

CHAPTER 2 (第3次课)

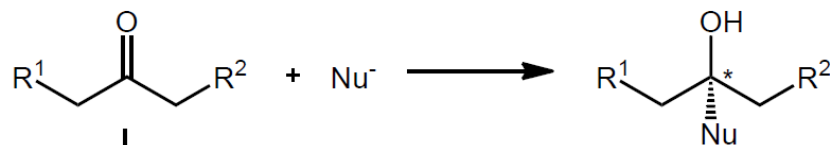
α -Alkylation and Arylation of Carbonyl Compounds

Jia-Rong Chen
2016-03-02

CHAPTER 2

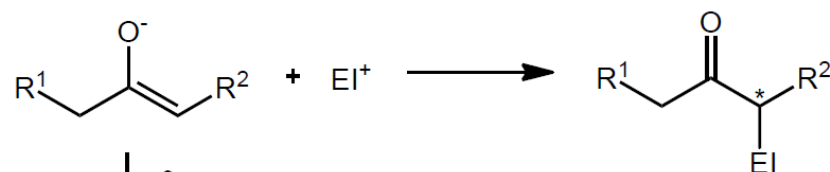
- 羰基化合物介绍
- 手性辅基
- 金属不对称催化
- 有机催化

羰基化合物的反应类型



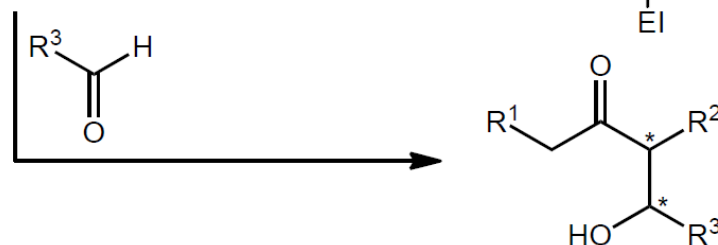
$\text{Nu} = \text{H}$, 还原反应

$\text{Nu} = \text{C}$, 加成反应

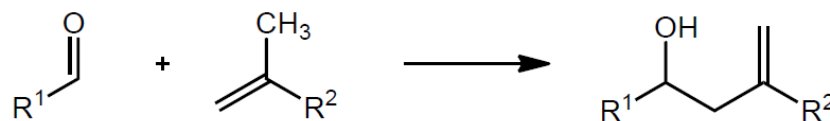


α -烷基化反应

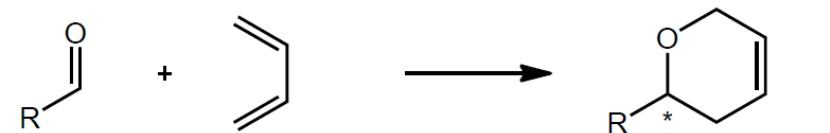
E = 亲电试剂



羟醛缩合反应



羰基-烯反应



杂-Diels-Alder反应

烯醇体催化模式

- (1) 通过Lewis酸与1,3-双羰基配位
- (2) 通过可以烯醇化的醛，酮与手性仲胺生成烯胺中间体
- (3) 通过手性亲核试剂对烯酮反应生成离子型的烯醇类物
- (4) 通过相转移催化剂与烯醇体的离子对
- (5) 手性叔胺作为手性碱催化剂

2.1 INTRODUCTION

Carbonyl compounds including ketones, aldehydes and carboxylic acid derivatives constitute a class of carbon acids, the acidity of which falls in the **pKa range of 25 to 35** in dimethylsulfoxide (DMSO).

To generate an **enolate** from a carbonyl substrate, **a suitable base** should be chosen to meet two criteria:

1. Adequate basicity to ensure the selective deprotonation process for enolate generation
2. A sterically hindered structure so that nucleophilic attack of this base on the carbonyl centers can be prevented.

2.1 INTRODUCTION

TABLE 2-1. pK_a Data for Representative Carbonyl Compounds and Related Substances in DMSO

Substrate	pK_a (DMSO)	Substrate	pK_a (DMSO)
H ₃ CCOCH ₃	26.5	NCCH ₃	31.3
PhCOCH ₃	24.6	EtOCOCH ₃	30–31
PhCOCH ₂ CH ₃	24.4	EtOCOCH ₂ Ph	22.7
PhCOCH ₂ OMe	22.9	EtOCOCH ₂ SPh	21.4
PhCOCH ₂ Ph	17.7	Me ₂ NCOCH ₃	34–35
PhCOCH ₂ SPh	17.1	CH ₃ SOCH ₃	35.1
HOH	27.5	NH ₃	41
CH ₃ OH	27.9	HN(CH ₃) ₂	44
(CH ₃) ₂ CHOH	29.3	(CH ₃) ₃ COH	29.4

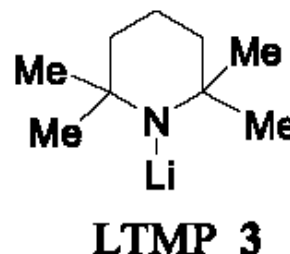
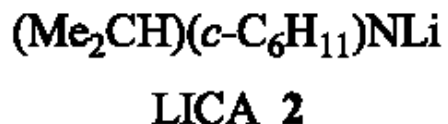
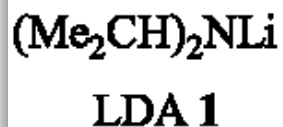
弱酸 \longrightarrow 烯醇化 (碱选择)

2.1 INTRODUCTION

The **metal amide bases** had enjoyed much popularity since the introduction of sterically more hindered bases 1-4.

Advantages:

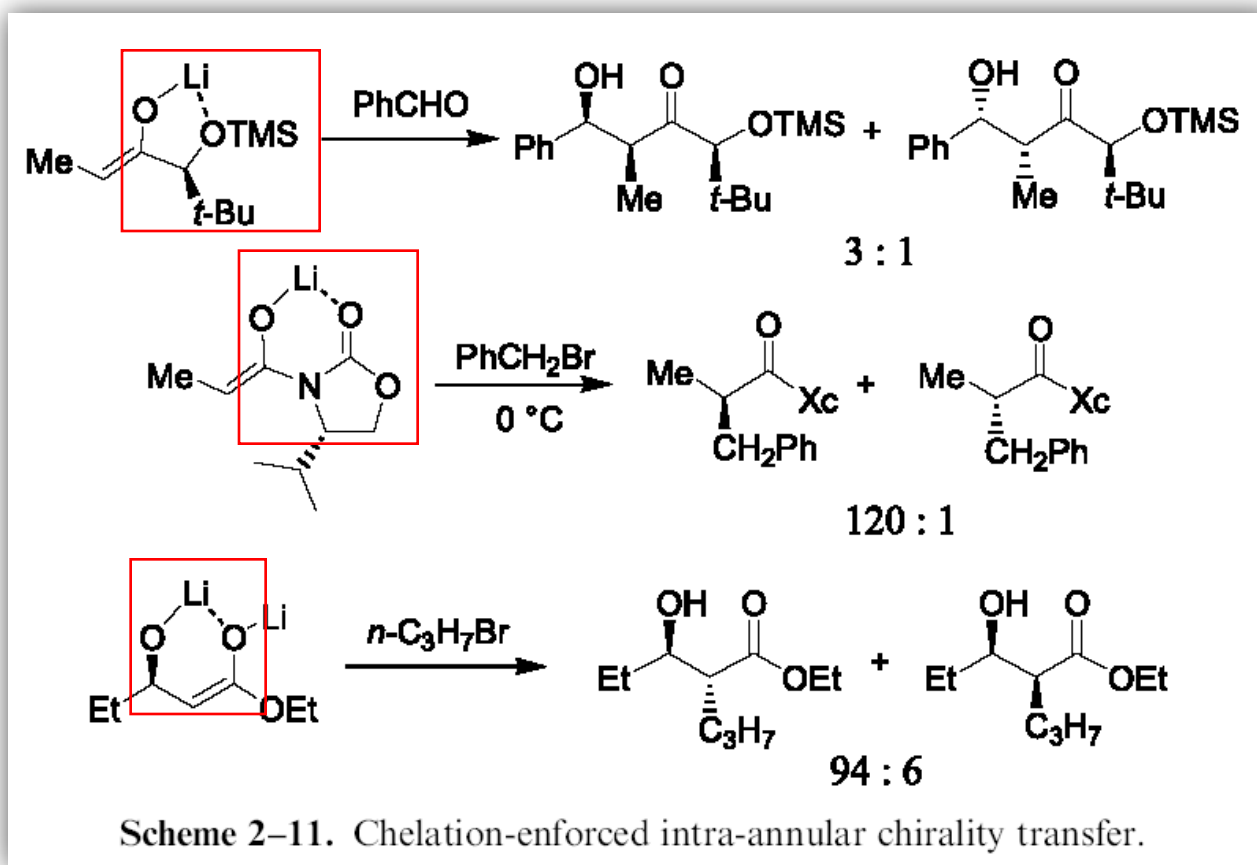
- most suitable and commonly used bases for carbonyl deprotonation.
- quite soluble in ethereal solvent systems.



2.2.3 Chelation-Enforced Intra-annular Chirality Transfer

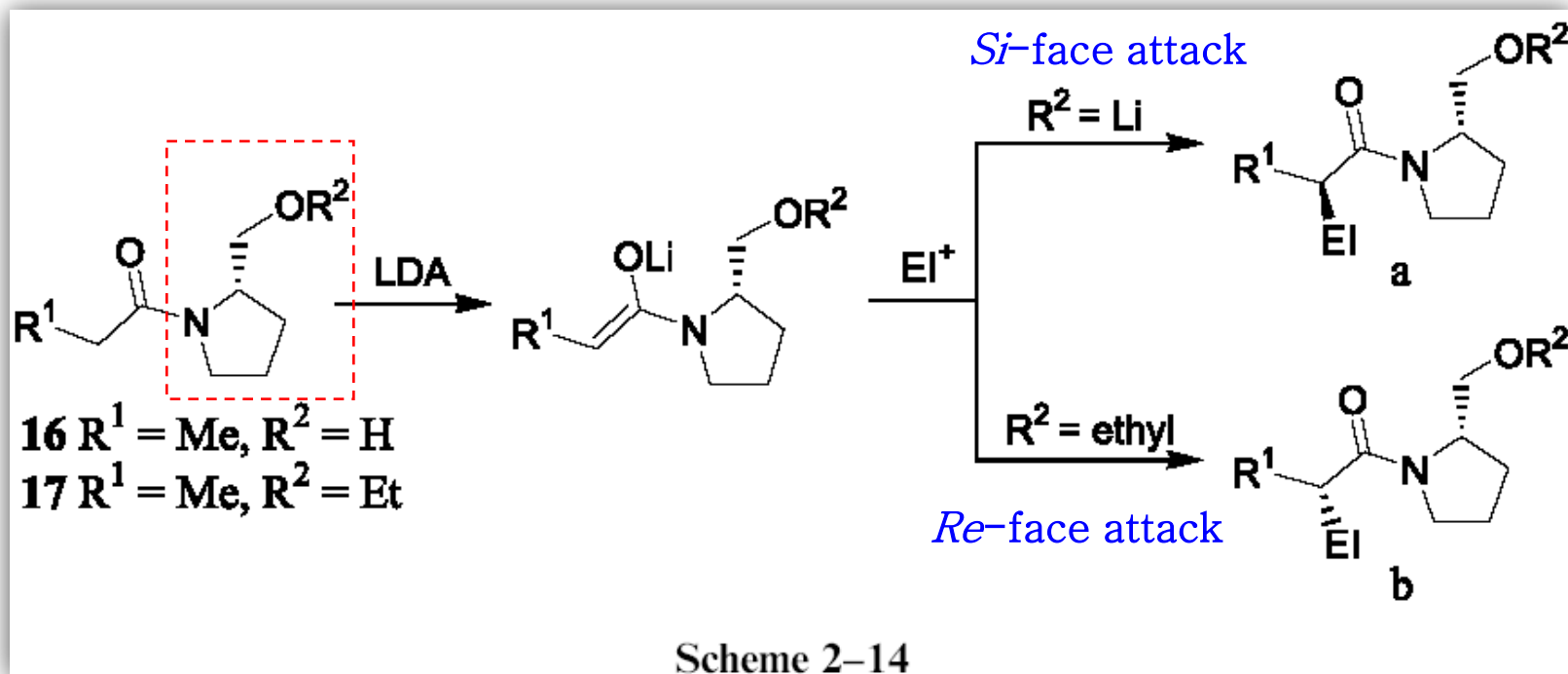
Transfer (配位型的环内不对称诱导)

As illustrated in the equations in Scheme 2-11. A lithium-coordinated five-membered or six-membered ring fixes the orientation between the inducing asymmetric center and the enolate:



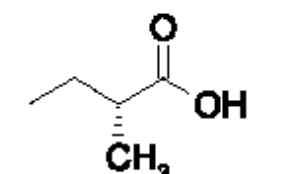
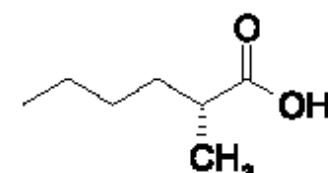
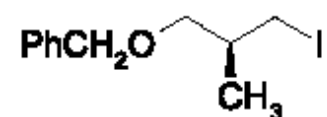
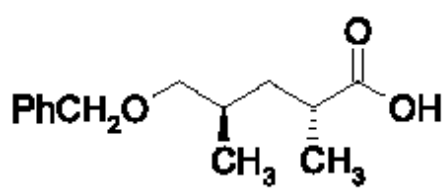
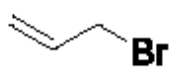
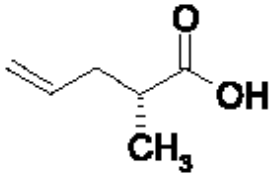
2.2.3.2 Prolinol-Type Chiral Auxiliaries

Evans and Takacs demonstrated a diastereoselective alkylation based on metal ion chelation of a lithium enolate derived from a prolinol-type chiral auxiliary. This method can provide effective syntheses of α -substituted carboxylic acids.

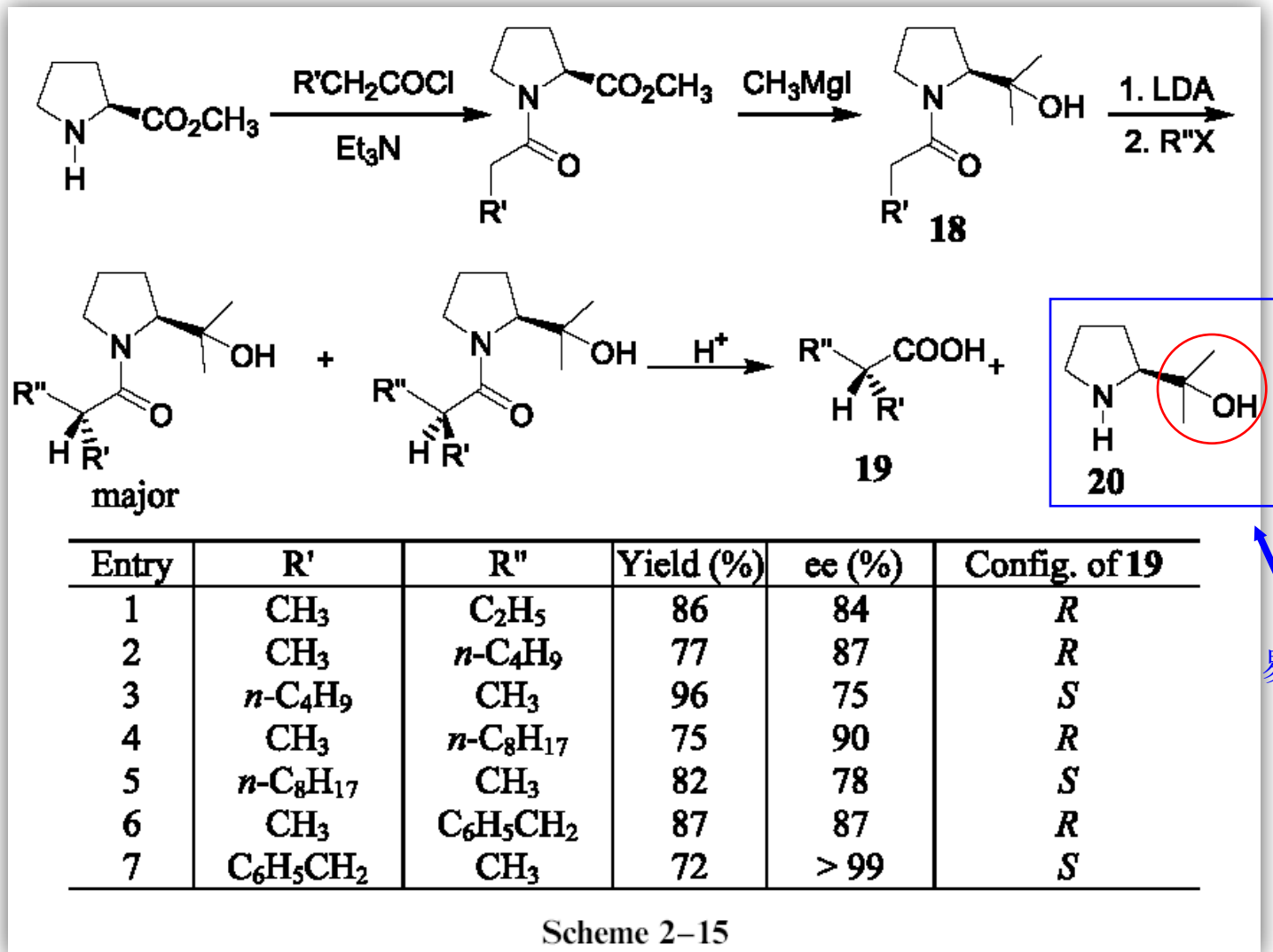


2.2.3.2 Prolinol-Type Chiral Auxiliaries

TABLE 2-3. Enantioselective Alkylations and Conversions of 16 to Carboxylic Acids

Entry	Electrophile	a:b	Hydrolysis products	Yield (%)
1	$\text{CH}_3\text{CH}_2\text{I}$	92:8		84
2	$n\text{-C}_4\text{H}_9\text{I}$	94:6		78
3		97:3		91
4		96:4		87

2.2.3.2 Prolinol-Type Chiral Auxiliaries



易回收

2.2.3.2 Prolinol-Type Chiral Auxiliaries (C₂-对称性)

外消旋二羧酸拆分

Evans et al

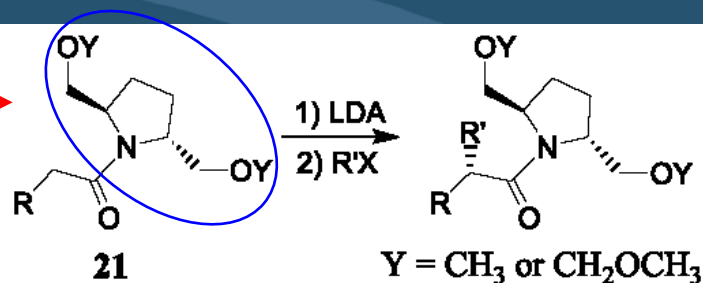


TABLE 2-4. Asymmetric Alkylation Using (2*R*,5*R*)-**21** in THF at -78°C

Entry	R in 21 Y = CH ₃	R'X	Yield (%)	de (%)	Configuration*
1	CH ₃	C ₂ H ₅ I	87	>95	<i>R</i>
2	CH ₃ [†]	C ₂ H ₅ I	78	>95	<i>S</i>
3	C ₂ H ₅	CH ₃ I	91	>95	<i>S</i>
4	CH ₃	C ₄ H ₉ I	81	>95	(<i>R</i>)
5	C ₄ H ₉	CH ₃ I	81	>95	(<i>S</i>)
6	CH ₃	PhCH ₂ Br	80	>95	<i>R</i>
7	PhCH ₂	CH ₃ I	76	>95	<i>S</i>
8	C ₁₆ H ₃₃	CH ₃ I	61	>95	(<i>S</i>)
9	CH ₃	CH ₂ =CHCH ₂ Br	81	>95	(<i>R</i>)
10	CH ₃	PhCH ₂ OCH ₂ Cl	74	>95	(<i>R</i>)
11	CH ₃	R''OCH ₂ CH ₂ CH ₂ Br [‡]	78	>95	(<i>R</i>)

* Tentative assignment in parentheses.

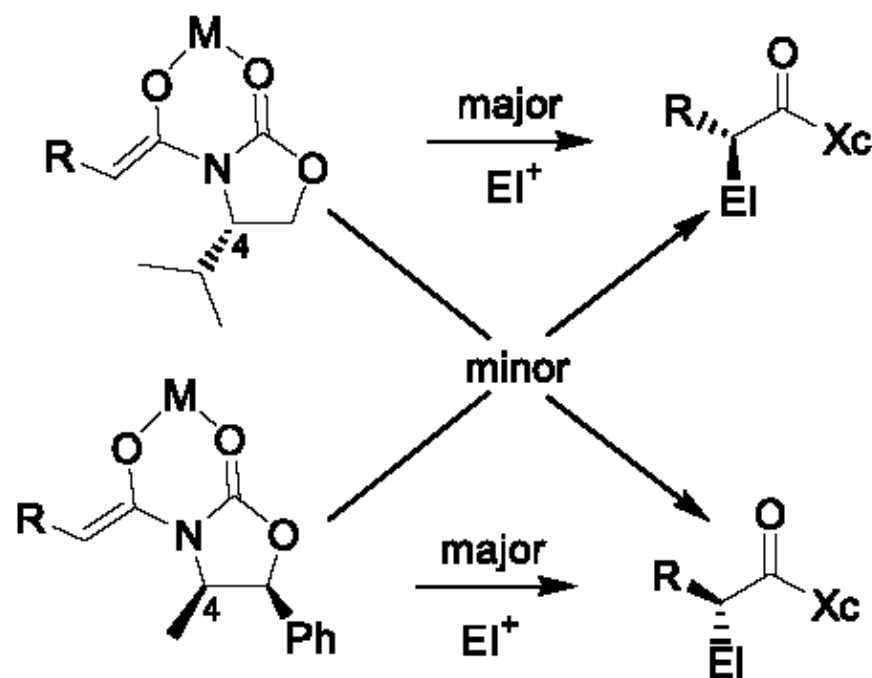
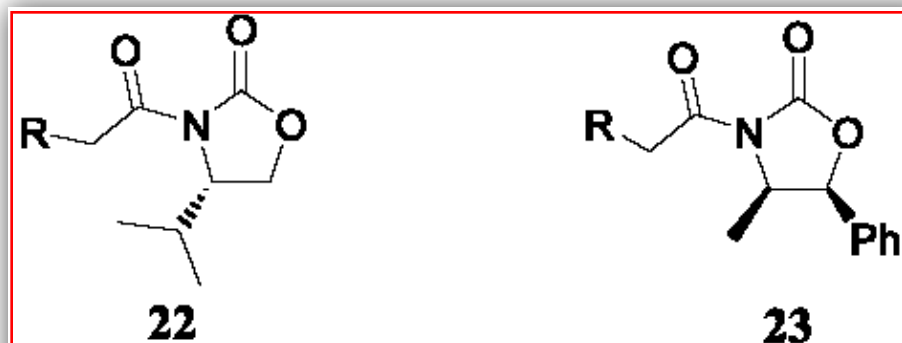
[†] (2*S*,5*S*)-enantiomer of **21** was used.

[‡] R'' = TBS.

de = diastereometric excess.

2.2.3.3 Imide Systems (酰亚胺体系)

Evans 试剂



Scheme 2-17

2.2.3.3 Imide Systems (酰亚胺体系)

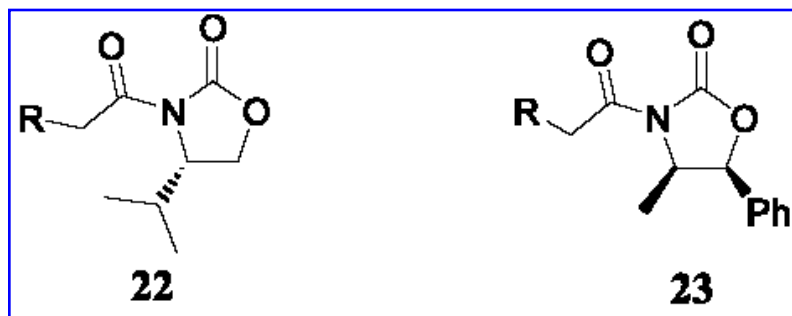
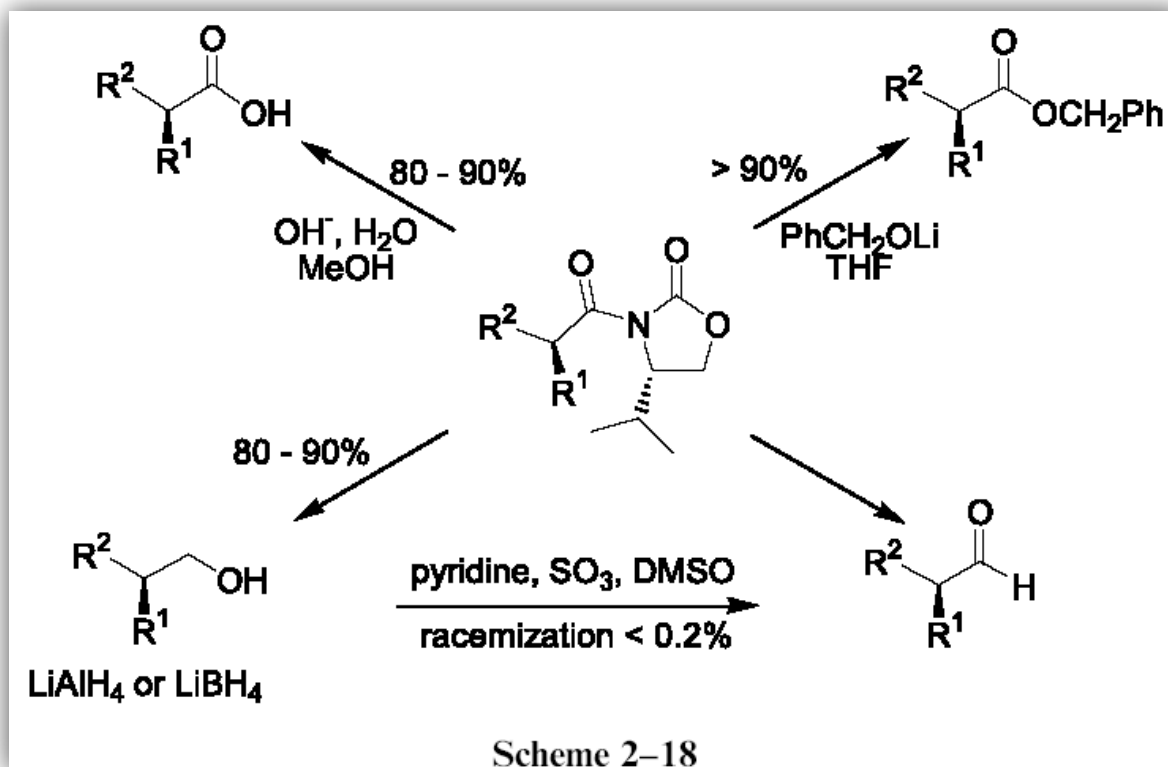


TABLE 2-5. Diastereoselective Alkylation Reaction of the Lithium Enolates Derived from Imides 22 and 23

Entry	Imide	EI ⁺	Ratio	Yield (%)
1	22 (R = CH ₃)	PhCH ₂ Br	99:1	92
2	23 (R = CH ₃)	PhCH ₂ Br	2:98	78
3	22 (R = C ₂ H ₅)	CH ₃ I	89:11	79
4	23 (R = C ₂ H ₅)	CH ₃ I	13:87	82
5	22 (R = CH ₃)	C ₂ H ₅ I	94:6	36
6	23 (R = CH ₃)	C ₂ H ₅ I	12:88	53
7	22 (R = CH ₃)	CH ₂ =CHCH ₂ Br	98:2	71
8	23 (R = CH ₃)	CH ₂ =CHCH ₂ Br	2:98	65

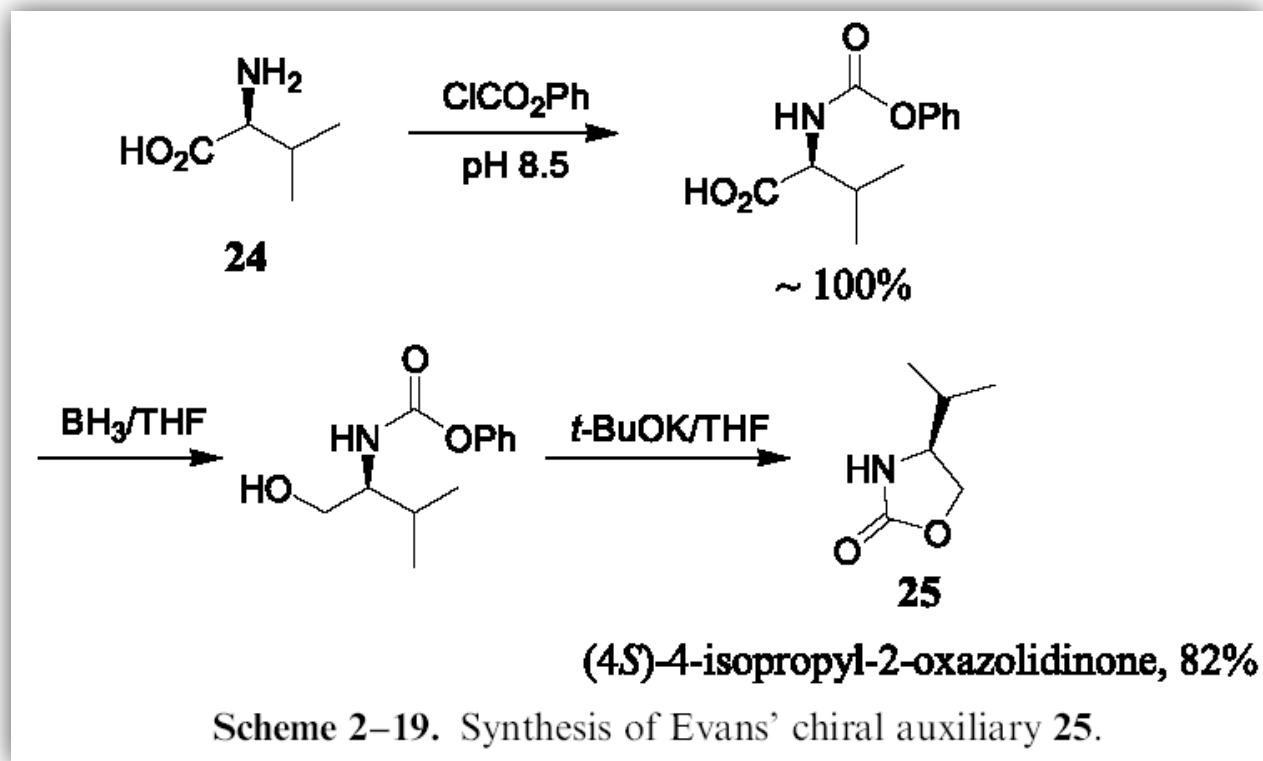
EI⁺ = electrophiles in Scheme 2-17.

2.2.3.3 Imide Systems (酰亚胺体系)



2.2.3.3 Imide Systems (酰亚胺体系)

Evans 试剂合成改进-Wuts (S-缬氨酸)



2.2.3.3 Imide Systems (酰亚胺体系)

Wenglowsky and Hegedus reported a more practical route to α -amino aldehydes via an oxazolidinone method.

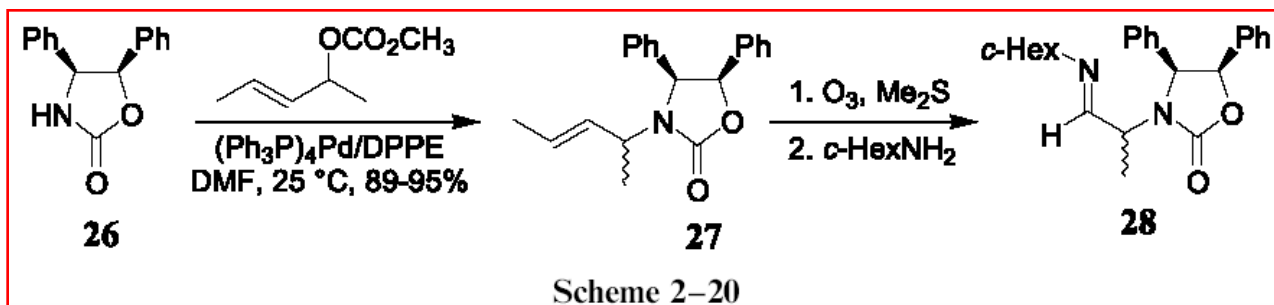
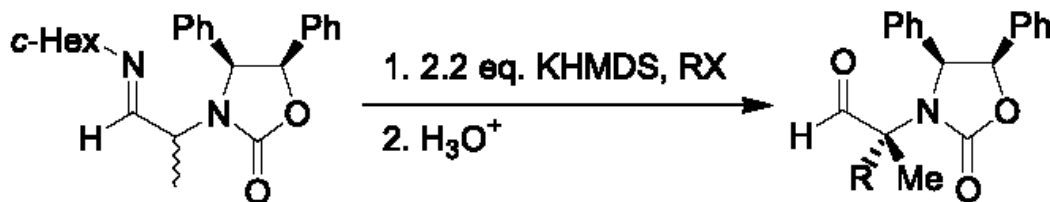


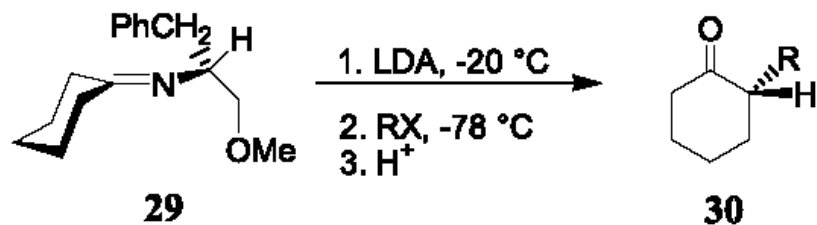
TABLE 2-6. Synthesis of α -Amino Aldehydes



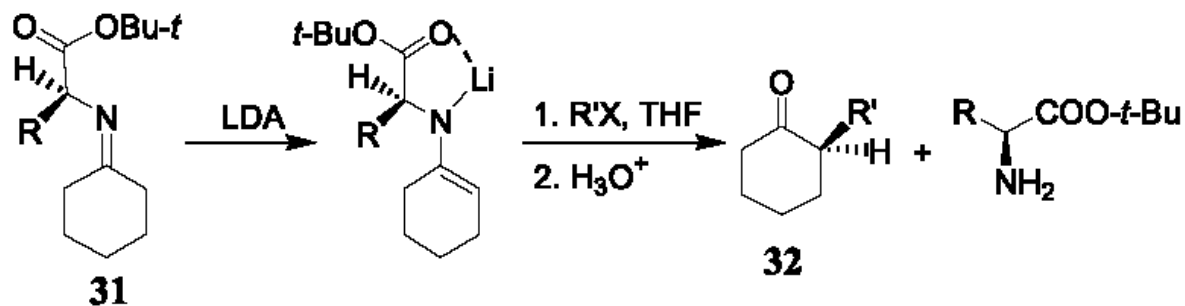
Entry	RX	de	Yield (%)
1	PhCH ₂ Br	94:6	62
2	3,4- <i>di</i> -MeOPhCH ₂ Br	90:10	47
3	CH ₂ =CHCH ₂ Br	92.5:7.5	62
4	(CH ₃) ₂ CHCH ₂ I	93.5:6.5	62
5	(CH ₃) ₂ CHI	97.5:2.5	48
6	<i>n</i> -BuI	92:8	75

de = diastereomeric excess; RX = electrophiles in the reaction.

2.2.3.4 Chiral Enamine Systems (烯胺体系)



R-X	ee (%)
Me ₂ SO ₄	82 (<i>R</i>)
<i>n</i> -C ₃ H ₇ I	> 95 (<i>R</i>)
CH ₂ =CHCH ₂ Br	> 90 (<i>S</i>)



R	R'-X	ee (%)
<i>i</i> -C ₃ H ₇	Me ₂ SO ₄	84 (<i>S</i>)
<i>t</i> -C ₄ H ₉	Me ₂ SO ₄	98 (<i>S</i>)
<i>t</i> -C ₄ H ₉	MeI	97 (<i>S</i>)
<i>t</i> -C ₄ H ₉	<i>n</i> -C ₃ H ₇ I	97 (<i>S</i>)

→ 机理?

2.2.3.5 Chiral Hydrazone Systems (手性脞)

In 1976, **Corey and Enders** demonstrated the great synthetic potential of metalated dimethylhydrazones as highly reactive intermediates in regio- and diastereoselective C-C bond formation reactions.

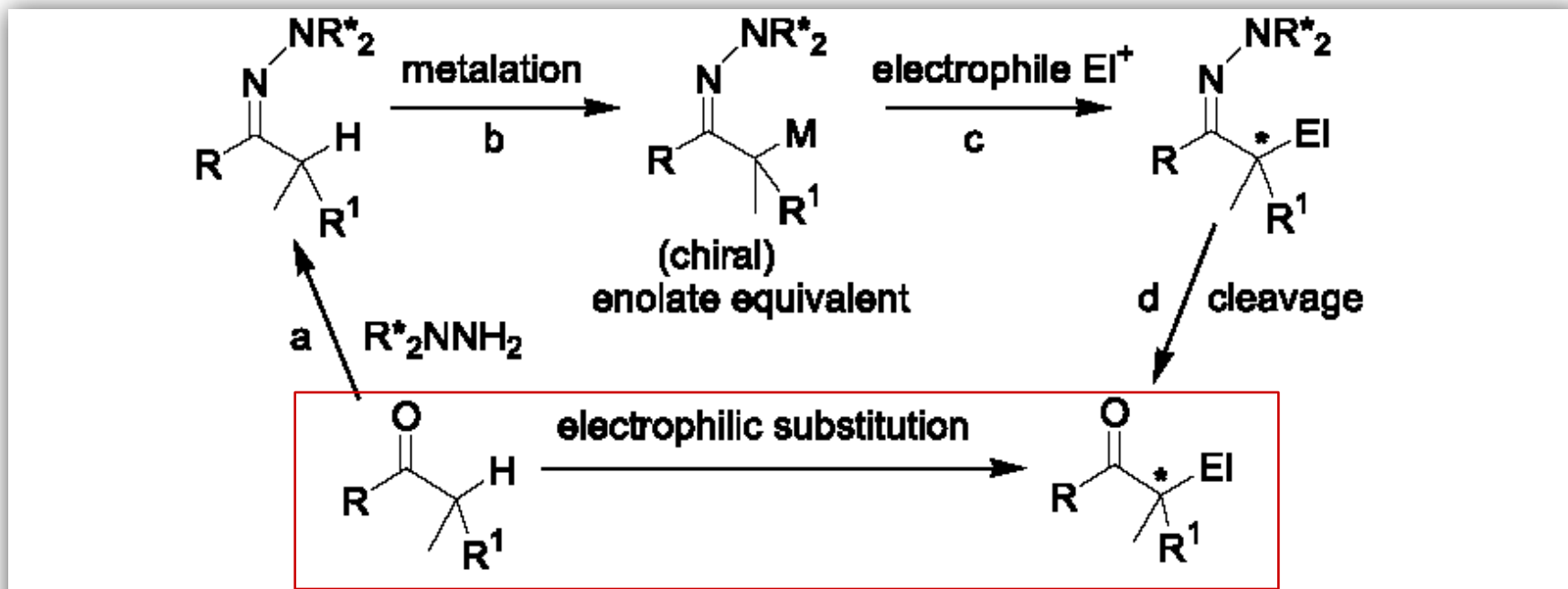
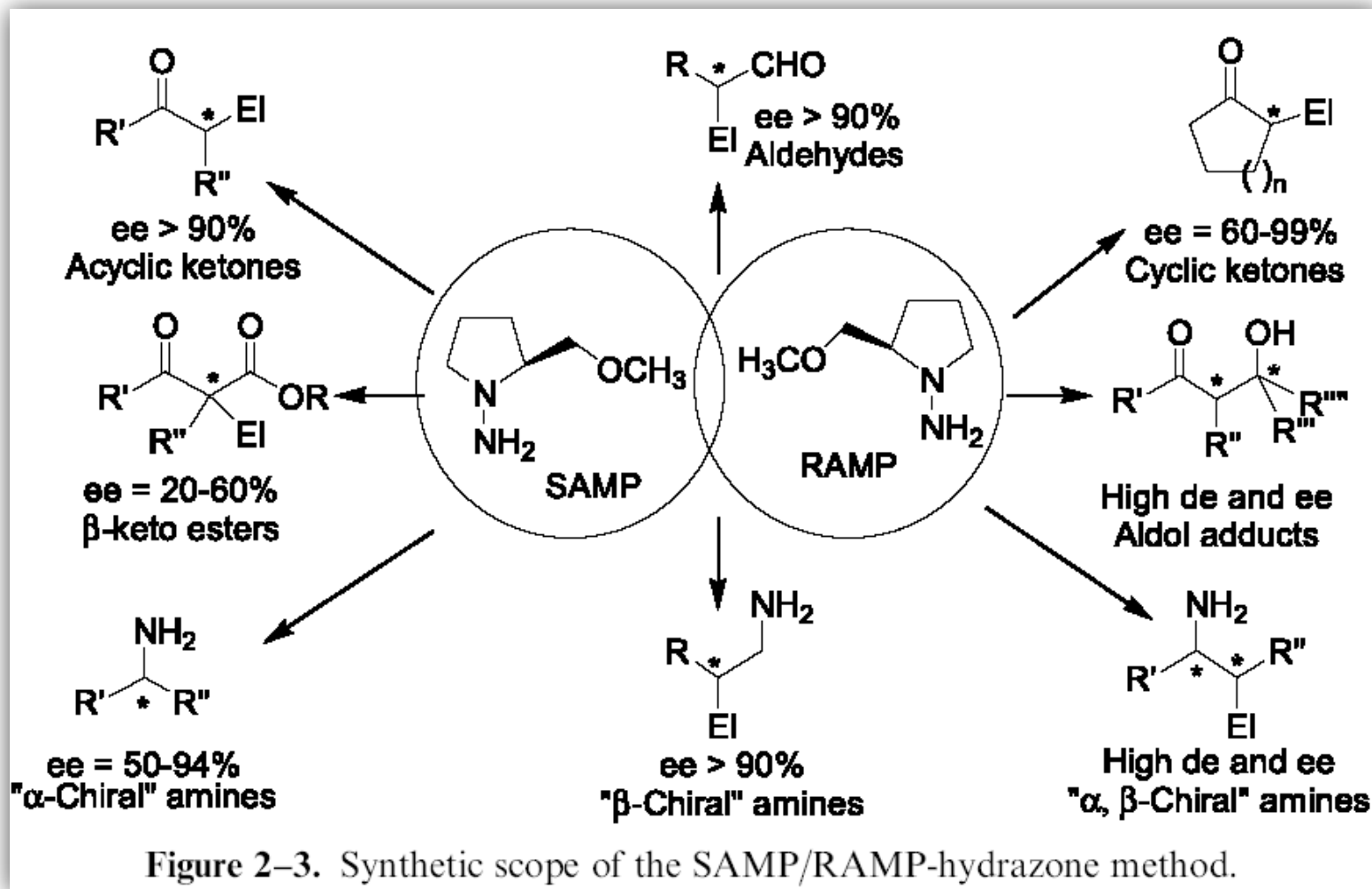


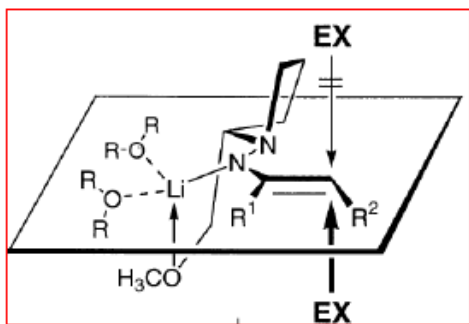
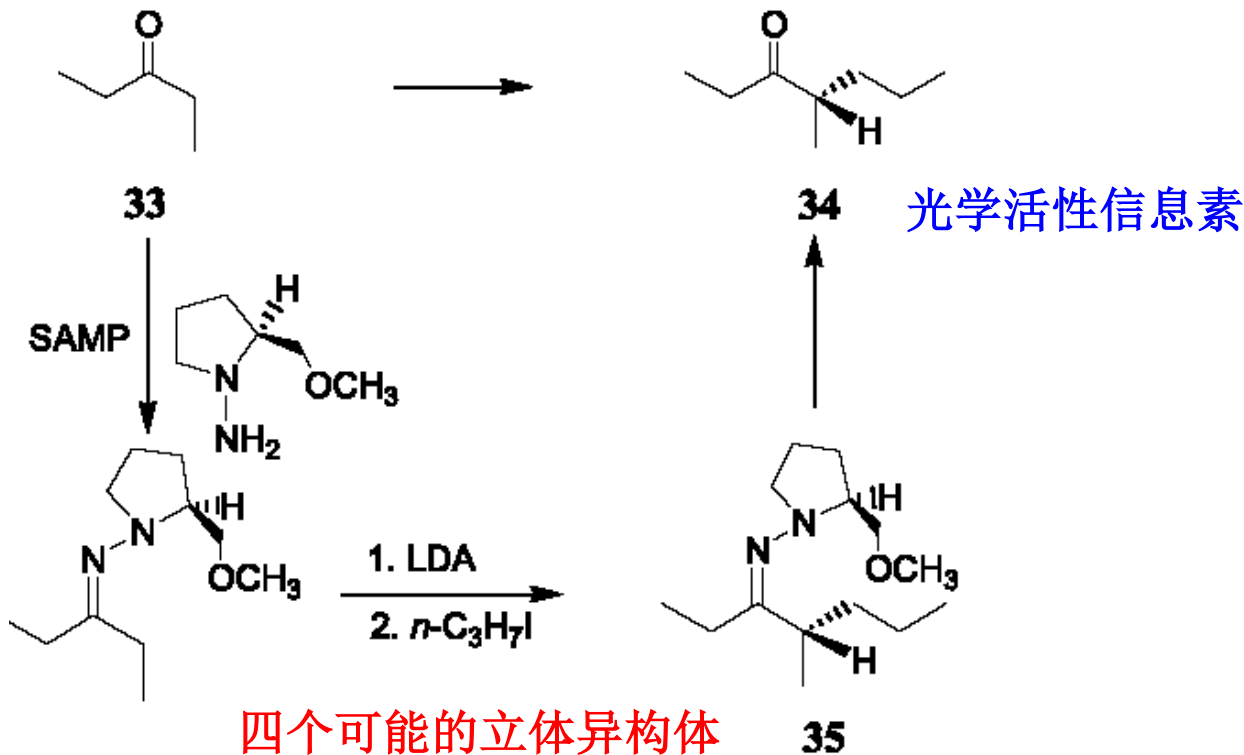
Figure 2-2. Electrophilic substitution to the carbonyl group of aldehydes and ketones via metalated (chiral) hydrazones.

2.2.3.5 Chiral Hydrazone Systems

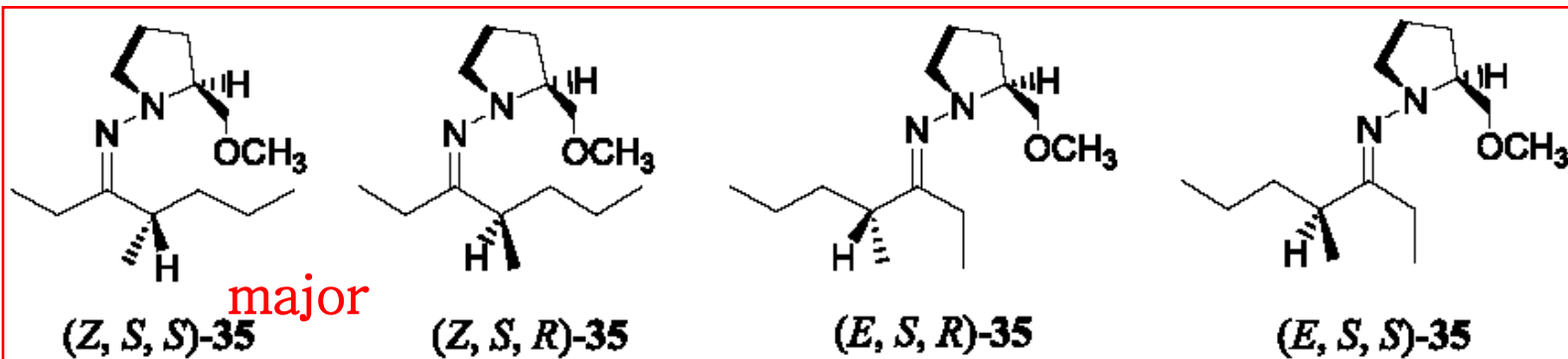


2.2.3.5 Chiral Hydrazone Systems

应用实例 1

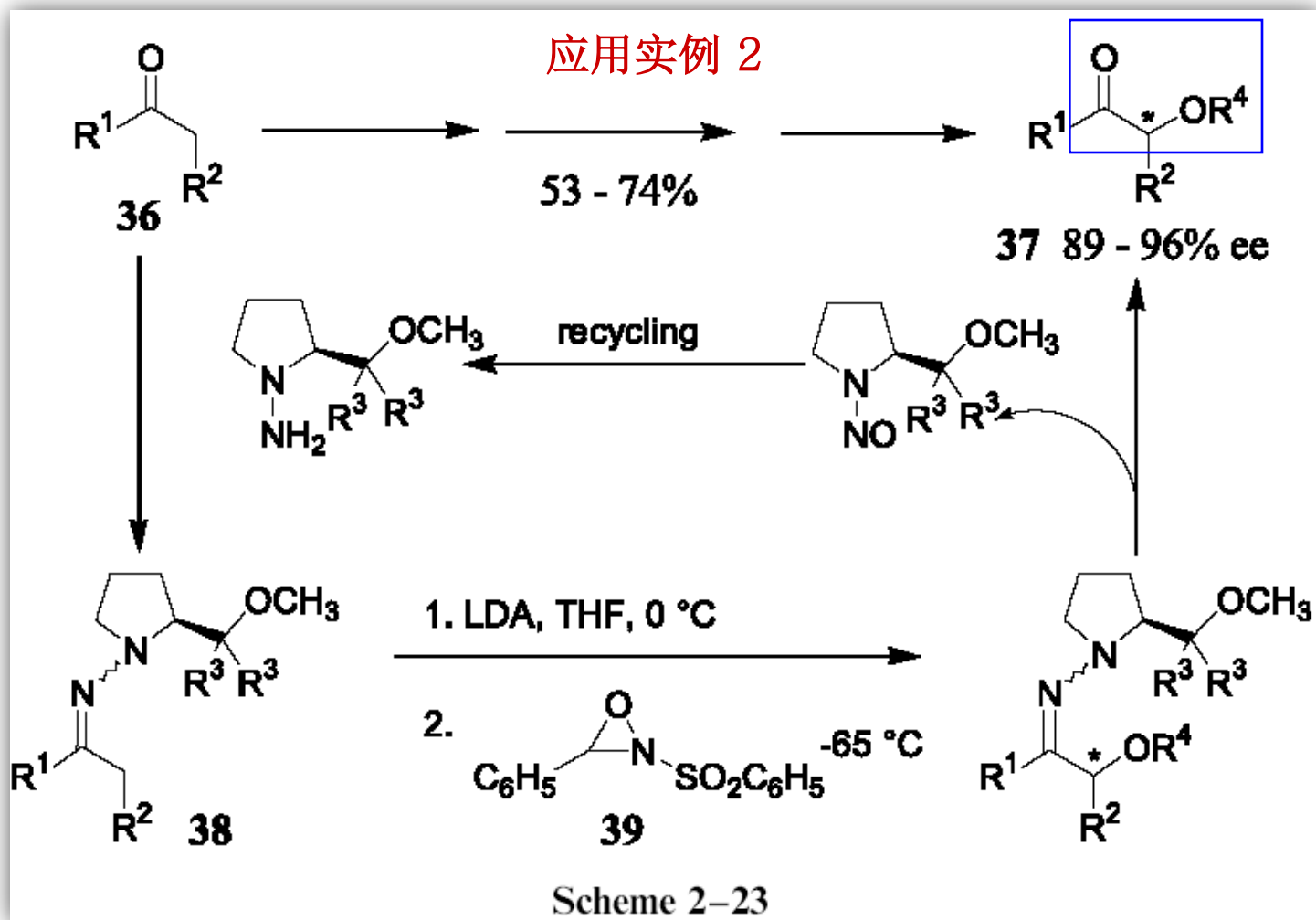


四个可能的立体异构体



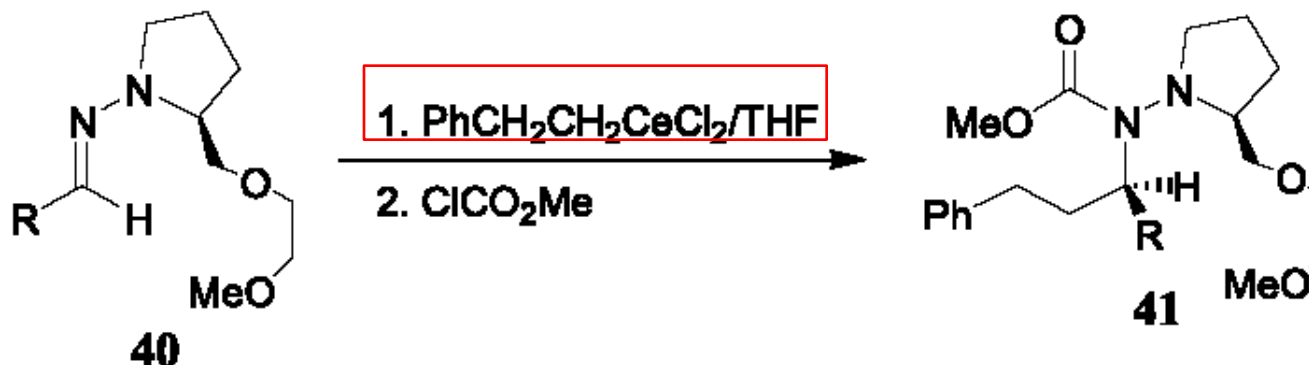
Scheme 2-22

2.2.3.5 Chiral Hydrazone Systems

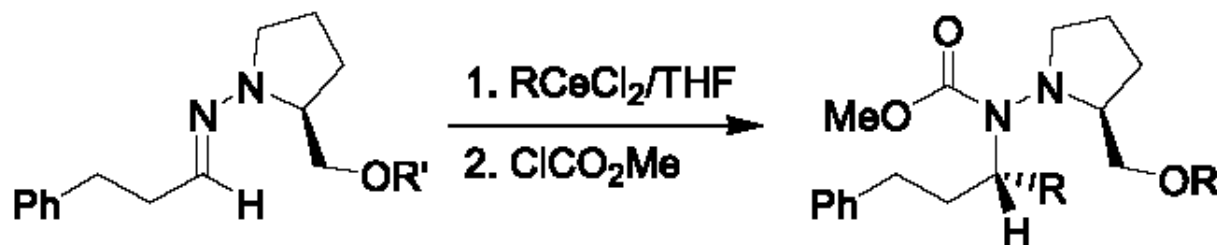


2.2.3.5 Chiral Hydrazone Systems

Denmark



(*S*)-1-amino-2-(2-methoxyethoxy
methyl)pyrrolidine (SAMEMP)



R	ds (R' = CH ₂ OCH ₃)	ds (R' = CH ₃)
Bu	97 : 3	93 : 7
Me	97 : 3	98 : 2
<i>t</i> -Bu	>99 : 1	96 : 4
Ph	95 : 5	96 : 4

Scheme 2-24. SAMEMP mediated reactions.

2.2.3.6 Oxazoline Systems (手性噁唑啉)

优点:

原料易制备, 稳定性好

潜在羧酸前体

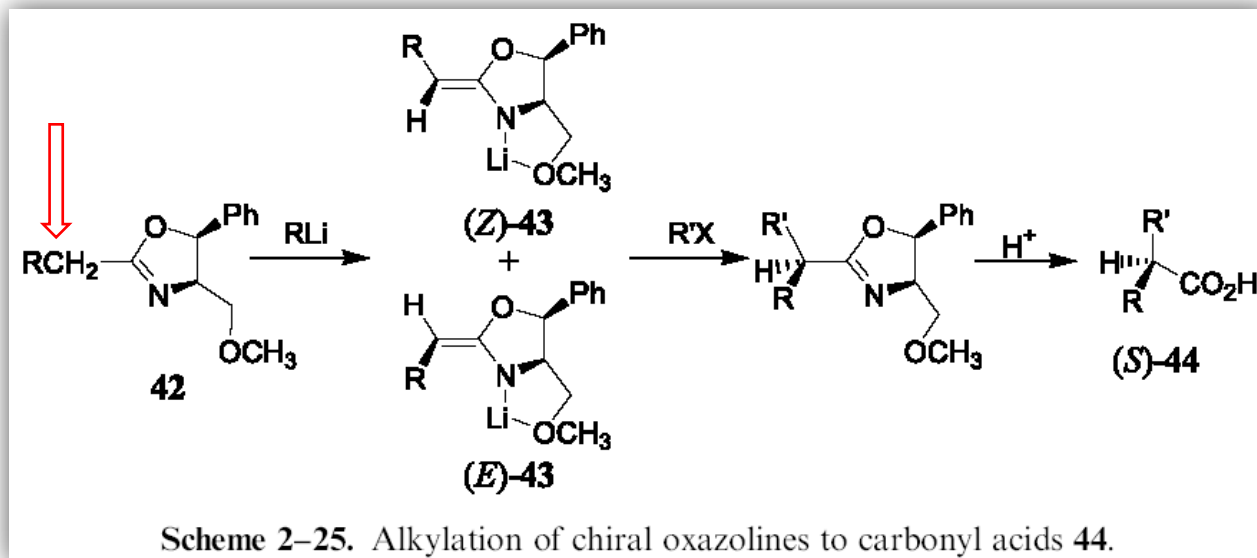


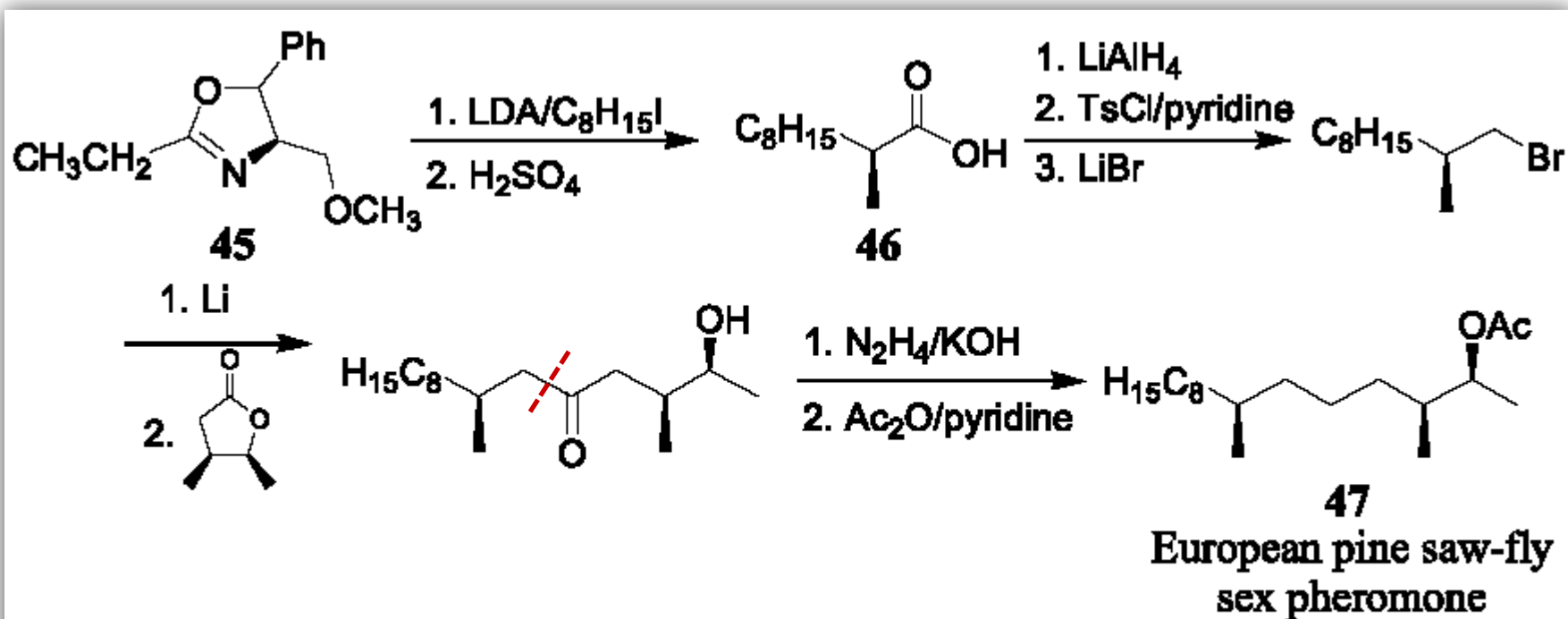
TABLE 2-7. Alkylation of Chiral Oxazolines to Carbonyl Acids 44

Entry	R	R'X	ee (%)	Config.	Overall Yield (%)
1	Me	EtI	78	<i>S</i>	84
2	Et	Me ₂ SO ₄	79	<i>R</i>	83
3	Me	<i>n</i> -PrI	72	<i>S</i>	79
4	<i>n</i> -Pr	Me ₂ SO ₄	72	<i>R</i>	74
5	Me	PhCH ₂ Cl	74	<i>S</i>	62
6	PhCH ₂	Me ₂ SO ₄	78	<i>R</i>	75

ee = Enantiomeric excess; R = R in **42**; R'X = R'X in Scheme 2-25.

2.2.3.6 Oxazoline Systems

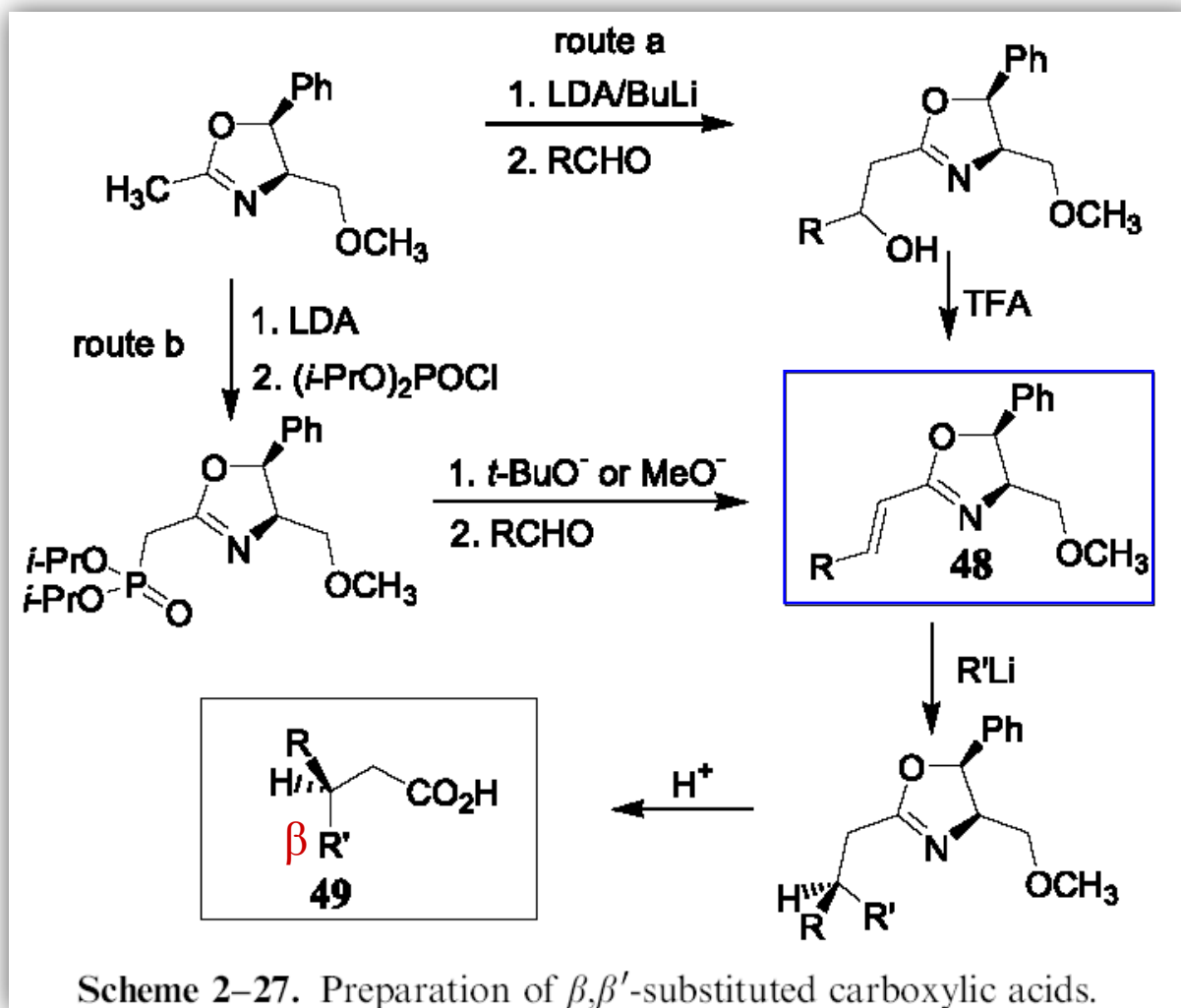
应用实例 1. 不对称烷基化



Scheme 2-26. Synthesis of European pine-saw fly pheromone.

2.2.3.6 Oxazoline Systems

应用实例 2. 1, 4-共轭加成



2.2.3.6 Oxazoline Systems

应用实例 2. 1, 4-共轭加成

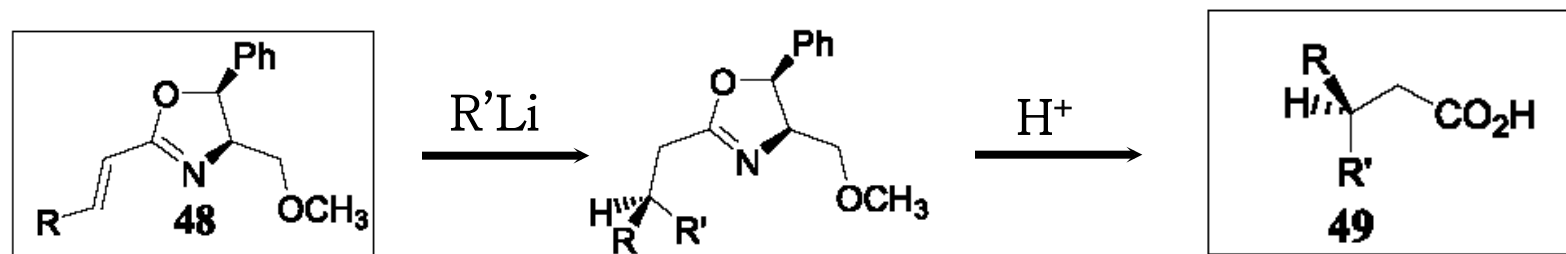


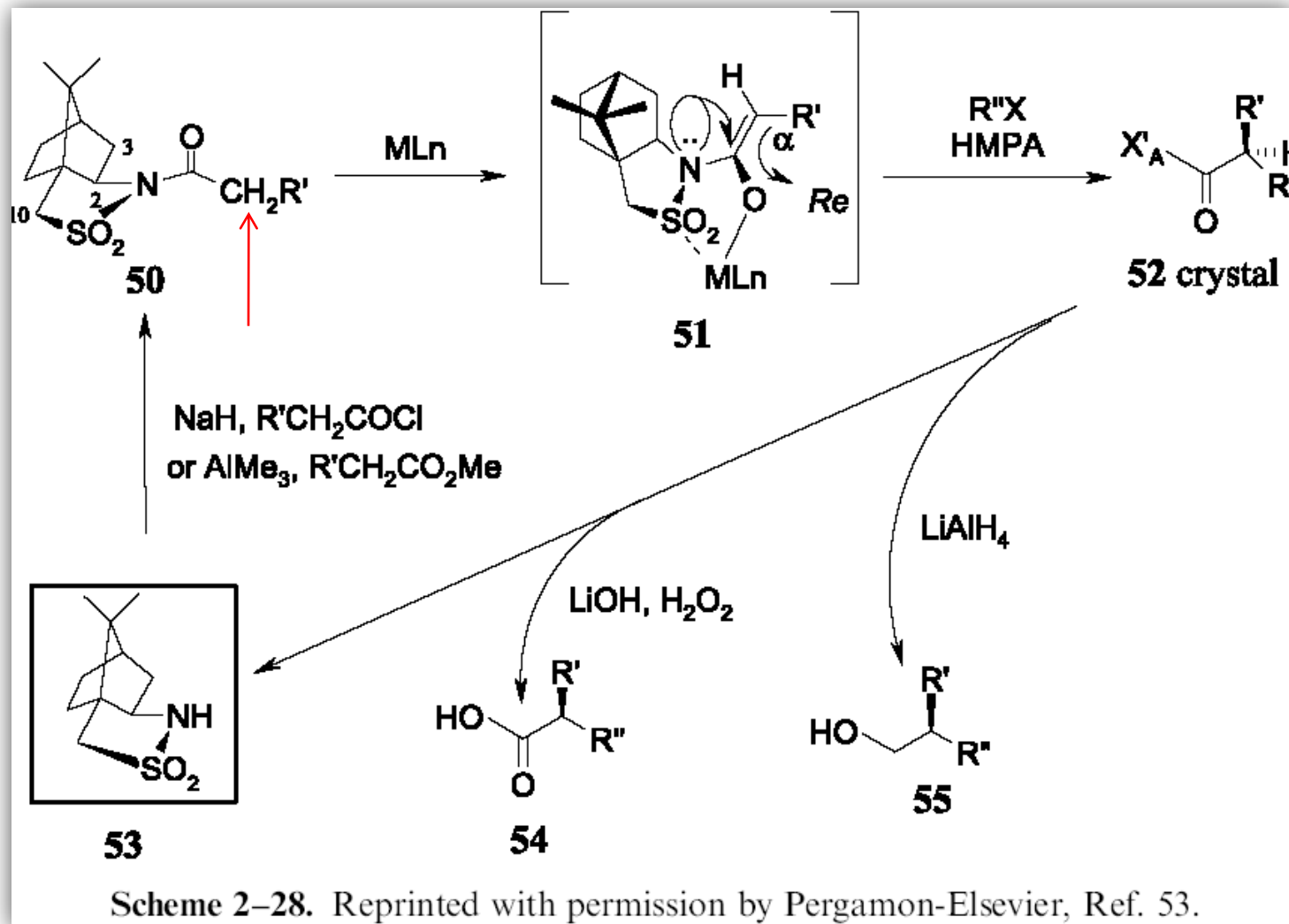
TABLE 2-8. Preparation of β,β -Disubstituted Carboxylic Acids **49**

Entry	R	R'	ee (%)	Config.	Yield (%)
1	Me	Et	92	<i>R</i>	30
2	Me	Ph	98	<i>S</i>	34
3	<i>i</i> -Pr	<i>n</i> -Bu	99	<i>R</i>	53
4	<i>t</i> -Bu	<i>n</i> -Bu	98	<i>R</i>	50
5	<i>c</i> -hexyl	Et	99	<i>R</i>	73
6	MeOCH ₂ CH ₂	<i>n</i> -Pr	99	<i>S</i>	50
7	<i>o</i> -MeOPh	<i>n</i> -Bu	95	<i>R</i>	75

ee = Enantiomeric excess; R = R in Scheme 2-27; R' = R' in Scheme 2-27.

2.2.3.7 Acylsultam Systems (酰基磺内酰胺)

Oppolzer 首创--- α, α -二取代羧酸



Scheme 2-28. Reprinted with permission by Pergamon-Elsevier, Ref. 53.

2.2.3.7 Acylsultam Systems (酰基磺内酰胺)

Oppolzer 首创

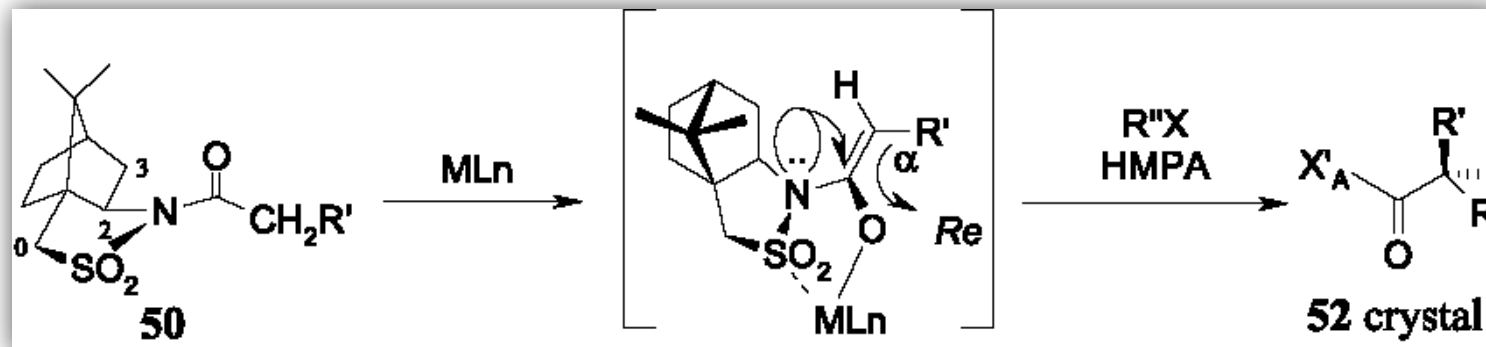


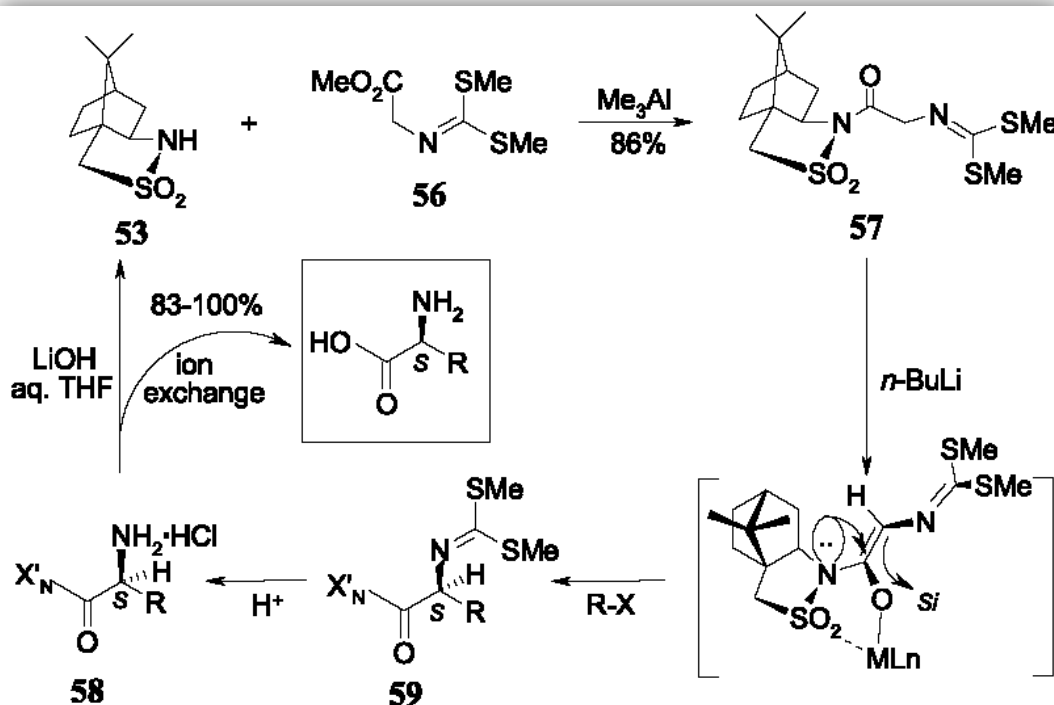
TABLE 2-9. Asymmetric Alkylation of **50**

R'	$R''X$	ML	de (% , crude)	de (% , crystal)
Me	PhCH ₂ I	NHDMS	96.5	98.4
Me	PhCH ₂ I	KHDMS	92.9	
Me	PhCH ₂ I	BuLi	96.9	98.5
Me	CH ₂ =CHCH ₂ I	NHDMS	94.2	94.5
Me	CH ₂ =CHCH ₂ I	BuLi	96.6	96.6
Me	CH ₂ =CHCH ₂ Br	BuLi	98.8	>99
Me	HC≡CCH ₂ Br	BuLi	98.3	>99

de = Diastereomeric excess; ML = ML_n in Scheme 2-28; $R' = R'$ in **50**; $R''X = R''X$ in Scheme 2-28.

2.2.3.7 Acylsultam Systems (酰基磺内酰胺)

非天然 α -氨基酸合成



Scheme 2-29

TABLE 2-10. Alkylation of Glycinate Equivalents

RX	ee (%)
MeI	>99.8
PhCH ₂ I	>99.8
CH ₂ =CHCH ₂ I	>99.8
<i>t</i> -BuOOCCH ₂ Br	>99.8
(CH ₃) ₂ CHCH ₂ I	>99.8
(CH ₃) ₂ CHI	99.5

ee = Enantiomeric excess; RX = R-X in Scheme 2-29.

2.2.3.7 Acylsultam Systems (酰基磺内酰胺)

1,4-共轭加成

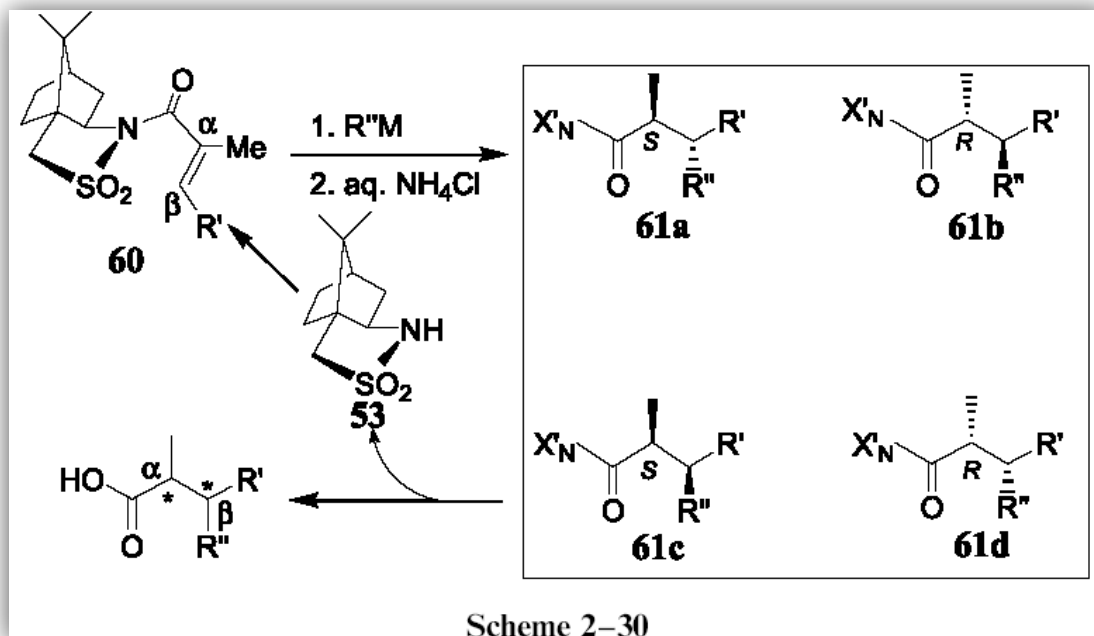


TABLE 2-11. Sultam 53 in the Preparation of 60c

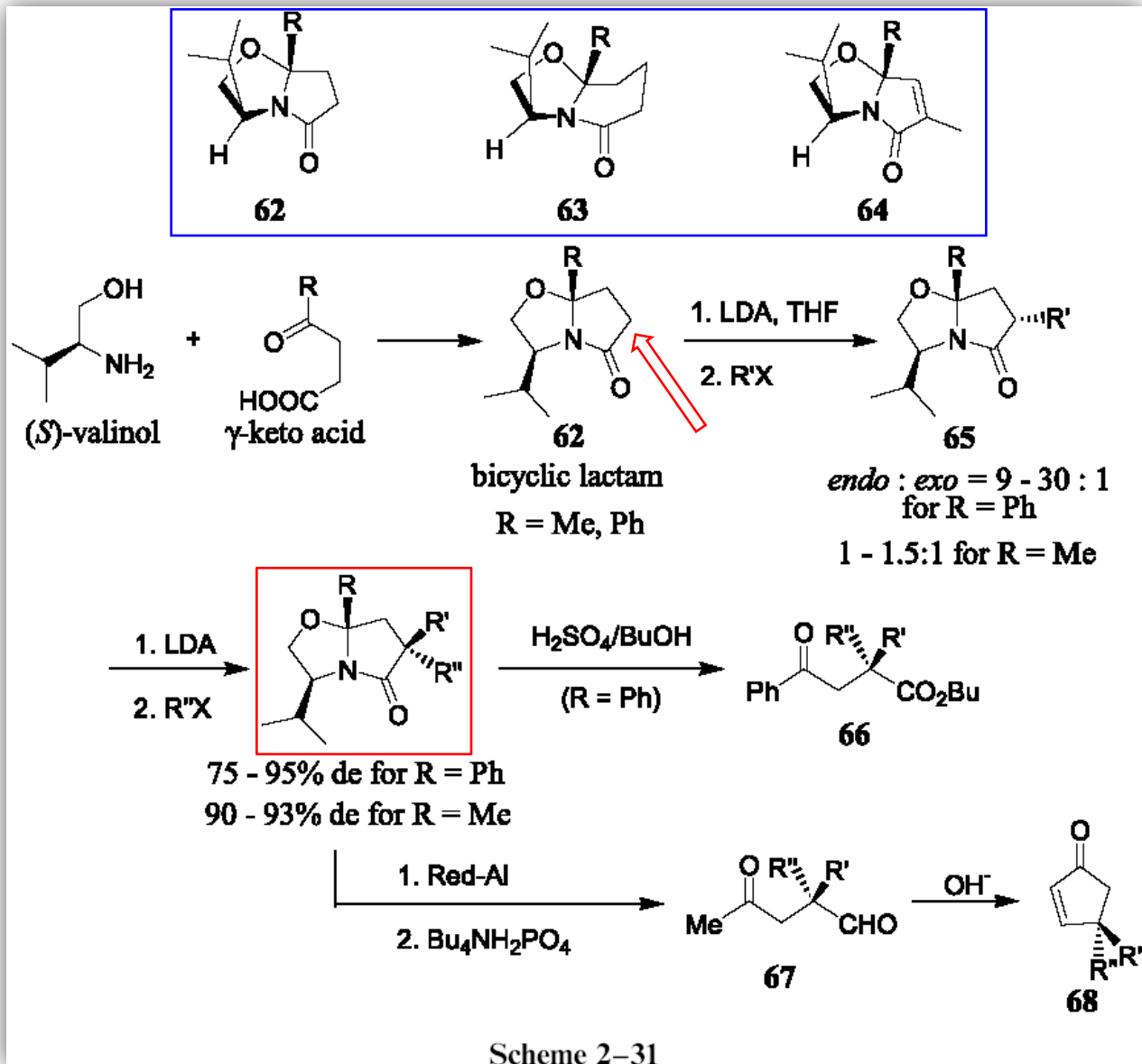
R'	R''	Cu(I) salt	Ratio (a:b:c:d)	Crystal purity (%)	Config.
Me	Bu	CuCl	2.1:0:86.3:11.6	97.7	2 <i>S</i> ,3 <i>S</i>
Me	Bu	CuCN	2.5:0:83.7:14.4	—	2 <i>S</i> ,3 <i>S</i>
Me	Et	CuCl	2.3:0:85.4:12.3	98.6	2 <i>S</i> ,3 <i>S</i>
Et	Bu	CuCl	0:0:91.5:8.5	99.8	2 <i>S</i> ,3 <i>S</i>
Bu	Et	CuCl	0:0:97.3:2.7	99	2 <i>S</i> ,3 <i>R</i>
TBSOCH ₂	Bu	CuCl	0:0:97.0:3.0	99.4	2 <i>S</i> ,3 <i>S</i>
Bu	Me	CuCl	10.5:8.2:68.6:12.7	—	2 <i>S</i> ,3 <i>R</i>
Me	Ph	CuCl	2.7:3.2:72.5:21.6	—	2 <i>S</i> ,3 <i>R</i>

R' = R' in Scheme 2-30; R'' = R'' in Scheme 2-30.

2.3 PREPARATION OF QUATERNARY CARBON CENTERS (手性季碳中心构建)

Mayers *et al*

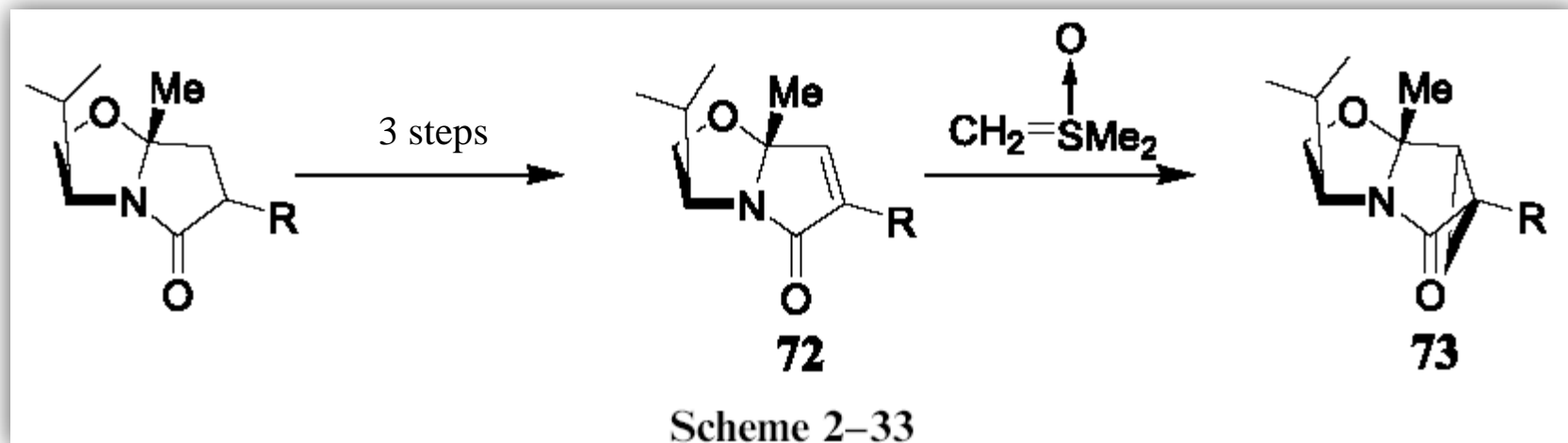
双环内酰胺



2.3 PREPARATION OF QUATERNARY CARBON CENTERS

Mayers et al

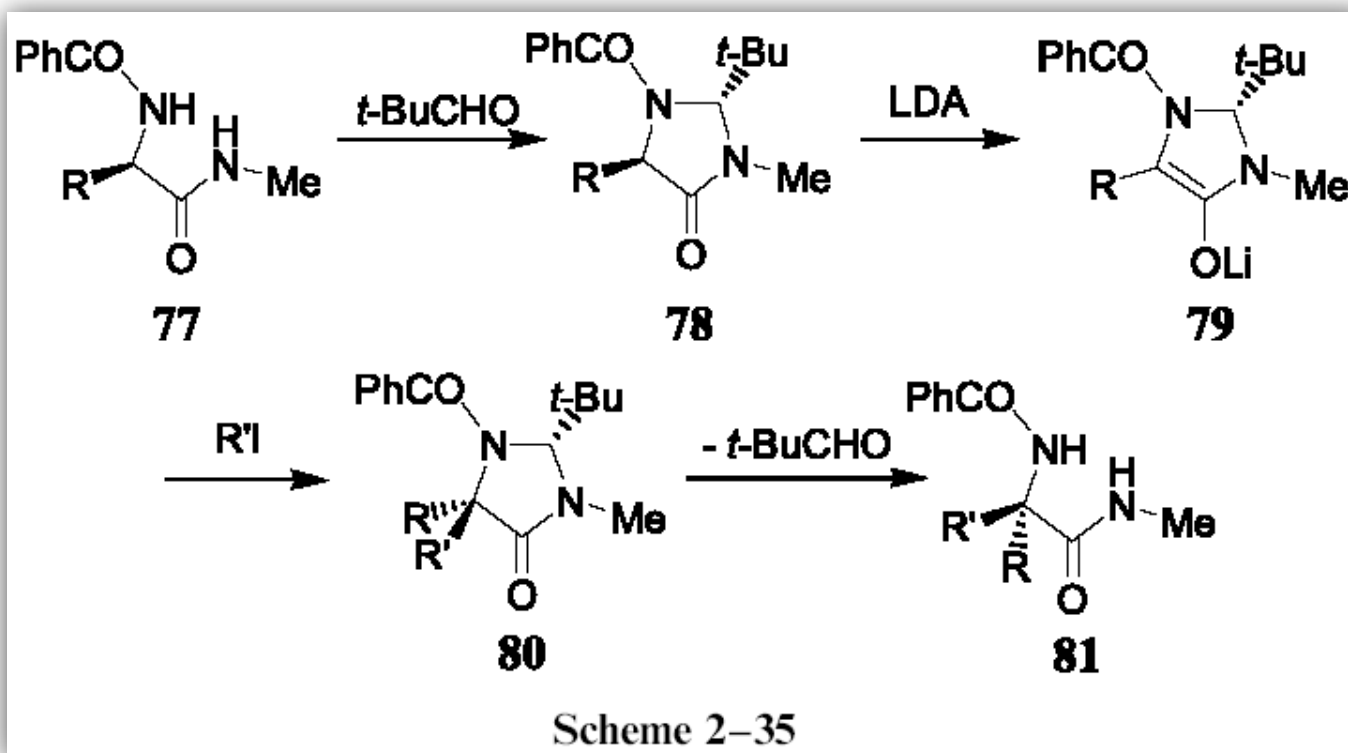
不对称环丙环化



2.3 PREPARATION OF QUATERNARY CARBON CENTERS

Seebach et al

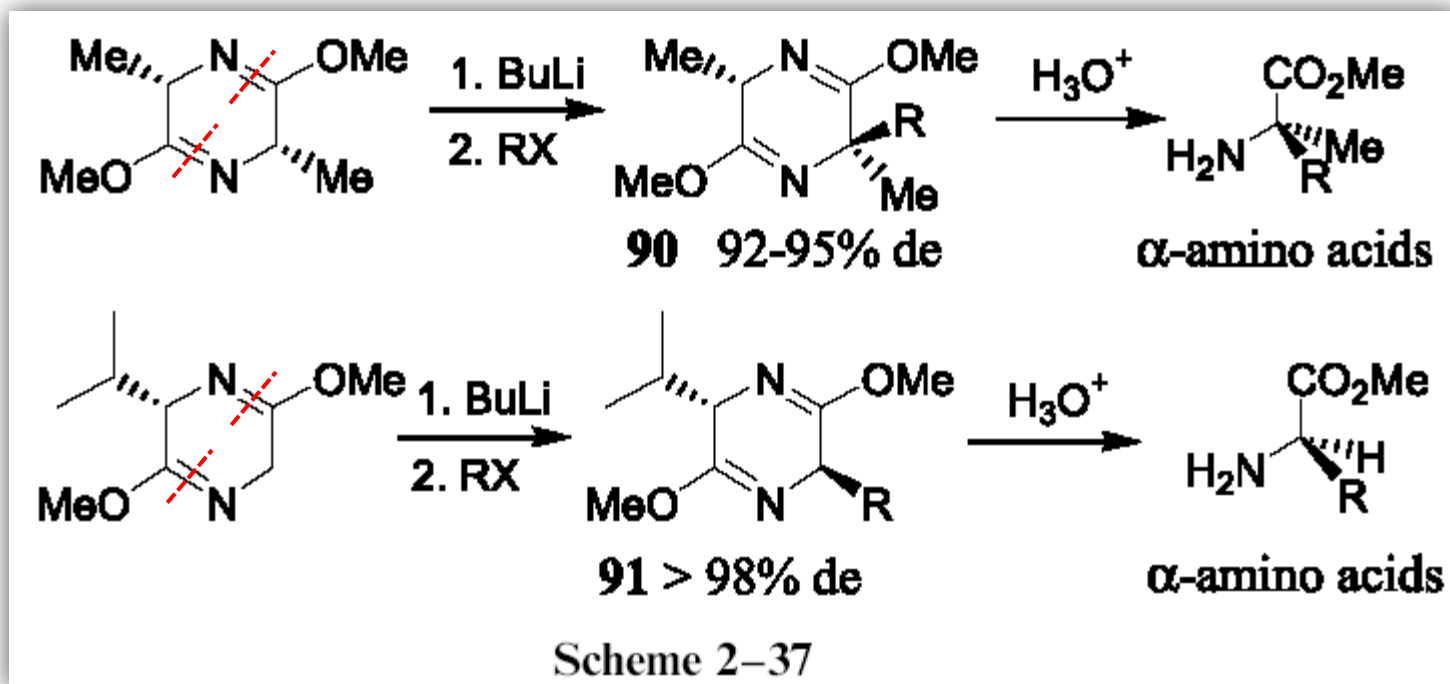
“手性中心自我再生法” (self-regeneration of stereocenters, SRS)



2.4 PREPARATION OF α -AMINO ACIDS

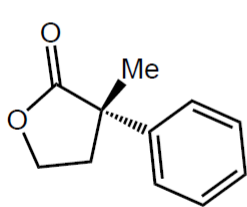
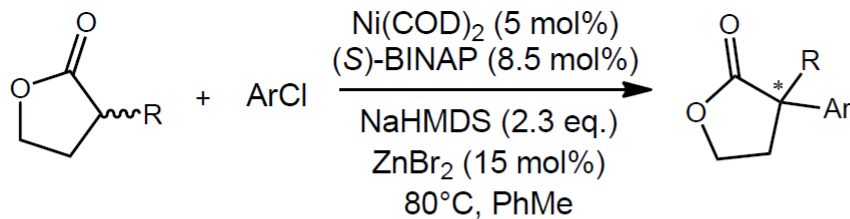
非蛋白氨基酸合成

二酮哌嗪-手性六元杂环

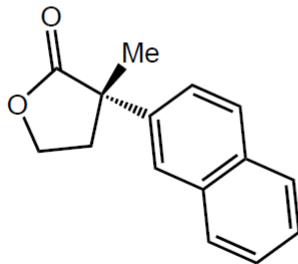


金属催化的 α -芳基化反应

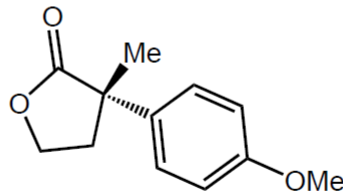
Buchwald, *JACS* 2002, 350



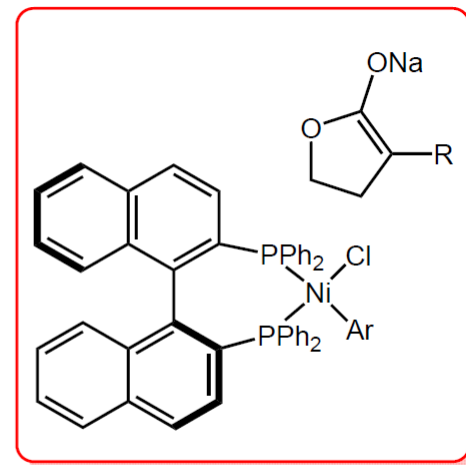
86% yield, >97% ee



95% yield, 94% ee

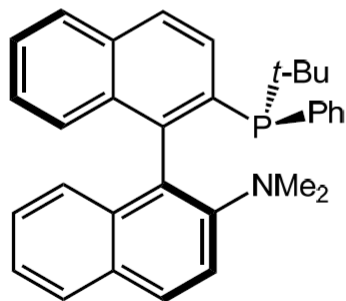
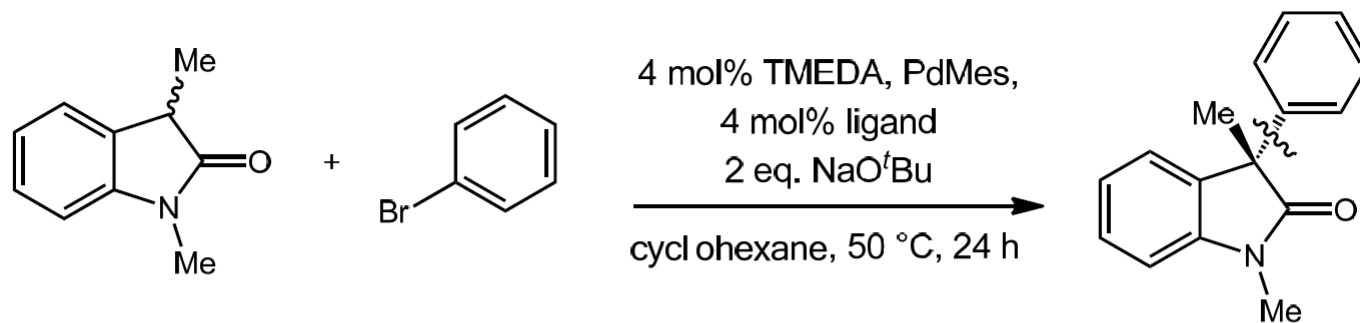


76% yield, 94% ee

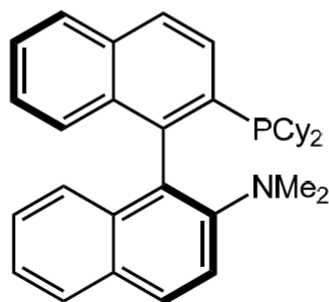


金属催化的 α -芳基化反应

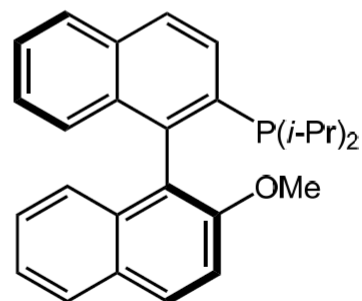
Buchwald, *JACS* 2009, 990



76%, 97% ee

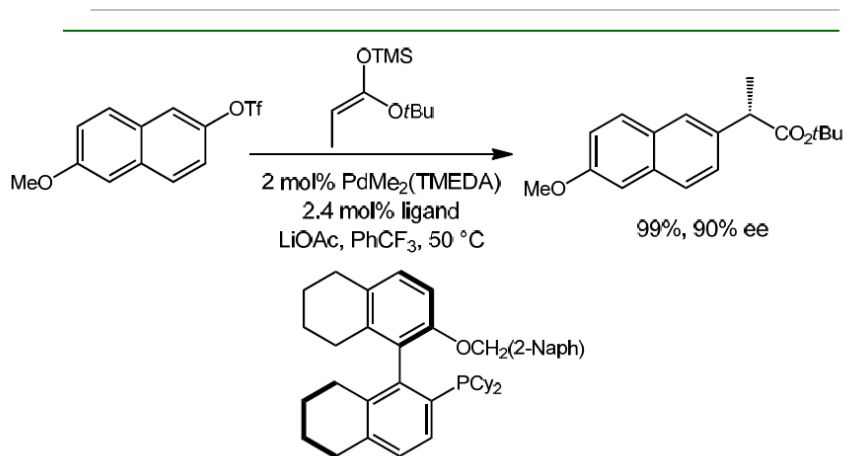


54%, 74% ee

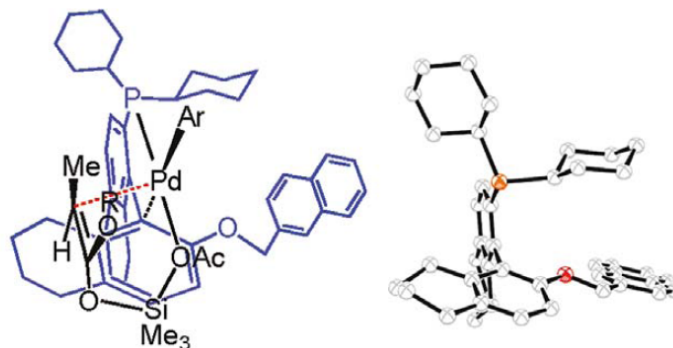
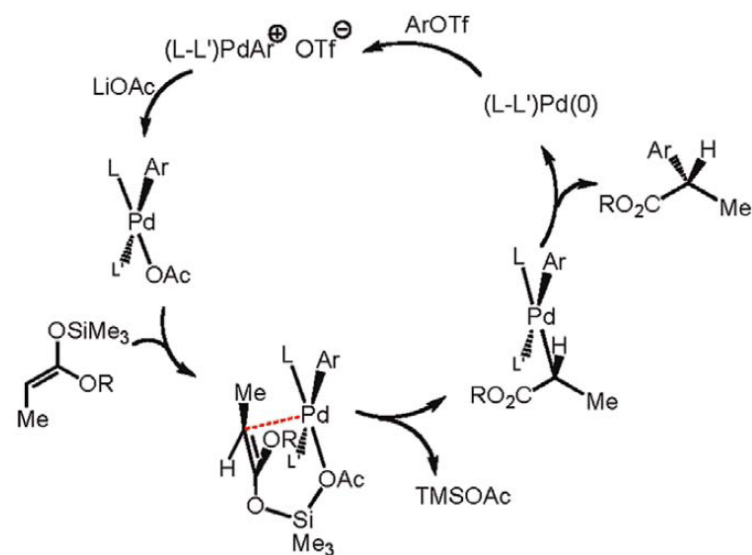


81%, 78% ee

金属催化的 α -芳基化反应:



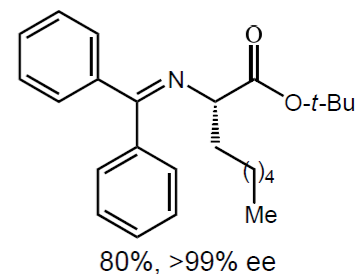
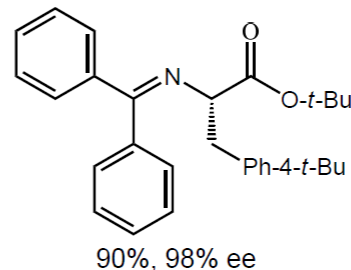
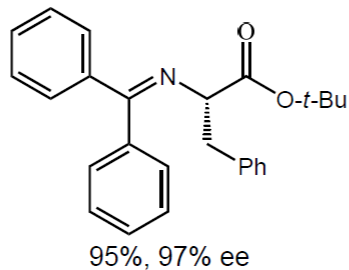
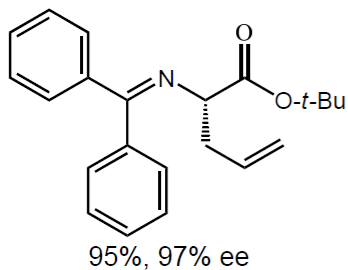
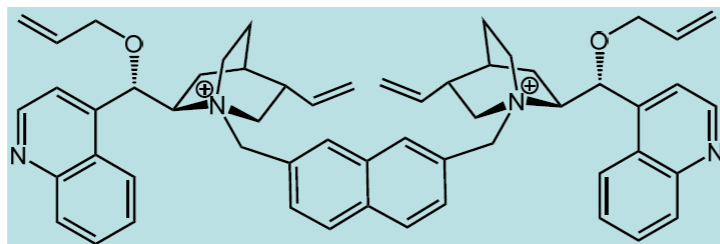
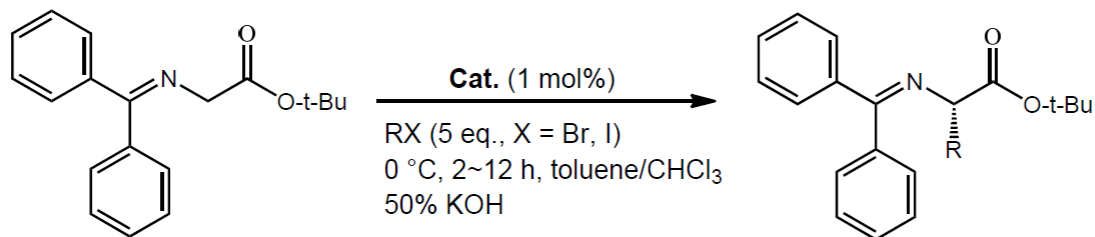
- tertiary chiral center easily racemized
- t-Bu ester is important for high ee
- big group in the ligand is important



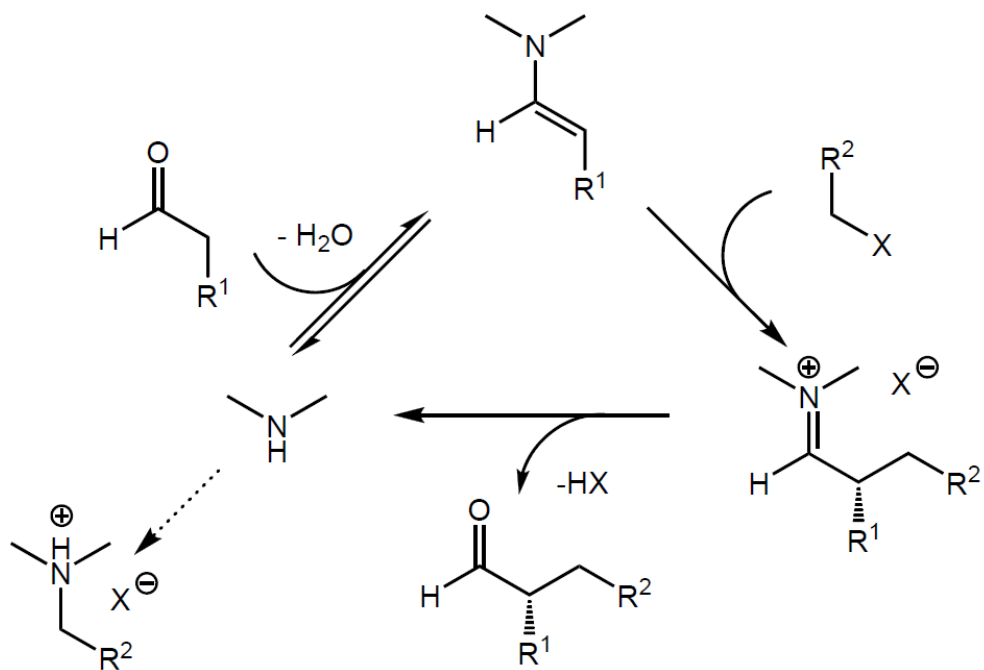
Huang, Z.-Y.; Liu, Z.; Zhou, J. S. *J. Am. Chem. Soc.* 2011, 133, 15882.

有机催化的 α -烷基化反应

O'Donnell, M. J. *Tetrahedron*. 1994, 4507.



有机催化的 α -烷基化反应

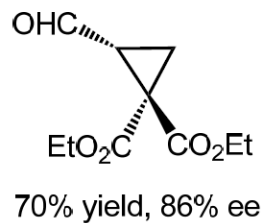
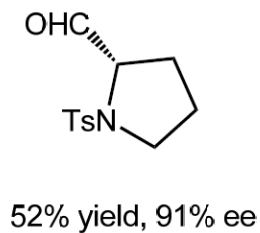
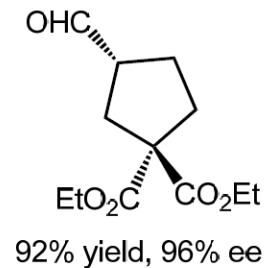
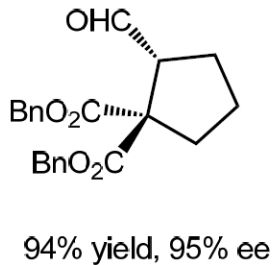
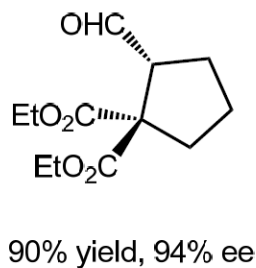
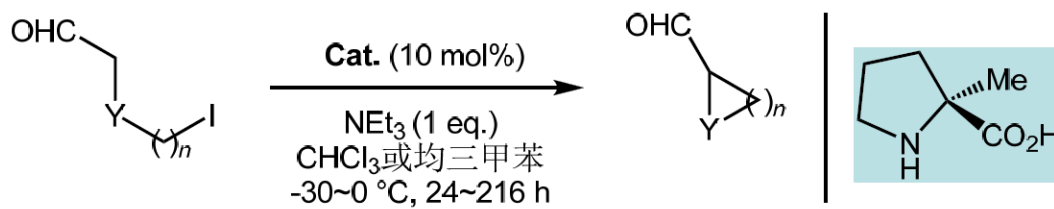


共价键催化:

- 催化剂用量大
- TON低
- 对映选择性控制优秀

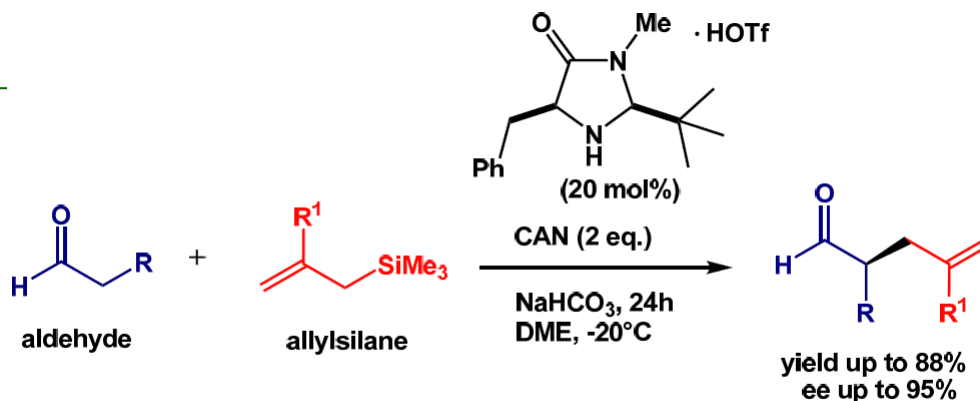
有机催化的 α -烷基化反应

List, B. *J. Am. Chem. Soc.* 2004, 450.



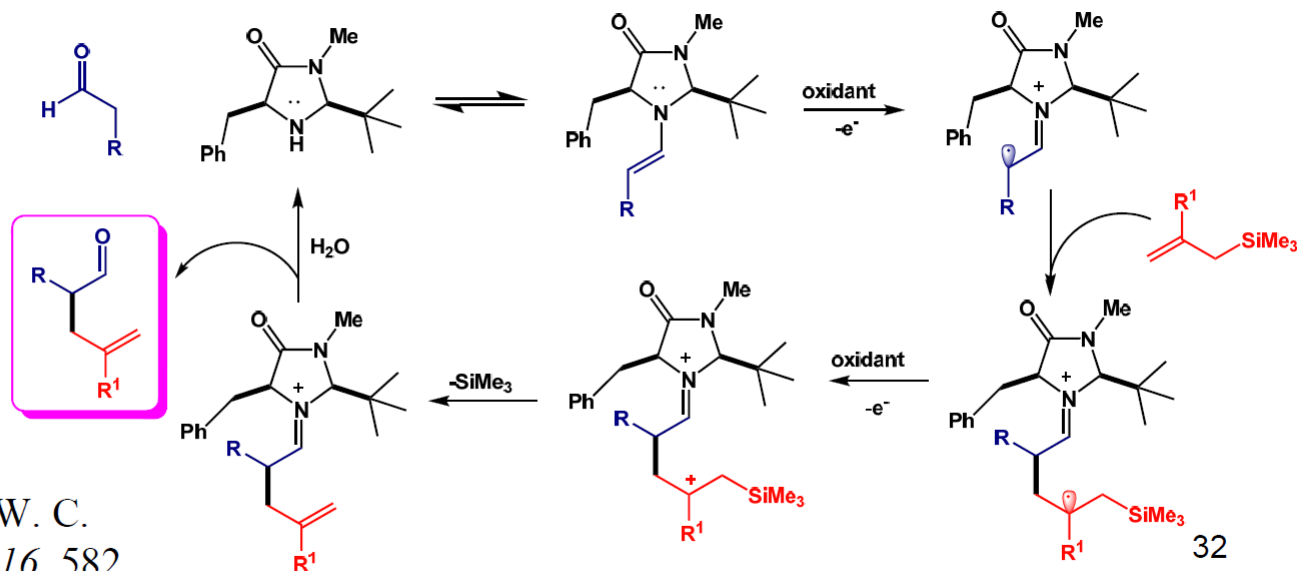
SOMO

Singly Occupied Molecular Orbital Activation



CAN: ceric ammonium nitrate

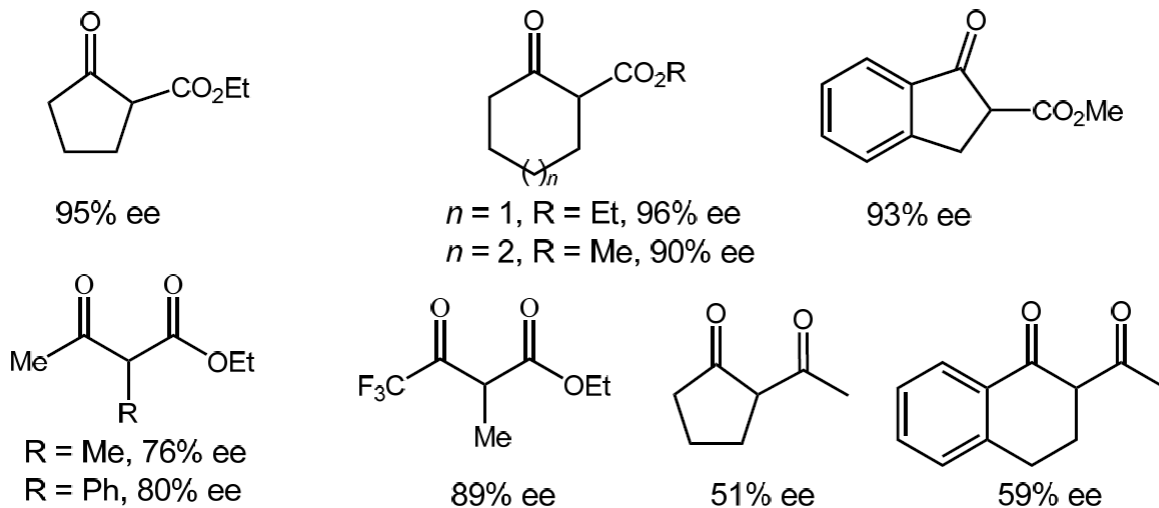
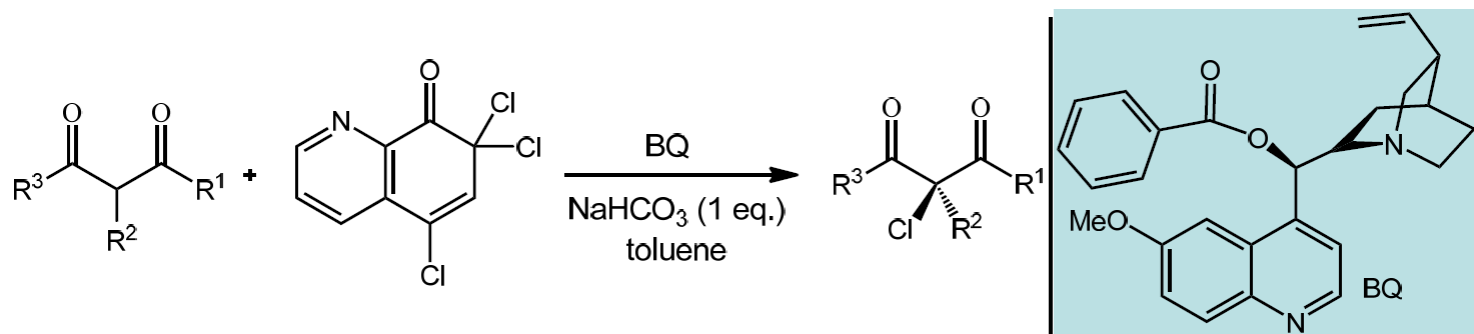
Mechanism



MacMillan, D. W. C.
Science **2007**, 316, 582

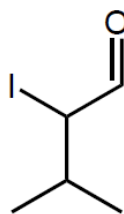
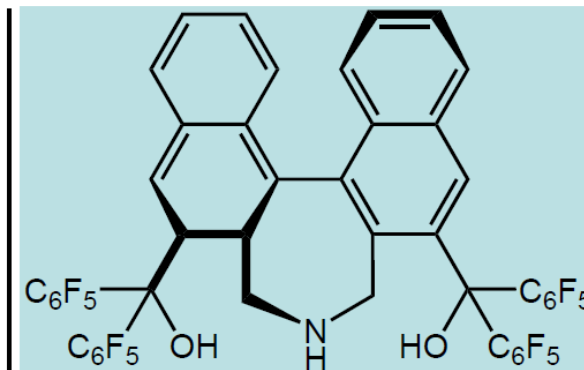
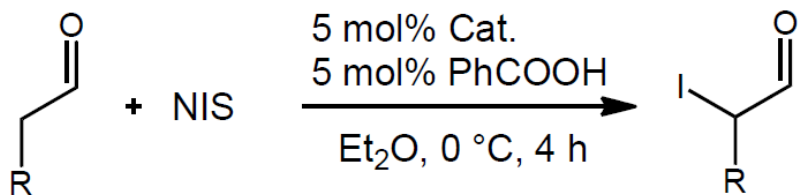
32

有机催化的羰基 α -卤代反应 Bartoli, G. *Angew. Chem. Int. Ed.* 2005, 6219.

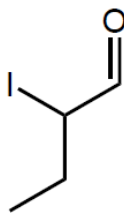


有机催化的羰基 α -卤代反应

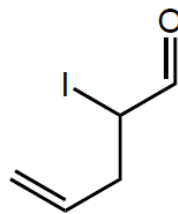
Maruoka, K. *J. Am. Chem. Soc.* 2008, 3728.



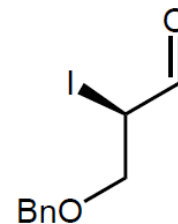
93%, 99% ee



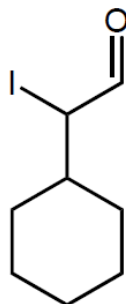
76%, 98% ee



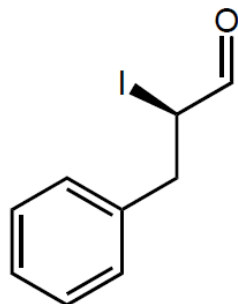
98%, 95% ee



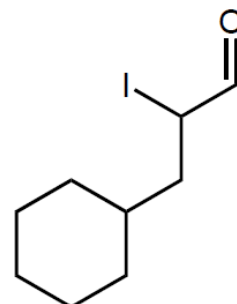
97%, 93% ee



86%, 98% ee



81%, 92% ee



74%, 90% ee

New Directions

- Cooperative catalysis
- Relay catalysis, sequential catalysis (metal/organo)
- Chiral anion directed catalysis (ACDC by List)