Sustainable Chemistry by Catalytic Design

AERI Seminar, July 2010

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The Weizmann Institute of Science

Major Goals of Catalysis:

Environmentally benign ("green") synthetic processes

Energy-related catalysis:

water splitting

CO_2 conversion

hydrogen from biomass

hydrogen storage

Synthesis based on inert molecules:

Hydrocarbons

N_2

CO_2

Environment, Energy, Economy

"Valley of the Drums" Louisville, Kentucky

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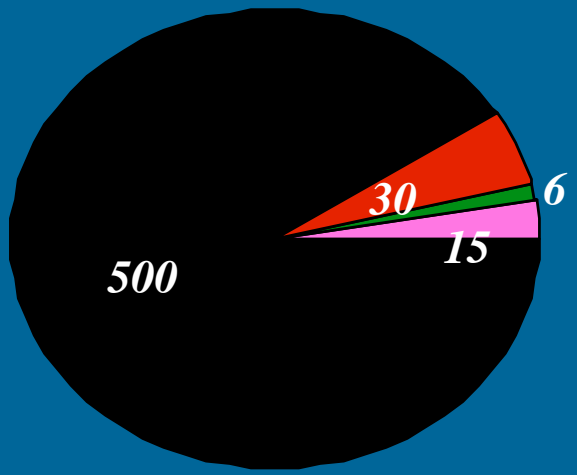
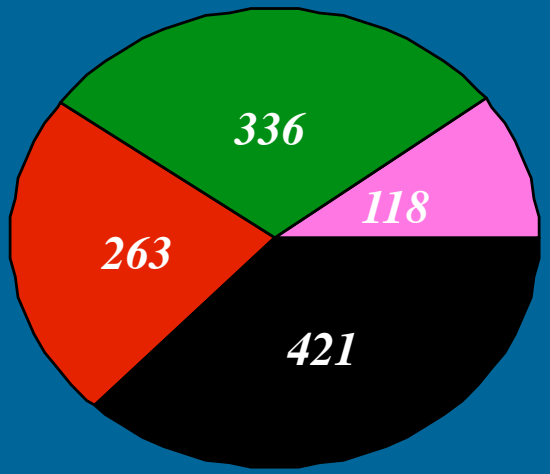
Chemicals - Facts and Figures

Annual – Worldwide (year 2000)

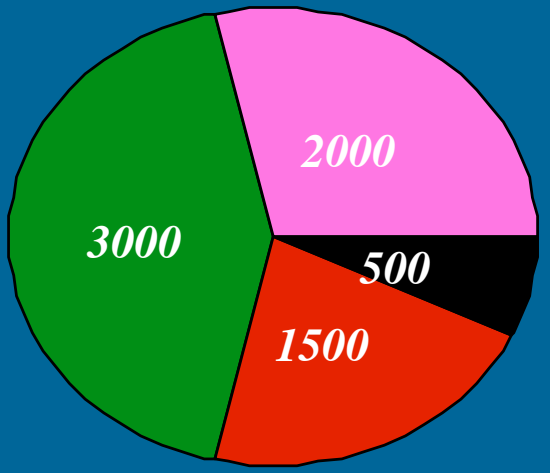
Production (Million tons)



Sales ($ Billions)



Waste (Million tons)



- Basic Chemicals
- Specialty Chemicals
- Pharmaceuticals and Agrichemicals
- Consumer Products

“Key green chemistry research areas—a perspective from pharmaceutical manufacturers”

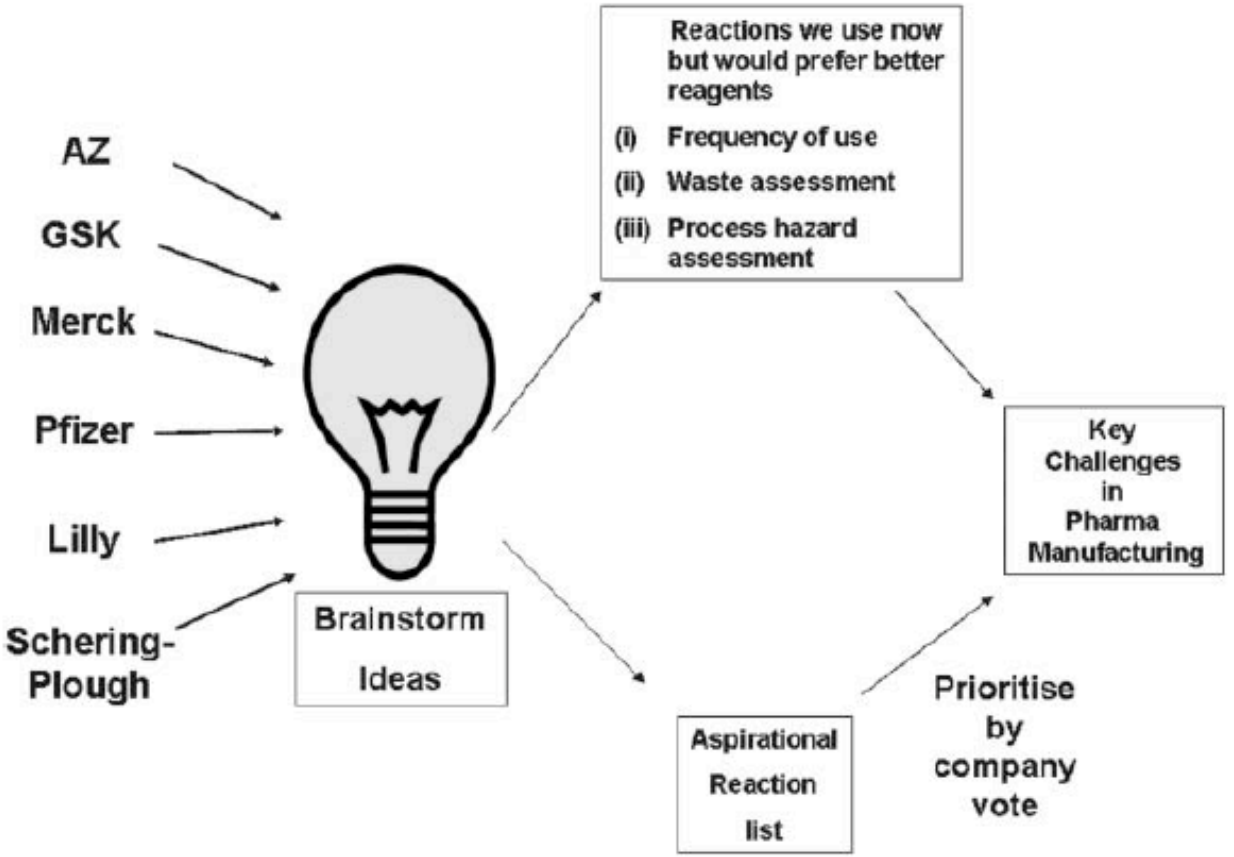


Fig. 1 The process for identifying and agreeing on the key research areas.

D. J. C. Constable, P. J. Dunn, J. D. Hayler,G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, Wells, A. Zaks, T. Y. Zhang, *Green Chem*. **2007**, 9, 411

Reactions in strong need

Reactions companies use now but would strongly prefer better reagents

Research area	Votes
Amide formation avoiding poor atom economy reagents	**6**
OH activation for nucleophilic substitution	**5**
Reduction of amides without hydride reagents	**4**
Oxidation/Epoxidation methods without the use of chlorinated solvents	**4**
Safer and more environmentally friendly Mitsunobu reactions	**3**
Friedel-Crafts reaction on unactivated systems	**2**
Nitrations	**2**

D. J. C. Constable, P. J. Dunn, J. D. Hayler,G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, Wells, A. Zaks, T. Y. Zhang, *Green Chem*. **2007**, 9, 411

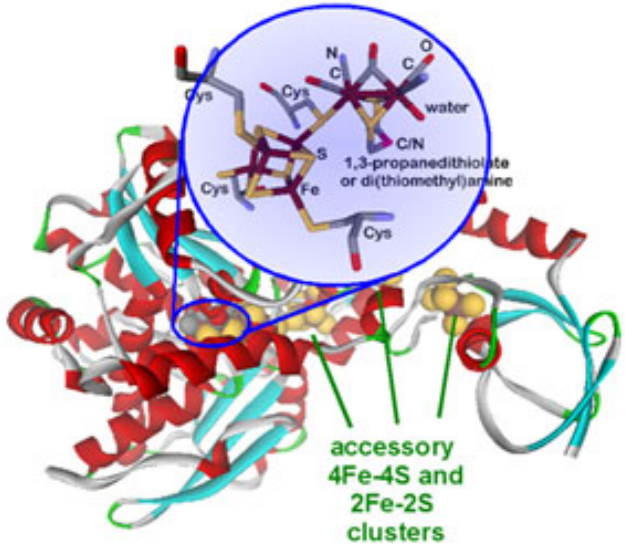
Catalytic design is essential

Needed: New modes of bond breaking and making

Approach: Metal-ligand cooperation

Metal-Ligand Cooperation: Hydrogenase

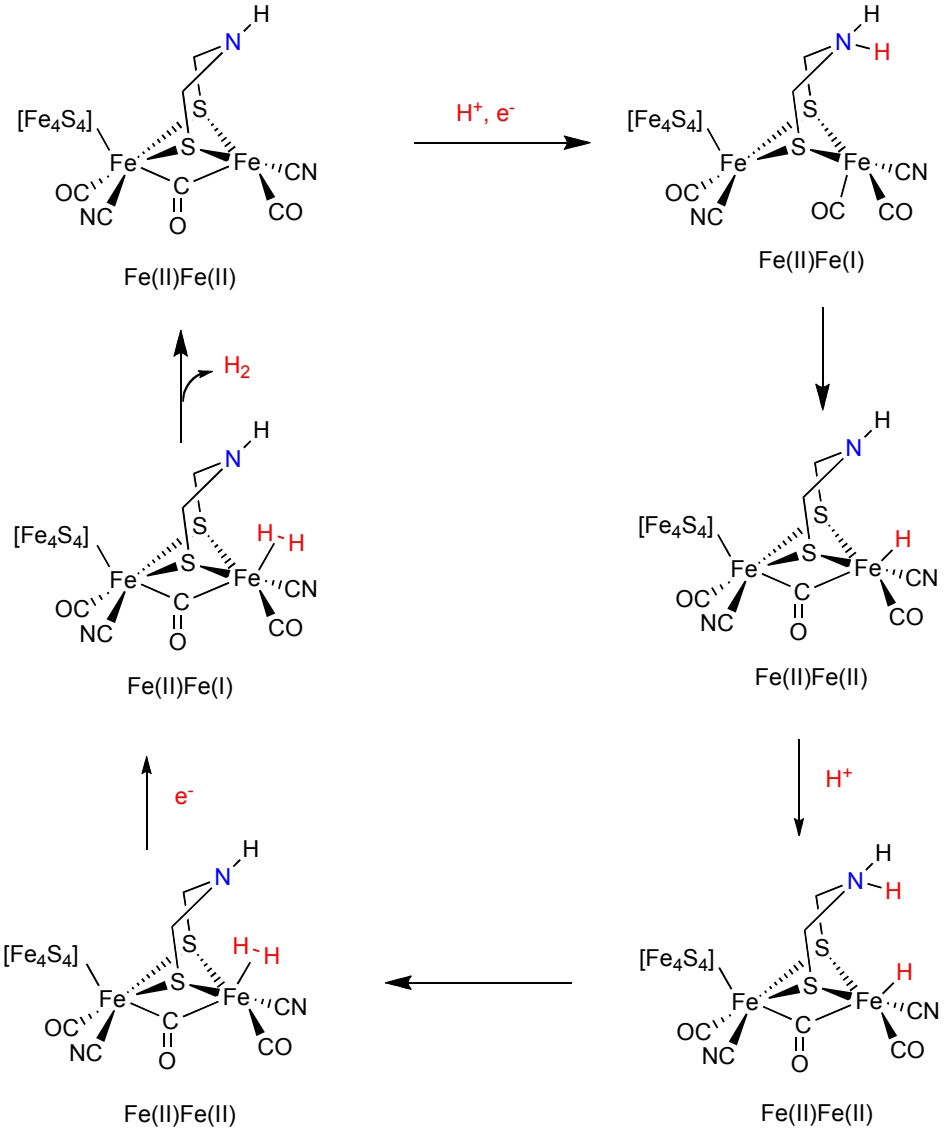
$H_2 \rightleftharpoons 2H^+ + 2e$



FeFe-hydrogenase
from Chlostridium pasteurianum

Structure:
Peters, J. W. et al. *Science* **1998**, 282, 185
Nicolet, Y. et al. *Struct. Fold Des.* **1999**, 7, 13.

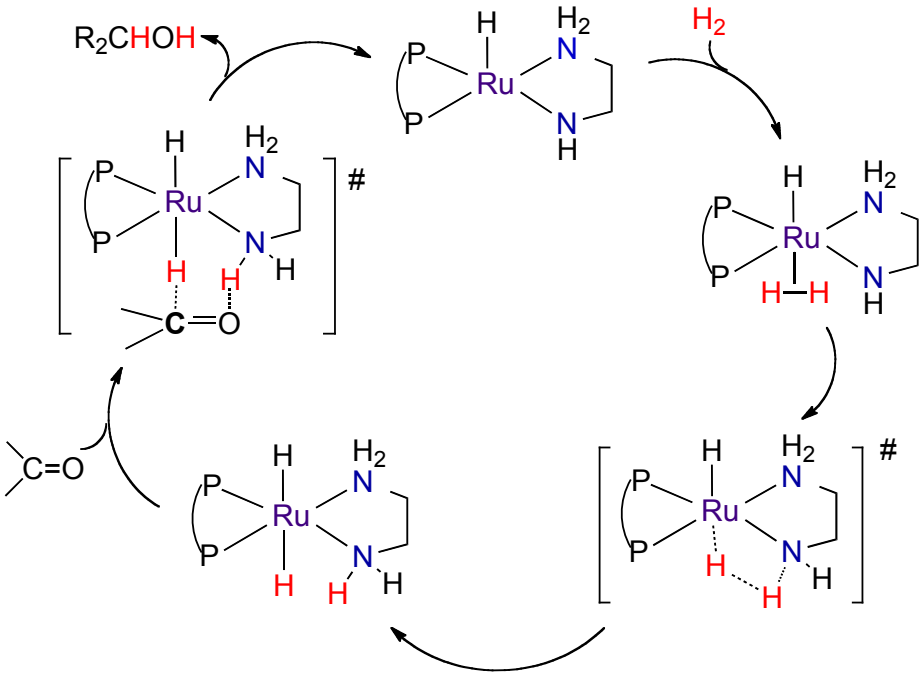
Pioneering studies on Fe-S Clusters: R. H. Holm



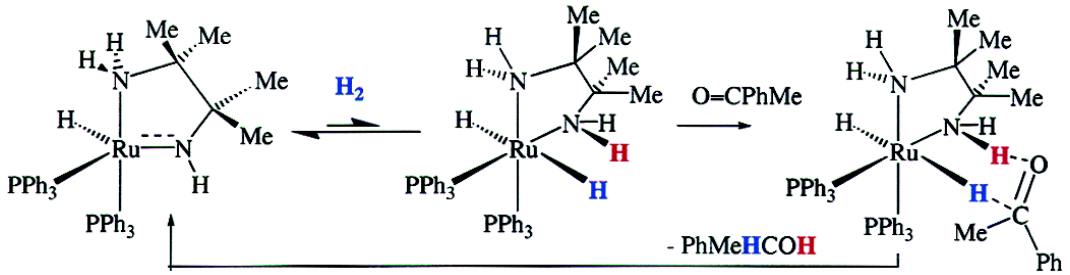
Proposed mechanism (DFT): Liu, Z-P. et al, *JACS* **2002**, 124, 5175; M. B. Hall et al, *JACS* **2001,** 123, 3828; L. de Gioia et al, *Inorg. Chem.* **2007**, 46, 5911

Metal-Ligand Cooperation: Hydrogenation of Polar Bonds

Noyori's catalysts

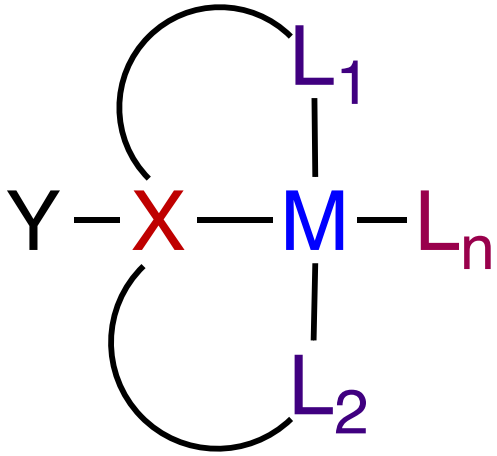


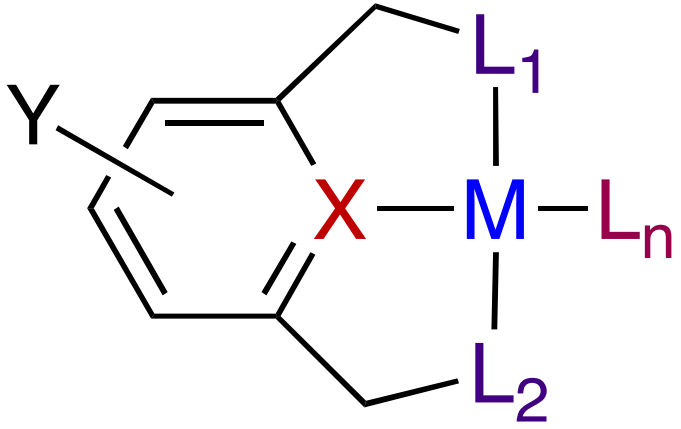
Review: R. Noyori and T. Ohkuma *Angew. Chem. Int. Ed.* **2001**, *40*, 40.



R. H. Morris *et al*, *JACS* **2002**, *124*, 15104 (scheme copied from this reference): *Turnover-limiting step: heterolytic H_2 splitting*

"Pincer" Complexes



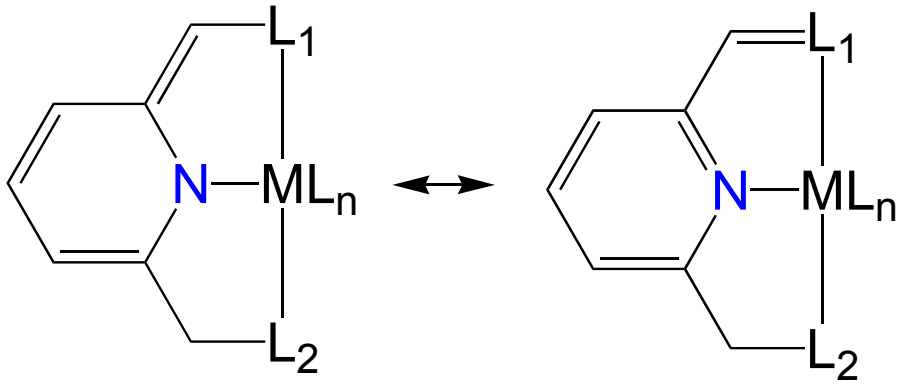


Bond activation
Mechanisms
Catalysis
Unusual complexes

Reviews:

D. Milstein, *Topics in Catalysis*, **2010**, *53*, 915
K. J. Szabo, *Synlett* **2006**, *6*, 811
M.E. Van der Boom and D. Milstein, *Chem. Rev*. **2003**, *103*, 1759
J. T. Singleton, *Tetrahedron*, **2003**, *59*, 1837
A. Vigalok and D. Milstein, *Accts. Chem. Res*. **2001**, *34*, 798
M. Albrecht and G. Van Koten, *Angew Chem. Int. Ed*. **2001**, *40*, 3750
B. Rybtchinski and D. Milstein, *Angew Chem. Int. Ed*. **1999**, *38*, 870
C.M. Jensen, *Chem. Comm*. **1999**, 2443

New Mode of Bond Activation: Metal-Ligand Cooperation by Pincer Complexes

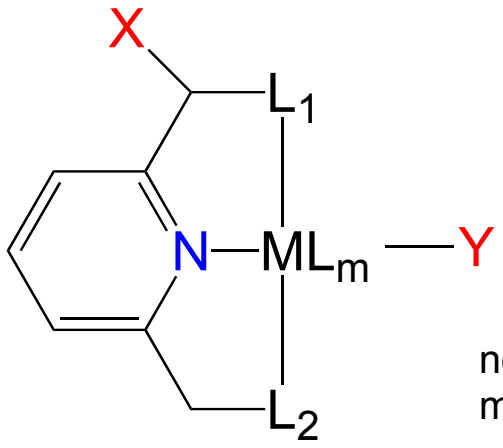


X-Y

aromatization

Low pyridine *trans* effect and influence
Acidity of benzylic H

<u>Resonance energy:</u>
Benzene: 36 kcal/mol
Pyridine: 28 kcal/mol

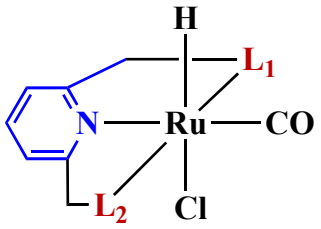


Bonds activated:
C-H, H-H, N-H, O-H

no overall change in
metal oxidation state

O-H Bonds

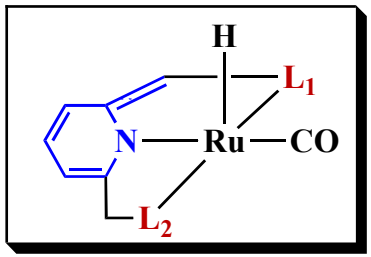
Development of a Ru Dehydrogenation Catalyst

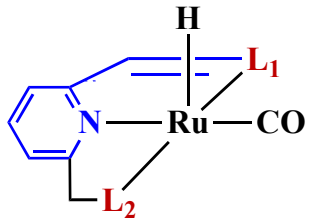


$L_1, L_2 = PPr^i_2$

$L_1 = PBu^t_2$; $L_2 = NEt_2$

$KOBu^t$



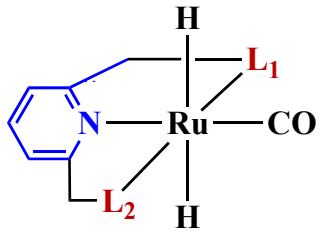


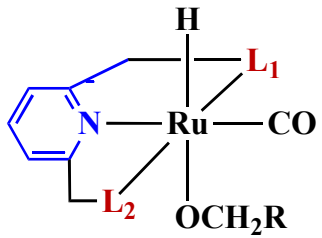
Minor Form

$-H_2$ $+H_2$

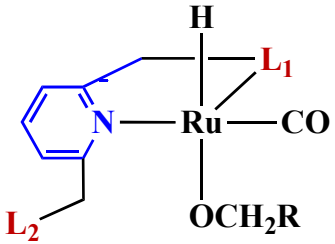
RCH_2OH

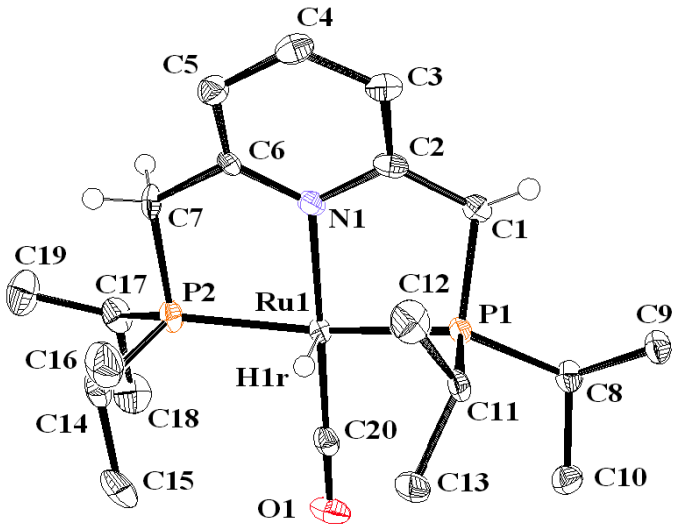
(R = Me, hexyl)





RCHO



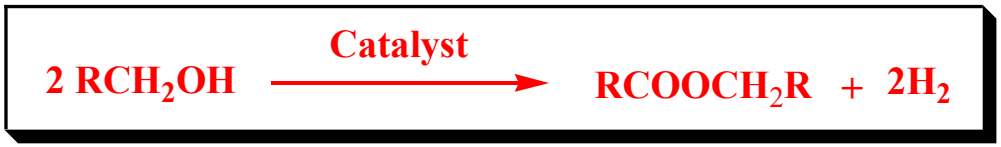


C1-C2 1.450 *C1-P1 1.803*

C7-C6 1.552 *C7-P2 1.843*

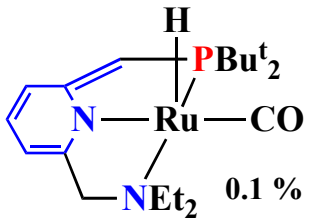
J. Zhang

Efficient alcohol dehydrogenation to esters



R = alkyl, aryl

Catalyst

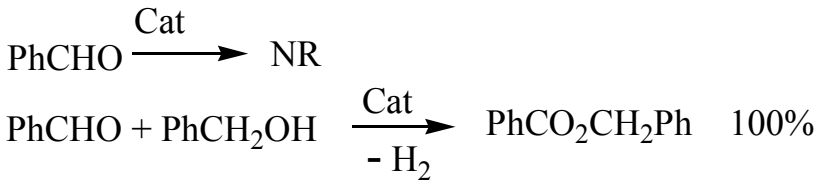


(PNP complex much less effective)

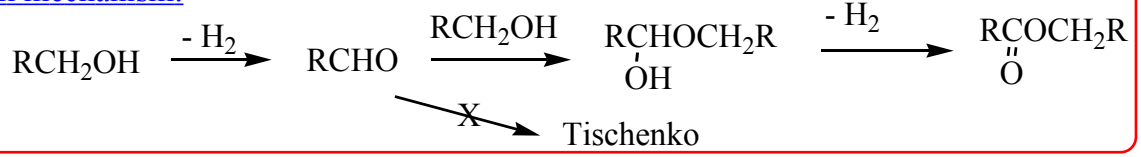
			Ester %	Aldehyde %
1- Butanol	117 °C	5 hrs	90	0.5
1- Hexanol	115 °C	6 hrs	99	0
Benzyl alcohol	115 °C	4 hrs	92	1

Neutral coditions
No waste
High efficiency

Observations:



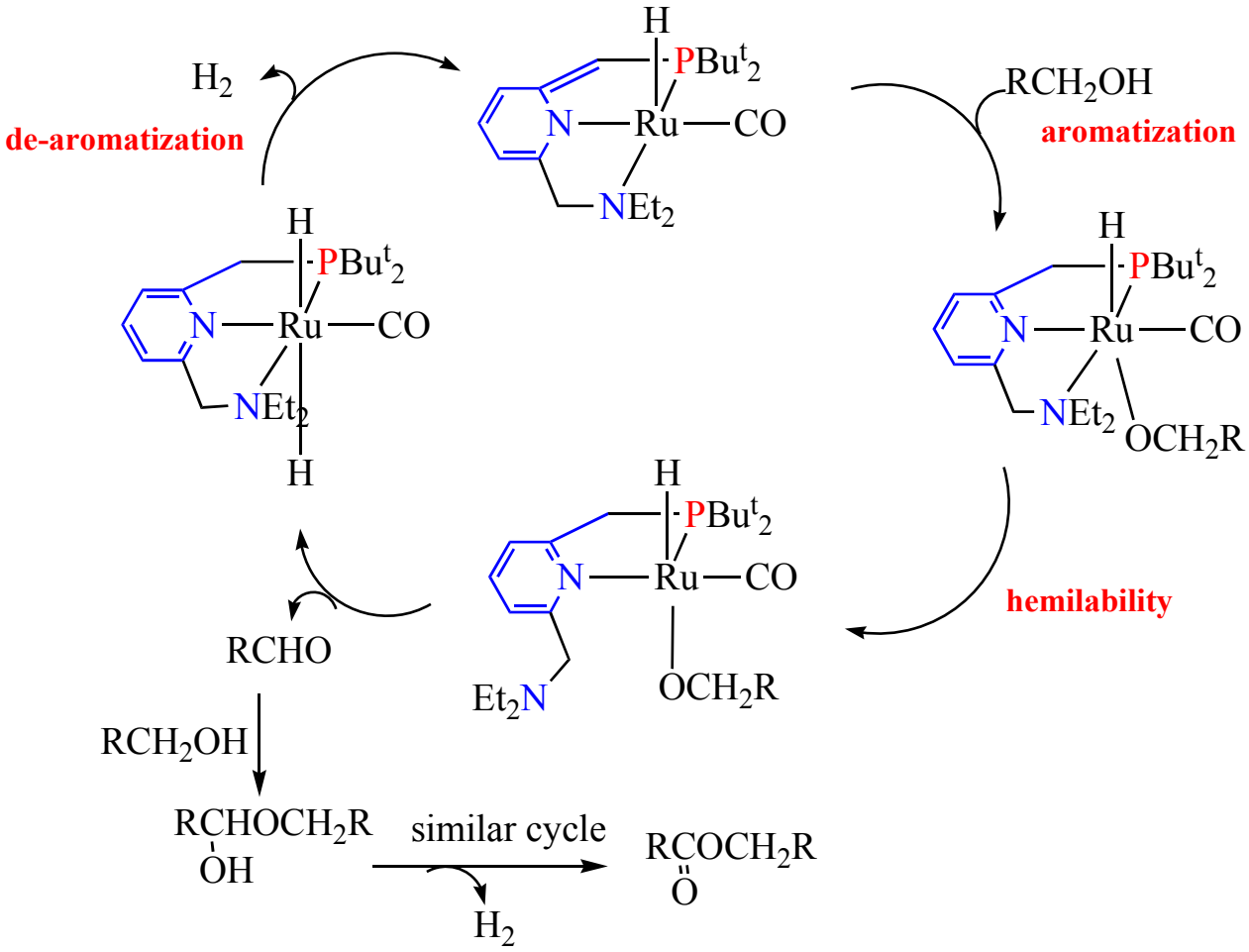
Overall mechanism:

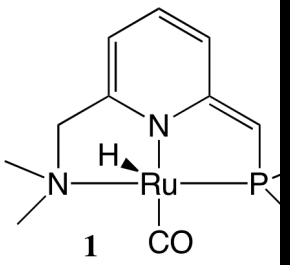


J. Zhang

J. Am. Chem. Soc. **2005**, *127*, 10840

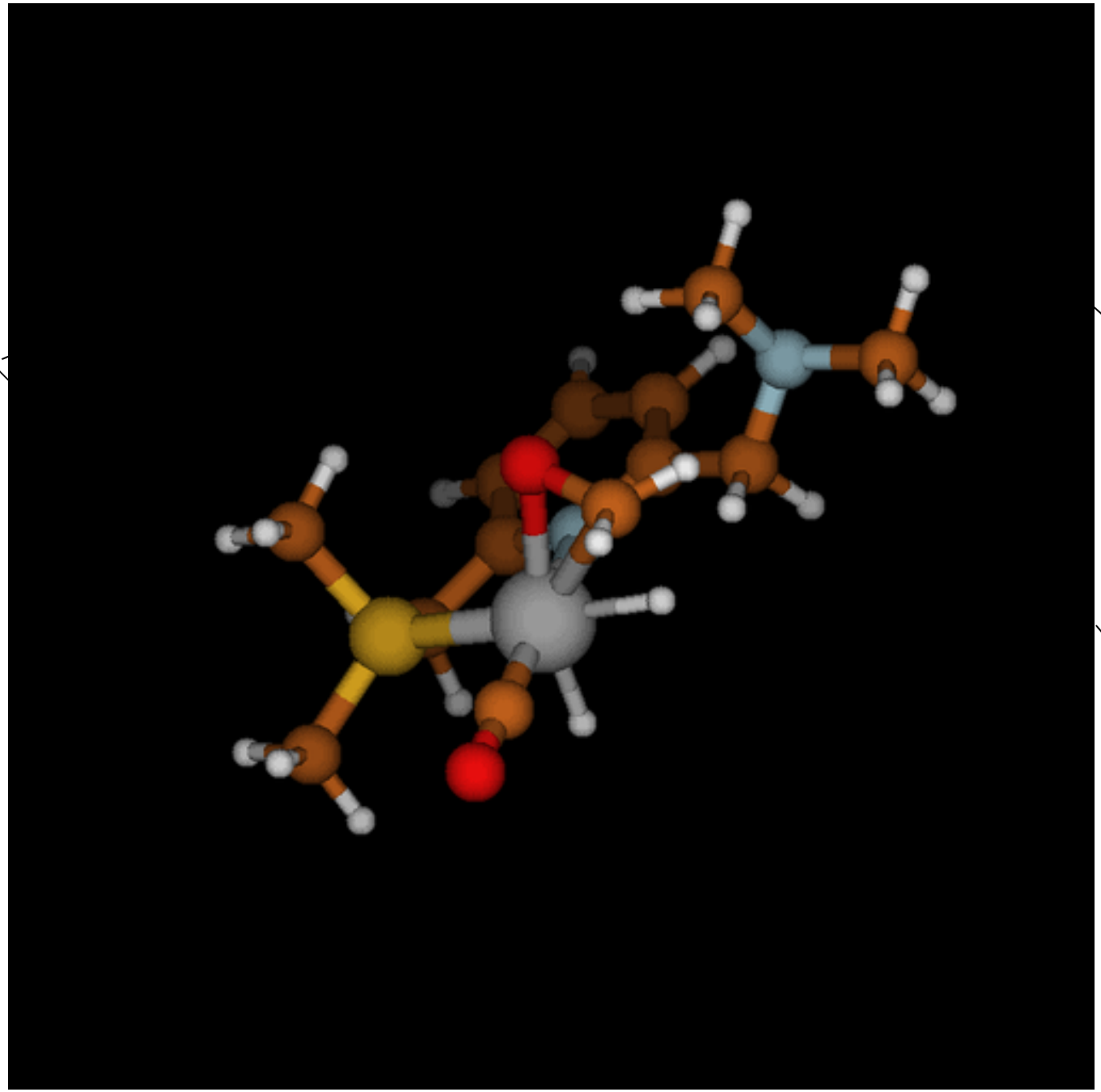
Mechanism: aromatization / dearomatization and hemilability

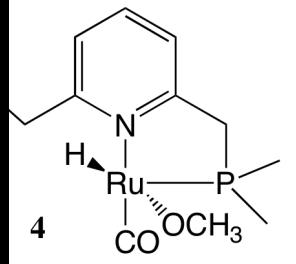




1

M. Iron

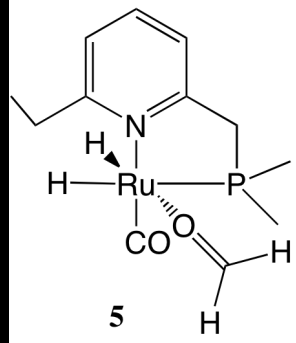




4

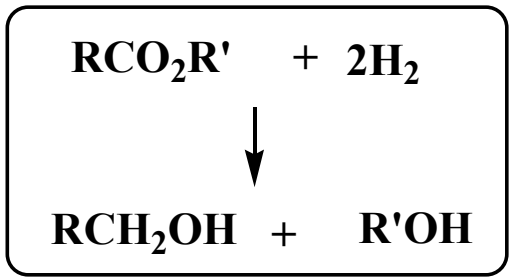
$\Delta G=7.4$

$\Delta G^{\ddagger}=15.4$

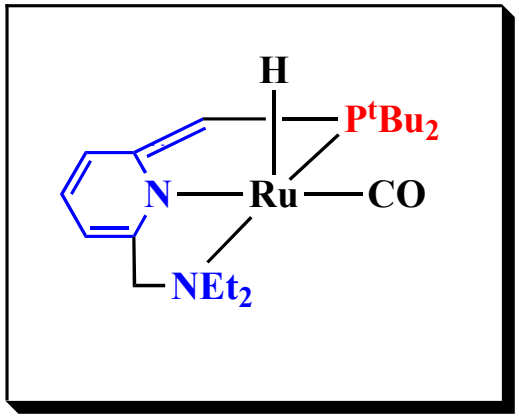


5

Ester Hydrogenation



Catalyst:

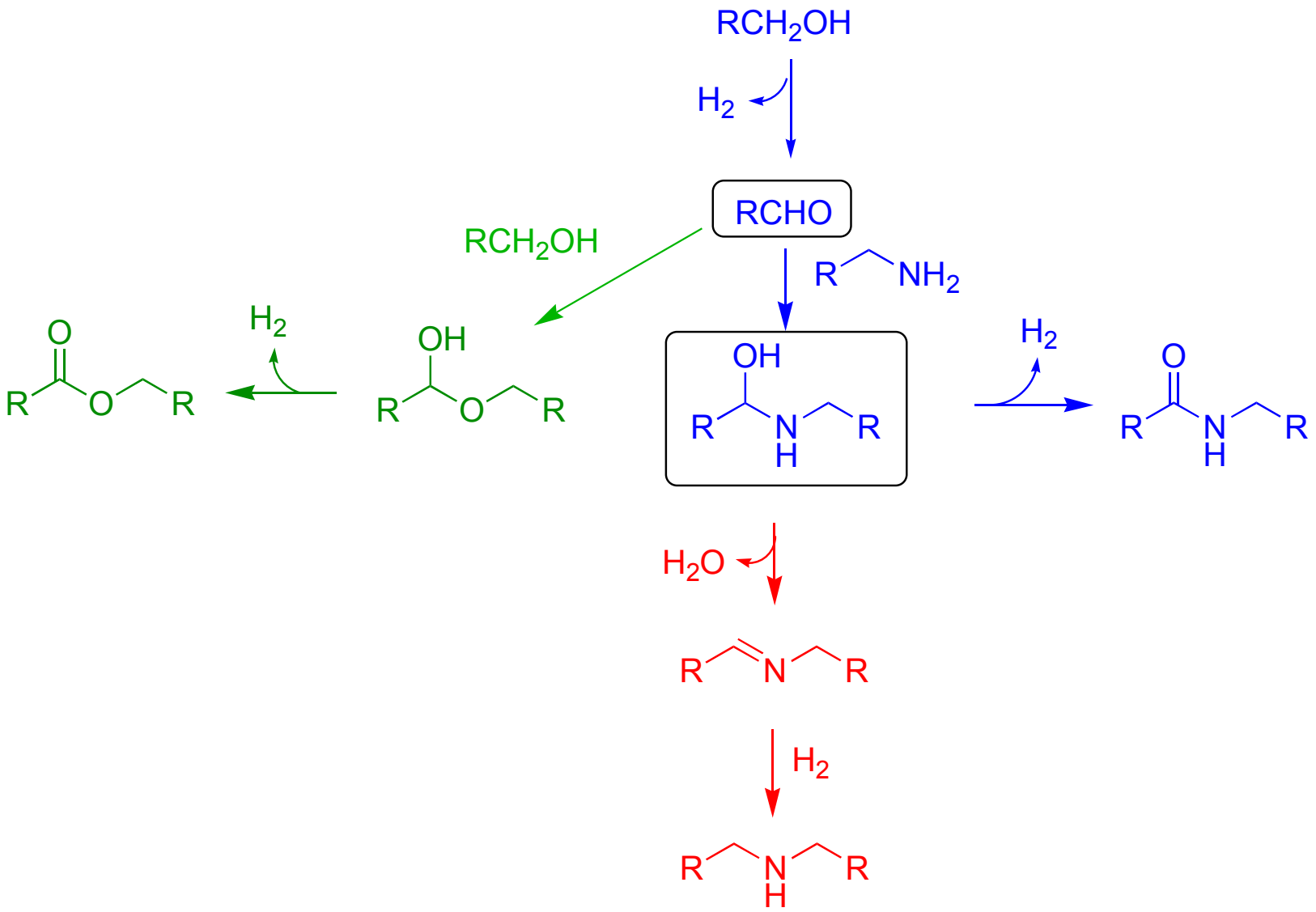


5 atm H_2 1% catalyst

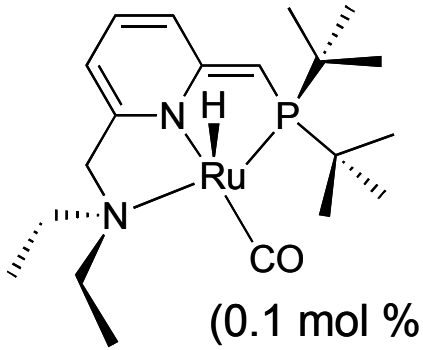
J. Zhang
Angew. Chem. Int. Ed.,
2006, *45*, 1113

Ester	Time (hr)	Temp. (°C)	Conversion (%)	Products (yield %)
Ethyl benzoate	4	115	99.2	Benzyl alcohol (96); Ethanol (99)[c]
Hexyl hexanoate	5	115	82.2	1-Hexanol (82.2)
Benzyl benzoate	7	115	98.5	Benzyl alcohol (98)
Methyl benzoate	4	115	100	Benzyl alcohol (97); Methanol (100)
Ethyl butyrate	4	115	100	1-Butanol (98); Ethanol (98.6)
Ethyl acetate	12	115	86	Ethanol (85.6)
t-Butyl acetate	24	115	10.5	Ethanol (10.5); t-Butanol (10.5)
Dimethyl terephthalate	5	115	100	1,4-Dimethanolbenzene (97); Methanol (100)

Coupling of alcohols with amines?



A New Way to Form the Amide Bond

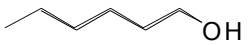
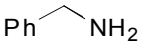
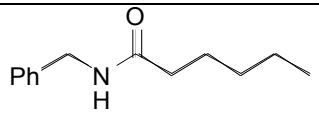
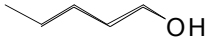
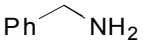
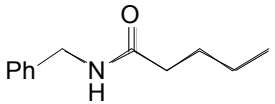
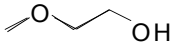
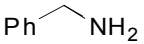
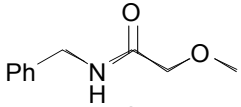
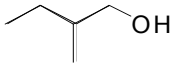
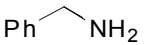
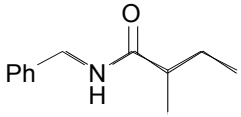
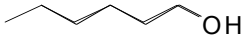
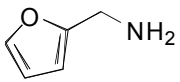
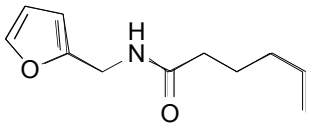
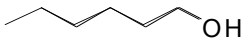
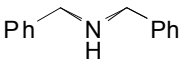
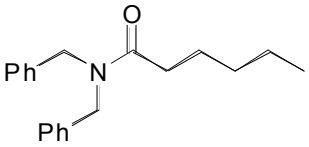
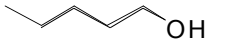
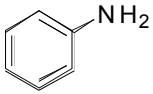
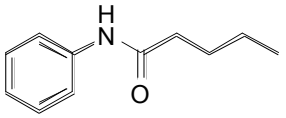
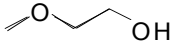
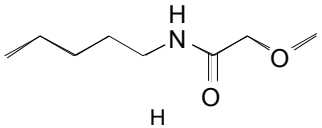
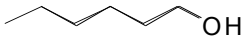
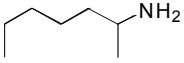
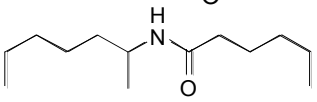
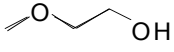
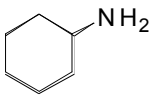
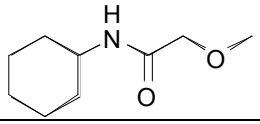


$R^1CH_2OH + R^2\text{-}NH_2 \xrightarrow[\text{Toluene, Reflux}]{\text{(0.1 mol \%),}} R^2NHCOR^1 + 2\ H_2$

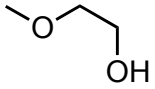
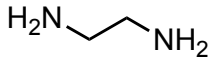
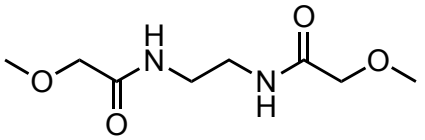
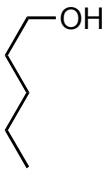
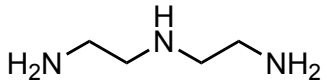
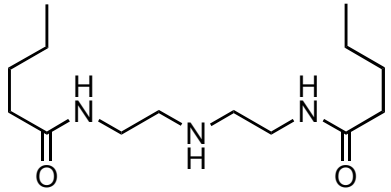
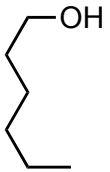
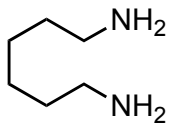
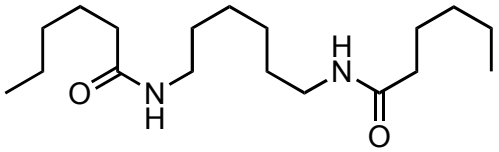
Neutral conditions
No waste
High yield
High turnover

C. Gunanathan, Y. Ben-David, D. Milstein *Science*, **2007**, *317*, 790

Amide Synthesis

Entry	R^1CH_2OH	R^2NH_2	Time (h)	Amides	Yield † (%)
1			7		96
2			7		97
3			9		99
4			12		70‡
5			8		78‡
6			8		0‡
7			8		58‡
8			8		99
9			8		72‡
10			8		99

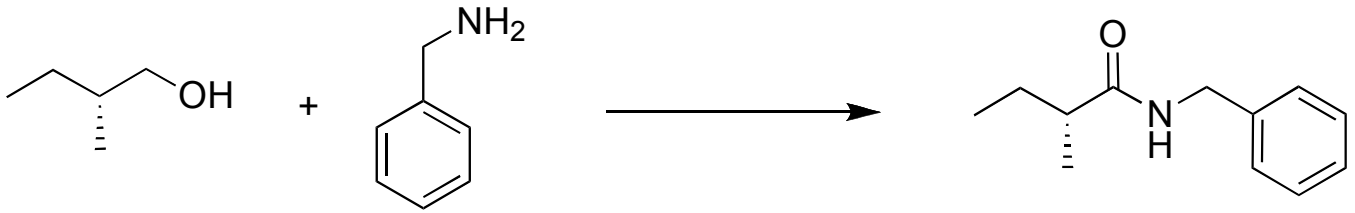
Chemoselective Bis-Amidation

Alcohol	Diamine	Bisamide	Yield (%)
			99
			88
			95

Selective to primary amines

C. Gunanathan

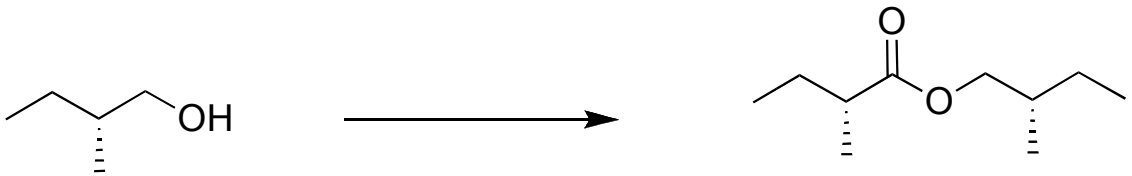
No Racemization



80% isolated yield

specific rotation

$[\alpha]_D^{20} = +17.2°$

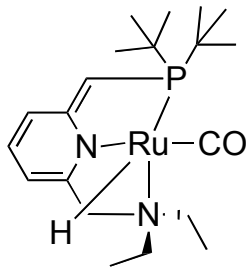


84% isolated yield

specific rotation

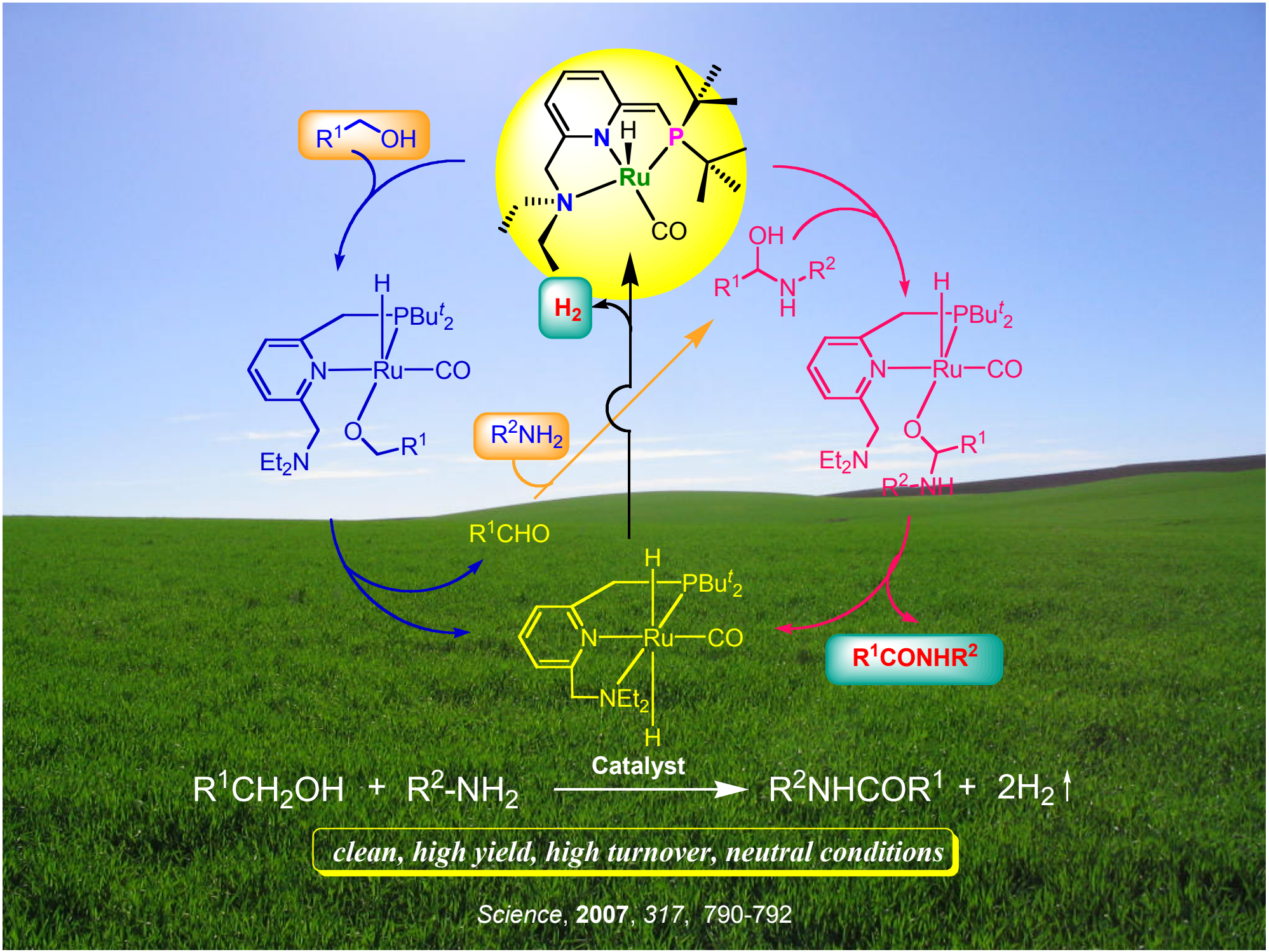
$[\alpha]_D^{20} = +14.2°$

Catalyst:

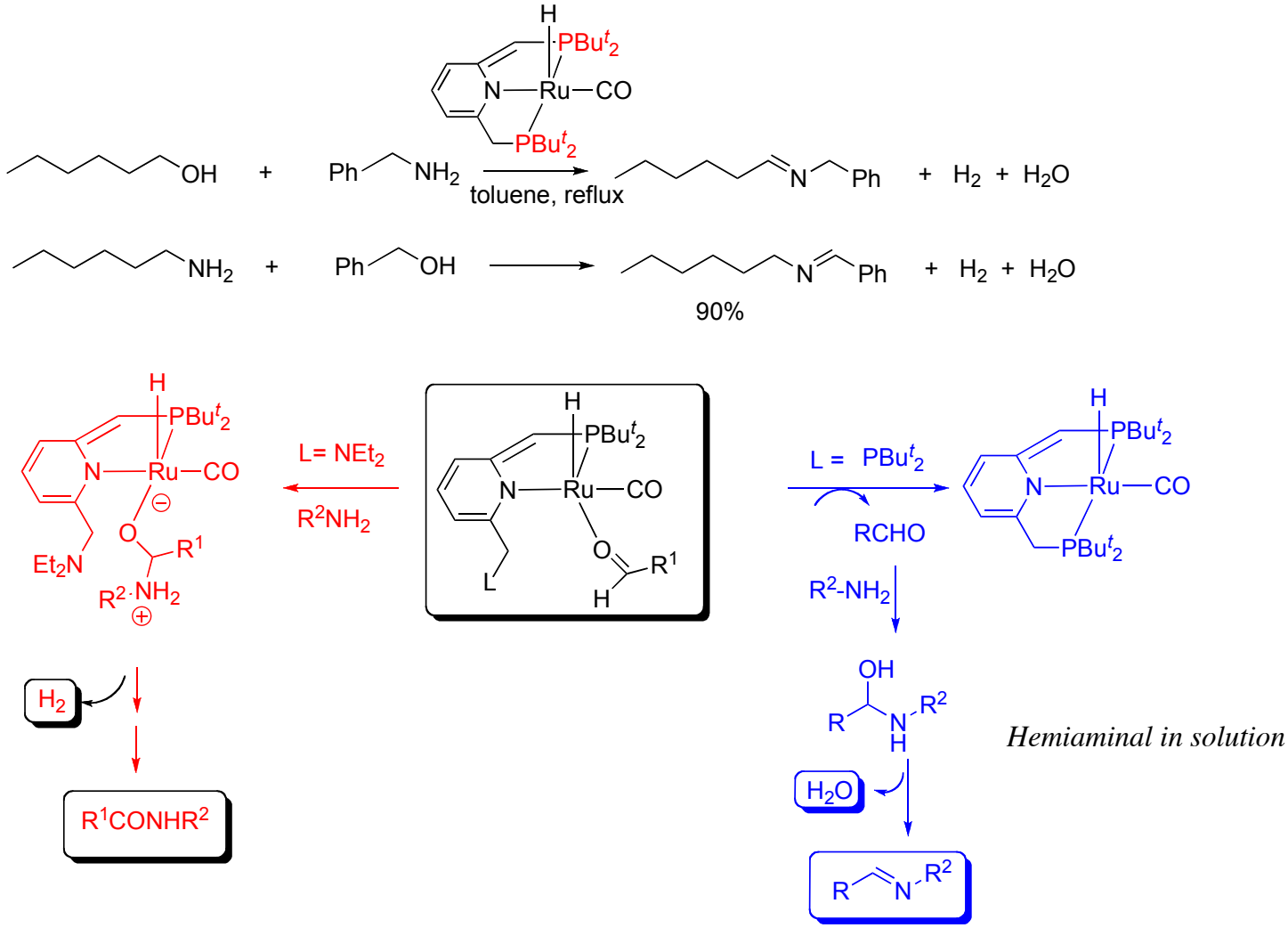


toluene, 14hrs, 115°C

B. Gnanaprakasam


R1CH2OH + R2-NH2
Catalyst
R2NHCOR1 + 2H2
clean, high yield, high turnover, neutral conditions
Science, 2007, 317, 790-792

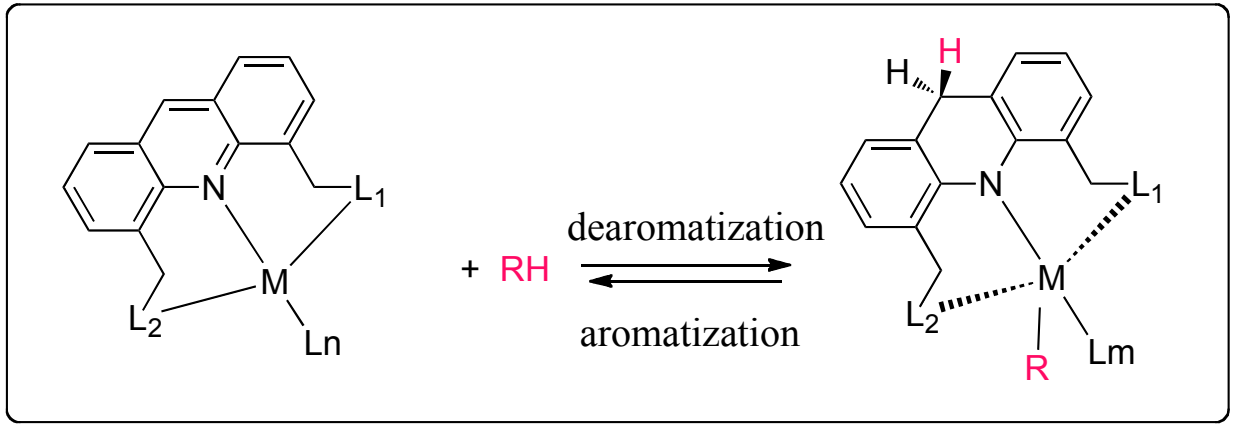
“Minor” Change- Different Reaction: Imines and H_2 from Alcohols and Amines



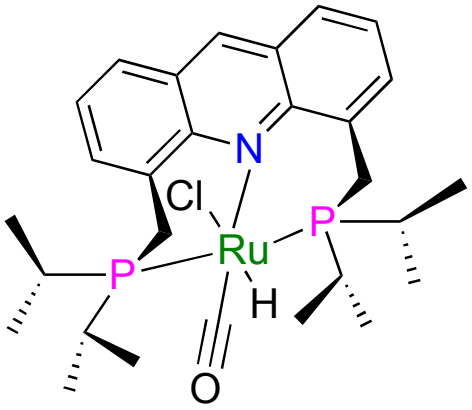
B. Gnanaprakasam

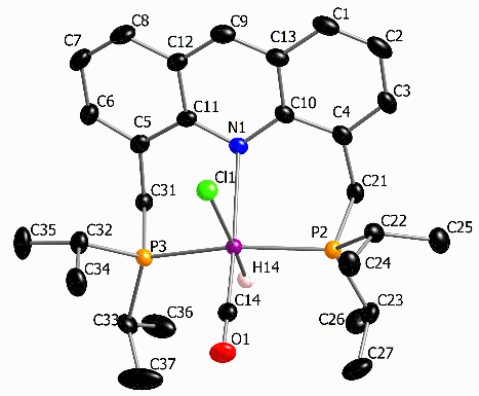
Angew. Chem. Int. Ed. **2010**, *49*, 1468

Acridine-Pincer Based Bond Activation



Long, "hemilabile" M-N bond
Position 9 is susceptible to nucleophilic attack



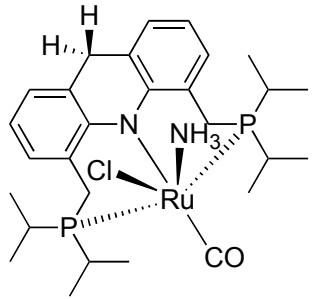


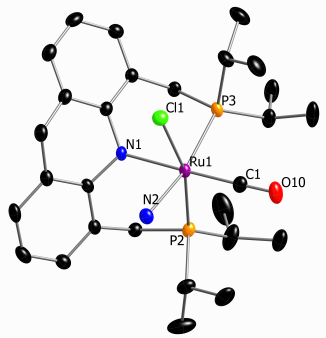
Middle aryl ring: boat-shaped, 167.6^0 dihedral angle. Ru-N 2.479 *Å*

C. Gunanathan

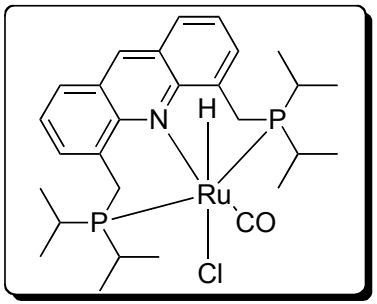
Reactions of Acridine-Based Complex

C. Gunanathan, B. Gnanaprakasam

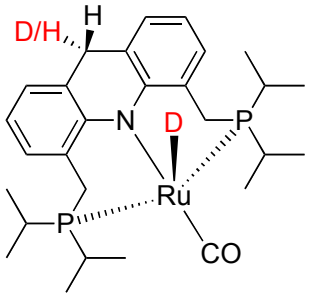




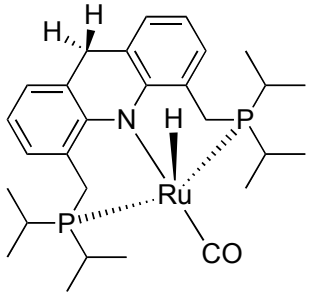
NH_3, Toluene, 135 C



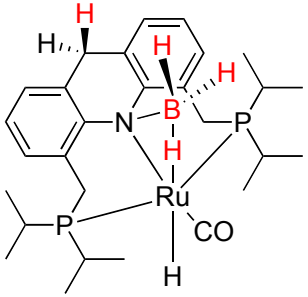
D_2, KOH

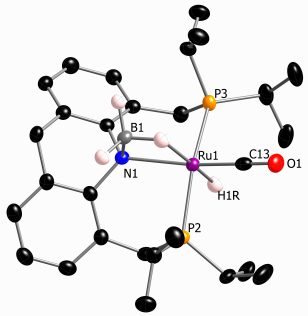


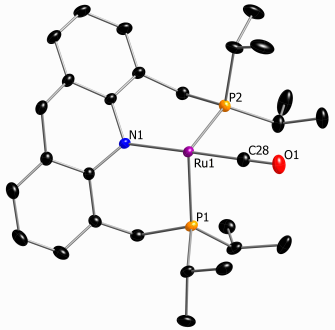
H_2 (5 at), 1eq KOH, 135 C



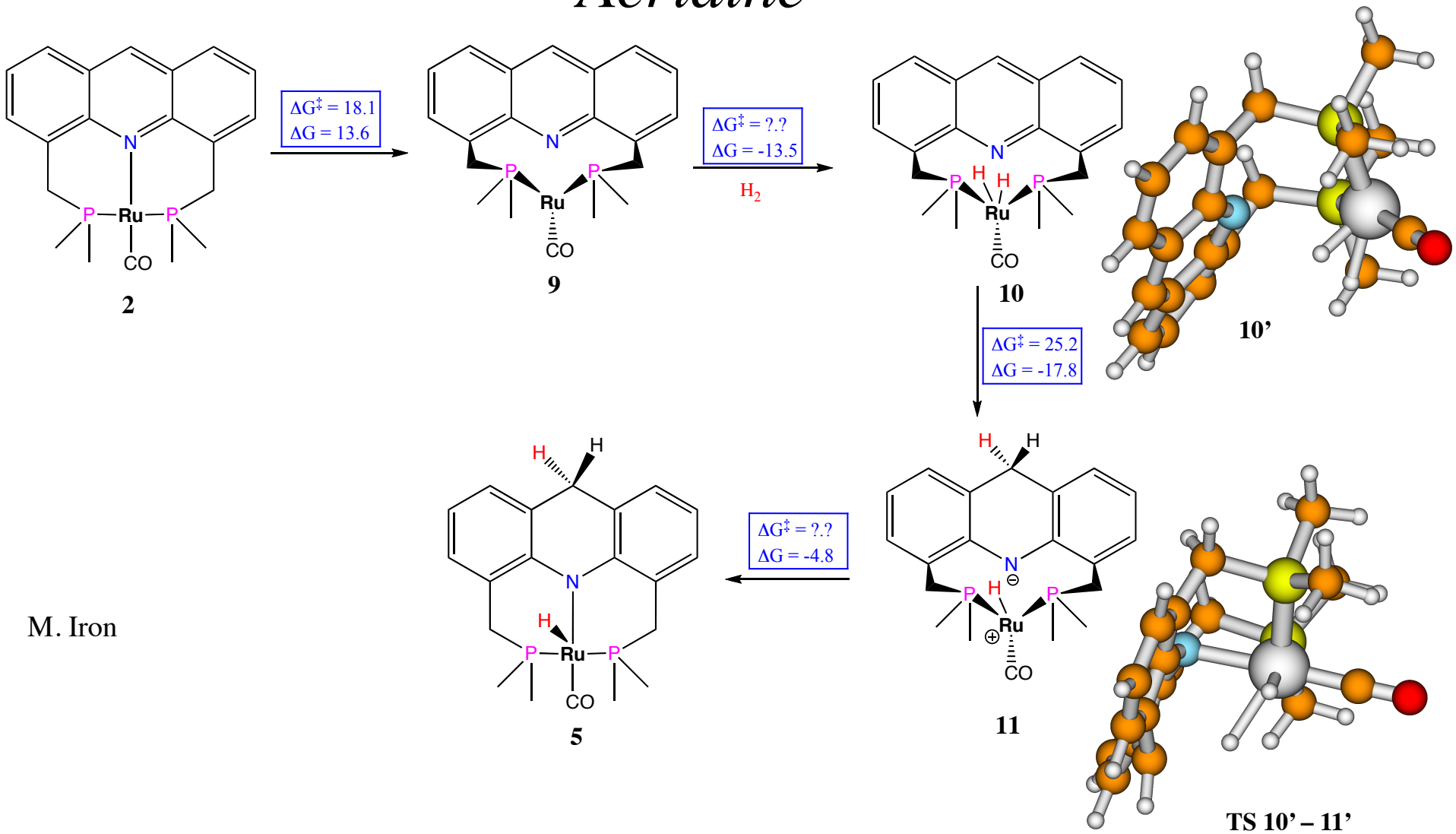
$NaBH_4$, 2h, rt



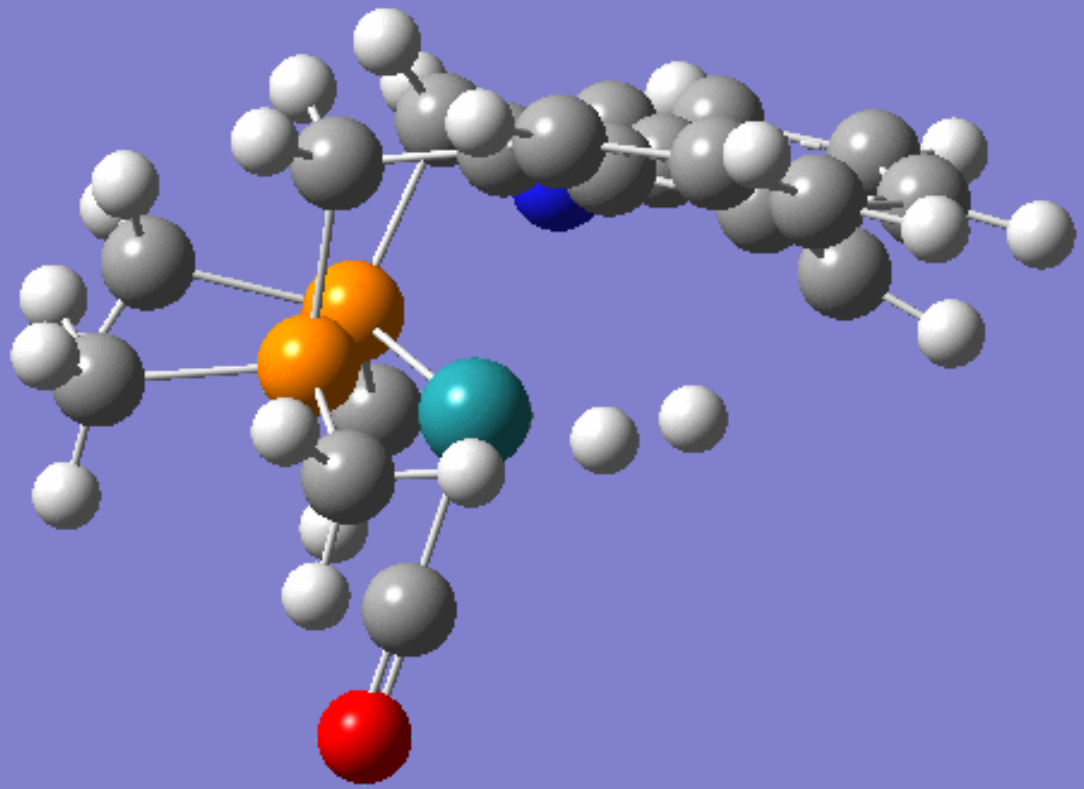




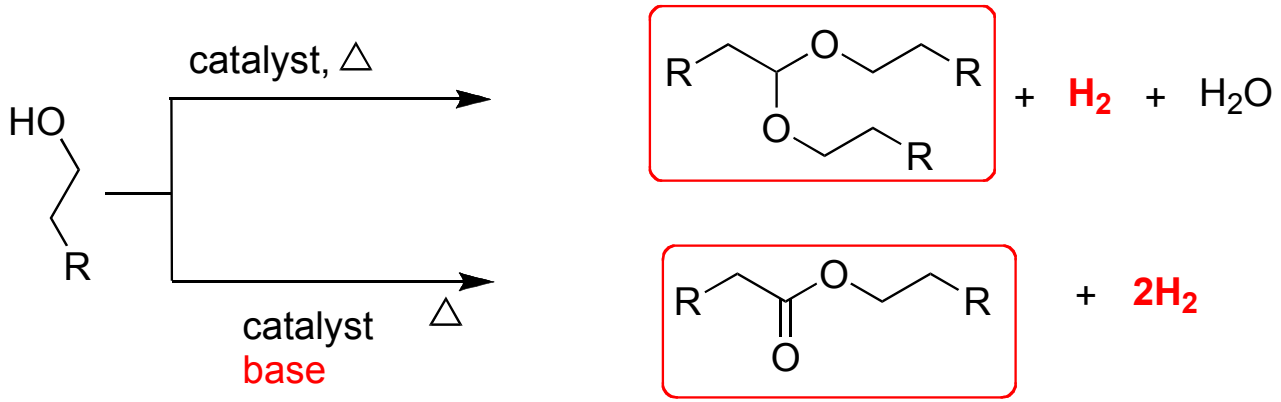
Mechanism of Cooperative H_2 Activation by Ru and Acridine



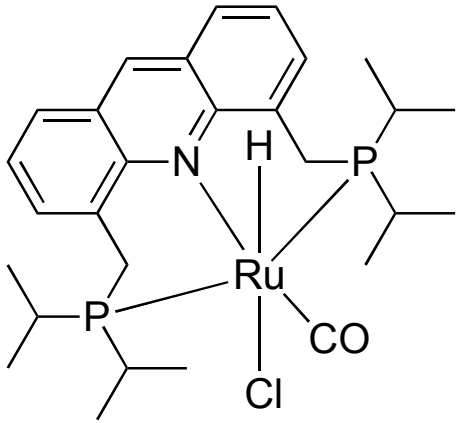
M. Iron



Acetals Directly From Alcohols With H_2 Liberation



Catalyst:



C. Gunanathan

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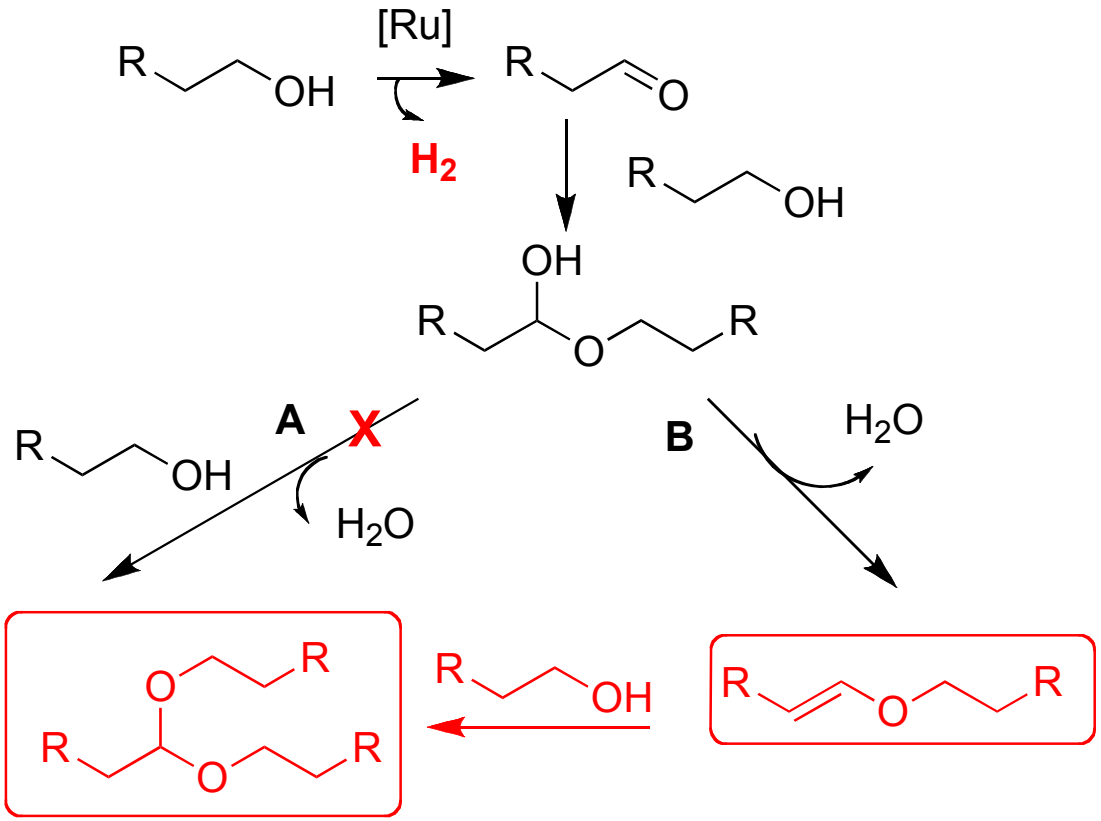
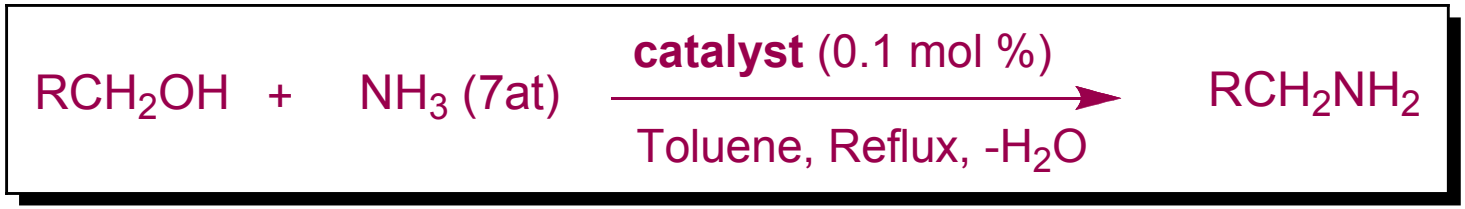
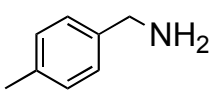
Mechanism: enol ether intermediacy



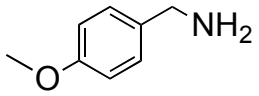
Enol ether intermediates detected
Benzyl alcohol does not yield acetals

Primary Amines From Alcohols and Ammonia





83%



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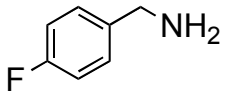
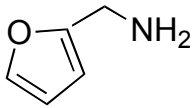


91%



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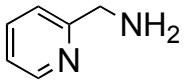
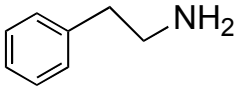
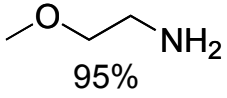


96%



69%



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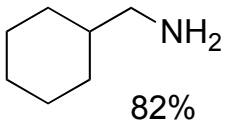

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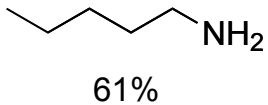

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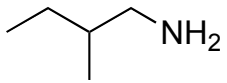

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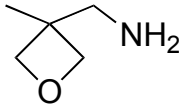

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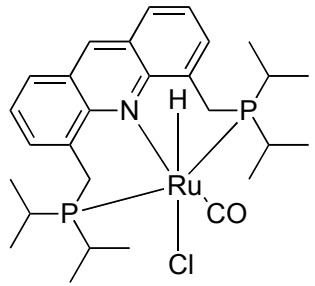
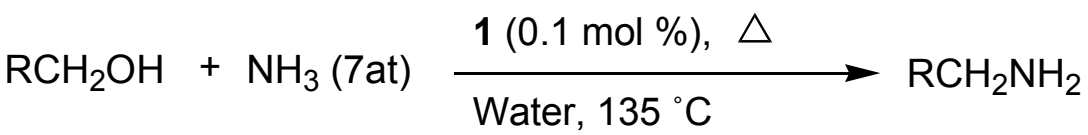


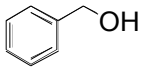
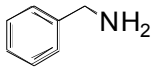
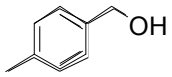
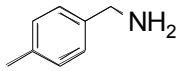
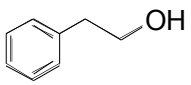
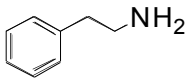
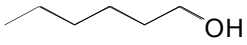
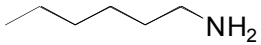
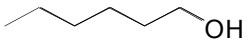
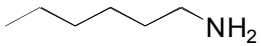
catalyst

C. Gunanathan

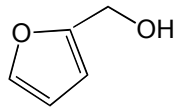
Angew. Chem. Int. Ed. ***2008****, 47, 8661*

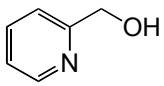
“On Water”



Entry	RCH_2OH	Time (h)	Convn.	RCH_2NH_2	Yield (%)[†]
1		18	100		95.4 (86)
2		18	100		91.7
3		36	100		80.4[‡]
4		24	92.4		54.8*
5[¶]		28	89.4		74.3

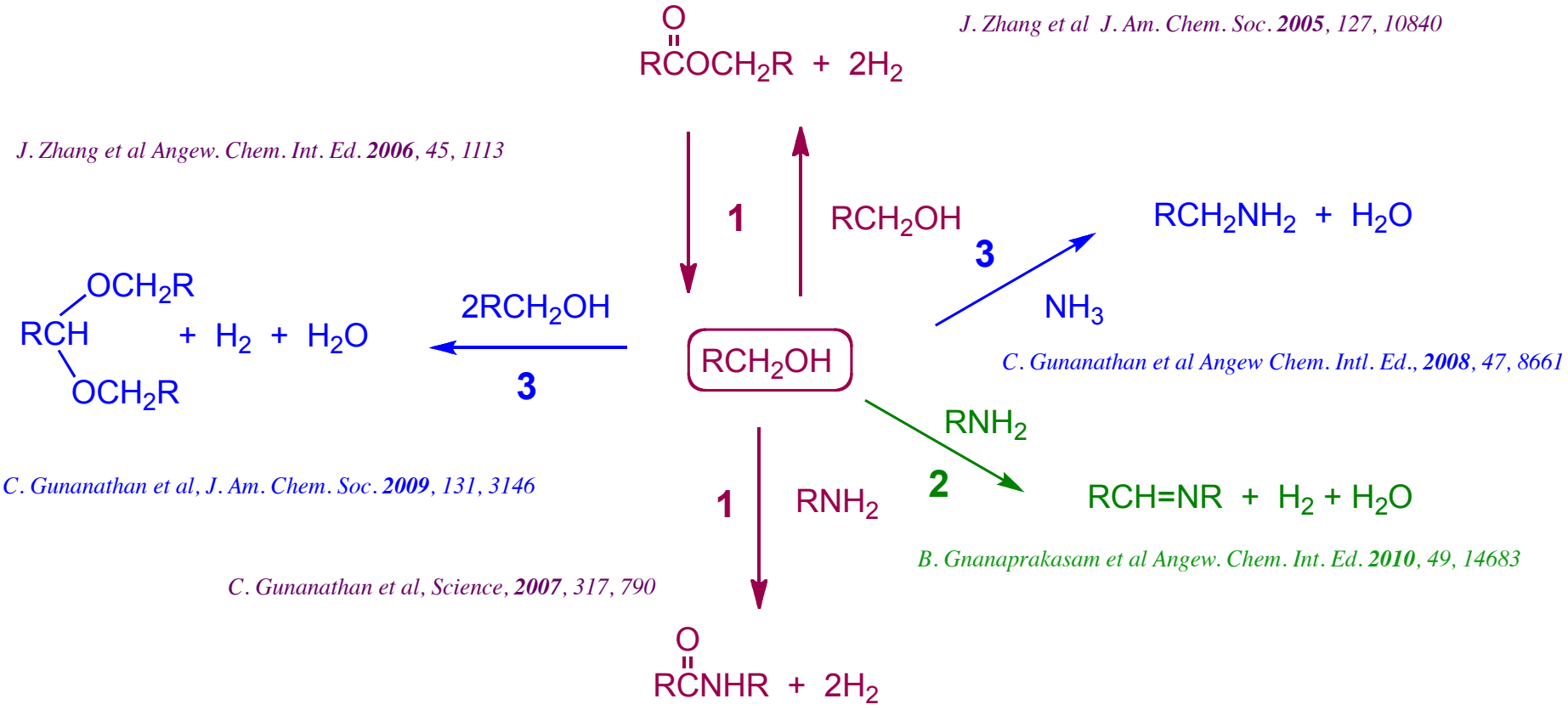
No reaction with the water soluble alcohols:





Higher selectivity to primary amine with hexanol, pentanol in water-dioxane

Choose Your (Alcoholic) Green Reaction



MILSTEIN CATALYST

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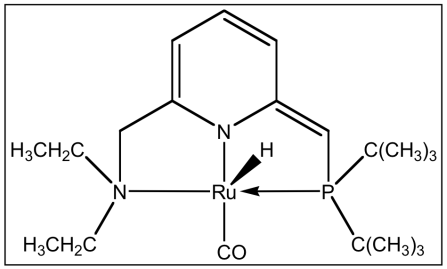
The Newburyport Greater Chamber of Commerce "2008 Business of the Year"

Offers a "Breakthrough of the Year" The Runners-up. *Science* **2007**, *318*, 1844-49.

and "Highlights of the Year 2007" *C&E News*, **2007**, *85 (52)*, 13-19.

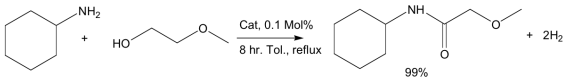


44-0091 **Carbonylhydrido[6-(di-t-butylphosphinomethylene)-2-(N,N-diethylaminomethyl)-1,6-dihydropyridine]ruthenium(II), min. 98%** *[863971-63-5]* 100mg 500mg

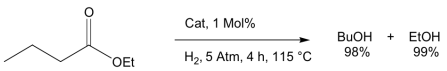
$C_{20}H_{35}N_2OPRu$; FW: 451.55; orange pwdr.

Technical Notes:

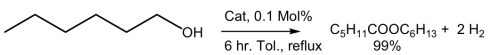
1. Ruthenium catalyst for the direct synthesis of amides from alcohols and primary amines.
2. Ruthenium catalyst for the hydrogenation of esters in high yields under mild pressure and neutral conditions
3. Ruthenium catalyst for the dehydrogenative coupling of alcohols to form esters in high yields under neutral conditions.



Tech. Note (1)
Ref. (1)



Tech Note (2)
Ref. (2)



Tech. Note (3)
Ref. (3-4)

References:

1. *Science* **2007**, *317*, 790
2. *Angew. Chem. Int. Ed.*, **2006,** *45,* 1113.
3. *J. Am. Chem. Soc,* **2005,** *127,* 12429.
4. *J. Am. Chem. Soc,* **2005,** *127,* 10840.

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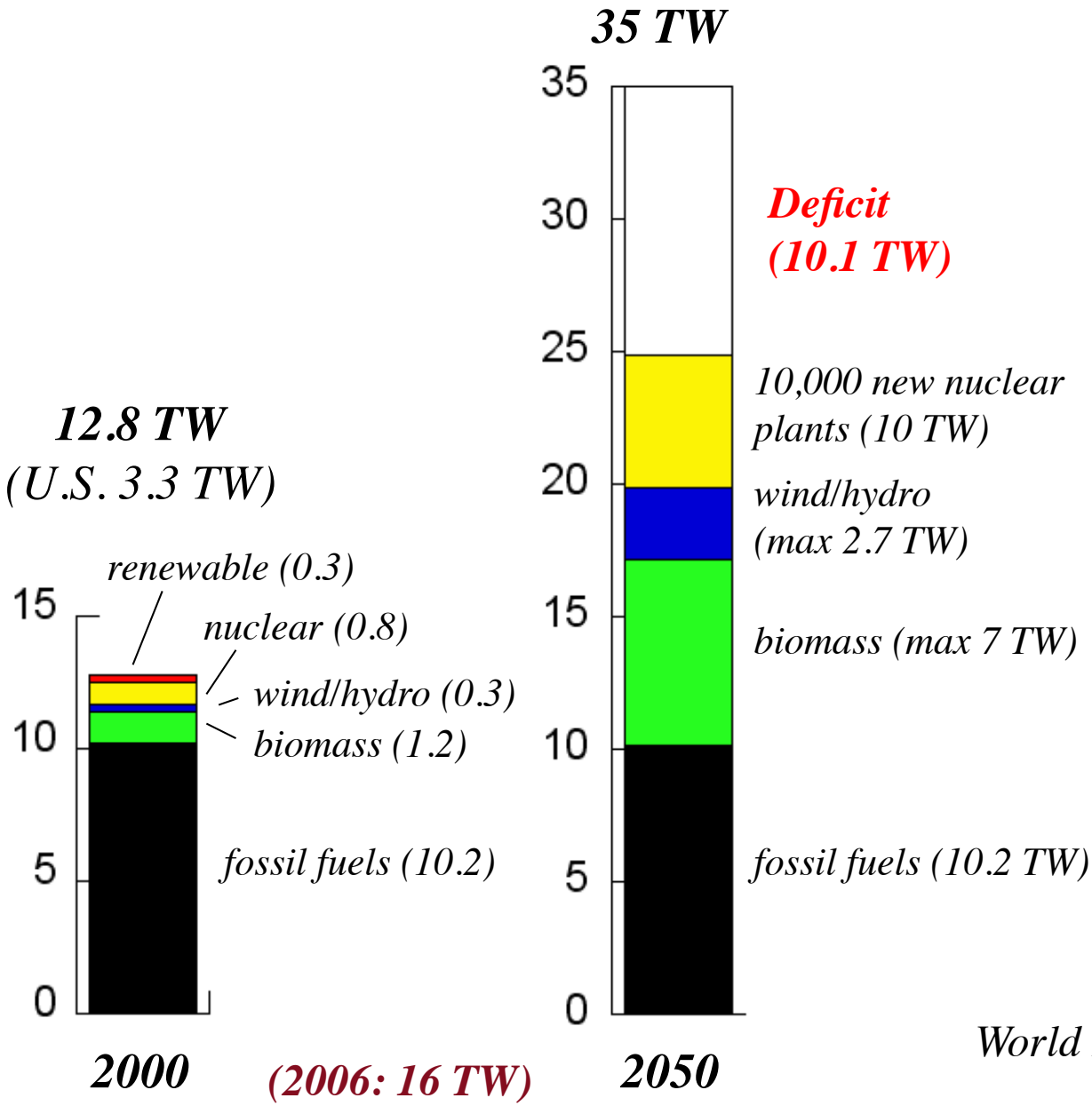
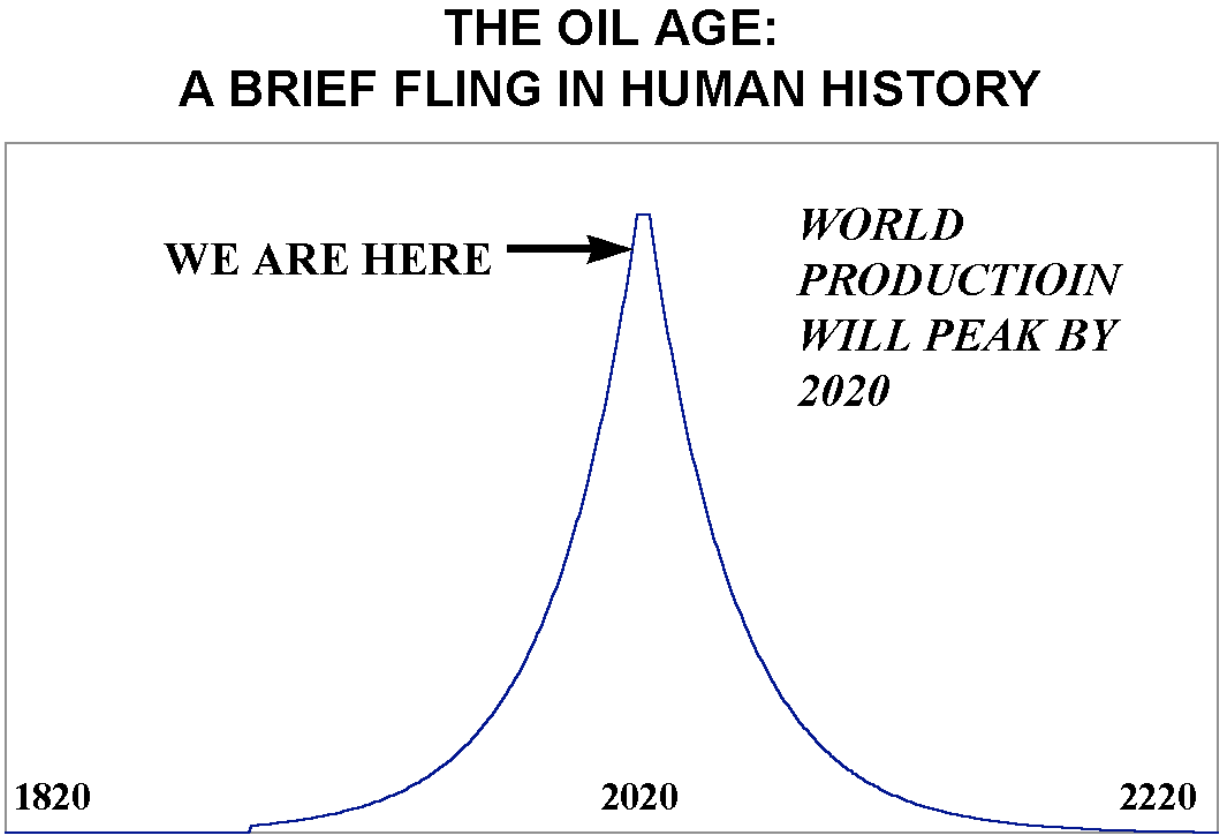
From Alcohol to Water?

Projected Global Energy Deficit



World Energy Assessment, 2000



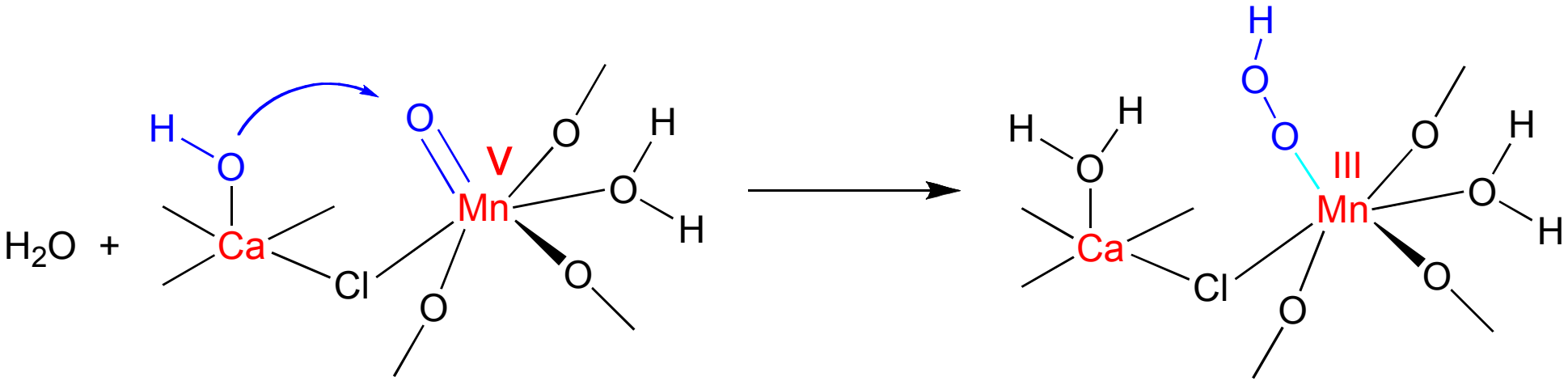
Source: INFORSE - International Network for Sustainable Energy
www.inforse.org/europe/dieret/WHY/why.html

Water Splitting

Bottleneck: O_2 generation

E^0 = 1.23V (vs hydrogen electrode) at pH=1

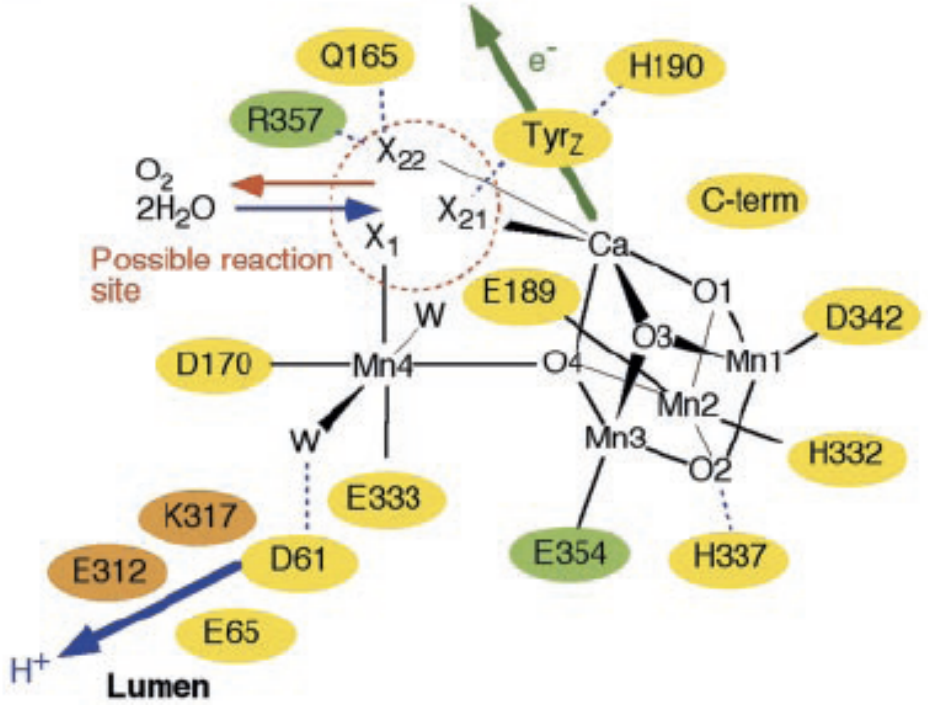
Postulated O-O Bond Forming Step in Photosystem II



Oxygen Evolving Complex (OEC) consists of an oxo-bridged Mn3Ca cluster linked by a μ-oxo bridge to a Mn site

X-ray: J. Barber *et al Science* **2004**, *303*, 1831

Review: C.W. Cady, R. H. Crabtree, G. W. Brudvig *Coord. Chem. Rev.* **2008**, *252*, 444

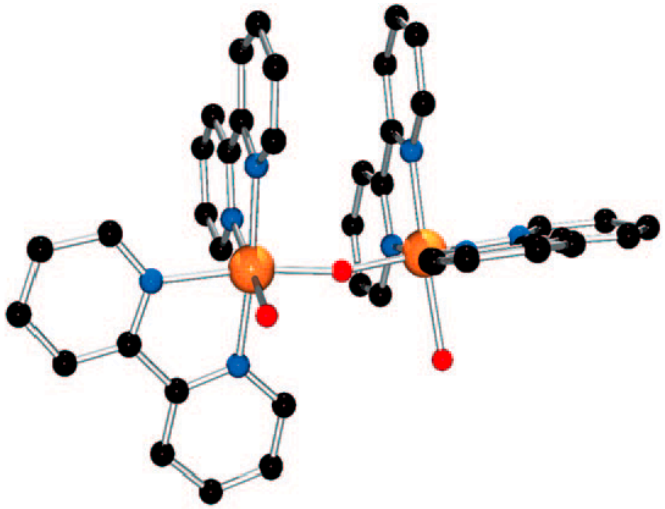


"Blue Dimer"

cis,cis-$[(bpy)_2(H_2O)Ru\text{-}O\text{-}Ru(H_2O)(bpy)_2]^{4+}$

"Blue Dimer"

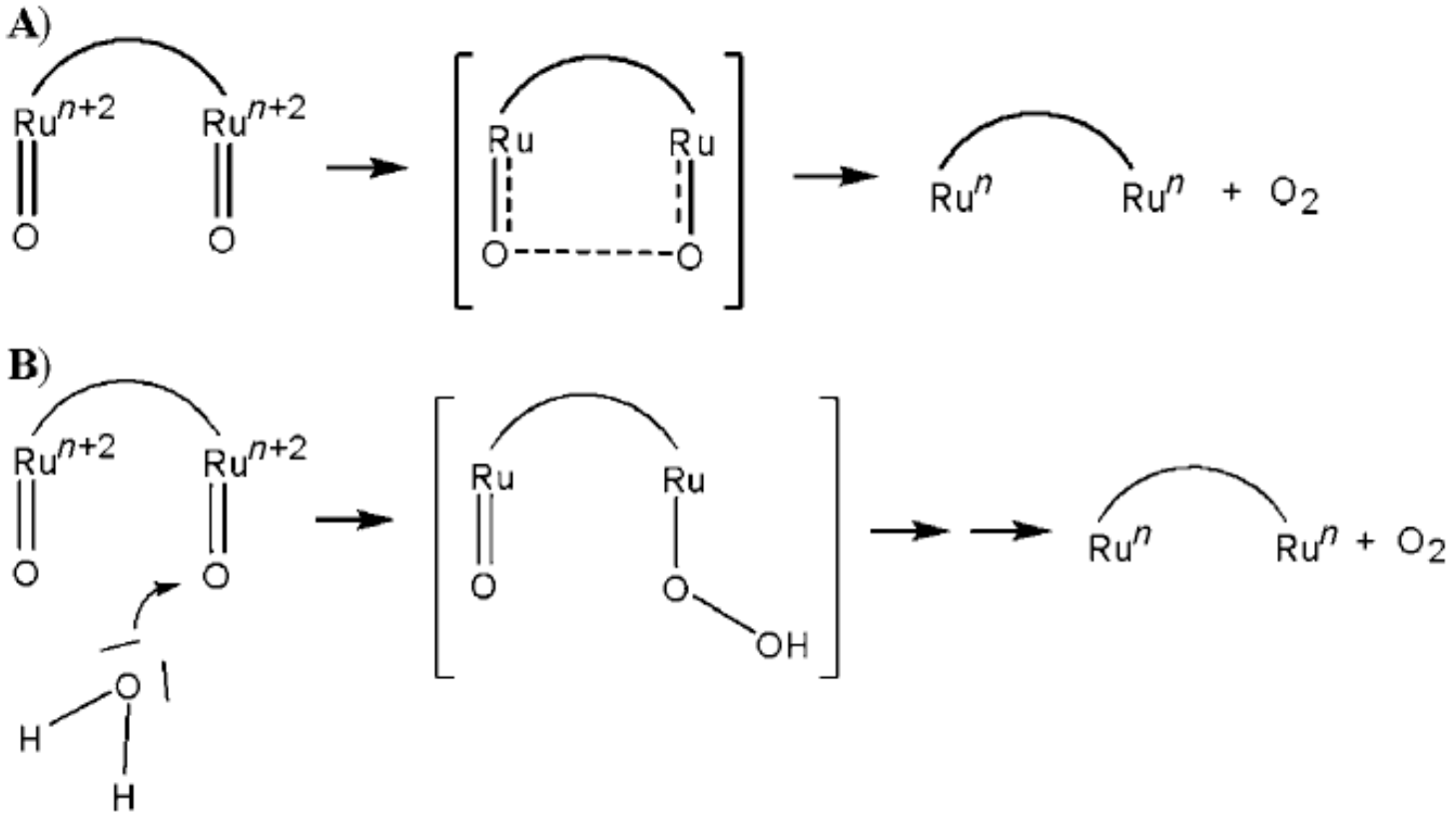
T. J. Meyer et al, *J. Am.Chem.Soc.* **1982**, *104*, 4029



$$4Ce^{IV} + 2H_2O \xrightarrow{\text{"Ru blue dimer"}} 4Ce^{III} + O_2 + 4H^+$$

J. P. Collin and J. P. Sauvage, *Inorg. Chem.* **1986**, *25*, 135

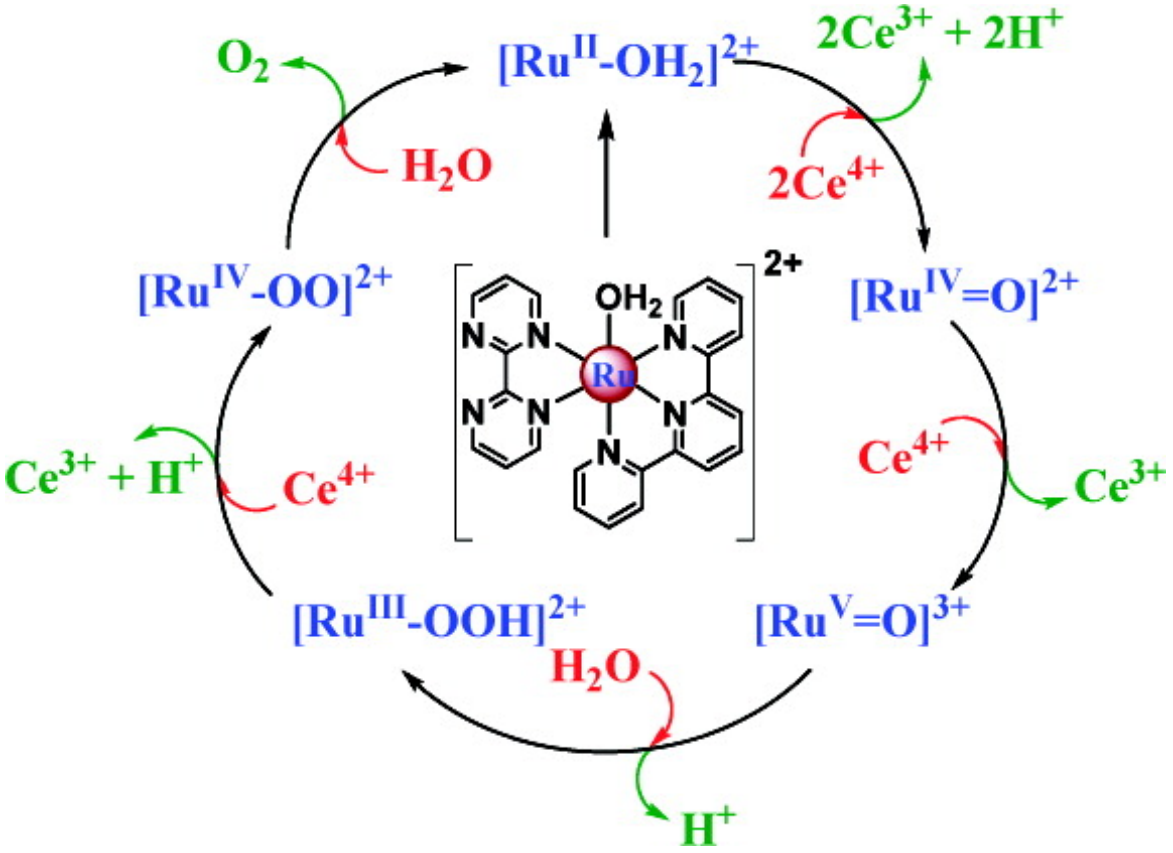
Suggested Mechanisms for O-O Bond Formation



A. Llobet et al, Angew. Chem. Int. Ed. ***2009****, 48, 2842*

Intermolecuar Mechanism B favored based on O-labelling: Hurst et al JACS, ***2004****,126,9786*

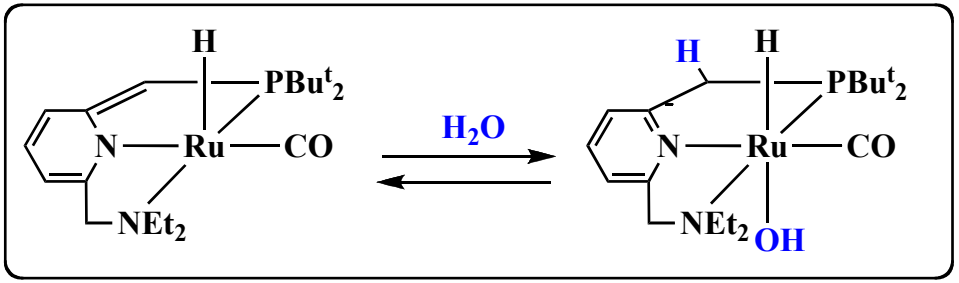
Suggested Mechanism for mono-Ru Catalyzed Water Oxidation by Ce^{4+}



$$4Ce^{IV} + 2H_2O \longrightarrow 4Ce^{III} + O_2 + 4H^+$$

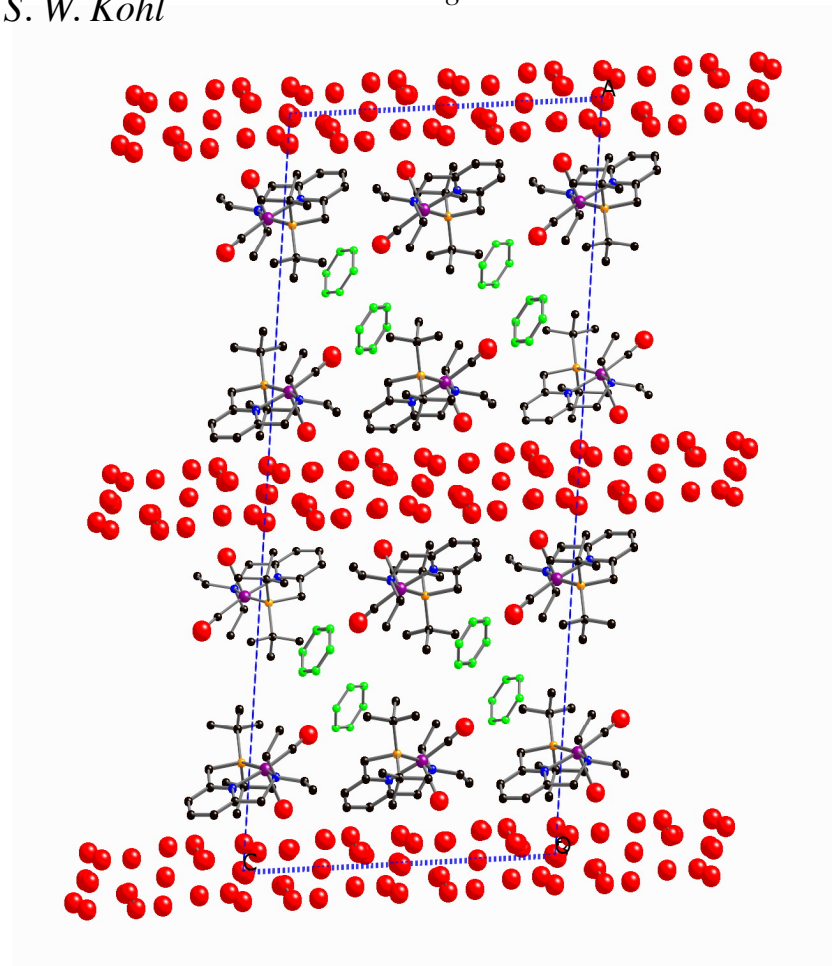
T. J. Meyer et al, ***2008***, *130, 16462*

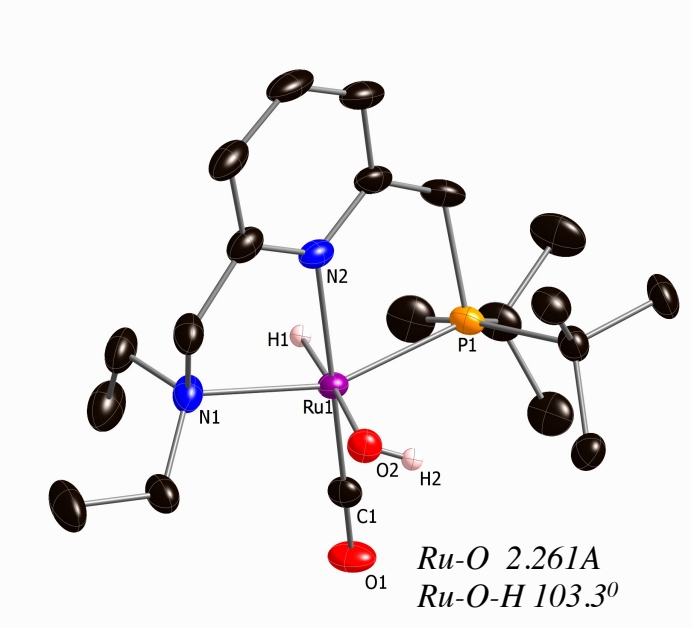
Metal - ligand cooperation in HO-H cleavage



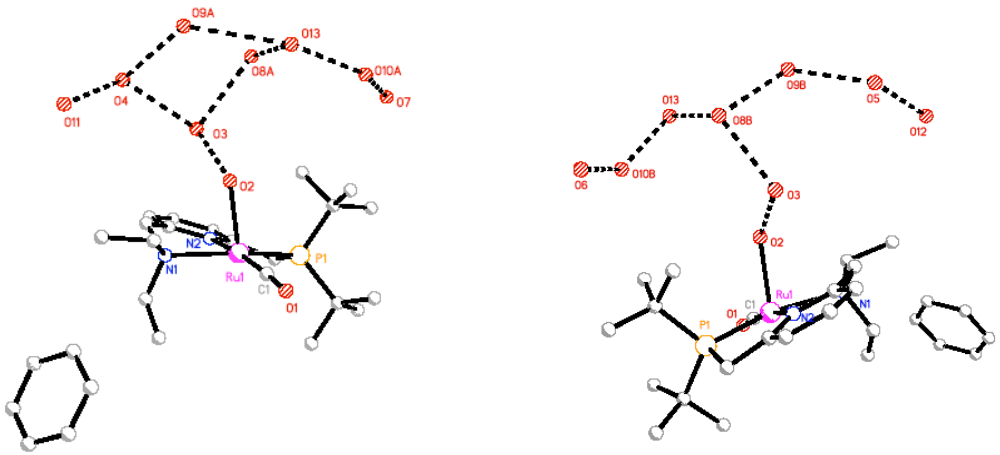
No change in metal oxidation state

S. W. Kohl



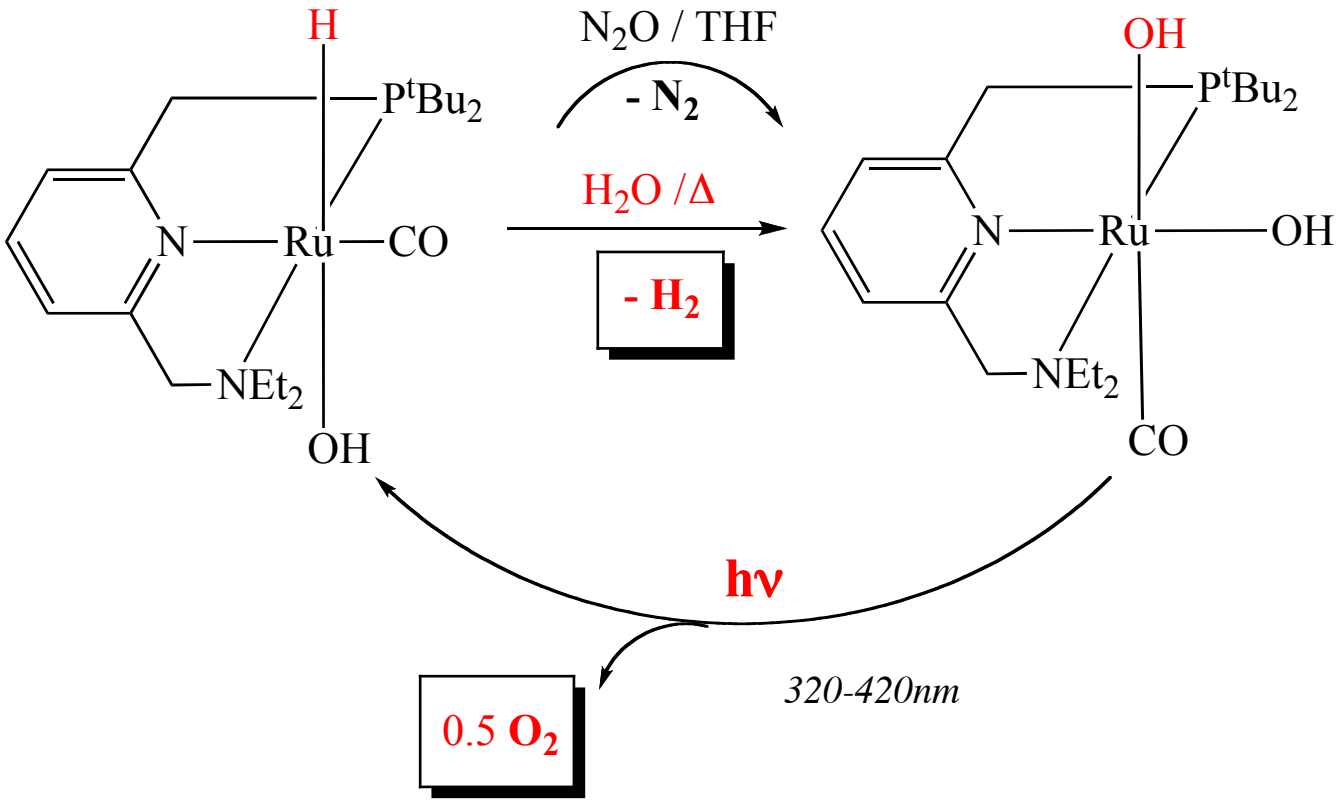


Ru-O 2.261A
Ru-O-H 103.3^0

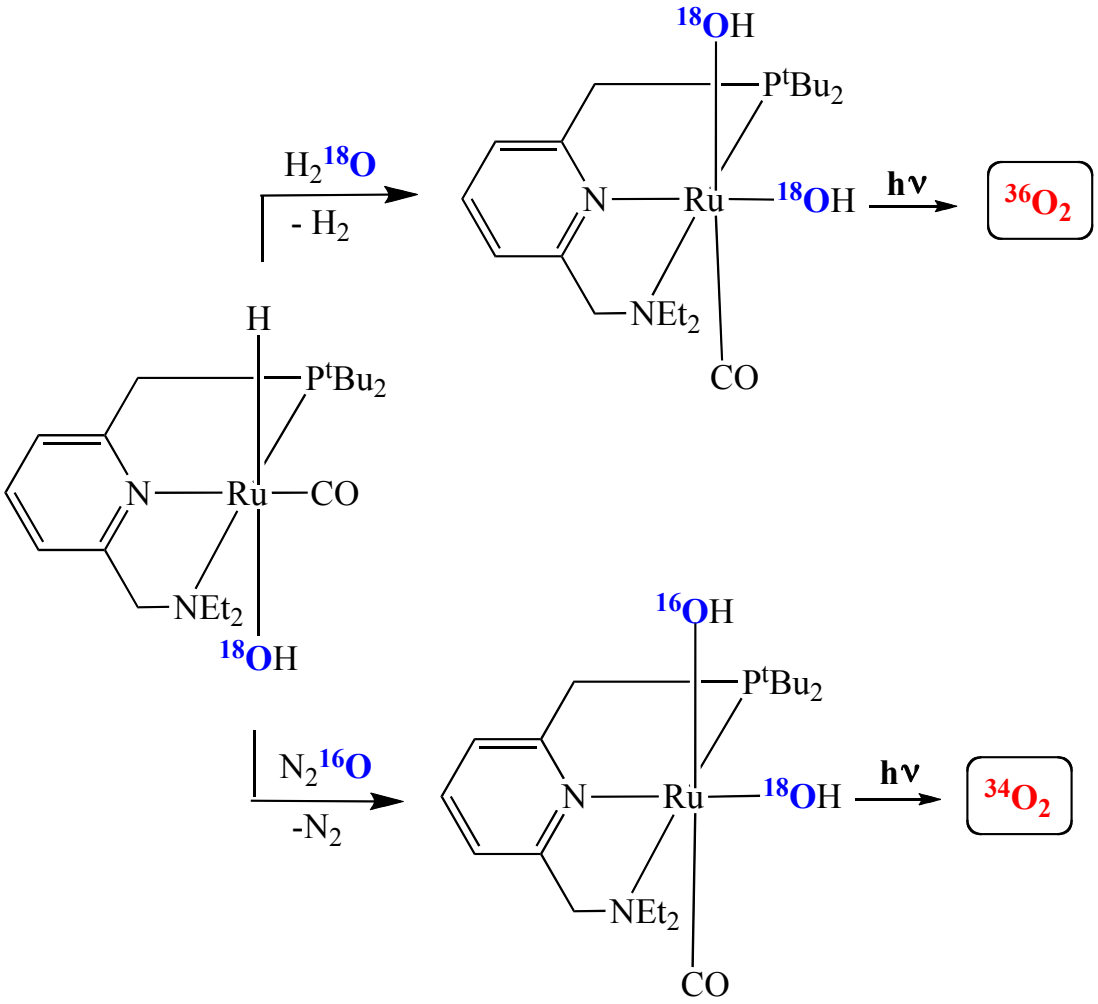


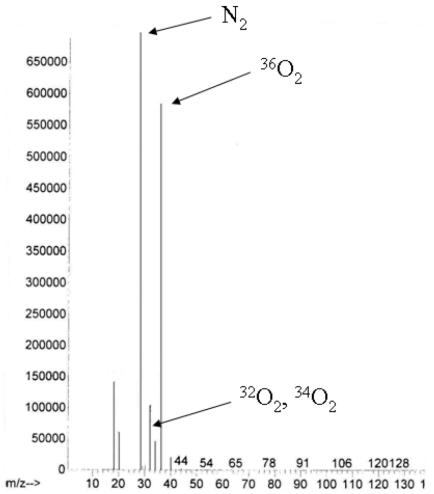
L. J. W. Shimon

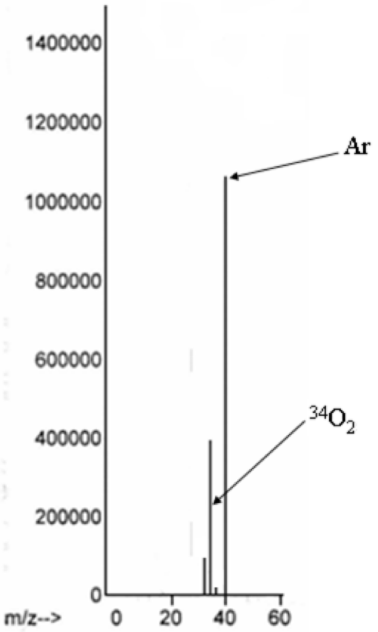
Consecutive Water Splitting



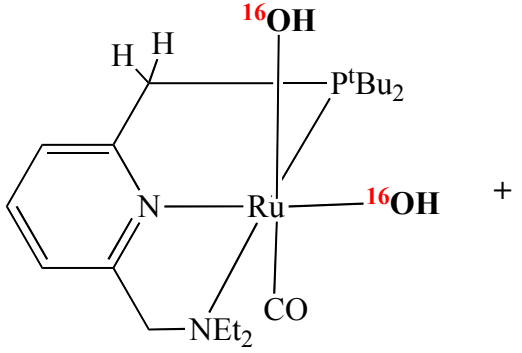
Isotopic Labelling Studies







No Cross-Over



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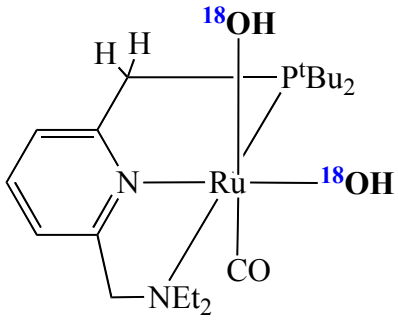
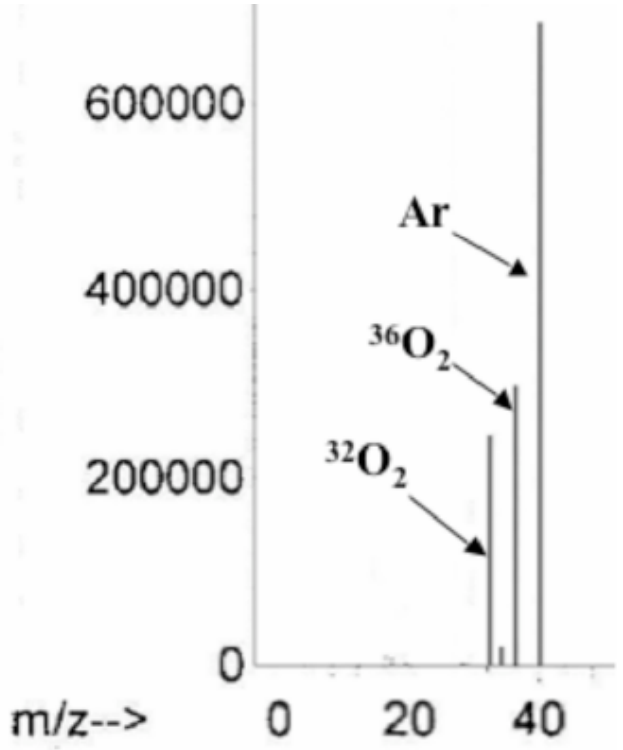


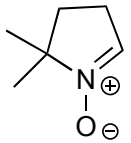


Intermediacy of H_2O_2 ?

Spin Trap Experiments: hydroxyl radicals detected; not involved in O2 generation; not formed in presence of Catalase

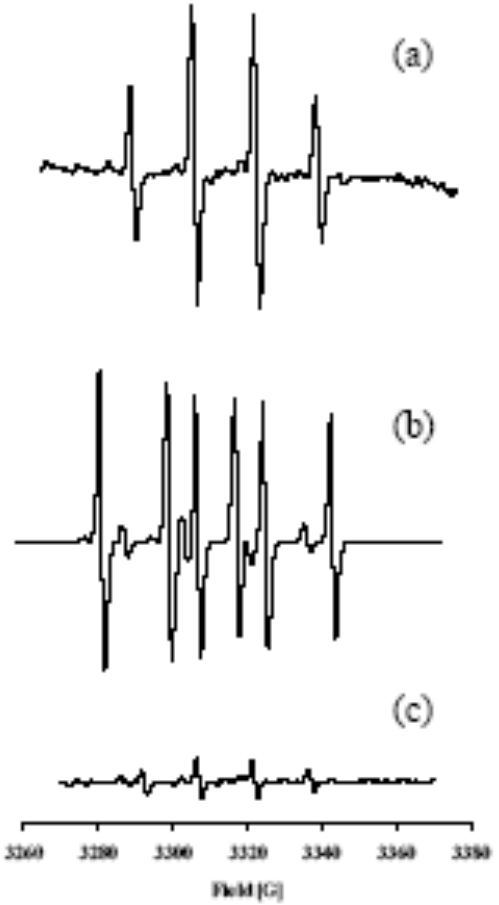
DMPO-OH spin adduct formed by the irradiation of the dihydroxo complex

DMPO



$DMPO\text{-}CH_3$ spin adduct by irradiation of the complex in presence DMSO

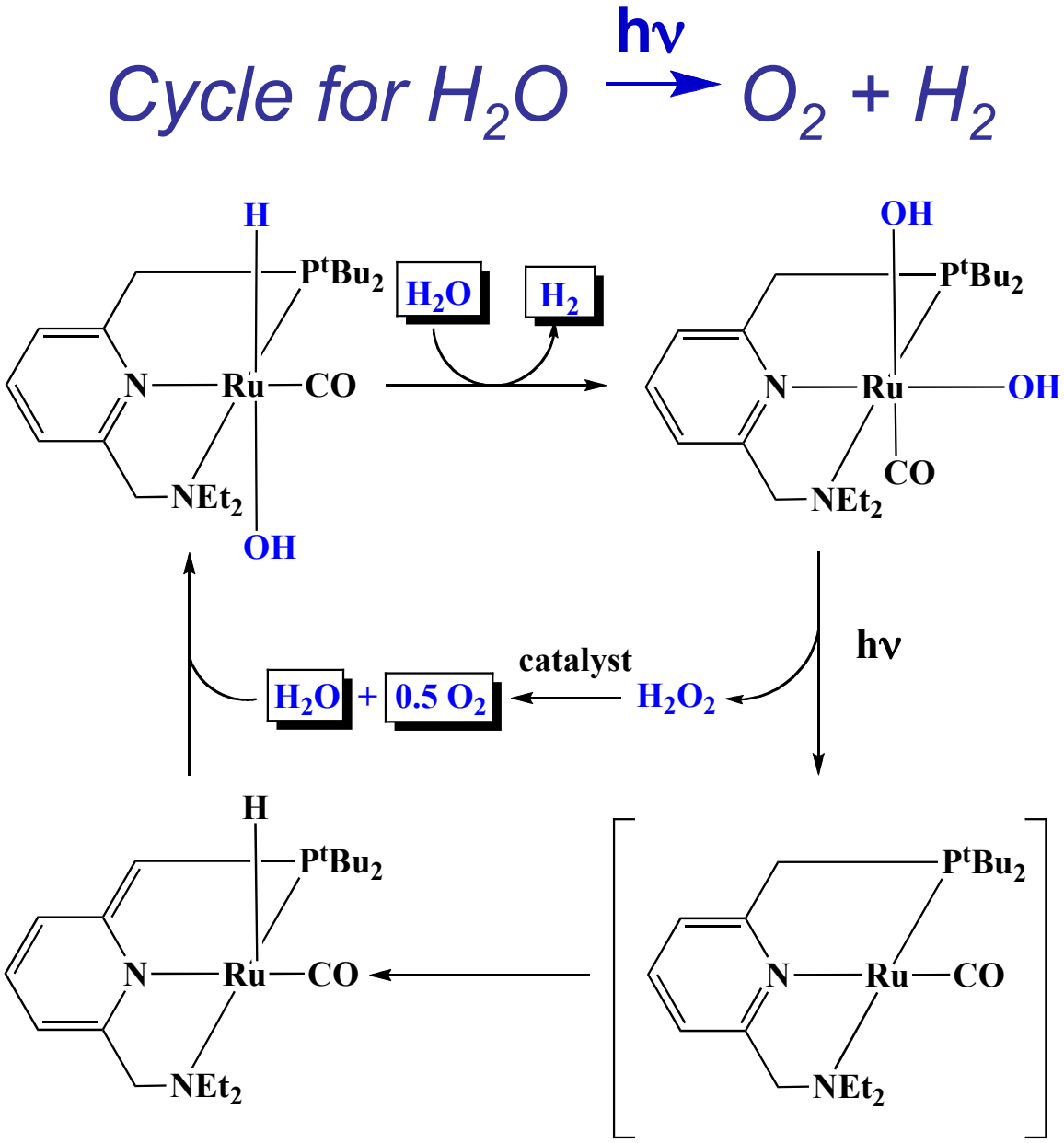
Irradiation in the presence of Catalase (~10^{-10}M)



Lev Weiner

O_2 liberation not affected by addition of hydroxyl radical traps (butanol, THF)

Hydroxyl radicals (formed from H_2O_2 side reaction) not involved in O_2 formation.



S. W. Kohl, L. Weiner, L. Schwartsburd, L. Konstantinovski, L. J. W. Shimon, Y. Ben-David, M. A. Iron, D. Milstein

Science, **2009**, *324*, 74

Summary
Metals and Ligands Acting in Concert

Design of "green" catalytic reactions:

* *Coupling of alcohols to form esters and H_2*
* *Mild hydrogenation of esters*
* *Conversion of alcohols to acetals and H_2*
* *Selective synthesis of primary amines from alcohols and ammonia*
* *Coupling of alcohols with amines to form amides and H_2*

A new approach towards water splitting:

* *Consecutive thermal H_2 , light induced O_2 generation*
* *O-O bond formation: intramolecular, single metal center, M=O not required*

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