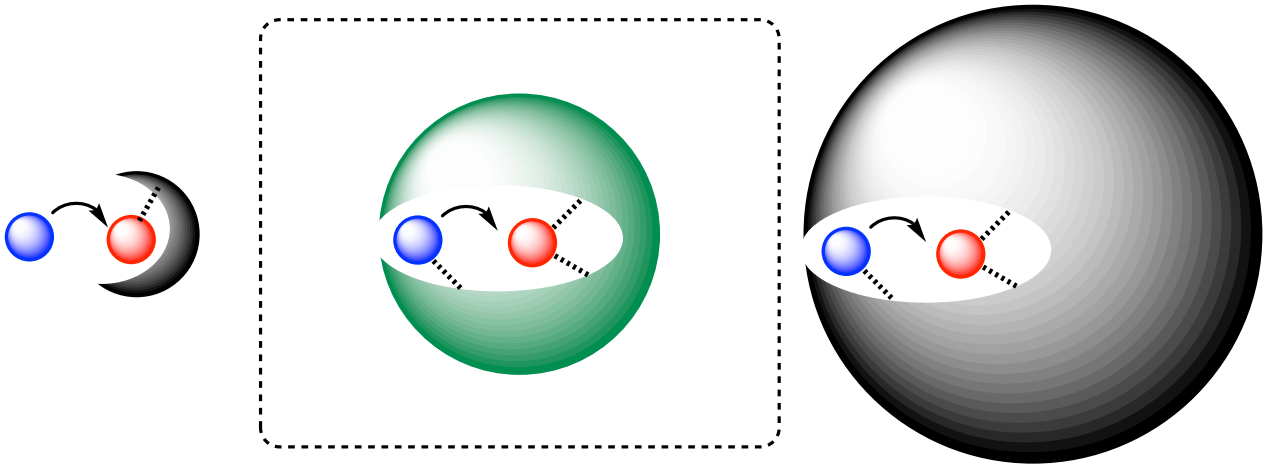
Middle molecule catalysis toward unique selectivities



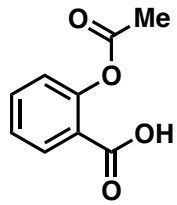
2021/ 11/ 27 (Sat)
Kai MATSUI

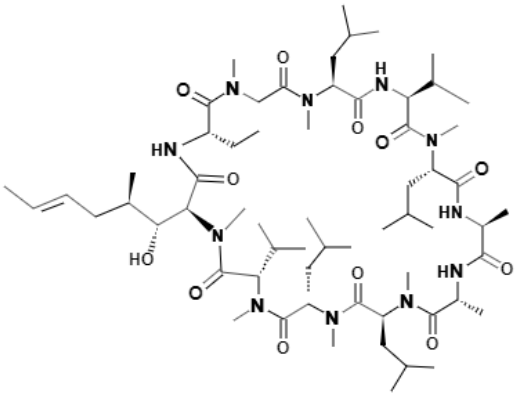
Contents

1. Introduction

1-1. Definition of middle molecule

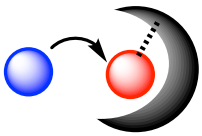
cf. Middle molecule drug

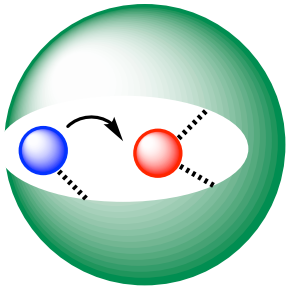


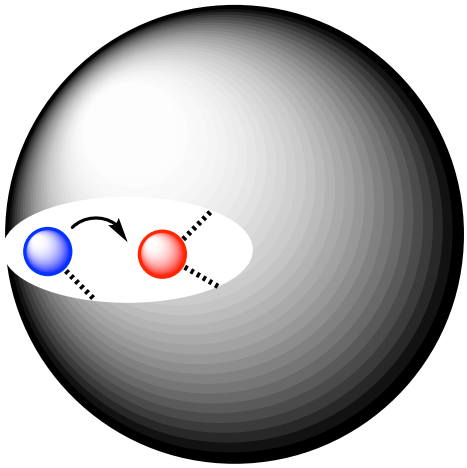


	Small molecule drug e.g. Aspirin etc. Mw: ~500 "Lipinski's rule of five"[1)]	Middle molecule drug e.g. Cyclic peptide, Nucleic acid Mw: 500~3000	Macromolecule drug e.g. Antibody Mw: 10000~
Organic synthesis	◎	○	×
Target selectivity	△	○	◎
Side effect	△	○	◎

Middle molecule catalyst







Small molecule catalyst conventional catalyst Mw: ~1000	Middle molecule catalyst Mw: 1000~3000	Macromolecule catalyst e.g. Enzyme Mw: 10000~

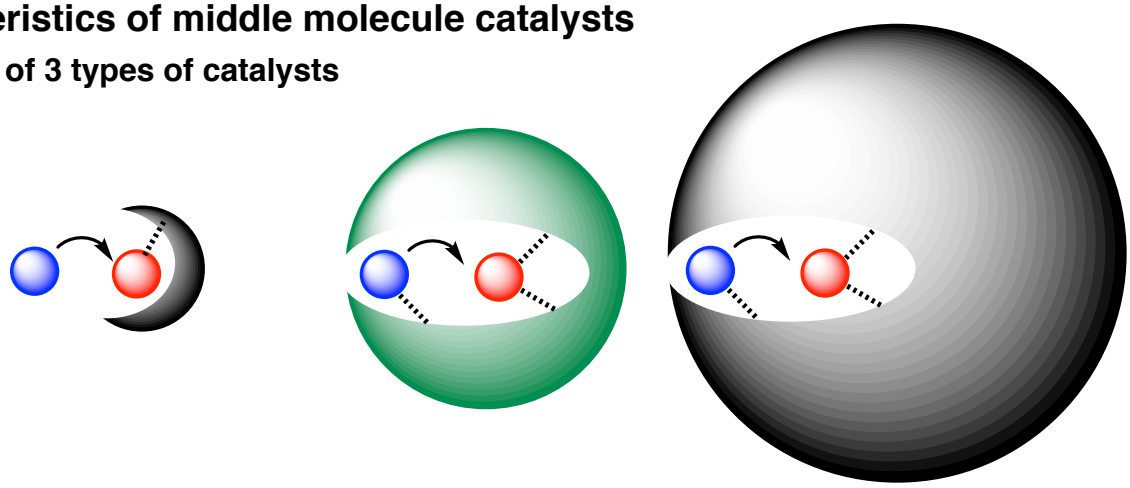
Refference

1) CA Lipinski, Adv. Drug Del. Rev. 1997, 23, 3

1. Introduction

1-2. Characteristics of middle molecule catalysts

Compariosn of 3 types of catalysts



	Small molecule catalyst	Middle molecule catalyst	Macromolecule catalyst (enzyme)
	Mw: ~1000	Mw: 1000~3000?	Mw: 10000~
Organic synthesis	◎	○ Multi-step synthesis needed (single molecule catalyst)	× Biosynthesis only
Reaction control (selectivity)	△ 1(or 2) selectivity can be controlled	○? Multi-selective? enantio-, diastero- regio-, reaction- etc	◎ Multi-specific enantio-, diastero- regio-, reaction- etc Advanced substrate recognition
Reaction condition	Organic solvent low to high temp.	Organic solvent low to high temp.	water around RT
Ratio of active site	◎	○	△

1-3. Requirements for middle molecule catalysts

Performance/Mw　　Mw

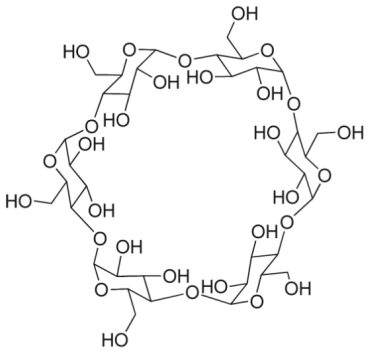
Catalytic function	Low	Middle	High
Low	○	△	△
Middle	◎	○	△
High	◎	◎	○

Not only middle Mw but also the function beyond small molecule catalysts'

⇨ **Artificial enzyme**

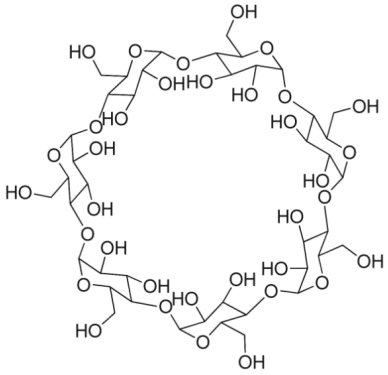
2. Examples of the catalysis based on key structure

2-1 Catalysts including Cyclodexitrin



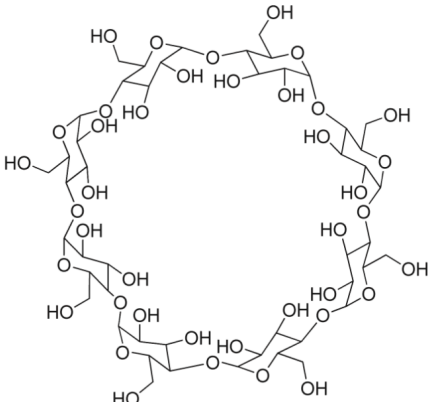
α-cyclodextrin
hexaamylose

Mw: 972.84



β-cyclodextrin
heptaamylose

Mw: 1134.98



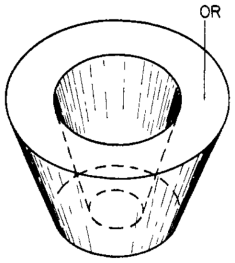
γ-cyclodextrin
octaamylose

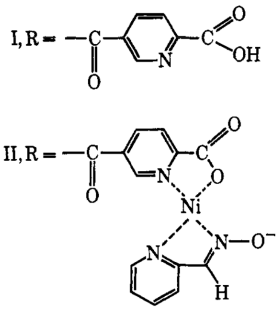
Mw: 1297.12

Outside: hydrophilic
Inside: hydrophobic cavity ⇨ **Enzyme mimic**

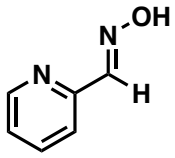
2-1.1 Pioneer work by Breslow (1970)[2)]

Hydrolysis of ester by artificial enzyme

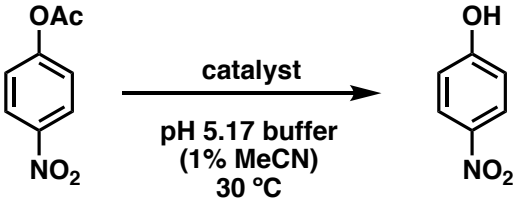




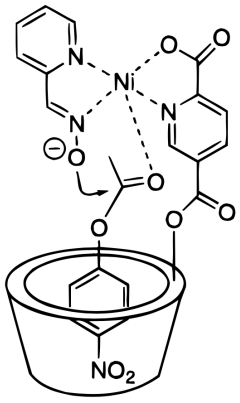
α-cyclodetrin derivative



PCA



catalyst	Relative reaction rate
none	1
$NiCl_2$ + PCA	366
II	1395



- **Rate acceleration by binding of substrate**
- **1st report of catalytic use of CD derivative**
- **Activation of SM without coordination to metal**

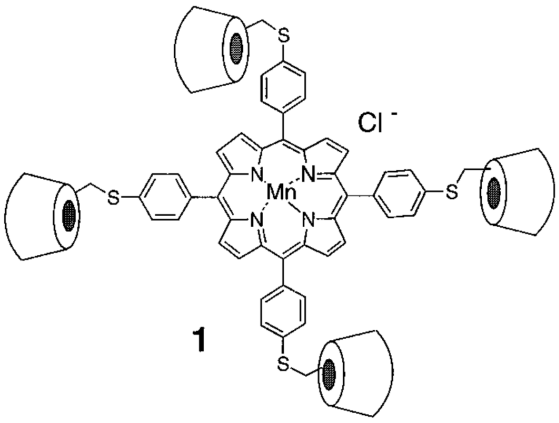
Refference

2) *a)* Breslow. R. *et al. J. Am. Chem. Soc.* **1970,** 92, 1075.
b) Review: Breslow. R. *et al. Chem. Rev.* **1998**, 98, 1997.

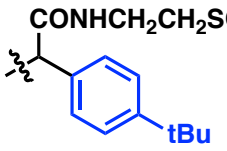
2. Examples of the catalysis based on key structure

2-1 Catalysts including Cyclodexitrin

2-1.2 Siteselective oxidation of steroid by Bresslow (1997)[3)]

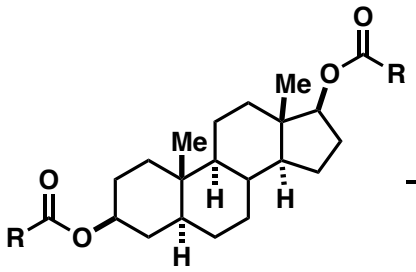


R = $CONHCH_2CH_2SO_3H$



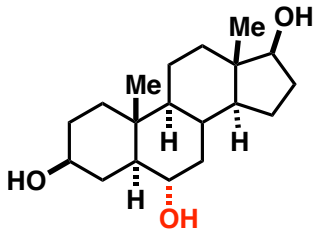
binding to CD

advanced molecular recognition



1 (10 mol%)
iodosobenzene (5 equiv)
py (10 equiv)
H_2O, rt, 2 h

then, hydrolysis

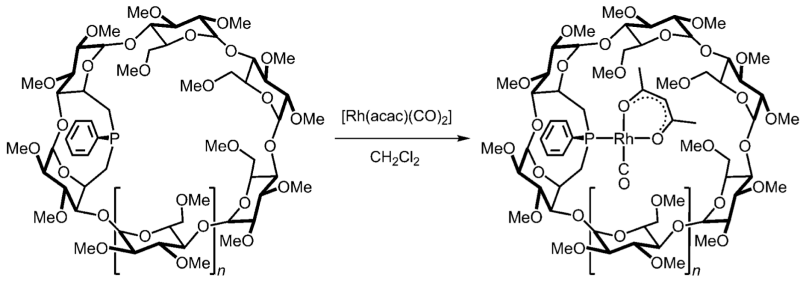


ca. 40% yield

not obtained without $tBu\text{-}C_6H_4$ of R

2-1.3 Regio-, enantioselective hydroformination by Armspach & Matt (2014)[4)]

High isoselectivity is incompatible with high enantioselectivity.[5)]

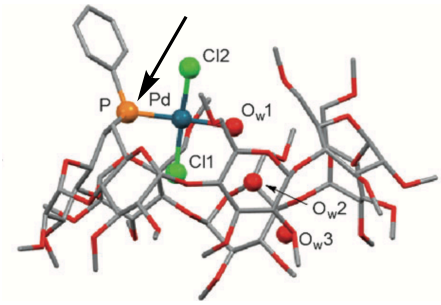


HUGPHOS-1 $n = 1$
HUGPHOS-2 $n = 2$

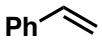
1 $n = 1$
2 $n = 2$

Air stable

Lone-pair is inside cavity

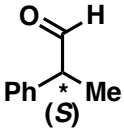


X-ray of $PdCl_2$(HUGPHOS-2)(H_2O)
Purified by C.C.



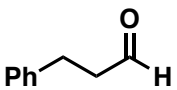
1 (10 mol%)

PhMe
temp., 24 h
H_2 / CO = 1:1 (40 bar)



branched

\+



linear

40 °C	96% yield (90% ee)	3%
20 °C	60% yield (95% ee)	1%

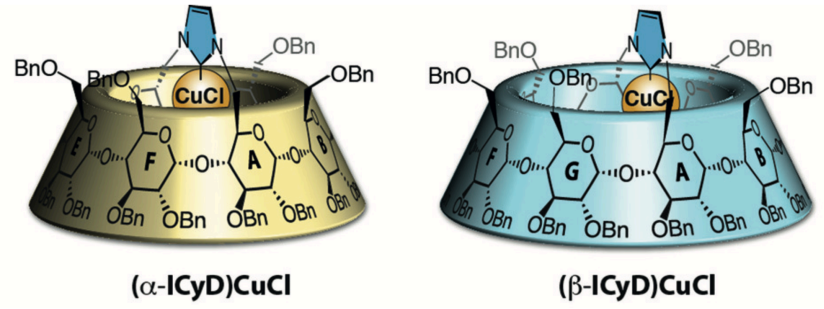
Refference

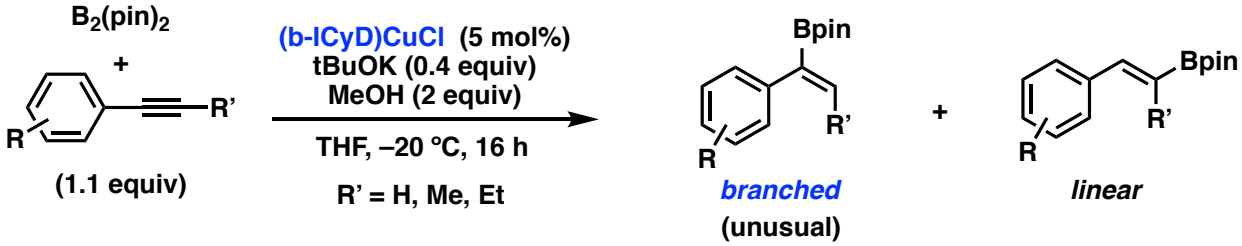
3) Breslow. R. *et al. J. Am. Chem. Soc.* **1997,** *119,* 4535.
4) Armspach. D, Matt. D. *et al. Angew. Chem. Int. Ed.* **2014**, 53, 3937.
5) Börner. A. *et al. Chem.Rev.* **2012**, 112, 5675

2. Examples of the catalysis based on key structure

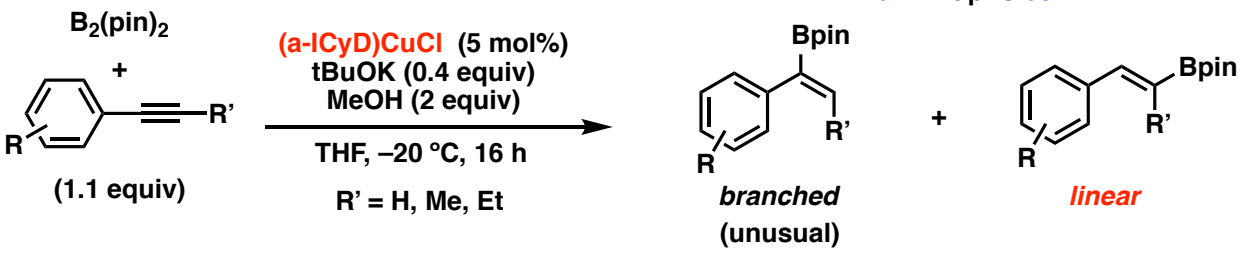
2-1 Catalysts including Cyclodexitrin

2-1.2 Regiodivergent Hydroboration by Sollogoub & Roland (2017)[6)]

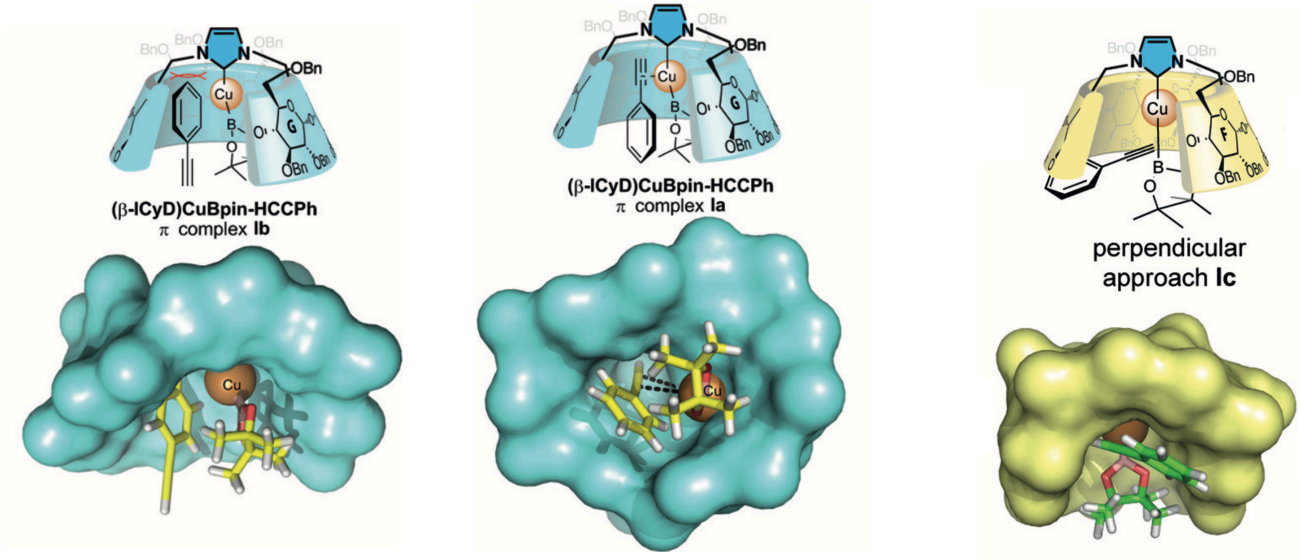




18 examples
up to 87% Yield
b : *l* = up to 98 : 2



18 examples
up to 70% Yield
b : *l* = up to 2 : 98



Refference

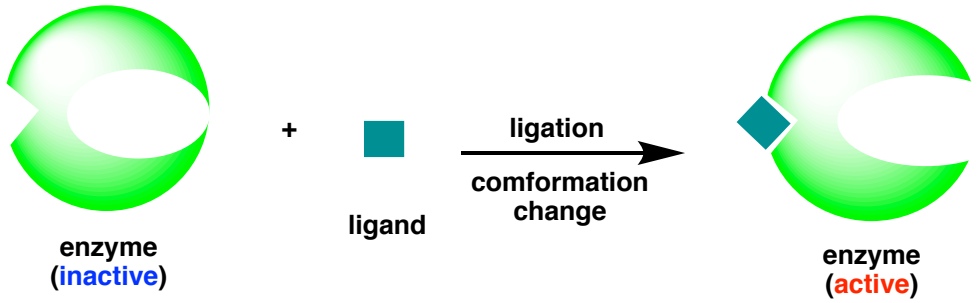
6) Sollogoub. M, Roland. S, *et al. Angew. Chem. Int. Ed.* **2017**, 56, 10821.

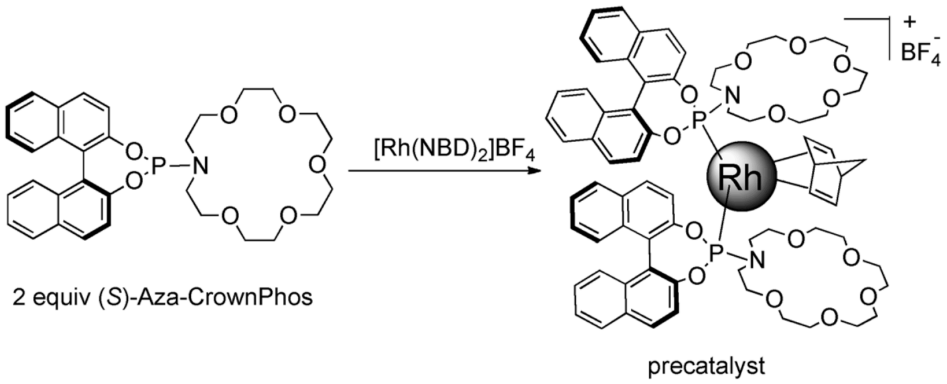
2. Examples of the catalysis based on key structure

2-2 Catalysts including Crown ether

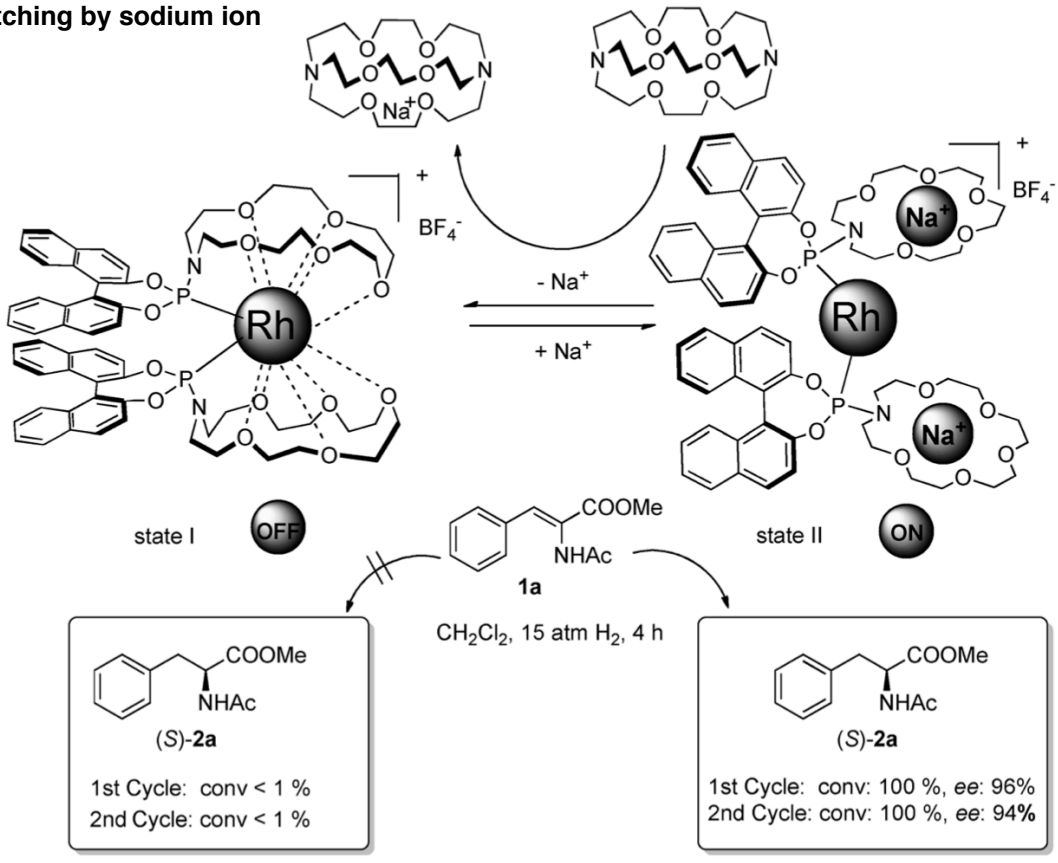
2-2.1 Reversible activity switching by Fan (2015)[7)]

One of the enzymes' function: Activity switching





Activity switching by sodium ion



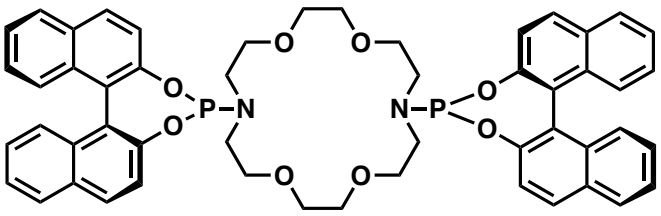
Refference

7) Fan. Q, *et al. Angew. Chem. Int. Ed.* **2015**, 54, 4334

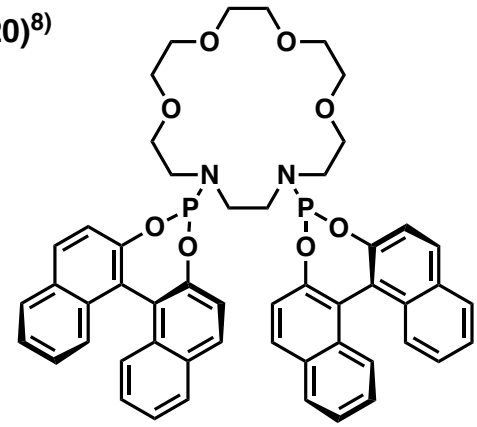
2. Examples of the catalysis based on key structure

2-2 Catalysts including Crown ether

2-2.2 alkali metal ion additive effect by Fan & He (2020)[8)]

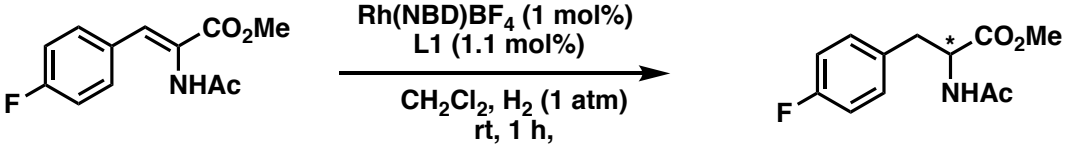


L1



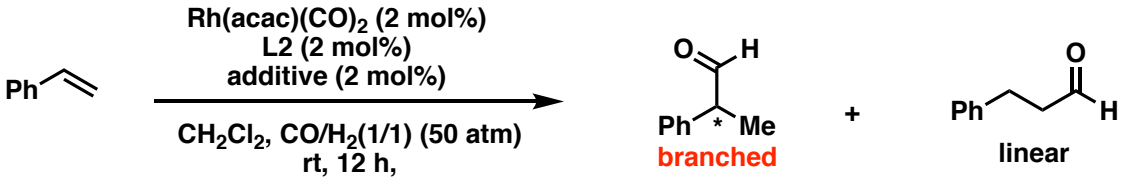
L2

Reactivity change by patassium ion



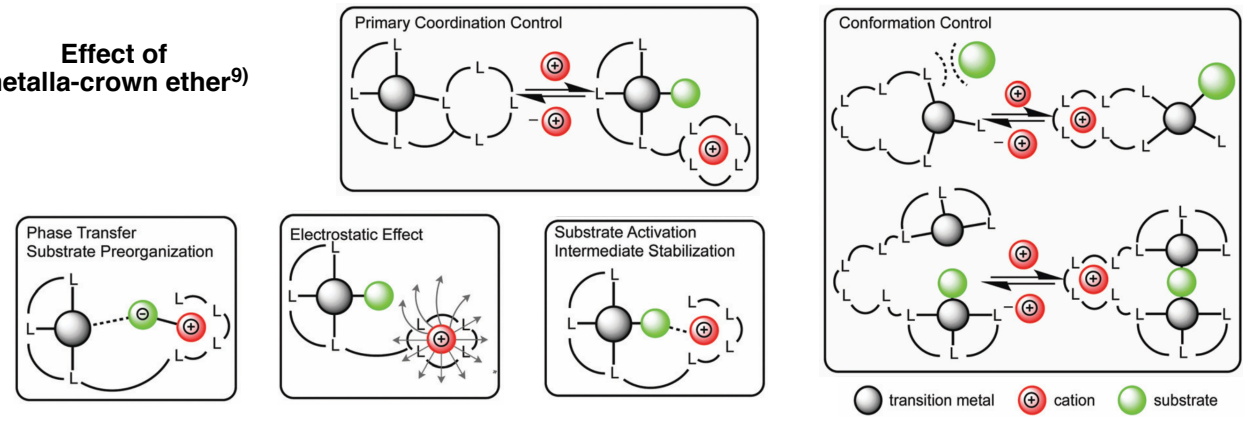
	additive	conv.	ee
1	none	70%	>99% (*R*)
2	KBArF	34%	97% (*R*)

configuration change by alkali metal ion



	additive	conv.	*b* : *l*	ee	
1	none	10%	90 : 10	26% (*S*)	configuration change
2	KBArF	10%	82 : 18	16% (*R*)	
3	NaBArF	43%	92 :8	70% (*R*)	
4	NaBArF	>99%	93 : 7	70% (*R*)	CO/H_2 (10 atm), rt ,24 h

Effect of metalla-crown ether[9)]



Refference

8) He. Y, Fan. Q, *et al. J. Org. Chem.* **2020**, 85, 8176

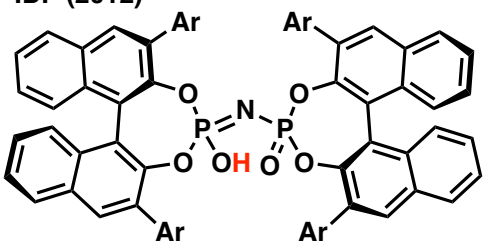
9) Miller. A. J. M. *et al. Chem.Commun.,* **2019**, 55, 5047

2. Examples of the catalysis based on key structure

2-3 IDP series by B. List

2-3.1 Overview of IDP series

IDP (2012)[10)]



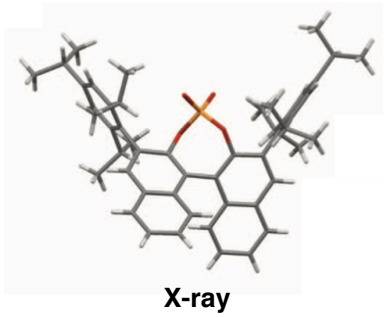
ImidoDiPhosphate

Well difined, confined cavity can do enatiodiscrimination of SM without sterically demanding PG or HB

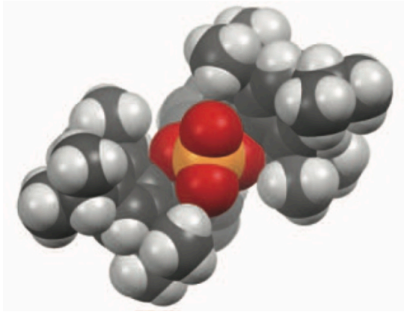
pKa (MeCN) = 11.5 [11)]

Comparison of IDP with TRIP

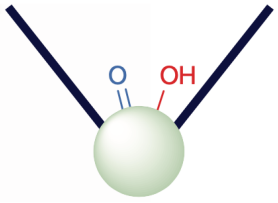
TRIP



X-ray

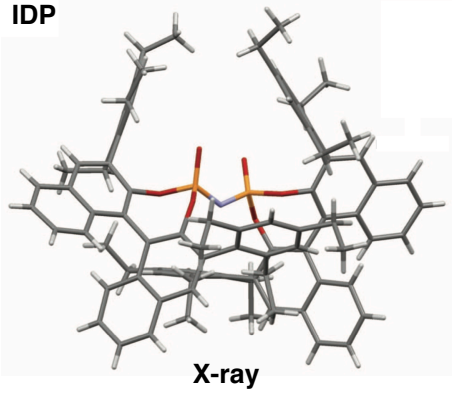


Top view

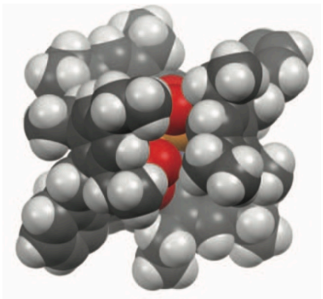


Open active site

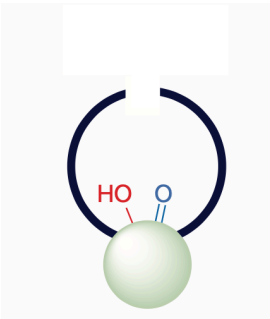
IDP



X-ray

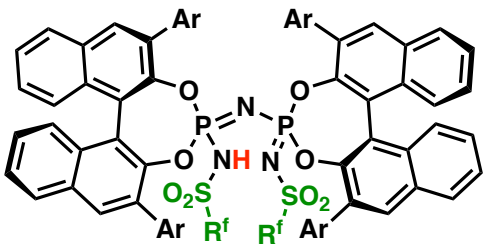


Top view



sterically constrained active site

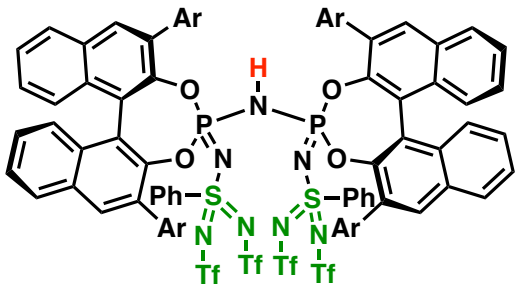
IDPi (2016)[12)]



pKa (MeCN) = 2~4.5 [11)]

R^f ⇨ fine tuning of cavity

IDPii (2021)[13)]



pKa (MeCN) = ~0 [13)]

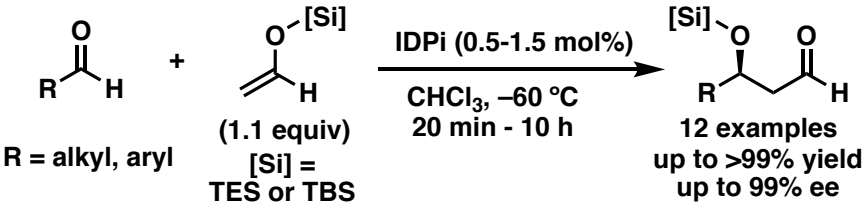
Refference

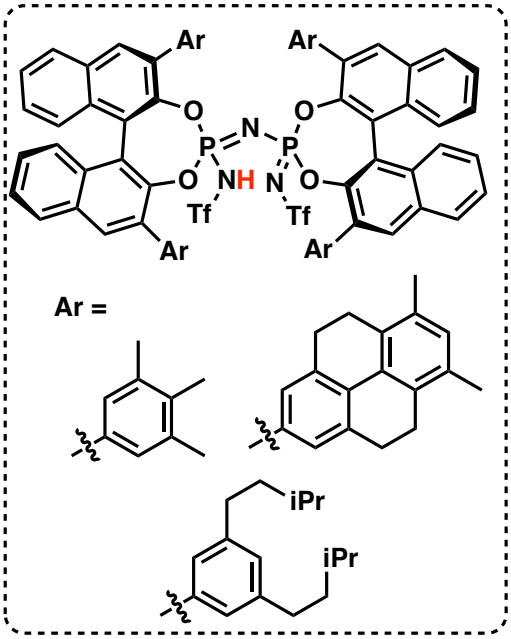
10) List. B, *et al. Nature* **2012**, 483, 315.
11) List. B, *et al. Angew. Chem. Int. Ed.* **2019**, 58, 12761.
12) List. B, *et al. Angew. Chem. Int. Ed.* **2016**, 55, 13200.
13) List. B, *et al. J. Am. Chem. Soc.* **2021**, 143, 14835.

2. Examples of the catalysis based on key structure

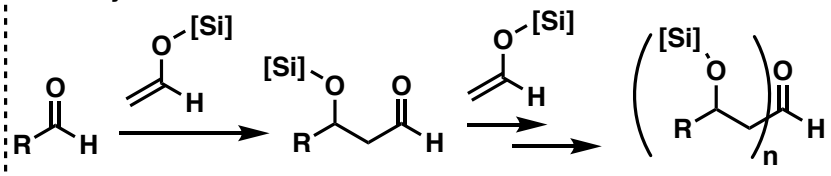
2-3 IDP series by B. List

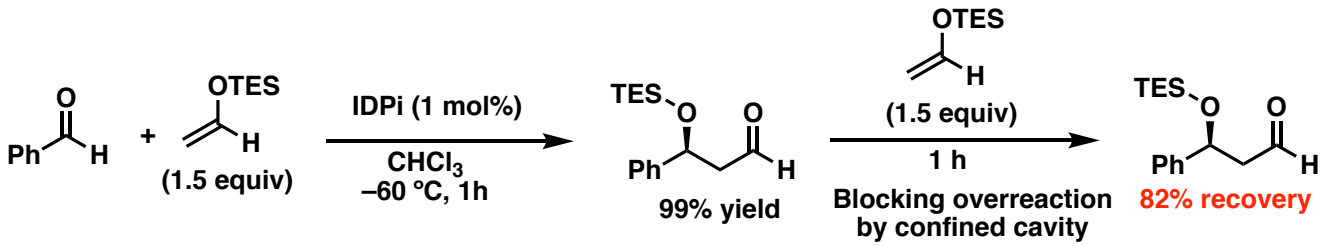
2-3.1 Single aldolization catalyzed by IDPi[14)]



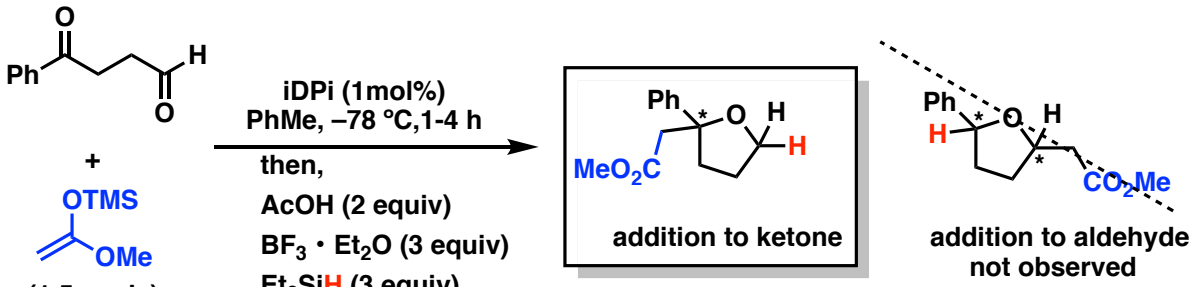


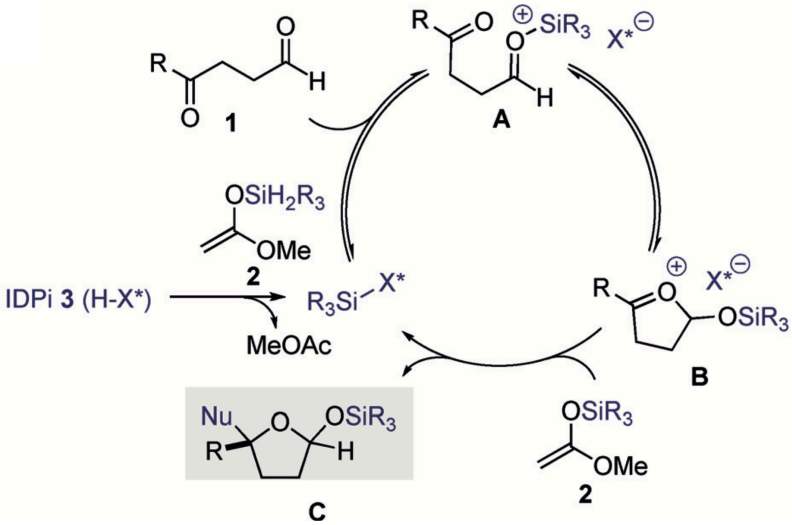
Difficulty of this reaction

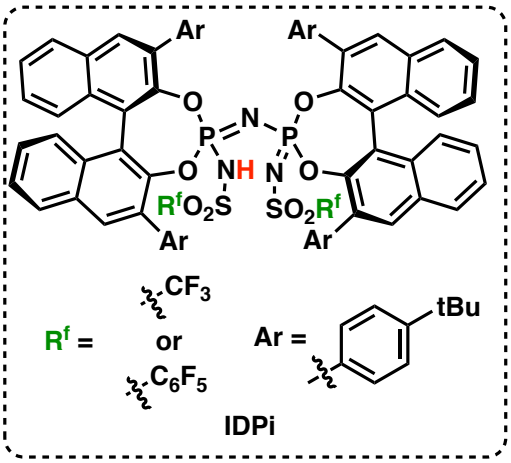




2-3.2 ketone selective addition of ketoaldehyde catalyzed by IDPi[15)]







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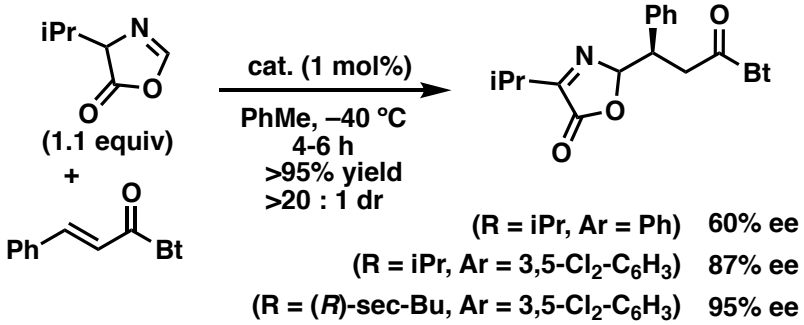
14) List. B, *et. al. Science* **2018**, 362, 216.
15) List. B, *et. al. Angew. Chem. Int. Ed.* **2018**, 57, 12162.

3. Examples of supramolecular catalysis

3-0) Types of supramolecule catalyst and its advantage

1. Hydrogen bond

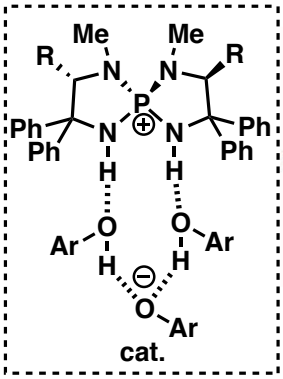
One of representative examples by Ooi & Uraguchi (2009)[16]

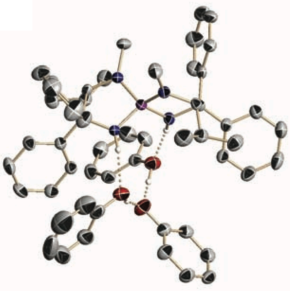


(R = iPr, Ar = Ph) 60% ee

(R = iPr, Ar = 3,5-Cl_2-C_6H_3) 87% ee

(R = (*R*)-sec-Bu, Ar = 3,5-Cl_2-C_6H_3) 95% ee

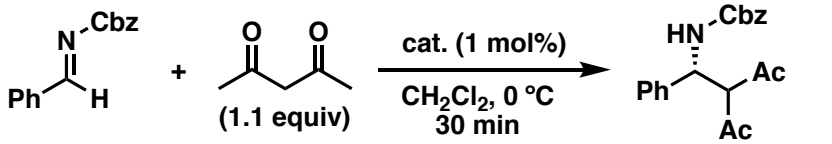




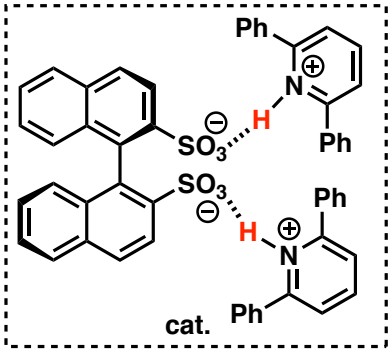
X-ray
(R = iPr, Ar = Ph)

2. Ion-pair

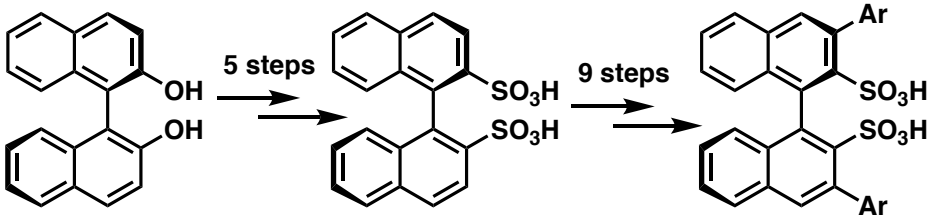
One of representative examples by Ishihara & Hatano (2009)[17]



74% yield, 92% ee

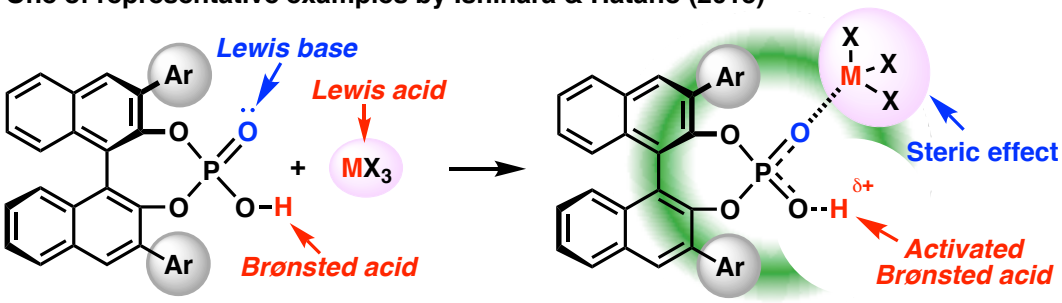


Synthetic difficulty of 3,3'-Ar_2-BINSA[18]

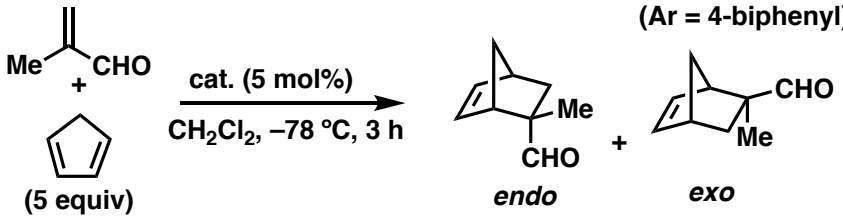


3. Lewis-pair

One of representative examples by Ishihara & Hatano (2015)[19]



cat.
(Ar = 4-biphenyl)



MX_3	yield	*endo*:*exo*	ee (*exo*)
none	0%	–	–
BCl_3	88%	4:96	62%
BBr_3	99%	2:98	89%

- **Many ways** to optimization
- Optimization **without multi-step synthesis**
- **Activation** by self-assembly

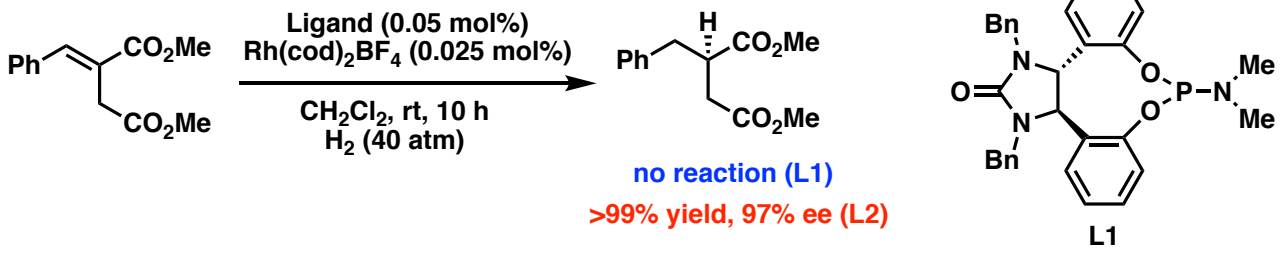
Refference

16) Uraguchi. D, Ooi. T *et al. Science* **2009**, 326, 120.
17) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2008**, 130, 16858.
18) Hatano. M, Ishihara. K *et al. Asian J. Org. Chem.* **2014**, 3, 352.
19) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2015**, 137, 13472.

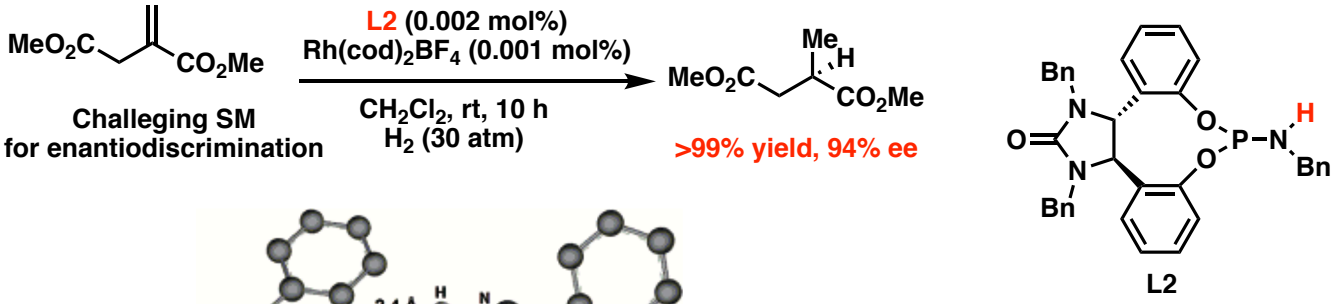
3. Examples of supramolecular catalysis

3-1) Supramolecule catalysts by hydrogen bond

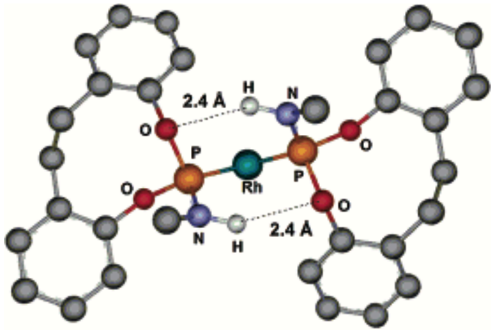
3-1.1 Inter-ligand hydrogen bond important for catalytic activity by Ding (2006)[20)]



L1

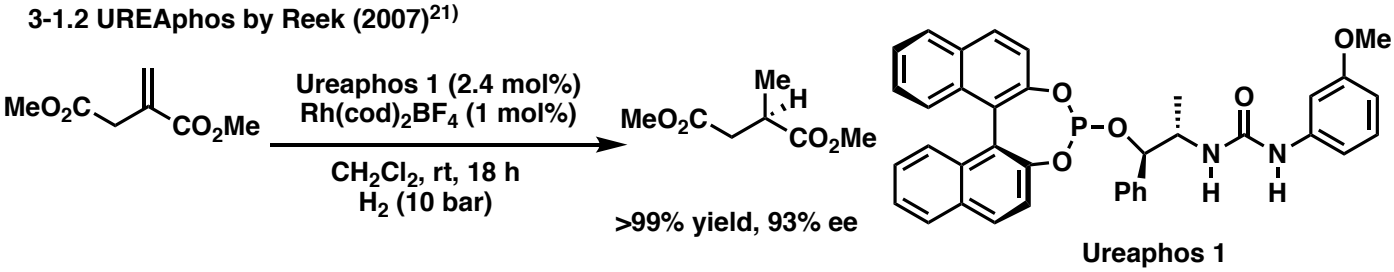


L2

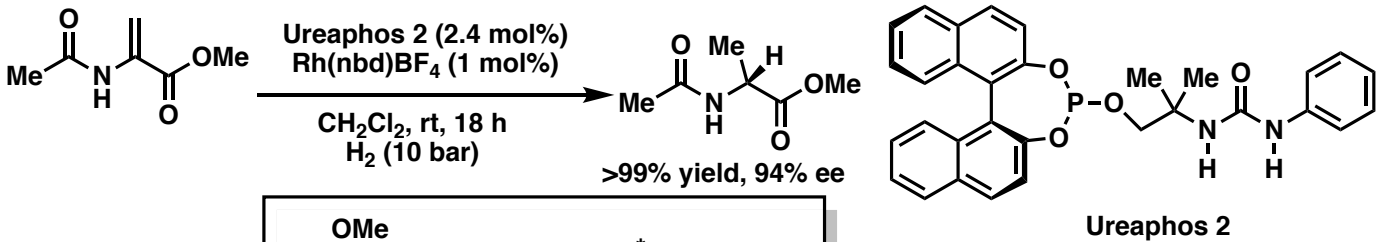


B3LYP/6-31G(d) optimized structure of the Rh/L2 structural mimic.

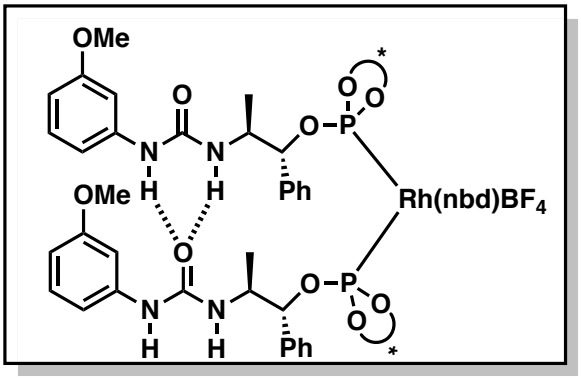
3-1.2 UREAphos by Reek (2007)[21)]



Ureaphos 1



Ureaphos 2



Refference

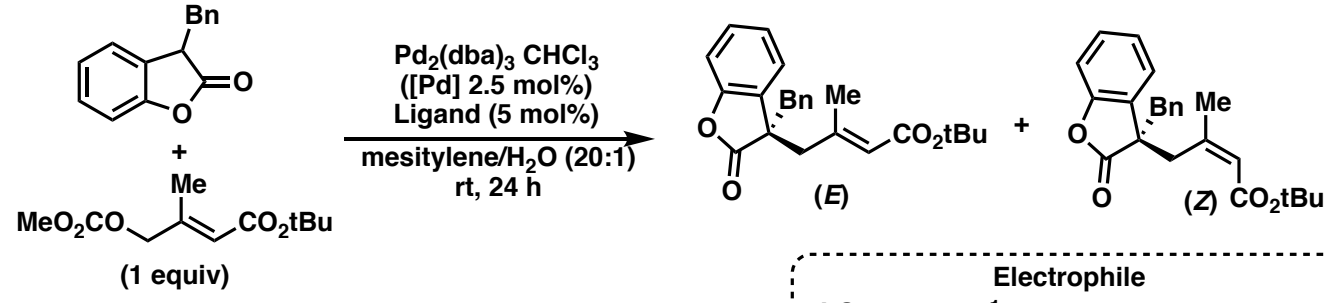
20) Ding. K *et al. J. Am. Chem. Soc.* **2006**, 128, 14212.

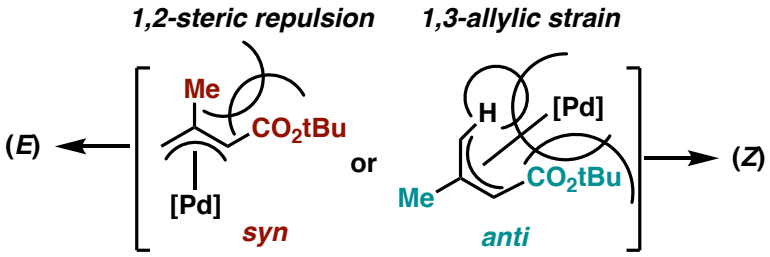
21) Reek. N. H *et al. Chem. Commun.* **2007**, 864.

3. Examples of supramolecular catalysis

3-2) Supramolecule catalysts by ion-pair

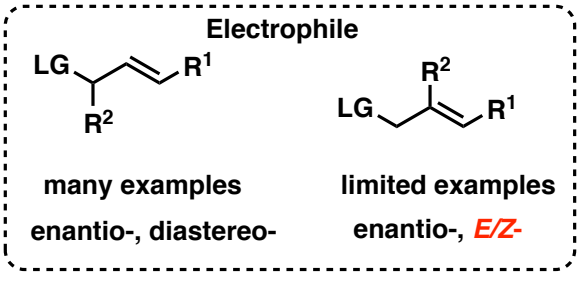
3-2.1 Cationic ligand-chiral anion pair by Ooi &Ohmatsu (2014)[22] Enantio-, *E/Z*-selective allylation

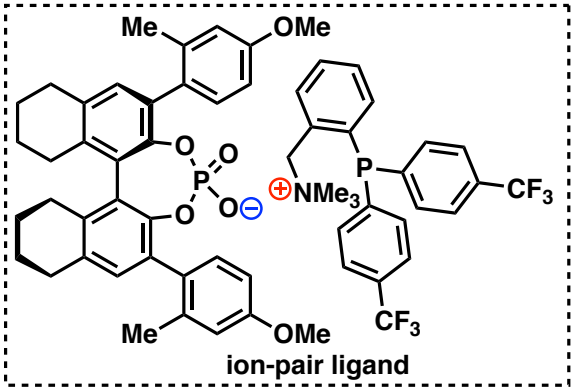




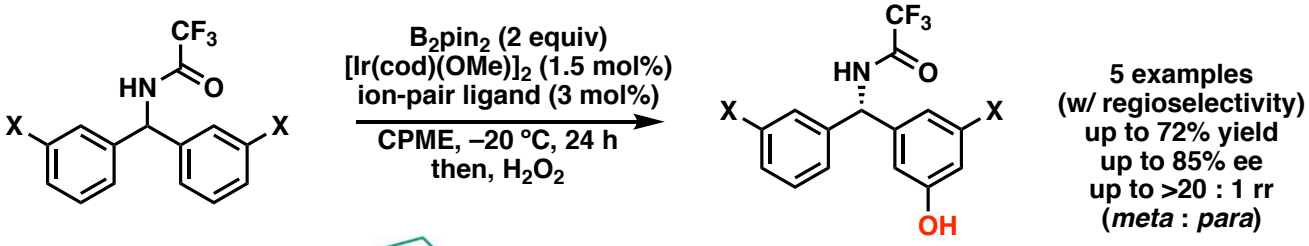
E/Z selectivity → depend on substrate

Ligand	yield	*E* / *Z*	ee	
PPh_3	99%	1 : 1	–	
ion-pair ligand	99%	>20 : 1	94% ee	
ion-pair ligand	91%	18 : 1	96% ee	SM of *E* / *Z* = 1.5 : 1

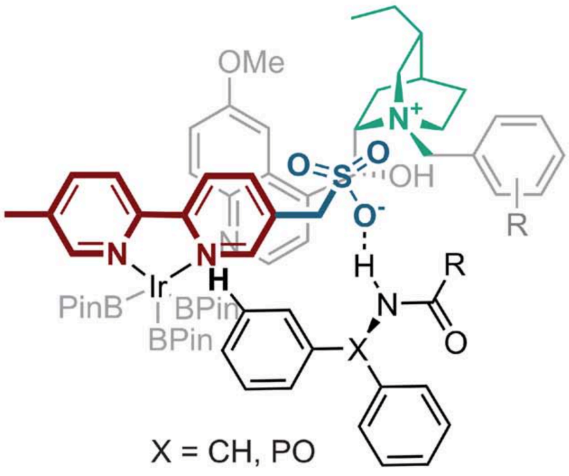




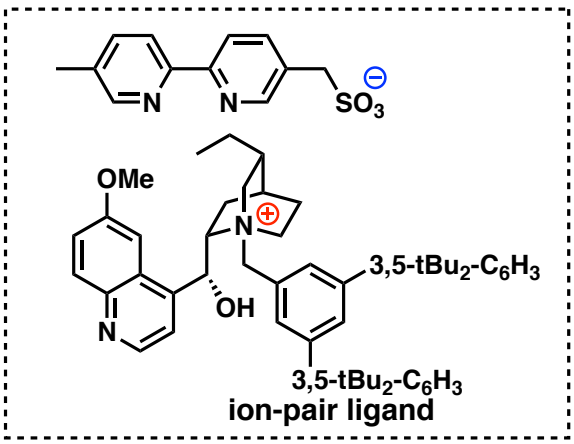
3-2.2 Anionic ligand-chiral cation pair by Phipps (2020)[23]
Long-range asymmetric induction and regioselective C-H borylation



5 examples
(w/ regioselectivity)
up to 72% yield
up to 85% ee
up to >20 : 1 rr
(*meta* : *para*)



Proposed TS



Refference

22) Ohmatsu. K, Ooi. T *et al. Chem. Commun.* **2014**, 50, 4554.

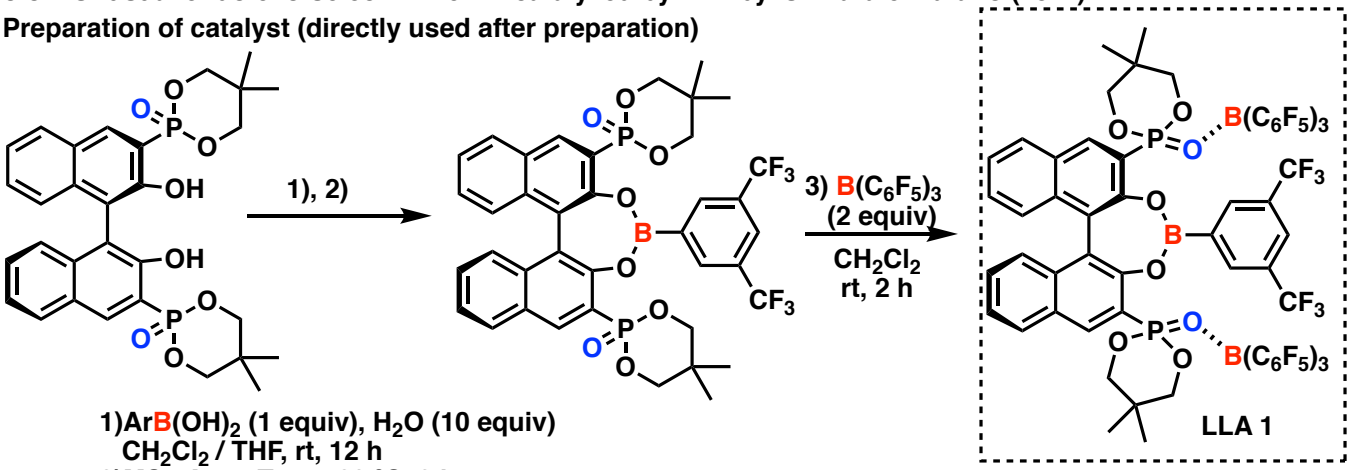
23) Phipps. R. J *et al. Science* **2020**, 367, 1246.

3. Examples of supramolecular catalysis

3-3) Supramolecule catalysts by Lewis-pair

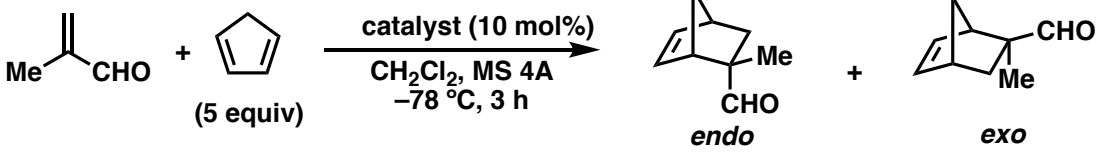
3-3.1 Unusual endo/exo-selectivitive DA catalyzed by LLA by Ishihara & Hatano (2011)[24)]

Preparation of catalyst (directly used after preparation)



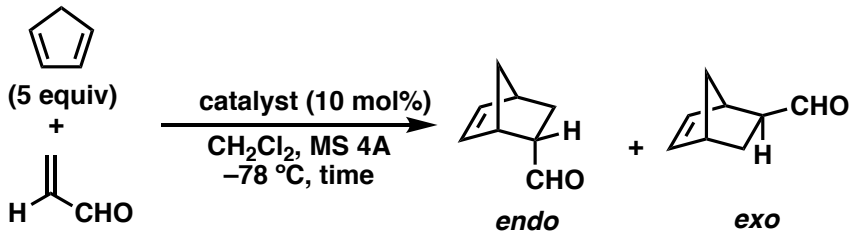
1)$ArB(OH)_2$ (1 equiv), H_2O (10 equiv)
CH_2Cl_2 / THF, rt, 12 h
2)MS 4A, <5 Torr, 100 °C, 2 h

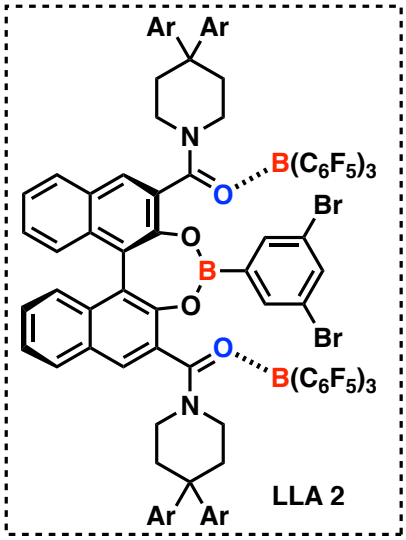
Unusual endo-selective Diels-Alder reaction



catalyst	yield	*endo* / *exo*	ee (*endo* / *exo*)	
$B(C_6F_5)_3$	93%	12 : 88	–	
LLA 1	99%	83 : 17	99% / 80%	unusual *endo !*

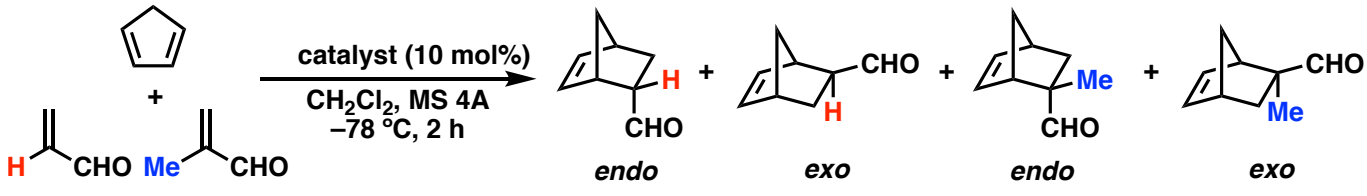
Endo/exo-divergent Diels-Alder reaction





catalyst	time	yield	*endo* / *exo*	ee (*endo* / *exo*)	
$B(C_6F_5)_3$	2 h	93%	86 : 14	–	
LLA 1	3 h	99%	>99 : 1	95% / –	usual *endo*
LLA 2	2 h	99%	20 : 80	23% / 94%	unusual *exo !*

Substrate-selective Diels-Alder reaction



catalyst	yield	H / Me	H *endo* / *exo*	Me *endo* / *exo*	H ee (*endo* / *exo*)	
$B(C_6F_5)_3$	>99%	63 : 37	86 : 14	9 : 91	–	
LLA 2	>99%	>99 : 1	20 : 80	–	44% / 95%	Acrolein-selective!

Substrate-, unusual exo-, enantio-, multi-selective!

Refference

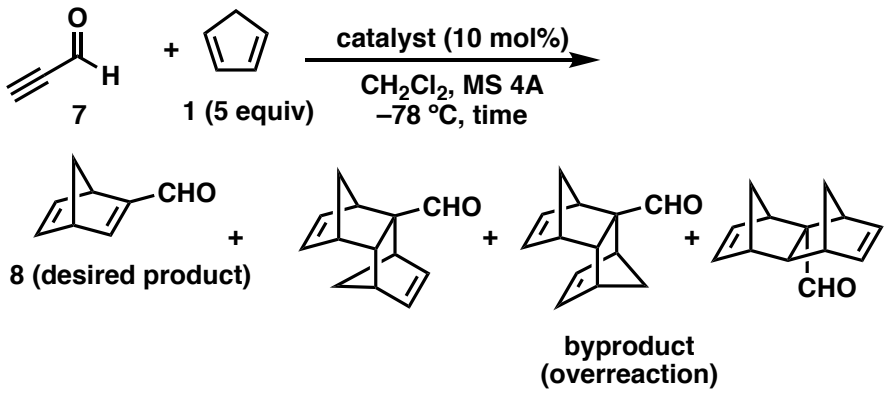
24) Hatano. M, Ishihara. K *et al. Angew. Chem. Int. Ed.* **2011**, 50, 12189.

3. Examples of supramolecular catalysis

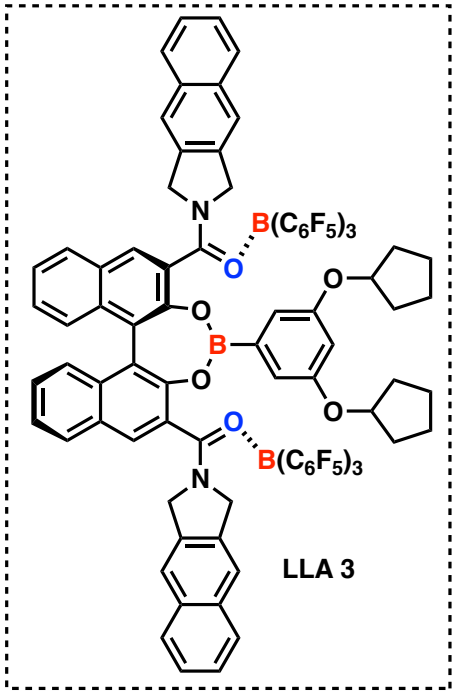
3-3) Supramolecule catalysts by Lewis-pair

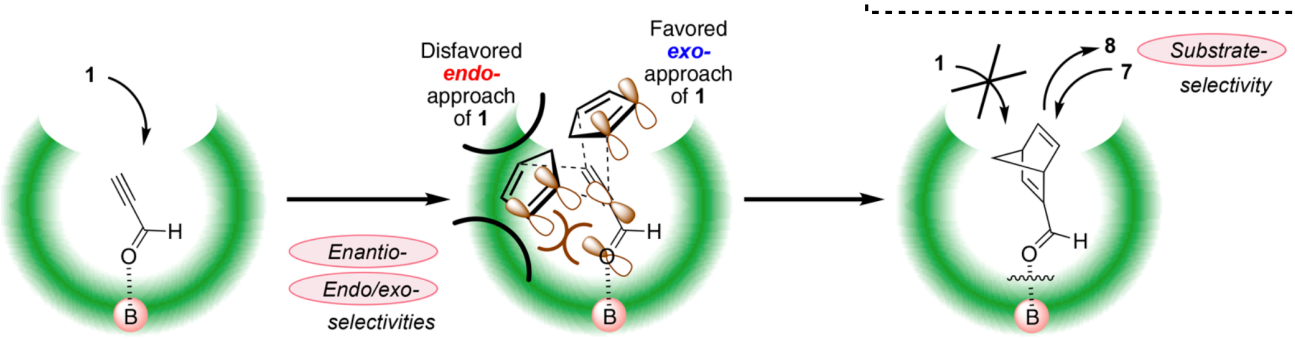
3-3.2 Multi-selectivitive DA of catalyzed by LLA by Ishihara & Hatano (2018)[25)]

Enantio-, endo/exo-, substrate-selective Diels-Alder reaction



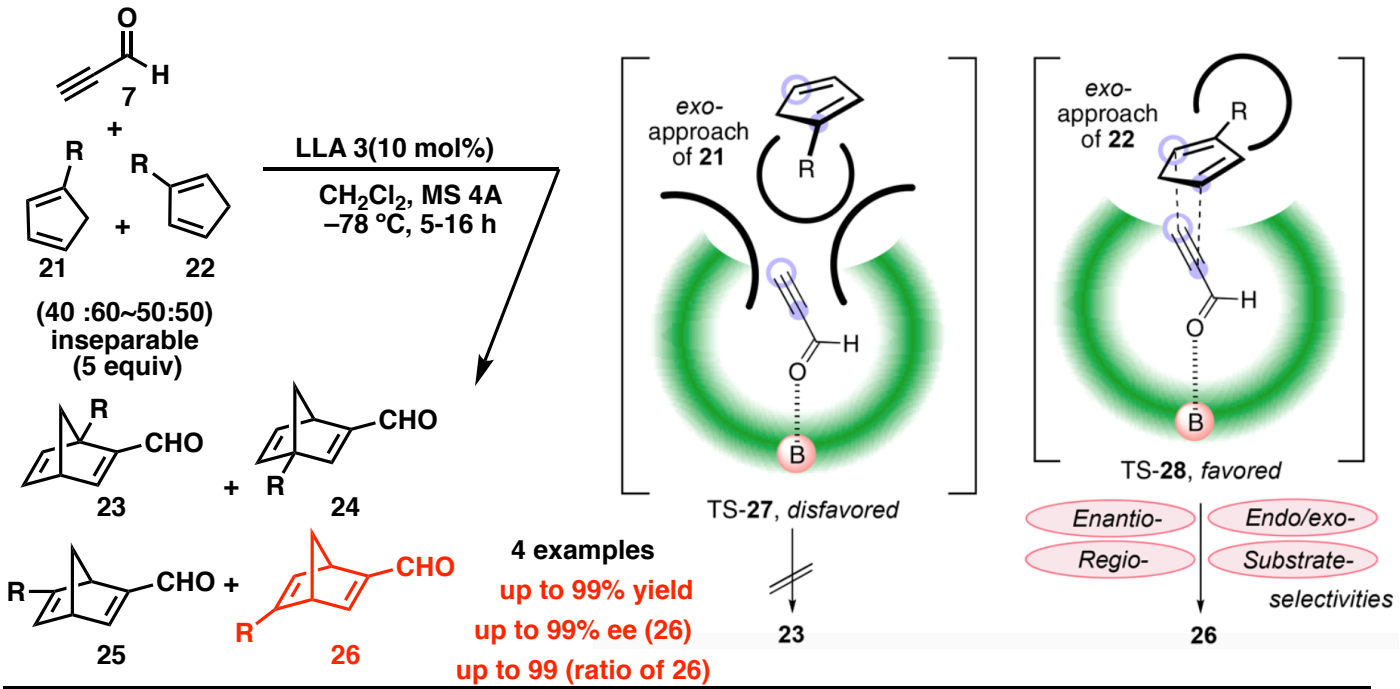
catalyst	time	yield (8)	yield (bypro.)	ee (8)	
$BF_3 \cdot OEt_2$	5 h	0%	89%	–	2nd-addtion of Cp is faster
LLA 3	3 h	95%	3%	90%	





-Chiral cavity can control exo-induced 1st. Diels–Alder reaction.
-Chiral cavity can prevent 2nd. Diels–Alder reaction (Substrate-selectivity).

Enantio-, endo/exo-, regio-, substrate-selective Diels-Alder reaction



Refference

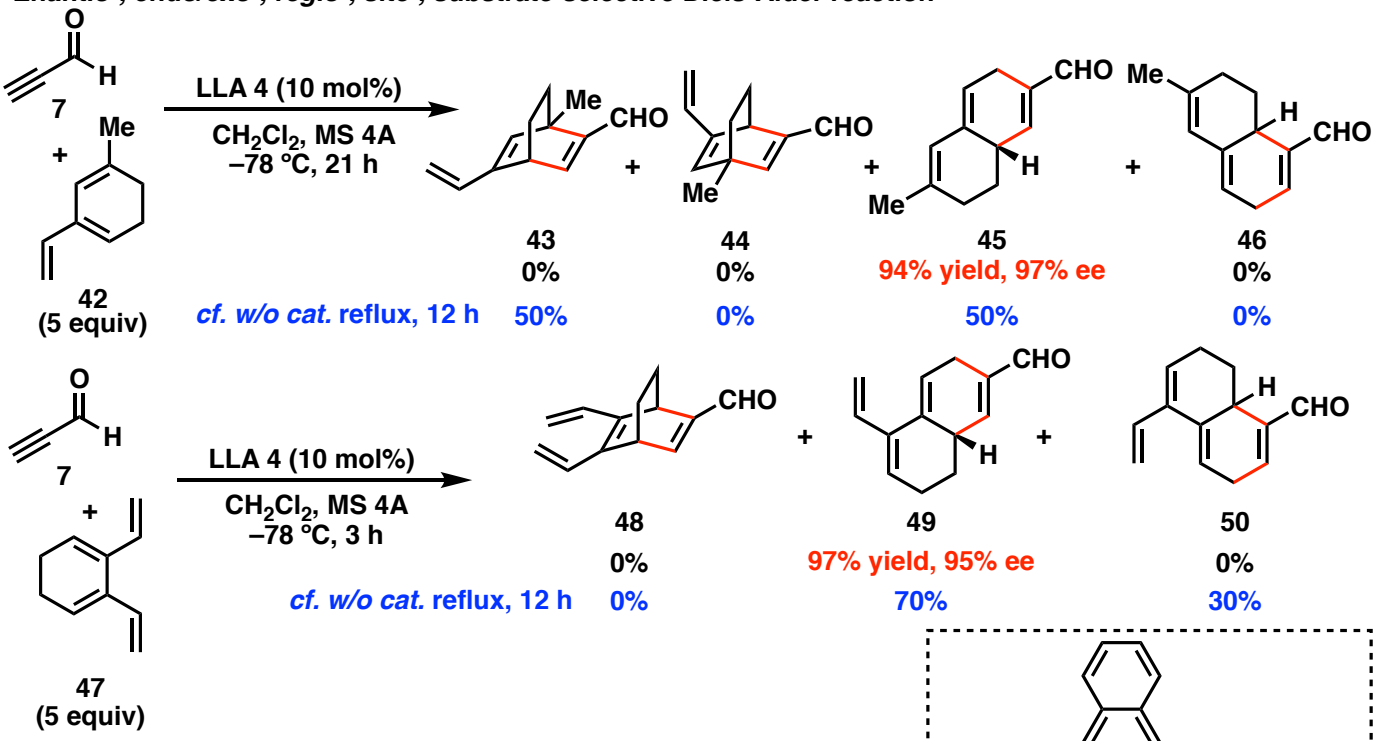
25) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2018**, 140, 16253.

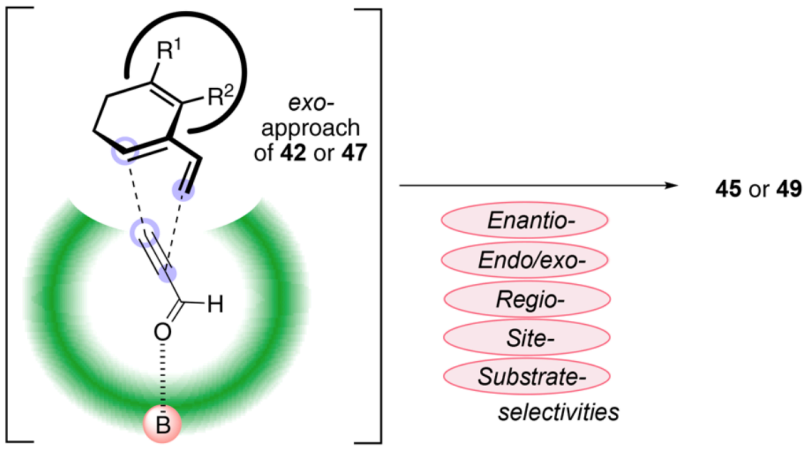
3. Examples of supramolecular catalysis

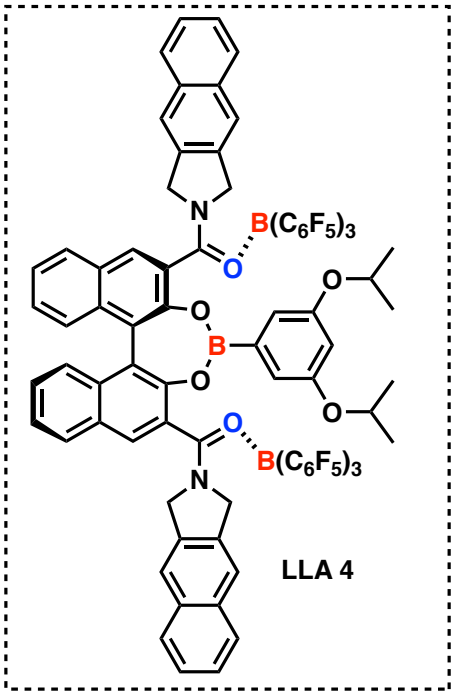
3-3) Supramolecule catalysts by Lewis-pair

3-3.2 Multi-selectivitive DA of catalyzed by LLA by Ishihara & Hatano (2018)[25)]

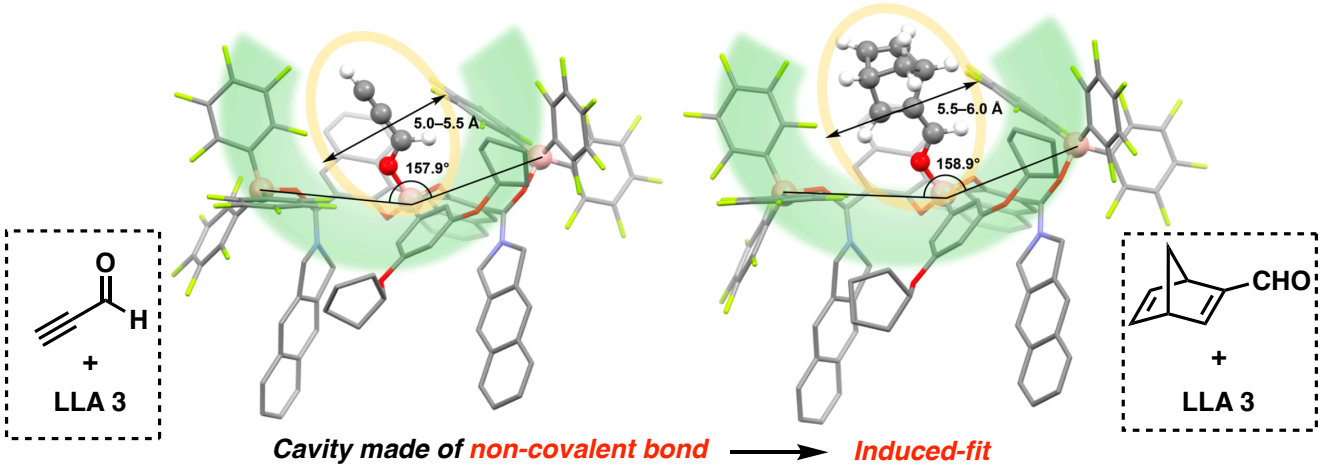
Enantio-, endo/exo-, regio-, site-, substrate-selective Diels-Alder reaction







DFT-optimized structure



Cavity made of non-covalent bond → ***Induced-fit***

Refference

25) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2018**, 140, 16253.

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4) Armspach. D, Matt. D. *et al. Angew. Chem. Int. Ed.* **2014**, 53, 3937.

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9) Miller. A. J. M. *et al. Chem.Commun.,* **2019**, 55, 5047

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12) List. B, *et al. Angew. Chem. Int. Ed.* **2016**, 55, 13200.

13) List. B, *et al. J. Am. Chem. Soc.* **2021**, 143, 14835.

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15) List. B, *et. al. Angew. Chem. Int. Ed.* **2018**, 57, 12162.

16) Uraguchi. D, Ooi. T *et al. Science* **2009**, 326, 120.

17) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2008**, 130, 16858.

18) Hatano. M, Ishihara. K *et al. Asian J. Org. Chem.* **2014**, 3, 352.

19) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2015**, 137, 13472.

20) Ding. K *et al. J. Am. Chem. Soc.* **2006**, 128, 14212.

21) Reek. N. H *et al. Chem. Commun.* **2007**, 864.

22) Ohmatsu. K, Ooi. T *et al. Chem. Commun.* **2014**, 50, 4554.

23) Phipps. R. J *et al. Science* **2020**, 367, 1246.

24) Hatano. M, Ishihara. K *et al. Angew. Chem. Int. Ed.* **2011**, 50, 12189.

25) Hatano. M, Ishihara. K *et al. J. Am. Chem. Soc.* **2018**, 140, 16253.

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27) Levine. M *et al. Chem. Rev.* **1998**, 98, 1997.

28) Zhang. Z *et al. Green Synthesis and Catalysis* **2021**, 2, 156.

29) Reek. J. N. H *et al. Nature Chem.* **2010**, 2, 615.

30) List. B, *et al. Chem* **2020**, 6, 2515.