Palladacycles as Reactive Intermediates☆

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Palladacycles are discussed as the key intermediates of some important preparative ring forming reactions; their reactivity depends strongly on the ring size. The existence of 5-membered palladacycles, and even 4-membered palladacyles, is now firmly established, whereas the knowledge of 6-membered and larger palladacycles is based mainly on mechanistic considerations. The role of 5-membered palladacycles as catalysts is described briefly.

Introduction

Methods for the construction of ring systems are of fundamental importance for organic syntheses. Very often a ring closure reaction is the crucial step in a multistep synthesis. In the last twenty years transition metal-mediated and -catalyzed reactions have emerged as powerful tools for the construction of carbo- and heterocyclic compounds, and in this respect palladium complexes prove to be the most versatile catalysts. Considering the multitude of different types of palladium-catalyzed reactions known it is amazing that a remarkable selectivity is regularly achieved by the correct choice of ligands and reaction conditions[1].

The subject of this review is the class of catalytic reactions that are assumed to involve palladacycles as reactive intermediates. The basic features of this type of reaction are best understood by comparison with the Heck reaction, the most renowned palladium-catalyzed process[2]. In a typical intramolecular Heck reaction palladacycles do not occur: the formation of the spirocyclic lactam **2** reported by Grigg and co-workers[3a] is explained mechanistically by three fundamental reaction steps (Scheme 1, additional ligands have been omitted for clarity; the term "Pd^0" symbolizes that a Pd^0 complex, which is generated in situ from a Pd^{II} complex, is assumed to be the active catalyst). Oxidative addition of the Pd^0 catalyst to the carbon–halogen bond affords the Pd^{II} intermediate **3**. The ring closing carbon–carbon bond formation is achieved by the carbopalladation of the appropriate CC double bond. The intermediate **4** is rapidly transformed to the final product **2** via a *syn*-β-hydrogen elimination. The hydrido-palladium halide undergoes a reductive elimination, mediated by a suitable base, regenerating the active Pd^0 catalyst. For the similar substrate **5** (Scheme 2)[3b] the first two reaction steps, oxidative addition and carbopalladation, proceed as for substrate **1**, but the third reaction step, the β-hydrogen elimination, is not possible, simply because the intermediate **7** lacks a suitable β-hydrogen. These are favourable conditions for a cyclopalladation to occur and they open up an alternative reaction pathway. In this case the 7-membered palladacycle **8** is a reasonable intermediate. The final ring closure proceeds, via reductive elimination, to give the polycyclic ring system **6**.

Palladacycles are assumed to be intermediates in Heck-type cyclization reactions when the crucial reaction step, the β-hydrogen elimination, is inhibited or, as it was pointed

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MICROREVIEWS: This feature introduces Berichte's readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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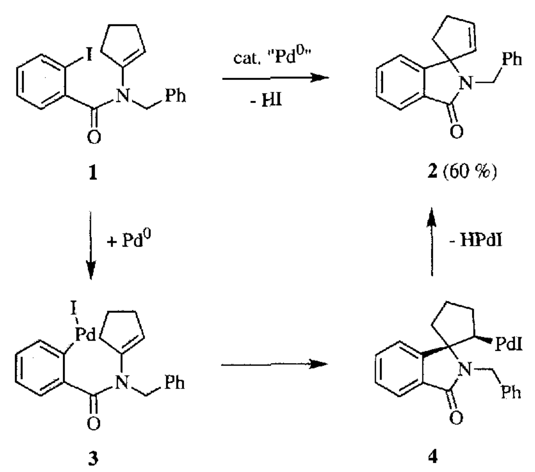
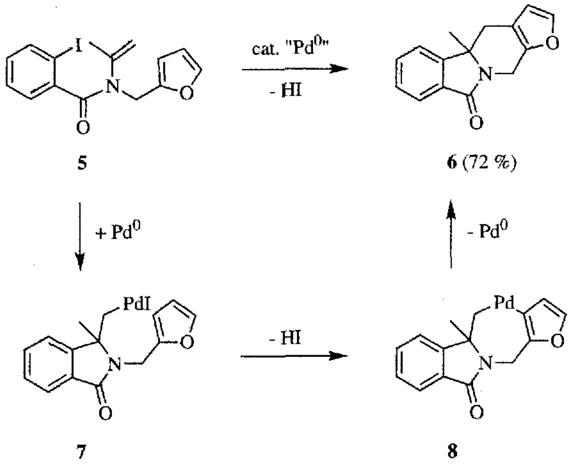
Scheme 1



Scheme 2



out in a recent review[2a] "*when Heck reactions don't know how to go on*". In fact, this is more often the case than one might anticipate. Moreover palladacycles are key intermediates in other types of palladium-catalyzed reactions, such as coupling reactions via CH activation and the intramolecular Stille reaction. Finally, palladacycles with enhanced stability turned out to be valuable catalysts with unique properties.

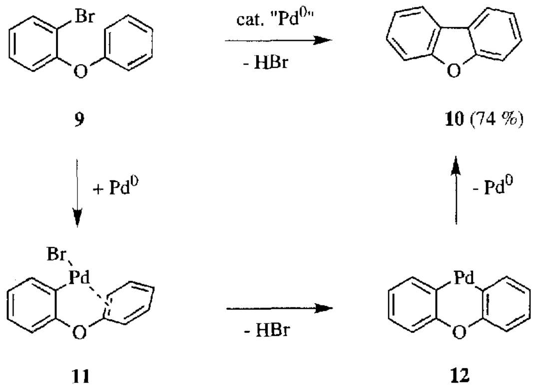
This review provides a brief overview of palladacycles as reactive intermediates, beginning with 6-membered and larger palladacycles that are clearly distinguished from 5-membered and smaller palladacycles in terms of their reactivity. In the third and final section examples of palladacycles as catalysts are discussed.

Palladacycles: 6-Membered and Larger

The typical reaction that 6-membered and larger palladacycles with two carbon–palladium σ bonds[4] undergo is reductive elimination. This is a facile process, thus explaining why it is difficult to detect these reactive intermediates[5]. For some palladium-catalyzed reactions their role as key intermediates is based on compelling mechanistic considerations (e.g. for the intramolecular Stille coupling reaction). For some other reactions the presence of 6-membered and larger palladacycles as intermediates has to be regarded as a working hypothesis, that is challenged by alternative mechanistic explanations.

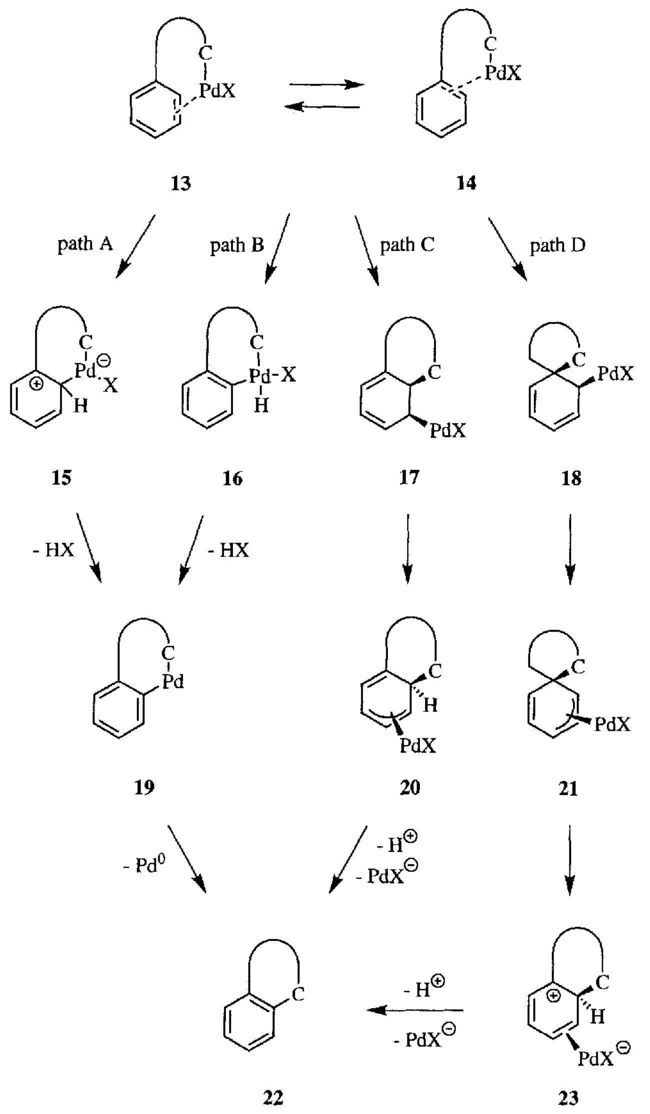
Ames and co-workers were the first to report on reactions supposed to proceed via intermediary 6- and 7-membered palladacycles[6]. Their intramolecular aryl-aryl coupling reaction under dehydrohalogenation turned out to be a very useful synthetic process. Thus, the biaryl ether **9** is efficiently cyclized using palladium catalysis to give dibenzofuran (**10**, Scheme 3)[6b][7]. A cyclopalladation/reductive elimination sequence is the mechanistic pathway usually proposed for this type of aryl-aryl coupling reaction. Presumably, the formation of a η^2-bound arene-palladium complex, **11**, preceeds the CH activation. The 6-membered palladacycle **12** rapidly undergoes a reductive elimination of Pd^0, closing the catalytic cycle and resulting in the formation of the final product **10**, with the central 5-membered ring.

Scheme 3



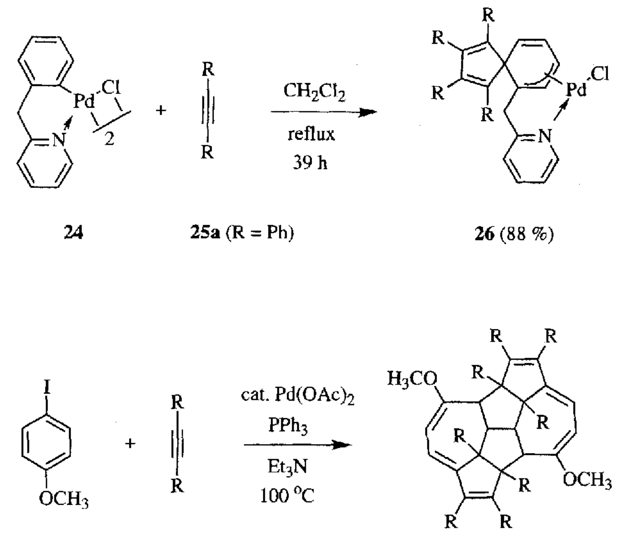
However, several alternative mechanistic pathways have to be considered[8][9]. The general mechanistic Scheme 4 presents the pathways A and B proceeding via palladacycles **19** (in analogy to Scheme 3) and introduces the pathways C and D, both proceeding via an intramolecular carbopalladation of the aromatic system. In any case η^2-bound arene palladium complexes **13** and **14** have to be considered as intermediates[10]. According to the pathway A the cyclopalladation is achieved by an intramolecular attack of the Pd^{II} center, in the sense of an electrophilic aromatic substitution. According to path B an oxidative addition, via the Pd^{IV} complex **16**, leads to palladacycles **19**. For the pathways C and D, the π-allyl palladium complexes **20** and **21**, rather than the palladacyles **19**, are the key intermediates. In particular the pathway D with the spirocyclic system **21**, and the rearrangement step to the intermediate **23**, appears to be a bit strange at first sight. Nevertheless, this type of process is very well precedented. Pfeffer et al. isolated the spirocyclic π-allyl palladium complex **26** from the stoichiometric reaction of the palladium complex **24** with diphenyl acetylene (**25a**, Scheme 5)[8b][8c]. The results reported by Rheingold and Heck suggest that an additional complexing group, such as the pyridyl ligand of **24**, is not required for the spirocyclization step to occur[9]: in addition spirocyclic π-allyl palladium complexes have to be taken into account as reactive intermediates for the formation of the hexacycle **28** from 4-iodoanisole (**27**) and 3-hexyne (**25b**).

Scheme 4



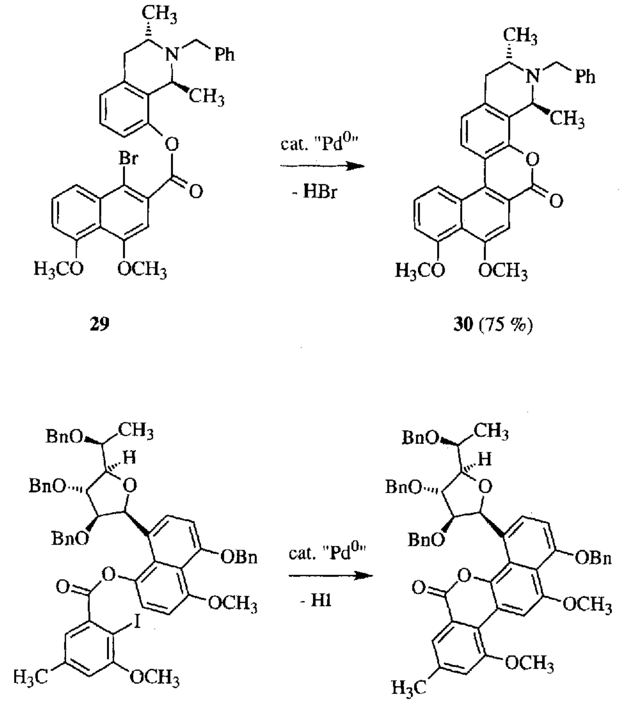
Clearly, for several of the palladium-catalyzed processes that involve CC-bond formation at aromatic systems, the experimental data obtained so far is insufficient to distinguish between the mechanistic pathways outlined in Scheme 4. Arguments and experimental hints for all four pathways can be found; therefore it is indeed likely that several pathways can occur, depending on the reaction conditions, the ligands at the palladium catalyst, and on the electronic properties of the substrates.

Scheme 5



Despite the mechanistic uncertainties the intramolecular[11] aryl-aryl coupling reaction first reported by Ames et al.[6] found numerous applications, ranging from polycyclic hydrocarbons to natural product synthesis. Some representative examples are given in the following schemes. Applications of this type of aryl-aryl coupling reaction[12][13] are highlighted by the facile synthesis of precursors for atropchiral naphthyl isoquinoline alkaloids by Bringmann et al. (Scheme 6)[14]. The biaryl axis of **30** is introduced via the palladium-catalyzed reaction step. A closely related example is the ring closure reaction of **31**, representing the key step in the synthesis of gilvocarcin by Suzuki et al.[15].

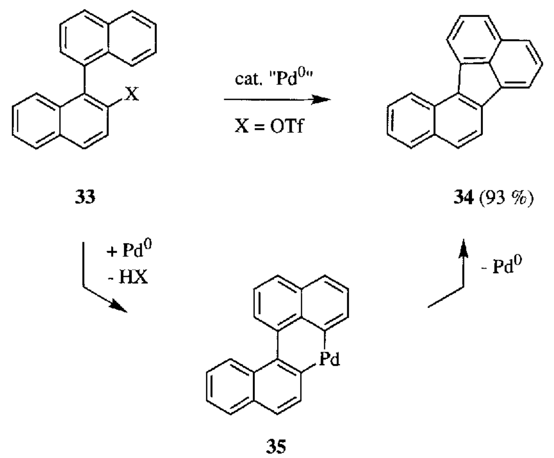
Scheme 6



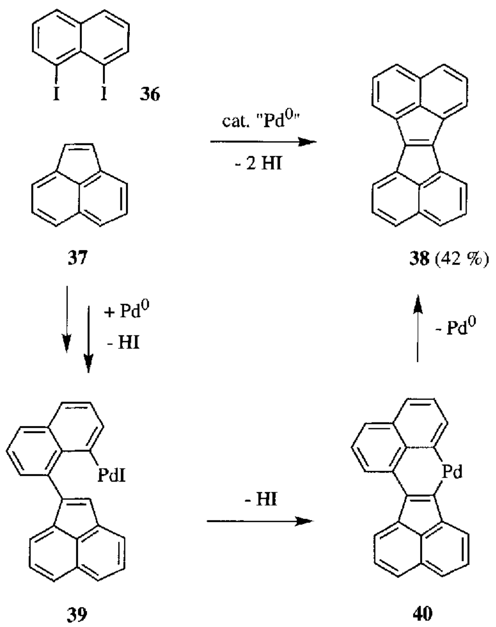
Rice et al. developed an efficient entry to substituted and annelated fluoranthenes such as **34** (Scheme 7)[16]. The aryl triflate **33** is a suitable substrate for the formation of the 6-

membered palladacycle **35** as a reactive intermediate. The cyclopalladation/reductive elimination sequence explains the facile introduction of such considerable ring strain; therefore the alternative pathway C (Scheme 4), via a direct carbopalladation of the naphthalene moiety, seems to be less likely in this case.

Scheme 7



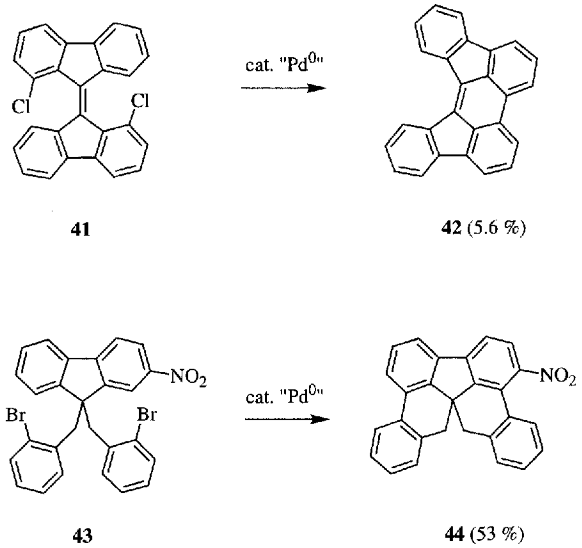
Scheme 8



The annelated pentalene system **38** is a valuable building block for the construction, via various cycloaddition reactions at the strained central double bond, of propellanes (Scheme 8)[17]. We found that it can be synthesized in a single preparative step by the coupling reaction of acenaphthylene (**37**) with 1,8-diiodonaphthalene (**36**)[13b][18]. In this case a 6-membered palladacycle **40** is also assumed to be the key intermediate, although the coupling reaction takes place at an olefinic double bond. A Heck-type ring closure for the intermediate **39** is not feasible; the intramolecular carbopalladation of the olefinic double bond in a *syn* manner would result in a extremely stained *trans*-fused ring system. Instead, the cyclometallation under CH-activation to give the 6-membered palladacycle **40** represents a reasonable reaction pathway.

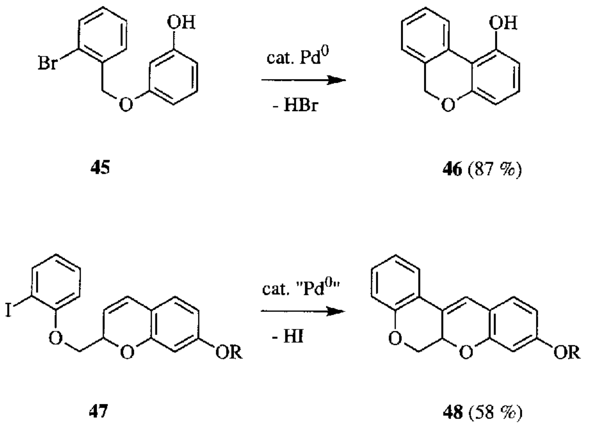
The fullerene fragment **42** is another strained polycyclic hydrocarbon, presumably formed via a 7-membered palladacycle (Scheme 9)[13c]. Starting from the dichlorosubstituted bifluorenylidene **41**, the ring closure is achieved with a low yield (6% absolute, 50% based on recovered starting material). Nevertheless, compared to the pyrolytic methods normally used for the synthesis of this type of compound, the palladium-catalyzed method proves competitive. The double cyclization at the substituted fluorene **43**, reported by Echavarren and co-workers[19], leading to the spirocyclic product **44**, is of both preparative and mechanistic importance. The facile cyclization at the electron-poor nitroarene strongly suggests that in this case the reaction does not proceed via an electrophilic aromatic substitution (path A of Scheme 4). In contrast, a recent publication by Rawal and co-workers confirms the electrophilic character of the intermediary arylpalladium halide (Scheme 10)[20]. According to their results the reactivity of the aryl moiety is significantly enhanced by the attached hydroxyl group. The aryl-aryl bond formation takes place regioselectively at the particularly electron rich 2-position of the phenolate, giving rise to the substituted dibenzopyran **46**. The differing results of Echavarren and Rawal are best reconciled by the assumption that this type of palladium-catalyzed aryl-aryl coupling reaction can proceed via more than one mechanistic pathway.

Scheme 9



The ring closure reaction of the vinylogous substrate **47** is a mechanistically interesting case. Considering the stereochemical requirements of the carbopalladation step and the β-H-elimination step, both proceed stereospecifically in a *syn* manner, and the standard mechanism of the Heck reaction cannot account for the formation of the heterocyclic product **48**[21]. Instead, a 7-membered palladacycle[22] could be formed from substrate **47** by an intramolecular electrophilic attack of a Pd^{II} species at the electron rich double

Scheme 10



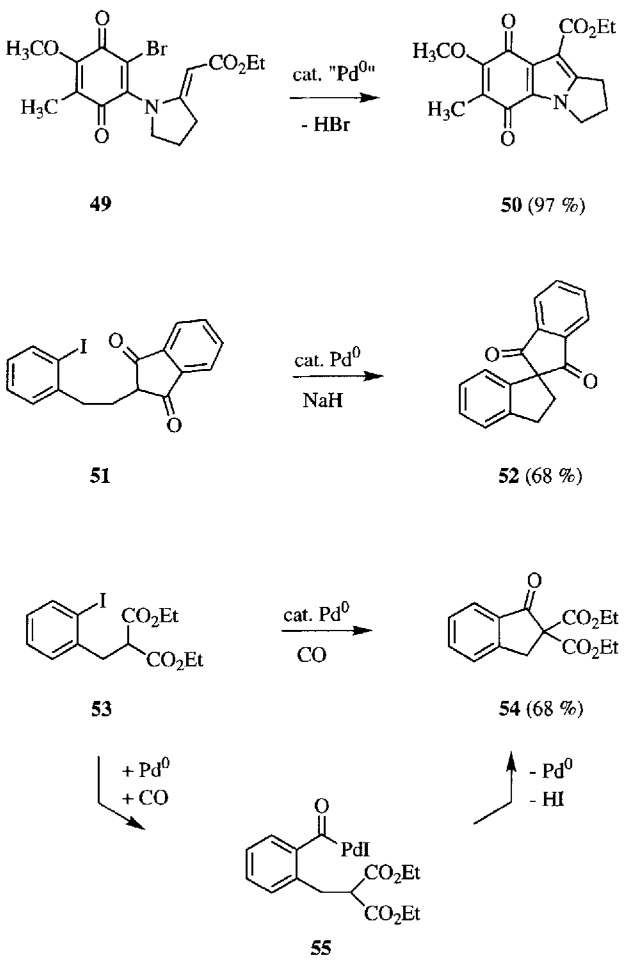
bond. Other mechanisms have been suggested to explain an apparant *trans*-β-H-elimination step: radical intermediates[21], "stereomutation" of benzylic palladium complexes[26b], and *trans*-β-H-elimination via a conformation with a dihedral angle of ca. 60° between Pd and hydrogen[23][24]. However, despite a considerable amount of experimental data, the mechanism of the coupling reaction of aryl halides with olefins under an apparant *trans*-β-H-elimination remains an unsolved problem of palladium chemistry.

Closely related to the cyclization reaction of phenol **45** are transformations of substrates with an internal nucleophile (Scheme 11); the enamine moiety of **49**[25][26] represents the electron rich center, that presumably takes part in a cyclopalladation step. In the case of the β-diketone **51** reported by Ciufolini et al.[27], the corresponding enolate gives rise to the formation of the spirocyclic product **52**, presumably via a 6-membered palladacycle.

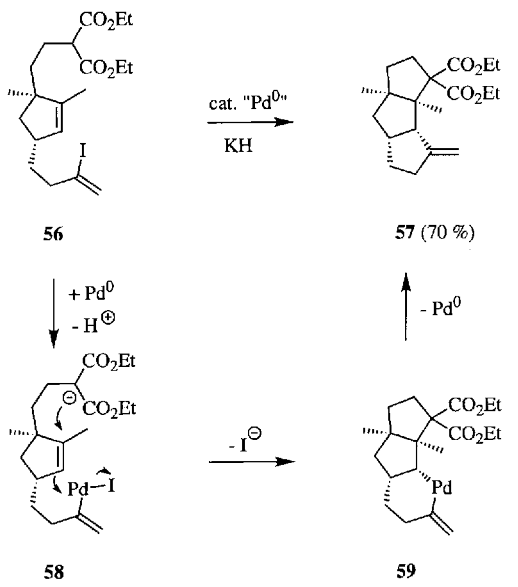
The synthesis of the indanone **54** from the functionalized aryl iodide **53** under carbonylation requires, according to Negishi et al., the intramolecular trapping of the acyl palladium intermediate **55** by the malonate moiety as the carbon nucleophile[28][29]. **55** was isolated under stoichiometric conditions in the absence of a suitable base. The nature of the ring closure reaction remains unclear in this case; as an alternative to the cyclopalladation step the direct nucleophilic attack of the malonate at the carbonyl group has to be considered.

A fascinating bis-cyclization was reported by Balme and Bouyssi as part of their synthesis of capnellene (Scheme 12)[30]. All three functional groups of the cyclopentene **56** are involved in this single step process. The electrophilic vinylpalladium halide of the intermediate **58** polarizes the neighbouring olefinic double bond by complexation, thus initiating the nucleophilic attack of the malonate. The tricyclic system **59**, with the annelated 6-membered palladacycle, is the result, being suitable for reductive elimination. These mechanistic considerations are in accord with the observed stereochemistry of the final product **57**.

Scheme 11

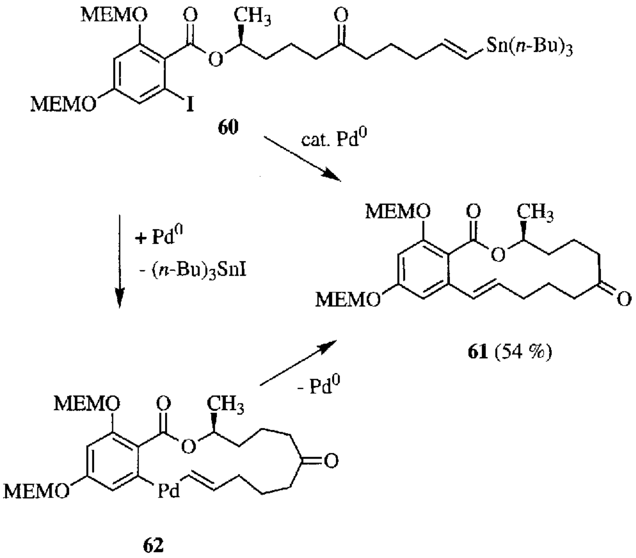


Scheme 12



Intramolecular palladium-catalyzed processes that involve a sequence of oxidative addition at aryl or vinyl halides, followed by a transmetallation step, generally proceed via palladacycles. These type of processes have found widespread application in the synthesis of naturally occuring macrocycles. An intramolecular Stille coupling reaction was the key step in the synthesis of zearalenone, a macrocyclic lactone (Scheme 13)[31][32][33]. The starting material **60** undergoes a sequence of oxidative addition of the polymer bound Pd^0 catalyst to the aryl iodide bond, and transmetallation with the vinylstannane, to give the 15-membered palladacycle **62**. The terminating reductive elimination under CC-bond formation closes the catalytic cycle. A similar strategy was also carried out successfully by Nicolaou[34] for the synthesis of rapamycin. In this case a twofold Stille coupling reaction was the final step of the total synthesis, involving an impressive 30-membered palladacycle.

Scheme 13



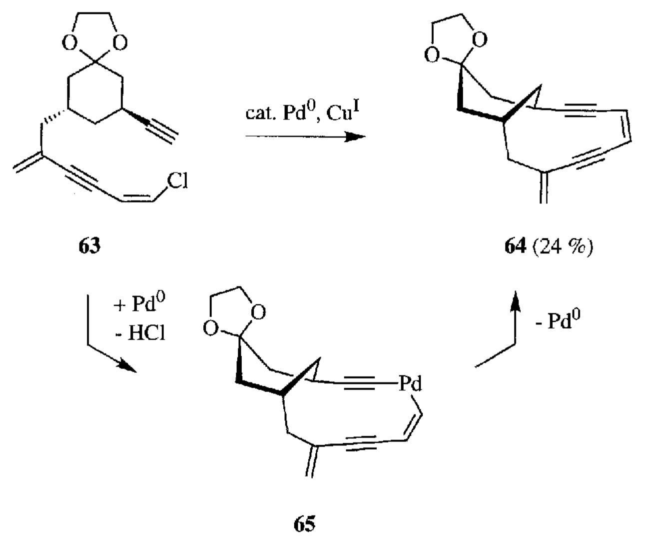
According to Schinzer and Kabbara the cyclic enediyne system **64** is accessible through an intramolecular Sonogashira coupling reaction (Scheme 14)[35]. This, and other examples[32d][36], underline the fact that palladacycles as intermediates offer opportunities for the construction, under mild reaction conditions, of highly unsaturated medium sized ring systems.

The selection of examples for CC-bond formation presented in this section demonstrates the diversity of products that are accessible via palladacycles as reactive intermediates. In comparison, the analogous carbon–hetero atom bond formation is clearly underutilized[37].

Palladacycles: 5-Membered and Smaller

No matter how 6-membered and larger palladacycles are formed, they generally undergo a facile reductive elimination. 5-Membered palladacycles behave differently; the formation of 4-membered rings via reductive elimination is unfavourable and restricted to special cases. Instead, 5-membered palladacycles can react with a second equivalent starting material, or with added reagents resulting in domino processes[38]. We have studied a variety of model compounds that fulfil the structural requirements for a cyclometallation to 5-membered palladacycles via an oxidative addition/CH-activation sequence. A typical example is the coupling reaction of the vinylic bromide **66** to give the anelated fulvene **67** with an excellent yield (Scheme 15)[39]. The reductive elimination of Pd^0 from the palladacycle **68** is inhibited in this case; the result would be a highly strained and antiaromatic benzocyclobutadiene. Instead, another equivalent starting material **66** is added, presumably to give the Pd^{II} intermediate **69**. The final ring closure proceeds in the sense of an intramolecular Heck reaction. Tricyclic derivatives of **66**, with a bridge between the phenyl substituents, undergo the same palladium-catalyzed domino coupling process. Thus, polycyclic hydrocarbons, such as **70** and **71**, are accessible from simple starting materials in a single efficient preparative step.

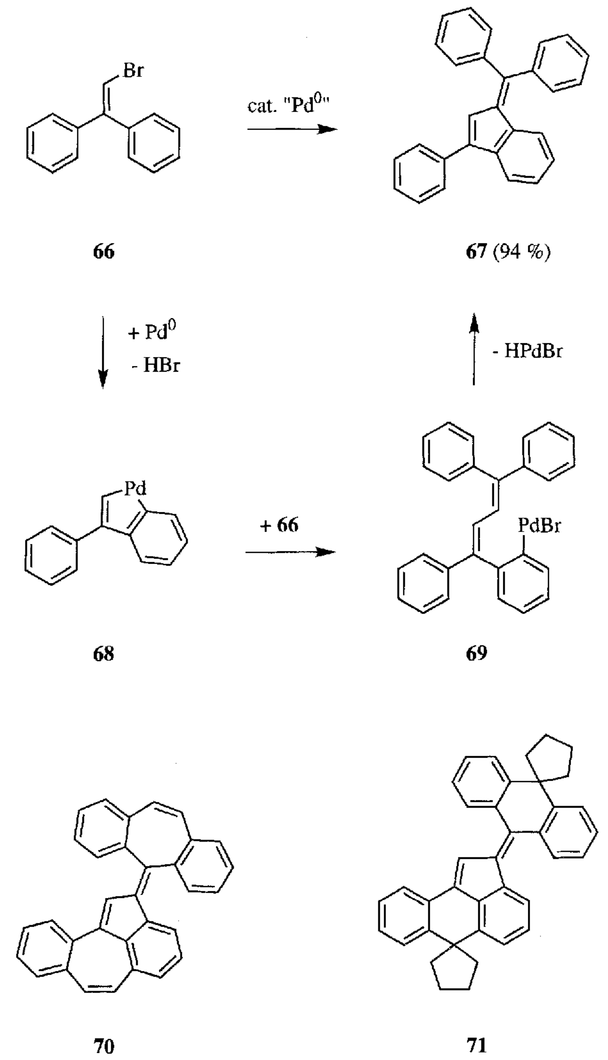
Scheme 14



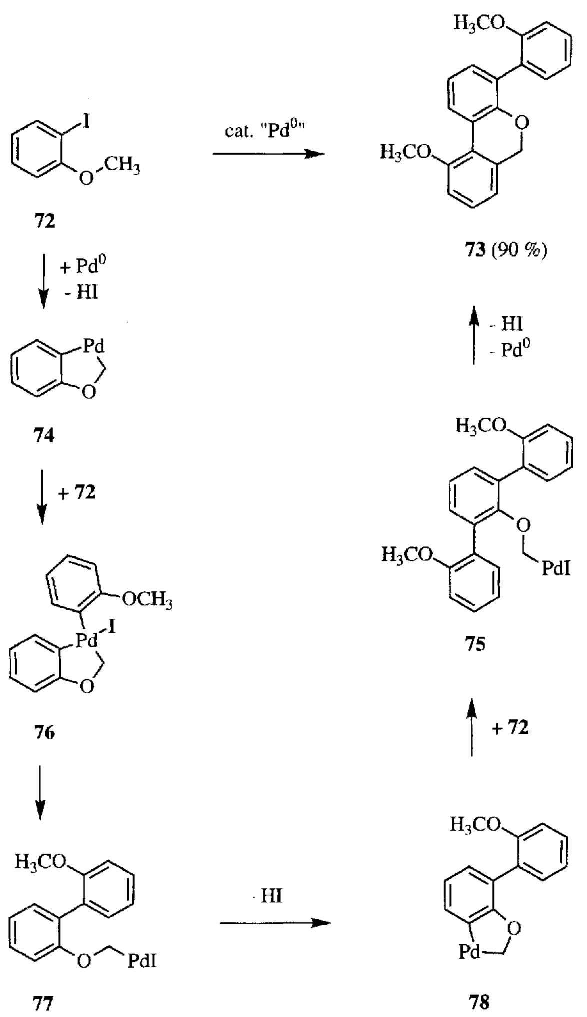
Surprisingly, the cyclopalladation turned out to be a facile process, even at sp^3-centered CH-groups that are regarded as unactivated. A fascinating domino coupling process condenses three equivalents of *ortho*-iodoanisole (**72**), selectively forming the substituted dibenzopyran **73** (Scheme 16)[40]. The mechanistic interpretation of this process involves several palladacycles: the 5-membered oxapalladacycle **74** is formed by an initial oxidative addition/cyclometallation sequence[41]. The direct addition of a second equivalent of the starting material **72** to give the Pd^{IV} complex **76**, and the subsequent reductive elimination, is a straightforward explanation for the formation of the biaryl linkage of intermediate **77**. A second cyclometallation to give **78** followed by the addition of the third equivalent of the starting material **72** would lead to the symmetrical intermediate **75**. Presumably, the final ring closure proceeds via one of the mechanistic pathways outlined in Scheme 4.

Evidence for the formation of Pd^{IV} intermediates by oxidative addition of alkyl halides to Pd^{II} complexes and subsequent reductive elimination, has been documented in detail[42]. Therefore catalytic cycles, that include oxidation states ranging from Pd^0 to Pd^{IV}, seem to be reasonable. Nevertheless, aryl halides are less reactive than alkyl halides where the oxidative addition to Pd^{II} complexes[43][44] is concerned, and for that reason ligand exchange reac-

Scheme 15



Scheme 16

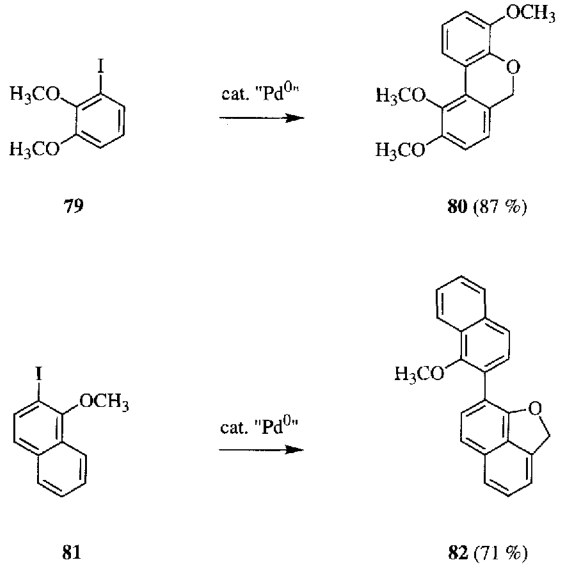


tions[40b][45] between palladacycle **74** and intermediary arylpalladium iodide complexes have to be considered as a slightly modified mechanistic pathway. Since the reaction conditions applied in this case (a catalytic amount of palladium acetate, potassium carbonate and tetraalkylammonium salts in dimethylformamide)[46a] are suitable for the formation of stabilized colloidal palladium[46b][46c], this type of reaction might actually take place at the surface of palladium clusters, a hypothesis that is currently under investigation.

In the case of 1-iodo-2,3-dimethoxybenzene (**79**) the additional methoxy group is blocking the crucial position for the second cyclopalladation, thus abbreviating the domino process (Scheme 17)[40]. The additional benzene ring of substrate **81** enables the favourable terminating ring closure, presumably via a 6-membered palladacyle, to give the naphthofuran **82**.

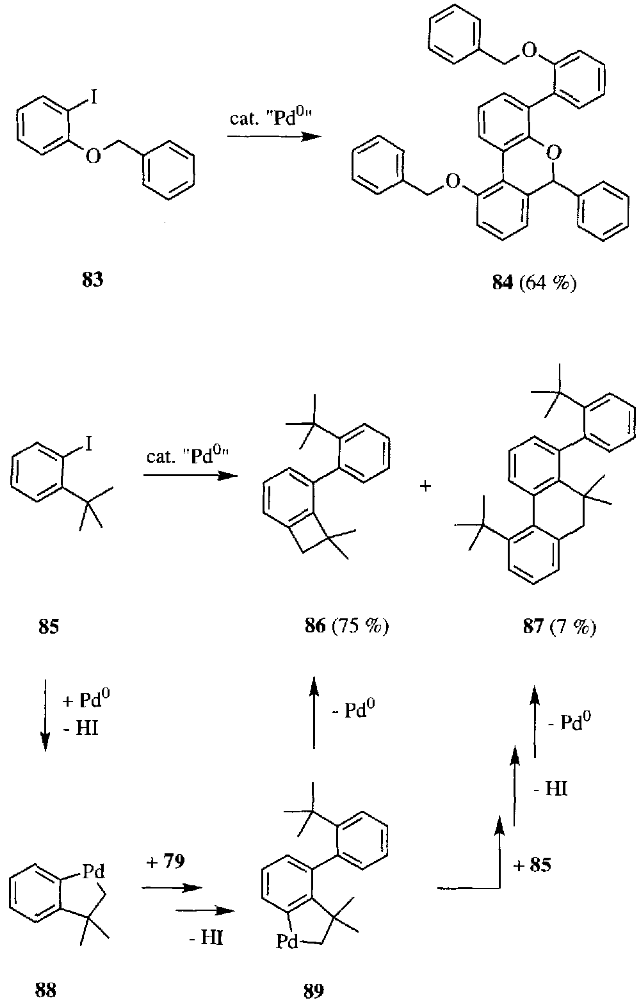
This type of domino coupling process, involving an intramolecular CH-activation at sp^3-hybridized centers, is not restricted to methoxy groups (Scheme 18). The reaction of the substrate **83**[47] with the *ortho*-benzyloxy group takes

Scheme 17



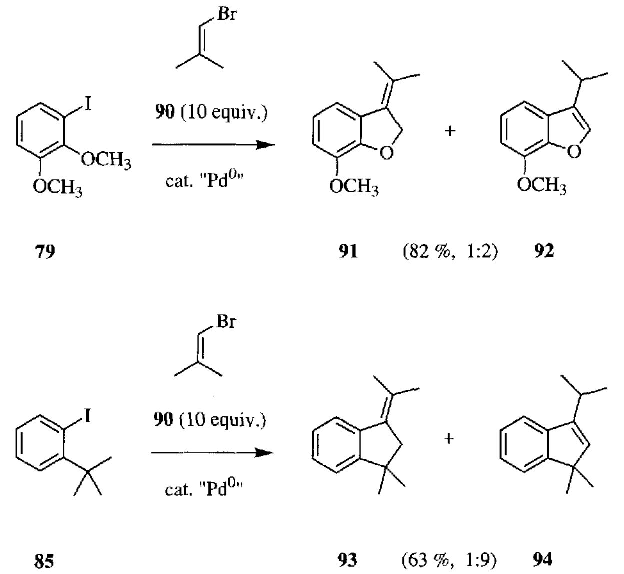
the same regiochemical course as is observed with *ortho*-iodoanisol (**72**, Scheme 16). Obviously, the formation of a 5-membered palladacycle under CH-activation at a benzylic position is prefered in comparison to the competing aryl-aryl coupling reaction (in analogy to the cyclization of **45** in Scheme 10). Surprisingly, the heteroatom does not have a marked influence on the C-H activation. Even a *tert*-butyl group can participate in this type of process. With 1-*tert*-butyl-2-iodobenzene (**85**) as the starting material the 9,10-dihydrophenanthrene derivative **87**, which corresponds to **73** and **84**, is a minor byproduct. Instead, the benzocyclobutene **86** is isolated as the main product (Scheme 18)[48]. The formation of the 4-membered carbocycle by reductive elimination at the intermediary 5-membered palladacycle **89** might, in this case, be favoured by the steric interaction of the aryl substituent with the dimethylmethylene group, and by the slightly increased temperature, which is required for the C-H activation at the *tert*-butyl group (110°C instead of 100°C at methoxy groups).

Scheme 18



The preparative value of this type of CH-activation is further enhanced by cross-coupling reactions with vinylic bromides, like **90**, as added reagents. The *tert*-butyl substituted substrate **85** leads to the isomeric indene derivatives **93** and **94**[48], whereas starting from the methoxy substituted substrate **79**, the corresponding benzofurans **91** and **92** are obtained (Scheme 19)[49].

Scheme 19



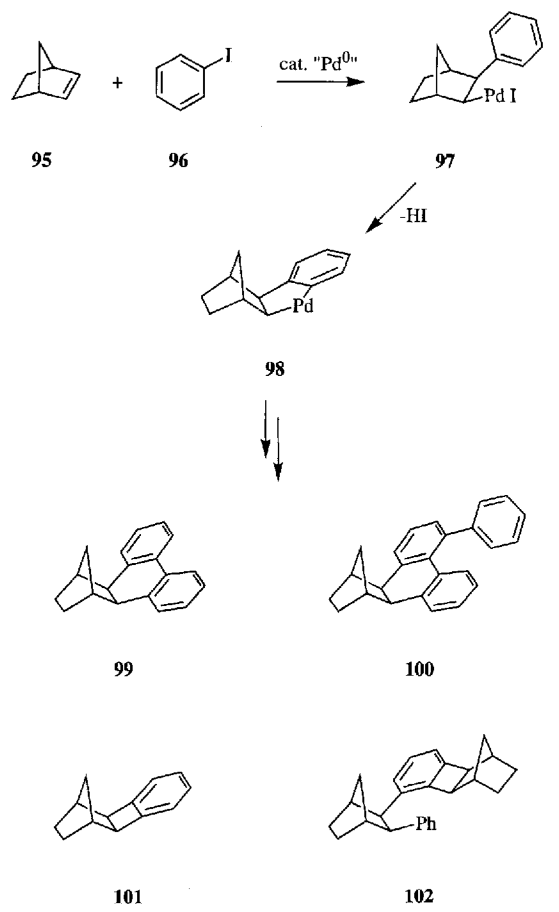
The substrates discussed so far are well suited for a direct cyclopalladation. In the following examples a suitable structural unit has to be assembled first; a carbopalladation of an alkene or an alkyne precedes the cyclopalladation step. The extensively investigated palladium-catalyzed annelation reaction of norbornene (**95**) with iodobenzene (**96**) illustrates this type of reaction (Scheme 20)[50]. The intermediary Pd^{II} complexes **97** and **98** can be isolated in the presence of stabilizing ligands[42][44]. The 5-membered palladacycle **98** finally leads to four different types of products, depending on the reaction conditions: the 1:2 product **99**[50a], the 1:3-product **100**[50b][50c] and the benzocyclobutene derivatives **101** and **102**[50d] as 1:1 and 2:2 products formed by reductive elimination from 5-membered palladacycles.

The 5-membered palladacycle **98** is also the key intermediate in a fascinating multicomponent reaction recently reported by Catellani et al. (Scheme 21)[44]. Surprisingly norbornene (**95**) is not incorporated into the final product **105**, revealing that retro-carbopalladation is possible under moderate conditions.

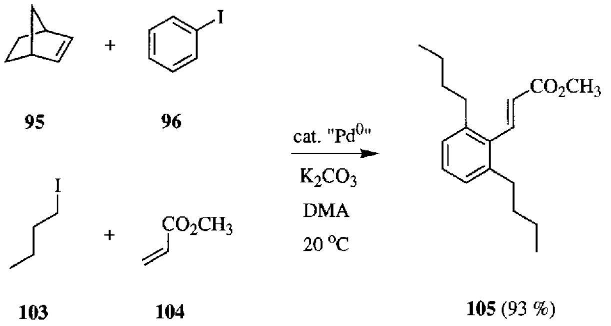
In analogy to norbornene (**95**) the pentalene system **38** is suitable for palladium-catalyzed annelation reactions with iodobenzene (**96**) and its derivatives (Scheme 22)[51]; propellanes with a hexaarylethane moiety are the result. Iodobenzene (**96**) leads to the [4.3.3]propellane **106**, presumably via an intermediary palladapropellane. The reaction with iodoprehnitene (**107**) took a surprising course; as the only isolated product we obtained the [3.3.2]propellane **108**. Because of steric hindrance the addition of a second equivalent of aryl iodide **107** to the intermediary palladapropellane is inhibited, and therefore the reductive elimination to the 4-membered ring is able to compete.

According to our own results tolan derivatives **109** undergo similar annelation reactions, via 5-membered and

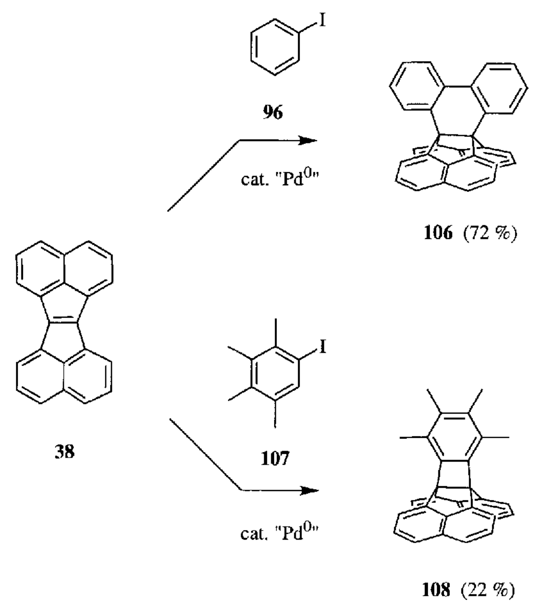
Scheme 20



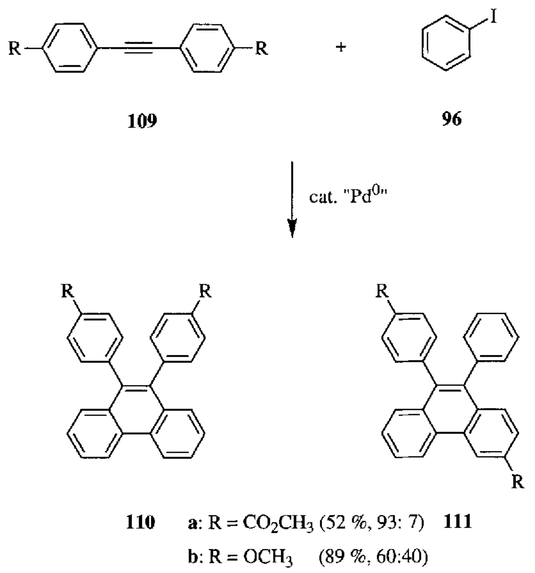
Scheme 21



Scheme 22



Scheme 23



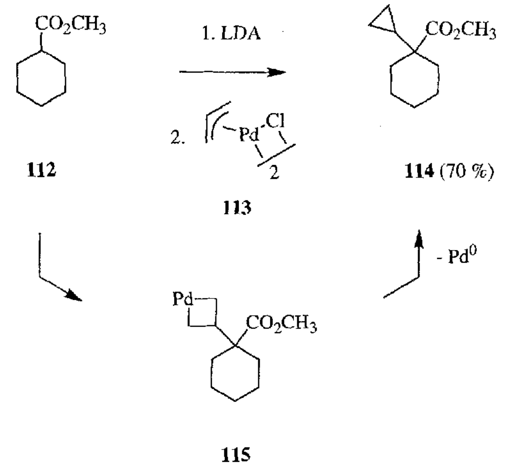
eventually 7-membered palladacycles, to give rise to the formation of a phenanthrene moiety (Scheme 23)[52]. The scrambling of the substituents, as revealed by the isolated products **110** and **111**, is explained through a *cis-trans* isomerization of vinylpalladium intermediates, a process favoured when electron-donating groups are present.

Palladacycles smaller than 5-membered are still a rarity. 4-membered palladacycles such as **115** are the key intermediates of the unusual stoichiometric reaction of π-allylpalladium complexes with the sterically demanding ester enolates, resulting in a cyclopropanation (Scheme 24)[53]. With the proper choice of the reaction conditions and the ligands, the usually favoured allylic alkylation[54] is suppressed. Recently, Hoffmann and co-workers[53e] succeeded in isolating a palladacyclobutane, thus determining its geometry and observing the facile reductive elimination in the presence of carbon monoxide.

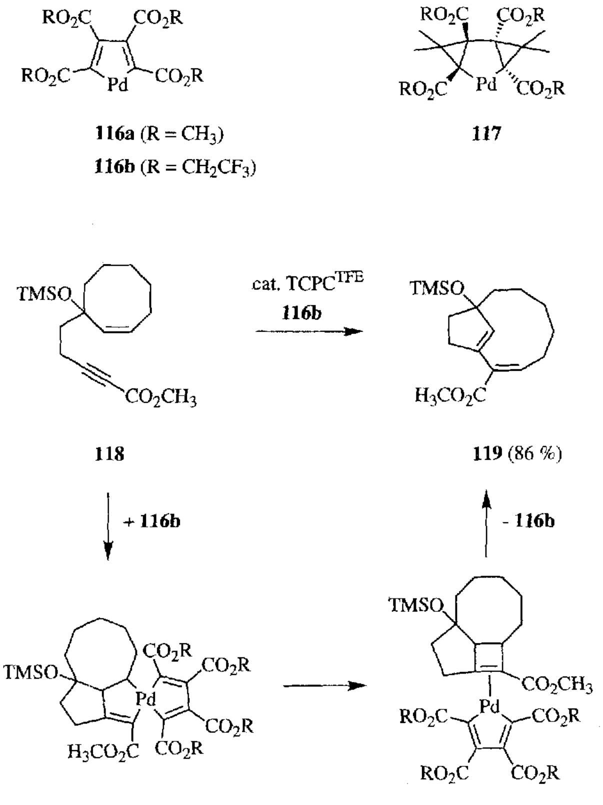
Palladacycles as Catalysts

Thermodynamic, as well as kinetic stability is necessary for palladacycles to be applicable as catalysts. 5-Membered palladacycles that fulfil these requirements are the TCPC-catalysts **116**[55] trakis(alkoxycarbonyl)palladacyclopentadiene], and the chiral THC-catalysts **117**[56] (palladatricycloheptane, Scheme 25). Reductive elimination is unfavourable in both cases.

Scheme 24



Scheme 25



The reactivity of the TCPC catalysts **116** is strongly influenced by the electronic effects of the substituents. The TCPC complex **116a**, with R = CH_3, is known to catalyze the intramolecular Alder-ene reaction of enynes[55a]. In contrast, with the TCPC catalyst **116b** (TCPC^{TFE}), with R = CH_2CF_3, an intramolecular enyne metathesis is achieved[55b][55c][55d]. The transformation of the cyclooctene **118** to give the bicyclic diene **119** is a representative example[55c]. Spirocyclic palladium complexes, such as **120**, are assumed to be key intermediates that undergo a reductive elimination to cyclobutene-palladium complexes **121**. Under certain conditions the free annelated cyclobutenes can be isolated in good yields[57].

Other reactions catalyzed by TCPC complexes **116** are cyclotrimerizations[58], cycloaddition reactions with intermediary palladadienes[59], and the dimerization of allenyl ketones leading to functionalized furans[60].

Conclusion

The studies presented here shed some light on the reactivity of palladacycles. The ring size of the palladacycles is of special importance: Whereas 6-membered and larger palladacycles rapidly undergo reductive elimination, the corresponding cyclobutane formation from 5-membered palladacycles is limited to special cases. Instead, 5-membered palladacycles as reactive intermediates offer opportunities to develop domino processes that lead from simple starting materials to complex ring systems. Their increased stability, when compared with that of the larger palladacycles, allows an extensive characterization of some derivatives, and in a few cases even application as catalysts.

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