The Potential of Palladacycles: More Than Just Precatalysts

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Received February 21, 2005

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1. Introduction

1.1. General

The past half century has witnessed enormous growth in transition-metal organometallic chemistry, both as a scientific discipline and as a subject for research and applications in industry. Organopalladium compounds have a very rich chemistry and are among the most readily available and easily prepared and handled of the plethora of known transition-metal complexes. The facile redox interchange between the two stable Pd(II)/Pd(0) oxidation states is mainly responsible for the rich chemistry enjoyed by palladium compounds. Doubtless, their compatibility with most functional groups also differentiates them from many other transition-metal complexes.[1] Palladium compounds containing at least one metal−carbon bond intramolecularly stabilized by at least one donor atom, termed cyclopalladated compounds or palladacycles, are one of the most popular class of organopalladium derivatives. These compounds, such as **1** (Scheme 1), were initially isolated and characterized from the cyclopalladation of azobenzene derivatives in the middle 1960s.[2] Since then, numerous reviews have been dedicated to their synthesis, structural aspects, and applications in organic synthesis, organometallic catalysis, and new molecular materials.[3] Moreover, the palladacycle skeletons are also often encountered as intermediate species in many reactions promoted by palladium.[4] Our review will concentrate on isolated and well-defined compounds that contain a Pd−C bond stabilized by the intramolecular coordination of one or two neutral donor atoms (N, P, As, O, Se, or S); i.e., the organic moiety acts as a C-anionic four-electron donor ligand or as a C-anionic six-electron donor ligand (Chart 1). Our review does not attempt to be comprehensive; it merely attempts to cover palladacycle chemistry that

10.1021/cr030681r CCC: $53.50
Published on Web 05/20/2005

Jairton Dupont was educated in Chemistry at PUCRS (Brazil) and received his Ph.D. in 1988 under the guidance of Dr. Michel Pfeffer at the Université Louis Pasteur, Strasbourg (France). After a Postdoc (1988–1990) with Prof. S. G. Davies at the Dyson Perrins Laboratory, University of Oxford (U.K.), he began work as a visiting scientist (1990–1992) at the Institute of Chemistry, UFRGS (Porto Alegre, Brazil). In 1992 he became a Professor of Organic Chemistry at the same Institute. He has been invited as Professor at the Faculté de Chimie de Strasbourg, France (2000 and 2004). His research interests are centered in synthetic organometallic chemistry with special emphasis on homogeneous and ionic liquid biphasic catalysis and nanocatalysis. He has authored around 100 scientific publications and several patents and book chapters, including an organometallic chemistry textbook.

Crestina S. Consorti, born in 1974 in Bento Gonçalves (Brazil), studied Chemistry at UFRGS and received her Ph.D. in the group of Prof. Jairton Dupont in 2004 in the field of palladacycles. She is coauthor of 14 publications. Currently she holds an Alexander von Humboldt Post-Doc fellowship at the Universität Erlangen-Nürnberg, working in the group of Prof. Dr. John A. Gladysz.

John Spencer obtained a B.Sc. in Chemistry with European Studies at the University of Sussex (U.K., 1990) and then a Ph.D. in palladacycle chemistry at the Université Louis Pasteur, Strasbourg, under the supervision of Dr. Michel Pfeffer (France, 1994). After spending 18 months at the ETH, Zurich (Switzerland) in Antonio Togni's group working on asymmetric catalysis, he went on to work in the pharmaceutical industry. He is co-inventor/author of a total of five patent applications and over twenty chemistry articles and reviews in international journals. His current interests include metal-mediated, microwave-enhanced, and parallel synthesis.

Scheme 1. Cyclopalladation of Azobenzene

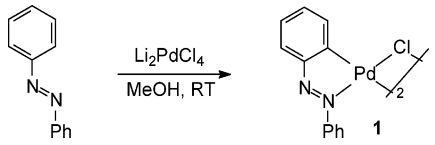


Chart 1. Anionic Four-Electron Donor (CY) and Anionic Six-Electron Donor (YCY) Palladacycles

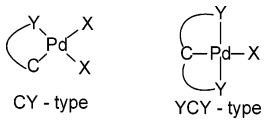
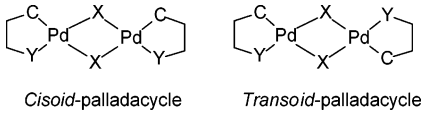


Chart 2. CY Halogen or Acetate Palladacycle Geometrical Isomers (X = Cl, Br, I, OAc, etc.)



has not already been covered in reviews.[3] The latter have dealt mainly with the synthesis and reactivity of the Pd−C bond and have appeared since the 1970s.[3a−o] There are excellent specialized reviews on the application of palladacycles in organic synthesis[3j,m−o,z′] and in organometallic catalysis[3q,s,t,w,x,z] and more recently on a particular class of palladacycles such as those of the pincer-type.[3p,r,u,v] However, the synthesis and structural aspects of palladacycles as well as their applications as chiral auxiliaries and as mesogenic and photoluminescent agents and their biological applications have only been marginally treated thus far. Moreover, the knowledge and applicability of palladacycles as precatalysts (catalyst precursors) over the last 2−3 years have increased exponentially. All of this coupled with the accumulated knowledge of the synthetic, mechanistic, and stability aspects allows for a systematic and rational review of this family of organometallic compounds. Our review will critically present the main achievements, potential, and limitations of palladacycles.

1.2. Types of Palladacycles

Palladacycles can be first divided into two types: anionic four-electron donor or six-electron donor, abbreviated hereafter as CY and YCY, respectively. The former usually exist as halogen or acetate bridged dimers, as two geometric isomers (*cisoid* and *transoid* conformations, Chart 2). CY-type palladacycles can be neutral (dimer (**2**),[2b] bis-cyclopalladated (**3**),[5] or monomeric (**4**)),[6] cationic (**5**),[7] or anionic (**6**)[8] depending on the nature of the other X ligands (Chart 3). The metalated carbon is usually an aromatic sp^2 carbon (see compounds **2**−**6** in Chart 3) and less commonly an sp^3 carbon (aliphatic or benzylic **7** and **8**)[9] or an sp^2 vinylic carbon (**9**, Chart 4).[10] The donor

Chart 3. Examples of Neutral (Dimer, Monomer, and Bis-cyclopalladated), Cationic, and Anionic CY-Type Palladacycles

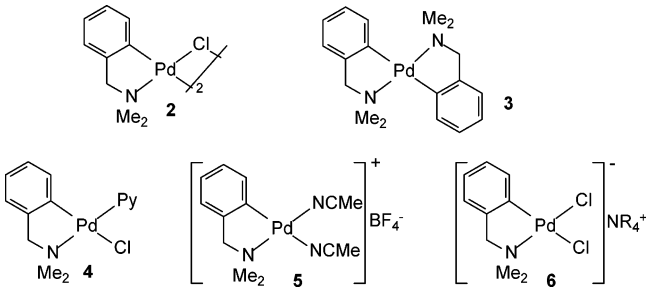


Chart 4. Various Types of Palladated Carbons Usually Present in CY-Type Palladacycles

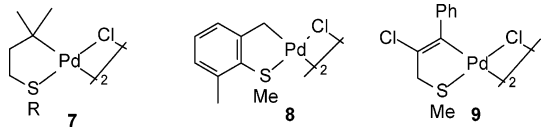
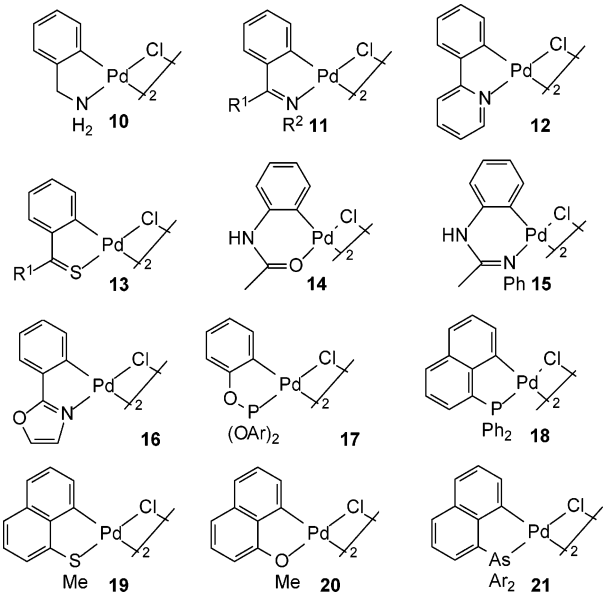


Chart 5. Examples of Chloro-Bridged Dimeric Palladacycles with Various Donor Groups



atom is usually found in azobenzenes (**1**),[2] amines (**10**),[11] imines (**11**),[12] pyridines (**12**),[13] thioketones (**13**),[14] amides (**14**),[15,16] amidines (**15**),[15] oxazolines (**16**), phosphorus (**17** and **18**) and arsine (III) containing ligands, (**21**),[17] thioethers (**19**),[9] and ethers (**20** etc.) (Chart 5). The most common palladacycles are derived from tertiary amines and imines and are usually five- or six-membered rings. Conversely, cyclopalladated complexes such as **10**, derived from primary amines, are rather rare.[18] The metalated ring of CY-type palladacycles can vary between 3 and 11 members.[19−24] Of note is that three-and four-membered palladacycles are not usually stable, and examples of isolated and well-characterized compounds are very rare (Chart 6). YCY pincer-type palladacycles are usually symmetrical[25−28] (two equivalent five- and, less commonly, six-membered rings) or are unsymmetrical[29−34] (mixed, five- and six-membered rings) (Chart 7).

Chart 6. Examples of Palladacycles Containing Three-,[19] Four-,[20] Five-,[21] Six-,[22] Seven-,[23] and Eight-Membered[24] Rings

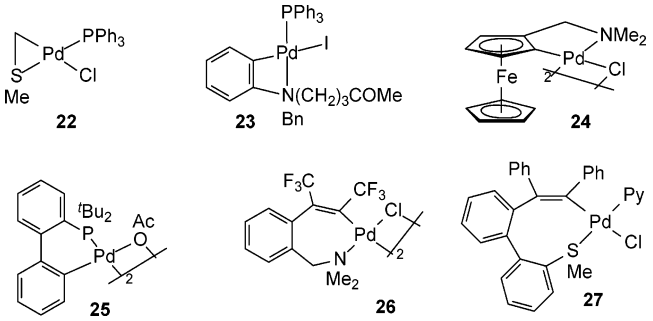
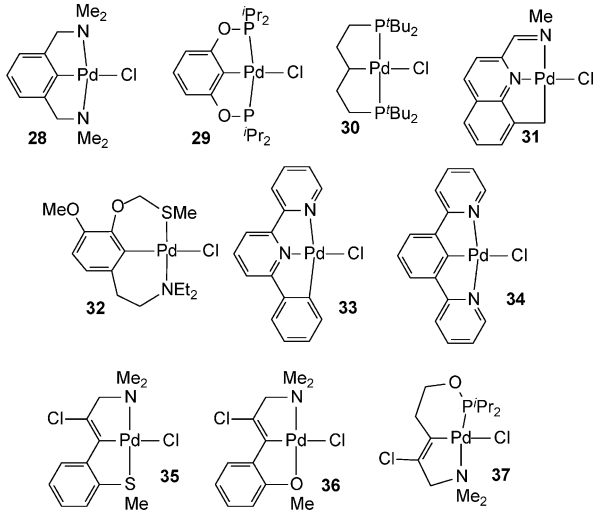
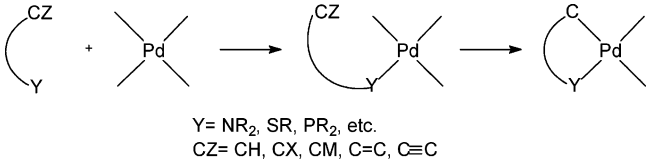


Chart 7. Types of Pincer Palladacycles: Symmetrical NCN (28[25] and 34[26]) and PCP (29 and 30[27]); Nonsymmetrical NNC (31[29] and 33[30]); and Mixed SCN (32[31] and 35[32]), NCO (36[33]), and NCP (37[34]) Containing Different Metalated Carbons (sp^3 and sp^2) and Ring Sizes (Five- and Six-Membered Rings)



Scheme 2. Methods for the Generation of Palladacycles



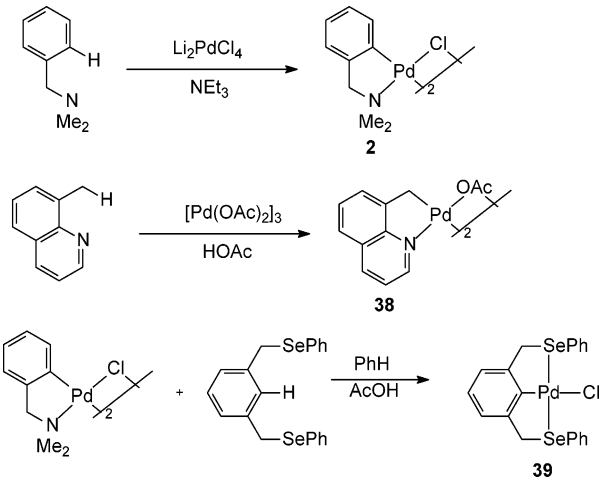
2. Methods of Preparation

There are several methods available for the generation of palladacycles (C−H activation, oxidative addition, transmetalation, or nucleophilic addition onto an unsaturated bond), and often a five- or six-membered chelate is formed as a result of the formation of a stable Pd−C bond, assisted by coordination of the two-electron donor group (Scheme 2).

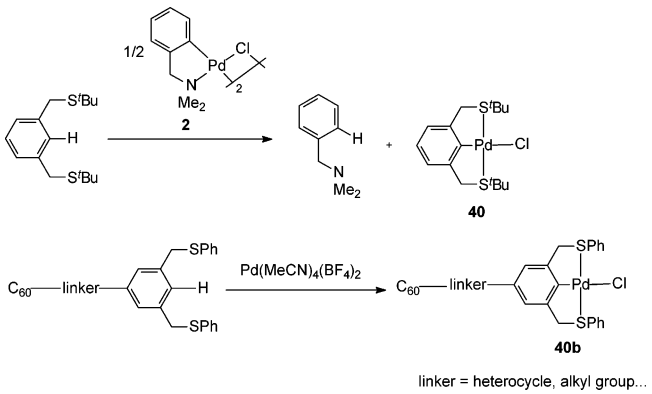
2.1. C−H Bond Activation

The direct chelation assisted palladation of C−H bonds is the most simple and direct method for the construction of palladacycles, also termed orthopalladation.[35] Common palladation agents include tetrachloropalladated salts (often the first choice method

Scheme 3. Examples of Cyclopalladation via C−H Bond Activation Using Different Palladating Agents: Li_2PdCl_4 (top); $[Pd(OAc)_2]_3$ (middle); and Ligand Exchange (bottom)



Scheme 4. Synthesis of SCS Pincer Complexes



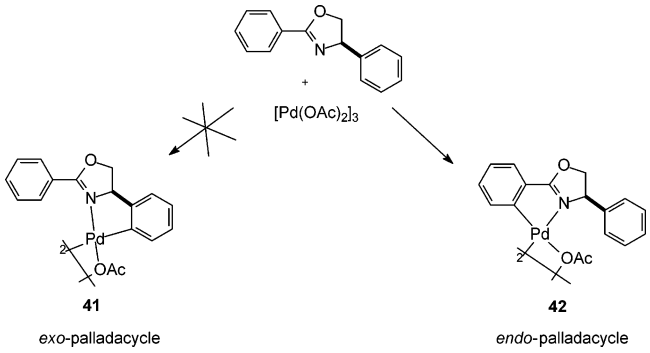
due to cost and ease of use), with a base,[36] or palladium acetate in acetic acid or benzene. Otherwise, a ligand exchange process is employed using another palladacycle (transcyclopalladation)[37] (Scheme 3). For example, for the synthesis of **40**, the Li_2PdCl_4 method was unsuccessful and a 10% yield was obtained with the $Pd(OAc)_2$/acetic acid procedure whereas transcyclopalladation gave the product in >90% yield (Scheme 4).[9] The cationic $[Pd(NCMe)]_4[BF_4]_2$ compound can also be employed as a palladation agent[38] and has been used for the generation of SCS pincer palladacycles attached to C_{60}.[39]

Detailed thermodynamic and kinetic investigations clearly show that the transcyclopalladation reaction takes place due to acidolysis of the starting palladacycle **2** in acetic acid. Palladium(II) is released from **2** by acidolysis, and the more acid resistant palladacycle, in this case complex **40**, is formed.[40]

Cyclopalladation reactions are known to proceed by a variety of mechanisms,[41] and the cyclopalladation of aromatic derivatives is generally considered to occur by a simple electrophilic aromatic substitution pathway (Scheme 5).[3a] Detailed mechanism investigations have been undertaken in the cyclopalladation of nitrogen-containing ligands by palladium acetate in chloroform and acetic acid such as in the cyclopalladation of primary[42] and tertiary aryl amines[43] and alkyl[44] and aryl phosphines.[45] There is some evidence that the C−H bond is only activated within the coordination plane of the metal center.[9,46]

The regioselectivity in the palladation of oxazolines and imines is highly directional (Scheme 6),[47] where

Scheme 6. Regioselectivity in the Cyclopalladation of Oxazolines



there is a tendency for the formation of the *endo*-palladacycle.[48] Apparently the size of the formed palladacycle (five- or six-membered ring, for example) and the type of the metalated carbon (sp^2 or sp^3) are not the driving force of this selectivity. However, it is probable that the *endo*-palladacycle is the thermodynamic isomer, since in some cases the *exo*-cyclic analogue can be isolated and undergoes isomerization (Scheme 7).[49] The cyclopalladation reaction can be used for the two- and three-fold palladation of a single benzene derivative including macrocycles (Chart 8).[50−52] Bimetallic (Ni) porphyrin complexes with a

Scheme 5. Proposed Mechanism for the Cyclopalladation of Aromatic Ligands

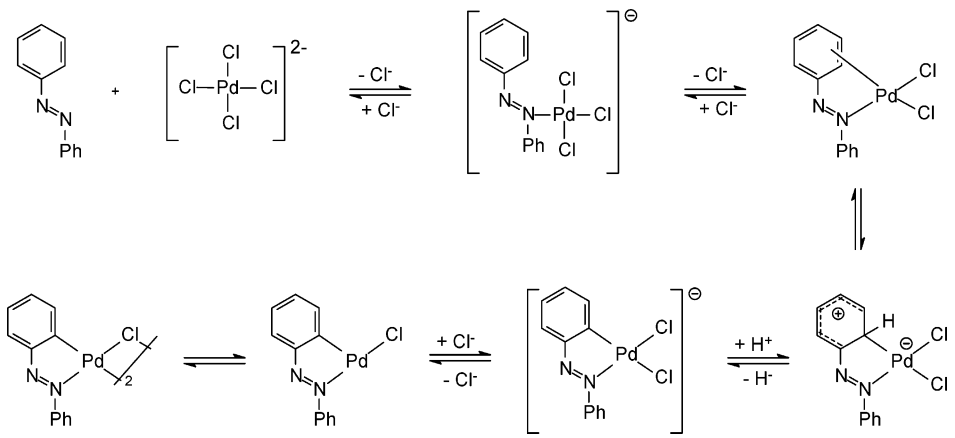
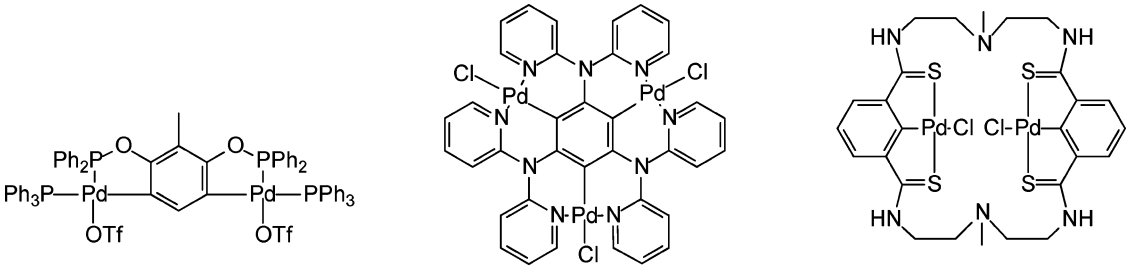
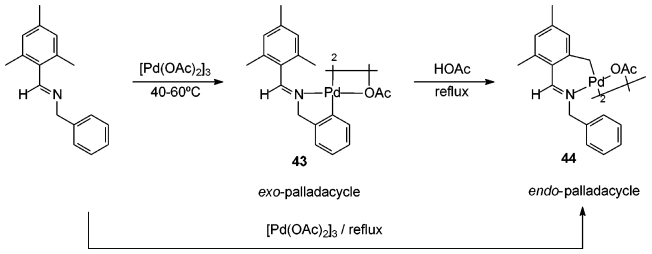


Chart 8. Palladacycles Derived from the Two- and Three-fold Palladation of a Single Benzene Derivative Ring

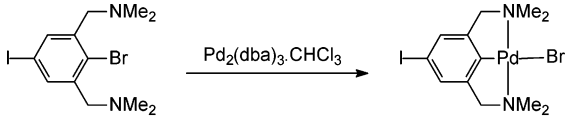


45 46 47

Scheme 7. Isomerization of Palladacycles Derived from Imine Ligands



Scheme 8. Palladacycle Formation via Oxidative Addition



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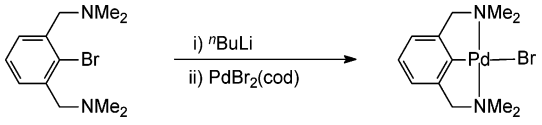
cyclopalladated phenylpyridine have also been reported.[53]

2.2. Oxidative Addition

The oxidative addition of aryl halides and, to a lesser extent, alkyl halides, containing a two-electron donor group, is also a useful method for the generation of various palladacycles that cannot usually be obtained by direct C−H bond activation procedures. The palladium starting materials used are, in most cases, $Pd(dba)_2$ or $Pd_2(dba)_3$ or $Pd(PPh_3)_4$, which will generate dimeric palladacycles containing halogen bridges, neutral pincer-type palladacycles, or PPh_3-bound monomers, depending on the palladating agent and the ligand employed. This procedure was successfully applied for the generation of three- and four-membered ring palladacycles (compounds **22** and **23** of Chart 6), which are not accessible by the C−H bond activation methodology. Moreover, this method is quite important for the generation of palladacycles that contain reactive functionalities, and the thus-formed palladacycle may undergo further transformations at the metalated ligand such as the synthesis of heterobimetallic systems or dendrimers (Scheme 8) (see also example **161**).[54] We must note that the major drawback of the oxidative addition methodology is the accessibility of the halo starting material, which in many cases is prepared by a multistep procedure.

Scheme 9. Palladacycle Formation via a Transmetalation Reaction



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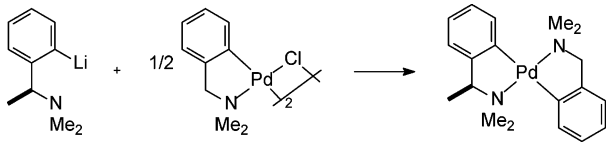
Scheme 10. Bis-cyclopalladated Compound Formed by a Transmetalation Reaction



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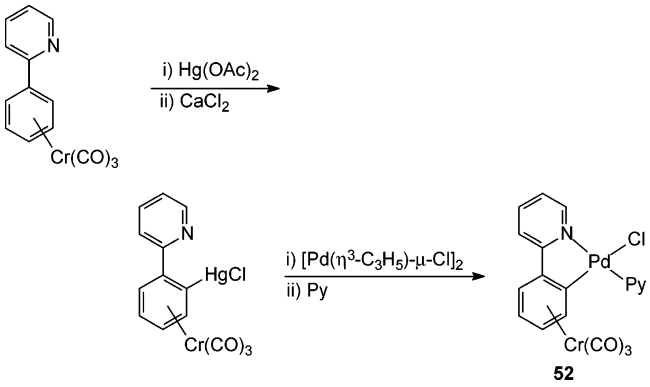
Scheme 11. Planar Chiral Palladacycle Formed by Transmetalation with Organo-mercurial Compounds



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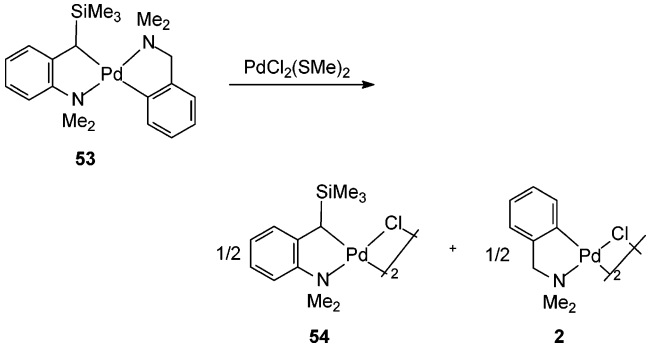
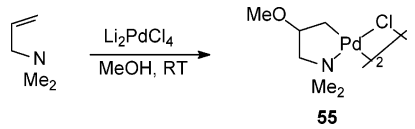
2.3. Transmetalation

The transmetalation reaction is an interesting and often-used methodology for the generation of palladacycles. In most cases the transmetalating agents are organolithium or organomercurial reagents. The organolithium reagents can be prepared directly by the selective lithiation of the ligand or by Li/halogen exchange, which is usually quantitative (Scheme 9).[55] Bis-cyclopalladated compounds are easily prepared by a transmetalation via organolithium or mercurial N- and O-containing ligands with halogen dimer palladacycles (Scheme 10).[17,56] The transmetalation reaction via organo-mercurial compounds is useful for the generation of planar chiral cyclopalladated complexes containing the $Cr(CO)_3$ moiety (Scheme 11).[57] Transmetalation reactions using $PdCl_2(SMe)_2$ with bis-cyclopalladated compounds are also an

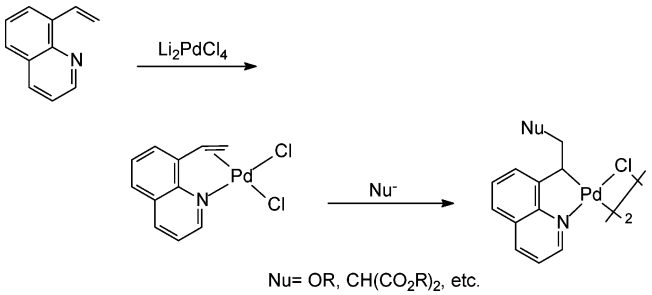
Scheme 12. Another Example of a Palladacycle Generated by a Transmetalation Reaction



Scheme 13. Palladacycle Generated by Alkoxypalladation of Allylamines



Scheme 14. Adduct Intermediate in the Formation of Palladacycles via Alkoxy- or Carbopalladation of Alkenes

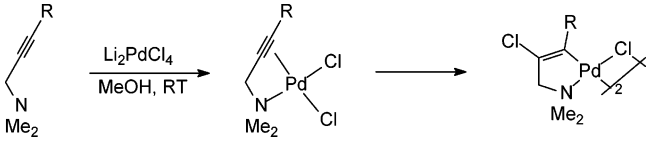


interesting method for the generation of halogen dimer palladacycles that are not accessible through other methods, such as those containing a labile $SiMe_3$ group located at the metalated carbon (Scheme 12).[58] In the case of transmetalation or oxidative addition processes, it is possible that the initial step does not involve coordination of the donor group to the metal, and indeed an ortho substituent decelerates such an addition through both steric and electronic effects.[59]

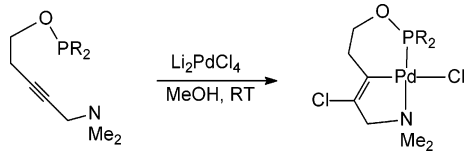
2.4. Alkoxy- and Carbopalladation of Alkenes and Halopalladation of Alkynes

The alkoxy- and carbopalladation of functionalized alkenes such as allyl or homo-allyl amines and thioethers by the addition of alkoxides or stabilized carbanions invariably yields five-membered palladacycles (Scheme 13).[60] The reaction proceeds through coordination of both the donor group and the C=C bond to the electrophilic Pd(II) center followed by nucleophilic addition to the unsaturated carbon, leading to the more stable palladacyclic ring, i.e., five-membered over six-membered rings (Scheme 14).[61] The formation of the intermediate adduct, generated through the chelation of both donor groups, is essential for the formation of the palladacycle, since attempts to use other allyl and homo-allyl alkenes failed. Terminal allyl and homo-allyl alkenes are much more prone to form palladacycles than internal

Scheme 15. Chloropalladation of Acetylenes in the Preparation of Palladacycles



Scheme 16. Pincer-type Palladacycles Generated from the Chloropalladation of Heterosubstituted Acetylenes



alkenes. Hard nucleophilic reagents tend to attack the metal center, leading to Pd-alkoxide species that decompose to metallic palladium. In opposition, stabilized carbanions lead almost exclusively to palladacycles by addition to the C=C bond. However, even relatively hard nucleophiles such as the alkoxide anion can add to the C=C bond at lower reaction temperatures.[61]

The reaction of propargylamines or thioethers with Li_2PdCl_4 in the presence of nucleophiles under the same conditions used for allyl amines or thioethers also generates palladacycles containing a Pd−vinyl bond. However, the product results from the nucleophilic addition of the chloride anion instead of the other nucleophiles present in the reaction mixture (Scheme 15).[10,33,62] This chloropalladation reaction is an interesting method for the generation of various types of palladacycles such as nonsymmetrical pincer-type palladacycles (Scheme 16)[32,34] or heterobimetallic compounds containing the $Cr(CO)_3$ moiety.[63] However, some of these palladacycles are not stable in solution, and in the case of dimeric derivatives, they can easily undergo a retro-chloropalladation reaction.[64] Moreover, palladacycles are not formed when terminal heterosubstituted alkynes are used.

2.5. Structural Aspects of Palladacycles

The Pd−C bond distance falls between 1.985 and 2.295 Å depending upon various structural and electronic aspects such as the nature of the palladated carbon (sp^2 aromatic, sp^2 vinylic, sp^3 benzylic, or sp^3 aliphatic), the nature of the donor group, the size of the ring, etc.[3l,65] Halogen dimer palladacycles usually adopt two isomeric forms—*cisoid* and *transoid*—but it is usually the *transoid* geometry that crystallizes, although palladacycles derived from the chloropalladation of heterosubstituted alkynes crystallize in the *cisoid* geometry. In all the halogen dimeric structures, the Pd−halogen bond located *trans* to Pd−C is longer than the one located in the *cis* position due to the stronger *trans* effect imposed by carbon compared with the heteroatom ligand.[33]

In acetate-bridged dimeric palladacycles, besides the *cisoid* and *transoid* isomeric forms, depending upon the nature of the ligand, *in*−*in*, *out*−*in*, and *out*−*out* structural isomers can also be formed.[66] The monomeric palladacycles formed through the bridge splitting reaction with L-type ligands such as py-

Scheme 17. Bridge-Splitting Reaction

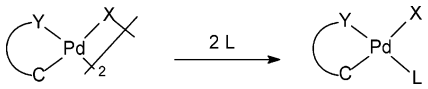
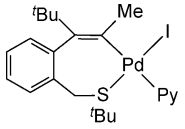
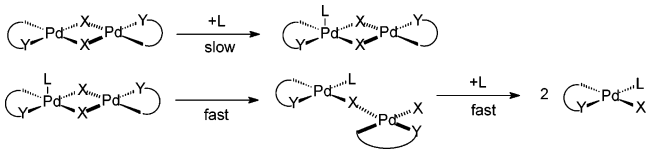


Chart 9. Palladacycle 56 with a *trans* C−Pd−Py Arrangement



56

Scheme 18. Mechanism of the Bridge-Splitting Reaction of Palladated *N*,*N*-Dimethylamino-phenethyl Ligands with Pyridine

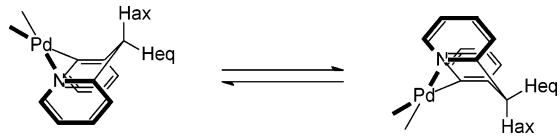


ridines or phosphines almost invariably have the L-type ligand located *cis* to the Pd−C bond (Scheme 17). However, a palladacycle with a *trans* C−Pd−Py arrangement has been structurally characterized (Chart 9).[67] The *cis* location of the iodine relative to the Pd−C bond is opposite to the geometry expected when taking into account the higher *trans* influence exerted by the C ligand compared with the two-electron donor groups of the metalated ring. However, theoretical calculations on model compounds clearly indicate that the *cis* C−Pd−L isomer is around 6 kcal·mol^{-1} more stable than its trans C−Pd−L counterpart.[33] This selectivity has been rationalized in terms of the *antisymbiotic* effect[68] (recently revisited and adapted for metallacycles as *transphobia*[69] and *trans* choice[70] concepts) of the soft Pd(II) center that will place the incoming ligand *cis* to the Pd−C bond. This is an indication that the stereochemical outcome of the bridge-splitting reaction is under thermodynamic control. The mechanism of the bridge-spitting reactions of palladated *N*,*N*-dimethylaminophenethyl ligands with pyridine has been investigated in some detail and is a fast, bimolecular, associatively driven reaction involving pentacoordinated species (Scheme 18).[71]

The fluxional behavior of most palladacycles can be generally investigated by variable-temperature NMR. The inversion of five-membered rings has a very low energy barrier, but in six-membered rings this process is often rapid at room temperature but can be "frozen" at low temperatures; e.g., palladacycles derived from the 2-benzylpyridine ligand show temperature-dependent ^{1}H NMR spectra attributed to the equilibria between two six-membered boat forms (Scheme 19).[72]

Pyramidal nitrogen and sulfur inversion processes are also quite common in palladacycles containing amine or thioether ligands.[10,73] Moreover, pincer-type palladacycles undergo facile ring puckering inversion processes (Scheme 20).[9]

Scheme 19. Inversion of a Six-Membered Ring Palladacycle



Scheme 20. Newman Projections along the Cl−Pd−C Axis of the Two Isomers of Palladacycle 57

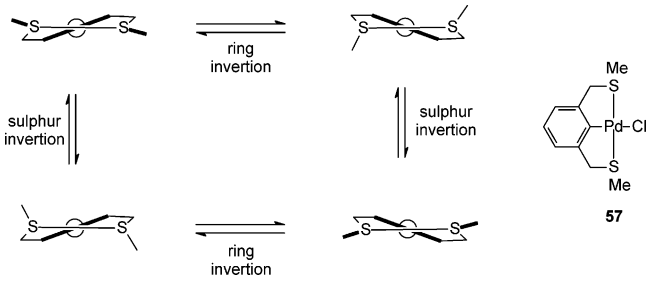
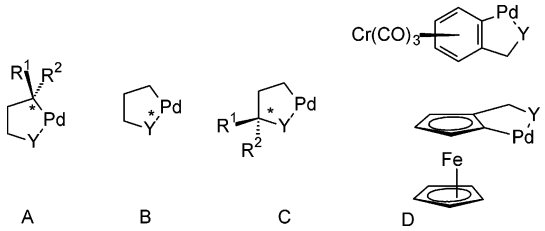


Chart 10. Schematic Representation of Some Types of Chirality Exhibited by Cyclopalladated Compounds[a]



[a] Other ligands are omitted for clarity. ∗ = stereogenic center.

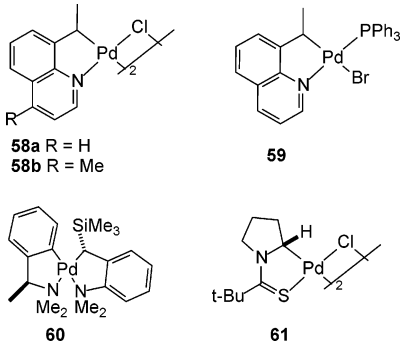
3. Chiral Cyclopalladated Compounds

Chiral cyclopalladated compounds existing in enantioenriched form may be subdivided into many different classes, and a schematic representation of the different types of chirality to be discussed hereafter is given in Chart 10. One rather rare class of chiral cyclopalladated compounds bears a stereogenic carbon atom directly σ-bonded to the metal as in **A**. In **B** the stereogenic center directly bound to palladium is an asymmetrically substituted donor group such as an amine, phosphine, or thioether. In **C** the stereogenic center is not directly bound to the metal but is elsewhere in the metalated ligand; this type of complex is often conformationally very stable and has, without a doubt, the most widespread applications. In **D**, planar chirality is exhibited by the molecule, usually courtesy of a ferrocenyl or η^6-chromium carbonyl moiety. This type of complex is becoming more popular and has many impressive applications in asymmetric synthesis.[74]

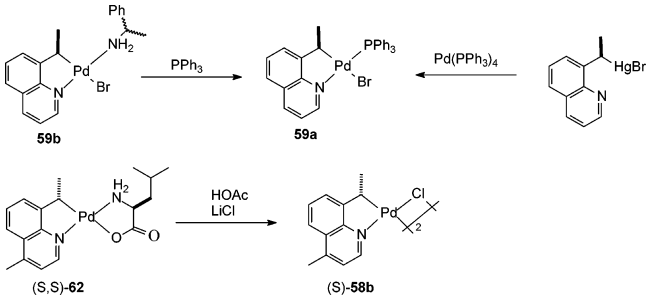
3.1. Complexes Containing a Stereogenic Center Directly Bound to the Metal

Examples of cyclopalladated compounds containing an asymmetric metalated sp^3 carbon atom are given in Chart 11. Complexes **58** and **59** can be made in racemic form by a C−H activation of a prochiral 8-ethylquinoline derivative with $Pd(OAc)_2$ followed by LiCl metathesis and can be resolved using the sodium salt of (*S*)-leucine. In the case of **62** (the (*S*,*S*)-

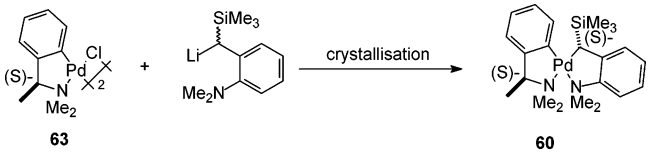
Chart 11. Palladacycles Containing an Asymmetric Metalated sp³ Carbon



Scheme 21. Enantioenriched Cyclopalladated Ethylquinoline Compounds



Scheme 22. Synthesis of a Heteroleptic Palladium Chelate

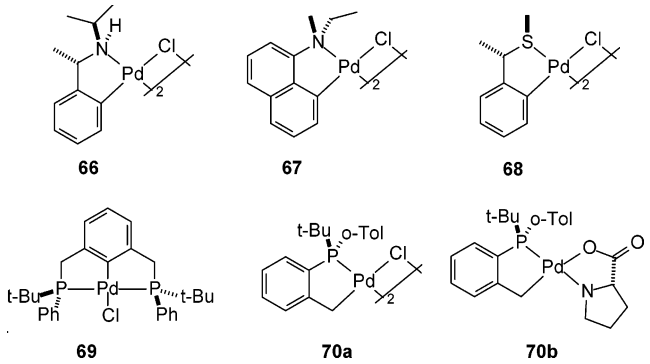


isomer is shown in Scheme 21), with a 4-methyl substituent on the quinoline ligand, the ratio of the two diastereomers (*R,S*) and (*S,S*)-**62** can be determined by simply examining the ratio of the H*o* or H*m* (AB system) protons in the aromatic region of the ^{1}H NMR spectrum, and the absolute configuration of (*S,S*)-**62** was determined by an X-ray diffraction study.[75,76] Enantioenriched **58b** is formed by liberation of the amino acid chiral template by reaction with mild acid followed by ligand metathesis with lithium chloride. The related monomeric complex **59a** has been synthesized by many different routes including the oxidative addition of metallic mercury onto an enantiopure 8-bromoethylquinoline derivative followed by transmetalation with Pd(PPh$_3$)$_4$. An alternative route involves separation of the two diastereomers of the palladium complex **59b** by fractional crystallization followed by phosphine−amine ligand exchange (Scheme 21).[77,78] The proline derivative **61** was synthesized and resolved using a method similar to that used for **58**.[79]

Complex (*S,S*)-**60** was synthesized by the reaction of orthopalladated (*S*)-(+)-dimethyl(1-phenylethyl)-amine (**63**) with a lithiated silylated dimethylaminotoluene derivative followed by fractional crystallization (Scheme 22).[80] A series of enantioenriched palladacycles was synthesized in high yield and diasteroselectivity starting from aryl triflate ligand **64** and palladium(0) diphosphine complexes (Scheme 23). Notably, these six-membered palladacycles containing accessible β-hydrogens are thermally stable even at 120 °C.[81] Epimerization at the stereogenic carbon only takes place at higher temperatures or in the presence of weak acids.

Examples of cyclopalladated compounds with an enantioenriched donor group Y are given in Chart 12. Derivative **67** was found to be conformationally

Chart 12. Cyclopalladated Complexes with an Asymmetric Y (donor) Group



labile and could not be isolated in optically enriched form due to rapid N-inversion,[82] whereas the less labile derivative **66** was used to resolve a monomeric phosphine, P(*t*-Bu)(Me)Ph, by the chloride-bridge splitting reaction of the latter with **66** and separation of the resulting diastereomers.[83] The chiral derivative **68** exists as a 3:1 anti/syn mixture in solution, and to confirm this ratio, its monomeric *trans*-(S−N) pyridine complex was formed, again as a 3:1 mixture of stereoisomers.[84] The P-chiral **69** was formed by a C−H activation of the pincer ligand *R,R*-{C$_6$H$_4$-2,6-(CH$_2$P*Ph*t*-Bu)$_2$}with PdCl$_2$(COD) in refluxing toluene.[85]

The interesting P-chiral derivative **70a**, synthesized as a "chiral Herrmann−Beller palladacycle"

Scheme 23. Chiral Palladacycles Containing an Asymmetric Metalated sp³ Carbon

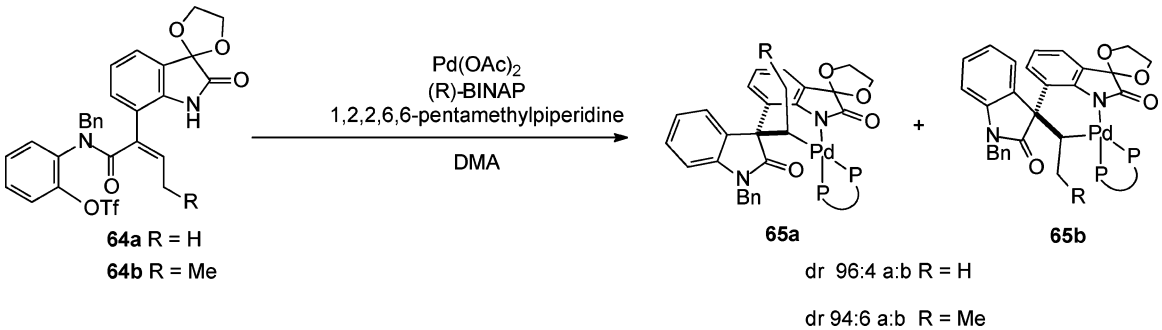
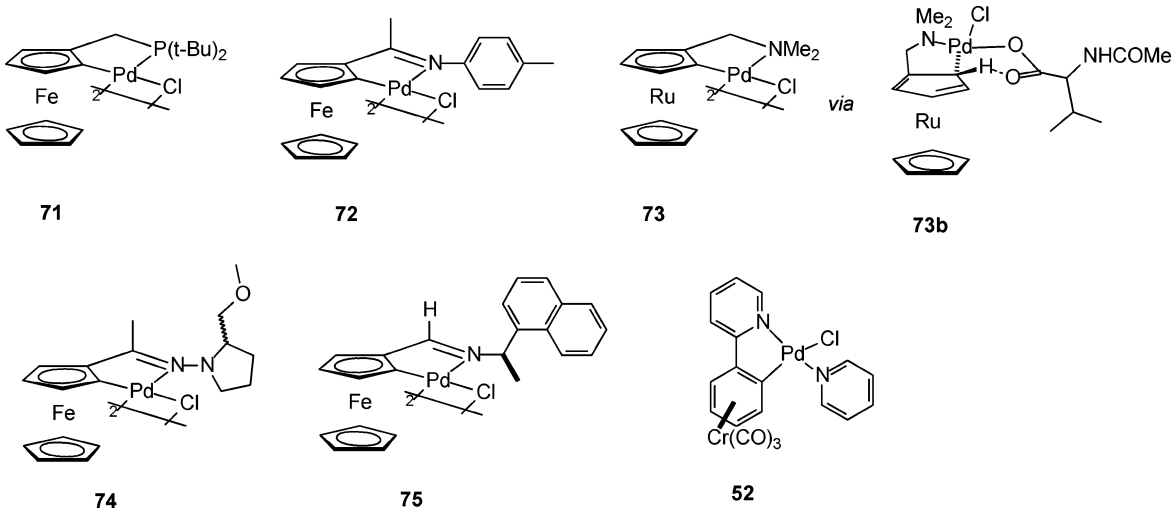


Chart 13. Planar Chiral Palladacycles



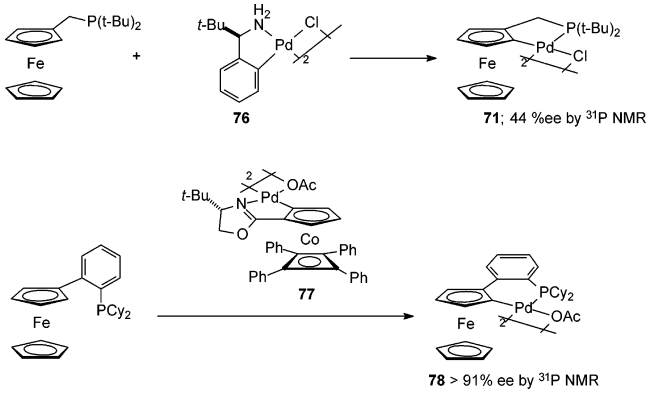
analogue, was made in racemic form by a benzylic sp^3 C−H activation of *tert*-butyldi-*o*-tolylphosphine with K_2PdCl_4 followed by heating in isobutyl alcohol. Separation of the enantiomers of the dimer was achieved by the formation of diastereomeric prolinate derivatives. Fractional crystallization of the latter afforded **70b** with a de >98% (by ^{31}P and ^{1}H NMR), and (S_p)-**70a** was recovered in enantioenriched form after treatment with HCl.[86]

3.2. Planar Chiral Palladacycles

These complexes typically contain metallocene or chromium carbonyl moieties (Chart 13). Direct C−H activation is a general route to racemic planar chiral palladacycles such as *rac*-**71**[87] and *rac*-**72**.[88] The resulting complexes are obtained in enantiopure form by a standard resolution technique analogous to those discussed earlier: derivatization with an amino acid ((*S*)-proline for **71**, (*S*)-leucine for **72**) and diastereomer separation by crystallization or chromatography, followed by regeneration of the chiral palladacycle by treatment with acid. Invariably, the absolute configuration of the metallacycle is determined by X-ray crystallography (Chart 13).

Three general methods for asymmetric C−H activation leading to enantioenriched planar chiral palladacycles have been reported: viz, enantioselective deprotonation using a chiral base, the use of a chiral directing group, and asymmetric ligand exchange. Under the hypothesis that carboxylate bases are directly involved in the generation of planar chirality with Pd(II) salts for the C−H activation of ferrocenyl derivatives, Sokolov devised an ingenious enantioselective version using chiral bases, which under optimal pH conditions afforded ee's of up to 90%. Enantioenriched palladacycles such as **73** were synthesized using Na_2PdCl_4 in the presence of the chiral base *N*-acetyl-(S)-valine, which effected the enantioselective deprotonation (see **73b** for a proposed deprotonation scenario involving the chiral base) of the starting ferrocenylamine.[89] For the synthesis of palladacycles **74**[90] and **75**[91] a chiral motif was attached to the ferrocene via the condensation of a ferrocenyl aldehyde/ketone with a chiral amine, and

Scheme 24. Planar Chiral Palladacycle by Asymmetric Transcyclopalladation



the C−H activation process was found to occur with moderate diastereoselectivity (de = ca. 10:1 and 3:1, respectively).

A very recent asymmetric ligand exchange/transcyclopalladation process was exploited as in the formation of **71** with ee's up to 44% ee using the primary amine coordinated palladacycle **76** containing an isolated stereogenic center (Scheme 24). As a recent, very impressive example, the ferrocene-containing palladacycle **78** was formed in >90% ee by a similar process.[92]

As a point of comparison, (S_pS_p)-**70a** was synthesized in 91% ee (by ^{31}P NMR) using **76**.[93] Not all attempts at asymmetric induction during the synthesis of planar chiral palladacycles have met with success. The C−H activation of a prochiral ferrocenylamine with a chiral sulfoxide palladium-containing complex led to racemic palladacycle **79**,[94] and the use of a chiral yet racemic phosphite as directing group afforded the metallacycle **80**[95] with a de = 0% (Scheme 25).

3.3. Cyclopalladated Compounds Containing an Isolated Stereogenic Center

Common enantiopure palladacycles including **63** and **76** and also the complexes shown in Chart 14, such as **81**,[96] **82**,[97] **83**,[98] **84**,[99] and **85**,[100] are typically formed by an orthometalation reaction of the enan-

Scheme 25. Racemic Planar Chiral Palladacycles

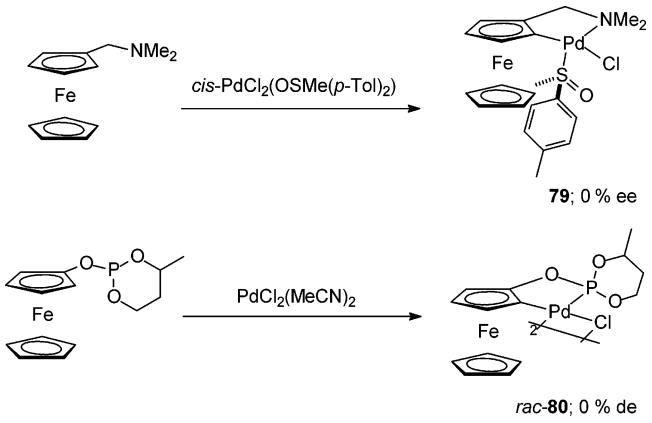
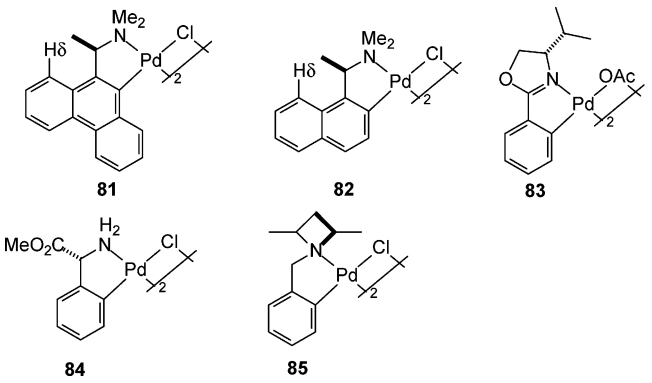


Chart 14. Cyclopalladated Complexes with an Isolated Asymmetric Center



tiopure amines (formed by either asymmetric synthesis or resolution). Many of these complexes have important uses in chiral recognition, e.g., in ligand resolution and structural studies in both solution and the solid-state.

3.4. NMR Studies and ee Determination

Chiral cyclopalladated compounds can be used to determine the enantiomeric excess of various species in solution in very much the way that chiral ligands such as amino acids can be used to determine the ee of chiral cyclopalladated complexes. The derivative **86**, containing a trifluoromethyl group, was prepared by the C−H activation of the racemic ligand and resolved using (*R*)-phenylglycine followed by HCl liberation of the enantioenriched palladacycle (ee >98%). **86** was used to determine the ee of α-amino acids by ^{19}F NMR.[101] Similarly, ^{31}P and ^{13}C NMR have been applied for the ee determination of phosphines as well as a study of phosphine-bound palladacycles in solution, as with **87** and **88** (Chart 15).[102,103]

NMR studies including NOESY and ROESY experiments of **63** and **82** and of their monodentate complexes with *N*,*N*,*N*′,*N*′-tetramethyl-2,3-butanediamine have revealed that **82** is more stereochemically rigid than **63** in solution due to the presence of the H_δ, which locks the conformation of the palladacycle (Chart 14). In a similar manner, **89**, the *N*,*N*,*N*′,*N*′-tetramethyl-2,3-butanediamine complex of **81**, was studied in solution by ROESY NMR and also found to be stereochemically rigid.[104] Complex **82** is probably the most extensively employed palladacycle for asymmetric synthesis and resolutions.

3.5. Chiral Cyclopalladated Compounds as Resolution Agents

The resolution of enantiopure biaryl ligands, of the type P−P, P−N, P−S, etc., remains an active area of research given the interest in probing steric and electronic effects in asymmetric catalysis.[105] Homochiral cyclopalladated compounds have been extensively employed for the resolution of such ligands, with complex **82** being one of the agents of choice, along with **63** and **81**, due to their attributes discussed in the previous section. A typical procedure involves treating a racemic biaryl with the chiral cyclopalladated agent, which is used either in its halo-bridged form or as a cationic monomeric complex. The reaction usually proceeds with little if any diastereoselection, often confirmed by NMR examination of the reaction mixture. Due to the high air and conformational stability of the diastereomers, separation is often possible by crystallization or chromatography. The absolute configuration of one or both of the diasteromers is typically determined by X-ray crystallography or NMR means, aided by the fact that the absolute configuration of the cyclopalladated ligand is known. The enantioenriched biaryl can be liberated from the metal by treating the complex with a chelating ligand such as dppe or a hard donor ligand such as cyanide. A few illustrative examples of biaryl systems prepared in this manner are displayed in Chart 16 accompanied by examples of typical binding modes (monodentate/bidentate) exhibited by the ligated complexes.[106]

The resolution of phosphines using cyclopalladated complexes is also an important area of research and was extensively reviewed by Wild, one of the leading contributors in the field, in 1997.[107] The few examples included hereafter mainly emanate from more recent publications. Granell's group found that the primary amine cyclopalladated derivative in **99** was an efficient resolving agent for monodentate phosphines,[108] and an impressive resolution of the diarylphosphine

Chart 15. Palladacycles and Their Applications in NMR Studies in Solution

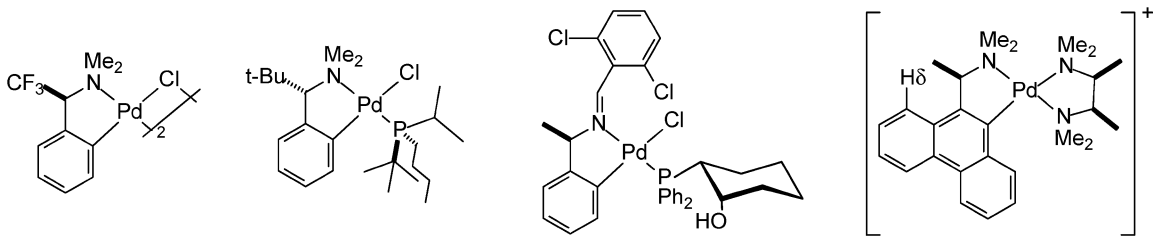


Chart 16. Biaryls Resolved Using Homochiral Cyclopalladated Complexes

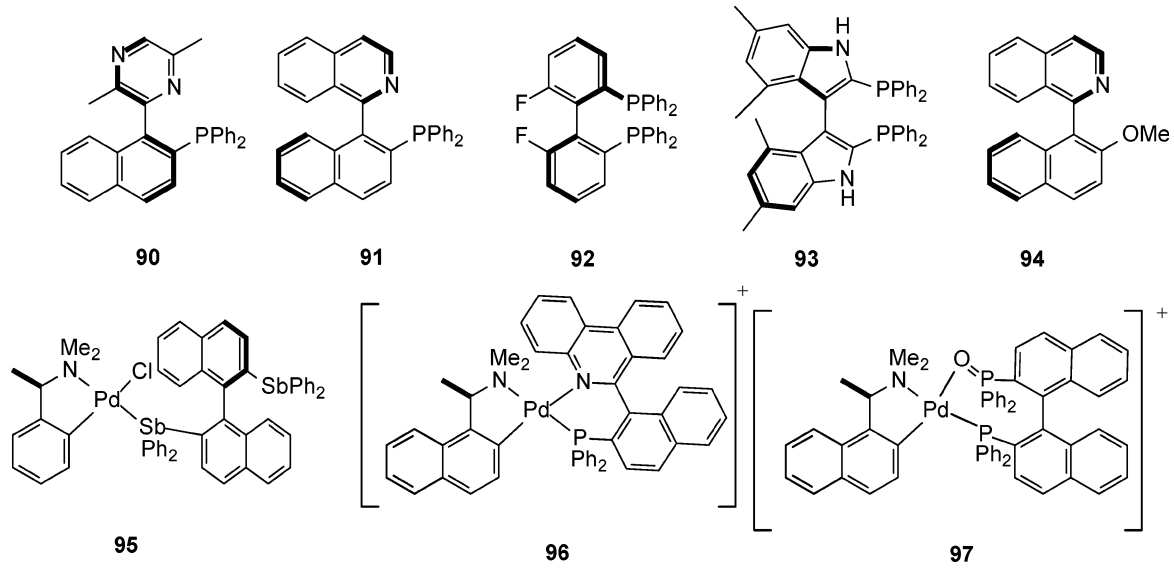
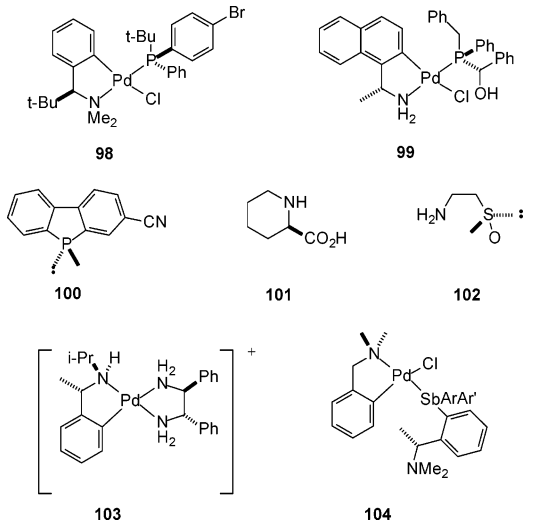


Chart 17. Other Systems Resolved by Cyclopalladated Complexes



in **98** was reported by Dunina et al., which was subsequently liberated by treatment with ethylenediamine (Chart 17).[109]

Other examples of resolutions involving cyclopalladated compounds are illustrated in Chart 17 including the chiral cyclic phosphine **100**.[110] Chelating ligands such as the important pharmaceutical feedstock **101**[111] and amino sulfoxides or diamines such as **102**[112] and **103**[113] have all been successfully resolved using the techniques described earlier. A curious resolution involving an *achiral* cyclopalladated complex is also worthy of inclusion in this discussion, since the diastereomers of a stibane were only separable once bound to a palladium as in the complex **104**. Decomplexation was here achieved by employing triphenylphosphine.[114]

3.6. Enantioselective Synthesis

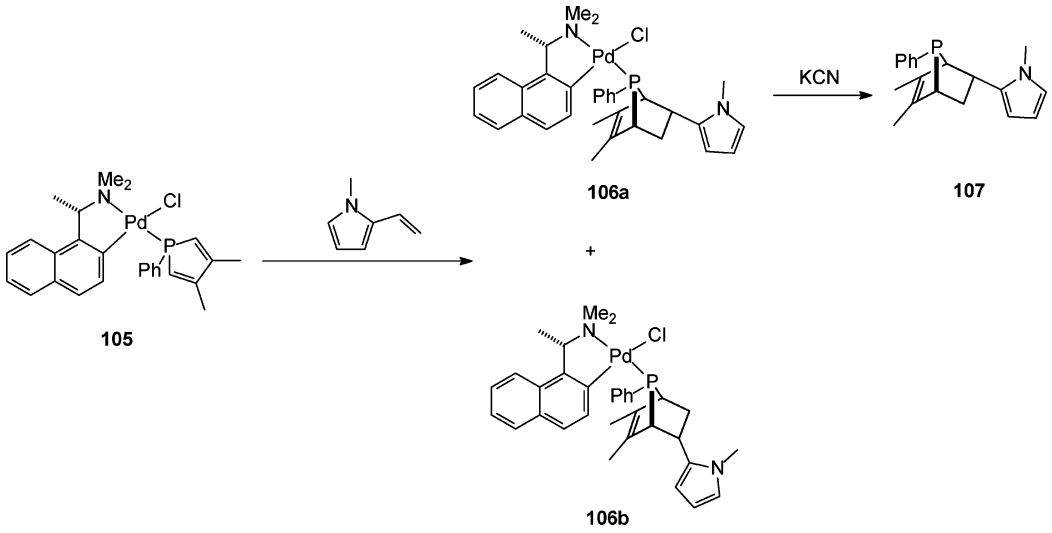
Homochiral cyclopalladated complexes are very useful in asymmetric synthesis both as stoichiometric templates as well as catalysts. *In these two cases the chiral ligand remains attached to the* Lewis acid Pd(II) center, often leading to high levels of enantiodiscrimination. *However, in some cases,* such as catalytic hydroarylation, cyclopropanation, and Heck reactions, involving a redox process (Pd(II) to Pd(0)), no enantiodiscrimination is observed. For these processes, the chiral ligand is no longer attached to the metal, which is presumably in the form of Pd(0) nanoparticles, and consequently, racemic product is obtained.

3.6.1. Stoichiometric Diels–Alder Chemistry

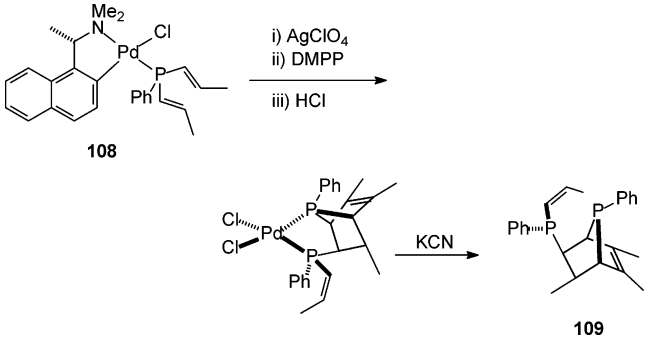
Cyclopalladated compounds have proven to be useful stoichiometric chiral templates for the synthesis of P-chiral phosphines. In many cases, 1-phenyl-3,4-dimethyl-phosphole (DMPP) is reacted with complex **82** and chirality is induced once the prochiral phosphine has been complexed to the metal. Such coordination destroys the aromaticity of the heterocylic system, and it can react with dienophiles to give a mixture of diastereomeric bicyclic phosphines that are typically separated by chromatography and decomplexed by reaction with potassium cyanide. Both *exo*- (intramolecular) and *endo*-cycloadducts (intermolecular) can be formed. The course of many of these reactions has been followed by multinuclear and 2D-NMR, and many of the complexes have been characterized in the solid state.[115] For example, **105** reacts with 1-methylvinylpyrrole to yield a 1:1 mixture of [4+2] adducts **106a** and **106b**, evidenced by two equal intensity singlets at around 120 ppm by ^{31}P NMR. The two diastereomers can be separated by chromatography, and the free ligand can be liberated stereospecifically by treatment with KCN (Scheme 26).[116]

Phenyldi[(*Z*)-prop-1-enyl]phosphine regiospecifically forms a complex **108** upon reaction with **82** whereby the phosphine and nitrogen atoms are mutually *trans*. After activation with a chloride scavenger, reaction with DMPP, and subsequent depalladation, the remarkable diphosphine **109** is formed (Scheme 27).[117] Many other chiral phosphines and arsines have been synthesized using similar methodology.[118]

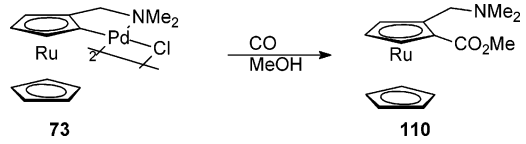
Scheme 26. Palladium-Promoted [4+2] Cycloadditions



Scheme 27. Diphosphine with 2P and 4C Stereogenic Centers via Palladium-Mediated Cycloaddition Chemistry



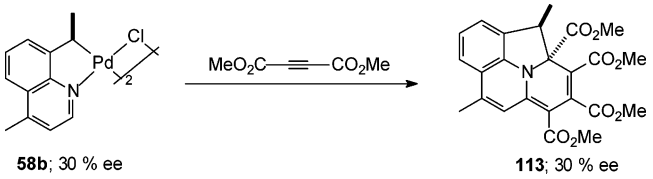
Scheme 28. CO Insertion into the Pd−C Bond



3.6.2. Stoichiometric Carbon Monoxide and Alkyne Insertions

Stoichiometric processes are known where the stereochemical integrity of the starting palladacycle is passed on to the product, another consequence of the metal remaining in the chiral environment, such as carbonylations (Scheme 28).[89a] Disubstituted alkynes readily insert into the Pd−C bond of planar chiral palladacycles with both mono- and di-insertions being observed (Scheme 29).[119] Enantioenriched **58b** reacts with DMAD, via a double alkyne insertion, to afford an enantioenriched [2.3.3] cyclazine product. Whether the initial alkyne insertion into the Pd−C bond involves retention or inversion of stereochemistry is still unknown, although the fact that the product is not racemic does point to a concerted mechanism (Scheme 30).[76]

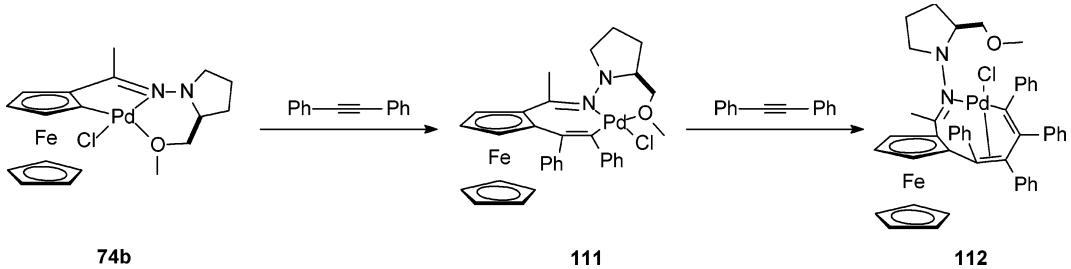
Scheme 30. Double Alkyne Insertion and Heteroannulation



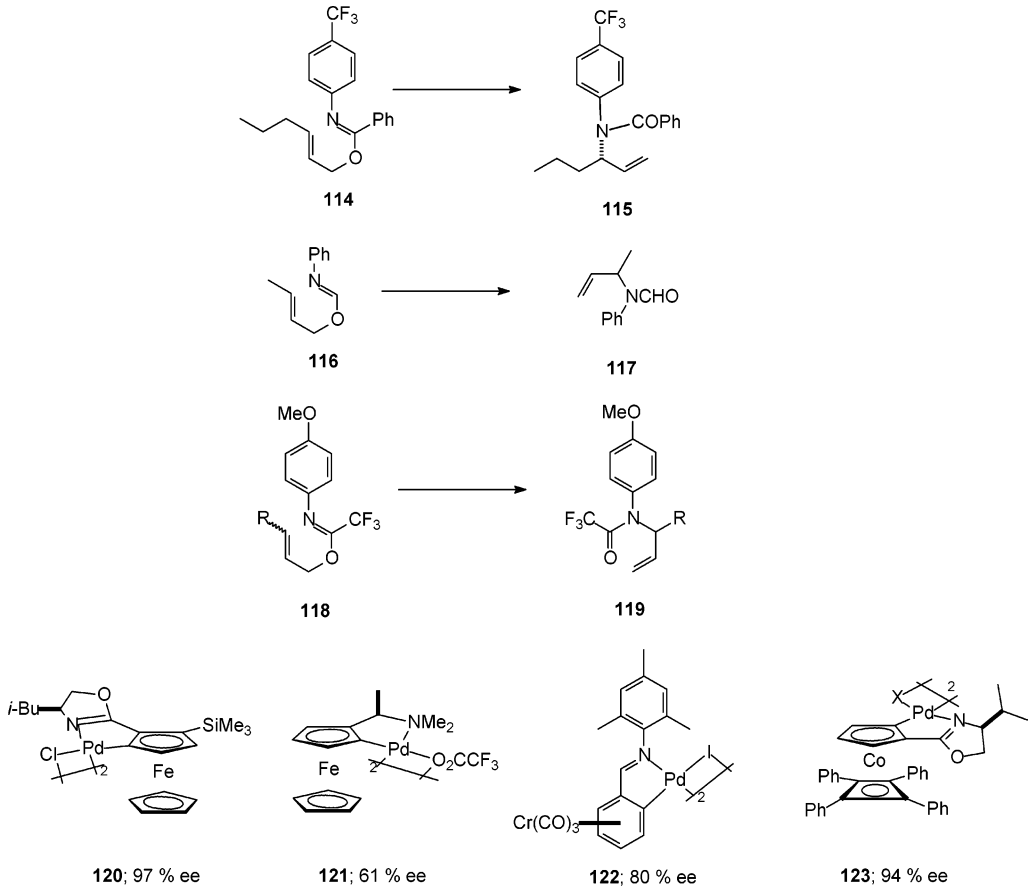
3.6.3. Catalytic Allylic Rearrangements

Overman's group have used homochiral cyclopalladated complexes for enantioselective catalysis, notably allylic rearrangements. This process is assumed to be via an associative mechanism with an axial approach of the olefin to the square planar palladium environment. Planar chiral palladacycles have consequently been very successful catalysts leading to a high degree of stereodifferentiation; e.g., the oxazoline derivative **120** catalyzed the transformation of **114** to **115** in 97% ee whereas the chromium-containing complex **122** led to **115** in 80% ee (Scheme 31).[120] However, complexes such as **63** were found to afford relatively poor ee's, e.g., 10% ee for the rearrangement of **116** to **117**, although **81** (10 mol %) led to a respectable 79% ee.[121] The novel cyclo-

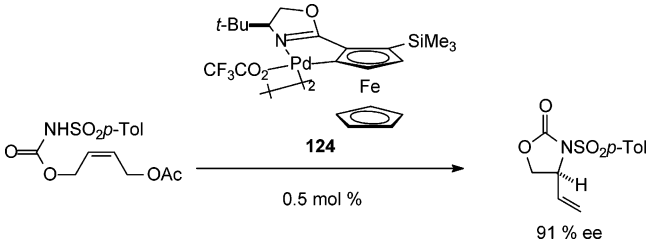
Scheme 29. Alkyne Mono- and Di-insertions



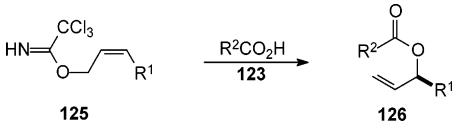
Scheme 31. Allylic Rearrangements Mediated by Cyclopalladated Complexes



Scheme 32. Oxazoline Palladacycle Catalysts for Intramolecular Aminopalladations



Scheme 33. Variant of the Asymmetric Allylic Imidate Rearrangement



butadiene-cobalt-containing analogue **123** conferred high enantioselectivities in allylic rearrangements leading to protected allylic amines.[122] Monomeric COPs (COP = cobalt oxazoline palladacycle) are more soluble than their chloro-bridged analogues and as effective in allylic rearrangements.[123] Other oxazoline-containing palladacycles, including **124** (Scheme 32), were excellent catalysts for intramolecular aminopalladations, achieving ee's over 90%.[124] Asymmetric allylic imidate rearrangements involving **125** and promoted by palladacycle **123** afford chiral allylic esters in nearly quantitative yield and excellent ee's (up to 99%) (Scheme 33).[125]

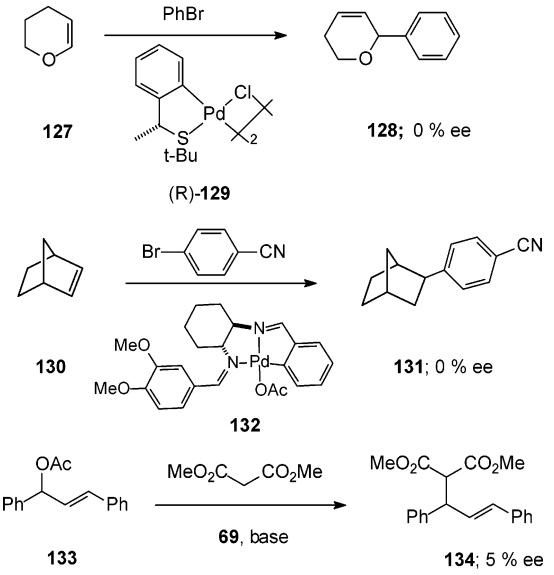
3.6.4. Catalytic C–C Bond-Forming Reactions

Heck reactions such as the formation of **128**, catalyzed by the homochiral palladacycle **129**, were found to proceed with zero enantioselectivity.[84] A similar observation was found for hydroarylations, as in the formation of **131**.[126] In these two cases, after activation, the Pd(0) catalyst is no longer bound to the chiral ligand. For allylic alkylations, poor enantioselectivity was observed, as in the formation of **134** (Scheme 34), and the authors proposed that the similarity of the substituents on phosphorus in the catalyst **69** may account for the poor stereodifferentiation.[85]

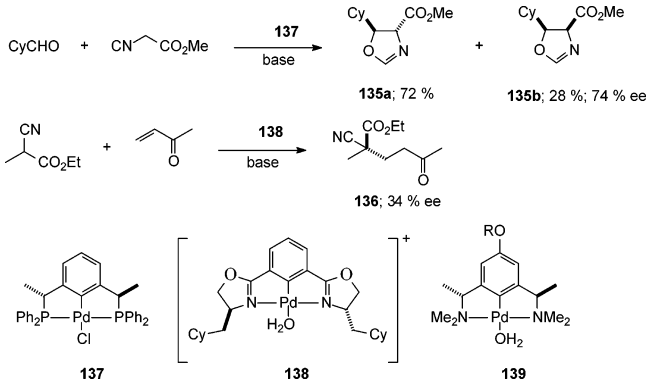
Palladacycles have also been employed as chiral Lewis acids (Pd(II) intact) for aldol- and Michael-type chemistry with reasonable success in terms of asymmetric induction (Scheme 35). The bisphosphine pincer complex **137** catalyzed the asymmetric aldol reaction between methyl isocyanoacetate and aldehydes, with, notably, a 74% ee for **135b**. With the related pincer **139**, only an 12% ee was observed.[127] The NCN pincer **138** catalyzed a Michael addition reaction affording **136** with 34% ee.[128]

Pincer complexes incorporating chiral hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolone chelating groups **140** have been synthesized via a remarkable condensation/ligand exchange process on a bis-(triphenylphosphine)-bound diformylarylpalladium precursor. These were shown to be impressive catalysts in Michael addition chemistry with ee's attaining 83% (Scheme 36).[129]

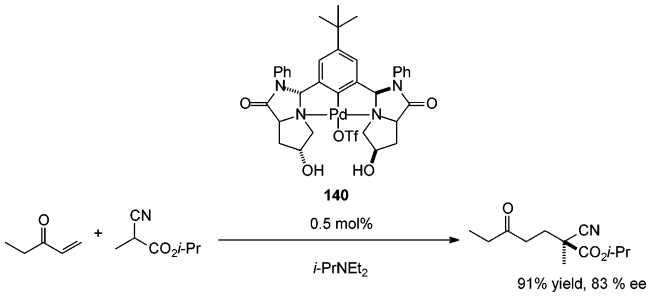
Scheme 34. Poor Enantioselectivity in Pd-Catalyzed C−C Bond Formations



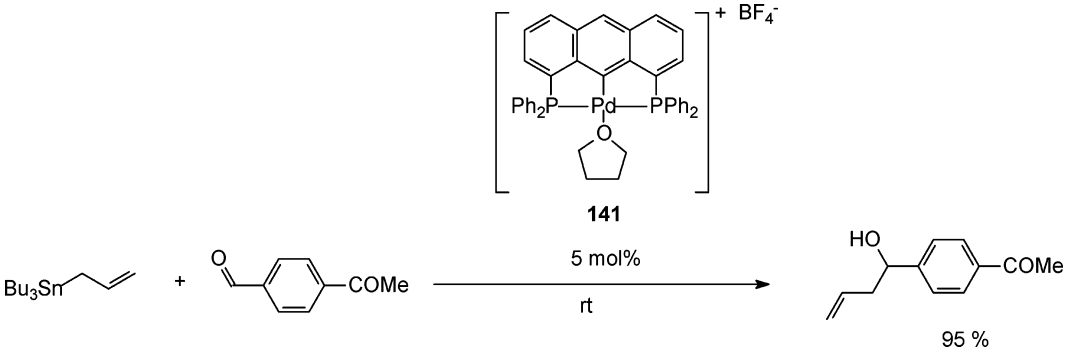
Scheme 35. Asymmetric Aldol and Michael Reactions Catalyzed by Palladacycles



Scheme 36. Asymmetric Michael Addition Promoted by Palladacycle 140

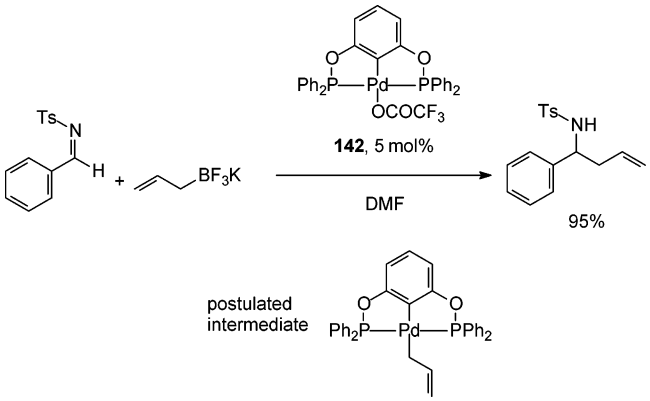


Scheme 37. Addition of Allylstannanes to Aldehydes



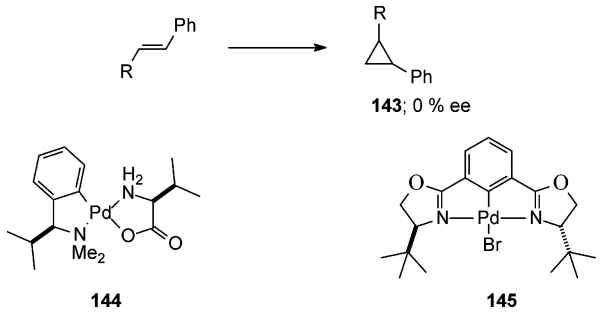
PCP pincer complexes catalyzed the addition of allylstannanes to aldehydes and imines, affording chiral, racemic products, with the advantage that few side products are formed, since the reactions proceed via monoallyl-Pd intermediates (Scheme 37).[130] The palladium pincer complex **142** catalyses the allylation of tosylimines with borate salts, showing that organotin substrates can be efficiently replaced by allylborates.[131] *Racemic products were obtained, although there is potential for chiral induction by, e.g., the use of ferrocenyl (planar chiral) analogues of* ***141*** *or* ***142*** *(Scheme 38).*

Scheme 38. Allylation of Tosylimines Promoted by Palladacycle 142

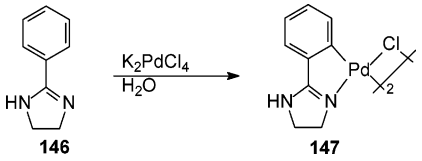


Cyclopropanation reactions have also been reported, yielding racemic product (Scheme 39). When using a menthol-containing diazoacetate starting material, de's reached only 20%. Dissociation from the chiral ligand through activation of Pd(II) to Pd(0) may explain this lack of enantioselectivity.[132,133]

Scheme 39. Cyclopropanations Catalyzed by Palladacycles



Scheme 40. 2-Phenylimidazoline-Derived Palladacycle



146 147

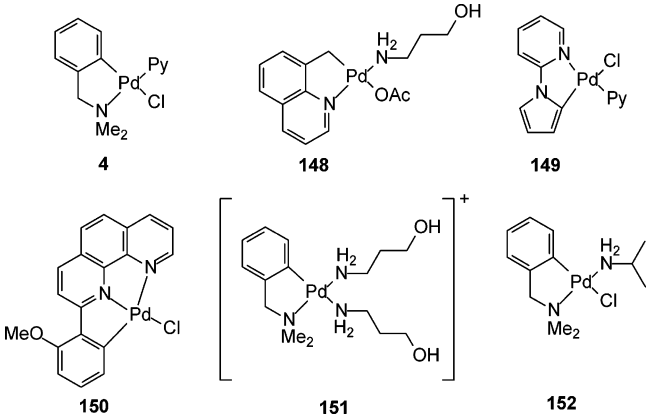
4. Palladacycles in Medicinal and Biological Chemistry

The success of *cis*-platin ($Pt(NH_3)_2Cl_2$) as an anticancer agent[134] has prompted chemists to investigate alternative metal-containing complexes as potential drug candidates,[135] especially since the former can give rise to toxic side effects and has a narrow spectrum of activity and tumor cells are known to develop resistance. Organometallic and transition metal complexes including palladacycles are indeed attracting attention as potential anticancer agents. *Due to the ease of synthesis, stability, and modular properties, with the potential for rapid library generation for structural activity studies and modifications of the physiochemical properties, it is hoped that this review may stimulate activity in this area as well as further investigation of the palladation of biologically relevant ligands*.

A number of reports have highlighted the potential of palladacycles as antineoplastic agents. These planar metal complexes can lead to possible alternative modes of cytotoxic action, such as intercalative DNA lesion, as opposed to the *cis*-platin-induced intrastrand guanine−guanine DNA lesion. For example, the 2-phenylimidazoline complex **147** (Scheme 40) was found to alter the T_m (melting temperature) of DNA, and further, DNA secondary structure modification was evidenced by circular dichroism. **147** had an $IC_{50} < 10\ \mu g\ mL^{-1}$ against HL-60 human leukemia cells (IC_{50} = inhibition constant; concentration of substrate leading to 50% inhibition of biological response).[136]

The structurally impressive complexes **4** and **148**−**152** (Chart 18) were formed by conventional C−H

Chart 18. Palladacycles Formed by CH Activation with Potential Biological Activity



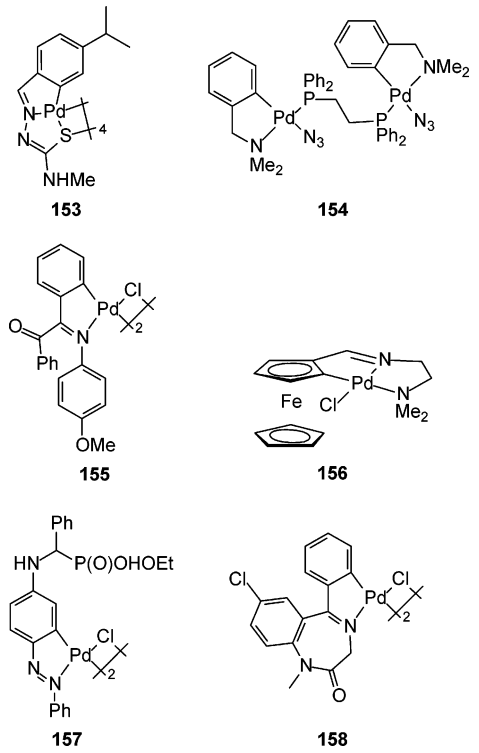
4 148 149

150 151 152

activation chemistry employing $Pd(OAc)_2$ or Li_2PdCl_4, followed by a bridge-splitting reaction by the addition of the appropriate amine. One rationale behind their synthesis was the good solubility profile imparted by the amine ligand, as the chloro dimers were often insoluble. The cationic complex **151** displayed poor cell permeability due to its low lipophilicity and positive charge. Complexes **4** and **148**−**152** were assessed for cytotoxicity against several different cancer cell lines in order to determine their differential cytoxicity, such that they are able to distinguish between cancer cells and normal healthy cells.[137] Most of the complexes displayed uniform cytoxicity across the cell panel, although complexes **4** and **152** were promising due to their 3−5-fold differential response between HT1376 and SW6020 cell lines. Furthermore, they bear little resemblance to *cis*-platin and may, hence, lead to different modes of cytotoxic action in terms of their DNA binding.

Other palladacycles assessed for anticancer activity or DNA-binding properties are displayed in Chart 19.

Chart 19. Other Palladacycles with Potential Biological Activity



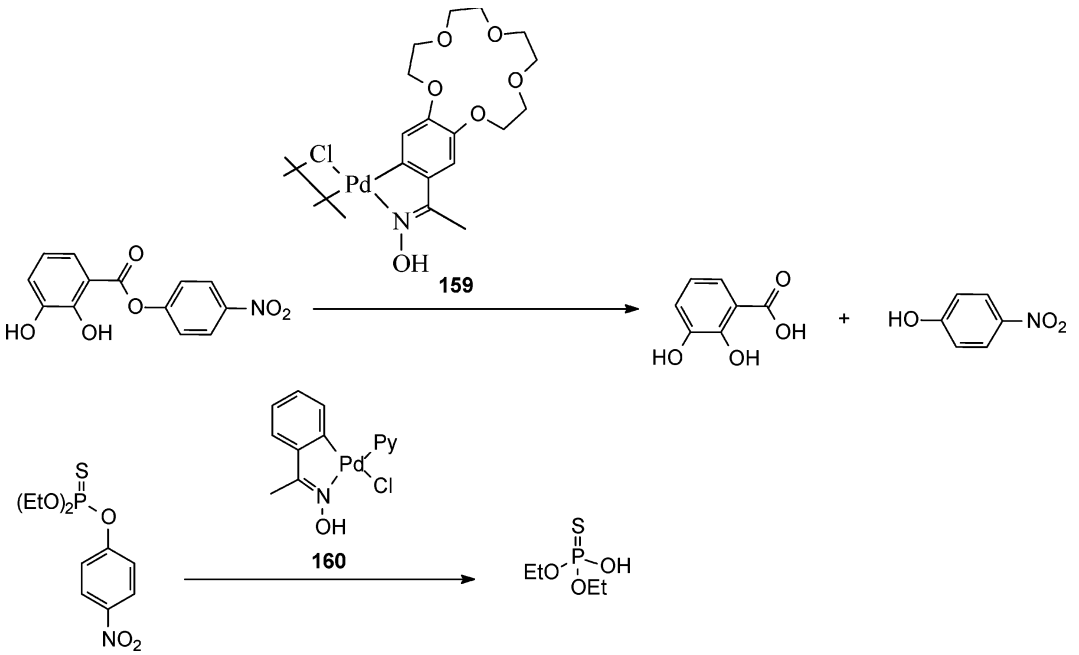
153 154

155 156

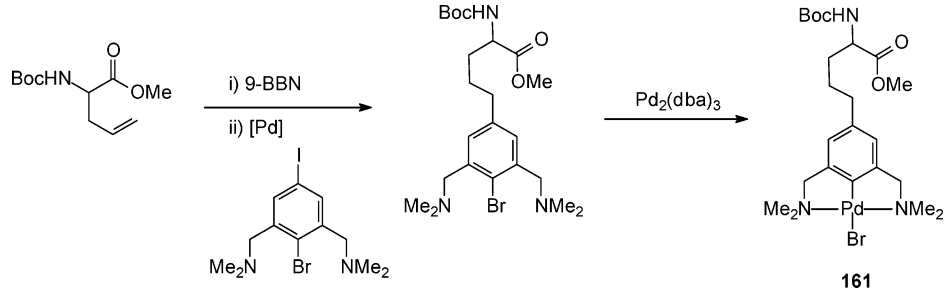
157 158

The tetrameric complexes **153** had micromolar activity against *cis*-platin-resistant cell lines and form DNA interhelical cross-links.[138] Dppe-coordinated complexes such as the dimethylbenzylamine dimer **154** had micromolar activity against human cancer cell lines, and some derivatives were tested in vivo, delaying tumor growth.[139] The cyclopalladated complex **155** was found to be significantly less potent than its platinum congener in terms of its antiproliferative behavior.[140] The ferrocenyl complex **156** displayed similar DNA-binding properties to those of *cis*-platin, evidenced by electrophoretic mobility studies.[141] The phosphonic acid derivative **157** had an IC_{50} of around 10^{-5} mol L^{-1} against a human KB cell line.[142] Complexes of medicinally relevant 1,4-benzodiazepin-2-ones have been synthesized, such as **158**,[143] although, surprisingly, no biological data have been reported (to our knowledge) for this

Scheme 41. Palladacycles Utilized for Biomimetic Hydrolysis of 4-Nitrophenyl Esters and Degradation of Thiophosphate Pesticide



Scheme 42. NCN Pincer Units Attached to Biological Scaffolds



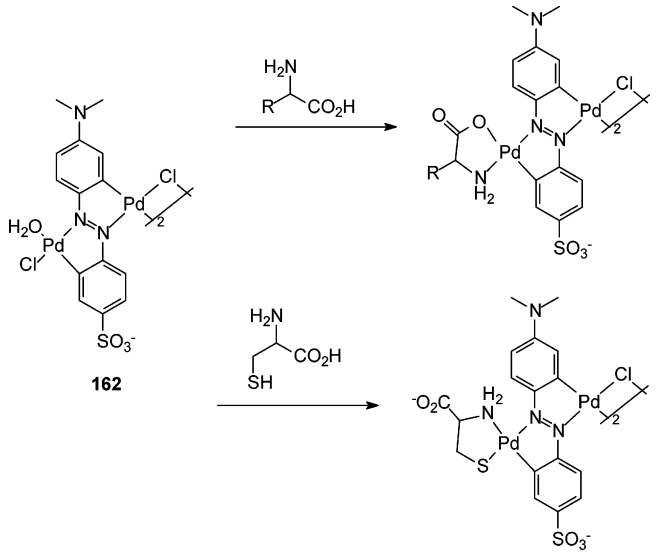
compound or for other palladacycles based on medicinally relevant heterocycles. This may merit further investigation.

A water soluble oxime-containing palladacycle was shown to effect a biomimetic (enzyme-like) hydrolysis of a 4-nitrophenol ester with a 120-fold rate increase compared with the uncatalyzed reaction.[144] Similar systems have also been used as green catalysts for the degradation of thiophosphate pesticides and neurotoxins (Scheme 41).[145] The same group has used the chiral palladacycle **63** for the enantioselective hydrolysis of amino acid analogues.[146]

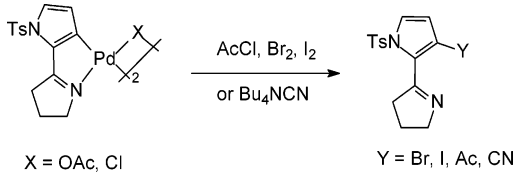
NCN pincer units can be attached to biologically relevant molecules such as amino acids via chemoselective Suzuki reactions. The organometallic units may be introduced thereafter into biomolecules in order to modify the properties of the pincer complex (e.g. nanosize, water solubility) or to use the resulting compounds as, e.g., color biomarkers for peptide libraries or for catalysis (Scheme 42).[147]

The palladium-azo complex **162** (Scheme 43) can be employed as a chromogenic sensor of amino acids in aqueous solution. The method is highly sensitive and can differentiate amino acids from complicated mixtures by virtue of the clearly distinguishable UV−vis spectra of the resulting complexes. Indeed, it has applications in the detection of specific amino acid residues such as methionine (in Alzheimer's disease) or for detecting a cysteine deficiency, implicated in liver damage and skin lesions, or in microscopy for protein detection. The coordination mode of amino acids to palladium atom is strongly dependent on the existence of donor atoms such as S, N, and O in the amino acid side chains.[148]

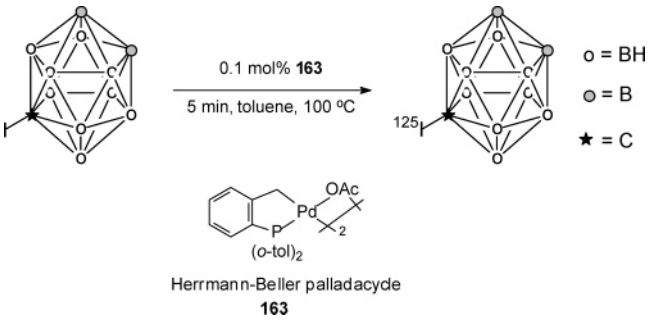
Scheme 43. Palladacycle as a Chromogenic Sensor



Scheme 44. Stoichiometric Functionalization of the Pd−C Bond



Scheme 45. Isotopic Iodine Exchange between [^{125}I] and I in Carboranes Using the Herrmann−Beller Palladacycle



5. Functionalization of Pd–C Bonds

5.1. Simple Functionalization

Stoichiometric functionalizations including acylations and isotope exchanges have been thoroughly covered in an earlier book and review.[1,3j] A few recent examples will follow: stoichiometric acylation, cyanation, and halogenations were carried out with cyclopalladated pyrroles (Scheme 44).[149] A highly impressive and general isotopic iodine exchange between [^{125}I] and I in various carboranes was developed using the Herrmann−Beller palladacycle in toluene without the need for quaternary ammonium salt stabilization (Scheme 45).[150] The rapidity and efficiency of this process signify that this may have medical applications as in boron neutron capture therapy.

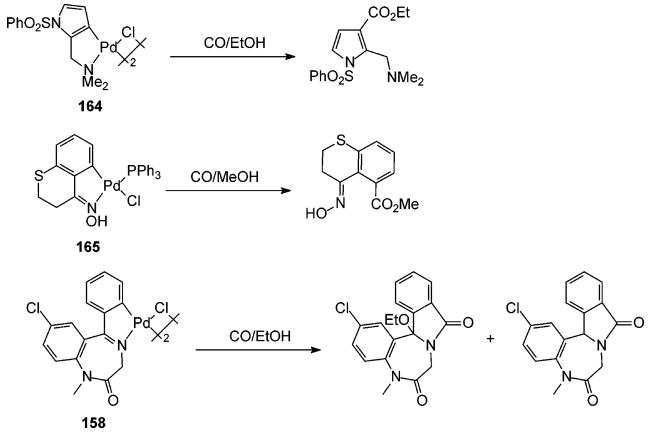
5.2. Carbonylations

The stoichiometric insertion of carbon monoxide into the Pd−C bond of palladacycles has been thoroughly investigated, and the outcome of the carbonylation reaction is influenced by many factors (e.g. temperature, solvent, size of the palladacycle ring, and nature of the ligands around palladium). In many cases, nucleophiles, including alcohols or amines, can be used to intercept the acyl−palladium intermediates (Schemes 46 and 47).[151]

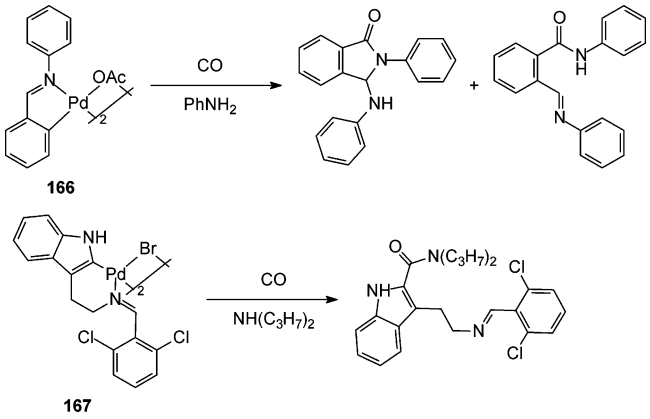
The carbonylation of palladacycles derived from the oxidative addition of 2-hydroxymethylbenzyl halides with $Pd(PPh_3)_4$ yields benzolactones in good yields (Scheme 48).[152] The structure of compound **168** was determined by an X-ray diffraction study and clearly indicates the coordination of the OH group to Pd(II). Isolation of the seven-membered palladacycle **169** shows unequivocally that the insertion of CO occurs into the Pd−C bond rather than the Pd−O bond.

In some instances, the attempted carbonylation process does not take place and a reduction process prevails. One unusual depalladation sequence led to

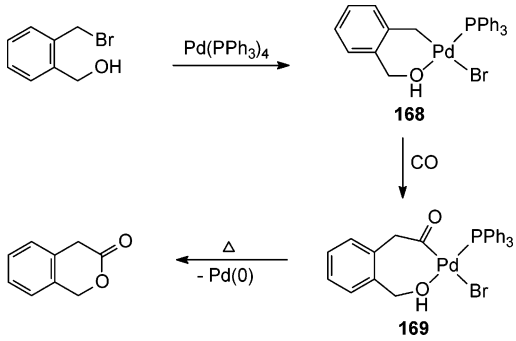
Scheme 46. Alkoxycarbonylation of Palladacycles



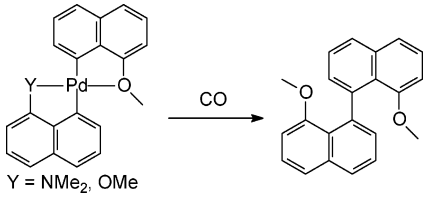
Scheme 47. Carbonylation of Palladacycles Employing Other Nucleophiles



Scheme 48. Carbonylation of Palladacycle 168



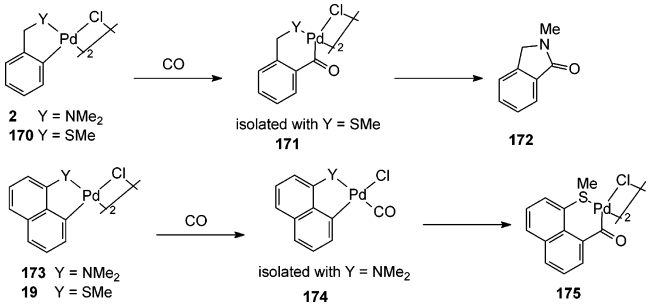
Scheme 49. Depalladation Sequence Leading to Biphenyl Formation



the formation of the symmetrical biphenyl, irrespective of whether the starting palladacycle was the symmetrical methoxy-bound analogue or the unsymmetrical amino-alkoxy-bound palladacycle (Scheme 49).[17]

In one study many important intermediates pertaining to the CO insertion mechanism were identified, which involves coordination of CO to palladium

Scheme 50. CO Insertion in Sulfur- and Nitrogen-Derived Palladacycles

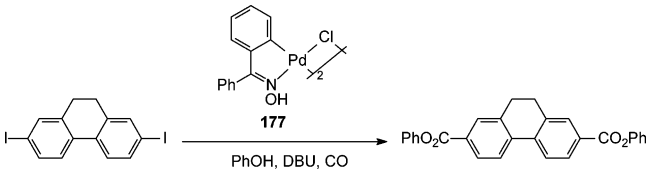


trans to the donor group, insertion in the Pd−C bond, and depalladation (Scheme 50).[153] For example, after removal of palladium black, a heterocycle, 2-methylisoindolin-1-one **172**, was isolated from the reaction of **2** with carbon monoxide in dichloromethane. However, in the case of the related thioether analogue, the enlarged palladacycle **171** was isolated, and such a reaction was reversible at 35 °C with no decomposition to metallic palladium. In the case of naphthyl analogues, the sulfur-bound palladacycle afforded the enlarged metallacycle **175** upon CO insertion, whereas, with its amino congener, a terminally bound carbonyl analogue **174** was obtained. It was concluded that CO insertion into sulfur-containing palladacycles was more facile than that for the corresponding amine congeners.

Catalytic room-temperature carbonylations have recently been developed; the aminocarbonylation of 2-iodobenzyl bromide was shown to proceed via initial nucleophilic substitution of the amine on the bromide prior to carbonylation, in the presence of the palladacycle **176**.[154] The latter was also shown to lead to Pd nanoparticle formation in the presence of CO, and the demetalated ligand and ketone were identified as the decomposition products in a stoichiometric reaction (Scheme 51).

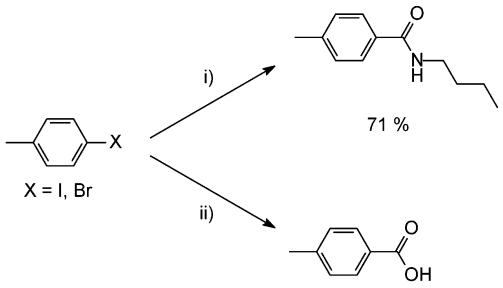
Oxime-containing palladacycles were employed for the carbonylation of aryl iodides, forming esters in excellent yields with TONs reaching 3905 and TOFs reaching 978. Dicarbonylations are especially attractive (Scheme 52).[155]

Scheme 52. Carbonylation of Aryl Iodides Promoted by Palladacycle 177



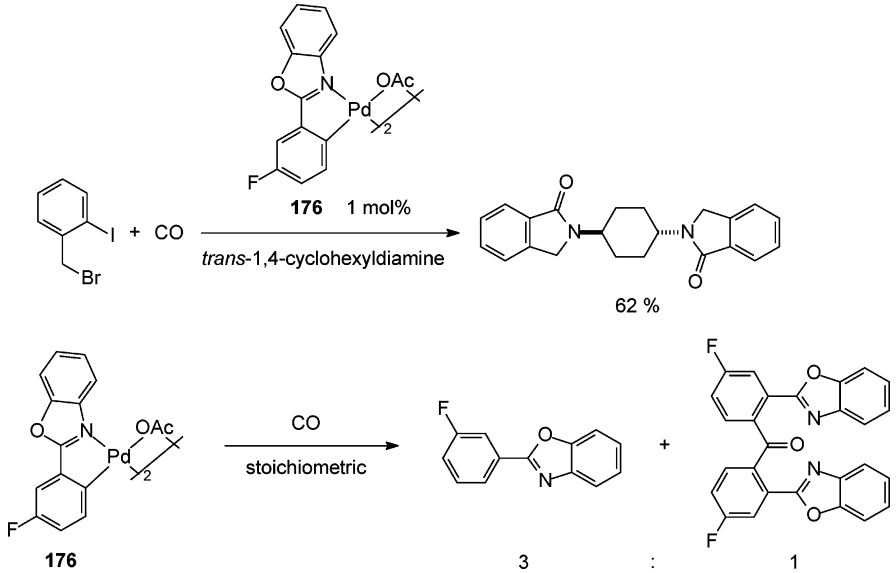
The incompatibility of carbonylation processes with the Herrmann−Beller palladacycle **163** has been reported.[3q] However, under microwave irradiation, using molybdenum hexacarbonyl as a source of CO, carbonylations and aminocarbonylations could be carried out using this catalyst along with *rac*-BINAP as a supplementary ligand (Scheme 53).[156]

Scheme 53. Herrmann−Beller Palladacycle in Carbonylation Reactions



Another very impressive process involves a catalytic CH activation using copper(II) as an oxidant, akin to a Wacker process, thus obviating the need for an aryl halide. A palladacycle intermediate has been proposed, and this assumption is supported by the high degree of regioselectivity attained when using the bis-chelating substrate **178** (Scheme 54).[157]

Scheme 51. Catalytic Room-Temperature Carbonylation Reactions Promoted by Palladacycles



Scheme 54. Catalytic CH Activation via a Palladacycle Intermediate

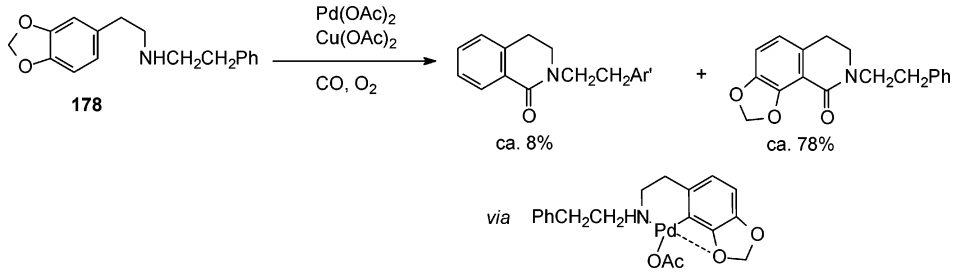
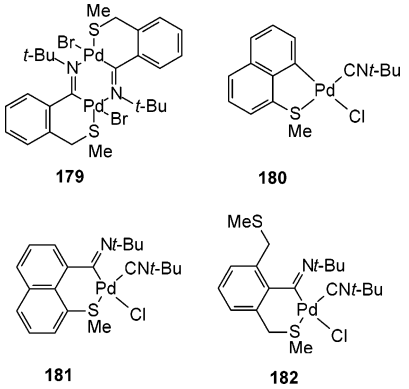
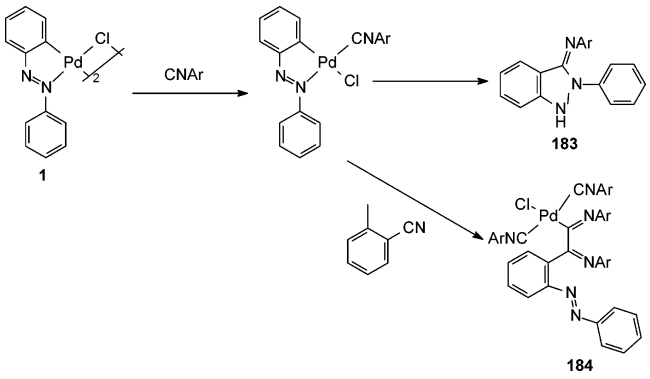


Chart 20. Palladacycles Resulting from Isocyanide Insertion or Coordination



Scheme 55. Isolated Species in Isocyanide Insertion Reactions



5.3. Isocyanides

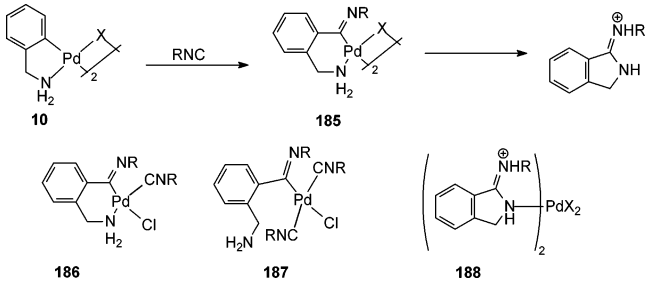
The behavior of isocyanides reflects that of the isoelectronic carbon monoxide in many instances. Organometallic complexes resulting from the monoinsertion and multiple insertion of isocyanides have been isolated, and in some cases these have been structurally characterized (Chart 20).[158] Heterocycles **183** or organometallic complexes **184** can be isolated depending on the conditions employed (Scheme 55).[159]

Isoindolinium salts were formed from the reaction of cyclopalladated benzylamine analogues with isocyanides (Scheme 56). A number of interesting species (**186**−**188**) were isolated during one study.[160] The same group has studied the insertion of isocyanides into the Pd−C bond of other arylpalladium complexes and characterized a remarkable palladacycle resulting from a triple isocyanide insertion and rearrangement (Scheme 57).[69c,161]

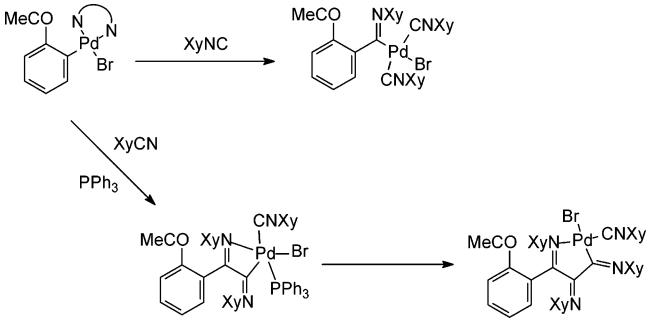
5.4. Allenes

Stoichiometric quantities of cyclopalladated tetralone ketimine **189** react with 1,1,-dimethylallene to

Scheme 56. Formation of Isoindolinium Salts in the Reaction of Cyclopalladated Benzylamine Analogues with Isocyanides



Scheme 57. Palladacycles Formed during Isocyanide Insertion into the Pd−C Bond



afford a mixture of heterocycles resulting from the nucleophilic attack of the imine nitrogen on both of the π-allyl terminals (Scheme 58). The kinetic product **190** is converted to the thermodynamic isomer **191** by reflux with catalytic amounts of a palladium complex.[162] Other heterocycles formed by this methodology are shown in Chart 21, and a second-order rate constant was found for this reaction.[163]

A library based on allene-insertion quaternary ammonium products shown in Chart 22 was tested for acetylcholine receptor binding. Compound **197** showed comparable activity to a reference compound with promise for future drug design.[164] Interestingly, since this study, the reaction of dimethylallene with palladacycle **200** was shown to afford **198** along with colloidal Pd that can be stabilized in imidazolium ionic liquids.[165] Catalytic versions of this heterocyclization are known, affording aromatic products when monosubstituted allenes are used (Scheme 59).[166]

Palladacycle-catalyzed cascade reactions are being increasingly employed for the synthesis of products with high degrees of complexity, including allene insertion−nucleophile incorporation reactions (Scheme 60).[167] This is also a powerful synthetic method for the synthesis of elaborated carbocyclic products (Scheme 61).[168]

Scheme 58. Heterocycles Formed during Allene Insertion into the Pd−C Bond of Palladacycle 189

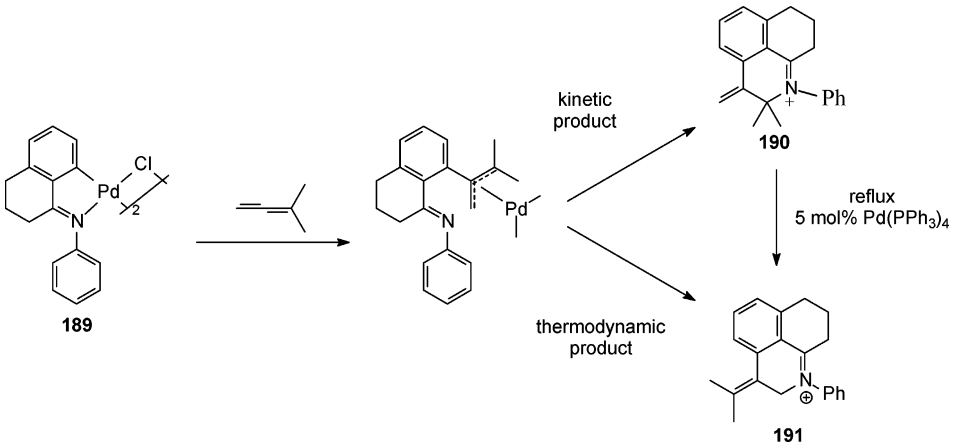


Chart 21. Other Heterocycles Generated by the Allene Insertion Reaction

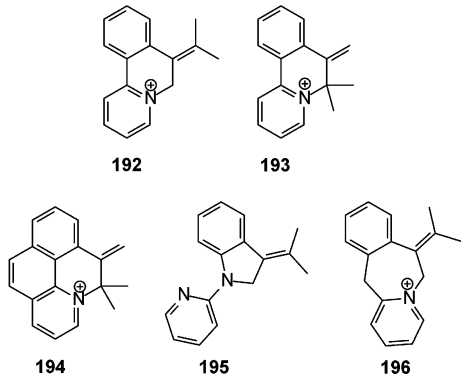
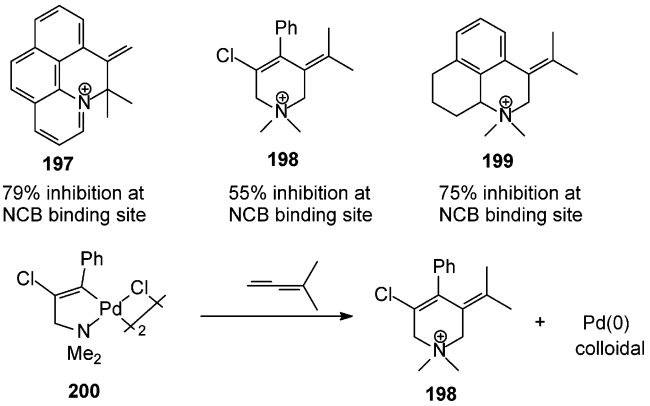


Chart 22. Inhibition at the NCB Binding Site

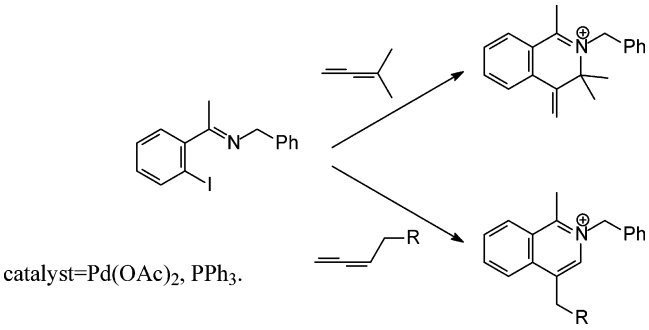


5.5. Diene and Alkene Additions

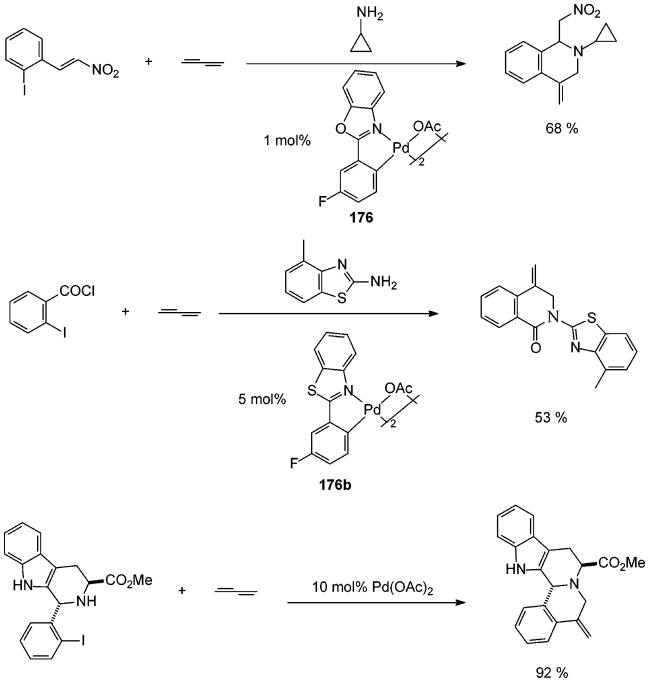
The intramolecular addition of tertiary amines to alkenes in the presence of stoichiometric quantities of Pd(II), as depicted in Scheme 62, can lead to heterocyclic products and proceeds via an allylic intermediate. In some instances, allylic and ortho C−H activations compete and a palladacycle can also be formed.[169]

Catalytic heterocyclizations involving the addition of a tertiary amine to a π-allyl intermediate have been developed using either an allyl acetate or a simple allylic starting material (Scheme 63).[170] Stoichiometric diene insertions also proceed via allylic

Scheme 59. Catalytic Heterocyclization Reaction



Scheme 60. Palladacycle-Mediated Cascade Reactions

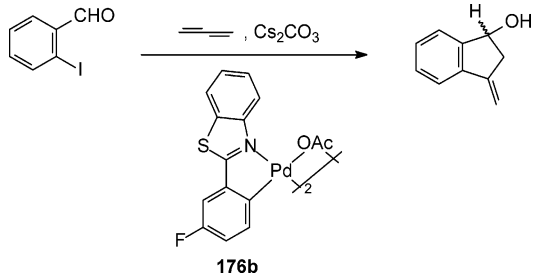


intermediates and lead to heterocycles when external ligands are employed such as PPh_3, to destabilize the organometallic intermediate (Scheme 64).[171]

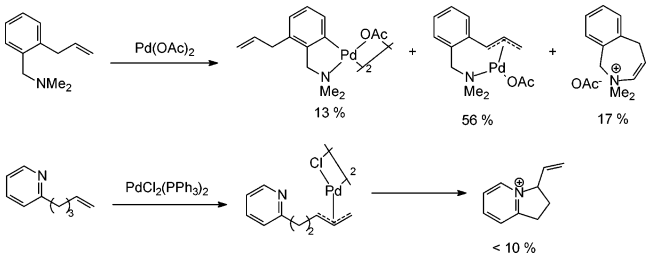
5.6. Alkynes

Internal alkynes can usually insert up to three times in the Pd−C bond of palladacycles depending on the conditions employed, the ligands around

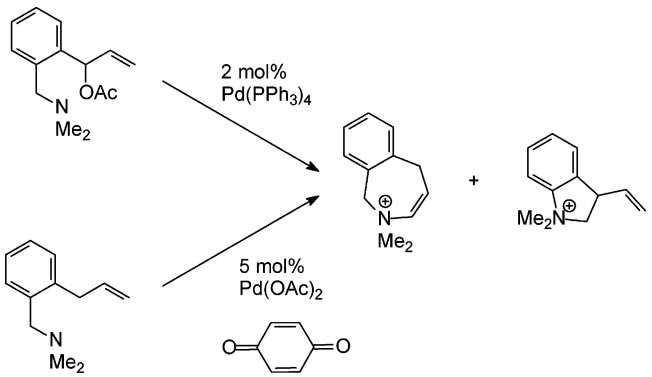
Scheme 61. Catalytic Intramolecular Nucleophilic Addition of Allene Promoted by Palladacycle 176b



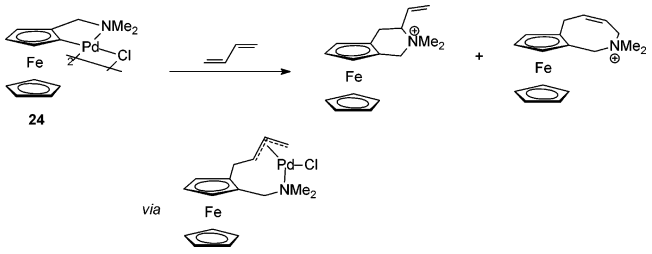
Scheme 62. Stoichiometric Intramolecular Addition of Tertiary Amines to Alkenes in Palladacycles



Scheme 63. Catalytic Heterocyclizations



Scheme 64. Stoichiometric Diene Insertion into Pd−C Bonds in Palladacycles



palladium, and the type of alkyne (Scheme 65). Intramolecular coordination to the metal is maintained in the resulting enlarged palladacycle. This is one of the most studied areas of palladacycle chemistry, and to avoid too much repetition, the reader is invited to refer to recent reviews of this chemistry,[3m−o] especially since triple-insertion chemistry will not be discussed hereafter.

For the initial insertion, theoretical and experimental studies have pointed to an η^2-preinsertion scenario as in Chart 23. Both structural and theoretical studies involving isolobal metallacarbynes have shown an alternative η^1 coordination mode of the carbyne to palladium.[172] From an early stage, the

Scheme 65. Alkyne Insertion into Pd−C Bonds in Palladacycles

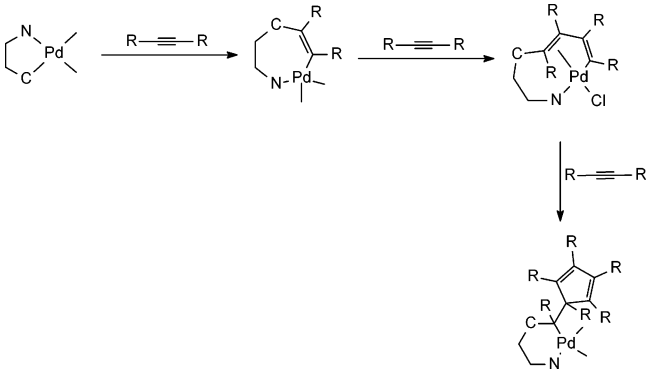
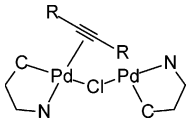


Chart 23. Postulated Intermediate in the Alkyne Insertion Reaction



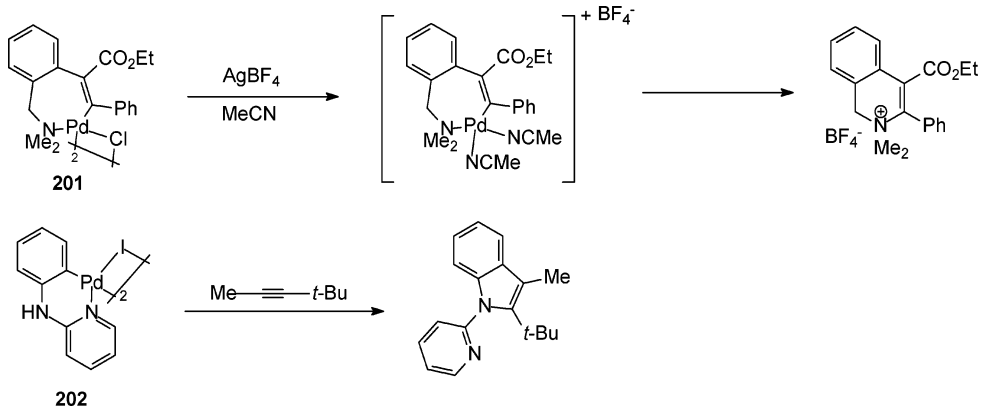
alkyne insertion process was found to be a useful method for the synthesis of heterocycles (Scheme 66). This often necessitates activation of either the starting palladacycle or the vinyl-palladated intermediate through the formation of the corresponding thermally labile iodo-bridged derivative or chloro bridge removal, often with a silver salt (the AgCl formed is removed by filtration) to yield a thermally labile monomeric cationic palladacycle. A high degree of regioselectivity is often observed when employing dissymmetric alkynes. As a general rule, the larger alkyne substituent, or the aromatic substituent, is found on the carbon adjacent to palladium in the vinyl-palladated metallacycle.[173] Other heterocycles formed via these stoichiometric heteroannulations are listed in Chart 24.[67,174]

Carbocyclic products have also been isolated from the reaction of a cyclopalladated *N*,*N*-dimethylbiphenylamine precursor with internal alkynes where it was assumed that the poor nucleophilicity or coordinating ability of the amine to palladium led to the formation of the spirocycle product (Scheme 67).[175] It is noteworthy that with the related SMe biphenyl analogues, where the thioether has a better coordinating ability to the metal, a heterocycle is formed.

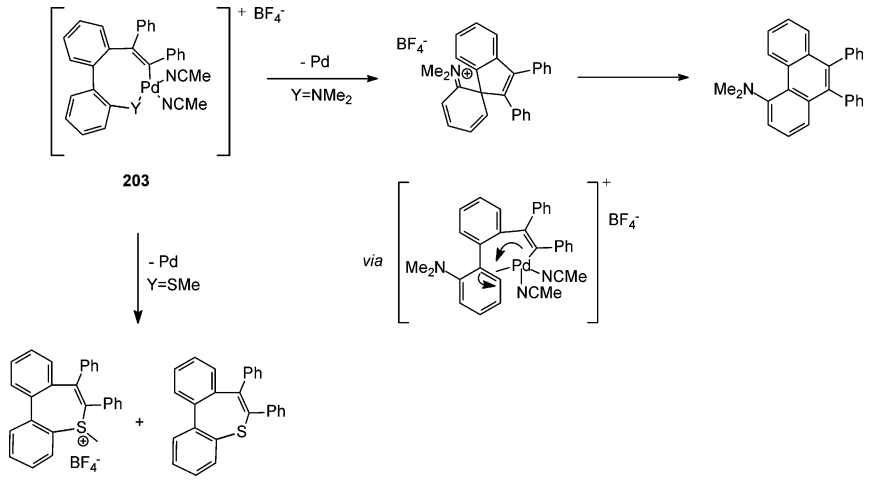
Indenones and indenols have been formed using stoichiometric or catalytic chemistry (Scheme 68).[3q,176] Precursors to the Aporphine skeleton and related isoquinolines were formed by the catalytic heteroannulation of tertiary amines with internal alkynes, with concomitant loss of methyl iodide, using palladacycle precatalysts.[177] Palladacycles were postulated intermediates in the heterocyclization of 2-iodoimine analogues (Scheme 69).

A variety of carbocyclic products can be synthesized by the double insertion of alkynes in the Pd−C bond of palladacycles. In the example outlined in Scheme 70, we can note the general *trans,cis*-geometry of the η^3-butadienyl fragment in compound **207**, adopted for maximal orbital overlap, achieved by a metallacyclic flip after the second alkyne insertion.[178] Often a strong nucleophile is employed, such as pyridine or

Scheme 66. Examples of Heterocycles Obtained by Alkyne Insertion Reactions



Scheme 67. Carbocycle versus Heterocycle Formation Depending on the Donor Group



Scheme 68. Indenones Formed Using Stoichiometric and Catalytic Alkyne Insertions

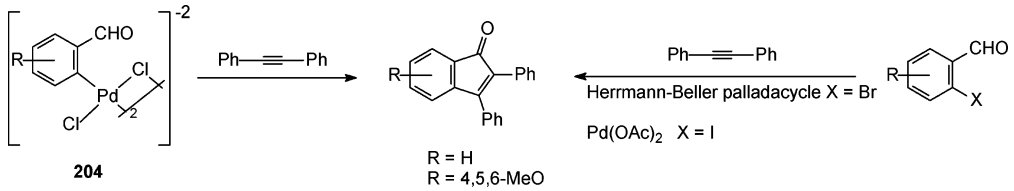
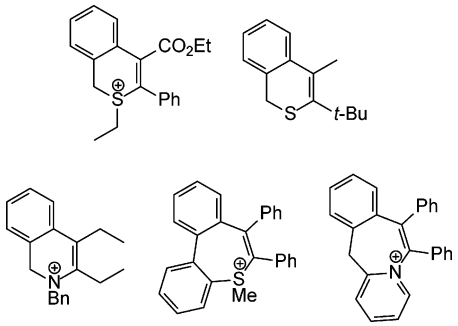


Chart 24. Other Heterocycles Obtained by the Alkyne Insertion Reaction



triphenylphosphine, to destabilize the metallacyclic framework, yielding organic products.[179]

Other unusual products obtained using similar methodology are outlined in Chart 25.[24,180] Spirocyclic intermediates and η^2-coordinated palladium complexes have often been proposed and, indeed, in some cases isolated, to rationalize the formation of some of the carbocyclic products (Chart 26).[181] The reaction of the monoinsertion complex **208** with a range of internal alkynes leads to cycla[2.3.3]zines and is believed to proceed via a carbene intermediate (Scheme 71).[182] Other interesting heterocyclic products can also be formed from the depalladation of η^3-butadienyl palladacycles (Chart 27).[183]

6. Palladacycles as Catalyst Precursors

6.1. General Remarks

The use of palladacycles as catalyst precursors is relatively recent, with the first applications being reported in the mid-1980s with the hydrogenation of C=C bonds by a cyclopalladated triphenyl phosphite,[184] followed by the use of cyclopalladated azobenzenes, hydrazobenzenes, or *N*,*N*-dimethylbenzylamine in the selective reduction of nitro-aromatic compounds, nitro-alkenes, nitriles, alkynes, alkenes, and aromatic carbonyl compounds.[185] However, it was not until the first report on the synthesis and applications in catalytic C−C coupling reactions of the palladacycle derived from the cyclopalladation of tris-*o*-tolylphospine[186] **163** that the rich chemistry of

Scheme 69. Heterocycles Formed by the Catalytic Heteroannulation of Tertiary Amines with Alkynes Using Palladacycle Precatalysts

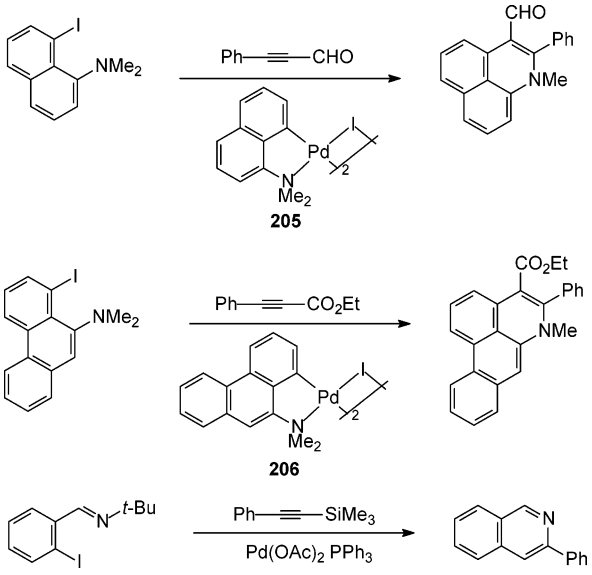
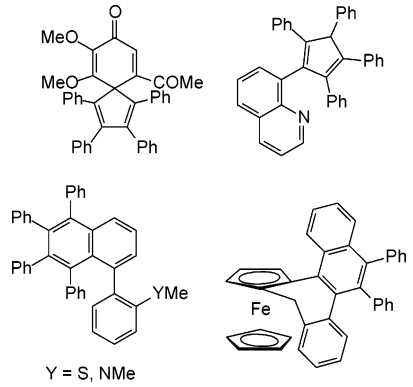


Chart 25. Other Heterocycles Generated by Double Alkyne Insertion into Pd−C Bonds in Palladacycles



these organo-palladium compounds received renewed interest, which still continues to flourish. Doubtless, there have been hundreds of reports over the last five years on the use of known and new palladacycles as catalyst precursors for C−C coupling reactions, in particular of the Heck- and Suzuki-type. *However, in the vast majority of these cases the palladacycles serve as a reservoir of catalytically active Pd(0) species,* and this behavior was recently addressed in an outstanding review[3z] together with specialized reviews on the use of palladacycles in catalysis. Therefore, it would be of little use to include these aspects herein, and we have, hence, decided to address the points that have been not covered in the recently published reviews[187] and/or can give a more in-depth approach on the mechanistic aspects of these C−C coupling reactions based on more recently published results as well as other palladacycle-mediated reactions.

Chart 26. Spirocyclic and η^2-Coordinated Intermediates Isolated during Alkyne Insertion Reactions

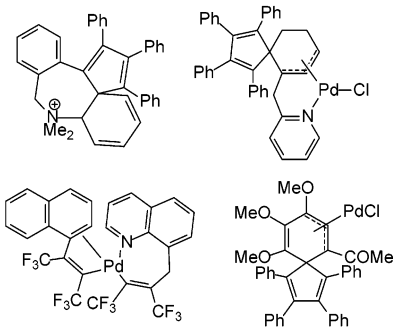
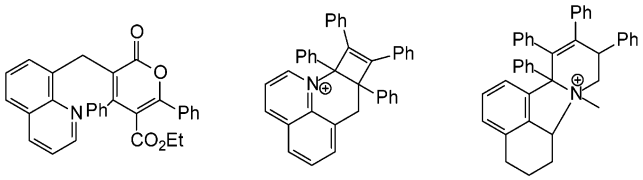


Chart 27. Heterocycles Formed from the Depalladation of Butadienyl Palladacycles



6.2. Heck Coupling

As already pointed out, since the introduction of the Hermann−Beller catalyst **163**, a commercially available robust and effective catalyst for the arylation of alkenes, a plethora of cyclopalladated compounds have been successfully used in this C−C coupling reaction. In fact, almost any palladacycle can promote the coupling of iodo and bromo arenes with alkenes at relatively elevated temperatures, often combined with a base and an additive such as tetrabutylammonium bromide (Chart 28). TON num-

Scheme 70. Heterocycles Generated by Double Alkyne Insertion into Pd−C Bonds in Palladacycles

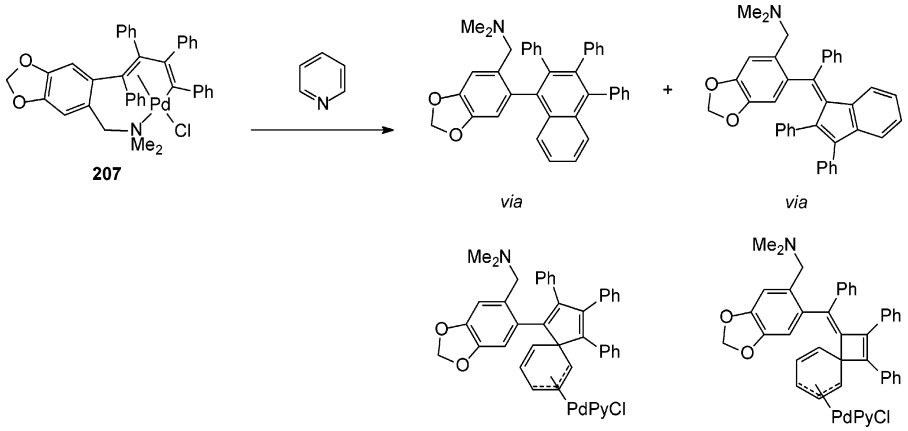
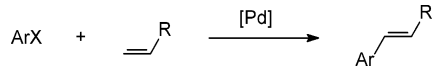


Table 1. Catalytic Performance of Palladacycles That Promote the Heck Coupling between Styrene or *n*-Butylacrylate and Aryl Chlorides (or an Aryl Iodide at Room Temperature)



entry	palladacycle	[Pd] (%)	R	Ar−X	*T* (°C)	*t* (h)	yield (%)	TON	ref
1	**211**	1.0	CO_2n-Bu	MeO-4-C_6H_4Cl	140	20	100	100	194
2	**129**	0.01	CO_2n-Bu	NO_2-4-C_6H_4Cl	170	2	49	4900	197
3	**200**	0.01	CO_2n-Bu	NO_2-4-C_6H_4Cl	150	24	100	10000	196
4	**212**	0.5	CO_2n-Bu	NO_2-4-C_6H_4Cl	130	8	93	186	193
5	**29**	0.67	CO_2n-Bu	C_6H_5Cl	180	24	99	147	27
6	**212**	0.5	Ph	C_6H_5Cl	160	24	60	120	193
7	**200**	1.0	CO_2n-Bu	C_6H_5I	RT	24	100	100	196
8	**213**	0.0023	Ph	Ac-4-C_6H_4Cl	150	24	75	32609	195
9	**214**	0.5	CO_2n-Bu	NO_2-4-C_6H_4Cl	140	15	89	178	198

Scheme 71. Proposed Carbene Intermediate in Cycla[2.3.3]zine Synthesis

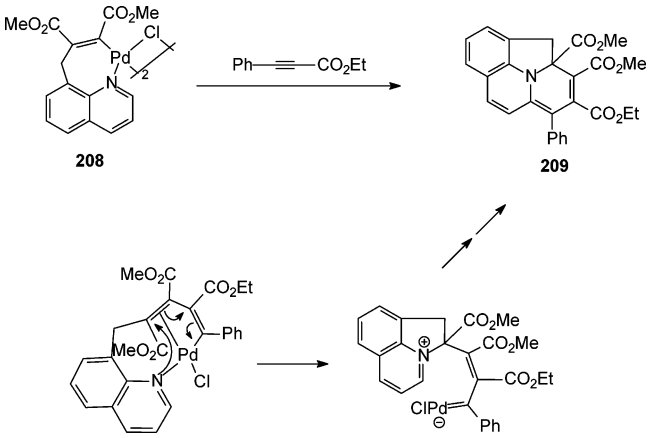


Chart 28. Herrmann−Beller, Milstein, and Dupont CP, NC, and CS Palladacycles, Respectively

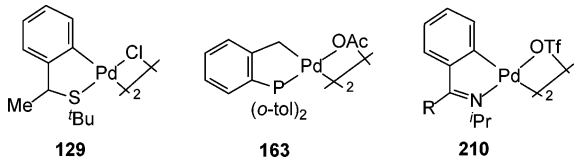
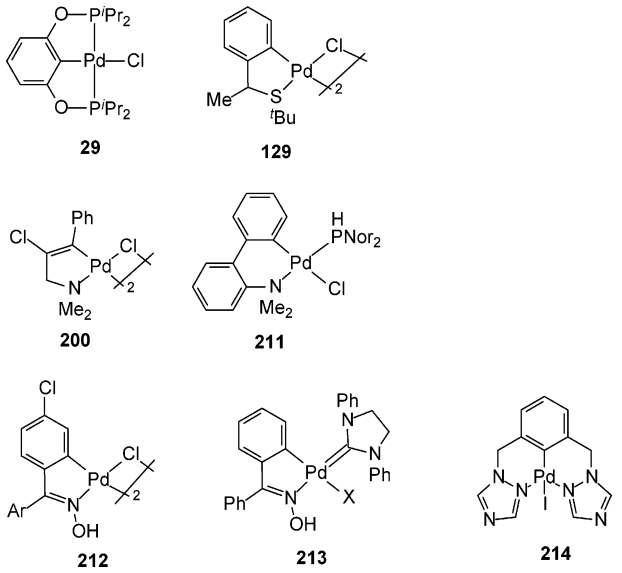


Chart 29. Efficient Palladacycle Catalyst Precursors That Promote the Heck Coupling Involving Chloroarenes (or Aryliodides at Room Temperature)

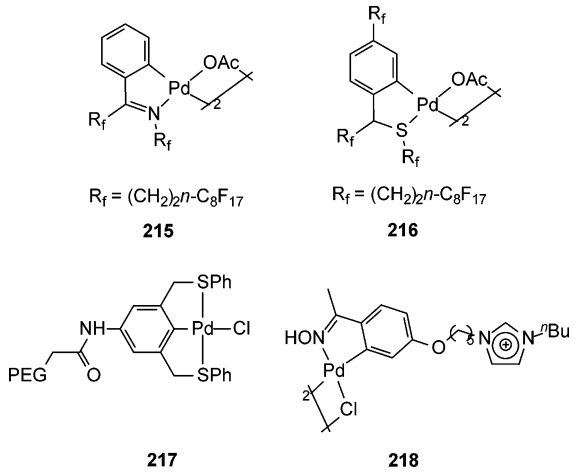


bers in these cases are usually on the order of 10^4−10^6 cycles, under homogeneous, supported, or two-phase conditions. Therefore, existing or new cyclopalladated derivatives (monomers, halogen- or acetate-bridged dimers, pincers) are known to catalyze the Heck coupling reaction. *However, it is well-known that under the reaction conditions used (temperatures above 100 °C) even palladium ultratraces in reaction vessels* promote the coupling of iodo and bromo arenes.[188] In this respect palladacycles are most likely to serve as a reservoir of catalytically active Pd(0) species that are similar to those formed in the denominated phosphine-free catalytic systems, and the reaction most probably follows the classical Pd(0)/Pd(II) catalytic cycle.[189] The catalytic activity differences observed with these different palladacycle precursors have been rationalized in terms of catalyst preactivation.[190] It has been proposed that the key step in these cases is the slow release of a low-ligated active Pd(0) species. *Therefore, the most efficient palladacycles will be those where the release of active Pd is neither too fast (typical of poorly thermally stable palladacycles that preferentially result in the formation of inactive metallic palladium) nor too slow (typical of thermally robust palladacycles, which would require higher temperatures to start the reaction in order to maintain a reasonable reaction rate).*[3z]

There are only a few examples of Heck reactions involving chloroarenes[191] promoted by palladacycles, and in most of these cases the reaction conditions use temperatures above 150 °C in molten salts and give similar results to those for a simple $PdCl_2$ salt in terms of yields and TONs.[192] Of note is the remarkable catalytic activity observed in the high-temperature Heck coupling of aryl chlorides with styrene with a cyclopalladated oxime **212**,[193] a pincer phosphinito palladacycle **29**,[27] or CN-palladacycles associated with bulky and electron-rich phosphines **211**[194] or carbenes **213**[195] (Chart 29). Moreover, there is only one example of a palladacycle that catalyzes the Heck coupling at room temperature (palladacycle **200**, Chart 22),[196]and in this case the chloropalladated propargylamine acts as a reservoir of catalytically active Pd(0) species. Other examples are given in Table 1.[197,198]

Some attempts have been made in order to transform highly active catalyst into biphasic systems where the catalyst can be easily separated and reused, including the introduction of imidazolium moieties in order to immobilize these complexes[199] in imidazolium-based ionic liquids.[200] However, leaching of palladium from the solid support to solution was

Chart 30. Modified Palladacycles Designed for Biphasic Catalysis



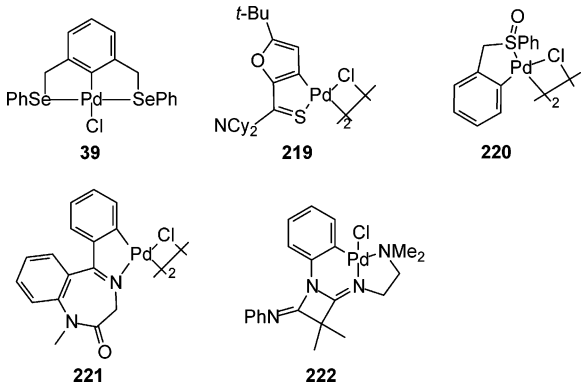
observed, and a significant amount of catalytic activity was assigned to palladium dissolved in the reaction solution. It has also been demonstrated that SCS pincer palladacycles can be covalently bound to a PEG polymer and used as catalytic precursors for the Heck reaction of iodoarenes and -alkenes. The catalyst can be reused up to three times without loss of catalytic activity, and no deactivation processes were observed by the authors.[201,202] However, detailed mechanistic studies indicated that in these cases the SCS palladacycles are actually reservoirs of catalytically active Pd(0) species.[203]

Gladysz's group exploited the temperature-dependent miscibility of palladacycles containing perfluoro chains in organic solvents and recently reported a highly efficient palladacycle catalyst precursor for the Heck reaction. However, the palladacycles act mainly as sources of highly active palladium colloids, as demonstrated by TEM analysis of the reaction samples.[204,205]

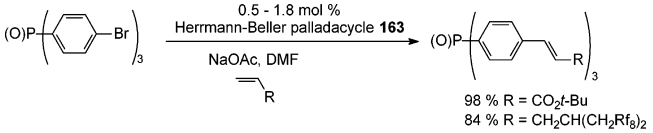
Other attempts to design heterogeneous Heck reactions include immobilization of the palladacycle in polymers,[206−208] MCM-41 mesoporous materials,[209,210] and silica.[211] The reaction can also be performed under biphasic conditions using ionic liquids[212] or H_2O[213] as solvents (Chart 30). In a polystyrene-immobilized imine−palladacycle system, no recyclability was observed in Heck chemistry involving iodobenzene and styrene.[214] However, the filtrate was found to have activity suggesting slow release of the true Pd(0) catalyst. A polystyrene-supported Herrmann−Beller palladacycle has also recently been disclosed, which can be reused six times when employing triethylamine as base.[208] *We can note, however, that iodo substrates, activated bromides, and/or relatively high palladium levels are often employed in these studies, which is somewhat different from the case when the actual catalyst precursor is employed in solution in homogeneous catalysis. A critical appraisal of the different approaches has been disclosed, which suggests that, in many of the cases, Pd(0) released from the solid support is probably the true catalyst.*[3t]

There is continuing interest in the synthesis of new palladacyclic systems and their evaluation in various

Chart 31. Palladacycles Used as Catalyst Precursors for the Heck Reaction



Scheme 72. Heck Reaction of Bromo-Substituted Phenylphosphine Oxides



catalytic model systems, many of which have been recently disclosed (Chart 31).[37,215] However, some groups are, unfortunately, in our opinion, still using electron-poor (activated) aryl bromides, such as 4-bromonitrobenzene, to test the effectiveness of palladacycles.[216] *At the very least, an electron-rich aryl halide such as 4-bromoanisole should be used as a benchmark substrate in the Heck reaction.*

Heck-type reactions employing palladacycles are gratifyingly not limited to simple substrates, and many recent examples will follow in order to illustrate their expanding synthetic scope. For example, functionalized arylphosphine ligands can be formed starting from bromo-substituted phenylphosphine oxides (Scheme 72). The products were formed with varying steric and electronic properties and were also capable of attachment to solid surfaces for immobilization[217] or for use as "ponytails" and "split pony tails" in fluorinated solvents.[218]

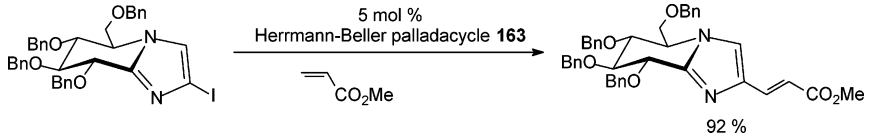
Improved yields for a Heck coupling were obtained when using the Herrmann−Beller palladacycle as in the synthesis of an imidazole derivative (Scheme 73).[219]

Double Heck reactions, one intermolecular process followed by an intramolecular process, were achieved using the Herrmann−Beller palladacycle along with 2,2′-dibromoaryls and ethyl acrylate (Scheme 74).[220]

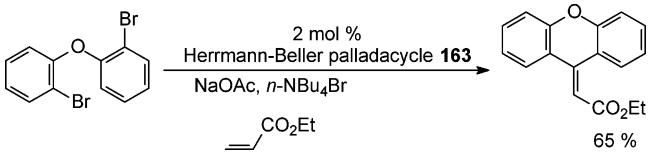
Heterocycles can be formed by intramolecular cyclizations mediated by palladium-based catalysts, for which **163** was found to be superior. The formation of regiomeric products can be suppressed by using symmetrical starting materials or by using a blocking group to avoid formation of the unfavorable product (Scheme 75).[221]

Domino Heck processes employing allylsilanes were mediated by the Herrmann−Beller palladacycle at high temperatures, and this impressive reaction led to carbocycles of varying, size as can be seen in Scheme 76. Systems based around $Pd(OAc)_2/PPh_3$ were unsuitable at higher temperatures, as they decomposed to palladium black.[222]

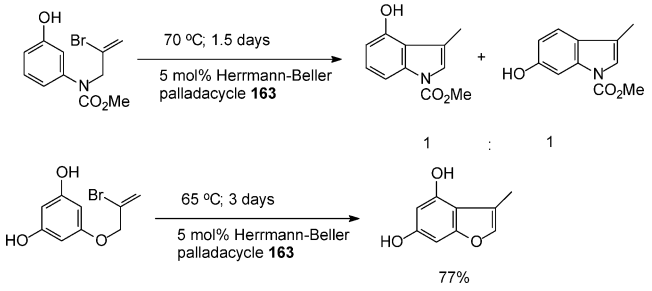
Scheme 73. Heck Reaction in the Production of Functionalized Imidazoles



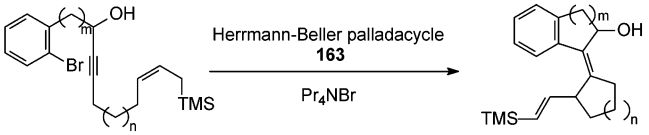
Scheme 74. Double Heck Reaction



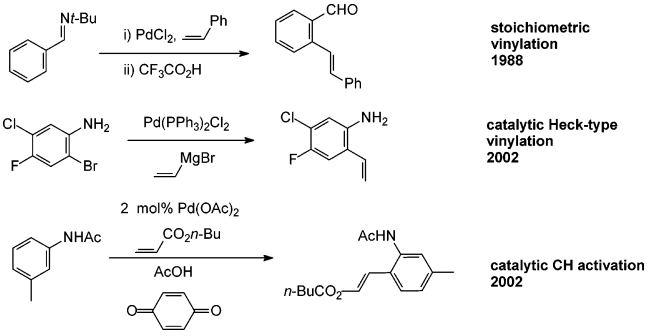
Scheme 75. Heterocycles by Intramolecular Cyclization



Scheme 76. Domino Heck Reaction Employing the Herrmann−Beller Palladacycle



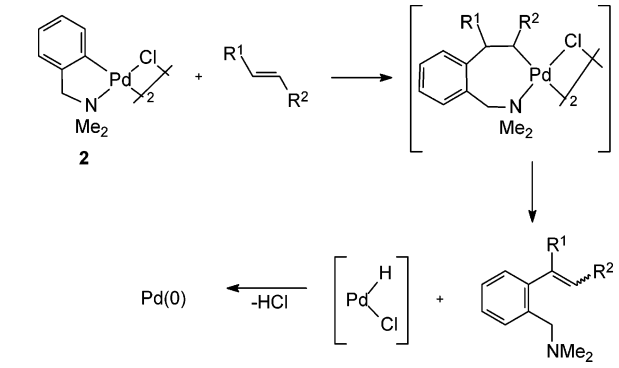
Scheme 77. Vinylation Reactions



Chemists are increasingly employing catalytic CH functionalization methods,[223] which are very attractive from an atom economy point of view (Scheme 77). Palladium-catalyzed room-temperature *ortho*-alkenylations of anilines have been recently reported and probably involve palladacyclic intermediates.[224] For comparative purposes, we have opted to include a stoichiometric vinylation process, reported barely 20 years ago[225] and a Heck-type vinylation of a 2-bromoaniline[226] (both probably involving palladacycle intermediates), to further underline the advances achieved in catalytic CH functionalization chemistry.

Although there are a legion of catalytic tests for the Heck coupling promoted by a plethora of palladacycles, little attention has been paid to the species involved and ultimately to the reaction mechanism. Nevertheless, evidence accumulated over the past

Scheme 78. Formation of a Catalytically Active Pd(0) Species



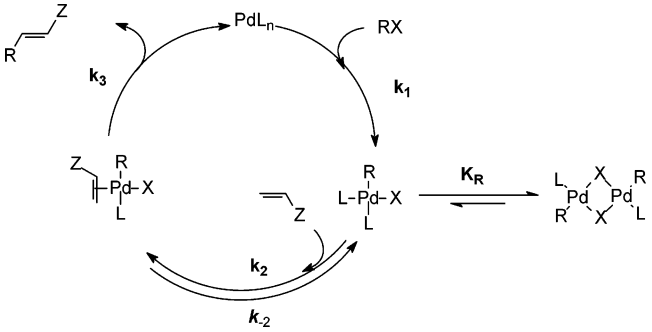
years from different studies indicates that the Heck reaction promoted by palladacycles occurs through a classical Pd(II)/Pd(0) catalytic cycle as opposed to Pd(IV) intermediates, which were postulated at an early stage for this reaction, and indeed, an earlier reference to such Pd(IV) intermediates was retracted.[3o,227]

The involvement of Pd(0) in the coupling of aryl halides with alkenes has been evidenced by positive mercury poisoning tests in reactions promoted by N- and P-containing palladacycles[196,228] (such a test can confirm the intervention of Pd(0) in the catalytic system). The formation of the Pd(0) catalytic active species from palladacycles most probably results from an olefin insertion into the Pd−C bond of the palladacycle followed by a β-hydride elimination and reductive elimination (Scheme 78).[190b,229,230]

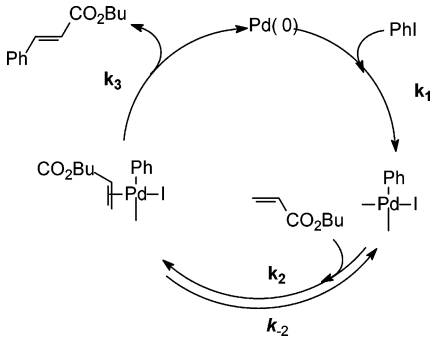
In two cases the formation of Pd(0) nanoparticles has been observed, after and during the Heck coupling of aryl iodides with acrylates, promoted by N- and S- palladacycles.[205,231] However, no colloidal palladium formation was observed in the Heck coupling promoted by the Herrmann−Beller P-containing palladacycle.[232] Nonetheless, the catalytically active species involved in the Heck reaction of phenyl halides with styrene promoted by a series of PCP palladium pincer complexes were studied, and evidence was found that the pincer complexes are precursors for metallic palladium. The identification of an induction period, the formation of palladium black, poisoning experiments (Hg, CS_2, thiophene, and PPh_3), and NMR studies were used to show that these complexes are precatalysts for highly active forms of metallic palladium.[228]

Detailed kinetic investigations and kinetic modeling of the Heck reaction of bromobenzaldehyde with *n*-butylacrylate promoted by palladacycle **167** have been performed.[233] The reaction progress was monitored by calorimetry, which allows for a very fast and reliable response of concentration changes as a function of time. The half-order dependence of the reaction rate on palladium concentration was used to test

Scheme 79. Kinetic Model for the Heck Reaction of Bromoarenes Promoted by Palladacycle 167



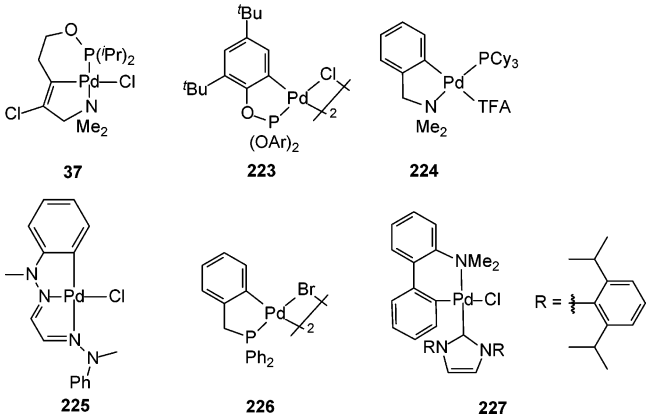
Scheme 80. Kinetic Model for the Heck Reaction of Iodoarenes Promoted by Palladacycle 200



the mechanism drawn in Scheme 79 as a model for the kinetic modeling. The oxidative addition step was found to be relatively fast, and as a consequence, the dominant species present in the catalytic cycle is the oxidative addition product. This intermediate is involved in equilibrium with a dimeric species, in such way that almost all the palladium involved in the reaction exists outside the catalytic cycle as a dimer. It was also shown that the relative concentration of substrate can have an effect on reaction order in the catalyst concentration determined experimentally by an initial velocity method and may lead to misinterpretation due to significant changes in the relative concentrations of the intermediates.

More recently the kinetics of the Heck coupling of iodobenzene with *n*-butylacrylate promoted by palladacycle **200** were investigated using in situ ATR−IR spectroscopy.[234] The iodobenzene consumption followed a sigmoidal curve indicating a preactivation step that disappears completely upon pretreatment of the palladacycle with the alkene and base. The significant reaction time reduction observed in these cases indicated that this preactivation step is not only related to the induction period but is also present during the entire catalytic reaction and should not be neglected in the kinetic modeling. The kinetic model depicted in Scheme 80 was simultaneously fitted to a set of experimental curves obtained after pretreatment of the catalytic precursor, showing good agreement with experimental curves. This kinetic model also predicts that relative concentrations of substrate will change the distribution of intermediates involved in the catalytic cycle. A slight excess of alkene relative to iodobenzene leads to a rapid rise in the Pd(0) concentration while when using a slight excess of iodobenzene, relative to alkene, the oxidative addition product is the resting state of the catalytic cycle.

Chart 32. Palladacycles Used in the Suzuki Cross-Coupling Reaction



Palladacycles were also tested in a Hammett competitive experiment involving the Heck reactions[235] of bromo- and iodoarenes with *n*-butyl acrylate. No significant changes were observed for the Hammett parameters obtained with different palladacycles, indicating that the same active species are in operation. It was also demonstrated that the oxidative addition step is responsible for the substituent effect on the reaction rate in competitive experiments performed with different bromo- and iodoarenes even if oxidative addition was not the rate-limiting step.

The chemistry of palladacyles would therefore appear to be closely related to the area of ultratrace, ligand-free palladium catalysis. Many groups are now looking at the use of "homeopathic" ligand-free palladium for very efficient Heck reactions.[189a,236] Of note is also a recent study by Leadbeater's group. Using microwave heating, reactions employing palladium concentrations at the 500 pbb level, found, for example, as traces in inorganic bases, can give rise to high-yielding coupling reactions.[237]

To compare palladacycle catalysis with homeopathic ligand-free palladium catalysis, the reaction of bromobenzene and *n*-butyl acrylate was carried out using 0.02 mol % [Pd] from either the Herrmann−Beller palladacycle or $Pd(OAc)_2$, and a similar kinetic profile was observed for the two reactions.[189b]

6.3. Suzuki Cross-Coupling

Palladacycles are also rather efficient catalyst precursors for the coupling of aryl boronic acids and aryl halides under relatively mild reaction conditions.[3w] In fact, almost any palladacycle promotes the coupling of aryl iodides or bromides with aryl boronic acids at temperatures above 80 °C, depending upon the nature of the base and the solvent. Of note is that TONs of up to 100,000,000 have been achieved for the coupling of phenylboronic acid with 4-bromoacetophenone in toluene using K_2CO_3 as base at 110 °C promoted by the phosphinito palladacycle **223** (Chart 32).[238]

This result is not exceptional since the Suzuki coupling involving aryl iodides and aryl bromides substituted with electron-withdrawing groups is pro-

Table 2. Catalytic Activity of Some Palladacycles that Promote the Suzuki Coupling between Phenylboronic Acid and Aryl Chlorides (or Aryl Bromides at Room Temperature)

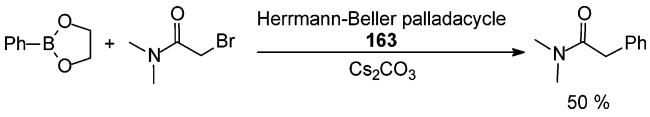
ArX + $PhB(OH)_2$ —[Pd]→ Ar—Ph

entry	palladacycle	[Pd] (%)	Ar−X	additive	T (°C)	t (h)	yield (%)	TON	ref
1	**212**	0.1	Ac-4-C_6H_4Cl	TBAB	130	2	86	860	242
2	**224**	0.01	Ac-4-C_6H_4Cl		100	17	100	10000	243
3	**212**	0.5	MeO-4-C_6H_4Cl	TBAB	160	2	40	80	242
4	**37**	0.5	MeO-4-C_6H_4Cl		130	27	85	170	34
5	**211**	1.0	MeO-4-C_6H_4Cl		100	20	95	95	194
6	**224**	0.01	MeO-4-C_6H_4Cl		100	17	80	8000	243
7	**223**	0.00005	Me-4-C_6H_4Cl	PCy_3	100	17	48	96000	238b
8	**225**	2.0	MeO-4-C_6H_4Br		RT	3	89	45	244
9	**129**	0.5	MeO-4-C_6H_4Br	TBAB	RT	38	95	190	245
10	**129**	0.5	NO_2-4-C_6H_4Cl	TBAB	RT	16	95	190	245
11	**226**	0.01	CHO-4-C_6H_4Cl		130	24	27	2700	246
12	**227**	2.0	Me-2-C_6H_4Cl		RT	1.5	95	47	247
13	*rac*-**78**	1.0	Me-2,5-C_6H_3Cl		RT	24	77	77	91b

moted by almost any palladium salt or complex such as palladium acetate even at room temperature.[239] The exceptionally high turnover numbers obtained for these substrate combinations suggest *that a reaction involving activated aryl halides is not a useful benchmark for testing new catalysts in Suzuki couplings*,[240] as we have already outlined in related Heck couplings in the previous section.

Palladacycles are being evaluated in more elaborate synthetic challenges, many of which will be discussed in the total synthesis section (section 7). For example, Suzuki-type cross-couplings involving 2-bromo-*N*,*N*-dimethylacetamide were catalyzed by the Herrmann−Beller palladacycle (3 mol %), although better yields were achieved with a combination of $Pd(dba)_2$ and PCy_3 (89%) (Scheme 81).[241]

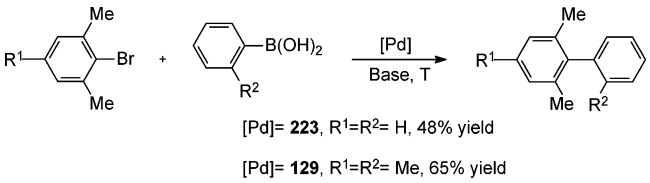
Scheme 81. Suzuki-Type Cross-Coupling Reaction Employing the Herrmann−Beller Palladacycle Precursor



The main challenges in Suzuki coupling are related to use of less reactive aryl halides such as aryl chlorides and aryl bromides substituted with electron-donating groups, under relatively mild reaction conditions, and in these cases only a few palladacycles have shown some catalytic activity (Table 2).[34,91b,194,238b,242−247] Of note is that the best results for the coupling of aryl boronic acids with chloroarenes were obtained with phosphapalladacycles or with palladacycles modified with carbenes or phosphorus-containing ligands (see entries 5 and 12 of Table 2). This might be rationalized by the extra stability provided by these ligands for the stabilization of the low-ligated catalytically active Pd(0) species involved in the main catalytic cycle.[3z]

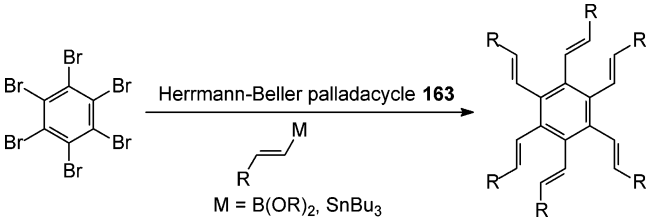
Moreover, Suzuki couplings of two sterically hindered substrates still remain a challenge,[248] and only in rare cases have such couplings been investigated with palladacycles. Of note is the coupling of phenylboronic acid and 2-bromo-1,3-dimethylbenzene promoted by phosphinito-based palladacycles in the presence of PCy_3 or the coupling of 2-tolylboronic acid with 2-bromo-1,3,6-trimethylbenzene catalyzed by a sulfur-containing palladacycle (Scheme 82).[249,245]

Scheme 82. Suzuki Coupling Reaction of Sterically Hindered Bromoarenes

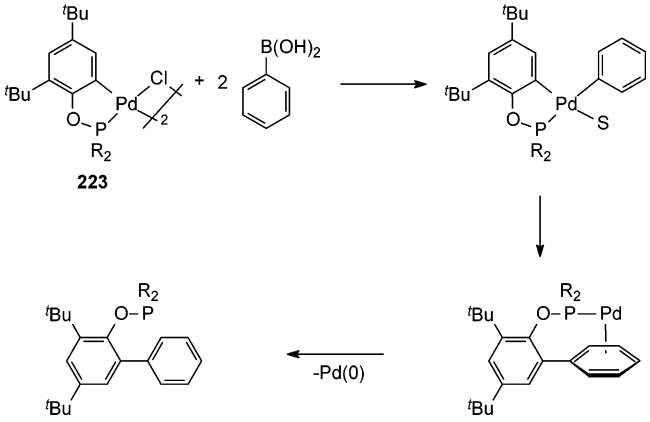


An impressive sixfold vinylation of a very hindered substrate was catalyzed by **163** (Scheme 83).[250] As

Scheme 83. Sixfold Suzuki/Stille Reaction

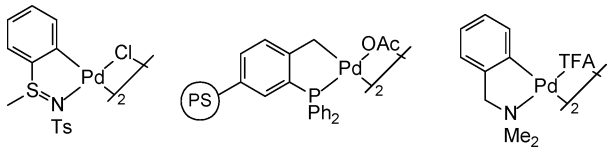


Scheme 84. Proposed Active Catalytic Species Formed during Suzuki Coupling Reactions (S = Solvent or Vacant Site)



observed in Heck coupling reactions, the catalytically active species are most probably Pd(0) species formed through a reductive elimination process between the palladated ligand and the aryl boronic acid derivative (Scheme 84).[251] Bedford's group has also shown that a phenylation/reductive elimination sequence is an activation step in the Suzuki reaction, leading to slow release of the true Pd(0) catalyst.[252] *A solid-supported palladacycle was an ideal mechanistic probe in their*

Table 3. Palladacycles and Palladacycle−Phosphine Adducts in Catalytic C−C and C−N Bond Formation

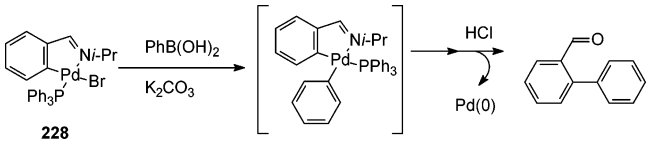


231 232 233

entry	palladacycle	substrate		conditions	yield (%)	TON	ref
				Sonogashira Coupling			
1	**231**	PhI	phenylacetylene	NEt_3, 80 °C, 12 h	84	336	254
2	**231**	PhBr	phenylacetylene	NEt_3, 80 °C, 12 h	25	100	254
3	**212**	PhI	phenylacetylene	NMP, NBu_4OAc, 110 °C, 24 h	72	7.2×10^4	255, 256
4	**212**	4-MeOPhBr	HC≡CSi(*i*-Pr)$_3$	NMP, NBu_4OAc, 130 °C, 1 h	85	340	255
5	**232**	4-COMePhBr	phenylacetylene	NEt_3, 90 °C, 72 h	98	490	208
6	**163**	4-COMePhBr	phenylacetylene	NEt_3, 90 °C, 5 h	99	990	3q
7	**200**	PhI	phenylacetylene	DMA, NBu_4OAc, 130 °C, 24 h		4.0×10^5	257
				Ullman Coupling			
8	**2**	4-MePhI		DMA, NEt_3, 132 °C, 4 h	99	495	258
9	**231**	PhI		NMP, K_2CO_3, 125 °C, 24 h	41	164	254
10	**212**	4-MeCOPhI		DMF, NEt(*i*-Pr)$_2$, 110 °C, 5 h	99	100	242
				Buchwald-Hartwig Coupling			
11	**223**	4-MeOPhCl	morpholine	2 equiv P(*t*-Bu)$_3$; toluene, NaO*t*-Bu, 110 °C, 17 h	96	960	259
12	**25**	4-MePhCl	morpholine	toluene, NaO*t*-Bu, 80 °C, 2 h	97	194	22
13	**227**	4-MeOPhCl	morpholine	dioxane, NaO*t*-Bu, 70 °C, 0.5 h	100	100	260
14	**233**	4-MeOPhCl	morpholine	1 equiv P(*t*-Bu)$_3$, toluene, NaO*t*-Bu, 110 °C, 17 h	92	920	261
15	**163**	4-CF_3PhCl	piperidine	toluene, KO*t*-Bu, LiBr, 135 °C, 24 h	98	980	262
16	**211**	4-MeOPhCl	morpholine	toluene, NaO*t*-Bu, 110 °C, 15 h	100	50	194
				Ketone arylation			
17	**227**	4-MeOPhCl	cyclohexanone	dioxane, NaO*t*-Bu, 70 °C, 2 h	100	100	263
18	**211**	4-MeOPhCl	ethylphenylketone	toluene, NaO*t*-Bu, 110 °C, 15 h	100	200	194
				Stille Coupling			
19	**223**	4-MeOPhCl	$PhSnBu_3$	2 equiv P(Cy)$_3$, dioxane, K_3PO_4, 100 °C, 18 h	100	100	264, 238b
20	**223**	4-COMePhBr	$PhSnBu_3$	toluene, 120 °C, 18 h	83	8.4×10^5	238a
21	**212**	4-COMePhBr	$PhSnBu_3$	toluene, 110 °C, 5 h	95	32	265
22	**163**	4-COMePhBr	$PhSnBu_3$	toluene, 110 °C, 4 h	96	19	266

study; although it was not recyclable, this in itself provided evidence for preactivation and loss of Pd(0) from the solid support. As a model for the activation of the precatalyst in the Suzuki reaction, with release of Pd(0), the stoichiometric reaction of an imine-bound palladacycle with phenylboronic acid led to 2-phenylbenzaldehyde and palladium black (Scheme 85).

Scheme 85. Formation of Pd(0) in a Suzuki Cross-Coupling Reaction Promoted by a CN Palladacycle



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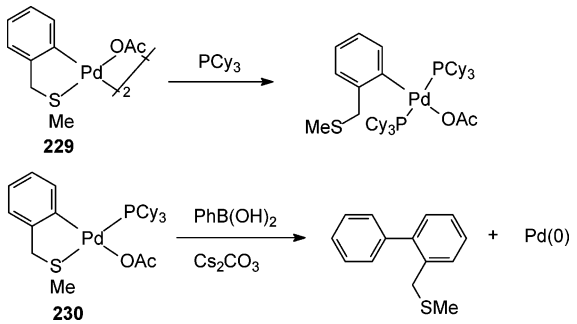
In-situ prepared alkylphophine adducts of S palladacycles are effective catalyst precursors in Suzuki couplings although overcoordination of the phosphine is detrimental to catalyst activity. The stoichiometric reaction of a monomeric PCy_3 adduct of a S palladacycle with phenylboronic acid led to a biphenyl product, suggesting a similar Pd(II)/Pd(0) pathway (Scheme 86).[253]

6.4. Sonogashira, Stille, Buchwald–Hartwig, and Other Cross-Coupling Reactions

Palladacycles have proven to be useful and versatile catalytic precursors for other C−C, C−N, and C−P catalytic bond-forming reactions such as Ullman, Stille, Kumada, Negishi, Sonogashira, and α-ketone arylation C−C coupling reactions and in the Buchwald−Hartwig arylation of amines (Scheme 87 and Table 3).[3q,22,194,208,238,242,254−266] As noted in the Suzuki reaction section, the best results for the activation of chloroarenes were obtained with phosphapalladacycles or with palladacycles modified with carbenes or phosphorus-containing ligands (see entries 11, 13, 14, 17, and 19 of Table 3).

A cyclopalladated biphenylphosphine analogue **25** was found to be effective for amination chemistry (Scheme 88).[22] 1-Aryl-*1H*-indazoles can be formed by an intramolecular amination reaction involving palladacyclic intermediates (Scheme 89).[267] There are only a few examples of Sonogashira, Ullmann, and Stille coupling reactions promoted by CN palladacycles, and in these cases, only marginal catalytic activities are obtained with less reactive chloroarene

Scheme 86. Formation of Pd(0) in a Suzuki Cross-Coupling Reaction Promoted by a CS Palladacycle



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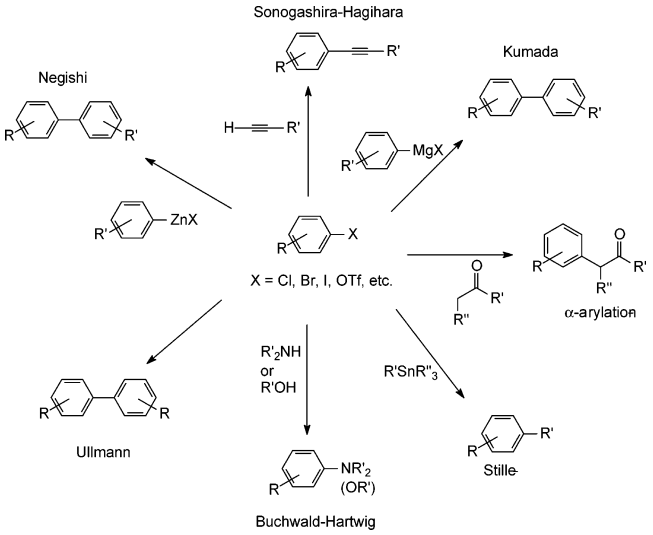
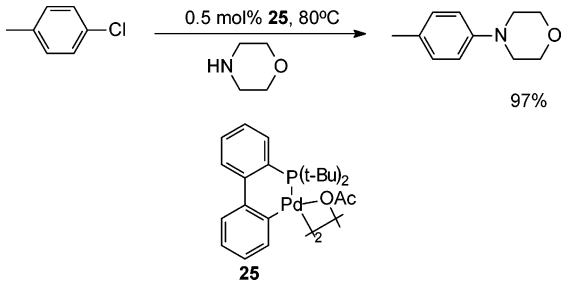
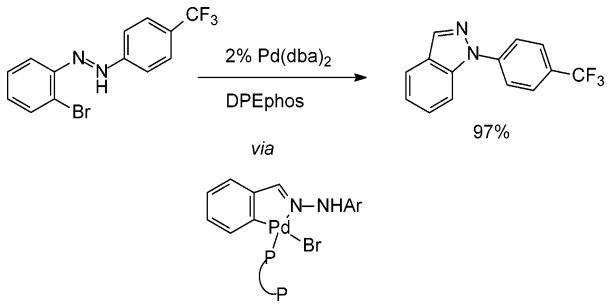
Scheme 87. Catalytic C−C and C−N Coupling Reactions Promoted by Palladacycles



Scheme 88. Palladacycle 25 as Catalyst Precursor for the Amination of Aryl Chlorides



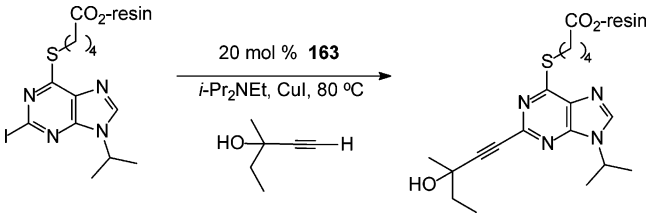
Scheme 89. Synthesis of 1-Aryl-1*H*-indazoles



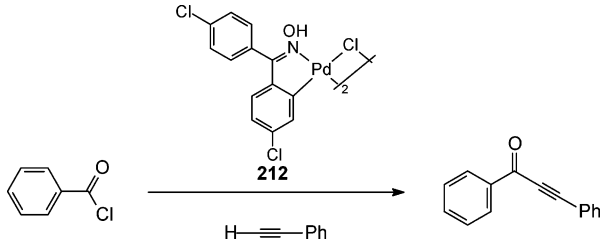
substrates.[254,255] Despite the poor activity with chloroarene substrates, CN palladacycles are exceptional catalytic precursors for promoting Sonogashira coupling with iodo- and bromoarenes under copper-free conditions, and an impressive TON of 400,000 can be achieved in the Sonogashira coupling of iodobenzene with phenylacetylene promoted by dimeric palladacycle **200**.[257] Solid-phase Stille couplings yielding biaryls, employing a resin-bound stannane, can also be carried out using the Herrmann−Beller palladacycle.[268]

Sonogashira reactions of terminal alkynes with iodoarenes can be performed on the solid phase using the Herrmann−Beller palladacycle, as in the synthesis of trisubstituted purines of potential biological interest (Scheme 90).[269] The oxime-containing palladacycle **212** was employed as a catalyst for the formation of ynones with TONs reaching 23,000 (Scheme 91).[270] Another interesting reaction medi-

Scheme 90. Sonogashira Cross-Coupling Reaction of a Polymer-Supported Substrate



Scheme 91. Palladacycle 212 as Catalyst Precursor for the Synthesis of Ynones



Scheme 92. Intramolecular *o*-Phenol-Coupling Reaction

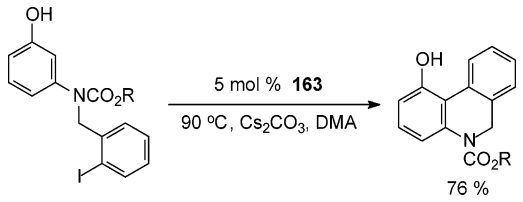
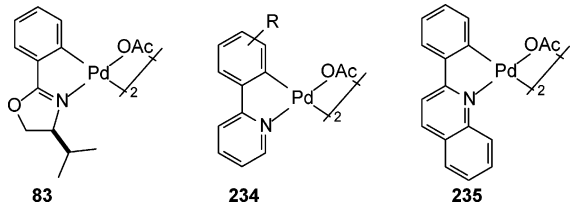


Chart 33. Palladacycles Employed as Catalyst Precursors to Oxidation Reactions



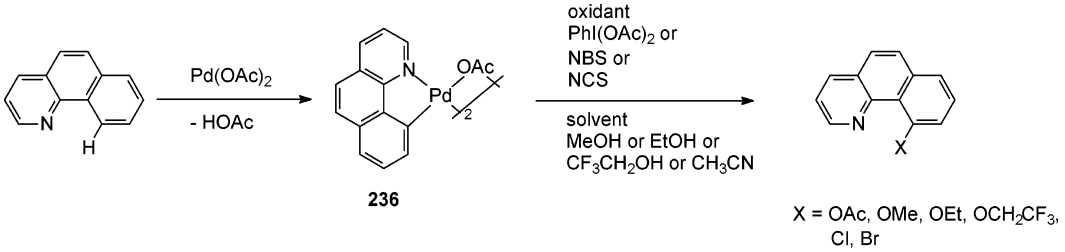
ated by the Herrmann−Beller palladacycle is an efficient intramolecular *o*-phenol-coupling reaction (Scheme 92).[271]

6.5. Oxidation Chemistry

Palladium-based catalysts are among the most important and investigated compounds used in catalytic oxidation methods that employ oxygen at atmospheric pressure. Such catalytic systems are nontoxic and environmentally friendly compared with classical stoichiometric oxidant methods. Palladacycles derived from 2-phenylpyridine, quinoline, and oxazoles (Chart 33) have been recently reported as effective catalysts for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones under an atmospheric pressure of air without the addition of any other reoxidants.[272] Theoretical calculations suggest that the β-hydride elimination step has the highest energetic barrier of the catalytic cycle.[273]

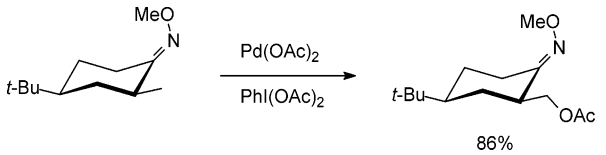
Regioselective Pd-catalyzed C−H bond activation can be used for the conversion of C_{sp^2} and C_{sp^3} C−H bonds to esters, ethers, and aryl halides. The reaction

Scheme 93. Catalytic C−H Bond Activation via a Palladacycle Intermediate

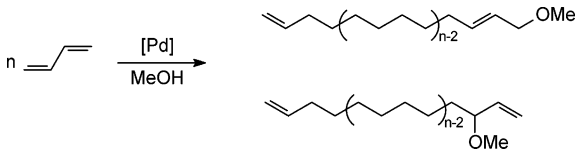


236

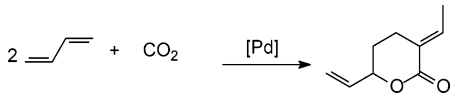
Scheme 94. Catalytic C_{sp^3} C−H Bond Activation



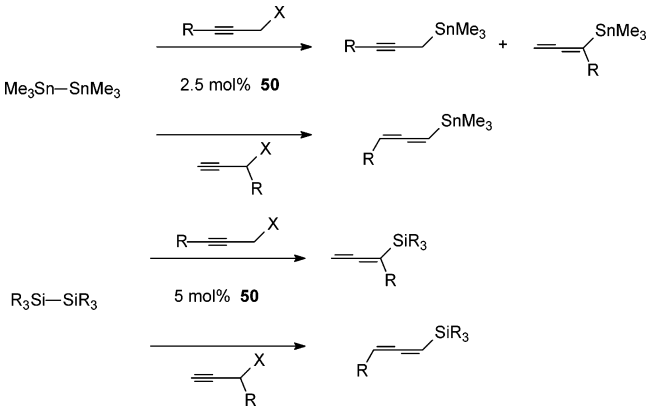
Scheme 95. Telomerization of 1,3-Butadiene with Methanol



Scheme 96. Telomerization of 1,3-Butadiene with CO_2



Scheme 97. Trialkylstannyl or Trialkylsilyl Transfer to Propargylic Substrates



involves a cyclopalladated intermediate (Scheme 93).[274] More interestingly, the oxidation of unactivated sp^3 C−H bonds of various O-methyl oximes can be easily accomplished via five-membered palladacycles (Scheme 94).[275]

6.6. Miscellaneous

6.6.1. Telomerization of Dienes

Palladacycles are also quite effective and selective catalyst precursors for the telomerization of 1,3-dienes with alcohols and carbon dioxide. Cationic complexes such as those derived from the cyclopalladation of 8-methylquinoline and *N*,*N*-dimethylbenzylamine promote the telomerization of 1,3-butadiene with methanol, affording the telomers $C_{16}OMe$ as the major products (Scheme 95, $n = 4$).[276]

Interestingly, the same palladacycles associated with phosphine enolate derivatives are quite effective for the coupling of two 1,3-butadiene units with carbon dioxide, affording the lactone 2-ethylidene-6-hepten-5-olide in selectivity up to 93% (Scheme 96).[277] The telomerization of isoprene with methanol was also performed using nonracemic cyclopalladated imines but without any asymmetric induction.[278]

6.6.2. Stannylations and Silylations of Propargyl Substrates

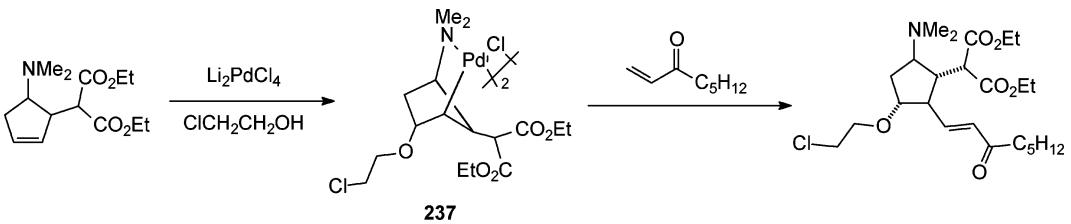
Palladium pincer complex **50** efficiently catalyses the regioselective transfer of stannyl or silyl groups to propargylic substrates as propargyl chlorides or epoxides.[279] The proposed reaction mechanism involves a transmetalation step in which the trialkylstannyl or trialkylsilyl groups are transferred to the palladium center followed by the transfer of the organometallic fragment to the propargylic substrate (Scheme 97).

7. Total Syntheses

An excellent early review covers mainly stoichiometric reactions involving palladacycles.[3j] One early impressive application of such complexes led to the synthesis of prostaglandin precursors via sequential stoichiometric alkoxypalladation and olefination reactions (Scheme 98).[280] The same group also disclosed an impressive synthesis of narwedine by means of a biomimetic oxidation (Scheme 99).[281]

Recently, Sames employed a series of remarkable stoichiometric CH activation reactions of sp^3 CH

Scheme 98. Synthesis of Prostaglandin Precursors



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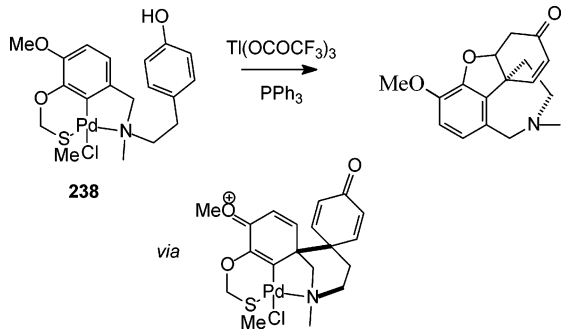
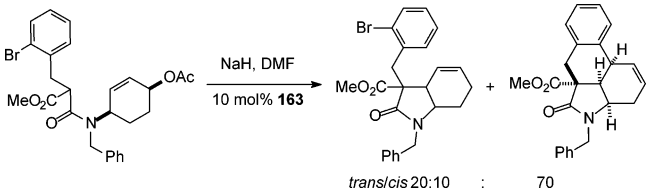
Scheme 99. Synthesis of Narwedine



bonds including transmetalation with a vinylboronic acid moiety to synthesize the core of Teleocidin B4 (Scheme 100).[282] A catalytic variant of this process has recently been disclosed, enabling C−C bond formation involving the palladacycle intermediate **240** (Scheme 101).[283] Polycondensed pyrrolidinone derivatives were formed via a distinct sequential allylic alkylation and Heck cyclization employing **163** in the presence of *n*-Bu_4NOAc (Scheme 102).[284] Heck couplings and electrocyclizations have been achieved using the Herrmann−Beller palladacycle for the synthesis of steroid analogues (Scheme 103).[285] The Herrmann−Beller palladacycle was found to be a more effective catalyst precursor than more "traditional" systems (e.g. $Pd(OAc)_2/PPh_3$) for Heck reactions leading to estrogen analogues (Scheme 104).[286] Dihydrochalcones were synthesized by a Heck coupling using the Herrmann−Beller palladacycle (Scheme 105).[287] Similar coupling reactions with Najera's oxime-based palladacycle led to stilbenes.[288] Bissteroidal analogues were synthesized using multifold coupling chemistry (Scheme 106).[289]

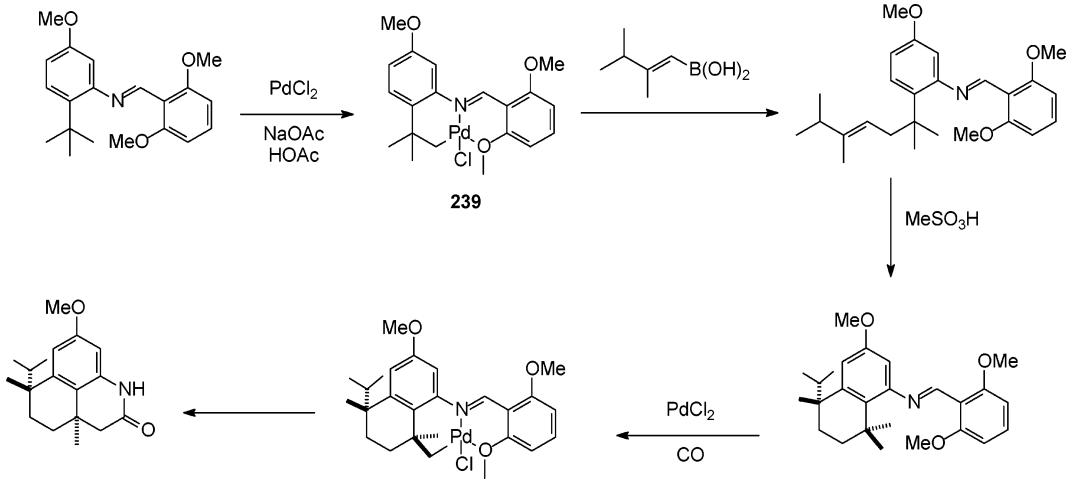
Synthetic studies aimed toward the antibiotic Mensacarcin compared various palladium analogues in effecting an intramolecular Heck reaction. The presence of a ketone function had a favorable effect on the cyclization yields, due in part to activation of the aryl bromide by electron withdrawal. High loadings of the palladacycle were required in order to achieve acceptable yields in product (Scheme 107).[290] Other intramolecular Heck couplings have been employed in the synthesis of the alkaloid cephalotaxine (Scheme 108).[291]

Scheme 102. Polycondensed Pyrrolidinone Formed via Sequential Allylic Alkylation and Heck Cyclization Employing the Herrmann−Beller Palladacycle

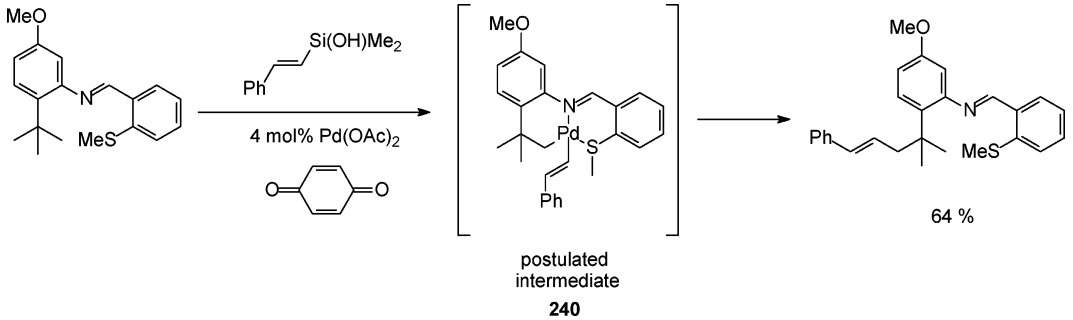


The desymmetrization of 3,8-dibromophenanthroline represents a formidable challenge; all attempts to make unsymmetrical analogues of **241**, via a single Sonogashira coupling reaction, were unsuccessful. However, the monoarylation of **241** led to the unsymmetrical dimethoxyaryl analogue **242**, which underwent a Sonogashira reaction via preferential reaction at the bromine adjacent to the chelating group. A

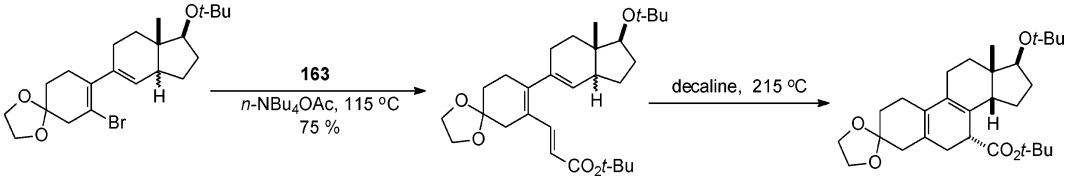
Scheme 100. Palladacycles in the Synthesis of the Core of Teleocidin B4



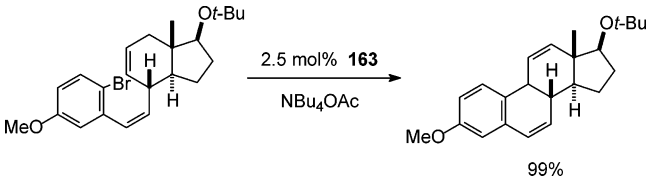
Scheme 101. C−C Bond Formation Involving Palladacycle Intermediates



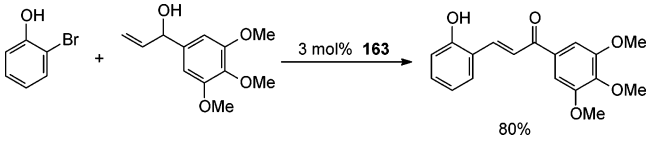
Scheme 103. Heck Couplings and Electrocyclizations Using the Herrmann−Beller Palladacycle



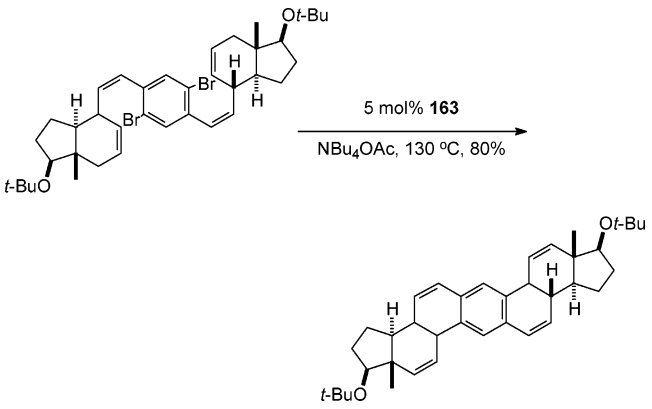
Scheme 104. Heck Reaction in Estrogen Analogue Synthesis



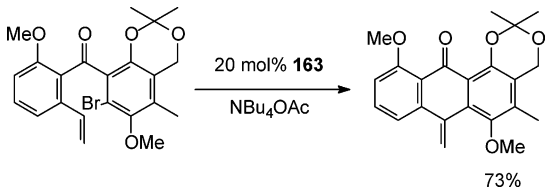
Scheme 105. Heck Coupling Using the Herrmann−Beller Palladacycle



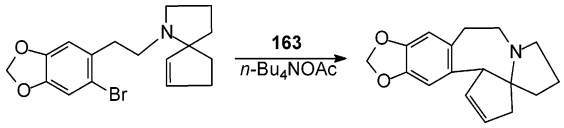
Scheme 106. Bissteroidal Analogues Formed by the Heck Reaction



Scheme 107. Intramolecular Heck Reaction



Scheme 108. Intramolecular Heck Coupling in the Synthesis of the Alkaloid Cephalotaxine



palladacyclic intermediate (**243**) was postulated to rationalize this regioselectivity (Scheme 109).[292]

High-speed microwave-induced Heck reactions employing **163** have been disclosed. [293] Although only simple substrates have been coupled so far, this might prove to be a useful method for synthesizing more elaborate synthetic targets, and already molecules targeting aspartic proteases have been made (Scheme 110).[294] A catalytic Sonogashira reaction, which probably proceeds via a palladacyclic intermediate (**245**), led to the alkaloid decumbenine B (Scheme 111).[295]

Pfeffer's group combined a series of stoichiometric palladacycle-mediated reactions, viz. C−H activation and heteroannulation of alkynes and allenes, toward the synthesis of berberinium derivatives (Scheme 112).[163] Biphenyl analogue precursors to biphenomycin antibiotics were synthesized in excellent yield via a Stille coupling employing **163** (Scheme 113).[296] Similarly, diazonium analogues couple with organotrifluoroborates to give biphenyl products.[297]

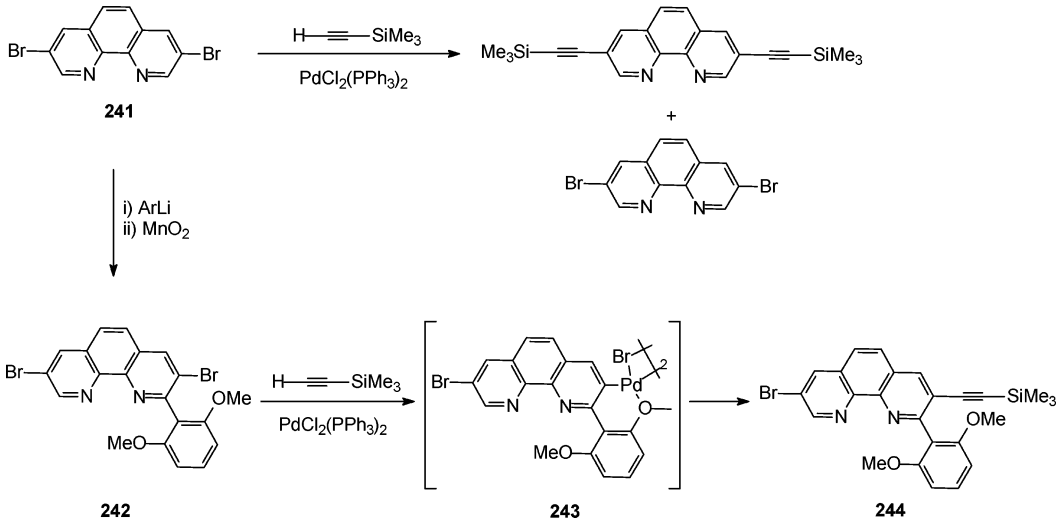
Intramolecular arylation reactions have been developed as milder alternatives to flash vacuum pyrolysis for the synthesis of fullerene-related fragments such as dibenzo[*a,g*]corannulene (Scheme 114).[298] Helicenes were synthesized using, as a key step, Heck chemistry with **163** (Scheme 115).[299] As can be seen from this and other sections, palladacycles, notably the Herrmann−Beller precatalyst **163**, have been used to great effect in organic synthesis. *However, we must note that in many cases the Herrmann−Beller palladacycle is employed in substoichiometric amounts, e.g. 10−20 mol % as opposed to ≪0.1 mol %, when used for coupling simple test substrates. This may be due to (i) the researchers having merely substituted a conventional catalyst with the palladacycle, keeping the [Pd] concentration constant, (ii) reaction times being too slow with <0.01 mol % of the palladacycle, so higher concentrations were used, or (iii) the palladacycle-mediated reaction simply not working at lower concentrations (e.g. catalyst posioning by substrate, functional group intolerance). In our view, to prove (or disprove!) the true synthetic potential of palladacycles, a systematic study of these reactions employing an elaborated aryl halide or an important synthetic precursor ought to be carried out, to see if high TONs and efficiencies can be achieved on substrates other than those used in benchmark couplings.*

8. Caveats

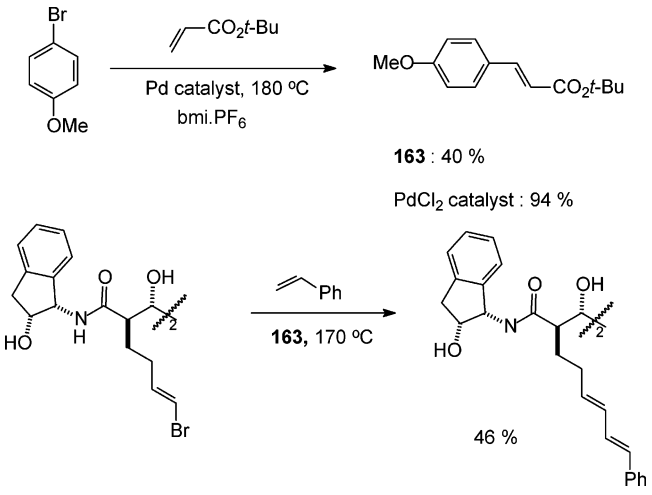
It is apparent that palladacycles can often be used to effect couplings that require harsh conditions and high temperatures (indeed palladacycles often require such conditions for activation) and in cases where the use of conventional Pd catalysts may be hampered due to palladium black formation and poor catalyst longevity. However, such harsh conditions may not always be tolerated by one of the coupling partners, and decomposition or rearrangements may ensue.

For example, not all Heck reactions and Suzuki couplings proceed as planned while employing palladacycles; while attempting an intramolecular Heck

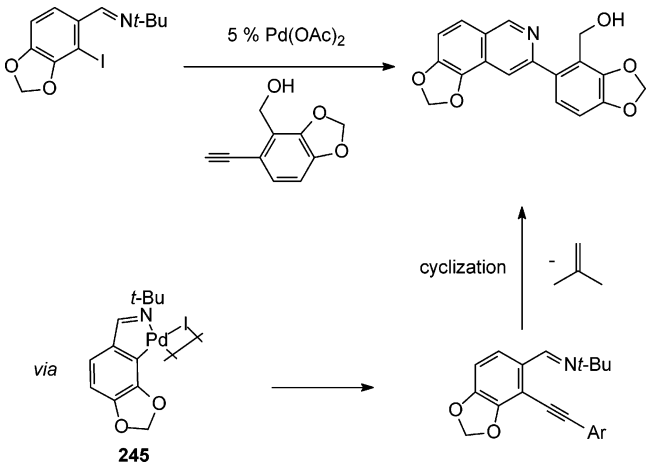
Scheme 109. Synthesis of Unsymmetrical Phenanthroline via a Palladacycle Intermediate



Scheme 110. High-Speed Microwave-Induced Heck Reactions in Ionic Liquids



Scheme 111. Synthesis of the Alkaloid Decumbenine B



cyclization toward the synthesis of the alkaloid huperzine A, employing **163**, an unexpected redox reaction was observed.[300] This protocol was consequently generalized for the transformation of 2-(2-bromobenzyl)-ketones to enones (Scheme 116).

The attempted intramolecular Heck cyclization of a diene substrate did not work due to poisoning of the precatalyst **246** by diene coordination to palladium. (Scheme 117). However, a $Pd(OAc)_2/PPh_3$ system catalyzes the cyclization.[301] However, both catalytic systems were effective in the cyclization of the cyclohexene analogue, which does not coordinate as effectively to Pd (Scheme 118).

The biologically important podophyllotoxin skeleton has been synthesized using an intramolecular Heck reaction, and the direction of the reaction, leading to the desired five- or six-membered fused ring, could be influenced by the choice of catalyst (Scheme 119). When using **163**, although the starting material was totally exhausted, under the high-temperature conditions (120 °C), only degradation products were detected.[302]

In the synthesis of the acetylcholinesterase inhibitor (−)-galanthamine, a mixture of isomeric products was formed when employing **163** for the intramolecular Heck cyclization, which was avoided by the use of a more conventional catalyst (Scheme 120).[303] Intramolecular reactions involving the trapping of a π-allyl species with an arylbromide mediated by **163** led to decarboxylation due to the high temperatures employed (Scheme 121).

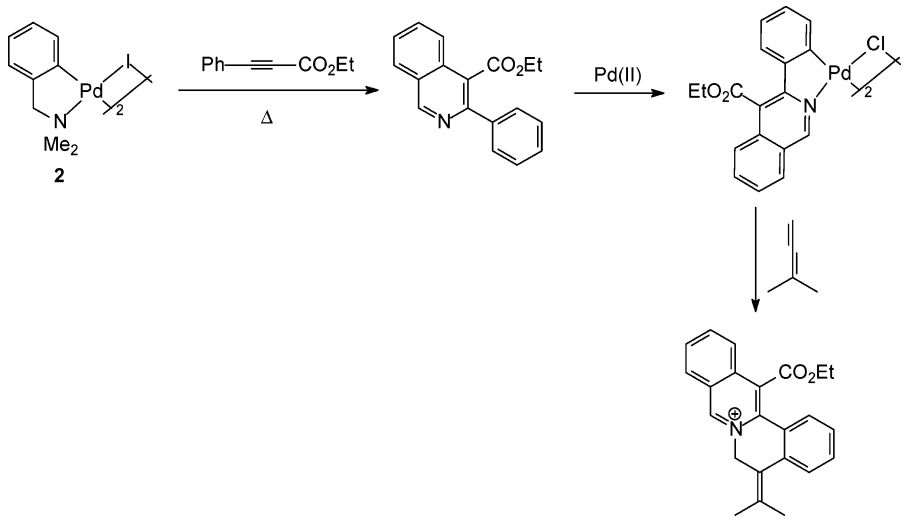
Suzuki couplings used to synthesize the disubstituted biphenylaldehyde led to protodeboronation when using **163** but proceeded smoothly with $Pd(PPh_3)_4$ (Scheme 122).[304] Similar protodeboronations were also observed, influenced by both the choice of catalyst and the nature of the aryl bromide (Scheme 123).[305]

To avoid many of these undesirable decomposition pathways, many of which are due to the high temperatures and long reaction times employed, it might be desirable to develop or employ (i) palladacycles that are active at lower temperatures (e.g. ***200****) or (ii) microwave-mediated palladacycle chemistry, which enables reaction times to be significantly reduced.*

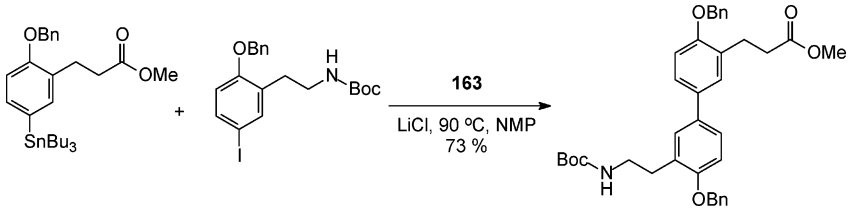
9. Photoluminescent Palladacycles

Over the past decades, luminescent organic and organometallic compounds have attracted a great deal of attention, especially for their practical applications in organic light-emitting devices (OLE-

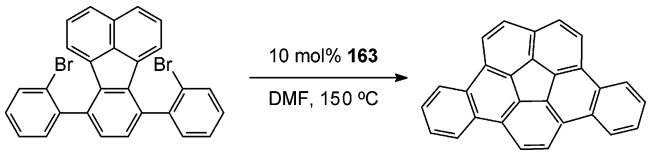
Scheme 112. Synthesis of Berberinium Derivatives via Stoichiometric Palladacycle-Mediated Reactions



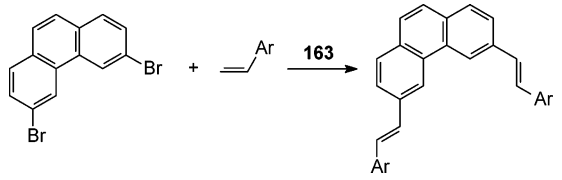
Scheme 113. Biphenyl Analogue Precursors to Biphenomycin Antibiotics



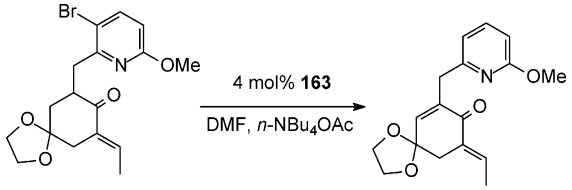
Scheme 114. Intramolecular Arylation Reactions for the Synthesis of Fullerene-Related Fragments



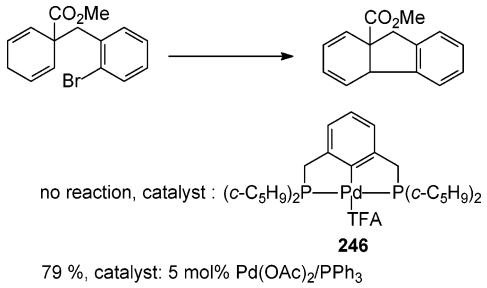
Scheme 115. Helicenes Synthesized Using a Heck Coupling Reaction



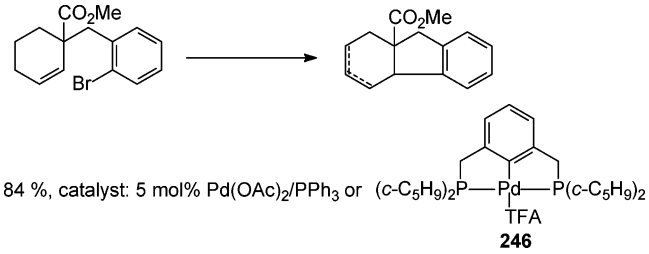
Scheme 116. Transformation of 2-(2-Bromobenzyl)-ketones to Enones Promoted by the Herrmann–Beller Palladacycle



Scheme 117. Poisoning of the Catalyst by the Diene Substrate in the Intramolecular Heck Reaction



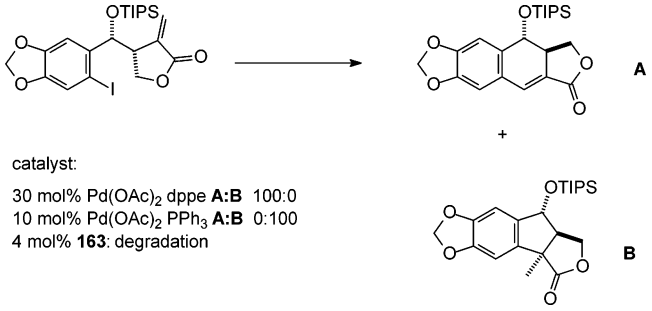
Scheme 118. Intramolecular Heck Reaction Promoted by a Pincer Palladium Complex



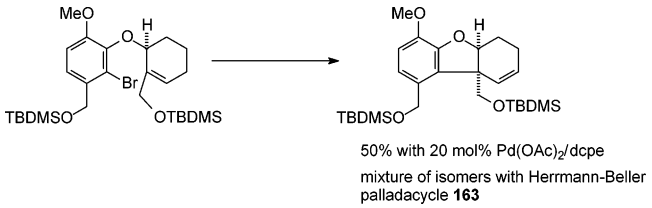
Ds).[306] Indeed, over the past decade OLEDs have been extensively studied for applications as next generation flat-panel displays because of their high luminescence, low drive voltage, fast response, and abundant range of colors. Since the strong spin–orbit coupling of heavy metal ions allows for efficient intersystem crossing between singlet and triplet excited states, high quantum efficiency can result. Therefore, research on heavy metal complexes as dopants for highly efficient OLEDs has received a great deal of attention recently.[307–309] Indeed, cyclometalated compounds, in particular, iridium complexes, are very efficient emissive dopants compared with those used in conventional fluorescent OLEDs.[307,308]

In this context, luminescent palladacycles are exceptions if compared with the innumerous analogous platinum and iridium compounds, and it is often found that the palladation of luminescent ligands causes a drastic decrease in luminescence. Nonethe-

Scheme 119. Synthesis of the Podophyllotoxin Skeleton Using an Intramolecular Heck Reaction Employing Different Pd Catalysts

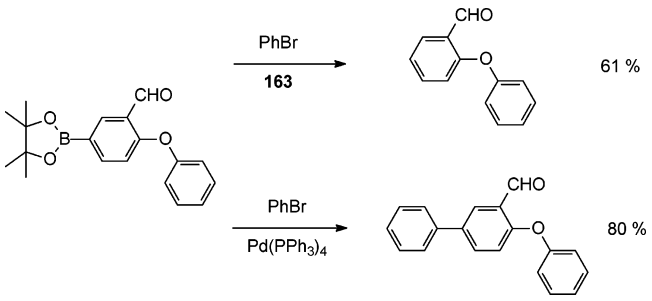


Scheme 120. Synthesis of the Acetylcholinesterase Inhibitor (−)-Galanthamine



Scheme 121. Intramolecular Cyclization Using the Herrmann−Beller Palladacycle

Scheme 122. Suzuki Coupling or Protodeboronation Using Different Sources of Palladium Catalyst



less, palladacycles can serve as model compounds for OLEDs, in particular for comparative purposes (structural and photophysical properties) with analogous cyclometalated platinum and iridium compounds.[310]

The first examples of palladacycles to exhibit luminescence at room temperature were provided by Kutal et al.[311] A series of palladacycles derived from the orthometalation of unsymmetrically disubstituted azobenzenes were synthesized and their photochemical properties determined (palladacycles **247**−**249**, Chart 34). The absorption spectra of these compounds were assigned as intraligand (IL) in character. All the palladacycles containing orthometalated 4-nitro-4′-(dimethylamino)azobenzene emit in the same region with a short lifetime (Table 4), and the luminescence has been assigned as an intraligand $\pi-\pi^*$ transition, while the 4-methoxyazobenzene palladacycles have an emission attributed to a ligand-centered $n-\pi^*$ fluorescence.

Scheme 123. Herrmann−Beller Palladacycle in the Coupling of Pinacolborate Borate Esters

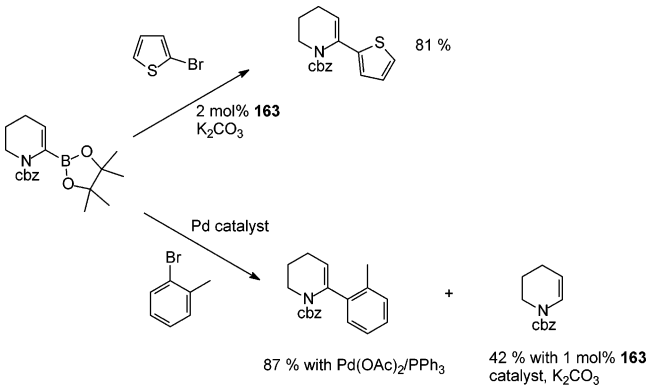
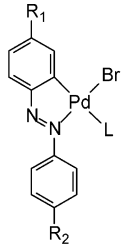


Chart 34. Luminescent Palladacycles Derived from the Orthometalation of Unsymmetrically Disubstituted Azobenzenes



247 $R_1 = NMe_2$, $R_2 = NO_2$, L = *cis*-4-stilbazole
248 $R_1 = NMe_2$, $R_2 = NO_2$, L = *trans*-4-stilbazole
249 $R_1 = H$, $R_2 = OMe$, L = *trans*-4-stilbazole

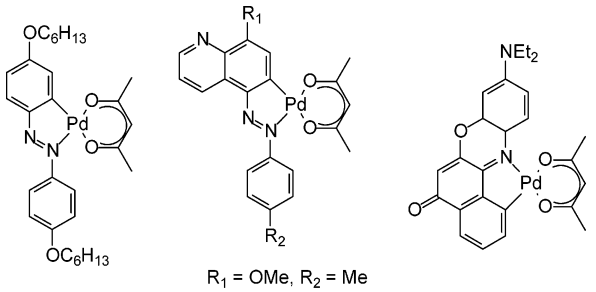
Table 4. Emission Spectra and Lifetimes for Palladacycles Derived from the Orthopalladation of Azobenzenes

palladacycle	λ_{max} emission (nm)	T (°C)	lifetime	Φ	ref
247	639	25			311
248	638	25	63 ps		311
249	550	25	*a*		311
250	560	25	1.7 ns	4.7×10^{-4}	312
251	600	25	<0.5 ns	0.001	313
252	660	25	4.4 ns	0.23	313

[a] Emission intensity remained unchanged after bubbling sample solution with O_2.

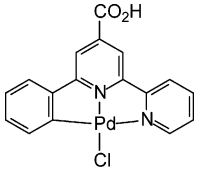
A comparative study of the photoluminescent properties of this class of palladacycles derived from azobenzenes has been performed by Ghedini.[312,313] The photophysical properties of the complexes have been investigated in solution at room temperature, showing, in some cases, high quantum yields. The best performance was obtained with the palladacycle derived from the dye Nile Red (**252**, $\Phi_{em} = 0.23$, $\lambda_{em} = 660$ nm at room temperature in CH_2Cl_2 solution), whose emission is greater than that in the free ligand ($\Phi_{em} = 0.13$, $\lambda_{em} = 602$ nm at room temperature in CH_2Cl_2 solution). A family of palladacycles derived from the Nile Red dye containing different β-diketonato bridge structures have been recently reported.[314] All palladacycles reported are efficient red emitters in room-temperature solutions, showing one of the highest reported quantum yields (up to 50%) (Chart 35).

Chart 35. Other Examples of Photoluminescent Palladacycles



250 251 252

Chart 36. Palladacycle Presenting Solid-State Eximeric Emission

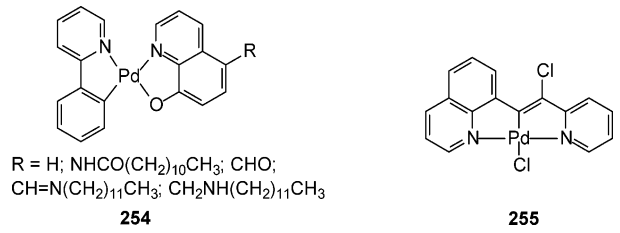


253

A series of papers report the photophysical properties of palladium complexes derived from the orthometalation of benzoquinoline and 2-phenylpyridine.[315−318] The emission and absorption spectra of glasses measured at 77 K showed lifetimes of the order of $10^{-6}-10^{-3}$ s. The absorption and emission spectra of this class of palladacycles have been attributed to transitions centered on ligands. The lack of fluorescence at room temperature has been attributed to the fact that the lowest exited state is a distorted MC exited state, which undergoes fast decay. The analysis of energy, lifetime, band structure, and solvent dependence was used to assign the nature of the emissions as ligand-centered (LC) transitions with some MLCT contribution.

The photochemical properties of a family of palladium complexes derived from the orthopalladation of 6-phenyl-2,2′-bipyridines[30,319−321] or ligands containing the azaindolyl moiety[322,323] have been studied over the last years. The great majority of cyclopalladated compounds reported exhibit fluorescent emissions only at 77 K for a rigid matrix. An interesting exception was given by Neve et al., who observed both solid-state fluorescence at room temperature and rigid matrix fluorescence at 77 K for the palladacycle **253** derived from the 6-carboxyl-2,2′-bipyridine ligand. The differences between luminescent data obtained in these cases allowed the authors to assign the luminescence observed at 77 K as a metal-perturbed LC state with a MLCT contribution, while solid-state room-temperature luminescence was ascribed to an excimeric emission. Due to the efficient packing of palladacycle **253**, which displays extended π-stacking and also short Pd···Pd interactions, the excimeric emission can be a combination of MMLCT and $\pi-\pi^*$ transitions from stacking interactions between the aromatic moieties (Chart 36). Noteworthy are the examples of room-temperature palladacycle emitters provided by Ghedini et al. (Chart 37).[324] These palladacycles derived from the cyclopalladation of 2-phenylpyridine containing various 5-substituted

Chart 37. Palladacycles Which Exhibit Room-Temperature Solution Luminescence



254 255

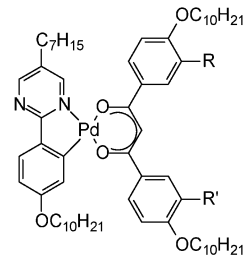
8-hydroxyquinolines **254** are efficient room-temperature emitters with photoluminescent quantum yields ranging from 0.24 to 0.8 depending on the R group nature. Recently, a remarkable example of a room-temperature luminescent palladacycle, derived from the chloropalladation of 2-pyridyl-8-quinolylacetylene, was reported.[26] The palladacycle **255** exhibits both solid-state and solution fluorescence at room temperature. Although the fluorescence observed in room-temperature solutions is quite low, this new architecture provides a unique example that luminescence is not restricted to palladacycles containing Pd−aryl bonds.

10. Liquid Crystals (Mesogenic Palladacycles)

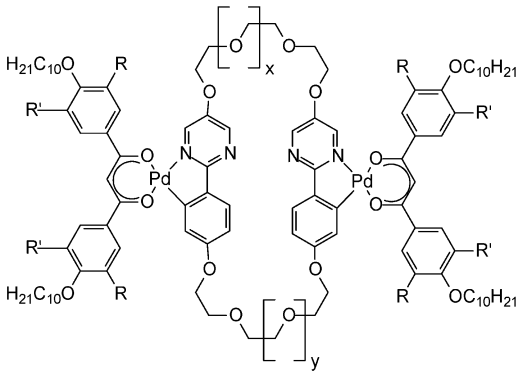
Mesogenic palladacycles have received much attention over the last years due to their promising proprieties.[325] The metalation reaction of a particular ligand is commonly performed, aiming to improve some desired property, such as reaching some particular mesophase, conductivity, or redox behavior. These palladium-containing liquid crystals consist, in the great majority of cases, of dimeric or monomeric five-membered orthopalladated organometallic complexes derived from aromatic imine,[326] phenylpyridine,[319,327] or phenylpyrimidine[328] ligands, and they were introduced mainly due to their high thermal stability and the versatility of the orthopalladation reaction in the construction of palladacycles of different molecular geometries. This class of palladacycles provided the first examples of ferroelectric[329] and cholesteric metal-containing liquid crystals[330] as well as the first spontaneous McMillan phase with an orthogonal alignment of the molecules.[328] However, no practical applications have yet been reported, in particular due to the melting point temperatures being too distant from room temperature and significant decomposition during prolonged heating.

Palladacycles **256a**−**256c** are important examples of how different ligand structures can affect the mesomorphic properties of analogous palladacycle complexes.[328] It was also demonstrated that binary mixtures of palladacycles **256a**−**256c** and 2,4,7-trinitrofluorenone (TNF) produce, spontaneously, an orthogonal alignment of the molecules characterizing a McMillan phase. In another impressive contribution to this field, the same group reported a series of metallomesogen palladacycles containing *para*-cyclophanes and 1,3-diketonato moieties named butterfly-like mesogens (palladacycles **257**, Chart 38). By changing the alkyl chains in the diketonato ligand, a change in molecular organization and in mesophases was observed.[331]

Chart 38. Palladacycles with Mesogenic Proprieties

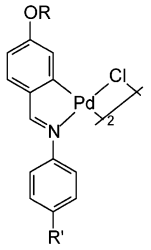


256a R = R' = H
256b R = $OC_{10}H_{21}$, R' = H
256c R = R' = $OC_{10}H_{21}$



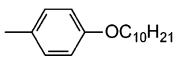
257a R = R' = H; x = 3, y = 1
257b R = $OC_{10}H_{21}$, R' = H; x = 3, y = 1
257c R = R' = $OC_{10}H_{21}$; x = 3, y = 1
257d R = R' = $OC_{10}H_{21}$; x = 1, y = 2
257e R = R' = $OC_{10}H_{21}$; x = 1, y = 3

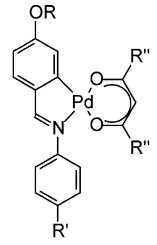
Chart 39. Mesogenic Palladacycles Derived from the Orthopalladation of Aromatic Imines



258a R = $C_{10}H_{21}$, R' = H
258b R = $C_{10}H_{21}$, R' = OC_2H_5
258c R = $C_{10}H_{21}$, R' = OC_6H_{13}
258d R = $C_{10}H_{21}$, R' = $OC_{10}H_{21}$

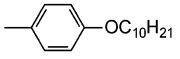
258e R =  , R' = $OC_{10}H_{21}$

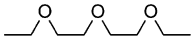
R'' = 

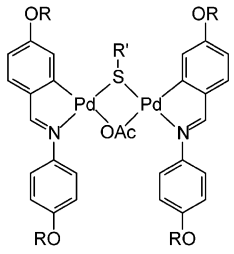


259a R = $C_{10}H_{21}$, R' = H, R'' = Me
259b R = $C_{10}H_{21}$, R' = OC_2H_5, R'' = Me
259c R = $C_{10}H_{21}$, R' = OC_6H_{13}, R'' = Me
259d R = $C_{10}H_{21}$, R' = $OC_{10}H_{21}$, R'' = Me

259e R =  , R' = $OC_{10}H_{21}$

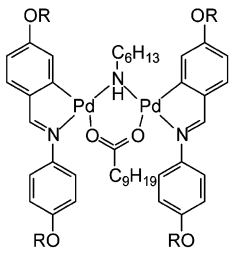
R'' = 

259f R = OR' = 
R'' = Me



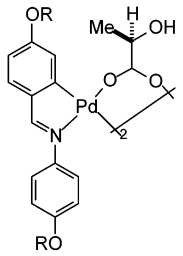
260 R = C_nH_{2n+1} (n = 6, 8, 10)

R'' = C_mH_{2m+1} (m = 6, 8, 10, 18)

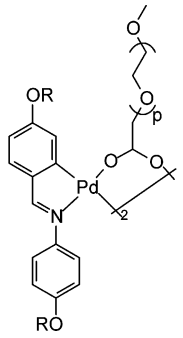


261 R = C_nH_{2n+1} (n = 2, 6, 10)

Chart 40. Mesogenic Palladacycles Containing Carboxylato Bridges



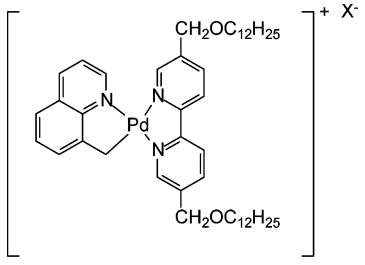
262



263

R = C_nH_{2n+1} (n = 6, 10)
p = 1,2

Chart 41. Mesogenic Palladacycle 264



$X^- = O_3SOC_{12}H_{25}$

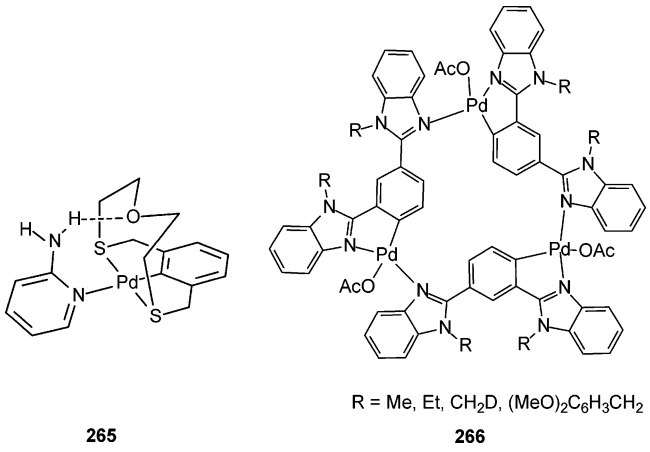
264

The most common class of liquid crystalline palladacycles are those derived from imine ligands.[326,332] The palladacycles presented in Chart 39 clearly show the efforts at lowering the symmetry of the early dimeric palladacycle mesogens (**258**) by changing the bridge structure or by a bridge splitting reaction with the known diketonato ligand. Several interesting proprieties were characterized in these studies, such as a significant lowering of the mesophase temperature formation and ferroelectric behavior. For example, compound **259f**, containing polyether substituents, shows liquid crystalline behavior at room temperature.[332e]

The mesogenic proprieties of imine palladacycles can be improved with the utilization of bulky carboxylato bridges.[333] Palladacycle **263**, containing a polyether-substituted carboxylate bridge, presents a large range of smetic A phases at temperatures lower than 50 °C. Interesting behavior was observed with palladacycle **262**, where the replacement of an acetate bridge by L-lactate produces a positive effect on mesomorphic properties, since the acetate-bridged palladacycle does not present liquid crystalline behavior (Chart 40).

It was also demonstrated that a cationic palladacycle derived from the C−H activation of the 8-me-

Chart 42. Palladacycles 265 and 266



265 266

thylquinoline ligand with alkyl-disubstituted biyridine **264** forms a smetic A phase (168 °C) and a columnar (131 °C) liquid crystalline phase.[334] A high thermal stability is observed for this palladacycle, and no sign of decomposition was found after 2 h at 185 °C (Chart 41).

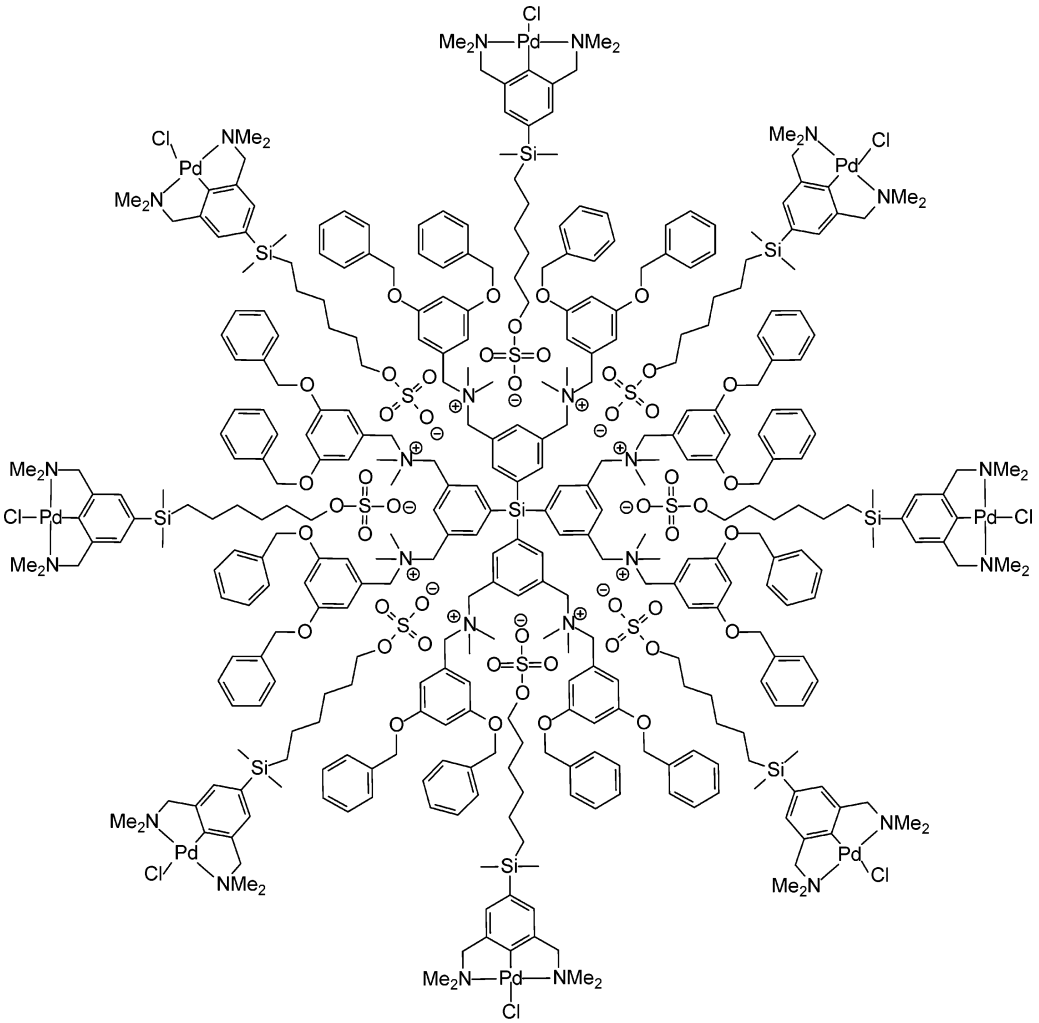
11. Supramolecules and Dendrimers

Supramolecular architectures of palladacycles have also been constructed employing impressive chemistry, and many of these display molecular recognition phenomena. These aspects have been recently elegantly addresed by van Koten et al.[3r] For example, the crown ether complex **265**[335] behaves as a metalloreceptor for 2-aminopyridine derivatives. The trimeric complex **266**, termed a molecular tricorn, was formed by a self-assembly process (Chart 42).[336] A tetranuclear Schiff base-containing tetranuclear complex, synthesized by a self-assembly process, comprising a central "Pd_4O_4" ring has also been described. The analogue **267**[337] comprises a polycationic dendrimeric assembly with eight anionic metal complexes and was used as a catalyst in an Aldol condensation with comparable results to those for the unsupported palladacycle (Chart 43).

12. Conclusions and Trends

It is doubtless that palladacycles possess a plethora of important and interesting properties, which can explain their popularity and ever-increasing applica-

Chart 43. Metalodendrimer 267



267

tions. Most of this interest centers on their facile synthesis and easily handling. Moreover, the possibility of modulating their electronic and steric properties simply by changing (i) the size of the metallacyclic ring (3−10 membered), (ii) the nature of the metalated carbon atom (aliphatic, aromatic, vinylic, etc.), (iii) the type of donor group (N-, P-, S-, O-containing group, etc.) and its substituents (alkyl, aryl, etc.), or (iv) the nature of the X ligands (halide, triflate, or solvent, e.g. MeCN, H_2O) renders them an interesting and varied family of organometallic compounds. Although in some cases the cyclopalladation process has been used for the functionalization of the Pd−C bond (mainly in organic synthesis), the vast majority of the applications of palladacycles involve an intact Pd−C bond; i.e., the palladated unit is used as an ancillary ligand. As well as proving useful as stoichiometric agents, palladacycles, notably since the discovery of the Herrmann−Beller system, now display potential for coupling chemistry and industrial applications. However, as pointed out recently, perhaps *in many regards*, palladacycles have not truly met their early promise.[3z,186] *A Pd(II)/Pd(IV) mechanism is highly unlikely, solid-based catalysts, designed for reusability, are probably only slow-releasing sources of Pd(0), and enantioselective reactions, where the Pd(0) has been released from the chiral environment, give invariably racemic product.* Rather than representing a whole new branch of chemistry, the catalytic potential of palladacycles is very similar to that of ligand-stabilized or homeopathic palladium chemistry, although in this respect palladacycles serve as a very useful mechanistic tool. Moreover, palladacycles may provide sources of more active Pd catalytic active species than classical metal sources for performing C−C coupling reactions, such as in the case of the Heck reaction that can be performed at room temperature using palladacycle **200**. Nevertheless, palladacycle chemistry is still a fascinating area. This interesting class of compounds represents a challenge to chemists not only in terms of their synthesis but also in terms of their structures, design, and types of ligands metalated. They have applications in domains as diverse as biological chemistry, material science, synthesis, ligand resolution, or chiral (Pd(II)) catalysts for asymmetric catalysis.

It is also quite fitting that most of the work cited herein, published over the last 10 years, is not limited to the use of palladacycles as catalyst precursors but also refers to important and "hot" areas such as in photoluminescent devices and medicinal and biological chemistry. This serves to underline that the chemistry of palladacycles will undoubtedly have a lot more to offer soon, in areas such as organometallic precursors for soluble Pd nanoparticles and catalytic CH activation chemistry.

13. Acknowledgments

Thanks are due to CAPES, CNPq, and Fapergs (Brazil) for partial financial support.

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CR030681R