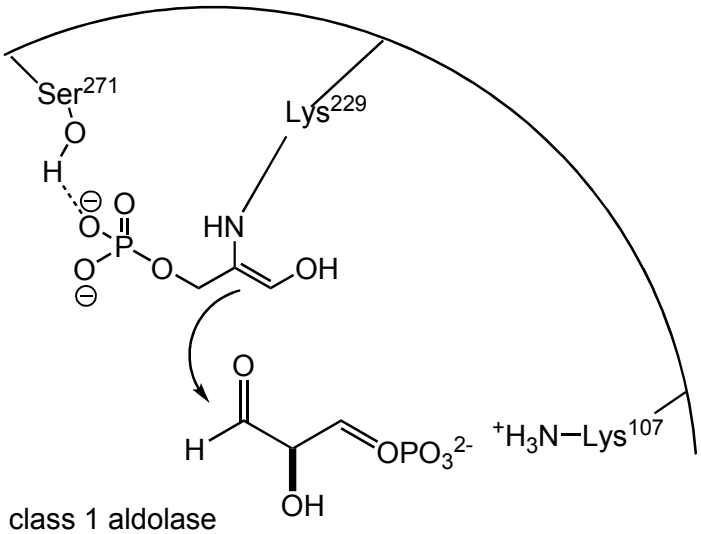
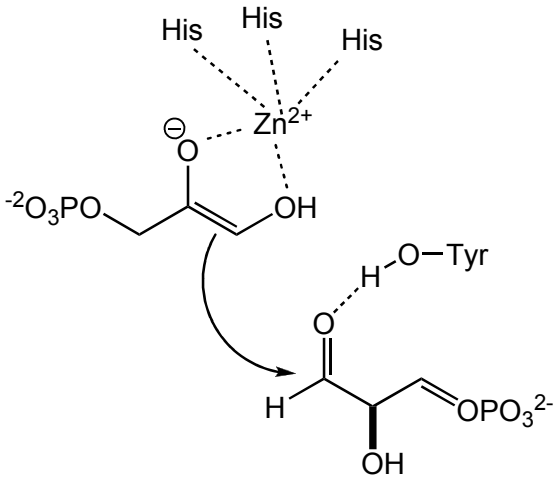
Reversible Interaction between Substrate and Ligand

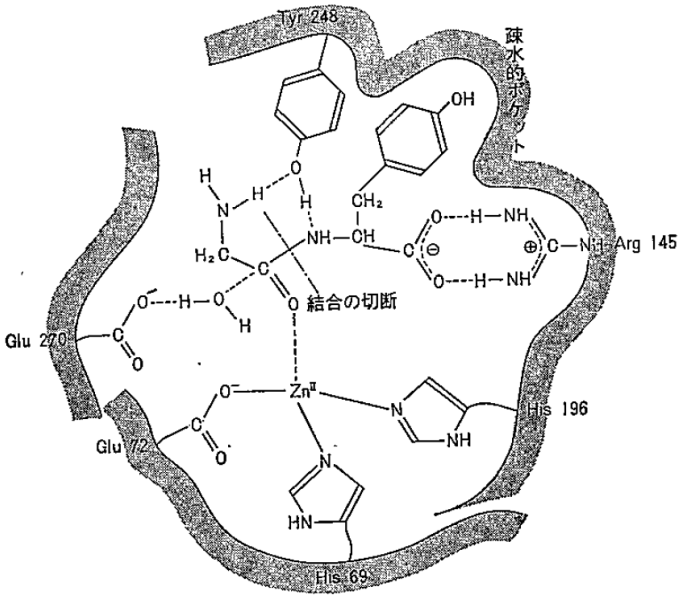
2010. 6. 9. Yohei Shimizu (D3)



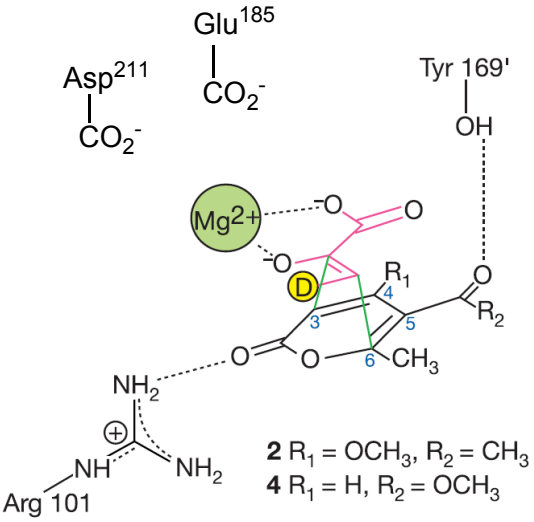
class 1 aldolase



class 2 aldolase



carboxypeptidase A



macrophomate synthase
(*Nature*, **2003**, *422*, 185.)

High substrate selectivity
(specific interaction in the active site)

Enzyme ⇕

Low substrate generality

⇨ **Mimic active site of enzyme with wide substrate generality.**

Contents

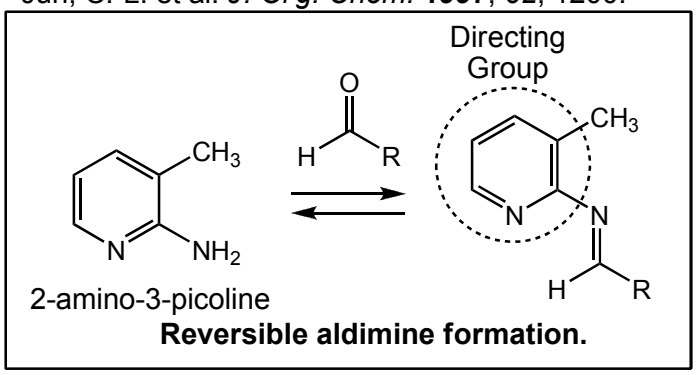
Reversible directing group with covalent bond

Noncovalent bond interaction between substrate and ligand

Reversible directing group with covalent bond

Utilize aldehyde/imine equilibrium for temporal directing group.

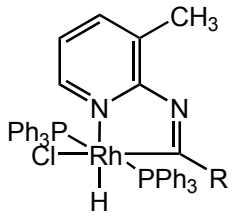
Jun, C.-L. et al. *J. Org. Chem.* **1997**, *62*, 1200.



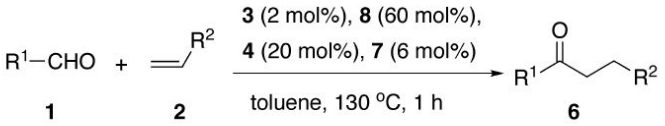
2-amino-3-picoline

Reversible aldimine formation.

for catalytic hydroacylation



Suggs, J. W.
J. Am. Chem. Soc. **1979**, *101*, 489.

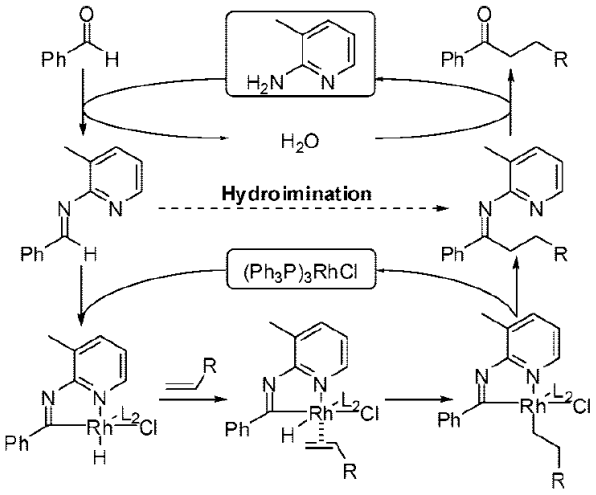


1 2 6

Entry	R^1 (1)	R^2 (2)[a]	Product	Yield [%][b]
1	Ph (**1a**)	*n*-C_4H_9 (**2a**)	**6a**	98 (100)
2	Ph (**1a**)	*n*-C_3H_7 (**2b**)	**6b**	83 (86)
3	Ph (**1a**)	*n*-C_6H_{13} (**2c**)	**6c**	99 (100)
4	Ph (**1a**)	*t*Bu (**2d**)	**6d**	84 (87)
5	Ph (**1a**)	Me_3Si (**2e**)	**6e**	95 (100)[c]
6	Ph (**1a**)	C_6F_5 (**2f**)	**6f**	98 (100)[d]
7	Ph (**1a**)	$PhOCH_2$ (**2g**)	**6g**	95 (100)[d]
8	*p*$MeOC_6H_4$ (**1b**)	*n*-C_4H_9 (**2a**)	**13**	79 (80)
9	*p*$CF_3C_6H_4$ (**1c**)	*n*-C_4H_9 (**2a**)	**6h**	71 (86)
10	*p*$Me_2NC_6H_4$ (**1d**)	*n*-C_4H_9 (**2a**)	**6i**	60 (64)
11	PhC_6H_4 (**1e**)	*n*-C_4H_9 (**2a**)	**6j**	95 (98)
12	$PhCH_2CH_2$ (**1f**)	*n*-C_4H_9 (**2a**)	**6k**	71[e]

[a] Five equivalents based on aldehyde were used. [b] Yield of product after isolation; GC yields are given in parenthesis. [c] 1.1 equivalents of **2e** was used. [d] Reaction time was 40 min. [e] 10% of the aldol condensation product of **1f** was obtained.

3: $Rh(PPh_3)_3Cl$ 4: 2-amino-3-picoline
7: benzoic acid 8: aniline

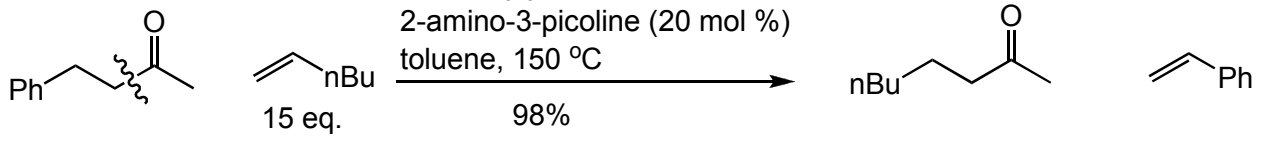


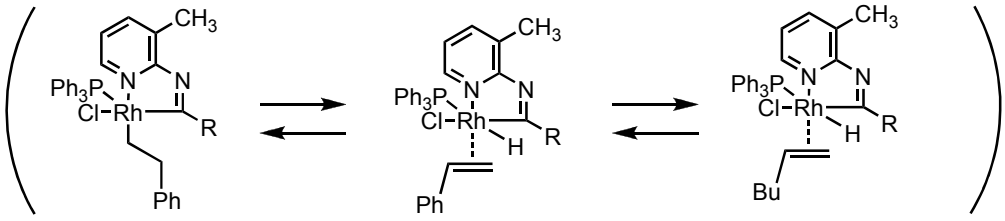
Jun, C.-L. et al.
Angew. Chem. Int. Ed. **2000**, *39*, 3070.

Without 2-amino-3-picoline, decarbonylation was serious problem.
Benzoic acid accelerated imine formation.
Aniline accelerated imine formation via transimination.

Application of this catalyst to other reactions.

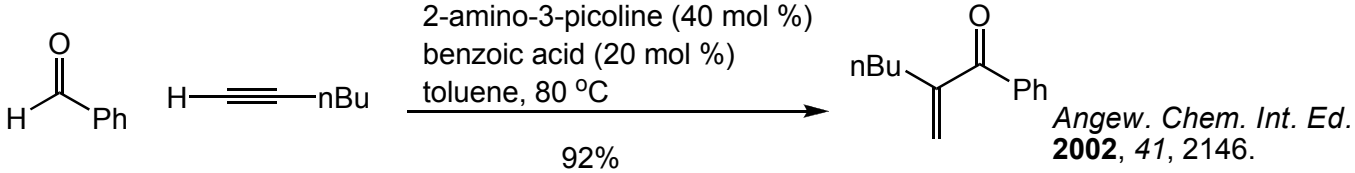
C-C bond activation





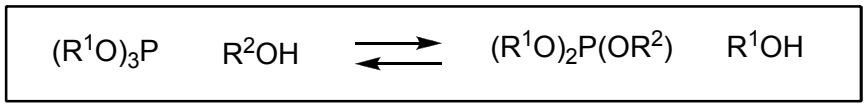
J. Am. Chem. Soc, **1999**, *121*, 880.

hydroacylation of alkynes



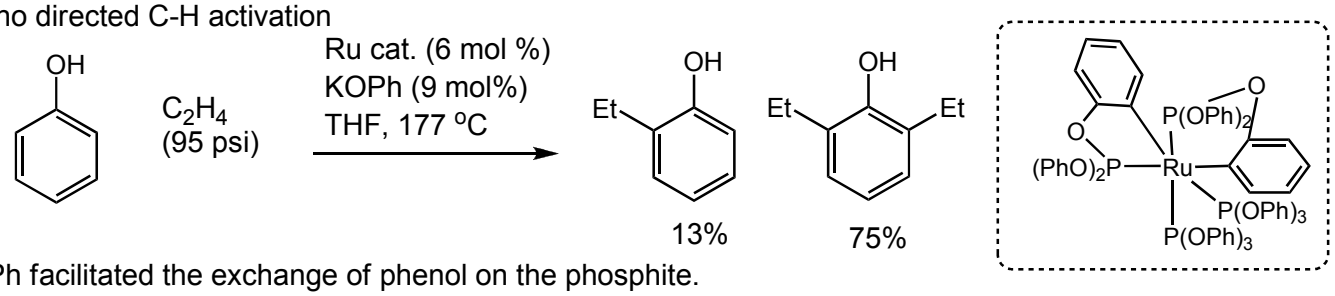
Angew. Chem. Int. Ed. **2002**, *41*, 2146.

Phosphite as reversible directing group

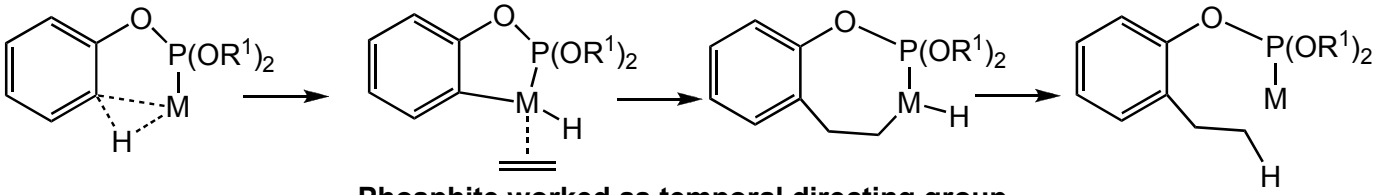


Lewis, N. L. et al. *J. Am. Chem. Soc.* **1986**, *108*, 2728.

Ortho directed C-H activation



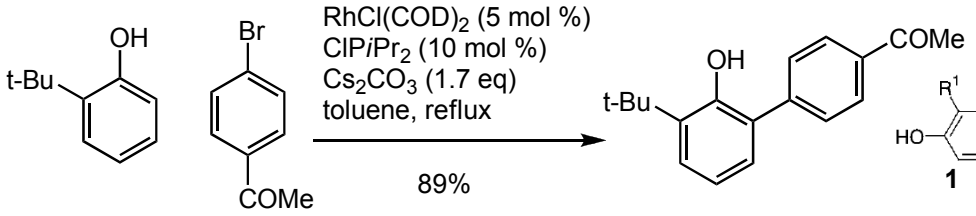
KOPh facilitated the exchange of phenol on the phosphite.



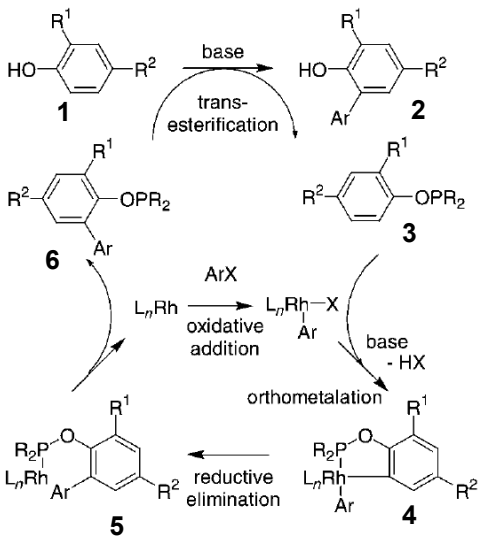
Phosphite worked as temporal directing group.

Recent application of this type of reversible directing group.

Orthoarylation via directed C-H activation

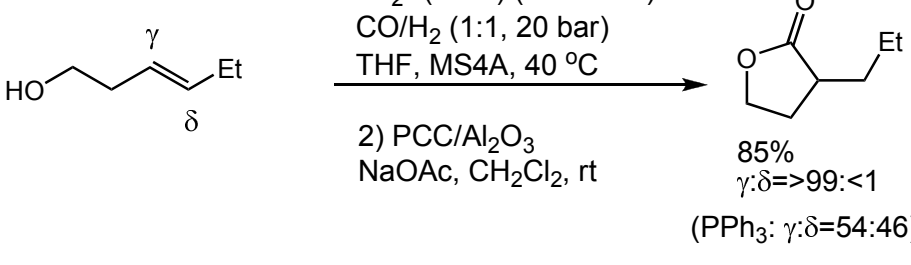


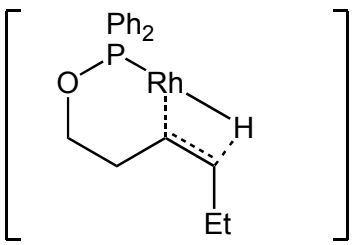
Phosphinite did the same work as phosphite.
To prevent contamination derived from phosphinite, substrate derived phosphinite was generated in situ.



Bedford, R. B. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 112.

Directed hydroformination

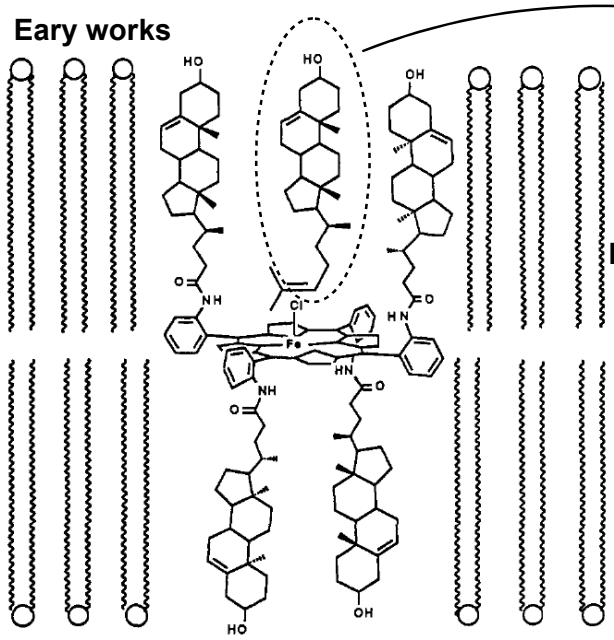




Breit, B. et al *Angew. Chem. Int. Ed.* **2008**, *47*, 7346.

Noncovalent bond interaction for molecular recognition

Eary works



organized space for specific substrate

lipid bilayer

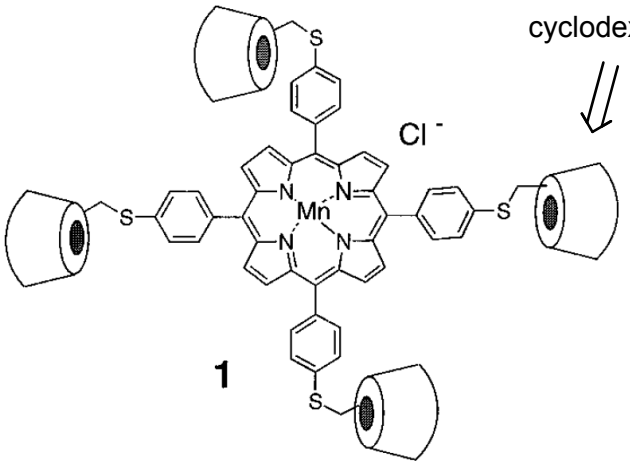
Epoxidation occured only at the olefin of the side chain.

Steroid attached porphirin catalyst in phospholipid bilayer organize rigid environmet which restrict the entrance of substrates.
Low catalyst efficiency because of strong product binding.

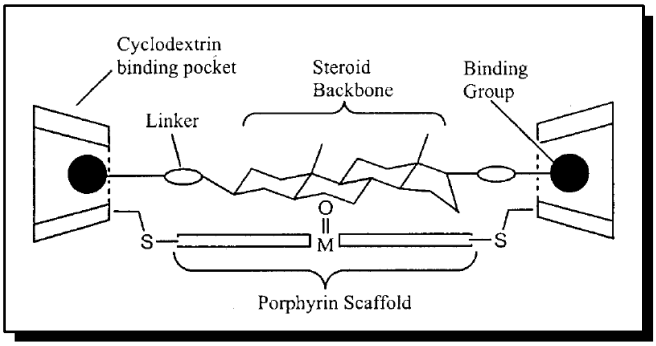
Groves, J. T. et al. *JACS*, **1987**, *109*, 5045.

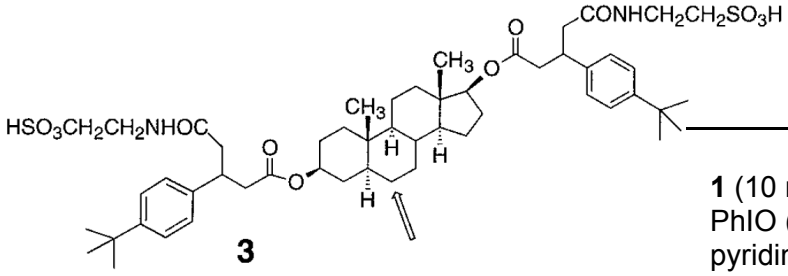
Early successful work by Breslow group.

cyclodextrin ⟹ Recognize hydrophobic group.
Fix substrate at appropriate position.
Release products (reversible interaction).



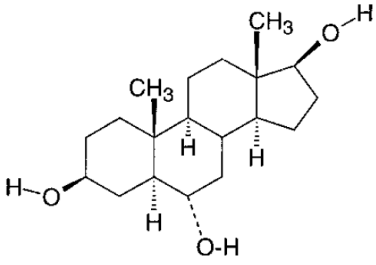
1





3

1 (10 mol %)
PhIO (5 eq.)
pyridine, H_2O;
KOH aq.



4
ca. 40%

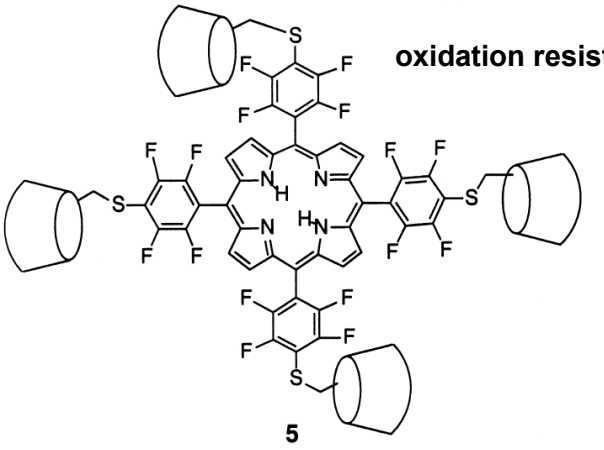
only 4 turnover

no oxidation without binding group
no over oxidation to ketone
>2 cyclodextrin was necessary to fix the substrate.

Problem: oxidation of porphyrin core under the condition ⟹ perfluorination

addition of excess of pyridine

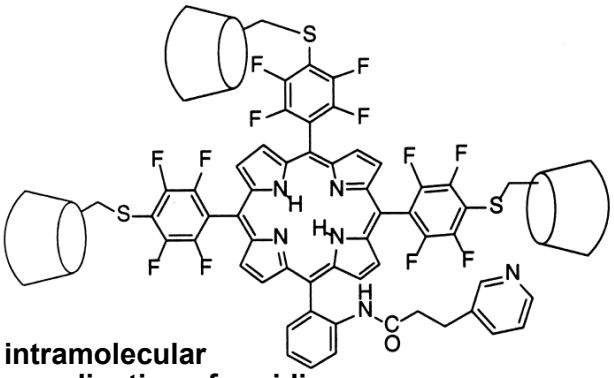
(Coordinates to Mn. (like thiolate in P450 system)
Directs oxigen and substrates to the other side.) ⟹ attachment of pyridine moiety on porphyrin



oxidation resistent core

5

0.1 mol% of cat. => 187 turnover
1 mol% of cat. => 95 turnover

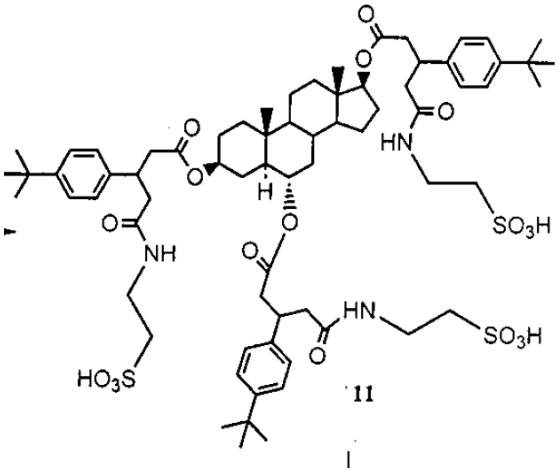


intramolecular coordination of pyridine

6

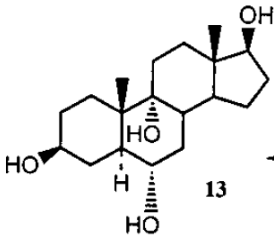
0.02 mol% of cat. => 2000 turnover

Change the oxdation site.



11

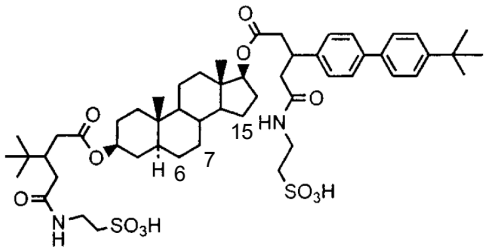
5 (10 mol %)
PhIO (5 eq.)
pyridine, H_2O;
NaOH aq.



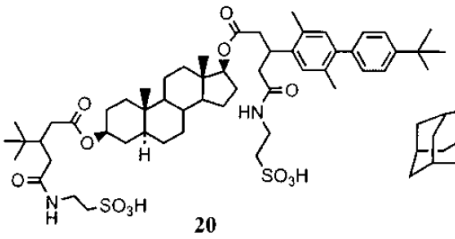
13

Third binding group
effeciently changed the regioselectivity.

Different binding groups also changed the regioselectivity.

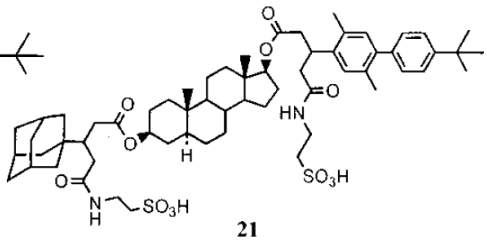


6α:7β:15α=1:3:1



20

6α:7β:15α=1:0:1



21

6α:7β:15α=1:1:2

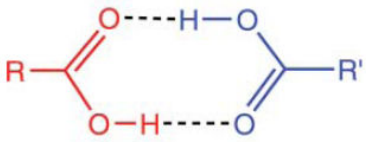
Flexible moving of binding group in CD resulted in low selectivity?

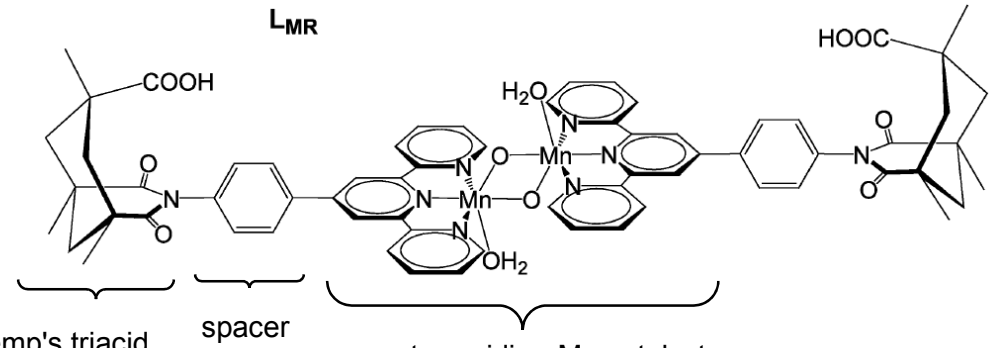
Hydrogen bond based recognition

Crabtree, R. H.; Brudvig, G. W. et al. succeeded in developing effecient molecular recognitioncatalyst.

Science, **2006**, *312*, 1941.

recognition mode
(two point hydrogen bond)





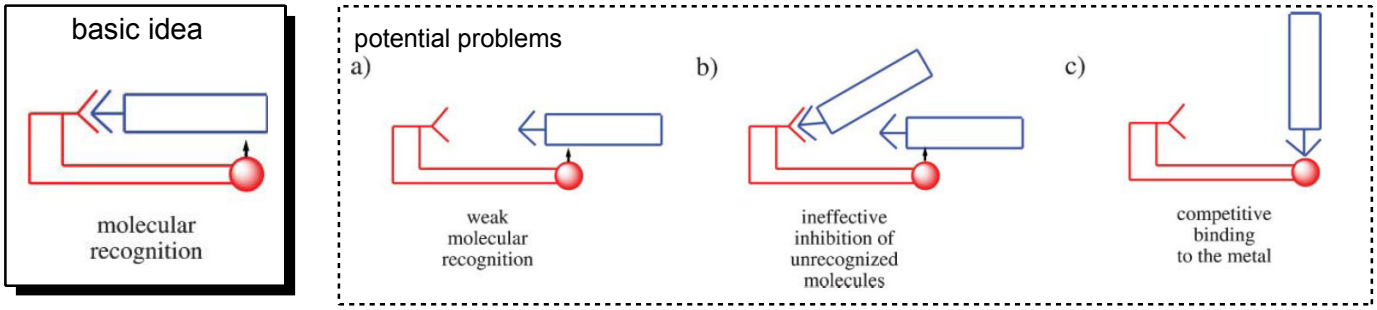
Kemp's triacid recognition site

spacer

terpyridine-Mn catalyst

originally developed for H_2O oxidation catalyst
oxdation resistant framework
high oxidation ability

Crabtree, R. H.; Brudvig, G. W. et al. *Science*, **1999**, *283*, 1524.



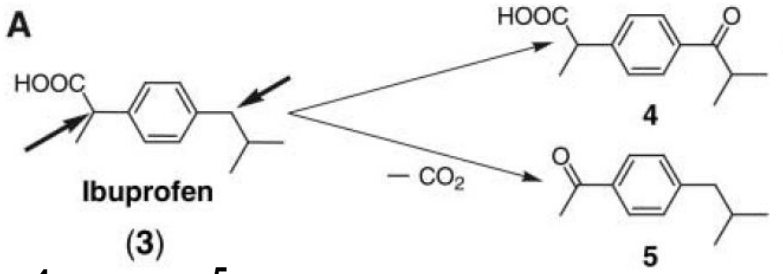
CO_2H-CO_2H hydrogen bonding => two point binding
inhibit the rotation of the substrate
Kemp's triacid U-turn motif => reasonably rigid
maintain low pKa condition => avoid calboxylate anion (potential ligand of center metal)

Ibuprofen as substrate

condition

CH_3CN, Oxone (5 eq.)
terpy-Mn cat. (1 mol%)

1b: recognition cat.
1c: lacking Kemp's triacid



	Temperature	Catalyst	Conversion	4 (Favored by recognition)	5 (Disfavored by recognition)	turnovers*
1	20°C	**1b**	50%	97.5%	2.5%	50
2		**1c**	53%	77%	23%	53
3	0°C	**1b**	53%	98.5%	1.5%	53
4		**1c**	54%	78%	22%	54
5	−20°C	**1b**	53%	98.5%	1.5%	53
6		**1c**	54%	77%	23%	54
7	20°C	**1b**†	56%	75%	25%	56
8		**1c**†	58%	77%	23%	58
9	0°C	**1b**§	58%	98.5%	1.5%	580
10	20°C	**1b**‡§	71%	96.5%	3.5%	710

*Total turnovers = mol products per mol catalyst; subtrate:catalyst:oxidant = 100:1:500. †Solutions contained excess acetic acid (400% with respect to substrate). ‡With CD_3CN as solvent instead of CH_3CN. §Subtrate:catalyst:oxidant = 100:0.1:500.

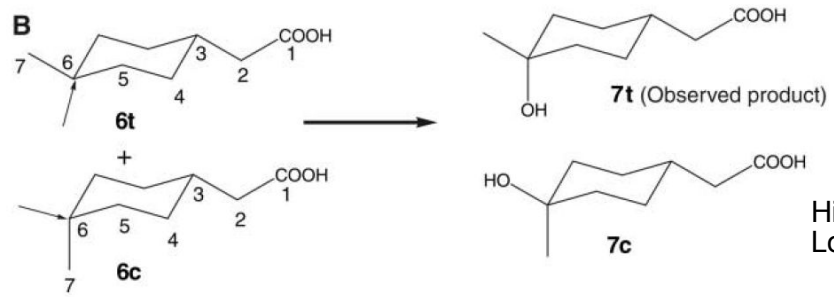
Competitive inhibition of recognition. (4eq. AcOH)

Low cat. loading prevent bimolecular self oxidation of cat.

CD_3CN is more oxidation resistant.

High regioselectivity was achived by molecular recognition catalyst.

(4-methylcyclohexyl) acetic acid



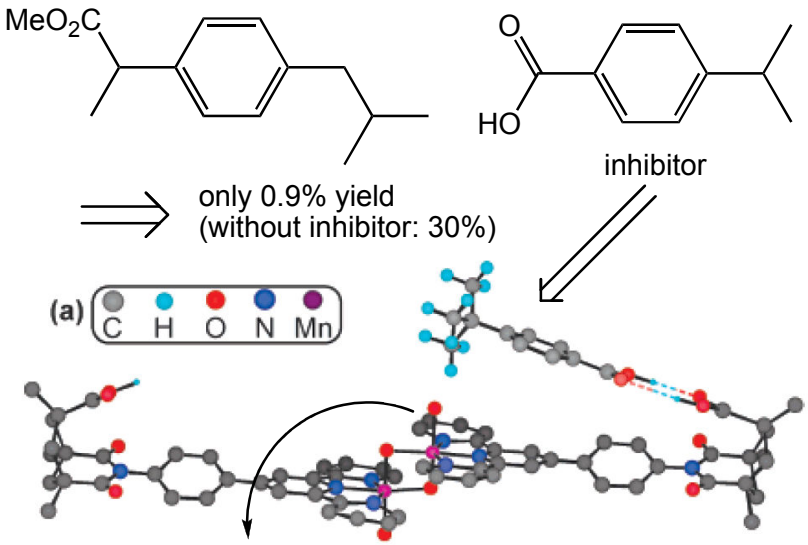
High regioselectivity and stereoselectivity.
Low conversion...

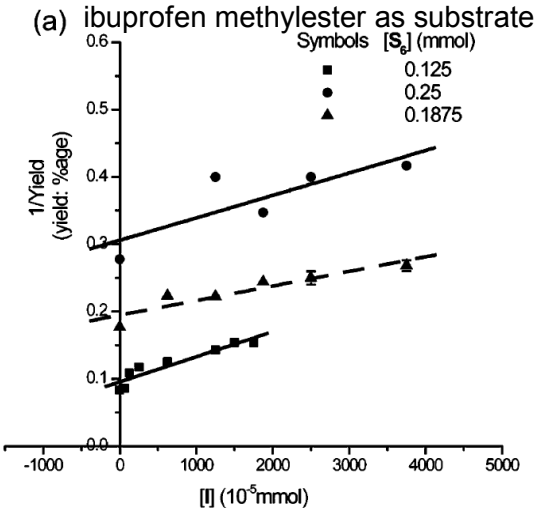
Temperature	Catalyst (0.1%)	Conversions	7t (favored)	7c (disfavored)	Other products	Total turnovers*
20°C	**1b**	13%	>99%	<1%	<1%	130
20°C	**1c**	~19%	~30%	~30%	~40%	190
20°C	**1b**†	18%	>99%	<1%	<1%	180

*Total turnovers = mol products per mol catalyst; subtrate:catalyst:oxidant = 100:0.1:500. †With CD_3CN as solvent instead of CH_3CN.

Inhibition by 4-tert-butyl benzoic acid ~How was background reaction suppressed?~

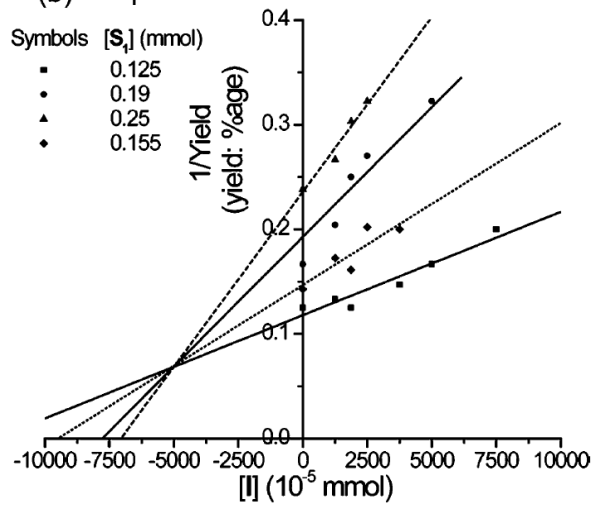
ibuprofen methylester





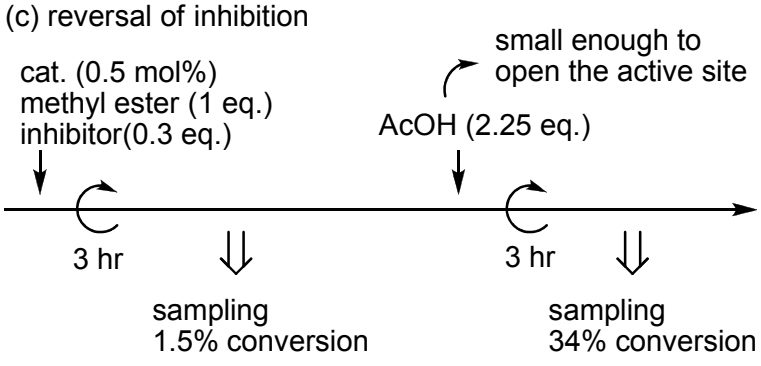
uncompetitive inhibition

(b) ibuprofen as substrate



competitive inhibition

(c) reversal of inhibition



These result suggested that
catalyst recognize carboxylic acid
reversible binding
active site was sterically inhibited

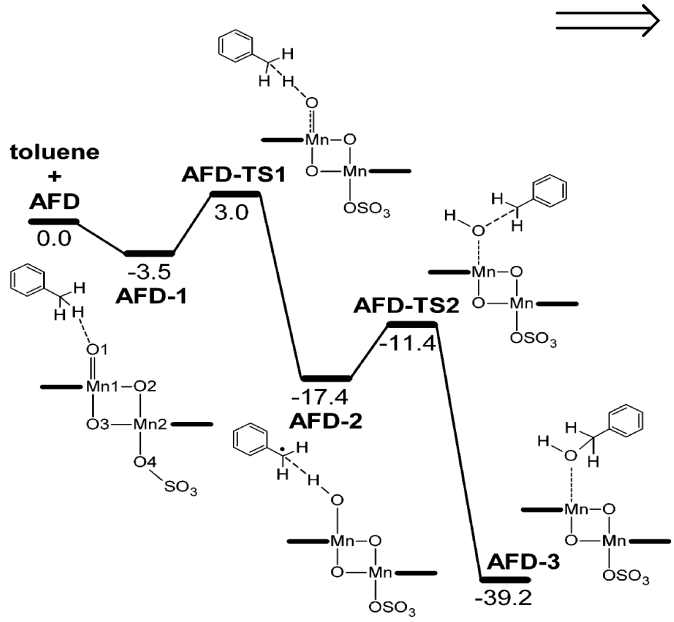
H abstraction-rebound mechanism

DFT calculation

$[(terpy)Mn(O)(\mu\text{-}O)Mn(SO_4)(terpy)]^+$

longer Mn-O bond (1.80~1.91 A compared to Mn=O: 1.60 A)
high spin dencity on O

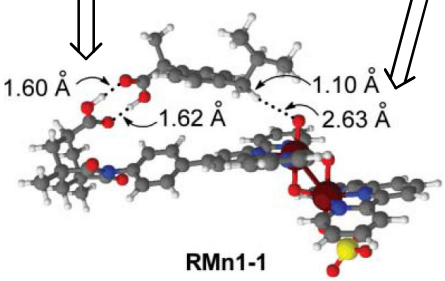
⟹ reactive center has a Mn^{IV}-O· character

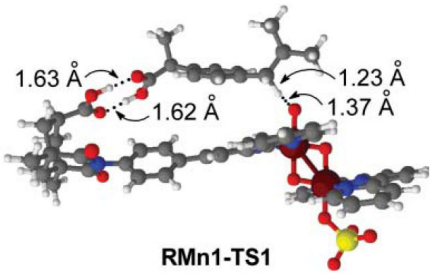


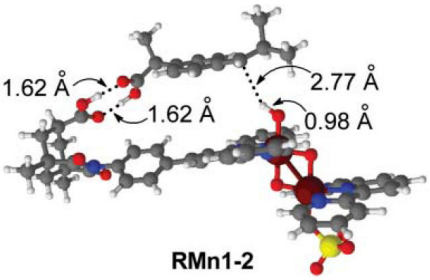
H abstraction step and rebound step are exothermic.
Energy barrier is low.
(6.5 kcal/mol for H abstraction)

hydrogen bond

C-H ------ · O-Mn







oxidized C-H bond
is relatively far from active site

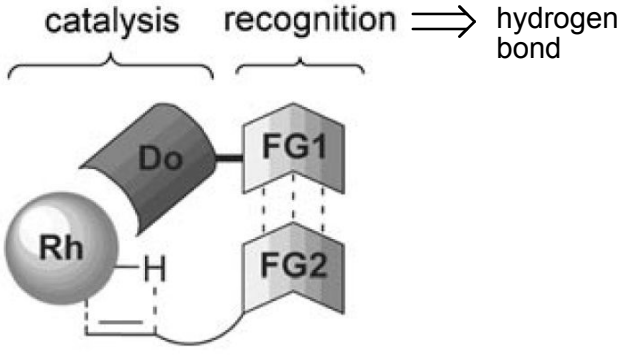
C-H can reach the active site
without losing recognition

⟹ The catalyst has enough flexibility enabling the approach of the substrate to the active site.

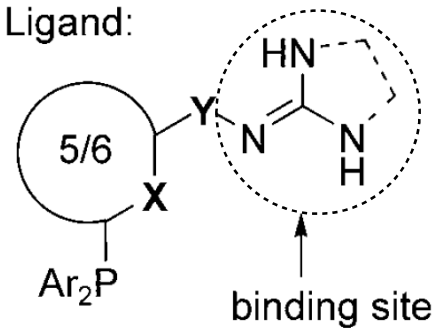
Feature of this catalyst
Suppresses the background reaction.
Catalyst has reasonable rigidity and flexibility.

Other than oxidation catalyst

Breit, B. et al. used similar approach to phosphine ligand.



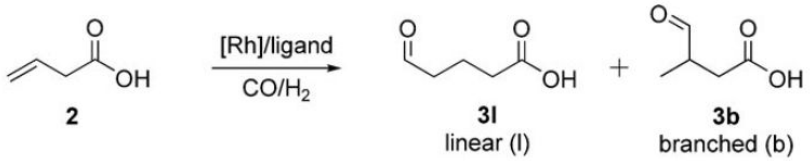
⟹ hydrogen bond

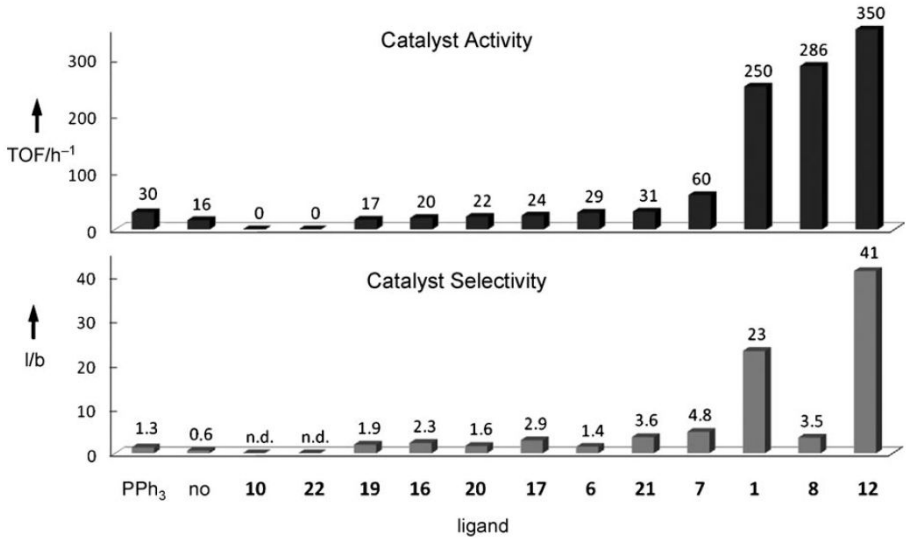


recognize carboxylic acid

target reaction: hydroformination

Linear/branch selectivity could be observed using proper ligand.

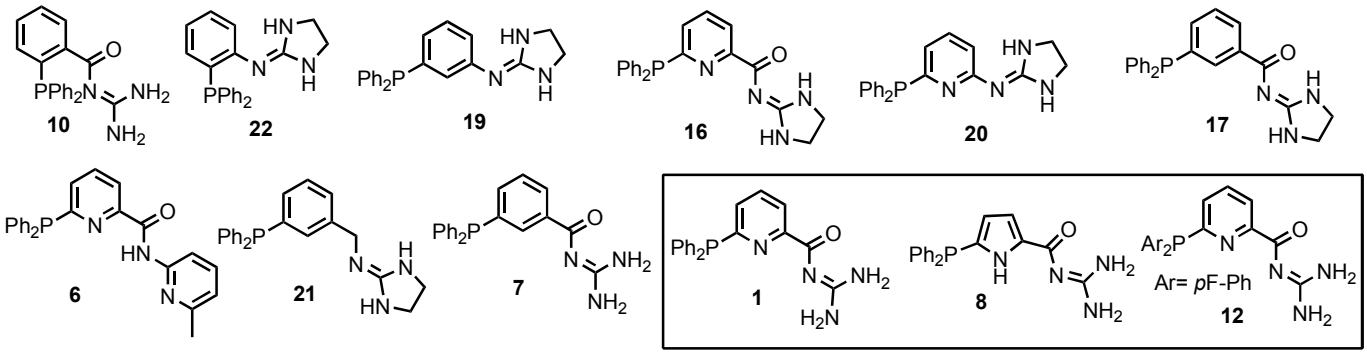




Ligand	v_L(rel)	v_B(rel)
PPh_3	1	0.77
1	14.13	0.61

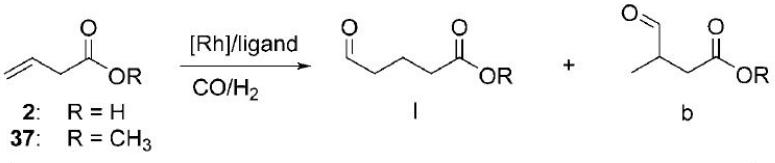
v_L: rate of linear product
v_B: rate of branched product

Only the lenear selective transition state was accelerated by the recognition catalyst.

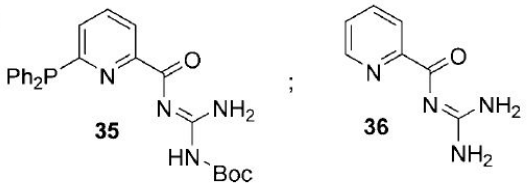


free guanidine > cyclic guanidine (**1** vs **16**) meta > ortho (**7** vs **10**) pyridine ring > benzene ring (**1** vs **7**)

control experiments



ligands:



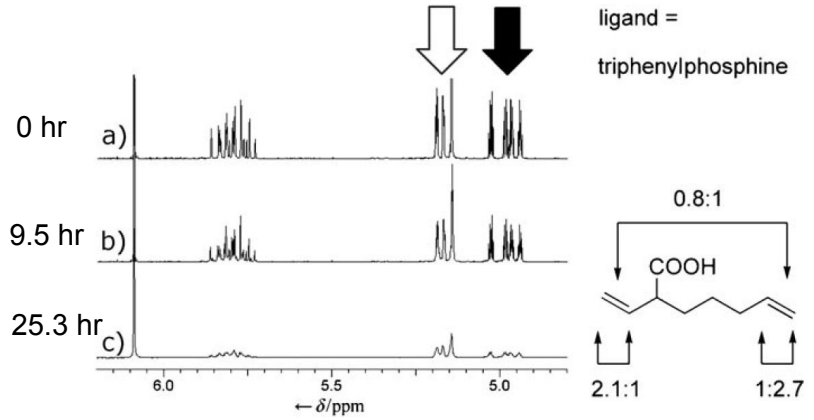
Entry	Ligand	Substrate	Conversion [%]	Regioselectivity [l/b ratio]	TOF [h^{-1}]
1	**1**	**2**	100	23	250
2	**35**	**2**	77	1.4	50
3	PPh_3/**36** (1:1)	**2**	20	1.5	12
4[b]	**1**	**37**	50	1.1	29
5	**1**	**37**/AcOH (1:1)	58	1.4	34

[a] [Rh(acac)$(CO)_2$]/ligand/substrate = 1:10:200, c_0(substrate) = 0.2 M, THF (2 mL), 10 bar CO/H_2 (1:1), 40 °C, 4 h; [b] Suspension (ligand **1** is practically insoluble in the reaction medium without a carboxylic acid); all other runs were clear solutions.

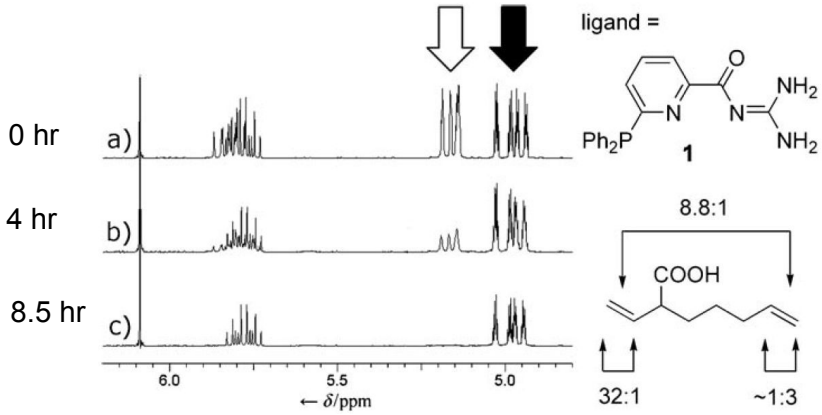
entry3: Ligand moiety and recognition moity should be in the same molecule.

entry4, entry5: Catalyst recognize the carboxylic group. It should be in the same molecule as the substrate.

differenciation of two terminal olefins



Both terminal olefin reacted almost same rate. Linear/branch selectivity was poor.



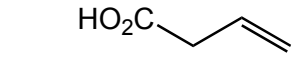
Reaction rate of each olefin was significantly different (8.8:1).
And linear/branch selectivity was also excellent.

Only the reaction at β,γ-unsaturated carboxylic group was accelerated by the recognition catalyst.

This system showed rate dependent differenciation.

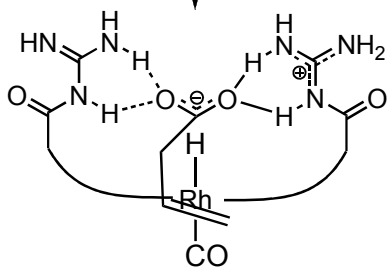
Direction of hydrogen bond is desirable in TS.

DFT calculation of hydrometalation step

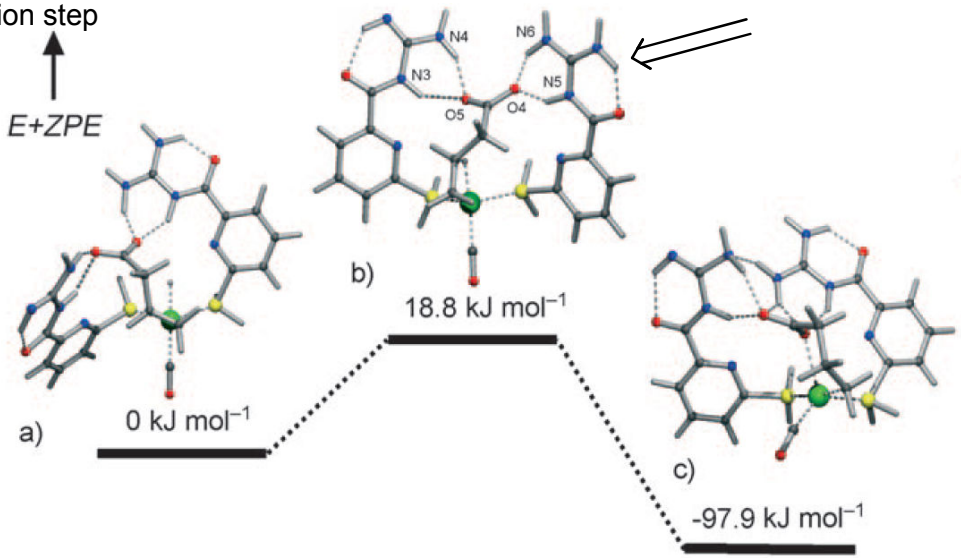


2 **Ligand 1**

$Rh(acac)(CO)_2$



E+ZPE



Carboxylic acid formed hydrogen bond with both guanidine ligands.

Rotation of the alkene is the main cause of activation energy. (assisted by hydrogen bonding)

One point hydrogen bonding resulted in higher activation energy.

Molecular recognition catalyst still need to be investigated.
Substrate generality is still limited.
Reaction pattern is also limited.