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Palladium-catalysed oxidation of primary and secondary alcohols

Jacques Muzart*

Unité Mixte de Recherche 'Réactions Sélectives et Applications', CNRS-Université de Reims Champagne-Ardenne, B.P. 1039,
51687 Reims Cedex 2, France

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1. Introduction

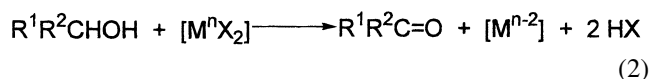
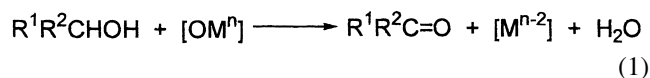
The transformation of the hydroxy group into the corresponding carbonyl is one of the most frequently used

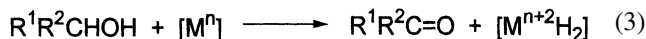
Keywords: oxidation; dehydrogenation; alcohol; palladium; catalysis.

Abbreviations: ADP, allyl diethyl phosphate; Adogen, 464[®], methyltrialkyl(C₈–C₁₀)ammonium chloride (Adogen 464[®] is a registered trademark of Ashland Chemical Co.); bpy, bipyridine; cat., catalytic; C₄mim, 1-butyl-3-methylimidazolium; cod, 1,5-cyclooctadiene; dba, dibenzylideneacetone; DME, 1,2-dimethoxyethane; ee, enantiomeric excess; equiv., equivalent; (–)-Me-DUPHOS, 1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene; MesBr, 2-bromomesitylene; MS, molecular sieves; nbd, norbornadiene; phen, 1,10-phenanthroline; py, pyridine; sc CO₂, supercritical carbon dioxide; TON, turnover number; wt, weight.

* Corresponding author. Tel.: +33-3-2691-3237; fax: +33-3-2691-3166; e-mail: jacques.muzart@univ-reims.fr

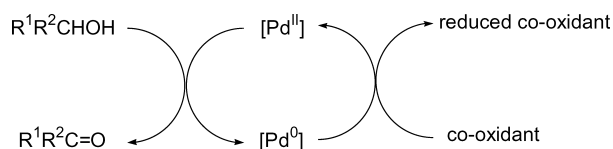
reactions in organic synthesis. Traditionally, stoichiometric and even over-stoichiometric amounts of metal oxides (Eq. (1)) or metal salts (Eq. (2)) are used for such oxidations. These procedures, which generate copious quantities of heavy metal wastes, are hardly compatible with environmental regulations. A number of metal-catalysed methods have been described as interesting alternatives; this has introduced a third type of reaction (Eq. (3)) which is often called 'dehydrogenation' or 'oxidative dehydrogenation' rather than 'oxidation.'





The aim of this review is to give an overview of the palladium-catalysed processes devoted to the oxidation of primary and secondary alcohols. This topic is evoked in various books and reviews, but with restricted reference to the literature.¹ Moreover, an active research in this area has been documented in recent years. In this field, Pd⁰ and Pd^{II} compounds are used as catalysts.

The oxidation of alcohols by stoichiometric quantities of Pd^{II} was discovered one and three quarter centuries ago.^{2,3} Since Pd^{II} is reduced to Pd⁰,⁴ the achievement of a catalytic cycle requires the regeneration of the oxidative species and this is obtained by the addition into the reaction of stoichiometric amounts of a co-oxidant (Scheme 1).

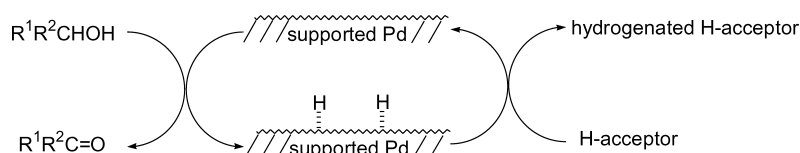


Scheme 1.

Pd⁰ catalysis is generally devoted to dehydrogenations which are carried out under heterogeneous conditions. Such reactions involve mainly the formation of palladium-hydride intermediates; the regeneration of the active Pd species is usually achieved by an H-acceptor (Scheme 2). Dehydrogenations in the vapour phase using flow reactors and/or using supported bi- or even multi-metallic catalysts, especially with bismuth, lead and platinum associated with palladium and in carbohydrate chemistry, have also been reported; these methods are out of the scope of the present review and only a few of them will be mentioned; in addition, several review articles^{5–7} have appeared on this subject.

In fact, the mechanism of many catalytic oxidation methods remains rather a black box, with essentially no more than suggestions from authors. It is also often difficult to ascribe with confidence the term 'oxidation' or 'dehydrogenation' to metal-catalysed transformations of alcohols to carbonyl compounds. Nevertheless, to suggest a mechanism might induce more work in the field and could thus lead to improvements of the process.

This review will be organised around the nature of the additives which have been used to mediate the catalytic cycle. To determine if an additive is a co-oxidant or a hydrogen acceptor is often tedious. As an example, O₂ can act as a co-oxidant, since it is able to coordinate to Pd⁰ to afford Pd^{II}O₂, but in the course of the oxidation of alcohols,



Scheme 2.

it leads finally to H₂O and is therefore also an H-acceptor. The classification of the additives in the present review is, for this reason, rather arbitrary.

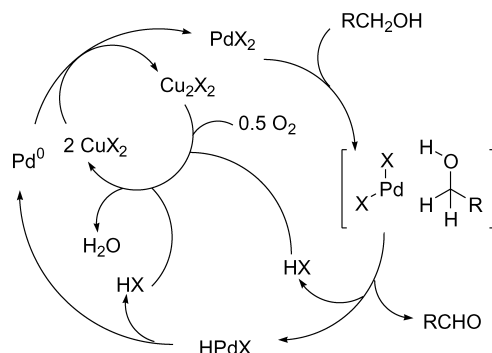
2. Oxygen as a co-oxidant

The ideal co-oxidant would be molecular oxygen, since it is readily available, inexpensive and non-toxic. The present section will be sub-divided taking into account the nature of the starting catalyst.

2.1. Using well-determined Pd^{II}-compounds

This section will concern the use of mainly palladium chloride (**1**), palladium acetate (**2**) and their complexes with organic ligands as catalysts.

In 1963, Moiseev et al. reported that acetic acid was produced by bubbling air into a heated aqueous solution of ethanol containing catalytic amounts of both **1** and CuCl₂.⁸ Four years later, Lloyd obtained a mixture of butyraldehyde, its di-*n*-butyl acetal and *n*-butyl *n*-butyrate with a low TON using undiluted 1-butanol under oxygen pressure (3 atm) and **1** as a catalyst at 100°C.⁹ Traces of these compounds were even obtained in the absence of **1**. The addition of catalytic amounts of Cu(NO₃)₂ to **1** increased the conversion of 1-butanol while 1/CuCl₂ and 1/1,4-naphthoquinone were much less satisfactory. It is not surprising that copper salts were used in conjunction with oxygen in these early attempts, because the Wacker process was the emerging palladium-catalysed reaction at this time. The suggested catalytic cycles additionally have strong similarities with the Wacker process (Scheme 3).^{8,9} The formation of water was demonstrated unambiguously.⁹ This method was extended to the oxidation of secondary saturated alcohols, benzylic alcohols⁹ and, subsequently, to 1,*n*-diols¹⁰ and a β-aminoalcohol.¹¹

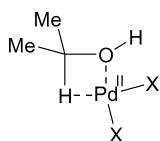


Scheme 3.

Ten years after the report of Lloyd, much milder conditions were described by Blackburn and Schwartz.¹² Their method, which involves 1 mol% of **1** and 1 atm of oxygen in solvents such as ethylene carbonate, sulpholane and acetone at 20–38°C, requires the addition of small amounts¹³ of NaOAc (5 mol%) to be efficient. The reaction is slow (up to 133 h), but led to high yields from secondary aliphatic alcohols and benzyl alcohol.¹⁴ A variety of other Pd complexes (**2**, PdCl₂L₂ (L=NH₃ or PPh₃), Na₂PdCl₄ and Pd black) were inefficient as catalysts under such conditions. In contrast to Lloyd's procedure, the authors noted that the presence of Cu^{II} salts retards the oxidation. The formation of water was also observed, an excess of which inhibited the catalysis. The oxidation of alcohols bearing a C=C double bond was thwarted because olefins poison the catalyst by strong complexation.¹⁵ The proposed mechanism involved deprotonation of the coordinated alcohol by NaOAc to afford a Pd^{II} alkoxide, followed by a β-hydride elimination which led to the carbonyl compound and a Pd^{II} hydride. This latter complex would react with O₂ to generate H₂O and an active Pd^{II} species, for which no structure was suggested.

The use of **1** at 80°C under an air atmosphere with hexane as the solvent and NaHCO₃ as base led to a low TON from 1-indanol, even in the presence of a phase transfer catalyst.¹⁶ Nevertheless, in the course of the formation of 1,7-naphthylpyridine from a Heck-type reaction of 3-amino-4-iodopyridine with allyl alcohol using **1**, P(*o*-tolyl)₃ and NaHCO₃ in HMPA at 140°C, the oxidation of the primary allylic alcohol adduct intermediate was suggested.¹⁷ Instead of such an oxidative step, the formation of the aldehyde intermediate could be explained by the classical Heck reaction of aryl halides with allylic alcohols.^{18,19} Actually, the authors retained the idea of the aldehyde as intermediate because they accomplished the reaction under an air atmosphere.²⁰

Kinetic studies of the oxidation of isopropanol to acetone catalysed at 66–96°C by **1** in aqueous ionic media have led Kozhevnikov et al. to propose that the proton of the hydroxy group is preserved in the transition state leading to the ketone (Scheme 4).²¹ Although this direct abstraction of hydride from the carbon atom is not totally unlikely, such a possibility was either not examined or ruled out²² in studies carried out by other researchers under different experimental conditions. Kozhevnikov et al. have also studied aerobic oxidation with the heteropolyacid H₅PMo₁₀V₂O₄₀ as the additive which reoxidised Pd⁰ to Pd^{II} and was regenerated by oxygen.²³



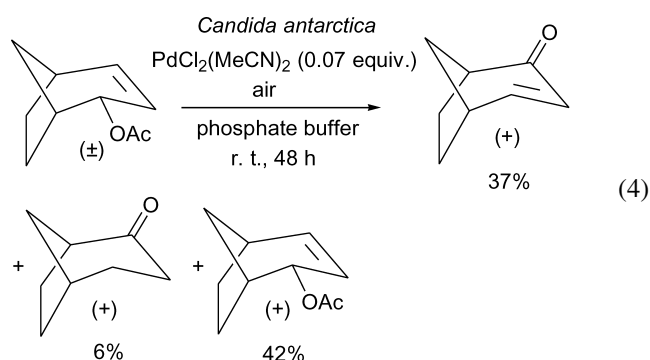
Scheme 4.

Kinetic studies have additionally been performed using mono- and bi-metallic catalysts obtained by the coordination of Pd^{II} to a polyphenylene polymer containing a β-di- or tri-ketone as the ligand. In phosphate buffered aqueous solutions at 25°C, it was shown that benzyl alcohol was

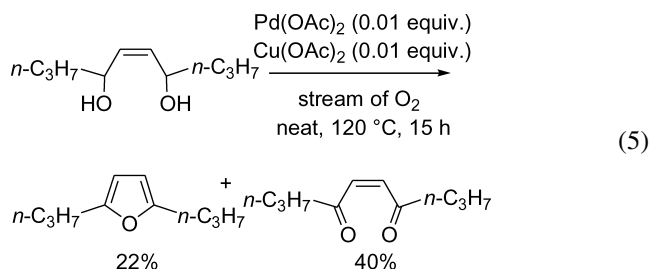
more reactive than aliphatic alcohols, allylic alcohols, diols and glucose. Allyl alcohol led to a mixture of acrolein and 3-hydroxypropanal, this latter resulting from Wacker-type oxidation of the C=C double bond.^{24,25}

Recently, the oxidation of alcohols to aldehydes or ketones using PdCl₂(PhCN)₂ fixed on hydroxyapatites (Ca_{10-2z}(HPO₄)_z(PO₄)_{6-2z}(OH)_{2-2z}·nH₂O; z=0–1; n=0–2.5) in benzotrifluoride at 90°C has been patented, 2-octanol yielding 91% 2-octanone.²⁶ In a subsequent paper, it was clearly shown that these aerobic heterogeneous conditions are highly efficient for the oxidation of aliphatic, allylic and benzylic alcohols to the corresponding aldehydes or ketones with high yields, TON's up to 236000 being reached.²⁷ In addition, no leaching of palladium occurred, allowing recycling experiments without loss of catalytic activity.

The resolution of an acetoxyated monoterpene by a lipase and oxidation of the resulting allylic alcohol catalysed by PdCl₂(MeCN)₂ has been successfully obtained in a one-pot reaction (Eq. (4));²⁸ the formation of small amounts of the saturated ketone may be explained by a concurrent reaction leading to hydrogen transfer, as exemplified in Section 7.

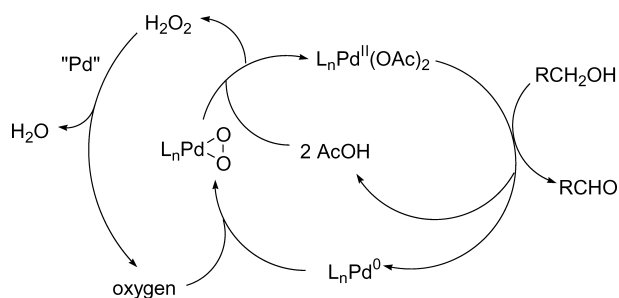


The catalysis by **2** of the oxidation of aliphatic alcohols in an oxygenated acidic medium was documented in 1969 by Brown et al.²⁹ In 1982, Siedle et al. reported that the amount of oxidised products was greatly increased when *n*-propanol was treated with palladium bis(hexafluoroacetylacetonate) under oxygen instead of nitrogen.³⁰ Simultaneously, Couturier et al. obtained furans and also a γ-dione from ethylenic diols using catalytic amounts of both **2** and Cu(OAc)₂ (Eq. (5)).³¹ These three reports have received little attention.

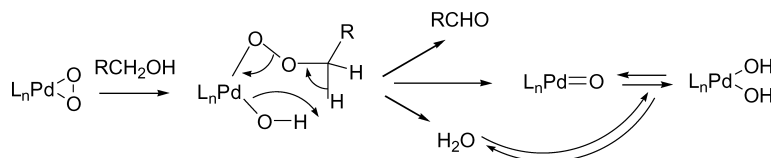


In 1998, Peterson and Larock disclosed the efficient oxidation of primary and secondary allylic and benzylic alcohols to the corresponding aldehydes and ketones using 5 mol% of **2** in DMSO³² (alcohol concentration 1 M) at 80°C under an atmosphere of oxygen.³³ The presence of a

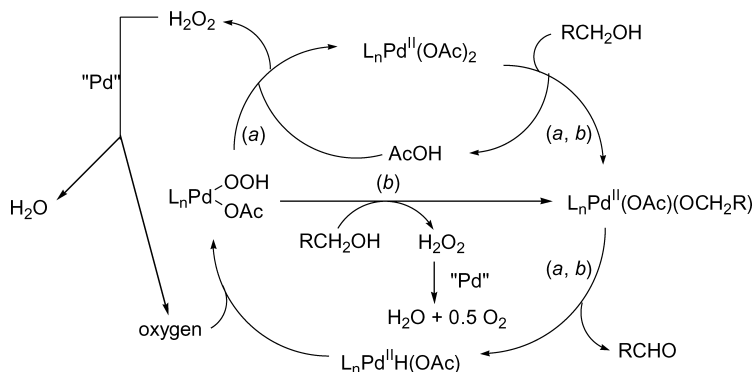
mineral base (2 equiv. NaHCO_3 , KHCO_3 , Na_2CO_3 or K_2CO_3) generally improved the rates and yields from the secondary substrates. Variations of these experimental conditions using substoichiometric quantities of the above bases, switching to (i) NaOAc , KOAc , LiOAc or NEt_3 ³⁴ as the base, (ii) either MeCN or a 9:1 mixture of $\text{DMSO}/\text{H}_2\text{O}$ as the solvent, or (iii) other Pd catalysts (**1**, $\text{Pd}(\text{O}_2\text{CCF}_3)_2$ or $\text{Pd}(\text{dba})_2$), or reducing either the reaction temperature or the amount of solvent were detrimental to the efficiency of the process. According to the authors, the Pd–H species produced in the catalytic cycle would undergo a reductive elimination to Pd^0 which would be oxidised to the active state by oxygen. A recent mechanistic study of this reaction by Stahl et al. using a primary benzylic alcohol in the absence of base has demonstrated that (i) DMSO does not participate in the redox chemistry and (ii) all four oxidising equivalents in dioxygen are used.³⁵ According to Stahl et al., Pd^0 is stabilised with regard to palladium black formation, owing to coordination with DMSO , and the regeneration of the catalyst is achieved through a peroxy-palladacycle intermediate, the addition of AcOH to this latter complex³⁶ regenerating the initial Pd^{II} catalyst and leading to the concomitant formation of H_2O_2 (Scheme 5; $\text{L}=\text{DMSO}$, $\text{R}=2,5\text{-dimethoxyphenyl}$). It has been shown that H_2O_2 disproportionates rapidly under these reaction conditions.³⁵



Scheme 5.

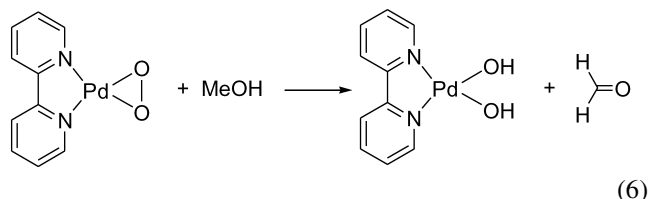


Scheme 6.



Scheme 7.

The formation of peroxy-palladacycles from L_nPd^0 and O_2 is well known.^{36,37} It was shown some years ago that methanol reacts with $(\text{bpy})\text{PdO}_2$ to afford $(\text{bpy})\text{Pd}(\text{OH})_2$ and formaldehyde (Eq. (6)).³⁸ If a peroxy-palladacycle is produced under the catalytic conditions of Stahl et al., it could therefore react with RCH_2OH rather than AcOH , at least at the beginning of the reaction, because of the high $\text{RCH}_2\text{OH}/\text{AcOH}$ ratio (Scheme 6).



(6)

The possibility of a hydroperoxy-palladium derivative as an alternative intermediate to the peroxy-palladacycle has not been considered in the mechanistic study of the **2**/ DMSO/O_2 process, although it has been previously suggested by Uemura under different reaction conditions³⁹ (vide infra). Such a hydroperoxy-palladium intermediate⁴⁰ could be hydrolyzed by AcOH ^{41,42} to regenerate the starting catalyst (Scheme 7, path *a*), but its competitive reaction with the substrate to reproduce the Pd^{II} alkoxide (Scheme 7, path *b*) could be more effective (vide supra).³⁹

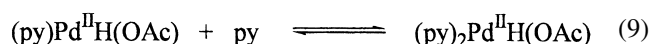
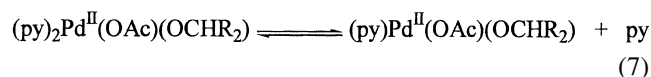
The reaction mechanisms illustrated in Scheme 5 and in Scheme 7, path *a*, are not compatible with Larock's reactions carried out in the presence of a base because of the capture of AcOH . Scheme 7, path *b*, in which the alcohol reacts with the hydroperoxy-palladium intermediate seems to be more in agreement with a basic medium. The base could enhance the nucleophilicity of the alcohol and could even possibly give the corresponding sodium or potassium alkoxide, as proposed for some metal-catalysed oxidations,^{43–45} which would promote the formation of the palladium alkoxide. According to the mechanism depicted

in Scheme 7, path *b*, a catalytic amount of base would be sufficient. Decreasing the amount of base, however, reduced the efficiency of Larock's method for the oxidation of secondary alcohols,³³ which could be due to some heterogeneous character of the reaction.

Here, it is interesting to note that the stability of H₂O₂ in the presence of palladium is highly dependent on the experimental medium. Indeed, the catalytic oxidation of undiluted alcohols at 70°C by O₂ (5 atm) using **2** complexed with a suitable bidentate nitrogen ligand, especially 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, and an acid cocatalyst has been proposed as a method for the production of H₂O₂.⁴⁶

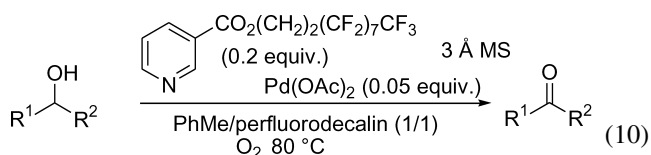
Since 1998, the group of Uemura has published a series of papers in which **2** was used as the starting catalyst. The optimum conditions were a 0.1 M substrate concentration in toluene at 80°C under an oxygen atmosphere in the presence of 3 Å MS and 4 equiv. of pyridine/palladium atom.^{39,47,48} A variety of primary and secondary—saturated, allylic or benzylic—alcohols led to the corresponding aldehydes and ketones with high yields and lactonisation was observed from suitable diols. A primary hydroxy group was oxidised more rapidly than a terminal alkene, 10-undecen-1-ol yielding 91% 10-undecenal.⁴⁹ Interestingly, air can be used instead of O₂, a longer reaction time and continuous bubbling of air being, however, required. The use of other Pd catalysts (**1**, PdCl₂(MeCN)₂, Pd(OCOFCF₃)₂, Pd(dba)₂ or Pd(PPh₃)₄) was ineffective. Lower yields were obtained in other solvents or with other bases. Geraniol, which initially led to disappointing results,³⁹ yielded finally 56% *E* and *Z*-aldehydes at 76% conversion.⁵⁰ Some limitations were, however, reported such as the lack of oxidation of 1-dimethylamino-2-propanol, 1-methoxy-1-phenyl-2-ethanol or 1-phenyl-1-propynol as examples.³⁹ The in situ formation of H₂O₂ has been demonstrated, its decomposition into water and oxygen being facilitated by MS. Since H₂O₂ may compete with the alcohol for binding to the palladium center, its removal by MS could promote substrate oxidation.^{39,51,52} Such in situ production of H₂O₂ was then exploited to perform a **2**-catalysed oxidation of terminal alkenes to the corresponding methyl ketones⁵³ using a 1/1 mixture of PhMe and 2-propanol in the absence of MS. Under these modified conditions, 10-undecen-1-ol yielded 71% undecan-10-on-1-ol, the terminal C=C bond being more rapidly oxidised than the primary hydroxy group.⁴⁹ The role of pyridine in the alcohol oxidation process was not determined with confidence. Uemura et al. suggested its possible coordination to Pd^{II} to give the (py)₂Pd(OAc)₂ complex. This coordination would stabilize the Pd^{II} hydride intermediate, preventing the reductive elimination of HOAc. A catalytic scheme involving a Pd^{II} complex as an active species throughout the reaction was proposed and, instead of the regeneration of the initial catalyst, (py)₂Pd(OAc)₂, the authors considered a ligand exchange of (py)₂Pd(OAc)(OOH) with the substrate to reform the Pd^{II} alkoxide (Scheme 7, path *b*; L=py, *n*=2). Recently, the mechanism of this alcohol oxidation procedure has been revisited by Stahl et al.⁵⁴ Since the turnover rate decreased when the ratio of py/Pd was higher than 1, they argued that the formation of the Pd^{II} hydride from the Pd^{II} alkoxide (Scheme 7) requires the reversible dissociation of one pyridine ligand to generate a three-

coordinate Pd^{II} species from which β-hydride elimination would proceed (Eqs. (7)–(9)). In contrast to Uemura, they retain a catalytic cycle regenerating (py)₂Pd(OAc)₂ from (py)₂Pd⁰ and, hence, the whole catalytic cycle would be similar to the one described in Scheme 5 (L=py). According to Stahl et al., the **2**/py system exhibited a >10-fold rate enhancement over the **2**/DMSO system.



Under experimental conditions close to those of Uemura, it has been incidentally observed that 2,4-cyclohexadien-1-ol and 2,4-cycloheptadien-1-ol lead to phenol and 2,4-cycloheptadien-1-one respectively.⁵⁵

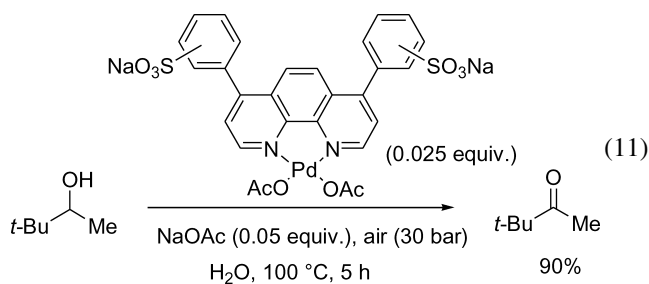
Uemura's team has designed two approaches, through either a fluorous biphasic system or a heterogenised catalyst, to turn their catalytic method into a recyclable process. Using perfluoroalkylated-pyridines as ligands in a toluene/perfluorodecalin solvent, aliphatic and benzylic alcohols led to the corresponding carbonyl compounds with good yields and a very slight leaching of palladium into the toluene phase (Eq. (10)).⁵⁶ Recycling of the fluorous phase was effective if small amounts of the ligand were added once every two runs. In contrast, allylic alcohols induced precipitation of palladium black. For the second system, a supported palladium catalyst was prepared from **2**, pyridine, hydrotalcite (Mg₆Al₂(OH)₁₆CO₃·4H₂O; a basic clay mineral) and toluene.^{50,57,58} This heterogeneous catalyst has to be used in the presence of at least 4 equiv. of pyridine in toluene at 65°C to selectively oxidize a number of aliphatic, benzylic or allylic alcohols, diols or benzoin with yields often higher than with the previous **2**/pyridine/3 Å MS method and without requiring the addition of MS, the hydrotalcite working better than the 3 Å MS to decompose H₂O₂. Recycling was also performed, although a slight leaching was detected. This system seems to be rather general, the limitations being similar to those with the **2**/py/3 Å MS method.



R¹ = Me(CH₂)₉, R² = Me, 9 h: 90%; R¹ = *t*-BuMe₂SiO(CH₂)₇
 R² = H, 9 h: 77%, R¹ = Ph, R² = H, 5 h: 94%; R¹ = Ph
 R² = Me, 5 h: 98%, recycling: 97, 88, 90, 80, 74%

Besides Uemura's recyclable systems, two other 'green' methods using either water or an ionic liquid as the solvent have been disclosed by the teams of Sheldon and Seddon, respectively.

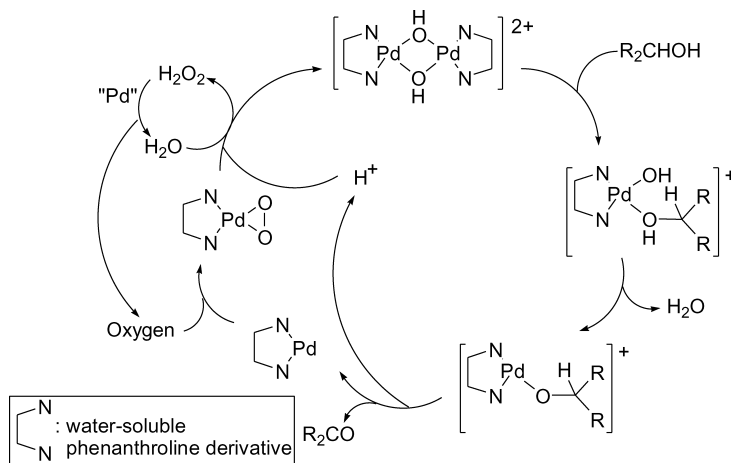
Sheldon et al. have been able to carry out the oxidation in water with the use of **2** coordinated to the disodium salt of a 4,7-diphenyl-1,10-phenanthroline disulfonic acid as the catalyst.^{22,59} The reaction was performed at 100°C under a high air pressure in the presence of small amounts of sodium acetate to afford good yields of ketones from secondary aliphatic and benzylic alcohols (Eq. (11)), while the oxidation of other alcohols was less selective. Etherification, migration and/or Wacker oxidation of the C=C bond were by-products from the secondary allylic alcohols. Primary allylic and benzylic alcohols led mainly to the corresponding aldehydes, while the major product from a primary aliphatic alcohol was the corresponding acid. We suggest that this difference in selectivity may in part be due to the different aptitudes of allylic, benzylic and aliphatic aldehydes towards hydration;^{6b} nevertheless, the formation of the acid has a radical character because the addition of a radical scavenger stops the reaction at the aldehyde.^{22,59,60} The oxidation of the terminal C=C bond of 10-undecen-1-ol was strongly preferred under these aqueous conditions which contrasts with the 2/py/3 Å MS method of Uemura (vide supra).⁴⁹ As with many procedures, no reaction was observed with alcohols containing functionalities able to coordinate strongly to the palladium. The recyclability of the catalyst solution has been demonstrated using 2-hexanol as the substrate.²² Extensive studies of the process using a range of concentrations, water-soluble ligands, palladium salts and pH²² have led to the proposal of a dihydroxy-bridged palladium dimer as the active catalyst and the reaction cycle depicted in Scheme 8, which involves the formation of a peroxypalladacycle from Pd⁰.



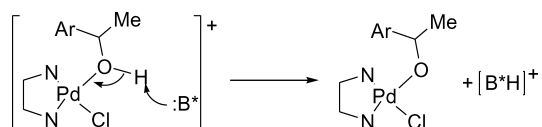
Seddon and Stark have quantitatively oxidised benzyl alcohol and 1-phenylethanol to benzaldehyde and aceto-

phenone respectively, using **2** as the catalyst and 1 atm of O₂ in an ionic liquid, [C₄mim][BF₄], at 80°C.⁶¹ Both the catalyst and the ionic liquid may be re-used for at least five recycles, but, to preclude overoxidation of the benzaldehyde to benzoic acid, the catalytic system has to be dried from time to time to remove the water that accumulates during the reaction and work-up.

The successes of the Pd^{II}-catalysed oxidations of alcohols using bidentate nitrogen ligands have undoubtedly stimulated research into oxidative kinetic resolution catalysts. In March 2001, the teams of Stoltz⁶² and Sigman⁶³ have independently reported some exciting results. In both laboratories, exploratory experiments have been carried out using 1-phenylethanol as the racemic substrate, 3 Å MS, 1 atm oxygen and **2** (0.05 equiv.) as catalyst associated to a structurally diverse set of chiral ligands (0.1⁶³ or 0.2⁶² equiv.) in PhMe at 70⁶³ or 80°C⁶². Both ligand screens established that (–)-sparteine was the most selective. Optimisation of the process led to three kinetic resolution procedures under 1 atm O₂: (i) PdCl₂(nbd) (0.05 equiv.), (–)-sparteine (0.2 equiv.), 3 Å MS and 0.1 M substrate in PhMe at 80°C,⁶² (ii) Pd(OAc)₂ (0.05 equiv.), (–)-sparteine (0.2 equiv.) and 0.5 M substrate in 1,2-dichloroethane at 60°C,⁶³ and (iii) PdCl₂(MeCN)₂ or PdCl₂(cod) (0.05 equiv.), (–)-sparteine (0.2 equiv.) and 0.5 M substrate in 1,2-dichloroethane at 70°C.⁶³ These conditions allow the kinetic resolution of a range of secondary benzylic alcohols with ees up to 99.8%; for an example, 3.4 g of optically-enriched (–)-(2-naphthyl)ethanol in 99% ee have been recovered.⁶² In applying the method to β-functionalized benzylic alcohols, Sudalai et al. have shown the influence of the β-function on the efficiency of the resolution (Eq. (12)).⁶⁴ One example of the kinetic resolution of an allylic alcohol, 4-phenyl-3-methyl-but-3-en-2-ol, has been disclosed, with 91.8% ee of the recovered alcohol obtained at 70.4% conversion.⁶³ The resolution of saturated alcohols was less selective^{62,63} (77.8% ee for 3,3-dimethyl-2-butanol at 58.5% conversion).⁶³ The scope of the reaction includes oxidative desymmetrisation of *meso*-diols (Eq. (13)⁶² and Eq. (14)⁶³). Surprisingly, the isolated PdCl₂[(–)-sparteine] complex was incompetent as a catalyst for the oxidation of alcohols without additional (–)-sparteine.⁶³ Intensive kinetic studies have demonstrated the dual role of (–)-sparteine as a ligand on palladium and as an exogenous

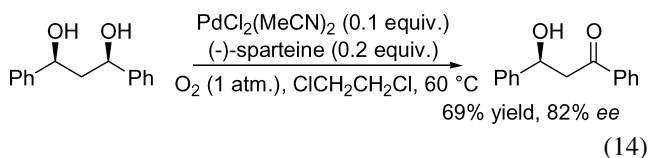
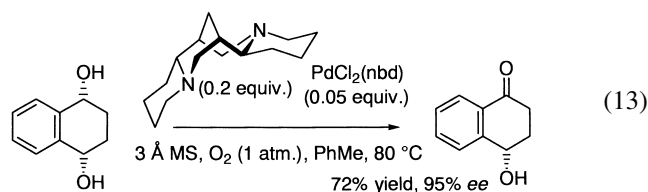
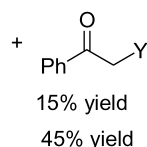
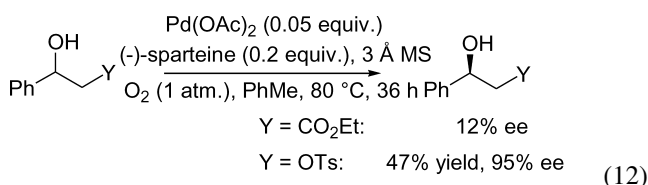


Scheme 8.



Scheme 9.

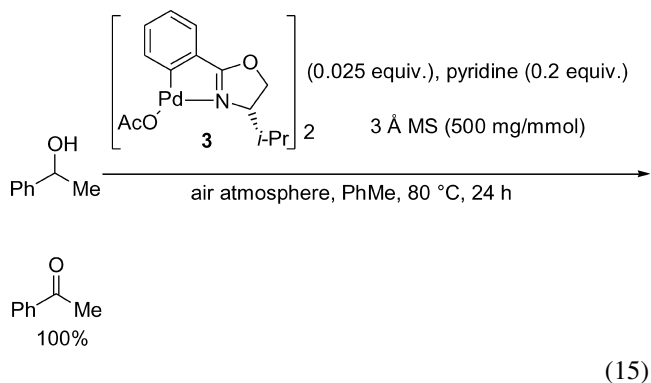
base.⁶⁵ Exogenous (–)-sparteine would deprotonate the Pd^{II}-bound alcohol (Scheme 9; B*=(–)-sparteine) and is involved in the β-hydride elimination leading to the ketone.^{65,66} Jensen and Sigman have also disclosed the use of various PdCl₂(*N*-heterocyclic carbene)₂ complexes as catalysts for which the ligand was not displaced by (–)-sparteine.⁶⁷ Such an achiral Pd-catalyst used with 0.15 equiv. of (–)-sparteine mediated the kinetic resolution of benzylic alcohols, affording up to 96% ee. With a chiral carbene ligand, ‘matched’ diastereoisomeric interactions⁶⁸ with the chiral exogenous base have allowed increases in the kinetic resolution.



Recently, Sigman et al. have reported that the use of triethylamine instead of a bidentate chelate as a ligand of **2** allowed the oxidation at room temperature of primary or secondary aliphatic, benzylic and allylic alcohols to the corresponding carbonyl compounds and the clean lactonisation of an aliphatic γ-diol.⁶⁹ The reaction was carried out in a THF/PhMe (15/85) mixture containing 3 Å MS using, in most cases, 0.03 equiv. of **2** and 0.06 equiv. of NEt₃ for 12 h. This report points out two examples of the influence of the nature of the substrate on the efficiency of these experimental conditions. While 2-(*p*-methoxyphenyl)-ethanol yielded 96% of the corresponding ketone, 2-(*o*-methoxyphenyl)ethanol was reluctant to react, this inhibition being explained by chelation of the substrate or the ketone product to the palladium. A cyclic allylic alcohol such as 3-methyl-2-cyclohexen-1-ol, was oxidised in 93%

yield on increasing the amount of NEt₃ (0.5 equiv.) whereas a linear allylic alcohol such as cinnamyl alcohol afforded low yields of cinnamaldehyde and precipitation of palladium metal. Sigman et al. have also tried to elucidate the role of the NEt₃. ¹H NMR analysis has shown the presence of both Pd(OAc)₂(NEt₃)₂ and Pd(OAc)₂(NEt₃), this differing from the reaction of **2** with pyridine, for which they observed a single adduct, Pd(OAc)₂(py)₂. The dependence of the oxidation rates on [NEt₃] has led to the assumption of catalysis by Pd(OAc)₂(NEt₃) rather than by Pd(OAc)₂(NEt₃)₂.⁶⁹ Nevertheless, we suggest that the influence of [NEt₃] could also be explained as proposed by Steinhoff and Stahl⁵⁴ for Uemura's alcohol oxidation procedure (vide supra and Eqs. (6)–(8) with NEt₃ instead of py).

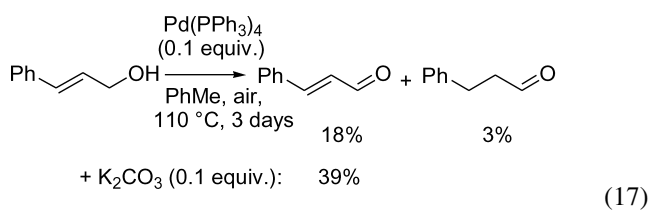
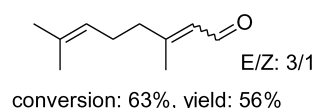
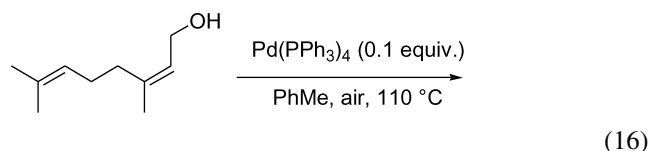
Using the palladacycle **3** and air as the re-oxidant, 1-octanol, 2-octanol and 1-phenylethanol led to the corresponding aldehyde and ketones.⁷⁰ For the latter substrate, Moberg et al. have studied various experimental conditions: (i) DMSO/NaHCO₃/80°C, (ii) *o*-xylene/K₂CO₃/130°C, (iii) PhMe/py/3 Å MS/80°C, and (iv) PhMe/perfluorodecalin/py/3 Å MS/80°C, to obtain higher yields and faster reactions than with **2** as the catalyst, the best result being shown in Eq. (15). Although **3** is chiral, no significant resolution was observed when the reaction was stopped at 50% conversion.⁷⁰



2.2. Using soluble Pd⁰ complexes

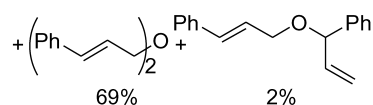
Uemura et al. have noted the inefficiency of Pd(*dba*)₂/py and Pd(PPh₃)₄ (**4**)/py as catalysts for the oxidation of benzyl alcohol with oxygen in PhMe at 80°C.³⁹ In contrast, Pd(*dba*)₂/PPh₃ and **4** are able to catalyse the oxidation of allylic alcohols by air in the same solvent at 100–110°C (Eq. (16)).⁷¹ In some cases, the formation of diallyl ethers was a concurrent reaction; this is surprising since **4** has no Lewis acid character.⁷² The selectivity was improved by the addition of small amounts of K₂CO₃ or NH₄PF₆ (Eq. (17)).⁷¹ According to the authors, who did not propose a catalytic cycle for the formation of α,β-unsaturated carbonyl compounds, the role of the additives was unclear. Although the O–H bond of the alcohols is normally reluctant to add to Pd⁰ complexes,⁷³ we nevertheless suspect the insertion of Pd⁰ into the allylO–H bond in this case. Indeed, the reaction of MeOH and ArOH with Pd⁰ to afford MeOPd⁷⁴ and ArOPdH,⁷⁵ respectively, has been documented and it has been proposed that oxidative

dehydrogenation of R_2CHOH over supported Pd^0 catalysts could involve $R_2CHO[Pd]H$ species.^{76,77} Interactions of the unsaturated alcohol with additives could make the alkoxy ligand ‘softer’ and therefore more compatible with the metal center⁷³ (see also Scheme 10, *vide infra*).



+ K_2CO_3 (0.1 equiv.): 39%

or NH_4PF_6 (0.1 equiv.): 90%

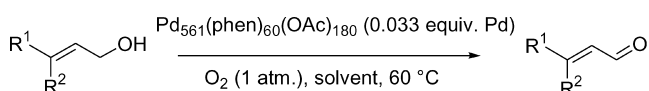


2.3. Using stabilised palladium particles

This section will cover catalysis by Pd clusters, nanoparticles and colloids. Indeed, the meaning of and differentiation between these terms are not always obvious.⁷⁸

The giant palladium clusters, $Pd_{561}(phen)_{60}(OAc)_{180}$ (**5**) and $Pd_{561}(phen)_{60}(PF_6)_{60}O_{60}$ (**6**), have been largely documented and used as catalysts by Russian workers.⁷⁹ The oxidation of methanol at 20°C catalysed by **5** led to methyl formate⁸⁰ while at 30–60°C with **5** and **6**, aliphatic primary alcohols led to mixtures,⁸¹ *n*-propanol, for example, affording propanal, propyl propionate, propionic acid, acetal, ethylene, ethane and carbon dioxide.⁸² With **5** as catalyst at 60°C, neat benzyl alcohol under 1 atm of oxygen led to benzaldehyde (70.2%, based upon the $PhCH_2OH$ consumed), benzoic acid (6.1%), toluene (21.8%) and benzene (1.9%). Since a 1/1 mixture of benzaldehyde and toluene was selectively produced under argon instead of oxygen, the formation of toluene under oxygen could be also due to disproportionation of the substrate.^{83,84} From these studies, it was concluded that **5** functions additionally as an efficient inhibitor of free radical oxidations.⁸⁴ Using **5** as a catalyst at 60°C, Kaneda et al. have reported a low catalytic activity for the oxidation of secondary allylic and benzylic alcohols, but indicate the formation of aldehydes from primary allylic alcohols in benzene with high yields (Eq. (18)).^{85,86} Changing benzene as the solvent to AcOH increased the rate of the reaction, but was often detrimental to the selectivity, some hydrogenation and/or esterification taking

place; a 9/1 ratio of PhH/AcOH was found to be a good compromise between the activity of the catalyst and the selectivity. Anchoring **5** on TiO_2 led to a catalyst with a similar efficiency and, interestingly, this supported cluster was re-usable without an appreciable loss of catalytic activity and selectivity. Under similar conditions, **1**, **2**, Pd/C, Pd/ Al_2O_3 and Pd/ SiO_2 were poor catalysts for the oxidation of cinnamyl alcohol (8–34% yield, instead of 94–99%). It was also noted that **5** showed low catalytic activity for oxidation of secondary allylic alcohols and benzylic alcohols.^{85,87}



$R^1 = Ph, R^2 = H, AcOH, 1 h: 94%$ or $PhH, 24 h: 97%$

$R^1 = n-Pr, R^2 = H, PhH, 24 h: 97%$; $R^1 = R^2 = Me, PhH, 24 h: 99%$

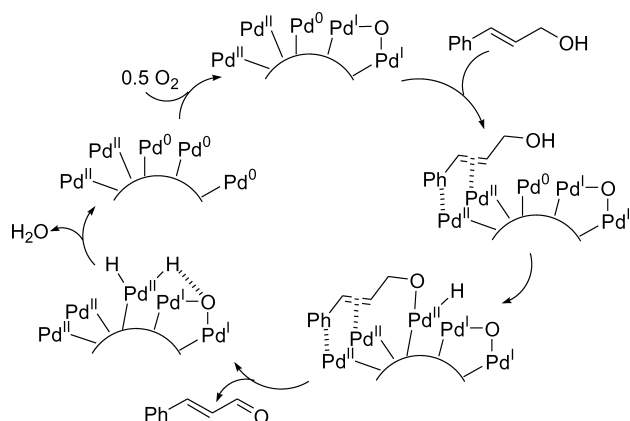
$R^1 = Me, R^2 = (CH_2)_2CH=CMe_2, 24 h, AcOH: 57%$ or $PhH: 39%$
or $PhH/AcOH (9:1 v/v): 95%$

(18)

Kaneda et al. have also prepared smaller palladium clusters, $Pd_4(CO)_4OAc \cdot 2AcOH$ (**6**) and $Pd_4(phen)_2(CO)(OAc)_4$ (**7**), from **2**.⁸⁸ A range of primary allylic alcohols was oxidised to the corresponding aldehydes with high yields using **6** and, in particular, mainly **7** in PhH at 50–80°C for 24–72 h, while secondary allylic alcohols and benzyl alcohol were reluctant to react. Nerol reacted slower than geraniol, an almost complete retention of the stereochemistry in the α,β -unsaturated aldehydes being observed for these substrates. Switching from PhH to AcOH as the solvent increased the rate of the process, but was detrimental to the selectivity, some esterification and hydrogenation of the aliphatic allylic alcohols taking place. Since the dehydrogenation was greatly reduced under nitrogen, the authors postulated the following mechanistic steps: (i) formation of an alkoxy-palladium complex, (ii) β -hydride elimination which yields the aldehyde and a Pd hydride intermediate, and (iii) reaction of this hydride with O_2 which leads to H_2O and the regenerated active Pd catalyst.^{85,88}

Quite recently, the same Japanese team has used the monodispersed Pd nanocluster, $Pd_{2060}(NO_3)_{360}(OAc)_{360}O_{80}$, prepared by the treatment of $Pd_4(phen)_2(CO)_2(OAc)_4$ with $Cu(NO_3)_2$ and oxygen to catalyse the efficient aerobic oxidation of primary allylic and benzylic alcohols in acetic acid at 60°C, the aromatic allylic alcohols being the most reactive. Concerning the secondary allylic alcohols, a good yield was obtained from 4-phenylbut-3-en-2-ol, while 4-methylpent-3-en-2-ol remained unchanged. Saturated alcohols were also reluctant to react. Having established the presence of Pd^{II} , Pd_2O and Pd^0 species at the surface of the cluster, Kaneda et al. ascribed the differences in reactivity to multiple and specific interactions between the substrate and these different Pd sites. The proposals led to a plausible mechanism for the catalytic oxidation of cinnamyl alcohol which involves the insertion of Pd^0 into the CO–H bond after interactions of the π -bonds with Pd^{II} (Scheme 10).⁸⁹

Uozumi and Nakao have prepared a catalyst by the coordination of **2** to a bis-pyridine ligand anchored to an



Scheme 10.

amphiphilic polystyrene-poly(ethylene glycol)-amino resin followed by treatment with benzyl alcohol, to provide a resin dispersion of Pd⁰ nanoparticles. In using 0.01–0.2 equiv. of these nanoparticles in refluxing water under 1 atm of oxygen, high yields of ketones were isolated from secondary benzylic, aliphatic and cyclic allylic alcohols. Interestingly, the recovered resin was reused with negligible loss of catalytic activity.⁹⁰ Under these conditions, benzyl alcohol led to 97% benzaldehyde, while primary aliphatic alcohols were reacted in the presence of 1 equiv. of K₂CO₃ to afford, after acidification, the acids almost quantitatively.

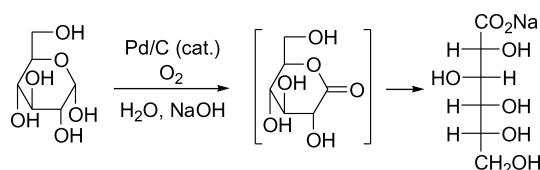
The dissolution of **2** and multi-dentate ligands in hot DMSO led, after cooling to room temperature, to stable metallogels which have been used as catalysts for the oxidation of benzyl alcohol to benzaldehyde by air (1 atm) at 90°C, the reaction taking place at the Pd^{II} centres.⁹¹ The best catalytic activity, obtained using a calix[4]arene-based tetradentate ligand, was twice that of **2**; metallogels prepared from [ethylenediamine-Pd(H₂O)₂](NO₃)₂ instead of **2** were much less effective. Other aerobic oxidations of benzyl alcohol in the presence of palladium colloids prepared in situ have also been reported.⁹²

2.4. Using supported Pd⁰ as the starting catalyst

A few aerobic heterogeneous procedures using supported palladium have already been included in Sections 2.1 and 2.2. The present section will concern Pd⁰ supported on simple mineral supports. Palladium on charcoal and

promote their activity,⁶ especially for carbohydrate oxidations, a topic which, as mentioned previously, is out of the scope of the present review.

Various alcohol oxidations with Pd/C,^{6b,7d,93–97} Pd/CaCO₃⁹⁸ and Pd/Al₂O₃^{97,99} have been carried out in aqueous basic solutions. With Pd/C, primary alcohols led mainly to the acids.^{94,96} The aqueous medium favours the formation of the acid in providing the hydrated form of the aldehyde.^{77,96} Nevertheless, the selectivity towards the aldehyde is good when the primary hydroxyl group is located next to an aromatic ring or a C=C double bond; this has been correlated with the lower hydration equilibrium constants.^{6b} A range of arylacetic acids has been prepared from ArCH₂CH₂OH over Pd/C with the selectivity enhanced by additives such as copper^{II} or lead^{II} acetate (Eq. (19)), two recyclings of the catalytic system have thus been performed without a notable deterioration of the selectivity or activity.^{94,100} At pH 11 and 40°C, one of the two primary functions of glycerol has been predominantly oxidised yielding 70% glyceric acid at 90% conversion.^{6b,101} At pH 8, a slight conversion of 9-decen-1-ol to 9-decenoic acid was obtained in a 1/1 dioxane/water mixture at 50°C.⁹⁶ In neutral aqueous solution, Pd/C has a low activity.^{5b} It was assumed that neutralisation of the acid as soon as it is formed is required to preserve the efficiency of the catalyst.¹⁰² In agreement with this assumption, a study of the pH effect on the oxidation of glucose to gluconic acid has shown the best reactivity to be in basic media, up to 99% yield being obtained at pH 9,¹⁰³ this transformation involving the oxidation of the anomeric hydroxyl (Scheme 11).¹⁰⁴ Additionally, the efficiencies of these Pd-catalysed oxidations, extensively studied for more than 60 years,^{6a,98} depend markedly on the particle size of the catalyst.^{6c,105} Pd/C has also been used to catalyse the aerobic oxidation of choline hydroxide, affording betaine with 95% selectivity at 95% conversion.¹⁰⁶

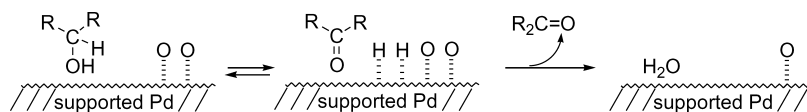


Scheme 11.

ArCH ₂ CH ₂ OH	5% Pd/C (0.03 equiv. Pd)		ArCH ₂ CO ₂ H + ArCH ₂ CHO + ArCO ₂ H		
	NaOH (1.9 equiv.), O ₂ (3–5 atm.)				
Ar: 4-methoxyphenyl	H ₂ O, 90 °C, 3 h		36.2%	0.7%	24.6%
	+ Cu(OAc) ₂ (0.05 equiv.):		72.4%	0.5%	11.9%
	or Pb(OAc) ₂ ·H ₂ O (0.05 equiv.):		93.8%	0.2%	0.6%

palladium on alumina have been extensively used as catalysts for the oxidation of alcohols with a molecular oxygen atmosphere. Unfortunately, many studies have been reported in the patent literature or in rarely available journals. Additionally, these two heterogeneous catalysts are often used in conjunction with other transition metals to

In organic solvents at 40–80°C, palladium-supported catalysts led to the formation of γ -butyrolactone from 1,4-butanediol¹⁰⁷ and to low or modest yields of cinnamaldehyde from cinnamyl alcohol.^{88,108,109} It is, however, worthwhile to note that studies of the oxidation of geraniol in toluene and acetonitrile have highlighted a strong



Scheme 12.

influence of the method of preparation of Pd/C on the efficiency and selectivity.⁷⁷ The catalytic activity of deposited thin film Pd catalysts vis a vis the oxidation of ethanol, for example, can be increased by resonance oscillations.¹¹⁰

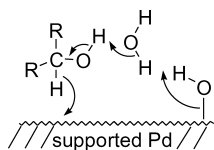
The use of sc CO₂ as a solvent and Pd/C as a catalyst has allowed the highly selective oxidation of primary alcohols to aldehydes with no metal leaching, and adding 1% Teflon to the catalyst dramatically increased its activity and lifetime.¹¹¹ In contrast, the selectivity with Pd/Al₂O₃ in sc CO₂ is low from 1-octanol, but excellent from 2-octanol.¹¹²

Palladium on zeolite has also been employed, up to 98% γ -butyrolactone being obtained from 1,4-butanediol at 118°C in *N*-methylpyrrolidin-2-one or *N,N*-dimethylpropionamide under 1 atm of oxygen.¹¹³

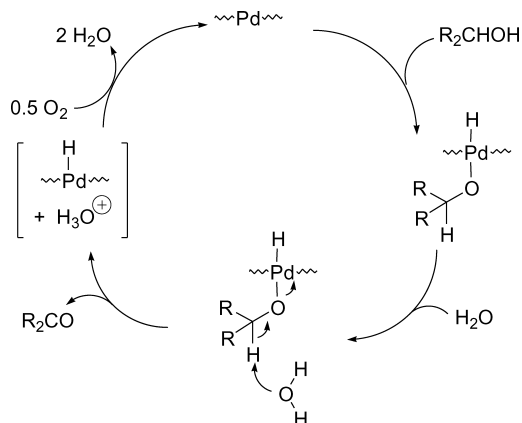
The mechanism of these heterogeneous reactions is far from being completely understood. A dehydrogenation mechanism, where the role of oxygen is to oxidize the co-produced hydrogen, was generally accepted (Scheme 12),^{92a} but this apparent agreement includes contradictory opinions.¹¹⁴

Kuster et al. have suggested that the production of R₂CO could operate in a single step, as depicted in Scheme 13.^{6f} In contrast, Griffin et al. have proposed a reaction in steps (Scheme 14).⁷⁷ In fact, alkoxide species have been identified at low temperatures from alcohols on the Pd(111) surface and they form the corresponding ketones on heating.¹¹⁵

A detailed study by Baiker et al. on the efficiency of the



Scheme 13.



Scheme 14.

oxidation of cinnamyl alcohol has concluded that, contrary to the general assumption, the major role of oxygen is the oxidative removal of CO which is produced by side reactions and this would ensure the availability of a large number of free Pd sites.¹¹⁴

3. Per-compounds as co-oxidants

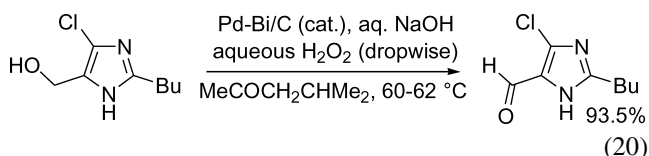
3.1. *tert*-Butyl hydroperoxide

Whereas Pd black¹¹⁶ and **5**⁸⁴ destroy *t*-BuOOH at ambient temperature, **4** slightly catalyses the oxidation of cyclohexanol: using 2 equiv. of *t*-BuOOH in acetone at room temperature for 3 h, 14% conversion of the substrate led to cyclohexanone with 93% selectivity, a lower conversion (7%) and selectivity (71%) being observed in the absence of a catalyst.¹¹⁷ In benzene at room temperature, catalysis by **2** of the oxidation of cyanohydrins with *t*-BuOOH led to unsatisfactory results.¹¹⁸

3.2. Hydrogen peroxide

Many of the aerobic procedures reviewed above produce H₂O₂ which leads to water and O₂ under the reaction conditions. Although **1** is ineffective in catalysing the decomposition of hydrogen peroxide,^{119,120} an oxidising system constituting **1**, small amounts of didecylmethylammonium bromide and an excess of 30% aqueous H₂O₂ in refluxing 1,2-dichloroethane showed a moderate activity,¹²⁰ since the conversion of benzyl alcohol reached 52% in 24 h to afford benzaldehyde and benzoic acid, the former compound being the main product.¹¹⁹

The Pd/C-catalysed oxidation of *n*-propanol by 50% H₂O₂ in trifluoroacetic acid at 90°C yields the cleavage compounds (acetic and formic acids).¹²¹ Although it was anticipated in Section 1 that bimetallic catalysts would not be included in the present review, both the efficiency and the selectivity of the heterogeneous oxidation of a functionalised imidazole accomplished by Heveling and Wellig should be mentioned (Eq. (20)).¹²²



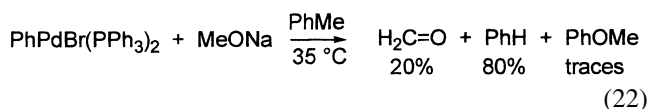
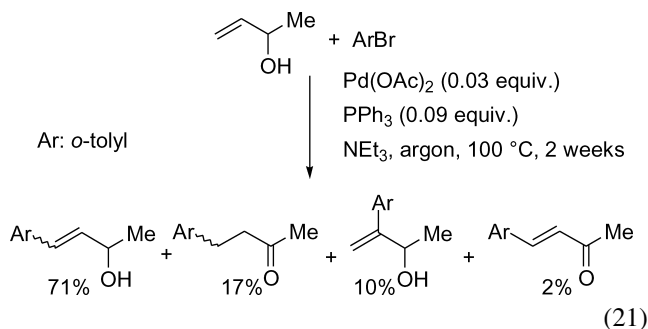
3.3. Potassium periodate

In the absence of palladium, periodic acid and periodates may lead to cleavage compounds from, in particular, alkenes and α -diols, but they are rather reluctant to react with simple alcohols.¹²³ Nandibewoor et al. have reported the addition of catalytic amounts of **1** to an alkaline aqueous

solution of KIO_4 and allyl alcohol to afford acrolein without the production of acrylic acid.¹²⁴

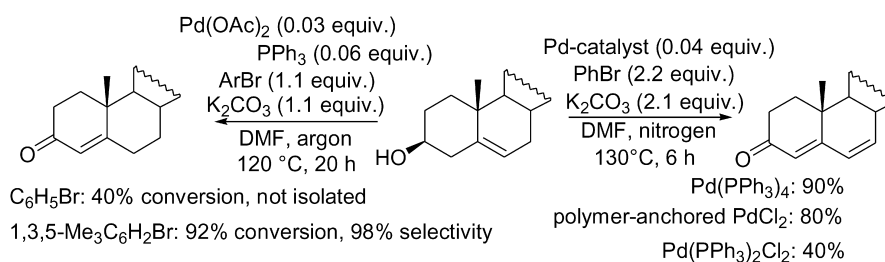
4. Halogen-based co-oxidants

In 1976, Heck and Melpolder did not comment on the formation of traces of 4-(*o*-tolyl)-3-buten-2-one that they observed as a by-product of the Pd-catalysed addition of 2-bromotoluene to 3-buten-2-ol (Eq. (21)).¹⁸ The same year, formaldehyde and benzene were obtained from the reaction of sodium methoxide and $\text{PhPdBr}(\text{PPh}_3)_2$ (Eq. (22)).¹²⁵ Two years later, it was mentioned in a footnote that formaldehyde and ArH were obtained from ArX and MeOH in the presence of $\text{Pd}(\text{PPh}_3)_4$ and NaOH.¹²⁶ We suspect that these reports have elicited research which has led to Pd-catalysed procedures for the oxidation of alcohols using aryl halides as co-oxidants.

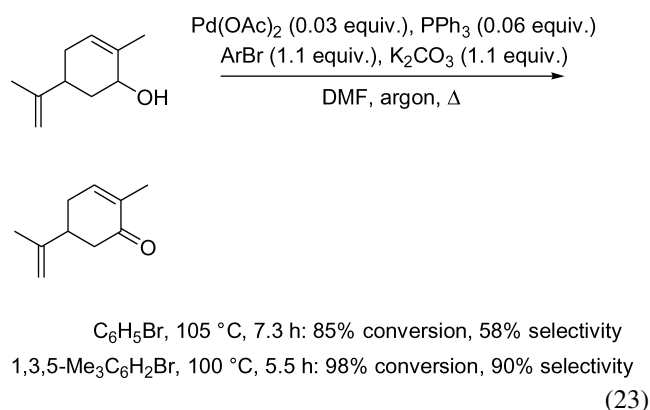


4.1. Aromatic halides

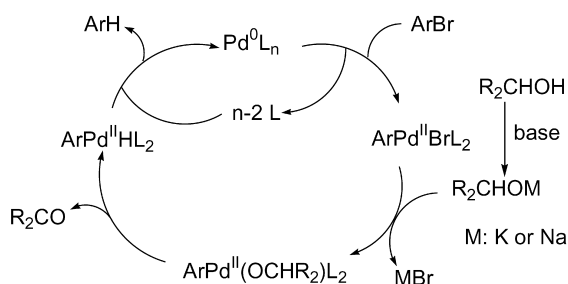
In 1979, Yoshida's team reported the effective Pd-catalysed oxidation of secondary aliphatic and benzylic alcohols using bromobenzene as the co-oxidant at 70–120°C in a basic medium.¹²⁷ Applying their protocol to secondary α,β -unsaturated alcohols was often disappointing, due to the formation of β -aryl ketones¹²⁸ through Heck reactions.^{18,19} From the examination of a range of aromatic halides as co-oxidants, they discovered that 2-bromomesitylene resulted in a much more selective oxidation procedure (Eq. (23)),¹²⁸ this sterically-hindered halide being much less prone to the Heck reaction.



Scheme 16.

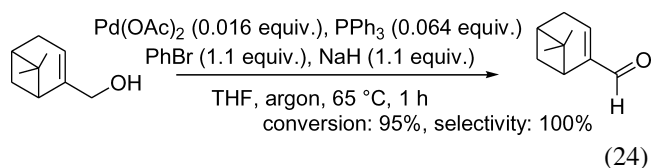


As catalyst, Yoshida's team used **4** or the association of **2** with **2** to **4** equiv. of PPh_3 (dppe as the ligand was less effective).⁴⁵ The optimum base/solvent combinations were NaH in THF or *N*-methylpyrrolidin-2-one and K_2CO_3 in DMF or DME; NaHCO_3 and NEt_3 were completely ineffective. Usually, K_2CO_3 is the base of choice, since it does not induce an aldol condensation of the products, but higher reaction temperatures and longer reaction times are required. Although the initial experiments on the oxidation of primary alcohols were disappointing,¹²⁷ a range of such alcohols was finally oxidised successfully, but the formation of a mixture of aldehydes and esters was often noted from saturated and benzylic substrates.¹²⁷ The formation of the carbonyl compound would involve a transmetalation of a sodium or potassium alkoxide with an arylpalladium^{II} complex^{129,130} (Scheme 15).^{45,131}



Scheme 15.

This methodology, even with PhBr as a co-oxidant, may be applied to the oxidation of primary allylic alcohols (Eq. (24)), but it lacks general applicability, the oxidation of geraniol being unsuccessful.¹²⁸ Various lactones have also been obtained from primary diols.⁴⁵

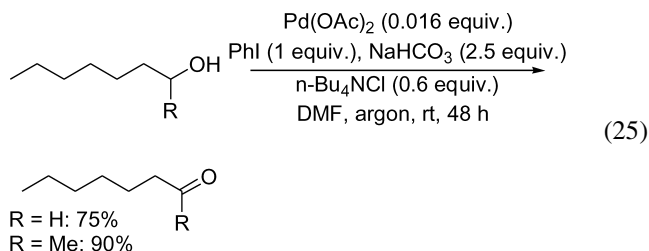


The results of the oxidation of cholesterol seem to be highly dependent on slight modifications of the experimental conditions. From Yoshida's team, the **2**/PPh₃/MesBr/K₂CO₃ method at 120°C in DMF for 20 h leads to 90% Δ⁴-cholesten-3-one,¹³² whilst with PhBr instead of MesBr,¹²⁸ cholesterol is reluctant to afford the ketone (Scheme 16). In contrast, Choudary et al. obtained Δ^{4,6}-cholestadien-3-one under various modified conditions (Scheme 16) including the use of a polymer-anchored palladium chloride containing phosphine (P/Pd=0.895).¹³³ This Pd polymer has been used for the oxidation of various sterols and it may be recycled, but with a strong decrease in activity.¹³³

We suggest that the dichotomy between Yoshida's and Choudary's results could be mainly due to the differences in the amount of the co-oxidant. When 2 equiv. of PhBr are initially present, 1 equiv. would be used for the co-oxidation of the hydroxyl group, while the other could regenerate a second stoichiometric quantity of a Pd^{II} species active for the formation of the η³-allylpalladium complex (Scheme 17). The synthesis of such a complex¹³⁴ from cholestenone and Pd^{II}, and the reductive hydride elimination from this complex leading to the diene,¹³⁵ are documented.

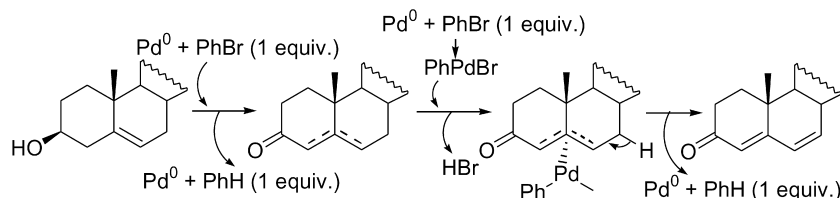
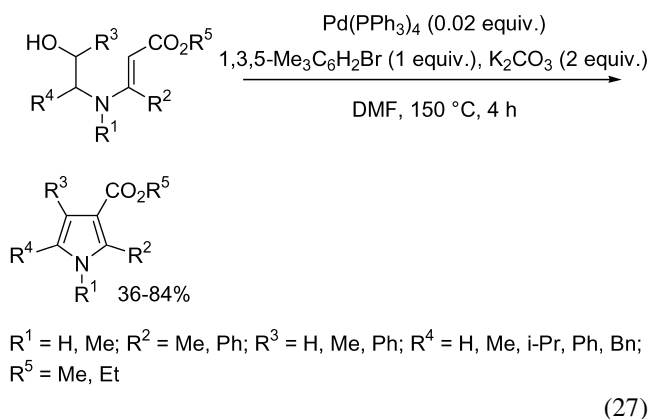
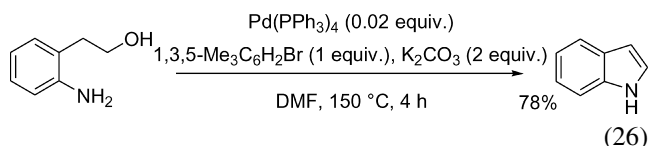
Yoshida's procedures require heating. Nevertheless, benzyl alcohol and aliphatic alcohols have been cleanly oxidised at room temperature using phenyl iodide as the co-oxidant under solid-liquid phase transfer conditions, as shown by Choudary et al. (Eq. (25)).¹³⁶ The nature of both the ammonium salt and the Pd catalyst are important: *n*-Bu₄NCl was superior to *n*-Bu₄NBr, *n*-Bu₄NI, Et₄NCl and Me₄NCl; similar yields were obtained with **1** instead of **2** while the reaction was very sluggish with PdCl₂(PPh₃)₂.¹³⁷ The relative inertness of the latter complex is surprising since the Pd/MesBr procedure requires the presence of PPh₃.¹²⁸ As an explanation, we suggest the influence of the reaction temperature: PPh₃ would be required to stabilise the Pd species at 65–105°C (Yoshida's conditions), while dissociation of the phosphine ligand from PdCl₂(PPh₃)₂,¹³⁸ which could be necessary to generate a reactive catalyst, would not be favoured at room temperature (Choudary's conditions). Since no palladium black was observed under the phase transfer conditions, we suspect stabilization of some palladium nanoparticles by the ammonium salt.^{139,140} Compared with the previous reaction conditions, the possibility of carrying out the oxidation at room temperature

may be ascribed to the more facile insertion of Pd⁰ into Ph–I than Ph–Br bonds.

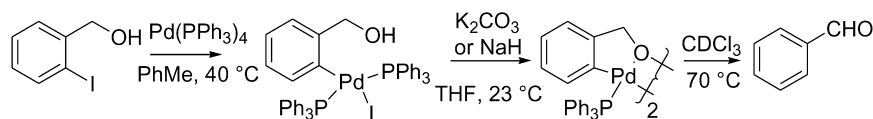


A few years later, Choudary's team disclosed a supported catalyst, montmorillonite-silylethyldiphenylphosphinepalladium^{II} chloride, to carry out molecular recognition between alcohols. This catalyst, used with PhI and K₂CO₃ in DMF at 80°C, is able to mediate oxidation in favour of *trans*-*t*-butylcyclohexanols, primary alcohols and *o*-benzyl alcohols as against *cis*-*t*-butylcyclohexanols, secondary alcohols and *p*-benzyl alcohols, respectively.¹⁴¹

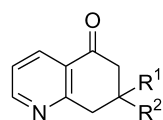
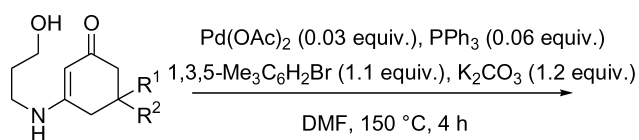
Yoshida's protocol has been applied to synthesis of indole,¹⁴² pyrroles,¹⁴² pyridines¹⁴³ and, additionally, to the effective oxidation of lactols¹⁴⁴ (Eqs. (26)–(29)).



Scheme 17.



Scheme 18.

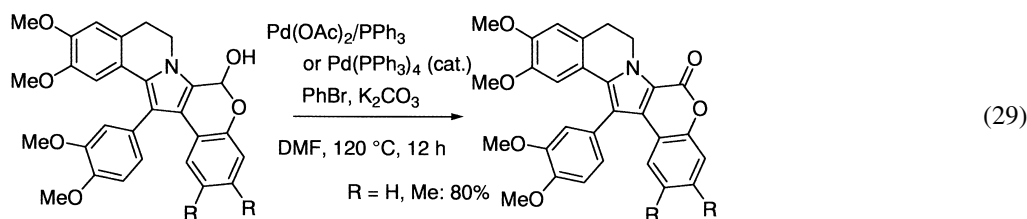


30–35%

R¹ = H, Me; R² = H, Me, CH₂OMe, CH₂OBn

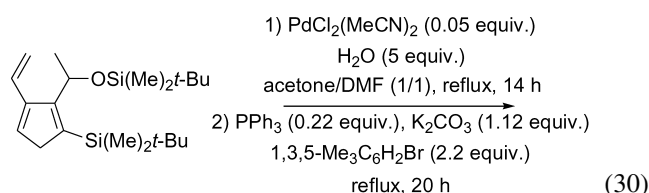
(28)

for various primary and secondary *t*-butyldimethylsilyl ethers, overoxidation of aldehydes being not detected, and it did not affect a range of other hydroxyl protecting groups, in particular, triisopropyl- and *t*-butyldiphenylsiloxy groups.^{147,148} The main limitation concerns allylic compounds, the desilylation-oxidation protocol applied to PhCH=CHCH₂OSi*t*-BuMe₂ leading to cinnamyl alcohol as the major product. A bromine atom attached to an aromatic ring of a *t*-butyldimethylsilyl ether was concomitantly removed under the reaction conditions (Eq. (31)). In this case, the role of MesBr was certainly limited, because the re-oxidation of the Pd⁰ may be mainly assumed by insertion into the Ar–Br bond of the substrate; consequently, the reaction could be, at least in part,

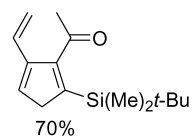


(29)

Various methods have been disclosed for the direct oxidation of silyl ethers to the corresponding carbonyl compounds, but *t*-butyldimethylsilyl ethers are reluctant to react when subjected to many of them.¹⁴⁵ Having improved Lipshutz's method¹⁴⁶ for the Pd-catalysed deprotection of these ethers by using acetone containing water as the solvent, Keay et al. proposed the one-pot procedure depicted in Eq. (30)^{147,148}



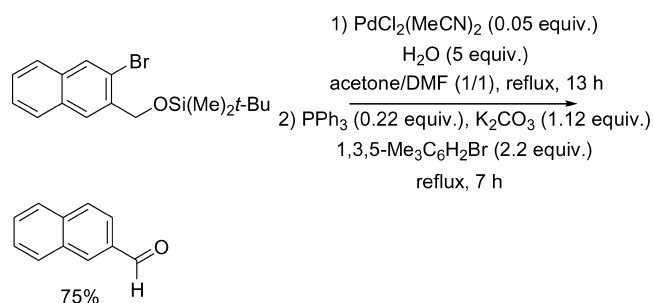
(30)



70%

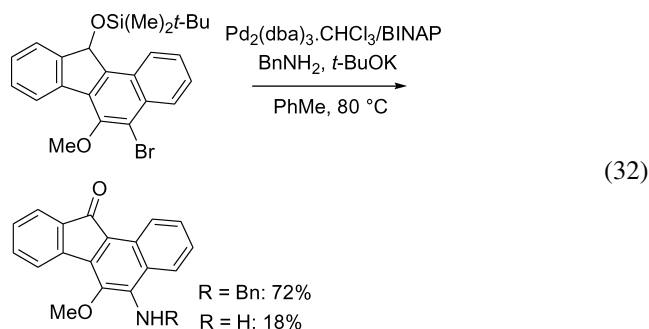
The deprotection requires the presence of water, but to perform the one-pot procedure with success, it is necessary to use a water/acetone/DMF mixture because desilylation does not take place in aqueous DMF while oxidation does not proceed in aqueous acetone. K₂CO₃ has to be introduced after the deprotection step, since this base inhibits the desilylation reaction. Interestingly, the procedure worked

intramolecular. In fact, dehalogenation–oxidation reactions from 2-bromophenethyl alcohol^{130a} and 2-bromo-3,4-dimethoxybenzyl alcohol¹⁴⁹ have been reported in the absence of aryl halide additives and, in addition, a palladacycle has been isolated from 2-iodobenzyl alcohol; on heating, it provided benzaldehyde cleanly (Scheme 18).^{150,151}



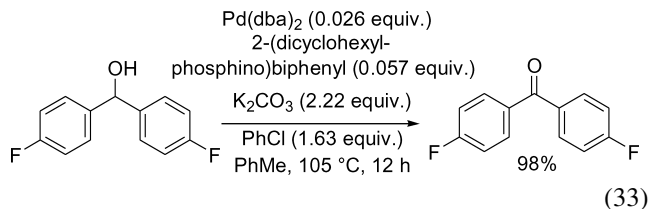
(31)

In the course of the synthesis of biologically active natural products, the reaction depicted in Eq. (32) was carried out using Buchwald's amination conditions.¹⁵² We suppose that the oxidation involves an intermolecular reaction between two substrate molecules.



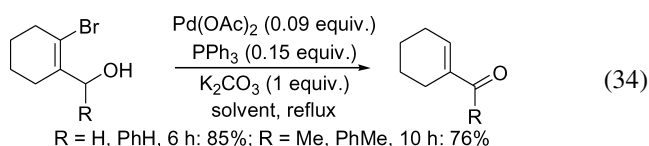
Ferreira and Stoltz, who reported the kinetic resolution of alcohols under aerobic conditions (vide supra), have briefly mentioned the moderate resolution of 1-cyclohexylethanol using **2**, (–)-Me-DUPHOS, *t*-BuONa and PhI in CH₂Cl₂ at 30°C, providing 65.5% ee at 58% conversion.⁶²

Aromatic chlorides are rather reluctant to react with palladium. Nevertheless, two patents, from Merck GmbH and from Symyx Technologies, disclose the preparation of carbonyl compounds from primary and secondary aliphatic or benzylic alcohols using either **1**, P(cyclohexyl)₃ and NaOH in refluxing 1,2,4-trichlorobenzene,¹⁵³ or Pd(dba)₂, 2-(dicyclohexylphosphino)biphenyl, K₂CO₃ and PhCl in PhMe at 105°C (Eq. (33)).¹⁵⁴



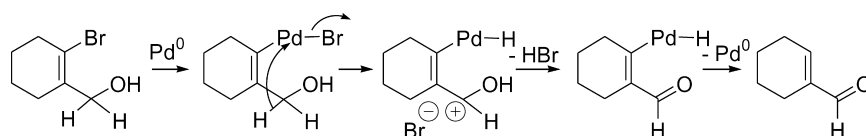
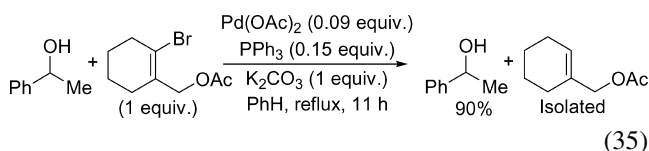
4.2. Vinylic bromides

Vankar et al. have obtained unsaturated carbonyl compounds from the intramolecular reaction of γ (or ω)-hydroxy vinylic bromides (Eq. (34)). They proposed a reaction scheme through a hydride transfer from a Heck-type complex (Scheme 19).¹⁵⁵

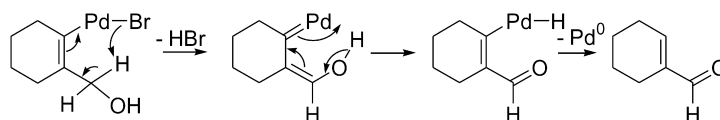


On the basis of the literature reports, we envision two alternative mechanisms, both starting from the Heck-type complex. The first would involve a palladium–carbene complex¹⁵⁶ (Scheme 20), whereas the second would implicate a palladacycle^{130d,150} (Scheme 21). This latter corresponds to the usual formation of an alkoxy-palladium intermediate from an alcohol and Pd^{II}, a reaction promoted by basic media, and has been established from 1-(*n*-hydroxyalkyl)-2-bromobenzene (vide supra).

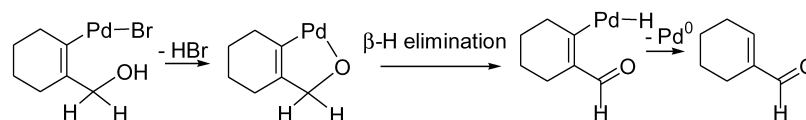
An intermolecular variation of the above procedure has been applied to the oxidation of secondary aliphatic and benzylic alcohols (Eq. (35)).¹⁵⁵



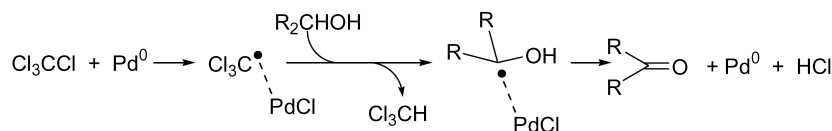
Scheme 19.



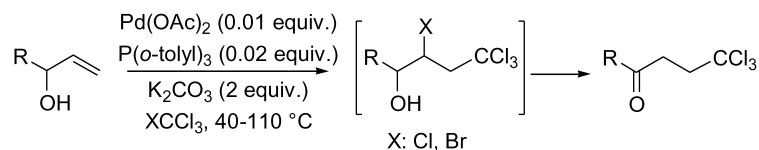
Scheme 20.



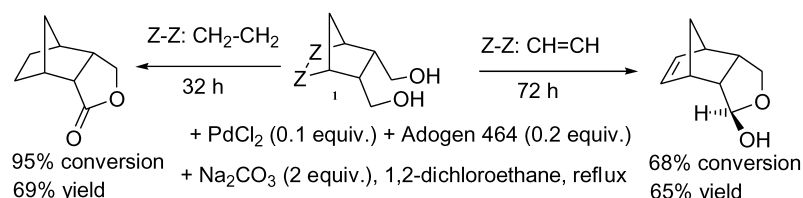
Scheme 21.



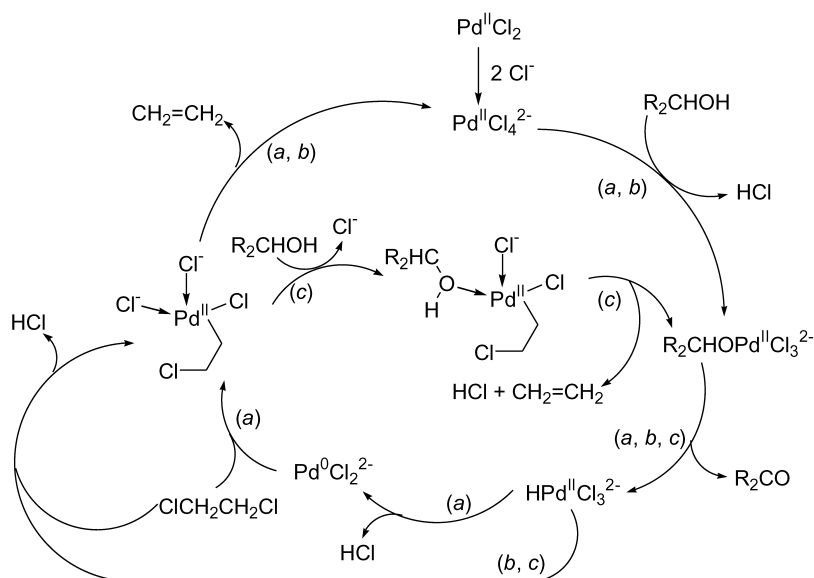
Scheme 22.



Scheme 23.



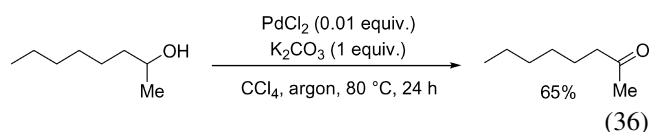
Scheme 24.



Scheme 25.

4.3. Carbon tetrachloride

Carbon tetrachloride has been used by Tsuji et al. as both a solvent and a co-oxidant for the oxidation of secondary aliphatic and benzylic alcohols (Eq. (36)). Instead of a mechanism similar to that of the reactions with aromatic halides (Scheme 15), the authors presented arguments for H-abstraction from the alcohols by a trichloromethyl radical generated by Pd⁰ catalysis (Scheme 22).^{157,158}



Primary alcohols are also oxidised, but esterification, especially from aliphatic substrates, takes place. Allylic alcohols having the double bond in a terminal position did not afford the corresponding ketones because CCl₄ readily underwent Pd-catalysed addition to the double bond. This addition, which occurred to a limited extent in the absence of phosphine, involves a halohydrin as an intermediate

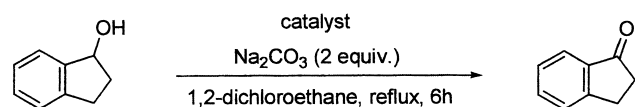
which provides the ketone by Pd catalysis (Scheme 23).^{158,159} Similarly, the conversion of isolated halohydrins to ketones was successfully catalysed by palladium.¹⁶⁰

4.4. 1,2-Dichloroethane

In screening the ability of various metal chlorides to catalyse the oxidation of 1-indanol by sodium percarbonate,¹⁶¹ we have disclosed the oxidation of primary and secondary, saturated, allylic or benzylic, alcohols in refluxing 1,2-dichloroethane using sodium carbonate and a 1/2 mixture of **1** and an ammonium salt, in particular Adogen 464[®], as the catalyst, neither hydrogen peroxide nor oxygen being required.^{16,162} Performing the reaction in the absence of the base or the ammonium salt greatly reduced the conversion of the alcohols. High selectivities were obtained from secondary saturated and benzylic alcohols (Eq. (37)), while primary alcohols afforded mixtures of aldehydes and esters (Eq. (38)). The migration of the double bond of linear allylic alcohols was a competing reaction (Eq. (38)). Under such conditions, various lactones have been obtained from 1,4 and 1,5-diols, but the presence of a C=C double bond in the substrate may stop the reaction at

the level of the lactol (Scheme 24).¹⁶³ This has been explained by inhibition of the β -hydride elimination because of the coordination of the double bond to an alkoxypalladium intermediate.¹⁶⁴

been used from time to time to improve the efficiency of the Pd-catalysed aerobic oxidation of alcohols. They have also been used in stoichiometric amounts for anaerobic oxidations, as shown below.



PdCl_2 (0.1 equiv.) + Adogen 464 (0.2 equiv.): 100% conversion, 86% yield

$\text{PdCl}_4(n\text{-Bu}_4\text{N})_2 \cdot 0.5\text{H}_2\text{O}$ (0.1 equiv.): 94% conversion, 92% yield

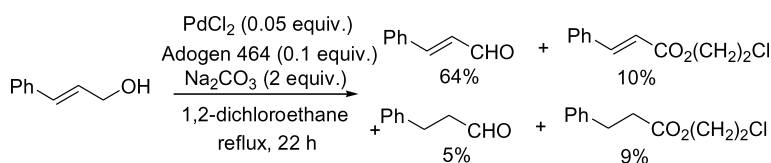
PdCl_2 (0.1 equiv.): 19% conversion, 0% yield^a

^adi(1-indanyl) oxide (19% yield) was obtained

$\text{PdCl}_2(\text{MeCN})_2$ (0.1 equiv.): 100% conversion, 0% yield^b

^bdi(1-indanyl) oxide (98% yield) was obtained

(37)



(38)

Since the oxidation reaction also produced ethylene arising from some concomitant dehalogenation of the solvent, we initially suspected a re-oxidation of Pd^0 by insertion into a C–Cl bond of the solvent, followed by a β -Cl elimination of $\text{Pd}^{\text{II}}\text{Cl}_2$.¹⁶ Such a reoxidation was already documented.¹⁶⁵ Subsequently, we observed that the complex $\text{PdCl}_4(n\text{-Bu}_4\text{N})_2 \cdot 0.5\text{H}_2\text{O}$ led to results similar to the combination 1/2 Adogen 464[®] (Eq. (37))¹⁶⁶ and we demonstrated the critical role of the coordination environment of palladium dichloride on the course of its reaction with secondary benzylic alcohols⁷² (Eq. (37)). Finally, a computational study was in agreement with the regeneration of Pd active species from $[\text{HPd}^{\text{II}}\text{Cl}_3]^{2-}$ (Scheme 25, path *b*), rather than $[\text{Pd}^0\text{Cl}_2]^{2-}$ (Scheme 25, path *a*).¹⁶⁷ In addition, a recent report led us to conclude the relative stability of the HPdCl species obtained from the reaction of **1** with alcohols,¹⁶⁸ and, besides, calculations suggest the possibility of a $\text{Cl}^-/\text{R}_2\text{CHOH}$ ligand exchange at the level of the $[\text{ClCH}_2\text{CH}_2\text{-Pd}^{\text{II}}\text{Cl}_3]^{2-}$ (Scheme 25, path *c*).¹⁶⁷ In this process, the base has, in all probability, the dual role of trapping HCl and promoting the formation of the alkoxypalladium intermediate.

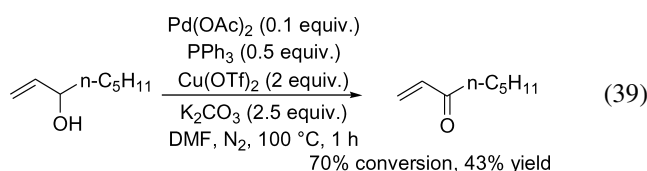
4.5. *N*-Halosuccinimides

N-Halosuccinimides have been used for the oxidation of alcohols in the absence of a metal catalyst.¹⁶⁹ Nevertheless, the influence of Pd^{II} catalysis on the kinetics of the oxidation of carbohydrates by *N*-bromosuccinimide in aqueous media has been studied.¹⁷⁰ Oxidation, in a basic medium, of allyl alcohol by *N*-chlorosuccinimide in the presence of catalytic amounts of **1** or $\text{Pd}(\text{NO}_3)_2$ afforded acrolein.¹⁷¹

5. Metal salts as co-oxidants

As described in Section 2, small amounts of metal salts have

In the course of studies of the Pd-catalysed arylation of allylic alcohols in the presence of stoichiometric amounts of $\text{Cu}(\text{OTf})_2$, Satoh et al. have observed the formation of β -aryl- α,β -unsaturated ketones as the main compounds.¹⁷² Traces of such products were previously observed on one occasion in the absence of copper under Heck experimental conditions (Eq. (21)).¹⁸ On repeating the experiment in the absence of halide, Satoh et al. have observed the oxidation of the allyl alcohol¹⁷² under nitrogen¹⁷³ (Eq. (39)).

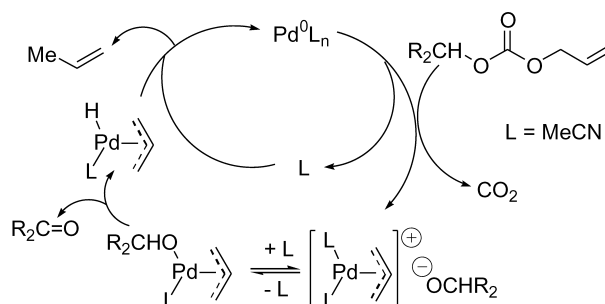


(39)

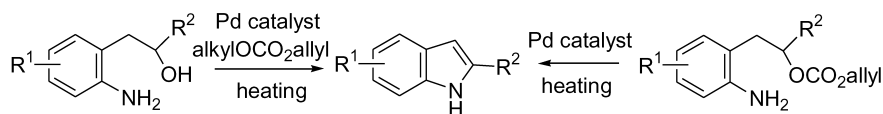
Manganese^{III} acetate has rarely been used for the oxidation of alcohols.¹⁷⁴ In combination with Pd^{II} , it affords acrolein as the main product from allyl alcohol.¹⁷⁵

6. Allyl-X as hydrogen acceptors

In 1984, Tsuji's team reported the conversion of alkyl allyl carbonates to ketones and aldehydes using catalytic

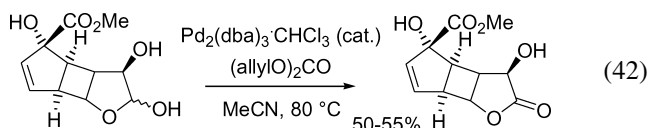
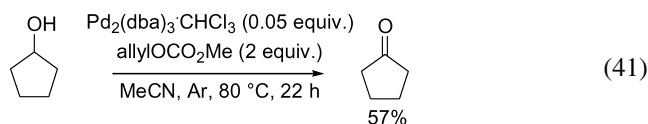
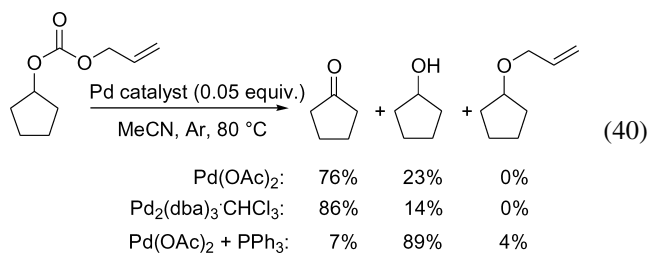


Scheme 26.

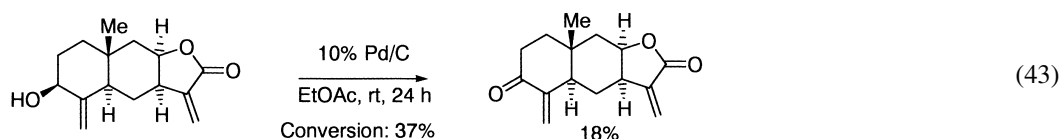


Scheme 27.

amounts of **2** in refluxing dry acetonitrile for 1–2 h.¹⁷⁶ High yields were obtained, except from carbonates derived from saturated primary alcohols. The cascade reaction was actually induced by Pd⁰, with Pd₂(dba)₃·CHCl₃ eventually improving the selectivity,¹⁷⁷ but it has to be carried out in the absence of phosphine (Eq. (40)). Since the catalytic cycle involves an η³-allylpalladium intermediate (Scheme 26), the oxidation was tentatively carried out directly from alcohols in the presence of allyl methyl carbonate, but a lower yield was obtained (Eq. (41)).¹⁷⁸ Nevertheless, this procedure of changing allyl methyl carbonate for diallyl carbonate has allowed the successful oxidation of highly-functionalised lactols to the corresponding lactones (Eq. (42)).¹⁷⁹ A Japanese patent has described the synthesis of indoles from *o*-aminophenylethanols using the above methodologies (Scheme 27), the reaction involving oxidation of the hydroxy group, addition of the amine to the carbonyl moiety, dehydration and migration of the formed double bond.¹⁸⁰



More recently, Shvo et al. obtained 10% of 2-cyclohexen-1-one from cyclohexanol and 75% cholesta-1,4,6-trien-3-one from cholesterol on submitting these ketones to catalytic amounts of **2** in refluxing THF in the presence of allyl



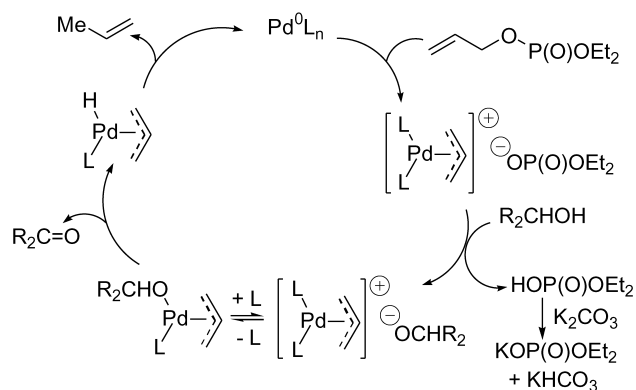
diethyl phosphate (ADP).¹⁸¹ These observations prompted the team to examine the Pd-catalysed oxidation of 2-octanol with ADP as a hydrogen acceptor.¹⁸² The screening of solvents (THF, DMF, DMSO or MeCN), bases (Na₂CO₃ or K₂CO₃), catalysts (**2**, **2**+PPh₃ or Pd₂(dba)₃·CHCl₃) and

other allyl systems (allylBr, allylOAc or allylOCO₂Me) at 86°C showed the formation of 2-octanone under these conditions except with allylBr, the best yield (85%) being obtained in DMF with K₂CO₃ (2 equiv.), ADP (1.3 equiv.) and **2** (0.04 equiv.). The method was successfully applied to primary and secondary benzylic alcohols, benzoin, menthol and cinnamyl alcohol. In contrast to benzylic alcohols, a primary alcohol such as 1-octanol led to octyl octanoate and this has been attributed to the difference in the facility of hemi-acetal formation between aromatic aldehydes and aromatic aldehydes. The selectivity was low from a secondary allylic alcohol, e.g. 47% for the oxidation of 1-octen-3-ol into 1-octen-3-one. Cyclohexanol led to a mixture of cyclohexanone and 2-cyclohexen-1-one. On the basis of ¹H NMR studies, Shvo et al. constructed the catalytic cycle depicted in Scheme 28. Since polar solvents have to be used, we suspect that their coordination to palladium stabilised the species implicated in the catalytic cycle.

7. Double bonds as hydrogen acceptors

The disproportionation in methanol of secondary aryl alcohols over Pd/C at room temperature under a nitrogen atmosphere was explained by the formation of PdH₂; under such conditions, benzyl alcohol and simple allyl alcohols were unaffected, while cinnamyl alcohol afforded cinnamaldehyde and 3-phenylpropanol.⁷⁶ These observations have prompted the hydrogenolysis of benzyloxy groups using PhCHOHMe as a hydrogen donor.⁷⁶ By heating to 80–110°C, benzyl alcohol also becomes a hydrogen donor and this has allowed crossover transfer hydrogenation to α,β-unsaturated carbonyl compounds.¹⁸³ Prior to these reports, Herz et al., in looking for a Pd-catalysed isomerization of the C=C double bond of a secondary allylic alcohol, incidentally discovered the first oxidation of an allylic alcohol over Pd/C (Eq. (43)), the best result, obtained with a pre-reduced Pd/C, leading nevertheless to a low transformation and selectivity (18% yield at 37% conversion).¹⁸⁴ Since the material balance of this reaction corresponds to a deficiency of 19%, we suspect that this deficit may be due to the formation of hydrogenated compounds by transfer hydrogenation.

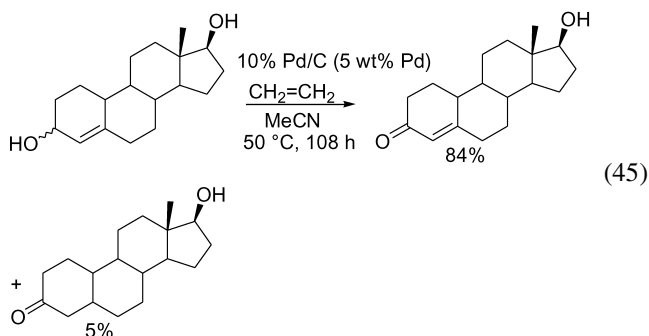
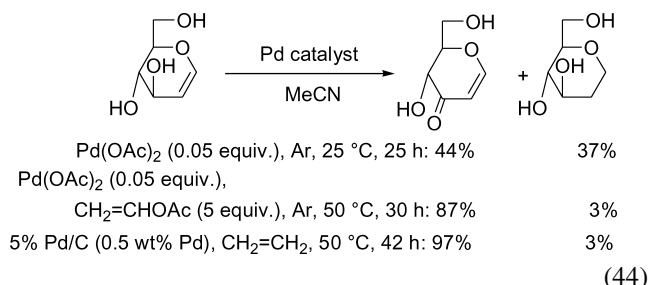
The oxidation of alcohols through Pd-catalysed hydrogen transfer was firstly developed by Hayashi's team. They originally observed the concomitant oxidation and hydrogenation of the secondary allylic alcohol of D-glycals leading to an approximately 1/1 mixture of the corresponding



Scheme 28.

α,β -unsaturated ketones and saturated alcohols using MeCN¹⁸⁵ or DMF as solvent and **2** as catalyst at 25°C (Eq. (44)).¹⁸⁶ The recovered palladium precipitate, which was formed immediately after mixing the solution, also catalysed the reaction. The use of **1** alone was ineffective, while its association with NaOAc (2 equiv./Pd) afforded results similar to **2**. These observations led Hayashi et al. to carry out the oxidation using ethylene¹⁸⁶ and vinyl acetate¹⁸⁷ as the hydrogen acceptor and the selectivity towards the ketone was greatly increased (Eq. (44)). Palladium also precipitated under these conditions, but its re-use now presented an activity similar to the original catalyst.^{1g,188} This led to the successful reaction with

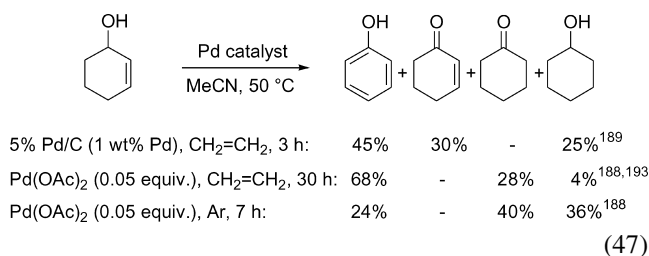
of compounds (Eq. (47)), phenol being quantitatively obtained when cyclohex-2-en-1-ol was submitted to the **2**/ethylene protocol.^{193,194}



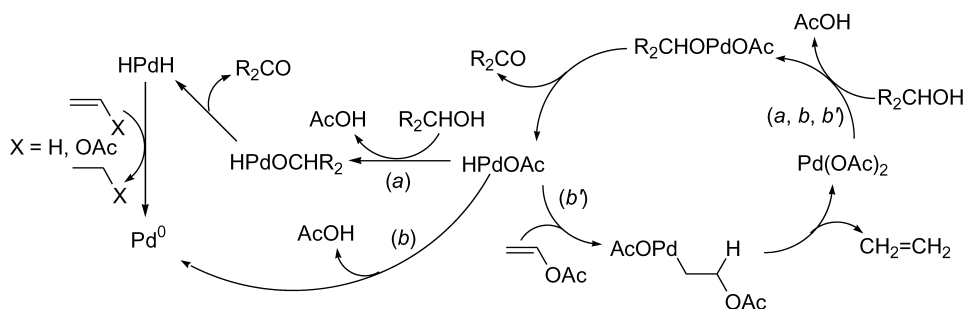
	Conv. %	Yield %
10% Pd/C (2 wt% Pd), CH ₂ =CH ₂ , MeCN, 50 °C, 48 h:	-	78 ^{188,193}
10% Pd/C (5 wt% Pd), CH ₂ =CH ₂ , H ₂ O, 80 °C, 16 h:	-	100 ¹⁹⁰
10% Pd/C (5 wt% Pd), CH ₂ =CH ₂ , neat, 80 °C, 16 h:	-	84 ¹⁹⁰
5% Pd/C (5 wt% Pd), C ₆ H ₁₀ (5 equiv.), C ₆ H ₁₂ , 80 °C, 1 h:	93	86 ²⁰¹
As above plus NEt ₃ (1 wt%):	91	90.5 ²⁰¹
5% Pd/Al ₂ O ₃ (5 wt% Pd), C ₆ H ₁₀ (5 equiv.), C ₆ H ₁₂ , 80 °C, 5 h:	93	93 ²⁰¹
5% Pd/CaCO ₃ (5 wt% Pd), C ₆ H ₁₀ (5 equiv.), C ₆ H ₁₂ , 80 °C, 5 h:	79	79 ²⁰¹
5% Pd/TiO ₂ (5 wt% Pd), C ₆ H ₁₀ (5 equiv.), C ₆ H ₁₂ , 80 °C, 5 h:	93	91 ²⁰¹
5% Pd/organopolysiloxane (5 wt% Pd), C ₆ H ₁₀ (5 equiv.), C ₆ H ₁₂ , 80 °C, 5 h:	96	95 ²⁰¹

(46)

commercial 5% Pd/C (Eq. (44)),¹⁸⁹ Pd black being less reactive.¹⁹⁰ Surprisingly, it was found that the choice of the best hydrogen acceptor depended of the nature of the catalyst, vinyl acetate exhibiting a higher reactivity than ethylene with **2**,¹⁹¹ while ethylene had to be used with Pd/C to obtain an efficient reaction.¹⁸⁹ These procedures were applied to the selective oxidation of primary and secondary benzylic or allylic alcohols to the corresponding carbonyl compounds. Inactivated alcohols were unmodified¹⁹² (Eq. (45))^{188,193} and, hence, ethanol^{1g} and even water¹⁹⁶ (Eq. (46)) could be used as the solvent. A limitation of the procedure for allylic alcohols is the oxidation of cyclohex-2-en-1-ol, which, under various conditions afforded a mixture



According to the authors, the details of the mechanisms are not clear at present.^{190,195} Even with **2** as the catalyst, the reaction was heterogeneous as the reaction proceeded. It is unquestionable that ethylene and vinyl acetate play the role

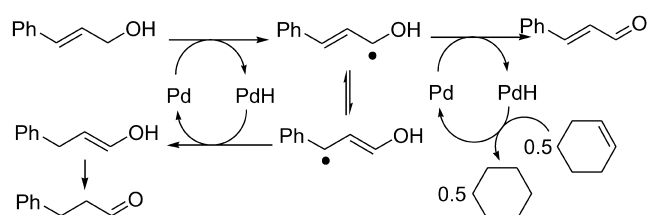


Scheme 29.

of hydrogen acceptors, since the generation of ethane and ethyl acetate has been confirmed by GLC analysis, and it was therefore concluded that the most probable catalytic cycle operates with a Pd^0 species independently of the nature of the initial catalyst.¹⁹⁰ It has been proposed that the formation of a Pd^0 species from **2** was due to the oxidation of two molecules of alcohol (Scheme 29, path *a*).^{186,187} With regard to the formation of Pd^0 through the customary elimination pathway of HOAc from HPdOAc (Scheme 29, path *b*), it is usually considered that this reaction is assisted by a base¹⁹⁶ and that its reversibility is possible under neutral conditions.^{73,197} Nevertheless, in the case of **2** as the initial catalyst, the higher reactivity with vinyl acetate as the hydrogen acceptor compared to ethylene led us to suspect some regeneration of $\text{Pd}(\text{OAc})_2$ owing to a β -OAc elimination, as shown in Scheme 29, path *b'*; similar β -OAc eliminations have been documented in particular for the Heck reactions on vinyl acetate.^{198,199} If path *b'* is operative, the oxidation process using **2** as the starting catalyst would operate following two concurrent mechanisms involving Pd^0 and Pd^{II} species, respectively, as the active catalyst. To examine this possibility, we carried out the **2**-catalysed oxidation of D-glucal in MeCN at 50°C in the presence of vinyl acetate to look for the production of ethylene with the methodology we used previously (trapping of ethylene by bromine).¹⁶ In fact, we did not detect the

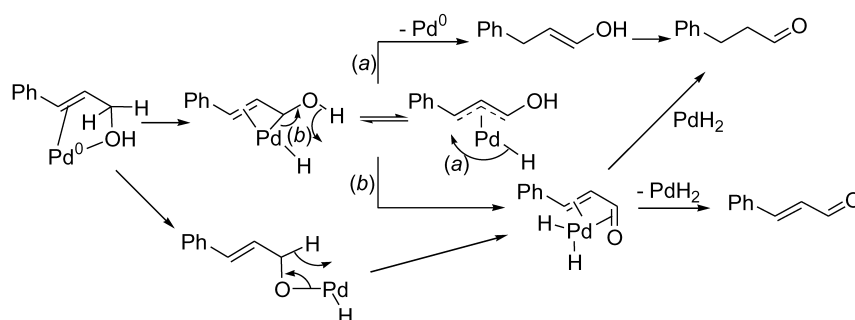
formation of ethylene.²⁰⁰ In conclusion, Hayashi's proposal (Scheme 29, path *a*) should be taken as the most plausible possibility for such oxidations.

The Pd/C protocol of Hayashi (ethylene atmosphere, MeCN as the solvent, 50°C) led to high yields from secondary allylic and benzylic alcohols, but the drawback of the method is the long reaction times, usually a few days (Eq. (46)). In screening a range of hydrogen acceptors, Baiker et al. have been able to obtain a faster reaction with cyclohexene in cyclohexane at 80°C.²⁰¹ With Pd/C as the catalyst and 1-phenylethanol as the substrate, NEt_3 was added to prevent the hydrogenolysis of the C–OH bond²⁰² (Eq. (46)). Changing the catalyst for other supported Pd catalysts did not require the presence of NEt_3 to maintain the high selectivity (Eq. (46)), Pd/ Al_2O_3 being the optimum catalyst which may be used in solvents such as heptane and toluene, while the oxidation is less efficient in acetonitrile. Various secondary benzylic alcohols were reacted using the Pd/ Al_2O_3 – C_6H_{10} method, but the success of the oxidations was highly dependent on the structure of the substrate. The method led to a low conversion from benzyl alcohol and a low selectivity from allylic alcohols, whereas aliphatic alcohols were unreactive. Baiker et al. explained the formation of some 3-phenyl-1-propanal and cinnamaldehyde from cinnamyl alcohol by a Pd-catalysed H-abstraction of a hydrogen *gem* to the hydroxy to afford the corresponding allylic radical; this intermediate would evolve either to the enol by isomerisation and fixation of H, followed by enol-keto tautomerisation leading finally to 3-phenyl-1-propanal, or by homolytic cleavage of the O–H bond to afford cinnamaldehyde (Scheme 30). Nevertheless, other mechanisms which show, in part similarities with that above, but without radical intermediates, are plausible (Scheme 31).

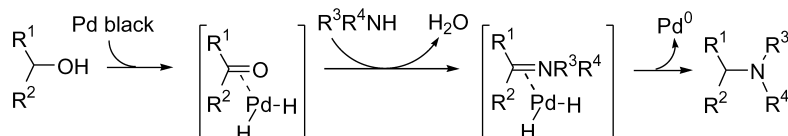


Scheme 30.

In using molten tetra-*n*-butylammonium bromide as the solvent, we have observed the oxidation of indan-1-ol to

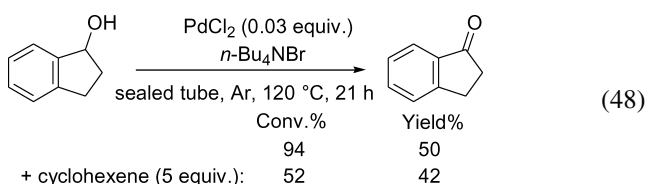


Scheme 31.

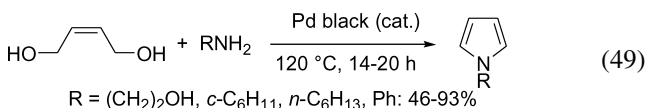


Scheme 32.

indan-1-ol in the presence of catalytic amounts of **1**, but with a low selectivity because of the concurrent hydrogenolysis reaction leading to indane. The use of cyclohexene as a hydrogen trap allowed a strong increase in the selectivity, but was detrimental to the conversion, probably because of the competitive coordination of palladium to the hydrogen acceptor (Eq. (48)).²⁰³



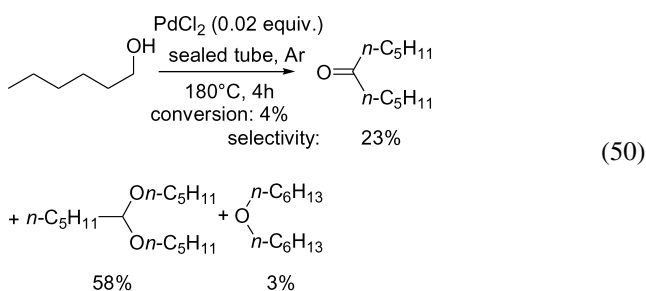
Another type of hydrogen transfer has been reported by Murahashi et al. for the synthesis of secondary and tertiary amines from the one-pot reaction of benzylic alcohols or allyl alcohol with primary or secondary amines over palladium black at 80–120°C²⁰⁴ and this appears to involve the reduction of in situ produced imines (Scheme 32).²⁰⁵ With this procedure, *N*-substituted pyrroles were also prepared in fair to excellent yields from but-2-en-1,3-diol and primary amines (Eq. (49)).²⁰⁴



8. Oxidations without co-oxidants or hydrogen acceptors

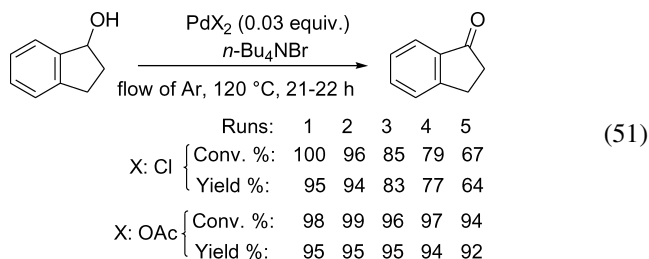
Pd-catalysed oxidations of alcohols in the absence of a co-oxidant or a hydrogen acceptor have often been carried out at high temperatures, leading to unselective production of the corresponding carbonyl compounds. Even at 80°C, palladium may induce dehydration of the alcohol,^{79c} and, hence, only a few papers related to these conditions will be mentioned here.

Heating 1-hexanol at 180°C in a sealed tube in the presence of catalytic amounts of **1** induced a low and unselective conversion of the substrate (Eq. (50)).²⁰⁶ A very low conversion and selectivity have also been obtained from cyclohexanol at 200°C over Pd/C in a flow reactor.²⁰⁷



The dehydrogenation of cinnamyl alcohol by **5** and **7** at 50–60°C was observed under nitrogen, but with **8** and **4** as the TONs instead of **26** and **30**, respectively, under oxygen.^{85,88} A low conversion of this alcohol was also reported over Pd/Al₂O₃ in PhMe at 65°C under argon.¹¹⁴

As noted in Section 7, indan-1-ol led to indan-1-one and indane when submitted to **1** catalysis in molten *n*-Bu₄NBr (Eq. (48)) but the same reaction carried out under a gentle flow of argon yielded 95% of indan-1-one. Interestingly, the system—**1**+*n*-Bu₄NBr—was recyclable, but gradually loses its oxidative properties (Eq. (51)). A high selectivity was also obtained using palladium black instead of **1** indicating a catalysis by Pd⁰.²⁰³ Quite recently, we have discovered that **2** as a catalyst improved the efficiency of the oxidation of 1-indanol and also the recycling ability (Eq. (51)).²⁰⁸ Preliminary studies suggest the formation of nanoparticles from **1** and **2** under these experimental conditions.²⁰⁹



The selectivity obtained using this protocol is due to the removal of hydrogen gas as soon as it is produced; this implies a low stability under these reaction conditions of the dihydridopalladium formed by dehydrogenation of the alcohol. Changing *n*-Bu₄NBr for *n*-Bu₄NCl, *n*-Bu₄NOAc or Adogen 464[®] was unsatisfactory. High selectivities have been observed from a range of secondary, linear or cyclic benzylic alcohols. In contrast, oxidation of primary benzylic alcohols was less satisfactory, naphthalenemethanols suffering from some hydrogenolysis, while benzyl alcohol led to benzaldehyde, toluene and *n*-butyl benzoate. This latter compound was the main product and was formed by the reaction of benzoic acid with the ammonium salt. We have proposed that PhCO₂H was produced by a dismutation-type of PhCO₂H mediated by palladium.²⁰³ Saturated alcohols were unreactive under these conditions while allylic alcohols yielded mainly saturated ketones (Eq. (52)).²⁰⁸

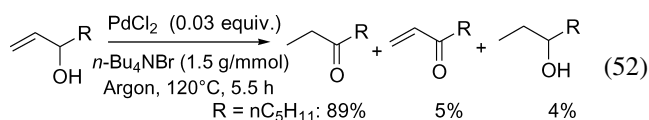


Chart 1. Reactivity of alcohols towards main convenient catalytic oxidation procedures

Method	Alcohol ^a					
	Aliphatic		Benzylic		Allylic	
	Prim.	Sec.	Prim.	Sec.	Prim.	Sec.
1, NaOAc, O ₂ , ethylene carbonate, 38°C		+++	+++		–	–
2, O ₂ , DMSO, 80°C			+++	+++ ^b	+++	+++ ^b
2, py, 3 Å MS, O ₂ , PhMe, 80°C	+++	+++	+++	+++	+++	+++
2, NEt ₃ , 3 Å MS, O ₂ , THF–PhMe, rt	+++	+++	+++	+++	+	+++
2, phen * ^c , NaOAc, O ₂ , H ₂ O, 100°C	+++ ^d	+++	++	+++	++	++
2, O ₂ , [C ₄ mim][BF ₄], 80°C			+++	+++		
3, py, 3 Å MS, O ₂ , PhMe, 80°C	++	+++		+++		
4, O ₂ , PhMe, 100–110°C					+++ ^e	++
5 or 7, O ₂ , neat or PhMe or AcOH, rt–60°C ^f	+	+	+	+	+++	+
Pd/C, aqueous basic medium	+++ ^g		+++		+	
2, PPh ₃ , base, ArBr, THF or DMF, 70–120°C	+++	+++	+++	+++	+++	+++
2, NaHCO ₃ , <i>n</i> -Bu ₄ NCl, PhI, DMF, rt	+++	++	+++			
1, K ₂ CO ₃ , CCl ₄ , 80–120°C	+++ ^h	++	+	++	i	i
1, Adogen 464, Na ₂ CO ₃ , ClCH ₂ CH ₂ Cl, 82°C	+	++	++	+++	++	++
2, K ₂ CO ₃ , ADP, DMF, 86°C	+	+++	+	++	+	+++
Pd/C, CH ₂ =CH ₂ , MeCN, 50°C	–	–	+	+++	+	++
Pd/Al ₂ O ₃ , cyclohexene, cyclohexane, 80°C	–	–	+	+++	+	+
1, <i>n</i> -Bu ₄ NBr, stream of argon, 120°C	–	–	+	+++	+	+

Efficiency of the formation of the corresponding carbonyl compound; high: +++, medium: ++, low: +, unreactivity of the alcohol.

^a Prim.: primary alcohol, sec.: secondary alcohol.

^b In the presence of 2 equiv. of NaHCO₃.

^c Phen*: 4,7-diphenyl-1,10-phenanthrolinedisulfonic acid.

^d In the presence of a radical scavenger.

^e In the presence of NH₄PF₆.

^f Reaction in aqueous solution of K₂CO₃; formation of the carboxylic acid.

^g Formation of the carboxylic acid.

^h Formation of the ester.

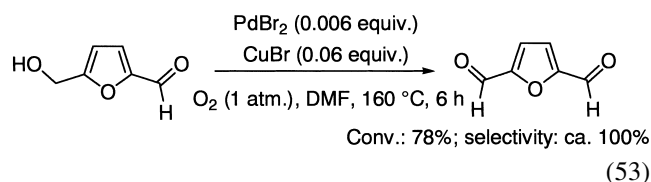
ⁱ Addition of CCl₄ across the double bond.

9. Conclusions

Since the discovery of the stoichiometric oxidation of alcohols by Pd^{II}, a variety of methods have been disclosed which require solely catalytic amounts of palladium to provide high yields of the corresponding carbonyl compounds from a range of alcohols, a possible limitation being multi-functionalised substrates which form too stable complexes with palladium. The mechanistic pathways associated with these methods are relatively well established, although some disputes may continue. In the context of ‘Green Chemistry’,²¹⁰ the recycling of the catalyst and even the solvent is without doubt an important advantage of some of these methods. The ability to use readily available, often commercial, catalysts is also of great interest because this allows an opportunity to quickly determine if a particular alcohol can be efficiently oxidised under Pd catalysis. The methods described in this review which seem to be the most convenient for use by bench organic chemists are summarized in Chart 1, to enable an easy visualisation of the possible reactivity of different alcohols under different procedures.

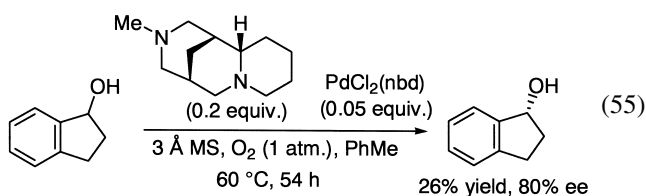
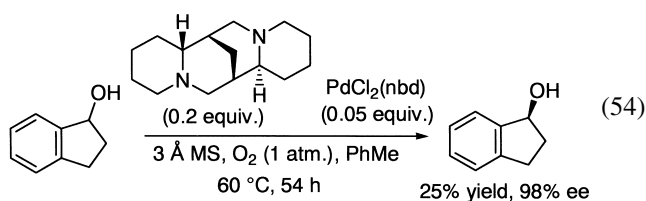
10. Note added in proof

Grushin et al. succeeded to oxidise 5-(hydroxymethyl) furfural to 2,5-diformylfuran using catalytic amounts of both PdBr₂ and CuBr under oxygen (Eq. (55)),²¹¹ while Larock’s method³³ led to less than 10% conversion and attempts with Sheldon’s catalyst⁵⁹ were unsuccessful.



Parallel experimentation methods have been used by Sheldon et al. to investigate the electronic effects in the (diimine)Pd^{II}-catalysed aerobic oxidation of alcohols in water from the viewpoint of the catalyst and the alcohol.²¹² The new results are in accordance with the mechanism they previously proposed (Scheme 8),²² and the evolution of the cationic alkoxy palladium intermediate, [(diimine)PdOCHR₂]⁺, by hydride migration from the alkoxide to palladium rather than through a bimolecular reaction involving the abstraction of the hydrogen by a base, was assumed.

Stoltz et al. have reported that the addition of Cs₂CO₃ and *t*-BuOH to their PdCl₂(ndb)/(–)-sparteine/O₂/3 Å MS/PhMe system⁶² provided a dramatic rate acceleration in the kinetic resolution of secondary benzylic and allylic alcohols, the selectivity of the process being maintained.²¹³ Using the initial conditions of Stoltz⁶² with either (–)-sparteine (Eq. (53)) or a (+)-sparteine surrogate (Eq. (54)) as resolving agent, O’Brien et al. have isolated (*S*)- and (*R*)-enantiomers of indanol respectively.²¹⁴ Mueller and Sigman have elucidated the mechanism details of these Pd^{II}/sparteine-mediated resolutions^{62–66} prior to catalyst turnover.²¹⁵



Additional studies of the aerobic oxidation of aliphatic alcohols in organic solvents²¹⁶ and glycerol in aqueous solutions²¹⁷ catalysed by supported Pd-catalysts have been reported by Griffin et al. In all cases, the addition of base in the system was beneficial for activity, and it was proposed that, for the glycerol, the base aids the dehydrogenation *via* H-abstraction of one of the primary hydroxy group.

A short account written in Japanese by Nishimura has resumed the work of their team^{39,47,50,56–58} on Pd-catalysed transformation of alcohols.²¹⁸

Singh et al. have studied the kinetic and the mechanism, in perchloric acid medium, of the 1-catalysed oxidation of carbohydrates by *N*-bromoacetamide in the presence of KCl, NaClO₄ and Hg(OAc)₂.²¹⁹

Aliphatic and aromatic primary alcohols have been dehydrogenated over Pd/C at 160°C, in diglyme containing sodium hydroxide, to provide the corresponding sodium carboxylates.²²⁰

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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^{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.