Homogeneous Catalysis

The syn/anti-Dichotomy in the Palladium-Catalyzed Addition of Nucleophiles to Alkenes

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How to add a nucleophile?

Palladium has an answer.
Abstract: In this review the stereochemistry of palladium-catalyzed addition of nucleophiles to alkenes is discussed, and examples of these reactions in organic synthesis are given. Most of the reactions discussed involve oxygen and nitrogen nucleophiles; the Wacker oxidation of ethylene has been reviewed in detail. An anti-hydroxypalladation in the Wacker oxidation has strong support from both experimental and computational studies. From the reviewed material it is clear that anti-addition of oxygen and nitrogen nucleophiles is strongly favored in intermolecular addition to olefin–palladium complexes even if the nucleophile is coordinated to the metal. On the other hand, syn-addition is common in the case of intramolecular oxy- and amidopalladation as a result of the initial coordination of the internal nucleophile to the metal.

1. Introduction

Electrophilic addition to olefins is one of the fundamental reactions in organic chemistry. Thus, bromine or hypobromous acid are readily added across an electron-rich olefinic double bond (1) in a process that is initiated by an electrophilic attack to generate the corresponding bromonium ion 2, which is then opened by Br\(^-\) (in the case of Br\(_2\)) or H\(_2\)O (when HOBr is employed) from the opposite side, to afford the anti-addition product (Scheme 1).\(^\text{[1,2]}\) Electrophilic metal cations M\(^{n+}\), such as Hg\(^{2+}\) and Tl\(^{3+}\), follow a similar pattern in both inter- and intramolecular reactions.\(^\text{[3,4]}\) By contrast, owing to the nature of the electron-rich C=C bonds, nucleophilic additions are rare and typically limited to intramolecular additions of an alkoxide moiety, generated from a suitable polycyclic alkenol by depuration with NaOH or tBuOK.\(^\text{[5]}\) Transition metals are known to form \(\eta^1\)-complexes 3 that can be attacked by nucleophiles to effect a formal nucleophilic addition upon the removal of the metal.\(^\text{[5]}\) However, the transition-metal-promoted process is more complicated, since the nucleophile can, a priori, attack the \(\eta^2\)-species either from the opposite side (3) in analogy to bromonium ions 2 and their congeners, or could first coordinate to the metal and then be delivered in a syn-fashion to the original alkene (4).\(^\text{[5]}\)

The first \(\eta^1\)-olefin metal complex 5 was prepared by Zeise (Scheme 2) via coordination of ethylene (generated by an in situ dehydrogenation of boiling ethanol) to K\(_2\)PtCl\(_6\).\(^\text{[6]}\) However, this complex was long considered as a rarity and it took more than 100 years before the nature of the \(\pi\) bond between an alkene and a metal was understood and its potential had been realized.

The present review is concerned with the stereochemistry of nucleophilic additions to \(\eta^1\)-alkene metal complexes of palladium (analogous to 5) and application of these reactions in synthetic organic chemistry. The experimental and theoretical findings, accumulated over the years, are submitted to a thorough mechanistic analysis in light of the most recent results, which are not included in previous reviews. The new results have allowed us to draw conclusions that were not explicitly expressed in previous reviews.\(^\text{[7]}\)

2. Wacker Oxidation

Apart from catalytic hydrogenation, the first large-scale industrial application of palladium was developed by Smidt and his colleagues at the Wacker company in the 1950s.\(^\text{[8]}\) This process, which converts ethylene into acetaldehyde, is known as the Wacker oxidation (Scheme 3). Here, the tetrachloropalladate first generates the corresponding \(\eta^1\)-ethylene-Pd complex (in analogy to the formation of Zeise’s salt 5), which then reacts with water to produce acetaldehyde, Pd\(^2+\), and two equivalents each of hydrogen chloride and chloride ions [Eq. (1)]. In order to make the process catalytic, the resulting Pd\(^2+\) needs to be reoxidized to its active form, that is, Pd\(^0\), which is effected by the reaction with CuCl\(_2\) (2 equiv), using the two equivalents of Cl\(^-\)
generated in the previous step [Eq. (2)]. The latter reaction produces CuCl, which is then reoxidized to CuCl₂ by molecular oxygen, consuming the two equivalents of HCl generated in the first step [Eq. (3)]. The reaction is thus catalytic in both Pd⁰ and Cu¹, with molecular oxygen serving as the terminal, stoichiometric oxidant. Note that direct reoxidation of Pd⁰ to Pd¹ by molecular oxygen in water under Wacker conditions is too slow and would not prevent aggregation and formation of metallic palladium.

\[ \text{CH}_2\text{CHO} + [\text{PdCl}_2]^{\circ} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{ClO} + \text{Pd} \]  

(1)

\[ 2\text{CuCl} + \text{Cl}^-- \rightarrow 2\text{CuCl}_2 \]  

(2)

\[ 2\text{CuCl} + \text{H}_2\text{O} \rightarrow 2\text{CuCl}_2 + \text{H}_2 \]  

(3)

Scheme 3. Wacker oxidation.

After the original publication on the Wacker process, this reaction became the subject of numerous mechanistic studies.²⁴ It was proposed that the intermediate η¹-complex 7 reacts with water to produce the 2-hydroxetyl palladium complex 8, which would undergo a η₁-H elimination to generate vinyl alcohol 10 (via 9a), tautomerization of which would produce acetaldehyde 11 (Scheme 4). However, deuterium labeling studies clearly demonstrated that the final stages of the cascade do not adopt this route: the η¹-complex 9a, primarily arising from 8 by the expected η₁-H elimination, does not dissociate to produce 10, but rather undergoes an insertion reaction to generate complex 12 (via rotamer 9b), which now uses the O–H (rather than C–H) for the final η₁-H elimination (12a or 12b) to produce acetaldehyde 11.²⁶ An alternative pathway, where a lone-pair on oxygen ejects Pd²⁺ as a leaving group (12b), was also considered,²⁷ which was later supported by theoretical calculations.²⁸

The latter mechanism has been inferred from isotopic labeling as follows (Scheme 5): If the reaction proceeded through enol 10, the molecule would abstract a proton from the envi-

Abstract in Czech: V tomto přehledném článku je diskutována stereochimie palladiu katalyzovaná adicí nukleofilů na olény a jsou zde uvedeny příklady aplikací v organické syntéze. Většina diskutovaných reakcí zahrnuje kysličaté a dusíkaté nukleofily. Zvláštní pozornost je věnována oxidaci etylenu, kterou vyvinula firma Wacker. V tomto případě experimentální i výpočetní studie jasně ukazují na anti-hydroxypalladaci jako dominantní mecha

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Scheme 5. Deuterium labeling in Wacker oxidation. Environment [note that there is free HCl available, according to Equation (1)]. However, the experiment with perdeuteriated ethylene [Eq. (4)] showed that all the label was retained, which is consistent with the mechanism depicted in Scheme 4, namely with the isomerization \( \text{9a} \rightarrow \text{9b} \rightarrow \text{12} \). The isotope effect [compare Eqs. (1) and (4) in Scheme 5] was found to be marginal.\(^9\)

In a complementary experiment, the specifically dideuterated ethylenes 13 and 14 (Scheme 6) were found to exhibit an internal competitive isotope effect (H vs D shift), demonstrating that the rate-limiting step must occur before the \( \beta \)-H elimination and formation of acetaldehyde.\(^9\) It was further argued that the rate-limiting step is the hydroxypalladation, and the results are better explained by a syn-migration since an anti-hydroxypalladation would seem to require a rate constant larger than diffusion control.\(^9\)

The proposed syn-migration of an oxygen nucleophile has been experimentally observed in a stoichiometric experiment with a Pt-olefin complex (Scheme 7). In this experiment the extremely electron-deficient tetrafluoroethylene (15) was treated with the Pt-Ome complex 16. The formation of intermediate 17 and product 18, as well as the kinetics, were monitored by NMR spectroscopy in [D\(_6\)]THF with added CD\(_3\)OD.\(^{14}\) Here, an external attack by CD\(_3\)OD (which should proceed with anti stereochemistry due to the steric hindrance from the Pt side) has not been observed, nor was the exchange of OCH\(_3\) with OCD\(_3\), so that the product 18 can only arise by the syn-migration of OCH\(_3\) from Pt. This may seem to support the syn-migration pathway in the Wacker process. However, it can be argued that the starting olefin 15 in this experiment is rather special, so that generalization of these findings, in particular to the Wacker oxidation of the electron-rich ethylene, cannot be made directly.

In order to elucidate the stereochemistry of hydroxypalladation, the trans-dideuteriated ethylene 19 was employed as a model compound (Scheme 8).\(^9,15\) Under catalytic hydroxypalladation conditions, using a mixture of PdCl\(_2\), LiCl, and CuCl\(_2\), the latter alkene was expected to generate the \( \eta^3 \)-complex 20, where the water molecule would have to be cis-coordinated toward the ethylene ligand (otherwise the syn-transfer would not be possible at all). The anti-attack by an external water molecule on 20 should generate complex 21, which in the presence of chloride ions should produce chlorohydrin 22 as a result of the \( \text{S}_2\text{O} \) displacement of palladium. Treatment of 22 with a base would then produce epoxide 23. The latter epoxide was found to be cis-configured (as shown), which is consistent with the pathway involving three inversions of configuration, that is, in each step starting with complex 20. Since the replacement of palladium by Cl\(^-\) was known from the previous work\(^{16}\) to proceed with inversion of configuration at carbon, and the stereochemistry of the chlorohydrin transformation into the corresponding epoxide is a textbook example of inversion, the key hydration 20 \( \rightarrow \) 21 must also occur with inversion, that is, via an external attack as shown. This study thus provides evidence for the anti-addition mechanism for the key hydroxypalladation step.

![Scheme 8](image-url)
first two complexes lie rather low, so that their interaction with the LUMO of the (coordinated) olefin will be weak and result in little stabilization. By contrast, the two latter complexes have high energy HOMO orbitals for the Pd–Nu bond (Nu = H– and CH3–), so that the interaction between the HOMO orbital of these complexes and the LUMO of the alkene should be stronger and lead to a considerable lowering of the energy of the system. Hence, it can be anticipated that the reactivity of H– and CH3– will be controlled mainly by orbital interactions, so that the transfer from the metal should be preferred. On the other hand, the orbital effects in the case of OH– are likely to be weak, so that the reaction should be dominated by ionic effects and thus proceed via anti-addition.17,18

Furthermore, the reactions controlled by ionic interaction (favoring the anti-pathway) can be expected to obey the Markovnikov rule like any other electrophilic addition and afford products, where the incoming nucleophile is planted on the carbon that can better stabilize a partial positive charge (24 in Scheme 10). On the other hand, in the orbital-controlled reactions (favoring the syn-pathway) the nucleophile should add to the less-substituted carbon (25), as the LUMO orbital at that carbon should be larger.17

A possible supramolecular interaction, involving several molecules of water and hydrogen bonding to the chloride bound to Pd, has also been considered for the Wacker oxidation (Figure 2).18

It has been argued that the chloride concentration in the experiments shown in Scheme 8 is higher (3 M) than in the Wacker process and in the kinetic experiments5,17,19 (≤ 1 M) and that the stereochemistry may not be the same at the different concentrations of Cl–.7,19,20 However, the chemistry of 1,4-difunctionalization of dienes, catalyzed by Pd(OAc)2, shows that while under chloride-free conditions, the acetate group is delivered preferentially to the intermediate allyl group from Pd (i.e., in the syn-fashion), addition of only catalytic amounts of LiCl (4 equiv per Pd) shuts down this reaction pathway. The chloride is replacing coordinated acetate on Pd, and in this way acetate can only be delivered in an anti-fashion by an intermolecular reaction.21 Further increase of the chloride concentration does not alter the latter stereochemistry and only increases the proportion of the product resulting from the Cl– attack on the η1-complex (rather than AcO– attack). This is in direct analogy to the formation of chlorohydrin 22 in the Wacker process, lending additional support for the argument that the stereochemistry should be the same at high and moderate concentrations of chloride ions.

Kinetic studies have demonstrated that the Wacker oxidation is actually inhibited by an increasing concentration of chloride ions [Eqs. (5)–(7) in Scheme 11].5,17,18 In fact, at ≤ 1 M concentration of Cl– and CuCl2 (industrial conditions for Wacker oxidation), acetaldehyde is the predominantly formed product (with small amounts of the corresponding chlorohydrin). By contrast, at 3 M concentration of Cl– (conditions used in the mechanistic study shown in Scheme 8), chlorohydrin becomes the predominant product (Scheme 12). It is highly unlikely that a change of the chloride ion concentration from 1 M to 3 M would change the stereochemistry of the hydroxypalladation of ethylene.

Finally, strong support for the anti-addition of AcO– and PdII under the chloride-free conditions has been obtained from the acetoxy palladation of deuteriated 3,3-dimethyl-1-butene 26 (Scheme 13).22 Here, the isomeric products 30 and 31 were shown to arise from predominant anti-addition of AcO– on the
However, an alternative pathway, namely the water-assisted deprotonation of 35 with concomitant syn-migration, eventually leading to 41, would proceed through the transition state 39 that is half-way down on the energy scale compared to 38, indicating that this pathway would be favored if the syn addition mechanism operated. Conversely, the anti-delivery of water (34) generates intermediate 36. Either of the transition states (39 or 40) would give rise to 41 by water-assisted deprotonation. Dissociation of the Pd–O bond in 41 would generate complex 43 ready for the expected β-H elimination. The calculations further found the energy of the corresponding transition state 42 (including the agnostic Pd–H interaction) to be 23.2 kcal mol$^{-1}$, which makes this species highest in energy.
in the whole cascade (via 39/40)\textsuperscript{[24]} so that this step can be regarded as rate-limiting.

However, there is a problem with this calculation since the transition state for the anti-attack is calculated on the negatively charged species 6. The kinetics of the Wacker process shows that two chlorides are displaced, so an anti-attack would occur on the neutral species PdCl\textsubscript{5}(OH\textsubscript{2})(CH\textsubscript{2}=CH\textsubscript{2}). It can be expected that the latter neutral species reacts much faster than the negatively charged species 6 in external anti-attack by water. This has also been confirmed later in other calculations (vide infra).

Subsequent calculations\textsuperscript{[24]} suggested that the anti-addition mechanism is strongly favored over the syn-pathway; this was disputed in a subsequent article\textsuperscript{[24]} and the quality of the calculation was questioned.

Calculations including CuCl\textsubscript{2} gave a slightly different picture,\textsuperscript{[11]} as shown in Scheme 15 (the structures here bear the same numbers as in Scheme 14 but with added “Cu” so that a direct comparison can be made). Here, the initial PdCl\textsubscript{5}/CuCl\textsubscript{2} complex 32-Cu first coordinates ethylene to produce 6-Cu (upon a loss of Cl\textsuperscript{−}), which then can be attacked by water either at Pd or at the carbon via transition states 33-Cu and 34-Cu, respectively, of which the latter is lower in energy by 4.0 kcal mol\textsuperscript{−1}, indicating that the anti-pathway is preferred. Furthermore, the energy of the TS\textsuperscript{33} 33-Cu is 26.0 kcal mol\textsuperscript{−1}, which is slightly higher than the experimentally observed value (22.4 kcal mol\textsuperscript{−1}). The two transition states would generate the hydrated species 35-Cu and 36-Cu that are almost equal in energy but the subsequent gradual conversion into 41-Cu should preferably proceed through TS\textsuperscript{35} 40-Cu that is by 4.4 kcal mol\textsuperscript{−1} lower in energy than its congener 39-Cu. The end-game from 41-Cu via 42-Cu and 43-Cu has been calculated to require lower energy in each step than the experimental value. Hence, the highest energy in this scenario (not exceeding the experimental value) is that of the transition state 34-Cu, so that the conversion of 6-Cu into 36-Cu can be regarded as the rate-limiting step (RLS) and the reaction should proceed predominantly via an anti-addition.\textsuperscript{[11]}

Again, one can argue that external attack on an (ethylene)palladium complex, where water has coordinated to Pd to remove negative charge (vide supra), should react faster than the negatively charged complex 6-Cu (34-Cu).

Recent computational studies, which included aqueous medium, namely a cubic box containing up to 26 molecules of water as a model that is more closely related to the “real” experimental conditions, arrived at the conclusion that anti-hydroxypalladation is the favored stereochemical pathway (Scheme 16)\textsuperscript{[24]} First, the initial coordination of tetrachloropalladate to ethylene (44) is known to produce the η\textsuperscript{2}-complex 6, which was taken as the starting point. The latter complex should then undergo a ligand exchange if syn-migration of the nucleophile from Pd is to be allowed. In view of the geometric restriction, previous study\textsuperscript{[24]} only considered the cis-complex 35. However, as the new study shows, the calculated activation barrier for its formation from 6 is 35 kcal mol\textsuperscript{−1}, which is more than twice as high as that for the pathway leading to its trans-isomer 45 (14 kcal mol\textsuperscript{−1}). Since the experimental value for the whole Wacker process has been found to be only 22.4 kcal mol\textsuperscript{−1}, the formation of 35 appears unlikely. Note that the conversion of 6 into 45 will be assisted by the trans-effect (absent in the formation of 35), which should considerably lower the activation energy, consistent with the calculations. Furthermore, the activation energy required for the syn-migration to generate complex 47 from 35 has been calculated to be 60 kcal mol\textsuperscript{−1}, far above the experimental value. By contrast, the activation barrier for the anti-attack by water on the trans-complex 45 to produce 46 was calculated to be only 19 kcal mol\textsuperscript{−1}. Hence, it can be clearly seen that none of the activation barriers in the anti-pathway (6 → 45 → 46) exceeds the experimentally established value\textsuperscript{[24]} for the whole process (22.4 kcal mol\textsuperscript{−1}), also indicating that the rate-limiting step should occur

![Scheme 15. Energies of various intermediates in the proposed syn-mechanism of the Wacker oxidation in the presence of CuCl\textsubscript{2}.](image-url)
after those initial steps, which is consistent with the previous findings.\textsuperscript{21} The mechanism in Scheme 16 is also consistent with the rate expression of the Wacker reaction [Eq. (7)], where the rate is inversely dependent on $[H^+]$ and the square of $[Cl^-]$. These advanced calculations thus allow to conclude that the \textit{anti}-hydroxypalladation should be the preferred pathway.\textsuperscript{22}

Another theoretical study, in combination with experimental results (Scheme 17), provides additional support for the \textit{anti}-hydroxypalladation pathway.\textsuperscript{23} In the latter study, the equilibria in the system of ethylene, tetrachloropalladate, and water were investigated. Starting with the tetrachloropalladate (32), there are two initial reactions to be considered: a ligand exchange with ethylene, generating $\eta^4$-complex 6, and partial hydrolysis, producing complex 48. Calculations suggest that the equilibrium should favor 48, as the energy of its formation is lower than that of 6 (by 5.1 kcal mol$^{-1}$). The experimentally established difference was found to be smaller (0.5 kcal mol$^{-1}$), indicating that both species should be considered for further reactions. Ligand exchange with water in the case of 6 would produce either the \textit{trans}-isomer 45 or its \textit{cis}-counterpart 35.\textsuperscript{24} As discussed in the previous paragraph,\textsuperscript{25} conversion of 6 into 45 should be associated with a barrier of 14.4 kcal mol$^{-1}$; the reversed process would require 17.0 kcal mol$^{-1}$, so that this equilibrium should be shifted toward 45. Formation of the \textit{cis}-complex 35 (from 6) would require 22.6 kcal mol$^{-1}$, according to these calculations, whereas the reversed reaction can proceed with a barrier of only 14.4 kcal mol$^{-1}$, so that the equilibrium should favor the starting complex 6. In other words, the displacement of $Cl^-$ in 6 by water should preferentially produce the \textit{trans}-complex 45. The other possible mechanism would be the ligand exchange starting with the aqua-complex 48. Its reaction with ethylene, generating the \textit{trans}-complex 45 was found to be associated with the activation energy of 23.8 and 24.5 kcal mol$^{-1}$ for the forward and reversed process, respectively. The latter difference is sufficiently small to allow the existence of both species in the equilibrium mixture. A completely different scenario was found for the conversion of 48 into the \textit{cis}-complex 35. Here, the forward process would require 19.4 kcal mol$^{-1}$, whereas the reversed reaction would be associated with merely a 6.1 kcal mol$^{-1}$ barrier, showing that the equilibrium should be heavily shifted toward 48. These finding are thus consistent with the previously suggested dominance of the \textit{trans}-complex 45 over its \textit{cis}-isomer 35. Since the barrier for the \textit{anti}-attack on 45 was previously calculated\textsuperscript{25a} to be 19 kcal mol$^{-1}$, whereas the syn-migration from 35 would require\textsuperscript{25a} 60 kcal mol$^{-1}$, the syn-pathway can be ruled out.\textsuperscript{26}

When extended beyond the original conversion of ethylene to acetaldehyde, the Wacker oxidation has served, with various modifications, as a standard method for oxidation of terminal olefins to produce methyl ketones\textsuperscript{27,28} (e.g., 49 $\rightarrow$ 50 in Scheme 18).\textsuperscript{29} However, alteration of the regioselectivity in favor of the corre-
sponding aldehydes 52 has recently been achieved simply by using tBuOH rather than water. The reaction presumably proceeds via the vinyl ether 51, resulting from the anti-Markovnikov attack of the bulky nucleophile at the sterically less hindered terminal carbon.\[20\]

3. Amination of Olefins

Related to Wacker oxidation, where the stereochemistry of the initial hydroxypalladation was discussed in detail in the previous chapter, is the amination of olefins. However, in contrast to water and alcohols, amines are not normally considered for analogous Pd-catalyzed reaction, as they are easily oxidized. Nevertheless, a stoichiometric Pd-mediated amination of (E)-2-butene (53) with dimethyl amine has been successfully investigated at low temperature (Scheme 19).\[51\] The initially formed aminopalladation product 54 was reduced in situ with LiAlD\(_4\) (with retention of configuration) to afford the deuteriated amine 55 in high yield. The relative configuration of the latter derivative was established in two steps, involving N-oxidation (55 \(\rightarrow\) 56) followed by Cope elimination, which is known to proceed with a syn-elimination mechanism. The product analysis (57–59) was consistent with an initial anti-addition of Pd\(^{II}\) and Me\(_2\)NH across the C–C bond,\[31\] in analogy to the mechanism discussed for the Wacker oxidation. Complementary experiments with (Z)-2-butene led to the same conclusions.\[31, 32\] Note that before the amine attacks the coordinated olefin, two amine molecules coordinate to palladium. A syn-migration of the amine from Pd to the coordinated olefin should be precluded, as this process apparently would be much higher in energy (Figure 1) than the intermolecular anti-attack by Me\(_2\)NH, generating 54. This is in contrast to the Pd-OAc \(\eta^1\)-species, where the syn-delivery via a cyclic transition state is allowed.\[33\] However, analogous syn delivery in the case of the corresponding \(\eta^1\)-complexes is disfavored (Scheme 13).\[22\]

4. Intramolecular Oxypalladation

The stereocontrolled intramolecular nucleophilic attack on a metal–olefin complex (as in 60), is an important reaction in synthetic organic chemistry.\[34\] and is analogous to halolactonization, haloetherification, and related reactions employing S, Se, Hg, Ti, Au, and other electrophiles [Scheme 20, Eq. (8)].\[21, 25\] When metals, such as Pd\(^{II}\) or Hg\(^{II}\), are employed as the electrophilic triggers of the reaction, the initially generated organometallic product 61 can be utilized in a subsequent reaction that would allow the construction of a new C–C bond from the C–M bond. The overall result would then be the formation of a C-X and C–C bond, where X is introduced as a nucleophile, and the new C-substituent formally as an electrophile (62).\[21\] Aside from this anti-mechanism [Eq. (8)], the syn-addition 63 \(\rightarrow\) 64 [Eq. (9)] may also operate (see also Scheme 1), due to the initial coordination (60 \(\rightarrow\) 63), known for instance from the vanadium-catalyzed epoxidation.\[31\] Examples of both mechanisms and the effects favoring one or the other will be discussed and analyzed in this and subsequent sections.

4.1. Intramolecular Oxypalladation Followed by Carbonylation

The first intramolecular oxypalladation was carried out in conjunction with carbonylation (Scheme 21).\[36\] Here, the reaction of alkenol 65 with CO and MeOH, catalyzed by Pd\(^{0}\), commenced with the \(\eta^1\)-coordination, followed by an anti-attack by the neighboring hydroxyl group. Of the two facial stereoisomers, one is consumed faster (66) and generates the tetrahydropyran derivative 67 with high stereoccontrol exercised by the original chiral center (note the “equatorial” methyl in 66). Coordination of carbon monoxide (68), followed by migratory

Scheme 19. Stereochemistry of the Pd\(^{II}\)-catalyzed amination of 2-butene.

Scheme 20. Neighboring group effects in the metal-catalyzed functionalization of olefins.

Scheme 21. Intramolecular hydroxypalladation controlled by a residing chiral center followed by carbonylation.
insertion then generated complex 69, which on reaction with methanol produced the desired methyl ester 70 and Pd\(^0\), whose reoxidation with Cu\(^2+\) completed the catalytic cycle.

Several other examples followed shortly, all featuring the initial anti-addition of the electrophilic Pd\(^{II}\) and the neighboring OH group across the C\(=\)C bond\(^{37–39}\), such as the cyclization of 71 and 73 (Scheme 22),\(^{39}\) and 76 (Scheme 23), followed by carbonylation, as detailed in the previous paragraph.\(^{38a}\)

**Scheme 22.** Carbonylative cyclization: the effect of alkene geometry on the regioselectivity.

**Scheme 23.** Carbonylative cyclization occurring with pure anti-stereosemetry.

All those reactions (Schemes 21—23) occurred with alkenols, whose structures allow 5-exo- or 6-exo-cyclizations. If the only option is a 4-exo process, as in the case of the homoallylic alcohol 78, the reaction has been found to take a different course (Scheme 24).\(^{40}\) Here, the C\(=\)C bond coordination to Pd\(^{II}\) (as described in Scheme 21) becomes unproductive, as cyclization to produce the corresponding oxetane 79 would be too high in energy. Instead, the reaction proceeds through a different channel, namely that involving the initial coordination of CO to Pd, followed by a reaction with the OH group and additional coordination to the C\(=\)C bond (80). These events are followed by reductive elimination to generate lactone 81 with Pd chelated to the exocyclic carbon in an \(\eta^1\)-fashion (which formally corresponds to a syn-addition across the C\(=\)C bond). The cascade is then completed by the second carbonylation to produce 82 (Scheme 24). The trans-configured alcohol 83 reacted in the same way to produce the diastereomeric lactone 84. The reaction conditions for these transformations are noteworthy: aside from the standard reoxidation of the resulting Pd\(^{II}\) by Cu\(^{2+}\), propene epoxide was employed to consume the Brønsted acid generated by the reaction, whereas trimethyl orthoacetate was added to secure anhydrous conditions.\(^{40}\)

Other examples of this reaction course, where the cyclization involving intramolecular oxypalladation is precluded by structural restrictions in the homoallylic arrangement, have been reported but without addressing the stereochemistry issues.\(^{41}\)

### 4.2. Intramolecular Oxypalladation Followed by \(\beta\)-Hydride Elimination

The stereochemistry of the Pd\(^{II}\)-catalyzed ring closure of alkenols has been investigated with the aid of the stereospecifically deuteriated substrate 85, using \(p\)-benzoquinone (\(p\)-BQ) as the terminal oxidant (Scheme 25).\(^{42}\) Since intermediates in a catalytic reaction are difficult to isolate, the steric course was inferred from the products of the subsequent \(\beta\)-H elimination, which is known to occur as a syn-process. With the weakly coordinating BF\(_4\)\(^-\) anion at Pd\(^{II}\), the free phenolic hydroxyl group tends to coordinate to the metal [as in Eq. (9), Scheme 20], which leads to a \(\pi\)-olefin complex where Pd is bound to the top face of cyclohexene. A syn-oxypalladation then produces 86, which on subsequent \(\beta\)-hydride elimination removed the cis-positioned deuterium. By contrast, coordination to the neighboring hydroxyl is precluded in the case the strongly co-

**Scheme 24.** Carbonylative cyclization occurring with pure syn-stereosemetry.

**Scheme 25.** Switching between syn- and anti-mechanism in the intramolecular hydroxypalladation as a function of the anion coordinated to Pd.
ordinating Cl− at PdII (especially when additional LiCl is present) and the reaction thus proceeded with anti-stereochemistry to give 87, as revealed by the β-H elimination of the cis-disposed proton.33,42,43

The latter study used phenolic hydroxyl as a neighboring group, whose coordination capability can differ from that of an ordinary alcohol due to the difference in the pKₐ. Therefore, two diastereoisomerically deuteriated substrates 88 and 89 were investigated by Stoltz and co-workers (Scheme 26).44 The catalyst employed possessed the weakly coordinating trifluoroacetate anions and the reaction was found, in both cases, to follow the syn-pathway, as revealed by the β-hydride elimination of 90 and 91 to give 92 and 93, respectively. These results are in full agreement with the first reaction shown in Scheme 25. Notably, the catalyst in Scheme 26 allowed the use of molecular oxygen as the stoichiometric oxidant, avoiding the requirement to employ a mediator, such as CuII or quinone/metal macrocycle.46 The use of the bipyridine ligand presumably keeps the reduced palladium in solution and gives it time to be reoxidized. This study clearly demonstrates that for intramolecular alkoxy palladation, coordination of the neighboring hydroxy group is a powerful process that favors syn-addition. When the alkoxy group is first coordinated to palladium in the π-olefin complex of 88 and 89, there will be no competing pathway via anti-attack.

Solvents (e.g., MeOH vs MeCN) have been found to have an effect on the regiochemistry of the β-hydride elimination but that study did not address the stereochemical issues.45

4.3. Intramolecular Oxypalladation Followed by Heck Addition

Phenolic olefin 94 has been reported to undergo a Pd-catalyzed cyclization (with p-BQ as the terminal oxidant) in the presence of Michael acceptors, such as methyl vinyl ketone, to produce 96 with high enantioselectivity, owing to the chiral ligand 97 (Scheme 27). Although the steric course of the initial step (94 → 95) has not been investigated, it can be assumed to proceed via a syn-mechanism, owing to the weakly coordinating anion (CF₃CO₂⁻) and the presence of 97, whose ligating properties are likely to mirror those of the bipyridine, featured in Scheme 26.46

4.4. Intramolecular Oxypalladation Followed by Arylation

The PdII species 100, generated in the catalytic cycle from the Pd0 complex 98 on an oxidative addition to aryl halide 99, has been shown to react with the alkoxide generated from the bishomoallylic alcohol 101, giving rise to the cyclization product 104 (Scheme 28).47 The corresponding alkenyl aryl ether that would be normally expected for these conditions (typical for the Hartwig–Buchwald coupling) has not been observed. The reaction has been suggested to proceed via the η²-complex 102 (with pentacoordinated Pd), predisposed to the syn-cyclopalladation, generating the tetrahydrofuran intermediate 103. The latter species then undergoes re-
ductive elimination to afford 104 as the final arylated product, thereby regenerating Pd⁰ 98 for the next catalytic cycle. Aldehyde 106 has been isolated as a byproduct, apparently arising from 105 via a β-hydride elimination.

The stereochemistry of the latter reaction was investigated with the aid of the cis-alkenol 107 (Scheme 29). As expected (based on the discussion in the previous paragraph), the reaction proceeded as a syn-addition to produce 108. However, by using DPPE as a strongly chelating ligand, which apparently prevents the alkoxide coordination to palladium, the mechanism was pushed toward anti-addition, giving rise to the diastereomeric product 109. Amine 110 reacted in the same way.

The syn-addition mechanism has been masterly utilized in the cyclization, where the stereochemistry was controlled by the residing chiral center in the secondary alcohol 111 (Scheme 30). Here, the initial oxidative addition to a Pd⁰ catalyst produces 112, where the C–C bond is coordinated to Pd. Two diastereofacial ways of this coordination can be considered, so that a mixture might be expected. However, the subsequent replacement of bromide in the Pd coordination sphere with the neighboring alkoxy group (to generate 113) is apparently faster for one stereoisomer (as, e.g., in Scheme 21), which in view of the reversibility of the η¹-coordination results in dynamic stereodifferentiation. Hence, isomer 114 is thus formed preferentially and the subsequent reductive elimination affords the cyclization product 115 of high diastereopurity.

Further investigation revealed that the stereochemistry of amidopalladation is subjected to delicate effects of the anion in the original PdX₂ catalyst and ligand (Scheme 33). With the monodeuteriated substrate 122, the cyclization was catalyzed by two Pd⁰ salts in the presence or absence of ligand 125 and the products were analyzed for the content of deuterium in the resulting cyclic olefins 123 and 124. The latter analysis demonstrated that the chelation of Pd (and thus the syn-pathway) is suppressed when the combination of (CF₃CO₂)₂Pd and ligand 125 is used, whereas the remaining reactions were dominated by the syn-pathway. To add to the complexity of the mosaic, the cyclic, stereo-specifically deuteriated sulfonamide 126 was found to be cyclized via the anti-pathway (with 127 and 128 as intermediates)

5. Intramolecular Amidopalladation

The first amidopalladation, analogous to alkoxypalladation, was explored in a stoichiometric experiment with enamide 116 and found to produce the azepine derivative 117 with the new C–N and C–Pd bonds related in a cis-fashion, which correspond to syn-addition (Scheme 31).

Further investigation revealed that the stereochemistry of amidopalladation is subjected to delicate effects of the anion in the original PdX₂ catalyst and ligand (Scheme 33). With the monodeuteriated substrate 122, the cyclization was catalyzed by two Pd⁰ salts in the presence or absence of ligand 125 and the products were analyzed for the content of deuterium in the resulting cyclic olefins 123 and 124. The latter analysis demonstrated that the chelation of Pd (and thus the syn-pathway) is suppressed when the combination of (CF₃CO₂)₂Pd and ligand 125 is used, whereas the remaining reactions were dominated by the syn-pathway. To add to the complexity of the mosaic, the cyclic, stereo-specifically deuteriated sulfonamide 126 was found to be cyclized via the anti-pathway (with 127 and 128 as intermediates).
ates), giving rise to 129, which lacks the label (Scheme 34).[54]

In this instance the reaction was catalyzed by Pd(OAc)$_2$ and would be expected to occur via the syn-addition pathway according to Scheme 33. However, in the previous study the final oxidant was molecular oxygen, whereas in Scheme 34 it was p-BQ, which is known to coordinate to Pd in an n$^1$-intermediate[55] and this should be regarded as a contributing factor. Also, the fact that the reaction was run under slightly acidic conditions may inhibit coordination of the tosylamide. Note that as a stoichiometric experiment with the cyclopentene analogue of 126, $N$-coordinated to (tBu$_2$bipy)PdCl, has been found to cyclize via the syn-pathway in DMSO in the presence of molecular oxygen (to simulate the catalytic conditions),[53a] clearly, more studies are required to define the relationship between the reaction conditions and the mechanism.

The syn-mechanism has been assumed (but not proven) for the cyclization of 130[56] and 131[57] (Scheme 35), where the chiral control is exercised by a chiral sulfinimide group and chiral ligand 132, respectively.

Two other amidation reactions have been reported recently (Scheme 36) but their stereochemistry has not yet been elucidated.[56] In accord with the previous observations (vide supra), the hydroxylamine derivative 133 produced the trans-configured pyrazolidine derivative 136 ($\geq 30:1$ dr).[56a] The latter products can be regarded as surrogates of 1,3-amino alcohols and diamines, respectively.

Finally, the O-allyl hemiaminal 137, prepared from the corresponding allylic alcohol and AcOHNHCbz, has been shown to undergo an analogous cyclization, giving rise to the trans-configured oxazolidine 138 (Scheme 37) but again without specification as to the actual stereochemistry of the cyclopalladation step.[59] This strategy has been developed as an approach to 1,2-syn-amino alcohols and employed in the synthesis of acosamine.[59]

5.2. Intramolecular Amidopalladation Followed by Arylation

The cascade of catalytic amidopalladation of olefins and arylation has been developed in parallel with oxypalladation (cf. Section 4.4). Thus, the Pd$^0$ species, generated from Pd(OAc)$_2$ and the diphosphine ligand 139 (Scheme 38),[60] and the diphosphine ligand 139 (Scheme 38) has been shown to catalyze the cyclization of the Boc-functionalized aminoalkene 142 to produce the piperidine derivative 145 with high diastereoselectivity. The latter outcome has been rationalized in a similar way as in the case of oxypalladation, namely by the initial oxidative addition to generate the Pd$^+$ complex 141, whose reaction with 142 (upon deprotonation with Cs$_2$CO$_3$) generates the Pd–N complex 143, where Pd is also coordinated to the C=C bond. The key addition across the C-N bond generates the piperidine derivative 145.
C=C bond thus occurs with a syn-mechanism to generate the $\eta^1$-complex \ref{144}, which affords the final product \ref{145} by reductive elimination and Pd\(^0\) that enters the next catalytic cycle.\cite{60,61}

The cyclization of the isomeric derivatives of hydroxylamine \ref{146} and \ref{148} (Scheme 38) was expected to proceed via the syn-mechanism\cite{62} in analogy to the related cyclizations highlighted in Scheme 38 (see also the evidence presented in Scheme 40). The syn-mechanism was than proved by isotopic labeling at the terminus of the double bond. Note, however, that while \ref{146} gave the cis-disubstituted isoxazolidine \ref{147} (typically with $\geq 20:1$ dr), its positional isomer \ref{148} that reacts by forming the C–O (rather than C–N) bond, furnished mainly the trans-product \ref{149} (7:1 dr). This change of stereochemistry was attributed to the steric interference by the Boc group 1,2-related to the phenyl in \ref{148}; a transition state leading to \ref{149} is believed to be lower in energy than that producing the cis-diastereoisomer (both using the syn-addition mechanism)\cite{62}.

Stoichiometric experiments (Scheme 40),\cite{63} employing the potassium salt \ref{150}, stereospecifically deuteriated at the terminus of the double bond, and the ArPdBr complex \ref{151}, lend further credence to the syn-mechanism (via \ref{152})\cite{63}. The same conclusion has been arrived at for an intermolecular, stoichiometric amination of (Z)-CHD=CHD with Ph$_3$N-[Pd]\cite{64} and for an intramolecular amidation of a deuterated cyclopentene substrate followed by $\beta$-H elimination.\cite{53a}

Another piece of complementary evidence was obtained from the catalytic cyclization of the deuteriated urea derivative \ref{154}. The relative configuration of the major product \ref{155} was found to be consistent with the syn-mechanism of the addition (Scheme 41).\cite{65}

On the other hand, cyclization of the deuteriated acetamide \ref{156a}, carried out in the absence of a strong base, afforded the arylated pyrrolidine derivative \ref{157a} (Scheme 42) as a result of an anti-amidopalladation ($\ref{156a} \rightarrow \ref{157a}$). The Pd\(^0\) species \ref{157a} thus generated is oxidized with N-fluorosulfonimide to afford the corresponding Pd\(^{IV}\) complex. The latter intermediate then effects an electrophilic attack on toluene with retention of configuration to produce the C-arylated derivative \ref{158} (thus accomplishing a C–H activation). The stereochemistry of the anti-amidopalladation has been confirmed by a stoichiometric experiment, in which \ref{156b} was converted into the stable bipy complex \ref{159}, characterized by NMR spectroscopy.\cite{66} The dramatic difference in the two mechanisms described in Schemes 41 and 42 apparently originates in the actual reaction conditions: in the former case, the amide-type nitrogen in \ref{154} is deprotonated by a strong base, which increases its propensity to coordinate the palladium catalyst. In the latter case the base is absent and the palladium apparently prefers to first coordinate to the C=C bond; the resulting species then undergoes a traditional attack from the opposite face as in any classical electrophilic addition. Numerous other examples highlight the application of this palladium-catalyzed intramolecular amidopalladation of alkenes...
in the synthesis of various nitrogen heterocycles.\textsuperscript{[67,68]} In the most recent examples both amidation and arylation were carried out as intramolecular processes to produce polycyclic structures.\textsuperscript{[69]} This area has also been reviewed.\textsuperscript{[70]}

### 5.3. Intramolecular Amidopalladation Followed by a Second Amidation

The amine-type nitrogen, being trivalent, offers another dimension in synthetic strategy that is not available to the divalent oxygen: while intramolecular alkoxypalladation produces a cyclic ether that cannot be further elaborated on the oxygen, the analogous amidopalladation features an additional \(N\)-substituent that can be involved in the subsequent events. Thus, the urea derivative 160 has been shown to undergo double cyclization to give the \textit{trans}-configured bicyclic product 163 (Scheme 43).\textsuperscript{[71]} The stereochimetry of this cascade was rationalized as follows: the initial amidopalladation (presumably proceeding with the established \textit{syn}-mechanism) generates the Pd-chelate 161, in which Pd is replaced by bromide from CuBr\(_2\) with \(S_N^2\) inversion and the resulting bromo derivative 162 undergoes cyclization with a second inversion to produce 163.\textsuperscript{[71]} However, an alternative pathway, involving \textit{anti}-amidopallada-

A different type of bis-amidation has been reported for the stilbene-derived bis-sulfonamide 169 (Scheme 45).\textsuperscript{[73]} Here, the first cyclization presumably proceeds with \textit{anti}-stereochemistry\textsuperscript{[74]} and the arising Pd\(^{\text{II}}\) species is believed to be oxidized by PhI(OAc)\(_2\) to generate Pd\(^{\text{IV}}\), which enables its replacement with the second sulfonamide group to produce 170.\textsuperscript{[75]}

The deuteriated substrate 156b was used again to elucidate the diamidation process that afforded the pyrrolidine derivative 172 (Scheme 46). The latter outcome corresponds to the initial \textit{anti} amidopalladation generating the Pd\(^{\text{II}}\) species 157b (as in Scheme 42). The latter complex then undergoes oxidation with (PhSO\(_2\))\(_2\)NF, giving rise to the Pd\(^{\text{IV}}\) species 171, which is then converted into the final product 172 on reaction with the imide anion via an \(S_N^2\) inversion.\textsuperscript{[76]}

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\textbf{Scheme 42.} Intermolecular amidopalladation followed arylation with C–H activation.

\textbf{Scheme 43.} Catalytic intramolecular bis-amidation.

\textbf{Scheme 44.} Catalytic intramolecular bis-amidation.

\textbf{Scheme 45.} Catalytic intramolecular double-amidation.
5.4. Intramolecular Amidopalladation Followed by Carbonylation

Intramolecular amidopalladation of olefinic amides, sulfonamides, and ureas 173–177 in the presence of carbon monoxide and methanol (Scheme 47) has been reported to afford products corresponding to the anti-mechanism, irrespective of the configuration of the C=–C bond in the starting molecule.

The reaction conditions are mild: atmospheric pressure of CO, room temperature, and CuCl₂ as the terminal oxidant. Both 5-exo and 6-exo cyclizations were attained. In the case of the urea derivatives 175 and 176, trapping of the acyl–Pd intermediate with the second nitrogen was observed in the absence of methanol to give 180 and 181. In the latter instance, the chloro derivative 182 was also obtained, apparently as a product of the S₂N₂ substitution of Pd in the intermediate by chloride ion (as in the case of 21 and 161).

With a free hydroxy group in the molecule as in 184, the initial amidation has been found to continue by lactonization to the neighboring hydroxyl (Scheme 48). The yield of the resulting lactone 186 was maximized by replacing MeOH (as a solvent and competitor) with AcOH. While the stereochemistry of the initial amidopalladation has not been investigated in this instance, it was assumed to correspond to the anti-delivery. The diastereoselectivity is controlled by the hydroxy group, presumably by Pd coordination (185).

Finally, the Boc-protected hydroxylamine derivative 189 has been shown to undergo the cyclization/carbonylation with an overall syn-addition across the double bond, giving rise to the isoxazoline derivative 191 (Scheme 49). The stereochromic outcome apparently originates from the initial coordination of the Boc group to Pd (190), followed by syn-amidopalladation and subsequent carbon monoxide cleavage of the Pd–
carbon bond with retention of configuration. The striking contrast between the stereochemistry of the carbonylative cyclization of the amides shown in Scheme 47 and the latter case is puzzling, as the reaction conditions are very similar. One explanation is that CuCl$_2$ was used in Scheme 47, whereas Cu(OAc)$_2$ was employed in the cyclization of 189 (Scheme 49). The use of CuCl$_2$ leads to a high chloride concentration, which makes it more difficult for the amide to coordinate to palladium, and hence the anti-pathway should be favored. Furthermore, the latter reaction was carried out in the presence MeC(OMe)$_3$, which could modify the pH of the mixture and thus improve the propensity of the ONHCO$_2$(tBu) group to coordinate to palladium.

6. Intermolecular Amidopalladation

The intramolecular amidopalladation has been shown to mostly proceed as a syn-addition, which apparently stems from the considerable entropic advantage of the neighboring group over an external nucleophile. This factor is absent in intermolecular additions, which may change the stereochemistry, as demonstrated convincingly for the Wacker oxidation (see Chapter 2).

6.1. Amidoacetoxylation

While terminal olefins have been shown to readily undergo intermolecular Pd-catalyzed amidoacetoxylation,$^\text{[79]}$ their internal counterparts resisted a number of attempts. Finally, cis-olefins, such as 192 (Scheme 50), have been successfully converted into the amidoacetoxylation products on reaction with phthalimide in the presence of PhI(OAc)$_2$, as the oxidizing agent of palladium. The reaction was originally formulated as proceeding via an initial syn-amidopalladation. However, recent re-investigation,$^\text{[80]}$ prompted by the results of the related diamidation (see the next subchapter), demonstrated that the original structural assignment of the product$^\text{[81]}$ was incorrect. This finding led to a revision of the mechanism, according to which the initial amidopalladation of 192, catalyzed by Pd$^\text{II}$, proceeds as a pure anti process (rather than syn) to generate the palladium(II) intermediate 193 that is subsequently oxidized by the hypervalent iodine reagent to produce the Pd$^\text{IV}$ species 194. The latter reaction prevents the usual $\beta$-elimination and is followed by the S$_\text{N}^2$ replacement of palladium with acetate (i.e., with inversion of configuration$^\text{[82]}$) to afford the final product 195 that is anti-configured (rather than syn), according to X-ray analysis.$^\text{[83,85]}$ Noteworthy is also the high regioselectivity of this cascade, owing to the preferential attaching of the palladium moiety to the benzylic position (193).$^\text{[84]}$

By contrast, the behavior of terminal olefins has been shown to be more complicated: Thus, with the aid of the stereospecifically deuteriated olefin 196 (Scheme 51), the reaction was found not to be stereoselective, giving rise to a ~4:3 mixture of diastereoisomeric amidopalladation products (analogous to 195). The latter outcome has been attributed to the poor stereoselectivity of the replacement of Pd with acetate in the final step. On the other hand, under aerobic conditions (i.e., in the absence of the hypervalent iodine reagent), the formation of the (E)-enamide 198 was ascribed to the syn-addition, generating 197, followed by the ordinary syn-stereoselective elimination of [PdH]. However, it is pertinent to note that the product 198 was isolated in merely 5% yield (together with 70% of the recovered starting material).$^\text{[80]}$

6.2. Diamidation

In analogy to acetoxyamidation, the recently developed diamidation (Scheme 52) has also been found to be specific to cis-olefins, such as 199. The formation of the anti-configured of final product 202 has been rationalized by the initial anti-addi-

![Scheme 50. Intermolecular amidoacetoxylation of internal olefins.](image)

![Scheme 51. Intermolecular aerobic amidoacetoxylation of terminal olefins.](image)

![Scheme 52. Intermolecular diamidation of internal olefins.](image)
7. Overview of the Stereochemical Outcome in Nucleophilic Addition

The syn/anti-dichotomy in the nucleophilic additions was discussed mainly for oxygen and nitrogen nucleophiles. The stereochemical trends are summarized in Table 1, which covers cyclization processes (entries 1–28) and intermolecular reactions (entries 29–33).

The intramolecular alkoxypalladation-carbonylation cascade with carbon monoxide and alcohol as the stoichiometric reactants (reaction A) preferentially proceeds via the anti-pathway (entries 1–3), except for the examples, where this mechanism is disfavored by geometrical restrictions in the substrate (entry 4). On the other hand, anti/syn dichotomy has been observed for the analogous amidopalladation–carbonylation (reaction H; entries 27 and 28). Here, the dramatic difference in the stereochemistry can be tentatively attributed to the difference in the pH (neutral vs acidic), which is likely to influence the coordination capabilities of the participating amionic group.

Stereochemistry of the intramolecular alkoxypalladation-β-elimination cascade (reaction B; entries 5–7) can be controlled by the anion: thus, with PdCl₂, that is, with strongly coordinating chlorides, especially in the presence of additional LiCl, the potential coordination of the participating alcohol group to Pd is disfavored and the reaction proceeds as an anti-addition (entry 5). On the other hand, with a weakly coordinating anion (BF₄⁻ or CF₃CO₂⁻), Pd₂ can become coordinated to the participating OH group, which results in the preferential syn-addition (entries 6 and 7), regardless of the oxidizing reagents or solvent.

### Table 1. Stereochemistry of the Pd²⁺-catalyzed addition of nucleophiles to C–C bond: intramolecular (entries 1–28) and intermolecular (entries 29–33).

| Entry | Reaction | Scheme | syn/anti | PdX₂ | Ligand | Oxidant | Solvent | Additive | T [°C] | Ref. |
|-------|----------|--------|----------|-------|--------|---------|---------|---------|--------|------|
| 1 A[b] | 21 | anti | PdCl₂ | – | CuCl₂ | MeOH | CO | RT | [36] |
| 2 A[b] | 22 | anti | PdCl₂ | – | CuCl₂ | MeOH | CO | RT | [39] |
| 3 A[b] | 23 | anti | PdCl₂ | – | CuCl₂ | MeOH | CO, LiCl | RT | [3a] |
| 4 A[b] | 24 | syn | PdCl₂ | – | CuCl₂ | MeOH, CH₂Cl₂ | CO, MeC(O)Me | RT | [40] |
| 5 B[b] | 25 | anti | PdCl₂ | – | p-BQ | THF | LiCl | reflux | – | [42] |
| 6 B[b] | 25 | syn | PdCl₂ | – | p-BQ | MeOH | – | 40 | [42] |
| 7 B[b] | 26 | syn | Pd(OCCF₃)₂ | bipy²⁺ | O₂ | tolue | 3 Å MS | 80 | [44] |
| 8 C[b] | 28 | syn | Pd(dbta)₂ | dpe-phos (139)²⁺ | – | THF | BuNona, ArBr | 65 | [47] |
| 9 C[b] | 29 | syn | Pd(dbta)₂ | (t-MeOC₃H₅)²⁺ | – | tolue | BuNona, ArBr | 105 | [48] |
| 10 C[b] | 29 | anti | Pd(dbta)₂ | dpee,C₅H₅²⁺ | – | tolue | BuNona, ArBr | 105 | [48] |
| 11 C[b] | 30 | syn | Pd(dbta)₂ | (t-MeOC₃H₅)²⁺ | – | tolue | BuNona, ArBr⁺²⁺ | 105 | [48] |
| 12 D[b] | 31 | syn | PdCl₂ | – | MeCN | – | MeCN | – | RT | [50] |
| 13 E[b] | 32 | syn | Pd(OAc)₂ | pyridine | – | – | calculations | RT | [51,52] |
| 14 E[b] | 33 | syn | Pd(OAc)₂ | 125⁷⁺ | O₂ | tolue | 3 Å MS | 25 | [52,53] |
| 15 E[b] | 33 | anti | Pd(OAc)₂ | 125⁷⁺ | O₂ | tolue | 3 Å MS | 25 | [52,53] |
| 16 E[b] | 33 | syn | Pd(OAc)₂ | – | O₂ | tolue | 3 Å MS | 25 | [52,53] |
| 17 E[b] | 34 | anti | Pd(OAc)₂ | – | p-BQ | THF, DMSO | AcO₂H, AcO₂Na | 50 | [54] |
| 18 E[b] | 38 | syn | Pd(OAc)₂ | 139⁷⁺ | – | dioxane | Cs₂CO₂, ArBr | 105 | [60,61] |
| 19 E[b] | 39 | syn | Pd(dbta)₂ | (Bu)Br²⁺ | – | tolue | BuNona, ArBr | 65 | [62] |
| 20 E[b] | 39 | syn | Pd(dbta)₂ | Xanphos²⁺ | – | tolue | BuNona, ArBr | 65 or 110 | [62] |
| 21 F[b,c] | 40 | syn | Pd(dbta)₂ | dppp²⁺ | – | THF | (Me₅Si)₅N, ArBr₂ | 23–60 | [63,64] |
| 22 F[b,c] | 41 | syn | Pd(dbta)₂ | Siphos-PE | – | xylene | BuNona, ArBr | 115 | [65] |
| 23 F[b,c] | 42 | anti | Pd(dbta)₂ | (PhSO₂)₂NF²⁺ | – | tolue | ArOH, tolue | RT | [66] |
| 24 G[b,c] | 43 | anti | Pd(OAc)₂ | NaBr₂, DMF | CuBr₂ | NaPO₂ | 40 | [71] |
| 25 G[b,c] | 44 | syn | Pd(OAc)₂ | NaBr₂, DMF | CuBr₂ | NaPO₂ | 40 | [72] |
| 26 G[b,c] | 46 | anti | Pd(OCCF₃)₂ | (PhSO₂)₂NF²⁺ | – | tolue | (PhSO₂)₂N | RT | [66] |
| 27 H[b] | 47 | anti | PdCl₂ | – | CuCl₂ | MeOH or AcO₂H | CO | RT | [75] |
| 28 H[b] | 49 | anti | PdCl₂ | – | Cu(OAc)₂ | MeOH, CO, MeC(O)Me | 50 | [77] |
| 29 I[b] | 50 | anti | Pd(OAc)₂ | – | p-BQ | AcO₂H | AcO₂Na | RT | [22] |
| 30 J[b] | 19 | anti | PdCl₂ | – | MeCN | – | THF | Me-NH₂ | –40 | [31] |
| 31 K[b] | 50 | anti | PdCl₂ | – | Ph(OAc)₂, (CH₂Cl₂) | O₂ | phthalimide, ArOH | 70 | [80] |
| 32 E[b] | 51 | syn | PdCl₂ | – | PdCl₂ | (CH₂Cl₂) | phthalimide, ArOH | 70 | [80] |
| 33 G[b] | 52 | anti | PdCl₂ | PhCN | Ph(OAc)₂, (CH₂Cl₂) | phthalimide, TsNH₂ | 70 | [85] |

[a] A = alkoxypalladation-carbonylation; B = alkoxypalladation-HPdX₂ elimination; C = alkoxypalladation-arylation; D = amidopalladation; E = amidopalladation-HPdX₂ elimination; F = amidopalladation-arylation; G = diamidopalladation; H = amidopalladation-carbonylation; I = acetoxypalladation; J = aminopalladation; K = amidooxetation. [b] Intramolecular reaction. [c] Note that the reaction cannot proceed via 4(O)exo-trig cyclization. [d] Stoichiometric reaction. [e] The starting amide was first deprotonated. [f] Intramolecular reaction. [g] A different interpretation suggests anti-stereochemistry; see the comments in the text. [h] Chelating ligand. [i] Required in the second step, where the Pd²⁺ intermediate 157 is oxidized to generate a Pd⁴⁺ species that then reacts with tolue via a C–H activation. [j] Required in the second step for the oxidation 157 (Pd⁴⁺) → 171 (Pd⁴⁺); the latter species then undergoes an S₂,2'-type introduction of the second nitrogen group. [k] Required in the second step for the oxidation 193 (Pd⁴⁺) → 194 (Pd²⁺); the latter species then undergoes an S₂,2'-type introduction of ACO. [l] ArBr is connected to the C–C bond by a linker. [m] Note the dynamic stereodifferentiation by the residing chiral center. [n] Only 5% yield.
The analogous intramolecular amidopalladation-β-elimination cascade (reaction E; entries 13–17) also exhibits the syn/anti dichotomy, depending on the actual conditions: thus, the reactions catalyzed by \( \text{Pd(OAc)}_2 \) or \( \text{Pd(O}_{2}\text{CCF}_3)_2 \) follow the syn-pathway (entries 13, 14, and 16); however, the presence of ligand \( \text{125} \) has been found to drive the reaction catalyzed by \( \text{Pd(O}_{2}\text{CCF}_3)_2 \) toward the anti-mechanism (entry 15). By contrast, this ligand effect was not observed in the case of \( \text{Pd(OAc)}_2 \) (entry 14), which is rather intriguing. The change of the oxidizing agent (p-BQ vs \( \text{O}_3 \)) and the solvent (THF-DMSO vs toluene) and additives, namely AcOH/\( \text{AcONa} \), has been found to also drive the reaction toward anti-mechanism (compare entries 14 and 16 with 17). Calculations predict the syn-mechanism (entry 13), which was also observed for the stoichiometric cyclization using \( \text{PdCl}_2 \) (reaction \( \text{D} \); entry 12), where the palladated product was isolated.

The intramolecular alkoxy palladation-arylation cascade (reaction C; entries 8–11) requires a strong base (as in the Hartwig-Buchwald arylation), which converts the participating alcohol into a strongly coordinating alkoxide. As a result, the initial alkoxy palladation favors the syn-mechanism (entries 9 and 11). Addition of a chelating ligand may change the stereochemical course to anti (entry 10) but apparently not always (entry 8), especially when THF is used as a solvent (entry 8) instead of toluene (entry 10).

In analogy, the intramolecular amidopalladation-arylation cascade (reaction F; entries 18–22), also occurring in the presence of a base, invariably proceeds as a syn-addition, regardless of the solvent or the nature of the ligand employed. On the other hand, the reaction that involves oxidation to \( \text{Pd}^{IV} \) in the second step (required for the C–H activation of the “nucleophile”) has been shown to proceed with anti-stereochemistry, even when catalyzed by \( \text{Pd(O}_{2}\text{CCF}_3)_2 \) (entry 23). The outcome in the latter case can be attributed to the absence of the base, which renders the participating N-nucleophile less prone to coordination of the \( \text{Pd}^{IV} \) catalyst.

Intramolecular diamidopalladation (reaction G; entries 24 and 25) has been found to prefer the syn-mechanism, apparently due to the same effects as those discussed for entries 18–22. Again, this reaction, involving the \( \text{Pd}^{III} \rightarrow \text{Pd}^{IV} \) oxidation and proceeding in the absence of a base, favors the anti-pathway (entry 26).

Intermolecular hydroxypalladation clearly prefers the anti-mechanism, as shown by the recent studies of the Wacker oxidation (Schemes 14–17). In analogy, intermolecular catalytic acetoxypalladation (reaction I; entry 29) also follows the anti-pathway. The same stereochemistry has been demonstrated for the stoichiometric intermolecular aminopalladation with Me₂NH (reaction J; entry 30).

Intermolecular amidoacetoxylation (reaction K; entry 31) and diamidopalladation (reaction G; entry 33), catalyzed by \( \text{PdCl}_2 \) (which disfavors coordination of the nucleophile to \( \text{Pd} \)), give the anti-addition products. By contrast, the intermolecular amidopalladation-β-elimination cascade (reaction E; entry 32), catalyzed by \( \text{Pd(OAc)}_2 \), favors the syn-mechanism, which seems to be the only experimentally proven example of syn-migration in intermolecular nucleopalladation with O- and N-nucleophiles (although only in 5% yield) to date. Note that this reaction proceeds with a different oxidizing agent (\( \text{O}_3 \)) than those cited in entries 31 and 33, and that it does not involve the \( \text{Pd}^{IV} \) species. This, however, is unlikely to have a major effect on the mechanism of the first step; it appears that the key point here is the use of \( \text{Pd(OAc)}_2 \) rather than \( \text{PdCl}_2 \) as the catalyst.

### 8. Conclusion

This review has discussed the stereochemistry of the palladium-catalyzed addition of nucleophiles to alkenes and application of these processes in organic synthetic transformations. The syn/anti-dichotomy in the nucleophilic additions was discussed, mainly with oxygen and nitrogen nucleophiles. A general picture is emerging that in intermolecular reactions the anti-addition of the oxygen and nitrogen nucleophiles to (alkene)\( \text{Pd}^{IV} \) complexes is strongly favored. However, in intramolecular reactions a special situation arises when the nitrogen or oxygen nucleophile coordinates to \( \text{Pd}^{IV} \). In this case there is no nucleophile available for external attack since there is a 1:1 ratio between the nucleophilic site and substrate. Therefore, the syn-attack is tremendously favored in the intramolecular cases where the nucleophile is coordinated to the metal. However, stereochemistry of the intramolecular reactions is dependent on the coordination capability of the internal nucleophile, which can be modified by the reaction conditions, so that the whole process can be driven either to the syn- or anti-pathway. In the intermolecular process, there will always be a considerable amount of free nucleophile in solution and therefore coordination of the nucleophile does not shut down the external anti-pathway as is done in the intramolecular case. As a result, external anti-attack is the predominant pathway in the intermolecular nucleophilic addition to (alkene)\( \text{Pd}^{IV} \) complexes.

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### Keywords:

alkenes · catalysis · nucleophilic addition · palladium · stereochemistry

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Originally, this transformation required PDCl₃, or the presence of Cl⁻ as in the original Wacker protocol. The chloride-free oxidation (with p-BQ as the terminal oxidant) was first shown to require the addition of a strong Bronsted acid (namely HClO₄), which prevents the precipitation of Pd-black by pushing the equilibrium HPdX⁺ + Cl⁻ ⇌ HX + PdCl₂ to the left:

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