is already produced by one sixth of the complete reaction time (table 2.3, entry 1), but this slowing of enolate production is expected due to the lowering of substrate availability as it is consumed, and increased competition of other reaction products as ligands. The drop in isolated product after extended reflux also indicates some decomposition under the reaction conditions (table 2.3, entry 4). In all cases unidentifiable material, presumably of a polymeric nature,

was recovered. Finally, the large quantities of ketone **36** isolated cannot be reconciled with the quantities of polyalkylated material, which suggests that ketone may already be present in the reaction mixture before the alkylation step.

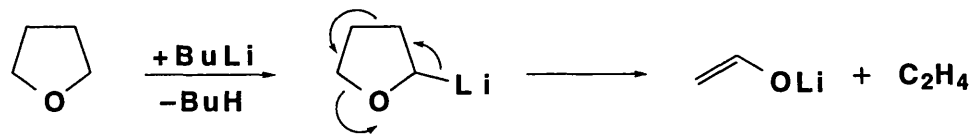
Equilibration can occur by two pathways: a second rhodium-catalysed isomerisation, or proton exchange. A rhodium-promoted second isomerisation would not benefit from the carbinolic activation of the first, and consequently should be much slower (scheme 2.2.54). In order for equilibration to 'keep-up' with the first isomerisation k_2 would need to be comparable to k_1, and this is likely only if a metal hydride addition-elimination mechanism is operating, requiring an hydridic catalytic species.



Scheme 2.2.54

The alternative proton exchange mechanism requires only a very small quantity of some proton source. The simplest explanation would be incomplete deprotonation of the substrate, but great care was taken at all times to use the minimum excess of butyllithium. This accuracy was indicated by the trace formation of coloured dianions from the benzylic alcohol substrates.

In order to be certain of complete deprotonation, the isomerisation was repeated using a 10% excess of butyllithium. Following the standard deprotonation procedure 1.1 molar equivalents of butyllithium were added dropwise to the substrate solution at 0°C and the resulting mixture stirred for approximately 15 minutes. Much of the excess butyllithium is slowly destroyed by the known reaction with THF leading eventually to ethylene and the lithium enolate of acetaldehyde (scheme 2.2.55).[57] As before, isomerisation was complete in 3 hours to give after alkylation the monoalkylated products **34** and **35** in 58% yield and in the similar ratio **34**:**35**=1.3:1.

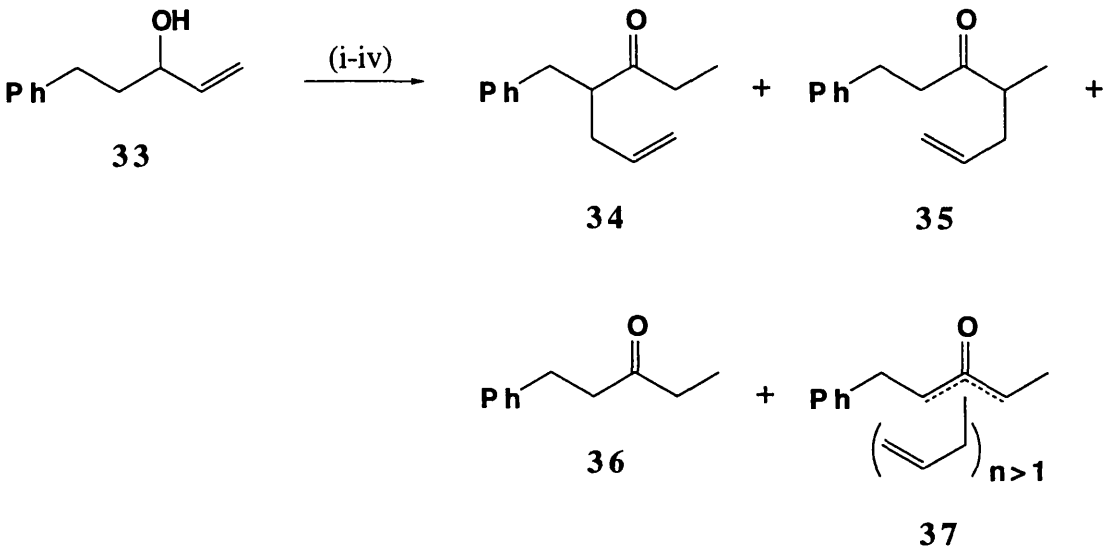


Scheme 2.2.55

A surprisingly large quantity of the parent ketone **36** was again recovered (14%), with the mixture of polyalkylated ketones **37** (*ca.* 5%). These results are summarised later (table 2.4, entry 1).

It is therefore highly unlikely that incomplete deprotonation is causing regiochemical equilibration. However protic materials may be generated during the reaction. It was considered that the presence of an excess of a strong, irreversible base in the reaction mixture during the isomerisation would remove any proton source as it was formed, and to this end an isomerisation was conducted using a 50% excess of butyllithium in the initial deprotonation. With this far larger excess a significant quantity was expected to remain during the reaction. This approach proved successful, as isomerisation produced the desired monoalkylated products in low yield (39%) but in the ratio **34**:**35**=1:9.7. Equivalent yields of ketone **36** and polyalkylated material **37** (6%) were, however, accompanied by recovery of a considerable quantity of starting material (44%) (table 2.4, entry 2). Although incomplete, this isomerisation had stopped after approximately six hours.

The regiochemical equilibration is therefore suppressed considerably, but at the expense of the catalyst rapidly becoming totally inactive. It would not be surprising if Wilkinson's catalyst reacts with butyllithium as reactive organometallic reagents are commonly used for the reduction of transition metal complexes. That some reaction occurs is apparent from the colour change when the alkoxide solution with the excess butyllithium is added to the solution of catalyst. Instead of the usual orange colour becoming gradually paler, an instant change to a deep claret-red was observed. Furthermore, once the reaction mixture had darkened and isomerisation had halted, work-up revealed the deposition of metallic rhodium.



Reagents: (i) ^{n}BuLi (equiv), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (mol%), THF, then reflux or r.t. (time); (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Entry	Catalyst (mol%)	BuLi (equiv)	Time (hours)	Isolated Yields (%) 33	34+35 (34:35)		36	37	Total
1)	2.0	1.1	3	-	58	(1.3:1)	14	5	77
2)	2.0	1.5	8.5	44	39	(1:9.7)	6	6	51
3)	2.0	1.5	4.5 (r.t.)	85	9	(1:10)	1	1	11
4)	5.0	1.5	1	8	18	(1:10)	15	14	47
5)	5.0	1.1	1.2	-	74	(1.3:1)	11	2	87

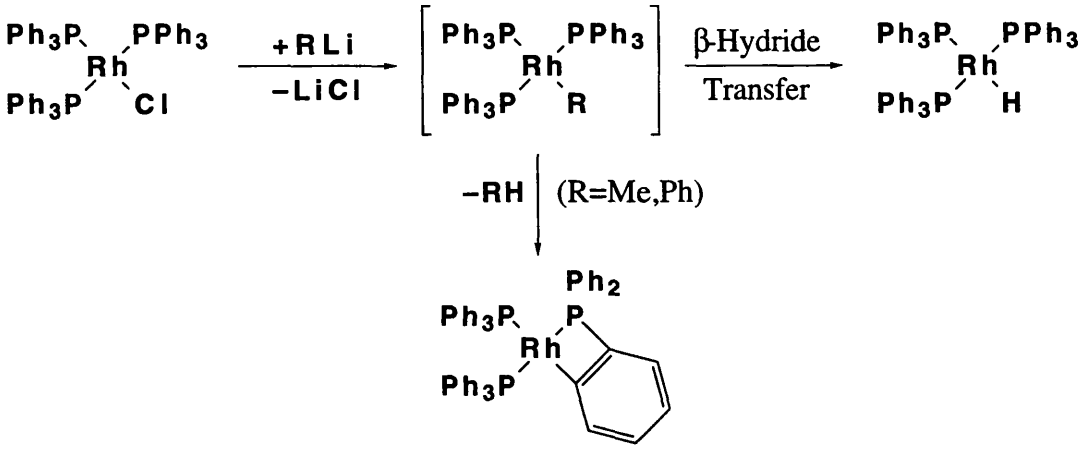
Table 2.4 – Isomerisations With Excess Butyllithium

In an attempt to complete the reaction by preventing thermal decomposition of the catalytic species the isomerisation was repeated at ambient temperature (table 2.4, entry 3). Similar results were obtained, with regiochemical equilibration again suppressed, but only a very low conversion was achieved with 85% starting material recovered. It appears that the isomerisation is significantly slowed while the rate of decomposition is not greatly affected. Consequently the quantity of catalyst was

increased from 2.0% to 5.0%. Isomerisation halted after one hour at reflux and produced a very poor 18% yield of the desired products, with an equally low 55% mass balance (table 2.4, entry 4). The regiochemical control was maintained, and both ketone **36** and polyalkylated materials **37** were major products.

In light of the decomposition of the catalytic species in the presence of a larger excess, isomerisation was attempted with a 10% excess of butyllithium and 5.0 mol% Wilkinson's catalyst (table 2.4, entry 5). Although the highest yield of desired products was recorded (74%), regiochemical equilibration again occurred (**34**:**35**=1.3:1) and a considerable quantity of ketone **36** was once again isolated.

The use of a large excess of butyllithium is clearly reducing equilibration, but slowly destroying the active catalyst and preventing complete reaction. Furthermore, the species produced when Wilkinson's catalyst is modified by reaction with butyllithium is probably hydridic, and may operate by an entirely different mechanism. Reaction with Grignard reagents has been shown to give alkyltris(triphenylphosphine)-rhodium (I), which is stable only when β-hydride transfer is not possible, with transfer otherwise proceeding to give hydridotris(triphenylphosphine)rhodium (I) (scheme 2.2.56).[132] This latter reaction is also known to occur with triisopropylaluminium. The alkylrhodium species can also decompose on heating by another route, involving insertion into a phosphine C-H bond to give a cyclic 'ortho-metallated' complex.[132b]



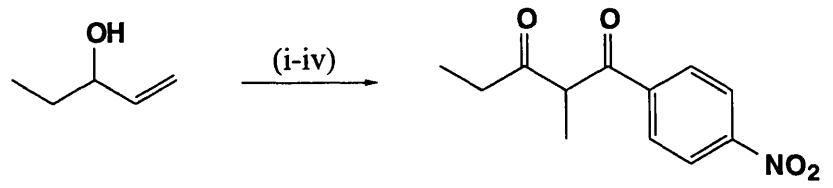
Scheme 2.2.56

With a hydridic catalyst species there may be a change of mechanism, but a metal hydride addition-elimination sequence would be more likely to cause equilibration of regioisomers, not less. Alternatively, as metallic rhodium is ultimately formed, it is quite possible that the catalyst is initially converted into a colloidal form which is catalysing isomerisation and undergoing slow aggregation to precipitate the element. A number of hydrogenation catalysts which were thought at first to be homogeneous have now been shown to in fact be colloidal platinum metals formed under the reducing conditions.[145]

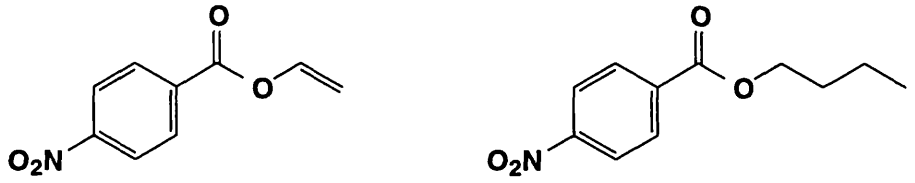
Examination of table 2.4 reveals an important point: with a small excess of butyllithium there is a much larger quantity of ketone **36** isolated than polyalkylated materials **37**, while with a larger excess these products are isolated in equivalent yields. This suggests that with a large excess of butyllithium **36** is produced only in the alkylation step (with a similar yield of **37**) while otherwise it is also present prior to alkylation. This supports the hypothesis of a proton source produced during the reaction.

The isomerisation of 1-penten-3-ol (**15**) was discussed earlier, and it was noted that attempts to trap the enolate products as non-volatile O-acyl derivatives were unsuccessful. However the reaction with 4-nitrobenzoyl chloride was unique in that volatile products could be trapped which would otherwise be lost. The major product was the 1,3-diketone **19** (63%), but esters **38** (*ca.* 1%) and **39** (6%) were also isolated (scheme 2.2.57). These unexpected products are thought not to be derived from the substrate **16** but 'yields' are included to indicate the relative molar quantities recovered.

Vinyl 4-nitrobenzoate (**38**) is undoubtedly produced by reaction of a small excess of butyllithium with THF as previously described (scheme 2.2.55).[57] The origin of butyl 4-nitrobenzoate (**39**) is less clear, but it is also thought to be derived from THF in a different manner. Conceivably, base-mediated elimination aided by coordination to a Lewis acid could give 3-buten-1-ol lithium alkoxide which is subsequently reduced by rhodium-catalysed transfer hydrogenation and esterified (scheme 2.2.58). No trace of 3-buten-1-yl ester was detected.



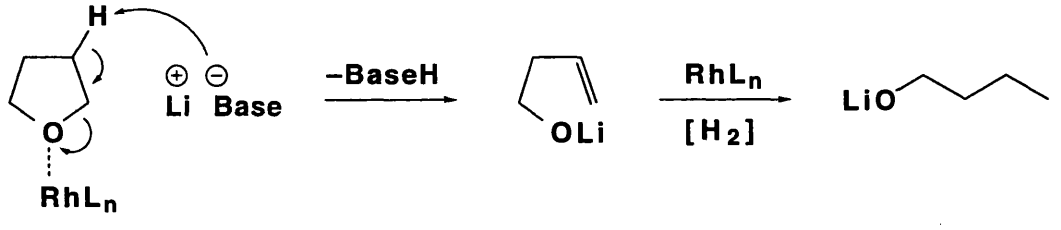
15 **19** (63%)



38 (*ca.* 1%) **39** (6%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 10 h; (iii) 4-NO_2-C_6H_4COCl (10), 3.0M in THF, –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.57

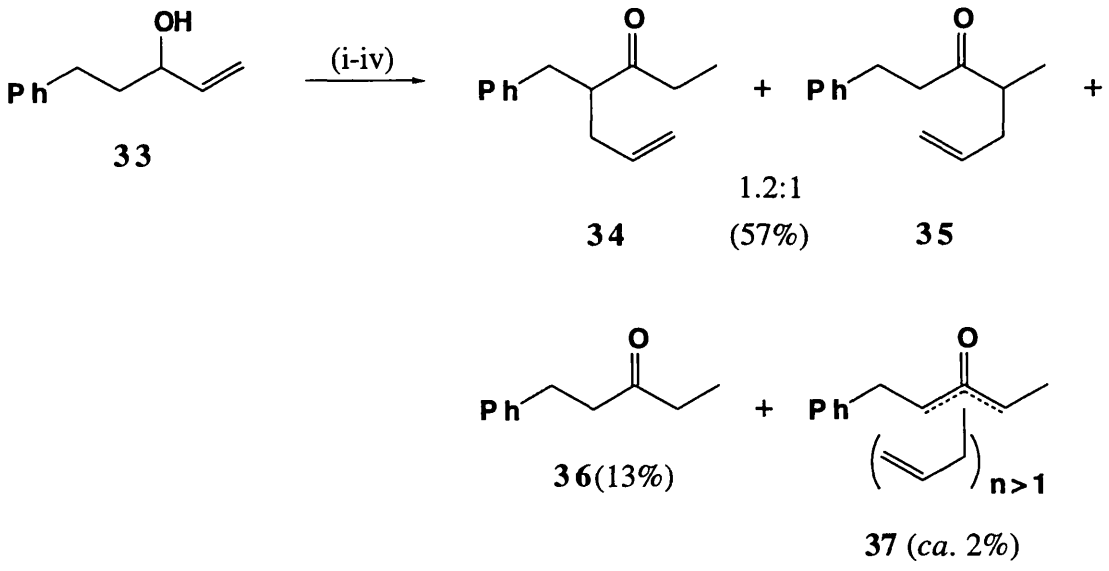


Scheme 2.2.58

A rhodium (I) phosphine complex is not a typical Lewis acid, but the unusual nature of the reaction suggests that rhodium is involved. The hydrogen source may be the substrate, since alcohols are commonly used as transfer reagents in conjunction with a weak base,[127,128] or another molecule of the solvent. It is interesting to note that THF has been used specifically as a source of hydrogen in transfer hydrogenation chemistry,[146] and is obviously present in far greater quantities.

We therefore have a mechanism by which THF can act as a proton source and

an isolated product to support the theory, so changing to an alternative solvent might prevent equilibration. Taking the usual precautions to ensure complete deprotonation, isomerisation of 5-phenyl-1-penten-3-ol (**33**) with 2.0 mol% of Wilkinson's catalyst at reflux in benzene solution was complete in 1.5 hours, half the reaction time observed in THF. This higher rate may be a consequence of both the higher reflux temperature and a less strongly solvated catalyst. Monoalkylated products **34** and **35** were isolated in 57% yield with the equilibrated ratio **34**:**35**=1.2:1, together with a large quantity of free ketone **36** (13%) and polyalkylated material (*ca.* 2%) (scheme 2.2.59).



Reagents: (i) ^{n}BuLi (1.0), benzene, 5°C; (ii) $(PPh_3)_3RhCl$ (2.1 mol%), benzene, then reflux 1.5 h; (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

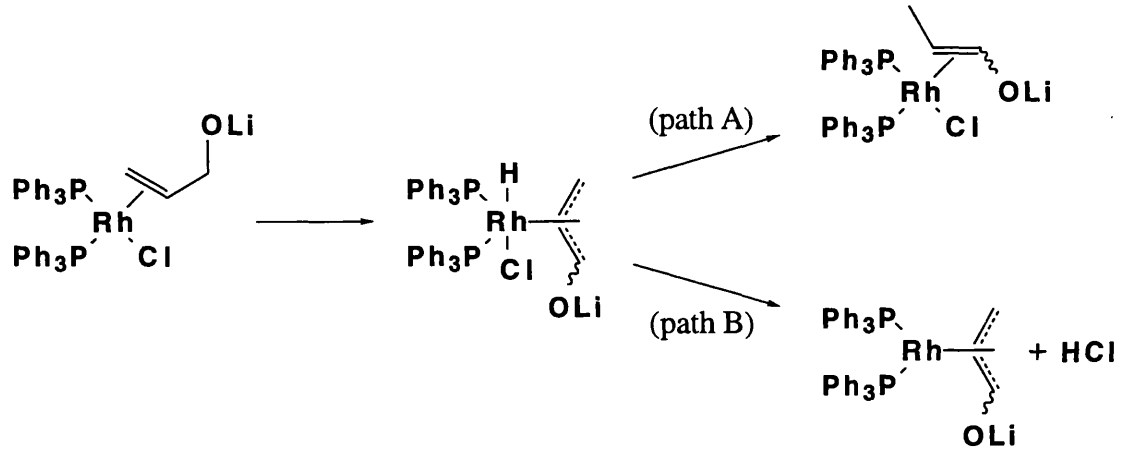
Scheme 2.2.59

There is no mechanism by which benzene can act as a proton source, so any further hypothesis to explain a proton-mediated equilibration must involve only the catalyst and substrate. With this in mind, there remain three feasible routes to a proton source. The first route to be discussed applies to the 'normal' π-allyl hydride mechanism. The remaining two routes, to be discussed subsequently, correspond to the alternative rhodium alkoxide mechanism.

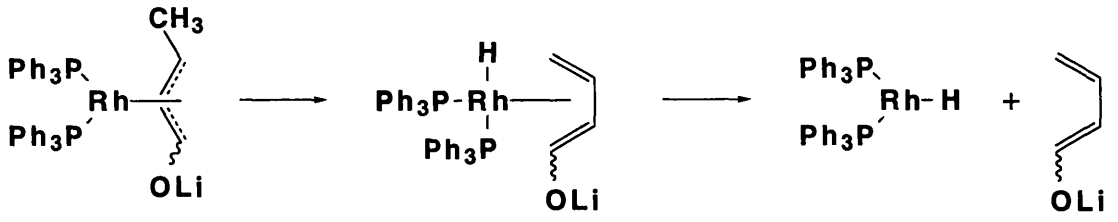
$$(PPh_3)_3RuCl_2 + H_2 + NEt_3 \longrightarrow (PPh_3)_3RuHCl + Et_3NHCl$$

Scheme 2.2.60

Under the basic conditions in which isomerisations are performed, a chlorohydridorhodium (III) intermediate might undergo reductive elimination to produce hydrogen chloride. A base-mediated reductive elimination is demonstrated in the synthesis of chlorohydridotris(triphenylphosphine)ruthenium (II) from the dichloro complex by hydrogenation in the presence of triethylamine (scheme 2.2.60).[147] A variety of bases increase the rate of reaction dramatically, although this may involve cleavage of a ruthenium (II) dihydrogen complex.[145b] An equivalent reaction in our rhodium system could follow oxidative addition of the substrate. Instead of the 'normal' reductive elimination to give the enolate complex (path A, scheme 2.2.61), loss of hydrogen chloride proceeds to give a rhodium (I) allyl complex (path B). An allyl complex is unlikely to be a suitable catalyst, but with a terminal alkyl substituent bearing a hydrogen at the β-position it can undergo hydride transfer and provide a route to a rhodium (I) hydride species (scheme 2.2.62). In THF an alternative rhodium (III) intermediate could be a chlorodihydrido complex formed by hydrogen transfer from the solvent; path B then gives rise to a rhodium (I) hydride more directly.

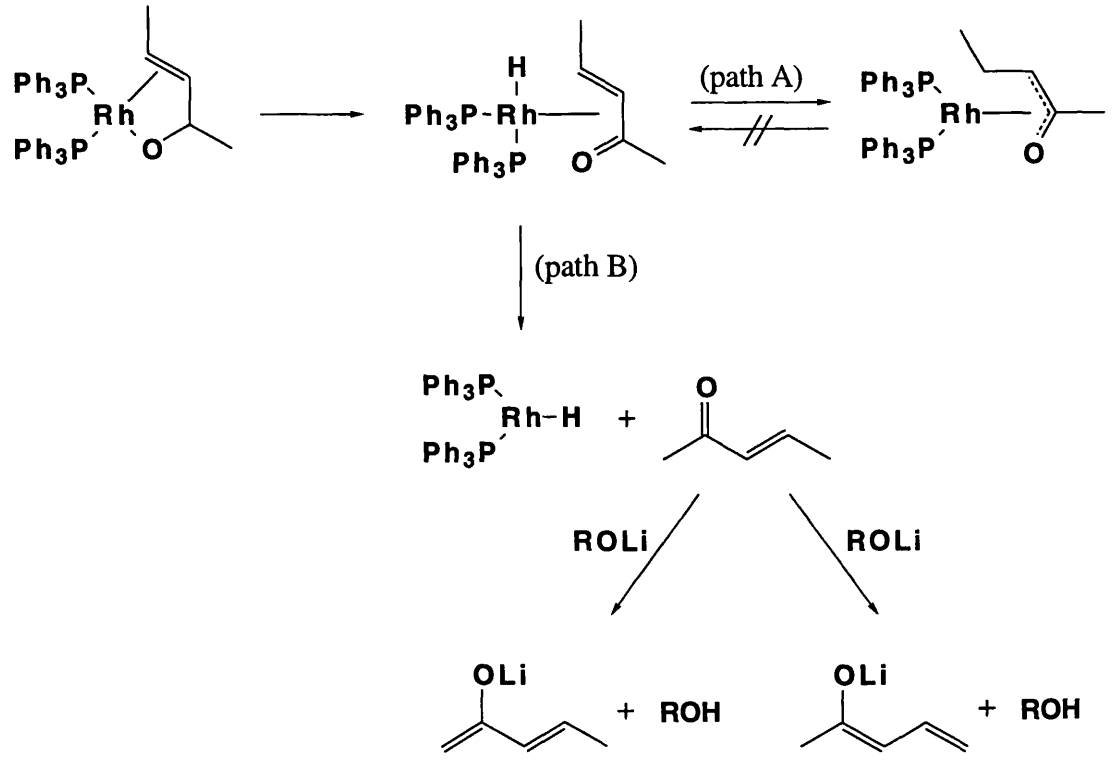


Scheme 2.2.61



Scheme 2.2.62

The second route applies most readily to the rhodium alkoxide mechanism and follows transfer of hydride to rhodium. If the reverse transfer of the hydride back to the substrate (path A) is relatively slow, dissociation of the dehydrogenated substrate might occur from the intermediate complex (path B, scheme 2.2.63). This unsaturated ketone can then be enolised in the basic medium. If path A is reversible then the rate of this forward process would be less important, as an equilibrium concentration of the hydrido-enone intermediate would be maintained and the alternative path B promoted.

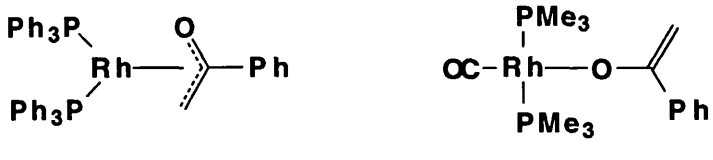


Scheme 2.2.63

In the forward direction path A gives the η^3-oxaallyl rhodium enolate. Cationic palladium (II) η^3-oxaallyl complexes decompose very rapidly by the reverse process, followed by path B, to give the palladium hydride and an enone.[148] Rhodium (I) η^3-enolates have however been shown not to decompose in this manner, suggesting that path A may in this case be irreversible.[135,138]

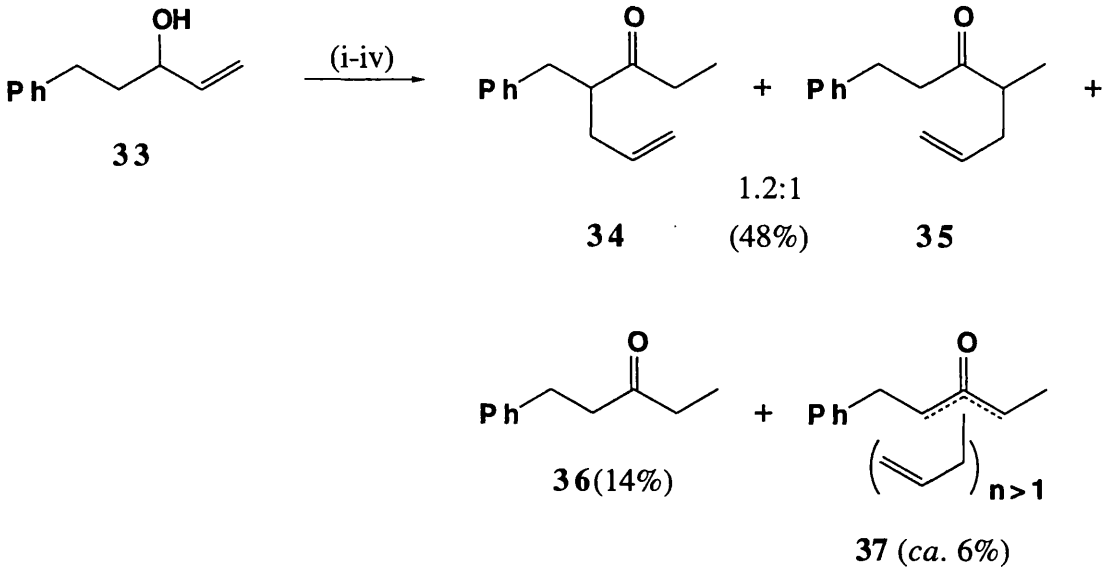
By either of these two routes the overall transformation is the same: one molecule each of lithium alkoxide and Wilkinson's catalyst are converted to lithium chloride, a rhodium (I) hydride, a dehydrogenated enolate anion product and 'a proton'. This means that the quantity of protic material produced is limited to the equivalent of the quantity of catalyst present.

The exact nature of the third route is uncertain, but it is the most clearly precedented. Although stable to dehydrogenation as described above, rhodium (I) enolates are thermally unstable. Slough noted that rhodium η^3-enolates decompose to yield the free ketone and unidentifiable rhodium products; the bis(triphenylphosphine)-rhodium (I) η^3-enolate of acetophenone (A, figure 2.13) has a half-life of 15.2 hours in benzene at 100°C.[138] Heathcock found that η^1-O rhodium enolates were even less stable, again giving free ketone and unidentifiable rhodium-containing products, and that the decomposition was particularly rapid in THF.[135] The carbonylbis-(trimethylphosphine)rhodium (I) η^1-O enolate of acetophenone (B, figure 2.13) has a half-life of just 50 minutes in THF at 25°C. Furthermore, decomposition in THF-d_8 yielded no deuterioketone, and it was concluded that the proton was derived from the phosphine ligand. Thus there are inherent problems associated with the intervention of rhodium enolates in the isomerisation process.



A B

Figure 2.13



Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), $SnCl_2$ (2.4 mol%), THF, then reflux 75 min; (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.64

A final attempt to prevent equilibration was made using the rhodium-tin system discovered previously, and a dramatic rate enhancement was again observed. Isomerisation of **33** with a mixture of Wilkinson's catalyst and tin (II) chloride under otherwise standard conditions was complete in just 75 minutes, giving alkylated products **34** and **35** in a lower 48% combined yield and in the ratio **34**:**35**=1.2:1 (scheme 2.2.64). The regioisomeric equilibration was therefore unabated. A large quantity of the parent ketone **36** (14%) was also isolated, together with polyalkylated materials (*ca.* 6%).

Proton exchange can therefore occur in a number of ways, and allow not only equilibration of enolate regioisomers but also stereoisomers. The scrambling of enolate stereochemistry is further aided by the presence of ketone in the reaction mixture through a rapid aldol/retro-aldol process.[11] However, the isomerisation reactions so far conducted have at least not all suffered equilibration. Only the (Z)-enol acetate of 1-penten-3-ol (**15**) was detected when it has been demonstrated that the lithium enolates form a equilibrium mixture (Z:E)=5.3:1 in the presence of 3-pentanone.[11]

2.2.6 The Preparation Of Tetrasubstituted Enolates

The ease with which a substrate is isomerised can be estimated from the degree of substitution around the allyl alcohol nucleus. The rate of isomerisation is expected to decrease with increasing double bond substitution, as the greater steric hindrance makes initial coordination less favourable.[114] Similarly, increased substitution about the double bond of the enolate product will hinder close approach of the catalyst, and probably further slow isomerisation despite the greater inherent thermodynamic stability of the product. Substrates can be judged on a combination of these two criteria, and a systematic investigation of the effects of substitution was therefore undertaken. Thus far in the series based on 1-phenyl-2-propen-1-ol (**1**), formed by introducing groups at the double bond (figure 2.14, R=H unless otherwise stated), only the monosubstituted parent **1** and disubstituted alcohols **7** (R_{trans}=Me) and **8** (R_{cis}=Me) have been studied.

The next substrate is logically the remaining disubstituted alcohol **40** (R_{gem}=Et). An ethyl group is chosen instead of a methyl to distinguish between the bond substituent and the newly-formed methyl group in the product, thus allowing the stereochemical course of the reaction to be followed.

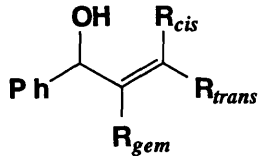
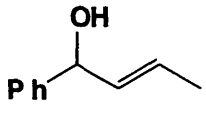
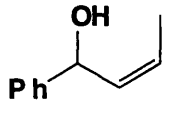


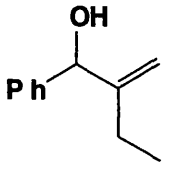
Figure 2.14



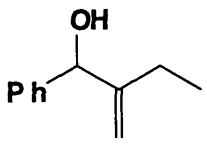
7



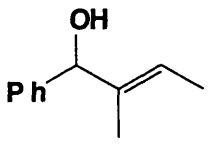
8



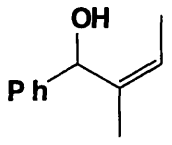
40



40



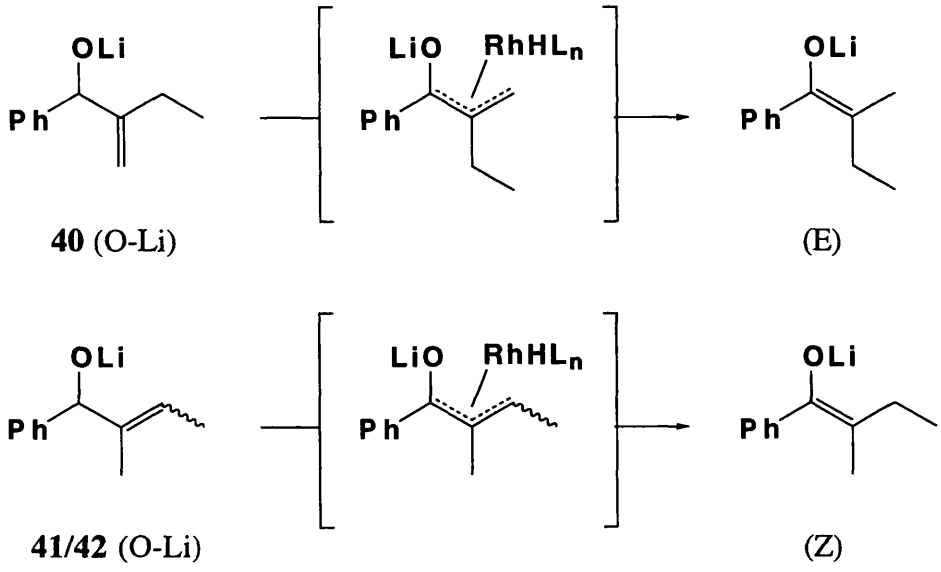
41



42

Importantly, alcohol **40** is also a precursor to a tetrasubstituted enolate, and so from the point of view of the product isomerisation would be a greater achievement than that of **7** or **8**. Substrates **41** (R_{trans},R_{gem}=Me) and **42** (R_{cis},R_{gem}=Me) are trisubstituted and give rise to tetrasubstituted enolates, and are therefore expected to be even more of a challenge. However examination of these three substrates reveals that they correspond to the same ketone, and the same enolates would therefore be produced. If the cisoid arrangement of the double bond and oxygen is still highly favoured, then enolate stereochemistry is substrate dependant, and a particular geometry could be selected by choice between **40** and the trisubstituted pair (scheme 2.2.65). At the present time, control of tetrasubstituted enolate stereochemistry is not generally possible.[65]

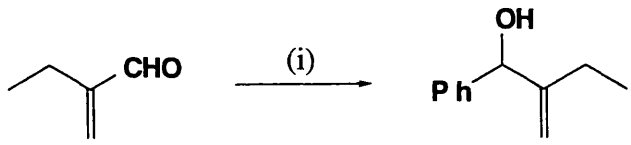
Alcohol **40** was prepared in 89% yield by reaction of phenylmagnesium bromide with 2-ethyl-2-propenal (scheme 2.2.66).



40 (O-Li) (E)

41/42 (O-Li) (Z)

Scheme 2.2.65

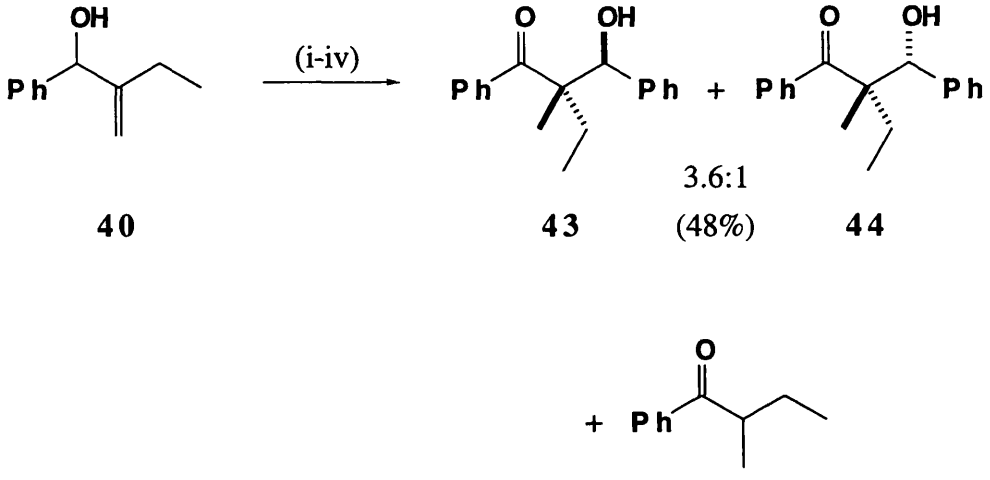


40 (89%)

Reagents: (i) Mg, PhBr, THF, 0°C.

Scheme 2.2.66

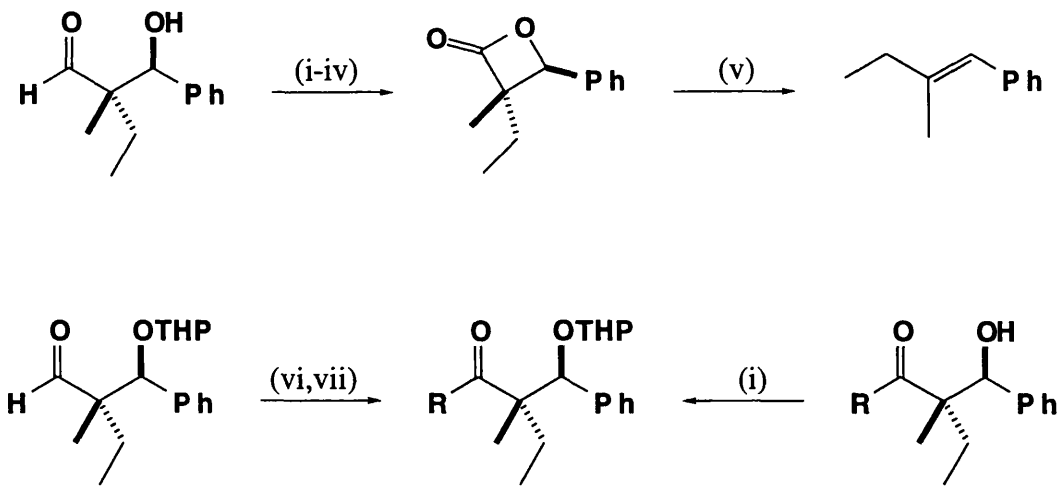
Isomerisation under standard conditions was complete in 24 hours, and aldol reaction gave aldols **43** and **44** in combined 48% yield and in the ratio **43**:**44**=3.6:1, with a large quantity of ketone **45** (14%) (scheme 2.2.67). With aldol products from tetrasubstituted enolates the relative stereochemistry cannot be assigned directly using ^{1}H NMR as there is no proton at the C-2 position to provide coupling information. Assignments have been made previously by a laborious chemical correlation procedure; an aldol derived from an aldehyde enolate was converted to an alkene which could be assigned spectroscopically, and related aldols from the corresponding ketone enolates are assigned by preparation from the former (scheme 2.2.68).[65]



40 **43** **44** **45** (14%)

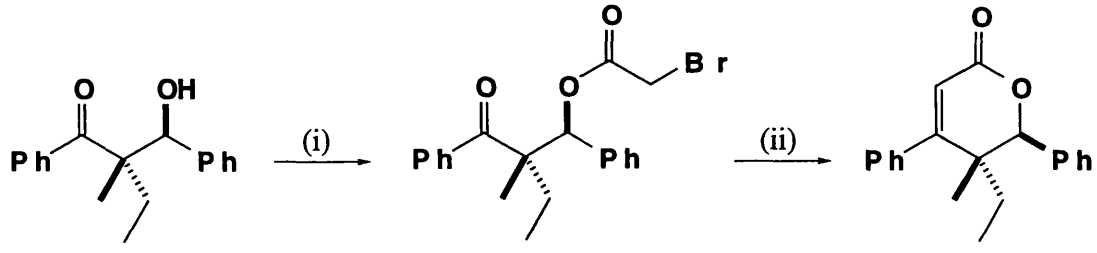
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 24 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.67



Reagents: (i) DHP, PTSA; (ii) $KMnO_4$; (iii) H_3O^+; (iv) $PhSO_2Cl$, NEt_3; (v) 110°C, Toluene; (vi) RLi; (vii) PCC.

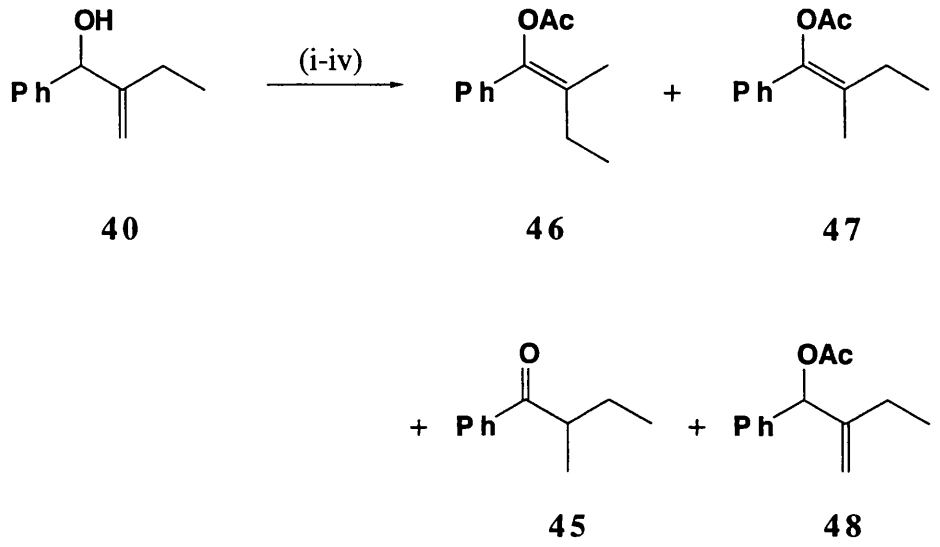
Scheme 2.2.68



Reagents: (i) $BrCH_2COCl$, Py; (ii) $2SmI_2$, THF.

Scheme 2.2.69

Attempts to prepare a rigid lactone derivative by a simpler procedure (scheme 2.2.69),[149] which might be assigned by ^1H NMR, were unsuccessful. As an unequivocal assignment of aldol stereochemistry was of secondary importance, the relative stereochemistry shown (scheme 2.2.67) was assigned by establishing enolate geometry *via* the corresponding enol acetates. Aldol reactions of tetrasubstituted lithium enolates have been shown to be consistent with the Zimmerman-Traxler transition state model.[65]



40 **46** **47**

45 **48**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux (time); (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Time (hours)	Isolated Yields (%)					
		46+47	**(46:47)**	**45**	**48**	**40**	Total
1)	21	40	(3.5:1)	3	–	–	43
2)	3	14	(3.4:1)	6	24	49	20

Table 2.5 – Preparation Of Enol Acetates

Isomerisation and quench after 21 hours with acetic anhydride provided enol acetates **46** and **47** in 40% combined yield and the ratio **46**:**47**=3.5:1, almost identical to the ratio of aldols (table 2.5, entry 1). The stereochemistry of the enol acetates was established by nOe experiments (figure 2.15), and thus, following Noyori's nomenclature,[2] the major aldol product was assigned as the *threo*-isomer **43**. In this case only a small quantity of ketone **45** was isolated (3%), with no starting material (or acetate **48**). That the (E)-enol acetate **46** was the major isomer is expected from the postulated cisoid arrangement of oxygen and the double bond, but as a stereochemical mixture was formed the complication of product equilibration is suggested once more.

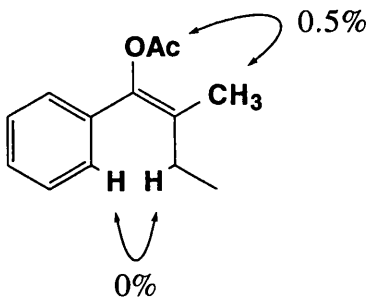
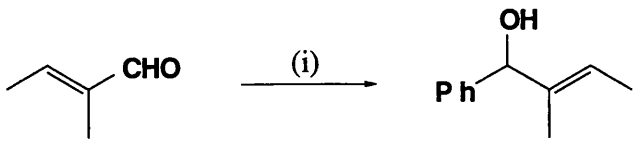


Figure 2.15 – nOe Experiments

It is notable that if isomerisation is discontinued after just 3 hours, the starting material **40** (30%) and acetylated starting material **48** (24%) are recovered unchanged—no conversion to the isomeric allylic alcohols is detectable (table 2.5, entry 2). The isolated enol acetates are in a similar ratio at this early stage of the reaction (**46**:**47**=3.4:1, 14%), despite the increased and variable proportion of ketone **45** (6%).

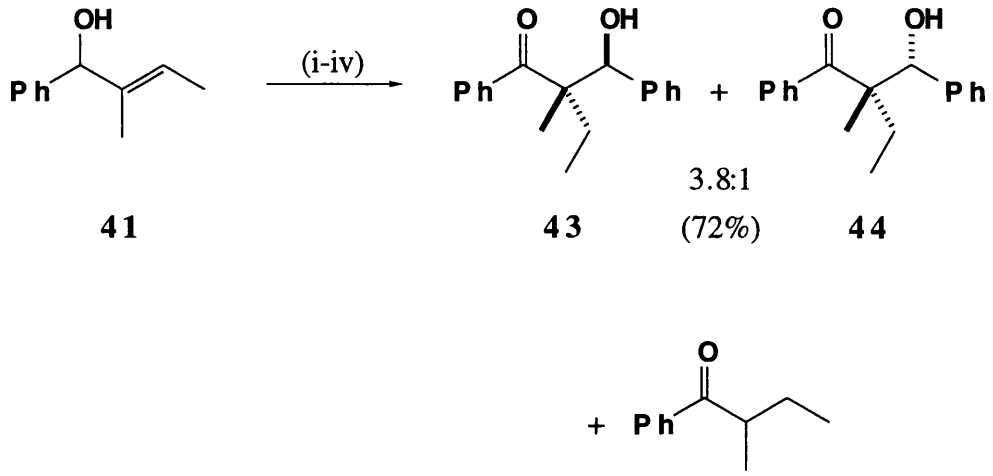
The substrate **41** was prepared previously by reaction of phenylmagnesium bromide with (E)-2-methyl-2-butenal (scheme 2.2.70).[102] Isomerisation under standard conditions was completed in 26 hours and kinetic aldol reaction gave the aldols in a comparatively excellent 72% yield, and in the ratio **43**:**44**=3.8:1 (scheme 2.2.71). With ketone **45** (15%) a total 87% yield of isomerised materials was isolated. Isomerisation of this substrate with a trisubstituted double bond was considerably more successful than disubstituted **40**, although the reaction was completed in a comparable time. The ratio of aldol products indicated a similar stereoselectivity, which was confirmed by preparation of enol acetates.



41

Reagents: (i) Mg, PhBr, THF, 0°C.

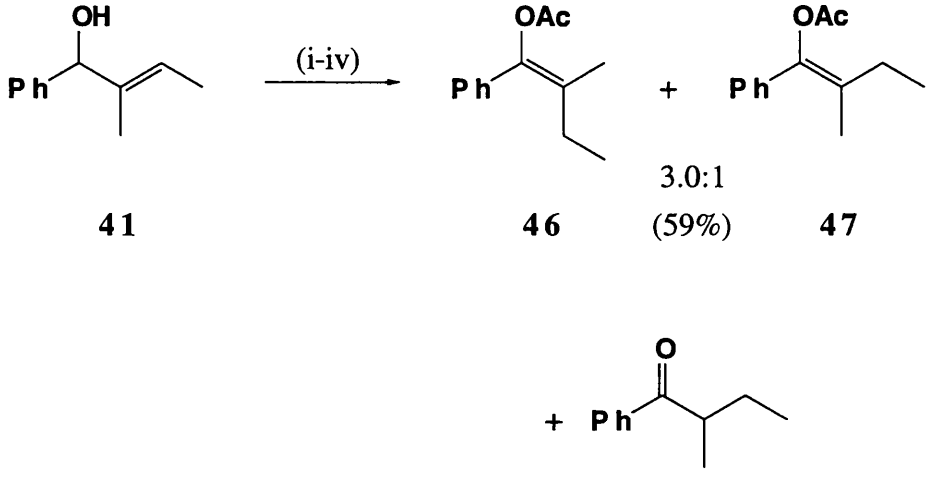
Scheme 2.2.70



Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 26 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

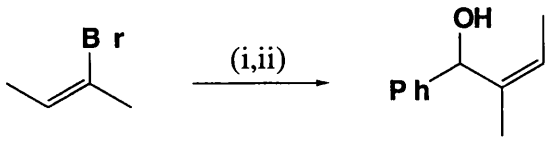
Scheme 2.2.71

Acetylation under standard conditions gave the enol acetates **46** and **47** in a good 59% combined yield and in the slightly lower ratio **46**:**47**=3.0:1 (scheme 2.2.72). Again a large quantity of the parent ketone **45** (15%) was isolated .



Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 24 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.72

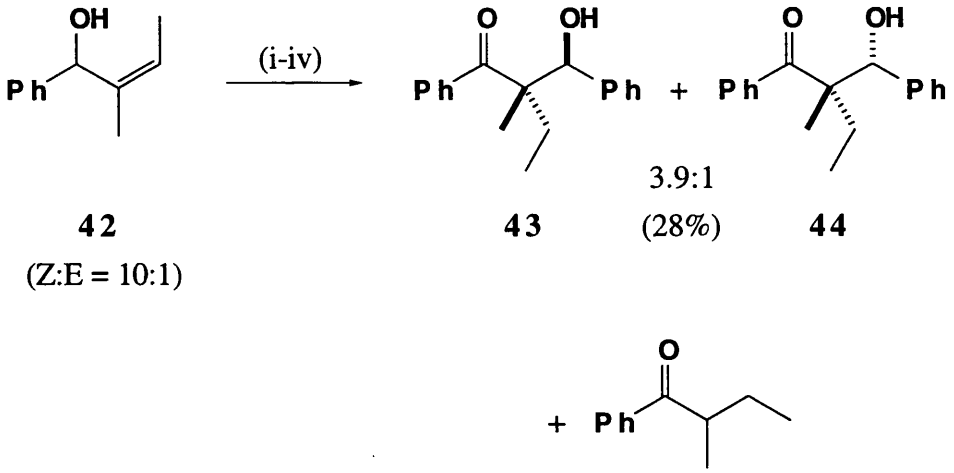


42

Reagents: (i) Mg, THF, reflux; (ii) PhCHO, THF, 0°C.

Scheme 2.2.73

The (Z)-substrate **42** had been prepared by reaction of benzaldehyde with the Grignard reagent derived from (Z)-2-bromo-2-butene (scheme 2.2.73).[102] However, a small quantity of the (E)-alcohol **41** was present as a result of some (E)-bromoalkene impurity. Isomerisation of **42** (Z:E=10:1) at reflux for 48 hours and reaction with benzaldehyde produced aldols **43** and **44** in a poor 28% combined yield and in the ratio **43**:**44**=3.9:1 (scheme 2.2.74). Considerable quantities of both starting material (32%) and ketone **45** (23%) give a total mass balance of 83%. The isomerisation was clearly incomplete and had most probably halted after approximately 24 hours. It is a general observation that residual lithium alkoxide lowers the efficiency of the aldol reaction.



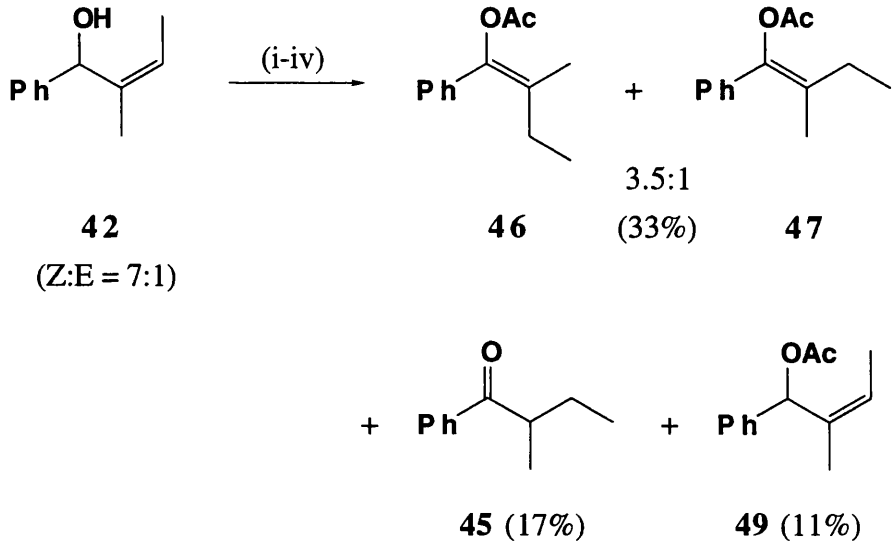
42
(Z:E = 10:1)

43 (28%) **44**

45 (23%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 48 h; (iii) PhCHO (1.1), –78°C, 5 s; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.2.74

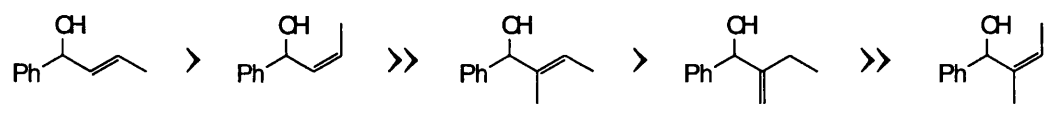


Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 16 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.75

Isomerisation of **42** (Z:E=7:1) for just 16 hours and formation of the enol acetates again reveals the same ratio of stereoisomers (**46**:**47**=3.5:1, 33%) (scheme 2.2.75). Also isolated were ketone **45** (17%), acetylated starting material **49** (11%) and starting material **42** (25%). Interestingly, in both reactions this starting material was pure (Z)-alcohol **42** as the (E)-geometry impurity **41** had been more rapidly consumed.

From the observed reaction times, isomerisation of the disubstituted substrate **40** would appear a more comparable challenge to the trisubstituted pair **41** and **42** than to the disubstituted substrates **7** and **8** (figure 2.16). Most surprising is that alcohol **40** seems to be less easily isomerised than **41**, even though a trisubstituted double bond is considered more sterically hindered and less accessible to the catalyst.

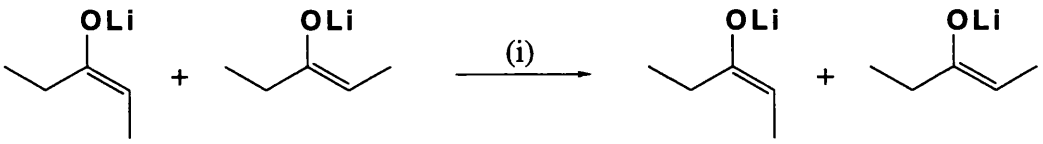


7 **8** **41** **40** **42**

Figure 2.16

Alcohol **42** is a much poorer substrate than the geometrical isomer **41**, an observation consistent with the more facile isomerisation of the (E)-isomer of 1-phenyl-2-buten-1-ol (**7**), and suggesting that the (Z)-methyl substituent interferes with the formation of some intermediate complex.

The three substrates studied in this section give rise to the same mixture of enolates. Hence there is either a mechanism for equilibration of the enolates or there is a common intermediate in the catalytic cycle. The simplest explanation for equilibration involves a proton source, and the ways in which this might be generated have been discussed in depth earlier. The presence of the parent ketone in the reaction mixture could allow scrambling of stereochemistry *via* a proton exchange mechanism. It has been shown however that an aldol/retro-aldol process can have the same effect: treatment of 3-pentanone lithium enolate with a catalytic quantity of ketone, even an aprotic ketone, results in equilibration (scheme 2.2.76).[11]

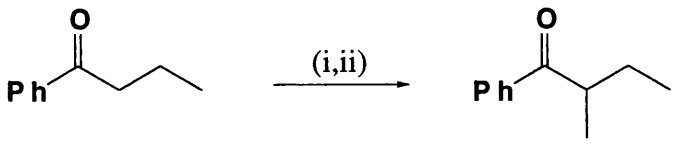


77 : 23 16 : 84

Reagents: (i) 3-Pentanone or Benzophenone (20 mol%), 0°C, 30 min.

Scheme 2.2.76

The work of Heathcock[135] and Slough[138] with rhodium enolates provides the most likely explanation—a rhodium-mediated interconversion process. It is postulated that isomerisation proceeds through a rhodium alkoxide to initially give a rhodium enolate. Bis(trialkylphosphine)rhodium (I) enolates have been shown to adopt the η^3-1-oxaallyl form, and the examples of triphenylphosphine complexes exhibit a rapid fluxionality which would be accentuated at the reflux temperatures used.[138] Thus, the isomerisations of all three substrates could converge on this common intermediate and the initial stereochemical differences be lost.

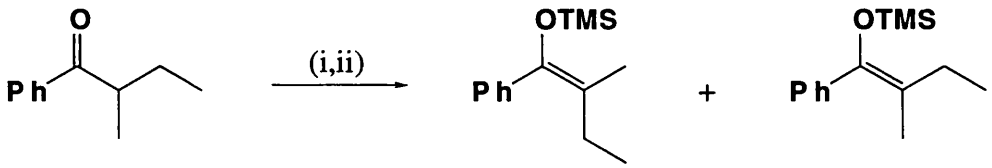


45 (97%)

Reagents: (i) LDA, THF, –78° to 0°C; (ii) MeI, THF, –78°C.

Scheme 2.2.77

In order to discover whether the lithium enolates themselves could undergo a rhodium-catalysed equilibration, the corresponding trimethylsilyl enol ethers were prepared so that a known, different ratio of the two stereoisomers could be generated and then exposed to the catalyst.[84] Ketone **45** was prepared by alkylation of 1-phenyl-1-butanone lithium enolate with methyl iodide in 97% isolated yield (scheme 2.2.77). This ketone was deprotonated under kinetic conditions with lithium diisopropylamide, and when quenched with chlorotrimethylsilane gave a mixture of the (E)-silyl enol ether **50** and the (Z)-silyl enol ether **51** in a combined 78% yield after fractional distillation and in the ratio **50**:**51**=1:3.0—fortunately the (Z)-isomer was predominant (scheme 2.2.78). This stereochemistry was assigned on the basis of nOe experiments (figure 2.17), and was further confirmed by conversion of the silyl enol ethers to the corresponding enol acetates. Thus, treatment of a mixture of **50** and **51** (**50**:**51**=1:3.0) with methyllithium and subsequent acetylation gave the enol acetates **46** and **47** in the identical ratio **46**:**47**=1:3.0 and in 80% isolated yield (scheme 2.2.79).



1 : 3.0

50 (78%) **51**

Reagents: (i) LDA, THF, –78° to 0°C; (ii) TMSCl, THF, –78°C.

Scheme 2.2.78

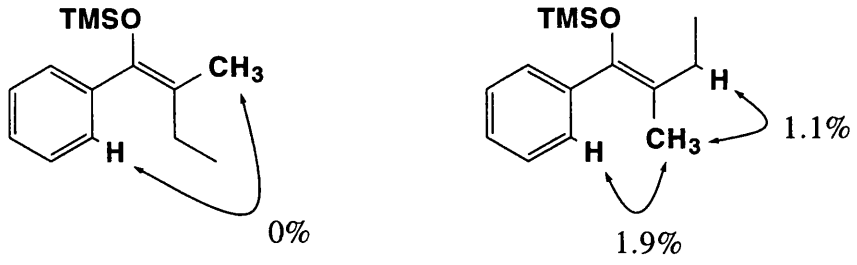
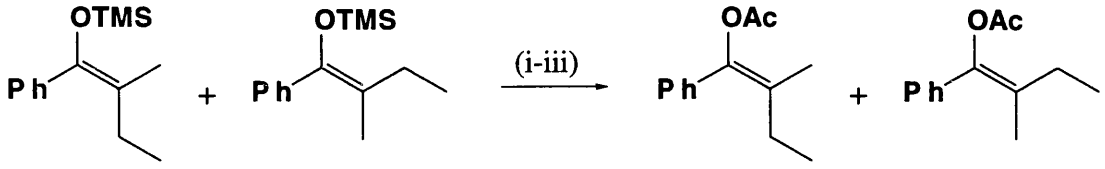


Figure 2.17 – nOe Experiments



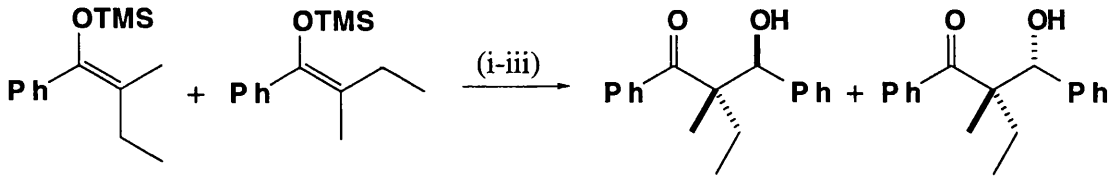
1:3.0 1:3.0

50 **51** **46** (80%) **47**

Reagents: (i) MeLi (1.0), THF, 0°C to r.t., 1.5 h; (ii) Ac_2O (10), –78°C; (iii) $NaHCO_{3(aq)}$.

Scheme 2.2.79

In contrast to the isomerisation reactions the (Z)-enolate isomer predominated, so in this case the isomerisation methodology gives a different result to conventional chemistry. This also allows another correlation between the ratio of the enolates and the aldol products **43** and **44**. Treatment of the trimethylsilyl enol ethers **50** and **51** (**50**:**51**=1:3.0) with methyllithium and kinetic aldol reaction gave **43** and **44** in 64% yield with no diastereoselection (**43**:**44**=1:1) (scheme 2.2.80; table 2.6, entry 1). This result is unexpected, since the methyl and ethyl groups are of similar steric requirement, but not unprecedented as the (Z)-lithium enolate of the equivalent methyl ketone is actually slightly *threo*-selective in the aldol reaction with benzaldehyde under the usual kinetic conditions (table 2.6, entry 2).[65] The aldol reactions of the enolates prepared by isomerisation (table 2.6, entry 3), and of the largely (E)-enolate of the equivalent methyl ketone (table 2.6, entry 4), are also included for comparison.

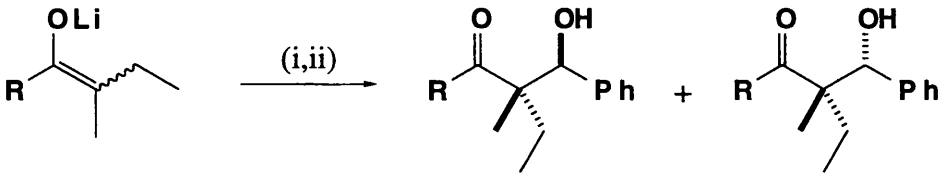


1:3.0 1:1

50 **51** **43** (64%) **44**

Reagents: (i) MeLi (1.0), THF, 0°C to r.t., 2 h; (ii) PhCHO (1.1), –78°C, 5 s; (iii) $NH_4Cl_{(aq)}$.

Scheme 2.2.80



threo *erythro*

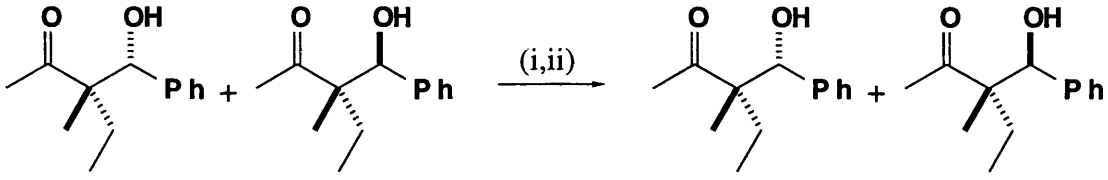
Reagents: (i) PhCHO, THF, –78°C, time; (ii) H^+.

Entry	Group (R)	Time (s)	Enolate Ratio (E:Z)	Aldol Ratio (*threo*:*erythro*)
1)	Ph	5	1 : 3.0	1 : 1
2)	Me	10	(Z)	1.2 : 1
3)	Ph	5	3.5 : 1	3.6 : 1
4)	Me	5	6.1 : 1	4.9 : 1

Table 2.6 – Aldol Stereoselectivity Of Tetrasubstituted Enolates

This analogous behaviour further confirms the stereochemical assignment of aldols **43** and **44**. In contrast to less-substituted enolates, for which the differences in aldol stereoselectivity between the two enolate stereoisomers has been explained by distortion

of the idealised chair transition state geometry,[118] these differences have been shown to be a result of product equilibration due to the rapidity of the retro-aldol process.[65] The expected kinetic stereoselectivity in the *erythro*-sense may be high but the lithium aldolate is destabilised by the increased steric crowding. This was demonstrated for the aldolates of the equivalent methyl ketone: a mixture of aldols greatly favouring the *erythro* isomer was equilibrated rapidly by treatment with butyllithium for five seconds (table 2.7, entry 1).



erythro (15.7:1) *threo* *erythro* *threo*

Reagents: (i) Base (1.0), THF, –72°C, time; (ii) AcOH, THF.

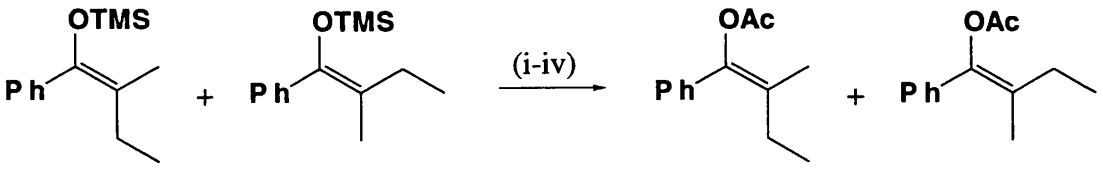
Entry	Base	Time (s)	Aldol Ratio (*erythro:threo*)	Recovery (%)
1)	^{n}BuLi	5	2.57 : 1	50
2)	LDA	5	2.85 : 1	75
3)	^{n}BuLi	600	1 : 3.00	30
4)	LDA	600	1.63 : 1	56

Table 2.7 – Base Dependant Equilibration Of Lithium Aldolates

Importantly, a similar equilibration using lithium diisopropylamide was far slower (table 2.7, entries 2,4). It seems that the presence of diisopropylamine in the reaction mixture, and the formation of mixed amine-aldolate oligomers, is in some way stabilising the lithium aldolate.[33] This is suppressing the retro-aldol process, and also

decomposition judging by the recovered yields. The catalytic isomerisation approach likewise gives lithium enolates free of amine, and consequently it can be concluded that the discrepancies noted previously between literature aldol diastereoselectivities and those observed in this work are not a result of different kinetic selectivities, but due to more rapid aldolate equilibration.

The trimethylsilyl enol ethers **50** and **51** were converted into the equivalent lithium enolates by reaction with methyllithium at ambient temperature.[84] The solutions were degassed and treated with a solution of Wilkinson's catalyst before being heated to reflux for 18 hours, and the resulting enolate solutions quenched with acetic anhydride under standard conditions to be analysed as the corresponding enol acetates (table 2.8, entries 1,4). Control experiments were studied by ^{1}H NMR analysis of the crude reaction mixtures and consequently yields are not given (table 2.8, entries 2,3).



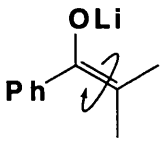
50 (1:3.0) **51** **46** **47**

Reagents: (i) MeLi, THF, 0°C to r.t., *ca.* 1.5 h; (ii) $(PPh_3)_3RhCl$ (mol% or none) then reflux 18 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Catalyst (mol%)	MeLi (equiv)	Starting Ratio (**50**:**51**)	Recovered Ratio (**46**:**47**)	Yield (%)
1)	2.0	1.0	1 : 3	3 : 1	73
2)	none	1.0	1 : 3	3 : 1	–
3)	none	1.1	1 : 3	1 : 3	–
4)	2.0	1.1	1 : 3	1 : 3	78

Table 2.8 – Equilibration Of Lithium Enolates

When one equivalent of methyllithium was used to generate the enolates equilibration of enolate stereoisomers had occurred after 18 hours reflux in the presence of the catalyst (table 2.8, entry 1). Notably, the parent ketone **45** was also isolated in 5% yield. However a subsequent control reaction, involving an identical reflux procedure but in the absence of catalyst, similarly showed an equilibration (table 2.8, entry 2). The methyllithium procedure was earlier shown to preserve the stereochemical integrity of the enolates at ambient temperature for 1.5 hours (scheme 2.2.79), and a proton-mediated equilibration would be expected to be sufficiently fast to occur during this time (scheme 2.2.76). A purely thermal equilibration would be an unlikely explanation, as the rotational activation free energy barrier of the enolate double bond for the similar 2-methyl-1-phenyl-1-propanone lithium enolate has been reported as $\Delta G^{\ddagger} \approx 27$ kcal.mol^{-1} (figure 2.18).[150] This corresponds to a rate constant for the inversion process $k = 2.7 \times 10^{-5}$ s^{-1} at reflux temperature in THF.



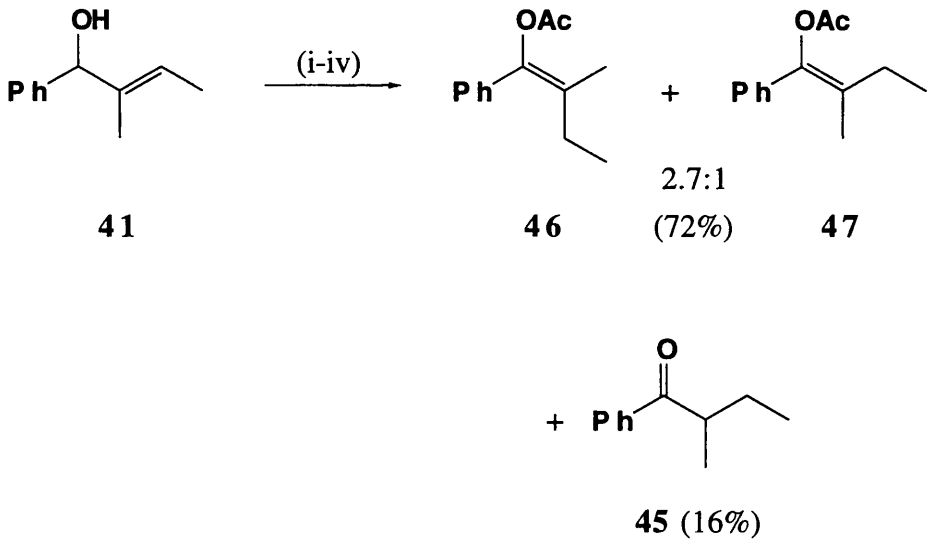
$\Delta G^{\ddagger} \approx 27$ kcal.mol^{-1}

Figure 2.18

Consequently, a control reaction was performed using 1.1 molar equivalents of methyllithium and the enol acetates were recovered in the starting ratio (table 2.8, entry 3). Again using 1.1 equivalents of methyllithium the enolates were exposed to Wilkinson's catalyst at reflux for 18 hours (table 2.8, entry 4). It is notable that the reaction of potassium enolates with rhodium (I) complexes even at low temperature has been used for the synthesis of rhodium enolates.[135,137,138] However no equilibration occurred as the enol acetates were again recovered in an unchanged ratio, and no ketone could be detected. Either a rhodium enolate complex was not forming from the lithium

enolate after extended reflux, or the enol acetate ratio recovered from the isomerisation reactions (**46**:**47**≈3:1) does not result from fluxional behaviour of the rhodium enolate.

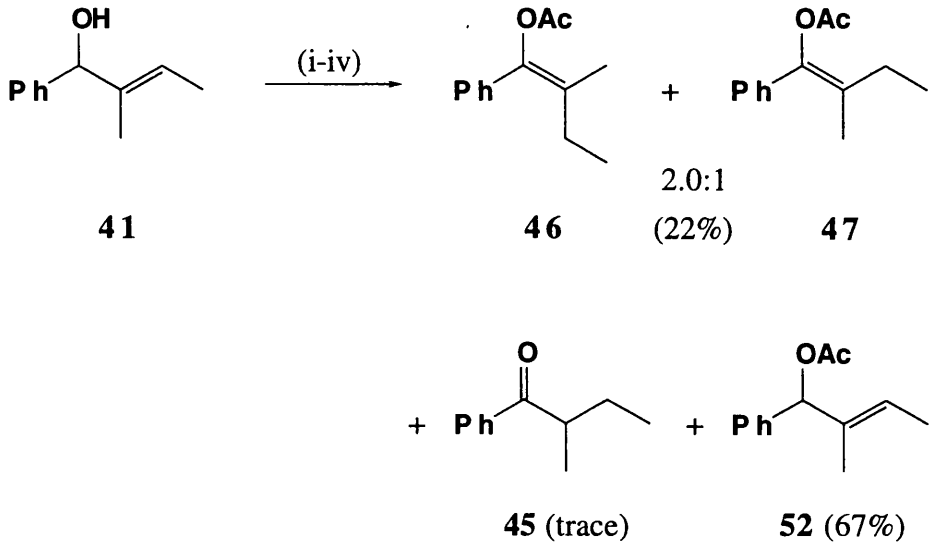
The fact that equilibration was suppressed when using 1.1 molar equivalents of methyllithium, but proceeded when using only one equivalent, lends credence to a proton-mediated equilibration mechanism. The isomerisation of alcohol **41** was therefore repeated using 1.1 equivalents of butyllithium in the initial deprotonation step to give a more direct comparison. Isomerisation was complete after 24 hours at reflux, giving enol acetates **46** and **47** in an increased 72% yield, but in the equilibrated ratio **46**:**47**=2.7:1 (scheme 2.2.81). A large quantity of parent ketone **45** (16%) gave an excellent 88% total isolated yield of isomerised material.



Reagents: (i) ^{n}BuLi (1.1), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 25 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.81

In a final attempt to suppress equilibration by persevering with the excess base approach, it was hoped that the use of potassium hydride might have advantages (scheme 2.2.82). As a heterogeneous, non-nucleophilic base the catalyst was expected to resist decomposition far better than with an alkyllithium, and the base was likely to remain a potent proton scavenger throughout the reaction.



Reagents: (i) KH (2.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 24 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.82

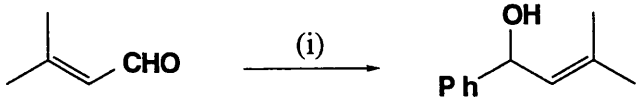
Approximately two molar equivalents of potassium hydride were used in the initial deprotonation, and the excess was clearly still highly reactive at the point of work-up. Isomerisation halted after several hours while still incomplete—the catalyst was in fact deactivated much more rapidly than normal. The enol acetates **46** and **47** were isolated in a very poor 22% yield, and in the ratio **46**:**47**=2.0:1, but only a trace of ketone **45** could be detected. The remaining starting material was isolated solely as the acetylated form **52** (67%), presumably as a result of the higher reactivity of potassium alkoxides.

At no time has it been possible to prevent the equilibration of stereoisomers. This latter experiment would seem to indicate that the process is not proton-mediated, but occurs during isomerisation. Although the lithium enolates do not equilibrate in the presence of Wilkinson's catalyst, this does not necessarily preclude an interconversion of rhodium enolates. It may be that lithium enolates do not react with the catalyst (being less reactive than their potassium counterparts), or do not convert from the initial η^1-O to the alternative η^1-C or η^3 forms. In a rhodium alkoxide mechanism the η^3 form is accessed directly. However it is interesting that the enol acetates were isolated in a lower ratio. This suggests that the potassium cation might be present during the

stereo-defining step.

The final substrate studied was the remaining trisubstituted alcohol in the series 3-methyl-1-phenyl-2-buten-1-ol (**53**) (figure 2.14, R_{cis},R_{trans}=Me). This is an important substrate as it is the first example with two substituents at the double bond terminus—this is the position where a new sp^3 centre is generated and successful isomerisation would introduce the possibility of asymmetric induction ($R_{cis} \neq R_{trans}$). The substrate had been prepared by reaction of phenylmagnesium bromide with 3-methyl-2-butenal (scheme 2.2.83).[102]

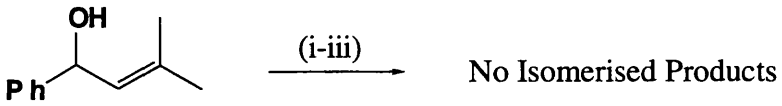
Treatment with Wilkinson's catalyst under standard conditions was ineffective. After reflux for 40 hours a complex reaction mixture was produced, and was quenched with ammonium chloride to avoid further complications (scheme 2.2.84). Crude ^1H NMR analysis and chromatography showed only starting material and no trace of the desired 3-methyl-1-phenyl-1-butanone. This result was unsurprising as substrates of similar substitution are frequently unreactive in related isomerisation chemistry.



53

Reagents: (i) Mg, PhBr, THF, 0°C.

Scheme 2.2.83



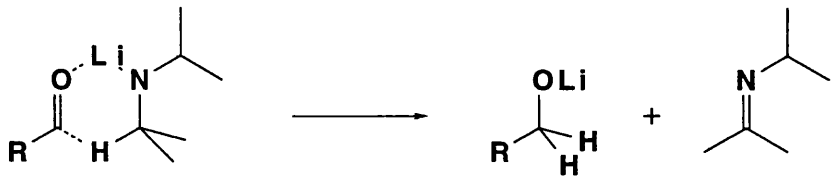
53

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 40 h; (iii) $NH_4Cl_{(aq)}$.

Scheme 2.2.84

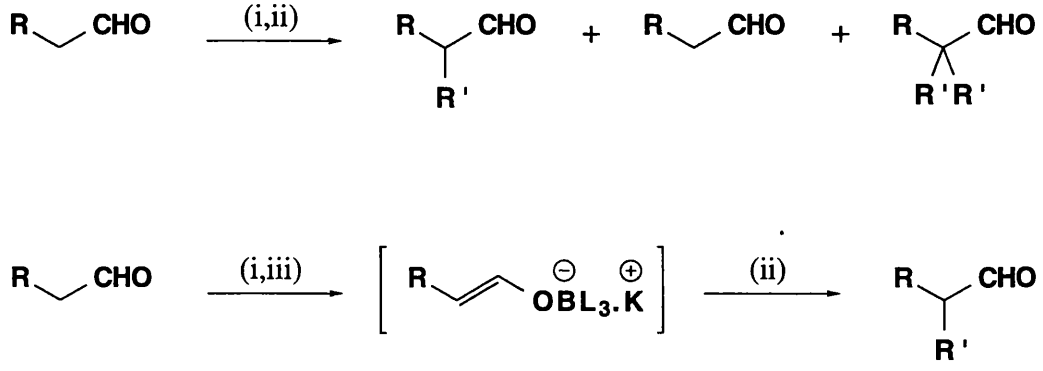
2.2.7 The Preparation Of Aldehyde Enolates

The preparation and reactions of aldehyde enolates present a number of problems. The conventional methods of kinetic deprotonation used with ketones are not applicable to aldehydes due to their higher electrophilicity; treatment with LDA results not in deprotonation but reduction to the primary alcohol.[151] Both hydride transfer (scheme 2.2.85) and electron transfer mechanisms may be involved.



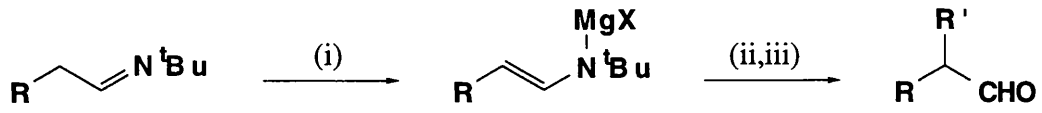
Scheme 2.2.85

Deprotonation may be achieved by the use of sodium or potassium hydride,[45,47,152] but aldehyde enolates suffer rapid proton exchange during alkylation (scheme 2.2.86), and competing aldol reactions of the aldehyde products also lower the yields.[153] Conversion to boron 'ate-complexes' can be helpful in both respects.[154]



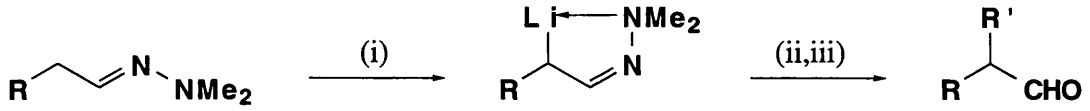
Reagents: (i) KH; (ii) R'X; (iii) BEt_3 or $B(OCH_2CH_2)_3N$.

Scheme 2.2.86



Reagents: (i) RMgX; (ii) R'X; (iii) H_3O^+.

Scheme 2.2.87



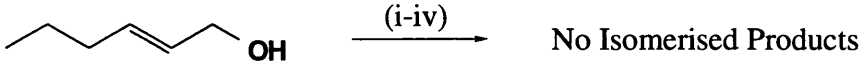
Reagents: (i) LDA; (ii) R'X; (iii) $NaIO_4$.

Scheme 2.2.88

Various methods have been developed to circumvent these problems, involving either the use of enolate equivalents, or the preparation of the enolates by indirect routes. *tert*-Butyl imine derivatives were developed as enolate equivalents by Stork; treatment with a Grignard reagent as a base gives an anion which may be alkylated and hydrolysed to the aldehyde product (scheme 2.2.87).[155] A similar methodology involves the use of *N,N*-dimethylhydrazone derivatives (scheme 2.2.88).[156] Aldehyde enolates may also be generated from enol acetates[83] or trimethylsilyl enol ethers[84,157] by treatment with methyllithium. In the former case lithium *tert*-butoxide is a by-product which can interfere with subsequent reactions.[153] The preparation of either of these precursors, particularly in a stereoselective manner, represents a further limitation.

In light of these difficulties, a new approach would seem to be of use. Aldol reactions of aldehyde enolates have been little studied and show no significant stereochemical dependence on enolate geometry,[13,65] but synthetic transformations involving vinyl triflates do require control of stereochemistry.[158] It was anticipated that isomerisation of a primary allylic alcohol would provide a simple, direct and possibly stereoselective route to aldehyde enolates.

The simplest primary alcohol substrate studied was (E)-2-hexen-1-ol (**54**), and isomerisation was expected to be facile. Formation of the lithium alkoxides at the standard concentration in THF proved problematic, as precipitation occurred if the solution was allowed to stand for more than a few minutes, and the alkoxide could not easily be redissolved. Consequently, solutions were degassed immediately after deprotonation with butyllithium. Treatment with 2.0 mol% of Wilkinson's catalyst under standard conditions and then acetic anhydride after reflux for 26 hours gave no trace of enol acetates (scheme 2.2.89). Chromatography yielded no identifiable products.



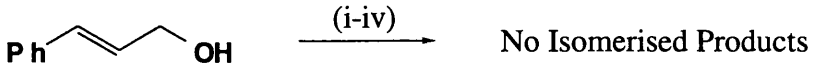
54

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%) [or 10 mol%], THF, then reflux 26 h [or 4.5 h]; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.89

Being the simplest of primary allylic alcohols, with the exception of allyl alcohol which was expected to present problems of volatility, this was a very disappointing result. It was hoped that using larger quantities of catalyst would promote isomerisation. Repeating the experiment using 10 mol% of Wilkinson's catalyst and acetylation after 4.5 hours at reflux gave a complex mixture. Although a trace of enol acetates was indicated by crude ^{1}H NMR analysis, no identifiable products could be isolated. There was no other evidence that isomerisation had occurred to any extent at all.

Our attention then turned to another linear primary alcohol, (E)-3-phenyl-2-propen-1-ol or cinnamyl alcohol (**55**), and similar results were obtained. Treatment with 2 mol% of Wilkinson's catalyst and acetylation after 18.5 hours gave no isomerised material, only a multi-component mixture containing acetylated and free starting material (scheme 2.2.90).



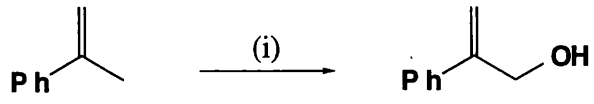
55

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 18.5 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.90

The (E)-geometry of the remaining substrate was unaffected. The thermal instability of the potassium alkoxide of this alcohol has previously been demonstrated in this group, giving numerous oligomeric products.[159] However when the lithium alkoxide was subject to reflux in THF solution for 13 hours, the alcohol was recovered quantitatively and stereochemically unaltered. Thus Wilkinson's catalyst served only to cause the decomposition of the substrate.

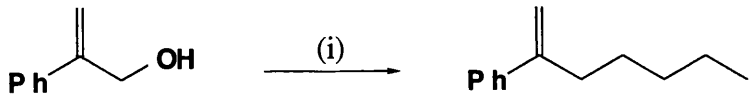
The third primary alcohol studied was 2-phenyl-2-propen-1-ol (**56**), prepared in 49% yield (56% based on a 12% recovery of starting material) by selenium dioxide oxidation of 2-phenylpropene (scheme 2.2.91). This substrate has also been prepared in *ca.* 30% yield by reaction of 1-phenylethenylmagnesium bromide with paraformaldehyde.[160] *tert*-Butyllithium must be used to generate the lithium alkoxide of **56** as a reaction occurs with *n*-butyllithium, equivalent to displacement of hydroxide ion, to give 2-phenyl-1-heptene in *ca.* 44% yield (scheme 2.2.92).[102] It appears that nucleophilic addition to give a benzylic anion occurs at a comparable rate to deprotonation.



56 (56%)

Reagents: (i) SeO_2 (1.5), $^{t}BuO_2H$ (1.5), DCM/2,2,4-trimethylpentane, r.t., 4 h.

Scheme 2.2.91

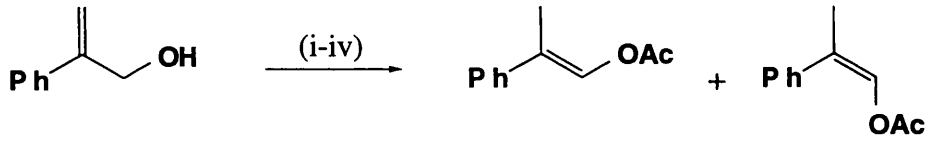


56 (44%)

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C.

Scheme 2.2.92

Isomerisation of the lithium alkoxide of **56** under standard conditions resulted in complete isomerisation in just 40 minutes, half the reaction time of 1-phenyl-2-propen-1-ol and the fastest recorded for any substrate. Acetylation gave the enol acetates **57** and **58** in an excellent combined yield of 83% and in the high ratio **57**:**58**=13:1 (scheme 2.2.93). That the major product was the (E)-isomer, corresponding to a 'cisoid' arrangement of the substrate, was confirmed by nOe experiments (figure 2.19).



13:1

56 **57** (83%) **58**

Reagents: (i) ^{t}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 40 min; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.93

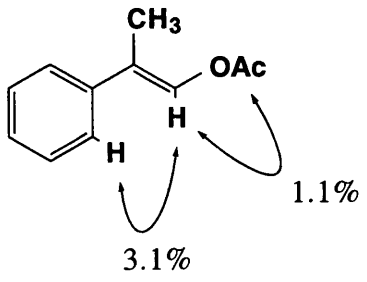
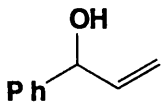
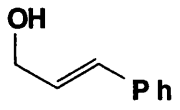


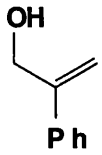
Figure 2.19 – nOe Experiments



1



55



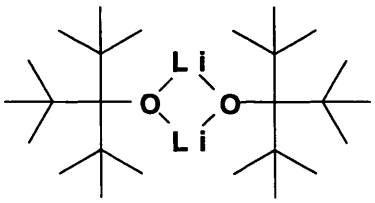
56

The substrate **56** represents the third isomer of an interesting group after alcohols **1** and **55**, each member comprising the allyl alcohol nucleus with a phenyl substituent. Although the vastly different steric requirements will distort the results, they allow some insight into electronic effects in the isomerisation process. Whereas isomerisation of alcohol **1** brings the double bond into cross-conjugation with the phenyl ring and oxygen, alcohol **55** loses the styryl-type conjugation when isomerised. Isomerisation of alcohol **56** brings the oxygen into linear conjugation with the styryl system. However, in all cases a relatively high energy allyl intermediate bears a phenyl substituent and is expected to be stabilised. If the initial oxidative addition is rate determining all three substrates might be expected to react faster than those bearing aliphatic substituents. With alcohol **1**, reductive elimination would kinetically favour the allyl terminus corresponding to isomerisation due to the greater conjugation in the transition state, and **1** is indeed rapidly isomerised. A similar argument applies to alcohol **56**, the most efficiently isomerised of all substrates. With **55** the favoured transition state would correspond to reversion to the starting material, but enolate products from even the slightest reductive elimination in the desired sense would build up due to the expected irreversibility of the isomerisation. As we have seen **55** is totally unreactive in this chemistry, and yet arguably the least hindered, suggesting that there is some other fundamental problem. The isomerisation of the free alcohol **55** with $[Rh(dppe)]^+$ is, in contrast, more rapid than that of the free alcohol **56**.[92]

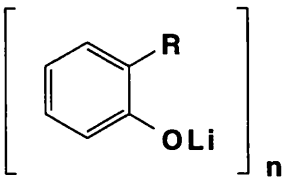
A clear difference between the unsuccessful primary alcohol substrates **54** and **55**, and alcohol **56** which undergoes facile isomerisation, is that the former are linear alcohols and **56** is branched at the C2-position. This is a curious result, since in the series of secondary alcohols studied substitution at the C3-position was greatly

preferred to substitution at C2 (compare substrates **7** and **8** with **40**). However the tendency of the lithium alkoxide of (E)-2-hexen-1-ol (**54**) to precipitate from THF solution suggests an explanation: the less hindered linear alcohols form more extensive aggregates in solution.

It is a common observation that aggregating species form higher oligomers when steric hindrance is minimal, and lower order species when the pendant group is large. This is a reported trend with lithium alkoxides (figure 2.20).[116] Linear alcohols would require a far smaller cone angle to accommodate the organic group than branched alcohols, and a greater number could fit spherically around a central lithium-oxygen framework (figure 2.21). Increasing aggregation would increase the steric crowding around the substrate double-bond, and would be expected to hinder approach of the catalyst and retard isomerisation.

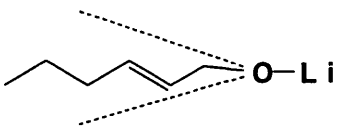


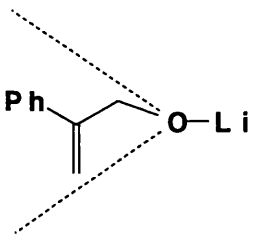
$[LiOC(^tBu)_3]_2$ [116a]



(R = Me, tetramer) [116b]
(R = ^{t}Bu, dimer) [116b]

Figure 2.20





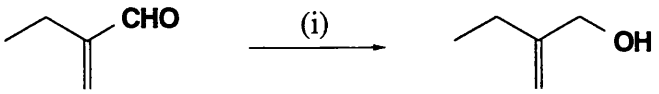
54 (O-Li)

Small cone angle, unreactive

56 (O-Li)

Large cone angle, isomerises

Figure 2.21

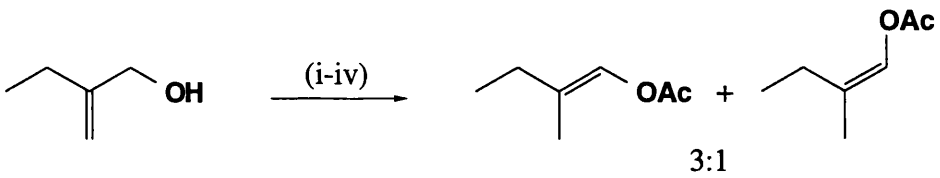


59 (64%)

Reagents: (i) $NaBH_4$ (0.5), $EtOH/H_2O$, 0°C.

Scheme 2.2.94

This theory was tested with a similarly branched, aliphatic alcohol. 2-Ethyl-2-propen-1-ol (**59**) was prepared by reduction of 2-ethylpropenal with sodium borohydride in 64% yield after distillation (scheme 2.2.94). Without the electronic effects resulting from conjugation with the phenyl ring this substrate is more comparable to (E)-2-hexen-1-ol (**54**). Isomerisation was complete under standard conditions in 9 hours, and acetylation gave the enol acetates **60** and **61** in a moderate combined yield of 49% and in the ratio **60**:**61**=3:1 (scheme 2.2.95).



59 **60** (49%) **61**

Reagents: (i) ^nBuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 9 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.2.95

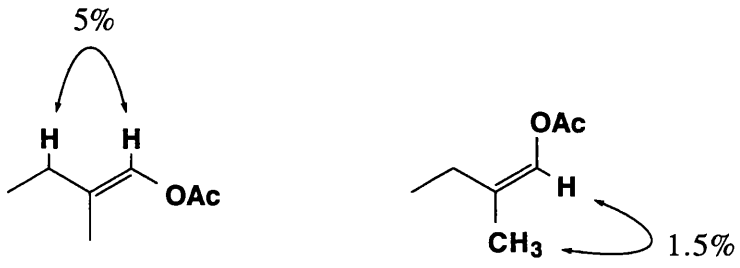
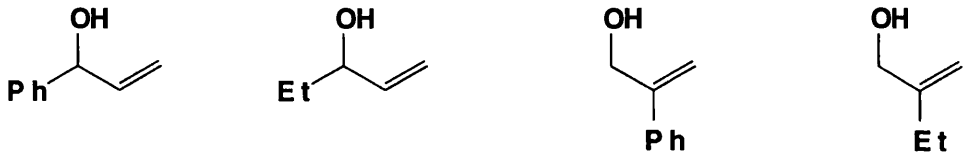


Figure 2.22 – nOe Experiments

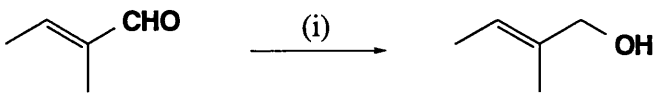


1 (1.5 h) **16** (10 h) **56** (40 min) **59** (9 h)

Figure 2.23 – Required Isomerisation Times

The stereochemistry was assigned on the basis of nOe experiments (figure 2.22). The high volatility of the enol acetate products contributed to the lower yield. The major product corresponds to a 'cisoid' arrangement of the substrate double bond and oxygen, but the selectivity is much lower and suggests equilibration. Again this branched substrate is readily isomerised, the reaction time being comparable to that of 1-penten-3-ol (**16**), an aliphatic secondary alcohol with a similar degree of substitution. The decrease in required reaction time on introducing a phenyl substituent in place of an ethyl was similar in both cases (figure 2.23). Thus, it seems that branching at the C2-position is more responsible for the facile isomerisation of **56** than electronic factors.

The possibility of generating a different ratio of the same enolates from the regioisomeric substrate was tested. (E)-2-Methyl-2-buten-1-ol (**62**) was prepared by lithium aluminium hydride reduction of (E)-2-methyl-2-butenal (scheme 2.2.96).[102] Again this is a branched substrate and so aggregation of the alkoxide should not pose significant problems. However, treatment with Wilkinson's catalyst under standard conditions for 24 hours gave a complex mixture, and acetylation gave no trace of enol acetates by ^{1}H NMR. No identifiable products could be isolated (scheme 2.2.97).



62

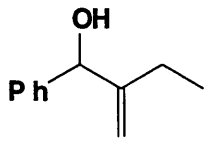
Reagents: (i) $LiAlH_4$, Et_2O, 0°C.

Scheme 2.2.96

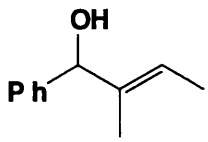
62

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 24 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

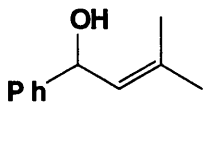
Scheme 2.2.97



40



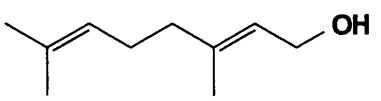
41



53

From a logical point of view, alcohol **62** should be less easily isomerised than the regioisomer **59** by virtue of having a tri-substituted double bond. However, this is in contrast to the secondary alcohol series, in which alcohol **41** is a significantly better substrate than **40** in this chemistry. It seems that primary alcohols display the expected reactivity pattern more closely than the secondary alcohols studied.

The most demanding substrates are those with two substituents at the C3-double bond terminus, such as alcohol **53** which is unreactive to isomerisation with Wilkinson's catalyst. When these two substituents are different a new stereogenic centre is created during isomerisation, and the use of a chiral catalyst can in principle induce asymmetry in the product. Although isomerisation of such a substrate would be difficult, the potential of the process warranted its investigation. Our attention therefore turned to (E)-3,7-dimethylocta-2,6-dien-1-ol (**63**), or geraniol, a naturally occurring achiral alcohol of this type. There was also the added complication of a second, isolated double bond which might isomerise or interfere with the desired process, but this too is tri-substituted and would not generally be prone to a transition metal catalysed side-reaction. Geraniol has been shown to be generally a very poor substrate in related isomerisations.[90,91d,126,161]

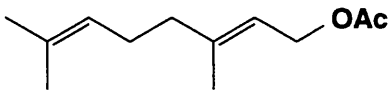


(i-iv) → No Isomerised Products

63

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (2.0 mol%), THF, then reflux 23 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

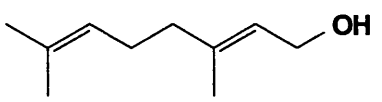
Scheme 2.2.98



64

Treatment with Wilkinson's catalyst under the usual conditions and acetylation after 23 hours gave no identifiable isomerised products, with only starting material (55%) and geranyl acetate **64** (28%) isolated (scheme 2.2.98). It is notable that the signal in the ^{1}H NMR corresponding to the isolated double bond vinylic proton is characteristic of the prenyl group and was significant in all recovered materials, and so it seems this group was unaffected. Geraniol was found to be similarly unreactive using the $[Rh(dppe)]^+$ catalyst.[102]

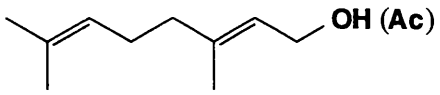
In view of the importance of this substrate to the future aims in this chemistry, several further attempts at isomerisation were made. It was hoped that isomerisation might be promoted by changing of reaction variables such as the alkoxide counter-cation, and the results of several experiments using alternative bases or additives are summarised below (table 2.9). The reaction times are an indication of the stability of the alkoxide, as the reactions were stopped when significant decomposition became apparent. At no time were the desired enol acetates detected, but the product of transfer hydrogenation citronellol (**65**) and the O-acetyl derivative (**66**) were produced in several cases. When present, the proportion of these products relative to the remaining starting material are given.



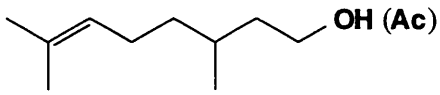
(i-v) → No Isomerised Products

63

Reagents: (i) Base (1.0), THF, 0°C; (ii) Additive (equiv); (iii) $(PPh_3)_3RhCl$ (2%), THF, then reflux (time); (iv) Ac_2O (10), –78°C; (v) $NaHCO_{3(aq)}$.



63 (64)



65 (66)

Entry	Base	Additive (equiv)	Time (hours)	Ratio **(63+64)** : **(65+66)**
1)	^nBuLi	–	23	–
2)	^nBuLi	$SnCl_2$ (0.02)	48	*ca.* 10:1
3)	^nBuLi	$SnCl_2$ (1.0)	48	–
4)	^nBuLi	HMPA (1.0)	24	–
5)	^nBuLi	$Al(O^tBu)_3$ (1.0)	24	–
6)	KH	–	18	*ca.* 1:1
7)	EtMgBr	–	48	–
8)	$(^iBu)_2AlH$	–	48	–

Table 2.9 – Attempted Isomerisation Of Geraniol

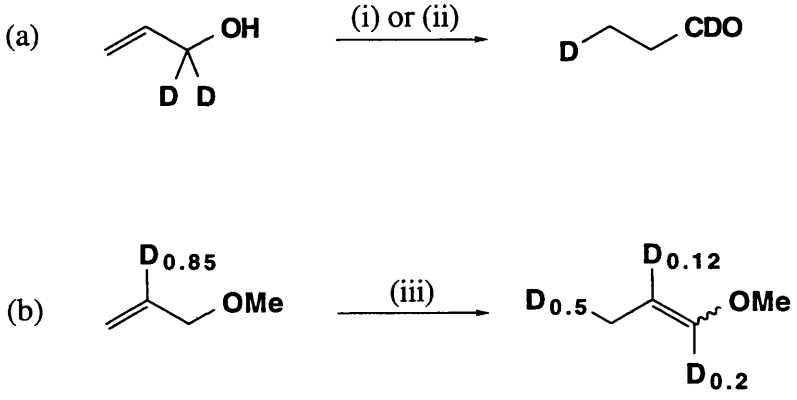
It is proposed that a small quantity of tin (II) chloride acts to modify the rhodium catalyst (table 2.9, entry 2; the additive was in this case added to the catalyst), but this approach was unsuccessful. As it is possible that a tin (II) alkoxide species is involved[162] a stoichiometric quantity was used, also without success. Similarly, metal alkoxides of varying covalency were tested (table 2.9, entries 6-8). It is unproven that

a di-*tert*-butoxyaluminium alkoxide was formed (table 2.9, entry 5), but it is noteworthy that these and magnesium alkoxides (table 2.9, entry 7) are utilised in Oppenauer-type oxidation for readily transferring the carbinolic hydride.[163] The use of HMPA (table 2.9, entry 4) was intended to disrupt aggregation,[164] but as in the case of similar experiments with the $[Rh(dppe)]^+$ catalyst, this had little effect.[102]

As an important and challenging substrate, the inability of Wilkinson's catalyst to isomerise geraniol (**63**) was disappointing, but unsurprising. Very few catalysts can isomerise the free alcohol, and it seems that alkoxides may generally be more demanding substrates. The isomerisation of geraniol represents a benchmark with which to gauge the capability of future catalytic systems.

2.2.8 Deuterium Labelling Experiments

Deuterium labelling has been used previously as a mechanistic probe in allylic isomerisation chemistry, specifically to differentiate between the metal hydride addition-elimination (A) and π-allyl hydride (B) pathways. Isomerisations catalysed by iron pentacarbonyl,[98a] or $[Rh(dppe)]^+$,[92] exhibit a regiospecific 1,3-deuterium migration and are consequently attributed to pathway B (scheme 2.2.99.a). A platinum hydride catalyst for the isomerisation of allyl ethers has, in contrast, been shown to distribute a C-2 deuterium label between all three allylic carbons, and is indicative of multiple metal hydride addition-elimination cycles (mechanism A) (scheme 2.2.99.b).[95c]

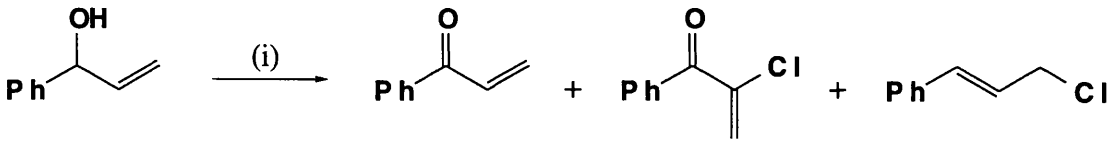


Reagents: (i) $Fe(CO)_5$; (ii) $[Rh(dppe)]^+$; (iii) $HPt(PPh_3)_2(acetone)$.

Scheme 2.2.99

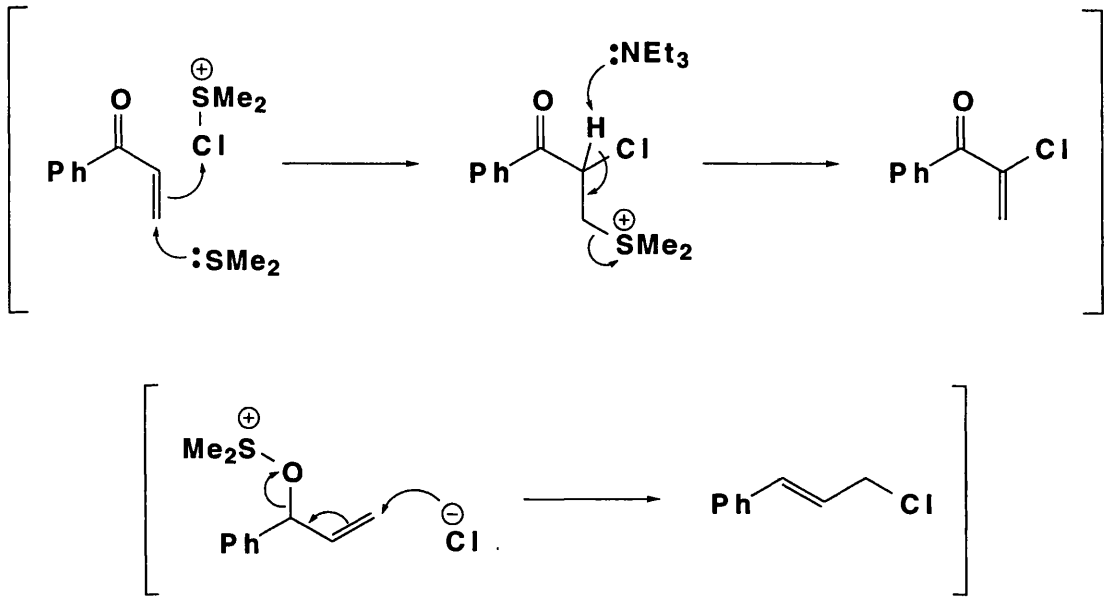
Differentiation between the classical π-allyl hydride pathway and the proposed rhodium alkoxide mechanism is, however, not possible. These two routes are closely related, in simplest terms involving a hydride abstraction–delivery cycle, and would give rise to identical products. Consequently, the similar π-allyl hydride and alkoxide routes are referred to jointly as the 'π-allyl hydride type' mechanism.

In order to perform a similar experiment 1-deuterio-1-phenyl-2-propen-1-ol (**71**) was required, and was prepared from alcohol **1** in two steps.



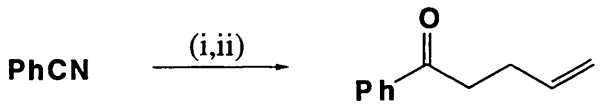
1 **67** (61%) **68** (12%) **69** (2%)

Reagents: (i) $(COCl)_2$, DMSO, NEt_3, DCM, –78°C.



Scheme 2.2.100

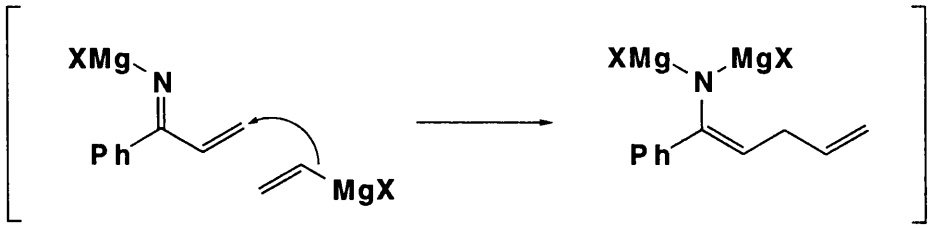
Swern-type oxidation gave 1-phenyl-2-propen-1-one (**67**) in 61% yield, together with chloroketone **68** (12%) and chloroalkene **69** (2%) (scheme 2.2.100). The enone **67** is thermally unstable and polymerises quite rapidly at ambient temperature. An attempt to make enone **67** directly[165] by reaction of vinylmagnesium bromide with benzonitrile led only to a very poor yield of 1-phenyl-4-penten-1-one (**70**) (scheme 2.2.101).



70 (9%)

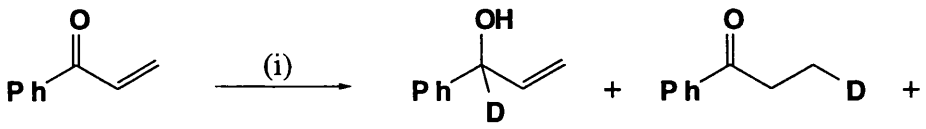
Reagents: (i) Vinylmagnesium bromide, THF/benzene, 10°C to reflux; (ii) $HCl_{(aq)}$.

Scheme 2.2.101

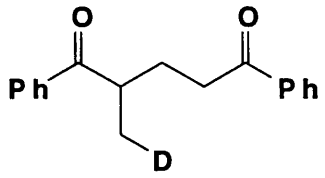


Scheme 2.2.102

A possible mechanism for the formation of **70** is shown (scheme 2.2.102). Reduction of **67** with lithium aluminium deuteride was less successful, giving the desired alcohol **71** in 18% yield (scheme 2.2.103). The major product was that of conjugate reduction **72** (33%), together with diketone **73** (24%).

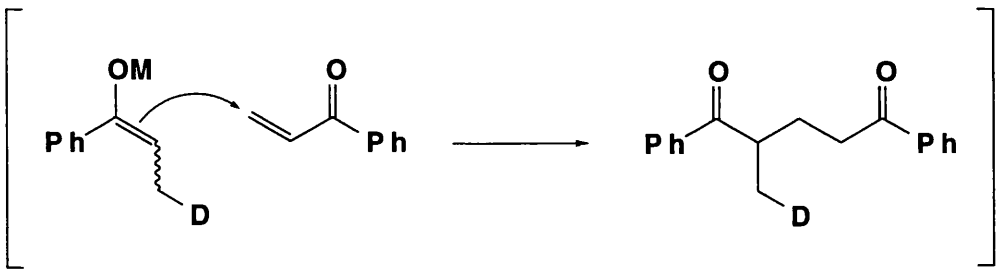


67 **71**(18%) **72**(33%)

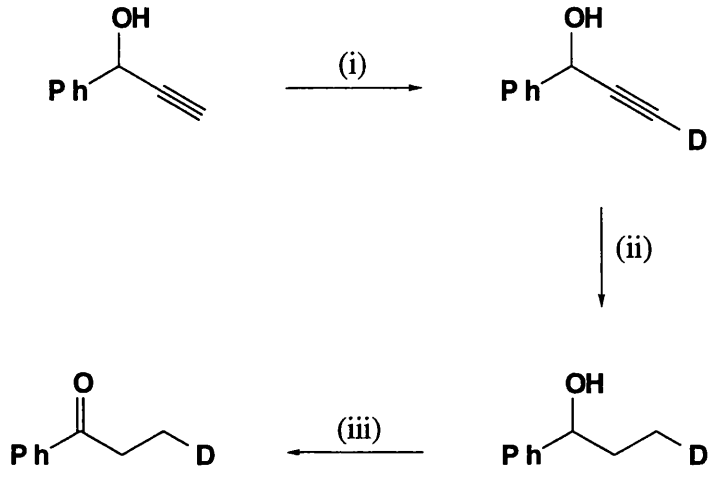


73 (24%)

Reagents: (i) $LiAlD_4$, Et_2O, 0°C.



Scheme 2.2.103



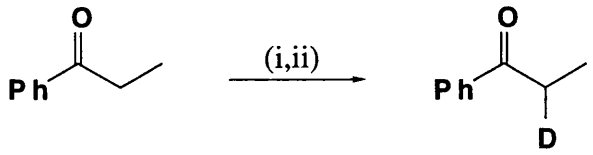
72

Reagents: (i) ^{n}BuLi (2.2), THF, –95°C to –30°C, then D_2O; (ii) H_2, Pd(C), acetone, 20°C; (iii) MnO_2, DCM, 20°C.

Scheme 2.2.104

The two possible monodeuterated isomerisation products were prepared separately by unambiguous routes. Formation of the dianion of 1-phenyl-2-propyn-1-ol by treatment with excess butyllithium and quenching with deuterium oxide gave the 3-deuterio analogue (scheme 2.2.104). Catalytic hydrogenation of the triple bond was achieved using a palladium catalyst supported on charcoal. Benzylic oxidation with manganese dioxide was extremely slow, and was stopped at approximately 50% conversion to give 3-deuterioketone **72** in >90% overall yield, taking into account the recovered intermediate.

2-Deuterio ketone **74** was prepared from propiophenone by treatment with lithium diisopropylamide and quenching the enolate with deuterium oxide (scheme 2.2.105). The degree of deuterium incorporation achieved was low, estimated at approximately 60% by ^{1}H NMR analysis. This was an unforeseen result of a reported phenomenon[33,166] The lithium enolate undergoes aggregate formation with diisopropylamine, and the amine hydrogen-bonds with enolate species such that the hydrogen atom that was initially removed (the amine NH proton) tends to be the one returned to the substrate on hydrolysis.

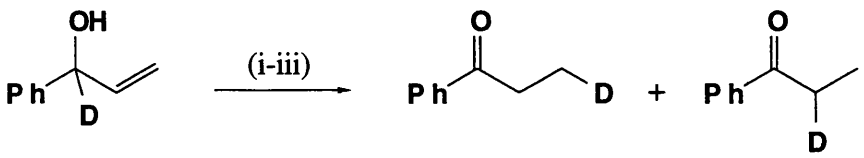


74

Reagents: (i) LDA, THF, –78°C; (ii) Add to D_2O, THF, 0°C.

Scheme 2.2.105

Isomerisation experiments were performed using 10 mol% of catalyst to allow a direct comparison with the equivalent experiments conducted using other catalysts.[102] Isomerisation of alcohol **71** under otherwise standard conditions proceeded rapidly and was quenched with saturated aqueous ammonium chloride after 30 minutes (scheme 2.2.106). The product ketones were isolated in 70% yield, a yield identical to the aldol reaction of the unlabelled substrate using 2 mol% catalyst. These ketone products are sufficiently volatile that a degree of product loss is inevitable (<10%). Analysis by proton-decoupled ^2H NMR reveals one peak only, corresponding to 3-deuterio-1-phenyl-1-propanone (**72**), and indicates a probable π-allyl hydride type mechanism. Regiospecific 1,3-deuterium transfer was also observed using the $[Rh(dppe)]^+$ catalyst for the isomerisation of both a free alcohol (scheme 2.2.99.a),[92] and the lithium alkoxide of substrate **70**.[102]



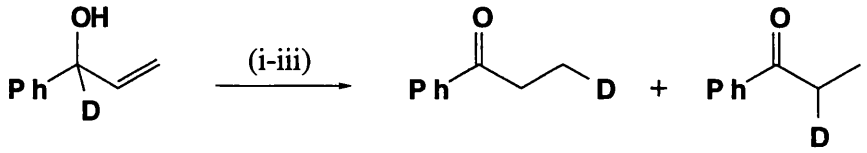
> 50 : 1

70 **72** (70%) **74**

Reagents: (i) ^nBuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl$ (10 mol%), THF, then reflux 30 min.; (iii) $NH_4Cl_{(aq)}$, 0°C.

Scheme 2.2.106

For comparison a second experiment was performed to study the catalyst when modified by excess butyllithium. Isomerisation with 10 mol% Wilkinson's catalyst, pre-treated at 0°C with one equivalent of butyllithium, was again complete within 30 minutes giving product ketones in 66% yield (scheme 2.2.107). In this case analysis by ^2H NMR reveals 3-deuterio-1-phenyl-1-propanone (**72**) to be by far the major product, but with a small quantity of the isomeric 2-deuterio-1-phenyl-1-propanone (**74**) also present.



≈ 30 : 1

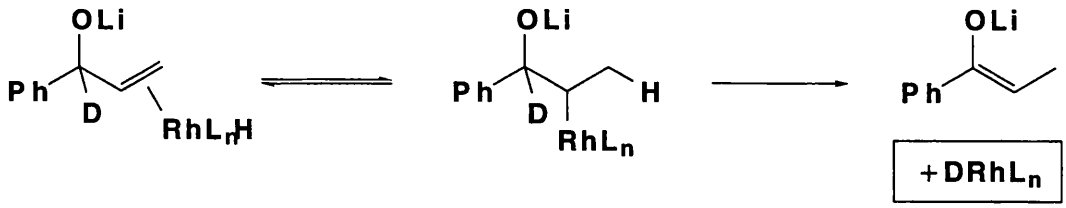
71 **72** (66%) **74**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PPh_3)_3RhCl/^n$BuLi (10 mol%), THF, then reflux 30 min.; (iii) $NH_4Cl_{(aq)}$, 0°C.

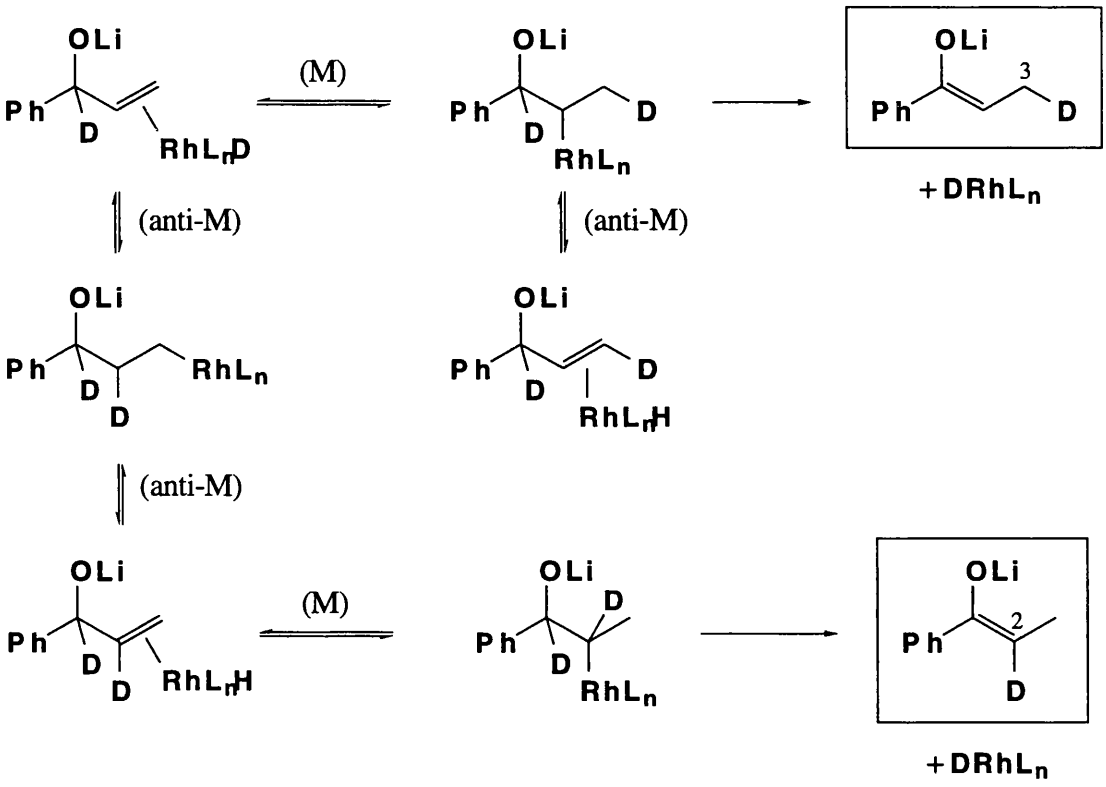
Scheme 2.2.107

Integration gives the ratio **72**:**74**≈30:1. This highly selective 1,3-migration of the deuterium label again indicates a probable π-allyl hydride type mechanism, but the small proportion of ketone (**74**) detected can only arise through mechanism A. It is most likely that reaction of butyllithium with Wilkinson's catalyst initially gives hydridic products,[132] and therefore surprising that a greater dependence on the hydrometallation route is not observed. It was earlier suggested that colloidal rhodium may be involved, in light of the deposition of the metal when excess butyllithium was employed. In such a case scrambling of the deuterium label would be expected to some extent, but the situation is less clear.

Isomerisation *via* a hydrometallation process (A) must result in elimination of a rhodium deuteride species (scheme 2.2.108). Reaction with a further molecule of substrate can then occur in two ways.



Scheme 2.2.108



(M) = 'Markovnikov' Hydrometallation
(anti-M) = 'Anti-Markovnikov' Hydrometallation

Scheme 2.2.109

Markovnikov addition produces a 2-metallated intermediate which can only revert to the starting materials or eliminate to give the enolate product; elimination to give a 1,3-di-deuterio alkoxide product serves no purpose (scheme 2.2.109). However anti-Markovnikov addition produces a 3-metallated species, which can revert with approximately equal likelihood either to the starting materials, or a 1,2-dideuterio

starting material-hydride complex. Thus, deuterium is incorporated into the 2-position, and isomerisation now gives the 2-deuterio enolate. Importantly, the Markovnikov addition route is the more favoured due to steric effects,[95c,167] and several Markovnikov addition-elimination cycles would usually occur with each substrate molecule prior to isomerisation. Isomerisation solely by the metal hydride mechanism (A) would give roughly equal proportions of 2-deuterio and 3-deuterio products. This reaction scheme requires the unlikely assumption that the catalyst-substrate complex does not dissociate prior to formation of the enolate. Dissociation would allow 'crossover', and the formation of undeuterated, and di- and trideuterated products (figure 2.24) which would be hard to differentiate from the monodeuterio products. However similar arguments would still apply, and the essentially specific formation of 3-deuterio products in both isomerisations is thus indicative of a π-allyl hydride type mechanism (B).

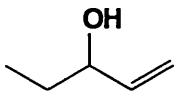
It is again emphasised that these experiments cannot differentiate between the π-allyl hydride mechanism and the closely related rhodium alkoxide mechanism. Both may be considered to be 'π-allyl hydride type' mechanisms and only differentiation between either one of these routes and the hydrometallation mechanism is possible.

Figure 2.24

2.2.9 Conclusions

We have shown that Wilkinson's catalyst efficiently catalyses the isomerisation of allylic alkoxides to generate lithium enolates in good yields and frequently with high stereoselectivity, and that the enolates produced in this way undergo the standard reactions with various electrophiles. In particular, the preparation of trisubstituted enolates provides the (Z)-isomer in a stereospecific way. With the α-phenyl alcohol substrates a similar level of selectivity can be attained using kinetic deprotonation techniques, but the isomerisation of 1-penten-3-ol (**15**) also provides the (Z)-stereoisomer, in contrast to kinetic deprotonation (scheme 2.2.18).[13] As expected, increasing double bond substitution slows the rate of isomerisation, whilst benzylic activation of the migrating hydrogen increases the rate of the process. However the alkoxide was not as reactive as was initially hoped. It was envisaged that an increase negative charge on oxygen would benefit isomerisation as a consequence of an 'oxy-anion' effect,[159] but this was not the case, possibly as a result of alkoxide aggregation. Isomerisation with Wilkinson's catalyst therefore follows very similar trends to those found in earlier studies using the $[Rh(dppe)]^+$ catalyst.[102,108]

Unwanted equilibration of enolate regioisomers was observed using both of these catalysts. Although the use of large excesses of butyllithium with Wilkinson's catalyst effectively halts the process, destruction of the catalyst and incomplete conversion of the substrate results. The mechanism of equilibration is uncertain, but a number of experiments have suggested that this may be an unavoidable consequence of using these rhodium catalysts. At no time was equilibration prevented using the $[Rh(dppe)]^+$ catalyst.



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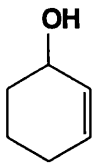

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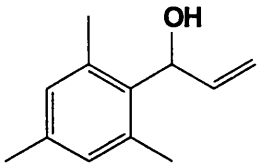


25

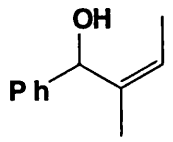
Although the preparation of tetrasubstituted enolates suffered poor stereoselectivity, this was in fact a similar degree of control to that encountered with kinetic deprotonation techniques, and in a complementary sense. Generation of the same stereochemical mixture of tetrasubstituted enolates irrespective of substrate regiochemistry or stereochemistry suggests a common intermediate in the isomerisation process, and once again mirrored our experience with the $[Rh(dppe)]^+$ catalyst. It was shown, however, that enolate stereochemistry was unaffected by treatment of a pre-formed mixture with Wilkinson's catalyst.

The regiospecific 1,3-migration of hydrogen has been demonstrated by experiments with a deuterium-labelled substrate, and a hydridorhodium catalytic species is discounted as a result. It has been proposed that isomerisation proceeds via a rhodium alkoxide, a mechanism consistent with this observation. The formation of a rhodium alkoxide species from Wilkinson's catalyst has been proposed previously,[129] and such an intermediate would explain the extremely poor reactivity of the cyclic substrate 2-cyclohexen-1-ol (**21**) (scheme 2.2.33). The consequent formation of a rhodium enolate could also rationalise the observed stereoselectivity. Selective formation of the (Z)-stereoisomer is expected under thermodynamic control, but alcohol **25** favours the (E)-enolate product (scheme 2.2.36), an observation most readily explained by interconversion of rhodium η^3-enolate stereoisomers.[138] This precedented fluxional behaviour similarly explains the substrate-independent formation of a stereochemical mixture of tetrasubstituted enolates. Comparable results have been obtained using the $[Rh(dppe)]^+$ catalyst, with 2-cyclohexen-1-ol (**21**) again resisting isomerisation completely. It is notable that formation of a rhodium alkoxide from the $[Rh(dppe)]^+$ catalyst is expected to be more facile, and a similar mechanism must be

considered in this case also.

The most dramatic differences between $[Rh(dppe)]^+$ and Wilkinson's catalyst were in the isomerisation of primary alcohols. $[Rh(dppe)]^+$ catalyses isomerisation of several primary alkoxides which are completely unreactive towards Wilkinson's catalyst, while branched substrates are isomerised in both cases. This has been attributed to aggregation phenomena; it is possible that the cationic catalyst can more readily 'abstract' a substrate molecule from these oligomers.

Despite a great many similarities between the two rhodium catalysts, comparison of yields and reaction times reveals unpredictable variations. In particular, Wilkinson's catalyst seems to be less susceptible to increasing bond substitution. Substrate **42**, for example, provides a *ca.* 50% yield of isomerised materials after 16 hours at reflux using 2 mol% of Wilkinson's catalyst (scheme 2.2.75), but is totally unreactive towards even 10 mol% of $[Rh(dppe)]^+$ after 24 hours.[102]



42

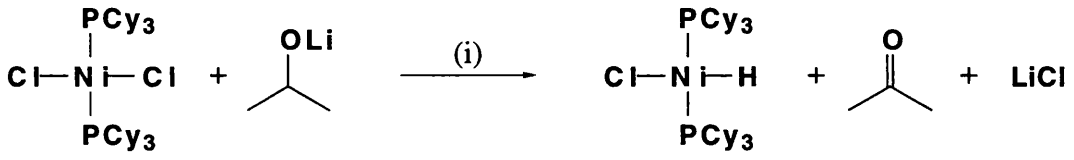
Wilkinson's catalyst therefore offers a viable and effective alternative to $[Rh(dppe)]^+$. From the practical point of view, Wilkinson's catalyst is far more easily prepared and used, requiring no *in situ* hydrogenation step to generate the active species. Although Schlenk-line techniques have been employed throughout this investigation to ensure the maximum efficiency, it is likely that simpler, more conventional handling procedures will also prove to be acceptable when using Wilkinson's catalyst. This study has both expanded the earlier methodology and allowed further insight into this isomerisation process.

2.3

Nickel Catalysed Isomerisation

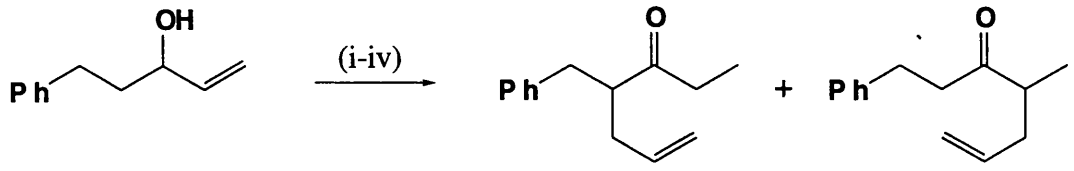
2.3.1 Introduction

The study of nickel catalysts in this group was originally prompted by the reported synthetic reduction of a nickel-phosphine complex with a lithium alkoxide.[168] Treatment of dichlorobis(tricyclohexylphosphine)nickel (II)[169] with lithium isopropoxide resulted in transfer of the carbinolic hydride, to give chlorohydridobis-(tricyclohexylphosphine)nickel (II)[169a,170] (scheme 2.3.1). It was envisaged that in a similar reaction using an allylic alkoxide, return of hydride to the substrate might proceed to constitute isomerisation. This complex has since been shown to be an effective catalyst in this chemistry.[102,171] It was further discovered that when the dichloro complex was pre-treated with either one or two equivalents of butyllithium, catalyst solutions of far greater activity were produced. Most importantly of all, enolate regiochemistry could be effectively controlled for the first time (scheme 2.3.2).



Reagents: (i) Toluene/THF, 70–80°C.

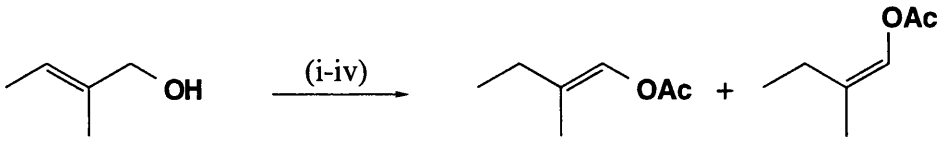
Scheme 2.3.1



33 **34** **35**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $(PCy_3)_2NiCl_2/^{n}$BuLi (10%), THF, then reflux; (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.3.2



62 **60** **61**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) (Catalyst), THF, then reflux; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Catalyst, reflux time	Ratio **60:61**	Yield (%) **60+61**
1)	$(PPh_3)_3RhCl$ (2%), 24 h	–	0
2)	$[Rh(dppe)]^+$ (5%), 1 h	3:1	46
3)	$(PCy_3)_2NiCl_2$ / ^{n}BuLi (10%), 4 h	3:1	53
4)	$(PCy_3)_2NiCl_2$ / 2^{n}BuLi (10%), 3 h	1:1.7	58

Table 2.10 – Comparison Of Catalyst Systems

The reactivity, and especially the stereoselectivity, varied depending on the quantity of organolithium used in the activation step, and was superior to that using the rhodium catalysts or the dichloro complex alone (table 2.10).[102] The equivalent complexes of other phosphines were less effective, giving generally lower yields and selectivities, and the complex $(dppe)NiCl_2$, bearing a chelating diphosphine ligand, was shown to be inactive in this chemistry.

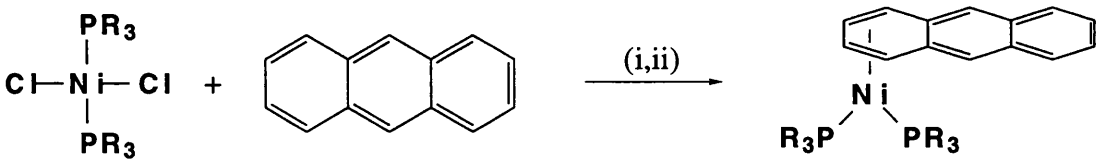
The second important discovery was that the nickel-based catalyst systems would isomerise geraniol (**63**). Geraniol has been shown to be a very demanding substrate in transition metal catalysed allylic isomerisation, with the trisubstituted double bond providing considerable steric crowding around the metal centre. There have been several reported attempts to isomerise the free alcohol, with varying degrees of success (table 2.11), but most catalytic systems show no significant activity.

63 **64**

Entry	Catalyst system	Yield of **64** (%)
1)[126]	$Cp(PPh_3)_2RuCl$ (5%), $Et_3NH^+Cl^-$	0
2)[91d]	$[Ir(cod)(PPh_2Me)_2]^+PF_6^-$ (0.5%)	14
3)[90,161]	$[Rh(cod)(BINAP)]^+$ (1%)	70

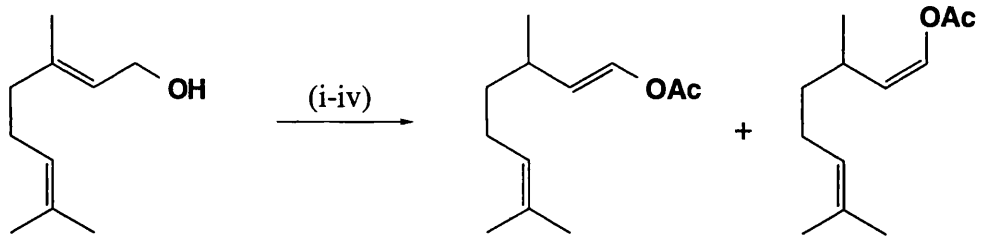
Table 2.11 – Isomerisation Of Geraniol

The nickel-tricyclohexylphosphine catalyst systems effectively isomerised the lithium alkoxide of geraniol, and the use of two equivalents of butyllithium resulted in higher selectivity (table 2.12).[102] Consideration of this mechanism of activation led to the conclusion that a nickel (0) complex might be the active species, and the recently reported synthesis of (π-arene)bis(phosphine)nickel (0) complexes added credence to this theory. Thus, treatment of dichlorobis(phosphine)nickel (II) complexes in the presence of the arene with two equivalents of methyllithium resulted in reduction (scheme 2.3.3).[172] Notably, this reaction was general with monophosphines but was not applicable to the chelating diphosphine ligand 1,2-bis(diethylphosphino)ethane.



Reagents: (i) MeLi (2.0), THF, –78°C; (ii) hν, *ca.* –50°C or Δ, 25°C, 1-3 h.

Scheme 2.3.3



63 **75** **76**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) (Catalyst), THF, then reflux; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Catalyst, reflux time	Ratio **75:76**	Yield (%) **75+76**
1)	$(PCy_3)_2NiCl_2$ / ^{n}BuLi (10%), 6 h	3.8:1	69
2)	$(PCy_3)_2NiCl_2$ / 2^{n}BuLi (10%), 6 h	10:1	52
3)	$Ni(cod)_2$ (20%), 3 h	4:1	75

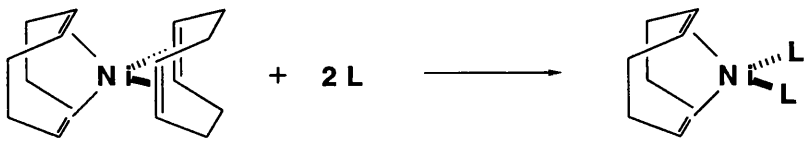
Table 2.12 – Isomerisation Of The Lithium Alkoxide Of Geraniol

It is suggested that reductive elimination of ethane from (dppe)$NiMe_2$ does not occur, and that nickel (0) is not formed. Similar behaviour would explain the inactivity of the (dppe)$NiCl_2$ catalytic system when treated with two equivalents of butyllithium.

It was subsequently found that bis(1,5-cyclooctadiene)nickel (0) alone, a nickel (0) olefin complex, effectively isomerised the lithium alkoxide of geraniol (table 2.12, entry 3).[102] $Ni(cod)_2$ has been shown to undergo ligand exchange with phosphines, yielding nickel (0) phosphine complexes.[173] With this clean and unambiguous route to nickel (0) species we could embark upon a study of the properties of various nickel (0) catalysts in this chemistry. Furthermore, since this approach is equally applicable to chelating diphosphines,[173b,c] we could generate chiral nickel (0) catalysts with the C2-symmetry most frequently successful in asymmetric induction,[174] and apply them to the asymmetric isomerisation of geraniol.

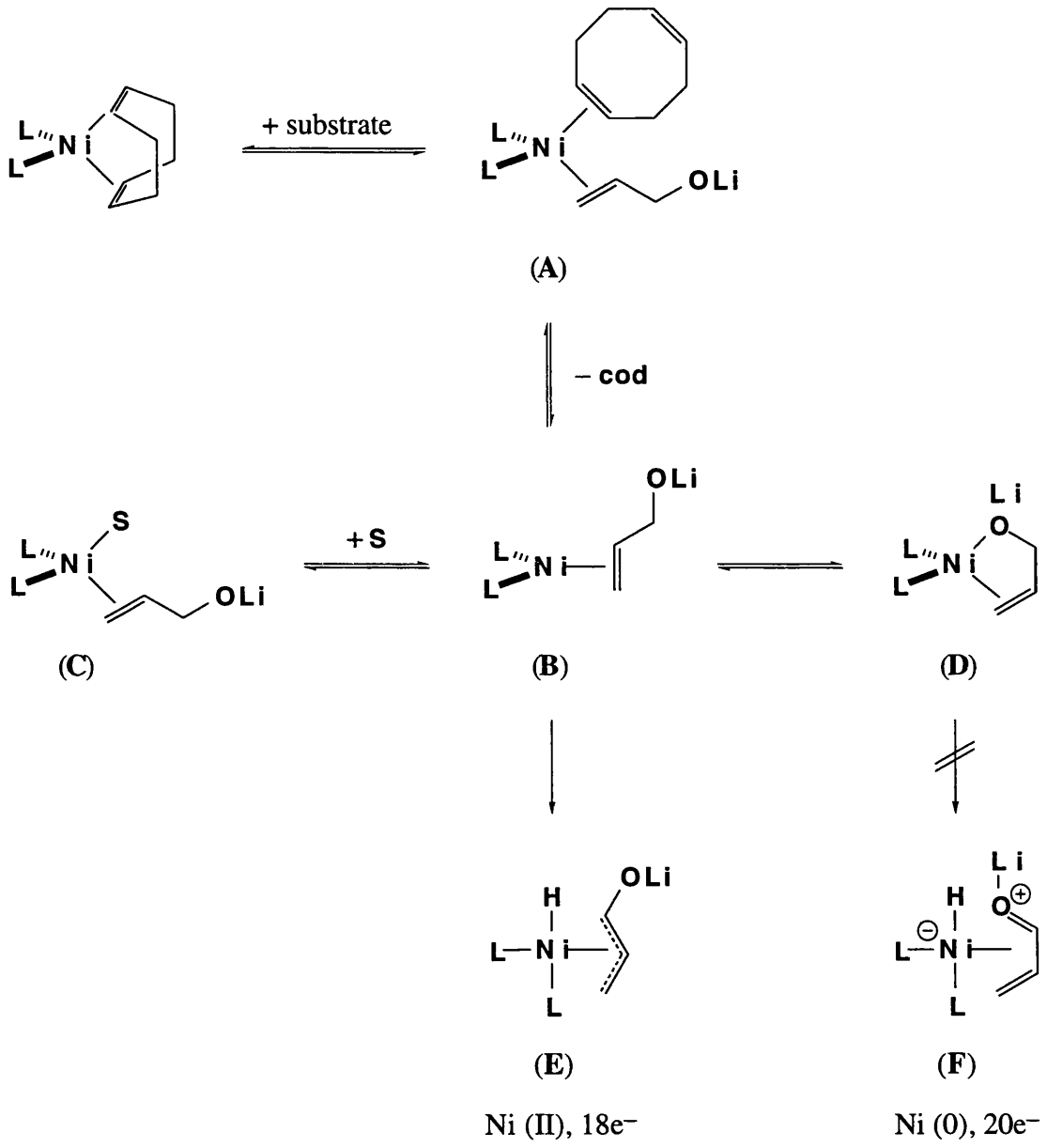
As potential catalysts in this isomerisation methodology, nickel (0) species differ in several ways from the rhodium (I) complexes studied previously. Wilkinson's catalyst is a square-planar, sixteen-electron complex. In contrast nickel (0) is a neutral d^{10} species, with the tendency to accept four ligands to give an electronically saturated eighteen-electron NiL_4 complex. Such complexes exhibit tetrahedral geometry,[173a] and because of the electron-rich nature of the metal centre strongly π-acidic ligands are favoured. In the starting complex $Ni(cod)_2$, the olefin ligands have poor electron-accepting properties and thermal decomposition to give elemental 'black nickel' occurs readily, but species generated from $Ni(cod)_2$ and more strongly π-acidic ligands are far more stable.[175]

Because of the eighteen-electron configuration, ligand exchange proceeds via a dissociative or concerted mechanism. Exchange with two added ligands generates the catalyst and leaves the second readily displaced 'cod' ligand occupying two coordination sites (scheme 2.3.4).



Scheme 2.3.4

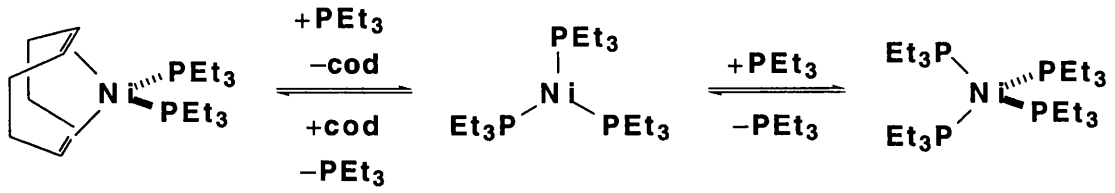
Introduction of the alkoxide requires displacement of this second 'cod' ligand, which will be disfavoured due to a chelate effect but aided by the greater quantity of substrate present. Subsequent dissociation of the monodentate 'cod' ligand then leaves a three coordinate, sixteen electron intermediate (**B**) which is capable of undergoing isomerisation (scheme 2.3.5). It is notable that electronic unsaturation is a requirement for oxidative addition of the carbinolic carbon-hydrogen bond, and consequently coordination of a second molecule of the substrate, a solvent molecule or 'cod' (**A** or **C**) will temporarily block the isomerisation process.



(**S** = solvent, or another molecule of substrate; **cod** = 1,5-cyclooctadiene)

Scheme 2.3.5

It is also apparent that chelation of the substrate through oxygen will form an electronically saturated complex (**D**). Isomerisation via such a chelate would produce a twenty electron π-(1-oxabutadiene) hydride type intermediate (**F**) and is extremely unlikely. However, due to the highly reduced state of the nickel centre, coordination of weak π-acid ligands is disfavoured and the formation of three- or even two-coordinate intermediates occurs readily. A number of such equilibria have been reported (scheme 2.3.6),[173c,176] including those of tricyclohexylphosphine-nickel (0) systems.[103]

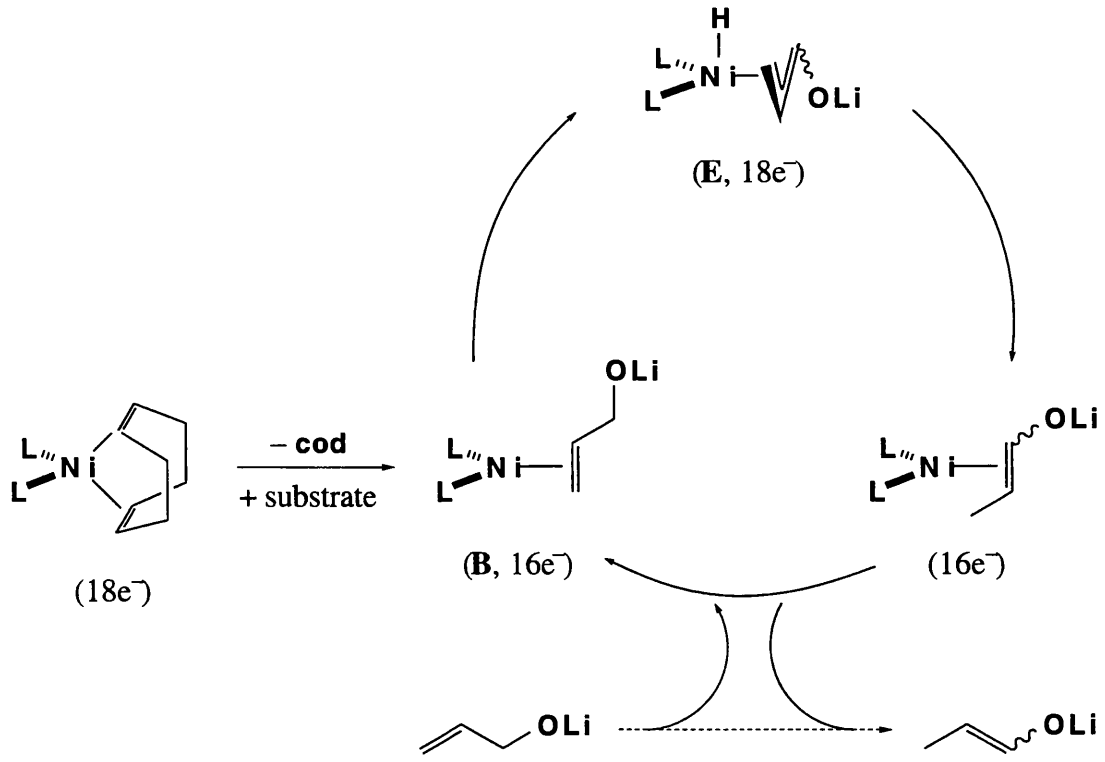


18e⁻ 16e⁻ 18e⁻

(Orange) (Purple, ambient temperature) (White, –20°C)

Scheme 2.3.6

In the case of tricyclohexylphosphine however, formation of the tetrakis(phosphine) nickel (0) complex is prevented by the extreme steric bulk of this phosphine ligand[177b] (the cone angle has been estimated as *ca.* 180°).[178] Clearly, as nickel (0) is neutral and coordination of a 'free' alkoxide anion is very unlikely, the alkoxide mechanism discussed previously is not possible. Thus a classical π-allyl hydride mechanism is postulated (scheme 2.3.7).



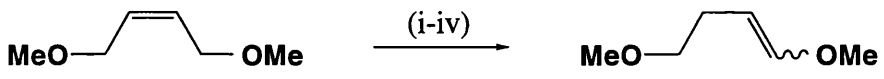
Scheme 2.3.7 – Proposed Isomerisation Mechanism

The proposed π-allyl hydride intermediate (**E**) is assumed to be square-pyramidal as this geometry is most common for complexes of the type $(\eta^3\text{-allyl})NiL_2X$.[179]

Nickel (0) catalysts have found wide utility in olefin oligomerisation and similar processes,[180] but olefin isomerisation has commonly been achieved using nickel (I) or hydrido-nickel (II) species.[181] It has also been proposed that the nickel (I) catalysts serve only as precursors to nickel (II) hydride species by reaction with the alkene substrate (scheme 2.3.8).[181a] The preference for non-hydridic catalysts in this chemistry was discussed earlier.

Scheme 2.3.8

The isomerisation of allylic compounds has been reported for only hydrido-nickel (II) catalysts. Lochow and Miller found that chlorohydridobis(tri-*o*-tolylphosphite)nickel (II), generated *in situ* from ethylenebis(tri-*o*-tolylphosphite)nickel (0) and hydrogen chloride, isomerised allylic alcohols to the corresponding carbonyl compounds.[181b] The same catalyst also isomerised isolated alkenes and allyl phenyl ether. Recently, Malanga and co-workers demonstrated that 2-butene-1,4-diol derivatives were isomerised to the corresponding enolic acetals using a catalyst prepared by reduction of dichloro-[1,2-bis(diphenylphosphino)ethane]nickel (II) (scheme 2.3.9).[182]



(100%)

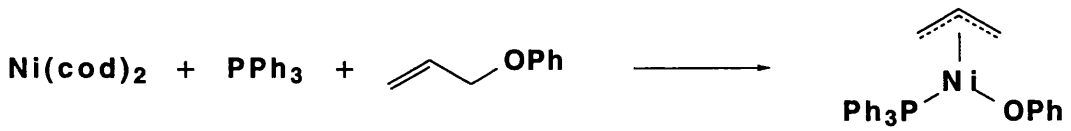
Reagents: (i) $Ni(dppe)Cl_2$ (2%), THF, 0°C; (ii) ^iPrMgBr (4%), THF, r.t.; (iii) TMSCl (1%), r.t., "a few seconds"; (iv) $NH_4Cl_{(aq)}$.

Scheme 2.3.9

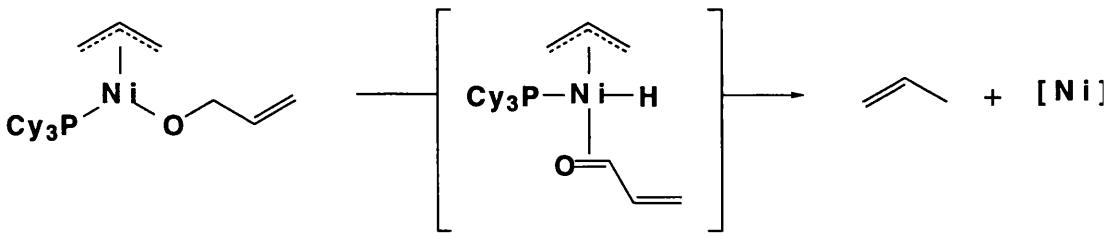
This reaction is remarkable in that isomerisation apparently proceeds to completion in only "a few seconds" at ambient temperature following addition of trimethylsilyl chloride. This procedure is not applicable to allylic alkoxides or simple allyl ethers.[183]

Investigations involving the treatment of allylic ethers with nickel (0) species resulted not in isomerisation but C-O bond cleavage. Treatment of allyl phenyl ether with $Ni(cod)_2$ and triphenylphosphine produces (η^3-allyl)phenoxytriphenylphosphine-nickel (II) (scheme 2.3.10).[184] Similar products are obtained using $Ni(PPh_3)_4$ or $Ni(cod)_2$ alone.[185] The corresponding complex derived from diallyl ether is thermally unstable, giving propene and unidentified nickel products (scheme 2.3.11).[184] Interestingly, this is presumably a result of carbinolic hydride abstraction from the allylic alkoxide.

Thus, to our knowledge, allylic isomerisation with a nickel (0) catalyst has been achieved for the first time with $Ni(cod)_2$ and the lithium alkoxide of geraniol, assuming that no drastic alteration of the catalyst occurred during the reaction.[102] It was therefore our intention to investigate a variety of nickel (0) catalysts bearing alternative ligands.



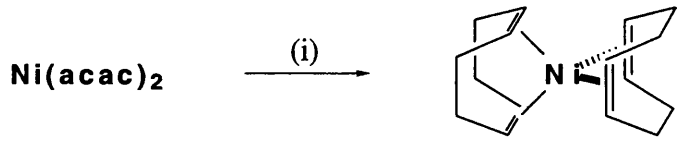
Scheme 2.3.10



Scheme 2.3.11

2.3.2 Nickel-Phosphine Catalysts

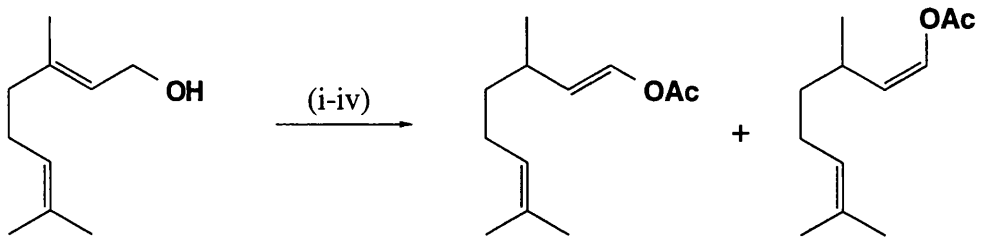
Bis(1,5-cyclooctadiene)nickel (0)[186] was prepared by the improved procedure recently reported by Krysan and Mackenzie.[186a] Treatment of bis(acetylacetonate)-nickel (II) with diisobutylaluminium hydride in the presence of 1,5-cyclooctadiene gives $Ni(cod)_2$ in approximately 70% yield (scheme 2.3.12). Subsequent recrystallisations allow recoveries of only 40-50% but are required to give a pure, stable product. Storage at –40°C in a fully equipped glove-box is then possible for several months.



Reagents: (i) $(^{i}Bu)_2AlH$ (2.5), 1,5-cyclooctadiene (4.0), THF, –78° to 0°C.

Scheme 2.3.12

Our initial aim was to prepare nickel (0) complexes of tricyclohexylphosphine, which may be the active species generated in the earlier work. The required 10 mol% of $Ni(cod)_2$ was weighed into Schlenk glassware in a glove-box, sealed and immediately cooled to –78°C. A degassed THF solution of two equivalents of tricyclohexylphosphine (20 mol%) was then transferred to the solid, and the mixture was allowed to warm to ambient temperature. In this way the thermally sensitive $Ni(cod)_2$ was intercepted by the stabilising ligand at the lowest possible temperature as it dissolved, giving a pale yellow solution. Initially, it was hoped that the cyclooctadiene could be effectively removed by hydrogenation of the phosphine complex in a process analogous to that with $[Rh(dppe)(cod)]^+$.[101] When the solution was subjected to a low positive pressure of hydrogen (*ca.* 30 mbar) for 20 minutes the colour gradually became dark orange-brown.



5.4:1

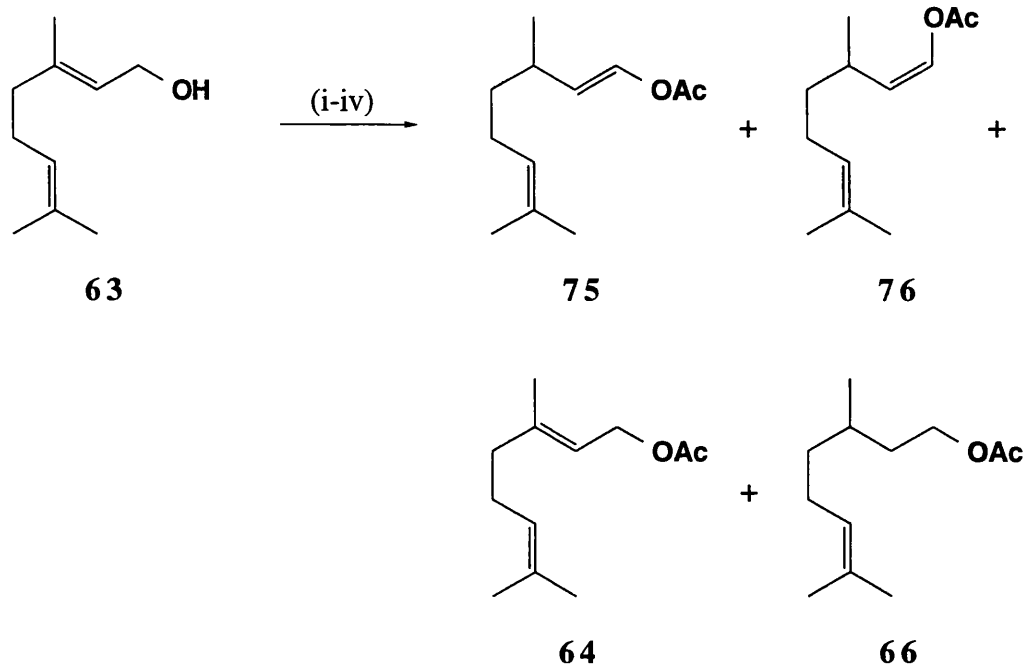
63 **75** (69%) **76**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $Ni(cod)_2/2PCy_3$ (10 mol%)/H_2 (20 min), THF, then reflux 26 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.3.13

Treatment of the lithium alkoxide of geraniol (**63**) in THF with this catalyst solution at reflux resulted in successful isomerisation in 26 hours. Quench with acetic anhydride as before gave, after chromatography, the enol acetates **75** and **76** in a combined yield of 69% and in the ratio **75**:**76**=5.4:1, with no other identifiable products isolated (scheme 2.3.13; table 2.13, entry 1). Stereochemical assignment of these products has been previously made,[187] and as with the earlier nickel catalysts the thermodynamically favoured (E)-isomer was predominant. Comparison with reactions using $Ni(cod)_2$ alone or $(Cy_3P)_2NiCl_2$ with one equivalent of butyllithium (table 2.12) indicates similar yields and superior stereoselectivity, and although $(Cy_3P)_2NiCl_2$ in conjunction with two equivalents of butyllithium was a more selective catalyst (**75**:**76**=10:1) a lower yield was isolated (52%).[102]

In all cases these earlier catalysts were considerably faster, and so twice the quantity of catalyst was employed. In light of the relatively slow colour change under a hydrogen atmosphere, the reaction was repeated with a slightly longer hydrogenation time. Using 20 mol% of $Ni(cod)_2/2PCy_3$ but hydrogenating at the same positive pressure for 30 minutes, reflux for 6 hours produced the enol acetates in only 22% yield but in the higher ratio **75**:**76**=10:1 (table 2.13, entry 2). The hydrogenated product citronellyl acetate (**66**) (8%) and acetylated starting material **64** (2%) were also isolated.



63 **75** **76**

64 **66**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $Ni(cod)_2$ (mol%)/PCy_3 (equiv)/H_2 (min), THF, then reflux (hours); (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	$Ni(cod)_2$ (mol%)	PCy_3 (equiv)	H_2 (min)	Reflux (hours)	Isolated Yields (%) **75+76**	**(75:76)**	**64**	**66**
1)	10	2	20	26	69	(5.4:1)	–	–
2)	20	2	30	6	22	(10:1)	2	8
3)	20	2	30	36	–	–	–	–
4)	20	2	–	1.75	65	(7.6:1)	–	–
5)	20	1	–	18	23	(4.4:1)	–	–

Table 2.13 – Effect Of Catalyst Hydrogenation

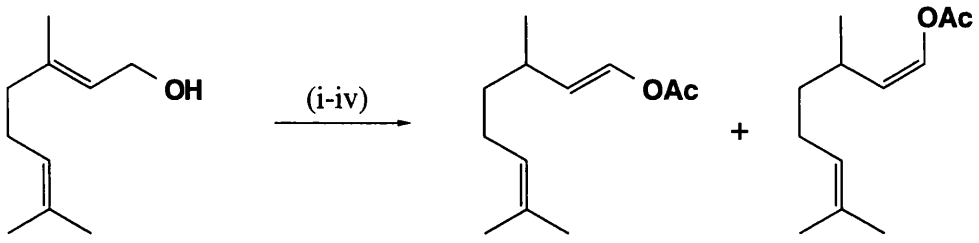
Reflux for 36 hours under identical conditions gave no identifiable products (table 2.13, entry 3). After hydrogenation for 30 minutes the catalyst solution was black.

From this survey it seemed that hydrogenation might be detrimental to catalytic activity, and worse, that a degree of capriciousness was evident. An experiment using

20 mol% of $Ni(cod)_2/2PCy_3$ but without prior hydrogenation was conducted, and isomerisation proceeded to completion in just 1.75 hours to yield the enol acetates in 65% yield and in the ratio **75**:**76**=7.6:1 (table 2.13, entry 4). Although the yield was lower than that for $Ni(cod)_2$ alone (75%), the stereoselectivity was superior, and the rate of isomerisation was roughly doubled. This was in fact the most active isomerisation catalyst yet discovered, and prior hydrogenation of the catalyst was accordingly abandoned in subsequent reactions.

It was postulated that dissociation of one phosphine ligand might precede isomerisation, in view of the large cone angle of tricyclohexylphosphine (*ca.* 180°).[178] However, the catalyst prepared from $Ni(cod)_2$ and one equivalent of PCy_3 was far less active. Isomerisation required 18 hours, and the enol acetates were isolated in just 23% yield and in the lower ratio **75**:**76**=4.4:1 (table 2.13, entry 5).

Having demonstrated the efficiency of nickel (0) catalysts in this approach, our attention then turned to chelating diphosphine ligands. Treatment of geraniol lithium alkoxide with an orange-yellow solution of $Ni(cod)_2$ and 1,2-bis(diphenylphosphino)-ethane ('dppe') at reflux for 10 hours produced a complex mixture after acetylation. The ligand was removed by crystallisation from the crude mixture, and crude ^1H NMR indicated the presence of the enol acetates in the ratio **75**:**76**=3.2:1 (scheme 2.3.14).



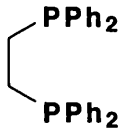
63 **75** (*ca.* 20%) **76**

Reagents: (i) ^nBuLi (1.0), THF, 0°C; (ii) $Ni(cod)_2$/dppe (20 mol%), THF, then reflux 10 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

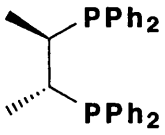
Scheme 2.3.14

Extensive chromatography gave an impure mixture of **75** and **76** in 20% estimated yield and the same ratio. Clearly 'dppe' is a poor ligand in comparison to tricyclohexylphosphine in this chemistry. It has far less steric bulk, and as a bidentate ligand there is an enforced *cis*-arrangement and a chelate effect. It is therefore probable that either a *trans*-arrangement or, more likely, that phosphine dissociation to give a further coordination site is required.

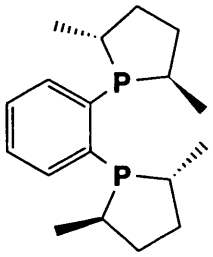
Despite this disappointing result we continued by investigating chiral diphosphine ligands. A number of chiral monophosphine ligands have been reported,[188] but with metal-phosphine bond rotation barriers typically in the range 7.6-9.1 kcal.mol^{-1},[189] a number of conformers are available. The steric interactions required to differentiate between the diastereomeric intermediates tend to be minimised, and the degree of asymmetric induction using such ligands has generally been low.[188] By using C2-symmetrical, bidentate ligands a single conformation can be enforced. Five such commercially available ligands were therefore selected for study.



dppe

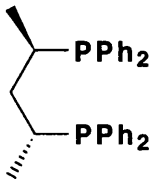


(*S*,*S*)-CHIRAPHOS



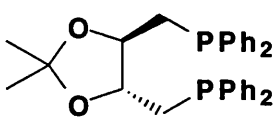
(*R*,*R*)-Me-DUPHOS [190]

5-Membered Rings

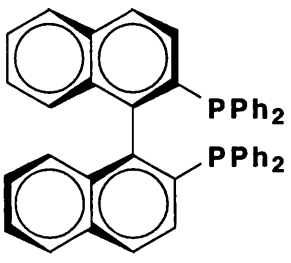


(*S*,*S*)-BDPP

6-Membered Ring

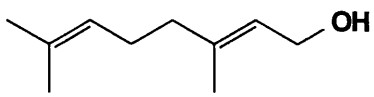


(*R*,*R*)-DIOP



(*R*)-BINAP [191]

7-Membered Rings



(i-iv) → No Isomerised Products

63

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) Ni(cod)$_2$/Ligand (5 mol%), THF, then reflux (time); (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Ligand	Reflux Time (hours)	Enol Acetates **75+76**
1)	CHIRAPHOS	48	–
2)	DUPHOS	48	–
3)	BDPP	48	–
4)	DIOP	24	Trace
5)	BINAP	87	–

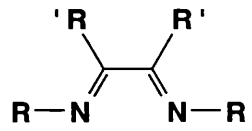
Table 2.14 – Attempted Isomerisation With Chiral Catalysts

It is notable that the ring sizes of the resulting chelates range from five to seven, and that the larger the chelate ring size the greater the 'bite angle' about the metal centre.[192]

The experiments were conducted using 5 mol% of catalyst. In all cases complex mixtures resulted, and no isomerised products were isolated (table 2.14), however when using the DIOP catalyst a trace quantity of enol acetates was detected by crude ^{1}H NMR. These ligands therefore produced even poorer catalysts than 'dppe', suggesting that chelating diphosphine complexes are inherently inactive in this chemistry and that successful asymmetric induction would require an alternative class of ligand.

2.3.3 Nickel-Bis(oxazoline) Catalysts

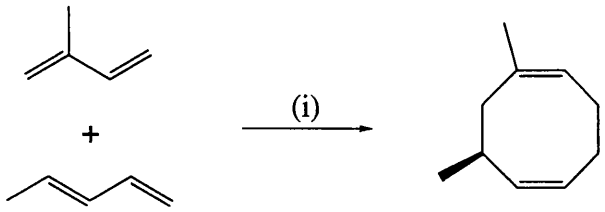
The use of nitrogen-donor ligands in catalysis and related organic chemistry has received increasing attention, and has been the subject of a recent review.[193] Whereas chiral phosphine ligands present synthetic problems, there are a great many naturally occurring, homochiral amines readily available as attractive ligand building blocks. Our attention was drawn to the 1,4-diaza-1,3-diene (DAD) class of ligands. It should be noted that this framework is also the core of the common 2,2'-bipyridyl ligand and similar systems.



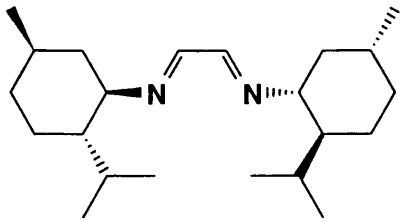
1,4-Diaza-1,3-diene (DAD)

Nickel (0) has been shown to form thermally stable complexes with 'DAD' ligands which are active in processes such as olefin oligomerisation.[194] These complexes benefit from delocalisation of the metal *d*-electrons, usually considered to be essentially non-bonding, by back-bonding with the ligand π-system.[173a,195] Also, there have been a number of recently reported catalytic processes involving complexes of chiral 'DAD' ligands, and closely related ligands based around the 'DAD' nucleus.

Dieck and co-workers have reported the asymmetric co-dimerisation of isoprene with *trans*-1,3-pentadiene using an iron catalyst with a simple C2-symmetrical 'DAD' ligand (scheme 2.3.15).[196] The complex was first activated by reduction with 'butadienemagnesium'. Very high chemo- and regioselectivity was observed, considering the number of possible products, and a remarkable 61% enantiomeric excess was achieved. A equally interesting example was the iridium-catalysed asymmetric transfer hydrogenation of ketones reported by Zassinovich and co-workers, a process related to the chemistry investigated here (scheme 2.3.16).[197]



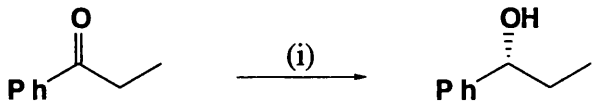
89%, 61% ee



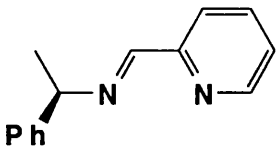
L = 1,4-Bis[(1*R*)-menthyl]-DAD

Reagents: (i) $LFeCl_2$ (0.5%), '$(C_4H_6)Mg$' (0.7%), –17°C, 14 days.

Scheme 2.3.15



75%, 33% ee

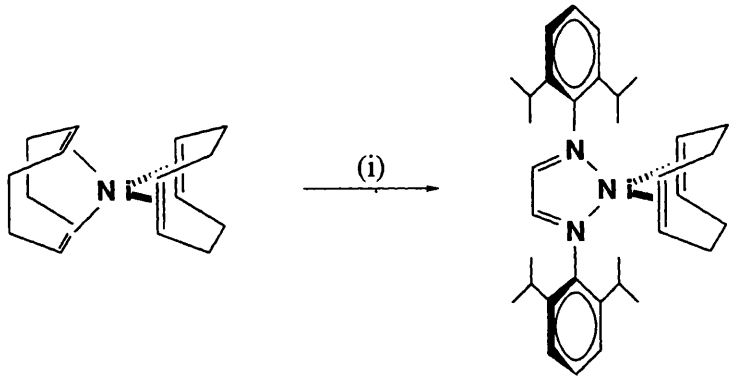


PPEI = (–)-2-Pyridinalphenylethylimine

Reagents: (i) $[Ir(PPEI)(cod)]^+.ClO_4^-$ (0.10%), KOH (0.14%), ^iPrOH (*ca.* 80 equiv), reflux, 2-3 h.

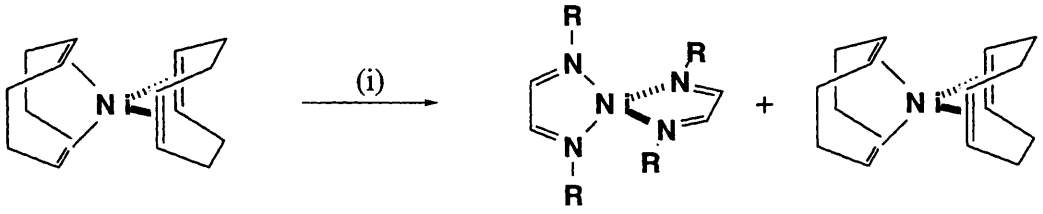
Scheme 2.3.16

Complexes of nickel (0) with 'DAD' ligands have been investigated by a number of workers. 'DAD'-nickel (0) complexes have been prepared specifically from $Ni(cod)_2$, but with varying results. Pörschke and co-workers found that Ni(DAD)(cod) could be obtained by treatment with one equivalent of the ligand at ambient temperature (scheme 2.3.17).[198] This product was thermally stable, decomposing only on melting (m.p. 131°C), and was also obtained from other $Ni(DAD)(olefin)_2$ complexes and 'cod'. Walther and co-workers studied a number of 'hetero-olefin' ligands including 'DAD', and reported that treatment of $Ni(cod)_2$ with one equivalent of the ligand gave only $Ni(DAD)_2$ and starting material (scheme 2.3.18).[199] However this was quite probably the result of selective crystallisation driving the equilibrium.



Reagents: (i) 1,4-bis(2,6-diisopropylphenyl)-1,3-diazabutadiene, pentane, 20°C.

Scheme 2.3.17



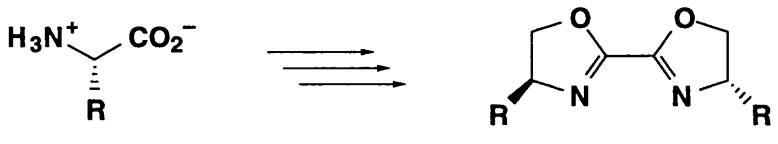
1:1

Reagents: (i) 1,4-di-*p*-Tol-(DAD) (1.0), Et_2O/THF, –10°C.

Scheme 2.3.18

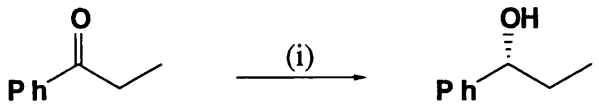
These complexes were again found to be thermally stable. There have been several reports of the preparation of $Ni(DAD)_2$ from the ligand and $Ni(cod)_2$.[198-200] $Ni(DAD)L_2$ complexes of phosphine and carbonyl ligands have also been reported, and are more stable again;[199-201] the complex $Ni(DAD)(CO)_2$ is air stable.[201] In comparison to similar phosphine complexes, these 'DAD' complexes exhibit several differences. Firstly, they are usually intense violet in colour instead of yellow to orange (phosphine complexes are occasionally violet[173c]). This is a result of a low energy transition between the new levels produced by *d*-orbital interaction with the lower energy π^*-molecular orbital Ψ^3, which also accounts for the π-acidity of the 'DAD' ligand.[199-201] The (DAD)Ni fragment also accepts olefinic ligands more readily than the phosphine counterparts, which do not form bis(ethylene) complexes.[202] As a result, $Ni(DAD)L_2$ complexes are well suited to the transformation of unsaturated organic molecules.[202,203]

The bis(oxazoline) class of ligands have been recently developed for application in organic synthesis and has been recently reviewed.[204] A variety of C2-symmetrical oxazoline ligands have been prepared, and found use in asymmetric cyclopropanation, hydride reduction, transfer hydrogenation, Diels-Alder reaction, conjugate organometallic addition and palladium-catalysed allylation. We were most interested in the 4,4'-dialkyl-4,4',5,5'-tetrahydro-2,2'-bi(oxazole) ligands (**77**), hereafter referred to simply as alkyl-bis(oxazolines), being closely related to the 'DAD' ligands so well precedented in conjunction with nickel (0) and likely to be most efficient at stabilising a low oxidation state. As with the other bis(oxazolines), these ligands are derived from amino acids and so readily available in enantiomerically pure form (scheme 2.3.19).

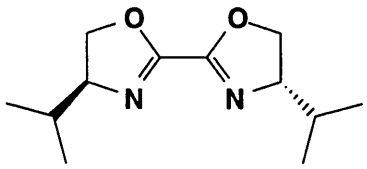


R-77

Scheme 2.3.19



74% ee



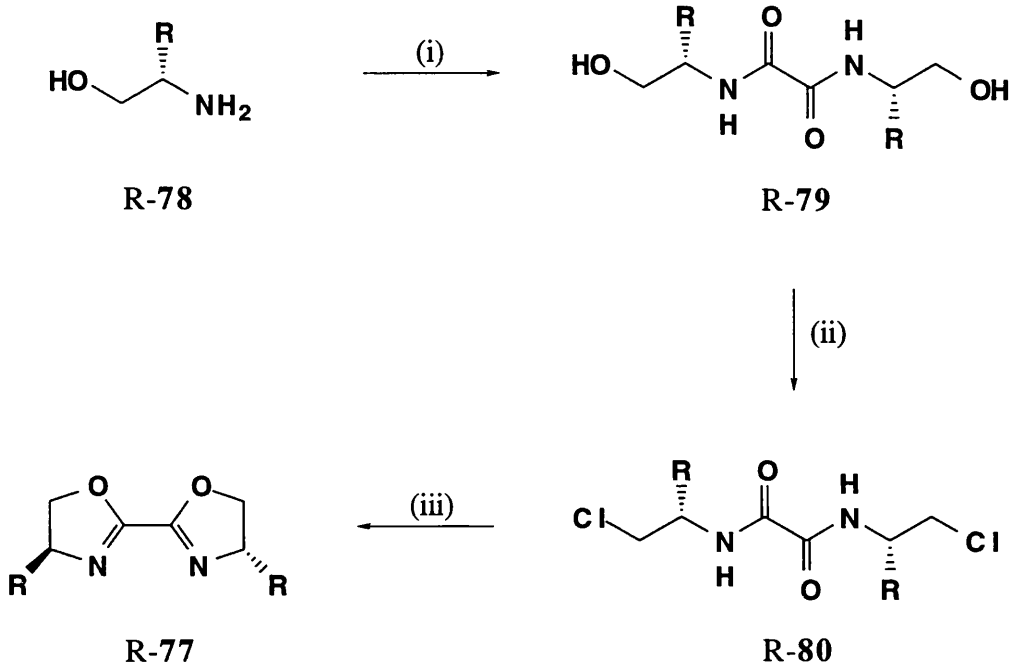
^{i}Pr-**77**

Reagents: (i) $[Ir(cod)Cl]_2$ (0.5%), ^{i}Pr-**77** (1.3%), KOH (2%), ^{i}PrOH, 80°C.

Scheme 2.3.20

Bis(oxazolines) **77** have been shown to be effective in the iridium-catalysed transfer hydrogenation methodology discussed earlier (scheme 2.3.16). In terms of asymmetric induction, ligand ^{i}Pr-**77** was far superior to 'PPEI', likely as a direct result of the C2-symmetry of the former (scheme 2.3.20).[205] Bis(oxazoline)-catalysts are also highly effective in ketone hydrosilation,[206] and palladium-catalysed allylation,[205] although poor results were obtained in asymmetric cyclopropanation using a bis(oxazoline)-copper catalyst.[207] To the best of our knowledge, no examples of bis(amidate) complexes of nickel (0) have been reported.

Amino alcohols were either obtained commercially or prepared by reduction of the corresponding acids using the sodium borohydride-sulphuric acid method of Abiko and Masamune.[208] The bis(oxazoline) ligands **77** were prepared from oxalate by modification of the three-step synthesis reported by Butula and Karlović (table 2.15),[209] one of the approaches used by Pfaltz and co-workers.[205] Thus, an oxalic diester is heated with the (*S*)-amino alcohols R-**78** to give the *N*,*N*'-bis(1-alkyl-2-hydroxyethyl) oxamides R-**79**. Treatment with thionyl chloride then yields *N*,*N*'-bis(1-alkyl-2-chloroethyl) oxamides R-**80**, which cyclise on treatment with sodium hydroxide to give the desired (*S*,*S*)-alkyl-bis(oxazolines) R-**77**.



R-**78** R-**79**

R-**77** R-**80**

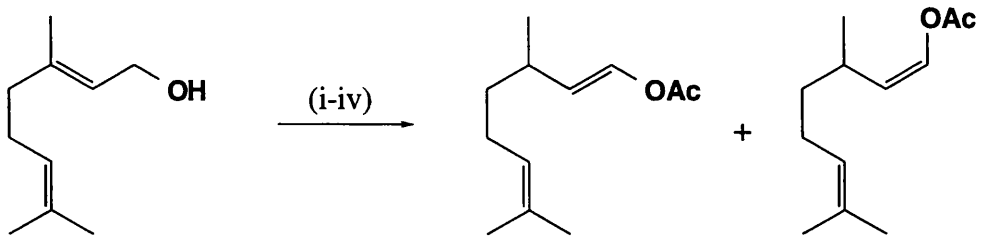
Reagents: (i) $(CO_2Me)_2$ or $(CO_2Et)_2$ (0.5), toluene or DCE, 80°C; (ii) $SOCl_2$, toluene or neat, reflux; (iii) NaOH, MeOH, reflux.

Entry	R	Isolated Yields (%)				$[\alpha]_D^{23}$ (**77**) (*c* 1.0 in $CHCl_3$)
		79	**80**	**77**	Overall	
1)	Me	63	90	70	40	-196.2
2)	^{i}Pr	–	72	75	54	-160.0
3)	^{t}Bu	–	–	60	60	-164.9
4)	Ph	–	–	–	(decomp.)	–

Table 2.15 – Bis(oxazoline) Synthesis

The bis(oxazoline) ligands R-**77** (R=Me, ^{i}Pr, ^{t}Bu) were successfully prepared in this manner. However the phenyl derivative Ph-**77** could not be isolated as the intermediates were gelatinous, and treatment of Ph-**80** with sodium hydroxide in the final step caused only decomposition. The equivalent benzyl-bis(oxazoline) ligand Bn-**77** was prepared by a colleague.[210]

Catalyst solutions were prepared as before, but it was decided to conduct the experiments with only 5 mol% of catalyst. A THF solution of the isopropyl-bis(oxazoline) ligand ^{i}Pr-**77** was degassed and added to the $Ni(cod)_2$ at –78°C, and the mixture allowed to warm to ambient temperature. The $Ni(cod)_2$ dissolved at a relatively low temperature, giving a yellow solution, but on warming to 0°C the colour began to change through green and pale blue to ultimately become very intense, deep blue. Clearly a new complex was formed. Treatment of the lithium alkoxide of geraniol with this solution at reflux resulted in complete conversion after just 1.5 hours. Acetylation under standard conditions gave enol acetates **75** and **76** in 75% combined yield and in the ratio **75**:**76**=4.8:1, with no other identifiable products (scheme 2.3.21; table 2.16, entry 1). This yield is the highest yet obtained, being equal to that obtained with $Ni(cod)_2$ alone, and in both cases a similar ratio of products was found.[102] However the most remarkable observation was the rate of the reaction using only 5.0 mol% of catalyst, which was approximately ten times more rapid than the fastest isomerisation previously observed. Repeating the reaction but quenching after 1 hour, the enol acetates **75** and **76** were isolated in 71% combined yield and in the similar ratio **75**:**76**=4.7:1, with starting material (**63**) (4%), hydrogenated starting material (**65**) (5%), and citronellal (**81**) (4%) (table 2.16, entry 2). This was notable as being the only reaction in which citronellal was isolated.

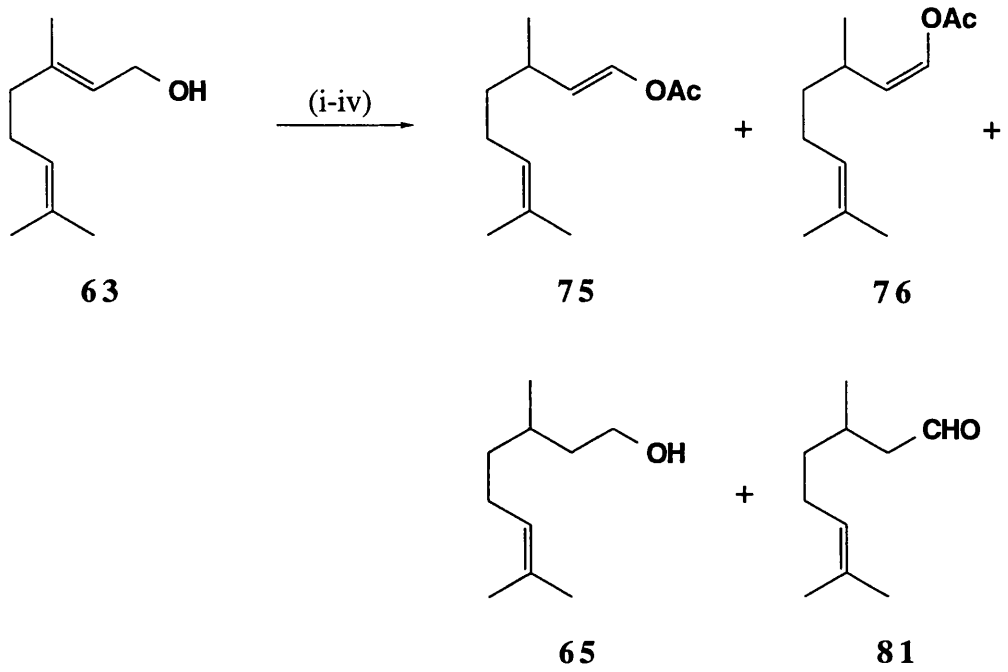


4.8:1

63 **75** (75%) **76**

Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) $Ni(cod)_2$/^{i}Pr-**77** (5 mol%), THF, then reflux 1.5 h; (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Scheme 2.3.21



63 **75** **76**

65 **81**

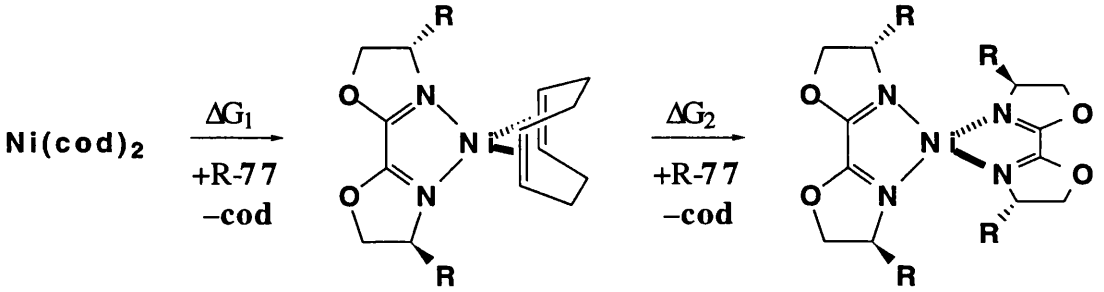
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) Ni(cod)$_2$/^{i}Pr-**77** (5 mol%), THF, then (temperature); (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	Temperature	Reflux Time (hours)	Isolated Yields (%) **75+76**	**(75:76)**	**65**	**81**	**63**
1)	Reflux	1.5	75	(4.8:1)	–	–	–
2)	Reflux	1	71	(4.7:1)	5	4	4
3)	40°C	48	–	–	12	–	10

Table 2.16 – Isomerisation With Ni(cod)$_2$ + ^{i}Pr-Bis(oxazoline)

An attempt to conduct the isomerisation at lower temperature was curiously unsuccessful. Treatment of the lithium alkoxide of geraniol with the same catalyst solution at 40°C led to a very slow reaction, with starting material still present after 48 hours. Quench with acetic anhydride as previously detailed yielded no isomerised products at all, with only the hydrogenated product citronellol (**65**) (12%) and starting material (**63**) (10%) being isolated (table 2.16, entry 3). No trace of enol acetates was detected, and the reason for this highly surprising result is unclear. It is possible that a

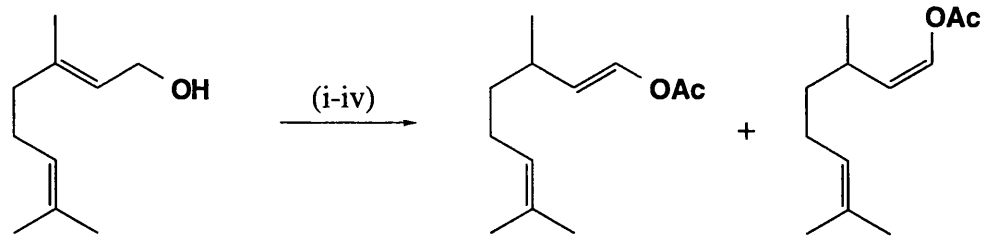
thermally-mediated activation of the catalyst is necessary. If, as was reported for a 'DAD' ligand,[199] formation of an Ni(R-**77**)$_2$ complex is favoured, then heating to reflux temperature might result in dissociation and ligand displacement to form the required Ni(R-**77**)L$_2$ complex. However, formation of Ni(R-**77**)$_2$ would seem unlikely unless it is an irreversible kinetic phenomenon. The electron density at the metal centre, and hence the π-acidic stabilisation gained, would not be as great on introduction of the second ligand as on introduction of the first (scheme 2.3.22). A lower energy system should result from formation of Ni(R-**77**)(cod). Also, some decomposition of unreacted Ni(cod)$_2$ would produce elemental 'black nickel', which was not observed. It is remarkable that in the isomerisation of diethylgeranylamine Noyori and co-workers found that the level of asymmetric induction was unchanged for reaction temperatures in the range 0–80°C.[100a]



$\Delta G_1 > \Delta G_2$ therefore $2\Delta G_1 > (\Delta G_1 + \Delta G_2)$

Scheme 2.3.22

Catalyst solutions were prepared using all four of the bis(oxazoline) ligands R-**77** (R=Me, ^{i}Pr, ^{t}Bu, Bn). An interesting correlation between the relative size of the group R and the colour of the mixture of Ni(cod)$_2$ and R-**77** was noted. The ligands Bn-**77** and ^{i}Pr-**77** both gave rise to deep blue solutions, although the solution of the benzyl ligand was deeper in colour. The less hindered ligand Me-**77** gave an extremely intense blue-violet, while the mixture of Ni(cod)$_2$ and ^{t}Bu-**77** did not noticeably change from the usual yellow colour of Ni(cod)$_2$ alone.



63 **75** **76**

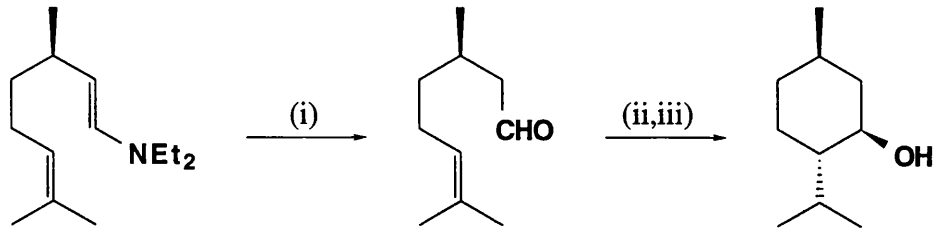
Reagents: (i) ^{n}BuLi (1.0), THF, 0°C; (ii) Ni(cod)$_2$/R-**77** (5 mol%), THF, then reflux (time); (iii) Ac_2O (10), –78°C; (iv) $NaHCO_{3(aq)}$.

Entry	R	Reflux Time (hours)	Colour (Ni(cod)$_2$ + R-**77**)	Isolated Yield (%) **75+76**	(**75**:**76**)
1)	Me	2	Deep blue-violet	41	(5.0:1)
2)	^{i}Pr	1.5	Deep blue	75	(4.8:1)
3)	Bn	2	Deep blue	56	(5.4:1)
4)	^{t}Bu	1.5	Yellow	59	(5.3:1)

Table 2.17 – Isomerisation With Ni(cod)$_2$ + Bis(oxazolines)

The results of the isomerisation experiments are tabulated above (table 2.17). The yields varied greatly depending on the ligand used (41–75%), but stereoselectivities varied only within a comparatively narrow range (**75**:**76**=4.8–5.4:1). Unfortunately, the ligand which provided the highest yield also gave the lowest ratio of products. In no case were identifiable by-products isolated.

It is notable that in terms of reaction rates, all the ligands produced catalysts of far higher activity than those previously studied. Although this was our primary objective in investigating this class of ligand, we had finally discovered a means of isomerisation with a chiral catalyst, and were obviously keen to assess the level of asymmetric induction. In order to measure the enantiomeric excess, if any, a number of techniques were tested.[211]



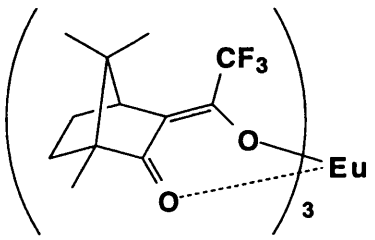
81

Reagents: (i) $AcOH_{(aq)}$, pH 4, <40°C; (ii) $ZnBr_2$, benzene, 5–10°C; (iii) Raney Ni, H_2, (100 $kg.cm^{-2}$), EtOH, 100°C, 2h.

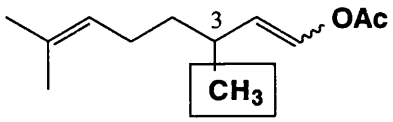
Scheme 2.3.23

It was initially hoped that chiral GC or HPLC technology would be suitable, but screening of several systems proved fruitless. Noyori and co-workers assessed the products of the asymmetric isomerisation of diethylgeranylamine by conversion of the enamine product in three steps to menthol (scheme 2.3.23).[100a] This then allowed the maximum optical rotation of the stereochemically pure enamine to be estimated. In this chemistry however, we isolated a variable mixture of enol acetates, and intended to obtain a measurement of the enantiomeric excesses for each stereoisomer individually. Hydrolysis would lose this information, and the optical rotation of the aldehyde citronellal (**81**) is in any case too small for accurate measurement.[212]

Chiral ^1H NMR shift reagents were also found to be ineffective under the usual conditions. However, using a 2.5 molar excess of tris(trifluoroacetylcamphorate)-europium (III), or $Eu(tfc)_3$, a small degree of resolution was achieved. The C3-methyl doublet of both enol acetate stereoisomers was split into two by *ca.* 1 Hz (figure 2.25).



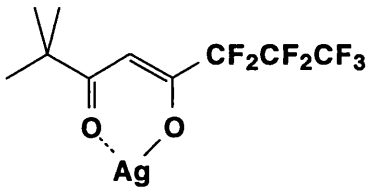
$Eu(tfc)_3$



$|\nu_R - \nu_S| = 1$ Hz

Figure 2.25 – ^{1}H NMR Of Enol Acetates + 2.5 Eu(tfc)$_3$

The absolute stereochemistry corresponding to each signal is not known, and therefore only the magnitude of the frequency difference for the enantiomeric pair is denoted by $|\nu_R - \nu_S|$. This method suffered both from poor resolution and overlapping with the broad signals from the large excess of the shift reagent, particularly with the minor (Z)-isomer. Not surprisingly, the enol acetates do not strongly coordinate to the 'hard' europium (III) reagent. This problem has been solved by the work of Offermann and Mannschreck, who have demonstrated that chiral, olefinic hydrocarbons can be resolved using a europium reagent in conjunction with silver (I).[213] (6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyl-3,5-octanedionato)silver (I), or Ag(fod), is soluble in non-polar organic solvents and readily coordinates alkenes, and by association of the resulting complex with europium, the silver ion acts as a bridge between the alkene and the chiral environment. The enolic double bond of the enol acetates **75** and **76** is clearly much closer to the asymmetric centre than the acetate oxygens which are expected to coordinate to europium (III). Thus, the (E)-enol acetate **75**, in a mixture with Eu(tfc)$_3$ and Ag(fod) in a 1:1:1 molar ratio, exhibits an increased resolution of the C3-methyl doublet of 10.1 Hz. Furthermore, the C2-vinylic proton is now resolved with a difference of 8.9 Hz (figure 2.26, appendix).



Ag(fod)

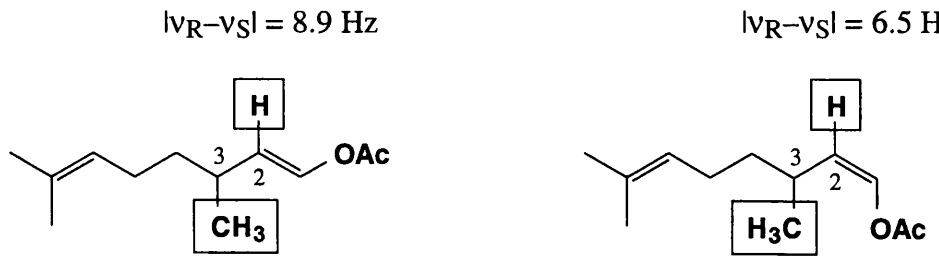
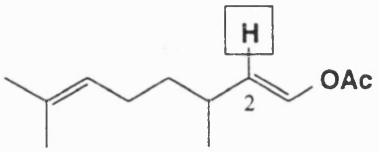


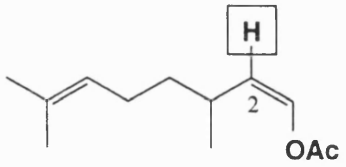
Figure 2.26 – ^{1}H NMR Of Enol Acetates + 1.0 Eu(tfc)$_3$ + 1.0 Ag(fod)

The (Z)-enol acetate **76** exhibits smaller splittings (figure 2.26, appendix). Importantly, the C2-signals of both isomers are free from overlapping signals from the shift reagent, and so more accurate integration is possible, even for the minor (Z)-isomer in some cases. Integration is, however, hampered by an curious effect found in the coupling pattern for the C2-resonances. In the ^{1}H NMR of the pure enol acetates both isomers show double-doublet signals (figure 2.27), as expected, but in the presence of the shift reagent mixture, these signals are apparently transformed into a triplet splitting pattern (figure 2.28, appendix). This is a result of the magnitude of the resolution matching the minor coupling constant. Surprisingly, this occurs with both enol acetates isomers, with the minor coupling and the resolution both measured as 8.9 Hz for the (E)-isomer **75**, and as 6.5 Hz for the (Z)-isomer **76**.

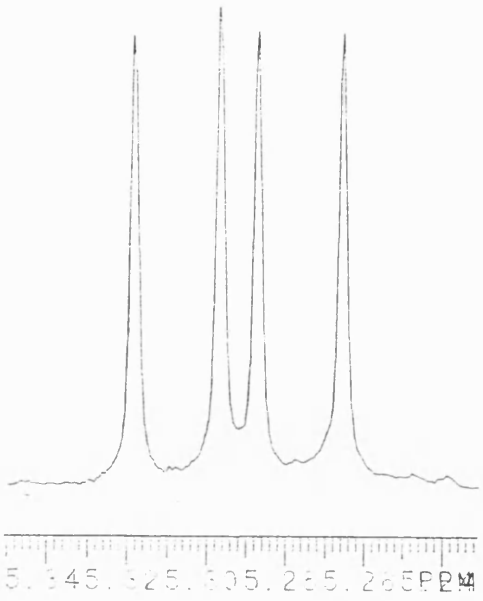
Thus, using this method of ^{1}H NMR analysis allowed measurement of the enantiomeric excesses for each stereoisomer. We were disappointed to measure a maximum value of 8%. Due to a combination of using partially overlapping signals, and the limited accuracy inherent in NMR integration, the given figures should be considered approximate with a maximum error of *ca.* 10%. We therefore conclude that there has been no asymmetric induction in any of the isomerisation experiments using the Ni(cod)$_2$/R-**77** catalyst system. Although this method is relatively inefficient, it is presently the only means of analysing the enol acetate products and provides useful qualitative information.

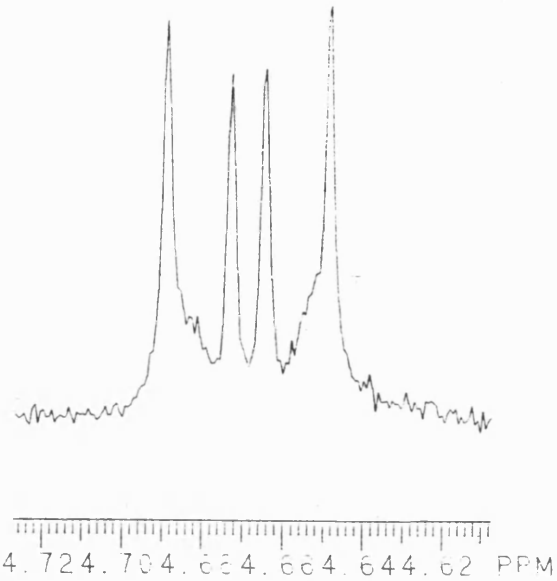


75



76

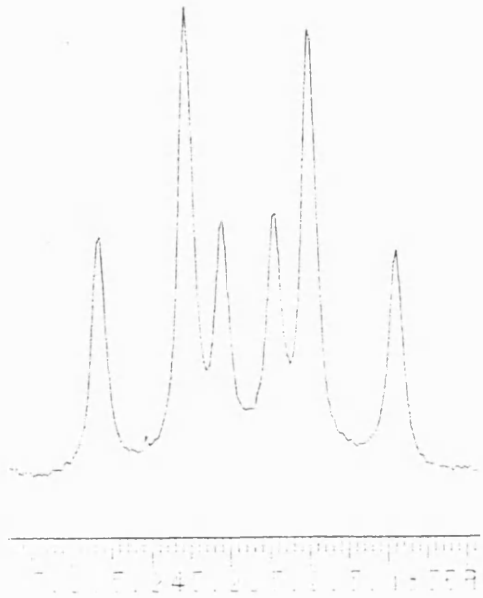


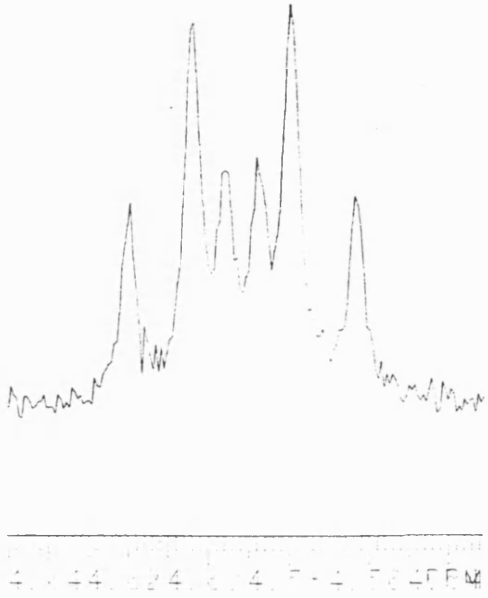


J = 12.4, 8.9 Hz

J = 9.6, 6.5 Hz

Figure 2.27 – ^{1}H NMR Of Enol Acetates 75 And 76



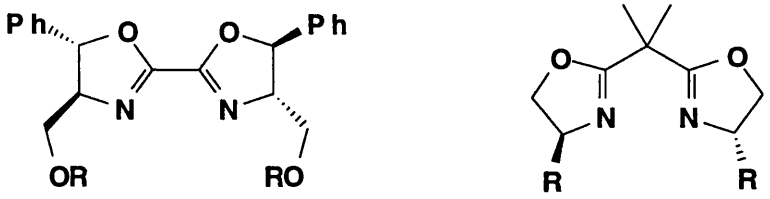


$|\nu_R - \nu_S|$ = 8.9 Hz

$|\nu_R - \nu_S|$ = 6.5 Hz

Figure 2.28 – ^{1}H NMR Of Enol Acetates + 1.0 Eu(tfc)$_3$ + 1.0 Ag(fod)

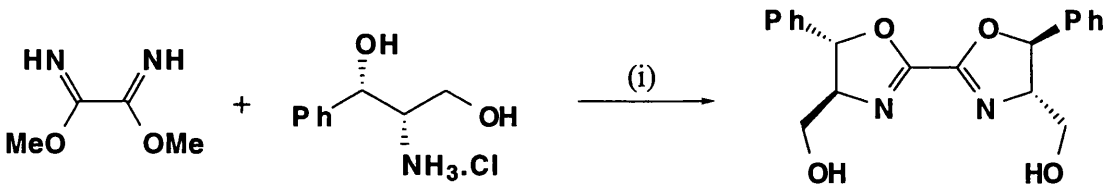
Preliminary attempts to use proton-decoupled ^{13}C NMR to measure the enantiomeric excess in future isomerisation experiments indicate complete resolution of the C3-methyl signals using this $Eu(tfc)_3/Ag(fod)$ shift reagent combination. It is hoped that the clearer resolution and simplicity of ^{13}C NMR spectra will allow greater accuracy.



A B

Figure 2.29

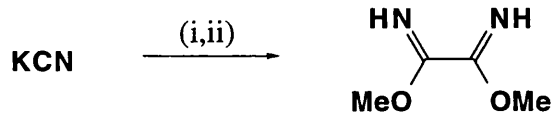
We were interested in studying alkoxymethyl-substituted bis(oxazolines) (**A**), and the related ligands of the 2,2-bis(oxazolinyl)propane class (**B**) (figure 2.29). Pfaltz has reported the synthesis of the dihydroxyl precursor to ligands of type **A** by the treatment of dimethyl diiminooxalate with the hyrdochloride salt of (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol (scheme 2.3.24).[205] The selective formation of 4-hydroxymethyl-5-phenyl-oxazolines in similar condensations with mono-iminoesters has previously been demonstrated by Meyers and co-workers, as a preparation of chiral ester enolate equivalents.[214] It was further demonstrated that these mono-oxazoline products could be O-methylated *via* the sodium salt.



42%

Reagents: (i) MeOH, 23°C.

Scheme 2.3.24



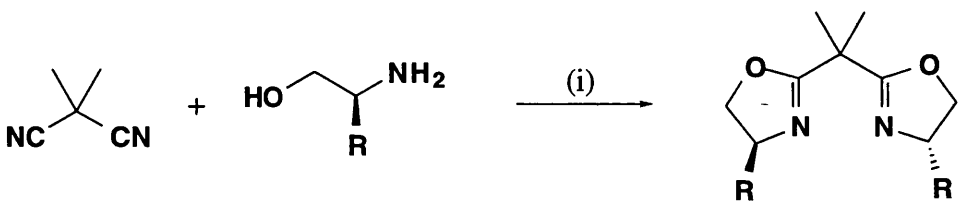
82 (25%)

Reagents: (i) Cl_2, H_2O:MeOH (9:4), 0°C; (ii) KCN (0.6), MeOH:H_2O (4:3), r.t., 6 h.

Scheme 2.3.25

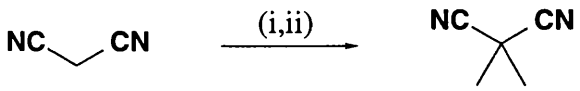
Dimethyl diiminooxalate (**82**) is commonly prepared by the reaction of methoxide with cyanogen;[215] treatment of oxamide with trialkyloxonium tetrafluoroborate results only in mono-alkylation.[216] However, in order to avoid the direct handling of this highly toxic gas, we chose to develop the method of Biddle.[217] Passage of chlorine through a solution of potassium cyanide in aqueous methanol at 0°C until the pH approaches neutral, and then treatment with further potassium cyanide at ambient temperature, produced **82** in 25% yield after distillation (scheme 2.3.25).

The 2,2-bis(oxazolinyl)propane ligands (**B**) have similarly been prepared in one step,[205] by cadmium acetate mediated condensation of the aminoalcohol with dimethylmalonitrile (scheme 2.3.26).[218,219] These ligands do not contain the 'DAD' framework and so present quite different electronic characteristics, and in forming a larger chelating ring are expected to exhibit a larger 'bite angle'. The pendant groups (R) would also be arranged more directly towards the other ligands. These ligands have been successfully applied to asymmetric cyclopropanation, Diels-Alder reactions and palladium catalysed allylation reactions.[204]



Reagents: (i) $Cd(OAc)_2$ (5 mol%), PhCl, reflux.

Scheme 2.3.26



82 (57%)

Reagents: (i) NaH (2.2), DMSO, 0°C; (ii) MeI (2.9), DMSO/benzene, 0°C to r.t.

[via **NaN= C= C= C=NNa**]

Scheme 2.3.27

Thus, dimethylmalonitrile was prepared following Pfaltz's modification[219] of the method of Bloomfield.[220] Treatment of the disodium salt of malonitrile with methyl iodide gave dimethylmalonitrile in 57% yield after distillation (scheme 2.3.27).

Several attempts to prepare ligands of types **A** and **B** by these methodologies have been unsuccessful. In both cases only mono- and uncyclised materials were isolated, and further work was precluded by the constraints of time. The 2,2-bis(oxazolinyl)propane ligands (**B**) might be more readily prepared the zinc chloride cyclisation methodology of Williams and co-workers,[221] or via the diiminoester (figure 2.30).[222] These ligands have also been prepared by Corey and co-workers following a more practically arduous route analogous to the three-step preparation of the bis(oxazoline) ligands R-**77**.[223] This latter approach, however, is not applicable to the alkoxymethyl-bis(oxazolines) **A**.

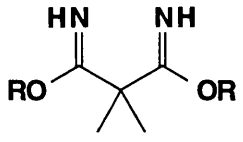


Figure 2.30

2.3.4 Conclusions

It has been demonstrated that nickel (0) catalysts generated from $Ni(cod)_2$ and tricyclohexylphosphine are highly efficient in the isomerisation of the lithium alkoxide of geraniol. Hydrogenation of these solutions is detrimental to catalytic activity. In view of the similarities with earlier studies,[102,171] and recent literature precedent (scheme 2.3.3),[172] it is likely that nickel (0) species are also generated from dichlorobis(tricyclohexylphosphine)nickel (II) in conjunction with two equivalents of butyllithium. However the catalysts prepared in this study are more active than any previously discovered, producing rates roughly twice the highest attained before, with good yields and (E)-selectivity. Chelating diphosphine ligands form considerably less active catalysts, and mixtures of $Ni(cod)_2$ with chiral diphosphines were completely inactive. This approach to asymmetric induction would therefore seem to warrant no further investigation.

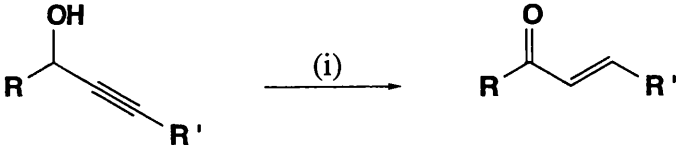
Catalysts prepared from $Ni(cod)_2$ and the bis(oxazolines) isomerised geraniol far more rapidly again, achieving similar rates to the $Ni(cod)_2$/tricyclohexylphosphine system but with one quarter the quantity of catalyst. The isopropyl-substituted ligand ^{i}Pr-**77** produced the highest yield of enol acetates yet recorded (75%), with reasonable stereoselectivity (E:Z=4.8:1). No significant asymmetric induction occurred, but an effective isomerisation catalyst involving a chiral, C2-symmetrical ligand has now been discovered, and future work should investigate nickel (0) complexes of related chiral nitrogenous ligands.

2.4

The Isomerisation Of Propargylic Alkoxides

2.4 A Preliminary Investigation Of Propargylic Isomerisation

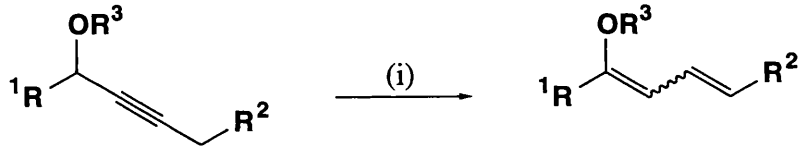
The catalytic isomerisation of propargylic substrates to the corresponding allenic and dienic systems has been reported.[224] The isomerisation of propargylic alcohols to give (E)-α,β-unsaturated ketones was demonstrated by Ma and Lu, using a non-hydridic ruthenium catalyst in conjunction with a trialkylphosphine (scheme 2.4.1).[225] In the absence of an added phosphine, or when using triphenylphosphine, no isomerisation products could be isolated. A metal hydride addition-elimination mechanism was proposed, as 2-propyn-1-ols are suggested to initially react with the catalyst to produce hydridic species.[226] Pre-formed ruthenium hydride species have also been utilised in propargylic isomerisation. Suzuki and co-workers reported the catalytic isomerisation of propargylic alkyl ethers and trimethylsilyl ethers with chlorohydridotris(triphenylphosphine)ruthenium (II) under even more forcing conditions, giving conjugated dienol derivatives (scheme 2.4.2).[193]



>20:1 (E)

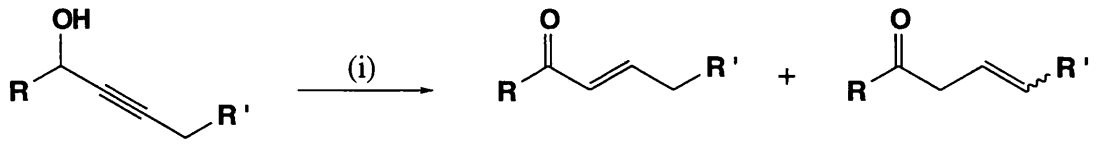
Reagents: (i) $Ru(PPh_3)_3Cl_2/2PR_3$ (2 mol%), toluene, reflux, 32–48 h, 63–85%.

Scheme 2.4.1



Reagents: (i) $Ru(PPh_3)_3HCl$ (10 mol%), toluene, 150–180°C, 24–100 h, 51–100%.

Scheme 2.4.2

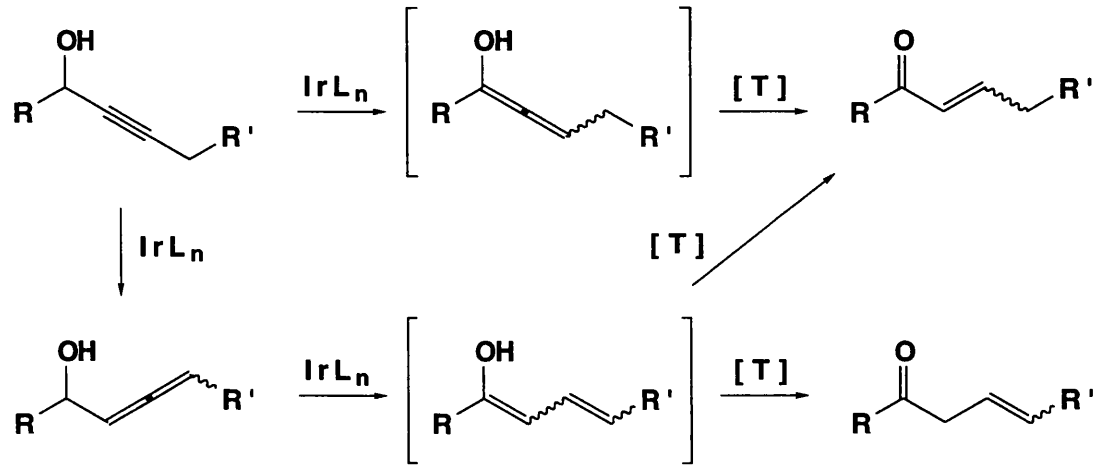


5.7–3.2:1

Reagents: (i) $Ir(P^iPr_3)_2H_5$ (1 mol%), toluene, reflux, 24–40 h, 70–92%.

Scheme 2.4.3

The unusual polyhydride catalyst pentahydridobis(triisopropylphosphine)-iridium (V)[228] has also been used, and in this case both (E)-α,β-unsaturated ketones and stereochemical mixtures of β,γ-unsaturated ketones were isolated (scheme 2.4.3).[229] This catalyst was the most active of those studied and, again, a metal hydride addition-elimination mechanism was proposed. The unconjugated products can only arise from a conjugated dienol intermediate, and as tautomerisation is likely to be rapid, these products are probably a result of an initial isomerisation in the unwanted sense. This route therefore requires two iridium-catalysed isomerisation steps (scheme 2.4.4). $Ir(P^iPr_3)_2H_5$ has also been found to catalyse olefin disproportionation.[230]

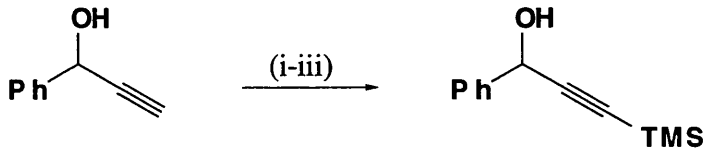


IrL_n = $Ir(P^iPr_3)_2H_5$; [T] = Tautomerisation

Scheme 2.4.4

It was envisaged that the similar isomerisation of a propargylic alkoxide would provide a route to allenolate or dienolate species, and to this end several preliminary experiments were conducted. It was decided to use a substrate that could form only an allenolate, and so could give only one product isomer. Transition metal complexes, and in particular those of ruthenium, are known to undergo oxidative addition of acetylenic carbon-hydrogen bonds,[229,231] and so substrates were chosen in which isomerisation to the dienolate product was blocked.

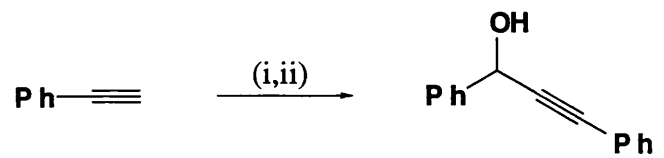
Alcohol **84** was prepared by treatment of the available alcohol 1-phenyl-2-propyn-1-ol with two equivalents of butyllithium to form the deep red dianion, and then trimethylsilyl chloride to give the silyl ether (scheme 2.4.5). Treatment with aqueous acid gave the alcohol **84** in 94% overall yield. Alcohol **85** was prepared in 56% yield by deprotonation of phenylacetylene with butyllithium and reaction with benzaldehyde (scheme 2.4.6).



84 (94%)

Reagents: (i) ^{n}BuLi (2.1), THF, –78°C, 30 min.; (ii) TMSCl (2.2), –78°C to r.t., then 2.5 h; (iii) $HCl_{(aq)}$ (2.0M), 45 min.

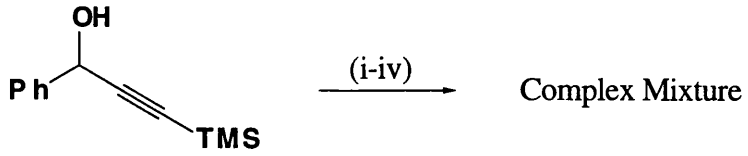
Scheme 2.4.5



85 (56%)

Reagents: (i) ^{n}BuLi (1.1), THF, 0°C, 45 min.; (ii) PhCHO (1.2), 30 min.

Scheme 2.4.6



84

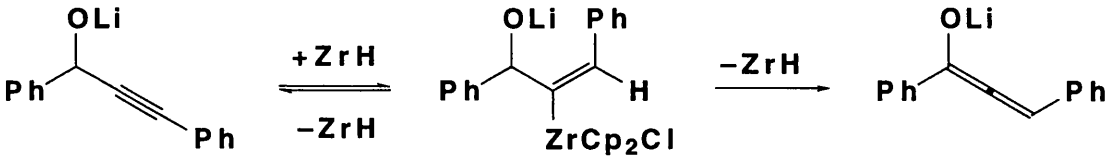
Reagents: (i) ^{n}BuLi (1.0), toluene, 0°C; (ii) Catalyst (mol%), toluene, then reflux (time); (iii) Allyl bromide (10), 0°C; (iv) $NH_4Cl_{(aq)}$.

Entry	Catalyst	(mol%)	(time)
1)	$Ru(PPh_3)_3Cl_2$, $2PBu_3$	1.1	3.5 days
2)	$Ru(PPh_3)_3Cl_2$	4.9	18 hours
3)	$Ru(PPh_3)_3HCl$	5.0	5 hours

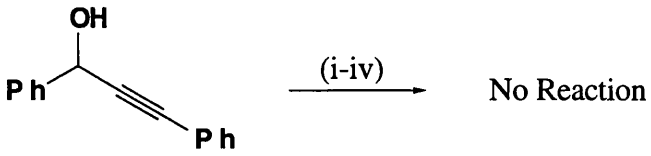
Table 2.18 – Attempted Isomerisation With Ruthenium Catalysts

Following the ruthenium methodology of Ma and Lu,[225] **84** was treated with several ruthenium based catalyst systems (table 2.18). The catalyst chlorohydridotris-(triphenylphosphine)ruthenium (II) was prepared by hydrogenation of the dichloro complex in refluxing benzene solution in the presence of triethylamine (scheme 2.2.36).[147] In all cases a complex mixture of products resulted from which no identifiable products could be isolated.

Zirconocene hydride species were also studied as potential isomerisation catalysts. Chlorobis(η^5-cyclopentadienyl)hydridozirconium (IV), or Schwartz's reagent,[232] is known to reversibly hydrometallate alkynes.[233] It was envisaged that isomerisation to the allenic derivative, not normally associated with this process, might nevertheless proceed due to carbinolic assistance to the desired hydride transfer (scheme 2.4.7). Attempted isomerisation in benzene at room temperature with protection from light, the usual conditions for hydrozirconation, gave no reaction, nor a similar experiment at reflux (table 2.19).



Scheme 2.4.7



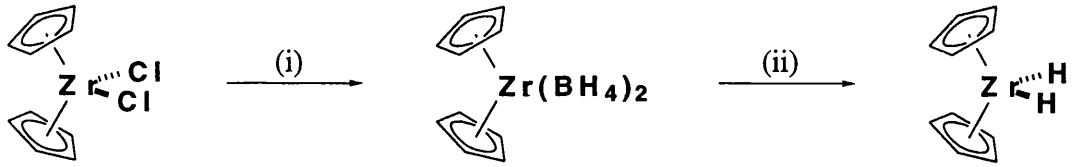
85

Reagents: (i) ^{n}BuLi (1.0), benzene, 0°C; (ii) Catalyst (mol%), reflux or r.t., dark, (time); (iii) Benzyl bromide (equiv), 0°C; (iv) $NH_4Cl_{(aq)}$.

Entry	Catalyst	(mol%)	(time)	BnBr (equiv)
1)	Cp_2ZrHCl, r.t.	10	16 hours	2.0
2)	Cp_2ZrHCl, reflux	11	22 hours	1.1
3)	Cp_2ZrH_2, reflux	3.5	18 hours	1.0

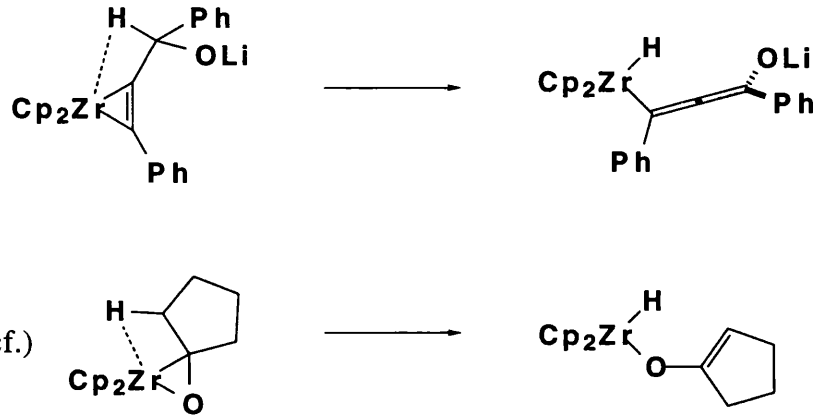
Table 2.19 – Attempted Isomerisation With Zirconium Catalysts

Bis(η^5-cyclopentadienyl)dihydridozirconium (IV) was prepared by treatment of the corresponding dichloro complex with lithium borohydride, to give a zirconium bis(borohydride) intermediate,[234] and then decomposition by reaction with triethylamine (scheme 2.4.8).[235] It was envisaged that reaction with the substrate would produce (formally) a reactive zirconocene (II) alkyne complex,[236] rearrangement of which might constitute isomerisation. A similar rearrangement is driven by the re-attainment of the favoured zirconium (IV) oxidation state (scheme 2.4.9).[237] However, no detectable reaction occurred at all (table 2.19).



Reagents: (i) $LiBH_4$; (ii) $2NEt_3$.

Scheme 2.4.8



Scheme 2.4.9

These preliminary experiments were unsuccessful, but further study is needed. Since the propargylic equivalent to the π-allyl hydride intermediate would have a linear π-system poorly suited to coordination to a metal centre (figure 2.31), it is expected to be relatively high in energy. It is likely that a hydrometallation route, and consequently pre-formed hydridic catalysts, will prove most effective. In particular, the iridium catalyst $Ir(P^iPr_3)H_5$ used by Ma and Lu warrants investigation.[229]

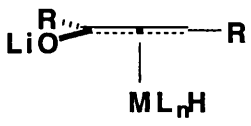


Figure 2.31

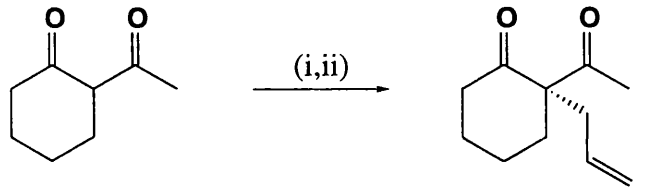
2.5

Conclusions And Perspectives

2.5 Overall Conclusions And Perspectives

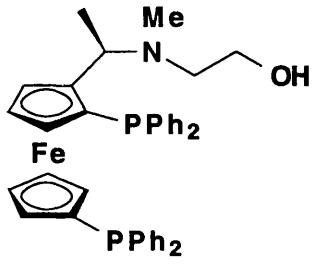
This work has demonstrated that the transition metal catalysed isomerisation of allylic alkoxides is a practicable new approach to enolate chemistry. Moreover, this route allows the preparation of 'clean' enolates, free of stoichiometric by-products such as amines. Thus, an allylic alcohol is a direct synthon for an enolate anion; traditional manipulation would require reduction, oxidation and deprotonation to achieve the same transformation. Wilkinson's catalyst is easily prepared and handled, and is effective particularly in the stereospecific preparation of trisubstituted lithium enolates. This catalyst is, however, sensitive to increasing substitution around the substrate double bond. Nickel (0) catalysts are far more active in this respect, readily isomerising demanding substrates which are unreactive towards Wilkinson's catalyst. However the use of nickel (0) catalysts by the current methodology is considerably less straightforward than the use of the rhodium catalyst, or than the *in situ* generation of active nickel-phosphine species from nickel (II) and butyllithium.[102] Clearly a simple preparation of these catalysts from more easily handled precursors is desirable.

Future work should involve the study of nitrogenous ligands related to the bis(oxazoline) class, in conjunction with nickel (0), with the aim of enantioselective isomerisation. In particular, the possible exploitation of ligand-substrate interactions seems attractive.[238] Such an approach is typified by the work of Hayashi and co-workers in palladium-catalysed asymmetric allylation (scheme 2.5.1).[239] Hydrogen bonding between the pendant hydroxyl group on the ligand and the approaching nucleophile serves to direct the addition. Sawamura and Ito[238] have pointed out the similarities between these processes and enzymatic catalysis, which relies on bonding interactions for enantioselection rather than the purely steric factors. Increased catalytic activity is desirable, as it is expected that catalysts which can operate effectively under milder conditions will be inherently more selective, and yet catalytic processes more commonly rely on sterically-based selectivity which by its nature blocks the catalytic site and impedes catalytic activity.

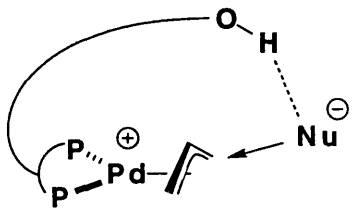


88%, 81% e.e.

Reagents: (i) NaH (1.25), THF; (ii) Allyl acetate (1.5), $[(\eta^3\text{-allyl})PdCl]_2$ (0.5%), L* (1.1%), THF, –60°C, 44h.



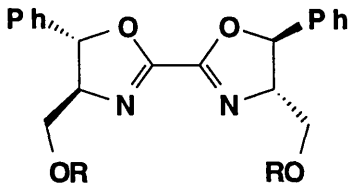
L*



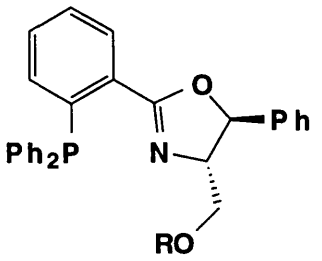
(via)

Scheme 2.5.1

The presence of a metal ion in our substrates suggests a similar approach, using a ligand with a pendant group bearing coordinating functionality (eg. figure 2.32). Interaction with the alkoxide substrate would provide highly ordered catalytic intermediates, and might aid both stereo- and enantioselectivity.



A



B

R = Me, CH_2CH_2OMe, etc.

Figure 2.32

C2-Symmetry is employed in asymmetric catalysis to ensure a maximum steric interaction between the substrate and the chiral blocking group. With a covalent interaction ordering the substrate complex C2-symmetry can be removed (figure 2.32.B), allowing a less hindered and so more active catalyst, and presenting greater opportunity to alter the electronic characteristics of the ligand. Such ligands, including the ferrocenyl ligands used by Hayashi and co-workers,[239] warrant future investigation.

Chapter 3

Experimental Section

General Procedures

^1H NMR spectra were recorded using a Bruker WM-250 instrument (250 MHz), a Jeol GSX-270 instrument (270 MHz), a Varian VXR-400 instrument (400 MHz) or a Bruker AM-500 instrument (500 MHz). ^{13}C NMR spectra were recorded on the Jeol GSX-270 instrument (67.9 MHz), the Varian VXR-400 instrument (100.6 MHz) or the Bruker AM-500 instrument (125.7 MHz), with broad-band decoupling at the ^1H resonance frequency. ^2H NMR spectra were recorded on the Varian VXR-400 instrument (61.4 MHz) or the Bruker AM-500 instrument (76.8 MHz). Unless otherwise stated $CDCl_3$ was used as solvent, stored over 4Å molecular sieves and filtered through basic alumina directly before use. Spectra were internally referenced against residual proton or other solvent signals. Infrared spectra were recorded either as thin films on sodium chloride plates or as potassium bromide discs, on the Perkin-Elmer 983-G or FT-IR 1600 instruments. Mass spectra and accurate mass measurements were recorded by electron impact (EI) studies with an Autospec Q, VG 7070 or VG 7070B instrument, unless fast atom bombardment (FAB) is stated in which case a ZAB-SE instrument was used. Elemental analyses were performed by the Imperial College Chemistry Department microanalytical service. Analytical gas chromatography was performed using a Hewlett Packard 5890 machine fitted with an SGE BPX5 capillary (25 m fused silica, 0.32 mm i.d., cross-linked 5% diphenyl-polydimethylsiloxane, 0.5 μm film) and flame ionisation detector. Split injection was used with helium or hydrogen carrier gas. Melting points were taken on a Reichert hot stage apparatus and are uncorrected. Optical rotations were taken with a 'POLAAR 2000' instrument by Optical Activity Ltd. and are given in the units 10^{-1} deg.cm^2.g^{-1}.

'Petrol' refers to light petroleum ether boiling in the range 40-60°C and '30-40 petrol' to that boiling in the range 30-40°C, both redistilled before use as chromatography eluents. 'Ether' refers to diethyl ether, used as received for this purpose, as were ethyl acetate, methanol and dichloromethane.

For use as reaction solvents ether, tetrahydrofuran and benzene were freshly

redistilled under dry nitrogen from sodium benzophenone ketyl, and toluene from molten sodium. Pentane was redistilled from sodium benzophenone ketyl and stored over a sodium mirror. Dichloromethane was freshly redistilled from phosphorous (V) oxide. Chlorobenzene and 1,2-dichloroethane were redistilled from phosphorous (V) oxide and stored over 4Å molecular sieves. Methanol was distilled from magnesium turnings and stored over 4Å molecular sieves. Unless otherwise stated 'ethanol' refers to absolute ethanol (>99.7%) and was used as received. Dimethyl sulfoxide and hexamethylphosphoric triamide were distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Chlorotrimethylsilane was freshly redistilled from sodium wire, or from calcium hydride and then treated with poly(4-vinylpyridine). Triethylamine, diisopropylamine and pyridine were distilled from and stored over potassium hydroxide. Acetic anhydride was distilled under reduced pressure from magnesium powder, and acetyl chloride from phosphorus (V) chloride and then quinoline. Benzaldehyde, allyl bromide, and methyl iodide were purified by accepted procedures prior to distillation.[240] Commercially obtained allylic alcohols were treated with potassium carbonate and distilled onto 4Å molecular sieves before use as substrates.

Preparative flash chromatography was performed using Merck Kieselgel 60 silica unless alumina (Brockmann Grade 1) is stated. A static positive pressure (≤ 0.2 bar) was provided by a compressed air cylinder. Products isolated by flash chromatography are listed in the order of elution.

Analytical thin layer chromatography was performed on Merck Kieselgel 60 F_{254} pre-coated glass plates. Visualisation was achieved with ultraviolet light (254 nm), iodine vapour, potassium permanganate solution [$KMnO_4$ (12.5 g), Na_2CO_3 (62.5 g), water (2.5 l)], acidic ammonium molybdate solution [$(NH_4)_6Mo_7O_{24}.4H_20$ (125 g), H_2SO_4 (conc., 0.25 l), water (2.25 l)] or iodoplatinatic acid [H_2PtCl_6 (1 g), KI (15 g), water (200 ml)] as appropriate.

Isomerisation Procedures

All isomerisation reactions were performed using Schlenk-line techniques and glassware (oven or flame-dried).[109] Solutions were prepared using standard air-sensitive handling procedures and twice degassed prior to mixing. 'Degassed' refers to one freeze-thaw cycle as described below. The Schlenk-line was served by a two-stage rotary oil pump and on-line vacuum maintained at between 0.01 and 0.05 mbar.

Argon was dried and deoxygenated by passage through a column of chromium (II) on activated silica:

> To a mechanically stirred solution of chromium (VI) oxide (60 g) in distilled water (2 l) was slowly added silica gel (1.5 kg, *ca.* 100 mesh). The resulting bright orange slurry was recovered by Büchner filtration and dried first at the pump (12 h) and then on several large crystallisation dishes in an oven at 100°C (48 h). The orange powder was placed in a large sintered glass chromatography column, in a cylindrical furnace, and dehydrated in a stream of oxygen at 250°C (3-4 h). After heating at 500°C (1h), and in a stream of dry nitrogen (30 min), a supply of carbon monoxide was attached and slow passage of the gas continued at >400°C until the transition through green to blue had run the length of the column (1-2 h). A flow of nitrogen was then maintained for several hours until the column had cooled to room temperature.

Absorption of oxygen was characterised by a gradual colour change to orange-brown moving in a distinct front in the direction of argon flow. The column was sufficient for several cylinders of gas and may be regenerated by the above procedure.

Commercially obtained solutions of *n*-butyllithium were regularly quantified by the 'double-quench and titration' procedure—subtraction of background base (hydroxide by reaction with 1,2-dibromoethane and then water) from total base (^{n}BuLi

and hydroxide by reaction with water). Determinations were performed twice and typically agreed to within 0.2%.

The catalysts chlorotris(triphenylphosphine)rhodium (I),[103] chlorocarbonylbis-(triphenylphosphine)rhodium (I),[136] (trichlorostannato)tris(triphenylphosphine)-rhodium (I)[119] and [1,2-bis(diphenylphosphino)ethane](1,5-cyclooctadiene)rhodium (I) perchlorate[101] were prepared by published procedures and stored under argon in air-tight bottles. Chlorodi(η^5-cyclopentadienyl)hydridozirconium (IV) and dichlorotris-(triphenylphosphine)ruthenium (II)[241] were used as purchased from Aldrich Ltd. Chlorohydridotris(triphenylphosphine)ruthenium (II)[147] and di(η^5-cyclopentadienyl)-dihydridozirconium (IV)[234,235] were prepared and handled under argon, and used immediately. Bis(1,5-cyclooctadiene)nickel (0), also prepared by published procedure,[186a] was stored at –40°C under argon in a fully equipped glove-box. Canula transfers of solutions of nickel (0) complexes were performed using teflon tubing.

The following trivial compound names are used for brevity: 'Wilkinson's catalyst' for chlorotris(triphenylphosphine)rhodium (I); 'geraniol' and 'geranyl acetate' for (E)-3,7-dimethylocta-2,6-dien-1-ol and the O-acetyl derivative; 'citronellol' and 'citronellyl acetate' for 3,7-dimethyl-6-octen-1-ol and the O-acetyl derivative; 'citronellal' for 3,7-dimethyl-6-octenal.

Standard Procedure For $Rh(PPh_3)_3Cl$ Catalysed Isomerisations

The alcohol substrate was weighed into a Schlenk flask, the flask was flushed with argon, and THF (6 ml) was added. The solution was cooled to 0°C and treated with *n*-butyllithium (1.00-1.05 equiv) dropwise over several minutes, and the mixture stirred for *ca.* 15 min. at that temperature. Into a second flask was placed solid Wilkinson's catalyst (2.0 mol%) and THF (5 ml), and the two solutions degassed twice by the freeze-thaw procedure *viz*, the solution is frozen in a bath of liquid nitrogen, the vessel evacuated for several minutes and then sealed, the solution is melted with the aid of a heat-gun and stirred momentarily, the solution is re-frozen, and the vessel again evacuated for several minutes. Freezing of solutions is begun from the bottom and melting from the top. The catalyst was transferred *via* canula to the alkoxide solution, a condenser fitted, and the mixture rapidly heated to reflux.

Standard Quench And Work-up Procedures:

Aldol reaction[13]

The reaction mixture was cooled to –78°C, and benzaldehyde (1.1 equiv) added via syringe as rapidly as possible. After exactly 5 s excess saturated aqueous ammonium chloride was added in a similar manner, and the mixture allowed to warm to ambient temperature. Water was added to dissolve any precipitated ammonium chloride. The mixture was extracted with ether (3 × *ca.* 30 ml), the combined organic phases washed with water (*ca.* 10 ml) and brine (*ca.* 50 ml), and dried over $MgSO_4$. Evaporation *in vacuo* gave the crude oil.

Acetylation

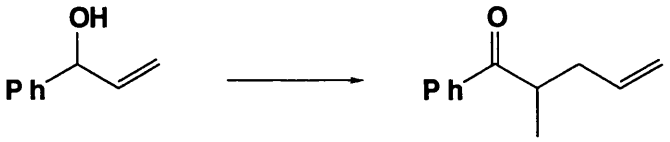
The reaction mixture was cooled to –78°C, and either acetyl chloride or acetic anhydride as stated (10 equiv) was added via syringe as rapidly as possible. After *ca.* 15 min at

–78°C excess aqueous sodium hydrogen carbonate was added, and the mixture allowed to warm to ambient temperature and stir for at least a further 20 min. Water was added to dissolve any precipitated solid, and the mixture extracted with ether as for an aldol reaction. Evaporation *in vacuo* gave the crude oil—for low molecular weight enol acetates careful evaporation directly onto flash silica was used.

Alkylation with allyl bromide

The reaction mixture was cooled to 0°C, and allyl bromide (10 equiv) added via syringe as rapidly as possible. After *ca.* 15 min excess saturated aqueous ammonium chloride was added, and water to dissolve any precipitated ammonium chloride. The mixture was extracted with ether as for an aldol reaction. Evaporation *in vacuo* gave the crude oil.

[Rh(dppe)(cod)]ClO_4 mediated isomerisation of 1-phenyl-2-propen-1-ol (1)



1 **2**

A solution of alkoxide was prepared from 1-phenyl-2-propen-1-ol (**1**) (324 mg, 2.41 mmol) in THF (15 ml) and *n*-butyllithium (1.00 ml, 2.5 M in hexanes, 2.5 mmol). A second solution of [1,2-bis(diphenylphosphino)ethane](1,5-cyclooctadiene)rhodium (I) perchlorate (38.4 mg, 54.2 μmol, 2.2 mol%) in THF (8 ml) was prepared, and both solutions were degassed twice. The catalyst solution was stirred at ambient temperature under a low positive pressure of hydrogen for 30 min, becoming bright orange, and transferred via canula to the alkoxide. The mixture was heated to reflux for 6.5 h. Quench with allyl bromide (2.0 ml, 23 mmol) and work-up as previously detailed gave after flash chromatography (5% ether in petrol elution) *2-methyl-1-phenyl-4-penten-1-one*[242] (**2**) (323 mg, 77%):

^{1}H NMR (270 MHz) δ_H: 1.21 (3H, d, J = 6.8 Hz, 2'-CH_3), 2.2 (1H, m, 3-CH_AH_B), 2.6 (1H, m, 3-CH_AH_B), 3.55 (1H, sextet, J = 6.8 Hz, 2-CH), 5.10 (2H, m, 5-CH_2), 5.79 (1H, ddt, J = 17.8, 10.3, 6.6 Hz, 4-CH), 7.5-7.7 (5H, m, ArH);

IR (film) ν_{max}: 3073, 2972, 2930, 1677, 1637, 1595, 1576, 1447, 1372, 1357, 1238, 1208, 975, 917, 792, 705 cm^{-1};

MS (70eV) m/z: 174 (M^+ 51%), 159 (19), 145 (8), 131 (20), 120 (21), 105 (100), 78 (65), 77 (84), 51 (49).

Preparation of 1-phenyl-2-propen-1-ol (1)

1

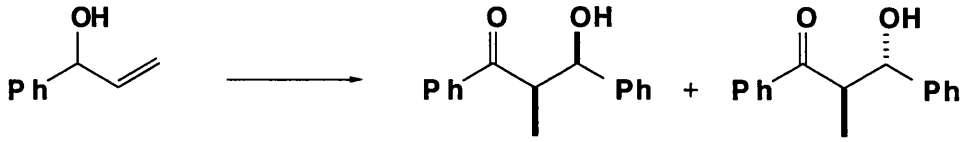
To a cooled (0°C) solution of vinylmagnesium bromide (51.0 ml, 1.0 M in THF, 51.0 mmol) diluted with THF (50 ml) was added a solution of benzaldehyde (5.68 g, 53.5 mmol) in THF (60 ml) dropwise over 40 min. The mixture was allowed to warm to ambient temperature over 2 h, treated with saturated aqueous ammonium chloride and stirred for a further 15 min. The mixture was extracted three times with ether, the combined organic phases washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (10-15% ether in petrol gradient elution) afforded *1-phenyl-2-propen-1-ol* (**1**)[243] as a clear, colourless oil (5.65 g, 83%):

^{1}H NMR (270 MHz) δ_H: 1.97 (1H, d, J = 3.7 Hz, OH), 5.05-5.15 (2H, m, 1-CH, 3-CH_{cis}), 5.27 (1H, dd, J = 17.1, 1.0 Hz, 3-CH_{trans}), 5.97 (1H, ddd, J = 17.1, 10.0, 6.1 Hz, 2-CH), 7.2-7.35 (5H, m, ArH);

IR (film) ν_{max}: 3399, 3029, 2870, 1674, 1600, 1491, 1450, 1197, 1115, 1026, 991, 927, 759, 700 cm^{-1};

MS (70eV) m/z: 134 (M^+ 55%), 133 (77), 117 (35), 115 (45), 107 (35), 105 (86), 92 (65) , 79 (58), 77 (100), 55 (47), 51 (49).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-phenyl-2-propen-1-ol (1)



1 **3** **4**

A degassed solution of alkoxide prepared from 1-phenyl-2-propen-1-ol (**1**) (200 mg, 1.49 mmol) in THF (6 ml) and *n*-butyllithium (1.00 ml, 1.49 M in hexanes, 1.49 mmol) was treated with a degassed solution of Wilkinson's catalyst (27.0 mg, 29.2 μmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 1.5 h. Quench with benzaldehyde (166 μl, 1.64 mmol) and work-up as previously detailed gave after flash chromatography (10-15% ether in petrol gradient elution) an inseparable mixture of aldols **3** and **4** (**3**:**4**=8.3:1, 250 mg, 70%) as a clear, colourless oil, and starting material (3.8 mg, 2%).

(syn)-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (**3**)[244]:

^1H NMR (270 MHz) δ_H: 1.21 (3H, d, J = 7.1 Hz, 2'-CH_3), 3.72 (1H, qd, J = 7.1, 3.4 Hz, 2-CH), 5.24 (1H, d, J = 3.4 Hz, 3-CH), 7.26 (1H, br t, J = 7 Hz, 3-*p*-ArH), 7.35 (2H, br t, J = 7 Hz, 3-*m*-ArH), 7.41 (2H, br d, J = 7 Hz, 3-*o*-ArH), 7.59 (2H, br t, J = 7 Hz, 1-*m*-ArH), 7.59 (1H, br t, J = 7 Hz, 1-*p*-ArH), 7.93 (2H, br d, J = 7 Hz, 1-*o*-ArH);

(anti)-3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (**4**)[244]:

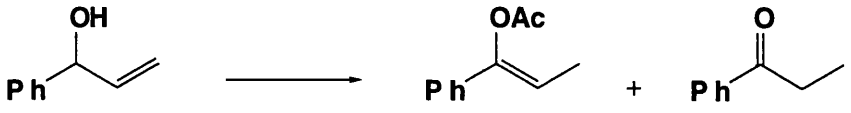
^1H NMR (270 MHz) δ_H: 1.26 (3H, d, J = 7.1 Hz, 2'-CH_3), 3.7-3.8 (1H, m, 2-CH), 5.02 (1H, d, J = 7.3 Hz, 3-CH), 7.2-8.0 (10H, obscured, 2 × ArH);

Mixture of **3** and **4**:

IR (film) ν_{max}: 3469, 3062, 2976, 2932, 1964, 1902, 1814, 1673, 1597, 1578, 1493, 1450, 1346, 1216, 1054, 1027, 972, 759, 703, 658 cm^{-1};

MS (70eV) m/z: 240 (M^+ 0.2%), 222 (2), 134 (23), 105 (100), 77 (48), 51 (20).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-phenyl-2-propen-1-ol (1)



1 5 6

A degassed solution of alkoxide prepared from 1-phenyl-2-propen-1-ol (**1**) (157 mg, 1.17 mmol) in THF (6 ml) and *n*-butyllithium (790 µl, 1.49 M in hexanes, 1.18 mmol) was treated with a degassed solution of Wilkinson's catalyst (21.5 mg, 23.2 µmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 1.5 h. Quench with acetyl chloride (832 µl, 11.7 mmol) and work-up as previously detailed gave after flash chromatography (10-15% ether in petrol gradient elution) a trace of ketone **6** (0.9 mg, <1%), (Z)-enol acetate **5** (115 mg, 56%) and starting material (9 mg, 6%).

1-Phenyl-1-propanone (**6**)[212]:

^1H NMR (270 MHz) δ_H: 1.22 (3H, t, J = 7.1 Hz, 3-CH_3), 3.01 (2H, q, J = 7.1 Hz, 2-CH_2), 7.46 (2H, br t, J = 7 Hz, *m*-ArH), 7.54 (1H, br t, J = 7 Hz, *p*-ArH), 7.97 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3063, 2980, 2939, 1689, 1598, 1583, 1450, 1378, 1353, 1221, 1181, 1078, 1014, 952, 746, 691 cm^{-1};

MS (70eV) m/z: 134 (M^+ 69%), 122 (9), 106 (65), 105 (100), 91 (14), 77 (100), 57 (28), 51 (91), 43 (42), 39 (53), 28 (78).

(Z)-1-Phenyl-1-propen-1-yl acetate (**5**)[244,245]:

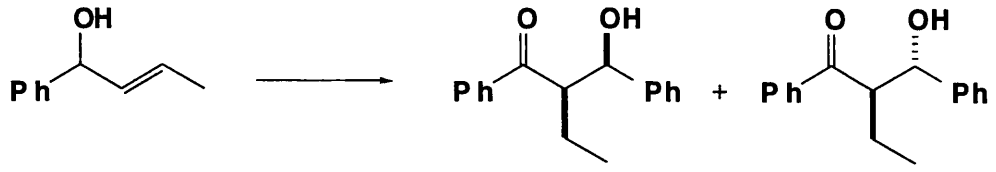
^1H NMR (500 MHz) δ_H: 1.73 (3H, d, J = 7.1 Hz, 3-CH_3), 2.31 (3H, s, $COCH_3$), 5.91 (1H, q, J = 7.1 Hz, 2-CH), 7.29 (1H, br t, J = 8 Hz, *p*-ArH), 7.33 (2H, br t, J = 8 Hz, *m*-ArH), 7.40 (2H, br d, J = 8 Hz, *o*-ArH);

IR (film) ν_{max}: 3062, 2937, 1758, 1694, 1601, 1584, 1496, 1450, 1371, 1272, 1209, 1116, 1027, 972, 754, 695, 640 cm^{-1};

MS (70eV) m/z: 176 (M^+ 17%), 134 (100), 133 (65), 115 (7), 105 (36), 77 (28), 56 (12), 51 (10), 43 (40);

HRMS m/z: M^+ = 176.0843 (176.0837 calcd for $C_{11}H_{12}O_2$).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-1-phenyl-2-buten-1-ol (7)



7 **9** **10**

A degassed solution of alkoxide prepared from (E)-1-phenyl-2-buten-1-ol (**7**)[102] (223 mg, 1.50 mmol) in THF (6 ml) and *n*-butyllithium (1.01 ml, 1.49 M in hexanes, 1.50 mmol) was treated with a degassed solution of Wilkinson's catalyst (27.9 mg, 30.1 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 5.5 h. Quench with benzaldehyde (168 μl, 1.65 mmol) and work-up as previously detailed gave after flash chromatography (20% ether in petrol elution) an inseparable mixture of aldols **9** and **10** (**9**:**10**=3.0:1, 351 mg, 92%).

(syn)-2-(Hydroxyphenylmethyl)-1-phenyl-1-butanone (**9**)[246]:

^1H NMR (500 MHz) δ_H: 0.78 (3H, t, J = 7.5 Hz, 4-CH_3), 1.7-1.8 (1H, m, 3-CH_AH$_B$), 1.9-2.0 (1H, m, 3-CH$_A$$H_B$), 3.24 (1H, d, J = 1.9 Hz, OH), 3.74 (1H, quintet, J = 4.6 Hz, 2-CH), 5.08 (1H, d, J = 4.1 Hz, 2'-CH), 7.21 (1H, t, J = 7.3 Hz, 2'-*p*-Ar), 7.31 (2H, t, J = 7.4 Hz, 2'-*m*-ArH), 7.39 (2H, d, J = 7.5 Hz, 2'-*o*-ArH), 7.44 (2H, t, J = 7.4 Hz, 1-*m*-ArH), 7.56 (1H, t, J = 7.4 Hz, 1-*p*-ArH), 7.90 (2H, d, J = 7.3 Hz, 1-*o*-ArH);

(anti)-2-(Hydroxyphenylmethyl)-1-phenyl-1-butanone (**10**)[246]:

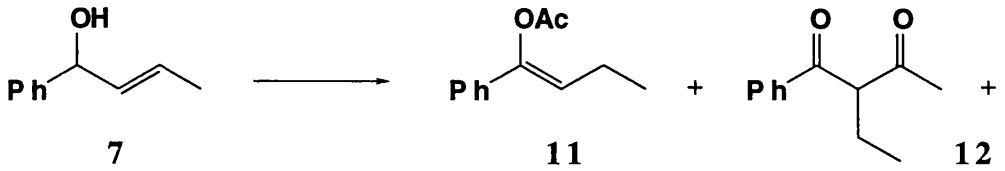
^1H NMR (500 MHz) δ_H: 0.81 (3H, t, J = 7.5 Hz, 4-CH_3), 1.5-1.6 (1H, m, 3-CH_AH$_B$), 1.7-1.8 (1H, m, 3-CH$_A$$H_B$), 3.12 (1H, d, J = 5.4 Hz, OH), 3.78 (1H, td, J = 7.1, 5.2 Hz, 2-CH), 5.02 (1H, dd, J = 6.9, 5.6 Hz, 2'-CH), 7.2-7.4 (5H, m, 2'-ArH), 7.44 (2H, t, J = 7.4 Hz, 1-*m*-ArH), 7.54 (1H, t, J = 7.4 Hz, 1-*p*-ArH), 7.92 (2H, d, J = 7.3 Hz, 1-*o*-ArH);

Mixture of **9** and **10**:

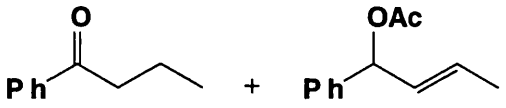
IR (film) ν_{max}: 3444, 3063, 3031, 2966, 2876, 1669, 1597, 1579, 1494, 1447, 1360, 1267, 1212, 1001, 848, 760, 703, 661 cm^{-1};

MS (70eV) m/z: 254 (M^+ 0.1%), 236 (0.4), 225 (2.3), 148 (21), 133 (13), 120 (6), 105 (100), 77 (63), 55 (9), 51 (21).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-1-phenyl-2-buten-1-ol (7); acetyl chloride quench



7 11 12



13 14

A degassed solution of alkoxide prepared from (E)-1-phenyl-2-buten-1-ol (**7**)[102] (199 mg, 1.34 mmol) in THF (6 ml) and *n*-butyllithium (824 µl, 1.63 M in hexanes, 1.34 mmol) was treated with a degassed solution of Wilkinson's catalyst (24.8 mg, 26.9 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 6 h. Quench with acetyl chloride (954 µl, 13.4 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) ketone **13** (17 mg, 9%), an inseparable mixture (70 mg) of (Z)-enol acetate **11** (Z:E>50:1, 19%) and allyl acetate **14** (8%), and diketone **12** (35 mg, 14%).

1-Phenyl-1-butanone (**13**)[212]:

^1H NMR (270 MHz) δ_H: 1.01 (3H, t, J = 7.3 Hz, 4-CH_3), 1.78 (2H, sextet, J = 7.3 Hz, 3-CH_2), 2.95 (2H, t, J = 7.3 Hz, 2-CH_2), 7.46 (2H, br t, J = 7 Hz, *m*-ArH), 7.55 (1H, br t, J = 7 Hz, *p*-ArH), 7.96 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3062, 2963, 2934, 2875, 1967, 1905, 1817, 1687, 1598, 1581, 1449, 1369, 1274, 1213, 1180, 1002, 896, 754, 736, 691, 668 cm^{-1};

MS (70eV) m/z: 148 (M^+ 49%), 120 (38), 105 (100), 91 (11), 77 (90), 65 (7), 55

(10), 51 (82), 39 (31), 27 (54).

(Z)-1-Phenyl-1-buten-1-yl acetate (**11**)[102]:

^{1}H NMR (500 MHz) δ_H: 1.08 (3, t, J = 7.6 Hz, 4-CH_3), 2.16 (2H, quintet, J = 7.5 Hz, 3-CH_2), 2.30 (3H, s, $COCH_3$), 5.83 (1H, t, J = 7.3 Hz, 2-CH), 7.27 (1H, br t, J = 7 Hz, *p*-ArH), 7.33 (2H, br t, J = 7 Hz, *m*-ArH), 7.41 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3034, 2968, 2936, 1760, 1665, 1601, 1494, 1447, 1370, 1207, 1035, 751, 691 cm^{-1};

MS (70eV) m/z: 190 (M^+ 12%), 148 (100), 133 (18), 105 (10), 77 (15), 51(8), 43 (21).

(E)-1-Phenyl-2-buten-1-yl acetate (**14**):

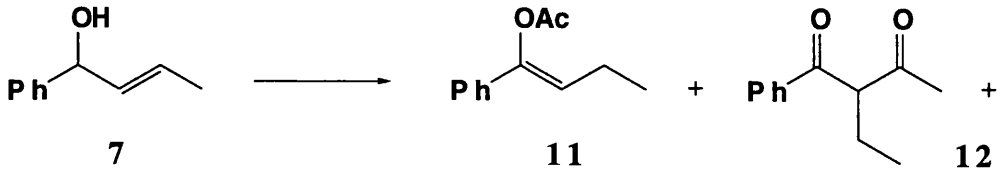
^{1}H NMR (500 MHz) δ_H: 1.73 (3H, dd, J = 6.3, 0.7 Hz, 4-CH_3), 2.10 (3H, s, $COCH_3$), 5.68 (1H, ddd, J = 15.3, 6.9, 1.4 Hz, 2-CH), 5.77 (1H, ddd, J = 15.3, 6.3, 0.7 Hz, 3-CH), 6.23 (1H, br d, J = 7.0 Hz, 1-CH), 7.25-7.45 (5H, m, ArH).

2-Ethyl-1-phenyl-1,3-butanedione (**12**)[247]:

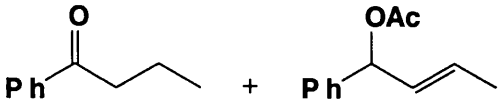
^{1}H NMR (270 MHz) δ_H: 0.94 (3H, t, J = 7.4 Hz, 5-CH_3), 1.9-2.1 (2H, m, 4-CH_2), 2.13 (3H, s, 1-CH_3), 4.35 (1H, t, J = 7.0 Hz, 3-CH), 7.48 (2H, br t, J = 7 Hz, *m*-ArH), 7.59 (1H, br t, J = 7 Hz, *p*-ArH), 7.98 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 2969, 2936, 1722, 1675, 1597, 1448, 1357, 1273, 1211, 735, 695 cm^{-1}.

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-1-phenyl-2-buten-1-ol (7); acetic anhydride quench



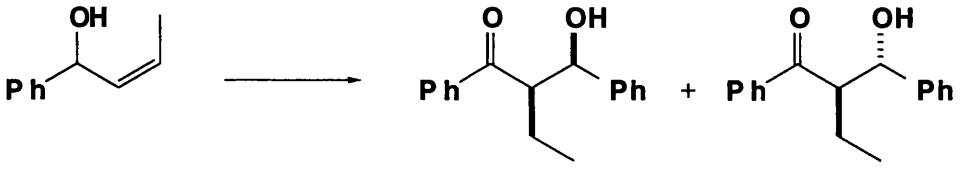
7 11 12



13 14

A degassed solution of alkoxide prepared from (E)-1-phenyl-2-buten-1-ol (**7**)[102] (190 mg, 1.28 mmol) in THF (6 ml) and *n*-butyllithium (785 µl, 1.63 M in hexanes, 1.28 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.7 mg, 25.6 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 8 h. Quench with acetic anhydride (1.21 ml, 12.8 mmol) and work-up as previously detailed gave after flash chromatography (5-33% ether in petrol gradient elution) *1-phenyl-1-butanone* (**13**) (17 mg, 9%), an inseparable mixture (102 mg) of *(Z)-1-phenyl-1-buten-1-yl acetate* (**11**) (Z:E>20:1, 32%) and *(E)-1-phenyl-2-buten-1-yl acetate* (**14**) (10%), and *2-ethyl-1-phenyl-1,3-butanedione* (**12**) (16 mg, 7%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (Z)-1-phenyl-2-buten-1-ol (8)

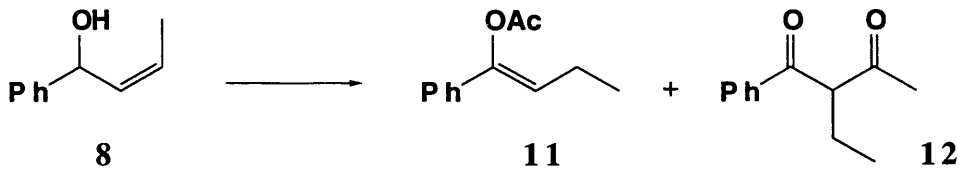


8 9 10

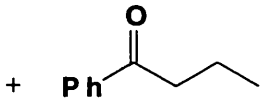
A degassed solution of alkoxide prepared from (Z)-1-phenyl-2-buten-1-ol (**8**)[102] (200 mg, 1.35 mmol) in THF (6 ml) and *n*-butyllithium (906 µl, 1.49 M in hexanes, 1.35 mmol) was treated with a degassed solution of Wilkinson's catalyst (25.5 mg, 27.6

μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 6.5 h. Quench with benzaldehyde (151 μl, 1.48 mmol) and work-up as previously detailed gave after flash chromatography (33% ether in petrol elution) an inseparable mixture of *(syn)-2-(hydroxyphenylmethyl)-1-phenyl-1-butanone* (**9**) and *(anti)-2-(hydroxyphenylmethyl)-1-phenyl-1-butanone* (**10**) (**9**:**10**=3.0:1, 257 mg, 75%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (Z)-1-phenyl-2-buten-1-ol (8)



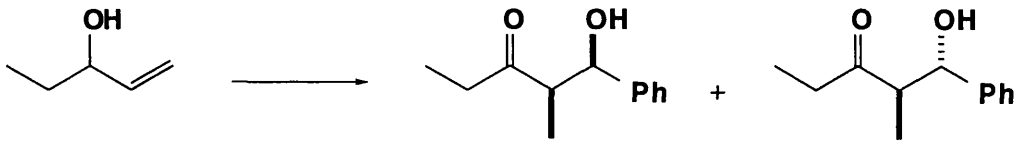
8 **11** **12**



13

A degassed solution of alkoxide prepared from (Z)-1-phenyl-2-buten-1-ol (**8**)[102] (199 mg, 1.34 mmol) in THF (6 ml) and *n*-butyllithium (824 μl, 1.63 M in hexanes, 1.34 mmol) was treated with a degassed solution of Wilkinson's catalyst (25.2 mg, 27.2 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 7 h. Quench with acetyl chloride (950 μl, 13.4 mmol) and work-up as previously detailed gave after flash chromatography (2-20% ether in petrol gradient elution) *1-phenyl-1-butanone* (**13**) (29 mg, 14%), *(Z)-1-phenyl-1-buten-1-yl acetate* (**11**) (Z:E>50:1, 115 mg, 45%) and *2-ethyl-1-phenyl-1,3-butanedione* (**12**) (31 mg, 12%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-penten-3-ol (15)



15 **16** **17**

A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (135 mg, 1.57 mmol) in THF (6 ml) and *n*-butyllithium (1.05 ml, 1.49 M in hexanes, 1.57 mmol) was treated with a degassed solution of Wilkinson's catalyst (29.4 mg, 31.8 μmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 10 h. Quench with benzaldehyde (176 μl, 1.72 mmol) and work-up as previously detailed gave after flash chromatography (20% ether in petrol elution) aldols **16** and **17** (**16**:**17**=3.5:1, 240 mg, 80%) as a clear, colourless oil and an inseparable mixture.

(syn)-1-Hydroxy-2-methyl-1-phenyl-3-pentanone (**16**)[13,248]:

^1H NMR (270 MHz) δ_H: 0.98 (3H, t, J = 7.1 Hz, 5-CH_3), 1.08 (3H, d, J = 7.1 Hz, 2'-CH_3), 2.4-2.55 (2H, m, 4-CH_2), 2.83 (1H, qd, J = 7.1, 4.1 Hz, 2-CH), 3.20 (1H, br d, J = 2.4 Hz, OH), 5.03 (1H, dd, J = 3.9, 2.2 Hz, 1-CH), 7.2-7.4 (5H, m, ArH);

(anti)-1-Hydroxy-2-methyl-1-phenyl-3-pentanone (**17**)[13,248]:

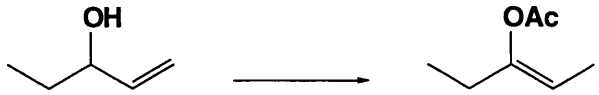
^1H NMR (270 MHz) δ_H: 0.92 (3H, d, J = 7.1 Hz, 2'-CH_3), 1.03 (3H, t, J = 7.3 Hz, 5-CH_3), 1.79 (1H, br s, OH), 2.2-2.4 (2H, m, 4-CH_2), 2.9-3.0 (1H, m, 2-CH), 4.73 (1H, J = dd, 8.0, 4.4 Hz, 1-CH), 7.2-7.4 (5H, m, ArH);

Mixture of **16** and **17**:

IR (film) ν_{max}: 3456, 3030, 2977, 2881, 1955, 1889, 1814, 1707, 1604, 1493, 1409, 1453, 1376, 1198, 1112, 1015, 975, 762, 702 cm^{-1};

MS (70eV) m/z: 192 (M^+ 1%), 174 (2), 145 (2), 117 (4), 106 (57), 105 (48), 86 (31), 77 (65), 57 (100), 51 (32), 29 (68).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-penten-3-ol (15)



15 **18**

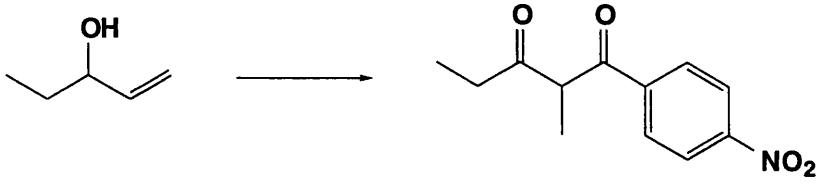
A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (127 mg, 1.48 mmol) in THF (6 ml) and *n*-butyllithium (907 µl, 1.63 M in hexanes, 1.48 mmol) was treated with a degassed solution of Wilkinson's catalyst (27.4 mg, 29.6 µmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 11 h. Quench with acetic anhydride (1.40 ml, 14.8 mmol) and work-up as previously detailed gave after flash chromatography (10% ether in 30-40 petrol elution) *(Z)-2-penten-3-yl acetate* (**18**)[134,249] (51.2 mg, 27%) as a clear, volatile oil.

^1H NMR (270 MHz) δ_H: 0.99 (3H, t, J = 7.3 Hz, 5-CH_3), 1.45 (3H, br d, J = 6.8 Hz, 1-CH_3), 2.1-2.25 (2H, m, 4-CH_2), 2.14 (3H, s, $COCH_3$), 5.04 (1H, br q, J = 6.8 Hz, 2-CH);

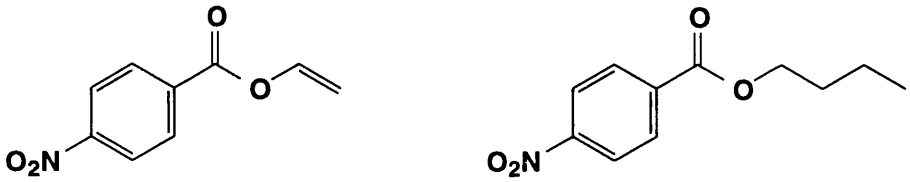
^{13}C NMR (67.9 MHz) δ_C: 168.8, 150.6, 109.5, 26.5, 20.6, 11.1, 10.6;

IR (film) ν_{max}: 2975, 2938, 2889, 1756, 1690, 1453, 1371, 1221, 1056 cm^{-1}.

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-penten-3-ol (15)



16 **19**



38 **39**

A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (105 mg, 1.22 mmol) in THF (6 ml) and *n*-butyllithium (819 µl, 1.49 M in hexanes, 1.22 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.9 mg, 24.7 µmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 10 h. Once cooled to –78°C a solution of 4-nitrobenzoyl chloride (2.26 g, 12.2 mmol, 10 equiv) in THF (4 ml) was added, followed by aqueous sodium hydrogen carbonate after 10 min. The reaction mixture was extracted three times with ether, the combined organic phases washed with more aqueous sodium hydrogen carbonate, water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (20-50% ether in petrol gradient elution) gave a mixture (21 mg) of vinyl ester **38** (*ca.* 1%) and *n*-butyl ester **39** (6%), and diketone **19** (181 mg, 63%) as an oil which crystallised on standing as clear, colourless plates, m.p. 65°C.

Ethenyl 4'-nitrobenzoate (**38**)[250]:

^1H NMR (270 MHz) δ_H: 4.80 (1H, dd, J = 6.3, 2.0 Hz, 2-CH_{cis}), 5.15 (1H, dd, J = 13.9, 2.0 Hz, 2-CH_{trans}), 7.50 (1H, dd, J = 13.9, 6.3 Hz, 1-CH), 8.2-8.4 (4H, obscured, ArH);

MS (70eV) m/z: 193 (M^+ 0.5%), 150 (100), 120 (9), 104 (45), 92 (11), 76 (29), 64 (3), 50 (16);

HRMS m/z: MH^+ = 194.0457 (194.0453 calcd for $C_9H_7NO_4$);

GC: retention time 6.90 min [H_2, capillary flow rate (70°C) 3.09 ml.min^{-1}, split ratio 40:1, initial temp. 100°C (2 min), ramp 20°C.min^{-1}];

Butyl 4'-nitrobenzoate (**39**)[251]:

^{1}H NMR (270 MHz) δ_H: 0.99 (3H, t, *J* = 7.4 Hz, 4-CH_3), 1.48 (2H, sextet, *J* = 7.3 Hz, 3-CH_2), 1.78 (2H, quintet, *J* = 7.1 Hz, 2-CH_2), 4.37 (2H, t, *J* = 6.6 Hz, 1-CH_2), 8.20 (2H, d, *J* = 9.0 Hz, ArH), 8.28 (2H, d, *J* = 9.0 Hz, ArH);

MS (70eV) m/z: 223 (M^+ 0.6%), 207 (0.6), 168 (45), 150 (87), 120 (9), 104 (37), 92 (9), 76 (30), 65 (9), 56 (100), 50 (14), 41 (33), 29 (25);

HRMS m/z: MH^+ = 224.0920 (224.0923 calcd for $C_{11}H_{13}NO_4$);

GC: retention time 8.53 min (as above);

Mixture of **38** and **39**:

IR (film) ν_{max}: 3114, 2962, 2875, 1739, 1733, 1717, 1648, 1609, 1533, 1465, 1411, 1351, 1278, 1134, 1103, 1015, 945, 874, 840, 720, 668 cm^{-1};

MS (Xe^+ FAB) m/z: 224 (**39**: MH^+ 33%), 207 (19), 194 (**38**: MH^+ 5%), 168 (40), 150 (100), 147 (29), 134 (28), 123 (13), 111 (21), 109 (22), 104 (23), 97 (34), 95 (28), 91 (11).

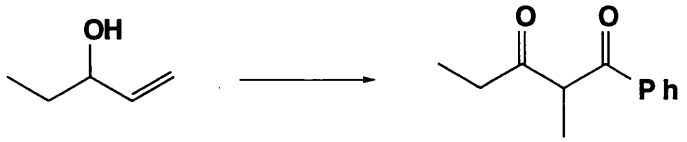
2-Methyl-1-(4'-nitrophenyl)-1,3-pentanedione (**19**)[252]:

^{1}H NMR (270 MHz) δ_H: 1.01 (3H, t, *J* = 7.3 Hz, 5-CH_3), 1.47 (3H, d, *J* = 7.0 Hz, 2'-CH_3), 2.51 (2H, q, *J* = 7.3 Hz, 4-CH2), 4.52 (1H, q, *J* = 7.0 Hz, 2-CH), 8.09 (2H, d, *J* = 9.0 Hz, *o*-ArH), 8.29 (2H, d, J = 9.0 Hz, *m*-ArH);

IR (film) ν_{max}: 2981, 2938, 1714, 1687, 1606, 1526, 1457, 1409, 1349, 1218, 1110, 974, 855, 712 cm^{-1};

MS (70eV) m/z: 235 (M^+ 0.8%), 218 (1), 206 (4), 179 (7), 150 (19), 120 (12), 104 (15), 92 (4), 76 (9), 57 (100), 29 (22); (Xe^+ FAB) m/z: 236 (MH^+ 100%), 222 (9), 176 (9), 150 (17), 137 (25), 104 (8), 89 (7), 77 (7), 57 (68), 29 (7).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-penten-3-ol (15)



15 **20**

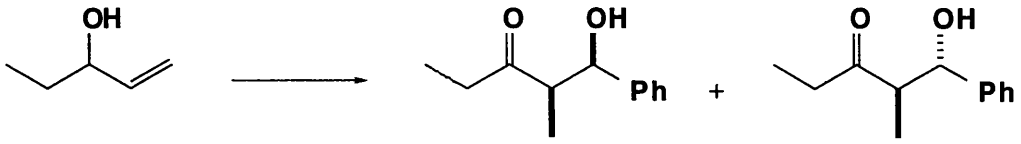
A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (106 mg, 1.23 mmol) in THF (6 ml) and *n*-butyllithium (755 µl, 1.63 M in hexanes, 1.23 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.6 mg, 25.5 µmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 11 h. Once cooled to –78°C a solution of benzoic anhydride (1.39 g, 6.15 mmol, 5.0 equiv) in THF (5 ml) was added, and the reaction mixture allowed to warm to ambient temperature and stir for 1 h. Treatment with aqueous sodium hydrogen carbonate, extraction three times with ether, washing of the combined organic phases with water and brine, and drying over $MgSO_4$ gave after evaporation *in vacuo* a crude oil which proved to be largely unreacted benzoic anhydride. The residue was dissolved in THF (20 ml) and water (5 ml) with lithium hydroxide (*ca.* 15 equiv) and stirred for 12 h at ambient temperature. Quench and work-up as before gave after flash chromatography (5-10% ether in petrol elution) *2-methyl-1-phenyl-1,3-pentanedione* (**20**)[249] (92 mg, 39%) as an clear, colourless oil:

^1H NMR (270 MHz) δ_H: 1.01 (3H, t, J = 7.1 Hz, 5-CH_3), 1.44 (3H, d, J = 6.8 Hz, 2'-CH_3), 2.35-2.65 (2H, m, 4-CH_2), 4.50 (1H, q, J = 6.8 Hz, 2-CH), 7.47 (2H, br t, J = 7 Hz, *m*-ArH), 7.58 (1H, br t, J = 7 Hz, *p*-ArH), 7.96 (2H, br d, J = 7 Hz, *o*-ArH);

^{13}C NMR (67.9 MHz) δ_C: 207.4, 197.5, 136.1, 133.7, 128.9, 128.7, 56.0, 34.0, 13.7, 7.8;

IR (film) ν_{max}: 3063, 2980, 2938, 1720, 1677, 1596, 1450, 1329, 1375, 1224, 971, 703 cm^{-1}.

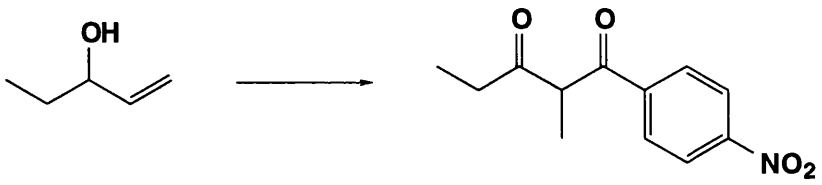
$Rh(PPh_3)_3Cl/SnCl_2$ mediated isomerisation of 1-penten-3-ol (15)



15 **16** **17**

A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (143 mg, 1.66 mmol) in THF (6 ml) and *n*-butyllithium (1.11 ml, 1.49 M in hexanes, 1.66 mmol) was treated with a degassed solution of Wilkinson's catalyst (31.1 mg, 33.6 μmol, 2.0 mol%) and tin (II) chloride (6.4 mg, 34 μmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 3 h. Quench with benzaldehyde (186 μl, 1.82 mmol) and work-up as previously detailed gave after flash chromatography (20% ether in petrol elution) *(syn)-1-hydroxy-2-methyl-1-phenyl-3-pentanone* (**16**) and *(anti)-1-hydroxy-2-methyl-1-phenyl-3-pentanone* (**17**) (**16**:**17**=3.3:1, 235 mg, 74%) as a clear, colourless oil.

$Rh(PPh_3)_3Cl/SnCl_2$ mediated isomerisation of 1-penten-3-ol (15)

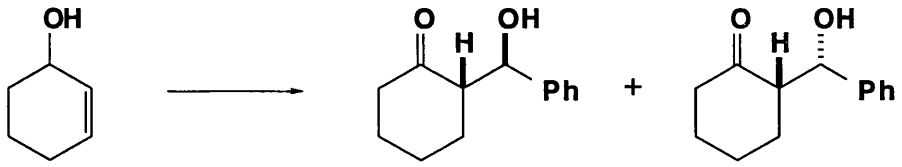


15 **19**

A degassed solution of alkoxide prepared from 1-penten-3-ol (**15**) (98 mg, 1.13 mmol) in THF (6 ml) and *n*-butyllithium (758 μl, 1.49 M in hexanes, 1.13 mmol) was treated with a degassed solution of Wilkinson's catalyst (21.0 mg, 22.7 μmol, 2.0 mol%) and tin (II) chloride (4.7 mg, 25 μmol, 2.1 mol%) in THF (4 ml), and the mixture heated to reflux for 3.25 h. Once cooled to –78°C a solution of 4-nitrobenzoyl chloride (2.10 g, 11.3 mmol, 10 equiv) in THF (4 ml) was added, followed by aqueous sodium hydrogen carbonate after 15 min. The reaction mixture was extracted three times with

ether, the combined organic phases washed twice with more aqueous sodium hydrogen carbonate, water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (20-50% ether in petrol gradient elution) gave *2-methyl-1-(4'-nitrophenyl)-1,3-pentanedione* (**19**) (174 mg, 65%) as an clear oil which crystallised on standing.

$Rh(PPh_3)_3Cl$ mediated isomerisation of 2-cyclohexen-1-ol (21)



21 **22** **23**

A degassed solution of alkoxide prepared from 2-cyclohexen-1-ol (**21**) (139 mg, 1.42 mmol) in THF (6 ml) and *n*-butyllithium (871 µl, 1.63 M in hexanes, 1.42 mmol) was treated with a degassed solution of Wilkinson's catalyst (65.2 mg, 70.5 µmol, 5.0 mol%) in THF (5 ml), and the mixture heated to reflux for 48 h. Quench with benzaldehyde (159 µl, 1.56 mmol) and work-up as previously detailed gave after flash chromatography (20-50% ether in petrol gradient elution) an inseparable mixture of aldols **22** and **23** (**22**:**23**=4.2:1, 19.5 mg, 7%) as a clear, colourless oil.

(anti)-2-(Hydroxyphenylmethyl)cyclohexanone (**22**)[13,133]:

^1H NMR (270 MHz) δ_H: 1.2-2.6 (8H, m, 3-, 4-, 5-, 6-CH_2), 2.55-2.7 (1H, m, 2-CH), 3.95 (1H, d, J = 0.7 Hz, OH), 4.78 (1H, d, J = 8.8 Hz, 2'-CH), 7.2-7.4 (5H, m, ArH);

(syn)-2-(Hydroxyphenylmethyl)cyclohexanone (**23**)[13,133]:

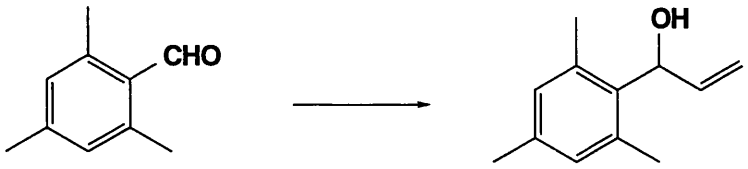
^1H NMR (270 MHz) δ_H: 1.2-2.7 (9H, m, 3-, 4-, 5-, 6-CH_2, 2-CH), 3.0 (1H, d, J = 3 Hz, OH), 5.39 (1H, m, 2'-CH), 7.2-7.4 (5H, m, ArH);

Mixture of **22** and **23**:

IR (film) ν_{max}: 3502, 2937, 2864, 1699, 1604, 1450, 1130, 1042, 776, 702 cm^{-1};

MS (70eV) m/z: 204 (M^+ 3%), 186 (100), 175 (8), 157 (10), 147 (17), 77 (11).

Preparation of 1-(2',4',6'-trimethylphenyl)-2-propen-1-ol (25)



25

To a cooled (0°C) solution of vinylmagnesium bromide (21.3 ml, 1.0 M in THF, 21.3 mmol) diluted with THF (30 ml) was added a solution of 2,4,6-trimethylbenzaldehyde (3.01 g, 20.3 mmol) in THF (40 ml) dropwise over 30 min. The mixture was stirred at 0°C for 30 min, allowed to warm to ambient temperature for 1 h, treated with saturated aqueous ammonium chloride and stirred until clear. The mixture was extracted three times with ether, the combined organic phases washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (10-20% ether in petrol elution) afforded *1-(2',4',6'-trimethylphenyl)-2-propen-1-ol* (**25**) (3.15 g, 88%) as white plates, m.p. 45°C:

^1H NMR (500 MHz) δ_H: 2.00 (1H, s, OH), 2.28 (3H, s, *p*-$ArCH_3$), 2.39 (6H, s, 2 × *o*-$ArCH_3$), 5.17 (1H, dt, J = 10.5, 2.0 Hz, 3-CH_{cis}), 5.22 (1H, dt, J = 17.1, 1.7 Hz, 3-CH_{trans}), 5.70 (1H, br t, J = 2 Hz, 1-CH), 6.16 (1H, ddd, J = 17.1, 10.5, 4.5 Hz, 2-CH), 6.85 (2H, s, *m*-ArH);

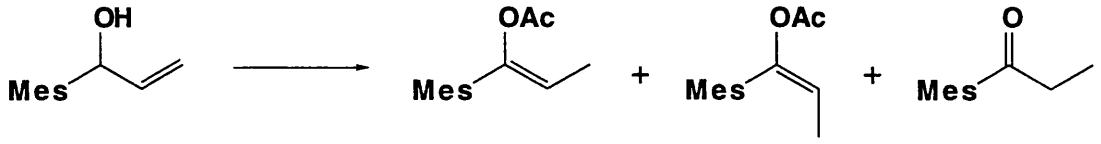
^{13}C NMR (126 MHz) δ_C: 20.5, 20.7, 71.5, 114.2, 130.0, 135.0, 136.5, 137.0, 138.8;

IR (film) ν_{max}: 3390, 2920, 1635, 1611, 1572, 1452, 1379, 1287, 1203, 1149, 1113, 1045, 990, 922, 850, 801 cm^{-1};

MS (70eV) m/z: 176 (M^+ 51%), 161 (37), 158 (41), 149 (34), 147 (100), 143 (65), 119 (58), 105 (45), 91 (32), 77 (21), 55 (34);

HRMS m/z: M^+ = 176.1200 (176.1201 calcd for $C_{12}H_{16}O$).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-(2',4',6'-trimethylphenyl)-2-propen-1-ol (25)



25 **26** **27** **24**

A degassed solution of alkoxide prepared from 1-(2',4',6'-trimethylphenyl)-2-propen-1-ol (**25**) (126 mg, 715 μmol) in THF (6 ml) and *n*-butyllithium (439 μl, 1.63 M in hexanes, 715 μmol) was treated with a degassed solution of Wilkinson's catalyst (13.2 mg, 14.3 μmol, 2.0 mol%) in THF (4 ml), and the mixture heated to reflux for 5.5 h. Quench with acetic anhydride (675 μl, 7.15 mmol) and work-up as previously detailed gave after flash chromatography (5-10% ether in petrol gradient elution) an inseparable mixture (99.6 mg) of ketone (**24**) (12%) and enol acetates **26** and **27** (**26**:**27**=1.69:1, 52%).

1-(2',4',6'-Trimethylphenyl)-1-propanone (**24**)[13]:

^1H NMR (400 MHz) δ_H: 1.20 (3H, t, J = 7.3 Hz), 2.19 (6H, s, 2 × *o*-$ArCH_3$), 2.27 (3H, s, *p*-$ArCH_3$), 2.72 (2H, q, J = 7.3 Hz, 2-CH_2), 6.85 (2H, s, *m*-ArH);

MS (70eV) m/z: 176 (M^+ 4%), 147 (100), 119 (31), 91 (9), 77 (5), 41 (5);

GC: retention time 5.20 min [H_2, capillary flow rate (70°C) 4.33 ml.min^{-1}, split ratio 30:1, isothermal 130°C];

(Z)-1-(2',4',6'-Trimethylphenyl)-1-propen-1-yl acetate (**26**):

^1H NMR (400 MHz) δ_H: 1.73 (3H, d, J = 6.8 Hz), 2.11 (3H, s, $COCH_3$), 2.29 (6H, s, 2 × *o*-$ArCH_3$), 2.33 (3H, s, *p*-$ArCH_3$), 5.21 (1H, q, J = 6.8 Hz, 2-CH), 6.86 (2H, s, *m*-ArH);

MS (70eV) m/z: 218 (M^+ 8%), 176 (14), 158 (4), 147 (100), 119 (10), 115 (4), 91 (5), 77 (3), 55 (3), 43 (13), 27 (2);

GC: retention time 9.10 min (as before);

(E)-1-(2',4',6'-Trimethylphenyl)-1-propen-1-yl acetate (**27**):

^1H NMR (400 MHz) δ_H: 1.45 (3H, d, J = 7.1 Hz), 2.06 (3H, s, $COCH_3$), 2.33

(6H, s, 2 × *o*-$ArCH_3$), 2.36 (3H, s, *p*-$ArCH_3$), 5.64 (1H, q, *J* = 7.1 Hz, 2-CH), 6.88 (2H, s, *m*-ArH);

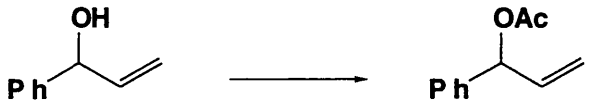
MS (70eV) m/z: 218 (M^+ 6%), 176 (14), 158 (5), 147 (100), 119 (10), 115 (3), 91 (6), 77 (3), 55 (3), 43 (14), 27 (2);

GC: retention time 8.52 min (as before);

Mixture **24**, **26** and **27**:

IR (film) ν_{max}: 3059, 2940, 1759, 1720, 1602, 1495, 1450, 1031, 951 cm^{-1}.

$Rh(CO)(PPh_3)_2Cl$—Attempted isomerisation of 1-phenyl-2-propen-1-ol (1)



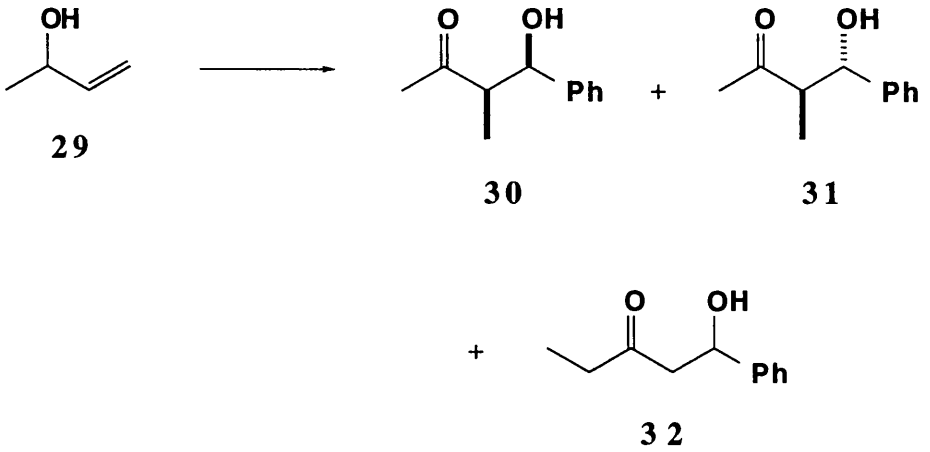
1 **28**

A degassed solution of alkoxide prepared from 1-phenyl-2-propen-1-ol (**1**) (219 mg, 1.63 mmol) in THF (6 ml) and *n*-butyllithium (1.09 ml, 1.49 M in hexanes, 1.63 mmol) was treated with a degassed solution of carbonylchlorobis(triphenylphosphine) rhodium (I) (22.7 mg, 32.9 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 9 h. Quench with acetyl chloride (1.16 ml, 16.3 mmol) and work-up as previously detailed gave after flash chromatography (15% ether in petrol elution) only acetylated starting material **28** (92 mg, 32%) and starting material (35 mg, 16%), and no trace of enol acetates.

1-Phenyl-2-propen-1-yl acetate (**28**)[253]:

^1H NMR (270 MHz) δ_H: 2.12 (3H, s, $COCH_3$), 5.25 (1H, d, *J* = 10.3 Hz, 3-CH_{cis}), 5.30 (1H, d, *J* = 17.1 Hz, 3-CH_{trans}), 6.01 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz, 2-CH), 6.27 (1H, d, *J* = 5.9 Hz, 1-CH), 7.3-7.4 (5H, m, ArH).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 1-buten-3-ol (29)



A degassed solution of alkoxide prepared from 1-buten-3-ol (**29**) (123 mg, 1.70 mmol) in THF (6 ml) and *n*-butyllithium (1.05 ml, 1.63 M in hexanes, 1.71 mmol) was treated with a degassed solution of Wilkinson's catalyst (31.5 mg, 34.1 μmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 3 h. Quench with benzaldehyde (190 μl, 1.87 mmol) and work-up as previously detailed gave after flash chromatography (20-50% ether in petrol gradient elution) an inseparable mixture (201 mg) of aldols **30** and **31** (**30**:**31**=3:1, 56%) and regioisomeric aldol **32** (10%).

(syn)-1-Hydroxy-2-methyl-1-phenyl-3-butanone (**30**)[248]:

^1H NMR (270 MHz) δ_H: 1.08 (3H, d, J = 7.1 Hz, 2'-CH_3), 2.13 (3H, s, 4-CH_3), 2.8 (1H, m, 2-CH), 3.09 (1H, br s, OH), 5.08 (1H, d, J = 3.7 Hz, 1-CH), 7.2-7.4 (5H, m, ArH);

(anti)-1-Hydroxy-2-methyl-1-phenyl-3-butanone (**31**)[248]:

^1H NMR (270 MHz) δ_H: 0.92 (3H, d, J = 7.3 Hz, 2'-CH_3), 2.21 (3H, s, 4-CH_3), 2.8 (1H, m, 2-CH), 4.72 (1H, d, J = 8.3 Hz, 1-CH), 7.2-7.4 (5H, m, ArH);

1-Hydroxy-1-phenyl-3-pentanone (**32**)[254]:

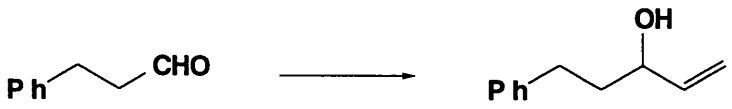
^1H NMR (270 MHz) δ_H: 1.06 (3H, t, J = 7.3 Hz, 5-CH_3), 2.8-3.0 (4H, m, 2-CH_2, 4-CH_2), 5.12 (1H, m, 1-CH), 7.2-7.4 (5H, m, ArH);

Mixture of **30**, **31** and **32**:

IR (film) ν_{max}: 3470, 2973, 2933, 1674, 1595, 1575, 1448, 1214, 971, 702 cm^{-1};

MS (70eV) m/z: 178 (M^+ 14%), 160 (15), 133 (7), 122 (9), 117 (17), 106 (95), 79 (63), 77 (87), 72 (100), 63 (10), 50 (78), 43 (50), 39 (31).

Preparation of 5-phenyl-1-penten-3-ol (33)



33

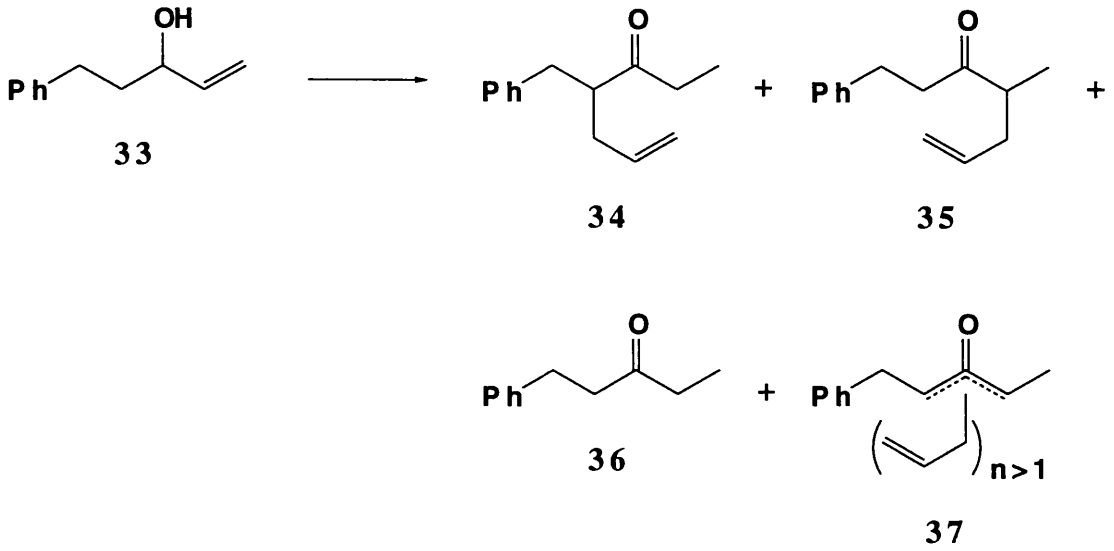
To a stirred, cooled (0°C) solution of 3-phenylpropanal (2.13 g, 15.9 mmol) in THF (25 ml) was added a solution of vinylmagnesium bromide (17.5 ml, 1.0 M in THF, 17.5 mmol) dropwise over 15 min. After a further 30 min at 0°C saturated aqueous ammonium chloride was added and the aqueous layer extracted twice with ether. The combined organic phases were washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (20% ether in petrol elution) afforded *5-phenyl-1-penten-3-ol* (**33**)[126b,255] as a clear, colourless oil (1.72 g, 67%):

^1H NMR (270 MHz) δ_H: 1.65 (1H, br s, OH), 1.80-1.95 (2H, m, 2-CH_2), 2.65-2.85 (2H, m, 1-CH_2), 4.14 (1H, q, J = 6.1 Hz, 3-CH), 5.15 (1H, dt, J = 10.5, 1.3 Hz, 5-CH_{cis}), 5.26 (1H, dt, J = 17.1, 1.3 Hz, 5-CH_{trans}), 5.92 (1H, ddd, J = 17.1, 10.5, 6.1 Hz, 4-CH), 7.2-7.35 (5H, m, ArH);

IR (film) ν_{max}: 3380, 3036, 2938, 1646, 1608, 1500, 1457, 1023, 996, 928, 704 cm^{-1};

MS (70eV) m/z: 162 (M^+ 15%), 144 (24), 133 (12), 129 (42), 105 (45), 91 (100), 79 20), 77 (18), 57 (43).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), reaction time 3 h



A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (211 mg, 1.30 mmol) in THF (6 ml) and *n*-butyllithium (861 µl, 1.51 M in hexanes, 1.30 mmol) was treated with a degassed solution of Wilkinson's catalyst (24.5 mg, 26.5 µmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 3 h. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (4-20% ether in petrol gradient elution) an inseparable mixture of alkylated ketones **34** and **35** (**34**:**35**=1.1:1, 143 mg, 54%), ketone **36** (14 mg, 6%) and an intractable mixture of poly-alkylated ketones **37** (15 mg, *ca.* 5%).

4-(Phenylmethyl)-6-hepten-3-one (**34**)[102]:

^1H NMR (270 MHz) δ_H: 0.90 (3H, t, J = 7.1 Hz, 1-CH_3), 2.0-2.45 (2H, m, 5-CH_2), 2.65-2.75 (1H, m, 4-CH), 2.75-3.0 (4H, m, 2-, 4'-CH_2), 4.95-5.1 (2H, m, 7-CH_2), 5.6-5.8 (1H, m, 6-CH), 7.1-7.35 (5H, m, ArH);

4-Methyl-1-phenyl-6-hepten-3-one (**35**)[102]:

^1H NMR (270 MHz) δ_H: 1.05 (3H, d, J = 6.8 Hz, 4'-CH_3), 2.0-2.45 (2H, m, 5-CH_2), 2.58 (1H, sextet, J = 7.1 Hz, 4-CH), 2.65-2.8 (2H, m, 2-CH_2), 2.8-3.0 (2H, m, 1-CH_2), 4.95-5.1 (2H, m, 7-CH_2), 5.6-5.8 (1H, m, 6-CH), 7.1-7.35 (5H, m, ArH);

Mixture of **34** and **35**:

IR (film) ν_{max}: 3064, 3028, 2975, 2935, 1710, 1639, 1604, 1495, 1452, 1410, 1375, 1112, 995, 917, 748, 701 cm^{-1};

MS (70eV) m/z: 202 (M^+ 4%), 173 (2), 161 (39), 145 (4), 133 (26), 111 (9), 105 (38), 91 (100), 77 (9), 69 (12), 57 (26), 41 (16).

1-Phenyl-3-pentanone (**36**)[126b, 256]:

^1H NMR (270 MHz) δ_H: 1.05 (3H, t, J = 7.3 Hz, 5-CH_3), 2.41 (2H, q, J = 7.3 Hz, 4-CH_2), 2.73 (2H, t, J = 7.1 Hz, 2-CH_2), 2.91 (2H, t, J = 7.1 Hz, 1-CH_2), 7.15-7.35 (5H, m, ArH);

IR (film) ν_{max}: 3062, 3027, 2976, 2937, 1711, 1604, 1495, 1452, 1412, 1374, 1113, 740, 700 cm^{-1};

MS (70eV) m/z: 162 (M^+ 6%), 161 (31), 145 (5), 133 (28), 111 (8), 105 (50), 91 (100), 77 (9), 69 (20), 57 (32), 41 (23).

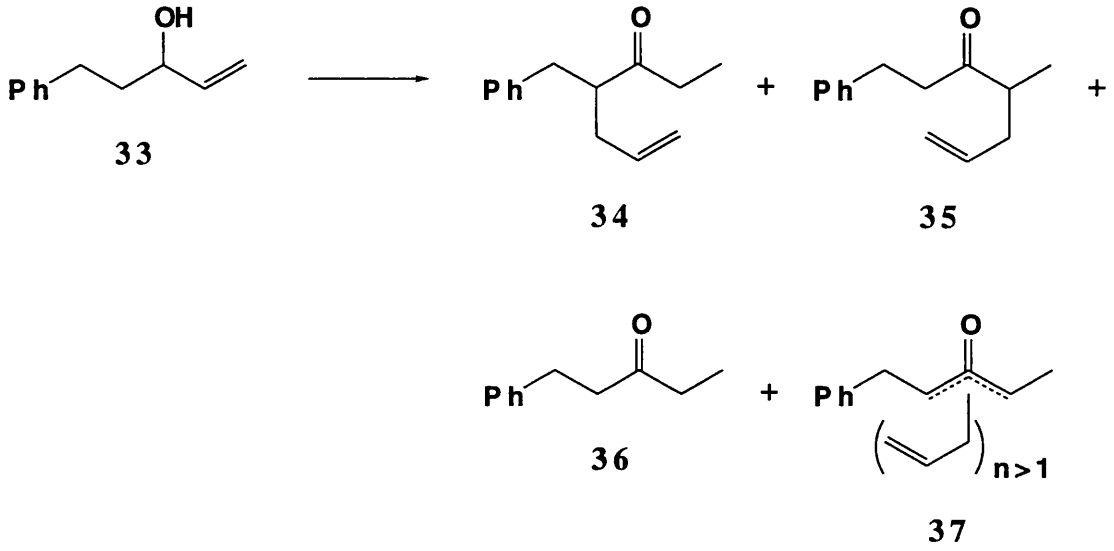
Polyalkylated mixture (**37**)[102]:

^1H NMR (270 MHz) δ_H: 0.70 (3H, d, J = 6.8 Hz, 4-allyl 5-CH_3), 0.96 (3H, d, J = 6.8 Hz, 4-allyl 5-CH_3), 1.10 (3H, s, 4,4-diallyl-5-CH_3), 1.7-2.5 (m, allyl 1'-CH_2), 2.6-2.8 (m, 2-CH, 4-CH and 4-CH_2), 2.8-3.05 (m, 1-CH_2, 2-CH_2), 4.8-5.2 (m, allyl 2'-CH), 5.4-5.8 (m, allyl 3'-CH_2), 7.1-7.3 (m, ArH);

IR (film) ν_{max}: 3077, 2975, 2929, 1708, 1639, 1603, 1494, 1454, 1373, 994, 916, 748, 700 cm^{-1};

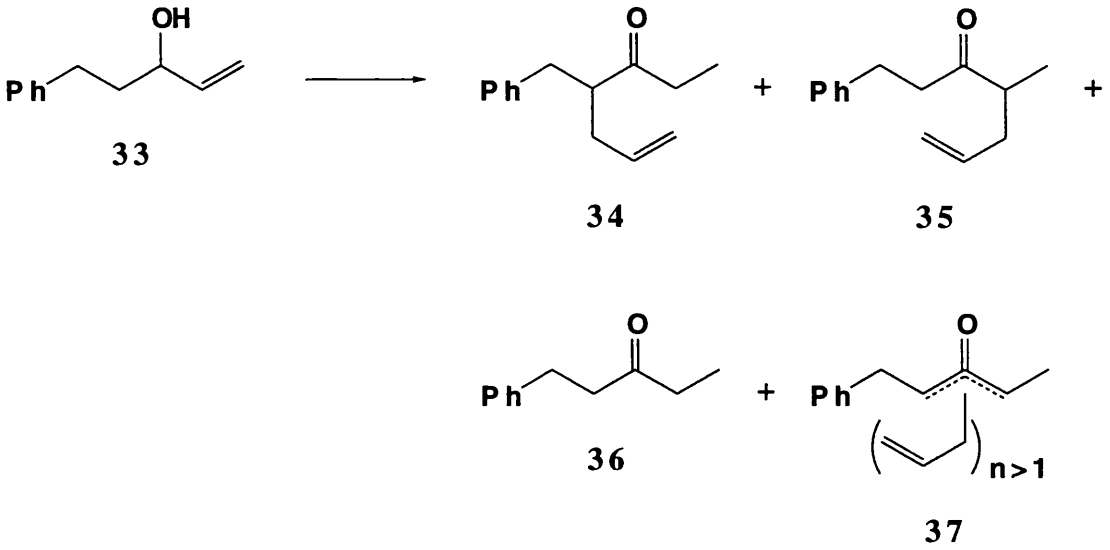
MS (70eV) m/z: 282 (triallyl: M^+ 0.3%), 242 (diallyl: M^+ 2%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), reaction time 30 min



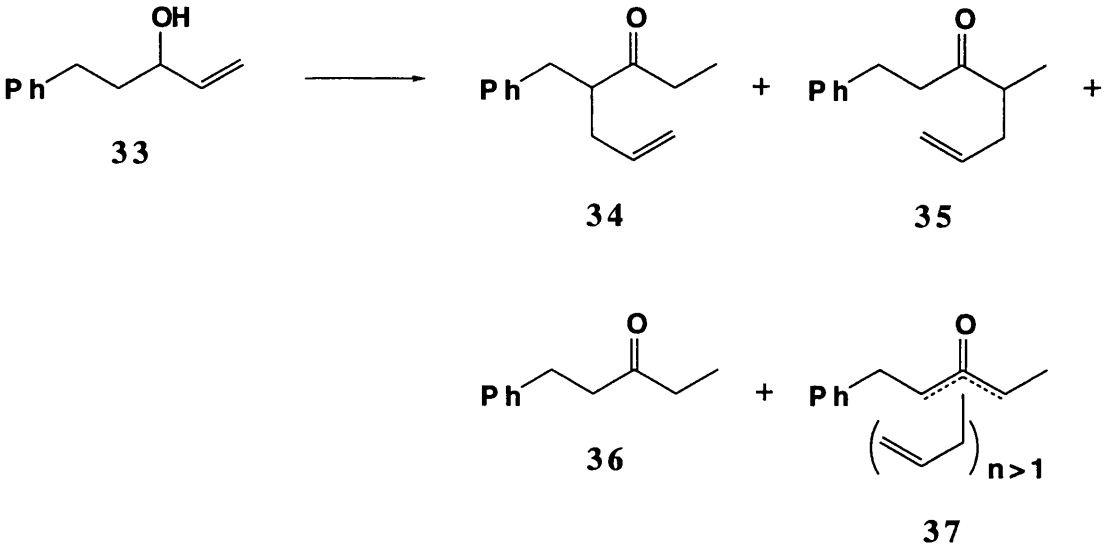
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (85.0 mg, 520 μmol) in THF (6 ml) and *n*-butyllithium (345 μl, 1.51 M in hexanes, 520 μmol) was treated with a degassed solution of Wilkinson's catalyst (9.8 mg, 10 μmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 30 min. Quench with allyl bromide (500 μl, 6 mmol) and work-up as previously detailed gave after flash chromatography (4-20% ether in petrol gradient elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.1:1, 19 mg, 18%), *1-phenyl-3-pentanone* (**36**) (9.3 mg, 11%), an intractable mixture of poly-alkylated ketones (**37**) (2.5 mg, *ca.* 2%), and starting material (43 mg, 51%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), half reaction time, 1.5 h



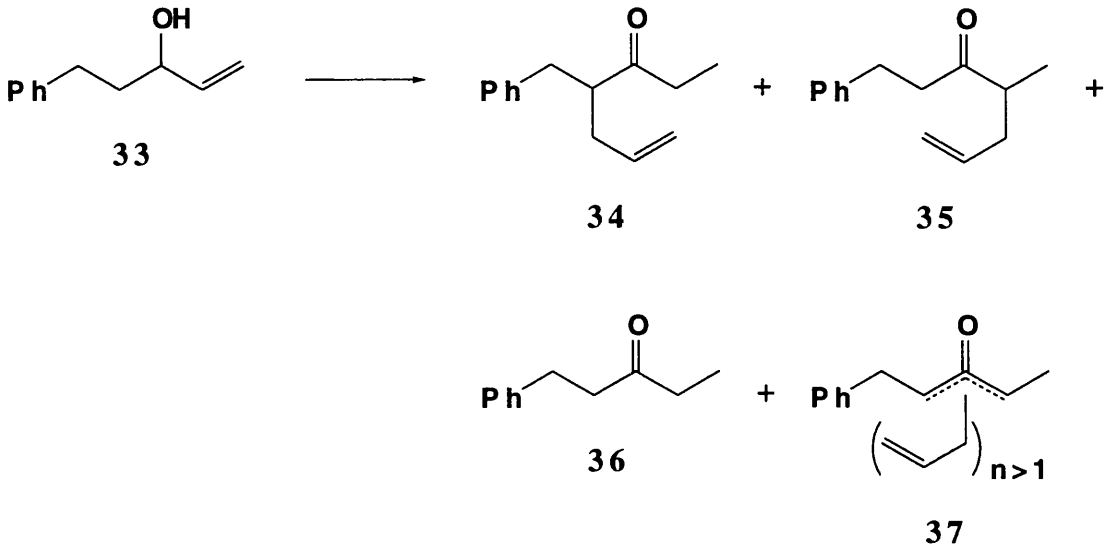
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (208 mg, 1.28 mmol) in THF (6 ml) and *n*-butyllithium (849 µl, 1.51 M in hexanes, 1.28 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.4 mg, 25.3 µmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 1.5 h. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (4-12% ether in petrol gradient elution)1 a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.3:1, 129 mg, 50%), *1-phenyl-3-pentanone* (**36**) (30 mg, 14%) and an intractable mixture of poly-alkylated ketones (**37**) (8 mg, *ca.* 3%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), double reaction time, 6 h



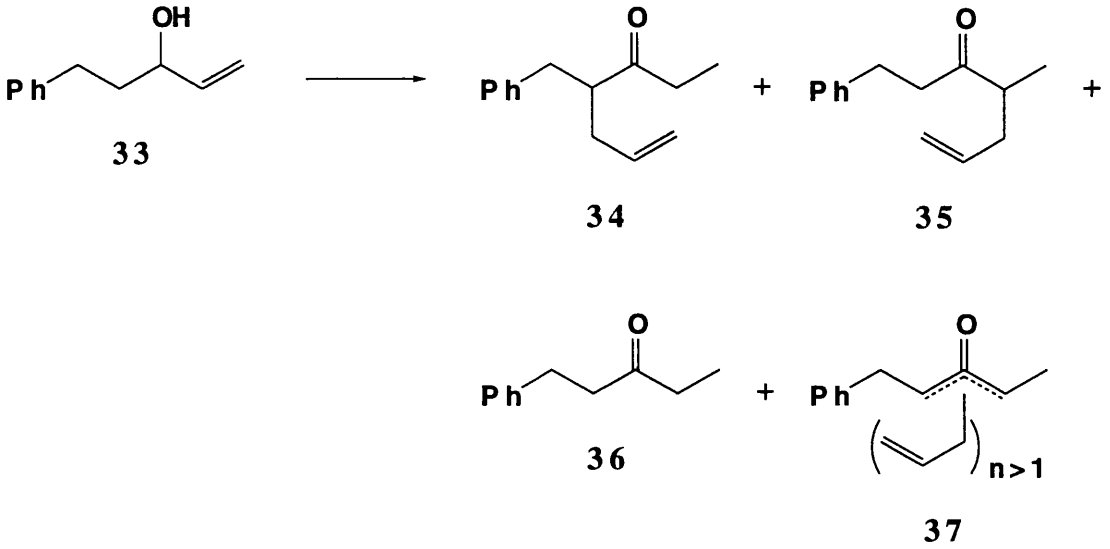
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (201 mg, 1.24 mmol) in THF (6 ml) and *n*-butyllithium (821 µl, 1.51 M in hexanes, 1.24 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.8 mg, 24.6 µmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 6 h. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (4% ether in petrol elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.4:1, 83 mg, 33%), *1-phenyl-3-pentanone* (**36**) (24 mg, 12%) and an intractable mixture of poly-alkylated ketones (**37**) (12 mg, *ca.* 4%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), 10% excess ^nBuLi



A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (202 mg, 1.25 mmol) in THF (6 ml) and *n*-butyllithium (907 µl, 1.51 M in hexanes, 1.37 mmol, 1.10 equiv) was treated with a degassed solution of Wilkinson's catalyst (22.9 mg, 24.8 µmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 3 h. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (4-20% ether in petrol gradient elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.3:1, 147 mg, 58%), *1-phenyl-3-pentanone* (**36**) (29 mg, 14%) and an intractable mixture of poly-alkylated ketones (**37**) (17 mg, *ca.* 5%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), 50% excess ^nBuLi

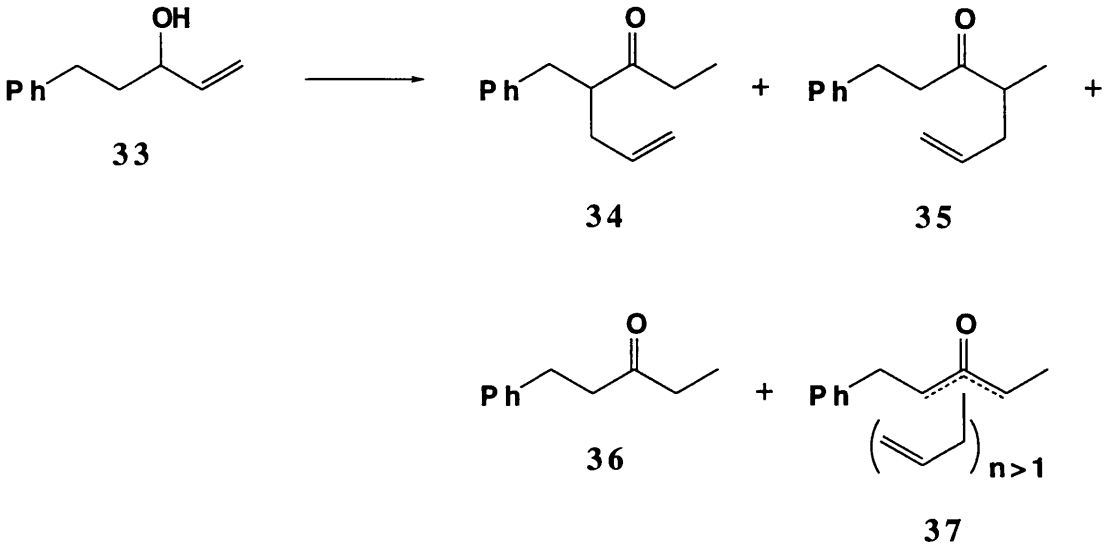


A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (211 mg, 1.30 mmol) in THF (6 ml) and *n*-butyllithium (1.31 ml, 1.51 M in hexanes, 1.95 mmol, 1.50 equiv) was treated with a degassed solution of Wilkinson's catalyst (24.0 mg, 25.9 μmol, 2.0 mol%) in THF (5 ml) and the mixture, a very deep red colour, heated to reflux for 8.5 h. At this time no further reaction was judged to be taking place by TLC analysis, and the mixture was quenched with allyl bromide (1.0 ml, 12 mmol) and worked-up as previously detailed. The stirrer bead was found to have a coating of metallic rhodium. Flash chromatography (4-20% ether in petrol gradient elution) gave a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1:9.7, 102 mg, 39%), *1-phenyl-3-pentanone* (**36**) (12 mg, 6%), an intractable mixture of poly-alkylated ketones (**37**) (2.5 mg, *ca.* 2%), and starting material (18 mg, *ca.* 6%).

4-Methyl-1-phenyl-6-hepten-3-one (**35**)[102]:

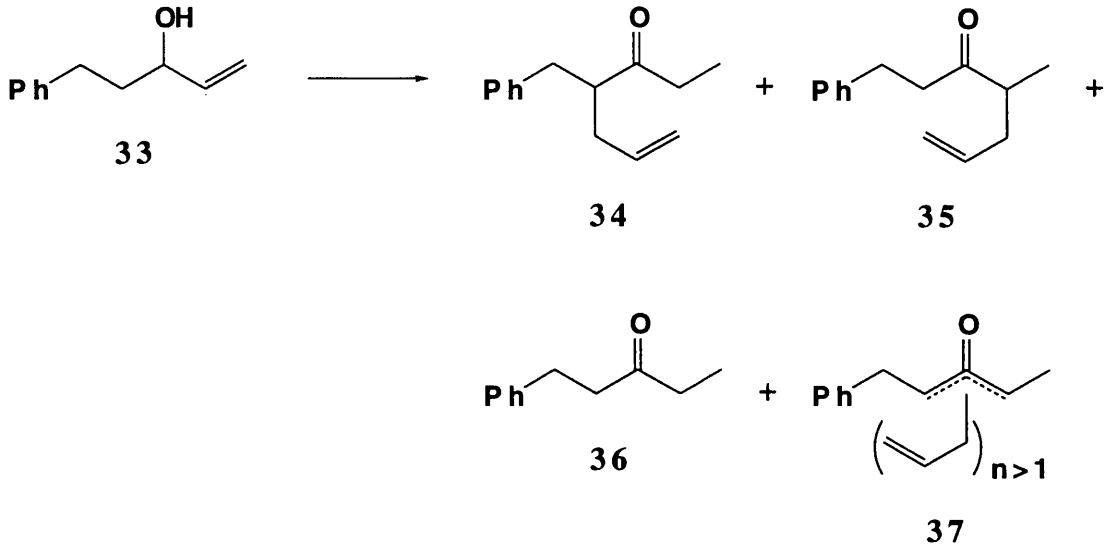
^1H NMR (270 MHz) δ_H: 1.05 (3H, d, J = 6.8 Hz, 4'-CH_3), 2.0-2.15 (1H, m, 5-CH_AH_B), 2.3-2.45 (1H, m, 5-CH_AH_B), 2.58 (1H, sextet, J = 7.1 Hz, 4-CH), 2.77 (2H, t, J = 7.3 Hz, 2-CH_2), 2.90 (2H, t, J = 7.3 Hz, 1-CH_2), 5.01 (1H, d, J = 9.5 Hz, 7-CH_{cis}), 5.02 (1H, d, J = 17.8 Hz, 7-CH_{trans}), 5.69 (1H, ddt, J = 17.8, 9.5, 7.1 Hz, 6-CH), 7.1-7.3 (5H, m, ArH).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), 50% excess ^nBuLi, ambient temperature



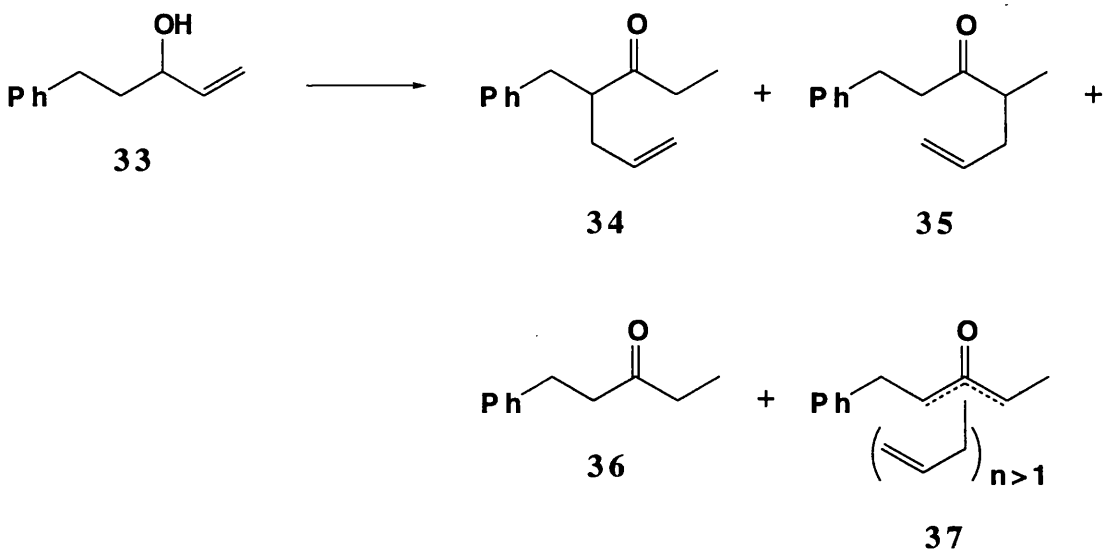
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (142 mg, 875 μmol) in THF (1 ml) and *n*-butyllithium (881 μl, 1.49 M in hexanes, 1.31 mmol, 1.50 equiv) was treated with a degassed solution of Wilkinson's catalyst (16.5 mg, 17.8 μmol, 2.0 mol%) in THF (2 ml) and the mixture, a very deep red colour, stirred at ambient temperature for 4.5 h. At this time no further reaction was judged to be taking place by TLC analysis, and the mixture was quenched with allyl bromide (700 μl, 8.4 mmol) and worked-up as previously detailed. The stirrer bead was found to have a coating of metallic rhodium. Flash chromatography (5-20% ether in petrol gradient elution) gave a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1:10, 15.9 mg, 9%), *1-phenyl-3-pentanone* (**36**) (1.5 mg, 1%), an intractable mixture of poly-alkylated ketones (**37**) (3.1 mg, *ca.* 1%), and starting material (120 mg, 85%).

5% $Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), 50% excess ^nBuLi



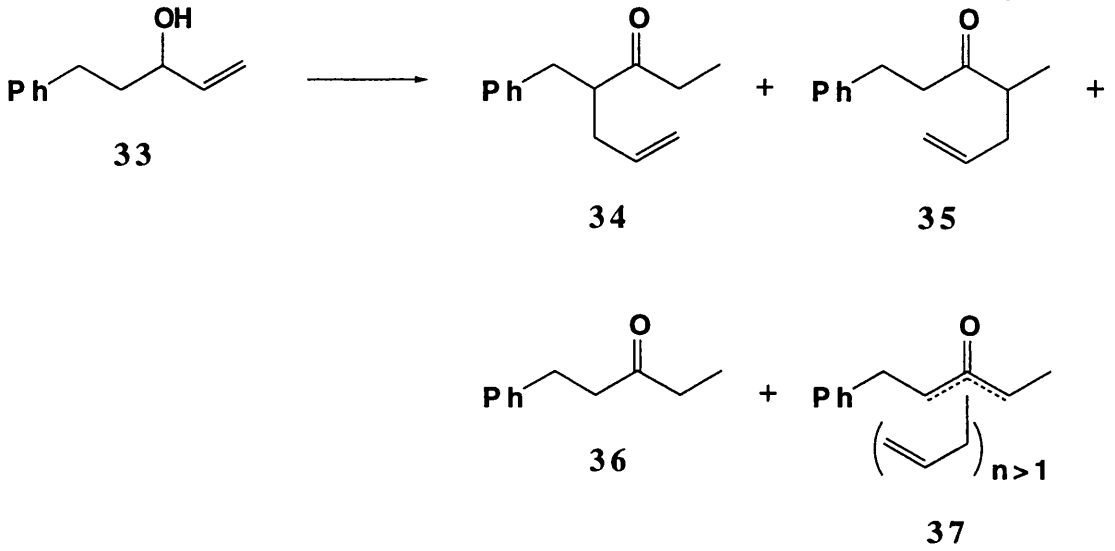
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (206 mg, 1.27 mmol) in THF (6 ml) and *n*-butyllithium (1.28 ml, 1.49 M in hexanes, 1.91 mmol, 1.50 equiv) was treated with a degassed solution of Wilkinson's catalyst (58.3 mg, 63.5 μmol, 5.0 mol%) in THF (5 ml) and the mixture, a very deep red colour, heated to reflux for 1 h. At this time no further reaction was judged to be taking place by TLC analysis, and the mixture was quenched with allyl bromide (1.0 ml, 12 mmol) and worked-up as previously detailed. The stirrer bead was found to have a coating of metallic rhodium. Flash chromatography (5-10% ether in petrol gradient elution) gave a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1:10, 46 mg, 18%), *1-phenyl-3-pentanone* (**36**) (30 mg, 15%), an intractable mixture of poly-alkylated ketones (**37**) (44 mg, *ca.* 14%), and starting material (16 mg, 8%).

5% $Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33), 10% excess ^nBuLi



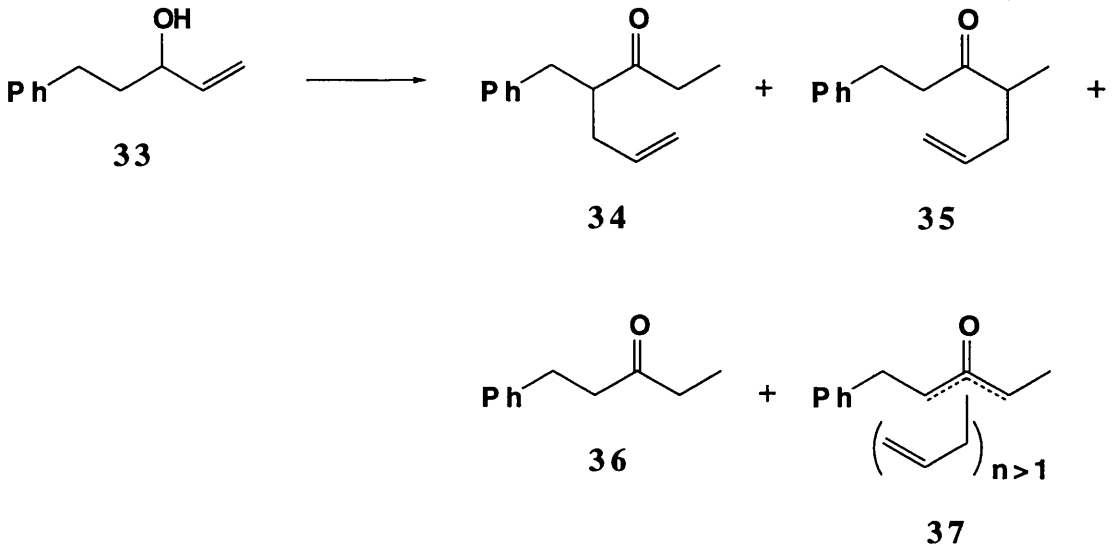
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (197 mg, 1.21 mmol) in THF (6 ml) and *n*-butyllithium (910 µl, 1.49 M in hexanes, 1.36 mmol, 1.12 equiv) was treated with a degassed solution of Wilkinson's catalyst (56.3 mg, 60.8 µmol, 5.0 mol%) in THF (5 ml) and the mixture, a very deep red colour, heated to reflux for 70 min. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.3:1, 181 mg, 74%), *1-phenyl-3-pentanone* (**36**) (22 mg, 11%), an intractable mixture of poly-alkylated ketones (**37**) (6 mg, *ca.* 2%), and a trace of starting material (<1%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33) in benzene



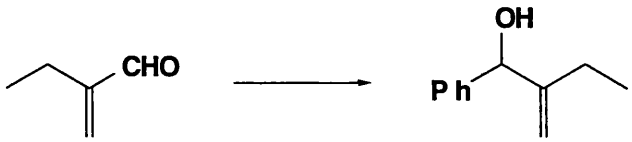
A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (212 mg, 1.31 mmol) in benzene (6 ml) and *n*-butyllithium (865 µl, 1.51 M in hexanes, 1.31 mmol) was treated with a degassed solution of Wilkinson's catalyst (26.2 mg, 28.3 µmol, 2.1 mol%) in benzene (5 ml) and the mixture heated to reflux for 1.5 h. Quench with allyl bromide (1.0 ml, 12 mmol) and work-up as previously detailed gave after flash chromatography (5% ether in petrol elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.2:1, 150 mg, 57%), *1-phenyl-3-pentanone* (**36**) (28.5 mg, 13%) and an intractable mixture of poly-alkylated ketones (**37**) (5 mg, *ca.* 2%).

$Rh(PPh_3)_3Cl/SnCl_2$ mediated isomerisation of 5-phenyl-1-penten-3-ol (33)



A degassed solution of alkoxide prepared from 5-phenyl-1-penten-3-ol (**33**) (216 mg, 1.33 mmol) in THF (6 ml) and *n*-butyllithium (905 µl, 1.47 M in hexanes, 1.33 mmol) was treated with a degassed solution of Wilkinson's catalyst (24.6 mg, 26.6 µmol, 2.0 mol%) and anhydrous tin (II) chloride (6.1 mg, 32 µmol, 2.4 mol%) in THF (5 ml) and the mixture heated to reflux for 75 min. Quench with allyl bromide (1.15 ml, 13.3 mmol) and work-up as previously detailed gave after flash chromatography (5% ether in petrol elution) a mixture of *4-(phenylmethyl)-6-hepten-3-one* (**34**) and *4-methyl-1-phenyl-6-hepten-3-one* (**35**) (**34**:**35**=1.2:1, 129 mg, 48%), *1-phenyl-3-pentanone* (**36**) (30 mg, 14%) and an intractable mixture of poly-alkylated ketones (**37**) (20 mg, *ca.* 6%).

Preparation of 2-ethyl-1-phenyl-2-propen-1-ol (40)



40

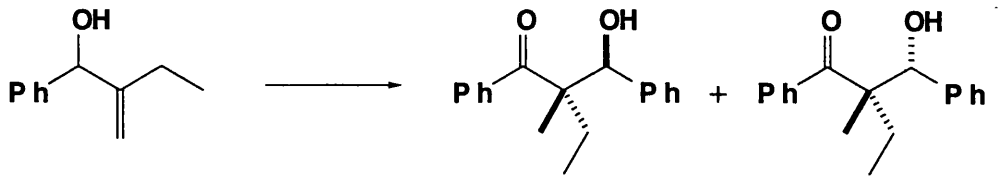
Oven-dried, coarse magnesium powder (1.50 g, 61.6 mmol) was dry-stirred under a flow of nitrogen and then suspended in THF (30 ml) with a small crystal of iodine. Bromobenzene (8.39 g, 53.4 mmol), freshly filtered through activated alumina, was dissolved in THF (20 ml) and added dropwise with stirring so as to maintain a gentle reflux. Once the reaction had moderated the mixture was heated to reflux for 30 min and then cooled to 0°C. A solution of freshly redistilled 2-ethyl-2-propenal (4.41 g, 52.5 mmol) in THF (40 ml) was transferred to the reaction mixture dropwise over 40 min. After a further 15 min the mixture was allowed to warm to ambient temperature for 1 h and quenched by the addition of ice and saturated aqueous ammonium chloride. Once cleared the mixture was diluted with ether, separated, and twice more extracted with ether. The combined organic phases were washed with water and brine, dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography (10-20% ether in petrol gradient elution) afforded *2-ethyl-1-phenyl-2-propen-1-ol* (**40**)[102] (7.56g, 89%) as a clear, colourless oil:

^{1}H NMR (400 MHz) δ_H: 0.98 (3H, t, J = 7.4 Hz, 2'-CCH_3), 1.7-2.05 (3H, m, 2'-CH_2, OH), 4.96 (1H, s, 1-CH), 5.16 (1H, s, 3-CH_AH$_B$), 5.25 (1H, q, J = 1.1 Hz, 3-CH$_A$$H_B$), 7.2-7.4 (5H, m, ArH);

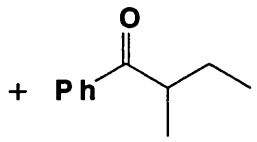
IR (film) ν_{max}: 3374, 3086, 3029, 2966, 2879, 1949, 1889, 1810, 1648, 1603, 1494, 1454, 1190, 1082, 1026, 903, 845, 763, 735, 700 cm^{-1};

MS (70eV) m/z: 162 (M^+ 28%), 147 (8), 133 (92), 120 (19), 115 (18), 107 (74), 91 (24), 79 (100), 77 (82), 63 (10), 55 (65), 51 (42), 39 (34), 27 (40).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 2-ethyl-1-phenyl-2-propen-1-ol (40); aldol reaction



40 43 44



45

A degassed solution of alkoxide prepared from 2-ethyl-1-phenyl-2-propen-1-ol (**40**) (192 mg, 1.18 mmol) in THF (6 ml) and *n*-butyllithium (726 µl, 1.63 M in hexanes, 1.18 mmol) was treated with a degassed solution of Wilkinson's catalyst (21.9 mg, 23.7 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 24 h. Quench with benzaldehyde (132 µl, 1.30 mmol) and work-up as previously detailed gave after flash chromatography (10-20% ether in petrol gradient elution) ketone **45** (27 mg, 14%) and an inseparable mixture of aldols **43** and **44** (**43**:**44**=3.6:1, 151 mg, 48%).

2-Methyl-1-phenyl-1-butanone (**45**)[257]:

^1H NMR (270 MHz) δ_H: 0.92 (3H, t, J = 7.4 Hz, 4-CH_3), 1.19 (3H, d, J = 6.8 Hz, 2'-CH_3), 1.50 (1H, m, 3-CH_AH$_B$), 1.84 (1H, m, 3-CH$_A$$H_B$), 3.39 (1H, sextet, J = 6.8 Hz, 2-CH), 7.46 (2H, br t, J = 7 Hz, *m*-ArH), 7.55 (1H, br t, J = 7 Hz, *p*-ArH), 7.96 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3060, 2969, 2934, 2875, 1680, 1597, 1581, 1448, 1378, 1263, 1219, 972, 702 cm^{-1};

MS (70eV) m/z: 162 (M^+ 5%), 149 (1), 134 (5), 120 (1), 105 (100), 77 (34), 73 (11), 61 (13), 51 (11), 45 (34), 43 (28), 29 (14).

(syn)-2-(Hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone (**43**)[102]:

^{1}H NMR (270 MHz) δ_H: 0.85 (3H, t, J = 7.6 Hz, 4-CH_3), 1.19 (3H, s, 2'-CH_3), 1.15-1.35 (1H, m, 3-CH_AH$_B$), 1.95-2.15 (1H, m, 3-CH$_A$$H_B$), 2.87 (1H, br s, OH), 5.08 (1H, s, 2"-CH), 7.25-7.65 (10H, m, ArH);

(anti)-2-(Hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone (**44**)[102]:

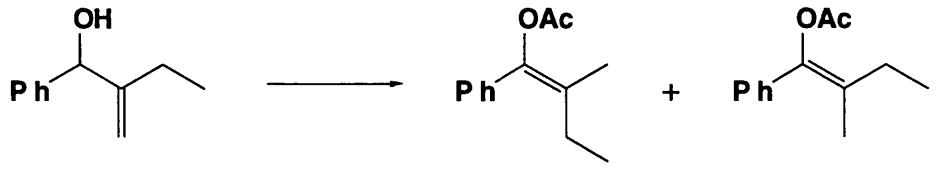
^{1}H NMR (270 MHz) δ_H: 0.87 (3H, t, J = 7.6 Hz, 4-CH_3), 1.21 (3H, s, 2'-CH_3), 1.55-1.75 (1H, m, 3-CH_AH$_B$), 2.1-2.3 (1H, m, 3-CH$_A$$H_B$), 1.85 (1H, br s, OH), 5.14 (1H, s, 2"-CH), 7.25-7.65 (10H, m, ArH);

Mixture of **43** and **44**:

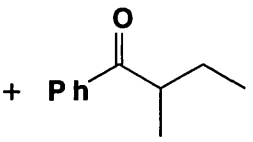
IR (film) ν_{max}: 3489, 3064, 2967, 2877, 1966, 1906, 1819, 1683, 1598, 1584, 1455, 1382, 1289, 1219, 1168, 1002, 961, 828, 747, 705, 650 cm^{-1};

MS (70eV) m/z: 268 (M$^+$ 22%), 252 (50), 236 (8), 196 (10), 181 (24), 163 (100), 148 (5), 121 (72), 105 (100), 91 (78), 77 (100), 69 (73), 51 (100), 41 (100), 27 (100).

Rh(PPh$_3$)$_3$Cl mediated isomerisation of 2-ethyl-1-phenyl-2-propen-1-ol (40); O-acetylation after 21 hours



40 **46** **47**



45

A degassed solution of alkoxide prepared from 2-ethyl-1-phenyl-2-propen-1-ol (**40**) (191 mg, 1.18 mmol) in THF (6 ml) and *n*-butyllithium (722 µl, 1.63 M in hexanes,

1.18 mmol) was treated with a degassed solution of Wilkinson's catalyst (21.8 mg, 23.5 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 21 h. Quench with acetyl chloride (837 μl, 11.8 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (5.8 mg, 3%) and an inseparable mixture of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3.5:1, 97 mg, 40%).

(E)-2-Methyl-1-phenyl-1-buten-1-yl acetate (**46**)[102]:

^{1}H NMR (500 MHz) δ_H: 1.08 (3H, t, J = 7.5 Hz, 4-CH_3), 1.73 (3H, s, 2'-CH_3), 2.12 (2H, q, J = 7.5 Hz, 3-CH_2), 2.13 (3H, s, $COCH_3$), 7.25-7.4 (5H, m, ArH);

(Z)-2-Methyl-1-phenyl-1-buten-1-yl acetate (**47**)[102]:

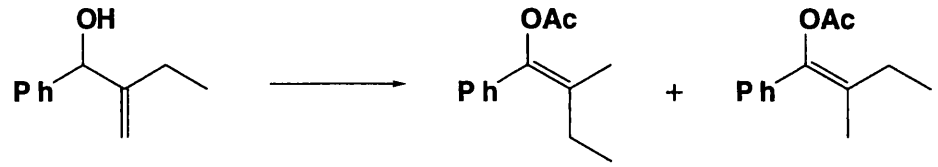
^{1}H NMR (500 MHz) δ_H: 1.06 (3H, t, J = 7.5 Hz, 4-CH_3), 1.79 (3H, s, 2'-CH_3), 2.14 (2H, q, J = 7.5 Hz, 3-CH_2), 2.14 (3H, s, $COCH_3$), 7.24-7.4 (5H, m, ArH);

Mixture of **46** and **47**:

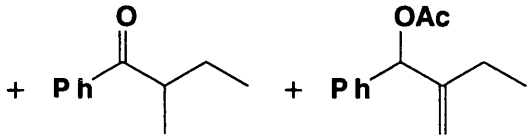
IR (film) ν_{max}: 3059, 2972, 2937, 2877, 2099, 1955, 1890, 1686, 1602, 1576, 1493, 1444, 1369, 1215, 1117, 1046, 1026, 961, 898, 780, 700 cm^{-1};

MS (70eV) m/z: 204 (M^+ 16%), 162 (100), 147 (100), 129 (64), 115 (22), 105 (100), 91 (38), 77 (100), 69 (61), 51 (76), 43 (100), 28 (99).

$Rh(PPh_3)_3Cl$ mediated isomerisation of 2-ethyl-1-phenyl-2-propen-1-ol (40); O-acetylation after 3 hours



40 46 47



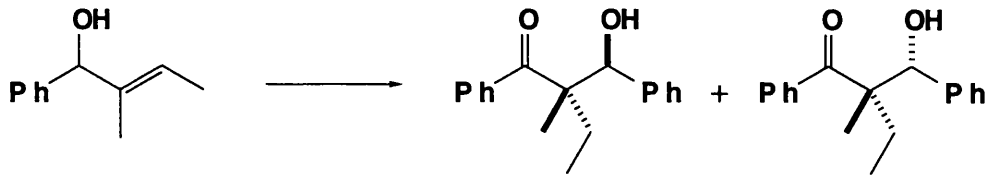
45 48

A degassed solution of alkoxide prepared from 2-ethyl-1-phenyl-2-propen-1-ol (**40**) (150 mg, 925 μmol) in THF (6 ml) and *n*-butyllithium (621 μl, 1.49 M in hexanes, 925 μmol) was treated with a degassed solution of Wilkinson's catalyst (17.1 mg, 18.5 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 3 h. Quench with acetyl chloride (660 μl, 9.30 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (9.3 mg, 6%), an inseparable mixture (73 mg) of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3.4:1, 14%) and acetylated starting material (**48**) (24%), and starting material (44 mg, 30%).

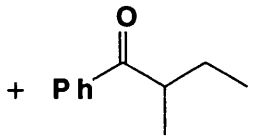
2-Ethyl-1-phenyl-2-propen-1-yl acetate (**48**):

^1H NMR (270 MHz) δ_H: 1.02 (3H, t, J = 7.3 Hz, 4-CH_3), 1.96 (2H, q, J = 7.3 Hz, 3-CH_2), 2.12 (3H, s, $COCH_3$), 5.01 (1H, s, 2'-CH_AH_B), 5.17 (1H, s, 2'-CH_AH_B), 6.23 (1H, s, 1-CH), 7.25-7.4 (5H, m, ArH).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (41) lithium alkoxide; aldol reaction



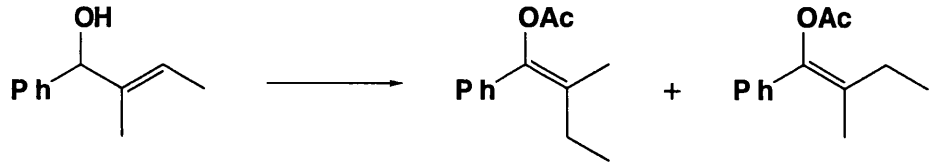
41 43 44



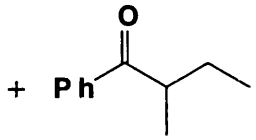
45

A degassed solution of alkoxide prepared from (E)-2-methyl-1-phenyl-2-buten-1-ol (**41**)[102] (194 mg, 1.20 mmol) in THF (6 ml) and *n*-butyllithium (808 µl, 1.63 M in hexanes, 1.32 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.2 mg, 23.9 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 26 h. Quench with benzaldehyde (134 µl, 1.32 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (29 mg, 15%) and an inseparable mixture of *(syn)-2-(hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone* (**43**) and *(anti)-2-(hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone* (**44**) (**43**:**44**=3.8:1, 232 mg, 72%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (41) lithium alkoxide; O-acetylation



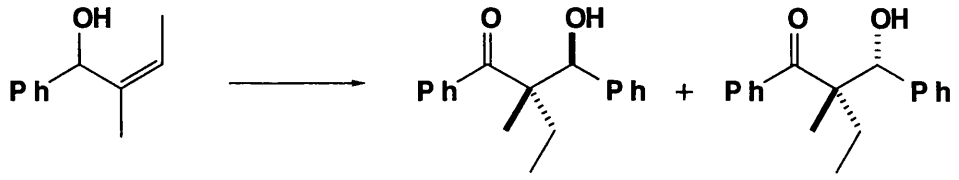
41 46 47



45

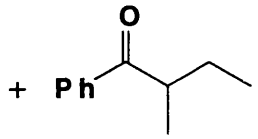
A degassed solution of alkoxide prepared from (E)-2-methyl-1-phenyl-2-buten-1-ol (**41**)[102] (202 mg, 1.25 mmol) in THF (6 ml) and *n*-butyllithium (764 µl, 1.63 M in hexanes, 1.25 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.0 mg, 24.9 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.17 ml, 12.5 mmol) and work-up as previously detailed gave after flash chromatography (5% ether in petrol elution) *2-methyl-1-phenyl-1-butanone* (**45**) (34 mg, 17%) and an inseparable mixture of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3.0:1, 150 mg, 59%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (Z)-2-methyl-1-phenyl-2-buten-1-ol (42) lithium alkoxide; aldol reaction



42 **43** **44**

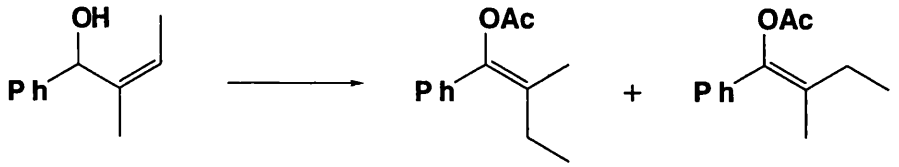
(Z:E = 10:1)



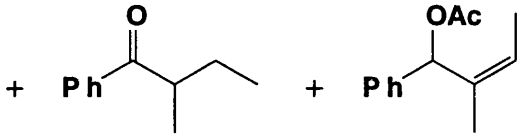
45

A degassed solution of alkoxide prepared from 2-methyl-1-phenyl-2-buten-1-ol (**42**)[102] (Z:E=10:1, 191 mg, 1.18 mmol) in THF (6 ml) and *n*-butyllithium (724 µl, 1.63 M in hexanes, 1.18 mmol) was treated with a degassed solution of Wilkinson's catalyst (21.8 mg, 23.5 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 48 h. Quench with benzaldehyde (132 µl, 1.30 mmol) and work-up as previously detailed gave after flash chromatography (10-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (44 mg, 23%), an inseparable mixture of *(syn)-2-(hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone* (**43**) and *(anti)-2-(hydroxy-phenylmethyl)-2-methyl-1-phenyl-1-butanone* (**44**) (**43**:**44**=3.9:1, 89 mg, 28%), and starting material (Z:E>50:1, 60 mg, 32%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (Z)-2-methyl-1-phenyl-2-buten-1-ol () lithium alkoxide; O-acetylation



42 (Z:E = 7:1) **46** **47**



45 **49**

A degassed solution of alkoxide prepared from 2-methyl-1-phenyl-2-buten-1-ol (**42**)[102] (Z:E=7:1, 201 mg, 1.24 mmol) in THF (6 ml) and n-butyllithium (761 µl, 1.63 M in hexanes, 1.24 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.9 mg, 24.8 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 16 h. Quench with acetic anhydride (1.17 ml, 12.4 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (34 mg, 17%), acetylated starting material (**49**) (Z:E>50:1, 29 mg, 11%), *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3.5:1, 84 mg, 33%), and starting material (Z:E>50:1, 64 mg, 25%).

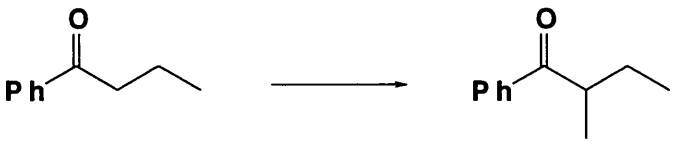
(Z)-2-Methyl-1-phenyl-2-buten-1-yl acetate (**49**):

^1H NMR (270 MHz) δ_H: 1.60 (3H, qd, J = 1.5, 0.7 Hz, 2'-CH_3), 1.86 (3H, dq, J = 7.1, 1.5 Hz, 4-CH_3), 2.17 (3H, s, $COCH_3$), 5.52 (1H, qq, J = 7.1, 0.7 Hz, 3-CH), 6.79 (1H, s, 1-CH), 7.25-7.4 (5H, m, ArH);

IR (film) ν_{max}: 3031, 2971, 2938, 2876, 1742, 1683, 1602, 1494, 1450, 1370, 1237, 1116, 1079, 1045, 1021, 978, 864, 741, 699 cm^{-1};

MS (70eV) m/z: 204 (M^+ 1.6%), 162 (52), 144 (42), 129 (100), 115 (12), 105 (14), 91 (21), 77 (16), 65 (4), 51 (9), 43 (100), 27 (7).

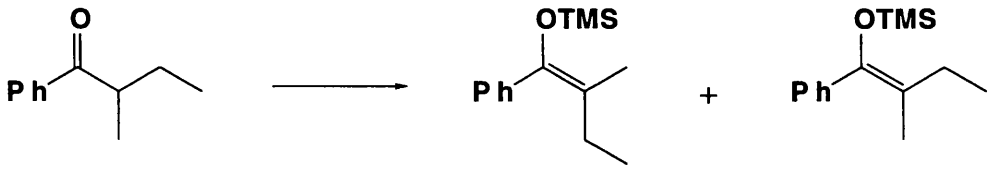
Preparation of 2-methyl-1-phenyl-1-butanone (45)



45

To a stirred, cooled (0°C) solution of diisopropylamine (15.7 g, 155 mmol) in THF (300 ml) was added a solution of *n*-butyllithium (60.0 ml, 2.5 M in hexanes, 150 mmol) over a period of 30 min. After a further 20 min the mixture was cooled to –78°C and 1-phenyl-1-butanone (20.96 g, 141.4 mmol) in THF (50 ml) added dropwise over 1 h. After stirring for 2.5 h the solution was transferred dropwise to a cooled (0°C) solution of iodomethane (50.2 g, 354 mmol) in THF (100 ml) and the mixture allowed to warm to ambient temperature overnight. Hydrochloric acid (0.1 M) was added, the mixture extracted three times with ether and the combined organic phases washed with aqueous sodium hydrogen carbonate, water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (10% ether in petrol elution) afforded *2-methyl-1-phenyl-1-butanone* (**45**)[257] as a colourless oil (22.34 g, 97%).

Preparation of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51)



45 **50** **51**

To a stirred, cooled (0°C) solution of diisopropylamine (15.0 g, 148 mmol) in THF (300 ml) was added a solution of *n*-butyllithium (60.5 ml, 2.5 M in hexanes, 150 mmol) over a period of 30 min. After a further 25 min the mixture was cooled to –78°C and 2-methyl-1-phenyl-1-butanone (**45**) (22.31 g, 137.5 mmol) in THF (130 ml)

added dropwise over 2 h. After stirring for 1 h chlorotrimethylsilane (19.2 ml, 151 mmol) was added and the mixture allowed to warm to ambient temperature over 2 h. Aqueous sodium hydrogen carbonate solution was added, the mixture extracted three times with ether and the combined organic phases dried over anhydrous sodium sulfate. Evaporation *in vacuo* gave a crude yellow oil, which when subject to fractional distillation yielded trimethylsilyl enol ethers **50** and **51** (**50**:**51**=1:3.0, 25.1 g, 78%) as a clear, colourless oil:

(E)-2-Methyl-1-phenyl-1-(trimethylsiloxy)-1-butene (**50**):

^{1}H NMR (500 MHz) δ_H: -0.03 (9H, s, $Si(CH_3)_3$), 1.04 (3H, t, J = 7.6 Hz, 4-CH_3), 1.77 (3H, s, 2'-CH_3), 2.23 (2H, q, J = 7.6 Hz, 3-CH_2), 7.2-7.35 (5H, m, ArH);

(Z)-2-Methyl-1-phenyl-1-(trimethylsiloxy)-1-butene (**51**):

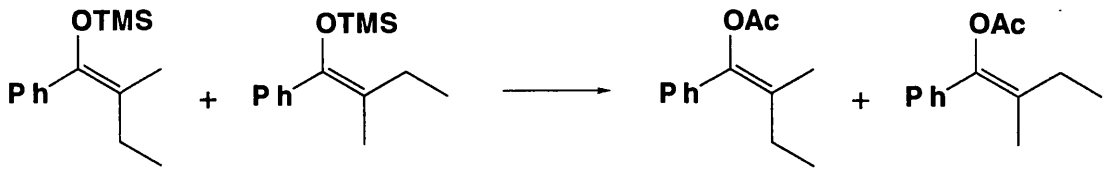
^{1}H NMR (500 MHz) δ_H: -0.03 (9H, s, $Si(CH_3)_3$), 1.05 (3H, t, J = 7.6 Hz, 4-CH_3), 1.64 (3H, s, 2'-CH_3), 2.24 (2H, q, J = 7.6 Hz, 3-CH_2), 7.2-7.35 (5H, m, ArH);

Mixture of **50** and **51**:

IR (film) ν_{max}: 2963, 2878, 1685, 1447, 1252, 1151, 1061, 1003, 885, 843, 752, 701 cm^{-1};

MS (70eV) m/z: 235 (M^+ +H 10%), 206 (10), 179 (79), 162 (12), 145 (100), 122 (40), 107 (94), 105 (100), 91 (18), 77 (100), 73 (100), 51 (94), 43 (85), 28 (96).

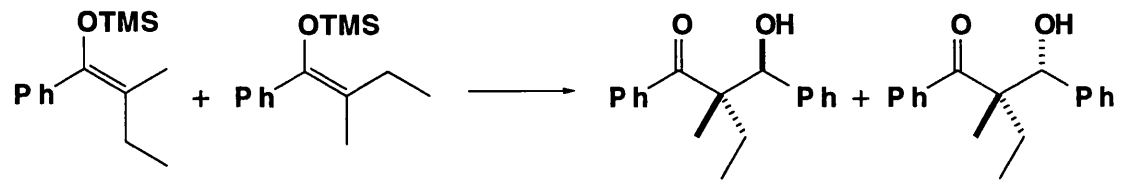
Conversion of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) to enol acetate derivatives (46 and 47)



50 **51** **46** **47**

To a stirred, cooled (0°C) solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 97 mg, 414 μmol) in THF (5 ml) was added methyllithium (335 μl, 1.36 M in ether, 455 μmol) dropwise, and after *ca.* 5 min the solution was allowed to warm to ambient temperature for 2 h. The mixture was cooled to –78°C and acetic anhydride (391 μl, 4.14 mmol) added in one go. After 15 min aqueous sodium hydrogen carbonate was added and the mixture extracted three times with ether, the combined organic phases washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (5-10% ether in petrol gradient elution) gave *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3:1) (68 mg, 80%) as a clear, colourless oil.

Conversion of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) to aldol derivatives (43 and 44)

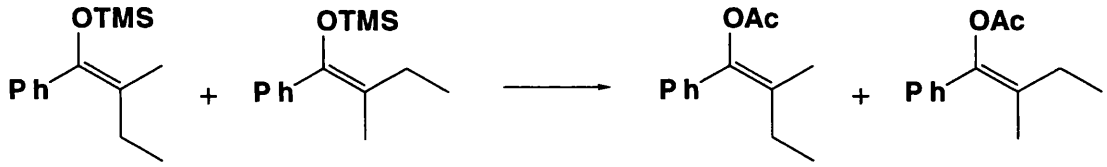


50 **51** **46** **47**

To a stirred, cooled (0°C) solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 3.52 g, 15.0 mmol) in THF (50 ml) was added methyllithium (12.1 ml, 1.40 M in ether, 16.5 mmol) dropwise, and after *ca.* 2 h the solution was cooled to –78°C. Benzaldehyde (1.68 ml, 16.5 mmol) was added in one

go, and after 5 s saturated aqueous ammonium chloride. The mixture was extracted three times with ether, the combined organic phases washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (20% ether in petrol elution) gave *(syn)-2-(hydroxyphenylmethyl)-2-methyl-1-phenyl-1-butanone* (**43**) and *(anti)-2-(hydroxy-phenylmethyl)-2-methyl-1-phenyl-1-butanone* (**44**) (**43**:**44**≈1:1) (2.57 g, 64%) as a clear oil.

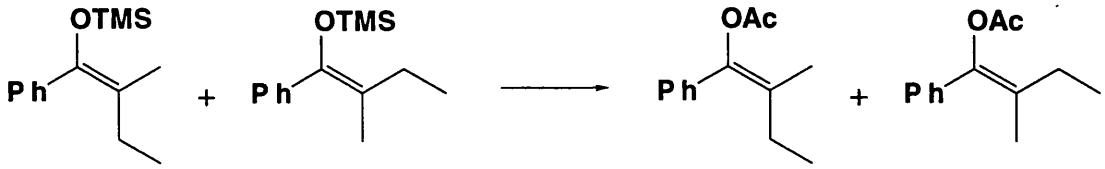
Attempted $Rh(PPh_3)_3Cl$ mediated equilibration of lithium enolates from 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) / 1.0 methyllithium



50 **51** **46** **47**

A solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 315 mg, 1.34 mmol) in THF (6 ml) was cooled to 0°C and treated dropwise with methyllithium (960 µl, 1.40 M in diethyl ether, 1.34 mmol). After stirring at ambient temperature for 2 h the resulting enolate solution was degassed, treated with a degassed solution of Wilkinson's catalyst (24.8 mg, 26.8 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 18 h. Quench with acetic anhydride (1.26 ml, 13.4 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) *2-methyl-1-phenyl-1-butanone* (**45**) (10 mg, 5%) and an inseparable mixture of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3:1, 200 mg, 73%).

Attempted thermal equilibration of lithium enolates from 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) / 1.0 methyllithium



50 **51** **46** **47**

A solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 173 mg, 738 µmol) in THF (10 ml) was cooled to 0°C and treated dropwise with methyllithium (527 µl, 1.40 M in diethyl ether, 738 µmol). After stirring at ambient temperature for 1 h the resulting enolate solution was heated to reflux for 18 h. Quench with acetic anhydride (700 µl, 7.4 mmol) and work-up as previously detailed gave a slightly yellowed crude oil. Crude 270 MHz ^{1}H NMR showed traces of *2-methyl-1-phenyl-1-butanone* (**45**), and *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=3:1).

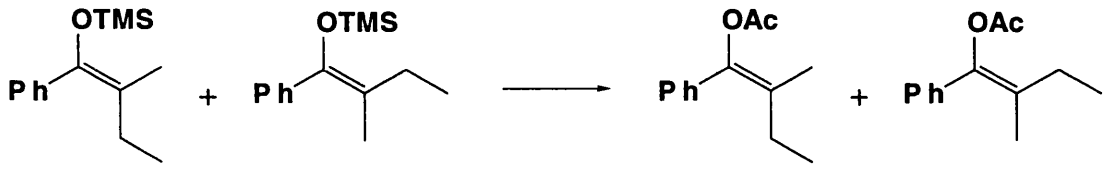
Attempted thermal equilibration of lithium enolates from 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) / 1.1 methyllithium

50 **51** **46** **47**

A solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 231 mg, 987 µmol) in THF (10 ml) was cooled to 0°C and treated dropwise with methyllithium (798 µl, 1.36 M in diethyl ether, 1.09 mmol). After stirring at ambient temperature for 1.5 h the resulting enolate solution was heated to reflux for 18 h. Quench with acetic anhydride (931 µl, 9.87 mmol) and work-up as

previously detailed gave a slightly yellowed crude oil. Crude 270 MHz ^{1}H NMR showed no trace of *2-methyl-1-phenyl-1-butanone* (**45**), but *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=1:3).

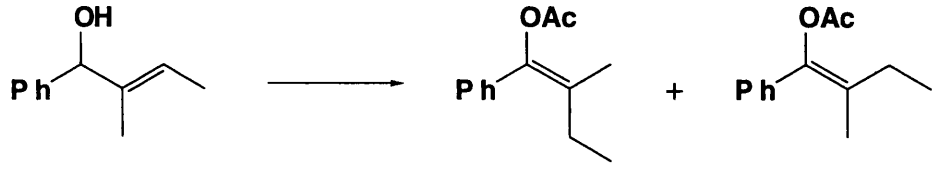
Attempted $Rh(PPh_3)_3Cl$ mediated equilibration of lithium enolates from 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (50 and 51) / 1.1 methyllithium



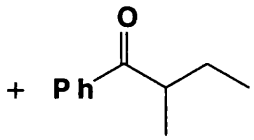
50 **51** **46** **47**

A solution of 2-methyl-1-phenyl-1-(trimethylsiloxy)-1-butenes (**50** and **51**) (**50**:**51**=1:3.0, 230 mg, 981 µmol) in THF (6 ml) was cooled to 0°C and treated dropwise with methyllithium (793 µl, 1.36 M in diethyl ether, 1.08 mmol). After stirring at ambient temperature for 1.5 h the resulting enolate solution was degassed, treated with a degassed solution of Wilkinson's catalyst (18.1 mg, 19.6 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 18 h. Quench with acetic anhydride (926 µl, 9.81 mmol) and work-up as previously detailed gave after flash chromatography (5-20% ether in petrol gradient elution) no trace of *2-methyl-1-phenyl-1-butanone* (**45**), but an inseparable mixture of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=1:3, 156 mg, 78%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (41) lithium alkoxide; 10% excess ^nBuLi



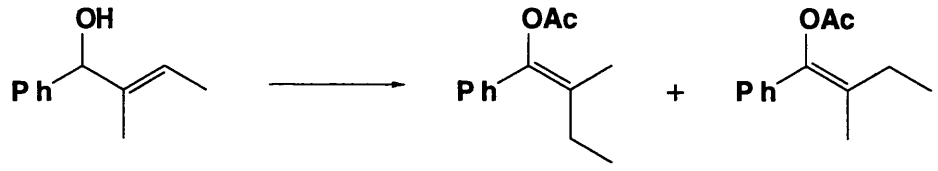
41 **46** **47**



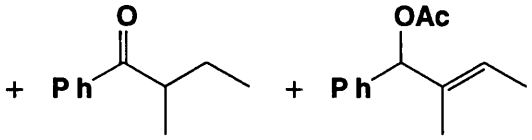
45

A degassed solution of alkoxide prepared from (E)-2-methyl-1-phenyl-2-buten-1-ol (**41**)[102] (219 mg, 1.35 mmol) in THF (6 ml) and *n*-butyllithium (910 µl, 1.63 M in hexanes, 1.48 mmol) was treated with a degassed solution of Wilkinson's catalyst (24.9 mg, 26.9 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 25 h. Quench with acetic anhydride (1.27 ml, 13.5 mmol) and work-up as previously detailed gave after flash chromatography (5% ether in petrol elution) *2-methyl-1-phenyl-1-butanone* (**45**) (36 mg, 16%) and an inseparable mixture of *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=2.7:1, 198 mg, 72%).

$Rh(PPh_3)_3Cl$ mediated isomerisation of (E)-2-methyl-1-phenyl-2-buten-1-ol (41) potassium alkoxide; excess potassium hydride



41 46 47



45 52

Potassium hydride (298 mg, 35% w/w dispersion in mineral oil, 2.6 mmol) in a Schlenk flask was washed free of oil with THF (3 × 6 ml) and cooled to 0°C. A solution of (E)-2-methyl-1-phenyl-2-buten-1-ol (**41**)[102] (208 mg, 1.28 mmol) in THF (4 ml) was added dropwise causing much effervescence, followed by a THF washing (2 ml). After warming to ambient temperature for 15 min the yellowed suspension was degassed twice and treated with a degassed solution of Wilkinson's catalyst (23.7 mg, 25.6 mmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.21 ml, 12.8 mmol) and work-up as previously detailed gave after flash chromatography (5-10% ether in petrol gradient elution) a trace of *2-methyl-1-phenyl-1-butanone* (**45**), and an inseparable mixture (231 mg) of acetylated starting material (**52**) (67%) and *(E)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**46**) and *(Z)-2-methyl-1-phenyl-1-buten-1-yl acetate* (**47**) (**46**:**47**=2.0:1, 22%).

(E)-2-Methyl-1-phenyl-2-buten-1-yl acetate (**52**):

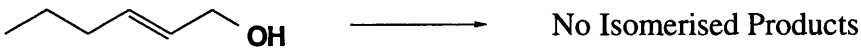
^1H NMR (270 MHz) δ_H: 1.54 (3H, t, J = 1.2 Hz, 2'-CH_3), 1.66 (3H, dt, J = 6.8, 1.0 Hz, 4-CH_3), 2.14 (3H, s, $COCH_3$), 5.68 (1H, qq, J = 6.8, 1.2 Hz, 3-CH), 6.21 (1H, s, 1-CH), 7.25-7.4 (5H, m, ArH).

Attempted isomerisation of 3-methyl-1-phenyl-2-buten-1-ol (53) with $Rh(PPh_3)_3Cl$

53

A degassed solution of alkoxide prepared from 3-methyl-1-phenyl-2-buten-1-ol (**53**)[102] (195 mg, 1.20 mmol) in THF (6 ml) and *n*-butyllithium (736 µl, 1.63 M in hexanes, 1.20 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.2 mg, 24.0 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 40 h. Quench with excess aqueous ammonium chloride and work-up as previously detailed gave a yellow oil. Crude 270 MHz ^1H NMR showed starting material as the only identifiable compound. Flash chromatography (10% ether in petrol elution) gave no trace of *3-methyl-1-phenyl-1-butanone*.

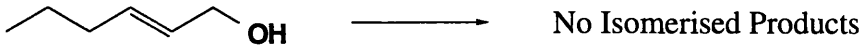
Attempted isomerisation of (E)-2-hexen-1-ol (54) with 2% $Rh(PPh_3)_3Cl$



54

A degassed solution of alkoxide prepared from (E)-2-hexen-1-ol (**54**) (160 mg, 1.60 mmol) in THF (6 ml) and *n*-butyllithium (980 µl, 1.63 M in hexanes, 1.60 mmol) was treated with a degassed solution of Wilkinson's catalyst (29.6 mg, 31.9 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 26 h. Quench with acetic anhydride (1.6 ml, 16 mmol) and work-up as previously detailed gave a complex mixture, with no trace of enol acetates by crude 270 MHz ^1H NMR. Flash chromatography (2-10% ether in 30/40 petrol gradient elution) gave no identifiable products.

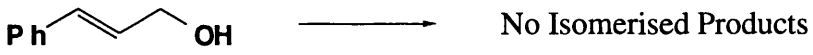
Attempted isomerisation of (E)-2-hexen-1-ol (54) with 10% $Rh(PPh_3)_3Cl$



54

A degassed solution of alkoxide prepared from (E)-2-hexen-1-ol (**54**) (116 mg, 1.16 mmol) in THF (6 ml) and *n*-butyllithium (711 µl, 1.63 M in hexanes, 1.16 mmol) was treated with a degassed solution of Wilkinson's catalyst (107 mg, 116 µmol, 10.0 mol%) in THF (5 ml), and the mixture heated to reflux for 4.5 h. Quench with acetic anhydride (1.09 ml, 11.6 mmol) and work-up as previously detailed gave a complex mixture. Flash chromatography (2-10% ether in 30/40 petrol gradient elution) gave a trace of enol acetates by 270 MHz ^1H NMR but no other identifiable products.

Attempted isomerisation of (E)-3-phenyl-2-propen-1-ol (55) with $Rh(PPh_3)_3Cl$



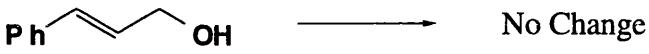
55

A degassed solution of alkoxide prepared from (E)-3-phenyl-2-propen-1-ol (**55**) (191 mg, 1.42 mmol) in THF (6 ml) and *n*-butyllithium (873 µl, 1.63 M in hexanes, 1.42 mmol) was treated with a degassed solution of Wilkinson's catalyst (26.3 mg, 28.5 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 18.5 h. Quench with acetic anhydride (1.34 ml, 14.2 mmol) and work-up as previously detailed gave a brown oil. TLC (50% ether in petrol elution) showed a complex mixture. Filtration through a pad of silica and crude ^1H NMR indicated no trace of enol acetates but a mixture of stereochemically pure starting material (**55**) and acetylated starting material (ca. 3:1).

(E)-3-Phenyl-2-propen-1-yl acetate[253]:

^{1}H NMR (270 MHz) δ_H: 2.11 (3H, s, $COCH_3$), 4.74 (2H, d, J = 6.4 Hz, 3-CH_2), 6.30 (1H, dt, J = 15.6, 6.4 Hz, 2-CH), 6.66 (1H, d, J = 15.6 Hz, 1-CH), 7.1-7.5 (5H, m, ArH).

Attempted thermal decomposition of (E)-3-phenyl-2-propen-1-ol (55) lithium alkoxide



55

A solution of (E)-3-phenyl-2-propen-1-ol (**55**) (147 mg, 1.09 mmol) in THF (5 ml) was treated dropwise at 0°C with *n*-butyllithium (671 µl, 1.63 M in hexanes, 1.09 mmol), and after stirring for 10 min the alkoxide was heated to reflux for 13 h. Quench with aqueous ammonium chloride and work-up as previously detailed gave a slightly yellowed oil. TLC (50% ether in petrol elution) and crude 270 MHz ^{1}H NMR indicated pure starting material.

Preparation of 2-phenyl-2-propen-1-ol (56)

56

To a stirred suspension of selenium dioxide (3.00 g, 27.0 mmol) in dichloromethane (10 ml) at ambient temperature was added a solution of *tert*-butyl hydroperoxide (9.00 ml, 3.0 M in 2,4,4-trimethylpentane, 27.0 mmol). After 10 min a solution of 2-phenylpropene (2.11 g, 17.9 mmol) in dichloromethane (15 ml) was added and the mixture stirred at ambient temperature for 4 h. Saturated aqueous sodium hydrogen carbonate was added, the mixture was extracted three times with dichloromethane and

the combined organic phases washed with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (20% ether in petrol elution) afforded starting material (254 mg, 12%), *2-phenyl-2-propenal* (51 mg, 2%), and alcohol (**56**) as a clear, colourless oil (1.18 g, 49%).

2-Phenyl-2-propenal [258]:

^{1}H NMR (270 MHz) δ_H: 6.19 (1H, d, J = 0.7 Hz, 3-CH_AH$_B$), 6.64 (1H, d, J = 0.7 Hz, 3-CH$_A$$H_B$), 7.2-7.5 (5H, m, ArH), 9.83 (1H, s, CHO);

IR (film) ν_{max}: 3060, 1735, 1697, 1639, 1599, 1493, 1447, 1168, 757, 696 cm^{-1};

MS (70eV) m/z: 235 (2M$^+$-CHO 19%), 132 (M$^+$ 12), 115 (8), 105 (100), 103 (29), 77 (46), 51 (18).

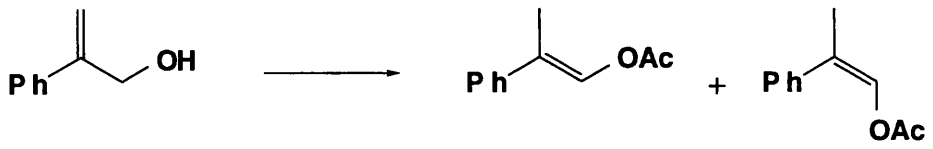
2-Phenyl-2-propen-1-ol (**56**)[160]:

^{1}H NMR (270 MHz) δ_H: 2.03 (1H, br s, OH), 4.54 (2H, s, 1-CH$_2$), 5.36 (1H, d, J = 0.7 Hz, 3-CH_AH$_B$), 5.48 (1H, d, J = 0.7 Hz, 3-CH$_A$$H_B$), 7.3-7.5 (5H, m, ArH);

IR (film) ν_{max}: 3352, 3056, 2923, 1629, 1599, 1573, 1494, 1444, 1026, 906, 779, 708 cm^{-1};

MS (70eV) m/z: 134 (M$^+$ 77%), 115 (21), 105 (59), 103 (100), 92 (66), 77 (77), 51 (36).

Rh(PPh$_3$)$_3$Cl mediated isomerisation of 2-phenyl-2-propen-1-ol (56)



56 **57** **58**

A degassed solution of alkoxide prepared from 2-phenyl-2-propen-1-ol (**56**) (176 mg, 1.31 mmol) in THF (6 ml) and *tert*-butyllithium (772 µl, 1.70 M in pentane, 1.31 mmol) was treated with a degassed solution of Wilkinson's catalyst (24.2 mg, 26.2 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 40 min. Quench

with acetic anhydride (1.24 ml, 13.1 mmol) and work-up as previously detailed gave after flash chromatography (10-20% ether in petrol gradient elution) enol acetates **57** and **58** (**57**:**58**=13:1, 192 mg, 83%) as the only identifiable products:

(E)-2-Phenyl-1-propen-1-yl acetate (**57**)[259]:

^{1}H NMR (500 MHz) δ_H: 2.12 (3H, d, J = 1.4 Hz, 3-CH_3), 2.23 (3H, s, $COCH_3$), 7.28 (1H, t, J = 7.5 Hz, *p*-ArH), 7.35 (2H, t, J = 7.5 Hz, *m*-ArH), 7.40 (2H, d, J = 7.4 Hz, *o*-ArH), 7.54 (1H, q, J = 1.4 Hz, 1-CH);

^{13}C NMR (126 MHz) δ_C: 13.5, 20.7, 121.5, 125.7, 127.2, 128.4, 132.5, 139.0, 168.0;

(Z)-2-Phenyl-1-propen-1-yl acetate (**58**)[259]:

^{1}H NMR (500 MHz) δ_H: 2.04 (3H, d, J = 1.4 Hz, 3-CH_3), 2.13 (3H, s, $COCH_3$), 7.2-7.45 (4H, m, 1-CH, *m,p*-ArH), 7.48 (2H, d, J = 7.5 Hz, *o*-ArH);

Mixture of **57** and **58**:

IR (film) ν_{max}: 3085, 2924, 1757, 1656, 1600, 1496, 1446, 1370, 1285, 1221, 1121, 1069, 1028, 918, 837, 759, 697, 643 cm^{-1};

MS (70eV) m/z: 176 (M^+ 6%), 134 (100), 118 (8), 105 (40), 91 (10), 79 (7), 77 (13), 43 (37).

Preparation of 2-ethyl-2-propen-1-ol (59)

59

To a stirred, cooled (0°C) solution of sodium borohydride (580 mg, 15.3 mmol) in water (5 ml) and ethanol (5 ml) was added 2-ethyl-2-propenal (2.56 g, 30.4 mmol) dropwise. After 10 min the solution was allowed to warm to ambient temperature, and after a further 30 min saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with ether three times, and the combined organic phases dried with K_2CO_3 and evaporated *in vacuo*. Flash chromatography (20-50% ether in 30-40

petrol gradient elution) gave a mixture of *2-methyl-1-butanol* and alcohol **59** (>10:1, 1.92 g), and subsequent short-path distillation afforded pure alcohol **59** (1.68 g, 64%) as a clear, colourless oil.

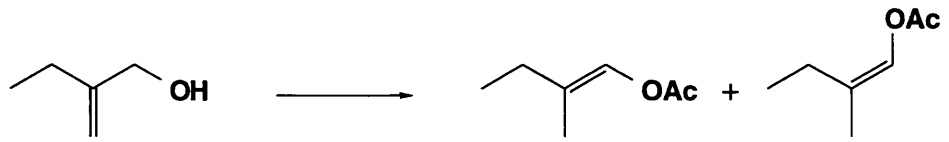
2-Ethyl-2-propen-1-ol (**59**)[93c]:

^{1}H NMR (270 MHz) δ_H: 1.07 (3H, t, J = 7.5 Hz, 4-CH_3), 1.48 (1H, t, J = 6.1 Hz, OH), 2.08 (2H, qd, J = 7.5, 0.5 Hz, 3-CH_2), 4.08 (2H, dd, J = 6.1, 0.5 Hz, 1-CH_2), 4.87 (1H, t, J = 0.5 Hz, 2'-CH_AH$_B$), 5.00 (1H, t, J = 0.5 Hz, 2'-CH$_A$$H_B$);

IR (film) ν_{max}: 3354, 2966, 2934, 2880, 1668, 1462, 1377, 1151, 1033, 898 cm^{-1};

MS (70eV) m/z: 86 (M$^+$ 14%), 71 (22), 68 (15), 57 (100), 44 (14), 29 (2).

Rh(PPh$_3$)$_3$Cl mediated isomerisation of 2-ethyl-2-propen-1-ol (59)



59 **60** **61**

A degassed solution of alkoxide prepared from 2-ethyl-2-propen-1-ol (**59**) (213 mg, 2.47 mmol) in THF (6 ml) and *n*-butyllithium (1.52 ml, 1.63 M in hexanes, 2.47 mmol) was treated with a degassed solution of Wilkinson's catalyst (45.8 mg, 49.5 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 9 h. Quench with acetic anhydride (2.36 ml, 24.7 mmol) and work-up as previously detailed gave after flash chromatography (10% ether in 30-40 petrol elution) enol acetates **60** and **61** (**60**:**61**=3:1, 156 mg, 49%):

(E)-2-Methyl-1-buten-1-yl acetate (**60**)[260]:

^{1}H NMR (270 MHz) δ_H: 1.00 (3H, t, J = 7.4 Hz, 4-CH_3), 1.65 (3H, d, J = 1.5 Hz, 2'-CH_3), 1.97 (2H, qd, J = 7.4, 1.0 Hz, 3-CH_2), 2.11 (3H, s, $COCH_3$), 6.87 (1H, sextet, J = 1.5 Hz, 1-CH);

(Z)-2-Methyl-1-buten-1-yl acetate (**61**)[260]:

^{1}H NMR (270 MHz) δ_H: 0.97 (3H, t, J = 7.6 Hz, 4-CH_3), 1.61 (3H, d, J = 1.5 Hz, 2'-CH_3), 2.10 (3H, s, $COCH_3$), 2.12 (2H, qd, J = 7.6 Hz, 3-CH_2), 6.79 (1H, m, 1-CH);

Mixture of **60** and **61**:

IR (film) ν_{max}: 2970, 2940, 2880, 1754, 1686, 1446, 1371, 1226, 1120, 1080, 916, 828 cm^{-1};

MS (70eV) m/z: 128 (M^+ 7%), 86 (100), 71 (12).

Attempted isomerisation of (E)-2-methyl-2-buten-1-ol (62) with 2% $Rh(PPh_3)_3Cl$

62

A degassed solution of alkoxide prepared from (E)-2-methyl-2-buten-1-ol (**62**)[102] (174 mg, 2.02 mmol) in THF (6 ml) and *n*-butyllithium (1.24 ml, 1.63 M in hexanes, 2.02 mmol) was treated with a degassed solution of Wilkinson's catalyst (37.4 mg, 40.5 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.91 ml, 20.2 mmol) and work-up as previously detailed gave a complex mixture, with no trace of enol acetates by crude 270 MHz ^{1}H NMR. Flash chromatography (2-10% ether in 30-40 petrol gradient elution) gave no identifiable products.

Attempted isomerisation of geraniol (63) lithium alkoxide with $Rh(PPh_3)_3Cl$

63

A degassed solution of alkoxide prepared from geraniol (**63**) (189 mg, 1.23 mmol) in THF (6 ml) and *n*-butyllithium (755 µl, 1.63 M in hexanes, 1.23 mmol) was treated with a degassed solution of Wilkinson's catalyst (22.7 mg, 24.5 µmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 23 h. Quench with acetic anhydride (1.16 ml, 12.3 mmol) and work-up as previously detailed gave a yellow oil. Flash chromatography (10-33% ether in petrol gradient elution) gave no trace of the desired enol acetates but *geranyl acetate* (**64**) (68 mg, 28%) and starting material (105 mg, 55%) as the only identifiable compounds.

(E)-3,7-Dimethyl-2,6-octadien-1-yl acetate (**64**)[212]:

^1H NMR (270 MHz) δ_H: 1.58 (3H, s, 3'-CH_3), 1.66 (3H, d, J = 1.0 Hz, 7'- or 8-CH_3), 1.68 (3H, d, J = 0.7 Hz, 7'- or 8-CH_3), 1.95-2.2 (4H, m, 4-, 5-CH_2), 2.03 (3H, s, $COCH_3$), 4.57 (2H, d, J = 7.3 Hz, 1-CH_2), 5.06 (1H, br t, J = 6.8 Hz, 6-CH), 5.32 (1H, tq, J = 7.1, 1.2 Hz, 2-CH);

IR (film) ν_{max}: 2968, 2926, 2858, 1742, 1670, 1446, 1378, 1366, 1232, 1024, 955, 830 cm^{-1};

MS (70eV) m/z: 196 (M^+ 0.8%), 154 (8), 136 (70), 121 (89), 107 (31), 93 (92), 85 (57), 80 (87), 67 (97), 53 (100), 39 (98), 43 (87), 41 (89), 29 (98), 27 (97).

Attempted isomerisation of geraniol (63) lithium alkoxide/HMPA with $Rh(PPh_3)_3Cl$

63

A solution of alkoxide prepared from geraniol (**63**) (183 mg, 1.19 mmol) in THF (6 ml) and *n*-butyllithium (729 µl, 1.63 M in hexanes, 1.19 mmol) was treated with hexamethylphosphoric triamide (207 µl, 1.19 mmol) dropwise at 0°C and degassed twice. The pale yellow solution was treated with a degassed solution of Wilkinson's catalyst (22.0 mg, 23.8 µmol, 2.0 mol%) in THF (5 ml), becoming immediately yellow, and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.12 ml, 11.9 mmol) as previously detailed and standard work-up including three aqueous copper (II) sulfate washes gave a yellow oil. Crude 270 MHz ^1H NMR showed no trace of the desired enol acetates, only *geranyl acetate* (**64**) and starting material.

Attempted isomerisation of geraniol (63) lithium alkoxide with $Rh(PPh_3)_3Cl/SnCl_2$

63

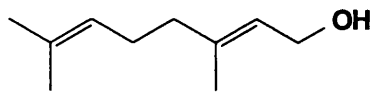
A degassed solution of alkoxide prepared from geraniol (**63**) (194 mg, 1.26 mmol) in THF (6 ml) and *n*-butyllithium (772 µl, 1.63 M in hexanes, 1.26 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.3 mg, 25.2 µmol, 2.0 mol%) and anhydrous tin (II) chloride (5.8 mg, 30.2 µmol, 2.4 mol%) in THF (5 ml), and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.19 ml, 12.6 mmol) and work-up as previously detailed gave a pale yellow oil. Crude 270 MHz ^1H NMR showed no trace of the desired enol acetates, but *geranyl acetate* (**64**) and *citronellyl*

acetate (**66**) (**64**:**66**=*ca.* 10:1) as the only identifiable compounds.

3,7-Dimethyl-6-octen-1-yl acetate (**66**)[212]:

^{1}H NMR (250 MHz) δ_H: 0.90 (3H, d, J = 6.1 Hz, 3'-CH_3), 1.59 (3H, s, 7'- or 8-CH_3), 1.67 (3H, s, 7'- or 8-CH_3), 1.0-2.1 (7H, obscured, 3-CH, 2-, 4-, 5-CH_2), 2.03 (3H, s, $COCH_3$), 4.08 (2H, t, J = 7.0 Hz, 1-CH_2), 5.0-5.15 (1H, m, 6-CH).

Attempted isomerisation of geraniol (63) tin (II) alkoxide with $Rh(PPh_3)_3Cl$

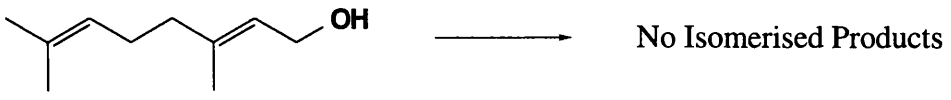


No Isomerised Products

63

A solution of alkoxide prepared from geraniol (**63**) (216 mg, 1.40 mmol) in THF (6 ml) and *n*-butyllithium (860 µl, 1.63 M in hexanes, 1.40 mmol) was treated with anhydrous tin (II) chloride (279 mg, 1.47 mmol) at 0°C and degassed twice. The pale yellow solution was treated with a degassed solution of Wilkinson's catalyst (25.9 mg, 28.0 µmol, 2.0 mol%) in THF (5 ml), becoming immediately deep red-brown, and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.32 ml, 14.0 mmol) and work-up as previously detailed gave a clear, colourless oil. Crude 270 MHz ^{1}H NMR showed no trace of the desired enol acetates, only *geranyl acetate* (**64**) and starting material.

Attempted isomerisation of geraniol (63) lithium alkoxide/aluminium *tert*-butoxide with $Rh(PPh_3)_3Cl$



63

A solution of alkoxide prepared from geraniol (**63**) (194 mg, 1.25 mmol) in THF (6 ml) and *n*-butyllithium (770 µl, 1.63 M in hexanes, 1.25 mmol) was treated with aluminium tri-*tert*-butoxide (279 mg, 1.47 mmol) at 0°C. Further THF (5 ml) was added to fully dissolve the solid and the resulting solution was degassed twice. This was treated with a degassed solution of Wilkinson's catalyst (23.2 mg, 25.1 µmol, 2.0 mol%) in THF (5 ml) and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.18 ml, 12.5 mmol) and work-up as previously detailed gave a yellow oil. Crude 270 MHz ^1H NMR showed no trace of the desired enol acetates, only *geranyl acetate* (**64**) and starting material.

Attempted isomerisation of geraniol (63) potassium alkoxide with $Rh(PPh_3)_3Cl$

63

Potassium hydride (295 mg, 35% w/w dispersion in mineral oil, 2.6 mmol) was washed free of oil with THF (3 × 5 ml), suspended in THF (2 ml) and cooled to 0°C. A solution of geraniol (**63**) (183 mg, 1.19 mmol) in THF (3 ml) was added dropwise causing much effervescence, followed by THF washings (4 × 1 ml), and after 5 min the mixture was allowed to warm to ambient temperature for 15 min. The mixture was filtered into a Schlenk flask (*via* glass filter-tipped canula) followed by THF washings (4 × 1 ml) and reduced in volume to *ca.* 6 ml by evaporation *in vacuo*. The clear,

yellowed alkoxide solution was degassed twice, treated with a degassed solution of Wilkinson's catalyst (24.0 mg, 25.9 μmol, 2.2 mol%) in THF (5 ml), and the mixture heated to reflux for 18 h. Quench with acetic anhydride (1.12 ml, 11.9 mmol) and work-up as previously detailed gave a brown oil. TLC (20% ether in petrol elution) and crude 270 MHz ^{1}H NMR showed a complex mixture with no trace of the desired enol acetates. *Geranyl acetate* (**64**), a large quantity of *citronellyl acetate* (**66**) and starting material (**63**) (**63+64:66**=*ca.* 1:1) were the only identifiable components of the mixture.

Attempted isomerisation of geraniol (63) magnesium alkoxide with $Rh(PPh_3)_3Cl$

63

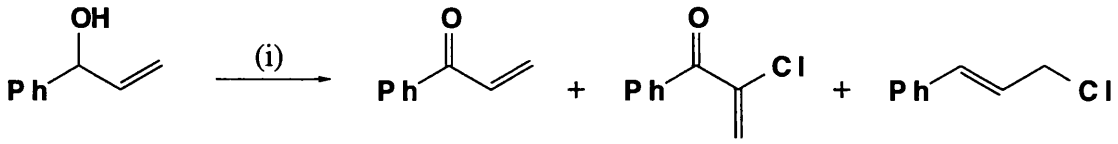
A degassed solution of alkoxide prepared from geraniol (**63**) (196 mg, 1.27 mmol) in THF (6 ml) and methylmagnesium bromide (907 μl, 1.40 M in 3:1 toluene-THF, 1.27 mmol) was treated with a degassed solution of Wilkinson's catalyst (23.5 mg, 25.4 μmol, 2.0 mol%) in THF (5 ml), and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.20 ml, 12.7 mmol) and work-up as previously detailed gave a pale yellow oil. Crude 270 MHz ^{1}H NMR showed no trace of the desired enol acetates, but *geranyl acetate* (**64**), and traces of *citronellyl acetate* (**66**) and starting material.

Attempted isomerisation of geraniol (63) diisobutylaluminium alkoxide with $Rh(PPh_3)_3Cl$

63

A solution of alkoxide was prepared from geraniol (**63**) (179 mg, 1.16 mmol) in THF (6 ml) and diisobutylaluminium hydride (775 µl, 1.50 M in toluene, 1.16 mmol) added dropwise at 0°C with much effervescence. The colourless solution was degassed twice, treated with a degassed solution of Wilkinson's catalyst (23.8 mg, 25.7 µmol, 2.2 mol%) in THF (5 ml) and heated to reflux for 48 h becoming a very pale, clear yellow colour. The mixture was quenched with acetic anhydride (1.09 ml, 11.6 mmol) at –78°C and allowed to warm to ambient temperature and stir for 24 h. Work-up as previously detailed gave a clear oil. Crude 270 MHz ^1H NMR showed a very clean reaction mixture with no trace of the desired enol acetates, but mostly *geranyl acetate* (**64**) and a small quantity of starting material.

Preparation of 1-phenyl-2-propen-1-one (67)



1 **67** **68** **69**

To a stirred, cooled (–78°C) solution of dimethyl sulfoxide (5.64 ml, 79.5 mmol) in dichloromethane (150 ml) was added oxalyl chloride (3.81 ml, 43.7 mmol) dropwise with visible evolution of gas. After 10 min a solution of 1-phenyl-2-propen-1-ol (**1**) (5.33 g, 39.7 mmol) in dichloromethane (50 ml) was added dropwise over 40 min with the formation of a white precipitate. After a further 30 min triethylamine (16.6 ml, 119 mmol) was added, the mixture stirred at –78°C for 15 min and then

allowed to warm to ambient temperature. The mixture was poured into water, extracted three times with dichloromethane, and the combined organic phases washed with water and brine, and dried over magnesium sulfate. Evaporation *in vacuo* and flash chromatography (10-20% ether in petrol gradient elution) afforded chloroalkene (**69**) (146 mg, 2%), chloroketone (**68**) (809 mg, 12%), and ketone (**67**) as a clear, colourless oil (3.22 g, 61%).

(E)-3-Chloro-1-phenyl-1-propene (**69**)[212]:

^{1}H NMR (270 MHz) δ_H: 4.26 (2H, d, J = 7.1 Hz, 3-CH_2), 6.33 (1H, dt, J = 15.6, 7.1 Hz, 2-CH), 6.67 (1H, d, J = 15.6 Hz, 1-CH), 7.25-7.5 (5H, m, ArH);

IR (film) ν_{max}: 3028, 2955, 1679, 1578, 1497, 1450, 1439, 1386, 1303, 1249, 1159, 1052, 964, 749, 694 cm^{-1};

MS (70eV) m/z: 154 (^{37}Cl-M$^+$ 8%), 152 (^{35}Cl-M$^+$ 22%), 117 (100), 115 (73), 91 (32), 89 (38), 77 (11), 65 (9), 63 (14).

2-Chloro-1-phenyl-2-propen-1-one (**68**)[261]:

^{1}H NMR (270 MHz) δ_H: 6.09 (1H, d, J = 2.1 Hz, 3-CH_AH$_B$), 6.28 (1H, d, J = 2.1 Hz, 3-CH$_A$$H_B$), 7.47 (2H, br t, J = 7 Hz, *m*-ArH), 7.59 (1H, br t, J = 7 Hz, *p*-ArH), 7.79 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3063, 1674, 1601, 1448, 1385, 1273, 1143, 967, 805, 770, 739, 671 cm^{-1};

MS (70eV) m/z: 168 (^{37}Cl-M$^+$ 1%), 166 (^{35}Cl-M$^+$ 3%), 149 (3), 147 (3), 122 (3), 105 (100), 77 (65), 51 (21), 43 (13).

1-Phenyl-2-propen-1-one (**67**)[262]:

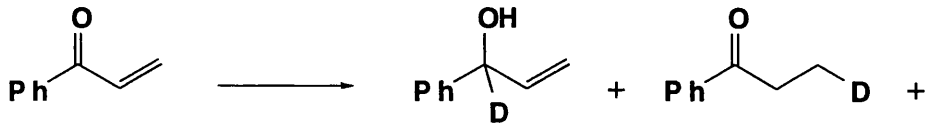
^{1}H NMR (270 MHz) δ_H: 5.94 (1H, dd, J = 10.5, 1.7 Hz, 3-CH_{cis}), 6.44 (1H, dd, J = 17.1, 1.7 Hz, 3-CH_{trans}), 7.16 (1H, dd, J = 17.1, 10.5 Hz, 2-CH), 7.48 (2H, br t, J = 7 Hz, *m*-ArH), 7.58 (1H, br t, J = 7 Hz, *p*-ArH), 7.95 (2H, br d, J = 7 Hz, *o*-ArH);

^{13}C NMR (126 MHz) δ_C: 128.46, 128.52, 129.9, 132.2, 132.8, 137.1, 190.8;

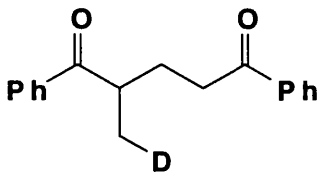
IR (film) ν_{max}: 3061, 1670, 1609, 1579, 1449, 1405, 1286, 1233, 1180, 994, 727, 689, 653 cm^{-1};

MS (70eV) m/z: 132 (M^+ 33%), 105 (100), 77 (66), 55 (12), 51 (24).

Preparation of 1-deuterio-1-phenyl-2-propen-1-ol (70)



67 70 71



72

To a stirred, cooled (0°C) suspension of lithium aluminium deuteride (480 mg, 11.4 mmol) in ether (150 ml) was added a solution of 1-phenyl-2-propen-1-one (**67**) (3.02 g, 22.9 mmol) in ether (50 ml) dropwise over 15 min. After a further 10 min several drops of water were added, followed by 3 M aqueous sodium hydroxide (*ca.* 50 ml), and the mixture extracted three times with ether. The combined organic phases were washed with aqueous sodium hydrogen carbonate, water, brine, and dried over $MgSO_4$. Evaporation *in vacuo* gave after flash chromatography (10-20% ether in petrol gradient elution) deuterio-ketone (**71**) (1.02 g, 33%), diketone (**72**) (730 mg, 24%), and deuterio-alcohol (**70**) (566 mg, 18%) as a clear, colourless oil.

3-Deuterio-1-phenyl-1-propanone (**71**)[102]:

^1H NMR (270 MHz) δ_H: 1.20 (2H, tt, J = 7.1, 2.0 Hz, 3-CH_2D), 2.98 (2H, tt, J = 7.1, 1.0 Hz, 2-CH_2), 7.44 (2H, t, J = 7 Hz, *m*-ArH), 7.52 (1H, t, J = 7 Hz, *p*-ArH), 7.96 (2H, d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3063, 2977, 2942, 1965, 1904, 1819, 1687, 1598, 1582, 1450, 1360, 1277, 1217, 1180, 1014, 951, 746, 720, 691 cm^{-1};

MS (70eV) m/z: 135 (M^+ 31%), 120 (5), 105 (100), 91 (12), 77 (100), 57 (7), 51

(38);

2-(Deuteriomethyl)-1,5-diphenyl-1,5-pentanedione (**72**):

^{1}H NMR (270 MHz) δ_H: 1.24 (2H, dt, J = 6.8, 2.0 Hz, 2'-CH_2D), 1.85-2.0 (1H, m, 3-CH_AH$_B$), 2.2-2.35 (1H, m, 3-CH$_A$$H_B$), 2.91 (1H, ddd, J = 17.1, 8.1, 6.4 Hz, 4-CH_AH$_B$), 3.10 (1H, ddd, J = 17.1, 8.3, 6.4 Hz, 4-CH$_A$$H_B$), 3.66 (1H, quintet, J = 6.8 Hz, 2-CH), 7.35-7.7 (6H, m, 1-*m*,*p*-ArH, 5-*m*,*p*-ArH), 7.9-8.1 (4H, m, 1-*o*-ArH, 5-*o*-ArH);

IR (film) ν_{max}: 3062, 2936, 1970, 1913, 1820, 1682, 1597, 1580, 1448, 1372, 1219, 1181, 1076, 1002, 975, 745, 691 cm^{-1};

MS (70eV) m/z: 267 (M$^+$ 14%), 224 (24), 191 (19), 162 (20), 148 (41), 135 (33), 120 (40), 105 (100), 91 (11), 77 (100), 51 (60), 28 (66).

1-Deuterio-1-phenyl-2-propen-1-ol (**70**)[243]:

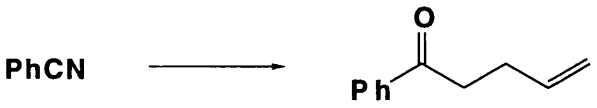
^{1}H NMR (270 MHz) δ_H: 5.21 (1H, dd, J = 10.3, 1.5 Hz, 3-CH$_{cis}$), 5.36 (1H, dd, J = 17.1, 1.5 Hz, 3-CH$_{trans}$), 6.06 (1H, ddt, J = 17.1, 10.3, 0.7 Hz, 2-CH), 7.2-7.5 (5H, m, ArH);

IR (film) ν_{max}: 3360, 3059, 3027, 1640, 1601, 1495, 1449, 1064, 1015, 991, 926, 700 cm^{-1};

MS (70eV) m/z: 135 (M$^+$ 66%), 134 (100), 118 (52), 116 (42), 105 (73), 92 (61), 80 (80), 78 (68), 77 (71), 55 (31), 51 (30);

HRMS m/z: M$^+$ = 135.0791 (135.0794 calcd for C_9H_9OD).

Preparation of 1-phenyl-4-penten-1-one (73)



73

To a water-cooled (10°C) solution of benzonitrile (5.16 g, 50.0 mmol) in benzene (100 ml) was added vinylmagnesium bromide (55 ml, 1.0 M in THF, 55 mmol)

dropwise over 20 min. The mixture was stirred at ambient temperature for 40 min., and then heated to reflux for 2 h. Once cooled, addition of ice, treatment with hydrochloric acid (200 ml, 1 M) for 1.5 h and extraction with ether produced an alkaline organic phase which was again treated with 1 M hydrochloric acid (100 ml) for 1 h. This mixture was extracted three times with ether, the combined organic phases washed with aqueous sodium hydrogen carbonate, water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography of the multi-component residue (2-10% ether in petrol gradient elution) afforded *1-phenyl-4-penten-1-one* (**73**)[242] as a clear, colourless oil (707 mg, 9%) and the only identified product:

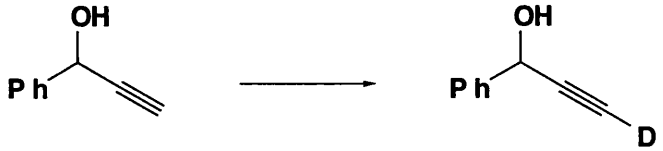
^{1}H NMR (270 MHz) δ_H: 2.50 (2H, qt, J = 6.6, 1.7 Hz, 3-CH_2), 3.07 (2H, t, J = 7.3 Hz, 2-CH_2), 5.01 (1H, dq, J = 10.3, 1.7 Hz, 5-CH_{cis}), 5.09 (1H, dq, J = 17.1, 1.7 Hz, 5-CH_{trans}), 5.91 (1H, ddt, J = 17.1, 10.3, 6.6 Hz, 4-CH), 7.45 (2H, br t, J = 7 Hz, *m*-ArH), 7.55 (1H, br t, J = 7 Hz, *p*-ArH), 7.96 (2H, br d, J = 7 Hz, *o*-ArH);

IR (film) ν_{max}: 3065, 2978, 2917, 1964, 1899, 1818, 1687, 1641, 1598, 1581, 1449, 1362, 1270, 1207, 1002, 916, 746, 690 cm^{-1};

MS (70eV) m/z: 160 (M^+ 61%), 145 (22), 129 (12), 120 (20), 106 (99), 105 (69), 91 (43), 78 (99), 77 (83), 65 (25), 55 (81), 50 (100), 39 (100).

Preparation of 3-deuterio-1-phenyl-1-propanone (71)

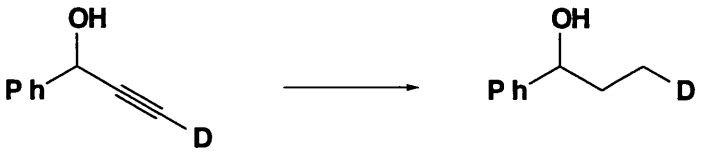
Preparation of 3-deuterio-1-phenyl-2-propyn-1-ol



To a stirred, cooled (–95°C) solution of 1-phenyl-2-propyn-1-ol (554 mg, 4.16 mmol) in THF (25 ml) was added dropwise *n*-butyllithium (6.1 ml, 1.5 M in hexanes, 9.2

mmol). The solution was allowed to warm to –30°C, becoming deep red-brown in colour, and then cooled again to –95°C. Deuterium oxide (0.5 ml, 28 mmol) was added, dispersing the colour, and the mixture was allowed to slowly warm to ambient temperature. After 30 min. saturated aqueous ammonium chloride was added and extracted three times with ether, the combined organic phases washed with water and brine, and dried ($MgSO_4$). Evaporation *in vacuo* gave a yellowed but clear residue, consistent with essentially pure *3-deuterio-1-phenyl-2-propyn-1-ol* by TLC.

Preparation of 3-deuterio-1-phenyl-1-propanol



Crude 3-deuterio-1-phenyl-2-propyn-1-ol was dissolved in acetone (20 ml) and a catalyst of palladium supported on powdered charcoal (*ca.* 50 mg, 1% w/w Pd, *ca.* 0.1 mol% cat.) suspended in the solution. The reaction flask was flushed with hydrogen and left to stir for 48 h at ambient temperature under a small positive pressure of the gas. Filtration through a pad of celite and evaporation *in vacuo* yielded crude *3-deuterio-1-phenyl-1-propanol* as an essentially pure, clear oil:

^{1}H NMR (270 MHz) δ_H: 0.91 (3H, tt, J = 7, 2 Hz, 3-CH_2D), 1.6-1.9 (2H, m, 2-CH_2), 2.15 (1H, s, OH), 4.58 (1H, t, J = 6.5 Hz, 1-CH), 7.2-7.5 (5H, m, ArH);

IR (film) ν_{max}: 3375, 3029, 2932, 2871, 1707, 1604, 1493, 1452, 1069, 1025, 760, 700 cm^{-1};

MS (70eV) m/z: 137 (M^+ 0.7%), 133 (22), 118 (21), 105 (91), 91 (100), 79 (23), 77 (49).

Preparation of 3-deuterio-1-phenyl-1-propanone (**71**)

(**71**)

Crude 3-deuterio-1-phenyl-1-propanol was dissolved in dichloromethane (30 ml) and activated manganese (IV) oxide (5.0 g, 58 mmol, 14 equiv) suspended in the solution. The mixture was left to stir under argon at ambient temperature for 24 h. Filtration through celite and evaporation *in vacuo* yielded a mixture of starting material and product (1:1 by crude ^{1}H NMR). Flash chromatography (10-20% ether in petrol gradient elution) afforded 3-deuterio ketone (**71**) (270 mg, 48% for three steps) as a mixture with 2-deuterio ketone (*ca.* 10:1 by ^{2}H NMR), and starting material (245 mg, 43%).

3-Deuterio-1-phenyl-1-propanone (**71**)[102]:

^{1}H NMR (270 MHz) δ_H: 1.20 (2H, tt, J = 7.1, 2.0 Hz, 3-CH_2D), 2.98 (2H, tt, J = 7.1, 1.0 Hz, 2-CH_2), 7.44 (2H, t, J = 7 Hz, *m*-ArH), 7.52 (1H, t, J = 7 Hz, *p*-ArH), 7.96 (2H, d, J = 7 Hz, *o*-ArH);

^{2}H NMR (76.8 MHz) δ_D: 1.19 (1D, tt, J = 2, 1 Hz, 3-CH$_2$*D*);

IR (film) ν_{max}: 3063, 2977, 2942, 1965, 1904, 1819, 1687, 1598, 1582, 1450, 1360, 1277, 1217, 1180, 1014, 951, 746, 720, 691 cm^{-1};

MS (70eV) m/z: 135 (M$^+$ 31%), 120 (5), 105 (100), 91 (12), 77 (100), 57 (7), 51 (38);

HRMS m/z: M$^+$ = 135.0789 (135.0794 calcd for C_9H_9OD).

Preparation of 2-deuterio-1-phenyl-1-propanone (74)

74

A cooled (–78°C) solution of diisopropylamine (209 µl, 1.49 mmol) in THF (10 ml) was treated with *n*-butyllithium (1.00 ml, 1.49 M in hexanes, 1.49 mmol) and stirred for 30 min. A solution of 1-phenyl-1-propanone (190 mg, 1.42 mmol) in THF (5 ml) was added dropwise and the mixture stirred a further 30 min, before dropwise transfer over 10 min to a cooled (0°C) solution of deuterium oxide (3.0 ml, *ca.* 170 mmol) in THF (7 ml). After 15 min ether was added and the separated organic phase dried over $MgSO_4$. Evaporation *in vacuo* and short-path distillation yielded *2-deuterio-1-phenyl-1-propanone* (**74**)[263] (157 mg, 82%, *ca.* 60% D) as a clear, colourless oil:

^1H NMR (270 MHz) δ_H: 1.21 (3H, dt, J = 7.3, 1.5 Hz, 3-CH_3), 2.98 (1H, qt, J = 7.3, 2.7 Hz, 2-C*H*D), 7.45 (2H, t, J = 7 Hz, *m*-ArH), 7.52 (1H, t, J = 7 Hz, *p*-ArH), 7.96 (2H, d, J = 7 Hz, *o*-ArH);

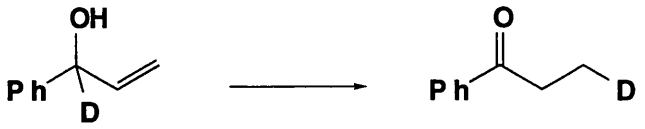
^2H NMR (76.8 MHz) δ_D: 2.98 (1D, dq, J = 3, 1 Hz, 2-CH*D*);

IR (film) ν_{max}: 3063, 2978, 2939, 1966, 1910, 1818, 1688, 1598, 1583, 1450, 1333, 1267, 1221, 1181, 1076, 1002, 952, 746, 724, 691 cm^{-1};

MS (70eV) m/z: 135 (M^+ 16%), 134 (12), 119 (2), 105 (100), 91 (3), 77 (43), 57 (5), 51 (15);

HRMS m/z: M^+ = 135.0796 (135.0794 calcd for C_9H_9OD).

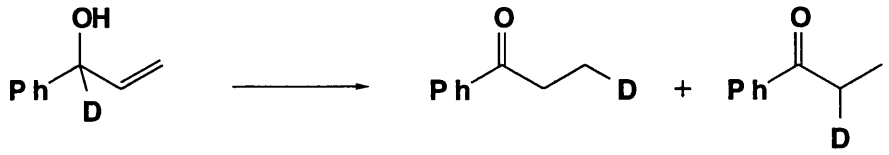
10% $Rh(PPh_3)_3Cl$ mediated isomerisation of 1-deuterio-1-phenyl-2-propen-1-ol (70)



70 **71**

A degassed solution of alkoxide prepared from 1-deuterio-1-phenyl-2-propen-1-ol (**70**) (32.0 mg, 237 μmol) in THF (2 ml) and *n*-butyllithium (145 μl, 1.63 M in hexanes, 237 μmol) was treated with a degassed solution of Wilkinson's catalyst (21.9 mg, 23.7 μmol, 10.0 mol%) in THF (3 ml) and the mixture heated to reflux for 30 min. Quench at 0°C with aqueous ammonium chloride and work-up as previously detailed gave after flash chromatography (10% ether in 30-40 petrol elution) *3-deuterio-1-phenyl-1-propanone* (**71**) (22.5 mg, 70%) as a clear, colourless oil.

10% $Rh(PPh_3)_3Cl/^nBuLi$ mediated isomerisation of 1-deuterio-1-phenyl-2-propen-1-ol (70)



70 **71** **74**

A degassed solution of alkoxide was prepared from 1-deuterio-1-phenyl-2-propen-1-ol (**70**) (35.2 mg, 260 μmol) in THF (2 ml) and *n*-butyllithium (160 μl, 1.63 M in hexanes, 261 μmol). A solution of Wilkinson's catalyst (24.1 mg, 26.0 μmol, 10.0 mol%) in THF (3 ml) was treated dropwise with *n*-butyllithium (16 μl, 1.63 M in hexanes, 26 μmol) at 0°C and degassed twice. This was added to the alkoxide solution and the mixture heated to reflux for 30 min. Quench at 0°C with aqueous ammonium chloride and work-up as previously detailed gave after flash chromatography (10% ether in 30-40 petrol elution) a mixture of *3-deuterio-1-phenyl-1-propanone* (**71**) and *2-*

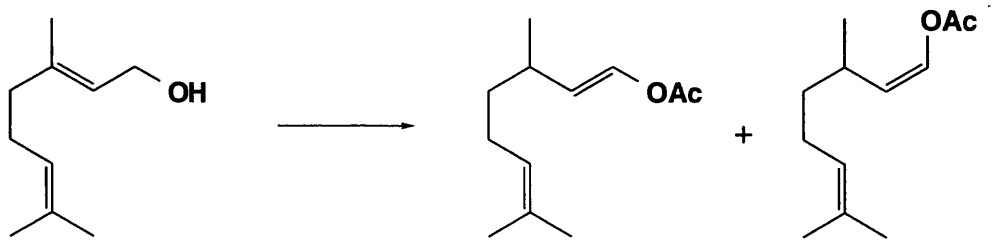
deuterio-1-phenyl-1-propanone (**74**) (**71**:**74**=30:1, 23.2 mg, 66%) as a clear, colourless oil.

Standard Procedure For $Ni(cod)_2$/Ligand Catalysed Isomerisations

In a fully equipped glove-box bis(1,5-cyclooctadiene)nickel (0) was weighed into a Schlenk flask which was sealed under a slight positive pressure of argon and immediately cooled to –78°C until used. The required quantity of the alcohol substrate, based on the quantity of $Ni(cod)_2$ used, was accurately weighed into a second Schlenk flask, the flask was flushed with argon, and THF (6 ml) added. The solution was cooled to 0°C and treated with *n*-butyllithium (1.00-1.05 equiv) dropwise over several minutes, and the mixture stirred for *ca.* 15 min. at that temperature. Into a third Schlenk flask was weighed the required quantity of ligand and the flask was flushed with argon, THF (5 ml) was added, and the two solutions degassed twice by the freeze-thaw procedure. The ligand solution was transferred *via* canula to the solid $Ni(cod)_2$, the complex dissolving as the mixture was stirred and allowed to warm slowly from –78°C to ambient temperature. In the case of the bis(oxazoline) ligands the appearance of a deep blue colour was characteristic at >0°C. The resulting solution was transferred *via* teflon canula to the alkoxide and the mixture rapidly heated to reflux.

The freeze-thaw degassing technique is described previously for $Rh(PPh_3)_3Cl$ isomerisations, as are quenching and work-up procedures. Deviations from the standard procedure are stated.

10% Ni(cod)$_2$/2PCy$_3$/H$_2$ mediated isomerisation of geraniol (63), 26 h (non-standard procedure)



63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (209 mg, 1.35 mmol) in THF (6 ml) and *n*-butyllithium (828 µl, 1.63 M in hexanes, 1.35 mmol), and a solution of tricyclohexylphosphine (75.4 mg, 269 µmol, 20 mol%) in THF (10 ml) were degassed twice. Under a blanket of argon bis(1,5-cyclooctadiene)nickel (0) (35 mg, 130 µmol, 10 mol%) was weighed into a Schlenk tube, which was flushed with argon and immediately cooled to 0°C. The phosphine solution, also cooled to 0°C, was transferred to the solid Ni(cod)$_2$ *via* canula. The resulting yellow solution was stirred at ambient temperature under a small positive pressure of hydrogen (*ca.* 30 mbar) for 20 min, becoming orange and then dark brown. This solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 26 h. Quench with acetic anhydride (1.27 ml, 13.5 mmol) and work-up as detailed previously gave after flash chromatography (2.5% ether in petrol elution) an inseparable mixture of (E)- and (Z)-enol acetates **75** and **76** (**75**:**76**=5.4:1, 183 mg, 69%) as a clear, colourless oil:

(E)-3,7-Dimethylocta-1,6-dien-1-yl acetate (**75**)[187]:

^{1}H NMR (400 MHz) δ_H: 1.01 (3H, d, J = 6.8 Hz, 3'-CH_3), 1.2-1.4 (2H, m, 4-CH_2), 1.58 (3H, s, 7' or 8-CH_3), 1.68 (3H, d, J = 1.0 Hz, 7' or 8-CH_3), 1.96 (2H, m, 5-CH_2), 2.11 (3H, s, $COCH_3$), 2.14 (1H, m, 3-CH), 5.1-5.0 (1H, m, 6-CH), 5.29 (1H, dd, J = 12.5, 8.9 Hz, 2-CH), 7.06 (1H, dd, J = 12.5, 1.0 Hz, 1-CH);

(Z)-3,7-Dimethylocta-1,6-dien-1-yl acetate (**76**)[187]:

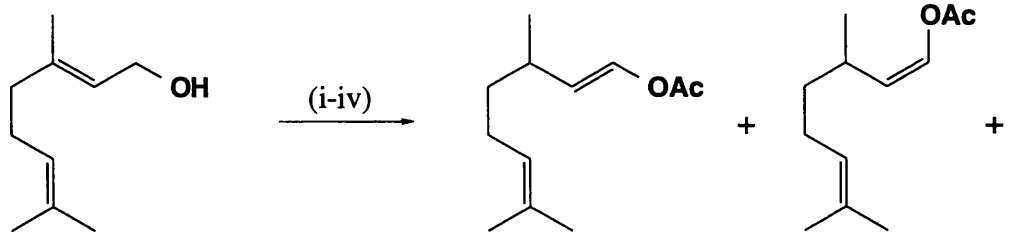
^{1}H NMR (400 MHz) δ_H: 0.98 (3H, d, J = 6.8 Hz, 3'-CH_3), 1.2-1.4 (2H, m, 4-CH_2), 1.58 (3H, s, 7' or 8-CH_3), 1.68 (3H, d, J = 1.0 Hz, 7' or 8-CH_3), 1.96 (2H, m, 5-CH_2), 2.11 (3H, s, $COCH_3$), 2.14 (1H, m, 3-CH), 4.67 (1H, dd, J = 9.6, 6.5 Hz, 6-CH), 5.1-5.0 (1H, m, 6-CH), 6.98 (1H, dd, J = 9.6, 1.0 Hz, 1-CH);

Mixture of **75** and **76**:

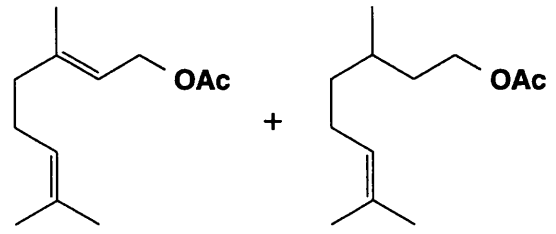
IR (film) ν_{max}: 2964, 2916, 2854, 1759, 1673, 1454, 1371, 1223, 1096, 1046, 934, 650 cm^{-1};

MS (70eV) m/z: 196 (M^+ <1%), 154 (41%), 136 (43), 121 (45), 109 (44), 101 (43), 95 (46), 84 (50), 71 (55), 69 (57), 55 (51), 43 (100), 41 (71), 27 (48);

20% Ni(cod)$_2$/2PCy$_3$/H$_2$ mediated isomerisation of geraniol (63), 6 h



63 **75** **76**

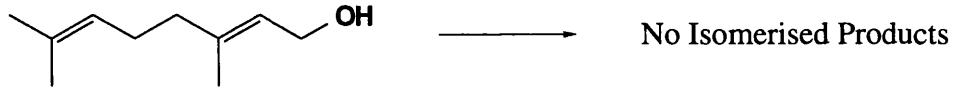


64 **66**

A solution of alkoxide prepared from geraniol (**63**) (180 mg, 1.17 mmol) in THF (8 ml) and *n*-butyllithium (718 µl, 1.63 M in hexanes, 1.17 mmol), and a solution of tricyclohexylphosphine (130 mg, 465 µmol, 40 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid Ni(cod)$_2$ (64 mg, 233 µmol, 20

mol%) at –78°C, and once warmed to ambient temperature the mixture was stirred under a positive pressure of hydrogen for 30 min. The resulting dark brown solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 6 h. Quench with acetic anhydride (1.10 ml, 11.7 mmol) and work-up as detailed previously gave after flash chromatography (1-2.5% ether in petrol gradient elution) a mixture (23.4 mg) of *geranyl acetate* (**64**) (2%) with *citronellyl acetate* (**66**) (8%), and an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=10:1, 50.5 mg, 22%) as the only identifiable products.

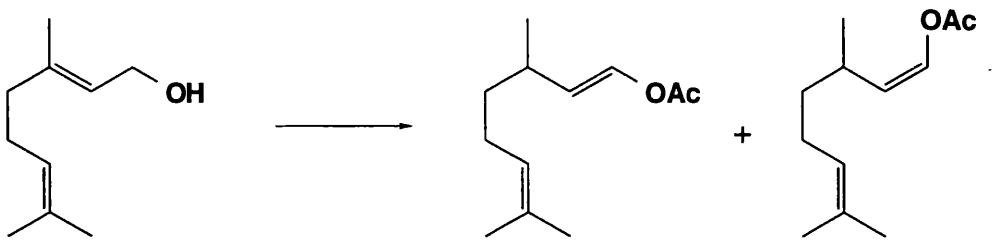
20% $Ni(cod)_2/2PCy_3/H_2$ mediated isomerisation of geraniol (63), 36 h (non-standard procedure)



63

In an argon-filled polythene glove-bag, $Ni(cod)_2$ (62 mg, 225 μmol, 20 mol%) was weighed into a Schlenk tube. Tricyclohexylphosphine (129 mg, 460 μmol, 40 mol%) was added, the flask was again flushed with argon and the mixture dissolved in degassed THF (10 ml). The resulting yellow solution was stirred at ambient temperature under a small positive pressure of hydrogen (*ca.* 30 mbar) for 30 min, becoming deep brown-black. In a second Schlenk tube a solution of alkoxide was prepared from geraniol (**63**) (191 mg, 1.24 mmol) in THF (6 ml) and *n*-butyllithium (761 μl, 1.63 M in hexanes, 1.24 mmol) and degassed twice. The alkoxide solution was transferred to the catalyst solution *via* canula, and the mixture heated to reflux for 36 h. Quench with acetic anhydride (1.17 ml, 12.4 mmol) and analysis by crude ^1H NMR indicated no identifiable products.

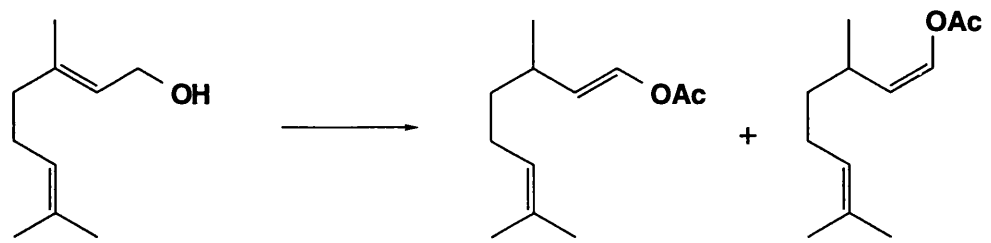
20% $Ni(cod)_2/2PCy_3$ mediated isomerisation of geraniol (63)



63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (250 mg, 1.62 mmol) in THF (8 ml) and *n*-butyllithium (1.02 ml, 1.63 M in hexanes, 1.64 mmol), and a solution of tricyclohexylphosphine (181 mg, 647 μmol, 40 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid $Ni(cod)_2$ (89 mg, 324 μmol, 20 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 1.75 h. Quench with acetic anhydride (1.51 ml, 16.0 mmol) and work-up as detailed previously gave after flash chromatography (2.5% ether in petrol elution) an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=7.6:1, 205 mg, 65%), with traces of *citronellyl acetate* (**66**).

20% $Ni(cod)_2/PCy_3$ mediated isomerisation of geraniol (63)

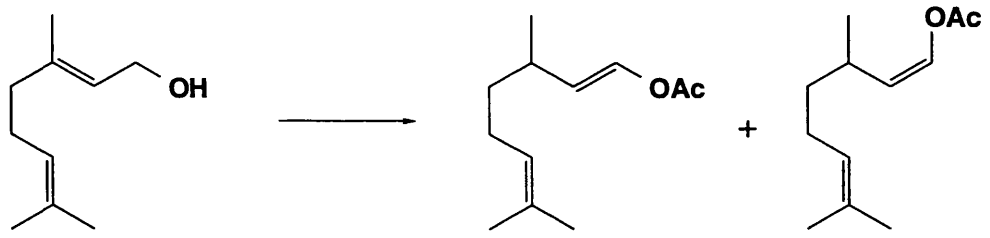


63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (212 mg, 1.37 mmol) in THF (8 ml) and *n*-butyllithium (859 μl, 1.60 M in hexanes, 1.37 mmol), and a solution of tricyclohexylphosphine (77.0 mg, 275 μmol, 20 mol%) in THF (12 ml) were degassed

twice. The phosphine solution was added to solid $Ni(cod)_2$ (75 mg, 273 μmol, 20 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 18 h. Quench with acetic anhydride (1.29 ml, 13.7 mmol) and work-up as detailed previously gave after flash chromatography (twice 1-2% ether in petrol gradient elution) a mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=4.4:1, 62.8 mg, 23%), with traces of *citronellyl acetate* (**66**).

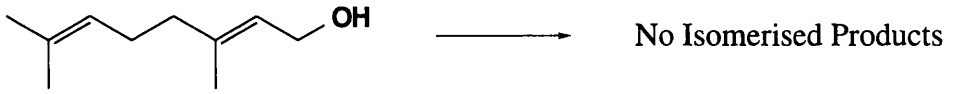
20% $Ni(cod)_2$/dppe mediated isomerisation of geraniol (63)



63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (182 mg, 1.18 mmol) in THF (8 ml) and *n*-butyllithium (738 μl, 1.63 M in hexanes, 1.18 mmol), and a solution of bis(diphenylphosphino)ethane (94.2 mg, 236 μmol, 20 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid $Ni(cod)_2$ (65 mg, 236 μmol, 20 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 10 h. Quench with acetic anhydride (1.11 ml, 11.8 mmol) and work-up as detailed previously gave after flash chromatography (three times 1-2.5% ether in petrol gradient elution) a mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=3.2:1, *ca.* 45 mg, *ca.* 20%).

5% Ni(cod)$_2$/CHIRAPHOS—Attempted isomerisation of geraniol (63)



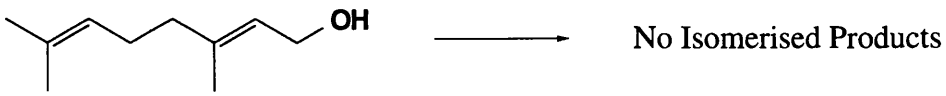
63

A solution of alkoxide prepared from geraniol (**63**) (292 mg, 1.89 mmol) in THF (8 ml) and *n*-butyllithium (1.18 ml, 1.60 M in hexanes, 1.89 mmol), and a solution of (*S*,*S*)-CHIRAPHOS (41 mg, 96 μmol, 5.1 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid Ni(cod)$_2$ (26 mg, 95 μmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.78 ml, 18.9 mmol) and work-up as detailed previously gave after flash chromatography (2.5-50% ether in petrol gradient elution) no trace of enol acetates, but a mixture (94 mg) of *citronellol* (**65**) (8%) and starting material (24%).

3,7-Dimethyl-6-octen-1-ol (**65**)[212]:

^{1}H NMR (250 MHz) δ_H: 0.87 (3H, d, J = 6.6 Hz, 3'-CH_3), 1.57 (3H, s, 7'- or 8-CH_3), 1.64 (3H, s, 7'- or 8-CH_3), 1.0-1.8 (6H, m, 3-CH, 2-, 4-CH_2, OH), 1.8-2.1 (2H, m, 5-CH_2), 3.64 (2H, t, J = 6.9 Hz, 1-CH_2), 5.0-5.15 (1H, m, 6-CH).

5% Ni(cod)$_2$/(Me)-DUPHOS—Attempted isomerisation of geraniol (63)

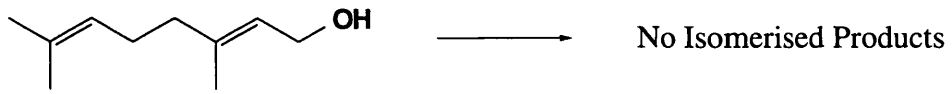


63

A solution of alkoxide prepared from geraniol (**63**) (252 mg, 1.63 mmol) in THF (8 ml) and *n*-butyllithium (1.02 ml, 1.60 M in hexanes, 1.63 mmol), and a solution of (*R*,*R*)-(Me)-DUPHOS (26 mg, 83 μmol, 5.1 mol%) in THF (12 ml) were degassed

twice. The phosphine solution was added to solid $Ni(cod)_2$ (22 mg, 80 μmol, 4.9 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.54 ml, 16.3 mmol) and work-up as detailed previously gave after flash chromatography (2.5-20% ether in petrol gradient elution) no trace of enol acetates, but *geranyl acetate* (**64**), *citronellyl acetate* (**66**) and *citronellol* (**65**).

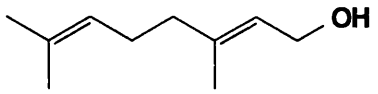
5% $Ni(cod)_2$/BDPP—Attempted isomerisation of geraniol (63)



63

A solution of alkoxide prepared from geraniol (**63**) (203 mg, 1.32 mmol) in THF (8 ml) and *n*-butyllithium (823 μl, 1.60 M in hexanes, 1.32 mmol), and a solution of (*S*,*S*)-BDPP (29 mg, 66 μmol, 5.0 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid $Ni(cod)_2$ (18 mg, 65 μmol, 4.9 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 48 h. Quench with acetic anhydride (1.25 ml, 13.2 mmol) and work-up as detailed previously gave a clear oil. Crude ^1H NMR (400 MHz) indicated no trace of enol acetates, but *geranyl acetate* (**64**), *citronellol* (**65**) and starting material (**63**) (**63+64**:**65**=*ca.* 3:1).

5% Ni(cod)$_2$/DIOP—Attempted isomerisation of geraniol (63)

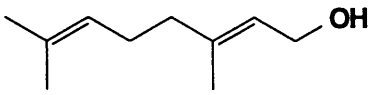


No Isomerised Products

63

A solution of alkoxide prepared from geraniol (**63**) (283 mg, 1.84 mmol) in THF (8 ml) and *n*-butyllithium (1.15 ml, 1.60 M in hexanes, 1.84 mmol), and a solution of (–)-DIOP (46 mg, 92 μmol, 5.0 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid Ni(cod)$_2$ (25 mg, 91 μmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 24 h. Quench with acetic anhydride (1.74 ml, 18.4 mmol) and work-up as detailed previously gave a clear yellow oil. Crude ^{1}H NMR (400 MHz) indicated a complex mixture with a trace of enol acetates, and *geranyl acetate* (**64**), *citronellol* (**65**) and starting material (**63**) (**63**+**64**:**65**=*ca.* 3:1).

5% Ni(cod)$_2$/BINAP—Attempted isomerisation of geraniol (63)



No Isomerised Products

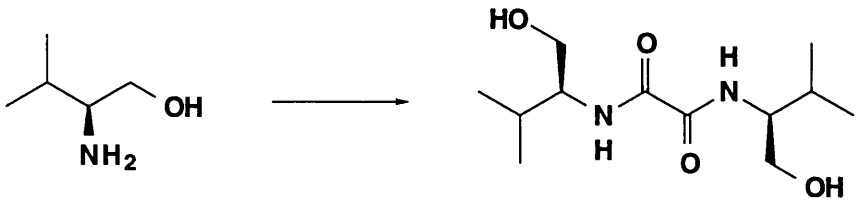
63

A solution of alkoxide prepared from geraniol (**63**) (172 mg, 1.11 mmol) in THF (8 ml) and *n*-butyllithium (695 μl, 1.63 M in hexanes, 1.11 mmol), and a solution of (*R*)-BINAP (34.7 mg, 56 μmol, 5.1 mol%) in THF (12 ml) were degassed twice. The phosphine solution was added to solid Ni(cod)$_2$ (15 mg, 55 μmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 87 h. Quench with acetic anhydride (1.05 ml, 11.1 mmol) and work-up as detailed previously gave a clear yellow oil. Crude ^{1}H NMR (400 MHz)

indicated no trace of enol acetates, only *citronellyl acetate* (**66**) and traces of *geranyl acetate* (**64**).

Preparation of *N,N'*-bis(*2S*-1-chloro-3-methyl-2-butyl)oxamide (^{i}Pr-77)

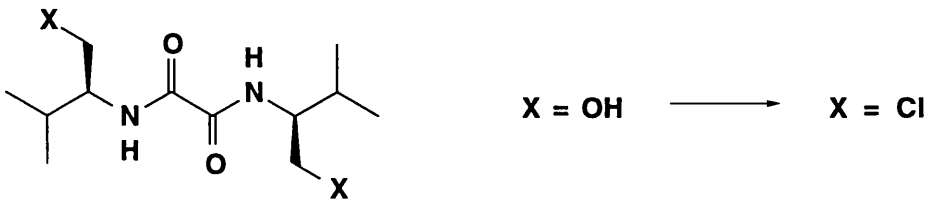
Preparation of *N,N'*-bis(*2S*-1-hydroxy-3-methyl-2-butyl)oxamide (^{i}Pr-**79**)



^{i}Pr-**78** ^{i}Pr-**79**

To a solution of (*2S*)-2-amino-3-methyl-1-butanol (^{i}Pr-**78**) (1.25 g, 12.1 mmol) in toluene (10 ml) was added diethyl oxalate (821 µl, 6.05 mmol). When heated to 80°C the mixture largely solidified but was diluted with further toluene (40 ml) and redissolved. After heating to 80°C overnight the solution was allowed to cool to ambient temperature giving a gelatinous mass, evaporation of which produced *N,N'*-bis(*2S*-1-hydroxy-3-methyl-2-butyl)oxamide (^{i}Pr-**79**) as a low-density white solid used subsequently without purification.

Preparation of *N,N'*-bis(*2S*-1-chloro-3-methyl-2-butyl)oxamide (^{i}Pr-**80**)



^{i}Pr-**79** ^{i}Pr-**80**

The crude *N,N'*-bis(*2S*-1-hydroxy-3-methyl-2-butyl)oxamide (^{i}Pr-**79**) was dissolved in thionyl chloride (6.0 ml, 82 mmol) and after 45 min at ambient temperature the solution heated to reflux for 1 h. Evaporation *in vacuo* gave a yellow solid, which was

triturated with ethanol (20 ml) and again evaporated twice. Recrystallisation of the discoloured residue from ethanol (*ca.* 60 ml.g^{-1}) yielded *N,N'-bis(2S-1-chloro-3-methyl-2-butyl)oxamide* (^{i}Pr-**80**) (1.29 g, 72% for two steps) as white needles, m.p. 213°C, $[\alpha]_D^{23}$ –95.7 (*c* 0.7 in $CHCl_3$):

^{1}H NMR (400 MHz) δ_H: 0.94 (3H, d, *J* = 7.0 Hz, CH_3), 0.98 (3H, d, *J* = 6.7 Hz, CH_3), 2.02 (1H, octet, *J* = 7.0 Hz, $CHMe_2$), 3.63 (1H, dd, *J* = 4.1, 11.5 Hz, CH_AH_BCl), 3.69 (1H, dd, *J* = 4.5 Hz, 11.5 Hz, CH_AH_BCl), 3.85-3.95 (1H, m, NCH), 7.55 (1H, br d, *J* = 8.9 Hz, NH);

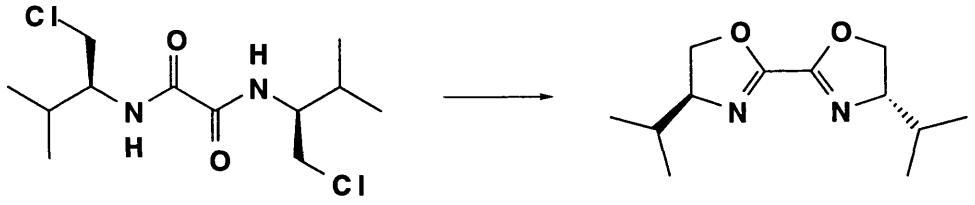
^{13}C NMR (101 MHz) δ_C: 18.5, 19.2, 29.3, 45.6, 56.0, 159.4;

IR (KBr disc) ν_{max}: 3278, 2971, 2941, 2875, 1660, 1531, 1496, 1473, 1392, 1232, 1188, 1140, 1060, 784, 765, 735 cm^{-1};

MS (70eV) m/z: 296 (^{35}Cl-M$^+$ 28%), 281 (1), 257 (5), 255 (32), 253 (50), 249 (15), 247 (46), 219 (3), 195 (32), 193 (100), 169 (5), 148 (10), 105 (27), 100 (21), 79 (35), 78 (100), 72 (61), 69 (100);

HRMS m/z: M$^+$ = 296.1054 (296.1058 calcd for $C_{12}H_{22}N_2O_2{}^{35}Cl_2$).

Preparation of (*4S,4'S*)-4,4'-bis(2-propyl)-4,4',5,5'-tetrahydro-2,2'-bis(oxazole) (^{i}Pr-77)



^{i}Pr-**80** ^{i}Pr-**77**

N,N'-bis(2*S*-1-chloro-3-methyl-2-butyl)oxamide (^{i}Pr-**80**) (1.25 g, 4.21 mmol) was dissolved in a methanolic solution of sodium hydroxide (8.43 ml, 1.00 M in methanol, 8.43 mmol) and the mixture heated to reflux for 1.5 h, rapidly becoming cloudy. Once cooled the mixture was filtered and evaporated *in vacuo*, the residue taken up in ether and refiltered through a pad of celite. Evaporation gave a clear oil which crystallised on

standing. Recrystallisation from petrol gave *4S,4'S-4,4'-bis(2-propyl)-4,4',5,5'-tetrahydro-2,2'-bis(oxazole)* (^{i}Pr-**77**)[205] (713 mg, 75%) as white needles, m.p. 55°C (lit.,[205] 50°C), $[\alpha]_D^{23}$ -160.0 (*c* 1.0 in $CHCl_3$) [lit.,[205] –158.8 (*c* 0.97 in $CHCl_3$)]:

^{1}H NMR (400 MHz) δ_H: 0.87 (3H, d, *J* = 6.8 Hz, CH_3), 0.97 (3H, d, *J* = 6.7 Hz, CH_3), 1.80 (1H, octet, *J* = 6.7 Hz, $CHMe_2$), 4.0-4.1 (2H, m, OCH_2CH), 4.35-4.45 (1H, m, OCH_2CH);

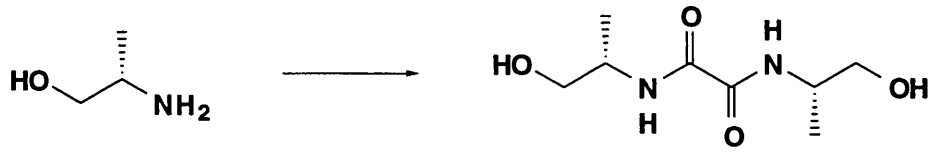
^{13}C NMR (101 MHz) δ_C: 18.2, 18.9, 32.4, 71.0, 73.1, 154.5;

IR (KBr disc) ν_{max}: 2960, 2878, 1616, 1482, 1470, 1449, 1362, 1345, 1276, 1260, 1111, 1028, 948, 895, 872, 810, 609 cm^{-1};

MS (70eV) m/z: 224 (M^+ 12%), 209 (5), 195 (2), 182 (90), 181 (100), 153 (8), 138 (31), 127 (8), 111 (20), 97 (6), 85 (30), 69 (16);

HRMS m/z: M^+ = 224.1529 (224.1525 calcd for $C_{12}H_{20}N_2O_2$).

Preparation of *N,N'*-bis(*2S*-1-hydroxy-2-propyl)oxamide (Me-79)



Me-**78** Me-**79**

A solution of (*S*)-2-amino-1-propanol (Me-**79**) (882.7 mg, 11.8 mmol) and dimethyl oxalate (1.39 g, 11.8 mmol) in 1,2-dichloroethane (18 ml) was heated to reflux for 3 h. When allowed to cool to ambient temperature a white solid precipitated, and evaporation of the mixture *in vacuo* gave a sticky amorphous solid. Recrystallisation from boiling 1:1 ethyl acetate-ethanol (*ca.* 50 ml.g^{-1}) and cooling to 0°C overnight afforded *N,N'-bis(2S-1-hydroxy-2-propyl)oxamide* (Me-**79**) (758 mg, 63%) as white needles, m.p. 205-7°C, $[\alpha]_D^{23}$ –4.2 (*c* 0.5 in 1:1 EtOH-H_2O):

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.06 (3H, d, *J* = 6.7 Hz, CH_3), 3.3-3.4 (2H, m, OCH_2), 3.75-3.85 (1H, m, CHN), 4.76 (1H, br t, *J* = 5.3 Hz, OH), 8.30 (1H, br d, *J* = 7.5 Hz, NH);

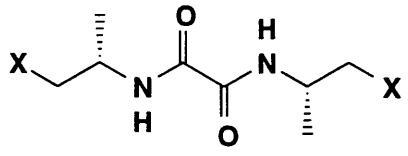
^{13}C NMR (101 MHz) δ_C: 16.6, 47.1, 63.8, 159.4;

IR (KBr disc) ν_{max}: 3290, 2977, 2946, 2888, 1652, 1538, 1476, 1456, 1384, 1306, 1251, 1216, 1135, 1106, 1047, 916, 871, 773, 643 cm^{-1};

MS (70eV) m/z: 204 (M^+ 12%), 187 (5), 174 (31), 173 (100), 147 (32), 129 (8), 102 (55), 84 (11), 70 (32);

HRMS m/z: M^+ = 204.1115 (204.1110 calcd for $C_8H_{16}N_2O_4$).

Preparation of *N,N'*-bis(*2S*-1-chloro-2-propyl)oxamide (Me-80)



X = OH ⟶ X = Cl

Me-**79** Me-**80**

N,N'-bis(*2S*-1-hydroxy-2-propyl)oxamide (Me-**79**) (676 mg, 3.31 mmol) was dissolved in toluene (25 ml) and thionyl chloride (1.5 ml, 20 mmol) added dropwise. After 15 min at ambient temperature the solution heated to 75°C for 18 h. Evaporation *in vacuo*, and trituration with ethanol (20 ml) and evaporation twice, gave a low density white solid. Recrystallisation of the residue from 1:1 ethyl acetate-ethanol (*ca.* 45 $ml.g^{-1}$) produced *N,N'-bis(2S-1-chloro-2-propyl)oxamide* (Me-**80**) (722 mg, 90%) as white needles, m.p. 197°C, $[\alpha]_D^{23}$ –71.7 (*c* 0.24 in $CHCl_3$):

^1H NMR (400 MHz, DMSO-d_6) δ_H: 1.16 (3H, d, *J* = 6.7 Hz, CH_3), 3.6-3.7 (2H, m, OCH_2), 4.0-4.1 (1H, m, CHN), 8.77 (1H, br d, *J* = 8.7 Hz, NH);

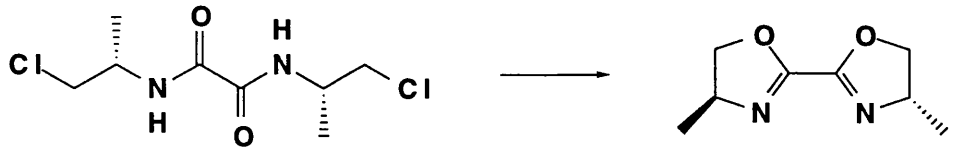
^{13}C NMR (101 MHz) δ_C: 17.8, 46.8, 47.3, 159.3;

IR (KBr disc) ν_{max}: 3285, 3071, 2981, 2953, 2878, 1700, 1684, 1652, 1541, 1498, 1458, 1377, 1321, 1241, 1192, 1149, 1092, 1066, 905, 871, 859, 774, 734 cm^{-1};

MS (70eV) m/z: 241 (2^{35}Cl-M^++H 10%), 204 (5), 193 (19), 191 (57), 167 (14), 165 (42), 120 (42), 86 (33), 83 (15), 79 (31), 77 (100), 72 (26), 58 (10);

HRMS m/z: M^++H = 241.0516 (241.0511 calcd for $C_8H_{15}N_2O_2{}^{35}Cl_2$).

Preparation of *4S,4'S*-4,4'-dimethyl-4,4',5,5'-tetrahydro-2,2'-bis(oxazole) (Me-77)



Me-**80** Me-**77**

To *N,N'*-bis(*2S*-1-chloro-2-propyl)oxamide (Me-**80**) (600 mg, 2.49 mmol) was added methanol (20 ml) and THF (10 ml) and the solution heated to reflux. A methanolic solution of sodium hydroxide (5.0 ml, 1.0 M in methanol, 5.0 mmol) was added and the mixture began to cloud. Reflux was maintained for 1 h. Once cooled the mixture was filtered, and evaporation *in vacuo* gave an amorphous white solid. Dissolution of the residue in ethyl acetate and filtration through a pad of celite removed more sodium chloride. Recrystallisation from 16:1 petrol-ethyl acetate (*ca.* 35 $ml.g^{-1}$) and storage overnight at 2°C gave *4S,4'S-4,4'-dimethyl-4,4',5,5'-tetrahydro-2,2'-bis(oxazole)* (Me-**77**) (296 mg, 70%) as white needles, m.p. 92°C, $[\alpha]_D^{23}$ –196.2 (*c* 1.0 in $CHCl_3$):

^{1}H NMR (400 MHz) δ_H: 1.30 (3H, d, *J* = 6.7 Hz, CH_3), 3.93 (1H, t, *J* = 8.2 Hz, OCH_AH_B), 4.34 (1H, ddq, *J* = 9.5, 8.2, 6.7 Hz, NCH), 4.48 (1H, dd, *J* = 9.5, 8.2 Hz, OCH_AH_B);

^{13}C NMR (101 MHz) δ_C: 20.8, 62.4, 74.7, 154.5;

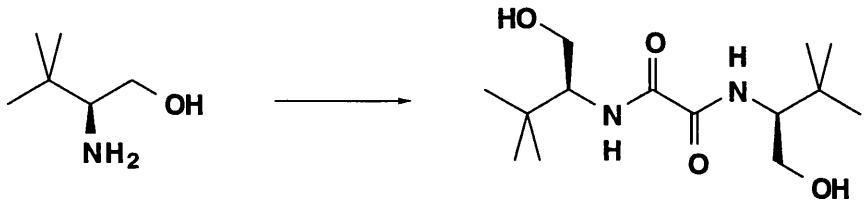
IR (KBr disc) ν_{max}: 2967, 2896, 2867, 1616, 1471, 1448, 1370, 1347, 1323, 1282, 1204, 1132, 1092, 1062, 945, 859, 834, 692, 609, 480 cm^{-1};

MS (70eV) m/z: 168 (M^+ 29%), 153 (17), 138 (11), 125 (13), 123 (10), 111 (5), 99 (23), 97 (46), 85 (14), 83 (21), 80 (6), 70 (100), 56 (42), 54 (21);

HRMS m/z: M^+ = 168.0894 (168.0899 calcd for $C_8H_{12}N_2O_2$).

Preparation of *4S,4'S*-4,4'-bis(2-methyl-2-propyl)-4,4',5,5'-tetrahydro-2,2'-bis(oxazole) (^{t}Bu-77)

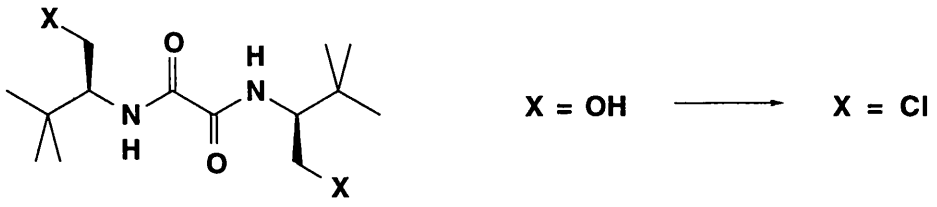
Preparation of *N,N'*-bis(2*S*-1-hydroxy-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**79**)



^{t}Bu-**78** ^{t}Bu-**79**

A solution of (2*S*)-2-amino-3,3-dimethyl-1-butanol (^{t}Bu-**78**) (1.28 g, 9.57 mmol) and dimethyl oxalate (566 mg, 4.79 mmol) in toluene (5 ml) and 1,2-dichloroethane (5 ml) was heated to reflux for 2 h. Once cooled to ambient temperature the clear solution was evaporated *in vacuo* to produce *N,N'*-bis(2*S*-1-hydroxy-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**79**) as a low-density white solid used subsequently without purification.

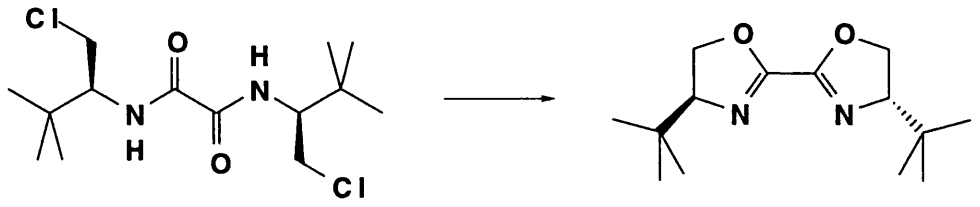
Preparation of *N,N'*-bis(2*S*-1-chloro-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**80**)



^{t}Bu-**79** ^{t}Bu-**80**

The crude *N,N'*-bis(2*S*-1-hydroxy-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**79**) was dissolved in toluene (10 ml) and thionyl chloride (4.5 ml, 62 mmol) added slowly. The mixture was stirred at ambient temperature for 1 h, and then heated to reflux for 1.5 h. Evaporation *in vacuo* gave a discoloured solid, which was triturated with methanol (5 ml) and again evaporated twice. Dissolution in 1:1 methanol-ethyl acetate and filtration through celite gave after evaporation *in vacuo* *N,N'*-bis(2*S*-1-chloro-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**80**) as a white solid used subsequently without purification.

Preparation of *4S,4'S*-4,4'-bis(2-methyl-2-propyl)-4,4',5,5'-tetrahydro-2,2'-bis(oxazole) (^{t}Bu-**77**)



^{t}Bu-**80** ^{t}Bu-**77**

The crude *N,N'*-bis(*2S*-1-chloro-3,3-dimethyl-2-butyl)oxamide (^{t}Bu-**80**) was dissolved in a methanolic solution of sodium hydroxide (19 ml, 1.0 M in methanol, 19 mmol) and the mixture heated to reflux for 1.5 h, rapidly becoming cloudy. Once cooled the mixture was filtered and evaporated in vacuo, the residue taken up in dichloromethane and refiltered through a pad of celite. Evaporation *in vacuo* gave a discoloured white solid. Recrystallisation from 5:1 ethyl acetate-methanol gave *4S,4'S-4,4'-bis(2-methyl-2-propyl)-4,4',5,5'-tetrahydro-2,2'-bis(oxazole)* (^{t}Bu-**77**)[205] (733 mg, 60% for three steps) as white plates, m.p. 196-7°C (lit.,[205] 190°C), $[\alpha]_D^{23}$ –164.9 (*c* 1.0 in $CHCl_3$) [lit.,[205] -164.4 (*c* 0.99 in $CHCl_3$)]:

^{1}H NMR (400 MHz) δ_H: 0.92 (9H, s, 3 x CH_3), 4.05 (1H, dd, *J* = 10.3, 9.0 Hz, OCH_2CHN), 4.20 (1H, t, *J* = 9.0 Hz, OCH_2CHN), 4.34 (1H, dd, *J* = 10.3, 9.0 Hz, OCH_2CHN);

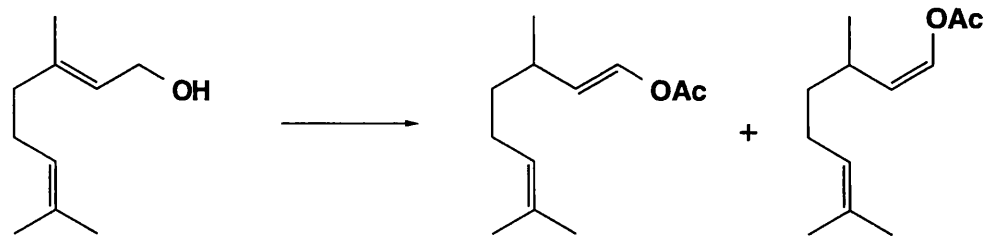
^{13}C NMR (101 MHz) δ_C: 25.9, 33.7, 69.5, 76.7, 154.4;

IR (KBr disc) ν_{max}: 2974, 2953, 2906, 2871, 1622, 1475, 1394, 1368, 1327, 1281, 1214, 1123, 1066, 1022, 946, 873 cm^{-1};

MS (70eV) m/z: 253 (M^++H 2%), 252 (M^+ 1%), 237 (9), 197 (22), 196 (100), 181 (2), 153 (3), 140 (34), 127 (3), 111 (21), 96 (8), 84 (20), 71 (19), 69 (30);

HRMS m/z: M^++H = 253.1912 (253.1916 calcd for $C_{14}H_{25}N_2O_2$).

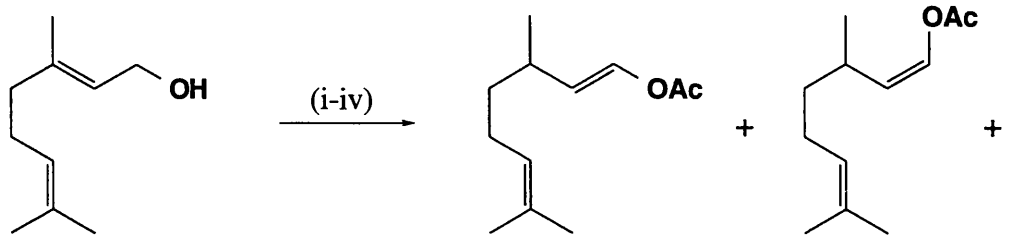
5% $Ni(cod)_2$/^{i}Pr-77 mediated isomerisation of geraniol (63), reaction time 1.5 hours



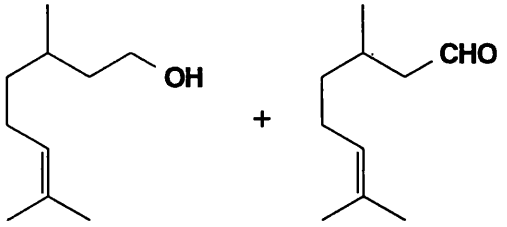
63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (202 mg, 1.31 mmol) in THF (8 ml) and *n*-butyllithium (818 µl, 1.60 M in hexanes, 1.31 mmol), and a solution of bis(oxazoline) ^{i}Pr-**77** (15 mg, 66 µmol, 5.0 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid $Ni(cod)_2$ (18 mg, 65 µmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting deep blue solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 1.5 h. Quench with acetic anhydride (1.24 ml, 13.1 mmol) and work-up as detailed previously gave after flash chromatography (2.5-20% ether in petrol gradient elution) an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=4.8:1, 193 mg, 75%).

5% Ni(cod)$_2$/^{i}Pr-77 mediated isomerisation of geraniol (63), reaction time 1 hour



63 **75** **76**



65 **81**

A solution of alkoxide prepared from geraniol (**63**) (229 mg, 1.48 mmol) in THF (8 ml) and *n*-butyllithium (928 µl, 1.60 M in hexanes, 1.48 mmol), and a solution of bis(oxazoline) ^{i}Pr-**77** (16.9 mg, 75.3 µmol, 5.0 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid Ni(cod)$_2$ (20 mg, 73 µmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting deep blue solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 1 h. Quench with acetic anhydride (1.40 ml, 14.8 mmol) and work-up as detailed previously gave after flash chromatography (2.5-50% ether in petrol gradient elution) an inseparable mixture (215 mg) of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=4.7:1, 71%) with citronellal (**81**) (4%) as a clear, colourless oil, and an inseparable mixture (21.5 mg) of *citronellol* (**66**) (5%) and starting material (4%).

(E)-3,7-Dimethyl-6-octenal (**81**):

^{1}H NMR (200 MHz) δ_H: 0.92 (3H, d, J = 7.4 Hz, 3'-CH$_3$), 1.1-1.4 (2H, m, 4-CH$_2$), 1.52 (3H, s, 7'- or 8-CH$_3$), 1.60 (3H, s, 7'- or 8-CH$_3$), 1.85-2.05 (2H, m, 5-CH$_2$), 2.05-2.45 (2H, m, 2-CH$_2$), 5.04 (1H, br t, J = 7.0 Hz, 6-CH), 9.69

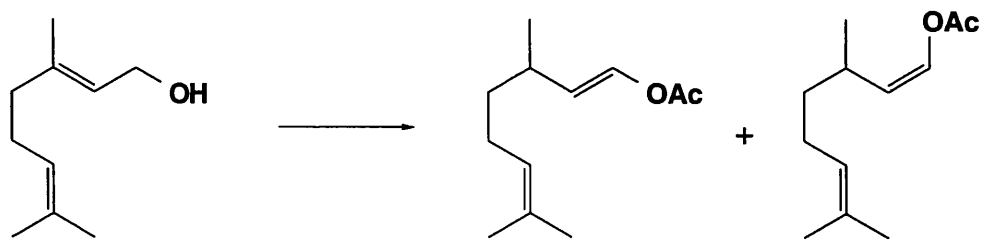
(1H, t, J = 1 Hz, CHO).

5% Ni(cod)$_2$/^{i}Pr-77 mediated isomerisation of geraniol (63) at 40°C

63

A solution of alkoxide prepared from geraniol (**63**) (190 mg, 1.23 mmol) in THF (8 ml) and *n*-butyllithium (771 µl, 1.60 M in hexanes, 1.23 mmol), and a solution of bis(oxazoline) ^{i}Pr-**77** (14 mg, 62 µmol, 5.0 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid Ni(cod)$_2$ (17 mg, 62 µmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting deep blue solution was transferred *via* teflon canula to the alkoxide solution and the mixture warmed to 40°C for 48 h. Quench with acetic anhydride (1.16 ml, 12.3 mmol) and work-up as detailed previously gave an orange-brown oil. Crude ^{1}H NMR (400 MHz) indicated no trace of enol acetates (**75**) and (**76**). Flash chromatography (2.5-50% ether in petrol gradient elution) yielded an inseparable mixture (43.1 mg) of *citronellyl acetate* (**66**) (12%) and starting material (10%).

5% Ni(cod)$_2$/Me-77 mediated isomerisation of geraniol (63)

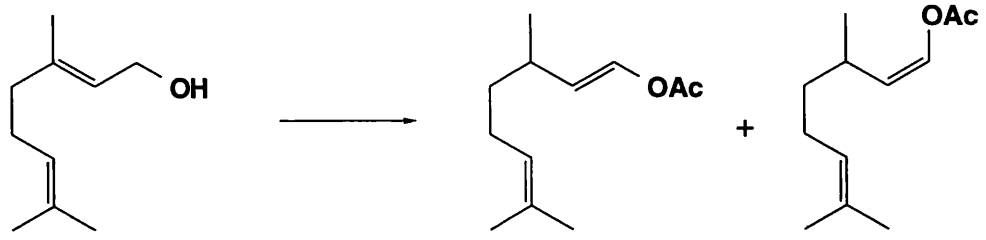


63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (193 mg, 1.25 mmol) in THF (8 ml) and *n*-butyllithium (781 µl, 1.60 M in hexanes, 1.25 mmol), and a solution of

bis(oxazoline) Me-**77** (10.5 mg, 62 μmol, 5.0 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid $Ni(cod)_2$ (17 mg, 62 μmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting deep blue-purple solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 2 h. Quench with acetic anhydride (1.16 ml, 12.5 mmol) and work-up as detailed previously gave after flash chromatography (1-2.5% ether in petrol elution) an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=5.0:1, 101 mg, 41%).

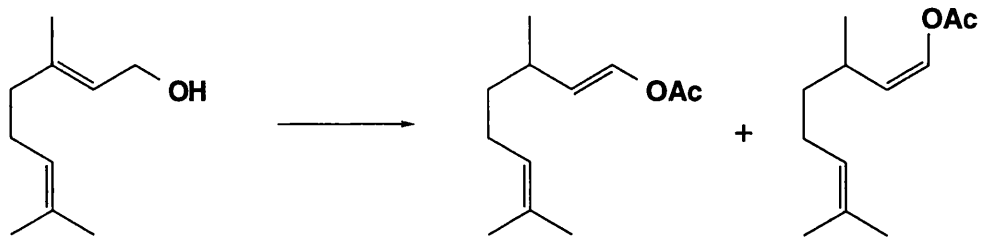
5% $Ni(cod)_2$/Bn-77 mediated isomerisation of geraniol (63)



63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (271 mg, 1.76 mmol) in THF (8 ml) and *n*-butyllithium (1.10 ml, 1.60 M in hexanes, 1.76 mmol), and a solution of bis(oxazoline) Bn-**77** (28 mg, 87 μmol, 5.0 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid $Ni(cod)_2$ (24 mg, 87 μmol, 5.0 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting deep blue-black solution was transferred *via* teflon canula to the alkoxide solution and the mixture heated to reflux for 2 hours. Quench with acetic anhydride (1.66 ml, 17.6 mmol) and work-up as detailed previously gave after flash chromatography (5-50% and then 2.5-5% ether in petrol gradient elution) an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=5.4, 192 mg, 56%).

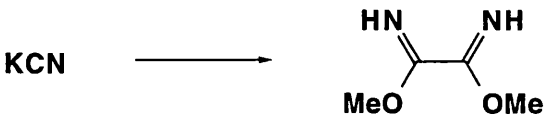
5% Ni(cod)$_2$/^{t}Bu-77 mediated isomerisation of geraniol (63)



63 **75** **76**

A solution of alkoxide prepared from geraniol (**63**) (348 mg, 2.26 mmol) in THF (8 ml) and *n*-butyllithium (1.41 ml, 1.60 M in hexanes, 2.26 mmol), and a solution of bis(oxazoline) ^{t}Bu-**77** (29.7 mg, 118 μmol, 5.2 mol%) in THF (12 ml) were degassed twice. The ligand solution was added to solid Ni(cod)$_2$ (32 mg, 116 μmol, 5.1 mol%) at –78°C, and the mixture allowed to warm to ambient temperature. The resulting yellow solution was transferred *via* teflon canula to the alkoxide solution and the golden yellow mixture heated to reflux for 1.5 h. Quench with acetic anhydride (2.13 ml, 22.6 mmol) and work-up as detailed previously gave after flash chromatography (2.5-5% and then 1-2.5% ether in petrol gradient elution) an inseparable mixture of *(E)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**75**) and *(Z)-3,7-dimethylocta-1,6-dien-1-yl acetate* (**76**) (**75**:**76**=5.3:1, 262 mg, 59%).

Preparation of dimethyl diiminooxalate (82)



82

Into a stirred, cooled (0°C) solution of potassium cyanide (15.4 g, 237 mmol) in water (90 ml) and methanol (40 ml) was conducted chlorine gas at such a rate that not all could be absorbed and a bubbling rate of *ca.* 2 ml.s^{-1} was observed. White fumes appeared and the solution became gradually orange; exit gases were connected to

aqueous sodium hydroxide and then aqueous sodium sulfite bubblers. Continual testing with pH paper showed a quite sudden drop from pH 12 initially to pH 8.5 (*ca.* 5 min) and the passage of chlorine was immediately ceased. A second solution of potassium cyanide (9.87 g, 152 mmol) in water (30 ml) and methanol (40 ml) was added, raising the pH to 12, and the mixture allowed to warm to ambient temperature and stir for 6 h. The resulting dark brown mixture was extracted with ether (5 × 100 ml), and the combined organic phases washed with water (20 ml) and brine and dried over $MgSO_4$. Evaporation *in vacuo* and short-path distillation yielded *dimethyl diiminooxalate* (**82**)[215a,217a] (5.74 g, 25%) as clear, colourless plates, m.p. 29.5-30.5 °C (lit.,[215a] 28-30°C; lit.,[217a] 29.5-30.5°C):

^1H NMR (400 MHz) δ_H: 3.82 (6H, s, 2 × CH_3), 8.31 (2H, br s, 2 × NH);

^{13}C NMR (101 MHz) δ_C: 54.2, 158.6;

IR (glass) ν_{max}: 3418, 2954, 1644, 1456, 1440, 1369, 1318, 1200, 1110, 923, 856 cm^{-1};

MS (70eV) m/z: 116 (M^+ 0.4%), 101 (24), 86 (20), 72 (13), 59 (21), 58 (100), 53 (8), 44 (36), 28 (34);

HRMS m/z: M^+ = 116.0586 (116.0586 calcd for $C_4H_8N_2O_2$).

Preparation of dimethylmalonitrile (83)

83

Sodium hydride (22.0 g, 60% w/w dispersion in mineral oil, 550 mmol) was washed with dry ether (2 × 40 ml then 3 × 20 ml) and suspended in dimethylsulfoxide (45 ml), and cooled to 0°C. A solution of malonitrile (16.5 g, 250 mmol) in dimethylsulfoxide (45 ml) was added dropwise over 45 min with much effervescence, and the grey-brown slurry allowed to warm to ambient temperature for 15 min. The reaction mixture was cooled again (0°C) and iodomethane (45 ml, 720 mmol) added dropwise over 45

min with evolution of more gas. The resulting viscous slurry was stirred for 30 min, diluted with benzene (60 ml) and allowed to warm to ambient temperature for 20 min. Further dilution with ether (60 ml) aided stirring for 10 min, and the mixture was poured into water (300 ml). Extraction with ether (3 × 200 ml) and evaporation *in vacuo* gave a dark brown oil which deposited clear crystals overnight at 0°C. Distillation at reduced pressure (49°C, 10 mmHg) gave a clear oil which crystallised on standing, and which was shown to contain an impurity by ^{1}H NMR and GC (*ca.* 2%). Flash chromatography (10-33% ether in petrol gradient elution) with GC analysis of the fractions yielded *dimethylmalonitrile* (**83**)[219,220] (13.5 g, 57%) as clear, colourless prisms, m.p. 31.5°C (lit.,[219] 31°C; lit.,[220] 33.7-34.4°C):

^{1}H NMR (400 MHz) δ_H: 1.80 (6H, s, 2 × CH_3);

^{13}C NMR (101 MHz) δ_C: 26.2, 105.2, 116.7;

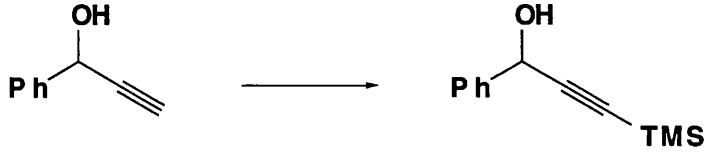
IR (glass) ν_{max}: 3003, 2951, 2890, 2252, 1658, 1456, 1374, 1224, 1131, 1058, 951, 603 cm^{-1}; ($CHCl_3$) ν_{max}: 3024, 3005, 2253, 1460, 1219 cm^{-1};

MS (70eV) m/z: 94 (M^+ 10%), 93 (100), 79 (10), 78 (8), 77 (6), 68 (9), 67 (32), 66 (24), 64 (5), 54 (3);

HRMS m/z: M^+-H = 93.0459 (93.0453 calcd for $C_5H_5N_2$);

GC: retention time 2.35 min [He, capillary flow rate (70°C) 2.55 ml.min^{-1}, split ratio 57:1, initial temp. 70°C (2 min), ramp 5°C.min^{-1}].

Preparation of 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (84)



84

To a stirred, cooled (–78°C) solution of 1-phenyl-2-propyn-1-ol (7.56 g, 57.2 mmol) in THF (100 ml) was added *n*-butyllithium (75.1 ml, 1.6 M in hexanes, 120 mmol) dropwise over 5 min. A deep red colour formed after addition of approximately half

the volume. The mixture was stirred at –78°C for *ca.* 30 min, and then treated with chlorotrimethylsilane (16.0 ml, 126 mmol) over 5 min, the deep red colour disappearing again after addition of approximately half the volume. The mixture was allowed to warm to ambient temperature for 2.5 h, treated with 2 M hydrochloric acid (50 ml) and stirred vigorously for a further 45 min. The resulting emulsion was diluted with ether (50 ml), and the organic phase washed with aqueous sodium hydrogen carbonate, water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (7.5% ether in petrol elution) afforded the silyl ether (805 mg, 5%), and alcohol (**84**) (10.4 g, 89%). Further treatment of the silyl ether with hydrochloric acid as previously gave alcohol (**84**) (11.0 g, 94%) as a clear, colourless oil.

3-Phenyl-3-(trimethylsiloxy)-1-(trimethylsilyl)-1-propyne:

IR (film) ν_{max}: 2956, 2174, 1663, 1448, 1249, 1065, 1012, 842, 758, 696 cm^{-1};

MS (70eV) m/z: 276 (M^+ 1%), 261 (15), 202 (10), 187 (100), 161 (16), 114 (19), 105 (38), 77 (42), 73 (75).

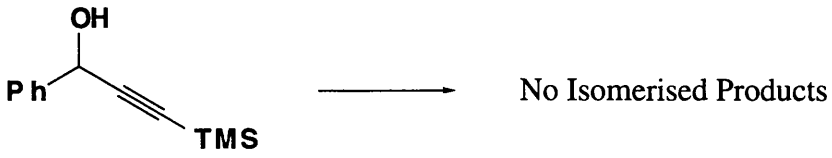
1-Phenyl-3-(trimethylsilyl)-2-propyn-1-ol (**84**)[264]:

^1H NMR (200 MHz) δ_H: 0.31 (9H, s, $Si(CH_3)_3$), 2.16 (1H, d, J = 6.4 Hz, OH), 5.45 (1H, d, J = 6.4 Hz, 1-CH), 7.3-7.6 (5H, m, ArH);

IR (film) ν_{max}: 3359, 3064, 3033, 2961, 2899, 2174, 1492, 1452, 1251, 1042, 982, 845, 761, 698 cm^{-1};

MS (70eV) m/z: 204 (M^+ 37%), 187 (38), 173 (10), 161 (76), 114 (86), 105 (59), 91 (24), 83 (100), 77 (79), 73 (60), 51 (31), 43 (26).

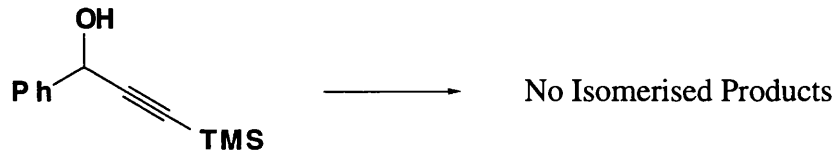
Attempted isomerisation of 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (84) with $Ru(PPh_3)_3Cl_2$ / $2PBu_3$



84

A degassed solution of alkoxide prepared from 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (**84**) (423 mg, 2.07 mmol) in toluene (10 ml) and *n*-butyllithium (1.34 ml, 1.51 M in hexanes, 2.03 mmol) was treated with a degassed solution of dichlorotris-(triphenylphosphine)ruthenium (II) (21.2 mg, 22.1 μmol, 1.1 mol%) and tri-*n*-butylphosphine (13 μl, 2 mol%) in toluene (6 ml), and the mixture heated to reflux for 3.5 days. The reddish-brown catalyst solution became green when the tributylphosphine was added. Quench with allyl bromide (1.8 ml, 21 mmol) and work-up as previously detailed gave after flash chromatography (2-15% ether in petrol gradient elution) no identifiable products.

Attempted isomerisation of 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (84) with $Ru(PPh_3)_3Cl_2$

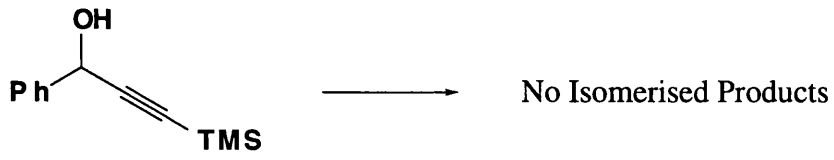


84

A degassed solution of alkoxide prepared from 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (**84**) (302 mg, 1.48 mmol) in toluene (5 ml) and *n*-butyllithium (928 μl, 1.51 M in hexanes, 1.40 mmol) was treated with a degassed solution of dichlorotris-(triphenylphosphine)ruthenium (II) (69.5 mg, 72.5 μmol, 4.9 mol%) in toluene (6 ml), and the mixture heated to reflux for 18 h. Quench with allyl bromide (1.28 ml, 14.8

mmol) and work-up as previously detailed gave after flash chromatography (0-20% ether in petrol gradient elution) starting material (82 mg, 27%) as the only identifiable compound.

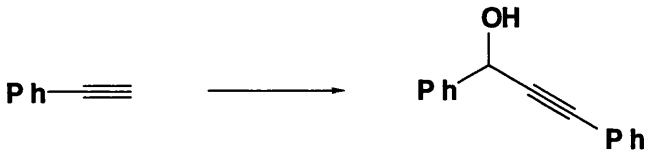
Attempted isomerisation of 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (84) with $Ru(PPh_3)_3HCl$



84

A degassed solution of alkoxide was prepared from 1-phenyl-3-(trimethylsilyl)-2-propyn-1-ol (**84**) (304 mg, 1.49 mmol) in toluene (5 ml) and *n*-butyllithium (987 µl, 1.51 M in hexanes, 1.49 mmol). Freshly prepared chlorohydridotris-(triphenylphosphine)ruthenium (II) (*ca.* 5 mol%), from hydrogenation of dichlorotris-(triphenylphosphine)ruthenium (II) (70.4 mg, 73.4 µmol) and triethylamine (31 µl, 220 µmol), was dissolved in toluene (15 ml) and the solution degassed. The catalyst solution was transferred to the alkoxide and the mixture heated to reflux for 5 h. Quench with allyl bromide (1.29 ml, 14.9 mmol) and work-up as previously detailed gave after flash chromatography (2-10% ether in petrol gradient elution) starting material (36 mg, 12%) as the only identifiable compound.

Preparation of 1,3-diphenyl-2-propyn-1-ol (85)



85

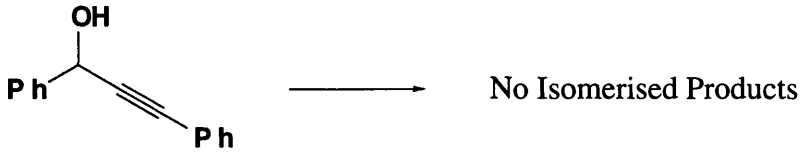
To a cooled (0°C) solution of phenylacetylene (10.0 ml, 91.0 mmol) in THF (50 ml) was added *n*-butyllithium (40 ml, 2.5 M in hexanes, 100 mmol) dropwise over 15 min, producing a dark brown solution. After *ca.* 30 min benzaldehyde (11.2 ml, 110 mmol) was added dropwise, the mixture stirred a further 30 min, treated with aqueous sodium hydrogen carbonate and extracted three times with ether. The combined organic phases were washed three times with aqueous sodium bisulfite, with water and brine, and dried over $MgSO_4$. Evaporation *in vacuo* and flash chromatography (2-10% ether in petrol gradient elution) gave a red oil which was subject to short-path distillation (170-220°C, 0.8 mmHg), thus affording *1,3-diphenyl-2-propyn-1-ol* (**85**)[264] (10.7 g, 56%) as a clear, colourless oil:

^1H NMR (270 MHz) δ_H: 2.31 (1H, d, J = 5.9 Hz, OH), 5.70 (1H, d, J = 5.9 Hz, 1-CH), 7.25-7.7 (10H, m, 2 × ArH);

IR (film) ν_{max}: 3349, 3058, 3029, 2973, 2869, 2228, 1596, 1487, 1450,1382, 1279, 1188, 1031, 997, 962, 916, 757, 719, 693, 639 cm^{-1};

MS (70eV) m/z: 208 (M^+ 18%), 191 (9), 178 (19), 133 (15), 129 (20), 105 (66), 102 (100), 77 (77), 51 (43).

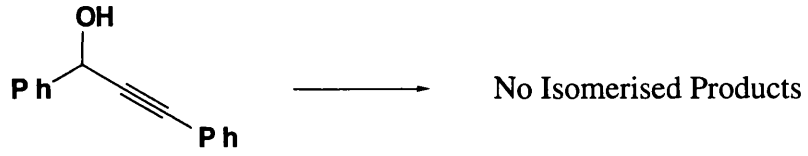
Attempted isomerisation of 1,3-diphenyl-2-propyn-1-ol (85) with Cp_2ZrHCl; non-standard procedure



85

To a solution of alkoxide prepared from 1,3-diphenyl-2-propyn-1-ol (**85**) (330 mg, 1.58 mmol) in benzene (10 ml) and *n*-butyllithium (1.05 ml, 1.51 M in hexanes, 1.58 mmol) was added solid chlorodi(η^5-cyclopentadienyl)hydridozirconium (IV) (41 mg, 159 μmol, 10 mol%) and the mixture stirred at ambient temperature in the dark for 16 h. Quench with benzyl bromide (0.38 ml, 3.2 mmol) and work-up as previously detailed for allyl bromide gave no new products as evidenced by TLC and crude 270 MHz ^{1}H NMR.

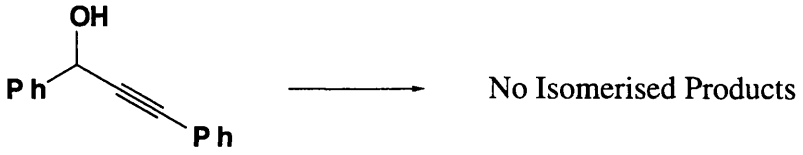
Attempted isomerisation of 1,3-diphenyl-2-propyn-1-ol (85) with Cp_2ZrHCl



85

A degassed solution of alkoxide prepared from 1,3-diphenyl-2-propyn-1-ol (**85**) (399 mg, 1.92 mmol) in benzene (20 ml) and *n*-butyllithium (1.27 ml, 1.51 M in hexanes, 1.92 mmol) was added to solid chlorodi(η^5-cyclopentadienyl)hydridozirconium (IV) (53.8 mg, 209 μmol, 10.8 mol%) and the mixture heated to reflux in the dark for 22 h. Quench with benzyl bromide (0.25 ml, 2.1 mmol) and work-up as previously detailed for allyl bromide gave no new products as evidenced by TLC and crude 270 MHz ^{1}H NMR.

Attempted isomerisation of 1,3-diphenyl-2-propyn-1-ol (85) with Cp_2ZrH_2

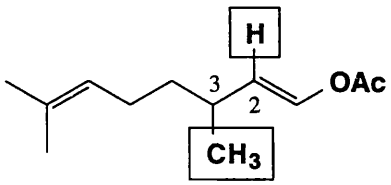


85

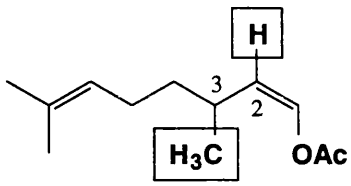
A degassed solution of alkoxide prepared from 1,3-diphenyl-2-propyn-1-ol (**85**) (318 mg, 1.53 mmol) in benzene (10 ml) and *n*-butyllithium (1.01 ml, 1.51 M in hexanes, 1.53 mmol) was added to solid di(η^5-cyclopentadienyl)dihydridozirconium (IV) (11.5 mg, 51.5 μmol, 3.5 mol%) and the mixture heated to reflux in the dark for 18 h. Quench with benzyl bromide (0.18 ml, 1.53 mmol) and work-up as previously detailed for allyl bromide gave no new products as evidenced by TLC and crude 270 MHz ^{1}H NMR.

Appendix

The ^1H NMR spectrum of the enol acetates **75** and **76** in the presence of $Eu(tfc)_3$ and Ag(fod) is presented, and the effects on the C3-methyl and C2-vinylic signals are tabulated below. Sections of this spectrum are included in the text (figures 2.27, 2.28). The absolute configuration corresponding to each signal is not known.



75



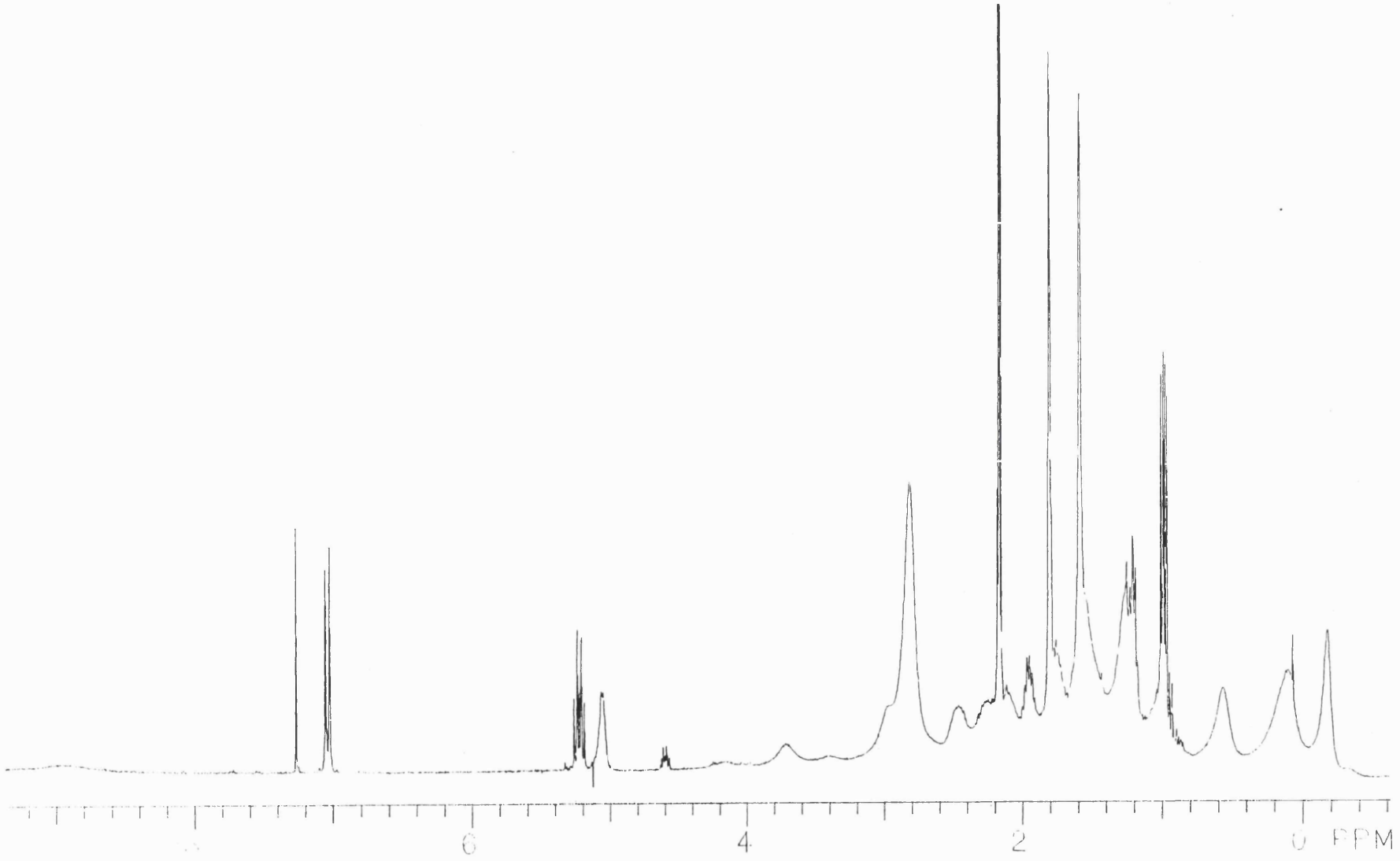
76

Additive (equiv)		**75** (3-CH_3)		**76** (3-CH_3)	
$Eu(tfc)_3$	Ag(fod)	δ_H (ppm)	$\lvert\nu_R-\nu_S\rvert$	δ_H (ppm)	$\lvert\nu_R-\nu_S\rvert$
–	–	1.01	–	0.98	–
2.5	–	1.01, 1.00	0.9 Hz	1.00, 0.99	1.4 Hz
1.0	1.0	0.99, 0.96	10 Hz	0.93, 0.89	*ca.* 10 Hz

Chemical Shifts For the C3-Methyl Signal (0.07M, $CDCl_3$, 20°C)

Additive (equiv)		**75** (2-CH)		**76** (2-CH)	
$Eu(tfc)_3$	Ag(fod)	δ_H (ppm)	$\lvert\nu_R-\nu_S\rvert$	δ_H (ppm)	$\lvert\nu_R-\nu_S\rvert$
–	–	5.29	–	4.67	–
1.0	1.0	5.23, 5.20	8.9 Hz	4.60, 4.58	6.5 Hz

Chemical Shifts For the C2-Vinylic Signal (0.07M, $CDCl_3$, 20°C)



400 MHz ^{1}H NMR Of Enol Acetates 75 And 76 (75:76=5:1) + Eu(tfc)$_3$ (1.0) + Ag(fod) (1.0)
[0.07M, $CDCl_3$, 20°C]

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