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Review

# The Reims Journey Towards Discovery and Understanding of Pd-Catalyzed Oxidations

Jean Le Bras and Jacques Muzart \*

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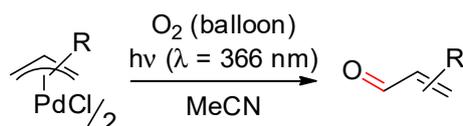


**Abstract:** This review recounts the development by the authors of the Pd-catalyzed procedures devoted to various kinds of oxidation. Starting with reactions assisted with UV light, the research has explored reactions under light-free conditions: allylic oxidation, alcohol oxidation, etherification, Wacker oxidation and dehydrogenations with, always, accompanying efforts towards mechanism determination.

**Keywords:** palladium; catalysis; oxidations; dehydrogenations; C–H activation

## 1. Introduction

Our initial studies on Pd-catalyzed oxidations results from our observation in the early 1980s of the formation of unsaturated carbonyl compounds from irradiation with UV light of bis( $\mu$ -chloro)bis( $\eta^3$ -allyl)dipalladium complexes in oxygenated acetonitrile (Scheme 1) [1]. That result urged us to look for such reactions under catalytic conditions. This activity progressively led us to study a variety of Pd-catalyzed oxidations under light-free conditions. The aim of the present account is to highlight the main results that we obtained in the area over the years.



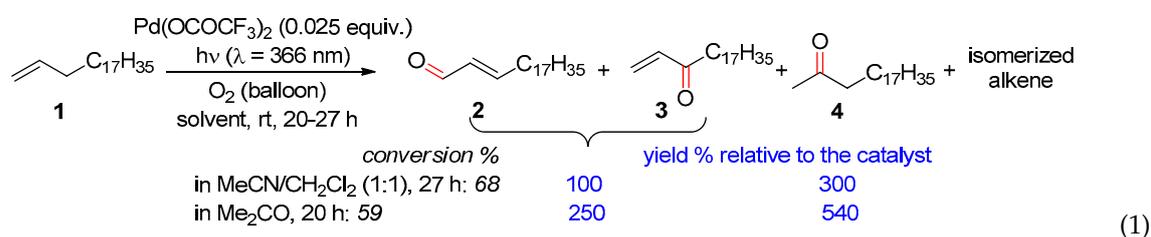
**Scheme 1.** Photocatalyzed oxidation of bis( $\mu$ -chloro)bis( $\eta^3$ -allyl)dipalladium complexes

## 2. UV-Light-Assisted Oxidation

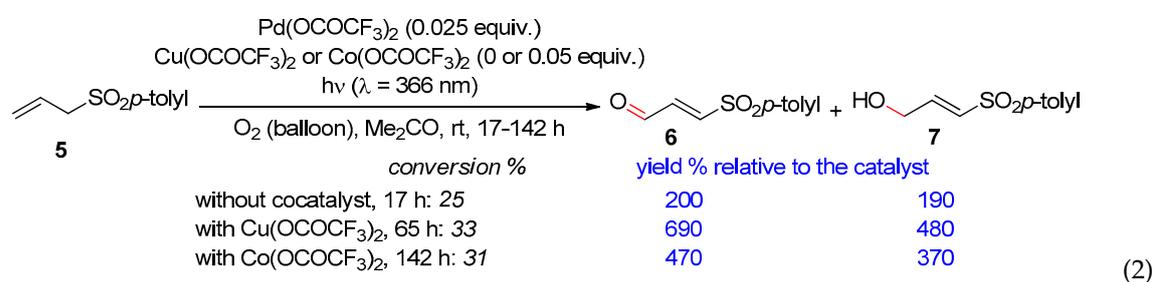
### 2.1. Ethylenic Compounds

The easy formation at room temperature of  $\eta^3$ -allylpalladium complexes from alkenes and Pd(OCOCF<sub>3</sub>)<sub>2</sub> reported by Trost and Metzner [2] urged us to use this Pd salt as a catalyst for the photo-assisted oxidation of alkenes [3,4]. For an example, the reaction of 1-eicosene (**1**) in MeCN/CH<sub>2</sub>Cl<sub>2</sub> afforded a mixture of saturated and unsaturated ketones **2** to **4** (Equation (1)). Some migration of the double bond of **1** was a competing reaction [5,6]. In contrast to the isomerization, ketones **2** to **4** were not produced in the absence of light. Switching to acetone as the solvent increased the ketone yields. Similar results were obtained using [( $\eta^3$ -CH<sub>2</sub>CHCHC<sub>3</sub>H<sub>7</sub>)Pd(OCOCF<sub>3</sub>)<sub>2</sub>] as the catalyst whereas the turnover number was inferior to 1 with Pd(OAc)<sub>2</sub> [4]. Under alkene-free conditions, monitoring the irradiation of an acetone solution of Pd(OCOCF<sub>3</sub>)<sub>2</sub> showed the adsorption of oxygen [4]. That led us to

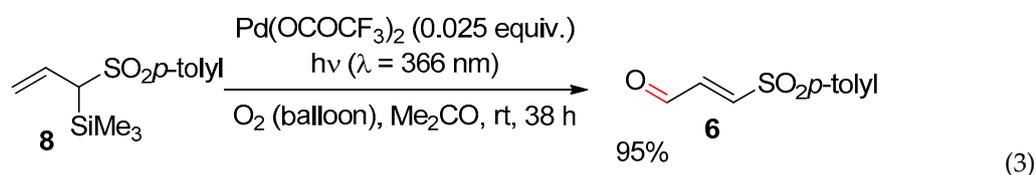
suspect the formation of peroxydic species. Nevertheless, ketones **2** to **4** were also produced from the reaction of **1** in the presence of radical and  $^1\text{O}_2$  traps [4].



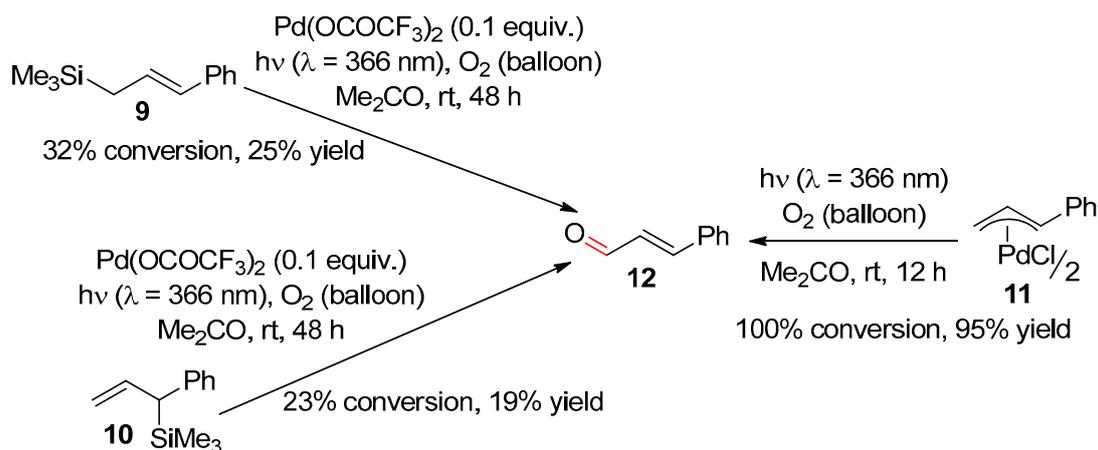
The process was used for the oxidation of allylsulfones [7]. Under the above conditions, **5** led to a mixture of unsaturated aldehyde **6** and alcohol **7** (Equation (2)). The yields were improved with a cocatalyst such as  $\text{Cu}(\text{OCOCF}_3)_2$  or  $\text{Co}(\text{OCOCF}_3)_2$ .



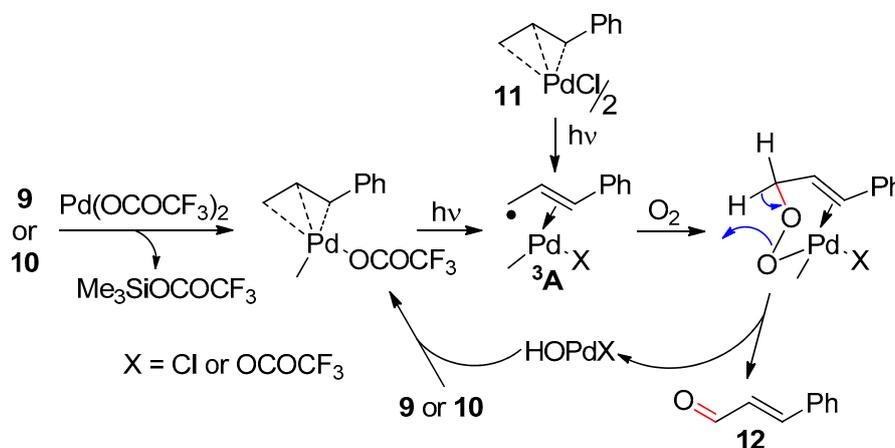
Under both  $\text{Pd}(\text{OCOCF}_3)_2$  catalysis and UV light, allylsulfones substituted with a trimethylsilyl group underwent cleavage of the allyl-Si bond. Thus, full conversion of **8** occurred in 38 h leading to **6** in 95% yield (Equation (3)) [8]. Lower conversions were mediated by other Pd catalysts.



The mechanism of the reaction of allylsilanes was studied using 1-phenyl-3-(trimethylsilyl)-1-propene (**9**) and 1-phenyl-1-(trimethylsilyl)-2-propene (**10**) as substrates, and comparison with the reactivity of corresponding allylpalladium chloride **11** [9]. The latter would be dissymmetric due to the different substitution of the allyl unit extremities [10–12]. Cinnamaldehyde (**12**) was selectively obtained from irradiation of either **9** and **10** in the presence of catalytic  $\text{Pd}(\text{OCOCF}_3)_2$ , or **11** (Scheme 2). That contrasts from oxidations of the free phenylallyl radical which gave mixtures of oxidation products in 1- and 3-position [9,13,14]. Consequently, the regioselectivity of the reactions of **9**, **10** and **11** excluded the formation of the free phenylallyl radical. The formation of  $\eta^3$ -allylpalladium complexes from allylsilanes and  $\text{Pd}^{\text{II}}$  salts is known [15]. Thus, a common intermediate, which would be a dissymmetric  $\eta^3$ -allylpalladium complex, has been proposed (Scheme 3). Light-mediated cleavage of the longer C–Pd bond would lead to intermediate  $^3\text{A}$  [16,17] which reacts with oxygen to afford a peroxopalladium complex. The latter evolves towards aldehyde **12**, liberating HOPdX which would be involved in the subsequent catalytic cycle.



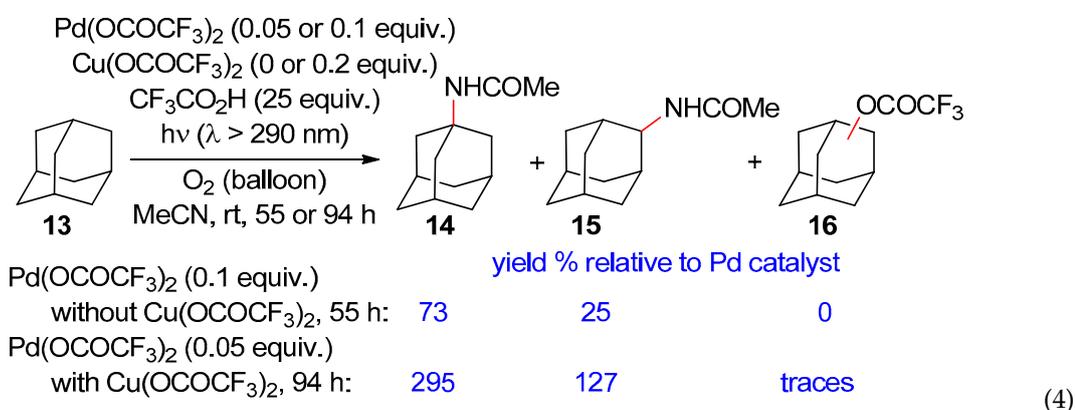
Scheme 2. Three photochemical reactions leading to cinnamaldehyde.



Scheme 3. Plausible reaction pathways leading to cinnamaldehyde from allylsilanes **9** and **10**.

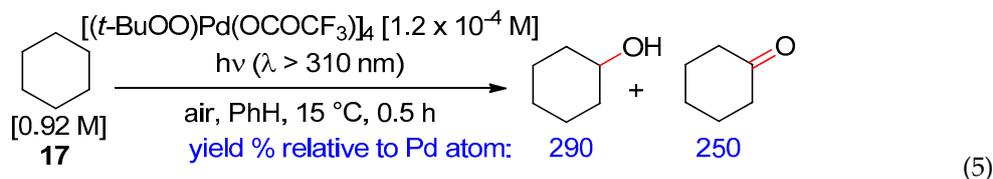
## 2.2. Alkanes

Irradiation with UV light of a MeCN solution of adamantane (**13**) containing trifluoroacetic acid and catalytic Pd(OCOCF<sub>3</sub>)<sub>2</sub> afforded adamantanyl acetamides **14** and **15** in quantitative yields versus the amount of palladium (Equation (4)) [18]. The reaction became catalytic with Cu(OCOCF<sub>3</sub>)<sub>2</sub> as the cocatalyst and provided traces of adamantanyl trifluoroacetates **16**. The mechanism of these reactions remains obscure, the %**14**/%**15** ratio indicating a radical or electrophilic process [19].



Oxidation of cyclohexane (**17**) and 3-methylhexane (**18**) was performed using light and peroxopalladium complexes [20]. Thus, [(*t*-BuOO)Pd(OCOCF<sub>3</sub>)<sub>2</sub>]<sub>4</sub> in air led, from **17**, to cyclohexanol

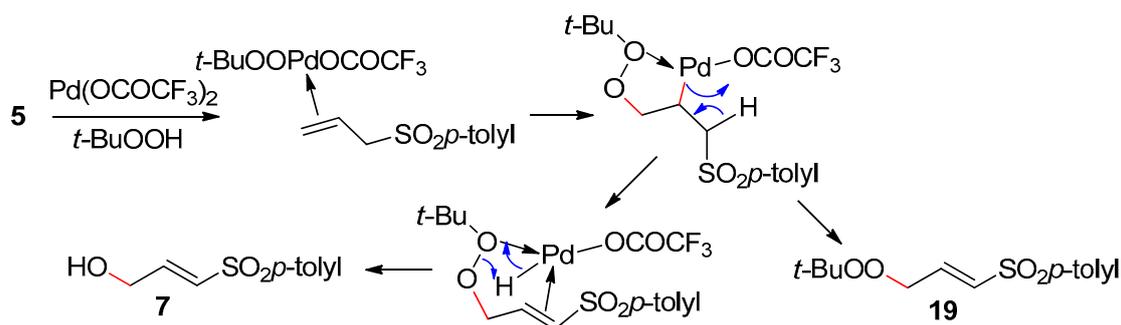
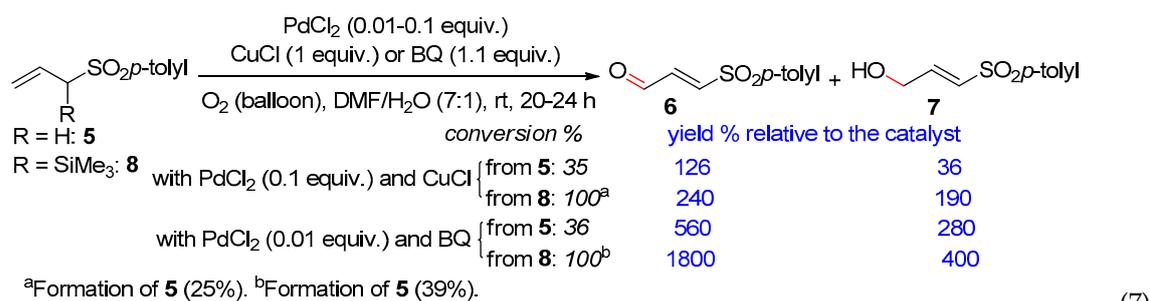
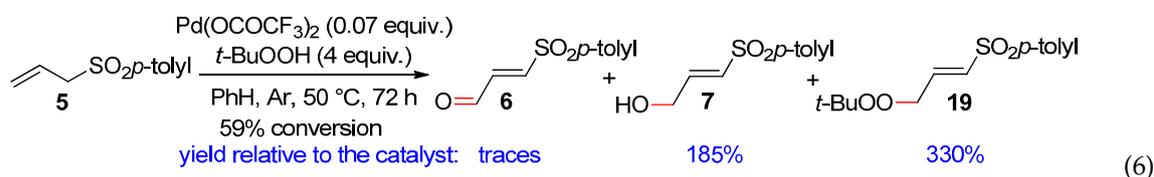
and cyclohexanone with a slight catalytic character (Equation (5)). A similar result arose with  $[(t\text{-BuOO})\text{Pd}(\text{OCOCH}_3)_4]$ . The oxidation of **18** mainly occurred at the level of the tertiary C–H bond.



### 3. Allylic Oxidation

#### 3.1. 1-(*p*-Toluenesulfonyl)-2-Propene and 1-(Trimethylsilyl)-1-(*p*-Toluenesulfonyl)-2-Propene

The Pd<sup>II</sup>-catalyzed oxidation of allylsulfone **5** was carried out with *t*-BuOOH or oxygen in conjunction with either CuCl or benzoquinone (BQ) (Equations (6) and (7)) [21]. Under the former conditions, the main products were alcohol **7** and peroxide **19**, which could be produced from a  $\eta^2$ -olefin palladium complex formed from **5** and *t*-BuOOPdOCOCF<sub>3</sub> (Scheme 4) [22].



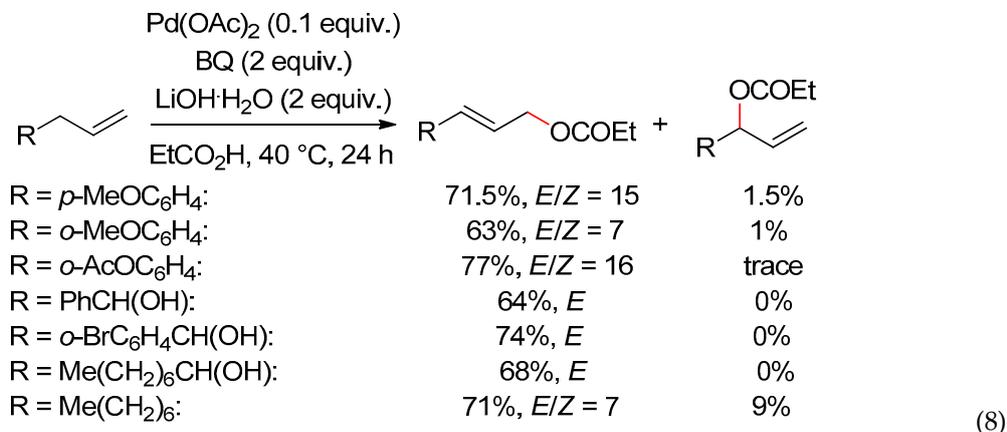
**Scheme 4.** Pd(OCOCF<sub>3</sub>)<sub>2</sub>-catalyzed oxidation of allylsulfone **5** with *t*-BuOOH.

Submitting allylsilane **8** to the PdCl<sub>2</sub>/CuCl or BQ system under oxygen mainly led to the desilylated compound **5**. (Equation (7)) [21]. Aldehyde **6** and alcohol **7** were concomitantly produced.

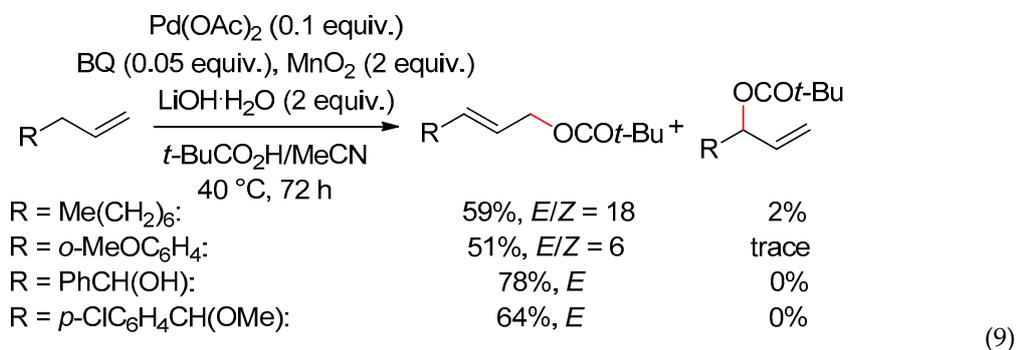
#### 3.2. Terminal Alkenes

Various conditions have been reported for the synthesis of allylic carboxylates via Pd<sup>II</sup>-catalyzed allylic oxidation of olefins in carboxylic acids [23,24]. After the observation of the improvement of

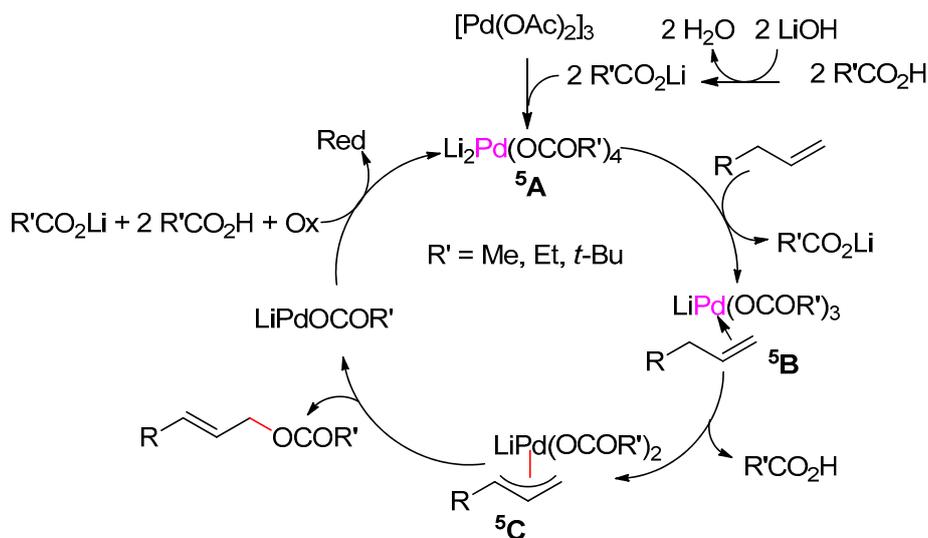
the Pd(OAc)<sub>2</sub>-catalyzed allylic acetoxylation of allylbenzene with BQ as the stoichiometric oxidant in the presence of base but with inconsistent yields, we performed the efficient, reproducible and regioselective allylic acyloxylation of terminal alkenes using lithium hydroxide as the additive and propionic acid as the solvent (Equation (8)) [25].



The reaction of 1-decene was less selective (Equation (8)). The regioselectivity increased with the more-hindered pivalic acid but to the detriment of the conversion. Improved results were finally obtained using a BQ/MnO<sub>2</sub> mixture as the oxidant (Equation (9)) [25]. This modified procedure was well adapted to the oxidation of homoallylic alcohols but led to lower yields with allylarenes (compare Equations (8) and (9)).



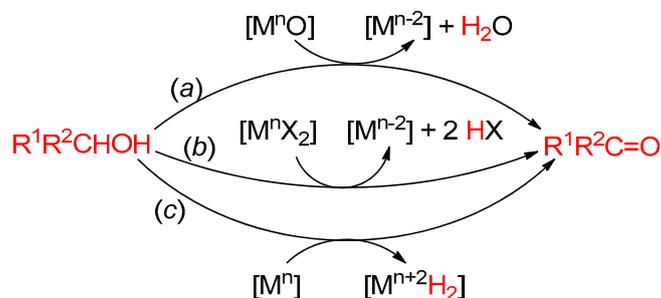
Careful analysis by Electrospray Ionization Mass Spectrometry (ESI-MS) of the allylic acyloxylation under the above conditions led to identification of different clusters, especially those corresponding to intermediates having the Pd atom (in mauve color) in the proposed catalytic cycle depicted in Scheme 5. Palladium acetate, which is a trimer in the solid state [26], reacts with the in-situ formed salt of the carboxylic acid to afford <sup>5</sup>A. Coordination of the substrate to <sup>5</sup>A leads to η<sup>2</sup>-alkenyl intermediate <sup>5</sup>B, which evolves towards an η<sup>3</sup>-allyl complex <sup>5</sup>C. Subsequent intramolecular acetoxylation delivers the product and Pd<sup>0</sup>. The reoxidation of Pd<sup>0</sup> completes the catalytic cycle.



**Scheme 5.** Proposed mechanism of the Pd-catalyzed allylic acyloxylation.

#### 4. Alcohol Oxidation

The transformation of alcohols into the corresponding carbonyl compounds with metal oxides and metal salts may occur through three pathways (Scheme 6). Instead of the term “oxidation” used for reactions following paths *a* and *b*, those arising via path *c* are often called “dehydrogenation” or “oxidative dehydrogenation”. Most Pd-catalyzed oxidation of alcohols occur via paths *b* and *c* [27]. As shown below, we have developed procedures for such reactions using various species to regenerate the catalyst.

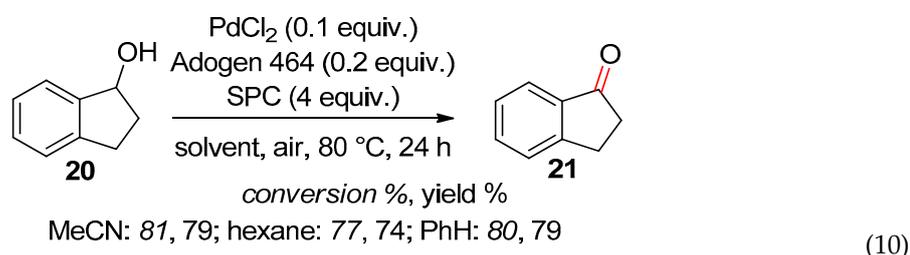


**Scheme 6.** The three pathways of metal-mediated oxidation of alcohols.

##### 4.1. With Sodium Percarbonate

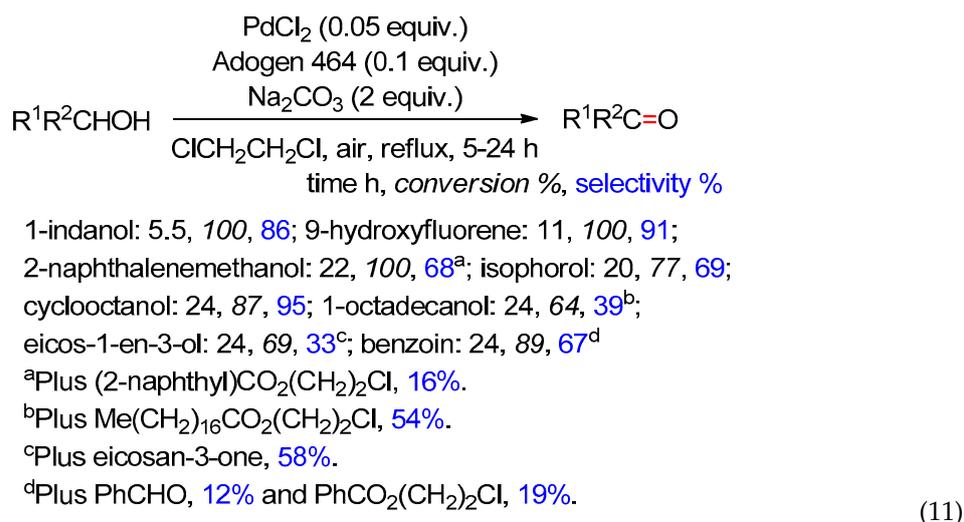
Despite its name, sodium percarbonate (SPC) is not a persalt. SPC, which is a versatile oxidizing agent for organic synthesis [28,29], is the association of sodium carbonate with hydrogen peroxide with the formula  $\text{Na}_2\text{CO}_3 \cdot 1.5 \text{H}_2\text{O}_2$ . In the course of the screening of metal chlorides for the catalytic oxidation of 1-indanol (**20**) by SPC in 1,2-dichloroethane (DCE) in the presence of Adogen 464 [30], we discovered that the reaction with  $\text{PdCl}_2$  effectively occurred even in the absence of SPC. That led

us to the procedure documented in Section 4.2. In contrast, SPC is required with solvents such as acetonitrile, hexane and benzene, leading selectively to 1-indanone (**21**) from **20** (Equation (10)) [31].

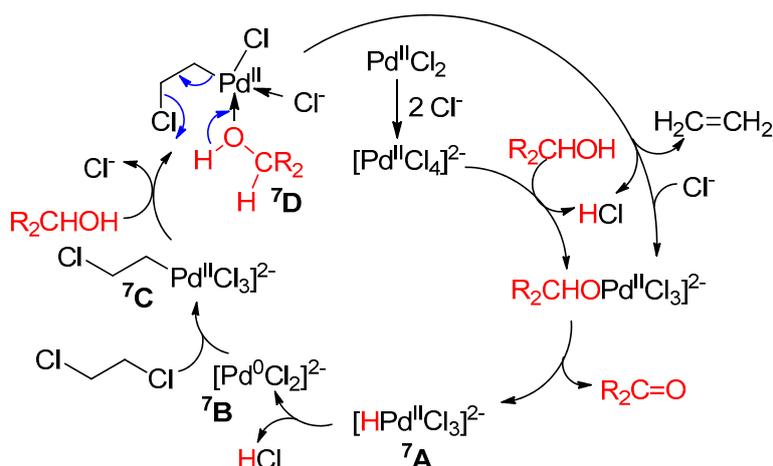


#### 4.2. With 1,2-Dichloroethane

The PdCl<sub>2</sub>-catalyzed oxidation of alcohols in DCE containing sodium carbonate and catalytic amounts of Adogen 464 (Equation (11)) involves the regeneration of active Pd species by the solvent, leading to the formation of ethylene. The formation of the latter has been highlighted by its reaction with iodine, giving 1,2-diiodoethane [32]. The method is efficient for saturated and benzylic secondary alcohols. Some overoxidation of primary alcohols occurred leading to acids which react with the solvent to afford esters. Isomerization of secondary allylic alcohols to saturated ketones may compete with the oxidation (Equation (11)).

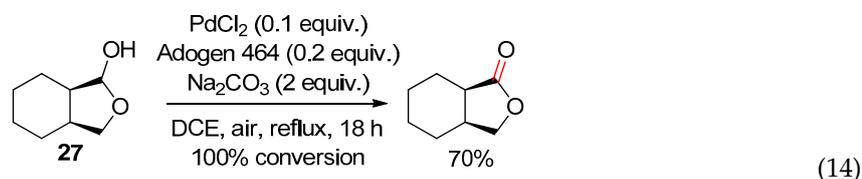
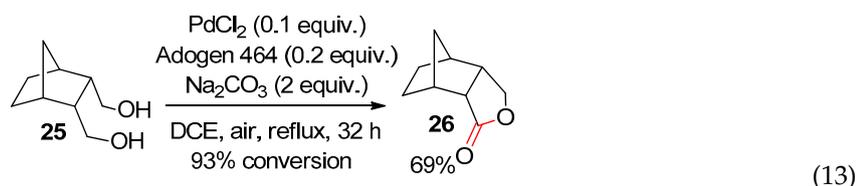
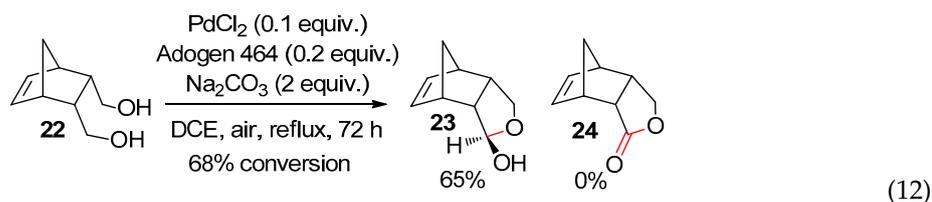


As the plausible mechanism, we initially suspected the insertion of Pd<sup>0</sup> into a C–Cl bond of DCE to afford ClCH<sub>2</sub>CH<sub>2</sub>PdCl which would undergo β-Cl elimination leading to ethylene and PdCl<sub>2</sub> [32]. According to a theoretical study, ClCH<sub>2</sub>CH<sub>2</sub>PdCl would rather be the active species reacting with the alcohol [33]. The process is, however, carried out in the presence of Adogen 464 which reacts with PdCl<sub>2</sub> to afford the soluble palladium salt [PdCl<sub>4</sub>]<sup>2-</sup> [34]. These remarks led us to propose the catalytic cycle depicted in Scheme 7. Hydridopalladium <sup>7</sup>A formed after the first alcohol oxidation leads to Pd<sup>0</sup> species <sup>7</sup>B via elimination of HCl. Insertion of <sup>7</sup>B into DCE affords <sup>7</sup>C. Coordination of the alcohol to the latter gives <sup>7</sup>D. Subsequent elimination of ethylene and HCl leads to an alkoxypalladium intermediate.



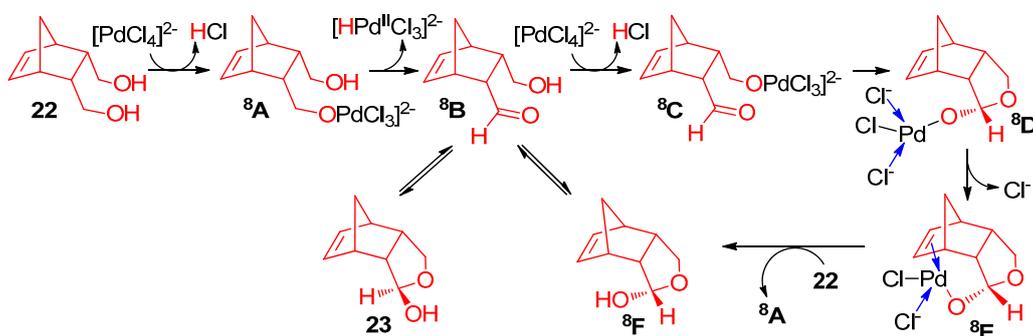
Scheme 7. PdCl<sub>2</sub>-catalyzed oxidation of alcohols with 1,2-dichloroethane.

The PdCl<sub>2</sub>/Adogen 464/DCE procedure effected the lactonisation of various 1,4- and 1,5-diols except that of *cis-endo*-2,3-bis(hydroxymethyl)bicyclo [2.2.1]hept-5-ene (**22**) which led to lactol **23** (96% selectivity) (Equation (12)) although the corresponding saturated diol **25** provided lactone **26** (Equation (13)) [35]. Oxidation of lactol **23** into lactone **24** did not occur under the Pd conditions, but arose using pyridinium dichromate in CH<sub>2</sub>Cl<sub>2</sub> (83% yield [36]) [37] or the Swern oxidation method [38]. The PdCl<sub>2</sub>/Adogen 464/DCE procedure is however able to oxidize α lactol such as **27** (Equation (14)).



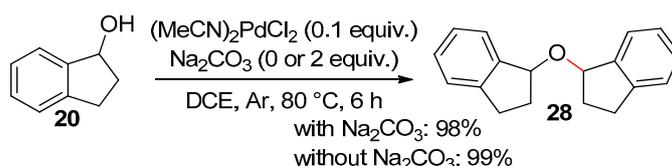
The above results clearly demonstrated that the lack of formation of **24** from **22** under Pd-conditions was attributable to the C=C bond. Analysis of both the plausible intermediates of the process and literature [39–41] led to the proposal of Scheme 8. The reaction of hydroxyaldehyde **8B** obtained via **8A** leads to alkoxy-palladium intermediate **8C**. Subsequent intramolecular reaction occurs through the stereoselective approach of the alkoxy-palladium moiety to one face of the aldehyde to afford **8D**. In contrast to the intermediate obtained from **25**, **8D** undergoes a ligand exchange leading to palladacycle **8E**. The syn relationship between O-Pd and C-H bonds, which would allow a β-H elimination leading to the carbonyl unit [42,43], is prevented in **8E**. That favors alkoxy exchange with diol **22** to afford **8F**. The latter is in equilibrium with **8B** which evolves towards **23**, that is, the more stable isomer [44–46]. The apparent absence of **23** evolution under the PdCl<sub>2</sub>/Adogen 464/DCE conditions would be a “no

reaction" reaction [47,48], which involves  $^8\text{B}$ ,  $^8\text{C}$ ,  $^8\text{D}$ ,  $^8\text{E}$ , alcoholysis and equilibration regenerating the starting substrate.



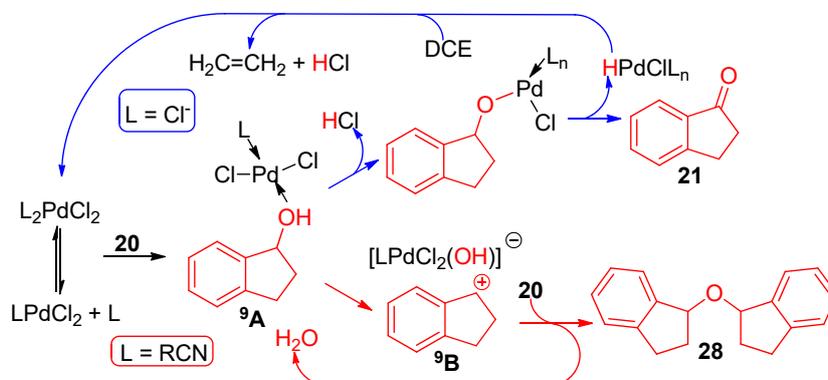
Scheme 8. The "no reaction" reaction of lactol 23.

As depicted in Equation (11), the  $\text{PdCl}_2/\text{Adogen 464}/\text{DCE}$  procedure efficiently oxidizes 1-indanol (**20**) into 1-indanone (**21**). The oxidation was also effective using the soluble catalyst  $(n\text{-Bu}_4\text{N})_2\text{PdCl}_4 \cdot 0.5 \text{H}_2\text{O}$  (92% conversion, 90% yield) instead of the  $\text{PdCl}_2/\text{Adogen 464}$  association [31]. Surprisingly, soluble  $(\text{MeCN})_2\text{PdCl}_2$  produced di(1-indanyl) oxide (**28**) in high yields, even in the absence of the base (Equation (15)) [49].



(15)

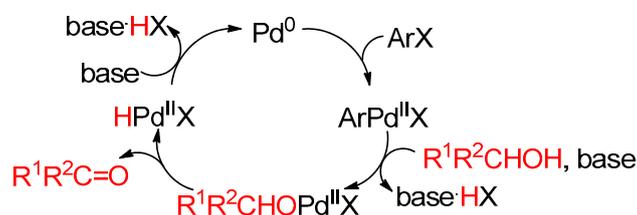
We rationalized the formation of **21** and **28** through two competitive pathways catalyzed with  $\text{L}_2\text{PdCl}_2$  ( $\text{L} = \text{Cl}^-$  or  $\text{RCN}$ ), that is with  $[\text{PdCl}_4]^{2-}$  and  $(\text{RCN})_2\text{PdCl}_2$ , respectively (Scheme 9) [49]. In contrast to the anionic catalyst ( $\text{L} = \text{Cl}^-$ ), the neutral catalyst ( $\text{L} = \text{RCN}$ ) is electrophilic [50–53]. Exchange of ligand between  $\text{L}_2\text{PdCl}_2$  and **20** affords  $^9\text{A}$ . The evolution of  $^9\text{A}$  depends on the electrophilicity of the  $\text{L}_2\text{PdCl}_2$ . Transition metals having Lewis acid properties mediate the formation of ethers from alcohols [31,54]. Consequently,  $^9\text{A}$  formed from the anionic catalyst evolves towards **21** via the ketonisation pathway [32,33], while  $^9\text{A}$  formed from  $(\text{RCN})_2\text{PdCl}_2$  undergoes heterolytic cleavage of the C–OH bond leading to ionic species  $^9\text{B}$ . The latter reacts with **20** to give ether **28**, water and the starting catalyst.



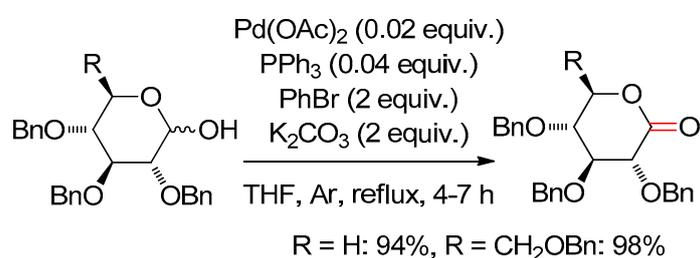
Scheme 9. Dependence of the reaction pathway on the electrophilicity of the catalyst.

### 4.3. With Aryl Bromide

The Yoshida procedure of oxidation of alcohols used a Pd catalyst with an aryl halide as hydrogen acceptor and a base (Scheme 10) [55,56]. We used this procedure for the oxidation with high yields of benzyl-protected sugar hemiacetals into lactones (Equation (16)) [57].



**Scheme 10.** Pd<sup>II</sup>-catalyzed oxidation of alcohols with aryl halides.



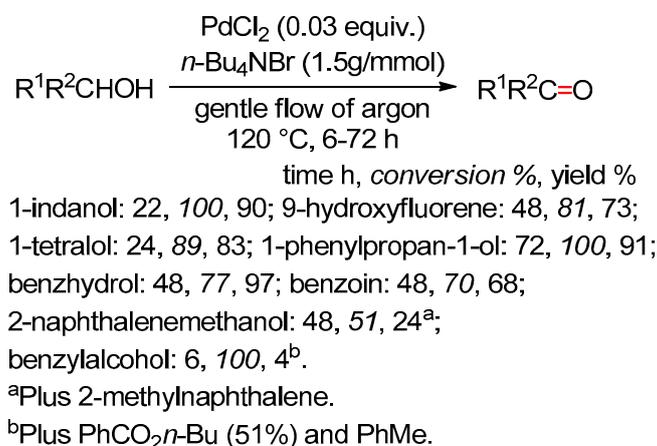
(16)

### 4.4. Dehydrogenation

Over the last thirty years, growing attention has been devoted to the use of ionic liquids and molten salts as solvents for organic synthesis [58–60]. The strong interest for catalyzed reactions is due to the immobilization of the catalyst in the ionic liquid or molten salt that would allow the recycling of the tandem catalyst/solvent. These unusual solvents have been used for various catalytic oxidations [61–63]. Our above studies with (*n*-Bu<sub>4</sub>N)<sub>2</sub>PdCl<sub>4</sub>·0.5 H<sub>2</sub>O (see Section 4.2) and Heck reaction in molten *n*-Bu<sub>4</sub>NBr [64] urged us to carry out Pd-catalyzed oxidations in this medium.

Initial experimentation using **20**, catalytic PdCl<sub>2</sub> and *n*-Bu<sub>4</sub>NBr at 120 °C led to a mixture of **21** and indane. The reductive cleavage of the C–OH bond of **19** indicated in-situ formation of hydrogen [65] and/or [Pd]H<sub>2</sub> species [66]. Addition of cyclohexene as a hydrogen acceptor increased the selectivity towards **21**. Finally, the best result was obtained under a gentle flow of argon which removes hydrogen gas (Equation (17)) [67]. Under these conditions, the recycling of both catalyst and *n*-Bu<sub>4</sub>NBr was relatively efficient. Secondary benzylic alcohols provided the corresponding ketones in good yields. The method is less selective for primary benzylic alcohols and is ineffective from allylic and saturated alcohols. Subsequent experiments showed that recycling was more efficient with Pd(OAc)<sub>2</sub> than

with PdCl<sub>2</sub>, the yield obtained from 4th reuse of the catalyst/*n*-Bu<sub>4</sub>NBr association being 92% (94% conversion) with the former and 64% (67% conversion) with the latter [68].

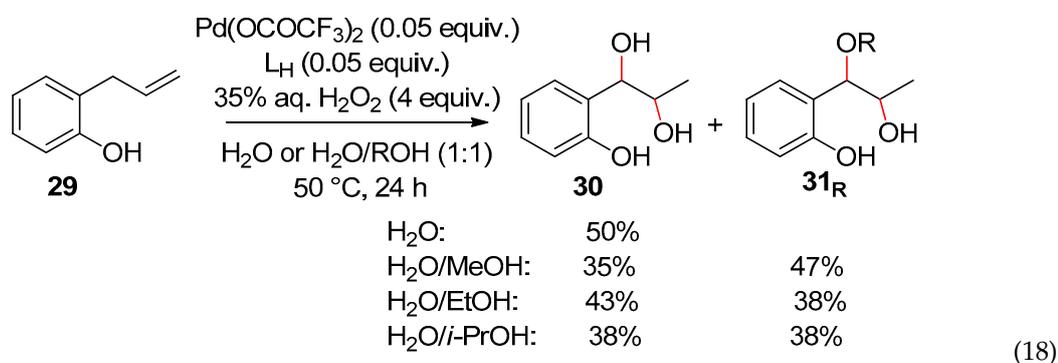


(17)

## 5. Allylphenols Oxidation

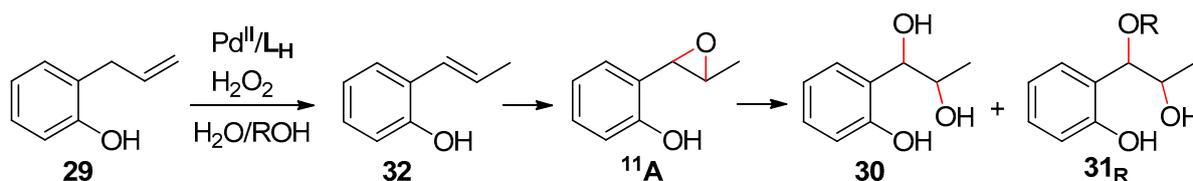
Green chemistry has led the chemical community to intensify research on aqueous procedures [69–75], and we previously used the hydrophilic ligand [(HOCH<sub>2</sub>CH<sub>2</sub>NHCOCH<sub>2</sub>)<sub>2</sub>NCH<sub>2</sub>]<sub>2</sub> (L<sub>H</sub>) for copper-catalyzed allylic oxidations in water [76]. The intramolecular Wacker oxidation of allylphenol (**29**) leads to 2-methylbenzofuran [77,78] or 2*H*-chromene [79] depending on the reaction conditions. Thus, we were interested in performing such a reaction in aqueous media with a Pd<sup>II</sup>/L<sub>H</sub> catalytic system.

Treatment of **29** with aqueous H<sub>2</sub>O<sub>2</sub> and catalytic amounts of both Pd(OCOCF<sub>3</sub>)<sub>2</sub> and L<sub>H</sub> at 50 °C in water afforded diol **30** instead of the cyclization products (Equation (18)) [80]. Reaction in a mixture of water and methanol led to **30** and hydroxyl methyl ether **31<sub>Me</sub>**. Similar compounds were produced in H<sub>2</sub>O/EtOH and H<sub>2</sub>O/*i*-PrOH, or using 2-allyl-4-methylphenol and 2-allyl-6-methylphenol.

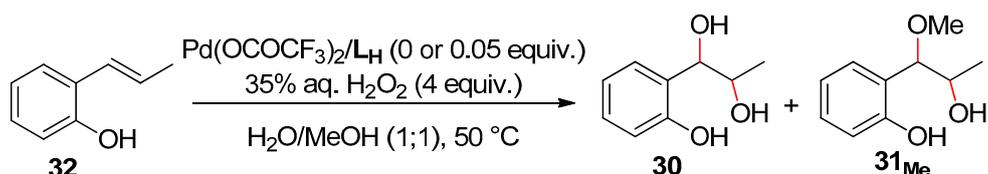


(18)

The report of Jacobs' team about the phenol-mediated epoxidation of alkenes by H<sub>2</sub>O<sub>2</sub> under metal-free conditions [81] led us to propose in 2005 the mechanism depicted in Scheme 11 [80]. Pd-catalyzed isomerization of **29** affords **32** [82]. Activation by the phenolic OH of the epoxidation of **32** provides <sup>11</sup>A. The high instability of such a compound [83] brings on spontaneous ring opening leading to **30** and **31<sub>R</sub>**. However, the strong acceleration of the palladium-catalyzed reaction of **32** (Equation (19)) indicates some participation of Pd(OCOCF<sub>3</sub>)<sub>2</sub>/L<sub>H</sub> in the process [80]. In fact, epoxides are very sensitive to Pd catalysis [84]. Complementary mechanistic experiments and ESI-MS studies supported the proposed reaction pathway [85].



Scheme 11. Domino reaction of 2-allylphenol.



with  $\text{Pd}^{\text{II}}/\text{L}_\text{H}$ , 24 h, 100% conversion, yield: 33%      55%  
 without  $\text{Pd}^{\text{II}}/\text{L}_\text{H}$ , 60 h, 55% conversion, yield: 7%      20%

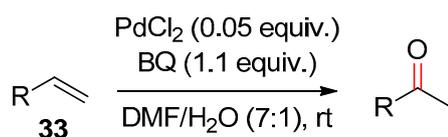
(19)

Recycling of the  $\text{Pd}(\text{OCOCF}_3)_2/\text{L}_\text{H}$  catalytic system led to gradual loss of activity, the 4th reuse in  $\text{H}_2\text{O}/\text{MeOH}$  yielding 35% and 24% of **30** and **31<sub>Me</sub>**, respectively, from **29** [85].

## 6. Wacker Oxidation

Tsuji's conditions of the Wacker reaction use  $\text{PdCl}_2$  catalyst in  $\text{DMF}/\text{H}_2\text{O}$  and oxidants such as copper salts/ $\text{O}_2$  or benzoquinone [86]. According to investigations through isotope effects, kinetic, stereochemical and theoretical studies [87–90], the mechanism involves alkene coordination to  $\text{PdCl}_2$ , followed by hydroxypalladation and  $\beta$ -hydride elimination leading to a palladium–enol  $\eta^2$ -complex. The latter evolves towards the ketone, liberating  $\text{HCl}$  and  $\text{Pd}^0$ . The catalyst is regenerated from  $\text{Pd}^0$  through reaction with BQ. Mechanistic details remain however matter of debate [87].

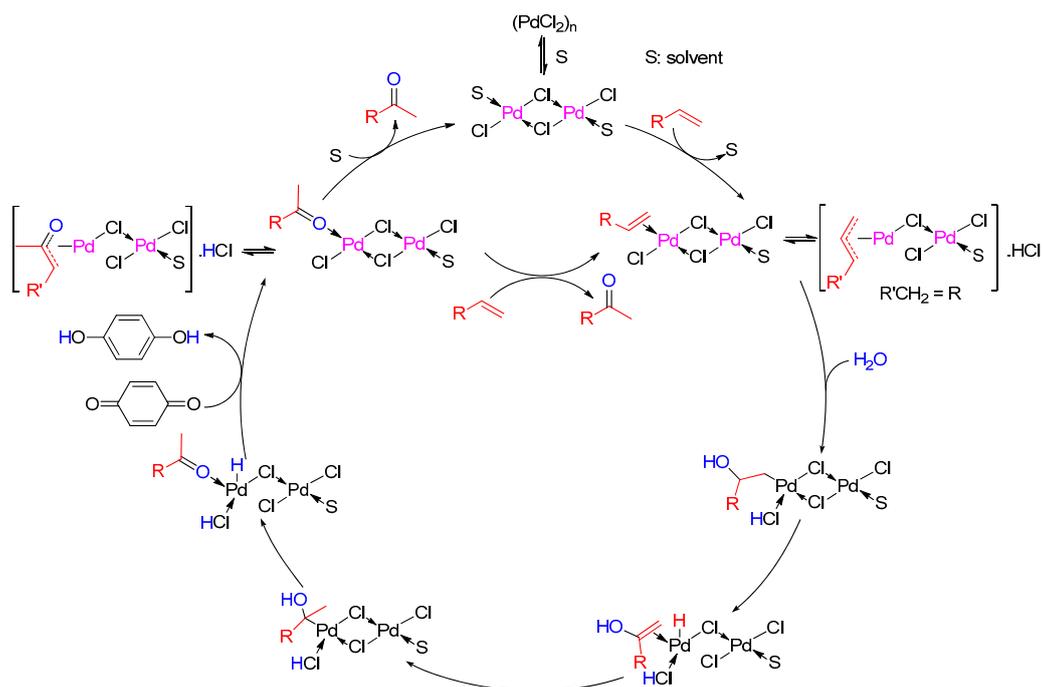
Our interest in the Pd-catalyzed oxidations and in the synthetic properties of DMF [91–93] and BQ [94] urged us to investigate the Wacker reaction of terminal alkenes **33** with ESI-MS, using BQ as the terminal oxidant (Equation (20)) [95].



**33a**: 1-octene, **33b**: 1-decene, **33c**: 4-allylanisole  
**33d**: 4-allyl-1,2-dimethoxybenzene  
**33e**: 5-hexenoic acid, **33f**: 10-undecenoic acid

(20)

ESI-MS monitoring of the reactions showed that dinuclear palladium complexes were more involved as active catalytic intermediates than mononuclear species. Tests of complexation suggested a reoxidation of Pd occurring before the decoordination of the product. These studies associated to kinetic experiments led us to propose the catalytic cycle depicted in Scheme 12, in which intermediates having the Pd atom in mauve color correspond to clusters detected by ESI-MS.

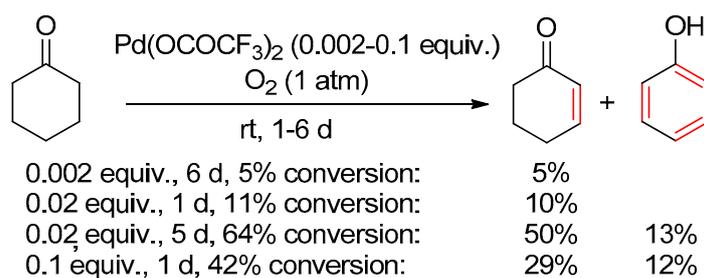


**Scheme 12.** Proposed catalytic cycle for the Wacker reaction in DMF/H<sub>2</sub>O in the presence of benzoquinone.

Compared with the usual mechanism, the most important differences are the involvement of mainly dinuclear Pd species and the reoxidation of a Pd-hydride complex before decomplexation of the ketone.

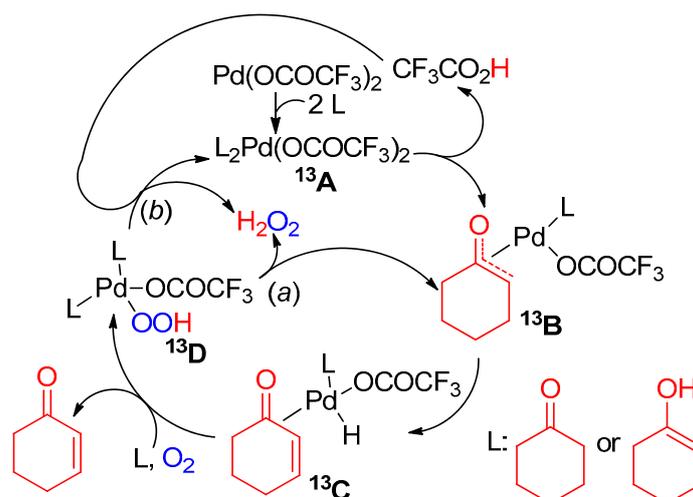
## 7. Cyclohexanone Dehydrogenation

In 1982, we disclosed the room temperature Pd(OCOCF<sub>3</sub>)<sub>2</sub>-catalyzed dehydrogenation of cyclohexanones under oxygen atmosphere (Equation (21)) [96]. Pd procedures were previously reported but using mainly stoichiometric amounts of Pd<sup>II</sup> [97].



(21)

Cyclohexenone was selectively produced at low conversion. Increase of the latter led to over-oxidation giving phenol. The proposed catalytic cycle (Scheme 13) maintains the formal oxidation state of Pd<sup>II</sup> throughout the reaction. Coordination of cyclohexanone or its enol form to Pd(OCOCF<sub>3</sub>)<sub>2</sub> provides <sup>13</sup>A, which led to oxo-η<sup>3</sup>-allyl palladium complex <sup>13</sup>B in liberating CF<sub>3</sub>CO<sub>2</sub>H. Hydrogen abstraction by palladium provides <sup>13</sup>C which undergoes insertion of oxygen and ligand exchange giving 2-cyclohexenone and hydroperoxy complex <sup>13</sup>D. The latter leads to H<sub>2</sub>O<sub>2</sub> and either <sup>13</sup>B (path a) or <sup>13</sup>A by reacting with CF<sub>3</sub>CO<sub>2</sub>H (path b).



**Scheme 13.** Pd(OCOCF<sub>3</sub>)<sub>2</sub>-catalyzed dehydrogenation of cyclohexanone.

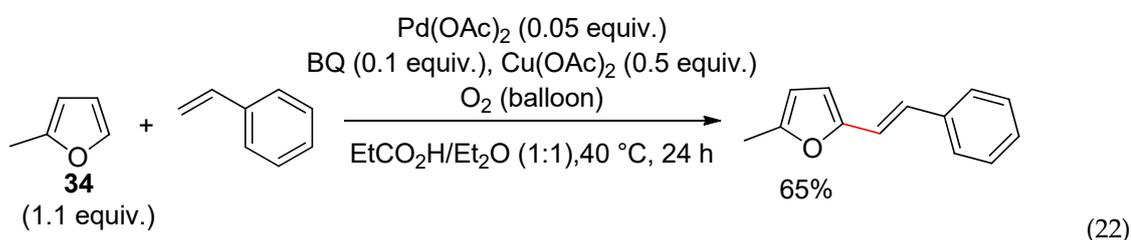
This oxidation process was, in 1982, one of the first reports on the regeneration of active Pd<sup>II</sup> species using only oxygen [98–100]. The pathway leading to PdOOH from PdH and O<sub>2</sub>, that is <sup>13</sup>D from <sup>13</sup>C remains however a matter of debate [98–101].

A number of procedures are now available for the Pd-catalyzed dehydrogenation of carbonyl compounds [102]. Moreover, such a dehydrogenation may be a step of a domino reaction involving the Heck reaction, decarboxylative Heck reaction or dehydrogenative Heck reaction [103].

## 8. Dehydrogenative Heck Reaction

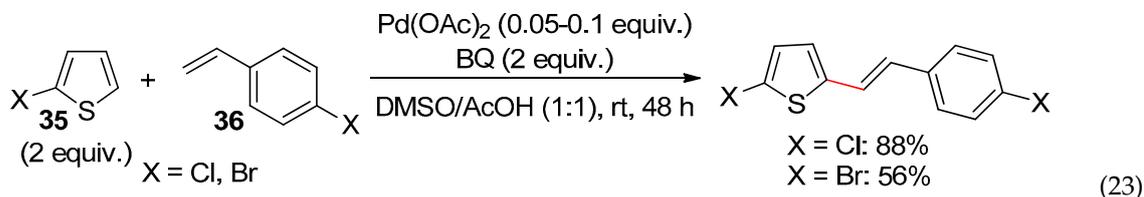
Disclosed in 1970, the Heck reaction is traditionally the synthesis of an arylalkene from the Pd<sup>0</sup>-catalyzed cross-coupling of an aryl halide with an alkene [104]. Previously, Fujiwara's team reported the synthesis of stilbene from the reaction of benzene with styrene and PdCl<sub>2</sub>, leading to two turnovers of palladium [105]. Such a cross-coupling, for which we adopted the name “dehydrogenative Heck reaction” (DHR) [106], may be more respective of the atom economic principle [107], and has been intensively studied over the last twenty years [108].

Our studies focused on the coupling of furan **34** with styrene. Screening various experimental conditions initially led to the best results with catalytic Pd(OAc)<sub>2</sub> and the BQ/Cu(OAc)<sub>2</sub>/O<sub>2</sub> oxidizing system (Equation (22)). The method was used for the DHR of various furans and styrenes with high regio- and stereoselectivities (30 examples, 50%–78% yields) [109].

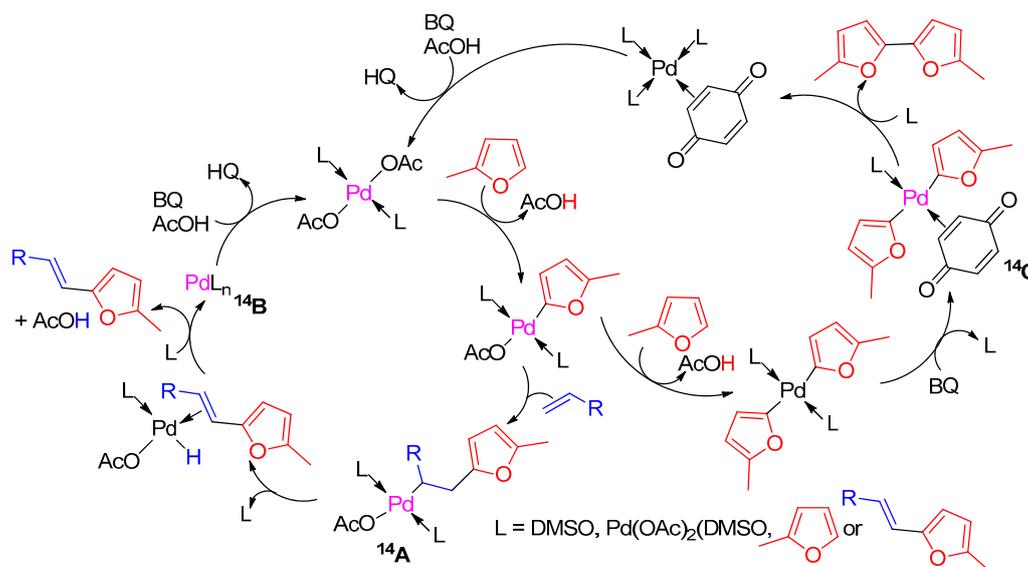
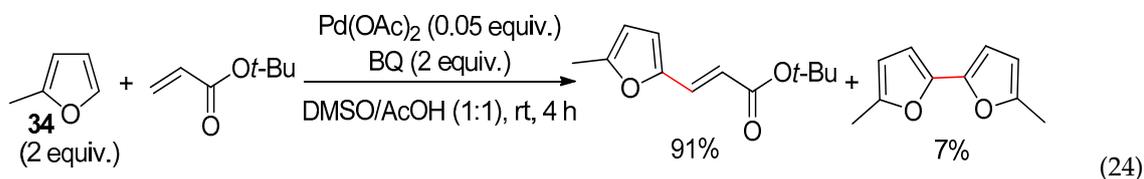


Kinetic investigations showed an induction period which depends on the nature of the furan, the transformation being faster with electron-rich furans. This led us to investigate the influence of ligands and solvents on the activity of the catalyst. The use of DMSO/AcOH as solvent mixture and BQ as oxidant led to a catalytic system showing no induction period at room temperature, leading to cross-coupling of furans and thiophenes with styrenes, and compatible with halogenated substrates such as **35** and **36** (Equation (23)) [110]. The positive influence of DMSO on the efficiency of Pd(OAc)<sub>2</sub>-catalyzed oxidations is largely documented in the literature [111,112]. Ligation of DMSO to the trimer [Pd(OAc)<sub>2</sub>]<sub>3</sub> affords the dimeric active species Pd(OAc)<sub>2</sub>(DMSO)<sub>2</sub> [113,114], which may

react with the arene leading to  $\text{ArPdOAc}(\text{DMSO})_2$ . Subsequent ligand exchange with BQ could give the less electron-rich species  $\text{ArPdOAc}(\text{BQ})(\text{DMSO})$ , which would be susceptible to easily coordinate to electron-rich styrenes [110].



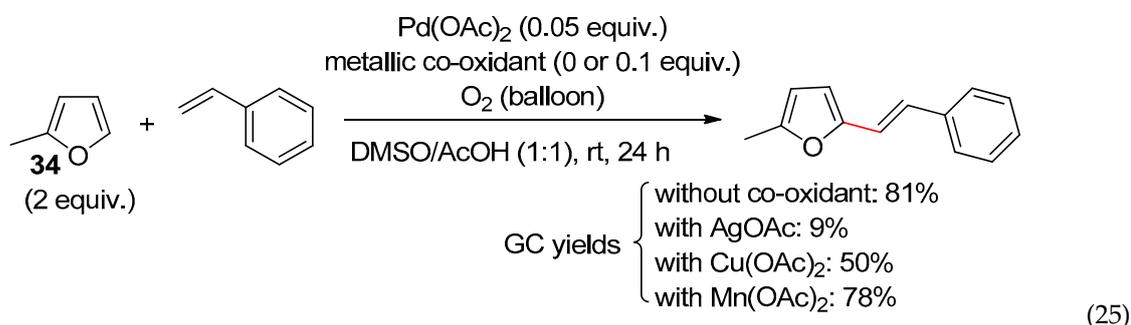
The mechanism of the reaction of **34** with *tert*-butyl acrylate under these conditions (Equation (24)) has been investigated by ESI-MS leading to identification of clusters corresponding especially to  $\text{Pd}^{\text{II}}$  and  $\text{Pd}^0$  intermediates **14A**, **14B** and **14C**, leading us to propose the catalytic cycle shown Scheme 14 [115].



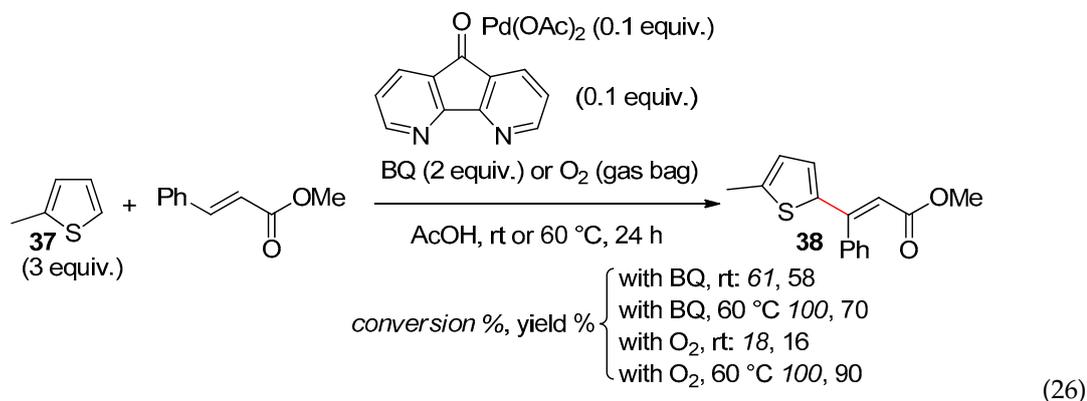
**Scheme 14.**  $\text{Pd}^{\text{II}}$ -catalyzed C-H activation.

Catalytic amounts of metallic co-oxidants are often required for efficient DHRs under oxygen [108]. We observed, however, that such additives are not always beneficial. Indeed, the room temperature  $\text{Pd}(\text{OAc})_2$ -catalyzed reaction of **34** with styrene in oxygenated DMSO/AcOH afforded the cross-coupling product in higher yield in their absence (Equation (25)). Thus, these mild experimental conditions were used for the efficient DHR of furans, thiophenes and indoles with styrenes (29 examples, 42%–95%

yields) [116]. ESI-MS studies of mixtures of Pd(OAc)<sub>2</sub> and AgOAc have shown the formation of mixed species; which could be inactive towards the DHR.

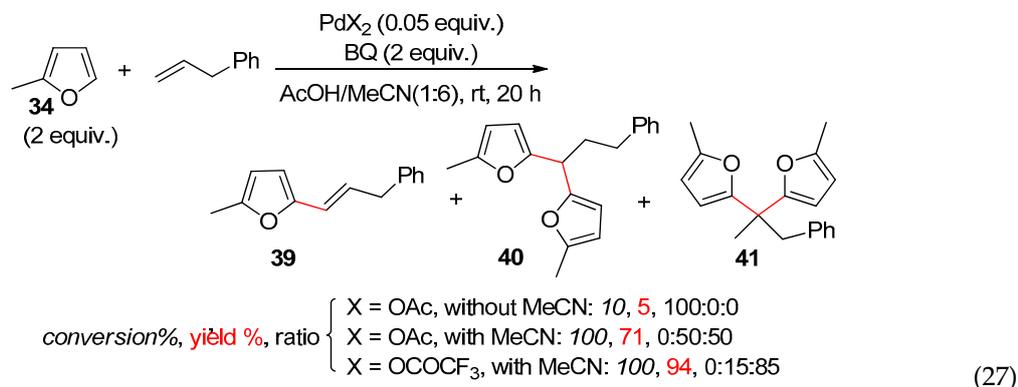


The reaction of thiophene **37** with a hindered alkene such as methyl cinnamate under conditions of Equation (24) occurred with 5% conversion leading to traces of DHR product **38** [117]. With AcOH as the solvent instead of the AcOH/DMSO mixture, the conversion increased to 20%. Testing various ligands led to an efficient DHR with 4,5-diazafluorenone (Equation (26)). Moreover, increase of the temperature to 60 °C with O<sub>2</sub> instead of BQ led to **38** in 90% isolated yield. Consequently, these conditions have been used for the cross-coupling of furans and thiophenes with various hindered alkenes (19 examples, 51%–96% yield). According to kinetics and competitive experiments as well as ESI-MS studies, 4,5-diazafluorenone influences the C–H bond activation, the alkene insertion, the stereoselectivity and the regeneration of the catalyst [117].

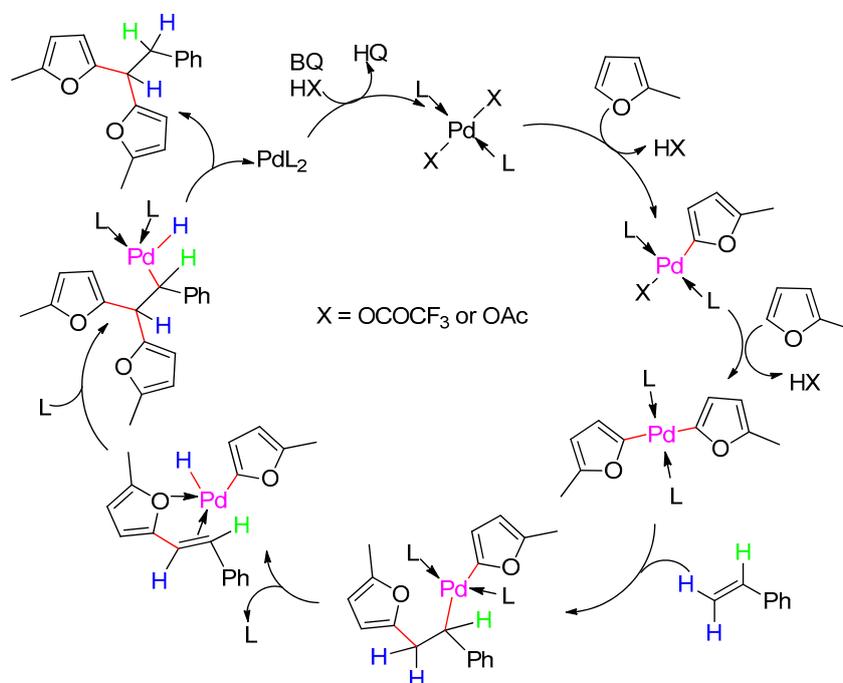
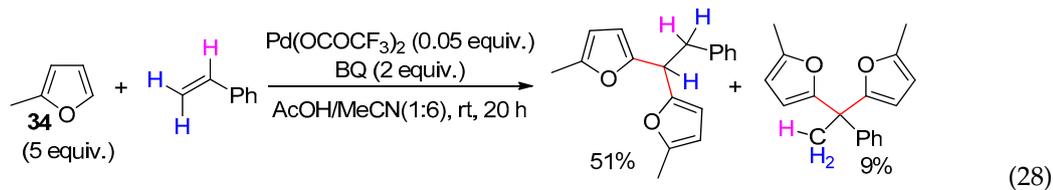


Under conditions of Equation (24) except the presence of DMSO, a low yield of the DHR product **39** was obtained from the sluggish reaction of **34** with allylbenzene (Equation (27)) [118]. Surprisingly, addition of MeCN as a co-solvent suppressed the formation of **39** and increased the conversion leading

to a 1:1 mixture of difurylalkanes **40** and **41**. Moreover, switching to  $\text{Pd}(\text{OCOCF}_3)_2$  as the catalyst increased the **40** + **41** yield to 94% (Equation (27)).



Suspecting the formation of **41** from prop-1-en-1-ylbenzene via isomerization of allylbenzene [82], the reaction was repeated with styrene [118]. Difurylalkanes were also obtained (Equation (28)). Labelling experiments led to assignment of the hydrogen shifts shown in Equation (28) and, associated ESI-MS studies, to propose the catalytic cycle depicted in Scheme 15 [118].



Scheme 15. Diaddition of 2-methylfuran to styrene.

## 9. Conclusions

Starting at the end of the 1970s with oxidations of CH or  $\text{CH}_2$  units under UV light, our research evolved towards light-free reactions in various media: organic solvents, water, molten salts, leading

to alcohol oxidation, dehydrogenation, etherification or formation of C–C bonds. We have always been strongly focused on the mechanisms; these lead us to various proposals, especially those based on ESI–MS results. Some reactions and mechanisms have been serendipitously discovered [119], but nevertheless, in most cases, they were the fruit of deep investigations and reflection, rather than good fortune.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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