Recent Advances in Oxypalladation of Alkenes

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Abstract: Intramolecular cyclizations involving oxypalladation as a key step provide useful entries to oxygen-atom containing heterocycles. The oxypalladation process is highly indispensable rout to synthesizing acetals or ketones. Surveyed in this article is recent progress relevant to these oxidations from both synthetic and mechanistic viewpoints, and particular attention will be paid to the role of molecular oxygen and copper salts in palladium catalysis.

1. Introduction

Nucleophilic attack on alkenes coordinated to PdX₂ (X=Cl, OAc, etc) is one of the fundamental reactions in the chemistry of palladium. Oxygen nucleophiles such as water, alcohols, phenols, and carboxylic acids thus react with alkenes to form oxypalladation intermediates, from which β-palladium hydride elimination takes place to give oxygenated products (Scheme 1). Typically, water reacts with terminal alkenes in the presence of PdCl₂ catalyst to give the corresponding methyl ketone, which represents an invaluable functionalization step in organic synthesis (ref. 1). Subjecting the reactive oxypalladation intermediate to a variety of substrates has enabled us to develop a myriad of synthetic reactions. In particular, intramolecular versions of the reaction have become a versatile tool for synthesizing heterocycles hitherto inaccessible (ref. 2, 3).

As for this type of reactions, much attention has been devoted to enhancing the catalytic efficiency of palladium species (ref. 4). These studies are largely dependent on the concept that Pd(0) arising from XPdH species is reoxidized to Pd(II) by chemical reoxidants such as CuX₂ (X=Cl, OAc, NO₃) (ref. 1a), benzoquinone (ref. 5), and heteropolyacids (ref. 6). The catalysis using CuX₂ and O₂ is usually represented by eqs. 1-2 where O₂ acts as a simple oxidant of CuX. In contrast to this, we have proposed an entirely different mechanism (ref. 3), in which the oxidation state of palladium(II) does not change during the reaction, but the catalysis is promoted by a Pd-Cu hydroperoxide species which is derived from the XPdH species and O₂ (eq. 3). In this mechanism, the role of O₂ is quite different from that

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\begin{align*}
\text{Pd}(0) & + 2 \text{CuX} \rightarrow \text{PdX}_2 + 2 \text{CuX} \quad (1)
\end{align*}
\]

\[
\begin{align*}
2 \text{CuX} + 1/2 \text{O}_2 + 2 \text{HX} \rightarrow 2 \text{CuX}_2 + \text{H}_2\text{O} \quad (2)
\end{align*}
\]

\[
\begin{align*}
\text{Pd} & \quad \text{Cu} \quad \text{H} \quad \text{O}_2 \rightarrow \text{Pd} \quad \text{Cu} \quad \text{OOH} \quad \text{X} \\
\end{align*}
\]

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conveyed by the conventional view. In line with such contexts, we describe here recent progress in the oxypalladation of alkenes based on their synthetic and mechanistic viewpoints, and particular attention will be paid to the role of molecular oxygen and copper salts in palladium catalysis.

2. Intramolecular Oxypalladation

Intramolecular oxypalladation of hydroxyalkenes shown in Scheme 2 has become a unique method for synthesizing oxygen-atom containing heterocycles in which $\beta$-palladium hydride elimination leads to vinyl substitution as an energetically favorable process in comparison with the exo-methylene substitution pathway. Subsequent to the elimination step, the reaction proceeds catalytically with Pd in the presence of copper salts and $O_2$. Typically, $\gamma$, $\delta$-unsaturated alcohol 1 can be converted to 2-vinyltetrahydrofuran 2 (eq. 4) (ref. 8), while homallylphenol 3 is transformed to 2-vinylchroman 4 which corresponds to a Vitamin A moiety (eq. 5) (ref. 9). In cyclizations of this type, regioselective nucleophilic attack of oxygen atom on alkenes depends on the nature of the anionic ligands (X) coordinated to Pd(II). Thus, the use of PdCl$_2$ in the cyclization of 5 (ref. 10) gives 6-membered chromene 6, whereas 5-membered tetrahydrofurans (7+8) are yielded as main products using Pd(OAc)$_2$.

![Scheme 2](image)

The enantioselective cyclization of 2-(2-butenyl)phenols 9 proceeds catalytically by using the optically active [(n$^3$-pinene)Pd(OAc)$_2$ (10) catalyst with Cu(OAc)$_2$ and $O_2$ to give 2-vinyl-2,3-dihydrobenzofurans 11 (eq. 6). The enantioselectivity of 11 (R= OCH$_3$, 26 %ee) correlates with the electronic properties of substituents R on the phenoxy group, and decreases in the order of OCH$_3$ $\lambda$ CH$_3$ $\lambda$ H $\lambda$ Cl $\lambda$ COCH$_3$ (ref. 11). The $[\alpha]D$ value of product 11 (R=H) has been found to be constant, irrespective of the reaction times (ref. 7). This means that the pinanyl ligand is retained by Pd(II) throughout the reaction. The rate of cyclization becomes faster as the relative ratio of added Cu(OAc)$_2$ to 10 increases and reaches a maximum when Cu/Pd is 1. These facts can be rationalized as shown in Scheme 3, where the Pd-OOH 13 species coupled with copper salt acts as the active catalyst. The copper salt is required to accelerate oxygenation of the Pd-H species 12 by $O_2$. The pinanyl ligand is retained by a Pd(II) species throughout the reaction, indicating that no decomposition of the H-Pd-OAc species 12 to $\ldots$
Pd(0) and HOAc takes place. Accordingly, the conventional redox couple of eqs. 1 and 2 is not operative in this reaction. If such is the case, then cyclization should proceed in the absence of a copper salt. Indeed, the cyclization of 2-(2-cyclohexenyl)phenol 14 does proceed catalytically in the presence of Pd(OAc)₂ and O₂ only (eq. 7), and 0.5 mol of O₂ is constantly consumed for the production of 1 mol of cyclized products (15+16+17) (ref. 12).

The isomer distribution in eq. 7 is sensitive to any small changes in the reaction conditions. For instance, reducing the relative ratio of substrate 14 to Pd(OAc)₂ decreases the portion of 15. Addition of cyclohexene to the reaction system or the use of a highly coordinating solvent such as CH₃CN leads to 15 predominantly. Obviously, some product selectivity in this reaction would be desirable. Semmelhack has reported an intriguing result concerning this point (ref. 13): the reaction of 18 with an stoichiometric amount of Pd(OAc)₂ in solvents such as DMF, AcOH, or THF gives a mixture of 19, 20, and other isomeric products; however, the use of DMSO solvent leads to 19 virtually as a single product (eq. 8). Using this condition, enantiomerically pure tetronomycine 24 was synthesized from 21 as shown in Scheme 4, where the tetrahydrofuran unit 22 was constructed by a
Pd(II)-mediated alkoxycarbonylation of 21 derived from D-arabinose (ref. 14).

Intramolecular oxypalladation of alkenoic acids using DMSO solvent has been recently reported to proceed by the aid of O₂ alone with Pd(OAc)₂ catalyst and NaOAc (2 equiv) to give unsaturated lactones (eqs. 9-10) (ref. 15). Use of excess amounts of Cu(OAc)₂ (2 equiv) leads to a poor yield of the lactone, while reducing the amount of Cu(OAc)₂ (10 mol%) or omitting it completely results in higher yields (90-86%). In the cyclization of o-allylbenzoic acid (25), the use of Pd(OAc)₂ as a catalyst affords 5-membered phthalide 27 (ref. 15), whereas PdCl₂ leads to 6-membered 3-methylisocoumarin 26 (ref. 16), similar to the case of oxypalladation of 5 (vide supra).

Methyl glyoxylate adducts of N-Boc protected allylic amines are similarly cyclized in the presence of O₂ alone as the oxidant to give oxazolidines (eq. 11) (ref. 17). In this case, the product yields are not affected by an excess use of Cu(OAc)₂ (3 equiv). Detachment of methyl glyoxylate moiety of the vinyloxazolidine using anodic oxidation gives N-Boc-protected β-amino alcohol (eq. 11). Application of this methodology to the synthesis of enantiopure natural products such as the sphingosines is expected to be realized. Formaldehyde aminals derived from N-Boc protected allylic amines are similarly converted into imidazolidines (eq. 12) by Pd(OAc)₂ catalyst and O₂ in DMSO (ref. 18). After removal of a formyl group from the 5-exo cyclized product shown in eq. 12, the N-protected vicinal diamine can be obtained by using anodic oxidation. The catalysis of Pd(OAc)₂/DMSO/O₂ system is thought to proceed in such a way that the palladium (0) cluster formed in the cyclization is stabilized by DMSO acting as a ligand and this is readily reoxidized by O₂ (ref. 19).

Intramolecular oxypalladation of hydroxyalkenes in the presence of alcohols and weak bases provides a useful method for synthesizing semiacetals. Thus, the treatment of (2S,3S)-2-allyl-hydroxybutyrate 28 with methanol in the presence of PdCl₂(MeCN)₂ catalyst, CuCl (3 equiv), and
Na₂HPO₄ under O₂ gives semiacetal 29. The reaction is thought to proceed via the vinyl ether intermediate 30 derived from intramolecular oxypalladation and Pd-H elimination (ref. 20). The C-2 methoxy group of 29 is readily replaced by an allylic moiety upon treatment with allylsilane in the presence of TiCl₄ to give 31 (>99 %de).

When an internal alkene bears an electron-withdrawing group, the cyclization is facilitated. Thus, the D-arabinose derivative 32 bearing an internal olefin is smoothly converted into β-furanoside 33 (ref. 21). Note that this type of cyclization is also catalyzed by PdCl(NO₂)(MeCN)₂ in the presence of CuCl₂ and O₂ (ref. 22).

Hydroxyalkenes derived from (R)-(−)- or (S)-(−)-phenethylamine and/or (S)-(−)-lactic acid or (1R, 2S)-(−)-ephedrine serve as the starting substrates for the synthesis of optically active tetrahydro-1,4-oxazines (morpholines) with high diastereoselectivity. An example is given in eq. 13 (ref. 23) where an excess amount of CuCl₂ was used as the oxidant in place of O₂. The high stereoselectivity is thought to be brought about by coordination of a Pd-Cu bimetallic complex toward the substrate as shown in 34.

Molecular oxygen in combination with CuCl also serves as the oxidant for Pd(OAc)₂-catalyzed intramolecular oxypalladation-olefination of hydroxyalkanes (eq. 14) (ref. 24).
3. Intermolecular Oxypalladation of Alkenes with Alcohols

Intermolecular oxypalladation of alkenes with alcohols is expected to produce acetals. Indeed, alkenes 35 (Z=COOMe, PhCO, CH(OAc)CN, Ph) bearing electron-withdrawing groups react with alcohols or diols to give terminal acetals 36 of aldehyde precursors in good yields (eq. 15) (ref. 25, 26). The use of chiral diols such as (R,R)-2,4-pentanediol gives the corresponding acetals which serve as the

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\begin{align*}
35 & \quad + \quad \text{ROH} \\
& \quad \xrightarrow{\text{PdCl}_2 (0.2 \text{ mmol}) \quad \text{CuCl} (2 \text{ mmol})} \quad \text{O}_2, \text{ DME} \\
& \quad \xrightarrow{\text{Z}} \quad \text{OR} \\
\end{align*}
\]

(15)

The use of chiral diols such as (R,R)-2,4-pentanediol gives the corresponding acetals which serve as the chiral reagents. The acetalization of vinyl ketones with 1,3-propanediol again proceeds catalytically by the aid of O₂ alone without using copper salt (ref. 27).

The acetalization of alkenes can be envisioned as shown in Scheme 5, where oxygen nucleophiles attack at the more electron-deficient C-1 carbon, giving rise to the oxypalladation intermediate 37. Elimination of Pd-H from 37 gives vinyl ethers 38 which coordinate to palladium. Readdition of Pd-H to the vinyl ethers followed by attack of ROH gives acetals 36 along with a XpdH species.

Scheme 5

Geminal disubstituted alkenes are less reactive because of ineffective coordination of Pd(II) to the alkenes. For example, methacrylic esters undergo only ~30% conversion under the same conditions in which acrylic esters are acetalized in more than 90% yield. However, the reactivity of methacryloyl moiety is enhanced by incorporation of oxazolidinones. Thus, prochiral geminal disubstituted alkenes 39 bearing chiral 4-tert-butyl or 4-phenyloxazolidine are smoothly acetalized with alcohols to give acetals 40 in high diastereoselectivity and good yields (ref. 28, 29). The acetals 40 are readily recrystallized to give single diasteromers which serve as a precursor of the optically active aldehyde 42 via 41. With this method, optically pure (S)-azetidinone 43 can be synthesized as shown in Scheme 6 (ref. 29). In addition to the synthetic utility of the present acetalization, the stereochemical outcome in the transformation of 39 into 40 provides detailed information on the reaction pathways such as 38 → 36 shown in Scheme 5 (ref. 28, 29).
The reaction of terminal alkenes bearing alkyl groups with alcohols or diols in the presence of Pd(II)-catalyst usually gives methyl ketones (eq. 16) (ref. 27, 30), where palladium attacks at the sterically less hindered site (C-1) of alkenes in an usual manner. The attack of alcohols occurs at C-2 carbon, and the resulting vinyl ethers or acetals having alkyl substituents are readily hydrolyzed under the reaction conditions to give methyl ketones. When bulky alcohols such as t-BuOH or i-PrOH are used as nucleophiles, the regioselectivity of ketonization is altered to a certain extent. Thus, the use of a catalyst system comprising of PdCl2(MeCN)2, CuCl2, CuCl, and LiCl in t-BuOH results in the formation of aldehyde 44 in 31% selectivity (eq. 17) (ref. 31). In this case, t-BuOH attacks Pd-coordinated to alkenes at the less hindered terminal carbon (C-1) to give t-butoxy vinyl ether intermediate which eventually leads to the aldehyde. When a Pd-NO2 catalyst, prepared by heating a mixture of PdCl(NO2)(MeCN)2 and CuCl2 in t-BuOH, is used, aldehyde 44 is also formed as the major product (60% selectivity) (ref. 32, 33). Certainly, aldehyde synthesis from simple alkenes using O2 holds much potential as an useful transformation in organic synthesis, but the results so far reported are not sufficient to warrant any practical application.

With terminal alkenes bearing heteroatom functionalities in allylic positions, nucleophilic attack of
MeOH occurs preferentially at the C-1 carbon to give terminal acetals of aldehyde precursors (eqs. 18, 19) (ref. 34, 35). The regioselectivity observed in eq. 18 is considered to be due to the chelation of a Pd-Cu heterometallic species to the substrate as depicted in 45 (ref. 34).

When acetic acid was allowed to react with cyclohexene in the presence of Pd(OAc)$_2$ catalyst, Cu(OAc)$_2$, and hydroquinone under O$_2$, cyclohexenyl acetate was formed in good yield (ref. 36). The reaction has been reported to involve acetoxypalladation followed by β-Pd-H elimination (ref. 37). A combination of Pd(OAc)$_2$ and Fe(NO$_3$)$_3$ also effects the allylic oxidation of alkenes (ref. 38).

4. Aspects of the Catalysis of Oxypalladation

The catalysis shown in Scheme 3 (Section 2) is promoted by a Pd-OOH species 13 coupled with copper salt which arises from the oxygenation of Pd-H species 12 by O$_2$. If a Pd-OOH species is formed in the absence of nucleophiles, the O atom transfer from this species to the alkene must take place. Indeed, when a catalyst system consisting of PdCl$_2$(MeCN)$_2$ (10 mol%), CuCl and hexamethylphosphoramide (HMPA) is used in anhydrous 1,2-dichloromethane (ref. 39), the oxidation of 1-decene proceeds catalytically to give 46 and 47 (eq. 20). The amount of O$_2$ uptake in this oxidation correlates well with that of products, and 0.5 mole of O$_2$ is consumed for the production of 46 and 47. Thus, two O atoms from molecular oxygen are incorporated into substrates to give methyl ketones. When the ratio of CuCl/PdCl$_2$ = 1/3, the rate of reaction reaches a maximum, suggesting the involvement of a Pd-Cu heterometallic species.

A reaction pathway of the oxidation is shown in Scheme 7. The reaction could be initiated via chloropalladation toward the alkenes followed by Cl-Pd-H elimination. Molecular oxygen activated by

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Scheme 7
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CuCl reacts with a Pd-H species to form Pd-OOH 48 from which hydroperoxypalladation (ref. 40) takes place to give 49. Cleavage of the Pd-C bond in 49 formally shown by arrow lines leads to methyl ketone...
and a Pd-OH species. Coordination of another alkene to palladium gives 50, and subsequent hydroxypalladation followed by \( \beta \)-Pd-H elimination affords another methyl ketone, completing the catalytic cycle. Thus, two O atoms of \( \text{O}_2 \) are incorporated into the alkene. The affinity of HMPA to strongly coordinate to metal salts (ref. 41) causes CuCl to be solubilized in the organic media by forming an HMPA-CuCl complex.

In homogeneous metal-catalyzed oxidations of simple alkenes by \( \text{O}_2 \), commonly a single O atom of \( \text{O}_2 \) is transferred to the substrate, and the other O atom is used for oxidation of co-substrates such as alcohols (ref. 42) (vide infra). In the light of this, the present oxidation is noteworthy in terms of both O atoms of \( \text{O}_2 \) being incorporated into substrates.

A remarkable feature of this catalyst system is the regioselective transformation of \( N \)-allylamide 51 into aldehyde 52, while methyl ketone 53 becomes the major product in the presence of water (eq. 21) (ref. 43). Among various oxidation of alkenes, there has been no precedent for such a complete reversal of the regioselectivity (ref. 44). The regioselective O atom transfer to the terminal olefinic carbon of \( N \)-allylamides must be attained via the chelating Pd-OOH species 54 as shown in Scheme 8. When water is present in the reaction system, coordination of \( \text{H}_2\text{O} \) to Pd(II) takes place to interfere in the chelation of the amide carbonyl. Attack of water to the alkene takes place in an usual manner to give methyl ketone 53. In other words, the present result justifies the existence of Pd-OOH species in this oxidation.

The oxidation of cyclopentene with PdCl\(_2\) catalyst and CuCl\(_2\) under \( \text{O}_2 \) in EtOH gives cyclopentenone (ref. 45). Co-oxidation of EtOH to MeCHO occurs here to give a Pd-H species which reacts with \( \text{O}_2 \) to afford Pd-OOH. Cyclopentenone is formed by this species. Of note is that involvement of Pd-OOH species derived from \( \text{O}_2 \) is increasingly being documented in several reactions such as PdCl\(_2\)-catalyzed oxidation of benzylic ethers into esters (ref. 46), PdBr\(_2\)-catalyzed oxidative rearrangement of propargyl esters into unsaturated aldehydes (ref. 47), PdCl\(_2\)-or Pd(OAc)\(_2\)-catalyzed conversion of silyl enol ethers to enones (ref. 39, 48), and PdCl\(_2\)-catalyzed hydroesterification of alkynes (ref. 49).

Recently our attention is being focused on the study to elucidate the involvement of Pd-Cu heterometallic species in the reaction depicted in Scheme 7 (ref. 50). When PdCl\(_2\)(MeCN)\(_2\) and CuCl were allowed to react with HMPA under an atmosphere of \( \text{O}_2 \) (eq. 22), isolation of the heterometallic cluster complex Pd\(_6\)Cu\(_4\)Cl\(_{12}\)O\(_4\)(HMPA)\(_4\) 55 and polymeric complex \([(\text{PdCl}_2\text{CuCl}_2\text{(HMPA)})_2]\)\(_n\) 56 was accomplished (ref. 51). Structures of these heterometallic complexes revealed by X-ray analyses are given below in which Cu and Pd atoms are linked to each other by a \( \mu \)-Cl ligand in both cases. Noteworthy is that the cluster complex 55 is the first example of a Pd-Cu \( \mu \)-O\(_4\) bridged complex derived from \( \text{O}_2 \).
The complex 55 readily undergoes O atom transfer to alkenes. Furthermore, either heterometallic complex 55 or 56 serves as a catalyst for the oxidation of alkenes with O_2 (eq. 23) in which both O atoms of O_2 are incorporated into alkenes. All these results indicate that the catalysis of PdCl_2 and CuCl with O_2 is certainly promoted by the Pd-Cu heterometallic species.

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\text{RCH=CH}_2 + \text{O}_2 \xrightarrow{\text{55 or 56 (cat)}} \text{RC(O)CH}_3
\]

References and Notes


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