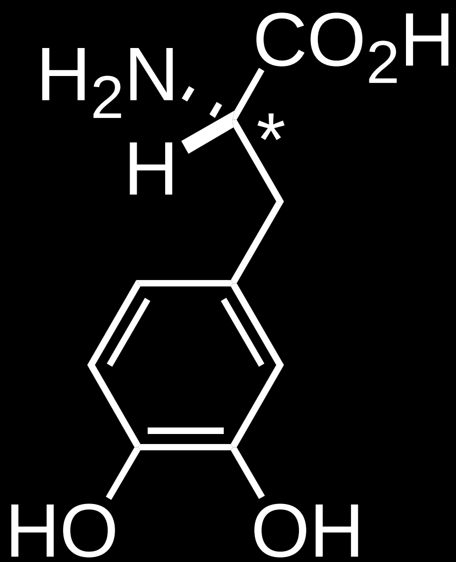
学術俯瞰講義

137億年の「物質」の旅
～ビッグバンからみどりの地球へ～

12月10日：物質と製造

東京大学大学院薬学系研究科
柴崎　正勝

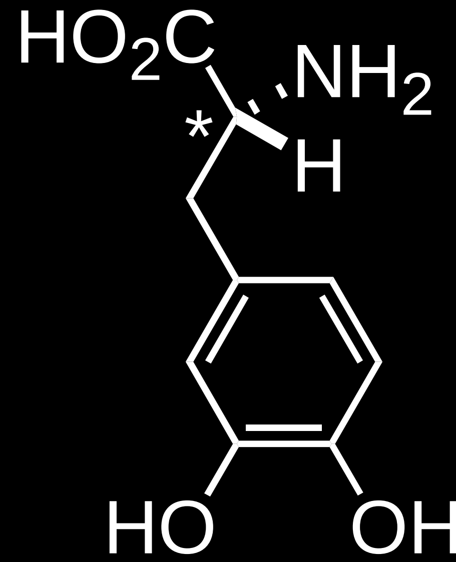
医薬における左手物質と右手物質



(*S*)–ドーパ

抗パーキンソン病薬

左手物質



(*R*)–ドーパ

毒性あり

右手物質

2001年ノーベル化学賞

触媒的不斉水素化
触媒的不斉酸化
― 官能基変化反応

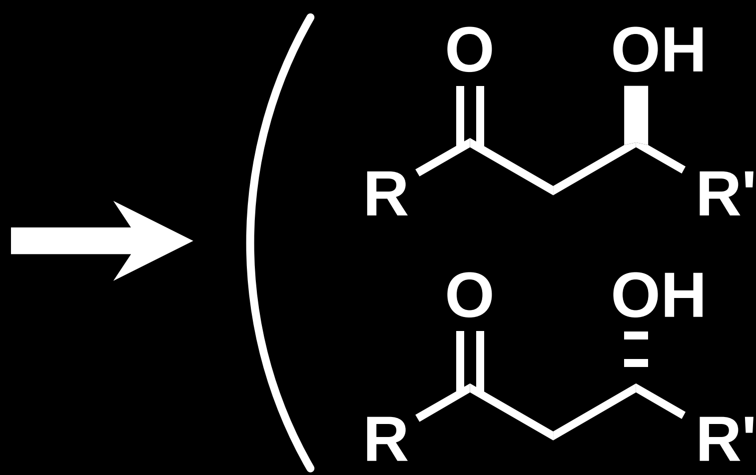
触媒的不斉炭素ー炭素結合形成反応 ― 分子構築の根源的反応

↓

将来ノーベル賞の光があたるか？

アルドール反応

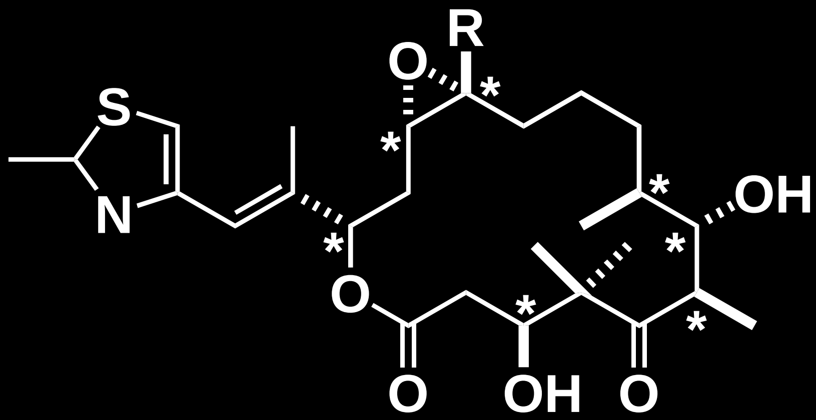
医薬重要合成
中間体



（左手物質）

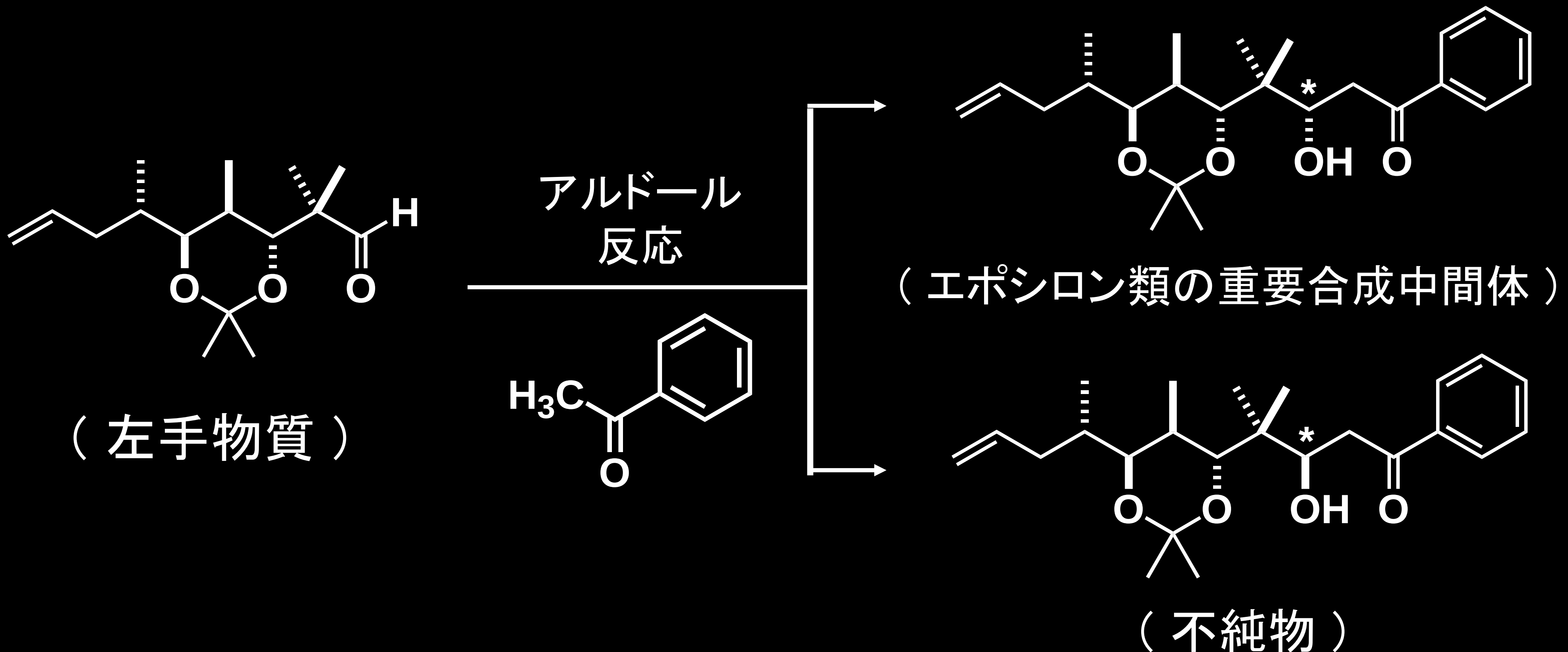
（右手物質）

触媒的不斉合成が可能か？

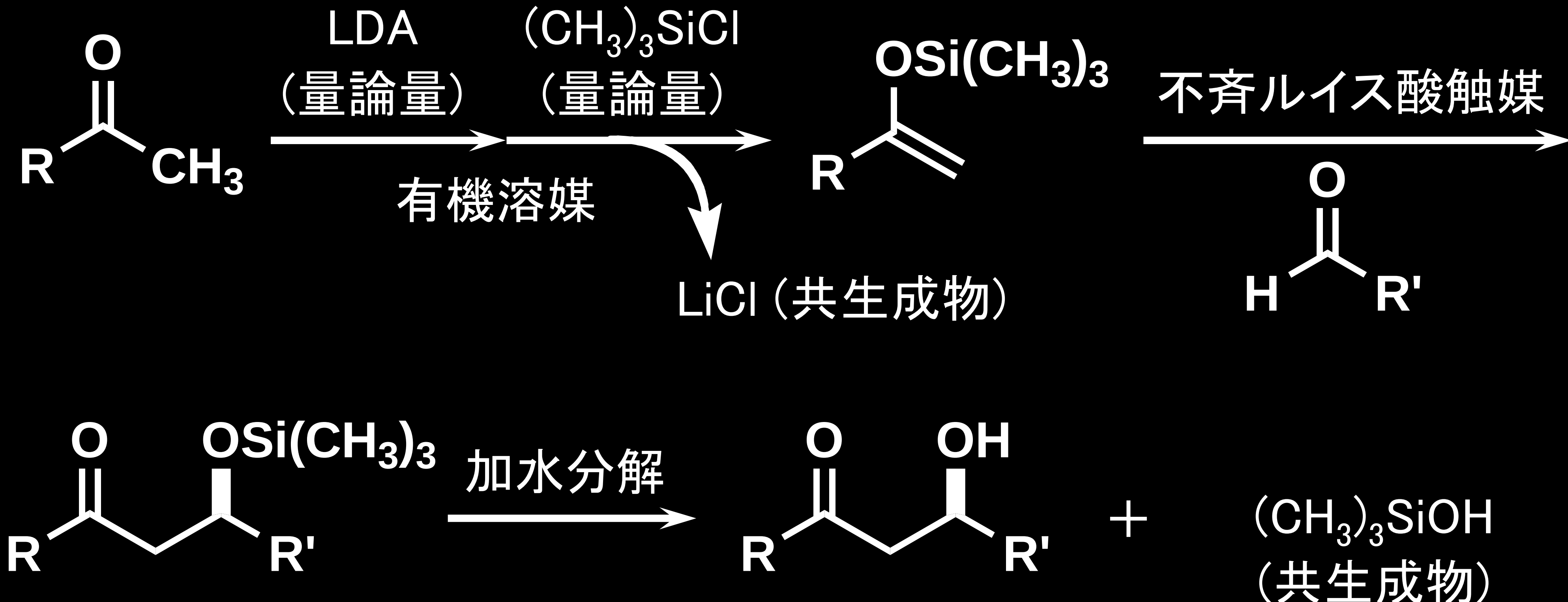


エポシロン類
（ R= H, Me ）

有望な抗癌剤：前立腺癌等



2000年当時における触媒的不斉アルドール反応の現状



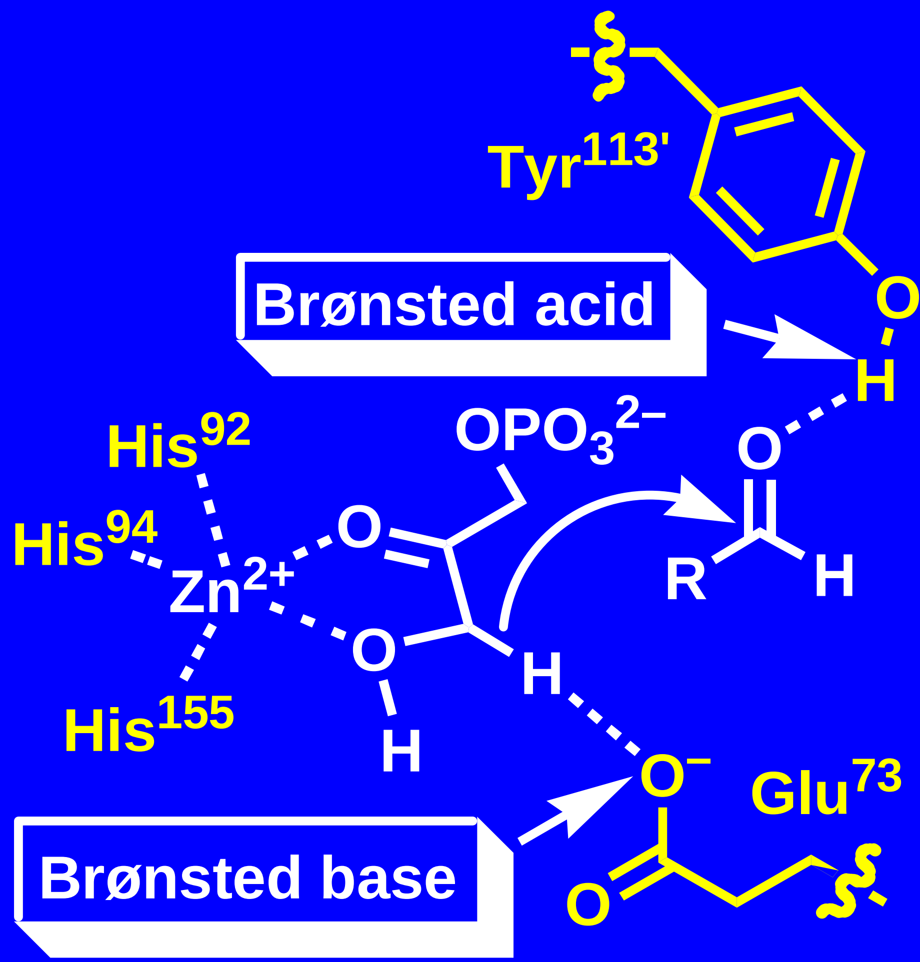
“大量のLiCl, $(CH_3)_3SiOH$, 有機溶媒等が蓄積”

世界最先端の研究

LiCl, $(CH_3)_3SiOH$,の共生成物なし

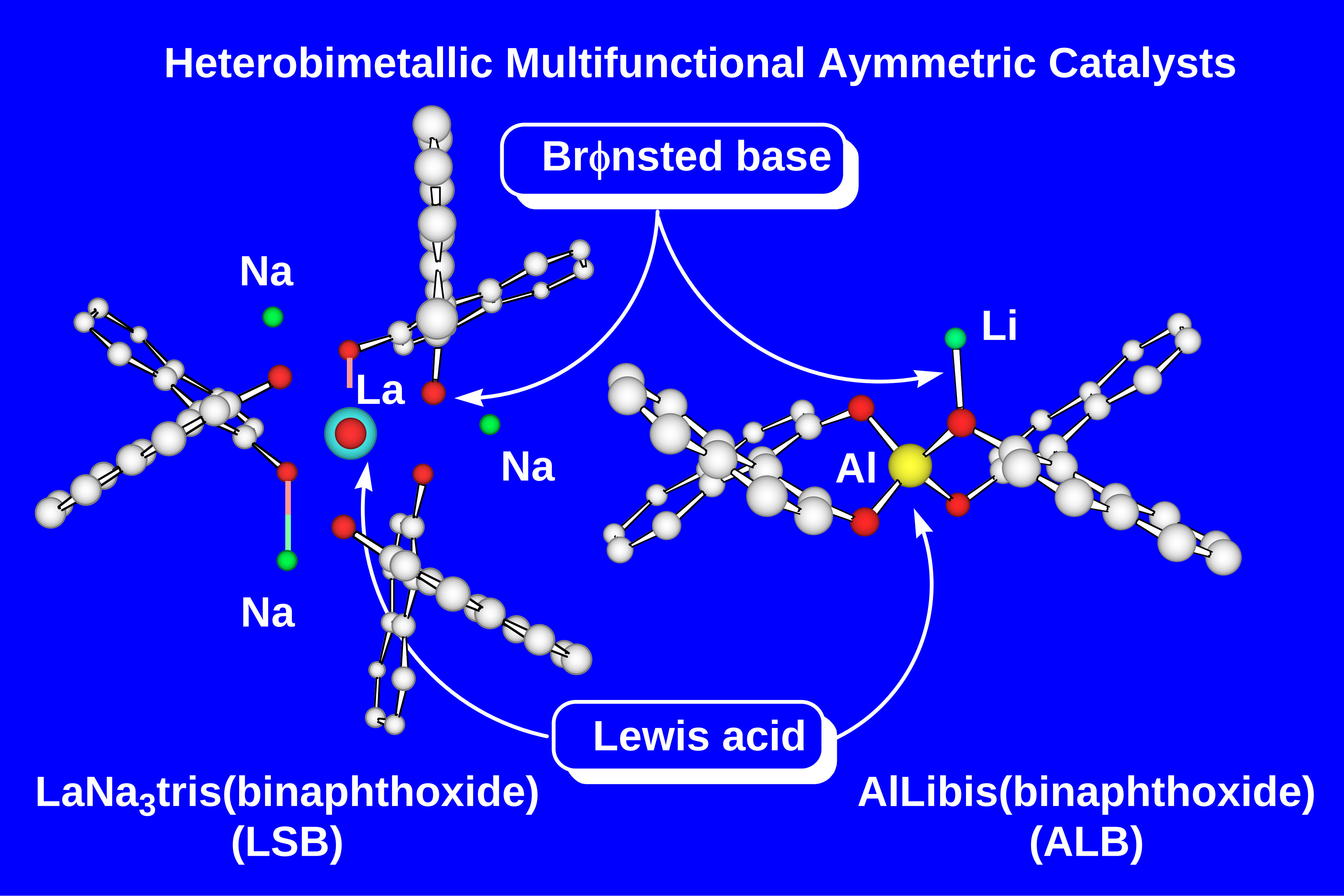
理想的な有機合成を実現するには
20世紀よりもより多くの困難がある。

Reaction Mechanism of Class-II Aldolase
–Multifunctional Catalyst–

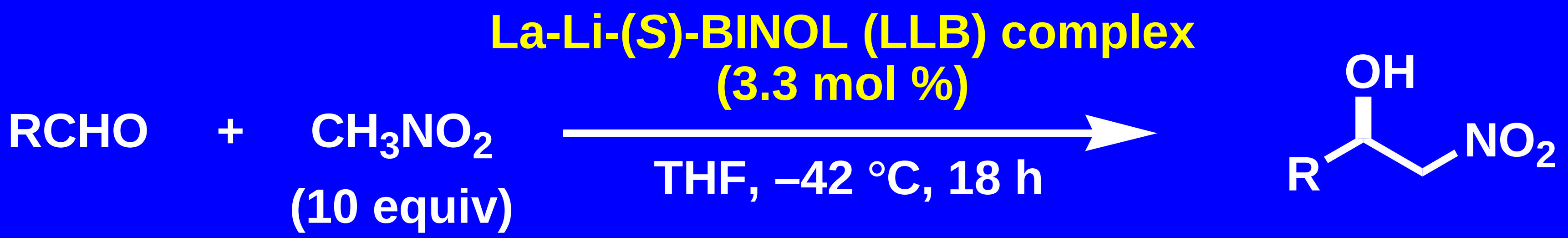


Class II, Metal–Dependent Aldolase

(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
Brϕnsted base
Na
La
Na
Na
Li
Al
Lewis acid
LaNa$_3$tris(binaphthoxide)
(LSB)
AlLibis(binaphthoxide)
(ALB)

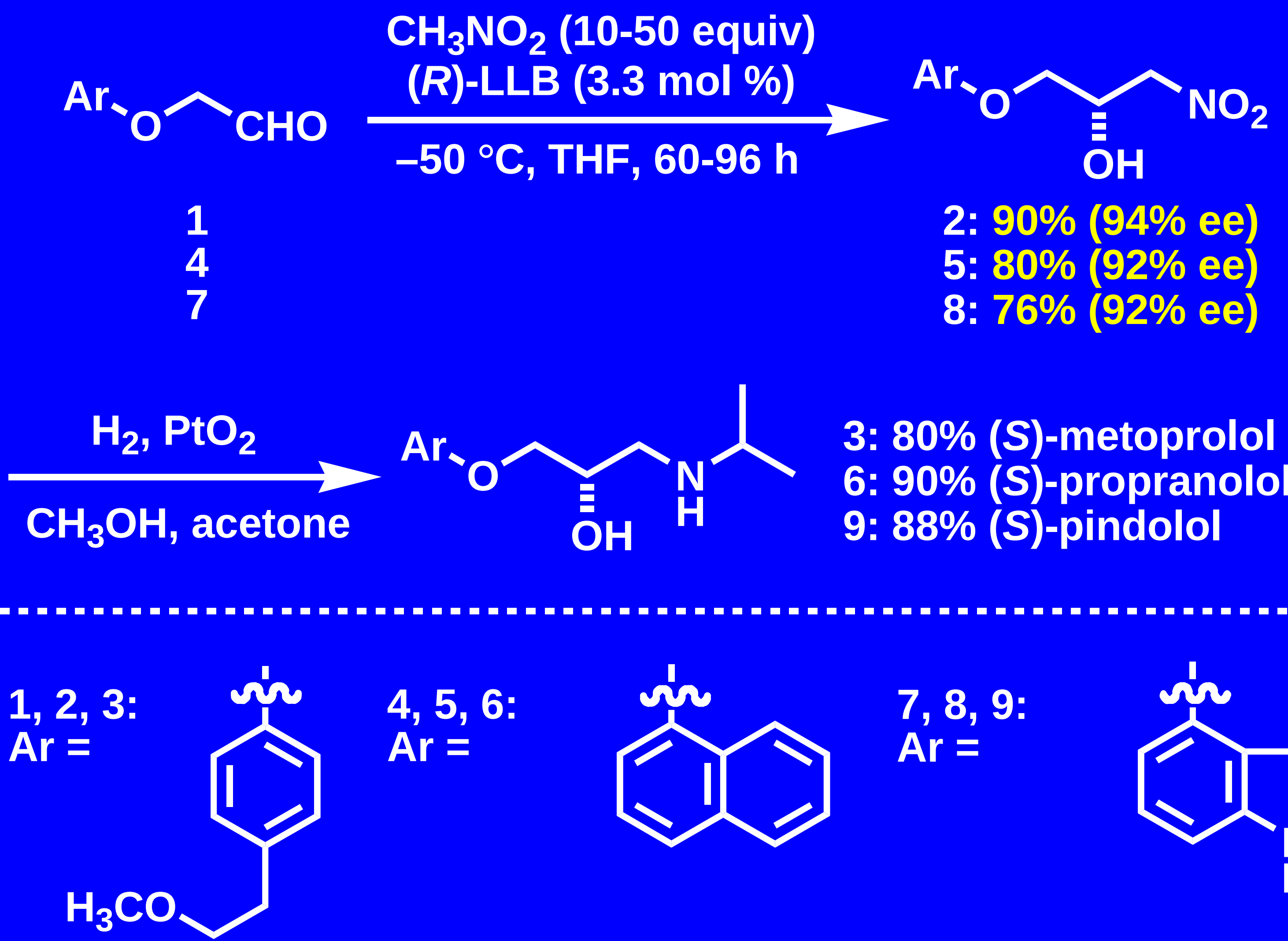
The First Catalytic Asymmetric Nitroaldol Reaction Catalyzed by Chiral Lanthanoid Complex



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

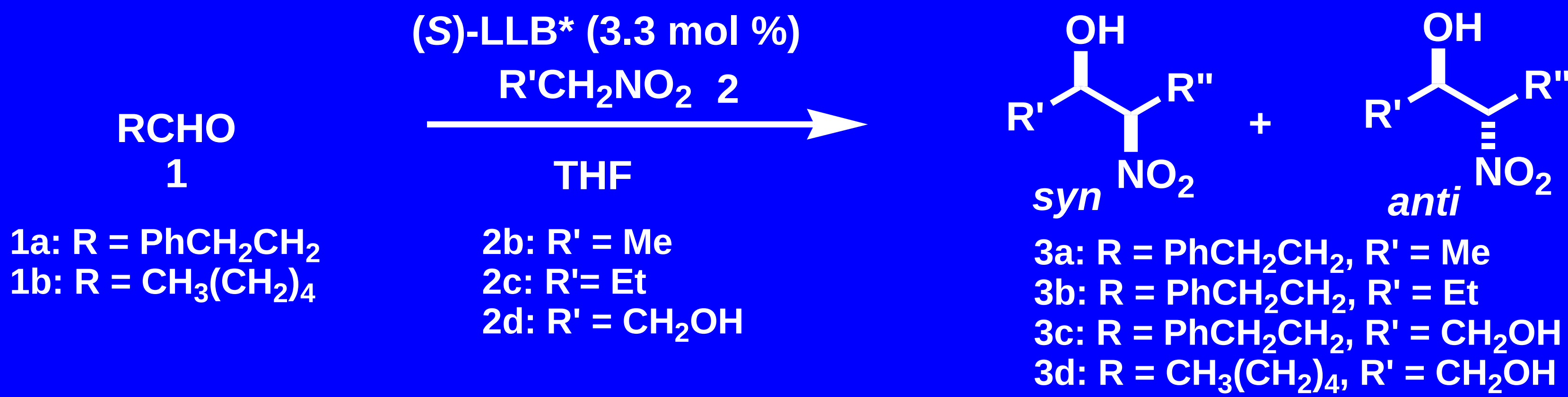
4: 79% (73% ee), R = $PhCH_2CH_2$
5: 80% (85% ee), R = *i*-Pr
6: 91% (90% ee), R = cyclohexyl

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



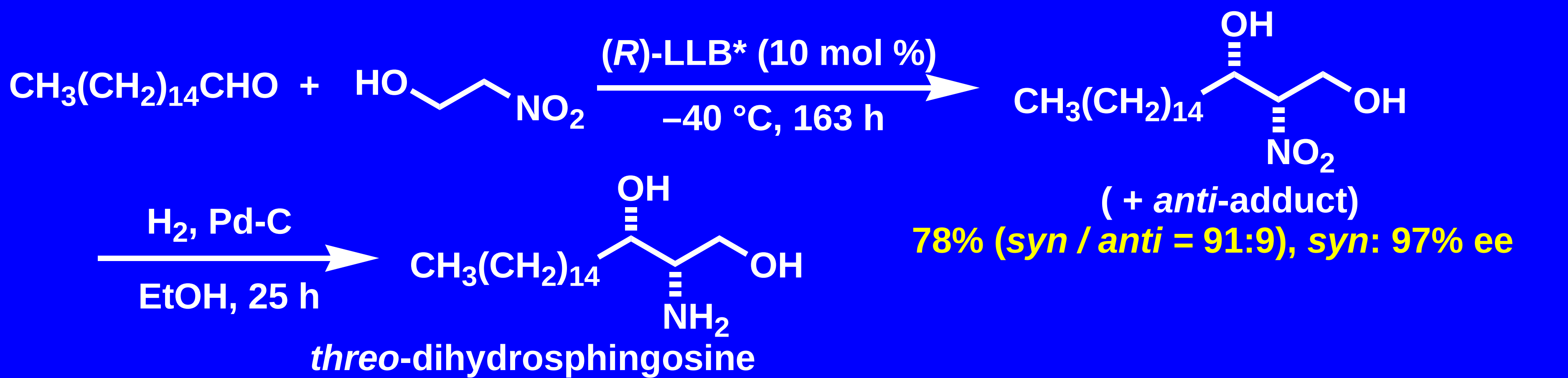
Recent Development of Catalytic Asymmetric Nitroaldol Reactions: Trost, Evans, Jørgensen

Diastereo- and Enantioselective Nitroaldol Reactions

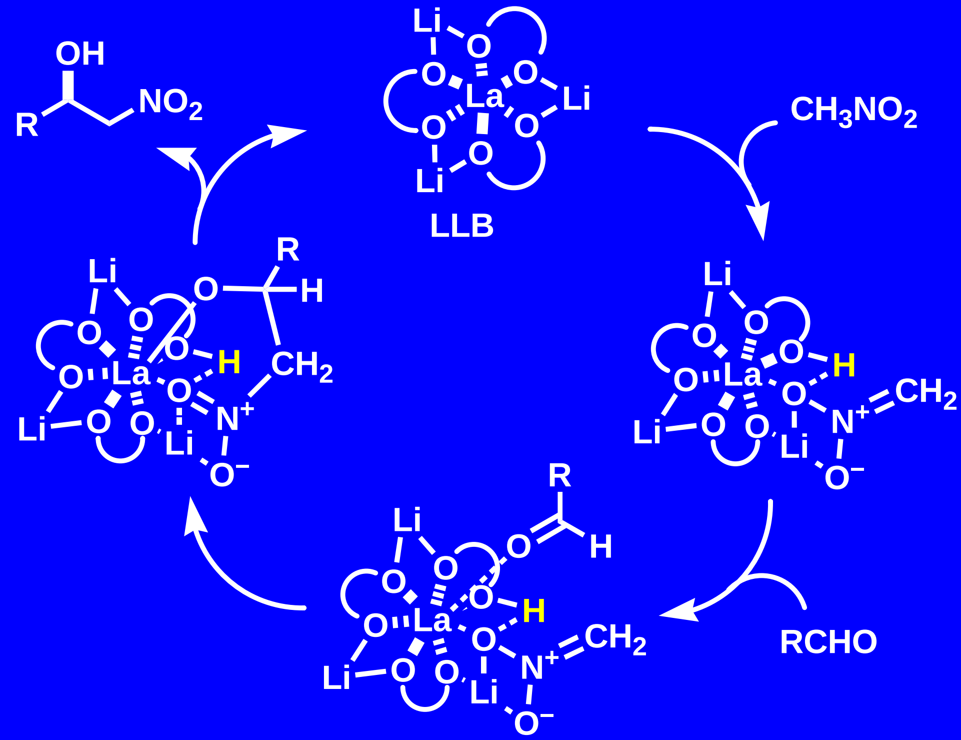


entry	aldehyde (R)	nitroalkane (R')	time (h)	temp (°C)	products	yield (%)	*syn*/*anti*	ee (%)
1	1a	2b	57	–20	3a	70	89/11	93
2	1a	2c	138	–40	3b	85	93/7	95
3	1a	2d	111	–40	3c	97	92/8	97
4	1b	2d	93	–40	3d	96	92/8	95

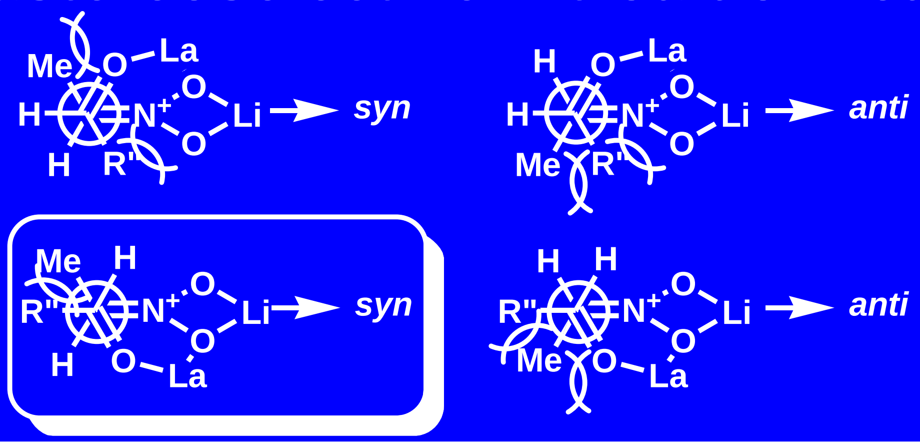
Catalytic Asymmetric Synthesis of *threo*-Dihydrosphingosine



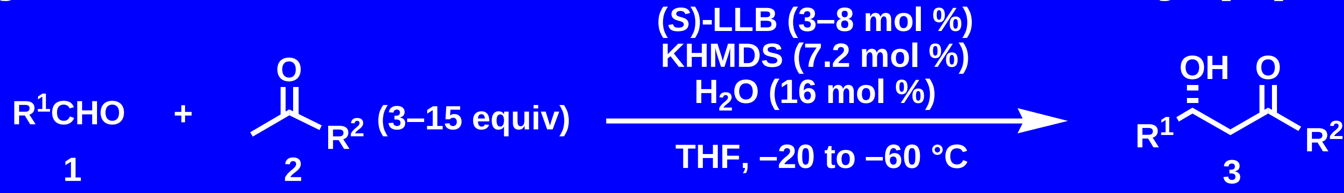
Plausible Mechanism for Catalytic Asymmetric Nitroaldol Reaction

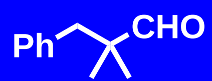
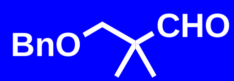
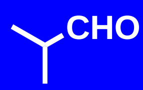
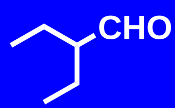
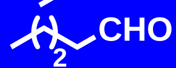
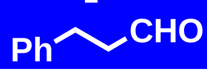


Newman Projections of Intermediates in the Diastereoselective Nitroaldol Reaction



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

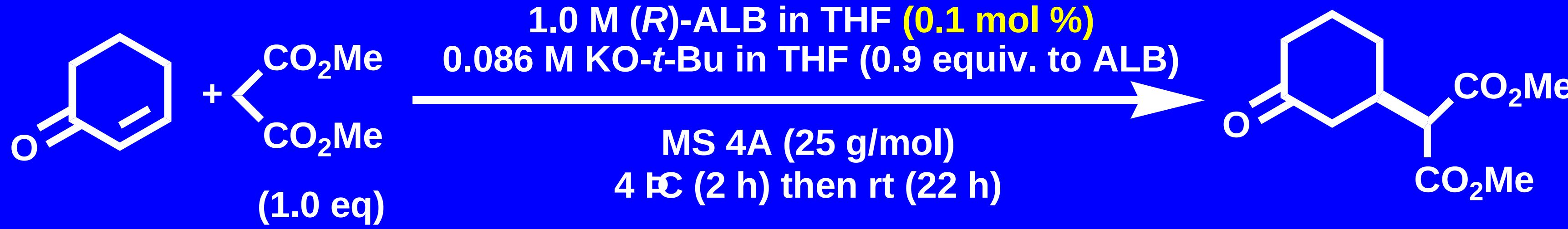


entry	aldehyde	ketone (equiv)	time (h)	yield (%)	ee (%)
1	 1c	-Ph 2a (5)	15	75	88
2	1c	-Ph 2a (5)	28	85	89
3	1c	$-CH_3$ 2b10)	20	62	76
4	1c	$-CH_2CH_3$ 2c (15)	95	72	88
5	 1d	-Ph 2a (5)	18	83	85
6[a]	1d	-Ph 2a (5)	33	71	85
7	 1e	-Ph 2a (5)	36	91	90
8	1e	-Ph 2a (5)	24	70	93
9	 1f	-Ph 2a (5)	15	90	33
10	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.

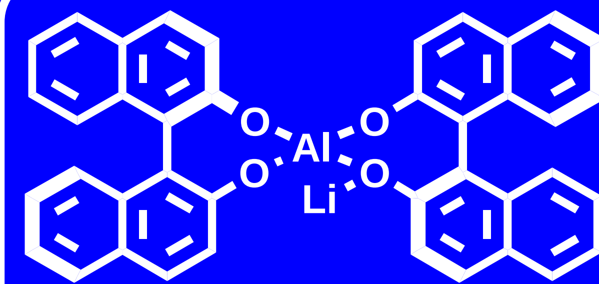
Recent Development: Trost, Evans, Shair, List, Barbas, MacMillan

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

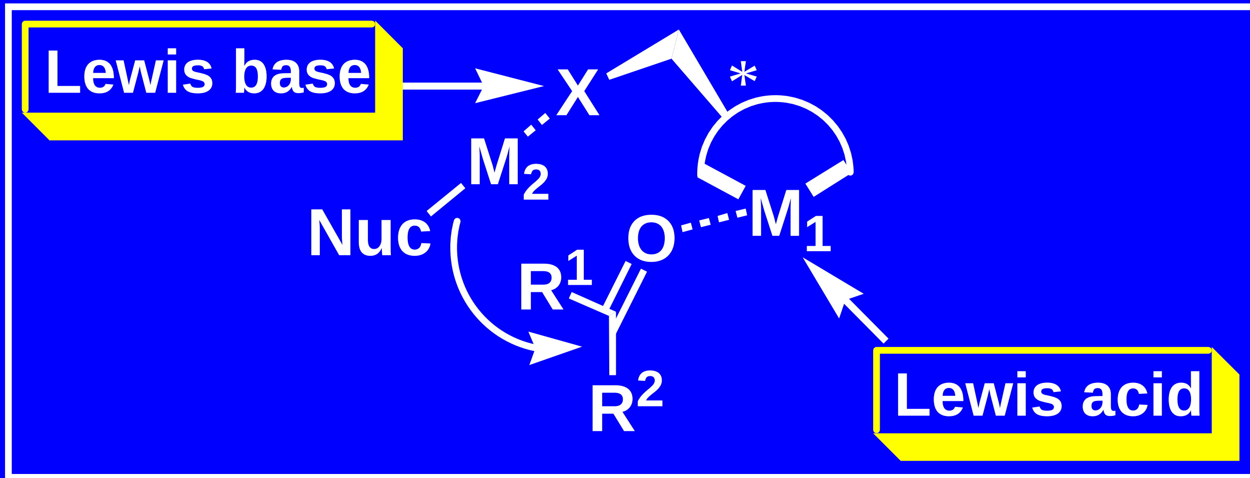
Cyclohexenone		581 mL (6.0 mol)
Dimethyl Malonate		686 mL (6.0 mol)
(*R*)-ALB in THF (0.1 mol%)	$LiAlH_4$	228 mg (6 mmol)
	(*R*)-BINOL	3.44 g (12 mmol)
	THF	60 mL
KO-*t*-Bu in THF (0.09 mol%)	KO-*t*-Bu	606 mg (5.1 mmol)
	THF	63 mL
MS 4Å		150 g



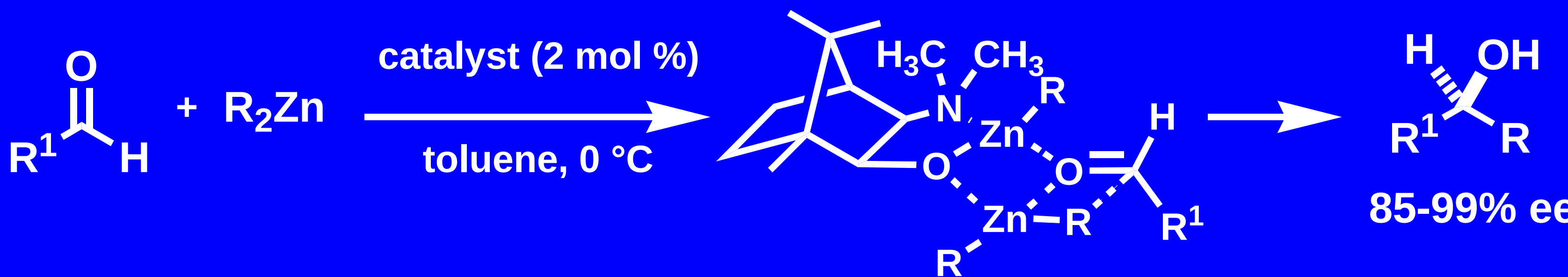
(*R*)-ALB Complex

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

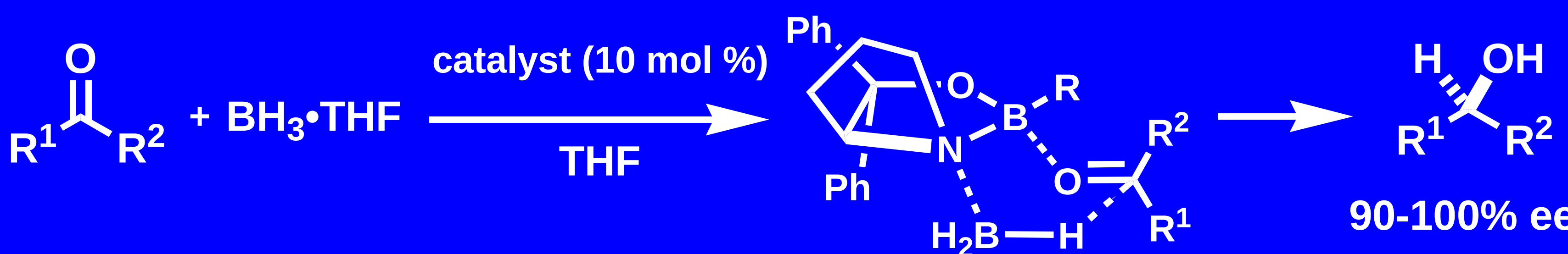
Lewis Acid-Lewis Base Asymmetric Catalysis



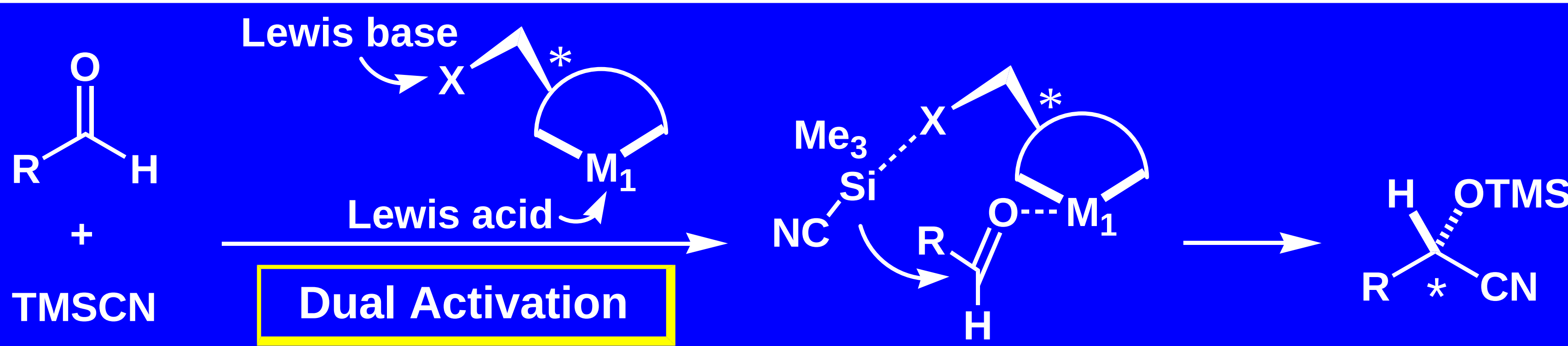
Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl*. 1991, *30*, 49-69 (review).



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



Our Hypothesis for Catalytic Asymmetric Cyanosilylation of Aldehydes



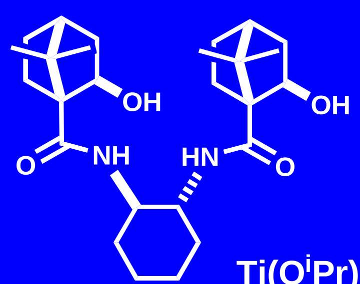
Catalytic Cyanosilylation of Aldehydes

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

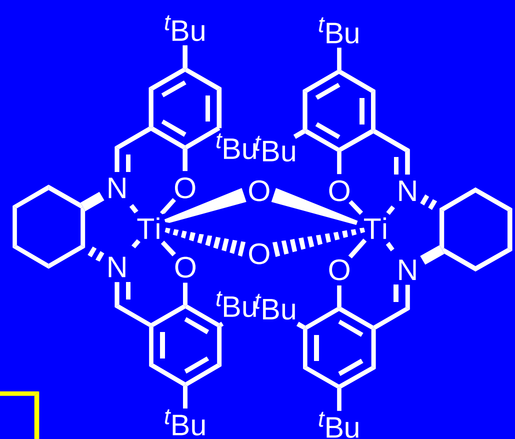
Uang (1998)



$Ti(O^iPr)_4$

< 97.5% ee (15 mol %)

Belokon' (1999)



< 92% ee (0.1 mol %)

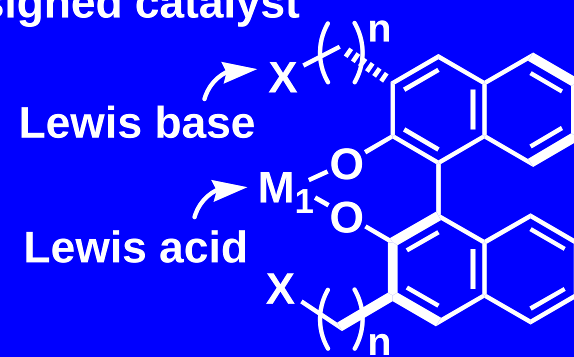
52% ee (EtCHO)

Problems

Low generality

High catalyst loading

designed catalyst



relative position

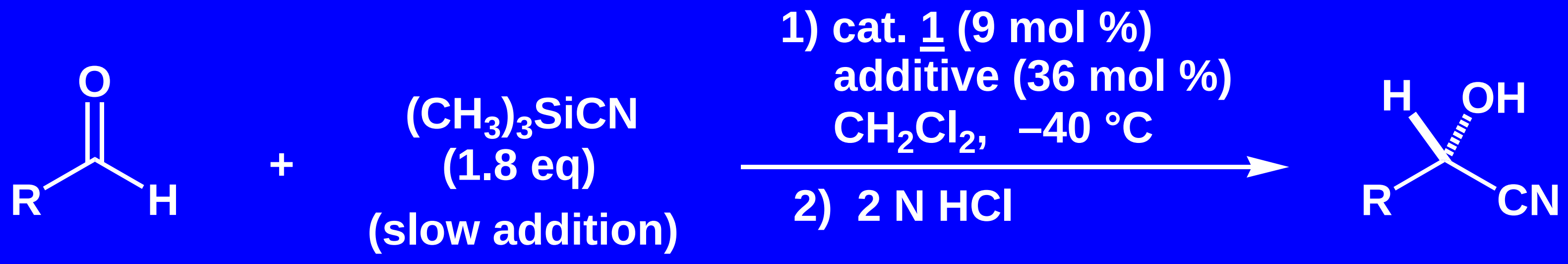
n = 0, 1, 2, ...

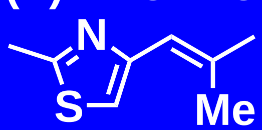
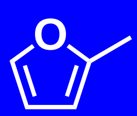
relative strength

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

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

Catalytic Asymmetric Cyanosilylation of Various Aldehydes

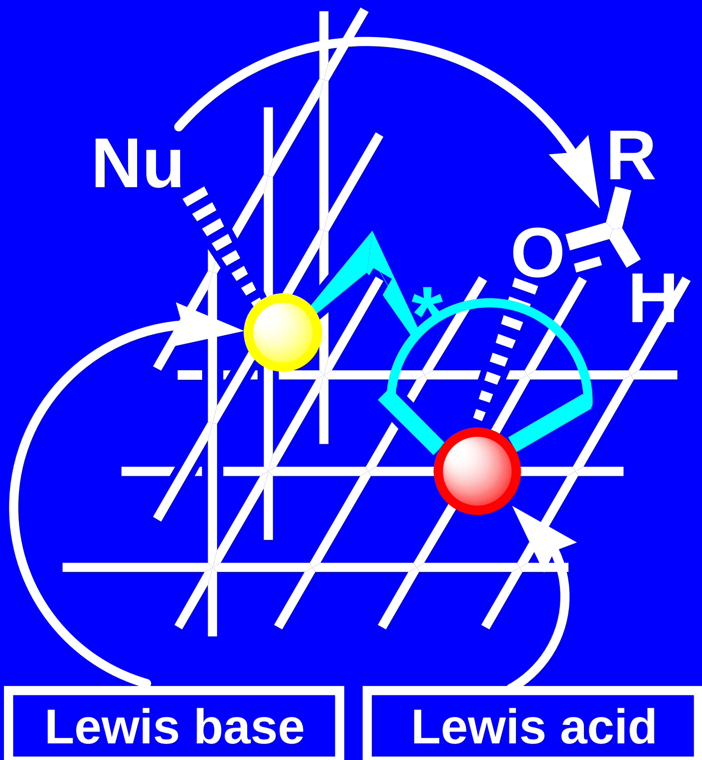


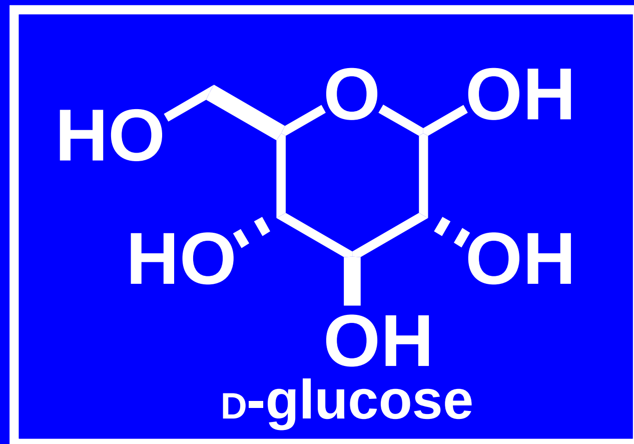
entry	R	additive	time (h)	yield (%)	ee (%)	config.
1	$Ph(CH_2)_2$	$Bu_3P(O)$	37	97	97	*S*
2	C_6H_{13}	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	$Bu_3P(O)$	40	96	90	*S*
4	$(C_2H_5)_2CH$	$Bu_3P(O)$	60	98	83	*S*
5	(*E*)-$C_4H_9CH{=}CH$	$Bu_3P(O)$	58	94	97	—
6	(*E*)-PhCH=CH	$Bu_3P(O)$	40	99	98	*S*
7		$Bu_3P(O)$	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.

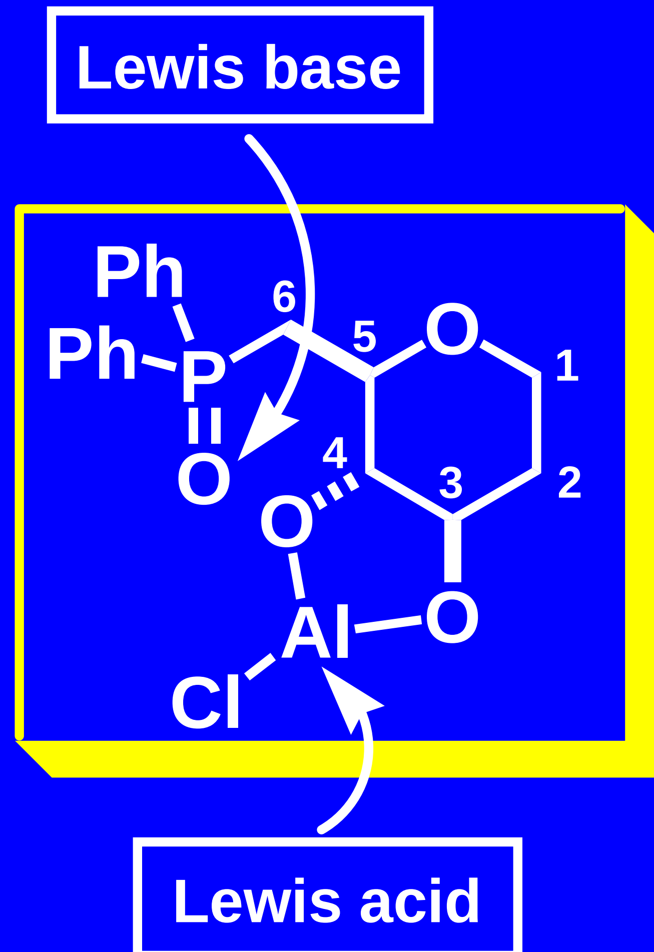
b. 18 mol % of catalyst 1 and 72 mol % of additive were used.

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





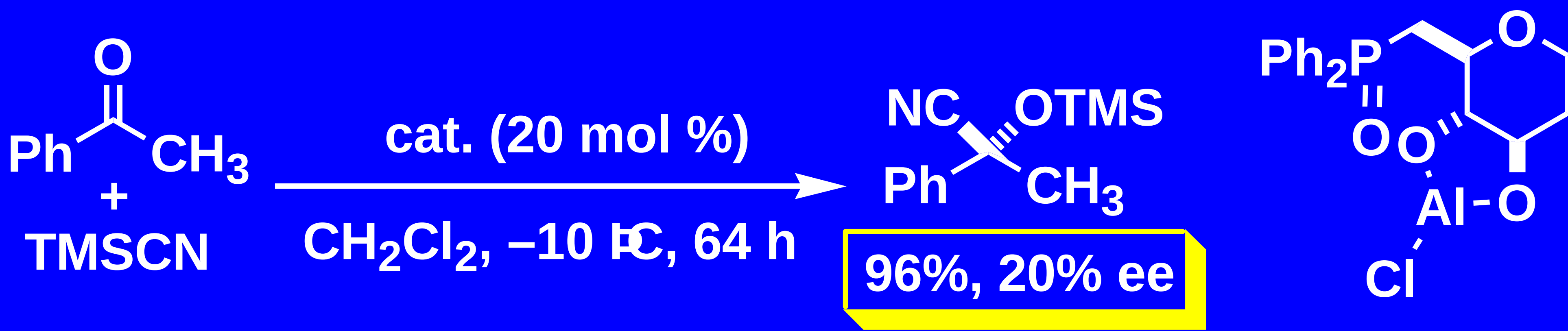
- 6-membered ring with defined conformation
- Multifunctionality

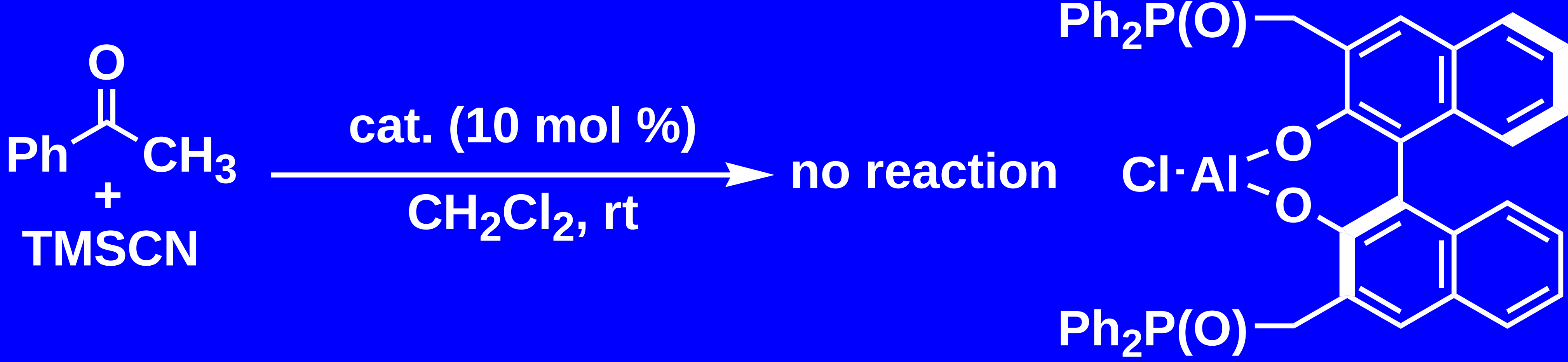


1. The balance of activation ability between the Lewis acid and Lewis base
2. The spatial arrangement of the Lewis acid and Lewis base

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

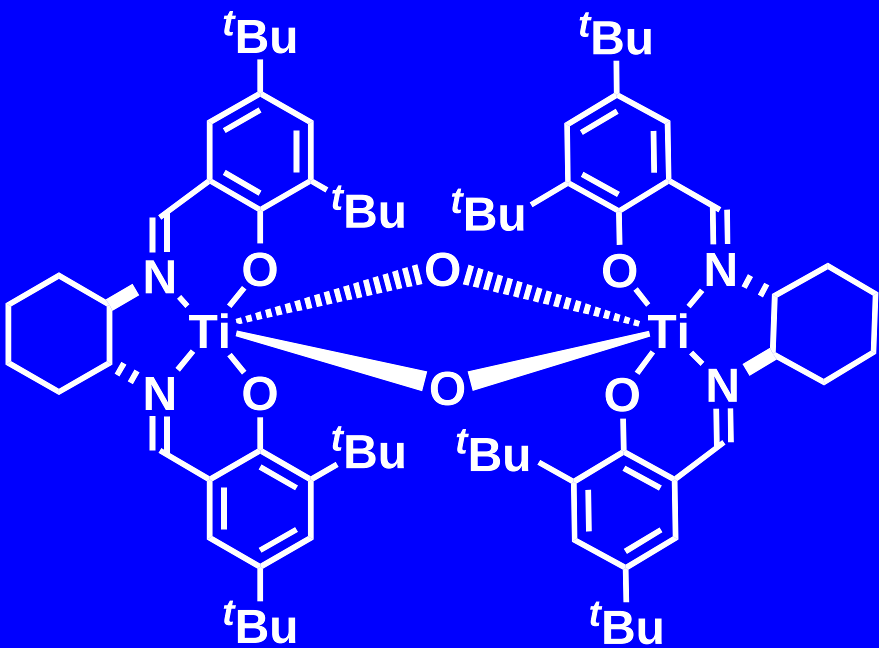
Catalytic Asymmetric Cyanosilylation of Acetophenone





Catalytic Asymmetric Cyanosilylation of Ketones

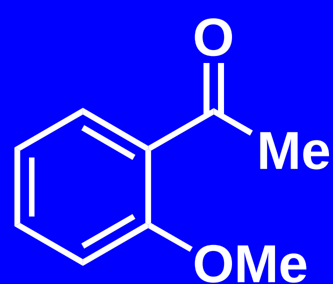
Only one artificial catalyst has been reported to promote the cyanosilylation of ketones under usual (1 atm) conditions.



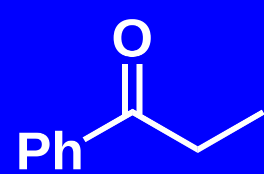
oxynitrilase

alkyl methyl ketones: good ee

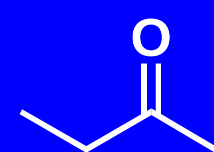
aromatic , Et, or Pr substituted ketones: low yield, low ee



66% ee (92%)

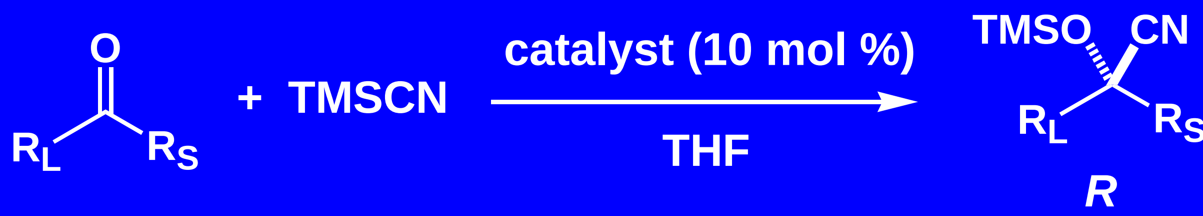


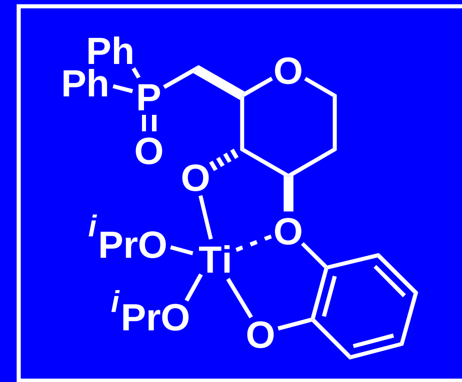
30% ee (100%)



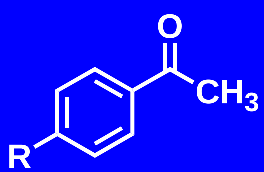
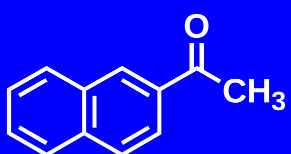
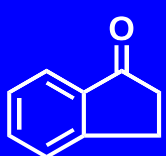
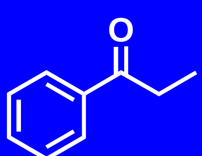
unsuccessful

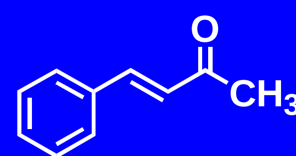
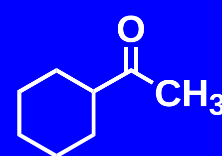
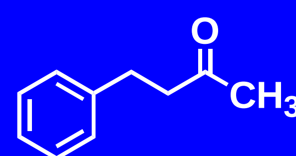
Catalytic Asymmetric Cyanosilylation of Ketones





Hamashima, Y.; Kanai. M.; Shibasaki, M.
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