Emergence of Palladium(IV) Chemistry in Synthesis and Catalysis

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1. Introduction

Palladium-catalyzed bond-forming processes (e.g., C−C, C−X, C−Y; X = F; Y = NR_2, OR, SR, etc.) represent essential tools for the synthetic chemist. A fascinating myriad of adventurous and unique Pd-catalyzed transformations are routinely found as key steps in target-oriented syntheses, affording complex natural products, functional advanced materials, fluorescent compounds, pharmaceutical lead compounds, and other high-value commercial products. Innovative Pd catalyst design, the identification of new synthetic methodologies, and the acquirement of detailed mechanistic insight, spanning both homogeneous and heterogeneous fields, underpin the numerous developments seen in this area over the past 40 years.

Most commonly, Pd-catalyzed bond-forming processes involve Pd^0/Pd^{II} complexes as intermediates. In recent times, the involvement of Pd^{IV} complexes have been implicated in many new synthetic methodologies, for which important advances have been made in the last 5 years or so. While observing the emergence of catalytic Pd^{IV} chemistry, particularly in organic synthesis, we identified the need to comprehensively review this area, which draws on aspects from both inorganic (organometallic) and organic chemistry fields. The historical background to organopalladium(IV) chemistry is therefore detailed. We have selected a wide range of diverse transformations where Pd^{IV} complexes are believed to act as key intermediates. It is clear that catalytic reaction manifolds involving Pd^{IV} intermediates offer new

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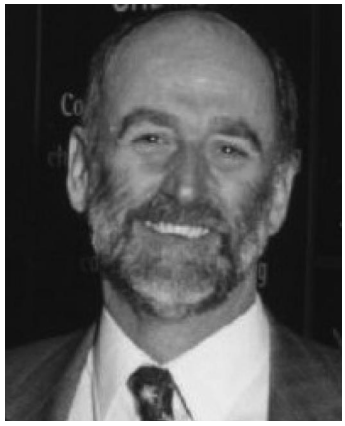
Petr Sehnal was born in Turnov, now Czech Republic, in 1979. He received his M.Sc. degree in chemistry in 2002 from Charles University, Prague. He obtained his Ph.D. in organic chemistry in 2006 under the guidance of Dr. Ivo Stary at IOCB Prague, where he worked on the synthesis of helical polyaromatics. He then moved to the University of York (U.K.) with the support of an EPSRC Postdoctoral Fellowship to conduct research in synthetic and mechanistic organic and organometallic chemistry. He has recently taken up a KTP Associate position at the University of Hull (U.K.). His main scientific interests are concerned with the development of new transition metal catalyzed reactions and the synthesis of novel functional materials.

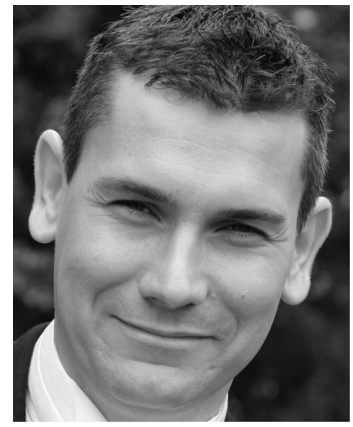


Richard Taylor graduated from the University of Sheffield with B.Sc. and Ph.D. (Dr. D. Neville Jones) degrees. Postdoctoral periods with Dr. Ian Harrison (Syntex) and Professor Franz Sondheimer (UCL) were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to the Chair of Organic Chemistry at the University of York. Taylor's research interests center on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the Tilden Medal (2000) and Pedler Lectureship (2007) of the Royal Society of Chemistry. Taylor is the current President of the International Society of Heterocyclic Chemistry, a past-President of the RSC Organic Division, and an Editor of Tetrahedron.

opportunities for the design of adventurous synthetic methodologies, which can complement or even in some cases supersede existing or related processes operating via Pd^0/Pd^{II} intermediates.

1.1. Common Palladium Oxidation States

Palladium is a member of the nickel triad of the periodic table. Palladium complexes exist predominantly in three oxidation states: Pd^0, Pd^{II}, and Pd^{IV}, although both Pd^I and Pd^{III} are known. Practically all characterized complexes in the Pd^{IV} oxidation state are octahedral and diamagnetic with a low-spin t_{2g}^6 configuration. Pd^{IV} complexes have traditionally been described as rare and elusive as compared to the both thermodynamically stable and kinetically inert Pt^{IV}



Ian Fairlamb was appointed to a lectureship in Organic Chemistry at the University of York in 2001, following Ph.D. study with Dr. J. Dickinson in Manchester at MMU (1999), and a post-doctoral research project with Prof. G. C. Lloyd-Jones in Bristol (2000−2001). Fairlamb is currently a Royal Society University Research Fellow (2004−2012) and was recently promoted to full Professor in York. Fairlamb's research interests interface through Catalysis, Synthesis, and Chemical Biology, particularly in ligand design for Pd catalysts and an understanding of the reaction mechanisms of cross-coupling processes. The group collaborates with industry (AstraZeneca, DSM Pharmaceuticals, GlaxoSmithKline, Johnson-Matthey, and Organon-Schering-Plough) and various academic groups from Europe, China, and the United States.

complexes. This is also reflected in the organometallic complexes. Consequently, Pt^{IV} complexes containing the $\{PtMe_3\}$ fragment have been known[1] since 1907, but the first methyl Pd^{IV} species[2] were not reported until 1986.

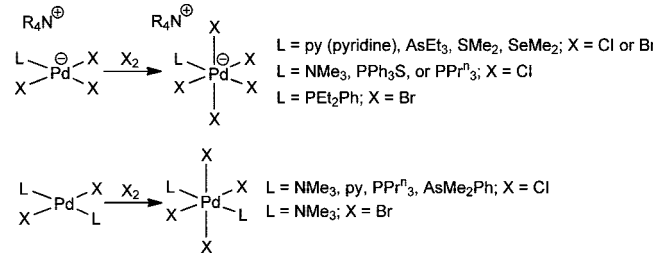
On thermodynamic grounds, the decreased stability of Pd^{IV} relative to Pt^{IV} is expected in view of the greater ionization potential [$Pd_{(g)} \rightarrow Pd^{4+}_{(g)} = 2546$ kcal mol^{-1}, $Pt_{(g)} \rightarrow Pt^{4+}_{(g)} = 2238$ kcal mol^{-1}], which is only slightly offset by the lower enthalpy of atomization of palladium [91.1 (Pd), 130.5 (Pt) kcal mol^{-1}].[3,4] The $t_{2g}^6 e_g^0$ configuration of the M^{IV} complexes results in a maximum ligand field stabilization energy for the octahedral complexes, and here too the larger Δ values for 5*d* elements (approximately 30% greater) contribute to greater stability for the Pt^{IV} complexes.[5]

2. Inorganic Pd^{IV} Compounds

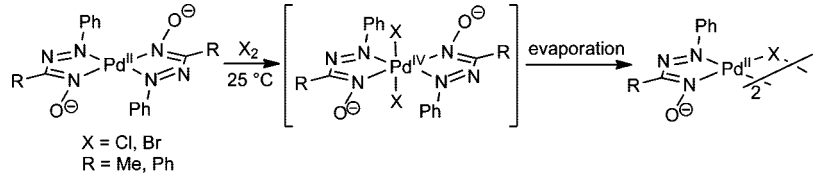
2.1. Complexes Prepared by Oxidation of Pd^{II} with Halogens

The simplest and the best characterized examples of inorganic Pd^{IV} compounds are the $[PdX_6]^{2-}$ anions (X = F, Cl, Br); the chloro and bromo complexes are readily prepared by halogen oxidation of solutions of the Pd^{II} analogues.[6–11] Interestingly, crystallographic studies show that in $[PdCl_4]^{2-}$ and $[PdCl_6]^{2-}$ the palladium atom has effectively the same atomic radius.[12] $[PdF_6]^{2-}$ has been used to stabilize O_2^+ salts;[13,14] Pd^{IV} tellurato complexes have been studied as

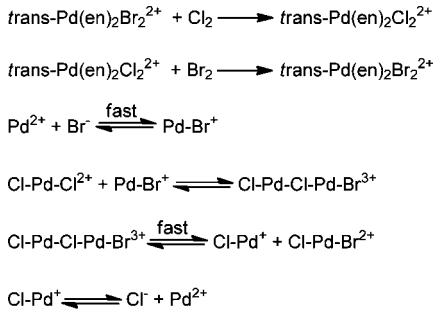
Scheme 1. Preparation of $[R_4N][PdLX_5]$ and $[PdL_2X_4]$



Scheme 2. Reactions of a Bis(arylazo-oximato) Pd^{II} Complex with Halogens



Scheme 3. Interconversion of *trans*-Dichloro- and *trans*-Dibromobis(ethylenediamine)Pd^{IV} Cation Species



multielectron oxidants. Furthermore, some antimicrobial effects have been reported for a Pd^{IV} complex of a tetradentate macrocyclic ligand.[15]

Pd^{IV} complexes with neutral ligands can be prepared, but most decompose very easily. As early as 1932, it was noted[16] that the oxidation of $Pd(NH_3)_2Cl_2$ with chlorine leads to the labile complex $[Pd(NH_3)_2Cl_4]$. Similar reactions occur with $Pd(en)C1_2$ and $Pd(py)_2C1_2$ (en = 1,2-ethylenediamine, py = pyridine), but in these cases the diamino Pd^{IV} tetrachlorides are more stable and can be isolated in a pure form (Scheme 1). Pd^{IV} complexes[17,18] and Pt^{IV} complexes[19,20] with neutral unidentate and bidentate ligands were studied extensively by Gulliver and Levason. Oxidation of $[R_4N][PdLX_3]$ with the corresponding halogen (X_2) gave octahedral Pd^{IV} anions $[R_4N][PdLX_5]$ [L = py, $AsEt_3$, SMe_2, or $SeMe_2$, X = Cl or Br; L = NMe_3, PPh_3S, or PPr^n_3, X = Cl; L = PEt_2Ph, X = Br]. Attempts to prepare analogues with L = $SbMe_2$, $TeMe_2$, or dimethyl sulfoxide were unsuccessful.

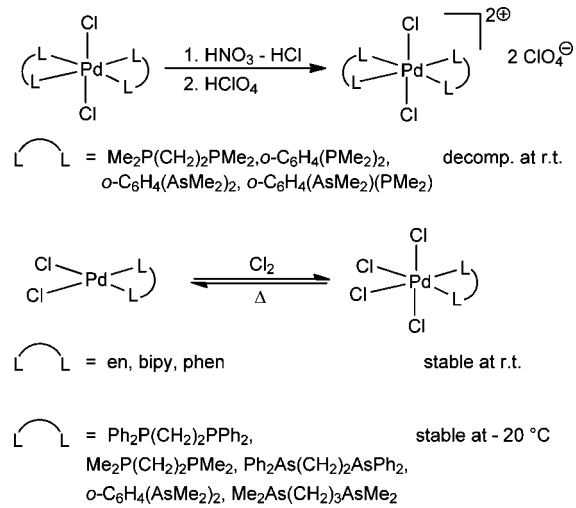
A thermogravimetric analysis (TGA) stability study revealed[18] that the $[PdLX_5]^-$ anions are more stable than the neutral complexes $[PdL_2X_4]$. The stability of the $[Pd^{IV}LX_5]^-$ complexes is very dependent upon the nature of the ligand L ($NR_3 \gg PR_3 \approx AsR_3 \approx SR_2 > SeR_2$ ($\gg SbR_3$, TeR_2)), but for the anions at least, the differences between chloride and bromide are small.

Oxidative addition of X_2 to give a Pd^{IV} complex was also observed in the reaction of bis(arylazo-oximato)Pd^{II} complexes (Scheme 2).[21] The intermediate was diamagnetic and showed ^1H NMR signals consistent with a symmetrical structure but decomposed to a dinuclear Pd^{II} complex during isolation.

The kinetics and mechanism of interconversion between *trans*-$[Pd(en)_2Cl_2]^{2+}$ and *trans*-$[Pd(en)_2Br_2]^{2+}$ has been studied by stopped-flow spectrophotometry.[22] A complex third-order kinetic model has been proposed (first order in entering halide, Pd^{IV} substrate, and $Pd(en)_2^{2+}$ that was found to catalyze the reaction through a redox ligand-transfer process as shown in Scheme 3).

Pd^{IV} complexes of phosphorus and arsenic donor ligands of the type $[Pd(L-L)Cl_4]$ have been prepared by chlorine oxidation of $[Pd(L-L)Cl_2]$ but exhibit even lower stability compared to the nitrogen ligand complexes and decompose at −20 °C to give chlorine and Pd^{II} (Scheme 4).[17] Cationic

Scheme 4. Preparation of Pd^{IV} Complexes with Bidentate Phosphorus and Arsenic Donor Ligands



complexes of the type *trans*-$[Pd(L-L)X_2](ClO_4)_2$ were also reported.

These studies suggest that $[Pd(L-L)_2X_2]^{2+}$ are kinetically more stable than $[Pd(L-L)X_4]$ species for constant L−L and X, which is probably due to the $[Pd(L-L)X_4]$ type having *cis*-halide ligands that reductively eliminate X_2 more easily (as shown by their thermal decomposition), while the *trans*-cations do not have this decomposition route available.

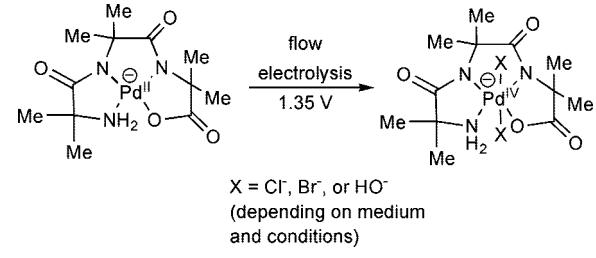
2.2. Complexes Prepared by Electrochemical Oxidation of Pd^{II}

Apart from strong oxidants, electrochemical methods have also been shown to produce stable Pd^{IV} complexes. A tripeptide amidate Pd^{IV} complex with sufficient stability in the absence of other strong oxidants has been characterized and studied (Scheme 5).[23] In another case, however, evidence for the oxidation state +III for organopalladium complexes has been obtained, but no further oxidation to Pd^{IV} was observed.[24]

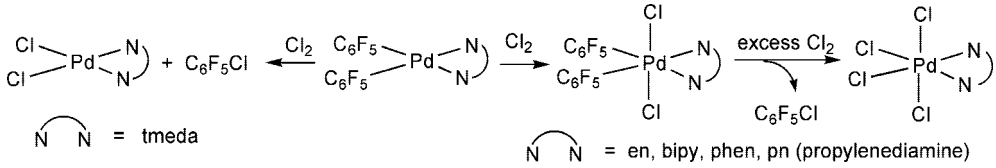
2.3. Applications of $Pd^{II} \rightarrow Pd^{IV}$ Compounds in Materials Chemistry

While Pd^{IV} compounds themselves are diamagnetic, halogen-bridged mixed valence $Pd^{II}-Pd^{IV}$ complexes show

Scheme 5. Electrochemical Synthesis of a Pd^{IV}−Amidate Complex



Scheme 6. Synthesis and Reactions of Bis(pentafluorophenyl) Pd^{IV} Complexes



very interesting one-dimensional electronic properties.[25,26] They consist of square-planar Pd^{II} species and tetragonal−bipyramidal Pd^{IV} species alternately arranged in $\cdots Pd^{II}\cdots X-Pd^{IV}-X\cdots Pd^{II}$ chains. Evidence for electronic interactions within the chains has been obtained from electrical conductivity and spectroscopy measurements.[27,28] A one-dimensional mixed-valence complex $[Pd^{II}L][Pd^{IV}Cl_2L](ClO_4)_4$ (L = 1,4,8,11-tetraazacyclotetradecane) has been reported.[29] In order to stabilize the $\cdots Pd^{II}\cdots Pd^{IV}\cdots$ chains with NH···O···HN hydrogen bonds, other tetradentate nitrogen ligands have also been used.[28]

3. Organometallic Pd^{IV} Compounds

The very first Pd^{IV} compounds containing a Pd−C bond were synthesized by Uson et al. in 1975 (Scheme 6).[30] An earlier report of Nyholm and Royo[31] claimed that two pentafluorophenyl groups of $BrTl(C_6F_5)_2$ could be transferred to the complex $Cl_2Pd(PPh_3)_2$ to give an organometallic Pd^{IV} complex, but it was later shown[32] that the reaction actually leads to a mixture of binuclear and mononuclear Pd^{II} complexes. Four organometallic complexes $Cl_2(C_6F_5)_2Pd(L-L)$ (L−L being a bidentate nitrogen-donor ligand) have been prepared by oxidative addition of chlorine to the corresponding bis(pentafluorophenyl) Pd^{II} complexes, $(C_6F_5)_2Pd(L-L)$. Interestingly, it was found that excess chlorine promotes reductive elimination of C_6F_5Cl, and when a more sterically hindered tmeda ligand is used, the Pd^{IV} intermediate is too unstable to be isolated.

3.1. Organometallic Pd^{IV} Compounds from Oxidative Addition of Pd^{II} into $C(sp^3)-X$ Bonds

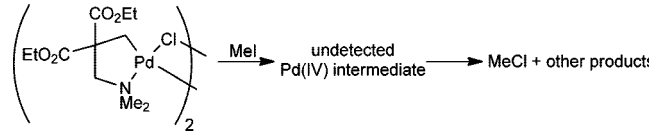
3.1.1. Alkyl Complexes

Despite the initial lack of direct evidence, organoPd^{IV} species were tentatively suggested as intermediates in various cleavage reactions of organoPd^{II} complexes, usually with dihalogens or other simple inorganics.

In 1977, Yamamoto reported[33] that reactions of complexes $[PdR_2L_2]$ (R = Me, Et, Pr^n; L = PEt_3, PPh_2Me) with iodine afforded $[PdI_2L_2]$ and RI, and of $[PdR_2(dppe)]$ with MeI gave CH_3H, CH_3CH_3, RH, RCH_3, R−R R−I, and alkene products together with $[PdI_2L_2]$, suggesting the presence of a six-coordinate intermediate Pd^{IV} species (Scheme 7). Interestingly, this was probably the first observation of transient organoPd^{IV} complexes supported by phosphine ligands.

An oxidative addition−reductive elimination mechanism was proposed for the hydrogen and hydrogen chloride

Scheme 8. Tentative Mechanism of the Reaction of a Pallada(II)cycle with Methyl Iodide



cleavage reactions of a pallada(II)cyclic compound shown in Scheme 8.[34]

Attempts to react the palladacycle with methyl iodide yielded a complex mixture, but significant amounts of methyl chloride were found, consistent with reductive elimination from a methyl Pd^{IV} intermediate, and a transient species with a methyl resonance at δ 2.20 ppm was detected by ^1H NMR spectroscopy.

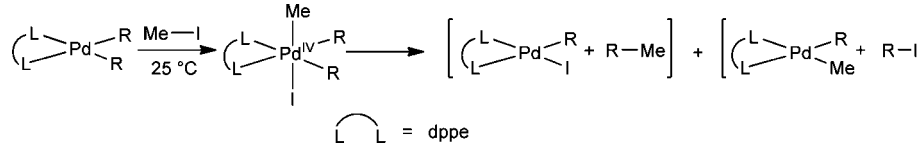
In 1986, a pioneering study was published by Canty et al.,[2] which reported the oxidative addition of iodomethane to dimethyl(2,2′-bipyridyl)palladium(II) and isolation of the first hydrocarbyl Pd^{IV} complex, *fac*-trimethyl(2,2′-bipyridyl)iodopalladium(IV) (Scheme 9). The complex was structurally characterized by NMR spectroscopy and X-ray diffraction (XRD) and reductively eliminates ethane in solution to form methyl (2,2′-bipyridyl)iodopalladium(II).

In the subsequent paper,[35] the complexes $PdIMe_3(L_2)$ (L_2 = bipy, phen) were shown to be stable on storage at ca. −20 °C, but in solution reductive elimination of ethane occurred with formation of $PdIMe(L_2)$. Pd^{IV} complexes with the other bidentate ligands could be detected in situ by ^1H NMR spectroscopy but could not be isolated. Further ^1H NMR studies conducted in CD_3CN showed that the bidentate ligand complexes form an equilibrium between $PdIMe_3(L_2)$ and $[PdIMe_3(L_2)(CD_3CN)]^+$, and oxidative addition of CD_3I or MeI to $PdMe_2(bipy)$ in $(CD_3)_2CO$ at low temperature indicates that a cation is formed prior to formation of $PdIMe_2R(bipy)$ as shown in Scheme 10. Kinetic studies of the reaction of iodomethane with "$Pd^{II}Me_2$" phosphine complexes, giving $Pd^{II}IMe$ complexes and ethane, are consistent with the occurrence of oxidative addition, with rapid elimination of ethane precluding spectroscopic detection of "$Pd^{IV}Me_3$" intermediates.

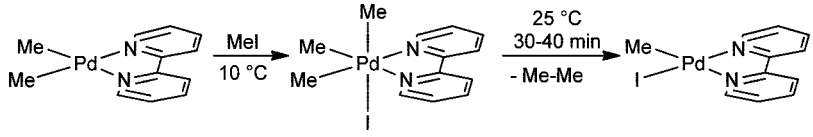
A rigid C,N,N′ ligand backbone was used by van Koten[36] to control the behavior in oxidative addition/reductive elimination reactions of a cyclometalated Pd^{II} complex (Scheme 11). An unusually stable organometallic Pd^{IV} dichloride adduct and reactions with alkyl halides were studied.

A dinuclear Pd^{II} complex of the biscyclometalating ligand 3,3′,5,5′-tetrakis[(dimethylamino)methyl]biphenyl was studied by van Koten et al.[37] Its oxidation with 2 equiv of $PhICl_2$

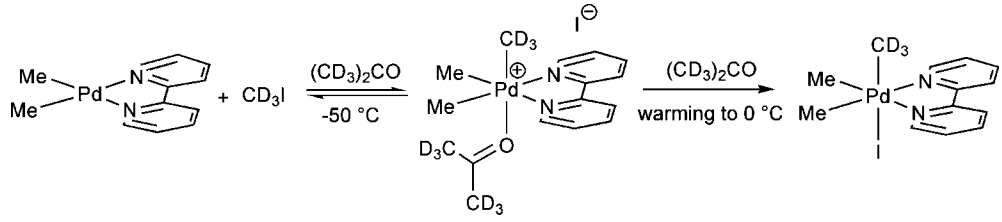
Scheme 7. Reactions of Bis(phosphine)Pd^{II} Dialkyl Complexes with Methyl Iodide and Decomposition of the Resulting Transient Pd^{IV} Complex



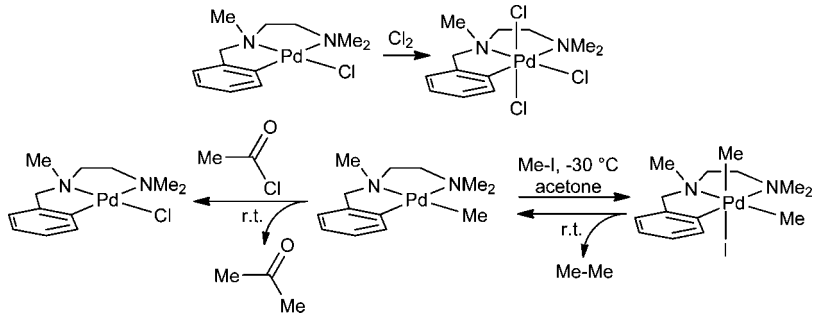
Scheme 9. Synthesis and Decomposition of *fac*-Trimethyl(2,2′-bipyridyl)iodopalladium(IV)



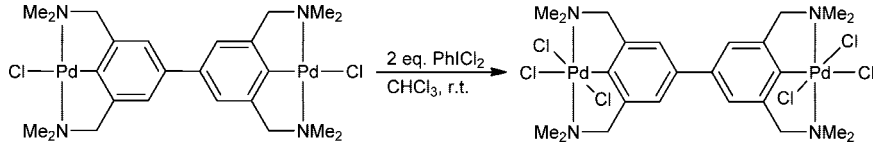
Scheme 10. Pre-equilibrium Cationic Pd^{IV} Species Prior to the Formation of $PdI(CD_3)Me_2(bipy)$



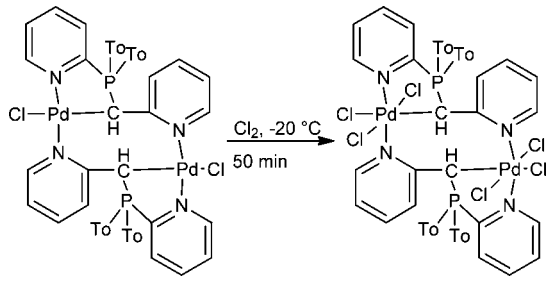
Scheme 11. {C,N,N′} Ligated Pd^{II} Complex and Its Reactions with Chlorine, Acetyl Chloride, and Methyl Iodide



Scheme 12. Formation of a Dinuclear Pd^{IV} Complex of the Biscyclometalated 3,3′,5,5′-Tetrakis[(dimethylamino)methyl]biphenyl



Scheme 13. Direct Chlorination of a Dimeric Pallada(II)cyclic Complex

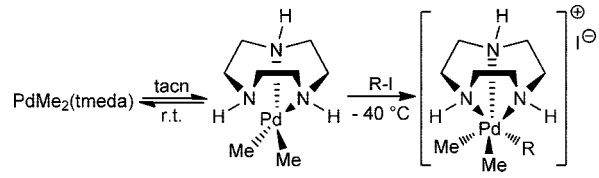


in solution leads cleanly to the double oxidative addition product (Scheme 12). Although the product could be isolated in a low yield (pure by ^{1}H NMR spectroscopy), its further characterization was prevented by decomposition, presumably by $Pd^{IV}-Cl$ reductive elimination.

Direct chlorination of an interesting dimeric cyclopalladated complex has been reported by Vicente et al. (Scheme 13).[38]

Facially chelating tridentate 1,4,7-triazacyclononane (tacn) was used[39] to produce stable *fac*-Me_3Pd^{IV} and *fac*-Me_2EtPd^{IV} complexes (Scheme 14). The pure compound $[PdMe_3(tacn)]^+I^-$ was characterized by elemental analysis, NMR spectroscopy, and electrospray mass spectrometry. As compared with other trimethyl Pd^{IV} compounds, this complex is thermally extremely stable, and it decomposes in the solid state at 152−154 °C. Solid *fac*-$[PdMe_3(bipy)I]$ violently decomposes at 100−110 °C.[2] Ethane rather than

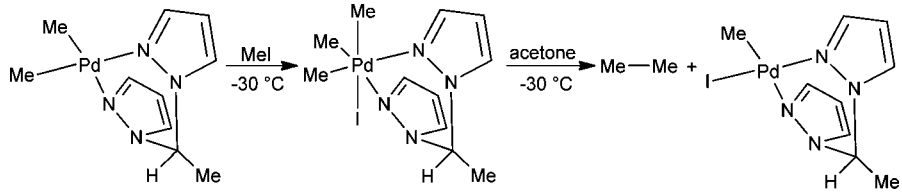
Scheme 14. Synthesis of Stable Trialkyl Pd^{IV} Complexes with 1,4,7-Triazacyclononane



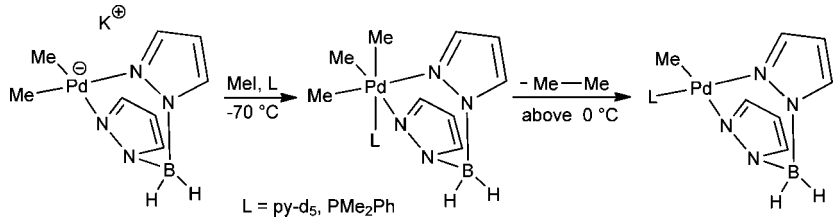
methane (with imine/enamine formation) is the sole hydrocarbon formed in the course of slow decomposition of $[PdMe_3(tacn)]^+I^-$ at 140 °C in a dimethyl sulfoxide (DMSO)-d_6 solution.

Scorpionate ligands (in particular the anionic bis(pyrazol-1-yl)borate and the neutral tris(pyrazol-1-yl)methane), have also been widely used to stabilize organoPd^{IV} centers. A comprehensive review of poly(pyrazolyl)borate ligands and their complexes is available.[40] The first synthetic, spectroscopic, and structural studies in hydrocarbyl Pd^{IV} chemistry were reported by Canty.[35] In a series of *fac*-Me_3Pd^{IV} complexes with varying ligands, the following stability trends were determined: $PdIMe_3(L_2) < [PdMe_3(L_3)]I$ (the complexes with bidentate ligands have to be stored below −20 °C, while the complexes with tridentate ligands are stable as solids at ambient temperature); $[PdMe_3((pyr)(mim)_2CH]I > [PdMe_3(pz)_3CH]I < [PdMe_3(pz)_3CH]BF_4$, (pyr = pyridin-2-yl, mim = 1-methylimidazol-2-y1, pz = pyrazol-1-yl). The enhanced stability of $[PdMe_3(L_3)]I$ compared to $PdIMe_3(L_2)$ at least partly

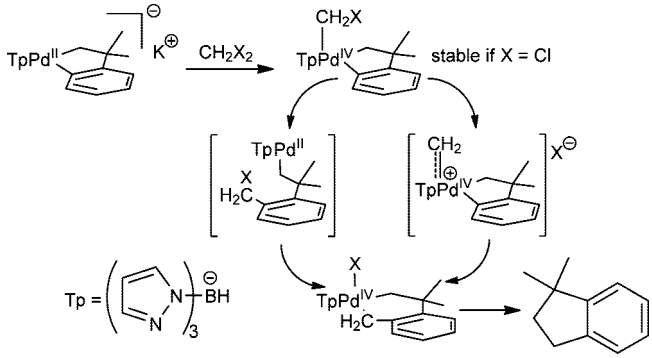
Scheme 15. Preparation and Decomposition of *fac*-PtIMe$_3${(pz)$_2$CHMe−*N*,*N*′}



Scheme 16. Preparation and Decomposition of Trimethyl Pd^{IV} Bis(pyrazol-1-yl)borate Complexes



Scheme 17. Synthesis and Possible Decomposition Mechanisms of [Pd(CH$_2$X)(CH$_2$CMe$_2$-*o*-C$_6$H$_4$(CH$_2$))(κ^3-Tp)]



results from the requirement for dissociation of one donor group of the tripod ligand prior to reductive elimination.

Other examples of Pd^{IV} complexes supported by the bidentate 1,1-bis(pyrazol-1-yl)ethane[41] and bis(pyrazol-1-yl)borate[42] have also been reported but show much lower stability compared to the tridentate analogues.

The Pt^{IV} complex *fac*-PtIMe$_3${(pz)$_2$CHMe-*N*,*N*′} has been fully characterized by NMR spectroscopy and XRD. However, the analogous Pd^{IV} complex could only be characterized at −30 °C, and it reductively eliminates above this temperature to give ethane and PdIMe{(pz)$_2$CHMe-*N*,*N*′} (Scheme 15).

The neutral Pd^{IV} complexes containing the bis(pyrazol-1-yl)borate ligand, PdMe$_3${(pz)$_2$BH$_2$}(L) [L = py-d_5, PMe$_2$Ph], were generated in solution by oxidative addition of iodomethane to [PdMe$_2${(pz)$_2$BH$_2$}]$^-$ at −70 °C followed by addition of L.[42] Being somewhat more stable, they reductively eliminate ethane above 0 °C (Scheme 16).

Reactions of the anionic Pd^{II} metalacycle [K{Pd(CH$_2$CMe$_2$-*o*-C$_6$H$_4$)(κ^2-Tp)}] with CH$_2$X$_2$ (X = Cl, Br, I) have been studied.[43] With CH$_2$Cl$_2$, the reaction leads to an extremely thermally stable Pd^{IV} chloromethyl complex (Scheme 17). The analogous reactions with CH$_2$Br$_2$ and CH$_2$I$_2$ gave rise to the six-membered metalacycles [K{Pd(CH$_2$CMe$_2$-*o*-C$_6$H$_4$(CH$_2$))(κ^3-Tp)}] (X = Br or I), as a result of the formal insertion of CH$_2$ into the Pd−carbon bond. However, the most interesting aspect of this process concerns the mechanism of the CH$_2$ migration. A likely route involves a reductive coupling of the CH$_2$X and aryl groups, to afford a Pd^{II} complex that subsequently undergoes an intramolecular oxidative addition of the CH$_2$−X bond. The relative stability of the intermediates suggests that the ability to undergo the CH$_2$ migration process increases in the order CH$_2$Cl < CH$_2$Br < CH$_2$I. This matches the trend in the strength of the Pd−CH$_2$X bonds that can be anticipated considering the group electronegativity and the size of the halomethyl ligand. The preference for alkyl−aryl coupling is substantiated by previous studies probing the selectivity of Pd^{IV} reductive elimination reactions. Notwithstanding the above, an attractive but alternative mechanistic pathway involving a transient Pd^{IV} carbene complex is conceivable as well. Interestingly, the observed reactivity trend fits in well with the degree of halide dissociation from the Pd−CH$_2$X linkage (I > Br > Cl). Carbene insertion reactions in isoelectronic complexes (compare Ir^{III}−Ir^{V} and Pd^{II}−Pd^{IV}) have been observed before.[44]

An independent study concerning the oxidative addition of methyl iodide into a Pd^{II} metalacyclic complex was conducted by Catellani.[45]

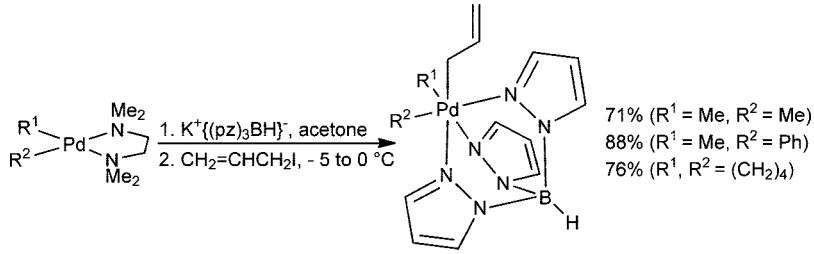
3.1.2. Allyl Complexes

The first allyl Pd^{IV} complexes were described by Canty et al.[46] Reaction of PdMe$_2${(pz)$_3$CH} with an excess of 2-propenyl iodide at ambient temperature in (CD$_3$)$_2$CO is rapid at ambient temperature but is followed by quantitative decomposition to ethane, free (pz)$_3$CH, and [PdI(η^3-C$_3$H$_5$)]$_2$ within 10 min. At −30 °C, the intermediate [*fac*-Pd(CH$_2$CH=CH$_2$)Me$_2${(pz)$_3$CH}]$^+$ cation could be characterized. In both [Pd(η^1-C$_3$H$_5$)Me$_2${(pz)$_3$CH}]I and [Pd(η^1-C$_3$H$_5$)Me$_2$-{(pz)$_3$CH}]Br, formed from PdMe$_2${(pz)$_3$CH} and 2-propenyl bromide, ^{1}H NMR spectroscopic analysis confirmed the η^1-binding mode of the allyl group. In fact, η^1-allylpalladium-pincer complexes are known intermediates in allylation reactions studied by Szabó et al.[47] Similarly in (allyl)$_2$Pd^{IV} species proposed by Kurosawa et al.[48] (Scheme 75), the second allyl group was introduced by reacting a Pd^{II}(η^3-allyl) complex with CH$_2$=CHCH$_2$X, which binds in an η^1-fashion.

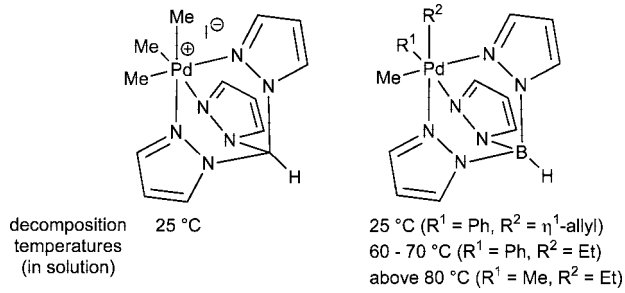
In a subsequent extensive synthetic study, Canty et al. showed[49] that very stable organoPd^{IV} complexes, Pd(CH$_2$CH$_2$-CH$_2$CH$_2$)R{(pz)$_3$BH} (R = Me, Et, PhCH$_2$, CH$_2$=CHCH$_2$), are accessible (Scheme 18).

The aryl- and η^1-propenyl Pd^{IV} complexes were stable above 0 °C and the ethylPd^{IV} complexes had stabilities in solution similar to that of the most stable ethyl Pd^{II} complexes. Again, the tris(pyrazol-1-yl)borate ligand considerably enhances the stability of Pd^{IV} complexes when compared with related neutral donor ligands[35] (Scheme 19).

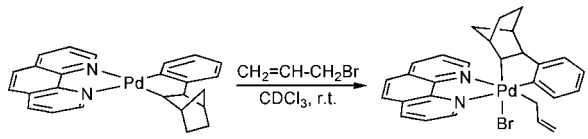
Scheme 18. Preparation of a Series of Allyl Pd^{IV} Complexes



Scheme 19. Stability Comparison of Neutral and Cationic Poly(pyrazolyl) Pd^{IV} Complexes



Scheme 20. Synthesis of a Pallada(IV)cyclic η^1-Allyl Complex



A later study concerning the oxidative addition of allyl bromide into a Pd^{II} metalacyclic complex was conducted by Catellani et al.[50] The product decomposed slowly at room temperature but could be characterized at −20 °C by NMR spectroscopy (Scheme 20).

Oxidative addition reactions of propargylic bromides (MeC′CCH_2Br and HC′CCH_2Br) with $[PdMe_2\{(pz)_3BH\}]^-$, $[Pd(CH_2CH_2CH_2CH_2)\{(pz)_3BH\}]^-$, and $PdMe_2$(bipy) were studied in detail by Canty et al.[51] Preference for adoption of the propargyl or allenyl tautomeric form of the Pd^{IV} products is dependent on ligand structure and substitution in the propargyl/allenyl fragment: for $Pd-C_3H_2Me$, propargyl is favored, whereas for $Pd-C_3H_3$, allenyl is favored for the $[(pz)_3BH]^-$ ligand and propargyl is favored for the bipy ligand (Scheme 21).

3.1.3. Benzyl Complexes

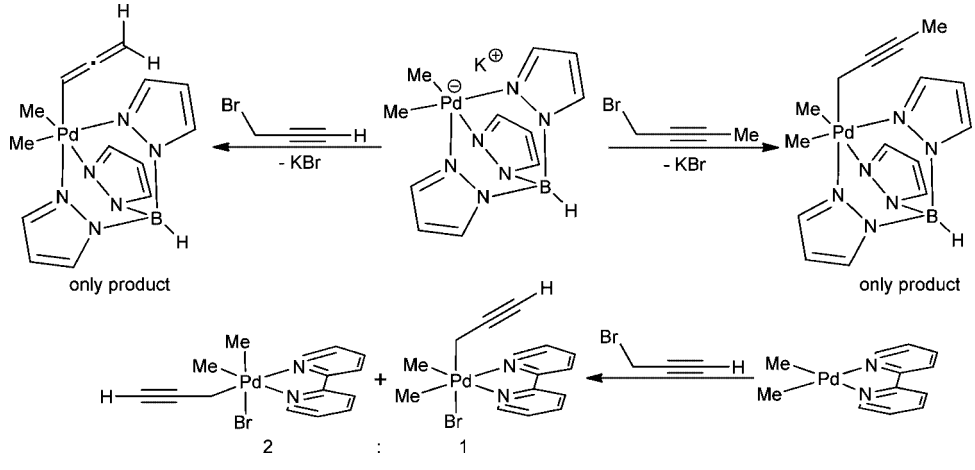
Pd^{IV} benzyl complexes were first proposed in the pioneering studies of Stille[52,53] that will be discussed in further detail later. It was found that $PdCl(CH_2Ph)(PPh_3)_2$ undergoes reaction with benzyl chloride and acyl chlorides at elevated temperatures, giving bibenzyl and benzyl alkyl ketones, respectively. It was proposed that an unstable Pd^{IV} species is generated and undergoes facile reductive elimination to yield $PdCl_2(PPh_3)_2$ and bibenzyl or benzyl alkyl ketone. A number of stable benzyl Pd^{IV} complexes have since been characterized, including outer periphery-palladated dendritic complexes.[54]

Benzyl and naphthyl bromides also react with dimethyl Pd^{II} complexes $PdMe_2(L_2)$ (L_2 = bipy, phen) to form the Pd^{IV} complexes $PdBrMe_2(CH_2Ar)(L_2)$ (Ar = p-C_6H_4X (X = H, Me, Br, NO_2), C_6F_5) and $PdBrMe_2(CH_2Ar)$(bipy) (Ar = 1-$C_{10}H_7$, 2-$C_{10}H_7$).[55] As shown in Scheme 22, the 2,2′-bipyridyl complexes and $PdBrMe_2(CH_2C_6F_5)$(phen) reductively eliminate ethane with formation of $PdBr(CH_2Ar)$(bipy) and $PdBr(CH_2C_6F_5)$(phen), respectively, on warming to ca. 40 °C in $(CD_3)_2CO$. The other 1,l0-phenanthroline complexes undergo less selective reductive elimination to form $PdBr(CH_2Ar)$(phen) and PdBrMe(phen) in a ca. 10:l ratio (Ar = p-C_6H_4Me) and approximately 3:l ratio (Ar = p-C_6H_4X where X = H, Br, NO_2).

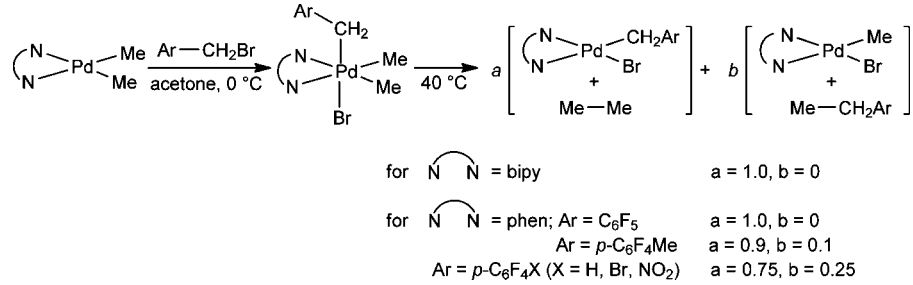
Interestingly, the stepwise addition of $PdMe_2$(bipy) and MMe_2(bipy) (M = Pd or Pt) allows for the preparation of μ-hydrocarbyl $Pd^{IV}-Pd^{IV}$ and $Pd^{IV}-Pt^{IV}$ dinuclear complexes.[55]

Oxidative addition reactions of 8-(bromomethyl)quinoline (mqBr) with $Pd(CH_2EMe_3)Ph$(bipy) result in the formation of octahedral Pd^{IV} complexes $[Pd(mq)(CH_2EMe_3)Ph(bipy)]Br$ (E = C, Si).[56] An X-ray structural analysis for the first example of a stable cationic aryl Pd^{IV} complex shows a *fac*-

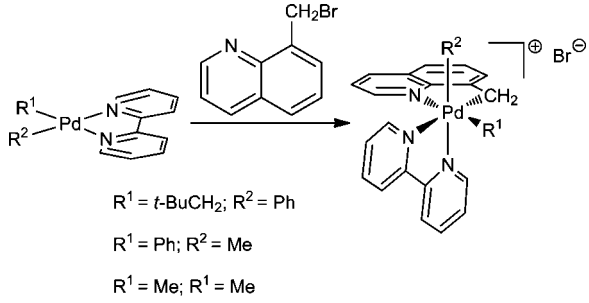
Scheme 21. Tautomeric Forms of Oxidative Addition Products of Pd^{II} Complexes and Propargylic Bromides



Scheme 22. Preparation and Reductive Elimination Behavior of Dimethyl(benzyl) Pd^{IV} Complexes



Scheme 23. Pd^{IV} Complexes from Oxidative Addition of Pd^{II} into 8-(Bromomethyl)quinoline



PdC_3N_3 configuration with the neopentyl group *trans* to the quinoline nitrogen donor atom (Scheme 23).

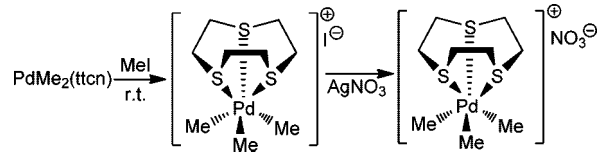
The cation $[Pd(mq)Me_2(bipy)]^+$ is less stable than the methyl(phenyl)Pd^{IV} analogue, decomposing in $(CD_3)_2CO$ by reductive elimination to form ethane and 8-ethylquinoline in 1:2 ratio, together with the Pd^{II} products [Pd(mq)(bipy)]Br and PdBrMe(bipy).

The neutral analogue, $\{Pd(mq)MePh\{(pz)_2BH_2\}$, was the first neutral aryl Pd^{IV} complex characterized by XRD.[57] The complex occurs as two isomers, and the one examined by X-ray crystallography has the *fac*-PdC_3 configuration with the phenyl group *trans* to the quinoline nitrogen donor.

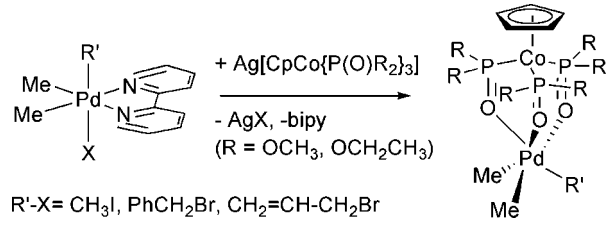
An independent study concerning the oxidative addition of *p*-nitrobenzyl bromide into a Pd^{II} metalacyclic complex shown in Scheme 24 was conducted by Catellani et al.[58] In solution, the complex is stable for several hours at room temperature, and then benzyl group migration to the aromatic site slowly occurs. Recently, Jutand and Catellani published an amperometric study concerning the oxidative addition/reductive elimination kinetics using a Pd^{II} metalacycle and benzyl halides.[59] It is interesting to note that, in these cases, selective benzyl−aryl reductive elimination is observed. On the other hand, in the $[Pd^{IV}BrMe(CH_2Ph)Ph(bipy)]$ complex reported by Canty,[60] exclusive alkyl−aryl reductive elimination to give toluene was found; this latter finding is likely a special case for the methyl group.

Pd^{IV} complexes show a strong preference for nitrogen donor ligands, and in line with this, the inorganic Pd^{IV} complex $[NPr_4][PdCl_5(SMe_2)]$ with a thioether ligand decomposes at room temperature.[18] Remarkably, with the exodentate ligand 1,4,7-trithiacyclononane (ttcn), the room temperature stable trimethyl Pd^{IV} complexes have been obtained as shown in Scheme 25.[61]

Scheme 25. Synthesis of Stable 1,4,7-Trithiacyclononane Trimethyl Pd^{IV} Complexes



Scheme 26. $\{Pd^{IV}Me_2R\}$ Fragment Stabilized by a Tris-chelating Oxygen Ligand



The dimethylPd^{II} complexes $[PdMe_2(tmeda)]$ and $[PdMe_2(bipy)]$ react with alkyl halides RX (=methyl iodide, benzyl bromide, and allyl bromide) in the presence of the sodium and the silver salts of the tris-chelating anionic oxygen ligands ($L^- = [CpCo\{PR_2(O)\}_3]^-$) to give the Pd^{IV} complexes $LPdMe_2R$[62] (Scheme 26). These represent the first trialkylPd^{IV} complexes, stabilized exclusively through oxygen donor ligands.

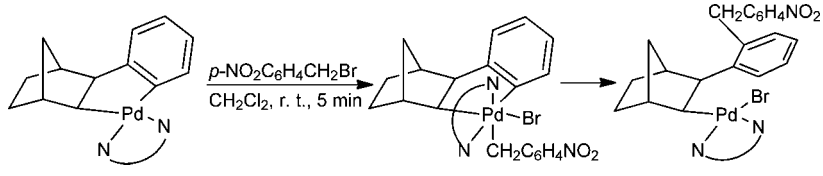
3.1.4. $C(sp^3)$−Pd^{IV} Complexes with P-Donor Ligands

Although it was originally believed that phosphine ligands cannot stabilize Pd^{IV} centers, various examples now exist of characterizable complexes containing the Pd^{IV}−PR_3 bond.

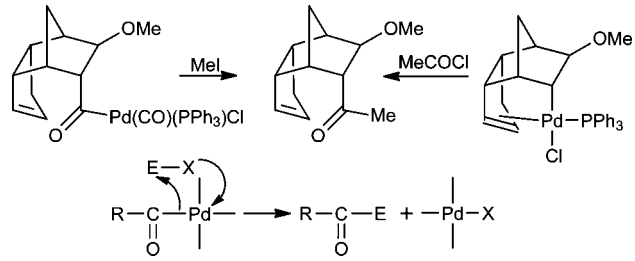
Pd^{IV}-containing complexes were probably involved in the reactions of palladated bicyclic compounds (Scheme 27).[63] The reactions with MeI and MeCOCl give the expected organic product of reductive elimination; however, the authors did not comment on a possible Pd^{IV} mechanism but suggested a cyclic transition state, followed by σ-bond metathesis type mechanism.

$PdX_2(PPh_3)_2$ (X = Cl, Br, I) reportedly react reversibly with saturated and aromatic hydrocarbons RH (RH =

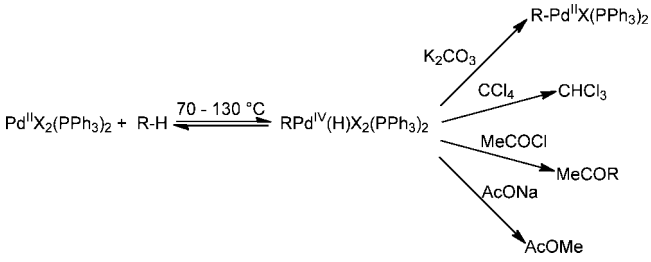
Scheme 24. Synthesis and Selective Benzyl−Aryl Reductive Elimination in a Cyclometalated (*p*-Nitrobenzyl) Pd^{IV} Complex



Scheme 27. Reactions of Pd^{II} Alkyl (or Acyl) Complexes Involving σ-Bond Metathesis or Pd^{IV} Intermediates



Scheme 28. Activation of Saturated and Aromatic Hydrocarbons with Bis(triphenylphosphine)palladium(II) Dihalides

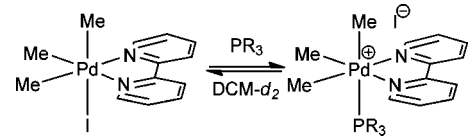


p-xylene, toluene, benzene, *n*-hexane, cyclohexane), slowly at ambient temperature and rapidly on heating at 70−130 °C, to produce Pd^{IV} complexes $Pd(H)(R)X_2(PPh_3)_2$ (Scheme 28). In the presence of bases, the Pd^{IV} intermediates eliminate HX, forming $Pd(R)X(PPh_3)_2$.[64] Activation of cyclohexane with $PdBr_2(PPh_3)_2$ and sodium alkoxides has also been reported.[65] A review on hydrido complexes of palladium is available,[66] and more Pd^{IV} hydride intermediates are discussed in sections 3.12 and 3.13.

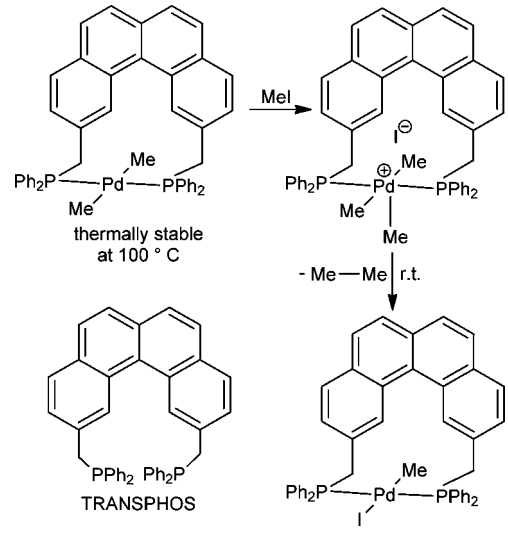
However, the authors have not provided any detailed spectroscopic characterization of these complexes due to rapid exchange processes and insufficient solubility at low temperatures.

Indirect introduction of a phosphine ligand via displacement of a weakly cordinating triflate has been demonstrated.[67] $PdMe_2$(bipy) was reacted with methyl triflate (CF_3SO_3Me) at −60 °C to form a Pd^{IV} complex, which was treated with a range of monodentate phosphines (PPh_3, $PMePh_2$, PMe_2Ph, PCy_3, $P(OMe)_3$, dppe, and *syn*,*syn*-1,5,9-triethyl-1,5,9-triphosphacyclodecane (tpcd)) to form complexes containing octahedral Pd^{IV} centers *fac*-[$PdMe_3$(2,2-bipy)(L)] (Scheme 29). All of the complexes reductively eliminate ethane on decomposition to form Pd^{II} species. The stability of Pd^{IV} complexes decreases in the order PMe_2Ph > $PMePh_2$ > PPh_3, and for complexes of PMe_2Ph there is a

Scheme 30. Equilibrium Phosphine−Iodide Exchange on Pd^{IV}



Scheme 31. Synthesis and Reactivity of Trimethyl Pd^{IV} Complex with a *trans*-Chelating Diphosphine Ligand



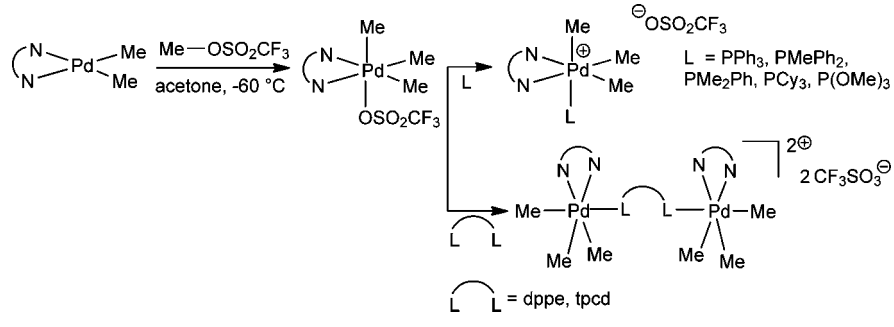
stability order phen > bipy > tmen for [$PdMe_3$(bidentate ligand)(PMe_2Ph)].

A very similar reaction has been reported with [$PdIMe_3$(bipy)].[68] Solutions containing unstable organoPd^{IV} complexes of phosphines, $[PdMe_3(bipy)(L)]^+$ (L = $PMePh_2$, PMe_2Ph, PPh_3), are generated on reaction of $PdIMe_3$(bipy) with phosphines. Using a more coordinating iodide ligand leads to faster reactions, which eventually reach equilibrium (Scheme 30). However, for the stronger donor ligands $PMePh_2$ and PMe_2Ph, displacement of iodide from $PdIMe_3$(bipy) in CD_2Cl_2 is approximately 2:3 complete for $PMePh_2$ and quantitative for PMe_2Ph at 0 °C.

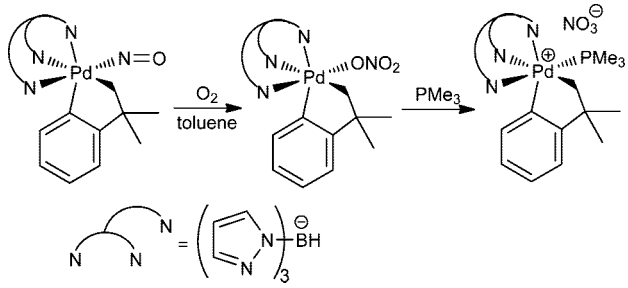
A reactive Pd^{IV} complex was generated from the thermally stable (TRANSPHOS)dimethylpalladium by Stille et al.[69] At room temperature, the addition of CD_3I induces rapid 1,1-reductive elimination of CD_3-CH_3, implicating a transient Pd^{IV} intermediate (Scheme 31).

A very unusual sequence of reactions in the coordination sphere of Pd^{IV} leading to a Pd^{IV}−phosphine complex has been disclosed by Carmona et al.[70] (Scheme 32).

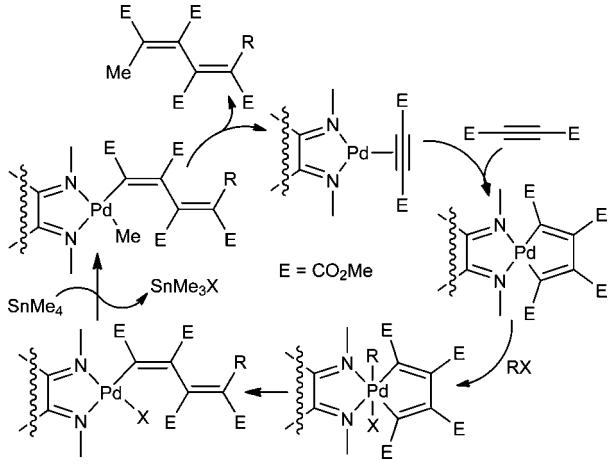
Scheme 29. Coordination of Mono- and Bidentate Phosphines to the {$Pd^{IV}Me_3$} Fragment



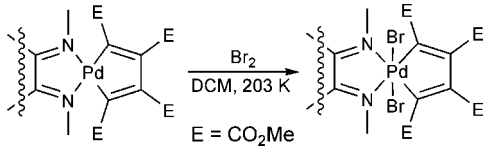
Scheme 32. Nitrosyl Ligand Oxidation and Nitrate−Trimethyl Phosphine Ligand Exchange in the Coordination Sphere of a Pd^{IV} Cyclometalated Complex



Scheme 33. Catalytic Cycle of a Three-Component Synthesis of Conjugated Dienes



Scheme 34. Stoichiometric Reaction of Bromine and a Pallada(II)cyclopentadiene Complex



3.1.5. Intermediacy and Catalytic Applications of Pd^{IV} Compounds from Oxidative Addition of Pd^{II} into $C(sp^3)-X$ Bonds

Oxidative addition of alkyl halides into Pd^{II} palladacyclic compounds has been developed into an elegant catalytic three-component methodology for the synthesis of conjugated dienes,[71,72] in which intermediate Pd^0, Pd^{II}, and Pd^{IV} species are involved (Scheme 33). In mechanistic studies, 2 equiv of Br_2 were reacted with a tetrakis(methoxycarbonyl)pallada(II)cyclopentadiene compound and the diorganoPd^{IV} dibromide formed instantaneously and quantitatively as shown by ^{1}H NMR spectroscopy at 200 K[73] (Scheme 34). The energy profile obtained from DFT-B3LYP calculations,[73] which have been carried out using [(HNCHCHNH)Pd($C_4-(CN)_4$)] and Br_2 as a model system, shows that this sequence of oxidative addition of molecular halogen to the palladacyclic compound, generating a Pd^{IV} species, followed by reductive elimination, with concomitant formation of a carbon−halogen bond, is energetically feasible.

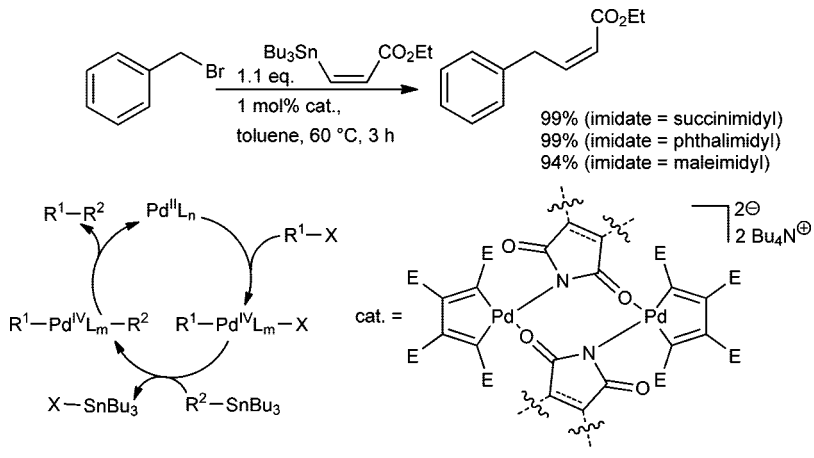
Fairlamb et al. reported the pseudohalide effects in Stille reactions of benzylic halides catalyzed by phosphine-free anionic palladacycles[74,75] (Scheme 35). In view of the accessibility of pallada(IV)cyclopentadiene intermediates reported by others, it now appears that the reaction could involve reductive elimination from benzylic Pd^{IV} intermediates.

Stable pallada(II)cycles L_2Pd-1-C_6H_5-2-$OCHCO_2$Et, featuring a Pd-bonded sp^3-hybridized stereogenic carbon and bipyridine or bis(imine) auxiliary ligands (L−L), reacted with allyl bromides via a $Pd^{II}-Pd^{IV}$ mediated process involving a direct C(sp^2)−H functionalization to afford highly substituted benzoxepines or benzopyrans.[76] An allyl Pd^{IV} complex, which was detected by low-temperature ^{1}H NMR spectroscopic analysis and characterized by X-ray crystallography, was shown to operate as an intermediate in the reaction sequence (Scheme 36).

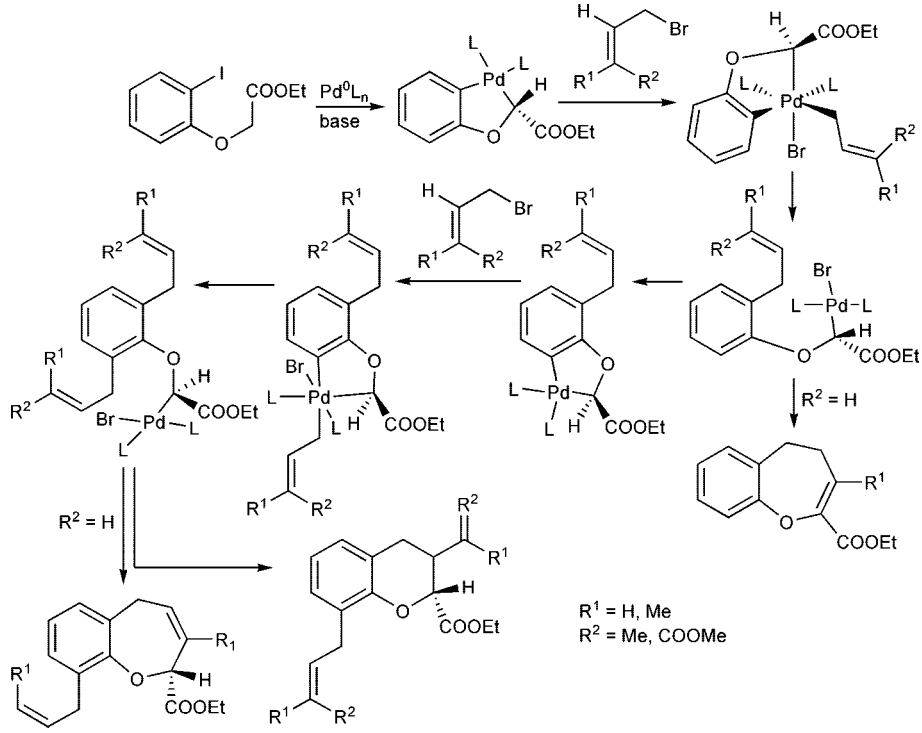
For the coupling of acetanilide with iodomethane (Scheme 37), the Pd^{II} cyclometalated complex is known to be an intermediate, and formation of the product was proposed to occur via either a benzonium Pd^{II} intermediate or an oxidative addition Pd^{IV} intermediate.[77] Tremont also suggested σ-bond metathesis as an alternative mechanistic possibility (not shown in Scheme 37).

A very robust, multistep four-component process leading to regioselective synthesis of *o*,*o*′-disubstituted vinylarenes was reported by Catellani[78] in 1997. The complex mechanism involves Pd^0, Pd^{II}, and Pd^{IV} species in a series of steps depicted in the simplified form in Scheme 38 along with other possible functionalization events. Oxidative addition of an aryl halide into Pd^0, insertion of norbornene, and base-promoted *o*-palladation lead to the crucial pallada(II) cyclic

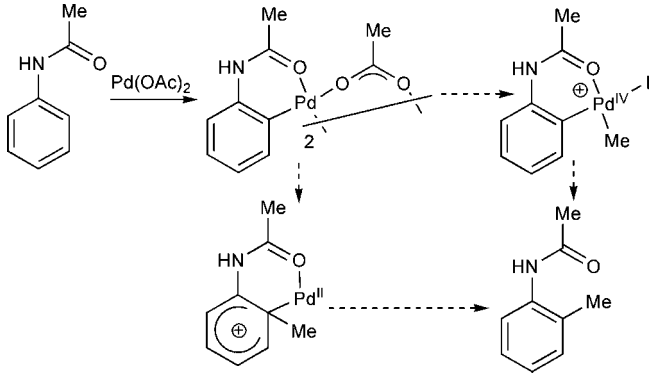
Scheme 35. Benzylic Stille Couplings Catalyzed by Anionic Palladacyclopentadienyl Imidate Catalysts and a Speculative Generalized $Pd^{II}-Pd^{IV}$ Catalytic Cycle



Scheme 36. Mechanistic Pathways and Possible Products of the Pd Catalyzed of Allylic Bromides with (2-Iodophenoxy)acetates



Scheme 37. Two Possible Mechanisms of the *o*-Directed Methylation of Acetanilide with Methyl Iodide

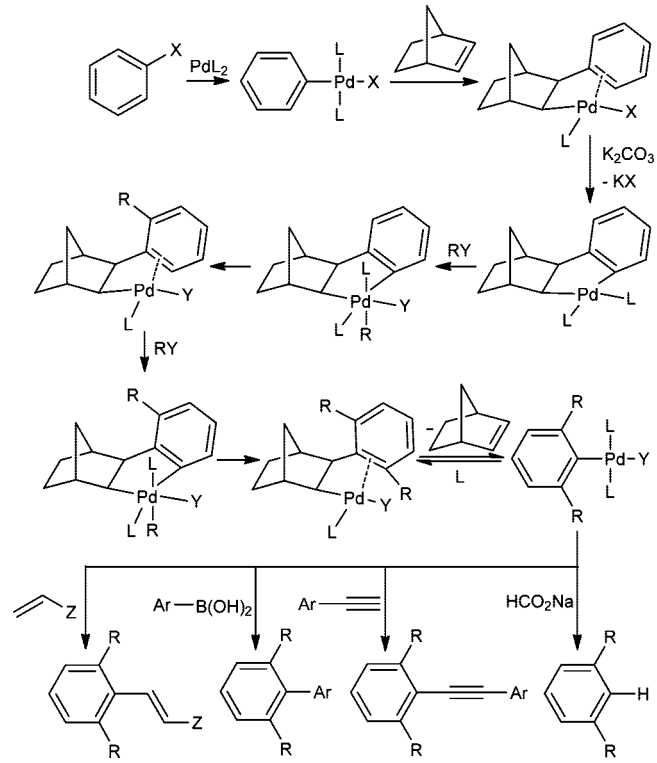


intermediate. As proved by earlier work of Catellani, complex **5** (L = phen) is able to undergo oxidative addition of some reactive organic halides such as methyl,[45] allyl,[50] and benzyl[58] halides to form a Pd^{IV} complex, which undergoes reductive elimination. At the end of this process, the scaffold is dismantled, with norbornene being spontaneously liberated owing to steric hindrance, and a new norbornene catalytic cycle starts, while palladium is cleaved from the organic product as soon as a suitable termination step is reached. Catellani has developed many modifications of this reaction varying in the type of termination event. Reductive dehalogenation, Heck, Suzuki, and Sonogashira-type products have been described (Scheme 38).[79–81] The use of iodothiophenes in place of iodobenzenes has also been reported.[82]

A modification developed by Lautens and co-workers gives six- and seven-membered condensed cyclic compounds through an intramolecular Heck reaction starting from an alkyl bromide containing a double bond.[83]

The synthesis of tetrahydroisoquinolines and tetrahydrobenzazepines was achieved using an alkyl bromide bearing a protected amine group, which gave rise, after

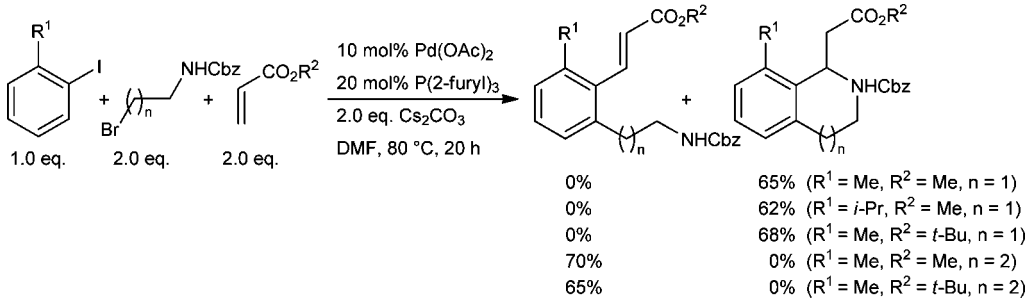
Scheme 38. Four-Component Synthesis of *o*,*o*′-Disubstituted Arenes from Aryl Iodides via Pd^{II} and Pd^{IV} Palladacycles



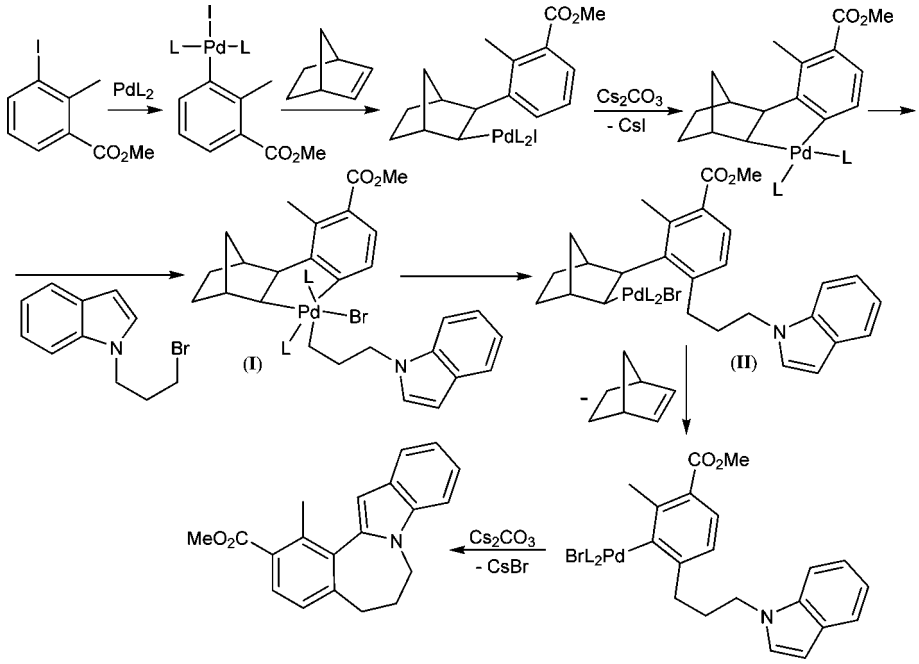
o-alkylation, to a final Michael reaction on the inserted olefin (Scheme 39).[84]

Synthesis of polycyclic heterocycles via a one-pot *ortho*-alkylation/direct heteroarylation sequence has been developed.[85,86] On the basis of modified Catellani conditions,[78] a bromoalkyl indole oxidatively adds into an aryl palladacyclic intermediate to give a Pd^{IV} species. *Ortho*-alkylation is then followed by intramolecular direct arylation to give the annulated product (Scheme 40).[85] It is important to note

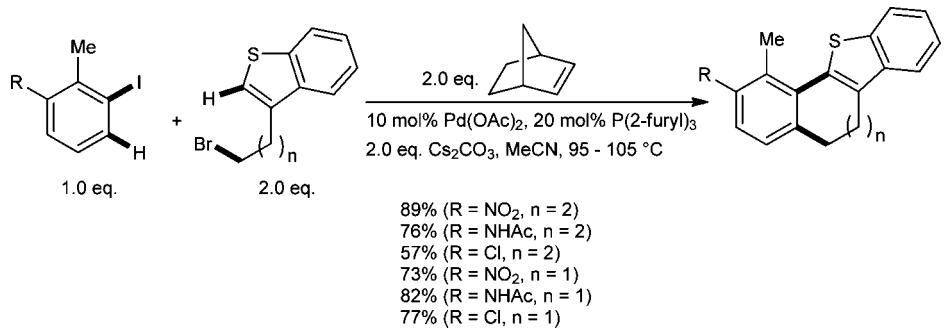
Scheme 39. Three-Component Synthesis of Difunctionalized Arenes and Tetrahydroisoquinolines from Iodoarenes



Scheme 40. Synthesis of Polycyclic Heterocycles via a One-Pot *ortho*-Alkylation/Direct Heteroarylation Sequence



Scheme 41. Modular Three-Component Synthesis of Polycyclic Benzothiophenes



that alkyl−aryl elimination (**I** → **II**) is proposed to occur in the presence of a β-hydrogen.

A variant with the bromoalkyl tether attached at the 3-position of benzothiophene (or benzofuran) has also been reported (Scheme 41).[86]

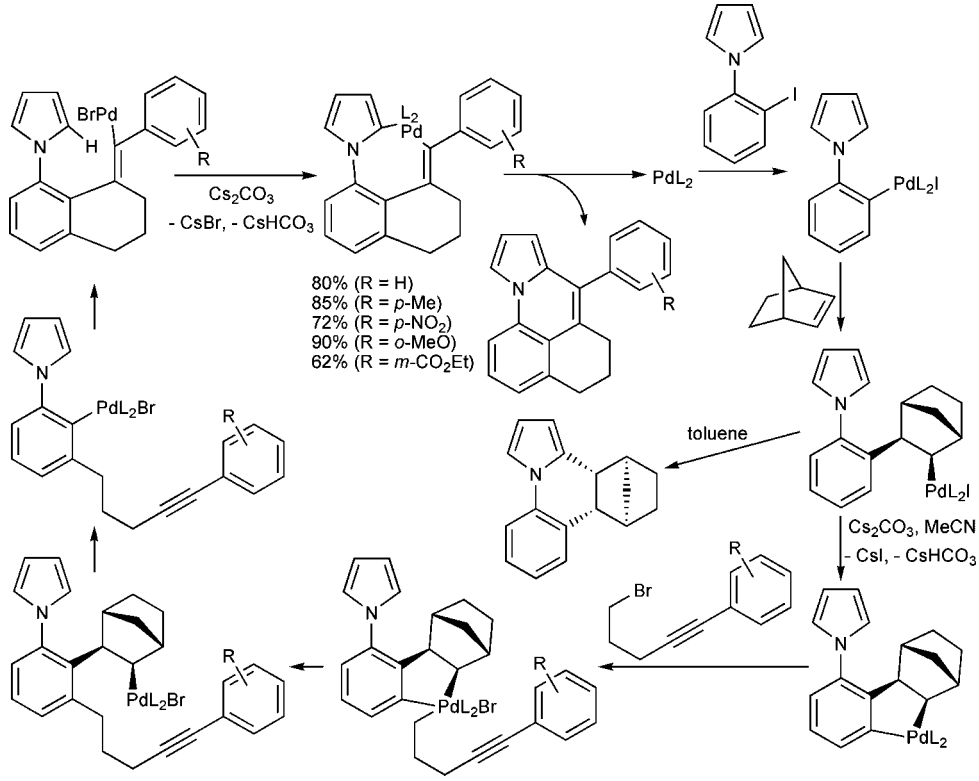
Lautens and co-workers[87] have also combined the *ortho*-alkylation/direct heteroarylation sequence with an intramolecular alkyne insertion, leading to polycyclic fused heterocycles (Scheme 42).

In another modification,[88] a domino synthesis of sterically encumbered tetrasubstituted helical alkenes was developed (Scheme 43); the incorporation of the norbornene fragment into the final product was observed. The reaction tolerates a variety of substituents on both the bromoalkyl aryl alkyne and the aryl iodide.

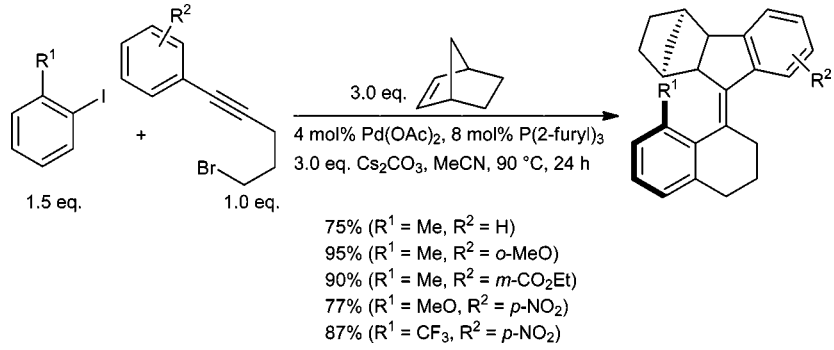
Using a secondary alkyl iodide tethered to the iodoaromatic, an interesting annulation leading to fused aromatic bi- and tricyclic ring systems was developed (Scheme 44).[89]

It is anticipated that the annulation of secondary alkyl iodides follows the same reaction mechanism as that proposed for the corresponding reaction of primary alkyl halides (vide supra). Using enantioenriched secondary iodides, it was possible to investigate the stereochemical course of the reaction[89] (Scheme 45). X-ray crystal structures of the starting material and a product (after derivatization as *p*-nitrobenzoate) were obtained, which revealed that the annulation reaction proceeded with overall inversion of configuration. The inversion of stereochemistry in this reaction likely occurs during the oxidative addition of the secondary alkyl iodide to Pd^{II} to form the Pd^{IV} intermediate.

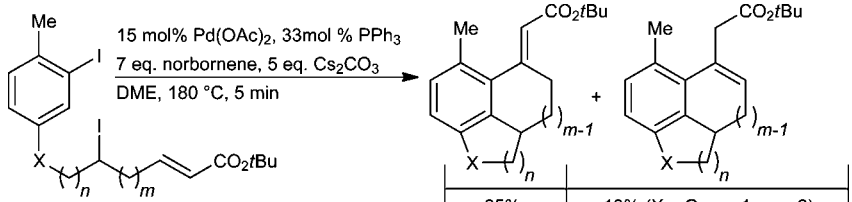
Scheme 42. Synthesis of Polycyclic Fused Nitrogen Heterocycles from *N*-(2-Iodophenyl)pyrrole



Scheme 43. Domino Synthesis of Sterically Crowded Tetrasubstituted Alkenes



Scheme 44. Annulation of Iodoaromatics with a Tethered Secondary Alkyl Iodide to Fused Polycycles

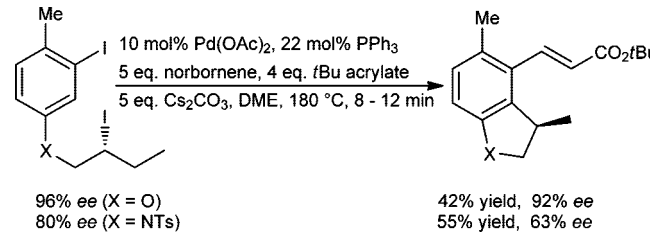


65%	13% (X = O, *n* = 1, *m* = 2)
74%	trace (X = O, *n* = 2, *m* = 2)
68%	0% (X = NTs, *n* = 1, *m* = 2)
62%	0% (X = NTs, *n* = 2, *m* = 2)

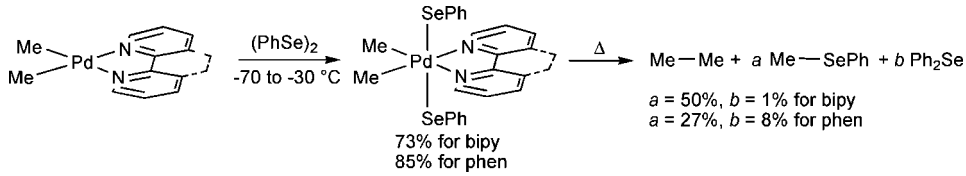
3.2. Organometallic Pd^{IV} Compounds from Oxidative Addition of Pd^{II} into Other Heteroatom−Heteroatom Bonds

In 1998, Canty et al. reported[90] that $PdMe_2(L_2)$ [L_2 = 2,2′-bipyridine, 1,10-phenanthroline] can be oxidized with diphenyl diselenide to provide the first examples of stable dimethyl Pd^{IV} complexes $PdMe_2(SePh)_2(L_2)$ and pallada(IV)-cyclic $Pd(CH_2CH_2CH_2CH_2)(SePh)_2(bipy)$ complexes (Scheme 46). The analogous Pd^{IV} species formed by oxidation of

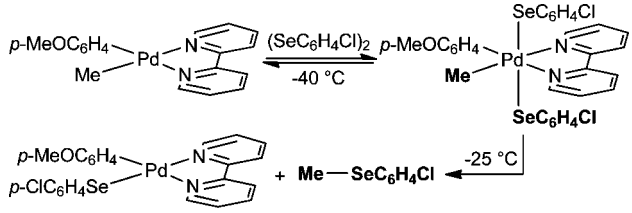
Scheme 45. Investigation of the Annulation Stereochemistry Using Enantioenriched Secondary Iodides



Scheme 46. Oxidative Addition of Dimethyl Pd^{II} Complexes into Diphenyl Diselenide and Decomposition of the Pd^{IV} Adduct



Scheme 47. Reversible Oxidative Addition of a Pd^{II} Complex into Bis(*p*-chlorophenyl) Diselenide and Decomposition of the Pd^{IV} Adduct



$PdMe_2$(bipy) or $Pd(CH_2CH_2CH_2CH_2)$(bipy) with $(O_2CPh)_2$ or $(SPh)_2$ are too unstable to be isolated. The $PdMe_2\{OC(O)Ph\}_2$(bipy) could be partially characterized by ^{1}H NMR spectroscopy at −50 °C, but it decomposed above this temperature. The detailed discussion of the reductive elimination selectivities will be given in the next section.

Reversible oxidative addition of $(SeC_6H_4Cl)_2$ to Pd^{II}Me(C_6H_4OMe)(bipy) to give $Pd(SeC_6H_4Cl)_2Me(C_6H_4OMe)$(bipy) (Scheme 47) was reported by Canty.[91] The Pd^{IV} complex is isolable at −40 °C, and when the equilibrium mixture is kept at −25 °C, a temperature at which the Pd^{II} complex is stable, selective reductive elimination of Me−SeC_6H_4Cl occurs very slowly from the Pd^{IV} complex to form $Pd(SeC_6H_4Cl)(C_6H_4OMe)$(bipy). Thermodynamic parameters for the Pd^{II}/Pd^{IV} equilibrium have been determined. An extension of this approach to include a complex containing a bidentate phosphine, $PdMe_2$(dmpe) [dmpe = 1,2-bis(dimethylphosphino)ethane], led directly to the reductive elimination products without detection of a potential Pd^{IV} intermediate.

Despite these well-documented examples of Pd^{IV}−S and Pd^{IV}−Se complexes, there are no reported synthetic applications of Pd^{II}−Pd^{IV} chemistry involving C−S and C−Se bond formation.

The reactions of $PdMeR(L_2)$ (R = Me, 4-tolyl; L_2 = tmeda, bipy) with diaroyl peroxides were later studied in more detail by Canty et al. (Scheme 48).[92] The initial reaction gives undetected "Pd$^{IV}(O_2CAr)_2MeR(L_2)$" (Ar = Ph, Ar_F; R = Me, Tol; L_2 = bipy, tmeda), which immediately undergoes methyl−carboxylate exchange with Pd$^{II}MeR(L_2)$ to give Pd$^{II}(O_2CAr)R(L_2)$ and Pd$^{IV}(O_2CAr)Me_2R(L_2)$. Reactions most likely occur via nucleophilic attack by a Pd^{II} reagent at an alkyl group bonded to a Pd^{IV} cationic species formed by dissociation of an anionic ligand, to generate a more stable Pd^{IV} product and a less nucleophilic Pd^{II} product.[92] On raising the temperature, the Pd$^{IV}Me_3$ complexes reductively eliminate ethane. The identity of Pd$^{IV}(O_2CR)Me_2R$(bipy) (R = Ph, Ar_F; R = Me, Tol) was confirmed by the independent synthesis of halogeno complexes with Ag[O_2CAr] by metathesis reactions.

In another study aimed at the mechanism of acetoxylation of arenes, Pd(O_2CPh)(NCN) (NCN = [2,6-(dimethylaminomethyl)phenyl-*N*,*C*,*N*]$^-$) was reacted with $(PhCO_2)_2$.[93] While a platinum analogue gave the expected Pt$^{IV}(O_2CPh)_3$(NCN), no reaction was detected by ^{1}H NMR spectroscopy at ambient temperature over several days.

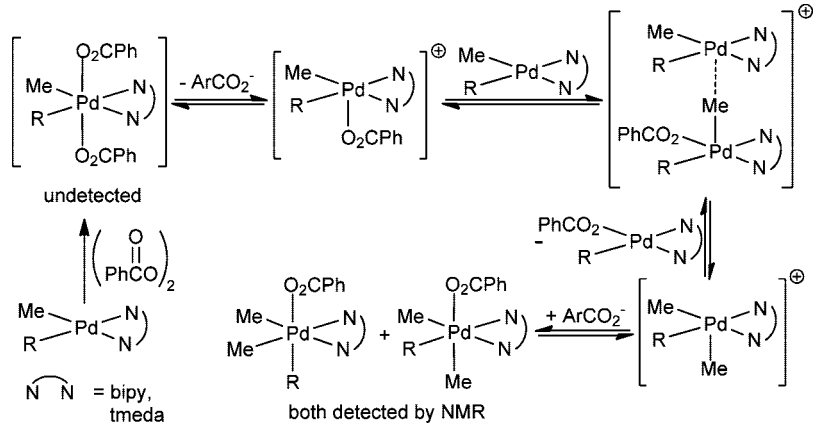
3.3. Organometallic Pd^{IV} Compounds Formed Using Other Oxidants

A new method for the synthesis of Pd^{IV} complexes based on the chemical oxidation of an anionic Pd^{II} precursor with 2 equiv of the one-electron oxidant $[FeCp_2][PF_6]$ has been reported,[94] together with some electrochemical analysis revealing that the stability of the +4 oxidation state is sensitive to the electron donor capability of the added coligand and to the steric features of the tris(pyrazolyl)borate ligand (Scheme 49).

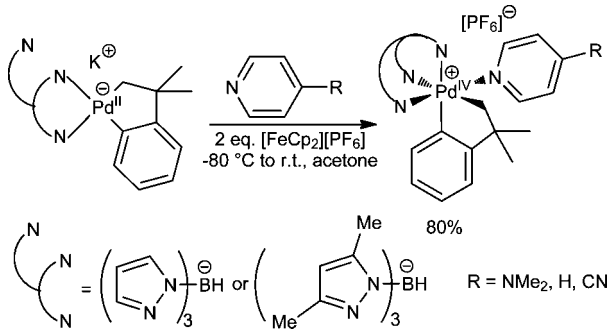
An unprecedented single-step assembly of dialkyl Pd^{IV} complex having a novel palladaspirocycle framework from $[Pd_2(dba)_3]$, *o*-chloranil, and norbornene was reported (Scheme 50).[95] The palladacycle fragment has C_2-symmetry and functions as a Lewis acid acceptor. The ligand exchange from tetrahydrofuran (THF) to pyridine caused a geometrical transformation to afford a bispyridine complex with a distorted octahedral geometry.

The structure was unambiguously confirmed by a single-crystal X-ray diffraction study. The complex has trigonal bipyramidal geometry. Two molecules of *o*-chloranil and

Scheme 48. Pd^{II}−Pd^{IV} Methyl Exchange, Following Oxidative Addition of Methyl Pd^{II} Complexes into Diaroyl Peroxides



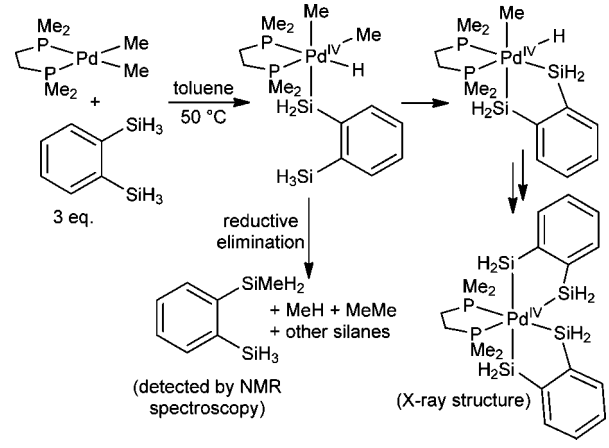
Scheme 49. Oxidation of an Anionic Tris(pyrazolyl)borate Cyclometalated Pd^{II} Complex with the Ferrocenium Cation



norbornene were coupled on the palladium center to form a pair of unprecedented seven-membered chelete rings. Interestingly, the product is stable in the solid state without any bidentate or tripodal donor spectator ligands, which normally prevent the formation of the five-coordinate intermediates that are required for facile reductive elimination of an alkane. On the other hand, the trigonal bipyramidal complex requires several days at ambient temperature in THF to decompose completely. The coordination number increased from five for the weaker THF donor to six for the stronger pyridine donor.

Similar pallada(IV)cyclic complexes were also formed from the reaction of $Pd_2(dba)_3$ with *o*-chloranil and benzonorbornadiene (Scheme 51).[96] The benzonorbornadiene-derived complexes exhibited pronounced stability in both the solid state and solution. The complete decomposition of the mono(pyridine) complex required several hours in C_6D_6 at 70 °C, and the addition of extra pyridine retarded the decomposition rate. Benzonorbornadiene was obtained as the main organic product, together with two isomeric adducts between *o*-chloranil and benzonorbornadiene. On the other hand, the decomposition of the pyridine complex took place

Scheme 52. Mechanism Leading to the First Silyl Pd^{IV} Complex via a Double Si−H Oxidative Addition

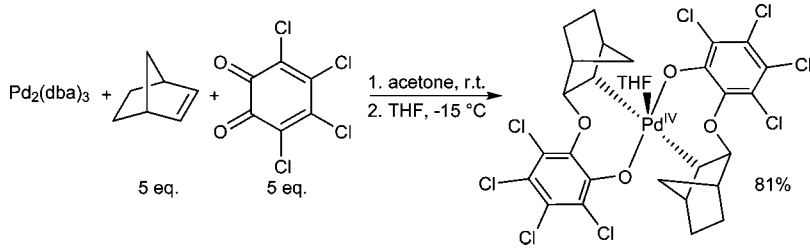


within 15 min even at −40 to −50 °C, upon exposure to HCl in a $CDCl_3$ solution.

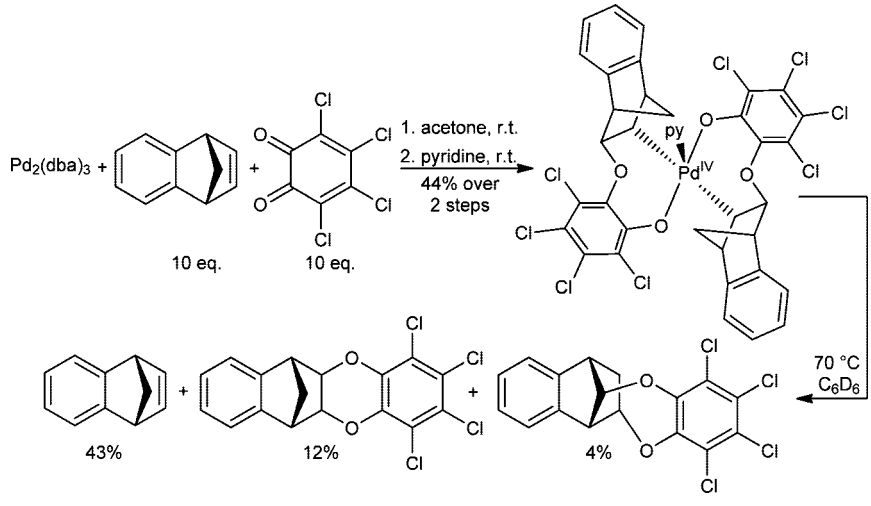
The first silyl Pd^{IV} complex was prepared and characterized by Tanaka et al.[97] On the basis of detection of the Si−C reductive elimination product, the authors proposed a tentative mechanism (Scheme 52).

A very unusual four-coordinate Pd^{IV} complex was produced by reacting 1,1,6,6-tetramethyl-1,5,6-trisilaspiro[4.4]-nonane with CpPd(η^3-allyl) (or Cp*Pd(η^3-allyl)) through the oxidative addition of Si−Si bonds (Scheme 53).[98] The complex is an air-stable colorless solid that can be purified by column chromatography on silica gel. Similarly, (η^5-Cp*)(η^3-allyl)palladium(II) afforded the corresponding Pd^{IV} complex, and its nearly perfect tetrahedral structure was confirmed by XRD. Excess 2,6-xylyl isocyanide (2.5 equiv) and an increased temperature induced double reductive elimination to give a five-membered disilane.

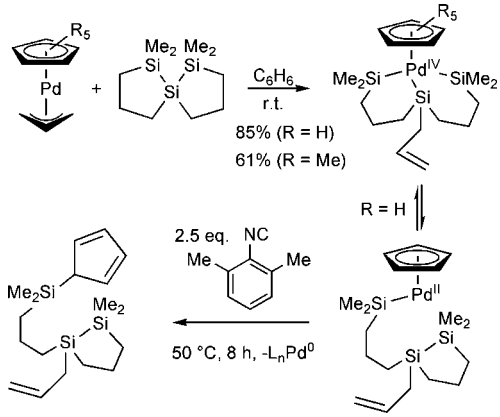
Scheme 50. Three-Component Assembly of a Novel OrganoPd^{IV} Complex from Norbornene and *o*-Chloranil



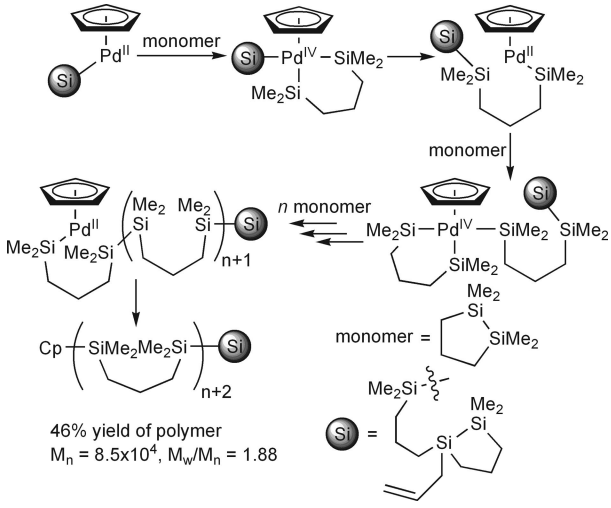
Scheme 51. Synthesis and Decomposition of a Benzonorbornadiene Based OrganoPd^{IV} Complex



Scheme 53. Synthesis and Decomposition of a Novel (η^5-Cyclopentadienyl) Pd^{IV} Disilane via Si−Si Oxidative Addition



Scheme 54. Pd^{II}−Pd^{IV} Catalytic Cycle of Polymerization of 1,1,2,2-Tetramethyl-1,2-disilacyclopentane

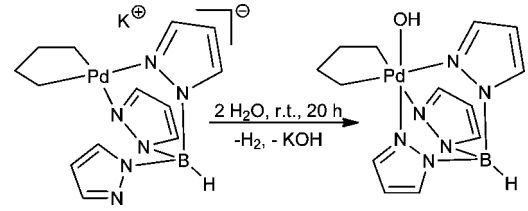


Interestingly, the (trisilyl)Pd^{IV} complex catalyzed the polymerization of 1,1,2,2-tetramethyl-1,2-disilacyclopentane at 50 °C to give organosilicon polymers of high molecular weight (Scheme 54).

Presumably, the polymerization is initiated by reductive elimination from the (trisilyl)Pd^{IV} complex, generating a (η^5-Cp)(monosilyl)Pd^{II} intermediate, which is then susceptible to oxidative addition of monomer forming a new (trisilyl)Pd^{IV} intermediate bearing the extended chain. Thus, formation of a new Si−Si bond through reductive elimination from a Pd^{IV} complex constitutes the propagation step for the ring-opening polymerization of 1,1,2,2-tetramethyl-1,2-disilacyclopentane.

Oxidative addition of reaction of a 1,4-bis(methoxypropyl)-2,3-dimethyl-1,4-diazabutadiene Pd^{II} cation with $HSiEt_3$ at −78 °C cleanly gives a product consistent with σ-silane coordination,[99] most probably $[(NN)Pd^{II}(Me)(\eta^2\text{-}HSiEt_3)]^+$ (Scheme 55). However, the complex is thermally unstable, and the two major volatile decomposition products, Et_3SiCl and $(Et_3Si)_2O$, are characteristic of heterolytic cleavage of the η^2-Si−H bond. An analogous reaction with a cationic Pt^{II} complex leads to oxidative addition of the Si−H bond to form an octahedral Pt^{IV} silyl hydride complex. On the basis of the ^1H NMR spectrum, which contains a very high-field signal at δ −9.87, a diimine Pd^{IV} silyl hydride structure was also considered as a possibility. The chemistry of Pt^{IV} silyl hydrides is well-precedented.[100]

Scheme 56. Pd^{IV} Hydroxo Complex Formed by Direct Oxidation of an Anionic Tris(pyrazolyl)borate Pd^{II} Complex with H_2O

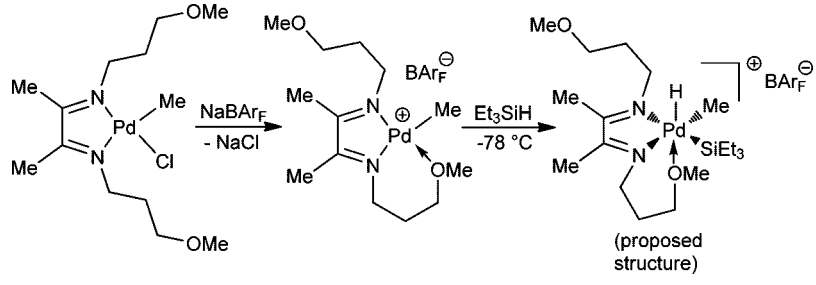


A very interesting reaction is the oxidation of diorganoPd^{II} complexes by water, published by Canty et al.[101,102] The pallada(II)cyclic complex ion $[Pd(CH_2CH_2CH_2CH_2)\{(pz)_3BH\}]$ is oxidized by water in acetone or THF to form $Pd^{IV}(CH_2CH_2CH_2CH_2)(OH)\{(pz)_3BH\}$ and H_2, and oxidation by H_2O_2 gives the same complex (Scheme 56). The various hydrogen-bonding modes of the Pd^{IV} hydroxo complex with phenols were studied.

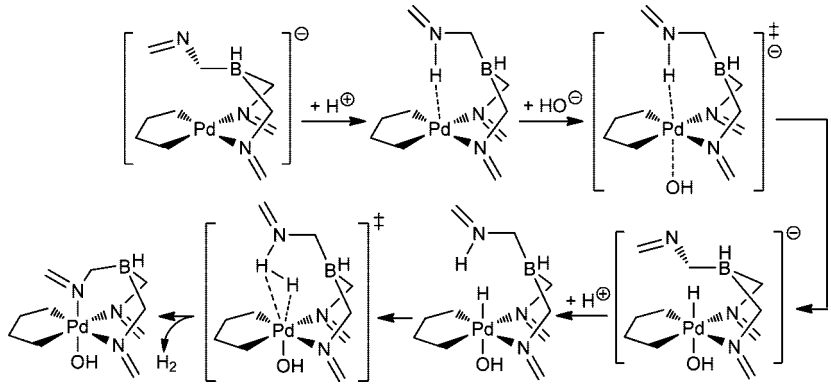
The complex ions $[Pd^{II}MeR\{(pz)_3BH\}]^-$ (R = Me, Ph) react with water to form $[Pd^{IV}Me_2R\{(pz)3BH\}]$, a $Pd^{II}R$ species and hydrogen. These reactions occur via initial oxidation to form undetected Pd^{IV} species, presumably $PdMeR(OH)\{(pz)_3BH\}$, which undergoes rapid methyl group exchange reactions with $[PdMeR\{(pz)_3BH\}]^-$ to form the detected products. The formation of hydroxo Pd^{IV} complexes upon reaction of water with Pd^{II} substrates is assumed to proceed via hydrido Pd^{IV} species formed by oxidative addition of water.

This was addressed in the next paper by ab initio theoretical calculations.[102] Using $[PdMe_2\{(H_2C{=}N{-}NH)_3BH\}]^-$ as a model for the pallada(II)cyclopentane reagent at the MP2//SCF level, the calculations suggest that the uncoordinated pyrazole group plays a major role as an intramolecular nucleophile in delivering $2H^+$ (per mole of H_2 formed) to the palladium center, with an eventual role as a coordinated group in the Pd^{IV} product. Thus, initial protonation leads to formation of a *N*-protonated Pd^{II} species $Pd(CH_2CH_2CH_2CH_2)\{(pz)_2(pzH)BH\text{-}N,N'\}$ containing a "Pd···H−N" interaction, followed by hydroxide coordination and hydrido ligand formation to give a Pd^{IV} species *trans*-$[Pd(CH_2CH_2CH_2CH_2)(H)(OH)\{(pz)_3BH\text{-}N,N'\}]^-$, a second

Scheme 55. Possible Cationic Pd^{IV} Silyl Hydride Product Formed by Oxidative Addition into Si−H Bond



Scheme 57. Mechanism of Water Oxidation of Anionic Tris(pyrazolyl)borate Pallada(II)cyclopentane Complex (As Shown by DFT Calculations)



protonation to form *trans*-Pd($CH_2CH_2CH_2CH_2$)(H)(OH){$(pz)_2$(pzH)BH-*N*,*N*′} prepared for a dihydrogen bond interaction "Pd−H···H−*N*", and finally by elimination of H_2 and coordination of the pyrazole group to form Pd(CH_2CH_2-CH_2CH_2)(OH){$(pz)_3$BH-*N*,*N*′} (Scheme 57).

3.4. Mechanistic and Selectivity Aspects of Oxidative Addition and Reductive Elimination in Pd^{IV} Chemistry

The details of mechanistic studies conducted on the fundamental steps of oxidative addition leading to Pd^{IV} and the reductive elimination have been reviewed by Canty.[103,104]

Oxidative addition of MeI to [$PdMe_2$(bipy)] occurs by an S_N2 mechanism.[105] Experimental evidence includes the observation of second-order kinetics in acetone solvent, with a large negative value for the entropy of activation, and the observation of a cationic species, [$PdMe_3$(bipy)(CD_3CN)]$^+I^-$ in CD_3CN solvent. The reaction occurs more slowly than the analogous reaction of [$PtMe_2$(bipy)], but the same mechanism operates. Reductive elimination from [$PdIMe_3$-(bipy)] to give ethane and [PdIMe(bipy)] follows clear first-order kinetics and occurs more rapidly in polar solvents, being strongly retarded by iodide anion. These observations are interpreted in terms of a mechanism that involves preliminary ionization of iodide followed by reductive elimination from the cation [$PdMe_3$(bipy)]$^+$. Studies by differential scanning calorimetry (DSC) allow an estimate of the Pd−C bond energy of −130 kJ mol^{-1} to be obtained. This value is considerably higher than the activation energy for reductive elimination of ethane from [$PdIMe_3$(bipy)] (*E*, values 65 kJ mol^{-1} in acetone, 78 kJ mol^{-1} in acetone with excess I^-, 39 kJ mol^{-1} in methanol with excess I^-). Although iodide dissociation is implicated in the reductive elimination, this step is unlikely to affect the Pd−Me bond energy significantly. The reductive elimination step is therefore concerted. However, an alternative pathway involving α-elimination, an agostic CHPd interaction, and Pd−hydride intermediates was also proposed (Scheme 58).[105]

Following the initial discovery of the $Pd^{IV}Me_3$ complexes, the detailed volume profile analysis of oxidative addition of MeI to $PdMe_2$(bipy) and reductive elimination from $PdIMe_3$(bipy) has been carried out.[106] The volume of activation ($\Delta V^{\ddagger}$) of -11.9 ± 0.6 cm^3 mol^{-1} for the addition process underlines the validity of the proposed S_N2 mechanism in the literature. The large positive value of $\Delta V^{\ddagger}$ (+17 $\pm$ 1 cm^3 mol^{-1}) for the reductive elimination suggests bond cleavage and/or the partial reduction from Pd^{IV} to Pd^{II} in the transition state. Addition of NaI to the Pd^{IV} compound slowed down the rate of reaction, but it did not affect the activation volume (Chart 1).

Scheme 58. Alternative Mechanisms of Reductive Elimination from a [$PdMe_3$(bipy)]$^+$ Cation

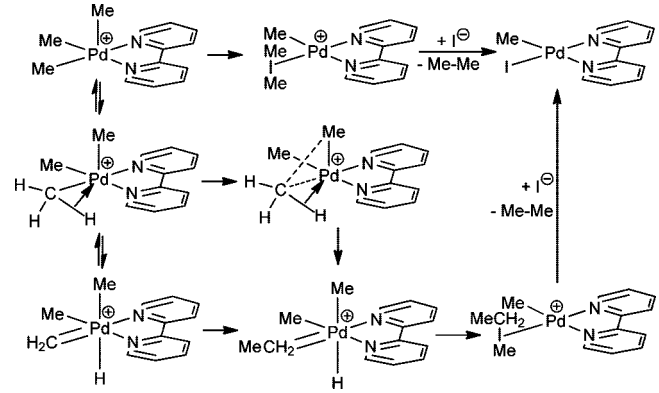
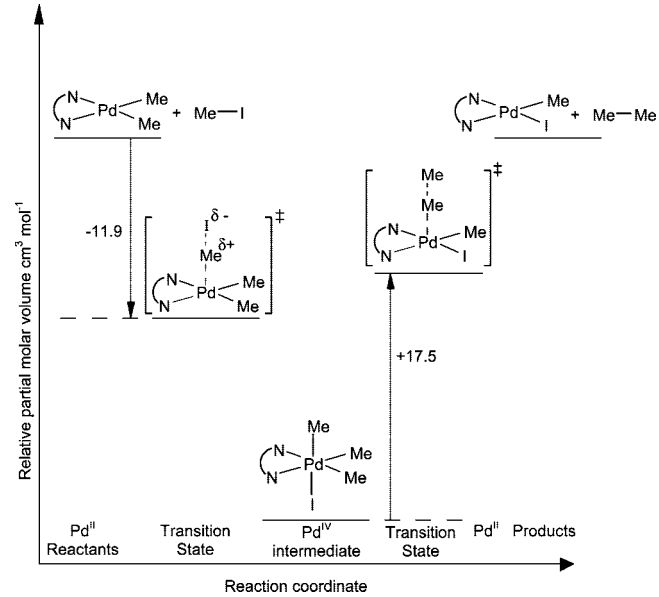
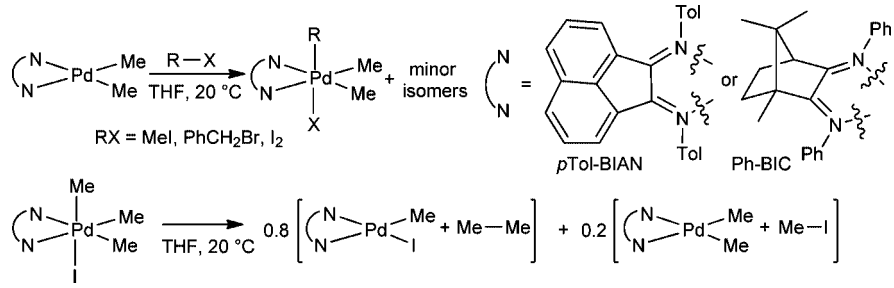


Chart 1. Activation Volume Profile of Oxidative Addition of MeI to $PdMe_2$(bipy) and Reductive Elimination from $PdIMe_3$(bipy)

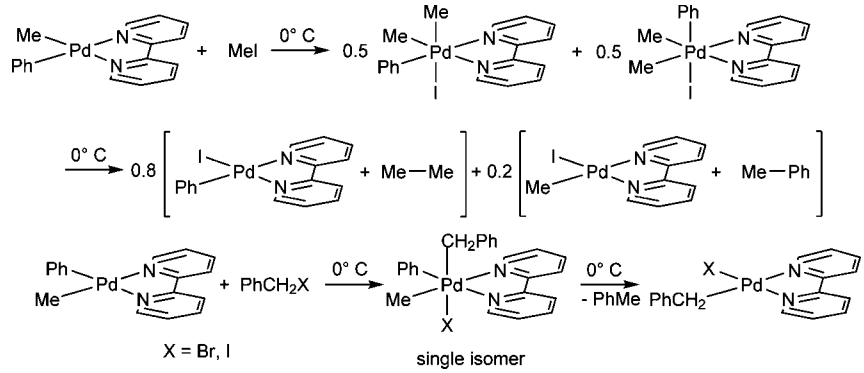


Reductive elimination from palladium complexes $Pd^{IV}Me_2$(R)X(NN) (RX = MeI, $PhCH_2Br$; NN = *p*Tol-BIAN, Ph-BIC) was studied by ^{1}H NMR spectroscopy.[107] First-order kinetics and slower rates than other reported triorganoPd^{IV} complexes were found. The new diorganoPd^{IV} complexes $PdMe_2I_2$(NN), synthesized via oxidative addition

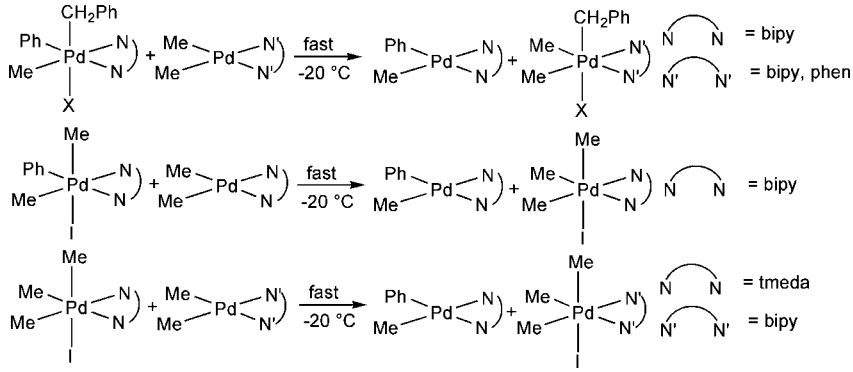
Scheme 59. Reactions of $PdMe_2(NN)$ Complexes with Electrophiles and Reductive Elimination Selectivity in the Decomposition of $[PdIMe_3(NN)]$ Complexes



Scheme 60. Preparation and Reductive Elimination Behavior of $Me_2(Ph)Pd^{IV}$- and $Me(Ph)(Bn)Pd^{IV}$-Type Complexes



Scheme 61. Study of $Pd^{II}-Pd^{IV}$ Methyl and Benzyl Group Exchange Processes



Scheme 62. Reductive Elimination Selectivity in Decomposition of $PdBrMeAr(CH_2Ph)(NN)$ Complexes

$PdBrMeAr(CH_2Ph)(bipy) \rightarrow PdBr(CH_2Ph)(bipy) + Ar\text{-}Me$ (Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$)

$PdBrMeAr(CH_2Ph)(phen) \rightarrow a[PdBr(CH_2Ph)(phen) + Ar\text{-}Me] + b[PdBrMe(phen) + Ar\text{-}CH_2Ph]$

a = 0.83, b = 0.17 (Ar = Ph) a = 0.87, b = 0.13 (Ar = 4-$MeOC_6H_4$)
a = 0.90, b = 0.10 (Ar = 3-$MeOC_6H_4$) a = 0.91, b = 0.09 (Ar = 4-MeC_6H_4)

of diiodine to $PdMe_2(NN)$, are much less stable than the triorganoPd^{IV} complexes (Scheme 59).

TrialkylPd^{IV} complexes decompose almost exclusively by C···C bond formation, and the C···halide reductive elimination is quite rare. MeI is a minor product in the decomposition of $PdMe_3I(p$Tol-BIAN),[107] and traces of MeBr are also produced from $Me_2(C_6H_5COCH_2)Pd(bipy)Br$ and $Me_2(C_6H_5COCH_2)Pd(phen)Br$.[108] A bromoalkene is the major product of decomposition of an unstable dibromopallada(IV)-cyclopentadiene complex.[73]

Methyl iodide reacts with PdMePh(bipy) to form the isolable *fac*-$[Pd^{IV}IMe_2Ph(bipy)]$. The complex occurs as a mixture of isomers in a 1:1 ratio, involving the phenyl group in a position *trans* either to bipy or to iodine (Scheme 60).[109] Reductive elimination at 0 °C in acetone-d_6 gives a mixture of ethane and toluene in a 4:1 molar ratio together with the respective Pd^{II}. The analogous benzyl Pd^{IV} complex, obtained as one isomer with the benzyl group *trans* to the halogen, has allowed elimination from a metal bonded to three different groups to be studied for the first time. Interestingly, toluene and $PdX(CH_2Ph)(bipy)$ are the exclusive products.

Another phenomenon that complicates the study of reductive elimination selectivity is the rapid alkyl halide transfer from Pd^{IV} to Pd^{II}.[109] On the basis of the mechanism proposed earlier for Pd^{II} to Pd^0 benzyl transfer,[110] it is assumed the reaction involves nucleophilic attack by the lower oxidation state reagent at an alkyl group attached to the higher oxidation state reagent. In the case of a Pd^{IV} with three different organo groups and $PdMe_2(NN)$, transfer of benzyl

Scheme 63. Solid-State Thermal Decomposition Studies of [PdBrMe$_2$(CH$_2$Ph)(NN)] Complexes

$$PdBrMe_2(CH_2Ph)(bipy) \xrightarrow{110\text{-}145\ ^\circ C} 0.8\ [PdBr(CH_2Ph)(bipy) + Me\text{-}Me] + 0.2\ [PdBrMe(bipy) + Me\text{-}CH_2Ph]$$

$$PdBrMe_2(CH_2Ph)(phen) \xrightarrow{85\text{-}120\ ^\circ C} 0.5\ [PdBr(CH_2Ph)(phen) + Me\text{-}Me] + 0.5\ [PdBrMe(phen) + Me\text{-}CH_2Ph]$$

Scheme 64. Selectivity in Pd^{IV}−Pt^{II} Methyl Versus Benzyl Exchange Reactions

$$[PdBrMe_2(CH_2Ph)(L_2)] + [PtMe_2(L_2)] \longrightarrow a\{PdMe_2(L_2) + [PtBrMe_2(CH_2Ph)(L_2)]\} + b\{PdMe(CH_2Ph)(L_2) + [PtBrMe_3(L_2)]\}$$

a = 0.75, b = 0.25 (L_2 = bipy); a = 0.85, b = 0.15 (L_2 = phen)

Scheme 65. Decomposition Study of a Series of Benzyl and Phenacyl Pd^{IV} Complexes Me$_2$RPd(NN)Br

$$Me_2RPd(L_2)Br \longrightarrow a\ [RPd(L_2)Br + Me\text{-}Me] + b\ [MePd(L_2)Br + R\text{-}Me]$$

(a = 1.00, b = 0.00 for L_2 = bipy, R = *p*-$XC_6H_4CH_2$ where X = H, Br, NO_2)
(a = 0.75, b = 0.25 for L_2 = phen, R = *p*-$XC_6H_4CH_2$ where X = H, Br, NO_2)
(a = 0.83, b = 0.17 for L_2 = bipy, R = *p*-$BrC_6H_4COCH_2$)
(a = 0.67, b = 0.33 for L_2 = phen, R = *p*-$BrC_6H_4COCH_2$)
(a = 0.75, b = 0.25 for L_2 = bipy, R = $C_6H_5COCH_2$)
(a = 0.50, b = 0.50 for L_2 = phen, R = $C_6H_5COCH_2$)

Scheme 66. Decomposition Study of a Series of [Me$_2$RPd^{IV}(tmeda)X] Complexes

$$PdRMe_2(tmeda)X \longrightarrow a\ [PdR(tmeda)X + Me\text{-}Me] + b\ [PdMe(tmeda)Br + R\text{-}Me]$$

a = 0.95, b = 0.05 (RX = $PhCH_2Br$ in acetone)
a = 0.85, b = 0.15 (RX = $PhCH_2Br$ in benzene)
a = 1.00, b = 0.00 (RX = CH_2=$CHCH_2Br$)
a = 0.00, b = 1.00 (RX = MeCOCl)

bromide is exclusively favored over methyl and phenyl bromide transfer (Scheme 61).

The reductive elimination/alkyl halide transfer selectivity was studied in detail[60] on a series of complexes: PdBrMeAr(CH$_2$Ph)(L$_2$) [L$_2$ = bipy, phen; Ar = C_6H_4X, X = H, Me, MeO, Me(O)C, O_2N] (Scheme 62). The complexes PdBrMeAr(CH$_2$Ph)(bipy) (Ar = Ph, 4-MeC_6H_4, 4-MeOC_6H_4) undergo selective reductive elimination of Ar−Me in $CDCl_3$ to form PdBr(CH$_2$Ph)(L$_2$), but PdBrMeAr(CH$_2$Ph)(phen) (Ar = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 3-MeOC_6H_4) gave mixtures of PdBr(CH$_2$Ph)(phen) and Me−Ar together with lesser amounts of PdBrMe(phen) and Ar−CH_2Ph (ca. 10−20%).

Kinetic studies by Canty and co-workers[111] showed that the S_N2 oxidative addition of MeI or $PhCH_2Br$ to [MMe$_2$(L$_2$)] occurs 7−22 times faster when M = Pt over Pd and 1.2−2.2 times faster when L$_2$ = phen over bipy. In the reductive elimination from [PdBrMe$_2$(CH$_2$Ph)(L$_2$)] in the solid state, there is a preference for methyl rather than benzyl group loss and, consistent with this, the thermal analysis indicates a relatively strong benzyl−Pd^{IV} bond (Scheme 63).

While no alkyl halide reductive elimination from Pd^{IV} has been detected, preferential benzyl halide compared to methyl halide transfer from Pd^{IV} to Pt^{II} occurs readily[111] (Scheme 64).

In another study, a series of benzyl and phenacyl complexes Me$_2$RPd(L$_2$)Br (L$_2$ = bipy, phen) was examined (Scheme 65).[108]

Reactions of PdMe$_2$(tmeda) with alkyl, benzyl, allyl, and acetyl halides were studied by van Koten.[112] The decomposition pathways of the respective Pd^{IV} intermediates PdRMe$_2$(tmeda)X are given in Scheme 66.

Full ^{1}H and ^{13}C NMR spectroscopic analysis revealed that reaction of PdMe$_2$(tmeda) with $PhCH_2Br$ and the reaction of PdMe(CH$_2$Ph)(tmeda) with MeBr both afford identical Pd^{IV} species *a*-benzyl-*b*-bromo-*cd*-dimethyl-*ef*-(tmeda)palladium(IV), in which the benzyl group and the bromine atom are in a *cis*-position.

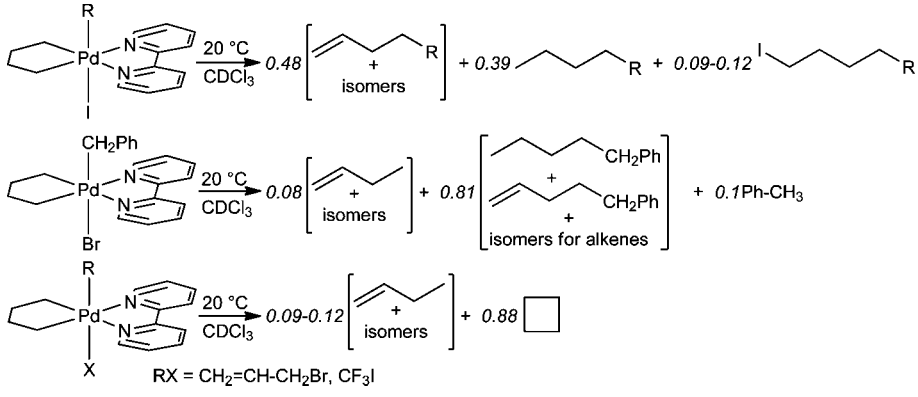
Canty et al.[113] have also studied the octahedral pallada(IV)-cyclopentane complexes PdX(C_4H_8)R(bipy) [RX = MeI, EtI, $PhCH_2Br$, CH_2=$CHCH_2Br$] and PdBr(C_4H_8)(CF_3)(bipy) (Scheme 67). Although the complexes exhibit different decomposition products, their decomposition is dominated by C···C reductive elimination as an early step in the process. Reductive elimination via C_4H_8···R coupling from PdX(C_4H_8)R(bipy) occurs for RX = MeI, EtI, and $PhCH_2Br$, followed by decomposition from monoalkyl Pd^{II} species; for RX = CH_2=$CHCH_2Br$ and CF_3I, direct elimination of cyclobutane is the dominant process. This difference in behavior may result from the inability of the latter R groups to form agostic interactions with the vacant site in [Pd(C_4H_8)R(bipy)]$^+$, and/or for R = CH_2CH=CH_2, an alternative Pd^{IV} (η^3-allyl) interaction may occur, which may disfavor reductive elimination and favor the formation of the Pd^{II} (η^3-allyl) product.

Deuteration studies implicate the occurrence of intermolecular hydrogen atom transfer for elimination of alkenes and alkanes, except for cyclobutane. Intramolecular β-hydrogen elimination from palladacyclopentanes appears to be not favored for steric reasons. The mechanistic proposal invoking Pd^{II} and Pd^{IV} hydrides that accounts for the observed products is shown in Scheme 68.

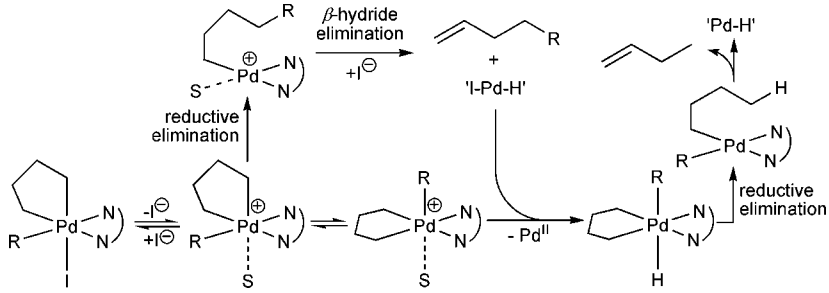
The results of other reductive elimination studies on PdBrMe$_2$(CH$_2$Ar)(L$_2$) (L$_2$ = bipy, phen)[55] and the [Pd(mq)Me$_2$(bipy)]$^+$ cation[57] have already been discussed (vide supra).

The most illuminating studies were reported in a series of papers by Stille, Milstein, and co-workers. They found that benzylic bromides strongly promote the reaction of tetraorganotin compounds (or Grignard reagents) and organohalogeno Pd^{II} complexes to give coupling products.[52] Low yields were obtained in the absence of the benzyl bromides, in

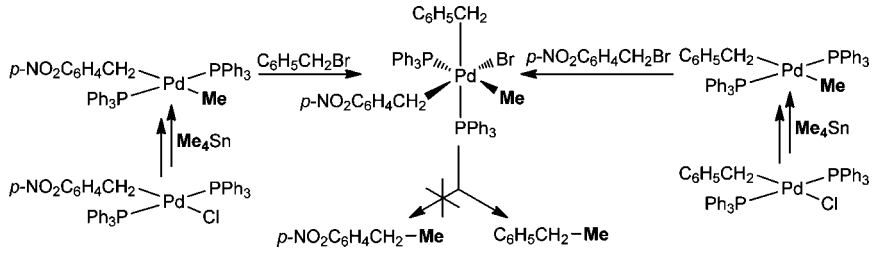
Scheme 67. Decomposition Study of a Series of Pallada(IV)cyclopentane Complexes [PdI(C_4H_8)R(bipy)]



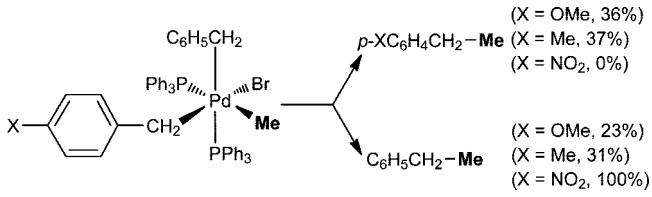
Scheme 68. Mechanism Accounting for the Formation of Butenes during the Decomposition of [PdI(C_4H_8)R(bipy)]



Scheme 69. Generation of $Pd^{IV}(CH_2C_6H_5)(CH_2C_6H_4-p-NO_2)MeBr(PPh_3)_2$ and Selective Reductive Elimination of Ethylbenzene



Scheme 70. Effects of *para*-Substituents in $(p-XC_6H_4CH_2)Pd^{IV}$ Complexes on Reductive Elimination Selectivity

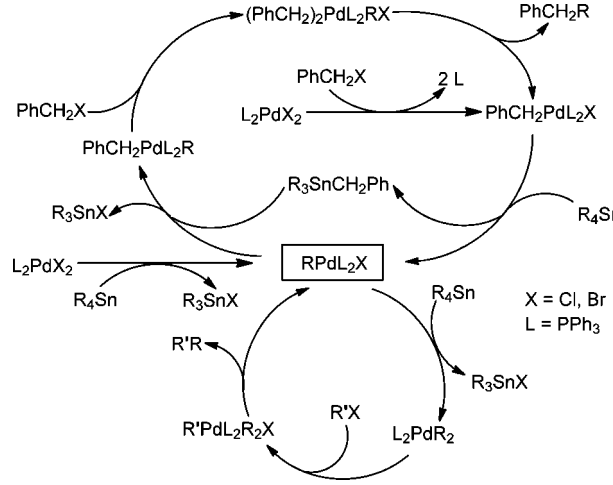


which case other decomposition pathways (e.g., α-elimination) take place, even in the presence of electron acceptors (e.g., oxygen, *m*-dinitrobenzene). They proposed a novel mechanism, where the *p*-nitrobenzyl bromide additive is responsible for the generation of $Pd^{IV}(CH_2C_6H_5)(CH_2C_6H_4-p-NO_2)MeBr(PPh_3)_2$ intermediate from $Pd^{II}(CH_2C_6H_5)MeBr(PPh_3)_2$. The completely selective reductive elimination of ethylbenzene (no *p*-nitroethylbenzene was detected) regenerates Pd^{II} (Scheme 69).

It was shown that the relative Pd−CH_2Ar bond strength is the decisive factor in determining reductive elimination selectivity (Scheme 70).[52]

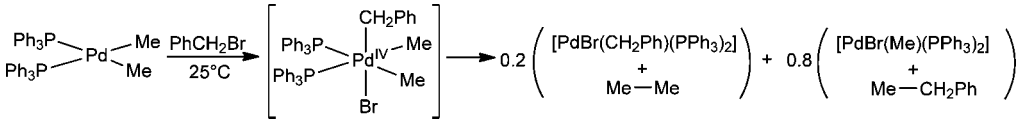
Also, it was shown that, overall, benzyl−methyl reductive elimination from Pd^{IV} is favored over methyl−methyl elimination, probably because of the lower Pd−CH_2Ph bond energy relative to Pd−Me (Scheme 71).

Scheme 73. Mechanistic Pathways of Stille Coupling of Organic Halides with Tetraorganotin Compounds

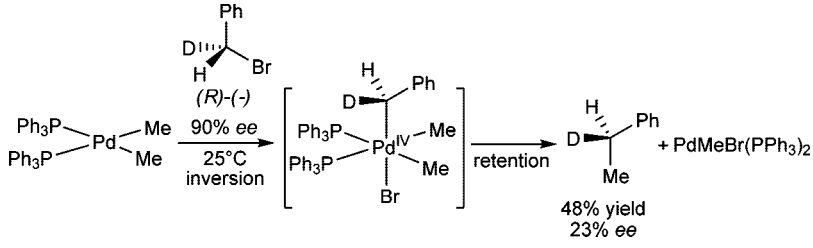


The stereochemistry of the reaction was investigated using (*R*)-(−)-α-deuteriobenzyl bromide (89.7 ± 0.3% ee).[52] Its reaction with $PdMe_2(PPh_3)_2$ at −78 °C gave (*R*)-(−)-α-deuterioethylbenzene in 47.5% yield and 22.9 ± 2% ee. Although palladium-catalyzed racemization of the benzyl halide was competing under the reaction conditions, it was estabilizhed by polarimetry that the reaction occurs with at

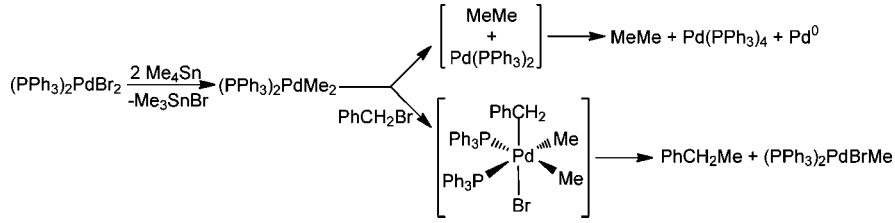
Scheme 71. Benzyl−Methyl Versus Methyl−Methyl Reductive Elimination in $[PdMe_2(CH_2Ph)Br(PPh_3)_2]$



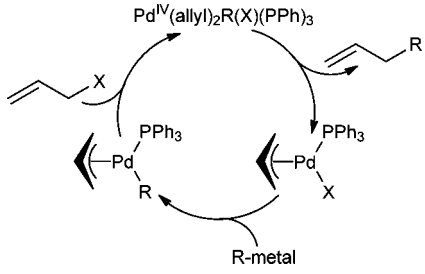
Scheme 72. Investigation of the Stereochemical Course of Oxidative Addition of $PdMe_2(PPh_3)_2$ into Benzyl Bromide and Subsequent Reductive Elimination of Ethylbenzene



Scheme 74. Mechanism and Decomposition Products of Reductive Elimination of $PdMe_2(PPh_3)_2$ in the Presence and Absence of Benzyl Bromide



Scheme 75. Possible $Pd^{II}-Pd^{IV}$ Mechanism of Cross-Coupling of Allylic Halides with Organometallic Reagents



least 25.5 ± 2.3% overall inversion (Scheme 72). Interestingly, later studies of alkene aminoacetoxylation by Stahl and co-workers[114] indicated that C−O reductive elimination from Pd^{IV} centers can also proceed with inversion of stereochemistry.

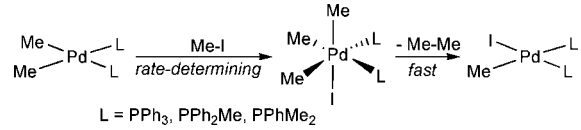
On the basis of previous results, Stille and Milstein suggested two concurrent catalytic cycles for the reaction of tetraorganotin compounds with organic halides. Benzyl halides were proposed to react in both the upper cycle and the lower cycle, whereas other organic halides (e.g., aryl halides) react by the lower one (Scheme 73).[115] This paper reports some convincing experimental evidence in support of this proposal (see below). However, in light of subsequent comprehensive mechanistic investigations, for example, by Espinet,[116–118] with Echavarren,[119] Lin[120] and others,[121,122] it could be a special case for tetramethyltin.

This was further corroborated by reactions of $PdBr_2(PPh_3)_2$ with tetramethyltin to form ethane and metallic palladium, whereas in the presence of benzyl bromide, $PdBrMe(PPh_3)_2$ and ethylbenzene are formed, while even traces of ethane could not be detected (Scheme 74).

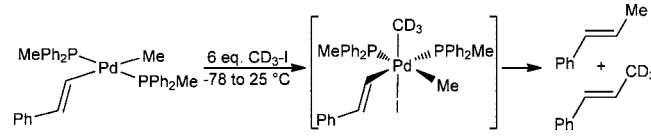
Interestingly, the opposite selectivity was seen by Canty in reductive elimination from $[PdBrMe_2(CH_2Ph)(bipy)]$ in the solid state, which shows a preference for methyl rather than benzyl group loss.[111]

A very interesting study, similar to the benzylic coupling of Stille,[115] was carried out by Kurosawa et al. using allylic halides (Scheme 75).[48] Allylic electrophiles used in Pd-catalyzed allylic alkylation greatly accelerated reductive elimination of η^3-allyl(organo) Pd^{II} complexes, via an $(allyl)_2Pd^{IV}$ intermediate, giving the coupling products and η^3-allylpalladium(II) salts.

Scheme 77. Relative Rates in the $Pd^{II}Me_2-Pd^{IV}Me_3I-Pd^{II}MeI$ Sequence



Scheme 78. Formation and Decomposition of $Pd^{IV}IMe(CD_3)((E)\text{-styryl})(PPh_3)_2$



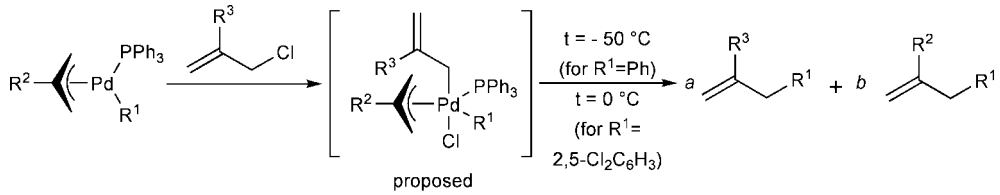
The crucial oxidative addition of allyl chlorides onto (η^3-allyl)Pd^{II} complexes was studied in more detail. Second-order kinetics in one example (using initial rate method) and rate constants were determined for various allylic electrophiles (for $CH_2{=}CHCH_2X$, the rate decreased in the order X = Br > OPh ≈ Cl > OAc). By examining the product selectivity for various combinations of substrates, they showed there is very slow or no allyl−methylallyl scrambling in the Pd^{IV} intermediate under the reaction conditions (Scheme 76).[48]

The energies and entropies of activation for the 1,1-reductive elimination of ethane from *cis*- $PdMe_2(PPh_3)_2$ were determined and compared with the $Pd^{II}Me_2-Pd^{IV}Me_3I-Pd^{II}MeI$ sequence.[123] In polar solvents (e.g., DMSO, acetone, and MeCN), the latter sequence is shown to be faster than the reductive elimination of ethane from dimethyl Pd^{II}, mostly because of the less negative entropies of activation for the oxidative addition step in the former sequence (Scheme 77). In nonpolar solvents (e.g., C_6H_6, toluene), these two pathways exhibit competitive rates.

Stille also reported[124] a reaction of $PdMe((E)\text{-styryl})(PPh_3)_2$ with CD_3I gives a mixture of deuterated and nondeuterated propenylbenzene, indicating the possible involvement of a Pd^{IV} intermediate in the *p*-bromostyrene−methylmagnesium bromide−PdL_n catalytic cycle (Scheme 78).

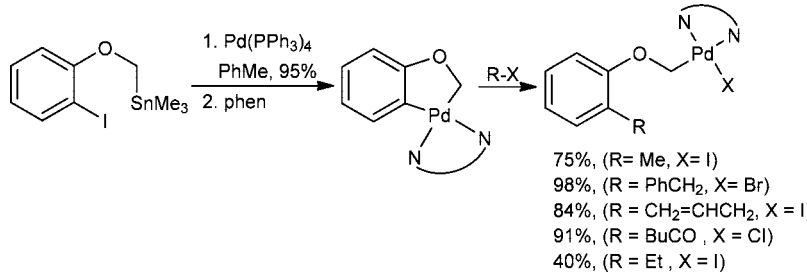
An interesting oxapalladacycle was prepared and studied by Echavarren (Scheme 79).[125]

Scheme 76. Proposed Pd^{IV} Intermediates in Allylic Cross-coupling, Explaining the Absence of Allyl−Methylallyl Scrambling



a = 0.66, b = 0.33 (R^1 = Ph, R^2 = H, R^3 = Me)
a = 0.66, b = 0.33 (R^1 =2,5-$Cl_2C_6H_3$, R^2 = H, R^3 = Me)
a = 0.75, b = 0.25 (R^1 = Ph, R^2 = Me, R^3 = H)
a = 0.83, b = 0.17 (R^1 = 2,5-$Cl_2C_6H_3$, R^2 = Me, R^3 = H)

Scheme 79. Reaction of an Oxapallada(II)cycle with Electrophiles



Scheme 80. Decomposition Pathways for the $PdMe_2(E)_2(bipy)$ Complexes

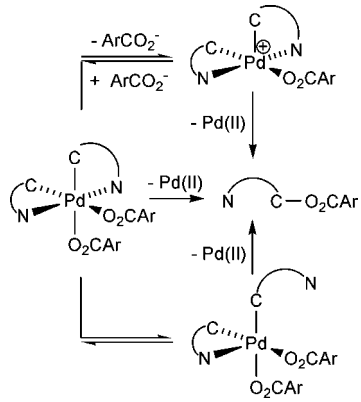
$PdMe_2(O_2CPh)_2(bipy) \rightarrow 0.6\ \{MeMe + Pd(O_2CPh)_2(bipy)\} + 0.4\ \{MeO_2CPh + PdMe(O_2CPh)(bipy)\}$

$PdMe_2(SPh)_2(bipy) \rightarrow MeMe + 0.17\ MeSPh + 0.49\ SPh_2$

$Pd(CH_2CH_2CH_2CH_2)(SPh)_2(bipy) \rightarrow cyclo\text{-}(CH_2)_4 + butenes + C_4H_7O_2CPh + C_4H_9O_2CPh + PhCO_2H$

$Pd(CH_2CH_2CH_2CH_2)(SPh)_2(bipy) \rightarrow cyclo\text{-}(CH_2)_4 + butenes + C_4H_7SPh + C_4H_9SPh + SPh_2$

Scheme 81. Three Possible Mechanisms for C−O Reductive Elimination from Cyclopalladated Bis(benzoate) Pd^{IV} Complexes



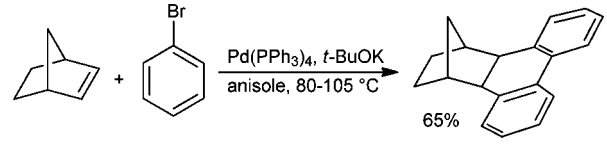
The reactions with the alkyl halides probably proceed by oxidative addition to give a Pd^{IV} intermediate, which undergoes aryl−alkyl or aryl−acyl reductive elimination to yield the observed Pd^{II} complexes. The reductive elimination is very selective in these cases, leading to exclusive C−C bond formation to the aryl ring.

3.5. C−Heteroatom Reductive Elimination from Pd^{IV} Complexes

The dominance of C−C bond formation from triorganoPd^{IV} complexes is not reflected in diorganoPd^{IV} complexes in the presence of group 16 donor atoms (E = O, S, Se) where C−E coupling becomes an important feature.[90] The decomposition pathways for the $PdMe_2(E)_2(bipy)$ complexes, generated in situ and characterized before decomposition at −50 °C (E = O_2CPh, SPh), are shown in Scheme 80.

The mechanism of C−O reductive elimination from Pd^{IV} complexes has been the subject of a systematic theoretical investigation.[126] The authors examined three possible mechanisms including pre-equilibrium dissociation of a benzoate ligand followed by reductive elimination from the resulting five-coordinate Pd^{IV} intermediate; direct reductive elimination from the six-coordinate Pd^{IV} intermediate; and dissociation of a pyridyl arm of one cyclometalated ligand followed by internal coupling (Scheme 81).

Scheme 82. Reaction of Norbornene and Bromobenzene Leading to a Fused Polycyclic Biaryl Product



On the basis of a match between calculated and experimental $\Delta G^{\ddagger}$, the direct reductive elimination mechanism appears to be the most successful (Scheme 81). The same theoretical model also correctly predicts the subtle solvent and substituent effects. Interestingly, these findings stand in contrast to the mechanistic studies of Canty[105] on trimethyl Pd^{IV} complexes, where iodide dissociation is a prerequisite for reductive elimination. However, in a later paper by Golberg et al.,[127] it was shown that, at least in some instances (C−H reductive elimination at Pt^{IV}), direct coupling without preliminary ligand loss is preferable.

3.6. Applications of $C(sp^2)-Pd^{IV}$ Complexes in Synthesis

While the key process of many palladium-catalyzed reactions, the oxidative addition of $C(sp^2)-X$ bonds to Pd^0, is very well established, related reactions of Pd^{II} substrates with $C(sp^2)-X$ bonds to form Pd^{IV} are much less documented. However, for Pt^{II}, oxidative addition into $C(sp^2)-X$ bonds is common and even activation of a C_6F_5 group via oxidative addition into a C−F bond has been demonstrated.[128]

The first Pd^{IV} aryl intermediate was proposed by Catellani and co-workers[129] in 1985 in the reaction of bromobenzene and norbornene (Scheme 82).

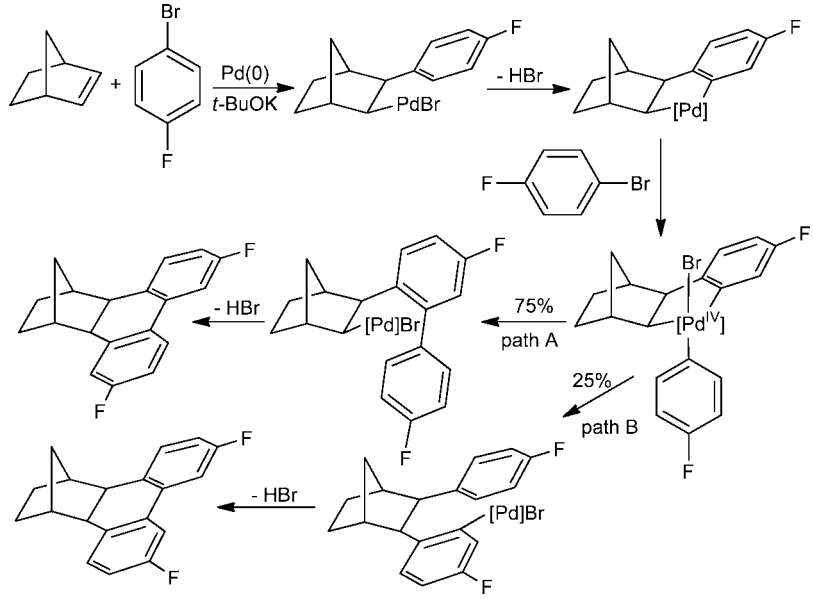
Catellani found that, when *p*-fluorobromobenzene was used instead, the reaction gave rise to two isomeric products depending on the sense of reductive elimination (paths A and B, Scheme 83). This led to the proposal of a novel mechanism involving the crucial pallada(II) and aryl pallada(IV) cyclic intermediates.

Later mechanistic studies with *p*-nitrobenzyl bromide[58] led to the isolation of a benzyl Pd^{IV} intermediate and a Pd^{II} complex containing the entire carbon skeleton. The selective benzyl−aryl reductive elimination is due to the extra stability associated with pallada(IV)cycle ring-formation.

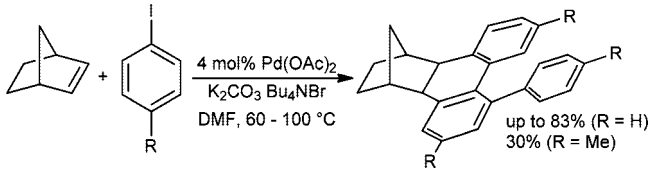
de Meijere and co-workers published a related reaction of *p*-substituted iodobenzenes,[130] though no specific aryl Pd^{IV} intermediate was implicated (Scheme 84).

The first identified transfer of Ph^+ to Pd^{II} from an aryl−halogen bond was achieved by Canty[131] using diphenyliodonium triflate. Pallada(II)cyclopentane complex $Pd(C_4H_8)(bipy)$ reacts with $[IPh_2][OTf]$ to form a 1:1 ratio of *cis*- and *trans*-$Pd(OTf)(C_4H_8)Ph(bipy)$; addition of halide ion gives a 1:3 ratio of *cis*-and *trans*-isomers for $PdI(C_4H_8)Ph(bipy)$ and $PdCl(C_4H_8)Ph(bipy)$ (Scheme 85).

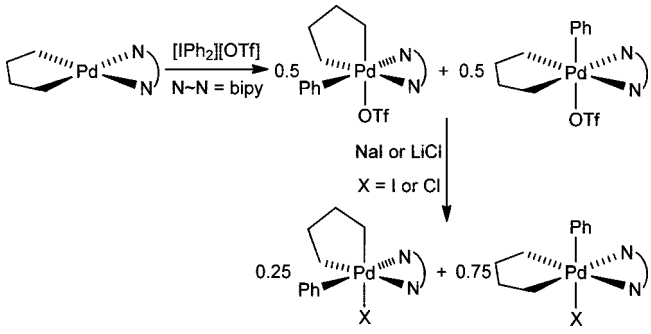
Scheme 83. Mechanism of Pd-Catalyzed Synthesis of 1,2,3,4,4*a*,12*b*-Hexahydro-1,4-methanotriphenylenes



Scheme 84. Reaction of Norbornene and Iodoarenes Leading to Polycyclic *o*-Terphenyls



Scheme 85. Arylation of [Pd(C$_4$H$_8$)(bipy)] with Diphenyliodonium Triflate



The decomposition behavior of PdX(C$_4$H$_8$)Ph(bipy) [X = OTf, I, Cl] is comparable to the more stable PdX(C$_4$H$_8$)(alkyl)(bipy) reported previously[113] (Scheme 86).

Analogous reaction of PdMe$_2$(bipy) with [IPh$_2$][OTf] in 1:1 molar ratio at −50 °C gave complex mixtures of products.[132] Addition of sodium iodide resulted in the detection of PdIMe$_3$(bipy), PdMePh(bipy), and a small amount of PdIMe$_2$Ph(bipy). These products are easily explained in terms of formation of the undetected Pd(OTf)Me$_2$Ph(bipy) and its methyl exchange reactions with PdMe$_2$(bipy).

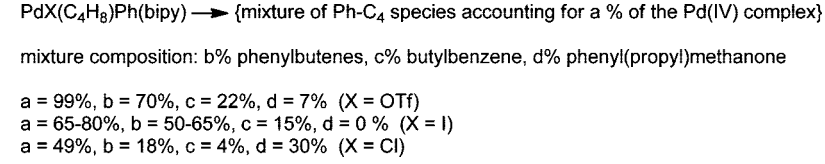
A number of theoretical studies have been conducted on the C(sp^2)−C(sp^2) reductive elimination on late transition metals. A detailed density functional study was performed for the vinyl−vinyl reductive elimination reaction from bis-σ-vinyl complexes [M(CH=CH$_2$)$_2$X$_n$].[133] It was shown that the activity of these complexes decreases in the following order: Pd^{IV}, Pd^{II} > Pt^{IV}, Pt^{II}, Rh^{III} > Ir^{III}, Ru^{II}, Os^{II}. The effects of different ligands were studied for both platinum and palladium complexes, which showed that activation barriers for C−C bond formation decrease in the following order: X = Cl > Br, NH$_3$ > I > PH$_3$. Activity order in C−C bond-formation process is as follows: PH$_3$ > I > Br, NH$_3$ > Cl. However, the solvent effect calculation shows that in polar media halogen complexes may undergo reductive elimination almost as easily as compounds with phosphine ligands.

Interesting studies on Pt^{IV} model complexes were reported by Vigalok and Vedernikov.[134] They found that *trans*-(dmpe)Pt^{IV}(Ar)$_2$I$_2$ can either reductively eliminate Ar−I or convert to the *cis*-isomer, which then undergoes Ar−Ar elimination selectively. Use of the rigid dmpe analogue, bis-1,2-dimethylphosphinobenzene (dmpbz), as the ligand shuts down the chelate ring-opening isomerization pathway and enables Ar−I reductive elimination to become the major pathway.

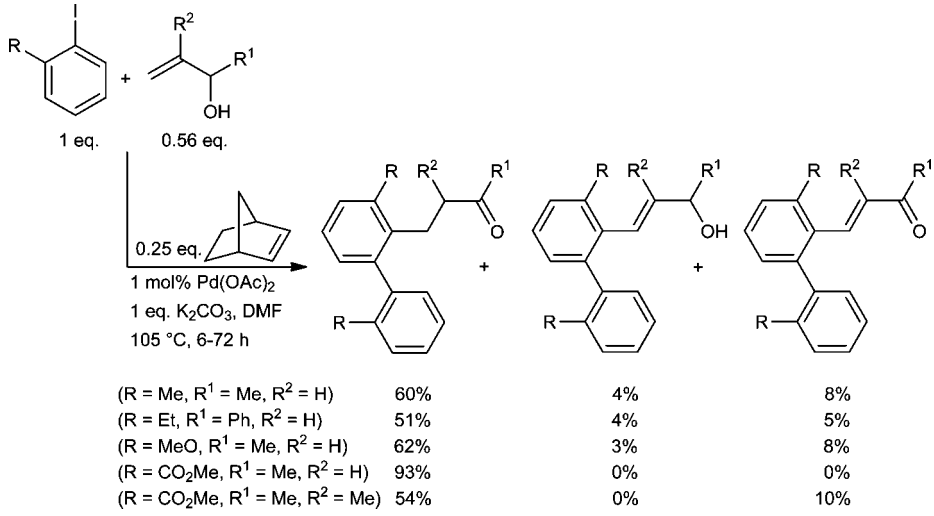
3.6.1. Applications of C(sp^2)−Pd^{IV} Complexes Formed from Oxidative Addition of Pd^{II} into Aryl Halides

Some of the early work on applications of aryl and vinyl Pd^{IV} species focused on stoichiometric reactions between hypervalent iodine compounds with Pd−aryl and vinyl complexes. These stoichiometric reactions generally result in clean and high-yielding functionalization/cleavage of a Pd−C bond.

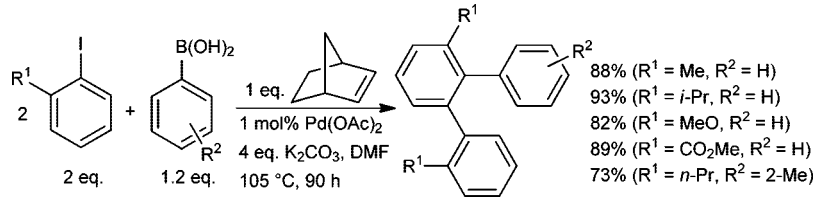
Scheme 86. Decomposition Behavior of the Pd^{IV}X(C$_4$H$_8$)Ph(bipy) Complexes



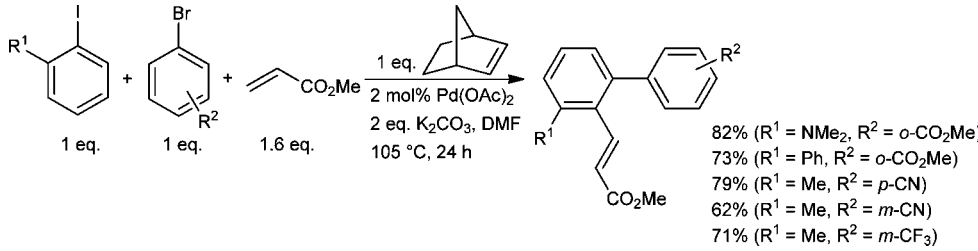
Scheme 87. Reaction of *o*-Substituted Iodobenzenes and Allylic Alcohols Leading to Functionalized Biphenyls



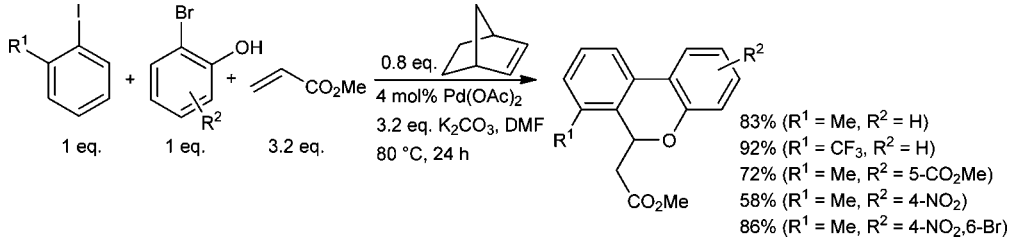
Scheme 88. Reaction of *o*-Substituted Iodobenzenes and Arylboronic Acids Leading to Functionalized *o*-Terphenyls



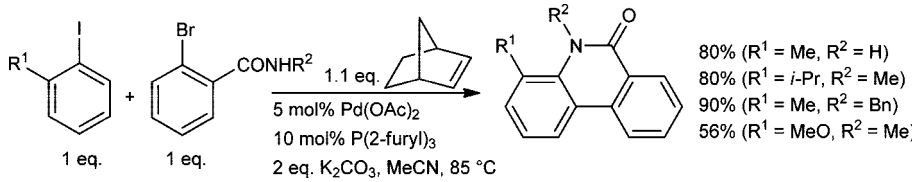
Scheme 89. Unsymmetrical Aryl Coupling−Olefination Sequence to Form Vinylbiphenyls



Scheme 90. Unsymmetrical Coupling of Iodobenzenes, Bromophenols, and Methyl Acrylate to Form Dibenzopyrans



Scheme 91. Coupling of Iodobenzenes and *o*-Bromocarboxamides to Form Phenanthridinones

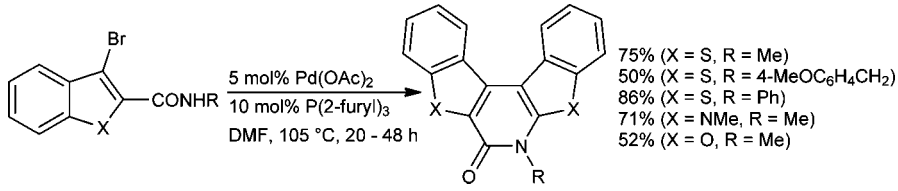


Oxidative addition of Ar−X leading to Ar−Pd^{IV}−X has been exploited by Catellani and co-workers in a reaction sequence leading to selectively substituted biphenyls (Scheme 87).[135]

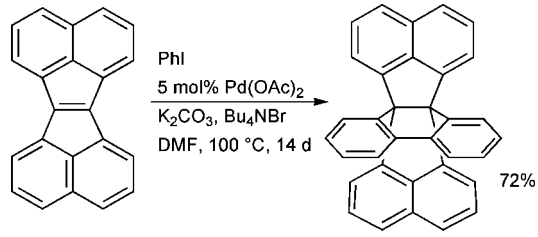
When combined with a Suzuki cross-coupling, the methodology leads selectively to 2,3-substituted 1,1′;2′,1″-terphenyl derivatives (Scheme 88).[136]

After a thorough study of the reaction factors, it was discovered that coupling of two differently substituted aryl groups can be achieved.[80] The methodology is based on the differing reactivity of Pd^0 and Pd^{II} complexes with aryl iodides and bromides. While under the conditions chosen the aryl iodides reacted faster than aryl bromides with palladium in both oxidation states, *o*-alkyl-substituted iodides

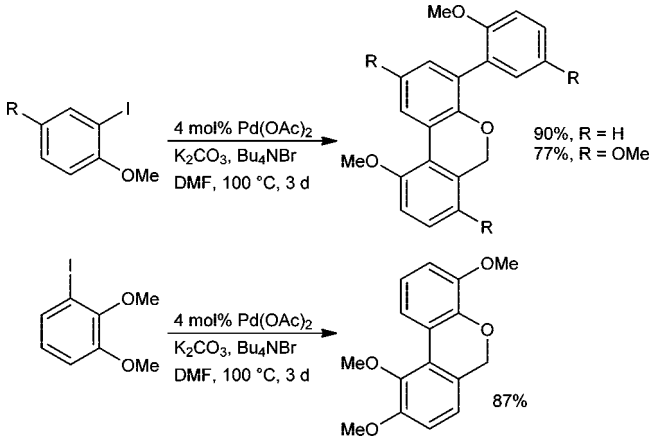
Scheme 92. Coupling of Two Molecules of *o*-Bromoaromatic Carboxamides to Polycyclic Pyridones



Scheme 93. Coupling of Iodobenzene with Acenaphtho[1,2-*a*]acenaphthylene to Give a Hexaarylethane-Type Propellane



Scheme 94. Condensation of Mono- and Dimethoxy-Substituted Iodobenzenes to 6*H*-Dibenzo[*b*,*d*]pyrans



reacted much more readily with Pd^0 than with Pd^{II} metalacycles, likely for steric and electronic reasons. On the contrary, aryl bromides substituted by electron-withdrawing or by certain chelating groups preferentially reacted with Pd^{II} rather than with Pd^0.

An example of this approach is the unsymmetrical aryl coupling−olefination sequence to form vinylbiphenyls (Scheme 89).[137]

Condensed heterocycles are accessible by utilizing appropriately placed functional groups on the aryl bromide. Michael addition of an *o*-hydroxyl gives dibenzopyrans (Scheme 90).[138]

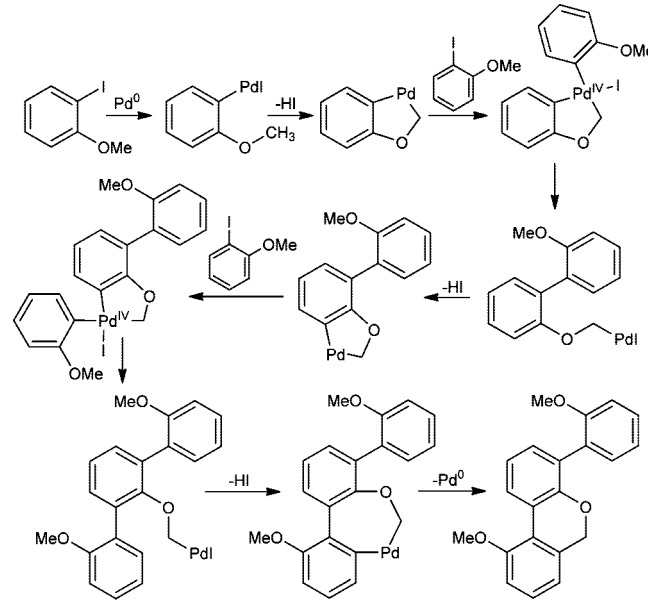
Another modification involves a C−N reductive elimination event to give phenanthridinone derivatives.[139] Interestingly, the reaction required tris(2-furyl)phosphine ligand to achieve high yields (Scheme 91).

Surprisingly, when using the $Pd(OAc)_2/P(2\text{-furyl})_3$ catalytic system in the absence of norbornene, coupling of two molecules of *o*-bromoaromatic carboxamide produced novel symmetrically condensed pyridones (Scheme 92).[140]

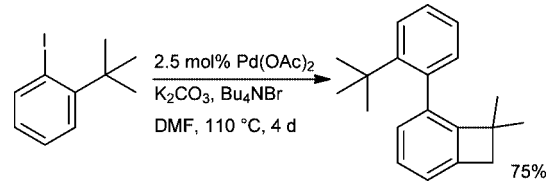
A summary of the catalytic multistep reactions via palladacycles developed by Catellani has been reported.[141]

Similar annelation reactions such as the one at norbornene also occur at a strained tetrasubstituted double bond in acenaphtho[1,2-*a*]acenaphthylene. The reaction with iodobenzene results in the formation of a hexaarylethane-type propellane structure (Scheme 93).[142]

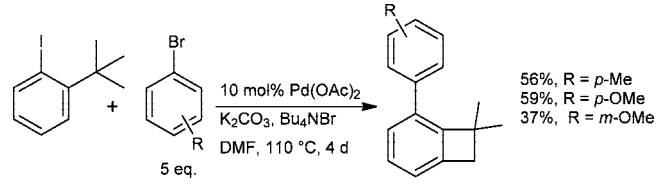
Scheme 95. Mechanism of the Condensation of Methoxy-Substituted Iodobenzenes via Aryl Pd^{IV} Intermediates



Scheme 96. Condensation of Two Molecules of 1-*tert*-Butyl-2-iodobenzene to 1,2-Dihydrocyclobutabenzene



Scheme 97. Unsymmetrical Coupling of 1-*tert*-Butyl-2-iodobenzene and Bromobenzenes to 1,2-Dihydrocyclobutabiphenyls

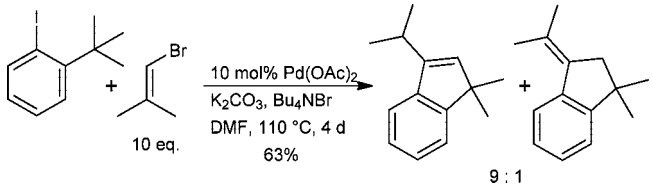


Dyker reported a novel type of palladium-catalyzed domino coupling reaction, where C−H activation at an aryl methoxy group occurs.[143] Mono- and dimethoxy-substituted iodobenzenes condense under palladium catalysis in high yields to substituted *6H*-dibenzo[*b*,*d*]pyrans (Scheme 94). When the crucial position for the third condensation step was blocked, a product originating from only two molecules of the starting arene was obtained.

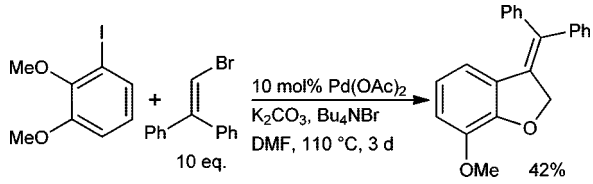
The following mechanism was proposed (Scheme 95).

Later, Dyker reported the first palladium-catalyzed C−H activation of a *tert*-butyl group.[144] It was found that 1-*tert*-

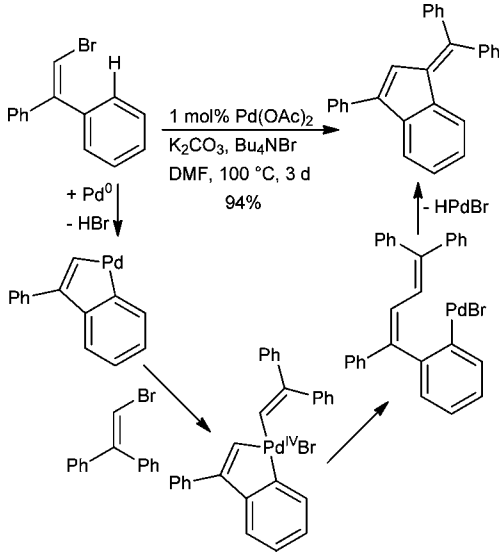
Scheme 98. Unsymmetrical Coupling of 1-*tert*-Butyl-2-iodobenzene and Bromoalkenes to Indenes



Scheme 99. Unsymmetrical Coupling of Dimethoxyiodobenzene and a Bromoalkene to Give a Condensed Oxygen Heterocycle



Scheme 100. Mechanism of Cyclodimerization of Phenyl-Substituted Bromoethenes to Indenes



butyl-2-iodobenzene condensed under palladium catalysis gave the strained 1,2-dihydrocyclobutabenzene in 75% yield (Scheme 96).

By adding an excess of a less-reactive aryl bromide, it was possible to develop a cross-coupling variant of this reaction (Scheme 97).

Bromoolefins also coupled successfully. In this case, the domino process is terminated by ring-closure, resulting in the formation of two regioisomeric indene derivatives (Scheme 98).

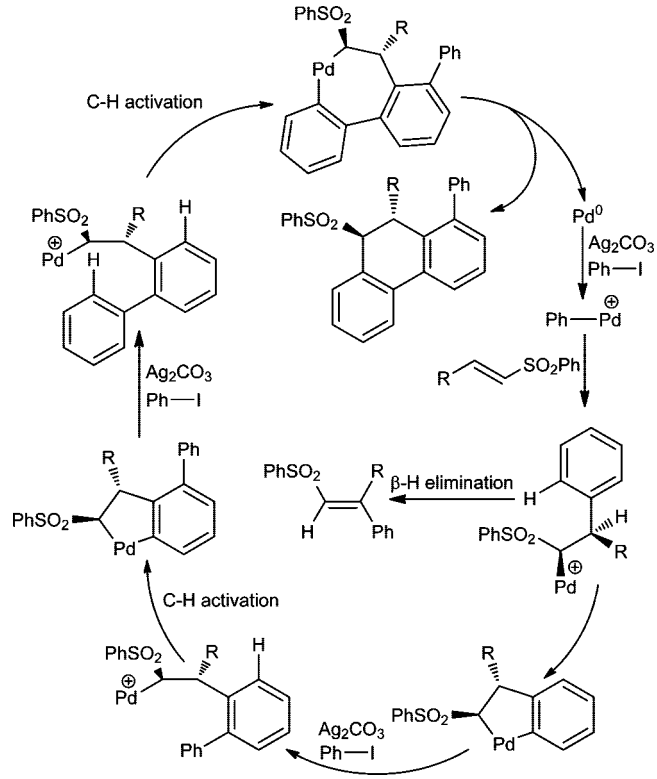
A combination of C−H activation at a methoxy group with a bromoolefin cross-coupling leads to the formation of oxygen heterocycles (Scheme 99).[145]

Indenes also originate from dimerization of phenyl-substituted bromoethenes, reported by the same group (Scheme 100).[146,147]

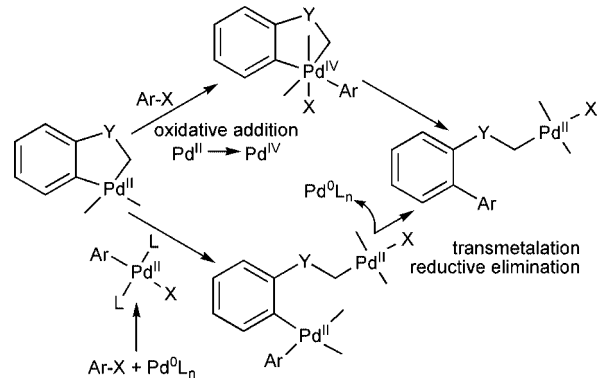
These and other reactions were later summarized by Dyker in a review of coupling reactions under C−H activation.[148]

A palladium-catalyzed four-component domino reaction of aryl iodides with unsaturated sulfones has been reported by Alonso and Carretero (Scheme 101).[149] For the key aryl−aryl bond-forming step, the authors propose two different mechanisms: an oxidative addition/reductive elimination pathway via a Pd^{IV} palladacycle intermediate or a ligand exchange reaction between two Pd^{II} complexes.

Scheme 101. Mechanism of Palladium-Catalyzed Four-Component Domino Reaction of Aryl Iodides with Unsaturated Sulfones



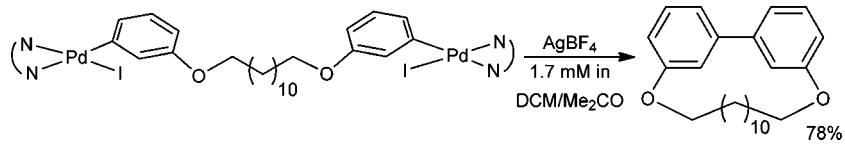
Scheme 102. Two Alternative Mechanisms for Arylation of Pallada(II)cycles (Bonds to Pd without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



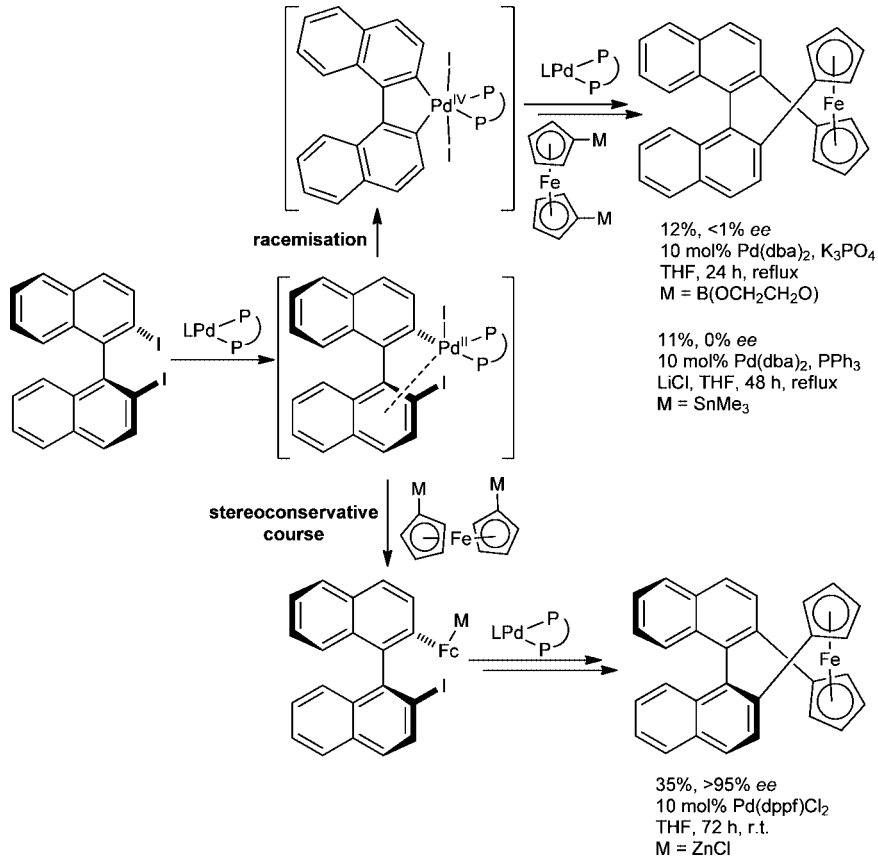
In view of an impressive array of Pd-catalyzed domino reactions described above, a computational study was performed by Echavarren and Martin-Matute[150] to determine the mechanism of the key steps in which $C(sp^2)-C(sp^2)$ are formed from aryl and alkenyl halides. Density functional theory (DFT) calculations were done on model complexes of the proposed intermediates, with PH_3 and H_2O as ancillary ligands, to explore two possible mechanisms: the oxidative addition of aryl or alkenyl halides to palladacycles to give Pd^{IV} intermediates and the transmetalation-type reaction of aryl or alkenyl ligands between two Pd^{II} centers, a palladacycle, and a Pd^{II} complex formed by oxidative addition of aryl or alkenyl halides to Pd^0 (Scheme 102).

The calculations showed that oxidative addition of iodoethylene to Pd^0 precursors is more favorable than oxidative

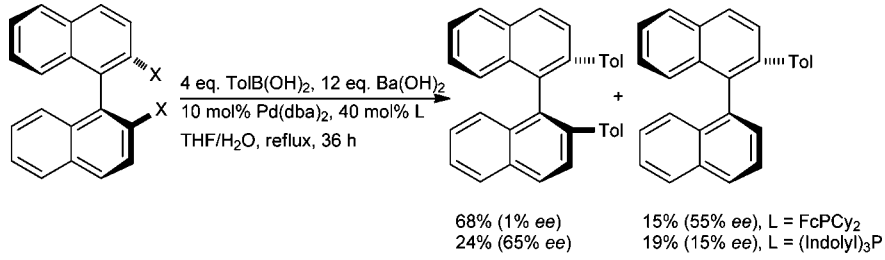
Scheme 103. Experimental Evidence for Transmetalation of an Aryl Group between Two Pd^{II} Centers



Scheme 104. Stereochemical Course of Cross-Coupling Reactions of 2,2′-Diiodo-1,1′-binaphthyl with Different 1,1′-Dimetalloferrocenes



Scheme 105. Products and Enantioselectivities of Suzuki Cross-couplings of 2,2′-Dihalo-1,1′-binaphthyls with *p*-Tolylboronic Acid



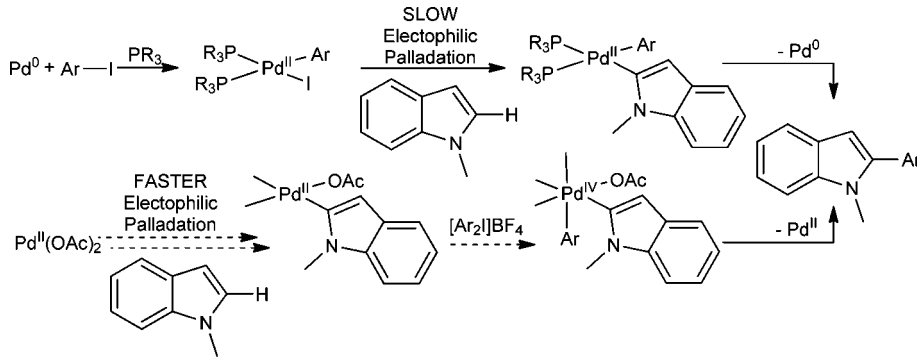
addition to Pd^{II} palladacycles, whereas transmetalation-type reactions between Pd^{II} complexes are facile. Similar results were obtained with iodobenzene instead of iodoethylene and formamide as the ancillary ligand. These results suggest that Pd^{IV} intermediates are not involved in these reactions. These findings clearly have implications for earlier experimental studies suggesting the intermediacy of Pd(IV) species.

Experimental evidence for the $Pd^{II}-Pd^{II}$ transmetalation route was provided by Osakada and co-workers.[151] Thus, reaction of a dinuclear aryl Pd^{II} complex with $AgBF_4$ directly gives rise to a macrocyclic biaryl product (Scheme 103).

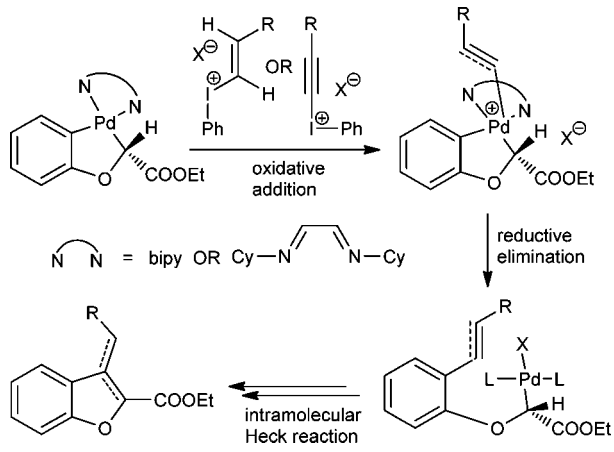
The stereochemical outcome of cross-coupling reactions of 2,2′-dihalo-1,1′-binaphthyl was studied by Putala et al.[152] Interestingly, when enantiopure 2,2′-diiodo-1,1′-binaphthyl was used, the enantiomeric excess of the product is strongly dependent on the type of organometallic cross-coupling partner. With 1,1′-dimetalloferrocenes, Negishi coupling proceeds stereoconservatively (affording enantiopure product), while complete racemization of binaphthyl moiety occurs during the reactions with less reactive boron and tin-based organometallics. A C_1-symmetric Pd^{II} intermediate was proposed for the former, and a configurationally unstable C_2-symmetric pallada(IV)cyclic intermediate was proposed in the latter case (Scheme 104).

In a later study, the authors examined Suzuki cross-coupling of enantiopure 2,2′-dihalo-1,1′-binaphthyls with benzeneboronic acids (Scheme 105).[153]

Scheme 106. Alternative Mechanistic Pathways for 2-Arylation of Indoles via Electrophilic Palladation (Bonds to Pd Without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



Scheme 107. Transfer of C(sp^2) or C(sp)-Moieties to Pallada(II)cycles from Vinyl or Alkynyl(phenyl)iodonium Salts and the Formation of Benzofuran-type Heterocycles



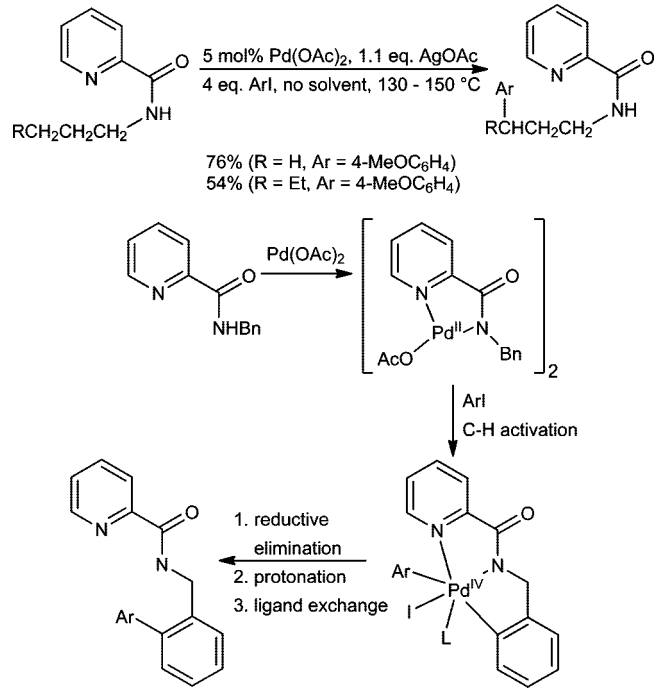
In accordance with the formerly proposed mechanism, the degree of racemization via the pallada(IV)cyclic intermediate can be controlled by electronic factors, which determine the rate of oxidative addition, i.e., electron-donating properties of the phosphine (L = $FcPCy_2$ gives 1% ee, L = $(Indolyl)_3P$ gives 65% ee) and leaving group of binaphthyl 2,2′-dielectrophile (7% ee for R = Me, X = I; 95% ee for R = Me, X = Br). Stereoconservativity in formation of monoarylated product does not exhibit strong dependence on leaving group.

However, later the stereoconservative Suzuki diarylations of 2,2′-diiodo-1,1′-binaphthyl were reported. Thus, a deracemization approach using binap ligand was developed, giving diarylation with 83% ee even when starting from racemic diiodide.[154]

3.6.2. Applications of C(sp^2)—Pd^{IV} Complexes Formed from Oxidative Addition of Pd^{II} into Diaryliodonium Salts

A room-temperature palladium-catalyzed direct C2-selective arylation of indoles was reported by Sanford and coworkers.[155] Compared to phosphine (aryl) Pd^{II} complexes, the more electron-deficient $Pd(OAc)_2$ is capable of rapid electophilic palladation of indole substrates. The resulting (2-indolyl) Pd^{II} complex is arylated with $[Ar_2I][BF_4]$, presumably via Pd^{IV}, and reductively eliminates to give 2-arylindole (Scheme 106). It was demonstrated that comparable yields and mild reaction conditions can be used when the $[Ar_2I][BF_4]$ is generated in situ from $ArI(OAc)_2$ and $ArB(OH)_2$.

Scheme 108. Chelation-Directed Regioselective Arylation of sp^3 C—H Bonds in Picoline and Quinoline Amides

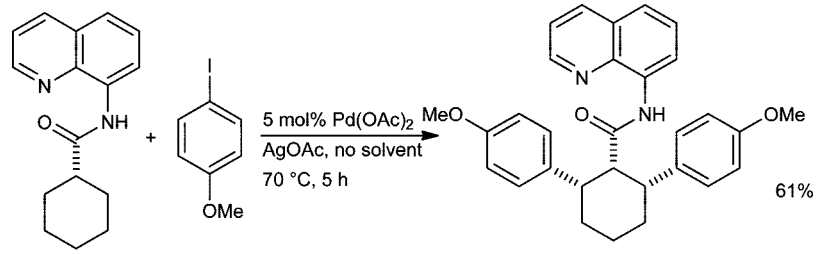


The *ortho*-directed arylation of acetanilides with $[Ph_2I][PF_6]$ has recently been highlighted in connection with the novel copper-catalyzed *meta*-arylation methodology reported by Gaunt et al.[156] A comprehensive review of applications and mechanistic aspects of hypervalent iodine reagents in palladium-catalyzed processes is available.[157]

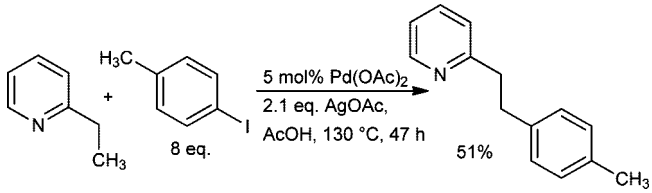
The ability of hypervalent vinyl- or alkynyl(phenyl)iodonium salts to transfer C(sp^2) or C(sp)-moieties, respectively, to pallada(II)cycles with the formation of Pd^{IV} has been exploited by Malinakova et al.[158] On the basis of a prior study with allylic bromides,[76] it was shown that two new geminal carbon—carbon bonds to the terminal carbon of the transferred substituent can be generated, providing benzofuran and dihydrobenzofuran heterocycles (Scheme 107). Since only one Pd^{II} complex is present in appreciable concentration, an alternative mechanism invoking transmetalation between two Pd^{II} centers[150] appears unlikely.

Palladium(II) acetate in combination with silver(I) acetate proved to be efficient for highly regioselective arylation of sp^3 C—H bonds in picoline and quinoline amides.[159] The timing of C—H activation process versus the oxidative addition of ArI to Pd^{II} remains unclear (Scheme 108).

Scheme 109. Stereoselective Double Arylation of a Cyclohexane Carboxamide with *p*-Methoxyiodobenzene



Scheme 110. Regioselective Arylation of 2-Ethylpyridine with *p*-Iodotoluene



Interestingly, when a cyclohexane carboxamide derivative was used, the reaction proceeded stereoselectively, giving the major product with a *cis,cis* relative configuration as determined by XRD analysis (Scheme 109).

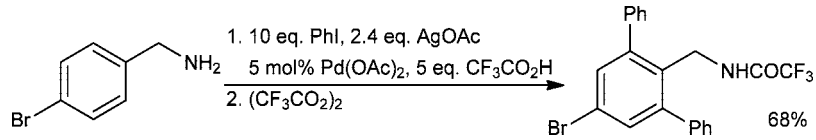
The same authors reported the catalytic coupling of unactivated C−H bonds and aryl iodides, where only a promixal pyridine moiety as a directing group was needed (Scheme 110).[160]

As in the case of anilide arylation, reactions generally are faster for electron-rich aryl iodides, which is distinct from the usual Pd^0-Pd^{II} catalytic processes. The most likely reaction mechanism involves electrophilic C−H activation by Pd^{II}, followed by oxidative addition of ArI to form a Pd^{IV} intermediate. Reductive elimination of the product, and then iodide exchange for acetate by Ag^+, completes the catalytic cycle.

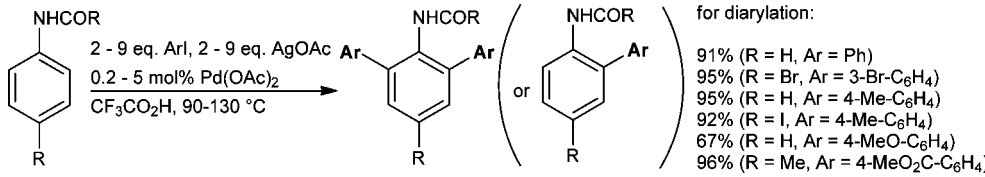
It was shown earlier that aminomethyl moiety is susceptible to decomposition under the reaction conditions.[159] However, this could be circumvented by adding 5 equiv of trifluoroacetic acid, proving a useful method for the direct *ortho*-arylation of benzylamines and *N*-methylbenzylamine (Scheme 111).[161] It was shown that the ca. 10% of *N*-trifluoroacetylated derivatives formed under the reaction conditions is not responsible for product formation. (*N*-trifluoroacetylbenzylamine and iodobenzene give no reaction. The final trifluoroacetylation of products is mainly to simplify purification.)

Later in the Daugulis group, direct *ortho*-arylation of anilides[162,163] (Scheme 112) and two methods for benzoic

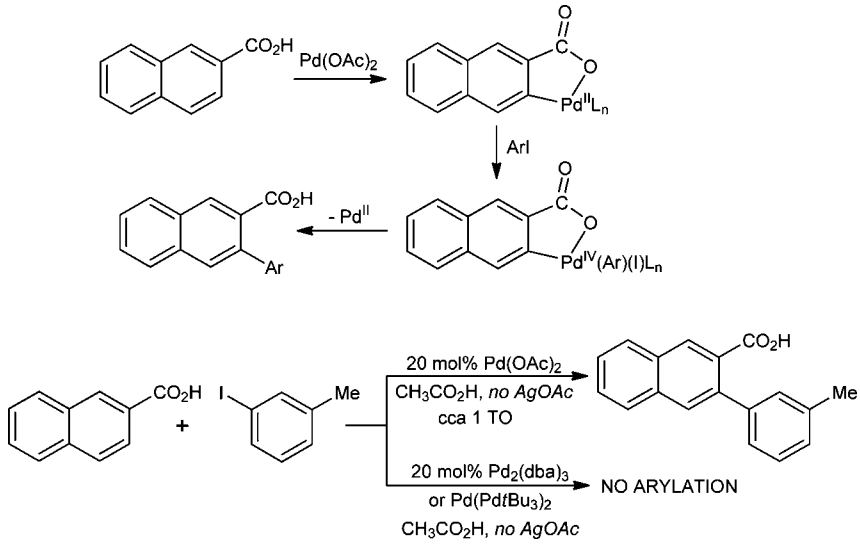
Scheme 111. Direct Double *ortho*-Arylation of Benzylamines



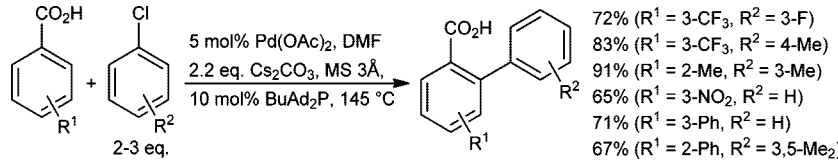
Scheme 112. Direct Single and Double *ortho*-Arylation of Anilides



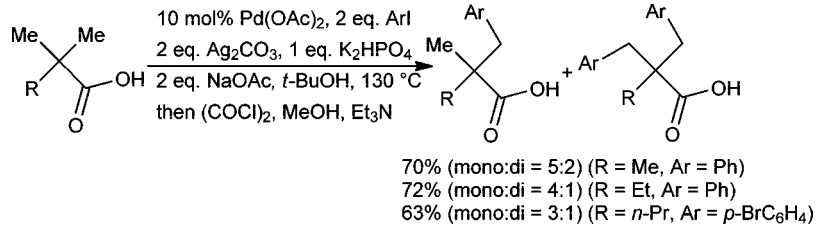
Scheme 113. Arylation of Moderately Electron-Poor to Electron-Rich Benzoic Acids with Aryl Iodides/AgOAc



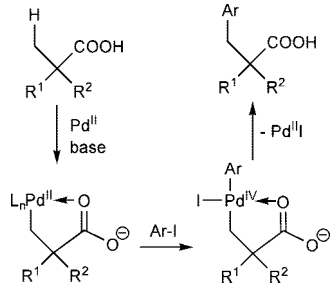
Scheme 114. General Method for Arylation of Benzoic Acids with Aryl Chlorides



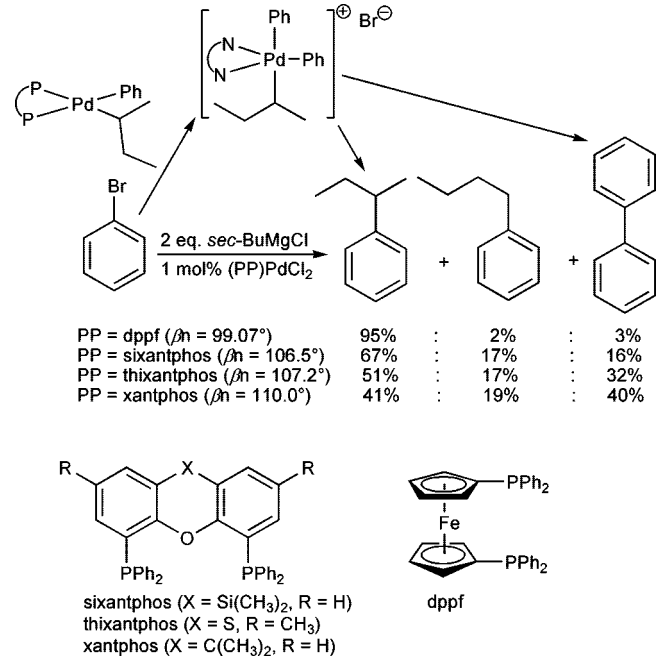
Scheme 115. β-Monoarylation and Diarylation of Aliphatic Acids with Aryl Iodides



Scheme 116. Mechanism of β-Monoarylation of Aliphatic Acids with Aryl Iodides



Scheme 117. Proposed Cationic Pd^{IV} Intermediate in Cross-Coupling of Bromobenzene with *sec*-Butylmagnesium Chloride



acid arylation[164] were developed (Schemes 113 and 114). The anilide (di)arylation reactions proceed in trifluoroacetic acid solvent at 110−120 °C. The method employs stoichiometric silver acetate for iodide removal. Anilides and aryl iodides of all electronic properties are reactive. Very similar conditions are also applicable to the *ortho*-arylation of benzoic acid amides.[165]

Moderately electron-poor to electron-rich benzoic acids are arylated with aryl iodides/AgOAc.

This method is tolerant of chloride and bromide substitution and most likely proceeds through a $Pd^{II}-Pd^{IV}$ coupling cycle (Scheme 113).[164] Mechanistic studies indicate that an electrophilic Pd^{II} acetate species is essential. Pd^0 sources give no arylation products.

The second method requires *n*-butyl-di-1-adamantylphosphine, Cs_2CO_3, molecular sieves, and an aryl chloride coupling partner. Benzoic acids of any electronic properties are reactive (Scheme 114).[164]

The area of palladium- and copper-catalyzed arylation has recently been reviewed.[166]

The first example of β-arylation of aliphatic acids using aryl iodides was provided by Yu and co-workers.[167] As shown by related experiments or aromatic acids, the role of the sodium counterion is crucial because a preformed Pd^{II} carboxylate in the absence of sodium counterions was unreactive. Thus, the use of 2 equiv of NaOAc as an additive substantially increases the combined yield of the mono- and diarylated products (70%). It was hypothesized that an electronically enriched carbonyl moiety instead of the *O*-anion of the sodium carboxylate binds the Pd^{II} in the C−H cleavage step (Scheme 115).

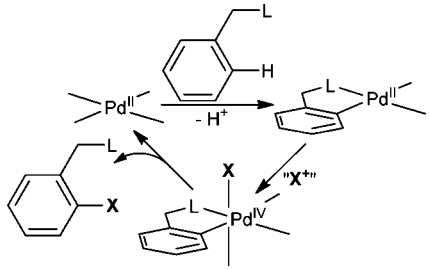
This arylation reaction most likely involves a carboxylic acid directed Pd insertion into C−H bonds and subsequent oxidation of the "RPd^{II}" complex to $(R)(Ar)Pd^{IV}I$ intermediate by ArI (Scheme 116). The formation of diarylated products is consistent with the Pd^{II}/Pd^{IV} pathway in which the Pd^{II}, unlike the Pd^0 species in the cross-coupling protocol, remains bound to the carboxylate and results in further arylation. Ag_2CO_3 is mainly responsible for the catalytic turnover by converting PdI_2 into the reactive Pd^{II} species.

The excess acetate could also displace the iodide from the $(R)(Ar)Pd^{IV}I$ intermediate and increase the turnover number as observed.

A hypothetical pentacoordinated cationic Pd^{IV} intermediate was proposed in the cross-coupling of bromobenzene with *sec*-butylmagnesium chloride (Scheme 117).[168] This complex could be stabilized by large bite-angle ligands; however, the competing aryl−aryl reductive elimination should lead to an increased amount of homocoupled product. While this was actually observed for sixantphos, thixantphos, and xantphos, which are most suitable for stabilizing trigonal bipyramids, an alternative mechanism could not be excluded.

The area of Pd^{II}-catalyzed C−H activation/C−C cross-coupling has recently been reviewed.[169]

Scheme 118. Catalytic Cycle for Pd-Catalyzed *o*-Directed C−H Bond Halogenation (Bonds to Pd Without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



3.6.3. Oxidative Cleavage of Pallada(II) Cyclic Compounds Leading to Functionalization of Proximal C−H Bonds with Chlorine and Heavier Halogens

The scope and selectivity in palladium-catalyzed chelate-directed C−H bond halogenation of arenes was studied in great detail by Sanford et al.[170,171] The proposed catalytic cycle for directed C−H bond halogenation is shown in Scheme 118. It involves ligand-directed *ortho*-palladation, oxidation of the resulting palladacycle to a Pd^{IV}−X intermediate, folowed by C−X reductive elimination and regeneration of Pd^{II}. The mechanism is corroborated by the earlier work of van Koten[36,37] and Elsevier,[73] who both directly observed transient Pd^{IV}−X intermediates in the oxidation of Pd^{II} complexes with molecular halogen or $PhICl_2$.

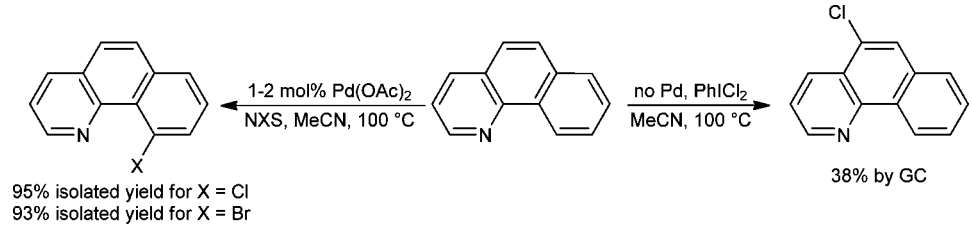
A palladium-catalyzed *ortho*-halogenation of azobenzene reported earlier[172] was low-yielding and used impractical molecular halogens. Sanford et al. introduced *N*-halosuccinimides as terminal oxidants for the palladium-catalyzed directed chlorination, bromination, and iodination (Scheme 119).

Selected examples in Scheme 120 illustrate the impressive scope and efficiency of the methodology.

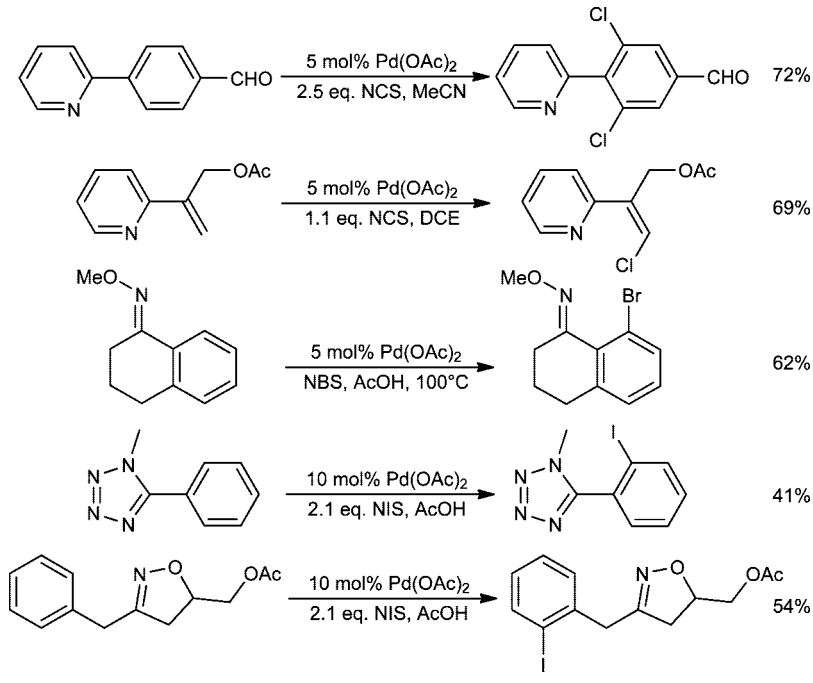
In 2007, by reacting $Pd^{II}(phpy)_2$ (phpy = 2-phenylpyridine) with both $PhICl_2$ and *N*-chlorosuccinimide (NCS), Sanford and co-workers have succeeded in isolating the first stable complexes containing a Pd^{IV}−Cl bond (Scheme 121).[173] Both complexes were fully characterized by ^1H and ^{13}C NMR spectroscopy and are stable at room temperature in the solid state for several weeks. X-ray structure of the Pd^{IV} imidate complex confirmed the proposed *cis* orientation between the chloride and succinimide ligands. Furthermore, it shows that the succinimide is *trans* to a σ-phenyl ligand, while the chloride is *trans* to a pyridine nitrogen. Thermal decomposition studies of both Pd^{IV} complexes revealed the dramatic solvents effects on the carbon···carbon versus carbon···hetero atom reductive elimination selectivity (Scheme 121). This is the first report of carbon−halogen bond-forming reductive elimination occurring in preference to C−C coupling at a Pd^{IV} center. The minor aryl···imidyl coupling route on Pd^{IV} can be compared to Pt^{IV}−sulfonamide complexes, where C−N versus C−C selectivity can easily be switched by solvent and conditions.[174]

An interesting dichotomy, with the platinum analogue $Pt^{II}(phpy)_2$ showing much more complex behavior in reactions with $PhICl_2$ and *N*-chlorosuccinimide, has been reported elsewhere.[175] It is pertinent to point out that other Pd^{II}

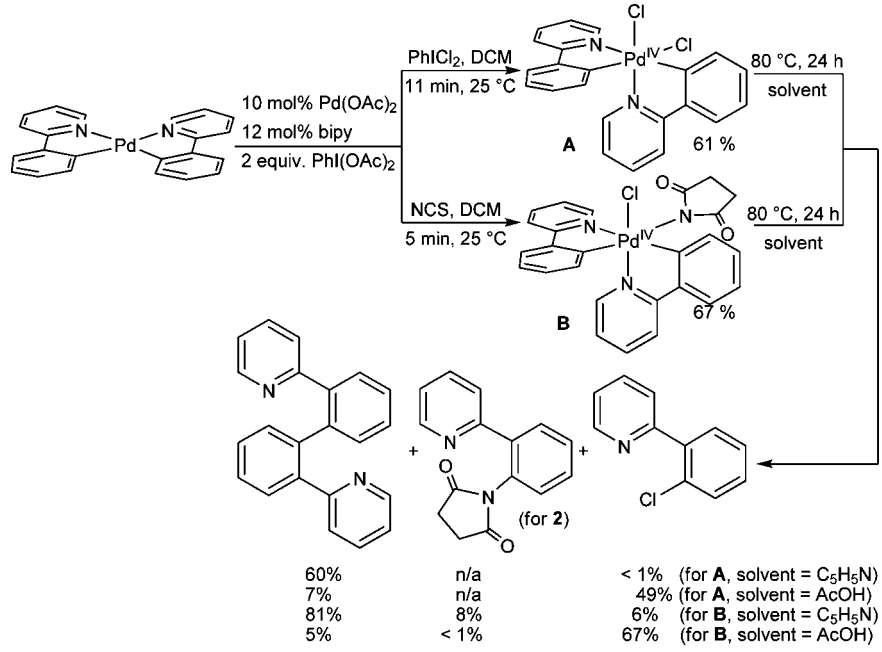
Scheme 119. Pd-Catalyzed Versus Uncatalyzed Halogenation of Benzo[*h*]quinoline with *N*-Halosuccinimides



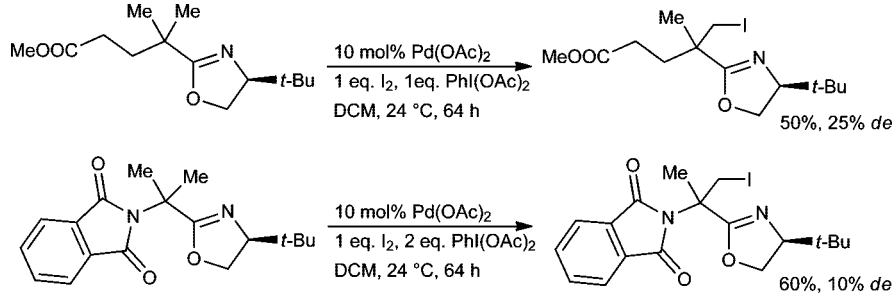
Scheme 120. Examples of Pd-Catalyzed *o*-Directed Halogenation



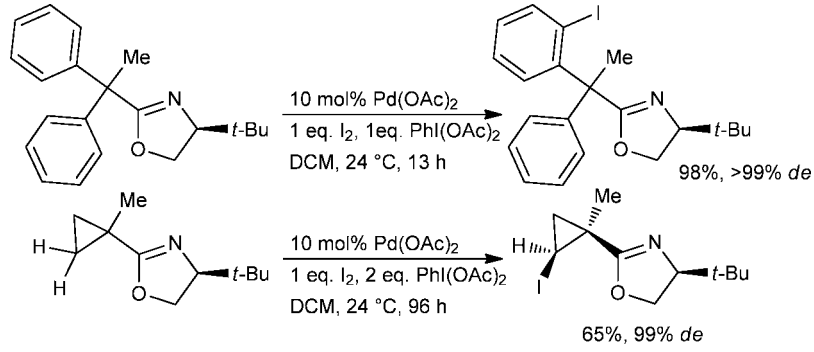
Scheme 121. Oxidative Addition of $PhICl_2$ and NCS to Bis(2-phenylpyridine)palladium(II)



Scheme 122. Selective Pd-Catalyzed Iodination of Methyl C−H Bonds Directed by a Proximal Oxazoline Group



Scheme 123. Highly Diastereoselective Iodination of Cyclopropane and Aryl C−H Bonds



precatalysts/catalysts possessing imidate ligands have been developed by Fairlamb, Taylor, and others.[176–181]

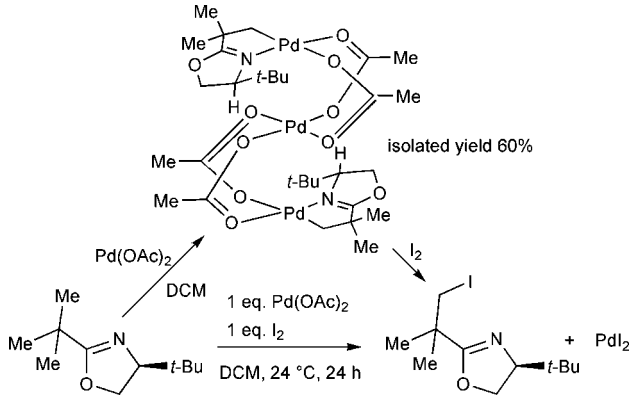
Synthetic and mechanistic efforts toward the development of selective catalytic directed iodination of C−H bonds have been reported by Yu and co-workers.[182,183] A large range of functional groups is tolerated[182] (Scheme 122).

In the case of methylene activation and aryl C−H activation of prochiral bonds, high diastereoselectivity can be achieved (Scheme 123).

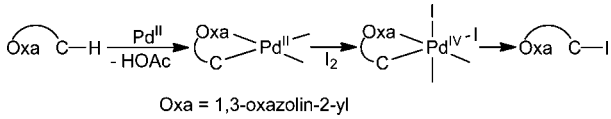
In order to elucidate the mechanism, a stoichiometric experiment was carried out (Scheme 124). PdI_2 was isolated in the reaction and found to be converted into $Pd(OAc)_2$ upon treatment with a combination of I_2 and $PhI(OAc)_2$ in situ to achieve catalytic turnover. It is worth noting that, in the absence of I_2, the combination of $Pd(OAc)_2$ and $PhI(OAc)_2$ results in an acetoxylation reaction in a similar manner to a recently reported Pd-catalyzed acetoxylation reaction.[184] It should be pointed out that, unlike the acetoxylation reaction, the role of $PhI(OAc)_2$ in this iodination reaction is not to oxidize Pd^{II} to Pd^{IV}. Instead, $PhI(OAc)_2$ reacts with I_2 to generate a new oxidant (most probably IOAc), which is responsible for converting PdI_2 into $Pd(OAc)_2$. The isolation of a trinuclear Pd^{II} complex from a stoichiometric experiment[183] shows the actual probable catalytic species. Addition of I_2 instantly converted the isolated complex into the iodinated product.

A simplified mechanism is shown in Scheme 125. Oxazoline-directed cleavage of the β-C−H bonds is followed

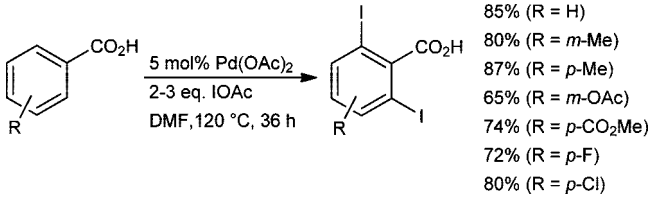
Scheme 124. Stoichiometric Palladation and Iodolysis Studies on a 2-*tert*-Butyloxazoline



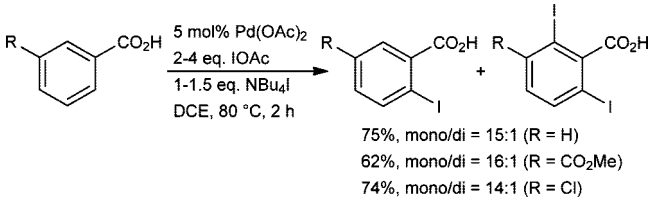
Scheme 125. Generalized Mechanism for Pd-Catalyzed Iodination by Cyclopalladation



Scheme 126. Pd(OAc)$_2$/IOAc System for Double *ortho*-Iodination of Benzoic Acids



Scheme 127. Pd(OAc)$_2$/IOAc/NBu$_4$I System for Monoselective *ortho*-Iodination of *meta*-Substituted Benzoic Acids



by reaction with I_2 to give a diiodo Pd^{IV} intermediate. The C−I reductive elimination then generates the iodinated coupling product.

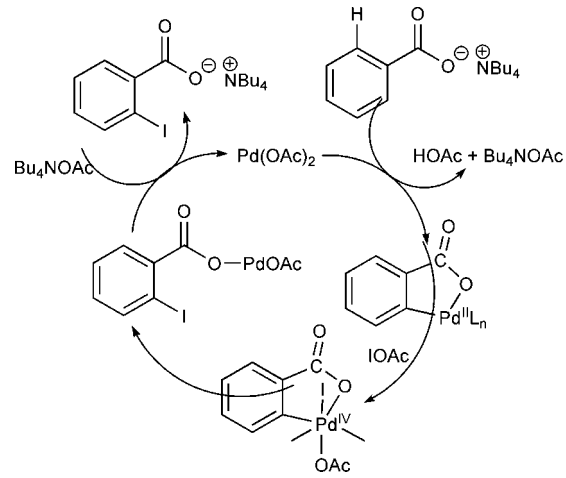
Further studies of remote C−H bond iodination using the Pd(OAc)$_2$/IOAc as the oxidant revealed an interesting distance-dependent isotope effect,[185] which is, however, beyond the scope of this review.

The Pd(OAc)$_2$/IOAc protocol is also effective for *ortho*-iodination of benzoic acids.[186] Similarly to β-arylation of aliphatic acids published by the same research group,[167] NaOAc was found to be a superior additive. Dimethylformamide (DMF) was also found to effectively promote this reaction, probably by abstracting a proton from carboxylic acids to a small extent to form $DMFH^+$ (Scheme 126). The noninnocent role of DMF and of its in situ decomposition products in many reactions are known[187,188] and have recently been reviewed.[189]

Monoselective *ortho*-iodination of *meta*-substituted benzoic acids assisted by NBu_4I was also demonstrated (Scheme 127).

Running the reaction with NBu_4Br instead leads to monoselective *ortho*-bromination in comparable yields,

Scheme 128. Mechanism of Monoselective *ortho*-Iodination of Benzoic Acids



presumably via IBr. The tetraalkylammonium cation appears to assist in the displacement of the monoiodinated (or monobrominated) product from the Pd^{II} center, thereby preventing undesired dihalogenation (Scheme 128).

Yu and co-workers have also developed related *o*-functionalization protocols based on copper catalysis,[190,191] which are outside the scope of this review.

The now well-established *o*-halogenation mechanism via $Pd^{II}-Pd^{IV}$ intermediates has very recently been challenged by the work of Ritter et al.[192] Unusual bimetallic Pd^{III} complexes were confirmed as products of oxidation of benzo[*h*]quinolinyl palladium acetate dimer with $PhICl_2$. Stoichiometric acetoxylation was also demonstrated using XeF_2/TMSOAc (Scheme 129).

On the basis of kinetic evidence and NMR spectroscopic studies, the following overall mechanism was proposed (Scheme 130).

It is important to note that analogous dimeric $Pt^{III}-Pt^{III}$ complexes containing a bridging acetate ligand were obtained by Sanford and co-workers[193] during C−H acetoxylation studies in AcOH (Scheme 130). Further support for bimetallic Pd(III) intermediates in Pd-catalyzed directed acetoxylation has been very recently reported.[194]

3.6.4. Oxidative Cleavage of Pallada(II) Cyclic Compounds Leading to Directed Fluorination

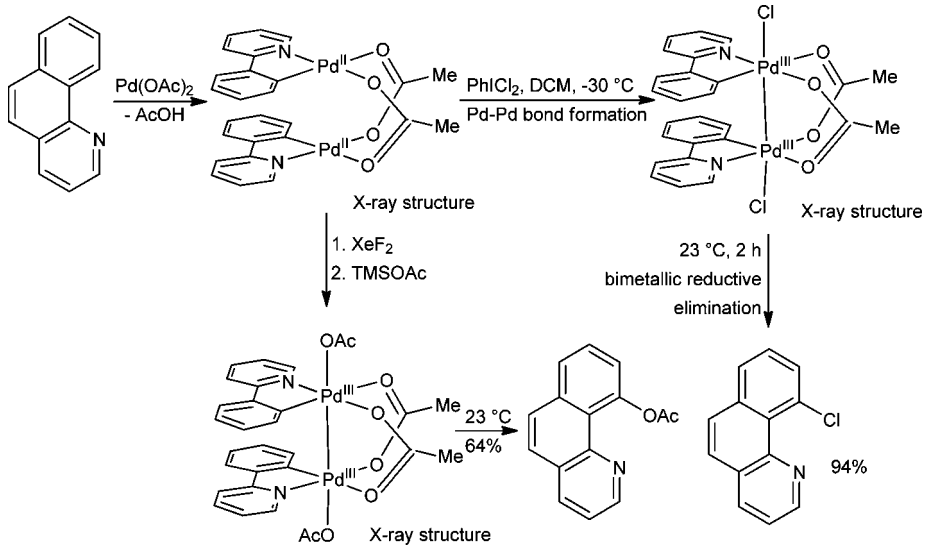
Despite the fact that selectively fluorinated organic compounds are highly desirable targets, transition metal-catalyzed methods for C−F bond construction have been particularly rare.

Having screened several common electrophilic fluorinating agents, Sanford and co-workers have found that *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate is a highly effective F^+ source for benzylic fluorination, particularly upon microwave irradiation.[195] In *ortho*-fluorination/difluorination of phenylpyridines, 2.5−4.5 equiv of *N*-fluoropyridinium tetrafluoroborate was found to be optimal (Scheme 131).

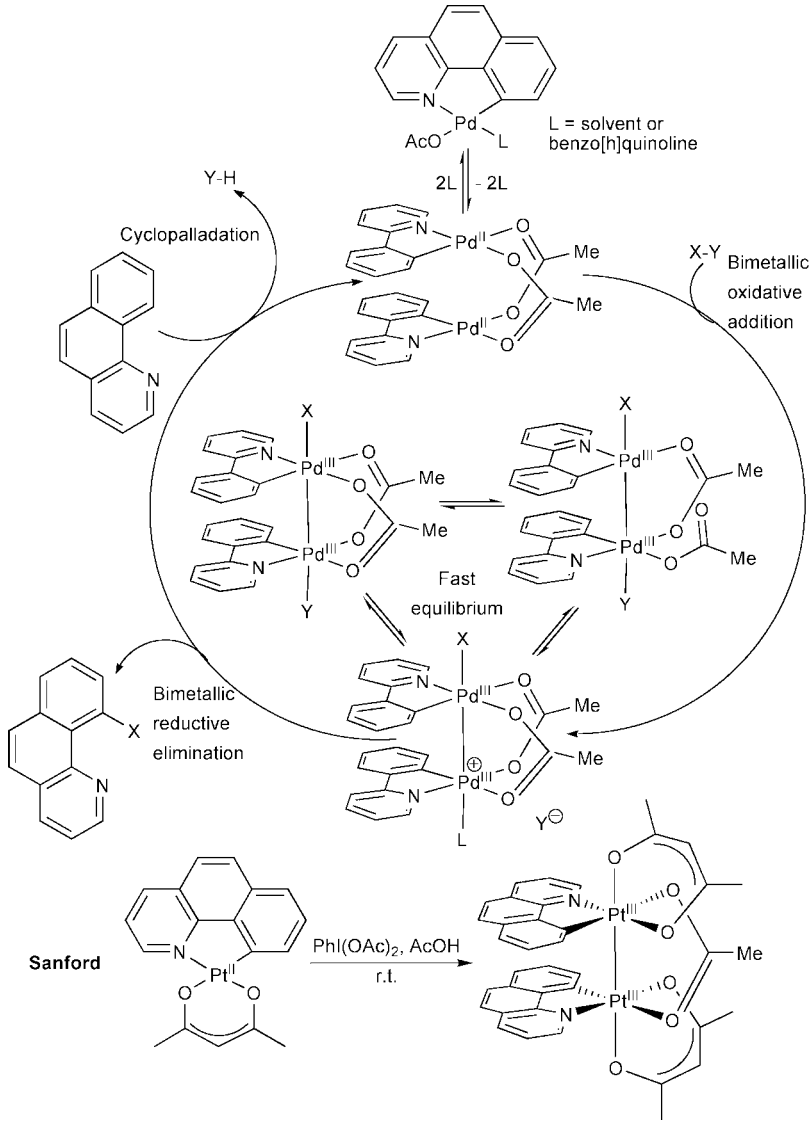
A related *ortho*-fluorination/difluorination of triflamide-protected benzylamines has been reported by Yu and co-workers.[196] The method uses *N*-fluoro-2,4,6-trimethylpyridinium triflate, palladium(II) triflate dihydrate, and, crucially, 0.5 equiv of NMP as promoter (Scheme 132).

The possible $Pd^{IV}-F$ intermediates and their properties were investigated by Vigalok et al.[197] They reported a

Scheme 129. Stoichiometric Reactions Demonstrating a Possible Bimetallic $Pd^{II}-Pd^{III}$ Mechanism of Directed Halogenation and Acetoxylation

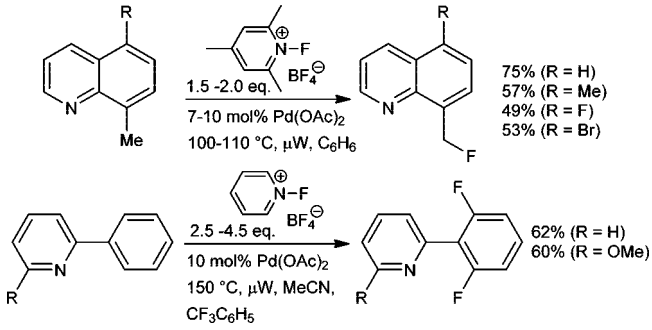


Scheme 130. Bimetallic $Pd^{II}-Pd^{III}$ Mechanism for Directed Functionalization of Benzo[*h*]quinoline and a Previously Reported Dimeric $Pt^{III}-Pt^{III}$ Complex

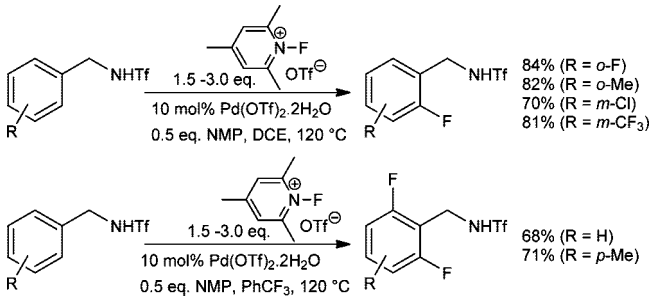


highly efficient and selective Ar−I reductive elimination reaction from a $Pd^{II}-Ar$ center triggered by reaction with xenon difluoride. The formation of a cationic $Pd^{IV}-F$ intermediate is responsible, probably proceeding by a S_N2-type mechanism (Scheme 133). Importantly, even the strong $C_6F_5-Pd^{IV}$ bond was readily cleaved under these conditions,

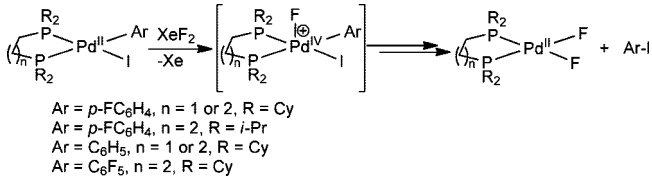
Scheme 131. Conditions for Chelation-Directed *ortho*-Fluorination/Difluorination



Scheme 132. Conditions for *ortho*-Fluorination/Difluorination of Triflamide-Protected Benzylamines



Scheme 133. Selective Ar−I Reductive Elimination from a Pd Center Triggered by Oxidation with Xenon Difluoride



which represents an unprecedented C_6F_5-X reductive elimination.

Later, a similar study was undertaken.[198] As opposed to the above-mentioned studies, use of a more stabilizing bipyridine-type ligand led to isolation of a stable $Pd^{IV}(Ar)F_2(FHF)$ complex that undergoes Ar−F bond formation in the presence of "F^+" sources. On the other hand, the respective biaryl coupling product was also generated as a side product in each case (Scheme 134).

The first conclusive evidence for C−F reductive elimination from Pd^{IV} and characterization of $Pd^{IV}-F$ complexes was provided by Ritter et al.[199] Fluorination of a benzo[*h*]quinoline cyclopalladated complex with Selectfluor in MeCN at 50 °C afforded 10-fluorobenzo[*h*]quinoline in 94% yield. A well-defined intermediate could be characterized by ^1H and ^{13}C NMR spectroscopy, with a half-life of ca. 70 min in MeCN at 23 °C. Its ^{19}F NMR spectrum ($\delta = -278$ ppm) is consistent with a cationic terminal Pd^{IV} fluoride structure shown in Scheme 135. Its treatment with XeF_2 provided an extremely air- and moisture-stable neutral Pd^{IV} difluoride. Its thermolysis at 150 °C gave cleanly the C−F reductive elimination product.

The very recent exploitation of Pd^{IV} fluoride intermediates for novel C−N bond formation by Yu and co-workers[200] will be discussed in section 3.6.6.

3.6.5. Oxidative Cleavage of Pallada(II)cyclic Leading to Directed Oxygenation

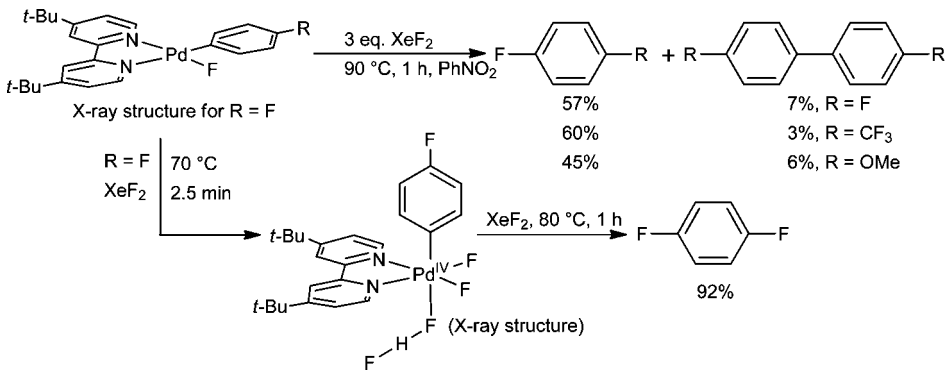
Stoichiometric oxygenation of cyclometalated as well as noncyclometalated Pd−C bonds with molybdenum peroxide [$MoO(O_2)_2 \cdot HMPT \cdot H_2O$] was reported by van Koten and co-workers (Scheme 136).[201]

Mechanistic studies indicate that the molybdenum peroxide oxidatively adds to the organopalladium substrate to afford a Pd^{IV} molybdate. Oxygen insertion into the Pd−C bond is only of minor importance for this peroxide. In the absence of steric hindrance, the Pd^{IV} molybdate reacts further via an oxidatively induced nucleophilic substitution of alkoxide on the palladated carbon atom to give products derived from oxygenation (Scheme 137).

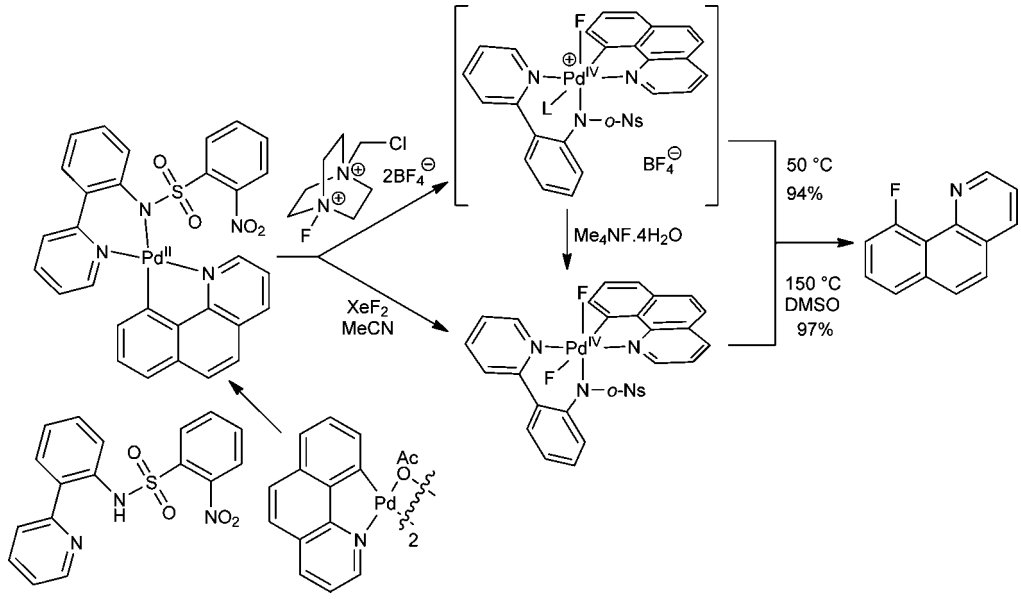
van Koten and co-workers also studied oxygenation of cyclopalladated *N,N*-dimethylbenzylamine complexes by *t*-BuOOH/$VO(acac)_2$ catalyst system.[202] The reactivity increases strongly with the nucleophilicity of the metal center, and for electron-rich diaryl Pd^{II} complexes, both vanadium-catalyzed and uncatalyzed oxygenation was possible. In the former case, vanadium alkylperoxide $VO(OOtBu)(OtBu)_2$ is likely the active catalyst, while for the latter, alcohol oxide species is involved. Both routes lead to a common Pd^{IV} oxo species that finally undergoes *O*-insertion (Scheme 138).

An early example of oxygen insertion into a Pd^{II}−naphthyl bond using iodosylbenzene as the oxidant was reported by Bandyopadhyay et al.[203] However, no mechanistic explanation was provided. Reactions of cyclometalated Pd^{II} complexes with $(ArI{=}O)_n$ (Ar = Ph, C_6F_5) were later extensively studied by the same group. Although no discrete aryl Pd^{IV} intermediates have been reported in these reactions, coordination of ArI(OR)(OH) to the palladacycle, oxidation to the Pd^{IV}−oxo species, and subsequent intramolecular insertion of the oxo group into the Pd^{IV}−C bond to afford a

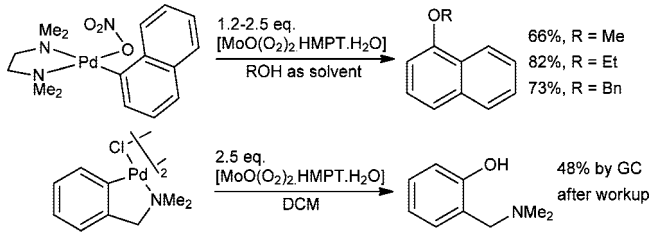
Scheme 134. Reactions of Pd^{II} Aryl Complexes with XeF_2, Isolation of a $Pd^{IV}(Ar)F_2(FHF)$ Complex, and Ar−F Bond Formation



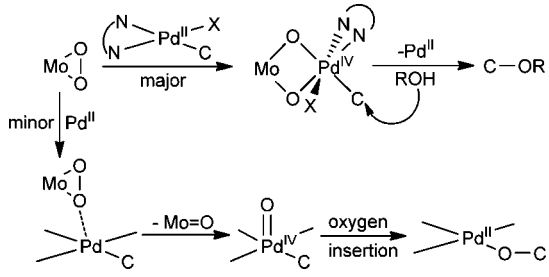
Scheme 135. Selectfluor and XeF_2 Oxidation of a Pd^{II} Complex to a Pd^{IV} Fluoride and Difluoride and Their Reductive Elimination



Scheme 136. Stoichiometric Oxygenation of Pd−C Bonds with Molybdenum Peroxide

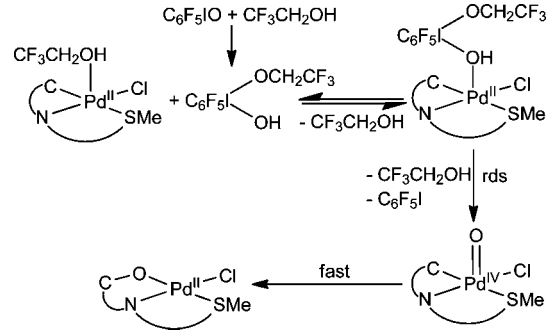


Scheme 137. Mechanism of Pd−C Bond Oxygenation with Molybdenum Peroxide (Bonds to Pd Without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



Pd^{II}−OAr complex has been proposed (Scheme 139).[204] A large negative value of $\Delta S^{\ddagger}$ supports an associative mechanism, and a smooth reaction in polar solvent supports a polar intermediate structure.

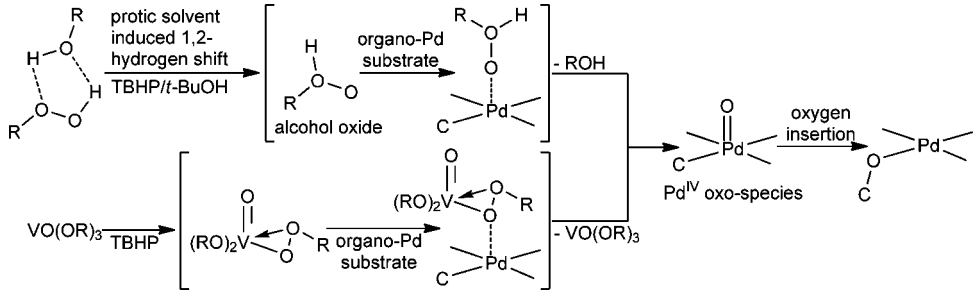
Scheme 139. Study of Oxygen Insertion into a Pd^{II}−Naphthyl Bond Using Pentafluoroiodosylbenzene



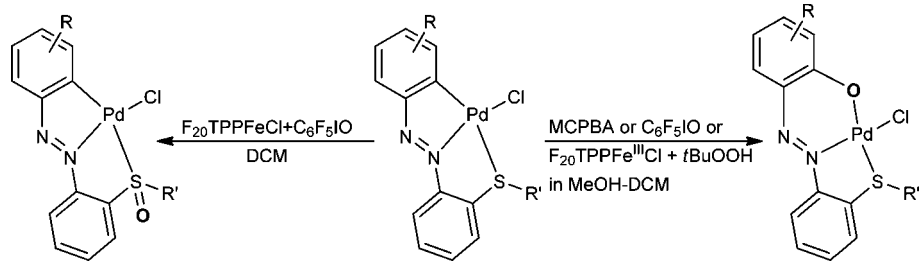
Among other oxidants, hydroperoxy radical (for example, *t*-BuOO•) is found to be extremely efficient, whereas the highly electrophilic oxoiron^{IV} porphyrin cation radical (oxene) is incapable of oxidizing the Pd−C bond. Oxene, however, selectively oxidizes the thioether functionality (Scheme 140). A modification using hydrogen peroxide with Fe^{III} porphyrin catalyst and some more mechanistic work have also been reported.[205,206]

The first practically applicable palladium-catalyzed directed oxygenation of sp^2 and sp^3 C−H bonds was reported by Sanford and co-workers.[207] Pyridine, azobenzene, pyrazole, and imine-type directing moieties can be utilized. Mono- vs dioxygenation selectivity can be governed by the amount of $PhI(OAc)_2$ oxidant used (1.1−1.6 equiv for mono-

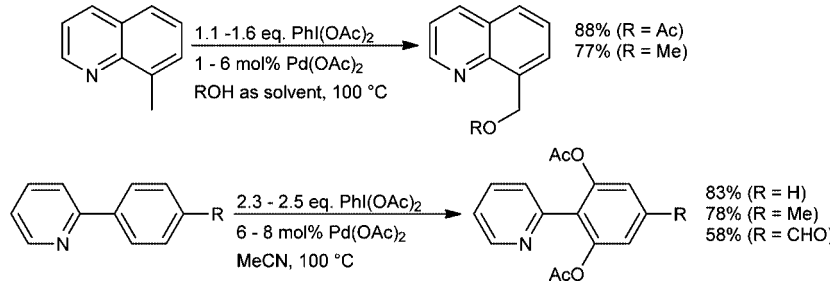
Scheme 138. Noncatalyzed and Vanadium Alkylperoxide-Catalyzed Oxygenation of the Pd−C Bond via a Common Pd^{IV} Oxo Species (The Structures of the Alcohol Oxide and Pd Intermediates Are Drawn As Specified in Ref 202.; Bonde to Pd without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



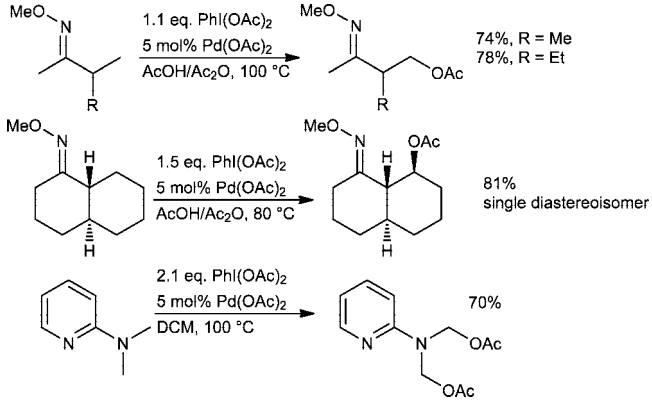
Scheme 140. Pd−C Versus Thioether Oxidation in an Cyclopalladated Complex



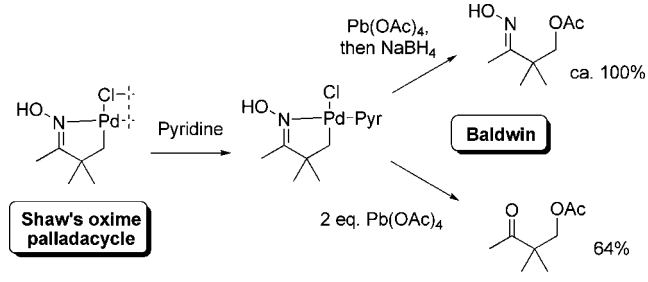
Scheme 141. Conditions for Effective Pd-Catalyzed Acetoxylation of sp² and sp³ C−H Bond



Scheme 142. Conditions for *O*-Methyl Oxime and Pyridine Directed Pd-Catalyzed Acetoxylation



Scheme 143. Stoichiometric Applications of Shaw's Original Pinacole Oxime Cyclopalladation Reaction

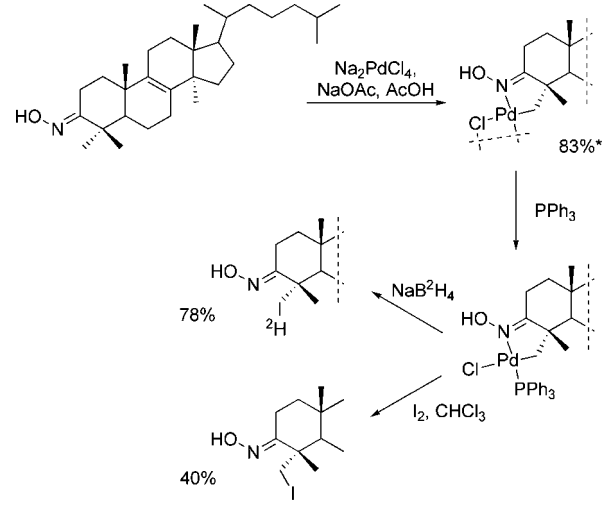


oxidation, 2.3−2.5 equiv results in clean formation of the dioxidized adducts) (Scheme 141).

The scope of this methodology was further expanded in the next report,[208] where *O*-methyl oxime and pyridine substrates with unactivated methyl groups and/or stereocenters were successfully acetoxylated (Scheme 142).

It is pertinent to point out early but related studies. Shaw's discovery of pinacole oxime cyclopalladation reported in 1978 arguably pioneered this class of reactions (Scheme 143).[209] Subsequent stoichiometric applications appeared in the literature several years later. The independent contributions of Baldwin[210] (Scheme 143) and Sutherland[211] (Scheme 144) showed that one can utilize these palladated

Scheme 144. Sutherland's Substitution of the 4-Methyl Group in Lanost-8-en-3-one

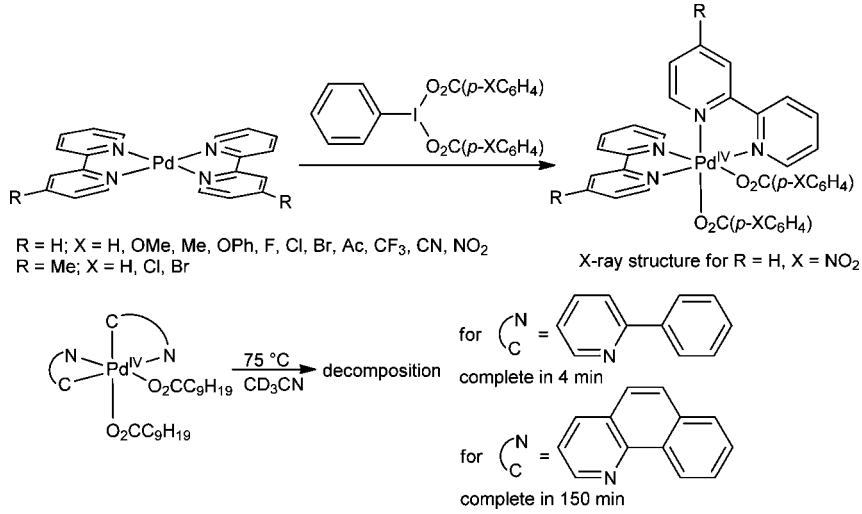


* not characterized (converted to PPh_3 adduct - no yield given).

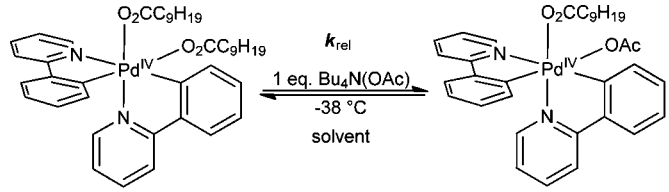
intermediates in real terms in organic synthesis. While mechanistic detail was lacking in these early studies, there is a possibility of Pd(IV) intermediacy. The influence of these pioneering studies on modern Pd chemistry, including catalytic processes, is clear. Recent applications have been reported by Sheppard and co-workers, which include an intriguing stereoselective cyclopropane-forming reaction.[212]

For detailed mechanistic investigation of the C−O bond-forming process, Sanford prepared a series of possible intermediate bis(benzoate) Pd^{IV} complexes $[Pd(phpy)_2\{O_2C(p\text{-}XC_6H_4)\}_2]$ (Scheme 145). Thermal decomposition of these unusually stable complexes was the subject of a kinetic investigation.[213] Surprisingly, the reactions proceeded at essentially identical rates in polar and nonpolar solvents (a bis(*n*-decanoate) complex was used for better solubility). Second, $\Delta S^{\ddagger}$ values close to zero were determined as well as a negative Hammett correlation ($\rho = -1.36 \pm 0.04$ with $R^2 = 0.98$) in the series of complexes containing *para*-substituted benzoate ligands. Furthermore, no crossover products were observed when a mixture of two differentially

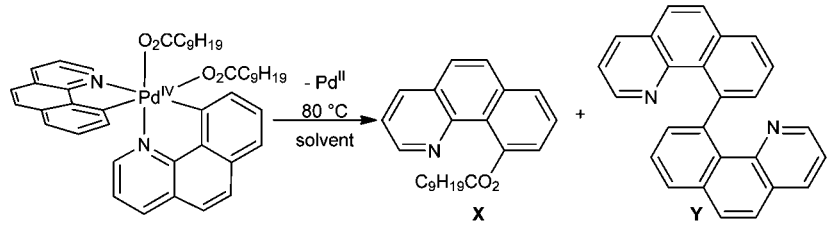
Scheme 145. Mechanistic Investigation of the C−O Bond-Forming Process on a Series of Bis(benzoate) Pd^{IV} Complexes



Scheme 146. Effects of Carboxylate Ligands, Solvents, and Additives on C−O Bond-Forming Process in Bis(benzoate) Pd^{IV} Complexes



solvent	toluene-d_8	acetone-d_6	CD_3CN	$CDCl_3$	acetone-d_6 2 eq. AcOH
k_{rel}	< 0.1	1.0 ± 0.1	2.0 ± 0.2	19 ± 1	4.5 ± 0.5

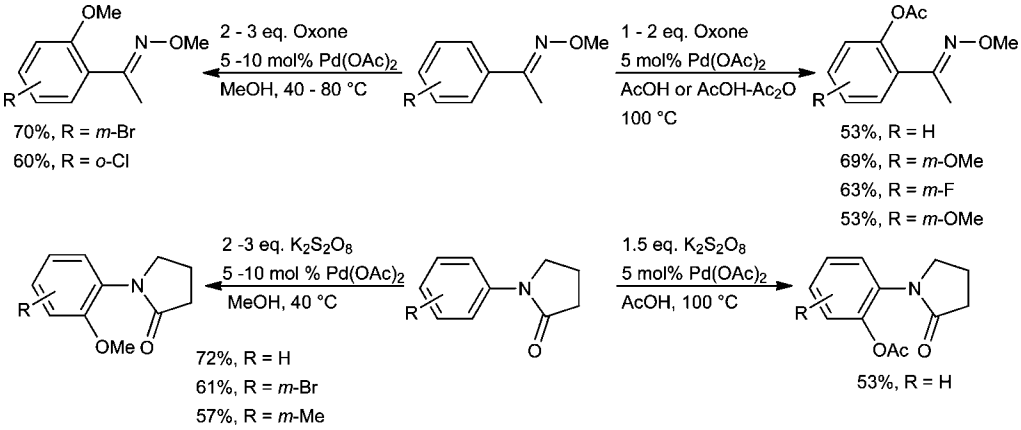


solvent	MeCN	$CHCl_3$	$PhNO_2$	DMSO	acetone	C_6H_6	acetone 5 eq. AcOH	acetone 0.1 eq. AgOTf	MeCN 1 eq. $Bu_4N(O_2CC_9H_{19})$
X : Y	0.2 : 1	0.77 : 1	2.2 : 1	3.3 : 1	13 : 1	>20 : 1	3.6 : 1	0.1 : 1	2 : 1

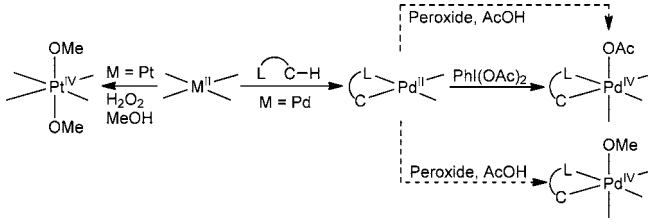
substituted Pd^{IV} complexes was allowed to decompose. This evidence strongly suggests that, unlike most other reductive eliminations from Pd^{IV} or Pt^{IV}, the above complexes predominantly decompose by either direct reductive elimination from the octahedral starting material or by dissociation of an arm of one of the chelating phenylpyridine ligands. The almost 40-fold difference in decomposition rate between cyclopalladated complexes with 2-phenylpyridine and the more rigid benzo[*h*]quinoline confirms that nitrogen dissociation in the chelate is crucial. Interestingly, a theoretical study of Liu et al.[126] supported direct reductive elimination without any ligand predissociation. In their theoretical model, the difference between the two complexes was explained on the basis of a different degree of ligand distortion in the transition state.

In another more comprehensive study of this reaction, Sanford investigated the effects of different carboxylate ligands, solvents, additives, and chelate rigidity in detailed Eyring analysis, Hammett plots, and crossover studies (Scheme 146).[214] Carboxylate exchange between $[Pd(phpy)_2(O_2CC_9H_{19})_2]$ and added acetate is possible even at low temperature, and its rate is solvent-dependent. Solvents also had a significant influence on the C−O vs C−C elimination product distribution. AcOH and AgOTf additives, which both accelerate carboxylate exchange, had a massive promoting effect on C−C versus C−O bond formation. On the other hand, addition of extra carboxylate anion biased the ratio in favor of C−O reductive elimination. Experiments with $[(Bzq)_2Pd^{IV}(OAc)]^+$ generated in situ from $[(Bzq)_2Pd^{IV}(Cl)(OAc)]$ and $AgBF_4$ further confirmed the trends. The authors concluded that C−O bond-forming reductive elimination proceeds via an ionic mechanism involving initial carboxylate dissociation, followed by C−O coupling from a 5-coordinate cationic intermediate. In contrast, the C−C bond-forming reaction involves direct reductive elimination from the

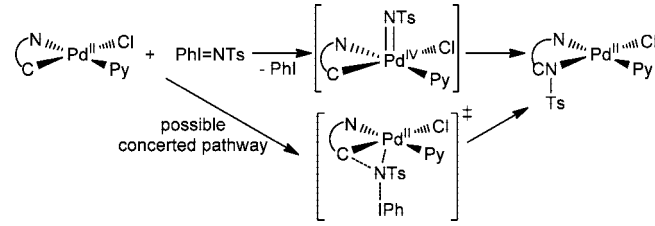
Scheme 147. $Pd(OAc)_2$/Oxone System for Efficient Methoxylation and Acetoxylation of Oxime Ethers and *N*-Aryl Pyrrolidones



Scheme 148. Proposed Pd^{IV} Methoxy and Acetoxy Intermediates and the Stable Pt^{IV} Dialkoxides



Scheme 150. Possible Concerted and $Pd^{II}-Pd^{IV}$ Pathways for Insertion of the "NTs" Fragment in the Pd−C Bond



octahedral Pd^{IV} starting material. Some crystallographic and mechanistic acetoxylation studies were also conducted with Pt^{IV}.[193]

By replacing the toxic $PhI(OAc)_2$ with inexpensive inorganic oxidant $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone), Sanford developed a robust protocol for methoxylation and acetoxylation of oxime ethers and *N*-aryl pyrrolidones (Scheme 147).[215] However, almost invariably, the yields are somewhat lower when compared with $PhI(OAc)_2$.

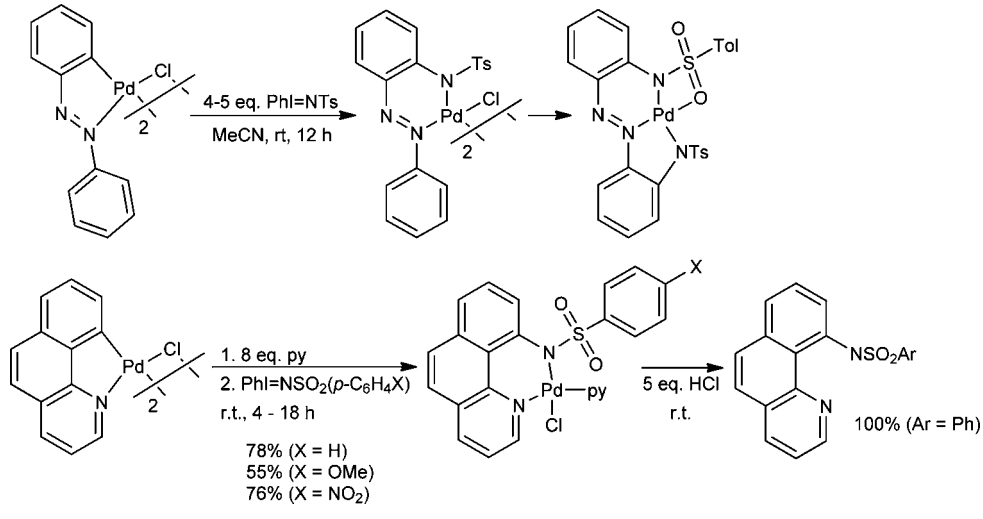
Mechanistically, the methoxylation is believed to proceed via a Pd^{IV} methoxide intermediate (Scheme 148). Stable Pt^{IV} dialkoxides are known to form in good yields from Pt^{II} starting materials and H_2O_2 in alcohols.[216]

3.6.6. Oxidative Cleavage of Pallada(II) Cyclic Compounds Leading to Directed Amination

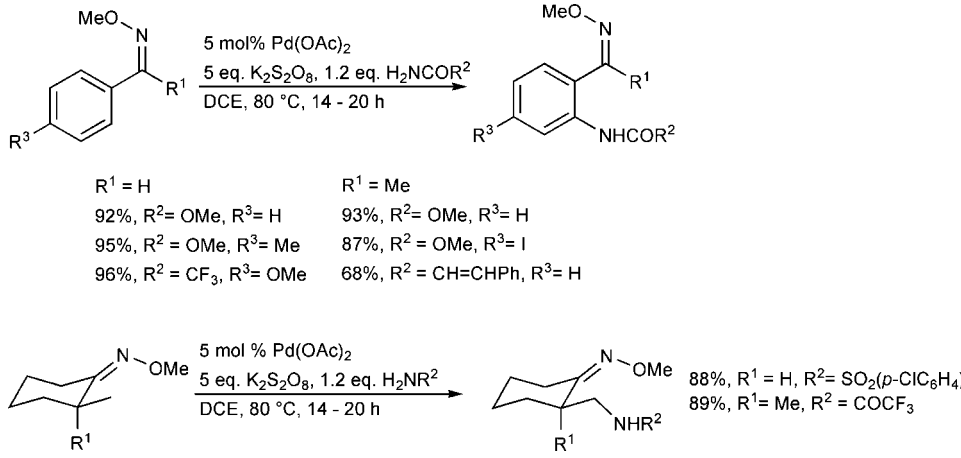
Analogously to the work of Bandyopadhyay on ArI=O, Sanford studied the reactions of Pd^{II} complexes containing bidentate cyclometalated CN chelating ligands and PhI=NTs, which lead to "NTs" insertion into the Pd−C bond.[217] Azobenzene, benzo[*h*]quinoline, and 8-ethylquinoline palladacycles are amenable, but excess of strong acid is required to liberate the aminated organic ligand from the metal center (Scheme 149).

This transformation is proposed to proceed via a stepwise mechanism involving a Pd^{IV}−imido intermediate, but an alternative concerted insertion of the NTs fragment into the Pd^{II}−C bond could not be ruled out (Scheme 150).

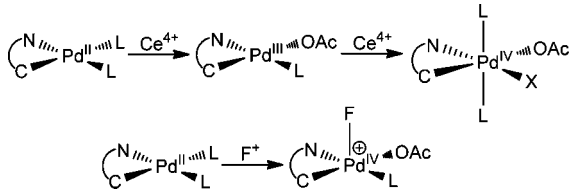
Scheme 149. Stoichiometric Insertion of the "NTs" Fragment into the Pd−C Bond Using PhI=NTs



Scheme 151. Pd-Catalyzed Amidation of *O*-Methyl Oximes Using the $Pd(OAc)_2-K_2S_2O_8$ System



Scheme 152. One- and Two-Electron Pathway for Oxidation of a Pd^{II} Cyclometalated Complex



Yu and co-workers[218] have succeeded in creating a high-yielding catalytic amidation protocol with $K_2S_2O_8$ as the stoichiometric oxidant. Primary aliphatic amides, sulfonamides, trifluoroacetamide, and cinnamide can be used. However, benzamide and secondary amides are unreactive (Scheme 151).

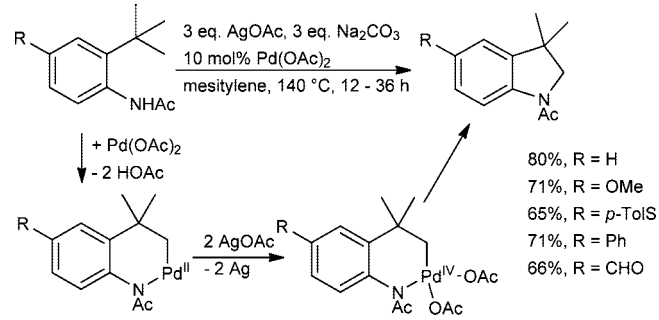
On the basis of electrospray ionization mass spectrometry (ESI-MS) analysis of a stoichiometric experiment, a reactive $Pd^{II}-$nitrene species or a $Pd^{IV}-$imido species was proposed as an intermediate.

A useful intramolecular amidation leading to substituted indolines has been reported by Yu and co-workers.[200] Very interestingly, the only efficient oxidants in this amidation variant were anhydrous $Ce(SO_4)_2$ (via one-electron oxidation pathway) and *N*-fluoro-2,4,6-trimethylpyridinium triflate (via F^+ two-electron oxidation pathway) (Scheme 152).

The reaction shows good selectivity for C−N bond formation (Scheme 153) and, similar to a related iodination protocol,[186] requires 1−6 equiv of DMF, possibly as a labile ligand. $K_2S_2O_8$ gave no conversion; other oxidants led to nonselective reductive elimination.

An intramolecular amination of involving C−H activation of a *tert*-butyl group has been reported by Glorius et al.[219] However, one of the proposed mechanisms involving Pd^{IV} seems unlikely in this case. First, the silver acetate oxidant is not strong enough to produce Pd^{IV} intermediates, as was shown in other related systems. Also, in polar solvents like DMSO, DMF, or MeCN, no product was obtained (Scheme 154).

Scheme 154. Intramolecular C−H Amination in 2-*tert*-Butylacetanilides Leading to Indolines

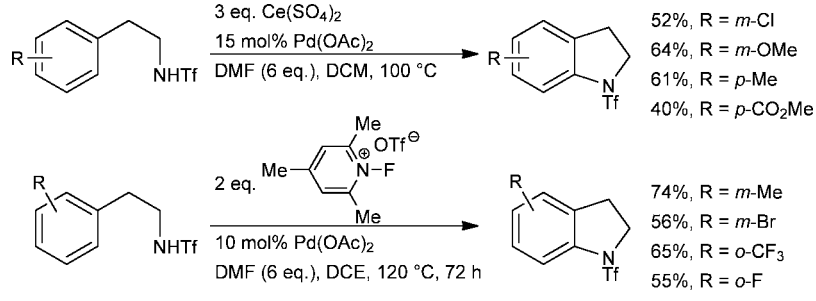


3.6.7. Oxidative Cleavage of Pallada(II) Cyclic Compounds Leading to C−C Coupling

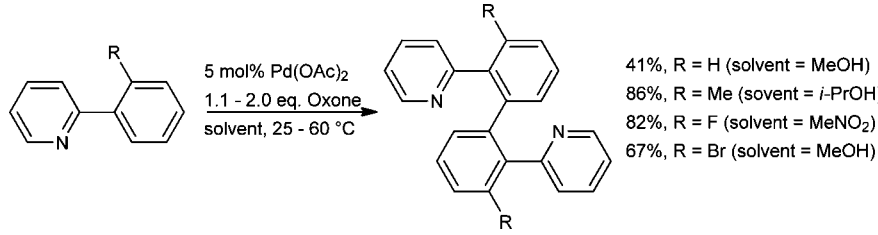
Highly regioselective catalytic oxidative C−C coupling of phenylpyridines was reported by Sanford (Scheme 155).[220] It was found that 5 mol % of $Pd(OAc)_2$ and 2 equiv of Oxone in *i*-PrOH at 25 °C served as optimal conditions for this transformation (using MeOH and/or increasing reaction temperature leads to significant amounts of *ortho*-ether products as reported previously[207,215]).

Sophisticated crossover, selectivity, and equilibration experiments led to the conclusion that two different C−H activation events, one at Pd^{II} and one at Pd^{IV}, must operate in the overall mechanism (Scheme 156). Therefore, this report represents the first example of C−H activation at a Pd^{IV} center. Arene C−H activation at Pt^{IV} centers[221] and other metals[44] have been reported previously.

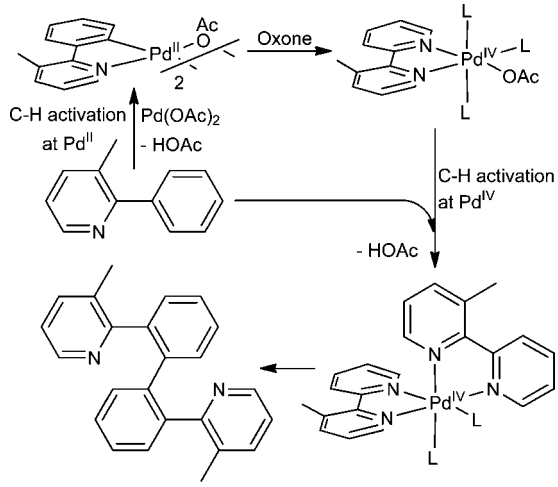
Scheme 153. Scope of the Intramolecular Amidation Leading to Substituted Indolines



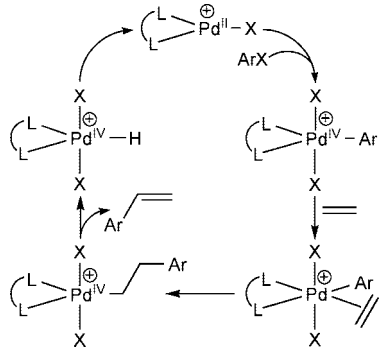
Scheme 155. Oxidative C−C Coupling of Phenylpyridines with the $Pd(OAc)_2$−Oxone Catalytic System



Scheme 156. Oxidative C−C Coupling of 2-Phenylpyridines Involving C−H Activation at Pd^{II} and Pd^{IV} Centers



Scheme 157. Proposed Pd^{II}−Pd^{IV} Catalytic Cycle for Heck Arylation of Alkenes



Because this reaction does not proceed at all with milder oxidants (air, Ag^{I}, Cu^{II}, benzoquinone), it is fundamentally different from the cross-coupling of benzo[*h*]quinolines with aromatic C−H substrates published by the same group, where the Pd^{0}−Pd^{II} cycle is operative.[222]

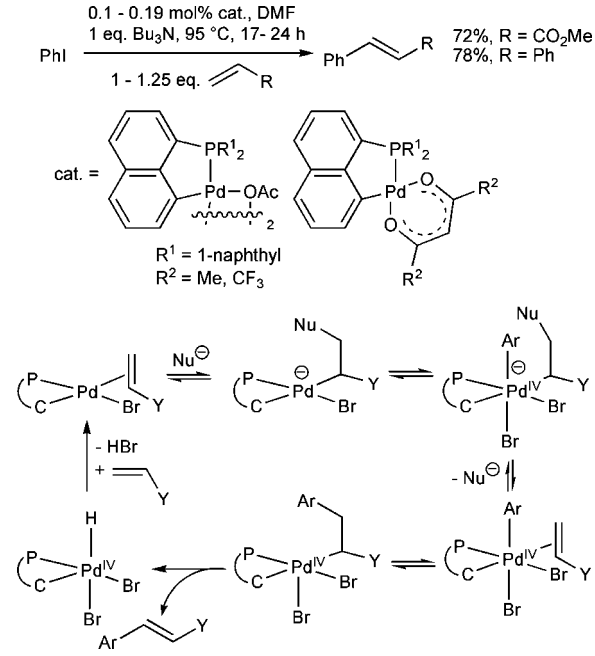
3.7. Pd^{IV} Intermediates in Heck Reactions?

Pd^{IV} intermediates in Heck-type reactions[223–225] have been invoked in connection with the highly active bischelated pincer palladacycles[226] of the type XCX (X = P, N, S). Their role in various other C−C bond-forming processes has been extensively reviewed.[227,228]

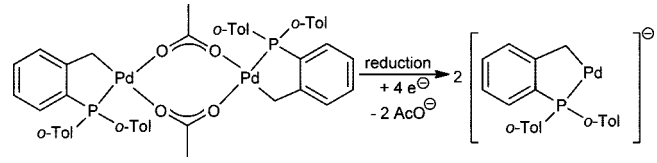
The involvement of Pd^{IV} intermediates in Heck arylation reactions, particularly when catalyzed by palladacycles, has been the subject of much controversy. In one case, this even led to the retraction of a report claiming that a Pd^{IV} intermediate was isolated from a phosphapalladacycle-catalyzed reaction.[229]

The group of Martin performed a DFT level calculation and found that the hypothetical Pd^{II}/Pd^{IV} mechanism (Scheme 157) and the usual Pd^{0}/Pd^{II} mechanism for the Heck reaction involve qualitatively similar stationary points.[230] The dissociation steps necessary to provide vacant coordination sites (i.e., dissociation of alkene products and iodide dissociation prior to starting alkene coordination) are likely to be rate-determining for the Pd^{0}/Pd^{II} mechanism. For the Pd^{II}/Pd^{IV} mechanism, the oxidative addition of Ph−I is the step with the highest activation barrier. The calculations show that intermediate ligand detachment and reattachment is necessary in the course of the oxidative addition to Pd^{II}. Therefore, the Pd^{II}/Pd^{IV} cycle is only feasible if a weakly coordinating ligand is present. Moreover, the β-elimination at Pd^{IV} to a Pd^{IV} hydride is completely without experimental precedent.

Scheme 158. Reaction Conditions and the Proposed Anionic Catalytic Cycle for Heck Arylation Catalyzed by PC-type Palladacycles

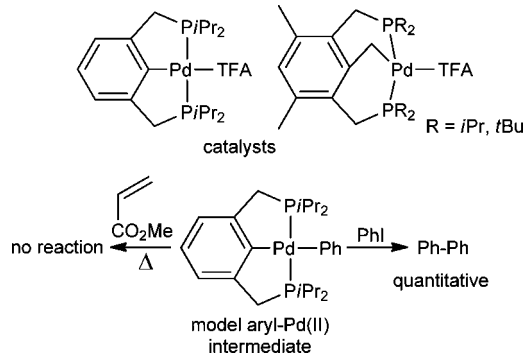


Scheme 159. Proposed In Situ Reduction of Dimeric Pallada(II)cycle Precatalysts to an Anionic Pd^{0} Complex

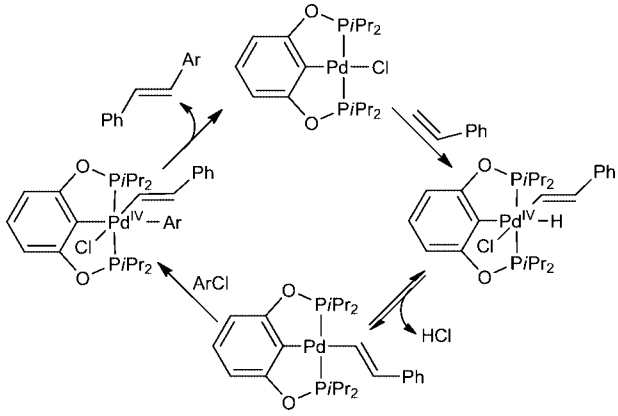


Arguably, a Pd^{II} species has to be relatively electron-rich to undergo second oxidative addition to Pd^{IV}. Shaw et al. proposed that a reversible attack by a nucleophile, such as AcO^{-}, $acac^{-}$, HO^{-}, Br^{-}, or I^{-}, to give a negatively charged alkyl Pd^{II} species, can increase nucleophilicity and lead to another ArX oxidative addition (Scheme 158).[231,232] No palladium metal formation was observed, and the final reaction solution was extremely pale yellow. A Pd^{II}−Pd^{IV}

Scheme 160. Stable PCP Catalysts and Mechanistic Investigations on a Model Aryl−Pd^{II} Intermediate



Scheme 161. Unusual Mechanistic Proposal for Heck Arylation Involving a Vinylic C−H Activation



mechanism was also favored by Shaw in Heck reactions using chelating diphosphine−Pd^{II} dihalides.[233]

Generation of Pd^{IV} species was suspected by Herrmann et al. in palladacycle-catalyzed Heck olefination of haloarenes[234] and alkynylation of aryl bromides.[235] Comparing the selectivity of [Pd^0{(*o*-Tol)$_3$P}$_2$] versus pallada(II)cycles as catalysts in vinylation of aryl bromides, they later concluded that the relatively small differences observed are inconsistent with a change from Pd^0−Pd^{II} to the Pd^{II}−Pd^{IV} mechanism.[236] Instead, reduction to a common highly active, cyclometalated anionic Pd^0 species was proposed (Scheme 159).

In situ formation of Pd^0 from a P,C-palladacycle was also reported by Jutand and co-workers.[237] The intermediacy of an anionic Pd^0 species was deemed unlikely in the study of Milstein et al.[238] The use of extremely stable PCP-type catalysts shown in Scheme 160 meant that reactions could be carried out in undried solvents in air. Interestingly, the expected intermediate in the Pd^0−Pd^{II} cycle was independently prepared but did not give any coupling products upon heating with methyl acrylate. Moreover, treating the model phenyl Pd^{II} complex with iodobenzene resulted in the quantitative formation of biphenyl, which was never detected in catalytic runs (Scheme 160). Therefore, direct reaction of the starting pallada(II)cycles with PhI to form Pd^{IV} might be involved.

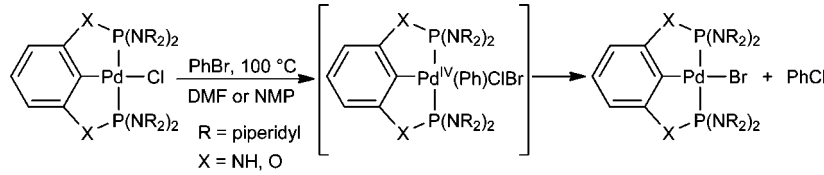
An unusual mechanism of the Heck arylation with aryl chloride via vinyl C−H activation was proposed by Jensen (Scheme 161).[239] However, experimental evidence for the Pd^{IV} intermediates was not gained.

Frech et al. has reported that aminophosphine-based pincer complexes shown in Scheme 162 are superior Heck catalysts even for electronically deactivated and sterically hindered aryl bromides and chlorides.[226] Interestingly, the pincer complexes react with bromobenzene, giving halide exchange in DMF (or NMP) at 100 °C, leading to bromide pincer complexes and chlorobenzene (Scheme 162). However, no halide exchange was observed for [C$_6$H$_3$-2,6-(OP*i*Pr$_2$)$_2$Pd(Cl)] or [C$_6$H$_3$-2,6-(CH$_2$P*i*Pr$_2$)$_2$Pd(Cl)]. These results and DFT calculations indicated that, at least for the extremely active aminophosphine pincer complexes, Pd^{IV} is principally accessible at elevated reaction temperatures. However, kinetic evidence (sigmoidal-shaped kinetics, induction periods highly sensitive to H$_2$O) overwhelmingly points to Pd nanoparticles.

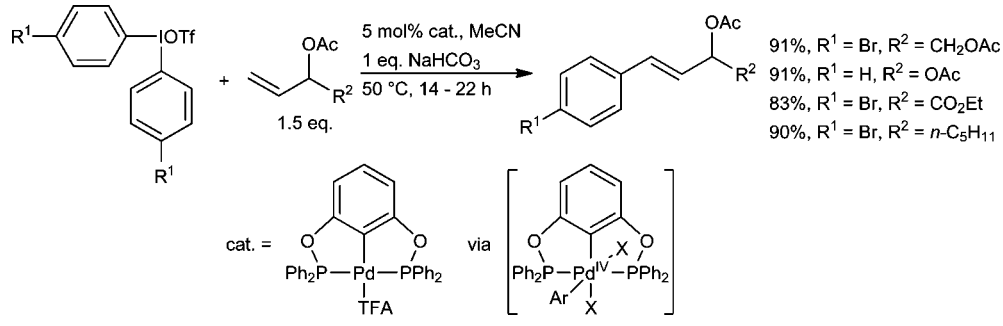
Similarly, a comprehensive study of a series of SCS pincer complexes by Bergbreiter indicated that, also in this case, Pd^0 colloids or highly active forms of low ligated Pd^0 species, rather than the intact palladacycles, are the actual catalytic species.[240] The involvement of palladium colloids and anionic species as a unifying feature in all high-temperature Heck reactions has been advocated by de Vries.[241] Hammett correlation studies of Dupont[242] and ESI-MS investigations of Nilsson[243] reached very similar conclusions.

Palladium PCP pincer complexes shown in Scheme 163 catalyze arylation of allylic acetates by diaryliodonium

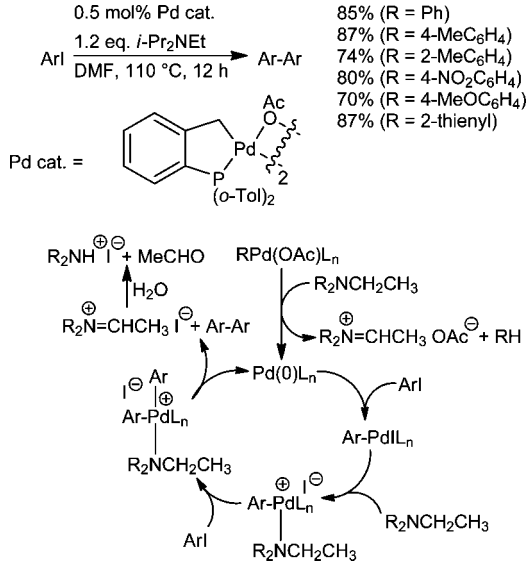
Scheme 162. Halogen Exchange Reaction between Aminophosphine Palladacycles and Bromobenzene



Scheme 163. Arylation of Allylic Acetates with Diaryliodonium Salts Catalyzed by Palladium PCP Pincer Complexes



Scheme 164. Scope a Mechanism of Pd-Catalyzed Homocoupling of Aryl Iodides with *N,N*-Diisopropylethylamine Oxidant



salts.[244] The mild conditions (50 °C, 14−22 h), resistance to Hg poisoning, and some DFT modeling suggest Pd^{IV} intermediates. In fact, stoichiometric oxidation of NCN pincer complexes with alkynyliodonium reagents has been reported by Canty and co-workers.[245]

A CP palladacycle has also been used for homocoupling of aryl iodides to biaryls with *N,N*-diisopropylethylamine as the oxidant (Scheme 164).[246] Two sequential oxidative additions lead to a key diaryl Pd^{IV} intermediate. The coordinated trialkylamine undergoes β-hydride elimination and is eventually converted into acetaldehyde and trialkylammonium iodide.

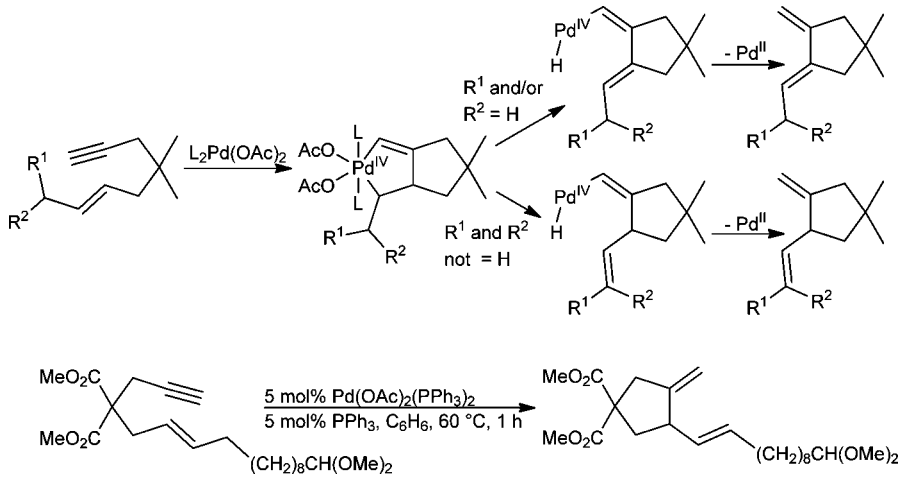
3.8. Pd^{IV} Intermediates in Various Isomerization Processes

The earliest example of cycloisomerization of 1,6-enynes to 1,3- and 1,4-dienes catalyzed by Pd^{II} salts was reported by Trost and Lautens.[247] The reactions proceeded in good to high yields under mild conditions (25−60 °C). A key mechanistic observation was made that a Pd^0 species such as $Pd(PPh_3)_4$ does not catalyze the reaction, but Lewis acidic Pd^{II} complexes (e.g., $(Ph_3P)_2Pd(OAc)_2$ and $\{(o\text{-Tol})_3P\}_2Pd(OAc)_2$) work cleanly and tolerate up to 6 equiv of excess phosphine without loss of activity. It was therefore argued that the isomerizations involve Pd^{IV} palladacycles (Scheme 165).

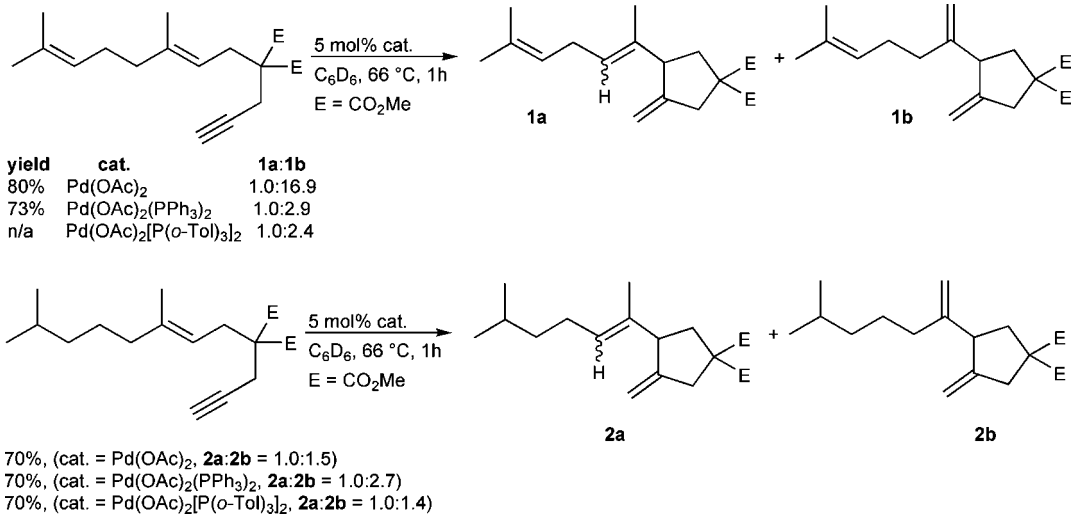
Other interesting features of this reaction were revealed in a detailed study (Scheme 166).[248]

In the absence of phosphines, the coordinatively unsaturated metal may complex with the remote double bond, which both stabilizes the metal and decreases the flexibility of the

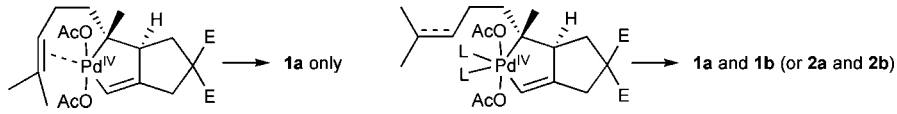
Scheme 165. Pd^{II} Catalyzed Cycloisomerization of 1,6-Enynes to 1,3- and 1,4-Dienes



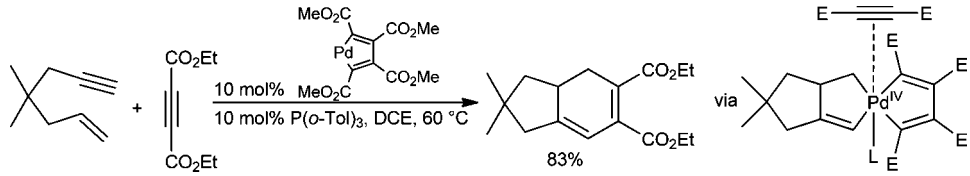
Scheme 166. Effect of a Distal Double Bond in Pd^{II} Catalyzed Cycloisomerization of 1,6-Enynes



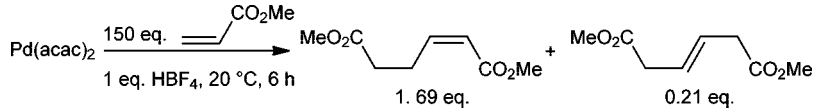
Scheme 167. Effect of a Distal Double Bond Coordination on Selectivity in Pd^{II} Catalyzed Cycloisomerization



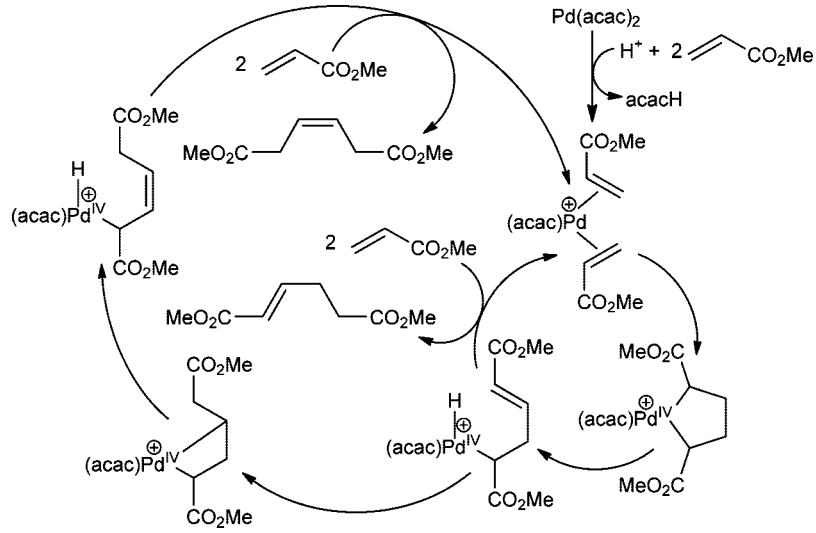
Scheme 168. Tandem 1,6-Enyne Cycloisomerization−Alkyne Insertion Sequence Leading to Bicyclic Cyclohexadienes



Scheme 169. $Pd(acac)_2 \cdot HBF_4$ Mediated Dimerization of Methyl Acrylate



Scheme 170. Proposed Catalytic Pathways in the $Pd(acac)_2 \cdot HBF_4$ Mediated Dimerization of Methyl Acrylate



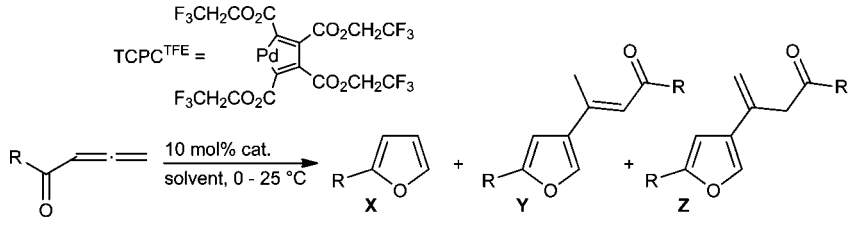
methylene side chain. The β-hydride elimination that follows is known to be a *cis*-process. Therefore, in the complexed form shown in Scheme 167, the methylene hydrogens cannot properly align themselves and thus elimination occurs toward the methyl group. However, upon addition of more strongly coordinating external ligands, such as phosphines, or when the double bond is absent, the additional rotational freedom created allows for correct alignment of the methylene as well as the methyl hydrogens (Scheme 167).

Trost et al. later applied the methodology successfully in the synthesis of the picrotoxane skeleton.[249]

The cycloisomerization can be extended by adding an electron-poor acetylene, which leads to bicyclic products (Scheme 168). A tetracarbomethoxypalladacyclopentadiene with added phosphite ligand is the catalyst of choice.

Interesting pallada(IV)cyclic intermediates were also proposed by Tkatchenko et al. in dimerization of methyl

Scheme 171. Scope of the Pd-Catalyzed Cyclization/Dimerization of Terminal Allenyl Ketones to 2,4-Disubstituted Furans



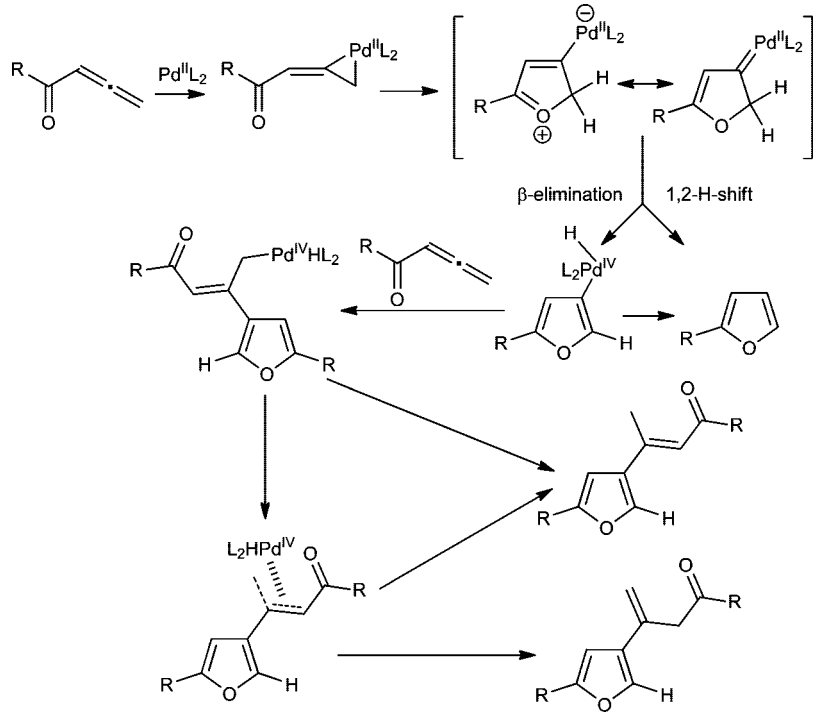
CONDITIONS: 10 mol% $TCPC^{TFE}$/acetone

R	X : Y : Z	yield of Y (%)
Me	1.0 : 8.8 : 0	86
CH_2Cl	1.0 : 2.2 : 0	60
2-IC_6H_4	1.0 : 11 : 0	91
2-furyl	1.0 : 4.1 : 0	72
$C(CH_3)_3$	1.0 : 1.0 : 0.2	33

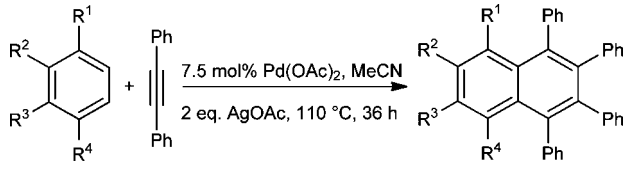
CONDITIONS: 10 mol% $PdCl_2(MeCN)_2$/MeCN

R	X : Y : Z	yield of Y (%)
Me	1.0 : 30 : 0	89
$CH(CH_2)_4$	1.0 : 3.8 : 0	82
$(CH_2)_3OH$	1.0 : 4.0 : 0	79
$C(CH_3)_3$	1.0 : 2.9 : 0	54
$CH(OMOM)CH_3$	1.0 : 17 : 0	83

Scheme 172. Proposed Catalytic Pathways for the Pd-Catalyzed Cyclization/Dimerization of Terminal Allenyl Ketones

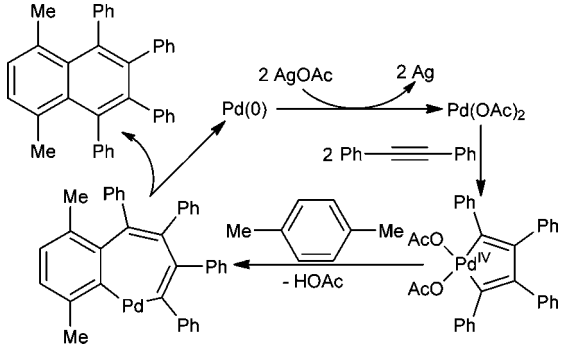


Scheme 173. Scope of the $Pd(OAc)_2$/AgOAc Catalyzed Synthesis of Highly Substituted Naphthalenes



R^1	R^2	R^3	R^4	yield (%)
Me	H	H	Me	60
Me	Me	H	Me	50
Me	Me	Me	H	52
OMe	Me	H	Me	47
OMe	H	Me	Me	48

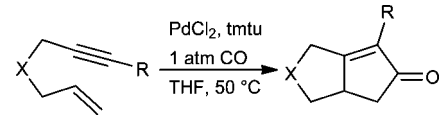
Scheme 174. Proposed TetraphenylcyclopentadienePd^{IV} intermediate in the $Pd(OAc)_2$/AgOAc Catalyzed Synthesis of Highly Substituted Naphthalenes



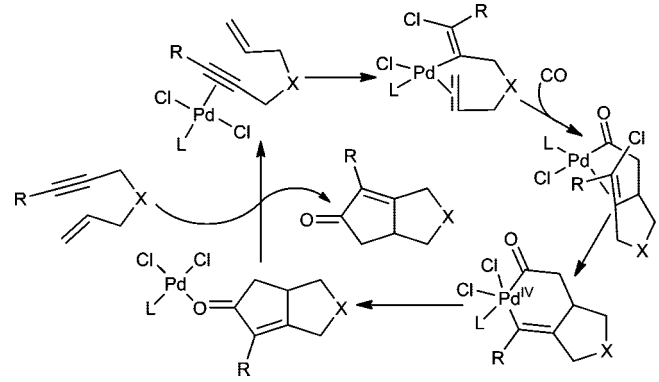
acrylate mediated by $Pd(acac)_2 \cdot HBF_4$ (Scheme 169).[250] However, very low TONs have been reported (1.3−1.9 with respect to Pd). Also, the transformation is very specific, failing completely for methyl methacrylate.

An elaborate mechanistic scheme was proposed (Scheme 170). The key dimerization event in the Pd^{II} coordination sphere leads to a cationic pallada(IV)cyclic intermediate. However, the subsequent endocyclic β-hydride elimination to a Pd^{IV} hydride and a four-membered pallada(IV)cycle would appear unlikely.

Scheme 175. $PdCl_2$−Thiourea Mediated Intramolecular Pauson-Khand-type Reaction



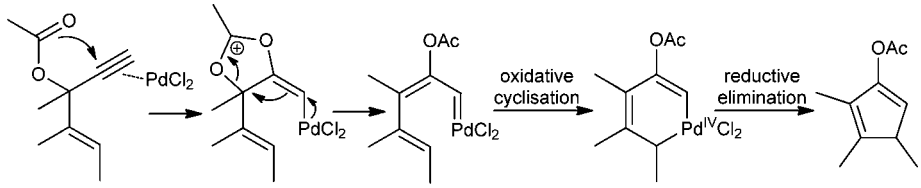
Scheme 176. Proposed Pd^{II}−Pd^{IV} Mechanism for the Intramolecular Pauson-Khand-type Reaction



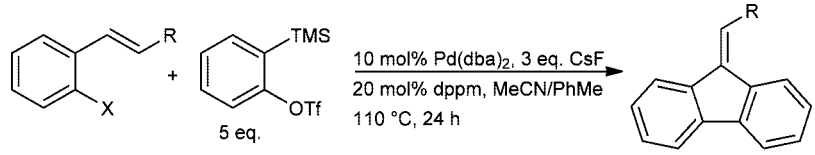
The scope of the palladium-catalyzed cyclization/dimerization of terminal allenyl ketones to 2,4-disubstituted furans was investigated by Hashmi (Scheme 171).[251]

The most probable pathway out of several mechanistic proposals is shown in Scheme 172. It involves a furyl Pd^{IV} intermediate, which leads to monosubstituted furans, and an allyl Pd^{IV} hydride species, leading to two isomeric dimers. Interestingly, the authors were able to conduct the dimerization of methyl allenyl ketone under 1 atm of pure dioxygen. Also, aryl iodide functionality was unaffected. While this is convincing evidence against Pd^0 catalytic intermediates, the ability of the starting materials and enone products to stabilize Pd^0 should be considered. Through

Scheme 177. Proposed $Pd^{II}-Pd^{IV}$ Mechanism for a Pd^{II}-Catalyzed Rearrangement of Propargyl Acetates

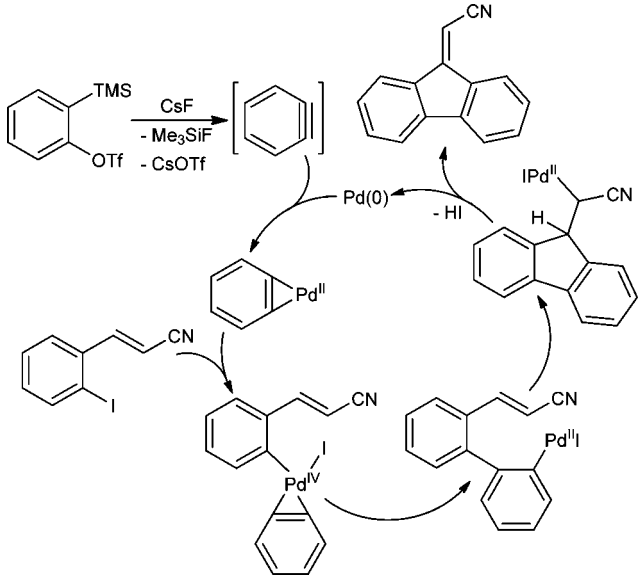


Scheme 178. Scope of Pd-Catalyzed Synthesis of 9-Fluorenylidenes through Aryne Annulation



91% (R = CN, X = I)
79% (R = CN, X = Br)
75% (R = CO_2Et, X = Br)
76% (R = CHO, X = I)

Scheme 179. Proposed Mechanism of Pd-Catalyzed Synthesis of 9-Fluorenylidenes



ingenious crossover and deuterium labeling experiments, the authors proved that the hydrogen-migration steps occur intramolecularly.

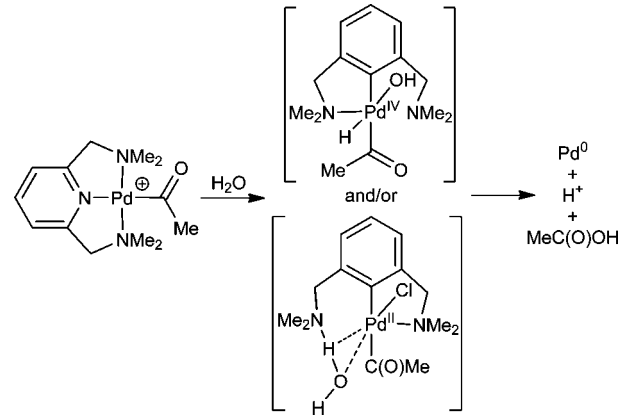
Several highly substituted naphthalenes have been synthesized in moderate yields by Wu and co-workers by treatment of electron-rich arenes with alkynes using $Pd(OAc)_2$ catalyst and AgOAc oxidant (Scheme 173).[252]

Although a tetraphenylcyclopentadienePd^{IV} complex has been invoked, direct electrophilic palladation of the arene followed by two alkyne insertions, cyclization, and Pd^0 recycling remains the most likely mechanistic path (Scheme 174).

Intramolecular Pauson-Khand-type reaction mediated by a $PdCl_2$−tetramethyl thiourea (tmtu) catalyst under mild conditions has been reported to involve Pd^{IV} intermediates (Scheme 175).[253,254]

More detailed DFT and experimental studies were carried out later in order to elucidate the mechanism of this tranformation.[255] The key step of the novel proposed mechanism is the oxidative addition of Pd^{II} into the vinylic C−Cl bond. In fact, $\Delta G^{\ddagger}$ values calculated for this pathway were

Scheme 180. Possible Routes of Hydrolysis of a Cationic Pd^{II} Acyl Complex



approximately 4 kcal mol^{-1} lower than the ones for the classical Magnus mechanism[256,257] initiated by oxidative coupling of the olefin (Scheme 176).

One of the routes for Pd^{II}-catalyzed rearrangement of propargyl acetates proposed by Frontier and co-workers involves a palladium carbene as reactive intermediate.[258] Its oxidative cyclization to a Pd^{IV} intermediate followed by reductive elimination leads to the observed product (Scheme 177).

3.9. Pd^{IV} Intermediates from Oxidative Addition of Pd^{II} into C−C Bonds

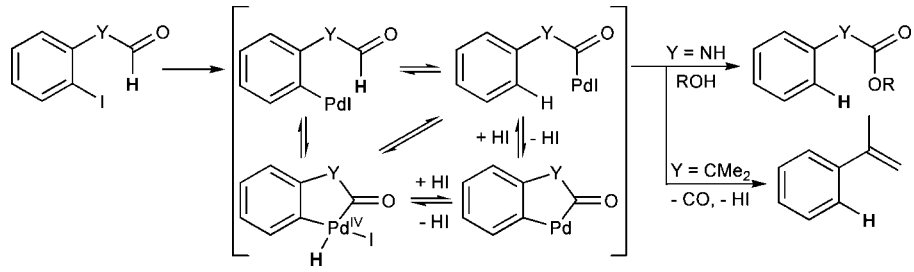
Palladium-catalyzed synthesis of 9-fluorenylidenes through aryne annulation was reported by Larock and co-workers (Scheme 178).[259]

Oxidative addition of Pd^0 into the benzyne sp^2-sp^2 bond, followed by oxidative addition of the aryl halide, generates an intermediate that might be formulated as an aryl Pd^{IV} species. Upon reductive elimination, and insertion, Pd^0 is regenerated (Scheme 179).

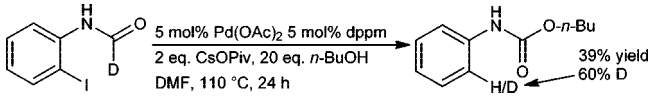
3.10. Pd^{IV} Acyl Intermediates

While there is no unequivocal evidence of Pd^{IV} acyl complexes, they might be involved as intermediates in reactions of acyl halides with Pd^{II}, C−H activation of aldehydes, and other reactions.

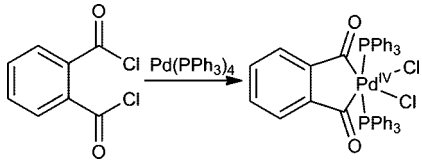
Scheme 181. Acyl C−H Activation of Aldehydes/Formamides via a Proposed "Through Space" Pd Migration



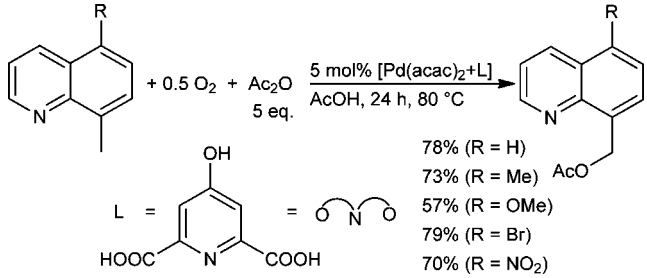
Scheme 182. Deuteration Study Elucidating the Pd-Transfer Mechanism



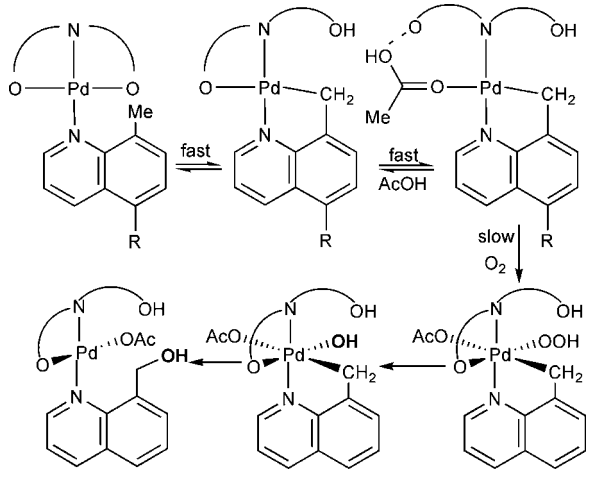
Scheme 183. Proposed Pd^{IV} Product of the Reaction of $Pd(PPh_3)_4$ with Phthaloyl Chloride



Scheme 184. Scope of Aerobic Pd-Catalyzed Benzylic Acetoxylation of 8-Methylquinolines



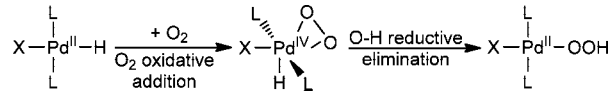
Scheme 185. Proposed Mechanism for Aerobic Pd-Catalyzed Benzylic Acetoxylation of 8-Methylquinolines Based on DFT Calculations



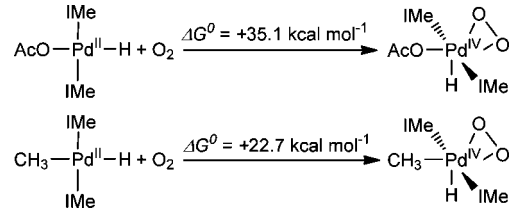
In studies reported by Graziani[63] described earlier (Scheme 27), both reactions of an unstable Pd^{II} acyl complex with MeI and an analogous Pd^{II} alkyl complex with MeCOCl rapidly gave the corresponding methyl alkyl ketone. However, no Pd^{IV} acyl complexes were implicated.

An interesting mechanistic possibility was discussed by Dedieu and Boersma.[260] Water acts as a nucleophile for the cationic Pd^{II} acyl complexes, leading eventually to Pd^0 and acetic acid. On the basis of the precedented $Pt^{II}\cdots H^+-NMe_2R$ motif and a discrete tautomeric $H-Pt^{IV}-NMe_2R$ species (both formed from CN cycloplatinated species and acids), the [Pd^{II}(acyl)(water)] and/or [Pd^{IV}(acyl)(hydride)(hydroxyl)] were proposed (Scheme 180).

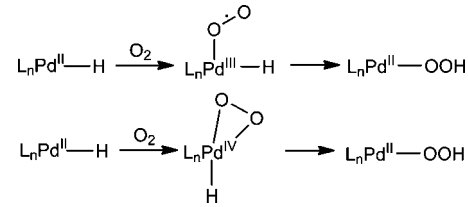
Scheme 186. Mechanistic Proposal for Pd^{II} Hydride Oxygenation via a η^2-Peroxo−Pd^{IV} Intermediate



Scheme 187. Activation Barriers for Oxygenation of Two Pd^{II} Hydride Complexes to the Respective η^2-Peroxo−Pd^{IV} Species



Scheme 188. Two Routes for Pd^{II} Hydride Oxygenation Evaluated with Unrestricted DFT



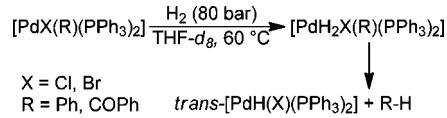
Acyl C−H activation of aldehydes/formamides was studied by Larock and co-workers.[261] The "through-space" migration of palladium from an aryl position to an acyl position by a five-membered ring palladacycle results in an acylpalladium species. Direct oxidative addition of $ArPd^{II}I$ into the C(O)−H bond would result in an acyl Pd^{IV} hydride. The acylpalladium species can be trapped by an alcohol, or in the absence of an alcohol, olefin products result from decarbonylation, followed by β-hydride elimination (Scheme 181).

A labeling study found 60% deuterium incorporation into the *ortho*-position of carbamate when a monodeuterated formamide was used, which is consistent with either of the two proposed mechanisms (Scheme 182).

From a synthetic point of view, the reaction is not practical as it leads to the loss of haloaryl functionality and proceeds in low to moderate yields.

A diacyl Pd^{IV} complex was proposed as a product of double oxidative addition of $Pd(PPh_3)_4$ into phthaloyl chloride (Scheme 183).[262] Although obtained in high yield, the material was only partially characterized by IR and NMR

Scheme 189. Possible Pd^{IV} Hydride Intermediate in Reactions of $[PdX(R)(PPh_3)_2]$ Complexes with H_2



spectroscopies. As the process showed no desired quinone-forming reactivity with alkynes, it was not studied further.

3.11. Pd^{IV} Peroxo Intermediates in Aerobic Oxidation Reactions

The intermediacy of Pd^{IV} in various Pd-catalyzed aerobic oxidations has been the subject of intense study. Vedernikov has reported regioselective aerobic acetoxylation of 5- and 6-substituted 8-methylquinolines in $AcOH-Ac_2O$ solution to produce corresponding 8-quinolylmethyl acetates in high yields (Scheme 184).[263]

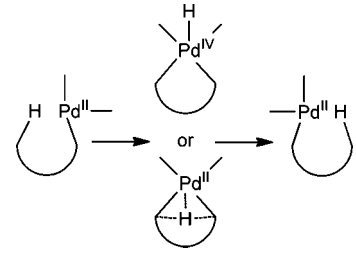
Thermodynamic accessibility of presumed key intermediates in Pd^0/Pd^{II} and Pd^{II}/Pd^{IV} (Scheme 185) catalytic cycles was analyzed with DFT calculations. Although transient Pd^{IV} were shown to be energetically accessible, the formation of a $Pd^{IV}-OOH$ species from $Pd^{II}-$substrate complex and O_2 was identified as a potential high-barrier reaction.

A recent summary of aerobic functionalizations achieved with Pt^{II} monoalkyl complexes is available.[264]

Detailed theoretical analysis of reactions between Pd^{II} hydride species and O_2 with respect to possible Pd^{IV} intermediates was carried out by Popp and Stahl (Scheme 186).[265,266]

The calculated free energy ($\Delta G°$) for formation of the η^2-peroxo$-Pd^{IV}$ complex was substantially higher than even the activation barriers ($\Delta G^{‡}$) associated with alternative pathways for palladium−hydride oxygenation. The more strongly donating methyl group in the second η^2-peroxo$-Pd^{IV}$ species in Scheme 187 makes the complex significantly more stable. Nevertheless, the acetate-for-methyl ligand exchange also dramatically lowers the barrier for a competing hydrogen atom abstraction mechanism. Thus, the Pd^{IV} pathway for palladium−hydride oxygenation appears to be energetically prohibitive.

Scheme 191. General Scheme for the Two Alternative Pd-Shift Mechanisms: Pd^{IV} Hydride Versus Proton Transfer (Bonds to Pd without Groups Are Empty Coordination Sites or Positions of a Labile Ligand, e.g., Solvent)



Later, the authors applied unrestricted DFT to the widely used $Pd(OAc)_2$/pyridine catalyst system (Scheme 188).[266] Both $Pd^{III}-$superoxide, resembling biological O_2 activation, and η^2-peroxo$-Pd^{IV}$ hydride intermediates were considered. In contrast to previous studies, the reductive elimination pathway (AcOH reductive elimination to yield a Pd^0 species that subsequently reacts with O_2) was significantly more favorable than any of the pathways proposed above.

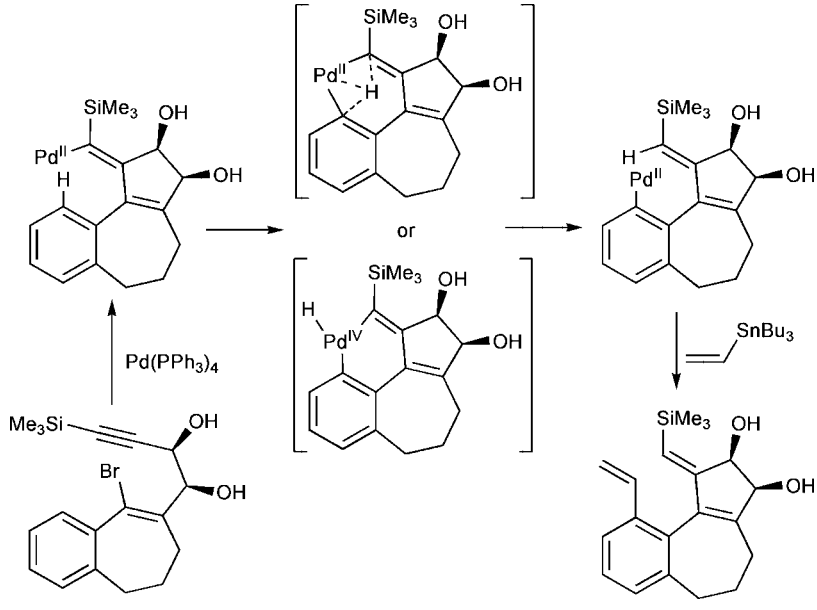
3.12. Pd^{IV} Hydride Intermediates and Pd-Transfer Processes

Although the chemistry of Pd^{II} hydrides is well-established and has been reviewed,[66] there is no solid experimental evidence for the existence of a $Pd^{IV}-H$ bond. In analogy to Pt^{IV}, similar Pd^{IV} hydride species have been suggested in the literature as possible intermediates in reactions of Pd^{II} complexes with HCl[66] and H_2 (Scheme 189).[267]

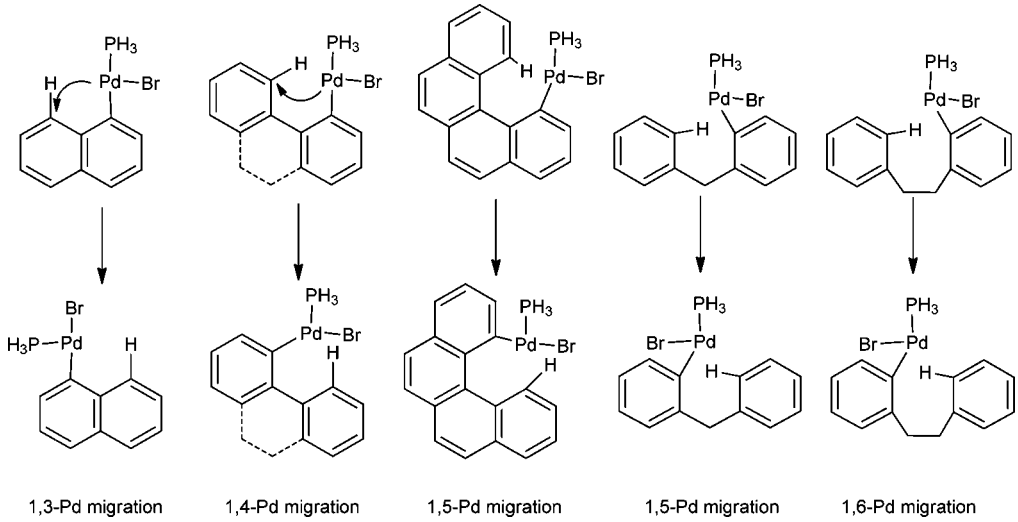
Extensive theoretical work of Mota and Dedieu has focused on intramolecular palladium-transfer processes.[268–270] A DFT/B3LYP model study focused on the mechanism of cyclocarbopalladation and on an unusual 1,5-vinyl to aryl−palladium shift.[270] The study was triggered by observation of unusual products of tandem reactions between various γ-bromopropargylic-1,2 diols and alkenyl or alkynyl stannanes catalyzed by $Pd(PPh_3)_4$ (Scheme 190).

However, on the basis of their calculations, the 1,5-vinyl to aryl−palladium shift is best represented as a proton

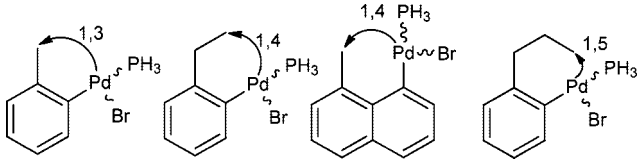
Scheme 190. Proton Transfer Versus Pd^{IV} Hydride Mechanism Explaining the Unexpected Products of Cross-Coupling between Alkenyl Stannanes and γ-Bromopropargylic-1,2-diols



Scheme 192. Variants of Model Intramolecular 1,*n* (*n* = 3−6) Palladium Migrations in Polycyclic Aromatic Hydrocarbons



Scheme 193. Variants of Model Intramolecular 1,*n* (*n* = 3−5) Aryl → Alkyl Palladium Migrations



transfer between the two formally negatively charged carbon atoms without a change in Pd oxidation state.

In subsequent work, Dedieu undertook a comprehensive study of model intramolecular 1,*n* (*n* = 3−6) palladium migrations in polycyclic aromatic hydrocarbons with a specific aim to determine whether a well-defined Pd^{IV} intermediate or the transition state is involved (Scheme 191).[268]

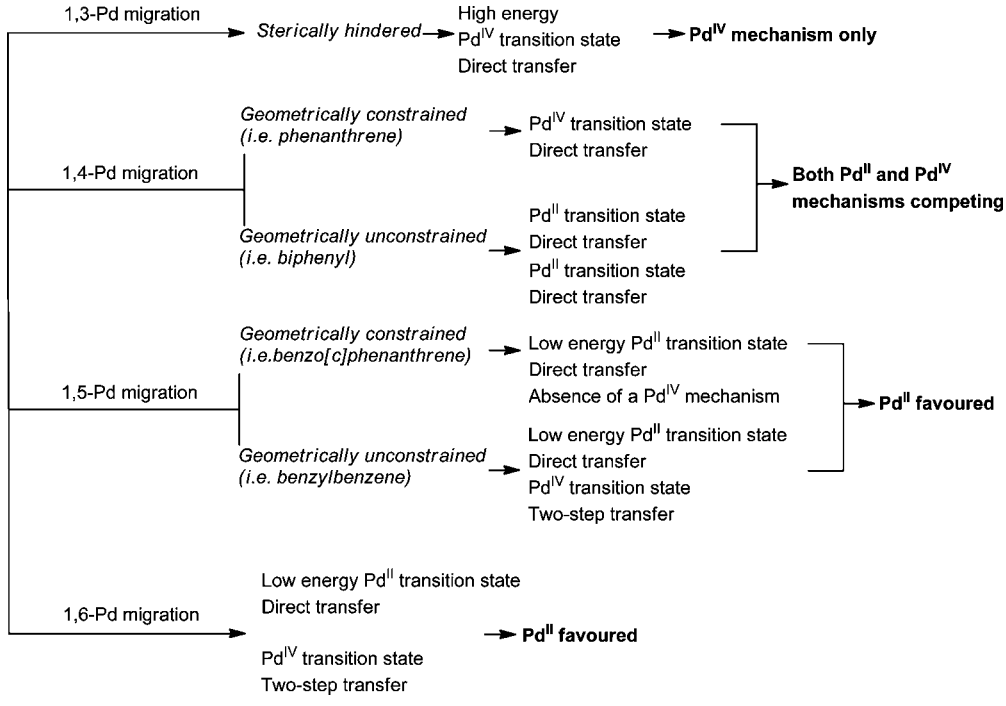
Examples of the many arrangements investigated are shown in Scheme 192.

The Pd^{IV} route (formally involving a hydride transfer in an oxidative hydrogen migration mechanism) is the preferred mechanism for 1,3-Pd migrations, whereas the Pd^{II} pathway (formally involving a proton transfer) turns out to be much more favorable in the case of 1,5- and 1,6-Pd migrations. In the case of 1,4-Pd/H interchanges, however, both mechanisms become competitive, displaying similar activation energies. The study was extended further to include aryl → alkyl palladium migration processes (Scheme 193).[269]

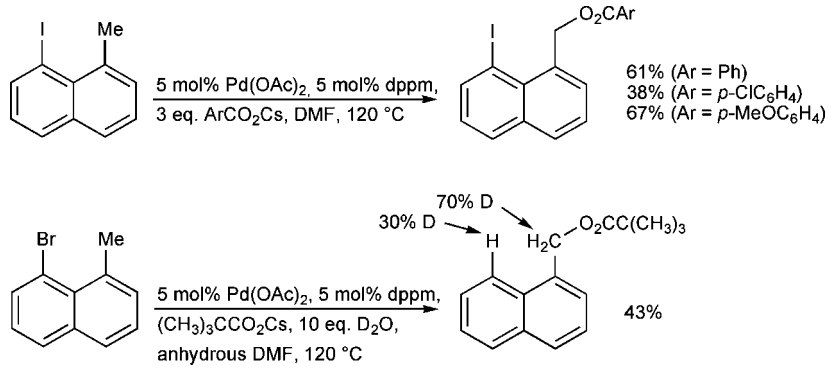
The results support the conclusions from the aryl → aryl study. The Pd^{IV} pathway can involve either a true Pd^{IV} intermediate (oxidative addition/reductive elimination mechanism) or a Pd^{IV} transition state (oxidative hydrogen migration mechanism). Conclusions from both studies are summarized in Scheme 194.

Experimental observations of 1,4-Pd migrations are known. A 1,4-aryl to benzylic migration followed by C−O bond formation has been reported by Larock.[271] Both naphthyl bromides and iodides react, giving benzylic esters and ethers

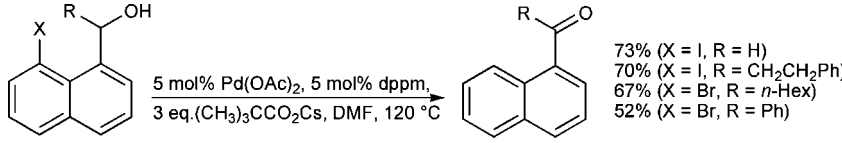
Scheme 194. General Mechanistic Conclusions for 1,*n* (*n* = 3−6) Palladium Migrations



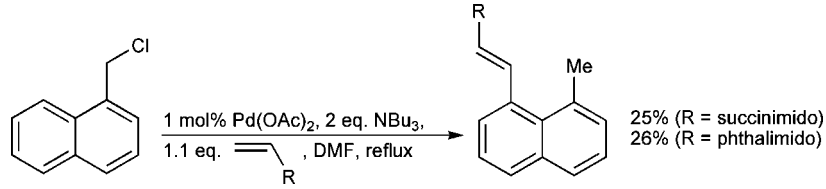
Scheme 195. Experimental Examples and Deuteration Studies of 1,4-Aryl to Benzylic Palladium Migration



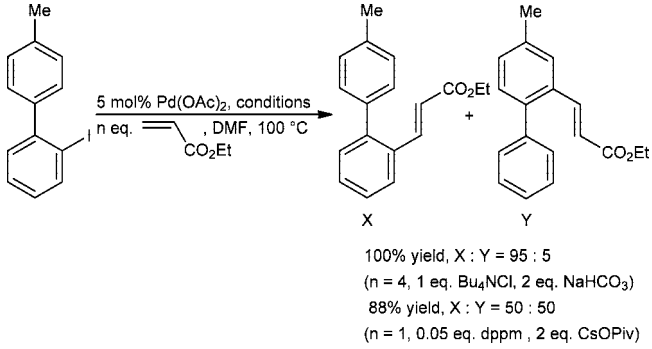
Scheme 196. 1,4-Aryl to Benzylic Palladium Shift Leading to Carbonyl Compounds



Scheme 197. Experimental Example of the Reverse Benzyl → Aryl 1,4-Pd Transfer



Scheme 198. Dependence of the 1,4-Pd-migration in 2-Iodobiphenyls on Reaction Conditions



in moderate to good yields via C−H activation of a proximal benzylic methyl group (Scheme 195). A deuteration experiment revealed that the palladium migration occurs reversibly between the aryl and benzylic positions. Reactions of substrates bearing a benzylic hydroxyl lead to carbonyl compounds (Scheme 196).

The reverse benzyl → aryl 1,4-Pd transfer was reported by Pan in reactions of α-chloromethylnaphthalene with *N*-vinyl olefins (Scheme 197).[272]

Many examples exist of the aryl → aryl 1,4-Pd migration in reactions of *o*-iodobiaryls, mainly from the group of Larock. The Pd migration can be switched "on" or "off" depending on the base used (Scheme 198).[273]

In the unsymmetrical iodo-3-phenylbenzofuran, there is strong preference for arylation of the more electron-rich benzofuran, irrespective of the position of iodine (Scheme 199).

A related study of retention versus crossover selectivity was conducted on Heck reactions of 4-aryl-3-bromopyridines by Gallagher and co-workers.[274] When combined with further C−H activation events, and/or alkyne insertion, the reactions represent a very powerful methodology for the synthesis of fused polycycles (Scheme 200).[275–278]

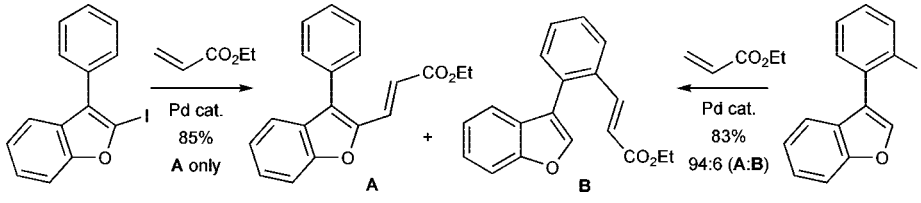
An aryl → imidoyl 1,4-Pd migration followed by cyclization is the basis of a very efficient methodology for the synthesis of fluoren-9-ones and xanthones (Scheme 201).[279]

The most plausible mechanism is shown in Scheme 202.

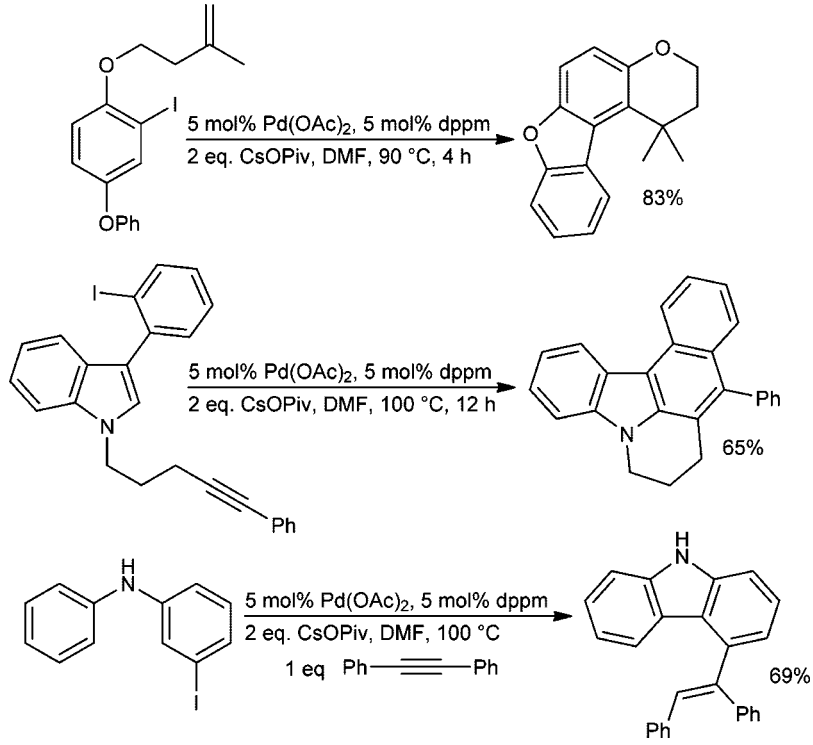
Larock and co-workers also reported an unusual dimerization of piperdin-2-ones with a 2-bromobenzyl substituent in the 5-position.[280] Apart from a 1,5-Pd migration process, the reaction involves an arylPd^{IV} intermediate (Scheme 203).

In the absence of a suitable functionality or a coupling partner, 1,4-Pd migrations can also result in dehydrogenation as demonstrated on reactions of dihydrocinnamates[281] and cyclopentanecarboxylic acids[282] (Scheme 204).

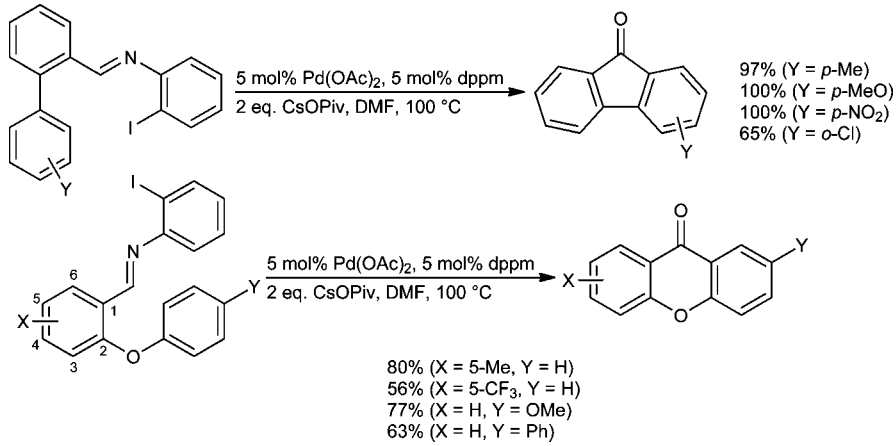
Scheme 199. Preference for Furan Ring Alkenylation in Isomeric Iodo-3-phenylbenzofurans



Scheme 200. Synthesis of Polycyclic Heterocycles Combining Pd-Transfer with Further C−H Activation and Insertion Events



Scheme 201. Efficient Synthesis of Fluorenones and Xanthones via Aryl → Imidoyl 1,4-Pd Migration



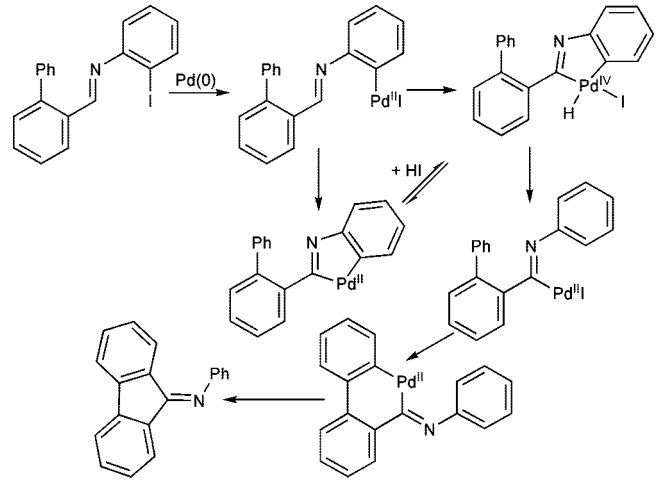
3.13. Applications of C(sp)−Pd^{IV} Complexes in Synthesis and Direct Oxidative Addition of Pd^{II} into C(sp)−H Bonds

Low-temperature studies of Canty and co-workers showed the first detection of alkynyl Pd^{IV} complexes [C_6H_3-2,6-(CH_2NMe_2)$_2$Pd(O_2CPh)(OTf)(C′$CSiMe_3$)] and $PdIMe_2$-(C′$CSiMe_3$)(dmpe) (Scheme 205).[245] Interestingly, attempts to prepare analogous NN stabilized Pd^{IV} species from $PdMe_2$(bipy) only led to decomposition. Compared to the known isolable platinum analogues,[283] the alkynyl Pd^{IV} complexes have turned out to be very unstable and decomposed at temperatures above −50 °C.

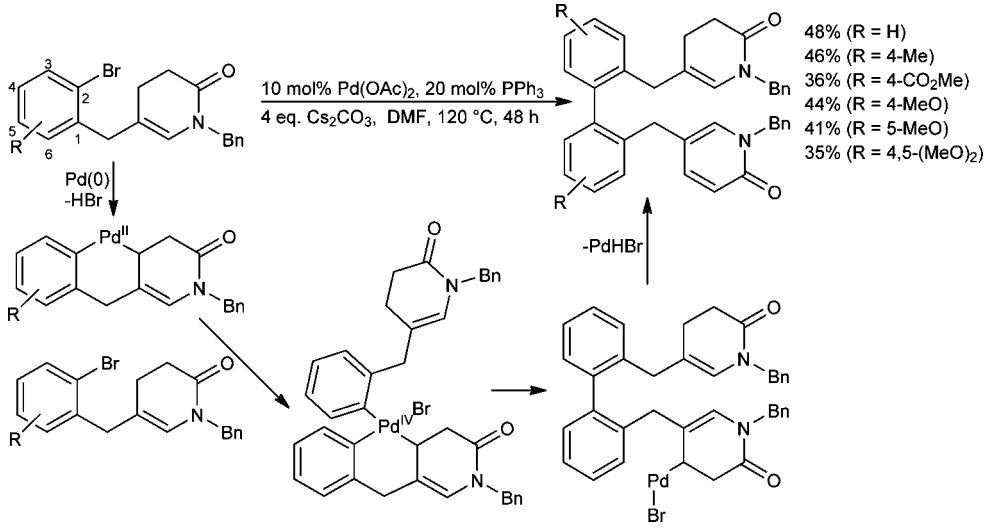
Trost et al. reported that attempted Pd-catalyzed cycloisomerizations of certain 1,6-enynes bearing a trisubstituted double bond do not lead to cyclization but give dimeric 1,3-enynes instead.[284] The same reactivity switch was seen in other substrates when using the highly sterically crowded tris(2,6-dimethoxyphenyl)phosphine ligand. With simple terminal alkynes, both homo- and heterodimerization is possible (Scheme 206).

The possible mechanism involves Pd^{IV} hydride intermediates (Scheme 207). This was corroborated by experiments

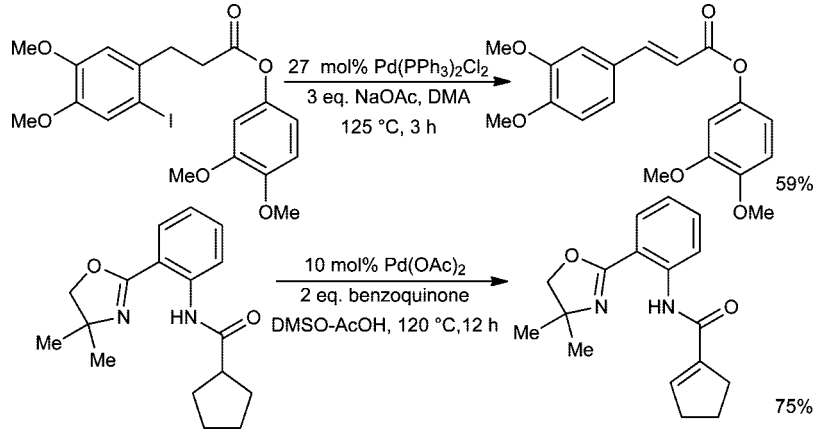
Scheme 202. Proposed Aryl → Imidoyl 1,4-Pd Migration Mechanism in Fluorenone Synthesis



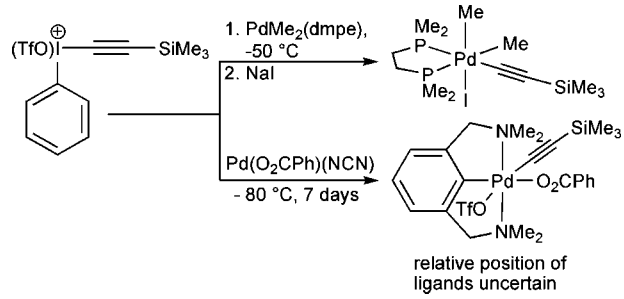
Scheme 203. Dimerization of 2-Bromobenzyl Substituted Piperdin-2-ones via 1,5-Pd Migration and ArylPd^{IV} Intermediate



Scheme 204. Examples of 1,4-Pd Migrations Resulting in Alkenic Products

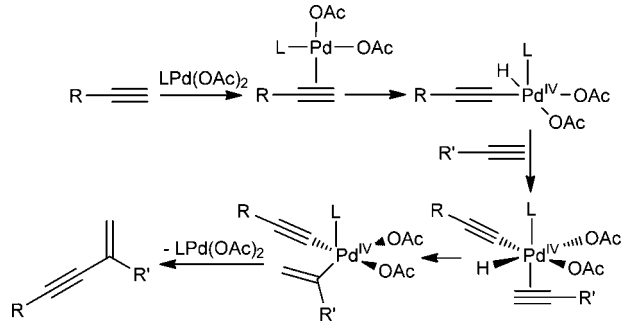


Scheme 205. C(sp)−Pd^{IV} Products from Alkynylation of Pd^{II} Complexes with an Alkynyliodonium Triflate



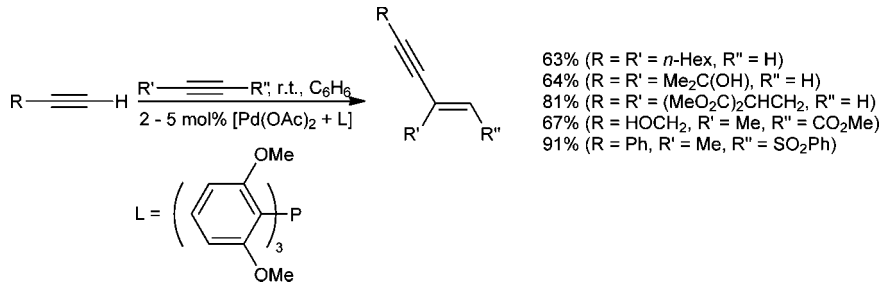
with $Pd_2(dba)_3 \cdot CHCl_3$, which gives dimerization products at an extremely slow rate. The rate is dramatically accelerated by addition of allyl acetate. More examples and some

Scheme 207. Possible Mechanism for Dimerization of Terminal Alkynes Involving C(sp)−Pd^{IV} Intermediates

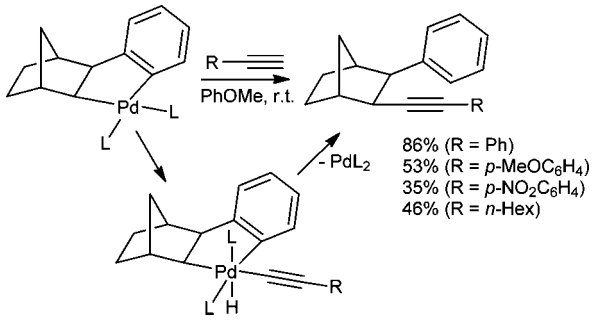


modified mechanistic hypotheses were reported in a later publication.[285]

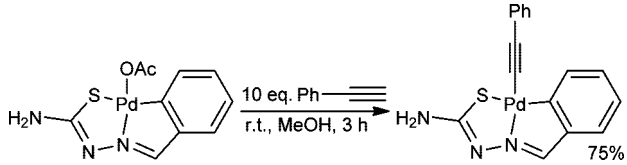
Scheme 206. Dimerization of Terminal Alkynes to 1,3-Enynes



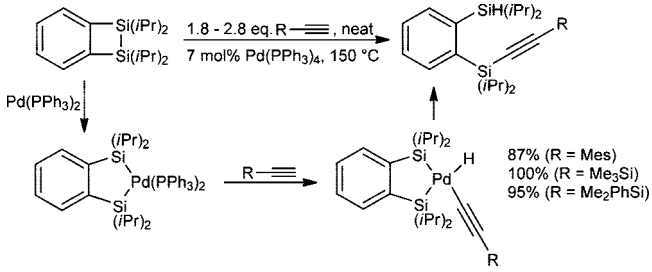
Scheme 208. Stoichiometric C(sp^3)−C(sp) Coupling via a Proposed C(sp)−Pd^{IV} Hydride Intermediate



Scheme 209. Acetate−Phenylethynyl Ligand Exchange on a Pallada(II)cyclic Complex



Scheme 210. Activation of Terminal Alkynes by a Disilapallada(II)cycle



The different behavior of terminal and internal alkynes in reactions with pallada(II)cyclic complexes led Catellani et al. to the conclusion that terminal alkynes do react through oxidative addition into the terminal C−H and reductive elimination to a ring-opened product regioselectively alkynylated only on the cycloaliphatic carbon (Scheme 208).[286]

In another instance, a direct reaction of a pallada(II)cyclic acetoxy complex with terminal alkynes gave alkynylpalladium(II) complexes in the absence of base under mild conditions (Scheme 209).[287] However, no Pd^{IV} hydride intermediates were invoked in this particular chemistry.

Activation of terminal alkynes by a disilapallada(II)cycle has been invoked in the studies reported by Ishikawa and co-workers.[288] The strained starting 1,1,2,2-tetra(isopropyl)-3,4-benzo-1,2-disilacyclobut-3-ene and terminal alkynes with bulky substituents give ring-opened products in very good to quantitative yields (Scheme 210). However, all attempts to detect any palladated intermediates by ^{1}H NMR spectroscopy were unsuccessful.

A palladium-catalyzed alkyne−oxalate ester reaction with a formal C−C bond cleavage was reported by Alper and co-workers (Scheme 211).[289]

A tentative mechanism involving oxidative additions into the terminal acetylene C−H and the oxalate C−C bonds is shown below (Scheme 212). Pd^0(dba)(dppb)(CO), the presumed active catalyst, sequentially reacts with two molecules of the terminal alkyne; oxidative addition into dialkyl oxalate C−C bond generates a key Pd^{IV} intermediate. The first molecule of alkyl cinnamate is produced from reductive elimination, and another alkyne molecule adds to form a Pd^{IV} hydride. After elimination of diaryl 1,3-butadiyne and a second alkyl cinnamate molecule, the Pd^0 catalyst is regenerated.

A related mechanism involving CO insertion and Pd^{IV}−alkynyl species has been proposed in aminocarbonylations of vinyl iodides, which is accompanied by the unexpected ynamide formation (Scheme 213).[290]

However, in both reactions described above, the proposed Pd^{IV}−alkynyl species remain highly speculative.

3.13.1. Allyl Pd^{IV} Hydrides

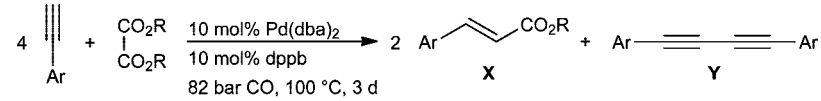
Direct evidence for discrete Pd^{IV} hydrides from direct oxidative addition of Pd^{II} into C−H bonds has been scarce and often inconclusive. Despite the systematic theoretical work of Vedernikov et al. on C−H activation of unactivated alkanes and arenes,[291–297] experimental work of the group[64,298–300] has not provided sufficient evidence for a Pd^{II}−Pd^{IV} catalytic cycle.

Allyl Pd^{IV} hydrides as intermediates in the formation of π-allyl complexes from olefins were first proposed by Trost[301] and later reiterated by others[302] (Scheme 214). It was argued that a base or $CuCl_2$ are key for the successful formation of $[(\eta^3\text{-allyl})PdCl]_2$ from this intermediate.

Kinetics of Pd^{II}-catalyzed H/D allylic exchange in alkenes has been studied in detail.[303] Very surprisingly, it was found that dimeric π-allylic species $[(\eta^3\text{-allyl})PdCl]_2$ cannot be an intermediate in the $Li_2Pd_2Cl_6$-catalyzed allylic H/D exchange. Neither H/D exchange in α-methylstyrene nor enrichment of $[(\eta^3\text{-2-PhC}_3H_4)PdCl]_2$ was observed when the latter complex was incubated at 100 °C in CD_3COOD either in the presence or in the absence of $PhC(CH_3)=CH_2$, respectively. Approximately 80% deuteration was observed on preparative scale for α-methylstyrene after 1 week. However, $[(\eta^3\text{-2-PhC}_3H_4)PdCl]_2$, which is a byproduct of the deuteration, was enriched to only 20%. This evidence pointed to a Pd^{IV} hydride mechanism (Scheme 215).

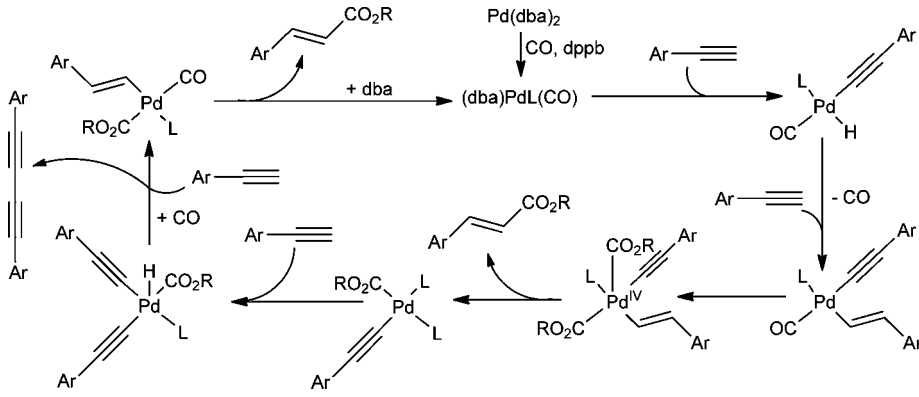
In order to explain some isotope redistribution effects in the deuteration studies of pentenes catalyzed by $PdCl_2$-

Scheme 211. Scope of the Pd-Catalyzed Alkyne−Oxalate Ester Reaction

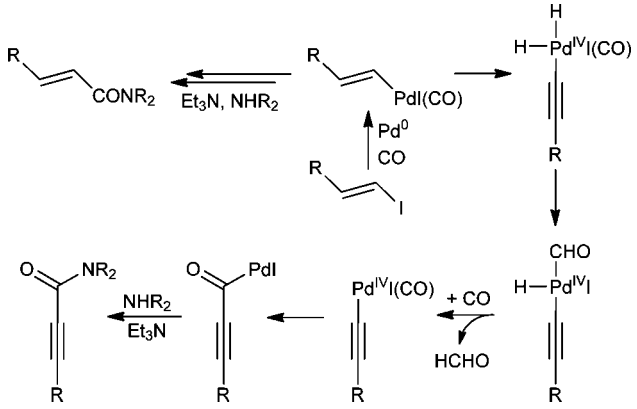


Ar	R	yield of **X** (%)	yield of **Y** (%)	solvent
Ph	Et	30	18	DME
Ph	Bu	30	0	DME
Ph	Me	57	24	4-methyl-2-pentanone
4-MeOC$_6$H$_4$	Et	32	0	4-methyl-2-pentanone
4-MeOC$_6$H$_4$	Me	37	0	4-methyl-2-pentanone

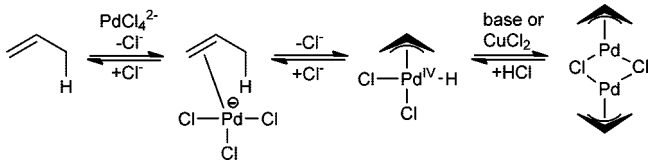
Scheme 212. Tentative Mechanism of the Alkyne−Oxalate Ester Reaction Involving Oxidative Addition of Pd^{II} into C−H and C−C Bonds



Scheme 213. Proposed Mechanism for Ynamide Formation in Aminocarbonylation of Vinyl Iodides



Scheme 214. Allyl Pd^{IV} Hydrides As Intermediates in the Formation of π-Allyl Complexes



$(PhCN)_2$, Wells suggested that a $(\eta^3\text{-allyl})_2Pd^{IV}$ dihydride might be involved.[304] However, no evidence was provided to support this proposal (Scheme 216).

3.13.2. Other Pd^{IV} Hydrides

Gas-phase ESI-FTICRMS studies of the fragmentation mechanism in a series of cationic Pd^{II} carboxylate fragments have revealed a stable Pd^{IV} hydride intermediate.[305] Semiempirical (PM3) calculations and deuterium-labeling experiments indicate that the protons of RCOOH lost from $[Pd(PPh_3)_2(O_2CR)]^+$ originate from the phenyl in the triphenylphosphine ligand (Scheme 217).

3.13.3. Functionalization of Unactivated Arenes

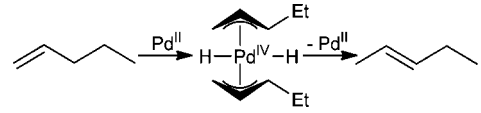
Stock and co-workers studied palladium(II) acetate catalyzed oxidation of benzene and other simple arenes in acetic acid.[306] A large excess of dichromate oxidant greatly increases the ratio of acetoxylation versus biphenyl formation. However, the presence or absence of dichromate had no effect in C_6H_6/C_6D_6 competition experiments. This suggested that phenylpalladium(II) acetate is oxidized by dichromate to an unstable phenyl Pd^{IV} triacetate. The thermal decomposition of this intermediate provides phenyl acetate and regenerates the electrophilic Pd^{II} catalyst (Scheme 218).

This was further substantiated by Crabtree and coworkers,[307] who established that $PhI(OAc)_2$ is a superior oxidant for this reaction and biphenyl formation is minimal.

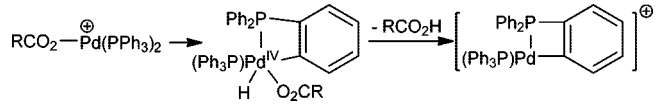
Despite the fact that the above acetoxylation shows poor *o*/*m*/*p* selectivity even for monosubstituted benzenes, a highly regioselective C−H activation of arenes without directing groups has recently been demonstrated (Scheme 219).[308]

Mechanistically, the reaction is similar to Pd-catalyzed alkene diamination discussed in the next section. Initial aminopalladation of the alkene gives a Pd^{II}−alkyl complex, and subsequent oxidation with "F^+" generates the key Pd^{IV} complex. In the presence of nucleophilic arenes, the Pd^{IV} center is intercepted and displaced in an electrophilic aromatic substitution reaction, forming the final product and regenerating the Pd^{II} catalyst (path a).

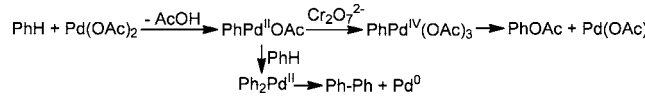
Scheme 216. $(\eta^3\text{-Allyl})_2Pd^{IV}$ Dihydride As Speculative Intermediate in Pentene Isomerization



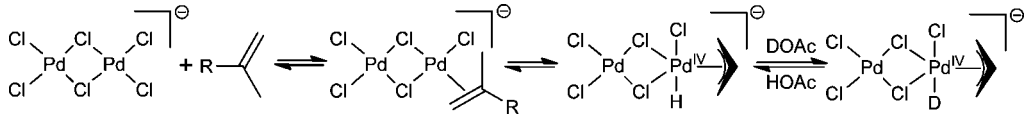
Scheme 217. Proposed ESI-FTICRMS Fragmentation Mechanism Involving a Pd^{IV} Hydride Species



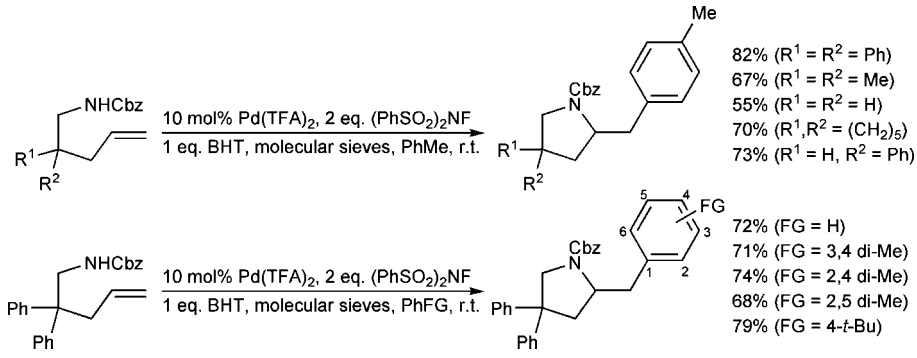
Scheme 218. Mechanism of Benzene Acetoxylation with Dichromate Oxidant



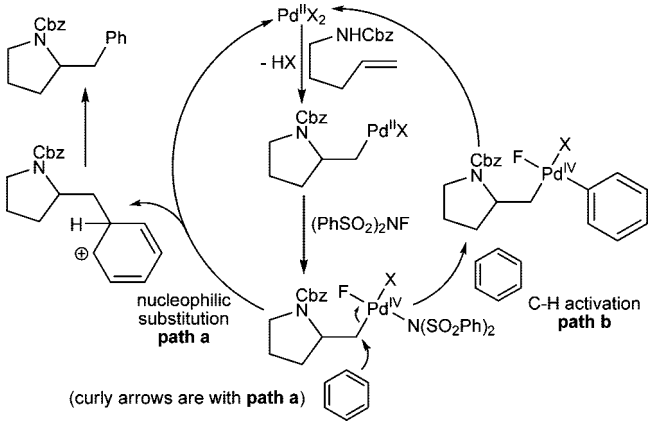
Scheme 215. Pd^{II}-Catalyzed H/D Allylic Exchange in Alkenes via Allyl Pd^{IV} Hydrides



Scheme 219. Scope of the Intramolecular Amination−Regioselective Arene Activation Sequence



Scheme 220. Proposed Mechanism for the Intramolecular Amination−Regioselective Arene Activation Sequence



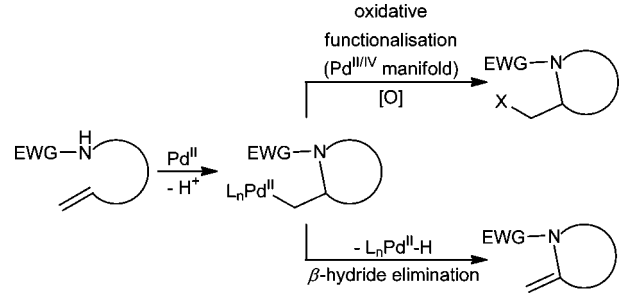
Alternatively, C−H activation of the arene by the Pd^{IV} species followed by reductive elimination is also a plausible route to the observed product (path b) (Scheme 220).

A rate limiting Pd−C bond protonolysis step in intramolecular alkene hydroamination was observed by Michael (Scheme 221).[309] Although a Pd^{IV} hydride intermediate was proposed, a direct S_E2 protonation is more likely.

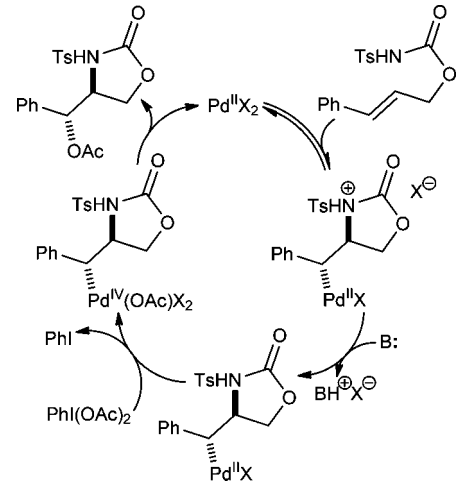
3.14. Oxidative Difunctionalization of Alkenes via Pd^{IV} Intermediates

The idea to combine alkene amination with a Pd^{II}/Pd^{IV} catalytic cycle was first successfully demonstrated independently by Sorensen[310] and Muñiz.[311] The Pd^{II} β-aminoalkyl species, generated by intramolecular aminopalladation, can be oxidatively intercepted to generate a Pd^{IV} intermediate.

Scheme 222. General Mechanism for Intramolecular Haloamination and Oxidative Amination to Enamines

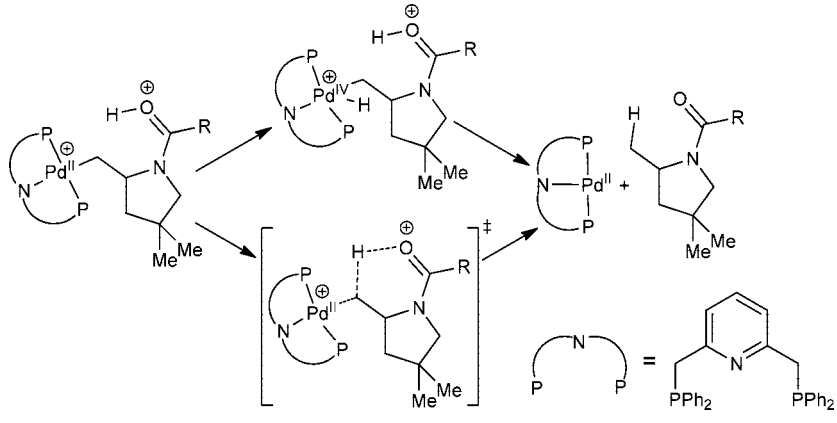


Scheme 223. Proposed Mechanism for Intramolecular Acetoxylation of Unsaturated Tosylamines

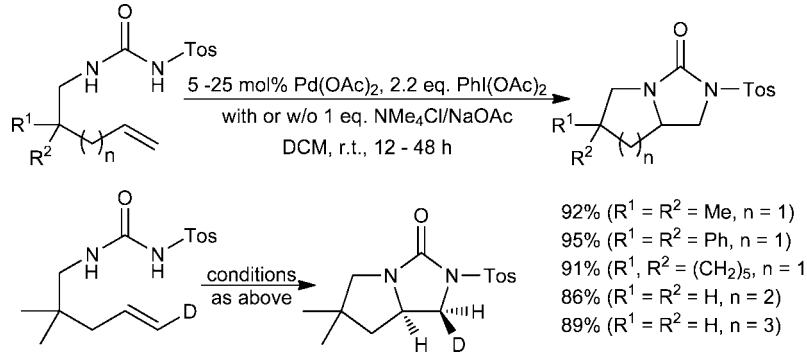


Reductive elimination from this intermediate then provides a difunctionalized product (Scheme 222).

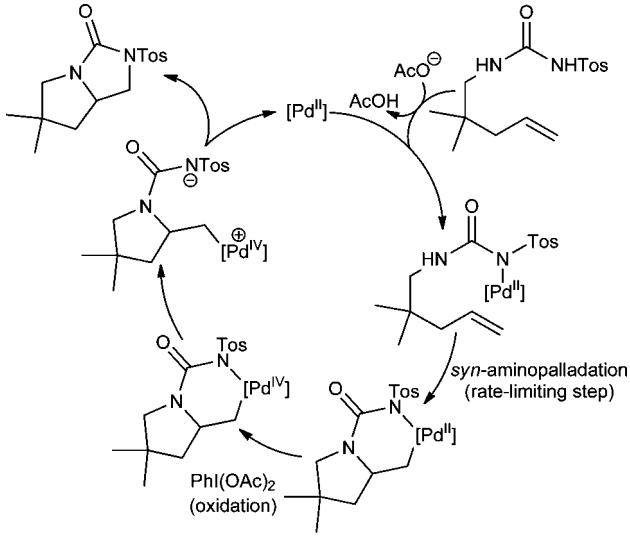
Scheme 221. Possible Pd^{IV} Hydride Intermediacy in Pd−C Bond Protonolysis



Scheme 224. Scope and Stereochemical Course of Intramolecular Alkene Diamination



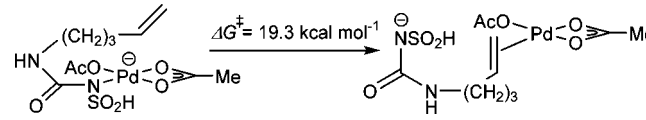
Scheme 225. Detailed Mechanism and Stereochemical Course of Intramolecular Alkene Diamination



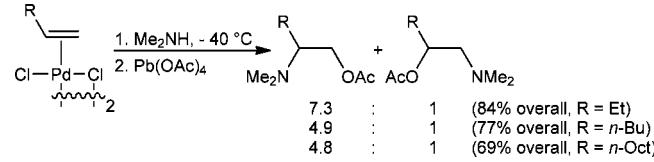
Sorensen devised ring-forming acetoxylation of unsaturated tosylamines and *N*-tosyl carbamates using $PhI(OAc)_2$ as oxidant in the presence of Bu_4NOAc.[310] On the basis of further experiments, the following mechanism was proposed (Scheme 223). Pd^{II}-mediated reversible *trans*-aminopalladation of the alkene generates a protonated intermediate that then undergoes an irreversible deprotonation step. The neutral alkyl Pd^{II} intermediate is oxidized by $PhI(OAc)_2$ to an alkyl Pd^{IV} intermediate. Finally, C−O bond-forming reductive elimination, which is stereospecific (with retention), completes the aminoacetoxylation process and regenerates the catalyst.

Muñiz developed a high yielding intramolecular diamination, closing a 5-membered and another 5−7-membered ring system (Scheme 224).[311]

Scheme 227. Rate-Determining Step in the Intramolecular Alkene *anti*-Aminopalladation



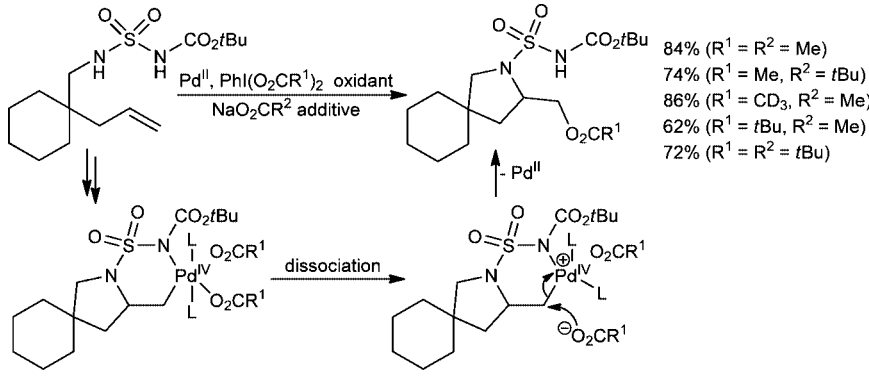
Scheme 228. Stoichiometric Aminoacetoxylation with Lead Tetraacetate As Terminal Oxidant



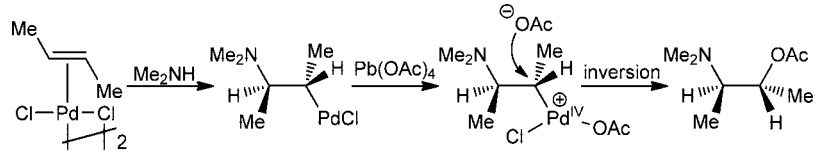
Diamination of selectively deuterated starting material produced diastereomerically pure product. The authors assumed that the aminopalladation step is *anti*-selective, and this indicated that the Pd^{IV} center was displaced in a S_N2 fashion by the amide nitrogen, with the stereochemistry inverted at the terminal carbon atom. However, in a later more comprehensive study,[312] the authors corrected the originally misassigned relative stereochemistry of the selectively deuterated product (Scheme 225) and put forward an amended mechanism containing the key aminopalladation with *syn*-stereochemistry as the rate-limiting step. The first C−N bond-formation event from within the coordination sphere of a Pd^{II}−urea complex was documented by NMR spectroscopic studies.

Further evidence for release of the nucleophile for the second C−N bond formation from the Pd^{IV} coordination sphere was obtained from reactions of sulfamides, where the nucleophile originates from the oxidant, and not from the anionic base (Scheme 226).

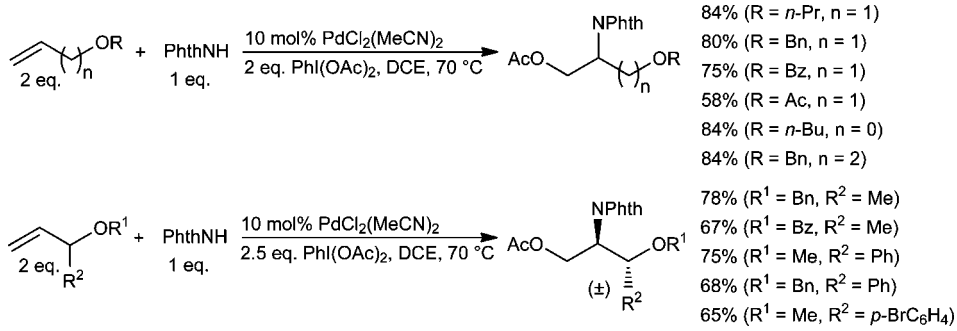
Scheme 226. Detailed Mechanism of Intramolecular Aminoacetoxylation of Unsaturated Sulfamides



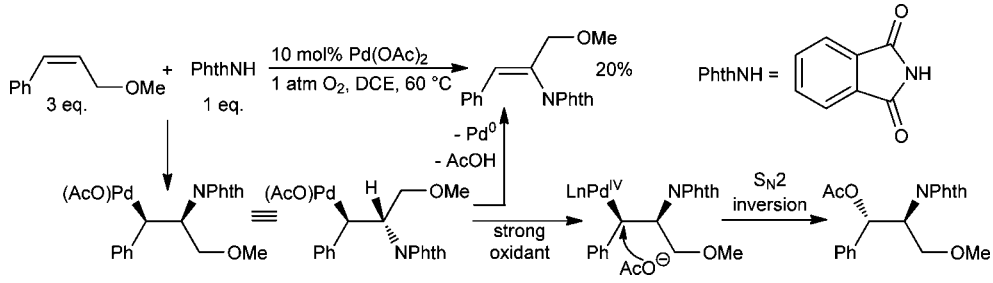
Scheme 229. Possible $Pd^{II}-Pd^{IV}$ Mechanism for Stoichiometric Alkene Aminoacetoxylation



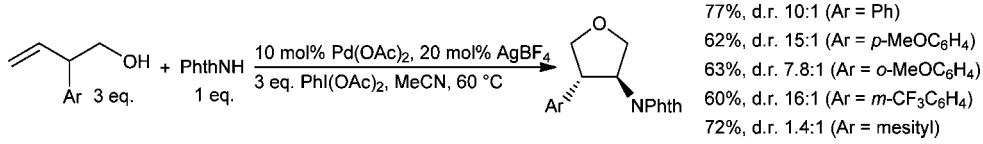
Scheme 230. Scope and Stereochemical Outcome of Intermolecular Aminoacetoxylation of Allylic Ethers



Scheme 231. Mechanism of Intermolecular Aminoacetoxylation via the Key *cis*-Aminopalladation Step



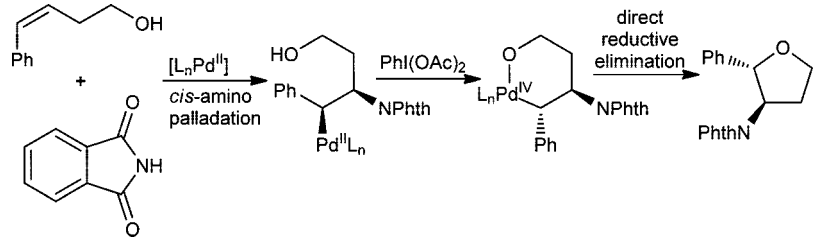
Scheme 232. Intermolecular Amination of Homoallylic Alcohols to Aminotetrahydrofurans



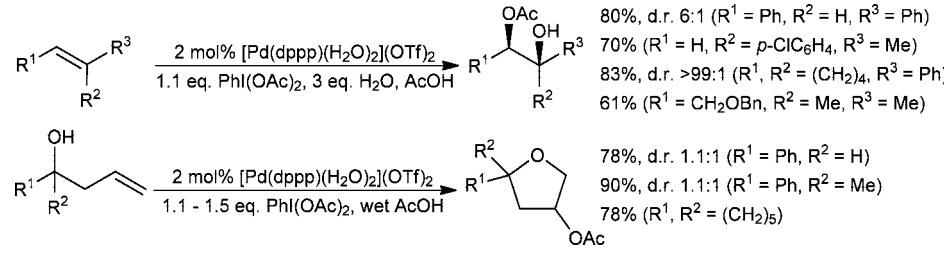
Contrary to experimental evidence, the DFT calucations of Lin and co-workers support *anti*-aminopalladation and direct reductive elimination from Pd^{IV} as the key steps.[313] The authors' predicted overall barrier for the diamination process of 19.3 kcal mol^{-1} is very close to the experimental value of ~22.0 kcal mol^{-1}.[312] The rate-determining step for their proposed mechanism is the transformation of the *N*-coordinated anionic Pd^{II} intermediate to the terminal alkene-coordinated Pd^{II} intermediate (Scheme 227).

An early study of Bäckvall demonstrated stoichiometric aminoacetoxylation using lead tetraacetate as stoichiometric oxidant (Scheme 228).[314]

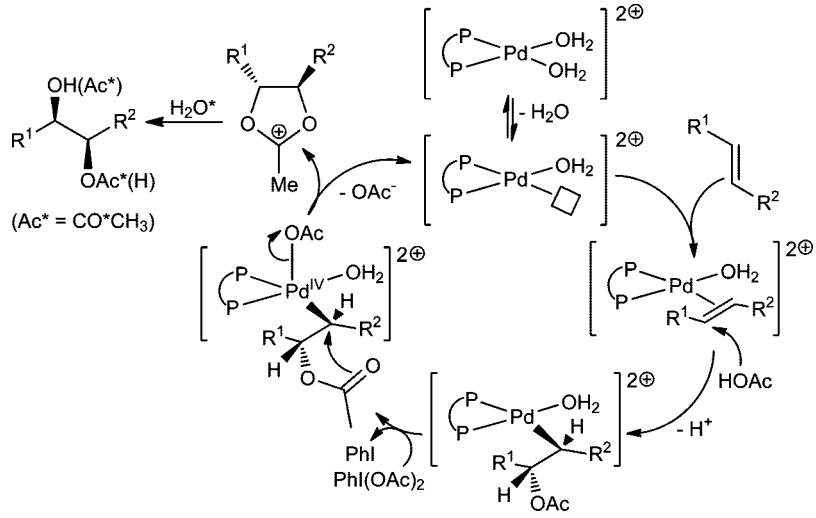
Scheme 233. Key *cis*-Aminopalladation Step in Intermolecular Amination of Homoallylic Alcohols



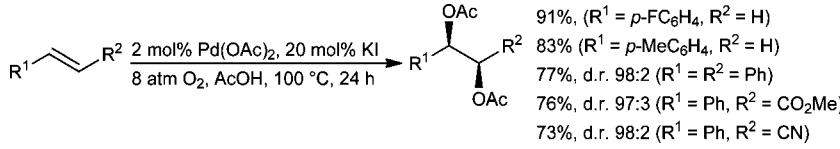
Scheme 234. Broad Scope Dioxygenation of Internal and Terminal Alkenes



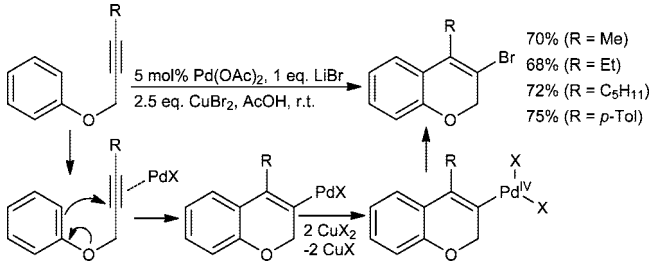
Scheme 235. Detailed Mechanism for Alkene Dioxygenation Using ^{18}O Labeling



Scheme 236. O_2-Mediated Pd-Catalyzed Diacetoxylation of Alkenes



Scheme 237. $Pd^{II}-Pd^{IV}$ Mechanism of Synthesis of 3-Bromo-*2H*-chromenes from Phenyl Propargyl Ethers

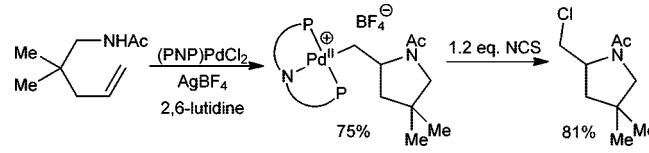


Reactions of *cis*- and *trans*-2-butene complexes were lower yielding but gave the respective *erythro*- and *threo*-3-dimethylamino-2-butanol with complete stereoselectivity. Although the author argued that a Pd^{II} to Pb^{IV} transmetalation is most likely involved, he also proposed an alternative Pd^{IV} mechanism (Scheme 229).

Intermolecular aminoacetoxylation of alkenes was first developed and probed by Stahl.[114] For steric reasons, terminal alkenes having an additional substituent in the allylic position give rise to only the *anti* diastereomer as detected by ^1H NMR spectroscopy (Scheme 230).

Reaction of *cis*-cinnamyl methyl ether confirmed that the aminopalladation proceeds with *cis* stereochemistry (Scheme 231). In order to explain the formation of *erythro*-products, the authors proposed a novel C−O reductive elimination from Pd^{IV} with inversion of stereochemistry, presumably via S_N2 displacement, which is known for Pt^{IV}.[315] It is interesting to note the difference with Stille's stereochemical investigations into the mechanism of $C(sp^3)-C(sp^3)$ cross-coupling (Scheme 72).[52]

Scheme 239. Isolation of the Aminopalladated Intermediate in Chloroamination of Unsaturated Acetamides



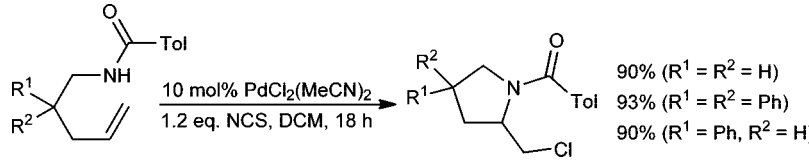
Sanford has reported an intermolecular amination of homoallylic alcohols leading to a range of 3-aminotetrahydrofurans with generally high diastereoselectivities (Scheme 232).[316]

On the basis of experiments with O_2 as the oxidant and the work of Stahl reported earlier,[114] Sanford concluded that the aminopalladation step proceeds with *cis*-stereochemistry (Scheme 233). Given the *trans*-stereochemistry of the product, this leaves just one alternative for the ring-closing event: direct ether-forming reductive elimination of a tethered alkoxide from Pd^{IV}. The C···OAc elimination from the acetate coordinated Pd^{IV} was not observed, most likely due to the lower basicity/nucleophilicity of AcO^- ligand.

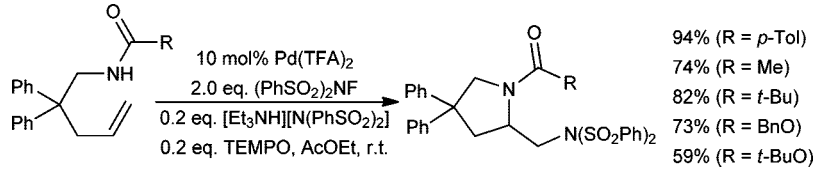
By employing cationic palladium diphosphine complexes with noncoordinating counterions, Song and Dong have demonstrated dioxygenation of alkenes.[317] The reaction is broad in scope and does not require terminal olefins and/or alkenes bearing a directing group (Scheme 234).

On the basis of experiments conducted in $H_2{}^{18}O$/anhydrous AcOH, the authors have drawn the following mechanism (Scheme 235).

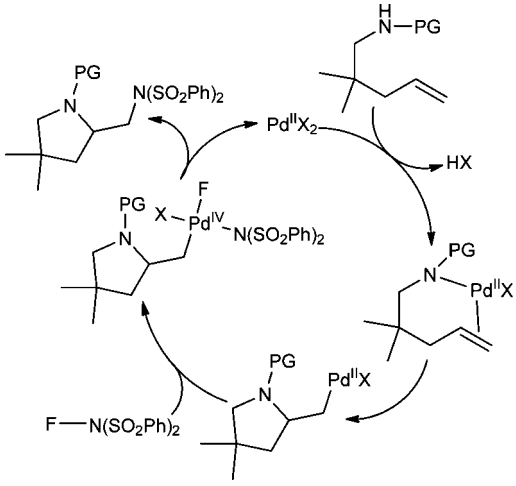
Scheme 238. Mild Intramolecular Chloroamination of Unsaturated Toluamides



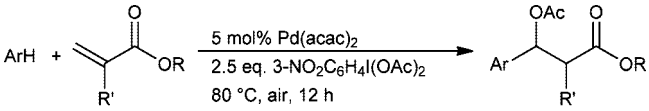
Scheme 240. Scope of Pd-Catalyzed Intermolecular Diamination



Scheme 241. Simplified Mechanism of Pd-Catalyzed Intermolecular Diamination



Scheme 242. Scope of 1,1-Difunctionalization of Activated Alkenes Leading to 3,3-Oxyarylpropionates



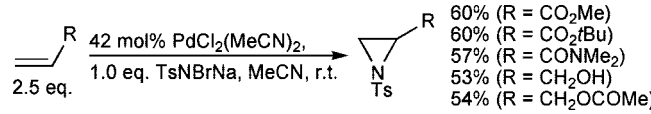
63% (Ar-H = C_6H_6, R = Me, R' = H)
25% (Ar-H = *p*-xylene, R = Me, R' = H)
65% (Ar-H = C_6H_6, R = *t*Bu, R' = H)
43% (Ar-H = C_6H_6, R = Bn, R' = H)
61% d.r. <2.5:1 (Ar-H = C_6H_6, R = Me, R' = Me)
67% d.r. <2.5:1 (Ar-H = C_6H_6, R = *t*Bu, R' = Me)

The group of Jiang developed a closely related highly stereoselective diacetoxylation of styrenes and other alkenes, but without the need for iodonium reagents.[318] The reaction appears to involve an unprecedented direct O_2-mediated Pd^{II} to Pd^{IV} oxidation with KI as additive (Scheme 236).

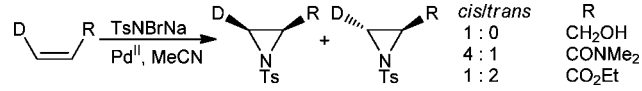
An early stoichiometric chloroacetoxylation study on (*Z*)-1-deuterio-l-decene using $PdCl_2/CuCl_2-LiCl$ system was published by Bäckvall.[319] Interestingly, he found that the cleavage of the palladium−carbon bond in the acetoxypalladated intermediate by $CuCl_2$ takes place with inversion. A more recent Pd^{II}-catalyzed asymmetric synthesis of chlorohydrins[320,321] and 1,2-dibromides[322] under similar conditions has also been reported by Henry.

Another example where a copper dihalide was implicated as oxidant of a Pd^{II} intermediate is the synthesis of 3-bromo-2*H*-chromenes reported by Perumal (Scheme 237).[323]

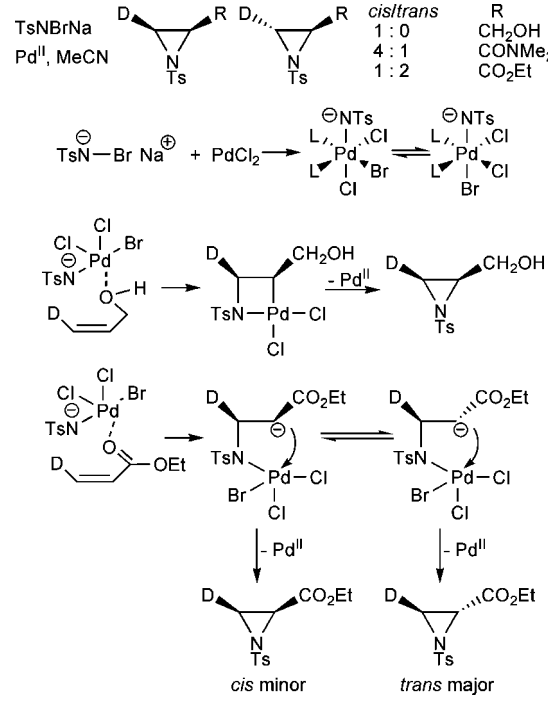
Scheme 244. Scope of Pd^{II}-Promoted Aziridination of Terminal Alkenes



Scheme 245. Dependence of Alkene Aziridination Stereochemistry on Substituents



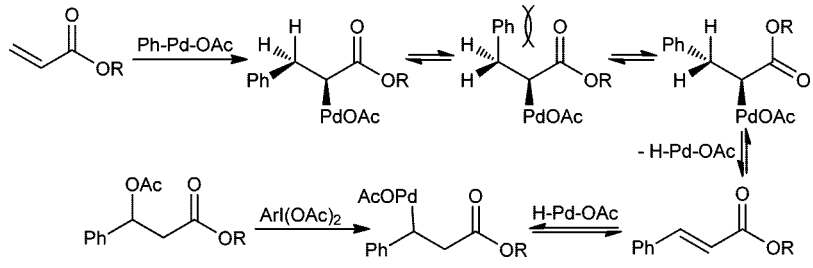
Scheme 246. Stereochemical Course of Alkene Aziridination Depending on the Coordinating Ability of Substituents



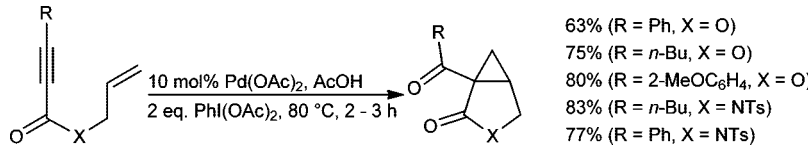
Michael developed a mild intramolecular haloamination of unactivated toluamides (Scheme 238).[324]

When using a tridentate PNP ligand (PNP = 2,6-bis(diphenylphosphinomethyl)pyridine), which prevents β-hydride elimination, the authors were able to isolate the intermediate palladium−alkyl complex and showed that it can be cleanly converted into the chloroamination product (Scheme 239).

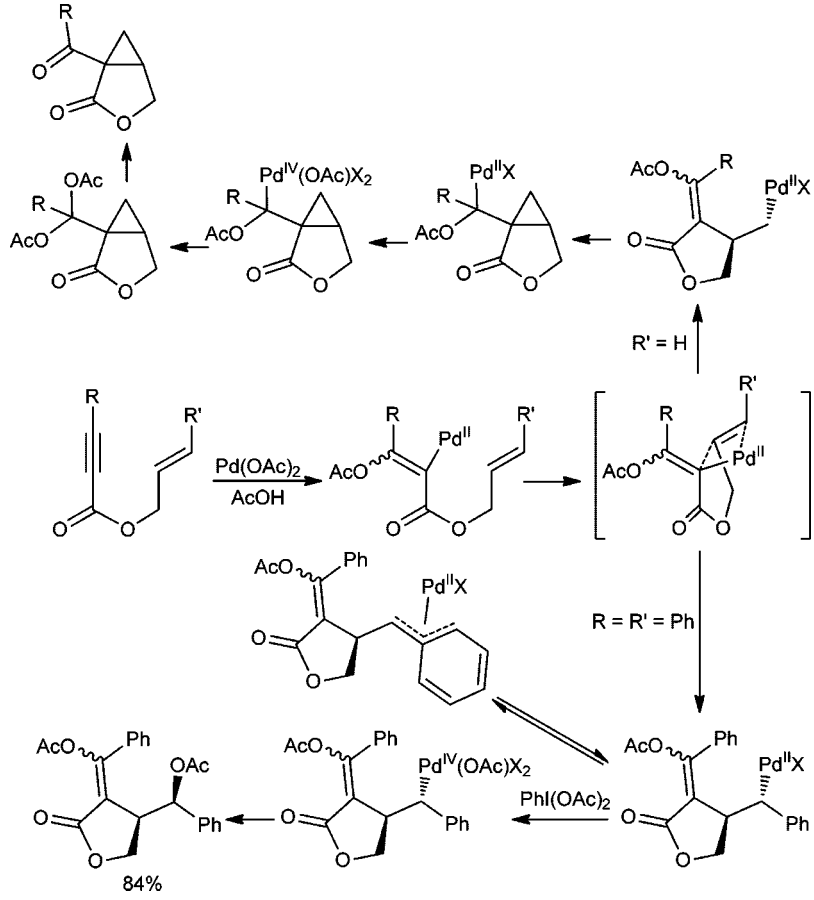
Scheme 243. Proposed Mechanism of 1,1-Difunctionalization of Activated Alkenes



Scheme 247. $Pd^{II}-Pd^{IV}$ Catalyzed 1,6-Enyne Cyclization Leading to Bicyclo[3.1.0]hexanes



Scheme 248. Two Alternative Mechanistic Pathways Leading to Isolated Products of $Pd^{II}-Pd^{IV}$ Catalyzed 1,6-Enyne Cyclization



Interestingly, attempted fluoroamination with $(PhSO_2)_2N-F$ led to the othogonally protected diamines (Scheme 240).[325]

A simplified catalytic cycle is shown below (Scheme 241).

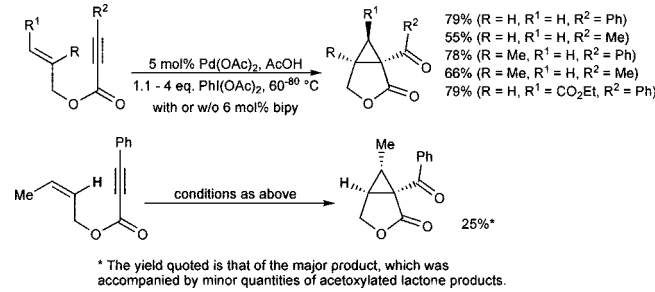
Further modification, in which the intermediate Pd^{IV} is intercepted by an electron-rich arene nucleophile leading to effective carboamination,[308] was discussed in the previous section.

A modular three-component 1,1-difunctionalization of activated alkenes was developed by Moran to access 3,3-oxyarylpropionate derivatives (Scheme 242).[326]

The mechanism of this transformation is proposed to proceed through electrophilic attack on Pd^{II} by the arene followed by Heck-type addition to the alkene. This Heck intermediate then undergoes β-hydride elimination, and the resulting Pd−H species re-adds to place the Pd at the benzylic site. Oxidation of Pd^{II} to Pd^{IV} by the hypervalent iodine reagent followed by displacement with acetate with inversion of configuration or reductive elimination then provides the observed products (Scheme 243).

Pd^{II}-promoted aziridination of olefins with bromamine-T to provide *N*-tosyl-2-substituted aziridines under mild conditions has been demonstrated by Branco (Scheme 244).[327]

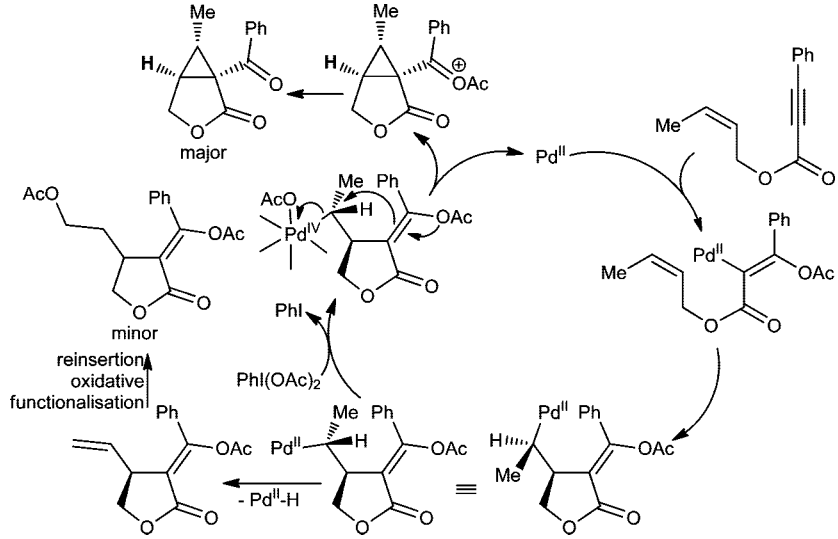
Scheme 249. Scope and Stereochemistry of Cyclization of 1,6-Enynes Bearing a Di- And Trisubstituted Double Bond



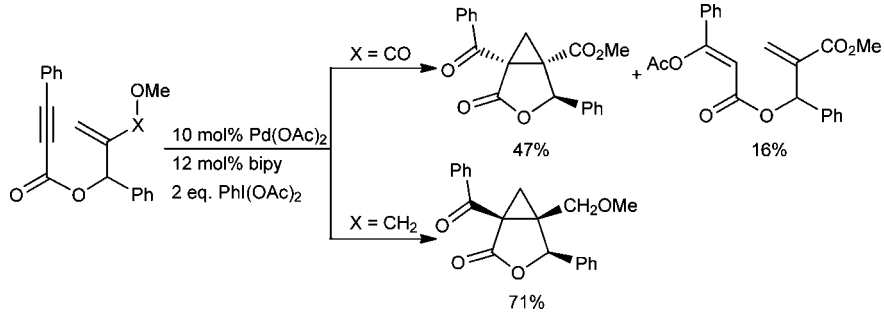
The study of reaction stereochemistry on deuterated olefins revealed interesting effects. *Cis*-deuteropropen-1-ol gave the *cis*-aziridine exclusively. However, aziridination of *cis-N,N*-β-deuterodimethylacrylamide was much less selective (*cis*/*trans* = 4:1), and for *cis*-β-deuteroethyl acrylate, the *trans*-aziridine was the major product (Scheme 245).

The difference has been ascribed to different coordinating abilities of the R-groups. Tightly bound OH leads exclusively to the *cis*-aziridine; the weakly bound ester carbonyl leads to certain ionic character in which some rotation about the central C−C bond becomes possible (Scheme 246).

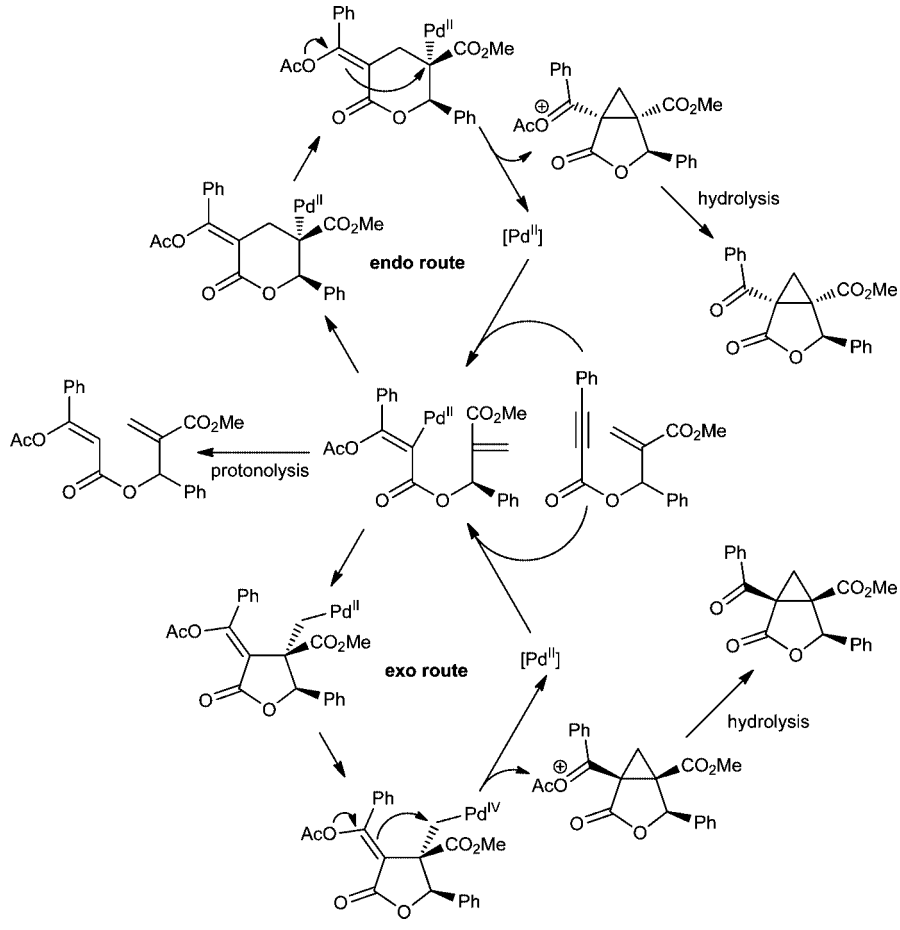
Scheme 250. Detailed Stereochemical Course of Cyclization of *cis*-Disubstituted 1,6-Enynes



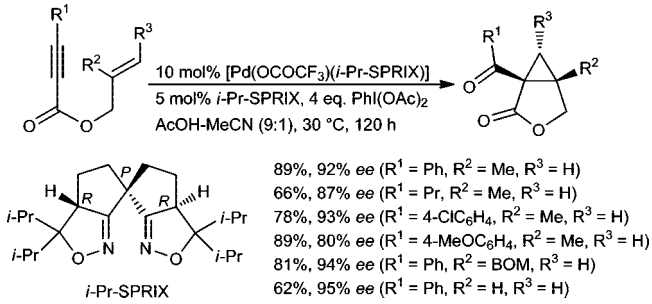
Scheme 251. Dependence of 1,6-Enyne Cyclization Outcome on the Alkene Functionality



Scheme 252. Two Alternative Catalytic Cycles for Cyclization of Functionalized 1,6-Enynes



Scheme 253. Scope of the First Enantioselective $Pd^{II}-Pd^{IV}$ Catalyzed 1,6-Enyne Cyclization



Tse[328] and Sanford[329] reported, practically simultaneously, two closely related $Pd^{II}-Pd^{IV}$ catalyzed cyclizations of 1,6-enynes leading to bicyclo[3.1.0]hexanes. The method of Tse gives good isolated yields of cyclized products containing a new keto carbonyl group (Scheme 247).

The key steps in one of the most plausible mechanisms are acetoxypalladation of the triple bond and alkene insertion to close the 5-membered ring. Since no β-hydride elimination product was detected, the closure of the cyclopropane ring is clearly rapid, followed by $PhI(OAc)_2$ oxidation to a Pd^{IV} intermediate. Finally, C−O bond formation and geminal diacetate solvolysis furnish the isolated bicyclo[3.1.0]hexane product. When the alkene carries a phenyl group, the reaction takes a different course. Because of η^3-benzylic stabilization and partially also because of steric hindrance of the phenyl group, a Pd^{IV} intermediate is produced before the second insertion event. Finally, selective C−O reductive elimination takes place with inversion of stereochemistry to give a monocyclic diacetate (Scheme 248).

Apart from the types of substrates studied by Tse,[328] Sanford has also focused more on enynes in which the alkene is 1,1- and 1,2-disubstituted (Scheme 249).[329]

From the outcome of experiments with *cis*- and *trans*-disubstituted enynes, it is apparent that the key cyclopropane-forming step could proceed via S_N2-type attack by the electron-rich tethered olefin on the Pd^{IV}-bound carbon to afford cyclopropane product with inversion of configuration. On the basis of these observations and identification of minor byproducts, the following mechanistic scheme was proposed (Scheme 250).

Further insights into the scope and mechanism of this transformation were reported later.[330]

An interesting dichotomy in the reactivity of substituted 1,6-enyne derivatives was discovered by Tong.[331] Depending on the electronic nature of the terminal alkene substituent, either the *trans*−*cis* isomer or the *all-cis*-isomer could be obtained as the major product (Scheme 251).

In order to explain the diference, a key 5-exo versus 6-endo alkene carbopalladation event was proposed for electron-rich and electron-poor alkenes, respectively (Scheme 252).

Interestingly, Sasai has managed to carry out the cyclization in a highly enantioselective manner on a number of substrates using a spiro-bis(isoxazoline)-type ligand and $Pd(CF_3CO_2)_2$ (Scheme 253).[332] The study represents the first example of asymmetric reaction proceeding through a Pd(IV) intermediate.

4. Summary

Chemistry exploiting the $Pd^{II}-Pd^{IV}$ catalytic manifold has enabled many novel reactions to be developed, which are often highly orthogonal to those possible within the more traditional, well-known Pd^0-Pd^{II} catalytic mode. However, there are still some drawbacks that limit the use of these novel Pd^{IV} methodologies. The low stability of Pd^{IV} intermediates means that poor selectivity is sometimes observed in C−C or C−X bond-forming steps. The isolated yields of products can be diminished because a mixture of similarly functionalized or mono- and oligofunctionalized products are formed. Contrary to traditional palladium "Pd^0-Pd^{II}" cross-coupling chemistry, where ppm-level Pd loadings are not exceptional, $Pd^{II}-Pd^{IV}$ catalysis commonly requires 2−20 mol % of a Pd^{II} catalyst (usually 10 mol %). Therefore, turnover numbers and frequencies need to be improved upon in the future, and there is clearly an opportunity here for new Pd^{IV} catalyst design strategies. Also, several equivalents of expensive additives, reagents, and oxidants are often required (e.g., silver and iodonium salts), and while this is not limited to the catalytic chemistry of Pd^{IV} per se, it is interesting to note that excess oxidant is often required to access the $Pd^{II}-Pd^{IV}$ cycle. Under reducing conditions (traditional cross-coupling), a Pd^0-Pd^{II} cycle is likely to predominate, and it is important that this difference is recognized.[333] In general, functional group tolerance is very broad in Pd^{IV} processes, and there are opportunities for researchers to develop generally applicable synthetic protocols based on Pd^{IV} intermediates. The opportunity to exploit enantioselective $Pd^{II}-Pd^{IV}$ transformations is another intriguing possibility warranting further exploration.

One ultimate challenge facing the Pd^{IV} field is to selectively activate sp^3 C−H and C−C bonds, without the need for proximal directing groups (e.g., imino or amino substituents). To this end, it might be interesting to explore the scorpinate-type ligands, and variants thereof, as an appropriate starting point.

When collating the references for this review, it became evident that some of the proposed mechanisms invoking Pd^{IV} intermediacy are not strongly supported by experimental evidence. While speculation about the possible mechanisms is no doubt useful for the community to debate, comprehensive experimental mechanistic studies, complemented by computational studies,[334] can reveal important details. The independent studies reported by Canty, Catellani, Echaverren, Milstein, Ritter, and Sanford are particularly noteworthy in this respect.

Finally, after the completion of this review paper, three further reviews have appeared in the literature, either discussing Pd^{IV} chemistry explicitly[335,336] or as part of a wider context[337] in transition metal catalyzed C−H functionalization processes.

5. References

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