

# Palladium-Catalyzed Alcohol Oxidation by Direct O<sub>2</sub>-Coupled Turnover

13th/Dec/2011 Ozawa Jun (B4)

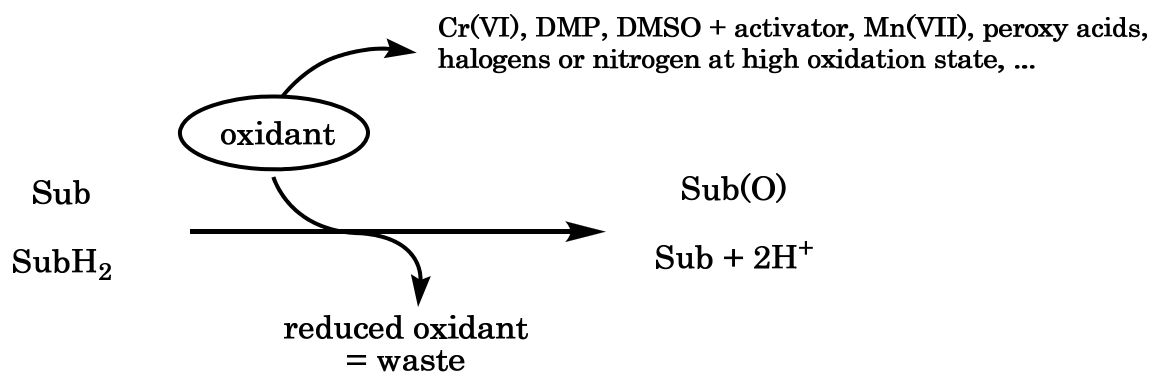
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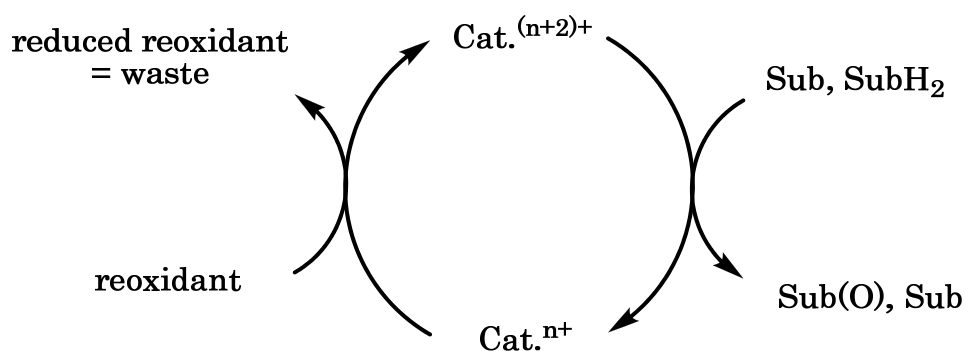
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## 1. Introduction

### \* stoichiometric oxidation



### \* catalytic oxidation

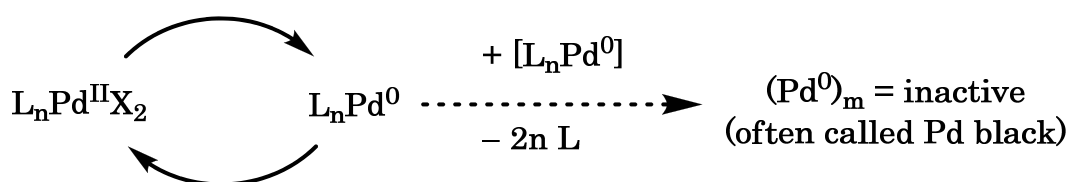


\* Molecular oxygen is the best oxidant of the catalyst from the viewpoint of reducing the wastes, lowering cost, facilitating product isolation, etc.

\* In many reactions, however, other reoxidants such as NMO, benzoquinone, or O<sub>2</sub> with cocatalyst like Cu(II) are often employed because molecular oxygen itself is not an effective oxidant.

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\* Direct aerobic oxidation of palladium often cannot compete kinetically with aggregation of the catalyst into inactive bulk metal.  
= catalyst decomposition



this results in low turnover number

To overcome this problem, many researches have been done.

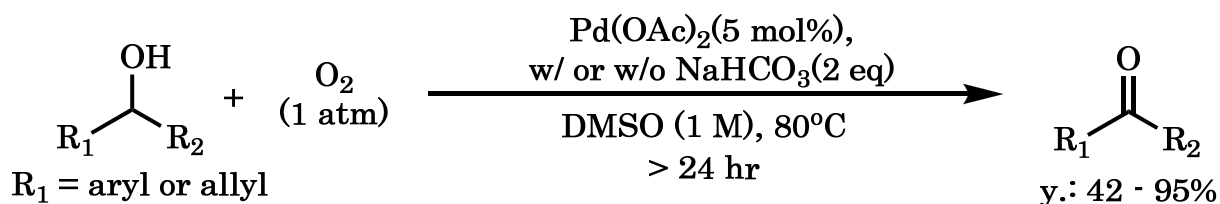
## 2. Alcohol Oxidation Reactions

Stoichiometric alcohol oxidation by Pd(II) was achieved by Berzelius in 1828, but it was 150 years later that catalytic alcohol oxidations by palladium and O<sub>2</sub> without cocatalyst was discovered.

In the last decade we have seen a lot of significant advances in the Pd-catalyzed aerobic alcohol oxidation.

### 2.1 The Pd(OAc)<sub>2</sub>/DMSO system

\* First reported by Larock group in 1998.



K. P. Peterson, R. C. Larock, *J. Org. Chem.* 1998, 63, 3185 - 3189

\* Alcohols are oxidized catalytically by Pd and O<sub>2</sub> without metal cocatalyst.

\* The base is thought to deprotonate the H of Pd(OAc)-HOR complex.

Δ High temperature and long reaction time is required.

Δ This method isn't applicable to aliphatic alcohols.

Table 2. Oxidation of Primary and Secondary Allylic and Benzylic Alcohols

entry	substrate	product	procedure	time (d)	% isolated yield
1			B	2	90 <sup>a</sup>
2			B	1	92
3			B	0.5	95
4			B	3	66
5			B	3	48 <sup>a</sup>
6			B	3	57
7			B	3	59
8			A	7	96
9			A	1	95

\* Substrate scope

{ procedure A: w/ NaHCO<sub>3</sub>  
procedure B: w/o NaHCO<sub>3</sub>

10			A	1	81
11			A	1	83
12			A	3	57
13			B	2	50 <sup>a</sup>
14			B	1.5	69 <sup>b</sup>
15			B	1	42 <sup>a,c</sup>
16			A	2	67
17			B	1	53 <sup>a</sup>

<sup>a</sup> Yield determined by gas chromatography. <sup>b</sup> Reaction used 1 mmol of substrate in 5 mL of DMSO. <sup>c</sup> Phenol observed in 37% yield by gas chromatography.

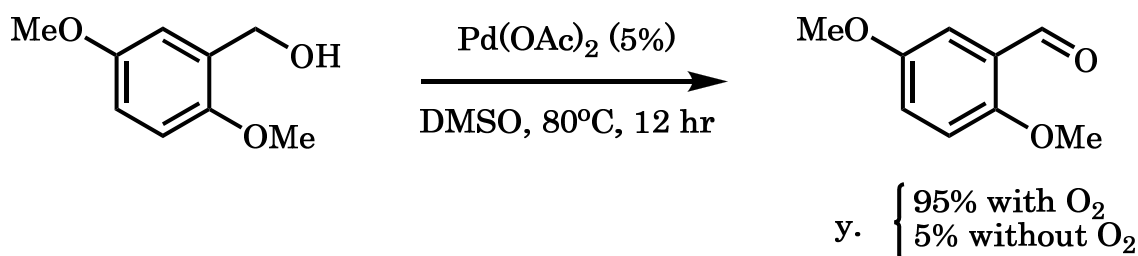
- \* Electron-rich aryl alcohols produce high yields (81 - 95 %).
  - \* Electron-poor aryl or allyl alcohols, and a hydroxybenzyl alcohol produce relatively low yields (42 - 69%).
  - \* In case of primary alcohols, better yields were obtained without NaHCO<sub>3</sub>; for bad mixture is produced with NaHCO<sub>3</sub> and the mixture makes it difficult to isolate the carbonyl products.
- Δ This system is ineffective for the oxidation of aliphatic alcohols.

\* the mechanistic study

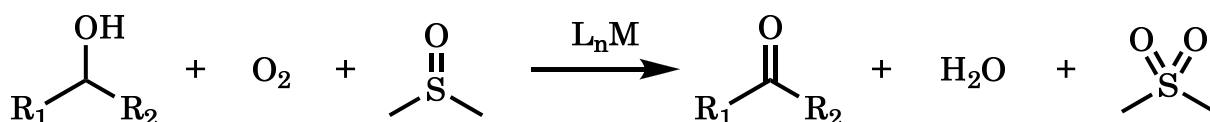
B. A. Steinhoff, S. R. Fix, S. S. Stahl, *J. Am. Chem. Soc.* 2002, 124, 766 - 767

- DMSO isn't involved in the redox cycle.

1) The reactions require O<sub>2</sub> or air atmosphere.



2) Only a trace of Me<sub>2</sub>S(O)<sub>2</sub> is produced during the alcohol oxidation, which means the reaction like the one below doesn't occur.

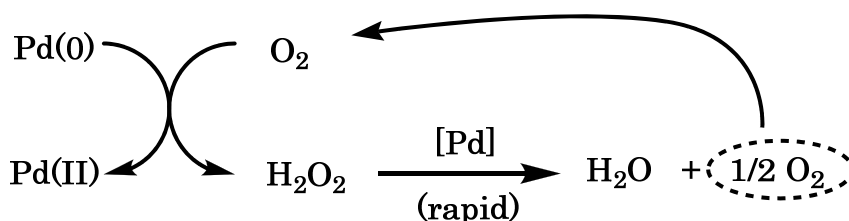


L<sub>n</sub>M = RhCl<sub>3</sub>, IrCl<sub>3</sub>, [Cu(MeCN)<sub>4</sub>]<sup>+</sup>

Trocha-Grimshaw, J.; Henbest, H. B. *Chem. Commun.* 1968, 1035 - 1036  
 Gamp, H.; ZuberbuNhler, A. D. *J. Mol. Catal.* 1980, 7, 81-88

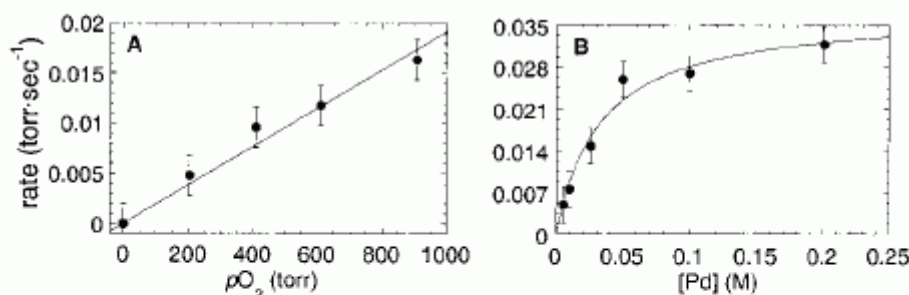
- \* Judging from 1) and 2), DMSO isn't involved in the redox cycle. DMSO-Pd coordination is thought to facilitate the oxidation of Pd(0) by O<sub>2</sub> and/or diminish the aggregation of Pd(0).

- 1 equiv. of O<sub>2</sub> yields 2 equiv. of carbonyl product. It appears that no H<sub>2</sub>O<sub>2</sub> is produced, but it isn't true. H<sub>2</sub>O<sub>2</sub> is produced, but it immediately turns into H<sub>2</sub>O under catalytic conditions.



(G. Bianchi, *et al. Electronica Acta.* 1962, 7, 457 - 473)

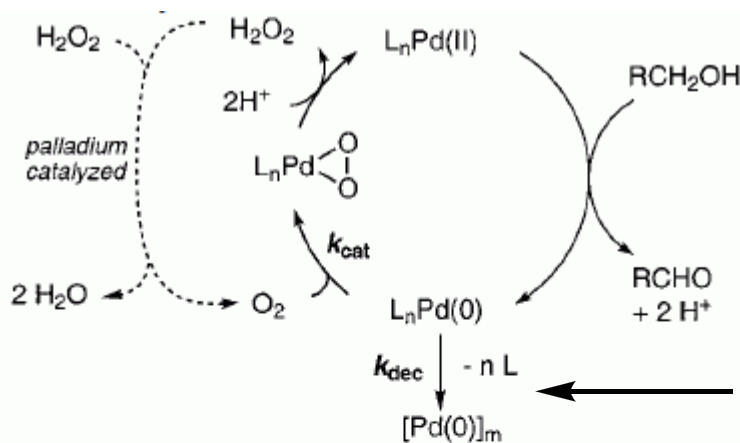
- The dependence of each factor on the reaction rate



\* The reaction rate doesn't depend on [alcohol] but on both  $pO_2$  and  $[Pd]$ ; therefore, reoxidation of  $Pd(0)$  by  $O_2$  is the rate-limiting step.

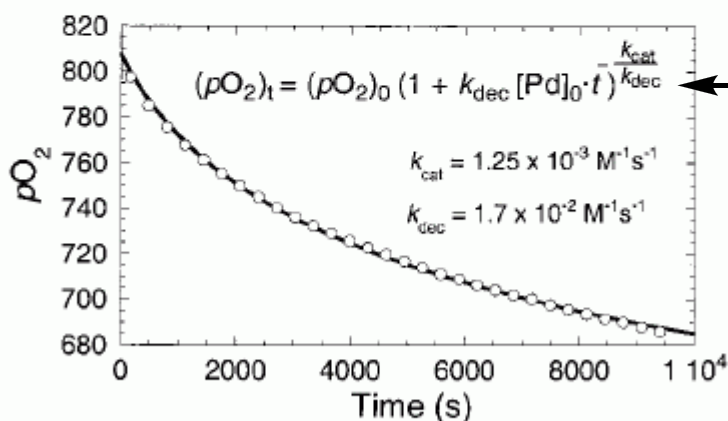
**Figure 1.** Dependence of the catalytic rate on initial dioxygen pressure, and catalyst and substrate concentrations at  $t = 800$  s. Rates were obtained by monitoring pressure changes during catalytic turnover. The curve in B is derived from a nonlinear least-squares fit of the data to eq 7. Reaction conditions: (A)  $[I] = 1.0$  M,  $[Pd(OAc)_2] = 0.05$  M,  $pO_2 = 0-908$  Torr, 2 mL of DMSO, 80 °C. (B)  $[I] = 1.0$  M,  $[Pd(OAc)_2] = 0.005-0.20$  M, 2 mL of DMSO, 80 °C, rates normalized to  $pO_2 = 1000$  Torr.

(the alcohol-rate graph isn't in the paper)



$$\frac{d[Pd]}{dt} = -k_{dec}[Pd]^2$$

substitute



$$\begin{aligned} \frac{d(pO_2)}{dt} &= k_{cat} \times [Pd]_t \times pO_2 \\ &= -k_{cat} \times \frac{[Pd]_0}{1 + k_{dec}[Pd]_0 t} \times pO_2 \end{aligned}$$

**Figure 2.** A 10 000 s time-course (O) for the catalytic oxidation of 1 (30 of 9500 data points shown). The fit (—) is based on integration of the rate expression in eq 7 (see inset). Reaction conditions:  $[I] = 1.0$  M,  $[Pd]_0 = 0.05$  M,  $(pO_2)_0 = 807$  Torr, 2 mL of DMSO, 80 °C.

\* The supposition that Pd decomposition is proportional to  $[Pd]^2$  is compatible with the experimental result (Fig. 2).

\* The lack of a rate dependence on [alcohol] is consistent with the independent observation that stoichiometric alcohol oxidation by  $Pd(OAc)_2$  occurs within seconds under anaerobic conditions, much faster than the initial catalytic turnover rates (4 - 5 turnovers/h).

♣ in relation to the rate-limiting step -Mass-Transfer-Limitation Effect of O<sub>2</sub>-

\* If the amount of Pd(OAc)<sub>2</sub> loading is reduced, the initial reaction rate become independent of O<sub>2</sub> pressure and dependent on [alcohol].

B. A. Steinhoff, S. S. Stahl, *JACS*, 2006, 128, 4348 - 4355

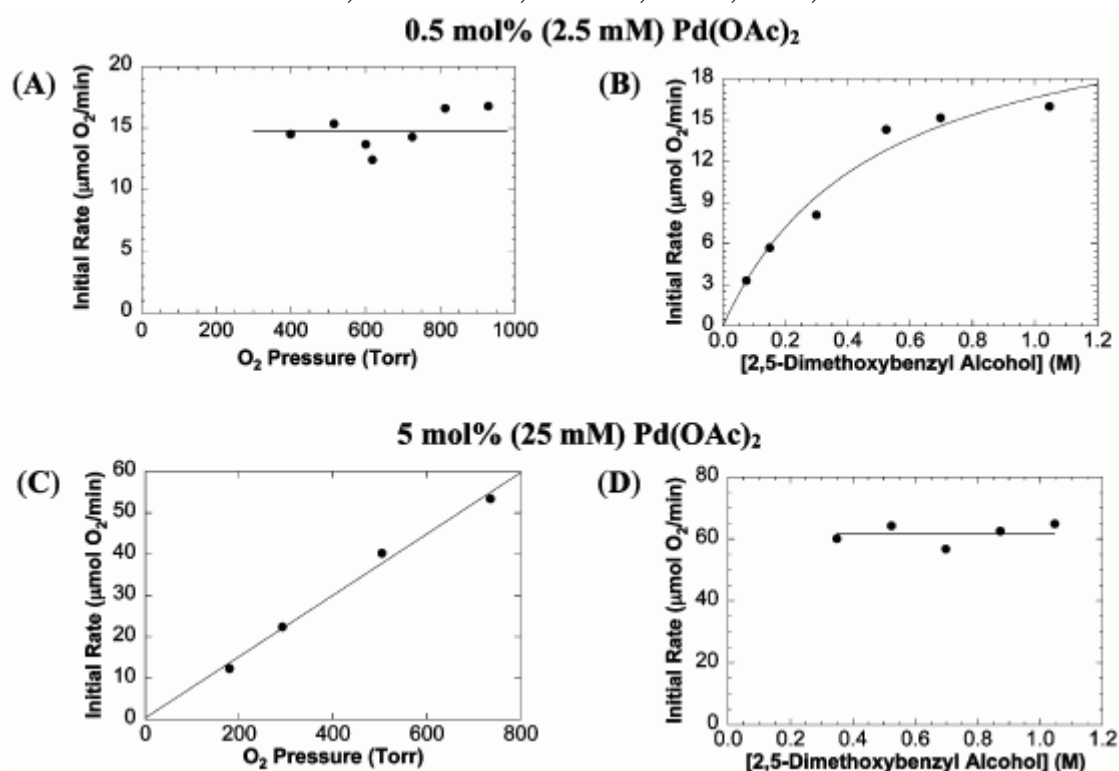


Figure 3. Dependence of the initial rate on oxygen pressure and alcohol concentration at both low and high catalyst loadings in the Pd(OAc)<sub>2</sub>/DMSO catalyzed aerobic oxidation of primary alcohol 1. Conditions: (A) 2.5 mM Pd(OAc)<sub>2</sub>, 399-913 Torr O<sub>2</sub>, 0.52 M 2,5-dimethoxybenzyl alcohol, 2 mL of DMSO, 80°C, in 25.4 mm OD tube; (B) 2.5 mM Pd(OAc)<sub>2</sub>, 730 Torr O<sub>2</sub>, 0.105-1.04 M 2,5-dimethoxybenzyl alcohol, 2 mL of DMSO, 80°C, in 25.4 mm OD tube, data fit to a hyperbolic curve; (C) 25.2 mM Pd(OAc)<sub>2</sub>, 179-735 Torr O<sub>2</sub>, 520 mM 2,5-dimethoxybenzyl alcohol, 2 mL of DMSO, 80°C, in 25.4 mm OD tube; (D) 24.9 mM Pd(OAc)<sub>2</sub>, 725 Torr O<sub>2</sub>, 0.349-1.05 M 2,5-dimethoxybenzyl alcohol, 2 mL of DMSO, 80°C, in 25.4 mm OD tube, rates normalized to 1 atm.



\* If an adequate supply of O<sub>2</sub> is available in solution, which accelerates the Pd(0) oxidation by O<sub>2</sub>, the alcohol oxidation step will be the turnover-limiting step instead of alcohol oxidation step in this system.

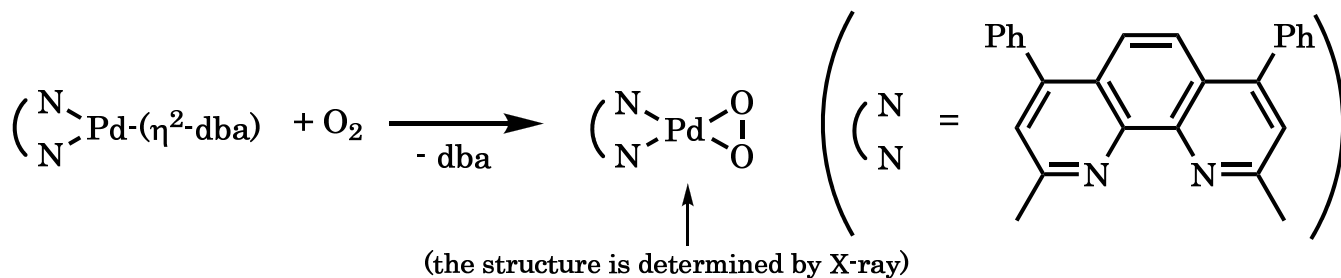
Table 2. Oxygen Gas Solubility in Common Solvents

solvent	O <sub>2</sub> solubility (mM) <sup>a</sup>	ref
perfluorobenzene	21.0	11c
<i>n</i> -hexane	15.7	11c
acetone	11.0	11b
chloroform	9.1 <sup>b</sup>	11a
ethyl acetate	8.9 <sup>c</sup>	11c
toluene	8.7	11c
acetonitrile	8.1	11b
<i>N,N</i> -dimethylformamide	4.5	11b
dimethyl sulfoxide	3.2 <sup>d</sup>	this work
dimethyl sulfoxide	2.2	11c
H <sub>2</sub> O	1.3	11c

<sup>a</sup> 25 °C unless otherwise indicated. <sup>b</sup> 16 °C. <sup>c</sup> 20 °C. <sup>d</sup> 80 °C.

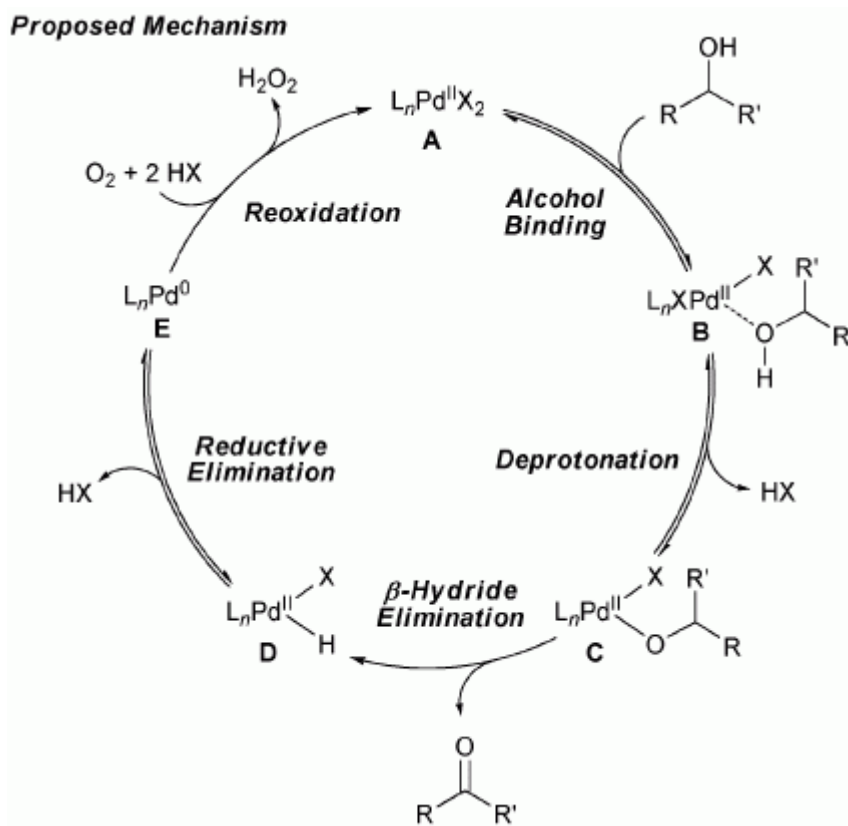
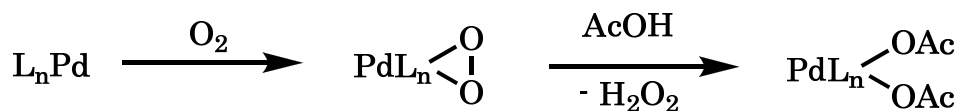
\* The main reason for this is the poor O<sub>2</sub> solubility in DMSO (about one third of that in toluene or CHCl<sub>3</sub>).

- The precedent implies the generation of Pd-peroxo complex.



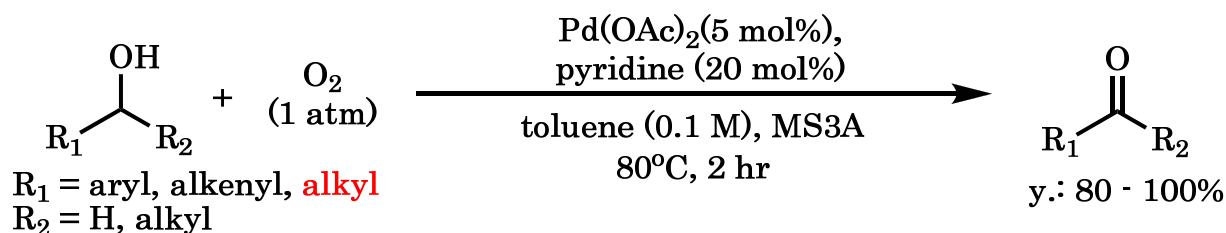
Stahl, S. S., Thorman, J. L., Nelson, R. C., Kozee, M. A. *J. Am. Chem. Soc.* 2001, 123, 7188 - 7189

\* According to the precedent above, it is not odd to think that Pd(0) is oxidized to Pd-peroxo complex and subsequently protonated by AcOH to reproduce Pd(OAc)<sub>2</sub>.



## 2.2 Pd(OAc)<sub>2</sub>/Pyridine system

\* First reported by Uemura group in 1998.

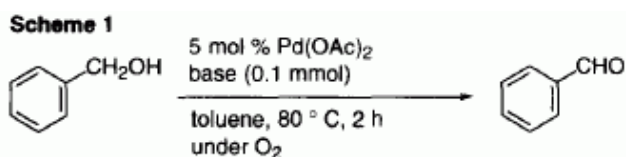


T.Nishimura, T. Onoue, K. Ohe, S. Uemura, *Tetrahedron Lett.* 1998, 39, 6011 - 6014

T.Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* 1999, 64, 6750 - 6755

- \* Py is the best base among the bases examined (see the tables below).
- \* At least 4 equiv. of Py to Pd(OAc)<sub>2</sub> is required for the effective conversion.
- \* High yields are obtained in short reaction time.
- \* MS3A works as a base and provides heterogeneous surface that hinders Pd aggregation (ref: *J. Org. Chem.* 2006, 71, 1861 - 1868).
- Δ High temperature is necessary.

### \* Ligand screening



**Table 1. Pd(OAc)<sub>2</sub>-Catalyzed Oxidation of Benzyl Alcohol by Molecular Oxygen<sup>a</sup>**

entry	base	conversion(%)	GLC yield(%) <sup>b</sup>
1	—	5	5
2	pyridine	86	86
3	2,6-lutidine	82	81
4	triethylamine	78	76
5	2,2'-bipyridine	5	5
6 <sup>c</sup>	pyridine	~100	quantitative

a) Reaction conditions; Pd(OAc)<sub>2</sub> (0.05 mmol), benzyl alcohol (1.0 mmol), base (0.1 mmol), toluene (10 mL), under atmospheric O<sub>2</sub> at 80 °C for 2 h.

b) Bibenzyl was used as an internal standard.

c) In the presence of MS3A (500 mg).

\* Other Pd(II) such as PdCl<sub>2</sub>, Pd(dba)<sub>2</sub>, PdCl<sub>2</sub>(MeCN)<sub>2</sub>, Pd(OCOCF<sub>3</sub>)<sub>2</sub>, and Pd(PPh)<sub>4</sub> proved ineffective, and other solvents such as CH<sub>2</sub>Cl<sub>2</sub>, THF, Et<sub>2</sub>O, and 1,4-dioxane were also ineffective.

**Table 1. Pd(II)-Catalyzed Oxidation of Benzyl Alcohol by Molecular Oxygen in the Presence of Various Pyridine Derivatives<sup>a</sup>**

entry	base	conv. (%)	GLC yield <sup>b</sup> (%)
1		~100	quantitative
2		~100	quantitative
3		93	90
4		71	71
5		5	5
6		5	5
7		30	22

<sup>a</sup> Reaction conditions: Pd(OAc)<sub>2</sub> (0.05 mmol), benzyl alcohol (1.0 mmol), base (0.2 mmol), toluene (10 mL), MS3A (500 mg), O<sub>2</sub>, 80 °C, 2 h. <sup>b</sup> Bibenzyl was used as an internal standard.



\* Substrate scope (extract)

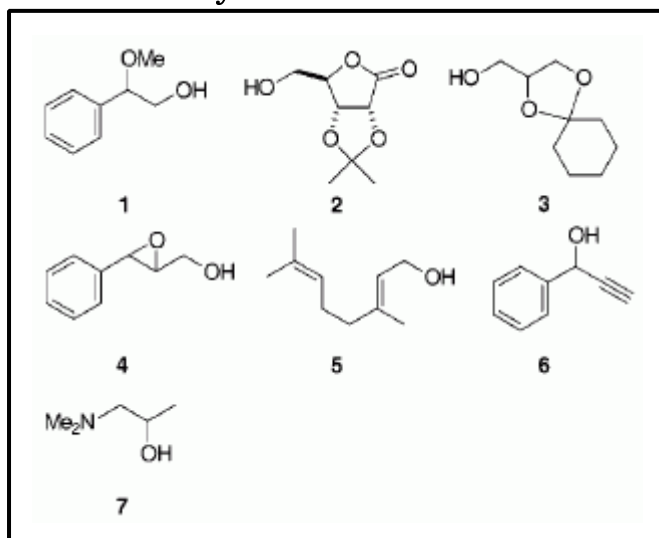
This method is applicable to wide range of alcohols.

Table 4. Pd(II)-Catalyzed Oxidation of Diols by Molecular Oxygen<sup>a</sup>

entry	substrate	product	isolated yield(%) <sup>b</sup>
1			85
2			80
3			64 <sup>c</sup>
4		 	91 (1/2=53/47) <sup>d</sup>

<sup>a</sup> Reaction conditions: see footnote a of Table 2. <sup>b</sup> Substrates were completely consumed. <sup>c</sup> GLC yield. <sup>d</sup> Determined by <sup>1</sup>H NMR.

hardly-oxidized substrates



\* 3 ~ 5 were oxidized relatively slowly, and a lot of unidentified products were obtained.

\* 1, 2, 6, and 7 failed to be oxidized (1 and 2 are not oxidized with TPAP, either).

Table 6. Pd(II)-Catalyzed Oxidation of Alkenic Alcohols by Molecular Oxygen<sup>a</sup>

entry	substrate	product	isolated yield(%) <sup>b</sup>
1			35 (46)
2 <sup>c</sup>			66 (77)
3 <sup>d</sup>			91 (96)
4 <sup>d</sup>			83 (90)
5 <sup>d</sup>			87 <sup>e</sup> (100)
6 <sup>f</sup>			75 (87)
7 <sup>g</sup>			81 (88)

<sup>a</sup> Reaction conditions: see footnote a of Table 2. <sup>b</sup> The value in parentheses is the conversion of the alcohol (%). <sup>c</sup> For 12 h. <sup>d</sup> Pyridine (5 mmol), for 4 h. <sup>e</sup> GLC yield. <sup>f</sup> For 15 h. <sup>g</sup> Pyridine (5 mmol), for 6 h.

\* Substrates containing olefin(s) require excess (25 times) pyridine.

\* Almost all of the alcohols in the tables produce excellent yields.

\* Chemoselective oxidation of asymmetric diol is not successful (see the entry 4 in Table 4).

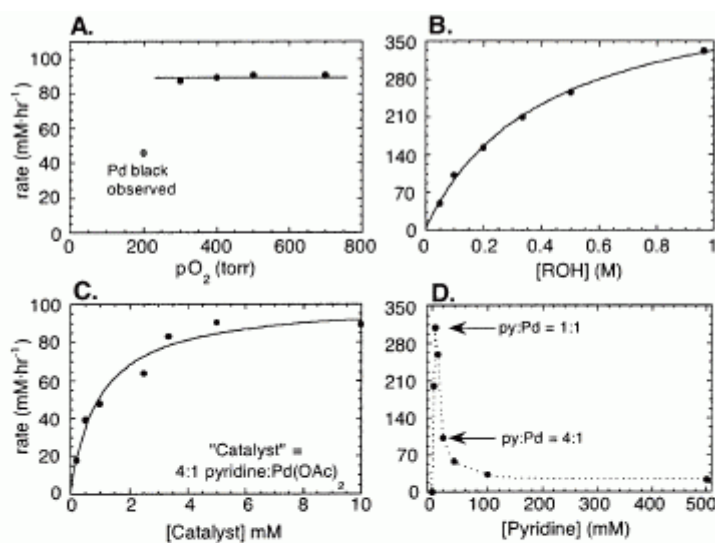
\* Alkenyl and allyl alcohols produce higher yields in Pd(OAc)<sub>2</sub>/Py system than in Pd(OAc)<sub>2</sub>/DMSO system (see Table 6).

\* Substrates containing vicinal heteroatoms are difficult to oxidize, probably because the heteroatoms form a chelate with Pd catalyst and deactivate it.

\* the mechanistic study

B. A. Steinhoff, I. A. Guzei, S. S. Stahl, *J. Am. Chem. Soc.* 2004, *126*, 11268 - 11278

• The dependence of each factor on the reaction rate



\* The initial reaction rate is independent of O<sub>2</sub> pressure, and dependent on [R-OH] and [Catalyst].  
 → The rate-limiting step is not the reoxidation of Pd(0) in which O<sub>2</sub> involves, but the step in which R-OH and Pd/Py catalyst involve, the alcohol dehydrogenation step.

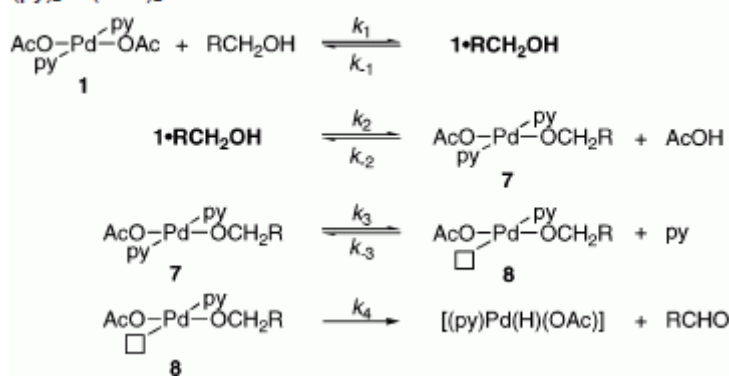
**Figure 1.** Initial rate dependence on oxygen pressure (A) and alcohol (B), catalyst (C), and pyridine (D) concentrations. Reaction conditions: (A) [Pd(OAc)<sub>2</sub>] = 5.0 mM, [py] = 20 mM, [PhCH<sub>2</sub>-OH] = 100 mM, pO<sub>2</sub> = 200–700 Torr, 10 mL of toluene, 80 °C; (B) [Pd(OAc)<sub>2</sub>] = 5.0 mM, [py] = 20 mM, [PhCH<sub>2</sub>-OH] = 50–970 mM, pO<sub>2</sub> = 700 Torr, 10 mL of toluene, 80 °C; (C) [Pd(OAc)<sub>2</sub>]:[py] = 1:4 (0.20–10 mM:0.80–40 mM), [PhCH<sub>2</sub>-OH] = 100 mM, pO<sub>2</sub> = 700 Torr, 10 mL of toluene, 80 °C; (D) [Pd(OAc)<sub>2</sub>] = 5.0 mM, [py] = 0–500 mM, [PhCH<sub>2</sub>-OH] = 100 mM, pO<sub>2</sub> = 700 Torr, 10 mL of toluene, 80 °C. The trendlines in (B) and (C) reflect nonlinear least-squares fits to eq 2 (see text).

\* Regarding Figure 1D

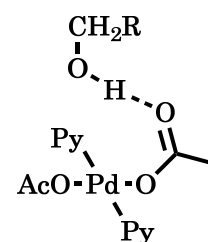
- When Py:Pd is below 4:1, catalytic turnover is accompanied by significant Pd black deposition and reduced substrate conversion.
  - When Py:Pd is above 100:1, no catalyst decomposition is observed even at low O<sub>2</sub> pressure (< 200 Torr).
- Py coordination enhances reoxidation of Pd(0) or hinders it from aggregating into inactive bulk metal, and slows down the β-H elimination.

• The alcohol oxidation step

**Scheme 3.** Stepwise Mechanism for Alcohol Oxidation by (py)<sub>2</sub>Pd(OAc)<sub>2</sub>



The structure of  $\mathbf{1}\text{-RCH}_2\text{OH}$  is unknown, but by density-functional-theory (DFT) calculation it's thought to be



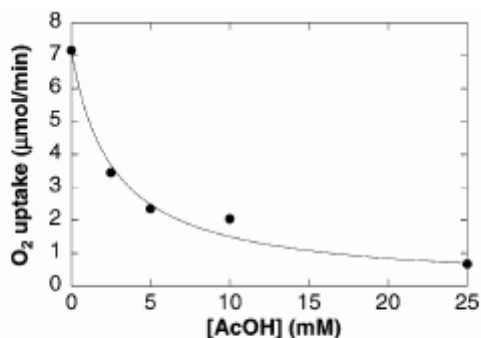
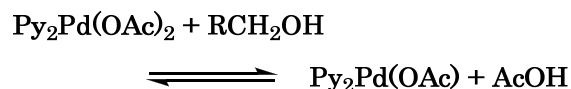


Figure 7. Dependence of the initial rate on acetic acid concentration. The curve fit results from a nonlinear least-squares fit to eq 16. Conditions:  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 20 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ ,  $[\text{AcOH}] = 0\text{--}25 \text{ mM}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ , 10 mL of toluene, 80 °C.

\* The initial rate decreases by adding extra AcOH, certainly because the equilibrium shifts to the left.



\* By adding  $\text{AcO}^-$  instead, however, the initial rate increases. It's because  $\text{AcO}^-$  traps AcOH and then the equilibrium shifts to the right.

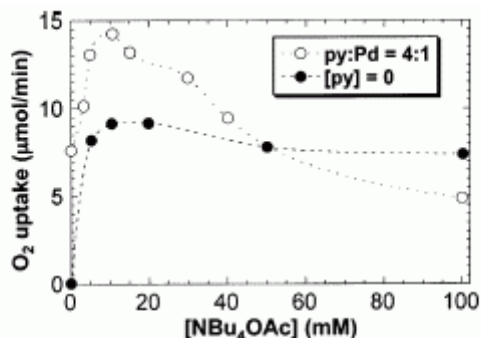
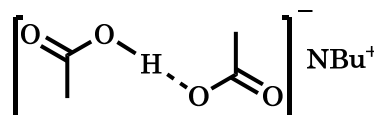


Figure 6. Dependence of the initial rate on  $\text{NBu}_4\text{OAc}$  concentration when the reaction is conducted in the presence (○) or absence (●) of pyridine. Conditions:  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 20 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ ,  $[\text{NBu}_4\text{OAc}] = 0\text{--}100 \text{ mM}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ , 10 mL of toluene, 80 °C (○);  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 0 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ ,  $[\text{NBu}_4\text{OAc}] = 0\text{--}100 \text{ mM}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ , 5 mL of toluene, 80 °C (●).

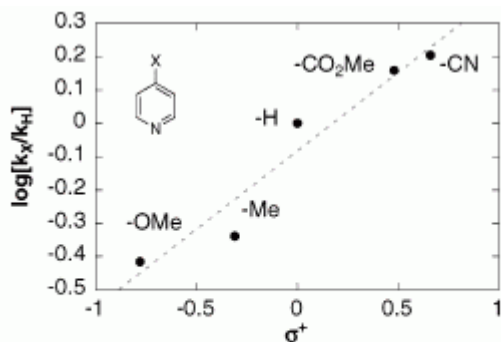


Figure 12. Hammett plot derived from the relative initial rates of catalytic alcohol oxidation conducted with a series of *para*-substituted pyridines. Conditions:  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 20 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ , 5 mL of toluene, 80 °C.

$$(\rho = +0.47)$$

\* Excess Py slows down the initial reaction rate (Fig. 1D).

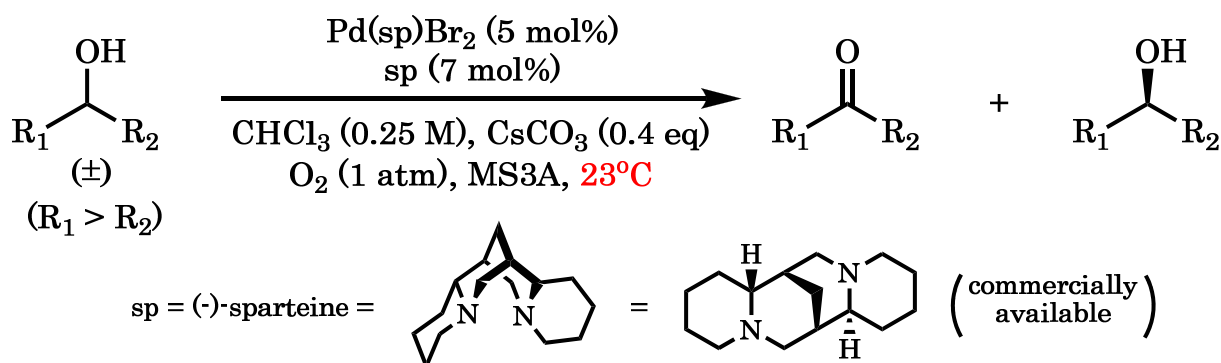
\* More electron-deficient Py derivative, that is, more labile ligand, increases the initial reaction rate (Fig. 12).

→  $\beta$ -H elimination occurs via 3-coordinate Pd complex prior to 4-coordinate one.

♠ According to Figure 1D, however, large excess of Py doesn't prevent the reaction, so  $\beta$ -H elimination via 4-coordinate complex does occur, but much more slowly.

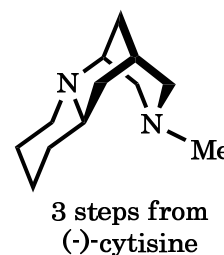
### 2.3 PdBr<sub>2</sub>/(-)-Sparteine system

\* First reported independently by the groups of Stoltz and Sigman in 2001, and an optimised method was reported by Stoltz group in 2008.



D.C. Ebner, R. M. Trend, C. Genet, M. J. McGrath, P. O'Brien, B. M. Stoltz, *Angew. Chem., Int.Ed.*, 2008, 47, 6367 - 6370

- \* *R* selective oxidation occurs with (-)-sparteine.
- \* The alternative of (+)-sparteine (hardly accessible) was discovered in 2008, which enables *S* selective oxidation.
- \* The reactions proceed at room temperature.
- Δ Long reaction time is required.
- Δ If there's little difference between the sizes of R<sub>1</sub> and R<sub>2</sub>, high ee isn't obtained.



**Table 1:** Optimization of conditions with [Pd(sp)X<sub>2</sub>].<sup>[a]</sup>

Entry	Solvent	T [°C]	Pd source	t [h]	Conv. [%] <sup>[b]</sup>	Alcohol ee [%] <sup>[c]</sup>	s
1 <sup>[d]</sup>	PhCH <sub>3</sub>	80	[Pd(sp)Br <sub>2</sub> ] (6)	76	32	27	5
2	PhCH <sub>3</sub>	60	[Pd(sp)Br <sub>2</sub> ] (6)	9	58	99	29
3	PhCH <sub>3</sub>	60	[Pd(sp)Cl <sub>2</sub> ] (4)	24	54	90	21
4 <sup>[f]</sup>	CHCl <sub>3</sub>	23	[Pd(sp)Cl <sub>2</sub> ] (4)	48	60	99	31
5 <sup>[f]</sup>	CHCl <sub>3</sub>	23	[Pd(sp)Br <sub>2</sub> ] (6)	4	56	96	28

[a] Pd source (5 mol%), (-)-sparteine (15 mol%), O<sub>2</sub> (1 atm), 0.25 M in solvent, unless otherwise noted. [b] Determined by GC analysis. [c] Determined by chiral HPLC methods.<sup>[e]</sup> [d] 0.1 M in PhCH<sub>3</sub>. [e] Pd black observed. [f] (-)-Sparteine (7 mol%), Cs<sub>2</sub>CO<sub>3</sub> (40 mol%). 3 Å M.S. = 3 Å molecular sieves; sp = (-)-sparteine.

- \* Pd(sp)Br<sub>2</sub> is ineffective at the originally employed temperature 80°C, but at lower temperature it shows better activity than Pd(sp)Cl<sub>2</sub>.
- \* Reaction temperature falls by using CHCl<sub>3</sub> as a solvent; in addition, reaction time shortens.

## \* Substrate scope

**Table 2:** Resolution of a variety of alcohols with [Pd(sp)Br<sub>2</sub>] (**6**).

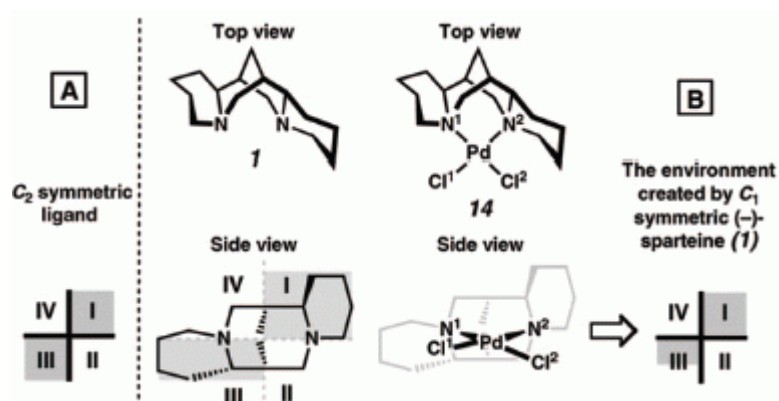
Entry	Alcohol <sup>[a]</sup>	t [h]	Conv. [%] <sup>[b]</sup> (yield [%]) <sup>[c]</sup>	Alcohol ee [%] <sup>[d]</sup>	s
1		4	56 (43)	96	28
2 <sup>[e]</sup>		5	55	95	27
3		4	59 (41)	95	17
4 <sup>[f]</sup>		8	59	97	20
5 <sup>[g]</sup>		24	60	98	20
6		41	64 (35)	97	14
7 <sup>[e]</sup>		30	63	96	13
8		24	60 (40)	93	14
9 <sup>[e]</sup>		21	65	99	15
10		15	60	91	12
11		48	62	97	16
12		49	58 (40)	91	15
13 <sup>[e]</sup>		45	58	91	15

[a] Major enantiomer shown. [b] Determined by GC or <sup>1</sup>H NMR methods. [c] Yield of the isolated enantioenriched alcohol. [d] Determined by chiral HPLC or GC methods.<sup>[10]</sup> [e] Performed under ambient air. [f] Performed at 10°C. [g] Performed at 4°C.

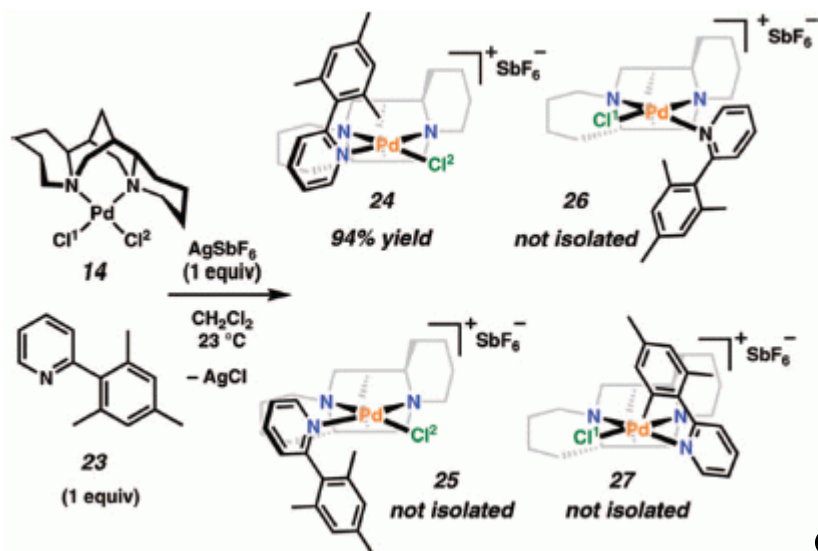
\* The substrates in the left table produce excellent ee and *k<sub>rel</sub>* ("s" in the table).

\* The use of air instead of pure O<sub>2</sub> is sufficient for obtaining high ee (entries 2, 7, 9, and 13).

## \* The mechanism of diastereoselectivity

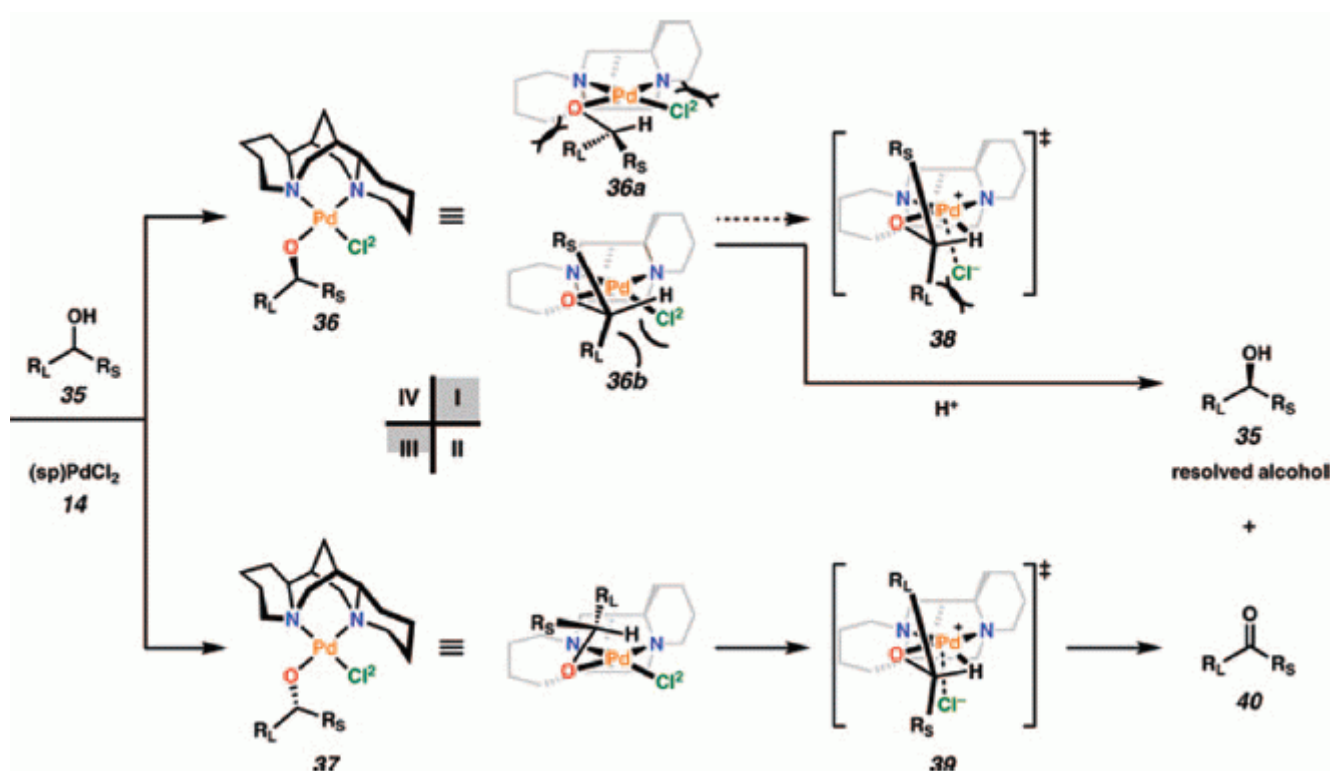


\* Quadrant I is fully hindered, and III is partially hindered by the pyrimidine unit of sparteine.  
\* Quadrant II and IV are less hindered.



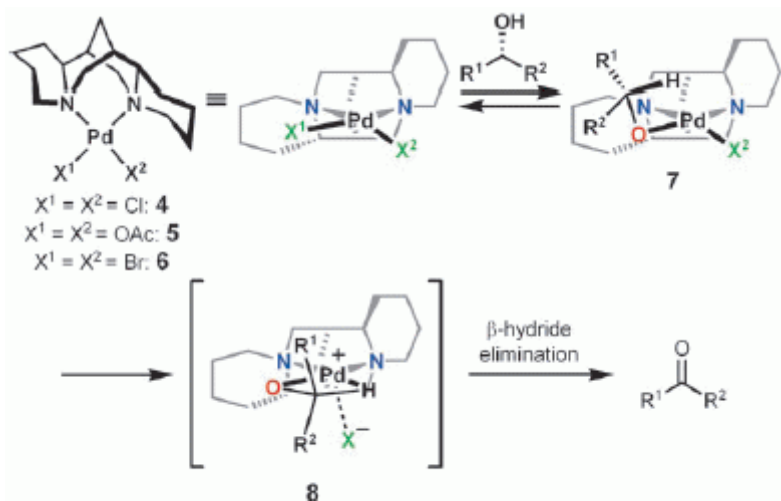
\* In the substitution reactions of Cl with pyridine derivatives,  $\text{Cl}^1$  is substituted selectively, and the substituent is located in IV.

(analyzed by X-ray crystallography)



\*  $\beta$ -H elimination of  $S$  alcohols hardly occurs because of steric hindrance; on the other hand,  $\beta$ -H elimination of  $R$  alcohols proceeds relatively smoothly via less hindered conformation (39).

\* Why Pd(sp)Br<sub>2</sub> is better than Pd(sp)Cl<sub>2</sub>?



\* It is important how many degrees the X<sup>2</sup> is out of the plane N,N,Pd,X<sup>1</sup> at the resting state, because the X<sup>2</sup> is pushed out of the plane at the TS of β-H elimination (8); that is, the more X<sup>2</sup> is distorted, the less the energy barrier to β-H elimination becomes.

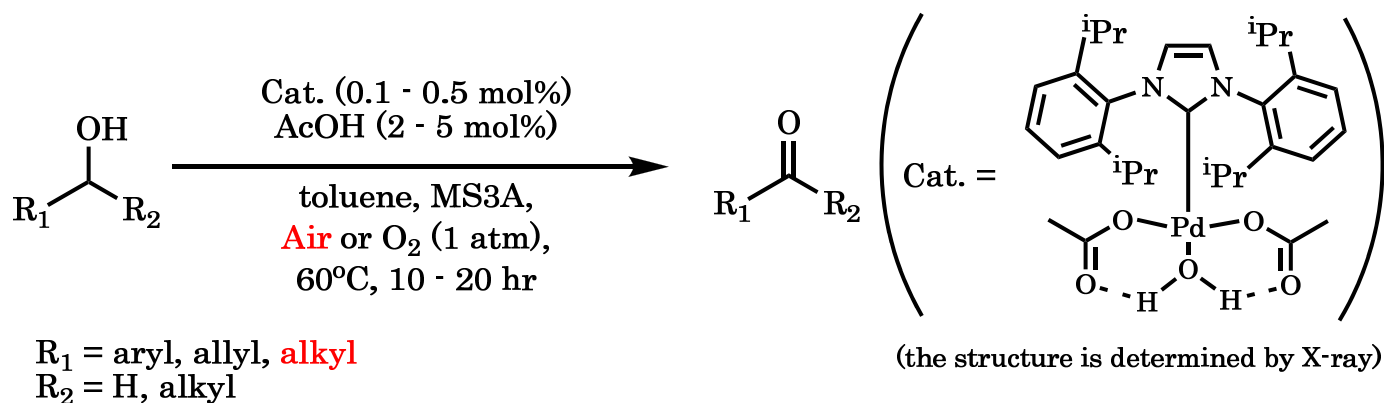
Scheme 1. Model of the alcohol oxidation with [Pd(sp)X<sub>2</sub>].

	X <sup>2</sup> deflection
Pd(sp)Cl <sub>2</sub>	9.9 deg
Pd(sp)(OAc) <sub>2</sub>	5.3 deg
Pd(sp)Br <sub>2</sub>	14.0 deg
TS (8)	15.4 deg

\* The X<sup>2</sup> deflection of Pd(sp)Br<sub>2</sub> is the nearest to that of TS (8).  
 → Pd(sp)Br<sub>2</sub> was thought to show the better activity than Pd(sp)Cl<sub>2</sub>, which is compatible with the experimental results.

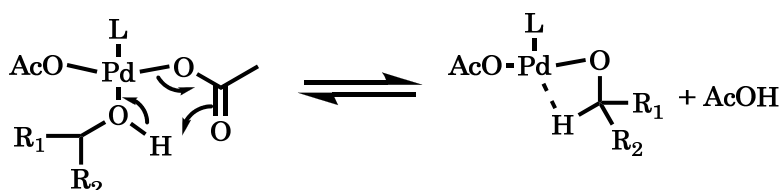
## 2.4 Pd(*i*Pr)(OAc)<sub>2</sub>(H<sub>2</sub>O) catalyst

\* First reported by Sigman group in 2003.



D. R. Jensen, M. J. Schultz, J. A. Mueller, M. S. Sigman, *Angew. Chem. Int. Ed.* 2003, 42, 3810 - 3813

- \* *i*Pr is employed because it is a monodentate ligand to Pd(OAc)<sub>2</sub>, which provides an open coordination site and facilitates β-H elimination.
- \* Lowering the amount of Pd(II) loading is achieved.
- \* A little amount of additional AcOH (~ 3 mol%) enables O<sub>2</sub> to be replaced by ambient air with slightly extended reaction time.
- \* Acetate unit is thought to behave as an intramolecular base to deprotonate R-OH, which enhances rate-limiting β-H elimination.



**Table 1:** Oxidation of alcohols using pure O<sub>2</sub>.

Entry <sup>[a]</sup>	Substrate	R	R'	t [h]	Yield [%] <sup>[b,c]</sup>
1 <sup>[d]</sup>	<b>2a</b>	Ph	CH <sub>3</sub>	5	> 99 (98)
2 <sup>[e]</sup>	<b>2a</b>			13	> 99
3 <sup>[d]</sup>	<b>2b</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	H	3.5	> 99 (99)
4 <sup>[d],[f]</sup>	<b>2b</b>			20	> 99
5 <sup>[d]</sup>	<b>2c</b>	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	12	> 99 (99)
6 <sup>[d],[g]</sup>	<b>2d</b>	Ph	<i>t</i> Bu	14	91
7 <sup>[d]</sup>	<b>2e</b>	1-cyclohexenyl	CH <sub>3</sub>	12	91 (84)
8 <sup>[h]</sup>	<b>2f</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	CH <sub>3</sub>	13	99 (93)
9 <sup>[d]</sup>	<b>2g</b>	3-Me-cyclohexenol		12	92
10 <sup>[h]</sup>	<b>2h</b>	<i>cis</i> -4-Me-cyclohexanol		13	> 99
11 <sup>[i]</sup>	<b>2i</b>	myrtenol		20	97
12 <sup>[k],[l]</sup>	<b>2j</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub>	H	10	85 (76)
13 <sup>[k],[l]</sup>	<b>2k</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub>	H	10	(85)

\* Substrate scope

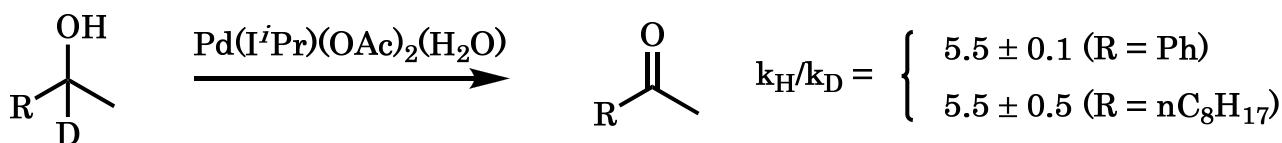
\* Aryl and aliphatic alcohols are oxidized in excellent yields. Δ This catalyst, like other systems, is also ineffective for oxidation of alkenic alcohols except ones in the table.

[a] See Supporting Information for details. [b] GC conversion. [c] Yield of isolated compound in parenthesis. [d] 2 mol% HOAc. [e] Catalyst prepared in situ using 0.5 mol% Pd(OAc)<sub>2</sub>, 0.65 mol% *i*Pr-HBF<sub>4</sub>, 0.7 mol% KO<sup>t</sup>Bu. [f] 0.1 mol% **1**. [g] 1 mol% **1**. [h] 1 mol% HOAc. [i] 5.0 mol% Bu<sub>4</sub>NOAc. [j] 0.75 mol% **1**. MS = molecular sieves.



\* Mechanistic study

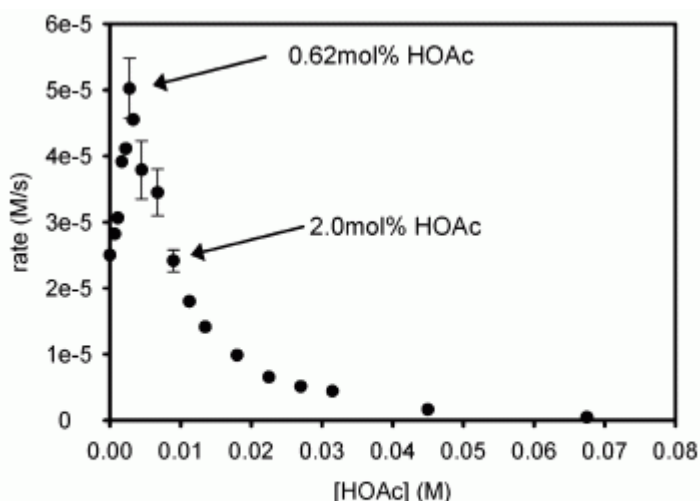
- Large KIE values were observed.



\* This result means the sole step of  $\beta$ -H elimination is the rate-limiting step under the optimized condition.

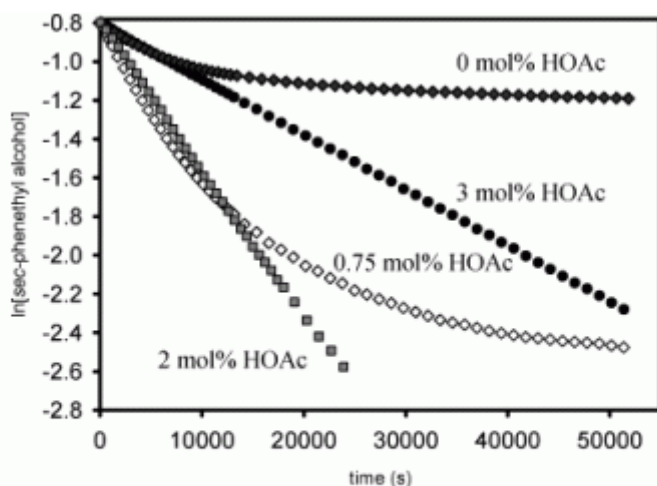
♠ Other systems (without  $\text{Pd}(\text{OAc})_2/\text{DMSO}$ ) show significantly smaller KIE values ( $\sim 1.3$ , at most 2) at the  $\beta$ -H elimination step, which means the rate-determining step consists of a few steps including  $\beta$ -H elimination.

- Initial rate depends on  $[\text{AcOH}]$ .



\* From 1.5 to 15 mol% of  $[\text{AcOH}]$ , the initial rate is proportional to  $[\text{AcOH}]^{-1}$ , but from 0 to 1.5 mol%, the graph draws a strange curve.

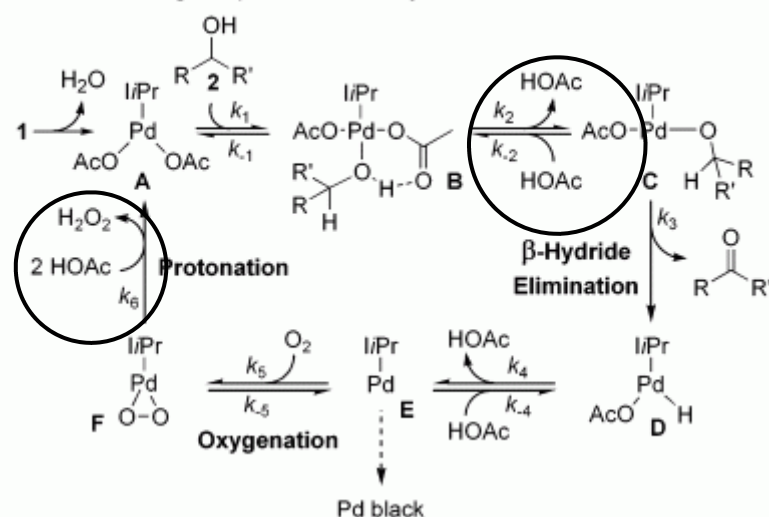
**Figure 10.** Rate dependence of *sec*-phenethyl alcohol oxidation using various HOAc concentrations at 50 °C. Conditions: 0.5 mol % **1**, 0.45 M alcohol in benzene, with 3 Å molecular sieves and a balloon charged with  $\text{O}_2$ . The range of  $[\text{AcOH}]$  is 0–67.5 mM (0–15 mol %).



\* When small amount of AcOH is added, the rate decreases as the reaction proceeds, which is thought to result from the decomposition of Pd catalyst.  
\* When adequate AcOH is added,  $[\text{alcohol}]$  decreases exponentially.

**Figure 12.** Natural logarithm of *sec*-phenethyl alcohol concentration vs time at various HOAc concentrations at 50 °C (every 10 time points displayed). Conditions: 0.5 mol % **1**, 0.45 M alcohol in benzene, with 3 Å molecular sieves and a balloon charged with  $\text{O}_2$ .

**Scheme 4.** Revised Proposed Mechanism: Possible Rate-Influencing Steps of Pd-Catalyzed Aerobic Oxidation



\* AcOH has two roles in the cycle; both of delaying and accelerating the cycle.

• Excess AcOH delays the deprotonation of the chelating alcohol but accelerates the protonation of Pd-peroxo complex.

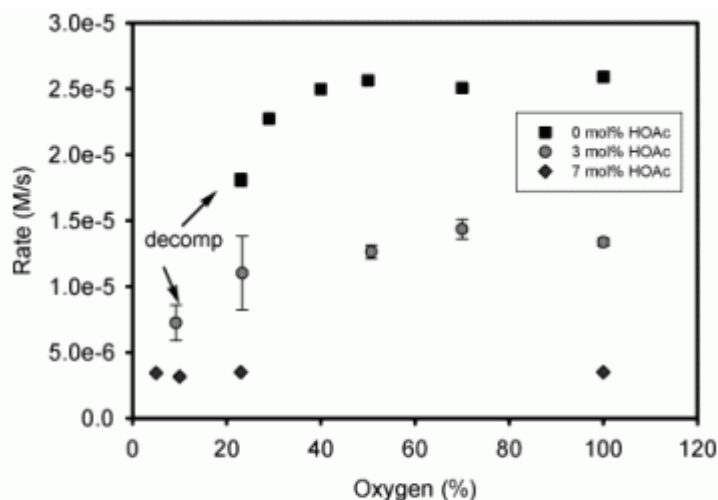
• Inadequate amount of AcOH brings the opposite result.

\* The dependence of the rate on [AcOH] implies the step of the oxygenation of Pd(0) is reversible.

\* Because of reversible oxygenation and irreversible Pd decomposition, adequate [AcOH] is necessary.

→ 2 mol% AcOH keeps the best balance between the efficient rate and Pd decomposition.

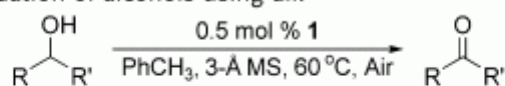
\* A little excess of AcOH (~ 5 mol%) enables the reaction to proceed under air.



\* The graph shows that 7 mol% AcOH prevents Pd from decompose in exchange for the decreased rate. → Air can replace pure O<sub>2</sub> by adding a little more AcOH.

**Figure 14.** Initial rates of the *sec*-phenethyl alcohol oxidation at 50 °C using various AcOH concentrations and oxygen/nitrogen mixtures. Conditions: 0.5 mol % **1**, 0.45 M *sec*-phenethyl alcohol, with 3 Å molecular sieves and a balloon charged with O<sub>2</sub>.

**Table 2:** Oxidation of alcohols using air.



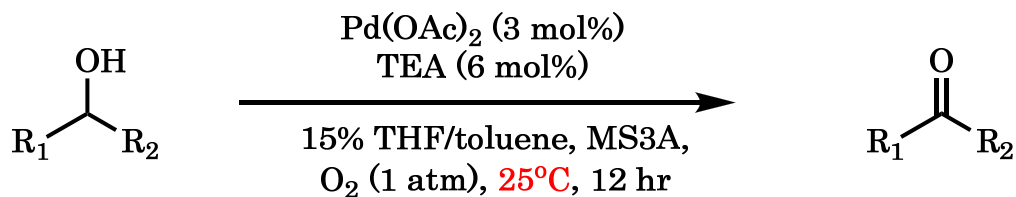
Entry <sup>[a]</sup>	Substrate	R	R'	t [h]	Yield [%] <sup>[b,c]</sup>
1 <sup>[d,e]</sup>	<b>2a</b>	Ph	CH <sub>3</sub>	14	> 99 (97)
2 <sup>[f]</sup>	<b>2l</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	14	> 99 (93)
3 <sup>[f]</sup>	<b>2c</b>	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	20	> 99
4 <sup>[f]</sup>	<b>2m</b>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	14	> 99
5 <sup>[g]</sup>	<b>2f</b>	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	CH <sub>3</sub>	14	99 (91)
6 <sup>[f]</sup>	<b>2n</b>	1-indanol		14	> 99
7 <sup>[f]</sup>	<b>2h</b>	<i>cis</i> -4-Me-cyclohexanol		14	96

\* Alcohols produce excellent yields under ambient air condition  
Δ Slightly longer reaction time is required.

[a] See Supporting Information for details. [b] GC conversion. [c] Yield of isolated product in parenthesis. [d] 5 mol% HOAc. [e] 1.0 g scale. [f] 4 mol% HOAc. [g] 2 mol% HOAc.

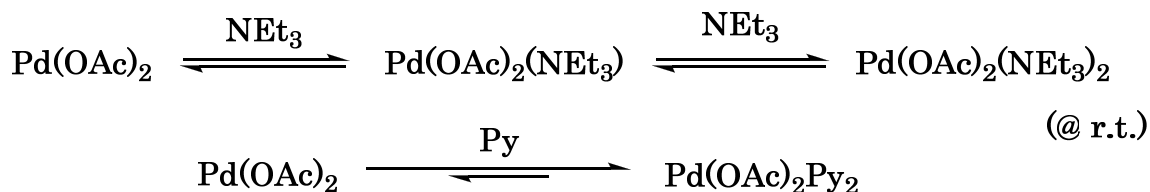
## 2.5 Other Pd(II) catalyst systems for aerobic oxidation

### (1) NEt<sub>3</sub> ligand



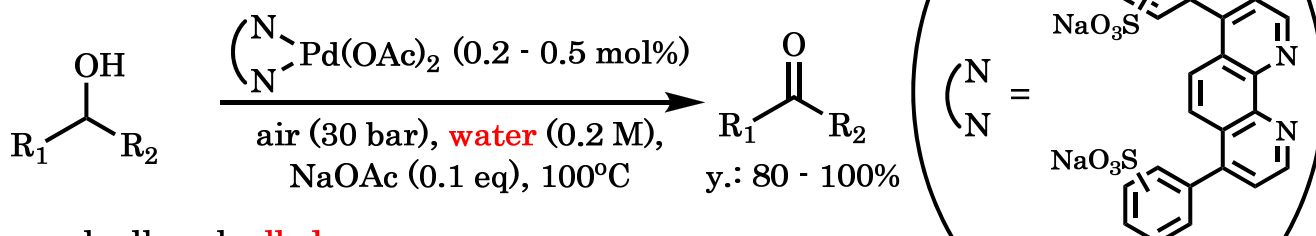
M. J. Schultz, C. C. Park, M. S. Sigman, *Chem. Commun.* 2002, 3034 - 3035

\* NEt<sub>3</sub> is a more labile ligand to Pd than Py, so the dissociation of NEt<sub>3</sub> occurs easier. It results in accelerating the alcohol oxidation and lowering the reaction temperature.



\* Substrate scope is similar to that of Pd(OAc)<sub>2</sub>/Py system, but shows relatively low yields for alkenyl substrates.

### (2) Bathophenanthroline Disulfonate (PhenS\*) ligand



R<sub>1</sub> = aryl, alkenyl, **alkyl**  
 R<sub>2</sub> = H, alkyl

G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Science* 2000, 287, 1636 - 1639

\* The catalyst is soluble in water, so the oxidation reaction can be done in water or biphasic system.

→ easier isolation, environmentally friendly wastes, reusable catalyst

\* High reactivity, that is, small amount of Pd loading is achieved.

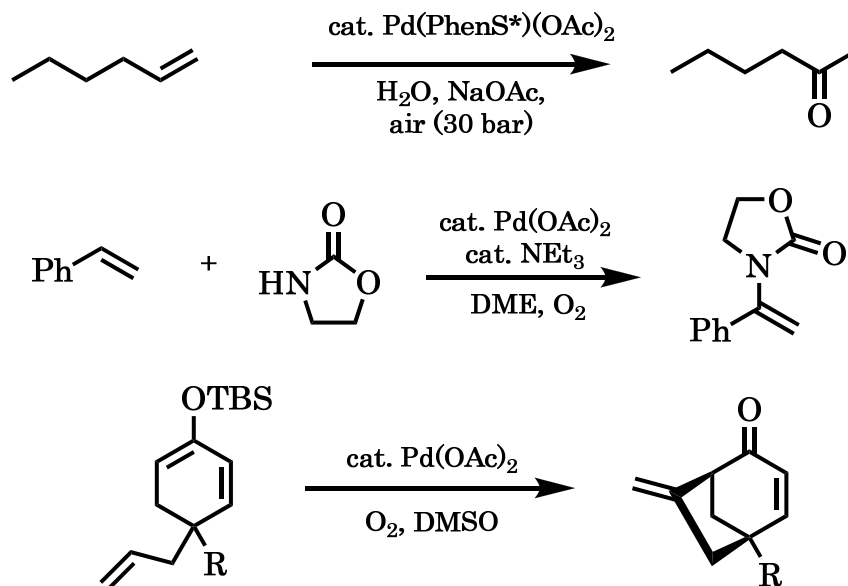
Δ High O<sub>2</sub> pressure and temperature is necessary.

Δ The reaction rate depends on the solubility in water of alcohols, resulting in the limiting substrate scope.

### 3. Prospects

The systems shown above are the foundations of other Pd-catalyzed oxidation reactions;

- 1) Olefin oxidation (Wacker-type reaction)
- 2) C-heteroatom coupling reactions
- 3) Oxidative C-C coupling reactions



\* The mechanistic studies of these systems will bring us more advanced procedure for catalytic aerobic oxidation.

There're problems to overcome;

- \* Many of the systems listed above require high temperature.
  - \* Limited substrate scope results in limited application;  $\text{Pd(OAc)}_2/\text{Py}$  system covers the widest range of substrates among the reactions listed above, but it still cannot compete with conventional methods.
  - \* To be applicable to various reactions means that the selectivity of functional groups is problematic.
- Further researches are necessary for better systems.

