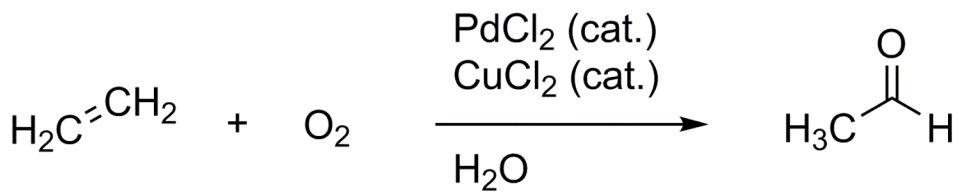
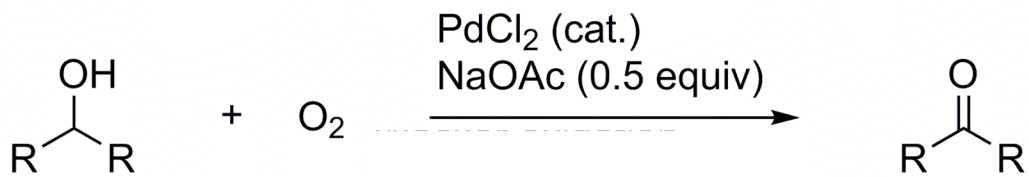
Mechanistic Studies on Palladium-Catalyzed Aerobic Oxidations

Peter J. Yao
Group Meeting
30 Jan 07

Historical background

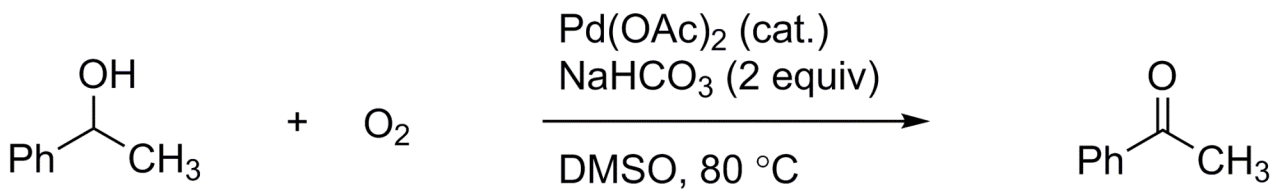


Wacker oxidation
Smidt *et al*. *Angew. Chem.* **1959**, *71*, 176.

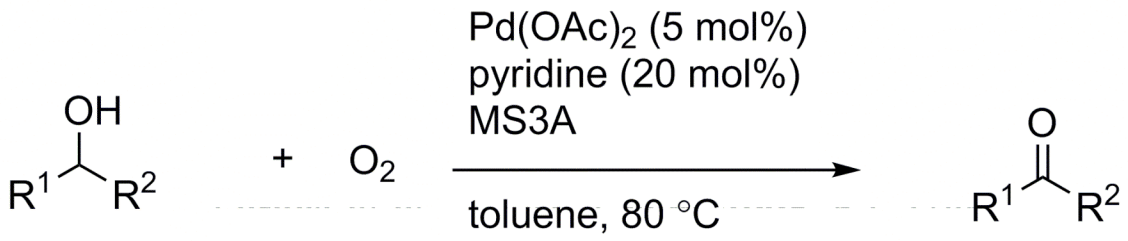


Copper free aerobic oxidation
Schwartz *et al*. *Chem. Commun.* **1977**, *157*.

Historical background

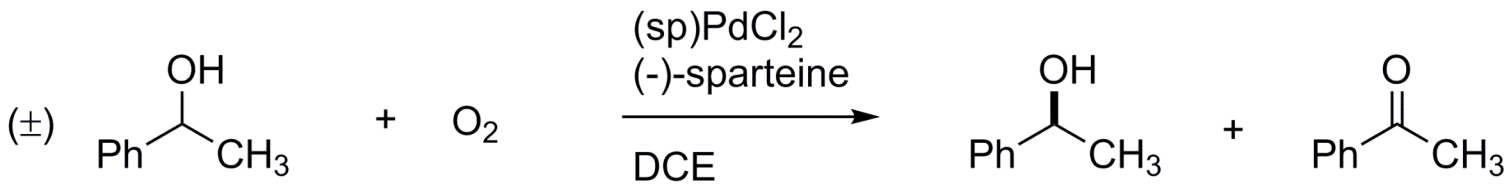


Larock *et al.* *J. Org. Chem.* **1998**, *63*, 3185.

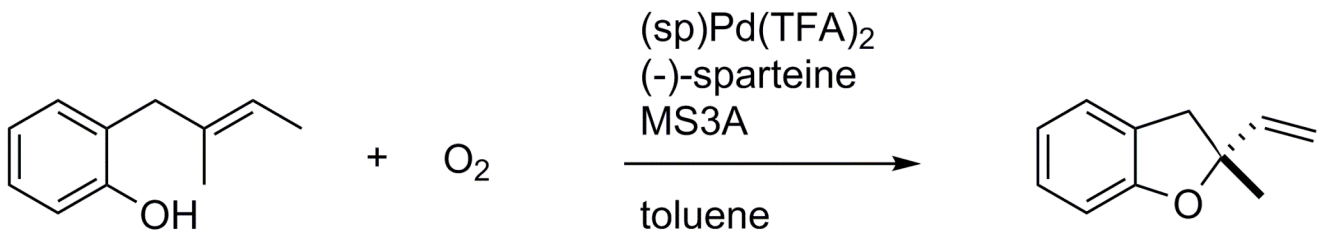


Uemura *et al.* *Tetrahedron. Lett.* **1998**, *39*, 6011.

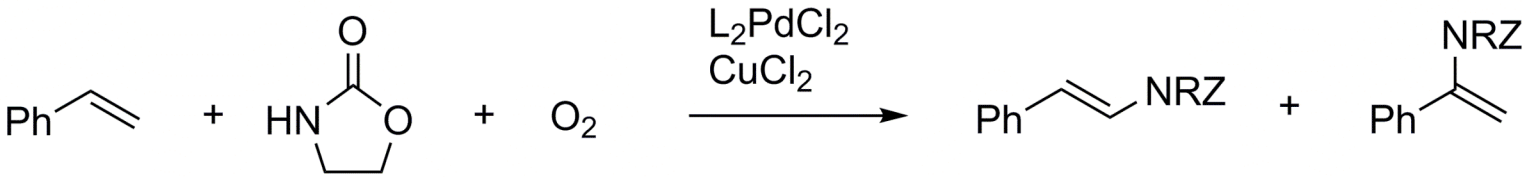
Synthetic applications



Sigman *et al.* *JACS* **2003**, *125*, 7005-7013.

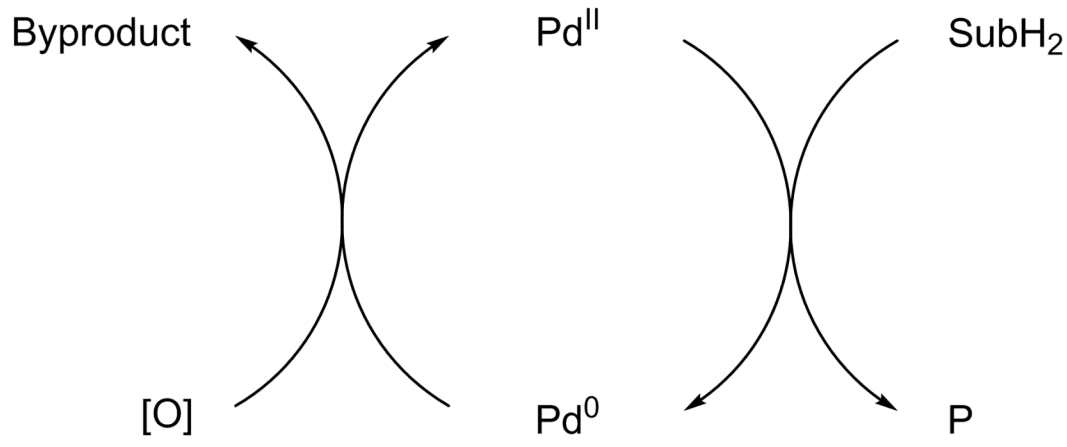


Stoltz *et al.* *JACS* **2005**, *127*, 17778-17788.



Stahl *et al.* *JACS* **2005**, *127*, 17888-17893.

Overview of the simplified catalytic cycle



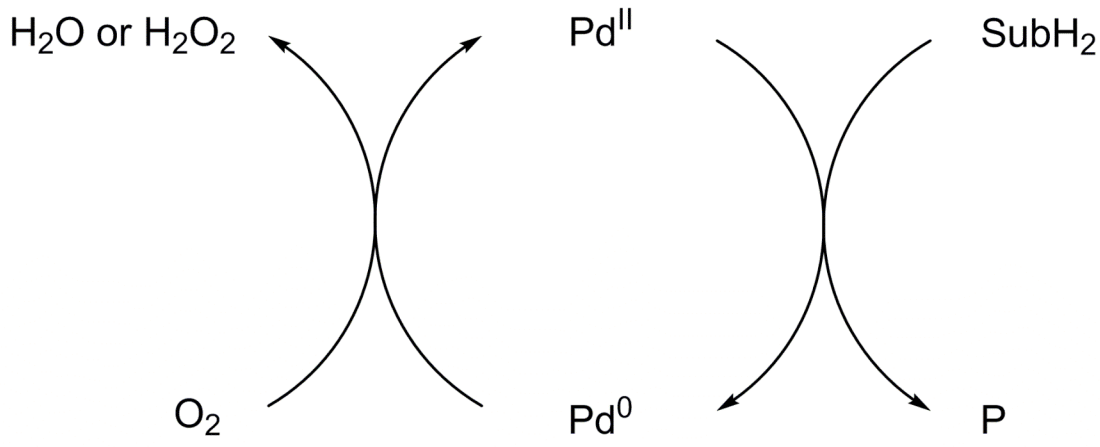
Two separate but coupled processes:

1. Substrate oxidation by Pd^{II}
2. Re-oxidation of Pd^0

Wacker process: reoxidation involves an additional redox cycle with copper
Backvall: reoxidation involves two addition redox cycles with benzoquinone and another metal

More recent advances allow reoxidation directly with O_2

Key issues to be addressed

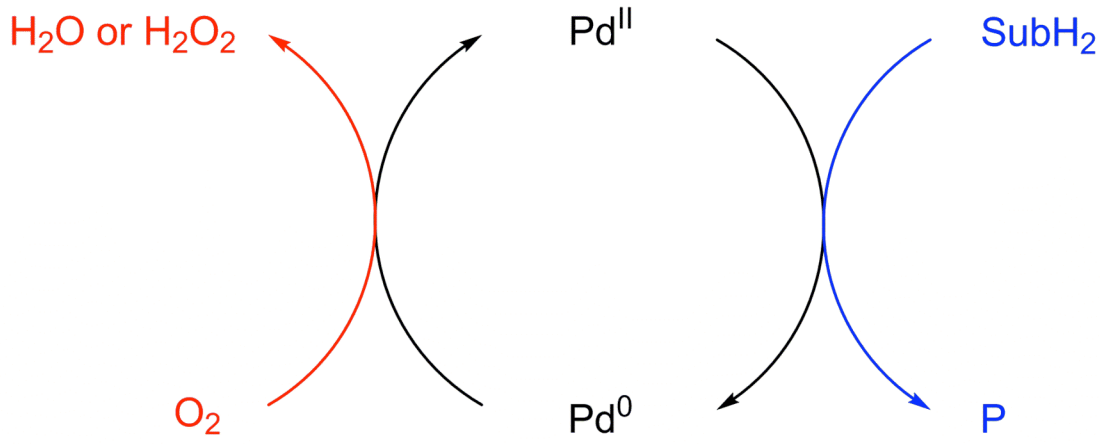


How is Pd^0 re-oxidized to Pd^{II} by O_2?

How are the hydrogen atoms removed?

What role do ligands and basic additives play
in each half of the catalytic cycle?

What has been studied so far?



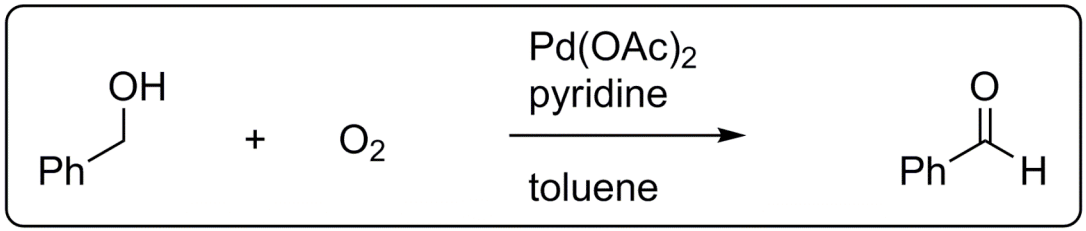
Stahl, Goddard, and others...
Kinetics and isolation of various complexes

Stahl, Sigman, Sheldon...
A **lot** of kinetics, KIE, and Hammett studies

Extensive computational modeling for both parts of the cycle

Most well-studied systems are simple alcohol oxidations

Stahl's analysis of the Uemura system



Stahl *et al*. *JACS* **2004**, *126*, 11268-11278.

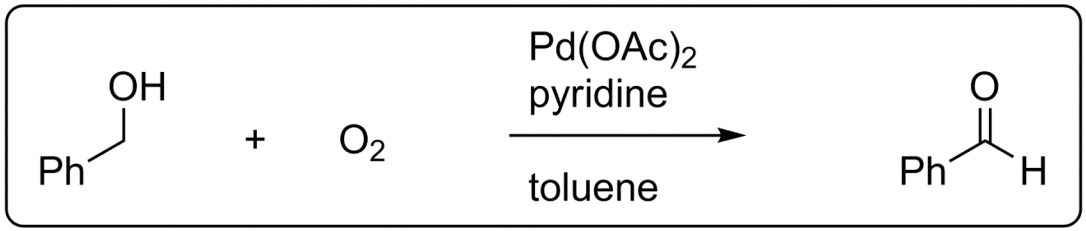
How was this reaction studied?

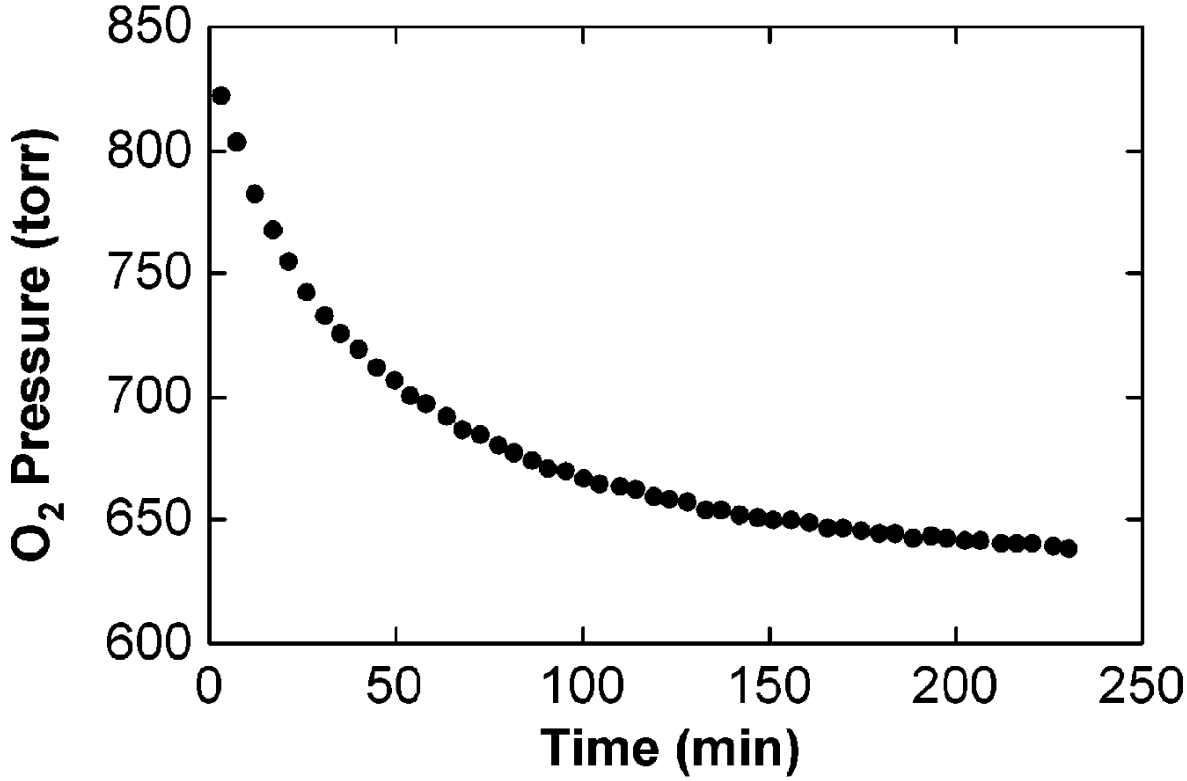
Kinetic analysis: order in O_2, RCH_2OH, $Pd(OAc)_2$, pyridine, and AcOH

KIE: $PhCD_2OH$ and PhCHDOH

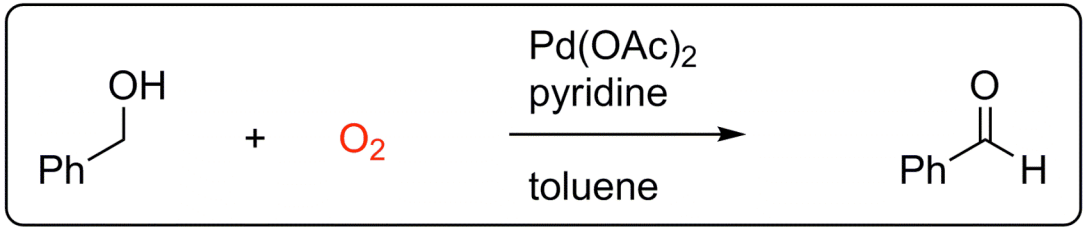
Hammett plots: (*p*-X-C_6H_4)CH_2OH and (*p*-X-C_5H_4N)

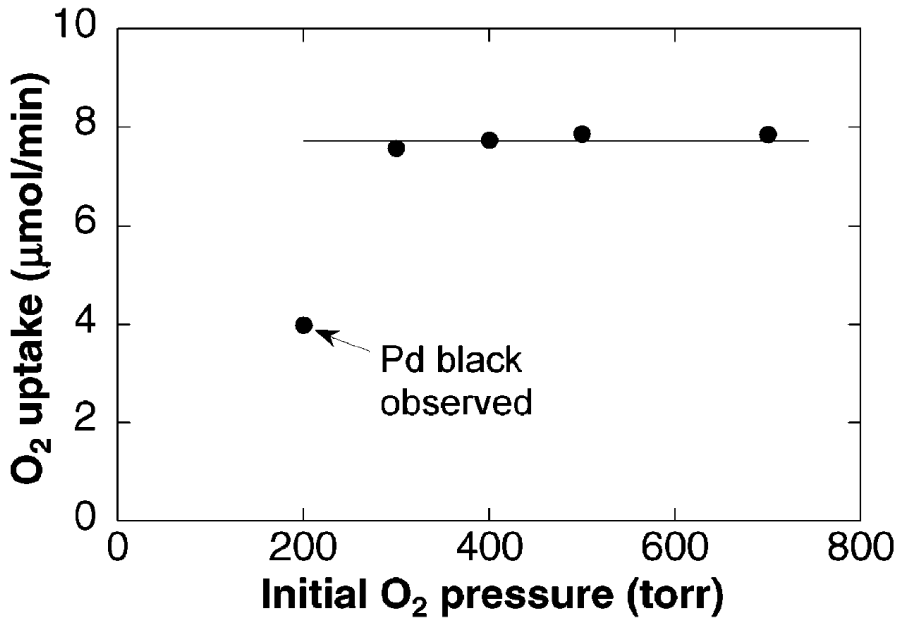
Kinetic analysis - initial rates measured by gas-uptake





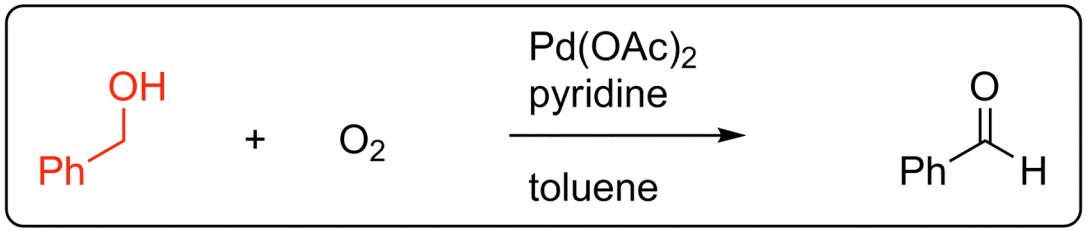
Kinetic analysis - O_2 order

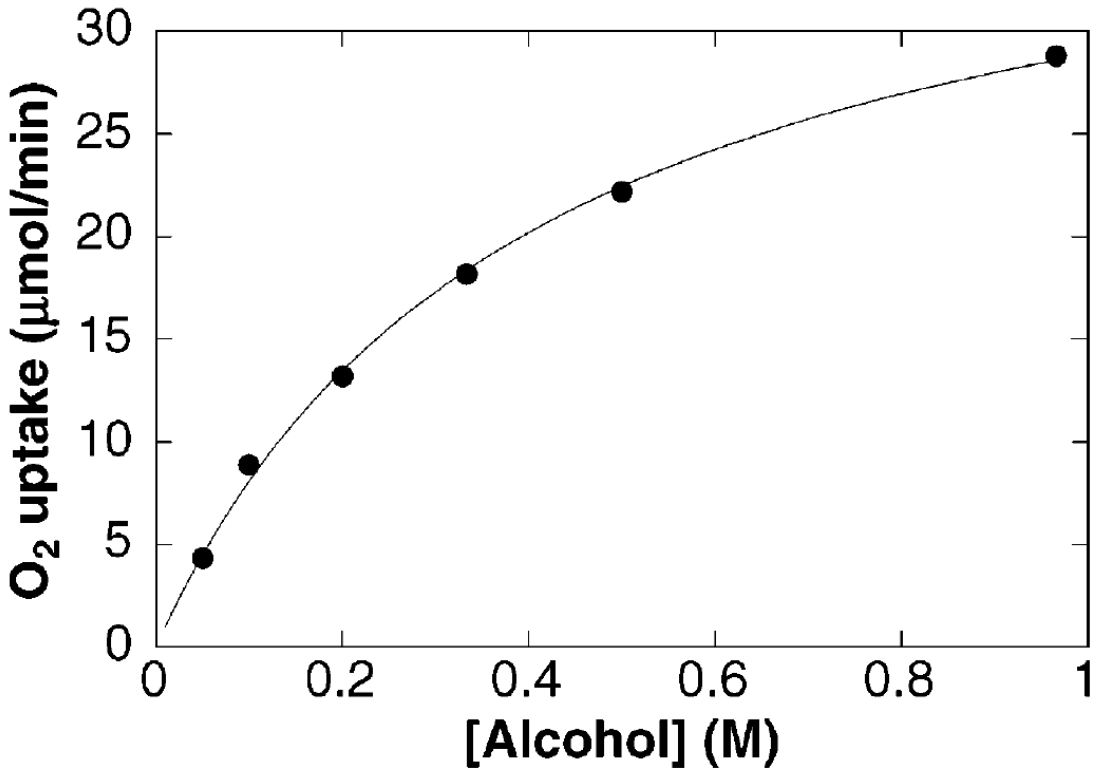




Which half of the catalytic cycle has the RDS?
At low [O_2] the catalyst dies... a common theme in this chemistry
(see: Stahl *et al.* *JACS* **2006**, *128*, 4348-4355.)

Kinetic analysis - RCH_2OH order





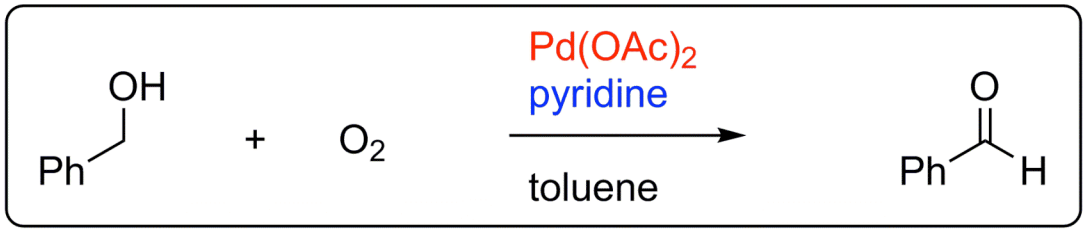
Kinetic isotope effect:

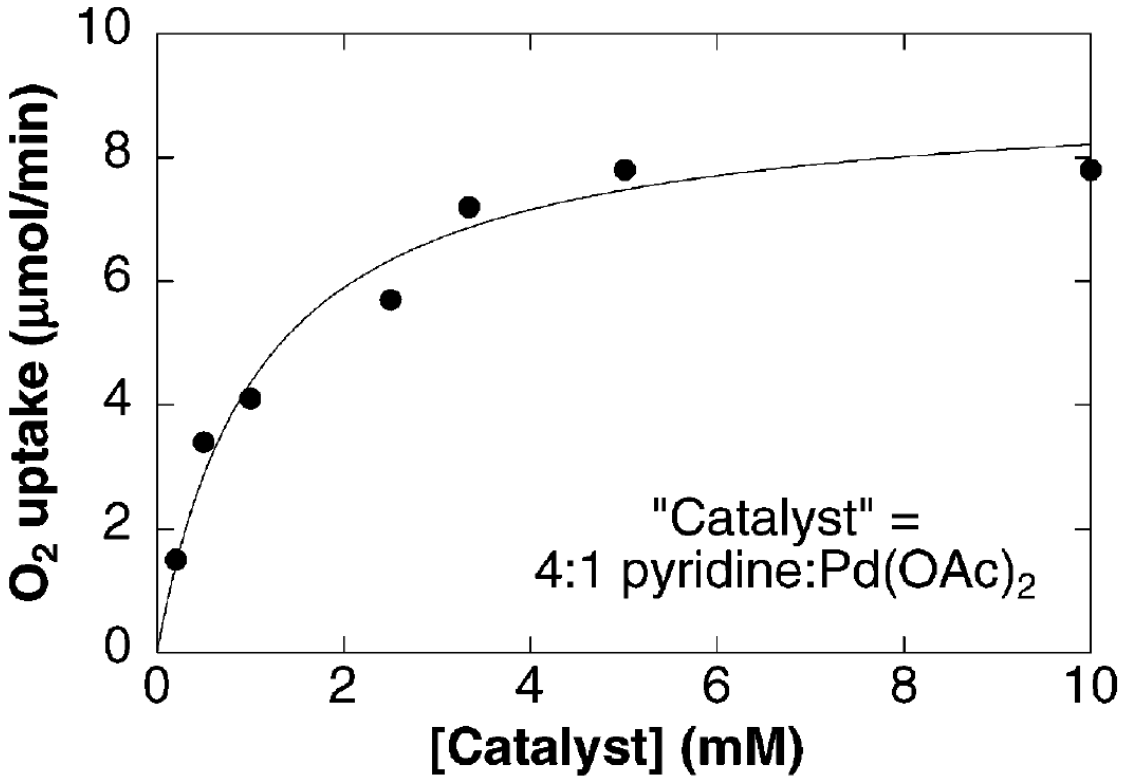
$PhCD_2OH$ *vs.* $PhCH_2OH$
KIE = 1.5

PhCHDOH
KIE = 2.6

What is the difference?

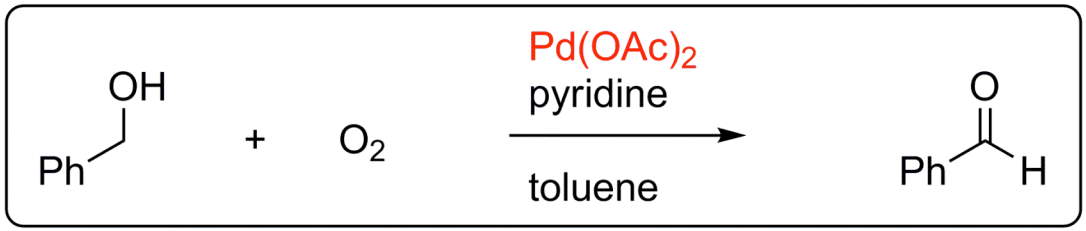
Kinetic analysis - catalyst order

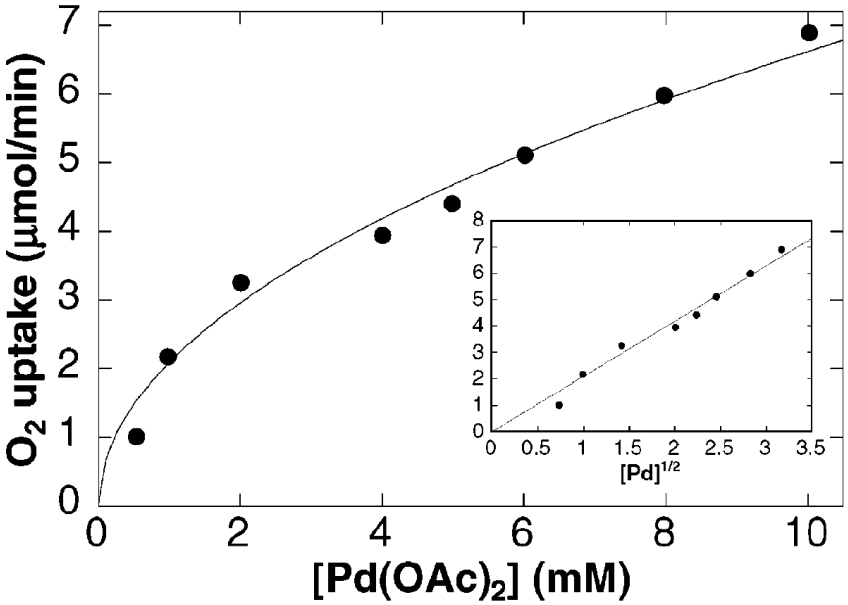




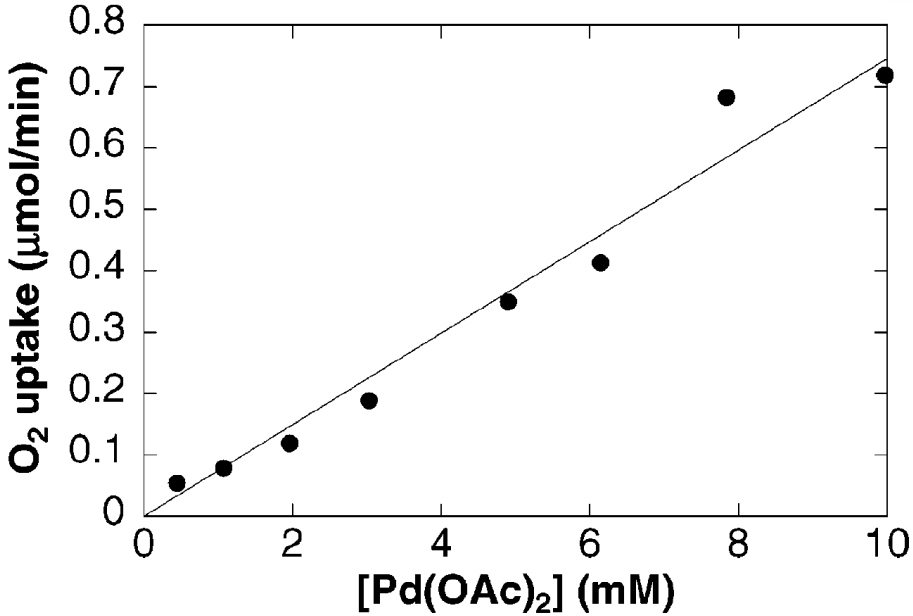
(10 mM = 10 mol%)

Kinetic analysis - catalyst order



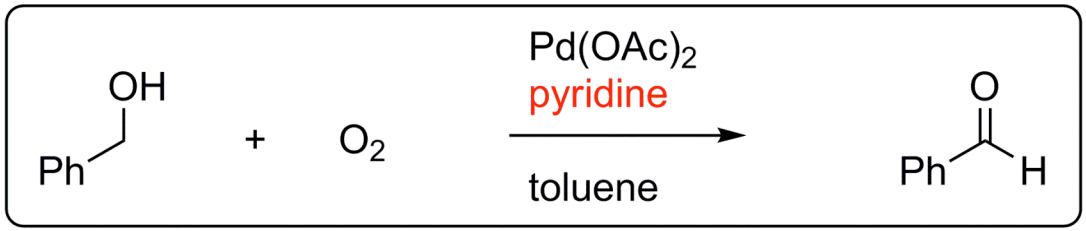


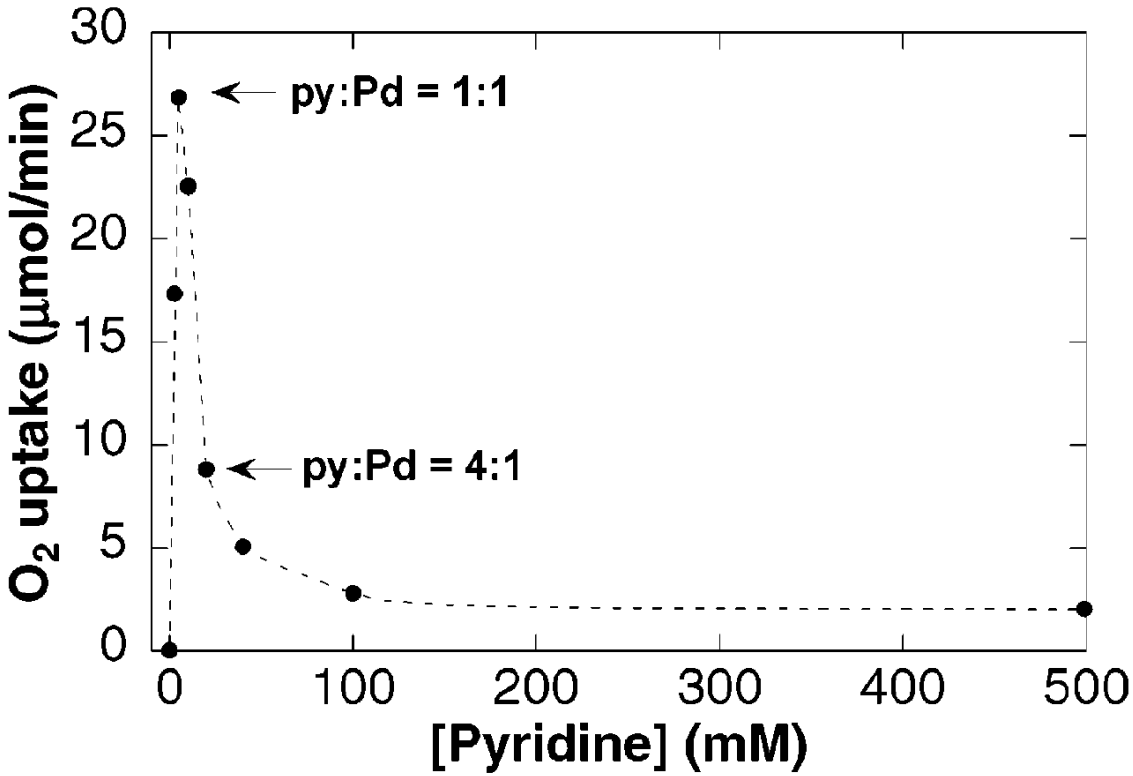
pyridine:Pd > 12.5



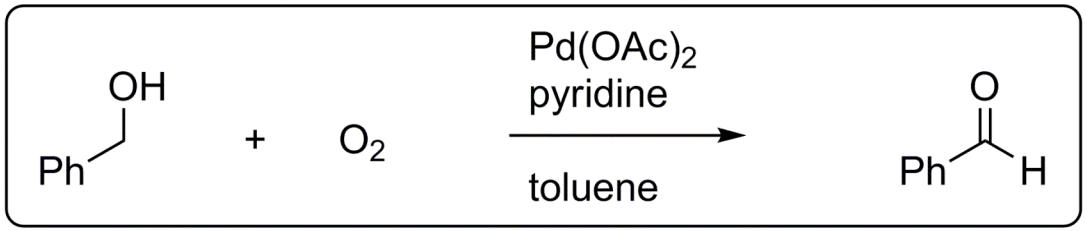
pyridine:Pd > 8
0.05 equiv AcOH

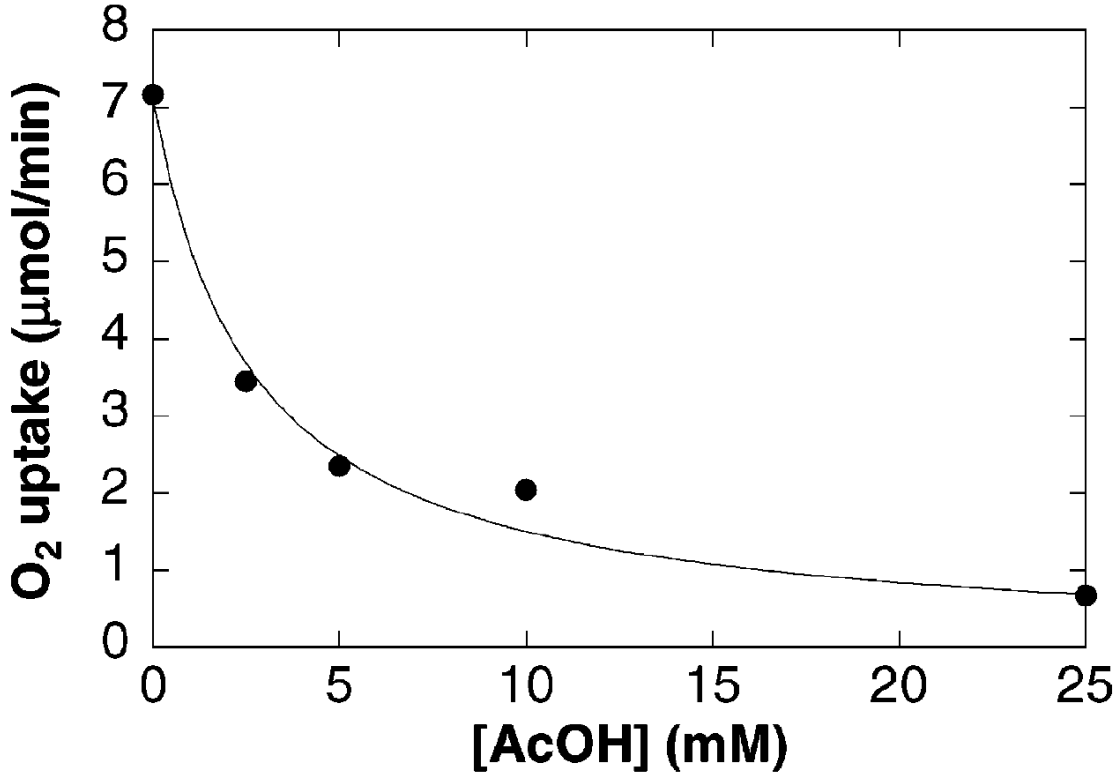
Kinetic analysis - pyridine order





Kinetic analysis - AcOH order





Kinetic analysis summary

The kinetics are quite complicated!

(1)	O_2:	0 order above a minimum pressure
(2)	RCH_2OH:	1st order at low conc., 0 order at high conc. (saturation)
(3)	Catalyst:	1st order in $Pd(OAc)_2$ with excess pyridine and AcOH
		<1 order in $Pd(OAc)_2$ with excess pyridine only
		<1 order in $Pd(OAc)_2$ at fixed pyr:Pd ratio (4:1)
(4)	pyridine:	inhibitory at pyr:Pd ratio > 1:1
(5)	AcOH:	inhibitory

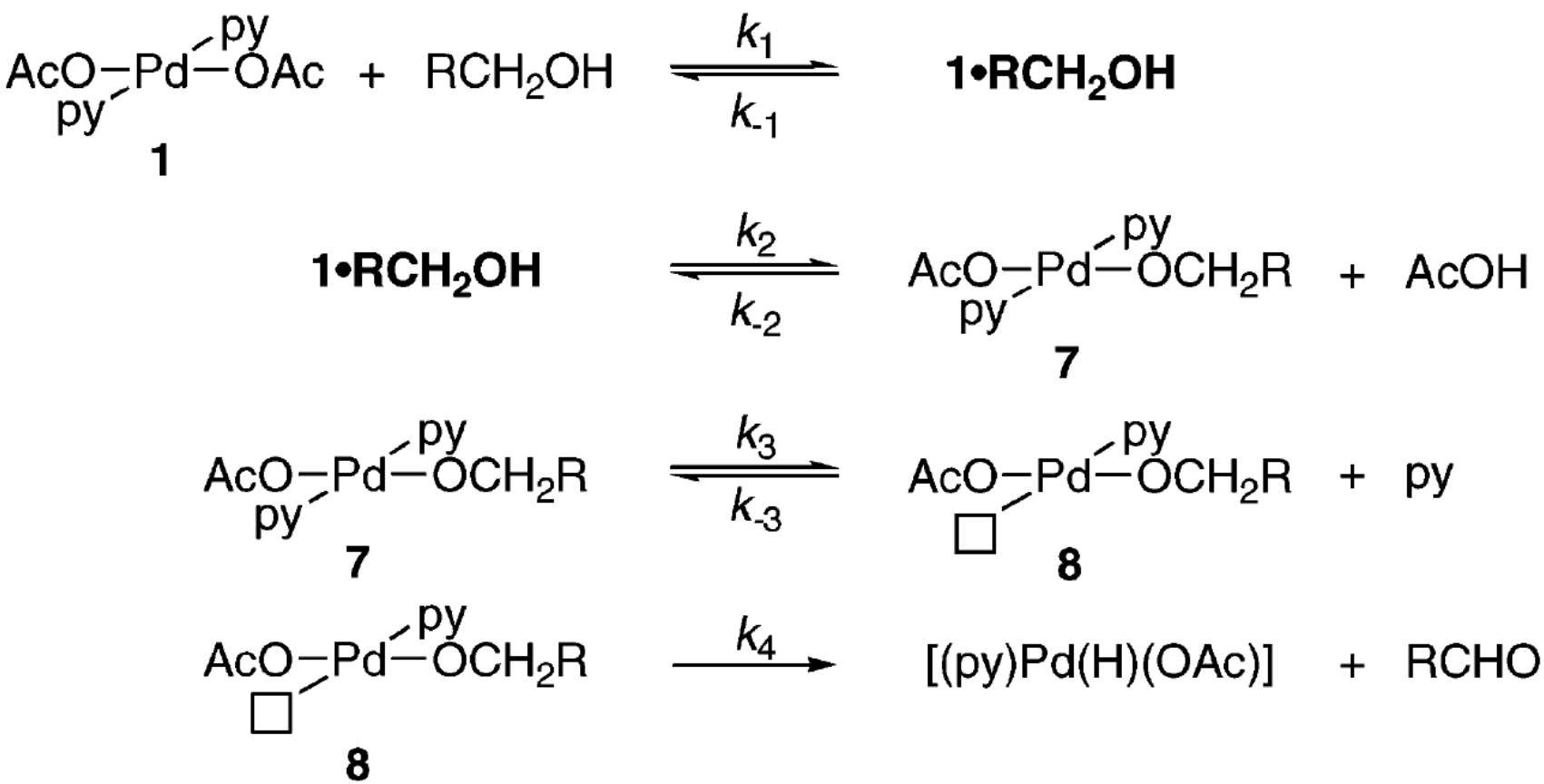
What does (2) suggest about the interaction of the alcohol with catalyst?

What does (4) suggest about ligand dissociation? How many ligands come off?

What does (5) suggest about formation of AcOH?

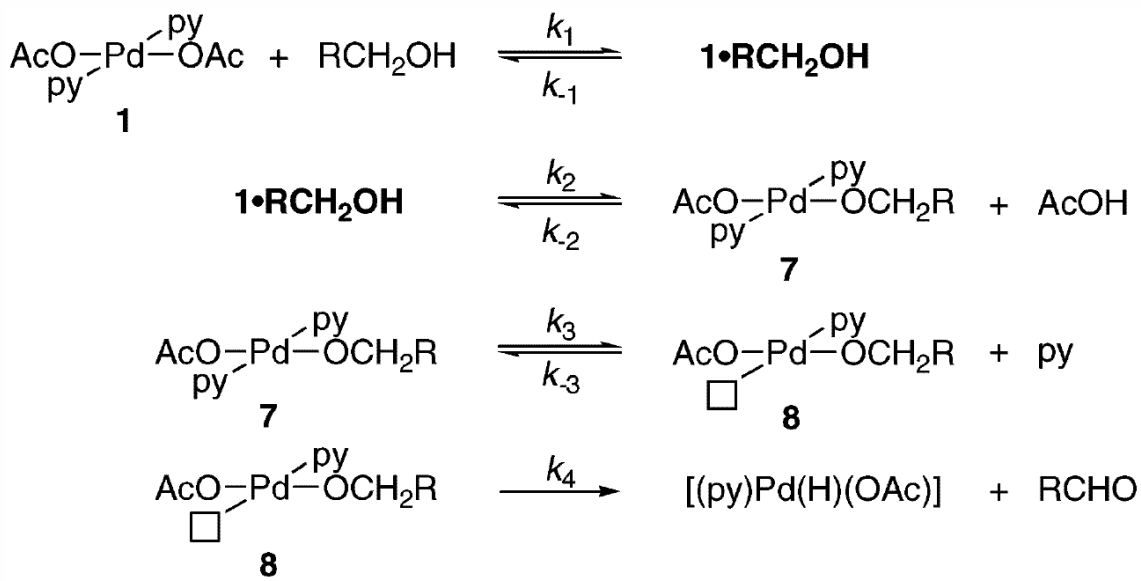
We will address (3) after the proposed mechanism...

Stahl's proposed mechanism



RDS is β-hydride elimination from Pd-alkoxide

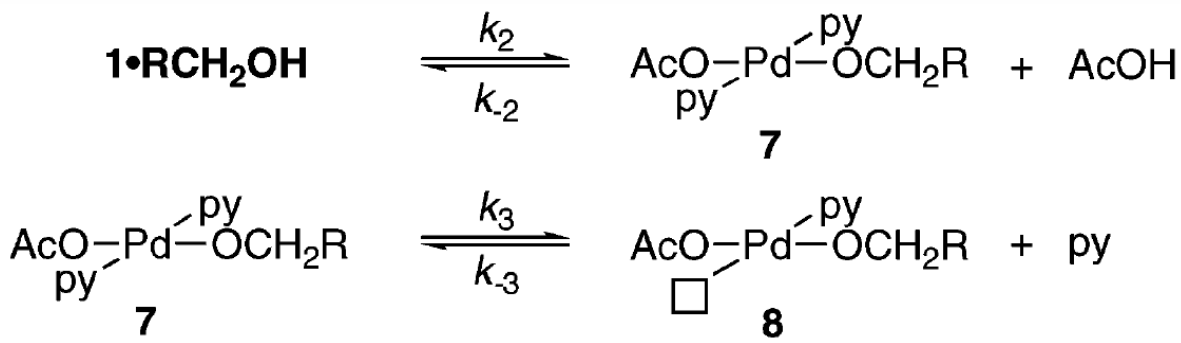
Stahl's proposed mechanism - rate law



$$\frac{d[\mathrm{RCHO}]}{dt} = \frac{K_1 k_2 k_3 k_4 [\mathrm{Pd}]_T [\mathrm{PhCH_2OH}]}{(1 + K_1[\mathrm{PhCH_2OH}])(k_{-2}[\mathrm{AcOH}](k_{-3}[\mathrm{py}] + k_4) + k_3 k_4)}$$

What happens at high [$PhCH_2OH$]?

Fractional order in catalyst



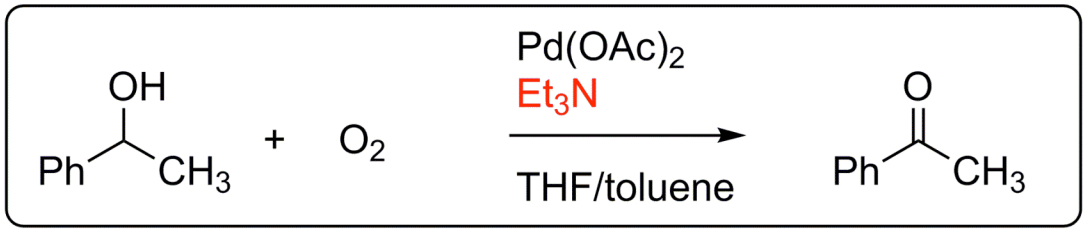
With no added AcOH, [AcOH] = [**7**]

Fractional-order arises from competition between unimolecular forward and bimolecular reverse reactions

$$\text{Rate} = \frac{k_3 k_4 \left(-k_3 k_4 + \sqrt{k_3^2 k_4^2 + 4 k_2 k_{-2} (k_{-3}[\text{py}] + k_4)^2 \left(\frac{K_1 [\text{Pd}]_\text{T} [\text{PhCH}_2\text{OH}]}{1 + K_1 [\text{PhCH}_2\text{OH}]} \right)} \right)}{2 k_{-2} (k_{-3}[\text{py}] + k_4)^2}$$

A formal derivation is in the SI of *JACS* **2004**, *126*, 11268-11278.

The role of the amine ligand



Sigman *et al*. *JACS* **2005**, *127*, 8499-8507.

Substitution of Et_3N for pyridine allows the reaction to proceed at RT... Why?

Summary of Sigman's kinetic analysis:

$PhCH(OH)CH_3$:	1st order at low conc., 0 order at high conc. (saturation)
Catalyst:	1st order at fixed Et_3N:Pd ratio 2:1
Et_3N:	inhibitory at Et_3N:Pd ratio > 1:1

Similar to Stahl's results so far...

The effect of Et_3N

(1) $Pd(OAc)_2 \rightleftharpoons Pd(OAc)_2(Et_3N) \rightleftharpoons Pd(OAc)_2(Et_3N)_2$

All three observed by ^{1}H-NMR

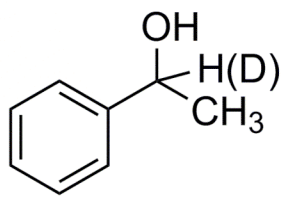
$Pd(OAc)_2 \rightleftharpoons Pd(OAc)_2(pyridine)_2$

Only species observed by ^{1}H-NMR

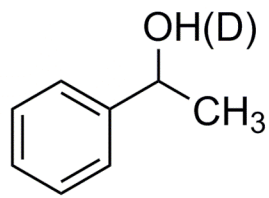
(2) $\Delta H^{\ddagger} = 10$, $\Delta S^{\ddagger} = -36$

compare to $\Delta H^{\ddagger} \approx 20$, $\Delta S^{\ddagger} \approx -5$ for other systems with RDS of β-hydride elimination

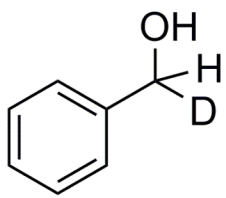
(3)



KIE = 1.09

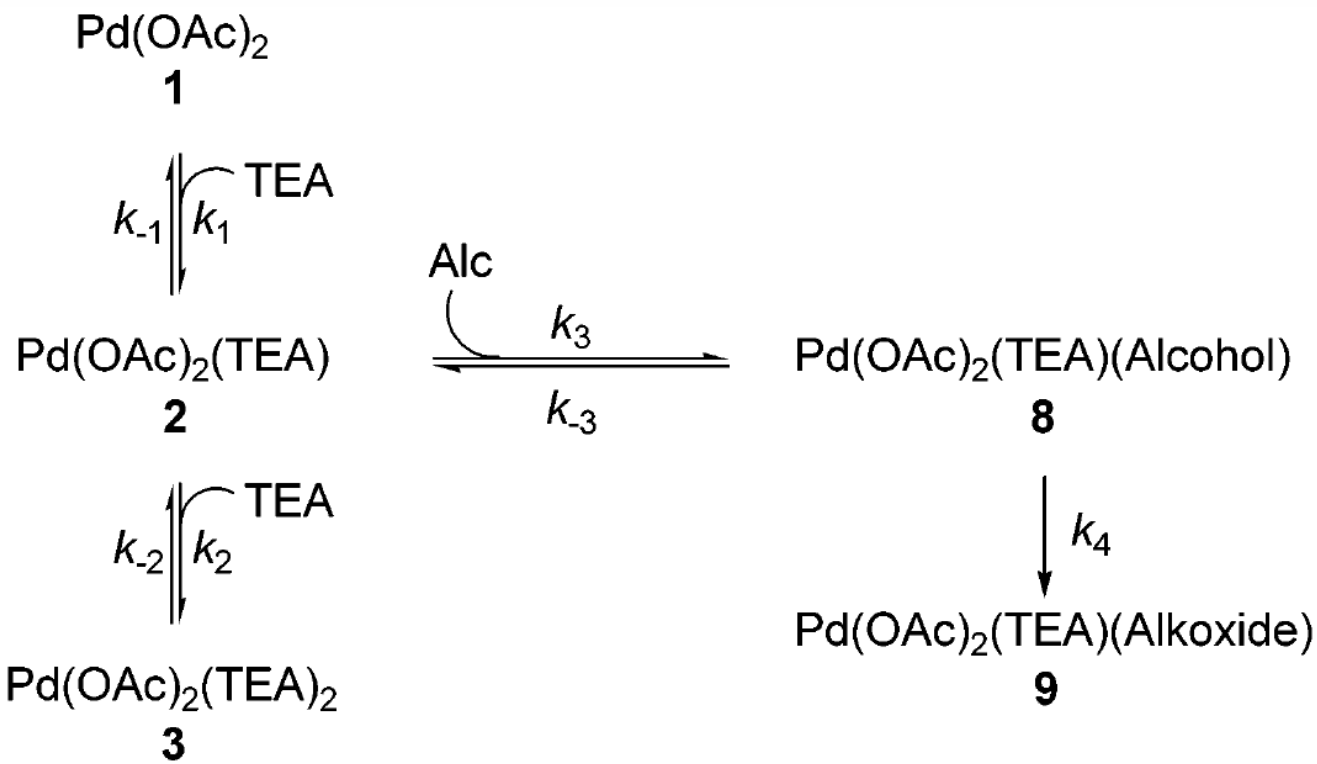


KIE = 1.26



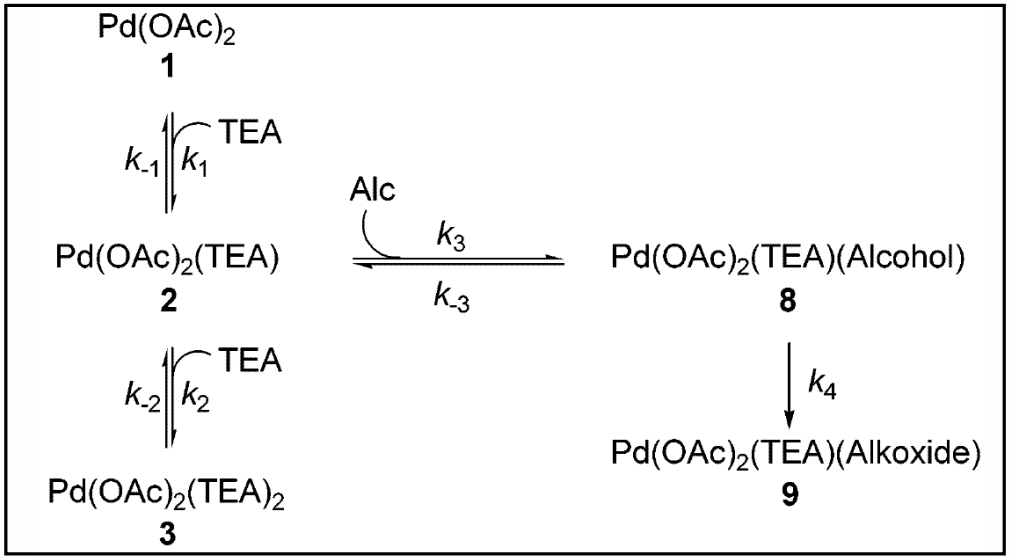
KIE = 4.3

Sigman's proposal for the Et_3N effect



β-hydride elimination is fast enough that deprotonation becomes RDS

Rate law derivation

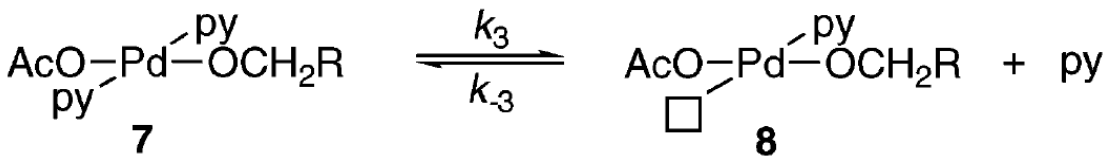


1. Write an expression for the rate of formation of **9**
2. Write equilibrium expressions for K_{eq1}, K_{eq2}, and K_{eq3}
3. Write an expression for $[Pd]_t$ (ignore [**9**])
4. Substitute each term in $[Pd]_t$ until they contain only [Alc], [TEA], [**8**], and K_{eq} terms
5. Solve for [**8**]

$$\text{rate} = \frac{K_{eq3}k_4[\text{Alc}][\text{Pdt}]}{\left(\frac{1}{K_{eq1}[\text{TEA}]}\right) + 1 + K_{eq2}[\text{TEA}] + K_{eq3}[\text{Alc}]}$$

Acceleration of β-hydride elimination

From Stahl's proposed mechanism with pyridine/$Pd(OAc)_2$

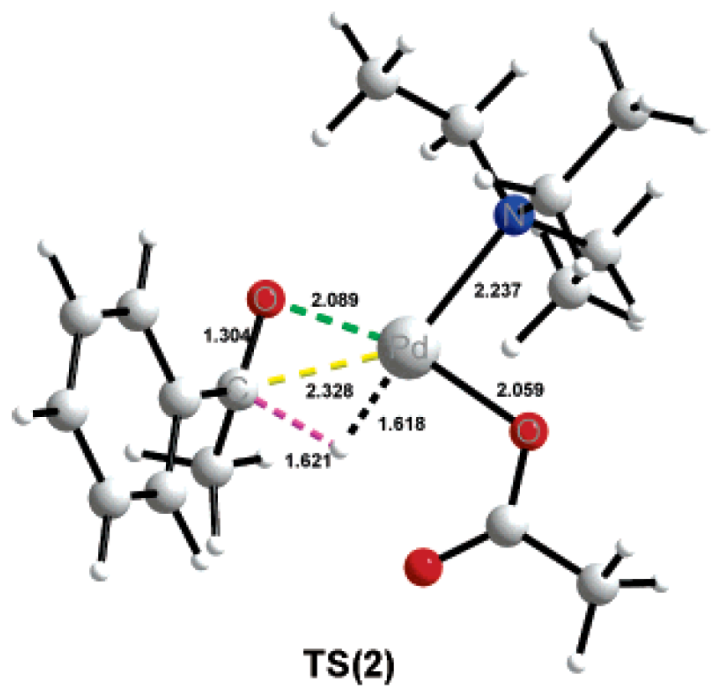


Hammett study also showed that electron-deficient pyridines lead to higher oxidation rates

Sigman proposes that the required dissociation of a pyridine ligand slows the rate of β-hydride elimination

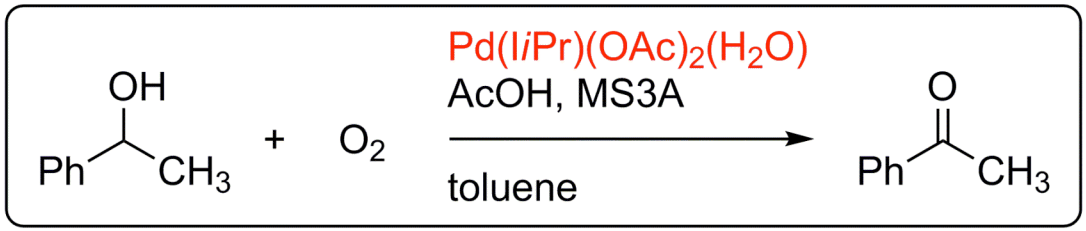
Computational modeling suggests that the Pd-alkoxide intermediate has two amine ligands with pyridine but only one amine ligand with Et_3N

TS of β-hydride elimination with one bound Et_3N:

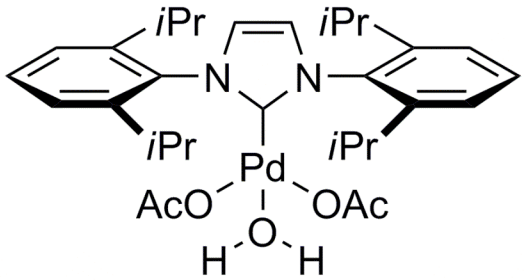


TS(2)

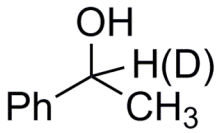
More on β-hydride elimination



Sigman et al. *JACS* **2004**, *126*, 9724-9734.

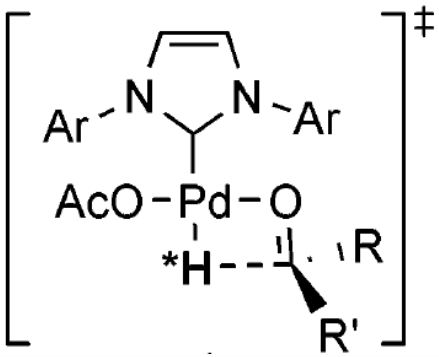


Pd(I*i*Pr)(OAc)$_2$(H$_2$O)



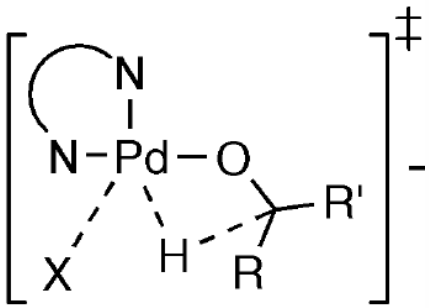
unusually large KIE of 5.5 especially compared to similar systems... what does this suggest about β-hydride elimination?

More on β-hydride elimination



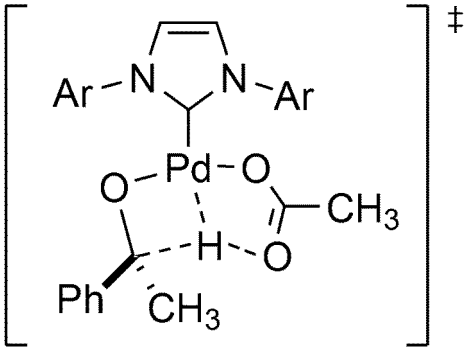
No external ligand, so no dissociation necessary

Late TS, large amount of Pd-H formation and C-H cleavage should lead to a large KIE



Bidentate ligand, associative pathway

Early TS, small amount of Pd-H formation and C-H cleavage should lead to a large KIE

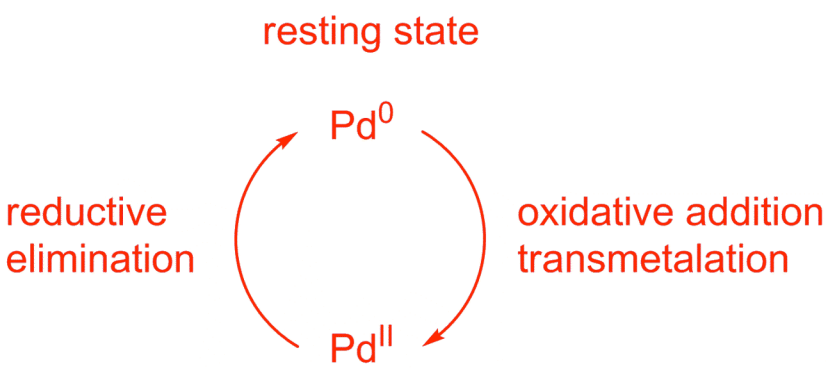


Goddard: "reductive β-hydride elimination"
Strong NHC σ-donation prevents Pd-H formation

JACS **2006**, *128*, 9651-9660.

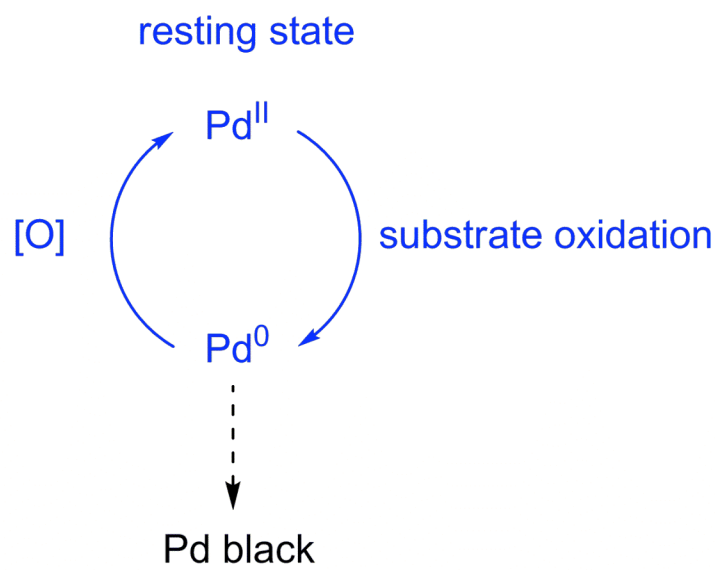
Stabilization of Pd^0

Simplified cross-coupling cycle



Phosphine ligands stabilize Pd^0

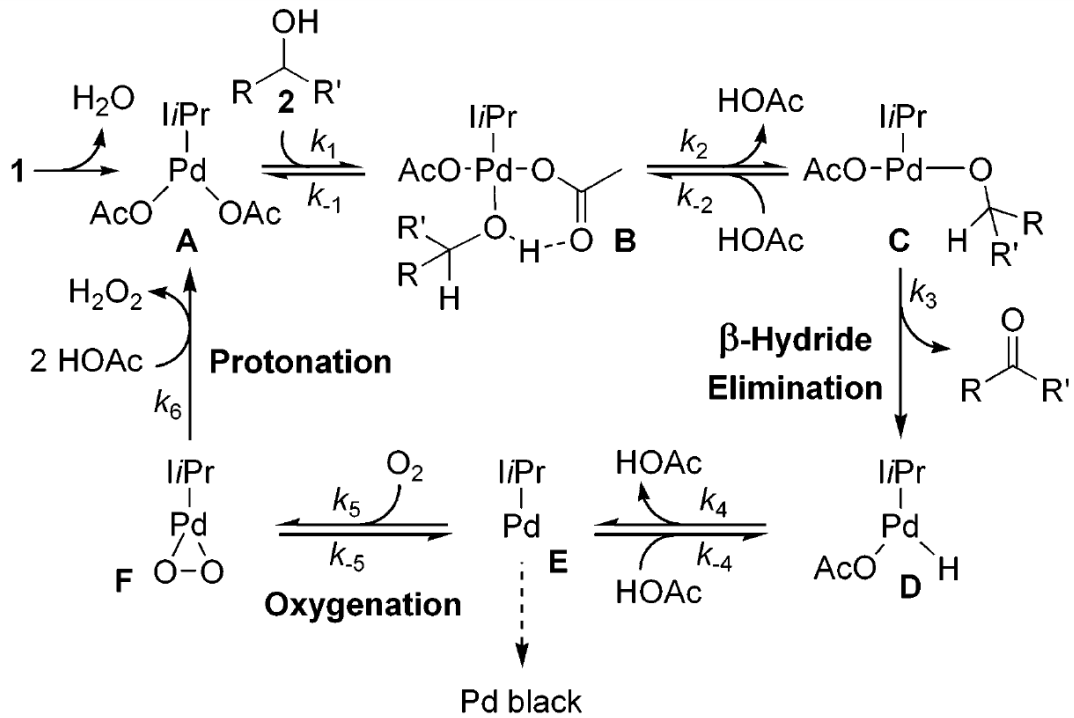
Simplified oxidation cycle



Phosphine ligands not stable under oxidizing conditions

High $[O_2]$ necessary to prevent Pd black formation

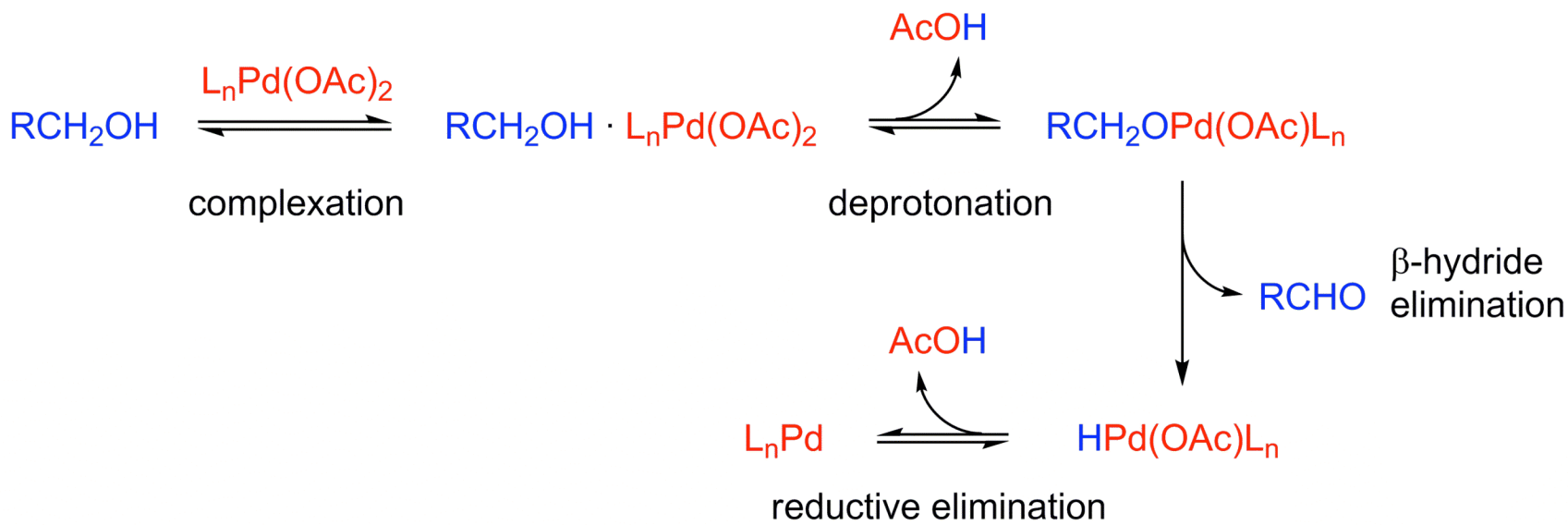
Stabilization of Pd^0



Sigman observed that a small amount (2 mol%) of AcOH can dramatically decrease the formation of Pd black

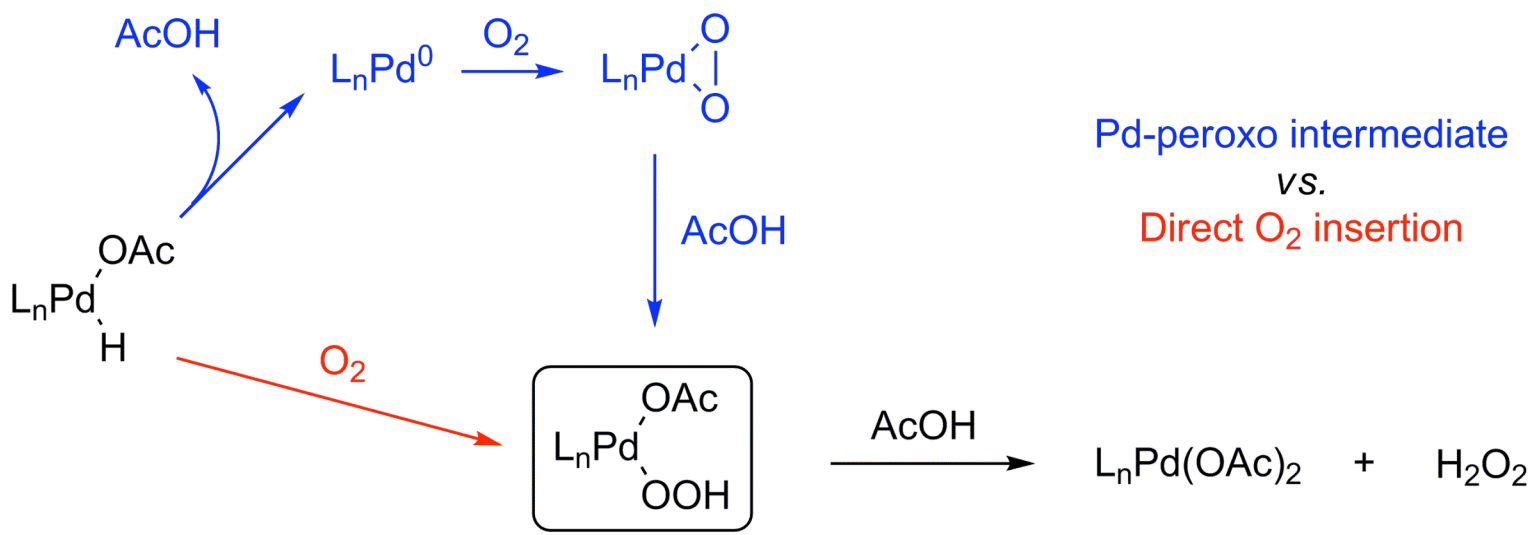
What two steps above can account for this effect?
(Which species, **A-F**, can lead to catalyst decomposition?)

Summary of mechanism for substrate oxidation



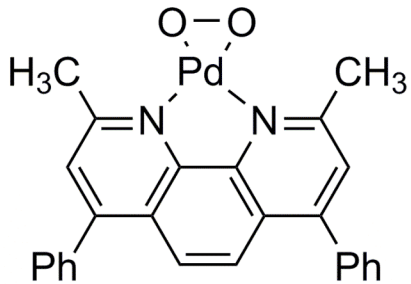
1. Geometry of alcohol-Pd adduct is not yet well established
2. Amine ligand can have significant effect on deprotonation *vs*. β-hydride elimination
3. β-hydride elimination can show large KIE, suggesting large amount of C-H cleavage in TS
4. Additives and reaction conditions have a subtle effect on Pd^0 stability

Palladium reoxidation by O_2

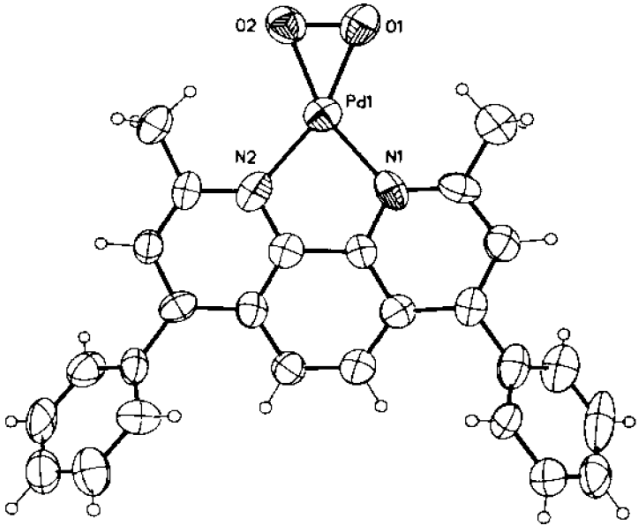


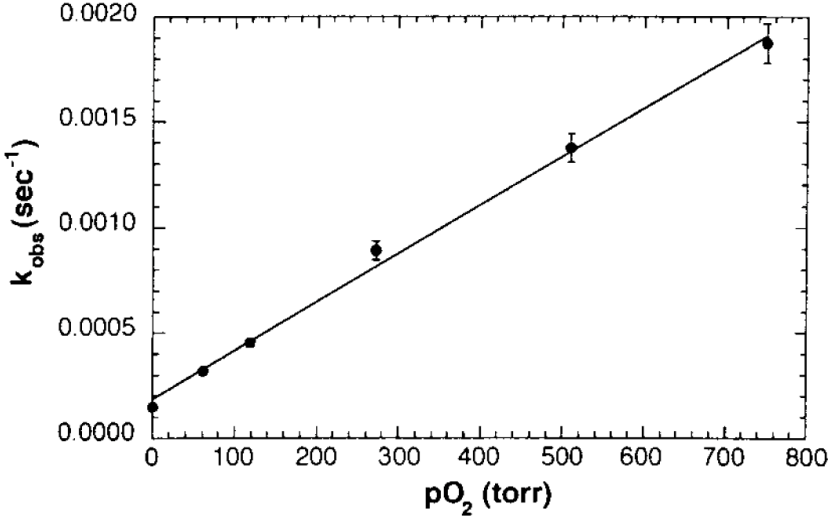
Highlight review: Sigman et al. *ACIE* **2006**, *45*, 6612-6615.

Evidence for palladium peroxo intermediate

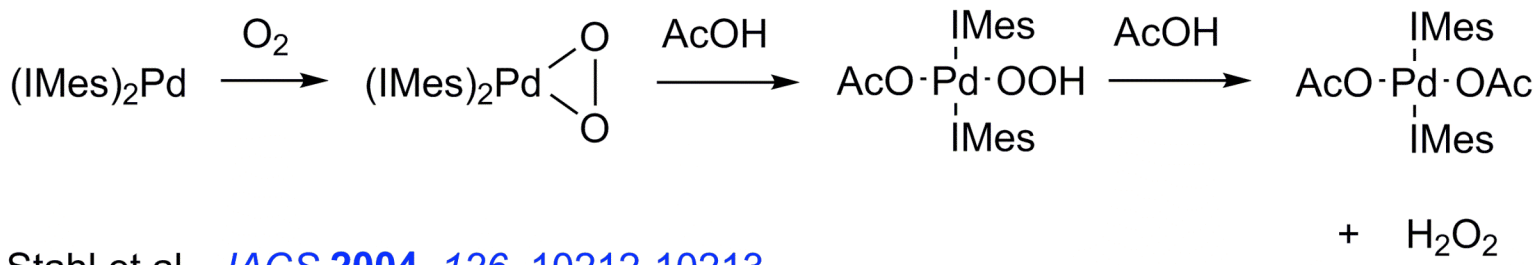


Isolated by Stahl *et al*.
JACS **2001**, *123*, 7188-7189.



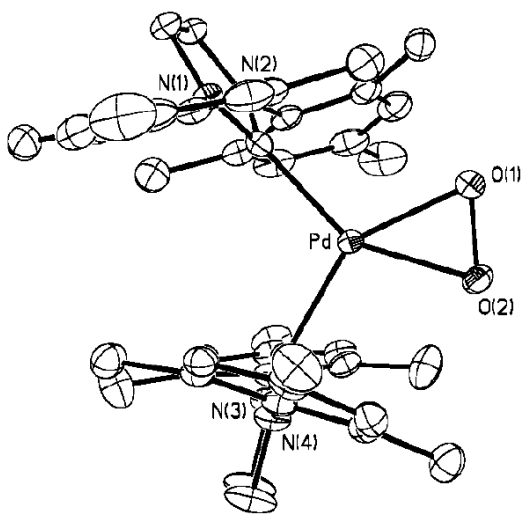


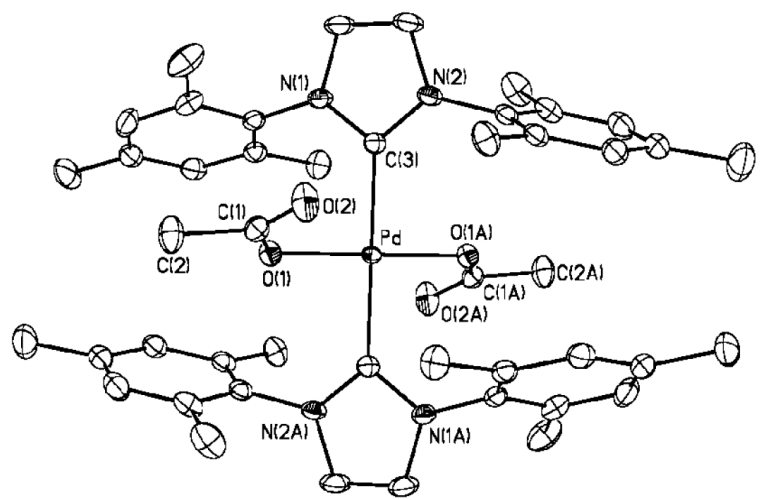
Evidence for palladium peroxo intermediate



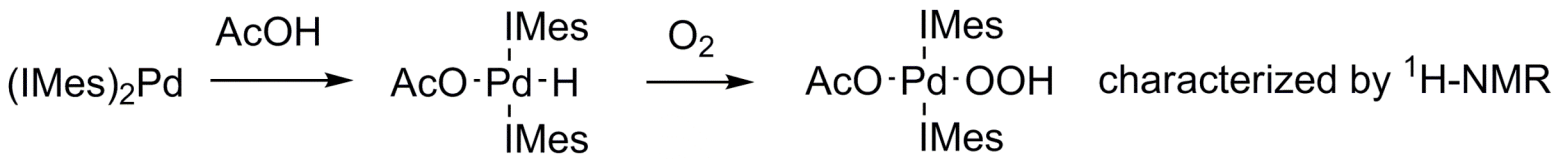
Stahl et al. *JACS* **2004**, *126*, 10212-10213.

detected by colorimetric assay

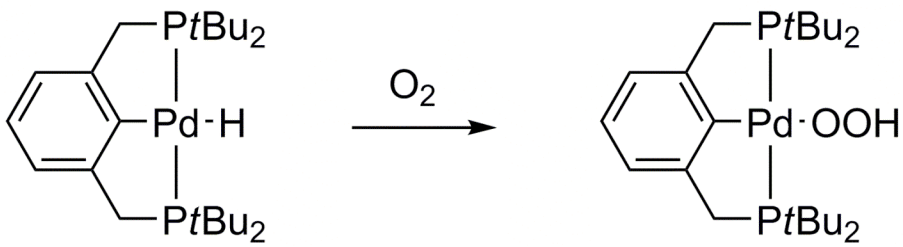


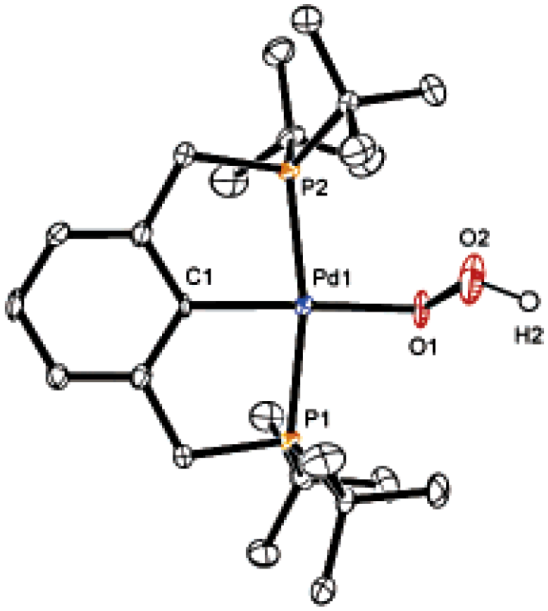


Evidence for direct O_2 insertion into Pd-H



Stahl et al. *ACIE* **2006**, *45*, 2904-2907.

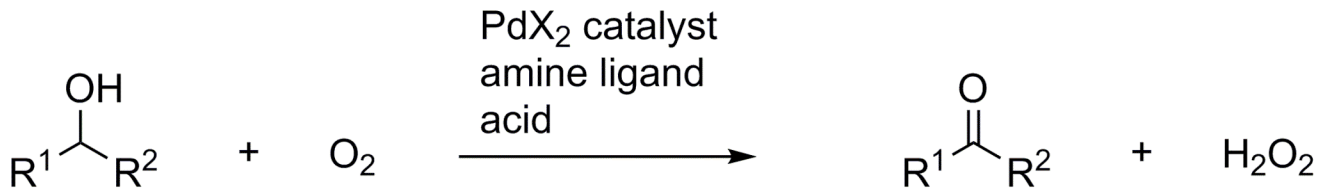




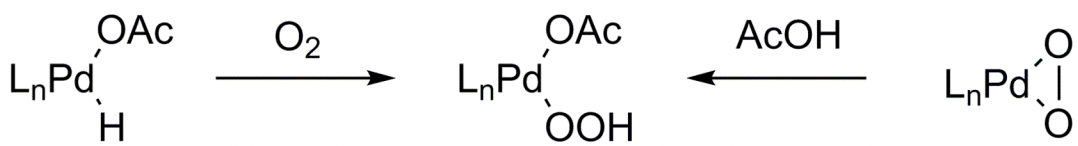
Kemp, Goldberg et al. *JACS* **2006**, *128*, 2508-2509.

Goddard has studied the O_2 insertion by computation
JACS **2005**, *127*, 13172-13179.
Inorg. Chem. **2006**, *45*, 9631-9633.

What is the current state of the field?



Relative rates of (1) deprotonation, (2) β-hydride elimination, and (3) catalyst decomposition are delicately balanced



Direct O_2 insertion to Pd-H and protonation of Pd-peroxo complex are both plausible pathways for catalyst turnover...

There is also recent work to suggest that the issue of stereochemistry in Wacker-type reactions (*syn vs. anti* oxypalladation) is not completely settled...