The Wacker Reaction and Related Alkene Oxidation Reactions

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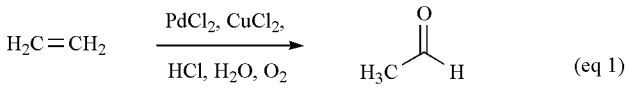
Abstract: The objective of this review is to survey the current state of the Wacker and related alkene oxidation reactions focusing on the reactions of higher alkenes and emphasizing the mechanistic pictures that have evolved, the current understanding regarding issues of selectivity, recent applications of the chemistry in synthesis, and the use of other transition metal catalysts to effect related oxidation reactions.

The Wacker oxidation reaction has been extensively studied over the years. There are a number of excellent reviews published on various aspects of the reaction [1], with a series of reviews by Tsuji deserving particular note for their special insight into the development of this reaction [2-4].

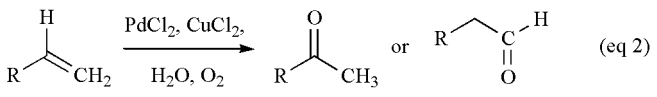
INTRODUCTION

The palladium(II)-catalyzed reaction of ethylene with water to form acetaldehyde, commonly known as the Wacker oxidation (eq 1), is one of the important industrial applications of transition metal catalysis. The oxidation reaction is typically promoted by a $PdCl_2/CuCl_2$ catalyst mixture in the presence of aqueous hydrochloric acid and an oxidizing agent. In the course of the reaction palladium(II) is reduced to palladium(0), then subsequently re-oxidized in situ by reduction of the Cu(II) co-catalyst, typically, $CuCl_2$ to CuCl. The ultimate oxidizing agent present in the reaction mixture is often molecular oxygen, and it serves to reoxidize Cu(I) to Cu(II) thus keeping the catalytic system active.



(eq 1)

The Wacker oxidation can be extended to higher alkenes, most commonly to terminal alkenes. In general, terminal alkenes **1** are converted to methyl ketones **2** rather than to aldehydes **3** (eq 2), but there are important exceptions (*vide infra*). The transformation has found significant use in organic synthesis. Alkenes are more stable to acid, base, and ketone liberated by the Wacker oxidation. A common variant of the palladium-catalyzed oxidation, that of running the nucleophiles than are most methyl ketones or aldehydes, and as such, the alkene can be thought of as a protected methyl oxidation in the presence of alcohols, affords ketals or acetals instead of the carbonyl compound.



(eq 2)

1 **2** **3**

MECHANISTIC ASPECTS OF THE PALLADIUM CATALYZED WACKER OXIDATION AND RELATED REACTIONS

The mechanism of the Wacker oxidation has been investigated using a number of approaches and techniques, including for example, kinetic studies [5-13], studies into the isotope effects [5,6], stereochemical studies [8,9,11-15], and theoretical studies using computational methods [16-18]. While the precise mechanistic details remain under investigation, the major features of the Wacker oxidation are generally accepted [8,19,20]. First, an alkene (e.g., **1**) coordinates to the palladium(II) salt (e.g., $PdCl_2$), to give the palladium-alkene π-complex **4**. At this stage, one of the chlorides is perhaps replaced by water forming a complex such as **5**. Then, addition of hydroxide to the alkene in a syn fashion (e.g., via **6**) or addition of water in an anti fashion (e.g., via **7**) forms a (β-hydroxyalkyl)palladium complex such as **8**. The partitioning between the *syn*- and *anti*-pathways likely depends on the precise reaction conditions employed. β-Hydride elimination affords the enol **9** which tautomerizes to the carbonyl compound **4**. Reductive elimination of Cl-Pd(II)-H gives HCl and Pd(0). As noted above, a copper co-catalyst is typically used to reoxidize Pd(0) to Pd(II) in situ by reduction of Cu(II) to Cu(I). The terminal oxidizing agent for the reaction mixture is usually molecular oxygen, a peroxide, or benzoquinone (BQ), and it serves to reoxidize Cu(I) to Cu(II), thus keeping the catalytic system active.

The details of the addition step (i.e., **5** to **8**) probably depend upon the precise conditions employed. Recent theoretical studies suggest that H_3O^+ has important role in the attack of the nucleophile on the alkene [17], and the nucleophile may be described by a chain of at least 3 water molecules bridging a chloride ligand and the point of attack on the alkene [18]. The stereochemical course of the addition (*syn* or *anti*) is also thought to be affected by such reaction details as the presence of oxygen nucleophiles or certain ligands and by the concentration of those ligands. The presence of chloride at low concentration [11-13,15], the

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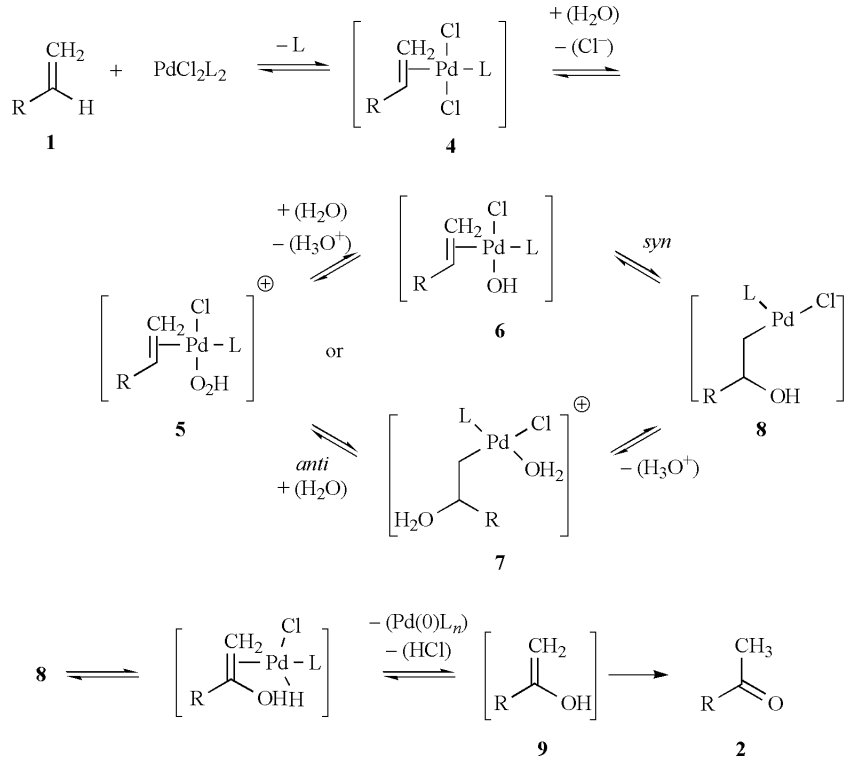
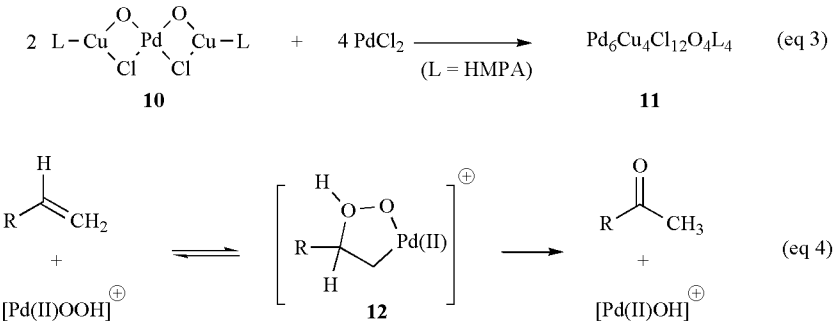


Scheme 1. A Simplified Model for the Mechanism of the Wacker and Related Alkene Oxidation Reactions.

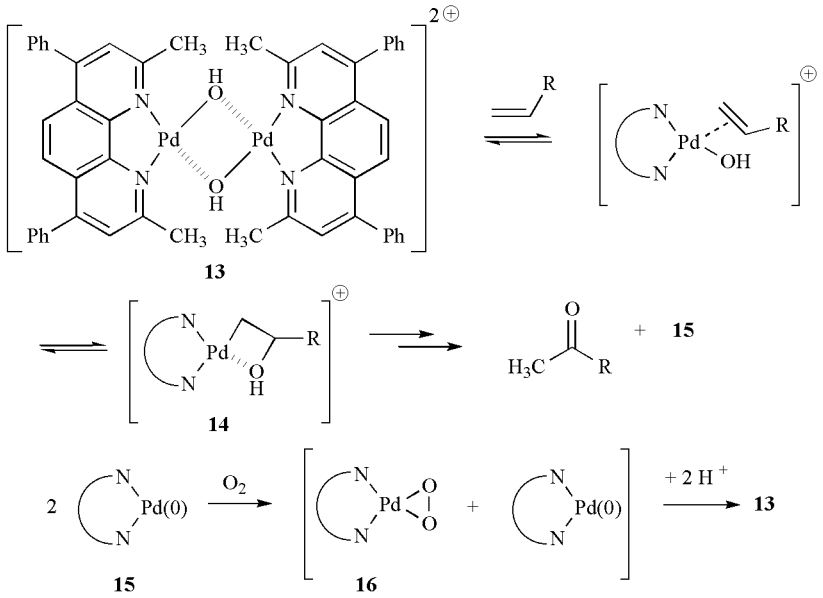


inclusion of a bidentate diamine [10], or the use of H_2O_2 [21] as both the nucleophile and the ultimate oxidant are thought to facilitate the *syn*-addition pathway (i.e., **5** to **6**). At high chloride concentration [8,9,12-15,22], or in the presence of pyridine [12] or hydroxide ion [23], the addition proceeds via the *anti*-addition mode (i.e., **5** to **7**).

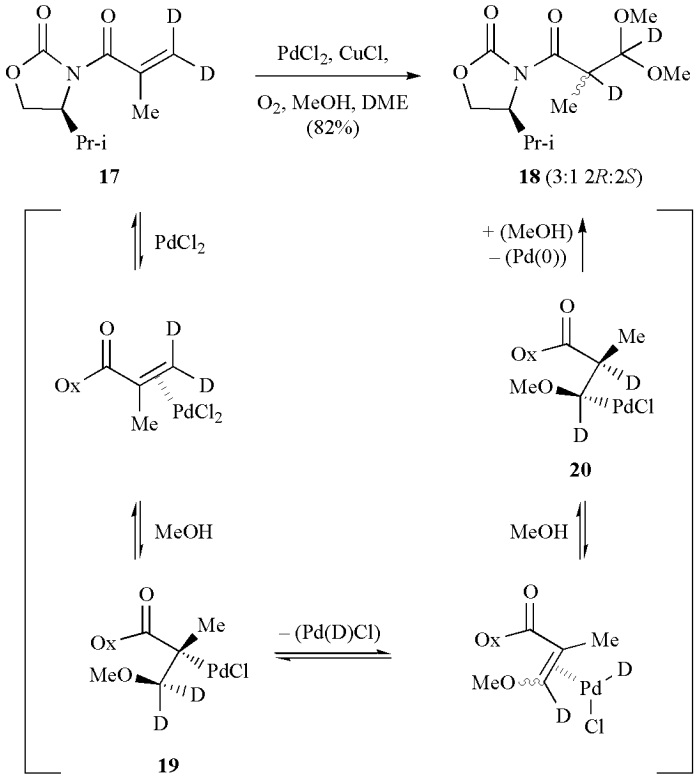
A number of alternative hypotheses for the nature of the active catalyst have been proposed. For example, a η3-allylpalladium complex was suggested to be an intermediate in the Wacker oxidation [24]. CuCl was reported to react with O_2 in coordinating solvent to give a μ-peroxocopper species L-Cu-O-O-Cu-L. When the $CuCl_2/O_2$ oxidizing system is employed, an oxidized Pd-Cu heterobimetallic complex has been proposed [25]. It is thought to possess an active site consisting of a cationic trimetallic Cu-O-Pd-O-Cu complex **10** with the reaction proceeding such that the formal +2 oxidation state of palladium remains constant throughout the reaction. Complex **10** could be generated by reaction of L-Cu-O-O-Cu-L with $PdCl_2$, and its presence was implicated by isolation of the Pd-Cu heterobimetallic complex **11**, formed by assembling of two units of **10** and four $PdCl_2$ (eq 6). Similarly, a Cu-O-Pd-O-Cu cationic working catalyst was proposed for Cu(II)-Pd(II) exchanged Y zeolites for the heterogeneous Wacker oxidation [20].

Another alternative mechanism has also been proposed, one in which a [Pd(II)OOH] species is formed. Several pathways to such species have been suggested; for example, by insertion of O_2 into an initially formed Pd(II)-hydride [26-29], via the addition of H_2O_2 to a palladium(II) complex [21,30], or by protonation of peroxopalladium(II) complex [31]. The [Pd(II)OOH] intermediate is then thought to transfer oxygen to the terminal alkene via a five-membered pseudo-pericyclic peroxypalladation mechanism (eq 4) [21,26-32]. Oxidation with alkyl peroxide has been proposed to proceed similarly [32].

Using the combination of palladium(II) diacetate and a rigid bidentate diamine such as a 1,10-phenanthroline derivative, it is possible to form a copper and chloride free catalyst system (scheme 2). The resting state of the active



Scheme 2. A Copper and Chloride Free Catalyst System.



Scheme 3. A Novel Mechanism for the Palladium Catalyzed Oxidation of Unsaturated N-Acyloxazolidinone **17**.

catalyst is thought to be a palladium dimer with two bridging hydroxide ligands, as illustrated by **13**. It is suggested that the dimer dissociates upon coordination of the alkene. The intramolecular addition of hydroxyl to the coordinated alkene would give a (β-hydroxyalkyl)palladium complex such as **14**, which could give the observed methyl ketone and a Pd(0) species such as **15**. The latter is then re-oxidized with dioxygen via an intermediate peroxo-palladium(II) complex (e.g., **16**). Its reaction with a second equivalent of **15** would regenerate the palladium(II) dimer **13** [10]. As evidence consistent with this mechanism, an isolable peroxopalladium(II) complex akin to **16** was synthesized via the aerobic oxidation of a palladium(0) complex [33].

A common variant of the palladium-catalyzed oxidation is to run the reaction in the presence of alcohols and thereby obtain an acetal or ketal as the product. α,β-Unsaturated carbonyl compounds can be used in this variant and an unusual mechanism for their reaction was proposed based on palladium catalyzed acetalization of the dideuterated N-methacryloyl-2-oxazolidinone **17** (scheme 3). When the

protio-analogue of **17** was oxidized in the presence of MeOD, the product showed no deuterium incorporation from solvent. Similarly, the dideutero-compound **17** shows no loss of deuterium to solvent (MeOH). Instead, an apparent 1,2-deuterium shift occurs in the course of the reaction. The proposed reaction pathway involves coordination of $PdCl_2$ with the double bond followed by nucleophilic attack of methanol on the terminal carbon to afford a σ-bonded Pd(II) intermediate such as **19**. β-deuteride elimination followed by readdition of Pd-D with the opposite regiochemistry affords intermediate **20**. While the details are not clear, it is suggested that the intermediate **20** undergoes substitution with methanol to give the acetal **18** and palladium(0) [34].

COMMENTS ON THE COMMONLY USED REACTION CONDITIONS

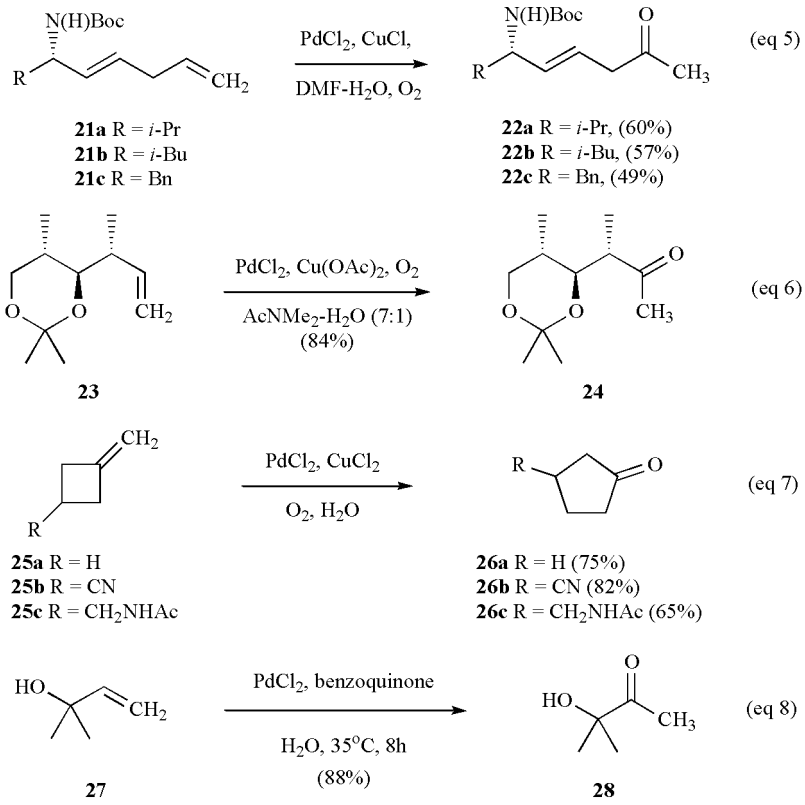
As noted above, the precise reaction conditions employed for the Wacker oxidations are important, and these can vary widely. The yield and rate of reaction depend upon the exact structure of the alkene and the reaction conditions employed. The industrial Wacker process is carried out in aqueous hydrochloric acid and under oxygen pressure using $PdCl_2/CuCl_2$ as the catalyst system. Newer reactors, such as a hollow fiber membrane reactor [35] and bubble column reactor [36], have been shown to exhibit higher production rates and efficiency. On a laboratory scale, the oxidation is most commonly carried out at room temperature using $PdCl_2$ and a copper salt under an oxygen atmosphere or with benzoquinone.

While $PdCl_2/CuCl_2$ is the most popular catalyst system for the Wacker oxidation, acidic conditions render the system highly corrosive, and the presence of a large amount of chloride ion in the reaction medium can lead to the formation of chlorinated by-products. To overcome these general deficiencies as well as other more substrate specific problems, a variety of other palladium catalyst systems are employed. These include, for example, soluble catalyst systems such as Na_2PdCl_4/H_2O_2 [30], Na_2PdCl_4/benzoquinone [21], RCO_2PdOO-t-Bu [32], dichlorobis(N,N-diethylacetamide)palladium(II) complex [37], bis(acetonitrile)chloronitropalladium(II) [38], $Pd(dba)_2/AgNO_3$ [39], $Pd(OAc)_2$/Fe(III) phthalocyanine/hydroquinone [40], $[Pd(P{Bu^t}_2H)(\mu\text{-}PB{u^t}_2)]_2$ [41], $M[PdCl_3(pyridine)]$ [42], $Pd(OAc)_2$/polyporrole [43], water soluble palladium complexes derived from $Pd(OAc)_2$ and bathophenanthroline disulfonate [44], $[(PdCl_2)_2CuCl_2(DMF)_4]_n$ [45], $Pd(OAc)_2$/molybdovanadophosphate/hydroquinone [46], $Pd(OAc)_2$/polyaniline derivatives [47], $[CF_3CO_2PdOO\text{-}Bu^t]_4$ [19], $Pd(OAc)_2$/hydroquinone/metal macrocycle, [8,48], $PdCl_2$/trimethyl ester of coenzyme PQQ [49], $Pd(OAc)_2$/pyridine [28], $PdCl_2/Cu(OAc)_2$ [50], and $(CH_3CN)_2Pd(NO_2)/AgSbF_6$ [51]. A number of heterogeneous catalyst systems have also been developed, including for example, γ-Al_2O_3- and TiO_2-supported Na_2PdCl_4 [52], or H_2PdCl_4/vanadate [53], $Pd(OAc)_2$/molybdovanadophosphate on activated carbon [54], $PdSO_4/V_2O_5$ supported on γ-Al_2O_3 [55], $PdSO_4/V_2O_5$ supported on titania [56], carbon supported $PdSO_4/VOSO_4/H_2SO_4$ [57], and $PdCl_2/CuCl_2$ prepared in molten CuCl/KCl and supported on Silica T1571 [58]. The latter catalyst system in particular was reported to be extraordinarily stable. Polymer-supported catalyst systems have also been developed. For example, polybenzimidazole [59,60] oligo(*p*-phenylene)terephthalamide [61], cyano-functionalized polyimide [62] and cyanomethylated and crosslinked-carboxymethylated polystyrene [63] have been used to support palladium(II) Wacker catalysts.

The addition of a strong inorganic acid to the palladium-catalyzed oxidation can lead to a significant rate enhancement in the reaction, as seen for example upon addition of perchloric acid to a palladium/benzoquinone catalyst system in chloride free solution [64,65]. Heteropolyacids can serve as Brønsted acid and oxidation catalysts and have inherent stability towards decomposition under extreme oxidation conditions. They have been used to re-oxidize Pd(0) to Pd(II) in the Wacker oxidation, for example, through the use of Pd-Cu exchanged Y zeolites [20,66], or the use of $H_{3+n}PV_nMo_{12-n}O_{40}$.[67,68]. The lifetime of the latter oxidizing agent is significantly prolonged by substitution of protons for transition metal cations [69]. Electrooxidation methods have also employed for the direct oxidation of Pd(0) to Pd(II) [70] or for generation of recyclable co-oxidants such as quinone [71,72] or triarylamines [73].

In general, the rate of oxidation of higher alkenes is much lower than that of ethylene or other low molecular weight alkenes, owing in part, to their low solubility in water. In such cases, DMF [74]. and NMP [75]. are commonly used as co-solvents. A number of other options have been explored. A reaction medium of formamide microemulsion was reported to give a much faster oxidation than classical media [76]. Surfactants such as sodium lauryl sulfate have been used to accelerate the oxidation reaction [77], terminal alkenes can be converted to ketones using the phase transfer catalyst, cetyltrimethylammonium bromide [78]. Both terminal and internal alkenes can be efficiently converted to ketones in aqueous PEG-400 [79]. Reverse phase transfer catalysts can also significantly facilitate the Wacker oxidation, including for example, the use of cyclodextrins [80,81], modified β-cyclodextrins [82], and a very interesting self-assembled nanocage [83]. A palladium(II) catalyst bearing a perfluorinated ligand, that imparts a high partition coefficient into a fluorous solvent which is immiscible with the organic solvent, forms the basis for running the Wacker oxidation in a fluorous biphasic system [84]. This latter strategy is appealing in that the fluorinated palladium catalyst is easily recovered from the reaction mixture.

Perhaps the most common side reaction that is observed during attempted Wacker oxidation is that of double bond isomerization [60]. The extent of isomerization is strongly influenced by solvent. The rate of the isomerization is generally faster in alcoholic solvents, but with increasing steric hindrance of that alcohol, the rate seems to reduce



considerably [39]. Dimethylformamide (DMF) is a good solvent for the reaction and competing isomerization appears to be retarded by this solvent [85].

FUNCTIONAL GROUP TOLERANCE

The Wacker oxidation conditions can be relatively mild, and a particularly notable feature of the reaction is that many common functional groups are well tolerated. While it is impossible to compile an exhaustive list, at least one example illustrating the compatibility of functionality from each of the following classes can be cited: alcohol [86-89], aldehyde [73,90-94], carboxylic acid [95], acetate [96,97], ester [98-102], lactone [87,103,104], carbonate [96,105], amide [96,98,106], lactam [29], β-lactam [107], carbamate [105,106,108,109], carbamoyl [96], benzyl ether [105,110-112], PMB ether [113], MOM ether [110,114-116], acetonide [50,90,94,106,111,117], benzylidene acetal [118,119], amine [21,120], oxazolidine [108], furan [121], sulfoxide [86], phosphonate [122], and nitro group [123]. The successful Wacker oxidation of substrates containing many of the functional groups listed here are illustrated in the specific examples discussed in the following sections.

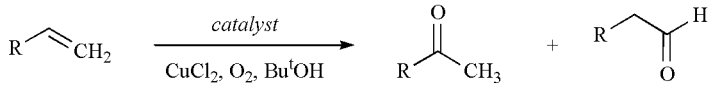
KEY FEATURES OF THE PALLADIUM CATALYZED OXIDATION OF TERMINAL AL-KENES

Additional substituents on the double bond tend to slow the rate of reaction substantially, and consequently, it is often possible to selectively oxidize an unhindered terminal alkene to the methyl ketone in the presence of internal alkenes [87,96,98,102,108,110,112, 113,121,124-126]. For example, the palladium-catalyzed oxidation of **21** to **22** is notable for its chemoselectivity (terminal versus internal alkene) and for the lack of double bond isomerization in either the starting diene or the β,γ¬unsaturated ketone product (eq 5) [108]. Similarly, the relatively acid sensitive alkene **23** was oxidized to corresponding chiral methyl ketone **24** without competing epimerization (eq 6); note the conditions employed here [50].

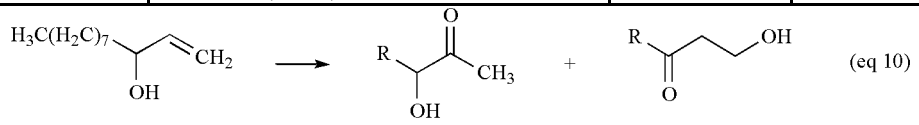
Again, additional substituents on the double bond tend to slow the rate of reaction, and 1,1-disubstituted alkenes are usually unreactive[127]. However, isolated cases have been reported where, in spite of the apparent mildness of the reaction conditions (see the examples in equations 5 and 6), strained or otherwise labile methylidenes rearrange under the reaction conditions. For example, the cyclobutyl derivatives **25** undergo palladium-catalyzed oxidation with rearrangement to the cyclopentanone **26** (eq 7) [128].

Steric hindrance about the terminal alkene is expected to slow the rate of the oxidation reaction [2,6], but the degree to which problems result from steric effects alone is unclear. There are several examples where relatively hindered terminal alkenes undergo palladium-catalyzed oxidation with facility [92,129]. For example, 2-methybut-3-en-2-ol (**27**) undergoes efficient palladium-catalyzed oxidation to 3-hydroxy-3-methylbutan-3-one (**28**) under mild condition (35°C) and the reported reaction time of 8 h is about average when compared to other less hindered substrates (eq 8) [129].

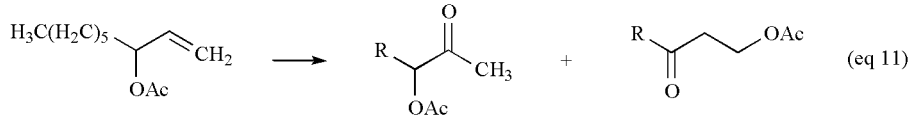
One of the more confusing and potentially problematic aspects of the Wacker oxidation is the issue of regiocontrol. In most cases, for example those illustrated in equations 5, 6



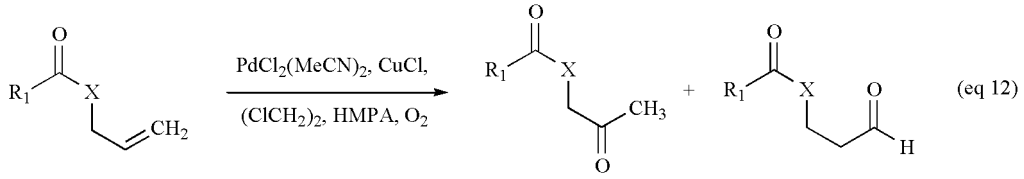
entry	R	catalyst	ketone	aldehyde	yield (%)
a	C_6H_{13}	$(MeCN)_2Pd(Cl)NO_2$-$CuCl_2$	45	55	43
b	C_8H_{17}	$(MeCN)_2Pd(Cl)NO_2$-$CuCl_2$	30	70	10
c	Ph	$(MeCN)_2Pd(Cl)NO_2$-$CuCl_2$	-	100	9
d	C_6H_{13}	$(MeCN)_2PdCl_2$-$CuCl_2$-CuCl	70	30	38
e	CH_2OAc	$(MeCN)_2PdCl_2$-CuCl-NaCl	14	86	75



29 **30** (60%) **31** (14%)



32 **33** (33%) **34** (17%)



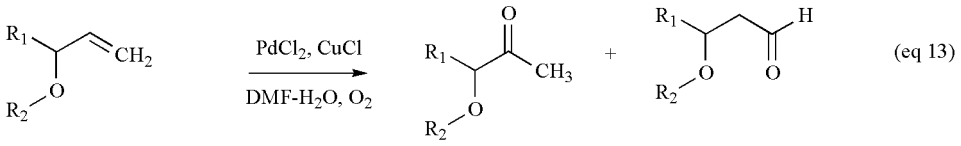
35 **36** **37**

35	X	R_1	36 (%)	37 (%)	yield (%)
a	O	Me	35	65	76
b	O	OEt	52	48	56
c	NMe	Ph	10	90	52
d	NPh	Me	10	90	52
e	$N(CH_2)_5$		10	90	52
f	$N(CH_2)_4$		10	90	52
g	$N(CH_2)_3$		11	89	52

and 8, the palladium-catalyzed oxidation of a terminal alkene follows Markovnikov's rule for addition, and ultimately, affords the methyl ketone. However, the regioselectivity can be switched to afford an aldehyde (or its acetal) by the use of certain catalyst systems or by the presence of certain neighboring groups. For example, palladium-catalyzed oxidation of a variety of simple terminal alkenes using $(MeCN)_2PdClNO_2$ [130] or $(MeCN)_2PdCl_2$[131] in *tert*-BuOH often affords more aldehyde than methyl ketone (eq 9). It was suggested that the reaction proceeds via formation of a *tert*-butyl acetal which is subsequently hydrolyzed. Cyanomethylated and carboxylated polystyrene resin supported palladium(II) catalysts have also been used to effect the anti-Markovnikov oxidation of 1-octene in *tert*-BuOH, however, the yield was lower than with $(MeCN)_2PdCl_2$ [63].

The presence of some neighboring groups can also strongly influence the regioselectivity of addition. In particular, heteroatoms such as nitrogen, oxygen or sulfur placed at a suitable position near the alkene can combine with the alkene to chelate palladium and direct the regiochemistry of the attacking nucleophile. It is typically reasoned that the observed regiochemistry is that which leads to the more favorable palladacyclic intermediate (that is, the more favorable, intramolecularly complexed alkylpalladium(II) intermediate) upon addition of water to the complexed alkene. Unfortunately, predicting the direction and level of such control is often difficult. The examples discussed in the following paragraphs will illustrate. As a further, but less frequent complication, while the oxidation of allylic alcohol **27** proceeds with high regioselectivity to afford the methyl ketone, other allyl alcohols and alcohol derivatives possessing a terminal double bond can give rearranged oxidation products. For example, the oxidation of **29** gives a mixture of methyl ketone **30** (60%) and 1-hydroxyl-3-one **31** (14%). Similarly, oxidation of **32** affords a mixture of methyl ketone **33** and the 1-acetoxy-3-one **34** in 33% and 17% yields, respectively (eq 10, 11) [2].

As suggested by the difference in the methyl ketone-to-aldehyde ratios in equations 12, 13 and 14, the nature of the allylic substituent strongly influences the observed partitioning between the regioisomeric oxidation pathways. For example, the palladium catalyzed oxidation of the propenyl acetate and carbonate (**35a** and **35b**, respectively) in anhydrous 1,2-dichloroethane containing HMPA gives a near 1 to 1 mixture of regioisomeric oxidation products (eq 12).



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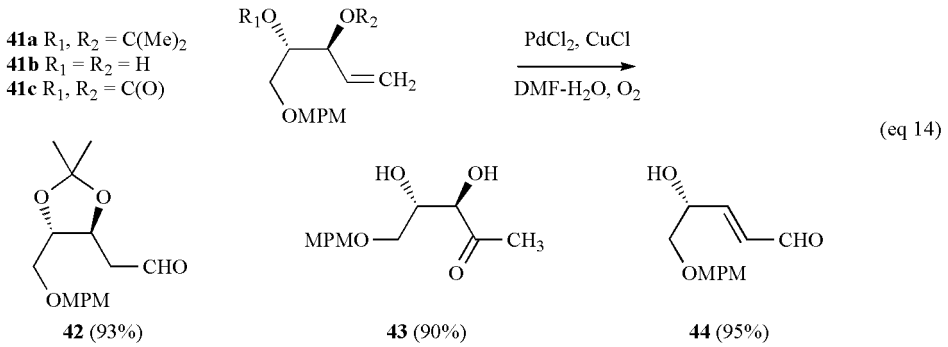

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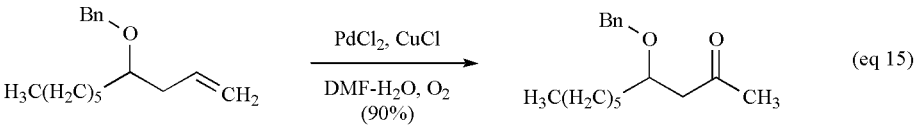
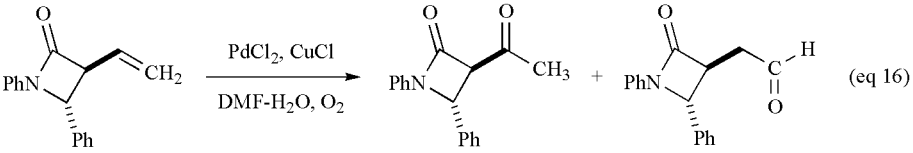


(eq 15)



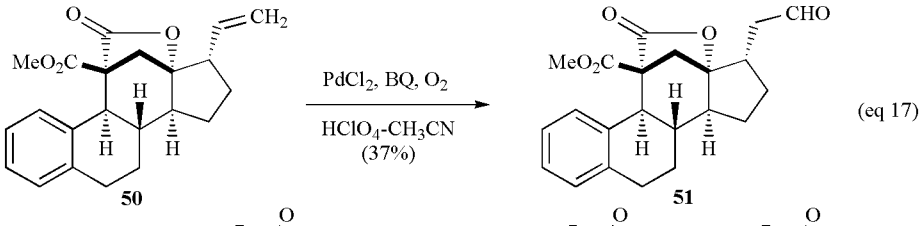
(eq 16)

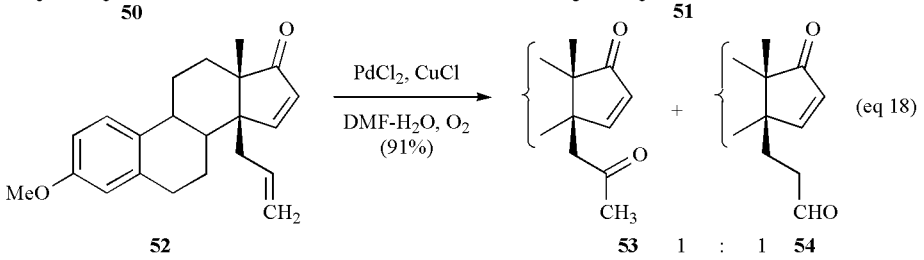
In contrast, under the same conditions, the propenylamides **35c-g** gave 90 percent of the aldehyde regioisomer [29]. To further highlight the importance of the precise nature of the allylic substituent, consider the influence of the allylic ether substituent in **38** (eq 13). The allylic benzyl ether **38a** affords a 1:1 mixture of methyl ketone **39a** and aldehyde **40a** [94]. In contrast, the TBS protected allylic ether **38b** affords only the methyl ketone **39b** [132].

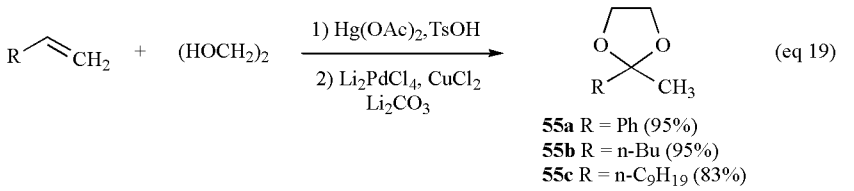
A series of examples from the groups of Jung and Kang further and dramatically highlight the influence of the allylic substituent and the unpredictability of its effect [94,117]. The five carbon unsaturated triol derivatives **41** give remarkably different results depending upon the choice or absence of diol protecting group (eq 14). Palladium-catalyzed oxidation of the acetonide **41a** gives the aldehyde **42** in excellent yield. The diol **41b** gives the methyl ketone **43**, again in excellent yield. Finally, the cyclic carbonate derivative **41c** reacts via a complementary pathway and gives the unsaturated aldehyde **44**. Three closely related substrates reacting under the same conditions and giving three different products, each obtained in excellent yield!

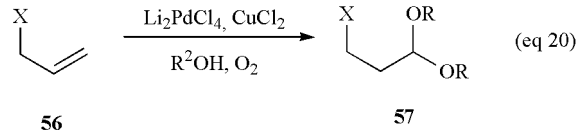
The examples illustrated above highlight the importance of the nature of the neighboring substituent. Not only the precise nature, but the precise position of the neighboring group is important. While the allylic benzyl ether **38a** gives a 1 to 1 regioisomeric mixture (eq 13), the homoallylic benzyl ether **45** gives only the methyl ketone **46** (eq 15) [94]. Once again, however, as the examples in equations 16-18 illustrate, it is difficult to generalize the effect. For example, the carbonyl group in the β-lactam **47** can occupy a similar position relative to the terminal alkene as the homoallylic ether oxygen in **45**. Nonetheless, it affords only 5% of the methyl ketone **48** and 65% of the aldehyde **49** (eq 16) [107].

The highly constrained nature of steroidal ring systems provides an interesting template upon which to explore the directing effect of remote substituents, and a number of very nice studies on steroid derivatives have been reported [86,103,133]. These also illustrate the rather unpredictable nature of this neighboring group effect. For example, the oxygen functionality positioned within the steroid skeleton in compound **50** again directs the oxidation of the terminal alkene to give the aldehyde (eq 17) [103]. Even more remote and/or non-obvious directing effects can influence the regioselectivity. The Wacker oxidation of **52** gave a mixture of methyl ketone **53** and aldehyde **54** in a ratio 1:1. It was suggested that participation of Δ^{15}-bond and hydrogen-





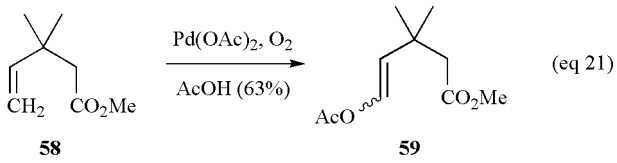




entry	X	R	yield (%)
a	NBn_2	Me	81
b	NBn_2	Et	81
c	NBn_2	$-CH_2CH_2-$	74
d	N(H)CH(Me)Ph	Me	10
e	SPh	Me	0
f	CH_2CH_2SPh	Me	56

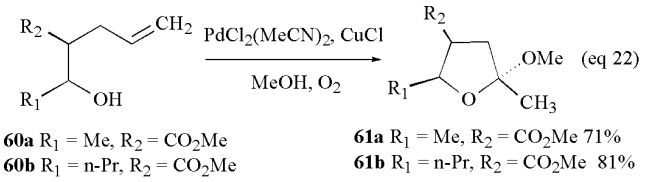
bonded association of water with the proximal 17-oxo group contribute to the unanticipated formation of substantial amounts of **54** (eq 18) [134].

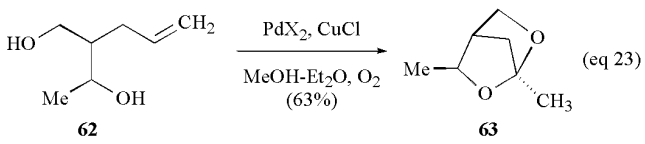
Usually the Wacker oxidation of terminal alkenes is carried out in an aqueous medium and affords the methyl ketone, but when the reaction carried out in the presence of an alcohol or a diol, the corresponding ketal is usually obtained. An older variant of the reaction variant initiates the process via oxymercuration. For example, oxymercuration of terminal alkenes in ethylene glycol followed by treatment with $PdCl_2$ leads to the ethylene ketal **55** (eq 19) [135]. The issue of regioselectivity again arises when the substrate bears a neighboring directing group. For example, the allylic tertiary amines **56a-c** efficiently give the corresponding acetals **57a-c**, but the allylic secondary amine **56d** gives only a low yield of acetal **57d** (eq 20) [136]. Similarly, the allylic sulfide **56e** gives none of the expected acetal **57e**, but the more remote phenyl sulfide gives **57f** in good yield. It is thought that the allylic NH and SPh substituents stabilize intermediates in the reaction that are intercepted to give chlorinated products, and thus, the yield of acetal in those two and related cases is low.

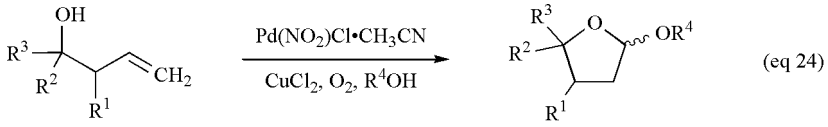


Another reaction mode related to the acetal formation is possible by again adjusting the reaction conditions. In the absence of chloride ion and in acetic acid, the palladium(II) catalyzed oxidation of ester **58** gave the vinyl acetate **59** in 63% yield (eq 27). It was suggested that chelation of palladium(II) by the double bond and a carbonyl oxygen lone pair induces the attack of nucleophile to terminal carbon of double bond [99]. Subsequent β-hydride elimination would account for formation of the enol acetate derivative.

The intramolecular addition of a suitably disposed hydroxyl group can be efficient and leads to formation of a cyclic ketal when the reaction is run in alcohol solvent or to a hemiketal when the reaction is run in aqueous solvent mixtures. For example, palladium-catalyzed oxidation of the unsaturated alcohol **60a-b** lead to the alkoxy tetrahydrofurans **61a-b** (eq 22). Diols such as **62** lead to the bicyclic ketal **63** (eq 23) [137,138].



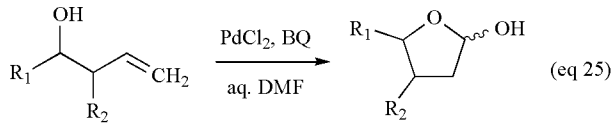




(eq 24)

64 **65**

entry	R^1	R^2	R^3	%yld 65 (R^4 = iPr)	% yield 65 (R = *t*-Bu)
a	H	H	H	26	94
b	H	Me	Me	100	100
c	H	Me	Et	95	100
d	H	Ph	Ph	80	75
e	Me	Me	Me	99	96



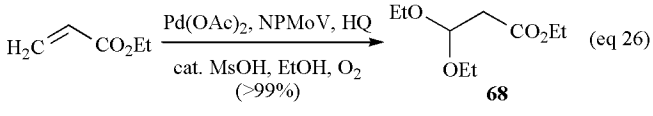
(eq 25)

66 **67**

entry	R^1	R^2	yield (%)
a	n-C_6H_{13}	Me	64
b	H	-$(CH_2)_7CO_2Me$	58
c	n-C_6H_{13}	CO_2Me	62
d	n-C_6H_{13}	(*p*-tolyl)SO_2	82
e	CH=C(H)Me	(*p*-tolyl)SO_2	50
f	CH_2OBz	OBn	81
g	CH_2OBn	OBn	87

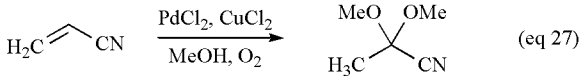
Regiochemistry is again an important issue, but the selectivity observed in this variant seems easier to rationalize. The unsaturated alcohols **60a-b** and **62** afford the ketals of methyl ketones (i.e., **61a-b** and **63)** and are derived via the facile five-membered ring forming cyclization of a pendant hydroxyl group. The facility of the ring closure seems to control the regioselectivity in similar substrates as well. For example, palladium-catalyzed oxidation of the homoallylic alcohols **64** afford the alkoxy tetrahydrofurans **65** (eq 24) [139]. The product obtained here is an acetal, that is, the product obtained via addition with the opposite regiochemistry as compared to **60** and **62**. Nonetheless, **65** is again derived via the more facile five-membered ring forming mode of cyclization. While it is reported that the reaction of 1-decen-4-ol (**66** R^1 = $(CH_2)_6CH_3$, R^2 = H) under the conditions given in equation 25 affords the methyl ketone (68% yield), other, more highly substituted homoallylic alcohols **66a-g** give the five-membered ring hemiacetals **67** under these conditions (eq 25) [140].

The palladium-catalyzed oxidation of an alkene bearing an electron-withdrawing substituent (e.g., phenyl vinyl ketone and ethyl acrylate) also produces the acetal when run in alcohol solvent [27,141,142]. For example, $Pd(OAc)_2$-catalyzed oxidation of ethyl acrylate using the chloride free reoxidation system molybdovanadophosphate (NPMoV)/-hydroquinone (HQ) in acidic ethanol affords ethyl 3,3-diethoxypropionate (**68**) in quantitative yield (eq 26) [46,143]. Surprisingly, it is reported that acrylonitrile is oxidized via a regioisomeric pathway to afford 2,2-dimethoxy propionitrile (**69**) (eq 27). However, when run with the same catalyst system but using ethylene glycol, the reaction gives the expected ethylene acetal rather than the isomeric ketal [141].



(eq 26)

68



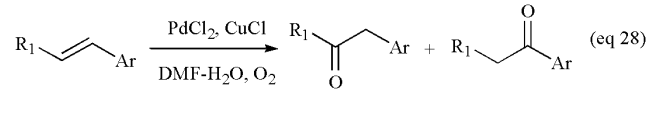
(eq 27)

69

KEY FEATURES OF THE PALLADIUM CATALYZED OXIDATION OF INTERNAL ALKENES

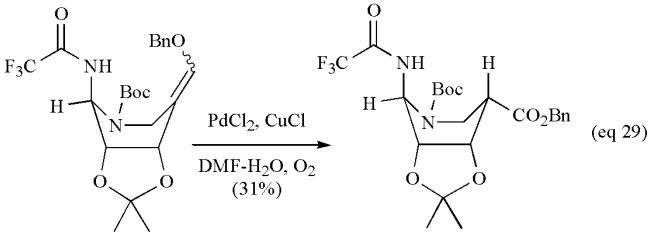
Under the standard Wacker oxidation conditions, simple internal and cyclic alkenes generally react slowly. However, under certain conditions, it is reported that such derivatives can be viable substrates for palladium-catalyzed oxidation. The reports include the use of bis(N,N-diethylacetamide)palladium(II) dichloride [37], water soluble palladium complexes derived from $Pd(OAc)_2$ and bathophenanthroline disulfonate [44], heteropolyacid co-catalysis [46,54,67], inorganic acid co-catalysis [64,65], electrochemical activation [72], and the use of fluorous biphasic systems [84].

As is the case with terminal alkenes, the regioselectivity observed in the oxidation of internal alkenes depends upon the precise reaction conditions, the structure of the starting alkene, and again, on the presence of neighboring groups capable of participation. Electronic effects can be important in determining the regioselectivity, as well. It is expected that a nucleophile such as water approaching a coordinated alkene should attack the carbon substituted by the better electron-donating group, or equivalently, at the position more remote from electron-withdrawing substituent. Comparing the palladium-catalyzed oxidations of β-methylstyrenes **70a** and **70b** tends to support this view(eq 28). β-Methylstyrene (**70a**) gives a mixture of the regioisomeric ketones **71a** and **72a** in 7.5: 1 ratio. Were a styrene derivative to bear a more electron rich aromatic ring, it should more highly favor addition at the adjacent site. In the event, the trimethoxystyrene analogue (1,3,5-trimethoxy-2-propenyl-benzene (**70b**)) did favor this mode to a relatively greater extent giving a 1 : 2.3 mixture of **71b** and **72b** [144,145], It should be noted however, that potentially the

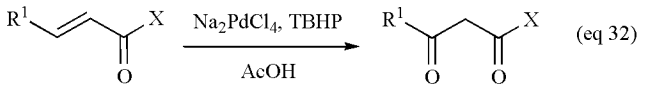


70a (R_1 = Ph)
70b (R_1 = 1,3,5-$(MeO)_3C_6H_2$)

71 **72**

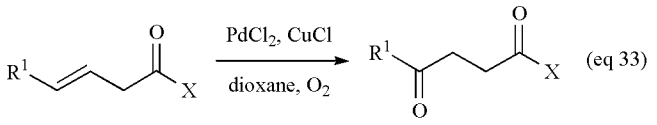


73 **74**



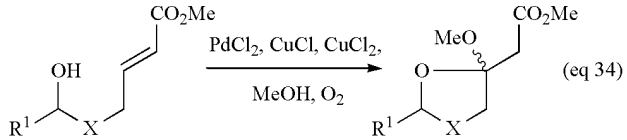
79 **80**

entry	R^1	X	yield (%)
a	Me	OMe	83
b	n-Pr	OMe	96
c	*i*-Pr	OMe	96
d	*i*-Bu	OMe	80
e	n-C_6H_{13}	Me	59
f	n-C_6H_{13}	Me	59



81 **82**

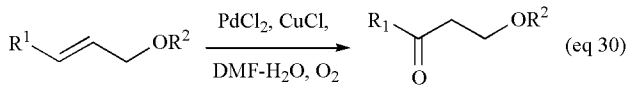
entry	R^1	X	yield (%)
a	Et	OMe	52
b	n-C_6H_{13}	OMe	61
c	Et	Me	45
d	n-C_6H_{13}	Me	61



83a R^1 = C_5H_{11}, X = CH_2
83b R^1 = Bn, X = CH_2CH_2
83c R^1 = C_7H_{15}, X = CH_2CH_2

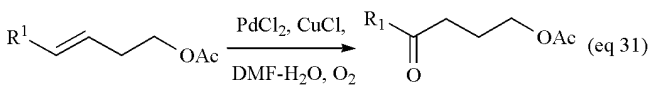
84a (87%)
84b (61%)
84c (79%)

1,3,5-trimethoxyphenyl ring can also participate as a neighboring group ligand, and this interpretation could as well account for the results. Based on the electronic



75 **76**

entry	R^1	R^2	yield (%)
a	Me	Bn	67
b	n-Pr	Me	65
c	*i*-Bu	Bn	76
d	n-C_5H_{11}	Ac	42



77e (R^1 = Me)
77f (R^1 = n-C_6H_{13})

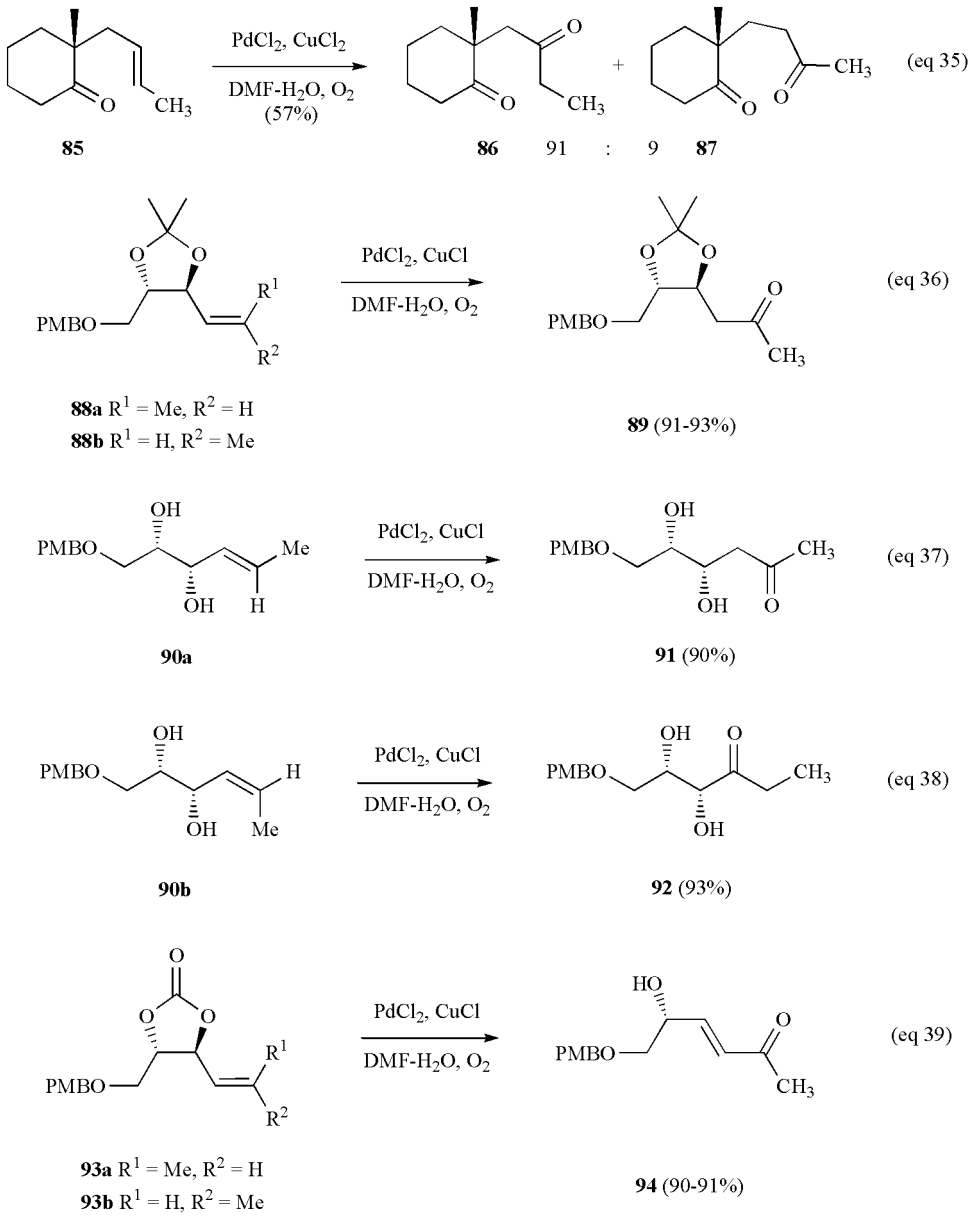
78e (80%)
78f (73%)

argument, enol ethers and related derivatives should favor attack of the nucleophile at the oxygen-substituted end, and palladium-catalyzed oxidation of enol ether **73** gives the ester **74** (eq 29) [106]. Note that this is one case where a trisubstituted alkene undergoes palladium-catalyzed oxidation; albeit, the yield is modest.

The palladium-catalyzed oxidations of acyclic, internal alkenes bearing allyl or homoallylic ether or acetate substituents proceed with high regioselectivity. For example, the allyl ethers **75a-c**, allyl acetate **75d** and homoallyl acetates **77e-f** were oxidized to corresponding β-alkoxy ketones **76a-c**, β-acetoxy ketones **76d**, and γ-acetoxy ketones **78e-f**, respectively (eq 30-31) [146]. These results again demonstrate the importance of the neighboring functional group, and the regioselectivity has been rationalized by invoking coordination of palladium with the oxygen functionality to direct the site of water addition.

α,β-Unsaturated esters and ketones as well as the corresponding β,γ-unsaturated derivatives also react with high regiocontrol. For example, α,β-unsaturated esters **79a-d** and ketones **79e-f** afford β-ketoesters **80a-d** and 1,3-diketones **80e-f**, respectively (eq 32). The β,γ-unsaturated esters **81a-b** and ketones **81c-d** afford the γ-ketoesters **82a-b** and 1,4-diketones **82c-d**, respectively (eqs 33) [147]. Intramolecular variants are also possible. For example, mixed ketals of structure **84** were formed via the regioselective intramolecular reaction of **83** in methanol. The five- and six-membered cyclic mixed acetals **84** were formed in generally good yields (61-87%) for several simple derivatives (eq 34) [148].

As was seen for certain terminal alkene substrates, rather remote functional groups positioned in rigid systems can significantly influence the observed regioselectivity. For example, palladium-catalyzed oxidation of **85** in aqueous DMF affords a mixture of ethyl ketone **86** and methyl ketone **87**, wherein the ethyl ketone **86** is strongly preferred (91:9 **86**:**87**, eq 35) [149]. However, the regioselectivity with internal alkenes depends upon the precise reaction conditions employed, and palladium-catalyzed oxidations of similar alkenes, when carried out in DME [101] with addition of

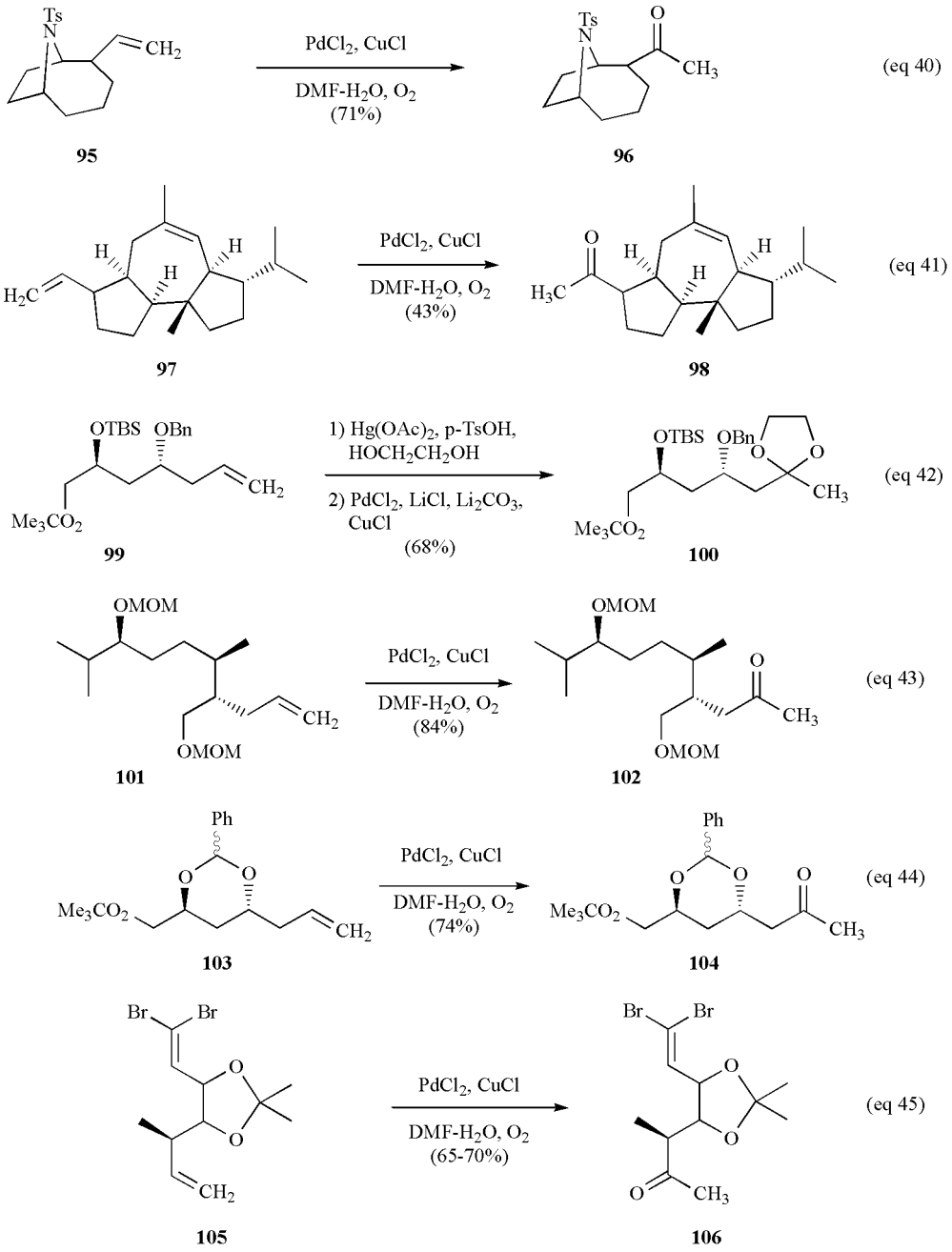


perchloric acid [64] or in the presence of PEG [80] afford methyl ketones as the major product.

Even relatively unconstrained systems can exhibit unusual regioselectivity as evident in a series of substrates studied by Kang and coworkers [94]. The (*E*)- and (*Z*)-acetonides **88a-b** (PMB = *para*-methoxybenzyl) undergo palladium-catalyzed oxidation to the methyl ketone **89** (93% and 91% yields, respectively) (eq 36). These results are consistent with what one might expect based upon the discussion above, and in particular, to the fairly close analogy shown in equation 30. However, the corresponding (*E*)- and (*Z*)-diols followed a much different course. Palladium-catalyzed oxidation of (*E*)-diol **90a** affords the methyl ketone **91** in 93% yield. In contrast, the (*Z*)-isomer **90b** affords the ethyl ketone **92** in high yield (90%) (eq 34). This dramatic difference in regioselectivity is ascribed to differences in steric hindrance around the double bond in the two isomers. The cyclic carbonates follow yet another course. Palladium-catalyzed reaction of either the (*E*)- or (*Z*)-carbonate (**93a** and **93b**, respectively) affords the α,β-unsaturated methyl ketone **94** in high yield (90% and 91%, respectively) (eq 39).

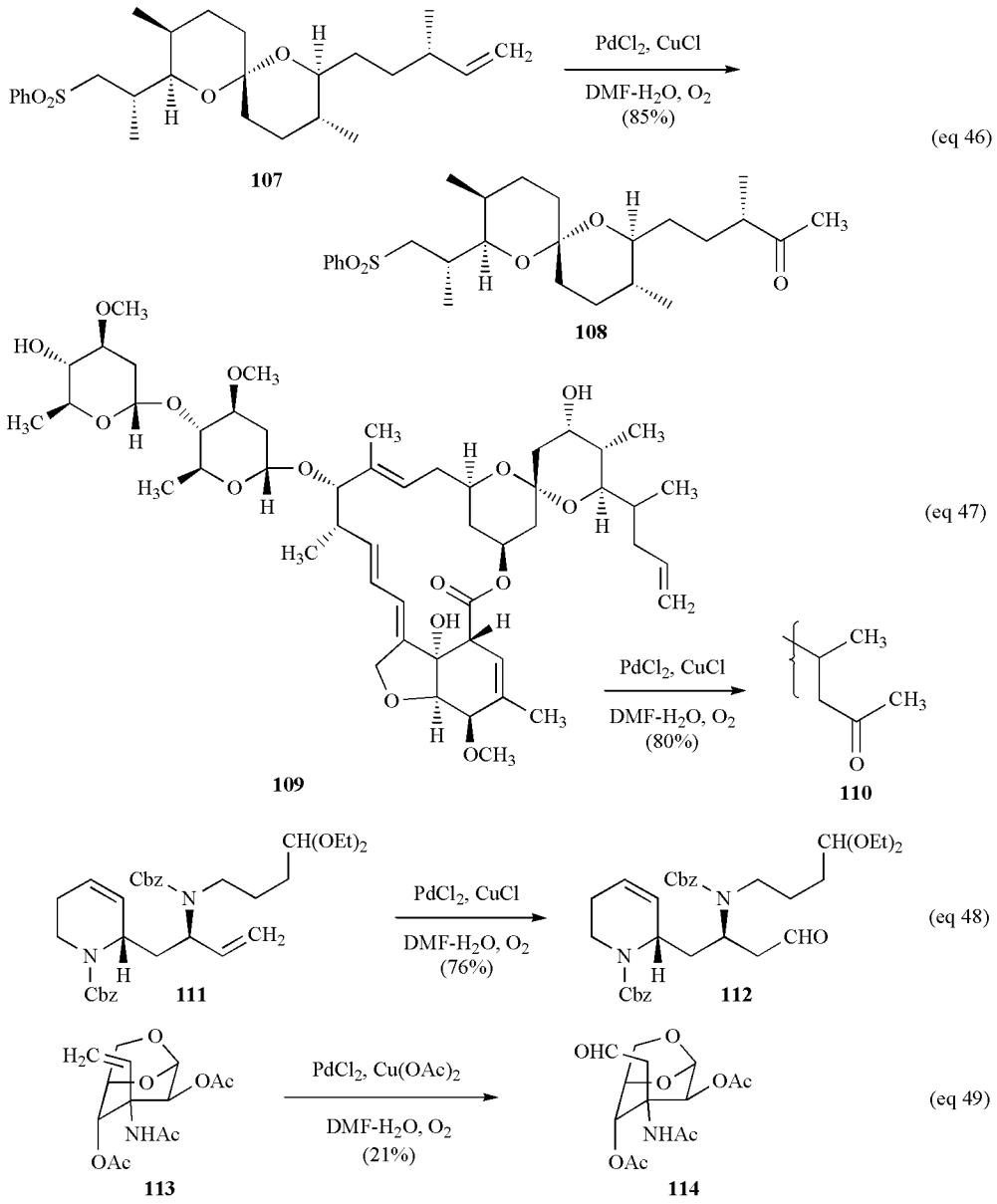
APPLICATIONS OF PALLADIUM-CATALYZED ALKENE OXIDATIONS IN TOTAL SYNTHESIS

The palladium-catalyzed oxidation of terminal alkenes to methyl ketones or to aldehydes has been used extensively in natural products total synthesis [2,3]. Recent applications involving the oxidation of an alkene to a methyl ketone include the total syntheses of calyculins A and B [50], sphydrofuran [97], queen's substance [102], the AB-ring of aklavinone [112], (-)-hennoxazole A [113,150], the BCD framework of richardianidins [121], (*dl*)-trichodiene [124], 18-oxo-3-virgene [125], the male sex pheromones of *Hylotrupes bajulus* and *Pyrrhidium sanguineum* [132], a



natural constituent of the perfume material civet [145], (*dl*)-dammarenediol [151], copalol [152], (±)-nakamurol-A [127], tautomycin [153], (+)-anatoxin-a [154], (±)-decarestrictine L [155], vitamin D_3 [115], clavularin A [126], the 1,3,5-triol fragment common to several polyene macrolides [156], nargenicin A_1 [157], and the preparation of dipeptide isosteres [158]. The palladium-catalyzed oxidation of an alkene to an aldehydes is less frequently applied; nonetheless, recent total syntheses using this variant include the synthesis of the carbocyclic core of tetradotoxin [159], the carbocyclic core of the tetraponerines [160], and the C25-C29 segment of rifamycin S [116].

As listed above, many complex substrates have been used successfully in the palladium-catalyzed alkene oxidation reaction to give methyl ketones or aldehydes. The examples described in this and the following several paragraphs are chosen so as to highlight the versatility of the reaction as well as to demonstrate the chemoselectivity of the palladium catalyzed oxidation and its tolerance of the common functionality. For example, the palladium-catalyzed oxidation of the aza-bicyclic compound **95** converts the terminal alkene to the methyl ketone **96**, a transformation that was used in the total synthesis of (+)-anatoxin-a (eq 40) [154]. The tricyclic ketone **98** was a key intermediate in the total synthesis of 18-oxo-3-virgene and was obtained by the selective palladium-catalyzed oxidation of the terminal alkene in compound **97** (eq 41) [125]. Recall that a common variant of the palladium-catalyzed oxidation of alkenes is one in which the reaction is carried out in the presence of alcohol or a diol and affords the ketal. Protected triol **99** contains two potentially acid labile protecting groups, and yet, the conversion of the terminal alkene to ketal occurs smoothly via the two step mercuric acetate then palladium dichloride

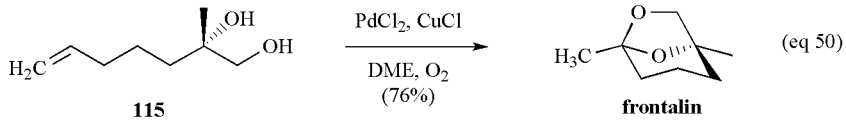


procedure. The transformation **99** to **100** was used for the C1-C7 segment of hennoxazole A (eq 42) [150].

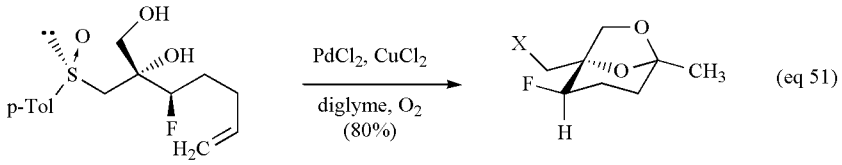
Acetals and ketals, whether acyclic or cyclic and whether used as a protecting group or present as key structural elements within the molecule of interest, are moderately acid labile functionalities often encountered in the course of synthesis. As the following examples illustrate, the conditions for palladium-catalyzed oxidation are very tolerant of such functionality. For example, in the synthesis of a ring D building block of vitamin D_3, doubly MOM ether-protected diol **101** was smoothly oxidized to the methyl ketone **102** (eq 43) [115]. The cyclic acetal **103** affords the methyl ketone **104**, a building block used in the synthesis of hennoxazole A (eq 44) [150]. The acetonide in **105** is stable toward palladium-catalyzed oxidation to the methyl ketone **106** (eq 45), a subunit used in an approach to nargenicin A_1 [157]. This example also illustrates the chemoselective oxidation of the terminal alkene in preference to the 1,1-dibromoalkene present in the same molecule, and in addition, the preservation of the methyl-bearing stereocenter alpha to the newly formed carbonyl in the course of the oxidation.

Even rather structurally complex acetal and ketal containing substrates undergo efficient palladium-catalyzed oxidation. For example, the spiroketal **107** gives methyl ketone **108**, which was used as segment C of tautomycin (eq 46) [153]. Again, the allylic stereocenter is preserved in the alkene to methyl ketone transformation. The palladium-catalyzed oxidation of avermectin derivative **109** to **110** provides access to avermectins with oxygen-containing functionalities at C-25 (eq 47) [87].

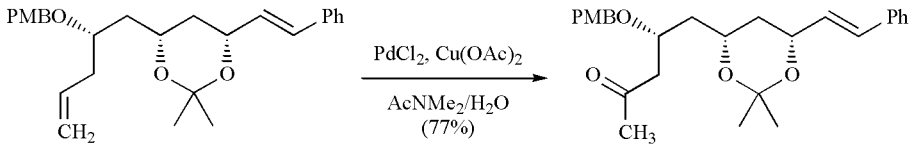
As stated previously, applications involving terminal alkenes that exploit the opposite regiochemistry in the palladium-catalyzed oxidation are less common. Nonetheless, it is found that tetrahydropyridine **111** is oxidized to aldehyde **112**, an intermediate in the total synthesis of tetraponerine (eq 48) [160]. It is likely that the allylic



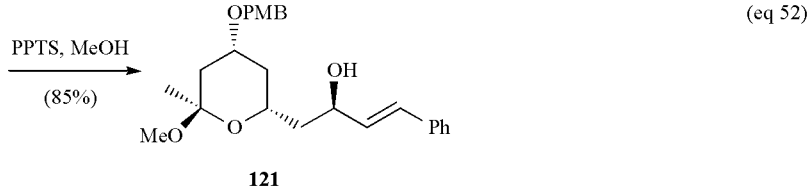
115 **frontalin** (eq 50)



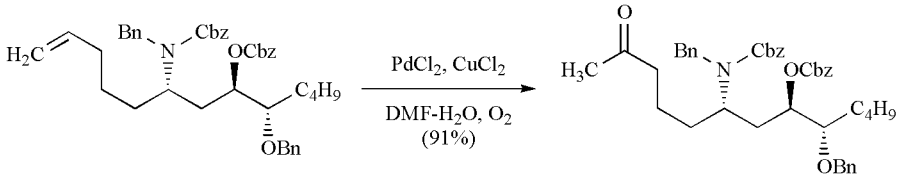
116 **117** (X = ArS(O)) **118** (X = H) (eq 51)



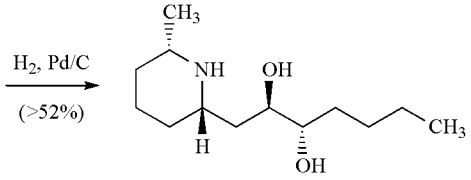
119 **120**



121 (eq 52)



122 **123**

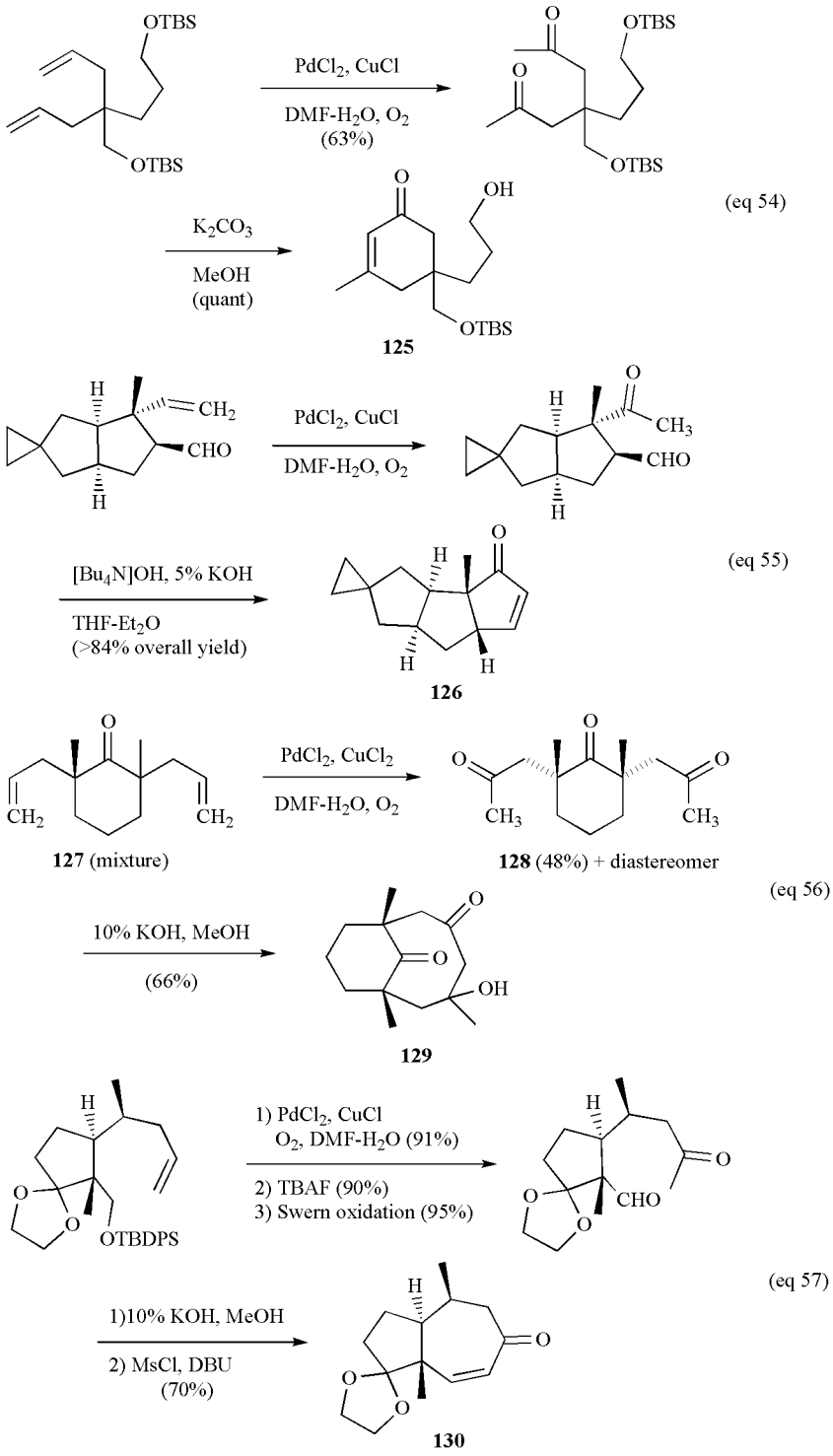


124 (eq 53)

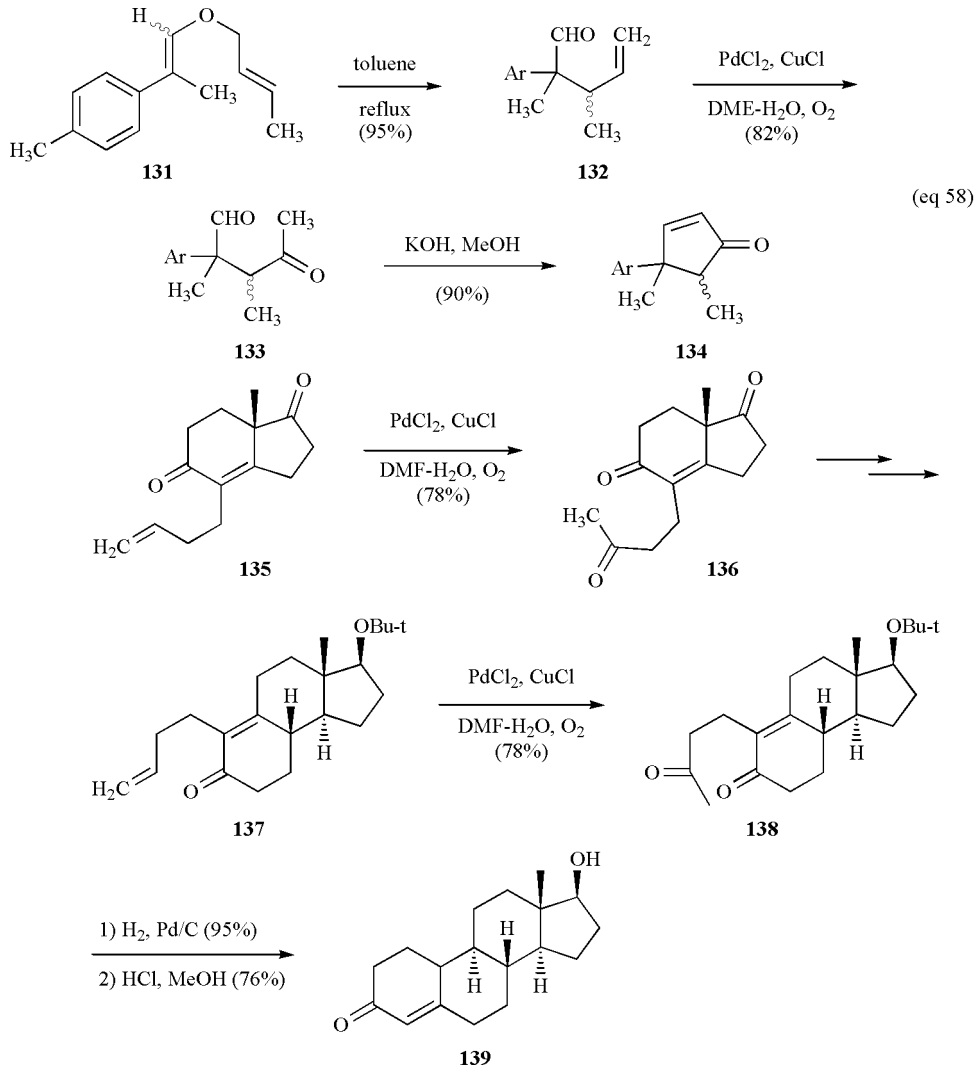
nitrogen substituent accounts for the regioselectivity, and of further note, the diethyl acetal is fully compatible with the palladium-catalyzed oxidation. Similarly, the 1,6-anhydro sugar **113** was converted into aldehyde **114**, a compound used as a key intermediate in the synthesis of carbocyclic core of tetradotoxin (eq 49) [159].

The various transformations effected via palladium-catalyzed oxidation have been successfully applied in a wide variety of substrate types, and the examples described above demonstrate some aspects of its chemoselectivity and its tolerance for common functionality. The reaction has also evolved into a strategy-level transformation that is useful in the context of synthetic planning. For example, the intramolecular palladium-catalyzed oxidation of certain unsaturated diols provides a versatile entry to bicyclic acetals. The shortest published synthesis of the aggregation pheromone frontalin is based on this strategy. Intramolecular acetalization of **115**, catalyzed by [$PdCl_2$/CuCl] under an atmosphere of oxygen, gives frontalin in 76% yield (eq 50) [161]. The more biologically active fluorinated analogue **118** was prepared from **116** via palladium-catalyzed acetalization to **117** (eq 51) [162]. This strategy has also been used to prepare (+)- and (–)-endo-brevicomin [163]. and the 2,8-dioxabicyclo[3.2.1]octane core of zaragozic acid [164].

While the direct conversion of an unsaturated diol to ketal is a frequently used approach, two step variants are also popular. For example, the functionalized tetrahydropyran **121** was prepared by palladium-catalyzed oxidation of **119** followed by mild acid catalyzed trans-ketalization (eq 52) [113]. The functionalized tetrahydropyran moiety **121** was used in the synthesis of (-)-hennoxazole A. A conceptual similar sequence used for the formation of a heterocyclic ring system, exploits palladium-catalyzed oxidation followed by intramolecular reductive amination. This latter variant is a convenient strategy for the preparation of nitrogen heterocycles as illustrated by equation 53. In the total synthesis of (+)-monomorine I, **123**, which was obtained via the oxidation of **122**, underwent a cascade of debenzylation and reductive cyclization to yield the cis-2,6-dialkylpiperidine **124** as a single stereoisomer [105].



While the palladium-catalyzed alkene oxidation is the key strategy for the synthesis of frontalin and related compounds, more commonly, the transformation is used in combination with a subsequent transformation(s) to define the synthetic strategy. The palladium-catalyzed alkene oxidation/reductive amination sequence in equation 53 illustrates the idea. The Wacker oxidation of an unsaturated aldehyde, an unsaturated ketone, or a doubly unsaturated substrate is frequently used to establish 1,4-, 1,5-, 1,6-, and 1,7-dicarbonyl relationships within a molecule. These functionalities then set the stage for subsequent intra-molecular aldol condensation or a related cyclization reaction. A variety of 5-, 6-, 7-, and 8-membered ring annulation sequences have exploited this strategy, and its utility is highlighted in the total syntheses of (±)-acorenone B [165], cephalotaxine [166], (-)-homogynolide-A [167], the AB ring model of Taxol [168], the AB ring system of 12-demethyltaxol [110], a number of angular and linear tetraquinanes [169], dysidiolide [100], the hydrindane systems of several natural products [170], and (-)-7-epibakkenolide-A [171]. Several other representative examples, the preparations of **125**, **126**, **129** and **130**, are illustrated in equations 54-57. These



Scheme 4. Strategy of Palladium-Catalyzed Alkene Oxidation Followed by Intramolecular Aldol/Dehydration in Steroid Synthesis

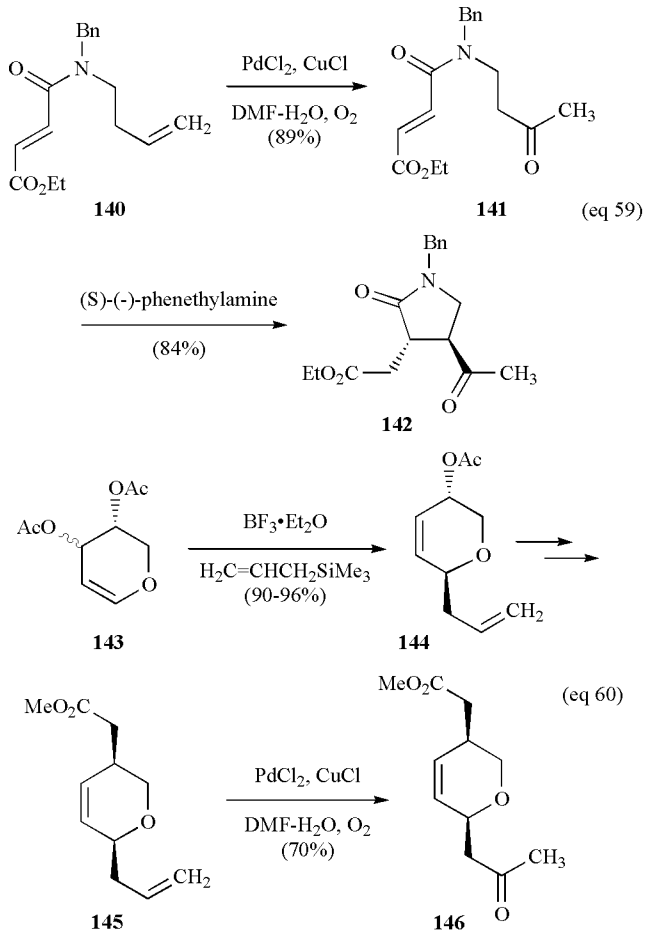
compounds (i.e., **125**, **126**, **129** and **130**) are intermediates in the syntheses of (±)-ptaquiosin [172], (±)-hirsutene [90], the ABC ring system of taxol [173], and pseudoguaianolide [174] respectively.

1,4-Dicarbonyl compounds can also be generated via a Claisen rearrangement-Wacker oxidation sequence. For example, Claisen rearrangement of **131** followed by Wacker oxidation affords keto-aldehyde **133**. The keto-aldehyde was converted to the rather sterically encumbered cyclopent-2-enone **134** (eq 58), which was used as a key intermediate in the total synthesis of (±)-laurene [91]. A similar strategy is used in the total syntheses of (±)-tochuinyl acetate and (±)-dihydrotochuinyl acetate [92,93].

The palladium-catalyzed oxidation/intramolecular aldol condensation sequence has found considerable use in preparations of the steroid skeleton [2,3,114,175-177] and various side chains derivatives [86,103,133,134,178]. In the preparation of the skeleton, the oxidation is used to construct 1,5-diketone building blocks for cyclohexenone annulation. For example, in a route to (+)-19-nortesto-sterone, the palladium-catalyzed oxidation of **135** gives 1,5-diketone **136**, and the latter compound was converted to BCD ring **137** (scheme 4) [176]. Similarly, compound **137** has been used to prepare the 1,5-diketone **138**. Hydrogenation of **138** followed by intramolecular aldol/dehydration and hydrolysis of *tert*-butyl ether furnished (+)-19-nortestosterone (**139**) [175]. Similar strategies have been used in the synthesis of D - homo - 19 - norandrosta - 4 - en - 3 - one, wherein the A ring is formed by the palladium - catalyzed alkene oxidation/intramolecular aldol-dehydration sequence [177], and in the synthesis of a 7-acetyl-D-homosteroid, wherein the B ring was constructed in a similar fashion [114].

Another of the cascade cyclization sequences exploits palladium-catalyzed oxidation followed by an intramolecular Michael addition reaction. For example, oxidation of **140** followed by treatment with (S)-(-)-1-phenylethylamine gives pyrrolidone (-)-**142**, an intermediate used as a key building block for α-allokainic acid (eq 59) [98].

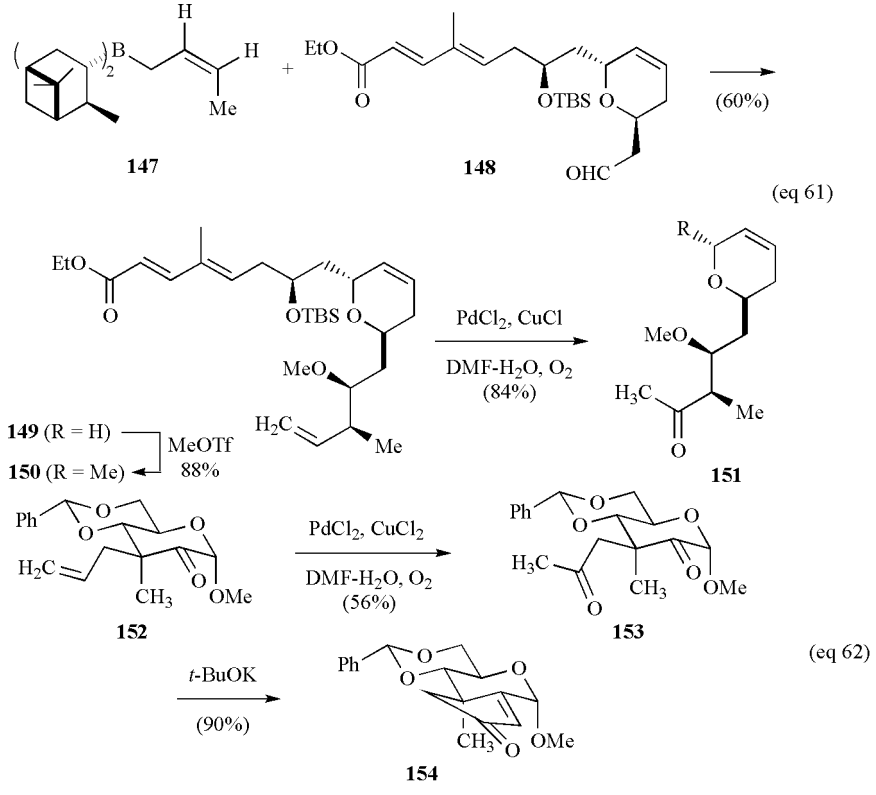
Another common strategic use of the Wacker oxidation is in conjunction with an asymmetric allylation to effect the equivalent of an asymmetric aldol reaction of acetone or other methyl ketone [88]. For example, allylation of diacetate of D-arabinal (**143**) gives the intermediate acetate **144** which serves as a precursor to the unsaturated ester **145**.

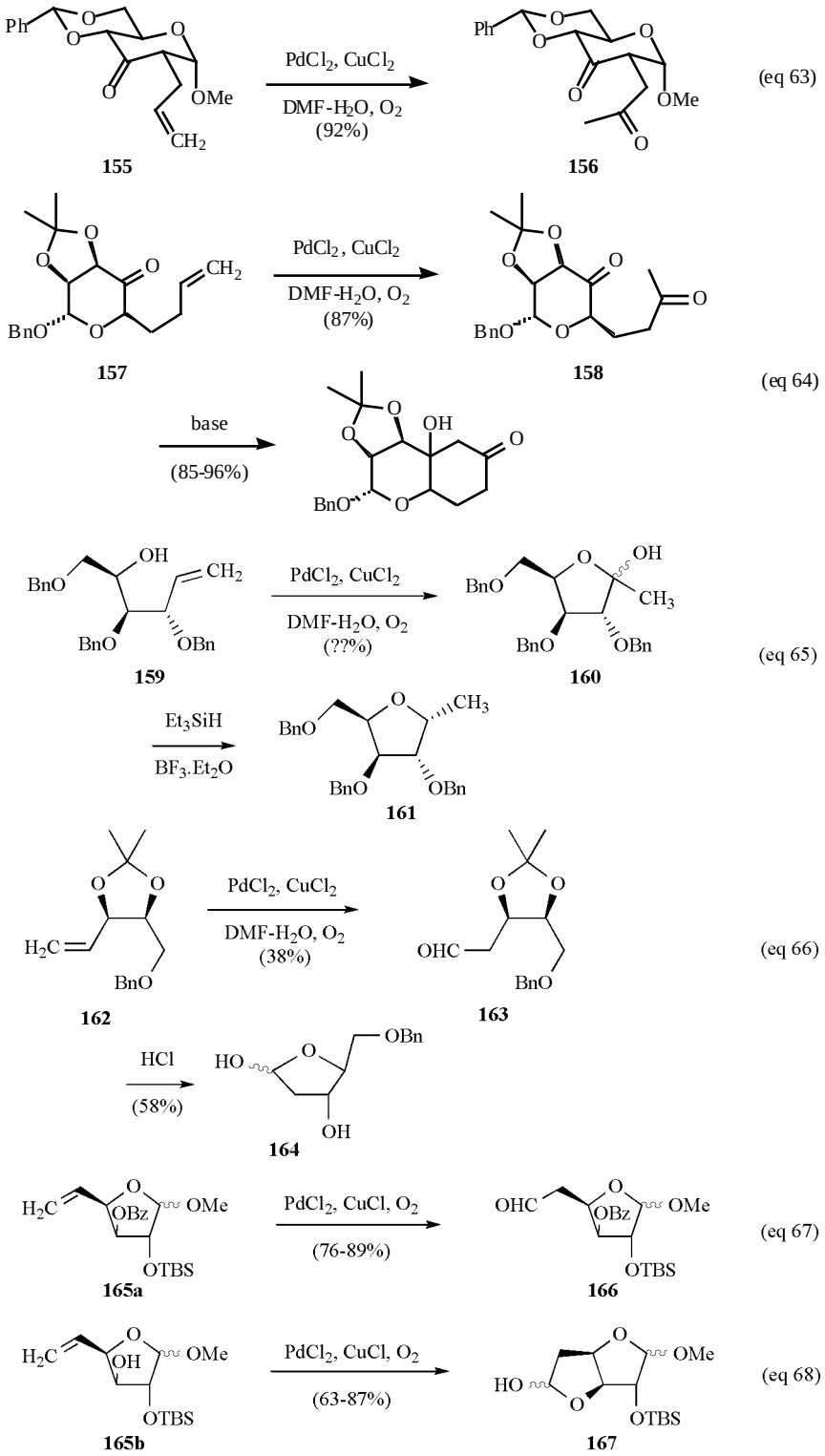


Palladium-catalyzed oxidation of **145** afforded multi-gram quantities of methyl ketone **146**, which was used in the total synthesis of pseudomonic acid (eq 60) [179]. A similar strategy has been applied in the total synthesis of rutamycins [180]. In the total synthesis of swinholide A, the syn-selective crotylboration of **148** with Brown's (-)-α-pinene-derived reagent **147** followed by methylation of the resulting hydroxyl group gives intermediate **150**. The Wacker oxidation of **150** affords methyl ketone **151** (eq 61) [181]. This example strikingly highlights the selectivity and functional group tolerance of the oxidation as well as the synthetic equivalency of the allylation/oxidation sequence to an asymmetric aldol reaction of a methyl ethyl ketone enolate. The presence of the dienoate, isolated double bond, TBS ether, tetrahydropyran ring, and potential β-methoxy leaving group are all tolerated in the reaction. In addition, epimerization at the methyl-bearing α-stereocenter is not a problem under the reaction conditions.

The palladium-catalyzed oxidation reaction has also been used in the modification of carbohydrates and in the synthesis of unnatural sugars. For example, oxidation of glucose derivative **152** affords the diketone **153** which was cyclized to the cyclopentenone **154** via base catalyzed intramolecular aldol reaction (eq 62). Surprisingly, the similar diketone **156**, which is obtained in good yield via the oxidation of **155**, fails to undergo the intramolecular aldol (eq 63) [119]. The palladium-catalyzed oxidation of 6-C-substituted D-mannose derivative **157** gives the methyl ketone **158** in high yield (eq 64) [111].

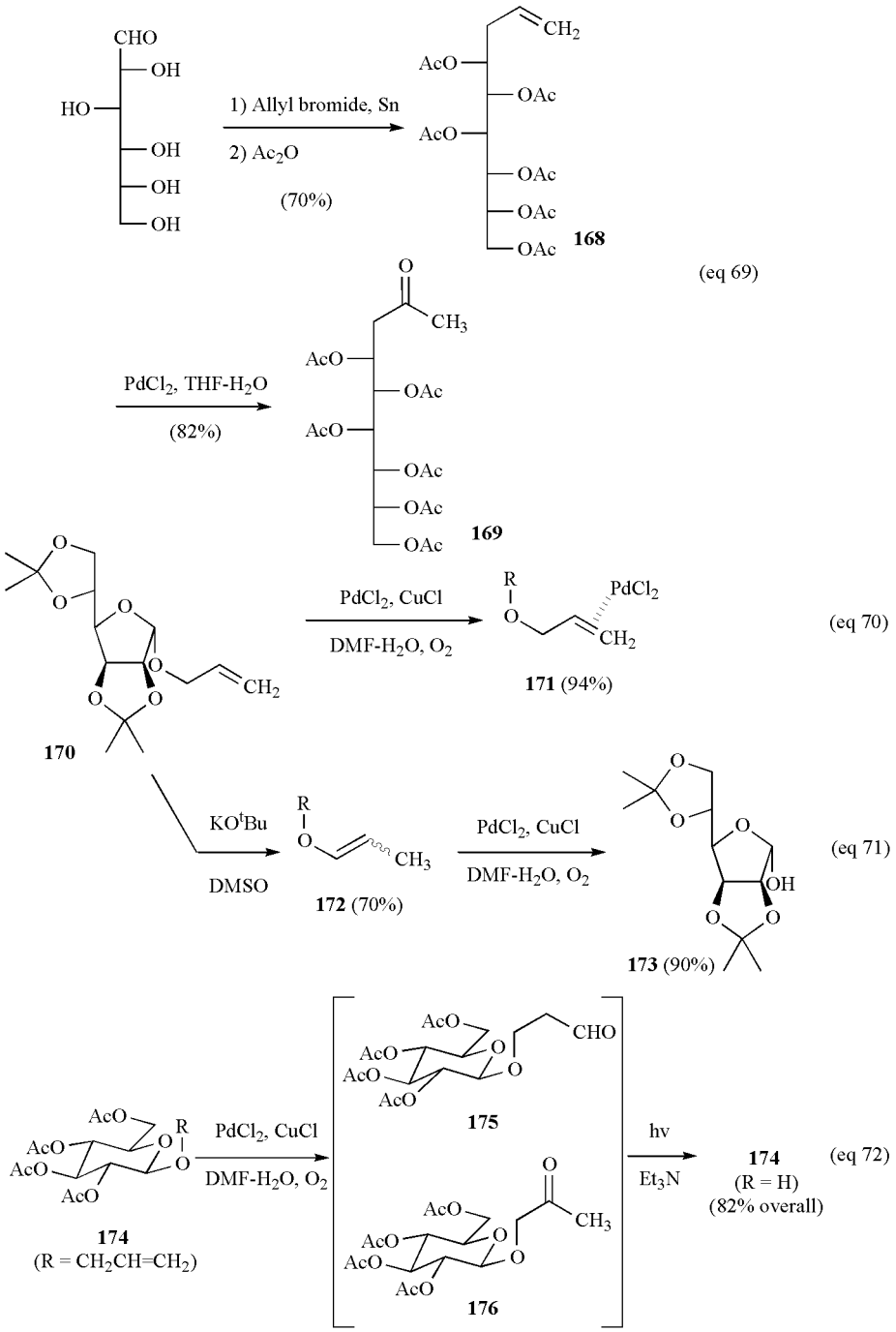
The examples described the preceding paragraph are in the six-membered ring pyranose series. In the furanose series, similar results have been obtained. For example, the unsaturated alcohol **159** undergoes palladium-catalyzed oxidation to give the hemiketal **160**. Reductive deoxygenation of **160** leads to the formation of the C-α-D-





glycoside **161** (eq 65) [138]. Formation of the aldehyde regioisomer is more commonly observed in the five membered ring series due to the frequent presence of a allylic oxygen substituent. For example, oxidation of acetonide **162** gives the aldehyde **163**. The latter compound was converted into 2-deoxy-L-ribose **164** upon treatment with HCl (eq 66) [117]. Similarly, the furanosides **165a-b**, afford the aldehyde or its lactol depending on the presence or absence of a protecting group on the neighboring oxygen; the benzoate **165a** leads to the formation of aldehyde **166** (eq 67), and free alcohol **165b** gives lactol **167** (eq 68) [182].

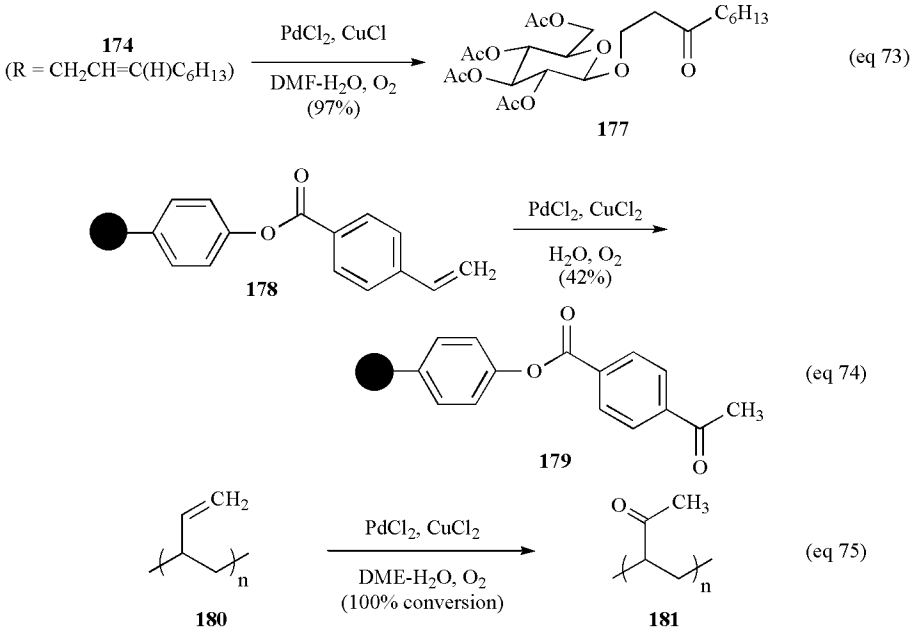
One example illustrating the use of the palladium-catalyzed oxidation of open chain sugar derivative is shown in equation 69. Tin mediated allylation of D-glucose followed by acetylation and palladium-catalyzed oxidation of the resulting polyacetate **168** gives the three carbon extended ketose **169** in high yield (eq 69) [183].



MISCELLANEOUS APPLICATIONS OF WACKER-TYPE OXIDATIONS

The Wacker oxidation has been applied in development of other synthetic strategies, including for example, the cyclizations of furan chromium carbenes [184], [3+4] and [3+5] annulation reactions [185], and the spiroannulation of cyclopentane rings [186]. In addition, allyl ethers are commonly used as protecting groups in carbohydrate chemistry [187]. Two closely related deprotection procedures based on palladium-catalyzed oxidation have been developed. Although the direct use of the Wacker oxidation conditions for the deprotection of allyl ethers has been reported [188], the methodology does not appear to be very general. For example, the oxidation of compound **170** under typical Wacker-type oxidation conditions gives only the η^2-palladium(II) alkene complex **171** (94%) (eq 70). Deprotection of the allyl ether in **170** could be achieved by first base-promoted isomerization to the corresponding propenyl ether **172** (*tert*-BuOK in DMSO at 140 °C) followed by palladium-catalyzed oxidation. Via this protocol, lactol **173** was obtained in 63% overall yield (eq 71) [189].

Alternatively, palladium-catalyzed oxidation of **174** (R = $CH_2CH{=}CH_2$) affords a mixture of aldehyde **175** and methyl ketone **176**, in which the **175**:**176** ratio is solvent dependent (1:4 in 1:1 DMF-H_2O and 2.3:1 in 6:1 DMF-H_2O). Photolysis of the mixture in the presence of triethylamine affords the glycol **174** (R = H) in overall 82% yield (eq 72) [96]. A variation on this method employs a more highly



substituted allyl glycoside, for example, **174** (R = $CH_2CH=C(H)C_6H_{13}$). In this case palladium catalyzed oxidation of the internal alkene occurs with high regioselectivity to afford the β-alkoxyl ketone **177** (97%) (eq 73). Subsequent base promoted elimination via treatment with DBU affords **174** (R = H, 81%) [190].

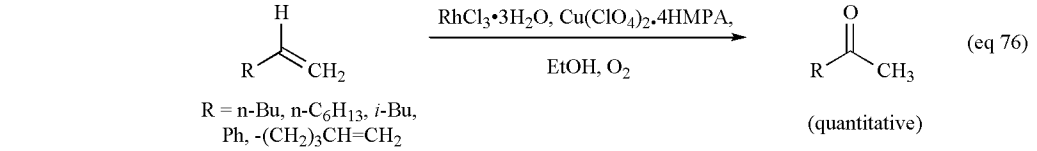
While a number of palladium-binding resins have been evaluated as polymer bound reagents for the Wacker oxidation (referenced in the discussion above), only a single recent report describes the Wacker oxidation of a resin bound alkene substrate. More work needs to be done on this application to make it attractive. Nevertheless, the preliminary study demonstrates the viability of the chemistry. Among several macroporous resins examined, the Wacker oxidation of alkenes **178** bound to a commercial polymer (Rohm & Haas) gives ketone **179** in moderate yield (eq 74; yield determined after cleavage) [191].

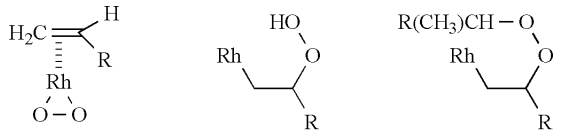
Polymeric polyketones are important materials because they can be converted to other functionalized polymers. Usually polyketones are prepared via the copolymerization of an α-alkene with carbon monoxide or via the polymerization of unsaturated ketones. Unfortunately, these two methods suffer from competing undesired side reactions and/or difficulty in controlling the degree of polymerization. Polybutadiene is a well-studied, readily available and commercially important polymer. Conditions (cat. $PdCl_2/CuCl_2$ in DME-water under low oxygen pressure) that effect the facile and complete palladium-catalyzed oxidation of polybutadiene **180** to polyketone **181** were reported (eq 75) [192].

RHODIUM-, IRIDIUM-, COBALT-, RUTHENIUM- AND PLATINUM-CATALYZED WACKER-TYPE OXIDATIONS

Compared with palladium, the use of other transition metals as Wacker-type alkene oxidation catalysts has been received limited attention. Nevertheless, number of other metals have been shown to catalyze similar oxidations using dioxygen or hydroperoxide as the ultimate oxidizing reagent. Among these, certain rhodium, iridium, cobalt and platinum catalysts have been shown to oxidize alkenes to ketones, and since the future of organic synthesis is intimately tied to the discovery and development of new reagents, we thought it appropriate to summarize these results, all of which are at an early stage of development, as part of our survey of the field, and perhaps, as food for thought.

Among the alternative metal catalysts for Wacker-type alkene oxidation, rhodium is the most extensively investigated thus far. Both Rh(I) and Rh(III) have been used in the oxidation of alkenes. In contrast to the palladium catalyst systems, most alkene oxidations using rhodium do not involve water as a nucleophile (although there are exceptions), and sometimes, the reaction is accelerated by the addition of a dehydrating agent such as 2,2-dimethoxypropane (DMP). For example, using dioxygen as the only oxidant, rhodium trichloride is a very inefficient and nonspecific catalyst. Water is formed during the course of the reaction, and its formation both inhibits the desired reaction and promotes isomerization of the double bond [193,194], These problems can be overcome by adding a oxidant such as a $Cu(II)X_2$ or $Fe(III)X_3$ salt, the former being preferred. The choice of counterion is important; perchlorate and nitrate are good, while chloride is less active, and bromide or iodide are inactive. The addition of ligands such as pyridine, bipyridine, phosphine, arsine or 1,5-cyclo-octadiene results in diminished catalytic activity. Generally, alcohols such as ethanol and isopropanol are the best reaction solvents. For example, a variety of simple, linear terminal alkenes can be quantitatively oxidized to the corresponding methyl ketones with $[RhCl_3•(H_2O)_3/Cu(ClO_4)_2•(HMPA)_4]$ (eq 76) [193]. Under the reaction conditions specified, isomerization of double bond occurs only to small extent, and aldehydes are not observed. While few more complicated alkenes have been examined, surprisingly, it is found that only one of the two terminal double bonds in 1,6-hexadiene is oxidized.



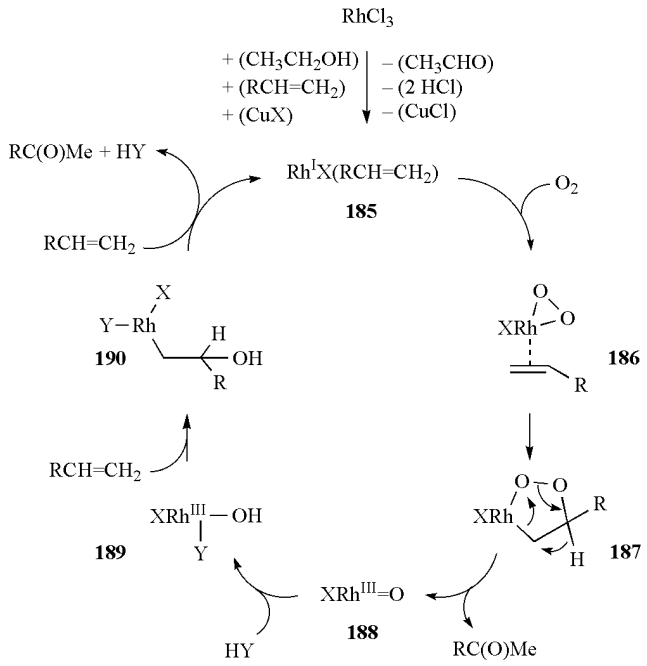


182 **183** **184**

A number of other catalyst systems show promise. Compared to $[RhCl_3•(H_2O)_3/Cu(ClO_4)_2•(HMPA)_4]$ for example, a catalyst system consisting of $[Rh(ClO_4)_3•(H_2O)_6/Cu(BF_4)_2$-LiCl] was found to be more effective with certain alkenes. In this latter catalyst system, 2-3 chloride ions per rhodium atom are necessary for maximum activity, but chloride present in larger excess leads to a sharp decrease in the catalytic activity. This catalyst system is not sensitive to the presence of 1 to 2 equivalents of added phosphine, but the addition of ligands such as pyridine results in inefficient catalysis [195]. Rhodium perchlorate is also reported to be a good catalyst for the oxidation of terminal alkenes to methyl ketones and is quite active in the absence of free water, chloride or copper ions [193]. $[Rh(CO)_2Cl]_2$ can be oxidized to a Rh(III) catalyst in ethanol [196], and it was found that either HOOH or t-BuOOH can be used as the oxidant in the oxidation of 1-hexene, run under inert atmosphere and catalyzed by $RhCl_3•(H_2O)_3$ and or a Rh(III)/Cu(II) catalyst system [194]. In contrast to many Rh complexes where the oxidation is strongly inhibited by water, it was found that $RhCl_3•(H_2O)_3$ or (1,5-hexadiene)rhodium(I) chloride can be used under the conditions of phase transfer catalysis [197]. In addition to the rhodium catalysts discussed above, rhodium oxide clusters have also been shown to catalyze oxidation of alkenes with O_2 to give ketones. Schwartz reported an oxide-bound (alumina)$Rh(O_2)$ species efficiently catalyzes the oxidation of alkenes to give ketones in the absence of a sacrificial co-reductant such as alcohol or phosphine [198]. Other rhodium oxide clusters have been investigated [199].

In general, the oxidation of internal alkenes are much slower than terminal ones. The reaction rate and the nature of products formed depend considerably on the structure of the alkene and the reaction conditions. Much effort has already been devoted toward developing an understanding of the catalytic mechanism of these rhodium catalysts, but at this point, the mechanistic picture remains rather complicated. Mimoun [193,200,201] and Drago [194,196] have proposed three mechanisms to rationalize the results of $RhCl_3$/Cu catalyzed oxidation of terminal alkenes to ketones by O_2. Each features a different key rhodium intermediate in the activation and transfer of dioxygen, the peroxo rhodium complex **182** [193,200-205], hydroperoxy rhodium **183** [194-196,201,205], and alkylperoxy rhodium **184** [194].

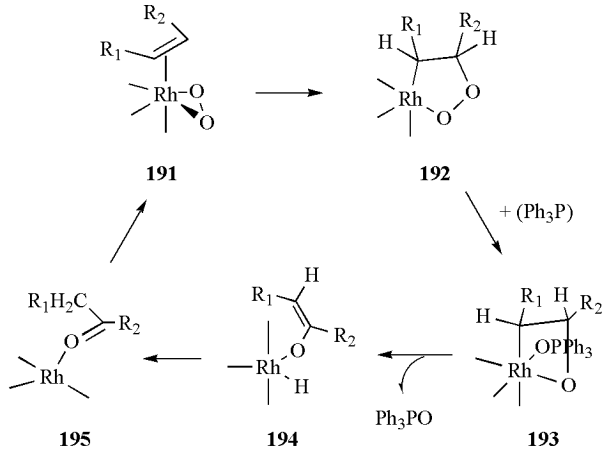
Mimoun's mechanism (Scheme 5) uses both oxygen atoms of dioxygen in reactions with alkene [193]. A rhodium(I)-alkene π complex such as **185** can be obtained



Scheme 5. Mimoun's Mechanism for the $RhCl_3/O_2$ Catalyzed Oxidation of Terminal Alkenes

from the reduction of $RhCl_3$ by the ethanol solvent in the presence of an alkene. It is postulated that **185** adds molecular oxygen to form a peroxo rhodium complex such as **186**. Alternatively, **186** might be generated by the reaction of a Rh(III) peroxo complex with the alkene [206]. Once formed, insertion of the alkene into a rhodium-oxygen bond would yield a five-membered peroxometallocycle such as **187** which decomposes to the observed methyl ketone product and a rhodium(III) oxo complex such as **188**. It is proposed that the addition of protic acid would give complex **189**, which in the presence of alkene forms an intermediate such as **190**. Complex **190** can undergo beta-elimination, releasing a second molecule of methyl ketone and an equivalent of HY. Coordination of alkene regenerates the initial rhodium(I) complex **185** completing the catalytic cycle. Drago offered two alternative proposals to account for the reaction [194].

The study of cationic Rh(I) complexes is at an early stage and their synthetic utility is yet to be established. Nonetheless, complexes such as [Rh(diphosphine)$_2$]X and [Rh(diphosphine)(diene)]X derivatives have been studied, but these suffer from a fall-off in activity, although they are capable of turnover numbers (TONs) in the range of 800- 900 [201,206]. Developing a better mechanistic under-standing of oxygenation at the rhodium center should be helpful in the design of future catalysts. Read proposed a mechanism for the rhodium-catalyzed alkene oxidation using Wilkinson's catalyst as illustrated schematically in Scheme 6 [204].



Scheme 6. A Pathway for Alkene Oxidation using $RhCl(PPh_3)_3$ and Dioxygen.

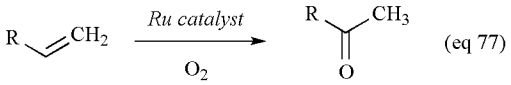
$RhCl(PPh_3)_3$ is thought to be converted to a peroxo Rh(III)(alkene) complex (e.g., **191**). The coordinated alkene is thereby activated toward isomerization to a peroxometallocycle such as **192**. Subsequent coordination of PPh_3, oxygen transfer and loss of Ph_3PO would allow for β-hydride elimination en route to the observed ketone. Gal and coworkers isolated several related model compounds that support this general mechanism [207].

Other metals have been used in alkene oxidation catalyst systems. Several ruthenium complexes have been investigated in the phase transfer catalyzed oxidation of 1-decene to 2-decanone (eq 77). $RuCl_2(PPh_3)_3$ and $RuCl_3$ showed activity, while $Ru(acac)_3$ and $[Ru(CO)_3Cl_2]_2$ were not effective [197]. Taquikhan reported the $RuCl_3$ catalyzed the oxidation of 1-hexene to 2-hexanone using oxygen as the ultimate oxidant (equation 77, entry d) [203]. A mechanism similar to Mimoun's mechanism for the rhodium catalyzed oxidation of terminal alkenes was proposed. Compared to the rhodium catalyst, an interesting feature of the ruthenium catalyst is that water is required [203].

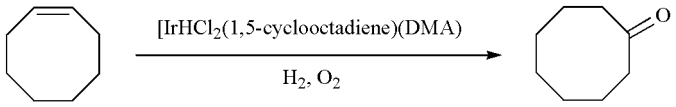
The reaction of cyclooctene, O_2 and H_2 to give cyclooctanone and water is catalyzed by an iridium(III) hydride complex, $[IrHCl_2(C_8H_{12})(DMA)]$ (eq 78, DMA = dimethylacetamide). The reaction is thought to proceed via an iridium-hydroperoxide intermediate [208], and may be related to the observation that $[\eta^5\text{-}Cp^*(Ph)IrPMe_3]^+$ can catalyze the insertion of ethylene into the Ir-OH bond of $[\eta^5\text{-}Cp^*(Ph)IrPMe_3]OH$. That insertion gives $[\eta^5\text{-}Cp^*(Ph)IrPMe_3]CH2CH2OH$, which is subsequently converted to $[\eta^5\text{-}Cp^*(Ph)IrPMe_3]CH2CHO$ [209].

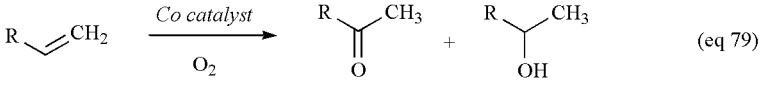
Cobalt complex **196** catalyzes the Wacker-type oxidation of terminal alkenes in the presence of dioxygen or hydrogen peroxide. Methyl ketones and their corresponding secondary alcohols are formed (eq 78) [210]. Internal alkenes such as 2-hexene and 3-hexene are oxidized to form mixtures of 2- and 3-hexanone and 2- and 3-hexanol.

Amidate-bidged Pt(III) binuclear complexes, $[Pt_2(NH_3)_4(Am)_2(H_2O_2)]^{4+}$ (Am = amidate ligand), catalyze the oxidation of alkenes in acidic aqueous solution ($[Pt_4(NH_3)_8(C_4H_6NO)_4](NO_3)_6\bullet(H_2O)_2$, $C_{12}H_{25}SO_3Na$, aqueous $H_2SO_4/(CH_2Cl)_2$, O_2) [211]. Linear alkenes (e.g., **197)** are oxidized principally to ketones (e.g., **198**), whereas cyclic alkenes are oxidized to epoxides (e.g., **199**); thus far, both proceed with only modest turnover numbers (eq 80). The

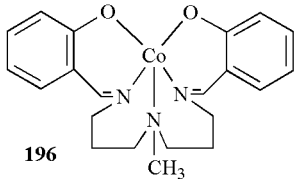


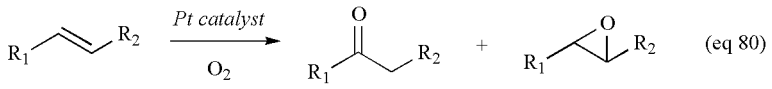
entry	R	*Ru catalyst*	yield (%)
a	n-C_8H_{17}	$RuCl_2(PPh_3)_3$-$CuCl_2$/cetyltrimethylammonium bromide	64
b	n-C_8H_{17}	$RuCl_2(PPh_3)_3\bullet CuCl_2/(Bu_4N)(HSO_4)$	28
c	n-C_8H_{17}	$RuCl_3\bullet CuCl_2$/cetyltrimethylammonium bromide	13
d	n-C_4H_9	$RuCl_3$, aqueous HCl	54





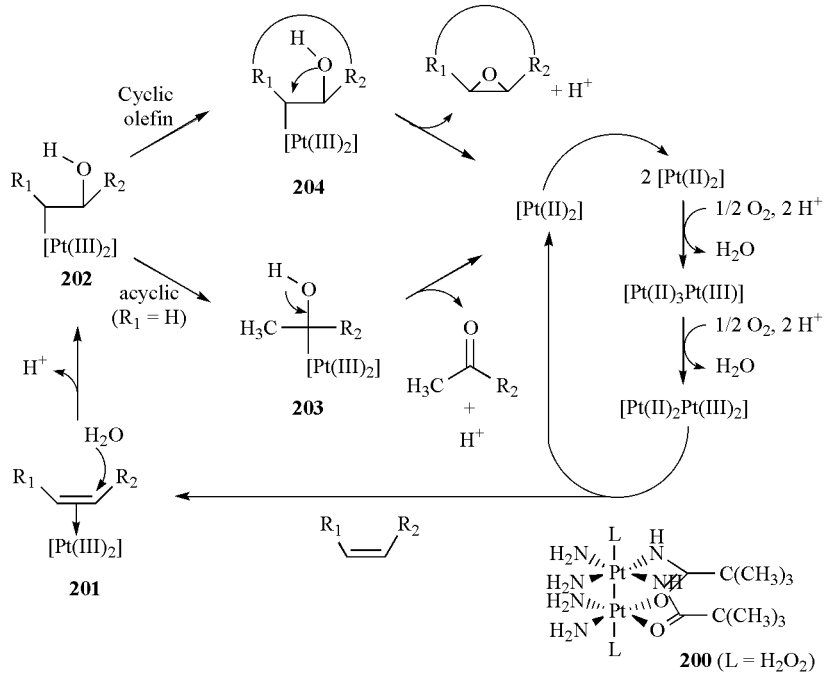
R = n-Bu, Ph, MeC(OH)H, *i*-C_5H_{11}





197 **198** **199**

R_1	R_2	198 (TON)	199 (TON)
n-Bu	H	11.9	8.6
n-C_5H_{11}	H	13.3	
n-C_6H_{13}	H	15.8	
n-C_5H_{11}	Me	1.7-2.2	
-$(CH_2)_4$-		1.9	22.8
-$(CH_2)_3$-		2.0	
norbornene		7.2	2.3



Scheme 7. Amidate-bidged Pt(III) Binuclear Complexes, $[Pt_2(NH_3)_4(Am)_2(H_2O_2)]^{4+}$

oxygen atoms incorporated come exclusively from water, suggesting that the reaction mechanism is basically similar to that of the Wacker reaction (scheme 7). It has been suggested that the catalytically active metal is a Pt(III) dimer **200**, and that in the first step of the reaction, the alkene is bound to the dimer to give a complex such as **201**. Nucleophilic attack by water at the more highly substituted carbon atom would afford **202**. At this stage, linear alkenes are thought to undergo 1,2-(H/Pt)-transposition to give an intermediates such as **203** which then serves as the precursor to the observed methyl ketone. In the case of cycloalkenes, which are more constrained, **204** leads to epoxide formation.

CONCLUDING REMARKS

The Wacker oxidation has been studied extensively. The largest part of research efforts have been devoted to palladium catalyzed the oxidation. Several mechanistic pathways have been proposed to explain the observed results. The regioselectivity of the palladium-catalyzed oxidation, both with terminal and internal alkenes, is influenced by each of the important reaction components: the structure of the substrate, the catalyst system, solvent and reaction conditions. The high chemoselectivity of this reaction is demonstrated in its applications in syntheses of complex natural products, and much common functionality is tolerated. In combination with other reactions, many useful synthetic strategies have been developed and used in the total syntheses of natural products. Other transition metal complexes can catalyze the Wacker oxidation and related reactions. These studies with other metals are at very early stages, however, the unique mechanisms by which these catalysts operate may provide new opportunities to achieve different selectivity and/or useful cascade pathways.

REFERENCES

[1] Dedieu, A. *Catal. Met. Complexes* **1995**, *18*, 167-195; Feringa, B. L. *Transition Metals for Organic Synthesis* **1998**, *2*, 307-315; Heumann, A.; Reglier, M. *Tetrahedron*

1996, *52*, 9289-9346; Jira, R., *Appl. Homogeneous Catal. Organomet. Compd.* **1996**, *1*, 374-393; Monflier, E.; Mortreux, A. *Aqueous-Phase Organometallic Catalysis* **1998**, 513-518.

[2] Tsuji, J. *Synthesis* **1984**, 369-384.

[3] Tsuji, J., *In Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon: Oxford* **1991**, *7*, 449-468.

[4] Tsuji, J., *Pure Appl. Chem.* **1999**, *71*, 1539-1547; Tsuji, J., *New J. Chem.* **2000**, *24*, 127-135.

[5] Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246-3250.

[6] Henry, P. M. *J. Am. Chem. Soc.* **1966**, *88*, 1595-1597.

[7] Moiseev, I. I.; Levanda, O. G.; Vargaftic, M. N. *J. Am. Chem. Soc.* **1974**, *96*, 1003-1007.

[8] Backvall, J. E.; Akermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411-2416.

[9] Wan, W. K.; Zaw, K.; Henry, P. M. *J. Mol. Catal.* **1982**, *16*, 81-87.

[10] Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Appl. Catal, A* **2000**, *194-195*, 435-442.

[11] Francis, J. W.; Henry, P. M., *Organometallics* **1991**, *10*, 3498-3503; Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832-2836.

[12] Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1996**, *112*, 317-326.

[13] Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082-7083.

[14] Backvall, J. E.; Akermark, B.; Ljunggren, S. O. *J. Chem. Soc. Chem. Commun.* **1977**, 264-265.

[15] Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745-7750.

[16] Armstrong, D. R.; Fortune, R.; Perkins, P. G. *J. Catal.* **1976**, *45*, 339-348; Eisentein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308-4320; Fujimoto, H.; Yamasaki, T. *J. Am. Chem. Soc.* **1986**, *108*, 578-581; Kragten, D. D.; Santen, R. A. *J. Phys. Chem. A* **1999**, *103*, 80-88. ; Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564-1568.

[17] Siegbahn, P. E. M. *J. Am. Chem. Soc.* **1995**, *117*, 5409-5410.

[18] Siegbahn, P. E. M. *J. Phys. Chem. A* **1996**, *100*, 14672-14680.

[19] Akermark, B. C. S. B. *Organometallics* **1987**, *6*, 2608-2610.

[20] Espeel, P. H.; Peuter, G.; Tielen, M. C.; Jacobs, P. A. *J. Phys. Chem. A* **1994**, *98*, 11588-11596.

[21] Antonsson, T.; Hansson, S. C. M. *Acta Chem. Scandia* **1985**, *B39*, 539-545.

[22] Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239-248.

[23] Saito, Y.; Koie, Y.; Shinoda, S. *Bull. Chem. Soc. Japan* **1986**, *59*, 2938-2940.

[24] Hamilton, R.; Mitchell, T. R. B.; Rooney, J. J. *J. Chem. Soc. Chem. Commun.* **1981**, 456-457.

[25] Hosokawa, T.; Nakahira, T.; Takano, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1996**, *118*, 3990-3991.

[26] Hosokawa, T.; Nakahira, T.; Takano, M.; Murahashi, S.-I. *J. Mol. Catal.* **1992**, *74*, 489-492.

[27] Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49-54. ; Hosokawa, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Japan* **1990**, *63*, 166-169.

[28] Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 1915-1918.

[29] Hosokawa, T.; Aoki, S.; Takano, M.; Nakahira, T.; Yoshida, Y.; Ichi, S. *J. Chem. Soc. Chem. Commun.* **1991**, 1559-1560.

[30] Roussel, M.; Mimoun, H. *J. Org. Chem.* **1980**, *45*, 5387-5390.

[31] Mimoun, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 734-750.

[32] Mimoun, H.; Charpentier, R.; Mitschler, A.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1980**, *102*, 1047-1054.

[33] Stahl, S. S.; Thorman, J. L.; Nelson, T. R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188-7189.

[34] Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S., *J. Org. Chem.* **1995**, *60*, 6159-6167.

[35] Rode, C. V.; A., B.; Chaudhari, R. V. *Can. J. Chem. Eng.* **1992**, *70*, 612-617.

[36] Chen, S.; Kao, Y.-K. *Chem. Eng. Commun.* **1990**, *88*, 31-47.

[37] Takethira, K.; Hayakawa, T.; Orita, H. *Chem. Lett.* **1985**, 1835-1838.

[38] Andrews, A. K.; Kelly, K. P. *J. Am. Chem. Soc.* **1981**, *103*, 2894-2896.

[39] Sage, J.-M.; Gore, J.; Guilmet, E. *Tetrahedron Lett.* **1989**, *30*, 6319-6322.

[40] Backvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160-5166. ; Srinivasan, S.; Ford, W. T. *J. Mol. Catal.* **1991**, *64*, 291-303.

[41] Sommovigo, M.; Alper, H. *J. Mol. Catal.* **1994**, *88*, 151-158.

[42] Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem.* **1995**, *99*, 77-86.

[43] Higuchi, M.; Yamaguhi, S.; Hirao, T. *Synlett* **1996**, 1213-1214.

[44] Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Chem. Commun.* **1998**, 2359-2360.

[45] Hosokawa, T.; Nomura, T.; Murahashi, S.-I. *J. Organomet.*

Chem. **1998**, *551*, 387-389.

[46] Yokota, T.; Fujibayashi, S.; Nishiyama, Y.; Sakaguchi, S.; Ishii, Y. *J. Mol. Catal. A: Chem.* **1996**, *114*, 113-122.

[47] Hirao, T.; Higuchi, M.; Hatano, B.; Ikeda, I. *Tetrahedron Lett.* **1995**, *33*, 5925-5928.

[48] Backvall, J.-E.; Hopkins, R. B. *Tetrahedron Lett.* **1988**, *29*, 2885-2888.

[49] Hirao, T.; Murakami, T.; Ohno, M.; Ohshiro, Y. *Chem. Lett.* **1989**, 785-786.

[50] Smith III, A. B.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765-8768.

[51] Wenzel, T. T. *J. Chem. Soc. Chem. Commun.* **1989**, 932-933.

[52] Heide, E. V.; Ammerlaan, J. A. M.; Gerritsen, A. W.; Scholten, J. J. F. *J. Mol. Catal.* **1989**, *55*, 320-329.

[53] Heide, E.; Zwinkels, M.; Gerritsen, A.; Scoholten, J. *J. Appl. Catal. A* **1992**, *86*, 181-198.

[54] Kishi, A.; Higashino, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 99-102.

[55] Stobbe-Kreemers, A. W.; Soede, M.; Makkee, M.; Scholten, J. J. F. *Appl. Catal. A* **1995**, *131*, 367-381.

[56] Stobbe-Kreemers, A. W.; Soede, M. M., M.; Scholten, J. J. F. *Appl. Catal. A* **1997**, *156*, 219-238.

[57] Izumi, Y.; Fujii, Y.; Urabe, K. *J. Catal.* **1984**, *85*, 284-286.

[58] Rao, V.; Datta, R. *J. Catal.* **1988**, *114*, 377-387.

[59] Tang, H. G.; Sherrington, D. C. *J. Catal.* **1993**, *142*, 540-551; Tang, H. G.; Sherrington, D. C. *Polymer* **1993**, *34*, 2821-2829.

[60] Tang, H. G.; Sherrington, D. C. *J. Mol. Catal.* **1994**, *94*, 7-17.

[61] Sherrington, D. C. *Pure Appl. Chem.* **1988**, *60*, 401-414.

[62] Ahn, J.-H.; Sherrington, D. C. *Macromolecules* **1996**, *29*, 4164-4165.

[63] Ma, J.; Sherrington, D. C. *J. Chem. Research [S]* **1995**, 119.

[64] Miller, D. G.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 2924-2927.

[65] Skumov, M.; Balbolov, E. *Catal. Lett.* **2000**, *69*, 103-107.

[66] Espeel, P. H.; Tielen, M. C.; Jacobs, P. A. *J. Chem. Soc. Chem. Commun.* **1991**, 669-671.

[67] Ogawa, H.; Fujinami, H.; Taya, K.; Teratani, S. *Bull. Chem. Soc. Japan* **1984**, *57*, 1908-1913; Kim, Y.; Kim, H.; Lee, J.; Sim, K.; Y., H.; Paik, H. *Appl. Catal. A* **1997**, *155*, 15-26.

[68] Stobbe-Kreemers, A. W.; Zon, M.; Makkee, M.; Scholten, J. J. F. *J. Mol. Catal. A: Chem.* **1996**, *107*, 247-253.

[69] Nowinska, K.; Dudko, D. *Appl. Catal. A* **1997**, *159*, 75-87; Nowinska, K.; Sopa, M.; Dudko, D.; Mocna, M. *Catal. Lett.* **1997**, *49*, 43-48.

[70] Otsuka, K.; Kobayashi, A. *Chem. Lett.* **1991**, 1197-1200.

[71] Riering, H.; Schafer, H. J. *Chem. Ber.* **1994**, *127*, 859-873.

[72] Miller, D. G.; Wayner, D. D. M. *Can. J. Chem. Eng.* **1992**, *70*, 2485-2490; Tsuji, J.; Minato, M. *Tetrahedron Lett.* **1987**, *28*, 3683-3686.

[73] Inokuchi, T.; Ping, L.; Hamaue, F.; Izawa, M.; Torii, S. *Chem. Lett.* **1994**, 121-124.

[74] Clement, W. H.; Selwitz, C. H. *J. Org. Chem.* **1964**, *29*, 241-243.

[75] Fabey, D. R.; Zuech, E. A. *J. Org. Chem.* **1974**, *39*, 3276-3277.

[76] Alandis, N.; Rico, I.; Lattes, A. *Bull. Soc. Chim. Fr.* **1989**, 252-255; Rico, L.; Couderc, F.; Perez, E.; Laval, J. P.; Lattes, A. *J. Chem. Soc. Chem. Commun.* **1991**, 669-671.

[77] Lepinte, C.; Riviere, H. *Tetrahedron Lett.* **1977**, 3817-3820.

[78] Januszkiewicz, K.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5159-5162.

[79] Alper, H.; Januszkiewicz, K.; Smith, D. J. H. *Tetrahedron Lett.* **1985**, *26*, 2263-2264.

[80] Zahalka, H. A.; Januszkiewicz, K.; Alper, H. *J. Mol. Catal.* **1986**, *35*, 249-253.

[81] Harada, A.; Hu, Y.; Takahashi, S. *Chem. Lett.* **1986**, 2083-2084.

[82] Monflier, E.; Blouet, E.; Barbaux, Y.; Mortreux, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2100-2102; Monflier, E.; Tilloy, S.; Fremy, G.; Barbaux, Y.; Mortreux, A. *Tetrahedron Lett.* **1995**, *36*, 387-388; Monflier, E.; Tilloy, S.; Blouet, E.; Barbaux, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1996**, *109*, 27-35; Karakhanov, E.; Maximov, A.; Kirillov, A. *J. Mol. Catal. A: Chem.* **2000**, *157*, 25-30.

[83] Ito, H.; Kusukawa, T.; Fujita, M. *Chem. Lett.* **2000**, 598-599.

[84] Betzmeier, B.; Lhermitte, F.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6667-6670.

[85] Kaszonyi, A.; Vojtko, J.; Hrousovsky, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 2128-2139.

[86] Cachoux, F.; Ibrahim-Ouali, M.; Santelli, M. *Synlett* **2000**, 418-420.

[87] Banks, B. J.; Fenner, B. R.; Voss, V. F.; Witty, M. J. *Synlett* **1991**, 875-877.

[88] Yatagai, H.; Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 4548-4550.

[89] Hiyama, T.; Sawahata, M.; Kusano, Y. *Chem. Lett.* **1985**, 611-612.

[90] Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 6099-6102.

[91] Kulkarni, M. G.; Pendharkar, D. S. *J. Chem. Soc. Perkin. Trans. I* **1997**, 3127-3128.

[92] Srikrishna, A.; Reddy, T. J.; Kumar, P. P.; Vijaykumar, D. *Synlett* **1996**, 67-68.

[93] Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 6311-6327.

[94] Kang, S.; Jung, K.; Chung, J.; Namkoong, E.; Kim, T. *J. Org. Chem.* **1995**, *60*, 4678-4679.

[95] Subramaniam, C. S.; Thomas, P. J.; Mamdapur, V. R.; Chadha, M. S. *Synthesis* **1978**, 468-469.

[96] Luning, J.; Moller, U.; Debski, N.; Welzel, P. *Tetrahedron Lett.* **1993**, *34*, 5871-5874.

[97] Maliakel, B. P.; Schmid, W. *J. Carbohydr. Chem.* **1993**, *12*, 415-424.

[98] Hirai, Y.; Terada, T.; Katoh, H.; Sonohara, S.; Momose, T. *Heterocycles* **1991**, *32*, 7-10.

[99] Tanaka, M.; Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1986**, *27*, 3165-3168.

[100] Paczkowski, R.; Maichle-Mossmer, C.; Maier, M. E. *Org. Lett.* **2000**, *2*, 3967-3969.

[101] Kulkarni, M. G.; Sebastian, M. T. *Synth. Commun.* **1991**, *21*, 581-586.

[102] Trhen, I. R.; Vig, R.; Singh, V.; Sharma, S.; Kad, G. L. *Indian J. Chem.* **1992**, *31B*, 257-259.

[103] Pellissier, H.; Michellys, P.; Santelli, M. *Tetrahedron* **1997**, *53*, 7577-7586.

[104] Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860-863.

[105] Ito, M.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *31*, 5065-5068.

[106] Nishimura, Y.; Kudo, T.; Kondo, S.; Takeuchi, T. *J. Antibiotics* **1994**, *47*, 101-107.

[107] Bose, A. K.; Krishnan, L.; Wagle, D. R.; Manhas, M. S. *Tetrahedron Lett.* **1986**, *27*, 5955-5958.

[108] Reginto, G.; Mordini, A.; Verrucci, M.; Degl'Innocenti, A.; Capperucci, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3795-3768.

[109] Esch, P. M.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Heterocycles* **1987**, *26*, 75-79.

[110] Shiina, I.; Iwadare, H.; Saitoh, M.; Ohkawa, N.; Nishimura, T.; Mukaiyama, T. *Chem. Lett.* **1995**, 781-782.

[111] Gonzalez, F. B.; Espina, M. R. *Bull. Chem. Soc. Japan* **1992**, *65*, 575-578.

[112] Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592-4597.

[113] Yokokawa, F.; Asano, T.; Shiori, T. *Tetrahedron* **2001**, *57*, 6311-6327.

[114] Pearson, A. J.; Ray, T. *Tetrahedron Lett.* **1985**, *26*, 2981-2984.

[115] Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965-973.

[116] Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Kusakabe, M.; Sato, F. *Heterocycles* **1987**, *25*, 549-561.

[117] Jung, M. E.; Nichols, C. J. *Tetrahedron Lett.* **1998**, *39*, 4615-4618.

[118] Wood, A. J.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc. Chem. Commun.* **1995**, 1567-1568.

[119] Wood, A. J.; Holt, D. J.; Dominguez, M.; Jenkins, P. R. *J. Org. Chem.* **1998**, *63*, 8522-8529.

[120] Kaufmann, W.; Venanzi, L. M. *J. Organomet. Chem.* **1991**, *417*, 205-209.

[121] Sanchez, M.; Bermejo, F. *Tetrahedron Lett.* **1997**, *38*, 5057-5060.

[122] Poss, A. J.; Smyth, M. S. *Synth. Commun.* **1987**, *17*, 1735-1740.

[123] Yamamoto, Y.; Nishii, S. *J. Org. Chem.* **1988**, *53*, 3597-3603.

[124] Tanaka, M.; Sakai, K. *Tetrahedron Lett.* **1991**, *32*, 5581-5584.

[125] Paquette, L. A.; Wang, X. *J. Org. Chem.* **1994**, *59*, 2052-2057.

[126] Tamura, R.; Watable, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 4477-4472.

[127] Bonjoch, J.; Cuesta, J.; Diaz, S.; Gonzalez, A. *Tetrahedron Lett.* **2000**, *41*, 5669-5672.

[128] Boontanonda, P.; Gragg, R. *J. Chem. Soc. Chem. Commun.* **1977**, 583-584.

[129] Derdar, F.; Martin, J.; Martin, C.; Bregeault, J. *J. Organomet. Chem.* **1998**, *338*, C21-C26.

[130] Feringa, B. L. *J. Chem. Soc. Chem. Commun.* **1986**, 909-910.

[131] Wenzel, T. T. *J. Chem. Soc. Chem. Commun.* **1993**, 862-864.

[132] Schroder, F.; Fettkother, R.; Noldt, U.; Dettner, K.; Konig, W. A.; Francke, W. *Liebigs Ann. Chem.* **1994**, 1211-1218.

[133] Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 10733-10742; Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron Lett.* **1994**, *35*, 6481-6484; Wilmouth, S.; Toupet, L.; Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron* **1998**, *54*, 13805-13812.

[134] Bull, J. R.; Mountford, P. G. *J. Chem. Soc. Perkin Trans. I* **1999**, 1581-1587.

[135] Hunt, D. F.; Rodeheaver, G. T. *Tetrahedron Lett.* **1972**, 3595-3598.

[136] Lai, J.; Shi, X.; Dai, L. *J. Org. Chem.* **1992**, *57*, 3485-3487.

[137] Hosokawa, T.; Nakajima, F.; Iwasa, S.; Murahashi, S. *Chem. Lett.* **1990**, 1387-1390; Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737-740.

[138] Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett.* **1997**, *38*, 9051-9054.

[139] Meulemans, T. M.; Kiers, N. H.; Feringa, B. L.; Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1994**, *35*, 455-458.

[140] Nokami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T. *Tetrahedron Lett.* **1988**, *29*, 5181-5184.

[141] Lloyd, W. G.; Luberoff, B. J. *J. Org. Chem.* **1969**, *34*, 3949-3952.

[142] Hosokawa, T.; Ohta, T.; Murahashi, S.-I. *J. Chem. Soc. Chem. Commun.* **1983**, 848-849.

[143] Kishi, A.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 523-525.

[144] Gaunt, M. J.; Yu, J.; Spencer, J. B. *Chem. Commun.* **2001**, 1844-1845.

[145] Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474-3480.

[146] Tsuji, J.; Nagashima, H.; Hori, K. *Tetrahedron Lett.* **1982**, *23*, 2679-2682.

[147] Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257-260; Nagashima, H.; Sakai, K.; Tsuji, J. *Chem. Lett.* **1982**, 859-860.

[148] Auclair, S. X.; Morris, M.; Sturgess, M. A. *Tetrahedron Lett.* **1992**, *33*, 7739-7742.

[149] Grattan, T. J.; Whitehurst, J. S. *J. Chem. Soc. Chem. Commun.* **1988**, 43-44.

[150] Shiori, T.; McFarlane, N.; Hamada, Y. *Heterocycles* **1998**, *47*, 73-76.

[151] Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587-9595.

[152] Toshima, H.; Oikawa, H.; Toyomasu, T.; Sassa, T. *Tetrahedron* **2000**, *56*, 8443-8450.

[153] Jiang, Y.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1997**, *53*, 5103-5122.

[154] Somfai, P.; Ahman, J. *Tetrahedron Lett.* **1995**, *33*, 3791-3794.

[155] Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381-6382.

[156] Schneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850-2858.

[157] Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502-7512.

[158] Ojima, I.; Wang, H.; Wang, T.; Ng, E. W. *Tetrahedron Lett.* **1998**, *39*, 923-926.

[159] Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666-6672.

[160] Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584-9591.

[161] Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S. *Chem. Lett.* **1985**, 1529-1530; Kongkathip, B.; Sookkho, R.; Kongkathip, N. *Chem. Lett.* **1985**, 1849-1850.

[162] Ambrosi, P.; Arnone, A.; Bravo, P.; Bruche, L.; Cristofaro, A.; Francardi, V.; Frigerio, M.; Gatti, E.; Germinara, G. S.; Panzeri, W.; Pennacchio, F.; Pesenti, C.; Potundo, G.; Roversi, P. F.; Salvadori, C.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 8336-8343.

[163] Kim, M.-J.; Choi, G.-B.; Kim, J.-Y.; Kim, H.-J. *Tetrahedron Lett.* **1995**, *36*, 6253-6256.

[164] Fallon, G.; Jones, E. D.; Perlmutter, P.; Selajarern, W. *Tetrahedron Lett.* **1999**, *40*, 7435-7438.

[165] Nagumo, S.; Suemune, H.; Sakai, K. *J. Chem. Soc. Chem. Commun.* **1990**, 1778-1779.

[166] Ikeda, M.; Matsubayashi, K.; Imoto, T.; Kitao, K.; Ishibashi, H.; Sato, T. *Heterocycles* **1994**, *38*, 1237-1240.

[167] Srikrishna, A.; Reddy, T. J. *Indian J. Chem.* **1995**, *34B*, 844-846.

[168] Mukaiyama, T.; Shiina, I.; Kimura, K.; Akiyama, Y.; Iwadare, H. *Chem. Lett.* **1995**, 229-230.

[169] Singh, V.; Prathap, S. *Tetrahedron* **1996**, *52*, 14287-14296.

[170] Srikrishna, A.; Reddy, T. J.; Nagaraju, S. *Tetrahedron Lett.* **1996**, *37*, 1679-1682.

[171] Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 11517-11524.

[172] Kigoshi, H.; Sawada, A.; Nakayama, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 1983-1986.

[173] Romero, M. A.; Franco, R. P.; Cruz-Almanza, R.; Pasilla, F. *Tetrahedron Lett.* **1994**, *35*, 3255-3258.

[174] Money, T.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 6307-6324.

[175] Tsuji, J.; Shimizu, I.; Suzuki, H.; Shimizu, I. *J. Am. Chem. Soc.* **1979**, *101*, 5070-5072.

[176] Shimizu, I.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 487-490.

[177] Tsuji, J.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 483-486.

[178] Johnson, W. S.; Chen, Y.; Kellogg, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 6653-6656; Ouvrard, P.; Tubul, A.; Santelli, M. *Bull. Soc. Chim. Fr.* **1993**, *130*, 772-778.

[179] Balog, A.; Yu, M. S.; Curran, D. P.; Yu, G.; Carcanague, D. R.; Shue, Y.-K. *Synth. Commun.* **1996**, *26*, 935-944.

[180] White, J. D.; Ohba, Y.; Porter, W. J.; Wang, S. *Tetrahedron Lett.* **1997**, *38*, 3167-3170; White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T.; Wang, S. *J. Org. Chem.* **2001**, *66*, 5217-5231.

[181] Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K.-S. *Tetrahedron* **1995**, *51*, 9437-9466; Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405-3408.

[182] Krishnudu, K.; Krisha, P. R.; Mereyala, H. B. *Tetrahedron Lett.* **1996**, *37*, 6007-6010.

[183] Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500-5507.

[184] Yamashita, A.; Toy, A.; Watt, W.; Muchmore, C. R. *Tetrahedron Lett.* **1988**, *29*, 3403-3406.

[185] Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931-5943; Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830-845.

[186] Srikrishna, A.; Kumar, P. P. *J. Indian Chem. Soc.* **1999**, *76*, 521-526.

[187] Guibe, F. *Tetrahedron* **1997**, *53*, 13509-13556.

[188] Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929-6930.

[189] Mereyala, H. B.; Lingannagaru, S. R. *Tetrahedron* **1997**, *53*, 17501-17512.

[190] Weigeilt, D.; Kraehmer, R.; Welzel, P. *Tetrahedron* **1996**, *37*, 367-370.

[191] Hori, M.; Gravert, D. J.; Wentworth Jr., P.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2363-2368.

[192] Ajjou, A. N.; Alper, H. *Macromolecules* **1996**, *29*, 5072-5074.

[193] Mimoun, H.; Machirant, M. M. P.; Roch, I. S. *J. Am. Chem. Soc.* **1978**, *100*, 5437-5444.

[194] Drago, R. S.; Zuzich, A.; Nyberg, E. D. *J. Am. Chem. Soc.* **1985**, *107*, 2898-2903.

[195] Faraj, M.; Martin, J. C. M.; Bregeault, J.-M. *J. Mol. Catal.* **1985**, *31*, 57-71.

[196] Nyberg, E. D.; Pribitch, D. C.; Drago, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 3538-3544.

[197] Januszkiewicz, K.; Alper, H. *Tetrahedron Lett.* **1983**, *24*, 5163-5164.

[198] McMillan, J. W.; Fischer, H. E.; Schwartz, J. *J. Am. Chem. Soc.* **1991**, *113*, 4014-4016.

[199] Friend, C. M.; Xu, X. *J. Am. Chem. Soc.* **1990**, *112*, 4571-4573; Friend, C. M.; Xu, X. *J. Am. Chem. Soc.* **1991**, *113*, 8572-8573; Takahashi, K.; Yamagushi, M.; Shido, T.; Ohtani, H.; Isobe, K.; Ichikawa, M. *J. Chem. Soc. Chem. Commun.* **1995**, 1301-1303.

[200] Igersheim, F.; Mimoun, H. *J. Chem. Soc. Chem. Commun.* **1978**, 559-560.

[201] Igersheim, F.; Mimoun, H. *Nouv. J. Chim.* **1980**, *4*, 161-166.

[202] Bortolini, O.; D., F. F.; Modena, G.; Seraglia, R. *J. Mol. Catal.* **1984**, *22*, 313-317.

[203] Taquikhan, M. M.; Rao, A. P. *J. Mol. Catal.* **1988**, *44*, 95-105.

[204] Read, G. *J. Mol. Catal.* **1988**, *44*, 15-33.

[205] Mimoun, H. *Pure Appl. Chem.* **1981**, *53*, 2389-2399.

[206] Bressan, M.; Morandini, F.; Morvillo, A. *J. Organomet. Chem.* **1985**, *280*, 139-146.

[207] Krom, M.; Coumans, R. G. E.; Smits, J. M. M.; Gal, A. W. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2106-2108; Bruin, B.; Verhagen, J. A. W.; Schouten, C. H. J.; Gal, A. W.; Feichtinger, D.; Plattner, D. A. *Chem. Eur. J.* **2001**, *7*, 416-422.

[208] Atlay, M. T.; Preece, M.; Strukul, G.; James, B. R. *J. Chem. Soc. Chem. Commun.* **1982**, 406-407.

[209] Woerpel, K. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 7888-7889. ; Ritter, J. C. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 2580-2581.

[210] Hamilton, D. E.; Drago, R. S.; Zombeck, A. *J. Am. Chem. Soc.* **1987**, *109*, 374-379.

[211] Matsumoto, K.; Nagai, Y.; Matsunami, J.; Mizuno, K.; Abe, T.; Somazawa, R.; Kinoshita, J.; Shimura, H. *J. Am. Chem. Soc.* **1998**, *120*, 2900-2907.