Tetrahedron: Asymmetry Vol. 3, No. 9, pp. 1089-1122, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

TETRAHEDRON: ASYMMETRY REPORT NUMBER 11

Selectivity in Palladium Catalysed Allylic Substitution

Christopher G Frost, Joshua Howarth and Jonathan M J Williams*
Department of Chemistry, Loughborough University of Technology,
Loughborough, Leicestershire, LE11 3TU, UK.

(*Received* 8 *August* 1992)

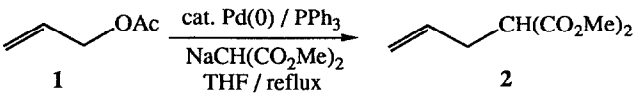
CONTENTS

1. Scope of the Reaction

i) Introduction

Transition metals are able to catalyse a wide range of synthetically useful organic reactions, very often with high levels of chemo- and stereoselectivity.[1] Palladium catalysed reactions in particular have found widespread utility in a number of important chemical processes,[2] including Stille couplings,[3] Heck reactions,[4] Wacker oxidation,[5] and allylic substitution reactions.[6] Central to all of these catalytic reactions is the ease with which palladium is able to undergo oxidative addition and reductive elimination reactions.

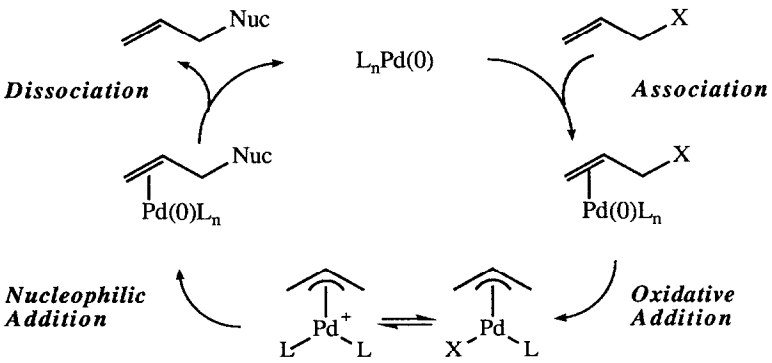
Palladium catalysed allylic substitution is a versatile process encompassing a wide range of allyl systems and their nucleophilic partners. Historically, η^3-allylpalladium complexes were first isolated and identified over 30 years ago, synthesised by the reaction of dienes with palladium(II) salts.[7] In 1965, Tsuji demonstrated that a limited range of nucleophiles react with palladium allyl complexes,[8] and in the early 1970's a catalytic variant was devised in which allylic alcohols reacted with amines to afford the allyl amine products.[9] The basic process is illustrated by the reaction of allyl acetate **1** with the sodium salt of dimethyl malonate in the presence of catalytic amounts of phosphine and palladium(0).[10] Typically, such reactions are conducted in a polar solvent such as THF to afford the substitution product **2** in good yield and with a high number of turnovers.



1 2

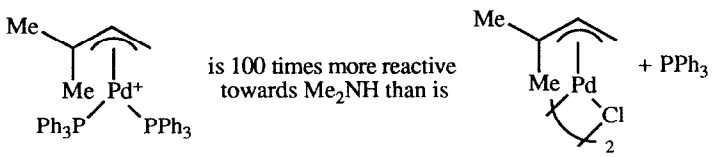
ii) Mechanism of palladium catalysed allylic substitution

It is believed that the mechanism of palladium catalysed substitution involves the initial co-ordination of palladium(0) to the alkene, followed by an oxidative addition process to afford an intermediate η^3-allyl complex. In the presence of phosphine, an equilibrium between a neutral and cationic complex results. The cationic complex is favoured by the use of bidentate phosphine ligands. Nucleophilic addition to the cationic complex is favoured, and occurs at one of the allylic termini to afford the palladium(0) complex of product. Dissociation of the palladium(0) liberates the product, and regenerates the active palladium catalyst, as shown in Scheme 1.[11]



Scheme 1

The issue of the involvement or otherwise of the cationic intermediates has not been fully resolved. Treatment of the neutral complex **3** with triphenylphosphine was not observed to afford any of the cationic species using either NMR or conductivity experiments, and it is possible that in the catalytic cycle the π-acceptor properties of the phosphine are sufficient to allow for reactivity. However, as this report indicates, the preformed cationic complex **4** is 100 times more reactive than the combination of the chloro complex **3** in combination with triphenylphosphine. Therefore if the equilibrium lies to the extent of just 1% of the cationic complex, then this would still be consistent with the kinetic data.[12]



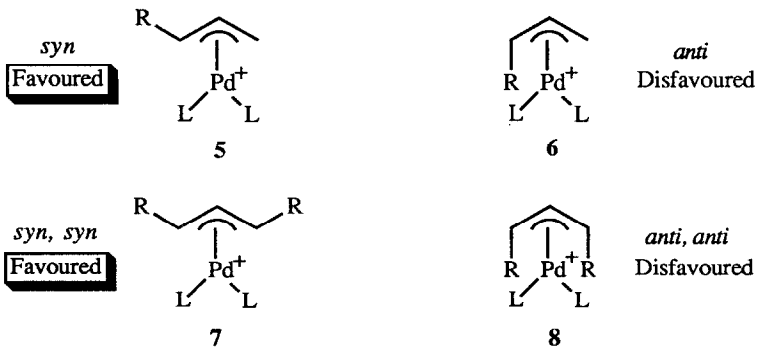
4 3

Under certain circumstances, it would appear that formation of a palladium(IV) species can accelerate the rate of the reductive elimination step, although this has not been as well studied as is perhaps warranted.[13] The addition of allyl chloride, bromide or acetate to the complex has been observed to accelerate the reductive elimination of a palladium(II) allyl complex. A plausible explanation for this is the oxidative addition of the allyl

substrate to afford a palladium(IV) species. This then facilitates the reductive elimination of the product, to revert to a palladium(II) intermediate.

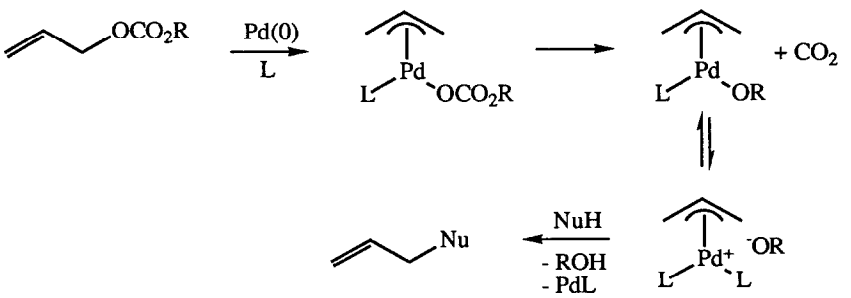
iii) The geometry of allyl complexes

For a mono-substituted allyl complex, there are two geometric isomers which may be considered, the *syn* isomer **5**, and the *anti* isomer **6**. Not surprisingly, the preferred geometry is *syn*, **5**. Similarly, di-substituted allyl complexes favour the *syn, syn* geometry **7**, and for more highly substituted allyl complexes, a similar geometrical preference is observed based on the steric requirements of the substituents involved. The isomeric forms are able to equilibrate by a π-σ-π mechanism (*vide infra*). In special cases, the choice of ligand L may result in a preference for the *anti* configuration, due to unusual steric considerations.[14]



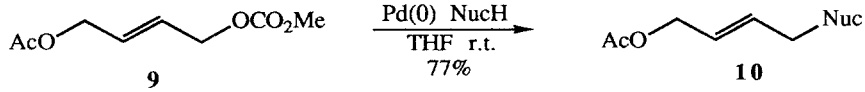
iv) The range of substrates

Whilst the most commonly employed substrates for palladium catalysed allylic substitution are the allylic acetates, a range of leaving groups will also function effectively. These include halides,[15] sulfones,[16] carbonates,[17] carbamates, epoxides[18] and phosphates.[19] The use of carbonates as leaving groups has gained in popularity since the development of these reagents by Tsuji.[20] The initially displaced carbonate loses carbon dioxide generating an alkoxide. The alkoxide is sufficiently basic to deprotonate many of the nucleophiles employed in these reactions. The mechanism is outlined in Scheme 2.



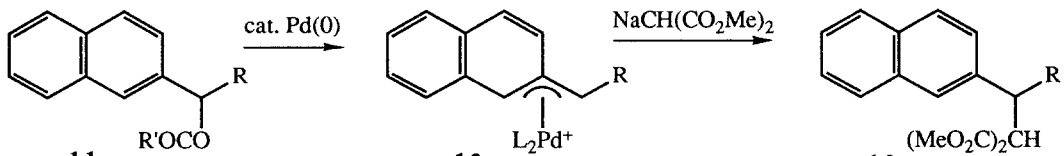
Scheme 2

For the substrate **9**, containing both carbonate and acetate leaving groups, carbonate functions as a better leaving group than acetate, thereby affording the substitution product **10**, representing another advantage of this leaving group for some applications.



9 **10**

It has been reported that as well as allyl substrates, palladium catalysed substitution proceeds in an analogous manner for the naphthyl substrate **11**, to give the product **13** *via* the intermediate palladium complex **12**. However, under similar conditions, the corresponding benzyl compound was found to be inert, the difference being ascribed to the greater loss of aromaticity in the latter case.[21] The use of allenyl substrates has been reported,[22] and dienes containing no leaving group have also been used recently.[23]

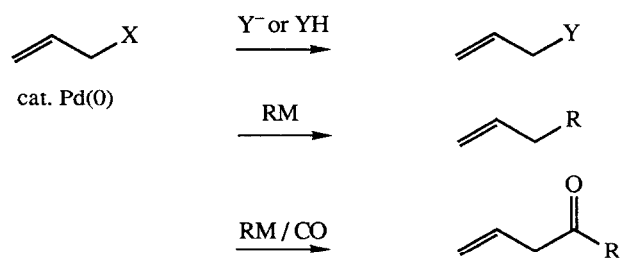


11 **12** **13**

v) The range of nucleophiles

A great number of nucleophiles have been employed, and there is much interest from both a synthetic and mechanistic stand-point in the development of many of these reactions.

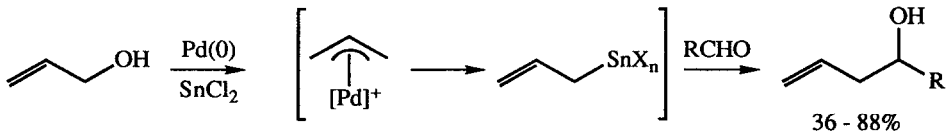
The most commonly employed nucleophiles are the 'soft' stabilised carbanions such as dimethyl malonate, but under suitable conditions, nitrogen based nucleophiles,[24] sulfur nucleophiles,[25] oxygen nucleophiles,[26] phosphorus nucleophiles,[27] silicon nucleophiles,[28] vinyl boranes,[29] hydrides (borohydrides / aluminohydrides[30] and formates[31]), tetraphenylborate,[32] organometallics (dialkylzincs,[33] Grignards,[34] organoaluminium reagents,[35] organozirconium reagents[36], organotin reagents[37]), have all been successfully employed.[38] In the presence of carbon monoxide and suitable nucleophiles, carbonylation reactions have also been achieved, as shown in Scheme 3.[39]



Scheme 3

vi) Transmetallation of palladium allyl complexes

π-Allyl palladium complexes function as electrophiles. However, by exchange with low valent metals, the so-formed allyl metal species can function as a nucleophile.[40] This approach has been used on several occasions, and is illustrated by a recent report of transmetallation with $SnCl_2$ to allow allylation of aldehydes. The use of $SnCl_2$ also permits the use of allyl alcohols directly, since activation by the tin gives a displacement reaction, illustrated in Scheme 4.[41]

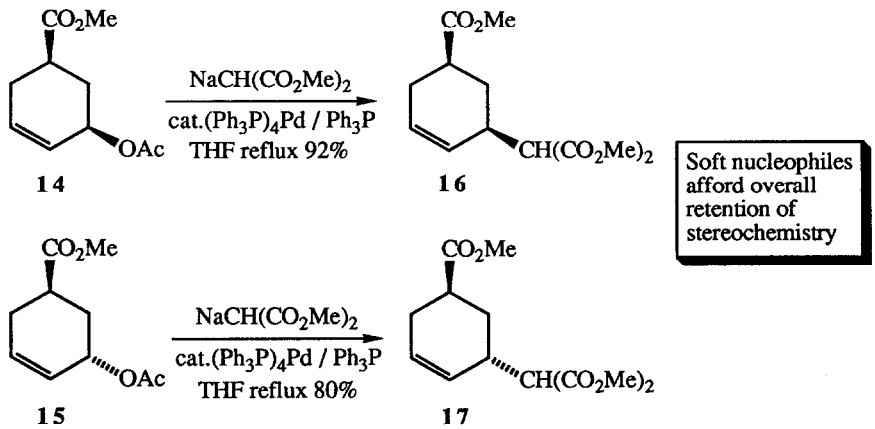


Scheme 4

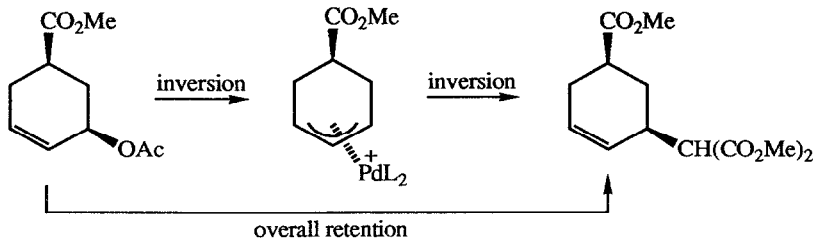
2. Mechanistic Aspects of Stereochemistry

i) Retention vs inversion of stereochemistry

A number of elegant studies have illustrated that net retention of stereochemistry is observed for soft nucleophiles in the palladium catalysed allylic substitution process.[42] Trost has employed the cyclohexenyl acetates **14** and **15** as models in which the carbomethoxy group functions as a stereochemical marker.[43] Reaction of the *cis*-substituted compound **14** affords the *cis*-substituted product **16**, whereas the *trans*-substituted compound **15** affords the *trans*-substituted product **17**.

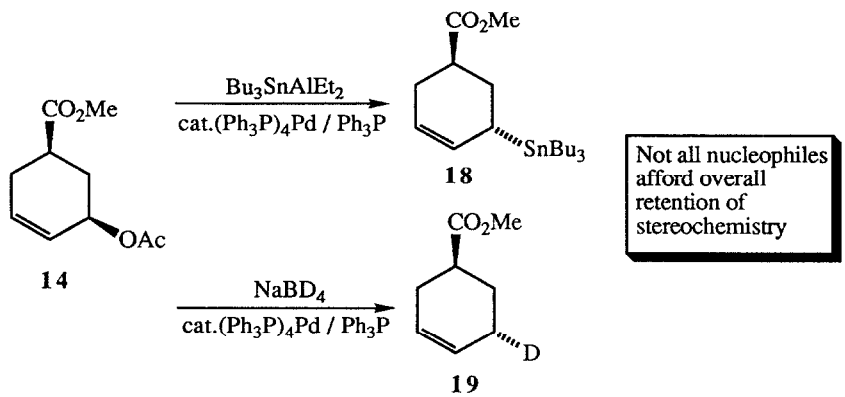


This stereochemical outcome is rationalised by two sequential inversion steps. The palladium displaces the leaving group with inversion, followed by the nucleophile which attacks from the *exo* face, again with inversion. Overall, this accounts for the observed net retention of stereochemistry, as shown in Scheme 5.

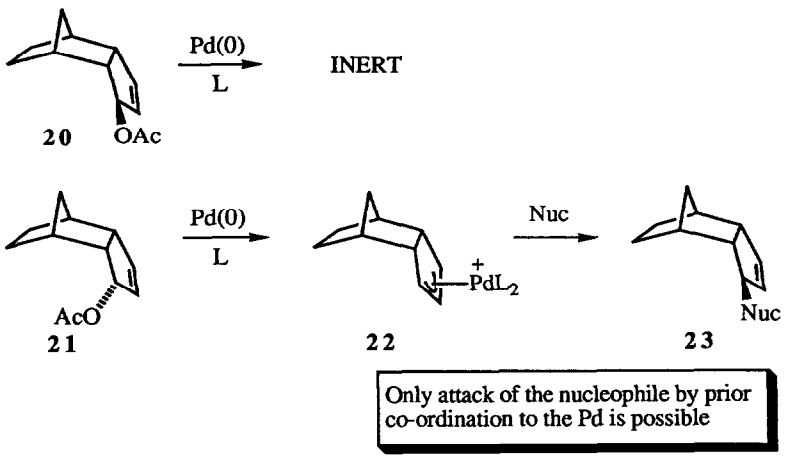


Scheme 5

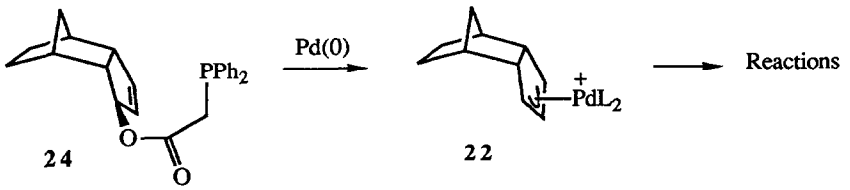
However, it was discovered that many nucleophiles do not afford retention of stereochemistry. For example, Trost showed that the nucleophile $Bu_3SnAlEt_2$ afforded the allylstannane **18** with clean inversion,[44] and Keinan has shown on the same system that sodium borodeuteride also affords inversion of stereochemistry, to afford **19**.[45] Using the same substrate, Negishi has demonstrated that phenylzinc chloride and alkenyl aluminium reagents also undergo reaction with overall inversion.[46]



Fiaud and Legros have introduced a classification of nucleophiles based on their ability to substitute the sterically hindered allylic acetates **20** and **21**.[47] The diastereomer **20** is inert to palladium catalysed allylic substitution with any nucleophile, since the palladium is sterically hindered from reacting, and thereby preventing palladium allyl formation. The diastereomer **21** is able to form a palladium allyl complex **22**. However, only nucleophiles which attack *via* prior co-ordination to the metal are effective, since nucleophiles are sterically blocked from approaching the complex from the face opposite the palladium. As a guide-line, nucleophiles with a pKa > 20 attack *via* the metal, whereas nucleophiles with a pKa < 20 attack the allyl ligand directly.

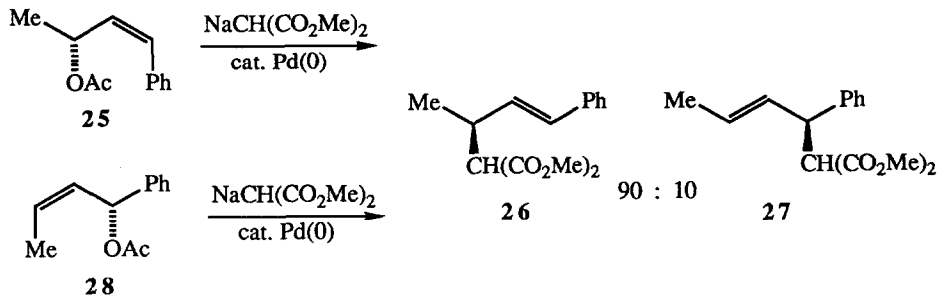


In certain circumstances, it has been demonstrated that it is possible to achieve an addition of palladium to the substrate as a *syn* addition. In the system **24**, where *anti* addition of palladium is not possible for steric reasons, π-allyl complexation by *syn* addition was observed, assisted by the directing group ability of the phosphine moiety. The resultant intermediate π-allyl complex **22** was reacted further, as with the previous example[48]

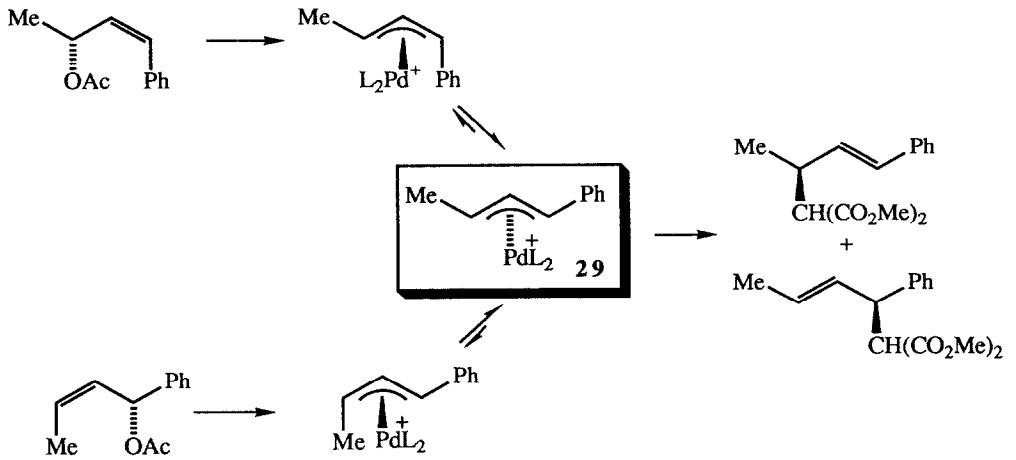


ii) (E)- and (Z)-Allyl acetates

There are differences in the stereochemical outcome for reactions involving (*E*)- or (*Z*)-allyl acetates. Whilst (*E*)-allyl acetates afford overall retention of stereochemistry for soft nucleophiles, (*Z*)-allyl acetates afford overall inversion of stereochemistry.[49] The (*Z*)-allyl acetate **25** reacts with catalytic palladium(0) and $NaCH(CO_2Me)_2$ to afford a 90:10 ratio of the two products **26** and **27**, and similarly the regioisomeric (*Z*)-allyl acetate **28** affords the same two products again with a 90:10 ratio.

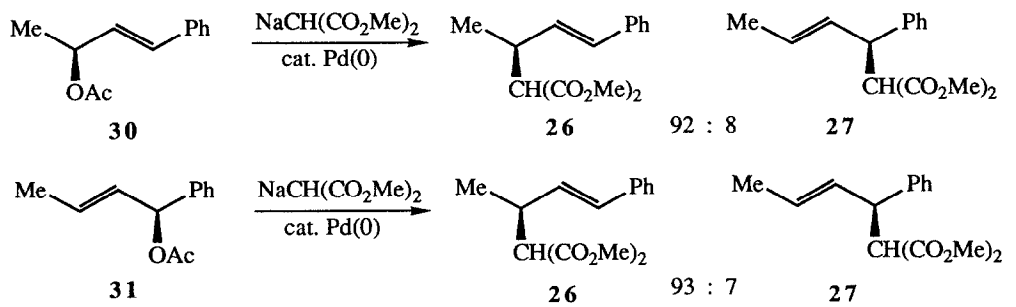


It has been suggested that the initially formed η^3-allyl complex rearranges for steric reasons by a π-σ-π mechanism, according to Scheme 6. The two regioisomers therefore proceed *via* a common intermediate **29**, which explains the consistency in the ratio of the products.



Scheme 6

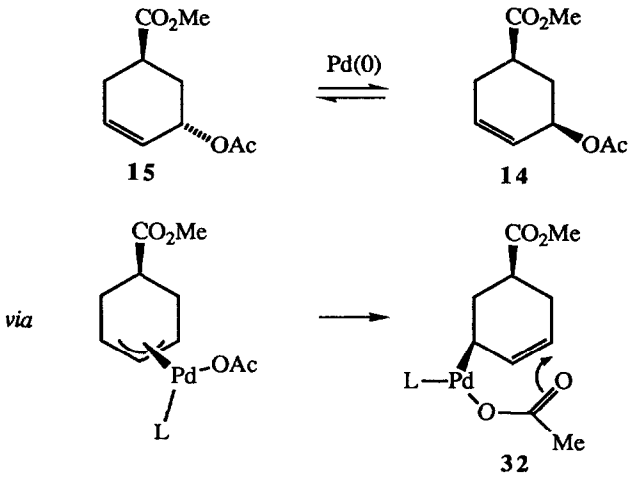
Interestingly, the same intermediate may be accessed using the (*E*)-allyl acetates **30** and **31** of the opposite absolute stereochemistry. Again, a very similar product distribution is observed in both cases.



iii) Loss of optical purity of palladium allyl complexes

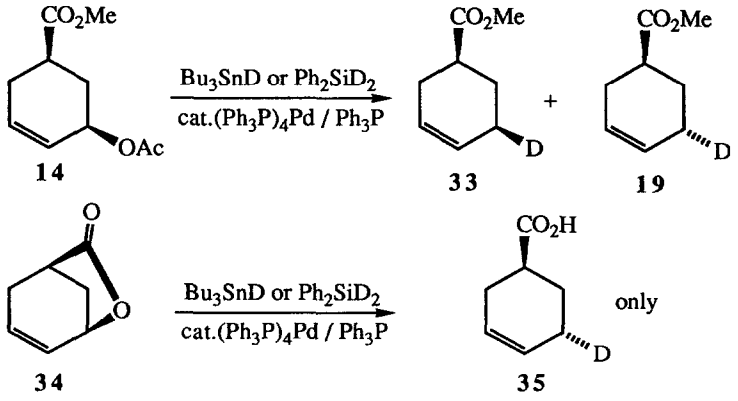
Erosion of the stereochemical integrity of the intermediate palladium allyl complexes may occur in a number of ways.

(i) Acetate is able to promote the erosion of enantiomeric purity of a palladium allyl complex, by delivery of acetate from palladium to the allyl moiety. Thus treatment of the allyl acetate **15** with catalytic palladium(0) and phosphine can lead to epimerisation as illustrated in Scheme 7. The epimerised acetate **14** has been re-isolated in the absence of an incoming nucleophile.[50] The mechanism of epimerisation by acetate is believed to proceed *via* an η^1-allyl complex **32**, as illustrated.[51]

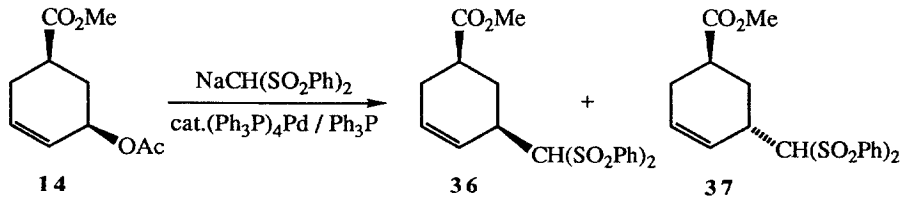


Scheme 7

This is elegantly illustrated in the reaction of the allyl acetate **14** with either tributyltin deuteride or diphenyldideuteriosilane.[52] These nucleophiles which are less reactive than sodium borodeuteride and afford a mixture of *cis*- and *trans*-substituted products **33** and **19**. However, for the related lactone **34**, no such problem arises, with the reaction only proceeding to afford the *trans* product **35**. Since a single product is observed in the case of the lactone, this suggests that the reaction is proceeding exclusively *via* prior co-ordination of the nucleophile to the metal, and this is also true for the reaction with the acetate. However, in the case of the acetate, since the reaction is relatively slow, this allows for epimerisation by acetate, prior to the reaction with nucleophile. However, for the lactone, such an epimerisation process is not allowed, because the formation of a *trans* lactone is not possible.



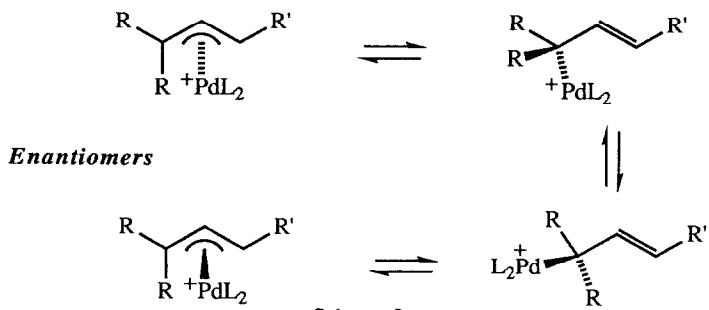
In a related example, the bulky nucleophile $NaCH(SO_2Ph)_2$ affords a mixture of products in the palladium catalysed allylic substitution of compound **14**. Due to the size of this nucleophile it reacts only slowly, and this allows time for epimerisation by acetate prior to the generation of the products **36** and **37**.[53]



14 **36** **37**

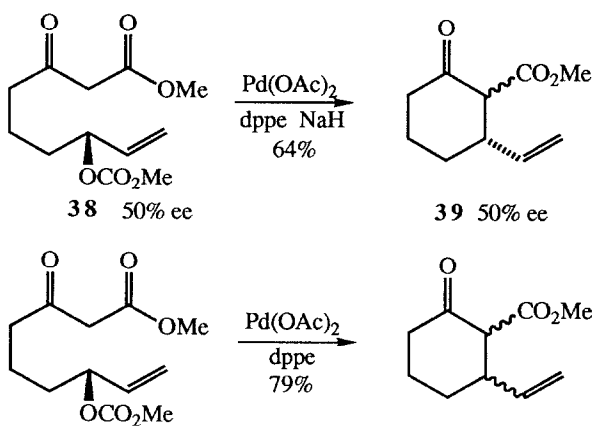
55 : 45

(ii) π-σ-π Isomerisation of η^3-allyl complexes is a well known process, and when one terminus of the allyl unit contains two identical groups, this process can occur rapidly.[54] The enantiomeric forms of such a complex are in equilibrium as demonstrated in Scheme 8.



Scheme 8

Depending on the speed at which such a palladium allyl complex reacts, complete loss of stereochemistry can occur. For example, in the cyclisation reaction of **38**, if the anion is preformed, it is possible to preserve stereochemical integrity in the formation of the substitution product **39**.[55] However, if the reaction relies on formation of the active nucleophile during the course of the reaction, then this allows time for the π-σ-π isomerisation to take effect, and the product is isolated with complete loss of enantiomeric purity.



38 50% ee **39** 50% ee

38 50% ee **39** 0% ee

dppe = 1,2-bis(diphenylphosphino)ethane

(iii) Palladium(0) is able to function as a nucleophile, and loss of stereochemical integrity can therefore arise by a displacement mechanism, as outlined in Figure 1.

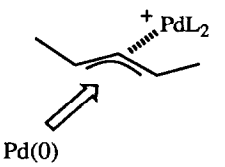
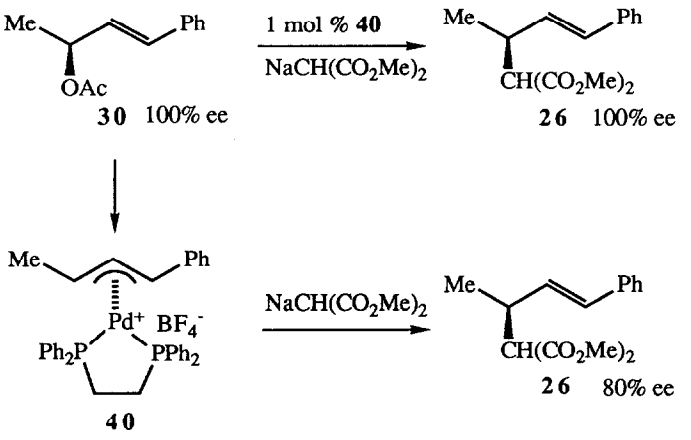


Figure 1

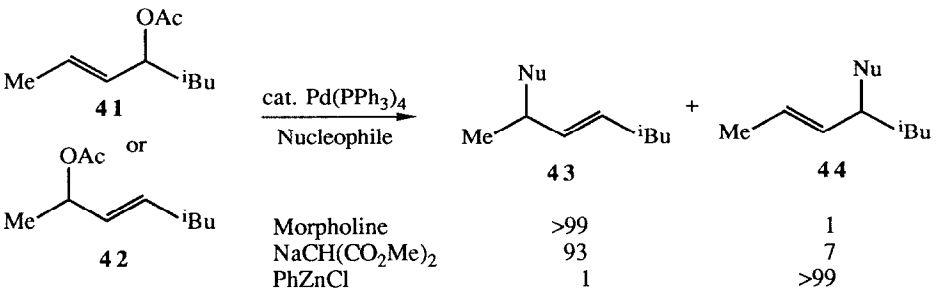
Hayashi has demonstrated that the use of stoichiometric amounts of palladium can lead to less preservation of stereochemical integrity.[48] The enantiomerically pure allyl acetate **30** was treated with 1 mol% of the cationic palladium complex **40** and $NaCH(CO_2Me)_2$ to afford enantiomerically pure product **26**. However, isolation of the intermediate complex, and treatment with a stoichiometric amount of $NaCH(CO_2Me)_2$ afforded the same product **26** with only 80% ee. This would be consistent with the notion of loss of stereochemical integrity by *exo* attack of palladium(0) on the allyl complex.



3. Control of Reaction Selectivity

i) Steric control of regiochemistry

Typically, nucleophiles approach palladium complexes from the least substituted terminus, with a good level of selectivity. For example, morpholine reacts with the allyl acetates **41** or **42** in the presence of a palladium(0) catalyst to afford a >99:1 ratio of the products **43** and **44**, and this regiochemical outcome is explained in terms of simple steric approach control arguments. However, for nucleophiles which react by transfer from the palladium to the metal, the opposite regiochemical outcome is observed. For example, the use of phenylzinc chloride as the nucleophile affords a 1: >99 ratio of the products **43** and **44**.[56]

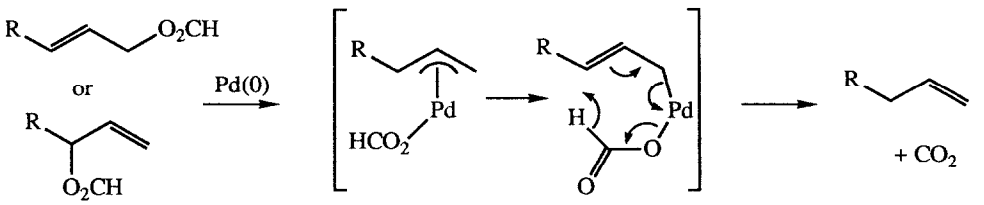


	43	44
Morpholine	>99	1
$NaCH(CO_2Me)_2$	93	7
PhZnCl	1	>99

The surprising behaviour of PhZnCl and other hard nucleophiles can be rationalised by considering the two possible isomeric intermediate complexes shown in Scheme 9. The sterically demanding triphenylphosphine ligand preferentially resides *trans* to the bulkier allyl terminus, in order to minimise steric interaction. The transfer of the phenyl group to the allyl group occurs in a *cis* fashion, thereby yielding the observed regioisomer as the major product. The levels of selectivity in both cases are remarkable.

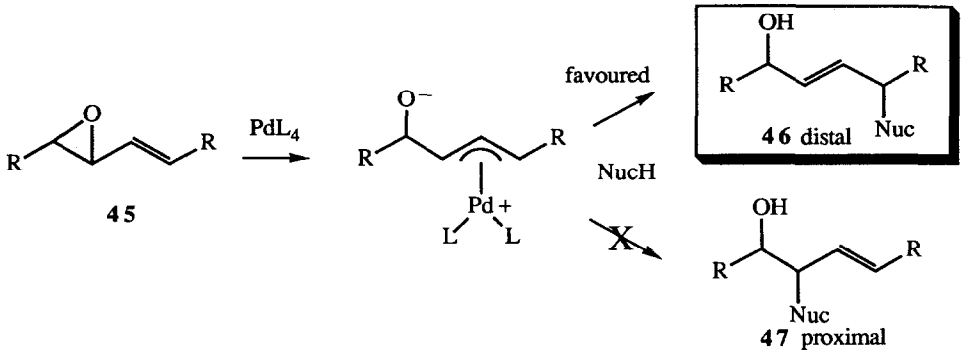
Scheme 9

Tsuji and co-workers have recently used the regiocontrol offered by hydride delivery from formates in the preparation of isopropenyl and vinyl groups from ketones.[57] None of the internal alkene is formed. Tsuji suggests the mechanism shown in Scheme 10.

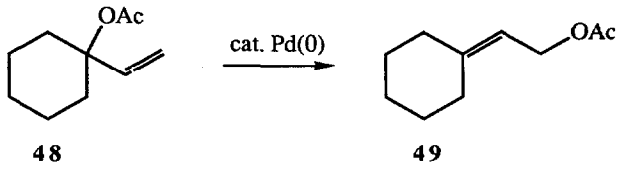


Scheme 10

Regiochemistry may also be controlled by other features of the allyl substrate. For example, in the palladium catalysed reaction of an allylic epoxide **45**, there is strong regiocontrol in favour of the product in which the incoming nucleophile and the resultant hydroxy are as far apart as possible, preferentially affording the product **46**. This is attributed to the desire of the nucleophile to stay away from the negatively charged alkoxide during the transition state, and therefore attack at the distal centre is observed over attack at the proximal centre.[58] Exceptions to this rule have been noted in some instances.[59]



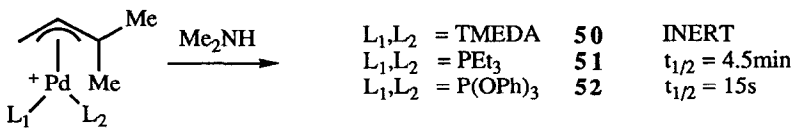
Acetate rearrangements have also been performed, and hence presumably the reaction is under thermodynamic control, to afford the more stable alkene **49** from the terminal alkene **48**.[60]



ii) Ligand effects on reactivity and regiochemistry

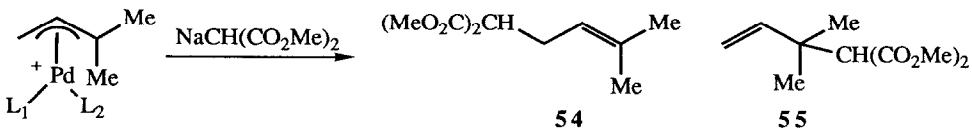
The nature of the ligand employed in palladium catalysed allylic substitution reactions has a significant effect on the rate of reaction and also on the control of the regioselectivity of the reaction. This is demonstrated by the work of Åkermark, Vitagliano and co-workers.[12,61]

The reaction is greatly accelerated in the presence of π-accepting ligands, such as phosphines, but not by ligands which are only able to function as σ-donors. For example, the half-life for the reaction between dimethylamine and a series of complexes **50-52** reflects this fact. The TMEDA (*N,N,N',N'*-tetramethylethylenediamine) complex **50** is inert under the reaction conditions employed, whereas the corresponding phosphine complex **51** has a half-life of 4.5 min, and for the phosphite complex **52**, the half-life is less than 15 seconds. It is well known that phosphites are better π-acceptors than are the corresponding phosphines.[62] The π-acceptor properties may be thought of as withdrawing electron density from the metal, which in turn increases the positive charge character of the allyl unit, rendering it more susceptible to nucleophilic attack.



Reaction of the sterically biased substrates **50**, **52** and **53** with nucleophiles causes predominant reaction from the less hindered end for all of the nucleophiles examined. However, whilst the regioselectivity was very high in the case of a nitrogen based ligand such as TMEDA to afford the product **54**, more of the regioisomer

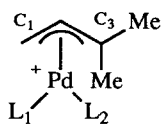
55 resulting from attack at the more substituted terminus was observed in the case where a π-acceptor ligand, triphenylphosphite was employed.



54 **55**

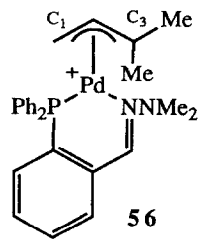
L_1,L_2 = TMEDA	**50**	>20	1
L_1,L_2 = PBu_3	**53**	4.8	1
L_1,L_2 = $P(OPh)_3$	**52**	1.3	1

The explanation suggested for this dichotomy considers the fact that the stronger π-acceptor creates more positive charge character in the allyl moiety. The more stable position for the positive charge character is the more substituted terminus, and therefore this centre becomes more reactive to an incoming nucleophile. An elegant series of ^{13}C NMR experiments support this idea. In the complexes **50** - **52**, the C_3 position is consistently observed downfield from the C_1 position, since in all cases, the C_3 carbon is better able to support the partial positive charge. As the allyl unit becomes more positively charged, the electron density is taken more and more from the more substituted terminus, as reflected in the increasing C_3-C_1 shift differences for better π-accepting ligands.



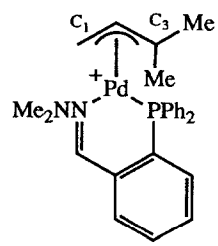
		C_3 - C_1 shift differences
50	L_1,L_2 = TMEDA	32
51	L_1,L_2 = PEt_3	56
52	L_1,L_2 = $P(OPh)_3$	64

Furthermore, it has been observed that the π-acceptor properties of the ligand are relayed predominantly in a *trans* manner across the complex. Therefore in ligands which contain both phosphorus and nitrogen donor atoms, the two termini of the allyl unit will respond differently to the electronic effects created by such a ligand. A comparison of the C_3-C_1 shift differences for the isomeric complexes **56** and **57**, show that when the C_3 carbon is *trans* to the π-accepting phosphine ligand, a large amount of positive character builds up, whereas, when the nitrogen ligand is *trans* to this position, the positive character is substantially reduced. The two complexes differ by a shift difference of 70 ppm, representing a major difference in the amount of positive charge character at this position.



56

C_3 - C_1 = 78 ppm



57

C_3 - C_1 = 8 ppm

X-ray crystal structure data support these arguments.[63] The bond lengths from palladium to the termini of the allyl unit are found to lengthen when they are *trans* to π-accepting ligands such as triphenylphosphine or trichlorotin, as illustrated in Figure 2. The cationic complex $(\eta^3\text{-}C_3H_5)Pd(TMEDA)^+$ has intermediate Pd-C bond lengths of 2.15Å.[64] Distortions within the allyl unit have been observed in the solid state[65] and also in solution.[66]

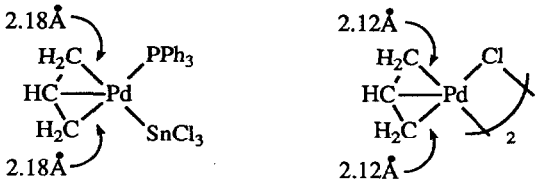
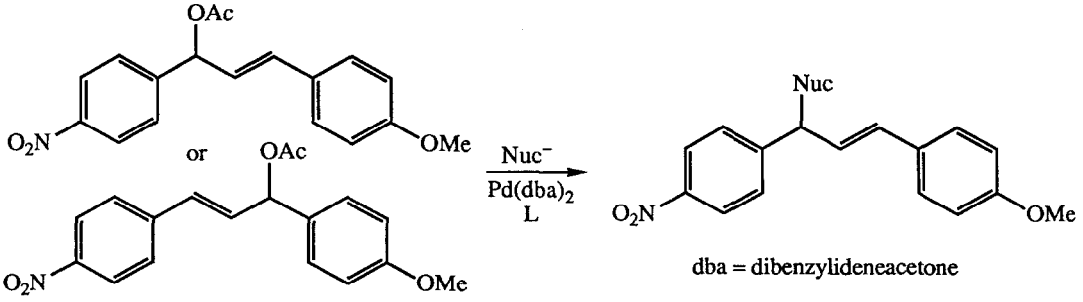


Figure 2

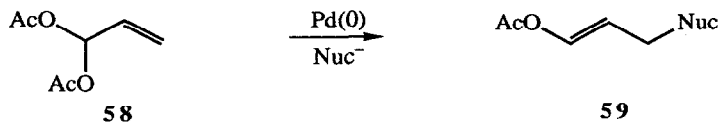
iii) Electronic control of regiochemistry

There are a number of instances where the regiochemistry of addition is controlled by electronic effects in the allyl unit. For example, when the two termini of the allyl unit are both aryl substituents, differing only in the substituent at the *para* positions, it would seem that since there is essentially no difference in the steric requirements of the two termini, and that electronic effects must play the more important role. In this example, illustrated in Scheme 11, the nucleophile attacks at the terminus containing the electron deficient aryl group, regardless of the regiochemistry of the starting acetate.[67]



Scheme 11

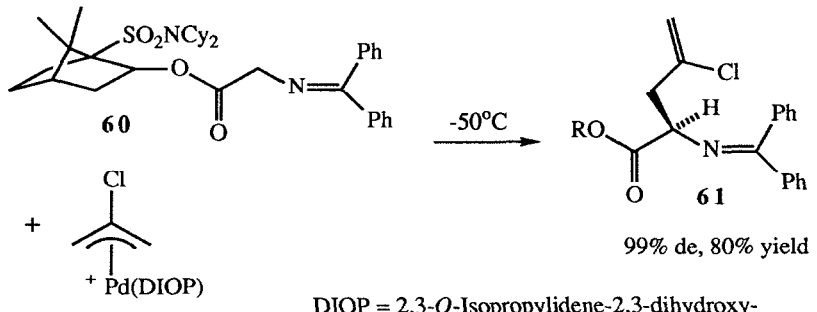
However, it is difficult to rationalise the regiochemical outcome of nucleophilic addition to all regiochemically biased allyl complexes based on simple electronic arguments. Most functionalities appear to direct nucleophilic attack to the remote terminus of the allyl moiety (more than based on simple steric arguments). There are very few cases where electronic and steric control can be completely distinguished. Phosphonates,[68] sulfides,[69] nitriles[70] and ketones[71] all direct to the remote terminus. The reaction of the *gem*-diacetate **58** with nucleophiles under palladium catalysis affords the product **59** with nucleophilic addition to the remote terminus. However, in related examples, steric factors can disrupt these preferences.[72]



58 59

iv) Diastereocontrol of reactions

Chiral nucleophiles have been employed to induce chirality in the substitution process. Genet and co-workers have used homochiral glycine derivatives **60** as nucleophiles in the preparation of protected amino acids **61**.[73] Asymmetric induction was enhanced to very high levels by using homochiral palladium complexes **62** as the electrophilic partner.[74] Asymmetric induction relying solely on the ligands also been achieved, and the use of this methodology in the preparation of racemic amino acids has also been documented.[75]

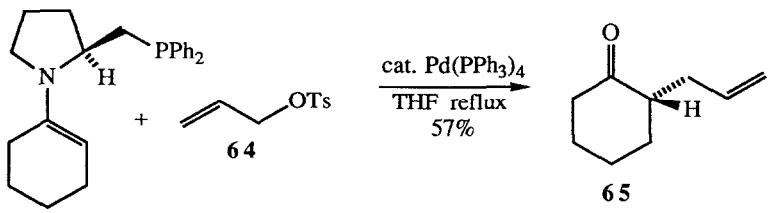


60 61 62

99% de, 80% yield

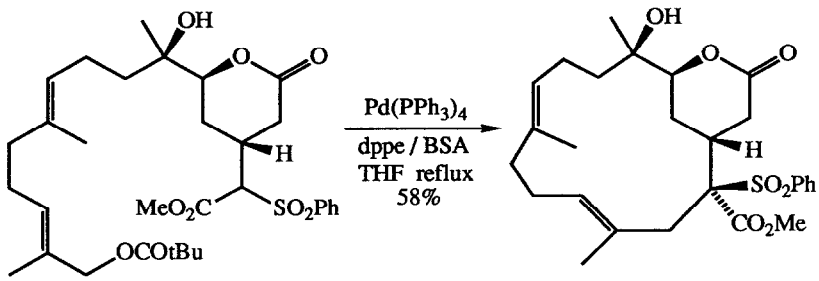
DIOP = 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

Homochiral enamines containing a phosphorus group have been used as nucleophiles, with the view that co-ordination of the nucleophile to the palladium will occur, and enhance asymmetric induction. The enamine **63** reacted with allyl tosylate **64** to afford the α-substituted ketone **65** with 65% ee. For related examples, higher selectivities were obtained (up to 88% ee).[76]



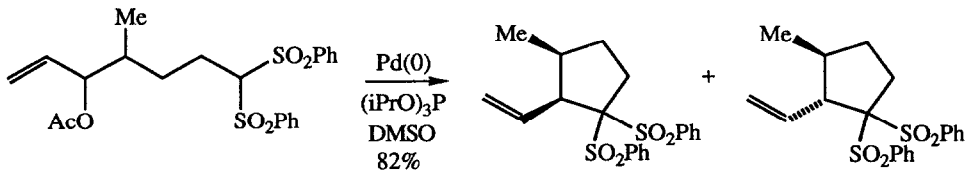
63 64 65

Marshall and co-workers only observed one diastereomer of product **66** in the macrocyclisation of the allylic carbonate **67** under palladium catalysis in the presence of the acid-scavenger BSA (*N*,*O*-bis(trimethylsilyl)acetamide).[77] Generally, the diastereoselectivity of such steps is of little consequence, since subsequent reaction destroys the chirality at these centres.



67 66

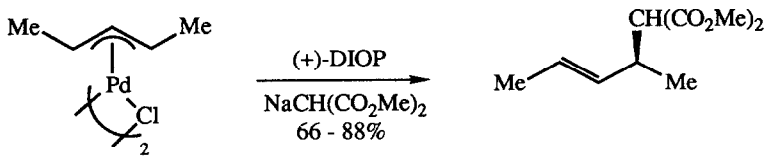
Trost has reported diastereoselectivity in the cyclisation of allylic acetate **68**. The levels of diastereoselectivity to afford **69** and **70** are reasonable, but highly dependent upon solvent, with the sense of induction being opposite for DMSO and THF.[78]



68 **69** 6.9 : 1 **70**

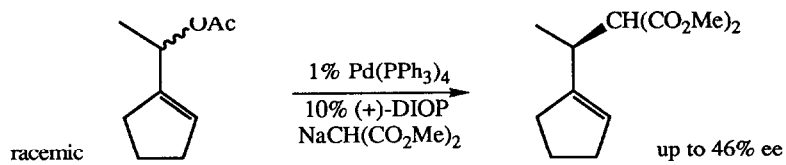
v) Enantiocontrol of reactions

Enantioselective reactions based on palladium catalysed allylic substitution are now reaching high levels of stereocontrol, and is currently an actively pursued research area. In 1973, Trost and Dietsche showed that the stoichiometric reaction of a palladium allyl chloride dimer **71** with $NaCH(CO_2Me)_2$ and chiral ligands afforded the substitution product **72** with 23% ee when (+)-DIOP was used as the ligand.[79]



71 **72**

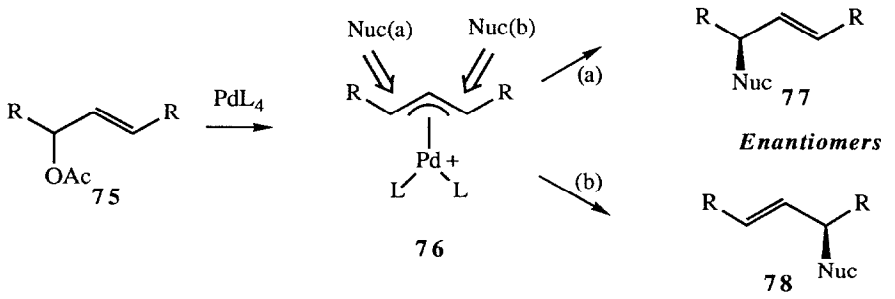
For catalytic asymmetric variants of this reaction, the first reported example was the conversion of the racemic allyl acetate **73** to the enantiomerically enriched product **74**, albeit with modest enantioselectivity of up to 46% ee.



73 **74**

a) Enantiocontrol via meso complexes

The majority of asymmetric palladium catalysed allylic substitution processes are based around the formation of an intermediate *meso* complex **76**. For example, in the absence of a chiral ligand, the allylic substrate **75** renders a *meso* complex, which can react by attack of the nucleophile from either terminus of the allyl unit to afford the enantiomers **77** and **78**. The ability to promote attack to one terminus in preference to the other results in an enantioselective reaction.



This is mechanistically a hard process to achieve with asymmetric induction, since the incoming nucleophile is approaching the ligand from the other side, and hence the use of chiral ligands leads to a large distance between the newly forming bond and the chirality-controlling centre.

Hayashi has devised a family of ligands, **79-81**, which are claimed to reach around to the *exo* face of the allyl unit, and selectively deliver the incoming nucleophile to one terminus of the allyl unit, as illustrated in Figure 3.[80]

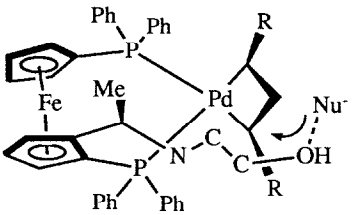
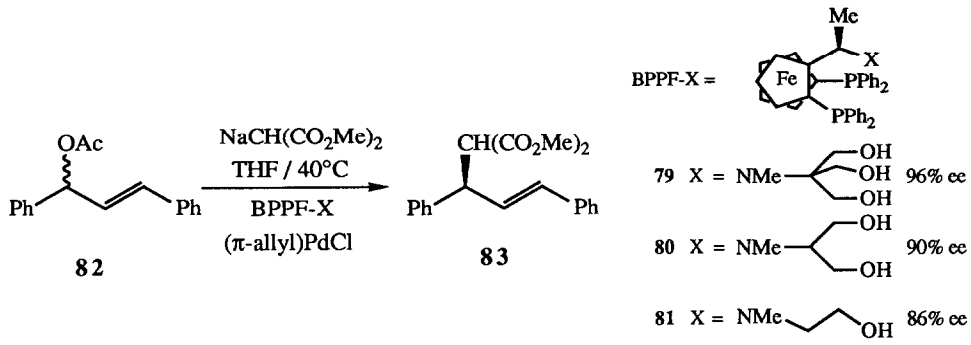
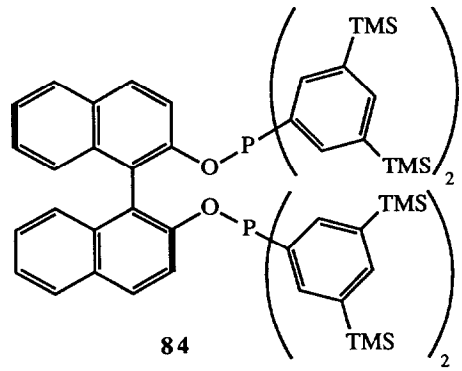


Figure 3

The enantioselectivities reported for the conversion of the allyl acetate **82** to the product **83** are very high (up to 96% ee). The directing group employed has been varied and found to have a significant effect on enantioselectivity. Ligands using crown ethers as directing groups have also been employed in these reactions.[81]



In a similar fashion, Trost has developed the sterically bulky ligand **84**, which is able to sterically block the approach of the nucleophile to one of the termini.[82] Reactions proceeding *via* a *meso* complex have been achieved with 69% ee employing this ligand.



However, many of the ligands which are able to impart appreciable levels of asymmetric induction are not able to reach around to the *exo* face of the allyl group in this manner, and it would seem that the effect may be caused, at least in some instances, by an electronic bias in the symmetry of the allyl unit, either by the association of a negatively charged group, such as hydroxyl or carboxyl, or alternatively by steric effects of the ligands forcing the allyl group away at one terminus, and thereby presumably generating an enhanced centre for nucleophilic addition, since it should carry more positive charge character, as represented in Figure 4.

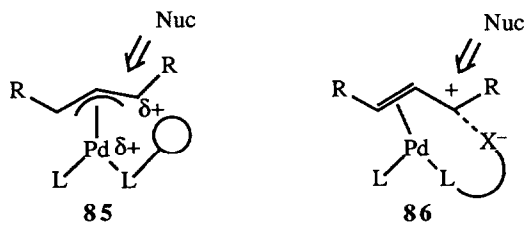
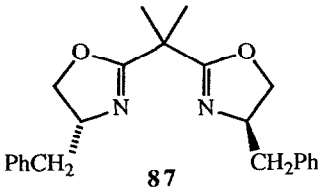
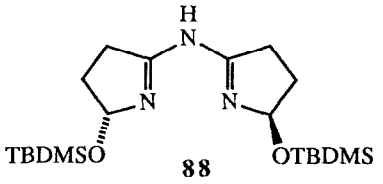


Figure 4

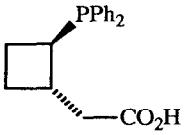
Ligands which may be considered in this category include, the bisoxazolines **87** and 5-azasemicorrins **88** employed by Pfaltz to obtain impressive levels of enantioselectivity (88%ee and 95%ee respectively),[83] and the cycloalkanecarboxylic acid phosphines **89** and **90** employed by Minami.[84] Pfaltz demonstrated that highest enantioselectivities were obtained with his ligands in the presence of the acid scavenger BSA, which allows for the use of less polar solvents.



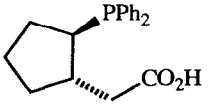
87



88

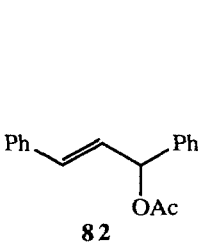


89

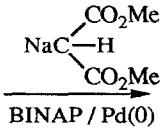


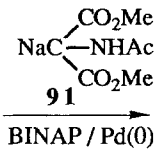
90

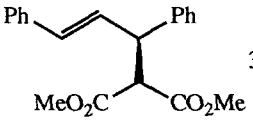
It has been demonstrated by Yamaguchi, Yamagishi and co-workers that the choice of incoming nucleophile can be of considerable importance in the enantioselectivity of these asymmetric reactions. For example, employing BINAP as the ligand in the reaction of allyl acetate **82**, a modest 34% ee is obtained for $NaCH(CO_2Me)_2$. However, for the acetamidomalonate **91**, the product **92** is obtained with 95% ee.[85]



82

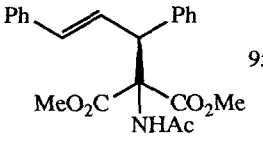






34% ee

83

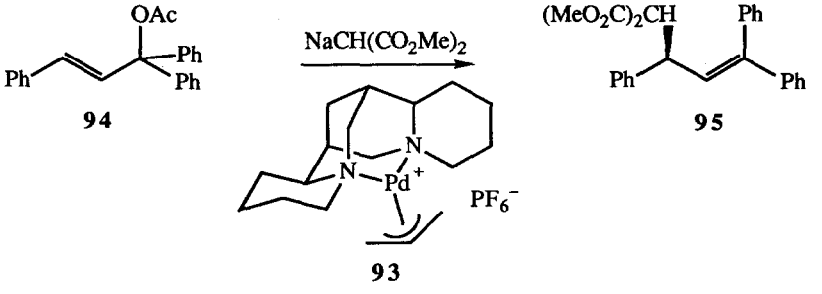


95% ee

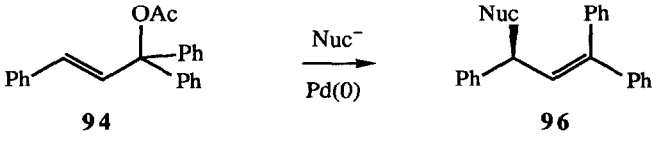
BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl **92**

The conditions under which the reaction is run, the choice of solvent, substrate and nucleophile all play a role in determining enantioselection. For example, the sparteine complex **93** has recently been used for the palladium catalysed allylic substitution of the substrate **94**, and despite early reports of only mediocre enantioselectivities, was able to produce the product **95** with 85% ee.[86] This reaction does not proceed *via* a *meso* intermediate, but the diastereomeric allyl complexes are in rapid equilibrium. An X-ray crystal structure of

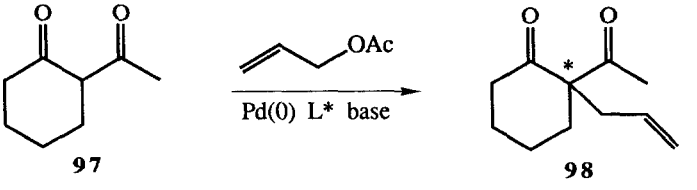
the proposed intermediate in this reaction has been solved, and the observed diastereomer is consistent with the stereochemical outcome for this reaction. COSY and NOESY 2D ^{1}H NMR techniques indicate that the structure of the complex in solution remains essentially unchanged.[87]



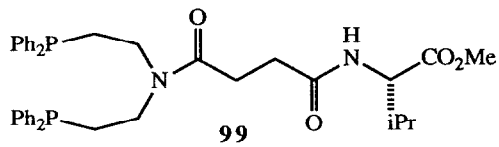
Bosnich has carefully investigated the mechanism of asymmetric palladium catalysed allylation, and has paid particular attention to systems of the type **94**.[88] The main conclusions that he arrived at were that the turnover-limiting step (and the one which determines the enantioselectivity) is the addition of the nucleophile to the π-allyl species. The major π-allyl complex in the equilibrium affords the major product, and the possible isomeric π-allyl complexes equilibrate more quickly than the nucleophilic addition to them. Again, a crystal structure of the proposed allyl intermediate has been determined, and used to analyse the stereochemistry of the observed products.[89]



The asymmetry generated adjacent to the allyl unit by non-symmetrical nucleophiles has been controlled in an enantioselective sense with a number of chiral phosphines.[90] Thus, the reaction of the diketone **97** to afford the allyl-substituted product **98** has been achieved with asymmetric induction.



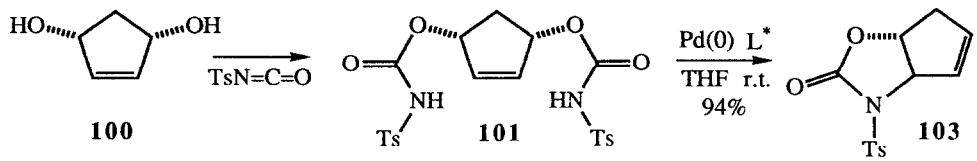
The enantioselectivities using the chiral diphosphine **99** are remarkable in view of how remote the existing stereocentre is from the newly created stereocentre, and are explained in terms of a transition state in which the ligand reaches around to the *exo* face of the allyl moiety in the palladium complex.[91] Likewise the family of ferrocenyl phosphine ligands **79-81** have been used with success in such reactions as well.[92]



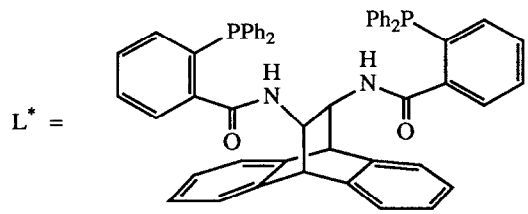
99

b) Enantiocontrol by replacement of prochiral leaving groups

Whilst there are less examples of enantiocontrol by replacement of prochiral leaving groups, it nevertheless offers an interesting and useful technique for introducing asymmetry. Trost employed the *meso* diol **100**, which was derivatised *in situ* with tosylisocyanate, generating the ditosylcarbamate **101**.[93] In the presence of the homochiral ligand **102**, the substrate was converted into the product **103** with 88% ee. This ligand, and a related family of ligands derived from 2-diphenylphosphinobenzoic acid, were designed to vary the ring size of the resulting palladium chelates, since increasing the ring size is expected to increase the 'bite angle' of the ligand, thereby bringing the chiral environment of the ligands closer to the allyl moiety, and hopefully increasing asymmetric induction.



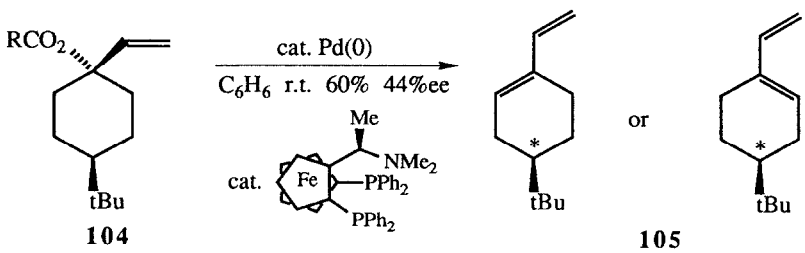
100 **101** **103**



102

c) Enantioselective elimination reactions

Hayashi has recently achieved modest enantioselectivities in the palladium catalysed elimination of the allyl ester **104** to form the diene **105**. In the absence of a suitable nucleophile, the intermediate palladium allyl complex may be deprotonated to afford a diene product. One diene enantiomer is formed preferentially.[94]



104 **105**

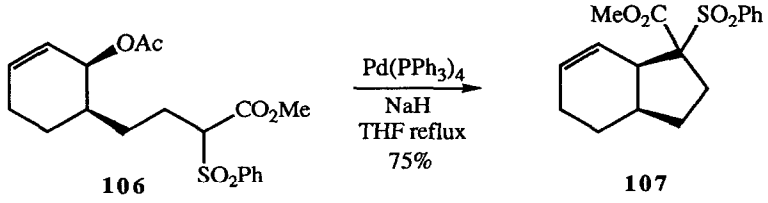
The elimination of palladium allyl complexes to give dienes, and catalytic variants of this process have been achieved in the absence of homochiral ligands.[95]

4. Uses of the Methodology

i) Cyclisations

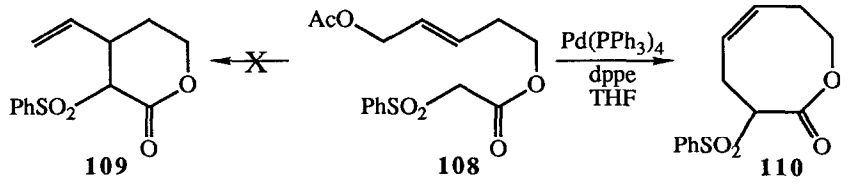
Whilst there are a wide range of synthetic applications in the use of palladium catalysed allylic substitution, many of these applications have been in the cyclisation of suitable substrates, and often, the further elaboration of such compounds into natural products. Trost and others have documented many of the unusual ring closures observed, and there is a review dedicated to cyclisation chemistry using palladium.[96]

In many instances, the outcome may be readily predicted from a knowledge of the reactivity of the acyclic systems. For example, reaction of the allylic acetate **106** with palladium(0) and base affords the ring-closed product **107** with retention of stereochemistry, as would be expected. If the nucleophile were not tethered, then a mixture of regioisomers might be expected, but in the cyclic case, cyclisation occurs to afford the *cis*-fused bicyclo[4.3.0]nonane system **107**.[97] The normal overall retention mechanism is observed with related cyclisations.[98]



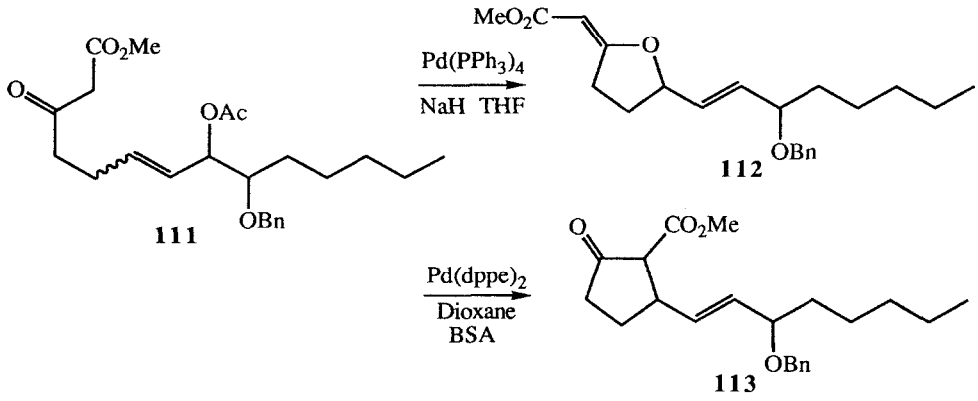
106 **107**

In certain instances, an apparently unusual regioselectivity may be observed, such as in the cyclisation of the allyl acetate **108**.[99] Whilst there is apparently a choice between the six-membered and eight-membered products **109** and **110**, only the eight-membered ring product is observed. However, the reason offered for this selectivity is that the nucleophile is adding to the least sterically crowded terminus of the allyl complex. Trost has observed that generally the regiocontrol in these instances can be attributed to the control by the palladium allyl complex, and not by the resultant ring size of the product. Consequently the larger ring size will generally be formed for medium-sized rings with palladium catalysed allylic substitution.[100]

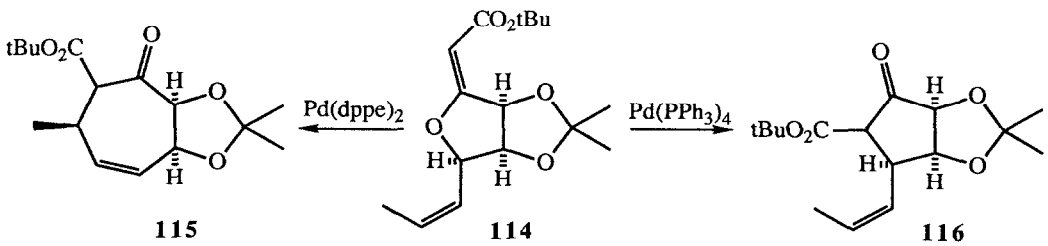


109 **108** **110**

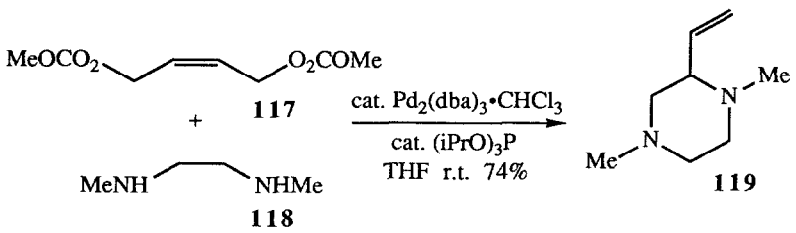
The choice of ligands employed can have a profound effect on the outcome of the reaction. The allyl acetate **111** may be cyclised to either **112** (O-alkylation) using $Pd(PPh_3)_4$ or to **113** (C-alkylation) using $Pd(dppe)_2$. This difference in reactivity arises because of the less sterically demanding nature of $Pd(dppe)_2$ compared with $Pd(PPh_3)_4$.[101]



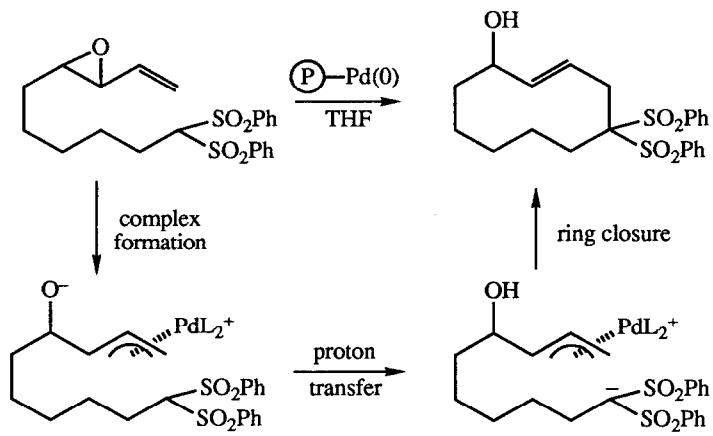
Trost has also reported examples of cyclisation reactions where the leaving group can function as the nucleophile.[102] The substrate **114** forms a π-allyl complex and recloses to form the seven-membered ring **115** using $Pd(dppe)_2$, whereas the five-membered ring **116** is formed in the presence of $Pd(PPh_3)_4$. In this instance the steric demand of the bulky triphenylphosphine ligands favours the product containing the least crowded alkene (alkene complex). A recent report notes the difference between these two catalysts, and describes the outcome in terms of the smaller cone angle of the bidentate dppe, which presents less steric bulk than triphenylphosphine.[103]



An interesting example of the cyclisation of the dicarbonate **117** with the diamine **118** affords the heterocyclic product **119** in 74% yield. Product formation occurs from two consecutive palladium catalysed substitution reactions.[104]



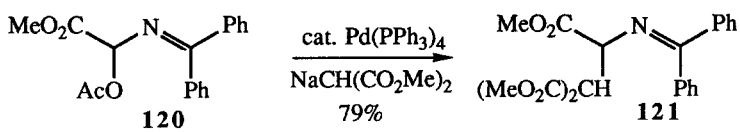
Many macrocyclisation reactions require high dilution techniques to ensure their successful outcome, due to competing intermolecular processes at more standard concentrations. Trost has developed a pseudo-dilution technique by employing polymer-supported phosphines and associated metal catalyst, illustrated in Scheme 12. The substrate needs to diffuse onto the polymer for reaction to occur. The so formed polymer-bound palladium allyl complex in the example below contains an alkoxide group which can deprotonate the nucleophilic moiety. In the non-polar environment created by the polymer, diffusion is hampered, and thereby facilitates addition of the nucleophile to the allyl complex.[102]



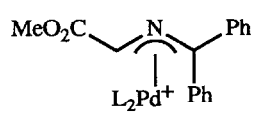
Scheme 12

ii) Heteroallyl palladium complexes

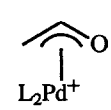
There are a number of reports of heteroallyl palladium complexes. O'Donnell has reported the alkylation of the imine **120** with palladium(0) and $NaCH(CO_2Me)_2$, which affords the product **121**, and presumably proceeds *via* the aza-allyl complex **122**.[103] The existence of oxo-allyl complexes **123** has been suggested, and may be considered as a variation of a metal enolate, since they are essentially the "halfway-point" between an O-bound enolate, and an α-metallated carbonyl compound.[104]



120 **121**



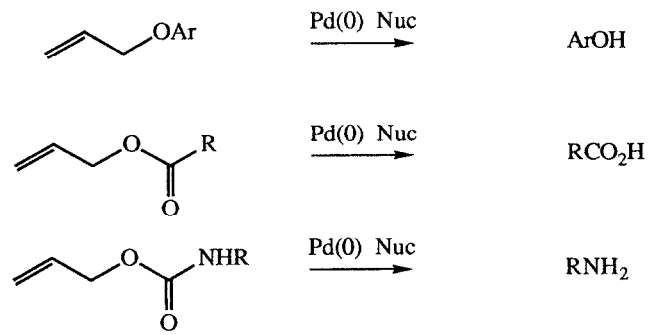
122



123

iii) Removal of allyl protecting groups

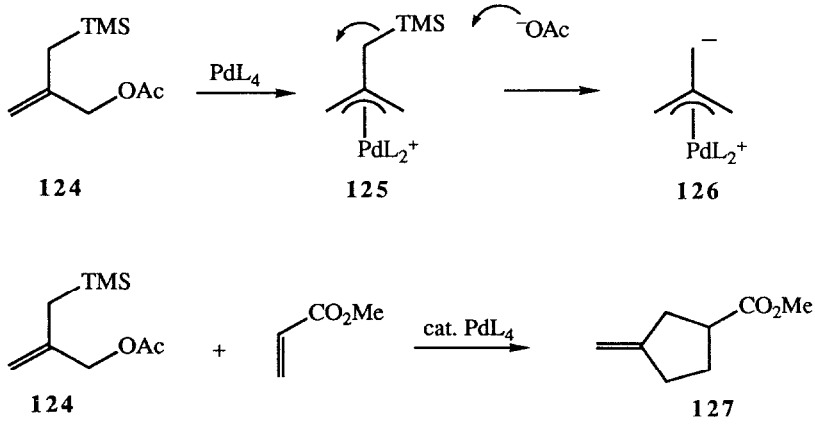
The allyl moiety has been employed as a protecting group for a number of functionalities, and may be removed from under mild and selective conditions by using palladium catalysed allylic substitution. The nucleophile is often chosen to be a hydride or morpholine or whatever nucleophile is believed to facilitate the work-up procedure. Recently, the use of silylated nucleophiles in the presence of a mild silylating agent has been recommended as most suitable, since palladium catalysed decarbonylation is avoided for deprotection of carbamates and carbonates, affording a cleaner reaction.[105] The following examples of the deprotection of phenols, acids, and amines are representative of this procedure, Scheme 13.[106]



Scheme 13

iv) Trimethylenemethane methodology

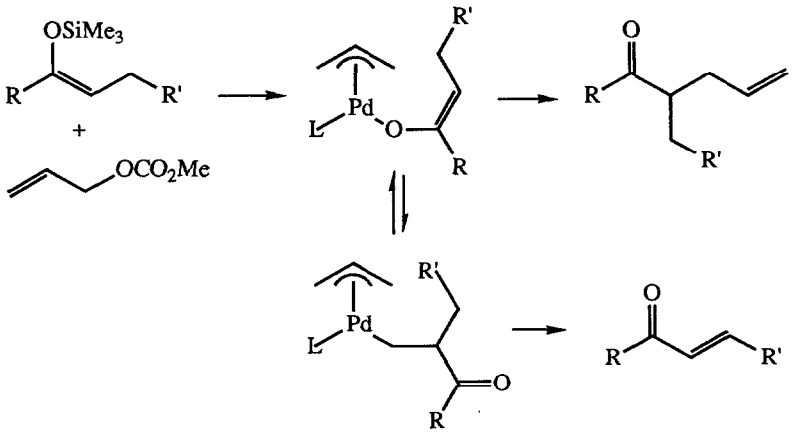
Treatment of the allyl acetate **124** with catalytic palladium(0) complexes results in the formation of a palladium allyl complex **125** which is prone to loss of the silyl group to afford a dipolar species, represented as **126**. This species is able to function in 1,3-dipolar reactions with a range of dipolarophiles. For example, the reaction with methyl acrylate affords the product **127**.[107] The control of regiochemistry with these systems has also been tackled.[108]



The aza-analogues of palladium trimethylenemethane complexes have recently been proposed as intermediates in the reactions of methylene oxazolidinones with palladium catalysts.[109]

v) Further synthetic applications

Tsuji has found a variety of applications for palladium allyl chemistry.[110] Certain enolates are able to function as nucleophiles in palladium catalysed allylic substitution reactions, although Tsuji has demonstrated that by choice of solvent, the reaction may be re-directed to give β-elimination of the intermediate palladium enolate, thereby affording an α,β-unsaturated product, as shown in Scheme 14. This represents a method for the conversion of enolates directly to the corresponding unsaturated carbonyl compound.



Scheme 14

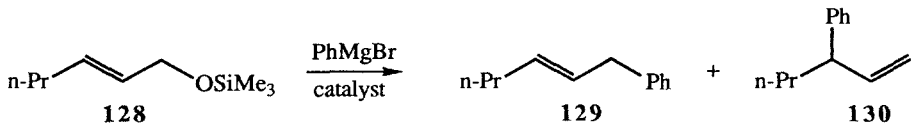
vi) Comparison of palladium with other metals

Palladium is not the only metal capable of catalysing allylic substitution reactions. Copper, nickel, molybdenum, tungsten, platinum,[111] rhodium[112] and iron catalysts have been reported. These metals each have their own characteristics in terms of selectivity, mechanism, and utility.

This section represents a brief overview of the behaviour of these systems in catalytic allylic substitution reactions, and is not intended to provide a complete account of such catalysts.

a) Nickel

Nickel catalysts have been used with allylic substrates and hard nucleophiles such as Grignard reagents, and the reactions proceed with overall inversion of configuration, as does the corresponding palladium catalysed reaction for such nucleophiles. However, the regiochemical outcome is different, since in the nickel catalysed process, nucleophiles are transferred to the more substituted terminus, whilst the opposite is true for the palladium catalysed reaction.[113] Thus, allyl ether **128** is selectively converted into **130**, whilst palladium catalysis affords **129** as the major product.

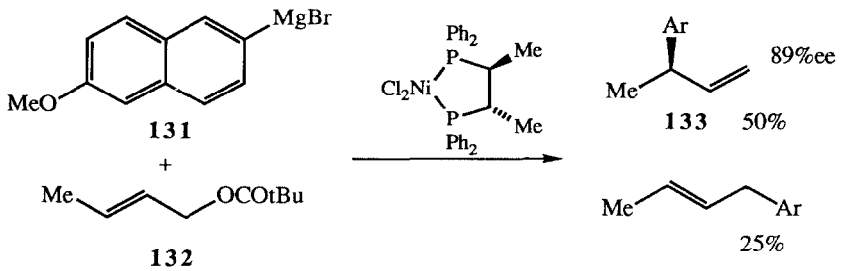


128 **129** **130**

	E/Z	
$NiCl_2$(dppf)	17 (16/1)	83
$PdCl_2$(dppf)	93 (87/6)	7

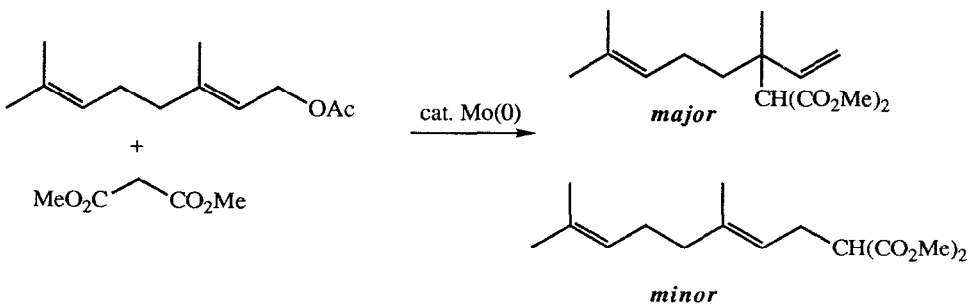
dppf = 1,1'-bis(diphenylphosphino)ferrocene

Nickel catalysed substitution of allylic acetals,[114] alcohols[115] and other derivatives[116] have been reported, and asymmetric variants of these processes using homochiral phosphine ligands have been achieved.[117] For example, the reaction of the Grignard reagent **131** with allyl carbonate **132** affords the substitution product **133** with 89% ee.



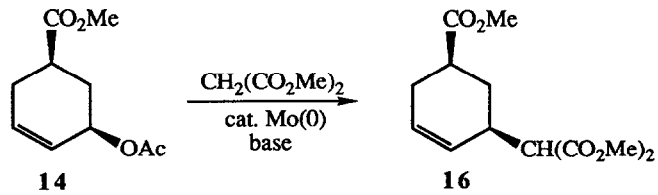
b) Molybdenum

The regiochemical and stereochemical outcome of molybdenum catalysed allylic substitution reactions have received a fair amount of interest, although there is still some uncertainty regarding the mechanism. A number of molybdenum catalysts including $Mo(CO)_6$, $Mo(CO)_4$(bipy) and $Mo(CO)_3(CH_3CN)_3$ have been successfully employed as catalysts for allylic substitution reactions. Molybdenum tends to promote alkylation at the more hindered terminus of the intermediate allyl complex, affording a regioselectivity of 97:3 when BSA is employed as the base, Scheme 15.[118] The regiochemical outcome of related systems has been discussed in terms of molecular orbitals.[119]



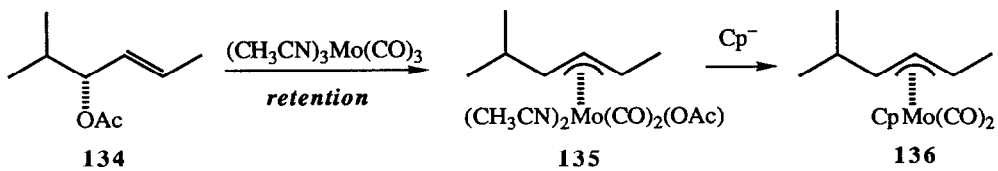
Scheme 15

Whilst the overall net retention mechanism seems to operate for molybdenum catalysed systems, the selectivity is highly dependent upon the choice of base, nucleophile and substrate.[120] Trost has recently recommended the use of $(tBuNC)_4Mo(CO)_2$ as a superior molybdenum catalyst in terms of reactivity, chemo-, regio-, and stereoselectivity. This catalyst promotes alkylations to the less substituted allylic carbon, but does proceed with overall net retention.[121] Thus, allyl acetate **14** is converted into the substitution product **16**.



14 **16**

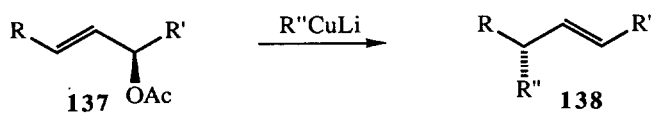
Faller's results suggest that the oxidative addition of the substrate to the metal occurs with retention, and that the overall net retention mechanism is therefore explained by two retention steps.[122] This was demonstrated by the reaction of the homochiral allyl acetate **134** with $(CH_3CN)_3Mo(CO)_3$, to afford the molybdenum allyl complex **135**, which was converted into the cyclopentadienyl complex **136**, which was shown to be of the absolute configuration shown. However, nucleophilic addition to this species occurred with inversion of stereochemistry.



134 **135** **136**

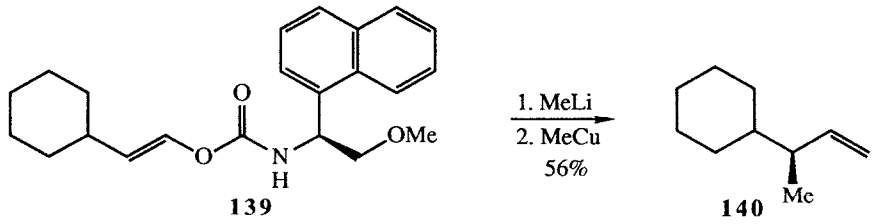
c) Copper

The reaction of copper reagents with allylic substrates generally proceeds *via* an S_N' *anti* mechanism, and the allyl acetate **137** affords the product **138** with high levels of stereoselectivity. This preference has been rationalised in terms of the interaction between the d-orbitals of the copper, and the orbitals of the substrate.[123] A symmetrical η^3-allyl intermediate is not believed to participate, since the stereochemistry and regiochemistry is transmitted with varying degrees of efficiency to the product. Occasionally, for steric reasons, the reaction of cuprates has been observed to proceed in an S_N' *syn* fashion, but this is very unusual.[124]



137 **138**

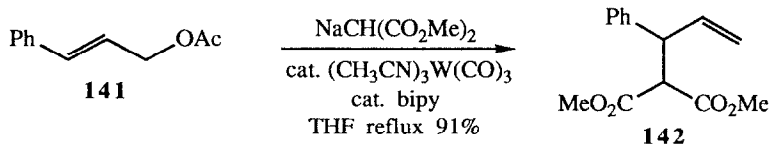
Denmark and Marble have achieved remote asymmetric induction with copper reagents by the use of enantiomerically pure leaving groups. The substrate **139** was converted with 95% ee into the substituted product **140**.[125]



139 **140**

d) Tungsten

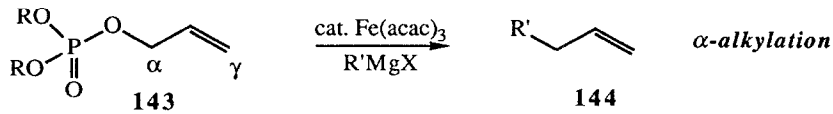
Tungsten (0) catalysts have been employed to effect an allylic substitution process. Whilst $W(CO)_6$ was found to be ineffective, $(CH_3CN)_3W(CO)_3$ was effective, and in the presence of the strong σ-donor bipyridine (bipy), the reaction was accelerated further.[126] The reaction of cinnamyl acetate **141** occurred regioselectively to afford the product **142** arising from addition to the more hindered terminus of the allyl.



141 **142**

e) Iron

Yamamoto has recently reported the iron-catalysed Kharash-type reaction between Grignard reagents and allylic phosphates **143**. The process is a highly S_N2 selective reaction, affording the product **144**.[127]



143 **144**

Summary

Palladium catalysed allylic substitution has emerged as one of the more useful synthetic methods for the construction of C-C and C-X bonds. The reaction offers the advantages of mild reaction conditions, as well as the ability to accomodate a wide range of nucleophiles and their electrophilc partners.

The issues of regiocontrol, diastereocontrol and enantiocontrol have been documented by a number of researchers over the last twenty years. The levels of selectivity in many cases are very high, and current research is driving these selectivities higher still. A greater understanding of the nature of the process is occuring as more detailed mechanistic and structural studies are being undertaken.

Many uses have been found for palladium catalysed allylic substitution methodology, since the strong stereocontrol allows for the selective formation of numerous products.

A few other metals are also able to catalyse allylic substitution, with modified stereochemical behaviour, although these are currently less well documented than for palladium catalysed process.

References

[1] (a) I. Ojima, N. Clos and C. Bastos, *Tetrahedron*, 1989, **45**, 6901. (b) S. L. Blystone, *Chem. Rev.*, 1989, **89**, 1663. For more general texts, see; (c) J. P. Collman, L. S. Hegedus, J. R. Norton and R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (d) S. G. Davies, *Organotransition Metal Chemistry: Applications to Organic Synthesis*, Pergamon Press: Oxford, England, 1982.

[2] (a) J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, Heidelberg, 1980. (b) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, London, 1985.

[3] J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 508.

[4] R. F. Heck, *Org. React.*, 1983, **27**, 1.

[5] K. Januszkiewicz and H. Alper, *Tetrahedron Lett.*, 1983, **24**, 5159, and references therein.

[6] (a) S. A. Godleski in *Comprehensive Organic Synthesis*, Ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol 4, p585. (b) G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257. (c) J. Tsuji, *Pure Appl. Chem.*, 1986, **58**, 869.

[7] (a) B. L. Shaw, *Chem. Ind. (London)*, 1962, 1190. (b) B. L. Shaw and N. Sheppard, *Chem. Ind. (London)*, 1961, 517.

[8] J. Tsuji, H. Takashashi and M. Morikawa, *Tetrahedron Lett.*, 1965, 4387.

[9] K. E. Atkins, W. E. Walker and R. M. Manyik, *Tetrahedron Lett.*, 1970, 3821.

[10] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435.

[11] (a) T. Yamamoto, M. Akimoto, O. Saito and A. Yamamoto, *Organometallics*, 1986, **5**, 1559. (b) H. Kurosawa, *J. Organomet. Chem.*, 1987, **334**, 243.

[12] B. Åkermark, S. Hansson, B. Krakenberger, A. Vitagliano and K. Zetterberg, *Organometallics*, 1984, **3**, 679.

[13] H. Kurosawa, M. Emoto and Y. Kawasaki, *J. Organomet. Chem.*, 1988, **346**, 137.

[14] B. Akermark, S. Hansson and A. Vitagliano, *J. Am. Chem. Soc.*, 1990, **112**, 4587.

[15] F. K. Sheffy and J. K. Stille, *J. Am. Chem. Soc.*, 1983, **105**, 7173.

[16] B. M. Trost, N. R. Schmuff and M. J. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 5979.

[17] J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, K. Takahashi and T. Sugiura, *J. Org. Chem.*, 1985, **50**, 1523.

[18] For example see; J. Tsuji, *Tetrahedron*, 1986, **42**, 4361.

[19] Y. Tanigawa, K. Nishimura, A. Kawasaki and S. Murahashi, *Tetrahedron Lett.*, 1982, **23**, 5549.

[20] For a review, see; J. Tsuji and I. Minami, *Acc. Chem. Res.*, 1987, **20**, 140.

[21] J-C. Fiaud and J-Y. Legros, *Tetrahedron Lett.*, 1992, **33**, 2509.

[22] J. Nokami, A. Maihara and J. Tsuji, *Tetrahedron Lett.*, 1990, **31**, 5629.

[23] B. M. Trost and L. Zhi, *Tetrahedron Lett.*, 1992, **33**, 1831.

[24] (a) R. Tanikaga, T. X. Jun and A. Kaji, *J. Chem. Soc., Perkin Trans. I*, 1990, 1185. (b) S. Murahashi, Y. Tanigawa, Y. Imada and Y. Taniguchi, *Tetrahedron Lett.*, 1986, **27**, 227. (c) S. E. Byström, R. Aslanian and J. E. Bäckvall, *Tetrahedron Lett.*, 1985, **26**, 1749. For a fuller list see reference 6(a).

[25] M. Julia, M. Nei and L. Saussime, *J. Organomet. Chem.*, 1979, **181**, C17.

[26] (a) J. Tsuji, K. Sakai, H. Nagashima and I. Shimizu, *Tetrahedron Lett.*, 1981, **22**, 131. (b) R. C. Larock, L. W. Harrison and M. H. Hsu, *J. Org. Chem.*, 1984, **49**, 3662.

[27] B. Akermark, J. E. Nystrom, T. Rein, J. E. Bäckvall, P. Helquist and R. Aslanian, *Tetrahedron Lett.*, 1984, **25**, 5719.

[28] B. M. Trost, J. Yashida and M. Lautens, *J. Am. Chem. Soc.*, 1983, **105**, 4494.

[29] N. Miyaura, T. Yano and A. Suzuki, *Tetrahedron Lett.*, 1980, **21**, 2865.

[30] (a) S. A. Godleski, K. B. Gundlach, H. Y. Ho, E. Keinan and F. Frolow, *Organometallics*, 1984, **3**, 21. (b) R. O. Hutchins and K. Learn, *J. Org. Chem.*, 1982, **47**, 4380. (c) D. H. R. Barton and A. Patin, *J. Chem. Soc., Chem. Commun.*, 1977, 799.

[31] J. Tsuji, I. Minami, I. Shimizu, *Synthesis*, 1986, 623.

[32] J-Y. Legros and J-C. Fiaud, *Tetrahedron Lett.*, 1990, **31**, 7453.

[33] (a) L. Zhu, R. M. Wehmeyer and R. D. Rieke, *J. Org. Chem.*, 1991, **56**, 1445. (b) T. Hayashi, A. Yamamoto and T. Hagihara, *J. Org. Chem.*, 1986, **51**, 723.

[34] T. Hayashi, M. Konishi, K. Yokota and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 1981, 313.

[35] J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.*, 1980, **102**, 7381.

[36] J. S. Temple, M. Riediker, J. Schwartz, *J. Am. Chem. Soc.*, 1982, **104**, 1310.

[37] (a) B. M. Trost and E. Keinan, *Tetrahedron Lett.*, 1980, **21**, 2595. (b) A. Gollaszewski and J. Schwartz, *Organometallics*, 1985, **4**, 417. (c) A. M. Echavarren, D. R. Teuting and J. K. Stille, *J. Am. Chem. Soc.*, 1988, **110**, 4039.

[38] For a review on the different nucleophiles employed see reference 6(a).

[39] (a) L. S. Hegedus and R. Tamura, *Organometallics*, 1982, **1**, 1188. (b) D. Milstein, *Organometallics*, 1982, **1**, 888. For a review see; (c) S-I. Murahashi and Y. Imada, *J. Synth. Org. Chem. Jpn.*, 1991, **49**, 919.

[40] P. Zhang, W. Zhang, T. Zhang, Z. Wang and W. Zhou, *J. Chem. Soc., Chem. Commun.*, 1991, 491, and references therein.

[41] J. P. Takahara, Y. Masuyama and Y. Kurusu, *J. Am. Chem. Soc.*, 1992, **114**, 2577.

[42] B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, 1975, **97**, 1611.

[43] B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, 1976, **41**, 3215.

[44] B. M. Trost and J. W. Herndon, *J. Am. Chem. Soc.*, 1984, **106**, 6835.

[45] N. Greenspoon and E. Keinan, *J. Org. Chem.*, 1988, **53**, 3723.

[46] H. Matsushita and E. Negishi, *J. Chem. Soc., Chem. Commun.*, 1982, 160.

[47] J-C. Fiaud and J-Y. Legros, *J. Org. Chem.*, 1987, **52**, 1907.

[48] (a) I. Stary and P. Kocovsky, *J. Am. Chem. Soc.*, 1989, **111**, 4981. (b) H. Kurosawa, S. Ogishi, Y. Kawasaki, S. Murai, M. Mioshi and I. Ikeda, *J. Am. Chem. Soc.*, 1990, **112**, 2813.

[49] T. Hayashi, A. Yamamoto and T. Hagihara, *J. Org. Chem.*, 1986, **51**, 723.

[50] L. E. Overman and F. M. Knoll, *Tetrahedron Lett.*, 1979, 321.

[51] H. Greenberg, V. Langer and J. E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1991, 1190.

[52] N. Greenspoon and E. Keinan, *Tetrahedron Lett.*, 1982, **23**, 241.

[53] B. M. Trost, T. R. Verhoeven and J. M. Fortunak, *Tetrahedron Lett.*, 1979, 2301.

[54] For a fuller account of π-σ-π equilibration, see reference 6(a).

[55] K. Yamamoto, R. Deguchi, Y. Ogimura and J. Tsuji, *Chem Lett*, 1984, 1657.

[56] E. Keinan and M. Sahai, *J. Chem. Soc., Chem. Commun.*, 1984, 648.

[57] T. Mandai, S. Suzuki, T. Murakami, M. Fujita, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, 1992, **33**, 2987.

[58] B. M. Trost and G. A. Molander *J. Am. Chem. Soc.*, 1981, **103**, 5969.

[59] T. Suzuki, O. Sato and M. Hirama, *Tetrahedron Lett.*, 1990, **31**, 4747.

[60] P. M. Henry, *J. Am. Chem. Soc.*, 1972, **94**, 5200.

[61] B. Akermark, B. Krakenberger, S. Hansson and A. Vitagliano, *Organometallics*, 1987, **6**, 620

[62] (a) C. A. Tolman, *J. Am. Chem. Soc.*, 1970, **92**, 2953. (b) G. M. Bodner, M. P. May and L. E. McKinney, *Inorg. Chem.*, 1980, **19**, 1951.

[63] (a) R. Mason and P. O. Whimp, *J. Chem. Soc. (A)*, 1969, 2709. (b) A. E. Smith, *Acta Cryst.*, 1965, **18**, 331.

[64] L. S. Hegedus, B. Åkermark, D. J. Olsen, O. P. Anderson and K. Zetterberg, *J. Am. Chem. Soc.*, 1982, **104**, 697.

[65] (a) A. Albinati, C. Ammann, P. S. Pregosin and H. Rüegger, *Organometallics*, 1988, **7**, 2130. (b) J. E. Gozum, D. M. Pollina, J. A. Jensen and G. S. Girolami, *J. Am. Chem. Soc.*, 1988, **110**, 2688. (c) J. W. Faller, C. Blankenship and B. Whitmore, *Inorg. Chem.*, 1985, **24**, 4483.

[66] A. Albinati, R. W. Kunz, C. J. Ammann and P. S. Pregosin, *Organometallics*, 1991, **10**, 1800.

[67] (a) M. Moreno-Mañas and J. Ribas, *Tetrahedron Lett.*, 1989, **30**, 3109. (b) M. Prat and M. Moreno-Mañas, *Tetrahedron*, 1992, **48**, 1695.

[68] Z. Zhu and X. Lu, *Tetrahedron Lett.*, 1987, **28**, 1897.

[69] S. A. Godleski and E. B. Villhauer, *J. Org. Chem.*, 1986, **51**, 486.
[70] J. Tsuji, H. Ueno, Y. Kobayashi and H. Okumoto, *Tetrahedron Lett.*, 1981, **22**, 2573.
[71] W. R. Jackson and J. U. Strauss, *Aust. J. Chem.*, 1977, **30**, 553.
[72] B. M. Trost and J. Vercauteren, *Tetrahedron Lett.*, 1985, **26**, 131.
[73] J. P. Genet, N. Kopola, S. Juge, J. Ruiz-Montes, O. A. C. Antunes, S. Tanier, *Tetrahedron Lett.*, 1990, **31**, 3133.
[74] J. P. Genet, D. Ferroud, S. Juge and J. Ruiz-Montes, *Tetrahedron Lett.*, 1986, **27**, 4573.
[75] J. P. Genet, S. Juge, S. Achi, S. Mallart, J. Ruiz-Montes and G. Levif, *Tetrahedron*, 1988, **44**, 5263.
[76] K. Hiroi and J. Abe, *Tetrahedron Lett.*, 1990, **31**, 3623.
[77] J. A. Marshall, R. C. Andrews and L. Lebioda, *J. Org. Chem.*, 1987, **52**, 2378.
[78] B. M. Trost and P. H. Lee, *J. Am. Chem. Soc.*, 1991, **113**, 5076.
[79] B. M. Trost and T. J. Dietsche, *J. Am. Chem. Soc.*, 1973, **95**, 8200.
[80] T. Hayashi, A. Yamamoto, T. Hagihara and Y. Ito, *Tetrahedron Lett.*, 1986, **27**, 191.
[81] M. Sawamura, H. Nagata, H. Sakamoto and Y. Ito, *J. Am. Chem. Soc.*, 1992, **114**, 2586.
[82] B. M. Trost and D. J. Murphy, *Organometallics*, 1985, **4**, 1143.
[83] V. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt and A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143.
[84] (a) Y. Okada, T. Minami, Y. Umezu, S. Nishikawa, R. Mori and Y. Nakayama, *Tetrahedron: Asymmetry*, 1991, **2**, 667. (b) Y. Okada, T. Minami, Y. Sasaki, Y. Umezu and M. Yamaguchi, *Tetrahedron Lett.*, 1990, **31**, 3905.
[85] M. Yamaguchi, T. Shima, T. Yamagishi and M. Hida, *Tetrahedron Lett.*, 1990, **31**, 5049.
[86] A. Togni, *Tetrahedron: Asymmetry*, 1991, **2**, 683.
[87] A. Togni, G. Rihs, P. S. Pregosin and C. Ammann, *Helv. Chim. Acta*, 1990, **73**, 723.
[88] P. B. Mackenzie, J. Whelan and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2046.
[89] D. H. Farrar and N. C. Payne, *J. Am. Chem. Soc.*, 1985, **107**, 2054.
[90] J. C. Fiaud, A. H. DeGournay, M. Lachevéque and H. B. Kagan, *J. Organomet. Chem.*, 1978, **154**, 175.
[91] T. Hayashi, K. Kanehira, H. Tsuchiya and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 1982, 1162.
[92] T. Hayashi, K. Kanehira, T. Hagihara and M. Kumada, *J. Org. Chem.*, 1988, **53**, 113.
[93] B. M. Trost and D. L. Van Vranken, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 228.
[94] T. Hayashi, K. Kishi and Y. Uozumi, *Tetrahedron: Asymmetry*, 1991, **2**, 195.
[95] (a) J. Tsuji, T. Yamakama, M. Kaito and T. Mandai, *Tetrahedron Lett.*, 1978, 2075. (b) F. M. Hauser, R. Tommasi, P. Hewawasam and Y. S. Rho, *J. Org. Chem.*, 1988, **53**, 4886.
[96] B. M. Trost, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 1173.
[97] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1977, **99**, 3867.
[98] T. Takahashi, Y. Jinbo, K. Kitamura and J. Tsuji, *Tetrahedron Lett.*, 1984, **25**, 5921.
[99] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1979, **101**, 1595.
[100] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4743.
[101] (a) B. M. Trost, T. A. Runge and L. N. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 2840. (b) B. M. Trost and L. N. Jungheim, *J. Am. Chem. Soc.*, 1980, **102**, 7910.
[102] B. M. Trost and T. A. Runge, *J. Am. Chem. Soc.*, 1981, **103**, 7559.
[103] T. Takemoto, Y. Nishikimi, M. Sodeoka and M. Shibasaki, *Tetrahedron Lett.*, 1992, **33**, 3527.
[104] T. Tsuda, T. Kiyoi and T. Saegusa, *J. Org. Chem.*, 1990, **55**, 3388.
[105] B. M. Trost and R. W. Warner, *J. Am. Chem. Soc.*, 1982, **104**, 6112.
[106] M. J. O'Donnell, X. Yang and M. Li, *Tetrahedron Lett.*, 1990, **31**, 5135
[107] Y. Ito, M. Nakatsuka, N. Kise and T. Saegusa, *Tetrahedron Lett.*, 1980, **21**, 2873.
[108] A. Merzouk and F. Guibé, *Tetrahedron Lett.*, 1992, **33**, 477.

[109] (a) J. E. Baldwin, M. G. Moloney and M. North, *J. Chem. Soc., Perkin Trans. 1*, 1989, 833. (b) F. Guibe, O. Dangles and G. Balavoine, *Tetrahedron Lett.*, 1986, **27**, 2365. (c) F. Guibe and Y. Saint M'Leux, *Tetrahedron Lett.*, 1981, **22**, 3591. (d) P. Four and F. Guibe, *Tetrahedron Lett.*, 1982, **23**, 1825.

[110] For a review on trimethylenemethane chemistry, see; B. M. Trost, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 1

[111] B. M. Trost and M. C. Matelich, *Synthesis*, 1992, 151.

[112] K. Ohe, T. Ishihara, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 1990, **112**, 9646.

[113] J. Tsuji, *Tetrahedron*, 1986, **42**, 4361.

[114] H. Kurosawa, S. Ogoshi, Y. Kawasaki, S. Murai, M. Miyoshi and I. Ikeda, *J. Am. Chem. Soc.*, 1990, **112**, 2813.

[115] J. Tsuji, I. Minami and I. Shimizu, *Tetrahedron Lett.*, 1984, **25**, 5157.

[116] T. Hayashi, M. Konishi, K-I. Yokota and M. Kumada, *J. Organomet. Chem.*, 1985, **285**, 359.

[117] H. Sugimura and H. Takei, *Chem. Lett.*, 1985, 351.

[118] (a) C. Chuit, H. Felkin, C. Frajerman, G. Roussi and G. Swierczewski, *J. Organomet. Chem.*, 1977, **127**, 371. (b) G. Consiglio, F. Morandini and O. Piccolo, *J. Am. Chem. Soc.*, 1981, **103**, 1846.

[119] T. Yamamoto, J. Ishizu and A. Yamamoto, *J. Am. Chem. Soc.*, 1981, **103**, 6863.

[120] (a) M. Chérest, H. Felkin, J. D. Umpleby and S. G. Davies, *J. Chem. Soc., Chem. Commun.*, 1981, 681. (b) T. Hiyama and N. Wakasa, *Tetrahedron Lett.*, 1985, **26**, 3259.

[121] (a) B. M. Trost and M. Lautens, *Tetrahedron*, 1987, **43**, 4817. (b) Y. Masuyama, K. Yamada and Y. Kurusu, *Tetrahedron Lett.*, 1987, **28**, 443.

[122] M. D. Curtis and O. Eisenstein, *Organometallics*, 1984, **3**, 887.

[123] B. M. Trost and M. Lautens, *J. Am. Chem. Soc.*, 1987, **109**, 1469.

[124] B. M. Trost and C. A. Merlic, *J. Am. Chem. Soc.*, 1990, **112**, 9590.

[125] J. W. Faller and D. Linebarrier, *Organometallics*, 1988, **7**, 1670.

[126] E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1984, **25**, 3063.

[127] S. M. Roberts, G. T. Woolley and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1729.

[128] S. E. Denmark and L. K. Marble, *J. Org. Chem.*, 1990, **55**, 1984.

[129] (a) B. M. Trost and M-H. Hung, *J. Am. Chem. Soc.*, 1983, **105**, 7757. (b) B. M. Trost and M-H. Hung, *J. Am. Chem. Soc.*, 1984, **106**, 6837. (c) B. M. Trost and R. Braslau, *Tetrahedron Lett.*, 1988, **29**, 1231.

[130] (a) A. Yanagisawa, N. Nomura and H. Yamamoto, *Synlett.*, 1991, 513. (b) Y. Xu and B. Zhou, *J. Org. Chem.*, 1987, **52**, 974. (c) B. Zhou and Y. Xu, *J. Org. Chem.*, 1988, **53**, 4419.