不对称合成
Asymmetric Synthesis

第4次课 (2016-03-09)

陈加荣

化学学院

Office:731

E-mail: chenjiarong@mail.ccnu.edu.cn

第4章 羟醛缩合及相关的反应

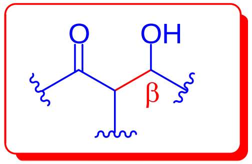
- 4.1 引言
- 4.2 底物控制的羟醛缩合反应
- 4.3 试剂控制的羟醛缩合反应
- 4.4 手性催化剂控制的不对称羟醛反应
- 4.5 双不对称羟醛反应
- 4.6 不对称烯丙基化反应
- 4.7 亚胺的不对称烯丙基化和烷基化反应

4.1 引言

❖ 羟醛反应，即亲核试剂与亲电的羰基基团（及类似基团的缩合反应；

✓ 羟醛反应在生物合成中是一种基本的键形成反应；

✓ 是构建不对称C-C键的最简单的，同时能满足不对称有机合成化学的最严格要求的一类化学转化。



Aldol adduct

❖ 几种用于对羟醛反应进行不对称控制的的方法：

✓ 底物控制(手性性醛)

✓ 试剂控制(手性烯醇盐)

✓ 双不对称羟醛反应

✓ 手性催化剂控制

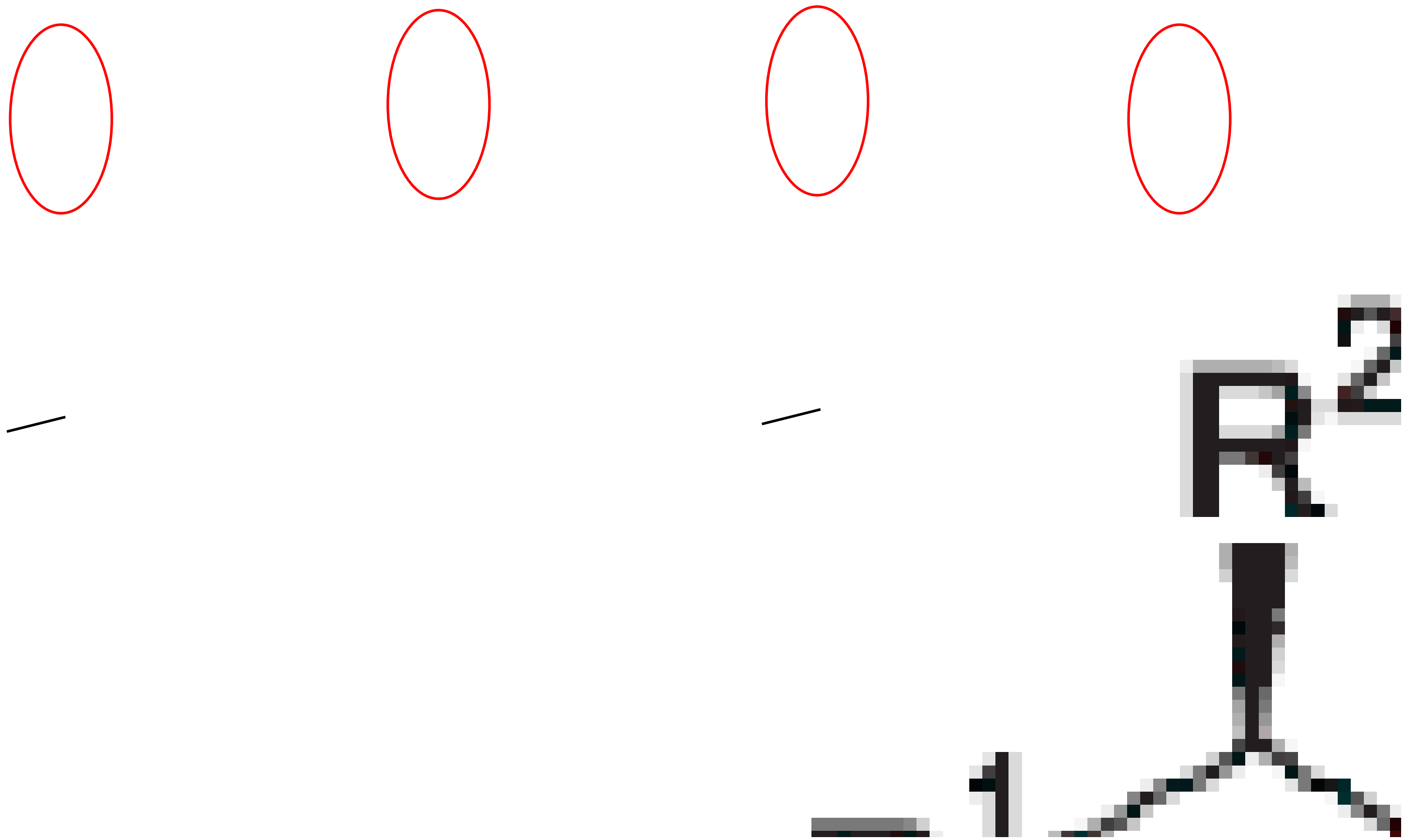
羟醛缩合的两种类型

Scheme 4.1

羟醛缩合反应的手性控制

底物控制

四个可能的立体异构体



结论: 烯醇盐的几何结构可以演变为产物的2,3-立体化学:Z-烯醇倾向于产生syn-产物(Z→syn), 而E-烯醇产生anti-产物(E→anti)

试剂控制

Masamune 羟醛缩合试剂

“羟醛给体 vs 羟醛受体”

Table 3.1用手性试剂5的非对应选择性醇醛缩合反应

Aldehyde	*syn:anti*	ds for *syn*	Yield (%)
EtCHO	93:7	97:3	95
PrCHO	94:6	>97:3	93
(*E*)-$CH_3CH{=}CHCHO$	93:7	>97:3	98
PhCHO	94:6	95:5	97

ds = diastereoselectivity.

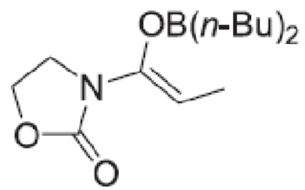
4.2 底物控制的羟醛缩合反应

4.2.1 噁唑烷酮作为手性辅剂参与的羟醛缩合型反应

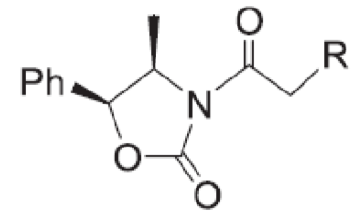
由7和8生成的手性硼烯醇盐由于其易于制备、优异的立体选择性、易于脱除和回收使用而备受青睐。---Evans试剂

获得一对对映体

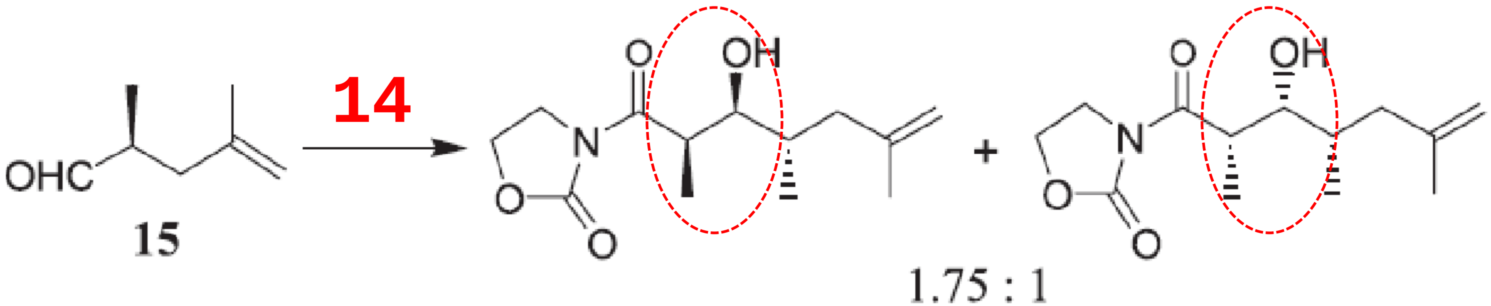
双不对称诱导：大大提高对映选择性

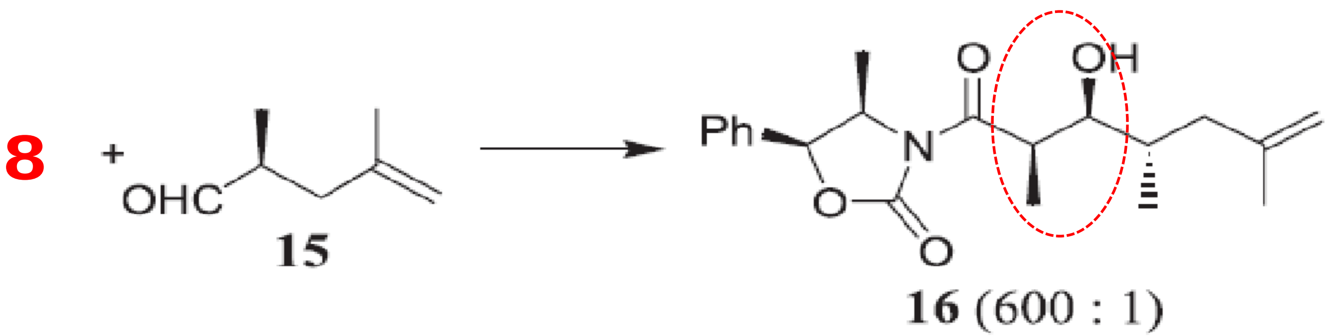


14



8



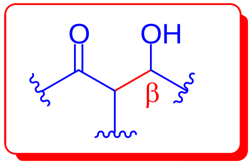


应用1：17(+)- Prelog-Djerassi 内酯酸片断立体中心构建

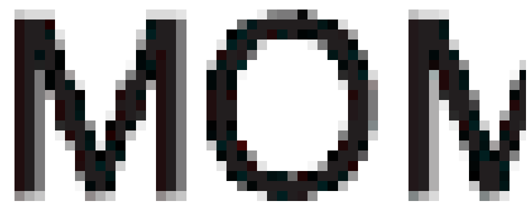
R

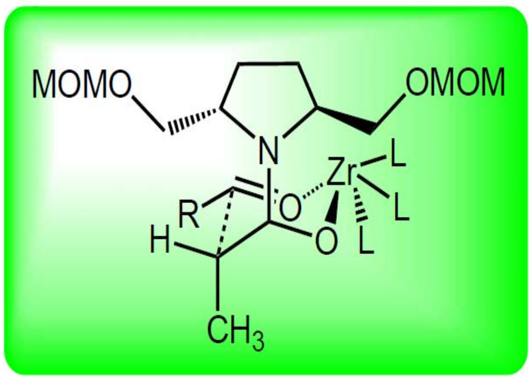
4.2.2 吡咯烷作为手性辅剂

合成β-羟基羰基单元最为成功的方法就是使用醛醇缩合反应



Aldol adduct



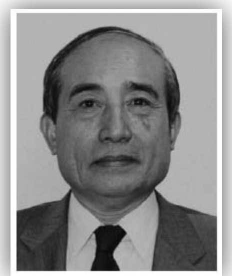


脯胺醇型手性辅剂

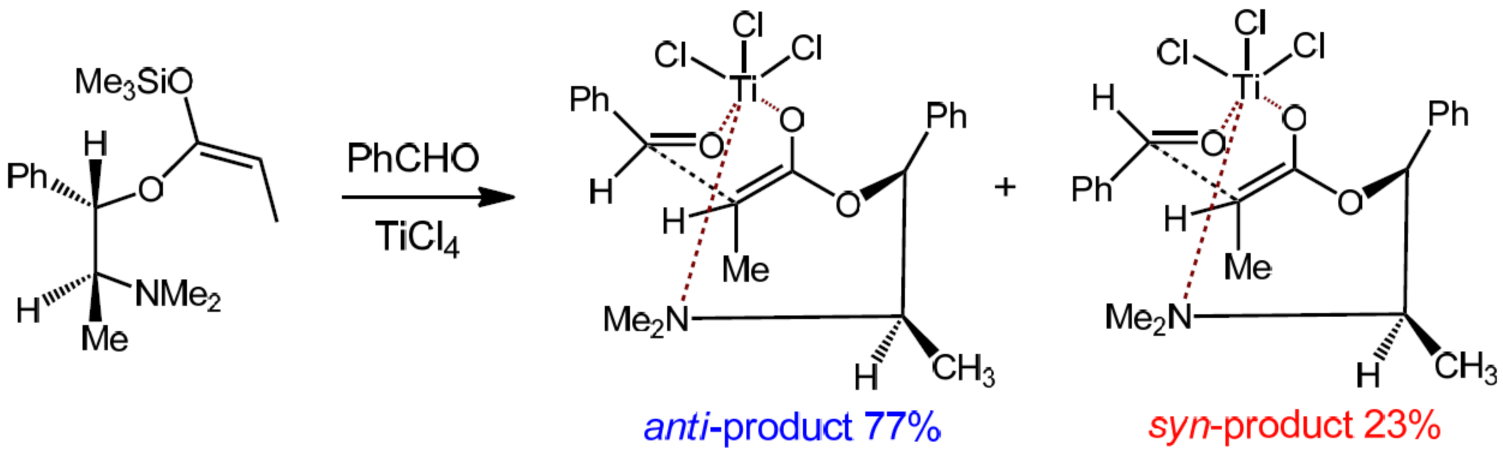
syn:anti 选择性达96%~98%,非对映选择性达50~200:1

4.2.3 氨基醇作为手性辅剂

Mukaiyama首次证明用$TiCl_4$和硅烷基烯醇醚作为稳定的烯醇等价物也能进行酸催化的醛醇缩合反应 (1973年)



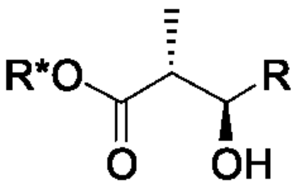
(*1R*, *2S*)-N-甲基麻黄碱-O-丙酸酯衍生的硅试剂-过渡态



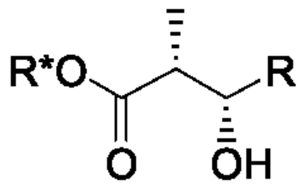
Scheme 4.15

(*1R*, *2S*)-N-甲基麻黄碱-O-丙酸酯衍生的硅试剂

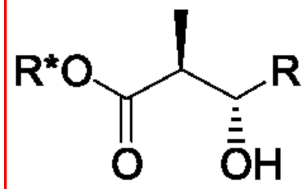
产物反式为主



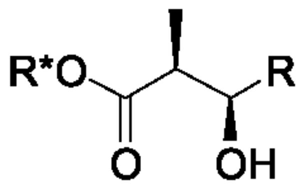
A



B

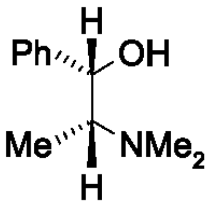
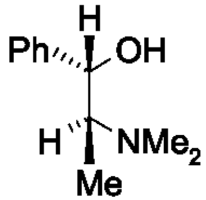


C

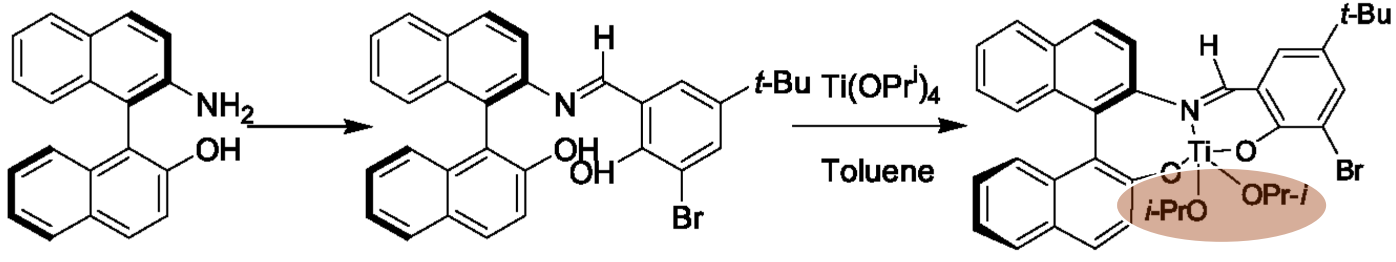


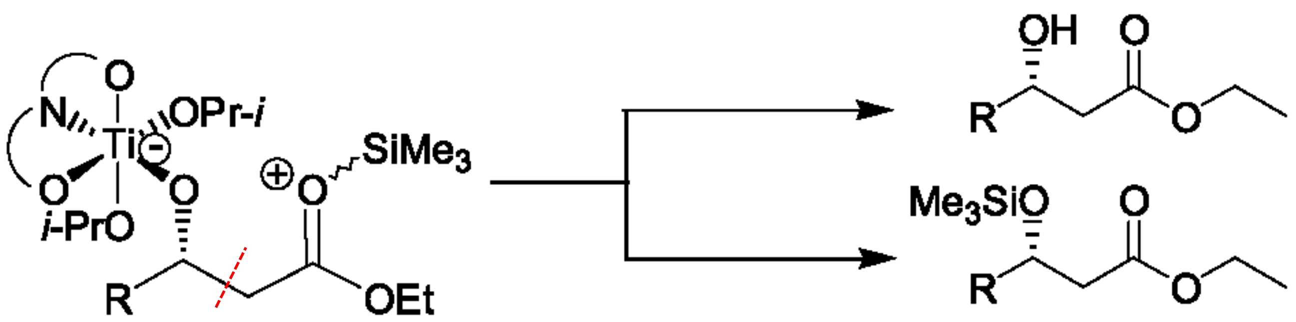
D

Table 4.4 硅烷基烯酮缩醛与醛的反应

Entry	R*OH	RCHO	*anti*/*syn*(**A** + **C**)/(**B** + **D**)	**A**/**C**
1		PhCHO	85:15	97:3
2	"	*n*-C_3H_7CHO	80:20	95.5:4.5
3		PhCHO	77:23	93:7

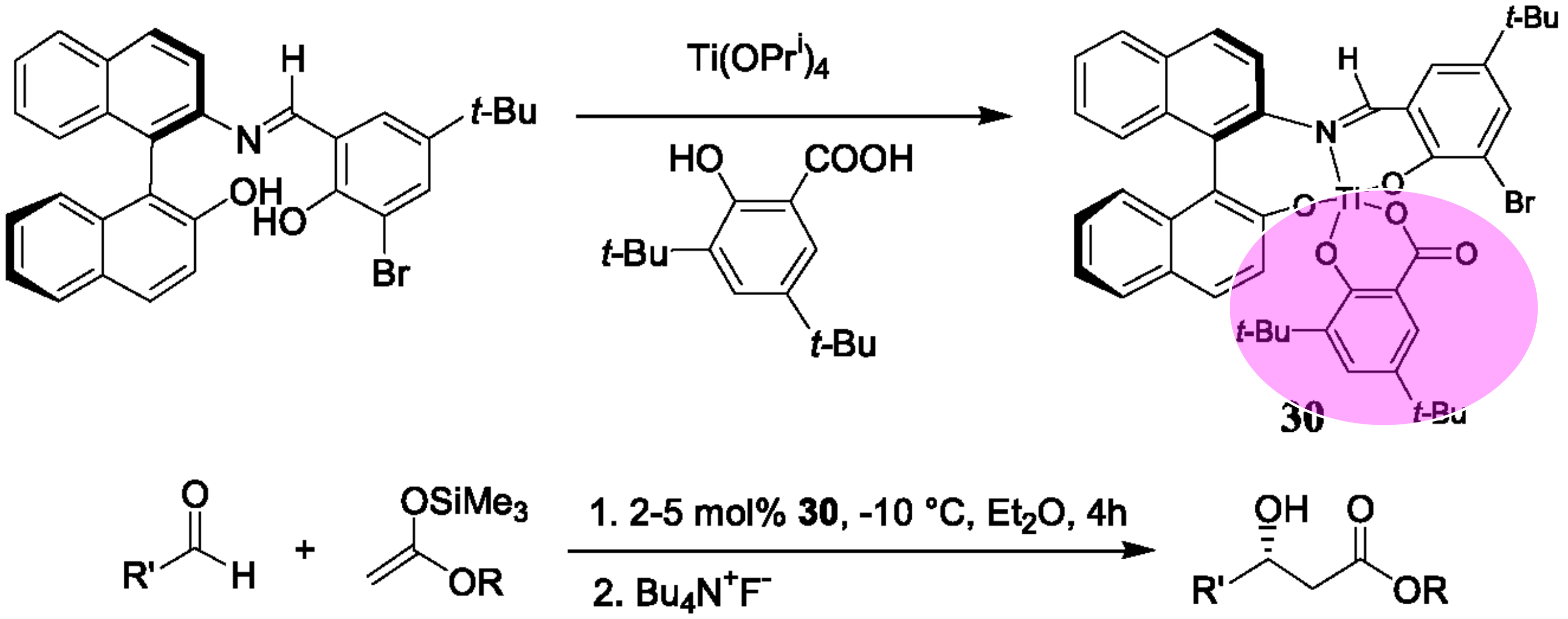
Mukaiyama羟醛反应-手性Lewis酸催化





Scheme 4.16 利用催化剂29产率和e.e.值都很低

Mukaiyama羟醛反应-手性Lewis酸催化

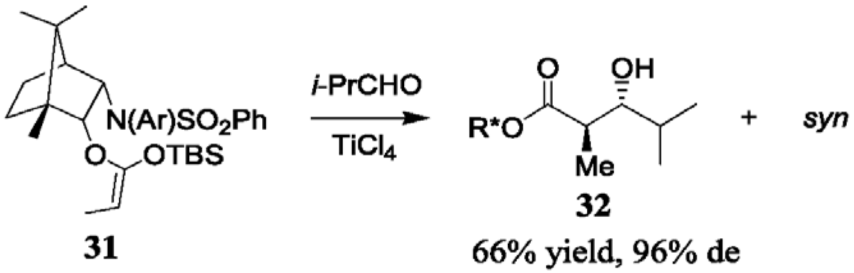


R = Et, ee 88 - 94%
R = Me, ee 94 -97%

Scheme 4.17

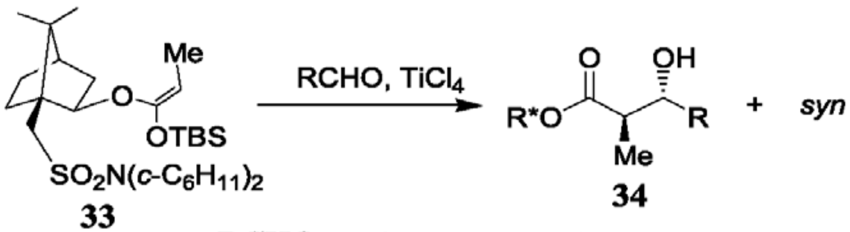
4.2.4 酰基磺内酰胺体系作为手性辅剂

O-硅烷基烯酮缩醛

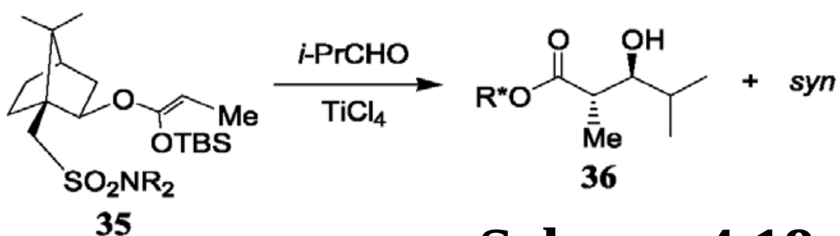


66% yield, 96% de

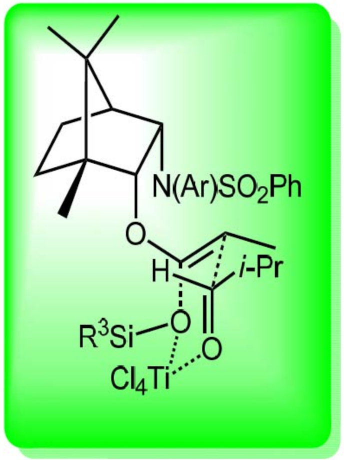
anti : *syn* = 93 : 7



RCHO	de, *anti*	*anti* : *syn*
PhCHO	90	81 : 19
n-PrCHO	85	94 : 6
i-PrCHO	85	98 : 2

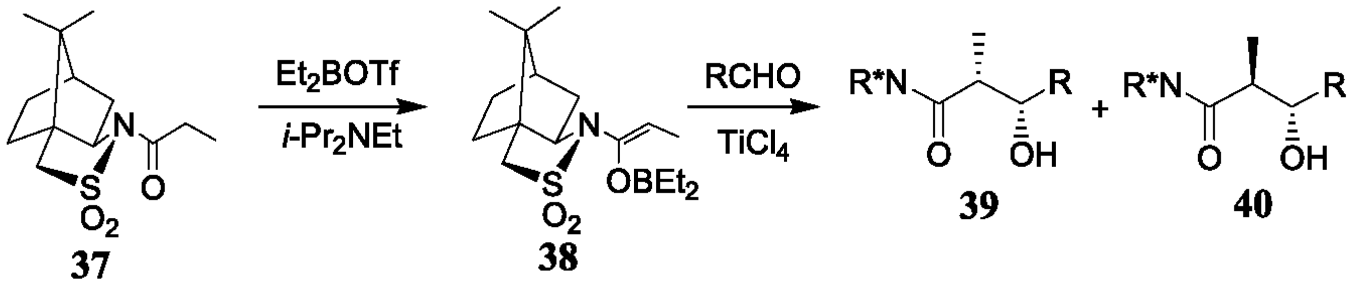


Scheme 4.18



4.2.4 酰基磺内酰胺体系作为手性辅剂

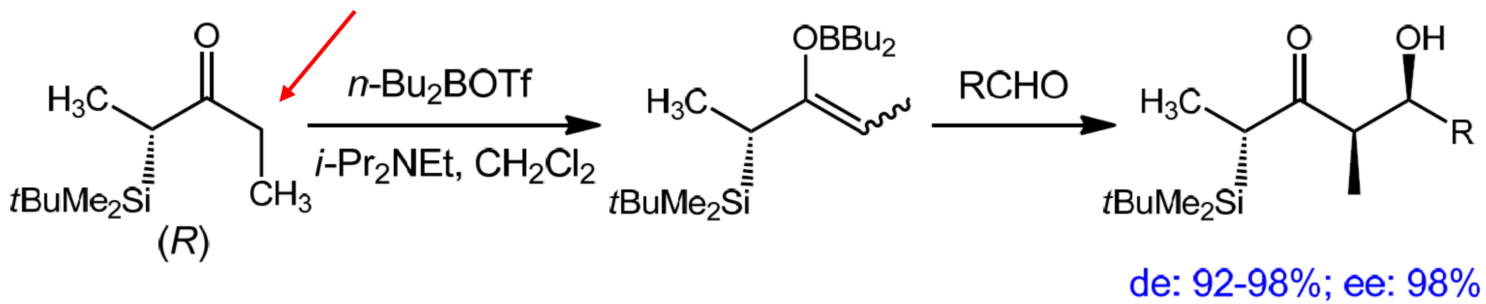
硼基烯醇盐

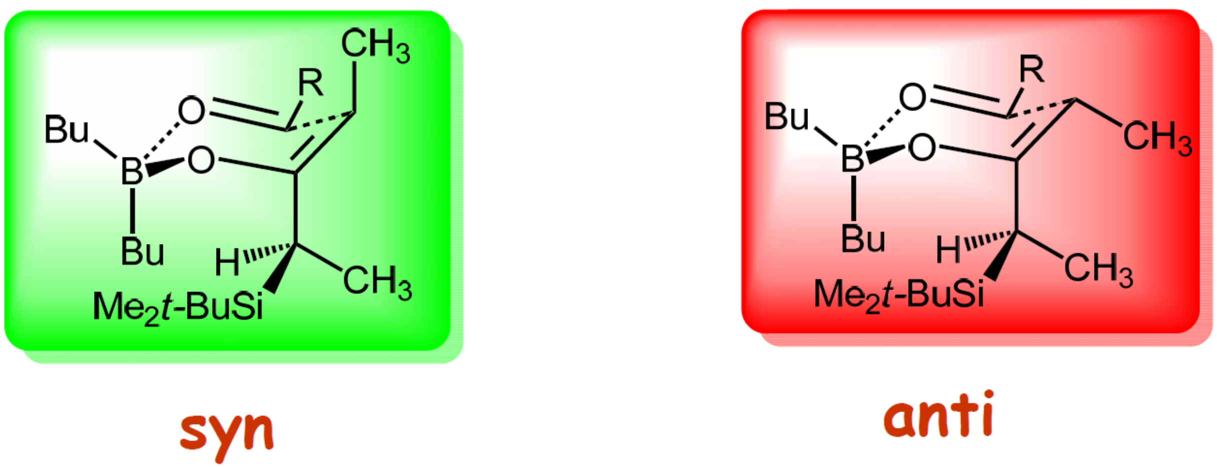


Lewis acid	mol. equiv. of Lewis acid/EtCHO	40/39/others
Et_2AlCl	2	27/37/36
Et_2BOTf	2	78/0/22
$TiCl_4$	2	98/0/2
$TiCl_4$	1	97/0/3
$TiCl_4$	0.5	93/0/7

Scheme 4.19

4.2.5 α-硅烷基酮的醛醇缩合反应-Enders

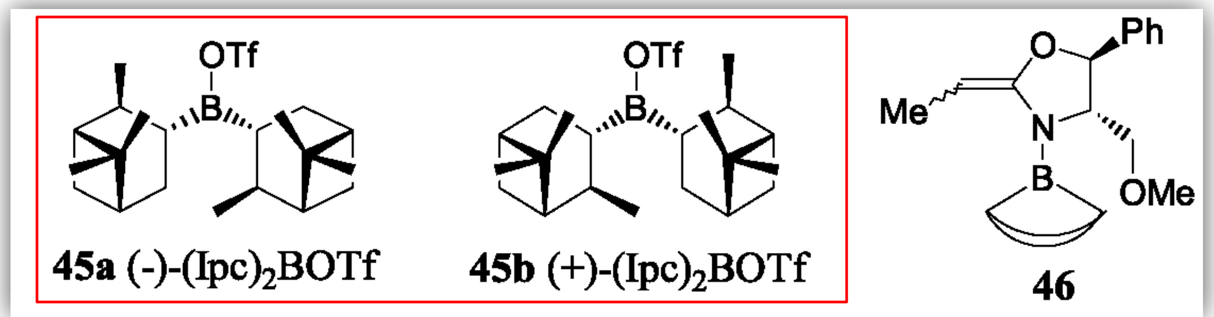


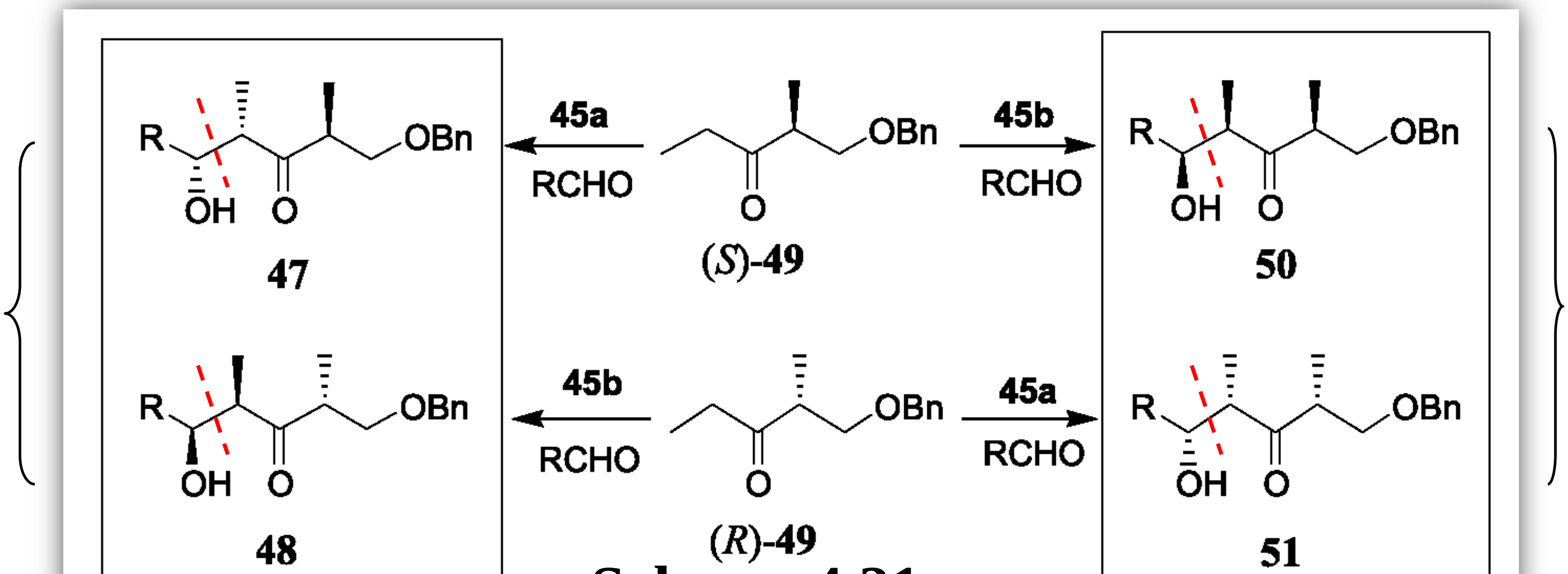


Scheme 4.20

4.3 试剂控制的羟醛缩合反应

4.3.1 由手性硼化合物诱导的羟醛缩合

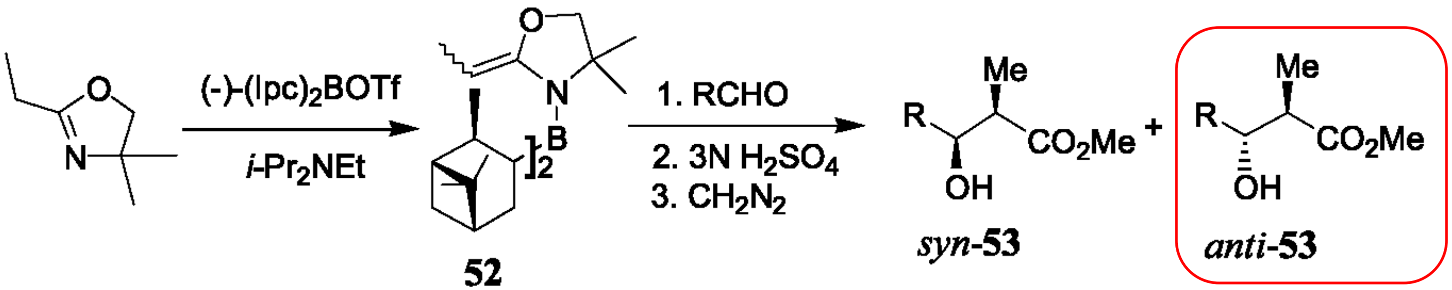




Scheme 4.21

4.3 .1 由手性硼化合物诱导的羟醛缩合

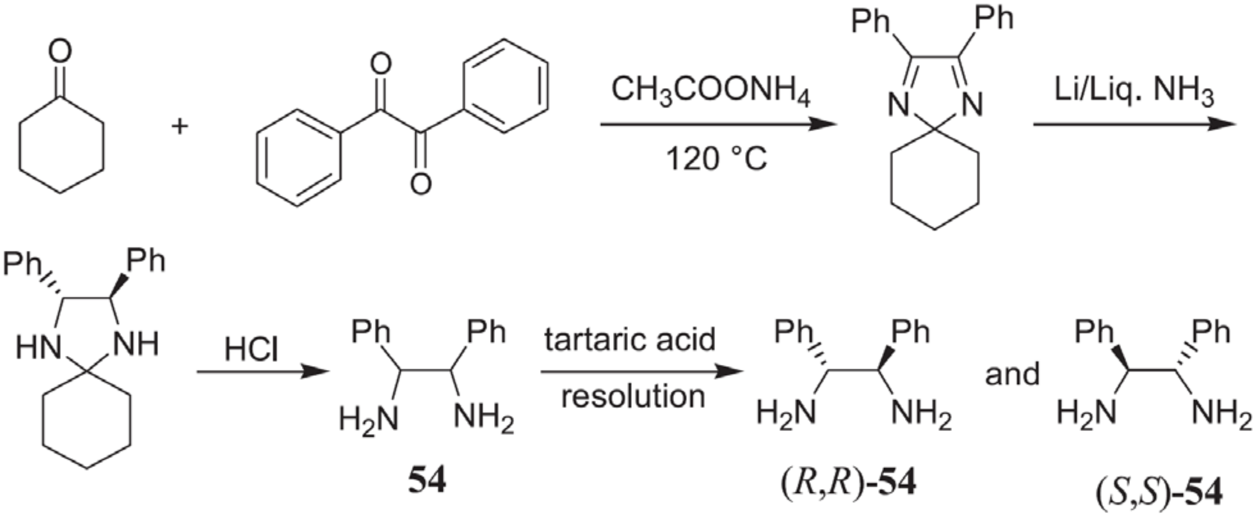
噁唑啉作为反应底物

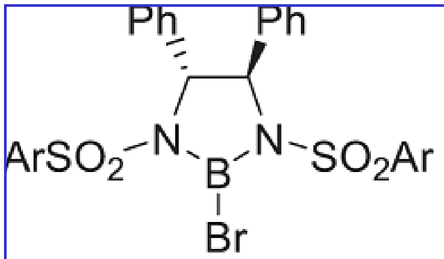


RCHO	ee (%) for *anti*	*anti*:*syn*
n-PrCHO	77	91:9
c-HexCHO	84	95:5
t-BuCHO	79	94:6

Scheme 4.22

4.3.2 Corey 试剂控制的羟醛反应



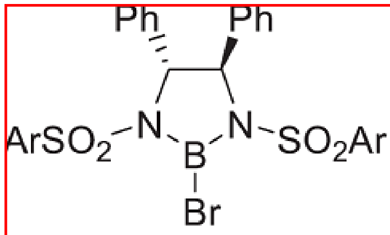


55a Ar = *p*-$CH_3C_6H_4$
55b Ar = *p*-$NO_2C_6H_4$

55 Corey试剂

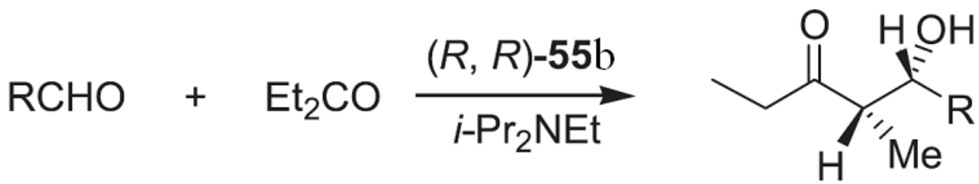
Scheme 4.23

4.3.2 Corey 试剂控制的羟醛反应



55a Ar = *p*-$CH_3C_6H_4$
55b Ar = *p*-$NO_2C_6H_4$

55



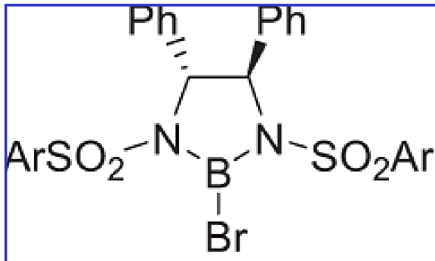
Scheme 4.24

Table 4.5 醛与二乙基酮衍生的烯醇盐和溴代硼烷(R,R)-55b反应

RCHO	Yield (%)	*syn*:*anti*	ee (%)
PhCHO	95	94.3:5.7	97
Me_2CHCHO	85	98:2	95
EtCHO	91	>98:2	>98

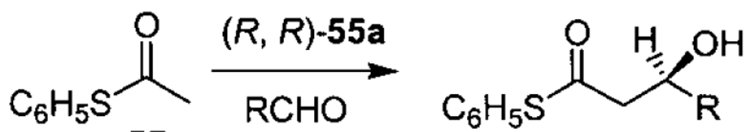
4.3.2 Corey 试剂控制的羟醛反应

Corey试剂应用-硫代乙酸苯酯



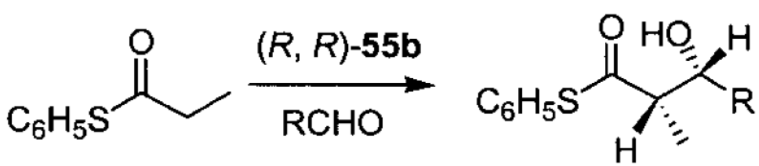
55a Ar = *p*-$CH_3C_6H_4$
55b Ar = *p*-$NO_2C_6H_4$

55 Corey试剂



57 **58**

R = Ph, 91% ee
R = *i*-Pr, 83% ee



59 **60**

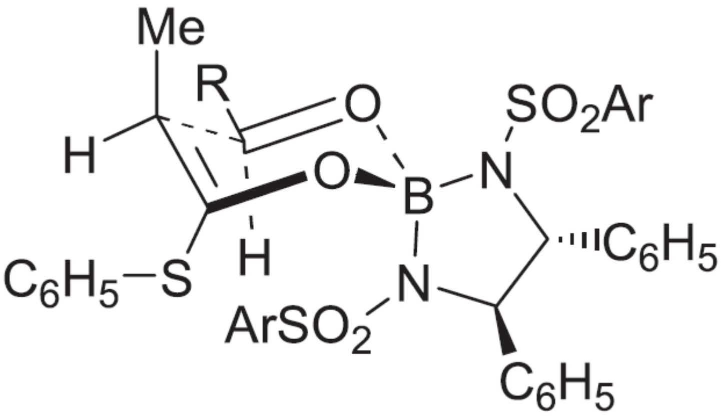
R = ph, 95% ee; *syn*/*anti* = 98.3 : 1.7
R = *i*-Pr, 97% ee; *syn*/*anti* = 94.5 : 5.5

Scheme 4.25

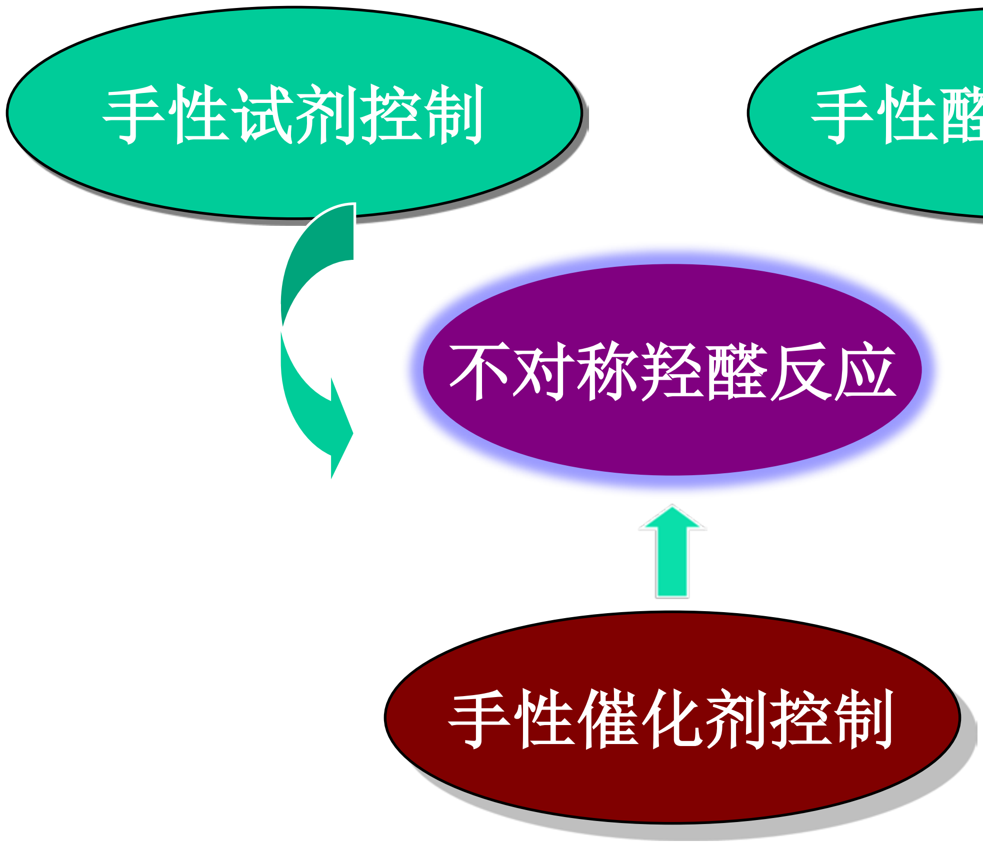
4.3.2 Corey 试剂控制的羟醛反应

反应可能过渡态

- 立体电子效应
- 空间效应

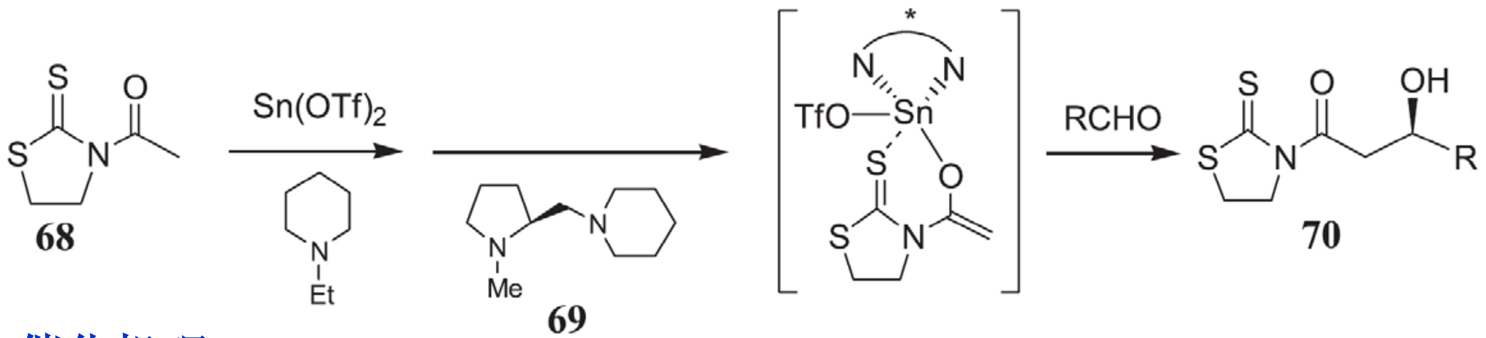


Scheme 4.26


手性试剂控制
手性醛底物控制
不对称羟醛反应
手性催化剂控制

4.4 手性催化剂控制的不对称羟醛反应

4.4.1 Mukaiyama 体系

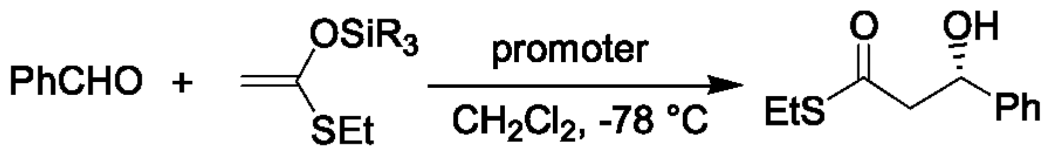


催化机理

Scheme 4.29

- Divalent tin has vacant d orbitals that enable it to form complexes with amines.
- The tin(II) metal is bonded with two nitrogen atoms, leaving one vacant orbital coordinatable to an aldehyde without losing the favorable chiral environment.

4.4.1 Mukaiyama 体系

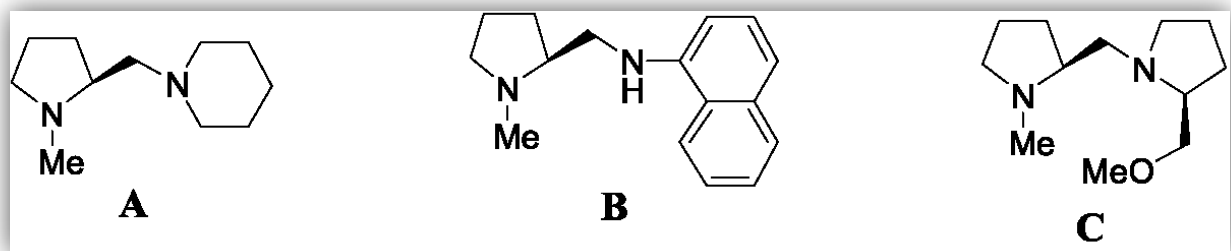


71 72

Table 4.6 S-乙基硫代乙酸酯的硅烷基烯醇醚与苯甲醛的反应

Promoter	Yield (%)	ee (%)
$Sn(OTf)_2$ + chiral diamine A	74	0
$Sn(OTf)_2$ + chiral diamine A+ n-Bu_3SnF	78	82
$Sn(OTf)_2$ + chiral diamine B+ n-Bu_3SnF	52	92
$Sn(OTf)_2$ + chiral diamine C+ n-Bu_3SnF	74	78

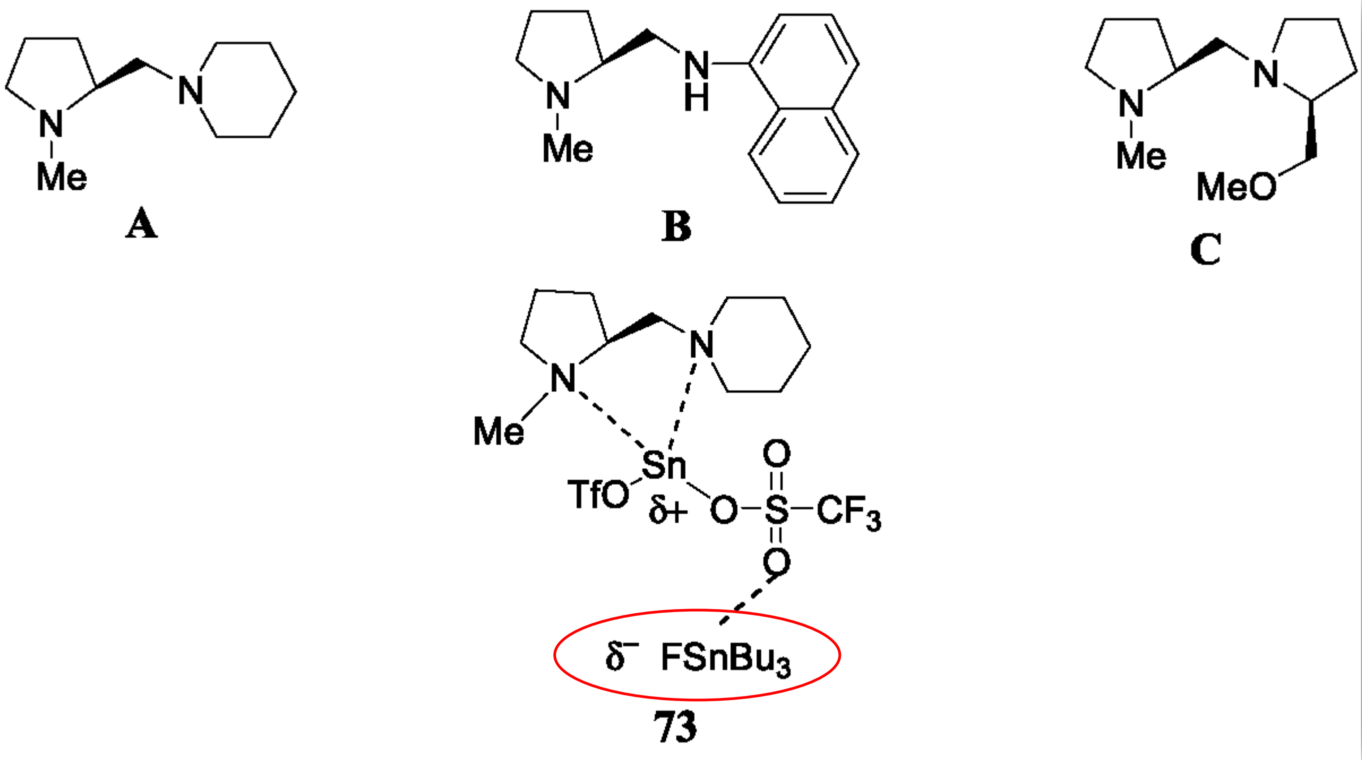
ee = Enantiomeric excess.



Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1989,** 1001.

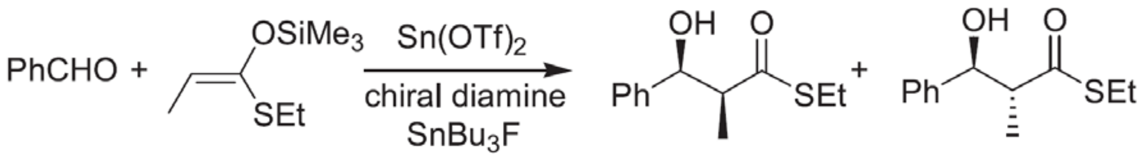
可能机理-添加剂影响

手性二胺



Scheme 4.30

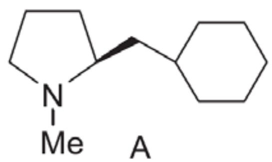
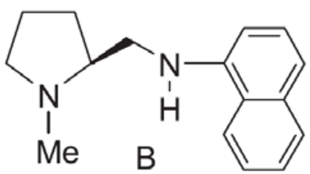
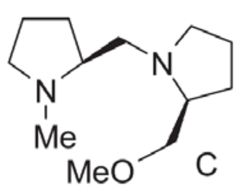
二胺配体影响



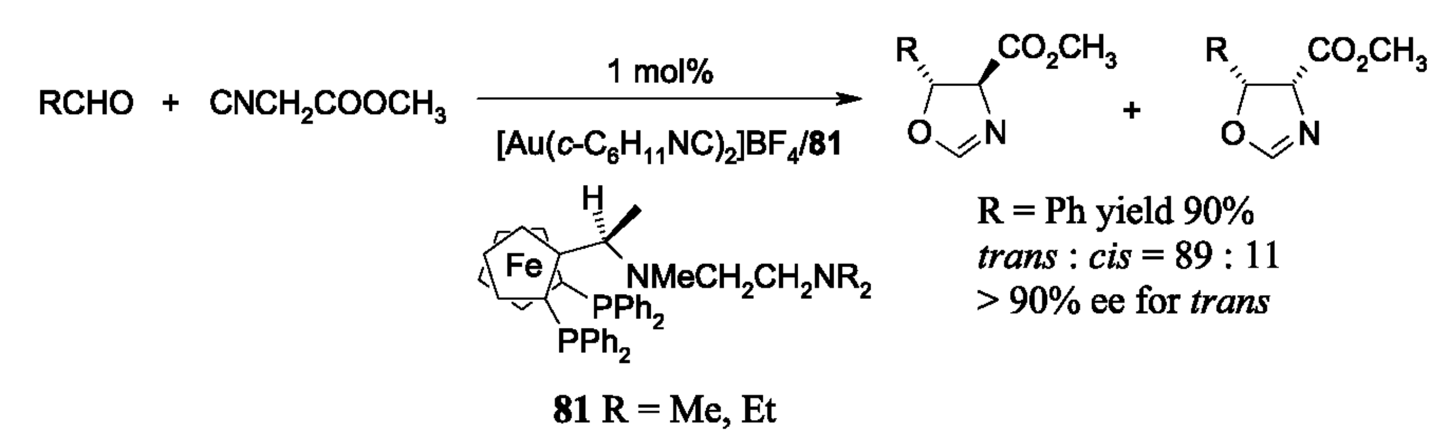
syn-**74** *anti*-**74**

Scheme 4.31

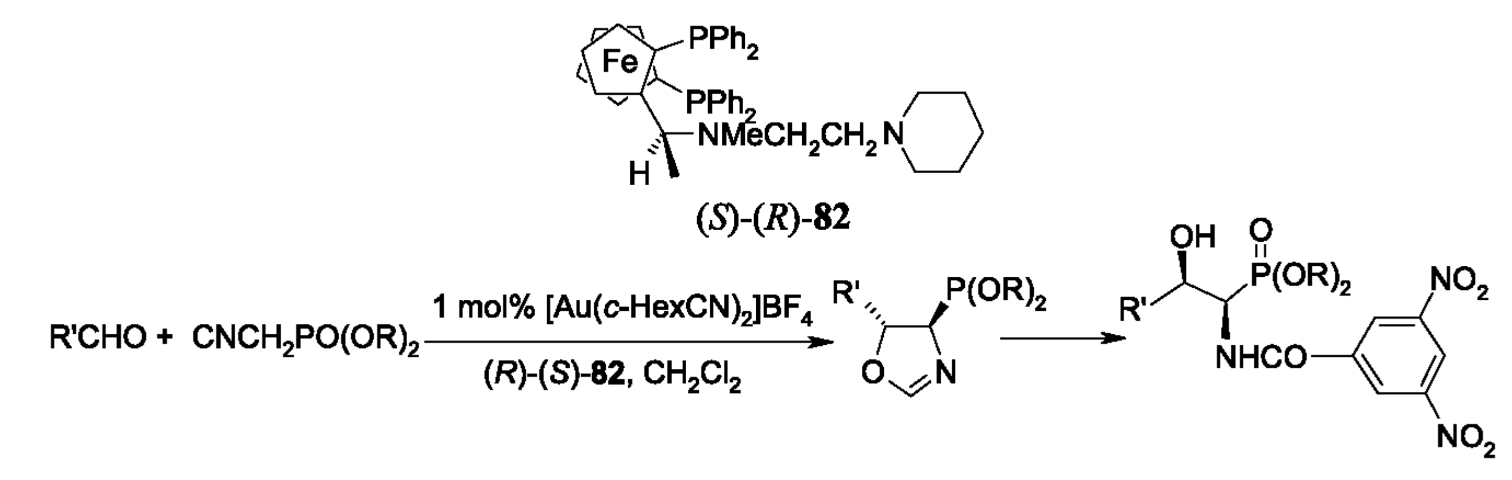
Table 4.7 手性二胺的作用

Chiral Diamine	Time (h)	Yield (%)	*syn*:*anti*	ee (%)
	20	80	93:7	80
	3	86	100:0	>98
	20	77	88:12	44

4.4.2 由Y.Ito报道的通过手性二茂铁基膦-金(I)的不对称羟醛反应



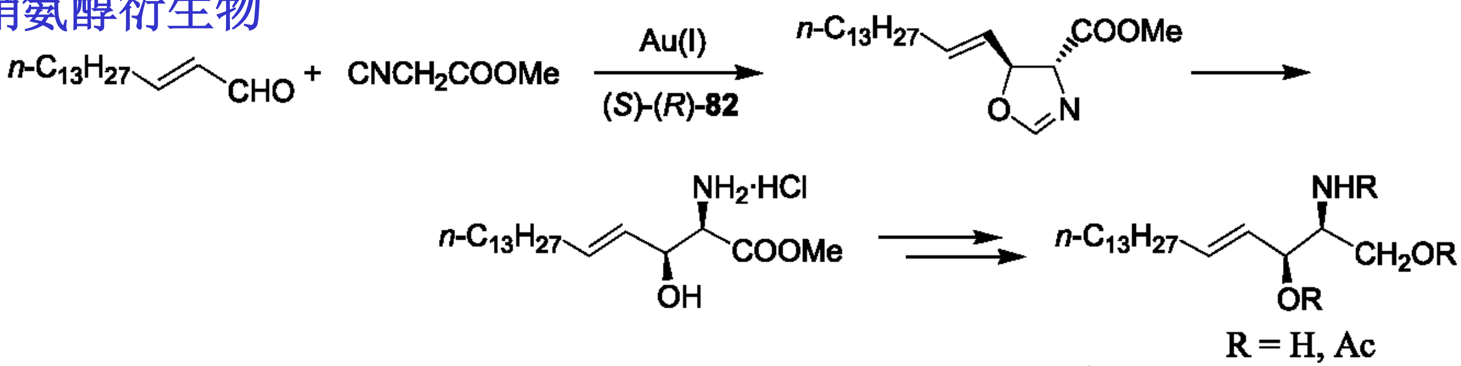
Scheme 4.33



Scheme 4.34

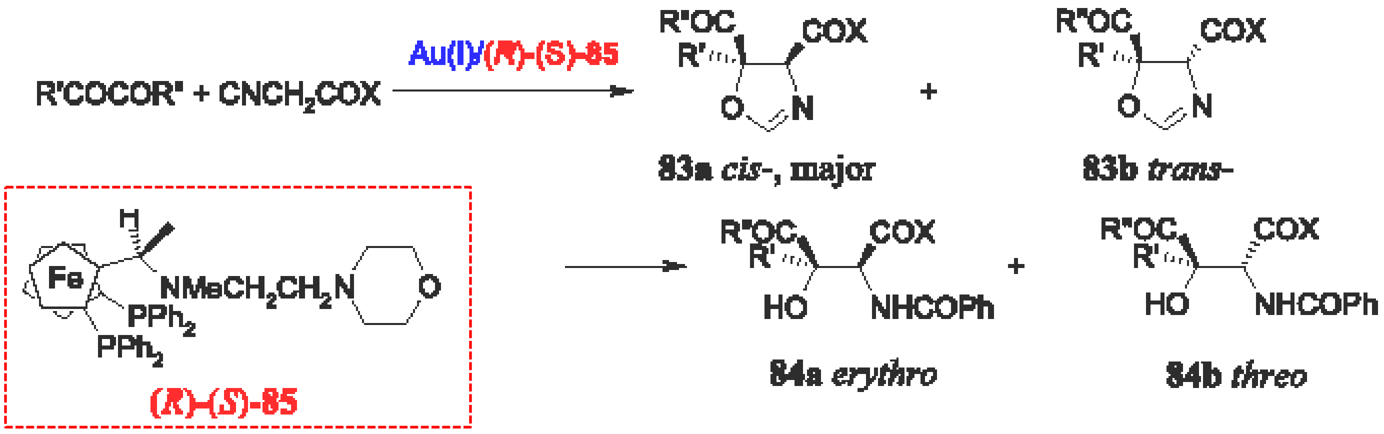
Y.I to催化体系---应用实例

D-赤式-鞘氨醇衍生物



Scheme 4.35 金(I)络合物催化的不对称醛醇反应

β-烷基-β-羟基天冬氨酸衍生物



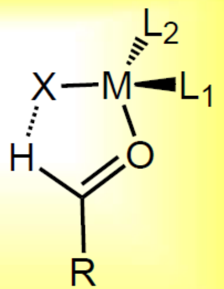
Scheme 4.36

Chiral Lewis Acids

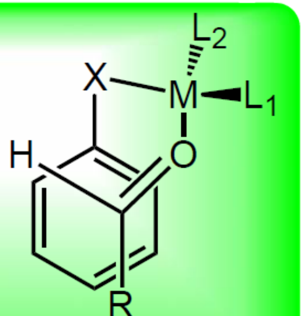
Several factors must be considered when designing the catalyst:

- mode of binding of the carbonyl group to the Lewis acid;
- the regiochemistry of complexation of the two available C=O lone pairs;
- establishing a fixed diastereofacial bias, therefore directing the enol/enolate addition to one of the two carbonyl p-faces.

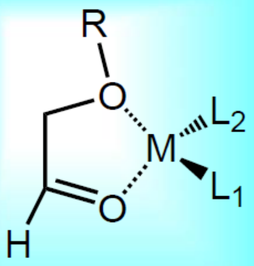
stabilizing interactions:



H-bonding

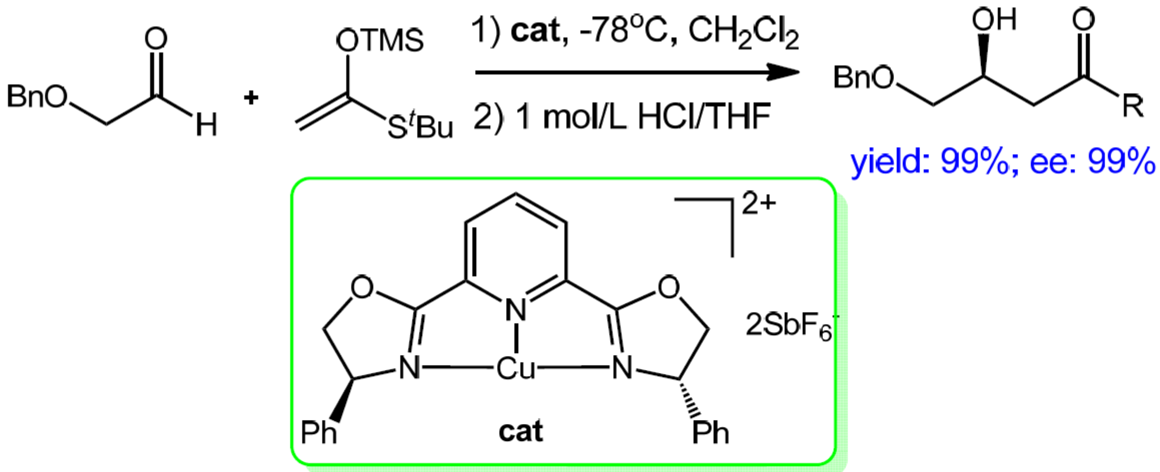


π–π-stacking

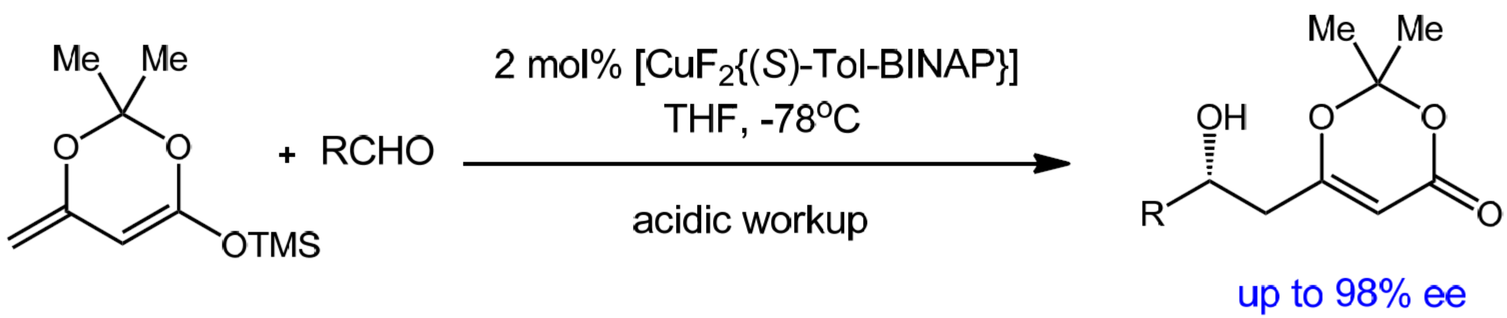


chelation

silyl enolate-mediated aldol reactions

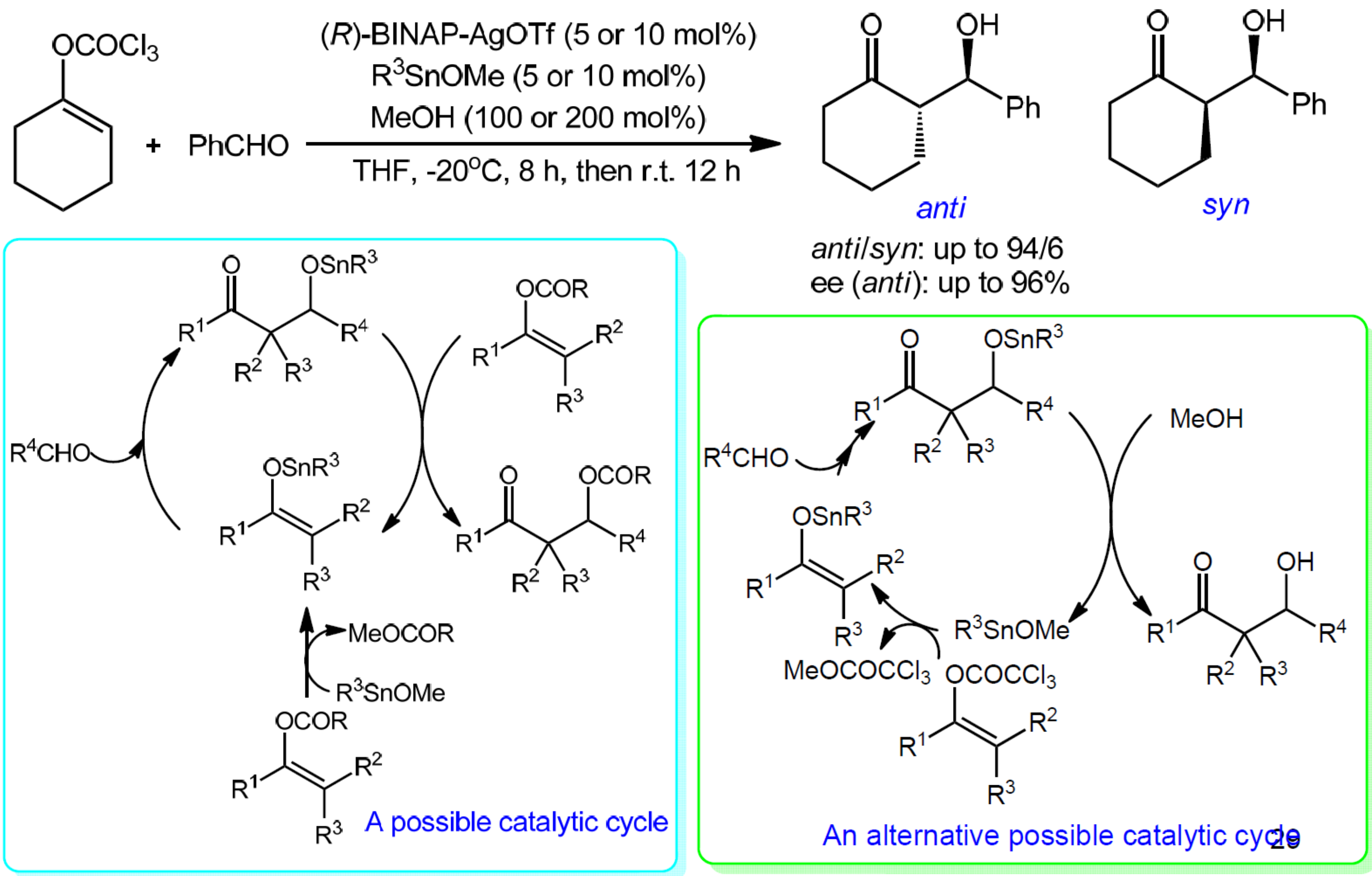


Evans, D. A. *JACS* **99**, *121*, 686.



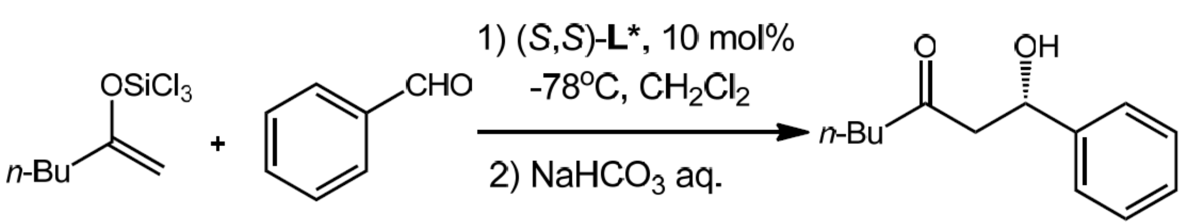
Carreira, E. M. *JACS* **98**, *120*, 837.

Organotin (IV)

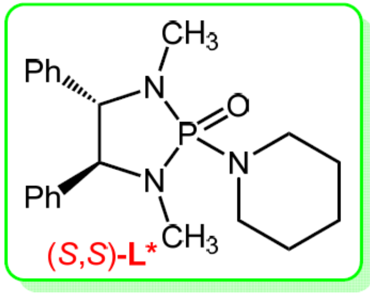


Yamamoto *JACS* **99**, *121*, 892.

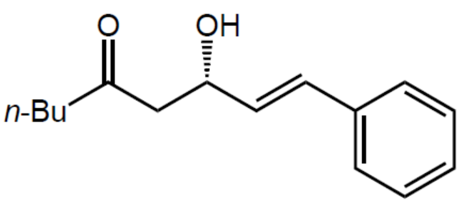
Lewis Bases



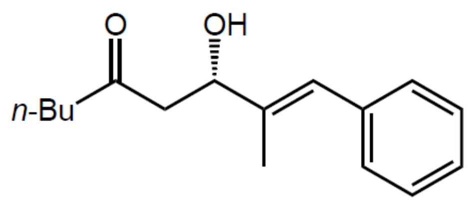
yield: 98%; ee: 87%



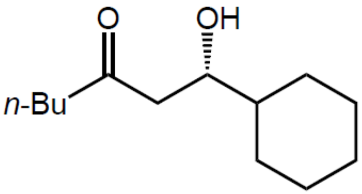
Selected examples:



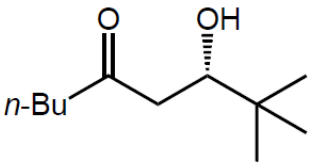
yield: 94%; ee: 84%



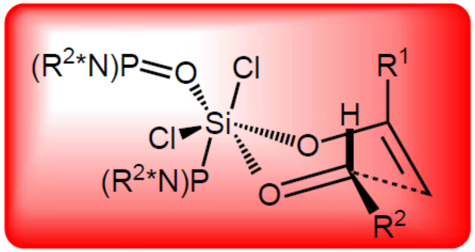
yield: 95%; ee: 91%



yield: 79%; ee: 89%



yield: 81%; ee: 92%



Denmark *JACS*, **00**, *122*, 8837.

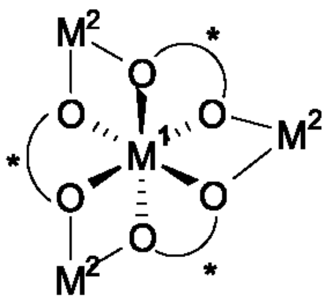
4.4.3 由双金属催化剂促进的直接的不对称羟醛反应

a chiral or achiral enolate ✓ OK

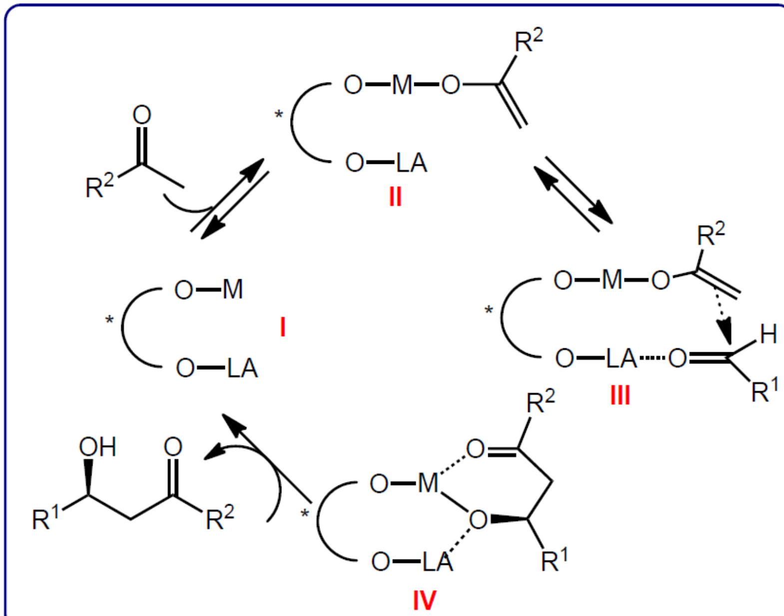
aldehydes or unmodified ketones ? How

----Shibasaki 体系

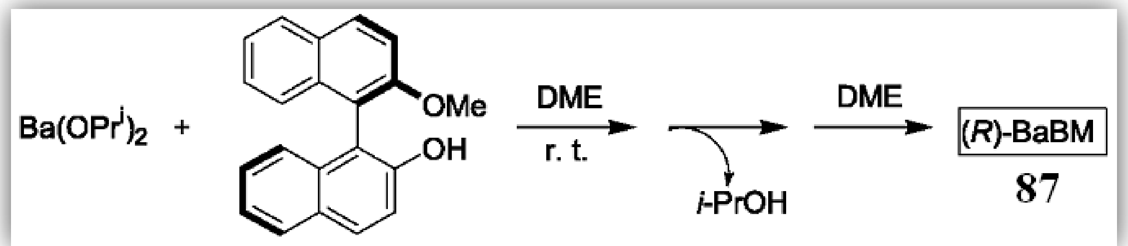
- 联萘酚和$LaCl_3$生成的双金属化合物
- 含Ba双金属配合物



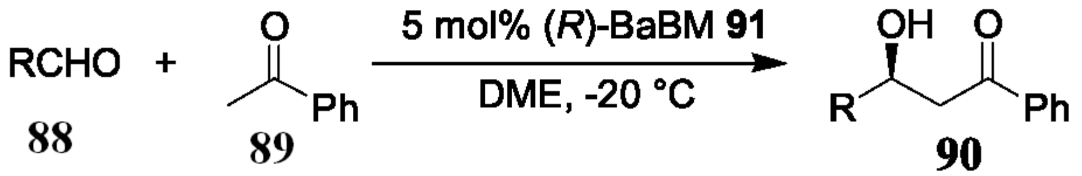
86



首例钡配合物催化的直接羟醛反应



- 含Ba双金属配合物



Scheme 4.38

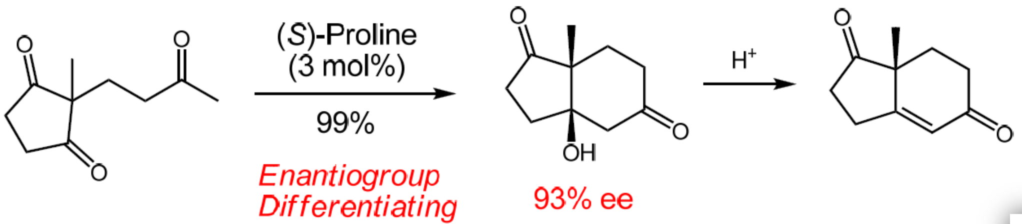
Table 4.8 由87促进的直接的醛醇反应

Entry	R in **92**	Yield for **94** (%)	ee for **94** (%)
1	*t*-Bu	77	67
2	$PhCH_2(CH_3)_2C$	77	55
3	*c*-C_6H_{11}	87	54
4	*i*-C_3H_7	91	50
5	$BnOCH_2(CH_3)_2C$	83	69
6	$BnO(CH_3)_2C$	99	70

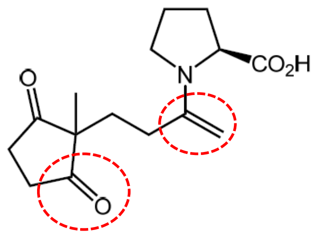
ee = Enantiomeric excess.

Enamine Catalysis-Organic molecule-direct Aldol reaction

The Hajos-Parrish-Eder-Sauer-Wiechert Reaction

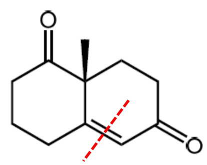


intramolecular reaction



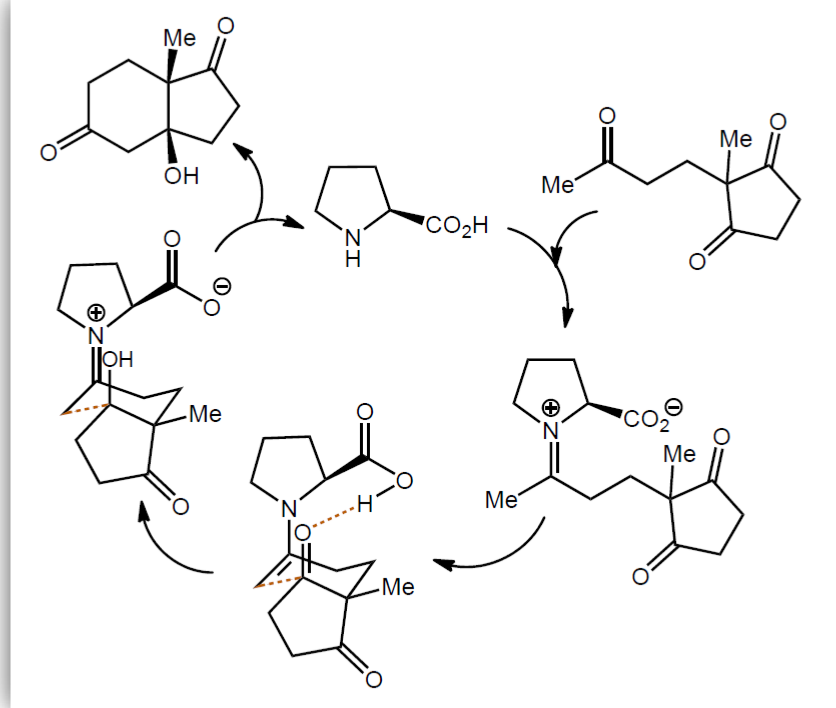
Enamine Catalysis
(Jung, Eschenmoser, Agami)

Hajos, Parrish
DE 2102623, July 29, 1971
J. Org. Chem. **1974**, 1615.

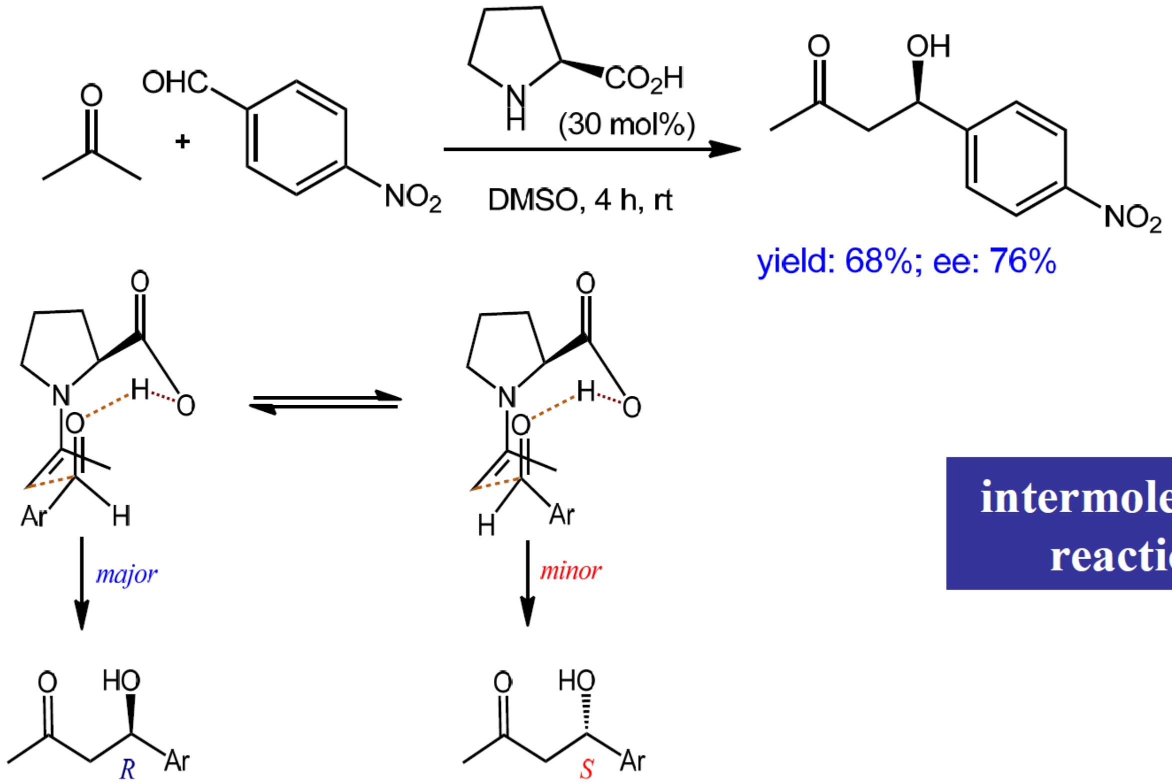


Wieland-Miescher-Ketone
(71% ee)

Eder, Sauer, Wiechert
DE 2014757, Oct. 7, 1971
Angew. Chem., Int. Ed. **1971**, 496.



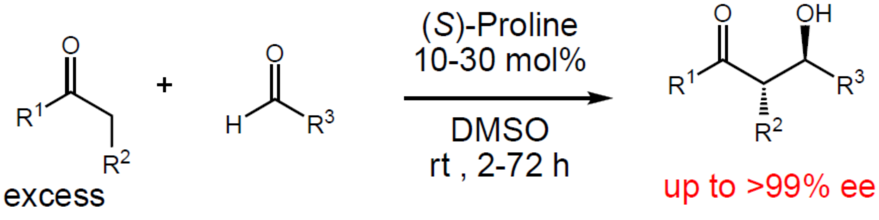
Enamine Catalysis-Organic Molecule-direct Aldol reaction

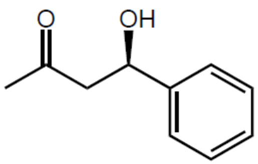


intermolecular reaction

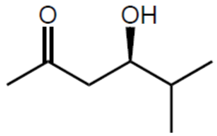
List, B.; Lerner, R. A.; Barbas, C. F. *JACS* **2000,** *122*, 2395.

Enamine Catalysis-Organic Molecule-direct Aldol reaction

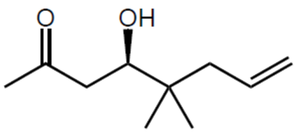




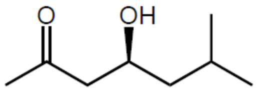
62%, 72% ee



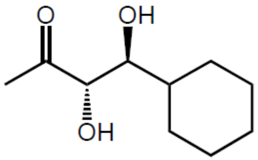
97%, 96% ee



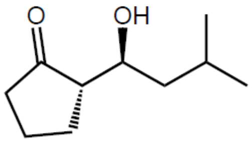
85%, >99% ee



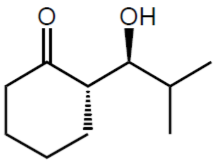
34%, 73% ee
(Reaction in Acetone)



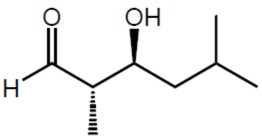
60%, >20:1 dr
>99% ee



77%, 2.5:1 dr
95% ee



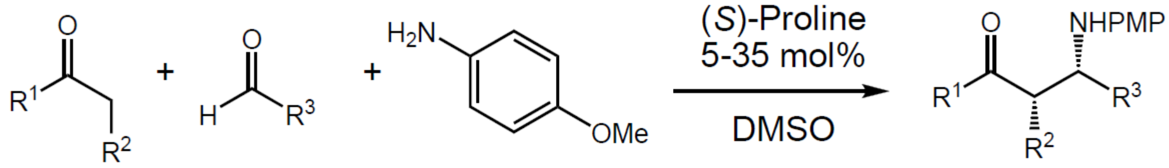
68%, >20:1 dr
97% ee

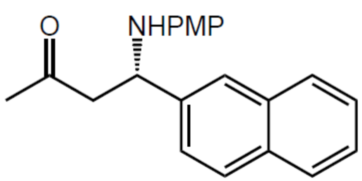


88%, 3:1 dr, 97% ee
Syringe Pump
MacMillan, *JACS* **2002**, 6798-9.

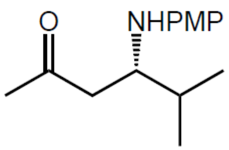
JACS **2000**, 2395 *JACS* **2000**, 7386 *Org. Lett.* **2001**, 573

The First Proline-Catalyzed Asymmetric Mannich-Reaction

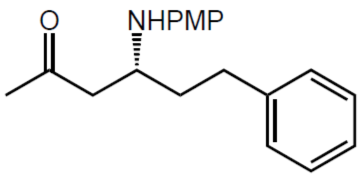




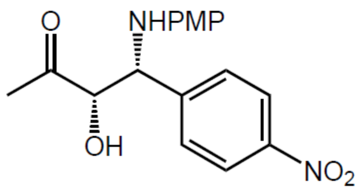
35%, 96% ee



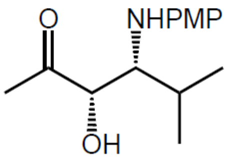
56%, 70% ee



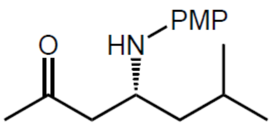
80%, 93% ee
(Reaction in Acetone)



92%, >20:1 dr, >99% ee



57%, 17:1 dr, 65% ee



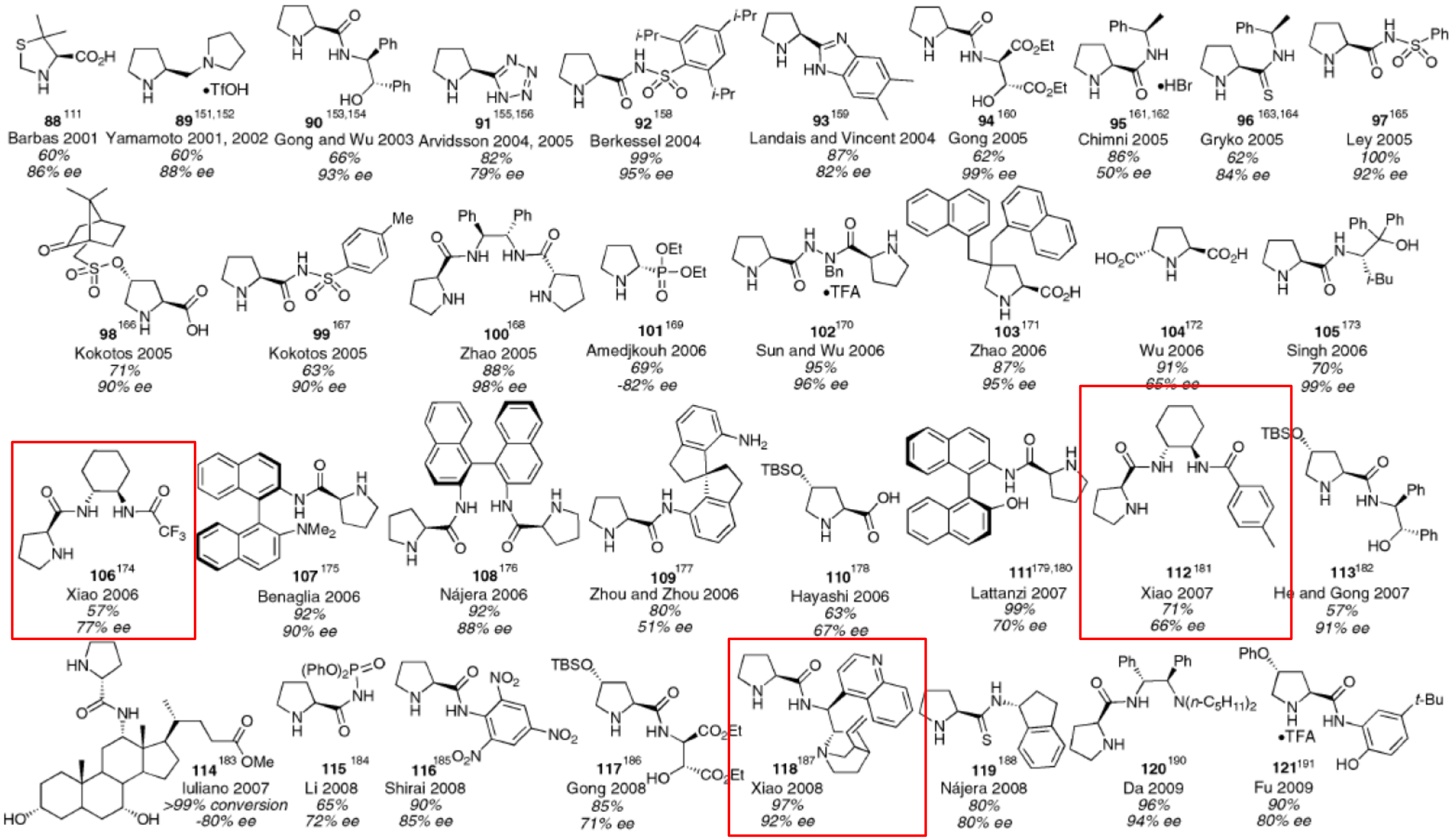
90%, 93% ee
(Reaction in Acetone)

JACS **2000**, 9336

JACS **2002**, 827

Synlett **2003**, 1903

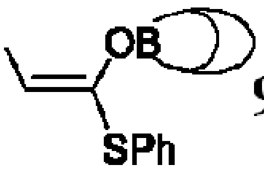
Catalyst screening: proline derivatives



Trost et. al., *Chem. Soc. Rev.*, **2010**, *39*, 1600.

4.5 双不对称羟醛反应

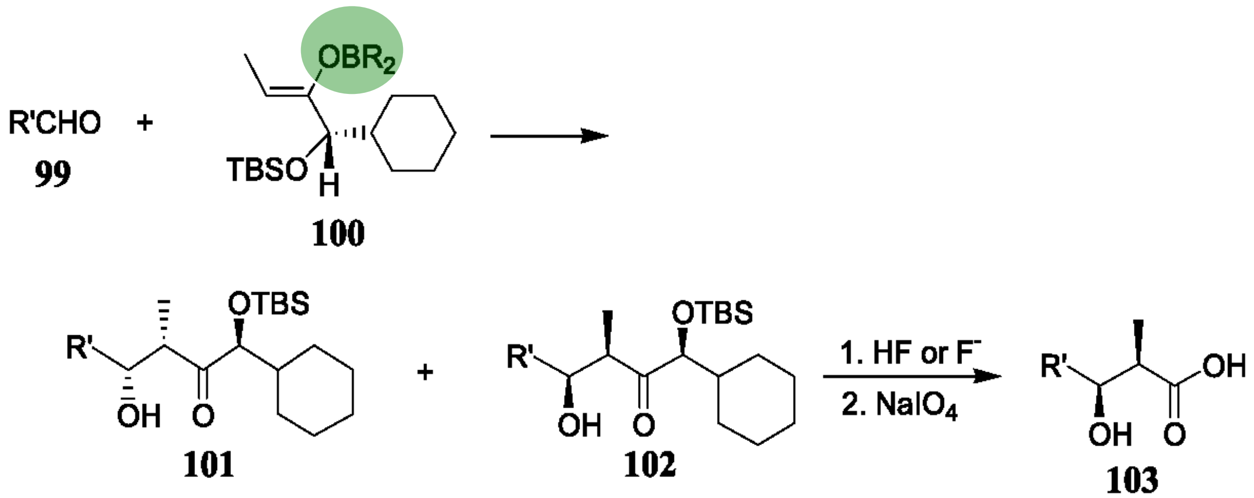
手性醛与非手性烯醇盐



95 (9-硼杂双环[3.3.1]壬-9-基烯醇盐)

Scheme 4.38

非手性醛与手性烯醇盐



(*S*)-**100a** BR_2 = B; (*S*)-**100b** R = *n*-C_4H_9; (*S*)-**100c** R = *c*-C_5H_9

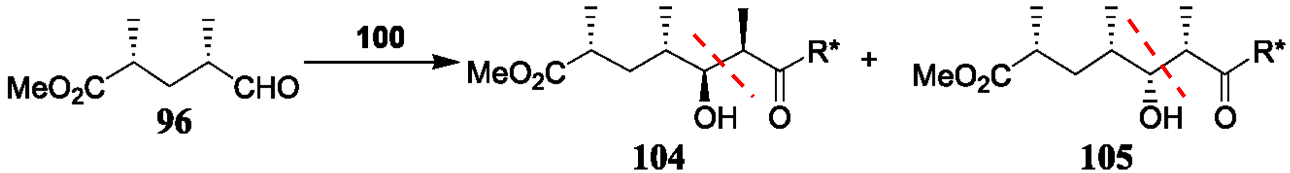
Scheme 4.39

Table 4.9 醛与硼烯醇盐的反应

Aldehyde	R′	Boron Enolate	**102:101**
99a	$PhCH_2OCH_2CH_2$	(*S*)-**100a**	16:1
		(*S*)-**100b**	28:1
		(*S*)-**100c**	100:1
99b	$(CH_3)_2CH$	(*S*)-**100a**	>100:1
		(*S*)-**100b**	>100:1
		(*S*)-**100c**	No reaction

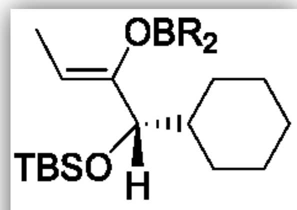
手性醛与手性烯醇盐

匹配对与错匹配对



96 + (*S*)-**100b**: matched pair　　**104** : **105** > 100 : 1

96 + (*R*)-**100b**: mismatched pair　　**104** : **105** = 1 : 30

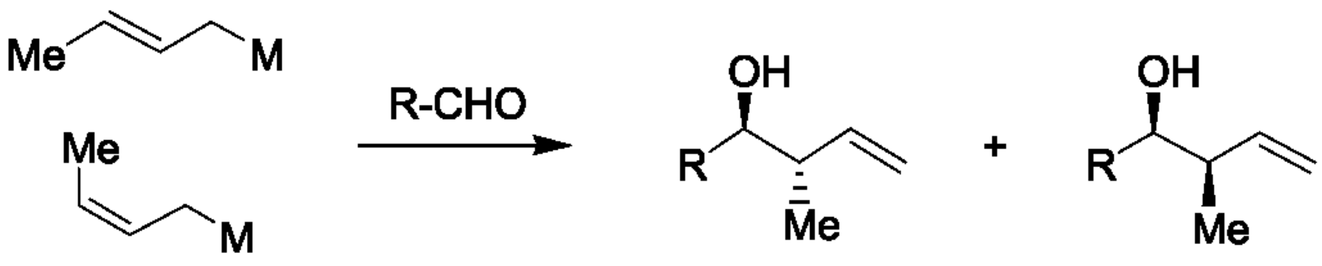


100

R= n-C_4H_9

Scheme 4.41

4.6 不对称烯丙基化反应

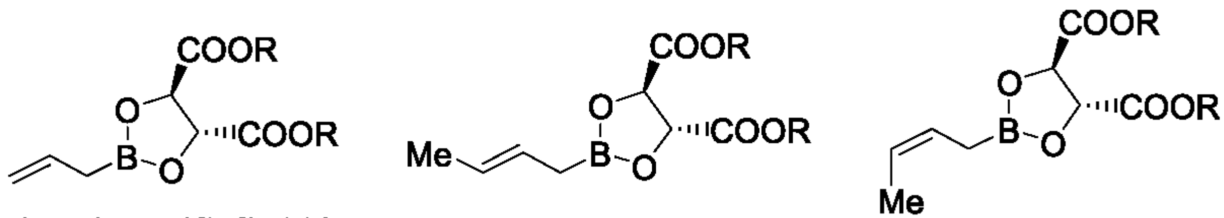


where M = $SiMe_3$; $SnBu_3$; BR_2; AlR_2; MgX; Li; CrX_2; $TiCp_2X$; $ZrCp_2X$,

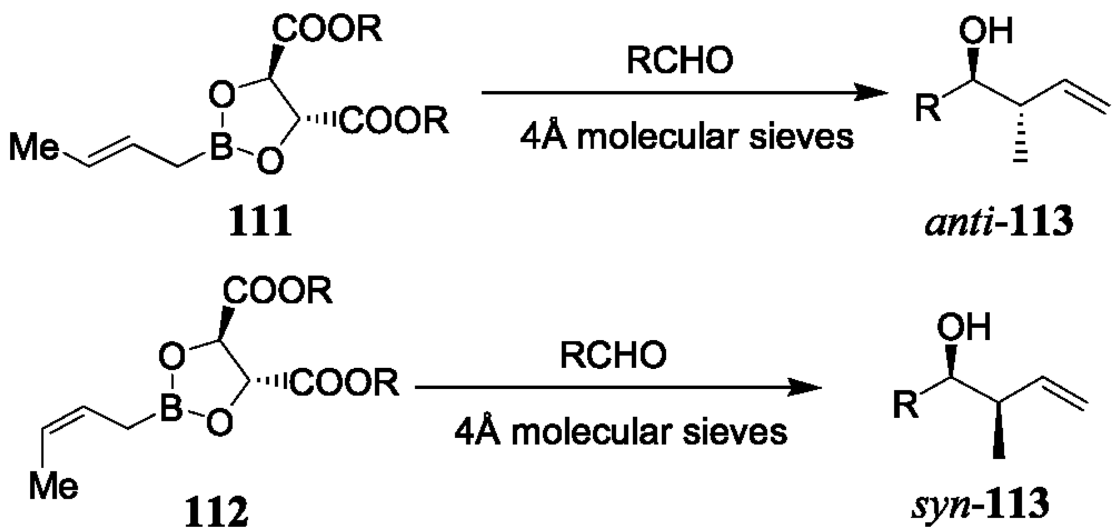
电子转移?

4.6.1 Rouch 反应

Rouch 硼试剂



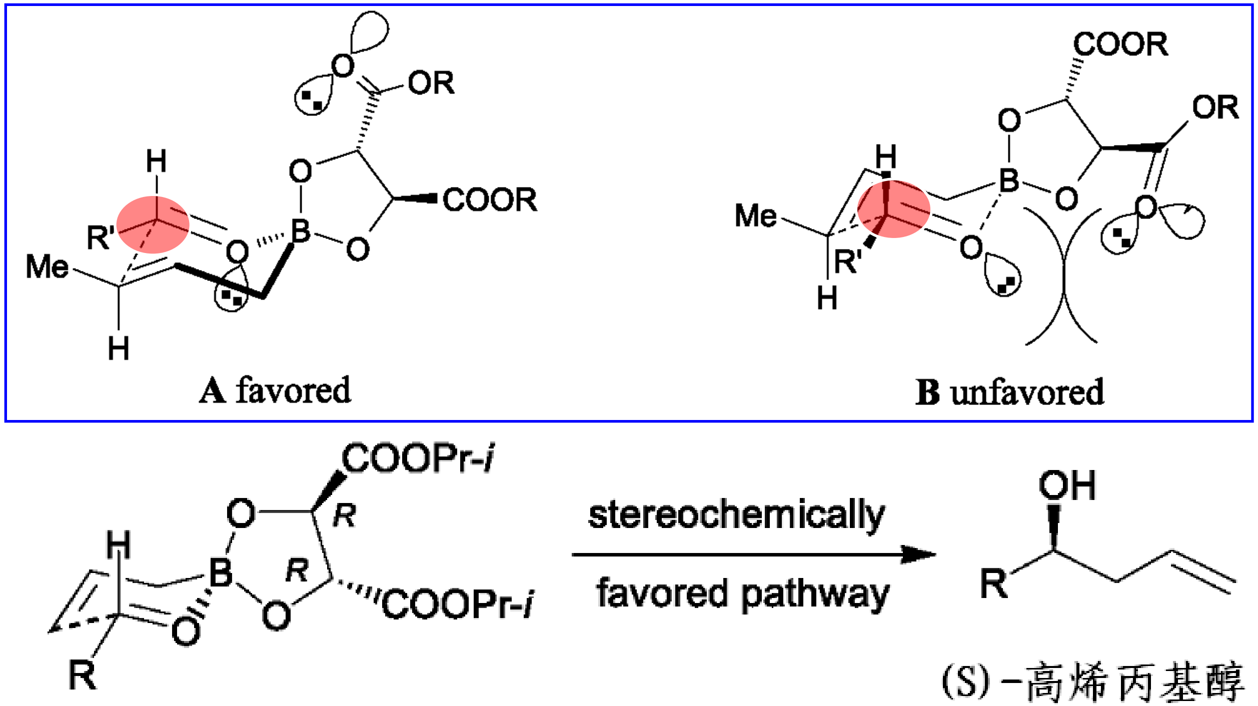
(*R*, *R*)- or (*S*, *S*)-**110** (*R*, *R*)- or (*S*, *S*)-**111** (*R*, *R*)- or (*S*, *S*)-**112**



Scheme 4.42

可能的机理

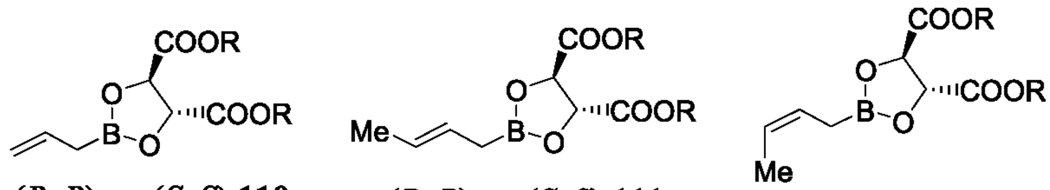
- 空间电子效应(主要因素)
- 空间立体位阻



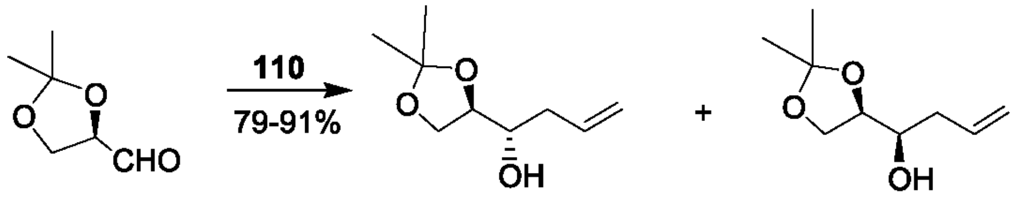
有利的孤对电子/偶极相互作用

Scheme 4.43

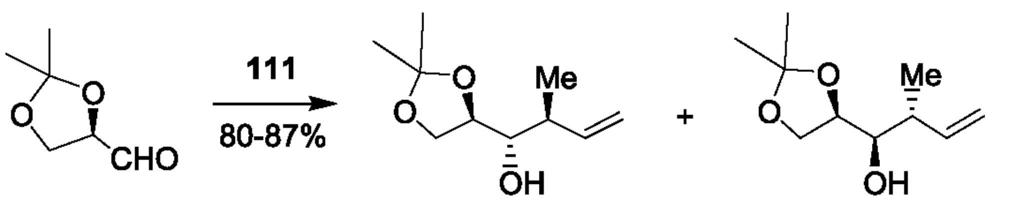
有张力手性醛作为底物-匹配对和错配对都有合成意义



(*R*, *R*)- or (*S*, *S*)-**110**　(*R*, *R*)- or (*S*, *S*)-**111**　(*R*, *R*)- or (*S*, *S*)-**112**



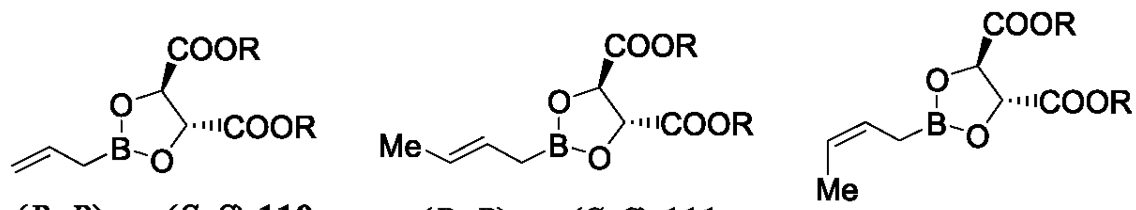
matched case, (*R*,*R*)-reagent, 98 : 2
mismatched case, (*S*,*S*)-reagent, 7 : 93



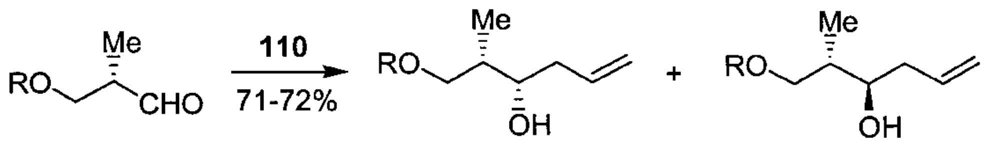
(*R*,*R*)-reagent, 91 : 9
(*S*,*S*)-reagent, 2 : 98

Scheme 4.44 与有张力的甘油醛的反应

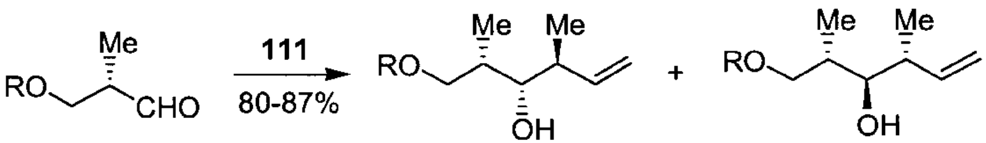
无张力手性醛作为底物



(*R*, *R*)- or (*S*, *S*)-**110** (*R*, *R*)- or (*S*, *S*)-**111** (*R*, *R*)- or (*S*, *S*)-**112**



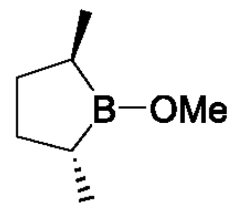
Aldehyde	Reagent	Selectivity
R = TBS	(*R*,*R*)-**110** (matched)	89 : 11
	(*S*,*S*)-**110** (mismatched)	19 : 81
R = TBDPS	(*R*,*R*)-**110**	79 : 21
	(*S*,*S*)-**110**	13 : 87
R = Bn	(*R*,*R*)-**110**	83 : 17
	(*S*,*S*)-**110**	20 : 80



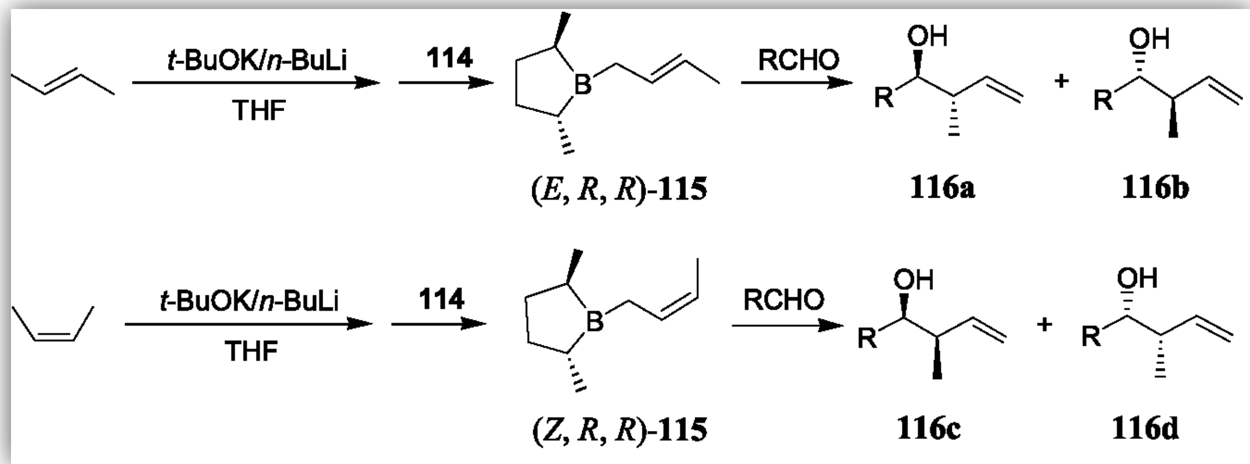
R = TBS	(*R*,*R*)-reagent (matched)	97 : 3
	(*S*,*S*)-reagent (mismatched)	16 : 84

Scheme 4.45 与无张力的醛的烯丙基化反应

Masamune试剂 (顺势烯烃vs反式烯烃)



114



Scheme 3.46

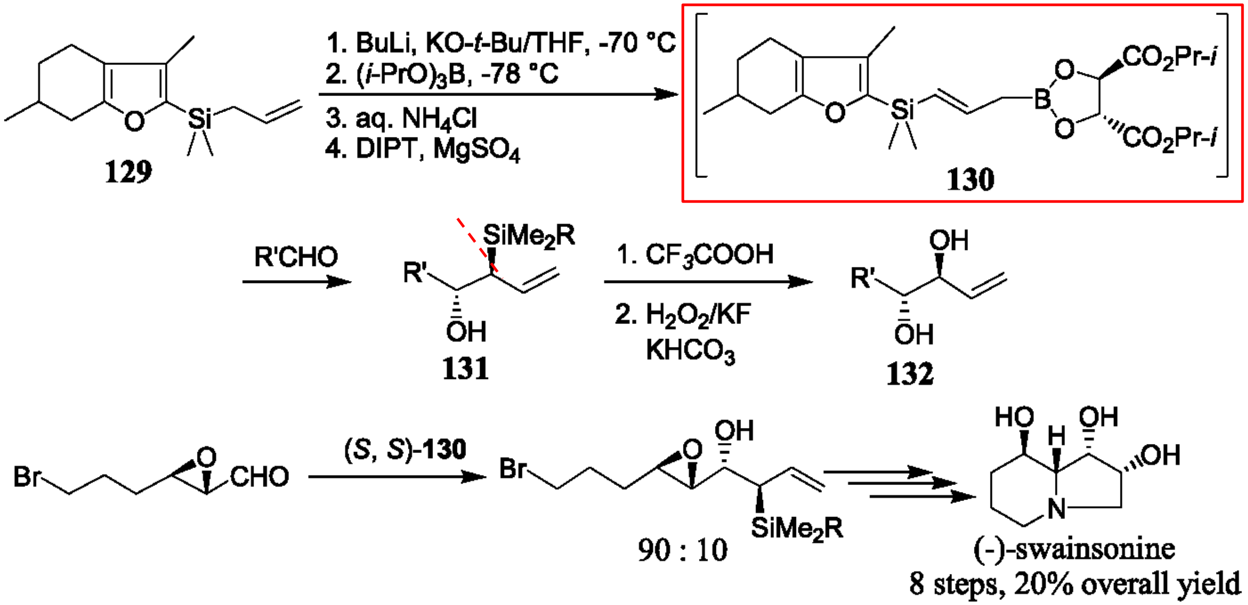
Table 3.10 巴豆基硼杂环戊烷(*E,R,R*)-115和(*Z,R,R*)-115与代表性的非手性醛的反应

Entry	Crotylborane	Aldehyde	Yield (%)	*anti*/*syn* Ratio	Major Product ee (%)
1	(*E*)-**115**	C_2H_5CHO	81	93/7	96
2	(*E*)-**115**	*i*-C_3H_7CHO	76	96/4	97
3	(*E*)-**115**	*i*-C_4H_9CHO	72	96/4	95
4	(*Z*)-**115**	C_2H_5CHO	73	7/93	86
5	(*Z*)-**115**	*i*-C_3H_7CHO	70	4/96	93
6	(*Z*)-**115**	*i*-C_4H_9CHO	75	5/95	97

2017/7/25

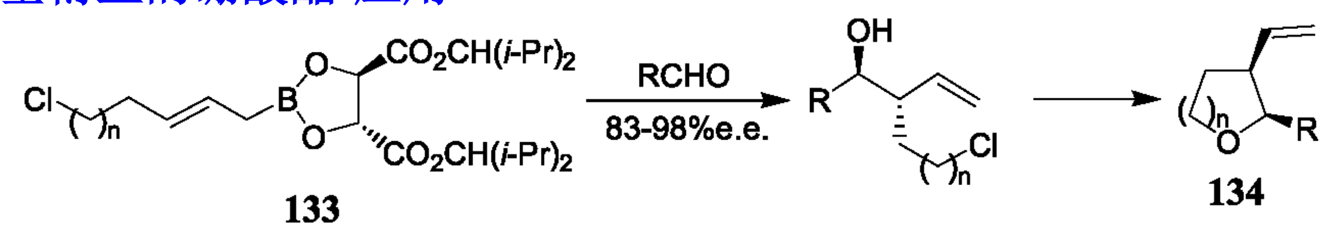
ee = Enantiomeric excess.

Roush-薄荷呋喃基衍生的硼酸酯-130



Scheme 4.48 新硼酸酯的应用

薄荷呋喃基衍生的硼酸酯-应用

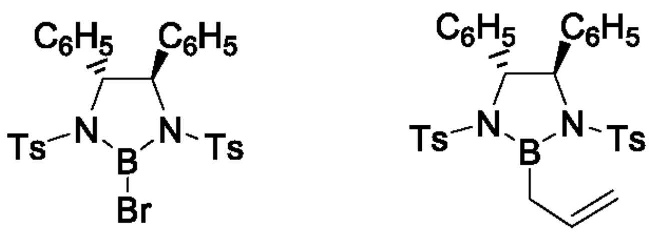


R = Me, *n*-Pr, Ph
n = 1, 2

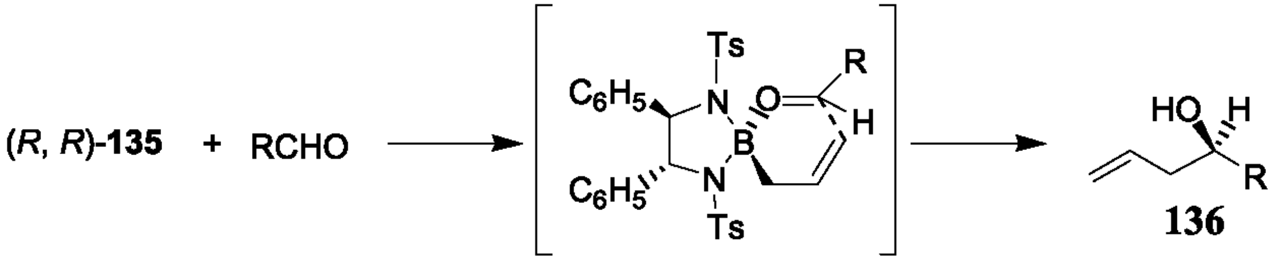
Scheme 4.49 α，β－二取代四氢呋喃和四氢吡喃的合成

4.6.2 Corey试剂-反应

手性烯丙基硼烷135与醛的反应



55　　135

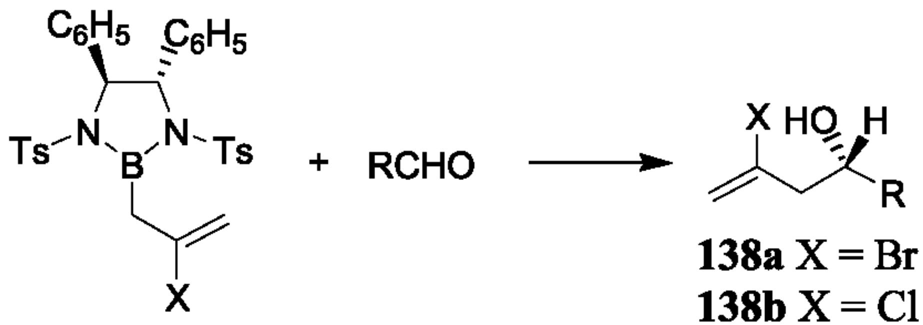


136

R of RCHO	Solvent	ee (%) of **136**	Config.
Ph	Toluene	95	*R*
(*E*)-PhCH=CH-	CH_2Cl_2	98	*R*
c-C_6H_{11}	Toluene	97	*R*
n-C_5H_{11}	Toluene	95	*S*

Scheme 4.50 醛与手性烯丙基硼烷135的反应

卤代手性烯丙基硼烷137与醛的反应



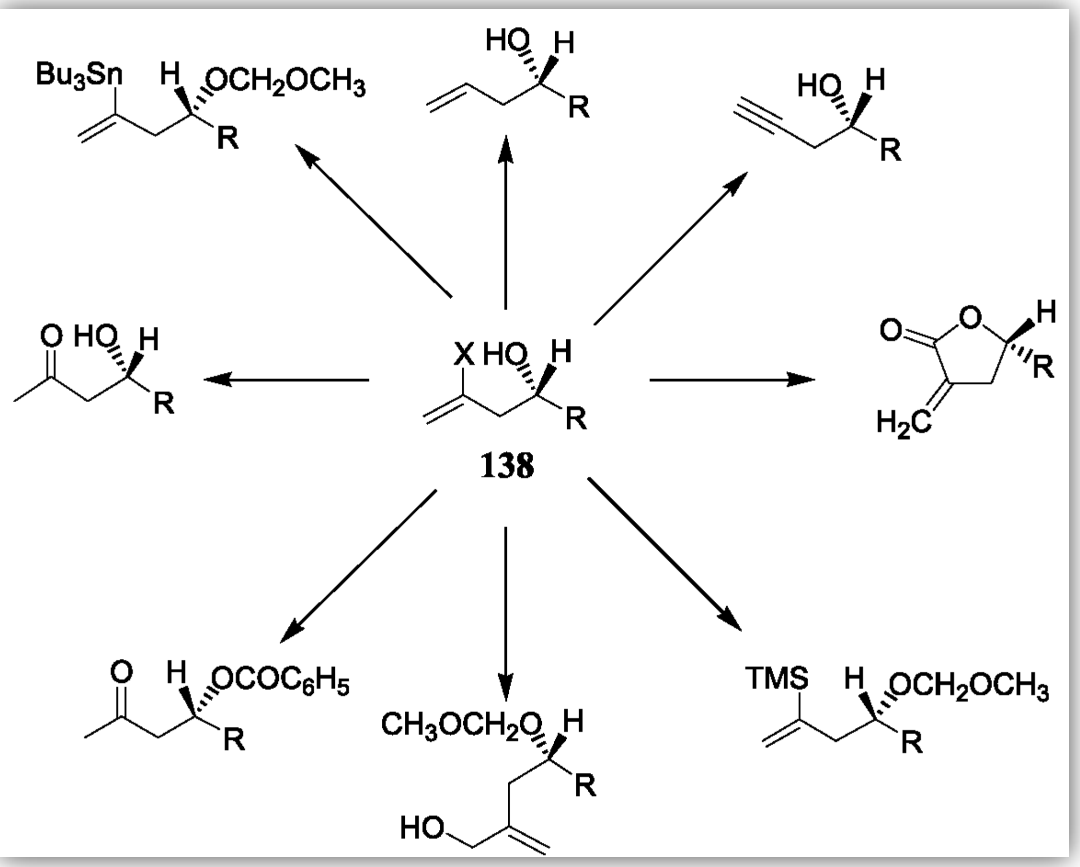
137a X = Br
137b X = Cl

138a X = Br
138b X = Cl

R of RCHO	Reagent	Yield (%)	ee (%) of **138**	Config.
Ph	**137a**	73	79	*S*
Ph	**137b**	79	84	*S*
(*E*)-PhCH=CH	**137a**	79	87	*S*
(*E*)-PhCH=CH	**137b**	84	92	*S*
c-C_6H_{11}	**137a**	75	94	*S*
c-C_6H_{11}	**137b**	81	99	*S*
n-C_5H_{11}	**137a**	71	94	*R*
n-C_5H_{11}	**137b**	77	99	*R*

Scheme 4.51 醛与手性2-卤代烯丙基硼烷的反应

卤代高烯丙基醇产物的合成应用



Scheme 4.52 化合物138 在有机合成中的应用

4.7 亚胺的不对称烯丙基化和烷基化

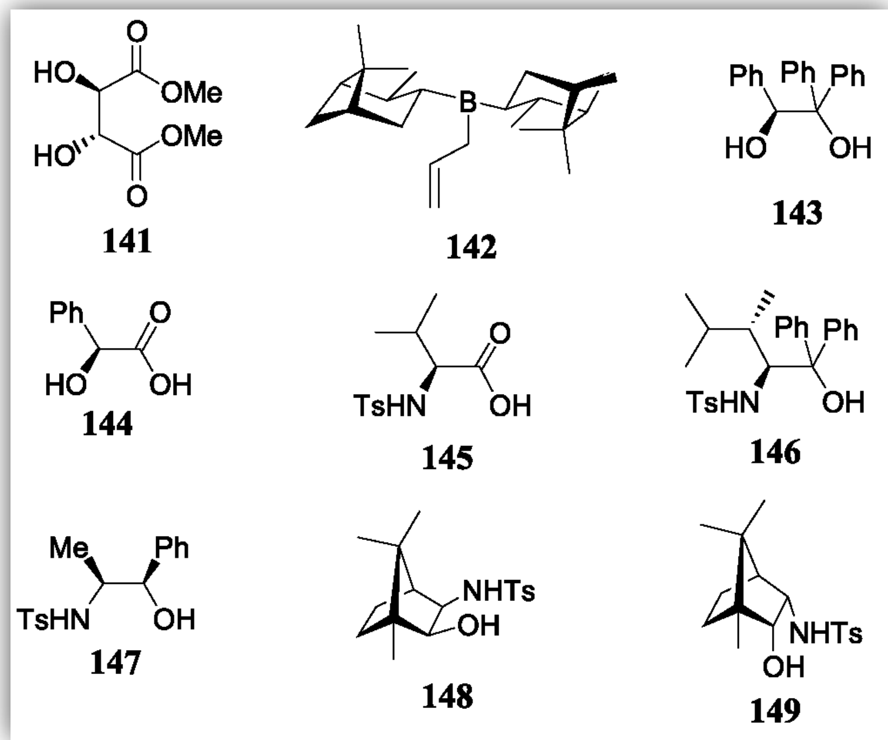
(对潜手性亚胺的C=N键的不对称烯丙基加成)

挑战:

1.亚胺的亲电性.

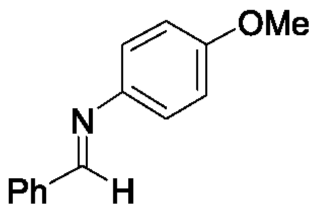
2. 亚胺E/Z异构化.

3. 反应产物胺具很强亲核性-毒化.

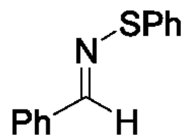


亚胺底物

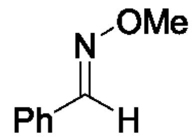
活化的亚胺底物



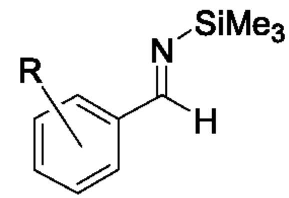
150



151

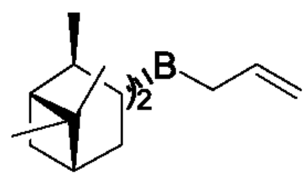


152

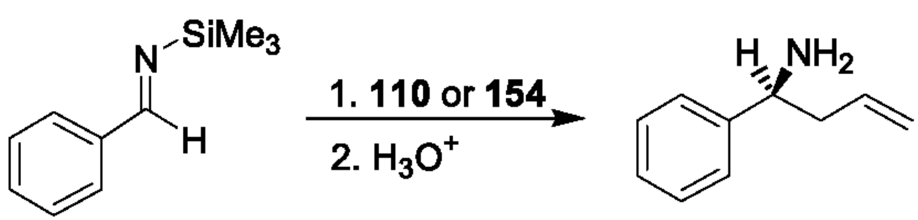


153a R = H
153b R = 2-Cl
153c R = 4-MeO

Watanabe 催化体系

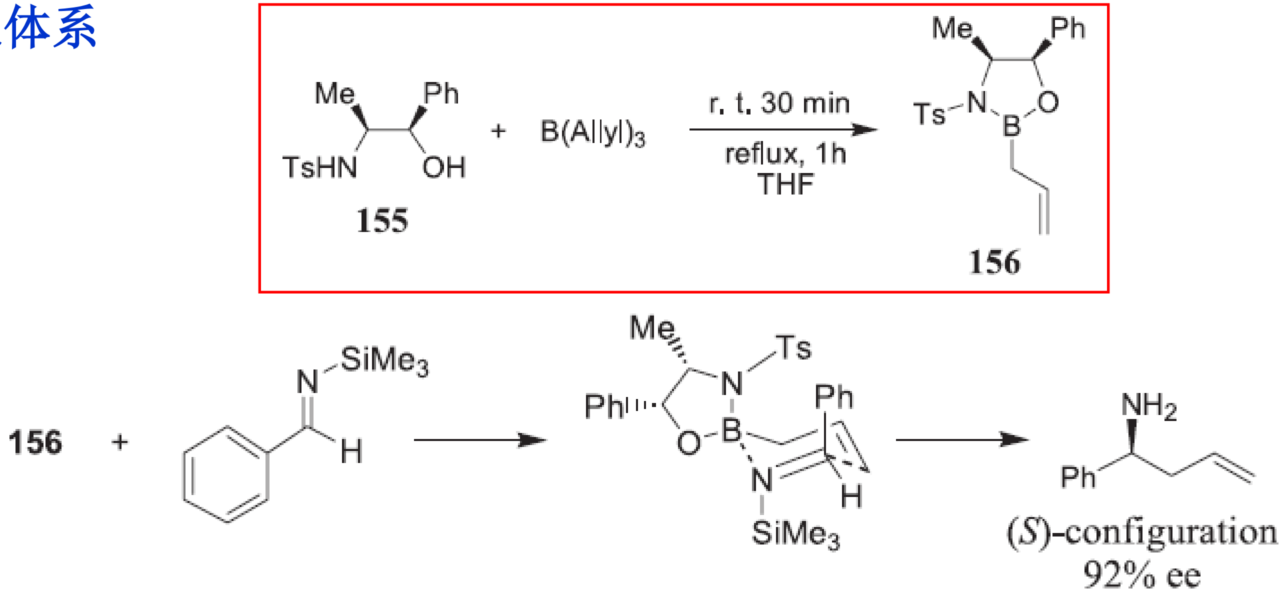


154



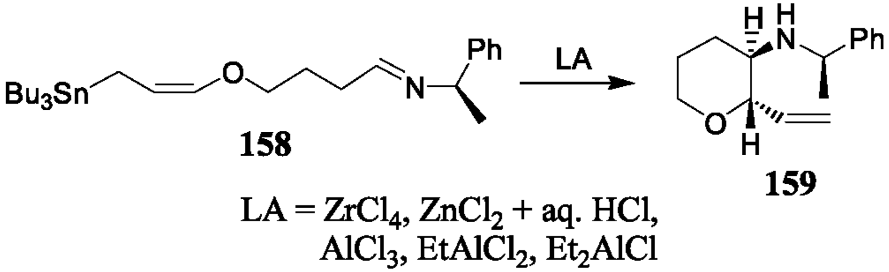
Scheme 4.56

Itsuno催化体系



Scheme 4.57

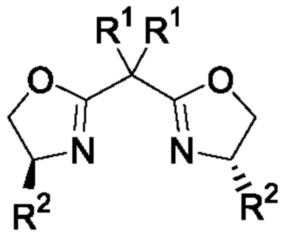
Yamamoto 分子内不对称烯丙基化反应-底物控制



Scheme 4.58

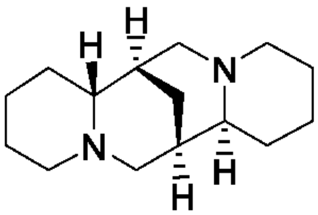
金属烷基试剂对亚胺加成

Li试剂加成



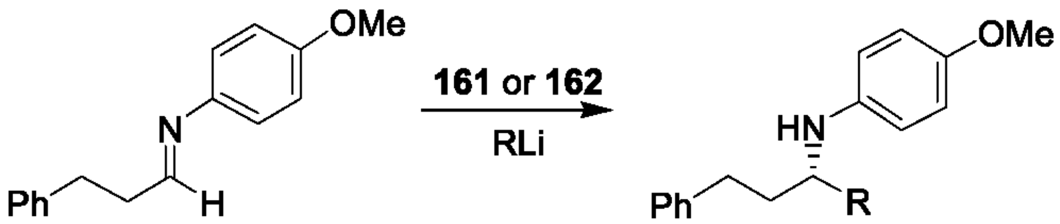
161

R^1 = Et, *i*-Bu
R^2 = CH_2Ph, *i*-Pr, *t*-Bu,
$PhCMe_2$, Ph_3C



162

(-)-sparteine

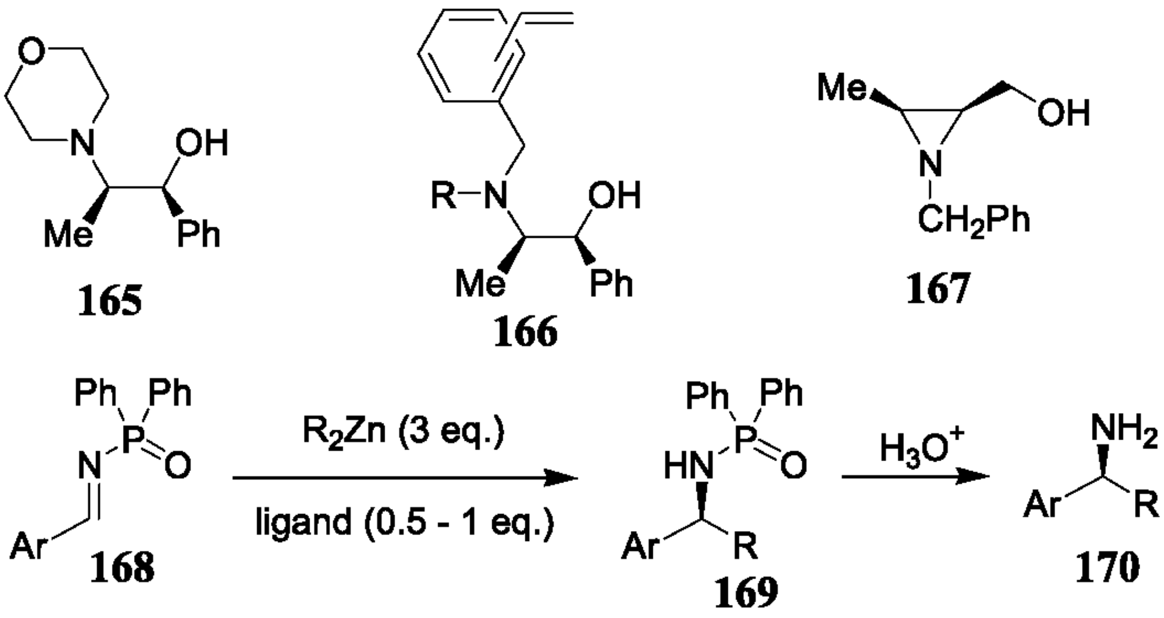


163 **164**

Scheme 4.59

金属烷基试剂对亚胺加成

Zn试剂加成



Scheme 4.60