Palladium Catalyzed Oxidative Reactions with Molecular Oxygen as Cooxidant ~ From the Mechanistic Viewpoint ~

1 Introduction

酸化還元反応

[酸化] $Zn \longrightarrow Zn^{2+} + 2e^-$

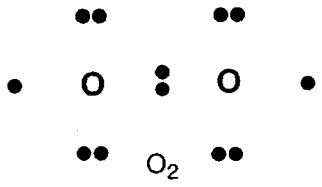
[還元] $Cu^{2+} + 2e^- \longrightarrow Cu$

electron transfer

酸化還元反応

$Cu^{2+} + Zn \longrightarrow Zn^{2+} + Cu$

表裏一体 ⟶ difficulty for the application of catalytic reaction



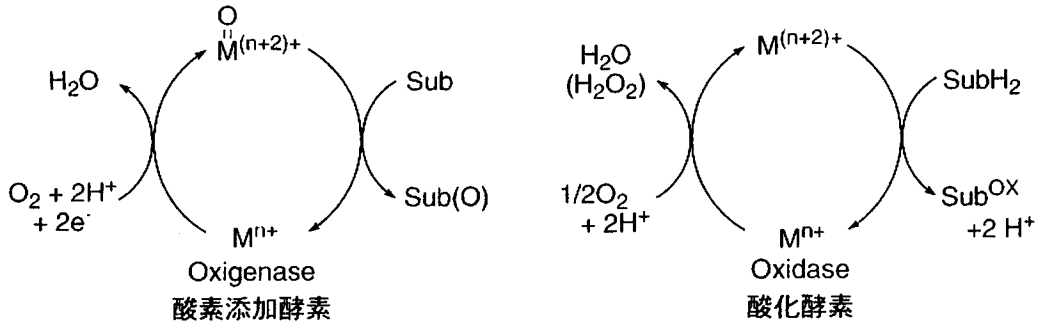
oxygen is good oxidant. (safe, cheap and abundant)

1/5 of air (volume) is O_2
about 47% of crust (weight) is O_2

¥520/1m^3(15MPa)
(鈴木商館価格)

copoduct is non-toxic. (H_2O_2 or H_2O)
thermodynamically capable to oxidize Pd^0 but always compete wiyh Pd aggregation.

Two types of aerobic oxidation



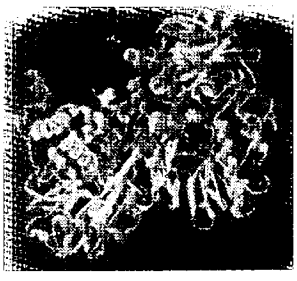
Shannon S. Stahl

Associate professor of
the University of Wisconsin-Madison

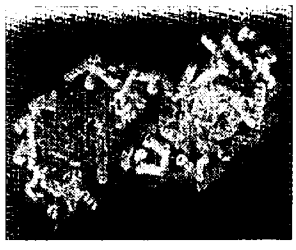
His research is focused
on metal-catalyzed reactions
for organic chemistry.

Review: *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.

bio-enzyme



cytochrome c
oxidase

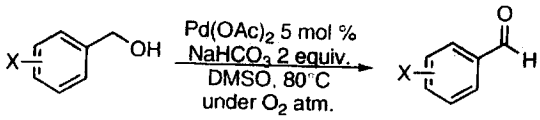


monoamine
oxidase

Contents

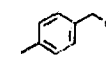
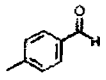
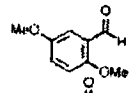
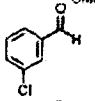
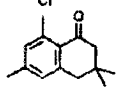
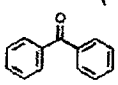
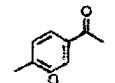
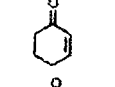
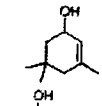
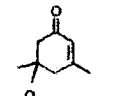
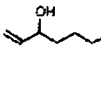
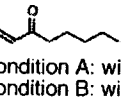
2 Oxidation of Alcohol
2.1 Early Work

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



significant breakthrough !
1 atm O_2 higher TOF but moderate yield

Table 1

entry	substrate	product	procedure	time (h)	% isolated yield
1			B	2	90
2			B	1	92
3			B	0.5	95
4			B	3	48
5			A	7	96
6			A	1	95
7			A	1	81
8			B	1	42
9			A	2	67
10			B	1	53

condition A: with base
condition B: without base

Uemura, S. et al. *J. Org. Chem.* **1999**, *64*, 6750.

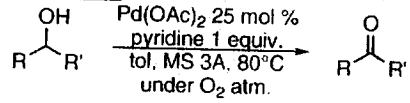
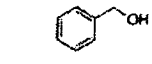
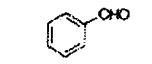
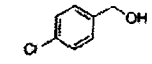
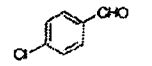
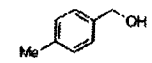
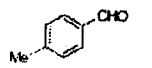
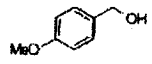
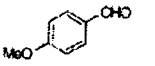
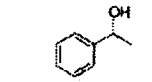
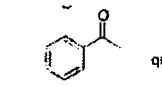
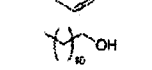
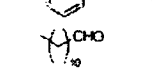
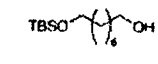
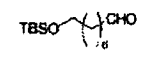
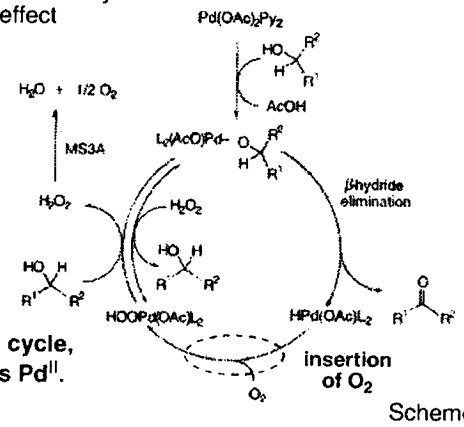


Table 2

entry	substrate	product	isolated yield(%)[b]
1			quant.[c] (100)
2			98[c] (100)
3			95 (97)
4			96 (100)
5			quant.[c] (100)
6			93 (97)
7[d]			92 (97)

exellent yiled.
EWG also OK.

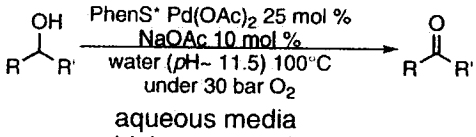
pyridine: stabilize Pd catalyst
MS 3A: positive effect



Throughout the cat cycle, palladium exists as Pd^{II}.

Scheme 1

Sheldon, R. A. et al. *Science*, **2000**, *287*, 1636.



aqueous media
high pressure (30 bar)

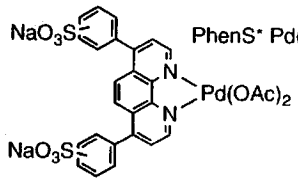
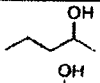


Table 3

Substrate	Product	Time (hour)	Conversion (%)	Selectivity (%)	Isolated yield (%)
		5	100	100	90
		10	90	100	85
		10	95	83*	79
		10	100	99.8‡	93

Scheme 2

Sigman, M. S. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7475.

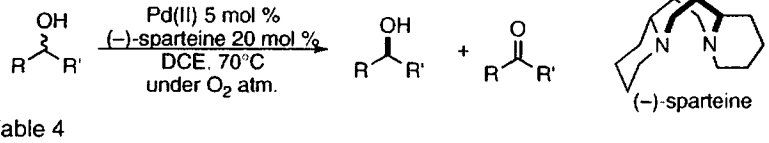


Table 4

entry		substituent R	substituent R^1	conditions[a]	% conv (% ee)[b,c]	average[d] k_{rel}
1	**1a**	C_6H_5	Me	A	65.9(98.2)	13.0
7	**1d**	*p*-MeC_6H_4	Me	A	60.8(96.6)	14.0
9	**1e**	*p*-$CF_3C_6H_4$	Me	A	59.4(83.2)	9.1
14	**1h**	*p*-FC_6H_4	Me	A	52.9(80.7)	12.2
15	**1i**	2-Naphthyl	Me	A	65.7(95.9)	10.1

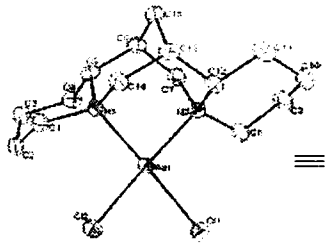
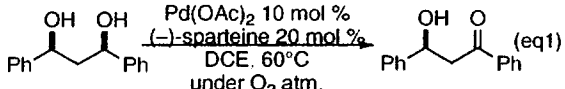


Figure 1

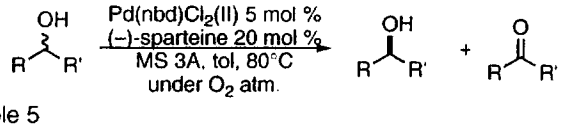
kinetic resolution
(–)-sparteine works as chiral template and amine base

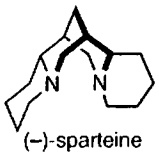


desymmetrization of 1,3-diol

82 %ee, 69% y.

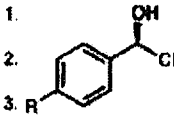
Stoltz, B. M. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7725.

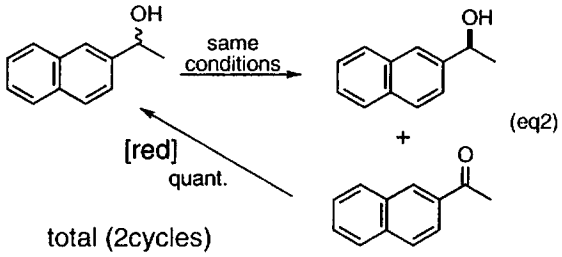




kinetic resolution
(–)-sparteine works as chiral template and amine base

Table 5

entry	unreacted alcohol, major enantiomer	time	C	isolated yield[b]	ee ROH[c]	s[d,e]
1.	 R = H	96 h	59.9%	37% (93%)	98.7%	23.1
2.	R = OMe	96 h	66.6%	32% (96%)	98.1%	12.3
3.	R = F	54 h	63.3%	32% (88%)	97.4%	14.4
4.	Ar = 1-Naphthyl	192 h	55.9%	43% (97%)	78.4%	9.8
5.	Ar = 2-Naphthyl	112 h	55.2%	44% (99%)	99.0%	47.1
6.	Ar = o-tolyl	144 h	48.4%	49% (96%)	68.7%	13.1



(eq2)

total (2cycles)

99 %ee, 68 %

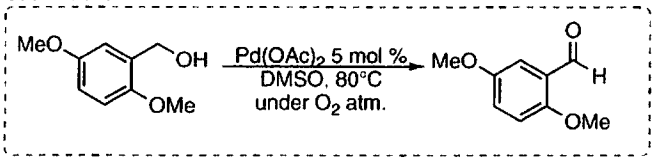
Enantiomer ((+)-sparteine) is not utilized easily.
Equivalent of (+)-sparteine did not work effectively.

2.2 Alcohol Oxidation Step

2.2.1 Mechanistic Study of Pd/DMSO System

ref. *J. Am. Chem. Soc.* **2002**, *124*, 766.

model reaction



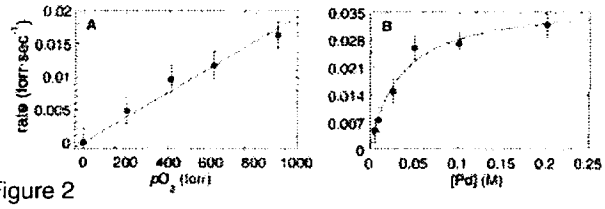


Figure 2

What is the role of the DMSO ?? involved in redox rxn ??
(DMSO can act as both oxidant and reductant)

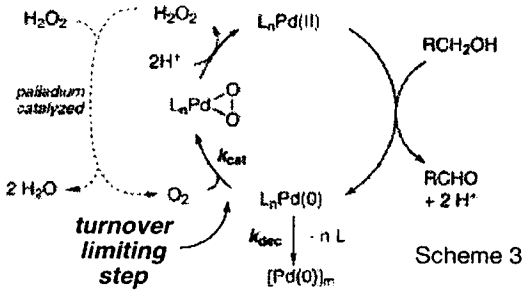
1st order dependence on pO_2. (A)
The saturation dependence on [Pd]. (B)
No dependence on [alcohol]. (no data is shown)

c.f.

$$H_2 + O_2 + Me_2SO \xrightarrow[DMSO]{RhCl_3\cdot 3H_2O} H_2O + Me_2S(O)_2 \quad \text{(eq3)}$$

$$\text{R}^{\text{OH}}_{\text{R'}} + O_2 + Me_2SO \xrightarrow[DMSO]{L_nM} \text{R}^{\text{O}}_{\text{R'}} + Me_2S(O)_2 + H_2O \quad \text{(eq4)}$$

⟶ ***DMSO had nothing to do with redox rxn.***
(Neither Me_2S nor $Me_2S(O)_2$ was detected.)



Scheme 3

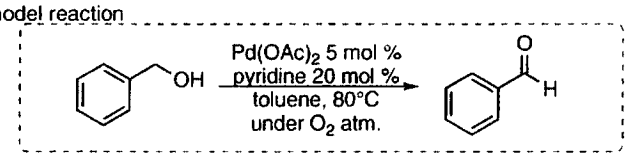
At higher [Pd], decomposition of Pd and catalyst regeneration steps were competed.

Summary
- DMSO acts as ligand and makes Pd more stable.
- Turnover limiting step is catalyst regeneration step.
- O_2 is consumed just for cat. regeneration.

2.2.2 Mechanistic Study of Pd/pyridine System

ref. *Org. Lett.* **2002**, *4*, 4179.
J. Am. Chem. Soc. **2004**, *126*, 11268.

model reaction



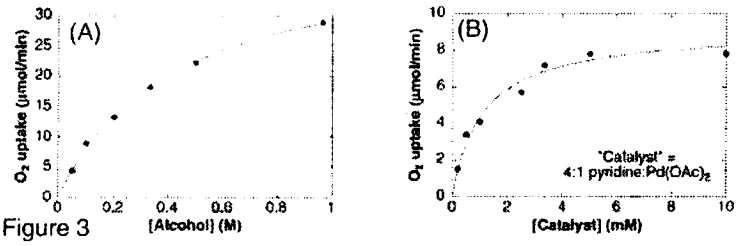
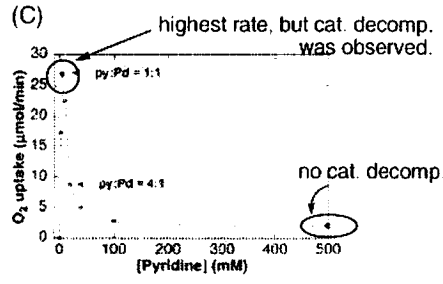


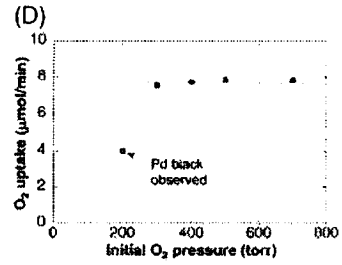
Figure 3

The saturation dependence on [alcohol] and [catalyst].



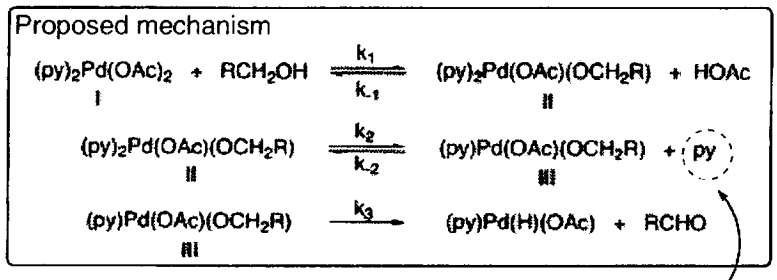
lower py amount: cat decomp.
higher py amount: slower rxn rate

⟶ ***$Pd(OAc)_2$/py= 1/4 system is best.***

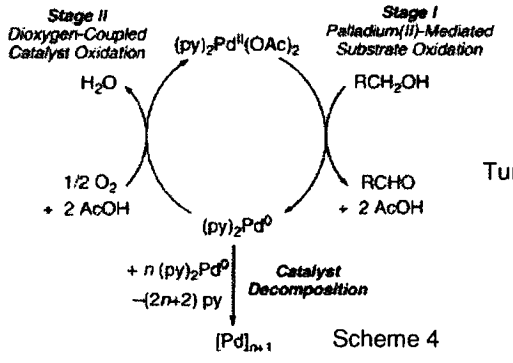


No dependence on O_2 pressure.
Under lower O_2 pressure, catalyst decomposition was observed.

Proposed mechanism



dissociation is essential ?
Using 2,2'-bipyridine, reaction proceeded slower.



Scheme 4

Turnover limiting step
$Pd(OAc)_2$/DMSO: **stage II**
$Pd(OAc)_2$/pyridine: **stage I** ⟶ especially β-hydride elimination is slow??

Addition of alcohol to cat solution (NMR study)

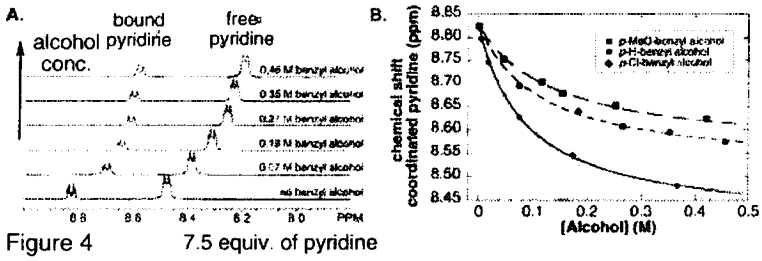
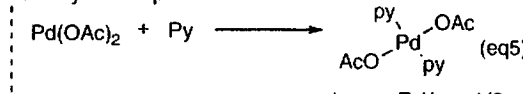


Figure 4 7.5 equiv. of pyridine

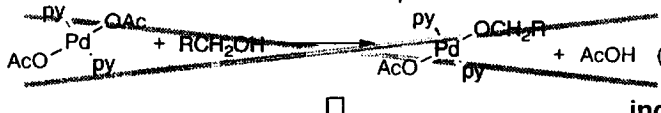
catalyst complex



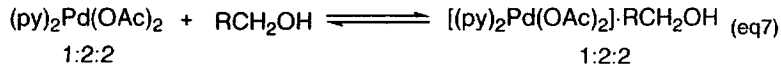
always Pd/py=1/2.

Chemical shift of both bound py and free py were changed. ⟶ free py: hydrogen bond
bound py: (1) rapid equilibrium formation of Pd alkoxide complex
(2) equilibrium coordination of the alcohol to Pd forming 5-coordinate adduct
(3) hydrogen bonding interaction between the alcohol and the acetate ligand

NMR Integration measurement:
always Pd/py/OAc= 1:2:2
even at high [alcohol]

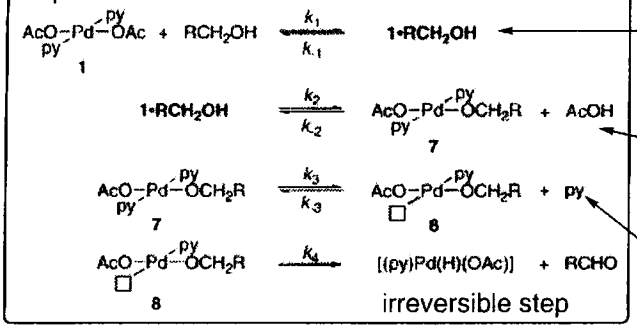


incorrect !



RCH_2OH	K_{12} (M^{-1}, 22 °C)
p-$ClC_6H_4CH_2OH$	11.5
$C_6H_5CH_2OH$	9.2
p-$MeOC_6H_4CH_2OH$	7.4

Proposed mechanism



With NMR analysis, **1** and **1**·RCH_2OH were observed.

This equilibrium might be the resting step.

Even in the presence of the excess amount of alcohol, no effect for the turnover rate, but **1**·RCH_2OH existed exclusively.

Dissociation of AcOH should be unfavourable from thermodynamic viewpoint.

(*p*Ka value:  v.s. )

Hammet plot

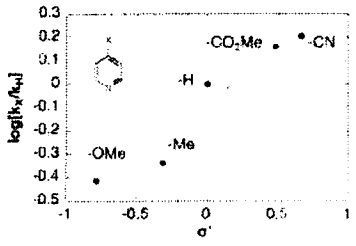
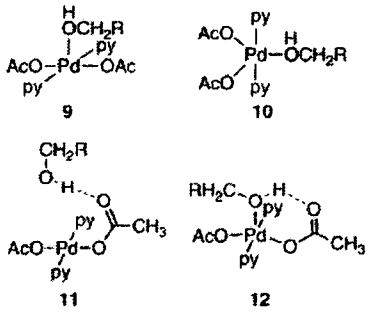


Figure 5

What is the structure of **1**·RCH_2OH complex ??



Normally five-coordinated palladium(II) complex possesses at least one strong π-acceptor ligand.

Complex **9** and **10** are exclusively σ (and π) donors.
11 is only stable intermediate

Summary

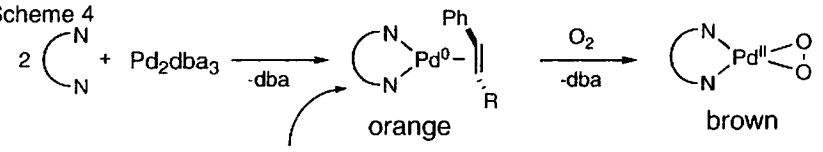
- Pyridine coordinates with Pd and makes Pd more stable.
- Excess pyridine retards the catalyst turnover due to inhibition of the pre-equilibrium of β-hydride elimination.
- Resting state of Catalyst is
  $(py)_2Pd(OAc)_2 + RCH_2OH \rightleftharpoons (py)_2Pd(OAc)_2 \cdot RCH_2OH$.
- The stage of catalyst regeneration is invisible so the mechanism is not clear yet.

2.3 Catalyst Regeneration

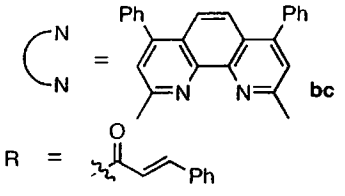
2.3.1 Coordination Manner of Pd(0) with Olefin

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

Scheme 4



two methyl groups are inequivalent



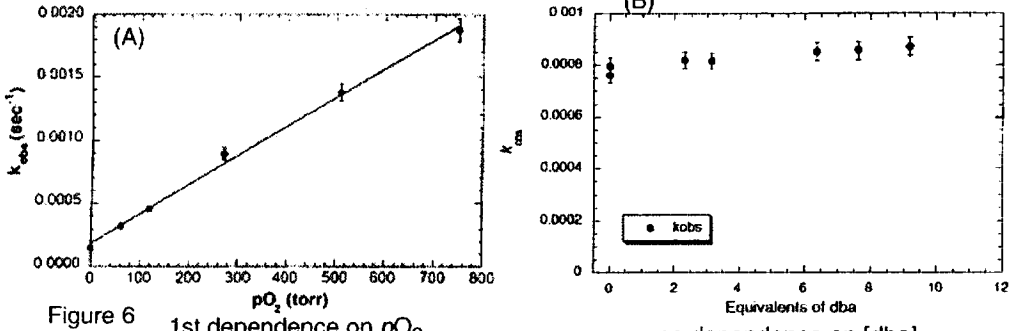


Figure 6

1st dependence on pO_2

no dependence on [dba]

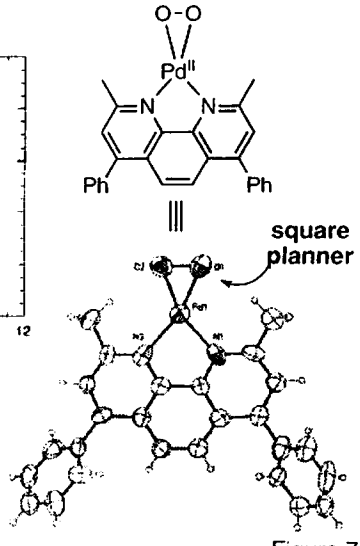
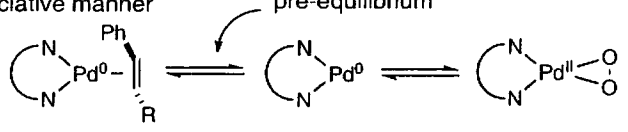


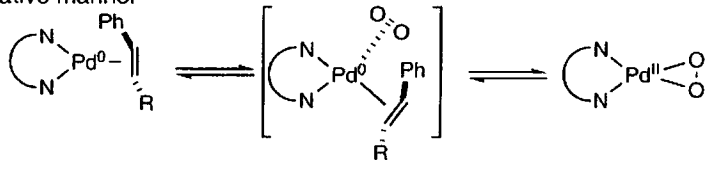
Figure 7

Ligand exchange : 2 manners

1 dissociative manner



2 associative manner



associative mechanism ??

Pd: 16-electron
excess dba: no inhibitory effect
inequivalence of two methyl group on bc of (bc)Pd(dba)

similarity with olefin exchange reaction

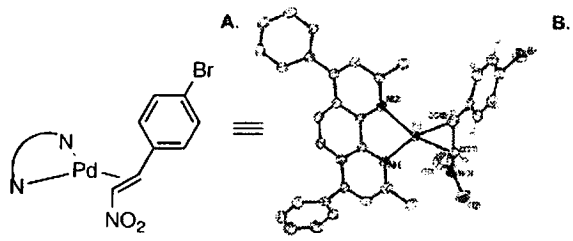
‖

simple ligand exchange ??

ref. *J. Am. Chem. Soc.* **2003**, *125*, 13.
J. Am. Chem. Soc. **2004**, *126*, 14832.

coordination manner (Pd-olefin)
using nitrostyrene derivertives.

square planner coordination manner



trigonal planner structure

Figure 8

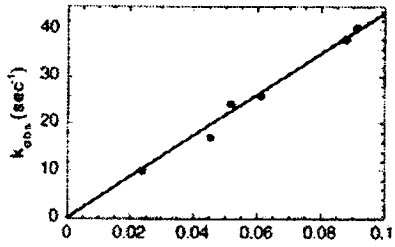
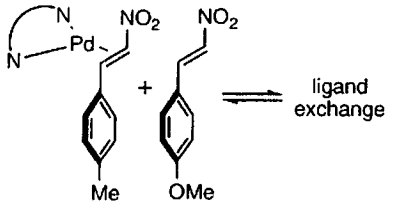


Figure 9

self exchange
· $[ns^{CF3}] = 0$: no olefin dissociation ⟶ pre-equiliburium does not exist.
· 1st order dependense on $[ns^{CF3}]$



Pseudo first order dependency

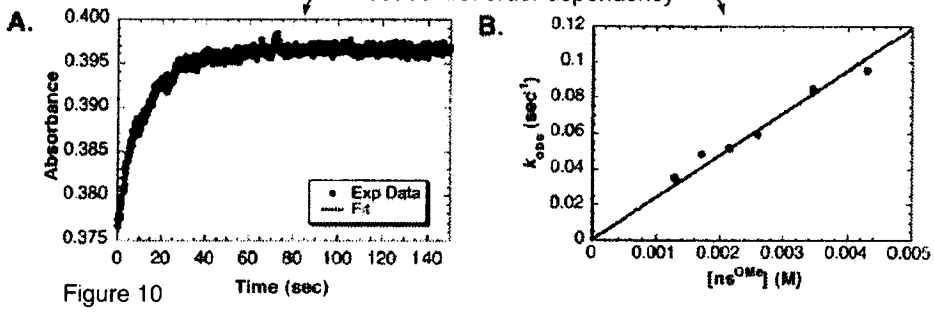


Figure 10

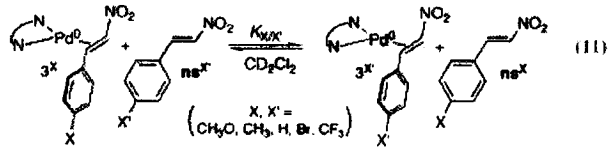


Table 6 **Equilibrium Constants and Thermodynamic Parameters for Equilibrium Olefin-Exchange Reactions (Eq 11)**[a]

entry	X	X'	$K_{X/X'}$ (−70 °C)	ΔH° (kcal/mol)	ΔS° (eu)
1	Br	CF_3	13.5	−0.9	0.7
2	H	Br	7.0	−0.7	0.7
3	CH_3	H	4.6	−0.7	−0.4
4	OCH_3	H	23.7	−1.7	−2.2
5	OCH_3	CH_3	5.56	−0.8	−0.5

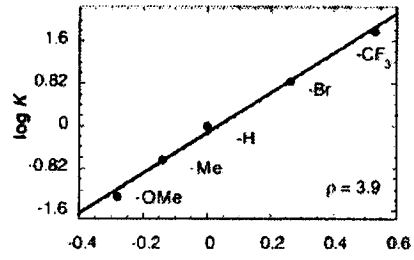
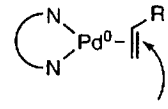


Figure 11



C-C bond length of coordinated olefin was longer than that of free olefin.

↓

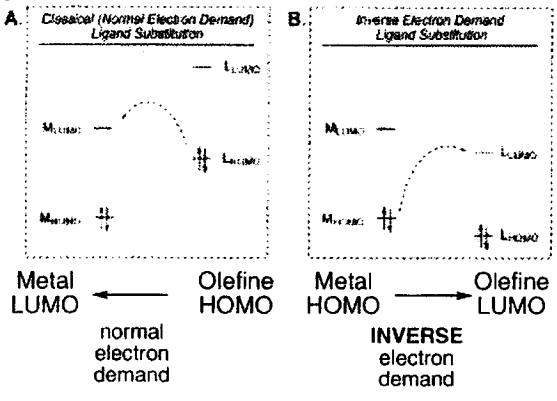
back bonding from Pd into the olefin π* orbitals??

Electron-deficient olefin coordinated with Pd^0 more strongly.

↓

Olefin have well-defined donor (filled π) and acceptor (empty π*)

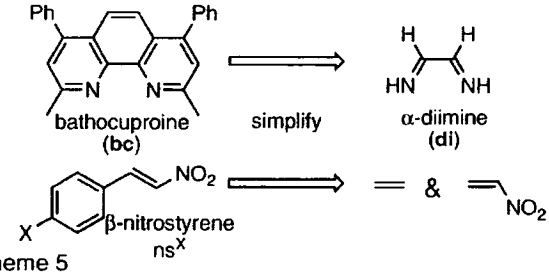
Figure 12



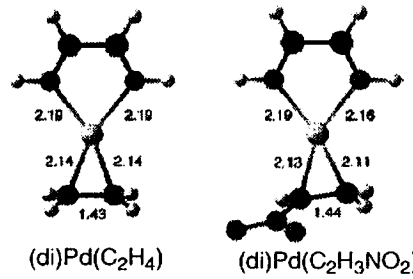
Opposite coordination manner.
" Inverse Electron Demand "

These Hammet plot implied....
HOMO of Palladium and LUMO of Olefin interacted.

Computational model study



Scheme 5



(di)Pd(C_2H_4) (di)Pd($C_2H_3NO_2$)

Figure 13

Olefin exchange occurred via 18e⁻ pseudo-octahedral TS.

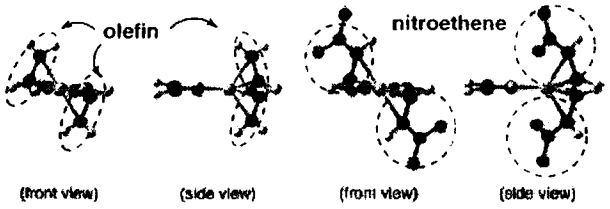


Figure 14 $4\text{-}C_2H_4$ $5\text{-}C_2H_3NO_2$

anti-parallel conformation
Nitro group locates opposite direction to minimize the molecular dipole.

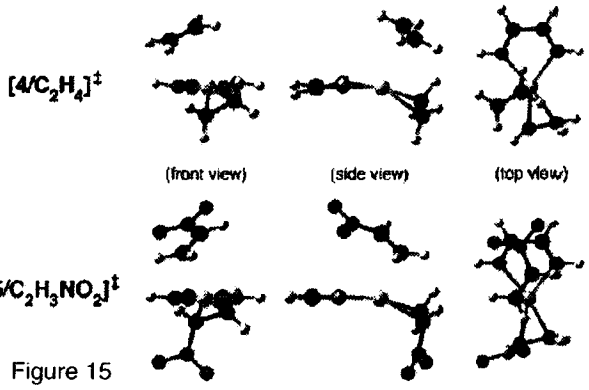


Figure 15

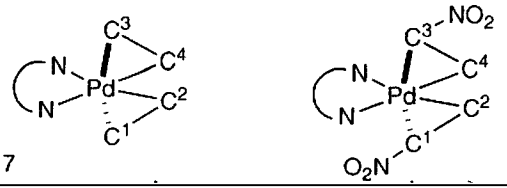


Table 7

		4	$[4/C_2H_4]^‡$	$4\text{-}C_2H_4$	5	$[5/C_2H_3NO_2]^‡$	$5\text{-}C_2H_3NO_2$
eq	Pd-C1	2.14	2.19	2.32	2.13	2.17	2.32
ax	Pd-C2	2.14	2.16	2.23	2.11	2.13	2.15
ax	Pd-C3	NA	2.91	2.32	NA	2.31	2.15
eq	Pd-C4	NA	3.08	2.23	NA	2.60	2.32

Free olefin approaches apical position of Pd center.
The angle (Pd and olefin) is around 105–110°

similar angle of
Bürgi-Dunitz trajectory

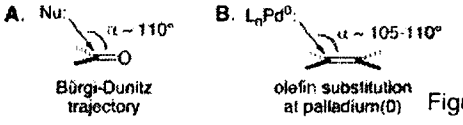


Figure 16

This suggests that nucleophilic attack of Pd toward the π* obital.

ref. *J. Am. Chem. Soc.* **2006**, *126*, 2804.

η^2-peroxopalladium complex.
can be converted to
Pd^0-olefin.
(required excess olefin)

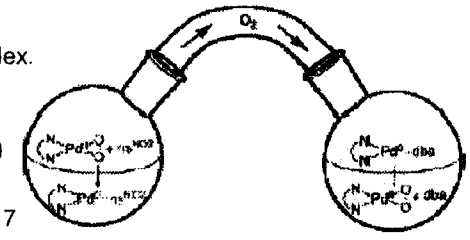


Figure 17

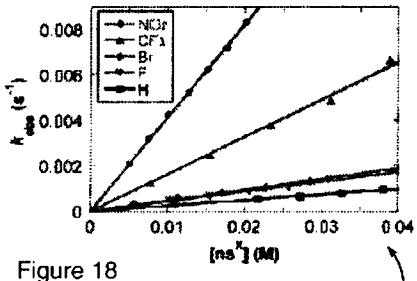
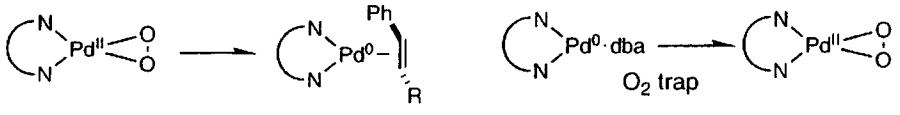


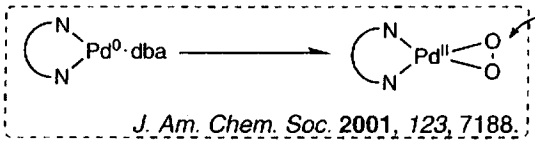
Figure 18



Electron deficient olefin exchanged more rapidly.

Summary
- (bc)Pd^0 reacts with O_2 and gives η^2-peroxopalladium complex.
- Exchange from dba to O_2 proceeds with associative manner and this step can be regareded as simple olefin exchange.
- Pd HOMO and olefin LUMO interact with "Inverse Electron Demand".
- Conversion proceeds via 18e⁻ pseudo-octahedral TS and free olefin approaches from apical direction.

2.3.2 Spin State of the Molecular Oxygen ref. *J. Am. Chem. Soc.* **2004**, *126*, 16302.



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

η^2-peroxopalladium
How does it form?
Forbidden step !!
(from the view of spin state of O_2)

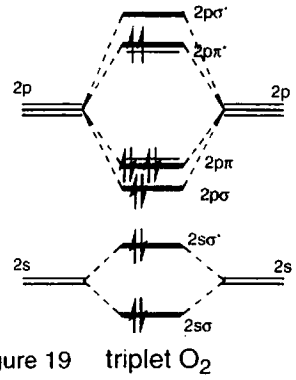
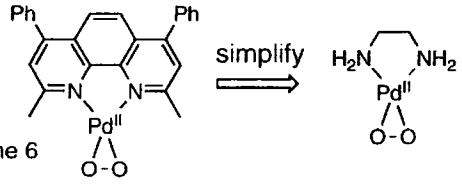


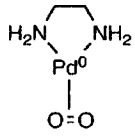
Figure 19 triplet O_2

– Question –
(1) Does O_2 approach the metal side-on or end-on?
(2) Is the two-electron transfer from palladium to O_2 stepwise or concerted?
(3) At what stage in the mechanism does spin-crossover occur?



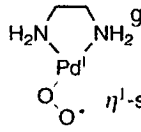
Scheme 6

(i) Pd-O distance > 5Å



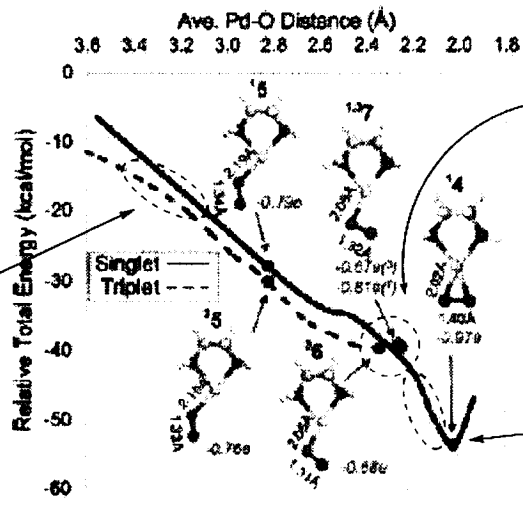
unpaired electrone of O_2 **triplet**

(ii) 2.3 Å < Pd-O distance < 4Å



gap shrinks rapidly

η^1-superoxide complex



(iii) Pd-O distance = 2.3 Å

Electron at the end of O_2 rotates into the coordination plane. Then energy levels of triplet and singlet cross over.

triplet to singlet: 0.2 kcal/mol uphill

(iv) Pd-O distance < 2.3 Å

singlet spin state

stabilize by 14 kcal/mol relative to crossover structure

Figure 20

lobe of spin dencity

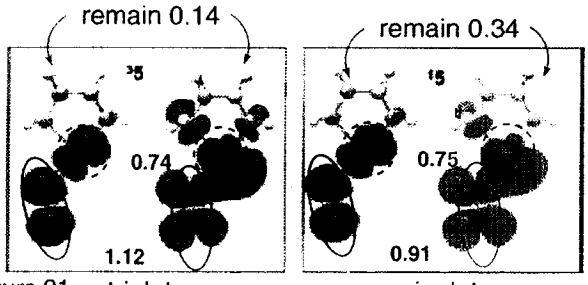


Figure 21 triplet singlet

Two electron delocalized.

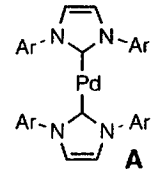
Mainly
- Pd -centered s-d combination
- π^* oribital of superoxide
- **The residue spin densities are on en ligand**

Summary
- When Pd and O_2 has enough distance, Pd coordinates with O_2 π electron.
- O_2 approaches the Pd side-on manner and forms η^1-superoxide complex.
- unpair electron delocalized included en ligand and this shrinks the gap between singlet and triplet state energy.

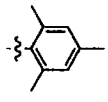
2.3.3 Generation of Hydroperoxide

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

They tried to synthesize monodentate ligand coordinated Pd complex **A**.

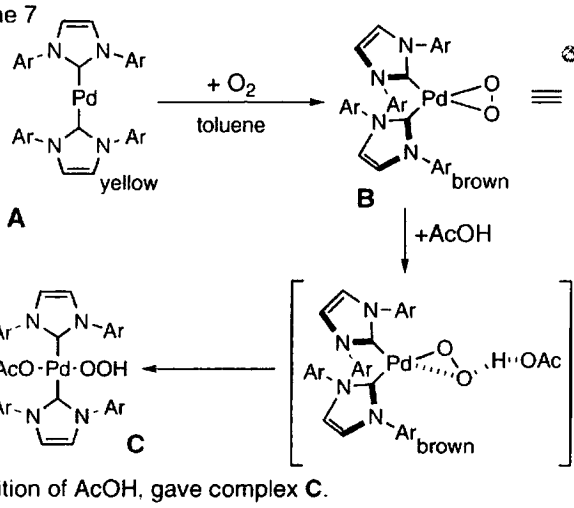


A

Ar- = 

However, their spectroscopic data differed from the date in literature.

Scheme 7



A **B** **C**

A solution of **A** in toluene at -78°C, color changed yellow to brown upon introduction of an atomosphere of oxygen.

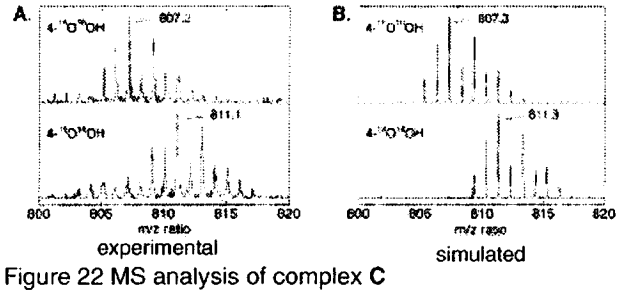
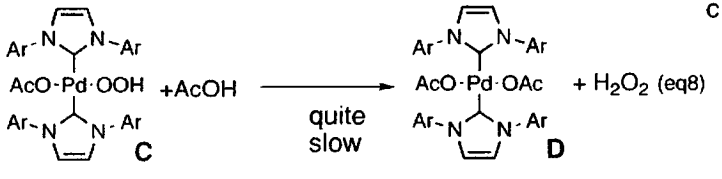


Figure 22 MS analysis of complex **C**

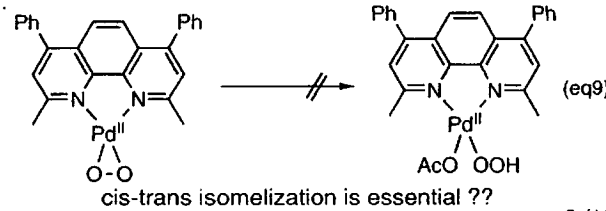
Addition of AcOH, gave complex **C**.

cis-tras isomelization of IMes ligand occurred.



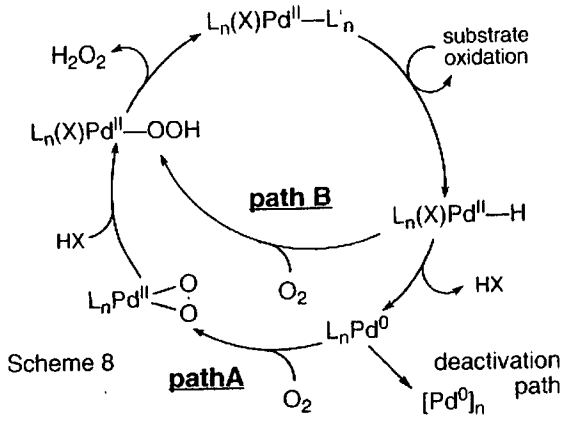
C **D**

c.f.



cis-trans isomelization is essential ??

ref. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904.



Scheme 8

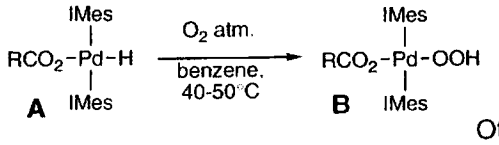
How does Pd^{II} regenerate ??

pathA reductive elimination, Pd^0 spiecies.
formation of η^2-peroxocomplex Pd^{II}-hydroperoxide
From other experiment, this spiecies can generate from Pd^0.

path B Insertion of molecular oxygen into Pd^{II}-hydride

Throughout the reaction oxidation state of Pd is +2.

They prepared the Pd^{II}-hydride complexes and it was exposed under O_2 atmosphere.



clean 1st order dependency on [Pd-H] exponential time-course of reaction → This suggested direct transformation to **B** (no Pd^0 intermediate)

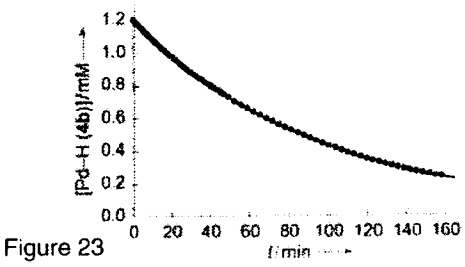
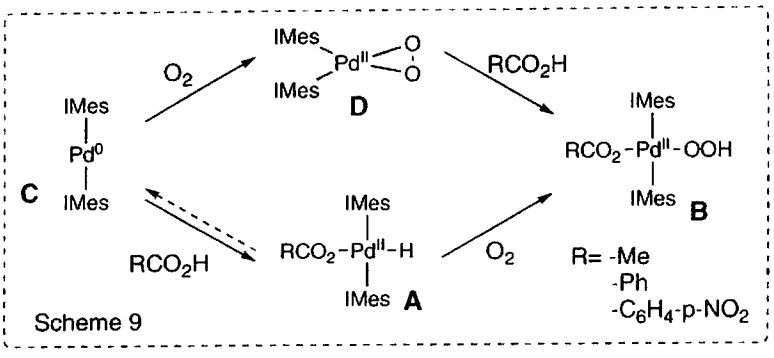


Figure 23

Other possible pathway.
- radical chain oxidation
  (Goldberg, K. I. et al. *J. Am. Chem. Soc.* **1999**, *121*, 11900. etc.)
- homolytic, non-radical chain oxidation
  (Goddard III, W. A. et al. *J. Am. Chem. Soc.* **2005**, *127*, 13172. etc.)
- direct insertion of O_2 into Pd-H bond
  (Goldberg, K. I., Kemp, R. A. et al.
  J. Am. Chem. Soc. **2006**, *128*, 2508. etc.)

Discussion **A → B** or **A → C → D → B**

- **D → B**
  cis-trans isomerization is essential ?
  sparteine, bathocuproine : impossible
  (bidentate ligand)
  → **A → B** ??
  pyridine, NHC : possible
  (monodentate ligand)



Scheme 9

- Deactivation of Pd catalyst occurred due to the aggregation of Pd^0 spiecies.
  → reductive elimination occurred and Pd^0 generated ?

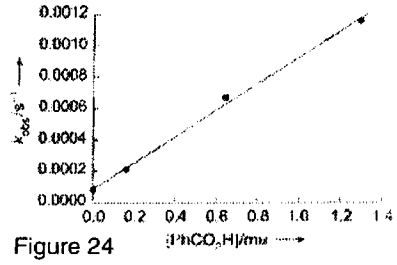
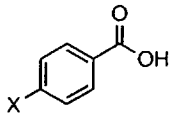


Figure 24

- More acidic RCO_2H promoted **A → B**.
  ↓
  Carboxylic acid promoted
  D → B
  &
  C → A



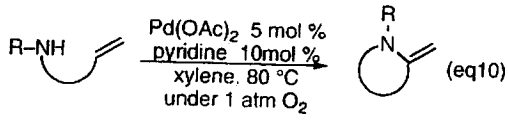
X = -H
= -NO2 → 8-fold faster

Anyway, further investigation is desired.

MEMO

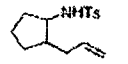
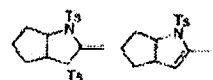
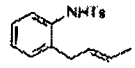
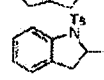
3 Oxidative Amination Reaction to Olefin

ref. *Angew. Chem., Int. Ed.* **2002**, *41*, 164.

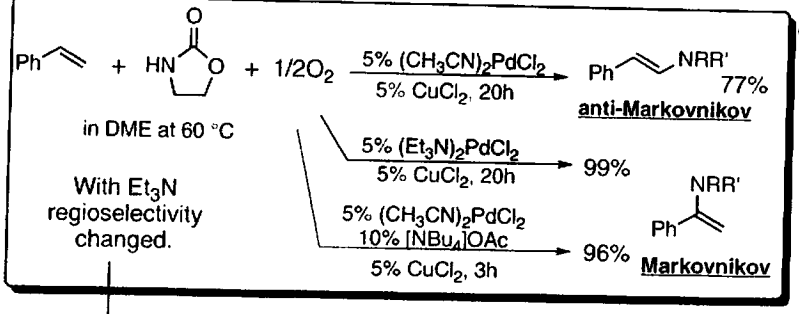


ambient O_2 pressure
no cooxidant (copper salt, BQ etc.)

Table 7

Entry	Substrate	t [h]	Product[b]	Yield[c]
1				
	R = Ts	2		87
	R = Ns	8		87
	R = Cbz	48		76
3		2		94 (1:1)
6		1.5		91

ref. *J. Am. Chem. Soc.* **2003**, *125*, 12996.



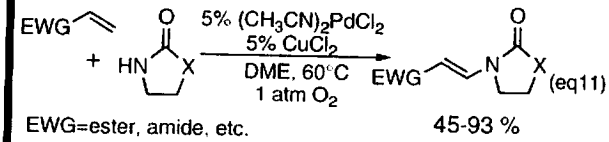
Et_3N was used as the ligand of Pd.

└→ steric effect ?? (cone angle = 158°)
However, addition of [NBu_4]OAc gave Markovnikov-type adduct

‖

Brönsted base effect ?

c.f. Hosokawa, T., Murahashi, S. -I. et al. *Tetrahedron Lett.* **1992**, *33*, 6643.



EWG=ester, amide, etc. 45-93 %

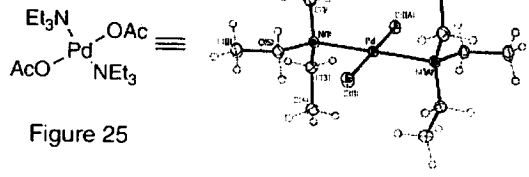
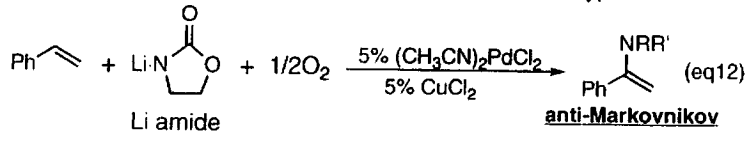
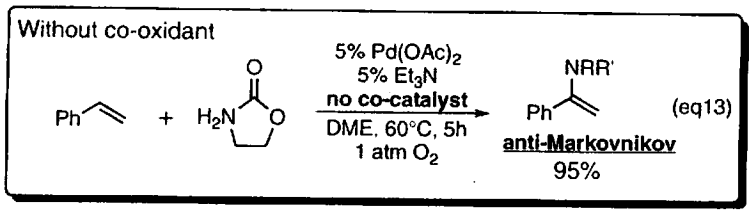


Figure 25

c.f. Li salt of oxazolidinone also gave anti-Markovnikov-type adduct.





Proposed mechanism

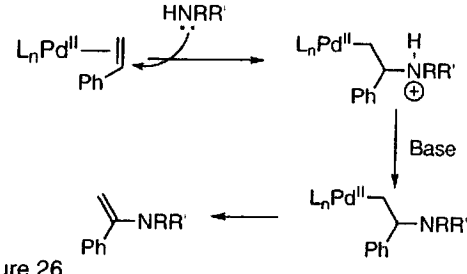


Figure 26

(N-H bond activation & insertion mechanism can be considered.)

ref. *J. Am. Chem. Soc.* **2005**, *127*, 17888.

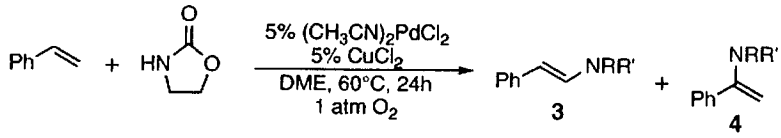
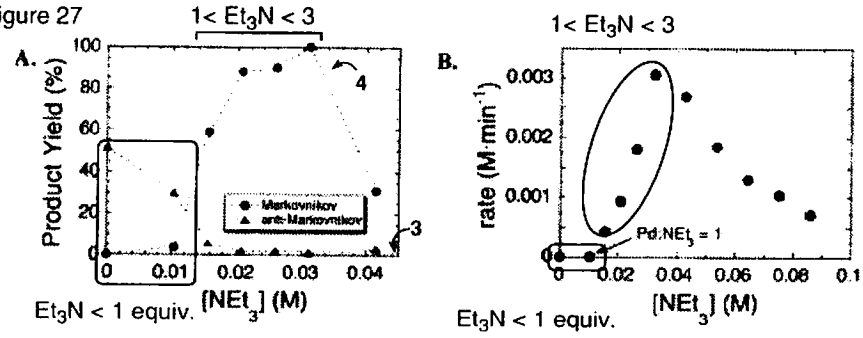


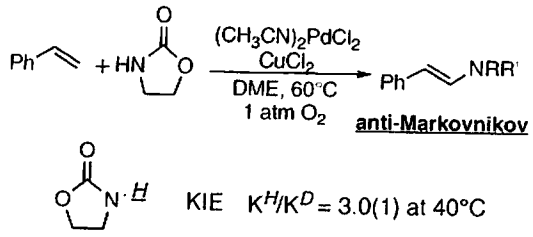
Figure 27



(i) Et_3N < 1 equiv.
yield of **4** decreased.

(ii) 1equiv.< Et_3N < 3 equiv.
yield of 5 jumped up.

No explanation was given from the view of steric effect .



KIE K^H/K^D = 3.0(1) at 40°C

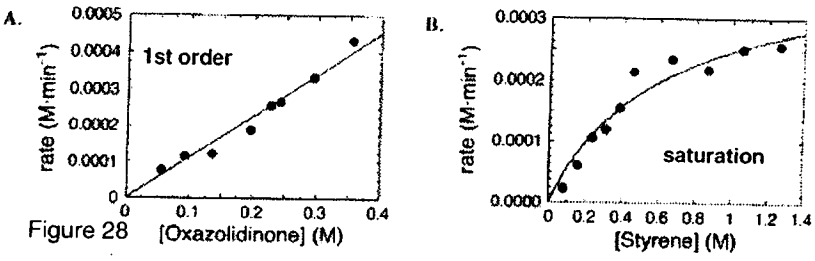
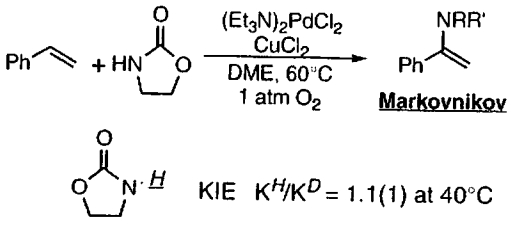


Figure 28



KIE K^H/K^D = 1.1(1) at 40°C

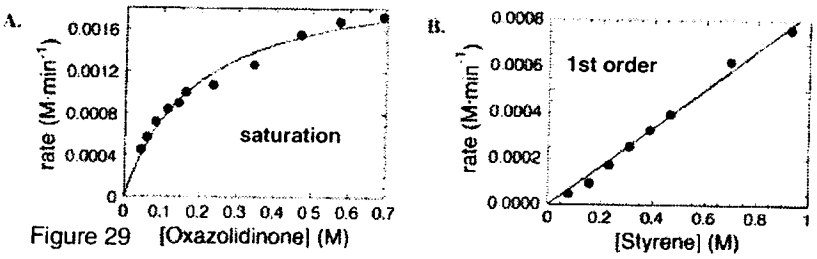


Figure 29

Scheme 10 Proposed mechanism

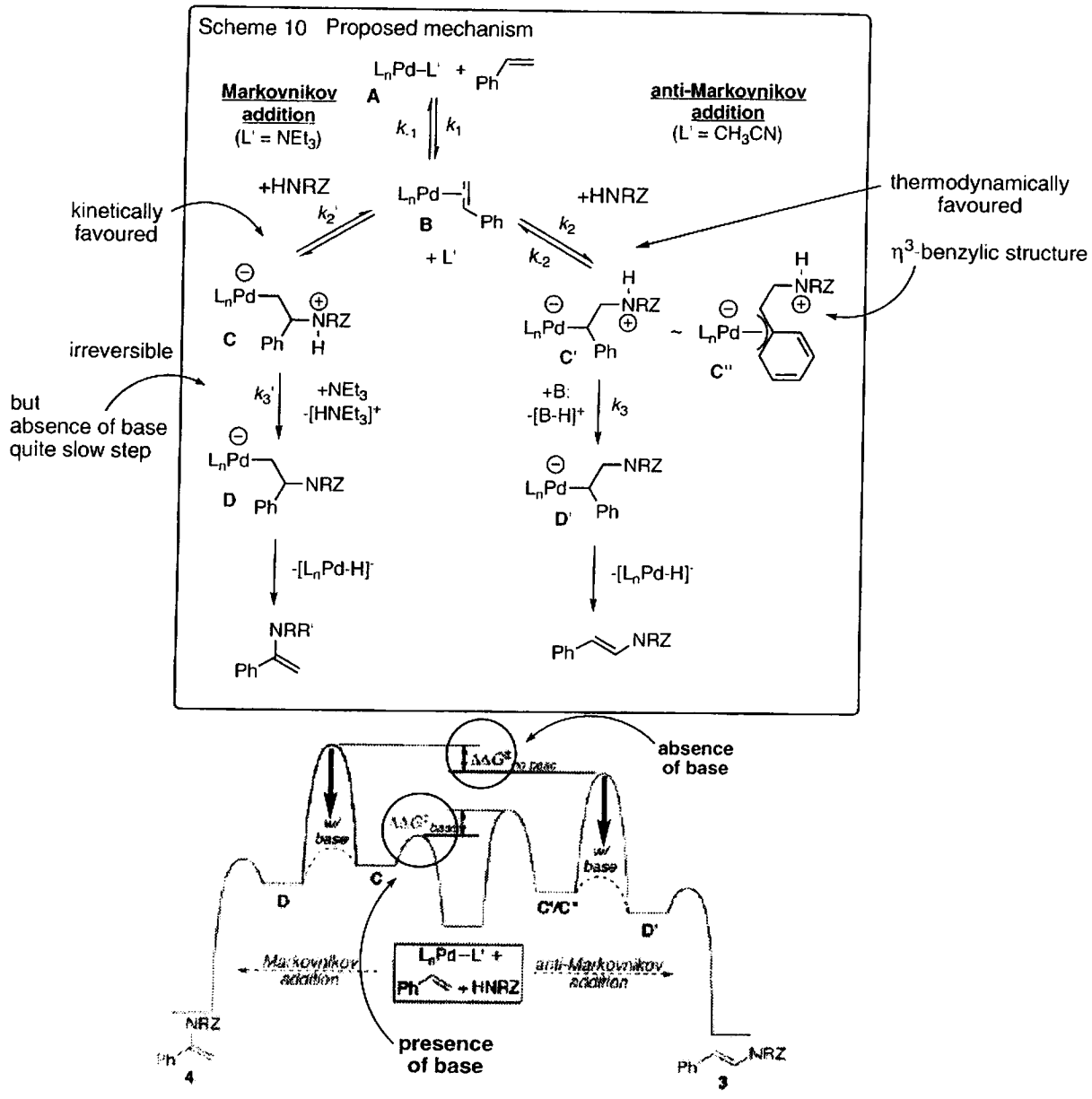


Figure 30

Summary

- In Pd^{II} catalyst system, oxidative amination reaction proceeds smoothly and the same reaction using molecular oxygen as the only cooxidant achieves.
- In the presence and absence of Brönsted base, regioselectivity changes.
- In the absence of Et_3N, aminopalladation step is the rate determining step.
- Addition of the base promotes deprotonation from zwitter ion intermediate and reaction proceeds under rather kinetic control.

4 Outlook & Remark

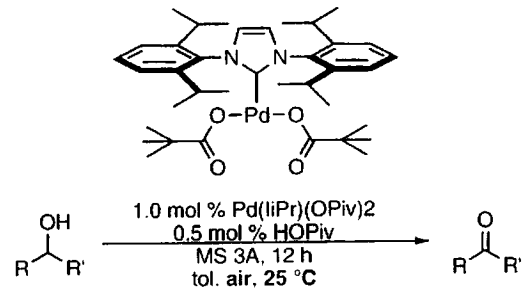
What's the supreme oxidative reaction ??

- milder temperature
- ambient O_2 pressure
- wide application range
- tolerance for other functionalities
- chemoselectivity

Other Oxidative Reaction.

Oxidative amination.

Oxidative coupling reaction etc.



Scheme 11

ref. Sigman, M. S. et al. *J. Org. Chem.* **2005**, *70*, 3343.
Sigman, M. S. et al. *Acc. Chem. Res.* **2006**, *39*, 221.