Palladium in Some Selective Oxidation Reactions

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Transition metals have become important tools in synthetic organic chemistry, and a great number of selective organic transformations can be achieved by the use of transition metals. The unique ability of transition metals to activate organic substrates and promote catalytic reactions was recognized early, but it was not until 30 years ago that studies of the organometallic chemistry involved in these reactions began. Some early uses of transition metals include heterogeneous hydrogenation of alkenes, Haber–Bosch reduction of nitrogen to ammonia, Fischer–Tropsch synthesis,[1] transition-metal-catalyzed reactions of acetylenes,[2] and cobalt-catalyzed hydroformylation.[3] In none of the early applications had palladium occurred in any important transition-metal-catalyzed reaction.

In the middle of the 1950s interest in the organic chemistry of palladium chemistry was aroused. One event that stimulated the development of palladium chemistry was the discovery of the Wacker process in 1956 by a German research team (eq 1).[4] They rec-

$$CH_2{=}CH_2 + {}^1/_2O_2 \xrightarrow[CuCl_2]{PdCl_2} CH_3CHO \qquad (1)$$

ognized the importance of a nucleophilic attack by water on an intermediate (π-olefin)palladium complex.[4,5]

During the last two decades oxidation reactions utilizing palladium have developed so fast that palladium has become one of the transition metals most frequently used in organic transformations. Contrary to what is found for other transition metals, which usually are useful for only one or a few types of transformations, palladium complexes are known to catalyze or promote many different types of organic reactions. This is in part because palladium is able to coordinate a great number of different organic substrates and, furthermore, because it is one of the few metals that is effective in almost all fundamental organometallic reactions such as oxidative addition, reductive elimination, nucleophilic addition, insertion reactions, and β-elimination. An important aspect of palladium in organic synthesis is that palladium-assisted reactions proceed with high stereospecificity; homolytic pathways to produce radicals are rare in palladium chemistry. Scheme I illustrates the principle of a typical metal-assisted reaction. We see that three criteria must be fulfilled: (i) the metal must coordinate the organic substrate to give an organometallic complex, (ii) the coordinated organic substrate must be activated enough to undergo the desired reaction, and (iii) the organic product thus

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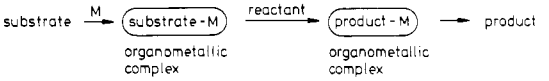
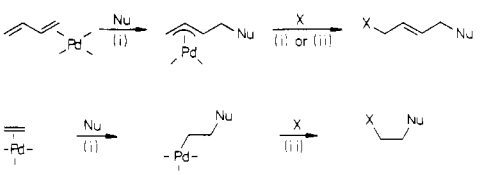
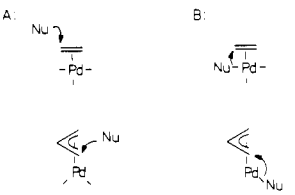
Scheme I



Scheme II



Scheme III



formed must now be released from the metal, which often involves the cleavage of a metal–carbon bond. In a catalytic process the cleavage reaction by which the organic product is released must occur spontaneously.

This Account will deal mainly with palladium-catalyzed or -promoted oxidations of alkenes and 1,3-dienes and related reactions. Often these reactions result in 1,2- and 1,4-functionalizations of the alkenes and dienes, respectively. The principle for these 1,2- and 1,4-additions is shown in Scheme II.

There are a few fundamental organometallic reaction steps involved in the functionalizations shown in Scheme II. These steps are (i) nucleophilic attack on (π-olefin)- and (π-allyl)palladium complexes and (ii) oxidative cleavage of palladium–carbon bonds.

Nucleophilic Attack on (π-Olefin)- and (π-Allyl)palladium Complexes

Nucleophilic addition to olefin and allyl groups coordinated to Pd(II) is known to take place with a variety of different nucleophiles. The stereochemistry and mechanism of these nucleophilic additions has been extensively investigated during the last decade.[6-20] Two

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(2) P. W. Jolly and G. Wilke, "The Organic Chemistry of Nickel", Academic Press, New York, 1975, Vol. 2, pp 94 and 194.
(3) M. N. T. Khan and A. E. Martell, "Homogeneous Catalysis by Metal Complexes", Academic Press, New York, 1974, Vol. 2, p 39.
(4) J. Smidt, W. Hafner, R. Jira, J. Sedlmeier, R. Sieber, R. Rüttinger, and H. Koijer, *Angew. Chem.*, **71**, 176 (1959).
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(6) (a) J. E. Bäckvall, in "Reaction of Coordinated Ligands", P. S. Braterman, Ed., Plenum Press, New York, in press; (b) F. J. McQuillin, *Tetrahedron*, **30**, 1661 (1974); (c) B. M. Trost, *ibid.*, **33**, 2615 (1977); (d) P. M. Henry, *Adv. Organomet. Chem.*, **13**, 363 (1975).
(7) (a) J. E. Bäckvall, B. Åkermark, and S. O. Ljunggren, *J. Am. Chem. Soc.*, **101**, 2411 (1979); (b) J. K. Stille and R. Divakaruni, *J. Organomet. Chem.*, **169**, 239 (1979).
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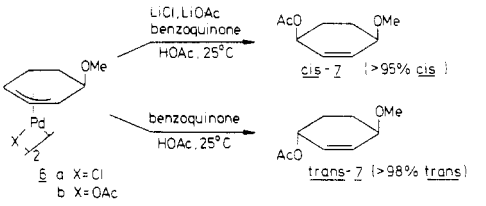
principal sterically different pathways for nucleophilic attack on (π-olefin)- and (π-allyl)palladium complexes have been observed (Scheme III). The nucleophile may either attack externally (trans attack, path A) or the nucleophile may attack the metal and subsequently migrate from the metal to carbon (cis attack, path B). In the case of olefinpalladium complexes, it has recently been suggested that the cis-migration pathway is frontier controlled.[6a] In the latter pathway the energy of the highest occupied molecular orbital of the metal–nucleophile bond (HOMO) will determine whether or not the nucleophile will migrate for a given olefin.

(π-Olefin)palladium complexes are spontaneously formed from palladium(II) and an olefin in solution.[21a] This is of great importance in preparative organic reactions involving nucleophilic additions to olefins and a necesssary requirement in a catalytic reaction. (π-Allyl)palladium complexes may also be spontaneously formed in solution from (i) 1,3-dienes and Pd(II)[21] or (ii) allylic halides or allylic acetates and Pd(0).[21,22] Another way of preparing (π-allyl)palladium complexes is from olefins by allylic C–H bond cleavage.[21,23]

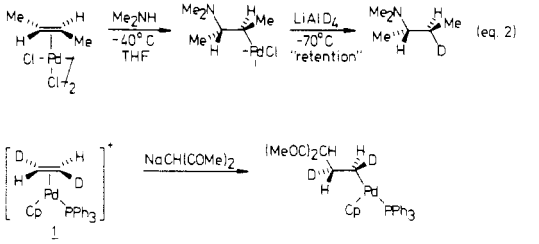
Nucleophilic addition to chelated dienes coordinated to Pd(II) affords stable adducts[24,25] and is known to occur with trans stereochemistry.[25] Although the corresponding adducts from monoolefins are less stable,

Scheme IV



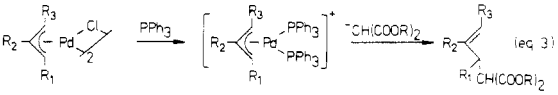
oxypalladation adducts are inferred in a number of oxidation reactions.[4,7,12] Stereochemical studies on nucleophilic addition of oxygen nucleophiles to monoolefins coordinated to palladium have shown that water,[7] methanol,[8,11a] and acetate[9] add with trans stereochemistry.

Addition of amines to monoolefin complexes of palladium at −40 to −50 °C proceeds smoothly with trans external attack (eq 2).[12,26] These adducts are relatively



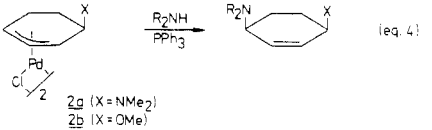
stable and can undergo further reaction with a variety of reagents, which will be discussed below. By working at low temperature (−50 °C) and using triethylamine as ligand, stabilized carbon nucleophiles can also be added to (π-olefin)palladium complexes.[27] Nucleophilic attack on the 18-electron complex 1 was shown to occur with trans stereochemistry.[11b] In the latter case the trans stereochemistry is greatly favored by the coordinatively saturated metal, however.

One of the first demonstrations of nucleophilic attack on (π-allyl)palladium complexes was by Tsuji in 1965, who studied the reaction of stabilized carbon nucleophiles with (π-allyl)palladium chloride.[28] The use of phosphines as ligands, later introduced by Trost[6c,13] enhances the rate of the reaction and enables the use of more substituted (π-allyl)palladium complexes (eq 3). Stereochemical studies have shown that the sta-



bilized carbon nucleophiles attack on the face of the π-allyl group opposite to that of palladium (cf. path A, Scheme III).[13]

Reaction of (π-allyl)palladium complexes with amines proceeds smoothly in the presence of phosphines.[29] In this case the nucleophilic attack also takes place by external trans attack (eq 4).[14a,b] From catalytic ami-



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(10) (a) P. M. Henry and G. A. Ward, *J. Am. Chem. Soc.*, **94**, 673 (1972); (b) A. Seignitz, P. M. Bailey, and P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, 698 (1973); (c) S. I. Murahashi, M. Yamamura, and N. Mita, *J. Org. Chem.*, **42**, 2870 (1977).
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(18) D. N. Jones and S. D. Knox, *J. Chem. Soc., Chem. Commun.*, 165 (1975).
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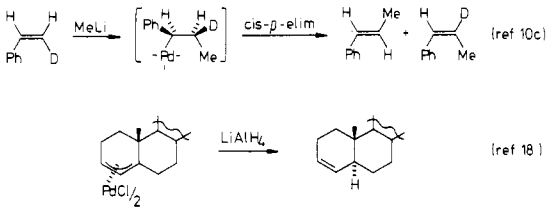
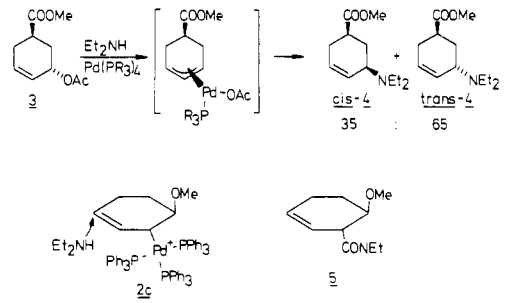
(29) (a) B. Åkermark and K. Zetterberg, *Tetrahedron Lett.*, 3733 (1975); (b) F. G. Stakem and R. F. Heck, *J. Org. Chem.*, **45**, 3584 (1980).

Scheme V



nation studies of allylic acetates it was suggested that both cis and trans attack by amine takes place.[14c] Thus, palladium(0)-catalyzed amination of *trans*-3-acetoxy-5-carbomethoxycyclohexene (**3**) gave a 35:65 mixture of *cis*- and *trans*-**4**. Similarly, *cis*-3-acetoxy-5-carbomethoxycyclohexene yielded a 65:35 mixture of *cis*- and *trans*-**4**. In contrast to these results is the high stereospecificity (>98% trans attack) for the amination of **2b** in the presence of phosphines.[14b] However, when the chloride was exchanged for BF_4^- (using $AgBF_4$), followed by addition of phosphine and subsequent amination, a less stereospecific reaction was observed (trans attack/cis attack ca. 90:10). In the latter case the small amount of cis attack might be the result of an S_N2' attack on a σ-allyl complex **2c**. In support for a σ-allyl complex, carbonylation of **2b** in the presence of diethylamine gave **5** as the only carbonylation product.[14b]

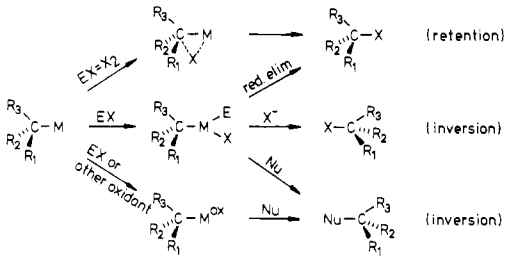


A change in regiochemistry from 3- to 1-attack by amine on (3,3-dimethyl-π-allyl)palladium chloride was observed when the chloride was exchanged for BF_4^-.[19]

Nucleophilic attack by acetate on (π-allyl)palladium complexes occurs under mild oxidative conditions.[16,30] In the presence of chloride ligands, acetate attack on **6** in acetic acid occurs exclusively by an external trans attack (Scheme IV).[16] In the absence of chloride ligands the acetate attack occurs exclusively by a cis-migration pathway. Thus, one can control the steric course of the nucleophilic addition by a slight change in the ligand concentration. The reason for this remarkable stereocontrol will be discussed below.

The nucleophiles so far mentioned include heteronucleophiles and stabilized carbon nucleophiles, which with one exception add trans to (π-olefin)- and (π-allyl)palladium complexes. Other types of nucleophiles such as hydride, alkyl anions, and aryl anions prefer to coordinate to the metal and be transfered to carbon in a cis-migration process (path A, Scheme III). Thus for π-olefin complexes cis nucleophilic attack has been demonstrated for hydride,[10a,21] aryl,[10a,b] and alkyl.[10c] For π-allyl systems cis attack has been established for hydride[15,18] and alkyl.[31a] Two examples of cis migration are shown in Scheme V.

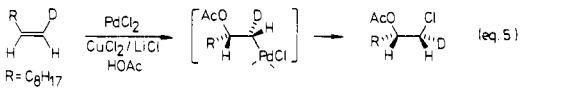
Scheme VI



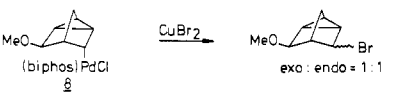
Oxidative Cleavage of Palladium-Carbon σ Bonds

The palladium–carbon bond, like most second and third row transition metal–carbon bonds, reacts very slowly in hydrolysis reactions. This is in contrast to alkaline and alkaline earth metal–carbon bonds, where hydrolysis is rapid. On the other hand, there is a broad spectrum of other methods for achieving metal–carbon bond cleavage for transition metals.[32] One such method, which is important in oxidation reactions, is through oxidative cleavage. Thus, an oxidizing agent usually labilizes palladium–carbon bonds in such a way that palladium is turned into a good leaving group. As a result, nucleophilic substitution of the metal may take place. A more general scheme for oxidative cleavage of transition-metal–carbon bonds is shown in Scheme VI.

Cupric chloride cleavage of palladium–carbon bonds takes place in a number of palladium-catalyzed oxidation reactions of olefins.[33] Thus, vicinal chloroacetates become the main product from $CuCl_2$ oxidation of intermediate acetoxypalladation adducts. More recent stereochemical results show that at least primary alkyl–palladium bonds are cleaved by $CuCl_2$ with predominant inversion at carbon in the presence of chloride ions (eq 5).[34] On the other hand, it was found that



$CuBr_2$ cleaves the palladium–carbon bond in **8** with complete scrambling of stereochemistry at carbon.[35] Also, the oxidation of bicyclic dienes appears to occur via a nonstereospecific cupric halide cleavage reaction.[36]



A more recent result of significance for the mechanism is the observation that phenyl participation takes place in the $CuCl_2$ cleavage of β-phenethyl–palladium bonds (Scheme VII).[37] Thus, anchimeric assistance by

(30) (a) S. Wolfe and P. G. C. Campbell, *J. Am. Chem. Soc.*, **93**, 1499 (1971); (b) W. Kitching, T. Sakakiyama, Z. Rappoport, P. D. Sleezer, S. Winstein, and W. G. Young, *ibid.*, **94**, 2329 (1972).

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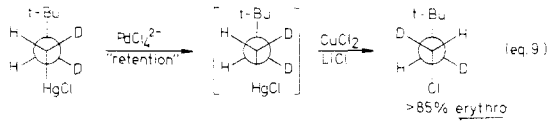
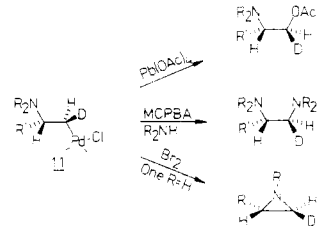
the phenyl group in the in situ generated phenethylpalladium complex **9a** results in metal–carbon bond cleavage with retention of configuration at carbon (eq 6). An electron-withdrawing group on the phenyl ring (**9b**) depressed the anchimeric assistance, and in this case the usual inversion product was observed. Conclusive evidence for phenyl participation in the $CuCl_2$ cleavage of β-phenethyl–palladium bonds was obtained by the reaction illustrated in eq 8. Generation of an unsymmetrically deuterated β-phenethylpalladium intermediate from the corresponding mercury compound, followed by $CuCl_2$ cleavage, produced **10a** and **10b** in equal amounts. Similar transmetalations followed by $CuCl_2$ cleavage were shown to occur with predominant inversion in acyclic systems (eq 9).[37] It thus appears



that the $CuCl_2$ cleavage of palladium–carbon bonds occurs via an oxidation induced nucleophilic substitution. The anchimeric assistance observed indicates that carbonium ion character is important in the cleavage process. It is therefore not very likely that loss of stereochemistry (i.e., in **8**) is a result of a radical process, as has been suggested,[35] but rather is due to the formation of a stable carbonium ion.

Halogenation reactions of alkylpalladium complexes also result in a similar oxidation induced nucleophilic displacement reaction in polar solvents.[38] In less polar solvents, however, the halide is introduced with retention of configuration at carbon,[38,39] probably via reductive elimination from an alkylpalladium(IV) halide intermediate. A classical three-centered electrophilic cleavage cannot be excluded, however.

Oxidative cleavage of palladium–carbon bonds by $Pb(OAc)_4$ to give alkyl acetates has been shown to occur with inversion of configuration at carbon.[40,41] $Pb(OAc)_4$ cleavage of the palladium–carbon bond in aminopalladium adducts **11** gave a clean inversion reaction.[40]



An analogous oxidative cleavage of the metal–carbon bond in the presence of amine also occurs stereospecifically to give a new carbon–nitrogen bond with inversion of configuration at carbon.[42] As with the $CuCl_2$ cleavage, the $Pb(OAc)_4$ cleavage of β-phenethyl–palladium bonds (generated as in Scheme VII) takes place with retention, most likely via an anchimeric assistance by the phenyl group.[43]

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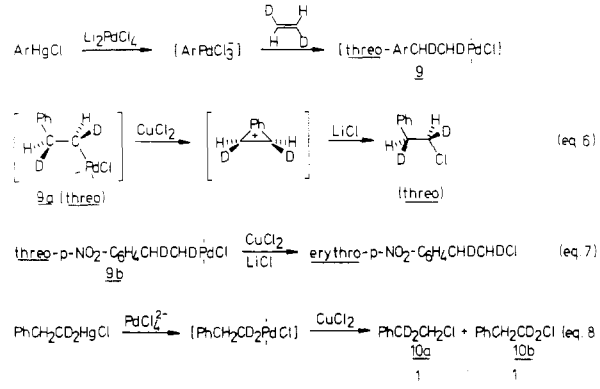
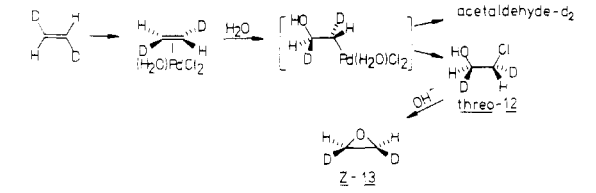
Scheme VII



Scheme VIII



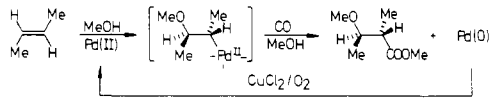
Related oxidative cleavage reactions of benzyl–platinum bonds and allyl–palladium bonds by peracids and peroxides to give alcohols proceed with retention of configuration at carbon.[44] In these reactions the peroxy group most likely coordinates to the metal followed by oxygen transfer from the metal to carbon.

Oxidation of Olefins

Oxidation reactions of olefins with Pd(II) usually involve nucleophilic addition to an olefinpalladium complex, followed by some cleavage reaction of the palladium–carbon bond in the intermediate σ-complex. In the Wacker oxidation of ethene to acetaldehyde (eq 1), ethene is oxidized by air in the presence of $PdCl_2$ and $CuCl_2$. The reaction involves nucleophilic attack by water on a (π-ethene)palladium(II) complex followed by a β-hydride elimination. It had been the subject of much discussion for many years whether nucleophilic attack takes place by a coordinated hydroxide (cis addition) or a free water nucleophile (trans addition) (cf. Scheme III). From the kinetics[45–47] of the reaction it was suggested that the rate-determining step was a cis addition of coordinated hydroxide and palladium across the coordinated ethene.[45] However, more recently hydroxypalladation of (*E*)- and (*Z*)-1,2-dideuterioethene under conditions similar to those employed in the Wacker process has been shown to take place with trans stereochemistry.[7a] Oxidation of (*E*)-1,2-dideuterioethene in water in the presence of high concentrations of cupric chloride and lithium chloride gave, except for acetaldehyde-d_2, a competing oxidative cleavage of the palladium–carbon bond by $CuCl_2$, resulting in chloroethanol-d_2 (Scheme VIII). Using microwave spectroscopy, the configuration of the chloroethanol-d_2 was established to be threo (*threo*-**12**). A more accurate quantitative analysis of the chlorohydrin *threo*-**12** was

(44) (a) I. J. Harvie and F. J. McQuillin, *J. Chem. Soc., Chem. Commun.*, 241 (1977); 369 (1976); (b) S. D. Knox and D. N. Jones, *ibid.*, 166 (1975).
(45) P. M. Henry, *J. Am. Chem. Soc.*, **86**, 3246 (1964); **88**, 1595 (1966).
(46) I. I. Moiseev, O. G. Levanda, and M. N. Vargaftic, *J. Am. Chem. Soc.*, **96**, 1003 (1974).
(47) R. Jira and W. Freiesleben, *Organomet. React.*, **3**, 1 (1972).

Scheme IX



done by conversion to epoxide (*Z*)-13 and subsequent analysis by microwave spectroscopy. Since cupric chloride cleavage of primary carbon–palladium bonds takes place with inversion at carbon in the presence of excess chloride ions,[7a,34,37] the formation of *threo*-12 requires that the hydroxypalladation step occurs with trans stereochemistry.

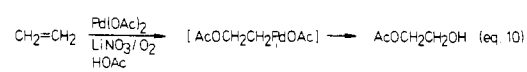
The same stereochemistry for the hydroxypalladation was observed in aqueous acetonitrile in the presence of carbon monoxide.[7b] Trans hydroxypalladation of (*Z*)-ethene-d_2 followed by insertion of carbon monoxide with retention at carbon gave the trans lactone.

The new mechanism suggested for the Wacker process,[7a] which accounts for these recent results, differs in three respects from the mechanism originally proposed:[6d,45] (i) there is an external trans attack by water on a neutral (π-olefin)palladium complex, (ii) the acid inhibition is a result of an equilibrium step, (iii) the rate-determining step is dissociation of a ligand before β-hydride elimination occurs. The rate-determining step for the Wacker process is still not conclusively established, and several recent studies have been directed toward this problem.[48,49]

An oxidation of olefins related to the Wacker oxidation, although via a completely different mechanism, takes place via peroxymetalation. Thus, $CF_3COOPdOO$-*t*-Bu oxidized terminal olefins to ketones,[50] most likely via a peroxypalladation followed by decomposition to ketone. No stereochemical data for the peroxypalladation are available.

If the metal atom in the σ-complex formed from nucleophilic attack on a (π-olefin)palladium complex is replaced by a group X according to Scheme II, the stereochemistry of the organometallic steps will be of importance for the overall organic reaction. If both steps are stereospecific, the result will be a stereospecific 1,2-functionalization.

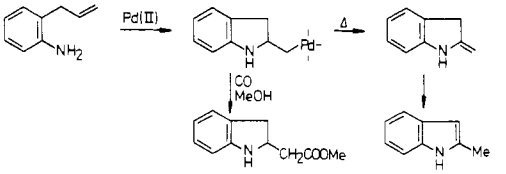
Palladium-catalyzed oxidation of alkenes in acetic acid using $LiNO_3$ as oxidant gives glycol derivatives.[51] The reaction proceeds via an acetoxypalladation of the olefin followed by an oxidative cleavage of the palladium–carbon bond (eq 10). Stereochemical studies



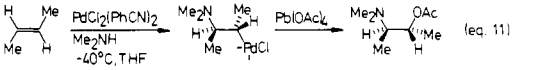
showed that the 1,2-addition is an overall cis acetoxyhydroxylation, consistent with a trans acetoxypalladation and subsequent oxidative cleavage with inversion.[51b]

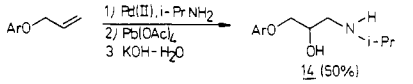
Oxidation of olefins in methanol in the presence of carbon monoxide results in an overall stereospecific trans methoxycarbonylation (Scheme IX).[8] The overall trans stereochemistry is the result of a trans methoxypalladation and subsequent insertion of carbon monoxide with retention of configuration at carbon. The reaction is catalytic in the presence of $CuCl_2/O_2$. The analogous reaction run in water resulted in the formation of β-lactone.[7b]

Scheme X



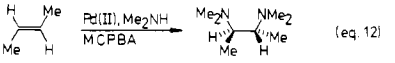
Another stereospecific 1,2-functionalization of use in organic synthesis is the oxyamination obtained from an aminopalladation oxidation sequence (eq 11).[40] The





overall cis stereochemistry is the result of a trans aminopalladation followed by oxidative cleavage of the palladium–carbon bond with inversion at carbon. Lead tetraacetate served as the oxidant, but Br_2 and NBS can also be used. The oxyamination has been applied[52] to the synthesis of (aryloxy)propanolamines 14, which are important β-adrenoceptor blocking drugs. By the use of chiral reagents, an asymmetric induction between 3% and 60% was obtained in the oxyamination reaction.[53]

In a similar manner, vicinal diamines were obtained if amine was used as nucleophile in the oxidative cleavage step (eq 12).[42] This reaction also occurs with



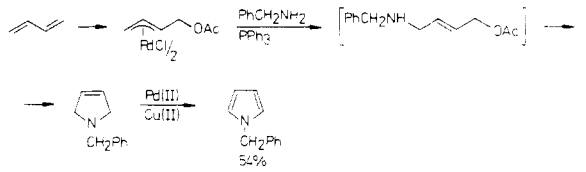
overall cis stereochemistry, consistent with an oxidative cleavage with inversion. Terminal olefins gave the best yields and *m*-chloroperbenzoic acid was the preferred oxidant. If the same reaction is performed with a primary amine, the main product is an aziridine.[54]

An intramolecular amination was used to prepare indole derivatives (Scheme X).[55] The reaction could be run with catalytic amounts of palladium, using benzoquinone as oxidant. Similar intramolecular oxypalladation reactions lead to benzofuranes.[56]

Only very few oxidative 1,2-functionalizations are known, where the initial nucleophilic attack is an intramolecular cis migration. Examples include palladium-catalyzed arylation reactions of ethene in the presence of $Pb(OAc)_4$ or $CuCl_2$, which gives $PhCH_2CH_2Cl$ and $PhCH_2CH_2OAc$, respectively.[57] In these reactions a phenylpalladium complex adds cis to the double bond, followed by an oxidative cleavage reaction. With both $CuCl_2$ and $Pb(OAc)_4$ as oxidants, the

(48) N. Gragor and P. M. Henry, *J. Am. Chem. Soc.*, **103**, 681 (1981); W. K. Wan, K. Zaw, and P. M. Henry, *J. Mol. Catal.*, **16**, 81 (1982).
(49) Y. Saito and S. Shinoda, *J. Mol. Catal.*, **9**, 461 (1980).
(50) H. Mimoun, R. Charpentier, A. Mitschler, J. Fischer, and R. Weiss, *J. Am. Chem. Soc.*, **102**, 1047 (1980).
(51) (a) M. Tamura and T. Yasui, *Chem. Commun.*, **1209** (1968); (b) N. Yoshimura and M. Tamura, *Abstr. Int. Conf. Organomet. Chem. Kyoto, 8th*, 252 (1977).
(52) J. E. Bäckvall and S. E. Byström, *J. Org. Chem.*, **47**, 1126 (1982).
(53) J. E. Bäckvall, E. E. Björkman, S. E. Byström, and A. Solladié-Cavallo, *Tetrahedron Lett.*, 943 (1982).
(54) J. E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 413 (1977).
(55) L. S. Hegedus, G. F. Allen, J. J. Bozell, and E. L. Waterman, *J. Am. Chem. Soc.*, **100**, 5800 (1978).
(56) T. Hosokawa, S. Yamashita, S. I. Murahashi, and A. Sonoda, *Bull. Chem. Soc. Jpn.*, **49**, 3662 (1976).
(57) (a) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5538 (1968); (b) *ibid.*, **90**, 5542 (1968).

Scheme XI

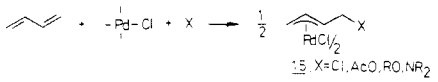


oxidative cleavage has been found[37,43] to take place with anchimeric assistance by the phenyl group and hence with retention of configuration at carbon.

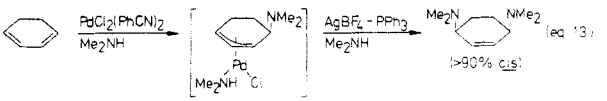
Oxidation of 1,3-Dienes

The palladium-catalyzed oxidation of butadiene to 1,4-diacetoxy-2-butene is of commercial interest and has been the subject of many reports, in particular patents.[58] Usually these reactions give a mixture of 1,2- and (*E*)- and (*Z*)-1,4-isomers. A related oxidation of 1,3-cyclohexadiene was reported by Brown and Davidson to give 1,4-diacetoxy-2-cyclohexene of unknown stereochemistry.[59]

(π-Allyl)palladium complexes **15** are spontaneously formed from a conjugated diene and palladium(II) in the presence of a nucleophile.[21,60,61]

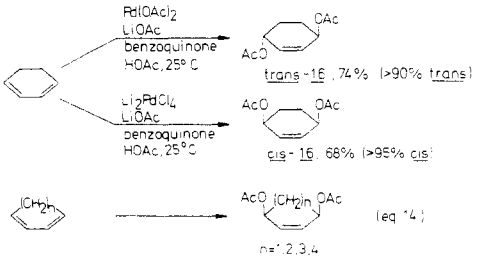


If 1,3-dienes are reacted with amines in the presence of palladium(II), (4-amino-1-3-η^3-alkenyl)palladium complexes are formed, which on further activation react with more amine to yield 1,4-diamino-2-alkenes.[14a] The reaction takes place with overall cis stereochemistry, a result of two trans additions by the amine (eq 13). An



intramolecular 1,4-cycloamination gave pyrrole derivatives (Scheme XI).[62] The aminoacetates obtained from attack by primary amines on **15** (X = OAc) are not readily isolated and undergo spontaneous palladium-catalyzed cyclization. The pyrroline thus formed is further oxidized to pyrrole under the reaction conditions.

Scheme XII



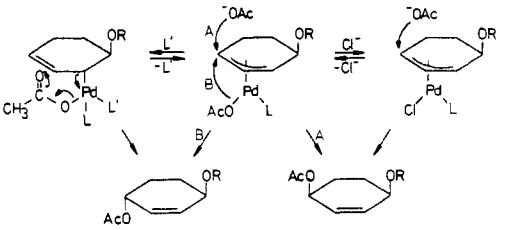
(58) K. Takehira, H. Mimoun, and I. S. DeRoch, *J. Catal.*, 58, 155 (1979) and references therein; P. M. Henry "Palladium-Catalyzed Oxidation of Hydrocarbons", D. Reidel Publishing Co., Dordrecht, 1980, p 244.
(59) R. G. Brown and J. M. Davidson, *J. Chem. Soc. A*, 1321 (1971).
(60) S. D. Robinson and B. L. Shaw, *J. Chem. Soc.*, 4806 (1963); 5002 (1964).
(61) J. M. Rowe and D. A. White, *J. Chem. Soc. A*, 1451 (1967).
(62) J. E. Bäckvall and J. E. Nyström, *J. Chem. Soc., Chem. Commun.*, 59 (1981).

Table I
Palladium-Catalyzed 1,4-Diacetoxylation of Cyclic 1,3-Dienes[a]

diene	LiOAc	LiCl	isolated yield, %	stereochemistry
	x	x	21	>95% cis
	x	x	68	>95% cis
	x		74	>91% trans
	x	x	57	>95% cis
			60	*cis/trans* = 1:1
			41[b]	*cis/trans* = 83:17
	x		47[c]	*cis/trans* = 23:77

[a] Unless otherwise noted all reactions were run in acetic acid at room temperature. [b] Reaction performed at 38 °C. [c] Reaction performed at 56 °C.

Scheme XIII (R = Me or Ac)



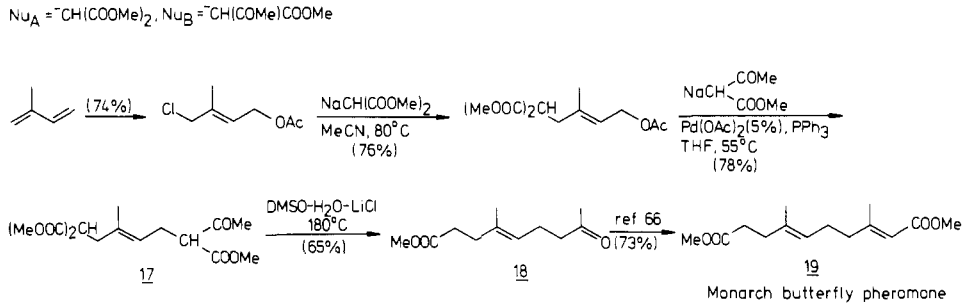
Addition of stabilized carbanions to **15** (X = OMe) resulted in regioselective nucleophilic attack and formally constitutes a 1,4-functionalization of butadiene.[63]

By ligand control, regio- and stereoselective 1,4-functionalizations of 1,3-dienes take place with catalytic amounts of palladium.[16,64] In most of these reactions, benzoquinone was employed as the oxidant. In the palladium-catalyzed diacetoxylation of conjugated dienes it was found that chloride and acetate ligands (as LiCl and LiOAc) have a profound effect on the stereochemical outcome of the reaction (Scheme XII).[16] Thus, palladium-catalyzed oxidation of 1,3-cyclohexadiene in acetic acid in the absence of lithium salts gave a 1:1 mixture of *cis*- and *trans*-1,4-diacetoxy-2-cyclohexene (*cis*- and *trans*-**16**). If the same oxidation reaction is performed in the presence of LiOAc, the reaction becomes stereoselective and gives *trans*-**16** (>90% trans). A remarkable change in stereochemistry takes place on addition of catalytic amounts of LiCl. A ratio of $[Pd]_{tot}/[Cl^-]_{tot}$ of 1:4, which was achieved by using Li_2PdCl_4 as the catalyst, gave exclusively *cis*-**16** (>95% cis). Other cyclic 1,3-dienes also underwent a stereoselective 1,4-diacetoxylation. For all cyclic dienes employed it was possible to stereoselectively prepare the cis isomer (eq 14). The results summarized in Table I show that for the six- and eight-membered rings it was possible to reverse the stereoselectivity toward the trans products. All the reactions were regioselective and gave only 1,4-isomer.

These stereocontrolled reactions suggest that two different modes of nucleophilic attack by acetate on the coordinated allyl group take place in the intermediate

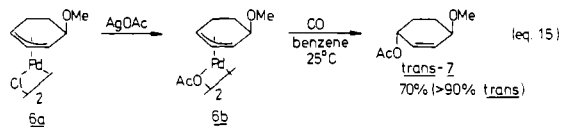
(63) B. Åkermark, A. Ljungqvist, and M. Panunzio, *Tetrahedron Lett.*, 22, 1055 (1981).
(64) J. E. Bäckvall, R. E. Nordberg, and J. E. Nyström, *Tetrahedron Lett.*, 1617 (1982).

Scheme XIV



(π-allyl)palladium complex. A likely mechanism, in which the role of chloride is to block the coordination of acetate, is shown in Scheme XIII. External attack by acetate on (π-allyl)palladium complexes is an expected pathway, whereas a cis migration is less precedented. It had previously been observed[17] that cyclic allylic acetates undergo cis–trans isomerization in the presence of $Pd(PPh_3)_4$. To account for this isomerization it was proposed that both cis and trans attack by acetate take place in an intermediate (π-allyl)palladium complex.

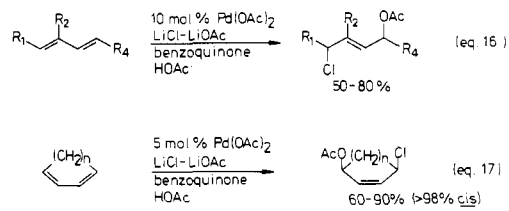
The first direct demonstration of a cis migration pathway for acetate was provided by the reaction shown in eq 15. Treatment of the (π-allyl)palladium complex



6b with carbon monoxide in benzene gave *trans*-**7**, which shows that a cis migration of acetate from palladium to carbon has occurred.[15]

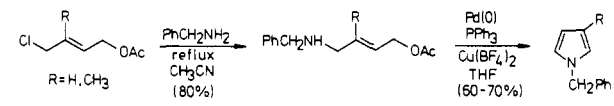
Thus, for acetate both cis and trans nucleophilic attack can occur depending on the reaction conditions. A direct demonstration of the duality of the acetate attack was provided by the stoichiometric reactions of (π-allyl)palladium complex **6** in acetic acid shown in Scheme IV.[16] Thus, treatment of **6b** with benzoquinone in acetic acid at room temperature resulted in a cis attack by coordinated acetate to give *trans*-**7**. When the same reaction was performed with the chloro complex **6a** in the presence of LiCl and LiOAc, a clean trans attack to give *cis*-**7** occurred (Scheme IV). This shows that it is possible to select the stereochemistry of the nucleophilic attack by a minor change in the ligand concentrations. The stereocontrolled reactions of (π-allyl)palladium complex **6** (Scheme IV) provide good evidence for the mechanism outlined in Scheme XIII for the palladium-catalyzed 1,4-diacetoxylation.

If the palladium-catalyzed oxidation of 1,3-dienes in acetic acid is performed at a slightly higher chloride concentration, the product pattern changes and 1,4-chloroacetate becomes the sole product (eq 16 and 17).[64]

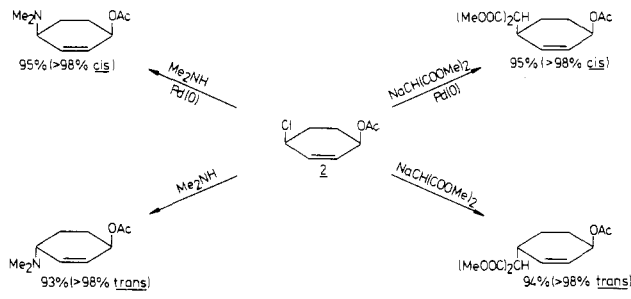


This reaction is highly stereospecific, proceeding with overall cis stereochemistry with cyclic 1,3-dienes. The

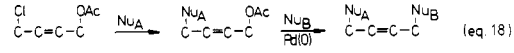
Scheme XV



Scheme XVI



synthetic utility of the palladium-catalyzed 1,4-acetoxychlorination is enhanced by the fact that the chloro and acetoxy groups of the product can be selectively substituted in two consecutive steps (eq 18). This is



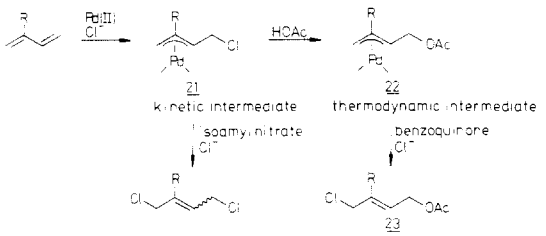
achieved by using a classical nucleophilic substitution (Nu$_A$) followed by a metal-catalyzed nucleophilic substitution (Nu$_B$) of the acetoxy group. This principle has been used in the synthesis of the Monarch butterfly pheromone (**19**) and is illustrated in Scheme XIV. Using dimethyl malonate and methyl acetoacetate as Nu$_A$ and Nu$_B$, respectively, and substituting on the isoprene adduct gave **17**, which on selective decarboxylation afforded **18**.[65] Since the transformation **18** to **19** in one step has been described in the literature,[66] the sequence in Scheme XIV constitutes a total synthesis of the pheromone from isoprene.

Another synthetic application of the 1,4-chloroacetoxylation is shown in Scheme XV. Substitution of the chloride with a primary amine followed by an intramolecular amination and subsequent oxidation gave pyrroles in good yield.[67] Contrary to the pyrrole synthesis mentioned previously (Scheme XI), the steps involving palladium in this procedure function with catalytic amounts of the metal.

The acetoxychlorination products from cyclic 1,3-dienes also allow a dual choice of stereochemistry (Scheme XVI). Thus, by utilizing either a mild palladium-catalyzed or a classical nucleophilic substitution, the chloro group in **20** was replaced with either reten-

(65) J. E. Nyström and J. E. Bäckvall, *J. Org. Chem.*, in press.
(66) B. M. Trost, M. J. Bogdanowicz, W. J. Frazee, and T. N. Salzmann, *J. Am. Chem. Soc.*, **100**, 5512 (1978).
(67) J. E. Bäckvall and J. E. Nyström, unpublished results.

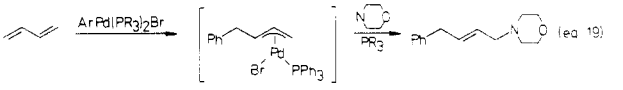
Scheme XVII



tion or inversion at carbon.[64] An important aspect of the products obtained in Scheme XVI is that they can be further functionalized by a stereospecific (retention) palladium-catalyzed nucleophilic substitution of the acetoxy group.

The high product selectivity for chloroacetate over diacetate and dichloride in the 1,4-acetoxychlorination reaction is remarkable. From a statistical point of view, one would expect the latter products to form to some extent. An explanation for this unusual product selectivity is offered in Scheme XVII. The chloro complex **21**, if initially formed, is expected to solvolyze rapidly in acetic acid (with anchimeric assistance by the metal) to afford the more stable acetoxy complex **22**. External chloride attack on **23** would give the observed chloroacetate. The regioselectivity observed for isoprene (**23**, R = Me) strongly suggests that the reaction proceeds via **22** and subsequent chloride attack. Further support for Scheme XVII is provided by the oxidation of butadiene with use of the more rapid oxidant isoamyl nitrite. In this case the sole oxidation product was 1,4-dichloro-2-butene.[64]

Palladium-catalyzed 1,4-functionalization of 1,3-dienes, where a phenyl group and an amine are added to the 1- and 4-positions, takes place according to eq 19.[29b,68] Addition of an arylpalladium complex (from



$ArBr + Pd(PR_3)_n$) to the diene produces an intermediate (π-allyl)palladium complex, which is attacked by amine. An analogous arylation reaction of butadiene using $Pb(OAc)_4$ as oxidant gave $PhCH_2CH(OAc)CH{=}CH_2$.[57b] Formation of 1,2-isomer in this case may be a result of anchimeric assistance by the phenyl group (vide supra).

Conclusions

Nucleophilic attack on (π-olefin)-, (π-allyl)-, and (σ-alkyl)palladium complexes and oxidative cleavage reactions are of importance in stereoselective 1,2- and 1,4-additions to olefins and 1,3-dienes, respectively. In some of these addition reactions a remarkable product control can be obtained by a minor change in the ligand environment. For example, in the palladium-catalyzed oxidation of 1,3-cyclohexadiene, one can selectively obtain different products by merely varying the LiCl concentration under otherwise identical conditions: (i) [LiCl] = 0, *trans*-1,4-diacetoxy-2-cyclohexene, (ii) [LiCl] = 0.2 equiv to the diene, *cis*-1,4–diacetoxy-2-cyclohexene, (iii) [LiCl] = 2 equiv to the diene, *cis*-1-acetoxy-4-chloro-2-cyclohexene.

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