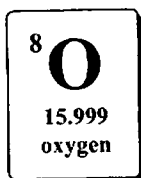


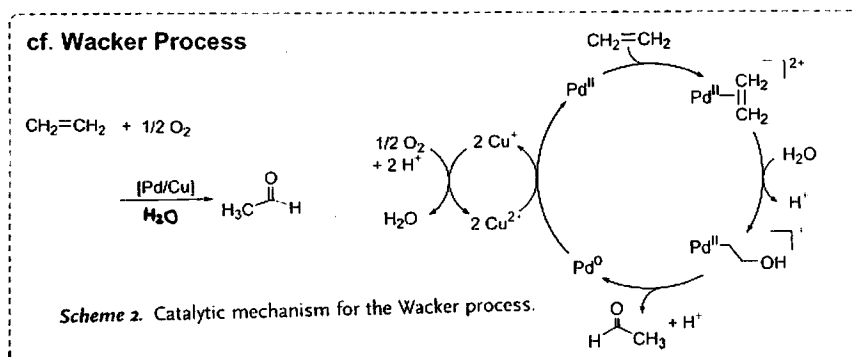
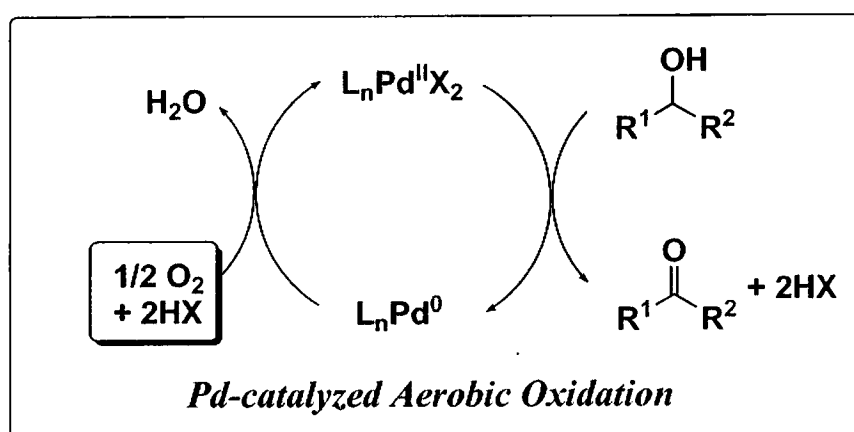
# Selective Oxidation of Organic Chemicals Under Aerobic Conditions

~ Catalytic Aerobic Alcohol Oxidation ~

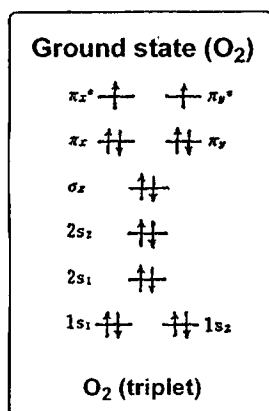
## ❖ Introduction ❖



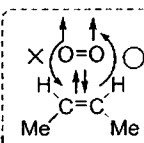
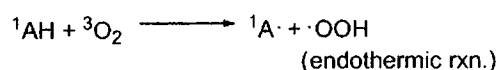
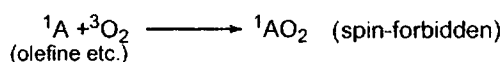
The conversion of alcohols into carbonyl compounds is an important transformation for laboratory and industrial chemistry. Recently catalytic method of aerobic oxidation have developed and without co-catalysts (such as  $\text{Cu}^{\text{II}}$  and benzoquinone) oxidation efficiently proceeds. In this seminar, recent progress of Pd-catalyzed aerobic oxidation is discussed.



## ❖ The basic character of $\text{O}_2$ ❖



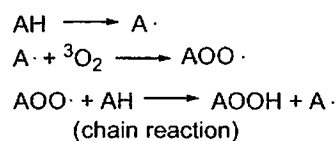
#  $\text{O}_2$  have a biradical character but usually that is less reactive because...



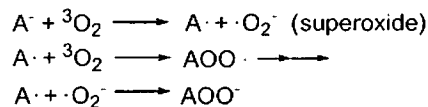
A change from one spin to the opposite involves a change in angular momentum and such a change would violate the law of conservation of angular momentum.

#  $\text{O}_2$  is reactive under below conditions.

1) With initiator (autoxidation)



2) Electron Transfer ( $\text{Fe}(\text{II})$ , anion of phenol etc.)



# 1. First example of Pd catalyzed aerobic oxidation without cocatalyst

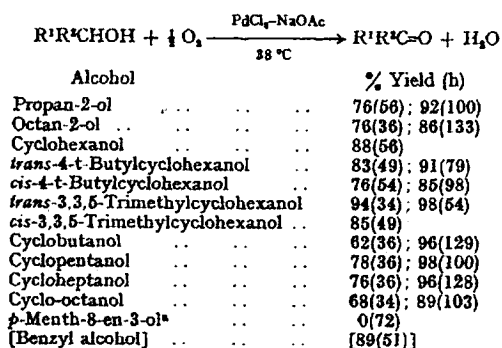
(2/12)

1977. Schwartz et al.

J.C.S. Chem. Comm. 1977, 157.

## Homogeneous Catalytic Oxidation of Secondary Alcohols to Ketones by Molecular Oxygen under Mild Conditions

By THOMAS F. BLACKBURN and JEFFREY SCHWARTZ\*



PdCl<sub>2</sub> : 1 mol%  
NaOAc: 5 mol%  
O<sub>2</sub>: 1 atm

# Reaction time is long.

# Olefine or unhindered amines poison the catalyst by strong complexation.

around 20 years...

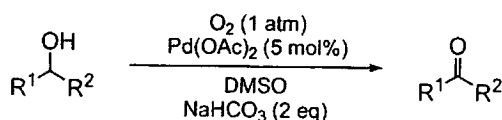
## 2. Pd(OAc)<sub>2</sub>/DMSO System

### Palladium-Catalyzed Oxidation of Primary and Secondary Allylic and Benzylic Alcohols

Karl P. Peterson and Richard C. Larock\*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

J. Org. Chem. 1998, 63, 3185-3189



# DMSO is the best solvent.  
(DMSO/H<sub>2</sub>O, CH<sub>3</sub>CN give moderate yield.)

# Primary and secondary allylic substrates were not as clean as the benzylic systems and lead to lower yields (entries 14-17).

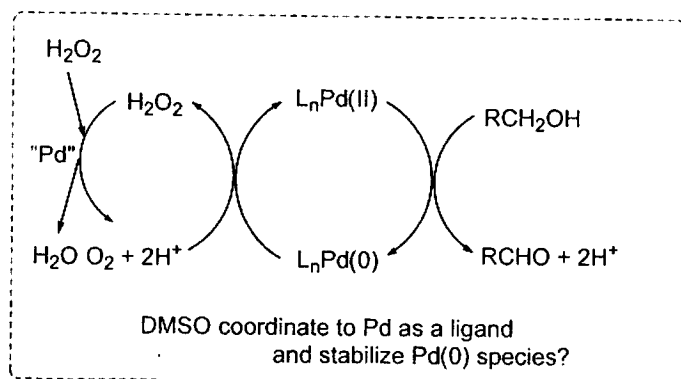


Table 2. Oxidation of Primary and Secondary Allylic and Benzylic Alcohols

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
8			A	7	96
14			B	1.5	69 <sup>a</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.

**procedure A:** Pd(OAc)<sub>2</sub> (5 mol%), NaHCO<sub>3</sub> (2 eq)  
DMSO (1 ml), 24 h at 80 °C, O<sub>2</sub> (1 atm)  
**procedure B:** Pd(OAc)<sub>2</sub> (5 mol%), DMSO (1 ml), 24 h  
at 80 °C, O<sub>2</sub> (1 atm) (base-free)

### 3. Pd(OAc)<sub>2</sub>/pyridine System

Uemura et al. *Tetrahedron Lett.* 1998, 38, 6011.  
*J. Org. Chem.* 1999, 64, 6750.

Scheme 1

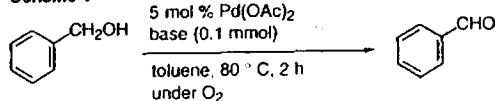


Table 1. Pd(OAc)<sub>2</sub>-Catalyzed Oxidation of Benzyl Alcohol by Molecular Oxygen<sup>a</sup>

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	—	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).

### Pd(OAc)<sub>2</sub>-Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Molecular Oxygen

Takahiro Nishimura, Tomoaki Onoue, Kouichi Ohe and Sakae Uemura\*

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering.

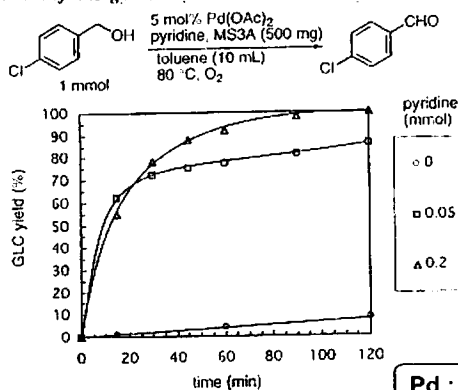


Figure 1. Time profile of the oxidation of *p*-chlorobenzyl alcohol: effect of the amount of pyridine to product yield.

Activated MS3A was used (by calcination).

### Scope and Limitation

Table 3. Pd(II)-Catalyzed Oxidation of Primary Alcohols by Molecular Oxygen<sup>a</sup>

entry	substrate	product	isolated yield(%) <sup>b</sup>
1			95 (96)
2 <sup>c</sup>			58 (61)
3			93 (97)
4			87 (93)
5 <sup>d</sup>			92 (97)
6 <sup>e</sup>			89 (92)
7 <sup>f</sup>			86 (97)

<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> In the absence of MS3A. <sup>d</sup> Pyridine (1 mmol), for 4 h.

Table 5. Pd(II)-Catalyzed Oxidation of Secondary Alcohols by Molecular Oxygen<sup>a</sup>

entry	substrate	product	isolated yield(%) <sup>b</sup>
1			97 (98)
2			93 (100)
3 <sup>c</sup>			80 (89)
4			83 (92)
5			93 (100)
6			93 (100)
7			92 (100)

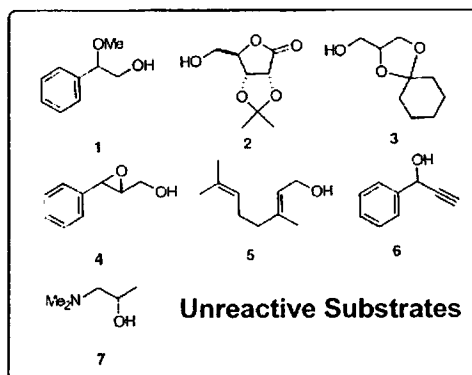
<sup>a</sup> Reaction conditions: see footnote a of Table 2. <sup>b</sup> The value in parenthesis is the conversion of the alcohol (%). <sup>c</sup> In the absence of MS3A.

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>e</sup>			83 (90)
5 <sup>f</sup>			87 <sup>g</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.

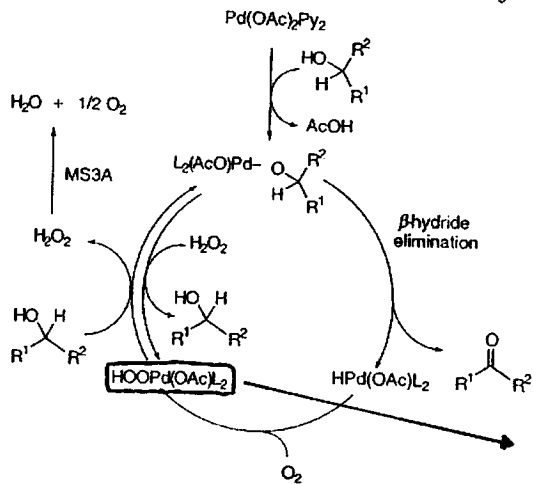
# Alkenic Alcohols were also oxidized. But a quite excess of pyridine (25 times compared with the standard conditions) was needed to avoid the production of Pd black.



Functional group such as amine coordinate to Pd.

Mechanistic Insights

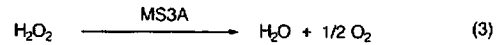
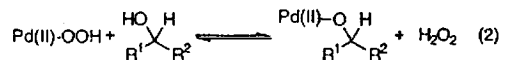
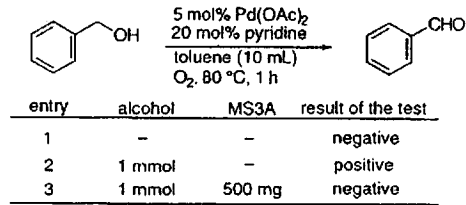
Scheme 1. Plausible Reaction Pathway



**MS3A absorbed or decomposed H<sub>2</sub>O<sub>2</sub> to O<sub>2</sub> and H<sub>2</sub>O?**

Pyridines coordinate with Pd(II) to stabilize the Pd(II)-H species to prevent reductive elimination of HX? The role of pyridines was unknown.

Scheme 2. Qualitative Analysis of Hydrogen Peroxide



4. Pd(OAc)<sub>2</sub> / Bathophenanthroline Disulfonate (PhenS\*) System  
**Green, Catalytic Oxidation of Alcohols in Water**

Gerd-Jan ten Brink, Isabel W. C. E. Arends, Roger A. Sheldon\*

3 MARCH 2000 VOL 287 SCIENCE 1636

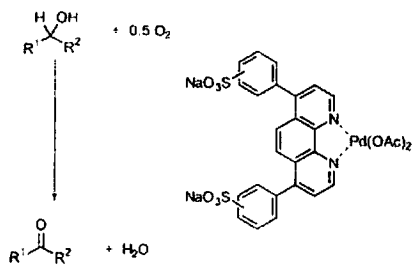


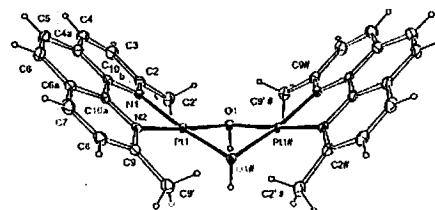
Fig. 1. Aerobic oxidation of alcohols catalyzed by water-soluble PhenS\*Pd(OAc)<sub>2</sub> (0.25 to 0.5 mole percent). R, alkyl, aryl.

other Ref. *Adv. Synth. Catal.* **2002**, 344, 355.  
*Adv. Synth. Catal.* **2003**, 345, 497.  
*Adv. Synth. Catal.* **2003**, 345, 1341.

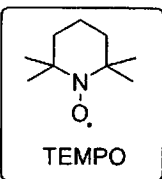
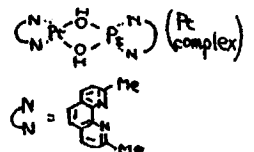
Substrate	Product	Time (hour)	Conversion (%)	Selectivity (%)	Isolated yield (%)
<chem>CCCC(O)C</chem>	<chem>CCCC(=O)C</chem>	5	100	100	90
<chem>CCCC(O)C</chem>	<chem>CCCC(=O)C</chem>	10	100	100	90
<chem>C1CCCC1O</chem>	<chem>C1CCCC1=O</chem>	5	100	100	90
<chem>c1ccc(cc1)C(O)C</chem>	<chem>c1ccc(cc1)C(=O)C</chem>	10	90	100	85
<chem>CC(O)C=C</chem>	<chem>CC(=O)C=C</chem>	10	95	83*	79
<chem>CCCC(O)CO</chem>	<chem>CCCC(=O)CO</chem>	10	100	100	92
<chem>CCCC(O)C</chem>	<chem>CCCC(=O)C</chem>	15	98	97†	90
<chem>CCCCCC(O)C</chem>	<chem>CCCCCC(=O)C</chem>	12	95	90‡	80
<chem>CC(O)C=C</chem>	<chem>CC(=O)C=C</chem>	10	100	96†	88
<chem>c1ccccc1CO</chem>	<chem>c1ccccc1C=O</chem>	10	100	99.8‡	93

Table 1. Conversion of primary and secondary alcohols. (All yields are for the pure, isolated products.) Conditions were as follows: 1° alcohol and 1-phenylethanol (10 mmol), 2° alcohol (20 mmol), PhenS\*Pd(OAc)<sub>2</sub> (0.05 mmol), substrate/catalyst ratio of 200 to 400, water (50 g), NaOAc (1 mmol), pH ~11.5, 100°C, and 30-bar air pressure. Selectivity is based on the yield determined by gas chromatography with an external standard.

\*Ether (17%) was formed. †TEMPO (4 equiv to Pd) was added. ‡Acid was formed as the major by-product. §Hexanal (7%) and hexyl hexanoate (2%) were formed.



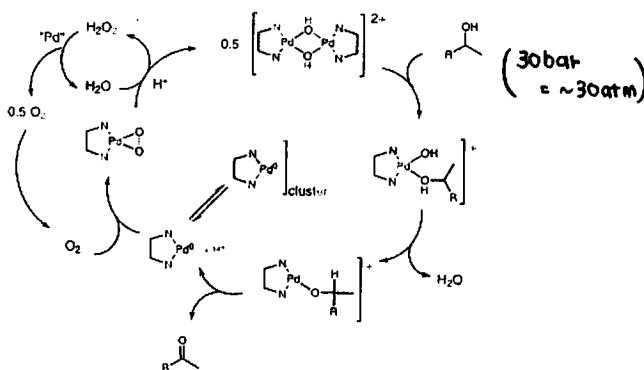
*Inorg. Chem.* **2001**, 40, 3247. Robinson et al.



Aliphatic alcohol (1-hexanol) reacted further to form hexanoic acid. The addition of TEMPO stops the reaction at aldehyde.

TEMPO (radical scavenger) inhibit autoxidation of the aldehyde?

Proposed Mechanism



# [alcohol]: first-order dependence, [catalyst]: 1/2-order dependence  
 # H<sub>2</sub>O<sub>2</sub> was not detected in the reaction mixture.

# 5. Mechanistic Study for The Improved Catalyst

(5/12)

## 5-1. Pd(0) or Pd(II)-H species?

Oxygenation of Nitrogen-Coordinated Palladium(0):  
Synthetic, Structural, and Mechanistic Studies and  
Implications for Aerobic Oxidation Catalysis

*J. Am. Chem. Soc.* 2001, 123, 7188.

Shannon S. Stahl,\* Joseph L. Thorman, Ryan C. Nelson, and  
Michael A. Kozec

Department of Chemistry  
University of Wisconsin–Madison

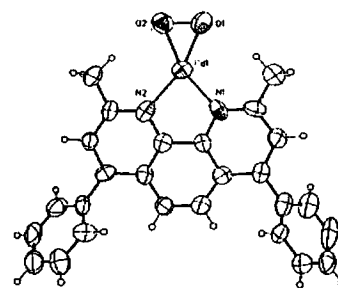
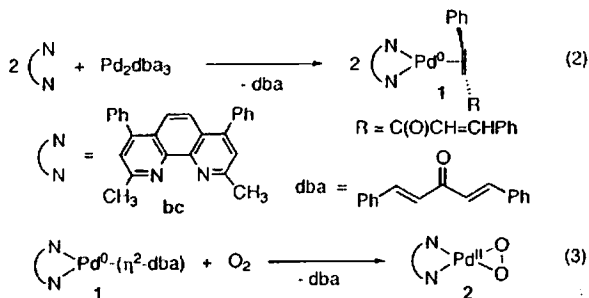


Figure 2. Molecular structure of (bc)Pd(O<sub>2</sub>). 2. Thermal ellipsoids are drawn at 50% probability.

O-O length : 1.415 Å

\* O<sub>2</sub><sup>2-</sup> (peroxide) : 1.49 Å

## 5-2. Pd(OAc)<sub>2</sub>/pyridine system

J|A|C|S

ARTICLES

Published on Web 08/21/2004

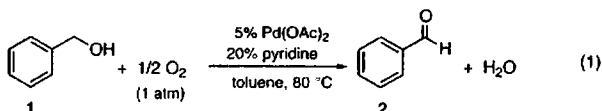
Mechanistic Characterization of Aerobic Alcohol Oxidation  
Catalyzed by Pd(OAc)<sub>2</sub>/Pyridine Including Identification of the  
Catalyst Resting State and the Origin of Nonlinear [Catalyst]  
Dependence

Bradley A. Steinhoff, Ilia A. Guzei, and Shannon S. Stahl\*

*Org. Lett.* 2002, 4, 4179.

*J. Am. Chem. Soc.* 2004, 126, 11268.

### Kinetic Studies



### 1) alcohol concentration

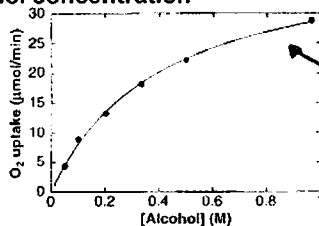


Figure 2. Dependence of the initial rate on alcohol concentration. The curve fit results from a nonlinear least-squares fit to a hyperbolic function of [alcohol] (eq 16). Conditions: [Pd(OAc)<sub>2</sub>] = 5.0 mM, [pyridine] = 20 mM, [alcohol] = 0.05–0.97 M, initial pO<sub>2</sub> = 700 Torr, 10 mL of toluene, 80 °C.

### 3) catalyst concentration

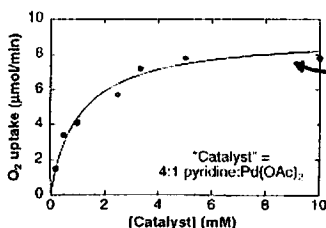
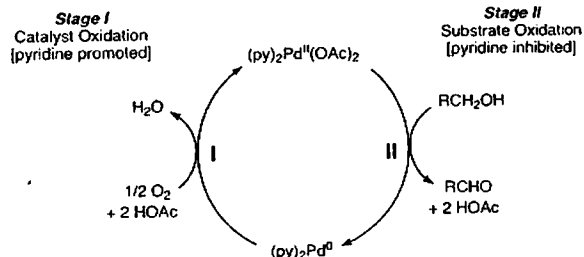


Figure 4. Dependence of the initial rate on catalyst concentration, where the "catalyst" is a 4:1 mixture of pyridine and Pd(OAc)<sub>2</sub>. The curve fit reflects a nonlinear least-squares fit to a generic hyperbolic function of [catalyst]: rate = C<sub>1</sub>[catalyst]/(C<sub>2</sub> + C<sub>3</sub>[catalyst]). Conditions: [Pd(OAc)<sub>2</sub>] = 0.20–10 mM, [pyridine] = 0.8–40 mM, [alcohol] = 0.10 M, initial pO<sub>2</sub> = 700 Torr, 10 mL of toluene, 80 °C.

### Scheme I. Catalytic Cycle



### 2) O<sub>2</sub> pressure

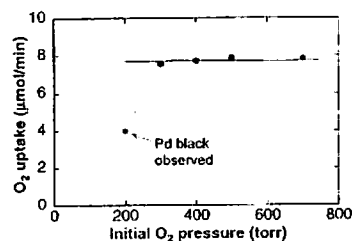


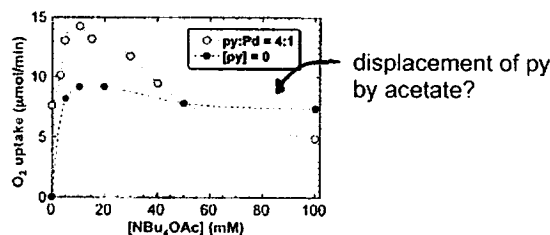
Figure 3. Dependence of the initial rate on the initial oxygen pressure. Conditions: [Pd(OAc)<sub>2</sub>] = 5.0 mM, [pyridine] = 20 mM, [alcohol] = 0.10 M, initial pO<sub>2</sub> = 200–700 Torr, 10 mL of toluene, 80 °C.

# At reduced oxygen pressure, Pd black was formed.  
Saturation rate dependence was observed.

- 1) Substrate oxidation (Stage II) is the rate-determining step.
  - 2) KIE (kinetic isotope effect) is also observed.
- ⇒ β-hydride elimination is rate-determining step?

The catalyst oxidation step is invisible.  
(Pd(II)-H or Pd(0)?)

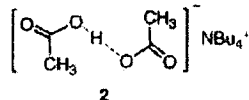
#### 4) acetate concentration



**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  $p\text{O}_2 = 700 \text{ Torr}$ ,  $10 \text{ mL}$  of toluene,  $80^\circ\text{C}$  (○);  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 0 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ ,  $[\text{NBu}_4\text{OAc}] = 0\text{--}100 \text{ mM}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ ,  $5 \text{ mL}$  of toluene,  $80^\circ\text{C}$  (●).

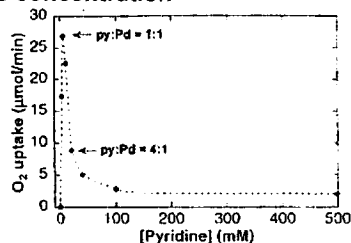
# pyridine :  $\text{NBu}_4\text{OAc}$  :  $\text{Pd}(\text{OAc})_2 = 4 : 2 : 1$  is the best.

# Acetic acid will be stabilized by formation of an acid-base complex. (Acetic acid is byproduct in the formation of a palladium alkoxide.)



#### 5) pyridine concentration

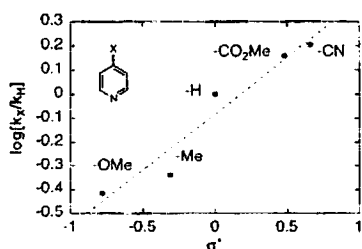
(6/12)



**Figure 5.** Dependence of the initial rate on pyridine concentration with the  $[\text{Pd}(\text{OAc})_2]$  held constant. Conditions:  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 0\text{--}500 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ , initial  $p\text{O}_2 = 700 \text{ Torr}$ ,  $10 \text{ mL}$  of toluene,  $80^\circ\text{C}$ .

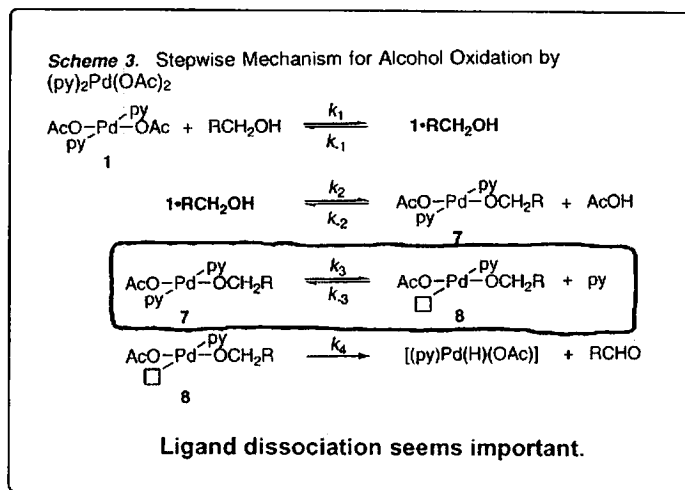
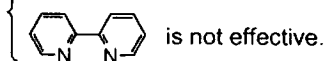
$\left\{ \begin{array}{l} \text{pyridine} : \text{Pd} < 4 : 1 \implies \text{Pd black is formed.} \\ \text{pyridine} : \text{Pd} > 4 : 1 \implies \text{The rate is quite low.} \end{array} \right.$   
 (Catalyst decomposition is not occurred.)

#### 6) Pyridine Substituent Effects

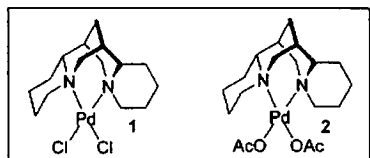


**Figure 12.** Hammett plot derived from the relative initial rates of catalytic alcohol oxidation conducted with a series of *para*-substituted pyridines. Conditions:  $[\text{Pd}(\text{OAc})_2] = 5.0 \text{ mM}$ ,  $[\text{pyridine}] = 20 \text{ mM}$ ,  $[\text{alcohol}] = 0.10 \text{ M}$ , initial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

Electron-deficient analogues promote turnover rates.



cf. Sigman et al. Stolz et al.



**Figure 1.** Structures of  $\text{Pd}((-)\text{-sparteine})\text{Cl}_2$  and  $\text{Pd}((-)\text{-sparteine})(\text{OAc})_2$ .

Sigman et al.

*J. Am. Chem. Soc.* **2001**, *123*, 7475.

*Org. Lett.* **2003**, *5*, 63.

*J. Org. Chem.* **2003**, *68*, 7573.

*J. Am. Chem. Soc.* **2003**, *125*, 7005.

Stolz et al.

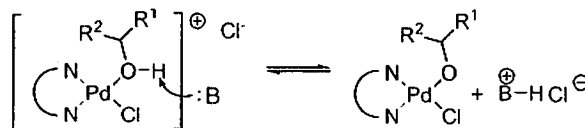
*J. Am. Chem. Soc.* **2001**, *123*, 7725.

*Org. Lett.* **2003**, *5*, 835.

**Table 1.** Base Screen for Pd-Catalyzed Oxidative Kinetic Resolution of Alcohols

entry	base	% conv. (% ee) <sup>a</sup>	$k_{rel}$ <sup>b</sup>
a	no base	0.0 (N.A.)	N.A.
b	(-)-sparteine	51.5 (82.4)	20.1
c	Hunig's base	28.0 (23.0)	5.1
d	$\text{Cs}_2\text{CO}_3$	52.9 (53.8)	4.7
e	KOt-Bu	14.0 (11.7)	6.9

<sup>a</sup> Conversion determined using internal standard. <sup>b</sup> Conversion <10% gives inaccurate  $k_{rel}$  values.



From previous mechanistic studies... (Stahl et al., Sigman et al., Sheldon et al.)

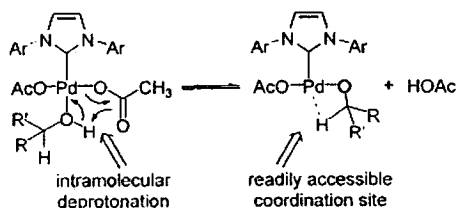
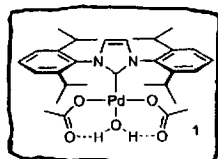
- # Base is necessary for catalysis.
- # A ligand must dissociate to allow alcohol binding and  $\beta$ -hydride elimination.
- # An excess ligand is needed to prevent catalyst decomposition.
- # Ligand must be stable under oxidation conditions.

N-heterocyclic carbene ligand: stabilization of Pd(II) and Pd(0) intermediates  
 Acetate ligand: base

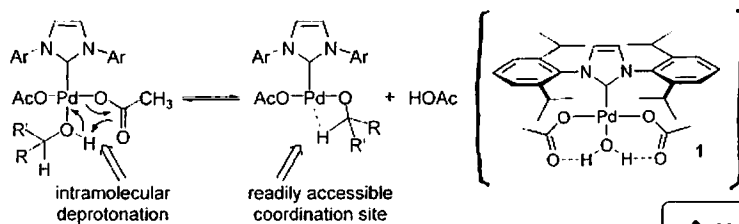
#### A Well-Defined Complex for Palladium-Catalyzed Aerobic Oxidation of Alcohols: Design, Synthesis, and Mechanistic Considerations\*\*

David R. Jensen, Mitchell J. Schultz, Jaime A. Mueller, and Matthew S. Sigman\*

*Angew. Chem. Int. Ed.* **2003**, *42*, 3810.



**Scheme 1.** Proposed intramolecular deprotonation.



Scheme 1. Proposed intramolecular deprotonation.

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>	2a	Ph	CH <sub>3</sub>	5	>99 (98)
2 <sup>[e]</sup>	2a			13	>99
3 <sup>[d]</sup>	2b	4-MeOC <sub>6</sub> H <sub>4</sub>	H	3.5	>99 (99)
4 <sup>[d],[f]</sup>	2b			20	>99
5 <sup>[d]</sup>	2c	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>	2d	Ph	tBu	14	91
7 <sup>[d]</sup>	2e	1-cyclohexenyl	CH <sub>3</sub>	12	91 (84)
8 <sup>[h]</sup>	2f	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	CH <sub>3</sub>	13	99 (93)
9 <sup>[d]</sup>	2g	3-Me-cyclohexenol		12	92
10 <sup>[h]</sup>	2h	cis-4-Me-cyclohexanol		13	>99
11 <sup>[h]</sup>	2i	myrtenol		20	97
12 <sup>[f],[i]</sup>	2j	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>10</sub>	H	10	85 (76)
13 <sup>[f],[i]</sup>	2k	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub>	H	10	(85)

[a] See Supporting Information for details. [b] GC conversion. [c] Yield of isolated product in parenthesis. [d] 2 mol% HOAc. [e] Catalyst prepared in situ using 0.5 mol% Pd(OAc)<sub>2</sub>, 0.65 mol% LiPr-HBF<sub>4</sub>, 0.7 mol% KOtBu. [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.

◆ Under Air conditions (instead of pure 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>	2a	Ph	CH <sub>3</sub>	14	>99 (97)
2 <sup>[f]</sup>	2l	4-MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	14	>99 (93)
3 <sup>[f]</sup>	2c	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	20	>99
4 <sup>[f]</sup>	2m	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	14	>99
5 <sup>[f]</sup>	2f	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	CH <sub>3</sub>	14	99 (91)
6 <sup>[f]</sup>	2n	1-indanol		14	>99
7 <sup>[f]</sup>	2h	cis-4-Me-cyclohexanol		14	96

[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.

# AcOH accelerates the reaction (later discussed).

◆ N-heterocyclic carbene (NHC) ligand ◆

Bertrand et al. *Chem. Rev.* 2000, 100, 39.

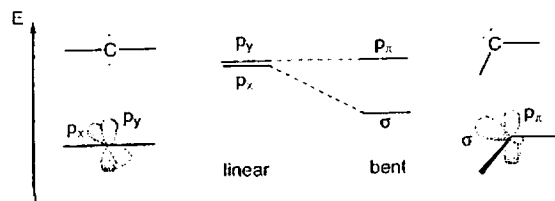


Figure 2. Relationship between the carbene bond angle and the nature of the frontier orbitals.

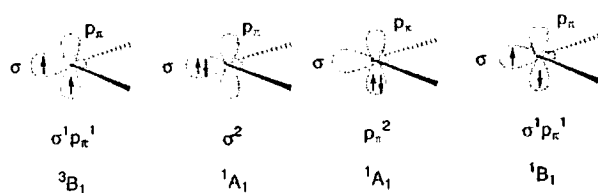
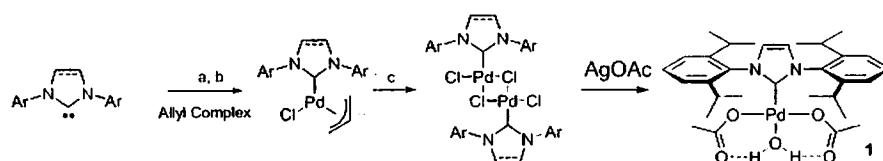


Figure 3. Electronic configurations of carbenes.

Synthesis of catalyst

Table 1. Synthesis of Pd(II)-Carbene Dimers<sup>[a]</sup>

<sup>a</sup> Reagents and conditions: (a) carbene, Pd(allyl)Cl<sub>2</sub>, THF (see Supporting Information for details); (b) flash chromatography; (c) HCl-ether (quantitative yield).

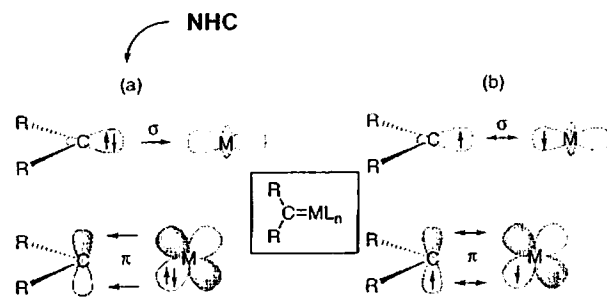
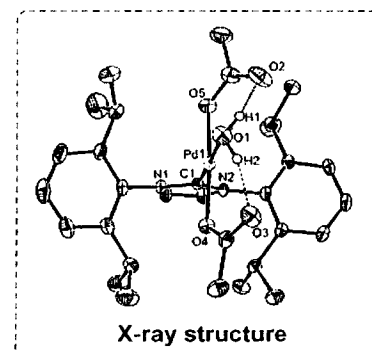


Figure 18. Schematic representations of (a) donor-acceptor bonding in Fischer carbene complexes and (b) covalent bonding in Schrock carbene complexes.

# NHC bind to transition metals only through  $\sigma$  donation,  $\pi$ -back-bonding being negligible.

Act as a strong ligand.



1) concentration of acetic acid

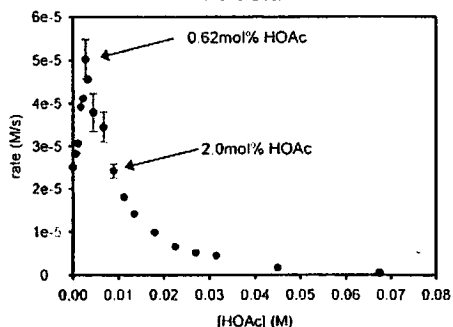


Figure 10. Rate dependence of *sec*-phenethyl alcohol oxidation using various HOAc concentrations at 50 °C. Conditions: 0.5 mol % 1, 0.45 M alcohol in benzene, with 3 Å molecular sieves and a balloon charged with O<sub>2</sub>. The range of [AcOH] is 0–67.5 mM (0–15 mol %).

2) reaction profile with acetic acid

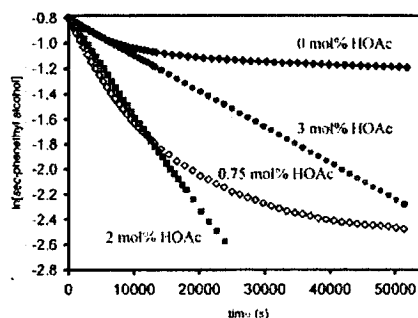


Figure 12. Natural logarithm of *sec*-phenethyl alcohol concentration vs time at various HOAc concentrations at 50 °C (every 10 time points displayed). Conditions: 0.5 mol % 1, 0.45 M alcohol in benzene, with 3 Å molecular sieves and a balloon charged with O<sub>2</sub>.

3) KIE value

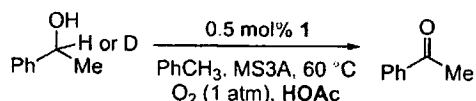


Table 3. KIE Values at Various HOAc Concentrations

[HOAc] (mM)	KIE value	[HOAc] (mM)	KIE value	[HOAc] (mM)	KIE value
0	1.7	2.79	3.1	6.75	5.2
2.12	2.7	4.50	3.4	9.00	5.5

(2 mol%)

The KIE value gradually increase as the concentration of additive acetic acid is increased.

# Point: O<sub>2</sub> ratio #

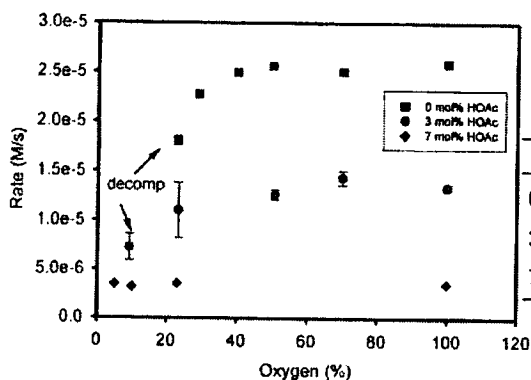
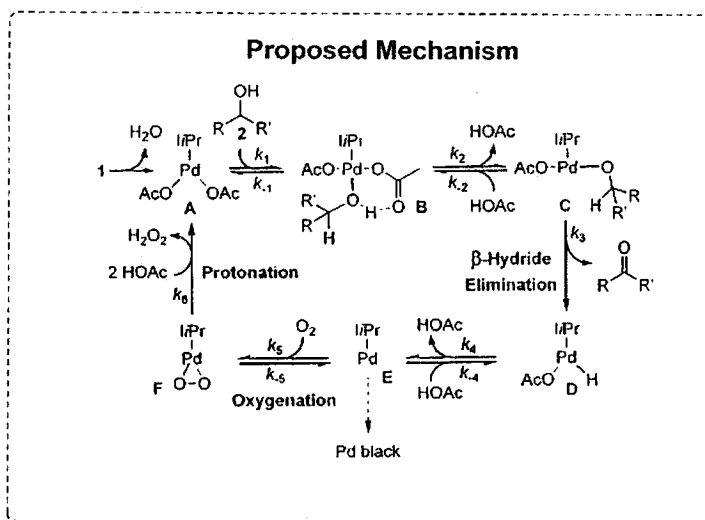


Figure 14. Initial rates of the *sec*-phenethyl alcohol oxidation at 50 °C using various AcOH concentrations and oxygen/nitrogen mixtures. Conditions: 0.5 mol % 1, 0.45 M *sec*-phenethyl alcohol, with 3 Å molecular sieves and a balloon charged with O<sub>2</sub>.



AcOH	catalyst decomposition
0 mol%	< 23% O <sub>2</sub> /N <sub>2</sub>
3 mol%	5 ~ 23% O <sub>2</sub> /N <sub>2</sub>
7 mol%	< 5% O <sub>2</sub> /N <sub>2</sub>

The catalyst decomposition is prevented as the concentration of acetic acid is increased.

- AcOH: 1) protonation F to A is promoted. (oxygenation proceeds smoothly) **large KIE?**  
 2) re-protonation C to B is also promoted. (only β-hydride elimination is rate limiting)

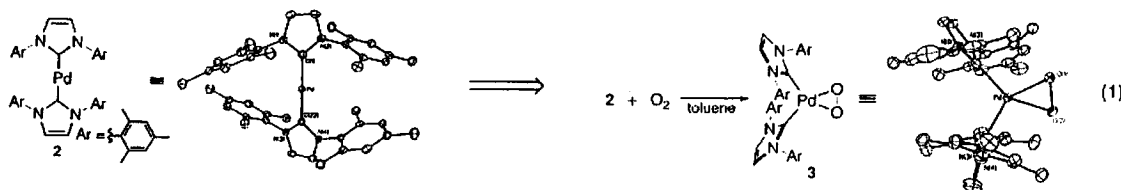
Acetic acid plays multiple roles in this reaction.

cf. Pd(II)-OOH species

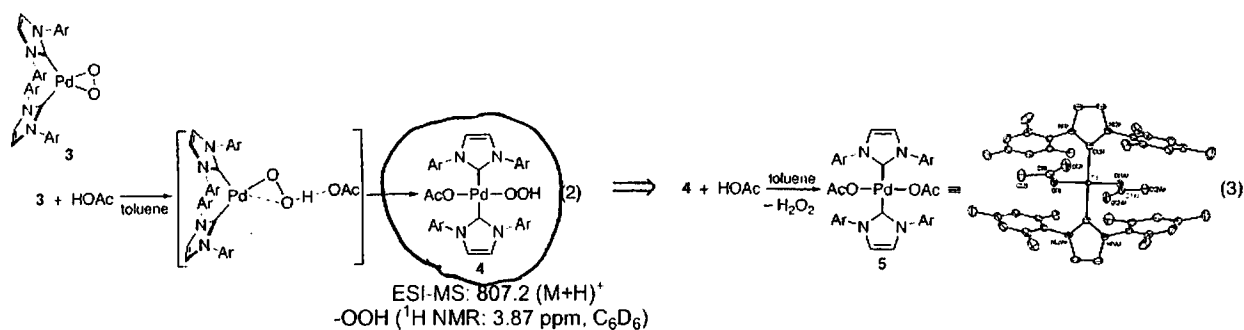
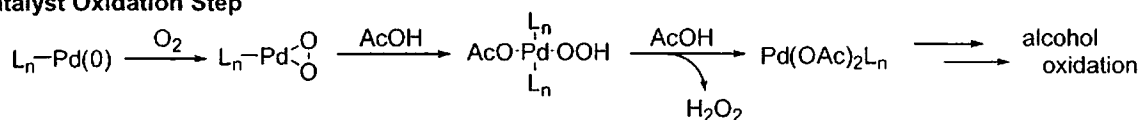
**Characterization of Peroxo and Hydroperoxo Intermediates in the Aerobic Oxidation of N-Heterocyclic-Carbene-Coordinated Palladium(0)**

Michael M. Konnick, Ilia A. Guzei, and Shannon S. Stahl\*

*J. Am. Chem. Soc.* 2004, 126, 10212.

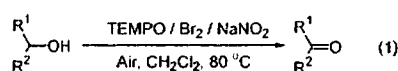
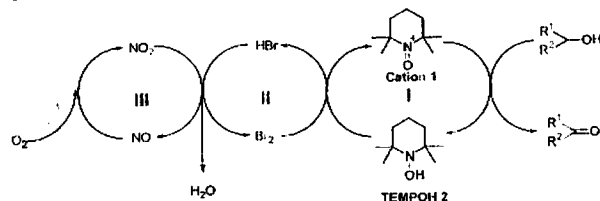




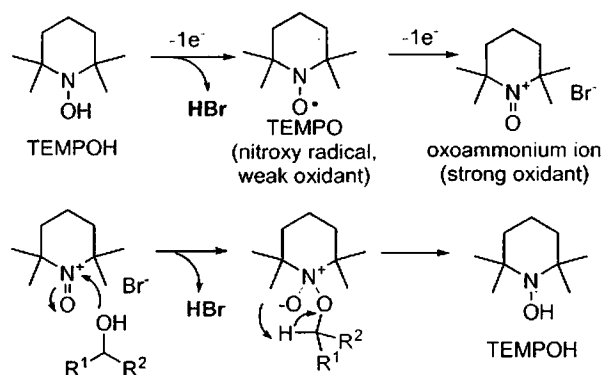
**Catalyst Oxidation Step****6. Metal-Free Aerobic Oxidation****Transition-Metal-Free: A Highly Efficient Catalytic Aerobic Alcohol Oxidation Process**

Renhua Liu, Xinmiao Liang,\* Chunyan Dong, and Xinquan Hu\*

Dalian Institute of Chemical Physics, the Chinese Academy of Sciences, Dalian 116023, P. R. China

*J. Am. Chem. Soc.* 2004, 126, 4112.**Scheme 1. Overall Catalytic Mechanism****Table 1. Catalytic Aerobic Alcohol Oxidation<sup>a</sup>**

Entry	Substrate	Product	Method	Time (h)	Conv (%)	Select (%)	Yield (%)
1			A	1	100	100	95
2			A	1.5	100	99	95
3			A	1.5	100	100	93
4			A	1.5	100	99.5	94
5			A	2	100	100	96
6			A	2	100	99.3	96
7			A	2	100	100	96

**Alcohol Oxidation using TEMPO**

8			A	1.5	100	99	98
9	1-C <sub>8</sub> H <sub>17</sub> OH	1-C <sub>7</sub> H <sub>15</sub> CHO	B	3	100	86 <sup>b</sup>	-
10	2-C <sub>8</sub> H <sub>17</sub> OH	2-Octanone	B	4	99.4	100	98
11	3-C <sub>8</sub> H <sub>17</sub> OH	3-Octanone	B	4	99.1	99.3	88
12			B	4	100	99.4	89
13			B	5	100	94.7	99 <sup>c</sup>
14			B	12	50.7	100	-
15			B <sup>d</sup>	5	94.4	100	98
16			B <sup>e</sup>	3	70.2	95.1	-

<sup>a</sup> Reaction conditions: alcohol (10 mmol), TEMPO (0.1 mmol), Br<sub>2</sub> (0.4 mmol), CH<sub>2</sub>Cl<sub>2</sub> (10 mL), 80 °C (oil bath temperature). Method A: NaNO<sub>2</sub> (0.4 mmol), 0.4 MPa air pressure; method B: NaNO<sub>2</sub> (0.8 mmol), 0.9 MPa air pressure. Conversions and selectivities are based on the GC with area normalization. All yields are for pure, isolated products. <sup>b</sup> Ester (14%) was formed. <sup>c</sup> 5-Bromo-thiophene-2-aldehyde was formed as major byproduct in 5.3%. <sup>d</sup> Conditions: 4 mol % of TEMPO, 8 mol % Br<sub>2</sub>, and 8 mol % NaNO<sub>2</sub> at 100 °C. <sup>e</sup> PyHBr<sub>3</sub> (4 mol %) was used in place of Br<sub>2</sub>.

( 0.4 MPa = ~4 atm  
0.9 MPa = ~9 atm.

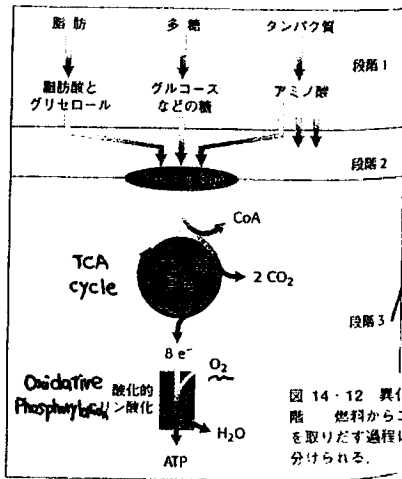


図 14-12 異化作用の段階 燃料からエネルギーを取り出す過程は3段階に分けられる。

② Oxidative Phosphorylation

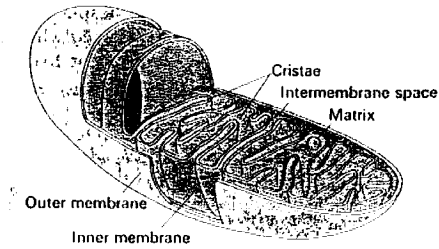


Figure 17-3 Diagram of a mitochondrion. [After Biology of the Cell by Stephen L. Wolfe. © 1972 by Wadsworth Publishing Company, Inc. Belmont, California 94002. Adapted by permission of the publisher.]

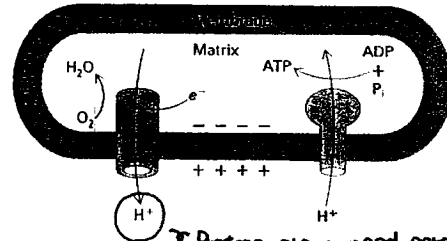


Figure 17-2 Protons are pumped across the membrane. Oxidation and ATP synthesis are coupled by transmembrane proton fluxes.

② Proton-Motive Force

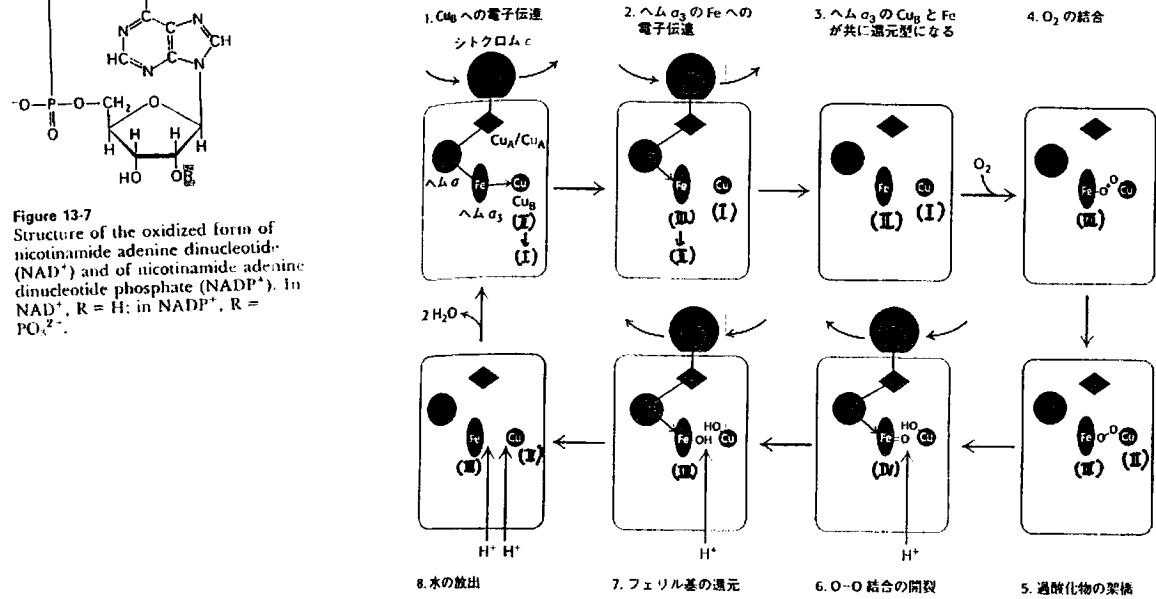
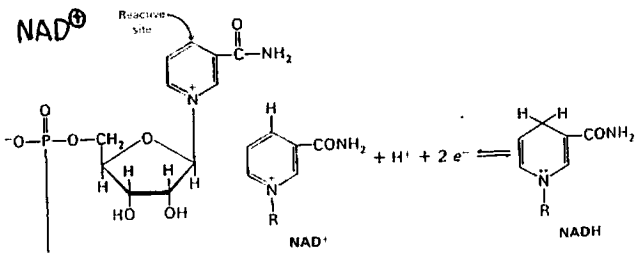
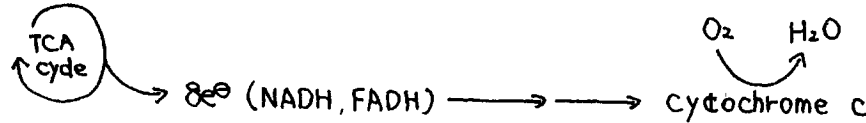
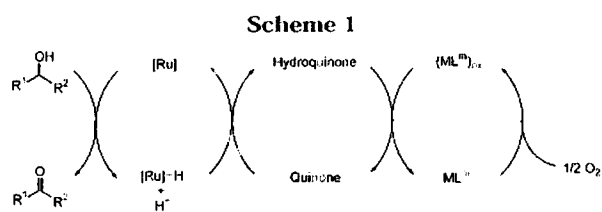


図 18-19 シトクロム c オキシダーゼの機構 このサイクルのすべての補次分子族は酸化型(青で示す)で始まる。還元型シトクロム c は、電子をもらい Cu<sub>B</sub>を還元する。2番目の還元型シトクロム c は heme a<sub>3</sub>の鉄を還元する。この Fe<sup>3+</sup>中心は酸素を結合する。二つの電子は、結合した酸素に移行して過酸化物を形成し、鉄と Cu<sub>B</sub>を架橋する。還元型シトクロム c の3番目の分子によって加えられた電子は、O-O結合を開裂し、マトリックスからプロトンを取り出す。最終的に取込まれる電子と三つのプロトンは二つの H<sub>2</sub>O分子を産生する。それは酵素から放出され最初の段階が再生する。水分子中の四つのプロトンは、マトリックスに由来している。

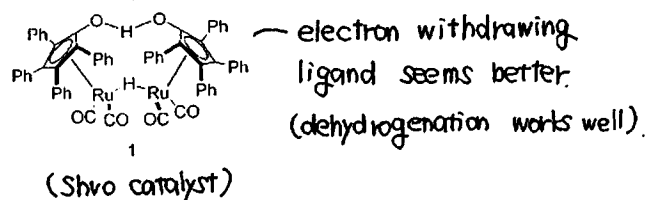
(ref. Biochemistry 3rd Ed. STRYER, L.)  
ストライプ-生化学 第5版

## Efficient Ruthenium-Catalyzed Aerobic Oxidation of Alcohols Using a Biomimetic Coupled Catalytic System

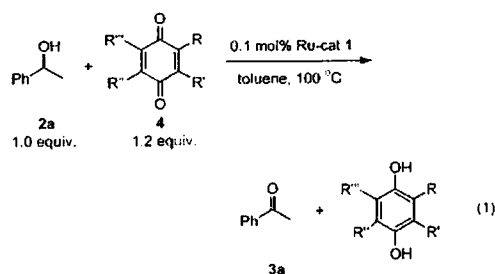
Gábor Csajenyik,<sup>†</sup> Alida H. Éll,<sup>†</sup> Luca Fadini,<sup>‡</sup> Benoit Pugin,<sup>‡</sup> and Jan-E. Bäckvall\*<sup>†</sup>



⊗ Ru catalyst.



⊗ Quinone Screening.



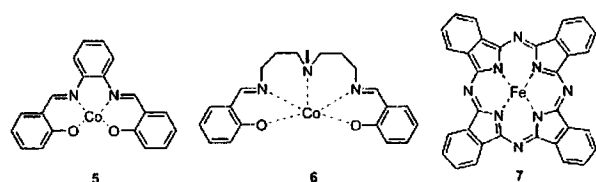
**Table 1.** Oxidation of 1-Phenylethanol (2a) with Stoichiometric Amounts of Quinones<sup>a</sup>

entry	benzoquinone	yield (%) <sup>b</sup>		
		10 min	30 min	1 h
1	tetrafluoro-1,4-benzoquinone (4a)	70	89	>99
2	2,6-dimethoxy-1,4-benzoquinone (4b)	61	84	>99
3	2-chloro-1,4-benzoquinone (4c)	58	82	>99
4	2,3-dimethoxy-5-methyl-1,4-benzoquinone (4d)	59	80	>99
5	1,4-benzoquinone (4e)	55	75	91
6	2,5-di- <i>tert</i> -butyl-1,4-benzoquinone (4f)	34	43	78
7	2,6-di- <i>tert</i> -butyl-1,4-benzoquinone (4g)	36	41	71

<sup>a</sup> The reactions were carried out on a 0.5 mmol scale with 0.1 mol % of catalyst **1** and 1.2 equiv of the benzoquinone in 3 mL of toluene at 100 °C under argon. <sup>b</sup> Determined by GC.

⊗ Oxygen-activating Catalyst

Ruthenium-Catalyzed Aerobic Oxidation of Alcohols



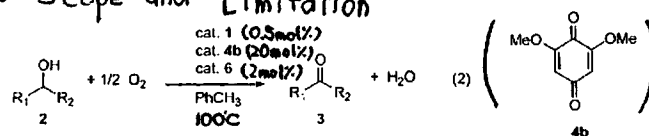
**Figure 1.** Oxygen-activating catalysts.

**Table 2.** Aerobic Oxidation of 1-Phenylethanol<sup>a</sup>

entry	solvent, temperature	ML complex	conversion (%) <sup>b</sup>
1	THF, 65 °C	<b>7</b>	58
2	THF, 65 °C	<b>6</b>	78
3	toluene, 100 °C	<b>7</b>	100
4	toluene, 100 °C	<b>6</b>	100 <sup>c</sup>

<sup>a</sup> The reactions were carried out on a 1 mmol scale in 5 mL solvent under a balloon filled with ca. 2% oxygen in nitrogen employing 0.5 mol % of catalyst **1**, 20 mol % of **4b**, and 2 mol % of metal–ligand (ML) complex. Reaction time: 48 h. <sup>b</sup> Determined by GC. <sup>c</sup> 24 h.

⊗ Scope and Limitation



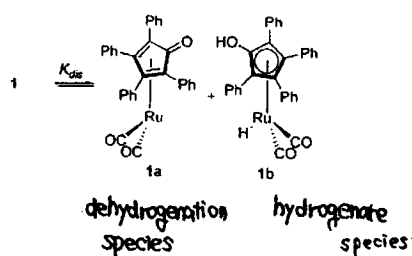
**Table 3.** Ruthenium-Catalyzed Aerobic Oxidation of Secondary Alcohols<sup>a</sup>

Entry	Substrate	Reaction Time (h)	Product	Yield (%) (Isolated)
1	2a	1	3a	89
2	2b	2.8	3b	88
3	2c	2	3c	81 <sup>c</sup> ~ 1 mol% of <b>1</b>
4	2d	1	3d	92
13	2m	2	3m	80
14	2n	1.5	3n	70 <sup>c</sup> ~ 1 mol% of <b>1</b>

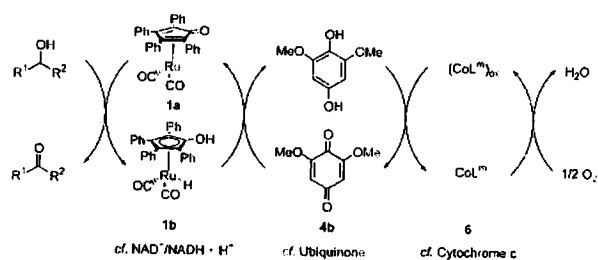
primary alcohol, is not reported.

## @ Mechanistic Insights.

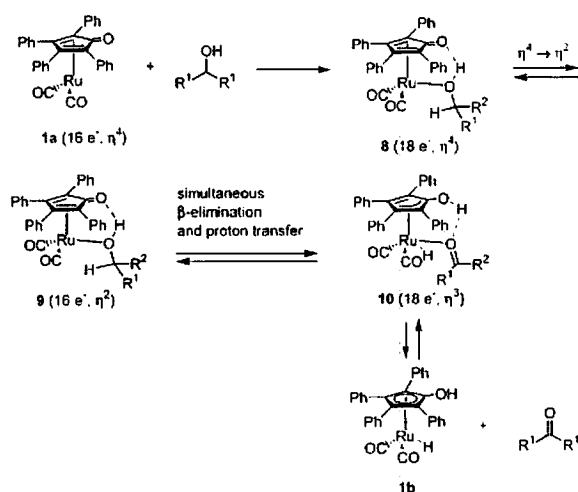
Scheme 2



Scheme 3. Biomimetic Aerobic Oxidation of Alcohols



Scheme 4



@ Close interaction (contact) between the redox couples achieves efficient reaction.