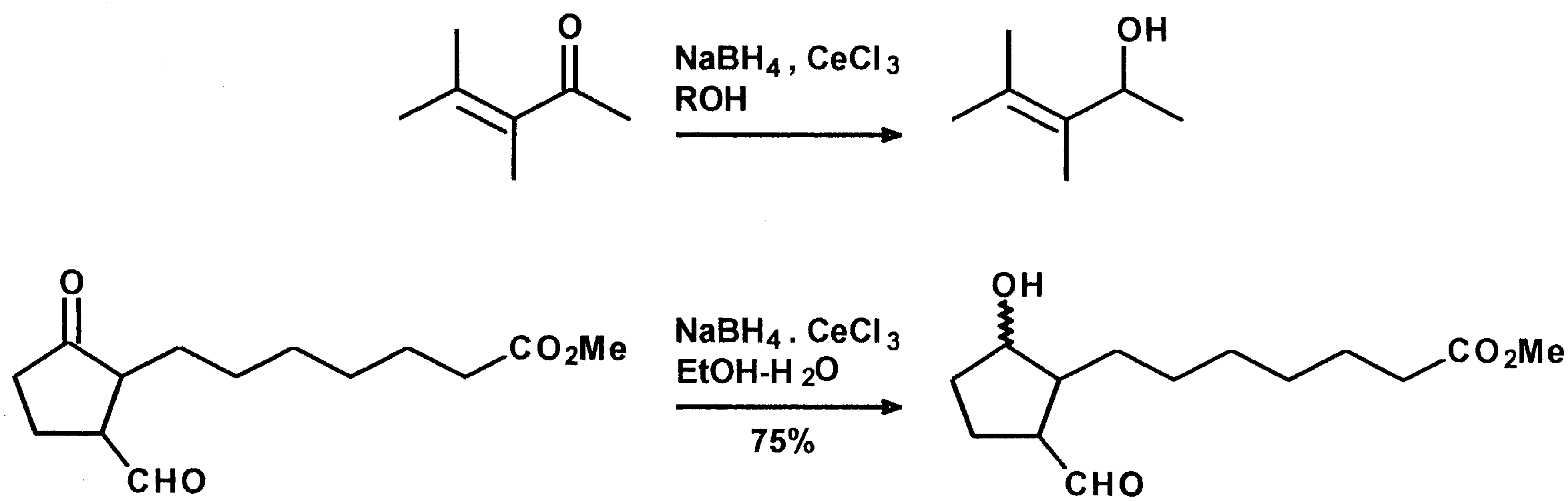
# *Cerium versus Titanium in Promoting Diastereoselective Reduction and Alkylation Reactions: a Step forwards Clean Chemistry*

*Prof. Giuseppe Bartoli*

*Università degli Studi di Bologna*

*Dipartimento di Chimica Organica "A. Mangini"*

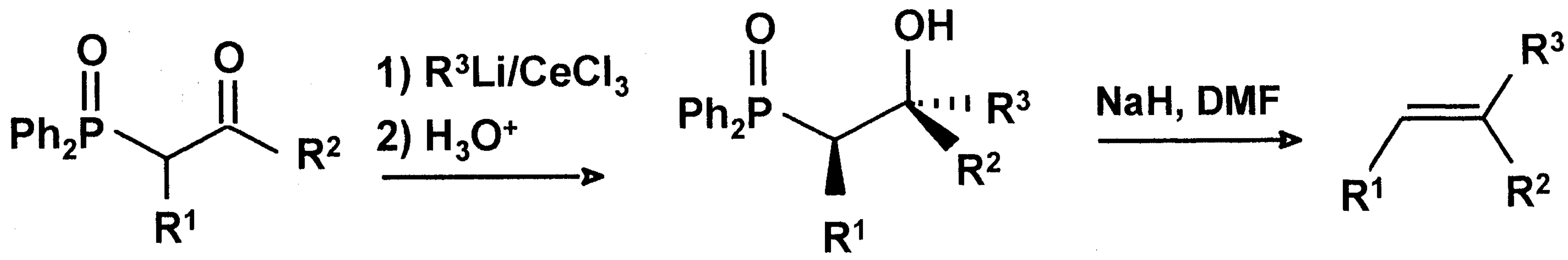
# Luche reduction




J.L. Luche, A.L. Gemal, *J. Am. Chem.Soc.,* 1981 , 5454

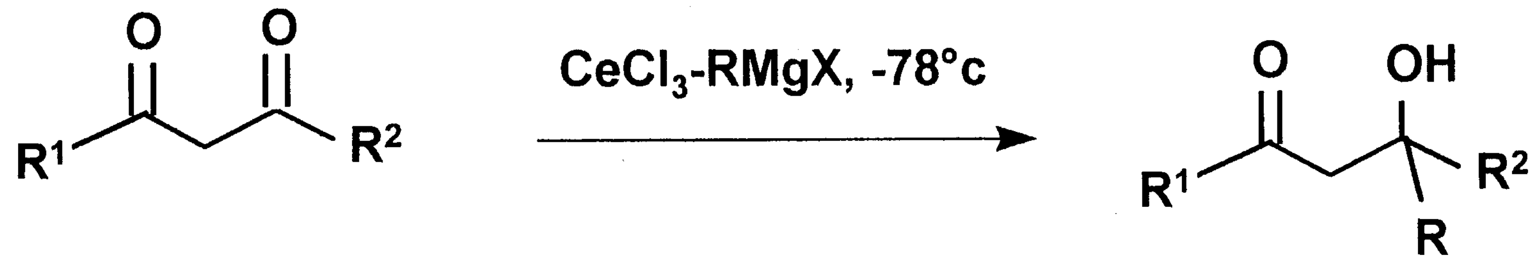
J.L. Luche, A.L. Gemal, *J. Am. Chem.Soc.,* 1979 , 5848

# Synthesis of trisubstituted olefins

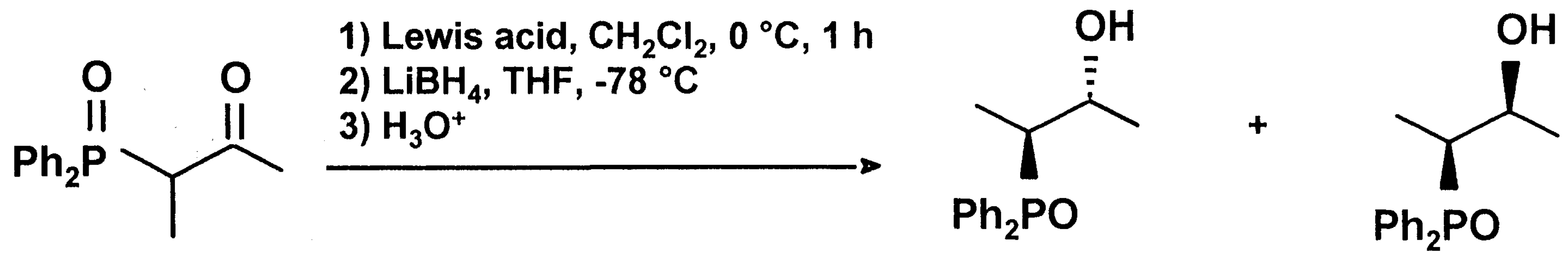



G. Bartoli *et al.*, *Angew. Chem. Int. Ed. Engl.*, 1995, *34*, 2046

# Monoalkylation of 1,3-diketones



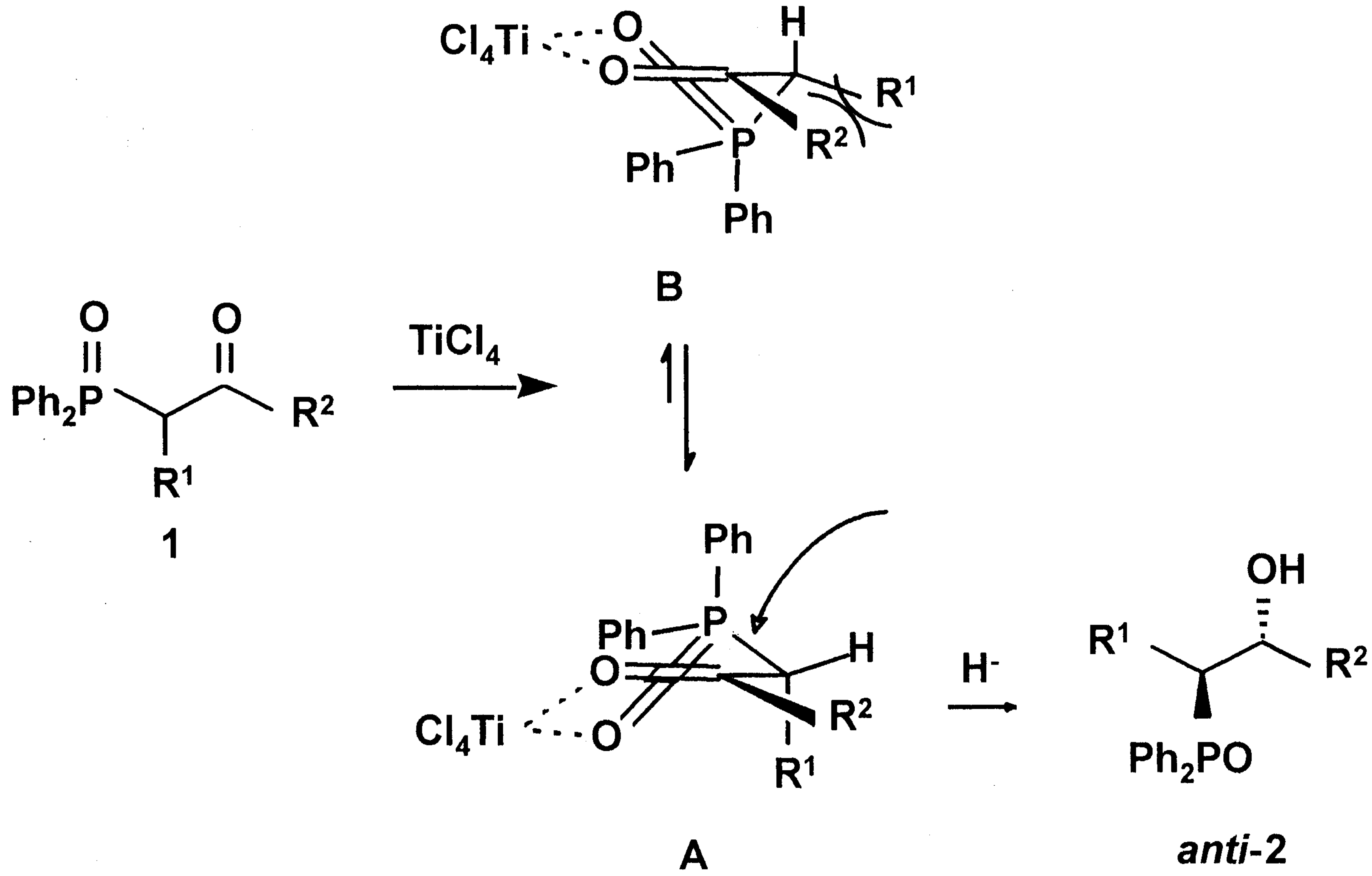

G. Bartoli *et al.*, *Angew. Chem. Int. Ed. Engl.*, 1993, *32*, 1061



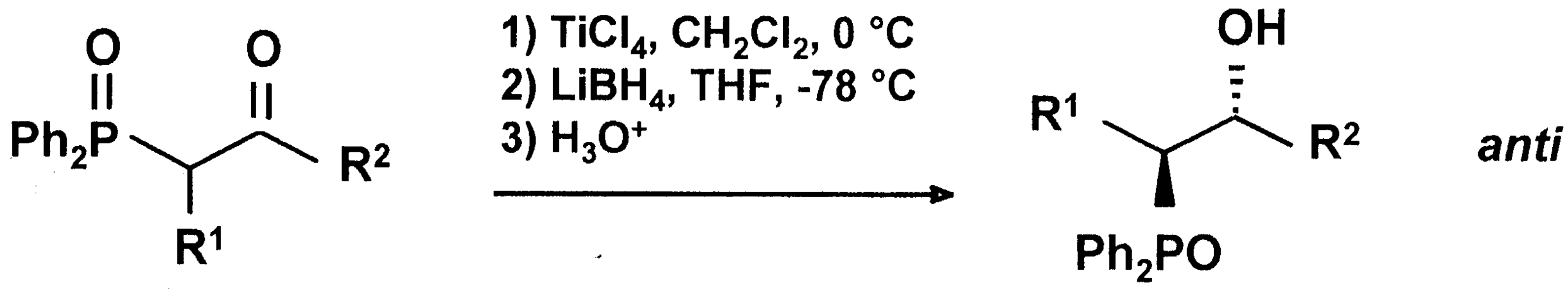

1      *anti*- 2      *syn*-2

| Lewis acid | Yield (%) | *anti / syn* |
|---|---|---|
| $TiCl_4$ | >98 | 75 / 25 |
| $CeCl_3$ | >98 | 25 / 75 |

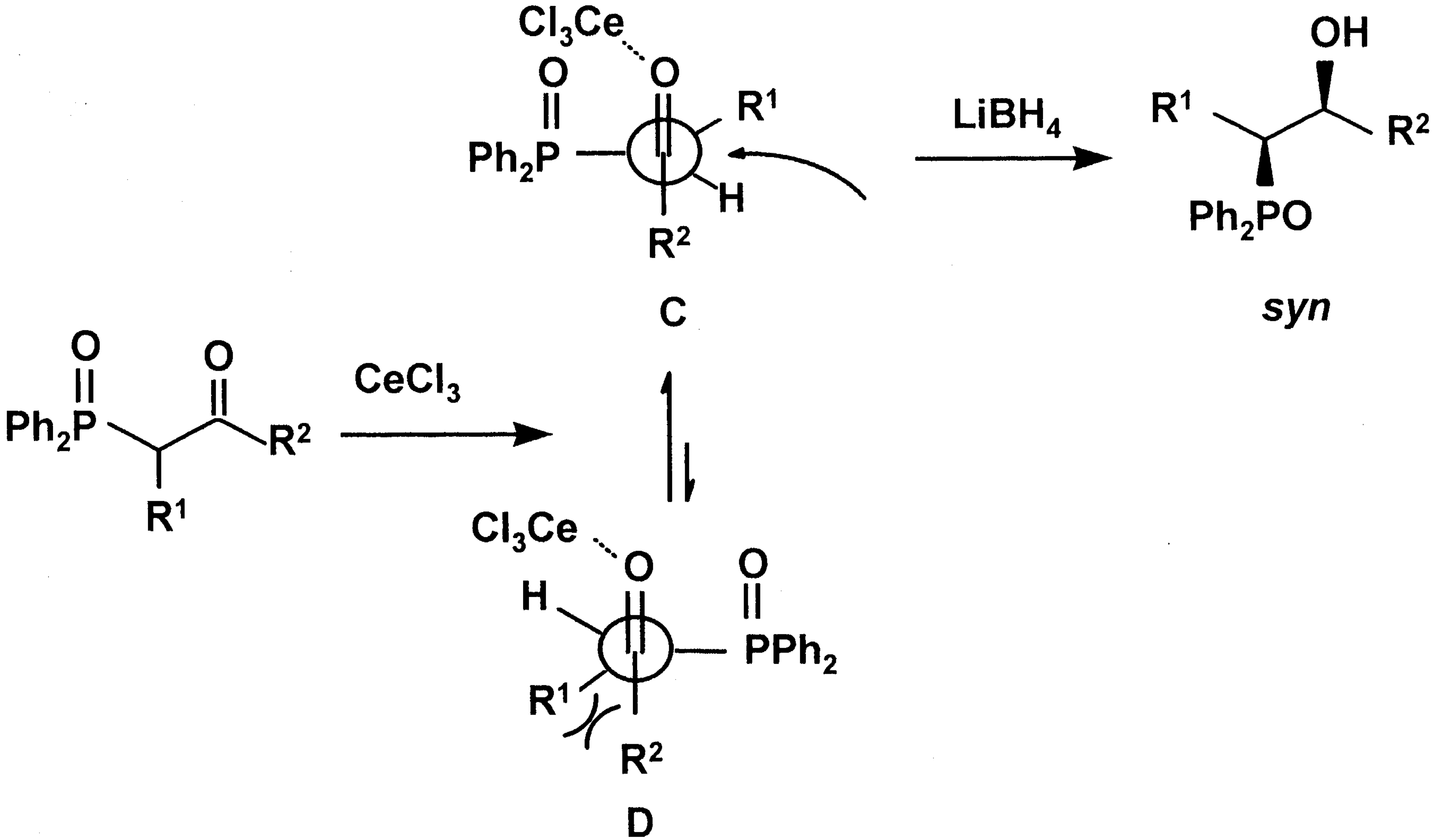
G. Bartoli *et al.*, *Chem. Eur. J.* , 1997, *3*, 1941

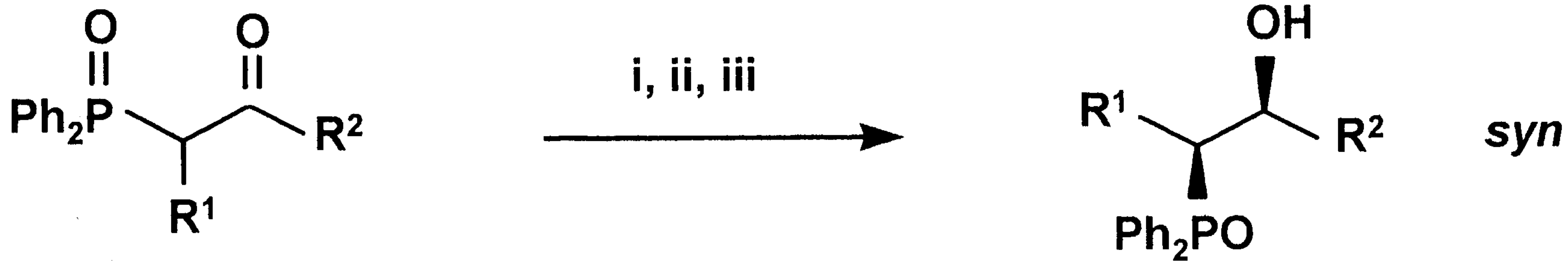


Cl4Ti
Ph
B
TiCl4
1
Ph
A
H-
OH
Ph2PO
anti-2




| $R^1$ | $R^2$ | *anti / syn* | Yield (%) |
|---|---|---|---|
| Me | Me | 75 / 25 | 98 |
| Pr | Bu | 87 / 13 | 95 |
| Me | Ph | 90 / 10 | 98 |
| Me | c-$C_6H_{11}$ | 98 / 2 | 97 |
| $CH_2Ph$ | Ph | 98 / 2 | 95 |
| c-$C_6H_{11}$ | Pr | 97 / 3 | 95 |
| Pr | Ph-C≡C- | 98 / 2 | 98 |

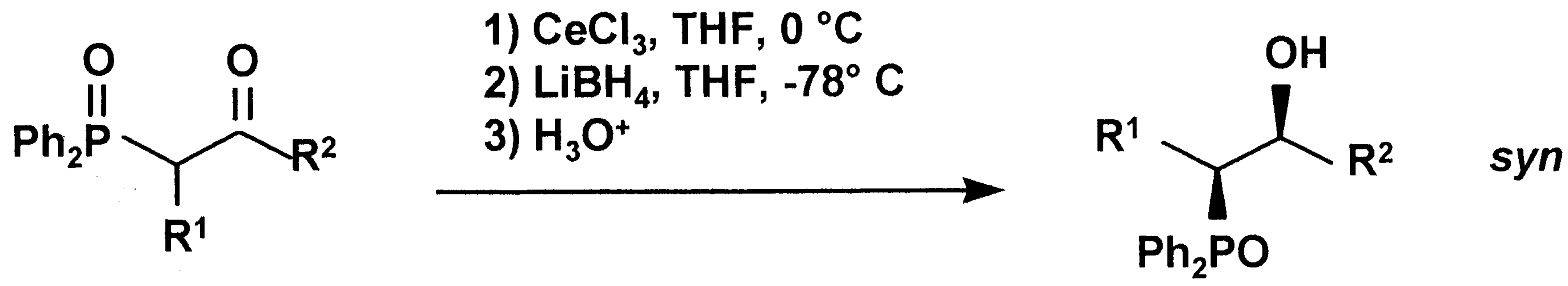

Cl3Ce
O
O
Ph2P
R1
H
R2
C
LiBH4
R1
OH
R2
Ph2PO
syn
O
O
Ph2P
R2
R1
CeCl3
Cl3Ce
O
O
H
PPh2
R1
R2
D



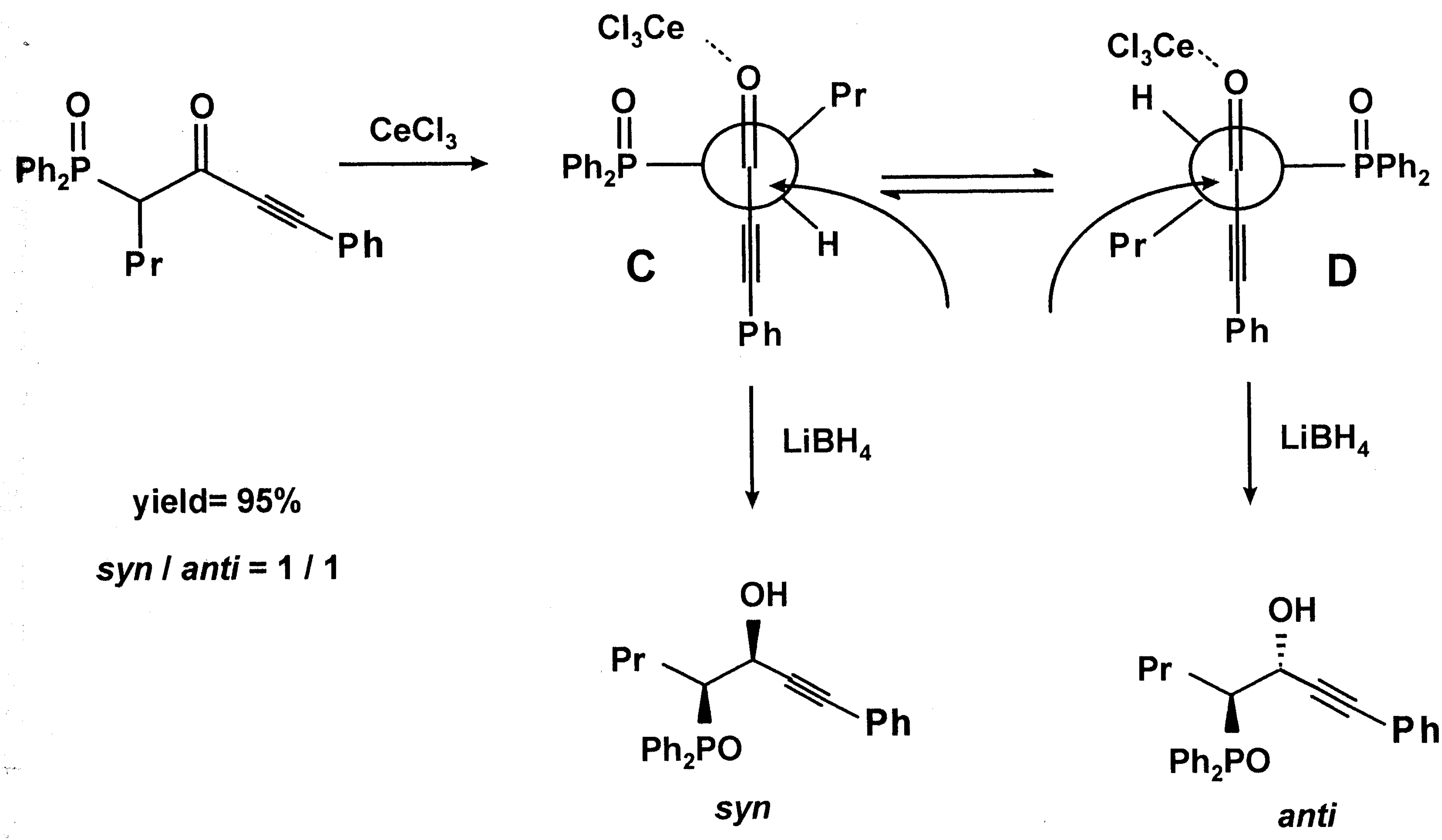

Method A: i) $CeCl_3$ (1.1 eq), $CH_2Cl_2$ , 0 °C; ii) $LiBH_4$ (1.1 eq), THF, -78 °C; iii) $H^+$

Method B: i) $CeCl_3$ (1.1 eq), THF, 0 °C; ii) $LiBH_4$ (1.1 eq), THF, -78 °C; iii) $H^+$

| Method | $R^1$ | $R^2$ | *syn / anti* | Yield (%) |
|---|---|---|---|---|
| A | Me | Me | 75 / 25 | 98 |
| B | Me | Me | 91 / 9 | 98 |
| A | Pr | Bu | 87 / 13 | 98 |
| B | Pr | Bu | 96 / 4 | 98 |
| A | $CH_2Ph$ | Me | 86 / 14 | 98 |
| B | $CH_2Ph$ | Me | 96 / 4 | 98 |

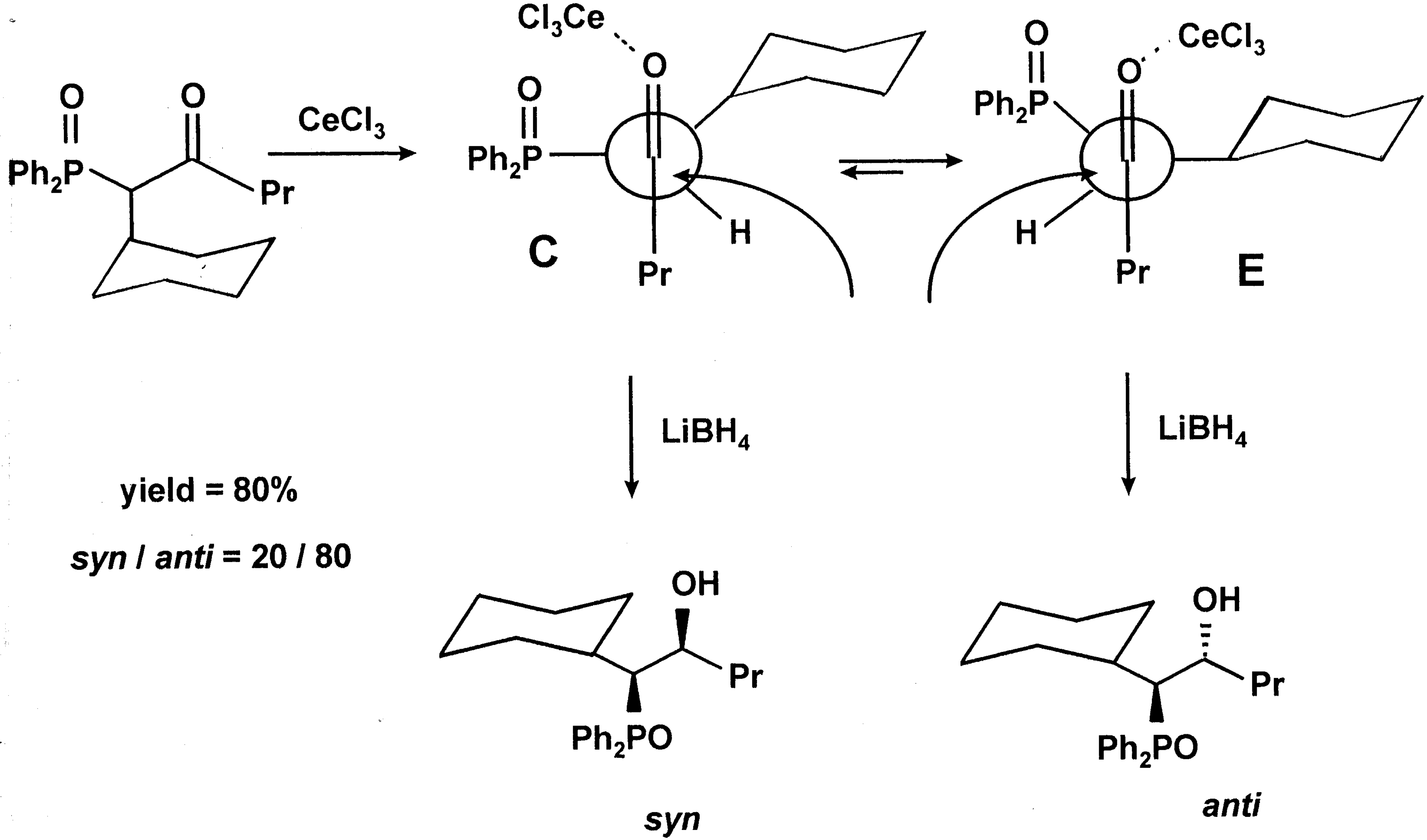



| $R^1$ | $R^2$ | *syn* / *anti* | Yield (%) |
|---|---|---|---|
| Pr | Ph-C≡C- | 50 / 50 | 95 |
| Me | Me | 91 / 9 | 98 |
| Me | c-$C_6H_{11}$ | 97 / 3 | 98 |
| $CH_2Ph$ | i-Pr | 95 / 5 | 98 |
| $C_8H_{17}$ | $C_{13}H_{27}$ | 90 / 10 | 98 |
| c-$C_6H_{11}$ | Pr | 20 / 80 | 80 |




yield= 95%

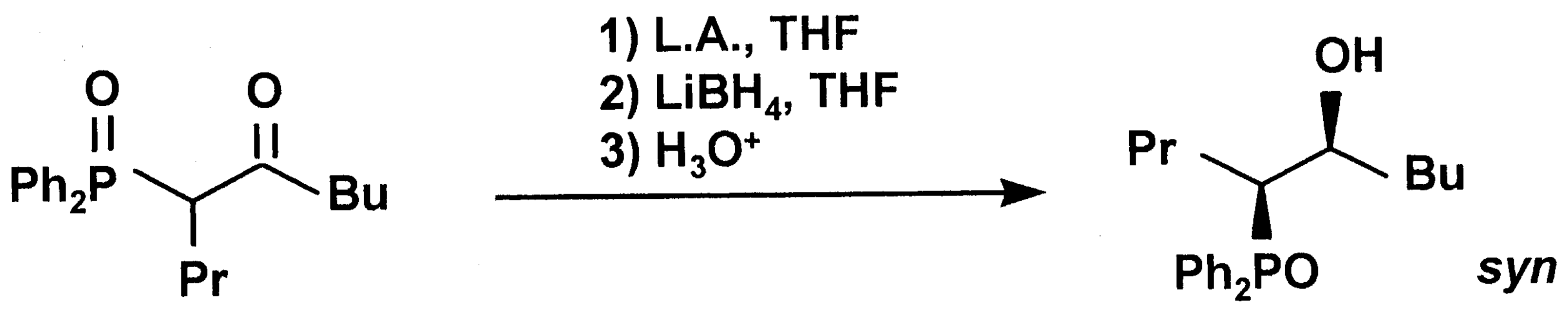
*syn* / *anti* = 1 / 1




yield = 80%

*syn* / *anti* = 20 / 80

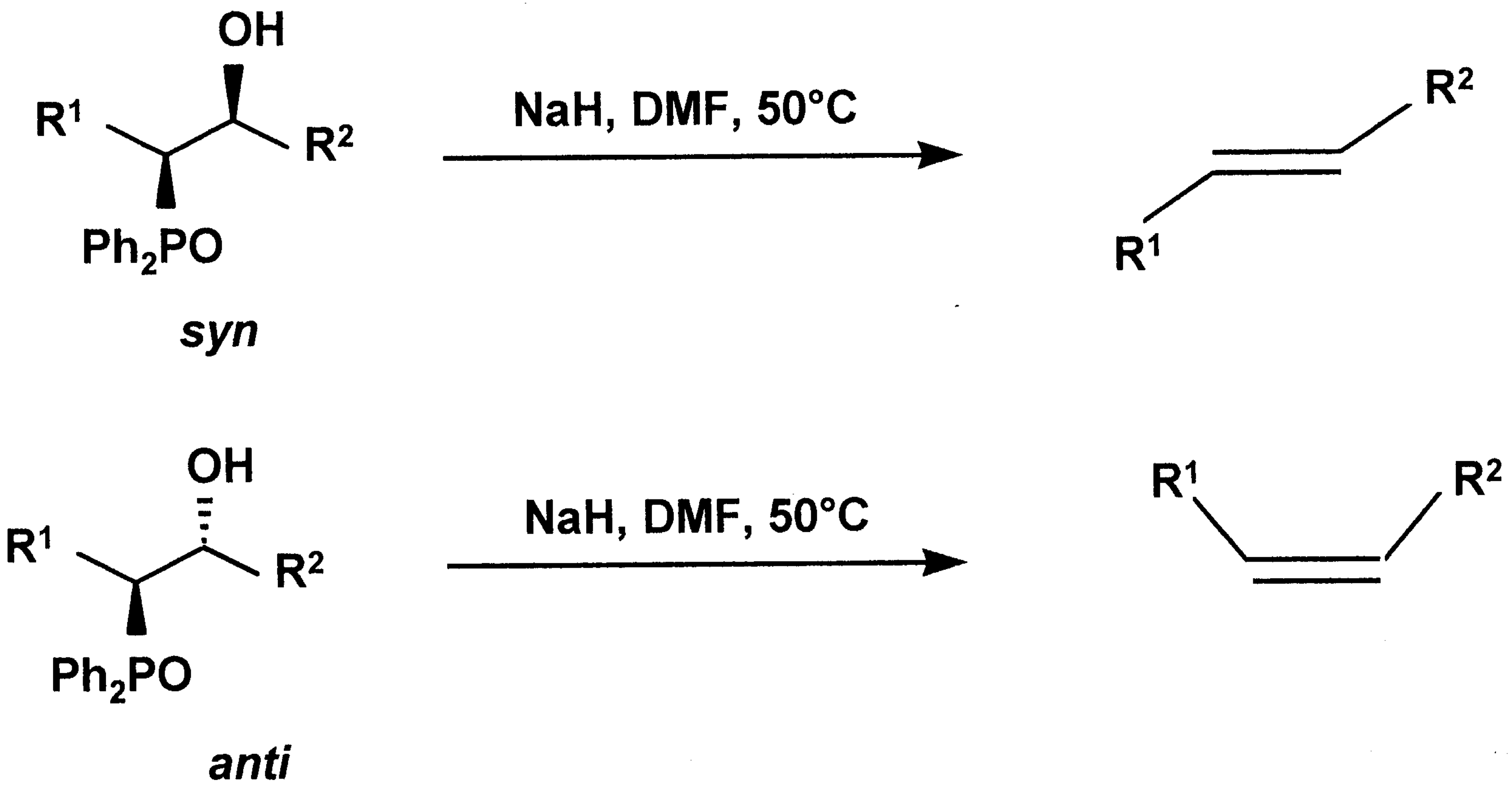
# The presence of $CeCl_3$ is essential to reach high diastereoselectivity



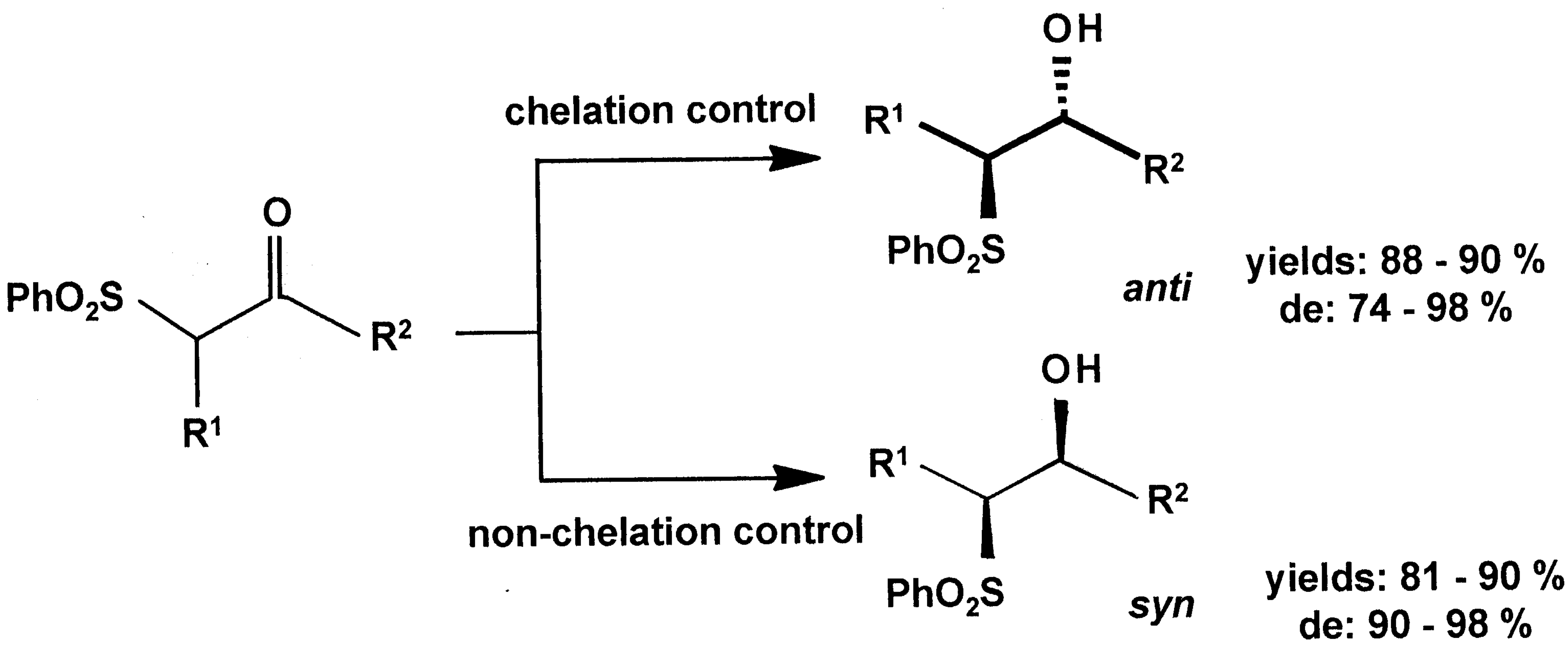

| Lewis Acid | Reaction Temperature | *syn* /*anti* | Yield (%) | Starting material (%) |
|---|---|---|---|---|
| none | -78 °C | - | 0 | 88 [a] |
| $CeCl_3$ | -78 °C | 96 /4 | 98 | 0 |
| none | 0 °C | 87 /13 | 60 | 10 [a] |
| $CeCl_3$ | 0 °C | 87 /13 | 98 | 0 |

[a] Formation of insoluble polymeric products was observed

# Stereodefined synthesis of disubstituted olefins




J. Clayden, S. Warren, *Angew. Chem. Int. Ed. Engl.* 1996, 241




Chelation control: 1) $TiCl_4$, $CH_2Cl_2$, 0 °C; 2) $BH_3$-Py, $CH_2Cl_2$, -78 °C; 3) $H_3O^+$

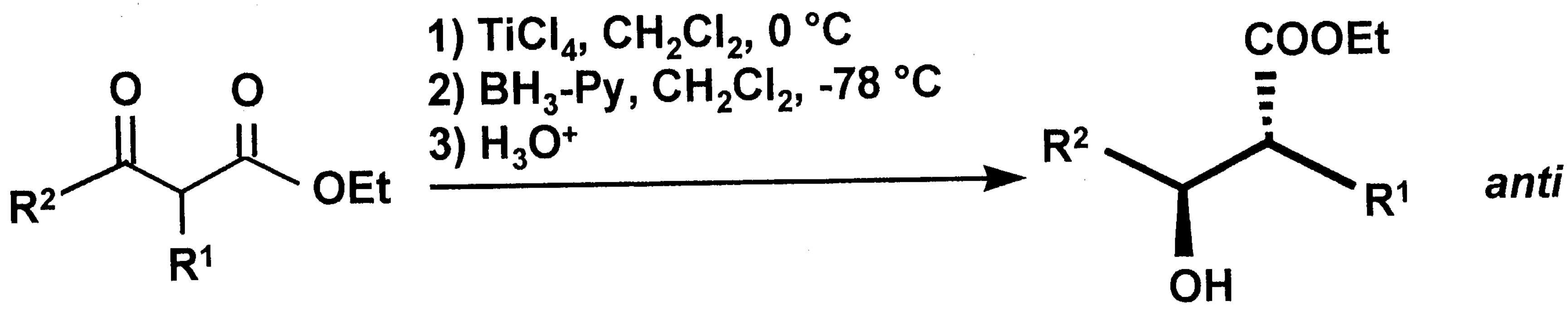
Non-chelation control: 1) $CeCl_3$, THF, 0 °C; 2) $LiBEt_3H$, THF, -78 °C; 3) $H_3O^+$

$R^1$ = Me, Et, Ph, *c*-$C_6H_{11}$, allyl, $CH_2Ph$

$R^2$ = Me, Ph, 4-MeOPh, 4-$NO_2$Ph

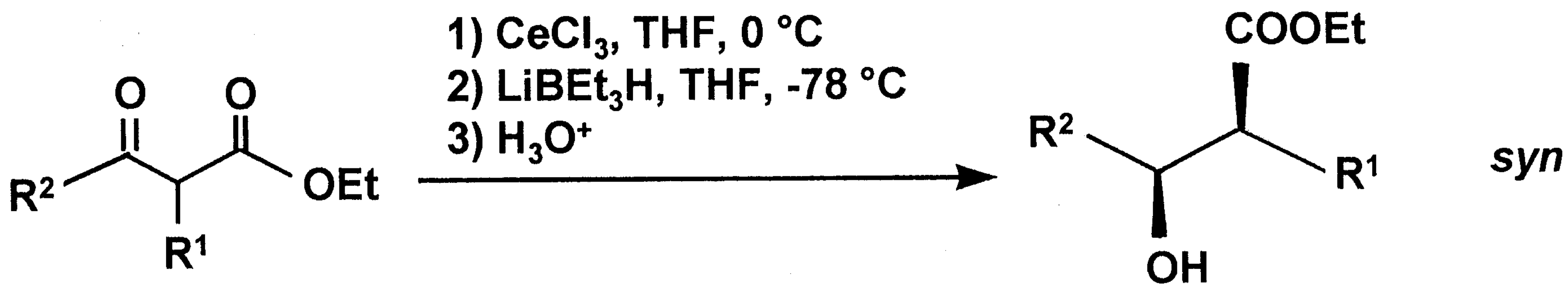
G.Bartoli , E. Marcantoni et al., *J. Org. Chem.*, 1998, *63*, 3624

# Reduction of α-alkyl-β-ketoesters under chelation control conditions



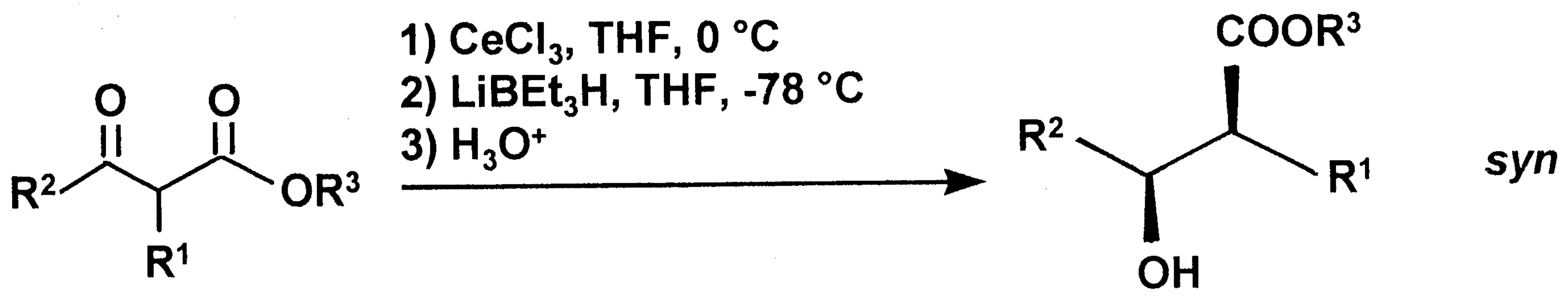

| $R^1$ | $R^2$ | *anti* / *syn* | Yield (%) |
|---|---|---|---|
| $PhCH_2$ | Me | 99 / 1 | 93 |
| Me | Ph | 99 / 1 | 99 |
| $CH_2$=$CHCH_2$ | Ph | 99 / 1 | 92 |
| $CH \equiv CCH_2$ | Ph | 88 / 12 | 95 |
| $EtOCO(CH_2)_3$ | Me | 95 / 5 | 89 |

# Reduction of α-alkyl-β-ketoesters under non-chelation control conditions



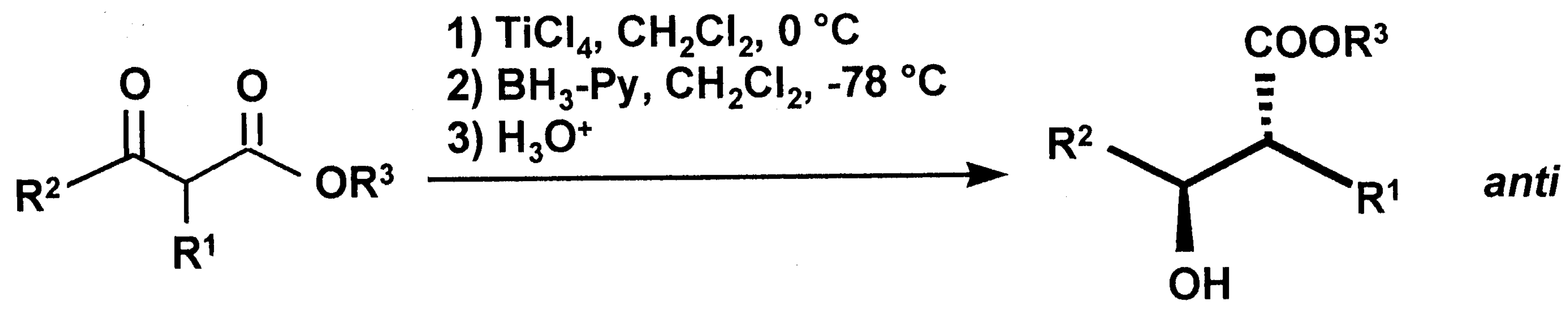

| $R^1$ | $R^2$ | *anti / syn* | Yield (%) |
|---|---|---|---|
| $PhCH_2$ | Me | 13 / 87 | 92 |
| Me | Ph | 9 / 91 | 85 |
| $CH_2{=}CHCH_2$ | Ph | 10 / 90 | 90 |
| $CH{\equiv}CCH_2$ | Ph | 11 / 89 | 90 |
| $EtOCO(CH_2)_3$ | Me | 13 / 87 | 79 |

# Dependence of *syn*-selectivity on the bulkiness of the ester group

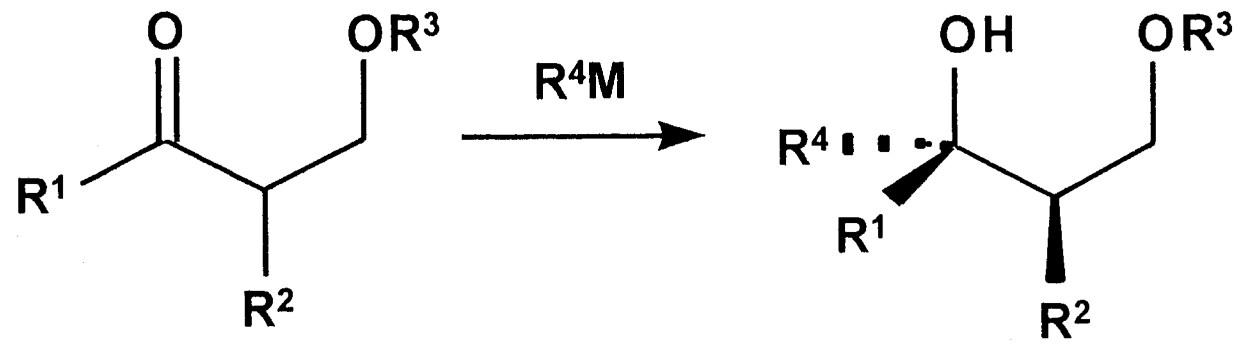


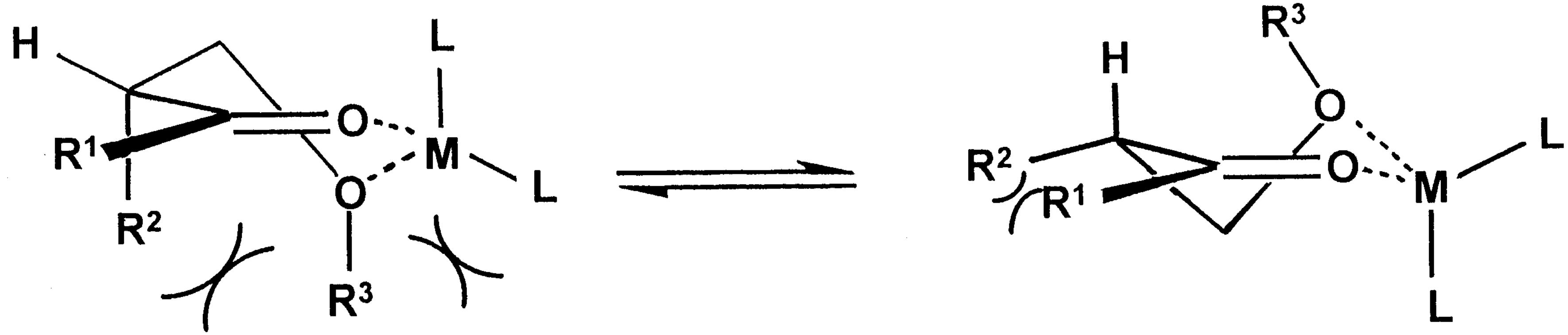

| $R^1$ | $R^2$ | $R^3$ | *anti* / *syn* | Yield (%) |
|---|---|---|---|---|
| $PhCH_2$ | Me | Et | 13 / 87 | 92 |
| $PhCH_2$ | Me | *t*-Bu | 1 / 99 | 94 |
| $CH_2$=$CHCH_2$ | Ph | Et | 10 / 90 | 90 |
| $CH_2$=$CHCH_2$ | Ph | *t*-Bu | 3 / 97 | 83 |

# Independence of *anti*-selectivity on the bulkiness of the ester group



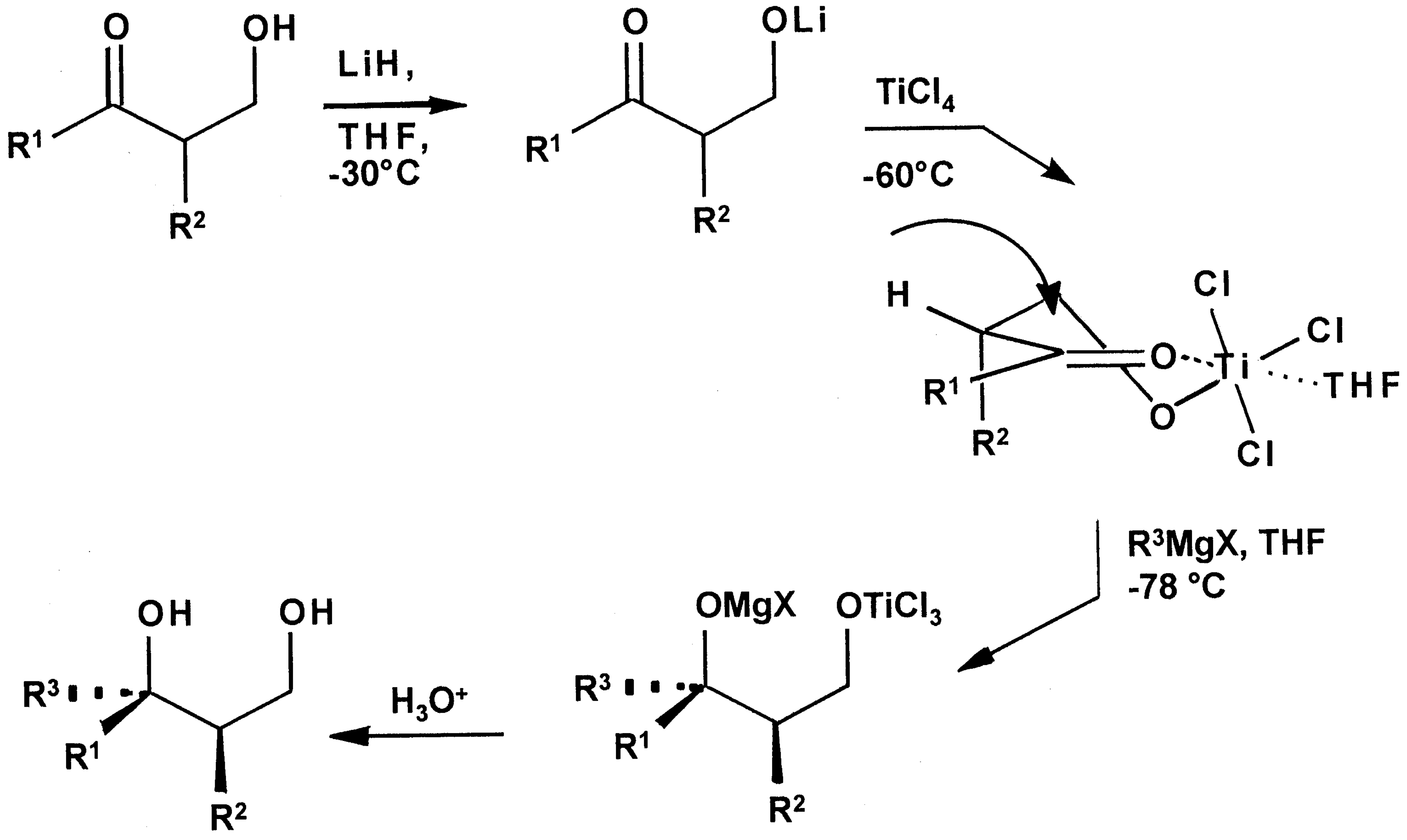

| $R^1$ | $R^2$ | $R^3$ | *anti* / *syn* | Yield (%) |
|---|---|---|---|---|
| $PhCH_2$ | Me | Et | 99 / 1 | 93 |
| $PhCH_2$ | Me | *t*-Bu | 99 / 1 | 94 |
| $CH_2{=}CHCH_2$ | Ph | Et | 99 / 1 | 92 |
| $CH_2{=}CHCH_2$ | Ph | *t*-Bu | 99 / 1 | 93 |



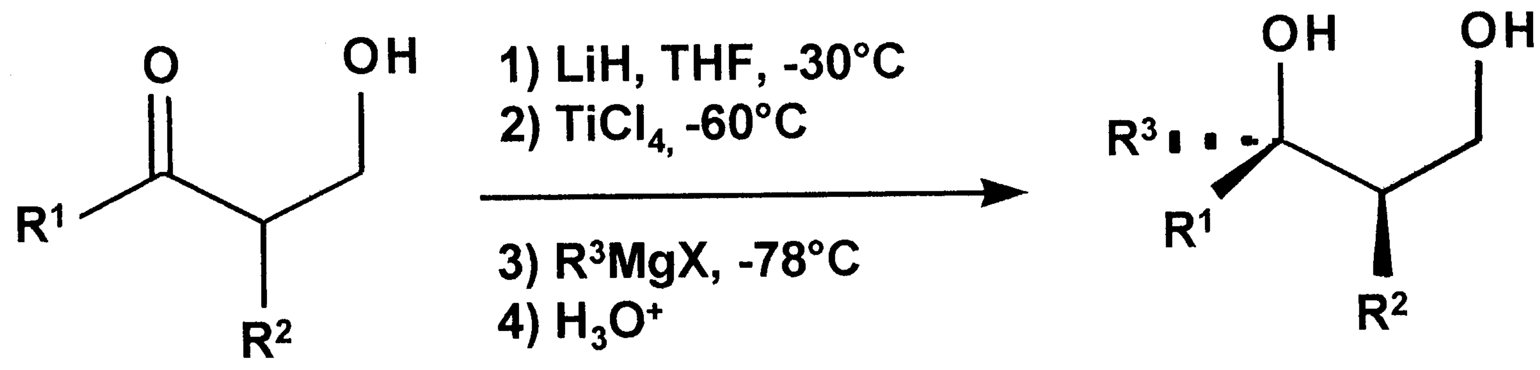

not stable

not stable



O
OH
R1
R2
LiH,
THF,
-30°C
O
OLi
R1
R2
TiCl4
-60°C
H
R1
R2
O
O
Ti
Cl
Cl
Cl
THF
R3MgX, THF
-78 °C
OMgX
OTiCl3
R3
R1
R2
H3O+
OH
OH
R3
R1
R2

# Diastereoselective alkylation of β-hydroxyketones



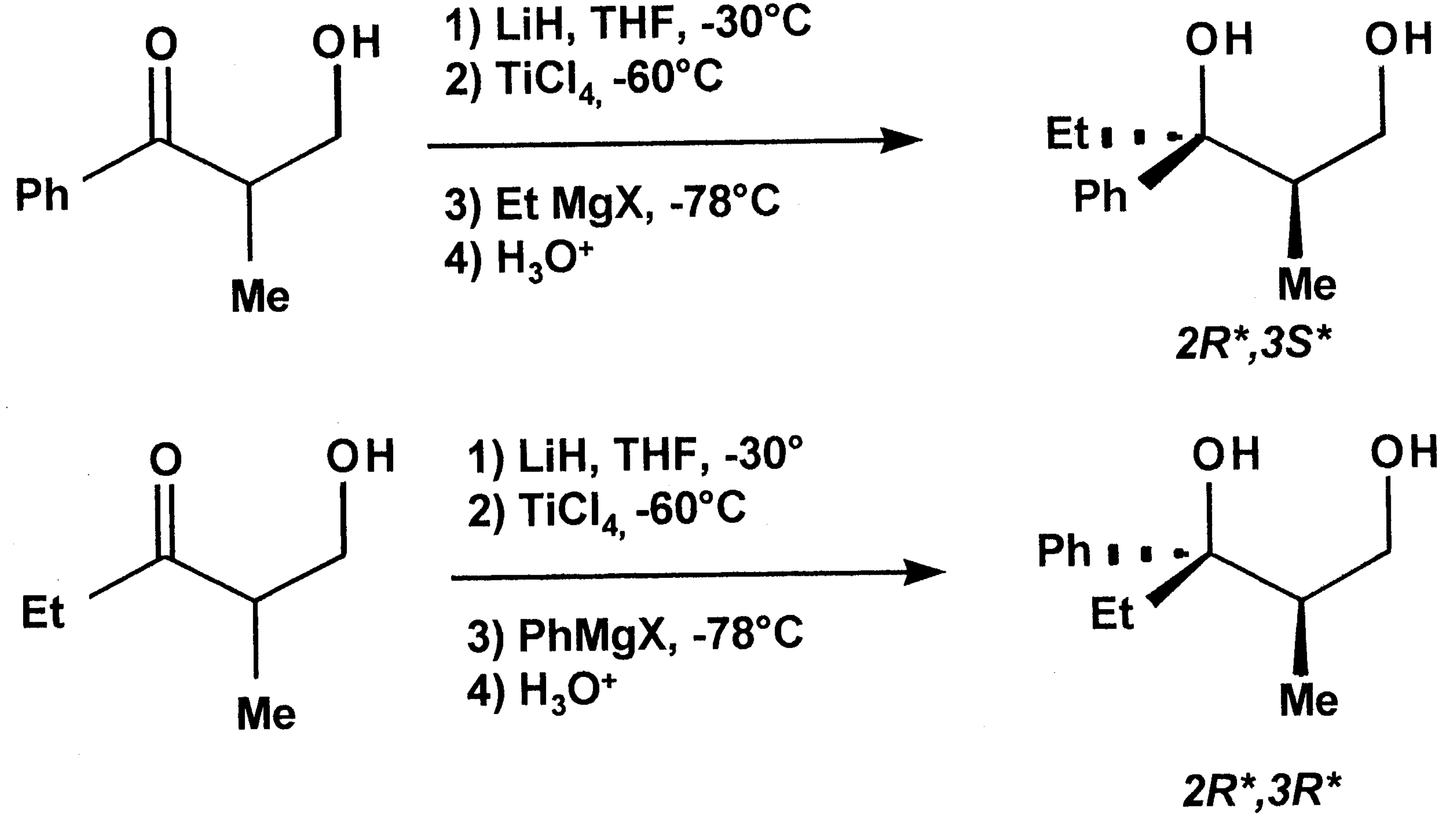

Yields = 75-98 %
de = 70-98 %

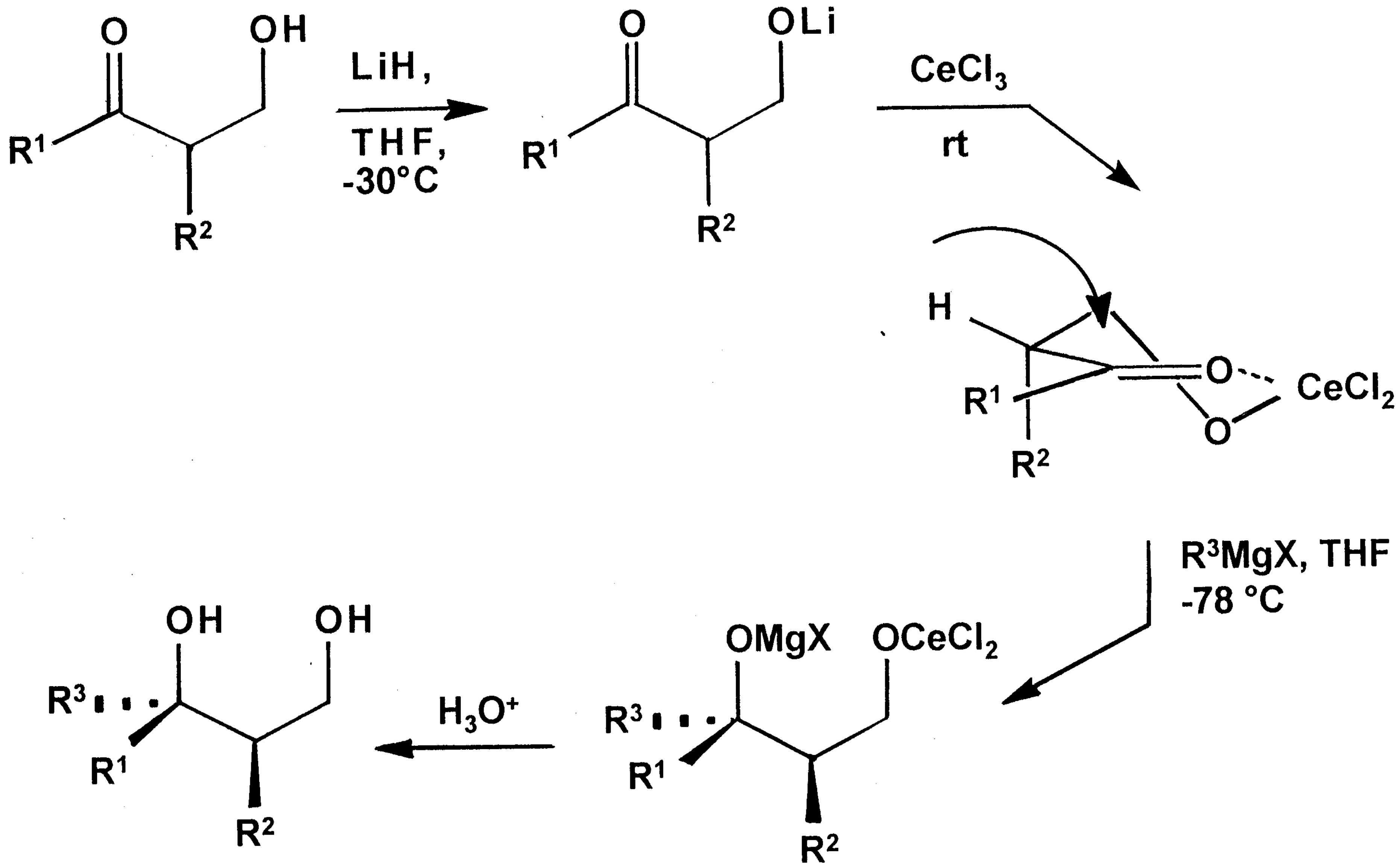
$R^1$ = Me, Et ,Ph

$R^2$ = Me, Et ,Ph

$R^3$ = Et, Ph, i-Pr, $CH_2$=CH, $PhCH_2$, Me, PhC≡C

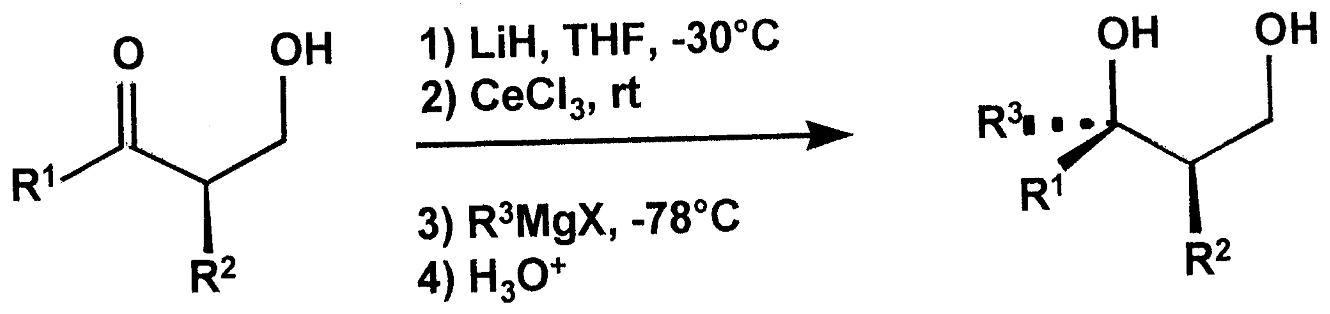
# Preparation of both diastereoisomers of 2-methyl-3-phenylpentan-1,3-diol





O
OH
R1
R2
LiH,
THF,
-30°C
O
OLi
R1
R2
CeCl3
rt
H
R1
R2
O
O
CeCl2
R3MgX, THF
-78 °C
OMgX
OCeCl2
R3
R1
R2
H3O+
OH
OH
R3
R1
R2

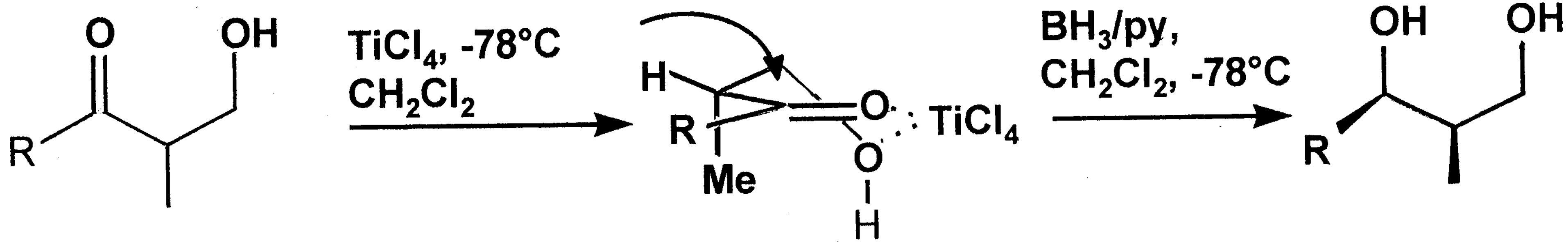
# Diastereoselective alkylation of β-hydroxyketones *via* Cerium alcoholate




| $R^1$ | $R^2$ | $R^3$ | Yield(%) | de(%) |
|---|---|---|---|---|
| Me | Me | Ph | 98 (80) | 74 (82) |
| Me | Me | *i*-Pr | 96 (90) | 89 (88) |
| Ph | Me | Et | 98 (96) | 86 (98) |
| Ph | Me | PhCH2 | 98 (98) | 88 (98) |

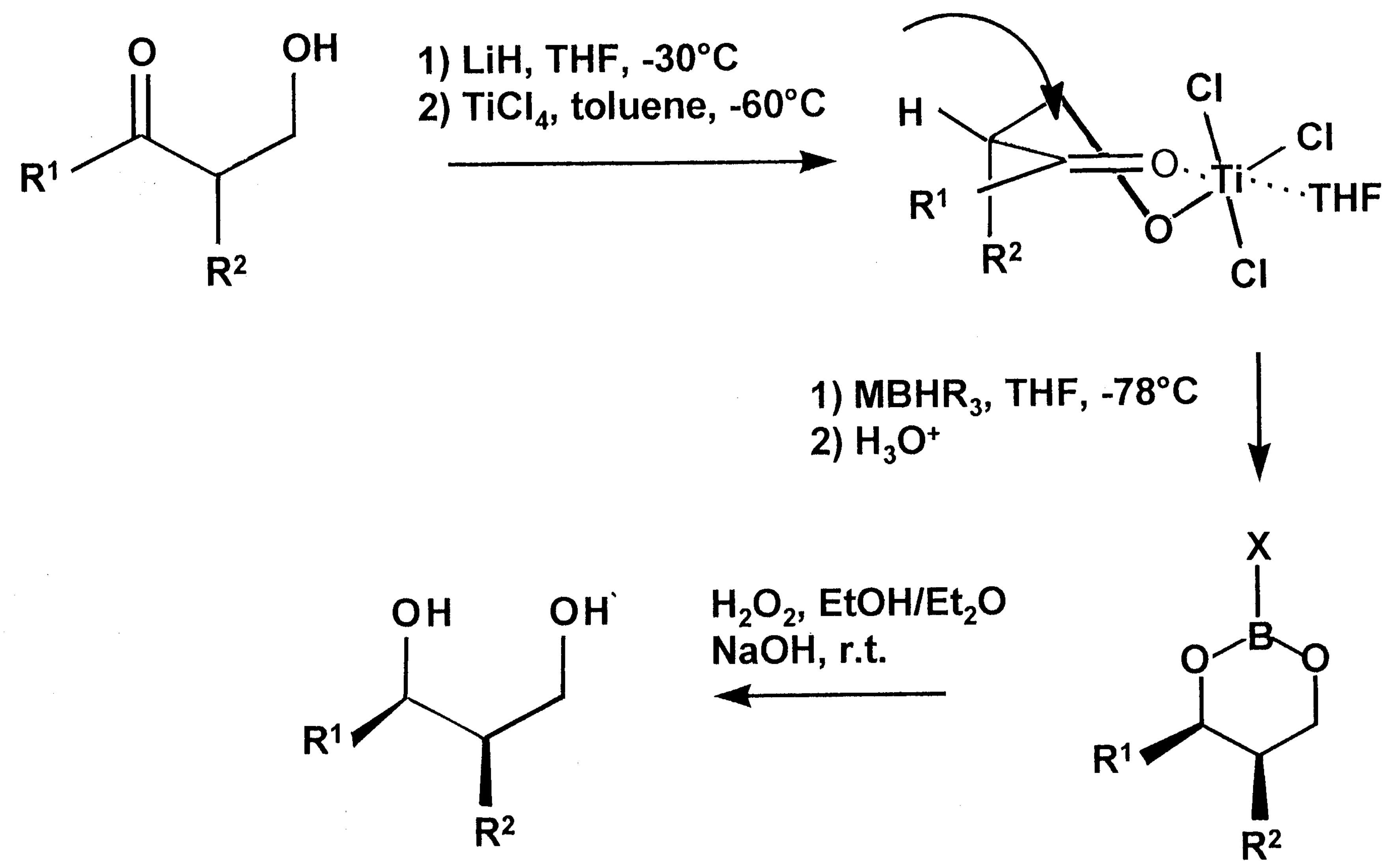
Data in parentheses refer to the reaction *via* Titanium alcoholate.

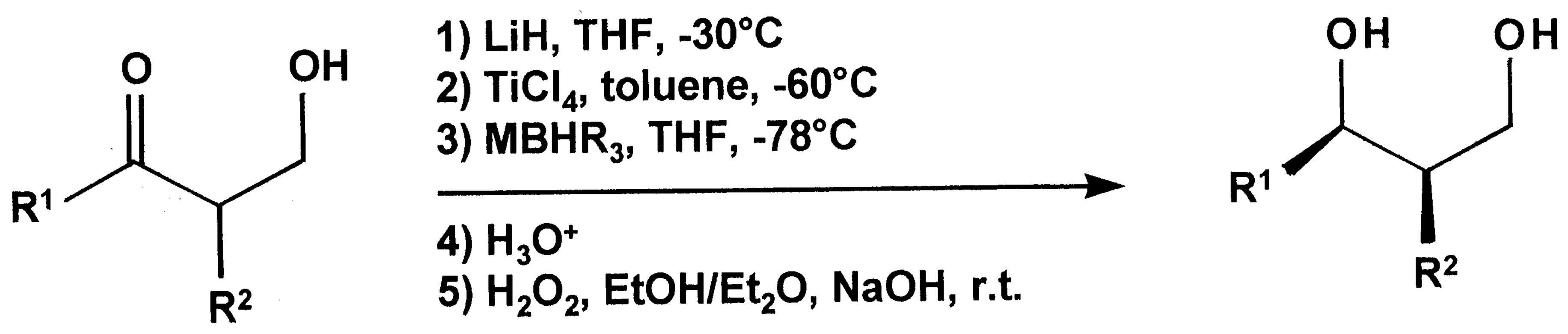
# Diastereoselective reduction of β-hydroxyketones




| R | Yield (%) | de (%) |
|---|---|---|
| Ph | 81 | 98 |
| *t*-Bu | 84 | 96 |
| Me | 87 | 26 |
| Et | 91 | 20 |

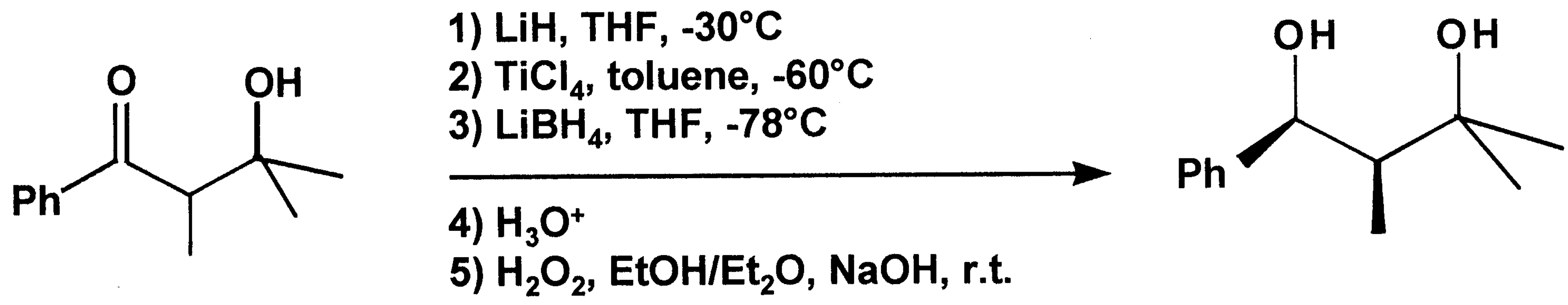
DiMare *et al.*, *J. Org. Cherm.*, 1996, *61*, 868


O
OH
R1
R2
1) LiH, THF, -30°C
2) TiCl4, toluene, -60°C
H
R1
R2
O
O
Ti
Cl
Cl
Cl
THF
1) MBHR3, THF, -78°C
2) H3O+
X
B
O
O
R1
R2
H2O2, EtOH/Et2O
NaOH, r.t.
OH
OH
R1
R2



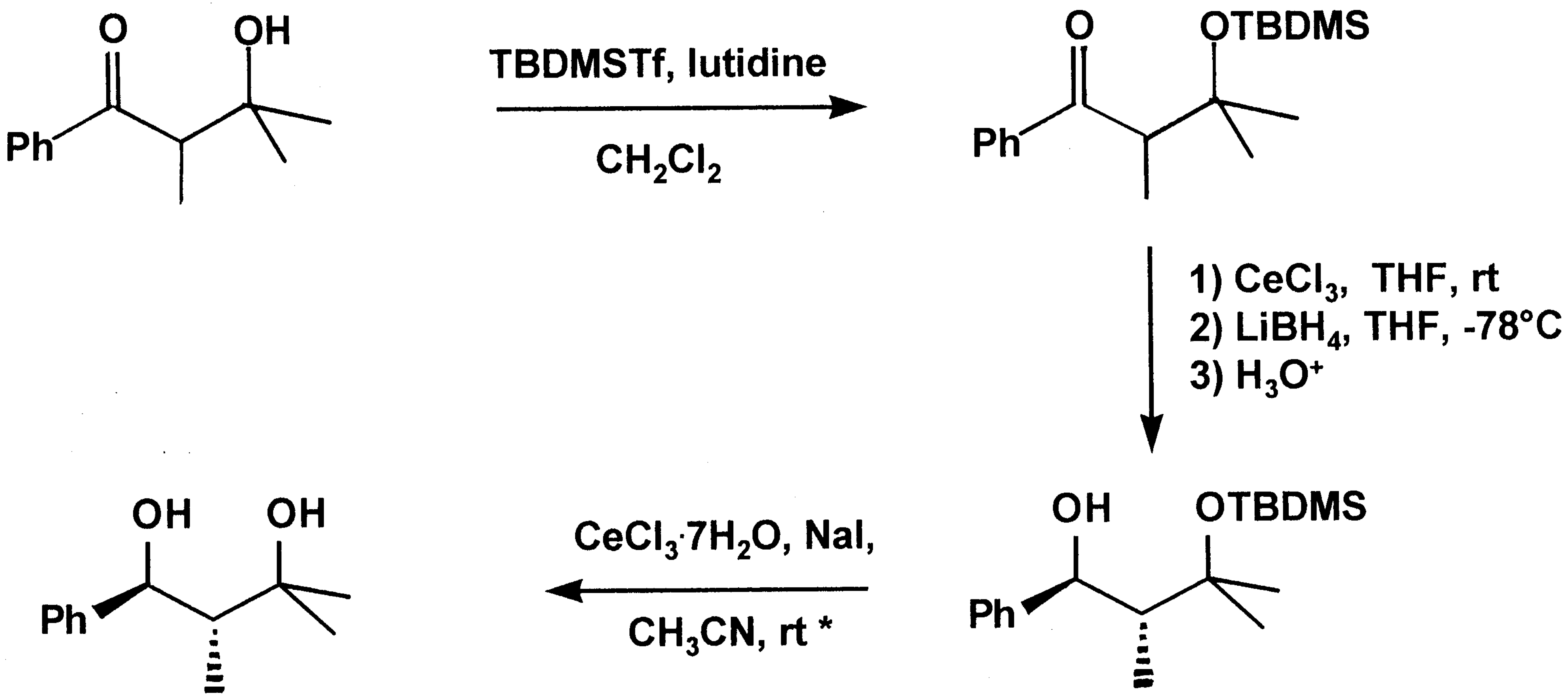

| $R^1$ | $R^2$ | $MBHR_3$ | Yield (%) | de (%) |
|---|---|---|---|---|
| Ph | Me | $LiBH_4$ | 95 | 98 |
| Ph | Et | $LiBH_4$ | 95 | 98 |
| Ph | Ph | $LiBH_4$ | 95 | 98 |
| Et | Me | $LiBH_4$ | 90 | 30 |
| Et | Me | L-selectride | 90 | 80 |
| Et | Me | N-selectride | 92 | 86 |
| Pr | Et | L-selectride | 91 | 90 |

# Synthesis of (1R*, 2S*)-1-phenyl-2,3-dimethyl-1,3-butandiol




yield= 92%
de= 98%

# Synthesis of (1R*, 2R*)-1-phenyl-2,3-dimethyl-1,3-butandiol




**yield= 81%**
**de= 98%**

*G. Bartoli *et al.*, *Syn Lett.*,1998, 209