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The Stereochemistry of Palladium Catalysed Cyclisation Reactions Part C: Cascade Reactions †

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Contents

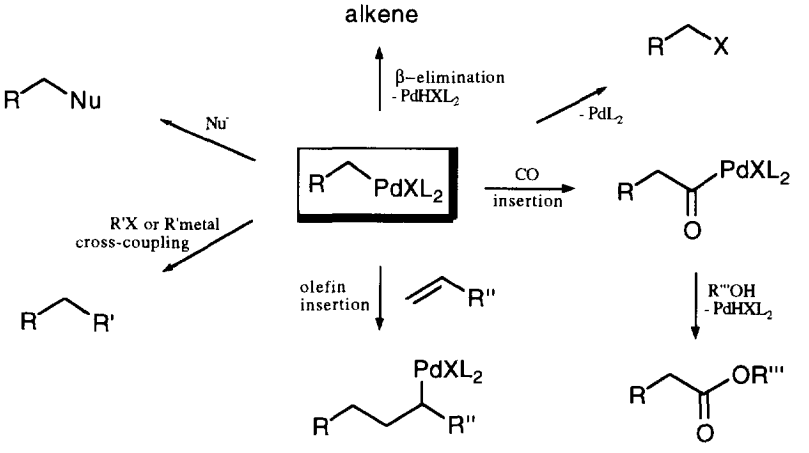
† Dedicated to the memory of Professor Wolfgang Oppolzer

1 Introduction

In the first article of this series[1] reactions were reviewed where the cyclisation step involved the addition of reactive species to carbon-carbon double bonds previously activated *via* coordination to palladium. In the second part[2] we reviewed the other principal intermediate in organic olefin-palladium chemistry, π-allyl palladium complexes. In this, ultimate part we will provide an overview of the rapidly growing field of tandem or cascade reactions.[3,4] In these transformations additional atoms are incorporated into the new molecule (CO for example) or a cascade of cyclisations[5,6] leads to polycyclic systems.[7]

Combining multiple reaction steps in the same chemical transformation is, in most cases, an elegant solution to synthetic problems. Transition metals, especially palladium, offer many possibilities of modifying a 'simple' organometallic reaction. This is particularly true for cyclisation reactions since attack on carbon-palladium bonds either leading to ring formation or simply to an intermolecular transformation are usually quite different in energy. Such cascade or tandem reactions have found ample use in the literature.

σ-Carbon palladium complexes are very reactive species which generally undergo fast reductive elimination or β-elimination processes. However, depending on reactant and reaction conditions, it is possible to trap these species before their decomposition by the insertion of carbon monoxide or olefins, nucleophilic attack or cross-coupling reactions with halides or organometallic complexes.

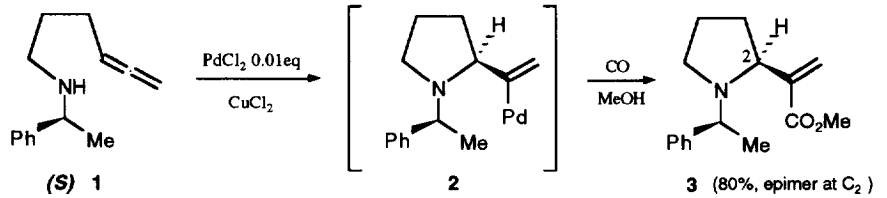


Scheme 1

The simplest and most investigated variation is the interception of an organometallic intermediate by small molecules like carbon monoxide.[8,9] This interception is possible before ring closure takes place or, as a termination reaction, after cyclisation. Moreover, if the trapping molecule is an olefin, the process may also be intramolecular, thus enabling several consecutive cyclisation steps according to the number of unsaturated groups present in the starting molecule.

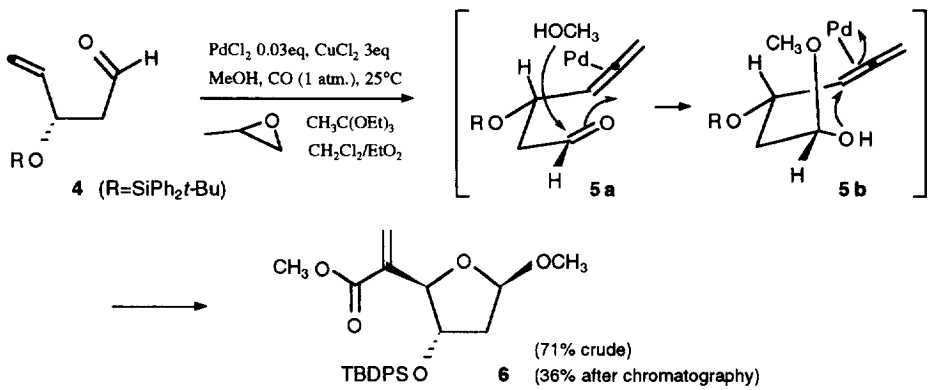
2 Interception of the cyclised organometallic species during the termination step

Some simple trapping reactions of a cyclised organometallic complex were discussed in the chapter of nucleophilic addition to palladium π-complexes[1] on 'tandem cyclisation-anion capture processes'[10,11] and the intramolecular alkoxycarbonylation of alkenols,[12,13] or the electrophile mediated cyclisation-incorporation of an allene moiety.[14,15] A recent contribution of the latter type of reaction, the Pd(II) mediated cyclisation of **1**[14c] is part of the enantioselective synthesis of the alkaloid pumiliotoxin 251D.



(S) **1** **2** **3** (80%, epimer at C_2)

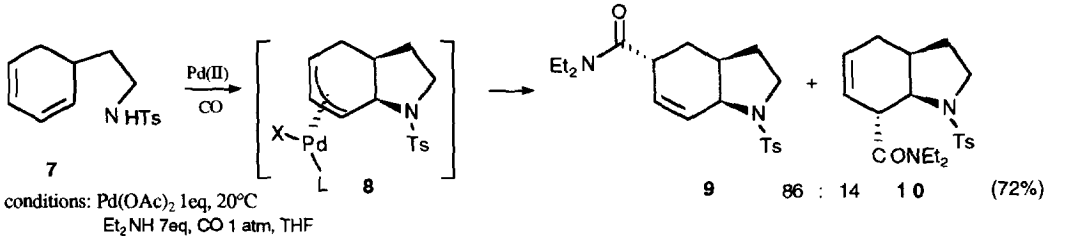
Oxoallenes lead to furans and synthetic exploitation for furanoside synthesis seems promising. The recent discovery of acetalisation-cyclisation-methoxycarbonylation of γ-allenic aldehydes[16] has been used as a key-step for the synthesis of nucleoside analogues.[17]



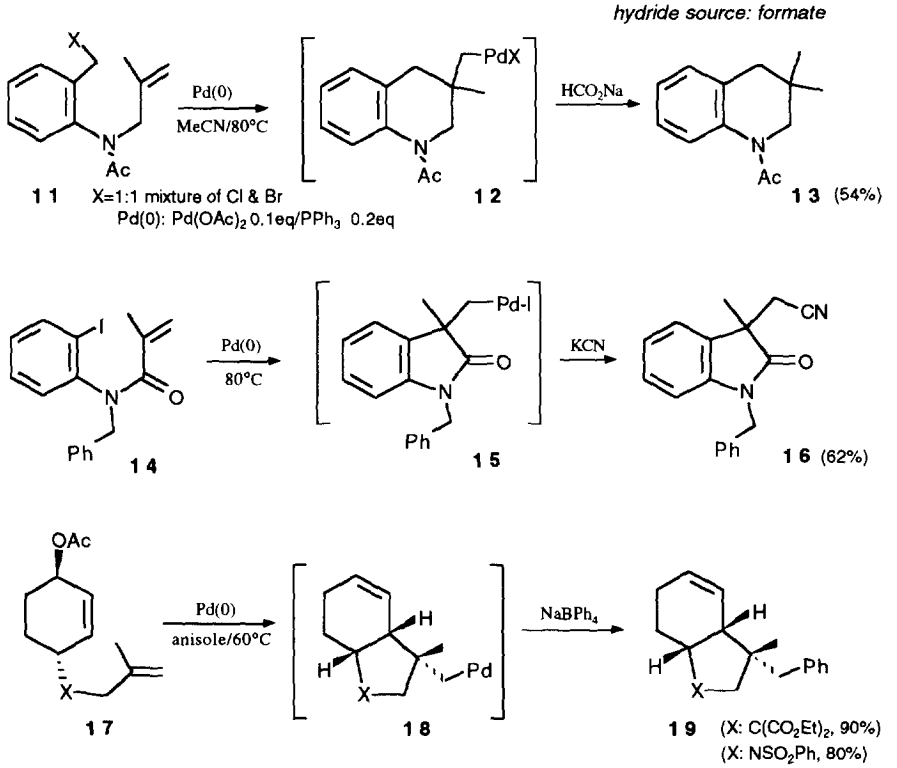
4 (R=$SiPh_2t$-Bu) **5a** **5b** **6** (71% crude) (36% after chromatography)

The excellent stereoselectivity for the D-deoxyribose geometry is rationalised by a combination of the effects exerted by the bulky alkylsilyl group and stereoelectronic requirements during the cyclisation step.

Recently, a new palladium-mediated cyclisation-carbonylation of 1,3-dienes[2,18] has been described.[19] The reaction, which proceeds *via* an intramolecular nucleophilic addition to dienes (nucleophile: OH, NHTs) followed by carbonylation of the π-allyl palladium intermediate, gives either an overall 1,2 or 1,4-addition across the diene. An improvement of the regiochemical outcome (1,4 vs. 1,2 addition = 6:1) can be achieved by the proper choice of reaction conditions (dichloromethane as a solvent and CO pressure of 1 atm.).

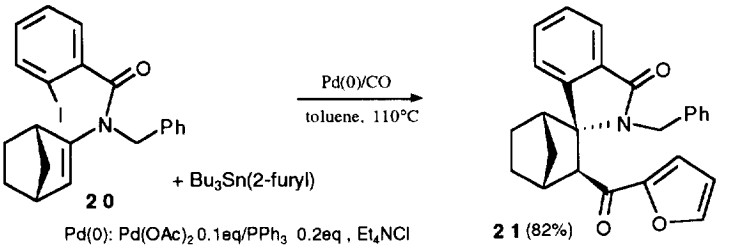


The interception through hydride[11] or cyanide ion capture and phenylation[20] with the $NaBPh_4$ nucleophile[11] is demonstrated by recent examples from Grigg's group. This approach allows the creation of quaternary carbon centres and concomitant elaboration of one of the carbon substituents.

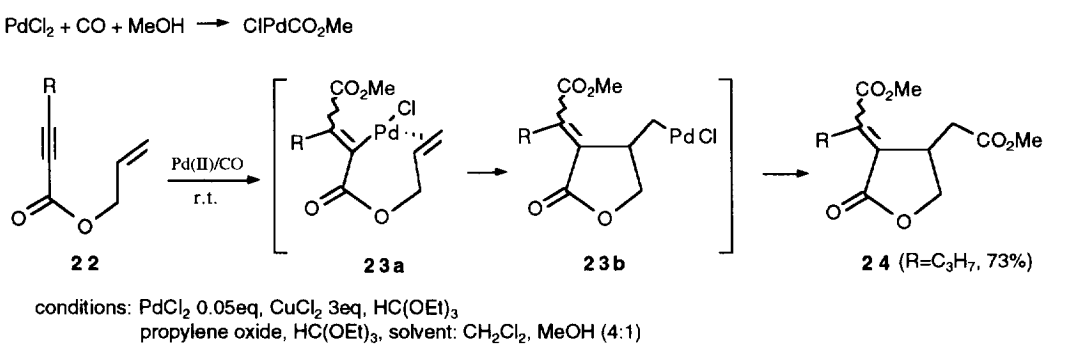


The cyclisation-anion capture *via* metallo-ene reaction of **17** nicely demonstrates that, potentially, many of metal catalysed reactions may be reoriented by interception with a reactive species. This is particularly useful in cases where other, more direct, termination steps are not possible, e.g. a ß-hydride elimination in the quaternary palladium σ-complexes **12**, **15** and **18**. Unlike the reactions discussed above, intercepting of metal-carbon bonds with carbon monoxide in metallo-ene type cyclisations[21] requires a nickel (0) catalyst.[22]

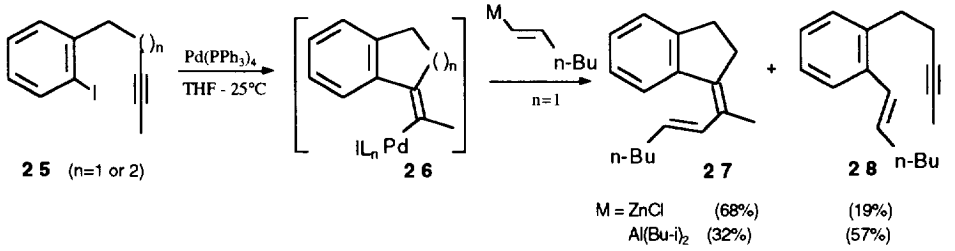
A three component version combines carbonylation with the cyclisation-anion-capture process.[23] Hydrocarbons and heterocyclic moieties are thus transferred, together with CO, from $NaBPh_4$ or Sn(IV) reagents to the cyclised annelated or spirocyclic species.[24]



Cyclisation-double carbonylation has been shown for allylic alkynoates in a 4:1 mixture of dichloromethane-methanol. The stereochemistry of the alkylidene group in **24** remained undetermined.[25]

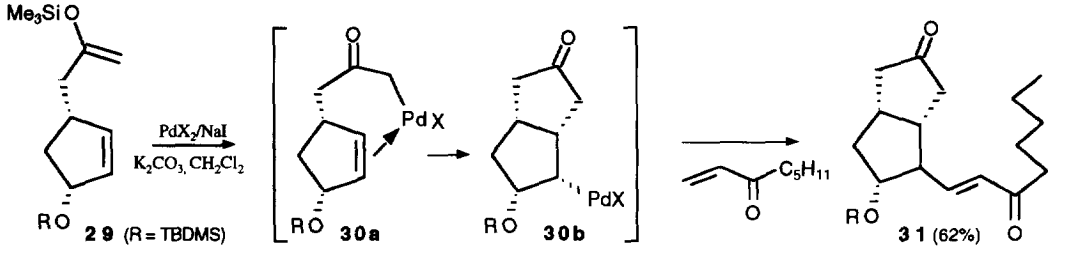


The interception by various unsaturated species[26] has been performed with acrylates,[27] allyl halides,[28,29] vinyl or aryl halides.[30,31] Vinylic, [32] acetylenic[33] or aromatic[34] organometallic species containing metals such as Cu, Zr, Sn, Al, B or Zn have been used as trapping agent.

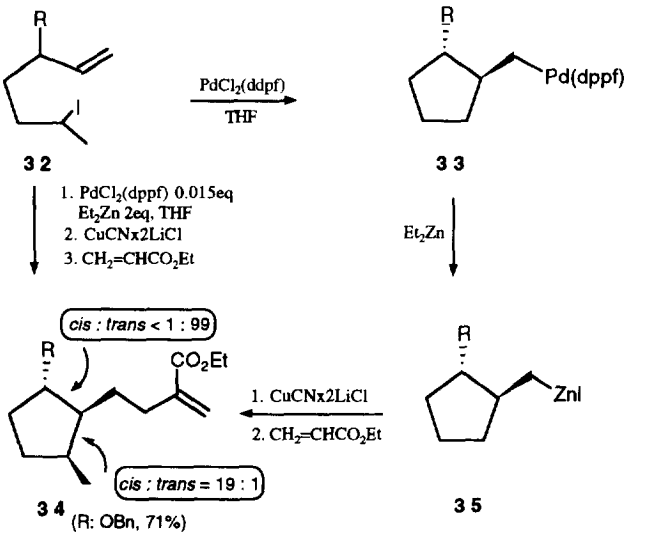


The cyclic carbopalladations of ω-(*Z*-ß-iodoalkenyl)- or ω-(*o*-iodoaryl)alkynes **25** followed by cross coupling is *cis* stereoselective (addition to the alkyne); thus the *trans* stereochemistry of the vinylic moiety is retained.[32b]

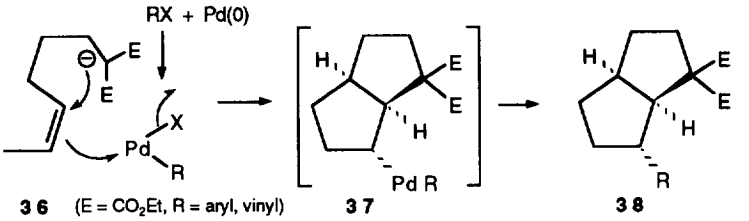
The cyclisation reaction is accompanied by direct cross-coupling to some extent. The role of the second metal is complex and zinc chloride, though being the more efficient metal during the cyclisation-interception of **25** (n=1), tends to direct cross-coupling when reacting with the higher homologue **25** (n=2).[32b] Among the many factors determining the outcome of the reaction the nature of the carbon ligands of the intercepting species is important, as is as the substitution pattern of the acetylenic group that is involved in the cyclisation step.[28] The interception by Michael acceptors has been recently applied in the stereoselective synthesis of carbacyclins.[35]



In this process, the bicyclic intermediate **30b** is relatively stable since it is blocked from *syn* β-hydride elimination by the silyloxy group. Unwanted β-elimination can also be avoided by transmetallation reactions. Knochel and co-workers[36] have shown that it is possible to transform σ-palladium species with Et_2Zn to the more stable zinc complexes **35** and react them with various electrophiles (e.g. acrylate, acid chloride, I_2, etc.).[37]

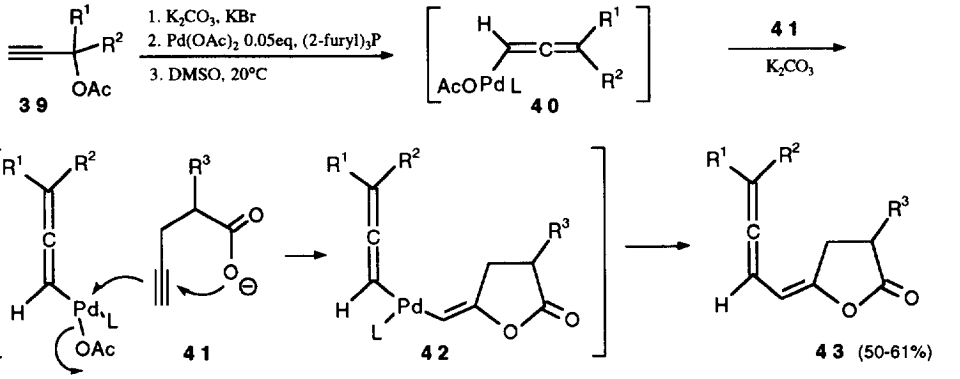


Cyclised Pd-organometallic species obtained from malonate type nucleophilic addition to alkenes[38] or alkynes[39] can be trapped with aryl or vinyl iodides. The interpretation of the stereochemistry of the cyclised compounds is a good argument for a mechanism proceeding *via* nucleophilic attack of the enolate to the coordinated double bond followed by a reductive elimination (trapping) step.

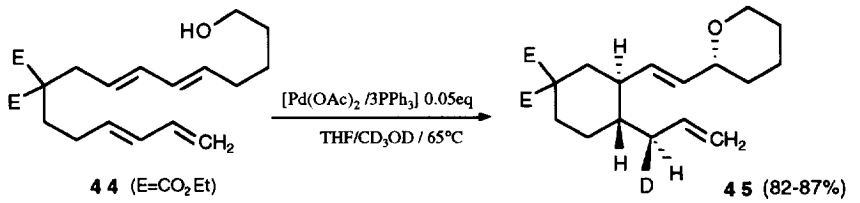


36 (E = CO_2Et, R = aryl, vinyl) **37** **38**

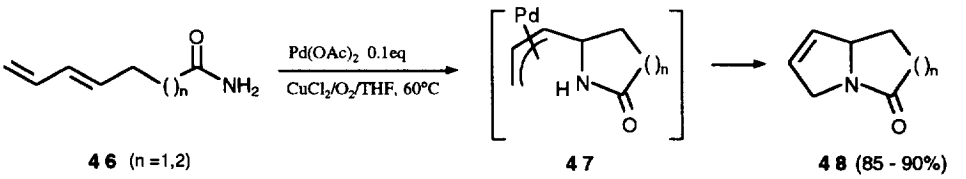
A similar cyclisation involves carboxylate addition to triple bonds and either capture by the triple[40] or allene bonds.[41] These conversions seem useful for the synthesis of biologically active tetrahydrofuranones.



The inter-[42] and intramolecular[43] trapping of functionalised tetraene compounds with various nucleophiles is discussed with other π-allyl-type reactions (part B).[2] The new carbon-carbon and carbon-heteroatom bonds are usually formed with high stereoselectivities. It has also been shown that also the protonation (deuteration) exocyclic to the carbocycle proceeds in highly diastereoselective manner.[44]



The intramolecular trapping of dieneamides makes use of the possibility of adding the same nitrogen nucleophile to the 1- and 4-positions of a conjugated diene (formal [4 + 1] intramolecular cycloaddition).[45]

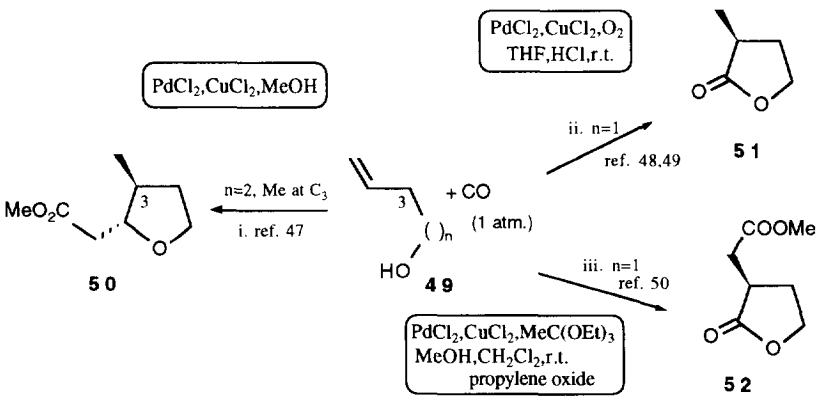


The catalytic oxidation reaction requires two equivalents of $CuCl_2$ and dioxygen at atmospheric pressure rather than the currently used *para*-benzoquinone[16] as the reoxidation system.[46]

3 Insertion into the newly formed ring

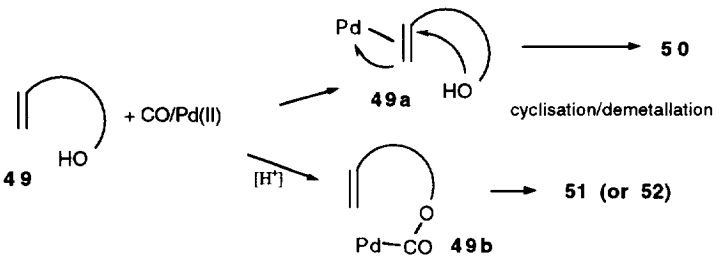
3.1 Addition to monoolefins

The choice between two (or more) different metal catalysed reaction pathways very often depends on minor modifications in the reaction system. When unsaturated alcohols react with carbon monoxide three different cyclisation-CO-insertion processes have been realised (Scheme 2): i. cyclisation *via* oxygen addition to the coordinated olefin followed by interception of the carbon-palladium bond,[1,12a,47] ii. CO insertion during the cyclisation step[48 - 50] and iii. a combination of Semmelhack's and Alper's reaction with the incorporation of two molecules of carbon monoxide (Tamaru).[51]



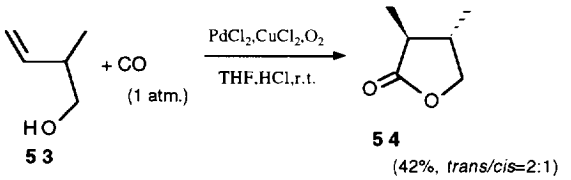
Scheme 2

Semmelhack's cyclic ether formation has been discussed extensively before.[1,12a] The key step consists of the nucleophilic attack of OH on the coordinated double bond, e.g. **49a** (Scheme 3). On the other hand the formation of lactones is catalysed by the typical Wacker[52] catalyst, $PdCl_2$-$CuCl_2$-O_2-HCl, under acidic conditions. Apparently these conditions are favourable for the intermediacy of **49b** instead of **49a**. α-Carbonyl palladium complexes of type **49b** have been shown to cyclise *via* insertion across the double bond,[53] provided a two carbon chain separates the double bond and hydroxyl group.

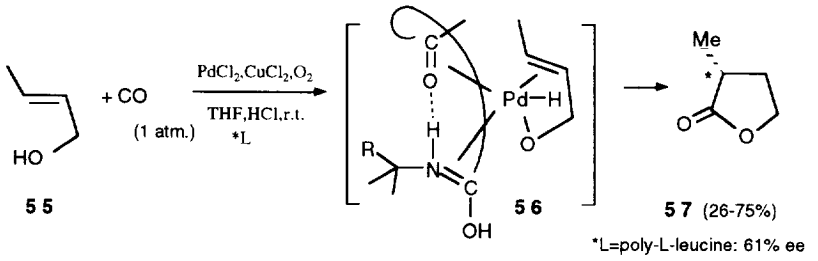


Scheme 3

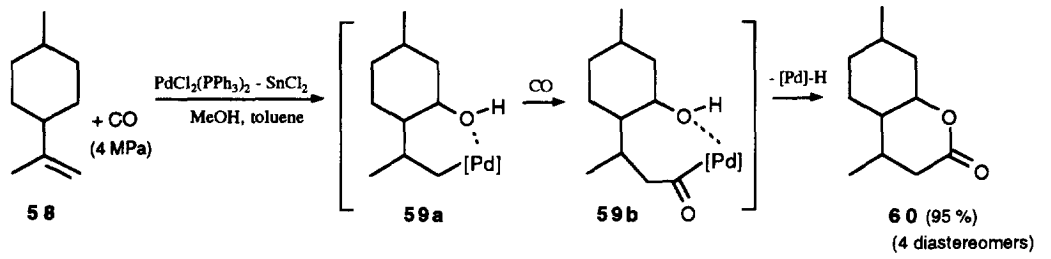
The catalytic reaction[48] also leads to cyclisation for longer chain molecules. Five or six membered rings form depending on both the chain length and substitution pattern of the initial allylic and homoallylic alcohols or 5-alkenols.



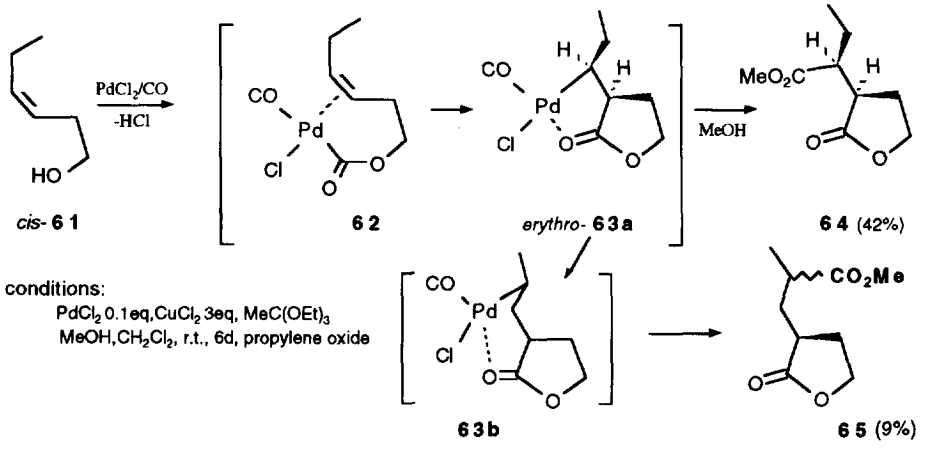
The *cis*/*trans* selectivity is rather low; however, in the presence of chiral ligands optically active α-methyl-γ-butyrolactone **57** is formed with up to 61% enantiomeric excess.[49]



More recently, Alper and co-workers[54] have described a new palladium catalytic system using $Pd(dba)_2$ and dppb as a ligand for the lactonisation of allylic alcohols under neutral conditions (DME) and in the absence of cupric chloride and dioxygen. This methodology is also applicable to propargylic alcohols (*vide infra*). With, $PdCl_2(PPh_3)_2/SnCl_2$ as catalysts, isopulegol **58** affords δ-lactone **60** after carbonylation.[55] During this reaction a $(SnCl_3)$Pd-H species, generated from the catalytic system, has been proposed to give a σ-alkyl palladium intermediate by addition across the carbon-carbon double bond. CO insertion and intrasphere attack of the hydroxyl group form the lactones and recycles the Pd-H species.

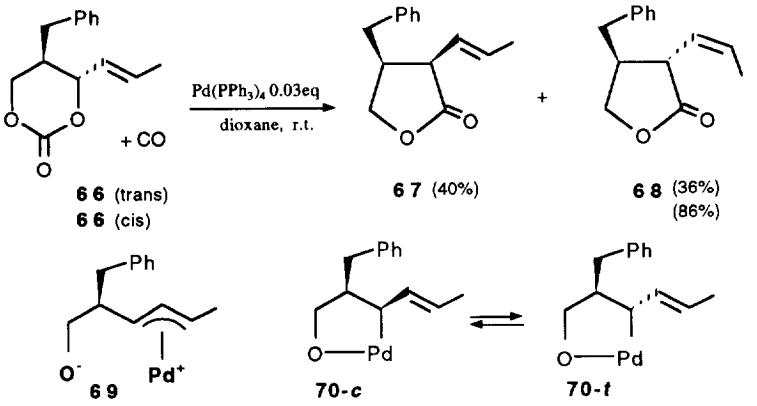


The very efficient double carbonylation of 3-buten-1-ols, e.g. **49** → **52** (Schemes 2 and 3), realised by Tamaru and coworkers[50,51] is the result of strictly neutral reaction conditions in the presence of propylene oxide. In the $PdCl_2/CuCl_2$/MeOH catalyst hydrogen chloride, necessary for efficient cyclisation,[48] is generated in every catalytic cycle. Quenching with propylene oxide eliminates HCl and a carbonylative termination (second carbonyl insertion) becomes possible. The formation of α-[(methoxycarbonyl)methyl-γ-butyrolactones is general for primary, secondary and tertiary homoallylic alcohols. Diastereoselectivities are moderate in the case of 1-substituted 3-butenols (at best 2.8:1 of 2 isomers with undefined stereochemistry). Both CO groups are incorporated with *cis* stereochemistry (*cis* olefin cyclised to erythro compound, e.g. **64**) and large catalytic turnover numbers (10-100) should be mentioned. The lack of direct nucleophilic attack by the OH group may be due to the ring strain of the resulting oxetanes. The effect of stereochemically unfavourable influences is demonstrated by the relatively difficult cyclisation of *cis*-**61**, which is accompanied by small amounts of the rearranged (hydride shift) lactone **65**.



Unlike the cyclisation of *trans*- **61** (2 days reaction time, 63% of *threo*-product), in the metallacyclic *erythro*-intermediate from *cis*-**61** the steric repulsions are sufficient to slow down the rate (6 days, lower yields) and thus permit the alternative hydride shift reaction leading to lactone **65**.

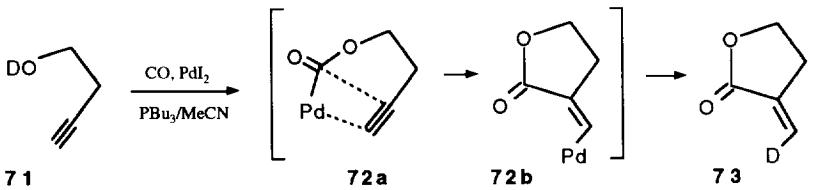
A similar lack of stereoselectivity is also found in the decarboxylative carbonylations of 3-vinyl-1-oxo-2,6-dioxacyclohexanes.[50]



High stereoselectivity in the formation of the π-allyl intermediate **69** (*syn* or *anti* according to *trans*- or *cis*-**66**) was only observed in case of the cyclisation of *cis*-carbonate **66**. This supports the intermediacy σ-allyl complexes **70**. The more stable *trans*-intermediate **70-*t***, formed from the *cis*-carbonate with inversion of configuration,[56] rapidly and specifically reacts to a carbon monoxide insertion product **68**. Intermediate **70-*c***, however, formed from the *trans*-carbonate, isomerises to **70-*t*** before inserting CO and cyclisation. Similar observations have been made by Bäckvall[57] and Oppolzer,[21,58] and the problem of non-selective allylic alkylations remains to be solved.[56,59]

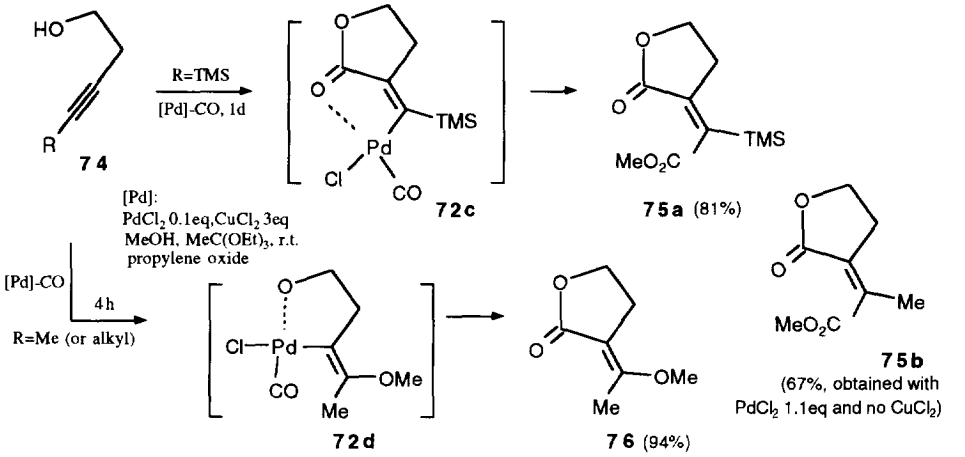
3.2 Addition to alkynes, allenes and related systems

The formation of methylene lactones through cyclocarbonylation of acetylenic alcohols has been studied in detail by Norton and co-workers.[60] Labelling studies[61] and extensive mechanistic work on isolated carboalkoxy palladium complexes **72** have provided evidence for the nucleophilic attack of the hydroxyl group on the coordinated carbonyl as well the *cis* addition across the triple bond.[1]



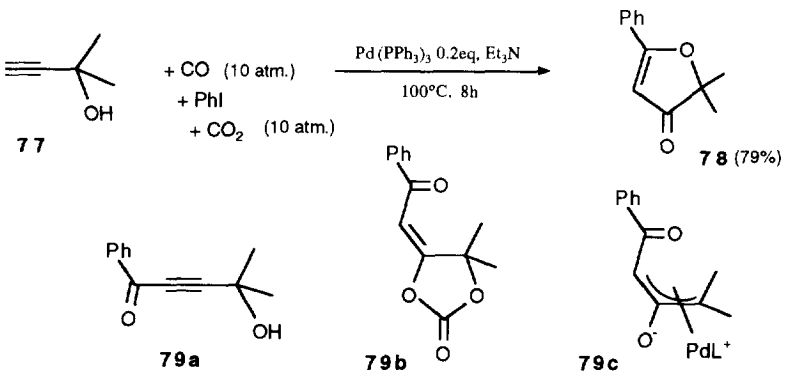
In the recent work of the Tamaru and co-workers[51] also the effect of triple bond substituents at the cyclisation of 3-butyn-1-ols has been studied under 'double carbonylation' conditions (propylene oxide, $MeC(OEt)_3$). Molecules with a trimethylsilyl group, **74** (R=TMS) follow the reaction pathway depicted by Norton, with the modification of a carbonylative termination step and the introduction of a second carbonyl unit *syn* to the first one (**75a**), whereas alkyl (or aryl) substituted acetylenes behave in a different way. The initiation of the sequence is the addition of methanol and palladium across the triple bond. The unusual *trans* stereochemistry may

be a result of alkyl or aryl group participation at the addition step. The incorporation of CO takes places only in the cyclisation step. The difference in the reaction of silylated or alkylated alkynes is attributed to the electropositive character of the Si-group, favouring intermediates with Si and the metal at the same carbon such as **72c**.



Interestingly, the copper chloride has a crucial role in these second reactions since the stoichiometric $PdCl_2$ reaction (absence of the reoxidant $CuCl_2$) of **74** (R=methyl) once more gives the product **75b**, according to Norton's mechanism. The effective promotion of the reaction between HCl and propylene oxide by the copper salt may be the rational explanation.

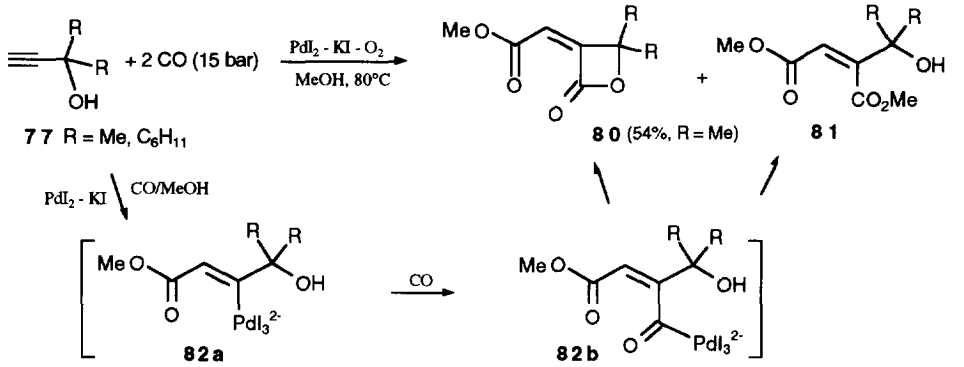
Propargylic alcohols have also been cyclised with various metals (Fe, Co, Ni, Ru, Pt, Pd) with concomitant



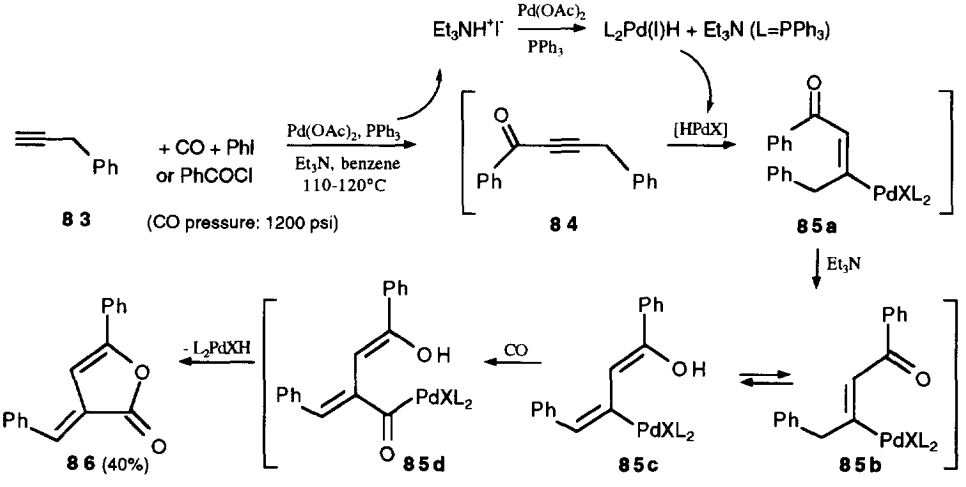
introduction of carbon monoxide into the 5-membered ring.[62] The mechanism involves incorporation of CO and CO_2 during the reaction.

The intermediacy of compounds **79a** and **b** during the formation of 3-(2H)-furanones has been shown. In the light of the results with 3-vinyl-1-oxo-2,6-dioxacyclohexane **66**[50] (*vide supra*) the involvement of **79c** (or analogous σ-allyl complexes) is probable.

In the presence of alcohols and catalytic amounts of PdI_2-KI, oxidative carbonylation of tertiary α-hydroxyalkynes gives β-lactones in reasonable yields (up to 50%) and selectivity (β-lactone vs. dicarbonylated byproduct with ratios higher than 3:1).[63] N-alkyl substituted propynylamines lead to β- and γ-lactames or oxazolines.[64]



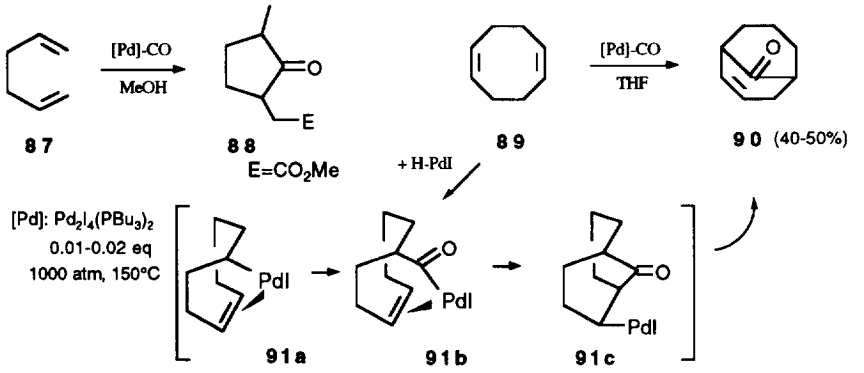
Simple 3-arylpropynes react with iodoarenes in the presence of CO and $Pd(OAc)_2$-PPh_3 to form *E*-arylydenebutenolides in 33-88% yields.[65]



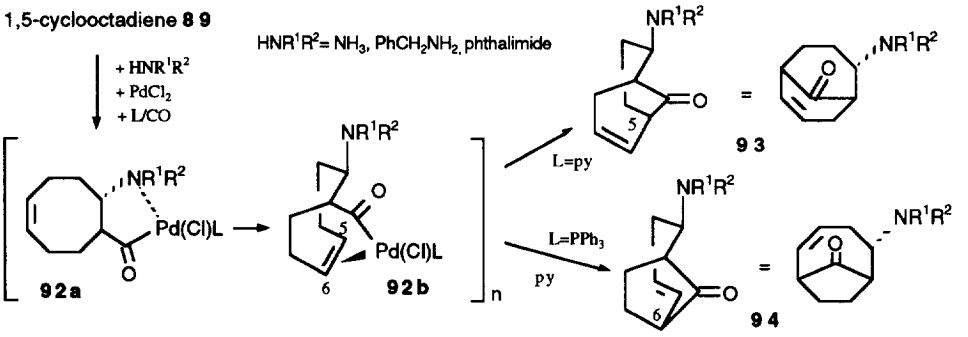
Since acid chlorides can be used instead of iodoarenes, the authors propose that the initial step involves generation of acetylenic ketones. During the reaction, $Et_3NH^+I^-$ can provide a route to Pd-H by reversible dehydroiodination. Addition of the palladium hydride to acetylenic ketones **84** may give the vinylpalladium complex **85a**. Enolisation, carbonylation insertion, ring closure leads to *E*-arylydenebutenolides **86** with regeneration of the catalytic species H-PdX.

3.3 Organopalladation-insertion of non-conjugated dienes

Known nearly as long as palladium catalysed oxidation of olefins, the combination of diene functionalisation and carbon monoxide insertion has been studied in cyclisation processes. Indeed the early reactions of 1,5-dienes involve the incorporation of CO into the new ring, and carboxylative interception in the termination step.[66] The reaction of 1,5-hexadiene under 'industrial-type' conditions (high pressure, high temperature) has been discussed in the part A of this review;[1] the transannular addition of carbon monoxide to 1,5-cyclooctadiene, yielding bicyclo[3.3.1]non-2-en-9-one most probably follows similar reaction pathways, except the last, palladium hydride elimination, step.[67,68]



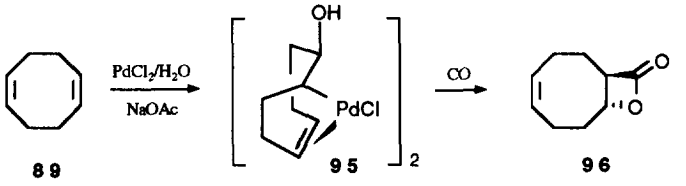
Trans aminopalladation-CO insertion of 1,5-cyclooctadiene proceeds under milder reaction conditions and the obtention (no yields are reported) of different (bridged bicyclic) ring sizes, **93** or **94**, seems to depend on the ligands present in the catalyst combination.[69]



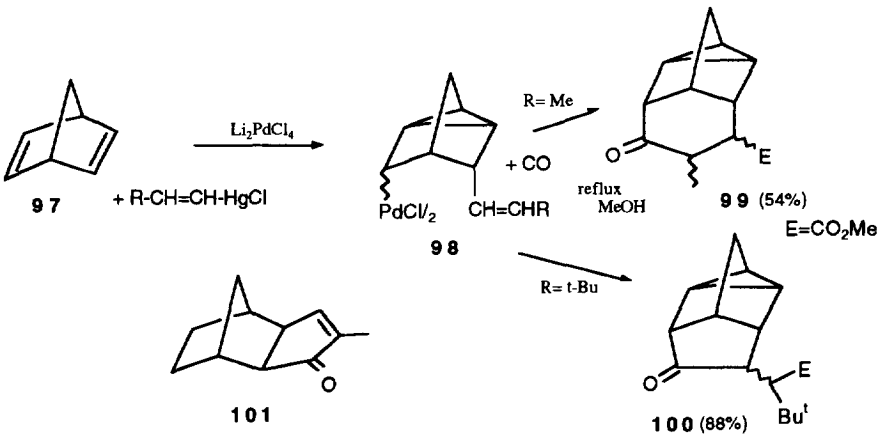
These few examples show interesting carbocyclisation reactions, however, the conditions leading to ring formation with 1,5-dienes are peculiar and in many cases simple carbonylation is the main reaction.[70]

In one case another type of cyclisation has been observed. Hydroxypalladation of one double bond of **89**

followed by CO insertion leads to bicyclic ß-lactone **96** but water addition and carbonylation do not affect the second double bond.[71] This reaction was one of the first examples that clearly demonstrated the *trans* stereochemistry of the nucleophile (water) addition across the coordinated double bond (cf. Wacker reaction).[46,72]

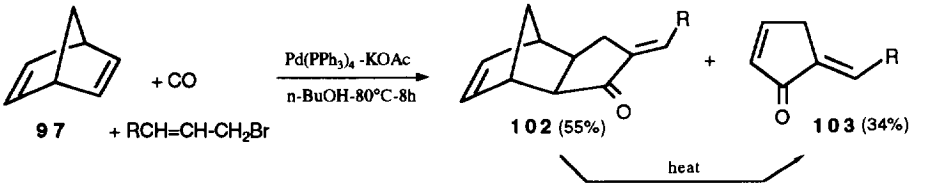


Norbornadiene can react with carbon monoxide and nucleophilic agents in different ways. When heteroatomic nucleophiles are added in the presence of palladium the carbonylation of the nortricyclene intermediates takes place exclusively during the termination step.[73] In case of vinyl palladium species R-CH=CH-PdCl, accessible *via* R-CH=CH-HgCl, several cyclisation-CO insertion reactions may lead to polycyclic ketones **99** or **100**[74] with the incorporation of CO into a new cyclic system combined with the carbonylative final interception according to the reaction conditions. The ring size of the lastly formed ring is controlled by the bulkiness of the olefin substituent.



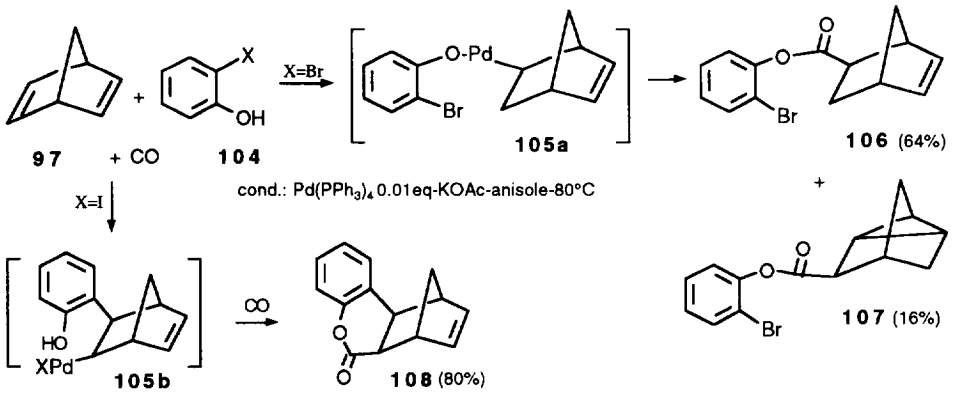
In comparable reactions of norbornene with palladium π-allyl complexes and subsequent treatment with CO annelated tricyclic ketones of type **101** are the reaction products. The *cis-exo* stereochemistry usually observed in this system is found in stoichiometric[74] as well in other catalytic reactions.[75]. In both carbonylations (norbornadiene and norbornene) the presence of triethylamine suppresses the cyclisation step, most probably due to decoordination of the double bond(s).

The usual *bis cis-endo* addition to norbornadiene (e.g. **98** and subsequent products), which is a consequence of coordination of palladium to this face of the diene,[1,76] may compete with the *cis-exo* mode when palladium π-allyl complexes are added to norbornadiene under conditions described by Chiusoli and co-workers.[75]



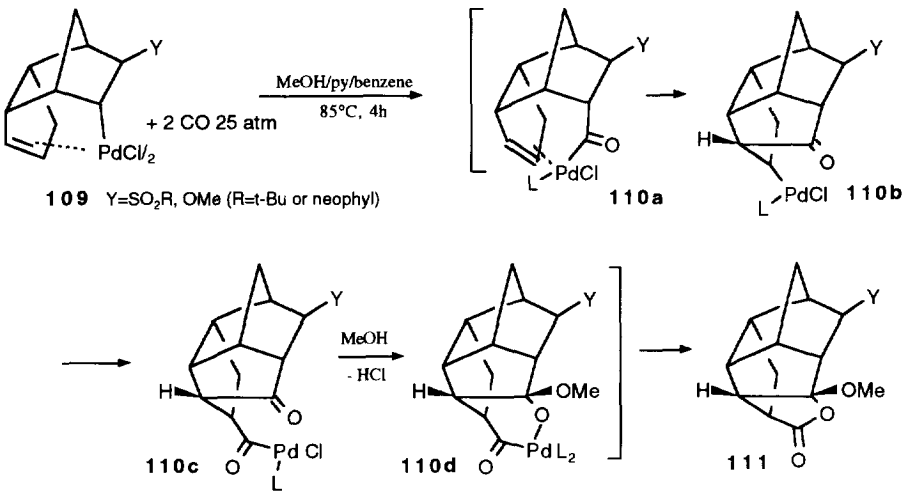
A subsequent retro Diels-Alder reaction yielding substituted alkylidene cyclopentenones **103**, which to some extent takes place during the carbonylation, is an interesting application of this transformation of norbornadiene.

Cis-exo addition to **97** is also observed with aryl palladium complexes favoured by an intramolecular η^2-arene coordination.[77] With *ortho*-halogenophenols and CO the mode of cyclisation is controlled by the nature of the halogen atom.[78]

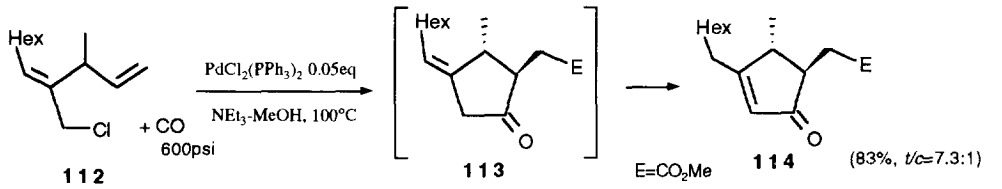


As a consequence of competition between OH or halogen activation in the metallation step palladium *O*-aryl complex **105a** or aryl norbornane σ-complex **105b** (X=I) are predominating intermediates, and ring closure to the polycyclic lactone **108** including CO insertion is possible with *ortho*-iodophenols exclusively. With this selective transformation of one of the two double bonds in **97**, heterocyclic ring systems are accessible (e.g. coumarin from **108**) after a retro Diels-Alder reaction.

Other alkenyl norbornene derivatives such as 5-vinyl-2-norbornene[79] or the palladium complexes from dicyclopentadiene such as **109**[73] cyclise selectively to polycyclic brendane type carbonyl compounds **111**.[80] This double carbonylation (quantitative yield) is highly *cis* stereospecific (twice: **110b** and **d**) with retention of configuration (**110a** and **c**) and constitutes, in principle, a one step synthesis of a functionalised pentacyclic compound from the dimer of cyclopentadiene. Spatial proximity and partial formation of the hemiacetal lead to a (rare) lactone-acetalisation demetallation step.



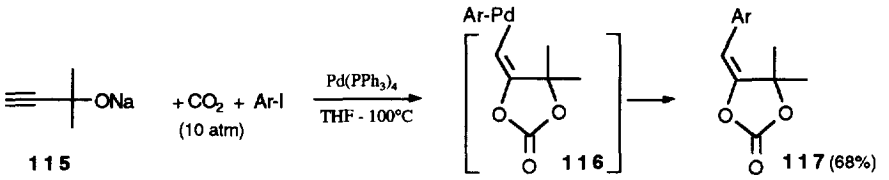
A different type of cyclisation-carbonylation is inherent, (which involves allylic electrophiles) for non-conjugated diene structures.[81,82] During cyclisation of **112** the high pressure conditions (CO: 600 psi, 100°C) favour double carbonylation and fairly good *cis/trans* selectivities (**114**, *trans/cis* = 7.3:1). On the other hand the extracyclic double bonds in the kinetically controlled reaction products **113** isomerise to the thermodynamically more stable intracyclic enone structure **114**.[82]



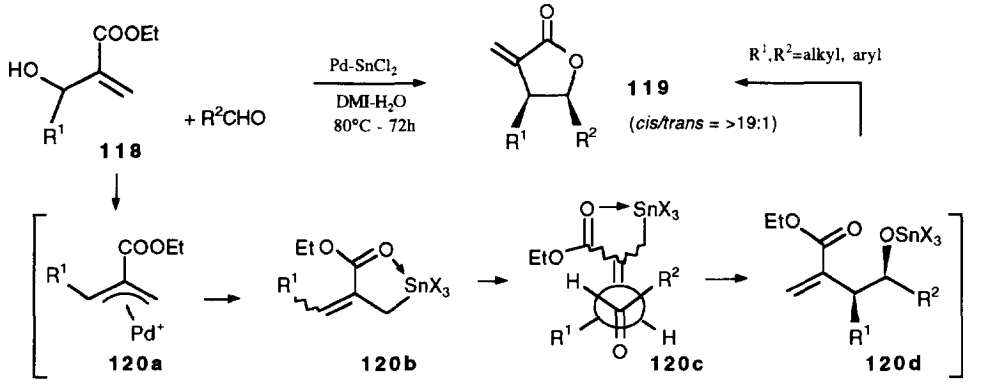
3.4 Insertion of CO_2, aldehyde or vinylether

In most of these cyclisation-insertion reactions carbon monoxide is the carbon unit that is easily incorporated into the new ring system. Nevertheless the reaction of other small molecules such as carbon dioxide,[83] aldehyde[84] or vinyl ethers[85] has been studied.

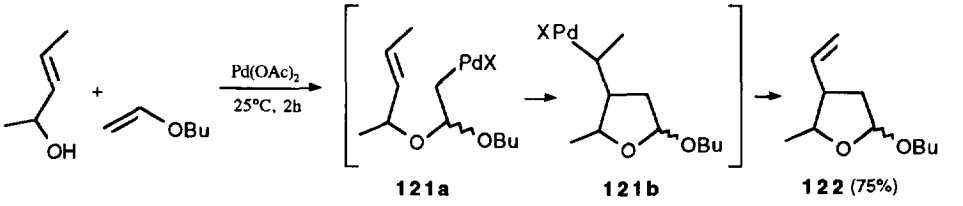
Inoue's[83] carboxylative cyclisation of propargylic alcohols involves the coordination of arylpalladium iodide to the acetylenic monoalkylcarbonate, formed from CO_2 and **115**, (*trans*) nucleophilic attack on the triple bond with concomitant cyclisation to **116** and reductive elimination.



Palladium-tin catalysed allylation of 2-(hydroxymethyl)acrylate compounds **118** leads *via* 'carbonyl insertion' to α-methylene-γ-butyrolactones **119**.[84] The most reactive carbonyl compounds are aldehydes, however, cyclohexanone can also be used (formation of spiro compounds). Poor to acceptable yields (< 61%) are combined with very high *syn* (*cis*) stereoselectivity in **119**. Coordination of the carboxylate C=O to Sn(IV) in **120b** as well as an acyclic antiperiplanar transition state **120c** are probably the origin of this remarkably high diastereoselectivity.



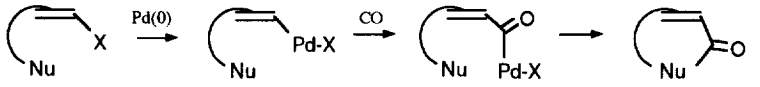
The stoichiometric (or catalytic, $Pd(OAc)_2$-$Cu(OAc)_2$) cycloalkenylation of allylic alcohols with vinyl ethers is conceptually interesting; however, these reactions do not show any stereodiscrimination in the cyclised tetrahydrofurans (e.g. **122**).[85]



The corresponding pyrrolidine derivatives are formed when the reaction is performed with allylic tosylamides instead of allylic alcohols.

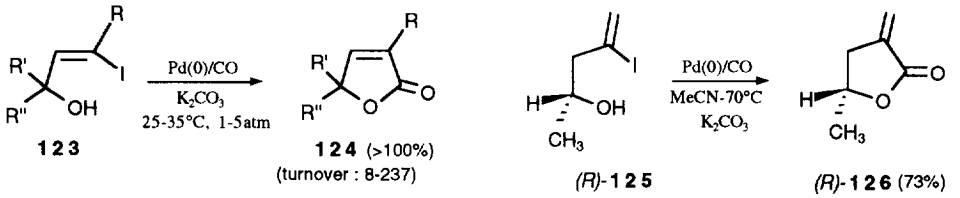
3.5 Heck-type reactions

The transformation of vinyl or aryl halides, *via* the corresponding palladium σ-complexes under Heck-type reaction conditions, has been studied extensively for cyclisation reactions.[1,6,86] Carbonyl insertion into these sp^2-carbon-palladium bonds was shown in numerous examples to be more rapid than the direct reaction with the nucleophile (cyclisation step), making this system highly suitable for tandem reactions (Scheme 4).



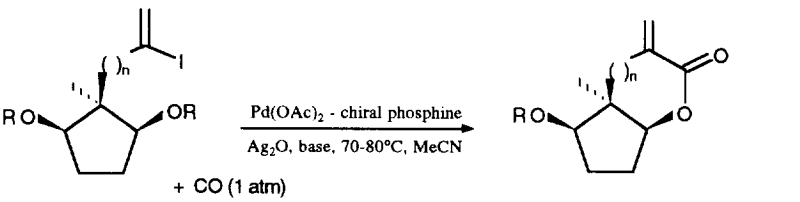
Scheme 4

According to Stille's[87] fundamental work, the palladium catalysed carbonylation of hydroxy vinyl halides or triflates[88] constitutes a general route to lactones. The sequence is illustrated by the cyclisation of vinylic iodides **123**[87] and (*R*)-**125**.[89] Under very mild reaction conditions vinyl and aryl halides containing alcohol groups lead to a variety of lactones with high turnover rates. The reaction is completely stereospecific as shown by the formation of optically pure α-methylene lactone (*R*)-**126** from (*R*)-**125**. This type of reaction[89] is complementary to Norton's carbonylation of homopropargyl alcohols.[60] If several ring sizes are possible the reaction selectively leads to γ-lactones.



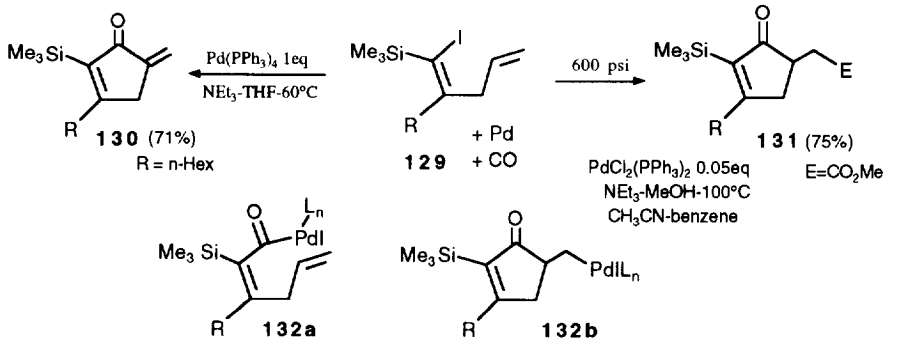
Similar amidation-cylisation of vinyl and aryl halides are interesting for the construction of nitrogen heterocycles,[90] particularly for the synthesis of ß-lactams[91] and ß-lactam antibiotics.[92]

A catalytic asymmetric synthesis of α-methylene lactones from prochiral alkenyl halides **127** (n=0, R=H or trimethylsilyl) was achieved with optically active bidentate phosphines such as (*R*)-binap, (*S,R*)-bppfa, (*S,S*)-bppm, (*S,S*)-chiraphos and (+)-norphos.[93]



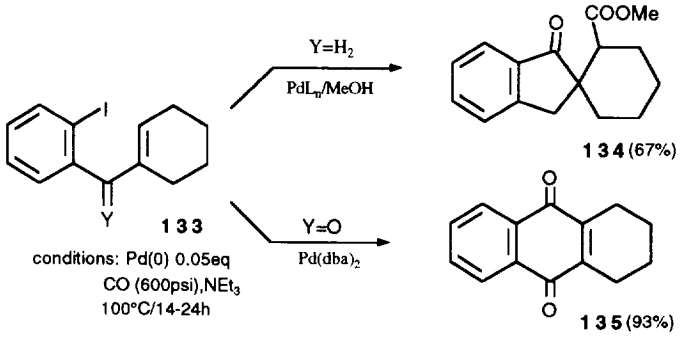
Best results (44%, 57% ee) are obtained with the alkenyl halide **127** (n=0, R=H) and (*R*)-binap/Ag_2O as selectivity controlling agents. Under the same conditions no induction was found for **127** (n=1, R=H) because of complete racemisation of the corresponding lactone **128** (n=1, R=H). This has been explained by the very close proximity of the hydroxyl group to the lactone ring. The racemisation is reduced considerably when the OH is silylated.

The participation of carbon nucleophiles in these carbonylations (double bond, stabilised soft malonate type nucleophiles, enolates vinyl metals) leads to the formation of two new carbon-carbon bonds. Negishi and co-workers,[94] have studied intramolecular Heck-type alkenylation-carbonylation of vinyl- and aryl iodides. Stoichiometric[94a] and catalytic[94b,c] transformation of 1,4- and 1,5-dienes, as well as the related aromatic compounds, selectively give rise to cyclisation in the *exo*-mode after carbon monoxide incorporation (formation of the five- and six-membered ring, respectively). The metal-elimination step is highly important for the overall selectivity and stoichiometry since polymerisation seems to accompany the formation of the conjugated exo-methylene double bond in the stoichiometric transformation to **130**. This problem has been overcome under catalytic reaction conditions by a second, terminative carbonylation in the presence of methanol to give **131**.[94b]

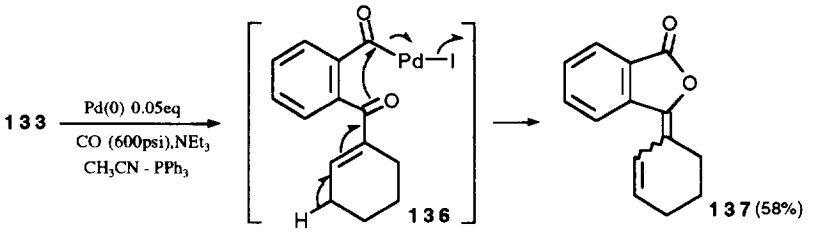


Intramolecular alkenyl- or arylpalladation[1] was shown to proceed easily without CO in olefinic compounds comparable to **129**. In this respect the carbonylative transformation of **129** exclusively *via* acyl- and alkyl palladium complexes **132a** and **b**, including a second carbonylation of the cyclic intermediate, is especially noteworthy.

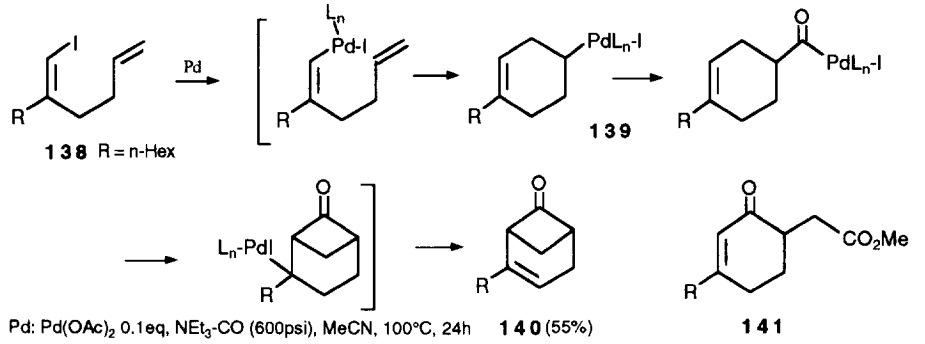
The following regiochemical directing effect from the '*exo*' to the '*endo*' mode is the consequence of the presence or absence of a carbonyl group in **133**.[94c]



The regiospecific quinone synthesis (**133** → **135**) is replaced by transposition and lactone formation in cases when either phosphines are present or the olefinic double bond is tetrasubstituted. Thus in the previous example phosphines retard the addition of the acyl palladium species to the alkene and competitive reactions can occur (**133** → **137**).[94c,d]



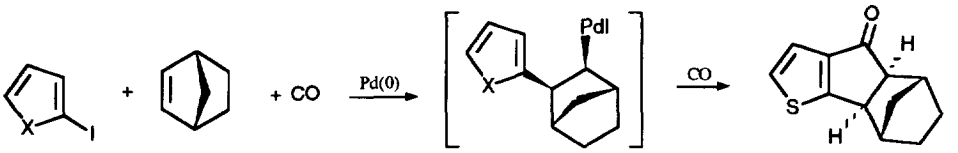
This enolate trapping cyclisation has recently been analysed in detail[95] and *O*-enolate trapping may efficiently compete with *C*-enolate trapping, more precisely when the formation of five- or six-membered enol lactones is possible.



The dependence of the final reaction products from the strict observation of certain reaction parameters can nicely be seen in the cyclisation of the 1-iodo-1,5-hexadiene **138**.[94b] Whereas double carbonylation in methanol gives rise to the 'normal' product **141** the absence of the alcoholic solvent orients the system to twofold cyclisation and the formation of the bridged bicyclic pinanone **140**. The mechanism *via* palladium intermediates **139** is tentative and the order of alkenylation/acylation may be different.

The formal introduction of one carbon monoxide between vinylic units (vinylic triflate and vinylstannane) was used as the ring-forming step in macrocyclic terpenes.[96] The double bond geometry in both unsaturated groups is retained. Combining aryl halides and enamine vinyl groups in acylpalladation leads to the quinolinone derivatives.[97]

By a similar way aryl iodides react in acetonitrile with norbornene derivatives in good yields in the presence of thallium acetate and palladium(0) to tetracyclic ketones **145**.[98]

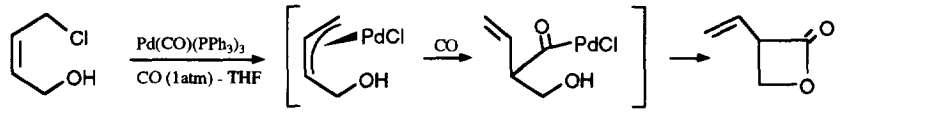


The carbonylative cyclisation of vinylic and aromatic halides together with malonate type carbon anions in the lateral chain has been reported by Negishi and co-workers.[99] The scope is reasonably broad and the reaction is useful for the obtention of five to seven-membered ring ketones, alicyclic in structure from vinylic precursors and annelated aromatic when aryl halides are cyclised . The transformation is, as 'usual' very specific with palladium (no direct alkenylation). However, this study also shows the feasibility of other late transition metals (Cu, Ni, Co, Fe) in the acylmetallation of unsaturated halides.

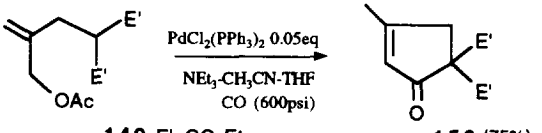
3.6 Cyclisation of allylic substrates including aromatic C-H activation

Cyclisation-carbonylation, involving allylic substrates has been studied only very scarcely. This may be attributed to the difficulties of the CO insertion into the allyl palladium bond.[100] Often pressure is necessary in order to enable carbonylative cyclisation with allylic and benzylic esters. Heteroatom (oxygen)[88] and stabilised carbon nucleophiles[99] may be used.

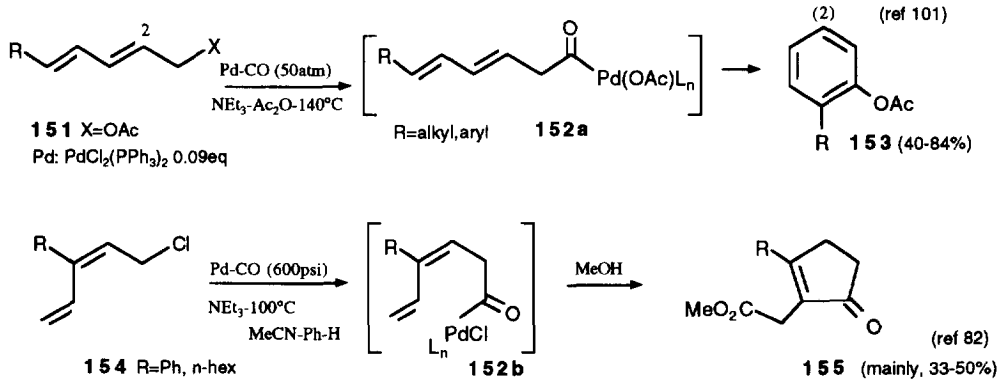
The low pressure and low temperature reaction of 4-chloro-but-2-en-1-ol **146** produces the ß-lactone - **148**.[88] The surprising absence of any δ-lactone (ring closure at C4), though CO insertion into primary palladium-carbon bonds is favoured over secondary ones, is rationalised by the intermediacy of the π-allyl palladium complex **147a**. From the different possible pathways to the ß-lactone, the direct carbonylation of the π-allyl complex **147a** is a reasonable alternative to the reaction *via* palladium σ-complexes.



Allylic acetates are generally poor substrates in catalytic allylic carbonylation reactions. Nevertheless, in the allylic acetate **149** the cyclisation with the carbon nucleophile can be driven with medium pressure to cyclopentenones **150**.[99]

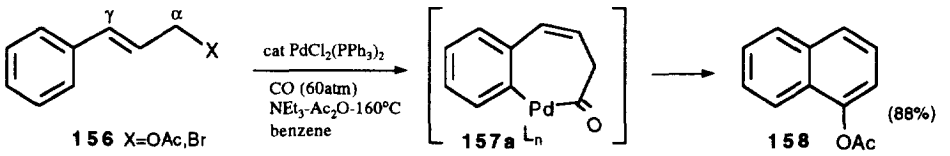


Moreover, conjugated dienyl allylic acetates show superior reactivity in cyclocarbonylation than allylic chlorides.[101] The α–ω cyclisation with incorporation of CO of penta-2,4-dienyl esters **151** (X=OAc) constitutes a selective synthesis of variably substituted phenyl acetates at *ortho*, *meta* and *meta'* positions (substituents at C2 and C4). The transformation of the *trans*-diene **151** involves *cis-trans* isomerisation of the internal double bond, intramolecular insertion of the terminal double bond into the Pd-CO σ-bond of **152a** as well as tautomerisation of the resulting cyclohexadienone and acetylation by acetic anhydride. Apparently these results are in contrast to Negishi's carbonylation of penta-2,4-dienyl halides.[82] These reactions, when performed in the presence of methanol as a nucleophile are inefficient with *trans*-olefins (**151**, X=Br does not cyclise) and dienes with *cis*-configuration **154** only form five membered unsaturated ketones after incorporation of two CO molecules, one into the cycle and another one into a terminal carbomethoxy group.



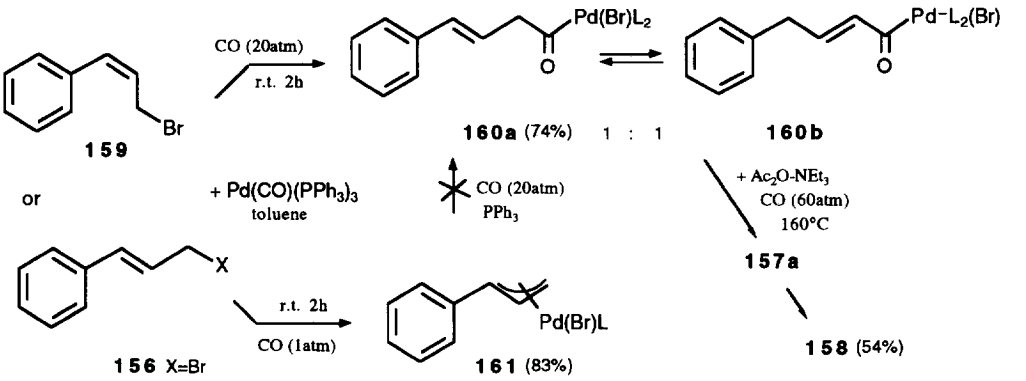
The reasons for this contradictory reactivity of penta-2,4-dienyl substrates under fairly comparable reaction conditions are not elucidated and need further investigations.

Closely related transformations of cinnamyl compounds under cyclocarbonylation conditions have been studied in more detail.



The phenol forming cyclisation[102] involves CO insertion as well *ortho* palladation of the aromatic ring. Acetic anhydride is necessary for the (final) esterification step. Substituents on the side chain and/or the aromatic ring lower the reactivity (ß-position on the allylic group, or *ortho* and *para* on the ring), or stop the reaction completely (α- and γ-position). *Meta*-substituted compounds can cyclise to two different isomers; the one with distant acetyl group being slightly favoured (*para*-cyclisation) and ratios of the isomers depending on the substituent (ratios of methyl substituent 58:42, and Cl 74:26). By reacting furans or 3-(2'-naphthyl)allyl acetates exclusive *ortho*-cyclisation takes place. In general, 3-(heteroaryl)allyl acetates undergo cyclisation in the case of 5-membered furyl-, thienyl-, pyrrolyl, and indolyl systems at the 2-position of the heterocyclic nucleus.[103]

A mechanistic study with cinnamyl bromides provided interesting mechanistic insights through the isolation of the palladium (and platinum) intermediates.[102,104]

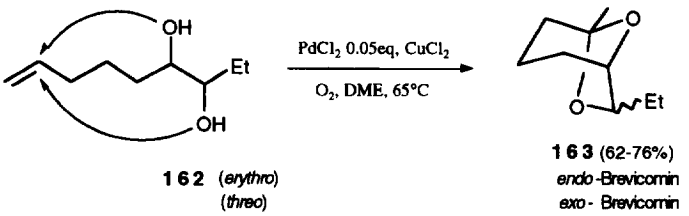


Though easily formed at 1 atmosphere CO pressure, the π-allyl complex **161** is not an intermediate in the cyclocarbonylation of cinnamyl compounds since it does not react to give σ-complex **160a**. The latter complex forms a 1:1 equilibrium with the conjugated acyl complex **160b** and is shown to lead easily to the cyclised aromatic acetate **158**. *Cis-trans* isomerisation, however, has to be a facile process at any stage of this cyclocarbonylation. *Cis-* or *trans*-configuration of the initial allylic bromide is unimportant for the overall reaction. On the other hand the reaction course from **160** to the final product requires *cis-rans* isomerisation, oxidative addition of the (*ortho*) aromatic C-H bond (**157a**), reductive elimination to the carbonyl compound followed by enolisation and acetylation to **158**.

4 Formation of more than one cyclic system

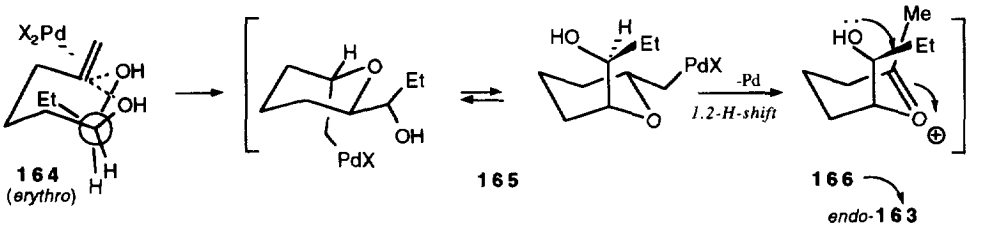
4.1 Addition of more than one heteroatom nucleophile to double and triple bonds

The geminal addition of two alcoholic functions across an olefin under Wacker-type reaction conditions is an elegant and direct synthesis of acetals and ketals.[105,106] The intramolecular version with vicinal diols easily leads to bridged dioxabicylo[n.m.1] systems.



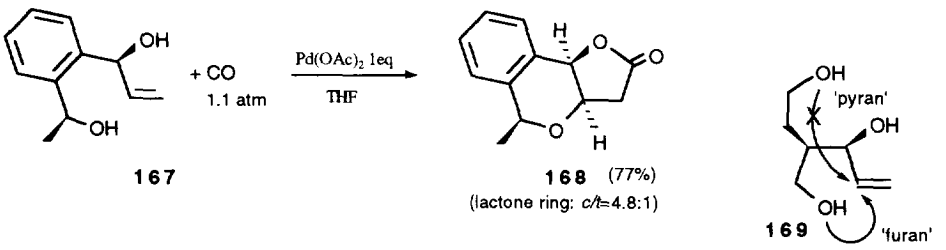
This is an interesting method for the obtention of oxabicyclic frameworks such as brevicomins, frontalins and other beetle natural products, and has been applied to the synthesis of di- or trioxabicyclic molecules of the

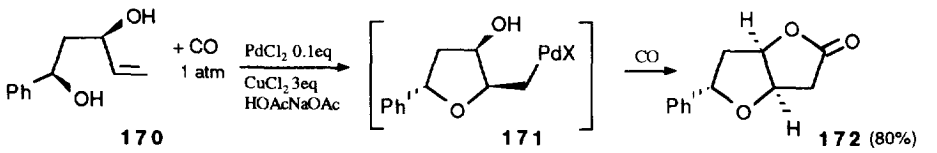
[3.2.1]-[107] [3.3.1]-,[108,109] and [4.2.1]-[107] skeleton, depending on the chain length and the relative position of the hydroxyl groups (1,2 or 1,3-diols).



In this intramolecular Wacker-type cyclisation the relative stereochemistry of the diol stereospecifically orients the cyclisation, e.g. *erythro*-**162** to the *endo*-brevicomin **163**.[107] The hydride shift that is involved cannot be a concerted process (S_N2-type substitution at the future methylated bridgehead position) because of the geometrical restrictions of the system. Thus, a reasonable alternative is the passage through the oxonium ion intermediate **166** (1,2-hydride shift) and the subsequent addition of the second OH group to carbon-oxonium bond.

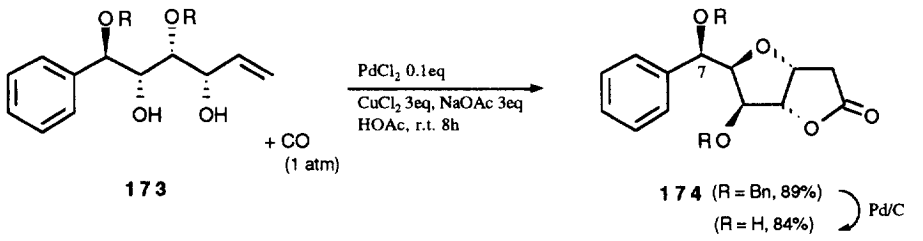
The double cyclisation, i.e. the addition of several nucleophiles across the same double bond becomes more versatile when carbon monoxide is incorporated at the same time. Semmelhack's[1,12] preparation of the fused γ-lactone **168**[110] has been the first of these reactions but other diol carbonylations,[111] addition of OH/COOH[112] or NHR/COOH[113] has been studied mainly by the Japanese group of Tamaru and Yoshida.



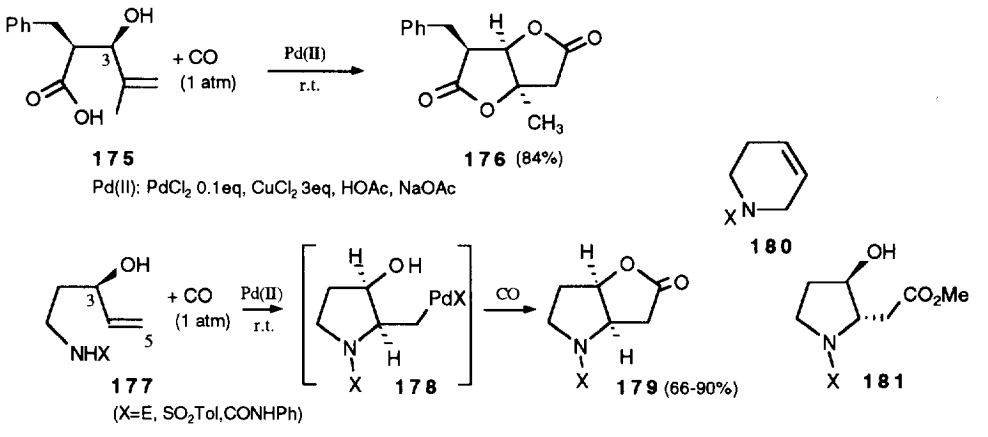


The stereoselectivity, which is moderately in favour of the *cis*-lactone (*cis*/*trans* = 5:1) in the alkoxycarbonylation of the bisbenzylic substrate **167**,[110] is high in the oxycarbonylation of 4-penten-1,3-diols such as **170**.[111] In addition, the highly efficient synthesis of *cis*-3-hydroxytetrahydrofuran 2-acetic acid lactones (**172**) requires catalytic reaction conditions. In the case of substituted double bonds (C4 or C5) the yields can drop. Cyclisation of **169** shows the high regioselectivity since this molecule, which has the choice between two cycles only cyclises to the bicyclic tetrahydrofuran compound (60% yield).

Oxycarbonylation of polyols, which are readily accessible from D-glucose, has been used for the syntheses of natural and unnatural enantiomers of goniofufurone **174** (R=H).[114]

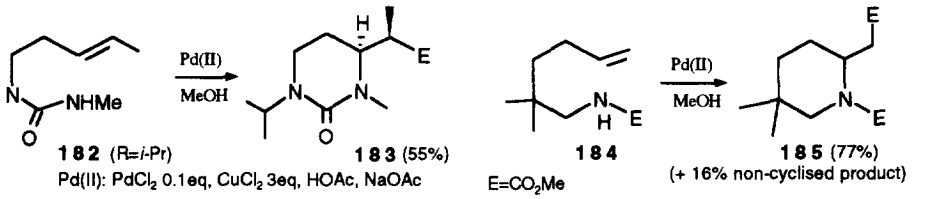


The scope of these intramolecular carbonylation reactions is quite broad since the second, non-allylic nucleophile may be a carboxy or an amido function. High yield stereoselective bis-lactonisation (**175** → **176**)[112] as well as aminolactonisation (**177** → **179**)[113] are the resulting *cis*-selective heterocyclic ring forming transformations.

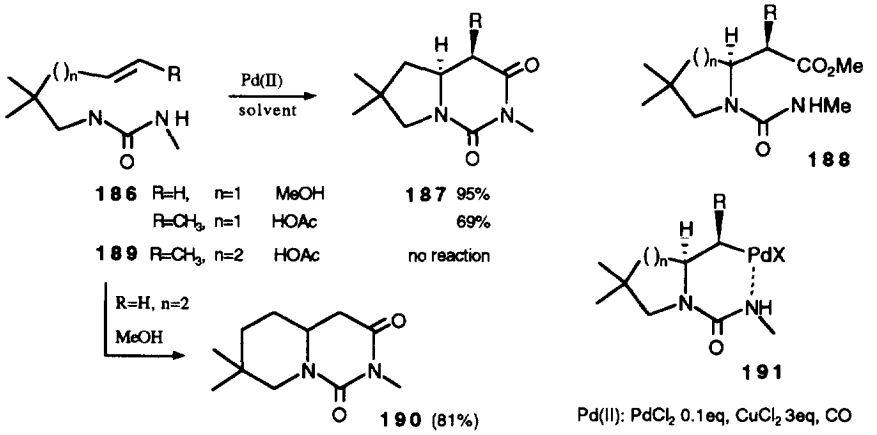


The intramolecular aminocarbonylation of protected 3-hydroxy-4-pentenylamines **177** (X=COOMe, SO_2Tol, CONHPh, CONHMe) constitutes a selective access to polyfunctionalised pyrrolidine derivatives.[113,115] Carbamate as a protecting group is more reactive than SO_2Tol. Acetic acid is the most useful solvent for the catalytic reaction. Monocyclisation products **180** and/or **181** together with non-cyclised compounds are formed in methanolic solutions. Substituents at C1 (*trans*-product), C3, C4 and C5 do not change the overall high stereoselectivity. Only a secondary carbon at position 2 leads to *cis/trans* mixtures (*cis*-lactone junction). On cyclising 4-hydroxy-5-hexenylamines similar reactions lead to 3-hydroxypiperidine-2-acetic acid lactones. However, these amidoalcohols are much less reactive, cyclise less stereoselectively and only urea is possible as a second nucleophile. Furthermore, the second amino function, only when carrying a methyl (and no aryl) group in the urea becomes competitive for a second cyclisation to annelated diazadiones (*vide infra*). The regio- and stereoselectivity in the second cyclisation is complex and despite a considerable amount of data no simple picture emerges.

The intramolecular amidation carbonylation of simple (non-allylic) carbon-carbon double bonds is a general transformation of protected alkenylamines[116,117] to five- and six-membered azacyclic systems. The notoriously bad reactivity of amines in aminopalladation of alkenes seems to be overcome when the Wacker oxidation system $PdCl_2$-$CuCl_2$ is combined to carbonylation conditions in protic solvents like methanol or buffered acetic acid. In addition to its influence on the reactivity of the system the nature of the protecting group can direct the ring formation to mono or biscyclisation.

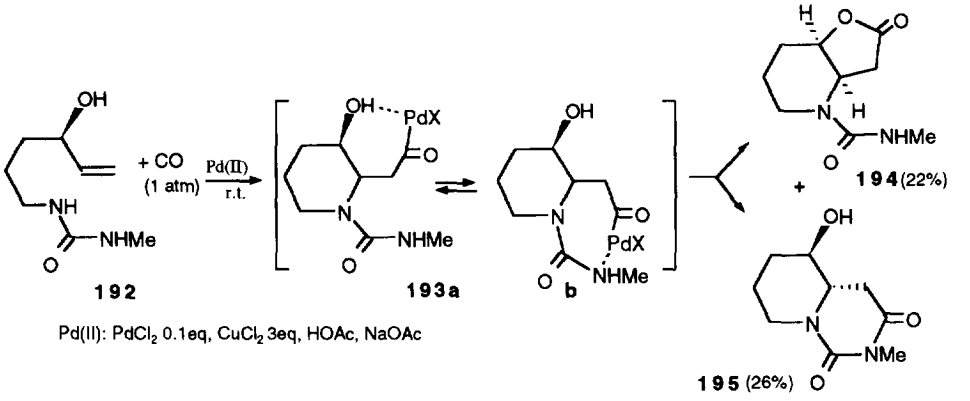


We present examples of cyclisation to six-membered rings which are much less abundant than those leading to cyclopentanes. The reaction supports substitution at the olefinic part and the stereochemistry of products (**183**) is the result of *trans* amino palladation (cyclisation step), insertion of CO and reductive elimination (termination step) with retention of configuration. The exact position and the nature of the amine protecting group are crucial. In **182** the second methyl amine of the urea is in the good position for the formation of a six-membered ring **183**. The ureidocyclisation proceeds most efficiently with moderately bulky substituents at the 'tandem' amino group. This is rationalised by the highest population of the conformer (C_{sp2}-N bonds) that is able to cyclise. When the amino group is placed at a 4-atom distance from the double bond different reaction patterns are possible. With carboxylate (E) or sulfonate groups at nitrogen monocyclisation-carbonyl insertion-termination is the principal reaction e.g. when **184** is oxidised to **185** with palladium-copper-CO catalyst (together with some direct carbonylation of the double bond). When applying urea as the protected amino unit two successive cyclisation reactions, involving both nitrogen atoms, lead to 1,3- and 1,4-diazabicycloalkane-2,4-diones **187** and **190**, respectively.



Substitution at the double bond slows down the rate and the better solvating ($PdCl_2$) acetic acid has to be used; in MeOH only monocyclisation seems possible (**188**, R=Me). This means that in these cases intermediate **191**, or its equivalent with carbon monoxide incorporated between C-R and Pd, is less favoured and intermolecular reductive elimination to **188**, or oxidative cleavage with copper chloride (chlorinated monocyclic compounds), instead of the intramolecular substitution, are the most favourable termination processes.

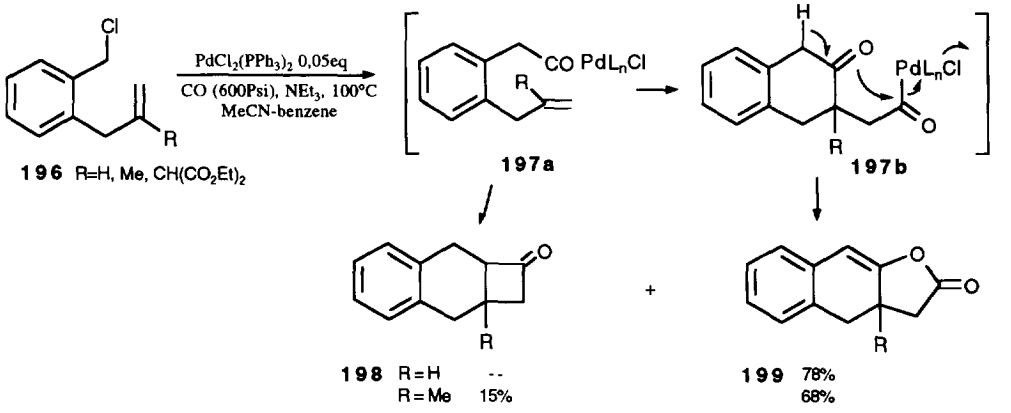
Two competitive intramolecular carbonylative terminations have been observed in 3-hydroxy-4-pentenylamines **192** with the urea protected amine.[113]

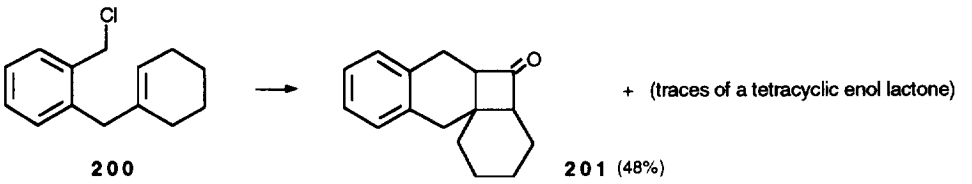


The sequential double addition to triple bonds in alkynediols and formation of spiro oxacyclic substrates was studied by Utimoto and co-workers.[118]

4.2 Addition of several CO groups to double bonds

The addition of two CO molecules to one double bond leads to intramolecular enol lactone formation with *o*-allylbenzyl chlorides *via* acyl-palladium intermediates. The reaction requires pressure and heat. Methanolysis gives mono- or non-cyclised carboxylic esters.

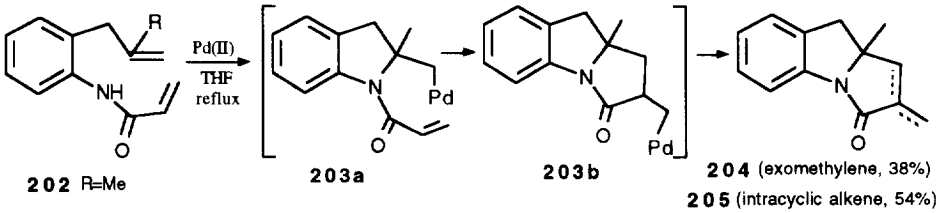




Replacement of MeOH by t-BuOH, or even better in the complete absence of an alcohol, substrates such as **196** lead to cascade cyclisation. Furthermore, increasing substitution of the alkene changes the reaction pathway to partial or exclusive formation of cyclobutanones.[119]

4.3 Multi-cyclisation by means of several unsaturated groups

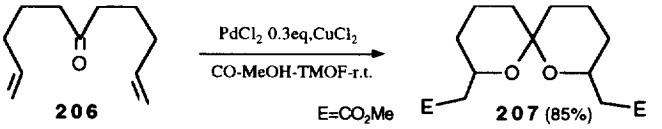
The direct access to tri- and polycyclic frameworks from relatively simple starting material is an interesting and rewarding challenge. In polyene systems effective multicyclisation is synonymous with the ability for rapid (and repetitive) olefin insertion into carbon-palladium bonds instead of palladium hydride elimination or intermolecular substitution. With the (stoichiometric) synthesis of functionalised tricyclic pyrroloindoles *via* oxidation of N-substituted *o*-allylanilines Hegedus and coworkers[120] have demonstrated the principle.



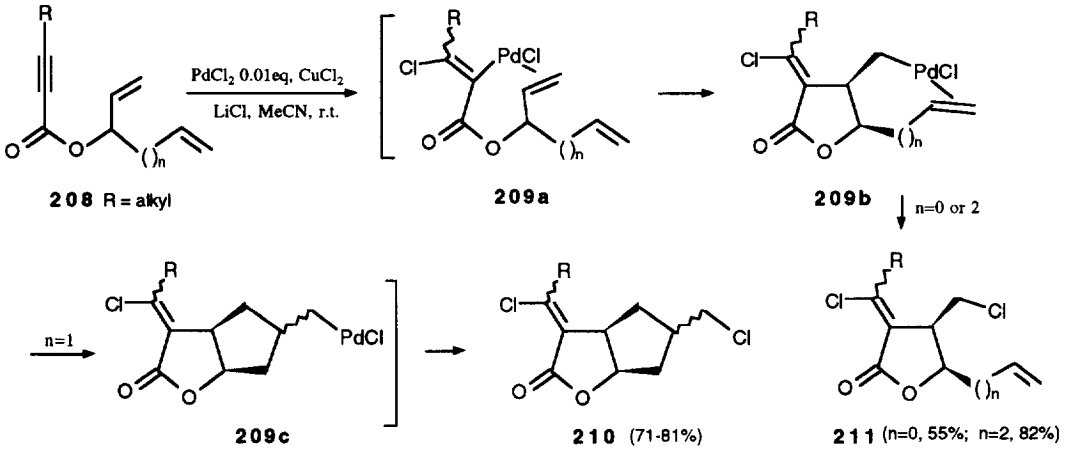
The inclusion of the quaternary methyl group to avoid ß-hydride elimination in the aminopalladated complex **203a** is not really necessary, since the noranilide **202** (R=H) cyclises (55% yield) readily to a comparable tricyclic indol derivative .[121] Even in **203b** the elimination can be avoided in favour of carbonylative cleavage.

4.3.1 Wacker-type oxidations

The catalytic oxidation-carbonylation of dienones in the presence of trimethylorthoformate (TMOF) and methanol is a convenient method for the construction of spiroacetals.[122] Stereochemistry and mechanism remain to be defined.

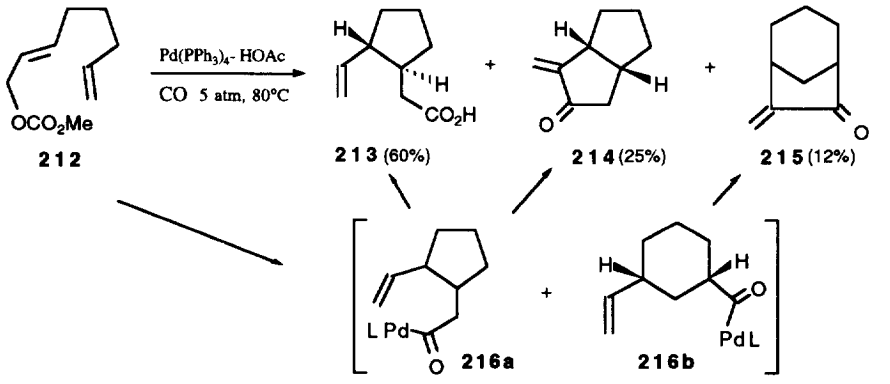


The oxidative cyclisation of allylic alkynoates has recently been developed by a Chinese group as a method for the construction of α-alkylidene-γ-butyrolactones.[123] The cascade carbopalladation-cyclisation, such as with 1,5-hexadiene 2-alkynoates **208** seems possible when the potential second cycle is a five-membered ring.[124,125]

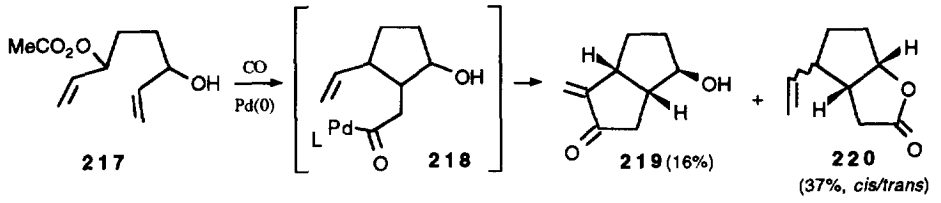


4.3.2 Metallo-ene reactions

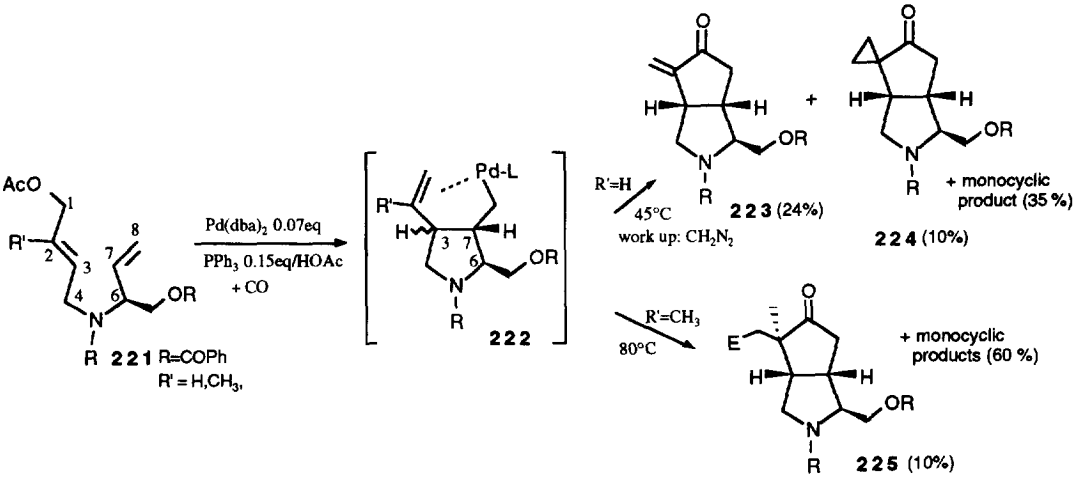
If we consider the role of σ-carbon-palladium bonds and the importance of protic solvents (HOAc) in tandem cyclisations it is clear that the metallo-ene cyclisation[21] of allylic substrates should also be prone to carbonyl insertion, and thus double cyclisation. Another of these variants of Oppolzer's metallo-ene reaction gives interesting bicyclic compounds. With 1,6-dienic allylic carbonate **212** the biscyclisation only takes place to a minor degree.[126] It is worth mentioning that the obtention of **215** (12%) is another example of an (unusual) cyclisation to the six-membered ring under carbonylation conditions.



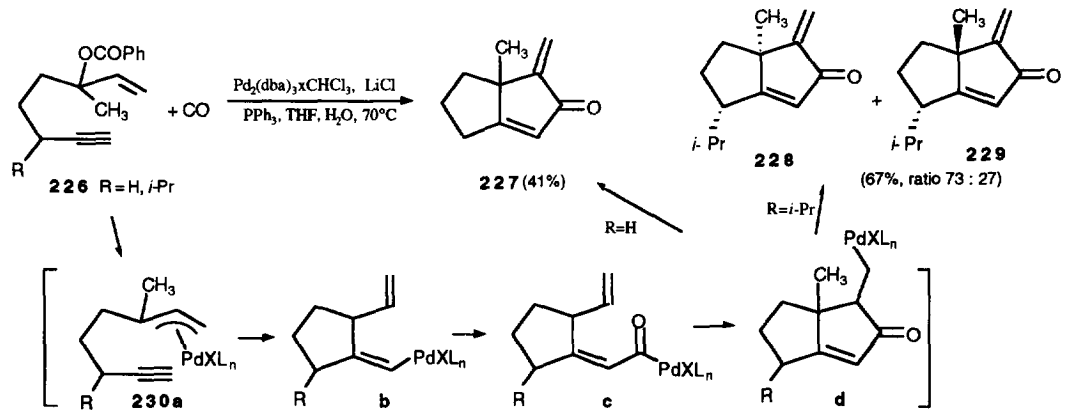
The incorporation of an OH group for potential intramolecular esterification is helpful since all mono cyclisation is suppressed. The system is still only moderately reactive. Nonetheless, it is interesting to find that both modes of second cycle ring closure (C-C or C-O bond) proceed with complete *cis*-control of the ring junction.



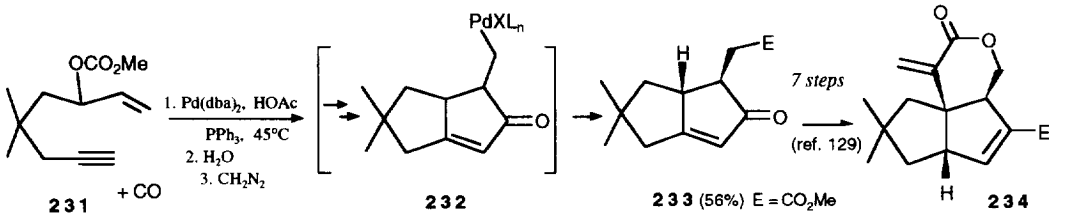
One such transformation, the carbonylation-olefin insertion of **221**[127] has already been discussed in part B.[2] The degree of bicyclisation as the minor reaction pathway depends on substitution pattern of the allylic acetate in **221**.

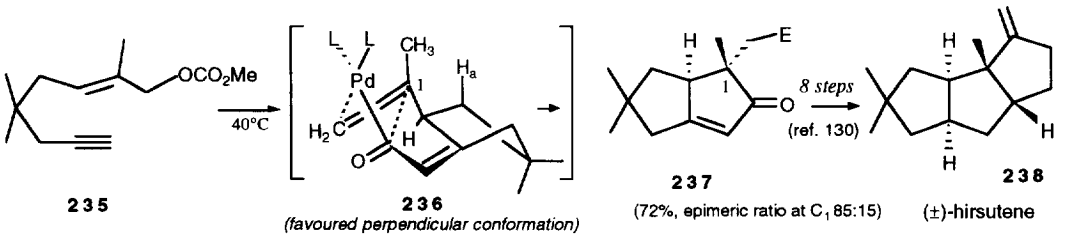


Another approach to the quinane skeleton uses tertiary allyl carboxylates as substrates.



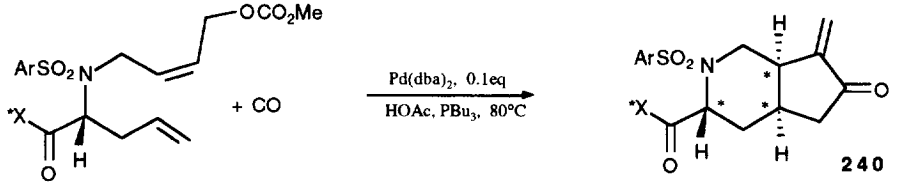
Fair to good yields and exclusive biscyclisation characterise the alkyne- and CO insertion cascade from **226** to α-methylenecyclopentenone fused to five-membered rings **227-229**.[128] These quinane forming cascade reactions are most interesting for natural product synthesis such as the key intermediate for the synthesis of (±)-pentalenolactone methyl ester **234**[129] or hirsutene **238**[130] by palladium-ene-cyclisation-methoxycarbonylation of alkyne allyl esters **231** and **235**, respectively.



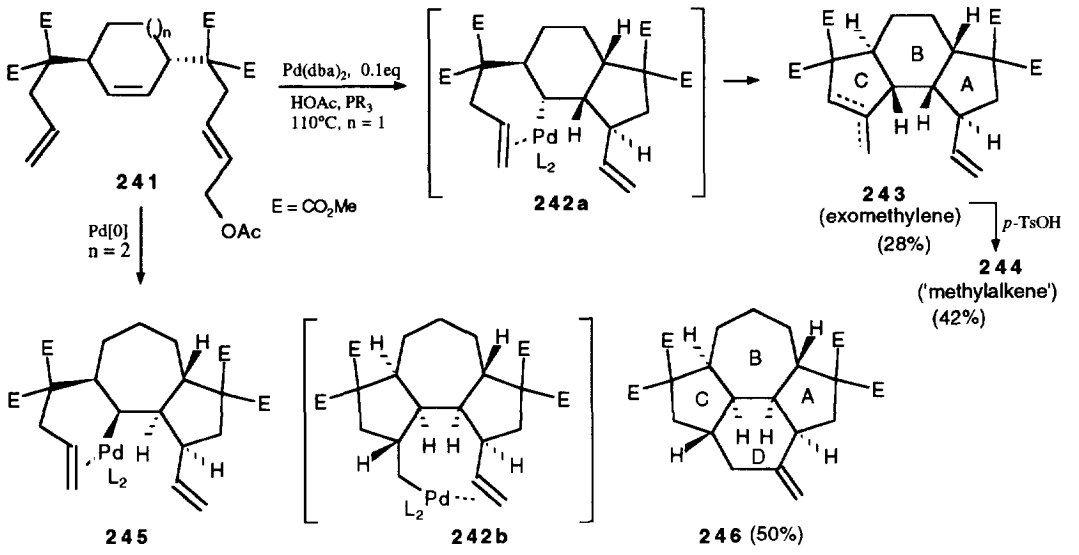


The stereochemistry of the quaternary C1 in **237** is a direct consequence of a favoured transition state conformation **236** which is free of strain and, according to Oppolzer, accommodates a suprafacial four-centre insertion of the alkene into the palladium-carbon bond.

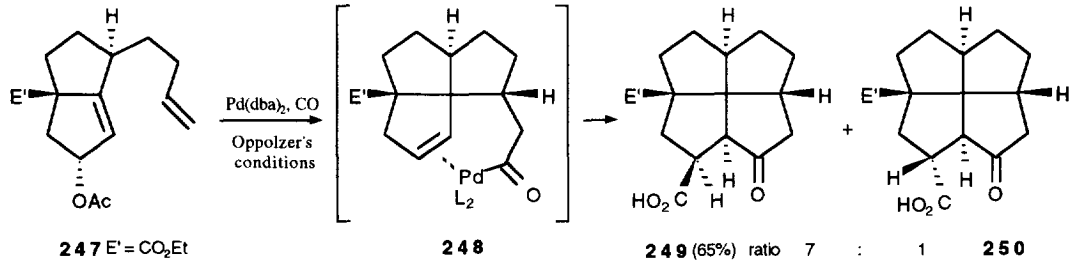
In the cyclisation of **239** the chiral sultam auxiliary controls the enantioselective palladium-ene-carbon monoxide-insertion cascade, which is the key step in the synthesis of (+)-3-isorauniticine.[131]



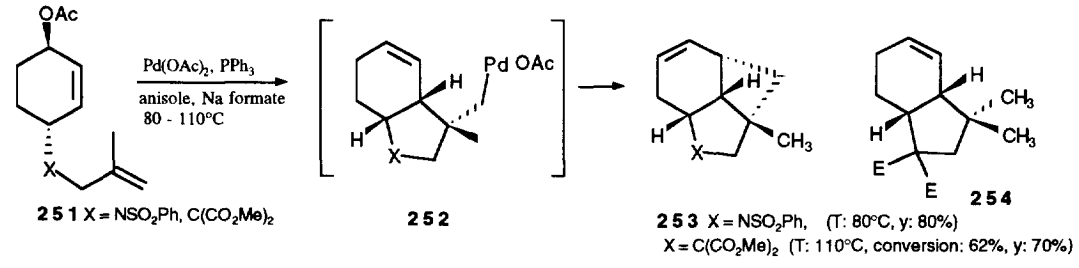
Polyfused rings are readily constructed when the final intermediate is (intramolecularly) trapped by alkenes instead of CO.[132] The topicity in (the first) A-ring is different according to the ring size of the disubstituted cycloalkene. The overall scheme is one (starting) Pd-ene reaction followed by one to two Heck-type insertion reactions.



The particular polyfused all-*cis*-[5.5.5.5]fenestranes **249** and **250**[133] are formed by double annulation-carbonylation of 1,6-enynes and 1,6-dienes **247**.[134] The double cyclopentane formation from cyclopentene palladium-ene/carbonylation seems conformationally less restrictive than the comparable addition to cyclo-hexene which does not lead to double annulation.



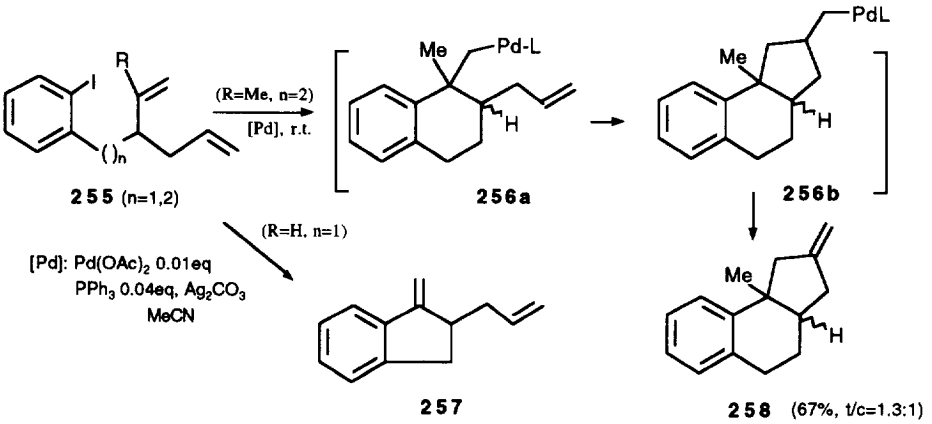
More strained polyfused rings form *via* double *exo*-trig cyclisations.[135]



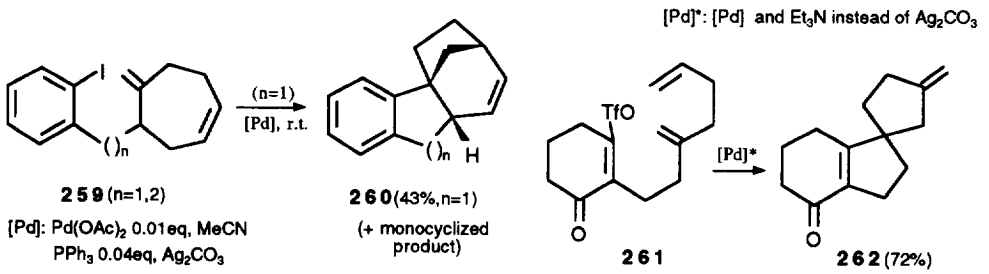
The bicyclisation to **253** is interrupted with the formic acid ion capture system[136] yielding only mono-cyclisation product **254**. This type of bicyclisation can also start with a (Heck) vinyl-Pd intermediate.

4.3.3 Heck-type reactions

The most important contributions to polycyclisation involving several unsaturated groups have been made by applying Heck-type chemistry.[6,7] This includes palladium(0) catalysis and carbocyclisation with several double and triple bonds. Polyene cyclisations of aryl, benzyl and vinyl halides or triflates have been studied by Overman,[137,138] Negishi[139] and Grigg.[140] The principle is easily perceptible from Overman's biscyclisation of **255** to fused tricyclic compounds **258**.[137]

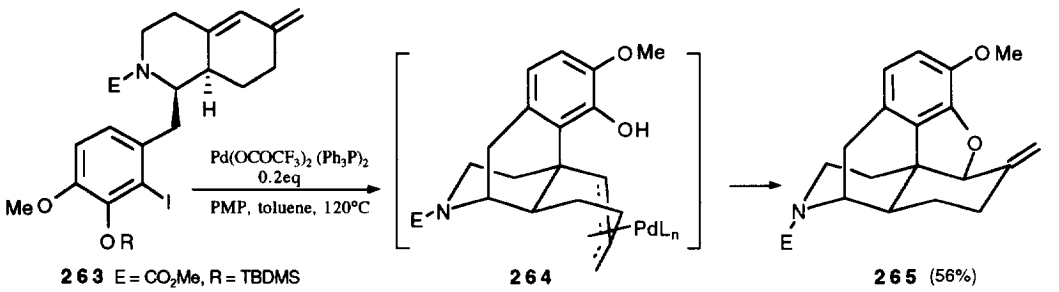


The key-tandem step is the intramolecular trapping of the first primary alkylpalladium complex (**256a**) by insertion of the alkenyl side chain (**256b**). Limited by the presence of a ß-alkyl group in order to suppress the simple hydride elimination e.g. **255** → **257**, the formation of **260** (and higher homologues) from **259** reveals the exciting possibilities in polycyclic synthesis. The application for spiro cyclisation-annelation is shown with trienyl triflate **261**.[138]



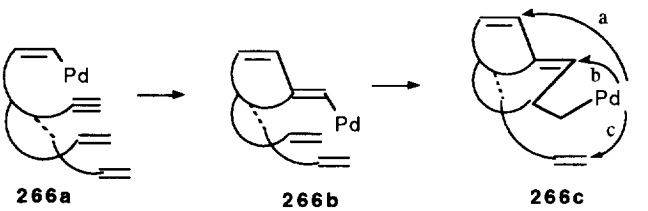
The utility of such polyene cyclisations has been demonstrated with other syntheses e.g. the tetracyclic diterpenic scopadulcic acids A[141] and B[142] (Table 1, entries 1 and 2).

A particular biscyclisation, which complements the asymmetric 'Heck-approach' to opium alkaloids[143] uses a tandem Heck carbocyclisation-intramolecular oxygen trapping thus allowing the one-step construction of the carbocycle and dihydrobenzofuran ring of the morphane framework.[144]



263 E = CO_2Me, R = TBDMS **264** **265** (56%)

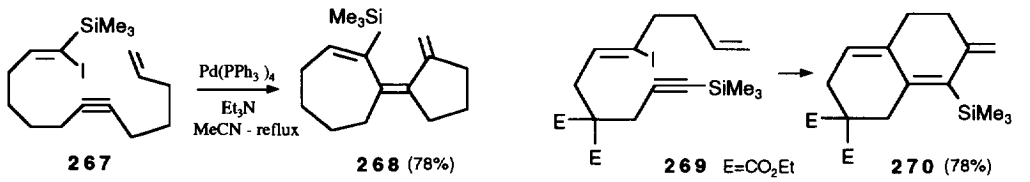
On combining alkenes and alkynes tri- and tetracyclic structures have been realised under carbopalladation conditions by Negishi and co-workers.[145 - 150] The increased stability of alkenylpalladium species (addition of Pd(II) to an alkyne) with respect to σ-alkyl palladium complexes is a very promising aspect for polycyclisation reactions (Scheme 5). The alkyl palladium species from vinylic or aromatic halides **266a** react with the triple bond to form **266b**, which will be intercepted by an additional double bond. The resulting bicyclic system **266c**, now may react *via* ß-hydride elimination or according to path a, b, or c, in cases when another double bond is present in the molecule, and thus allows the cascade transformation to continue.



266a **266b** **266c**

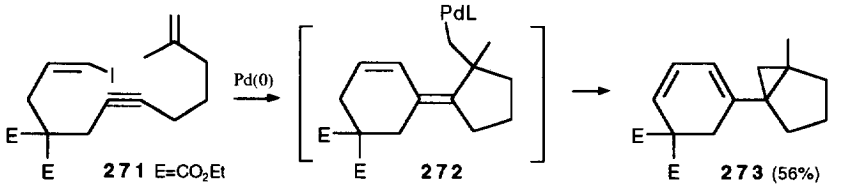
Scheme 5

The two simplest reactions with the double bond reacting in consecutively at the alkyne and the vinyl group, proceed in the prognosticated way and with final palladium hydride elimination for the conversion of **267** → **268** and **269** → **270**.[145]

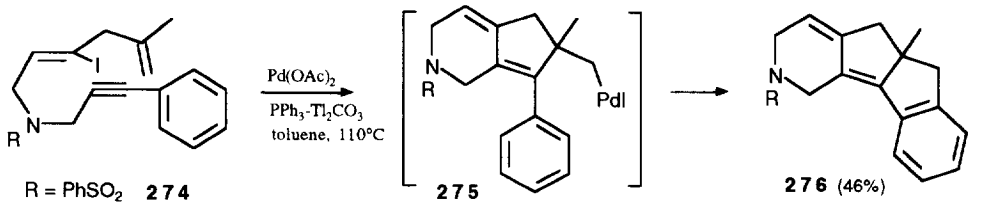


267 **268** (78%) **269** E=CO_2Et **270** (78%)

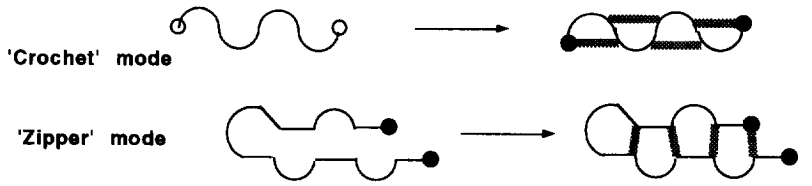
Exclusive termination-cyclisation at the proximal double *via* path b (Scheme 5) is the consequence of di-substitution at the terminal double bond.[145,151]



Multicyclisation processes can be also terminated by a formal Friedel-Crafts reaction involving attack of an σ-alkylpalladium(II) intermediate on an aryl or heteroaryl ring. Since these formal Friedel-Crafts alkylation reactions occur at both electron rich and electron poor heteroaromatic rings, the authors suggest a Pd(IV) intermediate by insertion into the sp^2 carbon-hydrogen bond of the cascade terminating aromatic ring.[152]

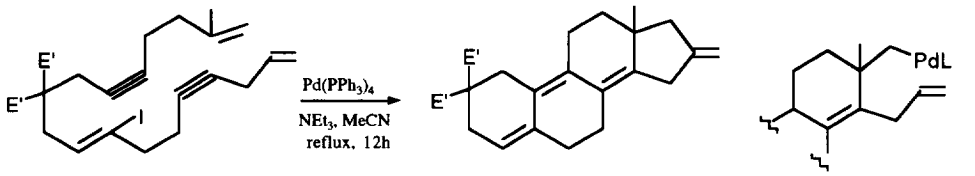


Other examples of these exciting multicyclisations concern those molecules where different unsaturations, including one or two triple bonds are arranged in order to react through multiple cyclisation, principally in the 'Zipper' mode.[146] Thus the catalytic palladium mediated polyenyne cyclisations are complementary to Johnson's biomimetic polyene cyclisations,[153] which proceed according to the the 'crochet mode' (Scheme 6).



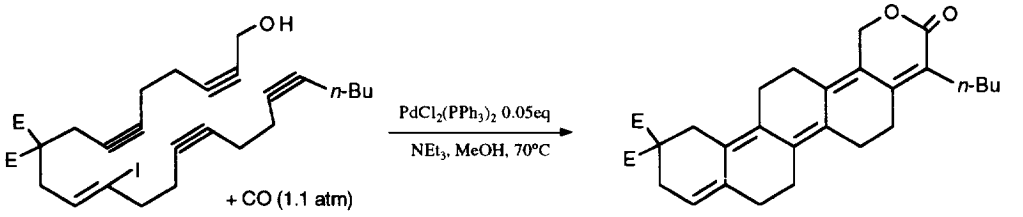
Scheme 6

Although the scope of these 'one-step' cyclisations is far from being reached at this time, it is possible to perform tri- and tetracyclisations, e.g. **277** → **278** in an extremely clean and selective manner with yields ranging from 76 to 95% (!).[146] In the penultimate, neopentyl like palladium intermediate **279** the cyclopropanation, observed previously with **271** becomes disfavoured, provided an 'ultimate' double bond is present (**266c** path c, Scheme 5).



277 E'=CO_2Et **278** (76%) **279**

The possible CO insertion in such polycyclisation reactions is deferred until the last, termination step and the carbometallation-carbonylation cascade of **280** yields the pentacyclic lactone 281.[149]



280 E=CO_2Me **281** (66%)

Some selected examples of various kinds of Heck-type cascade cyclisations combined with carbonylation and carbon or heteroatom anionic trapping[154,155] are shown in Table 1, among which are the stereoselective access to highly complex molecules,[156,157] synthesis of triquinanes,[158] and the formation of spiroheterocyclic systems[159-161] including the use of vinyl triflates as starting material.[162]

Table 1

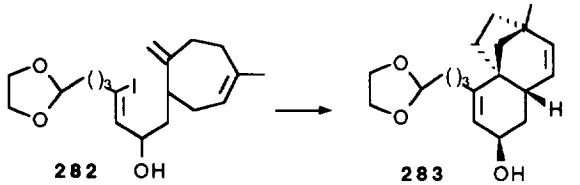
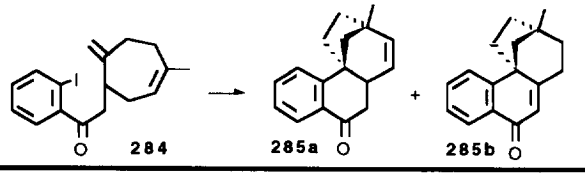
entry	reactions	conditions	comments	ref.
1	 **282** OH **283** OH	$Pd(OAc)_2$ PPh_3 (1:2, 0.1eq), Ag_2CO_3 THF, reflux y: 82%	total synthesis of scopadulcic acid A	142
2	 **284** **285a** **285b**	$Pd(OAc)_2$ PPh_3 (1:2, 0.05eq), MeCN, 80°C y: 80-85%	total synthesis of scopadulcic acid B	142

Table 1 continued

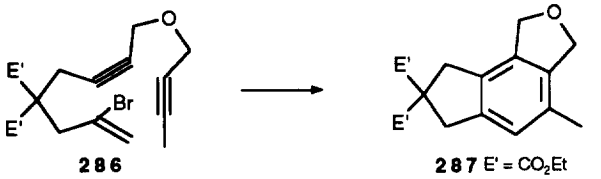
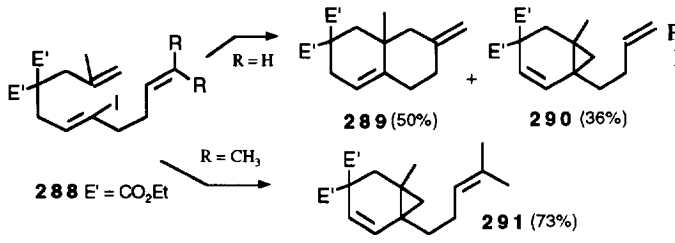
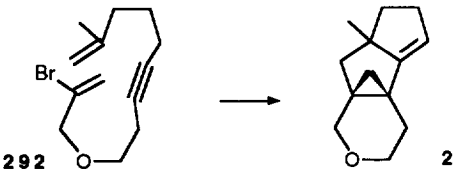
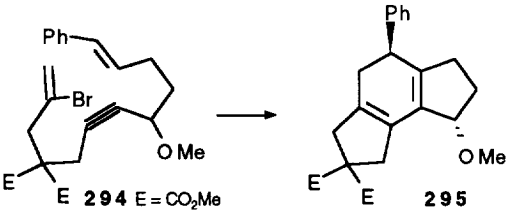
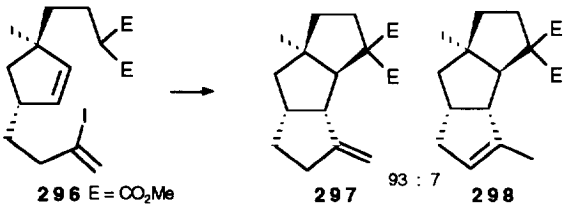
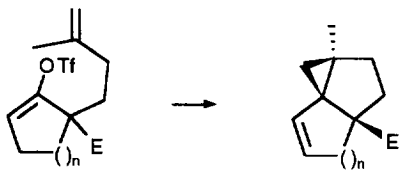
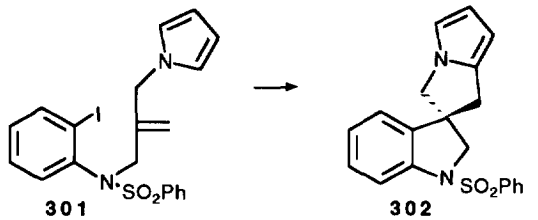
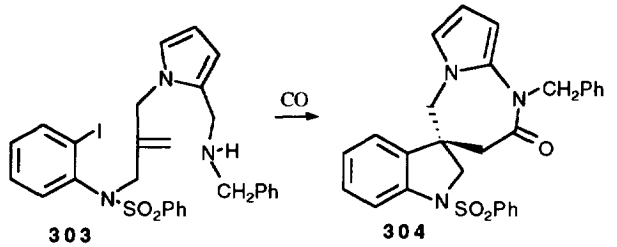
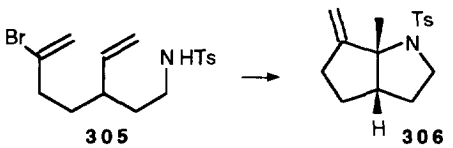
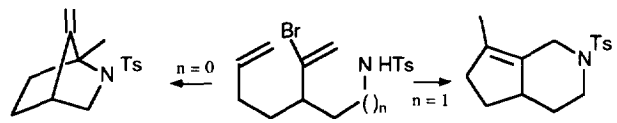
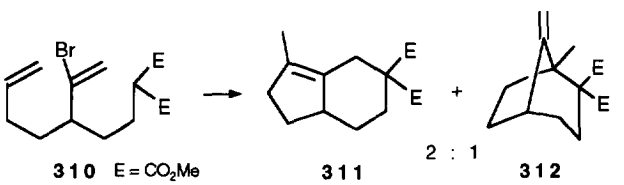
entry	reactions	conditions	comments	ref.
3	 **286** **287** E' = CO_2Et	$Pd(PPh_3)_4$ (0.03eq), MeCN, NEt_3, reflux y: 85%	route to benzene and fulvene derivatives	147
4	 **288** E' = CO_2Et **289** (50%) **290** (36%) **291** (73%)	$Pd(0)L_n$, NEt_3	cyclisation - cyclopropanation - rearrangement	148
5	 **292** **293**	$Pd(PPh_3)_4$, MeCN Ag_2CO_3 reflux y: 62%	synthesis of tetracyclic systems containing a three-membered ring	156
6	 **294** E = CO_2Me **295**	$Pd(OAc)_2$ PPh_3 (1:2, 0.1eq), K_2CO_3, MeCN, 60°C y: 83%	stereoselective route to complex polycycles	157
7	 **296** E = CO_2Me **297** 93 : 7 **298**	KH, THF, $Pd(OAc)_2$ dppe (1:2, 0.05eq), r.t. y: 70%	polycyclisation including carbon nucleophiles direct approach to triquinanes, (capnellene)	158
8	 **299** E = CO_2Me **300** n = 1-3	$Pd(OAc)_2$ PPh_3 (1:2, 0.1eq), Na_2CO_3 MeCN, 80°C TAAC y: 70-73%	cyclisation-cyclopropanation of vinyl triflates	162

Table 1 continued

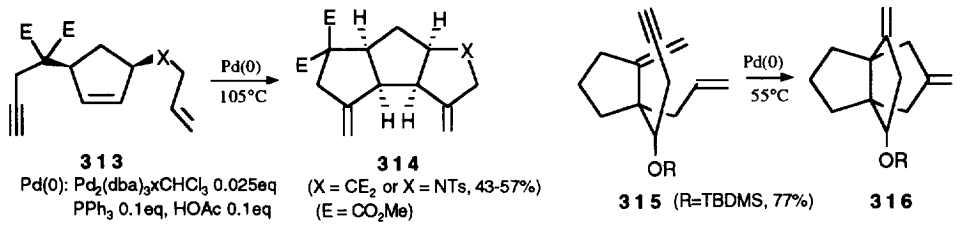
entry	reactions	conditions	comments	ref.
9	 **301** **302**	$Pd(OAc)_2$ PPh_3 (1:2, 0.1eq), anisole, KOAc, 130°C y: 59%	heteroatom spirocycles *via* cascade cyclisation	161
10	 **303** **304**	$Pd(OAc)_2$ PPh_3 (1:2, 0.1eq), TlOAc, MeCN, 80°C y: 45%	cascade spiro cyclisation - carbonylation - anion capture	160
11	 **305** **306**	$Pd(OAc)_2$ (0.05eq) (*o*-Tol)$_3$P,DMF, Na_2CO_3, NBu_4Cl, 65°C, 78%	tandem cyclisation and subsequent trapping of intermediate π-allyl Pd complex	154
12	 **308** (49%) **307** **309** (67%)	*idem* 65-75°C	synthesis of nitrogen heterocycles	154
13	 **310** E = CO_2Me **311** **312**	$Pd(OAc)_2$ (0.05eq) (*o*-Tol)$_3$P, NaH, DMF, NBu_4Cl, 50°C y: 74%	rapid construction of functionalised carbobicycles	155

4.3.4 Cycloisomerisations

Trost's[163] palladium catalysed cyclisation *via* isomerisation,[164] the other very general enyne conversion, was shown to be an extremely useful tool for ring construction in the cascade mode.[165]

The reactive vinyl palladium species that initiates the cyclisation(s) is generated through the addition of palladium hydride to the triple bond. The propagation proceeds *via* the successive insertions of the proximal double bonds into the carbon-palladium σ-bonds. The juxtapositions of the different unsaturations determine the size

and the topology of the ring systems. It allows formation of annelated, triquinane type molecules **314**, [3.3.3] or [3.3.4] propellanes e.g. **316** and spiro systems **318** and **319**.

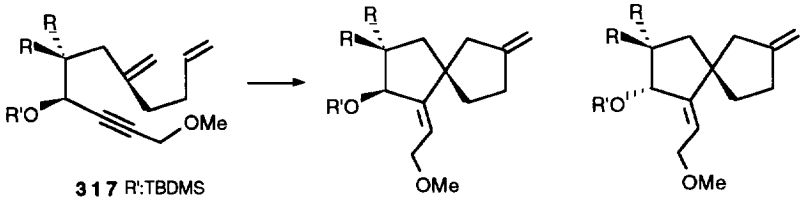


313
Pd(0): $Pd_2(dba)_3xCHCl_3$ 0.025eq
PPh_3 0.1eq, HOAc 0.1eq

314
(X = CE_2 or X = NTs, 43-57%)
(E = CO_2Me)

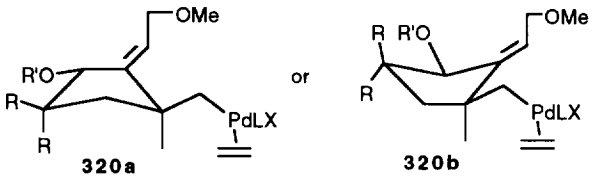
315 (R=TBDMS, 77%) **316**

The diasteroselectivity of spirocyclisation is efficiently controlled by alkyl substituents, apparently disfavouring transition states leading to **320a**, the precursor of the minor isomer **318b**.



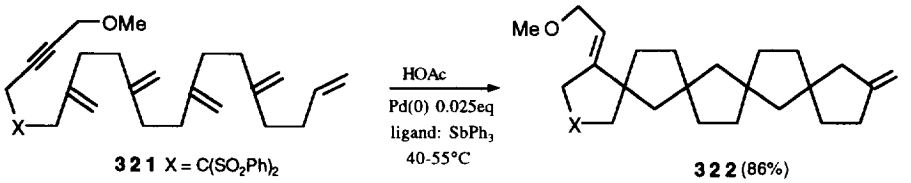
317 R':TBDMS

318a (R=H, 1 : 1.3) **319a**
318b (R=CH_3, <1 : >20) **319b**



320a **320b**

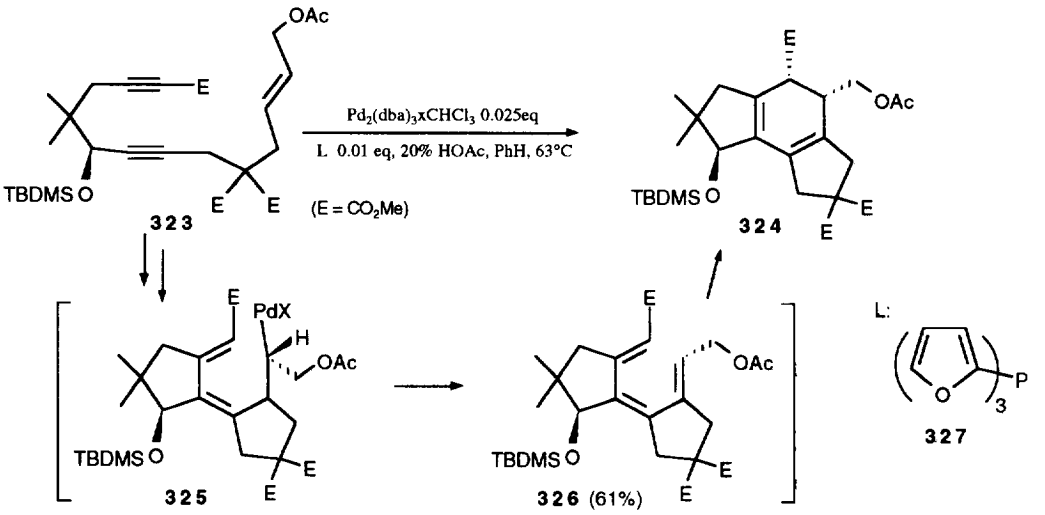
Trost[165] has demonstrated the potential scope of this cascade with the formation of a pentacyclic polyspiro framework **322**, composed of mainly two diastereoisomers in the incredible yield of 86%. Two higher cyclo-homologues e.g. six and seven cyclopentanes 'in line' have also been synthesised in the, respective, yields of 79 and 77%.



321 X = $C(SO_2Ph)_2$ **322** (86%)

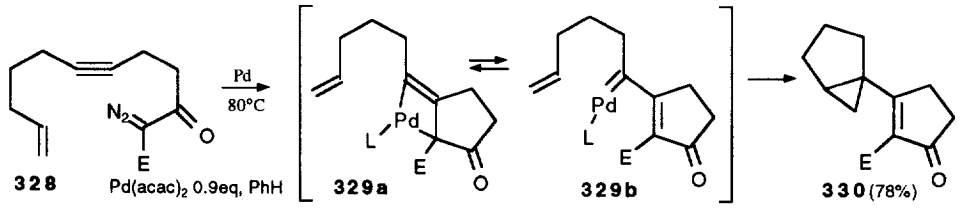
The cycloisomerisations of endiynes[166] creates tricycles with extraordinary diastereoselectivity.[167] The polycyclisation of **323** may serve as an example. The tricyclic diene **324** is obtained as a single diastereoisomer

and it has been shown on several compounds that the allylic oxygen directs the hydrogen β-elimination away from the acetate carbon thus generating the conjugated alkatriene which in turn undergoes intramolecular Diels-Alder[168] reaction, probably assisted by palladium coordination. The proper choice of reaction conditions prevents ordinary allylic functionalisation.

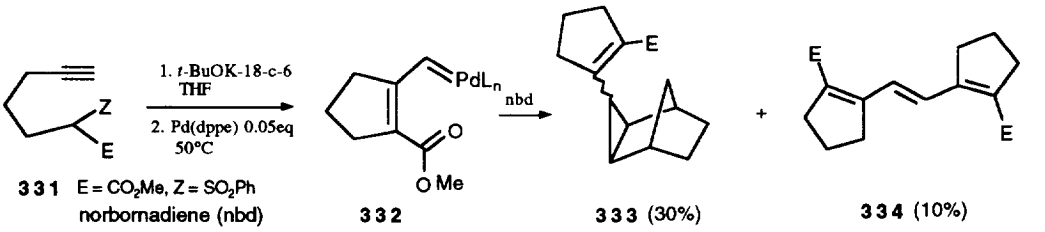


4.3.5 Cyclisation *via* carbenoids

Fairly uncommon is the tricyclisation reported by Hoye and co-workers,[169] suggested to be the result of metal carbenoid reactivity.



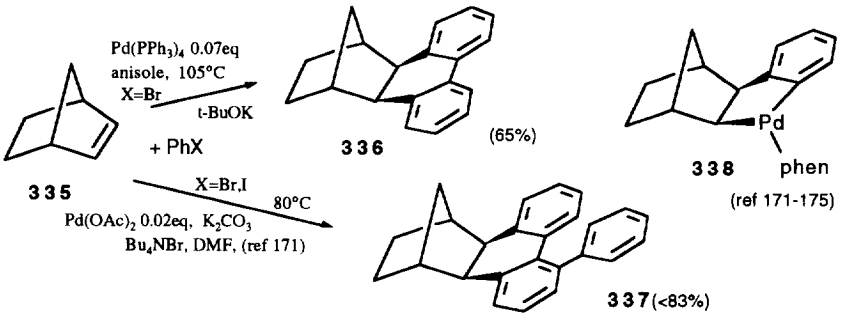
Palladium is the most reactive and selective catalyst in this reaction, and effectively the one that leads to polycyclic compounds. On the other hand, rhodium salts give rise to the formation of annelated ring compounds.



The cyclisation of certain α-sulfonyl ω-acetylenic esters has also been explained *via* the intermediacy of vinyl palladium carbenoids, such as **333**, which have been trapped by reactive dienes, for example the bridged bicyclic norbornadiene.[170]

5 Miscellaneous cyclisations

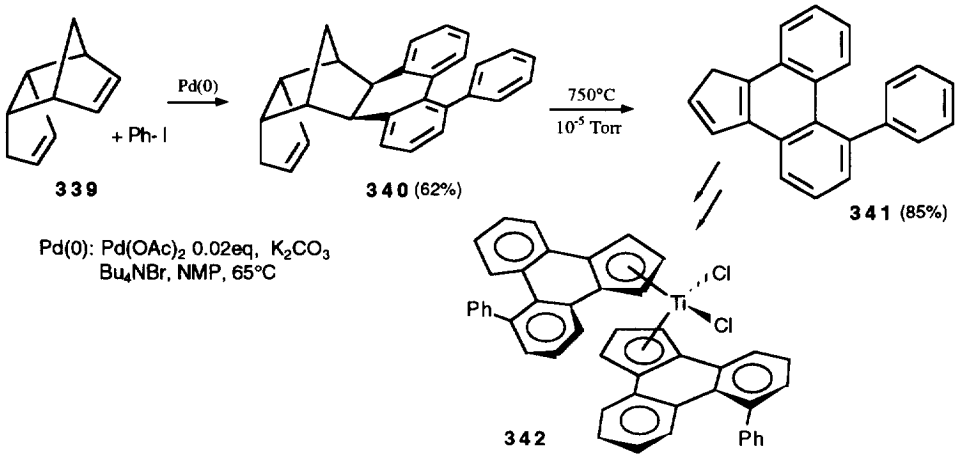
In this last part some isolated reactions shall be mentioned that lead in several consecutive reaction steps to bi- or polycyclic systems. Palladium catalysed aryl coupling can be repetitive at the same alkene, more precisely in the presence of the norbornene double bond. Annelated dihydrophenanthrenes such as **336** are the result of 1:2 Heck coupling.[171,172] Palladacyclic intermediates **338** have been suggested[173,174] and isolated after stabilisation with phenanthroline (phen) as a ligand. The *ortho* metallation step of intramolecular (σ-arene)palladium complexes was studied later.[175]



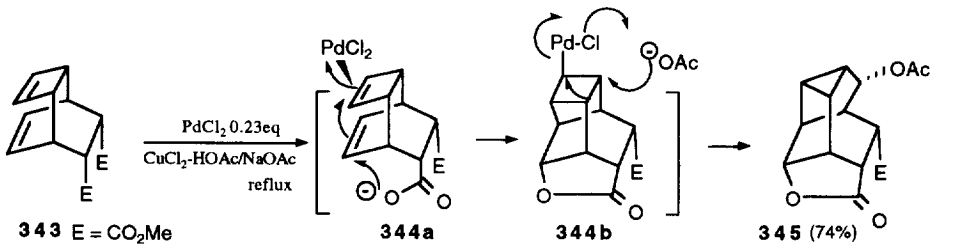
Switching to the 'Jeffery' conditions[176] (palladium acetate - carbonate - tetrabutyl ammonium bromide - DMF) one more aryl group is involved in the 'domino-Heck' coupling. This leads now to the 1:3 adduct **337**.[177]

When dicyclopentadiene **339** is used instead norbornene,[178] the domino-Heck coupling reaction of aryl halides gives polycyclic aromatic compounds **340** which after flash vacuum pyrolyses and complexation to titanium chloride are converted to **342**, complexes which might be potential catalysts for C—C bond forming reactions. The polyarylation of various norbornene derivatives with the control of 1:2 or 1:3 coupling products represents indeed a simple route to polycyclic aromatic compounds.[179] This type of polycyclisation is suppressed

in favour of *cis-exo*-2,3-diarylsubstituted norbornanes when the coupling occurs in the presence of tetraphenylborate anion.[180]

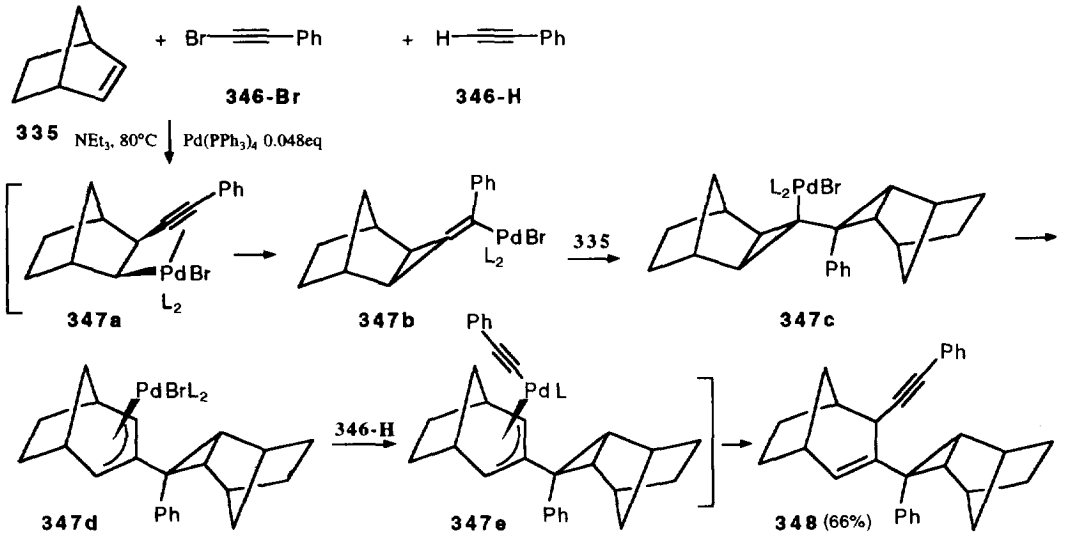


Sasaki's oxypalladation of the tricyclic diene **343**[181] follows a reaction pathway of intramolecular nucleophilic attack to the coordinated diene system with the formation of two new rings.

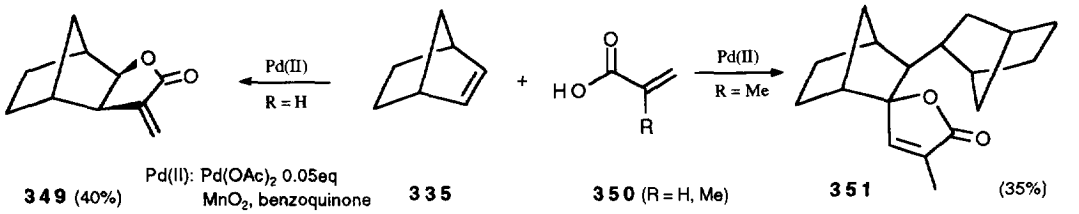


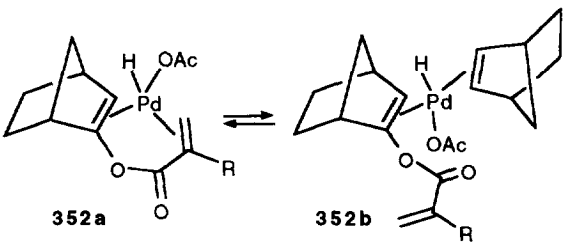
The termination step (substitution of the C-Pd σ-bond by OAc anion) is accompanied by a Wagner-Meerwein shift with *profound* rearrangement of the pentacyclic skeleton.

Also norbornene and norbornadiene provide, when subjected to palladium-catalysed alkyne addition, examples of *unusual ring formation and expansion reactions*.[182] The formation of the fairly complex reaction product **348** from two molecules of norbornene and one molecule of both alkyne and bromoalkyne, respectively, may proceed according to known organopalladium and norbornene chemistry and involves formal cycloaddition reaction to two norbornene double bonds.



Another particular addition-cyclisation reaction was reported with acrylates.[183] Unfortunately this oxypalladation-lactonisation is restricted to norbornene and terminal aliphatic alkenes.

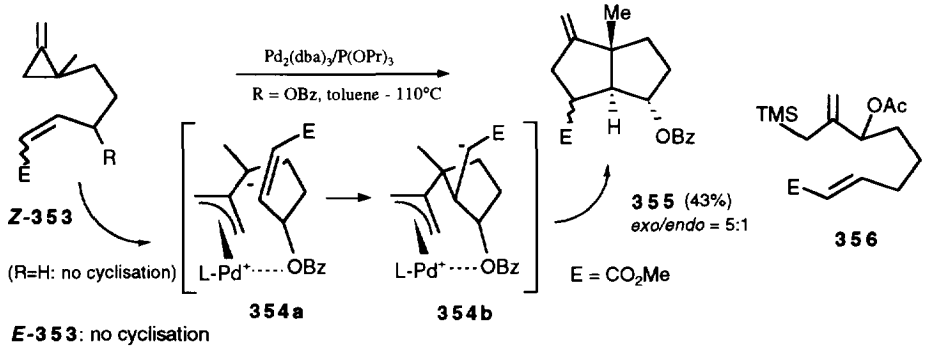




The product analysis reveals that the ring closure step depends on the substituent at the acrylic double bond with the putative intermediates **352a** (R = H) and **352b** (R = Me), leading to the annelated lactone **349** and spiro compound **351**, respectively. Tandem arylsulfonation with norbornene yields *cis exo*-2,3-norbornane fused benzo sulfones.[184]

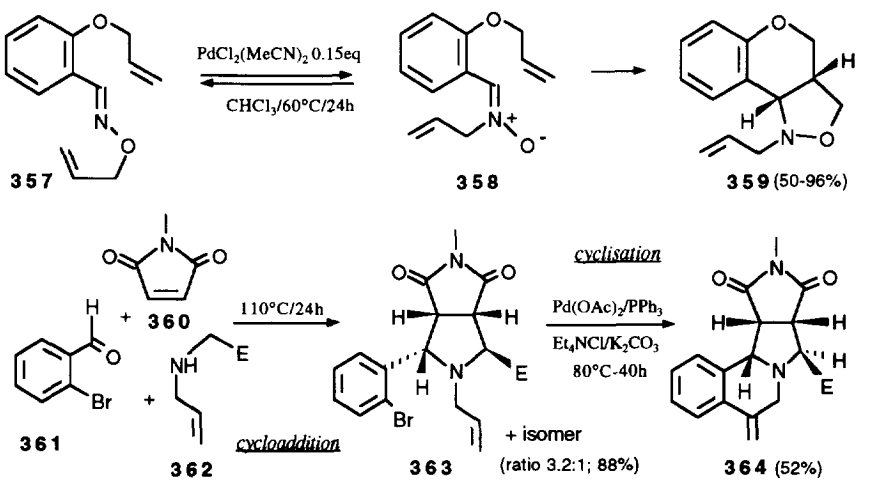
The cycloaddition *via* trimethylenemethane intermediates (TMM) is an important contribution to the palladium-cyclisation chemistry. The subject has been reviewed elsewhere.[185] In order to complete our survey on

methods leading to polycyclisation the recent results of Motherwell[186] are a good example that show the (unexpected) importance of chelation as well as of the nature of the 'generator' of the Pd-TMM intermediate. Different to Trost's intramolecular cycloaddition of allyl acetate **356** to the *cis*-fused bicyclo[3.3.0]octane derivative,[183] methylenecyclopropanes **353** (R=H, both *E*- and *Z*-stereoisomers) are completely unsuitable for ring closure reactions under palladium (0) catalysis. The desired reaction becomes possible when intramolecular chelation with an appended ether may stabilise cationic π-allyl palladium intermediates **354a** and **354b**, in which structures with non-bonded interactions are minimised. The intramolecular coordination of the ether group to the cationic palladium is not possible with ***E*-353**, and consequently cyclisation is observed only with the *Z*-isomer of **353**. The formation of the unfavourable *trans*-fused **355** reveals that inversion of the double bond geometry had occurred on cyclisation.



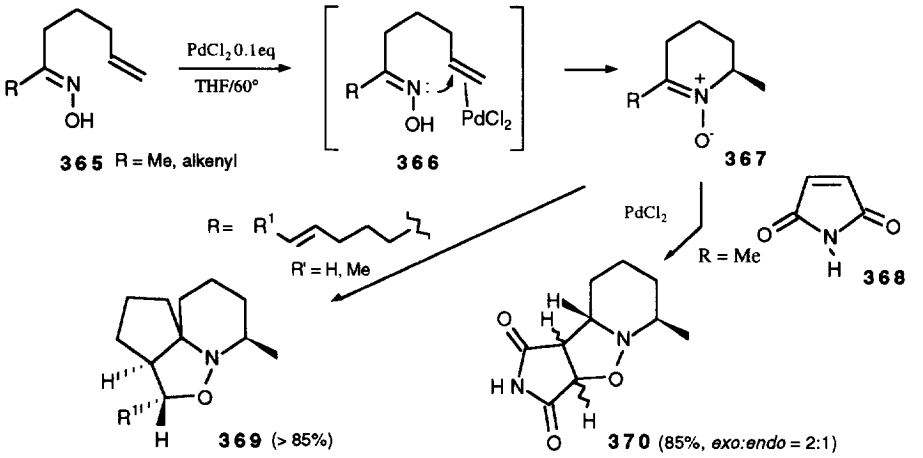
The reaction has been extended to methylenecyclopropanes with other olefinic and acetylenic acceptors.[187]

Grigg's recent contributions to the palladium (II) catalysed tandem [2,3]-sigmatropic shift-1,3-dipolar cycloaddition processes in oxime *O*-allyl ethers **357**,[188] as well as to sequential 1,3-dipolar cycloaddition - palladium catalysed cyclisation reactions,[189] for example in the synthesis of **364**, may considerably enlarge the arsenal of regio- and stereocontrolled multicyclisation processes.

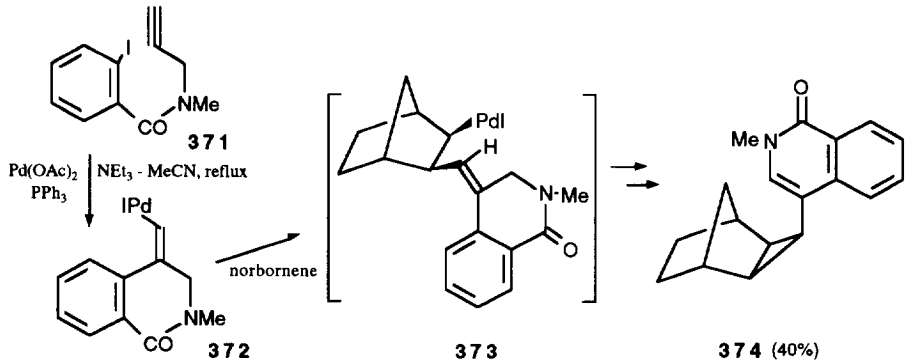


The cycloaddition of an *in situ* generated azomethine and subsequent palladium catalysed cyclisation, a sequence possible as one-pot reaction, is a mixed organic-organometallic application of so called Corey's Tactical Combination.

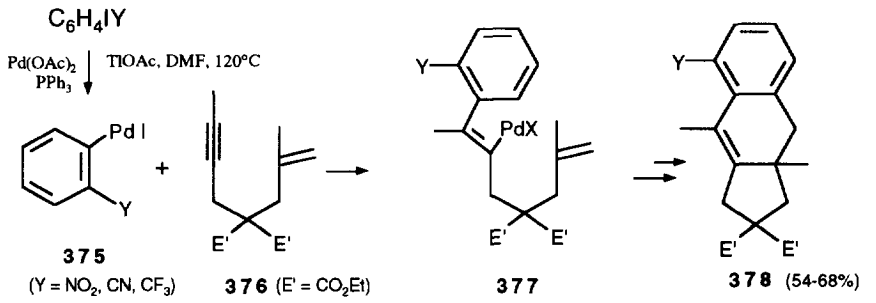
Cascade cyclisation-cycloadditions of alkenyl oximes[190] **365** (R=Me) catalysed by $PdCl_2$ occur regio- and facially-specifically in high yield. In this process, the intermediate six-membered cyclic nitrones, as a result of intramolecular nucleophilic addition of nitrogen to carbon-carbon double bond, undergo intermolecular cycloaddition to *N*-methylmaleimide. This cascade reaction can fully be realised when *bis*-δ-alkenyl oximes **365** are used. In this case when two different carbon-carbon double bonds are present in oxime **365** ($R=(CH_2)_3CH=CHMe$), the less substituted alkene is involved in the generation of the nitrone, whereas the more substituted alkene undergoes the cycloaddition reaction.



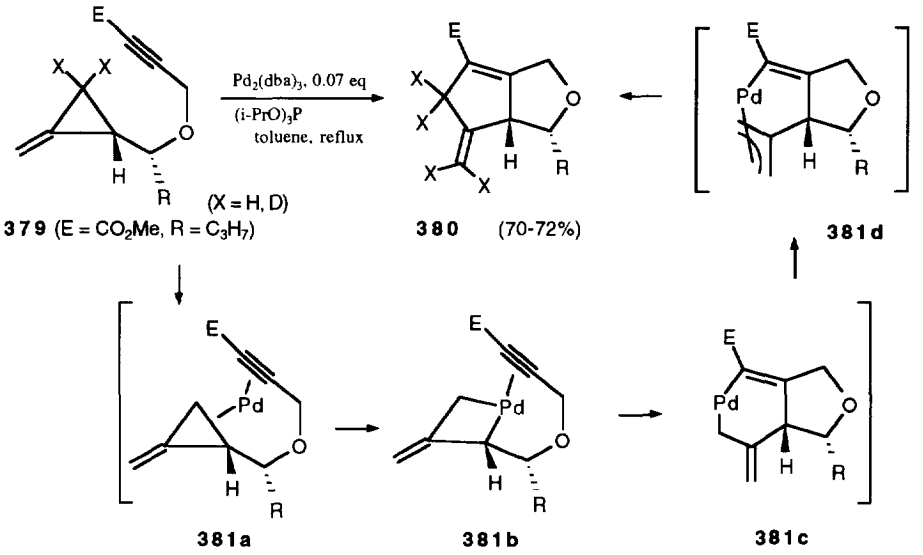
The possibilities of such combinations are numerous e.g. the cascade cyclisation/cycloaddition/cyclopropanation[191] in the synthesis of **374**, or the cascade [2+2+2] cycloaddition *via* carbopalladation of 1,6-enynes **376**.[152b]



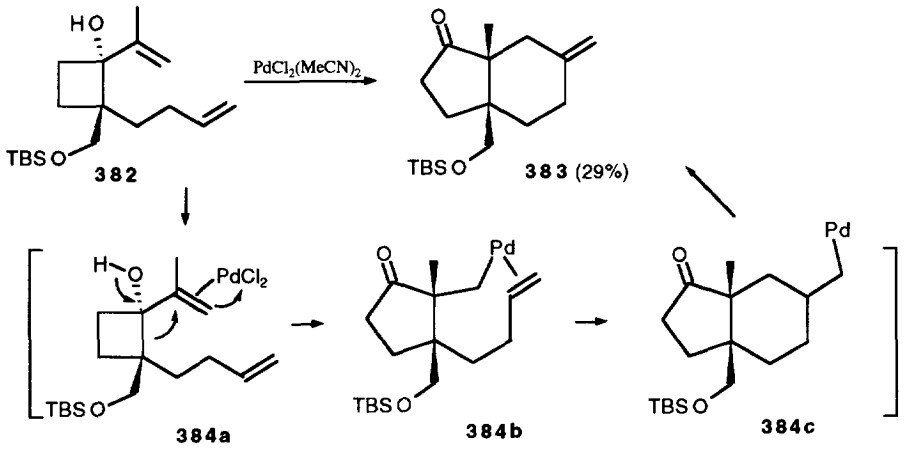
Also in these reactions [1+2] processes (and cyclopropane substrates) may dominate. Some general concepts were established for these reactions.[192]



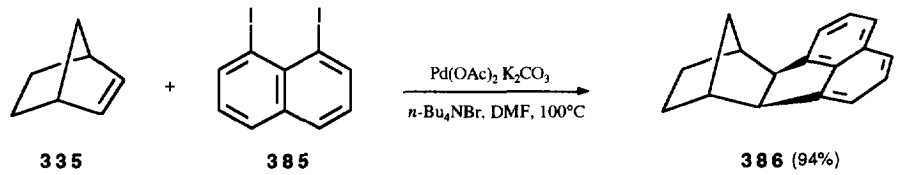
Cycloaddition of diastereoisomerically pure acetylenic methylene cyclopropane compounds **379** catalysed by $Pd_2(dba)_3$ with $(i\text{-PrO})_3P$ as ligand gives bicyclic ether **380** as a single isomer. Reaction of deuterated methylene cyclopropane **379** (X=D) leads to **380** with complete scrambling at the vinylic and allylic positions thus confirming the formation of a π-allyl complex **381d** as the final reaction intermediate.[193]



Fukumoto and co-workers[194] have recently described the synthesis of hydrindanes by a palladium mediated tandem (one-carbon) ring expansion-insertion reaction of alkenyl cyclobutanols **382**.



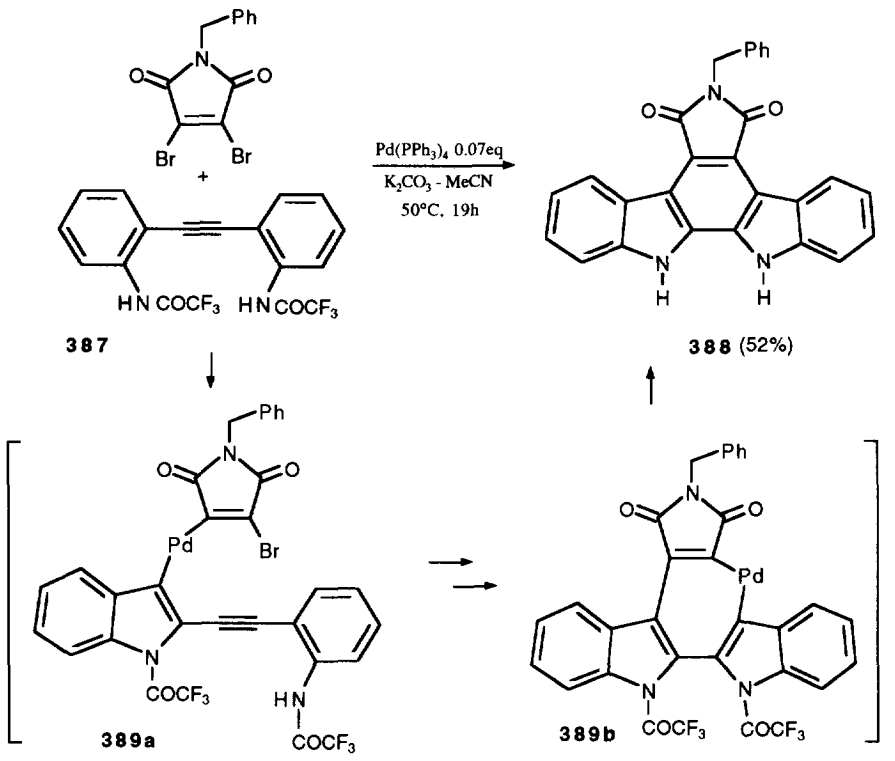
Palladium-catalysed coupling reactions of 1,8-diiodonaphthalene with alkenes or alkynes are useful for the synthesis of various acenaphthalene and acenaphthylene derivatives.[195] For example, with norbornene *exo,exo*-acenaphthalene **386** was obtained in high yield.[196]



335 **385** **386** (94%)

These reactions complement the 1:2 and 1:3 Heck domino coupling reactions with norbornenes (*vide infra*).[171-174, 177-180]

The synthesis of rebeccamycin-related indolo[2,3-a]carbazole **388** *via* polyannulation[197] demonstrates once more the power of palladium(0) in the accomplishment of complex synthetic organic chemistry. The assembly of the parent indolo[2,3-a]carbazole ring system is efficiently carried out by a novel palladium(0) catalysed reaction, wherein four bonds are formed in a single step from the simple monocyclic 1,3-diacetylene precursor **387**.



6 Conclusion

This review in three parts[1,2] is aimed to give an overview of the present state of the art of palladium catalysed ring forming reactions with particular emphasis on stereochemical questions. There was no ambition to cover this topic comprehensively, and other cascade or domino variations such as combinations of different reaction types were not incorporated. The use of this metal is now an integral part in the methodology of organic synthesis.[198] Palladium is certainly the most versatile catalyst with respect to selectivity and catalytic activity, but also multistep reactivity. The application to problems concerned with cyclic or polycyclic compounds only reflect the general trend in organic chemistry. It has been demonstrated throughout these articles that all kinds of carbo- and heterocyclic systems are practically synthesised *via* palladium(0) or palladium(II) catalysis. The extremely exciting results with cascade-type polycyclisation reactions are most probably only a good starting point for future challenges since an idea may emerge that with palladium 'everything' is possible. On the other hand these multistep transformations require more and more sophisticated starting material. This is perhaps the price to be paid unless, more convergently, the subsequent reacting functional units are introduced during the reaction sequence.

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