

High-Oxidation-State Palladium Catalysis: New Reactivity for Organic Synthesis

Kilian Muñiz*

coupling reactions · elimination ·
homogeneous catalysis · oxidation states · palladium

Recent years have seen the rapid development of a new field of palladium catalysis in organic synthesis. This chemistry takes place outside the usually encountered $\text{Pd}^0/\text{Pd}^{\text{II}}$ cycles. It is characterized by the presence of strong oxidants, which prevent further palladium(II)-promoted reactions at a given point of the catalytic cycle by selective metal oxidation. The resulting higher-oxidation-state palladium complexes have been used to develop a series of new synthetic transformations that cannot be realized within conventional palladium catalysis. This type of catalysis by palladium in a higher oxidation state is of significant synthetic potential.

1. Introduction

During the past few decades, reductive elimination from defined palladium(II) catalysts has enabled the development of seminal C–C and carbon–heteroatom bond-forming reactions.^[1,2] All these catalytic cycles involve $\text{Pd}^0/\text{Pd}^{\text{II}}$ states, and usually no other palladium oxidation states are involved.

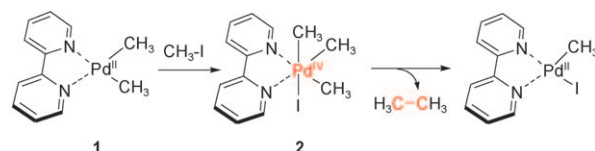
In contrast to $\text{Pd}^0/\text{Pd}^{\text{II}}$ catalysis, potential $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ cycles received little attention over a long period of time. Despite numerous comments on the potential involvement of Pd^{IV} intermediates in catalysis and synthesis, no definitive evidence was found for their existence.^[3] The strongest support for the feasibility of such cycles was provided by Canty and co-workers, who showed that the dimethylpalladium complex **1** readily undergoes oxidative insertion into methyl iodide to generate the trimethylpalladium(IV) complex **2**, which was subsequently isolated and characterized by X-ray crystallography (Scheme 1).^[4]

The structural chemistry of isolable palladium(IV) complexes of this type are characterized by the presence of neutral dinitrogen donor ligands, such as bipyridine, and by the presence of a large number of carbon-based ligands. Variations on this structural theme have led to a variety of low-spin d^6 Pd^{IV} complexes with benzyl, allyl, benzoyl, allenyl,

and propargyl substituents, among others.^[5–7] As a consequence of the carbon-rich coordination sphere of isolated Pd^{IV} complexes, C–C bond formation is typically their dominant reaction.

For the parent complex **2**, a detailed study suggested that iodide dissociation preceded ethane formation. Hence, this latter event occurs from a cationic pentacoordinated intermediate and was suggested to involve multiple steps including an α -agostic C–H interaction.^[5,8]

Palladium(IV) complexes have great potential for the development of new transition-metal-catalyzed reactions beyond C–C bond-forming processes owing to their inherent ability to accommodate up to four different groups for participation in subsequent reductive elimination processes. One of the key issues for catalytic transformations is the accessibility of a higher oxidation state of palladium at a given stage of the catalytic cycle and under given reaction conditions. This point is especially significant for aryl and alkyl palladium complexes, the redox potential of which is lower than that of simple palladium(II) salts. Hence, the inclusion of strong oxidants and the resulting change in the catalyst oxidation state have led to the development of unprecedented organic transformations that are not possible under conventional Pd^{II} catalysis. Furthermore, the domi-



Scheme 1. Pioneering synthesis of $[(\text{bipy})\text{Pd}(\text{Me})_3]$ (**2**; bipy = bipyridine) by Canty and co-workers, and the characteristic reductive elimination from this complex with the formation of a C–C bond.

[*] Prof. Dr. K. Muñiz^[†]
Institut de Chimie, UMR 7177, University of Strasbourg
4 rue Blaise Pascal, 67000 Strasbourg (France)
E-mail: muniz@unistra.fr

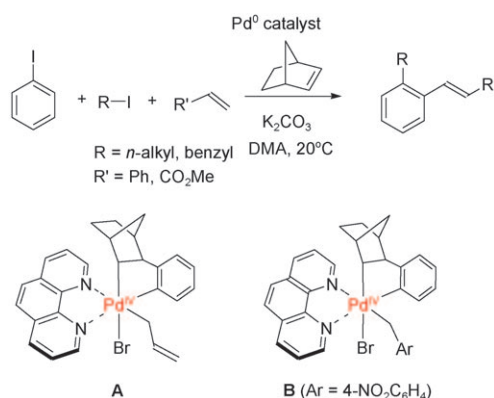
[†] New address: Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans, 16, 43007 Tarragona (Spain)
E-mail: kmuniz@iciq.es

nance of β -hydride elimination or the potential drawback of palladium-black deposition from Pd^{II} species would not be expected for Pd^{IV} catalysis. Also, process optimization by fine-tuning of the ligand is often necessary for reductive elimination from Pd^{II} complexes.^[2b] In contrast, this fine-tuning should not be a major concern for palladium catalysts in a higher oxidation state as such complexes should undergo reductive elimination more readily to stabilize the metal.

In this Minireview, recent progress in the area of Pd^{IV} catalysis is reviewed with a focus on the development of new organic transformations, in particular C–X bond formation.^[9]

2. C–C Coupling

The ethane formation from the Pd^{IV} complex **2** (Scheme 1) is the first demonstration of its type, and in general, reductive elimination to form a C–C bond represents the classical transformation for palladium(IV). It was subsequently observed for a variety of stoichiometric transformations involving $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$, $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$, and $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^2)$ coupling.^[5–7] The development of palladium(IV) catalyst states as intermediates in C–C bond-forming reactions began with the Catellani reaction (Scheme 2).^[10] This seminal reaction is based on the use of norbornene as a shuttle for the construction of up to three new bonds in a domino



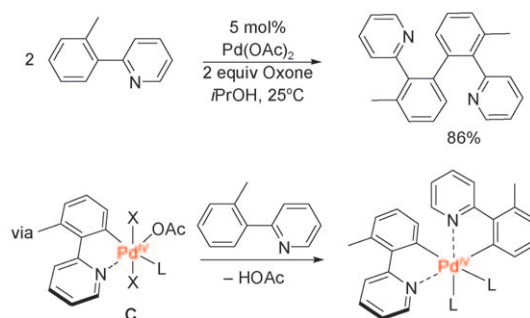
Scheme 2. Catellani reaction and observed Pd^{IV} complexes **A** and **B** with relevance to catalysis. DMA = dimethylacetamide.



Kilian Muñiz studied chemistry at the Universities of Hannover (Germany) and Oviedo (Spain), as well as at Imperial College London (UK). He obtained a doctorate in organic chemistry from the RWTH Aachen (Germany) in 1998, and then worked with Ryoji Noyori at Nagoya University (Japan) as an AvH/JSPS Postdoctoral Fellow (1999–2000). Following his habilitation at Bonn University (Germany) from 2001 to 2005, he accepted a professorship in catalysis at Strasbourg University (France). His current position is at the ICIQ Research Centre in Tarragona (Spain).

sequence.^[11] A proposed σ -norbornyl Pd^{IV} intermediate is central to the overall success of the reaction. Its existence was not proven outright, but derived from the isolation of phenanthroline-stabilized allyl and benzyl model compounds, such as **A** and **B**.^[12] However, some care must be exercised in assuming the presence of carbon-rich Pd^{IV} intermediates wherein two aryl coupling partners are concerned, for a study by Echavarren and co-workers provides evidence for an alternative mechanism of transmetalation between two monomeric Pd^{II} complexes.^[13]

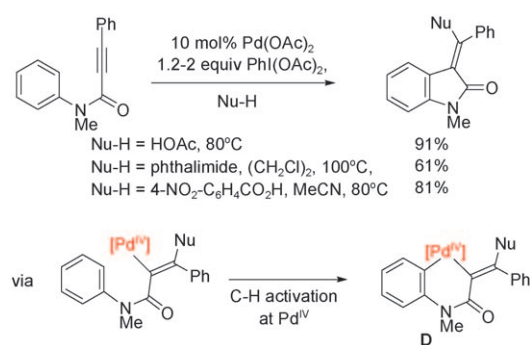
Hypervalent iodine reagents have been identified recently as suitable oxidants for catalytic C–C bond formation. These reagents enable selective metal oxidation at a given stage of the catalytic cycle, with a high preference for σ -aryl palladium intermediates. An authoritative review of developments in this field of research appeared recently.^[14] The presence of Oxone as an oxidant also enabled a biaryl synthesis through two consecutive C–H activation events.^[15] A series of control experiments showed that the second C–H activation proceeded on the Pd^{IV} complex **C** (Scheme 3). This finding



Scheme 3. C–C bond formation involving C–H activation at a Pd^{IV} center.

increases the synthetic potential of electrophilic palladium catalysis and also highlights the possibility of developing further organometallic reactions to take place at Pd^{IV} centers prior to the reductive elimination.

The efficiency of palladium(IV) complexes for C–H activation and reductive $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^2)$ bond formation was subsequently exploited for the construction of heterocyclic compounds through domino processes (Scheme 4). Following



Scheme 4. C–H activation at Pd^{IV} centers in domino catalysis.

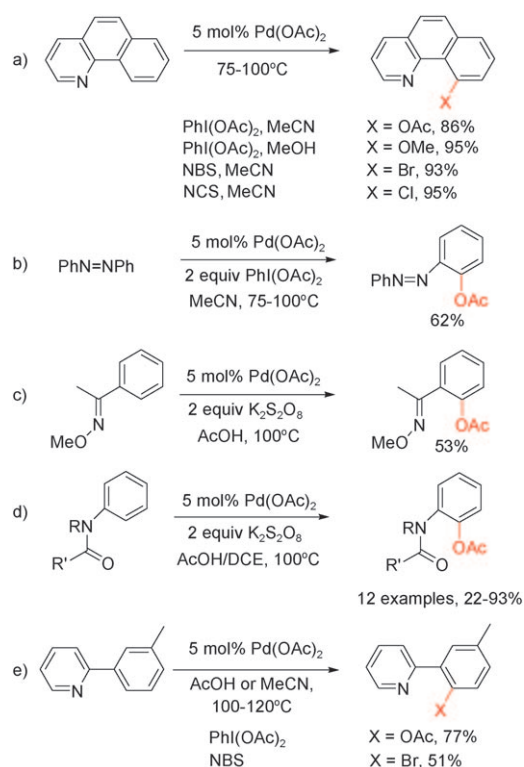
the well-established nucleopalladation of an alkyne with a palladium(II) catalyst, the resulting vinyl–palladium intermediate is oxidized rapidly to a Pd^{IV} complex in the presence of $\text{PhI}(\text{OAc})_2$. At this stage, in a step reminiscent of the process described in Scheme 3, Pd^{IV} initiates an intramolecular C–H activation of the neighboring aryl ring to give intermediate **D**. Reductive elimination then generates the oxindoline derivatives and regenerates the original Pd^{II} oxidation state. This reaction was shown to be general for a variety of differently substituted starting materials as well as for several carboxylate nucleophiles other than acetate.^[16] Michael and co-workers recently demonstrated the feasibility of intermolecular aromatic C–H activation at a Pd^{IV} center, following an intramolecular aminopalladation and metal oxidation.^[17]

3. Aryl–Heteroatom Coupling

3.1. C–O and C–X Bond Formation

The involvement of Pd^{IV} had been postulated for several transformations involving C–O bond formation, but the molecular basis for these processes remained unclear for a long time.^[18] Yoneyama and Crabtree reported that the combination of a palladium(II) catalyst and iodosobenzene diacetate led to the catalytic C–H activation of an arene, followed by acetoxylation.^[18c] This observation led Sanford and co-workers to develop a set of novel catalytic reactions for the functionalization of aromatic compounds. The underlying versatile strategy is based on chelation-controlled C–H activation to provide palladacycles. After carbopalladation, the metal center is oxidized by a strong oxidant in the reaction mixture, and carbon–heteroatom bond formation occurs by reductive elimination from a palladium(IV) intermediate.^[19,20] The general reactivity pattern is shown for benzo[*h*]quinoline (Scheme 5a).^[21] With the oxidant iodosobenzene diacetate, $\text{PhI}(\text{OAc})_2$, the corresponding acetoxylation product is formed in acetonitrile, whereas selective alkoxylation reactions are possible in alcoholic solvents. The C–H functionalization of single arenes proceeds with high selectivity^[22] for the *ortho* position; thus, this reaction provides unprecedented access to higher functionalized aromatic compounds, such as 2-acetoxiazobenzene (Scheme 5b). Replacement of the oxidant $\text{PhI}(\text{OAc})_2$ with a combination of Oxone and acetic acid gave a system of comparable efficiency for the *ortho* acetoxylation of acetophenone and aniline derivatives (Scheme 5c,d).^[23,24] The synthetically important regioselectivity issue was addressed by Kalyani and Sanford, who showed that for 3-substituted arenes, as in Scheme 5e, the functionalization proceeds with complete selectivity in favor of the 1,2,4-trisubstituted product over its 1,2,3-trisubstituted isomer.^[25]

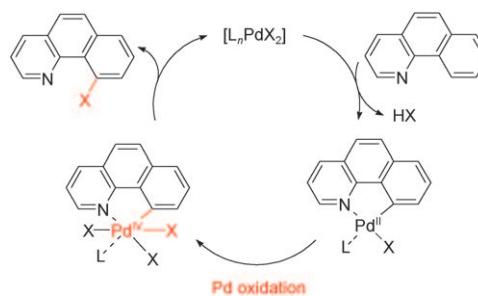
The same approach can be used for the introduction of halogen atoms with strong oxidants, such as PhICl_2 , NCS, or NBS. PhICl_2 , in particular, has a long history in the chlorination of $\text{C}(\text{sp}^2)$ atoms via presumed Pd^{IV} intermediates.^[26] For example, in one study, an oxidized trichloropalla-



Scheme 5. Catalytic C–O and C–X bond formation in Pd^{IV} intermediates. DCE = dichloroethane, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

dium(IV) pincer complex was detected by NMR spectroscopy, but the exact reduction product could not be identified.^[26e]

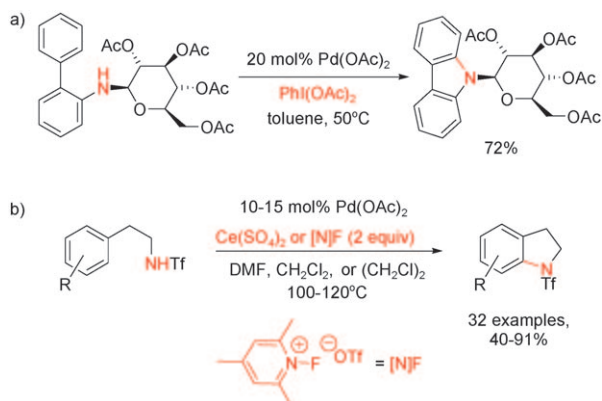
Halogenation reactions with palladium catalysts are usually comparable to palladium-catalyzed acetoxylation with $\text{PhI}(\text{OAc})_2$. For example, selective bromination and chlorination of benzo[*h*]quinoline was observed with NBS and NCS, respectively (Scheme 5a). Suitable directing substituents enable highly selective palladium-catalyzed *ortho*-halogenation reactions.^[27] Again, when substituted arene substrates are used, the 1,2,4-trisubstituted product is formed selectively (Scheme 5e).^[28] The catalytic cycle for chelation-controlled position-selective aryl oxidation is believed to proceed through palladacycle formation followed by palladium oxidation to Pd^{IV} and subsequent reductive carbon–heteroatom bond formation (Scheme 6).



Scheme 6. Suggested catalytic cycle for palladium(IV)-catalyzed aryl oxidation.

3.2. C–N Bond Formation

A catalytic intramolecular aryl–nitrogen bond formation was developed for carbazole synthesis from various 2-amino-biphenyls.^[29] This strategy is again based on regioselective C–H bond activation by palladium(II), whereby the aniline group is used as a tether to give a trinuclear palladium(II) complex. Selective metal oxidation with $\text{PhI}(\text{OAc})_2$ to a Pd^{IV} intermediate readily induces intramolecular C–N bond formation even at room temperature. This process is formally a palladium(IV)-based variant of the Buchwald–Hartwig C–N coupling.^[30,31] Its synthetic usefulness was demonstrated by the preparation of an *N*-glycosyl carbazole (Scheme 7a).

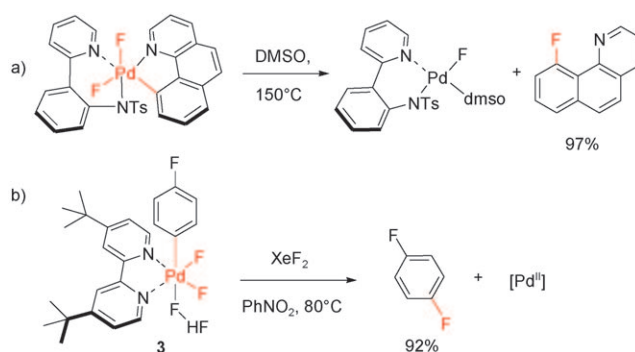


Scheme 7. Palladium(IV)-catalyzed carbazole and indoline syntheses. DMF = dimethylformamide, Tf = trifluoromethanesulfonyl.

Yu and co-workers recently described another unique aryl–nitrogen bond-forming reaction on the basis of high-oxidation-state palladium catalysis. In this case, *N*-trifluoromethanesulfonyl 2-aryl ethylamines underwent oxidative cyclization from a high-oxidation-state palladium catalyst to the corresponding indolines (Scheme 7b). A cationic fluoroorganic compound is used as a two-electron oxidant to form the Pd^{IV} intermediate. A sequential single-electron oxidation with $\text{Ce}(\text{SO}_4)_2$ is also feasible; this alternative process presumably proceeds via a Pd^{III} intermediate.^[32]

3.3. C–F Bond Formation

Additional work has recently dealt with the investigation of potential pathways for the reductive elimination of aryl–fluorine bonds from palladium(IV) complexes, which may constitute a useful alternative in view of the extreme difficulty of realizing this transformation within conventional $\text{Pd}^0/\text{Pd}^{\text{II}}$ systems.^[33] The feasibility of clean palladium(II) oxidation using xenon difluoride was first demonstrated by Vigalok and co-workers in their seminal synthesis of palladium difluoride complexes,^[34] and it was recently employed in the synthesis of new palladium(IV) difluoride complexes (Scheme 8).^[35,36] These compounds are capable of causing thermally or oxidatively induced reductive aryl–fluorine bond formation. In the latter case, xenon difluoride can be replaced with NBS;



Scheme 8. Reductive elimination from monomeric Pd^{IV} complexes with the formation of C–F bonds. DMSO = dimethyl sulfoxide, Ts = *p*-toluenesulfonyl.

the authors suggested that the role of the oxidant is to react with the FHF ligand. Not only is the reductive formation of C–F bonds in these reactions remarkable in itself, the isolation and structural characterization of **3**, which contains an aryl ligand without a supportive chelating group, is a striking accomplishment.^[37]

4. Mechanisms of Reductive Elimination from σ -Aryl Palladium(IV) Catalysts

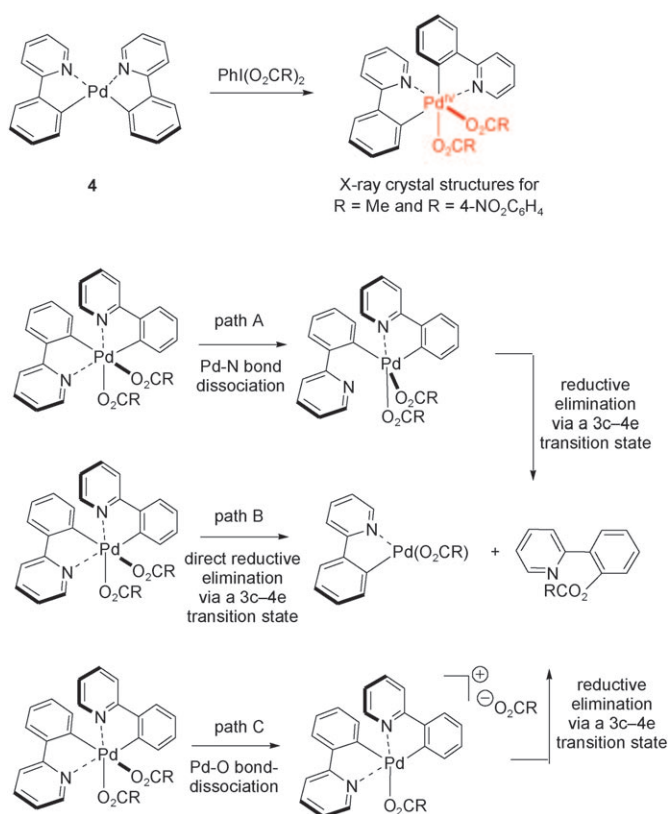
In principle, reductive elimination from σ -aryl palladium(IV) intermediates to produce aryl–aryl and aryl–X bonds is understood to proceed via a three-center, four-electron (3c–4e) transition state (Figure 1).

Although the geometry of the coordination spheres of the complexes involved differs significantly, the process itself may be comparable to related reductive elimination from Pd^{II} complexes.^[2] In the latter case, the precise mechanistic picture of the palladium(IV) complexes is not yet fully understood and may still provide mechanistic surprises. This potential is primarily a result of the fact that palladium(IV) complexes display too low a stability to allow structure isolation and advanced mechanistic studies. Palladium(IV) catalysis for aryl oxygenation is an exception to this rule. Sanford and co-workers isolated monomeric palladium(IV) complexes relevant to carbon oxygenation (Scheme 9).^[38,39] Treatment of the chelated bisaryl palladium(II) complex **4** with hypervalent iodosobenzene reagents led to stable isolable palladium(IV) complexes that were characterized by X-ray structure analysis.



Figure 1. Three-center, four-electron transition state for reductive elimination from σ -aryl palladium(IV) intermediates in aryl–aryl or aryl–X coupling reactions.

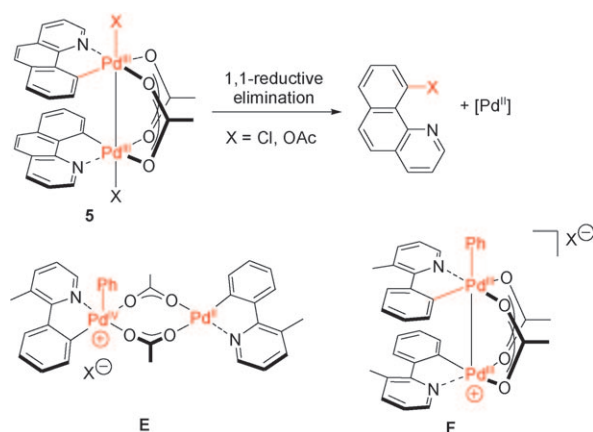
The subsequent reductive elimination may proceed through three alternative pathways (Scheme 9): On the basis of experimental results, it was initially proposed that chelate dissociation in a preequilibrium was followed by reductive elimination from a neutral pentacoordinate Pd^{IV} complex



Scheme 9. Synthesis of stable Pd^{IV} complexes relevant to C–O bond formation, and mechanistic alternatives for aryl–oxygen bond formation.

(path A).^[38] In contrast, a theoretical study predicted that reductive elimination occurred directly from the original octahedral Pd^{IV} complex (path B).^[40] A recent detailed study led Sanford and co-workers to conclude that the actual mechanism involves position-selective anion cleavage (path C).^[39] This anion dissociation is also the basis for the observed chemoselectivity, because in the presence of an excess of added anion, the competing C–C bond formation becomes the dominant pathway. This latter process appears to proceed directly from the parent octahedral Pd^{IV} complex without a pre-equilibrium.

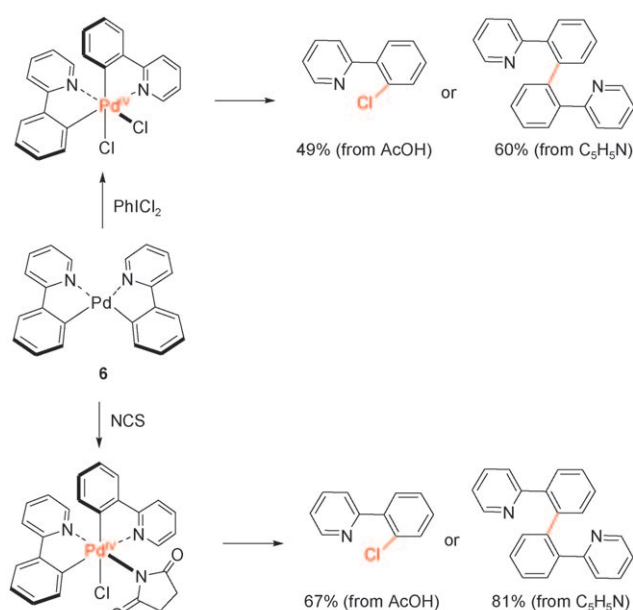
Recent results reported by Powers and Ritter suggest that high-oxidation-state palladium catalysis might also be possible with neutral dimeric palladium(III) complexes (Scheme 10).^[41] On the basis of kinetic data and orbital geometry, a concerted 3c–4e reductive elimination from one of the two metal centers was proposed in which one electron from each Pd^{III} atom is involved. This process generates a mixture of palladium(II) compounds of unknown composition. It was shown that this mixture could be reconverted into the dimer **5**, and a catalytic reaction was obtained by using NCS as the chlorine source. For catalytic chlorination, a reaction order of 1.0 was determined for a related bimetallic palladium complex with a bridging dicarboxylate group, which was interpreted in favor of the involvement of an aggregated Pd^{III} intermediate.^[41,42] An extensive investigation on the course of catalytic aryl–aryl coupling reactions of 2-



Scheme 10. A stable dimeric Pd^{III} complex **5** for reductive C–X bond formation, and dimeric palladium catalysts for aryl–aryl coupling reactions.

aryl pyridines with hypervalent iodine reagents^[14] led Deprez and Sanford to conclude that a bimetallic palladium species in a high oxidation state was formed as an intermediate. Depending on the bonding situation between the palladium centers, the catalyst state prior to reductive elimination can be formulated as a mixed-valent Pd^{IV}/Pd^{II} species **E** or as a symmetrical Pd^{III}/Pd^{III} dimer **F**.^[43]

Another investigation of isolated palladium(IV) complexes revealed that reaction conditions may influence competing pathways during the course of reductive elimination from these complexes. Oxidation of the diaryl palladium complex **6** with PhICl₂ gave the expected dichloropalladium(IV) complex, whereas oxidation with NCS led to the formation of a mixed-anion Pd^{IV} complex (Scheme 11). With both complexes, reductive C–Cl bond formation proceeds best under polar conditions in acetic acid. In contrast,



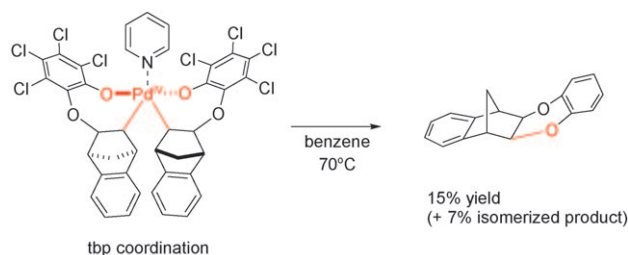
Scheme 11. Synthesis of stable chloropalladium(IV) complexes and reductive elimination from these complexes.

pyridine induces clean carbon–carbon bond formation when used as the solvent.^[44] This observation is in good agreement with the occurrence of a predissociation step for C–X bond formation, as discussed for related acetoxylation reactions.^[39]

5. Alkyl–Heteroatom Coupling

5.1. Alkyl Oxygenation

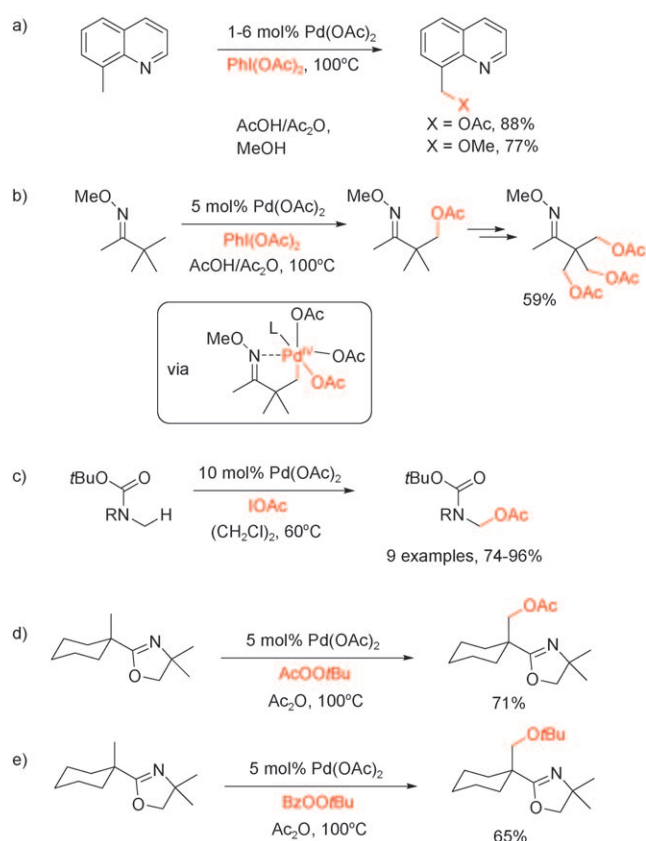
In contrast to aryl–heteroatom bond-forming reactions, there is little structural information available on the putative palladium(IV) intermediates involved in the oxidation of alkyl groups. An important exception was presented by Canty et al., who reported that the interaction of complex **1** with diphenyl diselenide resulted in clean oxidation to *trans*-[(bipy)Pd(SePh)₂Me₂]. This Pd^{IV} complex was characterized by X-ray crystallography and underwent carbon–selenium bond formation in solution.^[45a] Related complexes derived from the oxidation of dimethylpalladium(II) compounds with diaroyl peroxides were detected by NMR spectroscopy; however, reductive elimination led to C–C coupling.^[45b] A further example of reductive elimination was demonstrated by Yamamoto et al. They were able to isolate palladium(IV) complexes from stoichiometric alkene oxidation reactions using tetrachloro-1,2-benzoquinone and a palladium(0) precursor.^[46] Thermal treatment of an isolated Pd^{IV} complex then led to the expected bisoxygenated compound, among other products (Scheme 12).^[47] Although the strained cyclic carbon



Scheme 12. Reductive alkyl–oxygen bond formation from a stable Pd^{IV} complex. tbp = trigonal-bipyramidal.

framework of the alkyl ligands cannot serve as a general model for alkyl substituents at palladium, this reaction proved that the reductive oxygenation of alkyl groups is indeed a feasible pathway for alkyl palladium(IV) complexes. It also lent weight to Bäckvall's earlier proposal of palladium(IV) intermediates in stoichiometric oxidation reactions of alkenes.^[48]

In an extension of their studies on aromatic C–H functionalization,^[21] Sanford and co-workers described several examples of C–O bond formation as a result of aliphatic C–H activation.^[21,49] These reactions again rely on metal-coordinating groups for regioselective C–H activation at a Pd^{II} center prior to metal oxidation with PhI(OAc)₂. For example, 8-methylquinoline undergoes clean acetoxylation or methoxylation depending on the solvent (Scheme 13a). As well as pyridine groups, oxime ethers are particularly useful



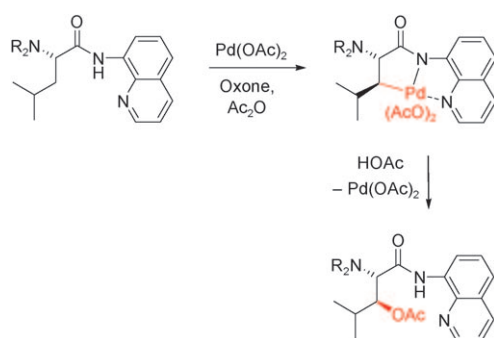
Scheme 13. Catalytic oxidative alkyl–oxygen bond formation. Bz = benzoyl.

(Scheme 13b). The activation of primary C–H groups in the β position with respect to the oxime nitrogen atom is the preferred pathway for the chelation-controlled C–H oxidation. Depending on the relative amount of the oxidant, each substrate molecule could undergo up to three C–O bond-forming events.

An alternative approach by Yu and co-workers is based on the use of *N*-methylcarbamates to direct C–H activation and depends upon stabilization of the resulting alkyl palladium intermediate through chelate formation. This oxidation is an important entry to masked carbonyl compounds.^[50] The same research group had earlier described the use of oxazolines as directing groups for cyclometalation.^[51–53] Under the strongly oxidizing conditions of these reactions, the functionalization of the alkyl–palladium bond is believed to proceed via a Pd^{IV} intermediate. In the case of iodination, a mixture of iodine and iodosobenzene diacetate served as a precursor to IOAc. This compound is required to generate mixed palladium iodide acetate from palladium diiodide, which is formed after the construction of two C–OAc bonds and is unreactive for further C–H activation (Scheme 13c).^[51] A further procedure developed by the same research group involves the use of acetyl *tert*-butyl peroxide for palladium oxidation (Scheme 13d). The authors suggest the formation of a Pd^{IV} complex upon oxidation by the peroxyester. Control experiments on an isolated trimeric palladium complex produced through C–H activation indicated that acetic anhydride is

crucial for subsequent reactivity. In general, monoacetoxylation reactions were encountered, as in the example in Scheme 13d. An interesting observation was made when the oxidation was carried out with benzoyl *tert*-butyl peroxide. In this case, selective ether formation was observed (Scheme 13e).^[52] Although the basis for this switch in anion incorporation is not yet understood, these two examples show that minor changes can have a significant effect on reactivity in palladium(IV) chemistry.

Corey and co-workers carried out a Pd^{II}/Pd^{IV}-catalyzed acetoxylation at an aliphatic position in a synthesis of highly functionalized amino acid derivatives (Scheme 14). In this sequence, regioselective aliphatic C–H activation with chelation-assisted palladacycle formation was followed by metal oxidation. Oxone was employed as the oxidant of choice in the presence of acetic acid anhydride. The resulting Pd^{IV} intermediate undergoes diastereoselective reductive elimination to give the product of alkyl oxidation.^[54]

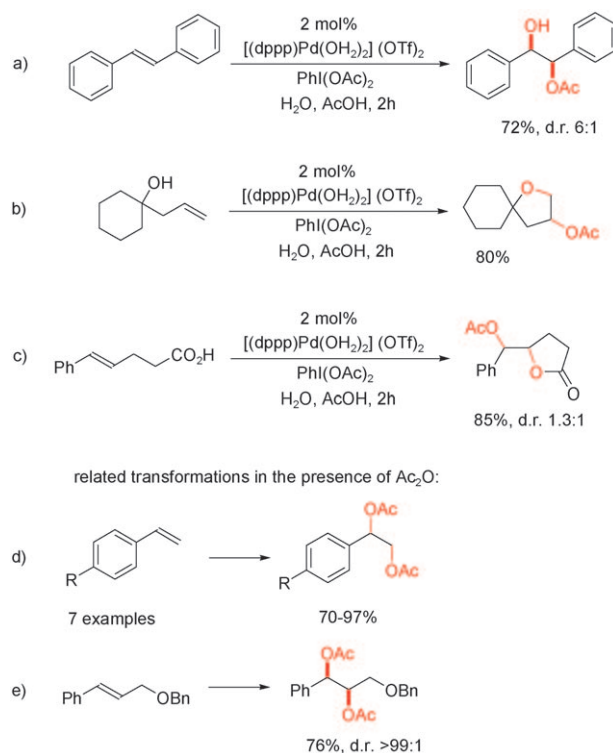


Scheme 14. Palladium(IV)-catalyzed amino acid functionalization. R₂ = phthaloyl.

5.2. 1,2-Difunctionalization of Alkenes: Dialkoxylation, Aminoalkoxylation, and Diamination

Reactions for vicinal alkene oxidation with a combination of palladium and a strong oxidant were first explored by Bäckvall.^[48,55–57] All follow a sequence of nucleopalladation of the alkene, followed by alkyl–heteroatom bond formation. In a seminal investigation under stoichiometric conditions, Bäckvall demonstrated that the presence of strong oxidants was essential for the second heteroatom substitution, which proceeded through the oxidation of the alkyl palladium intermediate. His suggestion of the involvement of Pd^{IV} intermediates was instructive for subsequent development of the field.

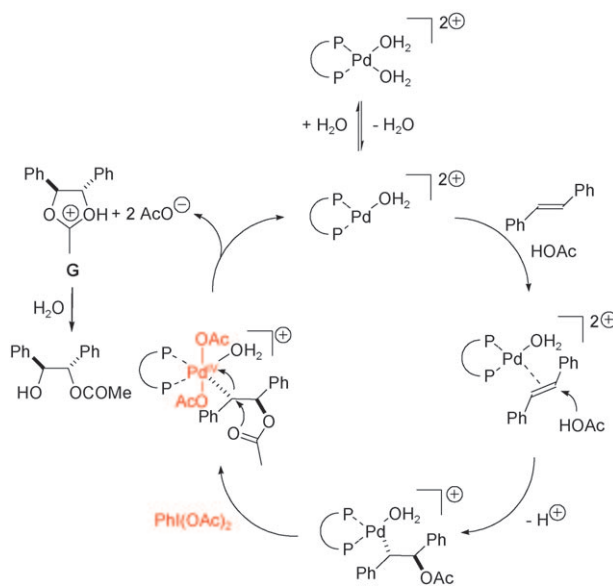
As in the case of related oxidative reactions for arene functionalization, the use of iodosobenzene diacetate is the key to clean and selective alkene oxidation. For example, Dong and co-workers developed a dioxygenation reaction of alkenes with bisphosphine-ligated palladium(II) complexes.^[58] Stilbene was converted into the vicinal hydroxyacetate as a 6:1 diastereomeric mixture in this reaction (Scheme 15a), and substrates bearing free OH groups were transformed into cyclized products, such as THF derivatives and lactones (Scheme 15b,c). Upon the addition of acetic



Scheme 15. Palladium(IV)-catalyzed diacetoxylation of alkenes. Bn = benzyl, dppp = 1,3-bis(diphenylphosphanyl)propane, OTf = tri-fluoromethane sulfonate.

anhydride, simple alkenes were converted cleanly into the corresponding diacetates (Scheme 15d,e).

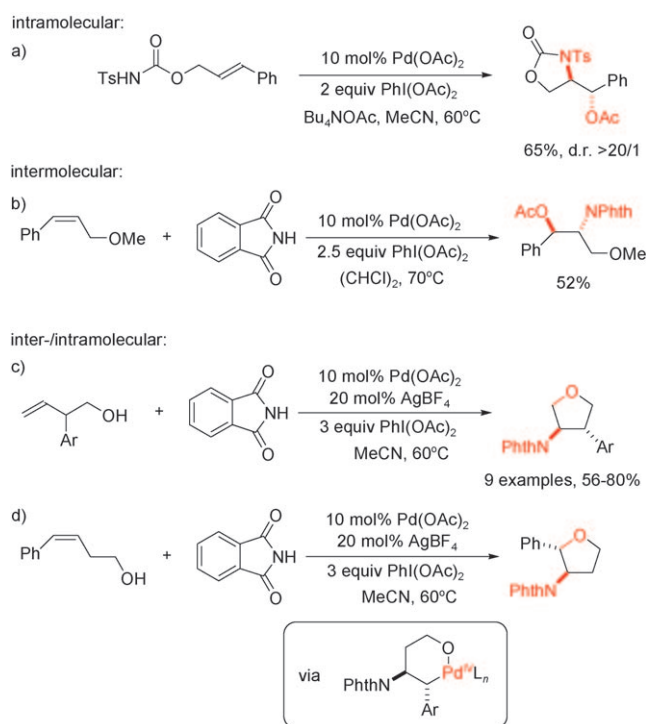
On the basis of control experiments, the authors proposed the catalytic cycle in Scheme 16 to explain the formation of the vicinal hydroxyacetate. Thus, *anti* acetoxypalladation is followed by Pd oxidation to give a σ -alkyl palladium(IV)



Scheme 16. Catalytic cycle for the palladium(IV)-catalyzed formation of a vicinal hydroxyacetate from an alkene.

intermediate. Intramolecular reductive metal displacement then creates the second C–O bond and regenerates the palladium catalyst. Through an experiment with isotopically labeled water, the authors proved that the oxygen atom from water is incorporated as the acetoxy carbonyl oxygen atom in the final product, thereby confirming the intermediacy of **G** and the origin of the hydroxyacetate product. The use of bisphosphine ligands in this oxidation reaction is important, as the corresponding palladium complexes are stable in the presence of the strong oxidant $\text{PhI}(\text{OAc})_2$; thus, the exclusive oxidation of alkyl palladium intermediates took place throughout catalysis. Recently, a related reaction under aerobic oxidation conditions was reported.^[59]

In the field of aminoalkoxylation, Sorensen and co-workers described the first catalytic intramolecular process (Scheme 17a).^[60] This reaction, in which $\text{PhI}(\text{OAc})_2$ is again

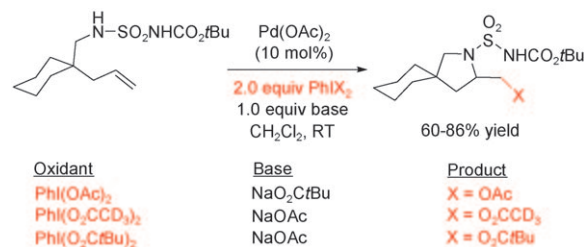


Scheme 17. Palladium(IV)-catalyzed aminoacetoxylation and aminoalkoxylation of alkenes. Phth = phthaloyl.

employed as the oxidant and source of acetate, was the first demonstration of the usefulness of this reagent in the oxidative vicinal difunctionalization of alkenes. The reaction proceeds at room temperature through aminopalladation^[61] with a palladium(II) catalyst, followed by oxidation to a palladium(IV) intermediate and C–O bond formation. Notably, the oxidation of an *E*-configured alkene led to diastereomerically pure material, the relative configuration of which indicated that at least one mechanistic step occurs with stereochemical inversion. The exact stereochemical course of the aminoacetoxylation was investigated by Liu and Stahl (Scheme 17b): For an intermolecular reaction with phthalimide as the nitrogen source, they concluded that the reaction proceeds through a two-step sequence of *syn* aminopallada-

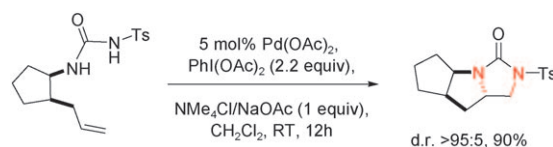
tion followed by *anti* alkoxylation from a Pd^{IV} intermediate.^[62] Desai and Sanford employed homoallylic alcohols for an inter-/intramolecular aminoalkoxylation reaction with phthalimide as the nitrogen source (Scheme 17c).^[63] These reactions yield 3,4-disubstituted THF products with high *anti* diastereoselectivity. THF formation from an internal alkene gives a final product with a configuration that suggests an unusual *syn*-selective reductive elimination from Pd^{IV} (Scheme 17d); a reductive elimination of this type apparently also occurs in the alkoxylation reactions in Schemes 9 and 13c.

Further aminoalkoxylation reactions comparable to that in Scheme 17a were found in oxidation reactions of alkenes with guanidine and sulfamide nitrogen groups.^[64,65] To identify the nucleophile involved in reductive elimination from Pd^{IV} catalysts, Muñiz et al. carried out cross-experiments with $\text{PhI}(\text{OAc})_2$, $\text{Ph}(\text{O}_2\text{CtBu})_2$, and $\text{PhI}(\text{O}_2\text{CCD}_3)_2$ in the presence of different carboxylate bases. The study demonstrated that carbon–alkoxide bond formation occurs exclusively with the anion derived from the oxidant (Scheme 18). Thus, this anion is introduced into the palladium(IV) coordination sphere prior to reductive elimination.^[66]



Scheme 18. Selectivity of anion transfer for the palladium(IV)-catalyzed aminoalkoxylation of alkenes.

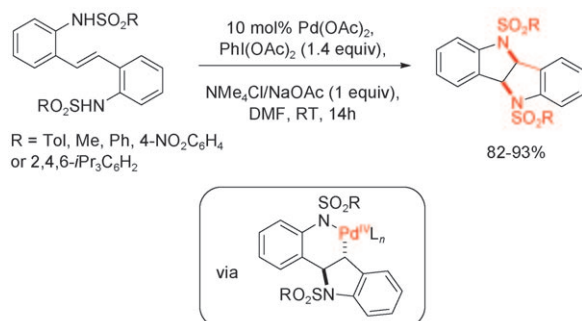
Palladium(IV) catalysis also proved key to the development of a catalytic diamination of alkenes.^[67] Initially, robust tosyl ureas were used as nitrogen sources for intramolecular vicinal alkene oxidation. Again, hypervalent iodine oxidants, such as $\text{PhI}(\text{OAc})_2$, proved most effective. A variety of five- and six-membered-ring annelation products of cyclic ureas could be synthesized by this method. Scheme 19 shows an example of diastereoselective alkene diamination. A detailed mechanistic investigation revealed the overall sequence to be a *syn* aminopalladation followed by *anti* alkyl–nitrogen bond formation from a Pd^{IV} intermediate.^[66] This mechanism is in agreement with that found by Liu and Stahl for related aminoacetoxylation reactions.^[62] The postulated involvement of a Pd^{IV} catalyst state resulting from the oxidation of the σ -



Scheme 19. Intramolecular palladium-catalyzed diamination of alkenes.

alkyl palladium intermediate formed by aminopalladation was recently confirmed by theoretical calculations.^[68]

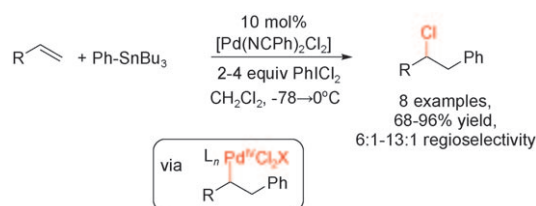
Studies on palladium-catalyzed diamination were subsequently extended to the oxidation of 2,2'-diamido stilbenes as a unique synthetic approach to bisindolines and related heterocyclic compounds, which are obtained as single diastereoisomers (Scheme 20).^[69] The C_2 symmetry of the products



Scheme 20. Palladium(IV)-catalyzed diamination of alkenes.

was established unambiguously by X-ray crystallography. The proposed catalytic cycle involves an η^1 -benzyl palladium(IV) catalyst state that, unlike related Pd^{II} derivatives, is configurationally stable. Metal oxidation must be remarkably fast to override β -hydride-elimination pathways to indoles. $PhI(OAc)_2$ is again the oxidant of choice for the selective formation of a palladium(IV) intermediate. Subsequent *anti* C–N bond formation regenerates the initial Pd^{II} catalyst and generates the diamination product with the correct configuration. In addition to this diamination through the $PhI(OAc)_2$ -induced creation of an alkyl–nitrogen bond from a Pd^{IV} complex, a diamination reaction involving intramolecular aminopalladation^[61] followed by oxidation with *N*-fluorobis(phenylsulfonyl)amide was recently developed.^[70]

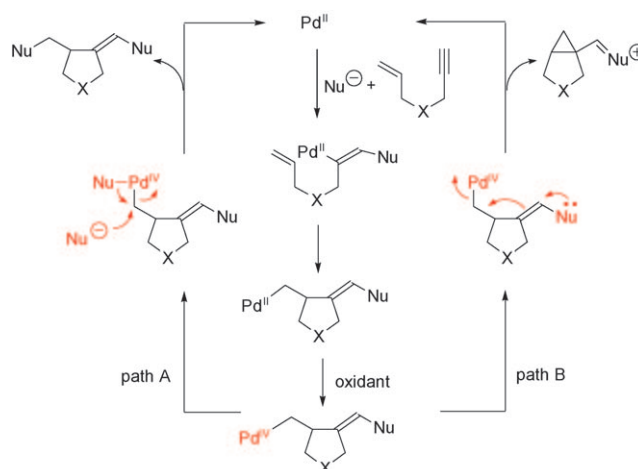
Kalyani and Sanford employed the oxidant $PhICl_2$ to devise an oxidative version of Heck chemistry. Again, this study demonstrates that pathways for conventional palladium(II) catalysis can be interrupted in the presence of strong oxidants. In this case, following the aryl palladation of an alkene, the usual β -hydride elimination that occurs in Pd^{II} catalysis is not possible as a result of fast selective metal oxidation. As a consequence, the dominant pathway becomes the reductive formation of an alkyl–chlorine bond (Scheme 21). Reactions in the presence of the conventional reagent copper(II) chloride proceed through a palladium(II) catalytic pathway and lead to the corresponding regioisomer.^[71,72]



Scheme 21. Palladium(IV)-catalyzed arylchlorination of alkenes.

5.3. Domino Catalysis Involving Pd^{II}/Pd^{IV} Catalysts

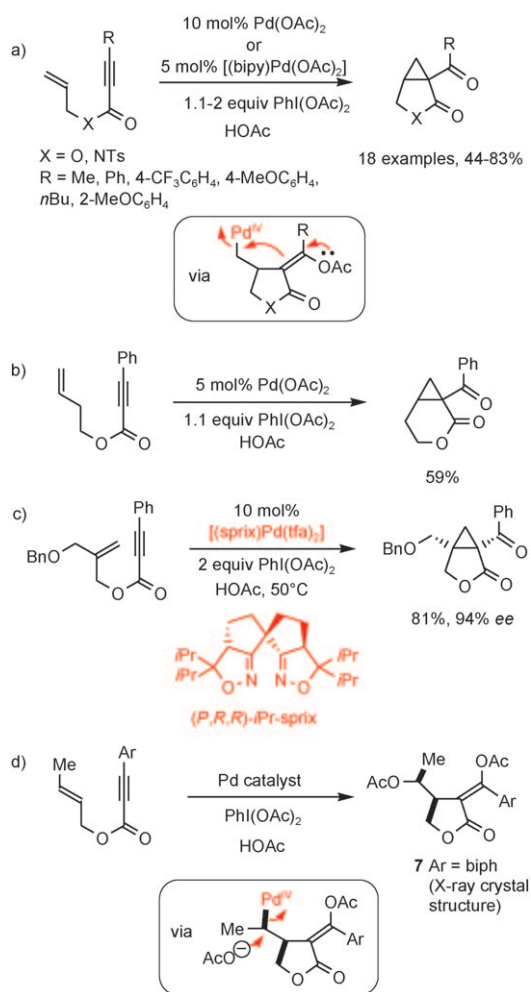
The oxidation with iodosobenzene diacetate was also employed for the development of domino reactions of 1,6-enynes through Pd^{II}/Pd^{IV} sequential catalysis (Scheme 22).



Scheme 22. Concept of domino bond formation through Pd^{II}/Pd^{IV} catalysis.

The reaction sequence starts with a palladium(II) catalyst, such as palladium diacetate, which in the presence of an external nucleophile promotes regioselective nucleopalladation of the alkyne. Subsequent 5-*exo*-trig cyclization onto the alkene gives rise to an alkyl palladium intermediate. This part of the reaction involves well-established Pd^{II} chemistry. At this stage, however, rapid oxidation of the metal takes place in the presence of the strong oxidant iodosobenzene diacetate to give a palladium(IV) intermediate. This oxidation suppresses alternative pathways, such as β -hydride elimination, and thereby enables new synthetic transformations. Two different reactions of the palladium(IV) intermediate were devised: In the first case, attack of the alkyl–palladium(IV) bond by a nucleophile, either from within the coordination sphere of the metal or from without, leads to reductive cleavage of the palladium moiety in the +II oxidation state and completes the catalytic cycle (path A). Alternatively, in the case of sufficiently electron rich alkenes, a nucleophilic attack at the position adjacent to the palladium(IV) center by the exocyclic double bond may result in cyclopropane formation, again with the liberation of the Pd catalyst in its original oxidation state (path B).

Suitable conditions for both pathways were developed (Scheme 23). The research groups of Beller and Tse, and Sanford independently reported conditions for cyclopropanation at a Pd^{IV} center to convert 1,6-enynes into bicyclo-[3.1.0]hexanes (Scheme 23a) and thus demonstrated the power of higher-oxidation-state palladium catalysis for C–C bond-forming reactions that are not possible through conventional Pd^{II} catalysis.^[73,74] The reaction was also extended to the formation of six-membered rings (Scheme 23b).^[74] A similar report describes related cyclizations on substituted acrylates as the alkene moiety.^[75]



Scheme 23. New domino C-X/C-C coupling reactions with a Pd^{II}/Pd^{IV} catalytic mechanism. tfa = trifluoroacetate.

Sasai and co-workers since developed the first example of enantioselective palladium(IV) catalysis by using their sprix ligands. In the presence of a preformed sprix-palladium catalyst, bicyclo[3.1.0]hexane formation proceeds with high enantioselectivity (up to 94 % ee; Scheme 23c). This result is an important proof of principle for enantioselective palladium(IV) catalysis.^[76]

Pathways involving the direct nucleophilic attack of acetate on the carbon atom α to the Pd^{IV} center were also described by the research groups of Beller and Tse, and Sanford.^[73,74] On the basis of the relative configuration, Beller and co-workers favored an S_N2-type carbon-acetate coupling. This stereochemical pathway was later confirmed unambiguously by Lyons and Sanford through X-ray crystal structure determination of the product **7** of a related transformation (Scheme 23d).^[77] Yin and Liu developed a related transformation for the formation of chloro-substituted lactones by performing the reaction under aerobic conditions in acetic acid in the presence of a large excess of lithium chloride. In this case, the opposite relative configuration of the products pointed to a direct reductive elimination from within the coordination sphere of the Pd^{IV} catalyst.^[78]

6. Mechanistic Basis for Reductive Elimination from σ -Alkyl Palladium(IV) Catalysts

Apart from the stoichiometric process in Scheme 12, few mechanistic details are known about the course of reductive elimination from σ -alkyl palladium(IV) intermediates.^[45,47] The high reactivity of monoalkyl palladium(IV) complexes has so far prevented their structural isolation and characterization, as indeed most catalysis involving monoalkyl palladium(IV) intermediates proceeds readily at room temperature. The high reactivity of these palladium(IV) intermediates is remarkable, especially if one considers that related σ -alkyl palladium(II) complexes are usually stable towards any kind of C-X reductive elimination. The involvement of a Pd^{IV} intermediate in oxidation reactions with PhI(OAc)₂ and other oxidants is supported by the formation of related σ -aryl palladium(IV) complexes with comparable electronic structures under similar or identical conditions. It is further substantiated by the fact that either a lack of reactivity or alternative reaction pathways are encountered in the absence of strong oxidants. These alternative pathways originate from well-established Pd^{II} reactions, such as β -hydride elimination. For example, the research groups of Stahl and Sanford demonstrated independently that without the addition of PhI(OAc)₂, the aminoacetoxylations reactions in Scheme 17 alter their course and result in enamide formation. These examples underline the notable absence of the classical β -hydride-elimination pathway of Pd^{II} catalysis when Pd^{IV} is involved.

In the vast majority of cases, reductive elimination from σ -alkyl palladium(IV) intermediates proceeds with inversion of configuration at the coordinated α carbon atom, as shown by the established relative configurations of products of several C-O,^[55,60,62] C-N,^[56,66,67,69] and C-C^[73,75,77] bond-forming reactions (Figure 2). Owing to the presence of the neighboring electron-deficient Pd^{IV} center, this carbon atom displays strong electrophilicity and is therefore unlikely to participate in reductive elimination via a three-center, four-electron transition state. Instead, anion dissociation from the coordination sphere takes place with subsequent nucleophilic attack on the coordinated α carbon atom through a transition state that is analogous to that of an S_N2-type reaction; within this topology, the Pd^{IV} atom functions as an effective leaving group. The differences between C-C and C-X bond formation from σ -aryl palladium(IV) complexes and C-C and C-X bond formation from σ -alkyl palladium(IV) complexes are hence reminiscent of those observed in classical substitution reactions. For alkyl-oxygen bond formation from Pd^{IV} intermediates, Liu and Stahl traced these differences back to the orientation and steric accessibility of the carbon-centered orbital involved in C-O bond formation.^[62] It appears that this model may also be true for related nitrogen nucleophiles^[56,66,67,69] and even stabilized carbon nucleophiles.^[73,75,77]

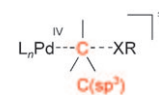


Figure 2. Transition state for reductive elimination from σ -alkyl palladium(IV) intermediates. This transition state leads to inversion of configuration at the α carbon atom.

7. Summary

Catalysis involving palladium in oxidation states higher than those of conventional Pd⁰/Pd^{II} cycles has great potential in the discovery of novel reaction pathways. Although the development of palladium(IV) catalysis has just begun, it has already enabled the development of a number of significant new transformations. These reactions are marked by their high selectivity and synthetic robustness, and almost all are based on the use of catalysts that are generated in situ from commercially available palladium salts. As supportive phosphine or N-heterocyclic carbene ligands, which are typical for related Pd⁰/Pd^{II} catalysis, are not required, higher-oxidation-state palladium(IV) catalysis is particularly attractive from the viewpoint of cost effectiveness. Future studies should broaden the spectrum of aryl palladium(IV) chemistry, for example, by removing the synthetic requirement for chelate-directed C–H activation in favor of direct C–H activation or transmetalation. A first step in this direction has been made with the preparation of the isolable complex **3**. With the recent identification of sprix compounds as suitable chiral ligands for enantioselective transformations, the design of general asymmetric palladium(IV) catalysis appears to be within reach. In any case, a solid arsenal of palladium(IV)-catalyzed reactions with enormous potential for future development is now available.

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