IASOC 2000:
New Challenges of Organic Synthesis in the 21st Century

New Dimensions of Lewis Acid Catalysis in Organic Synthesis

September 27, 2000

Shū Kobayashi
The University of Tokyo

Lewis Acids in Organic Synthesis

■ Reactions

Aldol, Michael, Friedel-Crafts, Diels-Alder, Ene, etc.

■ Lewis Acids

$TiCl_4$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, etc.

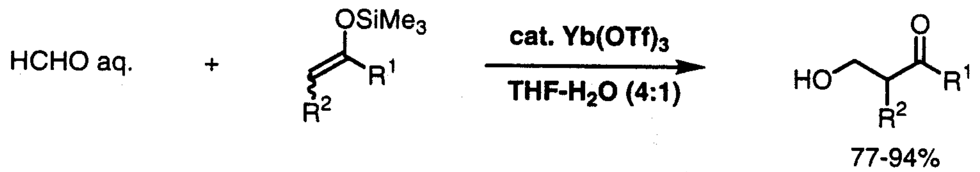
Problems:

- ◆ ***Stoichiometric Use***
- ◆ ***Moisture Sensitive***
- ◆ ***Not Reusable***

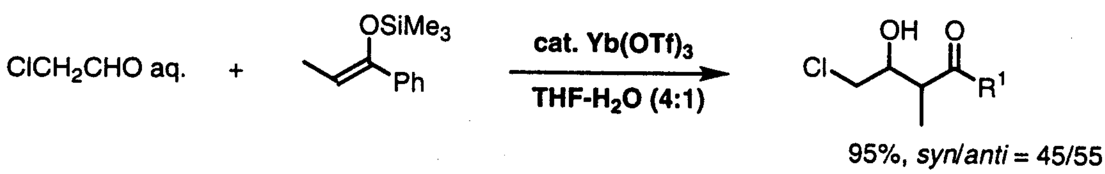
$Ln(OTf)_3$ Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

$Tf = SO_2CF_3$

- ■ ***Stable Lewis Acid in Aqueous Media***
- ■ ***Catalytic Use***
- ■ ***Reusable Catalyst***



S. Kobayashi, *Chem. Lett.*, **1991**, 2187.



S. Kobayashi, I. Hachiya, *Tetrahedron Lett.*, **33**, 1625 (1992).

Organic Synthesis in Water; Advantages

Cheap, Safe, and Clean Solvent

- *The cheapest solvent*
- *No Inflammable, explosive, mutagenic, carcinogenic*
- *Environmental-friendly (no pollution, recoverable)*

Synthetic Utility

- *Simple operation*
  Phase separation, Control of reaction temperature
- *Efficiency*
  No protective group, Water-soluble materials
- *Hydrophobic effect, Solvation, etc.*

Goal: *To perform enzymatic reactions in flasks without using enzymes*

*(High yield; High selectivity; Mild conditions + **Substrate generality**)*

Approach

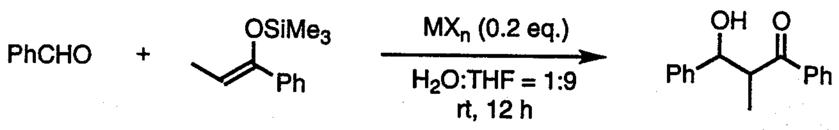
- To mimic enzymes
- To focus on *media* in which enzymes work

Media = Water

- *Hydrogen bonding; Hydrophilic and hydrophobic effects; Solvation; Acid and base*
- *Protein, Nucleic acid, Lipid, Carbohydrate, etc. work in water*

Final goal: *To perform catalytic enantioselective reactions in water; To study life and nature*

Effect of Metal Salts in the Aldol Reaction[a]



MX_n	Yield/%	MX_n	Yield/%	MX_n	Yield/%	MX_n	Yield/%
$AlCl_3$	trace	$CuCl_2$	25	$InCl_3$	**68**	**$Er(OTf)_3$**	**86**
$ScCl_3$	**70 (78)**[b]	**$Cu(ClO_4)_2$**	47 **(81)**[b]	$In(ClO_4)_3$	14	**$Tm(OTf)_3$**	**85**
$Sc(ClO_4)_3$	**82**	$ZnCl_2$	10	$SnCl_2$	4	$YbCl_3$	11 **(92)**[b]
$CrCl_3$	trace	**$Zn(ClO_4)_2$**	46 (57)[b]	**$La(OTf)_3$**	**80**	**$Yb(ClO_4)_3$**	**84**
$MnCl_2$	trace	$GaCl_3$	trace	**$Ce(OTf)_3$**	**81**	**$Yb(OTf)_3$**	**92**
$Mn(ClO_4)_2$	18 (40)[b]	YCl_3	5 **(86)**[b]	**$Pr(OTf)_3$**	**83**	**$Lu(OTf)_3$**	**84**
$FeCl_2$	39	$Y(ClO_4)_3$	**90**	**$Nd(OTf)_3$**	**78**	$IrCl_3$	trace
$Fe(ClO_4)_2$	26 (55)[b]	$RhCl_3$	trace	**$Sm(OTf)_3$**	**85**	$PtCl_2$	trace
$FeCl_3$	21	$PdCl_2$	trace	**$Eu(OTf)_3$**	**88**	$AuCl$	trace
$Fe(ClO_4)_3$	7	$AgCl$	trace	**$Gd(OTf)_3$**	**90**	$HgCl_2$	trace
$CoCl_2$	trace	$AgClO_4$	42 (36)[b]	**$Tb(OTf)_3$**	**81**	$HgCl$	trace
$Co(ClO_4)_2$	17 (7)[b]	$CdCl_2$	18	**$Dy(OTf)_3$**	**85**	$PbCl_2$	15
$NiCl_2$	trace	**$Cd(ClO_4)_2$**	49 **(72)**[b]	**$Ho(OTf)_3$**	**89**	**$Pb(ClO_4)_2$**	**59 (65)**[b]
$Ni(ClO_4)_2$	17 (7)[b]					$BiCl_3$	trace

[a]No adduct was obtained and the starting materials were recovered using LiCl, NaCl, $MgCl_2$, PCl_3, KCl, $CaCl_2$, $GeCl_4$, $RuCl_3$, $SbCl_3$, $BaCl_2$, $OsCl_3$. No adduct was obtained and the silyl enol ether was decomposed using BCl_3, $SiCl_4$, PCl_5, $TiCl_4$, VCl_3, $ZrCl_4$, $NbCl_5$, $MoCl_5$, $SnCl_4$, $SbCl_5$, $HfCl_4$, $TaCl_5$, WCl_6, $ReCl_5$, $TlCl_3$. [b]H_2O:EtOH:toluene = 1:7:3.

Yields (%) in the Aldol Reaction Using Metal Catalysts[a]

Li $^{+1}$ NR —	Be — —											B $^{+3}$ *NR* —	C — —	N — —
Na $^{+1}$ NR —	Mg $^{+2}$ NR —											Al $^{+3}$ trace —	Si $^{+4}$ *NR* —	P $^{+5}$ *NR* —
K $^{+1}$ NR —	Ca $^{+2}$ NR —	Sc $^{+3}$ 70 82	Ti $^{+4}$ *NR* —	V $^{+3}$ *NR* —	Cr $^{+3}$ trace —	Mn $^{+2}$ trace 40	Fe $^{+2}$ 39 55	Co $^{+2}$ trace 17	Ni $^{+2}$ trace 17	Cu $^{+2}$ 25 81	Zn $^{+2}$ 10 57	Ga $^{+3}$ trace —	Ge $^{+4}$ NR —	As — —
Rb — —	Sr — —	Y $^{+3}$ 86 90	Zr $^{+4}$ *NR* —	Nb $^{+5}$ *NR* —	Mo $^{+5}$ *NR* —	Tc — —	Ru $^{+3}$ NR —	Rh $^{+3}$ trace —	Pd $^{+2}$ trace —	Ag $^{+1}$ trace 42	Cd $^{+2}$ 18 72	In $^{+3}$ 68 14	Sn $^{+4}$ *NR* —	Sb $^{+5}$ *NR* —
Cs — —	Ba $^{+2}$ NR —	Ln $^{+3}$ 92 78-92	Hf $^{+4}$ *NR* —	Ta $^{+5}$ *NR* —	W $^{+6}$ *NR* —	Re $^{+5}$ *NR* —	Os $^{+3}$ NR —	Ir $^{+3}$ trace —	Pt $^{+2}$ trace —	Au $^{+1}$ trace —	Hg $^{+2}$ trace —	Tl $^{+3}$ *NR* —	Pb $^{+2}$ 15 65	Bi $^{+3}$ trace —

La $^{+3}$	Ce $^{+3}$	Pr $^{+3}$	Nd $^{+3}$	Pm	Sm $^{+3}$	Eu $^{+3}$	Gd $^{+3}$	Tb $^{+3}$	Dy $^{+3}$	Ho $^{+3}$	Er $^{+3}$	Tm $^{+3}$	Yb $^{+3}$	Lu $^{+3}$
—	—	—	—	—	—	—	—	—	—	—	—	—	92	—
80	81	83	78	—	85	88	90	81	85	89	86	85	92	84

[a]Upper column shows yields using metal chlorides. Lower column shows yields using metal perchlorates except for lanthanides. Lower column in lanthanides (La-Lu) shows yields using the corresponding triflates. NR: No product was obtained and the starting materials were recovered. *NR*: No product was obtained and the silyl enol ether was decomposed.

The Common Features of the Elements (Cations)!

■ Hydrolysis Constant (p*K*h = -log K_{xy})

4.3-10.08

$$x\,M^{z+} + y\,H_2O \rightleftharpoons M_x(OH)_y^{(xz-y)+} + y\,H^+$$

$$K_{xy} = \frac{[M_x(OH)_y^{(xz-y)+}]\,[H^+]^y}{[M^{z+}]^x} \bullet \frac{g_{xy}\, g_{H^+}^{\;y}}{g_{M^{z+}}^{\;x}\, a_{H2O}^{\;y}}$$

■ Exchange Rate Constant for Substitution of Inner-Sphere Water Ligands

$>3.2 \times 10^6\ M^{-1}S^{-1}$

Hydrolysis Constants[a] and Exchange Rate Constants for Substitution of Inner-Sphere Water Ligands[b]

Li $^{+1}$ 13.64 4.7×10^7	Be — —											B $^{+3}$ — —	C — —	N — —
Na $^{+1}$ 14.18 1.9×10^8	Mg $^{+2}$ 11.44 5.3×10^5											Al $^{+3}$ 1.14 1.6×10^0	Si $^{+4}$ — —	P $^{+5}$ — —
K $^{+1}$ 14.46 1.5×10^8	Ca $^{+2}$ 12.85 5×10^7	Sc $^{+3}$ 4.3 4.8×10^7	Ti $^{+4}$ ≤ 2.3 —	V $^{+3}$ 2.26 1×10^3	Cr $^{+3}$ 4.0 5.8×10^{-7}	Mn $^{+2}$ 10.59 3.1×10^7	Fe $^{+2}$ 9.5 3.2×10^6	Co $^{+2}$ 9.65 2×10^5	Ni $^{+2}$ 9.86 2.7×10^4	Cu $^{+2}$ 7.53 2×10^8	Zn $^{+2}$ 8.96 5×10^8	Ga $^{+3}$ 2.6 7.6×10^2	Ge $^{+4}$ — —	As — —
Rb — —	Sr — —	Y $^{+3}$ 7.7 1.3×10^7	Zr $^{+4}$ 0.22 —	Nb $^{+5}$ (0.6) —	Mo $^{+5}$ — —	Tc — —	Ru $^{+3}$ — —	Rh $^{+3}$ 3.4 3×10^{-8}	Pd $^{+2}$ 2.3 —	Ag $^{+1}$ 12 $>5\times10^6$	Cd $^{+2}$ 10.08 $>1\times10^8$	In $^{+3}$ 4.00 4.0×10^4	Sn $^{+4}$ — —	Sb $^{+5}$ — —
Cs — —	Ba 13.47 $>6\times10^7$	Ln $^{+3}$ 7.6-8.5 10^6-10^8	Hf $^{+4}$ 0.25 —	Ta $^{+5}$ (-1) —	W $^{+6}$ — —	Re $^{+5}$ — —	Os $^{+3}$ — —	Ir $^{+3}$ — —	Pt $^{+2}$ 4.8 —	Au $^{+1}$ — —	Hg $^{+2}$ 3.40 2×10^9	Tl $^{+3}$ 0.62 7×10^5	Pb $^{+2}$ 7.71 7.5×10^9	Bi $^{+3}$ 1.09 —

La $^{+3}$	Ce $^{+3}$	Pr $^{+3}$	Nd $^{+3}$	Pm	Sm $^{+3}$	Eu $^{+3}$	Gd $^{+3}$	Tb $^{+3}$	Dy $^{+3}$	Ho $^{+3}$	Er $^{+3}$	Tm $^{+3}$	Yb $^{+3}$	Lu $^{+3}$
8.5	8.3	8.1	8.0	—	7.9	7.8	8.0	7.9	8.0	8.0	7.9	7.7	7.7	7.6
2.1×10^8	2.7×10^8	3.1×10^8	3.9×10^8	—	5.9×10^8	6.5×10^8	6.3×10^7	7.8×10^7	6.3×10^7	6.1×10^7	1.4×10^8	6.4×10^6	8×10^7	6×10^7

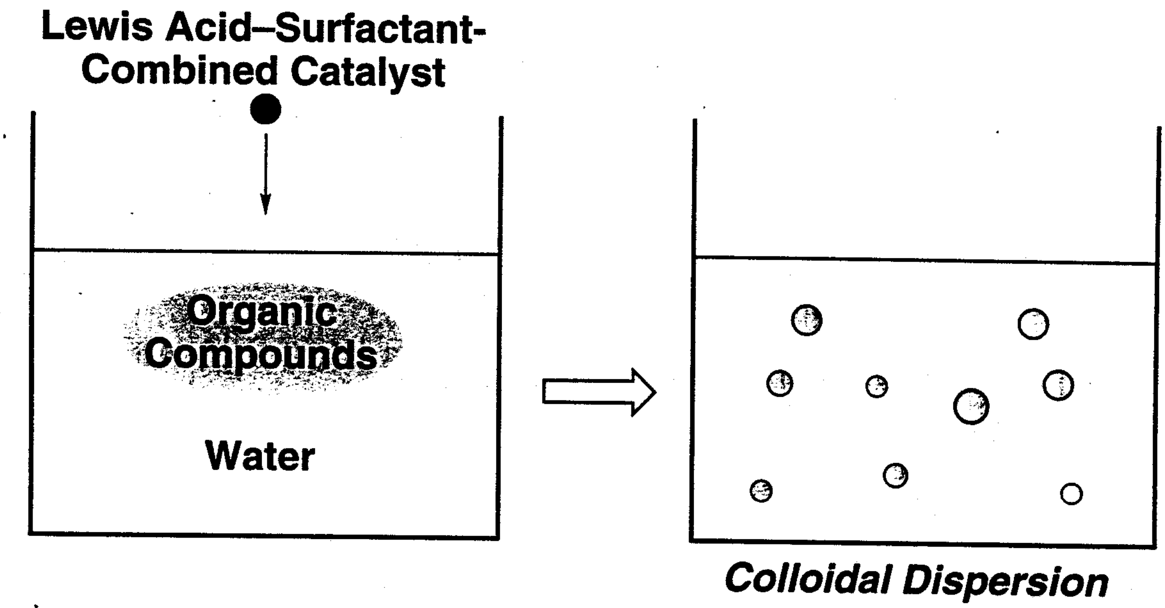
[a] p*K*h = -log K_{xy}

$$x\,M^{z+} + y\,H_2O \rightleftharpoons M_x(OH)_y^{(xz-y)+} + y\,H^+$$

$$Kxy = \frac{[M_x(OH)_y^{(xz-y)+}]\,[H^+]^y}{[M^{z+}]^x} \bullet \frac{g_{xy}\, g_{H^+}^{\;y}}{g_{M^{z+}}^{\;x}\, a_{H2O}^{\;y}}$$

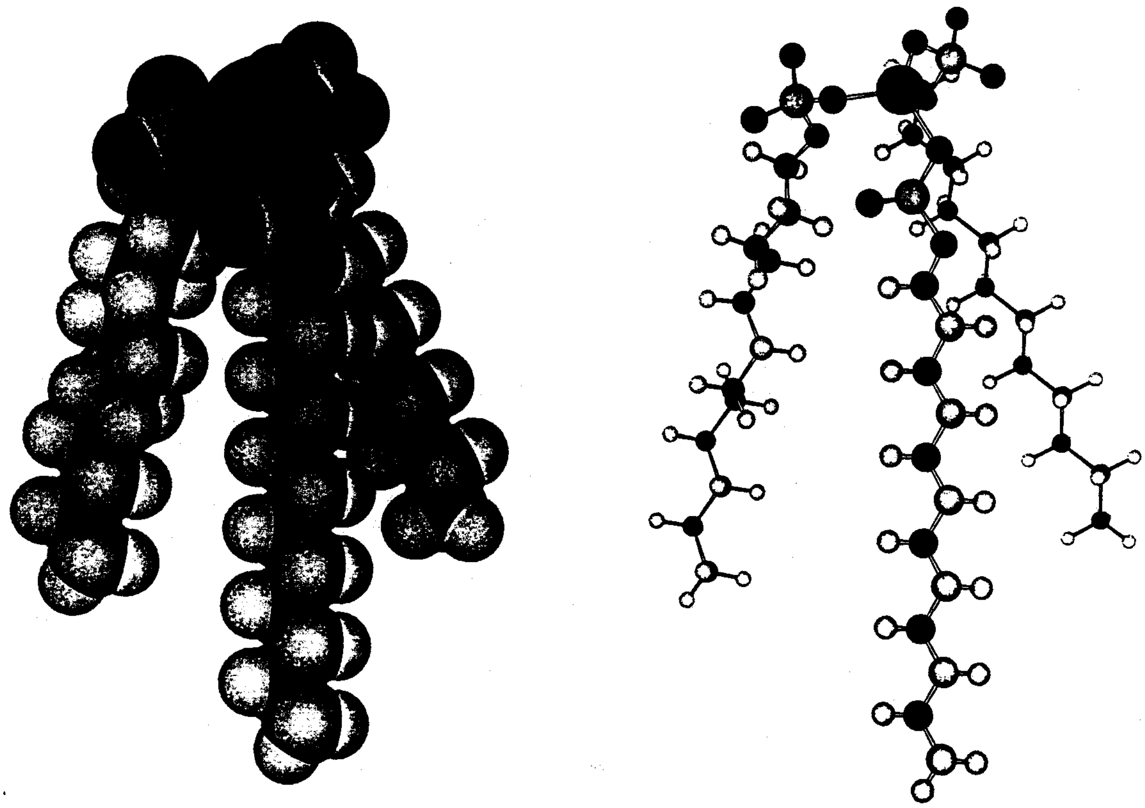
[b] Measured by NMR, sound absorption, or multidentate ligand method.

Lewis Acid–Surfactant-Combined Catalyst Forms Colloidal Dispersion in Water



Lewis Acid-Surfactant Combined Catalyst (LASC)

$Sc(OSO_3C_{12}H_{25})_3 = Sc(DS)_3$

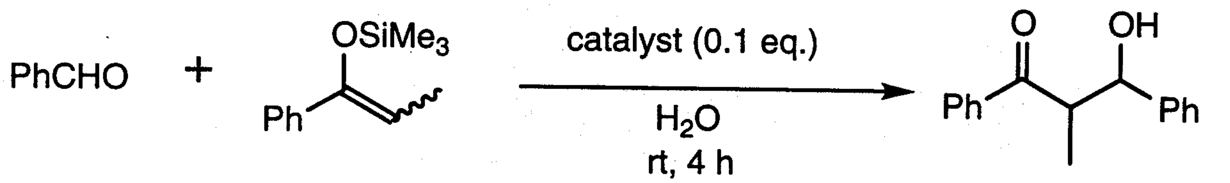


Preparation of $Sc(DS)_3$

$ScCl_3 \cdot 6H_2O$ + 3 $CH_3(CH_2)_{11}OSO_3Na$ —(H_2O, rt)→ **$Sc(OSO_3C_{12}H_{25})_3$**

Scandium Tris(dodecyl sulfate)
($Sc(DS)_3$)

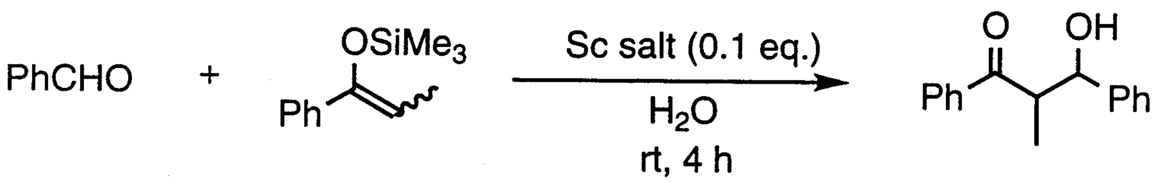
$Sc(DS)_3$-Catalyzed Aldol Reaction in Water



$Sc(DS)_3$; 92% Yield
$Sc(OTf)_3$; 3% Yield

Stable Dispersion System Forms!

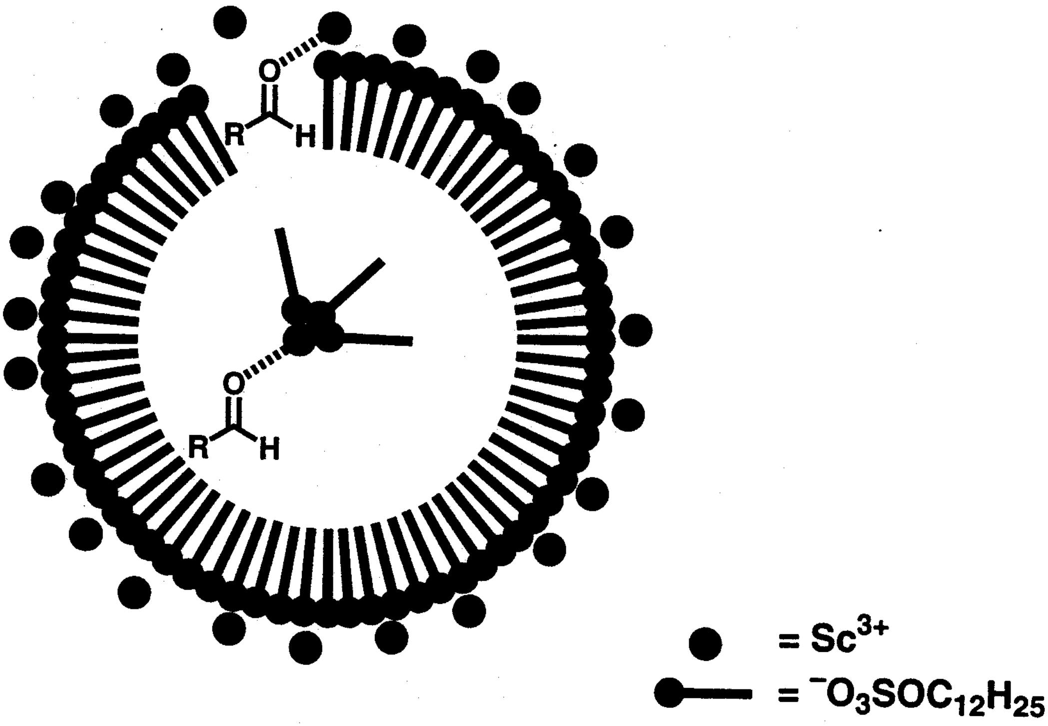
Effects of Alkyl Chains and the Scandium Salts



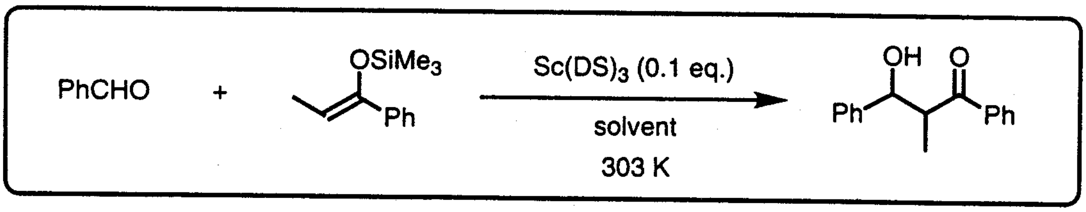
R	$Sc(OSO_3R)_3$	$Sc(OSO_2$*p*$\text{-R-}C_6H_4)_3$	$Sc(OSO_2R)_3$ / *Particle Size*
$C_{10}H_{21}$	—	**55**	**60** (*700 nm*)[a]
$C_{11}H_{23}$	—	—	**68**
$C_{12}H_{25}$	**92**	**91**	**83** (*1100 nm*)[a]
$C_{13}H_{27}$	—	—	**76**
$C_{14}H_{29}$	**73**	**33**	**19** (*400 nm*)[a]
$C_{16}H_{33}$	—	**14**	**12**

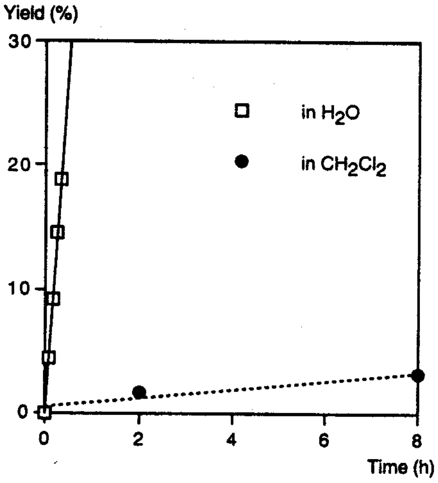
Numbers are isolated yields (%).
a) Particle sizes formed by $Sc(OSO_2R)_3$ and PhCHO in water are shown.

Carbonyl Activation by $Sc(O_3SOC_{12}H_{25})_3$ in Water



Kinetic Study of the $Sc(DS)_3$-Catalyzed Aldol Reaction

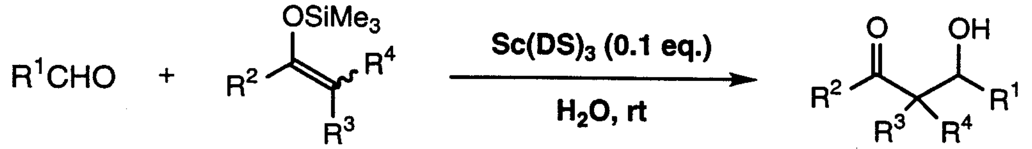




solvent	v (mol/l · sec)
H_2O	2.6×10^{-5}
CH_2Cl_2	2.0×10^{-7}

The reaction proceeded 1.3×10^2 times faster in water than in CH_2Cl_2.

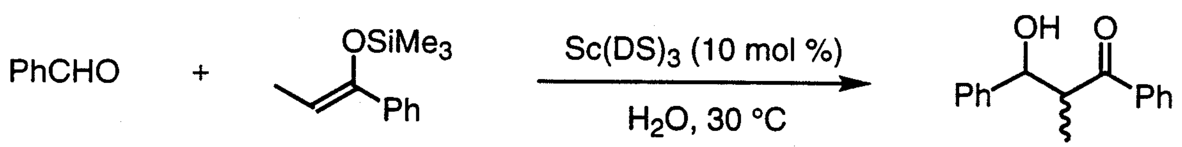
Sc(DS)$_3$-Catalyzed Aldol Reactions in Water

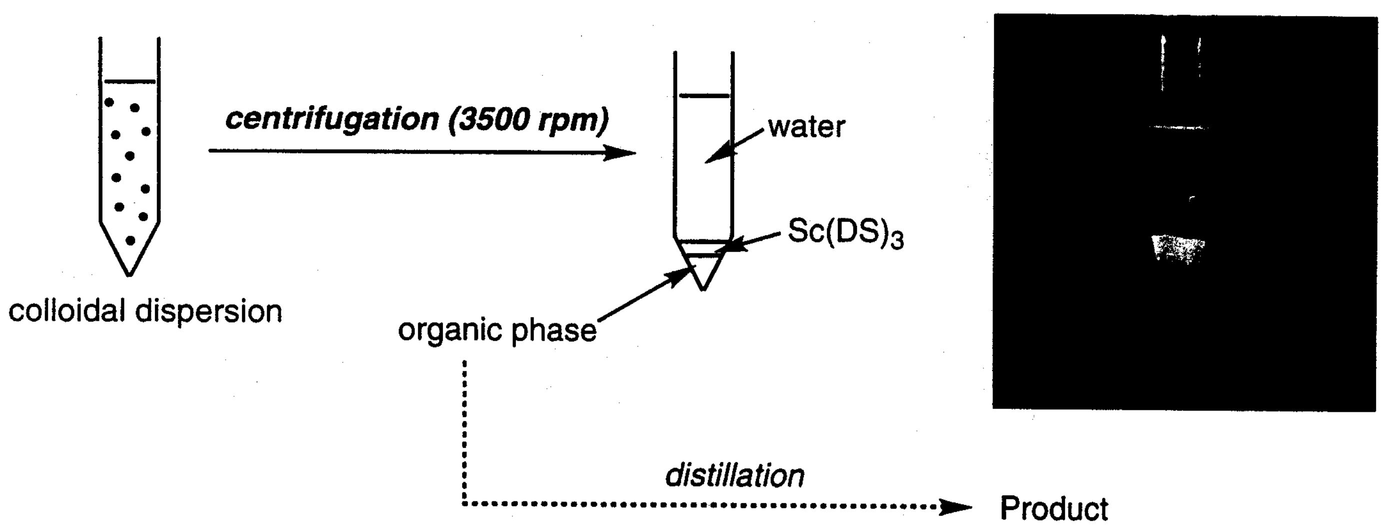


R^1	R^2	R^3	R^4	Yield/%
Ph	Ph	H	Me	**92**
$PhCH_2CH_2$	Ph	H	Me	**88**
PhCH=CH	Ph	H	Me	**91**
H	Ph	H	Me	**72**[a]
2-Pyridyl	Ph	H	Me	**84**[b]
PhCO	Ph	H	Me	**86**
p-Cl-Ph	Et	Me	H	**91**
Ph	-$(CH_2)_4$-		H	**77**
Ph	Ph	H	H	**94**[b, c]
Ph	EtS	Me	Me	**98**
Ph	MeO	Me	Me	**80**[b, d]

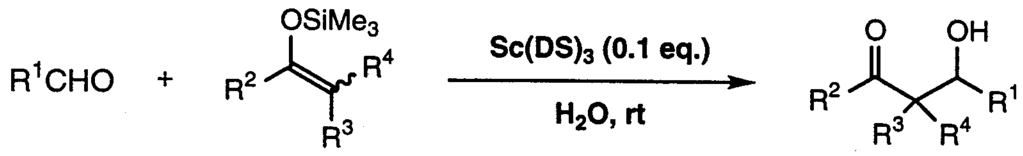
a) HCHO aq. (3 ml), silyl enolate (0.5 mmol), and Sc(DS)$_3$ (0.05 mmol) were combined. b) Sc(DS)$_3$ (0.2 eq.) was used. c) Additional silyl enolate (1.5 eq.) was charged after 4 h. d) Silyl enolate (3.0 eq.) was used.

Work-Up Procedure without Using Organic Solvents





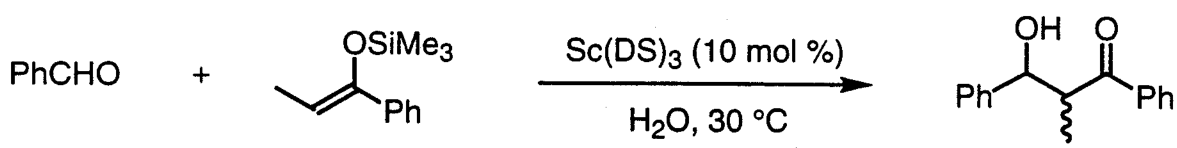
$Sc(DS)_3$-Catalyzed Aldol Reactions in Water

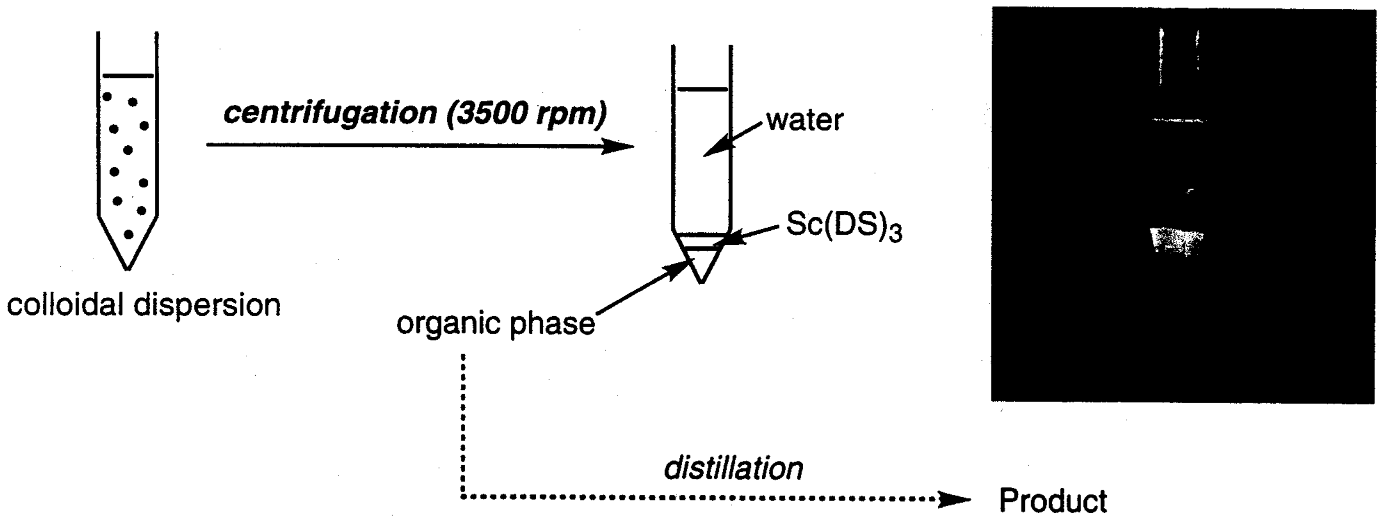


R^1	R^2	R^3	R^4	Yield/%
Ph	Ph	H	Me	**92**
$PhCH_2CH_2$	Ph	H	Me	**88**
PhCH=CH	Ph	H	Me	**91**
H	Ph	H	Me	**72**[a]
2-Pyridyl	Ph	H	Me	**84**[b]
PhCO	Ph	H	Me	**86**
p-Cl-Ph	Et	Me	H	**91**
Ph	$-(CH_2)_4-$		H	**77**
Ph	Ph	H	H	**94**[b, c]
Ph	EtS	Me	Me	**98**
Ph	MeO	Me	Me	**80**[b, d]

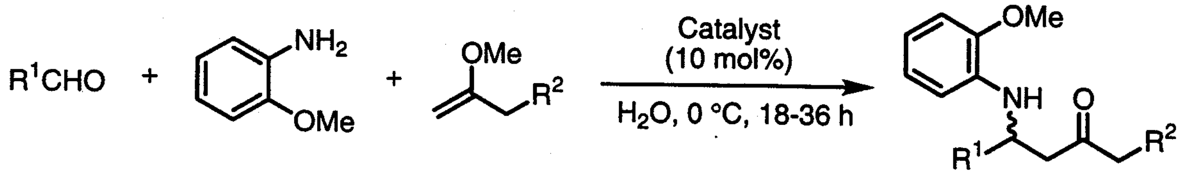
a) HCHO aq. (3 ml), silyl enolate (0.5 mmol), and $Sc(DS)_3$ (0.05 mmol) were combined. b) $Sc(DS)_3$ (0.2 eq.) was used. c) Additional silyl enolate (1.5 eq.) was charged after 4 h. d) Silyl enolate (3.0 eq.) was used.

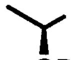
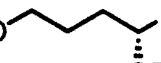
Work-Up Procedure without Using Organic Solvents



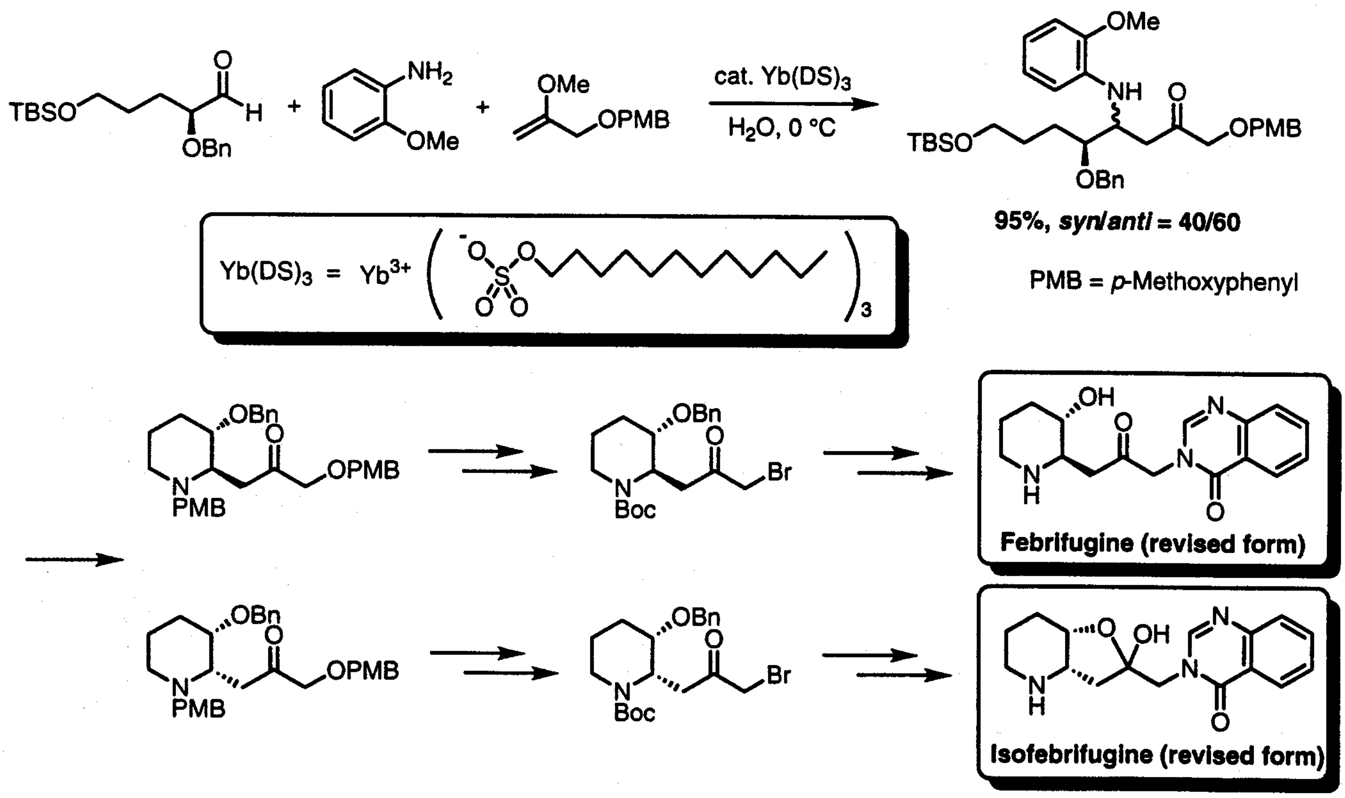


LASC-Catalyzed Mannich-Type Reactions in Water



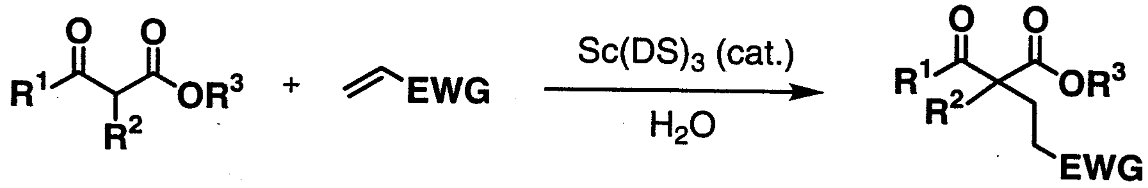
R^1	R^2	Catalyst	Yield (%)
Ph	H	$Cu(DS)_2$	**65**
c-C_6H_{11}	H	$Cu(DS)_2$	**86**
c-C_6H_{11}	H	$Yb(DS)_3$	**78**
 OBn	H	$Cu(DS)_2$	**82**
Ph	OPMB	$Cu(DS)_2$	**62**
 OBn	OPMB	$Cu(DS)_2$	**73**
 TBSO, OBn	OPMB	$Yb(DS)_3$	**91**

Synthesis of Febrifugine and Isofebrifugine

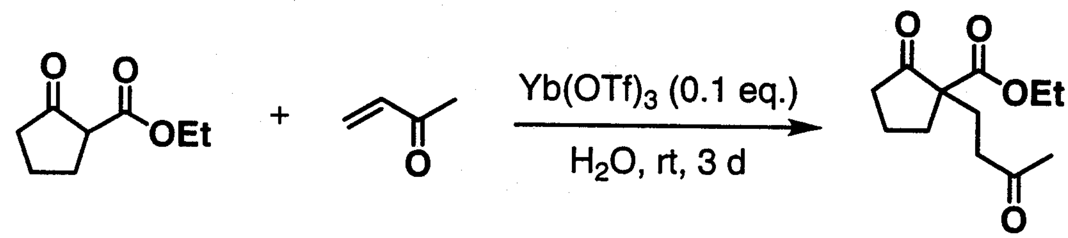


S. Kobayashi, M. Ueno, R. Suzuki, H. Ishitani, *J. Org. Chem.*, **64**, 6833 (1999).

Michael Reactions Mediated by Scandium Tris(dodecyl sulfate) (Sc(DS)3) in Water



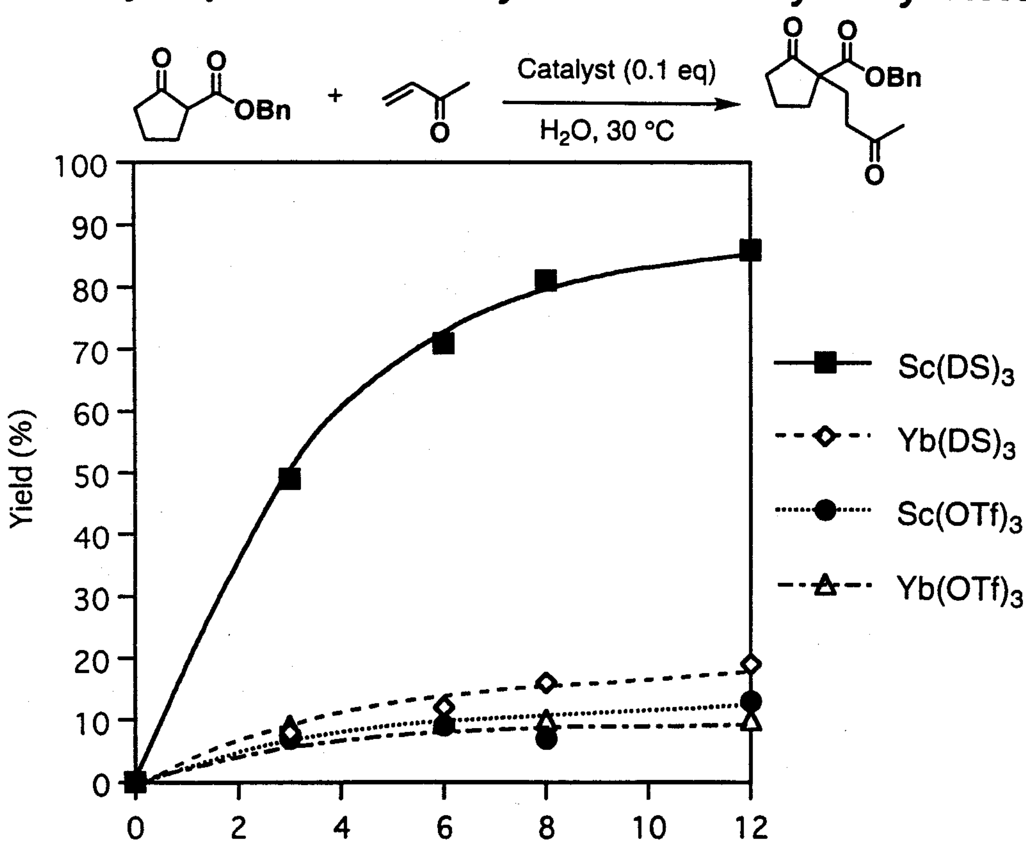
cf.)



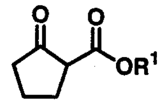
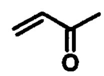
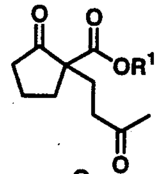
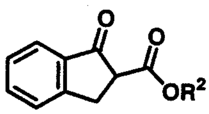
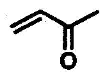
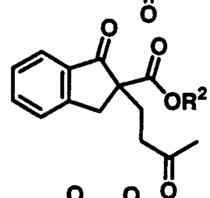
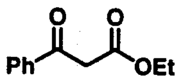
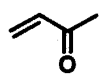
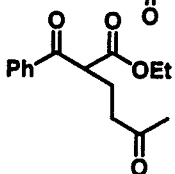
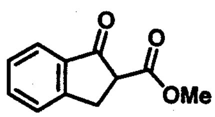
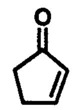
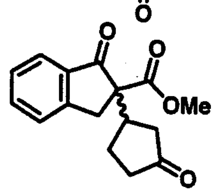
> 98% Yield

Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879.

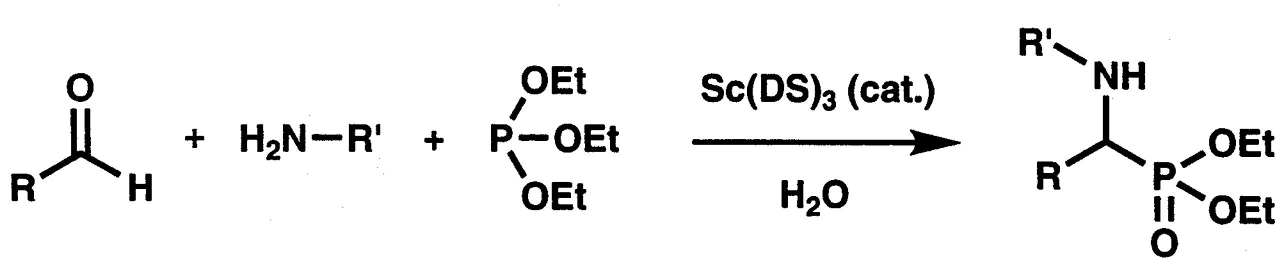
The Profiles of the Michael Reaction of Benzyl 2-Oxocyclopentanecarboxylate with Methyl Vinyl Ketone



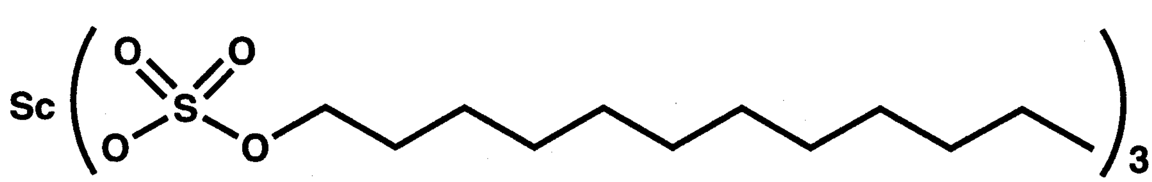
Sc(DS)$_3$-Catalyzed Michael Reactions of β-Ketoesters with Acceptors

Donor	Acceptor	Product	Yield (%)
			**91** (R^1 = Bn) **96** (R^1 = ^{t}Bu)
			**92** (R^2 = Me) **quant** (R^2 = Et)
			**87**
			**68**

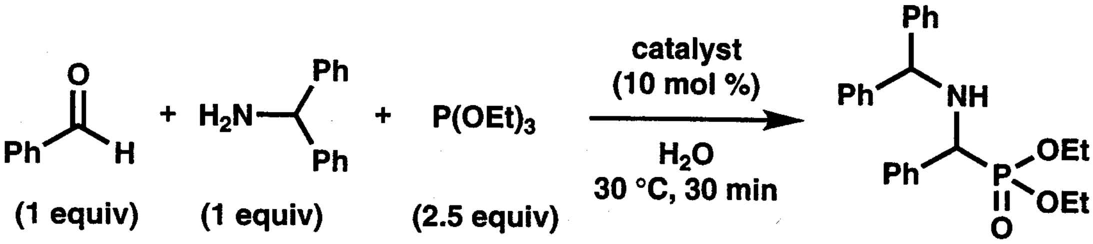
Sc(DS)$_3$-Catalyzed Synthesis of α-Amino Phosphonates in Water



Sc(DS)$_3$ =



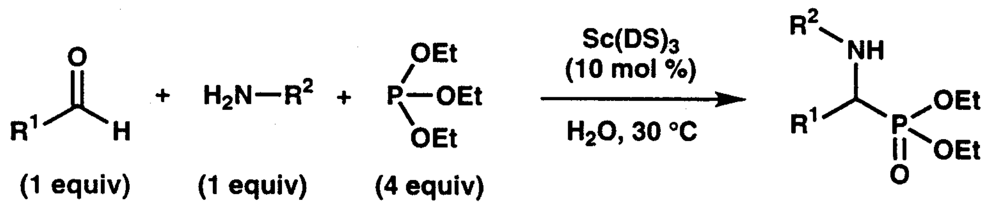
Effect of Catalysts

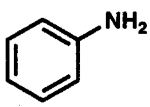
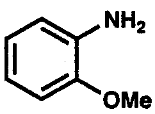
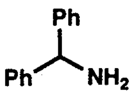
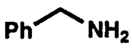


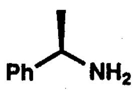
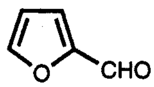
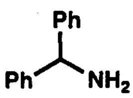
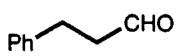
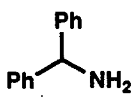
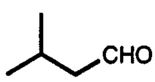
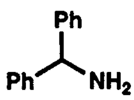
Entry	Catalyst	Yield (%)
1	$NaO_3SOC_{12}H_{25}$ (30 mol %)	8
2	$Sc(OTf)_3$	6
3	DBSA	18
4	**$Sc(DS)_3$**	**71**
5[a]	$Sc(DS)_3$	31
6[b]	$Sc(DS)_3$	trace

[a] Under neat conditions (without H_2O).
[b] $HOP(OEt)_2$ (2.5 equiv) was used instead of $P(OEt)_3$.

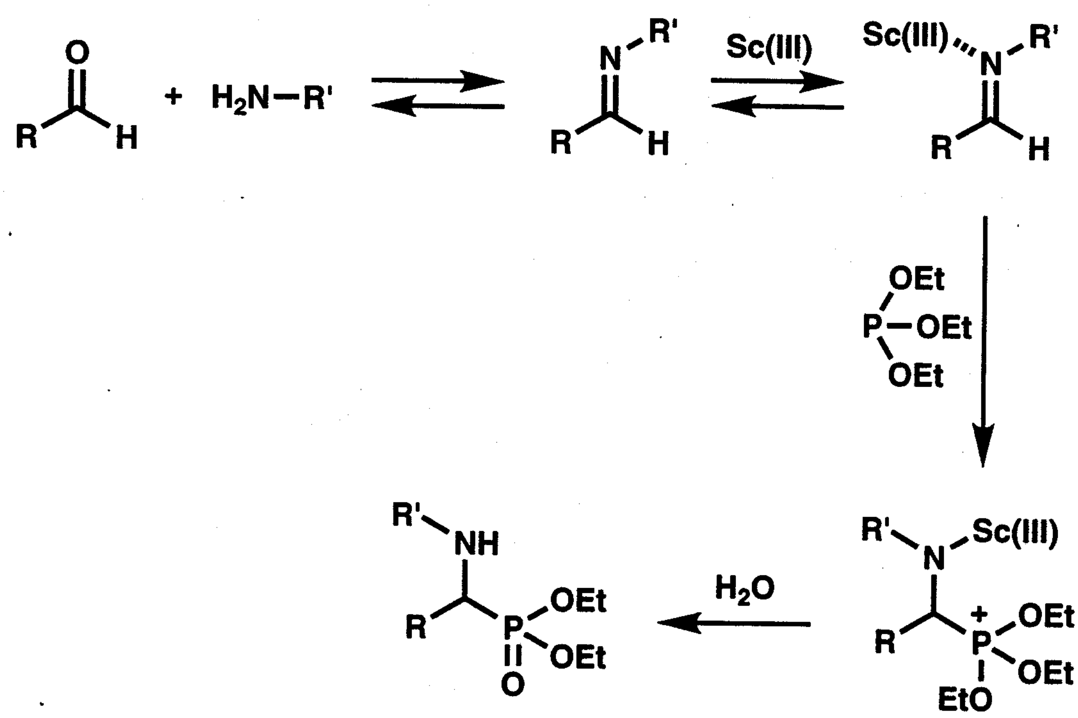
α-Amino Phosphonate Synthesis



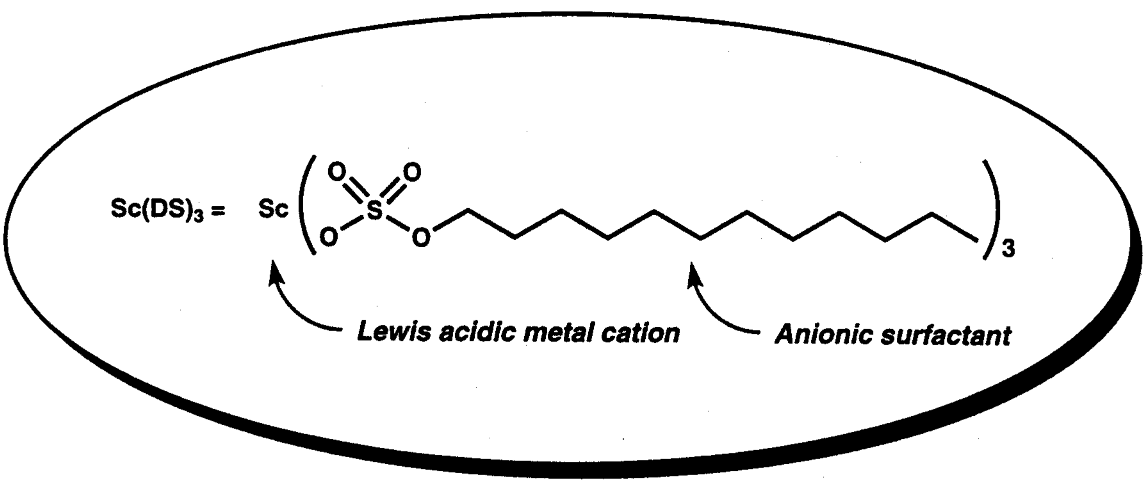
Aldehyde	Amine	Yield (%)
PhCHO		88
PhCHO		86
PhCHO		83
PhCHO		84

Aldehyde	Amine	Yield (%)
PhCHO		78[a]
		78
		95
		83

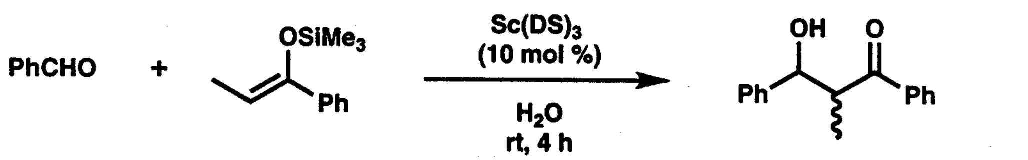
Mechanism of Sc(III)-Catalyzed Synthesis of α-Amino Phosphonates



Scandium Tris(dodecyl sulfate) (Sc(DS)₃) as a Lewis Acid–Surfactant-Combined Catalyst (LASC)



Effective Lewis acid catalyst for organic reactions in water



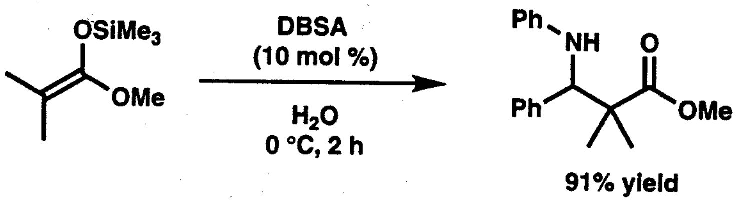
92% yield (*syn/anti* = 49/51)

Dodecylbenzenesulfonic Acid (DBSA) as a Brønsted Acid–Surfactant-Combined Catalyst (BASC)

DBSA =

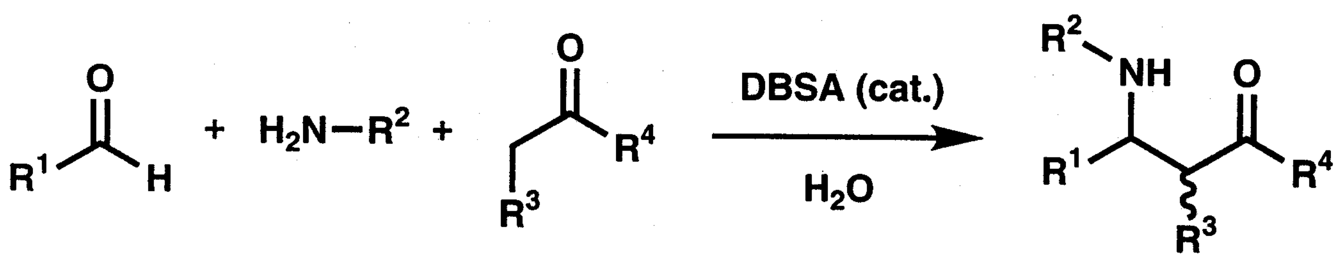
(soft type: mixture of isomers with a linear alkyl chain)

Effective Brønsted acid catalyst for organic reactions in water

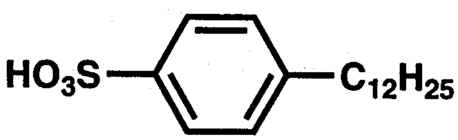


Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* 1999, 1401.

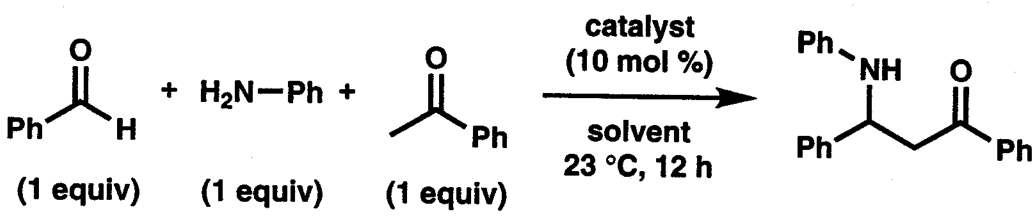
DBSA-Catalyzed Mannich-Type Reactions of Aldehydes, Amines, and Ketones in Water



DBSA =



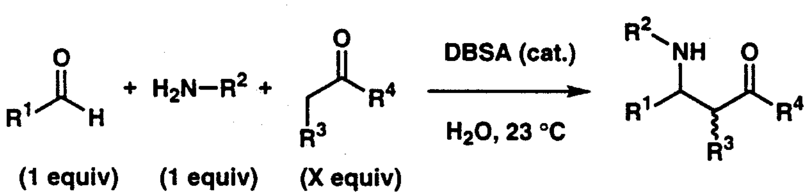
Effect of Catalysts and Solvents

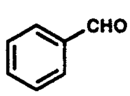
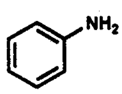
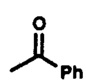
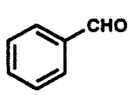
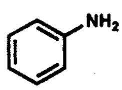
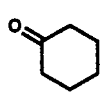
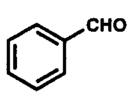
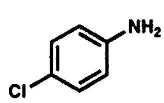
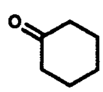
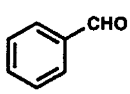
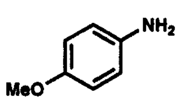
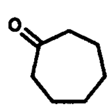
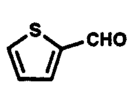
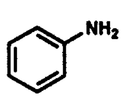
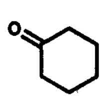
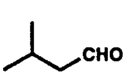
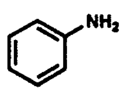
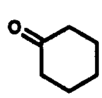


Entry	Catalyst	Solvent	Yield (%)
1	TsOH	H_2O	0
2	$NaO_3SOC_{12}H_{25}$	H_2O	5
3	TsOH + $NaO_3SOC_{12}H_{25}$	H_2O	56
4	$Sc(O_3SOC_{12}H_{25})_3$	H_2O	54
5	**DBSA**	**H_2O**	**69**
6	DBSA	MeOH	9
7	DBSA	CH_2Cl_2	4

DBSA = dodecylbenzenesulfonic acid (soft type)

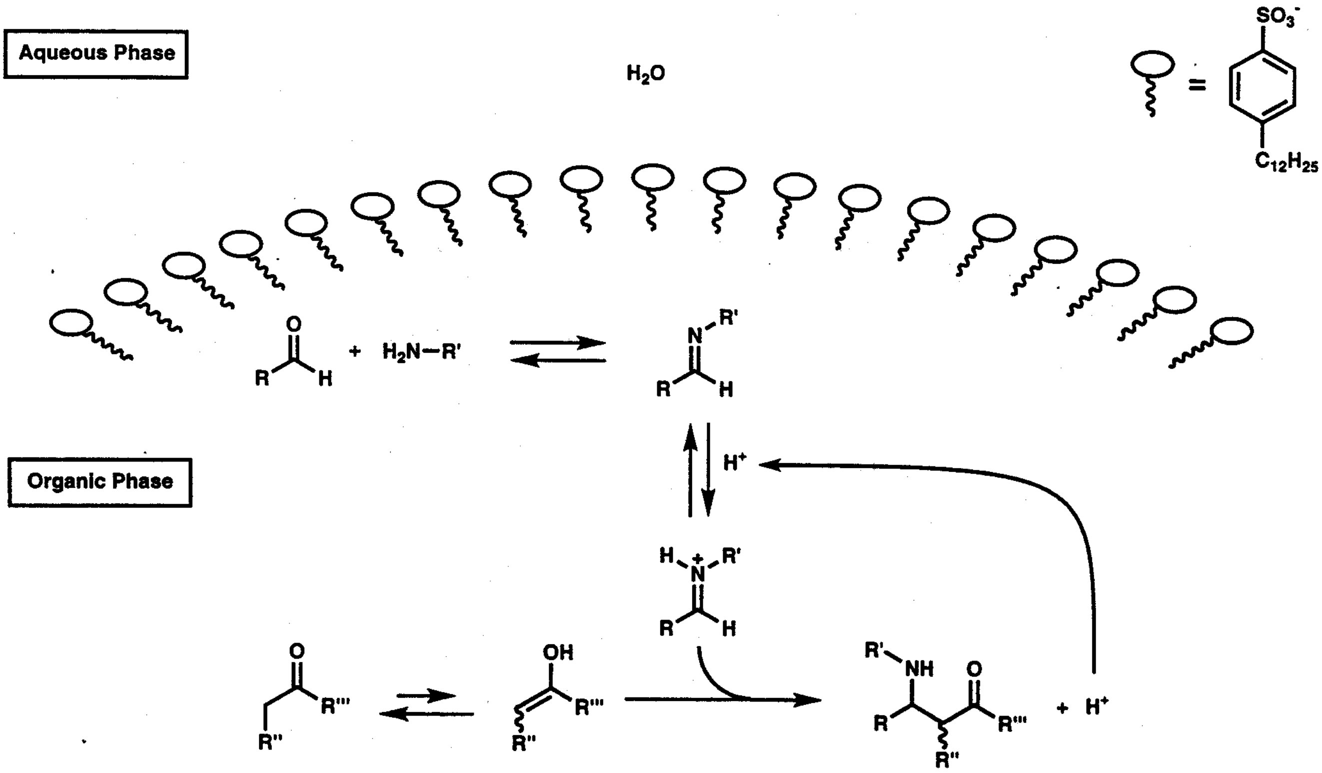
Mannich-Type Reactions in Water



Aldehyde	Amine	Ketone (equiv)	DBSA (mol %)	Time (h)	Yield (%)
		 (1)	10	24	**81**
		 (5)	1	1	**97**
		 (5)	1	1	**quant**
		 (5)	1	12	**89**
		 (5)	10	24	**87**
		 (5)	10	12[a]	**71**

[a] [illegible]

Assumed Mechanism of DBSA-Catalyzed Mannich-Type Reactions in Water



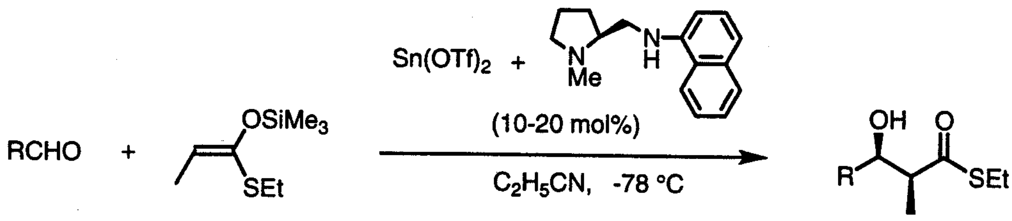
Catalytic Enantioselective Carbon-Carbon Bond-Forming Reactions in Aqueous Media

- *Enzymes do, but   limited examples*
- *Still very difficult in flasks*

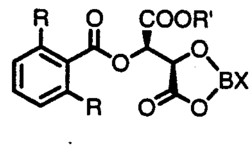
⇩

Challenging!!

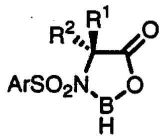
Asymmetric Aldol Reactions Using a Chiral Catalyst



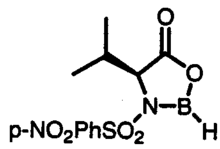
T. Mukaiyama, S. Kobayashi, *Chem. Lett.*, **1990**, 129; 1455.



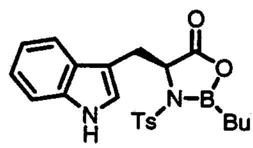
H. Yamamoto (1991)



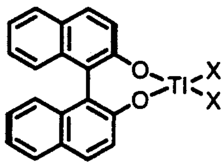
S. Masamune (1992)



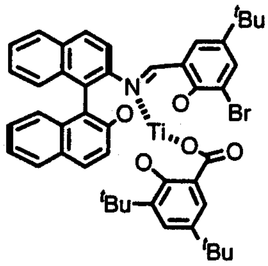
S. Kiyooka (1992)



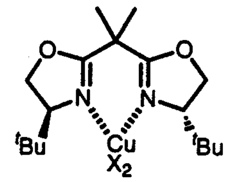
E. J. Corey (1992)



K. Mikami (1994)
G. E. Keck (1995)

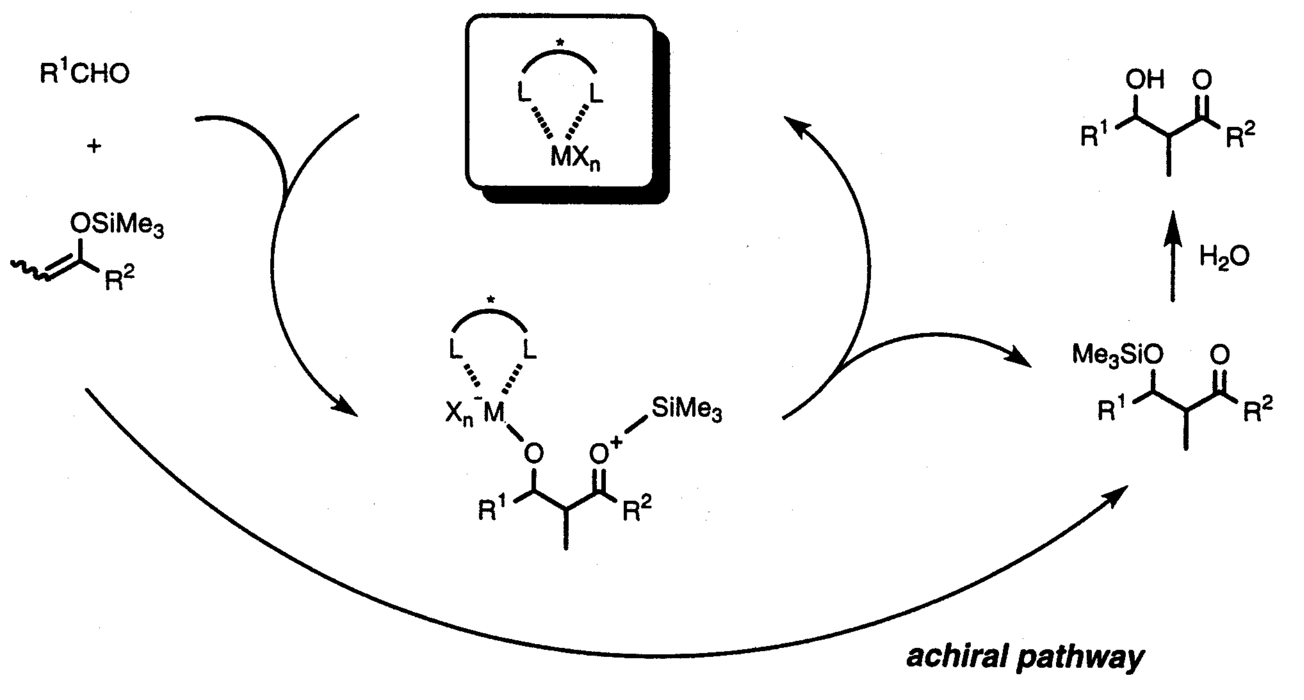


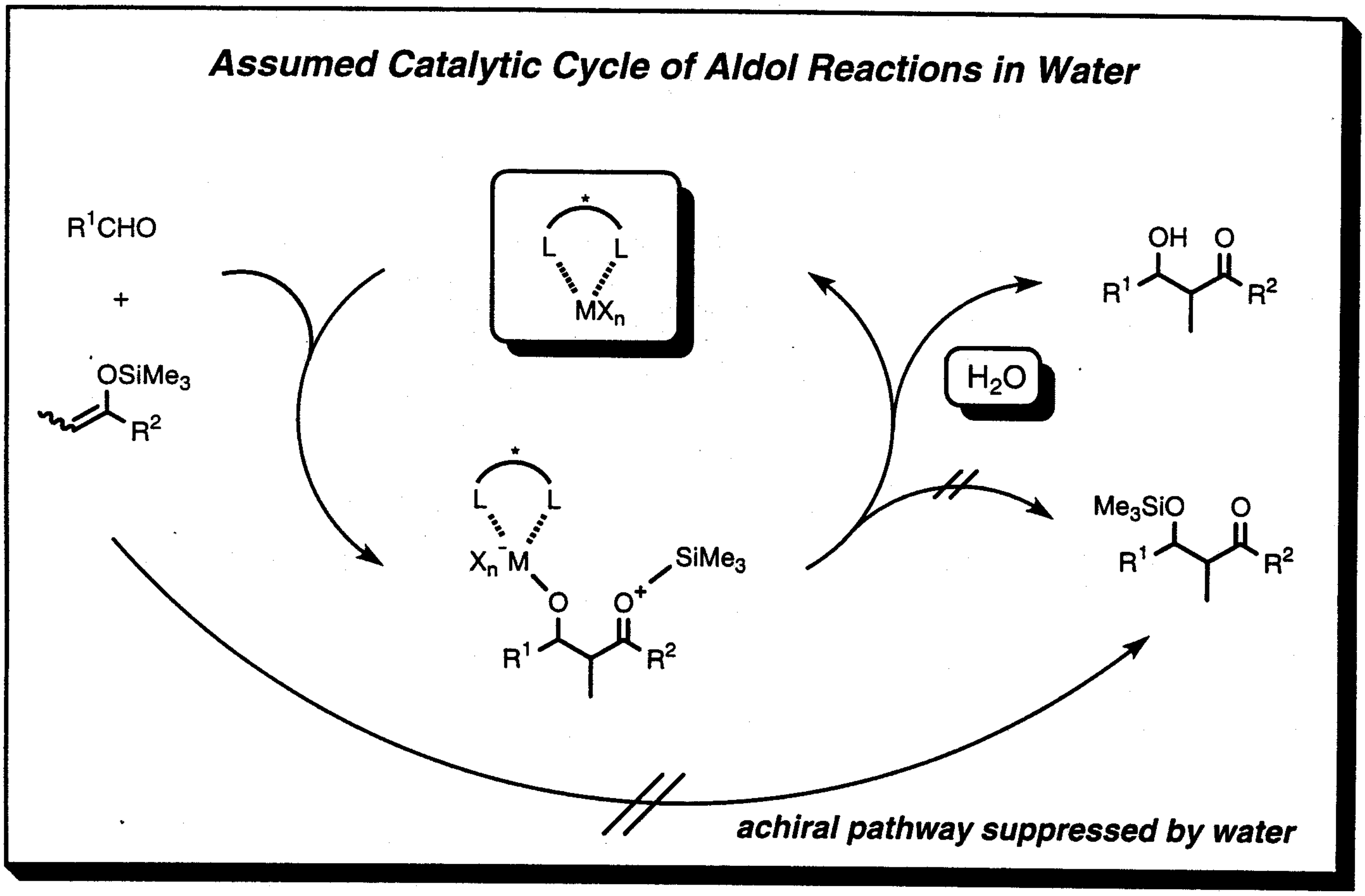
E. M. Carreira (1994)



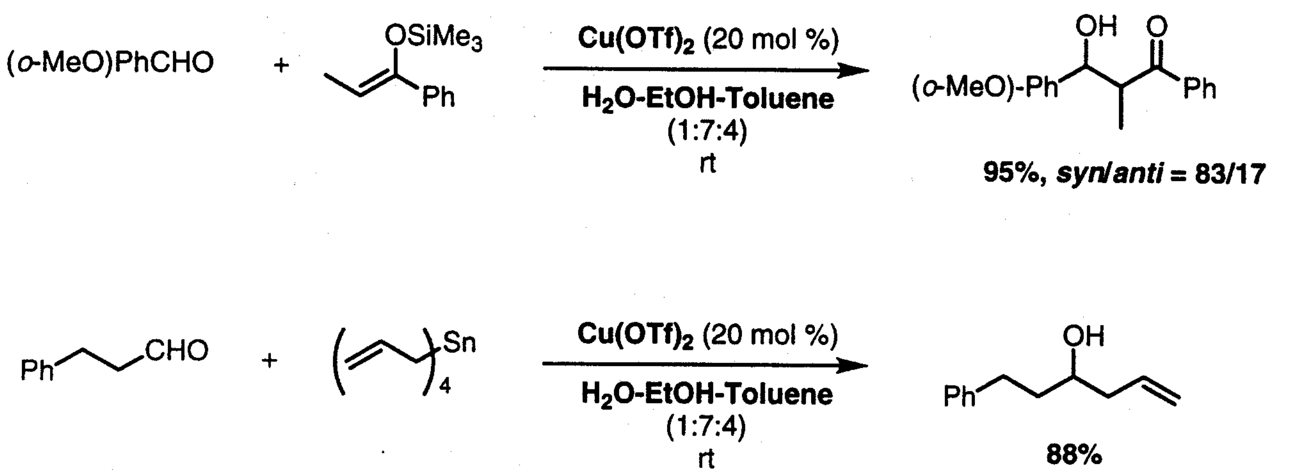
D. A. Evans (1996)

Assumed Catalytic Cycle of Aldol Reactions in Organic Solvents



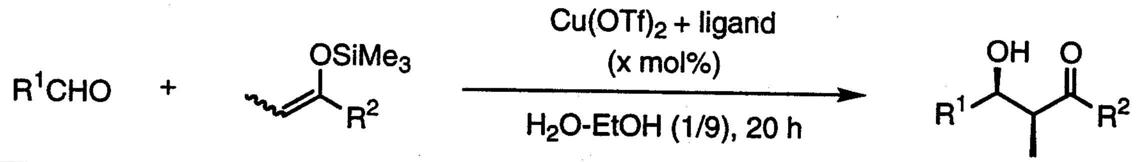


Cu(II)-Catalyzed C-C Bond-Forming Reactions in Aqueous Media



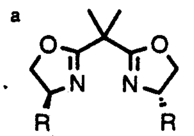
S. Kobayashi, S. Nagayama, T. Busujima, *Chem. Lett.* **1997**, 959.

Catalytic Asymmetric Aldol Reactions in Aqueous Media



Entry	R^1	R^2	*E*/*Z*	Ligand[a] (x/mol%)	Temp. /℃	Yield /%	*syn*/*anti*	ee/% (*syn*)
1	Ph	Et	*Z*	**1** (20)	-15	**81**	**3.5/1**	**81**
2	Ph	Et	*Z*	**1** (10)	-10	**79**	**3.3/1**	**77**
3	Ph	Ph	*Z*	**1** (20)	-10	**74**	**3.2/1**	**67**
4	Ph	Ph	*Z*	**2** (20)	0	**98**	**2.6/1**	**61**
5	2-naphthyl	*i*-Pr	*Z*[b]	**1** (20)	-10	**97**	**4.0/1**	**81**
6	2-furyl	Et	*Z*	**1** (20)	-10	**86**	**4.0/1**	**76**
7	PhCH=CH	Et	*Z*	**1** (20)	-10	**94**	**4.0/1**	**57**
8	$Ph(CH_2)_3$	Ph	*Z*	**2** (20)	0	**37**	**4.6/1**	**59**

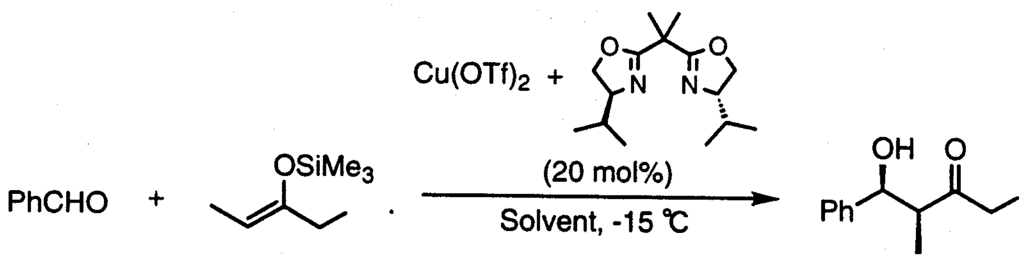
a



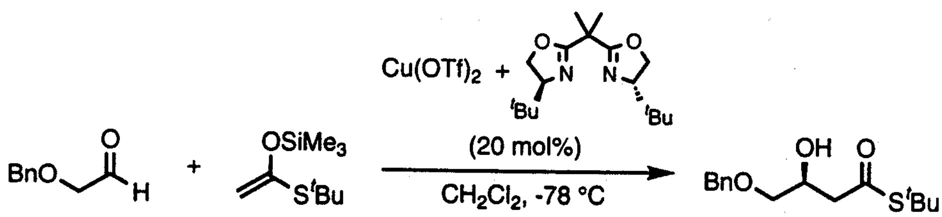
1: R = *i*-Pr
2: R = CH_2Ph

[b] *E*/*Z* = 2/98

Effect of Solvents

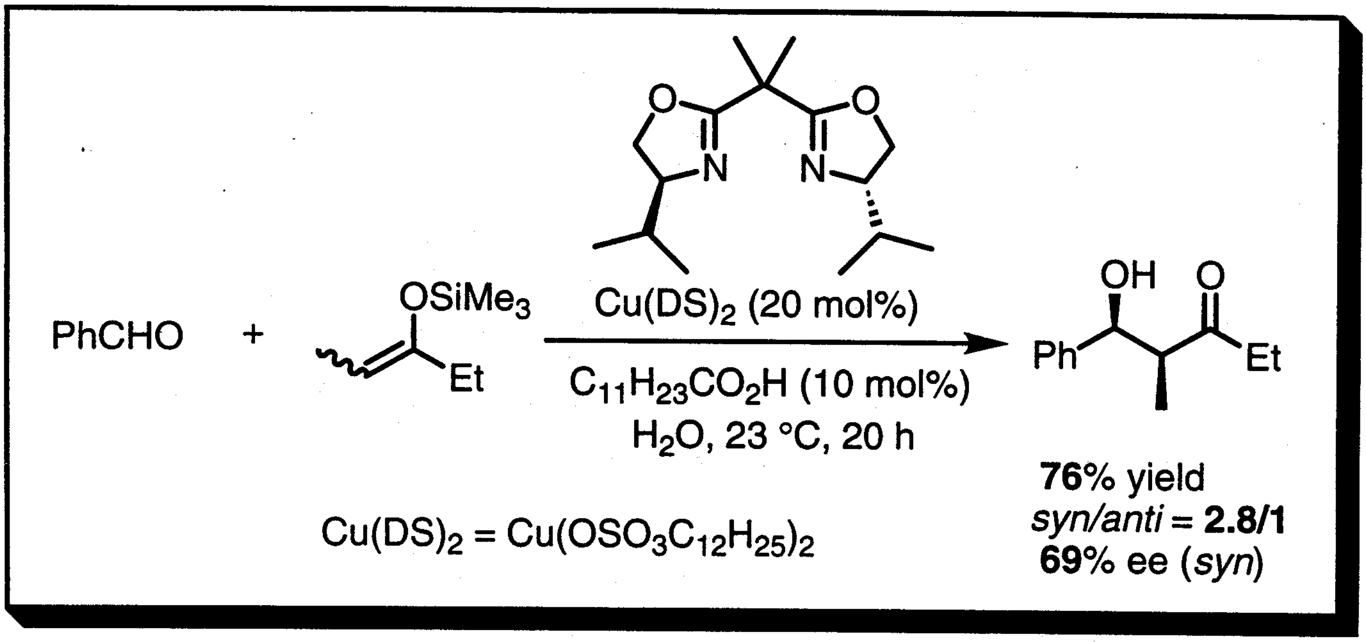


Solvent	Yield (%)	*syn*/*anti*	ee (%, *syn*)
CH_2Cl_2	**11**	**2.1/1**	**20 (2*R*,3*R*)**
H_2O/EtOH = 1/9	**81**	**3.5/1**	**81 (2*S*,3*S*)**

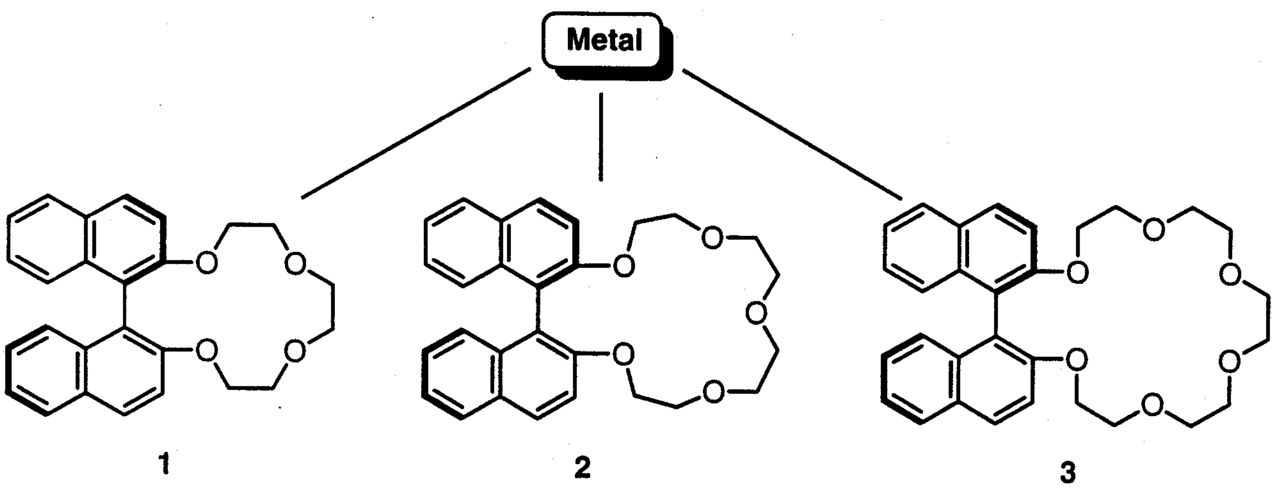


D. A. Evans *et al.*, *J. Am. Chem. Soc.* **1996**, *118*, 5814.

Catalytic Asymmetric Aldol Reactions Using Lewis Acid–Surfactant-Combined Catalysts (LASCs) in Water



Metal-Chiral Crown Ether Complexes as Chiral Lewis Acids



- **Suitable Combination of Metals and Crown Ethers (Ionic Radii and Hole Size)**
- **Lewis Acidity**
- **Asymmetric Environment**