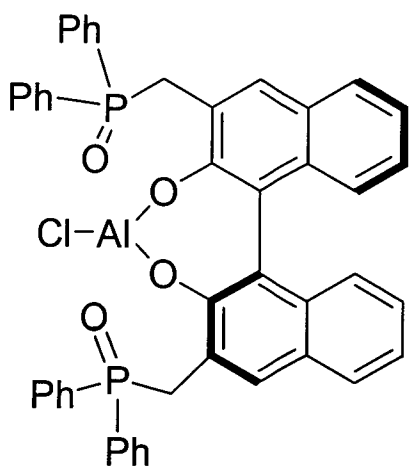
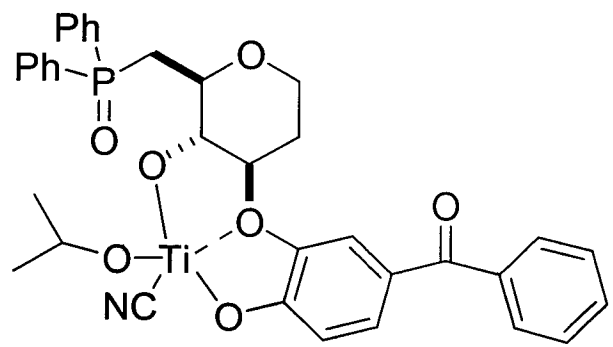
Multifunctional Asymmetric Catalysis

Selected Works of Masakatsu Shibasaki





Justin I. Montgomery

February 20, 2001

CATALYSIS

Chemist	vs.	Nature
• Conventional catalysts activate one side of a substrate.		• Enzymes activate both sides of a substrate AND control the orientation of the substrate with strategically placed functional groups in an asymmetric environment!

Advantage: Nature

Solution: Design catalysts that enhance the reactivity of substrates while securing their position in space – Chemzymes!

Lewis Acid – Brønsted Base Bifunctional Catalysis
Michael Reaction

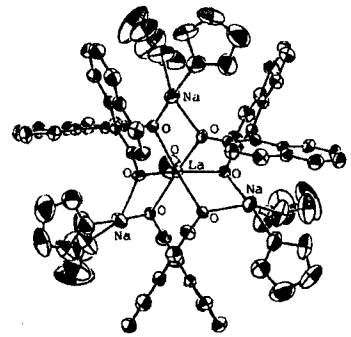
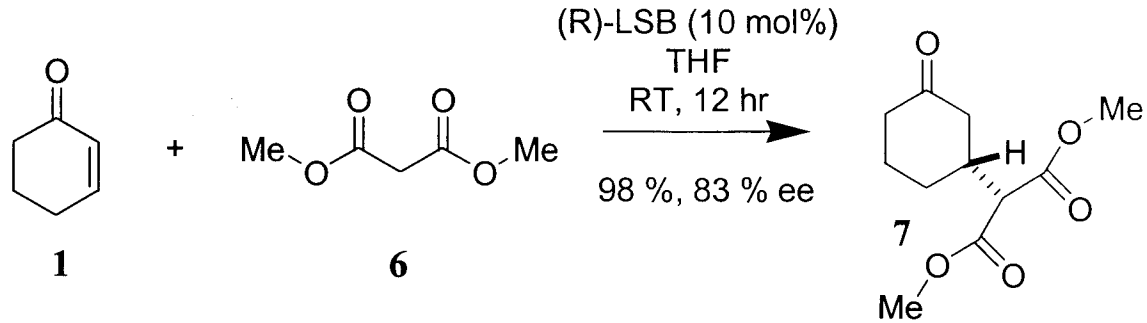


Figure 1. ORTEP representation of $LaNa_3tris((R)$-binaphthoxy)$\cdot 6THF\cdot H_2O$ ((R)-LSB).

(R)-LSB

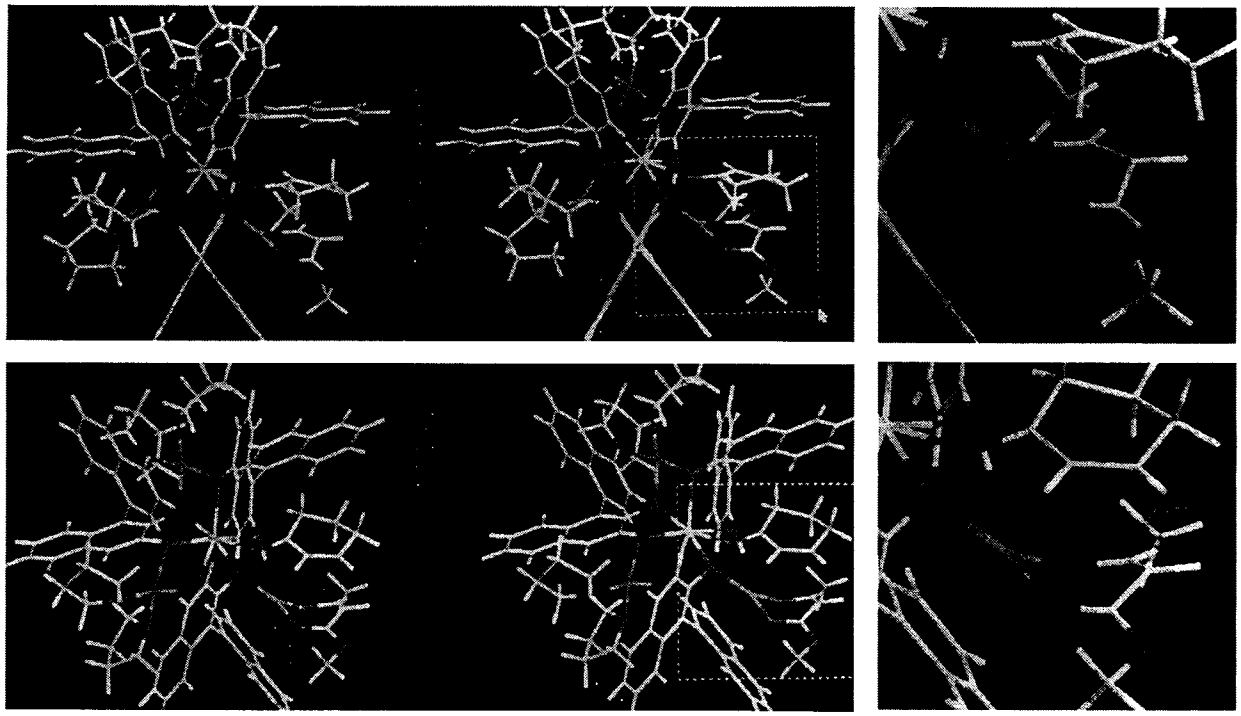


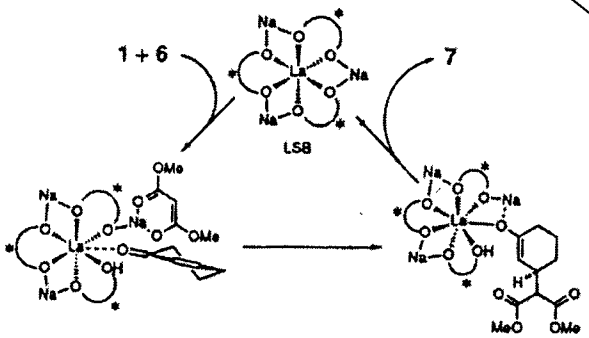
Favorable

$\Delta E = 4.9$ kcal/mol

(Rappe's Universal Forcefield Calculation)

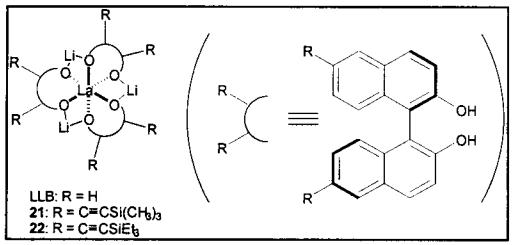
Unfavorable

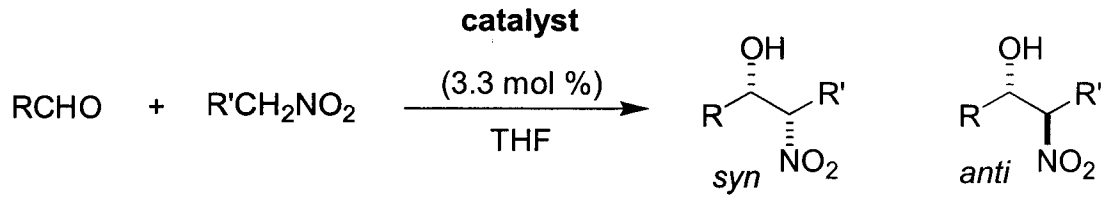




H. Sasai, T. Arai, Y. Satow, K.N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194.

Catalytic Asymmetric Henry Reaction





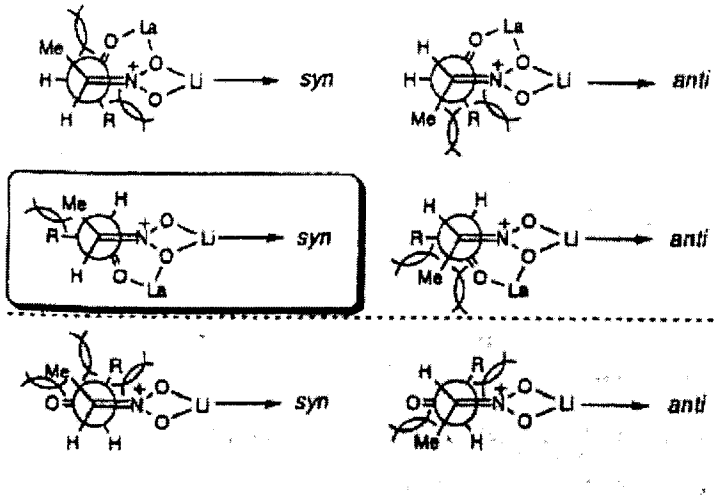
1: R = $PhCH_2CH_2$ **25**: R' = CH_3
28: R = $CH_3(CH_2)_4$ **29**: R' = Et
32: R' = CH_2OH

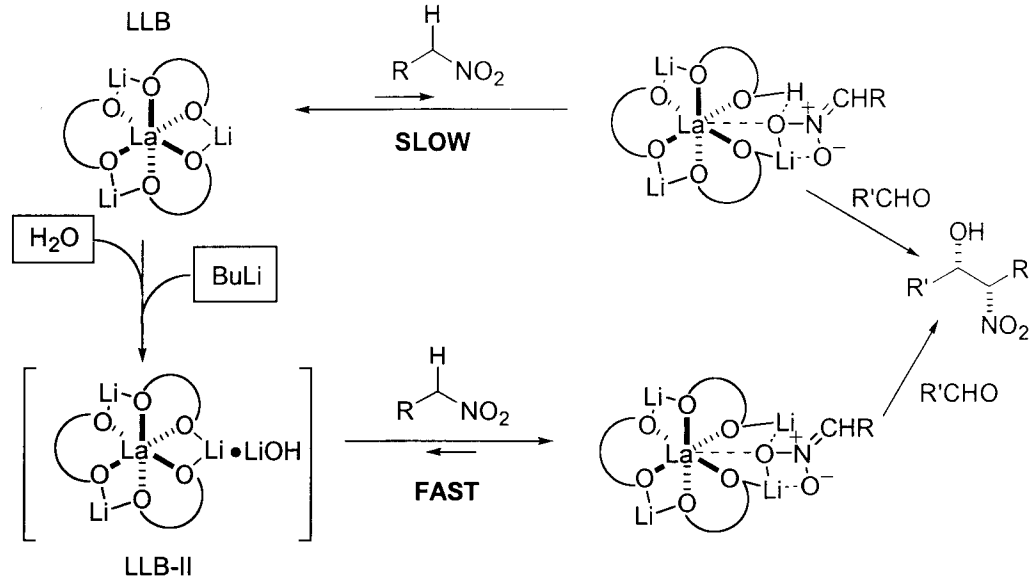
26 (*syn*), **27** (*anti*): R = $PhCH_2CH_2$, R' = CH_3
30 (*syn*), **31** (*anti*): R = $PhCH_2CH_2$, R' = Et
33 (*syn*), **34** (*anti*): R = $PhCH_2CH_2$, R' = CH_2OH
35 (*syn*), **36** (*anti*): R = $CH_3(CH_2)_4$, R' = CH_2OH

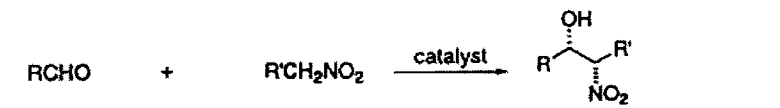
Entry	Aldehyde	Nitroalkane	Catalyst	Time (h)	Temp (°C)	Nitroaldols	Yield (%)	*syn/anti*	ee of *syn* (%)
1	1	25	LLB	75	-20	26 + 27	79	74 : 26	66
2	1	25	21	75	-20	26 + 27	72	85 : 15	92
3	1	25	22	75	-20	26 + 27	70	89 : 11	93
4	1	29	LLB	138	-40	30 + 31	89	85 : 15	87
5	1	29	22	138	-40	30 + 31	85	93 : 7	95
6	1	32	LLB	111	-40	33 + 34	62	84 : 16	66
7	1	32	22	111	-40	33 + 34	97	92 : 8	97
8	28	32	LLB	93	-40	35 + 36	79	87 : 13	78
9	28	32	22	93	-40	35 + 36	96	92 : 8	95

M. Shibasaki, *Enantiomer* **1999**, *4*, 513.
H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388.

Proposed Mechanism and Improved Catalyst







5: R = C_6H_{11}
1: R = $PhCH_2CH_2$

41: R' = H
25: R' = CH_3
29: R' = Et
32: R' = CH_2OH

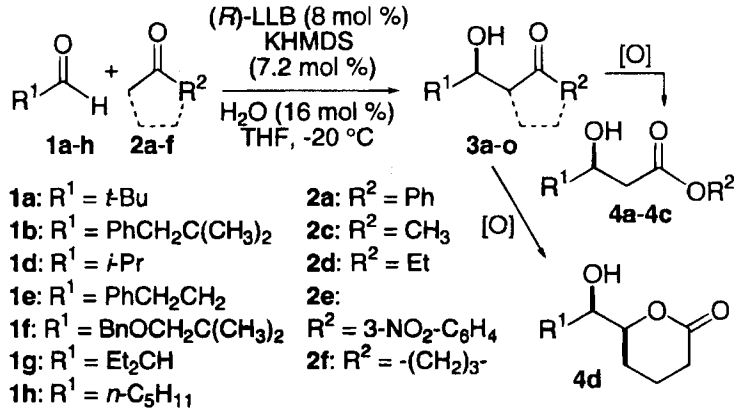
6: R = C_6H_{11}, R' = H
26: R = $PhCH_2CH_2$, R' = CH_3
30: R = $PhCH_2CH_2$, R' = Et
33: R = $PhCH_2CH_2$, R' = CH_2OH

Entry	Substrate	Catalyst[a] (mol%)	Time (h)	Temp (°C)	Product	Yield (%) (*syn*/*anti*)	ee (%) of *syn*
1	5 + 41	LLB (1)	24	−50	6	5.6	88
2	5 + 41	LLB-II (1)	24	−50	6	73	89
3	5 + 41	LLB-II (3.3)	4	−50	6	70	90
4	1 + 25	22 (1)	113	−30	26	25 (70/30)	62
5	1 + 25	22-II (1)	113	−30	26	83 (89/11)	94
6	1 + 29	22 (1)	166	−40	30	trace	—
7	1 + 29	22-II (1)	166	−40	30	84 (95/5)	95
8	1 + 32	22 (1)	154	−50	33	trace	—
9	1 + 32	22-II (1)	154	−50	33	76 (94/6)	96

[a]LLB-II: LLB + H_2O (1 mol equiv) + BuLi (0.9 mol equiv); 22-II: 22 + H_2O (1 mol equiv) + BuLi (0.9 mol equiv).

M. Shibasaki, *Enantiomer* **1999**, *4*, 513.
H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388.

Direct Catalytic Asymmetric Aldol Reaction

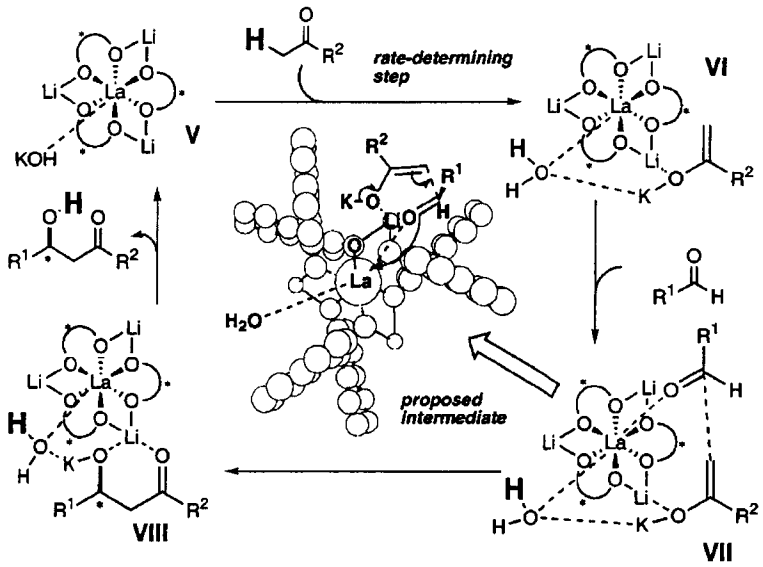


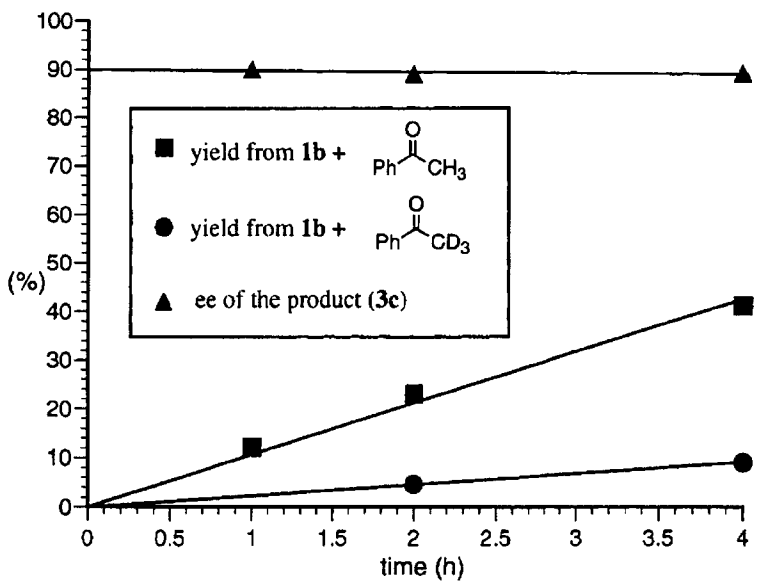
entry	aldehyde (R^1)	ketone[a] (R^2) (equiv)	aldol	time (h)	yield (%)	ee (%)	yield of ester[b]
1	**1a**	**2a** (5)	**3a**	15	75	88	
2	**1b**	**2a** (5)	**3c**	28	85	89	**4a**: 80%[c]
3	**1b**	**2c** (10)	**3g**	20	62	76	
4[d]	**1b**	**2d** (15)	**3i**	95	72	88	
5	**1f**	**2a** (5)	**3j**	36	91	90	
6[e]	**1f**	**2a** (5)	**3j**	24	70	93	**4b**: 73%[f]
7[g]	**1d**	**2a** (5)	**3e**	15	90	33	
8[h]	**1d**	**2e** (3)	**3k**	70	68	70	**4c**: 80%[i]
9[j]	**1g**	**2e** (3)	**3l**	96	60	80	
10[h,k]	**1h**	**2e** (5)	**3m**	96	55	42	
11[l]	**1e**	**2e** (3)	**3n**	31	50	30	
12	**1b**	**2f** (5)	**3o**	99	95	76/88	**4d**: 85%[c]
				(*syn*/*anti* = 93/7)		(*syn*/*anti*)	

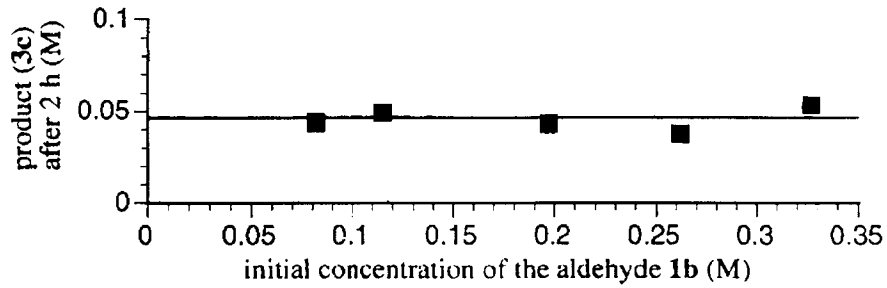
[a] Excess of ketone was recovered after reaction. [b] The yield from aldol product **3**. See ref 28. [c] Conditions: $SnCl_4$ (cat.), $(TMSO)_2$, ligand **8** (cat.), MS 4 Å, CH_2Cl_2. [d] 8 mol % of H_2O was used. [e] The reaction was carried out in 5.7 mmol (**1f**) scale. [f] Conditions: *m*CPBA, NaH_2PO_4, DCE. [g] The reaction was carried out at −30 °C. [h] The reaction was carried out at −50 °C. [i] Conditions: (i) PtO_2, H_2, MeOH; (ii) ZCl, Na_2CO_3, MeOH−H_2O; (iii) $SnCl_4$ (cat.), $(TMSO)_2$, ligand **8** (cat.), MS 4 Å, CH_2Cl_2. R^2 (**4c**) = 3-ZNH-C_6H_4. [j] Conditions: (*R*)-LLB (15 mol %), KHMDS (13.5 mol %), H_2O (30 mol %), −45 °C. [k] Conditions: (*R*)-LLB (30 mol %), KHMDS (27 mol %), H_2O (60 mol %). [l] The reaction was carried out at −40 °C.

N. Yoshikawa, Y.M.A. Yamada, J. Das, H, Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.

Mechanistic Studies







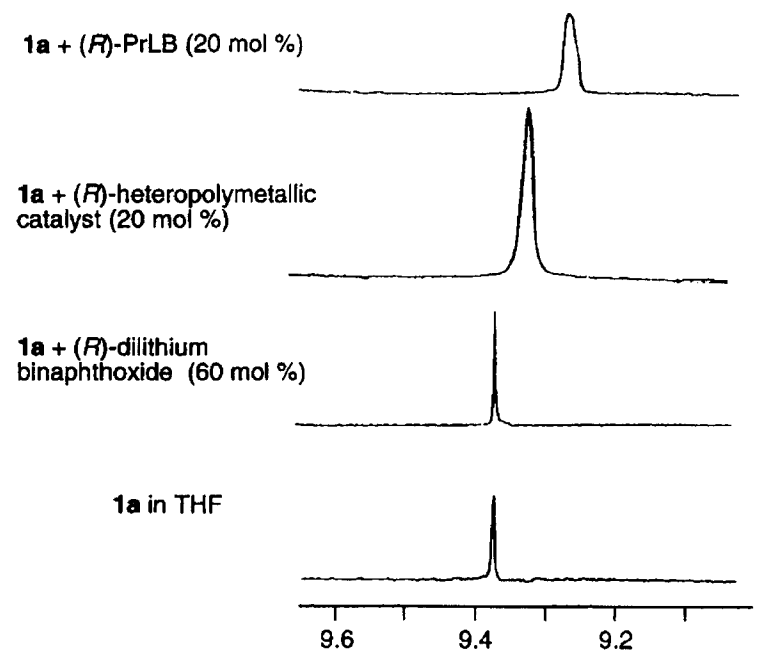
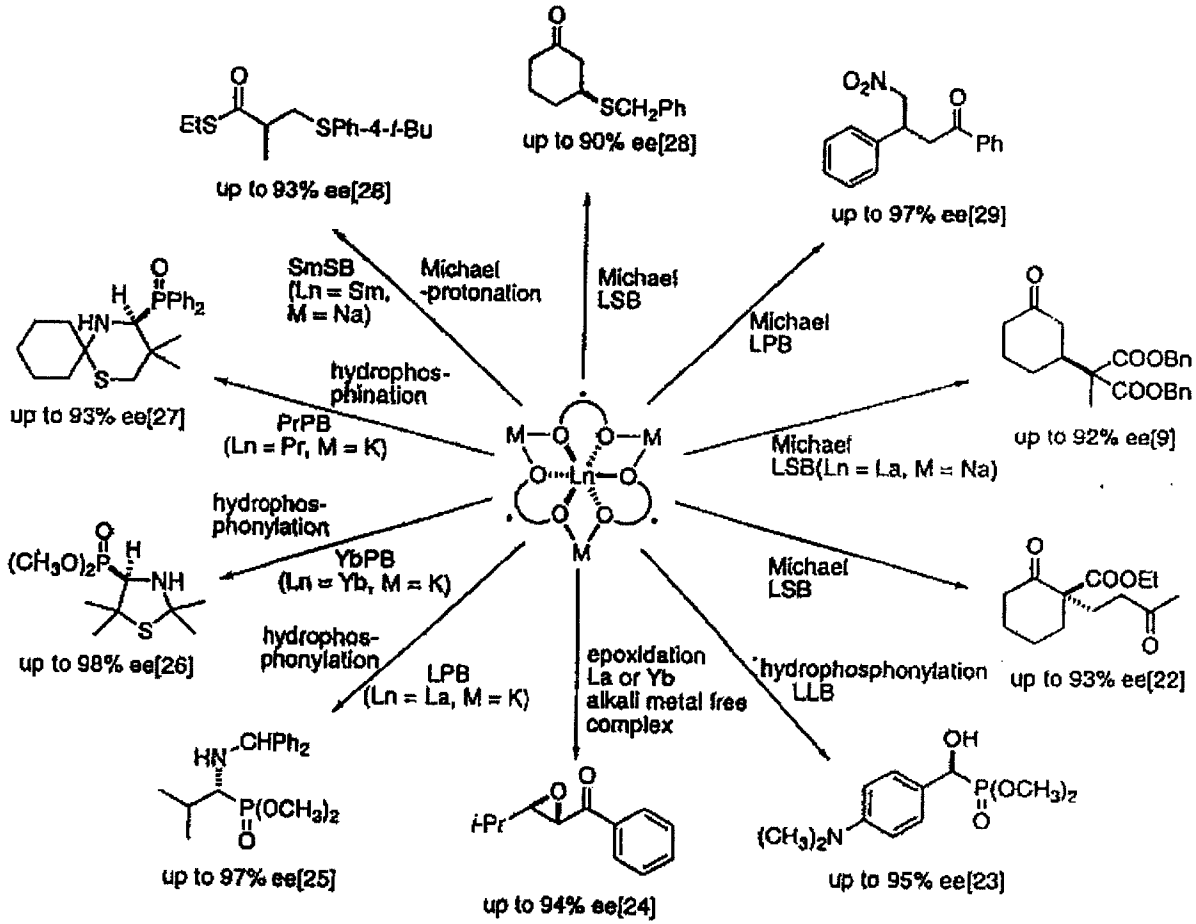


Figure 5. Chemical shift of formyl hydrogen in **1a**.

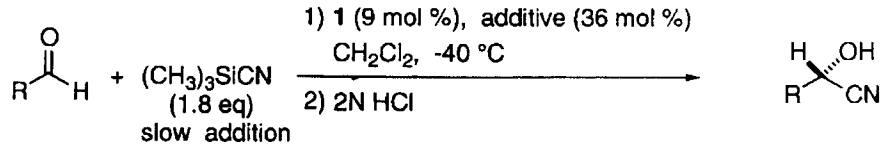
N. Yoshikawa, Y.M.A. Yamada, J. Das, H, Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.

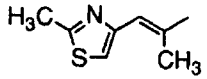
Other Catalytic Asymmetric Reactions Promoted by Heterobimetallic Complexes

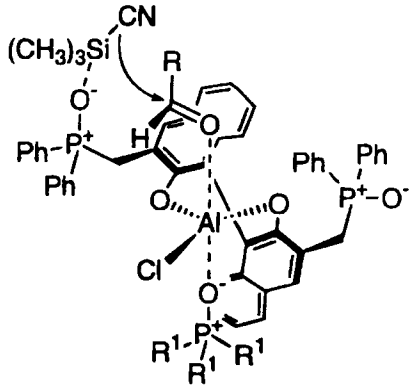


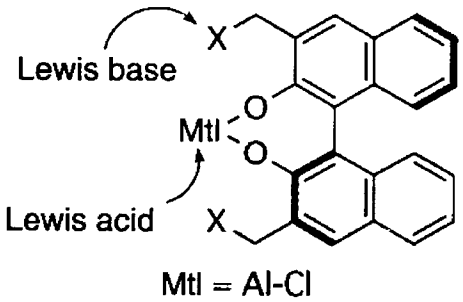
M. Shibasaki, *Enantiomer* **1999**, *4*, 513.

Lewis Acid – Lewis Base Bifunctional Catalysis
Asymmetric Cyanosilylation of Aldehydes



Entry	R	Aldehyde	Product	Additive	Time (h)	Yield (%)	Ee (%)[a]	*S/R*
1	$Ph(CH_2)_2$	**11a**	**12a**	$Bu_3P(O)$	37	97	97	*S*
2	$CH_3(CH_2)_5$	**11b**	**12b**	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	**11c**	**12c**	$Bu_3P(O)$	45	96	90	*S*
4	$(CH_3CH_2)_2CH$	**11d**	**12d**	$Bu_3P(O)$	60	98	83	*S*
5	*trans*-$CH_3(CH_2)_3CH{=}CH_2$	**11e**	12e	$Bu_3P(O)$	58	94	97	–[e]
6	$PhCH{=}CH$	**11f**	**12f**	$Bu_3P(O)$	40	99	98	*S*
7[b]		**11g**	**12g**	$Bu_3P(O)$	50	97	99	*S*
8[c]	Ph	**11h**	**12h**	$CH_3P(O)Ph_2$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	**11i**	**12i**	$CH_3P(O)Ph_2$	79	87	90	*S*
10[d]		**11j**	**12j**	$CH_3P(O)Ph_2$	70	86	95	*S*

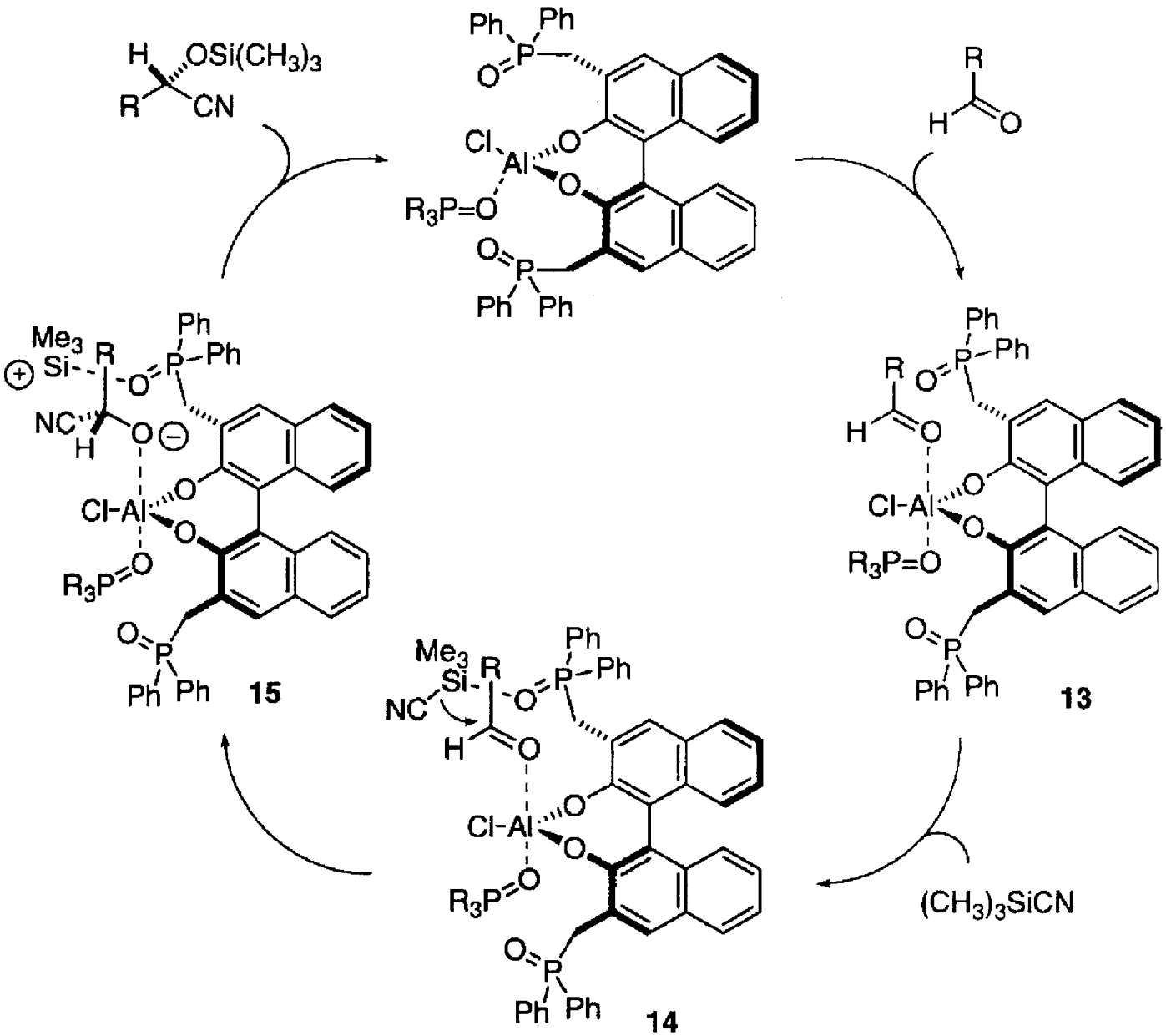




1: X = $P(O)Ph_2$
2: X = PPh_2
3: X = SEt
4: X = $CH_2P(O)Ph_2$
5: X = $CHPh_2$
6: X = $P(O)(PhN(CH_3)_2\text{-}p)_2$

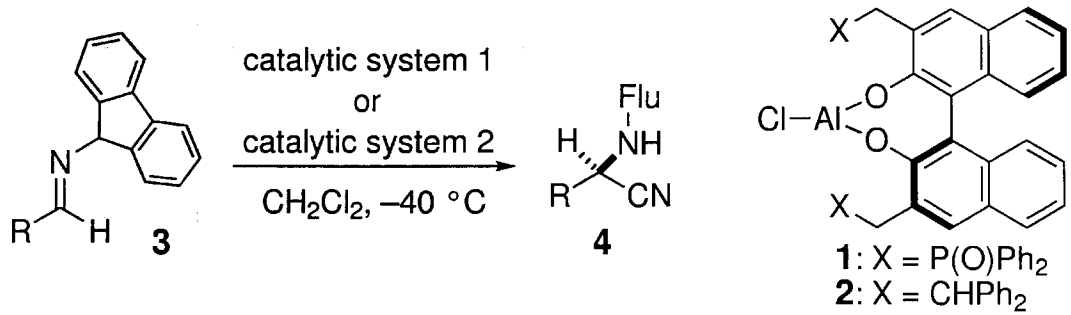
Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805.
Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641.
Review on Cyanohydrins in Nature and the Laboratory: R.J.H. Gregory, *Chem. Rev.* **1999**, *99*, 3649.

Proposed Mechanism



Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805.

Asymmetric Strecker-Type Reaction



Scheme 1. Catalytic system 1: **1** (9 mol%), TMSCN (2 mol equiv); PhOH (20 mol%, slow addition over 17 h). Catalytic system 2: **1** (9 mol%), TMSCN (20 mol%); HCN (1.2 mol equiv, slow addition over 24 h).

entry	R	**3a–m**	System 1 time [h]	System 1 yield [%][b]	System 1 *ee* [%][c]	System 2 time [h]	System 2 yield [%][b]	System 2 *ee* [%][c]
1	Ph	**a**	44	92	95	36	92	95
2	*p*-ClPh	**b**	44	92	95			
3	*p*-MeOPh	**c**	44	93	93			
4	1-naphthyl	**d**	68	95	89			
5	2-furyl	**e**	44	93	79			
6	3-furyl	**f**	44	92	90	36	92	87
7		**g**	58	90	89			
8	*trans*-PhCH=CH	**h**	41	80	96	36	78	92
9	*trans*-$CH_3(CH_2)_3CH{=}CH_2$	**i**	24	66	86[d]			
10	$CH_3(CH_2)_5$	**j**	24	80	80[e]	36	75	81
11	CH_3CH_2	**k**	44	84	70			
12	*i*Pr	**l**	44	89	72	36	92	71
13	*t*Bu	**m**	44	97	78	36	98	77

[a] See Experimental Section for the preparation of the catalyst and the general reaction procedure. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 50 mol% of PhOH was used. The aminonitrile was isolated as the corresponding trifluoroacetamide. [e] Without PhOH.

M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem., Int. Ed.* **2000**, *39*, 1650.

Kinetic Profile and Proposed Mechanism

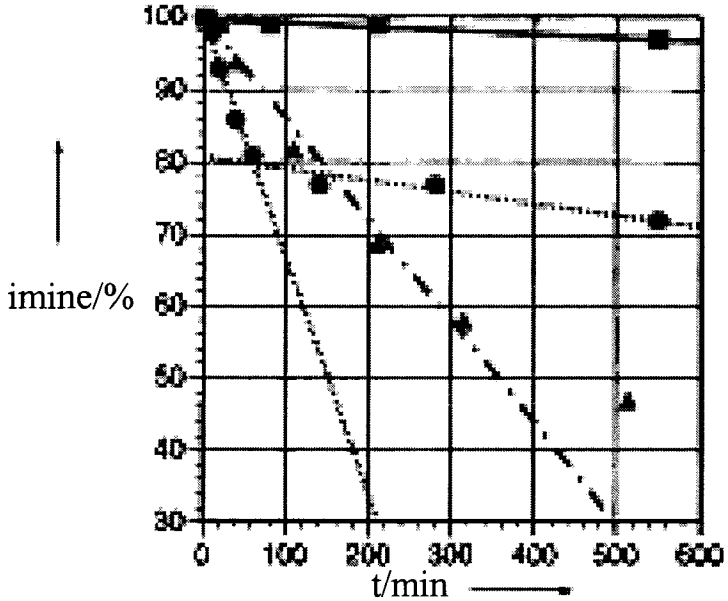
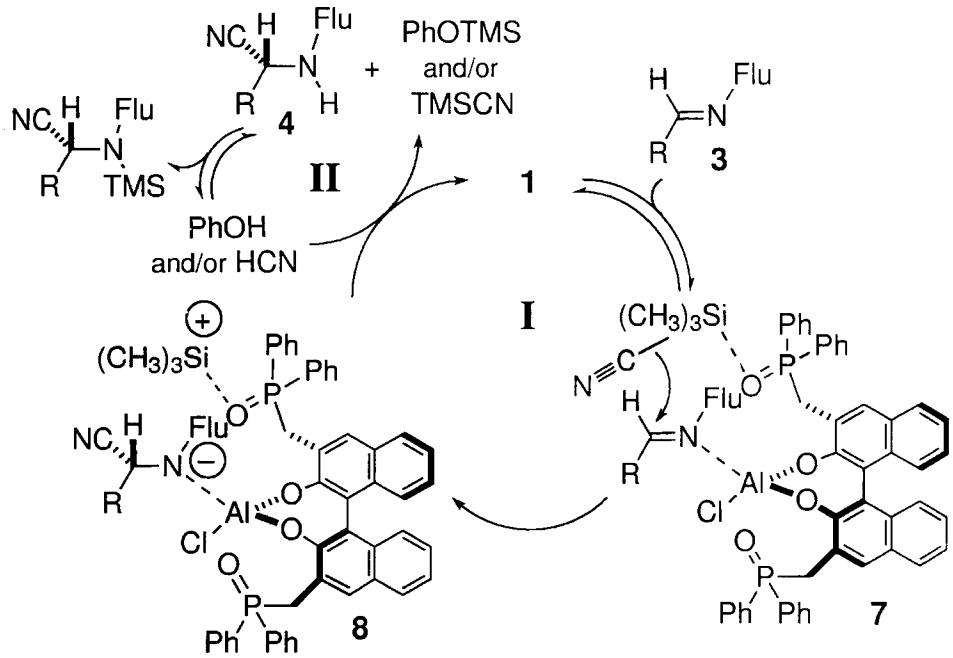
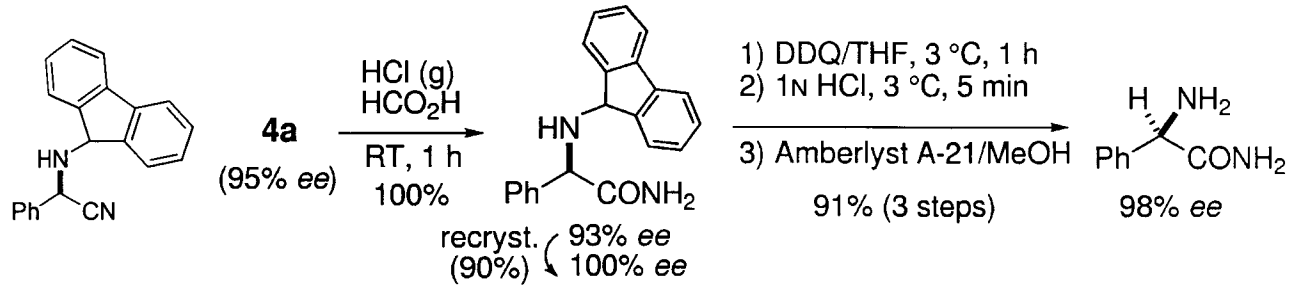


Figure 1. Initial reaction rate of **3a**. The disappearance of **3a** was monitored by ^{1}H NMR spectroscopy. For the experimental details, see the Supporting Information: the reaction of TMSCN in the absence (red ■) and in the presence of 20 mol% (blue ●) of PhOH, and the reaction of HCN (green ▲) are shown.

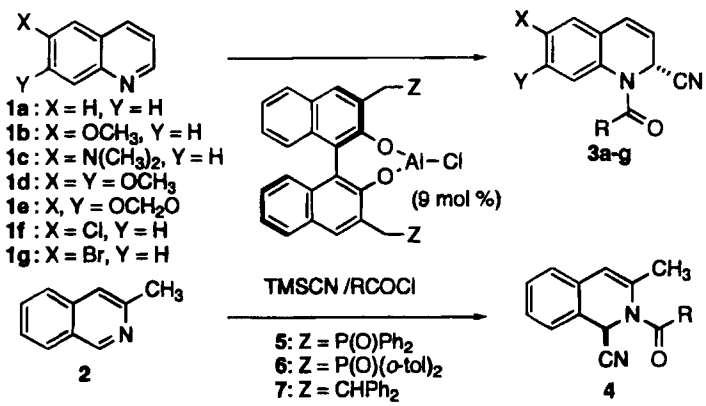


Conversion to α-amino acid derivatives



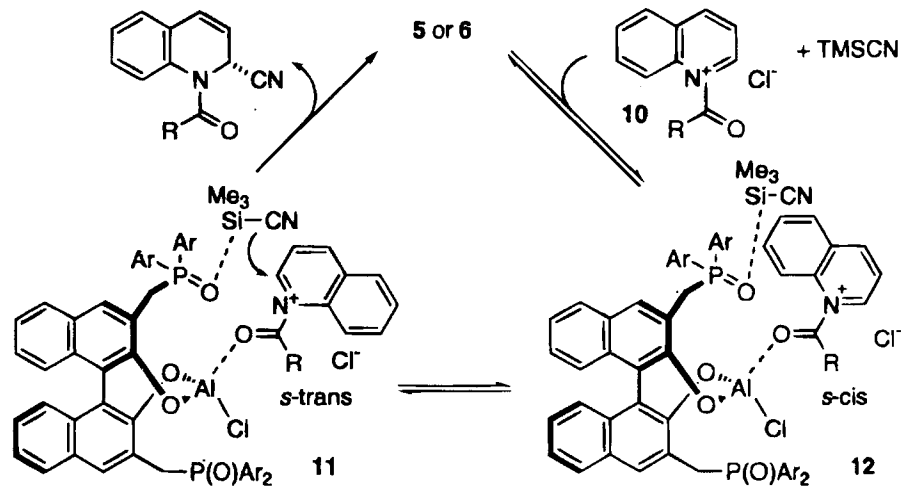
M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem., Int. Ed.* **2000**, *39*, 1650.
M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Chem. Pharm. Bull.* **2000**, *48*, 1586.

Asymmetric Reissert-type Reaction



entry	substrate	catalyst	solvent	R[b]	h	yield/%[c]	ee/%[d]
1	1a	5	CH_2Cl_2	Ph	24	70	71[i]
2	1a	5	CH_2Cl_2	2-furyl	48	58	73[i]
3	1a	5	CH_2Cl_2	o-MeOPh	24	68	64
4	1a	5	CH_2Cl_2	CH_3	24	42	58
5	1a	5	CH_2Cl_2	PhCH=CH	24	52	54
6	1a	5	CH_2Cl_2	1-naphthyl	24	63	46
7	1a	5	CH_2Cl_2/toluene[g]	Ph	24	27	78[i]
8	1a	5	CH_2Cl_2/pentane[g]	Ph	24	21	72[i]
9	1a	5	CH_3CN	Ph	24	67	37[i]
10	1a	6	CH_2Cl_2/toluene[g]	Ph	24	49	83[i]
11	1a	6	CH_2Cl_2/toluene[g]	2-furyl	64	91	85[i]
12	1b	6	CH_2Cl_2/toluene[g]	2-furyl	40	74	89
13[e]	1c	6	CH_2Cl_2/toluene[h]	2-furyl	40	72	89
14[e]	1d	6	CH_2Cl_2/toluene[g]	2-furyl	40	99	91
15[e]	1e	6	CH_2Cl_2/toluene[g]	2-furyl	60	77	83
16	1f	6	CH_2Cl_2	2-furyl	64	57	67
17	1g	6	CH_2Cl_2	2-furyl	112	63	67[i]
18[f]	2	5	CH_2Cl_2	CH_3	15	99	71

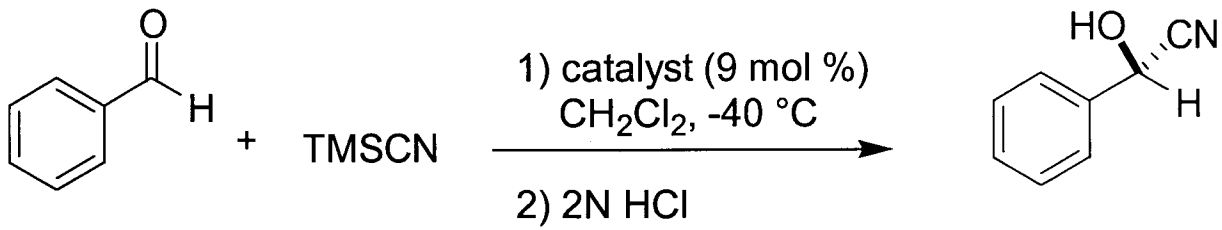
Proposed Catalytic Cycle

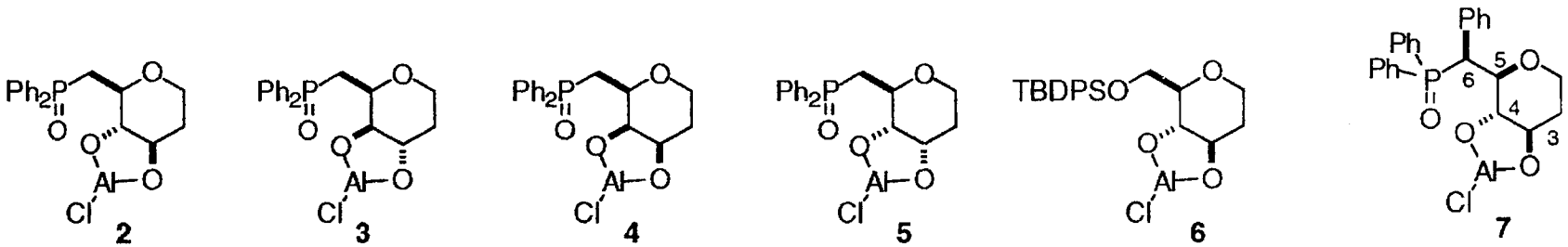


Slide 13
20-Feb-2001

M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327.

Carbohydrate Based Bifunctional Asymmetric Catalyst



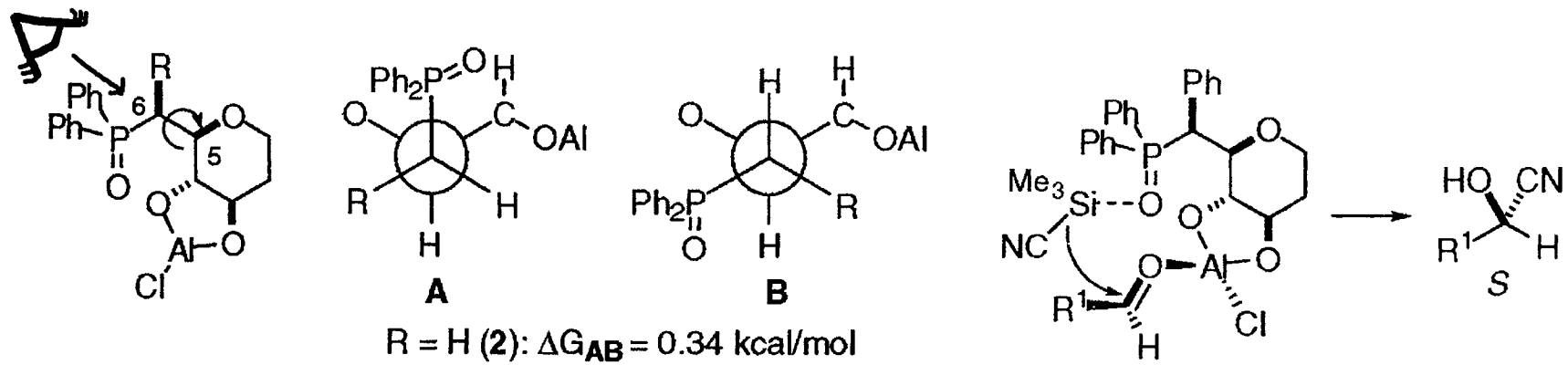


2	3	4	5	6	7
99% (21 h)	100% (69 h)	96% (38 h)	84% (23 h)	87% (96 h)	96% (50 h)
46% ee (*S*)	21% ee (*R*)	45% ee (*S*)	20% ee (*S*)	5% ee (*S*)	80% ee (S)

7 mol%
-60 °C

M. Kanai, Y. Hamashima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 2405.

Justification for Increased Enantioselectivity with C-6 Substitution



R = H (**2**): ΔG_{AB} = 0.34 kcal/mol

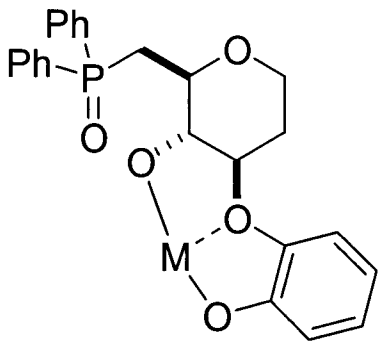
R = Ph (**7**): ΔG_{AB} = 4.2 kcal/mol

Computational Study

R=Ph favors desired conformation **A**

M. Kanai, Y. Hamashima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 2405.

Extension to Ketones: A New Carbohydrate-Based Catalyst



1

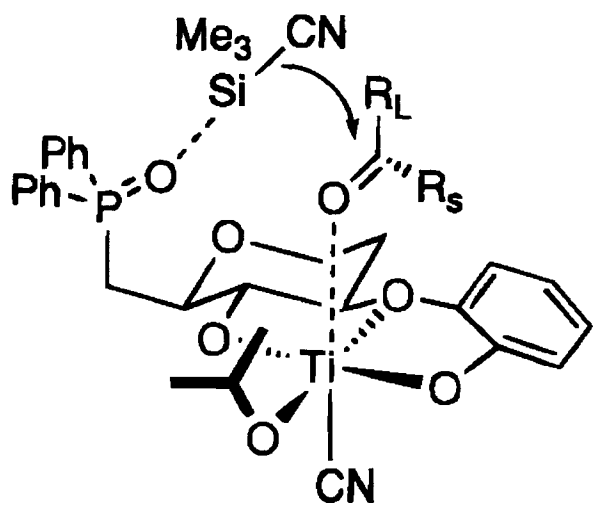
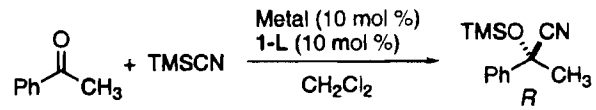
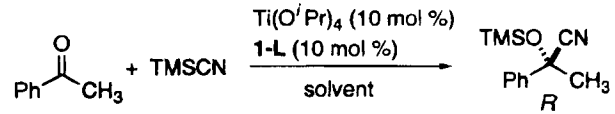


Table 1. Effect of Metals



entry	metal	temp/°C	time/h	yield/%	ee/%	*R*/*S*
1	Et_2AlCl	rt	48	0	-	-
2	$Yb(O^iPr)_3$	rt	2	90	18	*S*
3	$Zr(O^tBu)_4$	rt	36	52	14	*R*
4	$Ti(O^iPr)_4$	rt	48	78	35	*R*
5	$Ti(O^iPr)_4$	−20	36	44	73	*R*

Table 2. Effect of Solvents



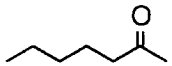
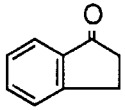
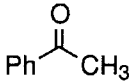
entry	solvent	conc/M	temp/°C	time/h	yield/%	ee/%
1	CH_2Cl_2	0.65	−20	36	44	73
2	toluene	0.65	−20	36	40	70
3	THF	0.65	−20	36	58	83
4	THF	3	−30	36	85	92

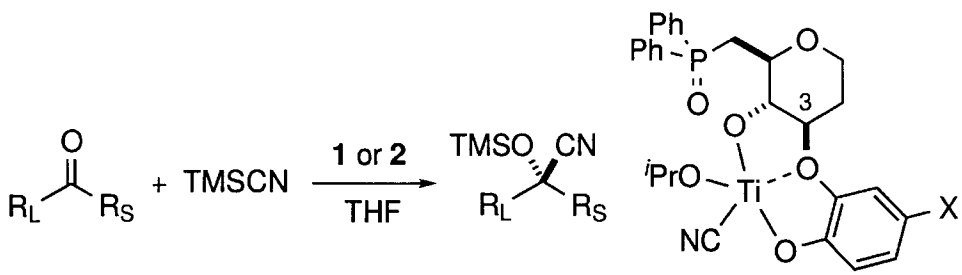
Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412.

Improvement of Enantioselectivity and Catalyst Turn-Over

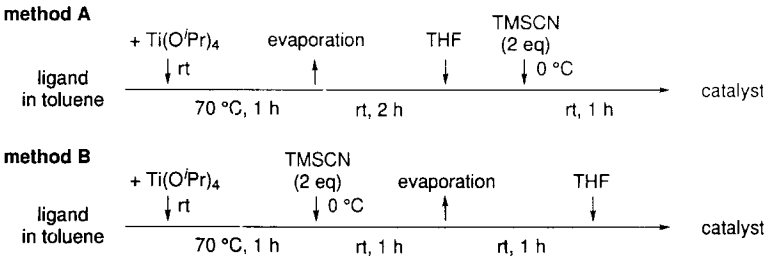
Experimental Design

- Ketone coordinates *syn* to phosphine oxide
- EWG will strengthen Ti-phenoxide bond

entry	ketone	catalyst (mol %) (method[a])	temp (°C)	time (h)	yield (%)	ee (%)
1	 **8a**	**1** (10) (A)	-50	36	88	76
2		**2** (10) (A)	-50	44	71	86
3	 **8b**	**1** (10) (A)	-40	96	72	69
4		**2** (10) (A)	-40	96	90	84
5	 **8c**	**1** (10) (A)	-30	36	85	92
6		**1** (1) (B)	-20	130	31	84
7		**2** (10) (A)	-30	44	76	97
8		**2** (5) (A)	-30	44	84	95
9		**2** (2.5) (A)	-30	48	84	96
10		**2** (1) (A)	-20	88	52	94
11		**2** (1) (B)	-20	88	92	94



1: X = H
2: X = COPh



Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691.

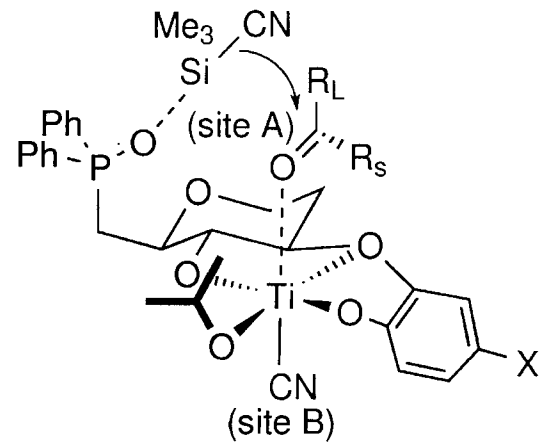
Proposed Transition State and Scope

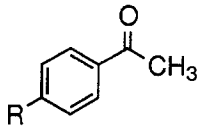
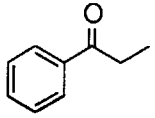
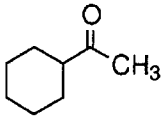
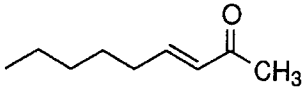
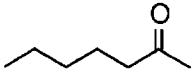
NMR Study

•Titanium cyanide does not act as a CN source

Importance of Phosphine Oxide

•Essential for favorable reactivity and enantioselection



entry	ketone		**2** (mol %) (method[a])	temp/°C	time/h	yield/%	ee/%
1		R = H **8c**	1 (B)	-20	88	92	94
2		R = Cl **8d**	1 (B)	-25	92	72	90
3		**8e**	1 (B)	-10	92	90	92
4		**8f**	2.5 (A)	-30	70	91	93
5		**8g**	2.5 (A)	-30	92	72	90
6		**8a**	2.5 (A)	-45	92	80	82

Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412.
Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691.

Conclusions

- Nature still wins but…
  - Chemists are making progress
- Benefits
  - High ee's for a range of products
  - Room for improvement with new research
  - Should have access to enantiomers
- Disadvantages
  - Long reaction times
  - No universal catalyst
  - Difficult substrates common