

# **Journey from Lanthanide Triflate to Metalloenzyme-Like Catalyst**

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# Today's topic ~S. KOBAYASHI's works~



Shu KOBAYASHI

1983 B. Sc.; The University of Tokyo (Professor T. Mukaiyama)  
1987 Assistant Professor; Science University of Tokyo (SUT)  
1988 Ph. D.; The University of Tokyo (Professor T. Mukaiyama)  
1991 Lecturer; Science University of Tokyo (SUT)  
1992 Associate Professor; Science University of Tokyo (SUT)  
1998 Full Professor, School of Medicine, The University of Tokyo  
2007 Full Professor, School of Science, The University of Tokyo

A leading chemist in the field of “water-tolerant Lewis acids”

1991 : Report that lanthanide and scandium triflates ( $\text{Ln}(\text{Otf})_3$ ,  $\text{Sc}(\text{Otf})_3$ ) is usable  
as Lewis acid in water.

2015 : Development of metalloenzyme-like catalyst  
(Very Important Paper of Chem. Asian J.)

In this seminar, focus on up to development of metalloenzyme-like catalyst  
from discovery of water-tolerant Lewis acids

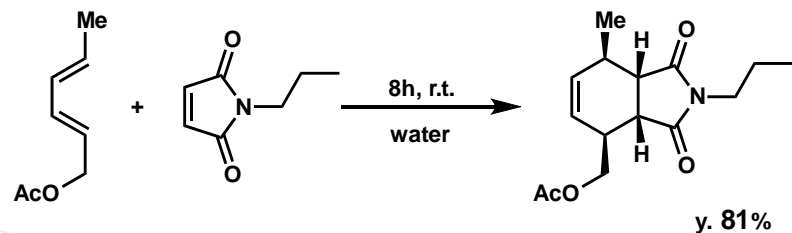
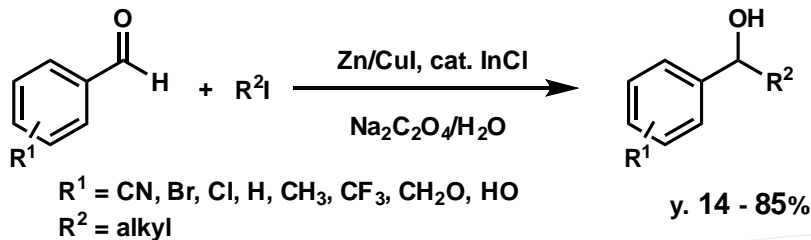
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# 1. Introduction

# Organic chemistry in water

Introduction



*Barbier-Grignard type reaction in water*

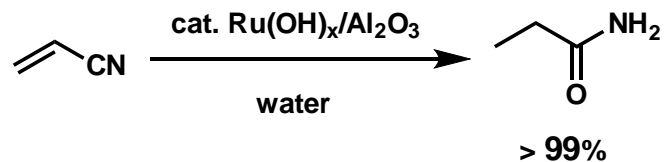
Organic reactions in water

Rate acceleration of Diels-Alder reactions by water solvent.

Solvent	Concentration[M]	Time to completion	Yield (%)
toluene	1	144 h	79
CH <sub>3</sub> CN	1	>144 h	43
MeOH	1	48 h	82
neat	3.7 <sup>a</sup>	10 h	82
H <sub>2</sub> O	3.7 <sup>a</sup>	8 h	81

a. Calculated from the measured density of 1:1 mixture of 1 and 2.

*Diels-Alder reaction in water*



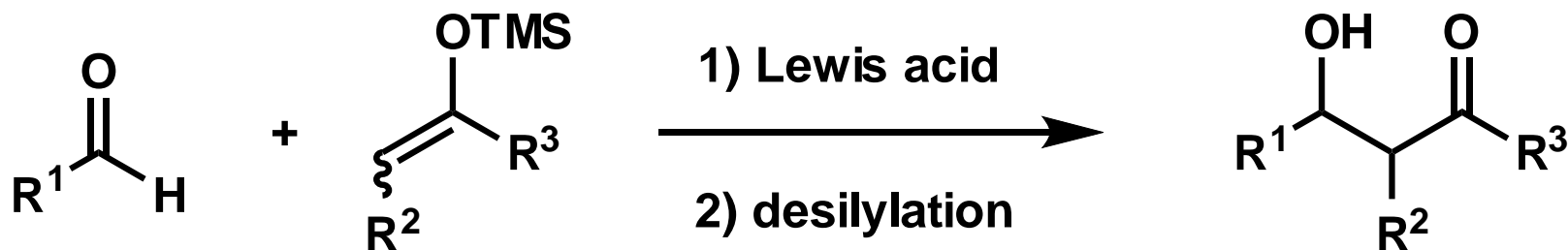
Chem. Soc. Rev., 2006, 35, 68–82

*Ru-catalyzed hydration of nitriles to amides in water*

- Advantage : safe, benign, environmentally friendly, and cheap
- Disadvantage : Most organic substances are insoluble in water.  
Many reactive substrates, reagents, and catalysts are decomposed or deactivated by water.

# Mukaiyama aldol addition

Aldol addition is a powerful method for forming a C-C bond.



typical Lewis acids :  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{BF}_3 \cdot \text{OEt}_3$

The Mukaiyama aldol addition is a type of aldol reaction between a silyl enol ether and an aldehyde or formate.

These reactants allow for a crossed aldol reaction between an aldehyde and a ketone or a different aldehyde without self-condensation of the aldehyde.

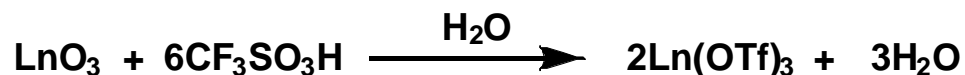
Lewis acids undergo hydrolysis by water molecules, so strict anhydrous conditions are needed in this reaction.

## 2. Lanthanide triflate as water-tolerant Lewis acids

# Use of Ln(OTf)<sub>3</sub> as Lewis acid

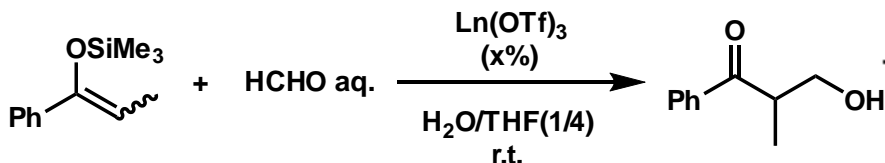
Lanthanide triflate  
as water-tolerant Lewis acids

Ln(OTf)<sub>3</sub> is prepared from the corresponding lanthanide oxides (Ln<sub>2</sub>O<sub>3</sub>) and trifluoromethanesulfonic acid in water.



Hydroxymethylation reactions by using Ln(OTf)<sub>3</sub>

Effect of Lanthanide Triflates in the Reaction of **1** with Commercial Formaldehyde Solution at r.t.



Chem. Lett., 2187-2190 (1991)

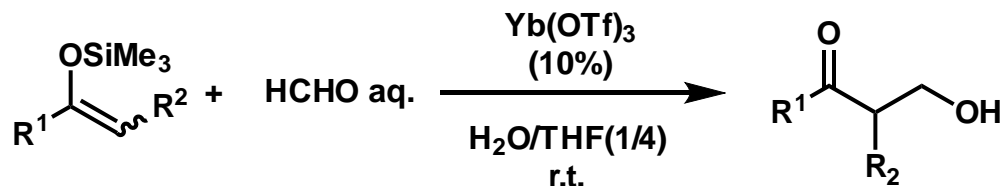
In most cases,  
the reactions proceeded smoothly.

Yb(OTf)<sub>3</sub> is the most reactive catalyst.

Ln(OTf) <sub>3</sub>	yield/%		
	100 mol %		20 mol % 36 h
	24 h	1 h	
La(OTf) <sub>3</sub>	90	23	88
Pr(OTf) <sub>3</sub>	92	40	80
Nd(OTf) <sub>3</sub>	74	6	89
Sm(OTf) <sub>3</sub>	92	51	91
Eu(OTf) <sub>3</sub>	92	28	93
Gd(OTf) <sub>3</sub>	92	20	79
Dy(OTf) <sub>3</sub>	89	20	85
Ho(OTf) <sub>3</sub>	91	38	86
Er(OTf) <sub>3</sub>	90	44	83
Yb(OTf) <sub>3</sub>	94	5	94



# Several examples of hydroxymethylation reaction



- 1) In every case, the reactions proceeded smoothly in high yield.
- 2) Di- and polyhydroxymethylated products were not observed.
- 3) The absence of equilibrium allowed for a regiospecific hydroxymethylation reaction.
- 4) Only a catalytic amount of  $\text{Yb}(\text{OTf})_3$  was required to complete the reaction.
- 5) Almost 100% of  $\text{Yb}(\text{OTf})_3$  was quite easily recovered from the aqueous layer after the reaction was completed and it could be reused (third use(93%yield)).

Lanthanide triflate  
as water-tolerant Lewis acids

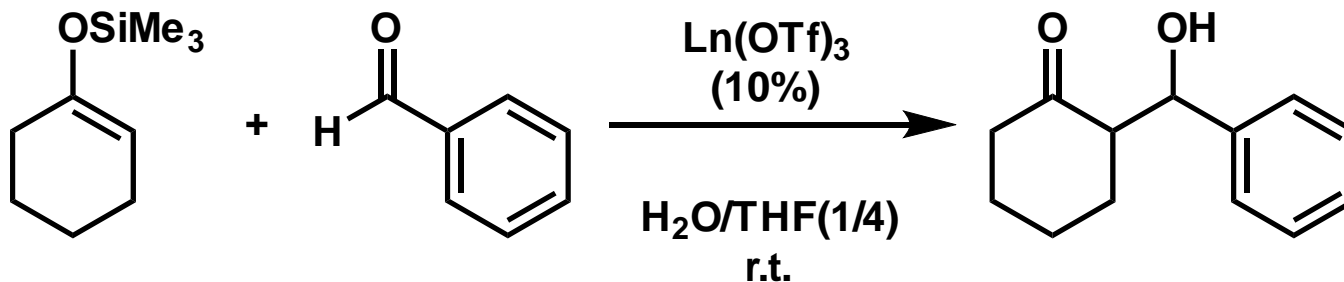
Reaction of Silyl Enol Ethers with Commercial Formaldehyde Solution Catalyzed by  $\text{Yb}(\text{OTf})_3$ .

entry	silyl enol ether	product	yield/%
1			94
2			85
3			77
4			82
5			86
6			92
7			92
8			88
9			83
10			90

<sup>a</sup>  $Z/E = >98/2$ . <sup>b</sup>  $Z/E = 1/4$ . <sup>c</sup> The mixture of the hydroxy thioester and the lactone (2:1) was obtained. The other diastereomers were not observed. <sup>d</sup> The mixture of the hydroxy thioester and the lactone (3:1) was obtained. Less than 3% yield of the other diastereomers were observed.

# Screening of Ln(OTf)<sub>3</sub>

Lanthanide triflate  
as water-tolerant Lewis acids



Effect of Lanthanide Triflates in the Reaction of 4 with Benzaldehyde at r.t. for 20 h in H<sub>2</sub>O-THF (1:4).

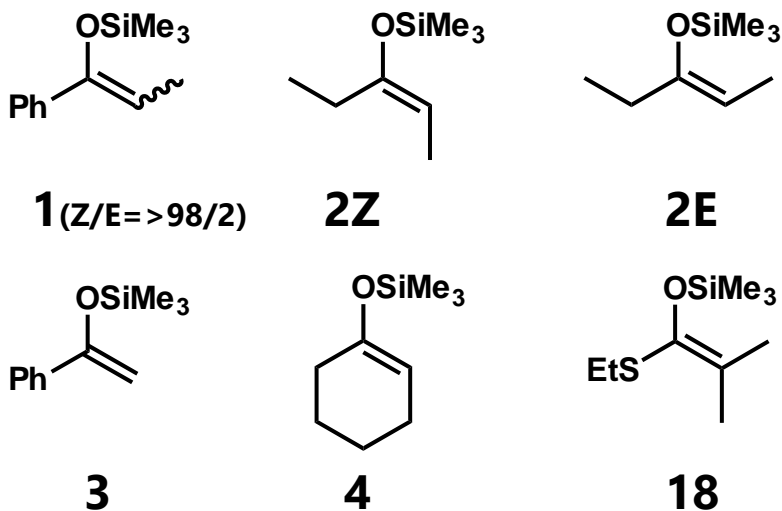
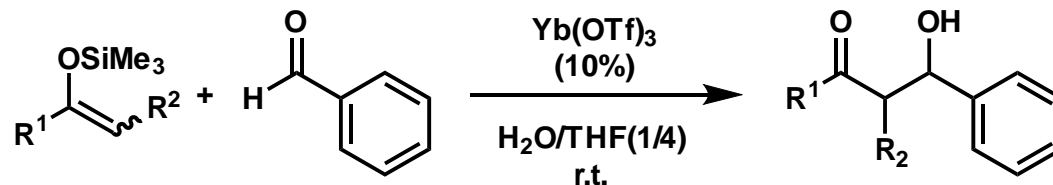
Ln(OTf) <sub>3</sub>	yield/%	Ln(OTf) <sub>3</sub>	yield/%
La(OTf) <sub>3</sub>	8	Dy(OTf) <sub>3</sub>	73
Pr(OTf) <sub>3</sub>	28	Ho(OTf) <sub>3</sub>	47
Nd(OTf) <sub>3</sub>	83	Er(OTf) <sub>3</sub>	52
Sm(OTf) <sub>3</sub>	46	Tm(OTf) <sub>3</sub>	20
Eu(OTf) <sub>3</sub>	34	Yb(OTf) <sub>3</sub>	91
Gd(OTf) <sub>3</sub>	89	Lu(OTf) <sub>3</sub>	88

High reactivity : Nd-, Gd-, Yb-, Lu(OTf)<sub>3</sub>

Low reactivity : La-, Pr-, Tm(OTf)<sub>3</sub>

# Several examples of hydroxymethylation reaction 2

Lanthanide triflate  
as water-tolerant Lewis acids



Lanthanide Triflate-Catalyzed Aqueous Aldol Reaction by Using Yb(OTf)<sub>3</sub> (10 mol %)<sup>a</sup>.

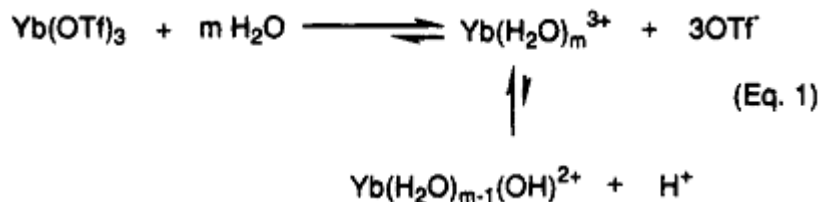
entry	aldehyde	silyl enol ether	product	yield/%
1	PhCHO	<b>4</b>	<b>22<sup>b</sup></b>	91
2	PhCHO	<b>2Z</b>	<b>23<sup>c</sup></b>	89
3	PhCHO	<b>2E</b>	<b>23<sup>d</sup></b>	93
4	PhCHO	<b>1</b>	<b>24<sup>e</sup></b>	81
5	PhCHO	EtSC(OSiMe <sub>3</sub> )=CMe <sub>2</sub> <b>18</b>	<b>25</b>	90
6	<i>p</i> -Cl-PhCHO	<b>4</b>	<b>26<sup>f</sup></b>	89
7	<i>p</i> -MeO-PhCHO	<b>4</b>	<b>27<sup>g</sup></b>	77
8	( <i>E</i> )-CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -CH=CHCHO	<b>4</b>	<b>28<sup>h</sup></b>	90
9	Ph(CH <sub>2</sub> ) <sub>2</sub> CHO	<b>2Z</b>	<b>29<sup>f</sup></b>	79
10	Ph(CH <sub>2</sub> ) <sub>2</sub> CHO	<b>2E</b>	<b>29<sup>i</sup></b>	72
11	CH <sub>3</sub> CHO	<b>1</b>	<b>30<sup>j</sup></b>	93
12	CH <sub>2</sub> =CHCHO	<b>1</b>	<b>31<sup>k</sup></b>	82
13	ClCH <sub>2</sub> CHO	<b>1</b>	<b>32<sup>l</sup></b>	95
14	ClCH <sub>2</sub> CHO	<b>3</b>	<b>33</b>	67
15	ClCH <sub>2</sub> CHO	<b>18</b>	<b>34</b>	66
16	PhCOCHO·H <sub>2</sub> O	<b>1</b>	<b>35<sup>m</sup></b>	67
17	<i>o</i> -HO-PhCHO	<b>1</b>	<b>36<sup>n</sup></b>	81
18	2-pyridinecarboxaldehyde	<b>1</b>	<b>37<sup>n</sup></b>	97

- 1) In every case, the reactions proceeded smoothly in high yield.
- 2) Diastereoselectivities were generally good to moderate

<sup>a</sup> Gd(OTf)<sub>3</sub> was used in entries 11 and 12. In entry 17, Lu(OTf)<sub>3</sub> was used. <sup>b</sup> *syn/anti* = 73/27. <sup>c</sup> 63/37. <sup>d</sup> 71/29. <sup>e</sup> 53/47. <sup>f</sup> 65/35. <sup>g</sup> 61/39. <sup>h</sup> 55/45. <sup>i</sup> 68/32. <sup>j</sup> 46/54. <sup>k</sup> 60/40. <sup>l</sup> 45/55. <sup>m</sup> 27/73. <sup>n</sup> 42/58.

# Mechanistic study 1

Lanthanide triflate  
as water-tolerant Lewis acids



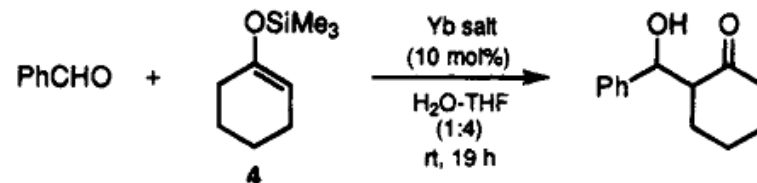
The dissociation equilibrium equation

The Yb salts with less-nucleophilic counter anions are more cationic and the high Lewis acidity promotes the desired reaction.

The results of screening of ligands, only water was effective.

In the presence of other polar molecules, the reaction proceeded very slowly.

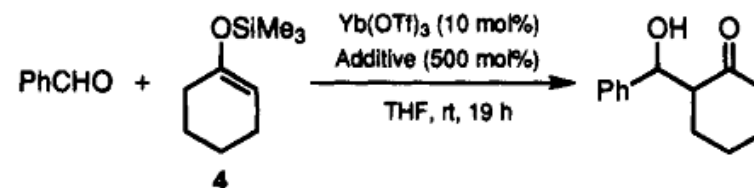
## Effect of Yb salts



Yb salt	yield/%
Yb(OTf) <sub>3</sub>	91 <sup>a</sup>
Yb(ClO <sub>4</sub> ) <sub>3</sub>	88 <sup>b</sup>
YbCl <sub>3</sub>	3
Yb(OAc) <sub>3</sub> ·8H <sub>2</sub> O	14
Yb(NO <sub>3</sub> ) <sub>3</sub> ·5H <sub>2</sub> O	7
Yb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·5H <sub>2</sub> O	trace

<sup>a</sup> *syn/anti* = 73/27. <sup>b</sup> 76/24.

## Effect of additive



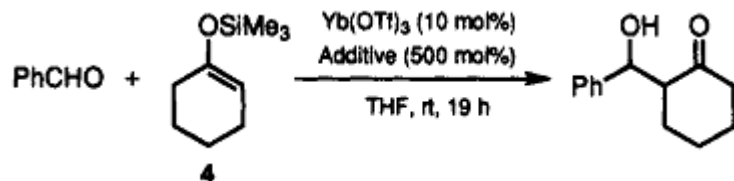
additive	yield/%
none	10
DMF	21 <sup>a</sup>
DMSO	trace
Et <sub>3</sub> N	trace
pyridine	23 <sup>b</sup>
Et <sub>2</sub> O	14
H <sub>2</sub> O	80 <sup>c</sup>

<sup>a</sup> *syn/anti* = 66/34. <sup>b</sup> 73/27. <sup>c</sup> 76/24.

# Mechanistic study 2

Lanthanide triflate  
as water-tolerant Lewis acids

Effect of water



In the absence or presence of small amount of water :  
THF predominantly coordinates to  $\text{Yb(OTf)}_3$

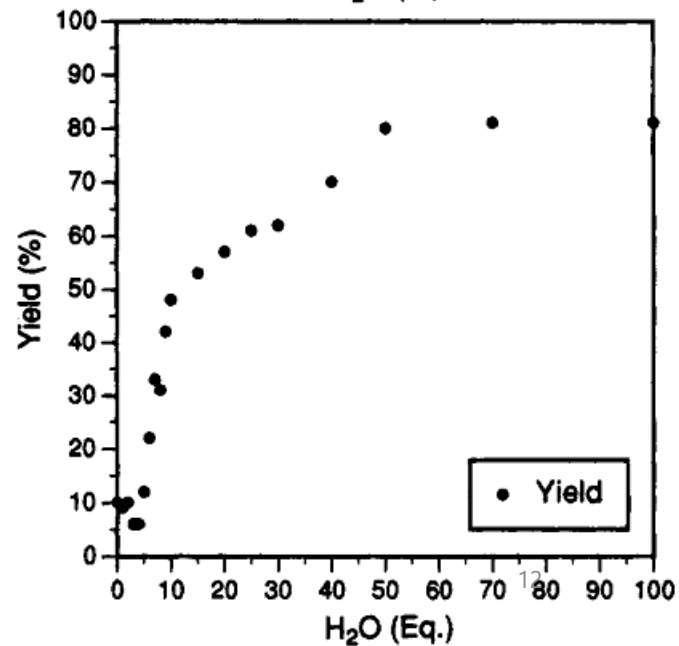
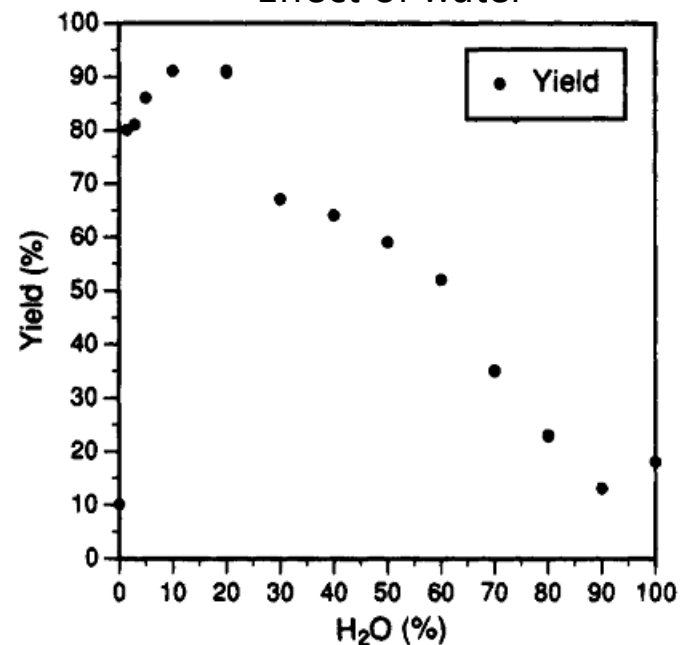
Lewis acidity is low.

When the equivalents of water are gradually increased :  
Water is prone to coordinate to  $\text{Yb(OTf)}_3$

Lewis acidity is high.

*There is a chance for an aldehyde activated.*

When the amount of water is further increased :  
Hydrolysis of the silyl enol ether precedes  
the desired aldol reaction



## *Discovery of lanthanide triflate as water-tolerant Lewis acids*

### Problem

- ◆ When the amount of water is further increased,  
a competitive reaction precedes the desired aldol reaction.

### 3. Development of "LASC"

- ◆ Lanthanide triflate could not be developed  
into enantioselective asymmetric reactions.

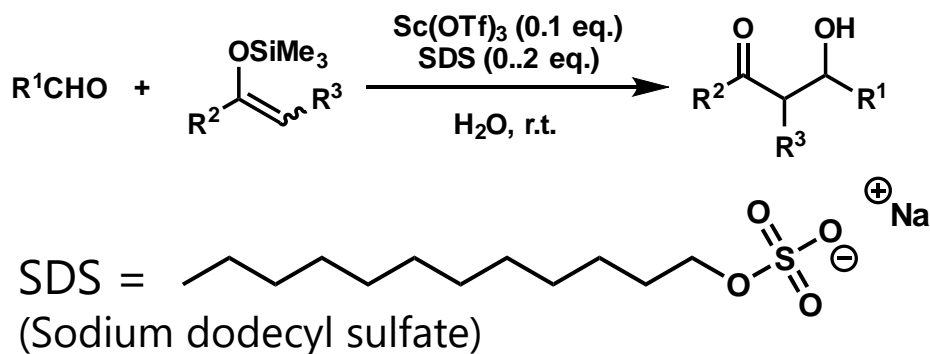
### 4. Asymmetric aldol reactions in aqueous media

### 3. Development of "LASC"

# Sc(OTf)<sub>3</sub>-SDS system

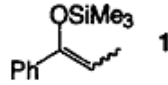
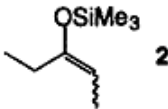
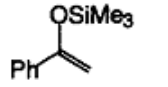
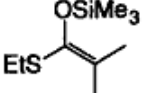
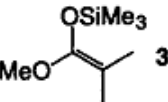
Development of "LASC"

Sc(OTf)<sub>3</sub>-catalyzed Mukaiyama aldol reactions have been successfully carried out in aqueous solutions of surfactants.



Not only aromatic, but also aliphatic and  $\alpha$ ,  $\beta$ -unsaturated aldehydes reacted with silyl enol ethers to afford the corresponding aldol adducts in high yields.

## Sc(OTf)<sub>3</sub>-SDS system

Aldehyde	Silyl Enol Ether	Yield/%
PhCHO	 1	88 <sup>a)</sup>
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO	1	86 <sup>b)</sup>
Ph-CH=CH-CHO	1	88 <sup>c)</sup>
HCHO	1	82 <sup>d)</sup>
PhCHO	 2	88 <sup>e)</sup>
Ph-CH=CH-CHO	2	80 <sup>f)</sup>
PhCHO	 3	75 <sup>g,h)</sup>
PhCHO		94
PhCHO	 3	84 <sup>h)</sup>

a) *Syn/anti* = 50/50. b) *Syn/anti* = 45/55. c) *Syn/anti* = 41/59. d) Commercially available HCHO aq. (3 ml), 1 (0.5 mmol), Sc(OTf)<sub>3</sub> (0.1 mmol), and SDS (0.1 mmol) were combined. e) *Syn/anti* = 57/43. f) *Syn/anti* = 69/31. g) Sc(OTf)<sub>3</sub> (0.2 eq.) was used. h) Additional silyl enolate (1.5 eq.) was charged after 6 h.

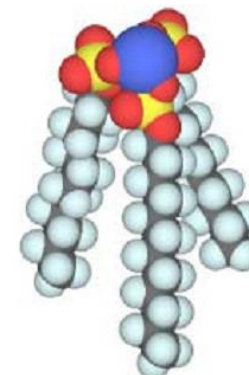
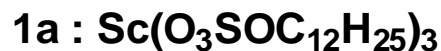


# Lewis-Acid-Surfactant-Combined Catalysts (LASC)

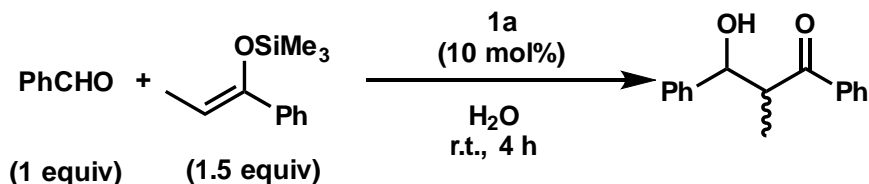
Development of "LASC"

*LASC is more simplified catalyst than Sc(OTf)<sub>3</sub>-SDS system*

1a-1f were prepared from ScCl<sub>3</sub> and the corresponding SDS or sodium alkanesulfonate.



Schematic representation of **1a**



Effect of Solvents on LASC (1a)-Catalyzed Aldol Reactions

solvent	yield (%)
H <sub>2</sub> O	92
CH <sub>3</sub> OH	4
DMF	14
DMSO	9
CH <sub>3</sub> CN	3
CH <sub>3</sub> Cl <sub>2</sub>	3
THF	trace
Et <sub>2</sub> O	trace
toluene	trace
hexane	4
- (neat)	31

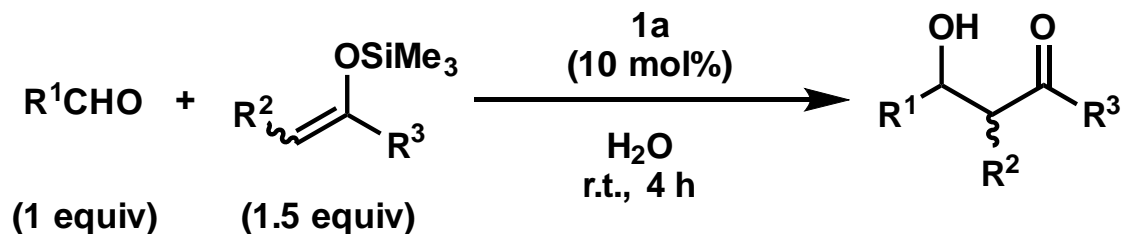
The reaction in water afforded the product in high yield.

Low yield were observed in other organic solvents.

Tetrahedron Letters 39 (1998) 5389-5392

*J. Am. Chem. Soc.*, Vol. 122, No. 30, 2000 7205

<sup>a</sup> When solvents other than H<sub>2</sub>O or CH<sub>3</sub>OH were used, the initially formed trimethylsilyl ether was converted to **3** (1 N HCl/THF (1/20), 0 °C).



## LASC (1a)-Catalyzed Aldol Reactions in Water

$R^1$	$R^2$	$R^3$	product	yield (%)	<i>syn/anti</i>
Ph	Me	Ph	<b>3</b>	92	49/51
Ph(CH <sub>2</sub> ) <sub>2</sub>	Me	Ph	<b>4</b>	88	44/56
PhCH=CH	Me	Ph	<b>5</b>	91	40/60
2-pyridyl	Me	Ph	<b>6</b>	84 <sup>a</sup>	24/76
PhCO	Me	Ph	<b>7</b>	86	66/34
Ph	Me	Et	<b>8</b>	84	78/22
<i>p</i> -ClPh	Me	Et	<b>9</b>	91	79/21
Ph(CH <sub>2</sub> ) <sub>2</sub>	Me	Et	<b>10</b>	82 <sup>a</sup>	72/28
PhCH=CH	Me	Et	<b>11</b>	87	71/29
PhCH=CH	-(CH <sub>2</sub> ) <sub>4</sub> -		<b>12</b>	85 <sup>a</sup>	52/48
Ph	H	Ph	<b>13</b>	94 <sup>a,b</sup>	
Ph	Me <sub>2</sub>	SEt	<b>14</b>	98	
Ph	Me <sub>2</sub>	OMe	<b>15</b>	80 <sup>a,b</sup>	

<sup>a</sup> **1a** (20 mol %). <sup>b</sup> Silyl enolate (3 equiv).

Aromatic as well as aliphatic,  $\alpha$ ,  $\beta$ -unsaturated, and heterocyclic aldehydes worked well.

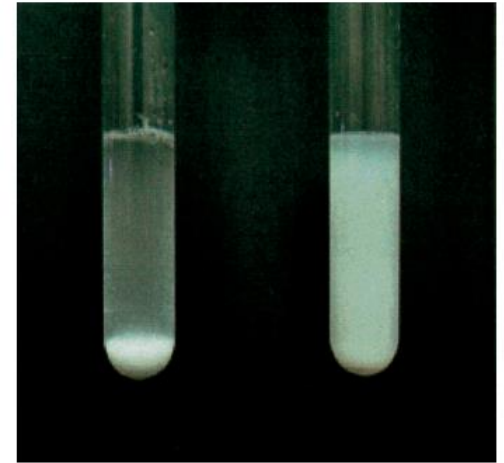
Silyl enol ethers, ketene silyl enol ethers, and an ester reacted well

to give the corresponding adducts in high yields.

# Characterization of the colloidal particle

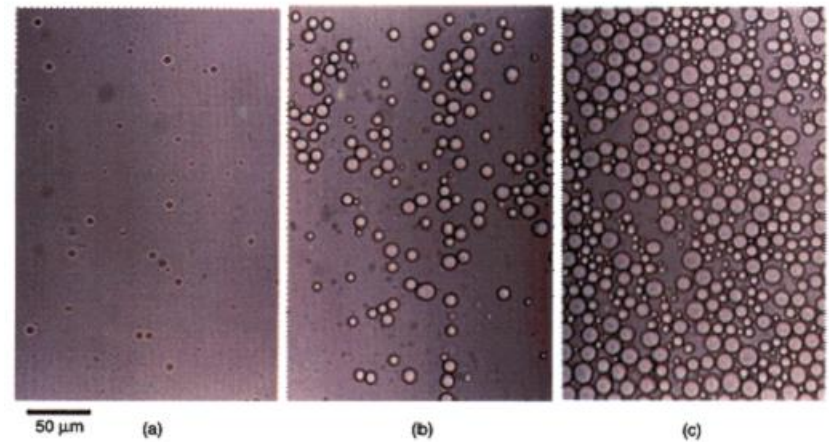
Development of "LASC"

- LASCs such as 1a and 1d do not dissolve in water.
- On the other hand, when the LASC was mixed with organic substrates in water, a white turbid mixture formed through colloid formation.

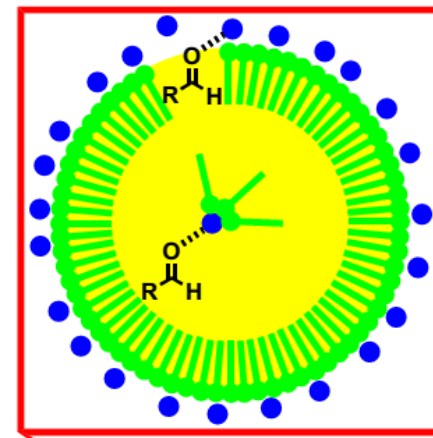
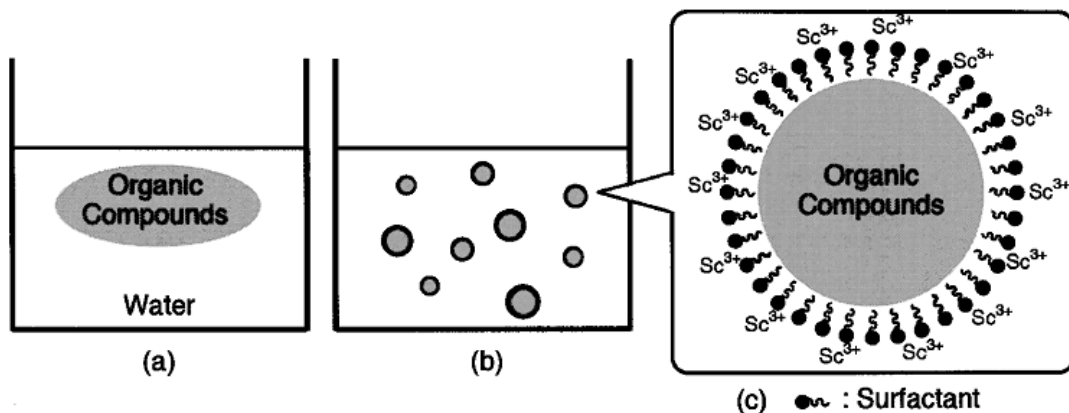


Mixtures of LASC 1d in water (left) and LASC 1d and benzaldehyde (1:10) in water (right)

- Light microscopic observations of the colloidal particles revealed their spherical shape.
- Finally, all of 1d formed the spherical colloidal particles.



Mixture of LASC 1d and benzaldehyde as detected by light microscopy. (a) 1d:benzaldehyde=1:10; (b) 1d:benzaldehyde=1:20; (c) 1d:benzaldehyde=1:100. In all cases, the concentration of 1d was 16.7 mM.



## Reaction mechanism

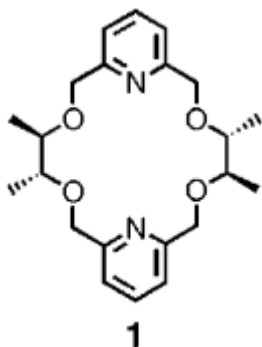
- 1) In the presence organic substrates, LASC molecules form stable colloidal particles. (the surfactant moiety of the LASCs surrounds the organic substrates.)
- 2) the countercations are attracted to the surface of the particles through electrostatic interactions between the anionic surfactant molecules and the cations.
- 3) Although each Sc(III) cation is hydrated by several water molecules, they can be readily replaced by a substrate.
- 4) The substrates to be activated move to the interface from the organic phase, coordinate to the cations, and then react with nucleophilic substances there.

## 4. Asymmetric aldol reactions in aqueous media

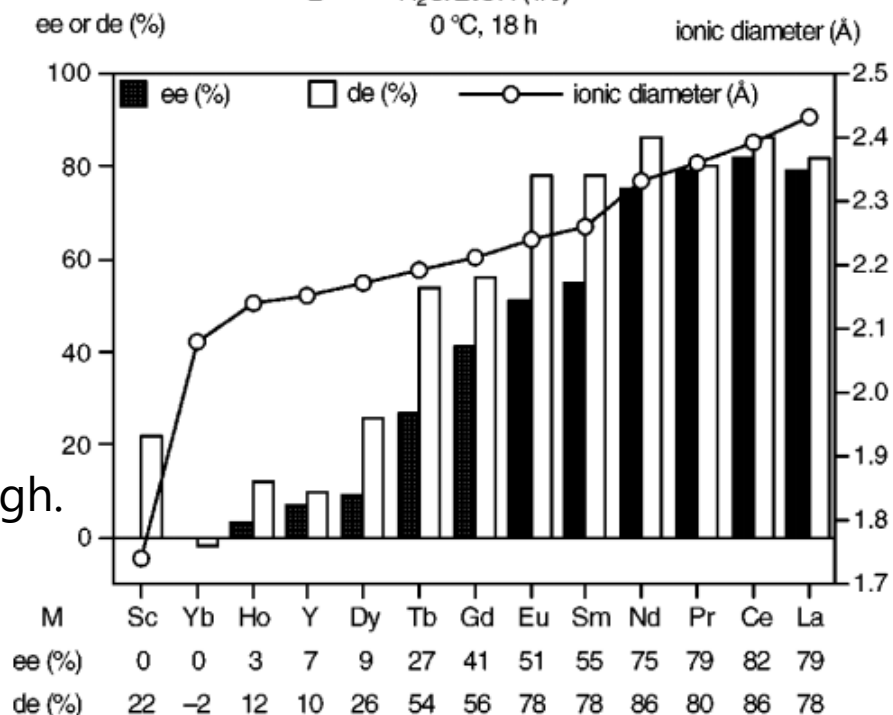
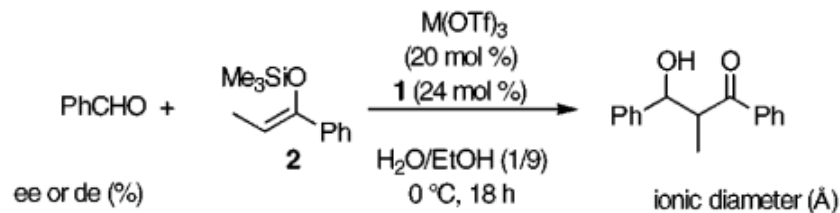
# Chiral ligand for $\text{Ln}(\text{OTf})_3$

Asymmetric aldol reactions  
in aqueous media

Need to finding a chiral ligand which has strong binding ability and does not significantly reduce the Lewis acidity of  $\text{Ln}(\text{OTf})_3$ .



Desirable ligand : chiral crown ether

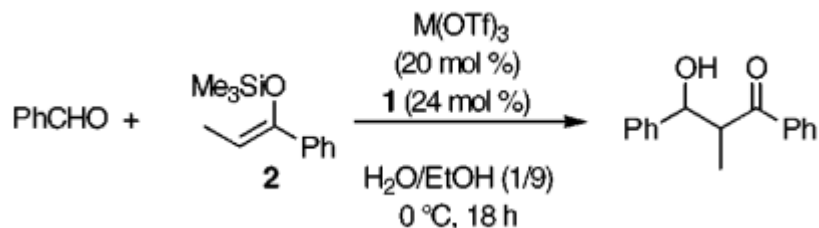


• For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high.

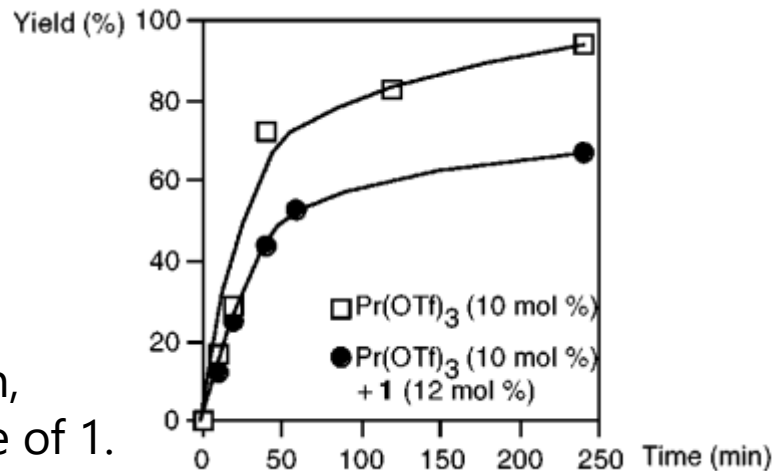
• The smaller cations such as Sc and Yb showed no enantioselection.

# Effect of chiral ligand

Asymmetric aldol reactions  
in aqueous media

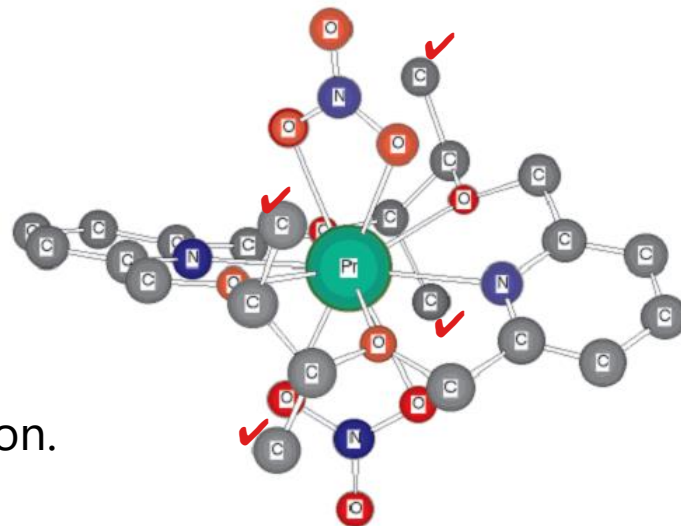


It should be noted that, although **1** slightly decelerated the reaction, sufficient reactivity still remained in the presence of **1**.



Reaction profiles for the Pr(OTf)<sub>3</sub>-catalyzed aldol reaction of benzaldehyde with **2** in water/ethanol (1/9) at 0 °C in the absence and presence of **1**.

- The methyl groups of **1** are all in axial positions.
- one or two of the nitrate anions are dissociated in aqueous media and that aldehydes to be activated coordinate in place of the nitrate anion.



**Figure 3.** [Pr(NO<sub>3</sub>)<sub>2</sub>·**1**]<sup>+</sup> moiety in the X-ray structure of [Pr(NO<sub>3</sub>)<sub>2</sub>·**1**]<sub>3</sub>[Pr(NO<sub>3</sub>)<sub>6</sub>]. Hydrogen atoms are omitted for clarity.

## 5. Metalloenzyme-Like Catalyst





## 1st generation :

## Asymmetric hydroxymethylation in water

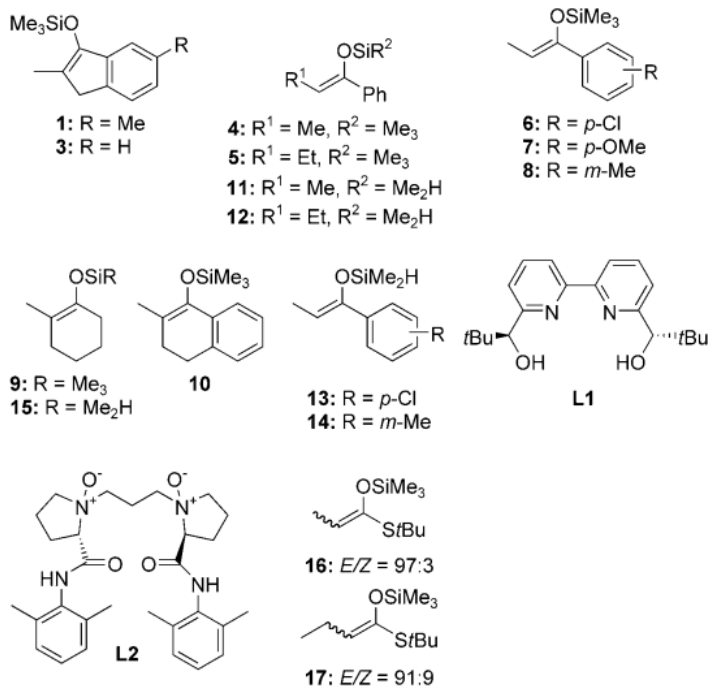
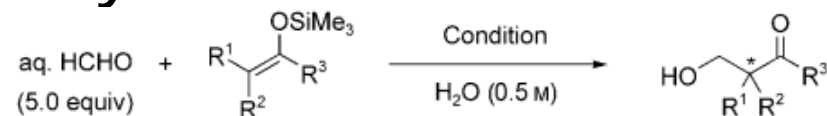


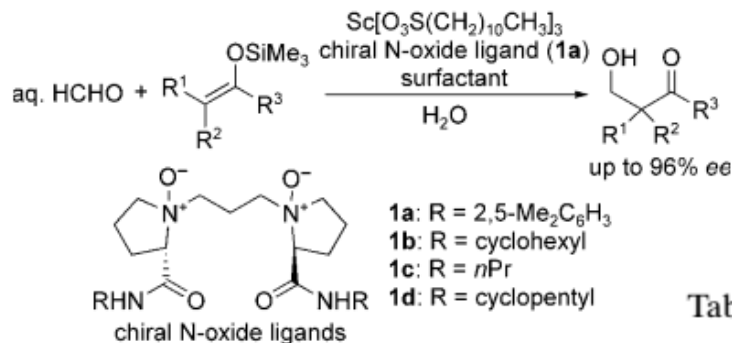
Figure 2. Substrates and ligands used.

Entry	Enolate	Conditions <sup>[a]</sup>	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	<b>1</b>	A	81	91 ( <i>R</i> )
2	<b>1</b>	B	85	90 ( <i>S</i> )
3	<b>3</b>	B	83	94
4	<b>4</b>	B	85	91 ( <i>R</i> )
5	<b>5</b>	B	85	90
6	<b>5</b>	C	82	91 ( <i>R</i> )
7	<b>6</b>	B	84	92
8	<b>8</b>	A	73	90
9	<b>9</b>	B	86	85
10	<b>10</b>	B	82	96
11	<b>10</b>	C	82	96
12	<b>11</b>	B	91	91 ( <i>R</i> )
13	<b>12</b>	B	92	90
14	<b>13</b>	B	83	94
15	<b>13</b>	C	83	94
16	<b>13</b>	D	83	90
17	<b>14</b>	B	90	92
18	<b>15</b>	B	84	91
19	<b>16</b>	A	73	91 ( <i>S</i> )
20	<b>17</b>	A	65	90

[a] Conditions A: Sc(DS)<sub>3</sub> (10 mol%), **L1** (12 mol%), Triton X-705, RT, 20 h. Conditions B: Sc[O<sub>3</sub>S(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]<sub>3</sub> (10 mol%), **L2** (12 mol%), CH<sub>3</sub>(CH<sub>2</sub>)<sub>10</sub>SO<sub>3</sub>Na, 5 °C, 48 h. Conditions C: Sc[O<sub>3</sub>S(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]<sub>3</sub> (2 mol%), **L2** (2.4 mol%), CH<sub>3</sub>(CH<sub>2</sub>)<sub>10</sub>SO<sub>3</sub>Na, 5 °C, 96–110 h. Conditions D: Sc[O<sub>3</sub>S(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>]<sub>3</sub> (1 mol%), **L2** (1.2 mol%), CH<sub>3</sub>(CH<sub>2</sub>)<sub>10</sub>SO<sub>3</sub>Na, 5 °C, 81 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

by using 2 mol% or 1 mol% of the catalyst (Conditions C and D) led to the same range in yields and enantioselectivities as those reactions employing 10 mol% of the catalyst.

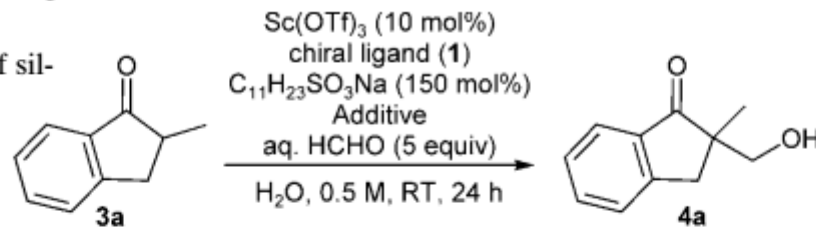
# 2nd generation : Direct asymmetric aldol reaction in water.



Scheme 1. Chiral Sc-catalyzed enantioselective hydroxymethylation of silicon enolates.

A cyclopentyl substituent on the amide moiety (1 d) was found to be the best in terms of both yield and enantioselectivity (entries 7–10).

Table 1. Optimization of reaction conditions.

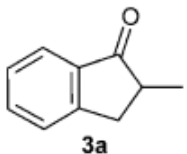
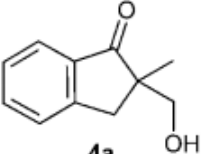
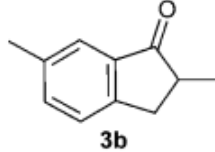
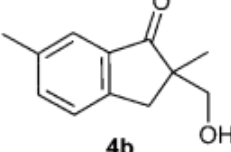
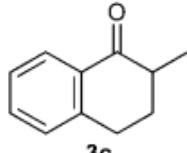
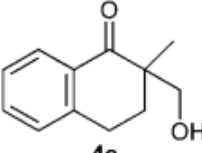
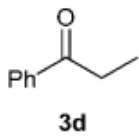
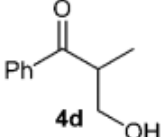
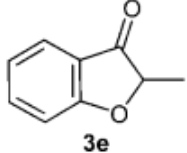
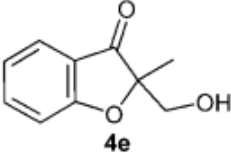


Entry	Ligand	Additive (mol %)	Yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	<b>1a</b>	none	20	41
2	<b>1a</b>	Et <sub>3</sub> N (20)	36	27
3	<b>1a</b>	NaOH (20)	37	38
4	<b>1a</b>	NaOH (50)	87	0
5	<b>1a</b>	2,6-lutidine (20)	16	46
6	<b>1a</b>	pyridine (20)	60	47
7	<b>1b</b>	pyridine (20)	57	67
8	<b>1c</b>	pyridine (20)	76	70
9	<b>1d</b>	pyridine (20)	76	73
10 <sup>[c]</sup>	<b>1d</b>	pyridine (20)	81	72

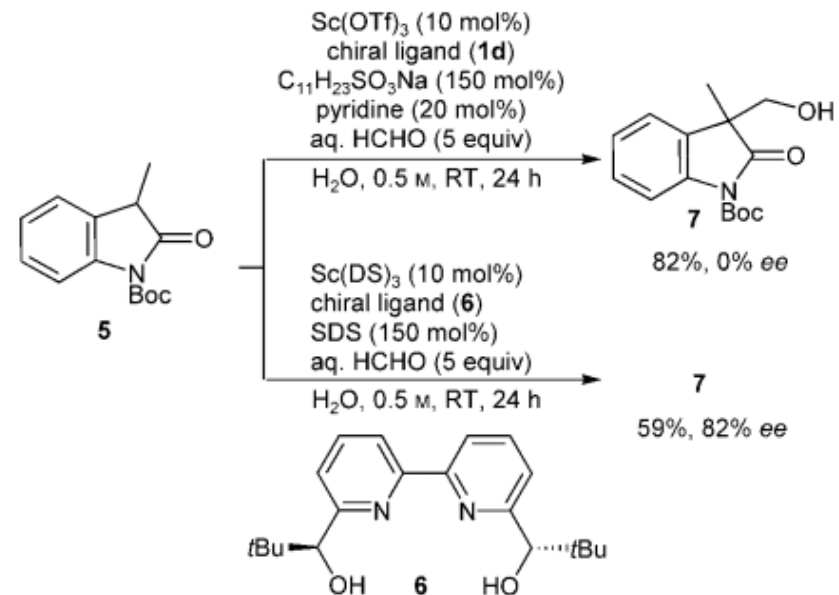
[a] Yield of isolated product after chromatography. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Reaction for 48 h.

# Substrate scope

Table 2. Asymmetric hydroxymethylation of ketones in water.<sup>[a]</sup>

Entry	Ketone	Product	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1			81	72
2			72	72
3 <sup>[d]</sup>			39	88
4 <sup>[d]</sup>			29	81
5			quant	67

[a] Conditions: Ketone **3** (0.3 mmol), Sc(OTf)<sub>3</sub> (10 mol%), N-oxide **1d** (12 mol%), C<sub>11</sub>H<sub>23</sub>SO<sub>3</sub>Na (150 mol%), pyridine (20 mol%), formalin (5 equiv), water, RT, 24 h. [b] Yield of isolated product after chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction was carried out at 40°C for 48 h.

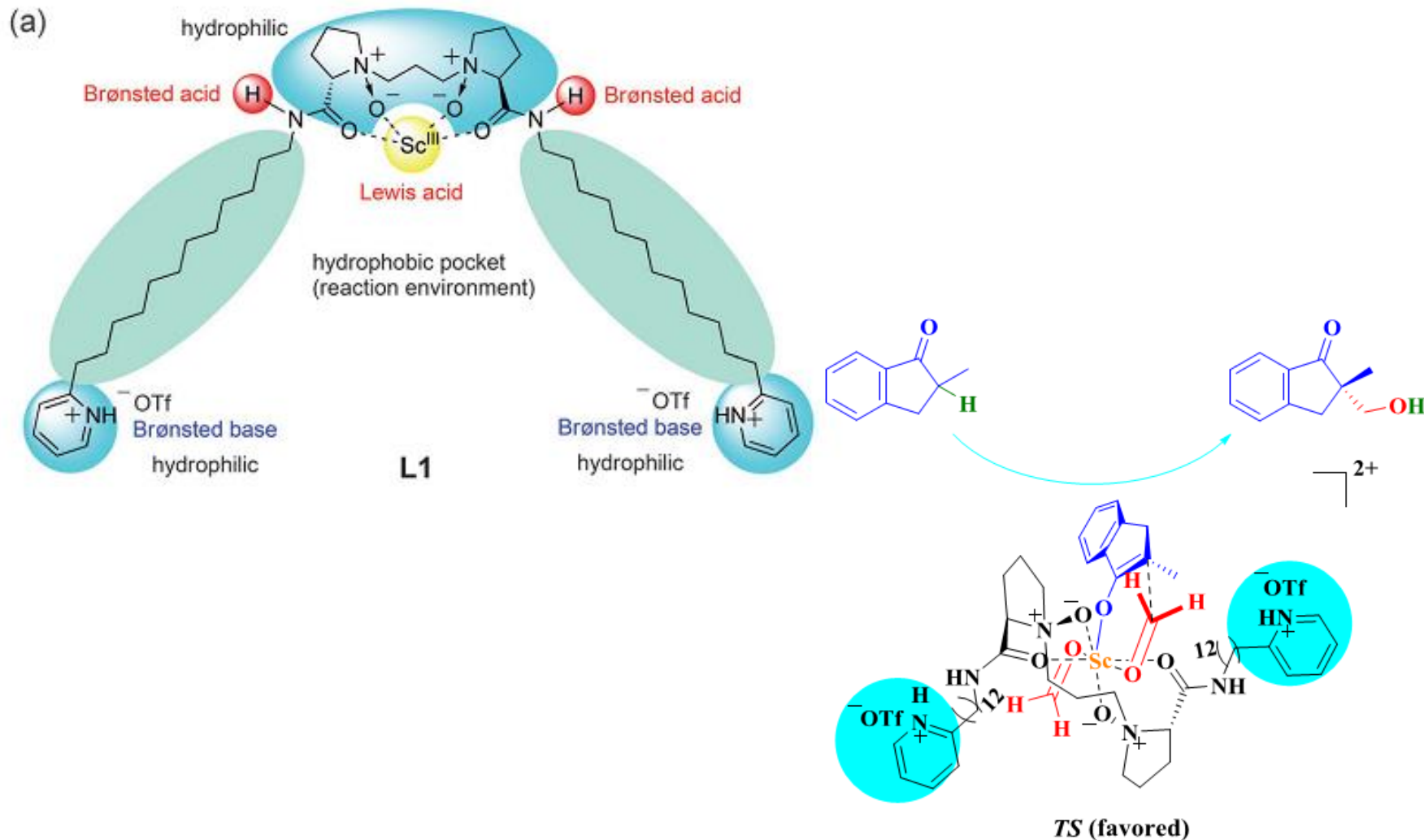


Scheme 2. Asymmetric hydroxymethylation of oxindole.

The addition of a catalytic amount of pyridine enabled us to use ketones directly in asymmetric hydroxymethylation reactions.

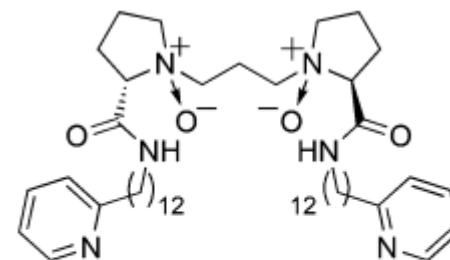
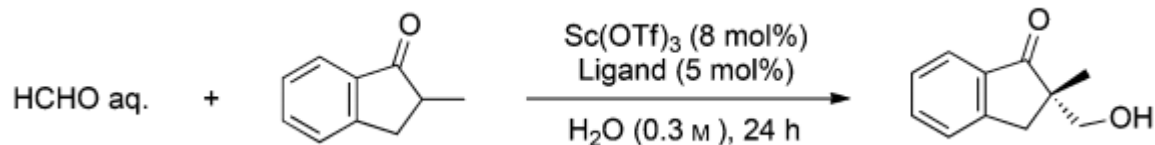
# 3rd generation : Metalloenzyme-Like catalyst

Metalloenzyme-Like Catalyst  
3rd generation

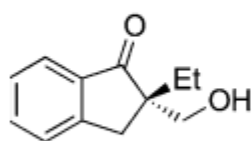
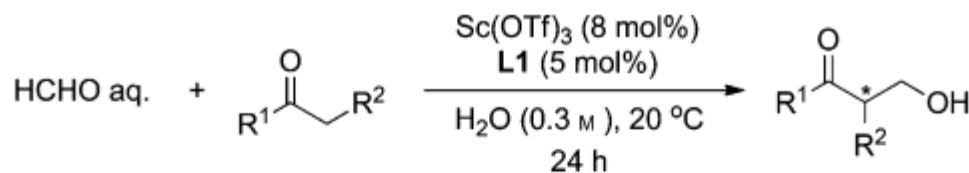


# Substrate scope

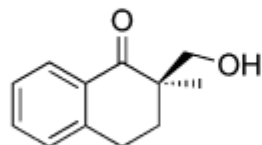
Metalloenzyme-Like Catalyst  
3rd generation



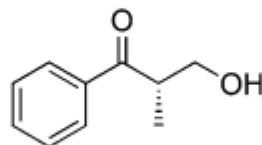
**L1:** 75% yield, 60% ee (S)  
91% yield, 60% ee (S)<sup>[b]</sup>  
<sup>[b]</sup> → 40 °C



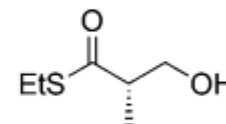
35% yield,  
58% ee (S)



53% yield,  
75% ee (S)  
[40 °C, 96 h]



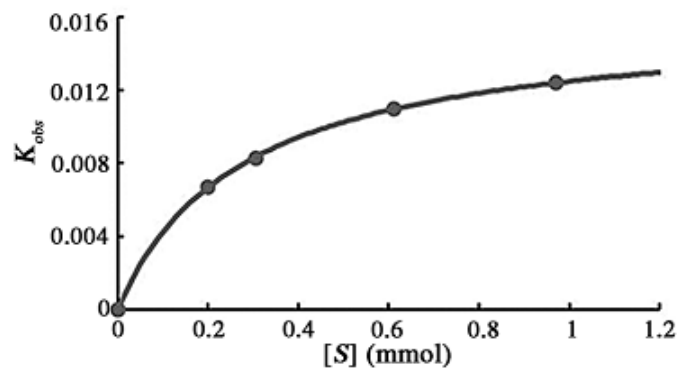
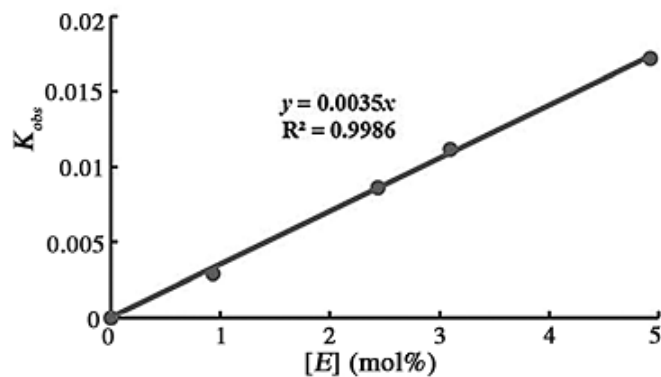
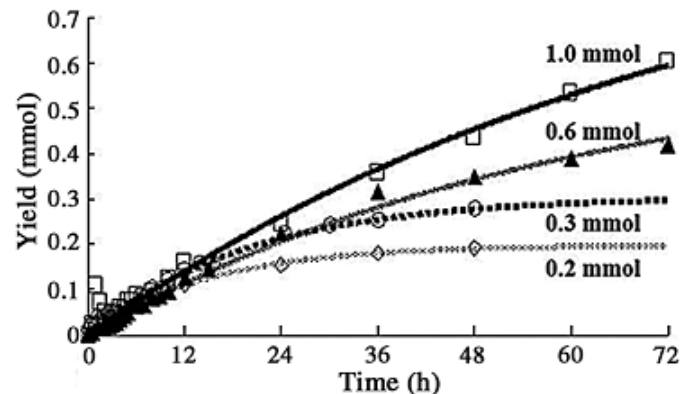
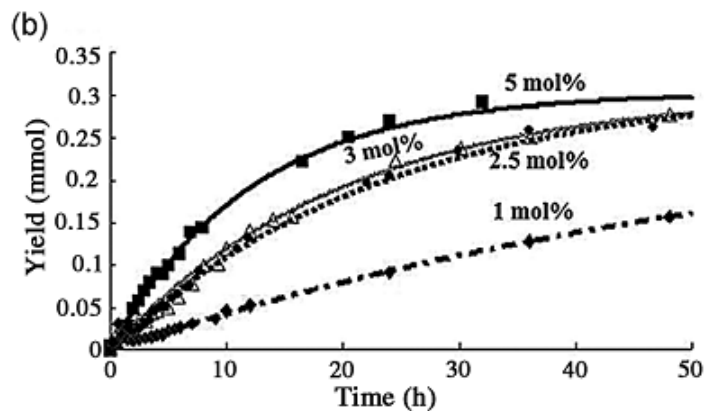
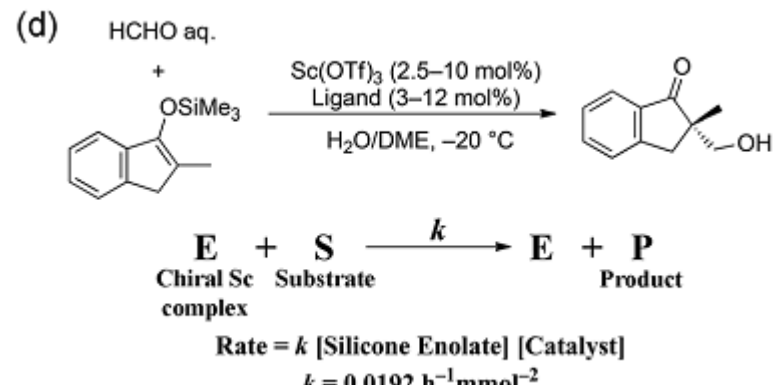
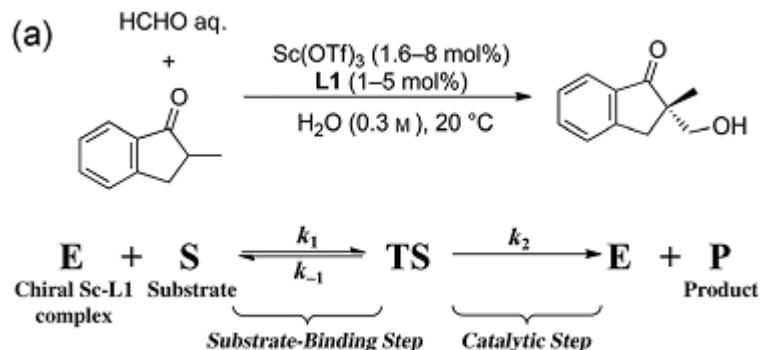
30% yield,  
62% ee (S)  
[40 °C, 20 mol% of pyridine  
was added]



23% yield,  
53% ee (S)  
[48 h, 20 mol% of pyridine  
was added]

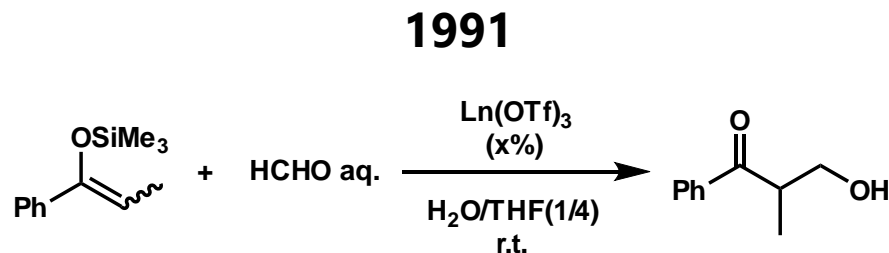
The addition of a catalytic amount of pyridine enabled us to use ketones directly in asymmetric hydroxymethylation reactions.

# Reaction mechanism



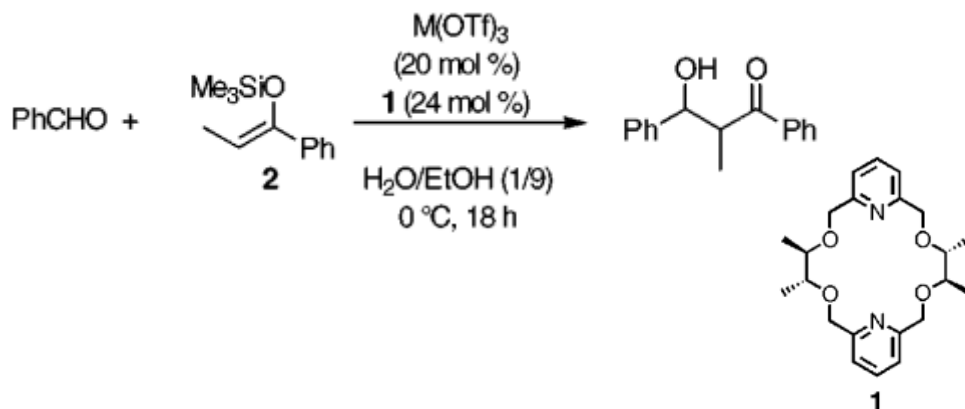
## 6. Summary

## Discovery of lanthanide triflate as water-tolerant Lewis acids



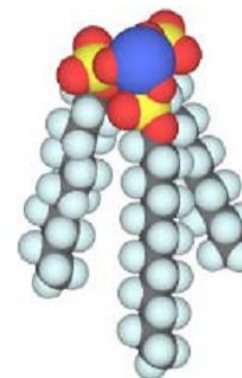
## Asymmetric aldol reactions in aqueous media

**2001**



## Development of "LASC"

**1998**

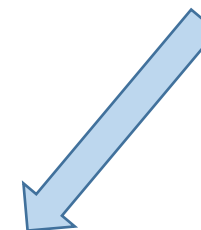
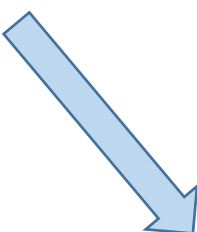
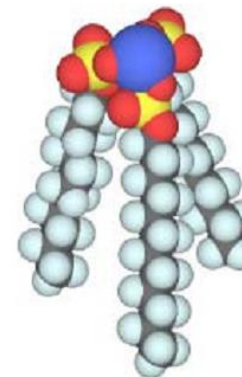




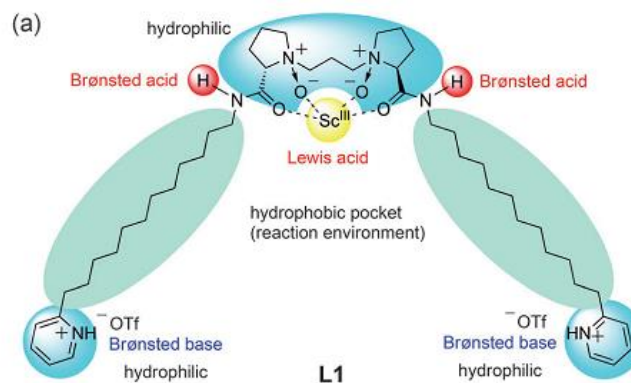
# Summary 2

Summary

## Development of "LASC" 1998



## Metalloenzyme-Like Catalyst 2015



## Asymmetric aldol reactions in aqueous media 2001

