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Aldehydes from Pd-catalysed oxidation of terminal olefins

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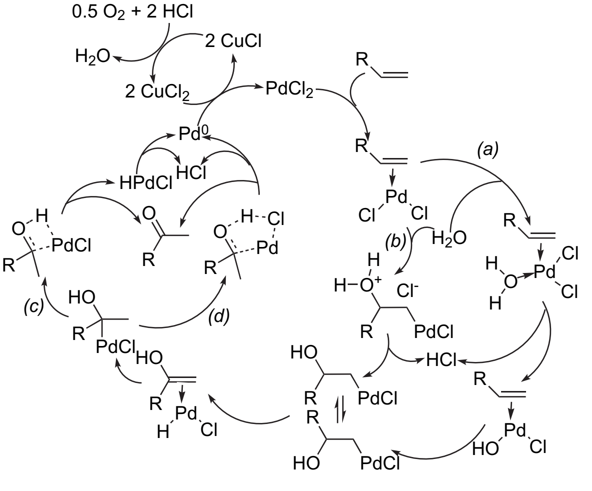
Contents

1. Introduction

The Pd^{II}-catalysed oxidation of alkenes to carbonyl compounds, usually referred to as the Wacker reaction,[1,2] is one of the most well-known reactions mediated by palladium, and has extensive synthetic applications.[3–6] This process involves coordination of the alkene to Pd^{II} and, subsequently, reaction of the η^2-Pd–alkene complex with water to afford, in the majority of cases, methyl ketones from terminal alkenes.[3–5,7] Scheme 1 depicts the simplified mechanism with $PdCl_2$ as the catalyst, and when catalytic amounts of copper chloride are used with oxygen to regenerate the active Pd^{II} species. In this scheme, the hydroxypalladation follows Markovnikov's rule; its stereochemistry, *syn* (path a) or *anti* (path b), depends on the experimental conditions,[3,8–11]



Scheme 1.

Keywords: Palladium; Alkenes; Aldehydes; Wacker reaction; Oxidation; Anti-Markovnikov addition.

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and remains a matter of debate.[12] Recently, other steps have also been the subject of investigations,[13,14] especially the formation of the ketone from ClPdCR(OH)Me (Scheme 1) with the proposal of a halide-mediated reductive elimination (path d), rather than the usually accepted β-hydride elimination (path c).[14]

The Wacker reaction has been so widely used in organic synthesis that terminal alkenes may be viewed as masked ketones. Nevertheless, aldehydes are sometimes produced but, except from particular substrates, usually in low yields.[8,15–17] Seeing the importance of aldehydes in synthesis, it seems of interest to highlight, with an overview, the investigations that have been carried out to obtain anti-Markovnikov regioselectivity in the Pd-catalysed oxidations of terminal alkenes. This is the aim of the present review. Most of the reports describe the oxidation via a Wacker-type procedure, but a few studies disclose methods that do not involve the hydroxypalladation as the key step, hence the organisation of the review with, mainly, also a chronological account of the reports.

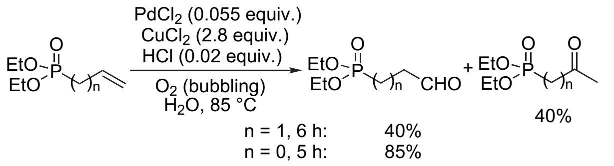
2. Wacker-type reactions

This section will not be limited to catalytic methods using water as the nucleophile and the association of copper salt/oxygen to regenerate the Pd^{II} active species, but will include all Pd procedures for which a hydroxy-, alkoxy- or acetoxy-palladation is suspected as an intermediate step leading to the aldehyde.

2.1. Hydroxypalladations

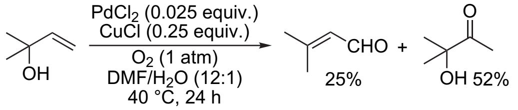
A few papers report the formation of the aldehyde with fair-to-high selectivity from the hydroxypalladation of simple terminal alkenes, but using stoichiometric quantities of a palladium salt[18] or with very low conversion of the substrate.[19] Catalytic procedures leading to aldehydes with useful yields have been disclosed only from substrates having a second chelating fragment, i.e., a heteroatom or unsaturation.

2.1.1. 1-Alkenes with P atom in α- or β-position. To our knowledge, the first efficient synthesis of aldehydes from the Pd-catalysed oxidation of terminal alkenes is due to Sturtz and Pondaven-Raphalen, who used vinylic and allylic phosphonates as the substrates (Eq. 1).[20] The authors ascribed the remarkable regioselectivity obtained from the vinylic substrate to the electron-withdrawing properties of the diethylphosphonate group. We suspect that the formation of aldehydes is also favoured by coordination of the phosphonate moieties to the palladium atom.



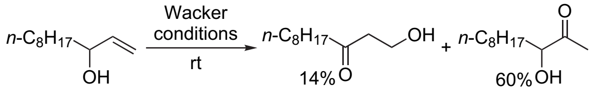
(1)

2.1.2. 1-Alkenes with O atom in β-position. In 1984, Tsuji disclosed briefly in a review that the oxidation under Wacker conditions of a tertiary allylic alcohol, namely 1-vinylcyclohexanol, led to low amounts of 1-acetylcyclohexanol and 2-cyclohexylideneacetaldehyde.[4] A similar observation has subsequently been reported by Brégeault et al. from 2-methylbut-3-en-2-ol (Eq. 2),[21] and they explained the formation of the aldehyde by isomerisation of the substrate[22] to the corresponding primary allylic alcohol followed by oxidation of the hydroxy group.[23]

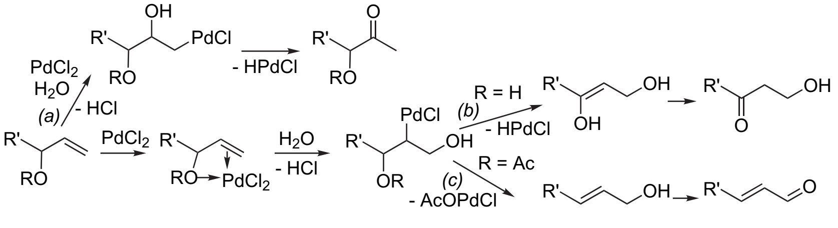


(2)

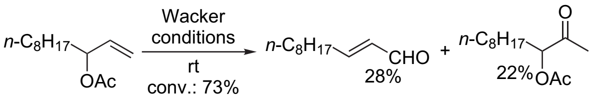
Tsuji reported, also without comment, that, at room temperature under Wacker conditions, 1-undecen-3-ol led to a mixture of 1-hydroxyundecan-3-one and 3-hydroxyundecan-2-one (Eq. 3), while 2-undecenal and 3-acetoxyundecan-2-one were isolated from 3-acetoxy-1-undecene (Eq. 4).[4] These methyl ketones are formed via the usual Wacker-type mechanism (Scheme 2, path a and Scheme 1). We suggest that the β-hydroxyketone (Eq. 3) ensues from the addition of water to the complex formed by coordination of the hydroxy group to palladium followed by the intramolecular abstraction by palladium of the hydrogen in C-3 to intermediately afford the hydroxyenol, as depicted in Scheme 2, path b. Such a reaction pathway has been proposed for the formation of β-hydroxypropanal from allyl alcohol and a stoichiometric amount of Li_2PdCl_4 in aqueous solution.[24] As for the α,β-unsaturated aldehyde (Eq. 4), the hydroxypalladation of the allylic acetate would be followed by the β-OAc elimination[25] and oxidation of the resulting allylic alcohol[23] (Scheme 2, path c).[26] Another possibility would be the formation of an η^3-allylpalladium intermediate followed by nucleophilic addition of water to afford the allylic alcohol.



(3)

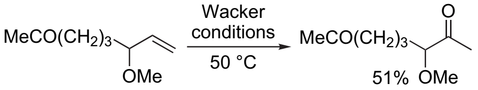


Scheme 2.

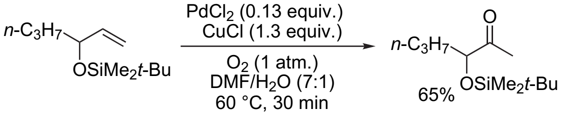


(4)

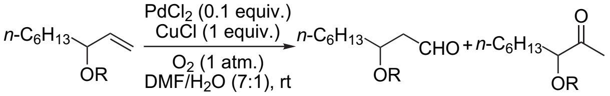
The methyl ketone has been the sole isolated product from a terminal olefin with an α-methoxy (Eq. 5)[4,27] or α-*tert*-butyldimethylsilyloxy substituent (Eq. 6).[28] In contrast, α-benzyloxy and α-methoxymethyloxy olefins led to the corresponding β-substituted aldehydes and α-substituted ketones in ratios of ca. 1:1 (Eq. 7).[29]



(5)



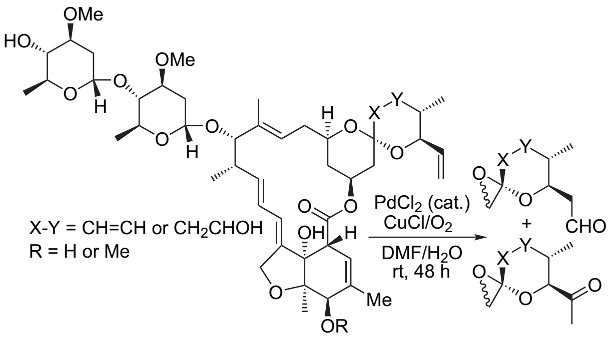
(6)



R = Bn: 75%, aldehyde/ketone = ca. 50:50
R = MOM: 65%, aldehyde/ketone = ca. 50:50

(7)

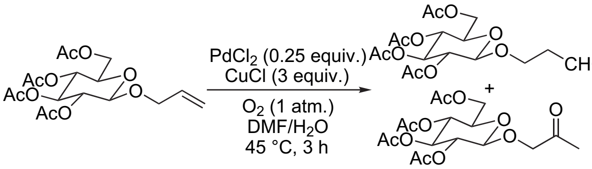
Banks et al. used the Wacker reaction of highly functionalised terminal olefins to synthesise a mixture of aldehydic and ketonic compounds providing access to a range of avermectins (Eq. 8).[30] The influence of the proximity of the oxygen heteroatom in the allylic position on the formation of aldehydes is determinant, since the procedure has only led to the methyl ketones when the vinyl substituent was exchanged for the CHMeCH$_2$CH=CH$_2$ group.



60%, aldehyde/ketone = 38:62

(8)

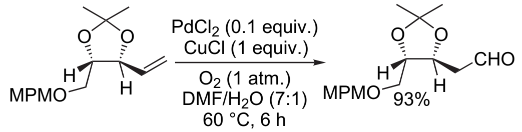
Welzel et al. have disclosed the solvent dependence of the aldehyde/methyl ketone ratio in the course of the Wacker oxidation of allyl glycosides in DMF/H$_2$O, an increase in the relative amount of water promoting the formation of the aldehyde (Eq. 9).[31] We suggest that the increase of the water concentration promotes its coordination to the palladium atom and, consequently, the *syn* delivery of the hydroxy group to the activated C=C bond.



DMF/H$_2$O = 6:1, near 100% yield, aldehyde/ketone = 30:70
DMF/H$_2$O = 1:1, aldehyde/ketone = 42:58

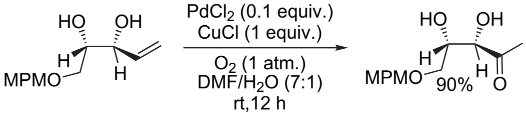
(9)

Kang et al. obtained selectively the aldehyde from the allylic acetonide depicted in Eq. 10. The authors presumed that the anti-Markovnikov attack of water was induced by the simultaneous chelation of palladium with the two adjacent oxygen atoms.[29] Nevertheless, the process led to the methyl ketone when this diol functionality was not protected (Eq. 11).[29]



(10)

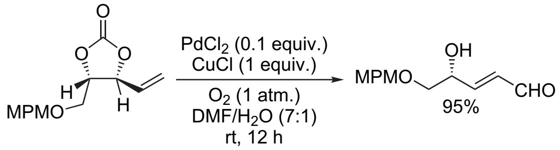
MPM = *p*-methoxyphenylmethyl



(11)

MPM = *p*-methoxyphenylmethyl

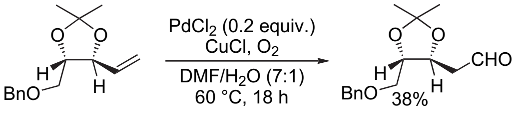
When a cyclic carbonate was used instead of the acetonide, the oxidation was accompanied by cleavage of this protective group to afford a γ-hydroxy-α,β-unsaturated aldehyde (Eq. 12).[29] This reaction is reminiscent of that of the allylic acetate depicted in Eq. 4, and could occur through a similar pathway, i.e., an η^3-allylpalladium intermediate or a mechanism similar to that depicted in Scheme 2, path c.



(12)

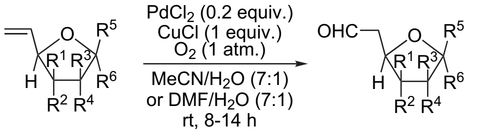
MPM = *p*-methoxyphenylmethyl

The oxidation of the allylic acetonide depicted in Eq. 10 seems to be difficult to reproduce since Jung and Nichols have, at best, obtained only traces of the aldehyde under the same experimental conditions. In using the benzyl group instead of the MPM protecting group, they isolated the corresponding aldehyde in 38% yield (Eq. 13).[32] This discrepancy between the results could be due to the instability of ketals in aqueous Pd^{II} solutions.[33]



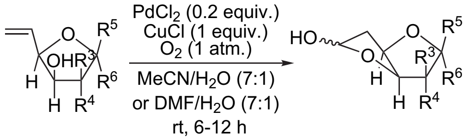
(13)

In 1996, Mereyala et al. reported the oxidation of a variety of 2-vinyl furanoside derivatives (Eqs. 14–16) that follow reaction pathways depending dramatically on the substitution in C-3.[34] With a protected 3-OH substituent, the aldehyde was invariably produced in high yield, irrespective of the cis or trans relationship between the vinyl and protected hydroxy groups (Eq. 14). With a 3-OH substituent cis to the vinyl moiety, the aldehyde was trapped by the alcohol to afford the lactol (Eq. 15), while a 3-OH substituent trans to the vinyl moiety led to a 1:1 mixture of aldehyde and methyl ketone (Eq. 16). A number of aldehydes and lactols obtained from the Pd-catalysed oxidation of 2-vinyl furanoside derivatives have been subsequently used as intermediates for the synthesis of natural products.[35,36]



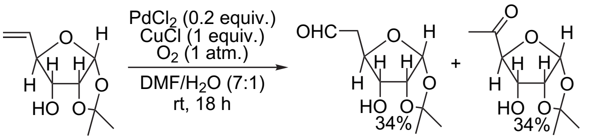
(14)

R^1-R^3 = $OCMe_2O$, R^2 = R^4 = R^5 = H, R^6 = OBn: 87%
R^1 = OBz, R^2 = R^3 = H, R^4 = $OSiMe_2t$-Bu, CR^5R^6 = CH(OMe): 82%
R^1 = OAc, R^2 = R^3 = H, R^4 = OAc, CR^5R^6 = CH(OBn): 86%
R^1 = OAc, R^2 = R^3 = R^5 = H, R^4-R^6 = $OCMe_2O$: 85%
R^1 = R^3 = R^6 = H, R^2-R^4 = $OCMe_2O$, R^5 = OBn: 76%
R^1 = R^3 = R^6 = H, R^2 = R^4 = OAc, R^5 = OBn: 89%



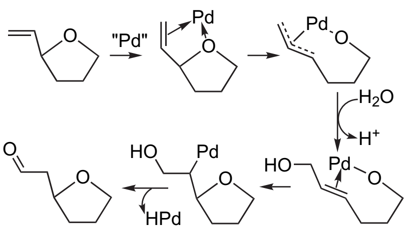
(15)

R^3 = OH, R^4 = R^5 = H, R^6 = OBn: 81%
R^3 = H, R^4 = $OSiMe_2t$-Bu, CR^5R^6 = CH(OMe): 81%
R^3 = H, R^4 = $O(CH_2)_2CBr{=}CH_2$, CR^5R^6 = CH(OMe): 63%
R^3 = H, R^4 = OH, CR^5R^6 = CH(OBn): 77%
R^3 = R^5 = H, R^4-R^6 = $OCMe_2O$: 83%



(16)

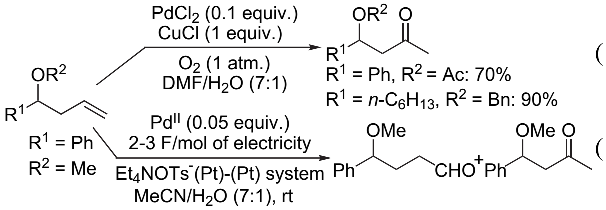
No scheme was included in Mereyala's report to explain the formation of aldehydes, but the authors wrote "It is perhaps due to the formation of the π-allylpalladium complex of the vinyl furanoside, which, being hindered, facilitates the anti-Markovnikov hydration to give aldehydes as exclusive products".[34] This sentence suggests the reaction pathway depicted in Scheme 3, that, in fact, is promoted by a Pd^0 catalyst. Whatever the correct mechanism, the C=C bond is liganded to palladium, and it seems that the oxygen of the tetrahydrofuran moiety is coordinated to the palladium atom. The coordination of this oxygen would play a determinant role in the selectivity. A 3-hydroxy cis to the vinyl (Eq. 15) would have no effect on this coordination or should improve the stability of intermediates. In contrast, a *trans*-3-hydroxy competes with the oxygen of the tetrahydrofuran for the coordination to palladium to afford a different palladium intermediate, hence the formation of the mixture of oxidised compounds (Eq. 16). The absence of an effect of a protected *trans*-3-OH (Eq. 14) is, nevertheless, surprising.



Scheme 3.

2.1.3. 1-Alkenes with O atom in γ-position.

Tsuji et al. expected to obtain the aldehyde from the Wacker oxidation of 1-acetoxy-1-phenyl-3-butene, but isolated the methyl ketone only (Eq. 17).[27] The same regioselectivity has been observed from 4-benzyloxy-1-decene (Eq. 17),[29] but slight amounts of the aldehyde have been obtained from 1-methoxy-1-phenyl-3-butene using an electrochemical Wacker-type reaction (Eq. 18).[37]

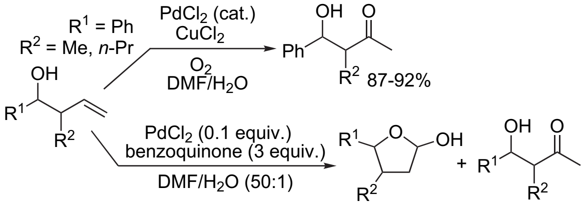


(17)

(18)

with $Pd(OAc)_2$ in a divided cell:	10%	82%
with $PdCl_2$ in an undivided cell:	0%	89%

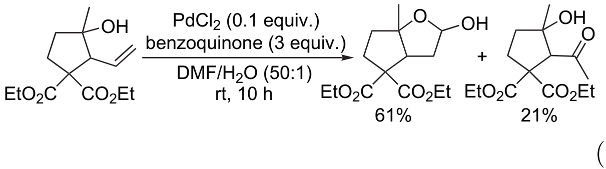
With an unprotected β-hydroxy group, the regioselectivity of the oxidation in DMF/H_2O could depend on the co-oxidants. With $CuCl_2/O_2$, Yamamoto et al. obtained selectively the methyl ketones from 2-methyl-1-phenylbut-3-en-1-ol and 2-propyl-1-phenylbut-3-en-1-ol (Eq. 19),[38] while, with either benzoquinone or $CuCl/O_2$, Nokami et al. have oxidised a range of secondary and tertiary 3-substituted-1-alken-4-ols, mainly at the terminal extremity, and obtained the corresponding lactols (Eqs. 20–22).[39]



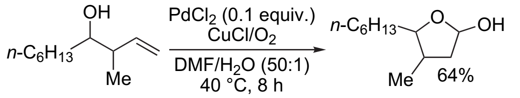
(19)

(20)

R^1 = n-C_6H_{13}, R^2 = Me, rt, 3 h:	43%	10%
R^1 = n-C_5H_{11}, R^2 = $(CH_2)_7CO_2Me$, 60 °C, 6 h:	74%	0%
R^1 = H, R^2 = $(CH_2)_7CO_2Me$, rt, 6 h:	58%	0%
R^1 = n-C_6H_{13}, R^2 = CO_2Me, 40 °C, 2 h:	62%	0%
R^1 = n-C_6H_{13}, R^2 = SO_2p-tol, 40 °C, 12 h:	82%	0%
R^1 = CH_2OCOPh, R^2 = OCH_2Ph, rt, 8 h:	81%	0%
R^1 = CH_2OCH_2Ph, R^2 = OCH_2Ph, rt, 18 h:	87%	0%
R^1 = n-C_6H_{13}, R^2 = H, rt, 8 h:	0%	68%



(21)



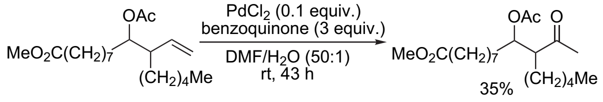
(22)

We envisage two hypotheses to explain the dependence of the selectivity on the oxidation state of the copper chloride (Eqs. 19 and 22), but we do not have any experimental evidence to prioritise any one of them:

(i) The selective formation of the methyl ketones under the conditions of Eq. 19 would be due to the higher concentrations of the chloride anion that preclude the coordination of the hydroxy substituent and water to the palladium atom. Henry et al. have disclosed the crucial influence of [Cl^-] on the stereochemistry of hydroxypalladation of C=C bonds, namely *syn* addition at low [Cl^-] and *anti* addition at high [Cl^-].[11] Unfortunately, the amounts of copper salts are not indicated in the reports of Yamamoto[38] and Nokami.[39]

(ii) The structure and the catalytic properties of the generated active complexes would depend on the oxidation state of the copper salt, these complexes being probably heterometallic. Indeed, Hosokawa et al. have disclosed the formation of polymeric complexes, $[(PdCl_2)_2CuCl_2(DMF)_4]_n$ and $(PdCl_2)_x(Cu)_y(DMF)_z$, from $PdCl_2(MeCN)_2$, CuCl, DMF and O_2 in 1,2-dichloroethane.[40]

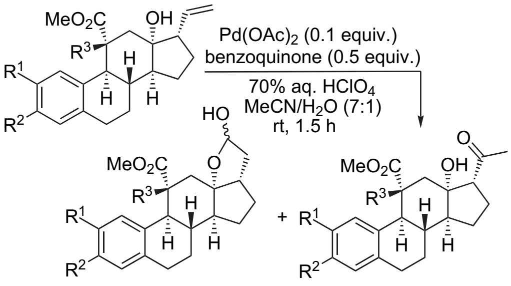
With the $PdCl_2$/benzoquinone methodology, 4-acetoxy-1-alkenes (Eq. 23) and 1-alken-4-ols without a substituent at C-3 (Eq. 20) gave only the methyl ketones.[39]



(23)

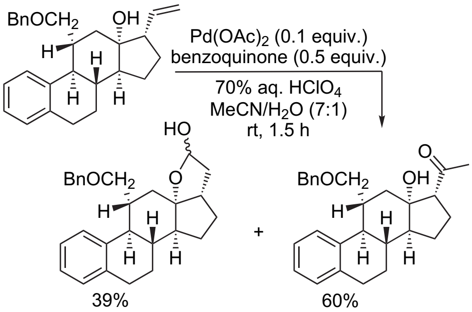
The anti-Markovnikov hydration of 3-substituted 1-alken-4-ols under Nokami's conditions is explained by coordination of both the C=C bond and the 4-hydroxy group to the palladium intermediates.[39] We presume that the requirement of the 3-substituent is due to its steric hindrance that would preclude or disfavour the addition of water at the 2-position of the distorted chelated palladium complex.

The team of Pellissier and Santelli has reported the Wacker-type oxidation of a range of steroids bearing a vinyl group at the 17α-position and various neighbouring oxygen functions. Unsatisfactory results being obtained with CuCl and O_2 as co-reagents, they used benzoquinone under the conditions of Miller and Wayner[41] that differ from those of Nokami mainly by the presence of perchloric acid. With a 13α-hydroxy group, the best lactol/methyl ketone ratio was 45:55 (Eqs. 24 and 25).[42,43] A substrate with a lactone connecting the 13α- and 11α-positions led, in most cases, to the aldehyde as the main product,[42,43] while, with the connection to the 13β- and 11β-positions, the yield of the aldehyde was very low (Eq. 26).[42–44] In other words, a lactonic bridge on the α-face promotes the anti-Markovnikov hydration of the 17α-vinyl moiety, while a lactonic bridge on the β-face has a low influence on the usual Wacker reaction pathway. As for the substrates studied by Nokami's team, the carbon bearing the vinyl group is tertiary, but, in contrast to Nokami's results (Eq. 23), the blocking of the hydroxyl group has a positive effect on the aldehyde selectivity. Although the two blocking systems are different, i.e., acetate (Eq. 23) and lactone (Eq. 26), respectively, this discrepancy in selectivities is surprising. Calculations have indicated that, in the key intermediate, the two lactonic oxygens are coordinated to palladium with the possibility of a cis-hydroxypalladation, but the calculations were also in agreement with the acetoxy group of 4-acetoxy-1-butene being linked to palladium by the two oxygen atoms.[45]



(24)

$R^1 = R^2 = R^3 = H$:	37%	46%
$R^1 = OMe$, $R^2 = R^3 = H$:	22%	58%
$R^1 = R^2 = OMe$, $R^3 = H$:	22%	54%
$R^1 = R^2 = H$, $R^3 = CO_2Me$:	37%	46%

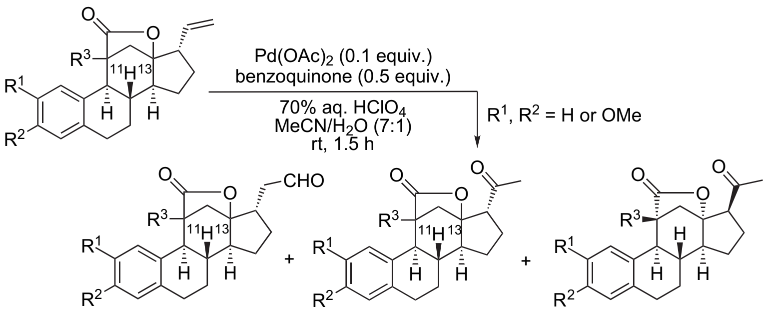


(25)

Santelli et al. have also carried out the oxidation of the 17α-vinyl group of steroids containing a heteroatom in cycle C. With a 13β-hydroxy and an SO or SO_2 in position 11, the methyl ketones were the main products (Eq. 27).[46,47] In contrast, with an oxygen atom in cycle C and a 13α-difluoro- or trifluoromethyl group, the aldehydes were obtained in high yields (Eqs. 28[48] and 29[49]). The selectivity towards the aldehyde was again rationalised by intramolecular coordination between the lactonic or ether function and the palladium atom.[48,49]

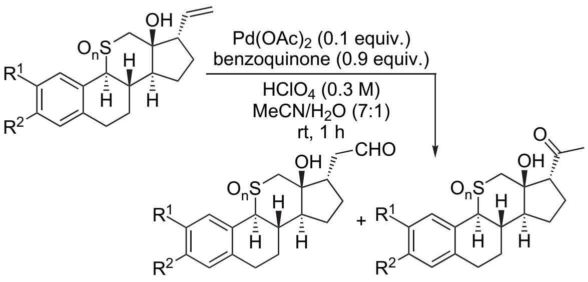
Contrary to the selectivity expected from the results depicted in Eqs. 28 and 29, the methyl ketone was the only isolated compound from the oxidation of 3-methyl-4-vinyltetrahydrofuran-2-ol, although its double bond is α-disubstituted (Eq. 30).[50] The experimental conditions were, however, quite different, and the moderate chemical yield of the ketone indicates the formation of by-products.

The methyl ketone was also the main product from the oxidation of methyl 2-((3*R*,6*S*)-6-allyl-3,6-dihydro-2*H*-pyran-3-yl)acetate, but low amounts of the corresponding aldehyde and of the isomerised substrate were identified (Eq. 31).[17]



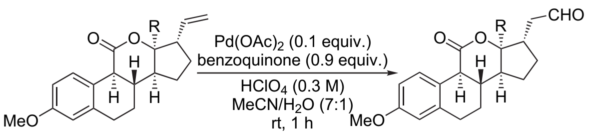
α-(C^{11}-CO), α-(C^{13}-O), R^3 = H and			
$R^1 = R^2$ = H:	35%	35%	10%
R^1 = OMe, R^2 = H:	28%	35%	8%
$R^1 = R^2$ = OMe:	30%	35%	10%
α-(C^{11}-CO), α-(C^{13}-O), $R^3 = CO_2Me$ and			
$R^1 = R^2$ = H:	37%	0%	0%
R^1 = OMe, R^2 = H:	45%	38%	0%
$R^1 = R^2$ = OMe:	28%	24%	0%
β-(C^{11}-CO), β-(C^{13}-O), R^3 = H and			
$R^1 = R^2$ = H:	7%	85%	0%
R^1 = OMe, R^2 = H:	14%	79%	0%
$R^1 = R^2$ = OMe:	9%	77%	0%

(26)



(27)

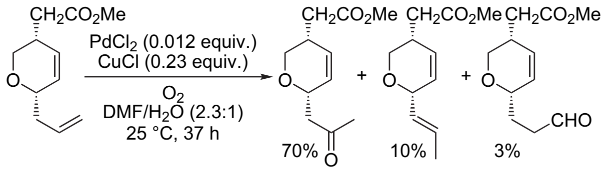
n = 1, R^1 = OMe, R^2 = H:	11%	85%
n = 1, R^1 = H, R^2 = OMe:	15%	81%
n = 1, R^1 = Br, R^2 = H:	0%	70%
n = 2, R^1 = H, R^2 = OMe:	10%	64%
n = 2, R^1 = OMe, R^2 = H:	17%	67%



R = CF_3 (80%), CHF_2 (85%)

(28)

The low aldehyde selectivity could be due to the absence of a substituent in the α-position of the C═C bond, or to isomerisation of the exocyclic C═C bond preceding the oxidation, or to saturation of the Pd coordination sphere by ligation of the intracyclic oxygen and the two double bonds of the substrate that precludes or renders more difficult the coordination of water to the palladium atom.

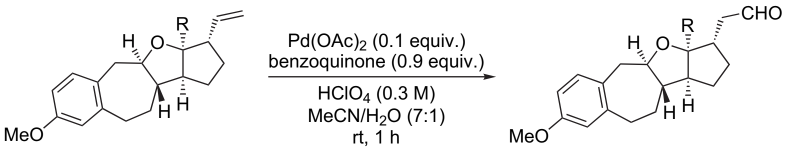


(31)

In fact, the literature contains various examples of the Pd-catalysed oxidation of terminal olefins containing an oxygen in the γ-position that, even in the presence of an α-substituent, led selectively to ketones.[51] Consequently, no rule can be established from the literature results.

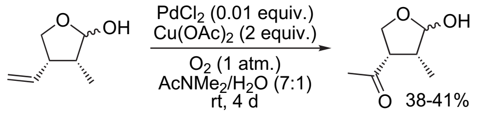
2.1.4. 1-Alkenes with O atom in δ-position.

Sunay and Fraser-Reid have oxidised 4-allyl-2-methyl-6,8-dioxa-bicyclo[3.2.1]octan-3-ol into a lactol, as shown in Eq. 32.[52] According to these authors, this transformation is an 'intramolecular oxypalladation'. In the absence of a mechanistic scheme in their report, we suspect that such a proposal corresponds to the reaction pathway depicted in Scheme 4,

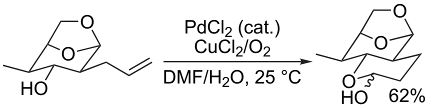


R = CF_3 (74%), CHF_2 (82%)

(29)

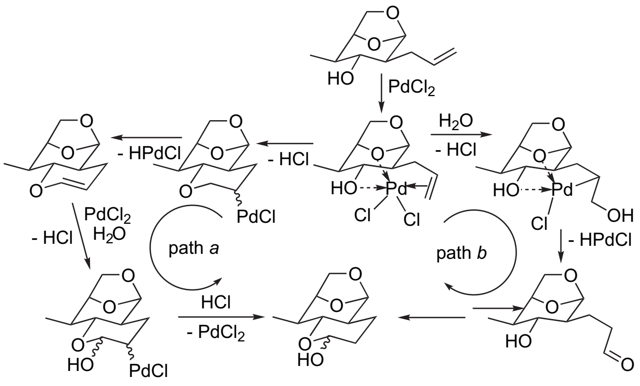


(30)



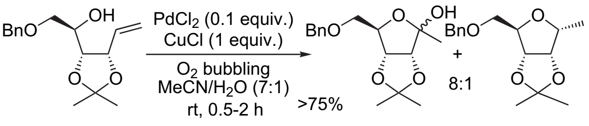
(32)

path a. Note that a similar reaction pathway could also explain the formation of lactols described in the previous sections, but this has not been retained by the corresponding authors, and is hardly compatible with some results.[53] We suggest that the process involves rather an anti-Markovnikov hydroxypalladation leading to the aldehyde and then to the hemiacetal, as shown in Scheme 4, path b.

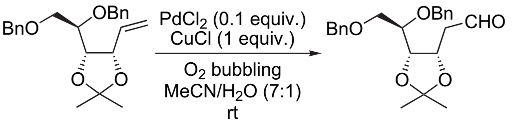


Scheme 4.

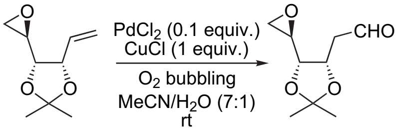
Sharma et al. have observed that a polyfunctionalised terminal olefin having a hydroxyl substituent in C-5, such as depicted in Eq. 33, led to Markovnikov addition with no trace of aldehyde. In contrast, the prior etherification of this hydroxyl group led exclusively to the aldehyde (Eqs. 34 and 35), but the reaction was very sluggish and a large amount of the starting material was recovered.[54] For the formation of the hemiketal depicted in Eq. 33, it seems that these authors envisaged a reactive pathway similar to the one shown in Scheme 4, path a, i.e., a mechanism involving the intramolecular nucleophilic addition of the hydroxyl group to the activated double bond rather than the formation of the methyl ketone as an intermediate step.



(33)

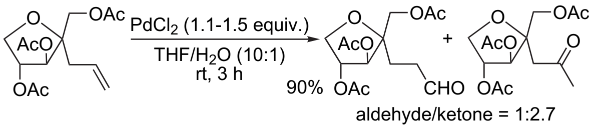


(34)



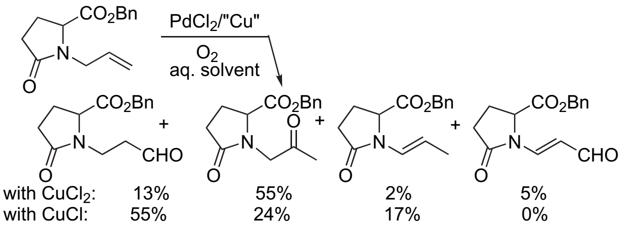
(35)

Maliakel and Schmid have obtained a lower selectivity of the hydroxypalladation using a triacetylated *C*-allylfuranose and a stoichiometric amount of palladium chloride (Eq. 36).[55]



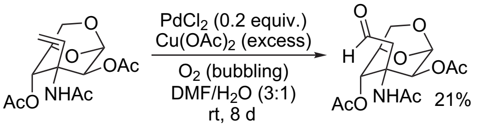
(36)

2.1.5. 1-Alkenes with N atom in β-position. In 1989, Mori et al. reported briefly the Wacker-type oxidation of benzyl 1-allyl-5-oxopyrrolidine-2-carboxylate (Eq. 37).[56] Interestingly, the selectivity towards the aldehyde was greatly increased using CuCl instead of $CuCl_2$ as the co-reagent. The hypotheses relating to the differences of regioselectivity induced by CuCl and $CuCl_2$, proposed in Section 2.1.3, can also be invoked here.



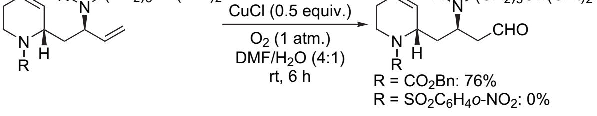
(37)

Having isolated only the aldehyde from the oxidation of the vinyl-acetamidopyranose derivative depicted in Eq. 38, Fraser-Reid et al. attributed this regioselectivity to the presence of the proximal oxygens and/or the acetamide function.[57] Note that this reaction was carried out with $Cu(OAc)_2$ as the copper salt.



(38)

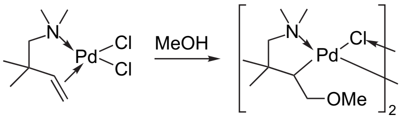
More recently, the $PdCl_2/CuCl/O_2$ procedure has been retained by Stragies and Blechert for the oxidation of allylic amines into the corresponding β-amino aldehydes.[58] The success of this reaction depended dramatically on the nitrogen substituents, as shown in Eq. 39: with a nosyl group, the cleavage of the allyl–N bond was the only observed process.



(39)

At this level, it seems of interest to point out that the addition of MeOH to dichloro(2,2,*N*,*N*-tetramethyl-3-buten-1-amine)-palladium (Eq. 40), in occurring exclusively at the terminal carbon, highlights the influence of the chelation on the regioselectivity.[59] Indeed, the treatment of simple terminal olefins with primary alcohols and catalytic amounts of

$PdCl_2$ and $CuCl_2$ under oxygen led generally to the ketones via the corresponding ketals.[60]

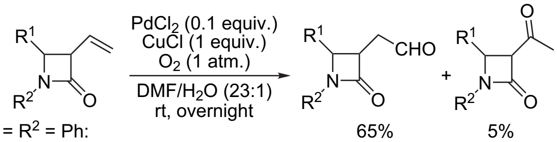


(40)

2.1.6. 1-Alkenes with C=O fragment.

Overman and Jacobsen suggested in 1982 that ‘oxypalladation of 5-hexen-2-one should occur some of the time to form a 6-hydroxy-5-pallada-2-hexanone intermediate’,[61] but, to our knowledge, such a reaction pathway has never been reported from this substrate.

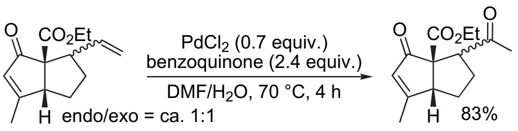
In 1986, Bose et al. disclosed the formation of aldehydes in fair yields from the oxidation of 3-vinyl-4-substituted-2-azetidinones under Wacker-type conditions (Eq. 41).[62] According to these authors, the regioselectivity is influenced by coordination of both the C=C bond and the carbonyl group of the β-lactam to the palladium atom.



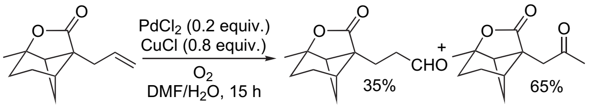
$R^1 = R^2$ = Ph:	65%	5%
R^1 = PhCH=C(Me)CH_2, R^2 = *p*-MeOC_6H_4:	60%	4%
$R^1 = R^2$ = *p*-MeOC_6H_4:	60%	5%
R^1 = Ph, R^2 = *p*-MeOC_6H_4:	60%	5%
R^1 = COPh, R^2 = *p*-MeOC_6H_4:	70%	0%

(41)

Although Moberg et al. obtained only the methyl ketone from the Pd-catalysed oxidation of a γ,δ-unsaturated ester (Eq. 42),[63] a tricyclic lactone α-substituted by an allyl group led, according to Rico and Bermejo, to a 35:65 mixture of the corresponding aldehyde and methyl ketone (Eq. 43).[64]



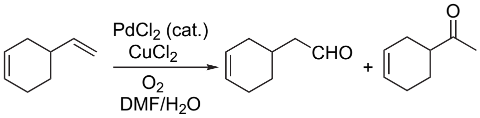
(42)



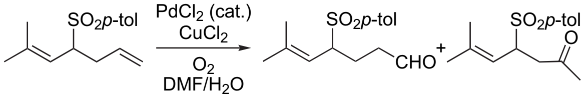
(43)

2.1.7. 1-Alkenes with C=C fragment.

The Pd-catalysed oxidation of 4-vinylcyclohex-1-ene (Eq. 44) and 4-(*p*-tolylsulfonyl)-6-methyl-hepta-1,5-diene (Eq. 45) to mixtures of the corresponding aldehydes and methyl ketones has been mentioned in a review by Tsuji, but without comment and, unfortunately, without any information on the products ratios.[4] For these reactions, we suspect that the formation of aldehydes originates from the coordination of both C=C bonds to the palladium atom. Indeed, it has been reported that the bis-η^2 complex formed from 4-vinylcyclohex-1-ene and Na_2PdCl_4 reacts with amines at the terminal carbon of the acyclic double bond,[65] while the palladium complex of terminal monoolefins reacts at the C-2 position.[66]

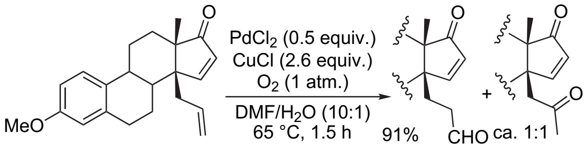


(44)



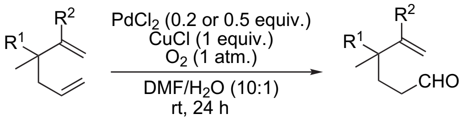
(45)

Subsequently, Bull and Mountford isolated a 1:1 mixture of Markovnikov and anti-Markovnikov oxidation products from the 14β-allyl Δ^{15}-17-ketone depicted in Eq. 46. Since the 15,16-dihydro derivative of this steroid underwent exclusive 2′-oxidation, the presence of the Δ^{15}-bond clearly affected the regioselectivity. The authors suspected that the C-2′ position in the coordination complex formed from the Δ^{15}-17-ketone is subject to some steric hindrance by the 13β-methyl group, and that attack at C-3′ of this complex is favoured by hydrogen-bonded association of H_2O with the proximal 17-oxo group.[67]



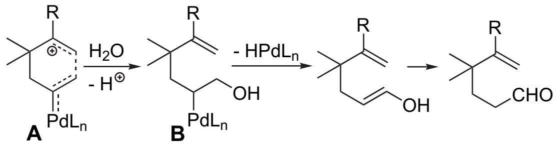
(46)

More recently, Ho et al. obtained aldehydes in good-to-high yields from substituted 1,5-dienes (Eq. 47).[68] To rationalise the regioselectivity, the authors proposed the capture of the unsymmetric intermediate **A** by water to give **B**, followed by β-H elimination to afford the enol and then the aldehyde (Scheme 5).



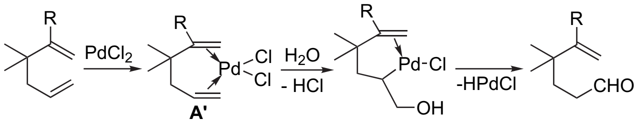
(47)

R^1 = Me, R^2 = *p*-tol: 73%; $R^1 = R^2$ = Me: 99%
R^1 = Me, R^2 = *n*-C_8H_{17}: 75%; R^1-R^2 = $(CH_2)_4$: 60%



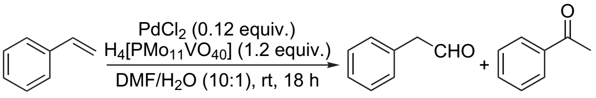
Scheme 5.

Intermediate **A** is reminiscent of that of the Pd^{II}-catalysed Cope rearrangement,[69] but, in our opinion, the regioselectivity of the hydroxy addition to **A** is surprising. Examples in the above sections have shown that chelation by heteroatoms of η^2-Pd-alkene complexes can promote the regioselective addition of water to the terminal carbon. The role of the chelation has been supported by calculations[45] and by the regioselective addition of methanol to a chelated complex (Eq. 40).[59] From the example depicted in Eq. 46, it is conceivable that the same regioselectivity might be induced by chelation with the second C=C bond. Consequently, we suggest a reaction arising from a (bis-η^2)-Pd-(1,5-diene) intermediate **A′** (Scheme 6), rather than from **A**. We are aware that the reaction of acetate anion with such complexes occurs at the internal position and rather through a trans attack relative to palladium,[70] but the reaction with amines can occur at the terminal carbon.[65] Moreover, methoxypalladation of 1,5-cyclooctadiene could be a *syn*-process,[71,72] and it has been suggested that the stereochemistry is dependent on the ligands attached to the metal.[73] The formation of aldehydes, rather than methyl ketones, from the 1,5-dienes of Eq. 47 should be particularly favoured if the attack of water on the double bond proceeds from palladium.[74] Recent studies from Spencer's team,[75] that will be discussed below, consolidate the mechanistic alternative depicted in Scheme 6. Nevertheless, complementary studies, especially on the effect of the diene substituents on the reactivity,[76] are required before making a choice between the above two mechanistic proposals.



Scheme 6.

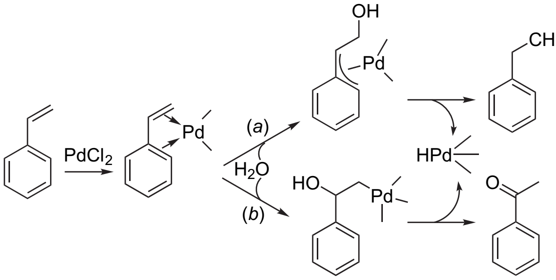
The oxidation of styrene under Wacker-type conditions leads to acetophenone, phenylacetaldehyde and its decomposition product, i.e., benzaldehyde. Generally, phenylacetaldehyde is not isolated, or is obtained only in low amounts.[77] With *p*- or *m*-substituted styrenes as substrates, Katsuyama et al. have reported that the regioselectivity depends on the electronic properties of the substitutent.[78] Recently, Spencer et al. have disclosed experimental conditions leading efficiently to phenylacetaldehyde from styrene (Eq. 48).[75]



75%, aldehyde/ketone = 86:14

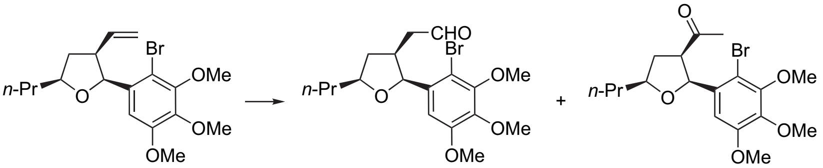
(48)

The regioselectivity of the reaction depicted in Eq. 48 is, at least, not mainly due to the use of a Keggin-type heteropolyacid to regenerate the Pd^{II} active species, since the use of the same heteropolyacid has subsequently led to more than 98% selectivity in butan-2-one from the Pd^{II}-catalysed oxidation of 1-butene.[79] Intensive mechanistic studies by Spencer et al. indicated the possible involvement of a η^4-palladium-styrene complex (Scheme 7).[75] These authors propose that internal attack of water, i.e., from prior coordination to palladium, leads to phenylacetaldehyde (path a), while external attack, i.e., from the solution, leads to acetophenone (path b).



Scheme 7.

Cassidy et al. have obtained a mixture of aldehyde and ketone from a *cis*-2-aryl-3-vinyltetrahydrofuran (Eq. 49).[80] For the aldehyde production, we suggest a reaction pathway similar to that of Scheme 6, with a palladium intermediate bearing both the vinyl and aryl groups as ligands.



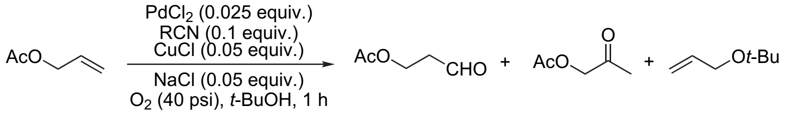
$PdCl_2$ (0.1 equiv.), O_2, DMF/H_2O: 73% yield, aldehyde/ketone = 50:50
$PdCl_2$ (0.1 equiv.), benzoquinone, $HClO_4$, $MeCN/H_2O$: 80% yield, aldehyde/ketone = 40:60

(49)

2.2. Alkoxypalladations

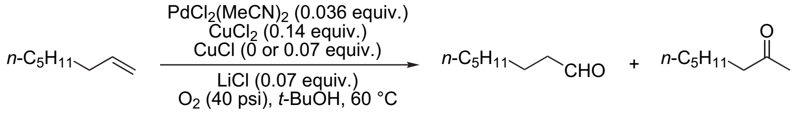
Alcohols instead of water have been used under Wacker conditions.[81] Of particular interest is the formation of acetals and/or vinyl ethers from the addition of the alkoxy moiety to the extremity of the double bond of terminal alkenes,[81,82] since their subsequent hydrolysis led to the corresponding aldehydes. Two reports disclose the direct formation of aldehydes in alcohols.

In 1993, Wenzel disclosed the formation of aldehydes from 1-octene and allyl acetate using *t*-BuOH as the solvent and a catalyst comprising $PdCl_2$, RCN and chloride salts. High conversions with up to 86% selectivity in the aldehyde were only obtained from allyl acetate (Eq. 50).[83] Nevertheless, with 1-octene as the substrate, an unelucidated role of chloride salts was observed (Eq. 51). The $PdCl_2(MeCN)_2/CuCl_2/CuCl/LiCl$ system (0.25:1:0.5:0:5 ratio) afforded mainly octan-2-one, while, in the absence of CuCl, the formation of the ketone was retarded and octanal was the main product at the beginning of the reaction, but the aldehyde/ketone ratio became inverted with reaction time. At first sight, this copper chloride effect is at variance with the hypotheses developed in Section 2.1.3 for reactions occurring via hydroxypalladations, but the oxidative conditions are quite different.



R = Me, 50 °C: 48% 8% 5%
R = p-$NO_2C_6H_4$, 60 °C: 55% 18% 0%

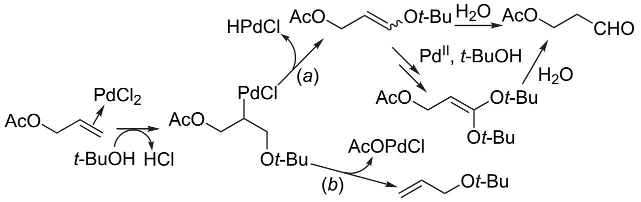
(50)



with CuCl, 0.5 h: conversion = 12%, yield = 8%, aldehyde/ketone = 30:70
with CuCl, 3 h: conversion = 49%, yield = 38%, aldehyde/ketone = 31:69
without CuCl, 0.5 h: conversion = 4%, yield = 1%, aldehyde/ketone = 57:43
without CuCl, 3 h: conversion = 56%, yield = 39%, aldehyde/ketone = 28:72

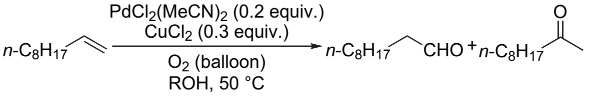
(51)

Wenzel's process should involve *tert*-butyl vinyl ether and, possibly, *tert*-butyl acetal as intermediates, and their attack by water (Scheme 8, path a). Water would be a trace contaminant in t-BuOH,[83] and is also generated from the $Pd^0 \rightarrow Pd^{II}$ reaction (see Scheme 1). In fact, water was mentioned as an additive in the patent issued from the same author.[84] According to this patent, 2-formylethyl acetate was thus obtained in 71.16% yield.



Scheme 8.

Recently, Hosokawa et al. reported that the selectivity towards aldehyde from 1-decene increased with the steric hindrance of the alcohol (Eq. 52).[85] This observation was in agreement with calculations, and a mechanism similar to that depicted in Scheme 8, path a was proposed. Unfortunately, the selectivity towards the aldehyde decreased with the conversion of the substrate (Eq. 52).

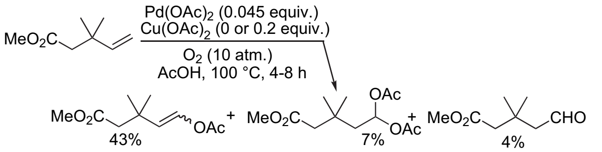


R = Me, 30 min: 26%, aldehyde/ketone = 3:97
R = Et, 30 min: 22%, aldehyde/ketone = 16:84
R = i-Pr, 30 min: 11%, aldehyde/ketone = 42:58
R = t-Bu, 30 min: 7%, aldehyde/ketone = 84:16
R = t-Bu, 60 min: 12%, aldehyde/ketone = 71/29

(52)

2.3. Acetoxypalladations

The Pd-catalysed reaction of terminal alkenes in acetic acid in the presence of oxygen and co-oxidants led, often, to complicated mixtures containing allylic and vinylic acetates.[3,72,86,87] The absence of migration of the C═C bond for substrates without allylic hydrogen led to more selective reactions. Fuchikami et al. have thus reported regioselective additions to the terminal carbon atom of *N*,*N*-diethyl-3,3-dimethylpent-4-enamide and 3,3-dimethyl-4-pentenoates.[88] The oxidation products are convertible into the corresponding aldehydes and this transformation partially occurred under the Pd experimental conditions (Eq. 53). The chelation of the palladium atom by the substrate was proposed to explain the regioselectivity of the acetate addition (Scheme 9). Interestingly, the $Pd(OAc)_2/O_2/AcOH$ system led to similar results in the absence of the copper salt (Eq. 53).[88,89]

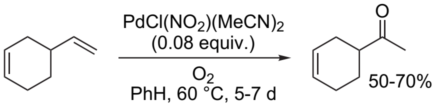


with $Cu(OAc)_2$: 43% 7% 4%
without $Cu(OAc)_2$: 46% 5% 3%

(53)

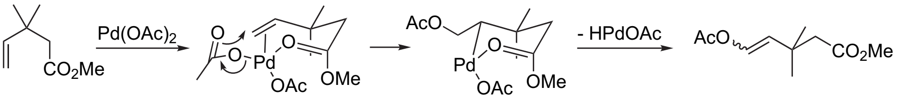
3. Palladium-nitro-nitrosyl redox couple

In contrast to the Wacker-type conditions (Eq. 44), only the ketone was observed by Heumann et al. from the $PdCl(NO_2)(MeCN)_2$-catalysed oxidation of 4-vinylcyclohex-1-ene with oxygen (Eq. 54).[90] This result could be due either to a different mechanism or to the higher steric hindrance of the palladium-nitro complex that would preclude the chelation of the palladium atom by the substrate.



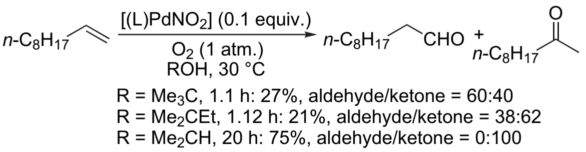
(54)

Feringa has used the above palladium complex with $CuCl_2$ and t-BuOH to prepare a catalyst denoted [(L)$PdNO_2$] that, in tertiary alcohols, mediates the catalytic aerobic oxidation of terminal alkenes to produce aldehydes with selectivities depending dramatically on the structure of both the

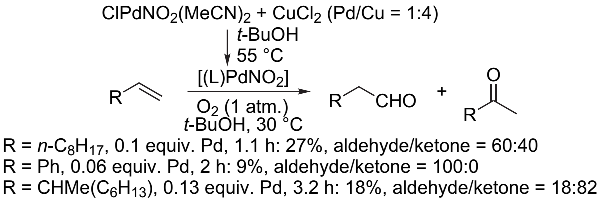


Scheme 9.

substrate (Scheme 10) and the tertiary alcohol (Eq. 55).[91] The exact constitution of the catalyst was uncertain, the symbol (L) indicating MeCN, $CuCl_2$ and *t*-BuOH. A high selectivity towards aldehydes can be obtained, even from alkenes without a chelating fragment (Eq. 55), but, in most cases, the process led to low yields. No aldehyde was formed with a secondary alcohol as the solvent (Eq. 55), or when either *t*-BuOH or $CuCl_2$ was omitted in the catalyst preparation.

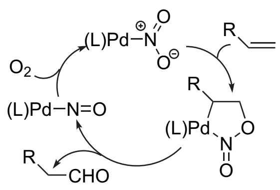


(55)



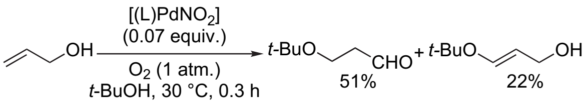
Scheme 10.

As proposed previously by the teams of Heumann and Andrews,[90,92] the reaction mechanism would involve the cycloaddition of the nitropalladium complex to the olefin followed by a β-H elimination (Scheme 11).[91] According to Feringa, the formal oxidation state of palladium does not change during the oxidation. Thereby, the role of the copper salt is different from that of the Wacker oxidation. A heterobimetallic catalyst comprising Cu^{II} and ROH, which determines the selectivity of the cycloaddition step, was suggested.[91,93] The tertiary alcohol has a crucial role as a component of the active catalyst on the reaction mechanism, since, according to Wenzel, no metal nitro catalyst was involved when a $PdCl(NO_2)(MeCN)_2/CuCl_2$ system was used in THF in the absence of ROH.[83]

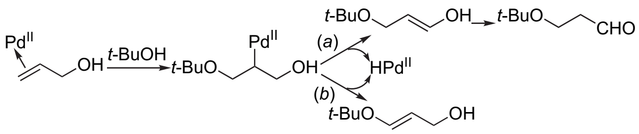


Scheme 11.

With allyl alcohol as the substrate, Feringa's procedure led to a mixture of 3-*tert*-butoxypropanal and 3-*tert*-butoxyprop-2-en-1-ol (Eq. 56).[91,94] We suspect that these two compounds were obtained from alkoxypalladation, as shown in Scheme 12.[89]

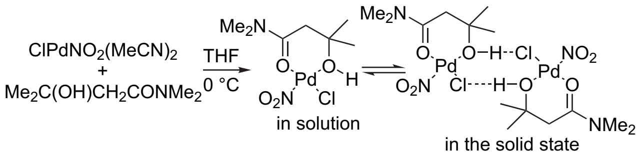


(56)



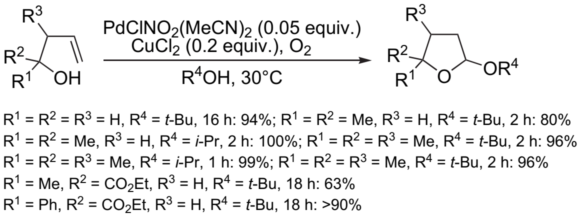
Scheme 12.

Subsequently, it has been disclosed that amides as ligands or co-solvents improved the rate of oxidation and the catalyst stability.[95] This observation led Feringa's team to synthesise a complex having an amide containing a tertiary hydroxy substituent as bidentate ligand (Scheme 13) that, associated to $CuCl_2$, led, in oxygenated *t*-BuOH, to a 30:70 mixture of octanal and octan-2-one from 1-octene.[96]



Scheme 13.

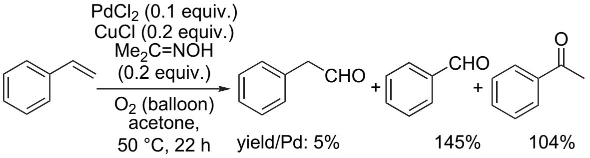
The $[(L)PdNO_2]/ROH/O_2$ system has also been used for the oxidation of homoallylic alcohols to α-alkoxytetrahydrofurans (Eq. 57).[97] The reactive pathways leading to these cyclic acetals are not obvious and were not commented by the authors. According to the mechanism previously ascribed to the oxidation of olefins with this procedure (Scheme 11), the formation of the aldehyde from the C=C bond should first occur. Its subsequent reaction with both the internal hydroxy group and the alcoholic solvent would afford the α-alkoxytetrahydrofuran. Another mechanistic possibility is the alkoxypalladation of the double bond of the substrate by the solvent to afford the corresponding vinylic ether, as previously depicted in Scheme 12, path b, followed by the intramolecular nucleophilic addition of the hydroxy group. Such a mechanism, not involving the aldehyde as an intermediate, was proposed by Inomata et al. for the synthesis of 2-methoxy-4-tosyltetrahydrofurans from 2-tosylbut-3-en-1-ols using $PdCl_2$, $CuCl_2$, a HCl quencher and nitrogen atmosphere in MeOH.[98] Whatever the correct mechanism, the results with Feringa's procedure contrast with those obtained using the method of Nokami et al. (Eqs. 20–22), since a substituent at the allylic position is not required for a highly selective reaction at the terminal position of the C=C bond.



$R^1 = R^2 = R^3 = H$, R^4 = *t*-Bu, 16 h: 94%; $R^1 = R^2 = Me$, $R^3 = H$, R^4 = *t*-Bu, 2 h: 80%
$R^1 = R^2 = Me$, $R^3 = H$, R^4 = *i*-Pr, 2 h: 100%; $R^1 = R^2 = R^3 = Me$, R^4 = *t*-Bu, 2 h: 96%
$R^1 = R^2 = R^3 = Me$, R^4 = *i*-Pr, 1 h: 99%; $R^1 = R^2 = R^3 = Me$, R^4 = *t*-Bu, 2 h: 96%
$R^1 = Me$, $R^2 = CO_2Et$, $R^3 = H$, R^4 = *t*-Bu, 18 h: 63%
$R^1 = Ph$, $R^2 = CO_2Et$, $R^3 = H$, R^4 = *t*-Bu, 18 h: >90%

(57)

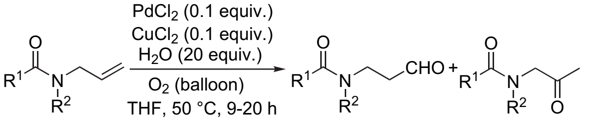
Hosokawa et al. have used molecular oxygen and a mixture of palladium chloride, copper chloride and acetoxime in anhydrous acetone to oxidise terminal olefins.[99] This procedure has a low efficiency, but led mainly to the oxidation at the terminal carbon of styrene to afford phenylacetaldehyde and benzaldehyde (Eq. 58). Experiments with 1-decene as the substrate in the presence of $H_2{}^{18}O$ and in the absence of either CuCl or acetoxime have led to the conclusion that the oxidation involves a $PdNO_2$ species, and the proposition of a mechanism involving a palladium-nitro-nitrosyl redox couple, as depicted in Scheme 11.



(58)

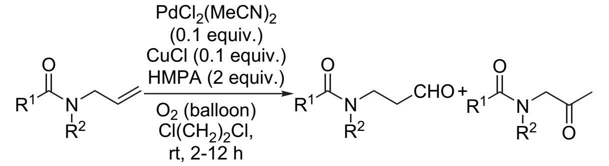
4. Peroxypalladium intermediates

Using *N*-allylamides as substrates, Hosokawa et al. have disclosed regioselectivity depending on the experimental conditions.[100] Under Wacker-type conditions, ketones were the main products (Eq. 59), while a complete reversal of the regioselectivity was observed in anhydrous 1,2-dichloroethane containing HMPA (Eq. 60). Note, however, that (i) $CuCl_2$ was used for reactions in the presence of water, while CuCl was used for reactions under anhydrous conditions, and (ii) we have, above, pointed out the possible role of the copper chloride on the selectivity (see Sections 2.1.3 and 2.1.5).



R^1, R^2 = Ph, Me; Me, Ph; Me, Me; $(CH_2)_3$; $(CH_2)_4$; $(CH_2)_5$:
50-86%, aldehyde/ketone = 4:96 to 17:83

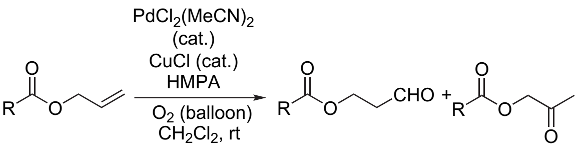
(59)



R^1, R^2 = Ph, Me; Me, Ph; Me, Me; $(CH_2)_3$; $(CH_2)_4$; $(CH_2)_5$:
50-68%, aldehyde/ketone = 85:15 to 90:10

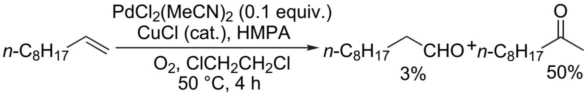
(60)

The water-dependent regioselectivity was also observed from allyl acetate and allyl carbonate. High amounts of aldehydes were formed in anhydrous dichloromethane (Eq. 61), while 95–100% regioselectivity towards the methyl ketones were observed under aqueous conditions.[100] The importance of the chelating group is highlighted by the oxidation of 1-decene under the anhydrous aerobic experimental conditions that led only to traces of the aldehyde (Eq. 62).[101]



R = Me: 76%, aldehyde/ketone: 65:35
R = OEt: 56%, aldehyde/ketone: 48:52

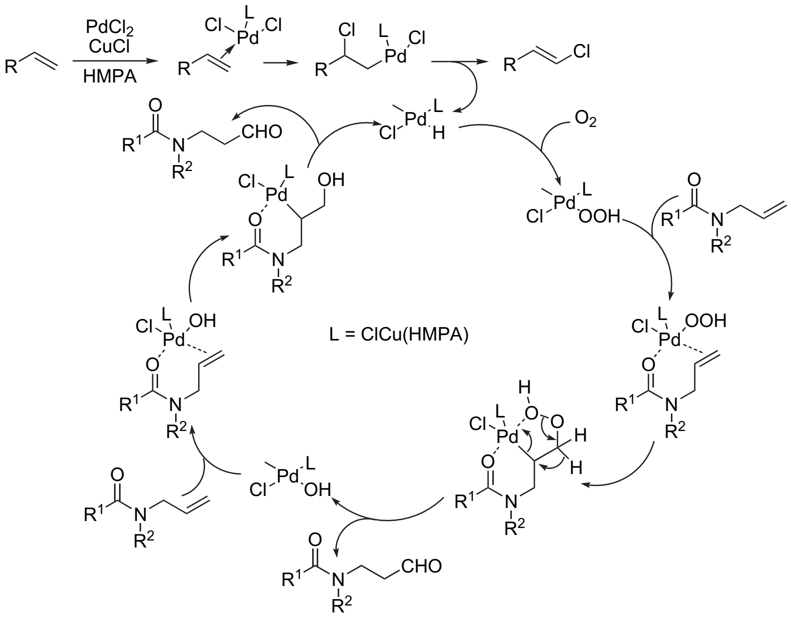
(61)



(62)

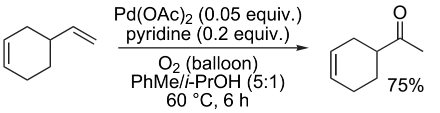
According to Hosokawa et al., (i) a hydrido bimetallic Cu/Pd complex containing HMPA as ligand is formed, (ii) HMPA facilitates the insertion of O_2 into the Pd–H bond, and (iii) the oxidation occurs via a pseudocyclic hydroperoxopalladation (Scheme 14). Monitoring the oxygen uptake has shown that 0.5 mol of O_2 was consumed for the production of 1 mol of the products. The incorporation of the two oxygen atoms of O_2 into the products implies that the Pd–OH species produced from the first oxygen transfer is also able to oxidise the substrate as depicted in Scheme 14.[100–102] Complementary studies by Hosokawa's team have led to the isolation of two complexes, namely $Pd_6Cu_4Cl_{12}O_4(HMPA)_4$ and $[(HMPA)_2CuCl_2(PdCl_2)_2]_n$, from $PdCl_2(MeCN)_2$, CuCl and HMPA in 1,2-dichloroethane under an oxygen atmosphere. These heterometallic complexes have been identified by X-ray analyses and the reaction of the former with 1-decene has led quantitatively to 2-decanone.[101,103]

In the mechanism proposed by Hosokawa (Scheme 14), molecular oxygen and the copper salt have roles quite different from those depicted in Scheme 1 for the Wacker process, and the aldehyde is produced from two different intermediates, namely a pseudo-peroxopalladacycle and a Wacker-type hydroxypalladate obtained from the *syn* addition to the double bond of a liganded OH. A mechanistic scheme with a similar pseudo-peroxopalladacycle leading to the carbonyl function via a 1,2-hydrogen shift has been previously proposed by Mimoun and Roussel for the Pd-catalysed oxidation of terminal olefins by hydrogen peroxide.[104,105]

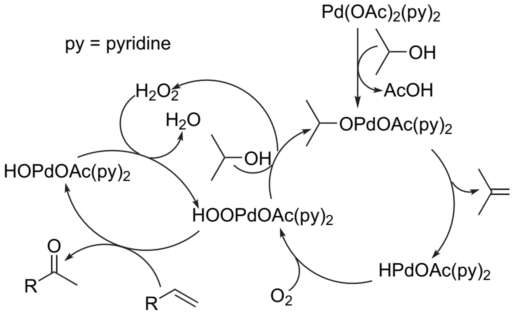


Scheme 14.

The formation of aldehydes under Hosokawa's conditions is not only due to the hydroperoxopalladium intermediate and to the use of a chelating substrate. The nature of the catalyst has probably a decisive role. Indeed, the $Pd(OAc)_2$/pyridine/2-propanol/O_2 catalytic system of Uemura's team led only to cyclohex-3-en-1-yl methyl ketone from 4-vinylcyclohex-1-ene (Eq. 63), although HOOPd species are implied in the oxidation step (Scheme 15),[106] and although the substrate, according Tsuji' results depicted in Eq. 44, should have chelating properties.

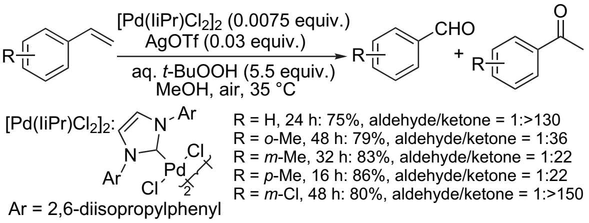


(63)

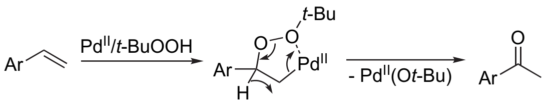


Scheme 15.

Cornell and Sigman have oxidised styrenes in MeOH using aqueous *t*-BuOOH as the oxidant and a palladium heterocyclic-carbene catalyst. The oxidation at the terminal carbon was a minor reaction pathway, the efficiency of which depended on the substitution of the substrate; the resulting arylacetaldehyde evolved under the reaction conditions to give the corresponding arylaldehyde (Eq. 64).[13] In agreement with Mimoun et al.,[105,107] Cornell and Sigman proposed a mechanism involving a pseudo-*tert*-butylperoxopalladacycle and a 1,2-hydrogen shift to explain the formation of the ketone (Scheme 16).[13,108] The arylacetaldehyde could be formed via a similar mechanism. The comparison of the results from styrene depicted in Eqs. 48 and 64 highlights the influence of the reaction conditions on the regioselectivity of the oxidation.



(64)



Scheme 16.

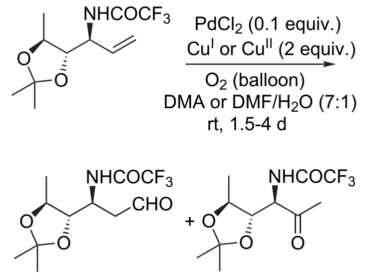
5. Conclusions

The synthesis of aldehydes with fair-to-high yields via the Pd-catalysed oxidation of terminal olefins is restricted to substrates containing a second coordinating centre located at an appropriate position for the formation of a four-electron donor-based palladacycle. Nevertheless, the possibility for such a key intermediate does not imply a selective anti-Markovnikov reaction. Although there is still a lot to discover about the factors leading to the oxidation at the terminal position and the corresponding mechanisms, it seems that the selectivity towards the aldehyde is improved when the oxygen transfer to the substrate occurs via coordination of this oxygen to the palladium atom, a reaction pathway depending, at least in part, on the experimental conditions.

Note added in proof

Propionaldehyde has been the main product obtained from the oxidation, at 100 °C, of propylene with oxygen using MeOH as the solvent and the $Pd(OAc)_2$/1,10-phenanthroline association as the catalyst.[109] The conversion of propylene and the selectivity towards propionaldehyde decreased strongly in the absence of 1,10-phenanthroline.[109,110]

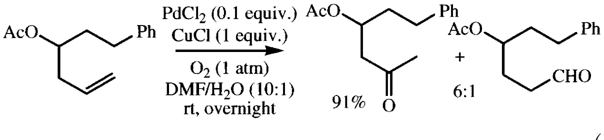
Friestad et al. have obtained a mixture of the aldehyde and the methyl ketone from the oxidation of the allylic trifluoroacetamide depicted in Eq. 65.[111] The increase of the aldehyde selectivity with the use of CuCl instead of a Cu^{II} salt as the additive is in agreement with the observations of Mori et al. (Eq. 37).[56]



(65)

$Cu(OAc)_2$: 83%, aldehyde/ketone = 54:46
$CuCl_2$: 80%, aldehyde/ketone = 65:35
CuCl: 85%, aldehyde/ketone = 75:25
CuCl + HMPA: ca 78%, aldehyde/ketone = 82:18

Kobayashi et al. have obtained a 6:1 mixture of the aldehyde and the methyl ketone from the aerobic oxidation of 1-phenylhex-5-en-3-yl acetate using copper salts and catalytic amounts of $PdCl_2$ in DMF/H_2O (Eq. 66). The use of excess $PdCl_2$ in the absence of copper salts has led to a strong increase of the ketone selectivity. These last conditions have been applied to the total synthesis of macrosphelide H.[112]



(66)

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Biographical sketch

Jacques Muzart was born in 1946 in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Champagne-Ardenne and received his degrees (Doctorat de 3$^{\text{ème}}$ cycle—1972, Doctorat d'Etat—1976) for his work with Jean-Pierre Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 as Stagiaire de Recherche and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with Elias J. Corey at Harvard University on natural product synthesis. On his return to Reims, he mainly studied the photoreactivity of η^3-allylpalladium complexes and anionic activation by supported reagents. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition metal catalysis with particular emphasis on oxidations, asymmetric reactions and mechanisms. Since a few years, he is also involved in the valorisation of agricultural by-products and in the use of water and molten salts as solvents for organic synthesis.