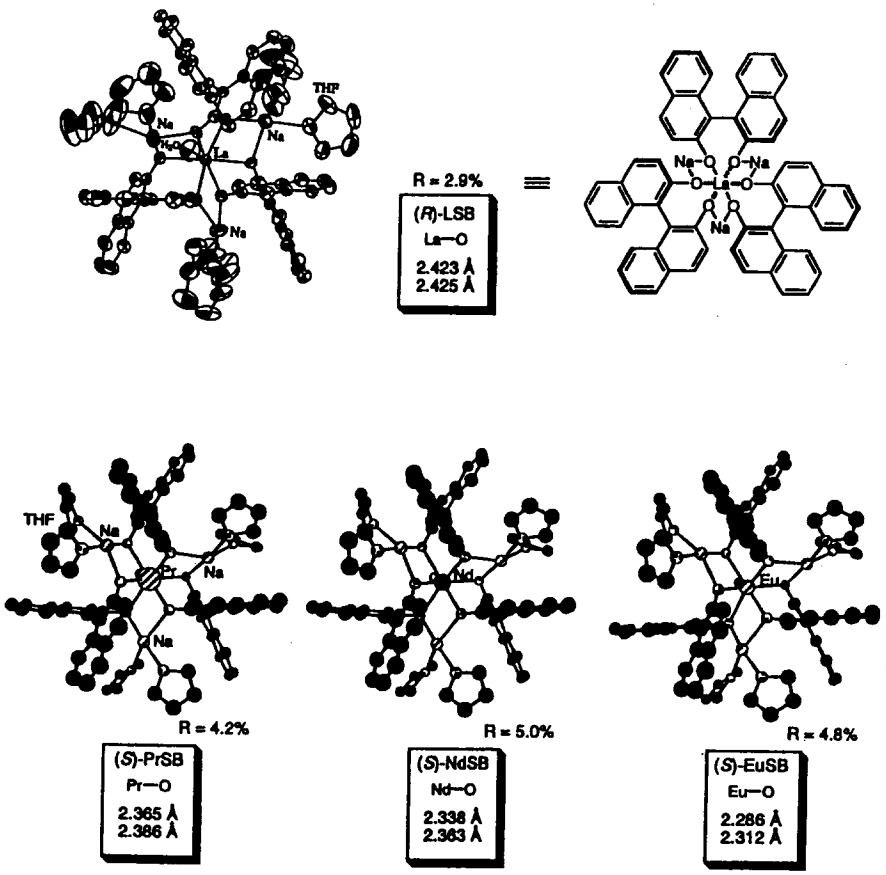
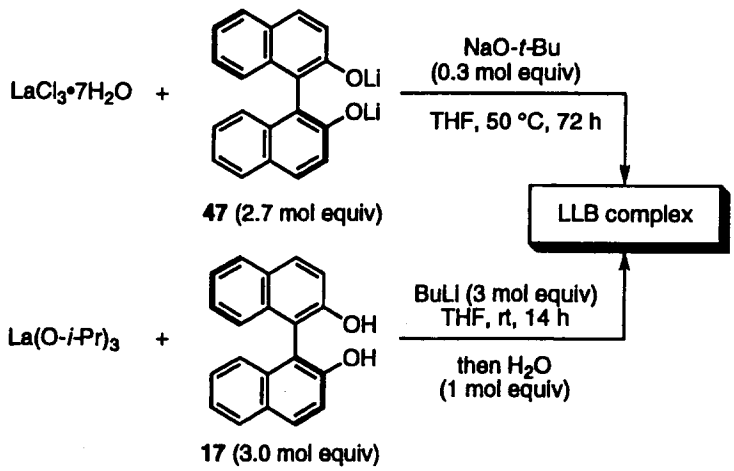
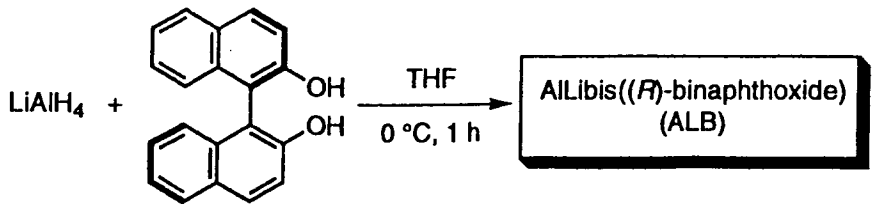


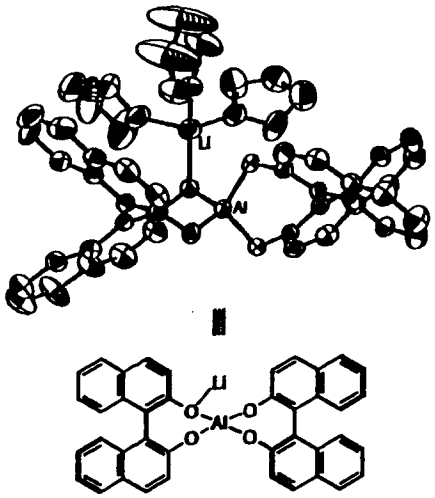
Structure of lanthanoid-sodium-BINOL complexes (LnSB).



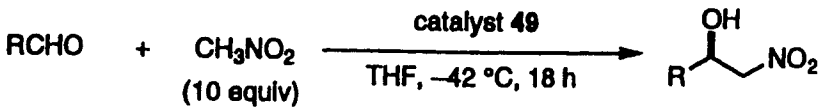
Best preparative procedures for LLB.



17 (2 mol equiv)



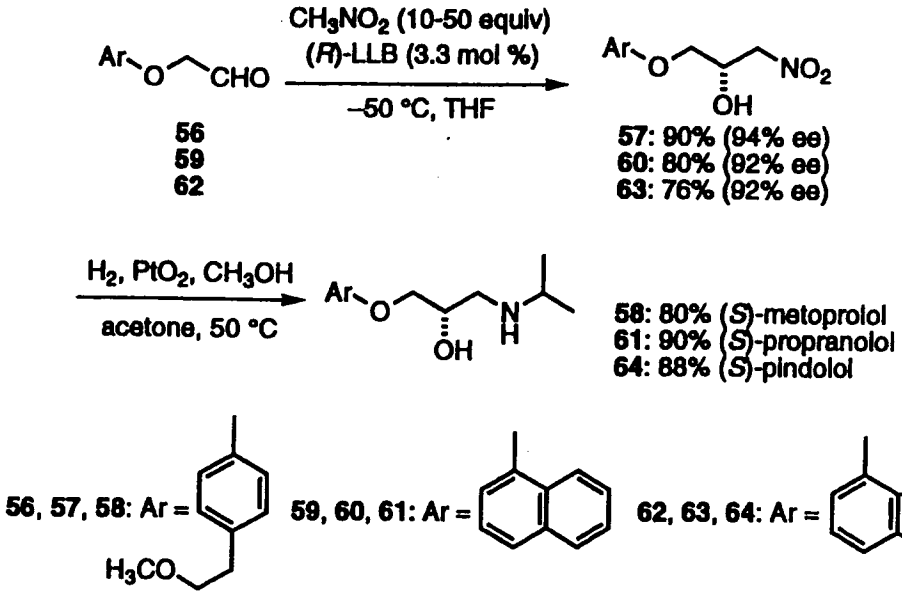
Crystal structure of ALB: $[C_{46}H_{34}AlLiO_4]\cdot 3THF$.



2: R = $PhCH_2CH_2$
50: R = *i*-Pr
52: R = cyclohexyl

13: 79% (73% ee), R = $PhCH_2CH_2$
51: 80% (85% ee), R = *i*-Pr
53: 91% (90% ee), R = cyclohexyl

Catalytic asymmetric nitroaldol reactions promoted by catalyst **49**.



56
59
62

57: 90% (94% ee)
60: 80% (92% ee)
63: 76% (92% ee)

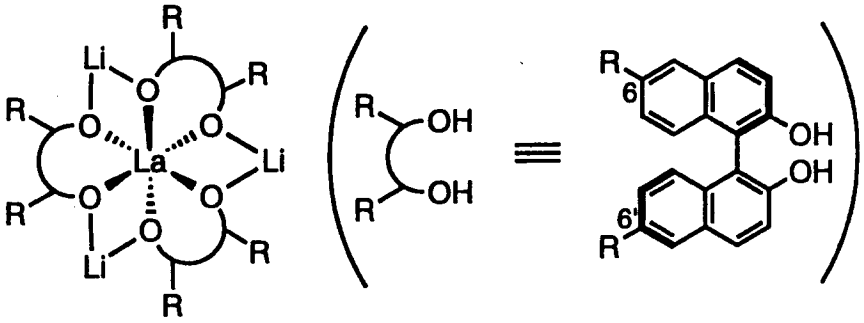
58: 80% (*S*)-metoprolol
61: 90% (*S*)-propranolol
64: 88% (*S*)-pindolol

56, 57, 58: Ar =

59, 60, 61: Ar =

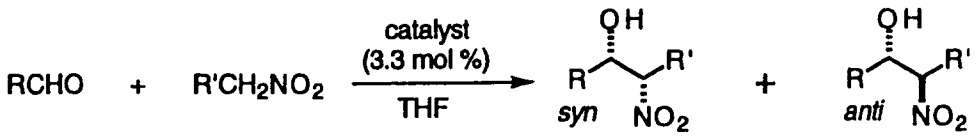
62, 63, 64: Ar =

Catalytic asymmetric syntheses of β-blockers using (*R*)-LLB as a catalyst.



LLB: R = H
69a: R = Br
69b: R = CH_3
69c: R = C≡N
69d: R = C≡CH
69e: R = C≡CPh
69f: R = C≡CSi$(CH_3)_3$
69g: R = C≡CSiEt_3
69h: R = C≡CTBS
69i: R = C≡CSi$(CH_3)_2$Ph

Structural modification of LLB.

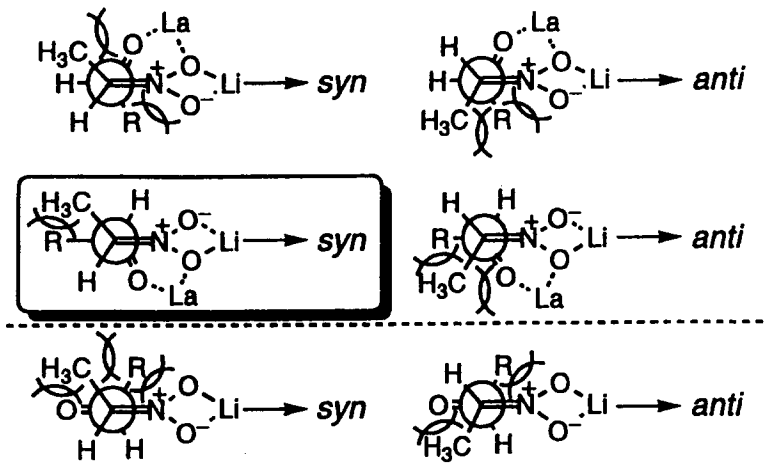


2: R = $PhCH_2CH_2$ **80**: R' = CH_3
89: R = $CH_3(CH_2)_4$ **83**: R' = Et
86: R' = CH_2OH

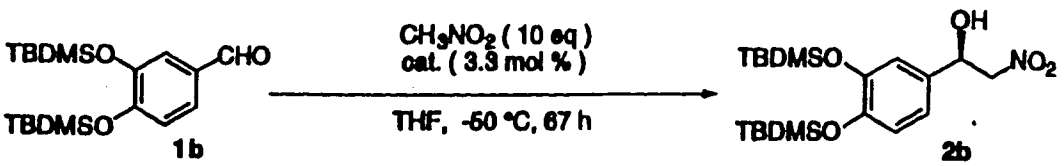
81(*syn*), **82** (*anti*): R = $PhCH_2CH_2$, R' = CH_3
84(*syn*), **85** (*anti*): R = $PhCH_2CH_2$, R' = Et
87(*syn*), **88** (*anti*): R = $PhCH_2CH_2$, R' = CH_2OH
90(*syn*), **91** (*anti*): R = $CH_3(CH_2)_4$, R' = CH_2OH

entry	aldehyde	nitroalkane	catalyst	time (h)	temp (℃)
	nitroaldols	yield (%)	*syn*/*anti*	ee of *syn* (%)	
1	**2** **80**	**LLB** 75	-20	**81** + **82** 79	74:26 66
2	**2** **80**	**69b** 75	-20	**81** + **82** 80	74:26 65
3	**2** **80**	**69d** 75	-20	**81** + **82** 77	84:16 90
4	**2** **80**	**69f** 75	-20	**81** + **82** 72	85:15 92
5	**2** **80**	**69g** 75	-20	**81** + **82** 70	89:11 93
6	**2** **80**	**69g** 115	-40	**81** + **82** 21	94:6 97
7	**2** **83**	**LLB** 138	-40	**84** + **85** 89	85:15 87
8	**2** **83**	**69g** 138	-40	**84** + **85** 85	93:7 95
9	**2** **86**	**LLB** 111	-40	**87** + **88** 62	84:16 66
10	**2** **86**	**69g** 111	-40	**87** + **88** 97	92:8 97
11	**89** **86**	**LLB** 93	-40	**90** + **91** 79	87:13 78
12	**89** **86**	**69g** 93	-40	**90** + **91** 96	92:8 95

Diastereoselective and enantioselective nitroaldol reactions.

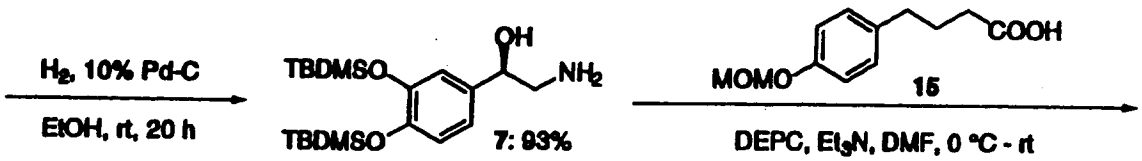


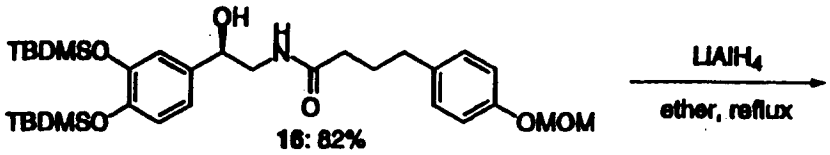
Proposed transition states of diastereoselective and enantioselective nitroaldol reactions.

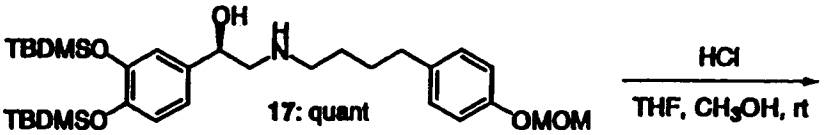


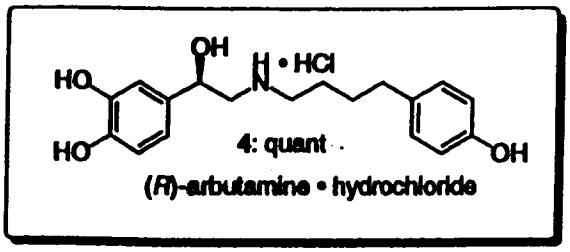
entry	cat.	yield (%)	ee (%)
1	(*S*)-SmLB*	74	92
2	(*S*)-SmLB* + H_2O + *n*-BuLi	93	92

Catalytic Asymmetric Nitroaldol Reactions Using SmLB*

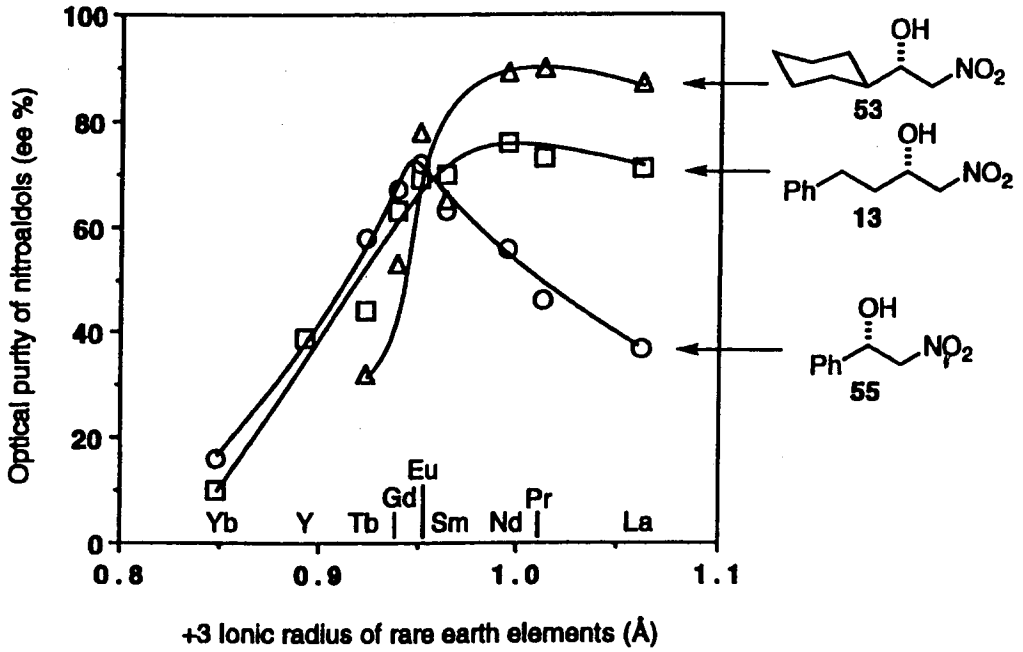




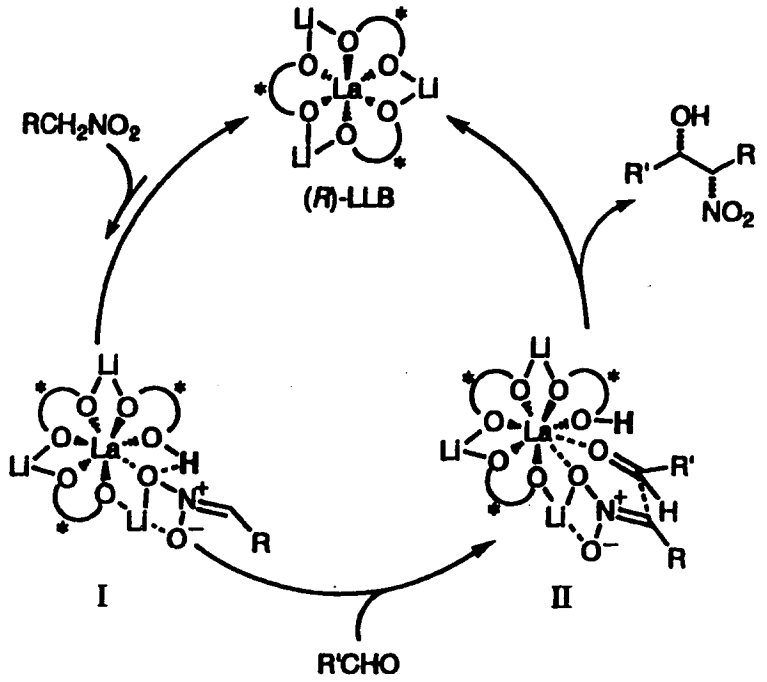




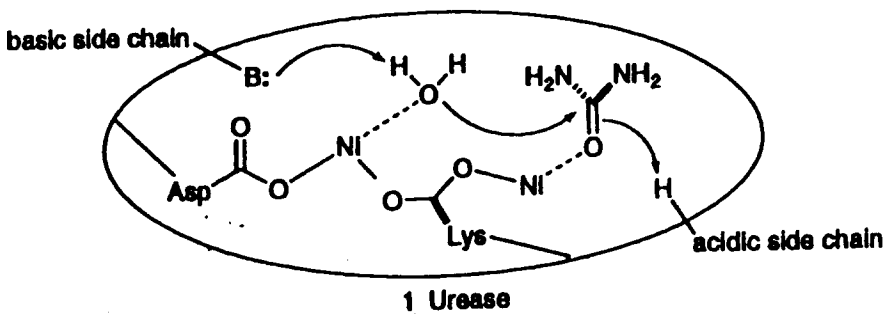
Catalytic Asymmetric Synthesis of (*R*)-Arbutamine Hydrochloride



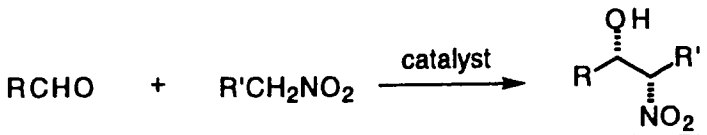
Effects of the ionic radii of rare earth elements on the optical purities of nitroaldol derivatives.



A possible mechanism for catalytic asymmetric nitroaldol reactions.



1 Urease



52: R = C_6H_{11}
2: R = $PhCH_2CH_2$

12: R' = H
80: R' = CH_3
83: R' = Et
86: R' = CH_2OH

53: R = C_6H_{11}, R' = H
81: R = $PhCH_2CH_2$, R' = CH_3
84: R = $PhCH_2CH_2$, R' = Et
87: R = $PhCH_2CH_2$, R' = CH_2O

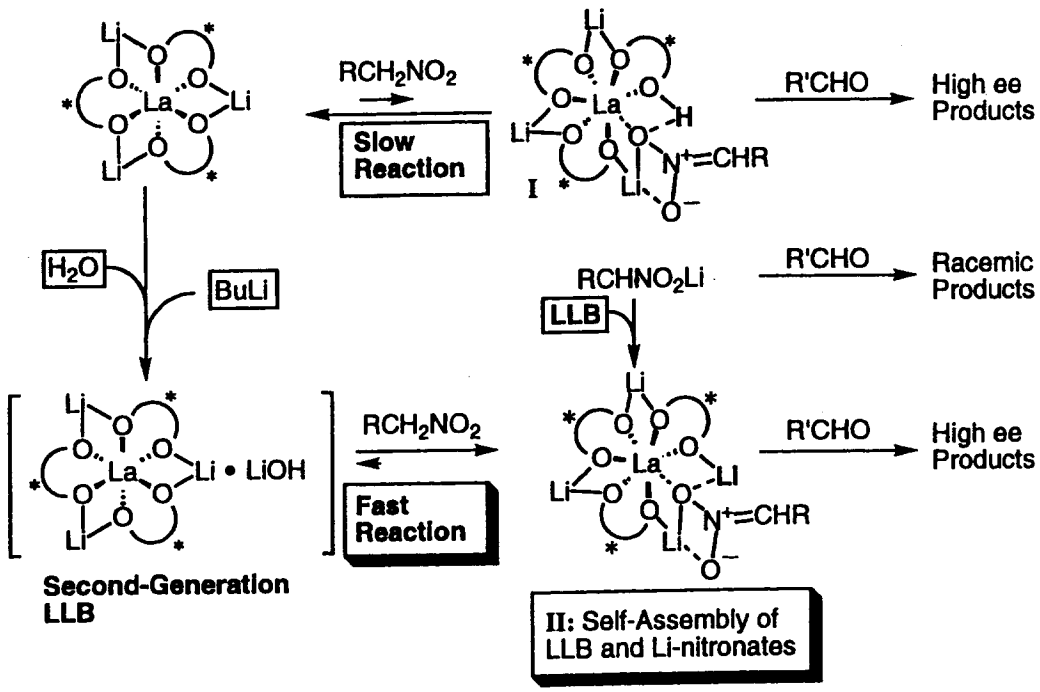
entry	substrate	catalyst (mol %)	time (h)	temp (°C)	productyield (%) (*syn/anti*)	ee (%) of *syn*
1	**52** + **12**	LLB (1)	24	-50	**53**	5.6	88
2	**52** + **12**	LLB-II (1)	24	-50	**53**	73	89
3	**52** + **12**	LLB-II (3.3)	4	-50	**53**	70	90
4	**52** + **12**	**A** (1)	42	-50	**53**	86	51
5	**2** + **80**	**69g** (1)	113	-30	**81**	25 (70/30)	62
6	**2** + **80**	**69g-II** (1)	113	-30	**81**	83 (89/11)	94
7	**2** + **83**	**69g** (1)	166	-40	**84**	trace	-
8	**2** + **83**	**69g-II** (1)	166	-40	**84**	84 (95/5)	95
9	**2** + **86**	**69g** (1)	154	-50	**87**	trace	-
10	**2** + **86**	**69g-II** (1)	154	-50	**87**	76 (94/6)	96

LLB-II: LLB + H_2O (1 mol equiv) + BuLi (0.9 mol equiv)

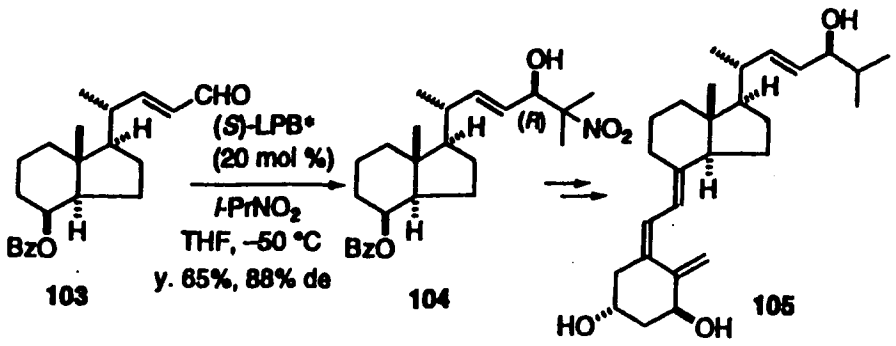
Catalyst **A**: LLB + H_2O (1 mol equiv) + BuLi (2 mol equiv)

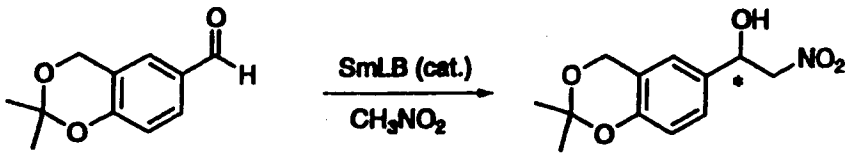
69g-II: **69g** + H_2O (1 mol equiv) + BuLi (0.9 mol equiv)

Comparisons of catalyst activity between either LLB and second-generation LLB (LLB-II) or **69g** and **69g**-II.



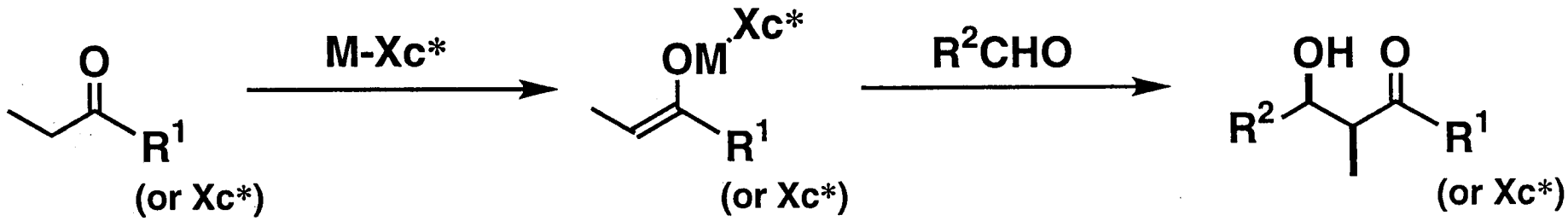
Proposed mechanism for the catalytic asymmetric nitroaldol reaction promoted by LLB, LLB-II or LLB-Li-nitronate.


CHO
(S)-LPB*
(20 mol %)
i-PrNO2
THF, –50 °C
y. 65%, 88% de
BzO
H
OH
(R)
NO2
HO
103
104
105

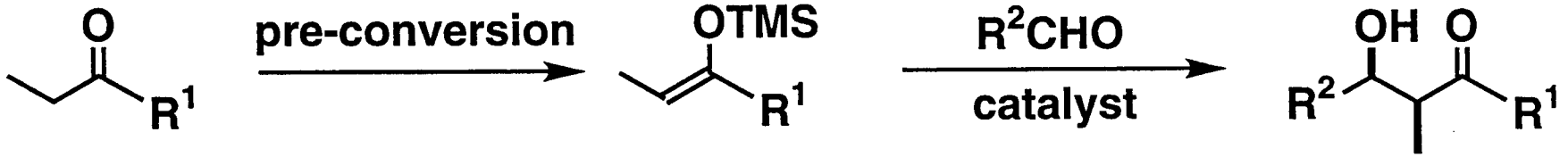

O
H
SmLB (cat.)
CH3NO2
OH
NO2
111: 100 g
112: 120 g, 90% ee

Scheme 17

1980's– Chiral Auxiliary Induced Asymmetric Aldol Reactions

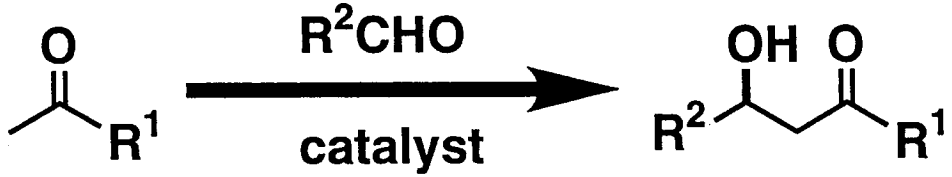


1990's– Catalytic Asymmetric Mukaiyama-type Aldol Reactions



1997–

Direct Catalytic Asymmetric Aldol Reactions



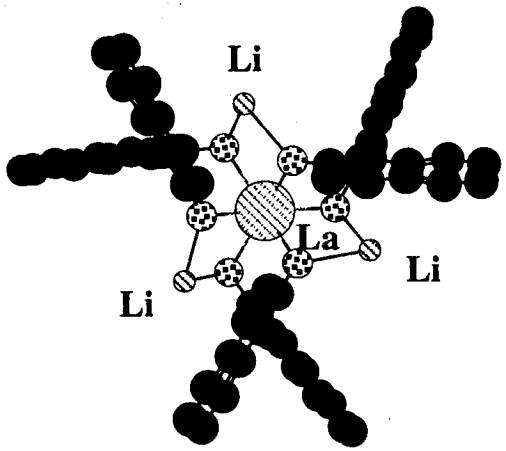
Predictable Problems

Self-condensation of Aldehydes

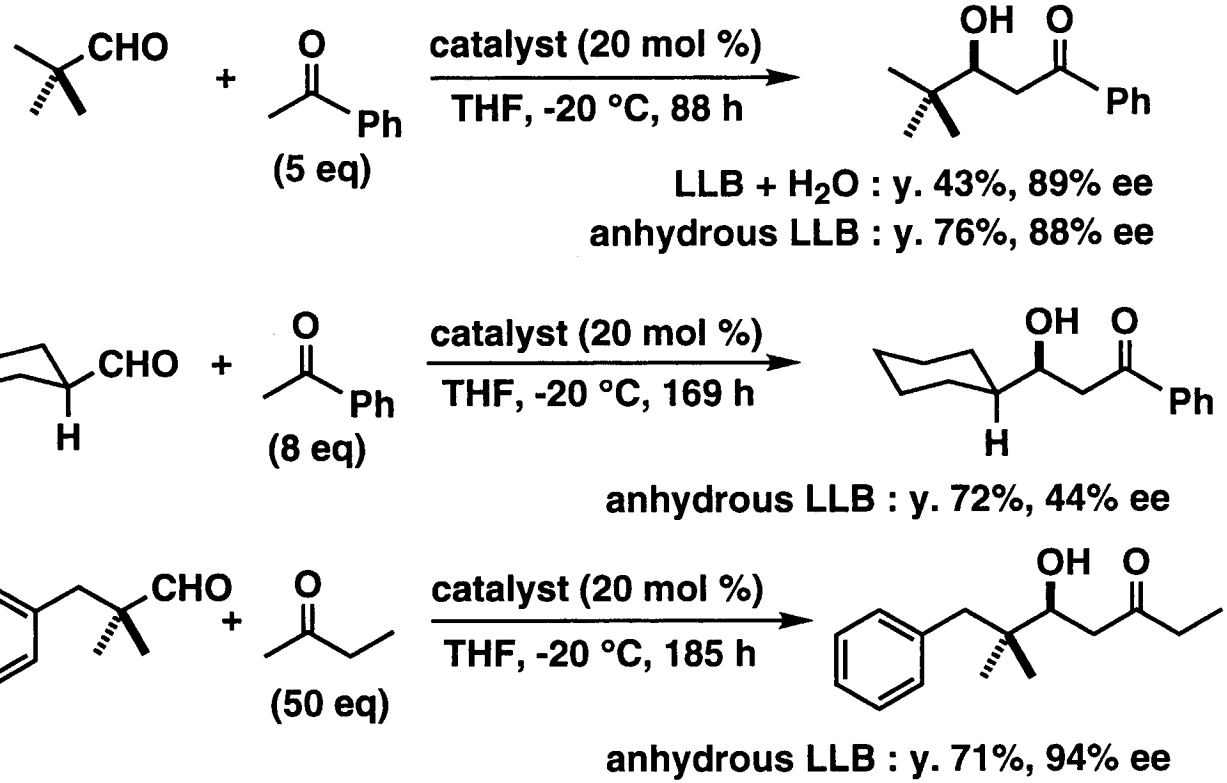
Catalytic Cycle

Enantiomeric Excess

Direct Catalytic Asymmetric Aldol Reactions of Aldehydes with Unmodified Ketones Promoted by LLB



Structure of
$LaLi_3$tris[(*R*)-binaphthoxide]
((*R*)-LLB)

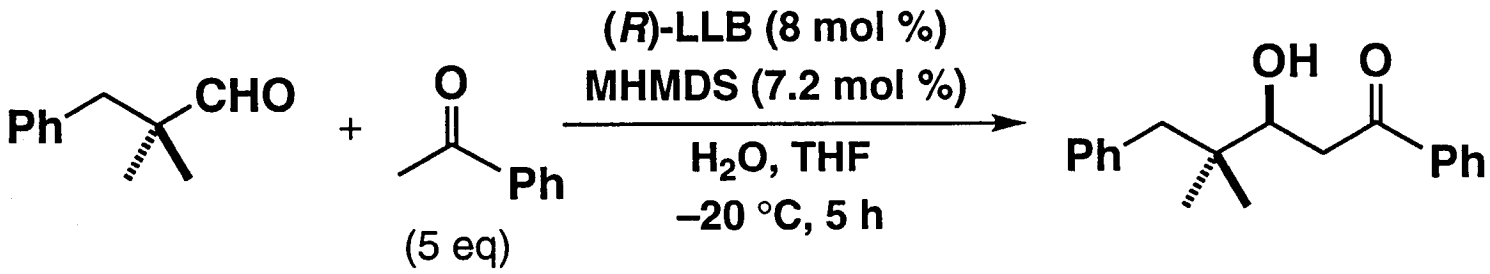


Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl,* 1997, *36*, 1871.
C&EN, September 8 (1997). *Chemistry and Industry*, October 20 (1997)

How to Increase the Catalytic Activity ?

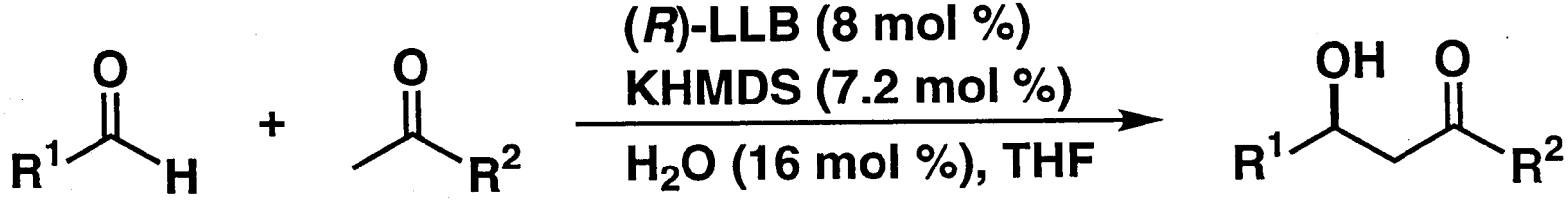
1) + Cocatalyst with Higher Basicity 2) Using More Basic Metal Naphthoxide

The Effects of Alkali Metal Hydroxides and Water



entry	Alkali Metal (M)	H_2O (mol %)	yield (%)	ee (%)
1	-	0	trace	-
2	KHMDS	0	83	58
3	KHMDS	4	85	65
4	KHMDS	8	89	79
5	KHMDS	16	83	85
6	KHMDS	32	67	89
7	LiHMDS	16	22	80
8	NaHMDS	16	28	86

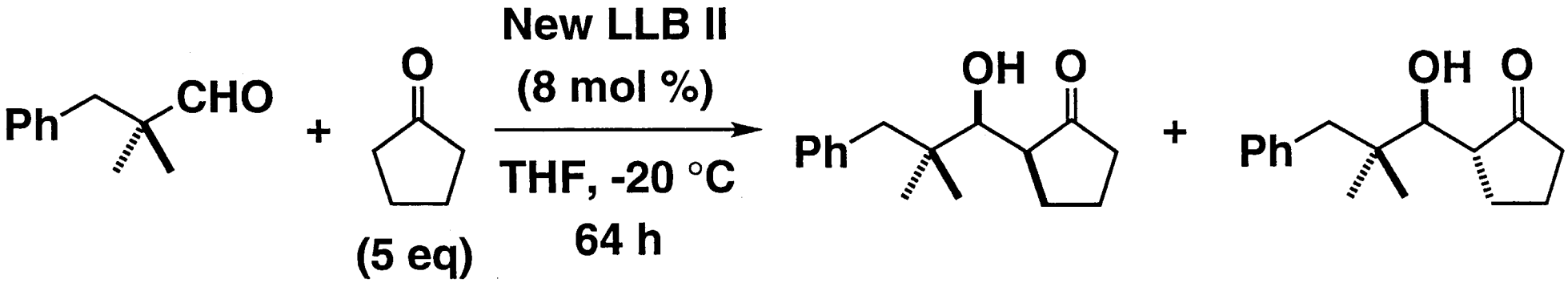
Direct Catalytic Asymmetric Aldol Reactions Using New LLB II with Various Aldehydes and Ketones



entry	aldehyde (R^1)	ketone (R^2)	temp. (°C)	time (h)	yield (%)	ee (%)
1	*t*-Bu	Ph (5 eq)	-20	15	75	88
2	$PhCH_2C(CH_3)_2$	Ph (5 eq)	-20	28	85	89
3	$PhCH_2C(CH_3)_2$	CH_3 (10 eq)	-20	20	62	76
4[1)]	$PhCH_2C(CH_3)_2$	Et (15 eq)	-20	95	72	88
5	$BnOCH_2C(CH_3)_2$	Ph (5 eq)	-20	36	91	90
6[2)]	$BnOCH_2C(CH_3)_2$	Ph (5 eq)	-20	24	70	93
7	*i*-Pr	*m*-NO_2-C_6H_4 (3 eq)	-50	70	68	70
8[3)]	Et_2CH	*m*-NO_2-C_6H_4 (3 eq)	-45	96	60	80
9[4)]	C_5H_{11}	*m*-NO_2-C_6H_4 (5 eq)	-50	96	55	42

1) water (0.8 mol %); 2) 1.1 g scale; 3) 15 mol % of cat was used; 4) 30 mol % of cat was used.

The First Diastereoselective Direct Catalytic Asymmetric Aldol Reaction

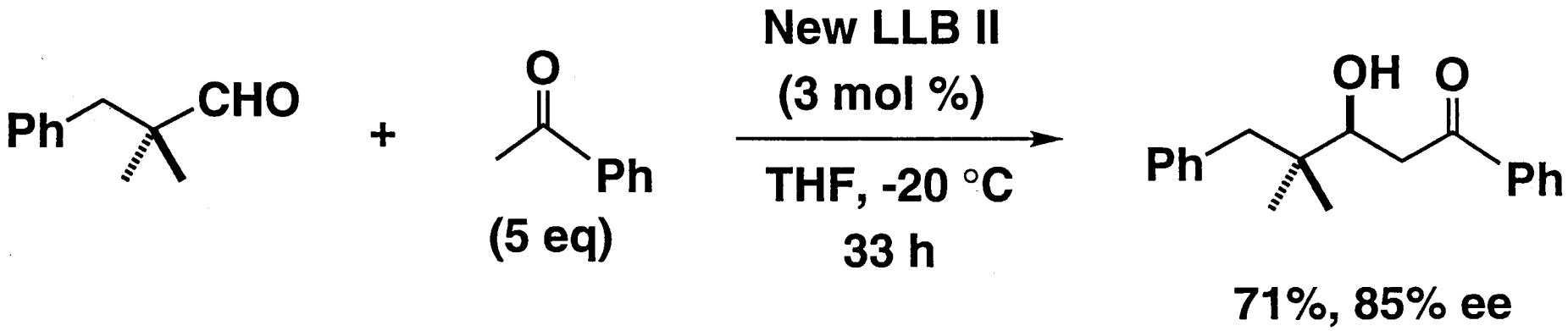


85%, *syn*/*anti* = 89 / 11

75% ee (*syn*)

New LLB II = LLB-KHMDS-H_2O

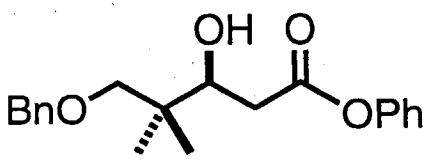
N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, and M. Shibasaki, *submitted.*



New LLB II = LLB-KHMDS-H_2O

"The powder obtained from the catalyst solution by evaporation of the solvent showed a similar result, which can be easily handled without the need of and inert atmosphere."

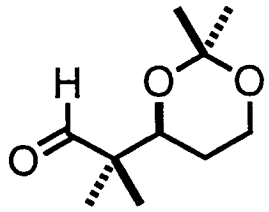
Catalytic Asymmetric Formal Synthesis of Epothilone A and Bryostatin 7



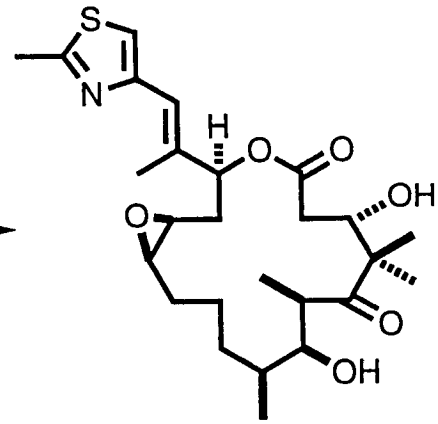
93% ee

1) $LiAlH_4$
2) $(CH_3O)_2C(CH_3)_2$
3) Li, NH_3;
$(COCl)_2$, DMSO, Et_3N

94% (3 steps)

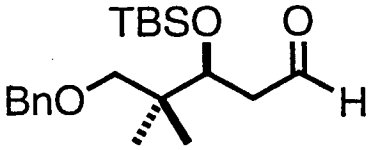


Schinzer's intermediate (1997)

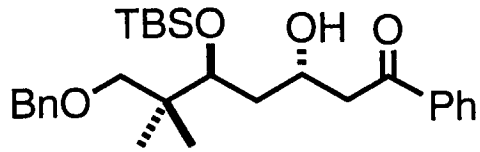


epothilone A

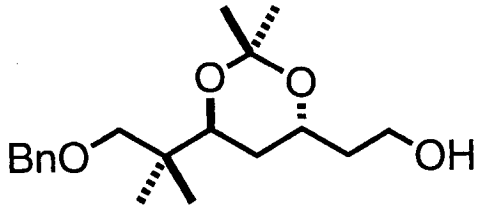
1) TBSOTf
2) DIBAL-H
3) PCC
87% (3 steps)



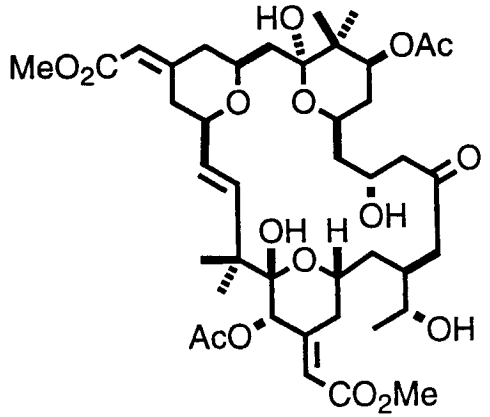
(*S*)-New LLB II
(20 mol %)
$PhCOCH_3$ (5 eq)
THF, -20 °C



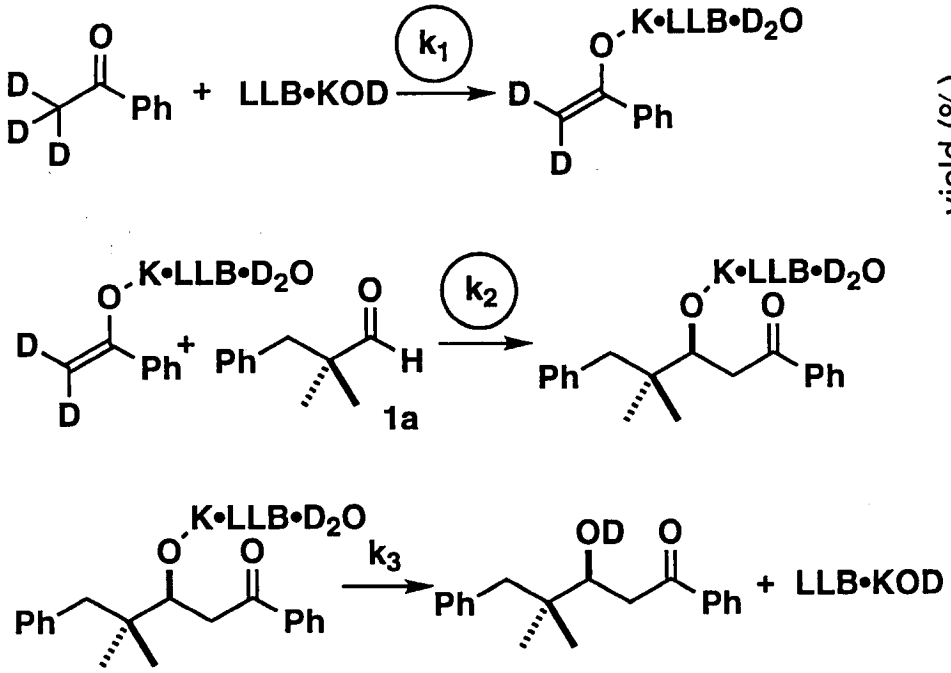
90%
***anti*/*syn* = 7/1, 95% ee (*anti*)**



Masamune's intermediate (1990)



bryostatin 7

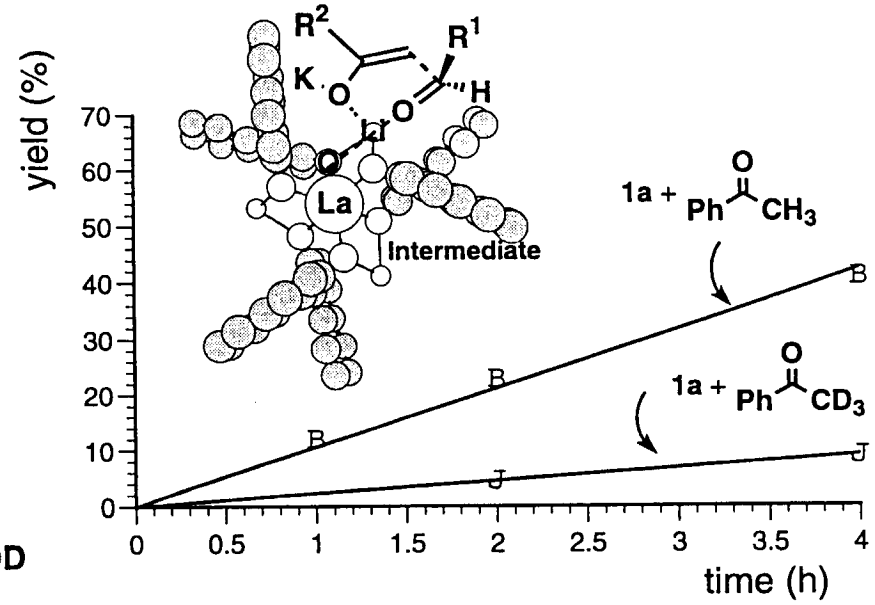


$$\frac{d[\text{aldol}]}{dt} \cong k_1[\text{ketone}][\text{LLB•KOD}]$$

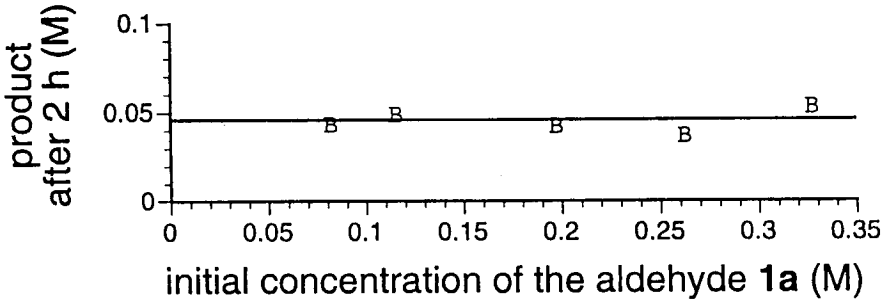
[cf. NaOEt catalyzed aldol reaction

$$\frac{d[\text{aldol}]}{dt} \cong k_2K_1[\text{ketone}][\text{NaOEt}][\text{aldehyde}]$$]

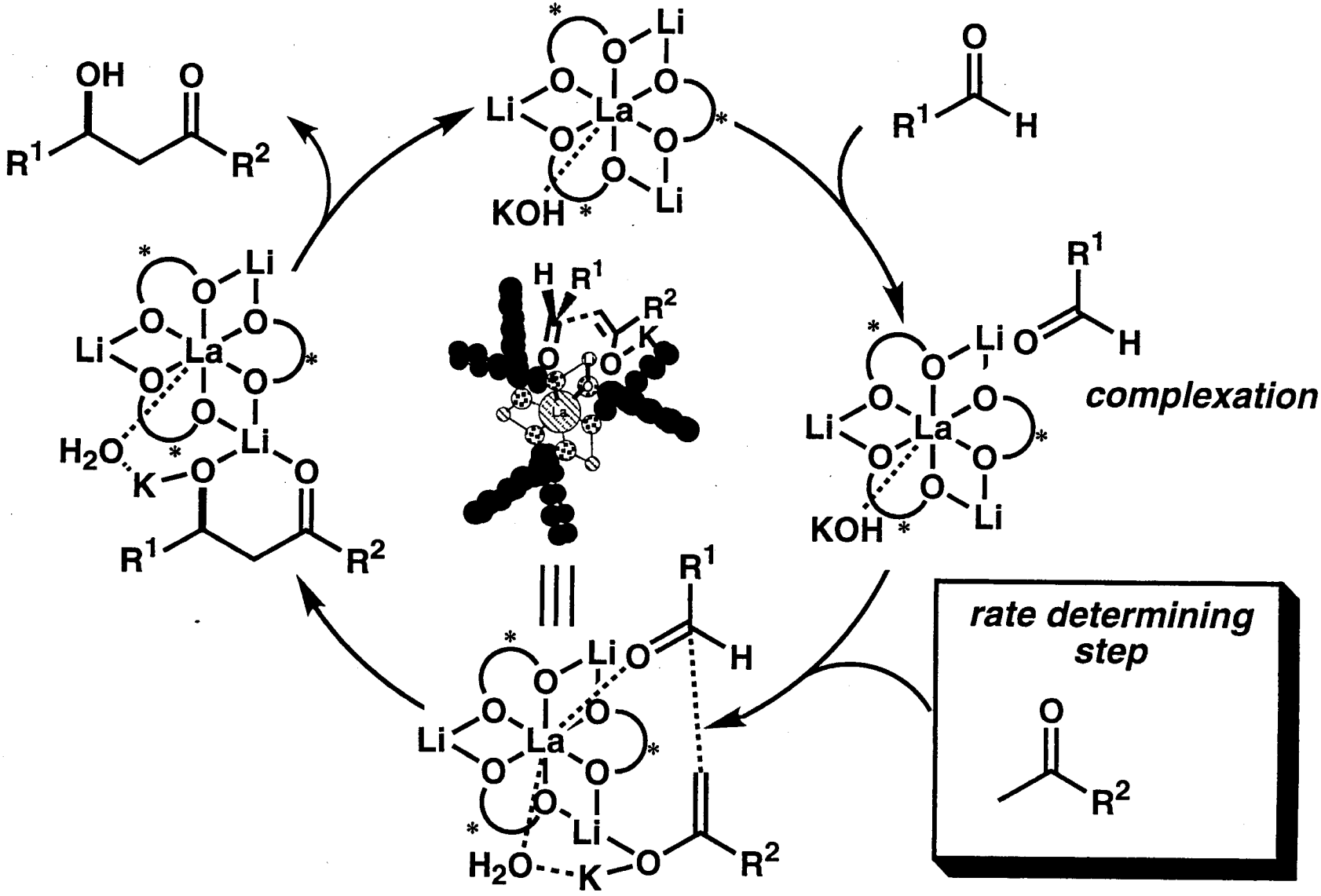
Isotope Effects of Aceto-d_3-phenone



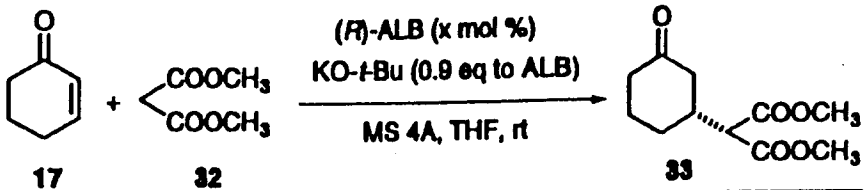
The Dependence of the Reaction (1a + Acetophenone) Rate on the Concentrationof the Aldehyde



The Proposed Mechanism of the Direct Aldol Reaction Catalyzed by New LLB II



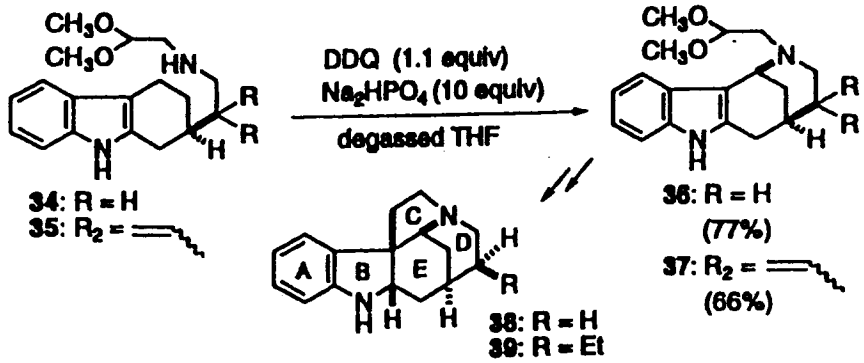
A greatly improved catalytic asymmetric Michael addition of **32** to **17**



17 **32** **33**

entry	ALB (x mol %)	KO-*t*-Bu	MS 4A	time (h)	yield (%)	ee (%)
1	10	–	–	72	90	93
2	5	+	–	48	97	98
3	0.3	+	–	120	74	88
4	0.3	+	+[a]	120	94	99
5[b]	1.0	+	+[c]	72	97	99

a) MS 4A (8.3 g) was used for ALB (1 mmol); b) 10 g scale reaction;
c) MS 4A (2.0 g) was used for ALB (1 mmol).



Catalytic asymmetric syntheses of 20-deethyltubifolidine (**38**) and tubifolidine (**39**)