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

New Dimensions of Lewis Acid Catalysis in Organic Synthesis

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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.

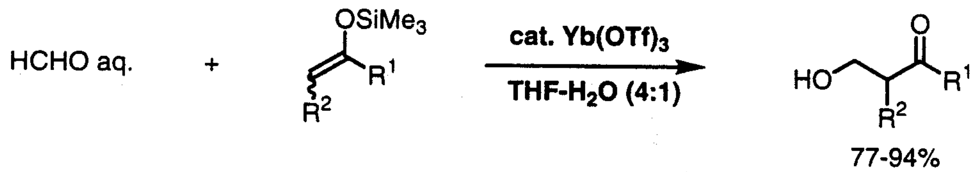
Problems:

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

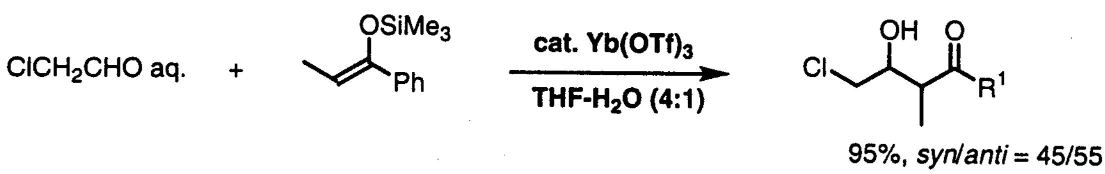
$Ln(OTf)_3$ Ln = Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu

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

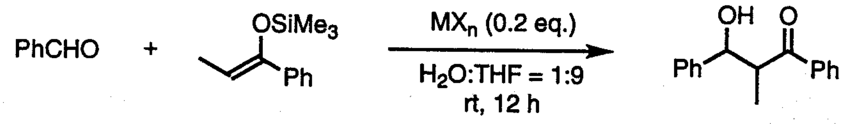
- To mimic enzymes
- To focus on *media* in which enzymes work

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 — 80	Ce +3 — 81	Pr +3 — 83	Nd +3 — 78	Pm — —	Sm +3 — 85	Eu +3 — 88	Gd +3 — 90	Tb +3 — 81	Dy +3 — 85	Ho +3 — 89	Er +3 — 86	Tm +3 — 85	Yb +3 92 92	Lu +3 — 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*Kh* = -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 $^{+3}$ 8.5 2.1×10^{8}	Ce $^{+3}$ 8.3 2.7×10^{8}	Pr $^{+3}$ 8.1 3.1×10^{8}	Nd $^{+3}$ 8.0 3.9×10^{8}	Pm — —	Sm $^{+3}$ 7.9 5.9×10^{8}	Eu $^{+3}$ 7.8 6.5×10^{8}	Gd $^{+3}$ 8.0 6.3×10^{7}	Tb $^{+3}$ 7.9 7.8×10^{7}	Dy $^{+3}$ 8.0 6.3×10^{7}	Ho $^{+3}$ 8.0 6.1×10^{7}	Er $^{+3}$ 7.9 1.4×10^{8}	Tm $^{+3}$ 7.7 6.4×10^{6}	Yb $^{+3}$ 7.7 8×10^{7}	Lu $^{+3}$ 7.6 6×10^{7}

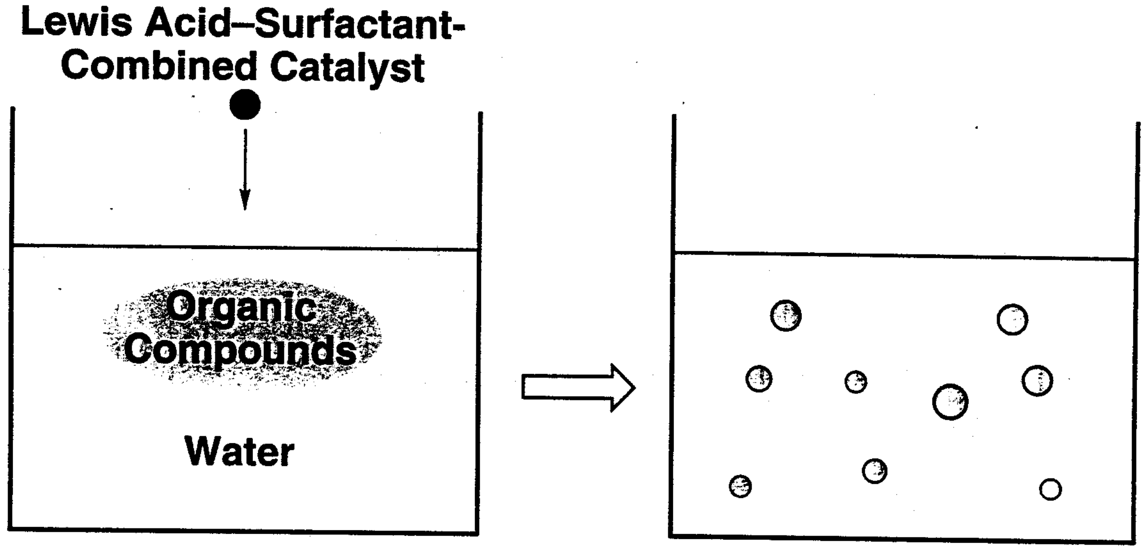
[a] p*Kh* = -log K_{xy}

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

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

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

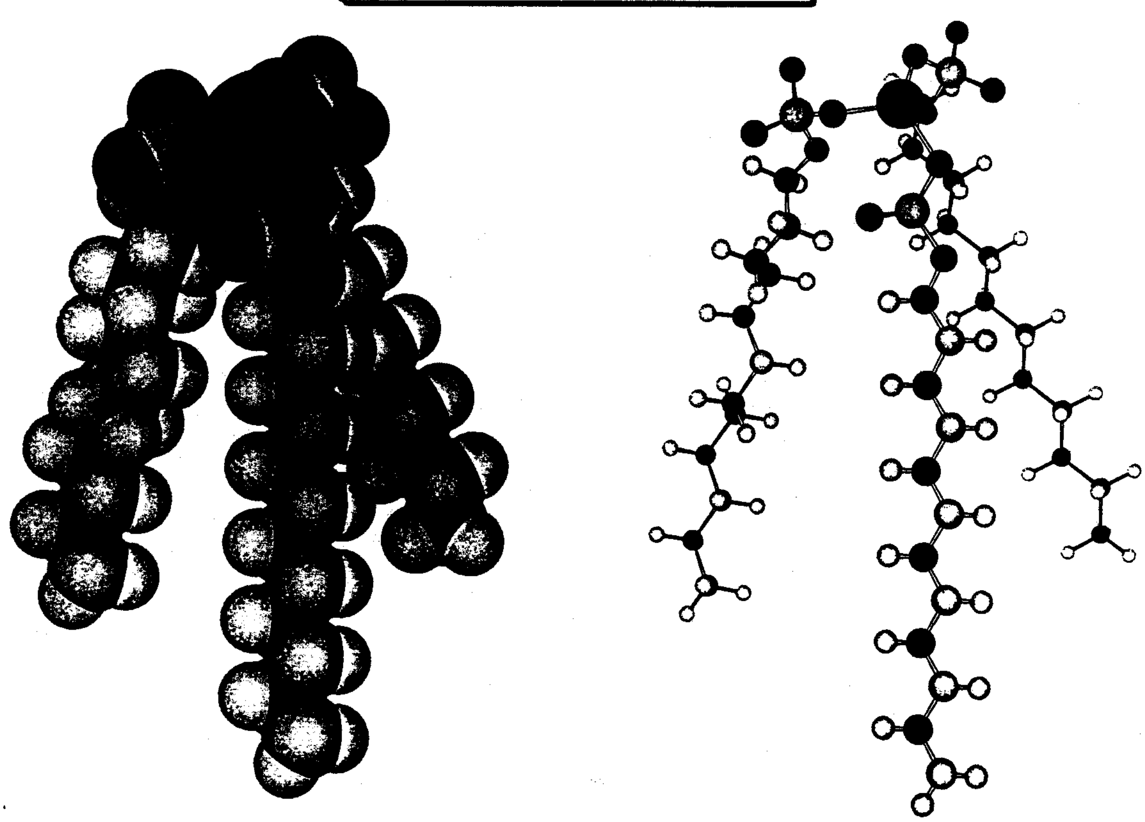
Lewis Acid–Surfactant-Combined Catalyst Forms Colloidal Dispersion in Water



Colloidal Dispersion

Lewis Acid-Surfactant Combined Catalyst (LASC)

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

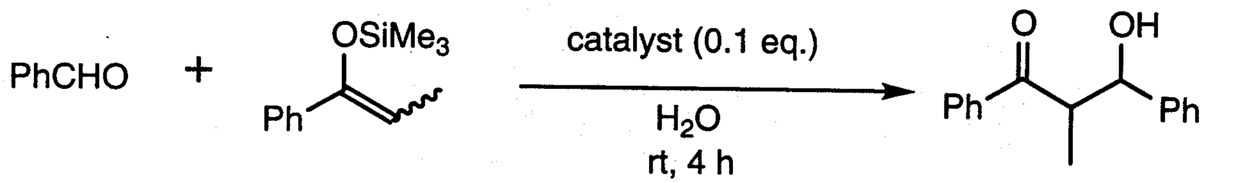


Preparation of $Sc(DS)_3$

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

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

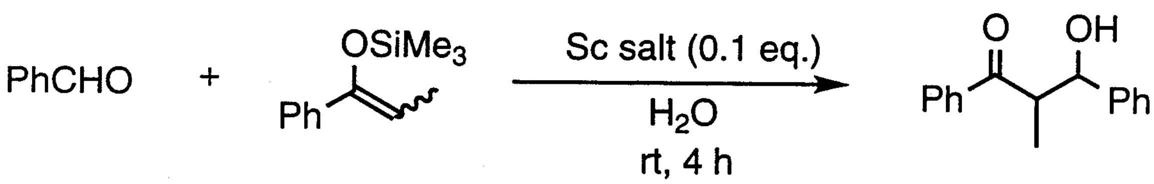
$Sc(DS)_3$-Catalyzed Aldol Reaction in Water



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

Stable Dispersion System Forms!

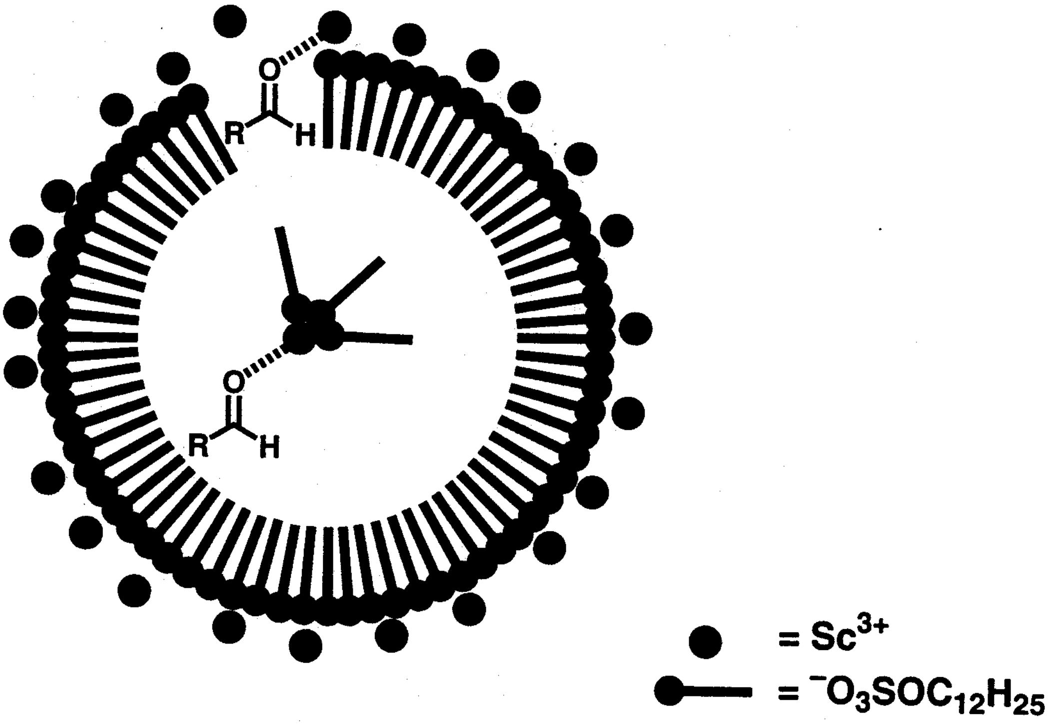
Effects of Alkyl Chains and the Scandium Salts



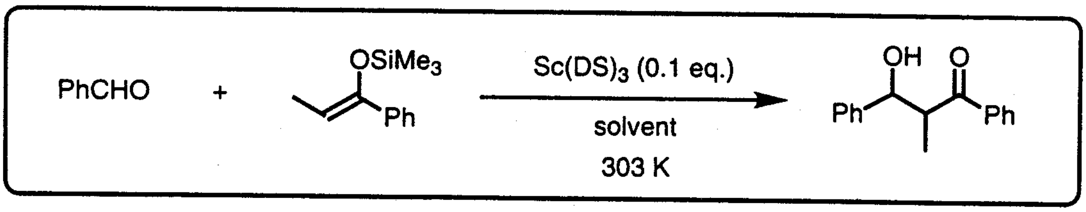
R	$Sc(OSO_3R)_3$	$Sc(OSO_2p\text{-}R\text{-}C_6H_4)_3$	$Sc(OSO_2R)_3$ / *Particle Size*
$C_{10}H_{21}$	—	**55**	**60** (*700 nm*)[a]
$C_{11}H_{23}$	—	—	**68**
$C_{12}H_{25}$	**92**	**91**	**83** (*1100 nm*)[a]
$C_{13}H_{27}$	—	—	**76**
$C_{14}H_{29}$	**73**	**33**	**19** (*400 nm*)[a]
$C_{16}H_{33}$	—	**14**	**12**

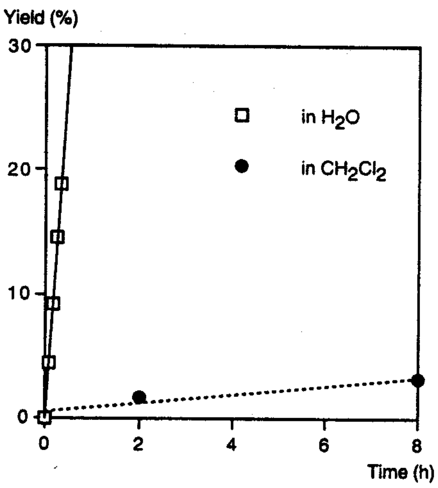
Numbers are isolated yields (%).
a) Particle sizes formed by $Sc(OSO_2R)_3$ and PhCHO in water are shown.

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



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

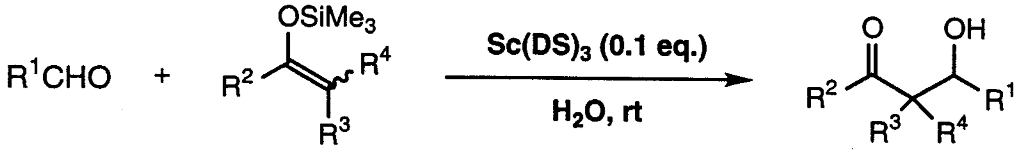




solvent	v (mol/l · sec)
H_2O	2.6×10^{-5}
CH_2Cl_2	2.0×10^{-7}

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

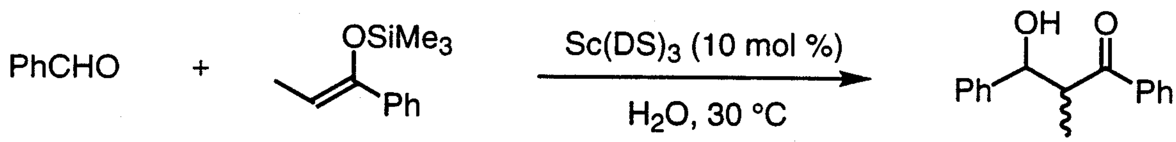
$Sc(DS)_3$-Catalyzed Aldol Reactions in Water

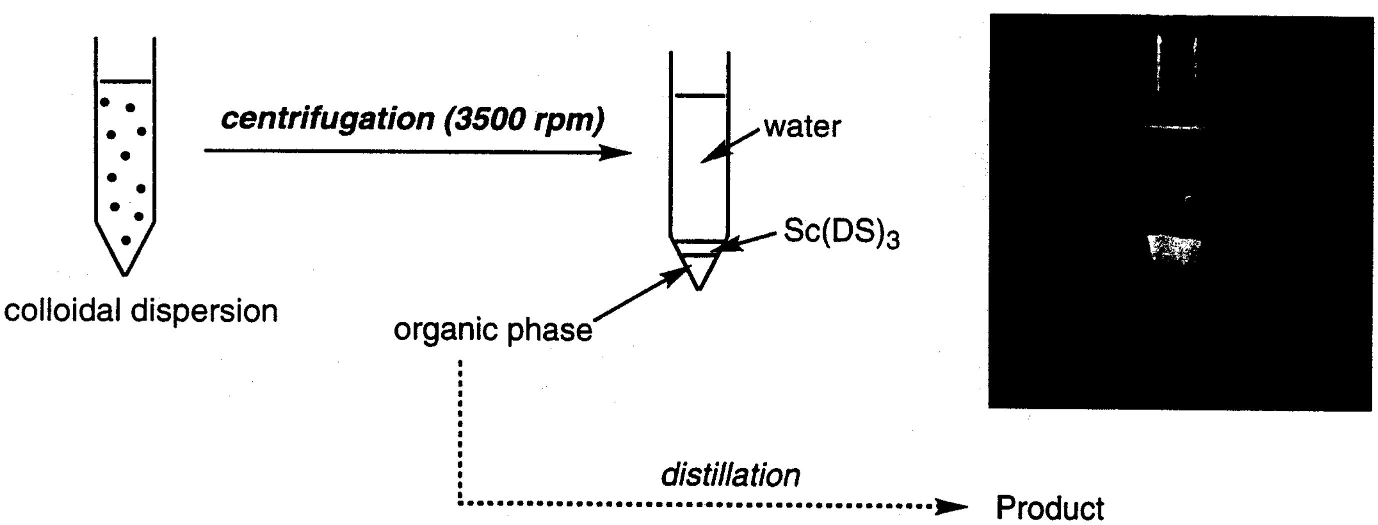


R^1	R^2	R^3	R^4	Yield/%
Ph	Ph	H	Me	**92**
$PhCH_2CH_2$	Ph	H	Me	**88**
PhCH=CH	Ph	H	Me	**91**
H	Ph	H	Me	**72**[a]
2-Pyridyl	Ph	H	Me	**84**[b]
PhCO	Ph	H	Me	**86**
p-Cl-Ph	Et	Me	H	**91**
Ph	-$(CH_2)_4$-		H	**77**
Ph	Ph	H	H	**94**[b, c]
Ph	EtS	Me	Me	**98**
Ph	MeO	Me	Me	**80**[b, d]

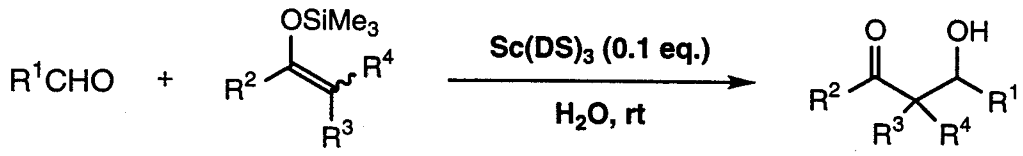
a) HCHO aq. (3 ml), silyl enolate (0.5 mmol), and $Sc(DS)_3$ (0.05 mmol) were combined. b) $Sc(DS)_3$ (0.2 eq.) was used. c) Additional silyl enolate (1.5 eq.) was charged after 4 h. d) Silyl enolate (3.0 eq.) was used.

Work-Up Procedure without Using Organic Solvents





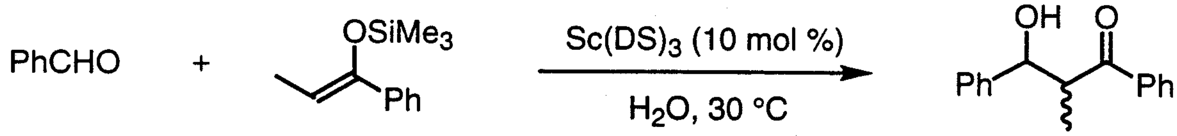
Sc(DS)$_3$-Catalyzed Aldol Reactions in Water

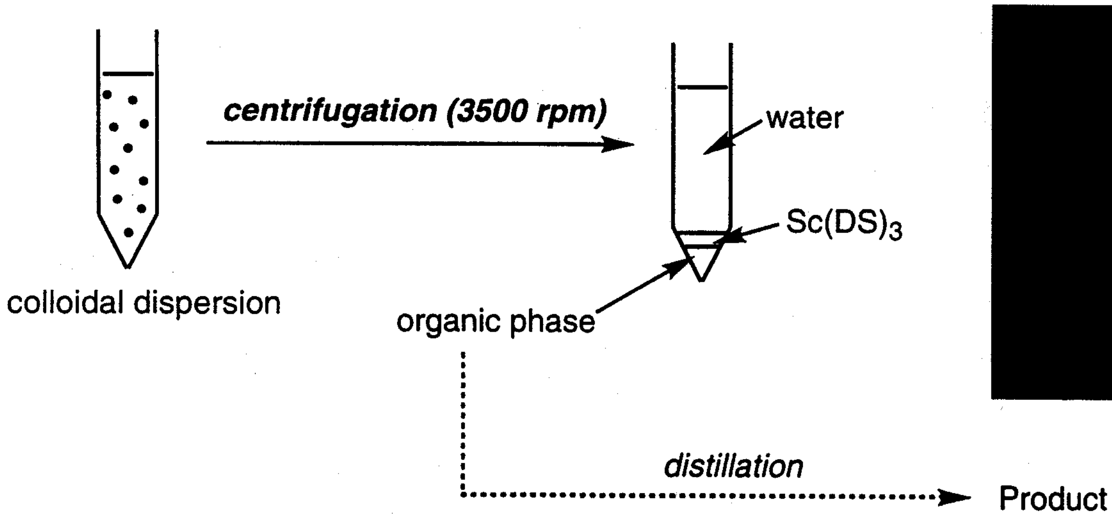


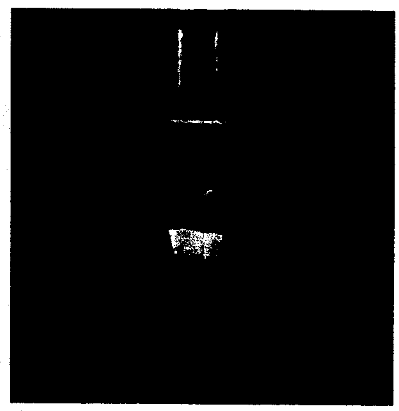
R^1	R^2	R^3	R^4	Yield/%
Ph	Ph	H	Me	**92**
$PhCH_2CH_2$	Ph	H	Me	**88**
PhCH=CH	Ph	H	Me	**91**
H	Ph	H	Me	**72**[a]
2-Pyridyl	Ph	H	Me	**84**[b]
PhCO	Ph	H	Me	**86**
p-Cl-Ph	Et	Me	H	**91**
Ph	-$(CH_2)_4$-		H	**77**
Ph	Ph	H	H	**94**[b, c]
Ph	EtS	Me	Me	**98**
Ph	MeO	Me	Me	**80**[b, d]

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.

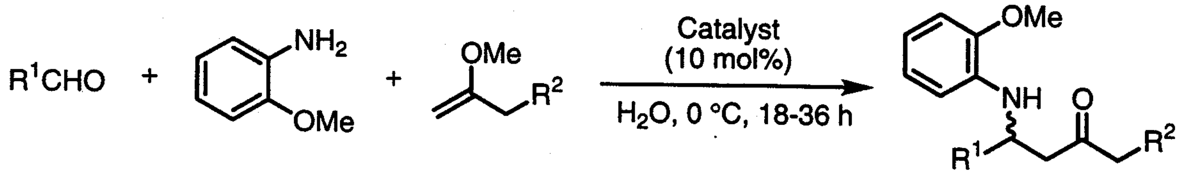
Work-Up Procedure without Using Organic Solvents

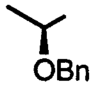
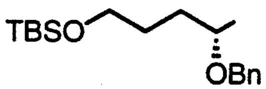




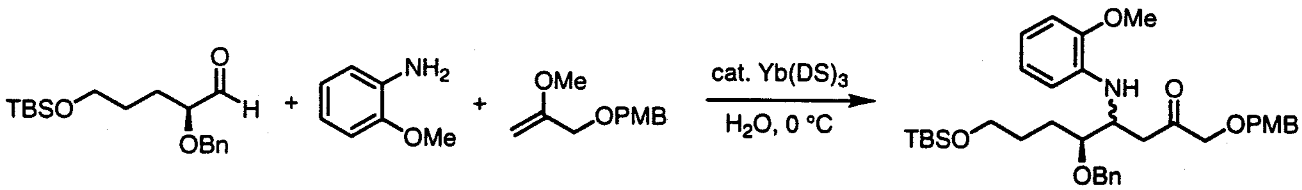


LASC-Catalyzed Mannich-Type Reactions in Water

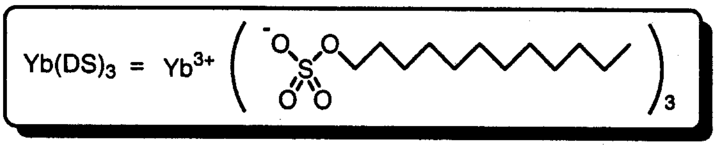


R^1	R^2	Catalyst	Yield (%)
Ph	H	$Cu(DS)_2$	**65**
c-C_6H_{11}	H	$Cu(DS)_2$	**86**
c-C_6H_{11}	H	$Yb(DS)_3$	**78**
	H	$Cu(DS)_2$	**82**
Ph	OPMB	$Cu(DS)_2$	**62**
	OPMB	$Cu(DS)_2$	**73**
	OPMB	$Yb(DS)_3$	**91**

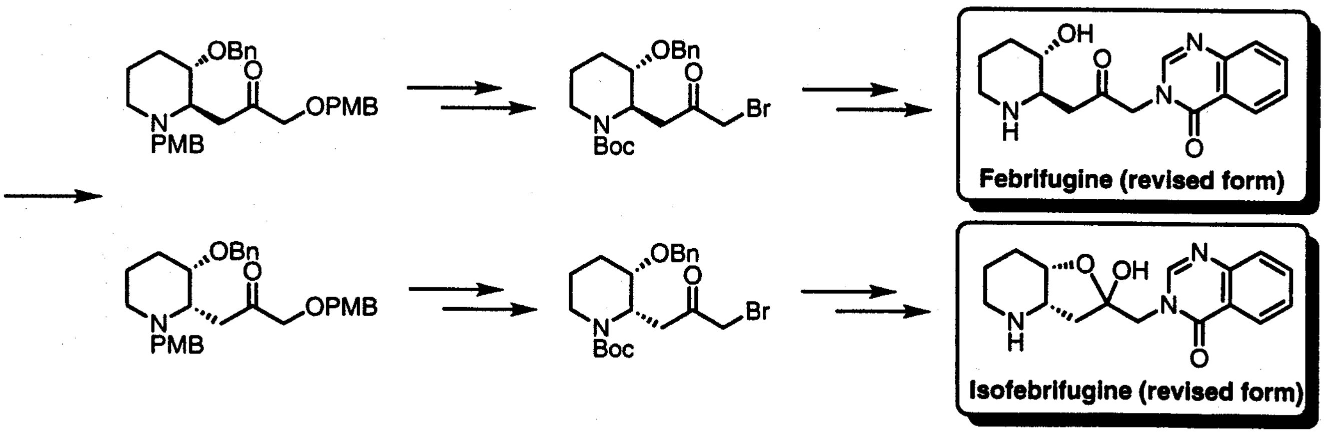
Synthesis of Febrifugine and Isofebrifugine



95%, *syn/anti* = 40/60

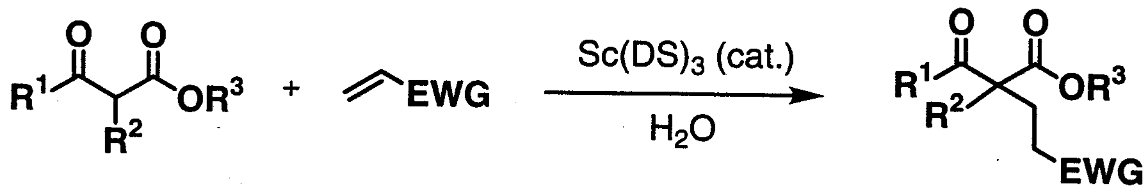


PMB = *p*-Methoxyphenyl

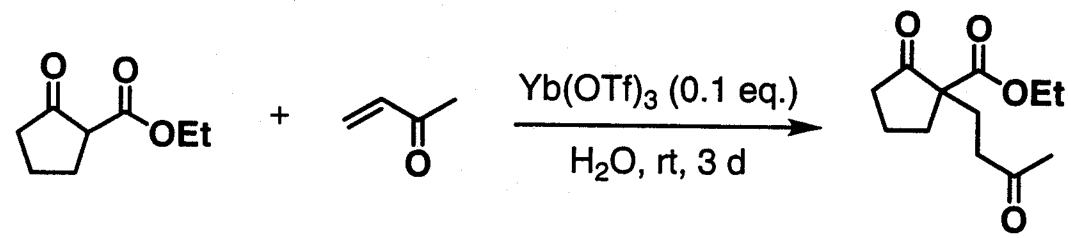


S. Kobayashi, M. Ueno, R. Suzuki, H. Ishitani, *J. Org. Chem.*, **64**, 6833 (1999).

Michael Reactions Mediated by Scandium Tris(dodecyl sulfate) ($Sc(DS)_3$) in Water



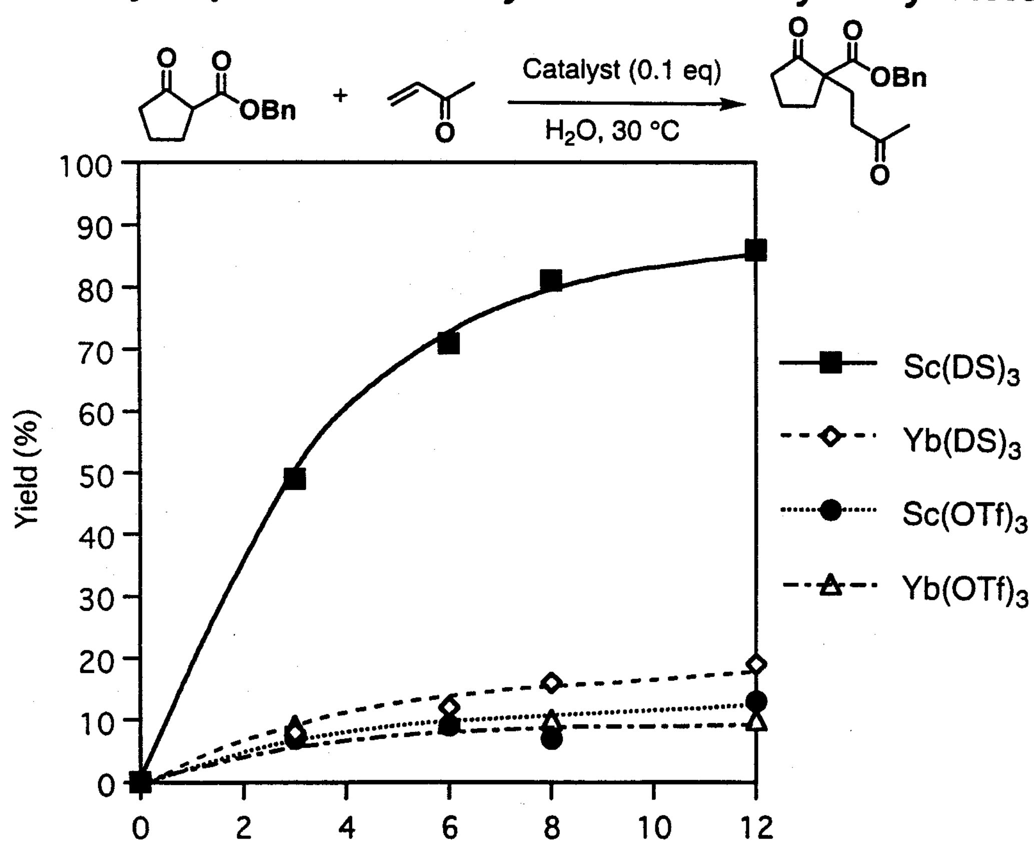
cf.)



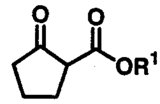
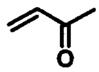
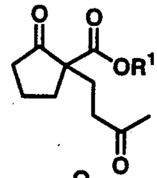
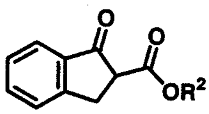
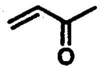
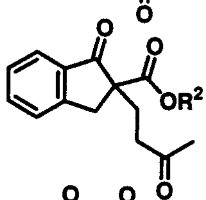
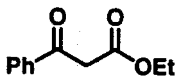
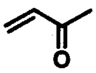
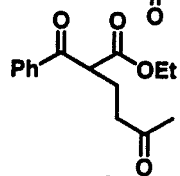
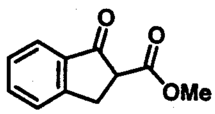
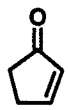
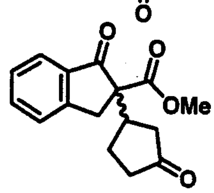
> 98% Yield

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

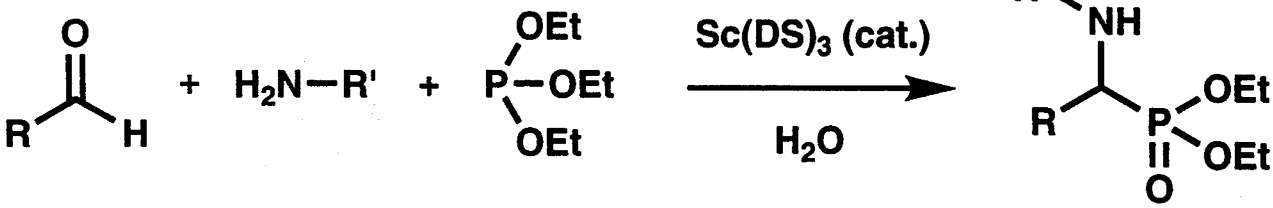
The Profiles of the Michael Reaction of Benzyl 2-Oxocyclopentanecarboxylate with Methyl Vinyl Ketone



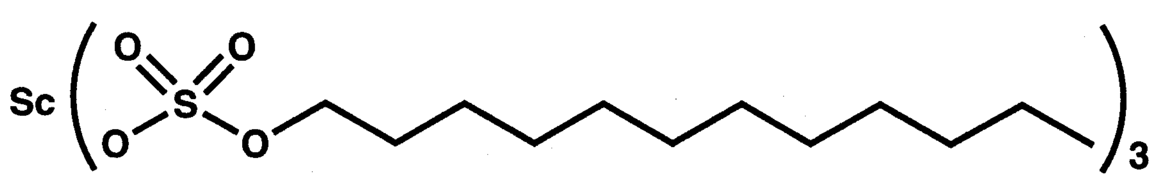
Sc(DS)$_3$-Catalyzed Michael Reactions of β-Ketoesters with Acceptors

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

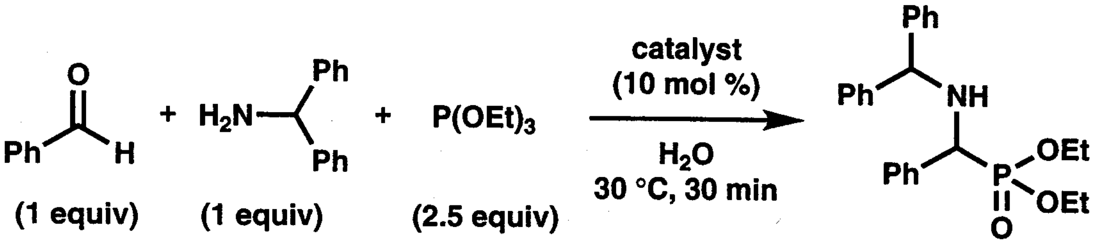
Sc(DS)$_3$-Catalyzed Synthesis of α-Amino Phosphonates in Water



Sc(DS)$_3$ =



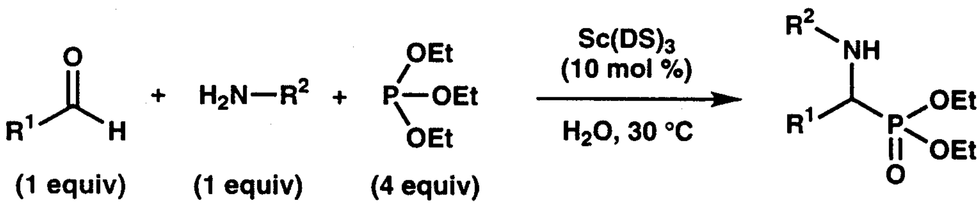
Effect of Catalysts

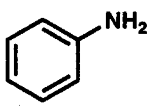
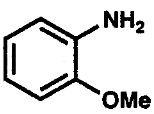
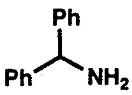
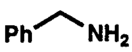


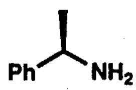
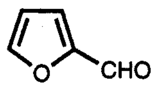
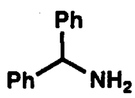
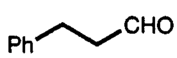
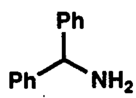
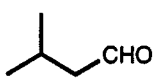
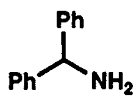
Entry	Catalyst	Yield (%)
1	$NaO_3SOC_{12}H_{25}$ (30 mol %)	8
2	$Sc(OTf)_3$	6
3	DBSA	18
4	**$Sc(DS)_3$**	**71**
5[a]	$Sc(DS)_3$	31
6[b]	$Sc(DS)_3$	trace

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

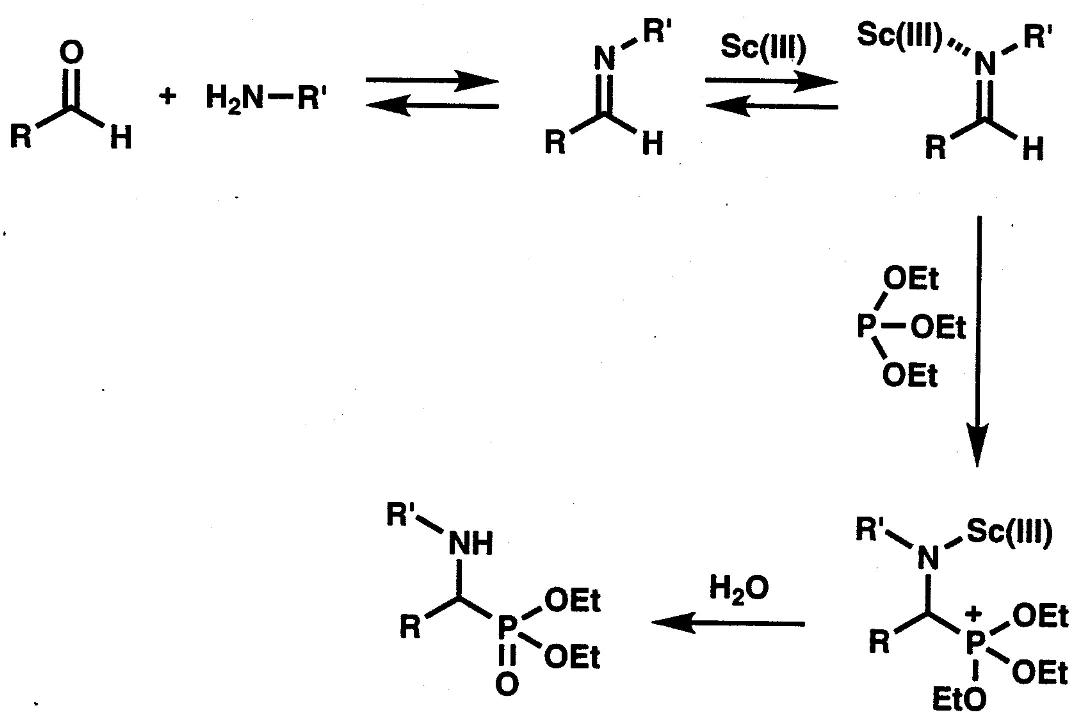
α-Amino Phosphonate Synthesis



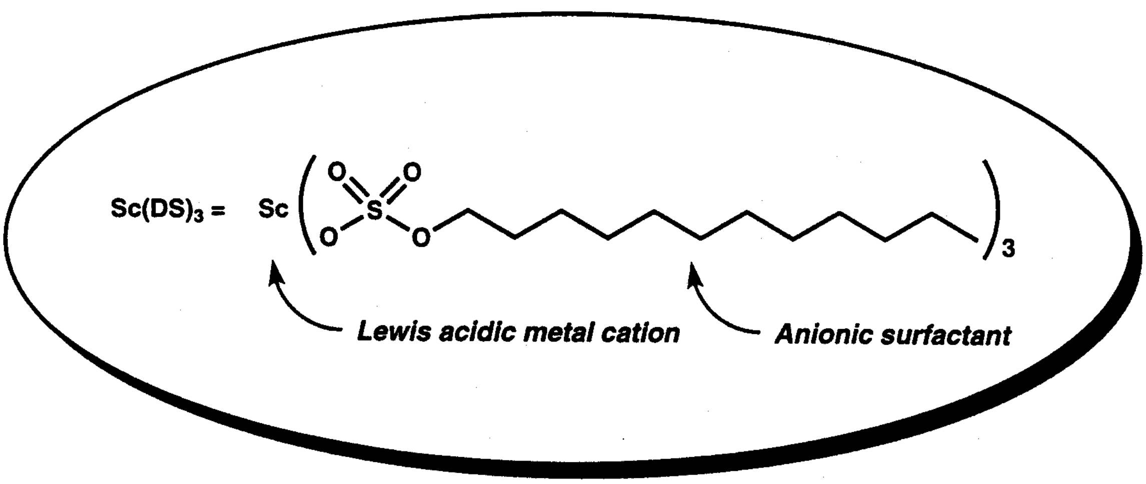
Aldehyde	Amine	Yield (%)
PhCHO		**88**
PhCHO		**86**
PhCHO		**83**
PhCHO		**84**

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

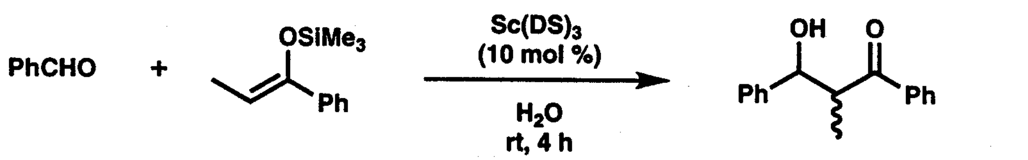
Mechanism of Sc(III)-Catalyzed Synthesis of α-Amino Phosphonates



Scandium Tris(dodecyl sulfate) (Sc(DS)$_3$) as a Lewis Acid–Surfactant-Combined Catalyst (LASC)



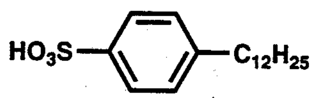
Effective Lewis acid catalyst for organic reactions in water



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

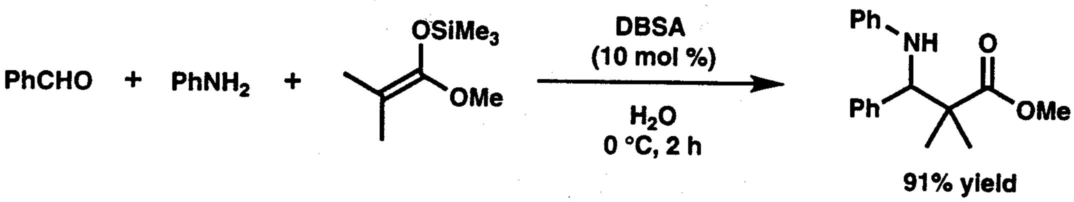
Dodecylbenzenesulfonic Acid (DBSA) as a Brønsted Acid–Surfactant-Combined Catalyst (BASC)

DBSA =



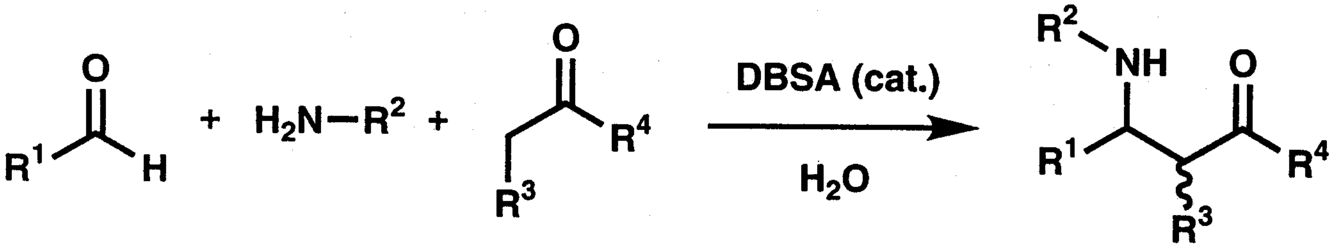
(soft type: mixture of isomers with a linear alkyl chain)

Effective Brønsted acid catalyst for organic reactions in water

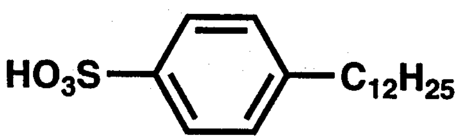


Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* 1999, 1401.

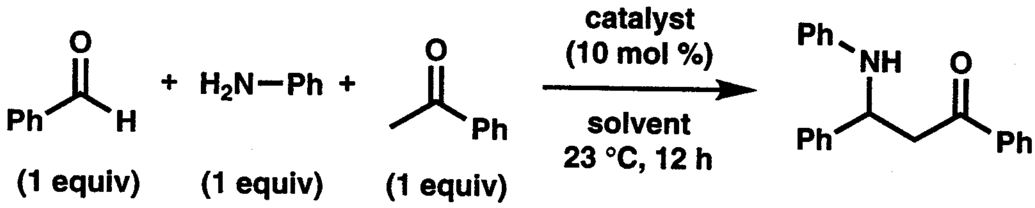
DBSA-Catalyzed Mannich-Type Reactions of Aldehydes, Amines, and Ketones in Water



DBSA =



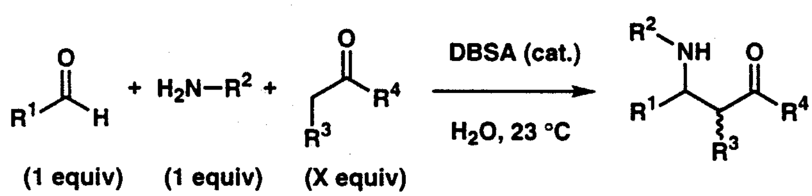
Effect of Catalysts and Solvents

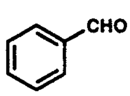
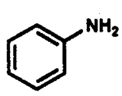
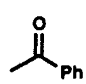
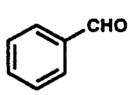
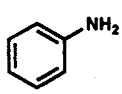
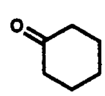
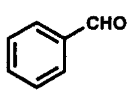
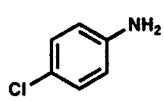
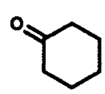
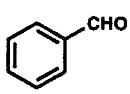
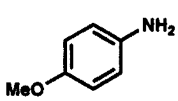
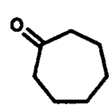
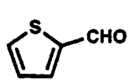
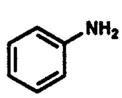
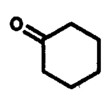
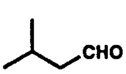
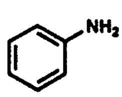
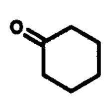


Entry	Catalyst	Solvent	Yield (%)
1	TsOH	H_2O	0
2	$NaO_3SOC_{12}H_{25}$	H_2O	5
3	TsOH + $NaO_3SOC_{12}H_{25}$	H_2O	56
4	$Sc(O_3SOC_{12}H_{25})_3$	H_2O	54
5	**DBSA**	**H_2O**	**69**
6	DBSA	MeOH	9
7	DBSA	CH_2Cl_2	4

DBSA = dodecylbenzenesulfonic acid (soft type)

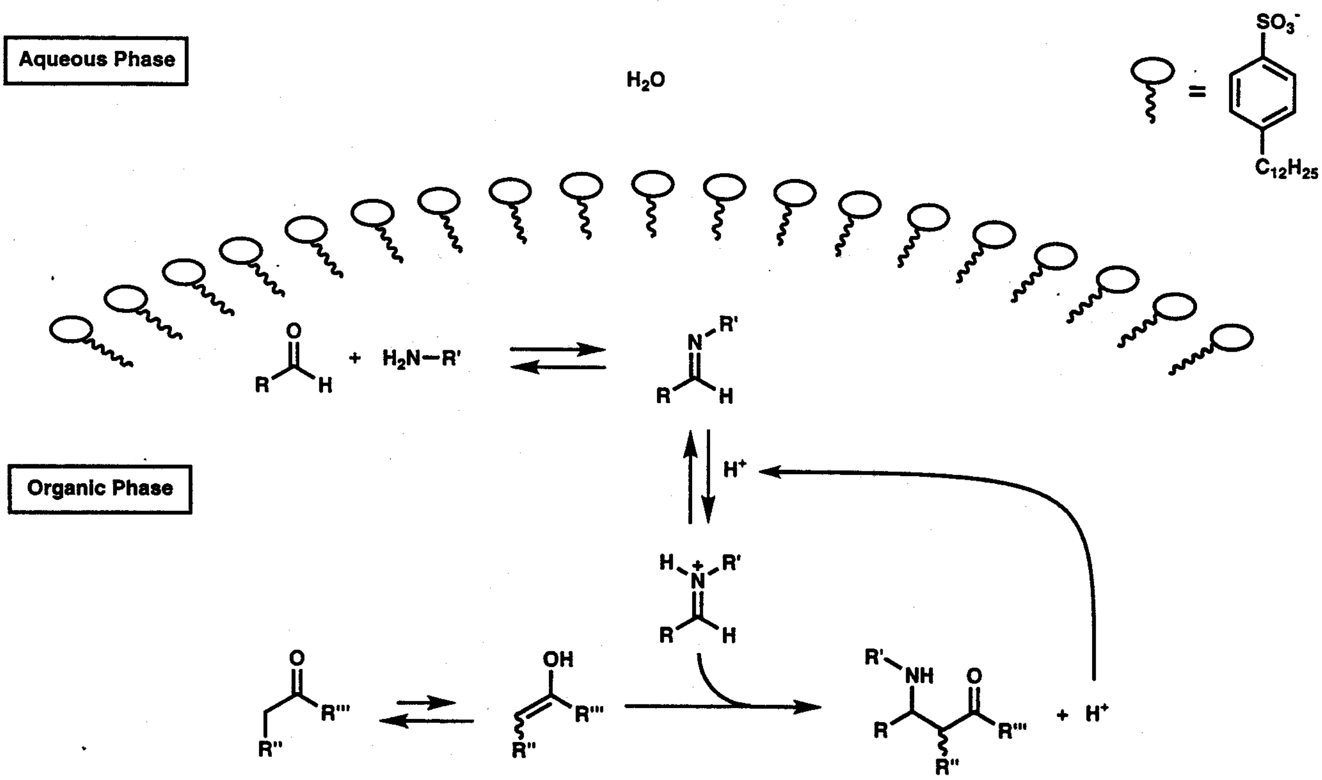
Mannich-Type Reactions in Water



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



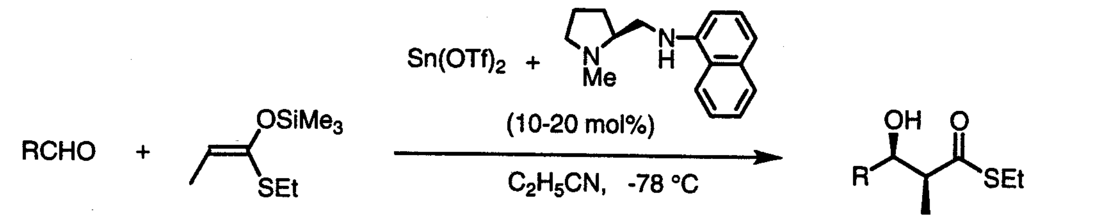
Catalytic Enantioselective Carbon-Carbon Bond-Forming Reactions in Aqueous Media

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

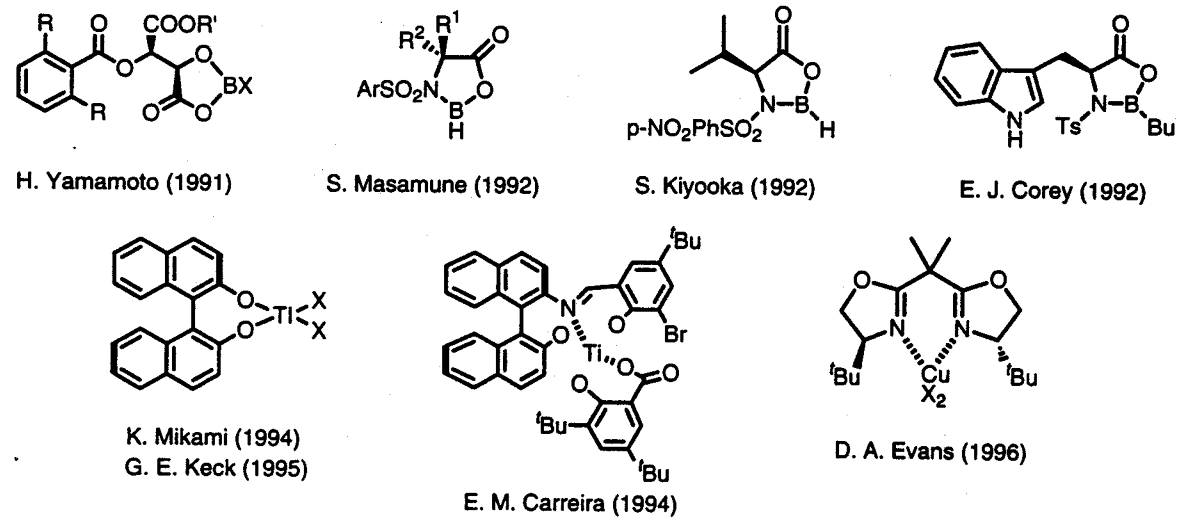
⇩

Challenging!!

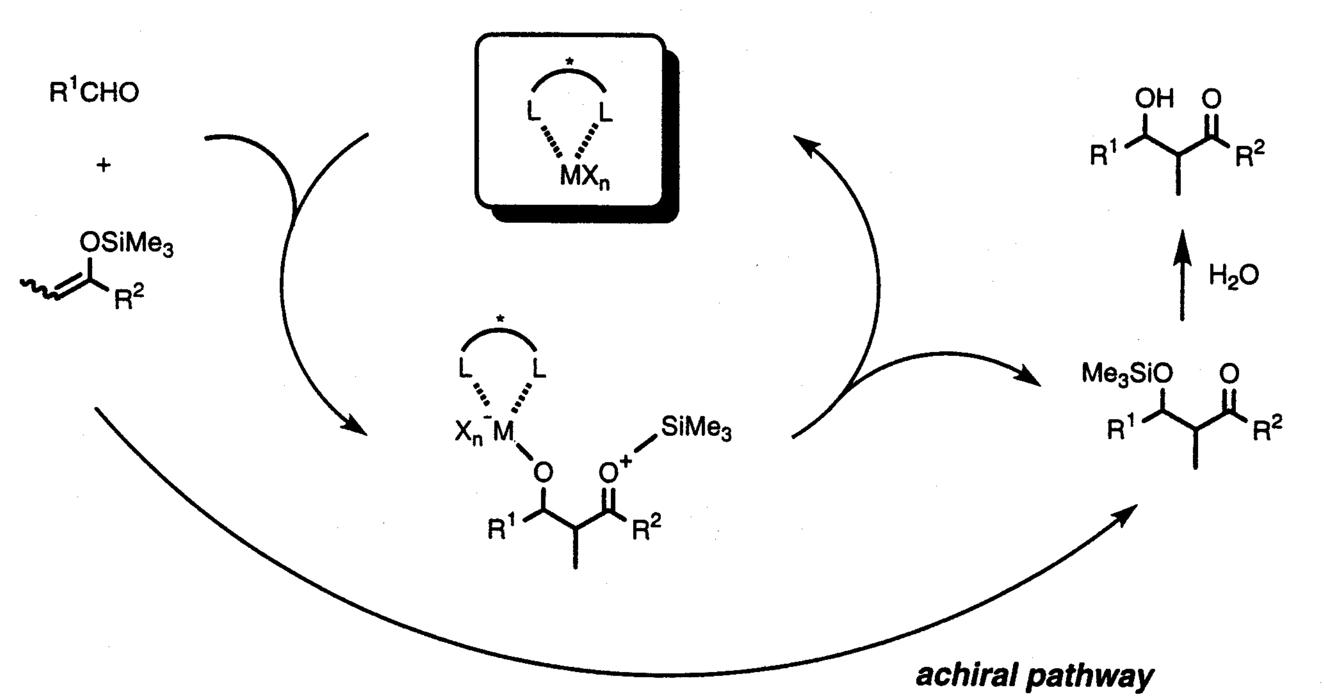
Asymmetric Aldol Reactions Using a Chiral Catalyst



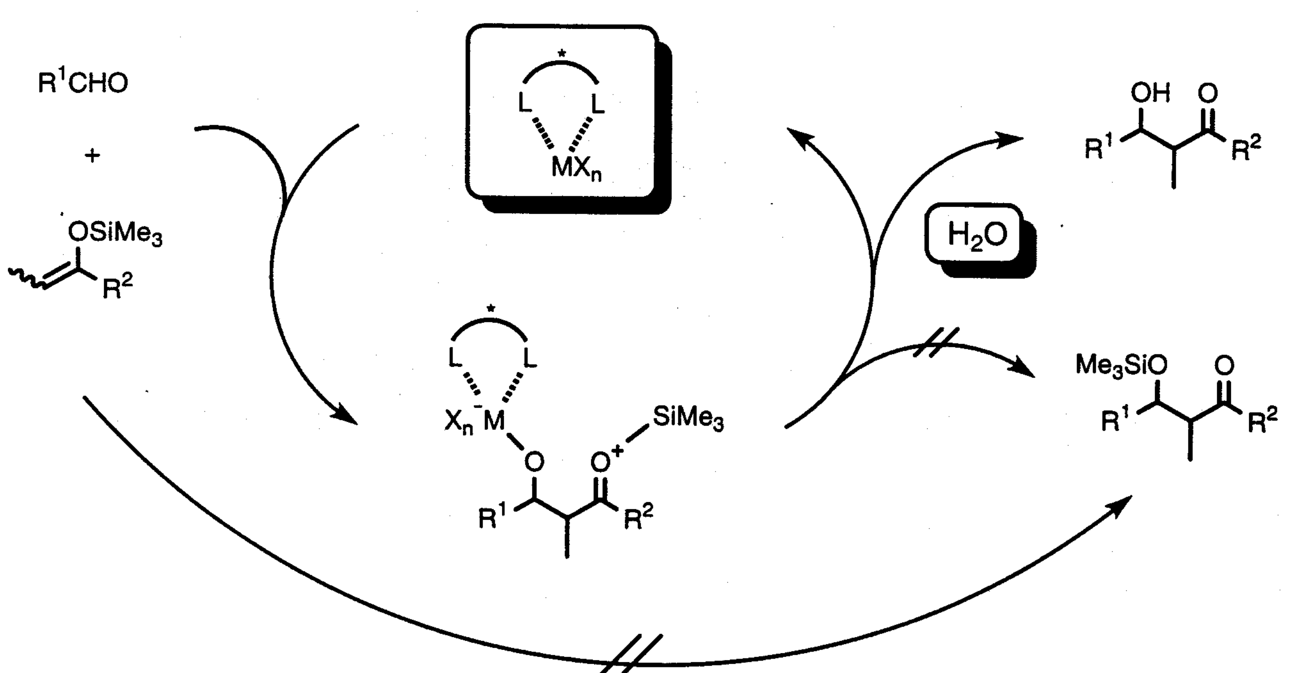
T. Mukaiyama, S. Kobayashi, *Chem. Lett.*, **1990**, 129; 1455.



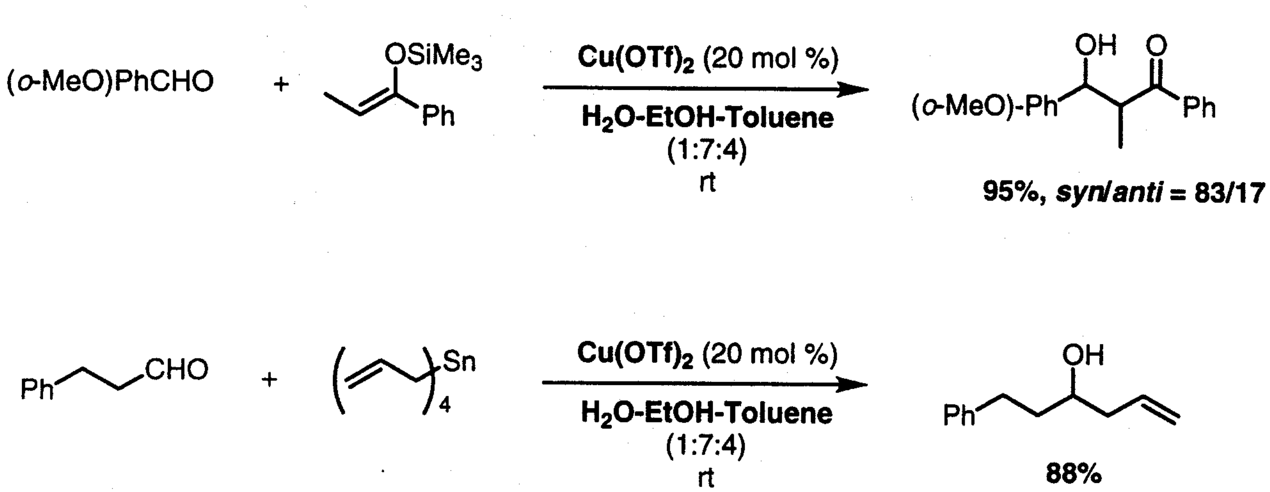
Assumed Catalytic Cycle of Aldol Reactions in Organic Solvents



Assumed Catalytic Cycle of Aldol Reactions in Water

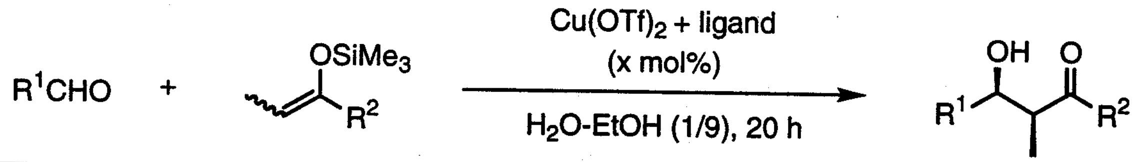


Cu(II)-Catalyzed C-C Bond-Forming Reactions in Aqueous Media



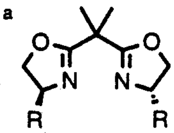
S. Kobayashi, S. Nagayama, T. Busujima, *Chem. Lett.* **1997**, 959.

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**

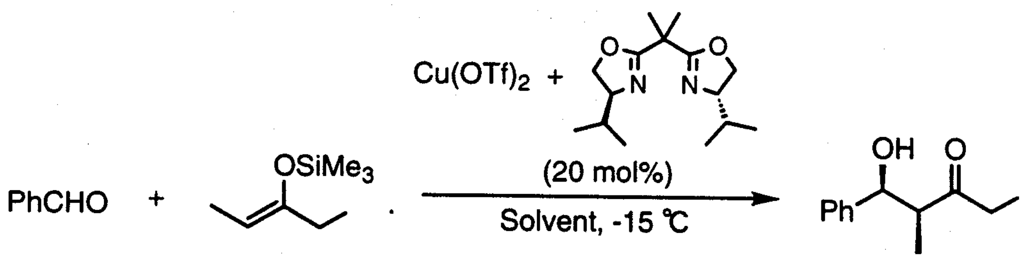
a



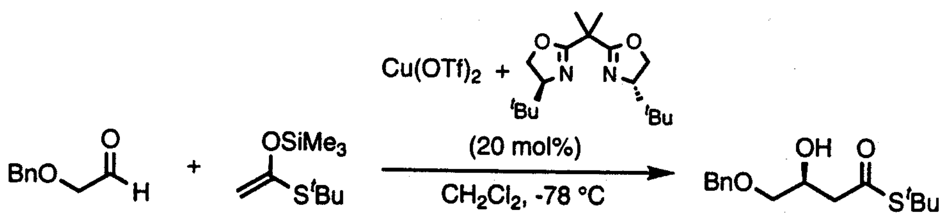
1: R = *i*-Pr
2: R = CH_2Ph

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

Effect of Solvents

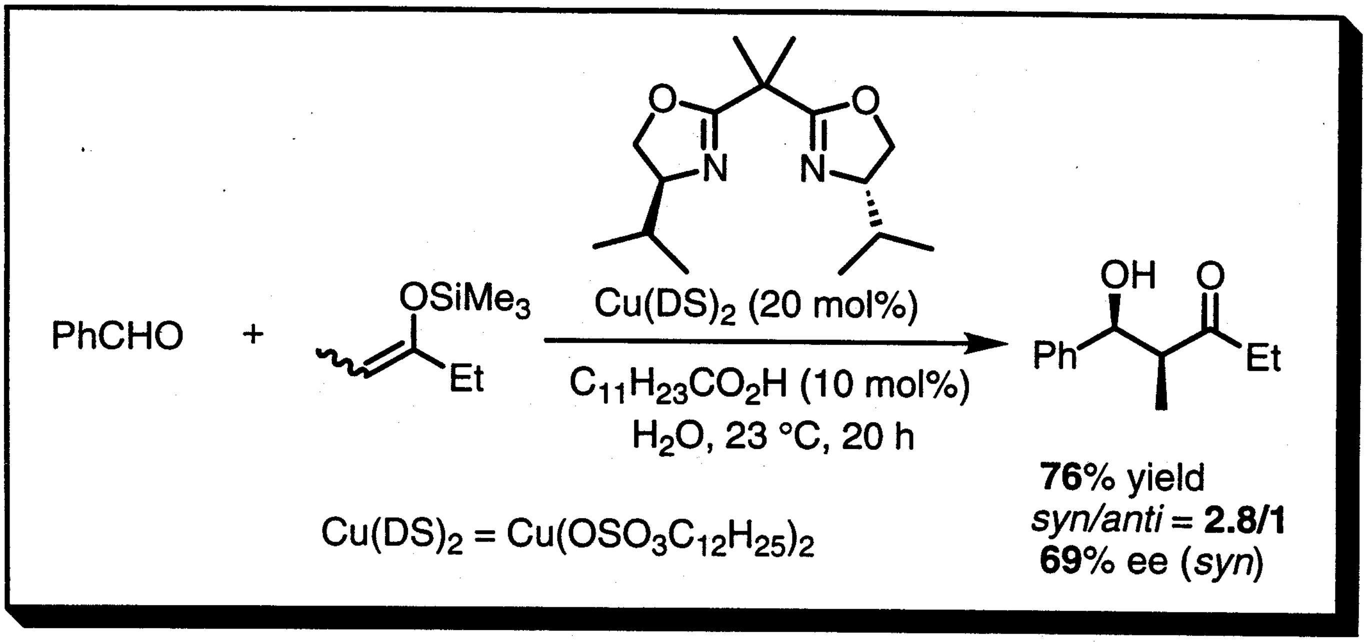


Solvent	Yield (%)	*syn/anti*	ee (%, *syn*)
CH_2Cl_2	**11**	**2.1/1**	**20 (2*R*,3*R*)**
H_2O/EtOH = 1/9	**81**	**3.5/1**	**81 (2*S*,3*S*)**

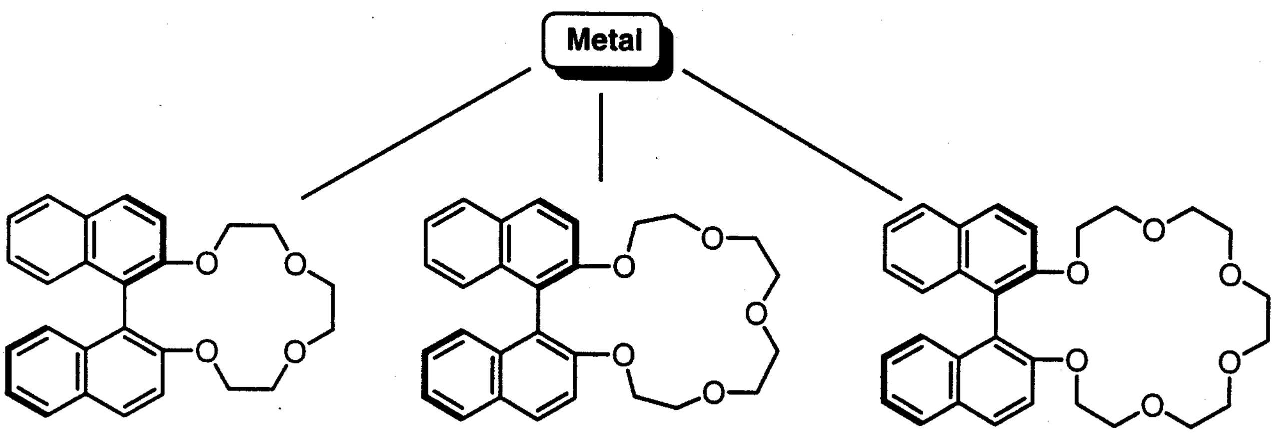


D. A. Evans *et al.*, *J. Am. Chem. Soc.* **1996**, *118*, 5814.

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



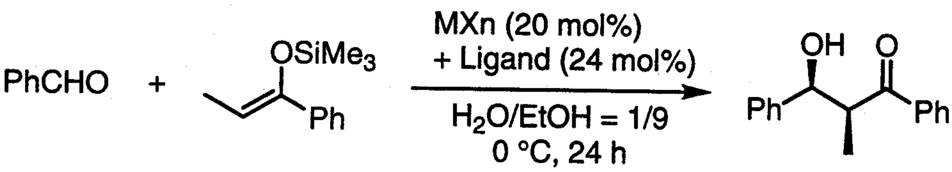
Metal-Chiral Crown Ether Complexes as Chiral Lewis Acids

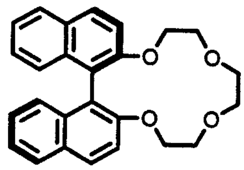


1 2 3

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

Effect of Metal-Ligand Combinations





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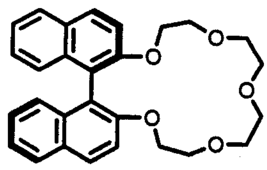

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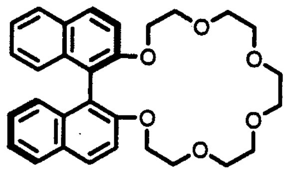
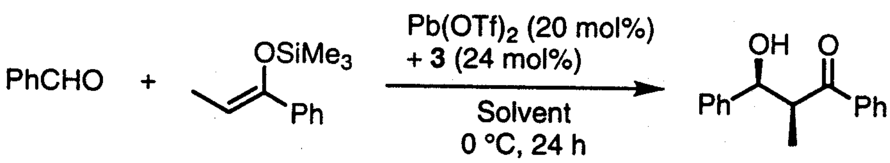


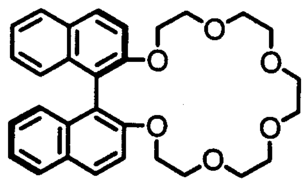
3

MXn	Ligand	Yield (%)	*syn*/*anti*	ee (%)[a]
$Zn(OTf)_2$	**1**	88	69/31	2
$Cu(OTf)_2$	**1**	86	87/13	0
$Sc(OTf)_3$	**2**	75	52/48	1
$Yb(OTf)_3$	**2**	74	63/37	1
AgOTf	**3**	61	75/25	5
$Pb(OTf)_2$	**3**	**62**	**90/10**	**55**
$Pb(OTf)_2$	**1**	78	89/11	0
$Pb(OTf)_2$	**2**	92	89/11	0

[a]Ee of *syn*-adduct.

Effect of Solvents[a]



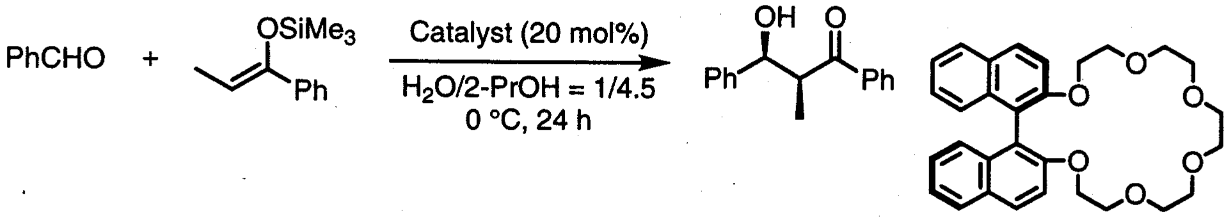


3

Solvent	Yield (%)	*syn*/*anti*	ee (%)[a]
H_2O/EtOH = 1/9	62	90/10	62
H_2O/EtOH = 1/4.5	92	88/12	57
H_2O/EtOH = 1/1	19	87/13	53
H_2O/2-PrOH = 1/9	92	91/9	62
H_2O/2-PrOH = 1/4.5	89	91/9	69
H_2O/*tert*-BuOH = 1/9	76	89/11	62
H_2O	4	70/30	15
H_2O-SDS (35 mM)	20	89/11	56
CH_2Cl_2	10	80/20	-8

[a]Ee of *syn*-adduct.

Comparison of $Pb(OTf)_2$- and $Pb(OTf)_2$-3-Catalyzed Reactions

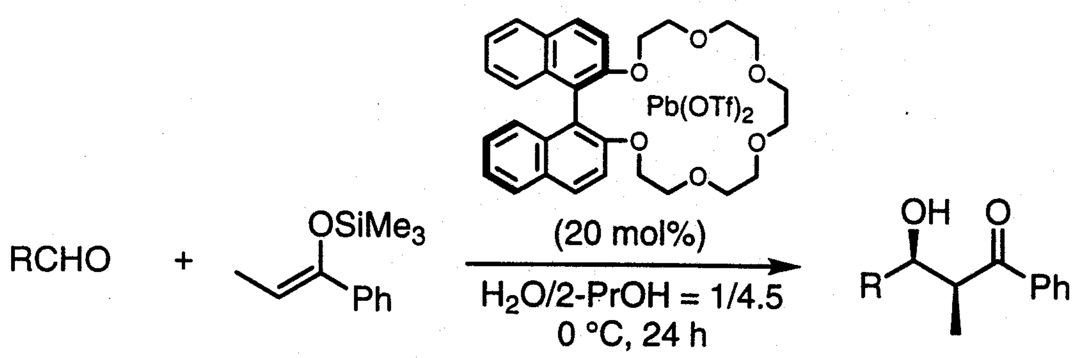


3

Time (h)	$Pb(OTf)_2$		$Pb(OTf)_2$-**3**		
	Yield (%)	*syn*/*anti*	Yield (%)	*syn*/*anti*	ee (%)[a]
3	15	85/15	14	92/8	67
6	33	86/14	34	92/8	68
9	47	85/15	47	92/8	68
24	87	85/15	89	91/9	69

[a]Ee of *syn*-adduct.

Pb-Crown Ether-Catalyzed Asymmetric Aldol Reactions



R	Yield (%)	*syn*/*anti*	ee (%)
Ph	**89**	**91/9**	**69**
C_5H_{11}	**82**	**92/8**	**80**
C_8H_{17}	**79**	**90/10**	**82**
$(CH_3)_2CHCH_2$	**99 (88)**	**94/6 (93/7)**	**87 (85)**[a]
$(CH_3)_2CH$	**65**	**90/10**	**78**

[a]10 mol%.

$Pb(OTf)_2$-Crown Ether 3 (X-ray)