Pergamon

Tetrahedron 56 (2000) 5959–5989

TETRAHEDRON

Tetrahedron Report Number 535

Palladium in Organic Synthesis: Fundamental Transformations and Domino Processes

Giovanni Poli,[a,*] Giuliano Giambastiani[b] and Andreas Heumann[c]

[a]*Laboratoire de Chimie des Organoéléments, UMR 7611 CNRS, Université Pierre et Marie Curie, Tour 44-45, 4, Place Jussieu, Boîte 183, F-75252, Paris Cedex 05, France*

[b]*Dipartimento di Chimica Organica 'Ugo Schiff' and Centro CNR di Studio per la Chimica e la Struttura dei Composti Eterocicli e loro Applicazioni, Via G. Capponi 9, I-50121 Firenze, Italy*

[c]*UMR-CNRS 6516, École Nationale Supérieure de Synthèses, de Procédés et d'Ingénierie Chimiques d'Aix-Marseille, Faculté de St. Jérôme, F-13397, Marseille Cedex 20, France*

Dedicated to the memory of Professor Wolfgang Oppolzer

Received 22 May 2000

Contents

Keywords: catalysis; palladium and compounds; domino; cascade reactions.

* Corresponding author; e-mail: poli@ccr.jussieu.fr

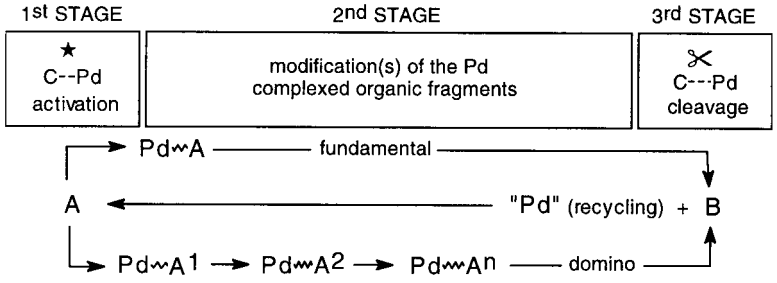
PII: S0040-4020(00)00438-5

1. Introduction

Transition metals have been invaluable reagents for the organic chemist since the beginning of this century. In particular, palladium, formerly used only for redox reactions, has recently achieved a prominent role in synthesis due to the manifold and unique transformations that it is capable of mediating, often in a catalytic mode.[1] In recent years, the pioneering work of a couple of scientists has demonstrated that, using a single catalytic starter, many reactions in cascade could be devised from suitable precursor substrates. Multiple consecutive one-pot reactions, thereafter named *domino* reactions,[2] are not, of course, confined to organometallic chemistry. The large number of organic transformations mediated, the wide functional group tolerance, and the catalytic nature of most of these processes, however, make palladium an ideal basis for devising unbeatable domino processes. In order to understand satisfactorily the palladium catalysed domino processes it is essential to survey briefly the basic organometallic chemistry associated with this metal.

2. The Single Elementary Steps in a Palladium Catalysed Process

Any reaction involving a transition metal can be systematised into few fundamental processes.[3] These can be ideally[4] subdivided into three main stages: (i) initial activation of the organic fragment by palladium; (ii) generation of the new organometallic bond, and (iii) removal of the metal from the modified organic moiety with possible recycling. The first stage involves ligand coordination, which, depending on the oxidation state of the Pd complex (vide infra), may be followed either by oxidative addition or by oxidative coupling; the second stage may involve addition of nucleophiles, either to palladium (ligand exchange) or to the coordinated ligand, and intramolecular migratory



Scheme 1.

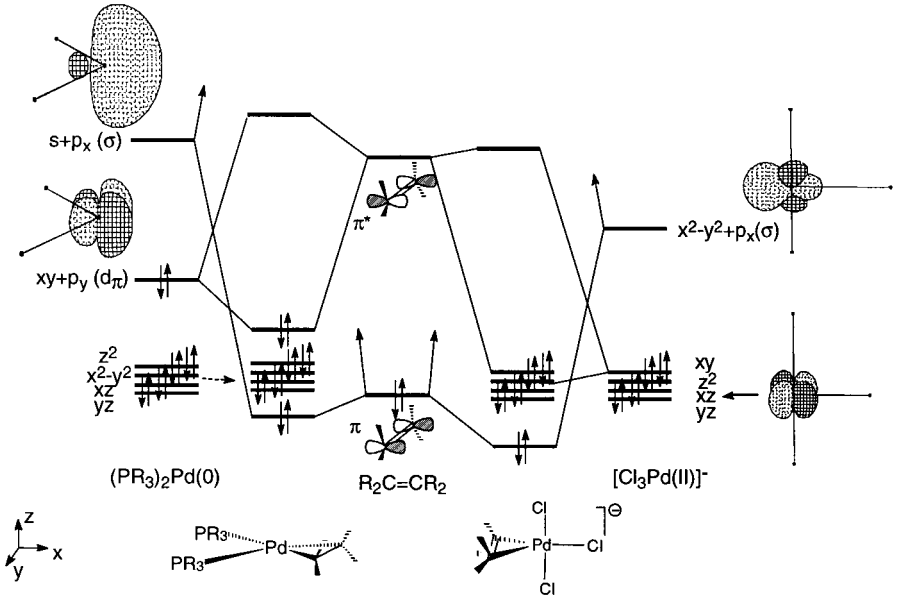


Figure 1.

insertion. All these transformations are characterised by the electrophilic nature of Pd(II). When several sequential and discrete chemical steps are involved, a *domino* process is at work. Finally, the third stage may take place via ligand dissociation, reductive elimination, dehydropalladation or oxidative cleavage (Scheme 1).

2.1. The interaction between palladium and an organic ligand (activation stage)

The interaction between an inorganic palladium derivative and an organic ligand represents the first step of a palladium mediated organic synthesis. Two distinct processes can occur depending on whether Pd(0) or Pd(II) is implicated. In both cases Pd(II) complexes are formed, and the transformations that later ensue (see stage 2) take place independently of the original oxidation state of the complex. Pd(0) and Pd(II) complexes are both capable of interacting with unsaturated systems such as alkenes or alkynes via π-coordination. The two complexes are however different in nature. Pd(0) is highly electron rich and back-donates to the ligand (Pd→L), whereas Pd(II) is electrophilic, and its main interaction is represented by σ-donation from the organic system to an empty orbital of palladium. A comparison of the orbital interactions between the alkene π and π^* levels and the frontier orbitals of $L_2Pd(0)$ and $L_3Pd(II)$ fragments accounts for the different ability of the metal dπ orbitals to give back-donation into the olefin π^* level.[5] As the CACAO drawing shows in Fig. 1,[6] the π fragment molecular orbital in $L_2Pd(0)$ is a hybrid formed by the d_{xy} and p_y atomic orbitals, whereas the corresponding in $L_3Pd(II)$ is a pure d_{xy} orbital one. Since the interaction between the orbitals is governed by their relative energies and overlap, it is apparent that the Pd(0) fragment is able to produce a much better back-donation than the Pd(II) moiety. The more efficient the back-donation into the C=C π^* level, the weaker the C=C bond. Bonding models, therefore, range between the *metalla-cyclopropane* where the double bond character is absent owing to the complete electron transfer into C=C π^* and simple *alkene coordination* where back-donation is insignificant, and the bonding stems only from the σ donation of the olefin π orbital into the empty metal σ hybrid.

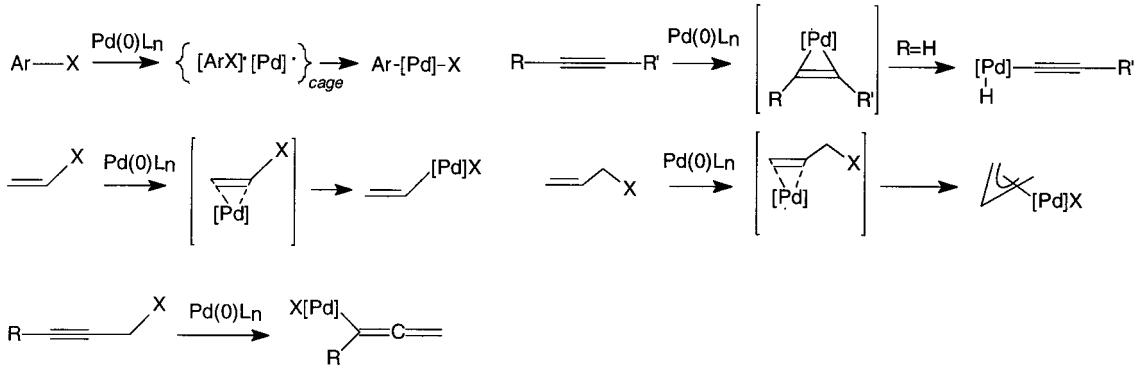
Similar arguments also predict a significant energy barrier for the olefin rotation in the $L_2Pd(0)(\eta^2$-olefin) complexes but free rotation in the $L_3Pd(II)(\eta^2$-olefin). In fact, the two dπ orbitals at 90° are equivalent in the $L_3Pd(II)$ fragment, but are energetically and spatially different in the $L_2Pd(0)$ group.

2.1.1. Pd(0) complexes.[7] The organic substrates that interact with Pd(0) are usually classified into polar and non-polar substrates. Polar substrates are represented by organic halides, susceptible to nucleophilic attack by palladium by virtue of their good leaving group. Non-polar substrates, such as arenes, activated alkanes and terminal alkynes react via C–H breaking. Aryl[8] and vinyl halides[9] afford the corresponding σ-aryl and σ-vinyl palladium complexes via oxidative addition, the order of reactivity being I>OTf>Br>Cl. Alkyl halides may additionally undergo a similar oxidative addition, but it must be born in mind that, whenever a *syn*-coplanar XPd–C–C–H arrangement is attained, palladium hydride will most likely be lost from the organic fragment (vide infra). Allylic systems such as allylic halides or acetates[10] or analogues, release the leaving group after coordination and give the corresponding π-allyl complexes. Alkynes give, via oxidative coupling,[7] transient palladacyclopropenes which may then break down into the corresponding σ-alkynyl complexes, if a terminal acetylene is used. It should be noted that many transformations that require Pd(0) actually use Pd(II) complexes, which are reduced in situ by other organic molecules present in the medium (carbon monoxide, alcohols, tertiary amines, alkenes, or phosphines) (Scheme 2).

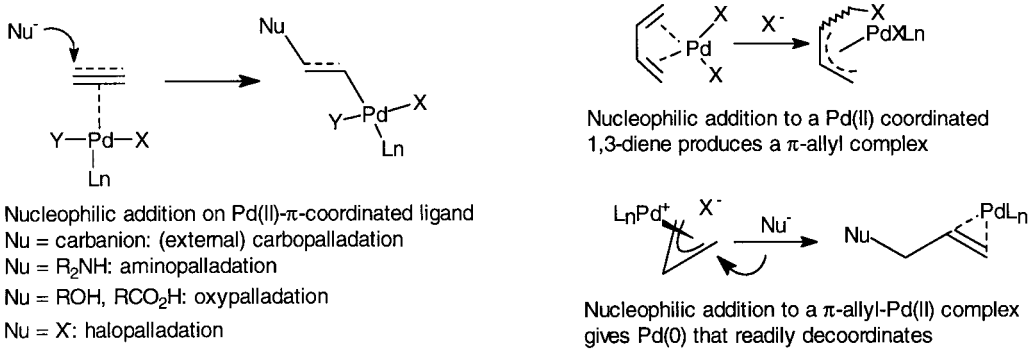
2.1.2. Pd(II) complexes. Alkenes reversibly π-coordinate to soluble Pd(II) complexes. Although these complexes are usually labile, the coordination is the crucial activating step that triggers the subsequent additions to the coordinated ligand. The Pd source may be totally inorganic (e.g. $PdCl_2$), or derived from the oxidative addition of a Pd(0) complex discussed above (e.g. Pd(0)+AcOH→H–Pd(II)–OAc).

2.2. Transformations of the Pd-complexed organic fragment

2.2.1. Nucleophilic *anti* addition to the Pd(II)-complexed organic ligands. The Pd(II)-complexes generated via either the oxidative (Section 2.1.1) or the electrophilic processes (Section 2.1.2) may then undergo typical transformations depending on the nature of the coordinated ligand and the reaction conditions. Pd(II) π-complexes of unsaturated ligands easily undergo nucleophilic additions at the electron



Scheme 2.



Scheme 3.

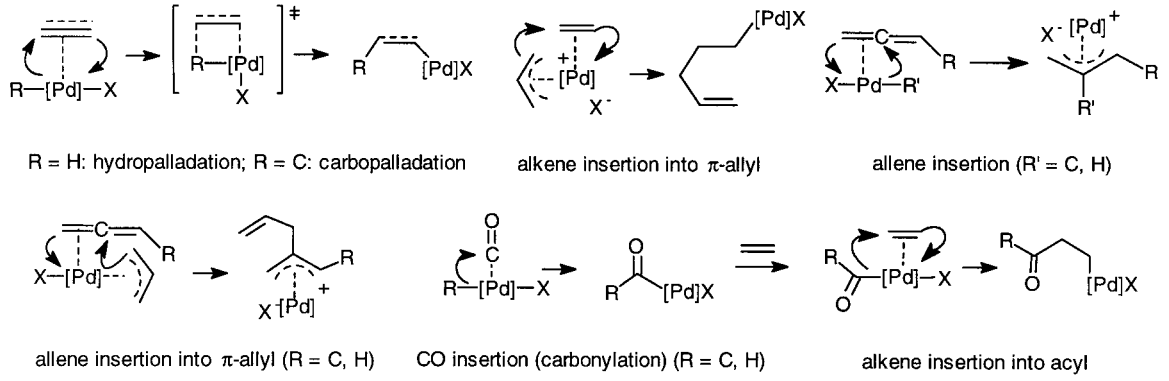
deficient coordinated fragment.[11] Under appropriate conditions, therefore, a wide variety of nucleophiles can add to coordinated alkenes or alkynes. On alkenes, the addition usually occurs at the more substituted position and *anti* to the metal. π-Allyl–Pd(II) complexes are also highly activated to nucleophilic addition, especially in the presence of suitable ancillary ligands such as phosphines. Stabilised carbanions, amines and phenoxides add to the external allylic terminus, *anti* to palladium (Scheme 3).

2.2.2. Migratory insertion processes. The most significant transformation of palladium catalysed domino processes is unquestionably migratory insertion. This intramolecular process involves migration of the atom σ-bonded to palladium to a coordinated adjacent (*cis*) ligand. A vacant coordination site is created during the reaction and the formal oxidation state of the metal is not changed. Depending on the relative position of the new M–L bond with respect to the group that has migrated, 1,1-(CO) and 1,2-insertions (alkynes and alkenes) may be distinguished. In the latter case, strict *syn* addition of the Pd-bound atom and Pd to the unsaturated fragment is observed, according to a four-centre transition state. The fact that alkynes are considerably more reactive than alkenes toward a Pd(II) species is of high relevance to domino processes. As illustrated in Scheme 4, allyl moieties may participate as migrating groups, whereas allenes[12] and acetylenes[13] easily undergo insertion to give π-allyl- and σ-vinyl–Pd(II) complexes, respectively. The latter may alternatively be obtained by the action of Pd(0) on the appropriate vinyl halide (Scheme 2). CO insertion gives an acyl–Pd(II) complex, from which the palladium can easily migrate onto a coordinated alkene in a new migratory insertion. Since alkene insertion into an acyl–Pd bond is easier than alkyl migration, alternating insertions of CO and alkenes are feasible[14] and these have actually been exploited in domino reactions.

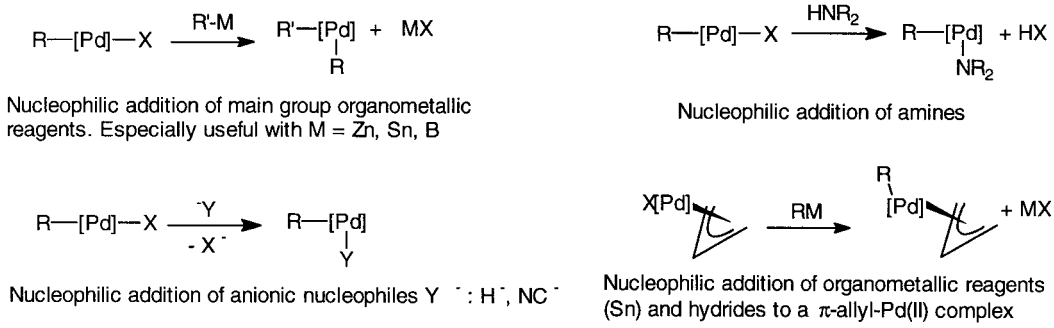
Examples of migratory insertion processes are the conversion of a Pd(II)-coordinated alkyne into a σ-vinyl–palladium complex, of a Pd(II)-coordinated alkene into a σ-alkyl palladium complex, and of a Pd(II)-coordinated CO into an acyl–Pd(II) complex. The migrating group is usually a carbon atom (carbopalladation) or sometimes a hydrogen atom (hydropalladation). Carbopalladations are normally irreversible, whereas hydropalladations and carbonylations are reversible processes (Scheme 4).

2.2.3. Nucleophilic additions at the metal in Pd(II) complexes. The Pd(II) σ-complexes generated as described above, can also undergo nucleophilic additions at the metal, a ligand exchange process that preludes metal cleavage. Main Group organometallic reagents R′M (M=Li, Mg, Zn, Zr, Sn, B, Al, Cu, Si, Ge, Hg, Tl, Ni) add to Pd(II) forming a new dialkyl–Pd(II) σ-complex. Among these, the B(III) (Suzuki–Miyaura),[15] Zn(II) (Negishi–Baba),[16] and Sn(IV) (Migita–Kosugi–Stille)[17] species are the most useful. Amines[18] and alkoxides[19] are additionally capable of exchanging a halide ligand with a mechanism analogous to transmetallation.

Since these ligand exchanges are almost invariably affecting the rate limiting steps, migratory insertions (e.g. of alkenes, alkynes or CO[20]) are also possible prior to transmetallation. As will be seen later, this feature is central to domino



Scheme 4.



Scheme 5.

reactions, since it enables the development of multiple subsequent discrete steps. Since the newly generated palladium complexes tend to release Pd(0), this ligand exchange process functions as an *external* way of catalyst regeneration (anion capture). In suitable cases, such nucleophilic displacements may even take place intramolecularly.

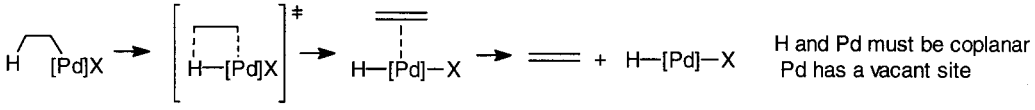
π-Allyl complexes, which are known to interact with soft nucleophiles at the allyl moiety (vide supra), react directly at palladium with hydrides[21] and other hard nucleophiles (Scheme 5).[22]

2.3. Metal release from the organic fragment

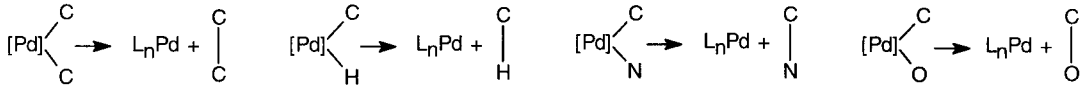
2.3.1. Dehydropalladation. Palladium(II) σ-alkyl complexes having a hydrogen atom in the β-*cis*-position readily undergo elimination, thereby forming an alkene. This reaction is the reverse of the hydropalladation insertion discussed above. CO insertion often competes with dehydropalladation. Since the transition state of the dehydropalladation requires a coordinated alkene, elimination is possible if the palladium complex is coordinatively unsaturated. On the other hand, σ-alkyl complexes lacking a β-*cis* hydrogen and σ-alkenyl complexes, cannot undergo dehydropalladation. They are in general thermally stable (*living species*) and, in the presence of other unsaturations, they give carbopalladations, allowing a domino process to start. Since dehydropalladation forms XPdH, which in turn is in equilibrium with HX and Pd(0), (vide infra) such a process represents an *internal* way of catalyst regeneration (Scheme 6).

2.3.2. Reductive elimination. The σ-palladium(II) complexes formed via any of the above shown paths may undergo intramolecular coupling of two ligands, extruding Pd(0). In this reaction, the reverse of the oxidative addition, a wide variety of ligand types can be coupled leading to the formation of C–C, C–H, C–N, and C–O bonds. The geometric requirements of the reductive elimination impose a *cis* disposition between the two ligands. It follows that two *trans* disposed ligands can couple only after *trans*→*cis* isomerisation. Since both *trans*→*cis* isomerisation and C–C coupling are fast processes compared with dehydropalladation, a β-hydrogen in the R group transferred from the organometallic reagent is tolerated. The reductive elimination produces a decrease of the positive charge at palladium. Thus, an opposite effect induced by the addition of good π-acceptor ligands or the dissociation of σ-donor ones favours the reaction. After the reductive elimination the released Pd(0) is ready to re-enter the catalytic cycle (Scheme 7).

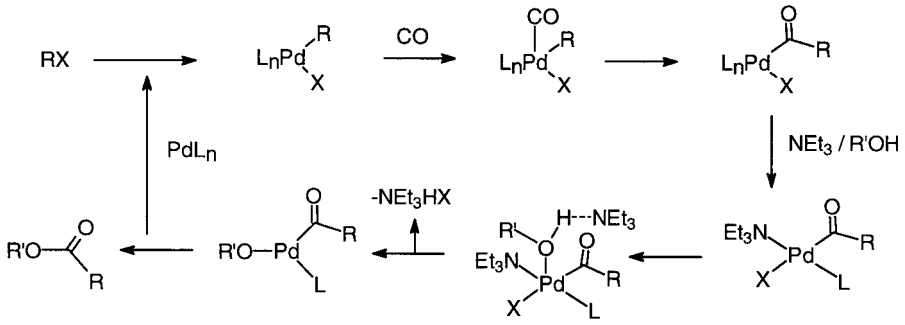
2.3.3. Anion capture and carbonylative trapping. The nucleophilic addition at palladium (Section 2.2.3) is always followed by the reductive elimination, and the combination of these two elementary steps is known as the *anion capture*. The transiently generated σ-alkylpalladium complexes can be alkoxycarbonylated, with concomitant regeneration of Pd(0), by treatment with carbon monoxide in the presence of an alcohol (usually methanol) or amines. Since the carbonylation reaction is a reversible process, when competitive reactions are possible, different results can be obtained as a function of the CO pressure and of the nature (e.g. inter- or intra-molecular) of the trapping alcohol (Scheme 8). Several mechanistic pathways may be operative depending on many factors such as the nature of the nucleophile, that of the ancillary ligands, or the pressure of CO used.[23,24] For example, the generation of esters in the presence of alcohols



Scheme 6.



Scheme 7.



Scheme 8.

and tertiary amines is expected to initially involve the migratory insertion of a coordinated carbon monoxide ligand to a σ-palladium(II) complex, to give an acylpalladium complex. Coordination of the amine, followed by alcohol coordination/deprotonation generates an acylpalladium alkoxide complex, which eventually undergoes reductive elimination to give the final ester function (Scheme 8).[25]

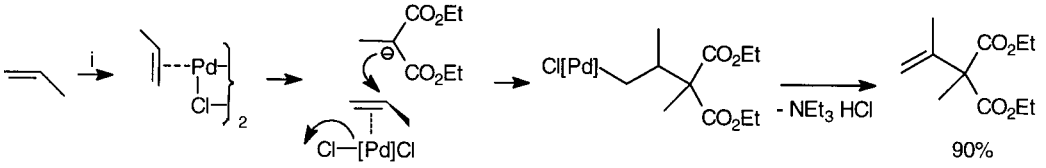
3. Single-stage Palladium Catalysed Transformations

The sequential and appropriate combination of stages 1, 2 and 3 give rise to a simple palladium catalysed transformations. Selected examples of those relevant for the understanding of the more complex domino processes are here illustrated.

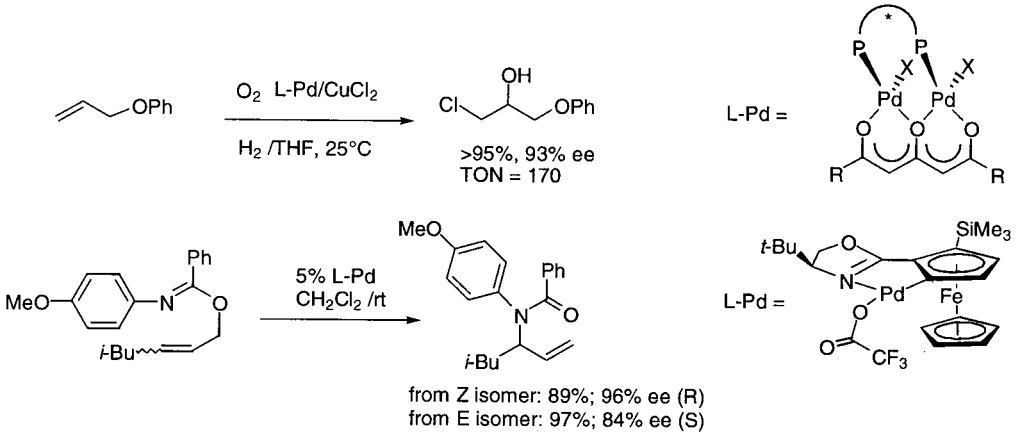
3.1. Pd(II) assisted nucleophilic additions to alkenes

The *anti* addition of nucleophiles to Pd(II) activated alkenes (*anti* palladation)[26] makes access to a variety of products possible. Water,[27] alcohols,[28] carboxylates,[29] aromatic and aliphatic amines protected with electron-withdrawing groups[30] can be used as nucleophiles.[31] These processes, that range from the industrial synthesis of acetaldehyde from ethylene and H_2O, (Wacker process) to the synthesis of various heterocycles,[32,28a] can also be made catalytic with Pd. This requires the addition of an oxidising agent (O_2/$CuCl_2$, $K_2S_2O_8$, benzoquinone) to regenerate Pd(II) from the Pd(0) generated by dehydropalladation of the initially formed σ-alkylpalladium complexes. A catalytic process, however, cannot be obtained where stabilised carbanions are used as the nucleophiles: in this case stoichiometric amounts of Pd(II) and the presence of a tertiary amine are necessary for the reaction to take place (Scheme 9).[33]

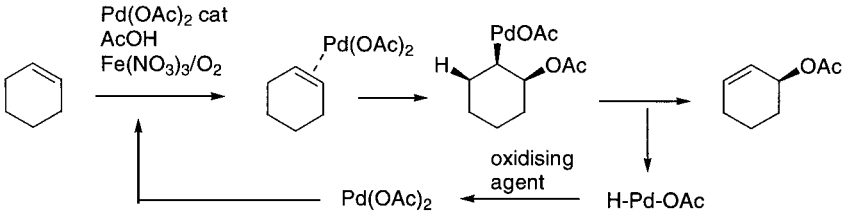
On carefully selecting the reaction conditions, it is possible to incorporate two (identical or different) heteroatoms into the alkene. Chlorohydrins are examples of potential products,[34] attracting intense mechanistic studies,[35] and, more recently, an interesting enantioselective variant of catalytic olefin oxidation (Scheme 10).[36] It may be recalled that these chlorohydrins are interesting precursors of



Scheme 9. (i) $(EtO_2C)_2$ CHMe, NEt_3 (2 equiv.), $PdCl_2(MeCN)_2$.



Scheme 10.



Scheme 11.

optically active oxiranes and allylic amides. The palladium catalysed rearrangement of allylic imidates into allylic amides is an intramolecular example of Pd(II) mediated catalysis, which has also recently been studied in enantioselective processes.[37]

3.2. Allylic oxidation

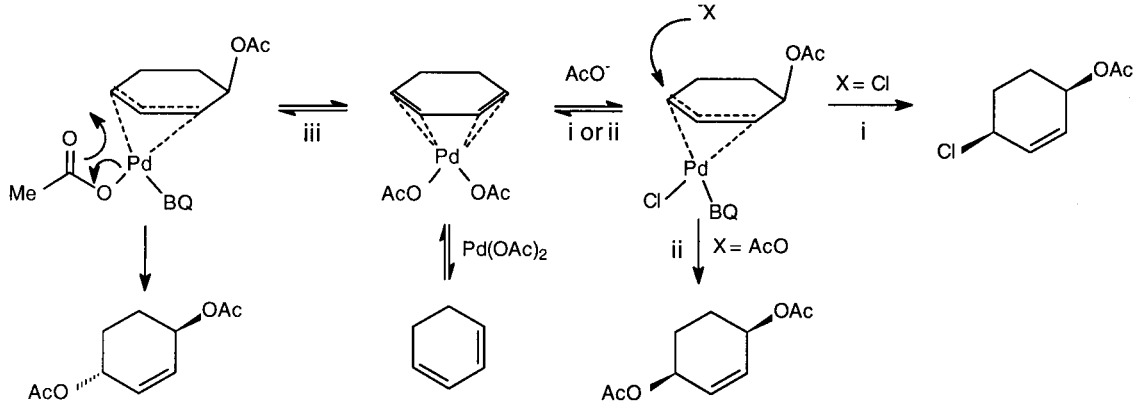
Palladium(II) is the reagent of choice for the allylic oxidation of simple alkenes,[38] and a preparative method was developed for allylic acetates[39] (Scheme 11).

Interaction between a nucleophilic species and a Pd(II)-coordinated 1,3-diene generates a π-(allyl)palladium complex which can be regio- and stereoselectively functionalised.[40,41] Some common examples of 1,4-functionalisation of 1,3-cyclohexadiene (diacetoxylation and chloroacetoxylation) are shown here below (Scheme 12). Recently, an enantioselective modification of this reactivity has been also reported.[42]

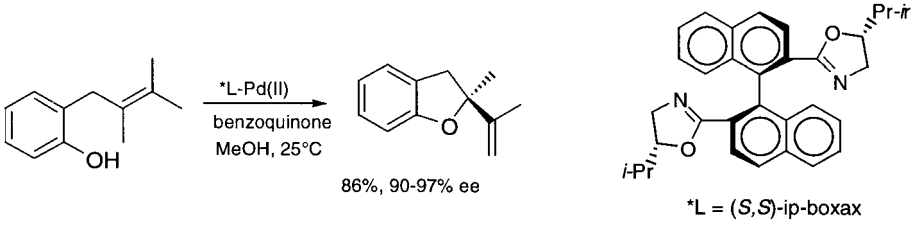
A large number of nitrogen-, oxygen-, carbon- or halogen-based nucleophiles have been added to Pd(II)-coordinated alkenes in an inter- or intramolecular manner. For example, Hosokawa's intramolecular phenoxypalladation[43] of allyl phenols is a recent example of such an allylic oxidation proceeding with very high asymmetric induction (Scheme 13).[44]

3.3. Allylic alkylation[45]

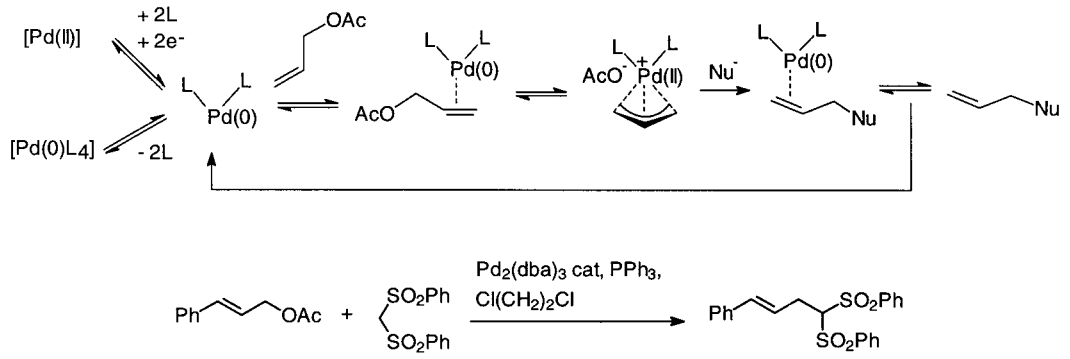
The mechanism of this reaction has been extensively studied. The first step involves the reversible coordination of the Pd(0)-catalyst to the allylic system. The subsequent rate determining departure of the leaving group takes place generally with *anti* stereochemistry generating a palladium(II) η^3-allyl complex, which is usually in dynamic conformational exchange. When two equivalents of an external ligand are available for coordination the square planar geometry on palladium is maintained by displacement of the allylic leaving group from the co-ordination sphere of the metal. If a suitable soft nucleophile is present in the medium it will add to a terminal position of the η^3-allyl complex from the site opposite the metal, thereby shifting the overall equilibrium to the right. As the nucleophile attacks, rotational displacement in the η^3-allylpalladium(II)



Scheme 12. (i) $Pd(OAc)_2$ cat, LiOAc, benzoquinone (BQ), AcOH, LiCl; (ii) $Pd(OAc)_2$ cat., LiOAc, BQ, AcOH, LiCl cat; (iii) $Pd(OAc)_2$ cat, LiOAc, BQ, AcOH.

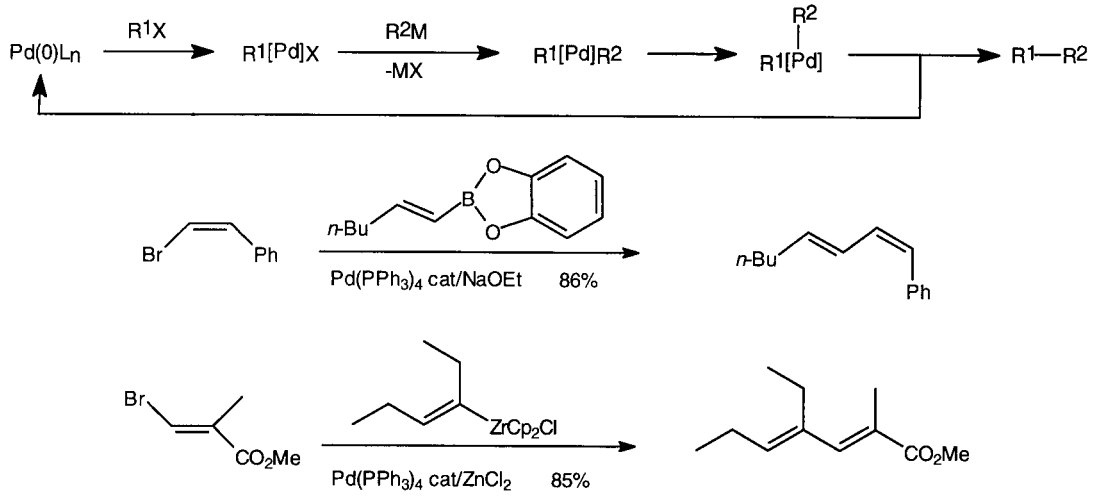


Scheme 13.

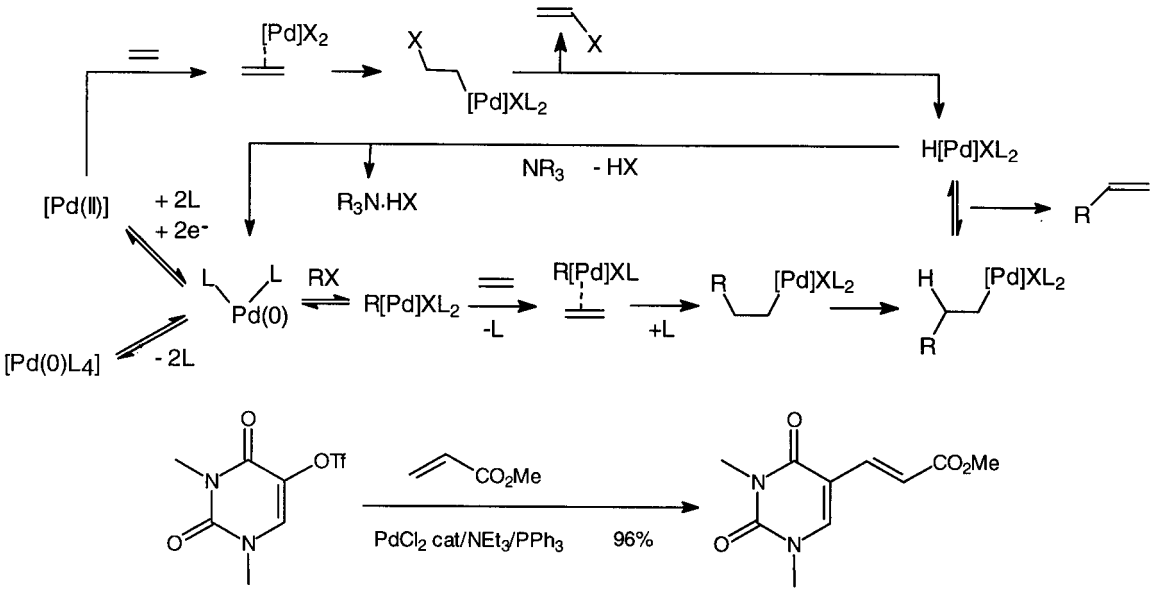


Scheme 14.

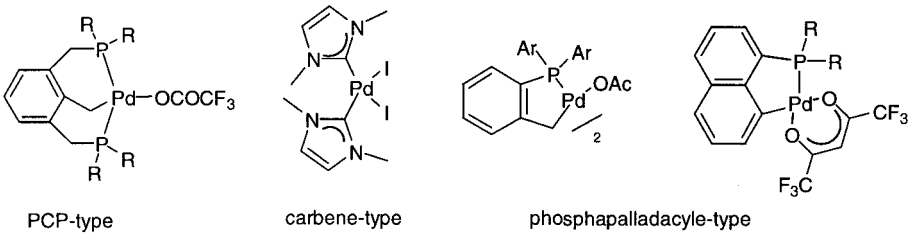
complex occurs, generating a η^2-alkenylpalladium(0) complex.[46] Decoordination of [Pd(0)] from the organic moiety closes the catalytic cycle. The manner in which a carbon acid pronucleophile is deprotonated to give a soft carbanionic species is dependent on some parameters. In particular, when the pK_a value of the conjugated acid of the displaced group is higher than that of the active methylene, deprotonation may take place in situ by the



Scheme 15.



Scheme 16.



Scheme 17.

displaced anion itself. Such an *endogenous* deprotonation mode can be at work on a wide variety of carbon acids when allylic carbonates,[47] phenoxides[48] and oxiranes are used.[49] With the more common allylic acetates, the carbanionic species is either preformed, or generated in situ, by the explicit addition of a stoichiometric amount of base. In this case *endogenous* deprotonation is also viable, though on a more restricted pK_a window.[50] The general mechanism, and a simple example are shown in Scheme 14.

Chiral versions[51] of this transformation have been developed over the last few years to become one of the most important tools in catalytic C–C bond formation. Many excellent new ligands are presently available and enantiomeric excesses close to 100% are now common.

3.4. Cross coupling

Aryl or alkenylpalladium halide complexes, formed by the oxidative addition of Pd(0), undergo transmetalation with alkyl, aryl, alkenyl, allyl and benzyl compounds of Main Group elements. C–C bond formation then takes place by reductive elimination (Scheme 15).[52]

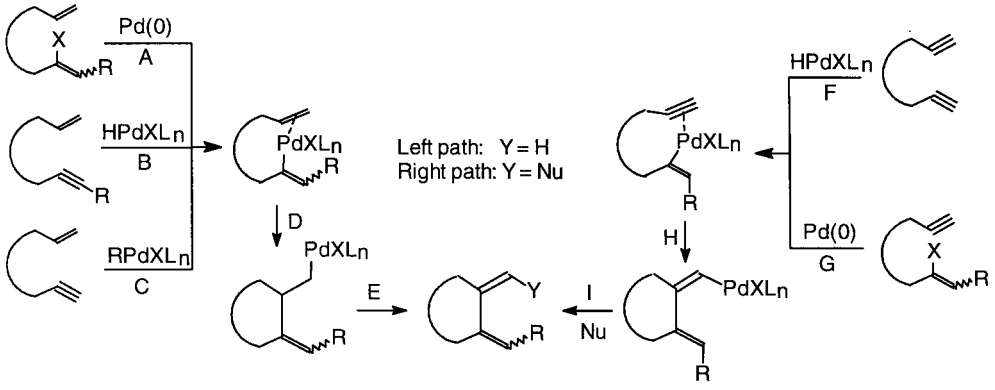
3.5. The Ozaki–Heck reaction

Unhindered alkenes insert into σ-vinyl- or σ-arylpalladium halides, or pseudohalides, formed by oxidative addition of Pd(0). Subsequent dehydropalladation generates a new alkene in which an original vinyl hydrogen is replaced by the organic moiety of the starting halide (Scheme 16).[53]

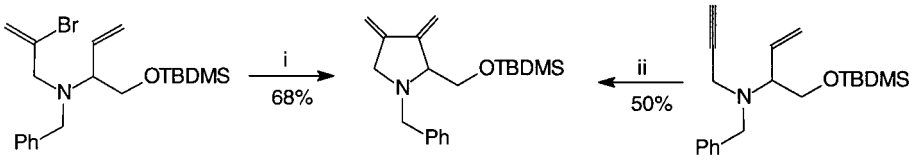
The arylation reaction is one of the most important industrial transformations, and the search for new, high-turnover catalysts is actively studied with carbon-centred ligands at the palladium-core like PCP-type ligands,[54] carbene complexes[55] and metallacyclic systems from e.g. *o*-tolyl phosphines (TON 250 000)[56] or tri(1-naphthyl)-phosphines (TON 1 120 000) (Scheme 17).[57]

3.6. The intramolecular Ozaki–Heck reaction

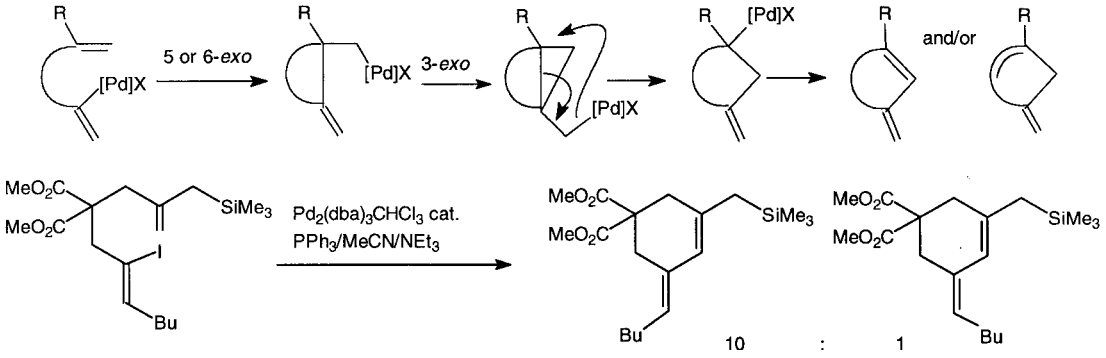
The Ozaki–Heck reaction is a milestone in organometallic chemistry,[58] and many variations are known. In particular, intramolecular versions have been extensively exploited in the synthesis of natural products and related complex molecules. The first step of this reaction involves the oxidative addition to Pd(0) on an alkenyl or aryl halide, which generates the corresponding Pd(II) σ-complex (path A).[59] If a juxtaposed unsaturation is present, intramolecular carbopalladation creates a new cyclic Pd(II) complex (path D), which can subsequently evolve, e.g. via dehydropalladation (path E). Interestingly, analogous cycloisomerisations[60] (vide infra) can be attained when the starting σ-alkenyl



Scheme 18.



Scheme 19. (i) 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, K_2CO_3; (ii) 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3.



Scheme 20.

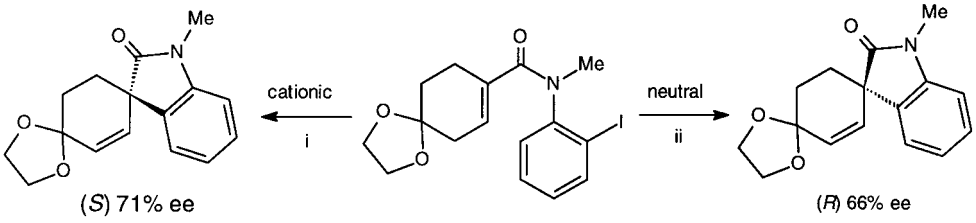
complexes are generated via hydro- (path B),[61] or carbopalladation (path C)[62] of alkynes. Furthermore, the transient alkenyl Pd(II) σ-complex may intramolecularly insert an alkyne thereby generating a new cyclic Pd(II) σ-complex (paths F,[63] G,[64] H) which can release the metal via nucleophilic addition (path I, e.g. hydride trapping) (Scheme 18).

Several cyclisations following the paths outlined in Scheme 18 have been reported in the literature. As an example, paths A and B have been compared in the synthesis of the same pyrrolidine derivative, starting from vinyl glycine (Scheme 19).[65]

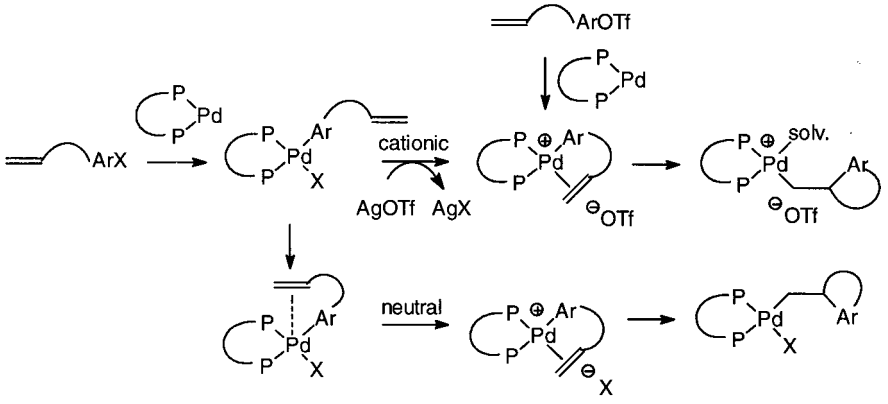
The *exo* mode of cyclisation is usually observed in path D. Some six- and seven-membered rings, however, may be formed via an apparent *endo*-mode of cyclisation. This unusual behaviour, known as *apparent endo mode cyclization* [62a,66] has been rationalised in terms of two subsequent 5-*exo* (or 6-*exo*), and 3-*exo* carbopalladations, followed by a cyclopropylcarbinyl-to-homoallyl rearrangement, and final dehydropalladation. The above rearrangement may take place as long as the cyclopropylcarbinylpalladium intermediate is not conformationally blocked. The mechanism and an example[67] are shown in Scheme 20.

The chiral intramolecular version of the Ozaki–Heck coupling is an important method to accede to optically active natural products[68,69] and at the same time has answered fundamental mechanistic questions.

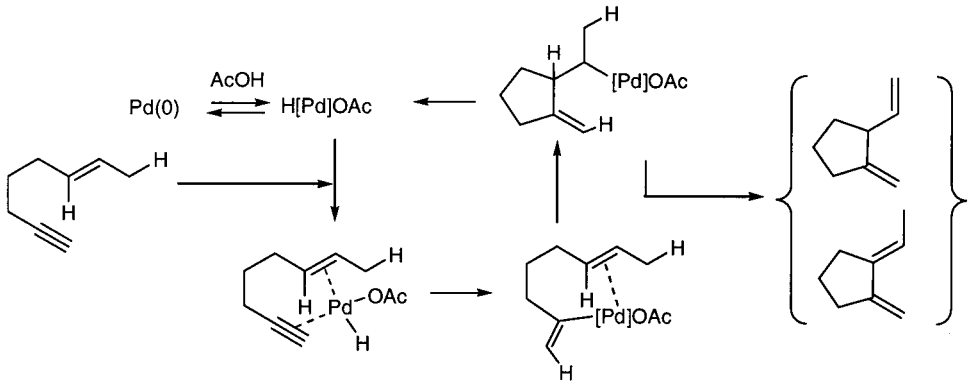
Overman[70,71] studied the intramolecular asymmetric Ozaki–Heck reaction of α,β-unsaturated 2-iodoamides using BINAP as the chiral ligand. Different, and usually high, enantioselectivities could be obtained as a function of the geometry of the unsaturation and/or the reaction conditions used. In particular, two distinct methods were developed, one exploiting halide ionisation via Ag(I) or Tl(I) salts



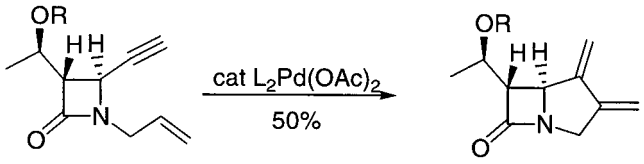
Scheme 21. (i) $Pd_2(dba)_3$ 5%; (*R*)-BINAP 11%; DMA; Ag_3PO_4, 80°C, (81%); (ii) $Pd_2(dba)_3$ 5%; (*R*)-BINAP 11%; DMA; PMP, 110°C, (71%).



Scheme 22.



Scheme 23.

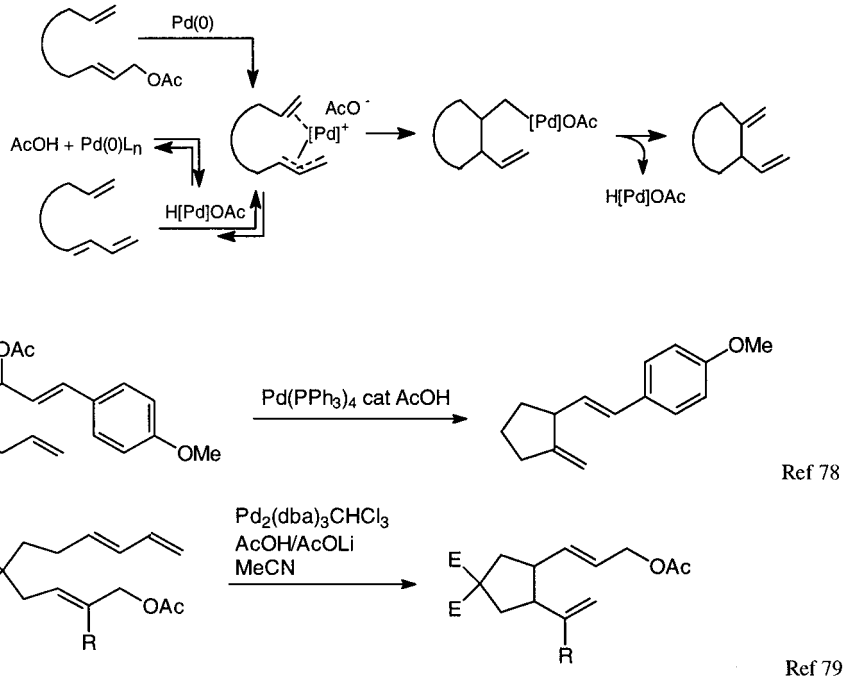


Scheme 24.

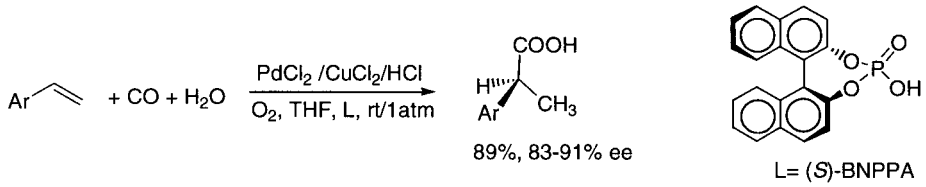
(cationic pathway), and an alternative route using a tertiary amine as the HI scavenger (neutral pathway). When spirocyclic products are generated the two methods provide opposite enantioselectivities (Scheme 21).

Overman also observed that when an acyclic unsaturation is involved in the cyclisation, the sense of enantioselectivity associated with the cationic pathway depends on the geometry of the starting alkene, whereas that obtained via the neutral pathway appears to be independent of the alkene geometry.

As expected, the two methods imply distinct mechanisms (Scheme 22). The cationic pathway involves the direct formation of a cationic four-coordinate square planar complex, and the enantioselectivity can be rationalised in terms of the most stable of the two possible diastereoisomeric cationic complexes. On the other hand, the neutral pathway has been proposed to initially involve formation of a pentacoordinate neutral complex, followed by halide ionisation to give a four-coordinate complex, and final migratory insertion. In this case the stage featuring stereoinduction is still a matter of speculation.



Scheme 25.



Scheme 26.

3.7. Cycloisomerisation[72] of alkyl- and alkenyl–Pd complexes

The ease of Pd–C and Pd–H bond formation from alkenes and alkynes and the coordination–insertion sequence with a second unsaturated group is a prerequisite for interesting cyclisation reactions from non-conjugated dienes, enynes, diynes and other possible functional combinations.[73] For example, 1,6-enynes and 1,7-enynes are known to undergo the Pd-catalysed Alder-ene reaction. In this reaction, a regioselective hydridopalladation is followed by an intramolecular carbopalladation. The final dehydropallation may take two different courses depending on which hydrogen is abstracted, affording 1,3- and/or 1,4-dienes (Scheme 23).

Such Alder-ene reactions are well documented and allow access to various, even sensitive cyclic systems, such as the carbapenem nucleus.[74] The related cycloisomerisation of 1,6-dienes requires cationic palladium complexes (Scheme 24).[75]

3.8. Intramolecular alkene insertion in π-allyl–Pd complexes

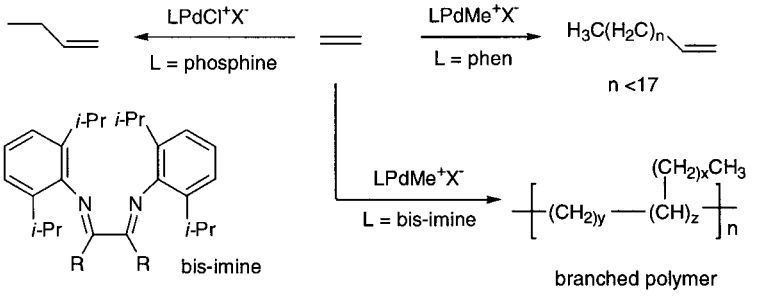
A conceptually different approach to obtain palladium catalysed cyclisations relies on the intramolecular insertion of alkenes on juxtaposed π-allyl–Pd complexes. These intriguing transformations, pioneered by Oppolzer, are known as *palladium-ene reactions*.[76,77] Interestingly, most of these reactions are successful only if performed in AcOH as the solvent. A possible explanation is that AcOH, being a source of palladium hydride, prevents collapse of the transient π-allyl complex to the corresponding triene (Scheme 25).[78,79] In this context, the intramolecular insertion of 1,3-dienes into π-allyl–Pd complexes has also been reported.

3.9. Carbonylation[80]

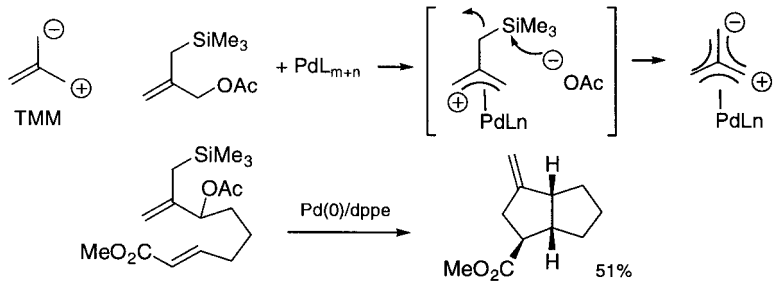
Carbon monoxide is the most interesting member of the C_1-family and its dual character of a stable but electronically unsaturated molecule provides enormous possibilities as an easy-to-handle building block in organic synthesis. The fundamental step of CO-insertion into almost any carbon–palladium bond is the archetype of a C–C bond forming reaction. Hydroformylation or hydrocarbonylation, hydroesterifications or carboxylations etc. are examples of these simple carbonylation reactions. A good illustration is the straightforward and highly selective preparation of the anti-inflammatory drugs ibuprofen and naproxen (Scheme 26).[81] Carbon monoxide is an ideal partner in domino reactions, for example when the C–Pd unit is already the result of several other reaction steps.

3.10. Hydrovinylation, oligomerisation, polymerisation, co-polymerisation of low molecular alkenes

The electrophilic character of certain palladium(II) complexes can be exploited for carbon–carbon bond formation in the homocoupling of α-alkenes. Connecting olefins with each other in an intermolecular manner to dimers (hydrovinylation),[82] oligomers or even polymers is largely controlled by the ligands coordinated to palladium. Dimerisation catalysts are simply cationic palladium phosphine complexes (in the presence of silver salts) whereas oligomerisation[83] or polymerisation[84] require more sophisticated control of the coordination sphere of the metal. In this context, the sterically bulky (bisimine)PdMe cation seems to be an ideal combination for the formation of high mass polyethylene with varied and unique microstructures (Scheme 27).[85] Polyketones are available via stereoregular palladium-catalysed co-oligomerisation or co-polymerisation of α-alkenes and carbon monoxide.[86]



Scheme 27.



Scheme 28.

3.11. [3+2] Cycloadditions, trimethylenemethane (TMM)

In cycloaddition reactions two chemical bonds are formed simultaneously during a ring-forming step. The template effect of transition-metals is extremely favourable in order to bring the reacting species together. A zwitterionic species like the TMM (trimethylenemethane) molecule is a valuable reagent, provided that it is stabilised and, more importantly, activated with palladium(0).[87] In 2-[(trimethylsilyl)methyl]-allyl esters the silyl group serves as the carbanionic equivalent whereas the acetate (or other more reactive sulfonates or chlorides) acts as the leaving group for the carbocationic part. This bifunctional palladium complex is reactive enough to attack electron-deficient double bonds (vinyl esters, nitriles, sulfones, and any activated alkenes in terms of a conjugate addition). The TMM cycloaddition is a powerful method for the access to quinanes and other cyclopentanoids. The example of Scheme 28 shows an intramolecular version leading to a bicyclo[3.3.0]octane structure.

4. Domino Processes[88]

Although palladium catalysed domino processes have only recently been extensively reported in the literature, the conception of sequential palladium mediated transformations was actually pioneered some time before the word 'domino' was coined. A comprehensive review of this topic is not the purpose of the present manuscript, which will be restricted to selected examples. A systematic classification of the palladium assisted domino reactions is not easy, since such transformations may, at least in principle, be combinations of several, among the elementary steps described above. In order to recognise and classify a domino process, it may be useful to locate three types of functional groups in the substrate: a *starting* functionality, one or more *relay* groups, and a *terminating* species. It is important to note that the second stage is invariably a migratory insertion (i.e. a carbopalladation or a CO insertion) and conditions must be met to in order to avoid premature termination of the relay species. This goal may be obtained if *living* (*stable*) σ-alkylpalladium complexes are generated, for

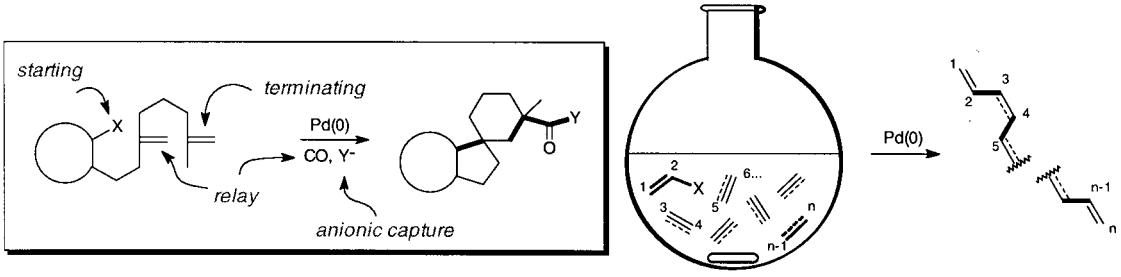
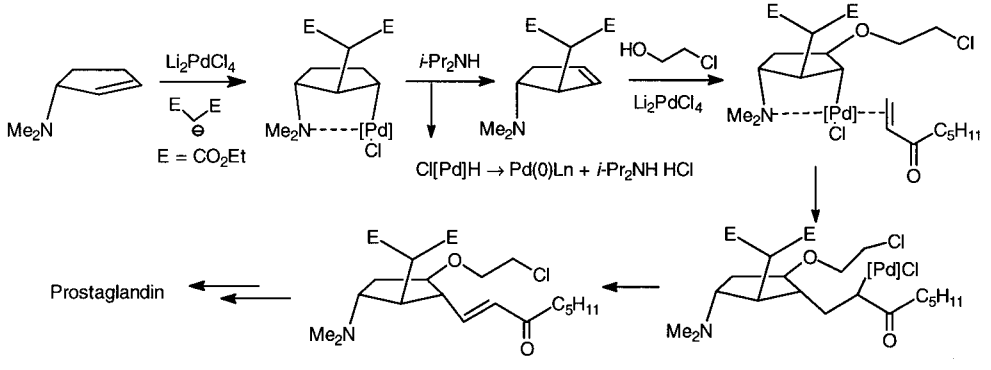
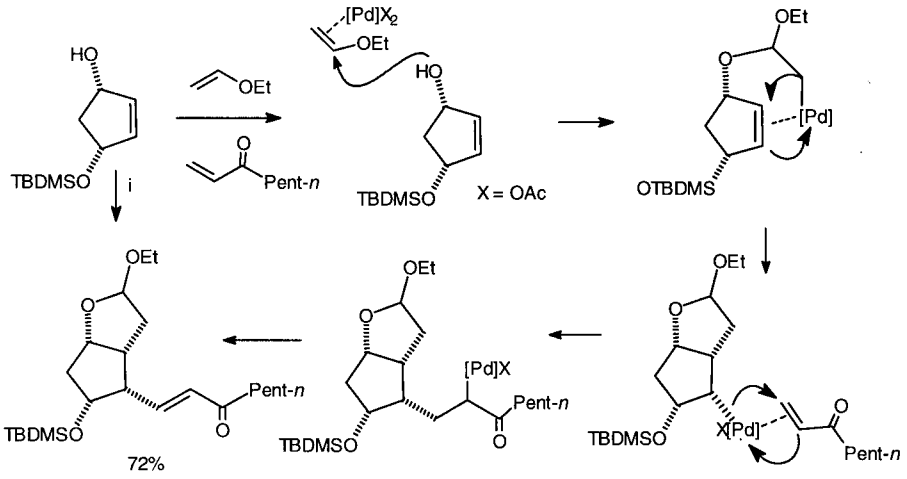


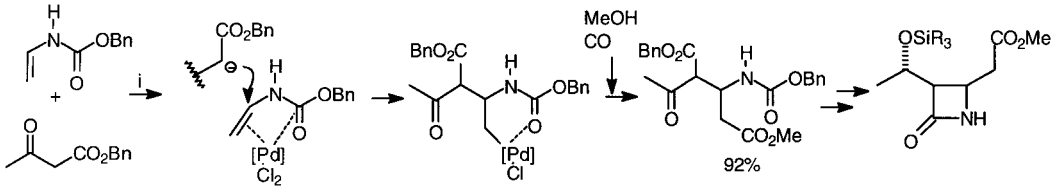
Figure 2.



Scheme 29.



Scheme 30. (i) 1.5 equiv .$Pd(OAc)_2$, AcONa, NaI, rt.

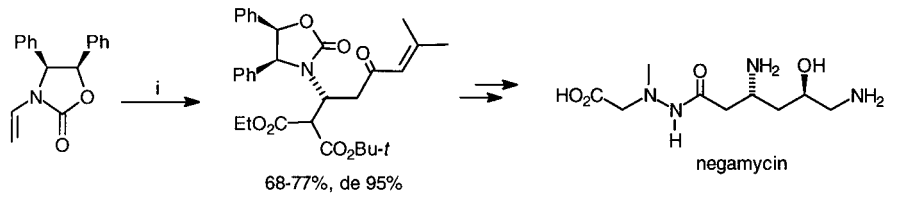


Scheme 31. (i) $PdCl_2(MeCN)_2$, NEt_3, CO, MeOH.

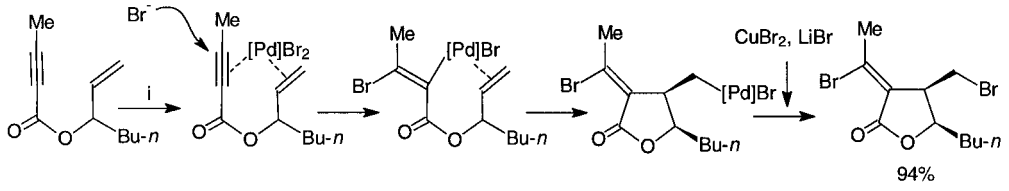
example, by preventing dehydropalladation. This concept is illustrated on the preceding page for an n-component domino process (Fig. 2). Termination of the cascade may take place internally (via dehydropalladation) or externally (via a trapping agent). In the latter case, the trapping agent must react slowly enough to allow the cascade to complete without premature termination, and, at the same time, rapidly enough to prevent undesired side reactions.

4.1. *anti* Palladations

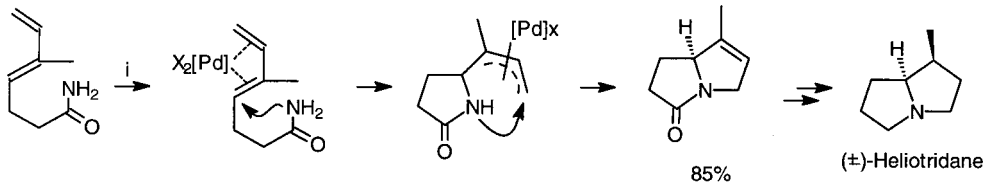
4.1.1. Intermolecular processes. The pioneering work of Holton on palladium mediated consecutive reactions led to an elegant prostaglandin total synthesis.[89] The product obtained by the Li_2PdCl_4-mediated regioselective coupling of 3-cyclopentylamine and diethyl malonate, upon treatment with an amine, underwent dehydropalladation. A further Li_2PdCl_4-promoted regioselective addition of 2-chloroethanol to the newly-generated alkene gave an alkyl–Pd(II) complex which carbopalladated 1-octen-3-one. The final dehydropalladation afforded the desired product which could eventually be converted to a prostaglandin. Unfortunately, the first carbopalladation could not be performed in the same pot as the subsequent alkoxypalladation/ketovinylation sequence, and stoichiometric amounts of the palladium salt were necessary (Scheme 29).



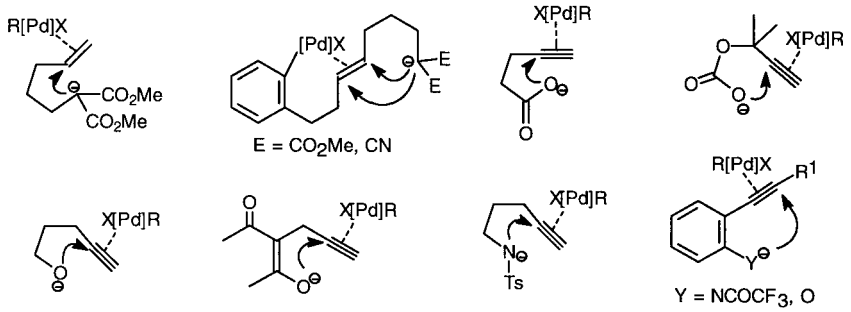
Scheme 32. (i) $PdCl_2(MeCN)_2$, NEt_3, $NaCH(CO_2Et)(CO_2Bu\text{-}t)$, CO, Me_3Sn–.



Scheme 33. (i) 5% mol. $Pd_2(dba)_3{\cdot}CHCl_3$, $CuBr_2$, LiBr, AcOH, rt.



Scheme 34. (i) $Pd(OAc)_2$, $CuCl_2/O_2$, THF, 60°C.



Scheme 35. R=π-allyl, σ-aryl, σ-vinyl, σ-alkynyl, σ-allenyl, σ-acyl. X=halide, triflate, acetate, alkoxide.

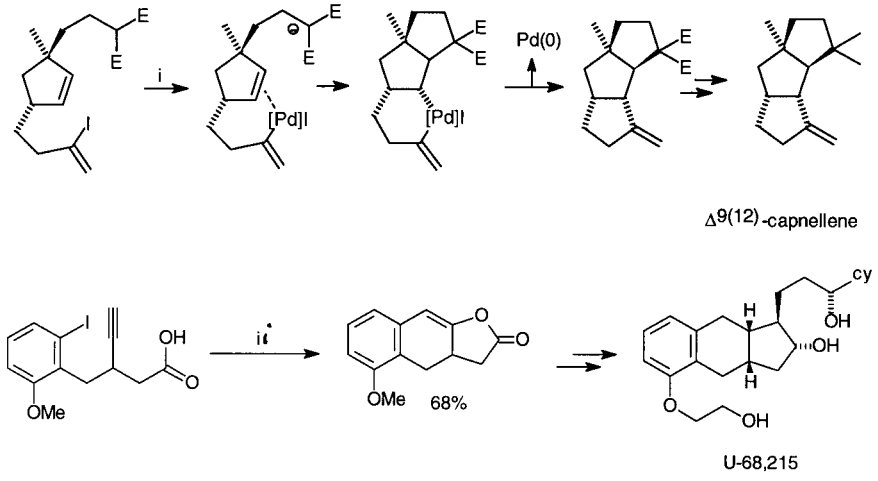
In the synthesis of a prostaglandin analog by Larock and coworkers,[90] alkoxypalladation of an enol ether is followed by two consecutive (intra- and inter-molecular) alkene insertions. A dehydropalladation completes this three component synthesis. Again, a stoichiometric amount of Pd(II) had to be used (Scheme 30).

Hegedus et al. developed very interesting Pd(II) assisted *anti*-carbopalladations of active methylenes on enamides. For example, the sodium salt of benzyl acetoacetate adds to $PdCl_2$-activated benzyl *N*-vinyl carbamate. The chelation-stabilised Pd(II) complex derived from this carbopalladation can undergo in situ sequential CO insertion/methanol trapping, to give an aminodiester, which can be converted into a β-lactam (Scheme 31).[91]

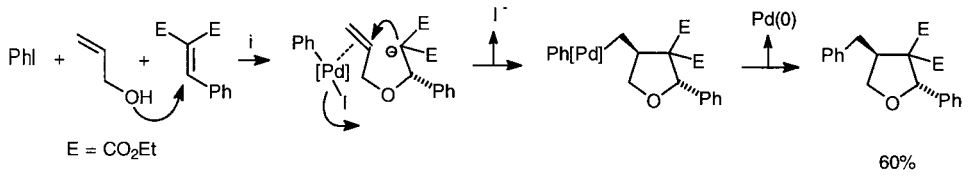
Further studies by the same authors demonstrated that highly diastereoselective carbopalladations on enantiopure enamides allow enantioenriched targets to be obtained, as exemplified by the synthesis of negamycin (Scheme 32).[92]

4.1.2. Ring formations. Pd(II) halides are capable of activating the halide anion addition to the triple bond of suitably substituted *O*-allyl butynoates[93] or *N*-alkenyl 2-alkynamides.[94] The resulting σ-alkenylpalladium complexes can interact with a juxtaposed alkene via an intramolecular carbopalladation. The final oxidative cleavage[95] affords the corresponding α-haloalkylidene-γ-butyro-lactones or -lactams (Scheme 33). The overall reaction regenerates Pd(0).

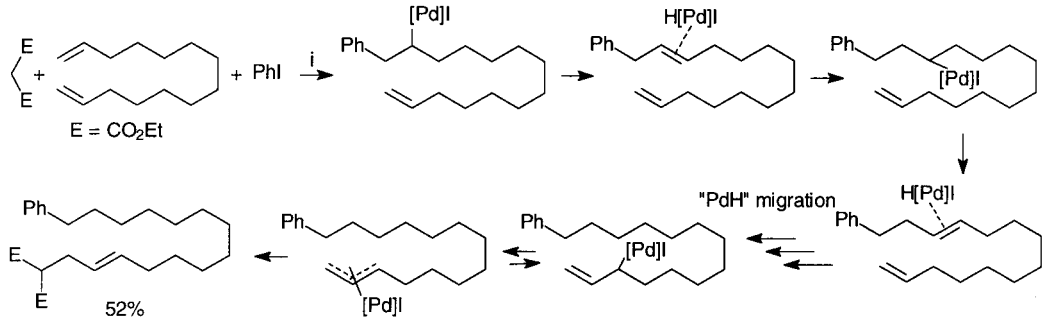
Bäckvall and his group have studied intensively the palladium-catalysed 1,4-oxidations of 1,3-dienes.[96] In these reactions Pd(II) coordination of the diene triggers the first *anti* heteropalladation by a nucleophilic species. The resulting π-allylpalladium complex is eventually trapped by a second nucleophile, thus forming a 1,4-heterodisubstituted 2-butene derivative. Since Pd(0) is ultimately produced, these reactions need a suitable oxidant to regenerate Pd(II) for a catalytic cycle. In a further extension of such a strategy, primary amides were chosen



Scheme 36. (i) 5% $Pd(OAc)_2$, 10% trifurylphosphine, KH, THF, rt, ~63%; (ii) 5% $Pd(OAc)_2$, 10% TFP, KF, DMSO, rt.



Scheme 37. (i) cat Pd(dppe), DMSO, KH, 50°C.



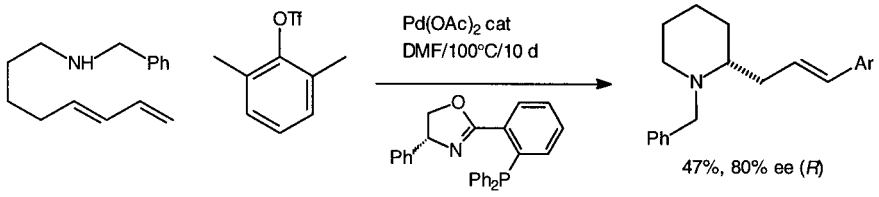
Scheme 38. (i) $Pd(dba)_2$, $NaHCO_3$, NBu_4Cl, DMSO, 80°C.

as nucleophiles capable of a twofold attack in the 1,4-positions of the 1,3-diene. This method enabled the synthesis of a heliotridane precursor in one step (Scheme 34).[97]

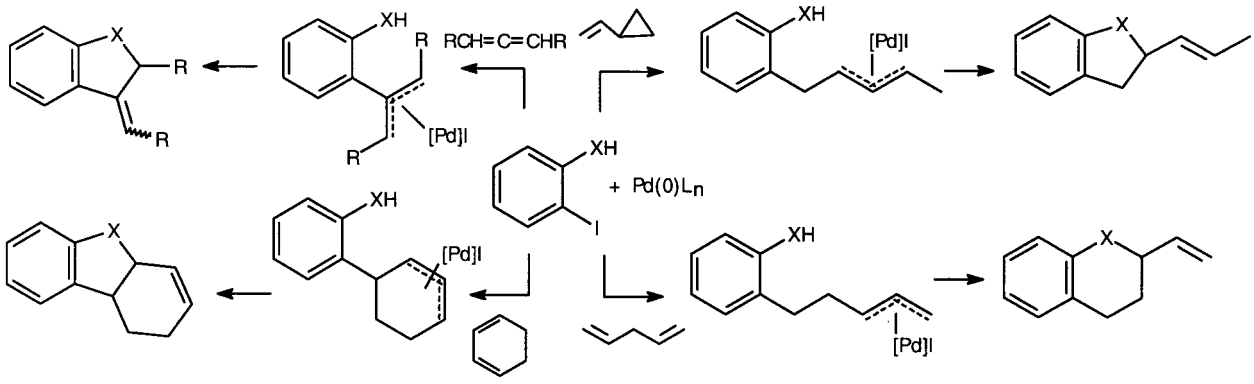
Alkenes and alkynes may also be electrophilically activated via in situ generated σ-aryl, σ-vinyl, or π-allyl palladium complexes. Such an interaction can trigger the addition of a juxtaposed nucleophilic function, providing, after reductive elimination, functionalised carbo- and heterocycles. In contrast to the analogous additions mediated by inorganic salts of Pd(II), the reaction is catalytic in Pd(0) and two new bonds are created in the overall process.[98] Unsaturated β-dicarbonyl compounds,[99] monoalkynylcarbonates,[100] substituted 4-pentinoic acids,[101] *o*-alkynyltrifluoroacetanilides,[102] 2-propargyl-1,3-dicarbonyl compounds,[103] *o*-alkynylphenols,[104] alkyl 3-oxo-6-heptinoates,[105] alkynes containing alcohols[106] or tosylamides[107] are suitable precursors for such interesting cyclisations. Some examples from the groups of Cacchi, Balme, Inoue and Luo are shown in Scheme 35.

Using this concept, Balme has achieved the total synthesis of the triquinane terpenoid $\Delta^{(9,12)}$-capnellene[108] and the formal total synthesis of the anti-ulcer agent U-68,215[99,109] (Scheme 36).

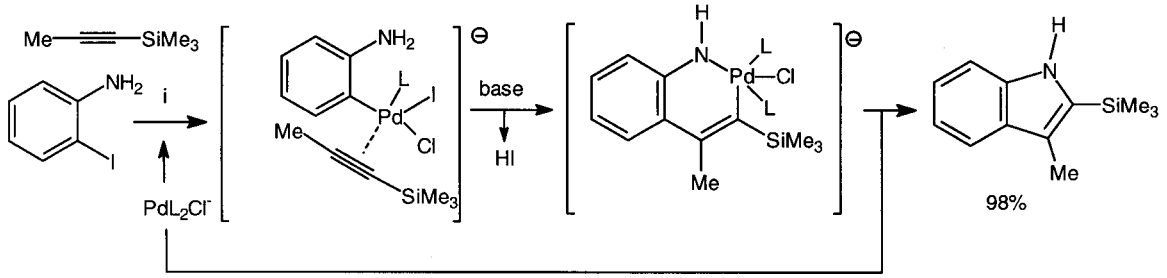
In a variation of this method developed by the same authors,[110] the conjugate addition of an allylic alcohol to a Michael acceptor generates a stabilised malonate anion,



Scheme 39.



Scheme 40. X=O, NR, CH_2O, CH_2NR, $C(CO_2,R)_2$, $CH_2C(CO_2R)_2$.



Scheme 41. (i) 5 mol% $Pd(OAc)_2$, 5 mol% PPh_3, NBu_4Cl, Na_2CO_3, 100°C.

which undergoes in situ intramolecular palladium catalysed coupling, thereby affording substituted tetrahydrofuran derivatives (Scheme 37).

4.2. *syn* Palladations

The carbopalladation reaction is especially suited to generate, by iterated inter and/or intramolecular C–C bond formations, structurally complex cyclic products.

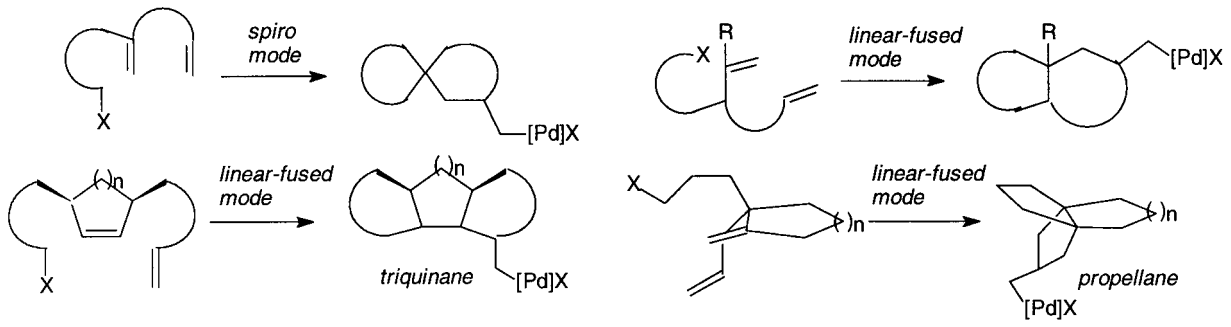
4.2.1. Intermolecular carbopalladations. If a σ-alkylpalladium complex is generated in a structure embodying an alkene, sequential reversible dehydropalladation/hydropalladation events may take place along the carbon backbone, until the randomly migrating palladium atom reaches the position allylic to the distal alkene. A π-allylpalladium complex is thus generated and this may be trapped in situ by a suitable nucleophilic species.[111] Aryl iodides react in this way with α,ω-dialkenes and active methylenes or amines, in the presence of Pd(0), to give an intermolecular three-component coupling. With the 1,13-diene described in Scheme 38, the XPdH migration involves 484 discrete mechanistic steps for the global process.

In an analogous manner, the Ozaki–Heck reaction between an amino-1,3-diene and an aryl halide generates an η^3-allyl complex, which can undergo intramolecular allylic amination in an enantioselective manner (Scheme 39).[112]

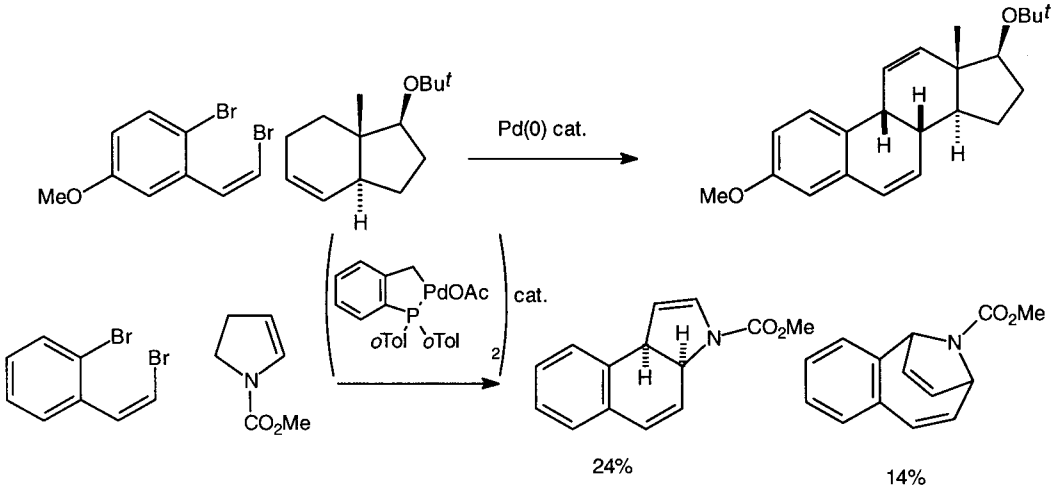
Larock et al. found that aryl halides bearing *o*-substituted heteroatoms or carbanion stabilising groups can couple with 1,2-,[12a] 1,3-,[113] 1,4-dienes,[114] unsaturated cyclopropanes and cyclobutanes,[115] under Pd(0) catalysis. These processes involve the initial oxidative addition of Pd(0) to the halide, followed by carbopalladation of the unsaturated system and final nucleophilic trapping by the internal nucleophile (Scheme 40).

In an analogous way, *o*-iodoaniline and its derivatives react with internal alkynes[116] to give indoles. The mechanism is expected to proceed through a regioselective *syn* insertion into the arylpalladium bond, followed by nitrogen dispacement of the halide in the resulting vinylpalladium intermediate to form a six-membered heteroatom-containing palladacycle, which eventually undergoes reductive elimination (Scheme 41).

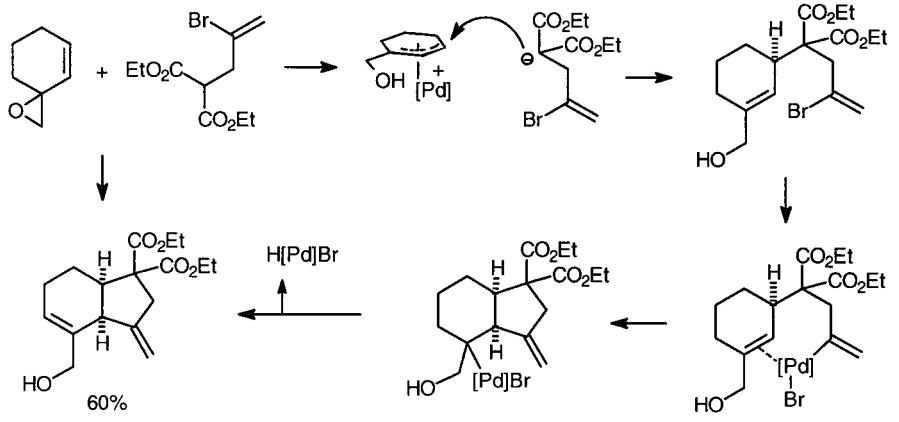
4.2.2. Intramolecular carbopalladations. *Linear-fused and spiro-mode carbopalladations.* Depending on the relative disposition of the unsaturations in the backbone of the precursor, and on the sequence of the reaction events, several modes can be distinguished in cyclic carbopalladations. A *linear-fused*-mode carbopalladation may be obtained with substrates having the starting, the relay, and the terminating groups each connected by a trisubstituted atom. For structural reasons the relay group has to be located vicinal to the tripodal atom.[117] When a 1,1-disubstituted alkene acts as relay, a *spiro-mode* cyclisation is realised.[118] If the relay function is an endocyclic alkene bearing the starting and the terminating moieties on two allylic *cis* disposed arms, triquinane-type structures may be obtained.[119] If the relay species is an exocyclic alkene, and the starting and the terminating species reside on the two vicinal geminally-disposed arms, propellane-type structures may be formed.[118] In all cases premature termination of the σ-alkylpalladium intermediate (not shown) is eluded



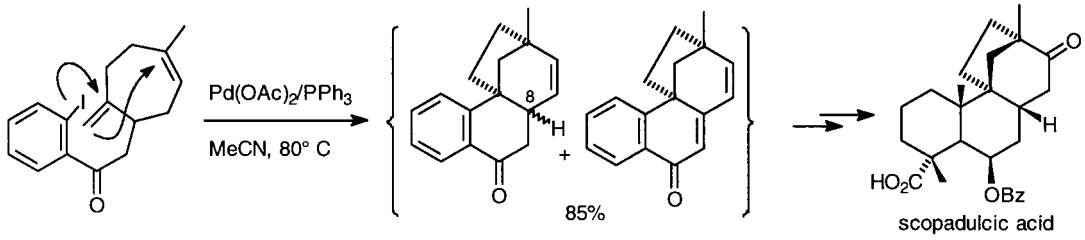
Scheme 42.



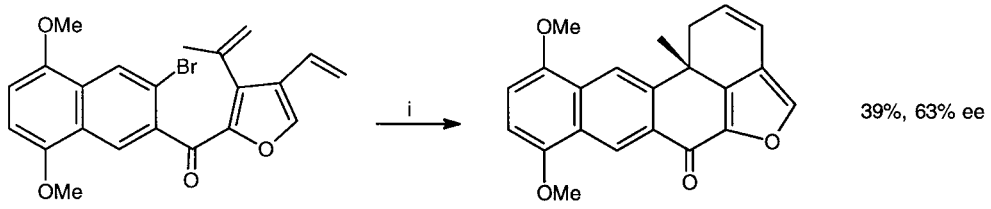
Scheme 43.



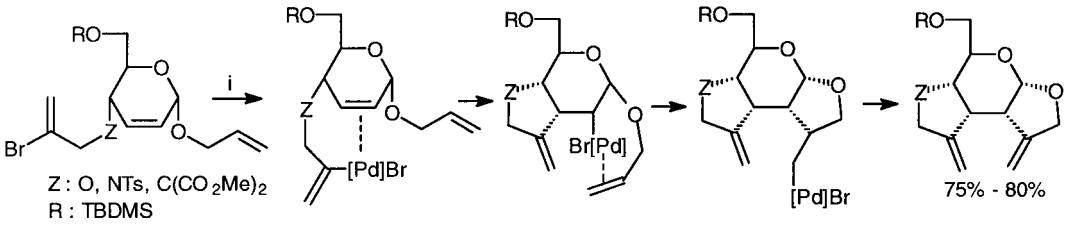
Scheme 44. (i) 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, NaH (1.1 equiv.), THF.



Scheme 45.



Scheme 46. (i) $Pd_2(dba)_3CHCl_3$ cat/(*S*)-BINAP cat/$CaCO_3$/Ag exchanged zeolite.



Scheme 47. (i) 10% mol $Pd(OAc)_2$, 20% mol PPh_3, NEt_3 (2.5 equiv.), Bu_4NHSO_4 (1 equiv.), CH_3CN, 80°C, 15–24 h.

thanks to the lack of a β-hydrogen *syn*-periplanar to palladium (Scheme 42).

The elegant use of two subsequent (inter and intramolecular) Ozaki–Heck reactions allowed Tietze et al. to build up a steroid derivative[120] and aza-heterocycles (Scheme 43).[121]

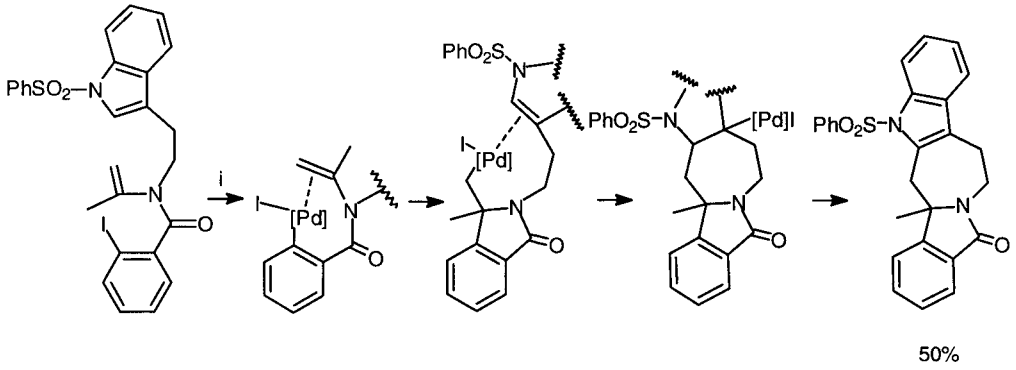
Gaudin[122] developed an interesting Pd(0) catalysed annulation between an allyl epoxide and a bromoallyl malonate, to form five-membered ring systems. The reaction proceeds via initial alkylation of the malonate anion with the epoxide-derived π-allylpalladium, followed by oxidative addition of Pd(0) on the vinylic bromide. The subsequent intramolecular carbopalladation, and dehydropalladation complete the sequence (Scheme 44). It should be pointed out that, although the global transformation is carried out using a single catalytic system, the process involves two independent catalytic cycles. This protocol cannot therefore be strictly defined as a true domino process.

The first experiments on sequential carbopalladation via generation of σ-alkylpalladium derivatives lacking β-*cis*-hydrogens (living) have been described by Overman in the first total synthesis of scopadulcic acid, the active principle of the medicinal plant *Scoparia dulcis*. In this elegant spiromode Pd(0) catalysed bis-cyclisation, the initial oxidative addition of the dienyl iodide is followed by two consecutive intramolecular carbopalladations and a final dehydropalladation. Since the first carbopalladation is not highly face-selective, a mixture of diastereoisomers is obtained in the final product (Scheme 45).[123]

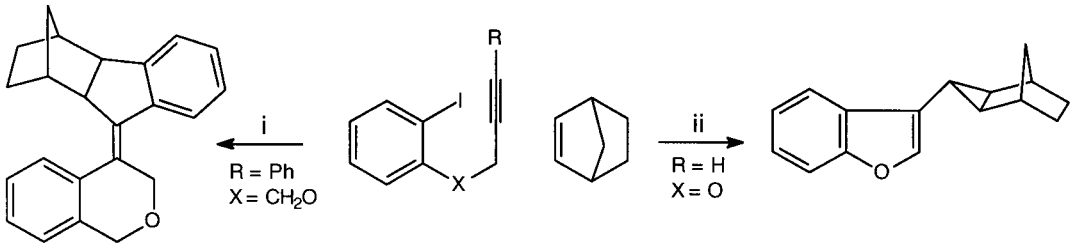
A related strategy has been elegantly developed by Shibasaki et al. in connection with the synthesis of (+)-xestoquinone. In this example (S)-BINAP is responsible for the enantioselectivity of the carbopalladation step (Scheme 46).[124]

Sinou[125] et al. have developed a one-component palladium-mediated intramolecular cyclisation on a glucal-derived template, obtaining an enantiopure triquinane-type product. The process starts with the formation of a σ-vinylpalladium intermediate which is followed by two consecutive intramolecular carbopalladations and by a final dehydropalladation (Scheme 47).

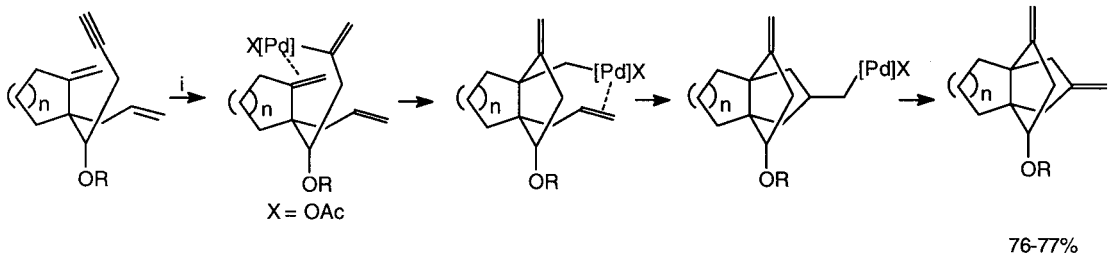
Grigg has recently reported examples of linear-fused bis- and tris-cyclisations which are terminated by a Friedel–



Scheme 48. (i) 10% mol $Pd(OAc)_2$, 20% mol PPh_3, 1 mol Tl_2CO_3, anisole, 130°C, 24 h.



Scheme 49. (i) $Pd(OAc)_2$ cat/PPh_3/TlOAc cat/MeCN (67%); (ii) $Pd(OAc)_2$ cat/PPh_3/NEt_3/MeCN (45%).



Scheme 50. (i) $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, AcOH, PhH, 50–55°C.

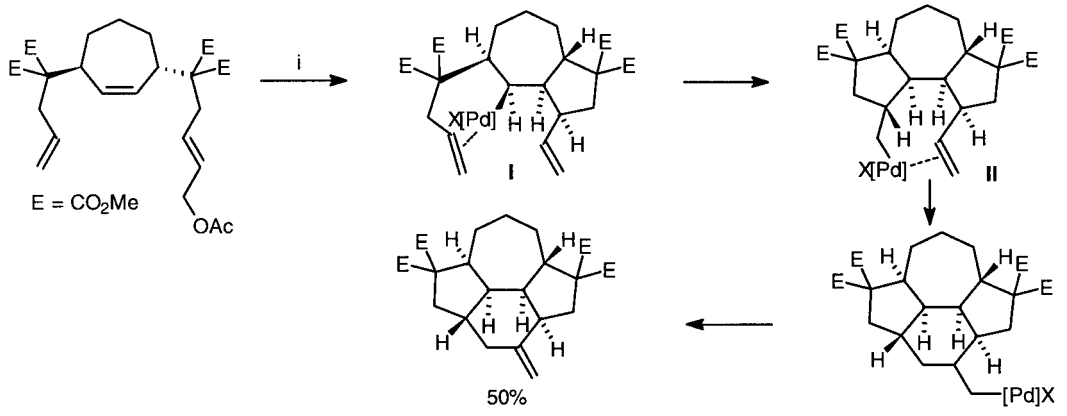
Crafts type alkylation.[126] These reactions occur on both electron rich and electron poor heteroaromatic rings (Scheme 48).

When such intramolecular *syn*-carbopalladations are followed by intermolecular *syn*-carbopalladation (norbornene capture), subsequent 3-*exo-trig* carbopalladation/dehydropalladation or Friedel–Crafts type condensation may take place, depending on the reaction conditions as well as on the nature of the substrate (Scheme 49).[127]

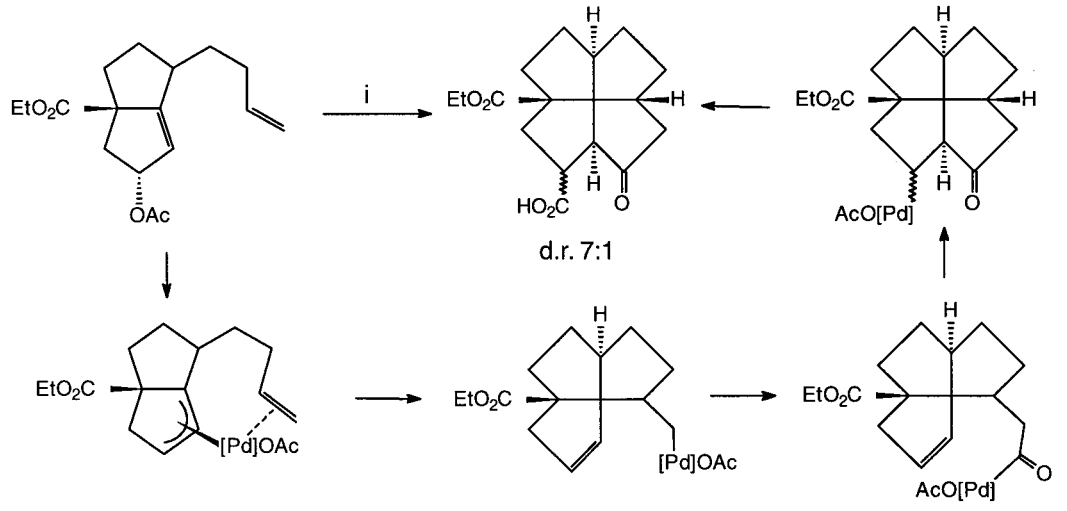
When the relay function is an allene, the addition takes place at the central carbon atom, thereby giving an η^3-allylpalladium complex. Trapping of such a complex by azide anion can eventually be followed by 1,3-dipolar cycloadditions.[128]

Propellane structures have been obtained by Trost et al. by reacting 2-allyl-2-homopropargyl-1-methylenecycloalkanes in the presence of $Pd_2(dba)_3$ and AcOH.[118] The success of the synthesis depends on the regioselective formation of the secondary vinylpalladium intermediate, and on its regioselective addition to the exocyclic double bond (Scheme 50).

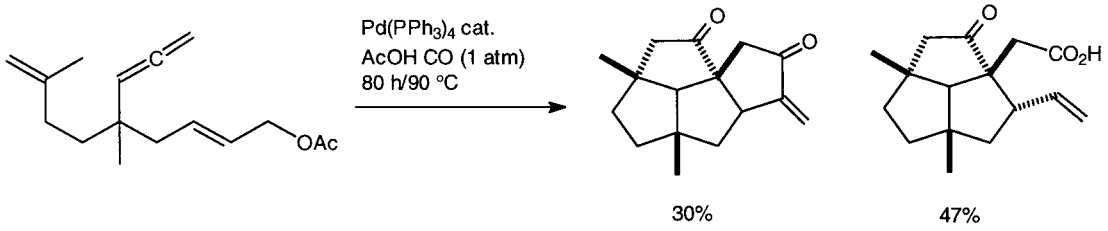
Oppolzer and De Vita[129] have reported an interesting linear-fused palladium catalysed tris-cyclisation of a bis-allylically



Scheme 51. (i) 10 mol% $Pd(dba)_2$, 40 mol% trifurylphosphine, AcOH, 110°C, 2 h.



Scheme 52. (i) $Pd(dba)_2$ cat/PPh_3/AcOH/CO (65%).



Scheme 53.

substituted cycloheptene (Scheme 51). The initially formed π-allylpalladium undergoes three subsequent intramolecular carbopalladations before the final dehydropalladation. Worthy of note, the two postulated alkylpalladium intermediates I and II undergo carbopalladation even if β-hydrogen atoms are present.

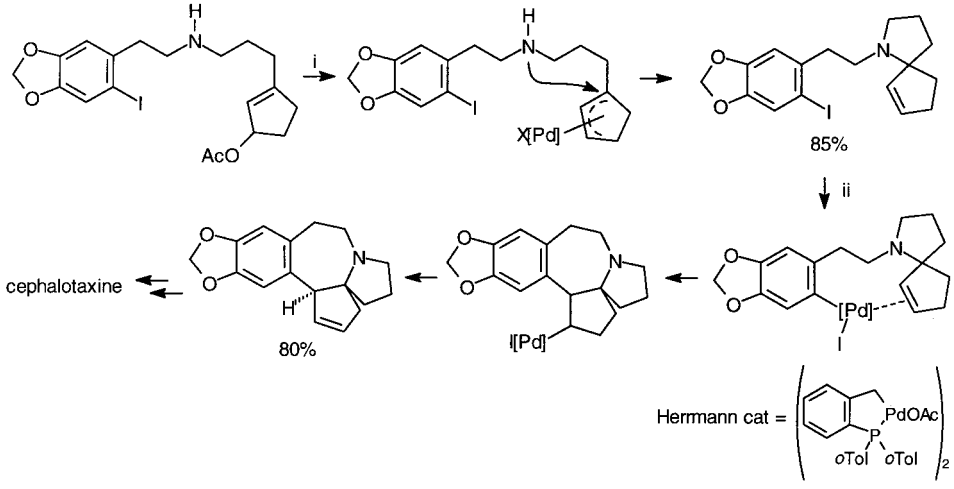
Keese et al. similarly succeeded in building up the fenestrane skeleton, the final product being obtained via a double intramolecular carbopalladation/CO insertion sequence (Scheme 52).[130]

Takahashi et al. submitted an alkenyl–allenyl–allyl acetate to domino cyclisation–carbonylation thereby achieving five and six consecutive C–C bond formations (Scheme 53).[131]

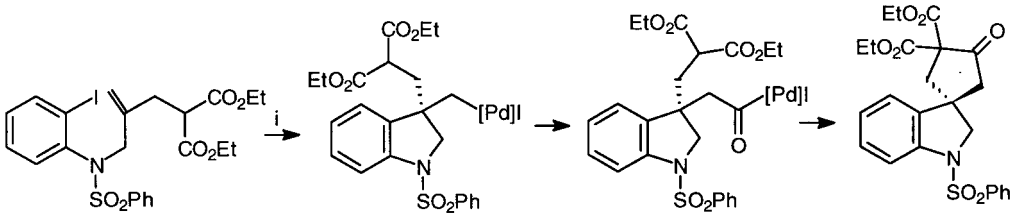
Tietze and Schirok[132] have recently reported the formal synthesis of the parent compound of a family of antileukemic drugs, cephalotaxine, by means of two sequential palladium-catalysed processes. The strategy relies on a 5-*exo* intramolecular allylic amination, followed by a totally diastereoselective intramolecular Ozaki–Heck reaction, to give the desired benzazepine (Scheme 54). The two transformations, however, need two different catalytic cycles and have been performed separately.

A wide variety of heterospirocyclic compounds have been obtained by Grigg et al. via intramolecular carbopalladation of a σ-arylpalladium complex into a 1,1-disubstituted alkene under carbonylative conditions. In the example shown below the anionic capture was effected by an internal malonate anion (Scheme 55).[133]

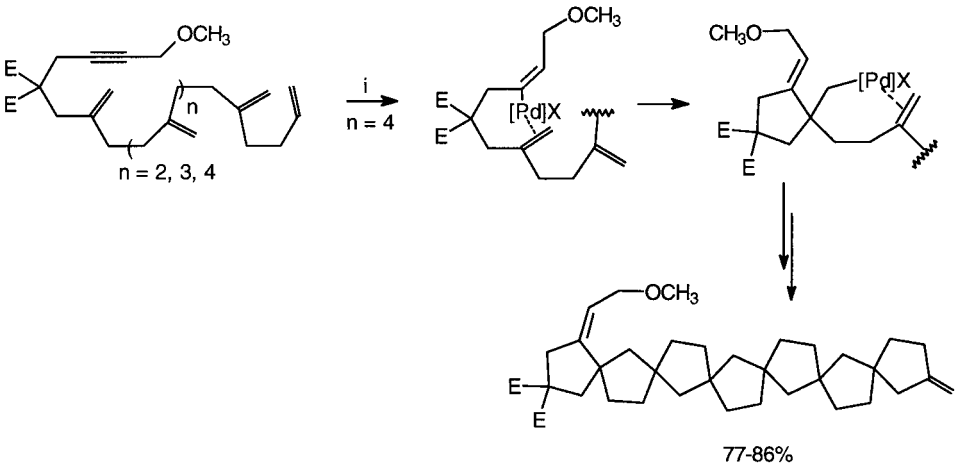
The intramolecular carbopalladation on a linear structure containing sequentially and properly disposed gem-disubstituted alkenes generates a cascade of *living* alkylpalladium complexes until the metal is internally or externally released. Using this strategy Trost et al.[118] succeeded in synthesising a hexaspirane system from a totally acyclic



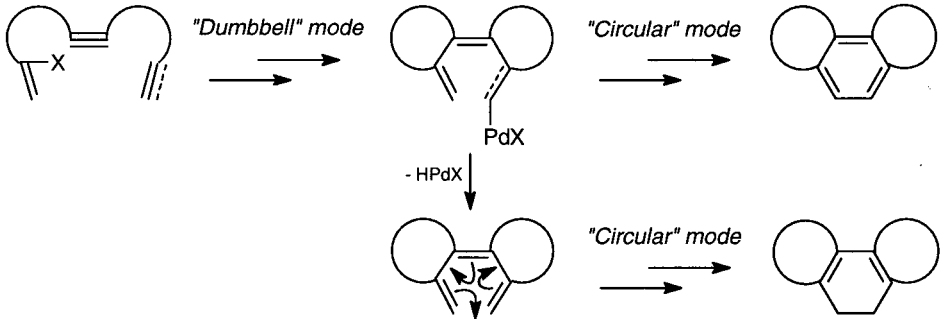
Scheme 54. (i) 8 mol% $Pd(PPh_3)_4$, NEt_3 (1.7 equiv.), CH_3CH, 50°C, 10 h; (ii) 6 mol% Herrmann cat., *n*-Bu_4NOAc (2.2 equiv.), $CH_3CN/DMF/H_2O$ (5/5/1).



Scheme 55. (i) $Pd(OAc)_2$, PPh_3, CO, CH_3CN, AcOTl, 80°C, 24 h (50%).



Scheme 56. E=$PhSO_2$ (i) 2.5% $(dba)_3Pd_2{\cdot}CHCl_3$, 10% Ph_3Sb, AcOH, PhH, 50–65°C.



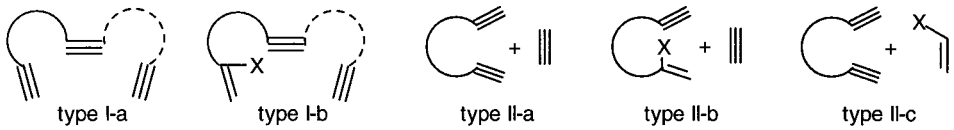
Scheme 57.

precursor, thereby generating seven new bonds in one synthetic operation (Scheme 56).

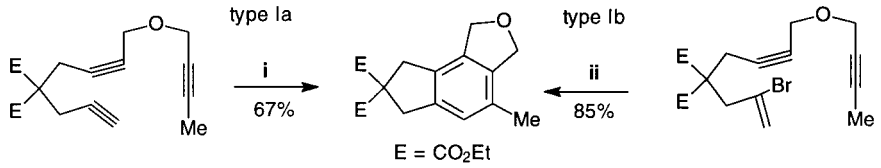
Dumbbell mode and circular carbopalladations. The *dumbbell*-mode carbopalladation cascade involves generation of the starting C–Pd bond in a linear structure in a distal position with respect to other juxtaposed unsaturations. This cyclisation mode, which works well with alkynes, allows the building up of pairs of C_{sp2}-linked ring systems.[134,63a] Upon iteration of the process, however, intramolecular processes may take over this linear process according to a *circular*-mode cyclisation. Pericyclic reactions such as Diels–Alder, ene, electrocyclic, and Cope, may serve as the final cyclisation step (Scheme 57).

When a σ-vinylpalladium complex interacts with two alkyne moieties a variety of substituted benzene derivatives can be obtained via a formal [2+2+2] cyclisation (Scheme 58).

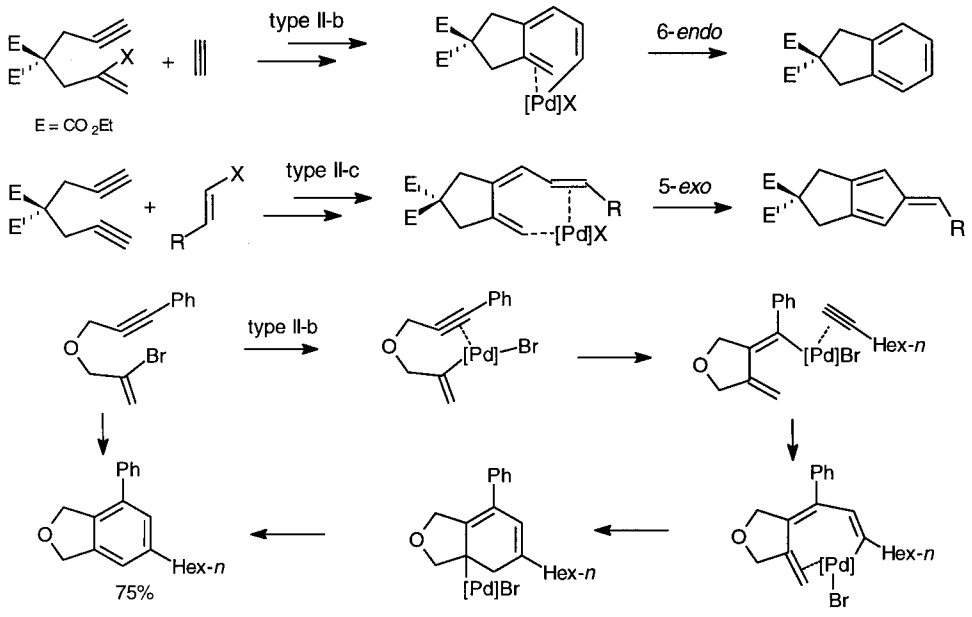
The totally intramolecular processes (type I-a and I-b) proceed smoothly and in good yield when leading to five- and/or six-membered rings.[135,63c] The initially formed alkenylpalladium derivative undergoes a dumbbell mode



Scheme 58.



Scheme 59. (i) 3% mol $Pd(PPh_3)_4$, 5 mol% AcOH; (ii) 3% mol $Pd(PPh_3)_4$, NEt_3.



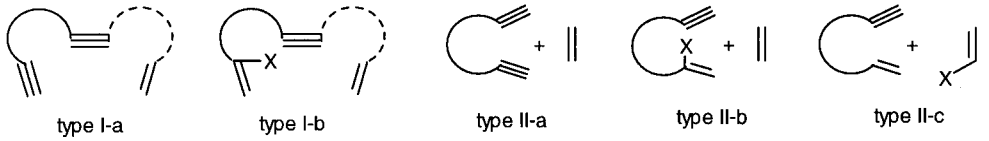
Scheme 60. (i) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% *n*-BuLi, NEt_3 (2 equiv.), DMF, 1-octyne.

exo cyclisation to give a bicyclic alkenylpalladium complex, which takes part in the last cyclisation (Scheme 59). Less obvious is the mechanism of the latter cyclisation, which could involve either an electrocyclic process or an *endo* carbopalladation, both being followed by dehydropalladation.[63c,135]

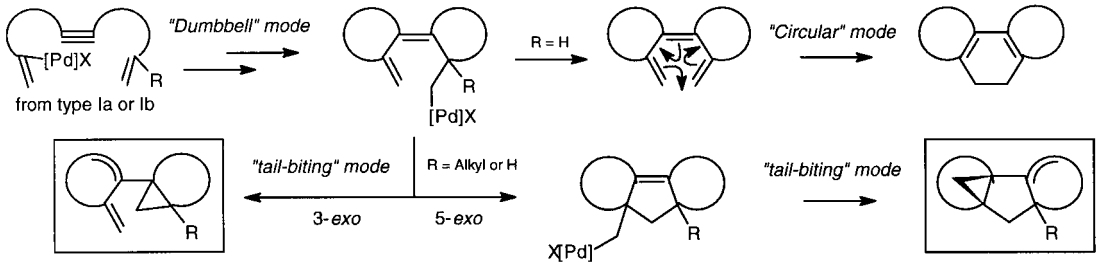
Reactions of type II-a are usually more complicated than those of types II-b, and II-c, where the vinyl halide serves to specify the starting site. Benzene derivatives or bicyclic fulvenes are formed in the last two reaction modes, respectively. In both cases, the rate of the intermolecular carbopalladation of the monoyne has to be greater than that of the unreacted haloenyne, and the termination must be faster than homooligomerisation of the monoyne. The 5-*exo* versus 6-*endo* preference can be understood on the basis of the different conformational rigidity of the trienylpalladium intermediates deriving from the two routes (Scheme 60).[136,59b]

Related cyclisation modes can occur with an alkene as the terminating species (Scheme 61).

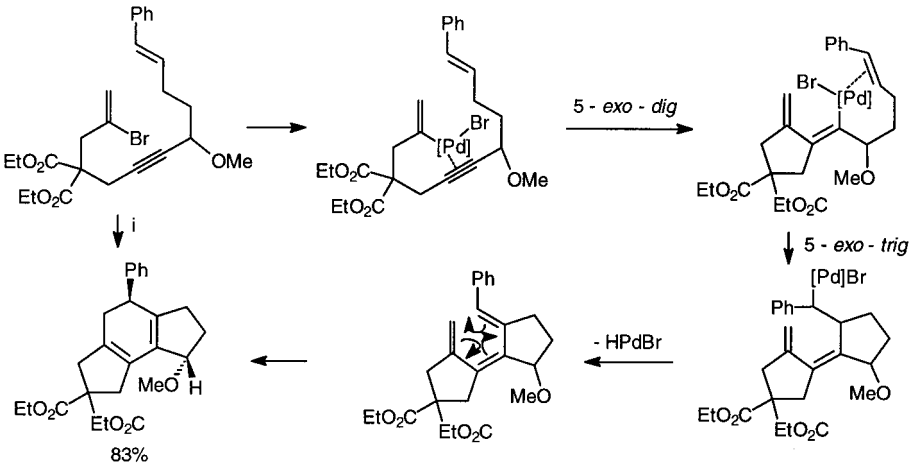
Enediynes and halodienynes (types I-a and I-b), undergo *dumbbell*-mode intramolecular bicyclisation processes. If the transient σ-alkylpalladium species carries a β-*cis*-hydrogen, dehydropalladation affords 1,3,5-trienes, which can in turn undergo an electrocyclic rearrangement to produce cyclohexadienes. If geminally disubstituted alkenyl groups are used as the terminating species, the *living* palladium complex may undergo either a 3-*exo*, or a 5-*endo* process followed by a 3-*exo* carbopalladation, before the final dehydropalladation.[137,63b] The 3-*exo* cyclopropanation process, known as *tail-biting*, is an intriguing side reaction that may short-circuit a carbopalladation cascade when a homoallylpalladium is transiently generated. Since it is a reversible process, the formation of cyclopropanated products can sometimes be prevented (Scheme 62).[62a]



Scheme 61.



Scheme 62.



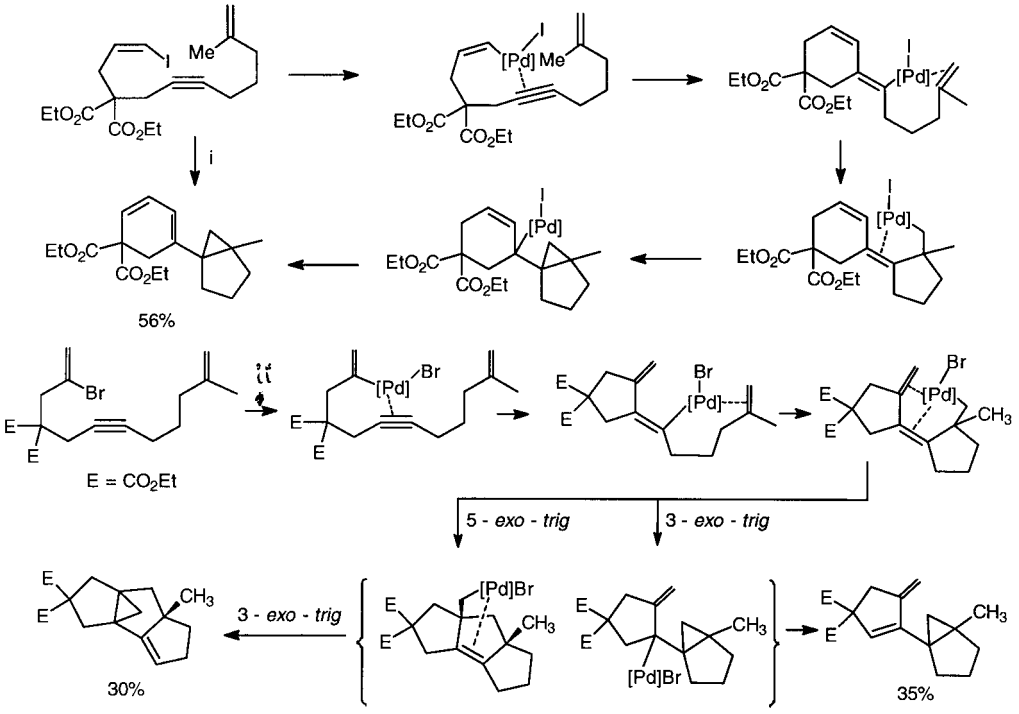
Scheme 63. (i) 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 3 equiv. K_2CO_3, CH_3CN, 60°C, 3 days.

Treatment of the 2-bromododeca-1,11-diene-6-yne shown in Scheme 63 with the palladium catalyst system gave a bisannelated cyclohexadiene. The mechanism involves an initial 5-*exo-dig*, followed by a 5-*exo-trig* cyclisation. Dehydropalladation affords the hexatriene intermediate which suffers 6π-electrocyclic rearrangement. The complete diastereoselectivity of the reaction depends on the influence of the methoxy group on the rotaselectivity of the final electrocyclic rearrangement. In fact, only one of the two possible thermally allowed disrotatory movements takes place, bringing the methoxy and the phenyl group in a *trans* relationship[136b,136c,63b,63d,138] (Scheme 63).

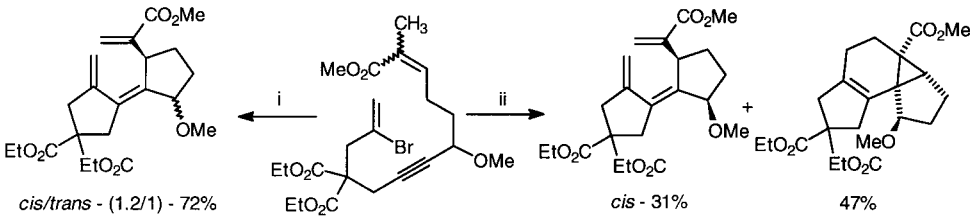
Further experiments by de Meijere[136c,137c] and Negishi[134] involved appropriate substrates where the final dehydropalladation is forbidden (Scheme 64). In the absence of β-hydrogens, the neopentylpalladium intermediate interacts with one of the adjacent alkenes, and competitive 3-*exo-trig*/dehydropalladation or a 5-*exo-trig*/3-*exo-trig*/dehydropalladation took place, facilitating access to complex tri- and tetracyclic structures.

Further studies involved the 2,12-dodecadiene substrate. The expected 1,3,6-trienyl system was obtained in the presence of silver carbonate at 80°C. When the reaction was run at 130°C in the presence of potassium carbonate, however, only the *cis*-disubstituted bicyclopentylidene derivative was obtained, along with the tetracyclic compound arising from the intramolecular Diels–Alder reaction of the *trans* isomer (Scheme 65).[136c]

As discussed earlier for the reaction between diynes and



Scheme 64. (i) 3 mol% $Pd(PPh_3)_4$, NEt_3 (2 equiv.), CH_3CN, 12 h, Δ; (ii) 3 mol% $Pd(OAc)_2$, 12 mol% PPh_3, Ag_2CO_3 (2 equiv.), DME/CH_3CN, 60°C.

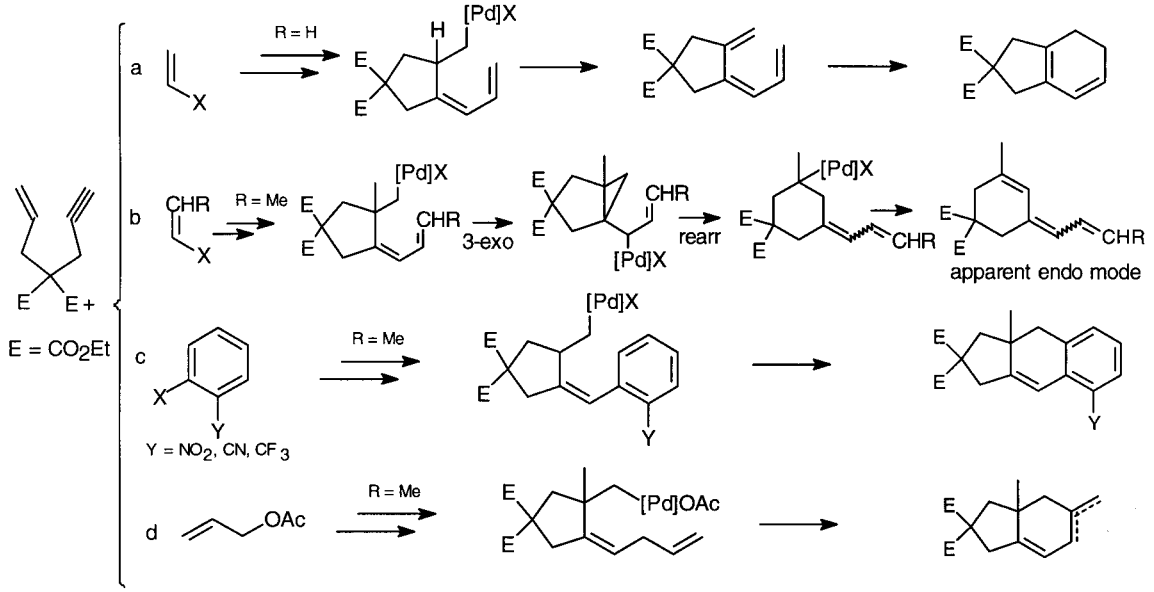


Scheme 65. (i) 3 mol% $Pd(OAc)_2$, 12 mol% PPh_3, 2 equiv., Ag_2CO_3, CH_3CN, 80°C, 8 h; (ii) 11 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 3 equiv. K_2CO_3, CH_3CN, 130°C, 14 h.

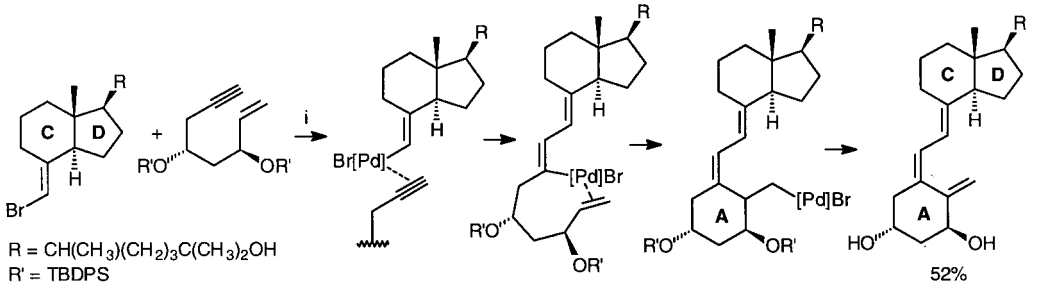
monoynes, the selective co-cyclodimerisation of diynes with monoenes (type II-a) is a disfavoured process. The type II-b process might be favourable provided that the monoene is more reactive than the alkyne of a second molecule. Type II-c is a known favourable process. When vinyl halides are used, a σ-alkylpalladium intermediate containing a conjugated diene moiety is generated. If a β-*cis*-hydrogen is available, dehydropalladation is the predominant path leading to conjugated hexatrienes (Scheme 66a).[62b] Further cyclisation to give cyclohexadienes can also be observed. If the β-hydrogen is lacking, *apparent endo mode* carbopalladation is observed (Scheme 66b).[66a] Five-membered rings are obtained via *exo* mode carbopalladation with aryl halides[66b] and allyl acetates (Scheme 66c,d).[62a]

Extension of the palladium catalysed cycloisomerisation to 1,7-enynes allowed Trost et al. to develop a new strategy for the synthesis of ring A of 1α-hydroxy-vitamin D.[139] In this type II-c cyclisation, the vinyl bromide undergoes oxidative addition and interacts with the alkyne function, starting the cyclisation process. Under these reaction conditions the undesired further electrocyclic cyclisation is prevented (Scheme 67).

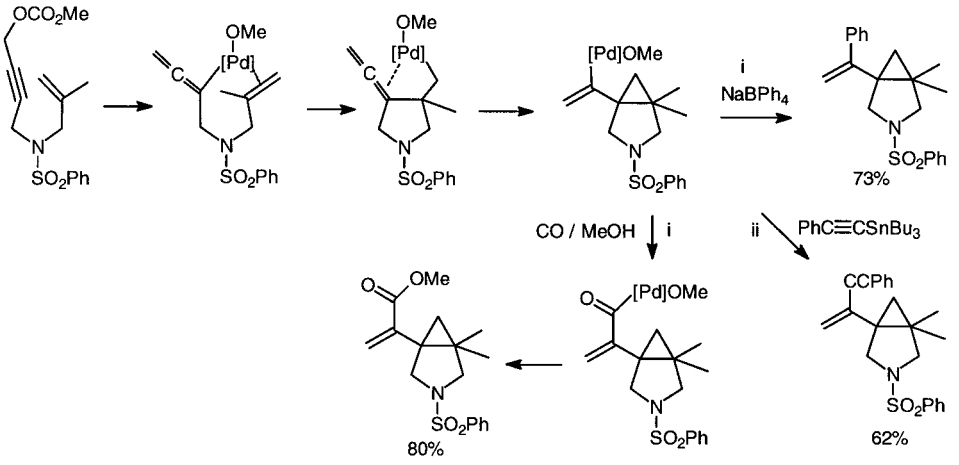
Propargyl carbonates are known to react with Pd(0) complexes to give the corresponding allenylpalladium derivatives. Their 5-*exo* intramolecular carbopalladation with a 1,1-disubstituted alkene generates a *living* σ-alkylpalladium complex which can *tail bite*. The resulting σ-vinylpalladium derivative can in turn undergo external nucleophilic



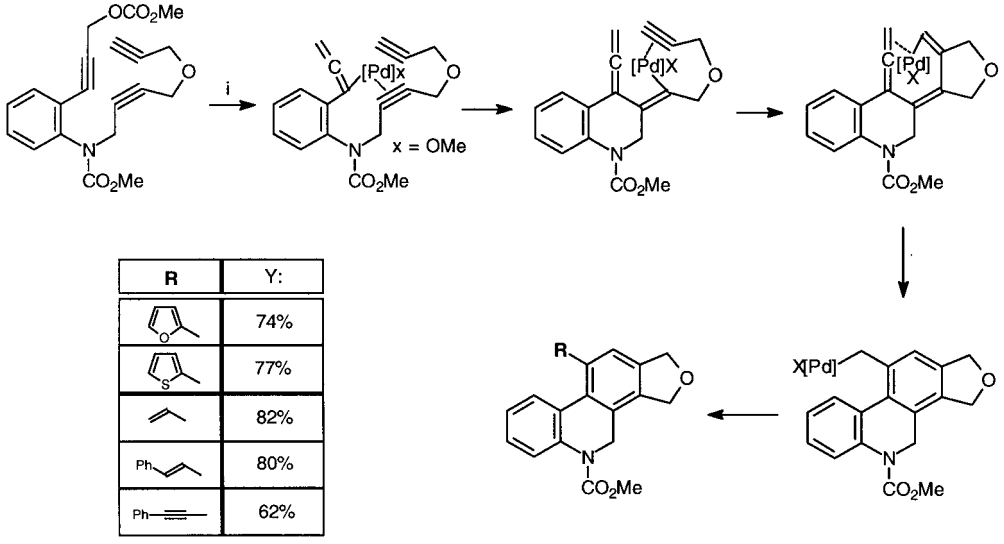
Scheme 66.



Scheme 67. (i) 2% $(dba)_3Pd_2{\cdot}CHCl_3$, 20% mol PPh_3, $PhCH_3$, reflux 2 h, TBAF (3 equiv.).



Scheme 68. (i) 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3; (ii) 10 mol% $Pd(OAc)_2$, 40 mol% $AsPh_3$.



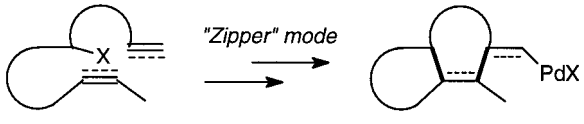
Scheme 69. (i) 10 mol% $Pd_2(dba)_3$, 40 mol% $AsPh_3$, $Bu_3Sn\mathbf{R}$, THF, reflux 16 h.

trapping with sodium tetraphenylborate, carbon monoxide/methanol, or organostannanes.[140] In the latter case the use of the milder donor triphenylarsine[141] as the Pd ligand is preferred. The sequence allows the one-pot construction of azabicyclo[3.1.0]hexanes (Scheme 68).

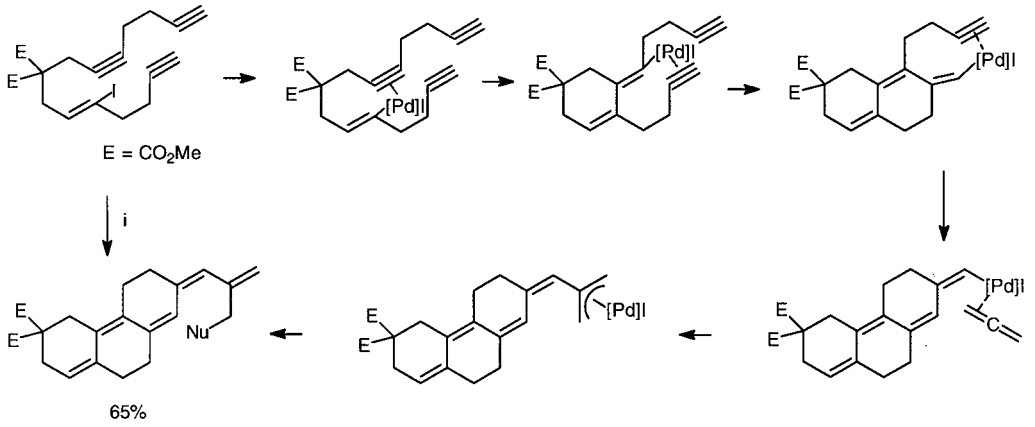
Using a propargylic carbonate as the starting group[142] and two juxtaposed alkynes as relay functions, Grigg et al effected a tricyclisation leading to a steroid-like backbone (Scheme 69).[143] A wide variety of stannanes could be used for the anionic capture. Although the exact mechanism of this circular carbopalladation is still a matter of speculation, it appears that the starting σ-allenylpalladium species is involved in three consecutive intramolecular carbopalladations followed by nucleophilic trapping.

Zipper-mode carbopalladations. The *zipper*-mode carbopalladation cascade can be performed when the starting C–Pd bond is located in a linear backbone between the reacting unsaturations (usually alkynes). Repeated carbopalladations sequentially join the unsaturations of the two opposite arms leading to a polycyclic structure.[134] These exceptionally selective and clean transformations rely on the fact that five- and six-membered ring formation is much faster than the formation of four-membered and medium-sized rings.[64b] This cyclisation represents an elegant approach to the synthesis of polyfused systems, and is complementary to the well-known enzymatic cyclisation of oxidosqualene to sterols (Scheme 70).[144]

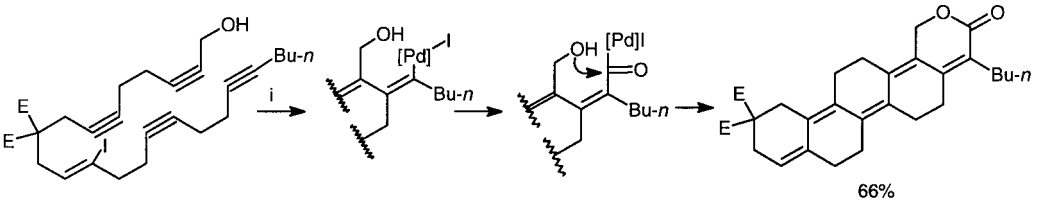
A zipper-mode cascade involving vinyl iodides as starting species, and alkynes or 1,1-disubstituted alkenes as relay, has been reported by Grigg.[143] In these cases allene carbopalladation could be achieved prior to the final nucleophilic trapping (Scheme 71).



Scheme 70.



Scheme 71. (i) Pd(0)/K_2CO_3, $C(CH_2)_2$ (1 atm), DMF 70–75°C, Nu=NaO_2SPh.



Scheme 72. (i) 5 mol% $Cl_2Pd(PPh_3)_4$, NEt_3 (2 equiv.), CO (1.1 atm), MeOH, 70°C, 1 day; E=CO_2Et.

These cascades can be terminated internally, by dehydropalladation, or externally, by anionic capture. A final carbonylative esterification could also be efficiently achieved by intramolecular trapping of the acylpalladium intermediate without premature CO incorporation (Scheme 72).[64b] These studies indicate that the intramolecular carbopalladation of alkynes to give five- or six-membered rings (as opposed to that of alkenes) are strongly favoured over cyclic acylpalladation (addition of acylpalladium bonds to alkenes) to give five-, six-, and seven-membered ketones. In line with the reversibility of the CO insertion process, competition between cyclic carbopalladation and CO insertion depends on CO pressure and on the availability of strategically positioned trapping species, such as an internal OH function. Similar intramolecular trappings of acylpalladiums could also be obtained with enolates.[145]

5. Concluding Remarks

The authors hope to have been able to give the reader a satisfactory picture of what organic chemists are able to achieve with the help of palladium in the domain of multistage processes. The discovery of the ability of this transition metal to interact with organic moieties, to connect inter- or intra-molecularly alkenes, alkynes, carbon monoxide, etc. in cascading processes is certainly a breakthrough in organometallic synthesis. It must be remembered that the astonishing simplicity of realising many complex polycyclisations is sometimes directly proportional to the labour required for the synthesis of the cyclisation precursor. The possible modes by which a living organopalladium complex can be engaged in consecutive bond formations, or the way in which two sequential palladium catalysed processes can be coupled by using a single catalytic system,[146] is only limited by a chemist's imagination and it is the authors' belief that more and more spectacular examples are still to come!

References

1. (a) Hegedus L. S. In *Organometallics in Synthesis*; Schlosser M., Ed.; Wiley: Chichester, 1994; Chapter 5, pp 385–459. (b) Tsuji, J. *Palladium Reagents and Catalysts, Innovation in Organic Synthesis*; Wiley: Chichester, 1995. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: New York, 1985. (d) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Sciences Books: Mill Valley, CA, 1987. (e) Harrington P. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson G., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, Chapter 8.2. pp 798–903. (f) Moreno-Mañas, M.; Pleixats, R. *Adv. Hetrocycl. Chem.* **1996**, *66*, 73. (g) Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975. (h) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, pp 585–661. (i) Consiglio, G.; Waymouth, M. *Chem. Rev.* **1989**, *89*, 257.

2. (a) Tietze, L. F. In *Selectivity—A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; VCH: Weinheim, 1984, pp 299. (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (d) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (e) Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1332. (f) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (g) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131. (h) Tietze, L. F. *Chem. Ind.* **1995**, 453. (i) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

3. Tolman, C. A. *Chem. Soc. Rev.* **1972**, *1*, 337.

4. The reader has, however, to bear in mind that this classification,

as any other elsewhere, is just an artefact for an easier understanding.
5. The FMOs (fragment molecular orbitals) of the principal transition metal fragments have been catalogued and those of the indicated fragments can be thought of as the hybrids which form upon removal of one ligand from planar L_3M or L_4M complexes, respectively. Albright. A., Burdett, J. K., Whangbo, M. H. *Orbital Interactions in Chemistry*; Wiley: New York, 1985.
6. Mealli, C.; Proserpio, D. M. *J. Chem. Ed.* **1990**, *67*, 399.
7. (a) Stille, J. K. In: *The Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, Chapter 9, pp 625–771. (b) Amatore, C.; Broecker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. (c) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. For the use of Pd(0) complexes in aqueous media see: (d) Genêt, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305.
8. Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598.
9. Jefferey, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
10. (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (b) Bäckvall J. E.; Granberg, K. L.; Heumann, A. *Israel J. Chem.* **1991**, *31*, 17.
11. Hegedus, L. S In *The Chemistry of the Metal–Carbon Bond*, Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, pp 401–512 (Chapter 6).
12. (a) Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. (b) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (c) Trost, B. M.; Michellys, P.-Y.; Gerusz, V. *J. Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1750.
13. (a) Trost, B. M.; Hipskind, P. A.; Chung, J. Y. L.; Chan, C. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1502. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
14. Drent, E.; Budzelaar, H. M. *Chem. Rev.* **1996**, *96*, 663.
15. (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (d) Miyaura, M.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (e) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
16. Erdik, E. *Tetrahedron* **1992**, *48*, 9577.
17. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803. (c) Shirakawa, E. Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 169.
18. (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066. (d) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
19. (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787.
20. Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.
21. Tsuji, T.; Mandai, T. *Synthesis* **1996**, 1.
22. Tamao, K. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3 (pp 435).
23. Stille, J. K. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4 (pp 932).
24. Copéret, C.; Sugihara, T.; Negishi, E. *Tetrahedron Lett.* **1995**, *36*, 1771.
25. Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466.
26. Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144.
27. (a) Tsuji, J. *Synthesis* **1984**, 369. (b) Tsuji, J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 449.
28. (a) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49. (b) Kasahara, A.; Izumi, T.; Ooshima, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2526. (c) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatekayama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248. (d) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.
29. Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.
30. (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (b) Åkermark, B.; Bäckwall, J. E.; Hegedus, L. S.; Zetterberg, K.; Siirala-Hansen, K.; Sjöberg, K. *J. Organomet. Chem.* **1974**, *72*, 127.
31. Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.
32. (a) Hegedus, L. S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113. (b) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 551 and 571. (c) Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079.
33. (a) Hegedus, L. S.; Williams, R. E.; Mc Guire, R. A.; Hayashi, T. *J. Am. Chem. Soc.* **1980**, *102*, 4973. (b) Hegedus, L. S.; Darlington, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 4980.
34. Stangl, H.; Jira, R. *Tetrahedron Lett.* **1970**, 3589.
35. Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.
36. El-Quisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790.
37. (a) Hollis, T. K.; Overman, L. E. *J. Organomet. Chem.* **1999**, *576*, 290. (b) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.
38. Grennberg, H.; Bäckvall, J.-E. In *Transition Metals for Organic Synthesis—Building Blocks and Fine Chemicals*, Bolm, C., Beller, M., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2 (pp 200).
39. (a) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (b) Heumann, A.; Åkermark, B.; Hansson, S.; Rein, T. *Org. Synth.* **1989**, *68*, 109.
40. Bäckvall, J.-E. In *The Chemistry of Dienes and Polyenes*, Rappoport, Z., Ed.; Wiley: New York, 1997; Vol. 1 (pp 653).
41. Bäckvall, J.-E. *Metal-Catalyzed Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; Wiley–VCH: Weinheim, 1998 (Chapter 8, pp 339).
42. Itami, K.; Palmgren, A.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6466.
43. Hosokawa, T.; Murahashi, S.-I. *J. Synth. Org. Chem. Jpn* **1995**, *53*, 1009.
44. Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063.
45. Heumann, A. In *Transition Metals for Organic Synthesis—Building Blocks and Fine Chemicals*, Bolm, C., Beller, M., Eds.; Wiley–VCH: Weinheim, 1998; Vol. 1 (pp 251).
46. Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189.
47. (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (c) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025.
48. Tsuji, J.; Okumoto, H.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1981**, *22*, 1357.
49. Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.
50. (a) Poli, G.; Giambastiani, G. *J. Org. Chem.* **1998**, *63*, 9608.

(b) Poli, G.; Giambastiani, G. Mordini, A. *J. Org. Chem.* **1999**, *64*, 2962.
51. (a) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (c) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (d) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (e) Williams, J. M. J. *Synlett* **1996**, 705. (f) Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189. (g) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195. (h) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203.
52. (a) Knoght, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 481. (b) *Metal-Catalyzed Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; Wiley–VCH, Weinheim, 1998; Chapters 1, 2 and 4.
53. (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 833. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. For recent enantioselective approaches see: (c) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (d) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N. Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16.
54. (a) Ohff, M.; Ohff, M. E.; van der Boon, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687. (b) Chen, L.-B.; Bergbreiter, D. E. *Chemtracts, Org. Chem.* **1998**, *11*, 845.
55. Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371.
56. (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fisher, H. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1844. (b) Beller, M.; Hartmut, F.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848. (c) Beller, M.; Riermeier, T. H.; Haber, S. H.; Kleiner, J.; Herrmann, W. A. *Chem. Ber.* **1996**, *129*, 1259. (d) Beller, M.; Riermeier, T. H. *Tetrahedron Lett.* **1996**, *37*, 6535. (e) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur.* **1997**, *3*, 1357. (f) Beller, M.; Riermeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073. (g) Beller, M.; Riermeier, T. H.; Zapf, A. *Top. Catalysis* **1997**, *4*, 301. (h) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29. (i) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem* **1999**, *576*, 23. (j) Poli G.; Scolastico, C. *Chemtracts, Org. Chem.* **1999**, *12*, 643.
57. Shaw, B. L.; Perera, S. D.; Staley, E. A. *J. Chem. Soc., Chem. Commun.* **1998**, 1361.
58. Bräse, S.; de Meijere, A. *Metal-Catalyzed Cross Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; Wiley–VCH: Weinheim, 1998 (pp 99).
59. (a) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033. (b) Torii, S.; Okumoto, H.; Nishimura, A. *Tetrahedron Lett.* **1991**, *32*, 4167.
60. Trost, B. M. *Janssen Chim. Acta* **1991**, *9*, 3.
61. (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161. (b) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211. (c) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (d) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. (e) Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 3027.
62. (a) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. (b) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923. (c) Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1994**, 134.
63. (a) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 791. (c) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. (d) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491.
64. (a) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1988**, *29*, 1231. (b) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (c) Grigg, R.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 2545. (d) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923.
65. Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1994**, *35*, 9537.
66. (a) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19. (b) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157.
67. Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1998**, 134.
68. Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371.
69. Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500.
70. Overman, L. E.; Poon, D. *J. Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 518.
71. (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (c) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. (d) Iserloh, U.; Curran, D. P. *Chemtracts, Org. Chem.* **1999**, *12*, 289.
72. Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
73. (a) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (b) Trost, B. M. *Janssen Chim. Acta* **1991**, *9*, 3.
74. Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.
75. (a) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1745. (b) Heumann, A.; Moukhliss, M. *Synlett* **1998**, 1211.
76. Oppolzer, W. In *Comprehensive Organomettalic Chemistry II*, Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12 (pp 905).
77. Gómez-Bengoa, E.; Cuerva, J. M.; Echavarren, A. M.; Martorell, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 767.
78. Oppolzer, W.; Swenson, R. E.; Pachinger, W. *Helv. Chim. Acta* **1989**, *72*, 14.
79. Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239.
80. (a) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011. (b) Nozaki, K.; Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 248.
81. Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.
82. Jolly, P. W.; Wilke, G. *Applied Homogeneous Catalysis by Organometallic Complexes*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996 (pp 1024).
83. Strömberg, S.; Oksman, M.; Zhang, L.; Zetterberg, K. *Acta Chem. Scand.* **1995**, *49*, 689.
84. (a) Mülhaupt, R.; Rieger, B. *Chimia* **1995**, *49*, 486. (b) Mülhaupt, R.; Rieger, B. *Chimia* **1996**, *50*, 10.
85. Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc.* **1995**, *117*, 6414.
86. Sen, A. *Acc. Chem. Res.* **1993**, *26*, 303.
87. Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1.
88. (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (b) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (c) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (d) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289. (e) Grigg, R.; Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65. (f) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88.
89. Holton, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 8083.

90. Larock, R. C.; Lee, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 7815.
91. (a) Wieber, G. M.; Hegedus, L. S.; Åkermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649. (b) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.
92. (a) Masters, J. J.; Hegedus, L. S.; Tamariz, J. *J. Org. Chem.* **1991**, *56*, 5666. See also: (b) Masters, J. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 4547. (c) Laidig, G. J.; Hegedus, L. S. *Synthesis* **1995**, 527.
93. Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160.
94. Jiang, H.; Ma, S.; Zhu, G.; Lu, X. *Tetrahedron* **1996**, *52*, 10945.
95. Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335.
96. (a) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Bäckvall, J.-E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
97. Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 8696.
98. Bouyssi, D.; Balme, G.; Fournet, G.; Monteiro, N.; Goré, J. *Tetrahedron Lett.* **1991**, *32*, 1641.
99. Bruyère, D.; Gaignard, G.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **1997**, *38*, 827.
100. Inoue, Y.; Itoh, Y.; Yen, I.-F. Y.; Imaizumi, S. *J. Mol. Cat.* **1990**, *60*, L1.
101. (a) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. See also: (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42.
102. (a) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (b) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915. (c) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363.
103. Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813.
104. Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
105. Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327.
106. Luo, F. T.; Schreuder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213.
107. Luo, F. T.; Wang, R.-T. *Tetrahedron Lett.* **1992**, *33*, 6835.
108. Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403.
109. (a) Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463. See also: (b) Coudanne, I.; Balme, G. *Synlett* **1998**, 999.
110. Cavicchioli, M.; Sixdenier, E.; Derrrey, A.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **1997**, *38*, 1763.
111. (a) Larock, R. C.; Wang, Y.; Lu, Y.; Russel, C. E. *J. Org. Chem.* **1994**, *59*, 8107. See also: (b) Larock, R. C.; Lu, Y.; Bain, A. C.; Russel, C. E. *J. Org. Chem.* **1991**, *56*, 4589.
112. Flubacher, D.; Helmchen, G. *Tetrahedron Lett.* **1999**, *40*, 3867.
113. Larock, R. C.; Berrios-Peña, N. G.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.
114. Larock, R. C.; Berrios-Peña, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.
115. Larock, R. C.; Yum, E. K. *Synlett* **1990**, 529.
116. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refuik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.
117. Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.
118. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701.
119. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.
120. (a) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124. (b) Tietze, L. F.; Nöbel, T.; Spescha, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2259.
121. Tietze, L. F.; Feraccioli, R. *Synlett* **1998**, 145.
122. Gaudin, J. M. *Tetrahedron Lett.* **1991**, *32*, 6113.
123. Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042.
124. Miyazaki, F.; Uotsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073.
125. (a) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 6827. See also: (b) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1893. (c) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341.
126. Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137.
127. Brown, D.; Grigg, R.; Sridharan, V.; Tambirajah, V.; Thornton-Pett, M. *Tetrahedron* **1998**, *54*, 2595.
128. (a) Gardiner, M.; Grigg, R.; Sridharan, V.; Vicker, N. *Tetrahedron Lett.* **1998**, *39*, 435. See also: (b) Grigg, R.; Brown, S.; Sridharan, V.; Uttley, M. D. *Tetrahedron Lett.* **1998**, *39*, 3247.
129. Oppolzer, W.; DeVita, R. J. *J. Org. Chem.* **1991**, *56*, 6256.
130. Keese, R.; Guidetti-Grept, R.; Herzog, B. *Tetrahedron Lett.* **1992**, *33*, 1207.
131. Doi, T.; Takahashi, M.; Nakanishi, S.; Yanagisawa, A.; Yamamoto, K.; Takahashi, T. *Bull. Chem. Soc. Jpn* **1998**, *71*, 2929.
132. Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124.
133. Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 7471.
134. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.
135. Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777.
136. (a) Negishi, E.; Sugihara, T.; Ay, M. *Tetrahedron* **1993**, *49*, 5471. See also: (b) Parsons, P. J.; Stefinovic, M.; Willis, D.; Meyer, F. E. *Synlett* **1992**, 864. (c) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545.
137. (a) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487. (b) Meyer, F. E.; Brandenburg, J.; Parson, P. J.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1992**, 390. (c) Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039.
138. Oh, H. C.; Rhim, C. Y.; Kang, J. H.; Kim, A.; Park, B. S.; Seo, Y. *Tetrahedron Lett.* **1996**, *37*, 8875.
139. Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836.
140. Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609.
141. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
142. Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.
143. a) Grigg, R., Rasul, R., Savic, V. *Tetrahedron Lett.* **1997**, *38*, 1825. (b) Grigg, R., Rasul, R. *9th IUPAC Symposium on Organometallic Chemistry—OMCOS 9* **1997**, Abstract p 278.
144. Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189.
145. Negishi, E.; Copéret, C.; Sugihara, T.; Shimoyama, I.; Zhang, Y.; Wu, G.; Tour, J. M. *Tetrahedron* **1994**, *50*, 425.
146. See for example: Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *Synthesis* **1998**, 581.

Biographical Sketch

Giovanni Poli was born in Milano on January 20, 1956. He received his laurea in 1980 and then his Ph.D degree at the University of Milano, under the direction of Professor Carlo Scolastico. During this period he was mainly engaged in asymmetric synthesis by the use of sulfoxides and oxazolidines. In 1986 and 1987 he continued his scientific education as Postdoctoral Fellow with Professor Wolfgang Oppolzer at the University of Genéve, where he devoted himself to asymmetric 1,4-additions to *N*-enoyl sultams, as well as to the total synthesis of the marine natural product (Pulo'upone). After having spent one year as an independent research associate at the University of Lausanne, and three further years back at the University of Milano, he joined the faculty at the University of Firenze in 1992, as an Associate Professor. He then reached faculty at the University Pierre et Marie Curie in Paris, as a visiting professor in 1999, then, as a full professor in 2000. His current interest is directed towards the study of new stereoselective transition metal catalysed transformations and heterocyclic chemistry.

Giuliano Giambastiani was born in Firenze on August 31, 1970. He received his laurea from the University of Firenze in 1997 under the direction of Professor Giovanni Poli. The same year he started his Ph.D thesis in the same research group in Firenze. He is now spending his third year of doctoral thesis in Paris, at the University Pierre et Marie Curie, under the supervision of Professor Giovanni Poli and the co-tutorship of Professor Max Malacria. During this period he has been engaged in the study of the allylic alkylation and the Heck reaction, which gave him the opportunity to gain a deep knowledge of palladium chemistry.

Andreas Heumann was born in Pforzheim, Germany, near the northern end of the Black Forrest (Schwarzwald). He received his academic education and his Dr. rer. nat. (1970) from the University of Tübingen. After two postdoctoral periods, first at the Université de Provence in Marseille 1970–1972 (Professor B. Waegell), and second, in Tübingen 1973–1974 (Professor W. Kraus), he joined the CNRS in 1974 and continued his research in Marseille. He has spent most of his career at the University of Marseille, where he was promoted to Directeur de Recherche in 1986. His research interests include synthetic organic and organometallic chemistry, homogeneous catalysis of palladium complexes, the selective transformation of alkenes and dienes, new reagents for the NMR determination of chiral compounds, and more recently, nitrogen-centered heterocyclic ligands in Ziegler–Natta type polymerisation catalysts.