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One-Pot Syntheses of α,β-Unsaturated Carbonyl Compounds through Palladium-Mediated Dehydrogenation of Ketones, Aldehydes, Esters, Lactones and Amides

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Keywords: Palladium / Dehydrogenation / Ketones / Aldehydes / Esters / Lactones / Amides

This review highlights the different direct stoichiometric and catalytic palladium procedures leading to α,β-unsaturated carbonyl compounds from the corresponding ketones, aldehydes, esters, lactones and amides. The proposed mechanisms are described, in some cases with personal observations.

Contents

1. Introduction

α,β-Unsaturated carbonyl compounds are highly useful synthetic blocks in organic synthesis, so their preparation from the corresponding saturated substrates is a synthetically important reaction. The use of palladium to achieve such transformations in single-step fashion, with ketones as substrates, emerged in the 1970s, with nearly simultaneous reports of stoichiometric and catalytic procedures. Methods for one-pot dehydrogenations of aldehydes, esters, lactones and amides were subsequently reported. Here we review the literature on this topic.

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2. Stoichiometric Procedures

In 1971, a patent from Kirschke and co-workers disclosed the preparation, in high yields (calculated with respect to Pd), of α,β-unsaturated ketones from the corresponding linear and cyclic ketones through the use of substoichiometric amounts of $PdCl_2$, $PdCl_2(PhCN)_2$ or $PdCl_2$(cyclohexenyl)$_2$ at 20–120 °C in *t*BuOH containing HCl.[1] This patent was rapidly followed by a paper from the same team in the open literature,[2] and by another patent in which a combination of $PdCl_2$ and HCl was used to perform the synthesis of linear α,β,α′,β′-unsaturated ketones from α,β-unsaturated ketones.[3] The authors suggested the intermediate formation of the η^1 complex $L_2ClPd\text{-}CH(CH_2R^1)COR^2$ (**A$_1$**, Scheme 1) from the reaction between $PdCl_2L_2$ and the enol of $R^1(CH_2)_2COR^2$. Hydrogen elimination from **A$_1$** produces the unsaturated ketone and unstable L_2ClPdH, leading to Pd^0. The authors isolated intermediates such as **A$_1$** from various cyclohexanones. The synthesis of oxocyclohexanecarboxylic acid by treatment of cyclohexanone with $PdCl_2(PhCN)_2$ in *t*BuOH/H_2O under CO (150 atm) also agrees with Kirschke's proposal. Nevertheless, oxo-η^3-allylpalladium complexes might

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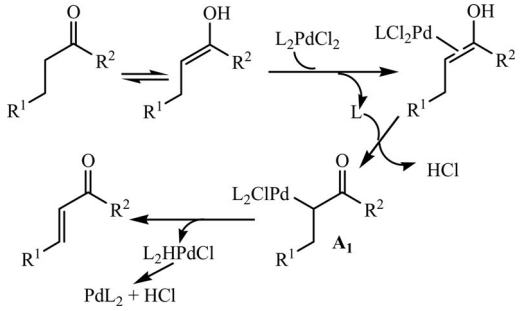
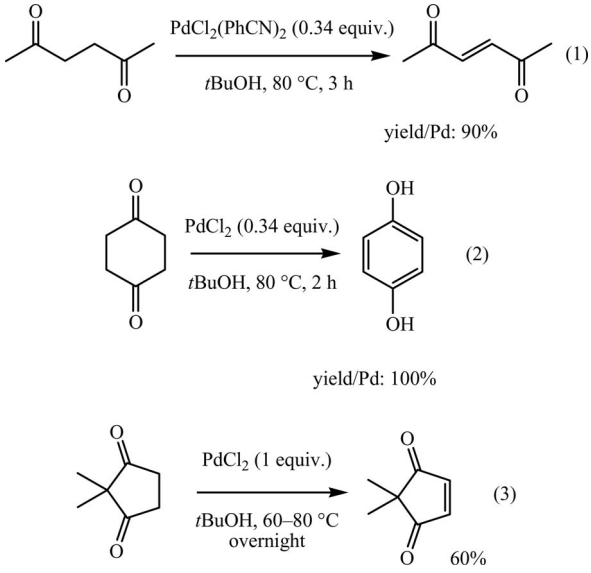
also be involved.[4,5] Subsequently, the team reported dehydrogenations of cyclic 1,2- and 1,3-diketones, as well as of linear 1,3-diketones [Equation (1)] and of unsubstituted cyclohexadiones, leading to the corresponding hydroquinones [Equation (2)].[6] The procedure has been used by Parker et al. to prepare 2,2-dimethylcyclopent-4-ene-1,3-dione [Equation (3)] for an approach to the synthesis of fredericamycin A.[7]

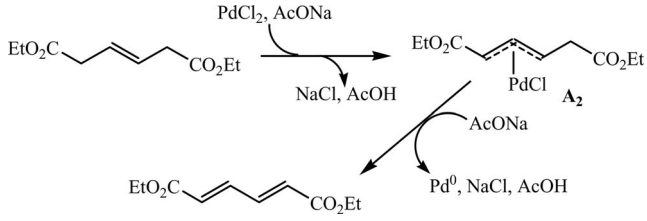


Scheme 1.



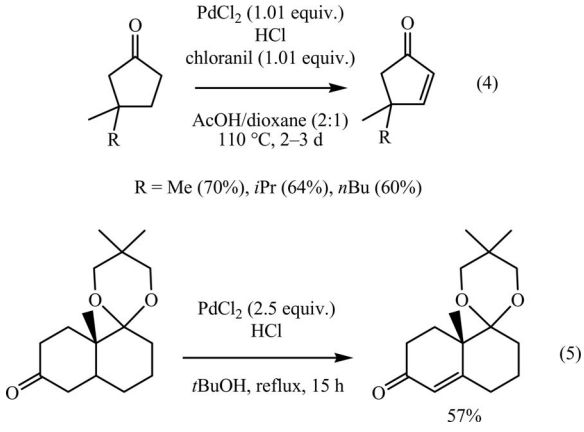
Suzuki and Tsuji dehydrogenated diethyl hex-3-enedioate with $PdCl_2$ at 70 °C in AcOH containing excess AcONa (78% yield/Pd).[8] The mechanism of this reaction (Scheme 2) differs from that above, because it involves the η^3-allylpalladium species **A_2** rather than the palladium enolate **A_1**. The abstraction of hydrogen required for the formation of **A_2** and then to give diethyl hexa-2,4-dienedioate are both mediated by AcONa. The authors claimed to have isolated **A_2** "when a part of the reaction mixture was taken out during the course of reaction". We suspect, however, that the isolated complex was the corresponding dimeric η^3-allylpalladium.

Wolff and Agosta have prepared cyclopentenones from 3,3-disubstituted cyclopentanones through the use of stoichiometric amounts of both $PdCl_2$ and chloranil at 110 °C for 2–3 d in AcOH/dioxane mixtures [Equation (4)].[9] To carry out these preparations, $PdCl_2$ was dissolved in concentrated aqueous HCl and the solution was

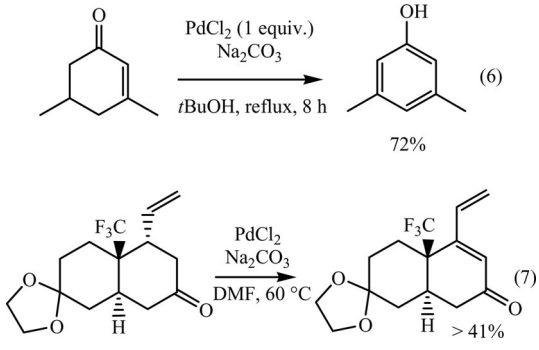


Scheme 2.

concentrated in vacuo, leading to a red-brown oil that was used to mediate the reaction. This procedure has been used by Mincione and co-workers for the α,β-dehydrogenation of a range of ketosteroids.[10] The reactions were regioselective, leading to 3-oxocholest-1-ene from 3-oxo-5α-cholestane and to 3-oxocholest-4-ene from 3-oxo-5β-cholestane. In a few cases the authors isolated the palladium-steroid complex as a yellow solid. Treatment of this complex on a SiO_2/$AgNO_3$ column afforded the expected α,β-unsaturated ketosteroid quantitatively. As shown in Equation (5), the $PdCl_2$/HCl system is tolerant to the presence of a ketal.[11]

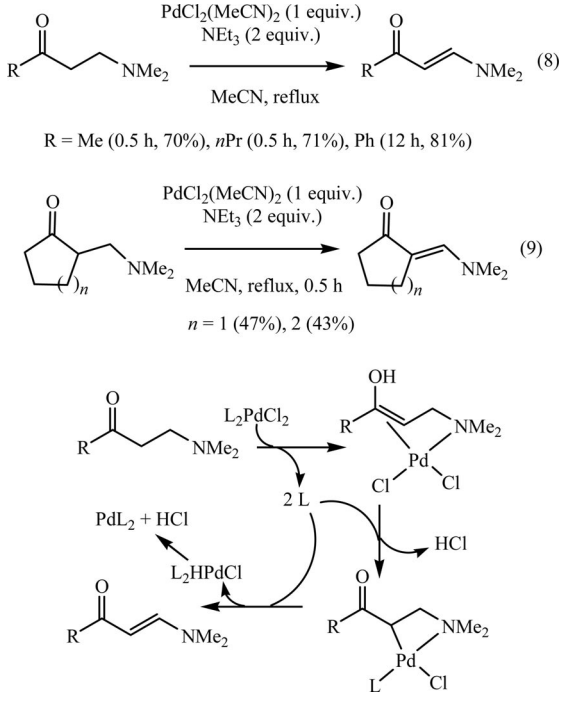


$PdCl_2$-mediated dehydrogenation of ketones can be carried out in the presence of base instead of HCl. Shan synthesised 3,5-dimethylphenol from 3,5-dimethylcyclohex-2-enone in the presence of $PdCl_2$ and Na_2CO_3 in *t*BuOH at reflux [Equation (6)].[12] Taguchi et al. used DMF in place of *t*BuOH as solvent to perform the dehydrogenation shown in Equation (7).[13] In fact, DMF could favour the formation of Pd/substrate intermediates.[14,15]



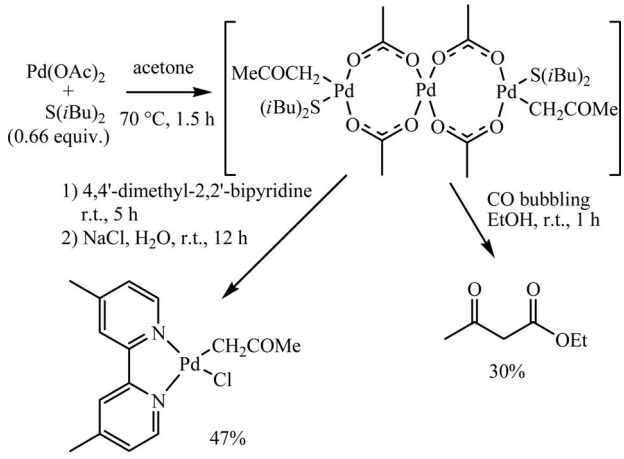
The synthesis of enaminones from β-amino ketones has also been mediated with a Pd^{II}/base system, as reported by Murahashi and co-workers. Optimum conditions were ob-

tained with $PdCl_2$ and NEt_3 in MeCN at reflux (Equations 8 and 9), the use either of $Pd(OAc)_2$ or of alternative bases and solvents being detrimental to the yields.[16,17] The regioselectivity of the reaction, particularly the formation of the exocyclic C=C bond [Eq. (9)], suggested to the authors the initial coordination of Pd^{II} to the amino group (Scheme 3). The use of a base is required because the enaminones are unstable in the presence of the acid liberated in the course of the process.



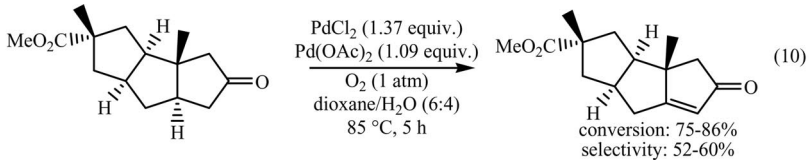
Scheme 3.

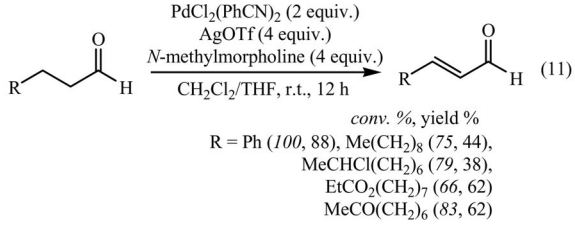
$Pd(OAc)_2$ also has a low efficiency in the mediation of the dehydrogenation of cyclopentanone and cyclohexanone, except when used with bis(isobutyl)sulfane as ligand, as disclosed by Fuchita and Harada.[18] These authors demonstrated the formation of palladium enolates from $Pd(OAc)_2$/$S(iBu)_2$ and acetone, methyl vinyl ketone and *tert*-butyl methyl ketone. They were able to isolate these complexes after ligand exchange and to perform their carbonylation (Scheme 4).

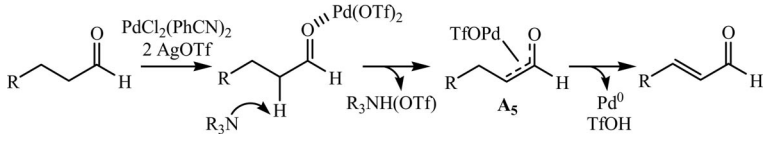


Scheme 4.

In the course of the synthesis of hirsutic acid C, Greene and co-workers screened various experimental conditions, based on Pd^{II}, to carry out the dehydrogenation depicted in Equation (10).[19] The best results were obtained under oxygen with excesses both of $PdCl_2$ and of $Pd(OAc)_2$ in dioxane/H_2O. This procedure was used by Sonawane's team to perform a step of the pathway leading to the synthesis of $\Delta^{9(12)}$-capnellene.[20]

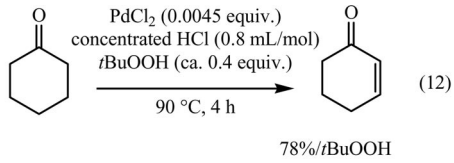


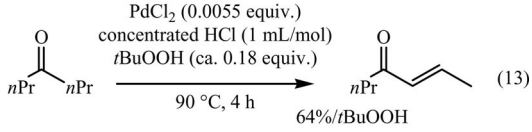


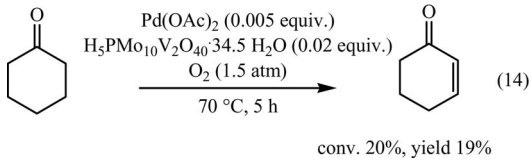


Scheme 5.

For the dehydrogenation of aldehydes, Mukaiyama et al. used large excesses of $PdCl_2(PhCN)_2$, AgOTf and *N*-methylmorpholine at room temperature [Equation (11)].[21] The authors proposed the coordination of the aldehyde to $Pd(OTf)_2$ and the formation of the oxo-η^3-allylpalladium intermediate $\mathbf{A_5}$ (Scheme 5) through the amine-mediated abstraction of a hydrogen. Because these conditions are ineffective for the dehydrogenation of ketones, the authors proposed for these substrates a protocol firstly involving the formation of a tin enolate, and secondly a transmetallation to afford the palladium enolate. Such a two-step reaction is beyond the scope of the present review. It seems worth mentioning, however, that this procedure has some analogy with the well-known Saegusa method involving the dehydrosilylation of silyl enol ethers with 1:1 mixtures of $Pd(OAc)_2$ and *p*-benzoquinone.[22]







3. Catalytic Procedures

Unlike the above section, this one, which summarises procedures leading to more cost-effective applications, is divided into four parts, depending on the natures of the substrates.

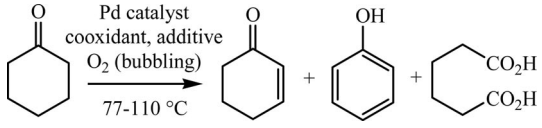
3.1. From Ketones

Kirschke's team patented catalytic methods almost simultaneously with their reports on stoichiometric Pd procedures. The first patents involve the dehydrogenation of cyclic and linear ketones with regeneration of active Pd^{II} species by means of H_2O_2 or, better, *t*BuOOH [Equations (12) and (13)].[23] Subsequently, the team proposed the use of various heteropolyacids associated to oxygen instead of peroxides [Equation (14)], sometimes with $Co(OAc)_2$ as a cocatalyst.[24]

Whereas Kirschke and co-workers patented their results with peroxides, Theisen reported, also in 1971 but in the open literature, a catalytic method based on the use either of a Cu^{II} salt/O_2 or of *p*-benzoquinone/O_2 as reoxidant.[25] Levels of conversion between 15 and 82% were attained at 77–110 °C from cyclopentanone, cyclohexanones, decalones and 3-oxo-5α-cholestane, but no more than 7% from cycloheptanone, cyclooctanone and linear ketones. The dehydrogenation of cyclohexanone was examined in particular (Table 1). Side-reactions were the formation of phenol and adipic acid. This aromatisation and this C–C bond cleavage are favoured by the reaction temperature. Indeed, Trost and Metzner have disclosed the $Pd(OCOCF_3)_2$-catalysed formation of 2-methylphenol from 2-methylcyclohexanone in bis(2-methoxyethyl) ether at reflux,[26] whereas the metal-catalysed oxidation of cyclohexanone to adipic acid with oxygen at 70 °C has also been reported.[27]

In 1982 we reported on $Pd(OCOCF_3)_2$-catalysed dehydrogenations of cyclohexanones under oxygen at room temperature.[28] Cyclohexanone afforded only cyclohex-2-enone at low levels of conversion. An increase in the level of conversion led to the appearance of phenol (Table 2). At room temperature, the aromatisation is favoured by an increase in the catalyst concentration (Run 9). This 1982 oxidation

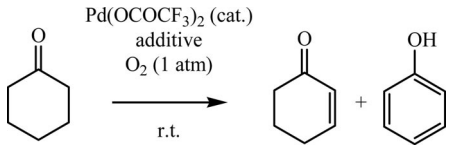
Table 1. Dehydrogenation of cyclohexanone under Theisen's conditions.[25]



Pd catalyst [equiv.]	Co-oxidant [equiv.]	O_2 [$cm^3\,min^{-1}$]	Additive [equiv.]	*T* [°C] *Time* [h]	Conversion [%]	Cyclohex-2-enone/ PhOH ratio
$PdCl_2(PPh_3)_2$ (0.0021)	$Cu(OAc)_2$ (0.042)	15	AcOH (0.82)	77 *10.5*	8	95:5[a]
$PdCl_2(PPh_3)_2$ (0.0028)	$CuCl_2(PPh_3)_2$ (0.015)	15	0	100 *6*	17	98:2[b]
$Pd(acac)_2$ (0.00016)	$Cu(acac)_2$ (0.021)	150	AcOH (0.87)	105 *24*	20–36	95:5[a],[b]
$Pd(acac)_2$ (0.00016)	*p*-benzoquinone (0.181)	10	AcOH (0.85)	110 *1*	15.3	98:2[b]
$Pd(acac)_2$ (0.00033)	*p*-benzoquinone (0.185)	15	$PhCO_2H$ (0.41)	110 *24*	43	88:12[a],[c]

[a] Some adipic acid formed. [b] Cyclohex-2-enone yield is approximately 15%. [c] Cyclohex-2-enone yield is approximately 36%.

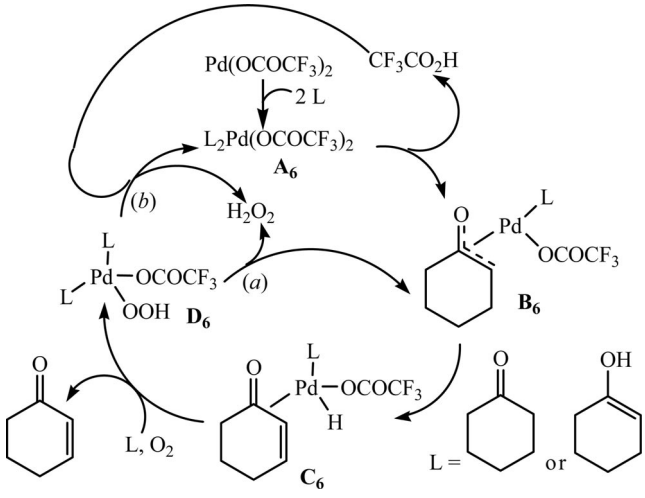
Table 2. Dehydrogenation of cyclohexanone under our conditions.[28]



Run	$Pd(OCOCF_3)_2$ [equiv.]	Additive [equiv.]	Time [d]	Conversion [%]	Cyclohex-2-enone/PhOH ratio	Yield [%] [a]	TON
1	0.002	0	1	1.2	100:0	1	6
2	0.002	CF_3CO_2H (0.01)	1	2.3	100:0	2	11
3	0.002	$Cu(OCOCF_3)_2$ (0.25)	1	4	100:0	4	20
4	0.002	PPh_3 (0.004)	1	0.21	100:0	0.2	1
5	0.002	0	6	5	100:0	5	25
6	0.02	0	1	11	100:0	10	5
7	0.02	0	5	64	79:21	50	32
8	0.02	molecular sieves [4 Å]	5	10	83:17	8	5
9	0.1	0	1	42	70:30	29	4

[a] Approximate yield of cyclohex-2-enone.

process was one of the first reports on the regeneration of active Pd^{II} species with use only of oxygen.[29] We proposed a mechanism in which the formal oxidation state of Pd^{II} remains constant throughout the reaction (Scheme 6).[30,31] Coordination of cyclohexanone or its enol form to $Pd(OCOCF_3)_2$ provides $\mathbf{A_6}$, which evolves to the oxo-η^3-allyl palladium complex $\mathbf{B_6}$ with liberation of CF_3CO_2H. Hydrogen abstraction by palladium affords $\mathbf{C_6}$. Insertion of oxygen into the Pd–H bond of $\mathbf{C_6}$ is accompanied by ligand exchange, giving cyclohex-2-enone and the hydroperoxy complex $\mathbf{D_6}$.[32] The latter species leads to H_2O_2, which has been characterised, and either $\mathbf{B_6}$ (path *a*) or $\mathbf{A_6}$ through a reaction with CF_3CO_2H (path *b*). The increase in the level of conversion with addition of CF_3CO_2H (Run 2) suggests the involvement of path *b*. As would be expected, use of $Cu(OCOCF_3)_2$ as an additive improved the process (Run 3). The decreases in the level of conversion in the presence either of PPh_3 (Run 4) or of molecular sieves (Run 8) could

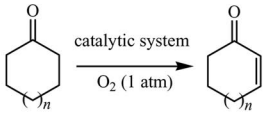


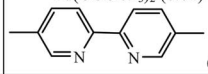
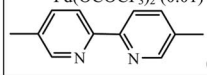
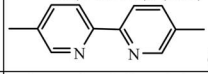
Scheme 6.

be due either to coordination of PPh_3 rather than substrate to the catalyst, or to trapping of CF_3CO_2H with the molecular sieves.

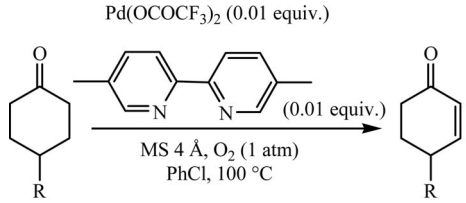
The above procedure was apparently unknown to the authors who subsequently reported studies in which Pd^{II}/O_2 systems were used to carry out the same transformation (Table 3).[18,33–36] Let us first consider the reports with $Pd(OCOR)_2$ (R = CF_3 or CH_3). More than ten years after our report, Fuchita and Harada used, under oxygen, the $Pd(OAc)_2/S(i\text{Bu})_2$ system that they had previously used under stoichiometric conditions (see Section 2): cyclohex-2-enone and cyclopent-2-enone were produced in <2% yields at 70 °C (Table 3, Entries 1 and 14).[18] The same reaction temperature was used for the dehydrogenation of cyclohexanone and cyclopentanone by Park and Oh, but with $Pd(OCOCF_3)_2$ as the catalyst.[34] These authors observed that the presence of phosphane and sulfide ligands could slightly increase the yields (compare Entries 3, 4 and 16, 17 with Entries 2 and 15, respectively), but they remained very low. A real improvement in the dehydrogenation of cyclohexanone was reported by Tokunaga and co-workers, who tested various bipyridine-type ligands, the best one being 5,5′-dimethyl-2,2′-bipyridine.[36] The reactions were carried out at 100 °C and, unlike in the previous reports, in a solvent. Chlorobenzene was more favourable for the process than toluene, but the increase in efficiency was accompanied by the appearance of phenol (compare Entries 5 and 6). The presence of molecular sieves was also beneficial to the process (compare Entries 6 and 7); this differs from our method, which, however, took place under very different conditions (Table 2, Entry 8). Under optimum conditions, the authors obtained an 84% yield of cyclohex-2-enone with only 4% phenol (Table 3, Entry 8). Similar experimental conditions afforded 51–78% yields from 4-substituted cyclohexanones [Equation (15)], whereas cyclohexanones substituted at their 2- or 3-positions, tetralone, cyclopentanone (Entry 18) and acyclic substrates gave lower yields.

Table 3. Pd^{II}-catalysed dehydrogenation of cycloalkanones under oxygen (see also Table 1 and 2).



Run	Cataytic system (equiv.)	Solvant	T °C, time	Yield %[a]	Turnover number
		$n = 1$			
1[18]	$Pd(OCOCH_3)_2$ (0.0046) $S(iBu)_2$ (0.0031)	substrate	70, 1.5 h	1.7	3.7
2[34]	$Pd(OCOCF_3)_2$ (0.0034)	substrate	70, 5 h	0.9	2.7
3[34]	$Pd(OCOCF_3)_2$ (0.0034) PPh_3 (0.0068)	substrate	70, 5 h	1.0	3.1
3[34]	$Pd(OCOCF_3)_2$ (0.0034) $(p\text{-}MeC_6H_4)_3P$ (0.0068)	substrate	70, 5 h	2	5.9
4[34]	$Pd(OCOCF_3)_2$ (0.0034) $S(nPr)_2$ (0.0068)	substrate	70, 5 h	1.4	4.2
5[36]	$Pd(OCOCF_3)_2$ (0.01)  (0.01)	PhMe	100, 24 h	25	25
6[36]	"	PhCl	100, 24 h	46[b]	46
7[36][c]	$Pd(OCOCF_3)_2$ (0.01)  (0.01)	PhCl	100, 24 h	70[d]	72
8[36][c]	"	PhCl	100, 48 h	84[b]	88
9[33]	$(MeCN)_2PdCl(NO_2)$ (0.013) AgOTf (0.013)	THF	r.t., 1 h	6	4.9
10[33]	$(MeCN)_2PdCl(NO_2)$ (0.024) AgOTf (0.024)	THF	r.t., 24 h	27[e]	11
11[35]	$Pd(NO_3)_2$ (0.0045) PPh_3 (0.0135)	substrate	75, 1.5 h	1	2.2
12[35]	$Pd(NO_3)_2$ (0.0045) $(p\text{-}MeC_6H_4)_3P$ (0.0135)	substrate	75, 1.5 h	1.2	2.7
13[35]	$Pd(NO_3)_2$ (0.0045) $S(iPr)_2$ (0.0068) (0.0135)	substrate	75, 1.5 h	0.9	2.0
		$n = 0$			
14[18]	$Pd(OCOCH_3)_2$ (0.0037) $S(iBu)_2$ (0.0025)	substrate	70, 1.5 h	1.5	4.1
15[34]	$Pd(OCOCF_3)_2$ (0.0027)	substrate	70, 5 h	0.4	1.6
16[34]	$Pd(OCOCF_3)_2$ (0.0027) $(p\text{-}MeC_6H_4)_3P$ (0.0054)	substrate	70, 5 h	0.5	2
17[34]	$Pd(OCOCF_3)_2$ (0.0027) $S(nPr)_2$ (0.0054)	substrate	70, 5 h	0.3	1.3
18[36][c]	$Pd(OCOCF_3)_2$ (0.01)  (0.01)	PhCl	100[f]	26	26
19[33]	$(MeCN)_2PdCl(NO_2)$ (0.011) AgOTf (0.011)	THF	r.t., 24 h	13	12
20[35]	$Pd(NO_3)_2$ (0.0036)	substrate	75, 1.5 h	0.9	2.6
21[35]	$Pd(NO_3)_2$ (0.0036) $(p\text{-}MeC_6H_4)_3P$ (0.0108)	substrate	75, 1.5 h	1.4	3.9
22[35]	$Pd(NO_3)_2$ (0.0036) SPh_2 (0.0108)	substrate	75, 1.5 h	1.1	3.2
		$n = 2$			
23[33]	$(MeCN)_2PdCl(NO_2)$ (0.013) AgOTf (0.013)	THF	r.t., 24 h	2.4	1

[a] Calculated on the basis of the initial amount of cycloalkanone. The levels of conversion were not published. [b] Formation of phenol (4%). [c] Reaction in the presence of molecular sieves (4 Å, 100 mg per mmol substrate). [d] Formation of phenol (2%). [e] Formation of phenol (0.6%). [f] Reaction time not indicated.



(15)

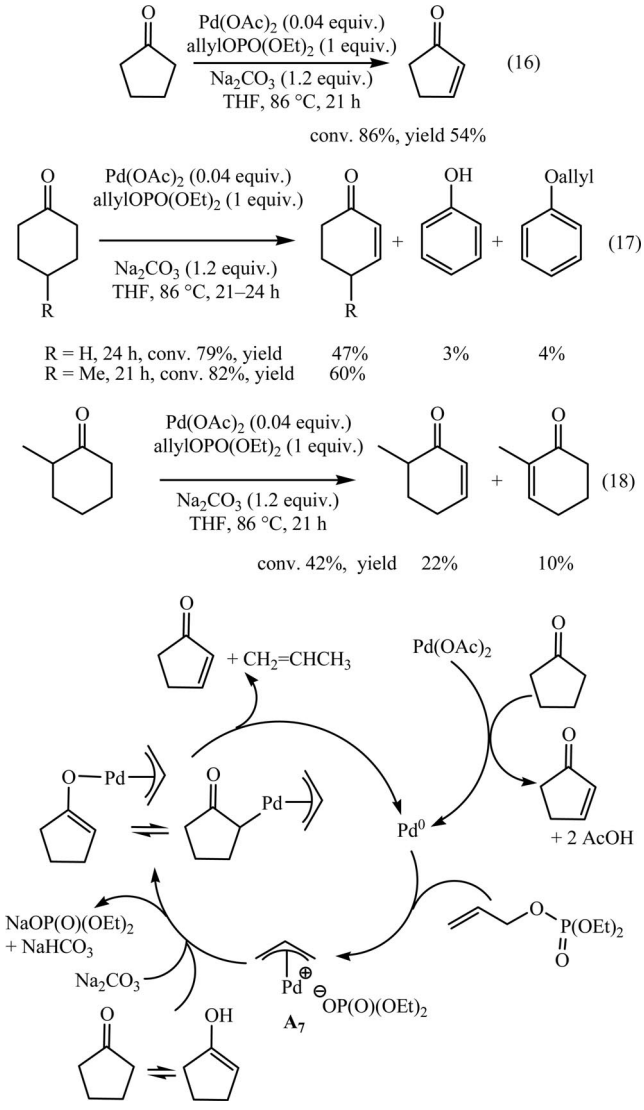
R = Me (96 h: 72%), Et (95 h: 78%), *t*Bu (44 h, 78%), Ph (48 h, 51 %)

Other types of Pd catalysts have also been used. In 1989, Wenzel disclosed the use, at room temperature, mainly in THF, of cationic palladium complexes, particularly $[(MeCN)_2PdNO_2][OTf]$, obtained in situ from $(MeCN)_2Pd(NO_2)_2$ and AgOTf.[33] Dehydrogenations of cycloalkanones occurred with yields decreasing from 27% with cyclohexanone to less than 3% with cycloheptanone (Table 3, Entries 9, 10, 19 and 23). Traces of but-3-en-2-one were detected from butan-2-one. A neutral nitro complex, $Pd(NO_3)_2$ associated with phosphane and sulfide ligands, was subsequently used by Park's team,[35] who had previously used such ligands with $Pd(OCOCF_3)_2$.[34] As shown in the main results depicted (Table 3, Entries 11–13 and 20–22), the yields were again very low.

In 1998, Shvo and Arisha submitted a new dehydrogenation procedure for cyclopentanone [Equation (16)] and cyclohexanones [Equations (17) and (18)], which consisted of heating in THF with 4 mol-% $Pd(OAc)_2$, Na_2CO_3 and allyl diethyl phosphate.[37] The allyl phosphate is a critical component of the method because no dehydrogenation occurred with a variety of other allylic compounds. A plausible mechanism with cyclopentanone as the substrate is depicted in Scheme 7. Stoichiometric dehydrogenation of cyclopentanone with $Pd(OAc)_2$ affords Pd^0, which reacts with the allyl phosphate to give the cationic η^3-allylpalladium species $\mathbf{A_7}$. Under basic conditions, the reaction between the substrate and $\mathbf{A_7}$ affords an η^3-allylpalladium enolate, which evolves to cyclopent-2-enone, propene and Pd^0.

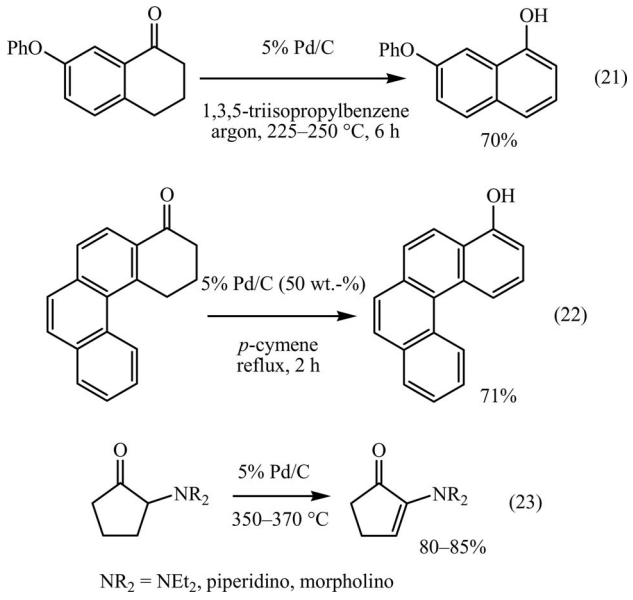
It seems worthwhile to mention dehydrogenations that were not really the researched reactions. The above $Pd(OAc)_2$/allyl diethyl phosphate/Na_2CO_3 procedure is also effective for the catalytic oxidation of alcohols.[38] When used with cyclohexanol or cholesterol as the substrate, dehydrogenation of the resulting ketone is observed [Equation (19)].[37,39] The Pd/ArBr/K_2CO_3 system, which oxidises alcohols,[38] also dehydrogenates cholesterol, although leading to cholesta-4,6-dien-3-one [Equation (20)][40] rather than cholesta-1,4,6-trien-3-one [Equation (19)]. In the course of study of the Wacker oxidation of cyclopentene, Takehira and co-workers observed the further oxidation of cyclopentanone into cyclopent-2-en-1-one.[41]

As noted above, the dehydrogenation of cyclohexanone can lead to phenol as a side-product. This potential overdehydrogenation has been used for the synthesis of phenols,[42] naphthols [Equation (21)][43] and 4-hydroxybenzo[*c*]phenanthrene [Equation (22)][44] from the corresponding ketones, usually under harsh experimental conditions.



Scheme 7.

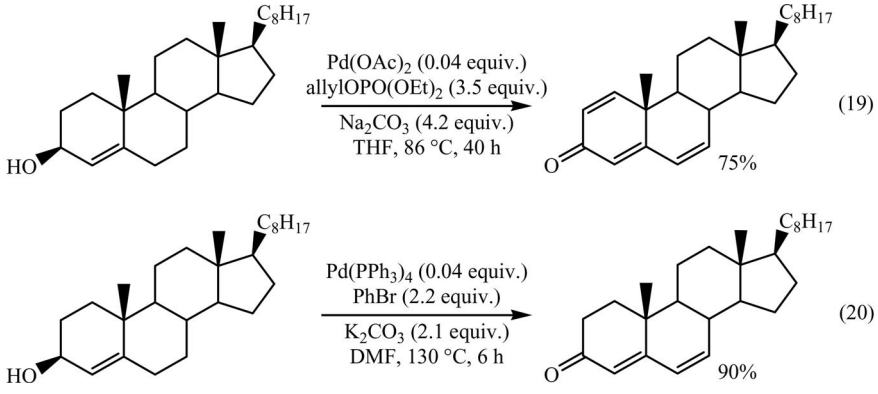
Such conditions have been used for the dehydrogenation of *N*,*N*-disubstituted 2-aminocyclopentanones [Equation (23)].[45]



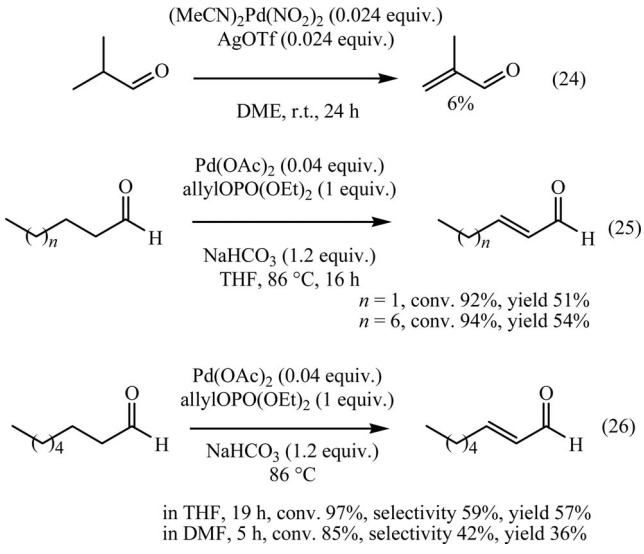
Before the end of this section it seems worthwhile also to mention catalytic systems that have been inefficient for the dehydrogenation of ketones. Miura et al. reported that no reaction of 1-phenyloctan-3-one was induced in DMF at 100 °C in the presence of the $Pd(OAc)_2/PPh_3$ catalytic system associated with over-stoichiometric amounts of $Cu(OTf)_2$ and K_2CO_3.[46] Li's team reported that their $Pd(OAc)_2$/amine/O_2/DMSO dehydrogenation methods for β-arylated aldehydes (vide infra) are not useful for reactions of β-arylated ketones.[47,48]

3.2. From Aldehydes

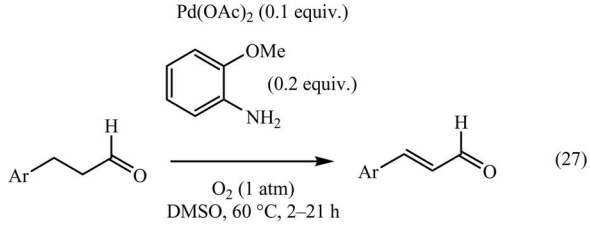
Two of the above catalytic methods have been tested for the dehydrogenation of aldehydes. The $(MeCN)_2Pd(NO_2)_2$/AgOTf/DME system afforded a 6% yield of methacrylaldehyde from isobutyraldehyde [Equation (24)],[33] whereas the $Pd(OAc)_2$/allyl diethyl phosphate/THF procedure, with $NaHCO_3$ instead of Na_2CO_3, gave fair yields from pent-



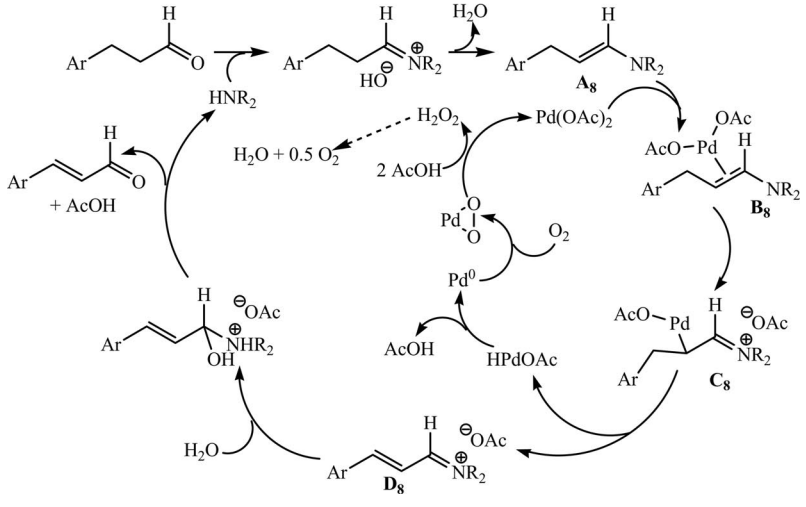
anal, octanal and decanal [Equations (25) and (26)].[37] Carried out in DMF, the reaction of octanal occurred more quickly than in THF but with a lower selectivity [Equation (26)]. The authors suggested that the rate difference might be attributable to the greater solubility of the carbonate salt in DMF. This, however, would not explain the selectivity difference. Our studies relating to the solvent-dependent Pd-catalysed isomerisation of allylic acetates in THF and DMF[49] led us to propose that the solvent-dependent selectivity of the Pd-catalysed dehydrogenation of octanal could be due to subtle differences in some palladium intermediates.



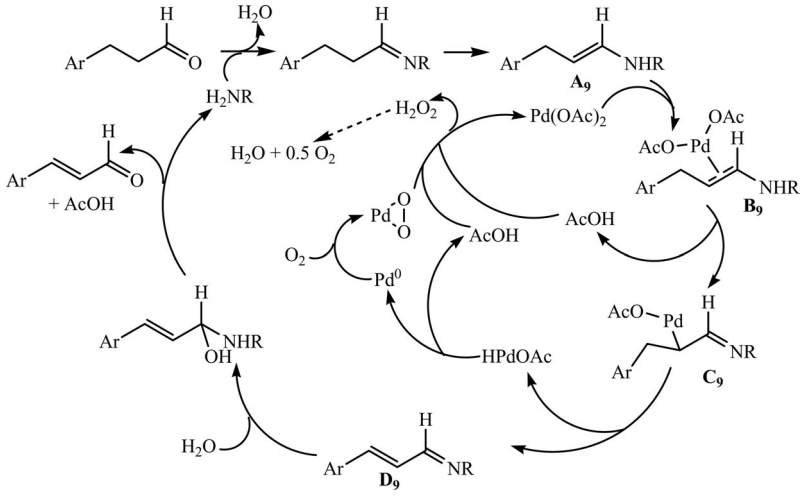
In 2009, Li and co-workers disclosed the $Pd(OAc)_2$-catalysed dehydrogenation of β-arylated aldehydes in the presence of oxygen and catalytic amounts of (*S*)-diphenylprolinol in DMSO.[47] In view of the price of (*S*)-diphenylprolinol, the team looked for a more cost-effective amine.[48] Screening of various amines led them to choose *o*-anisidine [Equation (27)]. Use of solvents other than DMSO led to lower yields. Interestingly, no oxidation of the aldehyde into the corresponding acid was observed. A limitation of the process, however, is the requirement for a substrate bearing an aryl group in the β-position, with no reaction occurring in the case of 4-phenylbutanal. The mechanisms proposed by the authors with either a secondary amine or a primary amine are similar (Schemes 8 and 9). Both involve the initial formation of an enamine (**A$_8$** or **A$_9$**) from the reaction between the substrate and the amine. Coordination of **A$_8$** (or **A$_9$**) to $Pd(OAc)_2$ affords the η^2 complex **B$_8$** (or **B$_9$**) which evolves to **C$_8$** (or **C$_9$**). β-H elimination of HPdOAc, which would be favoured by the Ar substituent through a conjugation effect,[47,48] gives iminium **D$_8$** (or imine **D$_9$**). Hydrolysis of this finally provides the α,β-unsaturated aldehyde, regen-



Ar = Ph (16 h, 54%), 2-MeC_6H_4 (21 h, 54%), 2-$MeOC_6H_4$ (19 h, 45%), 3-MeC_6H_4 (16 h, 58%), 4-MeC_6H_4 (2 h, 58%), 4-EtC_6H_4 (13 h, 62%), 4-AcC_6H_4 (2 h, 44%), 4-$MeOCOC_6H_4$ (10 h, 47%), 4-NCC_6H_4 (12 h, 55%), 4-$O_2NC_6H_4$ (18 h, 56%), 2,4-$Cl_2C_6H_3$ (9 h, 51%), 2-Me-4-$O_2NC_6H_3$ (11 h, 68%), 1-biphenyl (13 h, 72%), 1-naphthyl (13 h, 62%)



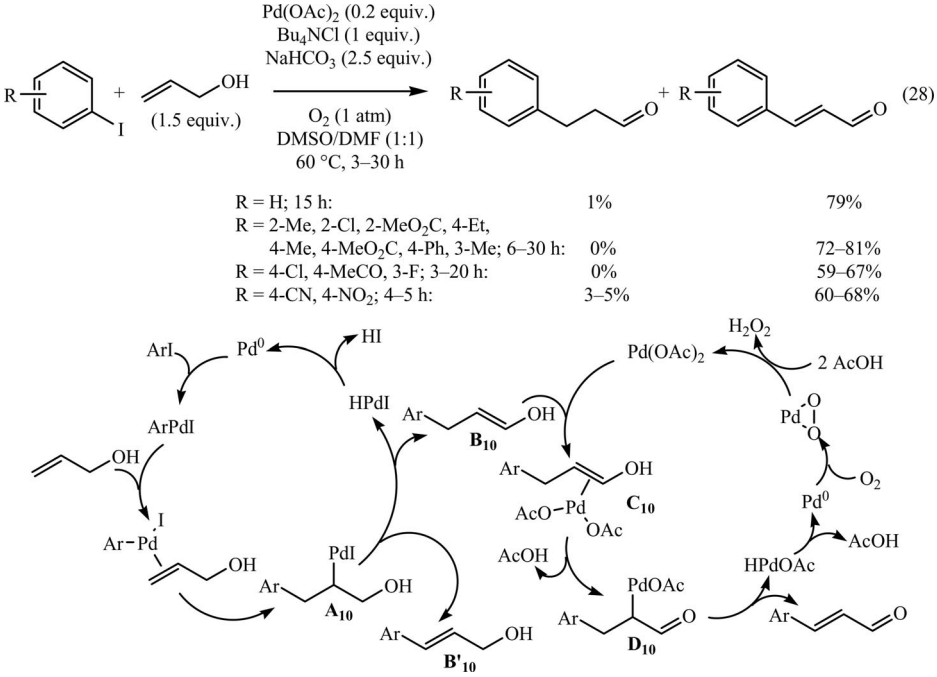
Scheme 8.



Scheme 9.

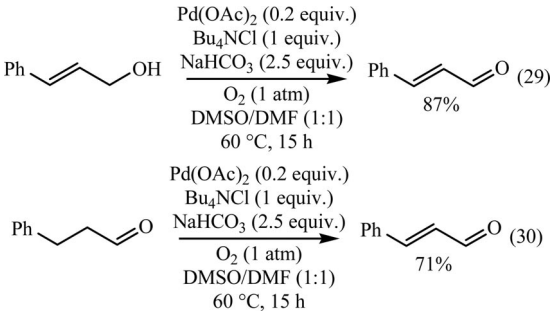
erating the amino cocatalyst. According to the authors, recycling of the Pd catalyst occurs through decomposition of HPdOAc into Pd^0. Oxidation of this with oxygen would afford PdO_2, reaction of which with AcOH gives $Pd(OAc)_2$. The authors argue that their mechanism proposals are "based on the established typical Saegusa oxidation reaction mechanism" reported by the teams of Larock and Mulzer.[50,51] The reactions reported by Saegusa,[22] Larock,[50] Mulzer[51] and their co-workers occur in the absence of any base, however, whereas the dehydrogenations under Li's conditions are performed in the presence of amine (2 equiv. per Pd). This amine can trap the acid required to generate $Pd(OAc)_2$ from PdO_2.[50] These factors, as well as the non-promoting effect of the addition of AcOH,[47] led us to suspect other possible mechanisms.[39]

Very recently, Li and co-workers reported an interesting and useful synthesis of enals from aryl iodides and allyl alcohol, through a reaction [Equation (28)] that they arbitrary called the "Pd-catalysed cascade Heck–Saegusa reaction".[52] Under the conditions depicted in Equation (28), use of (*S*)-diphenylprolinol or *o*-anisidine (0.2 equiv.) as additive decreased both the yield and the selectivity. Lower yields and selectivities were also obtained in DMSO or DMF instead of the DMF/DMSO mixture. As a mechanism leading to ArCH=CHCOH, the authors proposed the addition of ArPdI to the substrate to give $\mathbf{A_{10}}$ (Scheme 10). The authors consider that elimination of HPdI from $\mathbf{A_{10}}$ would afford $\mathbf{B_{10}}$ or $\mathbf{B'_{10}}$. Coordination of $\mathbf{B_{10}}$ to $Pd(OAc)_2$ would give $\mathbf{C_{10}}$, which would evolve to $\mathbf{D_{10}}$ by liberation of AcOH.[53] The β-arylated enal is obtained either from $\mathbf{D_{10}}$



Scheme 10.

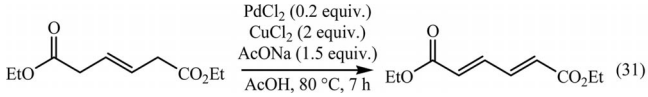
through elimination of HPdOAc or through oxidation of $\mathbf{B'_{10}}$. According to the authors, the formation of cinnamaldehyde both from cinnamyl alcohol [Equation (29)] and from 3-phenylpropanal [Equation (30)] under their experimental conditions corroborates their hypothesis. They did indeed assume the formation of the vinylic alcohol $PhCH_2CH{=}CHOH$ as an intermediate for the dehydrogenation of 3-phenylpropanal into cinnamaldehyde [Equation (30)]. This last reaction, which occurred without any (*S*)-diphenylprolinol or *o*-anisidine, led us to question the mechanisms depicted in Schemes 8 and 9.



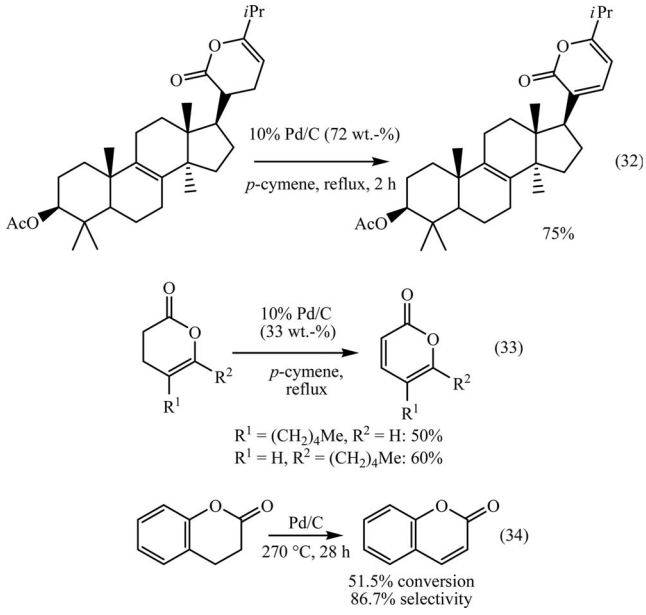
We also have a few remarks to add with regard to the synthesis of β-arylated enals from ArI and allyl alcohol, and the proposed mechanism. The formation of β-aryl α,β-unsaturated carbonyl compounds through Heck reactions of unsaturated alcohols had previously been observed.[46,54,55] It was proposed that these compounds were obtained either from the oxidation of β-aryl α,β-unsaturated alcohols, or from oxidation of the allylic alcohols followed by Heck arylation. In addition, the release of $\mathbf{B_{10}}$ from $\mathbf{A_{10}}$ could be a minor pathway, because Smadja and co-workers have shown that the β-H elimination gives mainly the Pd complex $\mathbf{B_{11}}$, which has the vinylic alcohol as ligand (Scheme 11).[56] Subsequent addition/elimination of HPdI would give arylated aldehyde $\mathbf{D_{11}}$, with the $\mathbf{C_{11}} \rightarrow \mathbf{D_{11}}$ step occurring either through the usually accepted β-hydride elimination or through an iodide-mediated reductive elimination.[57] According to the literature, Heck arylations of allyl alcohol in the presence of halide anions led to a large predominance of $\mathbf{D_{11}}$ over $\mathbf{B'_{10}}$.[54c,55,58,59] In view of the above remarks, we suspect that Li's cascade reaction occurs mainly via intermediate $\mathbf{D_{11}}$.

3.3. From Esters and Lactones

The above $Pd(OAc)_2$/amine/O_2/DMSO methods are not suitable for the dehydrogenation of β-arylated esters.[47,48] With $CuCl_2$ as the reoxidant, Suzuki and Tsuji dehydrogenated diethyl hex-3-enedioate in 64% yield [Equation (31)], a reaction described under stoichiometric $PdCl_2$ conditions in Section 2 (see Scheme 2 for the mechanism).[8]

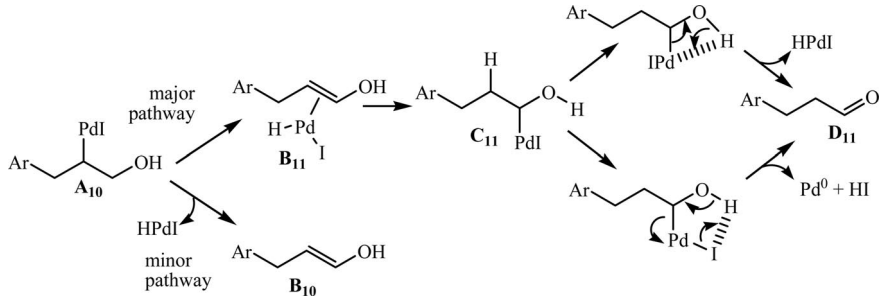


Dehydrogenations of tetrahydropyran-2-ones and 3,4-dihydropyran-2-ones have been carried out under the harsh conditions employed for the synthesis of phenols from cyclohexanones. A few examples are shown in Equations (32),[60] (33),[61] and (34).[62]



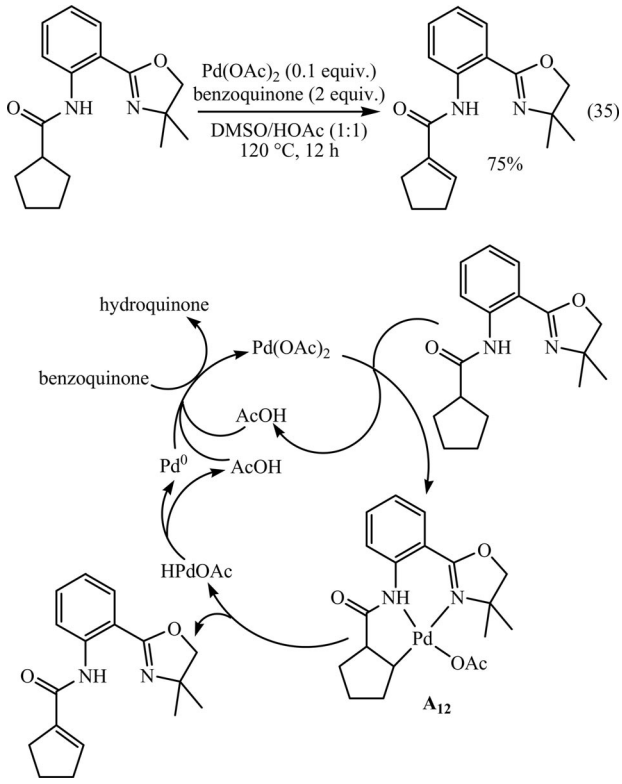
3.4. From Amides

Yu and co-workers reported the dehydrogenation of the cyclopentylcarboxamide shown in Equation (35).[63] According to other reactions they carried out with stoichio-



Scheme 11.

metric amounts of $Pd(OAc)_2$, it seems that the oxazoline moiety is involved in the reaction intermediates. This leads us to suspect the formation of complex $\mathbf{A_{12}}$ (Scheme 12) as an intermediate. The enamide would be obtained from $\mathbf{A_{12}}$ by elimination of HPOAc, with this leading to Pd^0, which would be reoxidised into $Pd(OAc)_2$ with the benzoquinone/AcOH system.[64]



Scheme 12.

4. Conclusion

Even when they occur with high selectivities, interest in the stoichiometric Pd methods to obtain α,β-unsaturated carbonyl compounds directly from the corresponding saturated substrates remains limited because of the price of the palladium salts. Palladium-catalysed procedures for such one-pot reactions have emerged over the years, but those leading to fair yields are limited to a few types of substrate. There is thus no doubt that the two-step procedures involving the successive synthesis and treatment of silyl enol ethers,[22,50,65,66] enol acetates[66,67] or allyl enol carbonates[68] with Pd catalysts[69] will continue to be widely used.

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