The carbonyl ene reaction

Literature Seminar(M1)

Sachiyo Nakanowatari

2010/09/30 @W5 18:00-

reference

Mikami, K.; Shimuzu, M. *Chem. Rev.* **1992**, 92, 1021-1050
Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, 64, 9003-9031
'Lewis Acid Catalyzed Carbonyl-Ene Reaction' Ober, M. **2003**,
(http://www.scs.illinois.edu/denmark/presentations/2003/gm-2003-12-16.pdf) 09/29/10 accessed

Contents

Part １－Basics

Mainly based on:

三上幸一、寺田真浩、清水正毅、中井武「有機合成化学」
（1990）vol. 48, No. 4, p292-303
Mikami, K.; Shimuzu, M. *Chem. Rev.* **1992**, 92, 1021-1050
Berrisford, D. J.; Bolm, C. *ACIE* **1995**, 34, 1717-1719

Koichi Mikami

- Born in 1953 and received his B.S. degree and Ph.D. from Tokyo Institute of Technology with Takeshi Nakai.

- Joined the faculty of TIT in 1982, where he is currently Professor of applied chemistry. From 1982 to 1983 he was a postdoctral fellow at the Yale University with Frederick E. Ziegler.

- His major research interests are the developments of new methods and strategies for organic synthesis, the asymmetric catalysis of synthetic organic reactions, and their application to natural product synthesis. His current research interests also include

photochemistry and

fluorine chemistry.
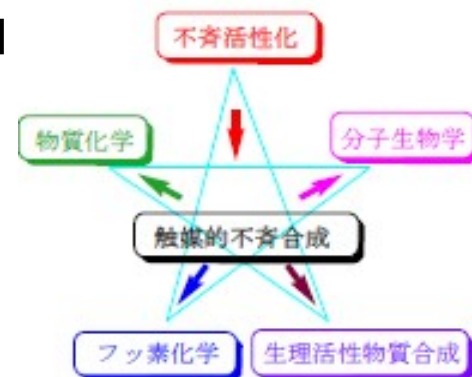
Masahiro   Terada

Born in 1964, received his B. S. degree and Ph. D. from Tokyo Institute of Technology

- 1989-1997, Assistant Professor Faculty of Engineering, Tokyo Institute of Technology

- 1997-2001, Assistant Professor Graduate School of Science and Engineering, Tokyo Institute of Technology

- 2001-2006, Associate Professor Graduate School of Science, Tohoku University

- 2006-present, Professor Graduate School of Science, Tohoku University

- 1999-2000, Visiting Researcher Harvard University, Prof. Matthew D. Shair

- 2005-2006, Visiting Associate Professor Catalysis Research Center, Hokkaidou University

Ene Reaction(Alder-Ene Reaction)

- Ene Reaction

Variation;
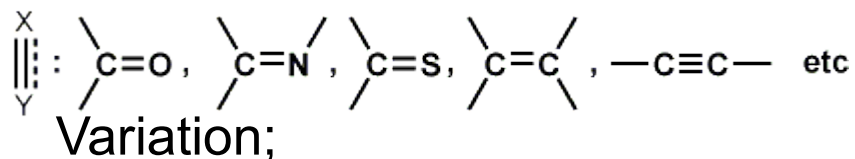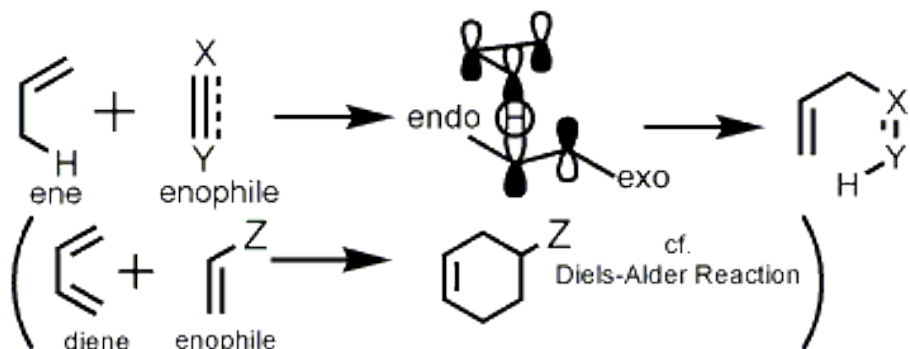
- Carbonyl ene reaction

- Conia reaction

- Singlet-oxygen ene reaction

- Metallo-ene reaction

- Thermal reaction; Higher temperature

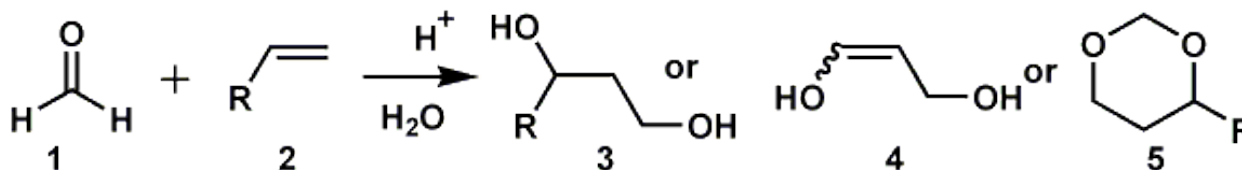 (more than 150℃ due to the high activation barrier)side reaction

- Recen 40 years:

  Lewis acid（AlMe$_2$Cl, SnCl$_4$, BF$_3$ OEt$_2$, Sc(OTf)$_3$, Yb(OTf)$_3$ etc.）

- 1980s-:Chiral Lewis Acid complex

- 2008-:Organocatalyst

Named Reactions

- ## Prins Reaction

  Acid-catalyzed addition of olefins to formaldehyde to give 1, 3-diols(**3**), allylic alcohols(4), or meta-dioxanes(**5**):
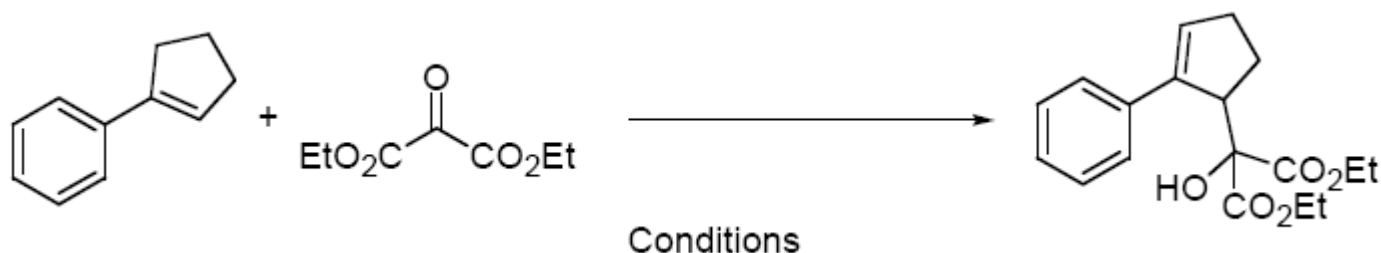

- ## Conia Reaction(Conia-Ene Reaction)

  The intramolecular ene reaction of unsaturated ketones, in which the carbonyl functionality serves as the ene component, *via* its tautomer, and olefinic moiety serves as the enophile:
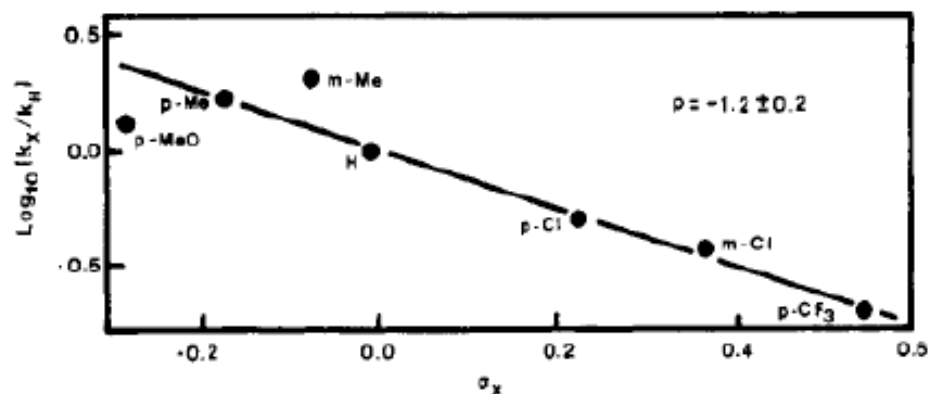
Thermal vs LA promoted

+

EtO₂C — CO₂Et

Conditions
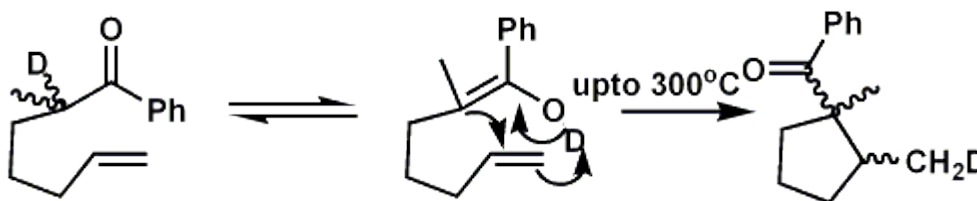
A : 185 °C
B : SnCl₄ (0.1 equiv), 0°C

$\rho = -1.2 \pm 0.2$

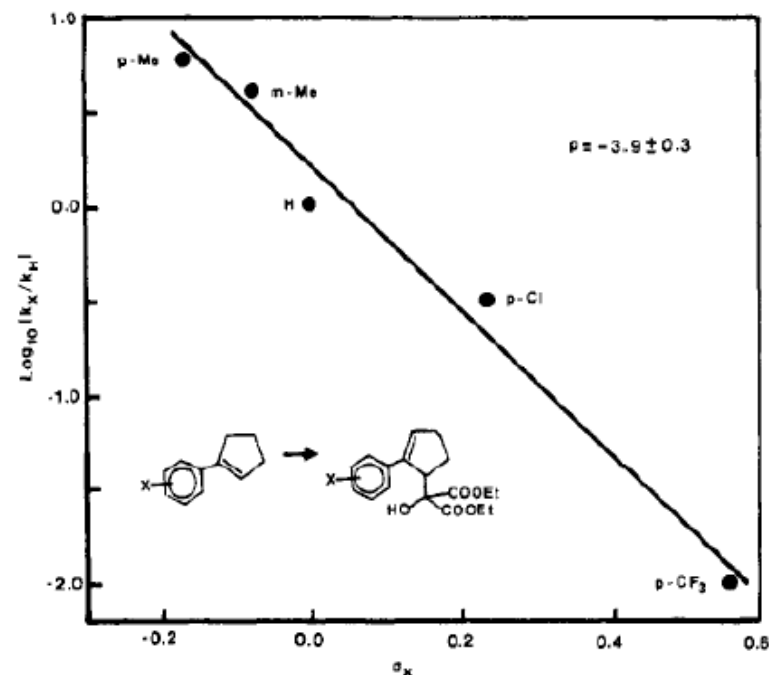**Figure 1.** Substituent effects on thermal ene reactions of diethyl oxomalonate with 1-arylcyclopentenes.

$\rho = -3.9 \pm 0.3$

Figure 2. Substituent effects on SnCl₄-catalyzed ene reactions of diethyl oxomalonate with 1-arylcyclopentenes.

Lewis Acid Catalyzed Carbonyl−Ene Reaction' Ober, M. **2003**
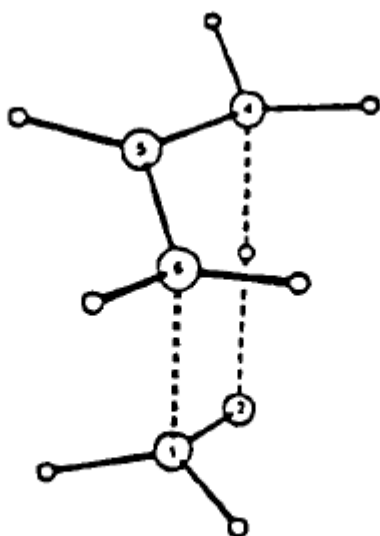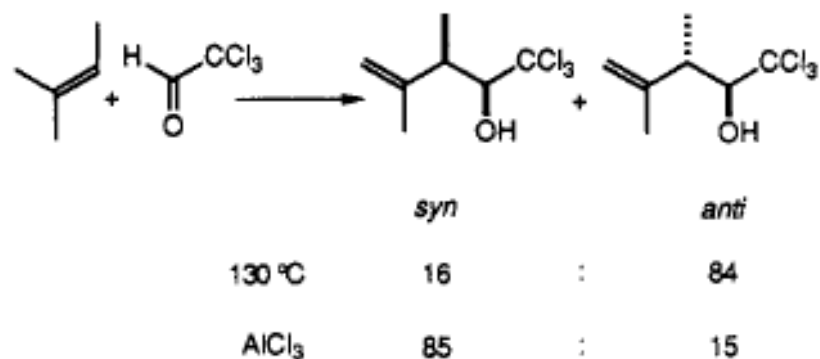
8

Thermal vs LA promoted

Figure 1. View of the 3-21G transition structure of the propene formaldehyde–ene reaction (from ref 124; copyright 1987 American Chemical Society).
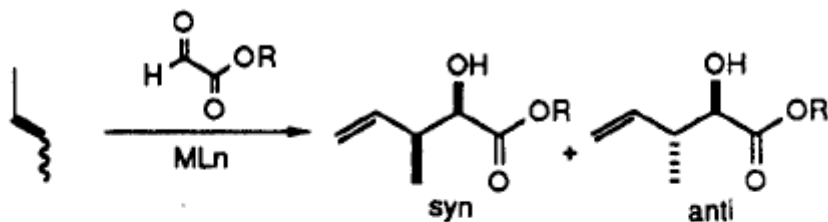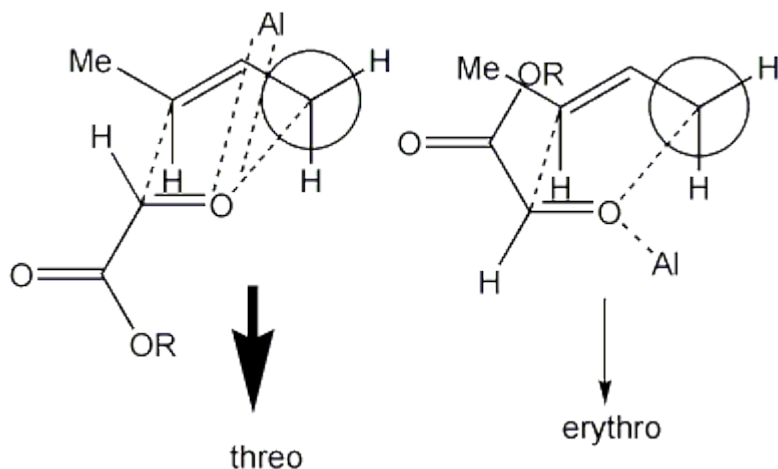
Scheme 20

	syn		anti
130 °C	16	:	84
AlCl₃	85	:	15

Lewis Acid Catalyzed Carbonyl–Ene Reaction' Ober, M. **2003**

Diaselectivity

Table 1. Glyoxylate–Ene Reactions with 2-Butene

butene	R	MLn	syn:anti
trans	Me	SnCl$_4$	18:82 (quant)
cis			28:72 (quant)
trans	i-Pr		8:92 (quant)
cis			29:71 (quant)
cis	Me	Me$_2$AlOTf	91:9 (65%)
trans			79:21 (29%)
		MeAl(OTf)$_2$	65:35 (41%)

- A dramatic changeover in diastereoselectivity by changing the Lewis acid

- Conventional 5 membered ring model does not explain the result.

Lewis Acid Catalyzed Carbonyl–Ene Reaction' Ober, M. **2003**
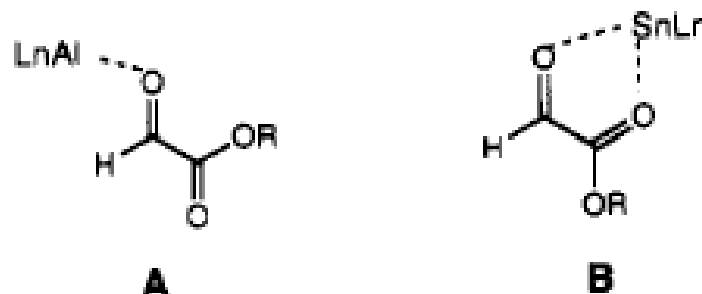
Diastereoselectivity -Chairlike Model

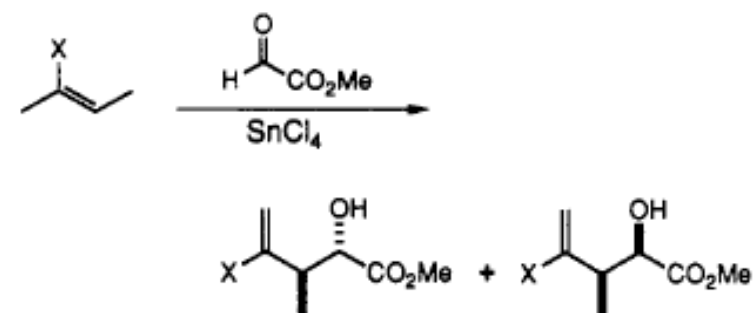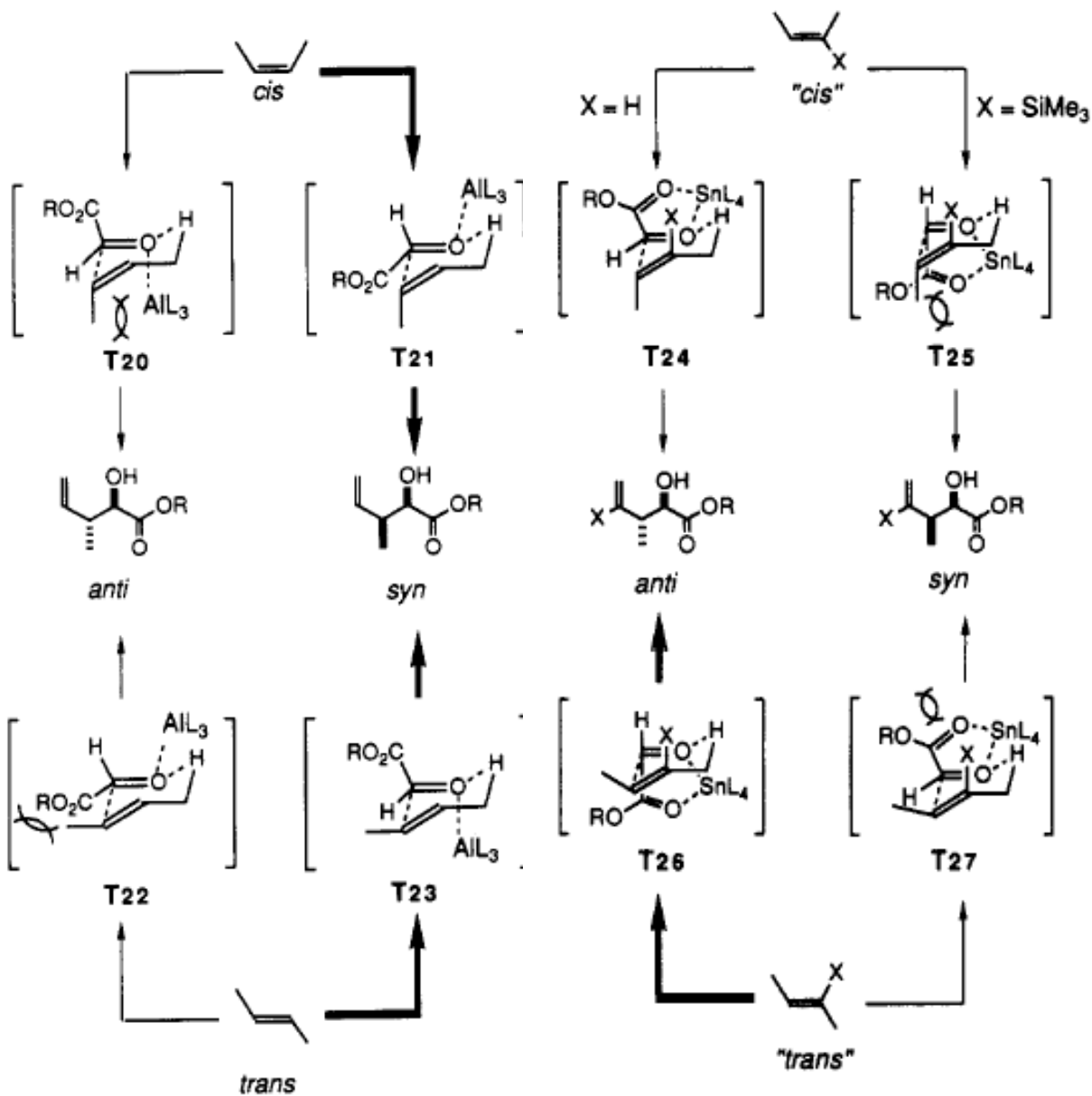# Part 2- The catalytic asymmetric Carbonyl ene reaction

Mainly based on:
Clarke, M. L.; France, M. B.
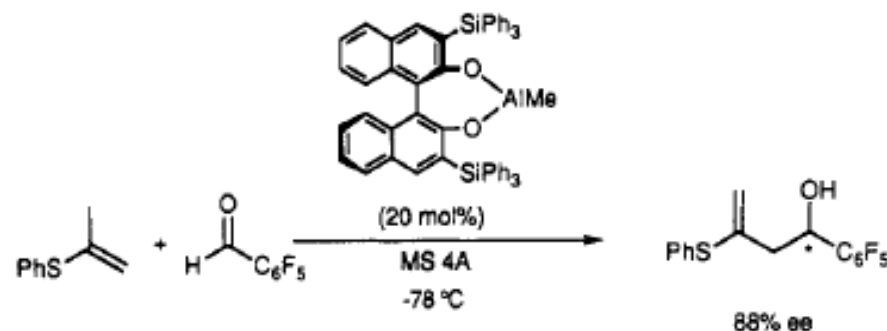*Tetrahedron* **2008**, 64, 9003–9031

In addition to guiding chemists towards reactions
that proceed effectively,
we hope this review has also
highlighted some of the
challenges that lie ahead.

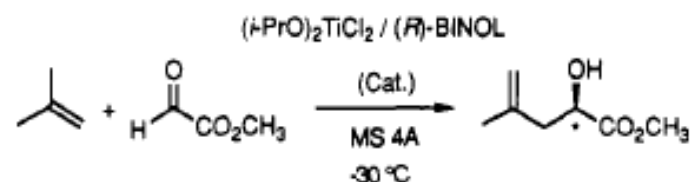# The development of Asymmetric Catalyst

- In 1988 and 1989; Pioneering work of Yamamoto(first;1988)'s aluminum-based and Mikami's titanium-based BINOL complex

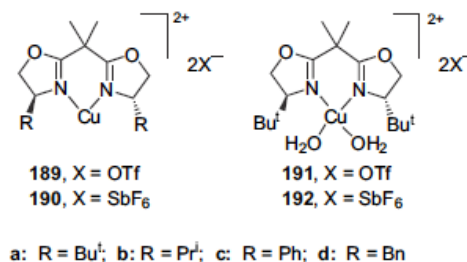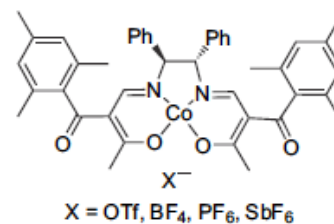- In 1995; Evan's Cu- Box catalyst(direct interaction between Metal and carbonyl oxgen)

- Other metals(Cr, Co, Pd, Pt, Ni, Sc, In etc.)

- In 2008 organocatalyst   by Terada and Rueping independently

- Polymer supported
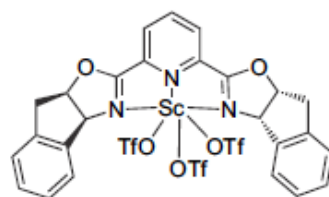
Ti-BINOL TS
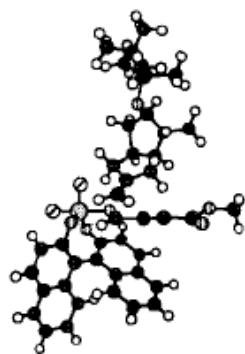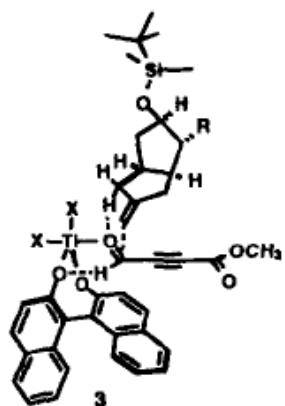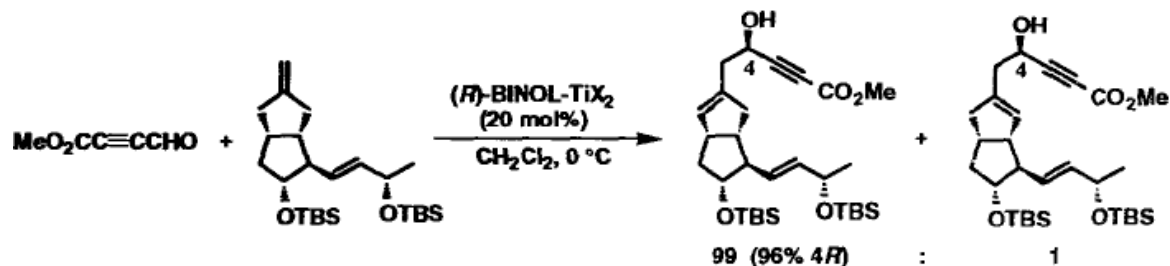
Stereopair representation of 3

Stereopair representation of 4
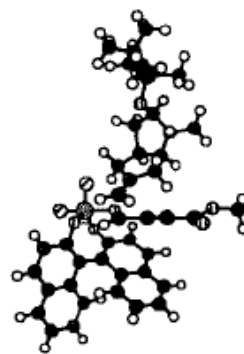
● C ○ H ⬒ O ⬢ Ti ⊘ X ● Si

- **3**; favored TS structure

- **4**; sterically disfavored

- Ene reaction like this is caliculated to be exothermic by *ca.*20kcal/mol.

- The reaction of the Lewis-acid coordinated aldehyde will be much more exothermic

-possibly 30kcal/mol

→TS should be SM like

Corey, E. J.; Barnes−Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron* **1997**, 38, 6513−6516

BINOL-Ti   NLE -1

(i - PrO)$_2$TiBr$_2$ / BINOL (33.0% ee)
(1.0 mol% each)

MS 4A, CH$_2$Cl$_2$
-30 °C

91.4% ee
(92%)

(R)-BINOL

(R)-1 a: (X = Br)
b: (X = Cl)

184

Figure 2.

- 4A MS; water donor & Base to trap HX

- NLE←isostructural dinuclear chelate complex **184.**

- Homochiral dimer is far more active than heterochiral *meso* dimer(*R,S*).

- Positeve Non Linear Effect

Product % ee

—○— (i-PrO)$_2$TiCl$_2$ / BINOL
—●— (i-PrO)$_2$TiBr$_2$ / BINOL

BINOL % ee

Fig. 2. (+)-NLE in asymmetric glyoxylate-ene reaction catalyzed by 1 (1.0 mol%).

Mikami, K.; Terada, M. *Tetrahedron* **1992**, 48, 5671−5680.

BINOL-Ti   NLE -2
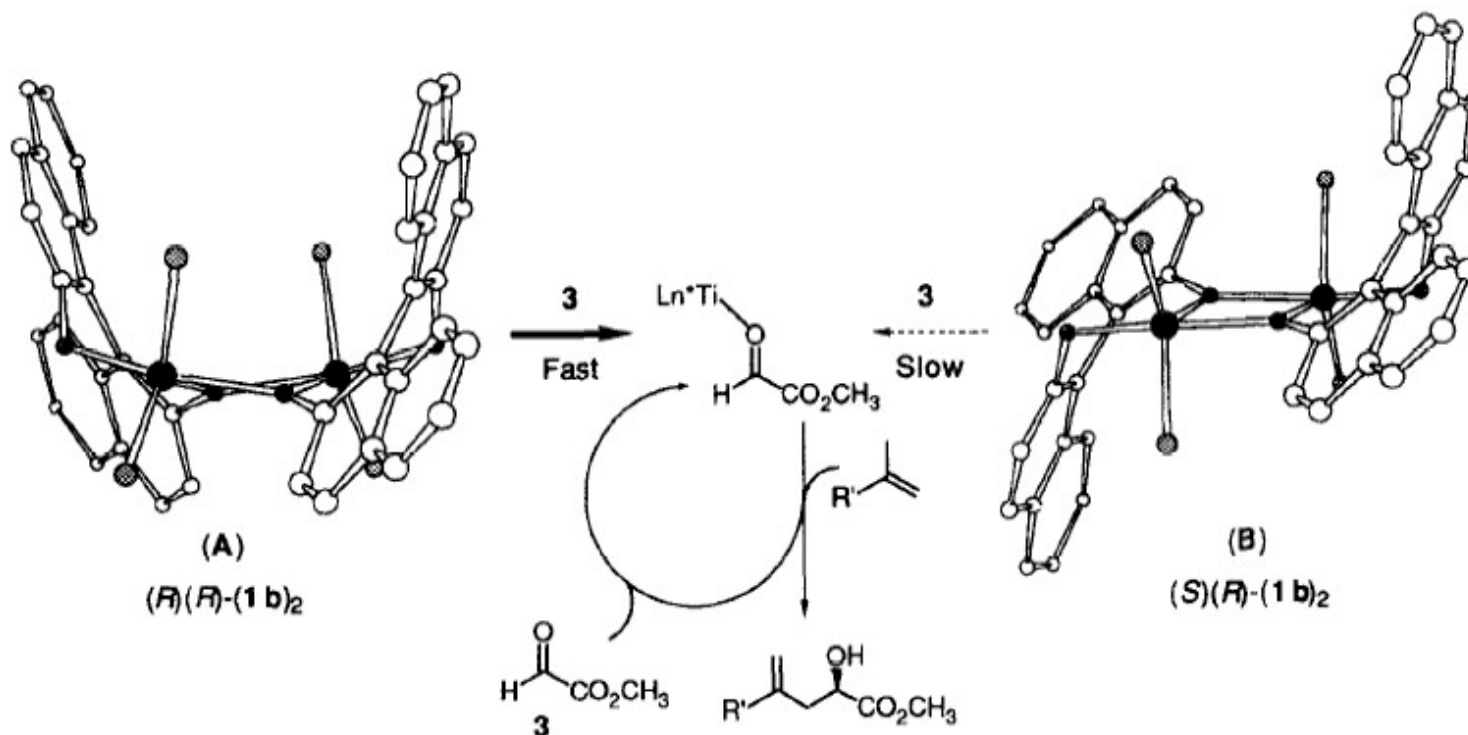
Fig. 3. 3-D representation of (R)(R)-(1 b)$_2$ and (S)(R)-(1 b)$_2$.

- The *meso* isomer is formed preferentially, leaving excess enantiomerically pure BINOL.

Mikami, K.; Terada, M. *Tetrahedron* **1992**, 48, 5671−5680.

Asymmetric synthesis by enantiomer-selective activation of racemic catalysts asymmetric activation

Substrate
$$\xrightarrow[k]{} \text{Product}\ (x\%\ \text{ee})$$ (1)

Substrate
$$\xrightarrow[k_{act}]{} \text{Product}\ (x_{act}\%\ \text{ee})$$

$$(k_{act} \gg k,\ x_{act} \gg x)$$ (2)
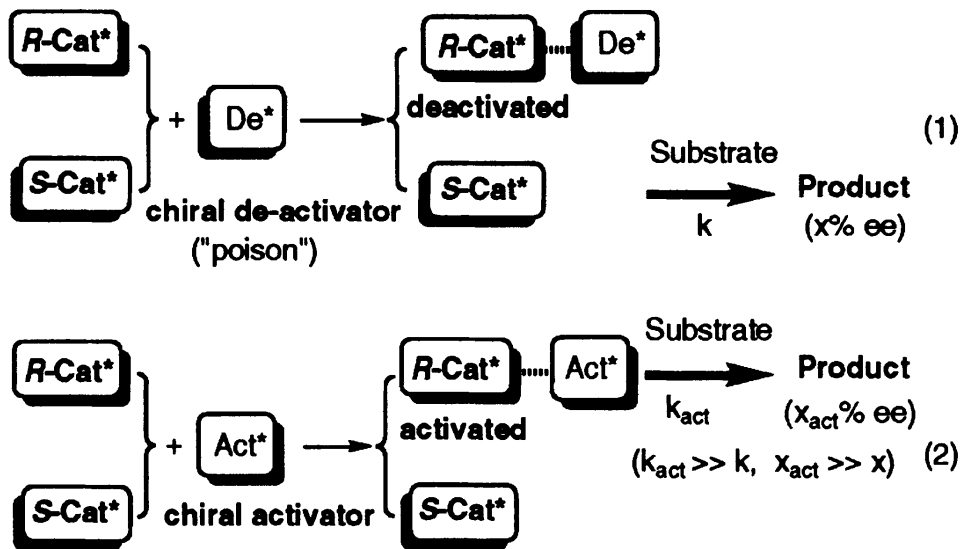
Table 1   Carbonylene reactions with racemic BINOLate-Ti complex
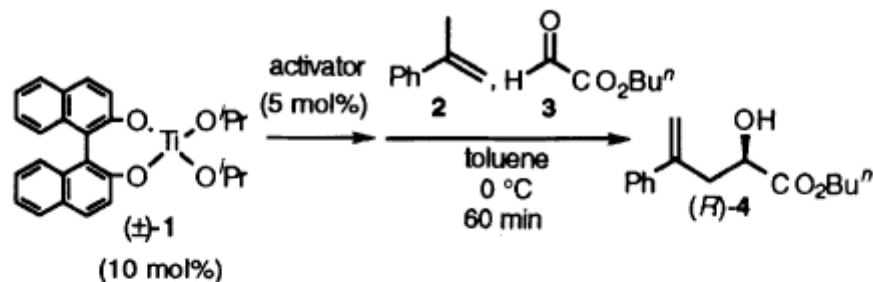
Run	Activator	Yield (%)	e.e. (%)
1	None	5.9	0
2		20	0
3	(R^2)	38	80.8
4	(R^2)	52	89.8
5*		35	80.0

Asymmetric synthesis by enantiomer-selective activation of racemic catalysts(2)

Table 2 Carbonylene reactions with enantio-pure (R)-BINOLate-Ti complex
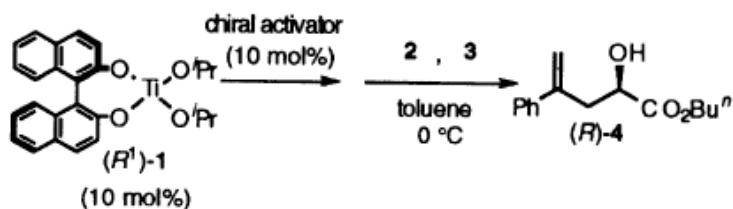
Run	Chiral activator	Time (min)	Yield (%)	e.e. (%)
1	None	60	19.8	94.5
2		1	1.8	94.5
3	(R^2)-5-Cl-BIPOL	60	66.0	97.2
4	(R^2)-BINOL	60	82.1	96.8
5		1	41.1	96.8
6		0.5	24.0	96.9
7	(S^2)-BINOL	60	48.0	86.0
8		0.5	2.6	86.0
9	$(\pm^2)$-BINOL	60	69.2	95.7
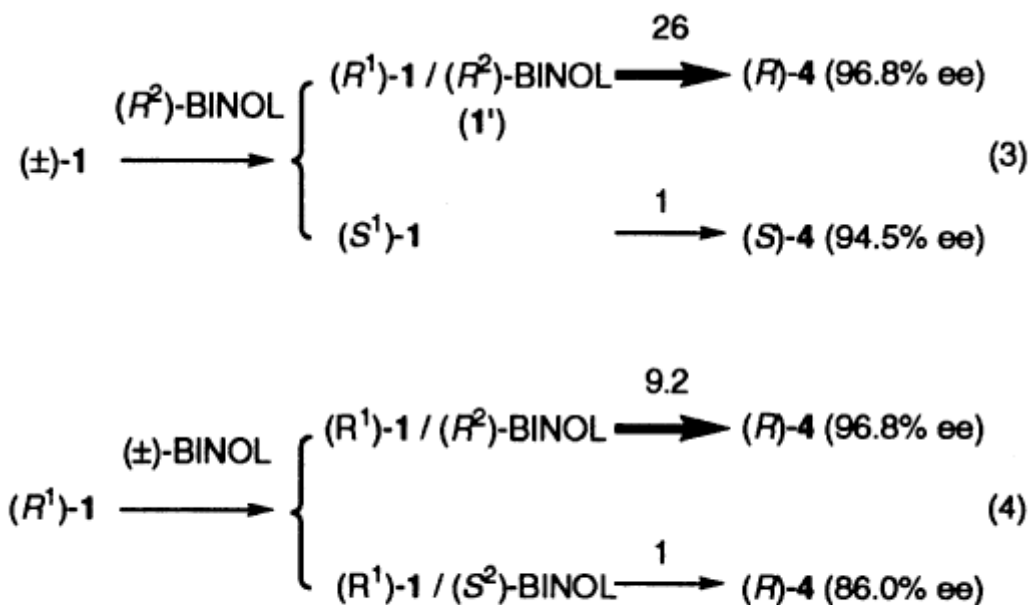
Figure 3 Kinetic studies in carbonylene reactions with racemic and single-enantiomer BINOLate-Ti complexes.

科学技術総合

新たなルイス酸触媒プロセス　開発

不斉合成で4級炭素構築
医薬品産業などへ展開期待

東工大

三上東工大教授

東京工業大学大学院理工学研究科の三上幸一教授らは、新たなルイス酸触媒プロセスを開発し、従来、触媒的不斉合成では困難とされていた4級不斉炭素の構築に成功した。

鏡像異性体の一方だけを作り出す不斉合成は、現代社会を支える基礎的で重要な化学技術である。三上教授グループは、これまで前周期遷移金属であるチタン触媒で、トリフルオロメチル基を持つケトン型化合物のエン反応を行うもの。従来実用化された触媒的不斉合成反応は、官能基の反応では収率、エナンチオ選択性はよいが、ケトン型不斉エン反応では収率、選択性が不十分と適応範囲があまり広くなかった。

金等の後周期遷移金属を中心金属とする不斉ルイス酸触媒で、トリフルオロメチル基を持つケトン型化合物め、これまで工業化された例がない。過去に開発したチタンのルイス酸触媒では、アルデヒド型化合物の不斉エン反応、アルドール反応などを可能にするなど、優れた触媒的不斉合成法を開発してきている。今回開発したのは、パラジウム、白金等の後周期遷移金属を中心金属とする不斉ルイス酸触媒を独自に開発し、高い不斉収率を与える高エナンチオ選択的なのエン反応を行う。有用なプロセスにルイス酸触媒が用いられなかったただ一つのプロセスにルイス酸触媒を転換し、後周期にあるソフトな金属にハードな特性を持たせたところ、カルボニル酸素との反応が進行するとともにソフトな特性が出て触媒がハードな生成物から速やかに解離し、触媒回転率が著しく増大することにより、反応時間が画期的に短くなった（実質的に1時間以内）。

結合生成と同時に、4級不斉炭素を生成することができる。不斉ルイス酸触媒反今回の研究では発想を転換し、後周期にあるソフトな金属にハードな特性を持たせたところ、カルボニル酸素との反応が進行するとともにソフトな特性が出て触媒がハードな生成物から速やかに解離し、触媒回転率が著しく増大することにより、反応時間が画期的に短くなった。実験では、0・0025

カルボニル酸素などのハードな官能基との反応は、ハードな金属を使った方が効率が良いと考えられるため、ルイス酸触媒としては周期表の前周期や典型、ランタノイドなどの金属を使うのが常識だった。しかし、

モル％という極少量の不斉触媒により、数十分でほぼ100％の生成物を得ることに成功した。あとは通常知られている手法で様々な医薬品を合成できる。こうした高価な貴金属を使った合成プロセスは触媒反応といえども経済的に工業化が難しいといえども、このプロセスではシンプルな不斉配位子の採用と触媒使用量が極少量であることから経済性に優れ、工業化できる可能性は非常に高いという。

三上教授は「エン反応は、極少量の触媒を使って、極少量の触媒を使って、原理的には無限の光学活性的かつ光学的に純粋に合成生成反応です。今後、さらに多くの金属についても検討を進め、価値のある不斉触媒を開発していきたい」と語っている。

共同研究を進めており、数年後には日本発の環境に優しい触媒的不斉合成プロセスとして世界中で使われるようになる可能性は高い。

失う分子が全くないという無駄のない炭素─炭素結合生成反応です。今後、さらに多くの金属についても検討を進め、価値のある不斉触媒を開発していきたい」と語っている。

医薬品産業等への展開が期待される。すでにセントラル硝子と

た炭素─炭素結合生成反応を利用した不斉合成プロセスは、経済性が高く、定量的かつ光学的に純粋に合成することに成功しており、医薬品産業等への展開が期待される。すでにセントラル硝子と

触媒的不斉合成は、廃棄物の少ない環境調和型不斉プロセスとして注目されている。

「これまで」; Mikami's titanium BINOL system has been used by Roche on a multi 100-kg scale in a pilot process.

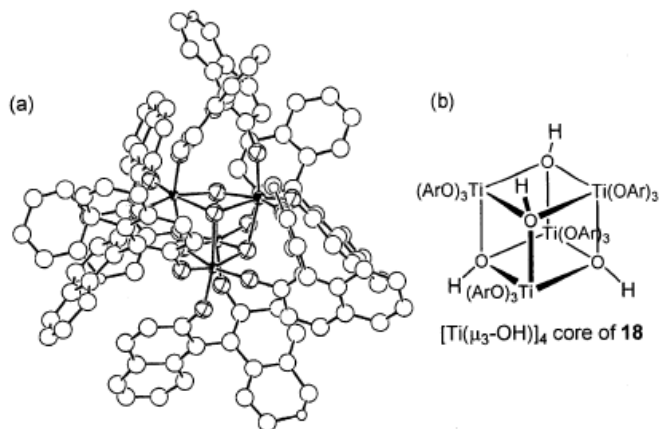# Structural Elucidation of Catalytically Active Species

(1)

(2)

(R)-BINOL (0.1 mmol)

(a)   (b)
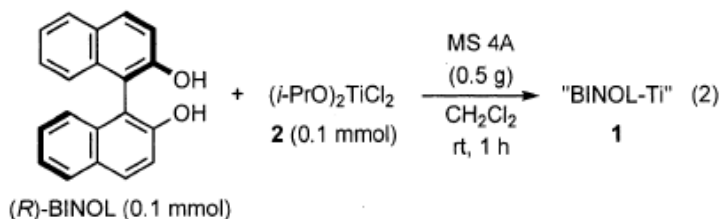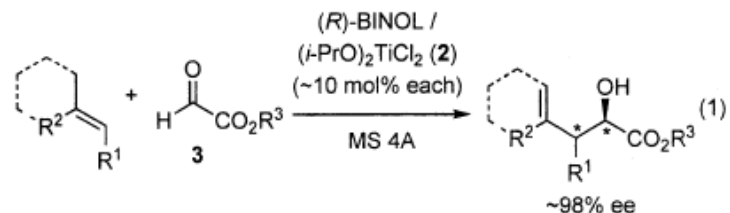
[Ti(μ_3-OH)]$_4$ core of **18**

Fig. 12 X-ray crystallographic analysis of [(BINOLato)$_6$[Ti(μ_3-OH)]$_4$] **18**: (a) ORTEP drawing of **18**. (b) [Ti(μ_3-OH)]$_4$ core structure of **18**.
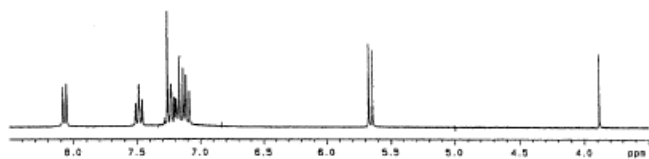
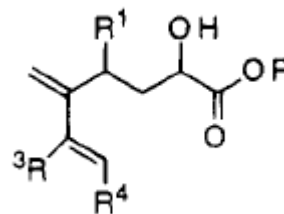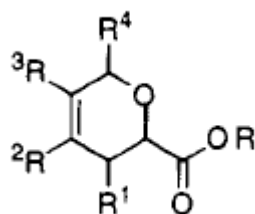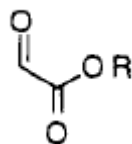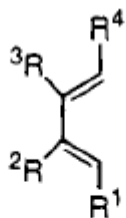Fig. 13 ^{1}H NMR spectrum of [(BINOLato)$_6$[Ti(μ_3-OH)]$_4$] **18** in CDCl$_3$.
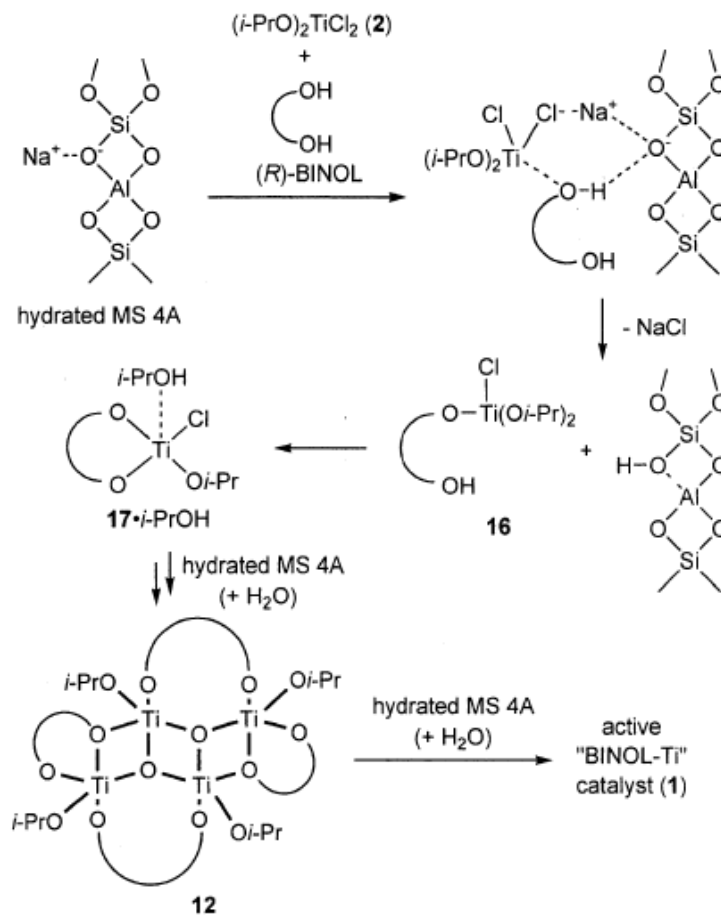
Fig. 11 Plausible mechanisms for generating the active "BINOL–Ti" catalyst 1 from BINOL and (i–PrO)$_2$TiCl$_2$ 2 in the presence of hydrated MS 4 A.

Asymmetric Hetero Diels–Alder Reactions and Ene Reactions Catalyzed by Chiral Copper(I1) Complexes
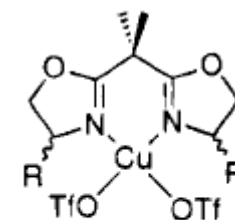
3a: $R^1 = R^2 = R^3 = R^4 = H$
3b: $R^1 = R^3 = R^4 = H$; $R^2 = Me$
3c: $R^1 = R^4 = H$; $R^2 = R^3 = Me$
3d: $R^1 = R^4 = (CH_2)_2$; $R^2 = R^3 = H$

4a: R = Me
4b: R = Et
4c: R = iso-Pr

(S)-1a (R = t-Bu)
(R)-1b (R = Ph)
(S)-1b (R = Ph)

Table 2. Hetero Diels−Alder Reactions and Ene Reactions of 2,3-Dimethyl-1,3-butadiene (3c) and Different Alkyl Glyoxylates 4a−c Catalyzed by (S)-1a and (R)-1b

entry	catalyst	glyoxylate	Diels−Alder product: yield/%[a] (ee/%)[b] (confg)	ene product: yield/%[a] (ee)[b,c]	Diels−Alder product:ene product ratio
1	(S)-1a	4a	5a, 25 (90) (S)	6d, 39 (85)	1:1.6
2	–	4b	5d, 20 (85) (S)	6c, 36 (83)	1:1.8
3	–	4c	5e, 12 (77) (S)	6d, 12 (83)	1:1
4	(R)-1b	4a	5c, 36 (81) (S)	6b, 50 (85)	1:1.4
5	–	4b	5d, 31 (83) (S)	6c, 50 (88)	1:1.6
6	–	4c	5c, 31 (87) (S)	6d, 40 (90)	1:1.3

[a] Isolated yield. [b] Ee determined by GC on a Chrompack Chirasil-DEX CB column. [c] Absolute stereochemistry not assigned.

Jorgensen, K. A. *J. Org. Chem.* **1995**, 60,5757

Asymmetric Hetero Diels–Alder Reactions and Ene Reactions Catalyzed by Chiral Copper(I1) Complexes

(si-face)

8

(si-face)

9

Cu-BOX catalyst

catalyst **2a**

CH_2Cl_2, 25 °C
48 h

26
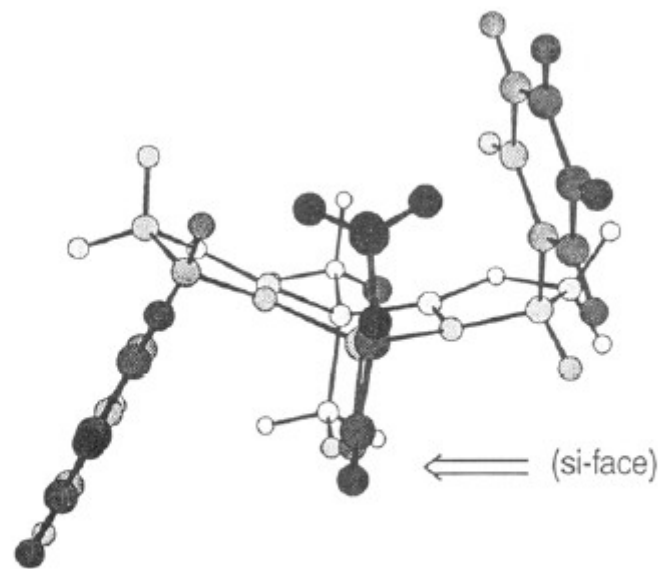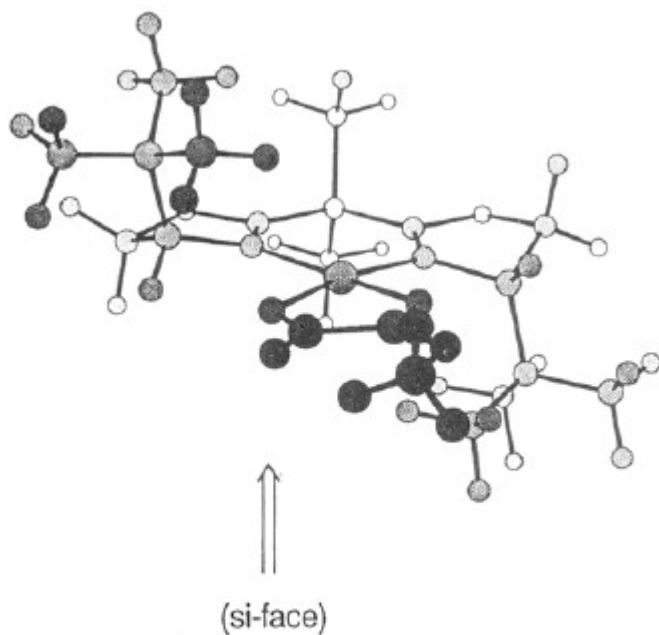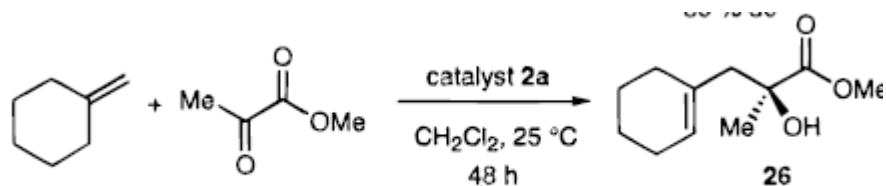
[Cu((S,S)-t-Bu-box)](SbF_6)$_2$ (**2a**) (10 mol%): >99 %ee, 35% yield

Table 11. Catalyzed Enantioselective Ene Reactions between Methyl Pyruvate and 1,1-Disubstituted Olefins[a]

olefin	product[b]	cat (mol%)	% ee[c]	% yield[d]
	26	**2a** (20)	98 (S)	84
	27	**2a** (5)	98 (S)	95
	28	**2a** (10)	98 (S)	76
	29	**2a** (5)	98 (S)	94

[a] All reactions performed at 0.33 M in substrate in CH_2Cl_2 at 40 °C. [b] Absolute configurations assigned by X-ray crystal analysis or by analogy (Supporting Information). [c] Enantiomeric excess determined by GLC (Cyclodex-β column). [d] Isolated yields.

endo–geometry   *exo –geometry*

Figure 2. Endo/exo approach of cyclohexene to the [Cu((S,S)-t-box)(glyoxylate)]$^{2+}$.

Evans, D. A. *J. Am. Chem. Soc.,* 2000, Vol. 122, No. 33,

Carbonyl-Ene Reactions Catalyzed by Box- Cu(II) Complexes Proceed by a Facile Stepwise Mechanism :DFT and ONIOM (DFT:PM3) Studies(1)

Scheme 1. Copper-Catalyzed Carbonyl-Ene Reaction

BOX リガンド（**4**）と銅（Ⅱ）錯体を触媒としたカルボニル–エン反応（**Scheme 1**）の反応機構のDFTによる研究がなされた。筆者らはDFT法と、DFT法よりも簡便なONIOM法の両方を用いて各計算を行った（**Figure 2**）。結果、ONIOMは正確な静止構造を算出したが、正確なエネルギーの算出にはDFTレベルの計算が必要であると結論付けた。また、計算結果を踏まえて、筆者らはこの反応はステップ・ワイズに進行すると結論づけた。TS 3のエネルギーがTS 2より高いことから、5のような4員環の中間体を経ずに進行する。更に、この反応における錯体金属の役割について、β水素転移がメタセシスや酸化的付加と異なり、錯体金属の直接の関与無しに起こることから、錯体金属は単に求電子性を上げる活性化の役割を果たしているとした。
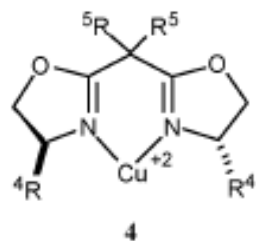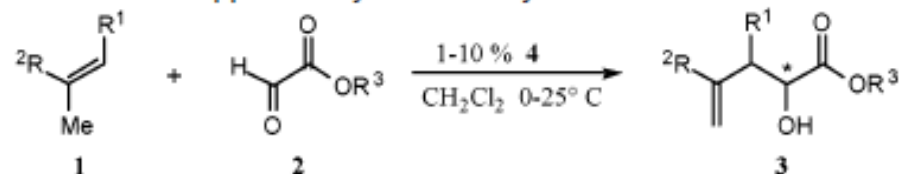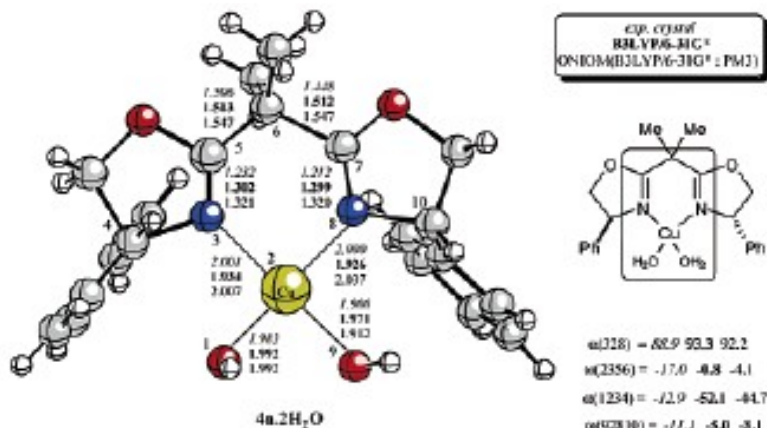
Figure 1. Main geometrical parameters for 4a·2H₂O. Selected bond lengths (Å) and angles (deg). Atoms included in the high level region are within the box.
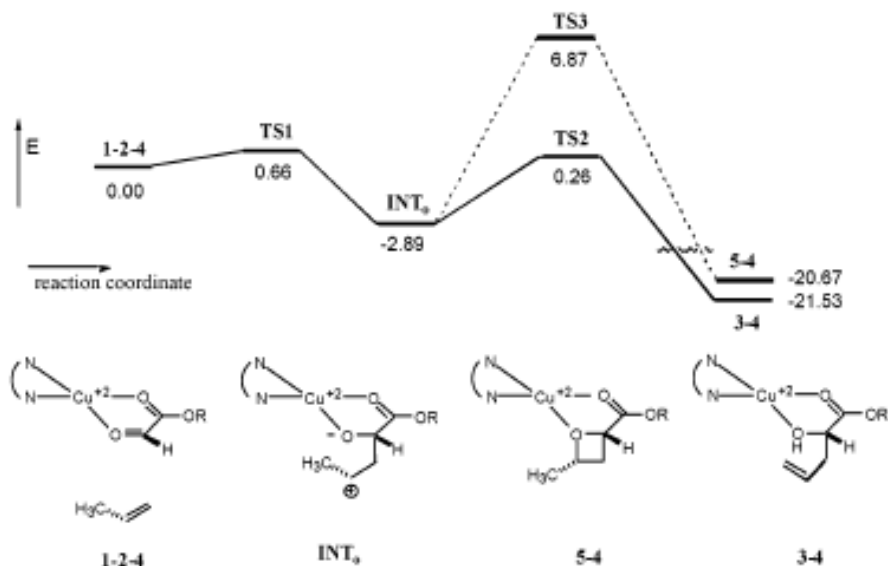
Figure 2. Relative free energies (in kcal/mol) on the pathway (1 + 2 → 3) catalyzed by 4 (solid lines) at the UB3LYP(PCM)/6-311G**//UB3LYP/6-31G* level. Only one enantiomer has been drawn (exo approach) for clarity. Alternative pathways are indicated by hashed lines.

Morao, I.; McNamara, J. P.; Hiller, I. H. *J. AM. CHEM. SOC.* **2003**, 125, 628–629

Enantioselective Syn-Selective Sc-Catalyzed Ene Reactions(1)

Table 1. Ene Reaction with 1,1-Disubstituted Olefins (eq 3)
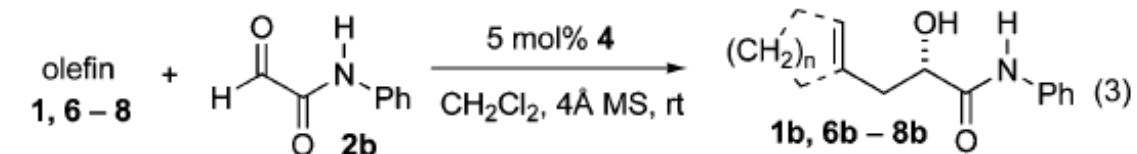
olefin	product		ee %[a]	yield %	mp °C
1: R = Ph		1b	92	73	115
6: R = Me		6b	94[b]	78	68
7: n = 1		7b	94	99	80
8: n = 2		8b	94	89	111

[a] Enantiomeric excesses were determined by HPLC using Chiracel OD-H or AD-H columns. [b] Absolute stereochemistry was determined by Mosher ester analysis. Remaining product configurations were assigned by analogy.

Syn-Selective Sc-Catalyzed Ene Reactions(2)

$$(4)$$
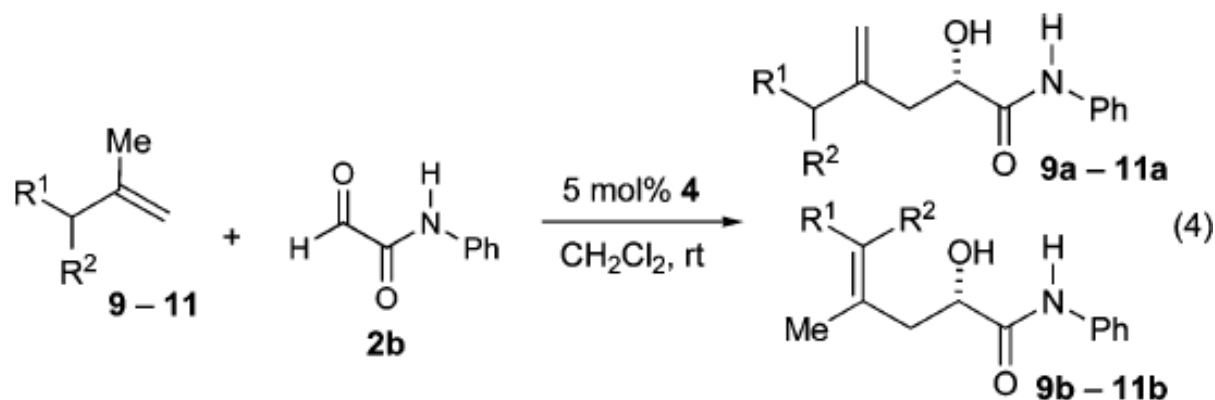
9: R^1 = i-Pr, R^2 = H   94% ee, 78% yield, 4:1 **9a/9b**
10: R^1 = R^2 = Me   96% ee, 60% yield, 5.3:1 **10a/10b**
11: R^1 = t-Bu, R^2 = H   94% ee, 81% yield, >99:1 **11a/11b**

Table 2. Ene Reaction with Trisubstituted Olefins (eq 5)

$$(5)$$

olefin	product	ee %[a]	yield %	dr	mp °C
12: R = Me	**12b**	94[b,c]	78	13:1	104
13: R = Et	**13b**	99	76	24:1	67
14: n = 1	**14b**	98	82	9.3:1	134
15: n = 2	**15b**	98[c]	78	9.3:1	133
16	**16b**	96[c]	58	9:1	87

Evans, D. A.; Wu, J. *J. AM. CHEM. SOC.* **2005**, 127, 8006-8007

26

Enantioselective Syn-Selective Scandium-Catalyzed Ene Reactions(3)

(6)
95% ee, 83% yield, 10:1 syn/anti

(7)
99% ee, 75% yield, 20:1 syn/anti

exo TS ‡

(8)
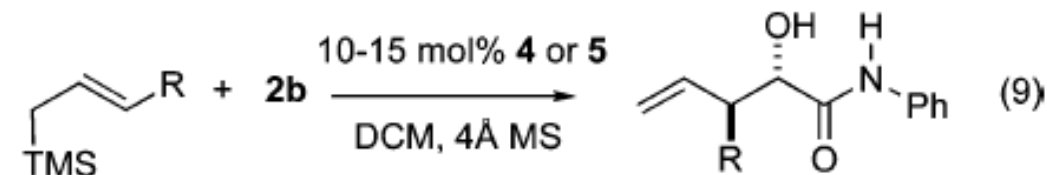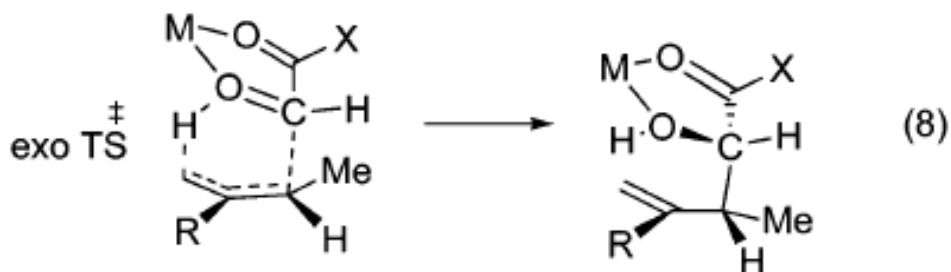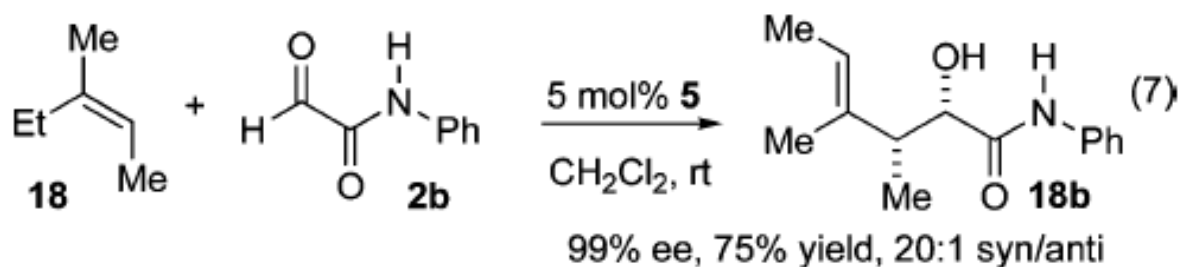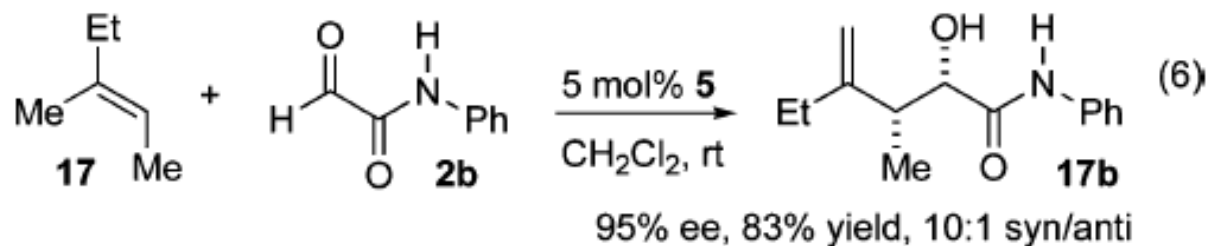
(9)
19: R = Me
20: R = Ph
19b: 94% ee, 15:1 anti:syn, 71% yield
20b: 99% ee, >99:1 anti:syn, 68% yield

Remarkably Broad Substrate Scope(1)

Zheng, K.; Shi, J.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2008**, 130, 15770-15771

四川大学

1a   **2a**   **3a**

Table 1. Optimization of the Reaction Conditions

L₁: R₁ = cyclopentyl
L₂: R₁ = phenyl
L₃: R₁ = 4-methoxylphenyl
L₄: R₁ = 2,6-diisopropylphenyl

L_1: R_1 = cyclopentyl
L_2: R_1 = phenyl
L_3: R_1 = 4-methoxylphenyl
L_4: R_1 = 2,6-diisopropylphenyl

L_5: n = 1
L_6: n = 2

entry	ligand	Ni(II)	x (mol%)	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	$Ni(ClO_4)_2$	20	CH_2Cl_2	32	51
2	**L2**	$Ni(ClO_4)_2$	20	CH_2Cl_2	42	57
3	**L3**	$Ni(ClO_4)_2$	20	CH_2Cl_2	57	63
4	**L4**	$Ni(ClO_4)_2$	20	CH_2Cl_2	75	99
5	**L5**	$Ni(ClO_4)_2$	20	CH_2Cl_2	70	80
6	**L6**	$Ni(ClO_4)_2$	20	CH_2Cl_2	99	99
7	**L6**	$Ni(ClO_4)_2$	20	DCE	99	>99
8	**L6**	$Ni(BF_4)_2$	20	DCE	99	>99
9[d]	**L6**	$Ni(ClO_4)_2$	5	DCE	95	96
10[d]	**L6**	$Ni(BF_4)_2$	5	DCE	98	>99
11[d]	**L6**	$Ni(BF_4)_2$	2.5	DCE	89	99
12[d]	**L6**	$Ni(BF_4)_2$	1	DCE	83	99

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of phenylglyoxal and 3.0 equiv of 2-phenylpropene in solvent (0.5 mL) at 25 °C for 64 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was performed at 60 °C for 16−32 h.

Remarkably Broad Substrate Scope(2)

Zheng, K.; Shi, J.; Liu, X.; Feng, X.
J. Am. Chem. Soc. **2008**, 130,
15770-15771

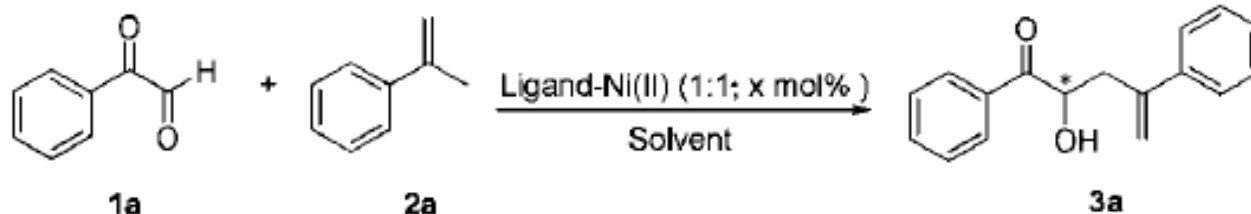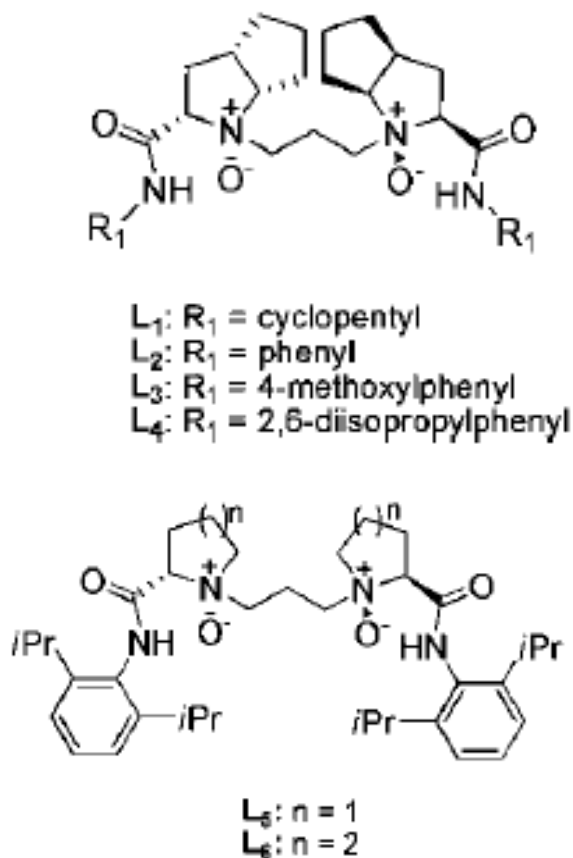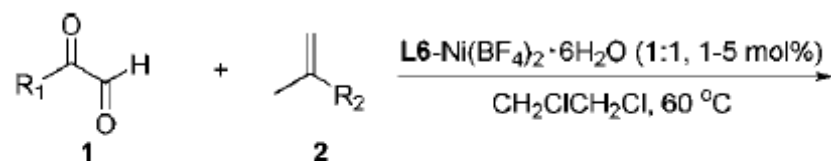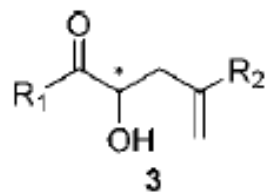**Table 2.** Substrate Scope for the Catalytic Asymmetric Carbonyl–Ene Reaction

L6-Ni(BF$_4$)$_2$·6H$_2$O (1:1, 1-5 mol%)
CH$_2$ClCH$_2$Cl, 60 °C

2a: R$_2$ = Ph
2b: R$_2$ = 4-FC$_6$H$_4$
2c: R$_2$ = 2-MeC$_6$H$_4$
2d: R$_2$ = ^{t}BuCH$_2$
2e: R$_2$ = ^{i}Pr

entry	R$_1$	2	yield (%)[b]	ee (%)[c]
1	Ph	2a	98 (83)	>99 (99)[g]
2	2-MeC$_6$H$_4$	2a	95 (78)	>99 (98)[h]
3	3-MeC$_6$H$_4$	2a	92 (82)	99 (98)[h]
4	4-MeC$_6$H$_4$	2a	97 (80)	>99 (97)[h]
5	3-MeOC$_6$H$_4$	2a	91 (78)	>99 (98)[h]
6	4-MeOC$_6$H$_4$	2a	99 (85)	>99 (96)[g]
7	3,4-(MeO)$_2$C$_6$H$_3$	2a	90 (87)	>99 (97)[h]
8	2-ClC$_6$H$_4$	2a	74	>99
9	3-ClC$_6$H$_4$	2a	92 (70)	99 (97)[h]
10	4-ClC$_6$H$_4$	2a	86 (75)	>99 (98)[h]
11	3,4-Cl$_2$C$_6$H$_3$	2a	92 (75)	99 (99)[h]
12	2-FC$_6$H$_4$	2a	85	99
13	4-FC$_6$H$_4$	2a	92 (73)	>99 (99)[h]
14	4-BrC$_6$H$_4$	2a	95 (70)	99 (97)[h]
15	3-NO$_2$C$_6$H$_4$	2a	72	>99
16	4-NO$_2$C$_6$H$_4$	2a	78	>99
17	2-naphthyl	2a	93 (77)	>99 (99)[h]
18	2-furyl	2a	95 (80)	>99 (98)[g]
19	2-thienyl	2a	90 (83)	98 (98)[h]
20	c-hexyl	2a	80	97
21	Me	2a	75	99
22	Ph	2b	93 (82)	>99 (99)[h]
23[e]	Ph	2c	73	>99
24	Ph	2d	84	98
25[e]	Ph	2e	86	>99
26[f]	OEt	2a	99	99 (S)[d]
27[f]	OEt	2b	94	97
28[e,f]	OEt	2c	77	99
29[f]	OEt	2d	87	98 (S)[d]

[a] Unless otherwise noted, the reaction was carried out with 5 mol% L6-Ni(BF$_4$)$_2$·6H$_2$O, 0.1 mmol of glyoxal derivative (glyoxylate), and 3.0 equiv of alkene in DCE (0.5 mL) at 60 °C for 14−48 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration was determined by comparison with literature data.[3r] [e] With 10 mol% catalyst. [f] The reaction was performed at 40 °C. [g] The results in parentheses were obtained with 1 mol% catalyst. [h] The results in parentheses were obtained with 2.5 mol% catalyst.

Organocatalyst
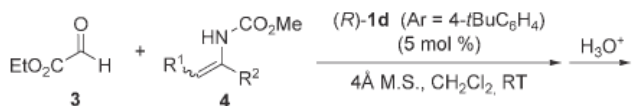## Aza-ene-type reaction catalyzed by chiral Bronsted acid

-the first example of the activation of aldehydes by using chiral phosphoric acid to efficiently accelerate an aza-ene-type reaction
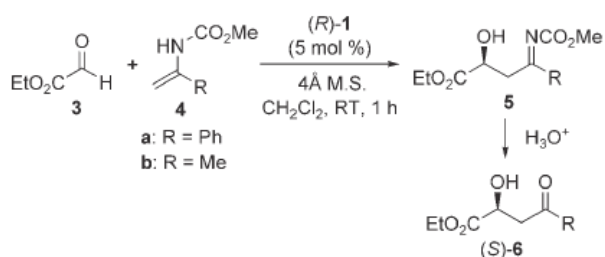
Table 1: Enantioselective aza-ene-type reaction of glyoxylate (3) with enecarbamate (4 a) catalyzed by (R)-1 ([Eq. (2)]).[a]

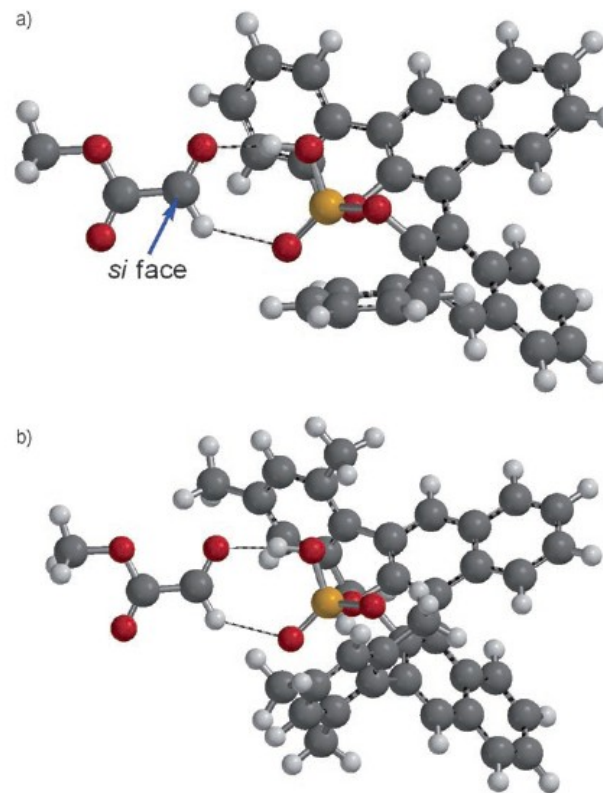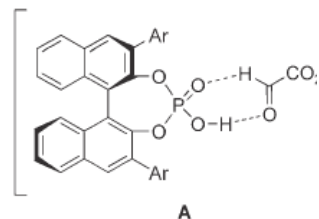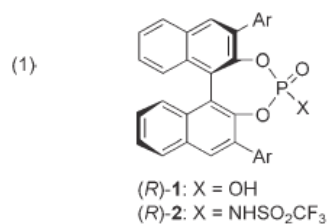| Entry	1: Ar	Yield [%][b]	ee [%][c]
1	1b: 4-CH$_3$C$_6$H$_4$	93	95
2	1c: 4-CF$_3$C$_6$H$_4$	82	94
3	1d: 4-tBuC$_6$H$_4$	99	98
4	1e: 4-β-naphthylphenyl	81	95
5	1f: β-naphthyl	80	91
6	1g: 3,5-tBu$_2$C$_6$H$_3$	37	2
7	1h: 2,4,6-(CH$_3$)$_3$C$_6$H$_2$	40	8[d]
8	1i: 9-anthryl	35	18

(R)-1: X = OH
(R)-2: X = NHSO$_2$CF$_3$

A

Figure 1. Three-dimensional structures of the hydrogen-bonded complexes formed between 1 and 3′. P tan, O red, C gray, H white. a) (R)-1a/3′; b) (R)-1h/3′.

c: R^1 = Me, R^2 = Ph
d: R^1 = Me, R^2 = Et
e: R^1 = Et, R^2 = Ph
f: R^1,R^2 = –(CH$_2$)$_4$–

anti 6   syn 6

Entry	4	t [h]	Yield [%][b]	anti:syn	ee [%][c] anti	syn
1	(E)-4c	2	73	>99:<1	>99	53
2	(E)-4d	2	73	96:4	99	56
3[d]	(E)-4e	4	75	99:1	99	74
4	4f	1	89	89:11	99	98
5	(Z)-4c	24	11	72:28	26	88
6	(Z)-4d	2	74	50:50	28	69
7[d]	(Z)-4e	24	67	92:8	8	74

Terada, M.; Soga, K.; Momiyama, N. *ACIE* **2008**, 47, 4122-4125

30

Organocatalyst

Carbonyl-ene reaction catalyzed by chiral Bronsted acid

-the first example of the highly enantioselective carbonyl-ene reaction with chiral phosphoric acid

Table 1: Survey of N-triflylphosphoramide catalysts for the enantioselective Brønsted acid catalyzed carbonyl-ene reaction.[a]
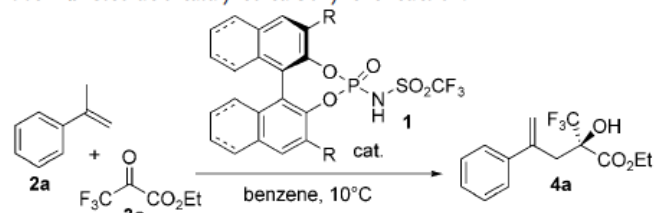
Entry	1	R	t [h]	Yield [%][b]	ee [%][c]
1	1a	phenyl	25	41	53
2	1b	2-naphthyl	23	63	81
3	1c	3,5-(CF$_3$)$_2$C$_6$H$_3$	26	32	36
4	1d	phenanthryl	23	52	28
5	1e	anthracenyl	38	24	26
6	1f	biphenyl	25	61	77
7	1g	p-NO$_2$C$_6$H$_4$	13	70	86
8	1h	SiPh$_2$Me [H$_8$]	26	34	56
9	1i	SiPh$_3$ [H$_8$]	38	15	7
10	1j	p-MeOC$_6$H$_4$ [H$_8$]	34	86	94

[a] Reaction conditions: 2a, 3a (2.0 equiv), 1 (5 mol%), benzene (2 mL).
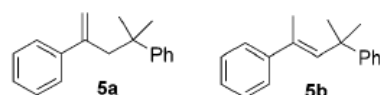
Table 3: Scope of the Brønsted acid catalyzed carbonyl-ene reaction.[a]
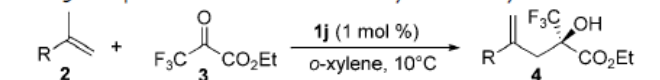
Entry	R	Yield [%][b]	ee [%][c]
1	Ph (2a)	76	96
2	p-MeOC$_6$H$_4$ (2b)	69	92
3	p-MeC$_6$H$_4$ (2c)	92	96
4	m-MeC$_6$H$_4$ (2d)	91	96
5	p-EtC$_6$H$_4$ (2e)	96	95
6	p-FC$_6$H$_4$ (2f)	88	92
7	2-naphthyl (2g)	95	95
8	biphenyl (2h)	87	97
9	p-tBuC$_6$H$_4$ (2i)	83	94
10	m,p-Me$_2$C$_6$H$_3$ (2j)	92	92
11	p-BrC$_6$H$_4$—C$_6$H$_4$ (2k)	87	96
12	tetralinyl (2l)	96	95
13	indanyl (2m)	93	95
14	p-ClC$_6$H$_4$ (2n)	55	93
15	p-iPrC$_6$H$_4$[d] (2o)	85	92
16	p-IC$_6$H$_4$[d] (2p)	89	97
17	p-BrC$_6$H$_4$[d] (2q)	71	93

[a] Reaction conditions: 2, 3a (2.0 equiv), 1j (1 mol%), 0.25 M solution in o-xylene. [b] Yield of the isolated product after column chromatography. [c] The ee value was determined by HPLC or GC on a chiral phase. [d] The reaction was carried out with catalyst 1g at −20°.
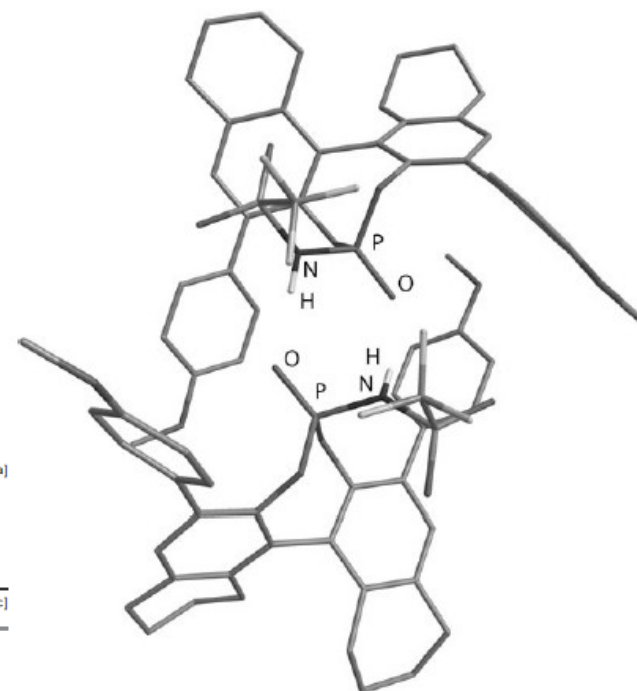
Molecular structure of the N-triflylphosphoramide catalyst 1j.

Sumary