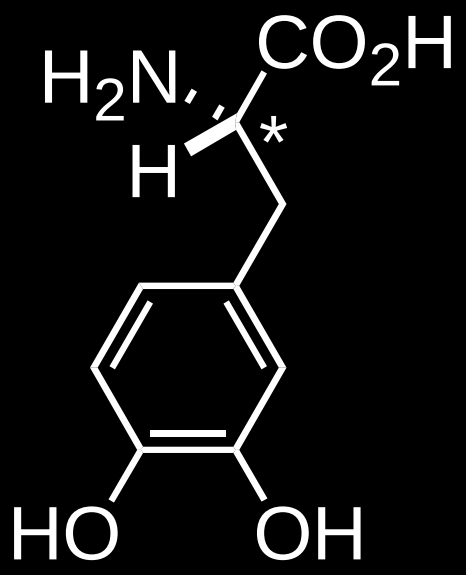
Global Focus on Knowledge

From the Big Bang to a Green Planet: The 13.7-Billion-Year Journey of Matter

Dec. 10: Matter and Manufacture

Masakatsu Shibazaki
Graduate School of Pharmaceutical Sciences
The University of Tokyo

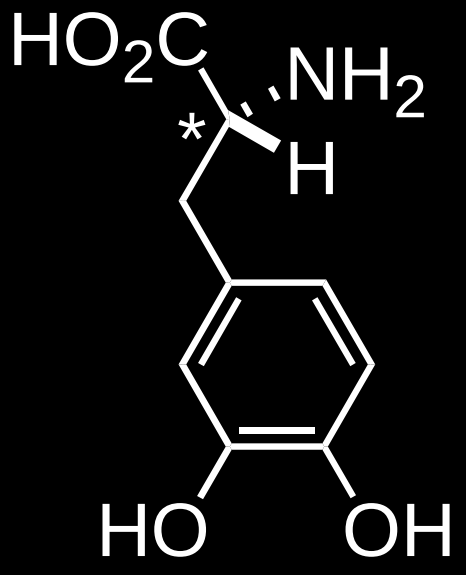
The Left-hand Substance and Right-hand Substance in Medicine



(*S*)-dopa

Anti-Parkinsons medication

Left-hand Substance



(*R*)-dopa

Toxicant

Right-hand Substance

The 2001 Nobel Prize in Chemistry

Catalytic Asymmetric Hydrogenation
Catalytic Asymmetric Oxidization

→ Functionality Change Reaction

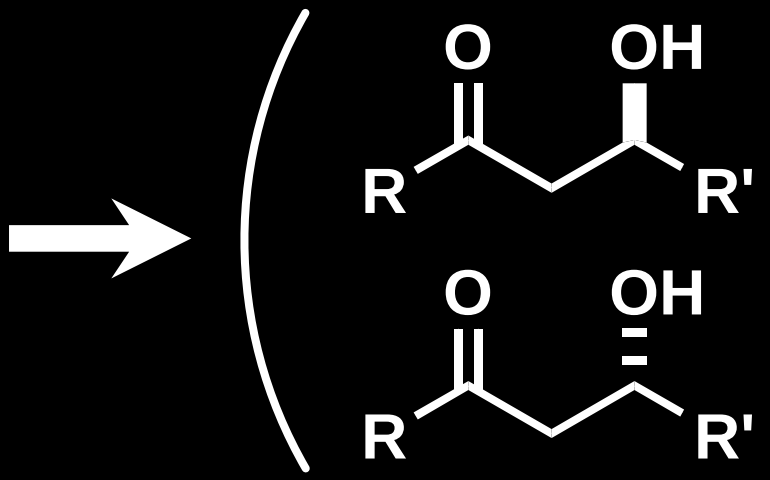
Catalytic Asymmetric Carbon—Carbon Bond Formative Reaction

→ Fundamental Reaction in Molecular Construction

A future Nobel laureate?

Aldol Reaction

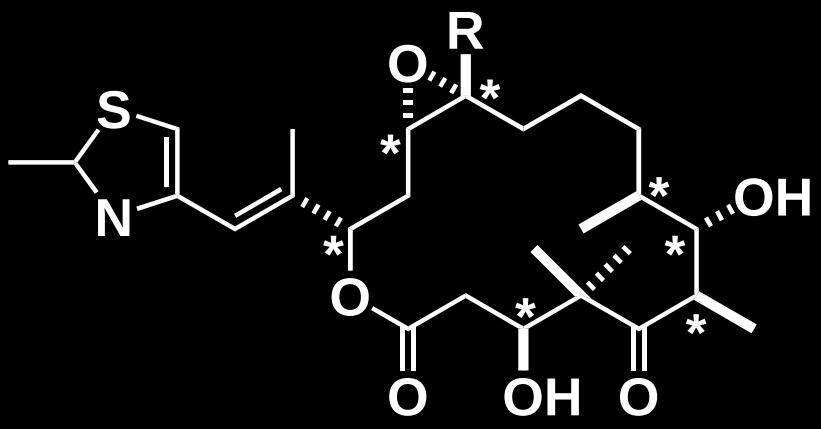
Important Synthetic Intermediates of Medicine



(Left-hand Substance)

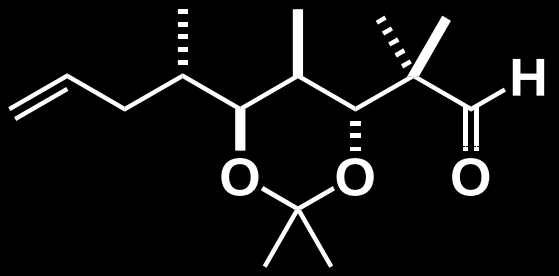
(Right-hand Substance)

Is catalytic asymmetric synthesis possible?



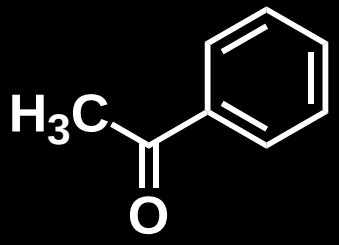
The epothilons
(R= H, Me)

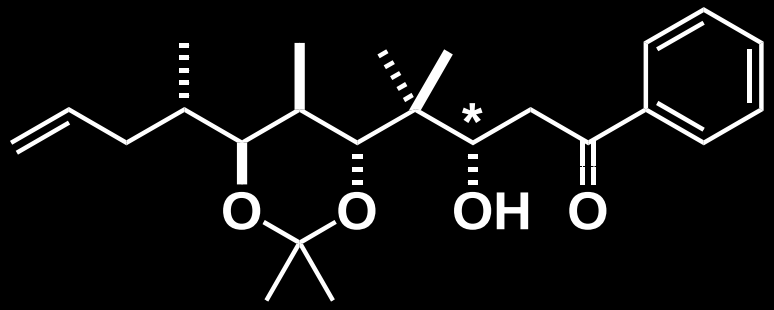
Promising anticancer agents:
against prostate cancer, etc.



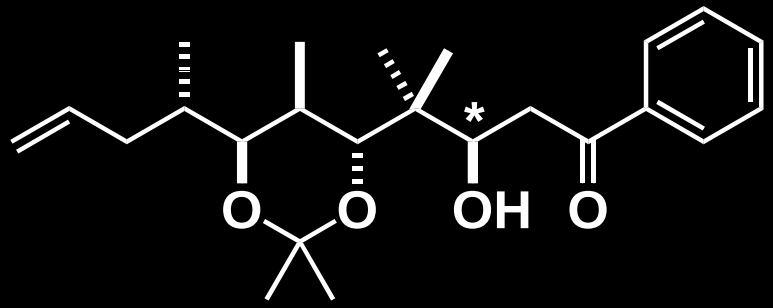
(Left-hand Substance)

Aldol Reaction



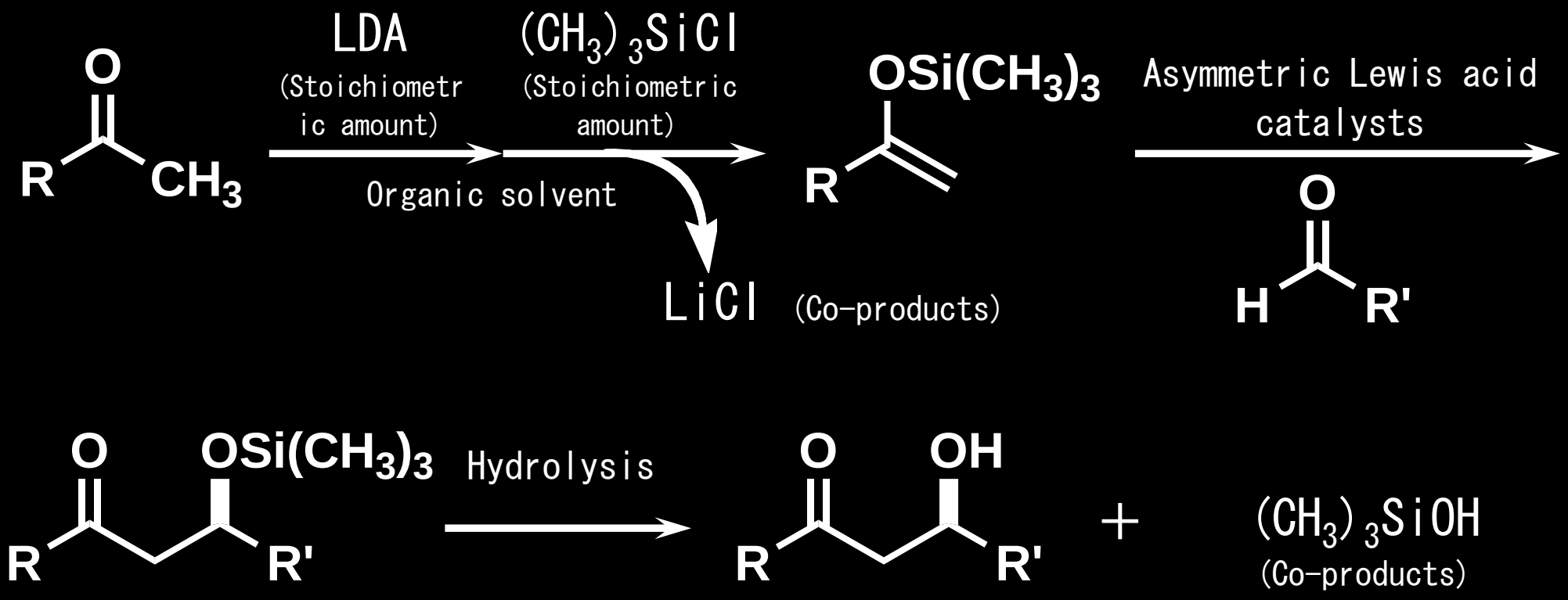


(Important synthesis intermediates of the epothilons)



(Impurities)

The Status of Catalytic Asymmetric Aldol Reactions in 2000



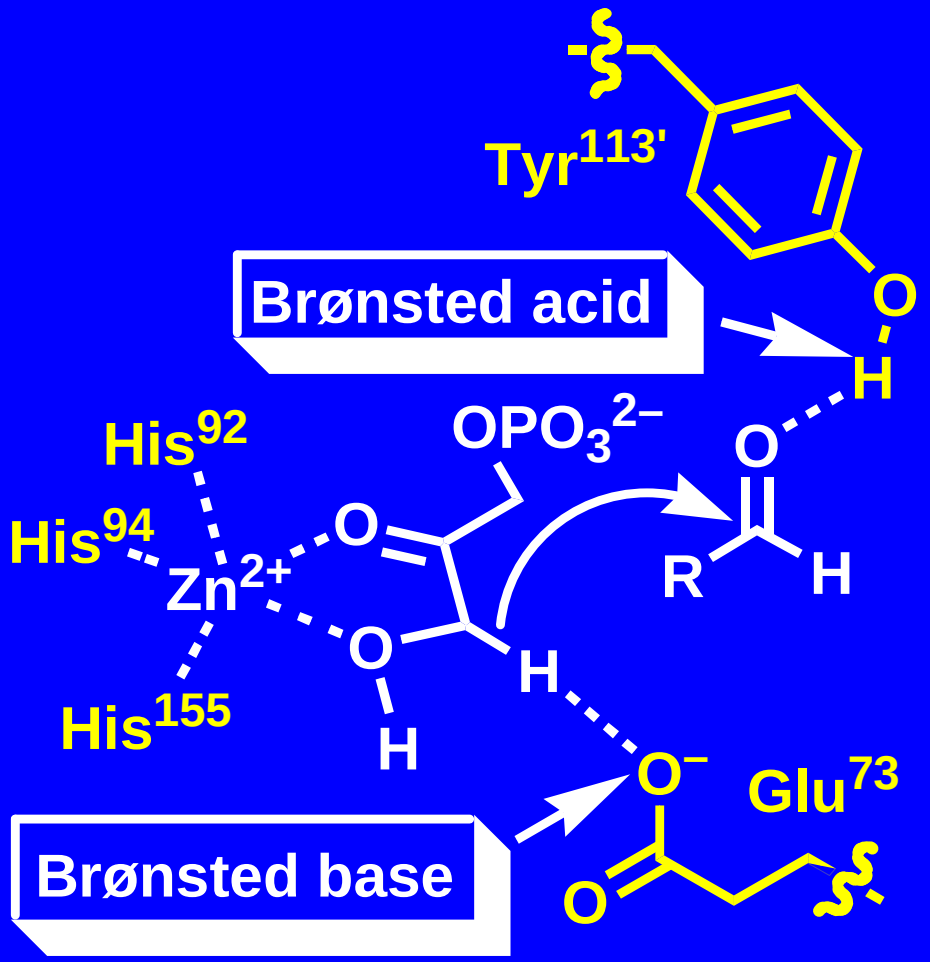
"A great amount of LiCl, (CH3)3SiOH and organic solvents, etc. accumulate."

The World's Most Advanced Sturdies

No co-products of LiCL and (CH3)3SiOH.

We will have many more difficulties than in the 20th century to realize ideal organic syntheses.

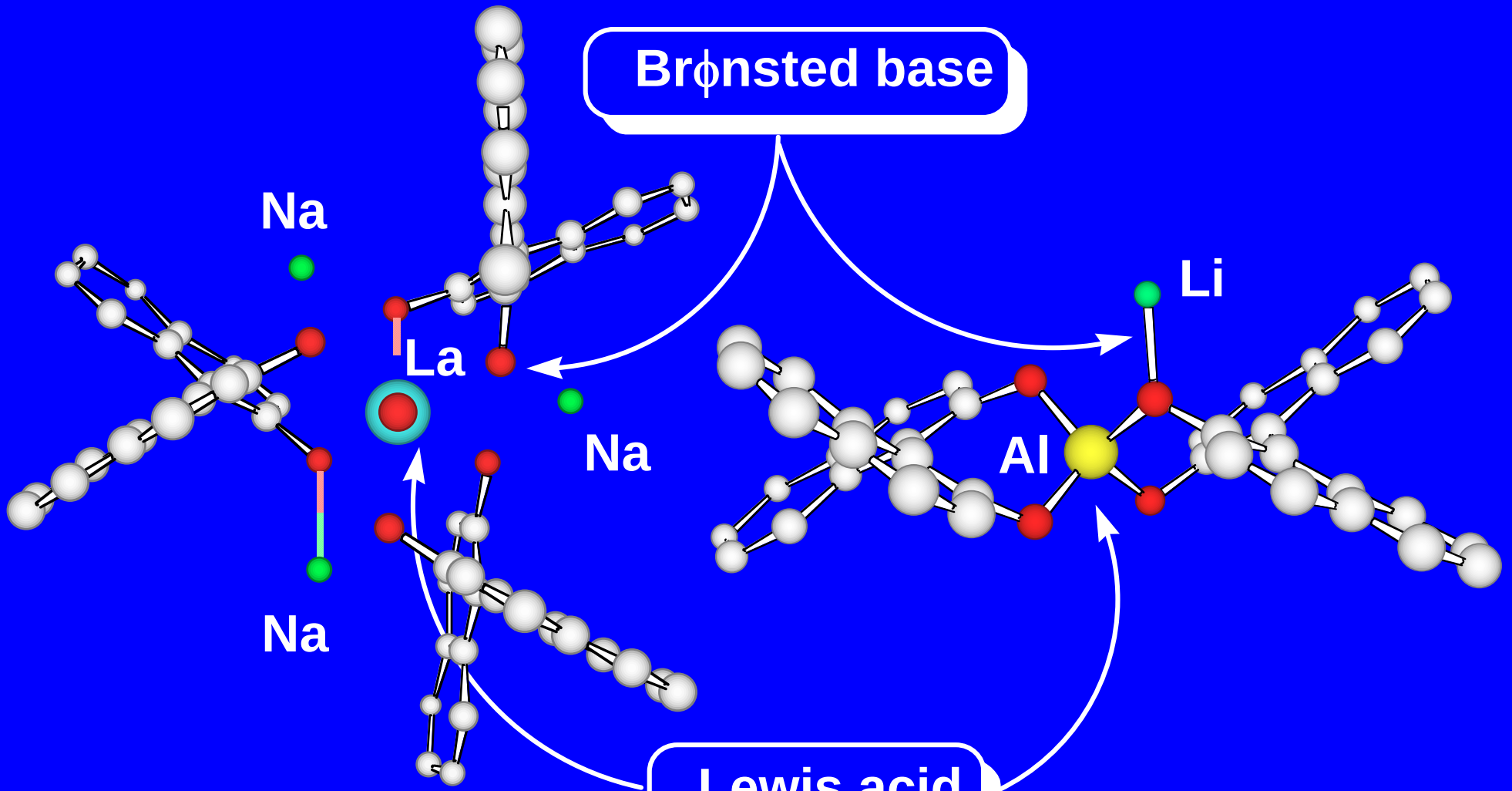
Reaction Mechanism of Class-II Aldolase
–Multifunctional Catalyst–



Class II, Metal–Dependent Aldolase

(a) Fessner, W. D.; Scloss, J. V. et. al. *Angew. Chem. Int. Ed. Engl*. 1996, *35*, 2219-2221.
(b) Dreyer, M. K.; Schultz, G. E. *J. Mol. Biol*. 1993, *231*, 549-553.

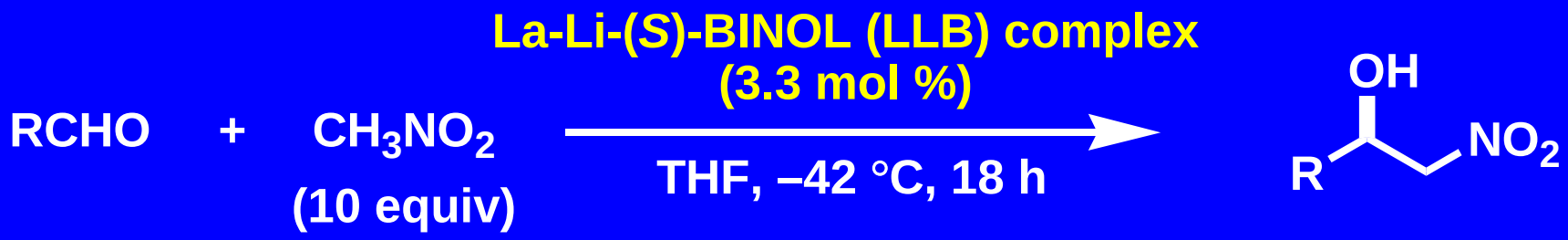
Heterobimetallic Multifunctional Aymmetric Catalysts



$LaNa_3$tris(binaphthoxide)
(LSB)

AlLibis(binaphthoxide)
(ALB)

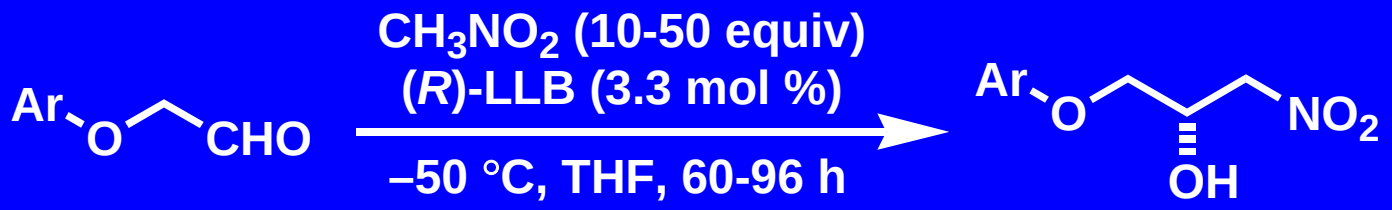
The First Catalytic Asymmetric Nitroaldol Reaction Catalyzed by Chiral Lanthanoid Complex



1: R = $PhCH_2CH_2$
2: R = *i*-Pr
3: R = cyclohexyl

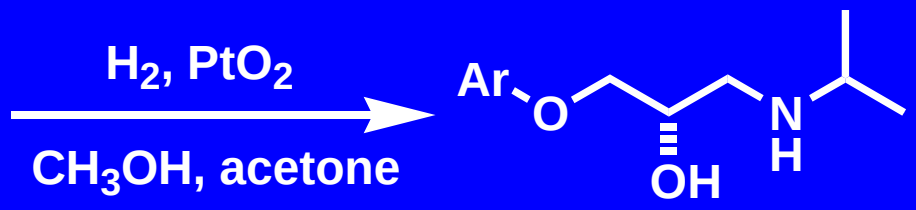
4: 79% (73% ee), R = $PhCH_2CH_2$
5: 80% (85% ee), R = *i*-Pr
6: 91% (90% ee), R = cyclohexyl

Catalytic Asymmetric Synthesis of β-Blockers Using (*R*)-LLB



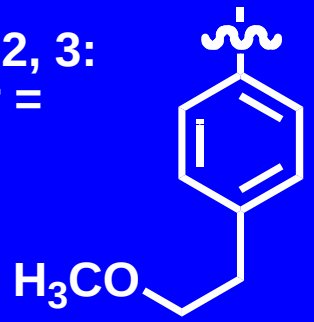
1
4
7

2: 90% (94% ee)
5: 80% (92% ee)
8: 76% (92% ee)

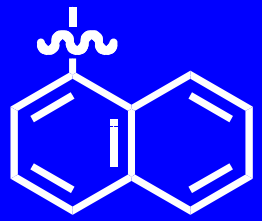


3: 80% (*S*)-metoprolol
6: 90% (*S*)-propranolol
9: 88% (*S*)-pindolol

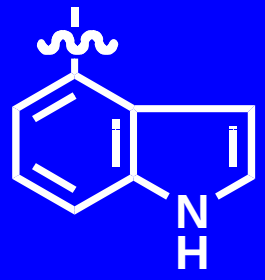
1, 2, 3:
Ar =



4, 5, 6:
Ar =

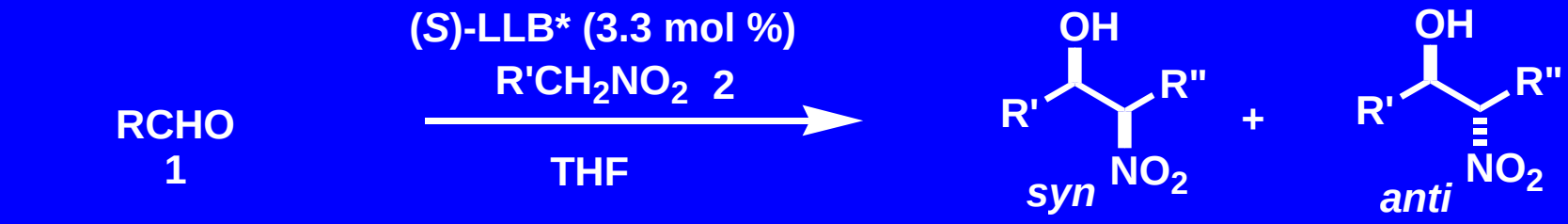


7, 8, 9:
Ar =



Recent Development of Catalytic Asymmetric Nitroaldol Reactions: Trost, Evans, Jørgensen

Diastereo- and Enantioselective Nitroaldol Reactions



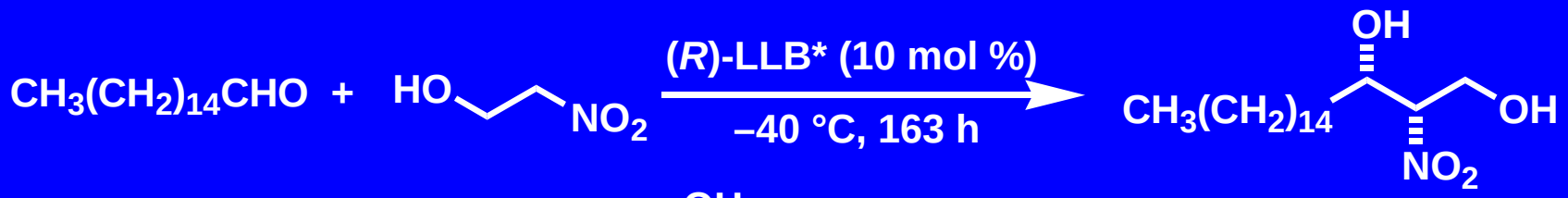
1a: R = $PhCH_2CH_2$
1b: R = $CH_3(CH_2)_4$

2b: R' = Me
2c: R'= Et
2d: R' = CH_2OH

3a: R = $PhCH_2CH_2$, R' = Me
3b: R = $PhCH_2CH_2$, R' = Et
3c: R = $PhCH_2CH_2$, R' = CH_2OH
3d: R = $CH_3(CH_2)_4$, R' = CH_2OH

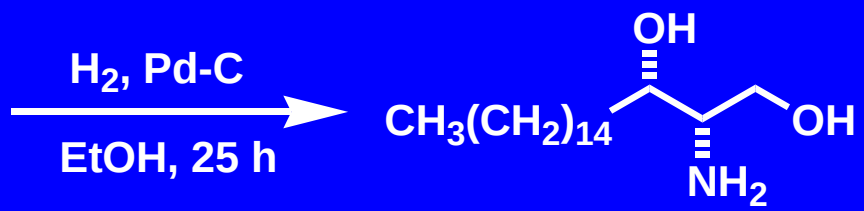
entry	aldehyde (R)	nitroalkane (R')	time (h)	temp (°C)	products	yield (%)	*syn*/*anti*	ee (%)
1	1a	2b	57	–20	3a	70	89/11	93
2	1a	2c	138	–40	3b	85	93/7	95
3	1a	2d	111	–40	3c	97	92/8	97
4	1b	2d	93	–40	3d	96	92/8	95

Catalytic Asymmetric Synthesis of *threo*-Dihydrosphingosine



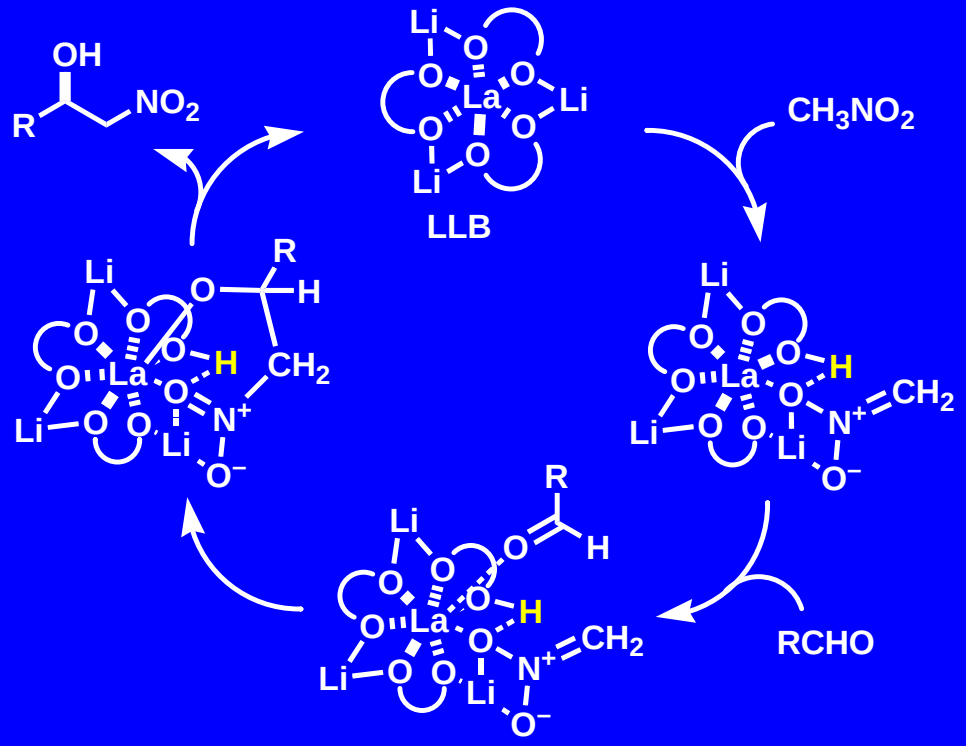
(+ *anti*-adduct)

78% (*syn* / *anti* = 91:9), *syn*: 97% ee

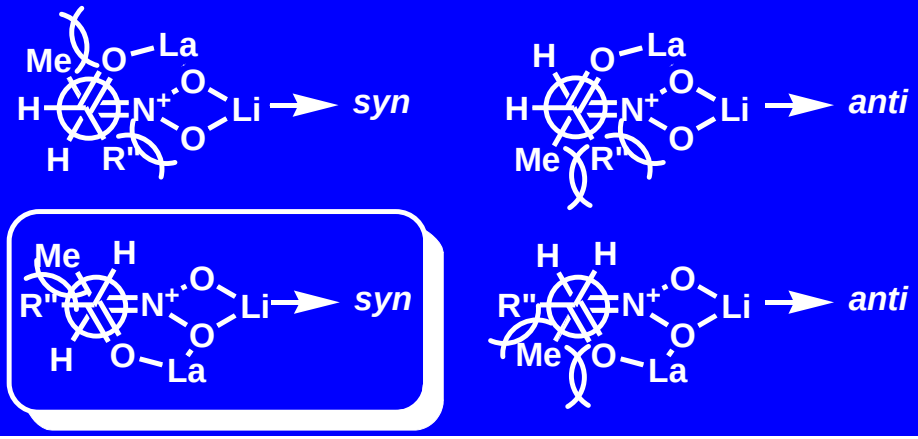


threo-dihydrosphingosine

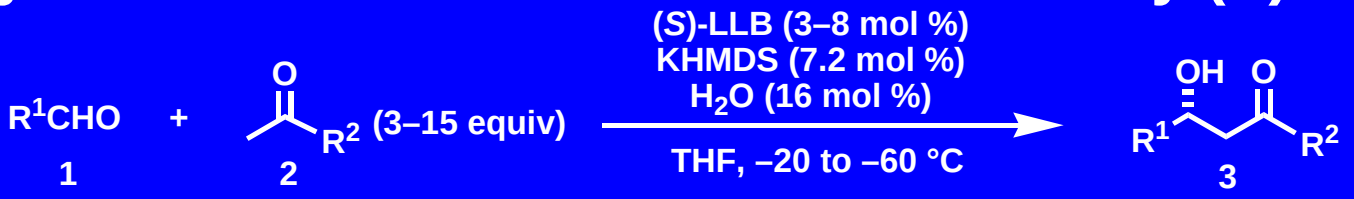
Plausible Mechanism for Catalytic Asymmetric Nitroaldol Reaction

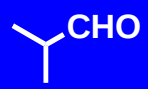
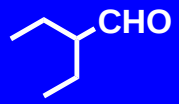
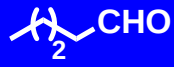


Newman Projections of Intermediates in the Diastereoselective Nitroaldol Reaction



The First Example of an Intermolecular Direct Catalytic Asymmetric Aldol Reactions Promoted by (*S*)-LLB•KOH

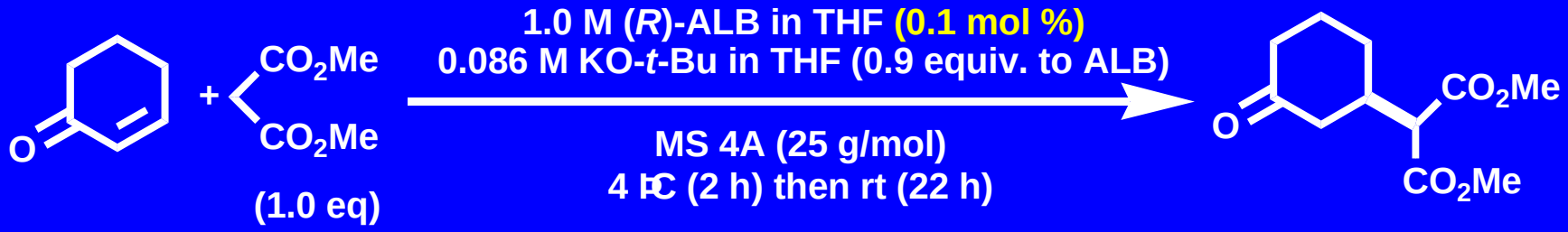


entry	aldehyde		ketone (equiv)		time (h)	yield (%)	ee (%)
1		1c	-Ph	2a (5)	15	75	88
2		1c	-Ph	2a (5)	28	85	89
3		1c	-CH_3	2b10)	20	62	76
4		1c	-CH_2CH_3	2c (15)	95	72	88
5		1d	-Ph	2a (5)	18	83	85
6[a]		1d	-Ph	2a (5)	33	71	85
7		1e	-Ph	2a (5)	36	91	90
8		1e	-Ph	2a (5)	24	70	93
9		1f	-Ph	2a (5)	15	90	33
10		1f	-*m*-NO_2-C_6H_4	2d (3)	70	68	70
11		1g	-*m*-NO_2-C_6H_4	2d (3)	96	60	80
12		1h	-*m*-NO_2-C_6H_4	2d (5)	96	55	42
13		1a	-*m*-NO_2-C_6H_4	2d (3)	31	50	30

[a] (*S*)-LLB (3 mol %) KHMDS (2.7 mol %) H_2O (6 mol %) were used.

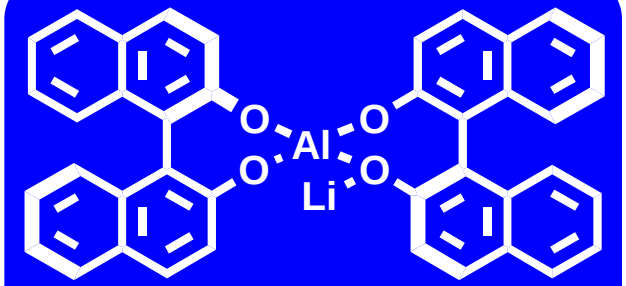
Recent Development: Trost, Evans, Shair, List, Barbas, MacMillan

Catalytic Asymmetric Michael Reaction Promoted by Al-Li-BINOL(ALB) Complex on Greater than Kilo Scale



581 mL 686 mL (91%, >99% ee) 1.24 kg

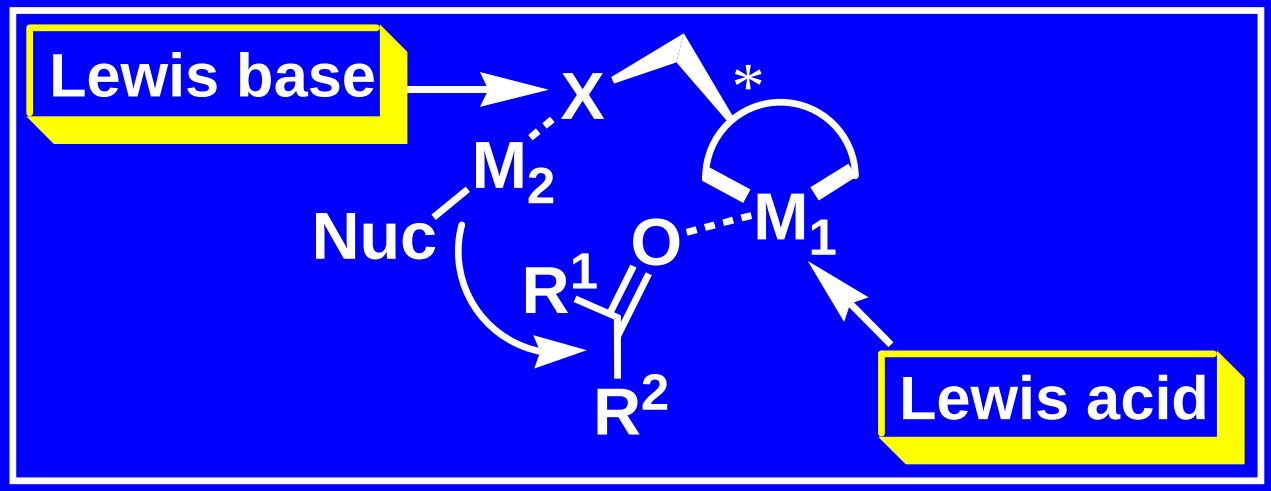
Cyclohexenone		581 mL (6.0 mol)
Dimethyl Malonate		686 mL (6.0 mol)
(*R*)-ALB in THF (0.1 mol%)	$LiAlH_4$	228 mg (6 mmol)
	(*R*)-BINOL	3.44 g (12 mmol)
	THF	60 mL
KO-*t*-Bu in THF (0.09 mol%)	KO-*t*-Bu	606 mg (5.1 mmol)
	THF	63 mL
MS 4Å		150 g



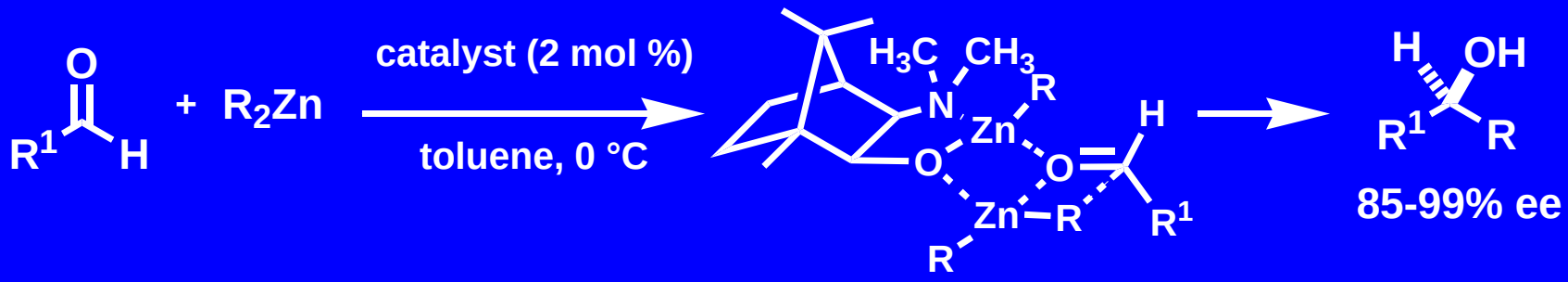
(*R*)-ALB Complex

Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* 2002, *58*, 2585.

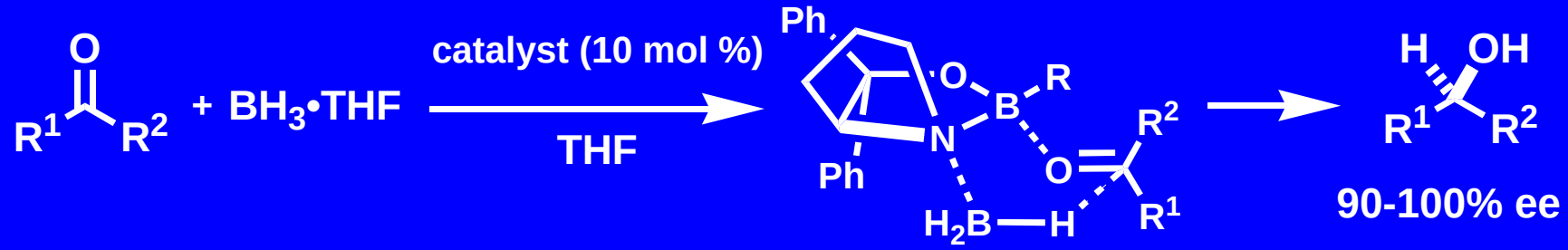
Lewis Acid-Lewis Base Asymmetric Catalysis



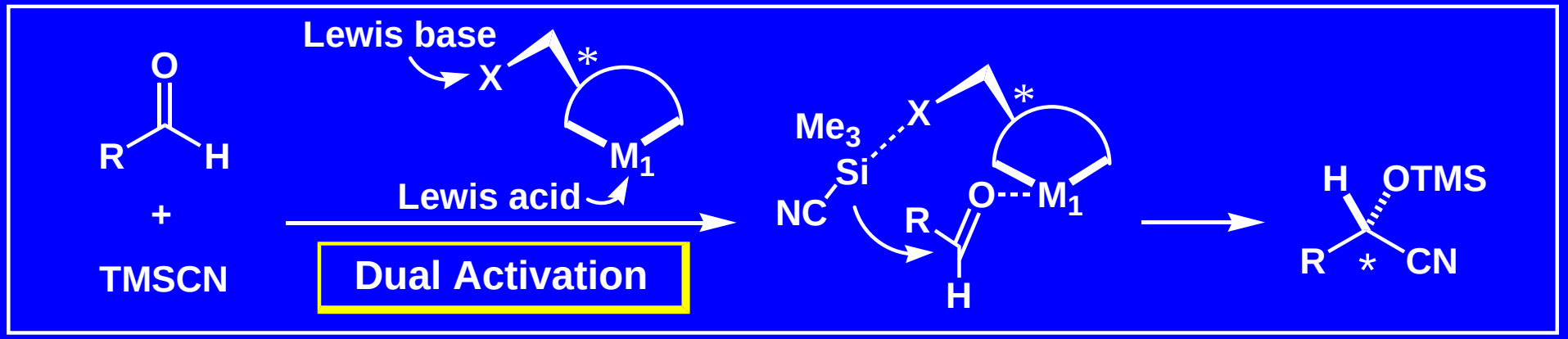
Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl*. 1991, *30*, 49-69 (review).



Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* 1998, *37*, 1986-2012 (review).



Our Hypothesis for Catalytic Asymmetric Cyanosilylation of Aldehydes



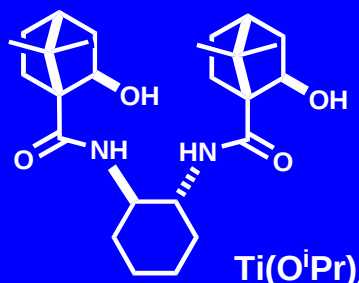
Catalytic Cyanosilylation of Aldehydes

Lewis acid catalyst: ZnI_2 (Evans (1973)), $AlCl_3$ (Sundermeyer (1973))

Lewis base catalyst: CN^-, P (Evans (1973)), N, P, As, Sb (Kobayashi and Mukaiyama (1991))

Selected Examples of Catalytic Asymmetric Cyanosilylation of Aldehydes

Uang (1998)



$Ti(O^iPr)_4$

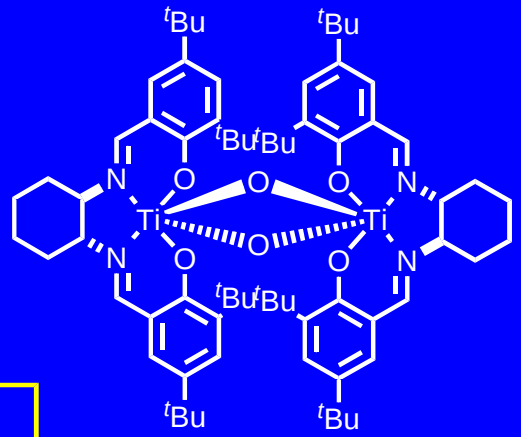
< 97.5% ee (15 mol %)

Problems

Low generality

High catalyst loading

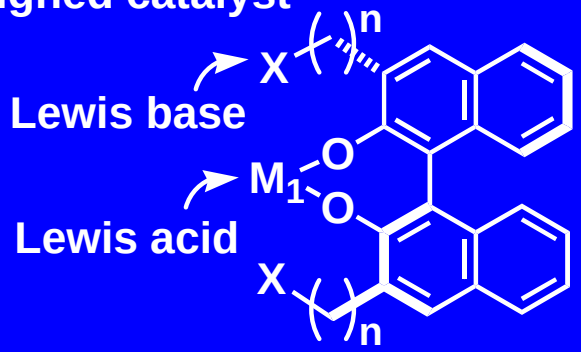
Belokon' (1999)



< 92% ee (0.1 mol %)

52% ee (EtCHO)

designed catalyst



relative position

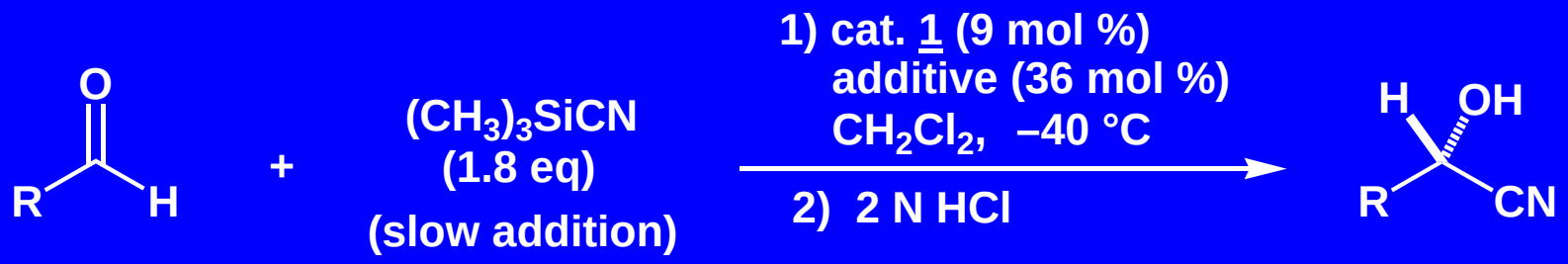
n = 0, 1, 2, ...

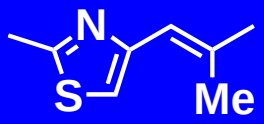
relative strength

M_1 = $TiCl_2$, $ZrCl_2$, GaCl, ... AlCl

X = SMe, PPh_2, ... $P(O)Ph_2$

Catalytic Asymmetric Cyanosilylation of Various Aldehydes

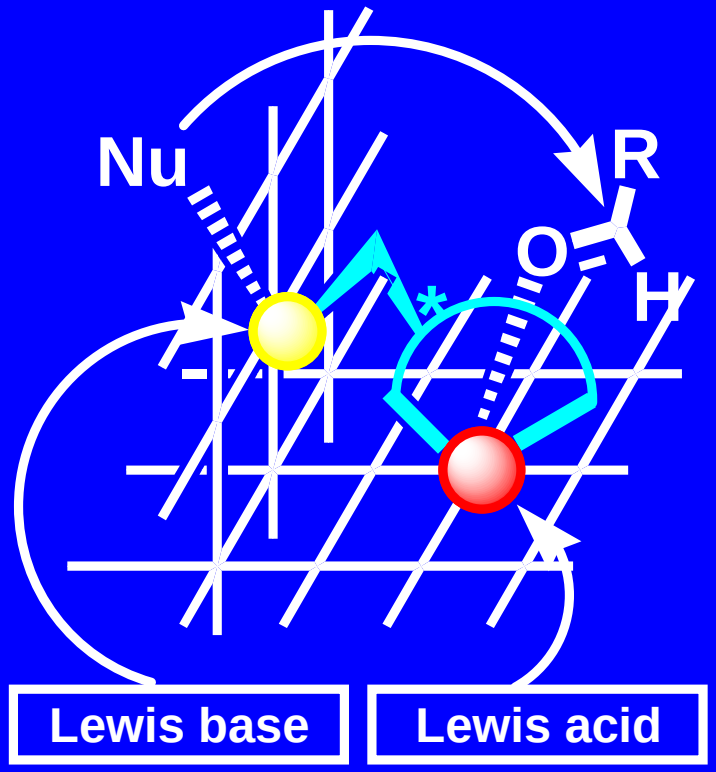


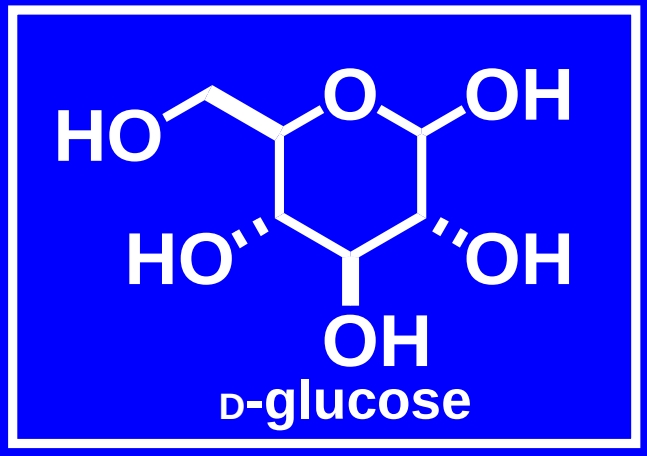
entry	R	additive	time (h)	yield (%)	ee (%)	config.
1	$Ph(CH_2)_2$	$Bu_3P(O)$	37	97	97	*S*
2	C_6H_{13}	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	$Bu_3P(O)$	40	96	90	*S*
4	$(C_2H_5)_2CH$	$Bu_3P(O)$	60	98	83	*S*
5	(*E*)-$C_4H_9CH{=}CH$	$Bu_3P(O)$	58	94	97	—
6	(*E*)-PhCH=CH	$Bu_3P(O)$	40	99	98	*S*
7		$Bu_3P(O)$	30	97	99	*S*
8[a]	Ph	$Ph_2P(O)CH_3$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	$Ph_2P(O)CH_3$	70	87	90	*S*
10[b]		$Ph_2P(O)CH_3$	70	86	95	*R*

a. 1.2 eq of TMSCN was added dropwise over 1 min.

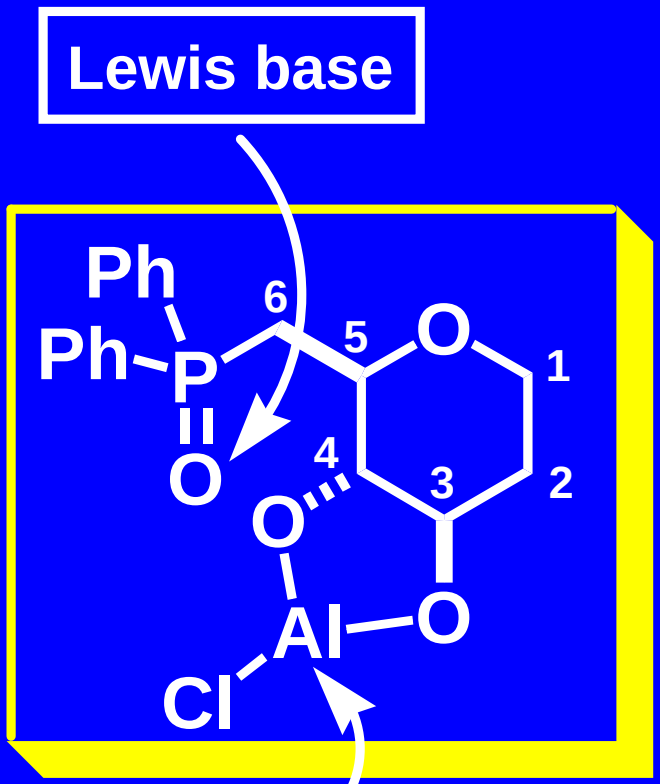
b. 18 mol % of catalyst 1 and 72 mol % of additive were used.

High Potentiality of Sugars for Lewis Acid-Lewis Base Bifunctional Catalyst





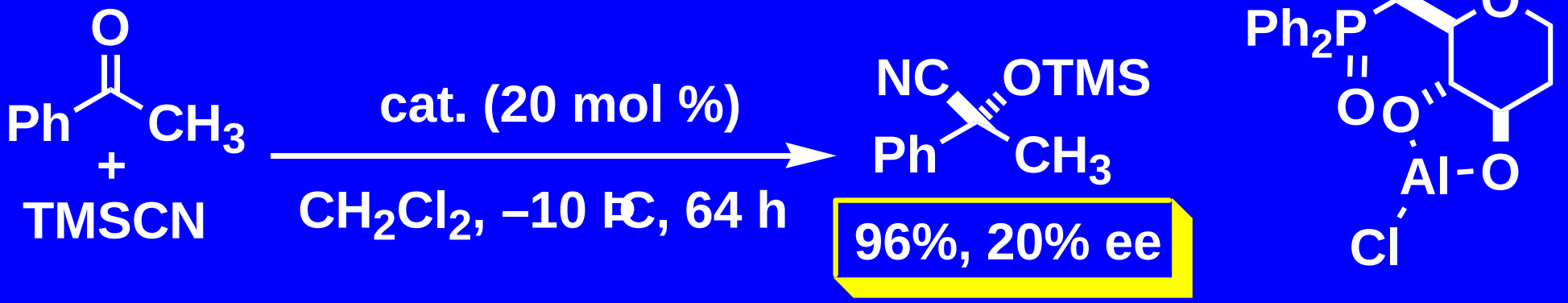
- 6-membered ring with defined conformation
- Multifunctionality

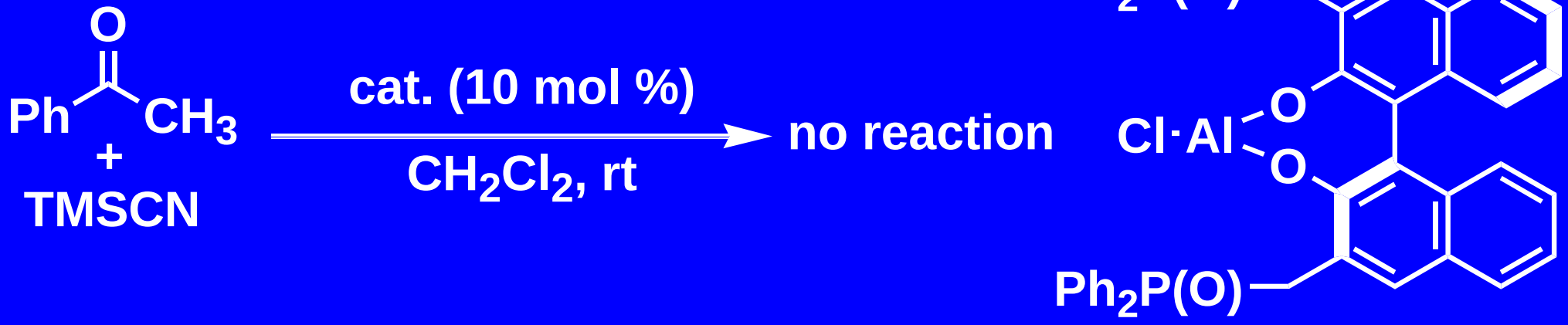


1. The balance of activation ability between the Lewis acid and Lewis base
2. The spatial arrangement of the Lewis acid and Lewis base

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

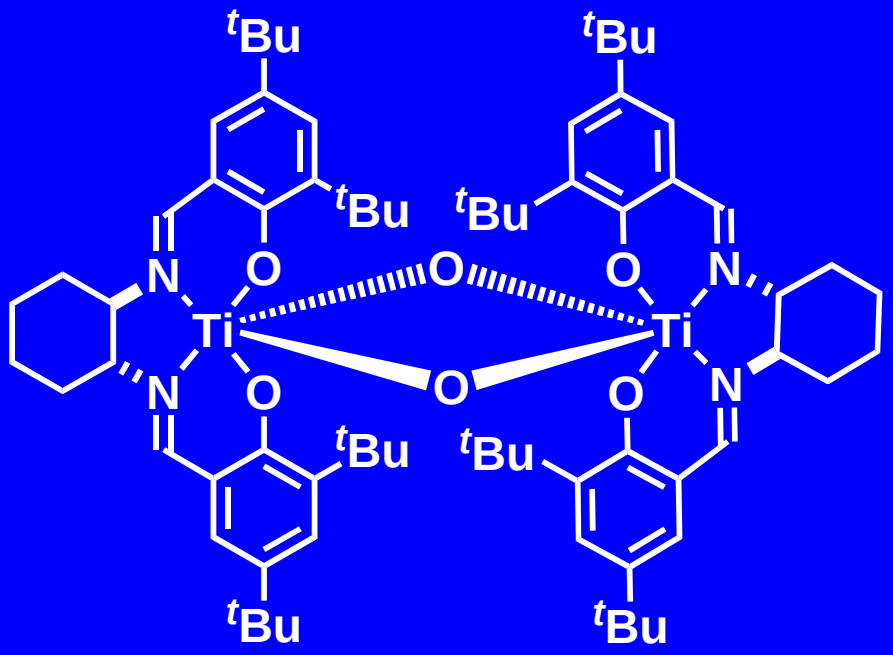
Catalytic Asymmetric Cyanosilylation of Acetophenone





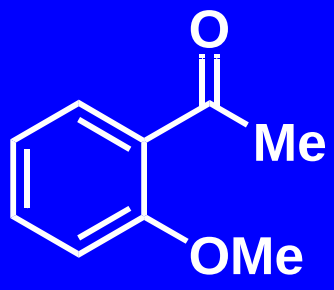
Catalytic Asymmetric Cyanosilylation of Ketones

Only one artificial catalyst has been reported to promote the cyanosilylation of ketones under usual (1 atm) conditions.

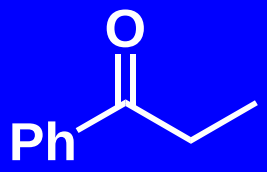


oxynitrilase

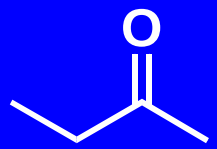
alkyl methyl ketones: good ee
aromatic , Et, or Pr
substituted ketones: low yield, low ee



66% ee (92%)

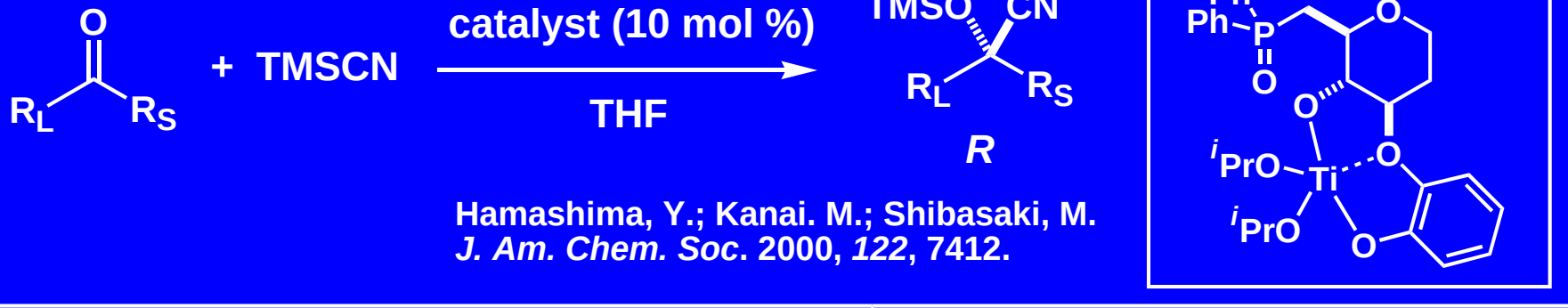


30% ee (100%)



unsuccessful

Catalytic Asymmetric Cyanosilylation of Ketones



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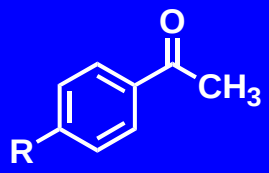
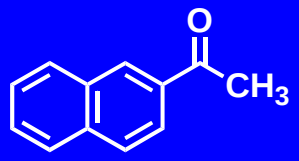
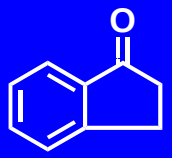
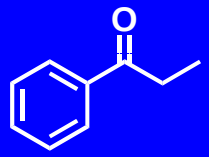
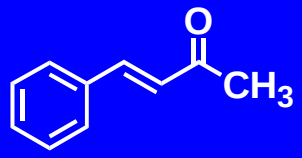
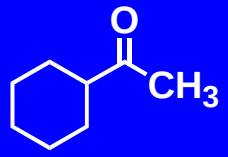
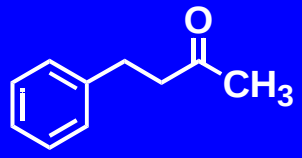
J. Am. Chem. Soc. 2000, *122*, 7412.

ketone	temp (°C)	time (h)	yield (%)	ee (%)
 R = H	–30	36	85	92
R = CH_3	–30	84	80	90
R = Cl	–40	80	82	92
	–40	80	82	95
	–40	96	72	69
	–20	64	89	91

ketone	temp (°C)	time (h)	yield (%)	ee (%)
	–50	24	79	84
	–50	88	72	91
	–50	36	86	90
	–50	36	92	85