Pergamon

Tetrahedron Vol. 51, No. 4, pp. 975-1015, 1995

0040-4020/95 $29.00+0.00

0040-4020(94)01011-0

TETRAHEDRON REPORT NUMBER 364

The Stereochemistry of Palladium-Catalysed Cyclisation Reactions
Part B: Addition to π-allyl intermediates

Andreas Heumann[a] **and Marius Réglier**[b]
Université d'Aix-Marseille, Faculté de St.-Jérôme,F 13013 Marseille, France
a. URA CNRS 1410, B. URA CNRS 1409

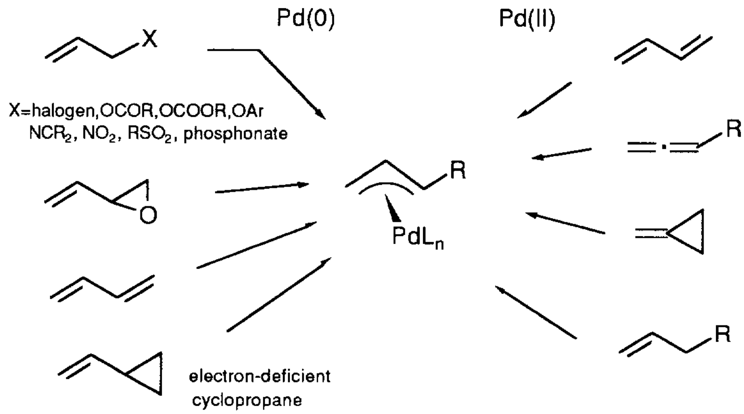
Contents

1. Introduction

In the first part of this series[1] a review was presented of reactions in which the cyclisation step consisted of the addition of reactive species to carbon-carbon double bonds that had been activated by coordination to palladium. This review will consider the other principal intermediate in organic olefin-palladium chemistry *viz* π-allyl palladium complexes and their use in cyclisation reactions. In a subsequent review we hope to give an additional atoms and incorporated into the new molecule (CO, for example) or a cascade of several cyclisations[3] lead to polycyclic systems.[4]

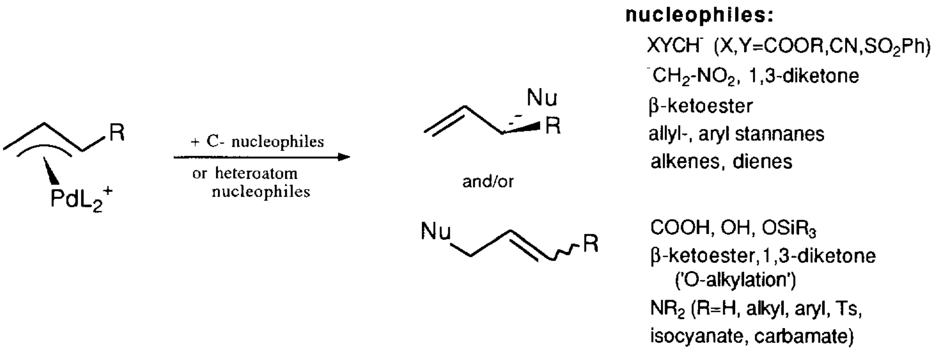
2 Addition to π-allyl intermediates

One of the most useful applications of palladium in organic chemistry is a consequence of the fact that an η^3 or π-allyl palladium species is easily formed in several different ways from various organic substrates that contain at least one double bond (Scheme 1),



Scheme 1

and in addition that this π-allyl palladium unit can be easily substituted by a number of carbon and heteroatom nucleophiles (Scheme 2). Depending on the organic starting material, both palladium(0) and palladium(II) catalysis can occur. Pd(0) requires an allylic leaving group in the form of an allylic ester or ether (including cyclic ethers like epoxides and higher oxacyclic systems) as well as an electron-deficient cyclopropane ring. Unsubstituted and unactivated organic compounds can form π-allyl complexes oxidatively with palladium(II).



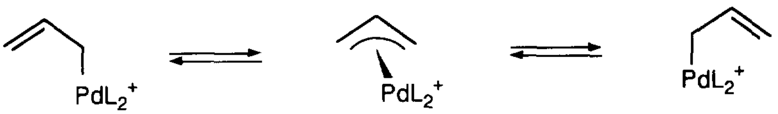
nucleophiles:

$XYCH^-$ (X,Y=COOR,CN,SO_2Ph)
$^-CH_2$-NO_2, 1,3-diketone
β-ketoester
allyl-, aryl stannanes
alkenes, dienes

COOH, OH, $OSiR_3$
β-ketoester,1,3-diketone
('O-alkylation')
NR_2 (R=H, alkyl, aryl, Ts, isocyanate, carbamate)

Scheme 2

The π-allyl complex, which may be in equilibrium with its canonical forms, two enantiomeric σ-allyl complexes (Scheme 3), is readily transformed to different allylic substrates by nucleophilic substitution. In many cases, catalytic reactions are possible. However, two completely differing mechanisms exist.



Scheme 3

In the case of the Pd(0) reactions with allylic substrates, only **replacement** of the allylic leaving group by another, generally organic, group is possible. This means that, in cyclisation, the leaving group is lost since the nucleophilic substitution proceeds in an intramolecular manner. In the overall reaction (oxidative addition - substitution - reductive elimination), the oxidation state of the palladium does not change. Conversely, the reaction with palladium(II) leads to an oxidized organic product; the catalyst is reduced to the zero oxidation state during the reaction. It is important to state that in the Pd(II) reaction at least one new allylic group is **introduced** into the molecule. In intramolecular reactions, the nucleophilic group is already present in the molecule and the oxidation simply consists of abstracting two hydrogen atoms. In this case, a Pd(II) regeneration system is also required. This might be the 'nucleophile' (Pd(0) + RX → R-Pd-X), but usually an independent reoxidation cycle (such as $CuCl_2$, benzoquinone, benzoquinone/oxidant) is used.[5]

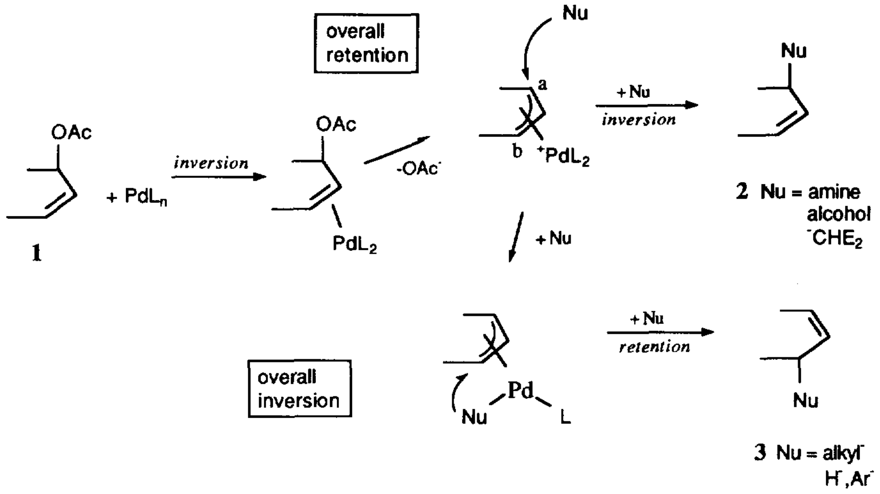
π-Allyl palladium chemistry[6] has been developed as a powerful tool in organic synthesis by several research groups, and reviews have appeared by Trost,[7] Tsuji,[8] Oppolzer[9] and Bäckvall[10] on these cyclisation methods.

2.1 Transformation of allylic substrates

2.1.1 Trost/Tsuji reaction

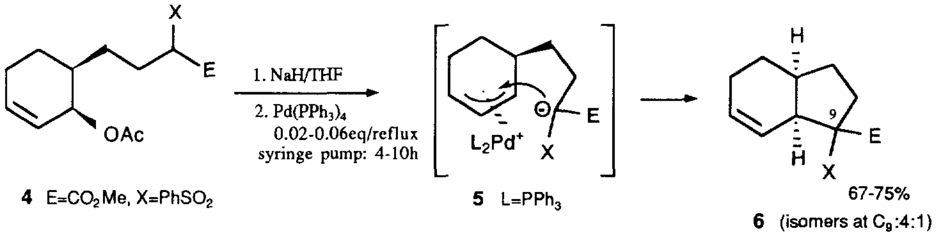
The palladium-catalysed substitution of allylic esters proceeds with a high degree of stereospecificity (Scheme 4). In the first reaction step, metallation, the leaving group is replaced by the metal with inversion of configuration *via* coordination of palladium to the allylic double bond. The subsequent reaction of the intermediate palladium-π-allyl complex, nucleophilic substitution, is dependent on the nature of the nucleophile: soft nucleophiles (stabilised carbanions and many heteroatom nucleophiles) react with a further inversion of the stereochemistry. Thus, the reaction of the allylic acetate **1** to give substrates **2** (Nu: amine, ether or malonate-type compounds) proceeds with overall retention of configuration.

If the incoming substituent is a hard nucleophile (such as hydride, nonstabilised carbon nucleophile) the attack at the carbon skeleton is preceded by coordination of the nucleophile to the palladium, and the final substitution proceeds *via cis* migration. The result is an overall inversion of configuration (**1** → **3**). There are only a few reactions known which do not follow this rule;[11] however, by carefully controlling the kinetics in these transformations side reactions can be diminished, such as those between the palladium(0) catalyst and the palladium π-allyl intermediate. Unselective alkylations with malonate type nucleophiles can be improved to give 100% selectivity.[12]



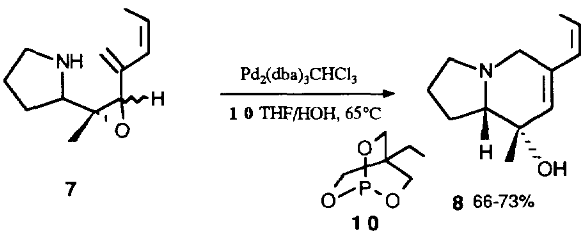
Scheme 4

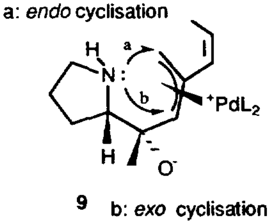
The first example of intramolecular substitution of a palladium-π-allyl complex with soft carbon anions demonstrates the general features of palladium-catalysed cyclisation of allylic substrates. Under the now 'classical' reaction conditions of strong base (NaH) followed by a palladium(0) catalyst in the presence of a phosphine ligand, the transformation proceeds with high yields and a high degree of selectivity. As mentioned before, the overall retention (double inversion) stereocontrol is characteristic of the soft malonate type nucleophile $^-CH(CO_2Me)(SO_2Ph)$.[13]



This reaction was the starting point for the still-growing development of this cyclisation methodology. An extensive review was published in 1989 by Trost,[7b] who discusses not only the synthetic aspects but also stereochemical and mechanistic questions of this type of reaction. Most of these cyclisations proceed with high chemo-, regio- and diastereoselectivities and also good enantioselectivities. Two points seem particularly interesting. Firstly, many different heteroatoms are compatible with these transformations. As well as carbon, oxygen and nitrogen have been shown to be extremely good nucleophiles in the formation of heterocyclic systems. Secondly, as well as a preference for the formation of five to seven-membered rings, medium and large rings are also easily formed. A limit on the ring size does not appear to have been reached; ring structures containing up to 26 carbons have been synthesised in good to excellent yields. This makes intramolecular nucleophilic addition an extremely versatile preparative tool for carbocyclic or heterocyclic systems. In this context, we will only discuss recent contributions which were not considered in Trost's review article.[7b]

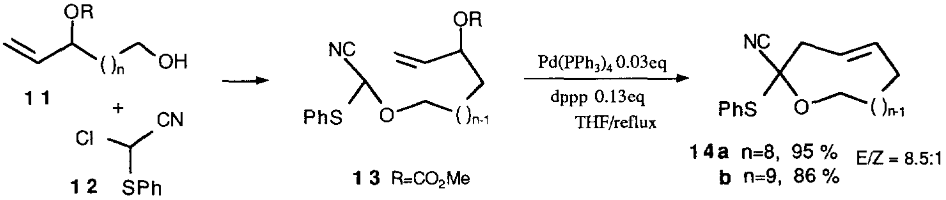
The preparative value of a synthetic method is considerably increased when the desired transformation can occur efficiently in the presence of other functional groups. This is the case for many palladium-catalysed organic reactions. The formation of annelated bicyclic amines such as **8**, a precursor of allo-Piumiliotoxin 339B, involving *endo*-cyclisation, not only shows the excellent diastereofacial selectivity which is obtained with allylic amination-cyclisations[14] but also the high chemoselectivity of this kind of transformation.





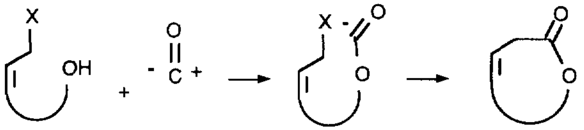
The intermediate π-allyl metal complex involves the allylic epoxide exclusively. The second, *cis* substituted conjugated double bond is not affected by the reaction with palladium. In terms of Balwin's rules[15] this reaction corresponds to a 6-*endo* cyclisation. The palladium-catalysed cyclisation takes place in a similar manner to conventional carbocyclisations in that the (unfavourable) 5-*endo* cyclisation does not occur with the appropriate allylic substrates.

The synthesis of larger cyclic compounds can be demonstrated by very recent work by Trost's group.[16] In the following macrolide synthesis, ring sizes from 14-17 carbons are easily achieved (such as **14**, n=8,9).



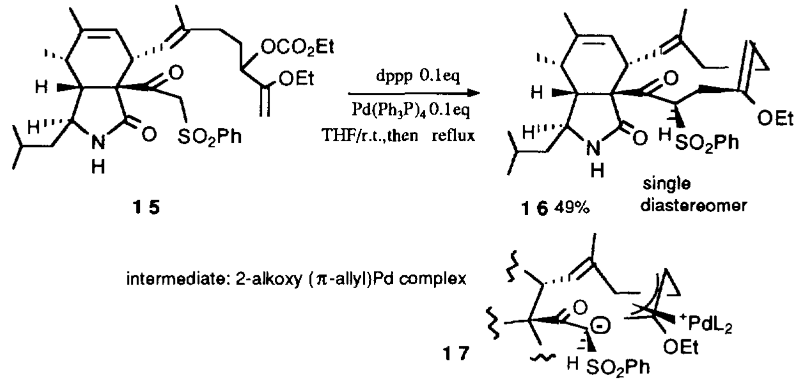
The palladium-π-allyl complex is generated from allylic carbonates of butadiene or isoprene monoepoxides. A specific carbon nucleophile, chloro(phenylthio)acetonitrile, allows the reaction to proceed under neutral conditions. It is easily hydrolysed by moist silica gel/silver nitrate to the lactone. The new carbon-carbon bond is created at the terminus of the allylic double bond in good to spectacular yields (>95%) with *E*:*Z* ratios of 4 - 8.5 : 1.[16b]

Chloro(phenylthio)acetonitrile can be considered a 1,1'-zwitterionic carbonyl synthon that is incorporated between two ends of an α-ω disubstituted carbon chain.

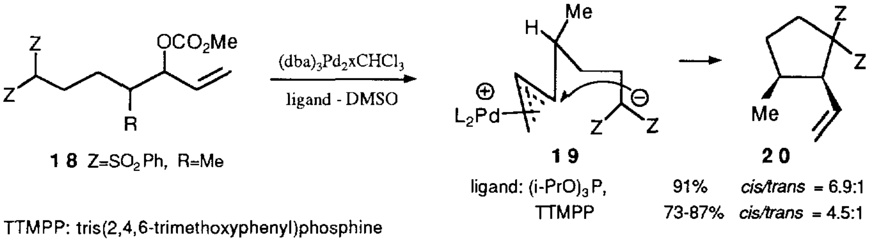


Scheme 5

The flexibility of the palladium-catalysed approach to macrocycles is demonstrated by another system involving the eleven membered ring **16** as an intermediate in the first synthesis of (-)-aspochalasin B.[16a]

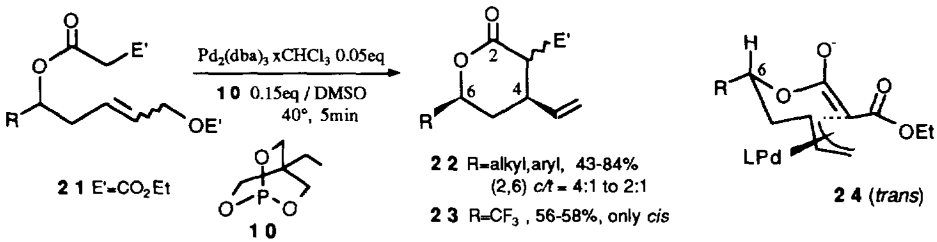


Cyclisation of **15** leads to one diastereoisomer (**16**) in which the enol ether group is found to have *Z*- geometry. This stereocontrol is a consequence of the preferred formation of a syn-π allyl intermediate (**17**). In the reaction of allylic substrates **18** (R=methyl, benzyl) to 5-membered rings, solvents like DMSO direct the cyclisation to the (thermodynamically unfavoured) *cis* **20**.[17]



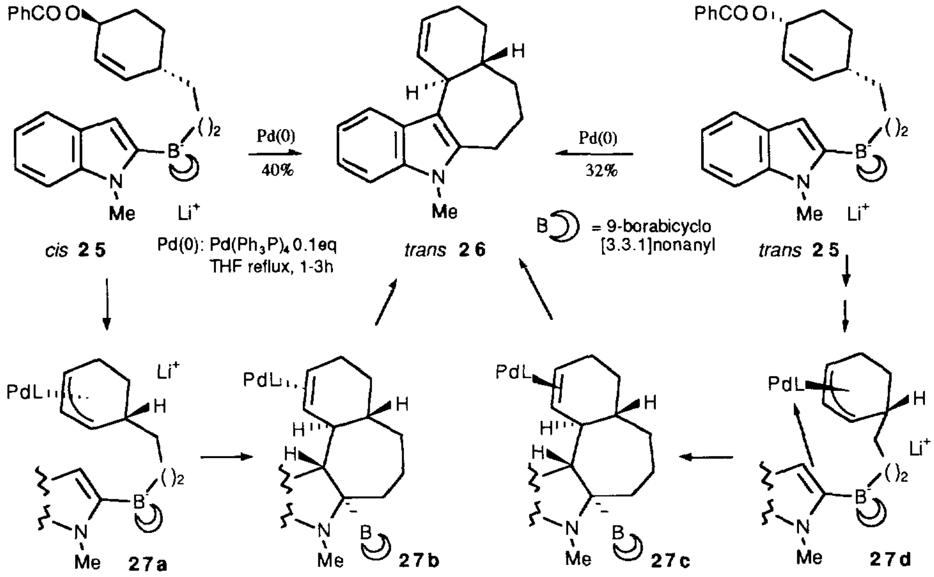
Electron-rich phosphine ligands proved particularly effective. Irrespective of their different electronic properties and steric bulk, triisopropyl phosphite and tris(2,4,6-trimethoxyphenyl) phosphine (TTMPP) give *cis/trans* selectivities of about 7:1 and 4.5:1 respectively. Apparently, these ligands, in combination with a strong solvent effect, maintain the palladium template in **19** in the (favourable) *anti*-conformation and thus control the *cis* configuration of **20**. Changing to substrates that give predominately O-alkylation, like the structurally related β-keto sulfones, the *cis/trans* ratios of the resulting tetrahydrofuran derivatives are in the same order of magnitude (6.2:1, with PPh3 as ligand in THF).

Other recently reported cyclisation reactions show selectivities caused by substituents. In the intramolecular lactonisation of allylic alcohol derivative **21**, an unusual substituent effect is observed caused by the trifluoromethyl group in the homoallylic position.[18]



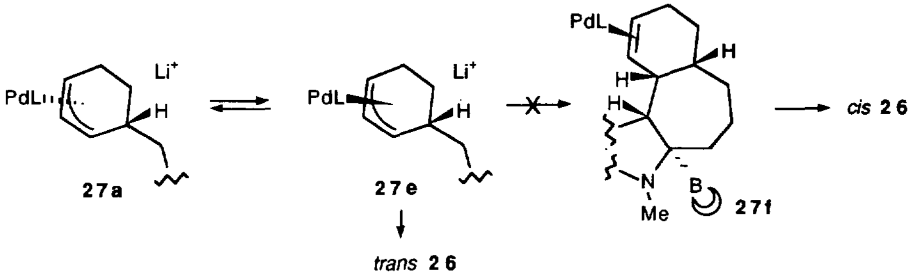
Whereas unsubstituted olefins lead, in a rapid (5 min. at 40°C) reaction, to cyclised lactones (**22**) with the moderate *cis/trans* selectivity of 2-4:1, the CF3 substituent directs the cyclisation to the 4,6-*cis*-disubstituted δ-lactone **23** exlusively. The absence of any *trans*-isomer in **23** can be rationalised by the strong electronegative effect of the trifluoromethyl group rather than simple sterics, since the isopropyl group, with comparable sterics, gave moderate *cis/trans* ratios of no better than 4:1. The irreversible reaction proceeds through a favoured transition state **24** (*trans*, R in pseudo-equatorial position) which involves the smallest possible steric and electronic repulsions between R (CF3) and the enolate anion.

In a one-pot cyclisation for [*b*]-annelated indoles, the final *trans* stereochemistry of **26** is controlled by

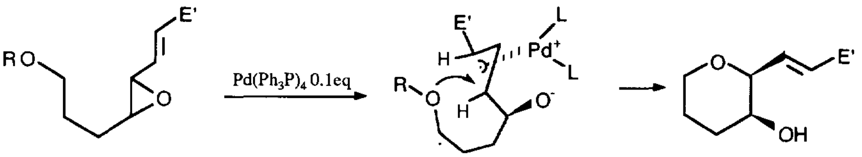


both steric and electronic factors.[19] Both *cis* and *trans* 1,4-disubstituted allylester **25** yield the same product *via* palladium π-allyl intermediates and borate complexes. The cyclisation step is accompanied by a 1,2-alkyl migration from boron to carbon. Steric repulsion between indole and cyclohexene rings in a putative *cis*-isomer (such as Pd π-complex **27f**) prevents the formation of *cis* **26**. The mechanistic interpretion of the transformation of *trans* allylic substrates to *trans* indoles presumes coordination of palladium to indole in the intermediate complex **27d** and *cis*-migration of the latter to an allylic carbon.

Another explanation could be the isomerisation of π-allyl intermediates **27a** and **27b** before the cyclisation step.



The formation of saturated oxacyclic systems from allylic substrates *via* the addition of alcohols to π-allylic intermediates has low selectivity and gives fairly poor yields, for example when unsaturated hydroxy epoxides **28** are treated with catalytic amounts of $Pd(PPh_3)_4$ in THF (**31**, 45% yield, *cis*/*trans* ratio = 74 : 26).[20] However, the absence of regio- and stereocontrol seems to question how the oxygen nucleophile is generated. In this regard, the desilylation of silylethers gives more reactive oxygen species. When *t*-butyl-diphenylsilyl (TBPS) ethers are used, an improvement of regio- and stereoselectivity (>98%) is combined with considerably higher yields, from 45% up to 90%. This is true for *cis* and *trans* epoxides. The *trans* isomer **29** leads to the *cis*-2-alkenyl-3-hydroxytetrahydropyran **31**, whereas the corresponding *cis* epoxide results in *trans* substituted tetrahydropyran products. An interesting solvent effect decreases the reaction times from several hours in THF (11.5 h) or acetonitrile (14.5 h) to a few minutes in chlorinated solvents $CHCl_3$ (5-10 min.) or CH_2Cl_2 (5-6 min.). When combined with the Sharpless epoxidation, this stereoselective cyclisation should give an easy access to chiral pyrans, which are present as oxygen heterocycles in numerous pharmacologically interesting natural products.



E'=CO_2Et

28 R=H,

29 R=TBPS,

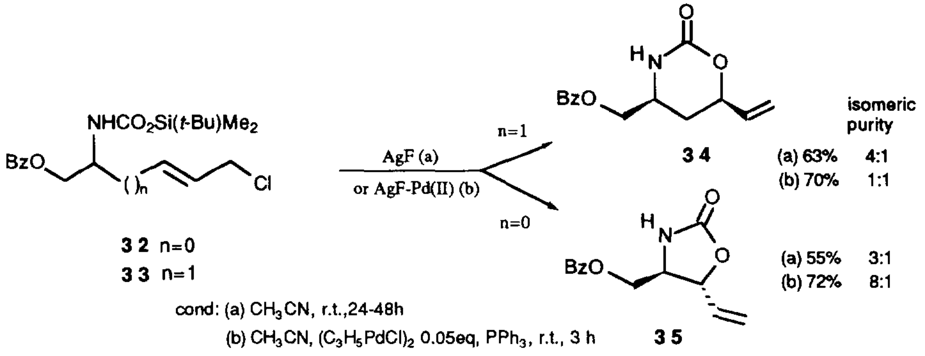
30

31

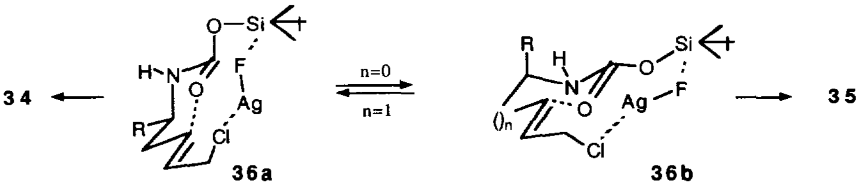
solvent: THF, 4h, *c/t*= 74:26 (y: 45%)

solvent: CH_2Cl_2, 5min, *c/t*= >99:1 (y: 90%)

In the intramolecular trapping of the *tert*-butyldimethylsiloxycarbonyl group with allylic esters, the presence of fluorinated reagents seems to be important. Cyclic carbamates, present in natural products as 1,2 or 1,3 hydroxyamino structural units, have been shown to be accessible from allylic chlorides of type **32**.

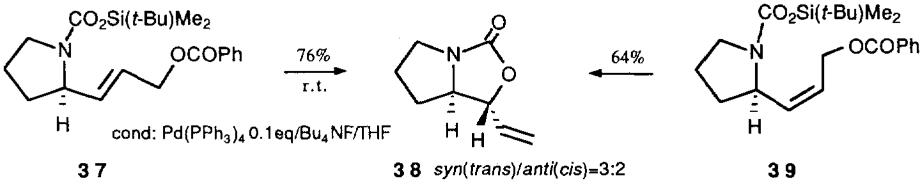


Activation and cyclisation, with moderate *cis*/*trans* stereoselectivity of 3-5:1, require fluoride in form of silver fluoride.[21] The addition of a catalytic amount of η^3-allyl palladium chloride dimer has two contradictory effects, according to the chain length of the allyl chloride. In the case of the 6-membered ring **34**, obtained from **33**, the stereoselectivity of the AgF catalysed reaction drops to zero. The opposite effect is observed for heterocyclic cyclopentane compounds **35**, from **32** (n=0), with *anti*/*syn* (*trans*/*cis*) selectivities reaching values of 15:1 in the best case.



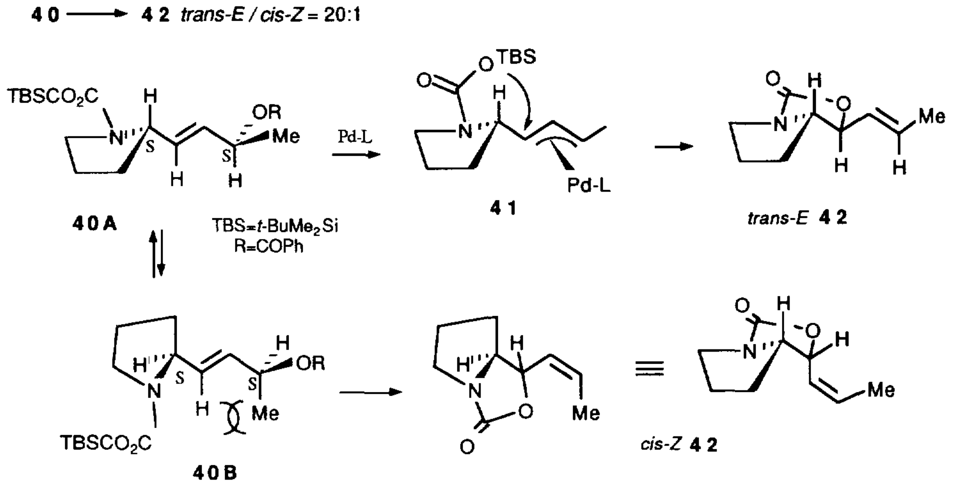
The difference in *syn* selctivity (6-membered ring) and *anti* selectivity (5-membered ring) is explained by two different transition states (**36a** and **36b**), leading to one or the other stereochemistry, and following a *syn* S_N2' mechanism. A good argument in favour of this mechanism is the unreactivity of Z-allyl chlorides.

The extension[22] of this cyclisation to cyclic carbamates and allylic esters (**37** or **39**) with palladium (in fair to good yields) still depends upon the presence of fluoride, and the reaction with 0.1 equivalent of Pd(0) requires 1 equivalent of Bu4NF.



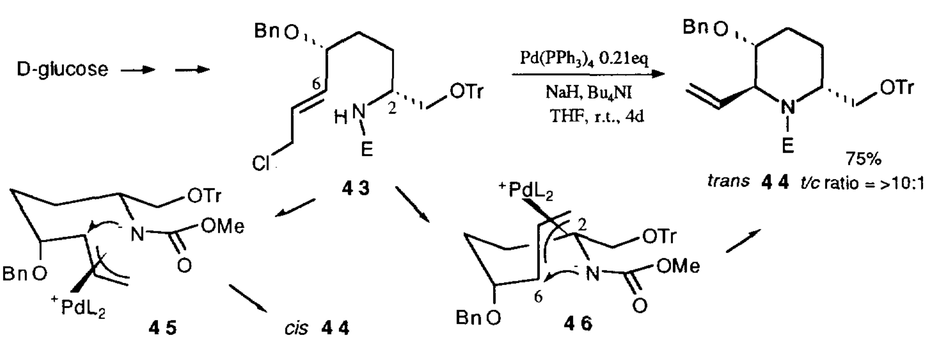
The best results were obtained with benzoate as a leaving group. The selectivities are comparable to those of the allylic chlorides;[21] however, the new conditions permit cyclisations of hitherto unreactive Z-allylic esters (yields 25-60%) as well as secondary allylic substrates. Annelated bicyclic substrates (**38**) have been obtained with moderate stereoselectivity.

The reaction of secondary allylic esters proved to be highly stereoselective, and reactions with pure isomers of a proline derivative such as (*S*,*S*)-**40** allowed mechanistic investigations.[22]



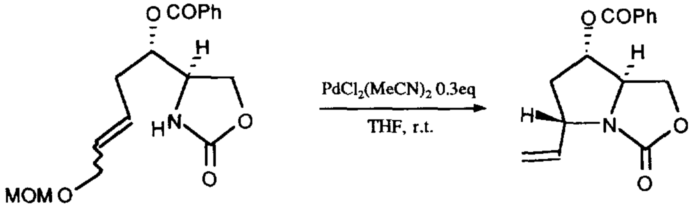
40A **41** *trans-E* **42** **40B** *cis-Z* **42**

The *trans-E* major isomer of **42** (isomeric ratio 20 : 1) is compatible with the following mechanism. As is well known for intermolecular reactions,[12] both formation and substitution of the π-allyl intermediates proceed with complete inversion of configuration. This means that the siloxycarbonyl group attacks at the same side as the benzoate leaving group. The formation of the major isomer (*trans*-E **42**) is controlled by the $A^{1,3}$ strain in the ground state conformation of **40** with the nucleophile and the leaving group at the same side of the molecule. From the corresponding (*S*,*R*) enantiomer, logically the main cyclised carbamate is in the *cis-E* form (ratio *cis-E*/*trans-Z* = 7:1). The diastereo-controlling factor in the intramolecular *N*-amidation of **43** is the benzyloxy group in position 5.[23]



43 *trans* **44** **45** *cis* **44** **46**

This *trans* selective piperidine formation is the key step in the stereospecific synthesis of prosopsis alkaloids from chiral pool sugars. The stereoselective formation of the pyrrolido[1,2-*c*]oxazolidin-3-one system **48** involves an allylic moiety.[24] The exclusive formation of *trans* -2.5-disubstituted pyrrolidines from either (*Z*)- or (*E*)-alkenes, as well as the mechanism in this *N* → π cyclisation, has not been further rationalised.

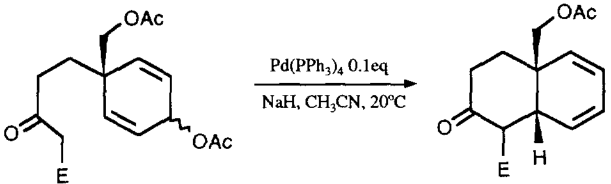


(*E*)- or (*Z*)- (-)- **47**

(+)- **48** 85 and 70% (96% ee)

Enantioselective allylic substitutions, involving π-allyl palladium intermediates have seen an explosive increase of investigation in the last couple of years.[25] A broad spectrum of phosphorus, nitrogen and other heteroatom-centred chiral ligands have allowed the chiral induction to be improved, at least in simple alkylation reactions, to nearly 100%.[26] The formation of optically active cyclic systems is an integral part of this development.

Chiral decalin derivatives are a structural feature of many bioactive molecules, such as steroids. Shibasaki and co-workers, who had contributed to the enantioselective synthesis of such bicyclic systems *via* asymmetric Heck reactions[1,27] were also able to show the feasibility of an intramolecular π-allyl approach to these systems. The diastereoselectivity was first checked by performing the reaction in the absence of chiral ligands.[28] Exclusive formation of *cis*-decalin derivatives **50** was seen from both stereoisomeric allylic acetates **49**. This implies inversion of the intermediate π-allyl complex and conformation-controlled formation of the *cis* isomer **50**.



+ 4% of a bridged bicyclic product **51**

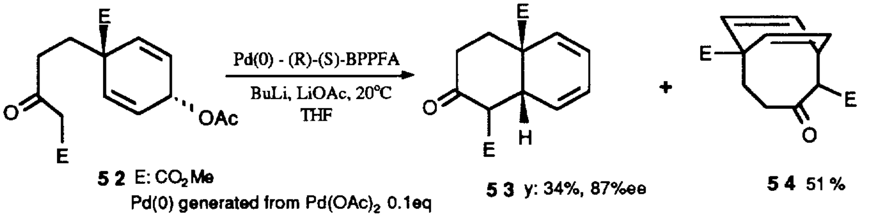
49 1:1 mixture, E: CO$_2$Me

50 96%

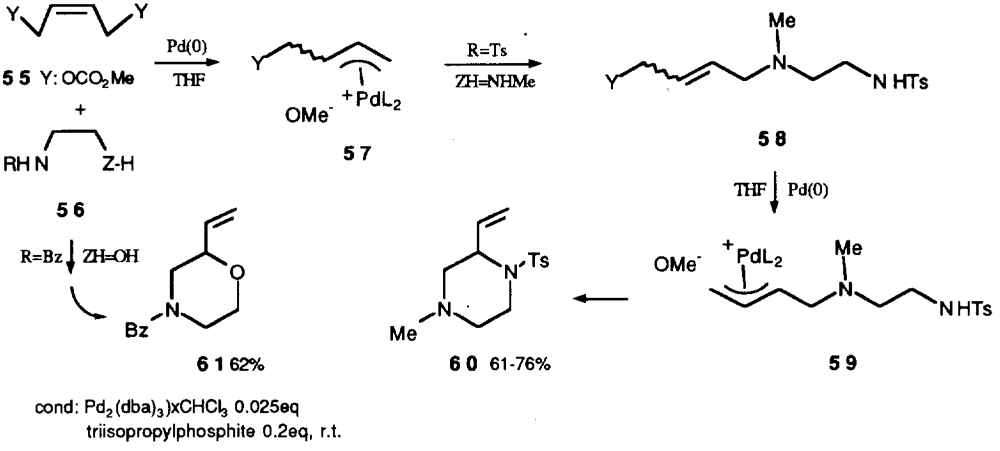
In the (achiral) cyclisation of **49**, the concentration of the phosphine ligand is important and the best yields of **50** were obtained without the use of any additional phosphine.

In order to achieve asymmetric cyclisation of **52**, the conditions had to be changed and the chiral ligand BPPFA had to be added.[29] Unfortunately, this increased the formation of the achiral bridged bicyclic **54**.

However, the chiral induction in the decalin **53** (yield 34%) is very high (87% ee), slightly better than obtained with CO2Me (E) as the angular substituent (**53**), compared to CH2OAc in **50** (yield: 15%, 71% ee).

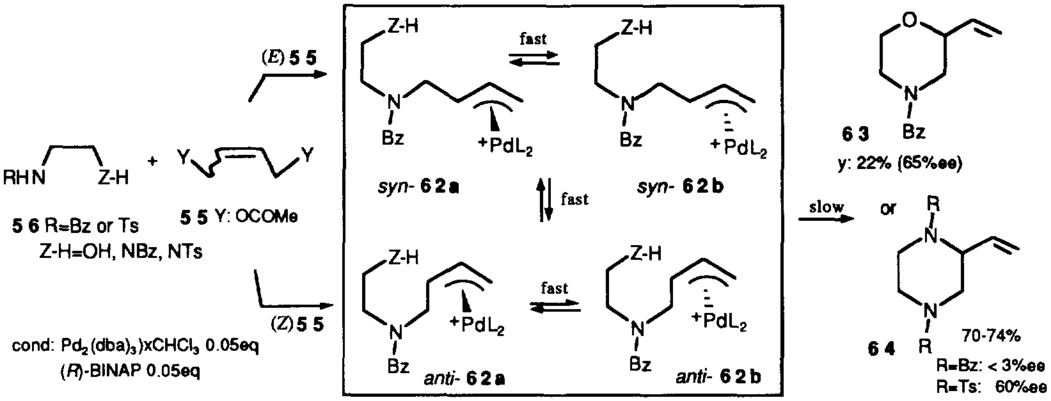


Bifunctional, 1,4-disubstituted 2-alkenes **55** (Y = carbonate or acetate) are readily double-substituted with heteroatom or carbon nucleophiles *via* π-allyl palladium complexes, provided the substituents are palladium-specific leaving groups. Saegusa[30] used this principle for the synthesis of diaza- and oxaza heterocyclic rings.

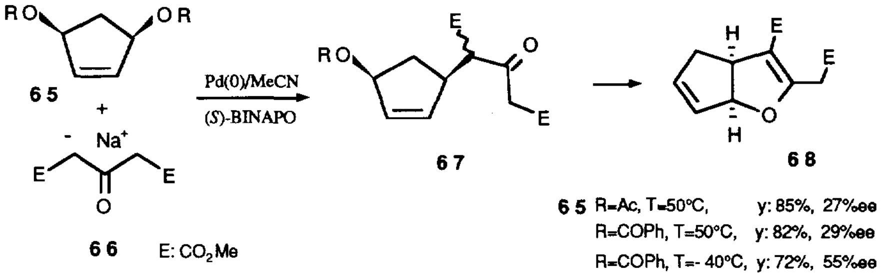


In the diamine or aminoalcohol, at least one amino group needs to be substituted. With two methylene groups connecting the amines or amino-alcohol, the cyclisation is regioselectively directed to six-membered-rings (piperazine **60** and morpholine **61**) containing an exocyclic vinyl group. Conversely, diamines containing three and four methylene groups lead to internal cyclononene and cyclodecene heterocycles respectively.

A couple of years later, Hayashi and co-workers[31] reported the asymmetric construction of morpholines and piperazines by means of a chiral version of these reactions. Inductions of at best 73% ee for morpholines and 60% ee for piperazines have been observed, depending on reaction conditions, substituents on heteroatoms and the heterocycle being formed, as well as the chiral phosphine ligand (BINAP). The chiral induction is controlled by the rapid equilibration of the four possible intermediate palladium π-allyl complexes *syn-anti*-**62a** and **62b**.



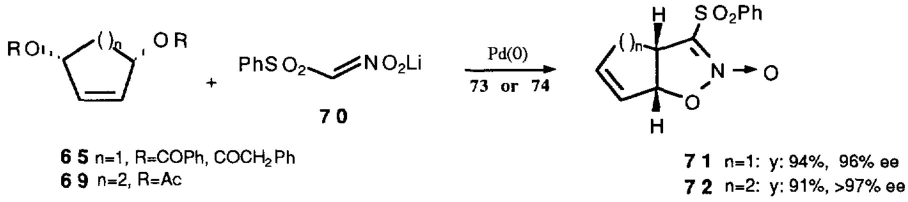
The double substitution of cyclopentenediol derivatives **65** with dimethyl sodio-3-ketoglutarate in the presence of Pd(PPh3)4 is a way to synthesise bicyclic cyclopentene derivatives **67**.[32] By the use of the chiral diphospine BINAPO, chiral inductions of up to 55% ee have been achieved.



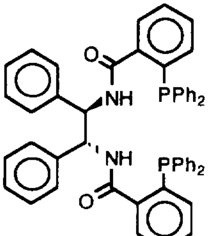
kinetic resolution:	67	68
time: 35h	(35%) 41% ee	(14%) 30% ee
time: 72h	(18%) 52% ee	(54%) 34% ee

The influence of the leaving group and temperature on enantiomeric purity suggest the importance of the oxidative addition step; however, the overall situation is more complicated since a kinetic resolution during the cyclisation step decreases the overall ee.

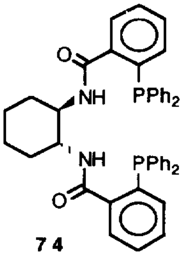
In a conceptually similar cycloalkylation reaction, chiral isoxazoline-2-oxides have been obtained by Trost and co-workers.[33] The bicephalic C,N-nucleophile is the lithium salt of [(phenylsulfonyl)methylene]-nitronate, and proves to be highly efficient in Pd(0) catalysis.



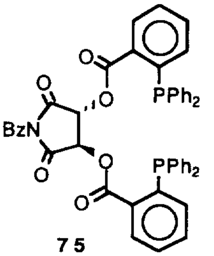
The heterocycles **71** and **72**, which are interesting building blocks for the asymmetric synthesis of carbanucleosides, have been synthesised in extremely good enantiomeric excess for the 5-membered 2-ene-1,4-diol derivatives **65** (n = 1, 96% ee) because of a new class of *modular asymmetric ligands* **73 - 75**. Even better asymmetric induction (> 97% ee) has been achieved with cyclohexene diesters **69**, a result which contrasts sharply with the enzymatic reactions of these systems.



73

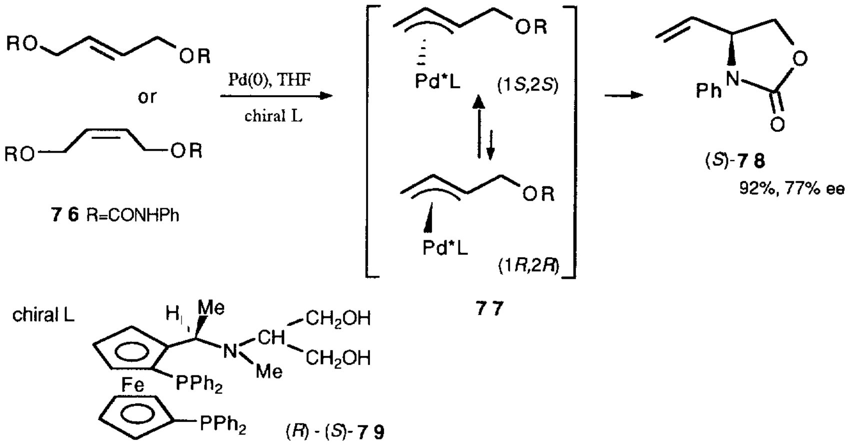


74

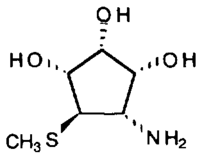


75

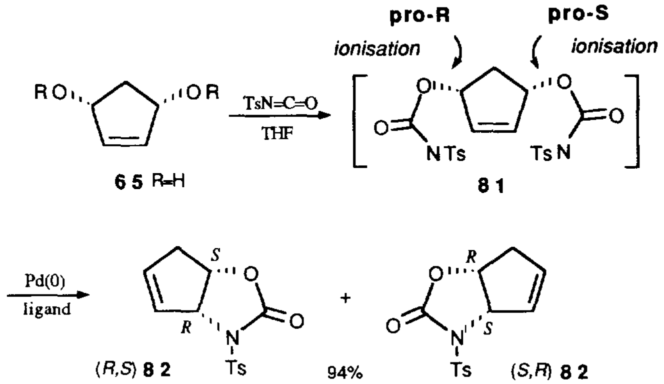
Hayashi, Yamamoto and Ito had demonstrated in 1988 that asymmetric cyclisation of 2-butenylene dicarbamates **76** leads to chiral vinyloxazolidines **78** in high yields and good enantiomeric excess (up to 77% ee).[34] More conventional chiral diphosphines are fairly inefficient (chiraphos: 18% ee, p-tolBINAP: 27% ee) than (hydroxyalkyl) ferrocenyl phosphines **79** with a chiral aminoalcohol lateral chain. The enantioselectivity results from the (fast, compared to the cyclisation step) equilibration of the the diastereomeric intermediate palladium π-allyl complexes.



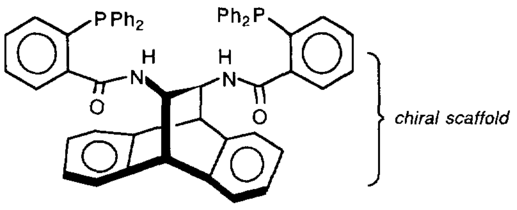
The same reaction has been found to be very useful for developing a general and flexible route to hetero-polyfunctionalised cyclopentanes such as mannostatin A **80**.[35] These glycosidase inhibitors are potential *anti*-HIV agents which could have therapeutic application. The *meso cis* cyclopenten-1,4-diol **65** (R=H) is transformed *in situ* into the bis tosylcarbamate **81** and subsequently, *via* cationic monopalladium π-allyl complexes, to the bicyclic vinyloxazolidines **82**. The two leaving groups are enantiotopic, and a chiral Pd-phosphine catalyst should lead to chiral induction. Ordinary chiral phosphines such as BINAPO only gave 28% chiral induction.[35] This kind of ligand when coordinated to the metal complex, is not able to direct the nucleophile that substitutes the π-allyl complex opposite to the Pd.



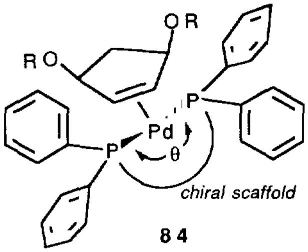
80



Previously in 1982, Hayashi and coworkers[36] presented ferrocenyl ligands like **79** that carried side arms which were able to direct nucleophiles and provoke optical inductions of up to 96 % ee in allylation, and up to 77% ee in asymmetric cyclisation reactions.[34] Trost proposed an original solution with a new class of ligands based on 2-(diphenylphosphino)benzoic acid of type **73** - **75** and **83**. The enantiomeric excess of one enantiomer (**82**) could be raised to 40-88% ee with these ligands by stepwise changes in the ligand structure[37] (ligand **83**, 88% induction).



83

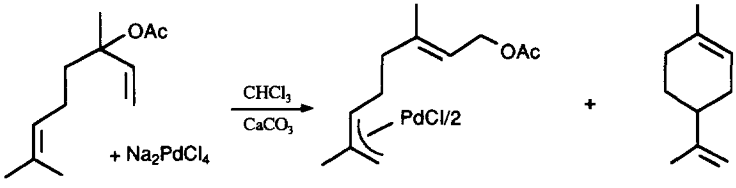


84

The ionisation of one enantiotopic allylic group is found to be the enantioselective step, and a large 'bite angle' θ" in Pd-alkene coordination compound **84** (with chiral diphosphine **83**) is required for good induction. This is caused by a subtle accommodation of rigidity of the amide/ester part structure and stereochemistry of the two-carbon part in the chiral scaffold of **83**. With these conceptually new ligands, not only can high inductions be achieved, but also the sense of the chiral induction becomes predictable.

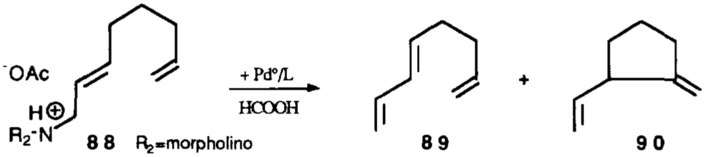
2.1.2 Palladium-ene reaction

In the palladium(II) catalysed oxidation of olefins, the olefin acts as an efficient nucleophile with respect to the metal. In catalytic allylation reactions, the first step consists of forming a palladium(II) species by oxidative addition to a substrate such as an allylic ester. We have seen that this species is easily substituted by carbon and heteroatom nucleophiles. It is of great interest that olefins can behave as carbon nucleophiles in the same way, and be the active functional group for efficient carbocyclisations. The first notice of this type of reaction appeared in the early 1970s; however, it was not exploited for organic synthetic purposes at the time:[38]



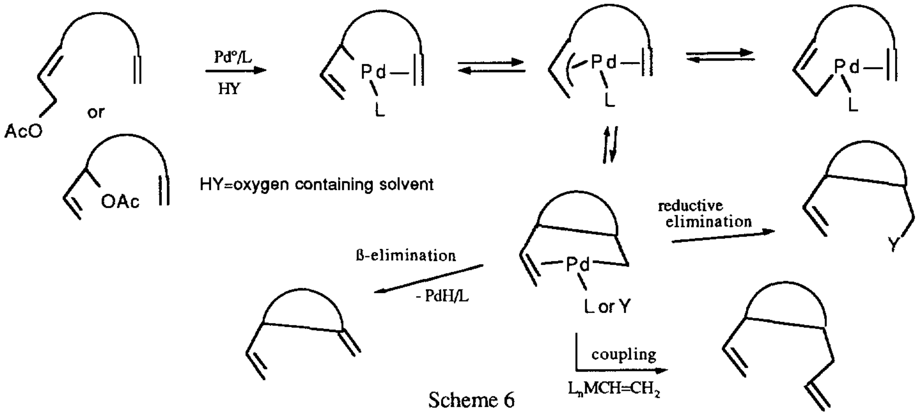
85 86 two Pd-complexes and uncomplexed organic material 87

At this time, the researchers were interested only in the preparation of metal complexes, and the isolation of cyclised limonene (**87**) from linalyl acetate (**85**) was merely recorded as part of the uncomplexed organic material. Another research group studied the reactions of 1,6-dienic allylic substrates,[39,40] and cyclisation of the allylic amine **88** was observed in addition to simple elimination:



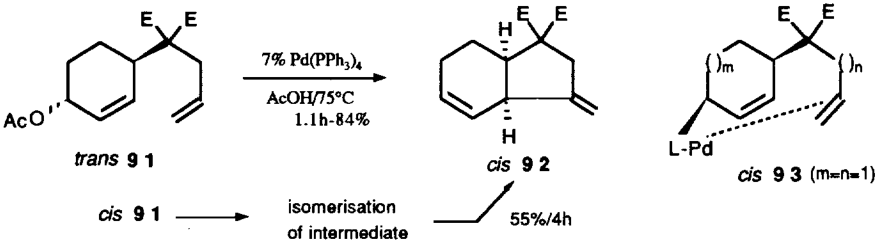
88 R_2=morpholino 89 90

Some years later, Oppolzer and co-worker developed this kind of cyclisations, which are now called palladium-ene reactions.[9] The principle of these reactions is set out in Scheme 6.

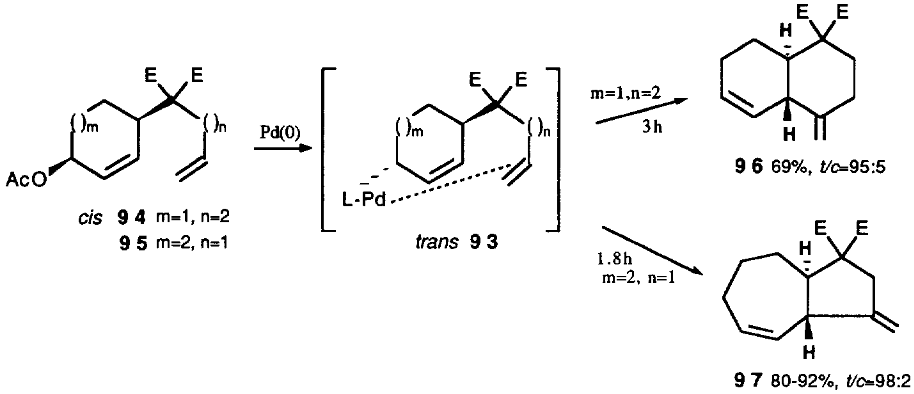


Scheme 6

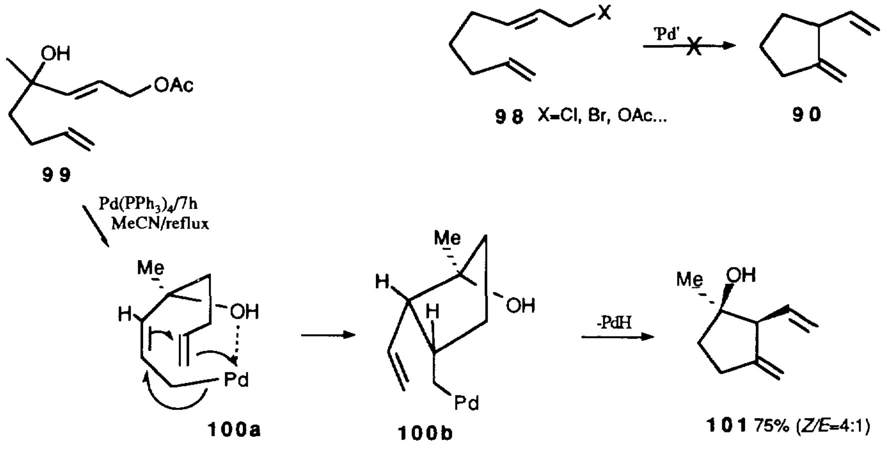
One important point concerns the solvent, which has to contain oxygen functionality (THF, methanol or acetic acid). Acetic acid appears to be the best choice. The cyclisation of *cis* and *trans* **91** demonstrates the synthetic utility of this interesting reaction, and also the stereochemical implications of the method. The formation of hydrindane system **92** is controlled by the allylic palladium intermediate **93** (m=n=1), which has the palladium in *cis*-relationship relative to the inserting double bond. This means that *trans* **91** should isomerise to *cis* **91**, since a *trans* oriented enophile seems to be highly unfavourable for coordination in the corresponding metallic intermediate.



It has been shown that, in molecules where *trans* interactions between the metal and enophilic double bond are possible, cyclisation takes place with the predicted high stereoselectivity. Larger rings or longer side chains increase the flexibility of the system, and the conversion of **94** and **95** to *trans* fused bicyclodecanes **96** and **97**, respectively, is possible without noticeable isomerisation.



The strong interaction of an oxygen atom in the intramolecular palladium-ene reaction was also exploited by Negishi.[41] He discovered that simple allylic dienes **98** could not be cyclised under several palladium(0) conditions. The effect of the oxygen atom in promoting cyclisation was shown by molecules such as the *tert.* alcohol **99** which cyclised easily to give **101**. The oxygen not only enables the reaction to take place, but also influences the stereochemistry of the products. The *cis*-relationship of vinyl and OH in **99** suggests the coordinated palladium intermediate **100a**, leading to the *Z*/*E* **101** with diastereomeric ratio of 4:1.

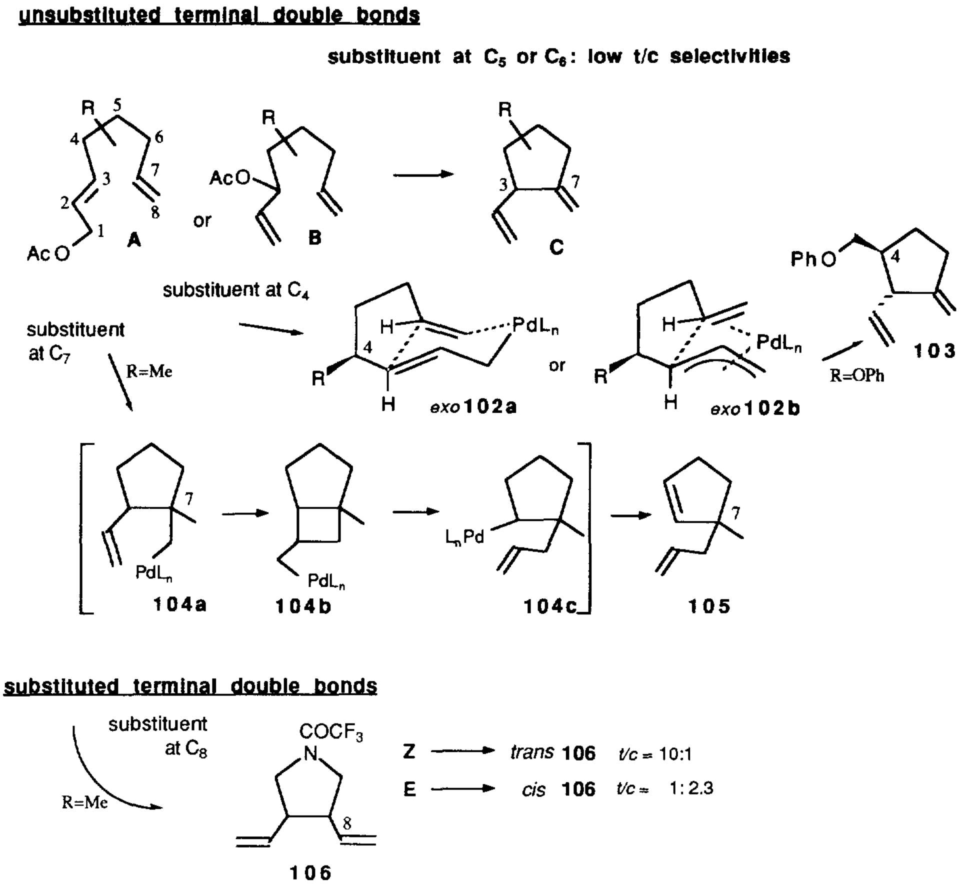


In other compounds, such as the one leading to a bicyclo[3.3.0]bicyclooctane skeleton, this intramolecular coordination is less favoured and the products are 1:1 mixtures of stereoisomers.

Oppolzer defined various structural implications that can influence the outcome of the metallo-ene cyclisation, the most important target being control in non-rigid aliphatic systems. Different outcomes of previously investigated reactions are detailed in Scheme 7.[9,42] Five or six-membered rings are formed according to the chain length. Usually, the cyclised diene contains both a vinyl- and an exomethylene double bond. Substitution of the terminal (non-allylic) double bond alters the final Pd-H ß-elimination to a bis vinyl compound **106**. The formation of **106** shows also the compatibility of the reaction with heteroatoms like nitrogen or oxygen. Non-terminal substitution of the alkene group necessarily leads to an intermediate **104a** with the quarternary C-CH_2-Pd arrangement, and thus metal-hydride β-elimination cannot take place. These systems rearrange *via* carbometallation/retrocarbo-metallation to diene **105**. From the different carbons in the saturated part of the ring being formed only substitution at C_4 is suitable for the creation of high *trans*/*cis* selectivities in the cyclised products **103** (*t*/*c*=12.5:1).

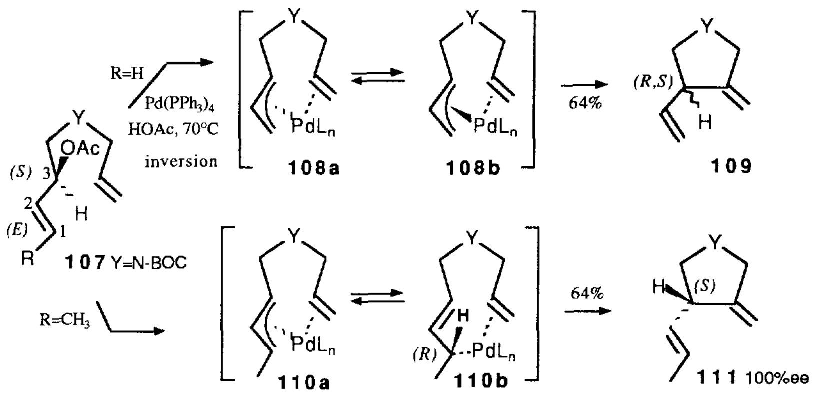
In this case, palladium seems to have a preference for an exo transition state (of the ene-metal or π-allyl intermediate **102a** or **102b**, respectively) leading to the *trans* product **103**.[43] Substitution at C_5 or C_6 has only a moderate effect on the stereoselectivity of the reaction. With any of these substituted (C_4, C_5 or C_6) substrates, nickel complexes are much better catalysts when high stereodifferentiation is required.[42a]

One major point concerns the complete control of absolute stereochemistry in some reactions. Chirality transfer (ee >96%) has been described in compounds such as *trans* **94** (m=0, n=1).[9a] Indeed, the chiral information has been transmitted from the carbon bearing the leaving group to the newly created bridgehead position. The question of whether this could also be possible in acyclic systems has been answered by the reactions of optically active substrates **107** and **112**.[42b]

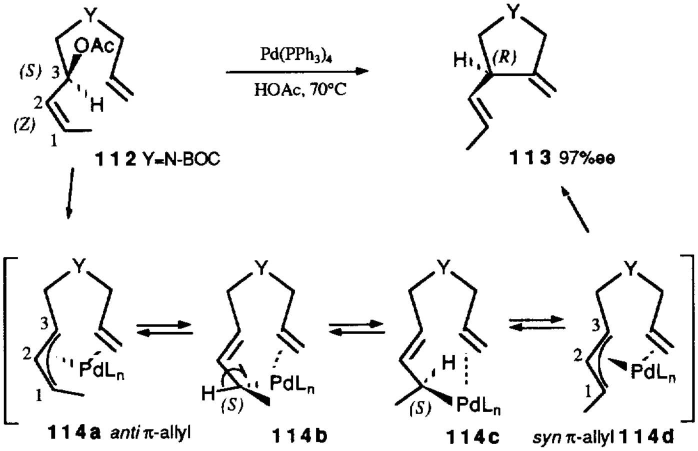


Scheme 7

In diene **107**, the pathway of the asymmetric reaction depends strongly on the substitution pattern of the allylic double bond.



As shown by the fact that product **109** is racemic, lack of substitution leads to complete loss of stereochemical configuration at carbon-3, a fact that is attributed to the easy isomerisation of π-allyl intermediate **108**. When substituting the terminal CH_2 by an alkyl group, the steric strain prevents the allylic intermediate from racemising.



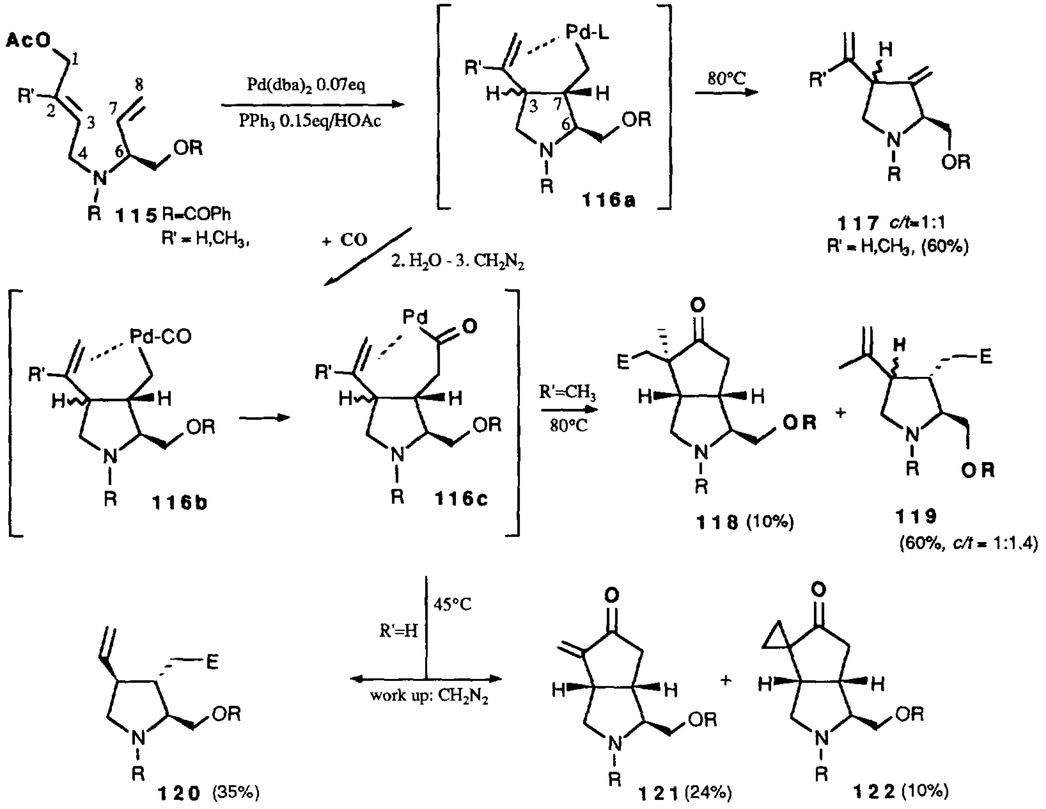
112 Y=N-BOC

113 97%ee

114a *anti* π-allyl **114b** **114c** *syn* π-allyl **114d**

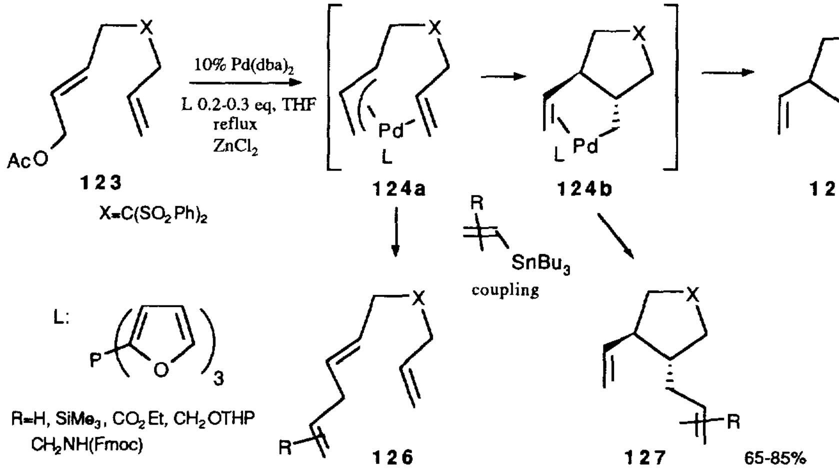
In the case of *E* configuration in **107** (R=Me), the inversion of configuration in the first metallation step is not reversed in the cyclisation (olefin insertion step), and the chiral integrity is thus transferred to the cyclised product **111** (100% ee). In case of a *Z* substituted allylic part in **112**, the *anti* π-allylic intermediate **114a** rapidly isomerises to the more stable *syn* system **114d** *via* a π-σ-π mechanism and rotation of the palladium-ene intermediate **114b**. The stereochemical result of this operation is that the original stereochemistry at carbon-3 is recreated by an overall double inversion in the reaction **112** → **113**. From these interesting stereochemical results, it should be noted that the non-chiral *cis-trans* isomerism of the double bond directs the chirality of the final products to *S* or *R* configuration.

Oppolzer's Pd(0)-catalysed formal ene reaction has been extended to the synthesis the α-kainic acid system.[44] The approach is applied to two starting dienes **115** which differ in the substituents on the allylic acetate. Under Pd(0)/HOAc conditions, a *cis/trans* mixture of the five-membered cyclic amines **117** is formed. This means that the side chain at C_6 is not able to control the stereochemistry at C_3 (cf. Scheme 7). However, the addition of carbon monoxide reveals several interesting aspects of this system: (i). the palladium elimination step is modified by the creation of a carboxylate group at C_8, (ii). the stereocontrol imparted by the configuration at C_7 and (iii). the possibility of a subsequent tandem type[2,4] second cyclisation reaction. The stereocontrolled carbonylation-olefin insertion sequence, leading to **118** or **121**, requires a *cis*-relationship of the lateral chains at C_3 and C_7 in the monocyclic intermediate palladium-σ species **116a**.

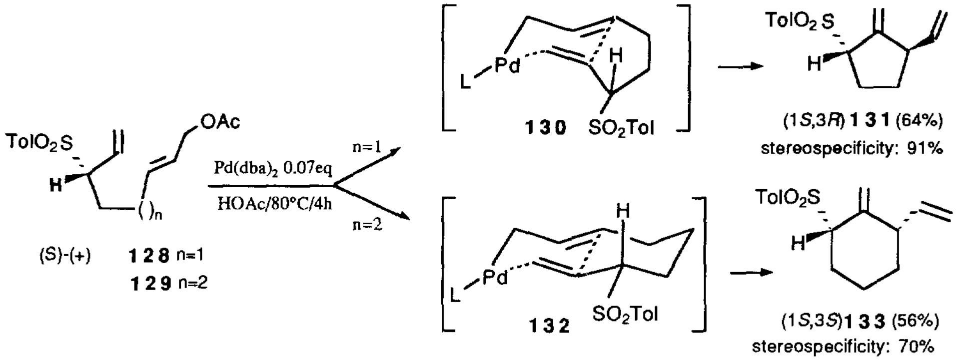


In case of the comparable reaction (R'=H), the *trans/cis* form of **116a** leads to the annelated *cis* azabicyclic product **121** whereas the *trans/trans* isomer of **116a** is simply carbonylated to yield (after hydrolysis and diazomethane treatment) the 4-vinyl pyrrolidine ring **120** exclusively. On substituting the allylic acetate (R'=CH_3), the second cyclisation is slowed down and the normal carbonylation to give **119** (60%, *cis/trans*=1:1.4) is the favoured reaction for both intermediates **116a**. Only 10% of the bicyclic amino ketone **118** is found, and as the rate of the first cyclisation is slowed down in this case, more forcing conditions (80°C) are necessary in order to produce any cyclic product.

Another cyclisation-capture[2] process (coupling) with vinylic metal species (M = Sn)[45] has been described (Scheme 7). Under the classical conditions, dienyl acetate **123** (X=$C(SO_2Ph)_2$) affords the cyclised β-elimination product **125**. However, a monocyclic palladium-σ-species **124b** can be trapped by vinyl tributylstannanes in the presence of 2 equivalents of $ZnCl_2$ to give the cyclisation/coupling product **127**. When cyclisation/coupling is attempted with the sterically more demanding stannanes, only diene **125** is found. The other limiting factor is the relatively small differentiation between cyclisation (**123** → **124b**) and allylic coupling (**123** → **124a**) of dienyl acetates **123** with X = $C(SO_2Ph)_2CH_2$, $C(COOMe)_2$ or NTs. With these substituents, non-cyclised allylic coupling products **126** are favoured.

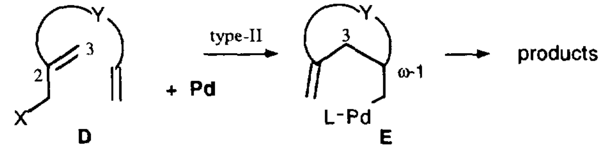


Chiral allylic sulphones can be transformed to optically active trisubstituted cyclopentane and cyclohexane derivatives.[46] The stereochemical relationship of the substituents at C_1 and C_3 is *trans* in **131** and *cis* in **133**. Once more, a chirality transfer reaction proceeds with high stereospecificity. The degree of this depends on the palladium catalyst as well as on the ring size of the ring system to be formed.



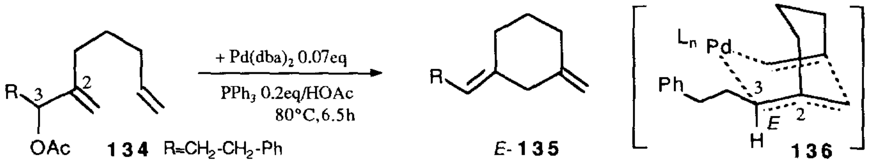
Relatively low selectivities are observed with $Pd(PPh_3)_4$ (39-41%), whereas the $Pd(dba)_2$ complex catalyzes the transformations with 70% (six-membered ring) and 91% (five-membered ring) stereoselectivity respectively. The stereochemical pathway can be rationalised by the intermediacy of annelated bicyclic transition states **130** and **132**. In the cyclisation of **128**, a *cis* five-six-membered transition state **130** with the tosyl group in the favourable *endo* position results in the *trans* (1*S*,3*R*) cyclopentane ring **131**. The one carbon-longer chain in **129** leads to a *trans* decalin-type transition state **132** with the tosyl group in the equatorial position. The orientation of the SO_2 tolyl substituent is the same in both systems; however, the pseudo-ring fusion in the transition state is different. As a consequence, the 1,3-stereochemistry in **133** has to be *cis* (absolute configuration 1*S*,3*S*). It is interesting to note that the tosyl group in the $Pd(dba)_2$ complex is the high selectivity inducing factor, even in a system where selective reactions seem to be unfavourable with palladium[42a] (Scheme 7, low *t/c* selectivities with C_6-substituted 1,6-dienes). Chiral cyclopentane derivatives and heterocyclic analogues have been obtained from carbohydrate templates.[47]

Less well investigated, but potentially also of interest with respect to chiral problems, are cyclisation reactions of substrates in which the chain with the second double bond is connected to the central carbon of the allylic group.[9a] These type-II reactions lead to cyclic bis exomethylene systems.



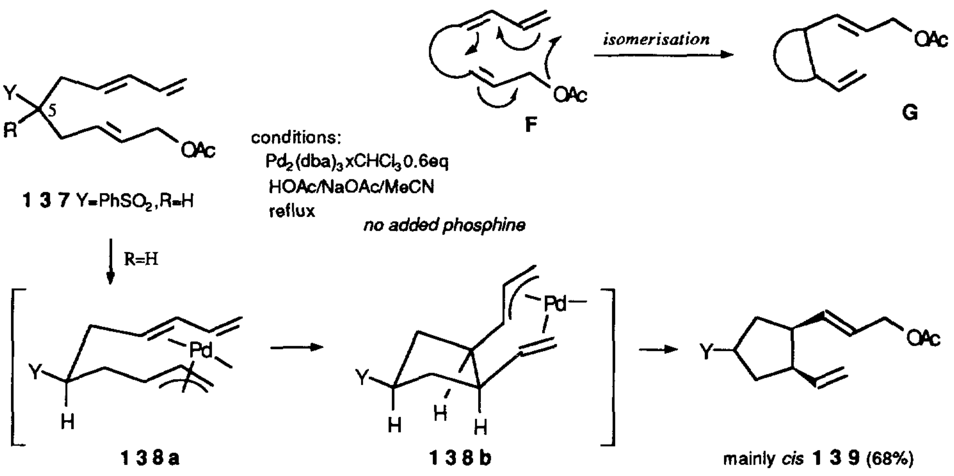
Scheme 8

From the cyclisation of diene **134**, it is evident that the regioselective ring closure takes place at the less substituted allylic part. The high degree of *E*-configuration in the substituted exomethylene group can be rationalised by involving a bridged bicyclic transition state **136** (*E*-configuration, substituent in the *'endo'* position).



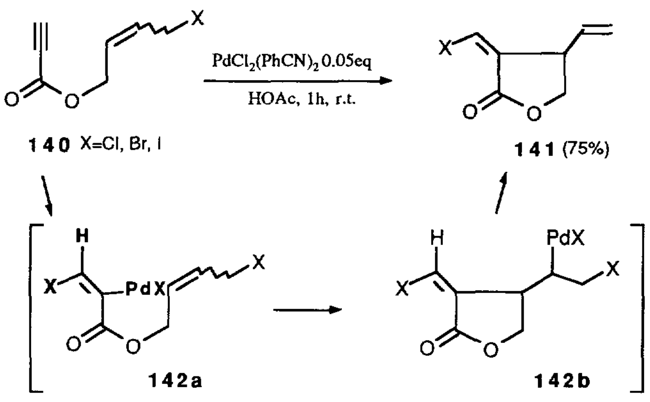
Reactions with other unsaturated carbon nucleophiles are less developed. In case of the combination of allylic acetate and 1,3-diene, the cyclisation developed by Trost and co-workers,[48,49] is effectively a metal-catalysed isomerisation in the presence of acetic acid (Scheme 9). The *cis*-diastereoselectivity is very high when monosubstituted compounds like **137** (R=H) or cyclohexene derivatives that lead to annelated bicyclo[4.3.0]nonane compounds are cyclised. Indeed, the insertion of the 1,3-diene into the first π-allyl complex **138a** generates a second cyclic π-allyl complex **138b** which is readily substituted by the acetoxy nucleophile; the *cis* relationship at C_3-C_7 reflects the concurrent coordination of Pd to the vinyl and the π-allyl group in **138b**.

The presence of two bulky groups at C_5 in **137** (for example E or SO_2Ph) seem to destabilise intermediates of type **138b**, and as a result *cis/trans* mixtures of the cyclised diene are obtained. The stereochemistry of the original allylic acetate has no influence on the reaction; however, the lack of reaction of the system when THF, DMSO or chloroform are used as solvents, as well as a similar non-reaction in the absence of phosphine ligands in the catalyst should be mentioned.



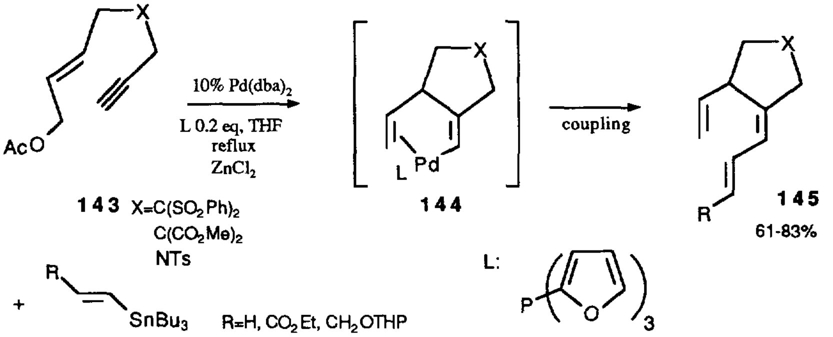
Scheme 9

Alkynes have also been reacted with the allylic system. In **140**, two allylic esters are connected with the intention of constructing α-methylene lactones *via* cyclisation of the corresponding propiolate.[50] The palladium chloride bis benzonitrile catalyst does not react with the allylic carboxylate, and only the triple bond and the allylic halide are involved in the cyclisation reaction.

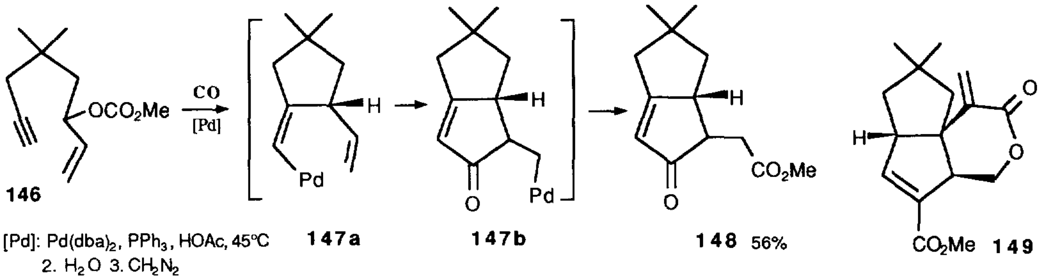


α-(Z)-Halomethylene-ß-vinyl-γ-butyrolactones **141** are formed by *trans*-halopalladation of the triple bond followed by insertion of the allylic double bond. Thus, this acetylene reaction does not seem to follow the usual π-allyl reaction pathway.

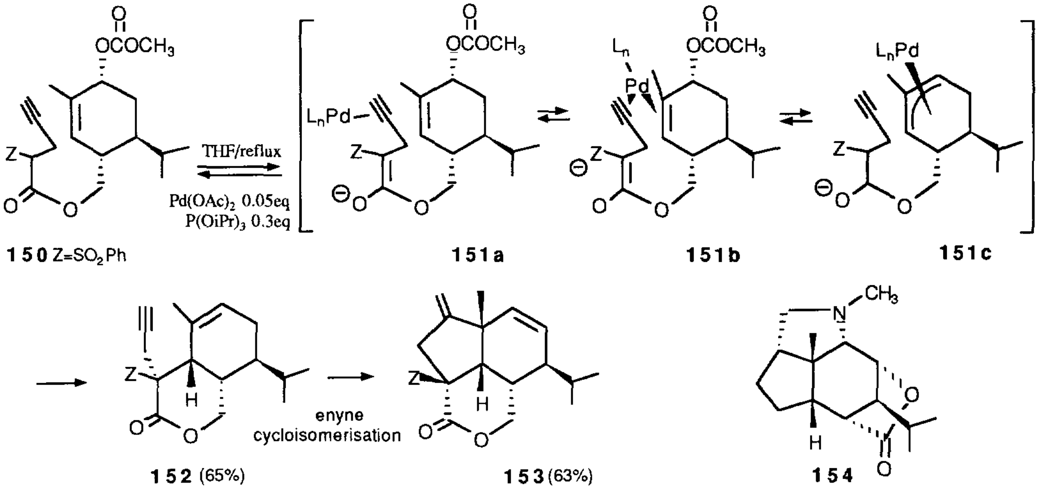
Metallo-ene-type cyclisation proceeds faster with an alkyne enophile and does not encounter the problem of β-elimination (Scheme 6). This fact turns out to be advantageous when the reaction is terminated by (1-alkenyl)(tributyl)stannane capture[45] such as in the cyclisation-coupling of **143** in the presence of ZnCl$_2$.



Cyclised vinyl-Pd species **147a** can also be trapped (twice) by CO to afford bicyclic ester **148** in good yield and high stereoselectivity. This Pd-catalysed tandem[2] intramolecular alkyne allylation/carbonylation reaction has been used in the elegant and straightforward synthesis of an advanced key intermediate in the synthesis of racemic pentalenolactone **149**.[51]



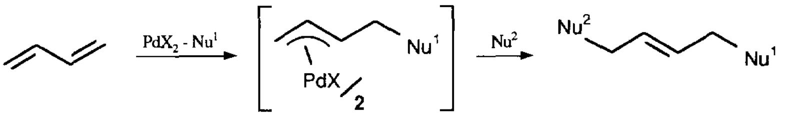
Unusual chemoselectivities are observed in the highly diastereoselective cyclisation of an allylic ester, **150**, that normally should follow known allylic alkylation methodology.[52]



In Trost's asymmetric synthesis of (-)-dendrobine **154**, a compound used in the Chinese herbal medicine, two palladium-catalysed cyclisation reactions (allylic alkylation and enyne cycloisomerisation[53]) should lead to the skeleton of **154**. Of the two intermediates that have been suggested to be involved in the first of these ring closure reactions, only the supposedly less reactive species reacted to give the desired cyclic product. It turned out that the acetylene group was vital for the cyclisation of **150** as it acted as a remote binding site for the palladium and thus promoted ionisation. The acetylene side-arm is long enough for the metal to lie in the appropriate *trans* configuration with respect to the leaving ester-group, even in this case where sterically hindered reactions would not usually occur. This useful principle could find application in other metal catalysed reactions.

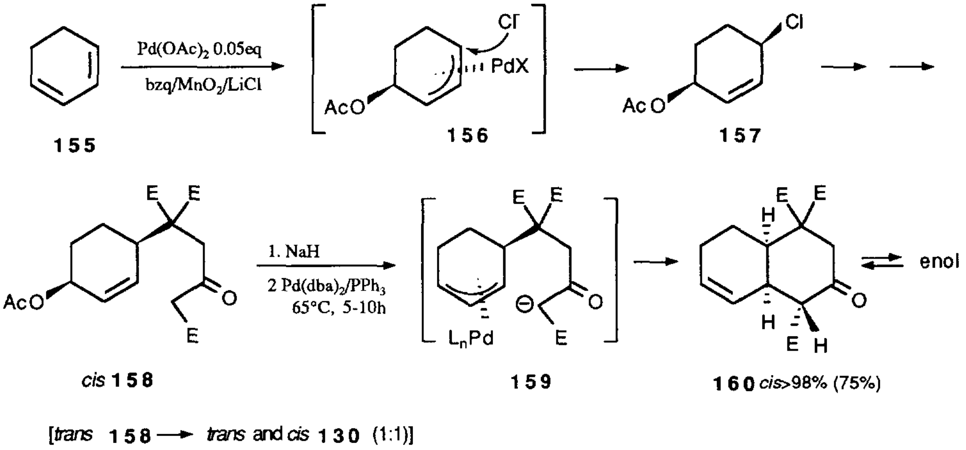
2.2 Addition to conjugated and cumulated dienes

The reaction of palladium(II) with conjugated dienes selectively generates π-allyl complexes with concomitant incorporation of a nucleophile. The easy and rapid substitution of the metal species by a second nucleophilic agent leads to bis substituted monoalkenes (Scheme 10). The high degree of regioselectivity (1,4-addition) as well as *cis* or *trans* stereocontrol according to reaction conditions are also highly successful in intramolecular reactions. Bäckvall and co-workers[6m,10] have developed this reaction into a powerful, synthetically useful reaction for the synthesis of differentially functionalised allylic substrates. For example, high chloride (LiCl) concentration in acetic acid solvolytic conditions permits the controlled 1,4-disubstitution of 1,3-dienes with both Cl and acetate nucleophiles in the same molecule.

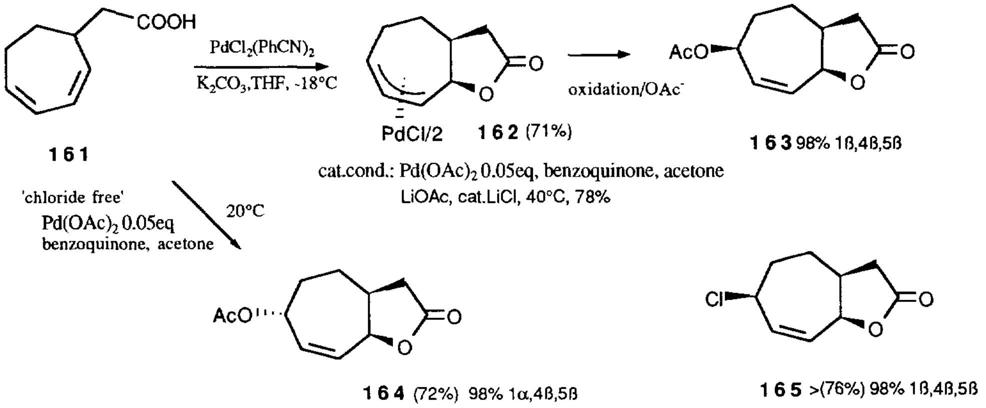


Scheme 10

In their first set of reactions,[54] this chloroacetoxylation is used to synthesise the *cis* chloroester **157** *via* **156**. The annulation[10] through the π-allyl intermediate **159** follows known pathways for intramolecular allylic alkylation. The stereoselectivity (overall retention) is remarkably high (98%) in the case of *cis* **158**. When the *trans* substituted six-membered ring **158** is cyclised, complete isomerisation takes place. This unselective alkylation is unusual and reflects secondary side reactions that are not understood.[12] In the case of seven-membered ring compounds, the reaction of both *cis* and *trans* 1,4-disubstituted alkene is stereospecific. If, more straighforwardly, the second nucleophile is incorporated in the starting diene, direct cyclisation is possible using the 1,4-disubstitution protocol.[10] Both oxygen[55,56] and nitrogen nucleophiles[57] react successfully. In all these reactions, the virtues of the intermolecular bisfunctionalisation of 1,3-dienes are evident: increased regio- and stereocontrol as well the free choice of *cis* or *trans* stereochemistry and the ability to vary the nucleophiles according to the reaction conditions. In annulation reactions,[10,55-57] the degree of stereocontrol is even higher since the configuration of a further carbon is completely ensured as the ring junction is always *cis*.



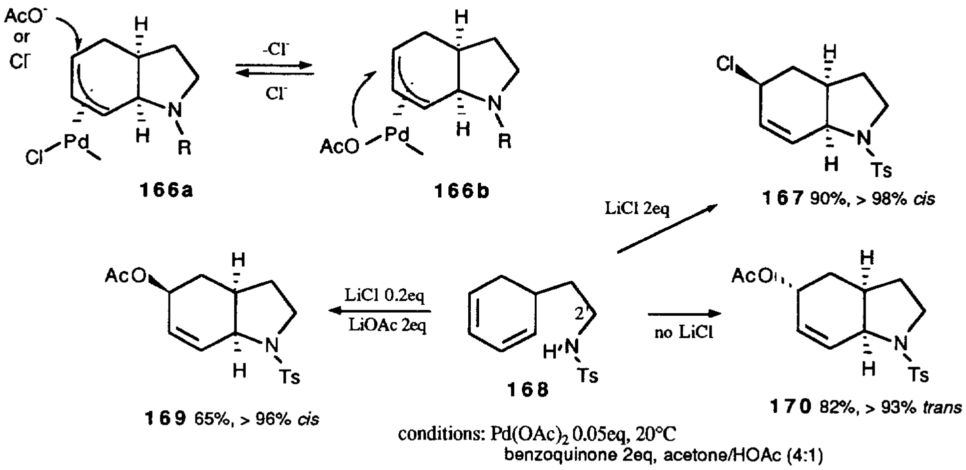
Lactonisation reactions of olefins are well known. The potential of Bäckvall's acetoxy- or chlorolactonisation of conjugated dienes lies in the possibility of directing the cyclisation to either *cis* or *trans* substituted lactones.[55] The stereochemical 'joker' is the lithium chloride which determines the chloro- or acetoxylactonisation and, at the same time, directs the overall addition of carboxylate and acetate either under chloride free conditions to *trans* addition (**164**), or with catalytic amounts of LiCl to *cis* addition (**163**); alternatively high chloride concentration leads to the addition of chloride instead of acetate as second nucleophile (**165**). It is interesting to note that in these catalytic reactions, palladium π-allyl intermediates **162** can easily be isolated, thus supporting the mechanistic considerations (*vide infra*).



The lactonisations have been performed with six- and seven-membered rings, and only in case of the *cis* acetoxylactonisation of the corresponding cyclohexadiene acid is the stereoselectivity less high (*cis*/*trans* = 3:1).

Selective oxidations using amides as nucleophiles are less common, and have not been described hitherto with conjugated dienes. The intramolecular 1,4-addition of nitrogen-centred nucleophiles to the *cis* annelated five-membered ring occurs with four different amido groups (NHTs, $NHCO_2Bz$, NHAc and NHCONHBz) under slightly acidic conditions.[57]

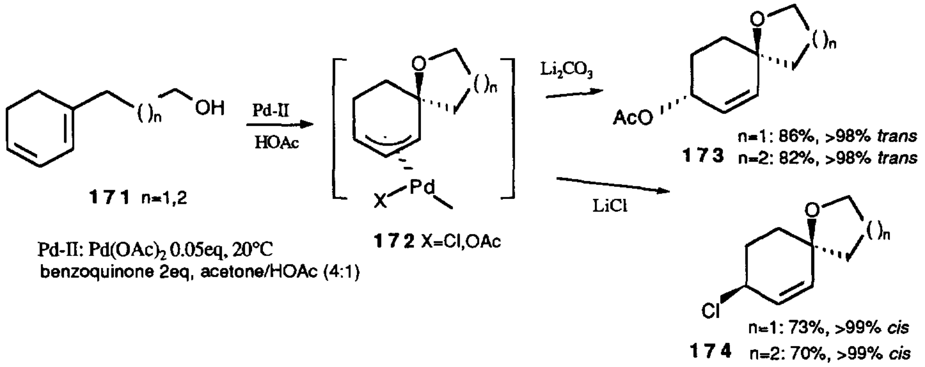
Scheme 11



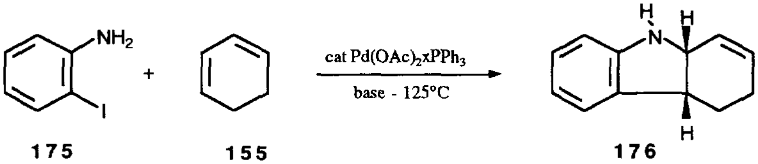
conditions: $Pd(OAc)_2$ 0.05eq, 20°C
benzoquinone 2eq, acetone/HOAc (4:1)

In contrast to lactonisation, the highest selectivities are seen in the cyclohexadiene series. In the first step, a *trans* addition of Pd(II) and the nitrogen nucleophile generates the *cis* annelated azabicyclononane system. In this, the palladium coordinates to the olefinic bonds from the side opposite to the lateral chain. The controlling activity of Cl^- is obvious from Scheme 11: chloride, if present, blocks the coordination site of the palladium and thus orients any second nucleophilic attack *trans* with respect to Pd, a high chloride ion concentration favouring the attack of Cl^-. If the chloride concentration is low, the second nucleophile will be the O-acetyl group. Unlike the chloride ion, acetate has a dual nucleophilic character; it may also coordinate to the palladium and give rise to a *cis* migration. Indeed, this is only possible when chloride (the better coordinating group) is absent from the reaction. Nonetheless, one restriction should be mentioned: the position of the amide carbonyl group is important since cyclisation is kinetically disfavoured for amides of type **168** with the amide oxygen at C2'.

The palladium-catalysed cyclisation of 1,3-dienes is not limited to the construction of fused ring systems. The recent oxaspirocyclisation reactions of dienic alcohols **171** are synthetically interesting.[56a] The stereochemical integrity of *trans* acetoxy and *cis* chloro oxaspirocyclic compounds **173** and **174** respectively is still extremely high with six-membered cyclic dienes. The presence of lithium carbonate promotes the activation of the hydroxy group. However, the overall *cis* addition of the two oxygen functions is not very efficient in this case (34% yield, 76% *cis*).

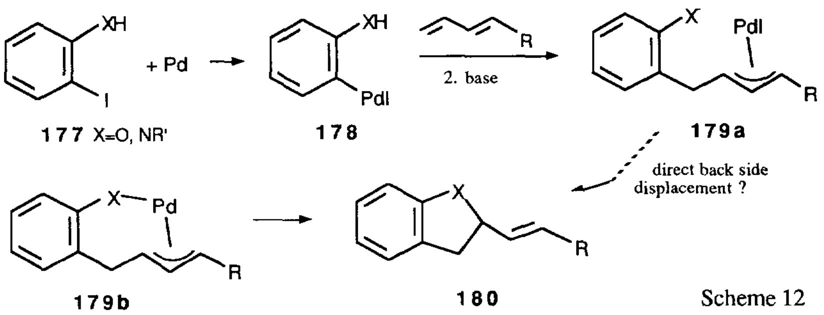


Heterocycles can also be obtained from the heteroannulation of conjugated diolefins under Heck-type reaction conditions[58,59] *via* formal 1,2-cycloaddition to 1,3-dienes.



The initial observation of Dieck and coworkers[58] that o-iodoaniline reacts easily with cyclohexadiene to give the azabicyclic olefin **176** has recently been elaborated by Larock[59a] to a quite general synthesis of annulated aromatic oxygen and nitrogen heterocycles. The reaction is general for a variety of 1,3-dienes (cyclohexadiene, isoprene, terminal *cis*- or *trans*-substituted butadienes) and the nucleophiles can be phenols and anilides as well as benzylic alcohols and tosyl- or acetoxy amides.

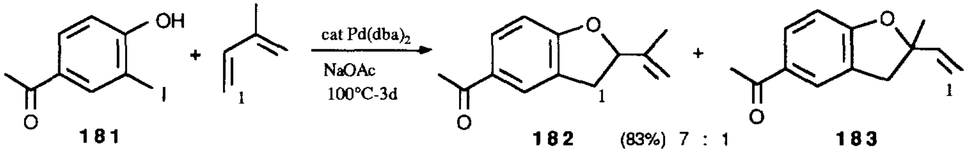
The π-allyl species **179a** is formed through the addition of aryl palladium complex to the 1,3-diene, whereas the cyclisation step consists of the nucleophilic displacement of Pd by the heteroatom X (O or NR'); in the case of cyclic dienes, this step is a *cis* process *via* coordination of the heteroatom to the palladium prior to the insertion reaction (**179a** → **179b** → **180**).



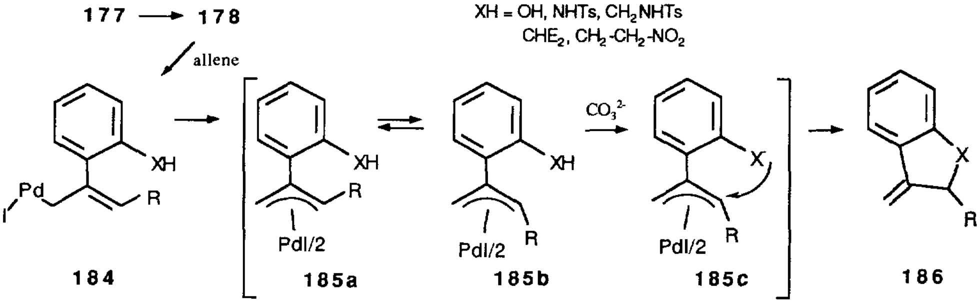
Scheme 12

With butadienes the possibility of direct backside nucleophilic displacement of **179a** cannot be discounted (Scheme 12).

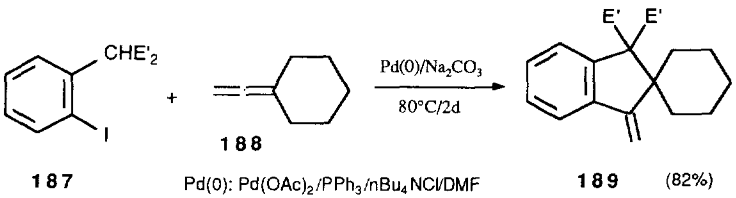
This process is potentially a valuable tool for natural product synthesis of compounds such as dihydrobenzofurans and alkaloids. An example is the synthesis of the toxic ketone **182** isolated from white snakeroot. It is directly accessible by this method in good yields (83%) and with high (7:1) regiochemical integrity from isoprene and the acetyl iodophenol **181**



An interesting extension of this annulation involves the use of cumulated dienes.[60,61]

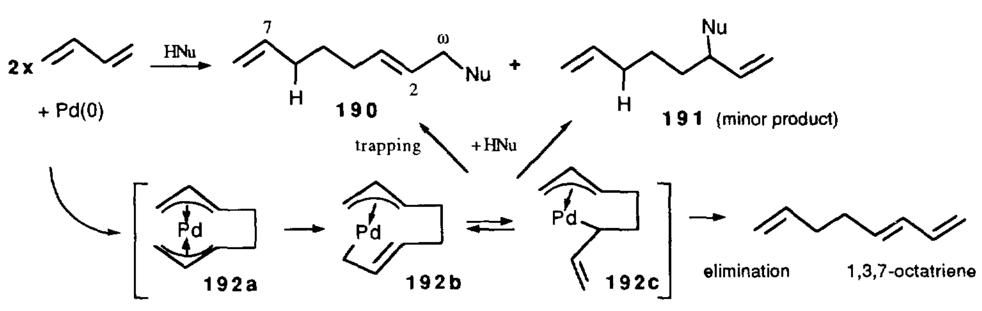


In contrast to the cyclisation of non-aromatic allenes,[62] the cyclisation with substituted aryl halides proceeds *via* π-allyl-palladium intermediates. The nucleophilic groups XH are similar to those in the annulation of 1,3-dienes.[58,59] Hetero- as well as carboannulation[59b] (XH = CHE_2 and nitroethylene group) to five- and six-membered ring systems is possible. The regioselectivities are usually high, and in the case of the cyclopentane ring the annulation always takes place across the more highly substituted C-C double bond. This is the most striking feature of the allene addition.



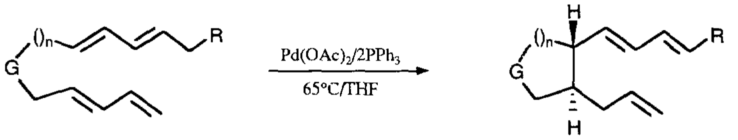
2.3 Telomerisation of tetraenes

A new carbocyclisation reaction is based on the palladium-catalysed telomerisation of butadiene in the presence of nucleophilic trapping reagents.



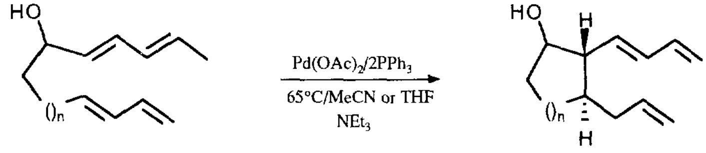
Scheme 13

When two butadienes contained in the same carbon chain (3 or 4 carbons between the 2 dienes), trapping of the π-allylic palladium intermediates leads selectively to *trans* 1,2-disubstituted five- and six-membered rings, respectively. The new ring junction in **194** is predominantly *trans* with two unsaturated lateral groups in the 1,2 positions, and good to very good diastereoratios (*t*/*c* = 5:1 to >20:1).[63]



193 n=1, 2; G=CE$_2$', NSO$_2$Ar, R=H, Et **194** 75-95%, *t*/*c* = 19:1

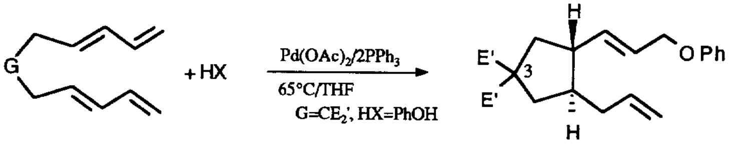
In the same way, alcohols **195**, in acetonitrile or THF and in the presence of 5-10 equiv. of triethylamine, afford cyclised products **196** in good yields with compounds with substituents in an all-equatorial arrangement predominating (1.6/1 for n=1 and 5/1 for n=2).



195 n=1, 2 **196** 62-76%

The reaction can be performed in the presence of trapping reagents such as phenol leading to similar yields and good selectivity. No stereocontrol is exerted by the asymmetrical group G in **197**.

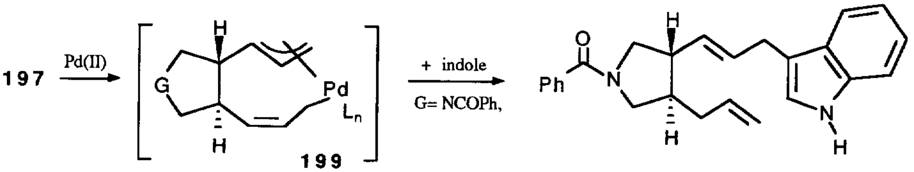
The controlled dimerisation of butadienes by palladium(0) catalysis (palladium acetate triphenylphosphine) is a general reaction leading to acyclic products, such as octatriene or, when nucleophiles are present, to monosubstituted octadienes with the substitutent at either the terminal (ω) or ω-3 position. This extensively studied reaction[64] has also been shown to be very efficient for the stereoselective construction of functionalised cyclopentanes and pyrrolidines.[65]



197 $G=CE_2'$,CE'CN, NCOPh,CSO_2Ph,

198 94%, t/c = 15:1

A large variety of nucleophilic trapping reagents HX lead to the regioselective formation of terminal (*trans*) allylic ethers, amines, acetates, sulfones, nitromethanes or malonates. The formation of a second carbon-carbon bond in allylic nitromethanes or malonates has been extended to other carbon nucleophiles like enamines.[66] This permits regioselective incorporation of cycloalkanones at the terminal allylic position, even when the enamine is part of an aromatic system (such as indole, **200**).



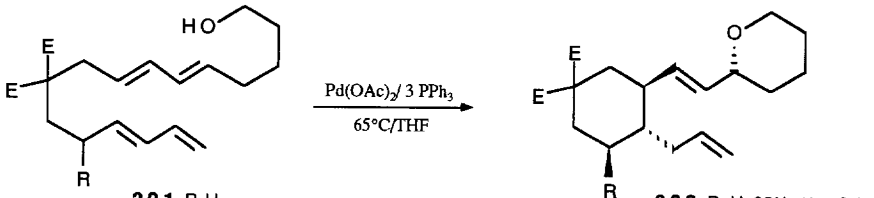
199

Pd(II):$Pd(OAc)_2$ 0.05eq/L/CH_2Cl_2/40°C

200 L=$(o\text{-}Tol)_3P$, 19h, 91%, t/c = 11:1

The *trans/cis* selectivities (>20:1) are appreciable. The influences of both ligand and solvent have been studied, and the formation of a triene (the cyclic pendant to 1,3,7-octatriene, Scheme 13) that is sometimes observed in THF or benzene can be avoided by the use of chlorinated solvents (chloroform, dichloromethane) or acetonitrile.

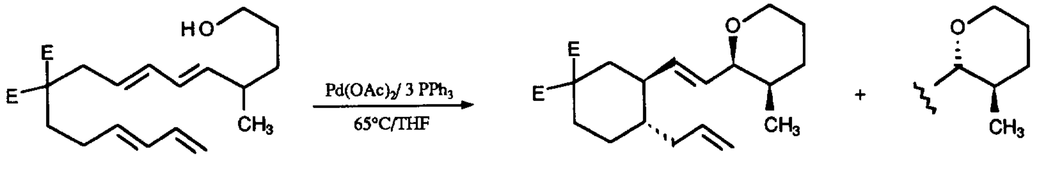
Another way to optimise results is to exploit an intramolecular strategy.[67]



201 R=H
202 $R=CH_3$

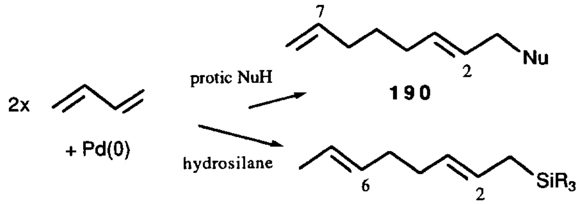
203 R=H, 82%, t/c = 9:1
204 $R=CH_3$, 82%, t/c = >20:1

In contrast to the intramolecular trapping of **201**, only small amounts (10%) of the product arising from competing tetraene to triene cycloisomerisation are observed with tetraene **201**. This cyclisation proceeds with a high level of 1,2-stereoinduction (>20:1) when stereocentres are present in the cyclohexane ring being formed. Stereoselection is almost absent in the trapped oxacycle (**206**/**207** = 1 : 1.6).



205 **206** 88% 1 : 1.6 **207**

The telomerisation of butadienes with hydrosilanes (HY) as trapping reagents is presumed to proceed through a different mechanism[68] and, contrary to reactions involving protic nucleophiles, 2,6-octadienes **208** are the reaction products.

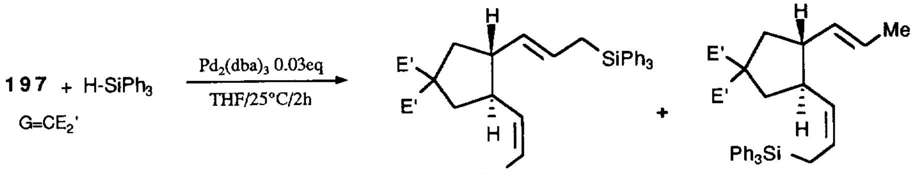


190

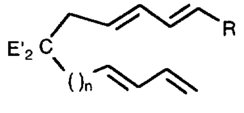
208

Scheme 14

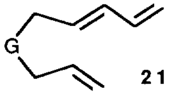
Vicinal *trans* divinyl substituted sililated compounds **209** and **210** (isomeric ratio 6:1) are easily obtained from the intramolecular hydrosililation of tetraenes **197**.[69]



209 6 : 1 (94%) **210**



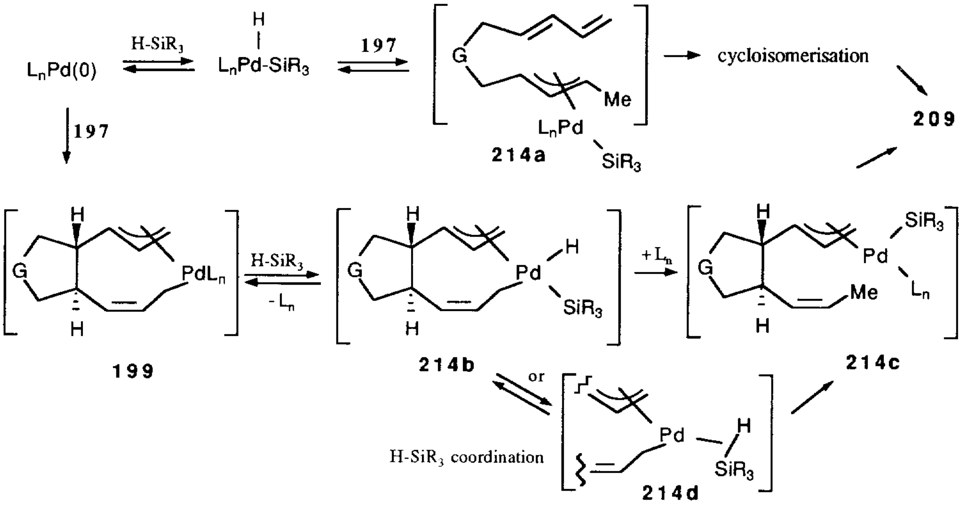
211 R=Me, n=1
212 R=H, n=2



213

The tetraene cyclisation has also been extended to dienes **212** that form six-membered rings, or those carrying an alkyl group at one terminal double bond (**211**). In the latter case, the regioselectivity was unexpectedly low for silyl addition to the less substituted alkene, with a yield of only 65%.

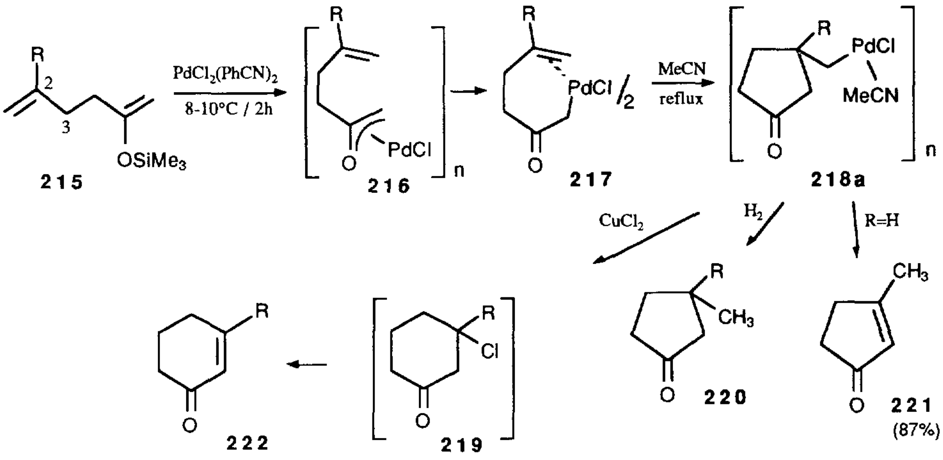
In these reactions, all the products belong to the 2,6-octadiene series and a hydrosilylation/carbocyclisation mechanism *via* the non-cyclised hydrosilylated palladium complex **214a** would account for the formation of the cyclised products. However, crossover experiments with deuteriosilanes and mixtures of trialkylsilane-d and trialkylsilanes, as well as the fact that triene **213** does not react, provided good arguments for the mechanism that is operative in the intramolecular telomerisation with protic trapping agents. Thus, the first step is the carbocyclisation of **197** in the presence of Pd(0) to the π-allyl-σ-complex **199** and the role of hydrosilane seems to be to capture this intermediate *via* oxidative addition (**214a**) or coordination (**214d**). Ligand transfer or reductive elimination leads to **214c** and finally to **209**.



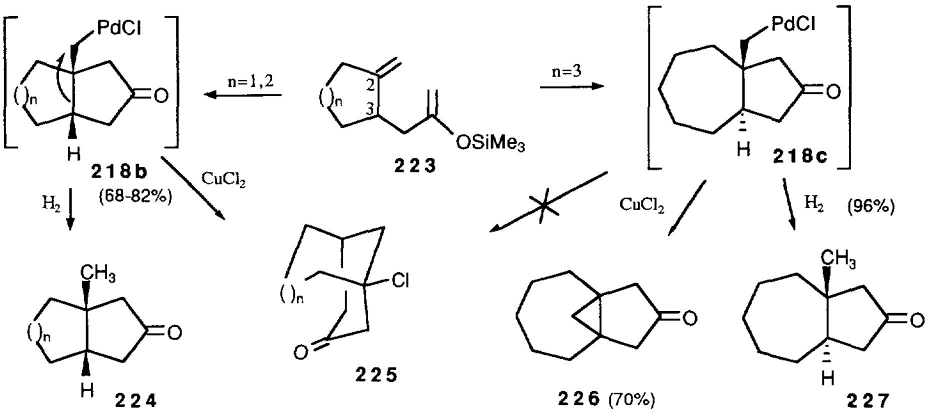
This reaction pathway explains both the high stereoselectivity of products such as **209** and **210**, but also the poor regioselectivies encountered during the cyclisation of **211**. The greater reactivity of tetraenes in cyclisation-telomerisation compared to the intermolecular hydrosilylation (poor reactivity) of substituted butadienes is in accordance with two different mechanisms. The fast carbocyclisation compared to the interaction of the nucleophile is a good argument to extend this reaction to any trapping agent. Indeed, the tetraene cyclisation is easily performed with tributylstannanes in place of hydrosilanes.[69]

2.4. Cyclisation *via* oxo-π-allylpalladium(II) intermediates

Oxo-π-allylpalladium intermediates have been postulated to exist in the oxidative transformation of silyl enol ethers **215** to carbocyclic ring systems.[70] The process requires stoichiometric amounts of palladium(II) and the outcome of the reaction depends on the reaction conditions. The cyclised key intermediate **218a** is formed by the slow insertion of the carbon-carbon double into the CH_2-palladium bond of **217**. These two σ complexes can been isolated when C_2 is substituted in **218a** (R=alkyl, Ph) and ß-elimination is not possible to give **221**. Subsequent hydrogenation leads to saturated cyclopentanones **220**. In the cyclisation of **223** having C_2-C_3 incorporated in a ring system, the final products are 1-methylbicyclo[n.3.0]alkanones. The exclusive *cis* stereochemistry observed in five- and six-membered rings **224** (n=1 or 2) and *trans* ring connection in the seven-membered ring **226** is noteworthy, but has not been rationalised.



A completely different reaction of complex **218a** leads, in the presence of copper chloride, to ring enlargement, and thus to six-membered rings. This type of transposition is already known in organic palladium chemistry[71] when a primary carbon-palladium σ-bond is involved.[72]

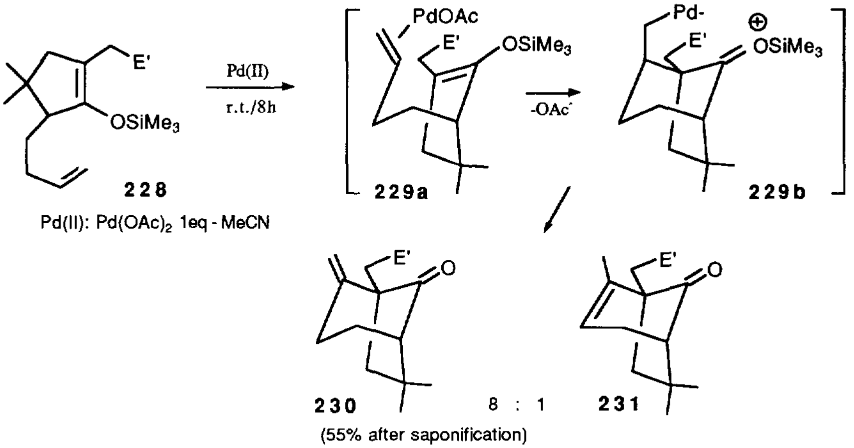


With cyclic silylenol ethers **223**, this transposition provides a route to bridgehead substituted bridged bicyclic ketones. Nevertheless, the seven-membered starting diene **223** (n=3) reacts in a different way with

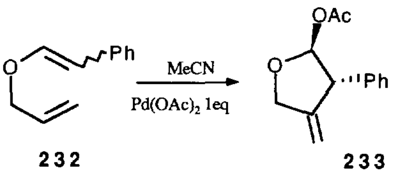
$CuCl_2$ and transannular palladium hydride elimination is observed in **218c** instead of the alkyl migration such in **218b**.

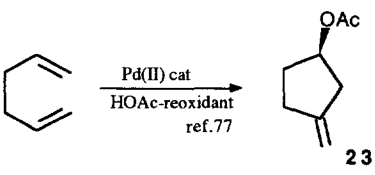
The dual reactivity of silylenol ethers seems to be restricted to dienes with a vinylic silyl substituted vinyl group at a terminal position. When this arrangement is involved, the R-C(O)CH_2-Pd complex is involved as key intermediate in Wagner-Meerwein-type transpositions. With the ene-silyl group incorporated in a cycloalkane[73,74] or in a non-terminal position of the chain[75] the cyclisation with palladium acetate follows the simple cyclisation mode that does not involve alkyl migration. Depending on the position of the O-silyl group, the annelated[74] or bridged bicyclic skeleton[73] is formed. Cyclisation of silylenol ether **228**, the key step in the total synthesis of antitumor agent (±)-quadrone, is a good example for these cyclisations.

The rearrangement of **228** demonstrates that this cyclisation is also possible with 1,6-dienes. Kende and co-worker group also showed that the cyclisation is not limited to silylenol ethers, since ordinary alkyl ethers could also be used.[76]



Considering the unreactiveness of lithium enolates in these reactions the oxo-π-allyl mechanism is disfavoured. Nucleophilic attack of the enol ether double bond on the coordinated terminal double bond and subsequent olefin insertion was postulated instead. The similarity of the palladium-catalysed cyclisations of vinyl allylether **232**[76] and 1,5-hexadiene[77] are good arguments for the latter reasoning.





However, the reaction pathway in many palladium-catalysed oxidation processes strongly depends on the geometry and nature of the double bond(s); both reactions, the palladium π-allyl or coordination-insertion mechanism can both occur in the same molecule.[77] It has also been postulated that the simple 1,1'-disubstitution of the terminal alkene siloxy group directs the cyclisation to the six-membered ring instead of cyclopentanes.[75] As the structures of the starting dienes are extremely diverse it seems unwise, without more data available, to propose one unique mechanism for the cyclisation of alkene enol ethers.[70,73-76]

3. References and Notes

1. Part A: Heumann, A. *The Stereochemistry of Palladium Catalysed Cyclisation Reactions. Addition to Carbon-carbon Double Bonds (π-route)* in *Stereochemistry of Organometallic and Inorganic Compounds Volume 5: Chains, Clusters, Inclusion Compounds, Paramagnetic Labels, and Organic Rings*; Zanello, P. Ed.; Elsevier, Amsterdam, 1994; pp 557-623.
2. Part C: *Cascade reactions*; Heumann, A.; Reglier, M., manuscript proposed to appear as a *Tetrahedron Report*.
3. A list of cyclisation reviews may be found in *Comprehensive Organic Chemistry, The Synthesis and Reaction of Organic Compounds,* Barton, D, Ollis, W. D., Eds.; Pergamon: Oxford, 1979, pp. 877-878.
4. Ho, T.-L. *Tandem Organic Reactions*; Wiley: Chichester, 1992; pp 512 .
5. Heumann, A.; Jens, K.-J.; Reglier, M. *Palladium Complex Catalysed Oxidation Reactions* in *Progress in Inorganic Chemistry*; Karlin, K. D. Ed.; Wiley: New York, Vol 42, 1994; pp 483-576.
6. (a) Trost, B. M. *Tetrahedron* **1977**, *33,* 2615-2649. (b) *Acc. Chem. Res.* **1980**, *13,* 385-393. (c) Trost, B. M.; Verhoeven, T. R. in *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, Vol 8, 1982; pp 799-938. (d) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1985**, *25,* 1-20. (e) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1980 .(f) *Tetrahedron* **1986**, *42,* 4361-4401. (g) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985. (h) Åkermark, B.; Bäckvall, J. E.; Zetterberg, K. *Acta Chem. Scand.* **1982**, *B36,* 577-585. (i) Bäckvall, J.-E. *Acc.Chem.Res.* **1983**, *16,* 335-342. (k) *Pure Appl.Chem.* **1983**, *55,* 1669-1676. (l) *Bull. Soc. Chim. France* **1987**, 665-670. (m) *Metal-Mediated Additions to Conjugated Dienes* in *Advances in Metal-Organic Chemistry;* Liebeskind, L. S.; Ed.; JAI Press: London 1989; Vol. 1, pp. 135-175.
7. (a) Trost, B. M. *Pure Appl. Chem.* **1979**, *51,* 787-800. (b) *Angew. Chem. Int. Ed. Engl.* **1989**, *28,* 1173-1192.
8. (a) Tsuji, J. *Top. Curr. Chem.* **1980**, *91,* 29-74. (b) *Application of Palladium Catalysts to Natural Products Synthesis* in *Fundamental Research in Organometallic Chemistry*; Tsutsui, M.; Ishii, Y. Yaozeng, H. Eds.; Van Nostrad Reinhold Company: New York, 1982; pp 305-326. (c) *Pure Appl.Chem.* **1982**, *54,* 197-206.

9. (a) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39-48. (b) *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38-52. (c) *Pure Appl. Chem.* **1990**, *62*, 1941-1948.
10. (a) Bäckvall, J.-E. *New J. Chem.* **1990**, *14*, 447-452. (b) *Pure Appl. Chem.* **1992**, *64*, 429-437. (c) *Recent Advances in Organopalladium Chemistry* in *Organic Synthesis via Organometallics (OSM 4)*; Enders, D.; Gais, H.-J. Keim, W. Eds.; Vieweg: Wiesbaden, 1993; pp 165-174. (d) *Stereocontrol in Palladium-catalysed Reactions* in *Organometallic Reagents in Organic Synthesis*; Academic Press: New York, 1994; pp 81-97.
11. some representative examples: Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779-7781; Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730-4743; Nordberg, R.-E.; Bäckvall, J.-E. *J. Organomet. Chem.* **1985**, *385*, C24-C26; Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558-3566; Moreno-Manas, M.; Ribas, J.; Virgili, A. *J. Org. Chem.* **1988**, *53*, 5328-5335.
12. Bäckvall, J.-E.; Granberg, K. E.; Heumann, A. *Isr. J. Chem* **1991**, *31*, 17-24.
13. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867-3868.
14. Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988-4990.
15. Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734-736; Baldwin, J. E.; Cutting, W.; Dupont, L.; Cruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Comm.* **1976**, 736-738.
16. (a) Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8281-8284. (b) Trost, B. M.; Granja, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 1044-1046.
17. Trost, B. M.; Lee, H. L. *J. Am. Chem. Soc.* **1991**, *113*, 5076-5077.
18. Hanzawa, Y.; Ishizawa, S.; Ito, H.; Kobayashi, Y.; Taguchi, T. *J. Chem. Soc., Chem. Comm.* **1990**, 394-395.
19. Ishikura, M.; Terashima, M.; Okamura, K.; Date, T. *J. Chem. Soc., Chem. Comm.* **1991**, 1219-1221.
20. Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747-4750.
21. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987-3990.
22. Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 5339-5342.
23. Tadano, K.; Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Ogawa, S. *Synlett* **1993**, 565-567.
24. Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893-7894.
25. (a) Bosnich, B. *Pure Appl. Chem.* **1982**, *54*, 189-195. (b) Fiaud, J. C. *Mechanisms in Stereo-Differentiating Metal-Catalysed Reactions. Enantioselective Palladium-Catalysed Allylation* in *Metal Promoted Selectivity in Organic Synthesis*; Graziani, M.; Hubert, A. J. Noels, A. F. Eds.; Kluwer Academic Publishers: Dordrecht, 1991; pp 107-131. (c) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089-1122. (d) Reiser, O. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 547-549. (e) Togni, A.; Venanzi, L. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497-526.
26. Some very recent examples: Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062-4066; Breutel, C.; Pregosin, P. S.; Salzmann, R.; Togni, A. *J. Am. Chem. Soc.* **1994**, *116*, 4067-4068; Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*,

4089-4090; Brenchley, G.; Merifield, E.; Wills, M.; Fedouloff, M. *Tetrahedron Lett.* **1994**, *35*, 2791-2794.

27. Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371-382 and references cited.
28. Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3527-3530.
29. Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3531-3534.
30. Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388-3390.
31. Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826-6832.
32. Mori, M.; Nukui, S.; Shibasaki, M. *Chem. Lett.* **1991**, 1797-1800.
33. Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745-8747.
34. Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99-102.
35. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317-6318; Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444-458.
36. Hayashi, T.; Kanehira, K.; Tsuchiya, H.; Kumada, M. *J. Chem. Soc., Chem. Comm.* **1982**, 1162-1164; Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113-120; Hayashi, T. *Pure Appl. Chem.* **1988**, 60, 7-12.
37. Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 228-230; Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327-9343.
38. Dunne, K.; McQuillin, F. J. *J. Chem. Soc. (C)* **1970**, 3987-3990.
39. Chalk, A. J.; Wertheimer, V.; Magennis, S. A. *J. Mol. Catal.* **1983**, *19*, 189-200.
40. *cf.* also Chatterjee, S.; Negishi, E. *J. Organomet. Chem.* **1985**, *285*, C1-C4.
41. Negishi, E.; Iyer, S.; Rousset, C. J. *Tetrahedron Lett.* **1989**, *30*, 291-294.
42. (a) Oppolzer, W.; Keller, T. H.; Kuo, D. L.; Pachinger, W. *Tetrahedron Lett.* **1990**, *31*, 1265-1268. (b) Oppolzer, W.; Birkinshaw, T. N.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 6995-6998.
43. It is interesting to note that,under the same conditions, rhodium-ene reactions lead preferentially the to *cis* product **103** (*t*/*c* = 14:86). It was expected that the Rh-ene process offers additional stereochemical perspectives owing to the octahedral hexacoordination of Rh(III) complexes; Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* **1993**, *76*, 2329-2337.
44. Yoo, S.-E.; Lee, S.-H.; Yi, K.-K.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 6877-6880.
45. Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266-1274.
46 Hiroi, K.; Kurihara, Y. *J. Chem. Soc., Chem. Comm.* **1989**, 1778-1780.
47. Engelbrecht, G. J.; Holzapfel, C. W. *Tetrahedron Lett.* **1991**, *32*, 2161-2164; *Heterocycles* **1991**, *32*, 1267-1272.
48. Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239-8241.
49. *cf.* also Takacs, B. E.; Takacs, J. M. *Tetrahedron Lett.* **1990**, *31*, 2865-2868.
50. Ma, S.; Lu, X. *J. Chem. Soc., Chem. Comm.* **1990**, 733-734.
51. Oppolzer, W.; Xu, J.-Z.; Stone, C. *Helv. Chim. Acta* **1991**, *74*, 465-468.
52. Trost, B. M.; Tasker, A. S.; Rüther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670-672.
53. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34-42.
54. Bäckvall, J.-E.; Vagberg, J.-O.; Granberg, K. L. *Tetrahedron Lett.* **1989**, *30*, 617-620.

55. Lactonisation: (a) Bäckvall, J. E.; Andersson, P. G.; Vagberg, J. O. *Tetrahedron Lett.* **1989**, *30*, 137-140; Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.* **1993**, *58*, 5445-5451. Chiral lactones: (b) Bäckvall, J. E.; Gatti, R.; Schink, H. *Synthesis* **1993**, 343-348.
56. (a) Oxaspirocyclisations: Bäckvall, J.-E.; Andersson, P. G. *J. Org. Chem.* **1991**, *56*, 2274-2276; Andersson, P. G.; Nilsson, Y. I. M.; Bäckvall, J.-E. *Tetrahedron* **1994**, *50*, 559-572. (b) Andersson, P. G.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5349-5353. (c) Bäckvall, J.-E.; Andersson, P. *J. Am. Chem. Soc.* **1992**, *114*, 6374-6381.
57. Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683-3685. Bäckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988-2993.
58. O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807-809.
59. (a) Larock, R. C.; Berrios-Pena, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447-3450. (b) Carboannulation: Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882-5884. (c) Annulation of vinylic cyclopropanes: Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529-530. (d) annulation of 1,4-dienes: Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509-4510.
60. Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615-2617.
61. Internal alkynes: Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690.
62. (a) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009-6012; Shaw, R.; Lathbury, D.; Anderson, M.; Gallagher, T. *J. Chem. Soc. Perkin Trans.1* **1991**, 659-660. (b) Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697-4710; Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652-2656.
63. Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992**, *114*, 773-774.
64. Tsuji, J. *Adv. Organomet. Chem.* **1979**, *17*, 141-193. Ref. 4e, p. 90. Ref. 4g, p. 327.
65. Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193-5195.
66. Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990**, *31*, 1117-1120.
67. Takacs, J. M.; Chandramouli, S. V. *J. Org. Chem.* **1993**, *58*, 7315-7317.
68. Seitz, F.; Wrighton, M. S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 289-291.
69. Takacs, J. M.; Chandramouli, S. *Organometallics* **1990**, *9*, 2877-2880.
70. Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494-496; Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 4519-4521.
71. Heumann, A. *Regio-, Stereo-, and Enantioselectivities in Palladium and Platinum Catalysed Organic Reactions* in *Metal Promoted Selectivity in Organic Synthesis*; Graziani, M.; Hubert, A. J. Noels, A. F. Eds.; Kluwer Academic Publishers: Dordrecht, 1991; pp 133-159.
72. Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Comm.* **1977**, 583-584; Bäckvall, J.-E.; Nordberg, R. *J. Am. Chem. Soc.* **1980**, *102*, 393-395; Sen, A.; Lai, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 4627-4629; Heumann, A.; Reglier, M.; Waegell, B. *Tetrahedron Lett.* **1983**, *24*, 1971-1974; Heumann, A.; Bäckvall, J. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 207-208; Wells, A. P.; Kitching, W. *J. Org. Chem.* **1992**, *57*, 2517-2519.

73. (a) Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784-1785. (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808-5810. (c) Kende, A. S.; Sanfilippo, P. J. *Synth. Commun.* **1983**, *13*, 715-719. (d) Kende, A. S.; Battista, R. A.; Sandoval, S. B. *Tetrahedron Lett.* **1984**, *25*, 1341-1344.
74. Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090-2091.
75. Torres, L. E.; Larson, G. L. *Tetrahedron Lett.* **1986**, *27*, 2223-2226.
76. Kende, A. S.; Wustrow, D. J. *Tetrahedron Lett.* **1985**, *26*, 5411-5414.
77. Antonsson, T.; Moberg, C.; Tottie, L.; Heumann, A. *J. Org. Chem.* **1989**, *54*, 4914-4929.

(*Received* 4 *November* 1994)