# Chiral Supramolecular Catalyst for Asymmetric Reaction

**2017/1/21 (Sat.)**

**Literature Seminar**

**Taiki Fujita (B4)**

# Introduction

## Conventional Chiral Catalyst

Central metal atom

Fine tuned chiral ligands

Rational design of chiral ligands remains very difficult.

Numerous trial-and-error attempts are needed.

Conventional chiral ligands are constructed with covalent bonds.

Synthesis of chiral ligands require multi-step operation and can be complicated.

**Optimizing ligands is time-and-energy consuming**

# Supramolecular Chiral Catalyst

Rene Descartes
(1596 -1650)

Le second était de diviser chacune des difficultés (...)

non-covalent interactions

Supramolecular chiral catalyst

combinatorial methods

self assembly

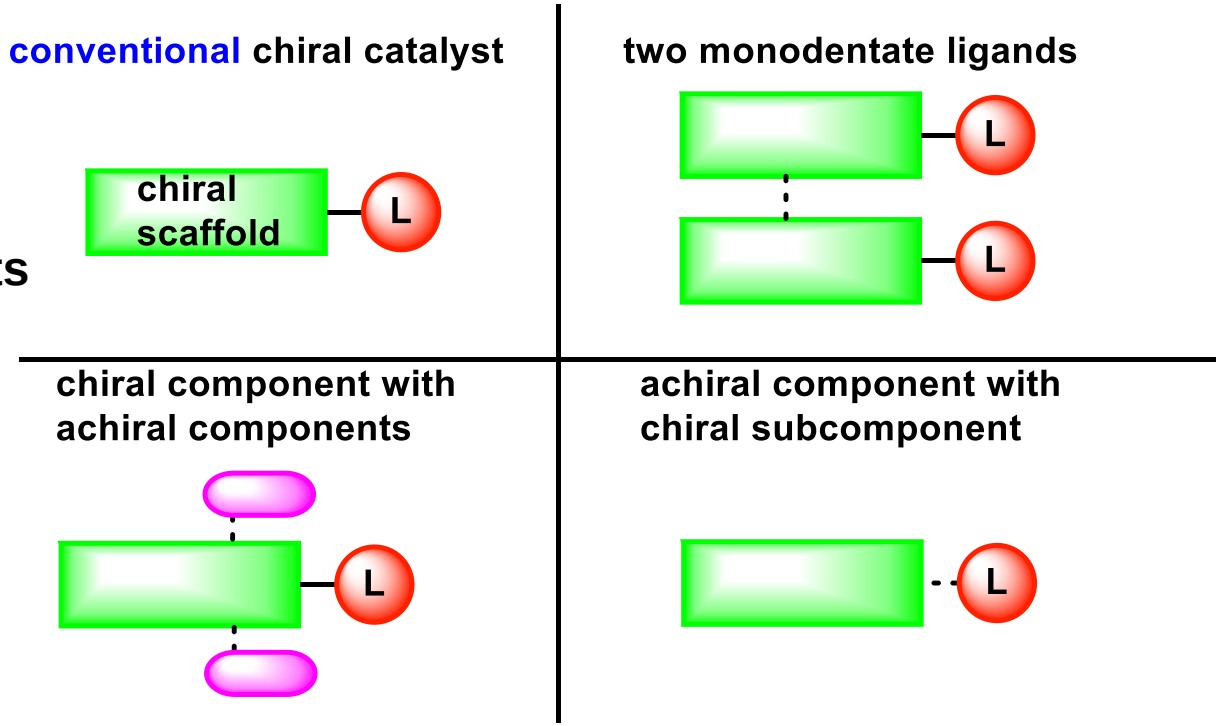
These attributes are induced by small components of supramolecular catalyst.

# Supramolecular Chiral Catalyst

**What is the advantage of supramolecular chiral catalyst?**

- **Synthesis of each small component is much easier than complex conventional large ligand.**
- **The ligands can be tuned easily by changing each component.**
- **Combinatorial methods can be used for screening ligands**

**To date, some strategies for supramolecular catalysts have been developed.**

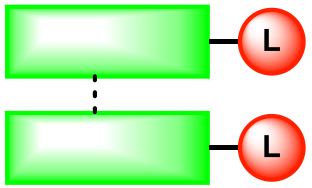


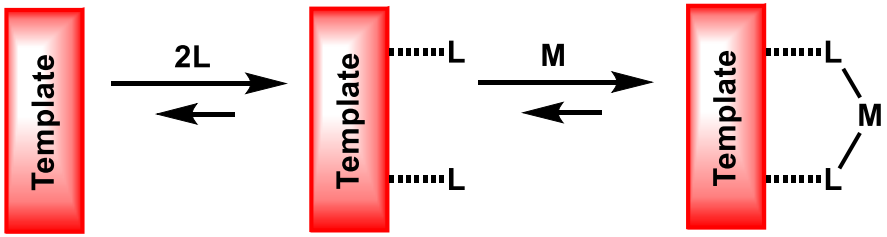

L = coodinating group
- - - = non-covalent interaction

# Supramolecular Catalysis Strategy 1

## 1)Zn-pyridine interactions

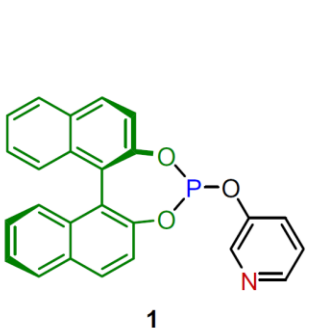
two monodentate ligands



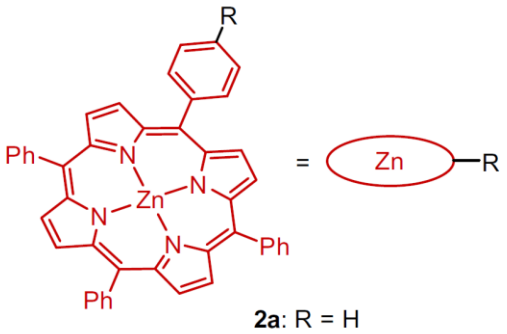




Zn-pyridine interaction is indeed selective

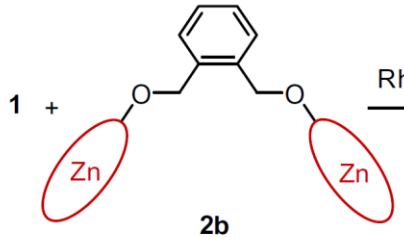
**L=monodentate ligand**
**M=transition metal**



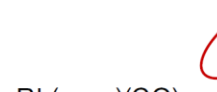

1

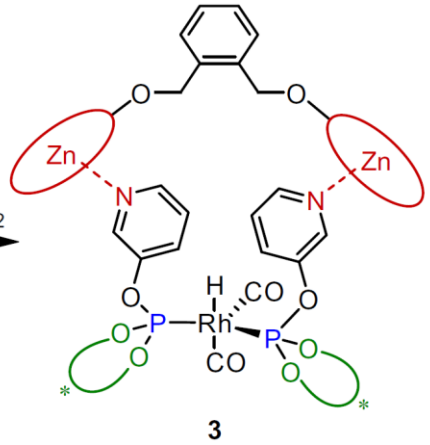



**2a**: R = H

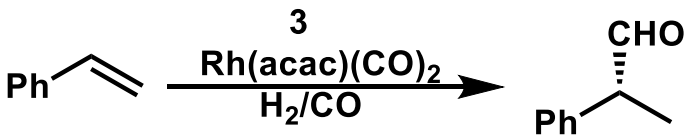



**2b**




3




**33% ee**

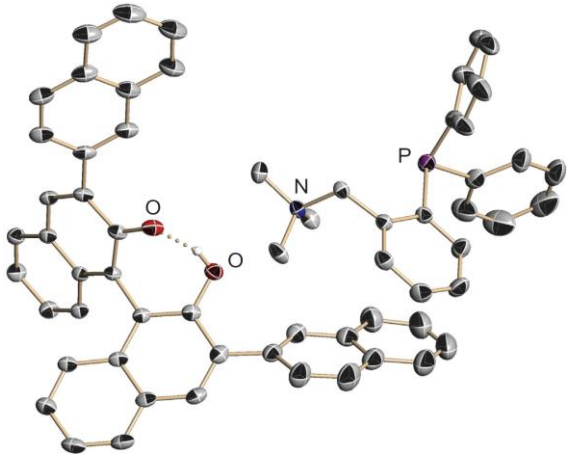
**6% ee with $HRh(1•2a)_2(CO)_2$**

First example of supramolecular bidentate ligands

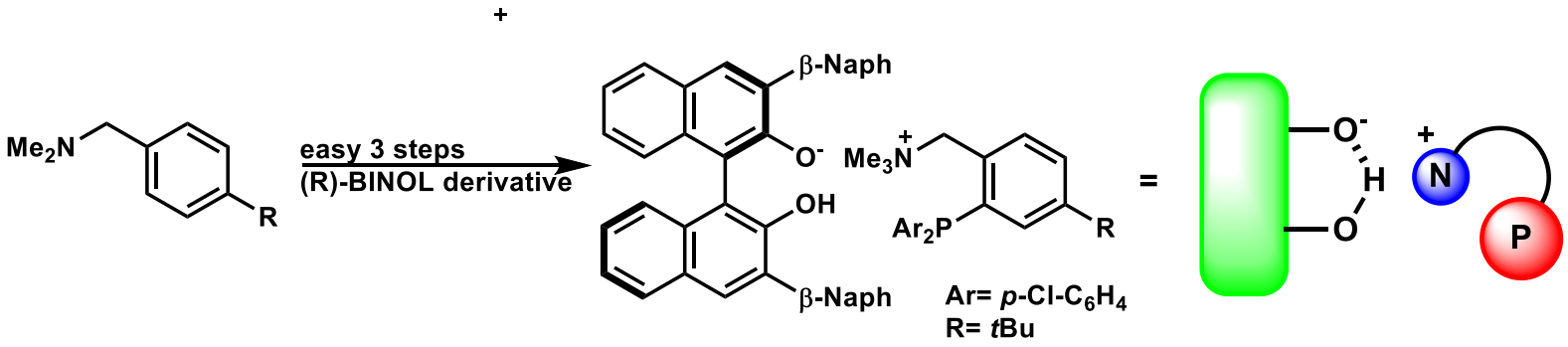
N. H. Reek, *et al. Chem. Commun.* **2003**, *89*, 3446.

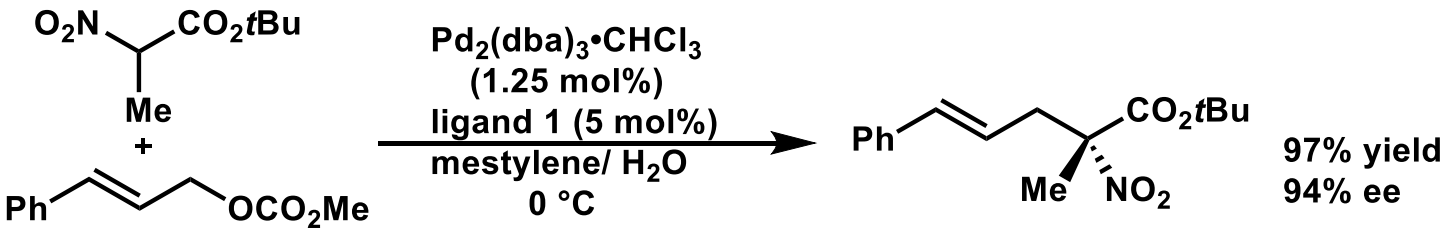
# Supramolecular Catalyst Strategy 2

**Achiral ligand upon chiral scaffold**



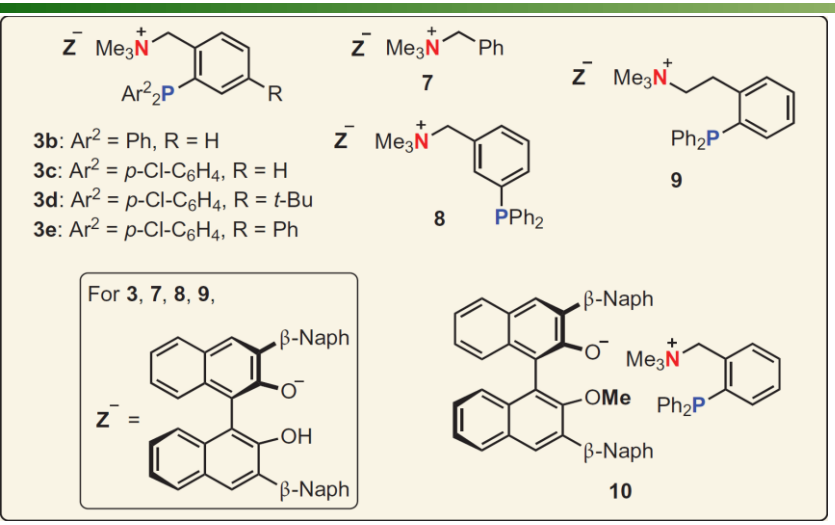

## 1) ion-paired chiral ligands



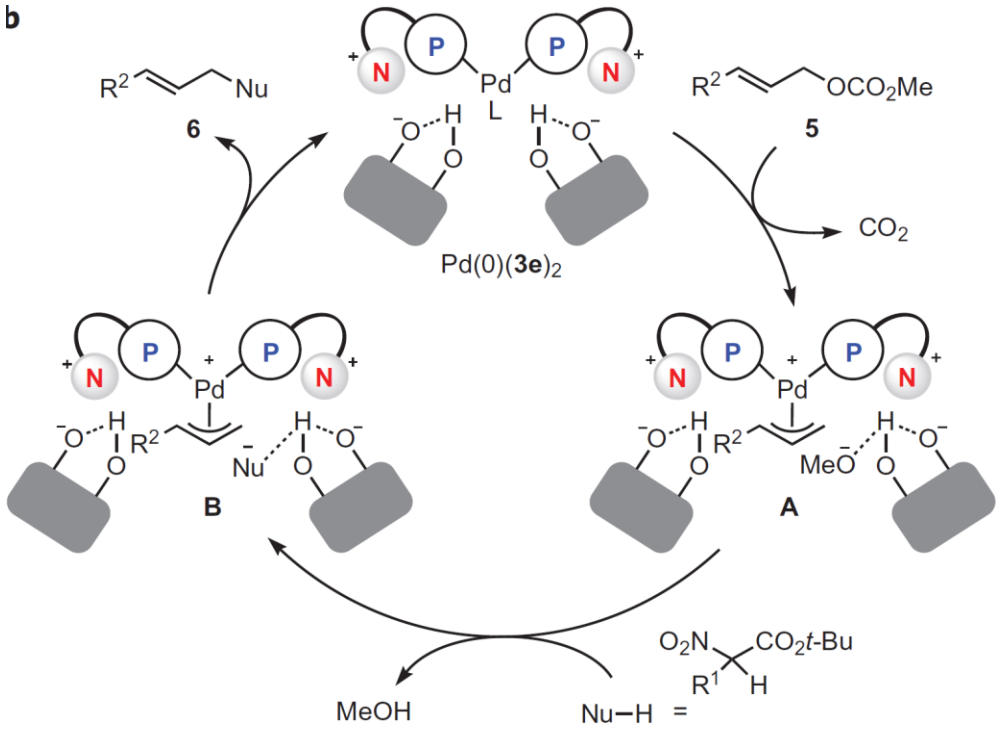




T. Ooi, *et al. Nat Chem.* **2012**, *4*, 473

# Reaction Mechanism

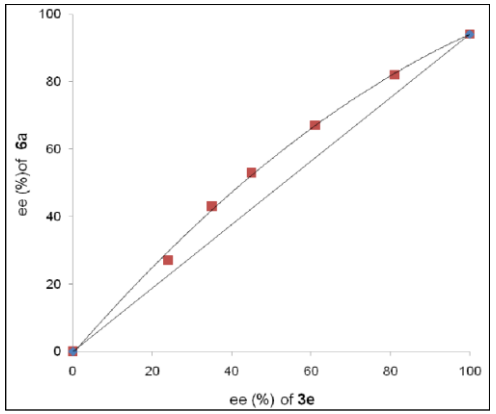



| Entry | Ligand | Conditions | Yield (%)* | e.e. (%)† |
|---|---|---|---|---|
| 1 | **3a** | r.t., 5 h | 56 | 38 |
| 2 | **3b** | r.t., 5 h | 78 | 68 |
| 3 | $PPh_3$ | With **7** (5 mol%), r.t., 5 h | 99 | <1 |
| 4 | **1**·Br | With **2b** (5 mol%), r.t., 5 h | 85 | <1 |
| 5 | **8** | r.t., 5 h | 99 | <1 |
| 6 | **9** | r.t., 5 h | 83 | <1 |
| 7 | **10** | r.t., 5 h | 92 | −3 |
| 8 | **3c** | r.t., 5 h | 99 | 73 |
| 9 | **3d** | r.t., 5 h | 99 | 75 |
| 10 | **3e** | r.t., 5 h | 99 | 83 |
| 11 | **3e** | 0 °C, 24 h | 78 | 88 |
| 12 | **3e** | Toluene/$H_2O$ (20:1. v/v), 0 °C, 12 h | 97 | 94 |




Hydrogen bond is critical for enantio selectivity.

co-solvent system is efficient?

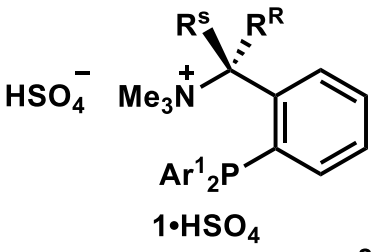


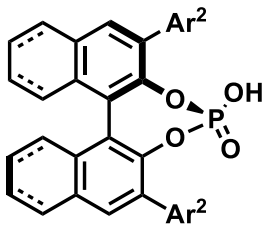

T. Ooi, *et al. Nat Chem.* **2012**, *4*, 473

# In Situ Generation and Deconvolution Method

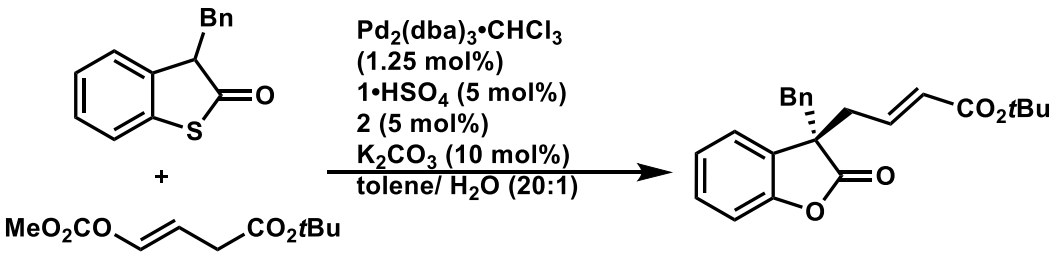
In situ generation of chiral ligands enables us to use combinatorial strategy much easier.

Just mixing reagent is enough to evaluate ligand selectivity.




2: octahydrobinaphthyl (H8) or binaphthyl (B)




| 1 | $R^S$ | $R^R$ | $Ar^1$ |
|---|---|---|---|
| 1a | H | H | 4-Cl-$C_6H_4$ |
| 1b | H | H | 4-MeO-$C_6H_4$ |
| 1c | H | H | 4-F-$C_6H_4$ |
| 1d | H | H | 4-$CF_3$-$C_6H_4$ |
| 1e | H | Me | 4-Cl-$C_6H_4$ |
| 1f | H | Me | 4-MeO-$C_6H_4$ |
| 1g | H | Me | 4-F-$C_6H_4$ |
| 1h | H | Me | 4-$CF_3$-$C_6H_4$ |
| 1i | Me | H | 4-Cl-$C_6H_4$ |
| 1j | Me | H | 4-MeO-$C_6H_4$ |
| 1k | Me | H | 4-F-$C_6H_4$ |
| 1l | Me | H | 4-$CF_3$-$C_6H_4$ |

| 2 | | $Ar^2$ |
|---|---|---|
| 2a | H8 | 2,6-$Me_2$-4-MeO-$C_6H_2$ |
| 2b | H8 | 2,6-$Et_2$-4-MeO-$C_6H_2$ |
| 2c | H8 | 2,4,6-$(MeO)_3$-$C_6H_2$ |
| 2d | H8 | 2,4,6-$Me_3$-$C_6H_2$ |
| 2e | H8 | 4-Ph-$C_6H_4$ |
| 2f | H8 | β-Naph |
| 2g | B | 2,6-$Me_2$-4-MeO-$C_6H_2$ |
| 2h | B | 2,6-$Et_2$-4-MeO-$C_6H_2$ |
| 2i | B | 2,4,6-$(MeO)_3$-$C_6H_2$ |
| 2j | B | 2,4,6-$Me_3$-$C_6H_2$ |
| 2k | B | 4-Ph-$C_6H_4$ |
| 2l | B | β-Naph |

| Step 1 | 2a-2f | 2g-2l |
|---|---|---|
| 1a-1d | 71% ee (97%) | 72% ee (99%) |
| 1e-1h | 75% ee (98%) | 79% ee (99%) |
| 1i-1l | 75% ee (86%) | 74% ee (94%) |

values in parentheses are isolated yields of **8a**

| Step 2 | 2g-2i | 2j-2l |
|---|---|---|
| 1e, 1f | 82% ee (95%) | 66% ee (96%) |
| 1g, 1h | 85% ee (93%) | 65% ee (91%) |

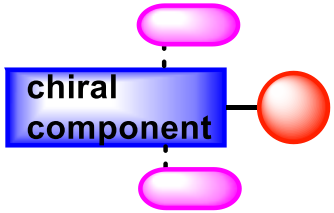
| Step 3 | 2g | 2h | 2i |
|---|---|---|---|
| 1g | 89% ee (95%) | 78% ee (89%) | 70% ee (90%) |
| 1h | 92% ee (89%) | 94% ee (99%) | 79% ee (86%) |

Only 16 experiments were enough!

Ooi T, *et al. Chem. Sci.* **2014**, *5*. 3645

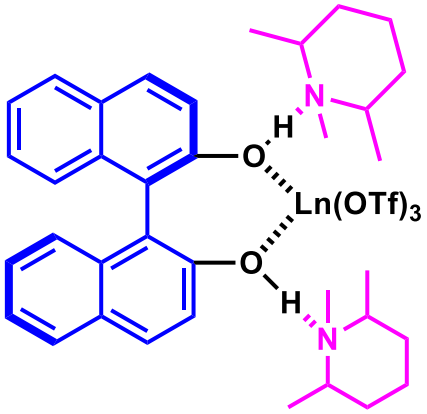
# Supramolecular Catalyst Strategy 3

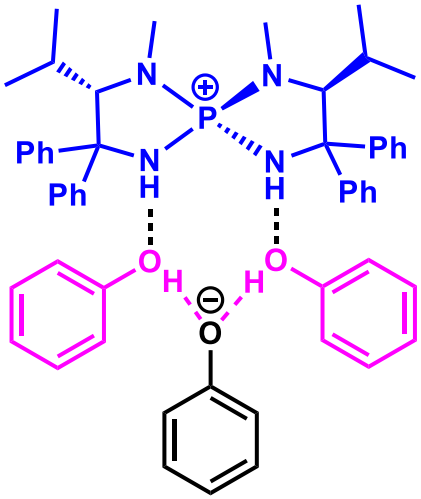
chiral component with achiral components

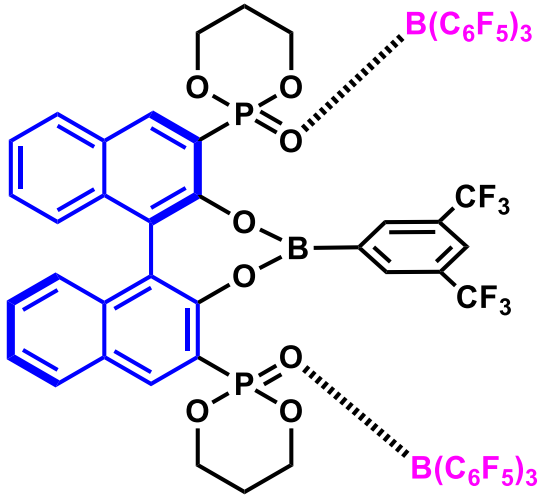



In order to get higher ee, the reaction field should be bulkier dissymmetrical environment. But such catalysts are often very complicated and the synthesis of the catalysts is very laborious.

Using hydrogen bond, Lewis acid-base pair and selective molecules interaction is attractive strategy to make better dissymmetrical environment based on chiral scaffold.

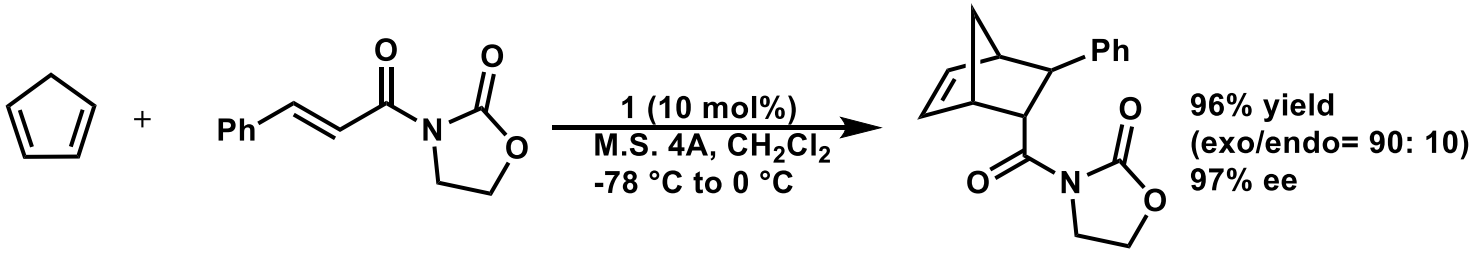


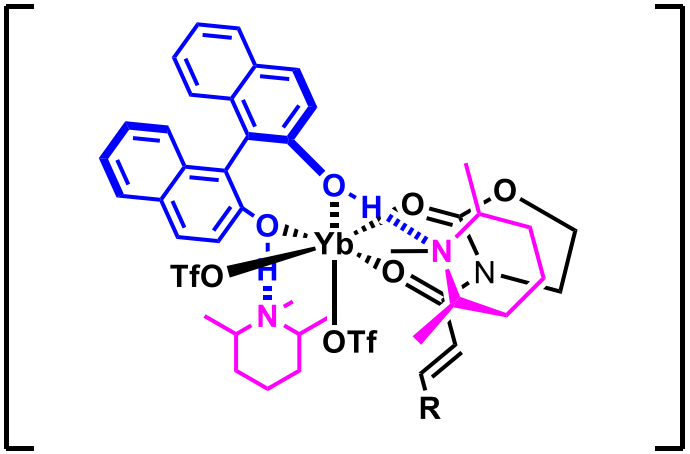



# Early Attempt to Use Supramolecular Catalyst

## Transmission of the chiral scaffold to other molecules

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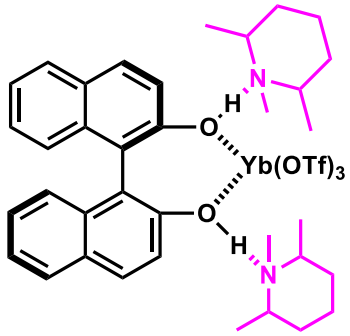
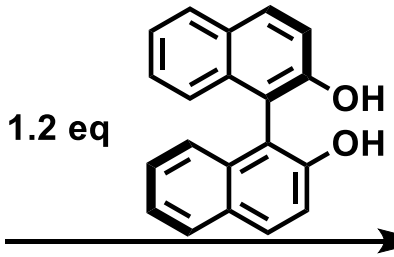



Catalyst1 is prepared from Yb(Otf)$_3$, (*R*)-BINOL, and a tertiary amine

The axial chirality is transferred to the amine part, which work as a "wall" in the transition state to shield one side of the dienophile.

S. Kobayashi, *et al. J. Am. Chem. Soc.* **1994**, *116*, 4083.
*Tetrahedron.* **1994**, *50*, 11623.

# The Effect of Tertiary Amine




1.2 eq

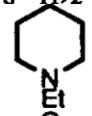
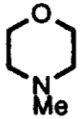
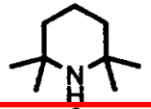
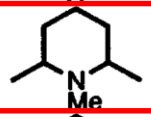
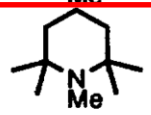
$Yb(OTf)_3$ (20 mol%)

MS 4A

2.4 eq amine

0 °C, 30 min

"chiral Yb triflate"

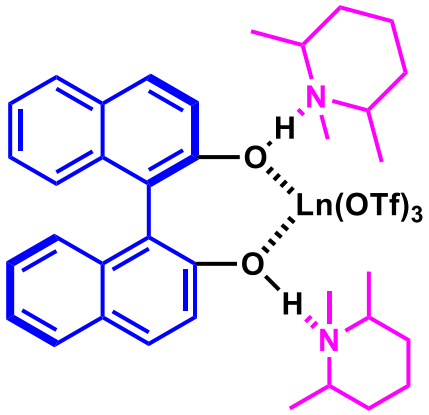
| Entry | Amine | MS [b] | Yield (%) | endo/exo | ee (%) |
|---|---|---|---|---|---|
| 1 | $Et_3N$ | — | 87 | 76/24 | 33 |
| 2 | $Bu_3N$ | — | quant. | 83/17 | 68 |
| 3 | $^iPr_2NEt$ | — | 82 | 85/15 | 70 |
| 4 | $^iPr_2NBu$ | — | 77 | 84/16 | 66 |
| 5 | $^iPr_2NH$ | — | 67 | 82/18 | 57 |
| 6 | $^iPr(c\text{-}C_6H_{11})NH$ | — | 90 | 82/18 | 54 |
| 7 | $(c\text{-}C_6H_{11})_2NH$ | — | 43 | 81/19 | 46 |
| 18 |  | — | 85 | 81/19 | 50 |
| 19 |  | — | 71 | 76/24 | 16 |
| 20 |  | — | 93 | 80/20 | 51 |
| 21 |  (*cis*) | — | 96 | 85/15 | 71 |
| 22 |  | — | 96 | 85/15 | 69 |

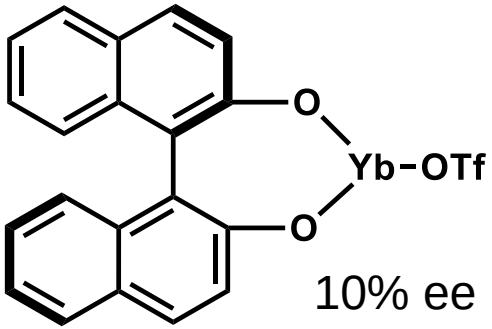
The amine strongly influenced the diastereo- and enantioselectivities.

+MS 4A → 77% yield, *endo/exo*= 89/11, 95% ee

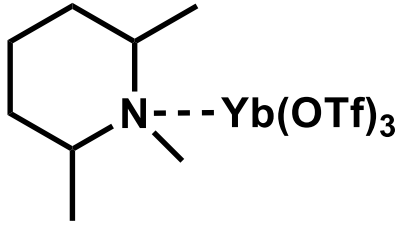
S. Kobayashi, *et al. Tetrahedron.* **1994**, *50*, 11623.

# The Existence of Weak Interaction




10% ee




sluggishly

**Table 6.** Comparison of $^{13}C$ NMR Chemical Shifts ($CD_2Cl_2$) of the Carbons of the *N*-Methyl Groups of *cis*-1,2,6-Trimethylpiperidine (TMP) and IR Wave Numbers ($CH_2Cl_2$) in the Region 930-1000 $cm^{-1}$

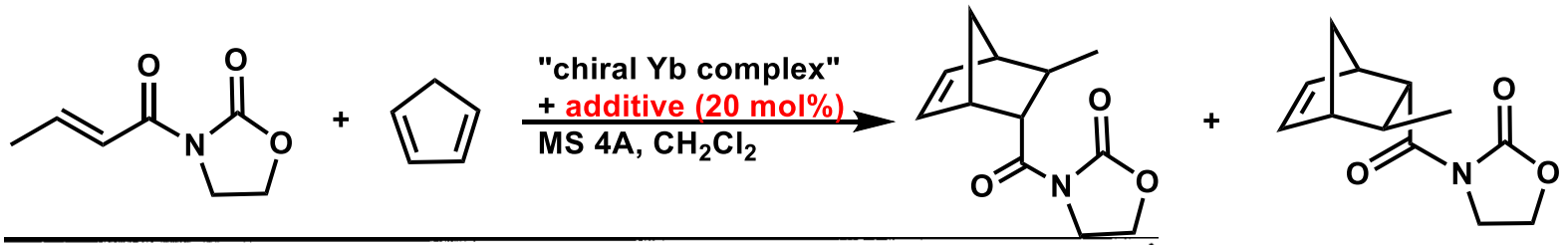
| Compound | δ (ppm) | Wave Number ($cm^{-1}$) |
|---|---|---|
| TMP | 38.2 | 947 |
| TMP + (R)-(+)-binaphthol ( 1 : 1 ) | 35.1 | 989, 947 |
| TMP + TfOH ( 1 : 1 ) | 34.1 | 958 |
| TMP + $Yb(OTf)_3$ + (R)-(+)-binaphthol + 3-acetyl-1,3-oxazolidin-2-one (Catalyst A) | 37.5 | 997, 955 |
| TMP + $Yb(OTf)_3$ + (R)-(+)-binaphthol + PAA (Catalyst B) | 38.5 | 982, 935 |

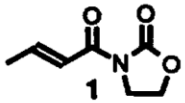
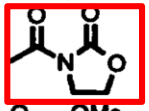
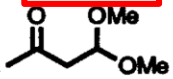
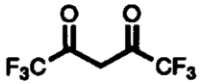
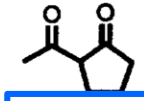
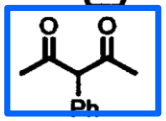
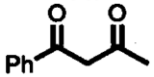
This table indicate that the existence of a weak interaction.

S. Kobayashi, *et al. J. Am. Chem. Soc.* **1994**, *116*, 4083.
*Tetrahedron.* **1994**, *50*, 11623.

# Additive is also Important Factor

S. Kobayashi, *et al. Tetrahedron.* **1994**, *50*, 11623.



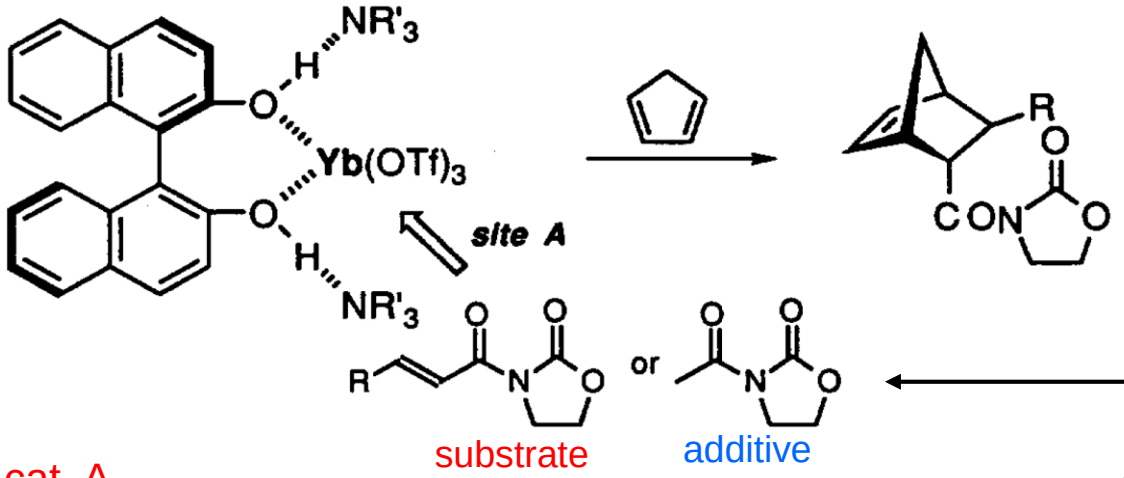

| Entry | Additive | Yield (%) | endo/exo | 2S,3R/2R,3S (ee (%))[b] |
|---|---|---|---|---|
| 1 |  | 66 | 87/13 | 94.0/ 6.0 (88) |
| 2 |  | 77 | 89/11 | 96.5/ 3.5 (93) |
| 3 |  | 81 | 86/14 | 90.5/ 9.5 (81) |
| 4 | | 54 | 77/23 | 53.5/46.5 (7)[d] |
| 5 |  | 58<br>80 | 78/22<br>79/21 | 75.5/24.5 (51)<br>55.0/45.0 (10)[d] |
| 6 | | 80<br>81 | 88/12<br>85/15 | 22.5/77.5 (55)<br>22.5/77.5 (55)[d] |
| 7 |  | 36 | 81/19 | 19.0/81.0 (62) |
| 8 |  | 69<br>83 | 88/12<br>93/ 7 | 15.5/84.5 (69)<br>9.5/90.5 (81)[c] |
| 9 |  | 77 | 78/22 | 33.0/67.0 (34)[d] |
| 10 | | 77<br>78 | 72/28<br>75/25 | 42.5/57.5 (15)<br>39.0/61.0 (22)[d] |

Additive are effective not only in stabilizing the catalyst, but also in **controlling the enantiofacial selectivity**.

**Both enantiomers could be prepared by the same chiral source!!!!!**

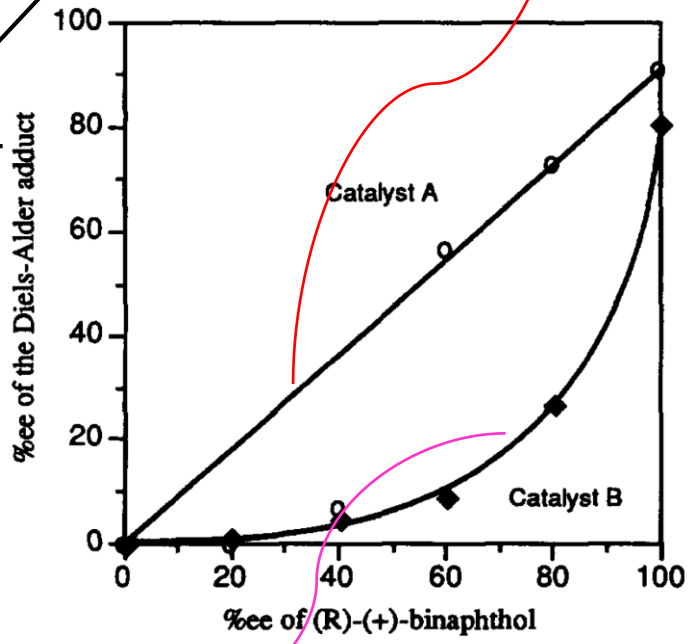
The enantioselectivities were controlled by the achiral ligands.

# Mechanism

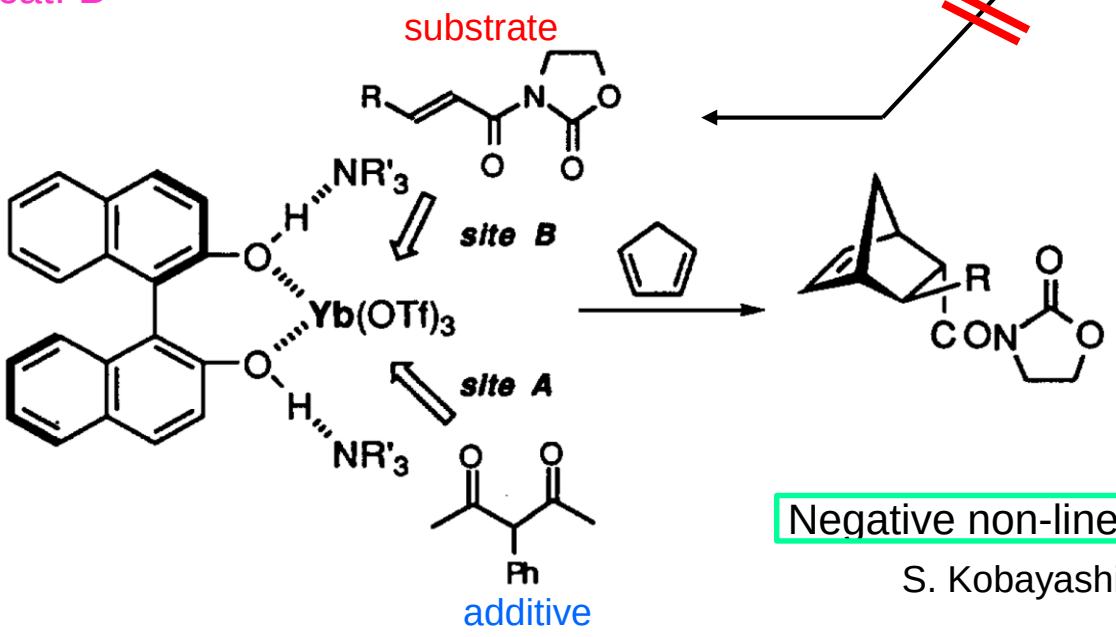



substrate and additive are under equilibrium condition.

Turnover…?




cat. B

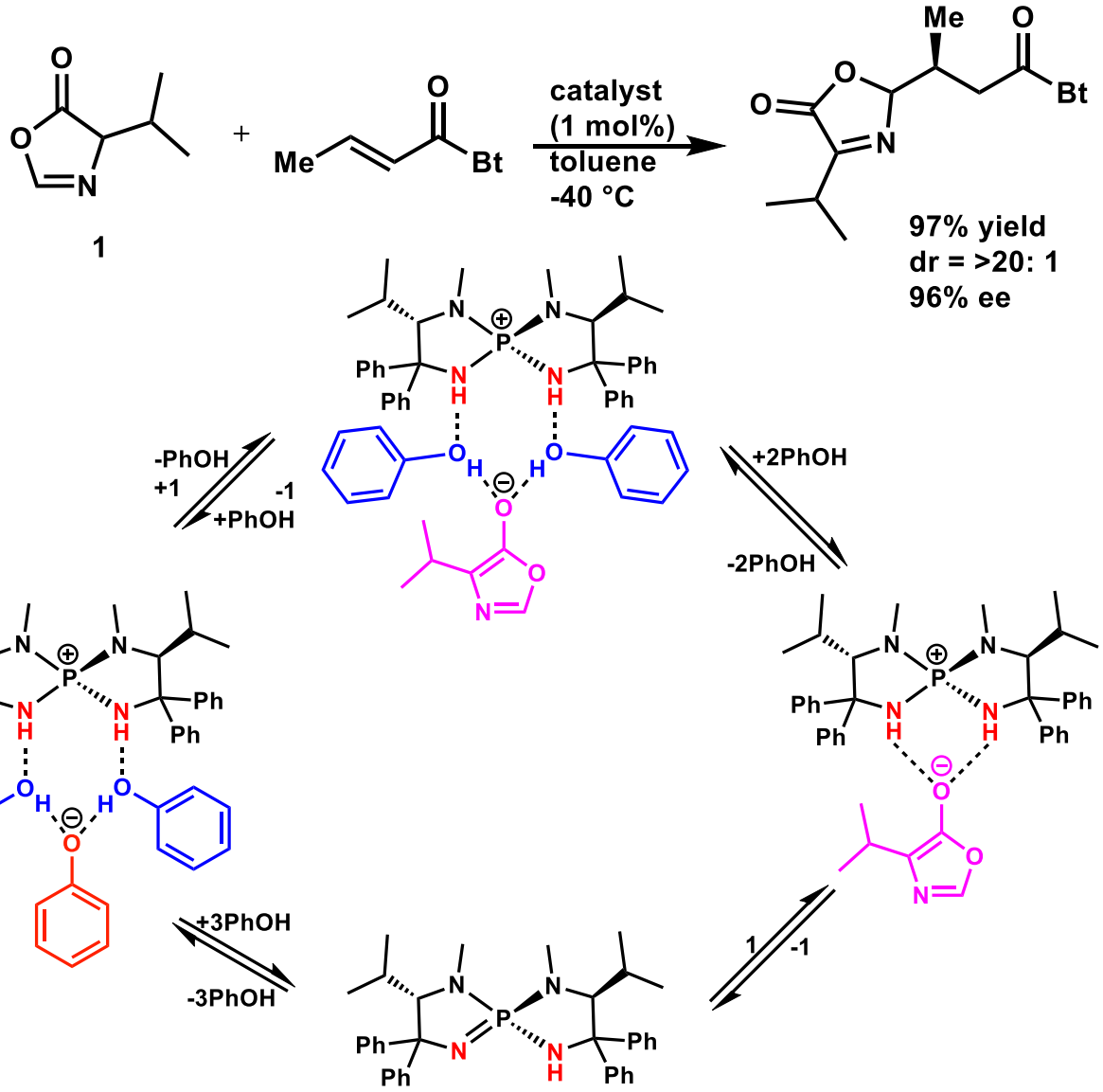



Negative non-linear effect

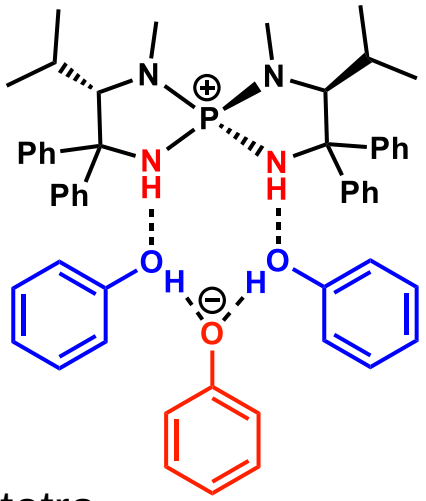
S. Kobayashi, *et al. J. Am. Chem. Soc.* **1994**, *116*, 4083.
*Tetrahedron.* **1994**, *50*, 11623.

# Supramolecular Catalyst Strategy3

## 1) Hydrogen bond + ion pair catalyst




catalyst 1a



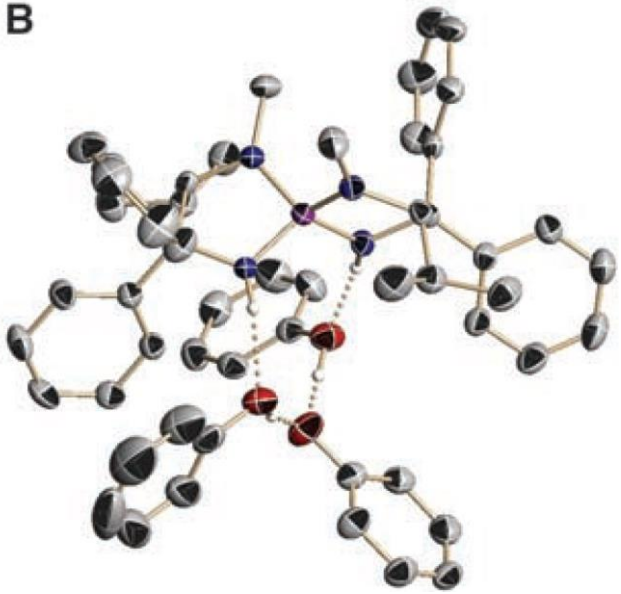
Chiral tetra-aminophosphonium cation is hydrogen-bonded via two phenol molecules to phenolate.

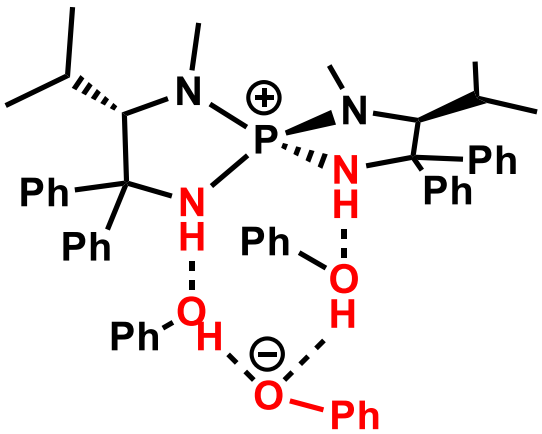
The chirality of aminophosphonium is relayed over two achiral phenols.

T. Ooi, *et al. Science*. **2009**. *326*. 120.

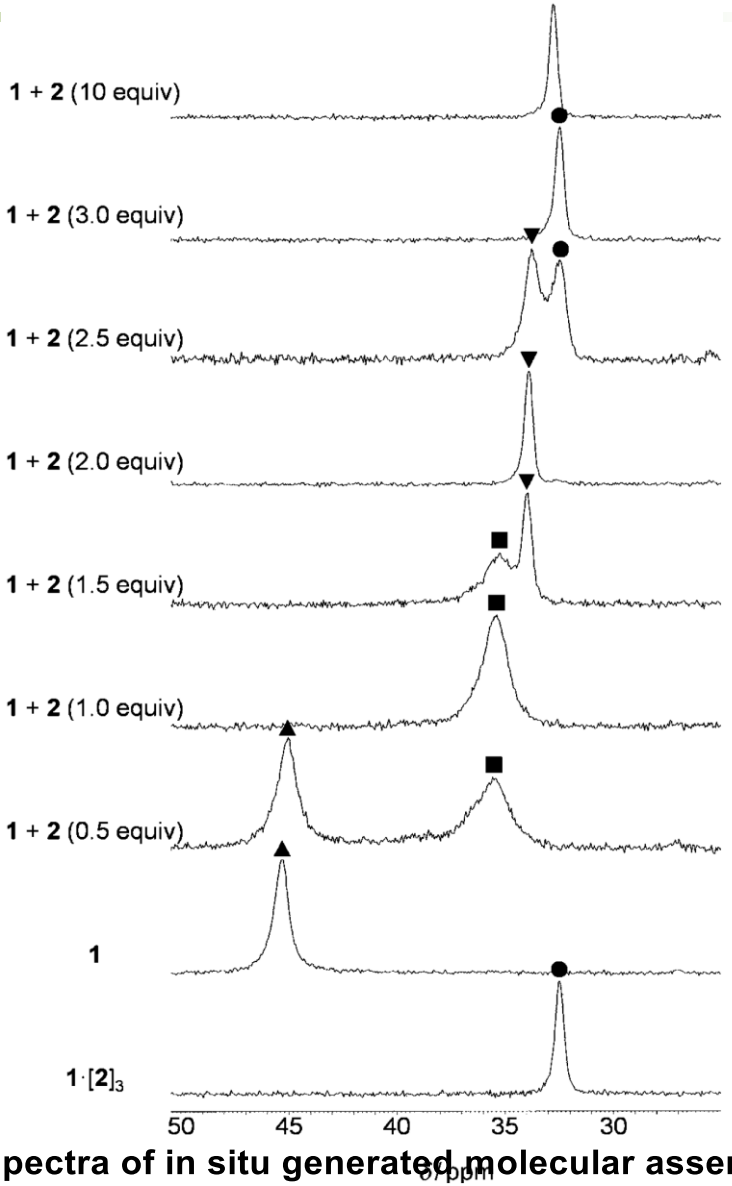
# Analysis of Interaction

Single-crystal x-ray diffraction analysis



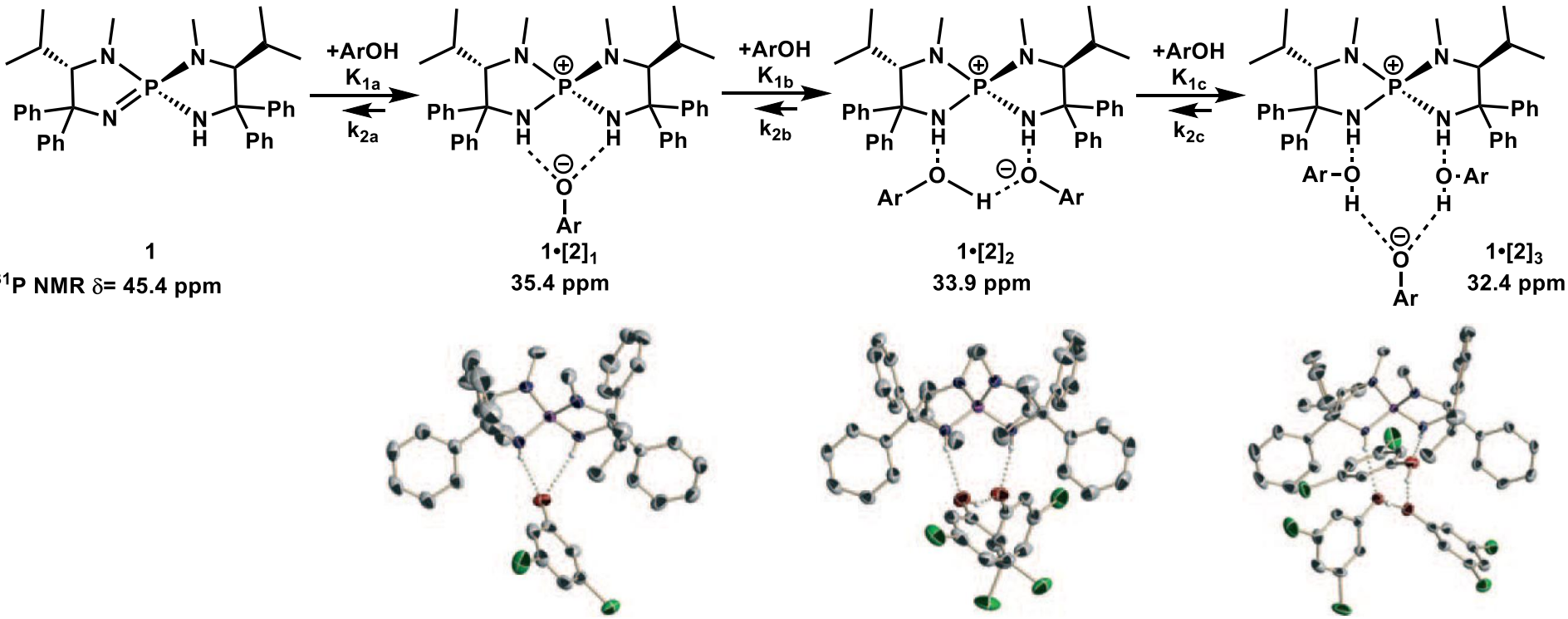

Ooi T, *et al. Science.* **2009**, *326*, 120.




**$^{31}$P NMR spectra of in situ generated molecular assembries of catalysts at -98 °C in toluene**

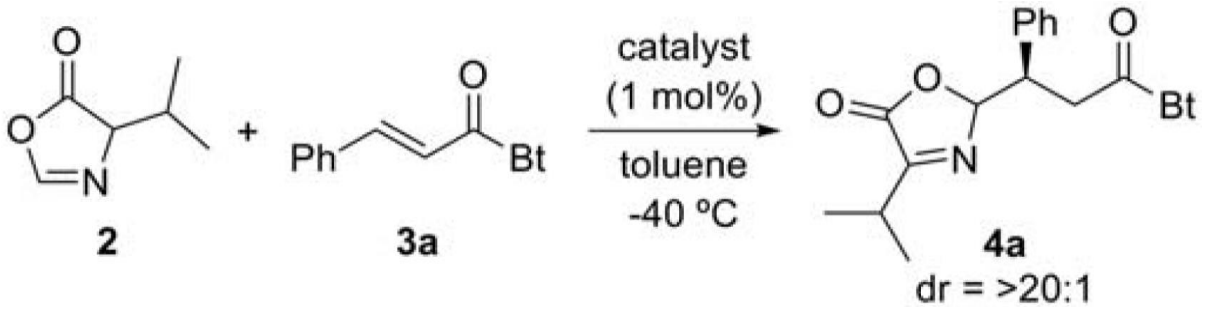
Ooi T, *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3681

# X-ray Crystal Analysis of Interaction




Ooi T, *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3681

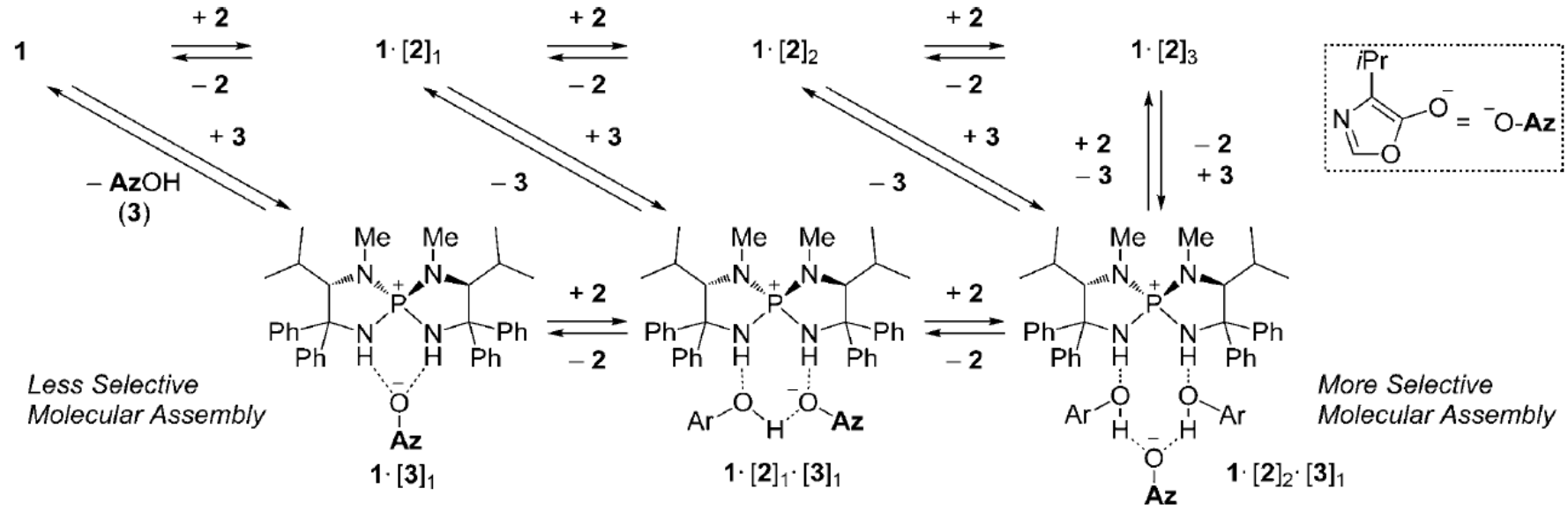
# The Effect of Phenol Derivative

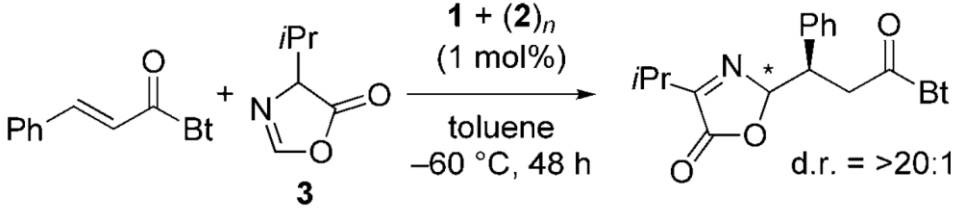



| ntry | Catalyst | Conc (mM) | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **1a**·$(PhO)_3H_2$ | 1 | 6 | 99 | 60 |
| 2 | **1a'** | 1 | 2 | 99 | 34 |
| 3 | **1a'** + 3PhOH | 1 | 10 | 98 | 62 |
| 4 | **1a·2'** + 3PhOH | 1 | 16 | 87 | 61 |
| 5 | **1a**·(4-Me–$C_6H_4O)_3H_2$ | 1 | 4 | 96 | 58 |
| 6 | **1a**·(4-Cl–$C_6H_4O)_3H_2$ | 1 | 10 | 97 | 75 |
| 7 | **1a**·(2-Cl–$C_6H_4O)_3H_2$ | 1 | 12 | 94 | 63 |
| 8 | **1a**·(3-Cl–$C_6H_4O)_3H_2$ | 1 | 6 | 93 | 70 |
| 9 | **1a**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 1 | 16 | 92 | 80 |
| 10* | **1a**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 2 | 24 | 99 | 85 |
| 11† | **1a**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 5 | 18 | 98 | 89 |
| 12‡ | **1a**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 10 | 20 | 94 | 89 |
| 13§ | **1a**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 10 | 4 | 99 | 87 |
| 14§ | **1b**·(3,5-$Cl_2$–$C_6H_3O)_3H_2$ | 10 | 4 | 95 | 95 |

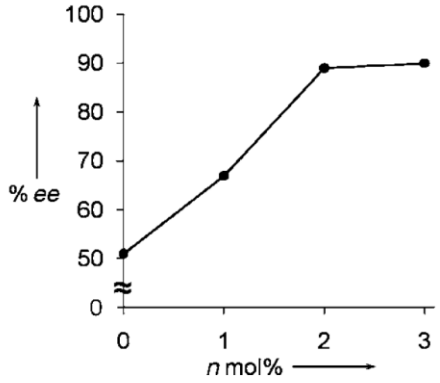
T. Ooi, *et al. Science*. **2009**. *326*. 120.

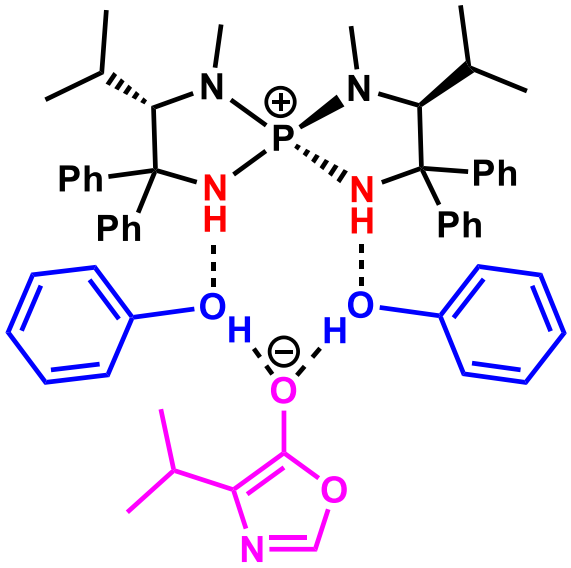
# The Importance of Phenols



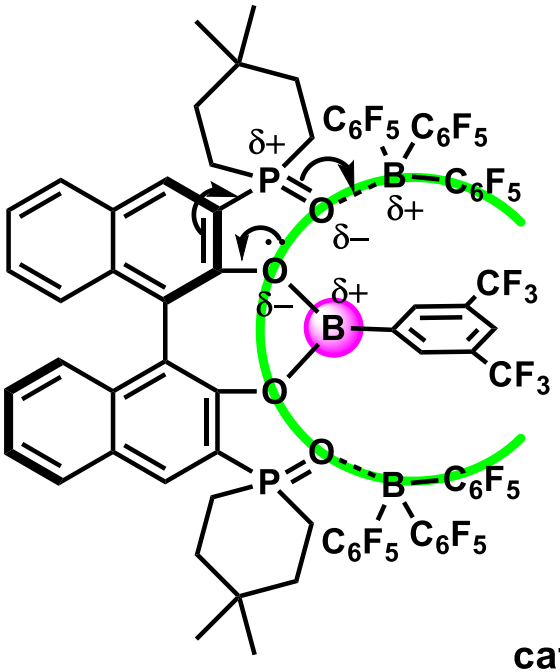

*n* = 0: 85%, 51% *ee*
*n* = 1: 81%, 67% *ee*
*n* = 2: 82%, 89% *ee*
*n* = 3: 89%, 90% *ee*



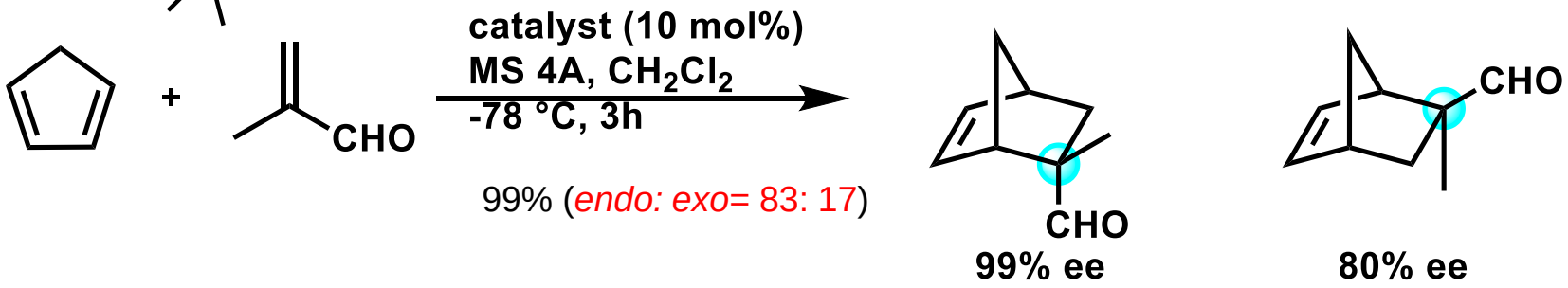




Ooi T, *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 3681

# Supramolecular Catalyst Strategy 3



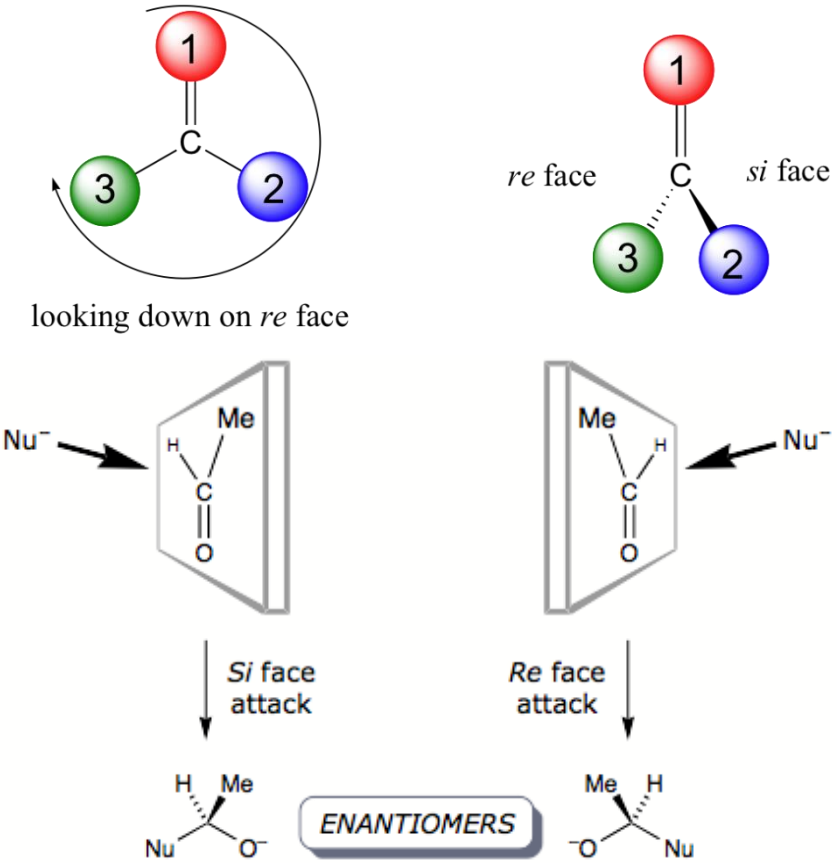

Subcomponents(=2B($C_6F_5$)$_3$ )act as a bulky functional group to make a **chiral cavity**. And at once, they increase the activity of catalyst center.

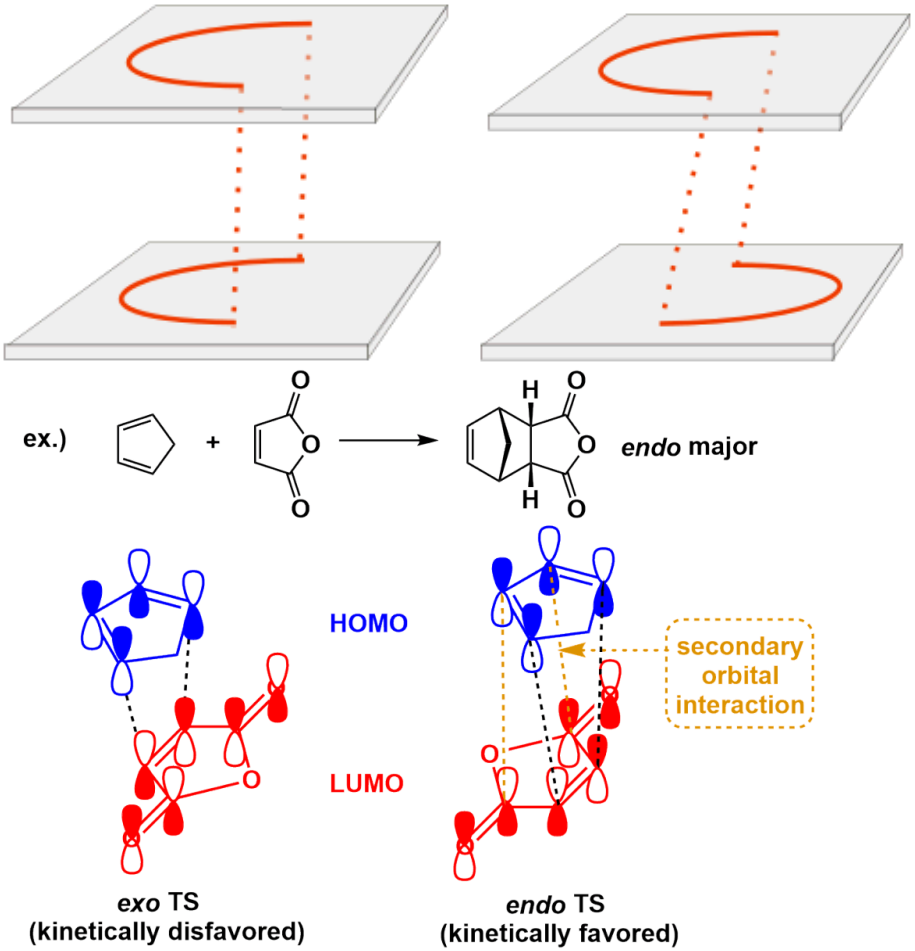



Chiral cavity which consists of subcomponents is effective for anomalous Diels-Alder reaction.

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.

# Enantio Selectivity VS *endo/exo* Selectivity



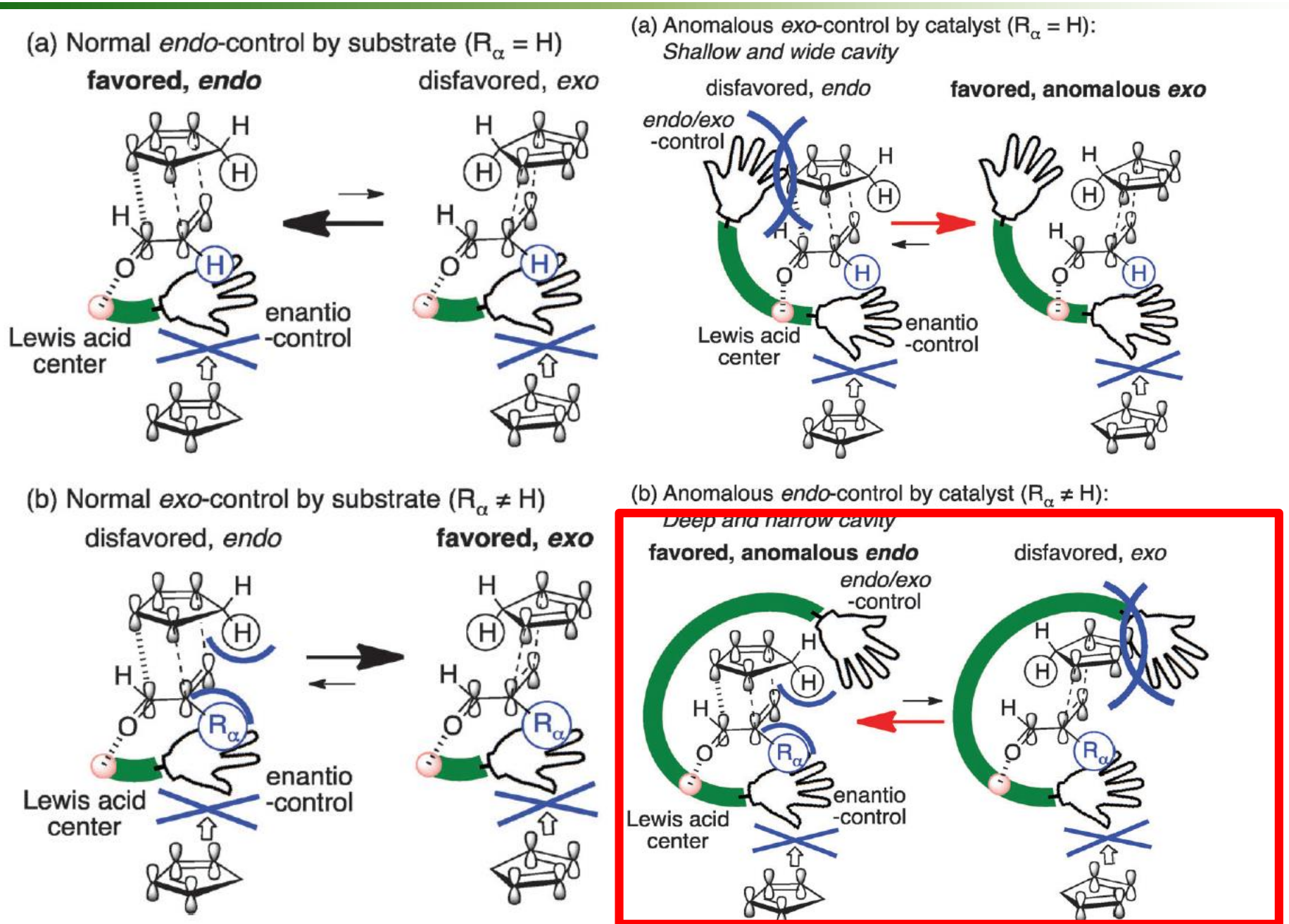




Covering the re or si face is enough to get enantiomer.

Covering one of the faces doesn't matter.

➡ Completely different two strategies are necessary to get endo/exo-enantio- selectivity.

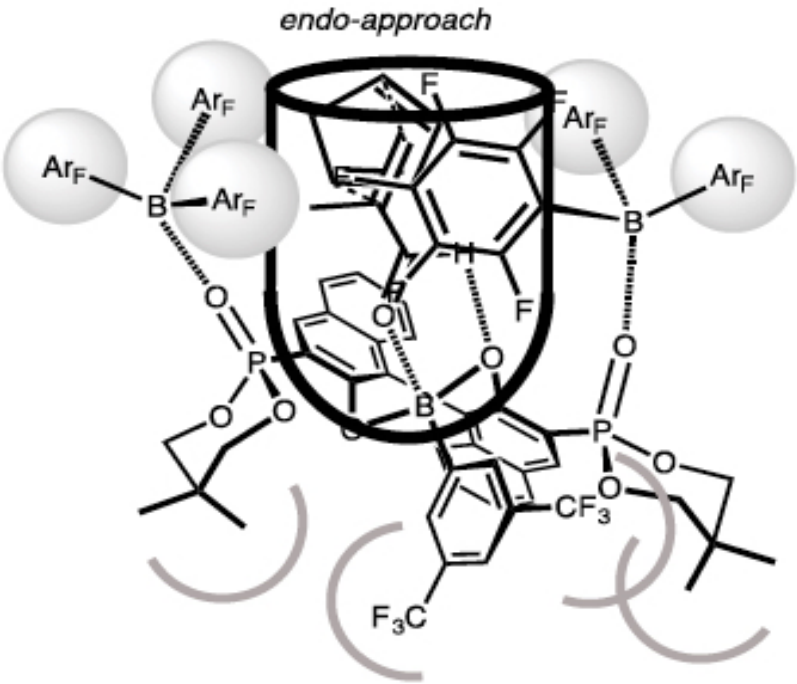
# Prof. Ishihara's Strategy



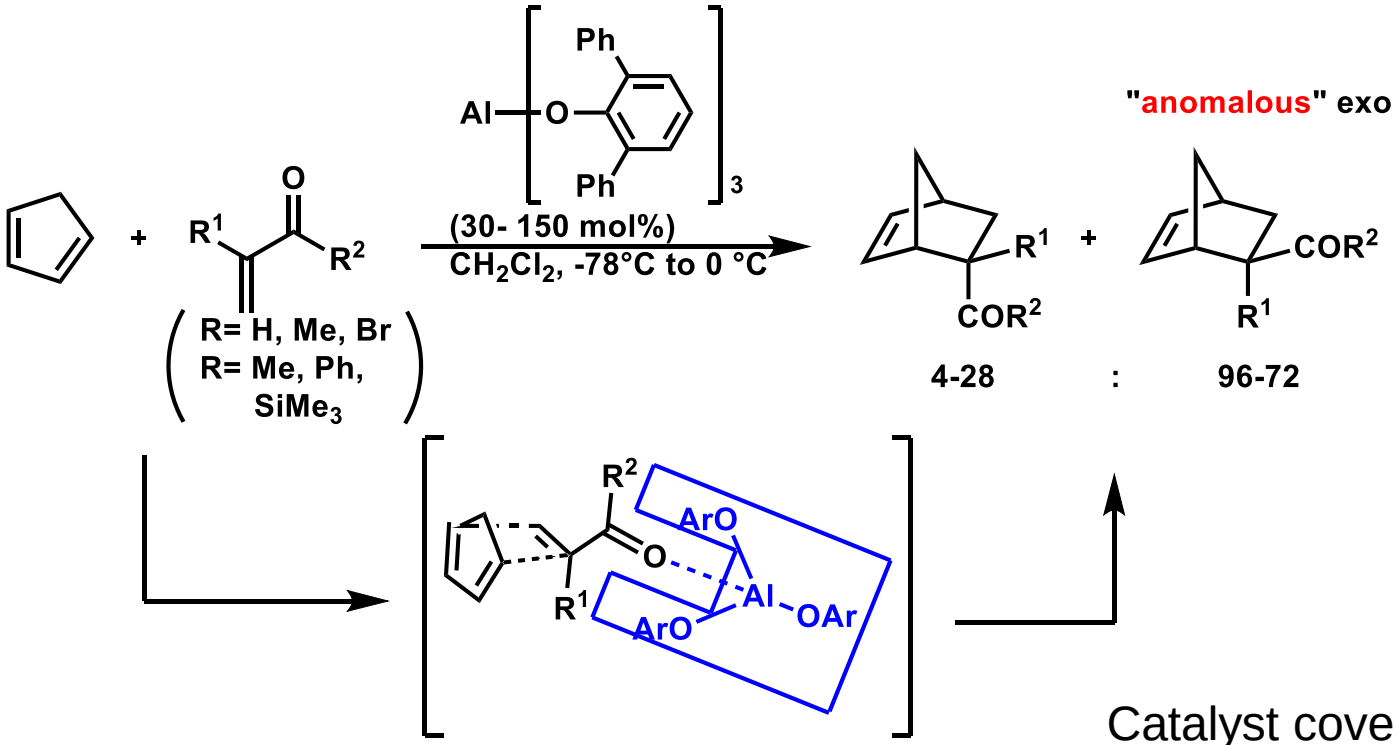
# Supramolecular Chiral Cavity

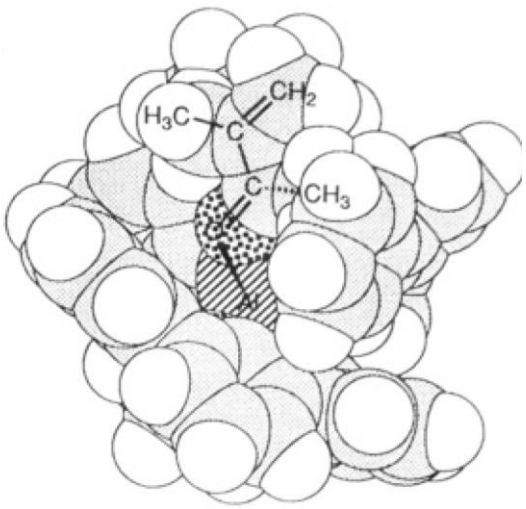
**Kazuaki Ishihara**

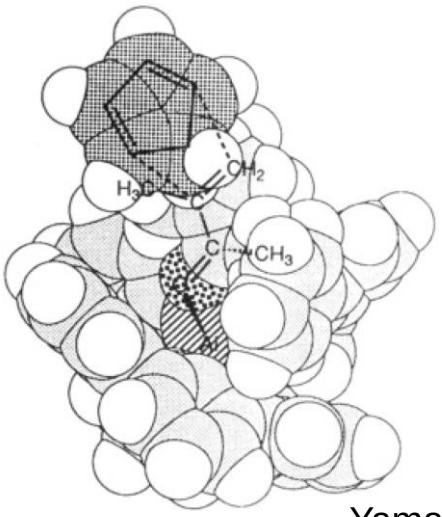
*Kazuaki Ishihara was born in Aichi, Japan, in 1963, and received his PhD from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for three months in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After he completed his postdoctoral studies with Professor E. J. Corey at Harvard University (15 months beginning in 1991), he returned to Japan and joined Professor Hisashi Yamamoto's group at Nagoya University as an assistant professor in 1992, and became associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis toward green and sustainable chemistry, acid–base combination chemistry, and designer supramolecular acid–base combined catalysts.*



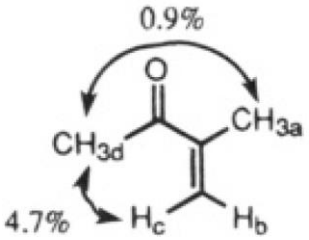
# The First Anomalous Diels-Alder Reaction

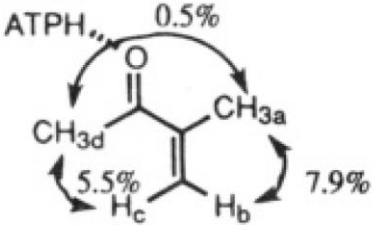




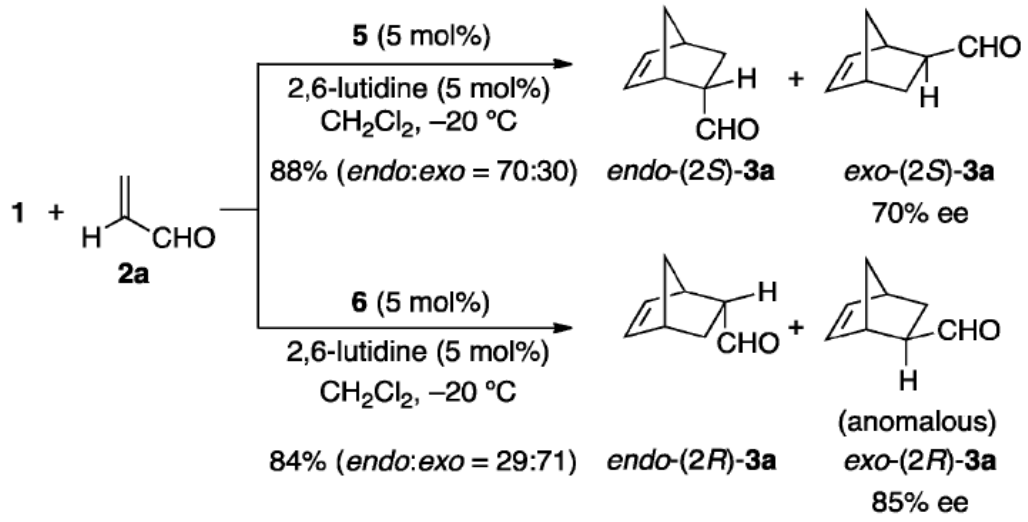
Catalyst covers around carbonyl group and inhibit the "secondary orbital interactions".

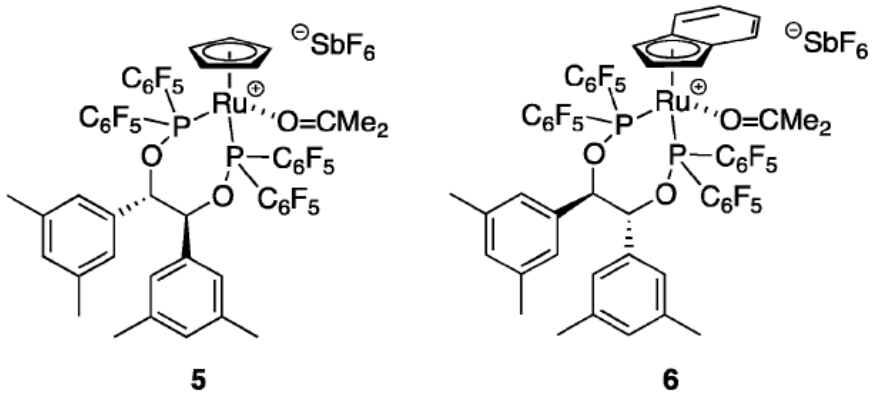


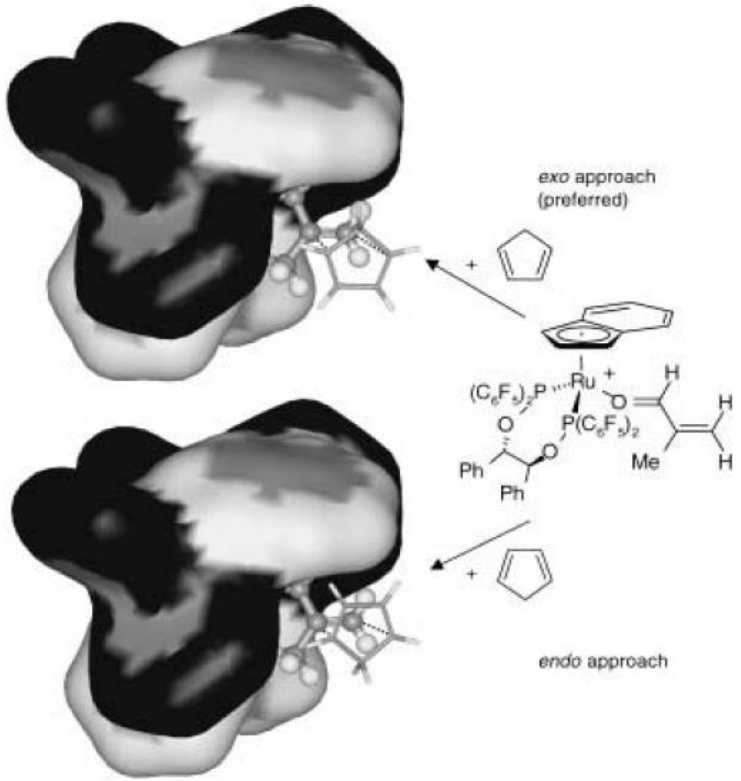

Yamamoto H, *et al. J. Am. Chem. Soc.* **1994.** *116.* 4131.

# The First Enantio and *endo/exo* Control



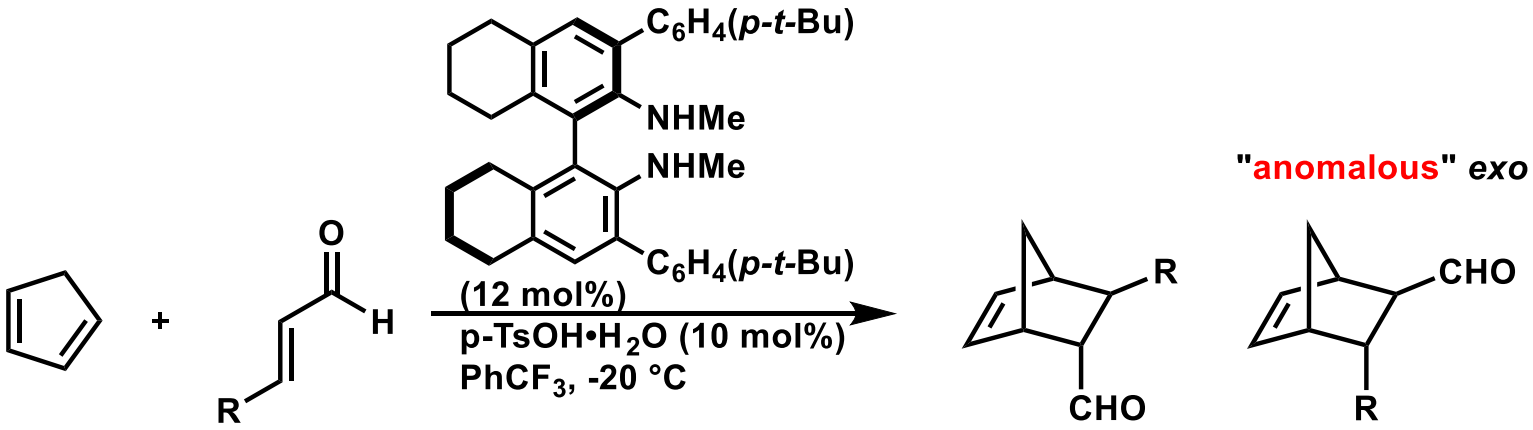

**5** **6**



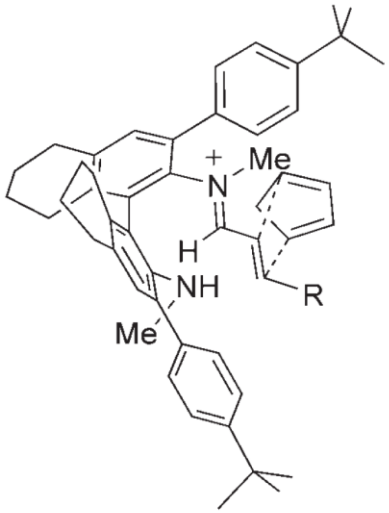

Heteroleptic complex coveres carbonyl group
and at once, makes enantiomeric reaction field.

Kündig, *et al. Angew. Chem. Int. Ed.* **2001**, *40* 4481.

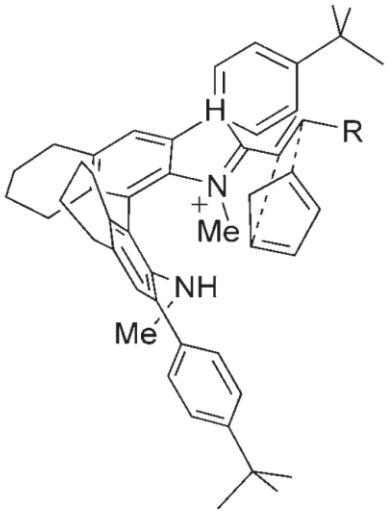
# The First Organic Catalyst




| | | |
|---|---|---|
| R= Ph: 160h, 80% (endo/exo= 7:93) | 91% ee | 92% ee |
| R= H: 45h, 93% (endo/exo= 34:66) | 68% ee | 86% ee |



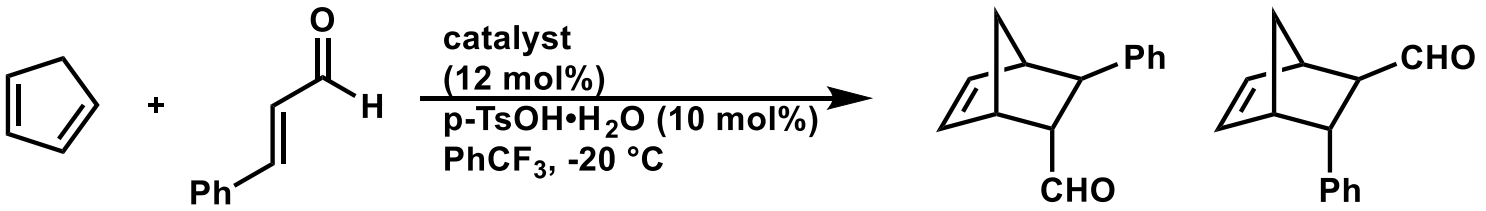

TS1



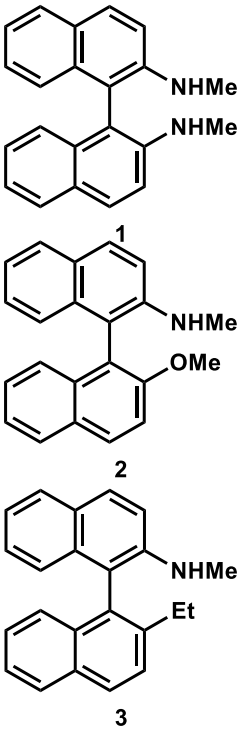

TS2

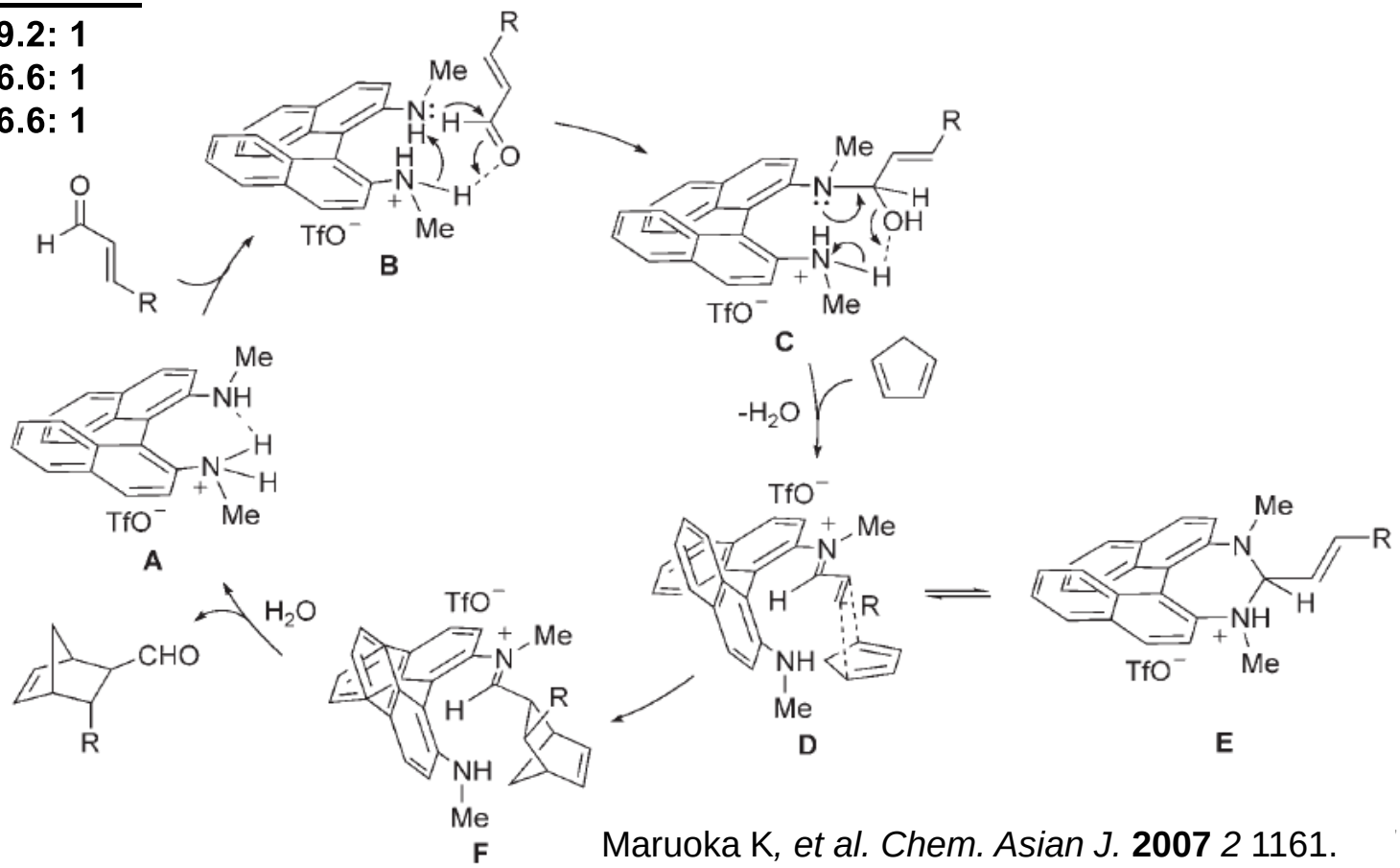
Maruoka K, *et al. Org. Lett.* **2006**, *8*. 2687.
*Chem. Asian J.* **2007** *2* 1161.

# Mechanism



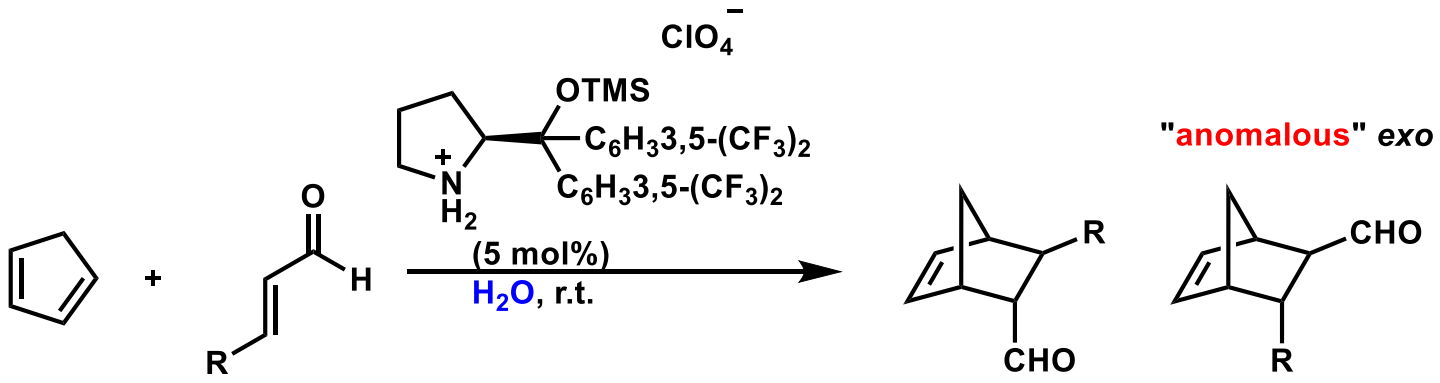

| catalyst | yield | *exo: endo* |
|---|---|---|
| 1 | 99% | 9.2: 1 |
| 2 | 12% | 6.6: 1 |
| 3 | 13% | 6.6: 1 |



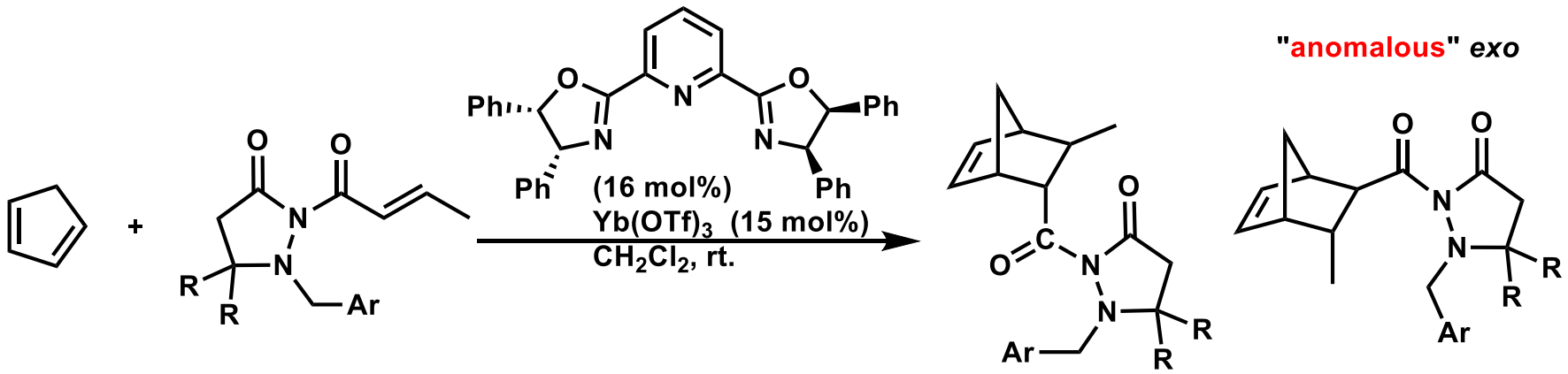

Maruoka K, *et al. Chem. Asian J.* **2007** *2* 1161.

# Other Example




R= Ph: 7h, 93% (endo/exo= 20: 80) 91% ee 92% ee
R= H: 24h, 85% (endo/exo= 38:62) 68% ee 86% ee

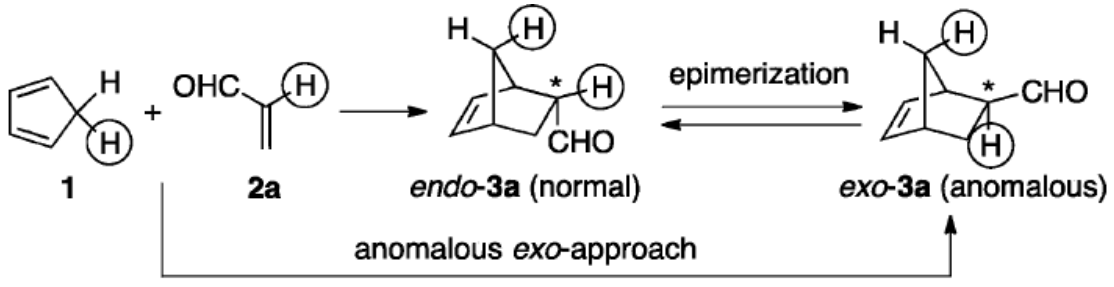
Hayashi Y, *et al. Angew. Chem.* **2008**, *120*. 6736.
*Angew. Chem. Int. Ed.* **2008**, 47. 6634.



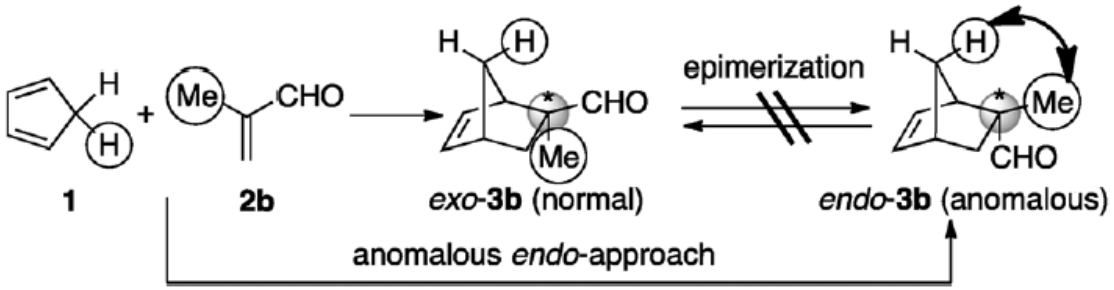

R= Et, Ar= 2,4,6-$Me_3C_6H_2$: 62%[*endo:exo*= 16:84 (93% ee)]
R= Me Ar= Ph : 93%[*endo:exo*= 56:44 (84% ee)]

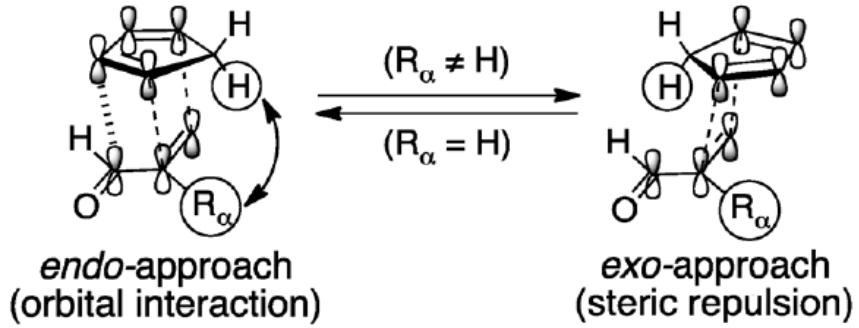
M. P. Sibi, *et al. Synlett.* **2008**,2655

# Epimerization



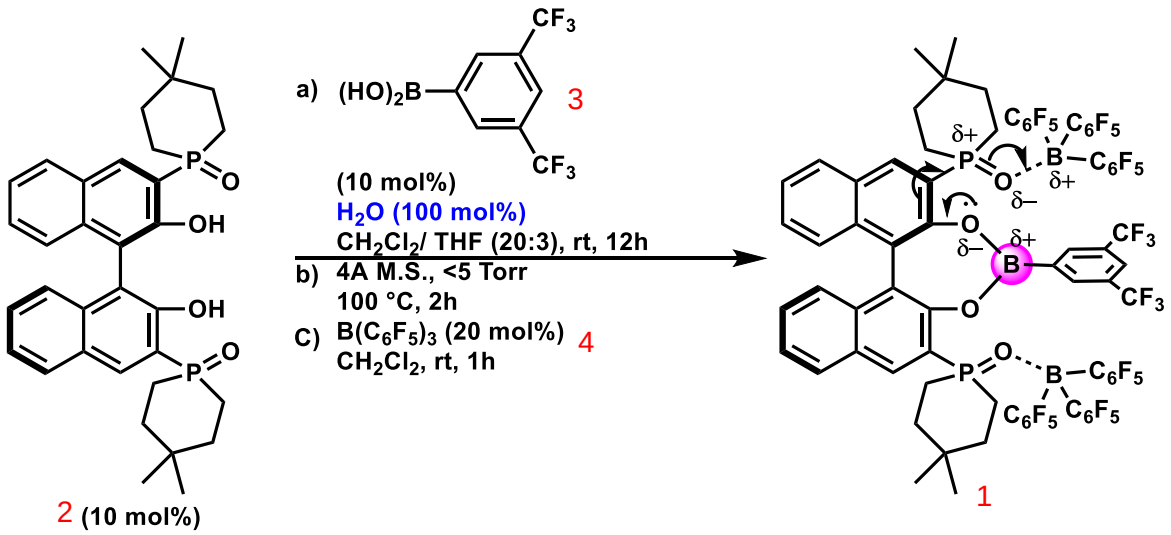

(1)

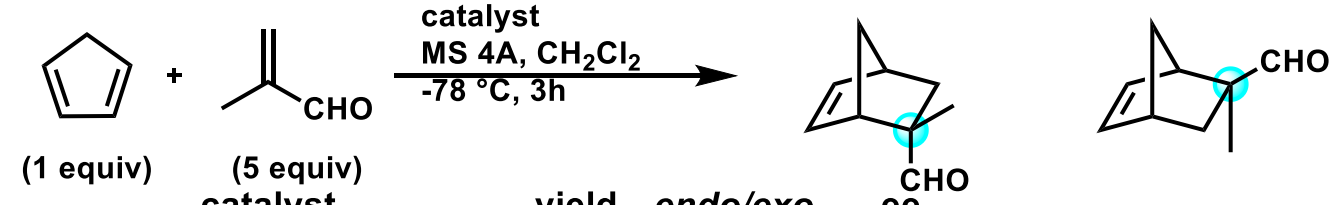



K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.

# $B(C_6F_5)_3$ Function as Bulky Groups and LLA




| catalyst | yield | *endo/exo* | ee |
|---|---|---|---|
| 1 (10 mol%) | 99% | 83:17 | 99% (*endo*) |
| 2 (10 mol%) | 0% | | |
| 3 (10 mol%) | >99% | 6:94 | |
| 4 (10 mol%) | 93% | 12:88 | |
| 2 (10 mol%) + 3 (10 mol%) | 2% | | |
| 2 (10 mol%) + 4 (20 mol%) | 0% | | |

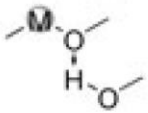
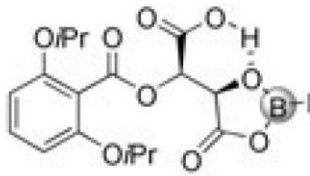
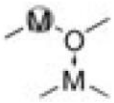
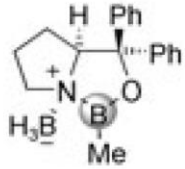
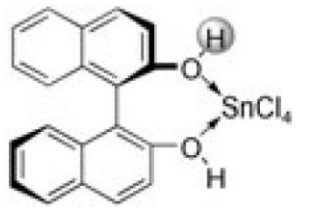
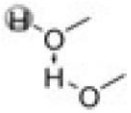
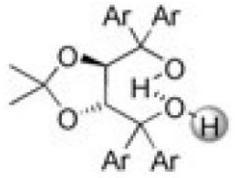
Catalytic anomalous end-selective enantioselective Diels-Alder ractions with α-substituted acroleins

P=O…$B(C_6F_5)_3$ moieties are critical not only for bulky functional group, but also for LLA catalyst.

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.

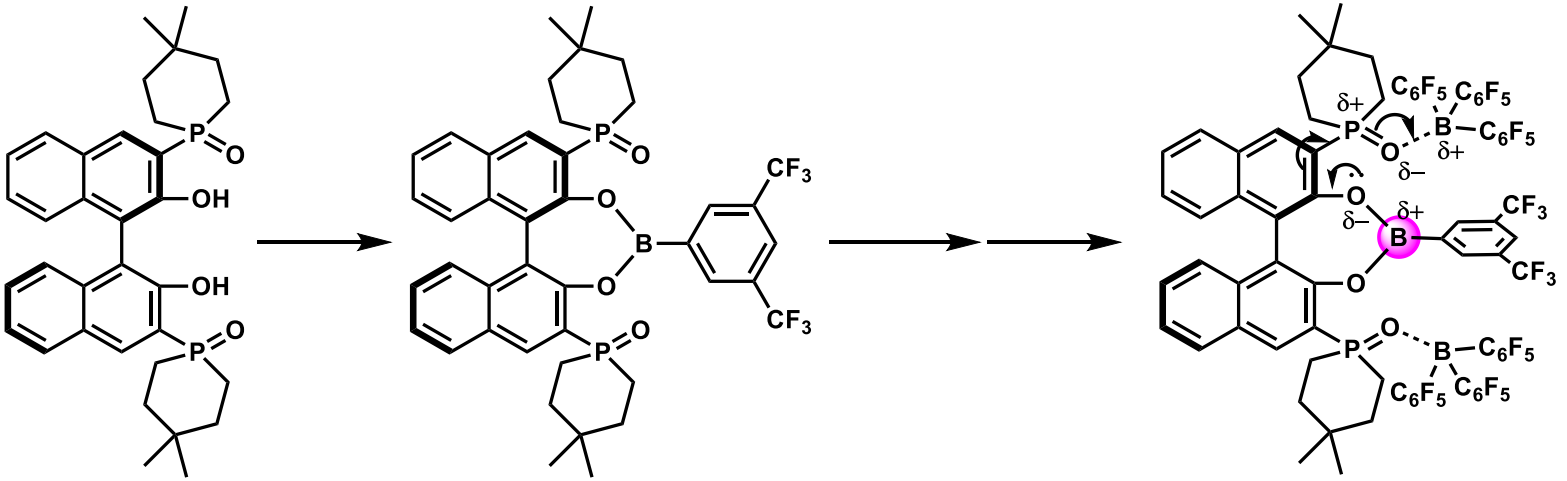
# What is LLA?

LLA= Lewis acid assisted Lewis acid catalyst
LLA is one of the combined acid catalysis strategies.

| Catalyst system | General structure | Examples |
|---|---|---|
| Brønsted acid assisted Lewis acid catalyst (BLA)<br>Enhancement of Lewis acidity by the combination with Brønsted acid |  |  |
| Lewis acid assisted Lewis acid catalyst (LLA)<br>Enhancement of Lewis acidity by the combination with Lewis acid |  |  |
| Lewis acid assisted Brønsted acid catalyst (LBA)<br>Enhancement of Brønsted acidity by the combination with Lewis acid | |  |
| Brønsted acid assisted Brønsted acid catalyst (BBA)<br>Enhancement of Brønsted acidity by the combination with Brønsted acid |  |  |

Yamamoto H. and Futatsugi K, *Angew. Chem. Int. Ed.* **2005**, *44*. 1924

# NMR and Intermediate

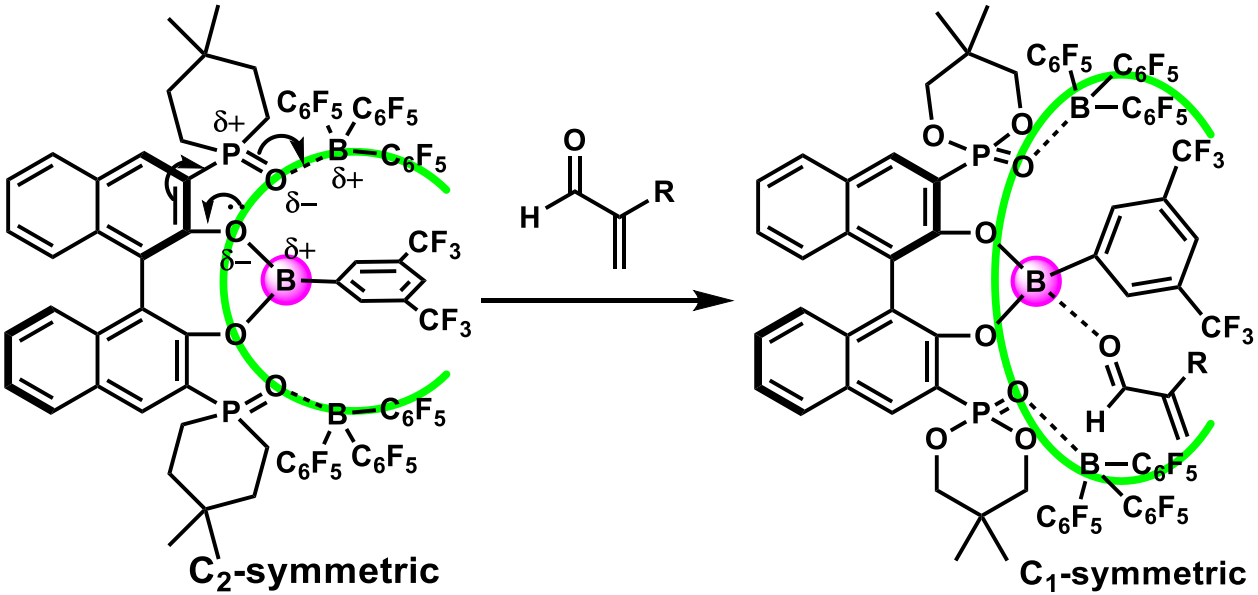


$^{31}$P NMR ($CDCl_2$)
δ 19.16 ppm

$^{31}$P NMR ($CDCl_2$)
δ 17.91 ppm

$^{31}$P NMR ($CDCl_2$)
δ 9.42 ppm

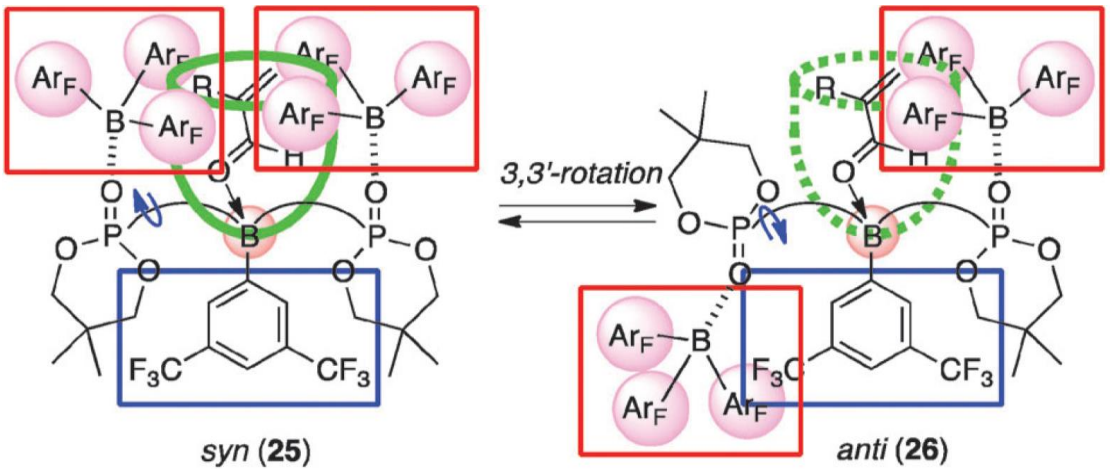
Ishihara K, *et al. Chem. Commun*. **2012,** *48*. 4273



$C_2$-symmetric

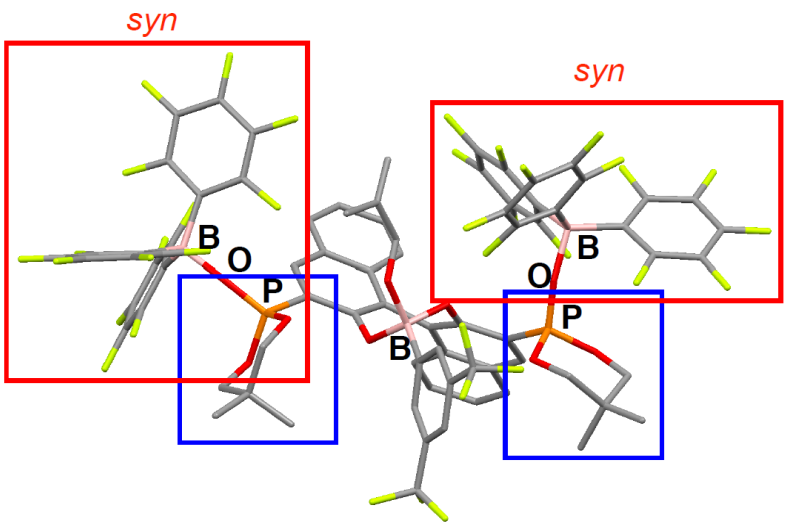
$C_1$-symmetric

# Theoretical Calculation

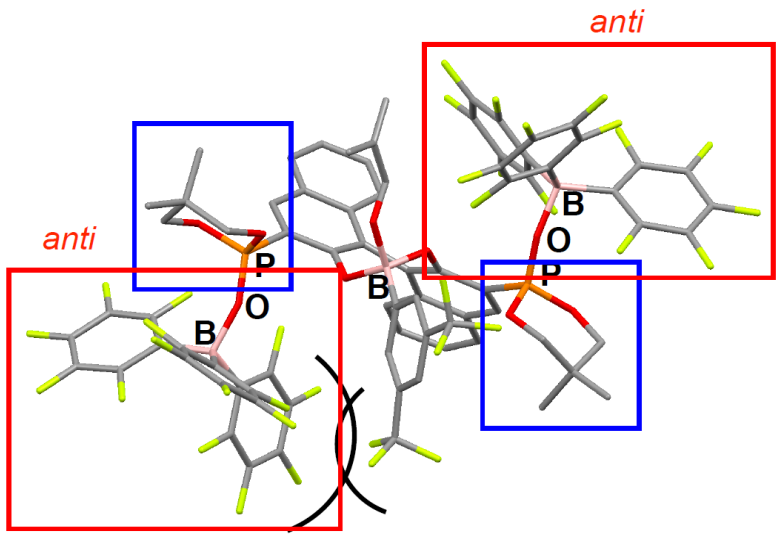



*syn* (**25**) *anti* (**26**)

In fact, the two flexible subcomponents could have a *syn* conformation.
It is more stable than the *anti* conformation by 3.86 kcal/ mol.



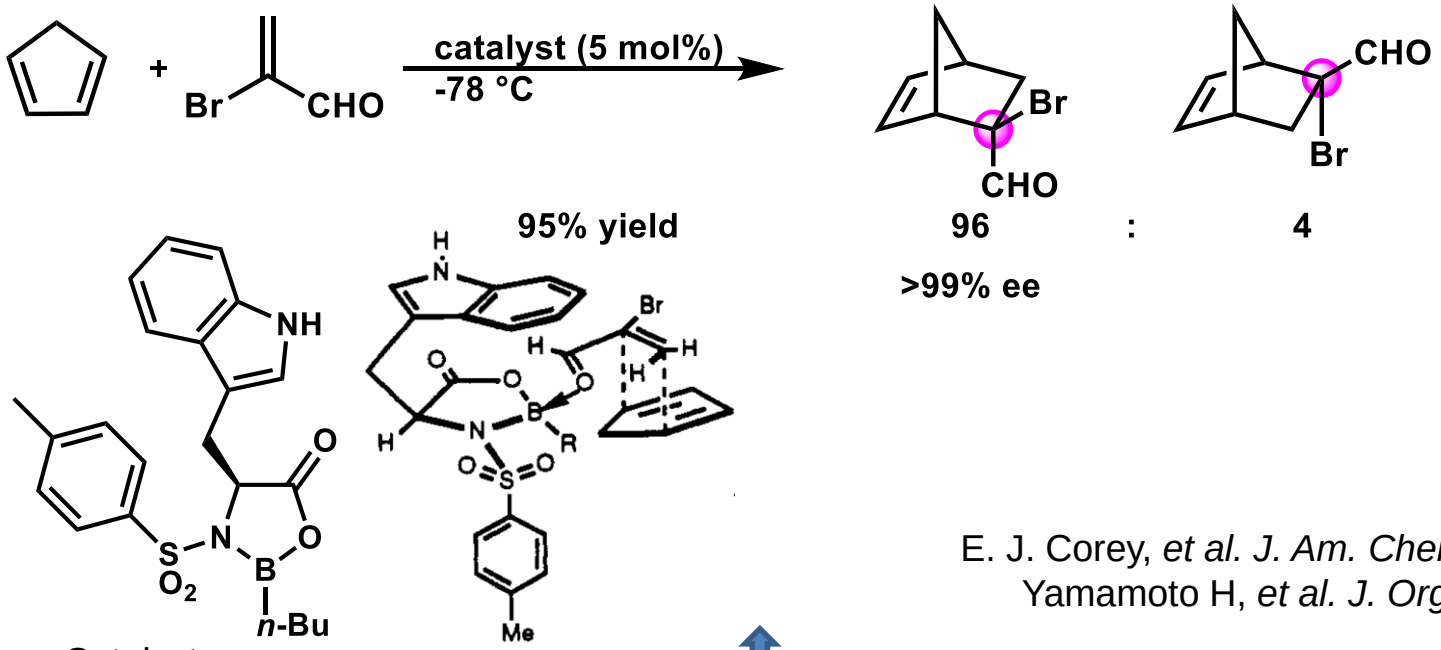

*syn*-form (**S13**) (0 kcal/mol)



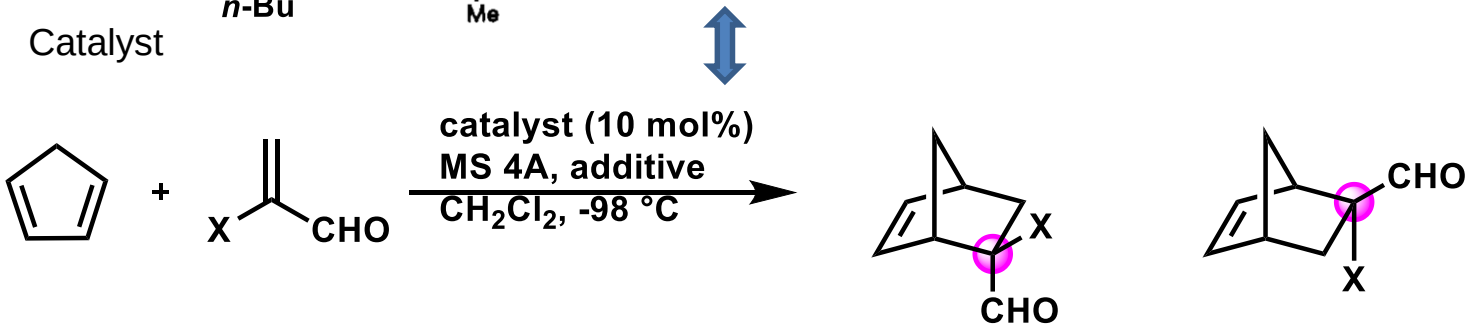

*anti*-form (**S14**) (+ 3.86 kcal/mol)

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.
*Chem. Commun*. **2012,** *48*. 4273.

# Precedent Works and Results



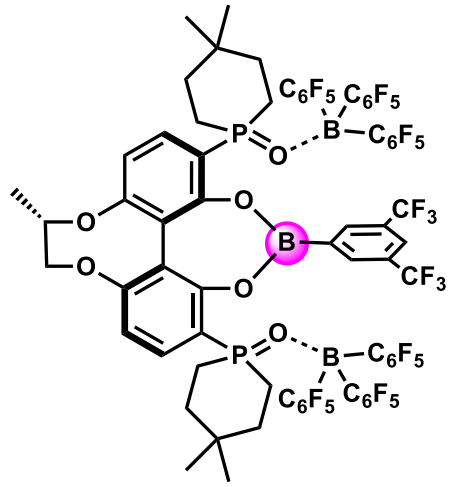

E. J. Corey, *et al. J. Am. Chem. Soc.* **1991**, *113.* 8967.
Yamamoto H, *et al. J. Org. Chem.* **1989,** *54*. 1481.



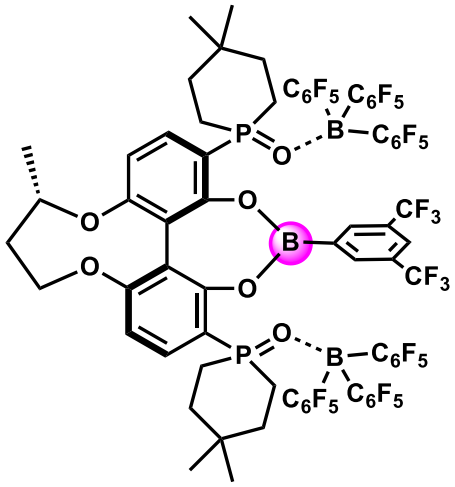

| X | catalyst | yield | *endo:exo* | ee | | catalyst | *endo:exo* |
|---|---|---|---|---|---|---|---|
| Br | 1 | 94% | 93:7 | >99% | | $B(C_6F_5)_3$ | 15:85 |
| Cl | 2 | >99% | 88:12 | >99% | | $B(C_6F_5)_3$ | 10:90 |
| F | 3 | >99% | 82:18 | 98% | | $B(C_6F_5)_3$ | * 49:51 |

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.
*Chem. Commun*. **2012,** *48*. 4273.

# Tuning for α-halo-acrolein



1



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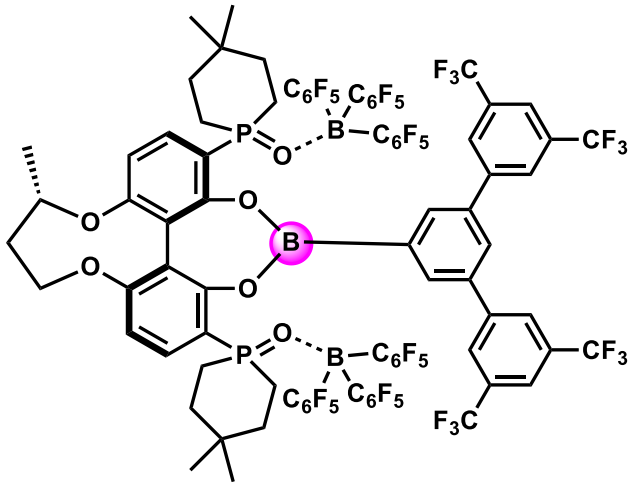
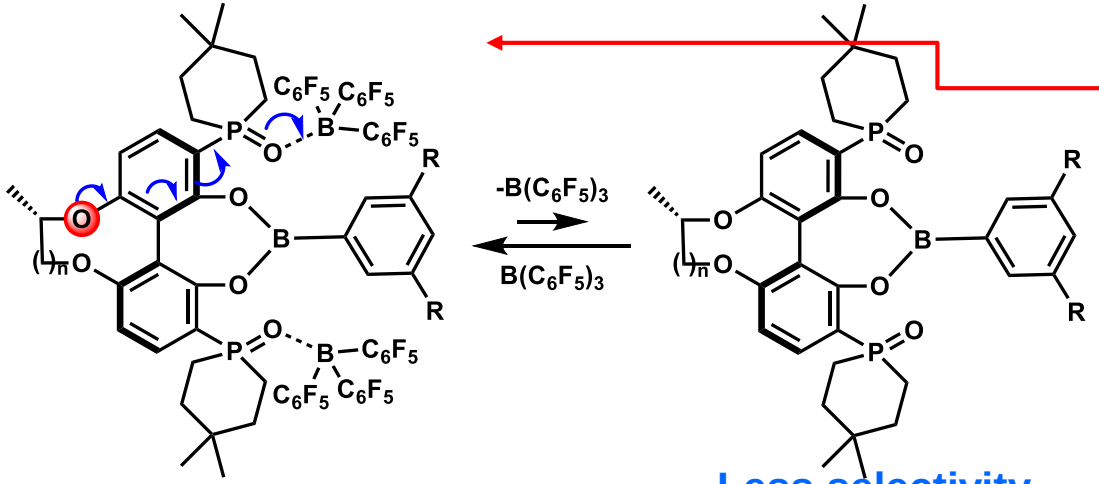
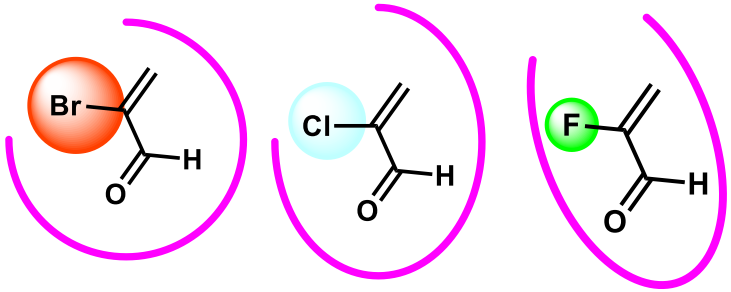


3

Is resonance effect important?




Less selectivity




dihedral angle? Resonance effect?

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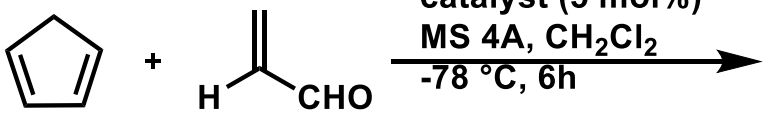
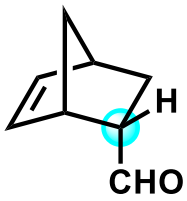
*Chem. Commun*. **2012,** *48*. 4273.

# The Cavity can be Applied for Acrolein

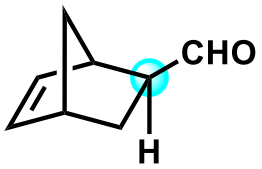
Same strategy




23% ee

"anomalous" exo

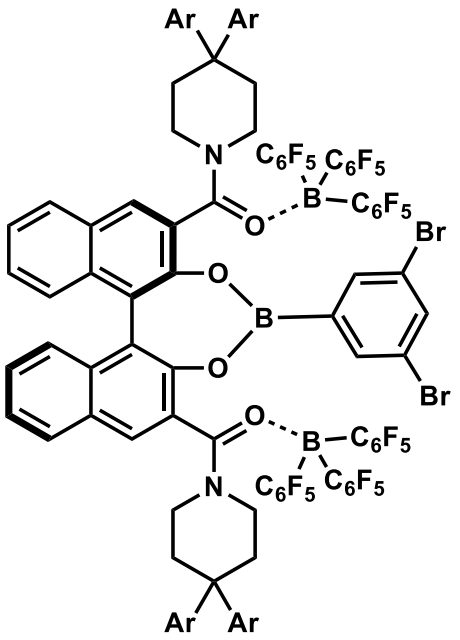



94% ee

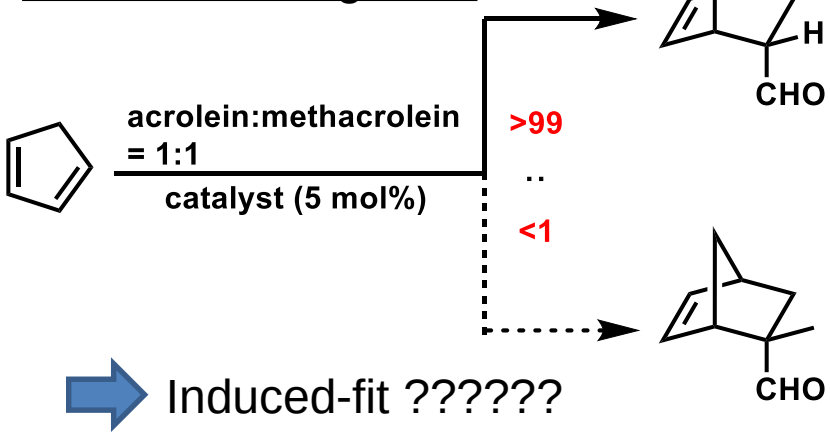
>99% yield
endo/exo= 20/80

with $B(C_6F_5)_3$

>99% yield
endo/exo= 86/14

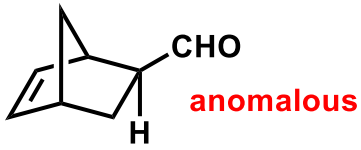



Molecular recognition




*endo*

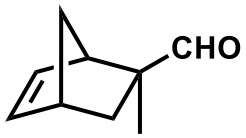
*exo*




anomalous

20:80

95% ee




cf. with $B(C_6F_5)_3$
acrolein: methacrolein
= 63:37

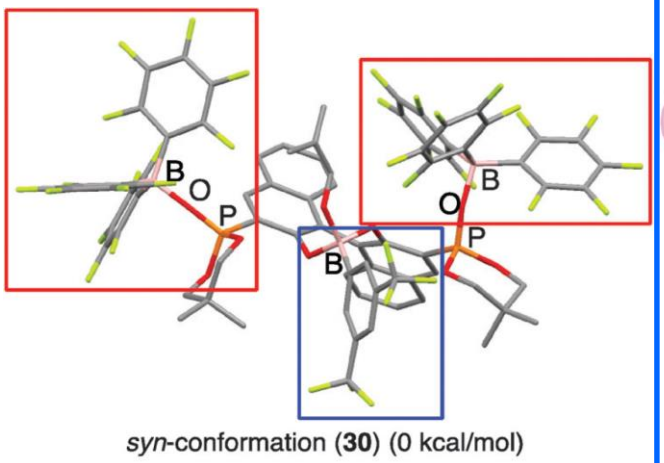
Induced-fit ??????

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.

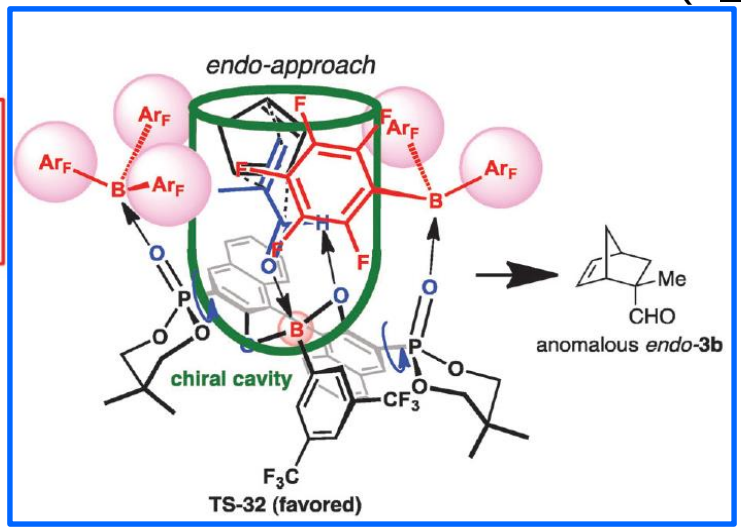
# Mechanism

methacrolein-catalyst complex
A chiral, narrow and deep cavity is assumed.

the B-O(Naph) moiety was doubly coordinated with the C(=O)H and C(=O)H parts.

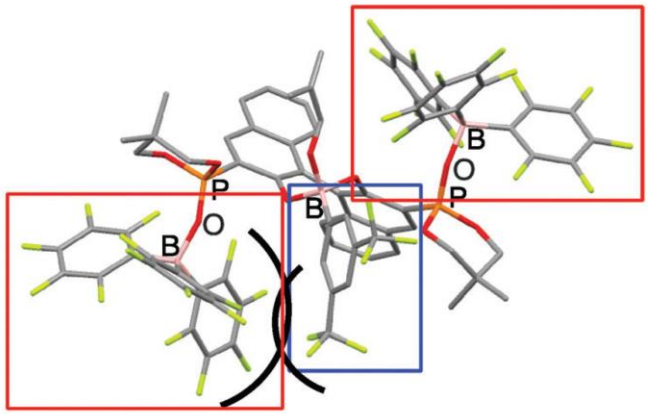



*syn*-conformation (**30**) (0 kcal/mol)

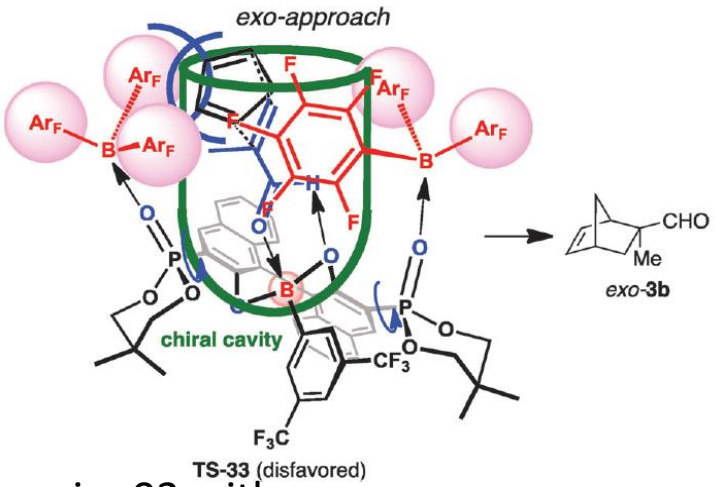



TS-32 (favored)

anomalous *endo*-**3b**

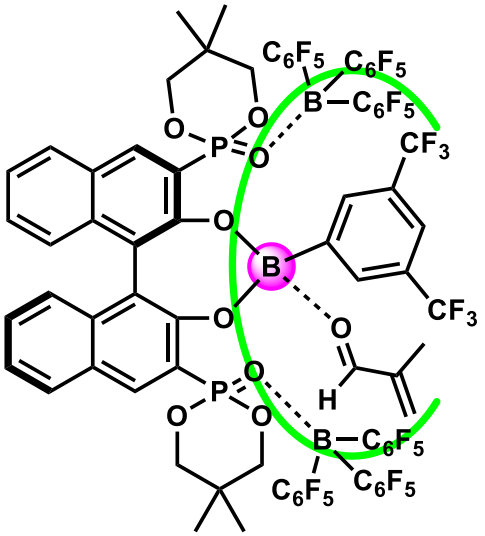



*anti*-conformation (**31**) (+ 3.86 kcal/mol)




TS-33 (disfavored)

*exo*-**3b**

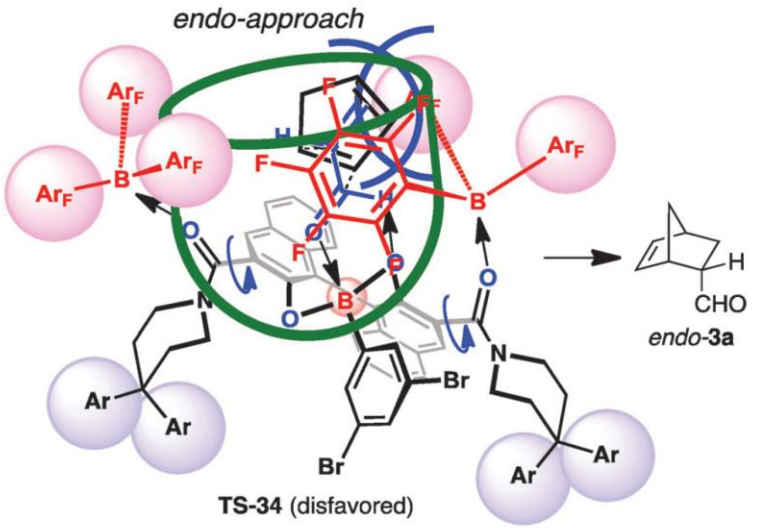


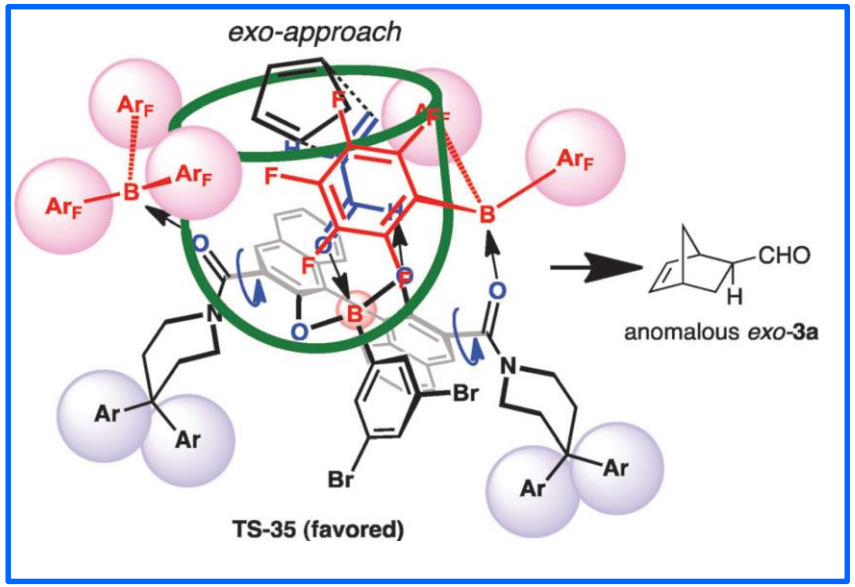

Theoretical calculations using Gaussian03 with B3LYP/6-31G* basis set.

Ishihara K, *et al. Chem. Commun*. **2012,** *48*. 4273.

# *Endo*-Selective Diels Alder

What is the difference between *endo-* and *exo-* selective catalyst ?




Acrolein-catalyst complex
A chiral, shallow and wide cavity.

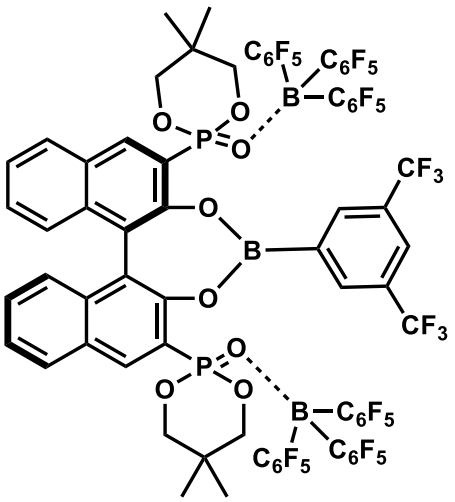
Non-covalent amide-B($C_6F_5$)$_3$ moiety turn outside the complex.

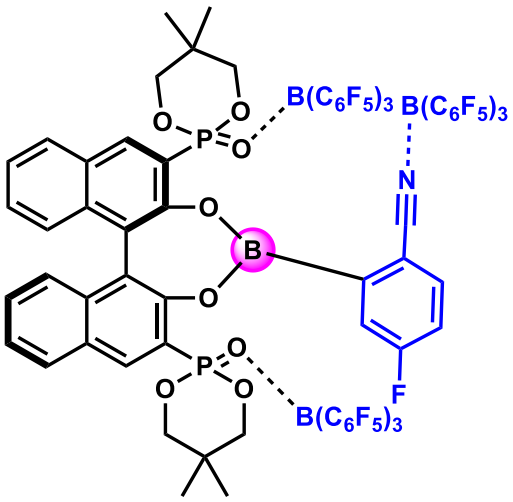
The amide has a less-hindered planar structure.

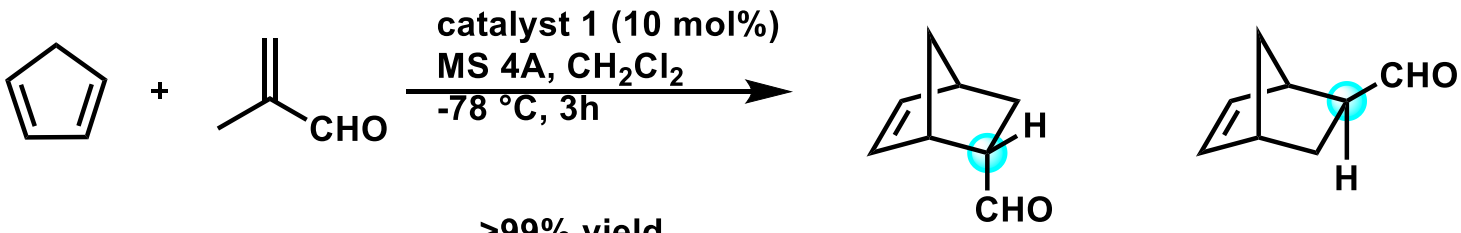
Pseudo-tetrahedral phosphorus structure

K. Ishihara, *et al. Angew. Chem. Int. Ed*. **2011**, *71*. 6474.
*Chem. Commun*. **2012,** *48*. 4273.

# Develop New Type Cavity



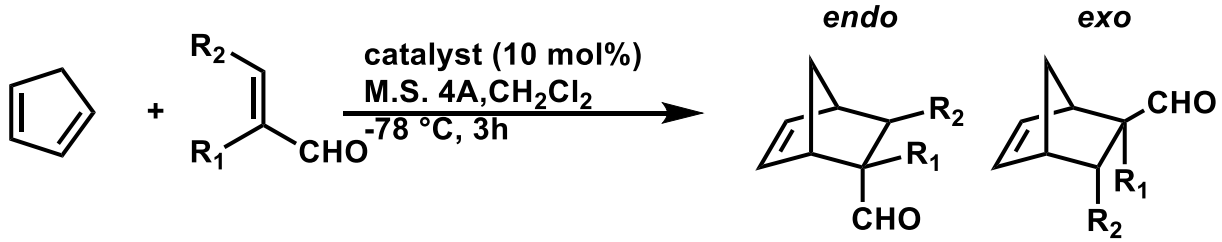




**>99% yield**
***endo/exo*= 9:91**
**6% ee(*exo*)**

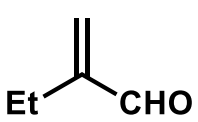
Excessive interaction between three bulky groups is the reason of low ee?

Ishihara K, *et al. Synlett.* **2016**,*227*. 1061.

# Substrate Scope




| catalyst | | $R_1$ | $R_2$ | yield | *endo:exo* | ee (major) |
|---|---|---|---|---|---|---|
| 1 | a | Et | H | >99 | 3:97 | 85 |
| 2 | | | | >99 | 2:98 | 92 |
| 1 | b | Br | H | 98 | 10:90 | 44 |
| 2 | | | | 98 | 9:91 | 0 |
| 1 | c | Me | Me | 80 | 1:>99 | 91 |
| 2 | | | | 16 | 1:>99 | 28 |
| 1 | d | H | H | 89 | 76:24 | 86 |
| 2 | | | | 89 | 73:27 | 42 |
| 1 | e | H | $CO_2Et$ | 72 | 86:14 | 85 |
| 2 | | | | 78 | 86:14 | 10 |



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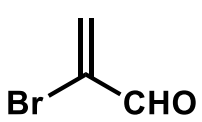

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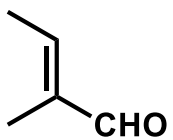

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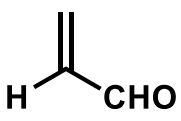

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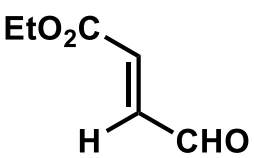

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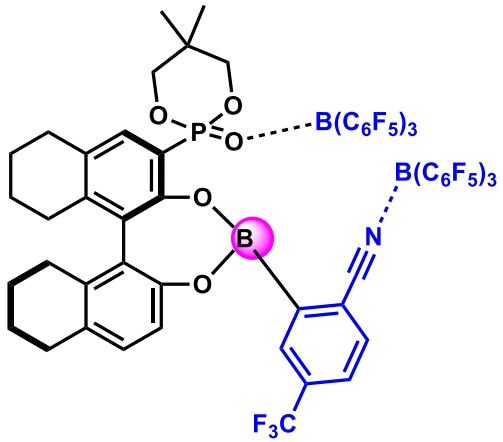

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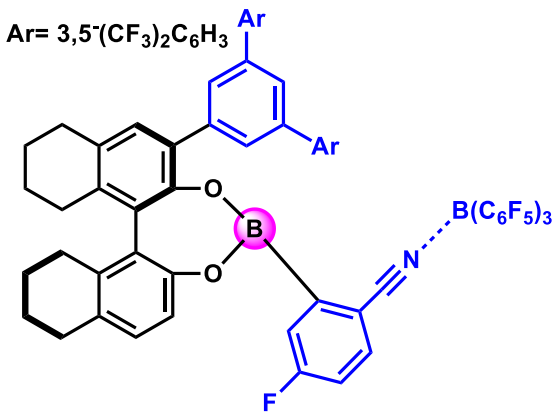
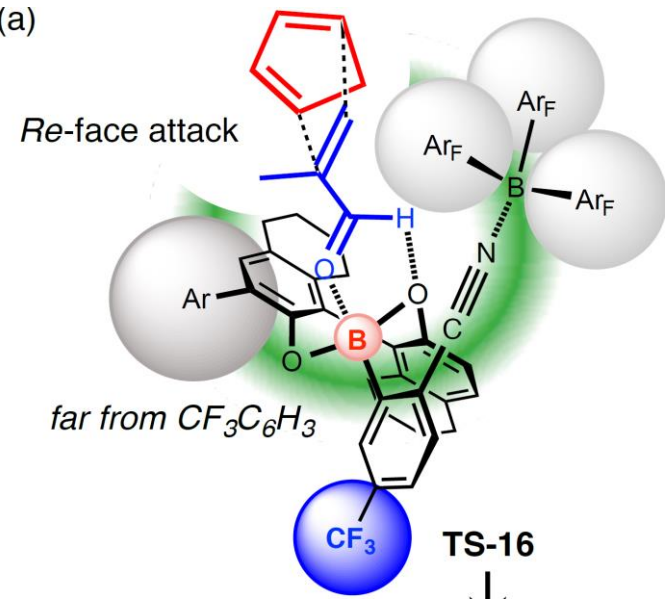


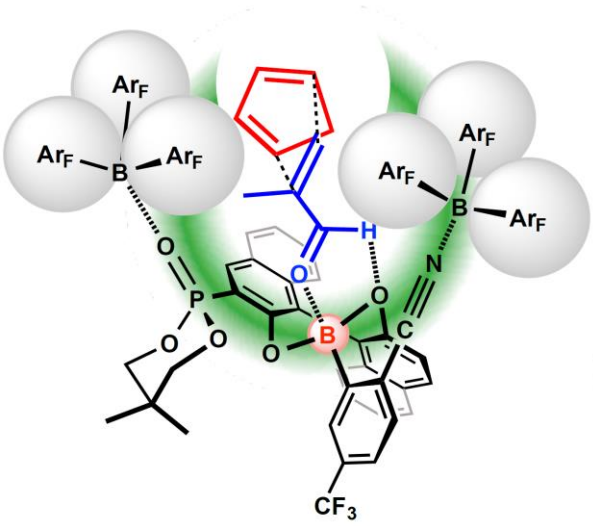
2

Ishihara K, *et al. Synlett.* **2016**,*227*. 1061.

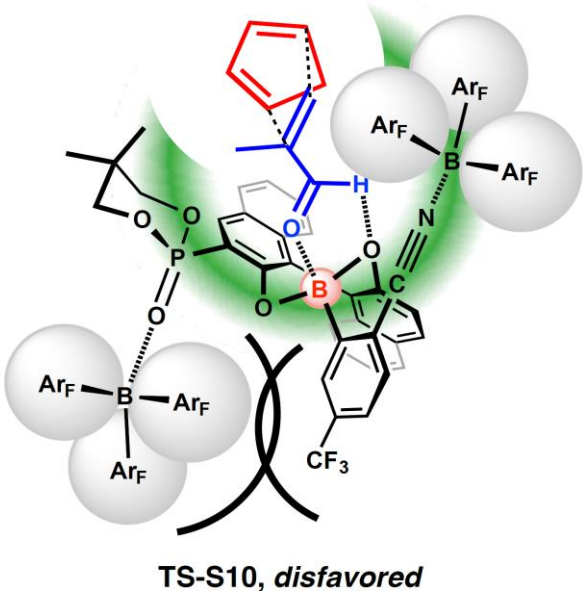
# The Importance of Two $B(C_6F_5)_3$




Low to high ee




High ee



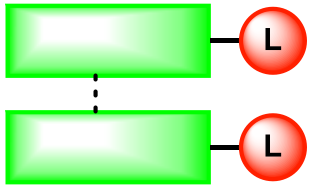

Ishihara K, *et al. Synlett.* **2016**,*227*. 1061.

# Summary

**conventional** chiral catalyst

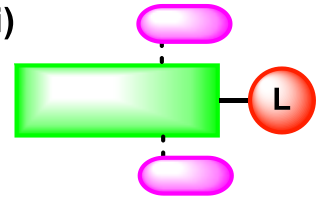
two monodentate ligands

(i)




chiral component with achiral components

(iii)

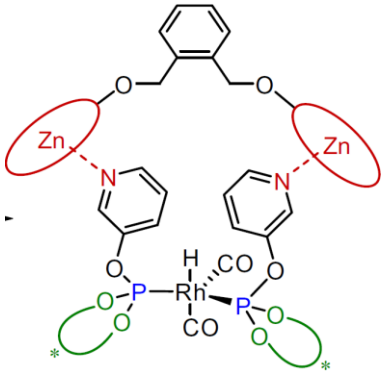


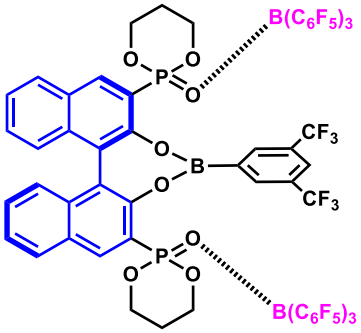

achiral component with chiral subcomponent

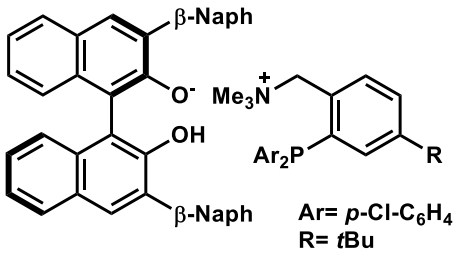
(ii)

L = coodinating group

- - - = non-covalent interaction




Hydrogen bond, acid-base pair,
selective interaction….
Deconvolution strategy….

Supramolecular strategy could develop a new field which conventional catalysts are useless in it.

Chiral cavity strategy

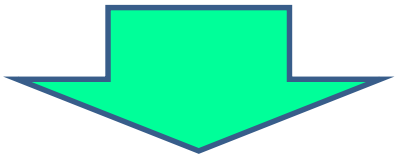
# Future Prospect

Problems

Each component is **still difficult to synthesize**.

The search for **non-covalent interactions** is an important task.

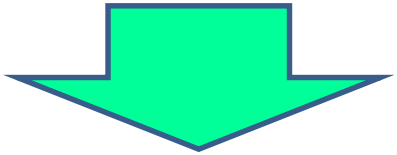
To date, most supramolecular catalytic asymmetric reaction **proceed even with conventional catalysts**.



***but!***

**Conformationally flexible catalysts are promising!**

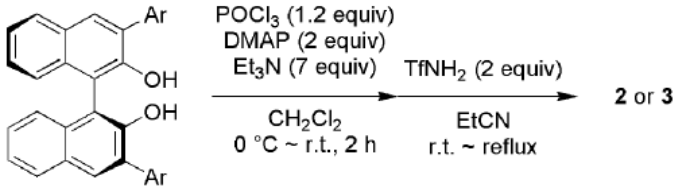
Induced-fit, tailor-made….

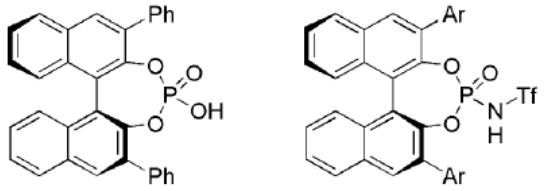


May supramolecular catalysis be ***beyond enzyme mimics?***

# 以下おまけ

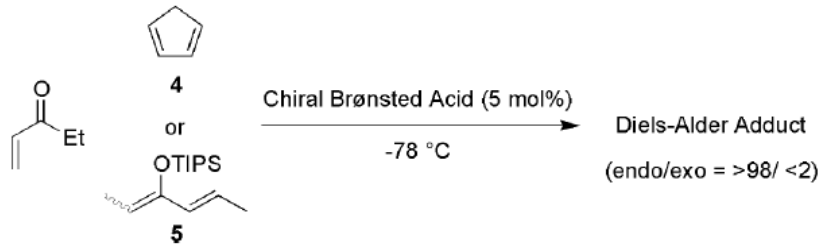
***Scheme 1.*** Preparation of Chiral Phosphoramide




**1** **2**: Ar = Ph
**3**: Ar = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$

***Table 1.*** Reactivity for the Diels–Alder Reactions[a]



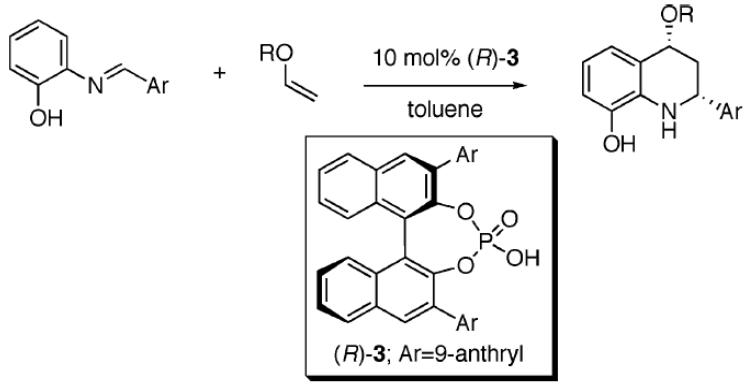

| en try | diene (equiv) | chiral Brønsted acid | solvent | time (h) | yield (%) | ee[b] (%) (config.) |
|---|---|---|---|---|---|---|
| 1 | **4** | **1** | $CH_2Cl_2$ | 2 | 0 | n.d. |
| 2 | (1.2) | **2** | $CH_2Cl_2$ | 2 | 91 | 9 (*S*) |
| 3 | | **3** | $CH_2Cl_2$ | 1 | 86 | 32 (*R*) |
| 4 | **5**[c] | **1** | toluene | 3 | 0 | n.d. |
| 5 | (1.5) | **2** | toluene | 3 | <10 | n.d. |
| 6 | | **3** | toluene | 3 | 95[d] | 92 |

[a] Only endo product was observed by $^1$H NMR. [b] Enantiomeric excess was determined by GC analysis. [c] (*Z*,*E*):(*E*,*E*) = 86:14. [d] Mixture of olefin regio isomer; see Table 2.

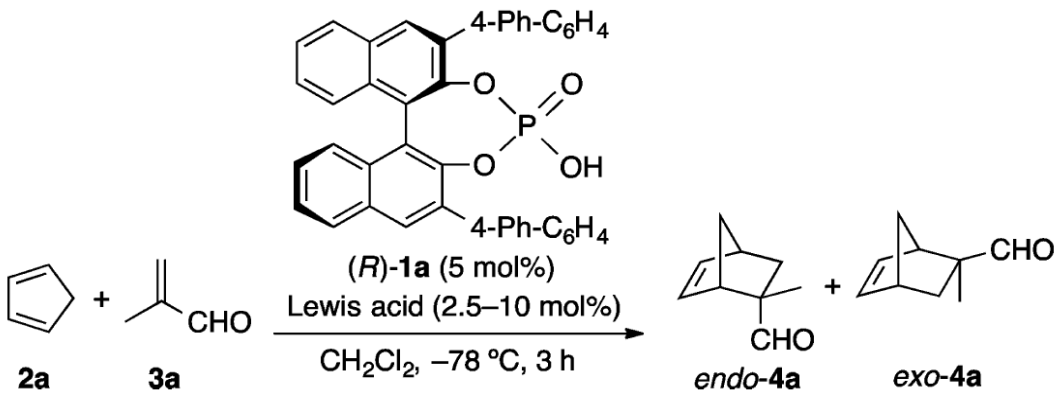
***Table 1.*** Chiral Brønsted Acid-Catalyzed Aza Diels–Alder Reaction of Aldimines with Vinyl Ethers[a]

| entry | Ar | R | yield (%) | cis/trans | ee(%)[b] |
|---|---|---|---|---|---|
| 1[c] | Ph | Et | 89 | 99:1 | 94 |
| 2[c] | Ph | *n*-Bu | 82 | 99:1 | 96 |
| 3[d] | Ph | Bn | 76 | 99:1 | 91 |
| 4[c] | Ph | **4a** | 86 | 99:1 | 90 |
| 5[d] | Ph | **4b** | 95 | 99:1 | 97 |
| 6[c] | 4-Br$C_6H_4$ | Et | 77 | 99:1 | 90 |
| 7[c] | 4-Br$C_6H_4$ | *n*-Bu | 86 | 99:1 | 89 |
| 8[c] | 4-Cl$C_6H_4$ | Et | 79 | 99:1 | 88 |
| 9[d] | 4-Me$C_6H_4$ | Et | 59 | 99:1 | 91 |
| 10[d] | 2-Cl$C_6H_4$ | Et | 72 | 96:4 | 87 |
| 11[d] | 2-naphthyl | Et | 74 | 99:1 | 95 |
| 12[d] | 2-naphthyl | *n*-Bu | 80 | 99:1 | 88 |

[a] The reaction time is 10–55 h by use of 10 mol % of (*R*)-**3**. [b] ee of the cis isomer. [c] The reaction was carried out at −10 °C. [d] The reaction was carried out at 0 °C.

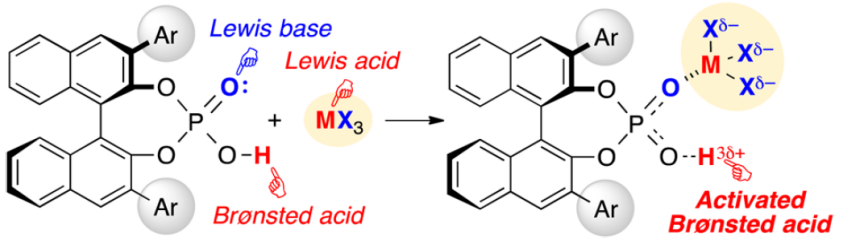


# using Chiral phosphoric acid for diels-alder



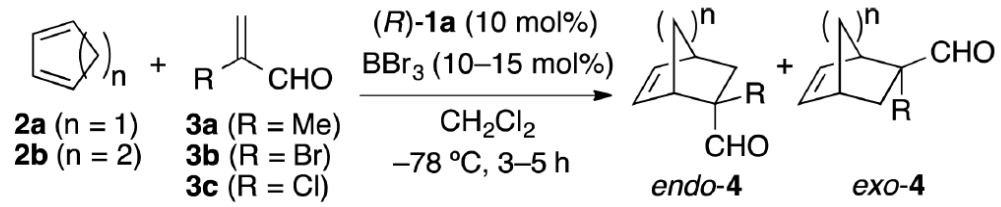

| entry | Lewis acid (mol%) | yield (%) | *endo*:*exo* | ee (%) of *exo*-**4a** |
|---|---|---|---|---|
| 1 | – | 0 | – | – |
| 2[b] | – | 51 | 13:87 | –7 |
| 3 | $B(C_6F_5)_3$ (5) | 64 | 10:90 | 5 |
| 4[c] | $BF_3{\cdot}Et_2O$ (5) | 87 | 3:97 | 52 |
| 5 | $BCl_3$ (5) | 88 | 4:96 | 62 |
| 6 | $BBr_3$ (2.5) | 92 | 3:97 | 61 |
| 7 | **$BBr_3$ (5)** | **99** | **2:98** | **89** |
| 8 | $BBr_3$ (7.5) | 78 | 2:98 | 85 |
| 9 | $BBr_3$ (10) | 64 | 8:92 | 18 |
| 10 | $BI_3$ (5) | 98 | 7:93 | 37 |
| 11[d] | $BBr_3$ (5) | 66 | 10:90 | – |

**Scheme 1. Achiral Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts as Chiral Acid–Base Cooperative Catalysts**



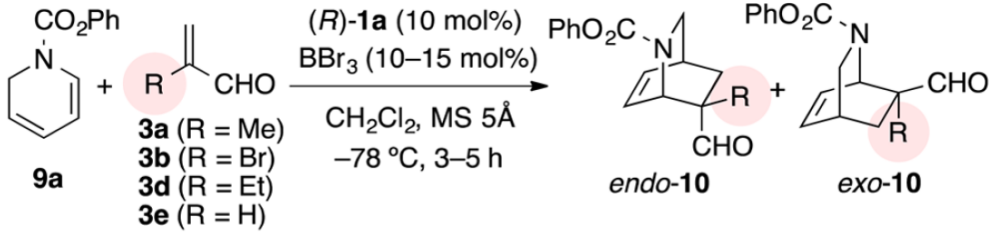

Ishihara K, *et al. J. Am. Chem. Soc.* **2015**, *137*. 13472.

# PBP Rhodium Complex




Products **4**, reaction time, yield, and enantioselectivity.

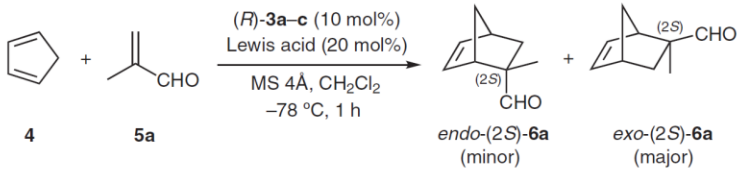
| *exo*-**4b** | *endo*-**4c** | *endo*-**4d** | *endo*-**4e** |
|---|---|---|---|
| 3 h, >99% yield[a] | 4 h, 88% yield[b] | 3 h, >99% yield[a] | 5 h, 88% yield[a] |
| *endo*:*exo* = 5:95 | *endo*:*exo* = 97:3 | *endo*:*exo* = 94:6 | *endo*:*exo* = 94:6 |
| 86% ee (*exo*) | 87% ee (*endo*) | 91% ee (*endo*) | 94% ee (*endo*) |



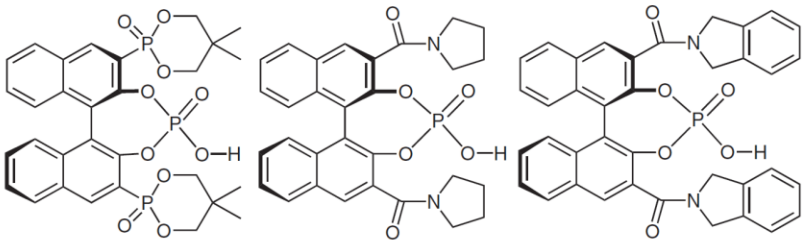

Products **10**, reaction time, yield, and enantioselectivity.

| *endo*-**10a** | *endo*-**10b** | *endo*-**10c** | *endo*-**10d** |
|---|---|---|---|
| 3 h, 82% yield[a] | 5 h, 63% yield[b] | 5 h, 58% yield[a] | 3 h, 96% yield[a] |
| *endo*:*exo* = >99:1 | *endo*:*exo* = >99:1 | *endo*:*exo* = >99:1 | *endo*:*exo* = 99:1 |
| 95% ee (*endo*) | 98% ee (*endo*) | 92% ee (*endo*) | 94% ee (*endo*) |

**Table 1** Screening of Chiral Supramolecular Catalysts[a]



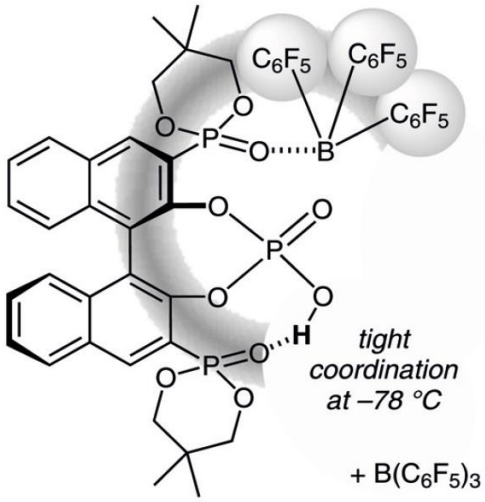

**4** **5a** *endo*-(2*S*)-**6a** (minor) *exo*-(2*S*)-**6a** (major)

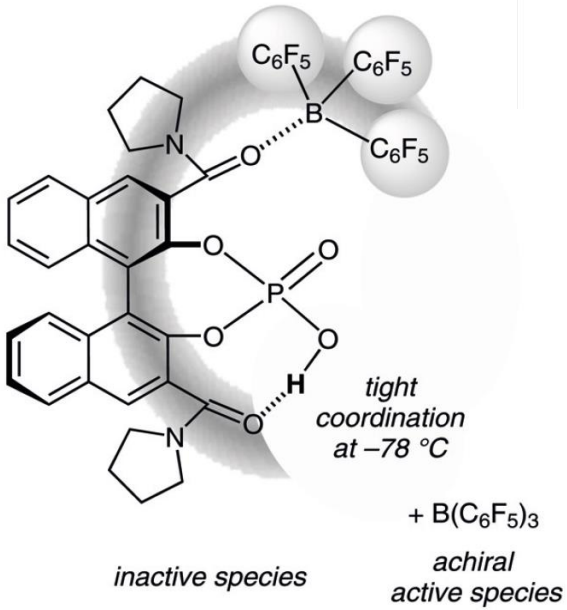


(*R*)-**3a** (*R*)-**3b** (*R*)-**3c**

| Entry | (*R*)-**3** | Lewis acid | Yield (%) | *endo*-**6a**/*exo*-**6a** | ee (%) of *exo*-**6a** |
|---|---|---|---|---|---|
| 1 | (*R*)-**3a** | – | 0 | – | – |
| 2 | (*R*)-**3a** | $BF_3{\cdot}Et_2O$ | >99 | 7:93 | 2 |
| 3 | (*R*)-**3a** | $BBr_3$ | 98 | 8:92 | 14 |
| 4 | (*R*)-**3a** | $B(C_6F_5)_3$ | 98 | 8:92 | –53[b] |
| 5[c] | (*R*)-**3a** | $B(C_6F_5)_3$ | >99 | 8:92 | –31[b] |
| 6[d] | (*R*)-**3a** | $B(C_6F_5)_3$ | 20 | 19:81 | –1[b] |
| 7 | (*R*)-**3b** | – | 0 | – | – |
| 8 | (*R*)-**3b** | $BF_3{\cdot}Et_2O$ | >99 | 7:93 | 0 |
| 9 | (*R*)-**3b** | $BBr_3$ | >99 | 5:95 | 0 |
| 10 | (*R*)-**3b** | $B(C_6F_5)_3$ | >99 | 5:95 | 90 |
| 11[c] | (*R*)-**3b** | $B(C_6F_5)_3$ | 62 | 11:89 | 8 |
| 12[d] | (*R*)-**3b** | $B(C_6F_5)_3$ | 0 | – | – |
| 13 | (*R*)-**3c** | – | 0 | – | – |
| 14 | (*R*)-**3c** | $BF_3{\cdot}Et_2O$ | 98 | 6:94 | 0 |
| 15 | (*R*)-**3c** | $BBr_3$ | 96 | 10:90 | 0 |
| 16 | (*R*)-**3c** | $B(C_6F_5)_3$ | >99 | 8:92 | 90 |
| 17[c] | (*R*)-**3c** | $B(C_6F_5)_3$ | >99 | 9:91 | 85 |
| 18[d] | (*R*)-**3c** | $B(C_6F_5)_3$ | 0 | – | – |
| 19[e] | – | $B(C_6F_5)_3$ | >99 | 7:93 | – |

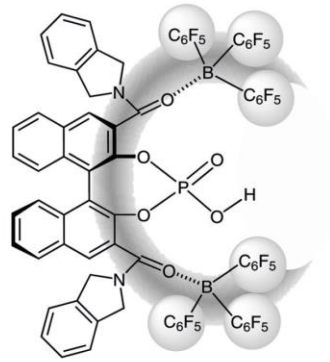
# PBP Cobalt Complex




(*R*)-**3c** (1 equiv)
$^{31}$P NMR ($CD_2Cl_2$): 4.0 ppm
+
$B(C_6F_5)_3$ (2 equiv)
$^{19}$F NMR ($CD_2Cl_2$): –130.2 (6F) ppm, –147.1 (3F) ppm, –161.4 (6F) ppm.

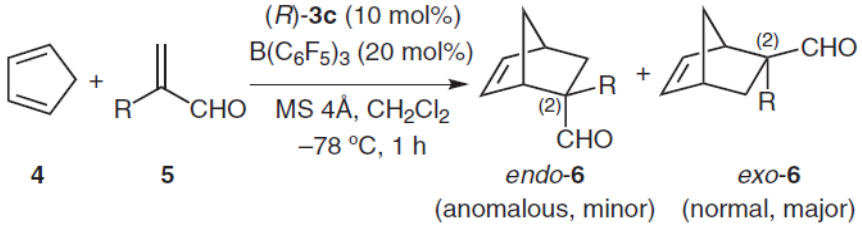
$CD_2Cl_2$
r.t., 30 min



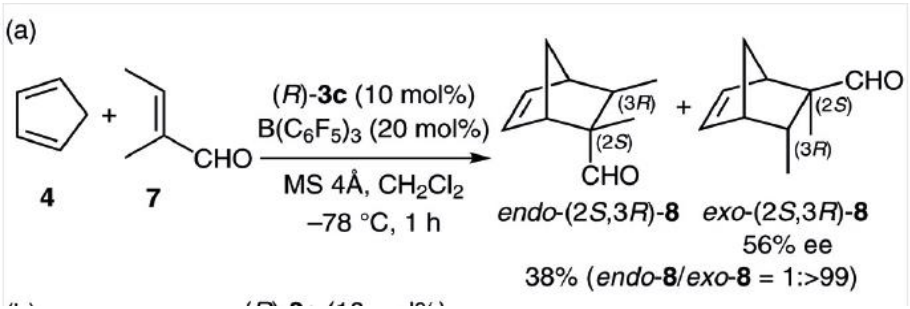
$^{31}$P NMR ($CD_2Cl_2$): 4.6 ppm
$^{19}$F NMR ($CD_2Cl_2$): –137.0 (6F) ppm, –159.5 (3F) ppm, –166.3 (6F) ppm.
ESI-MS (–): calcd for $C_{74}H_{30}B_2F_{30}N_2O_8P^-$ $[M + 2H_2O - H]^-$ 1697.1463, found 1697.1459

# PBP Cobalt Complex

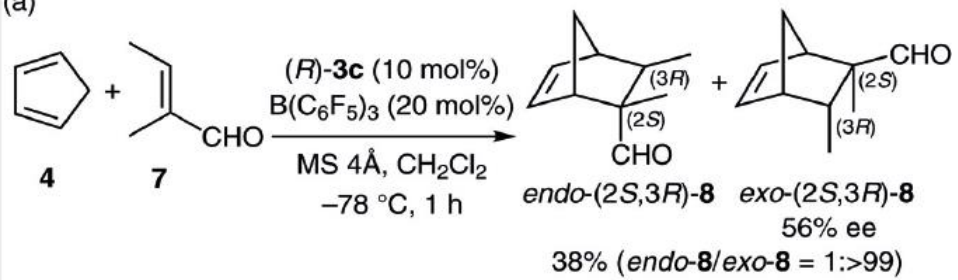
**Table 2** Substrate Specificity with the Use of $2B(C_6F_5)_3$–(*R*)-**3c**[a]



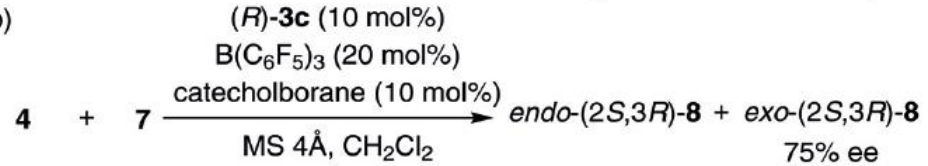

| Entry | **5** (R) | Product | Yield (%) | *endo*-**6**/*exo*-**6** | ee (%) of *exo*-**6** |
|---|---|---|---|---|---|
| 1 | **5a** (Me) | **6a** | >99 | 8:92 | 90 (2*S*) |
| 2[b] | **5a** (Me) | **6a** | 94 (40 °C, 3 h) | 16:84 | – |
| 3 | **5b** (Et) | **6b** | >99 | 2:98 | 84 (2*S*) |
| 4[b] | **5b** (Et) | **6b** | 73 (110 °C, 24 h) | 24:76 | – |
| 5 | **5c** (*i*-Pr) | **6c** | 72 | 15:85 | 23 (2*R*) |
| 6[b] | **5c** (*i*-Pr) | **6c** | <5 (110 °C, 3 h) | – | – |
| 7 | **5d** (Br) | **6d** | >99 | 15:85 | 18 (2*R*) |
| 8[b] | **5d** (Br) | **6d** | >99 (r.t., 3 h) | 15:85 | – |



(a)




(b)



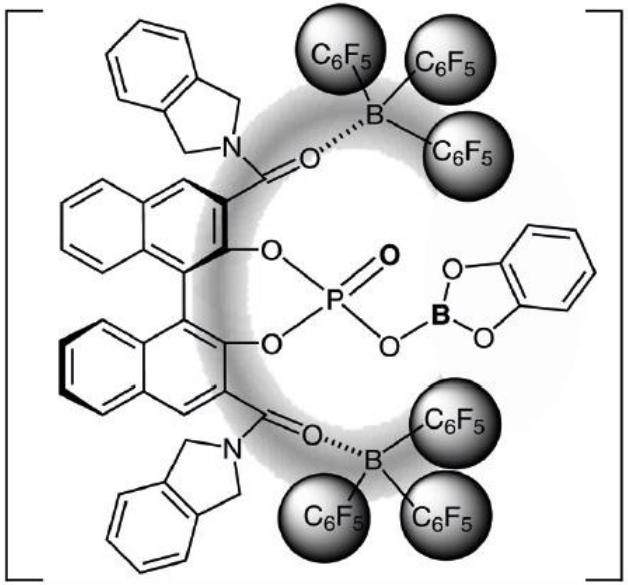
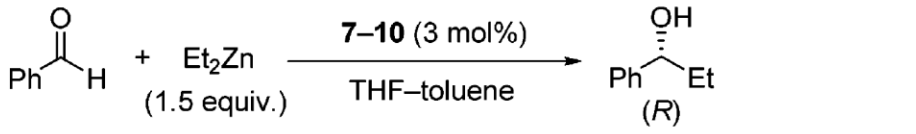
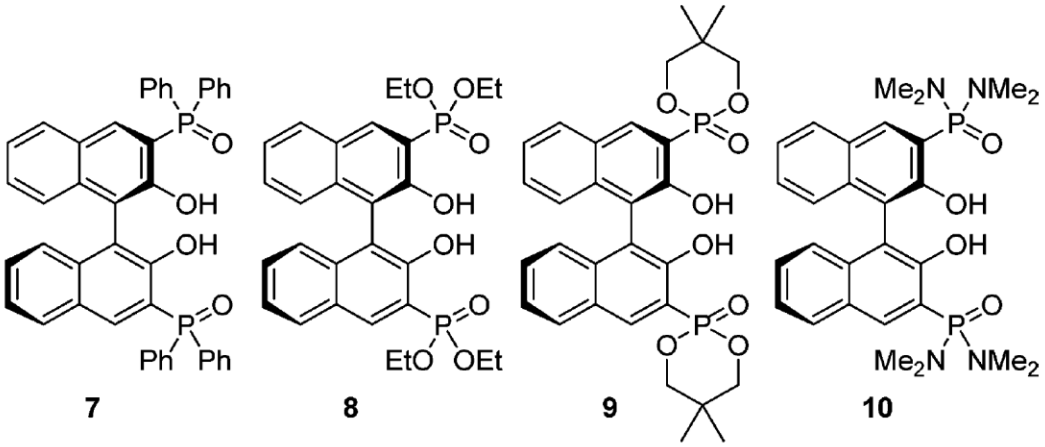
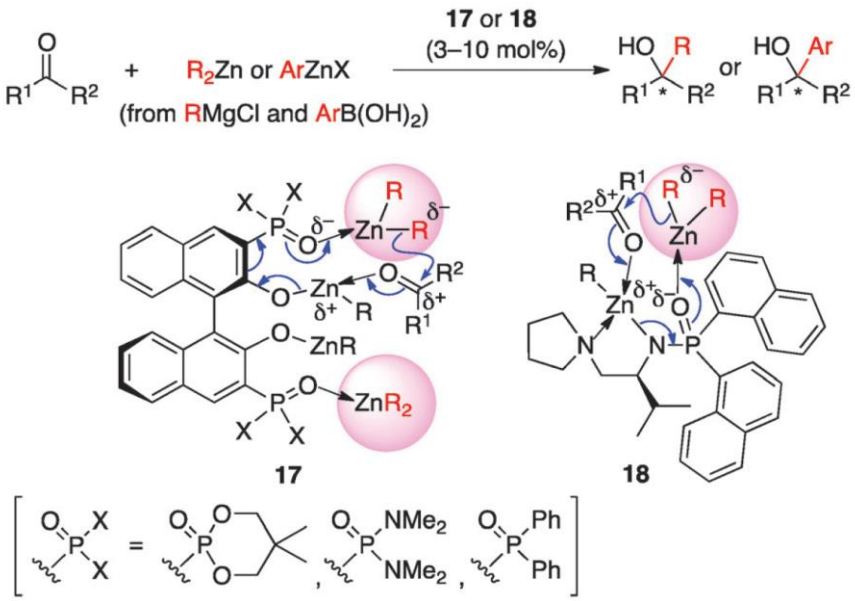


C6F5
C6F5
C6F5
C6F5
C6F5
C6F5
B
N
O
P
O
O
O
O
O
B
O
O
O
O
O

**TABLE 2. Enantioselective Diethylzinc Addition to Benzaldehyde with Conjugate Acid–Base BINOL–Zn(II) Catalysts**




| entry | ligand | temp | time (h) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | (*R*)-**7** | rt | 72 | 77 | 93 |
| 2 | (*R*)-**8** | rt | 48 | 70 | 94 |
| 3 | (*R*)-**9** | rt | 48 | 81 | 97 |
| 4 | (*R*)-**10** | rt | 24 | 98 | 97 |
| 5 | (*R*)-**7** | 50 °C | 12 | 60 | 91 |
| 6 | (*R*)-**8** | 50 °C | 12 | 65 | 94 |
| 7 | (*R*)-**9** | 50 °C | 12 | 76 | 96 |
| 8 | (*R*)-**10** | 50 °C | 4 | >99 | 95 |

[a] Isolated yield. [b] Absolute configulation of product was *R*. The ee valu were determined by chiral GC analysis.