

# 手性合成——不对称反应及其应用

## Chapter 5

### 不对称Diels-Alder 反应

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(第7次课)

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# 提 纲

5.1 概述

5.2 传统的不对称Diels-Alder 反应

5.3 催化不对称Diels-Alder 反应(手性Lewis  
酸催化和手性有机催化)

5.4 杂Diels-Alder 反应

5.5 分子内Diels-Alder 反应

5.6 逆-Diels-Alder 反应

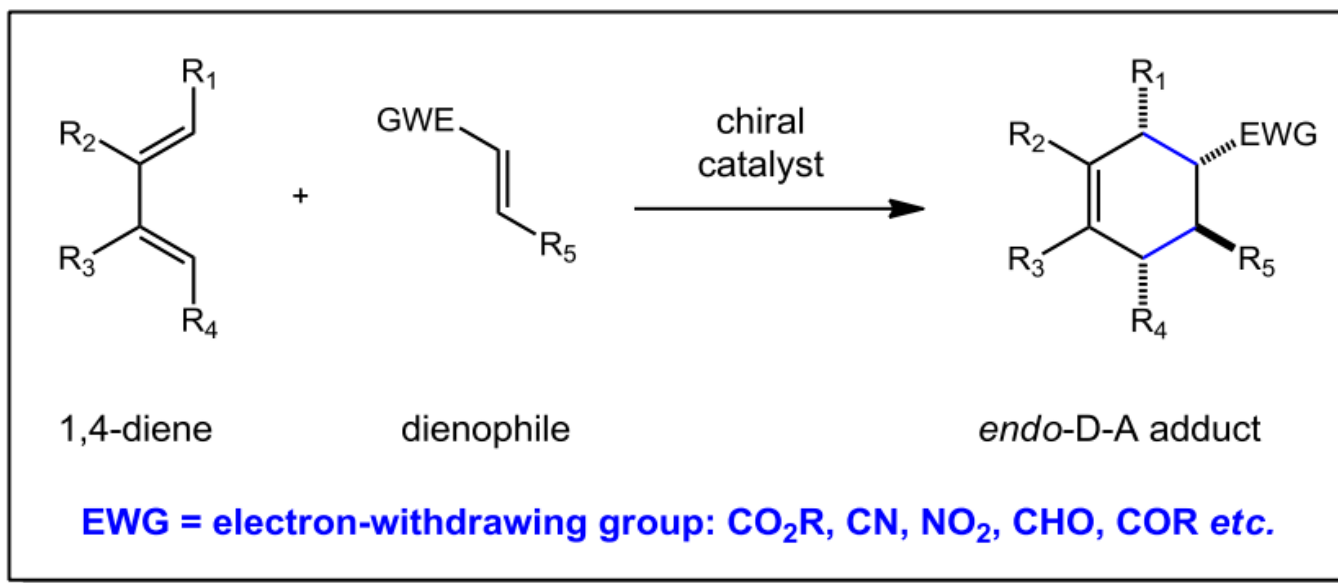
# Diels-Alder反应:

**Early 1900s** Wieland, Staudinger *etc.* Report [4+2] cyclization

**1928** Diels and Alder First establish the correct structure of cycloadduct

**1975** Corey First asymmetric D-A reaction employing chiral controller group

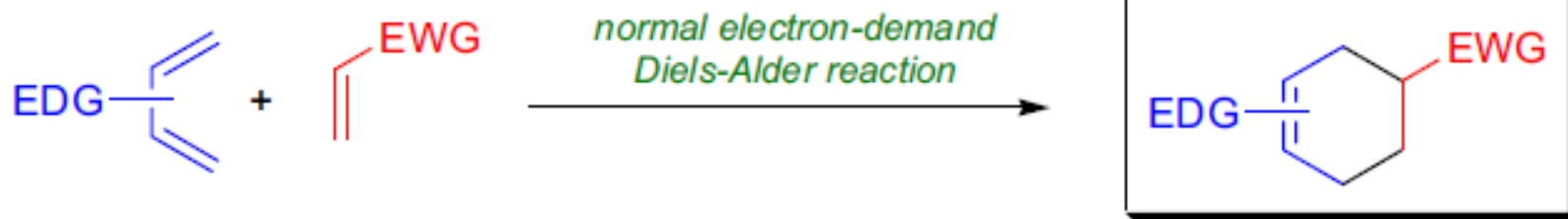
**Diels-Alder reaction:** The  $[4\pi + 2\pi]$  cyclization of diene and alkene to form a cyclohexene derivative.



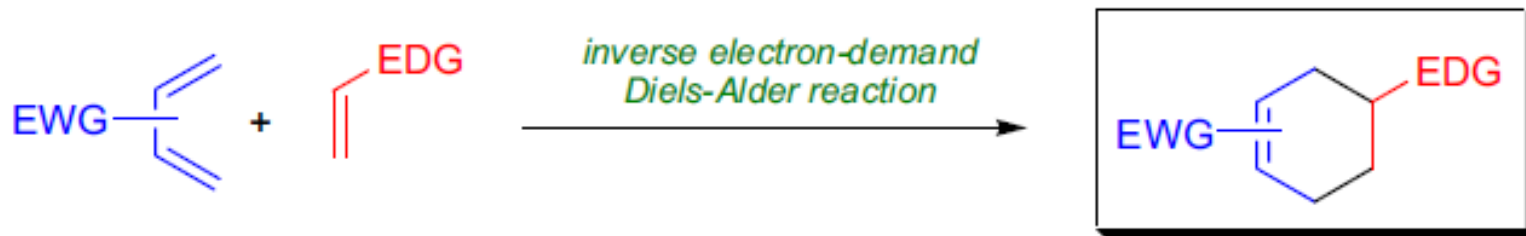
Reviews: Merino, P. *Synthesis* **2010**, 1. Tadano, K. *Chem. Rev.* **2005**, 105, 4779.  
Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, 41, 1650.

# Diels-Alder反应的分类:

# *normal electron-demand D-A reaction*



# *inverse electron demand D-A cyclization*

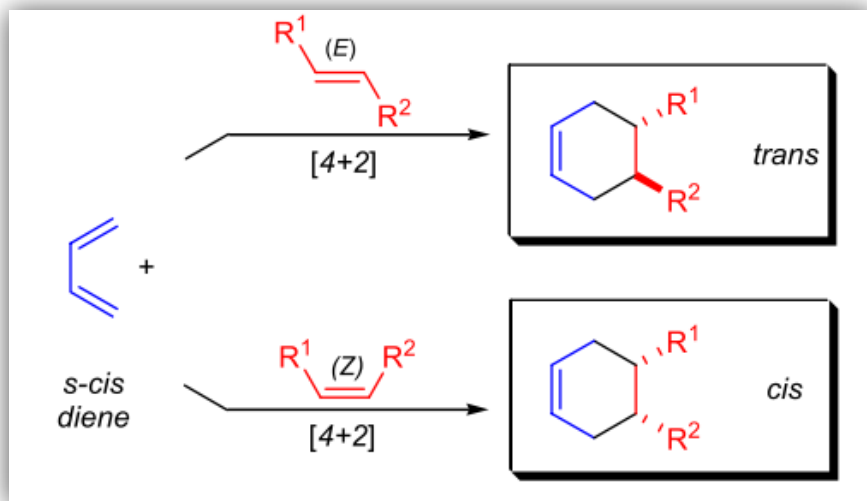


# *hetero-D-A reaction; eg: O, N, S*

# *retro-D-A reaction*

# 立体专一性和立体选择性

Diels-Alder反应是同步发生的，以致二烯和亲二烯体均无时间进行旋转，故它们的立体化学必然如实地重现于产物之中，顺式亲二烯体给出顺式产物(例如3)，反式亲二烯体(例如10)给出反式产物。

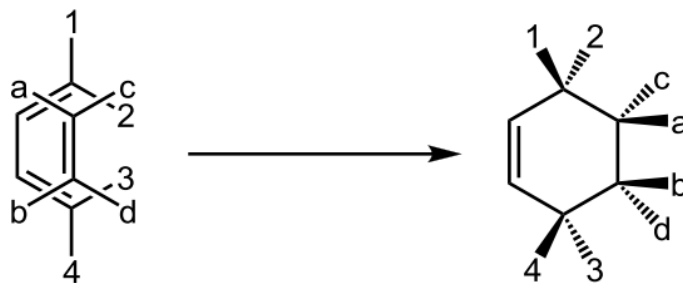


# 内式选择性(*Endo*)

尽管每一原料的立体化学必定被保留，但在许多情况中仍能生成两种产物。这不难从环状体系，例如(16)中看出。

这两个产物称做外式和内式，这些名称所指的是亲二烯体的Z基(此处为CO)与新的环己烯环中的双键之间的相互关系。实际上，反应是有利于生成内式的，因为它是动力学产物，尽管外式产物通常更为稳定些。亲二烯体中的吸电子基Z的作用在于在内式过渡态(17)中通过空间吸引二烯。这是一种次级轨道相互作用，它并不导致形成键，但却确实有助于使过渡态合为一体。

以D-A反应过渡态对*endo*和*exo*的表示法

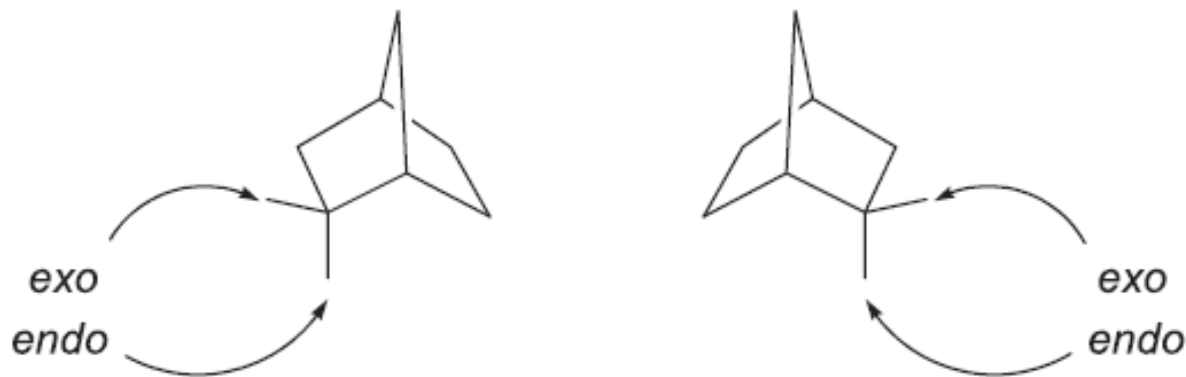


*exo*: c/d is in the back of the plane  
*endo*: a/b is in the front of the plane

# Endo or Exo ?

**bridge ring system**

桥环体系中的endo和exo取代基表示法



当不含取代基的两个桥具有不相等的长度时：

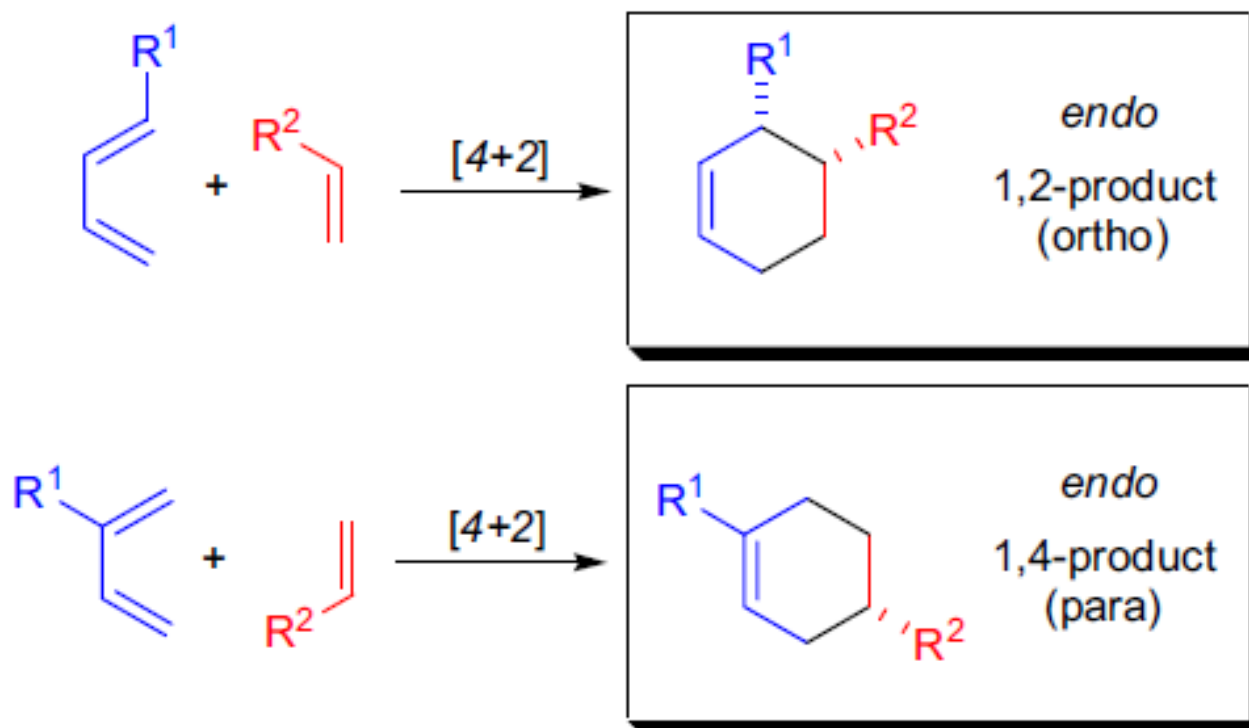
endo (环内)：指比较靠近未取代的桥中较长的那个桥的取代基

exo (环外)：指比较靠近较短的那个桥的取代基。

## Diels-Alder反应的区域选择性

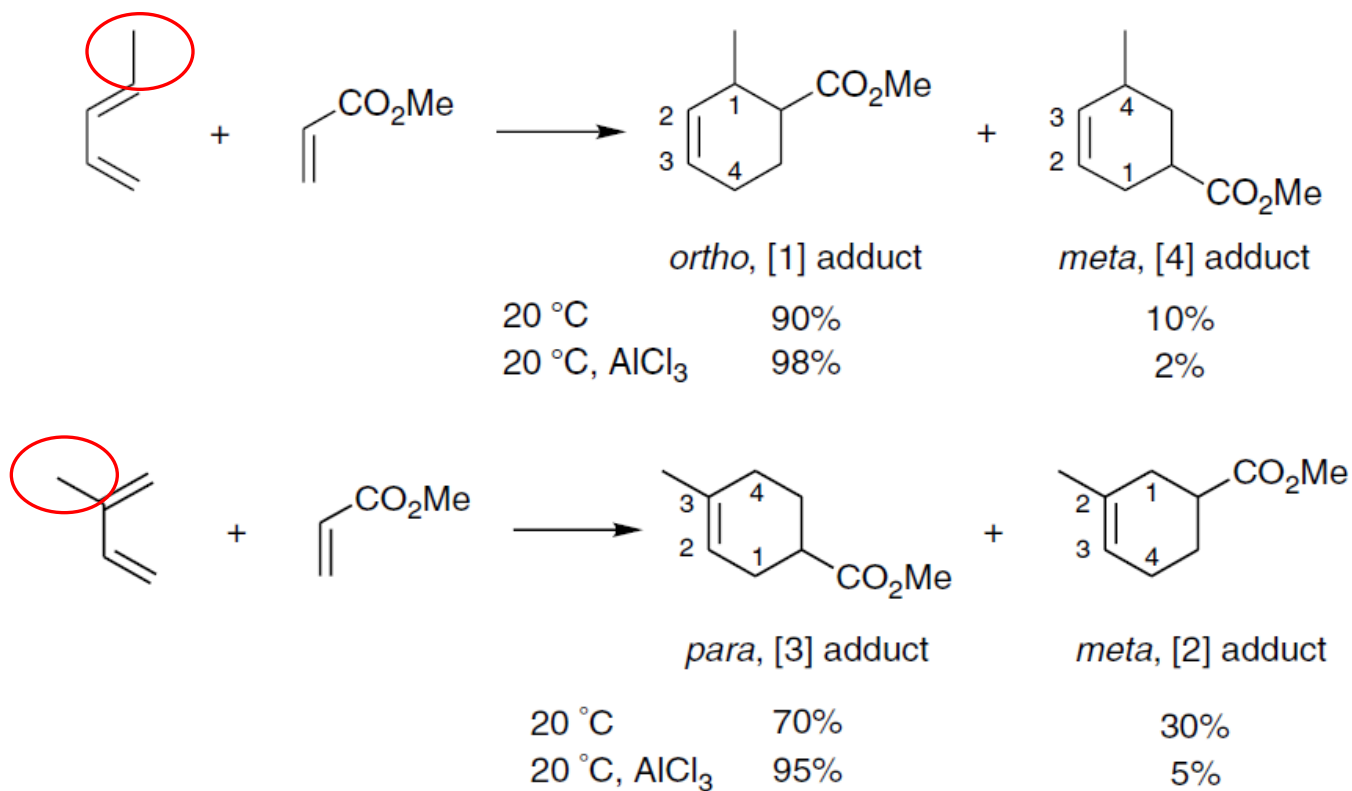
不对称二烯和不对称亲二烯体间的反应也是区域选择性的。

Diels-Alder反应是“邻、对位”定位的。



## Diels-Alder反应的区域选择性

1-取代的丁二烯给出“邻位”产物(1)，而2-取代的丁二烯给出“对位”产物(3)，在路易氏酸催化下尤其如此。“间位”产物(4)和(2)很难按此法制得。



## Chapter 5.2 传统的不对称Diels-Alder 反应

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早期，不对称Diels-Alder 反应使用手性的反应物进行。这类反应可分为手性亲双烯体、手性双烯体以及双不对称Diels-Alder 反应。

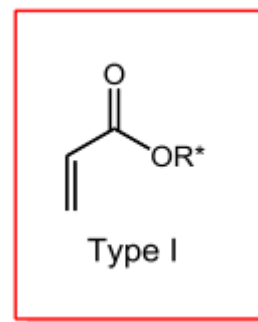
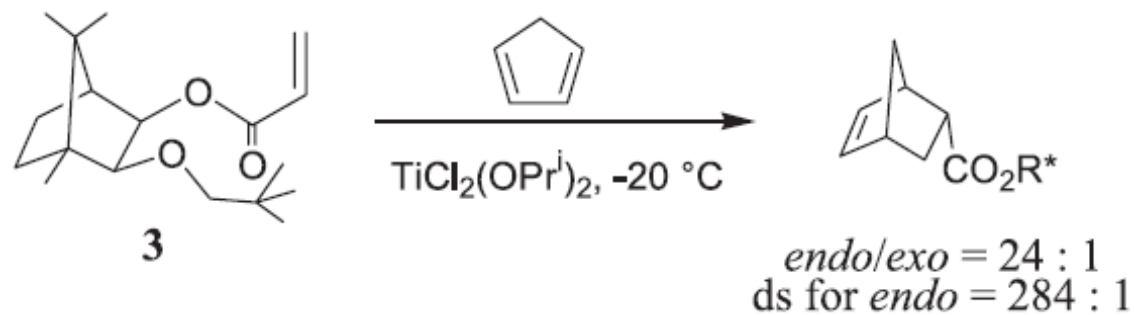
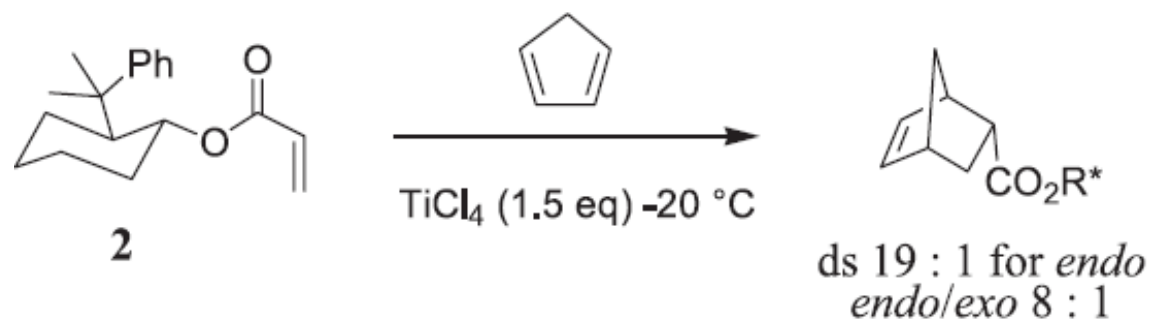
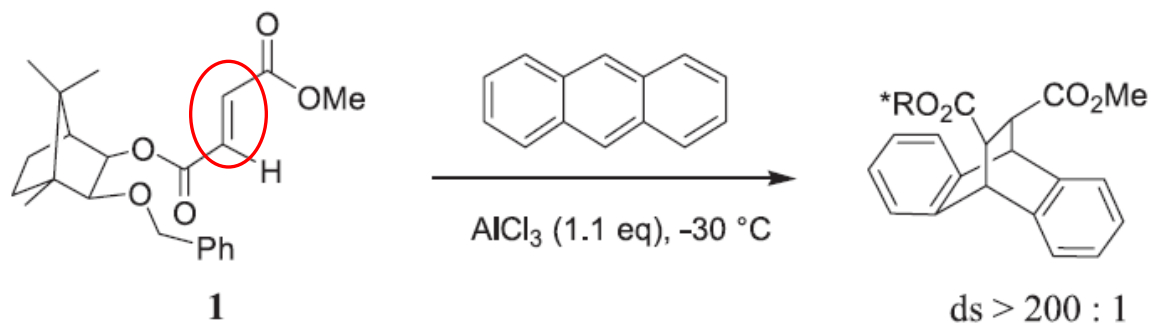
# 手性亲双烯体

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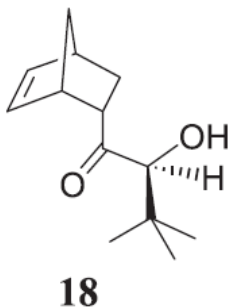
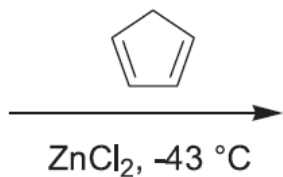
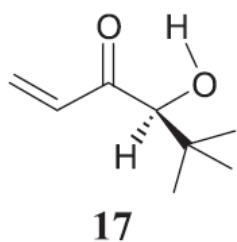
1) 大部分例子利用手性亲双烯体实现不对称 Diels—Alder 反应。

2) 作为最常用的手性亲双烯体, 有三种类型: I型是手性**丙烯酸酯**, 简单直接的方式与手性基团结合; II型 (**不饱和酮类**) 与I型比较, 其手性基团与双键更靠近一个原子, 合成较难, 且手性基团的循环使用也麻烦; III型是**丙烯酰胺**, 活性高。

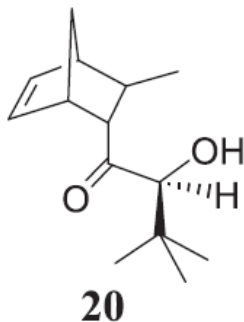
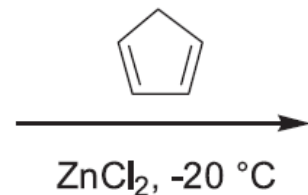
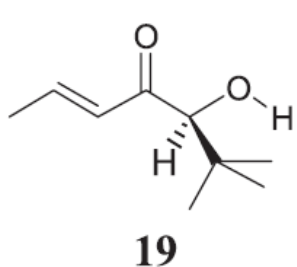
## Chapter 5.2.1 丙烯酸酯类亲双烯体 (I型试剂)



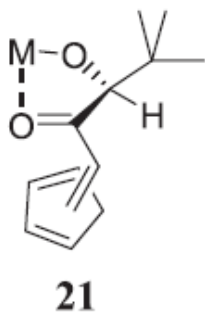
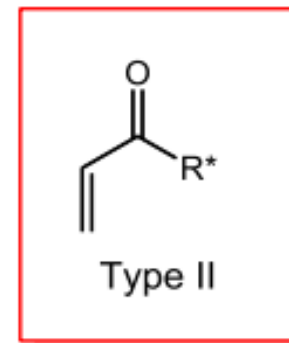
## Chapter 5.2.2 $\alpha$ , $\beta$ -不饱和酮类亲双烯体 (II型试剂)



*endo/exo* = 15 : 1  
*de* > 100 for *endo*



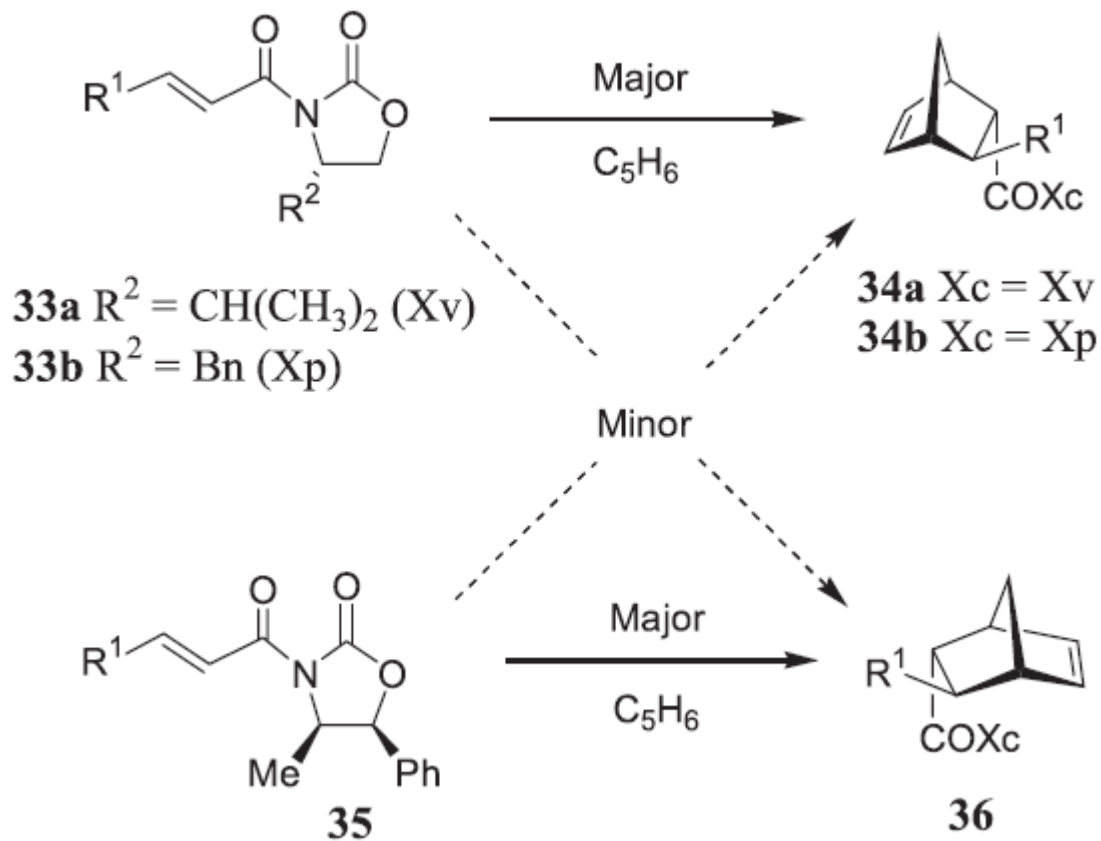
*endo/exo* = 15 : 1  
*de* > 100 for *endo*



高对映选择性：首先，Lewis酸中的金属与亲二烯体17或19的 $\alpha$ 羟基酮部分的配位，形成了刚性的五元环螯合物21，使烯酮体系的二个非对映面能够实现区分；其次，从已形成的18和20的绝对构型看，在21分子内烯酮片段的Diels-Alder反应是按顺向面(syn平面)进行的

## Chapter 5.2.3 $\alpha$ , $\beta$ -不饱和 *N*-酰基噁唑烷酮 (III型试剂)

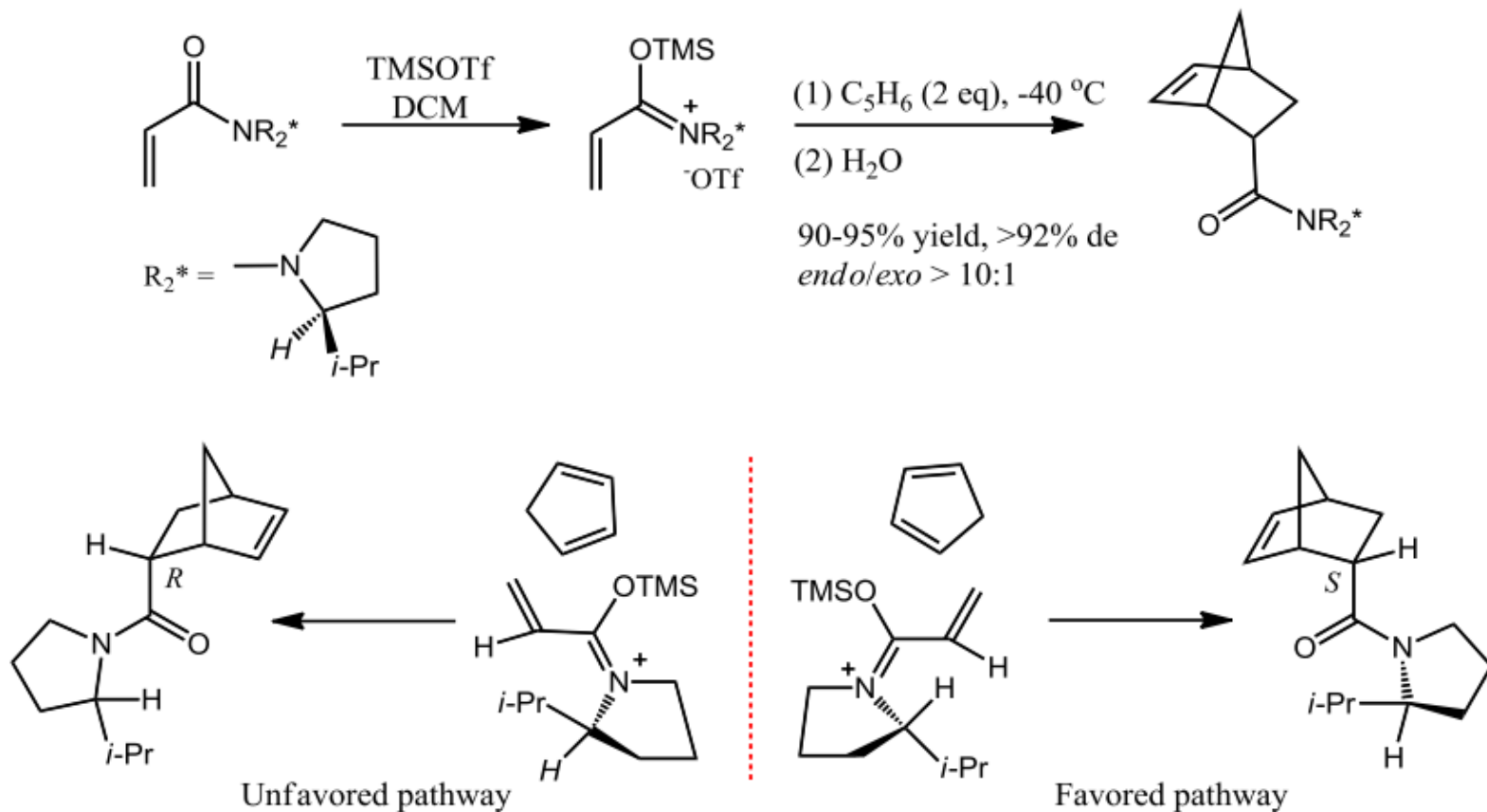
手性  $\alpha$ ,  $\beta$ -不饱和 *N*-酰基噁唑烷酮被看作是I型亲双烯体试剂的补充。这类手性亲双烯体由Evans 首次报道。



Evans, D. A. et al. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

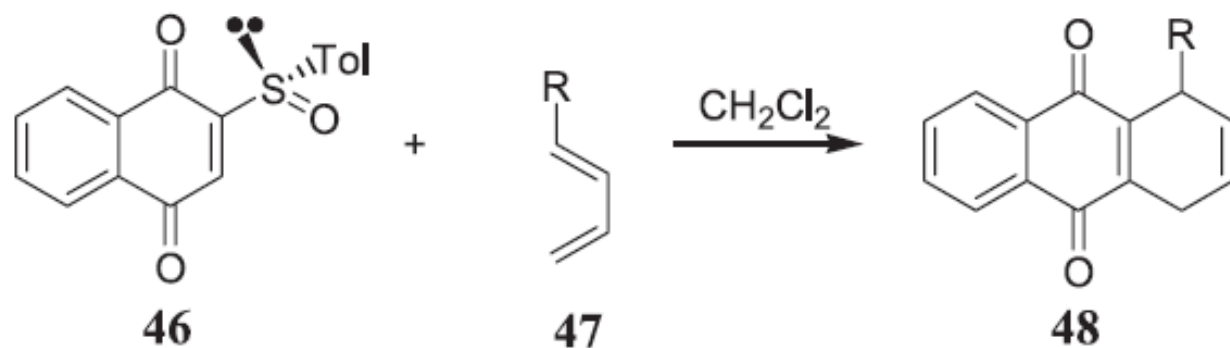
## Chapter 5.2.4 手性烷氧基亚胺盐

无论是实验结果还是前线轨道理论都表明，含有拉电子基团的亲双烯体在进行Diels-Alder 反应时会表现出较高的活性



Jung, M. E. et al. *Tetrahedron Lett.* **1989**, 30, 1893.

## Chapter 5.2.5 手性取代亚砷作为亲双烯体



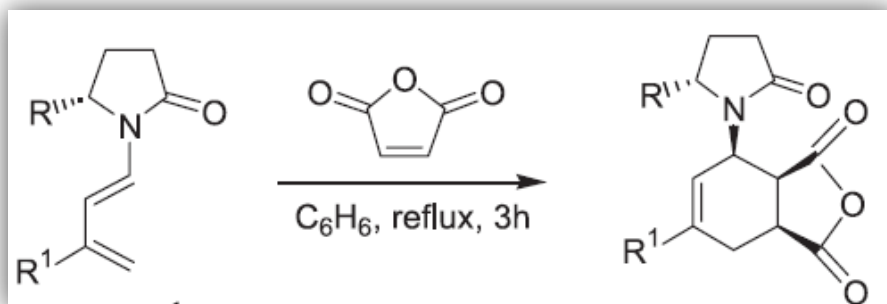
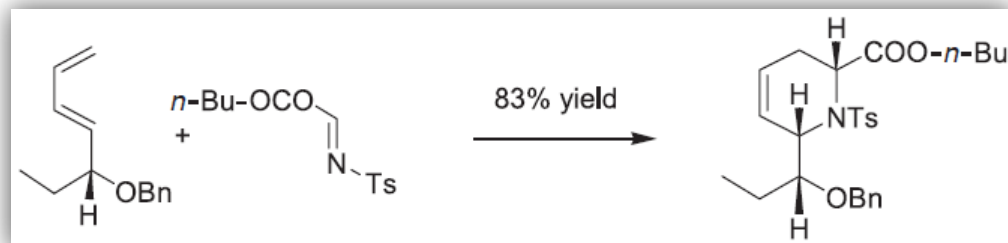
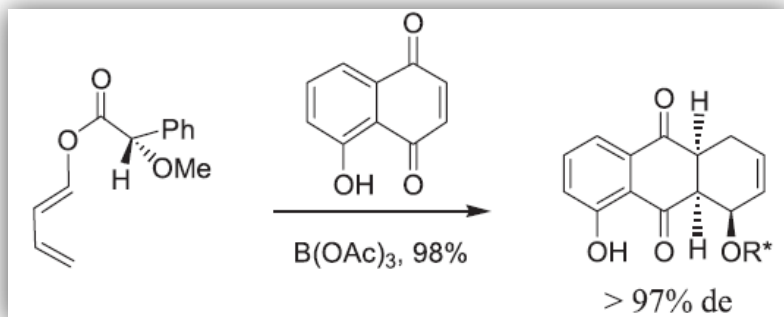
**ee: 68-82%**

优点：反应结束后手性辅基经过热消除即可脱去。

Carreno, M. et al. *Tetrahedron Asymmetry* **1998**, 9, 2965.

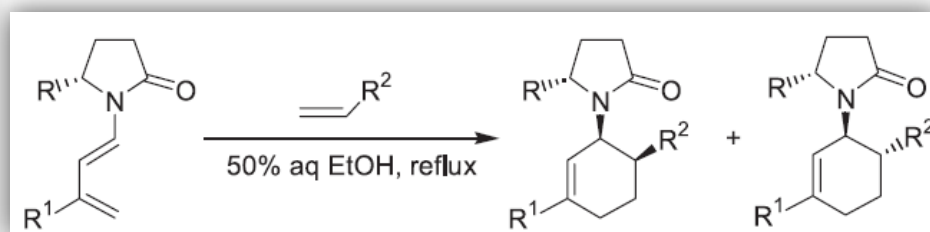
## Chapter 5.2.6 手性双烯体

连接手性辅基的双烯组份的报道很少见，原因是由于这些修饰的双烯较难制备。



$R = CO_2Et$ ;  $R^1 = H$ ;  
 $R = CO_2Et$ ;  $R^1 = Me$

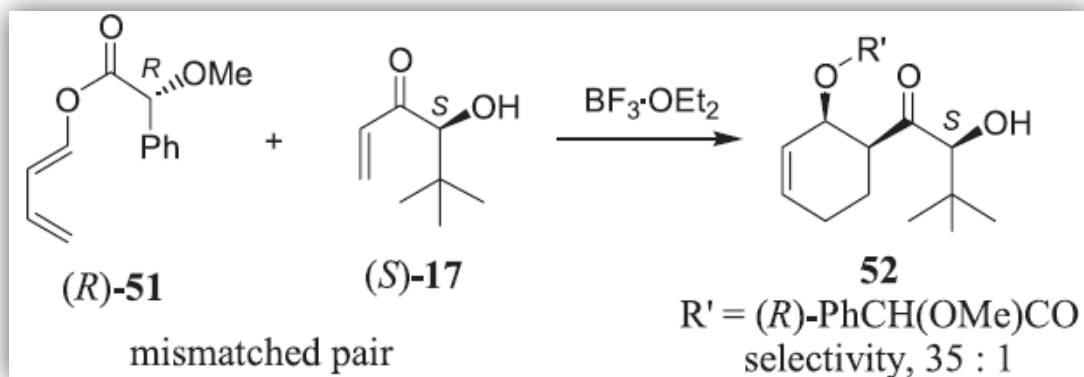
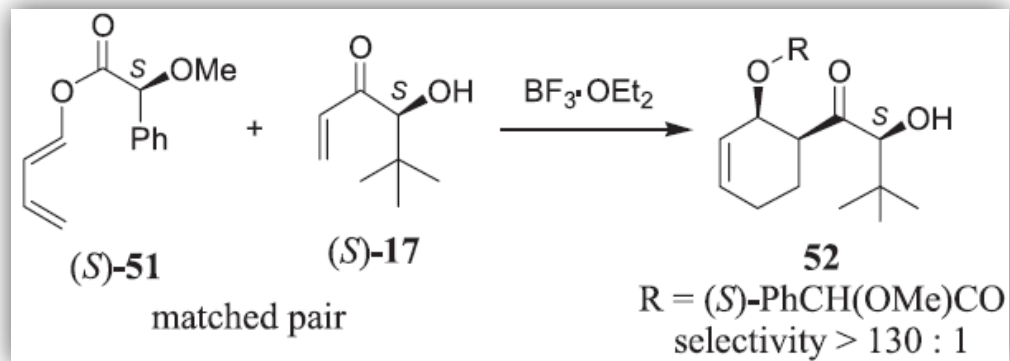
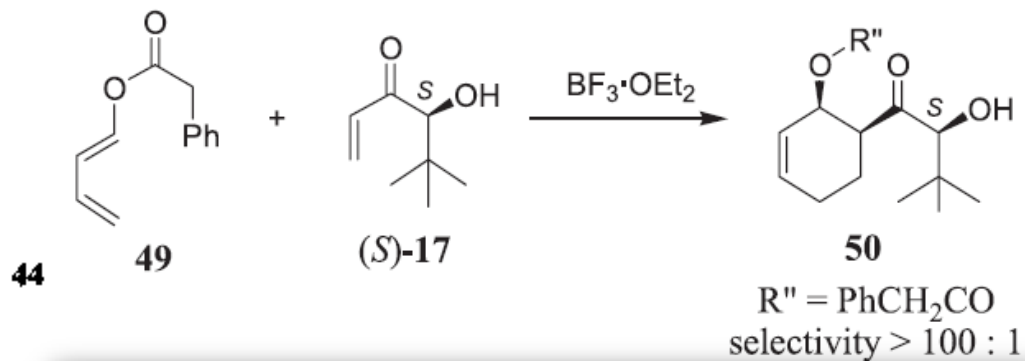
single diastereomer



	<i>cis</i> (ds)	<i>trans</i> (ds)
(a) $R = CO_2Et$ , $R^1 = H$ , $R^2 = CO_2Et$	93 (91.5/1)	7 (65 : 1)
(b) $R = CO_2Et$ , $R^1 = Me$ , $R^2 = CO_2Et$	92 (18/1)	8 (84 : 1)
(c) $R = CO_2Et$ , $R^1 = H$ , $R^2 = COMe$	82 (40/1)	18 (180 : 1)

## Chapter 5.2.7 双不对称环加成

### 手性亲双烯和手性双烯的一系列反应.



## Chapter 5.3 催化不对称Diels-Alder 反应-手性Lewis酸催化

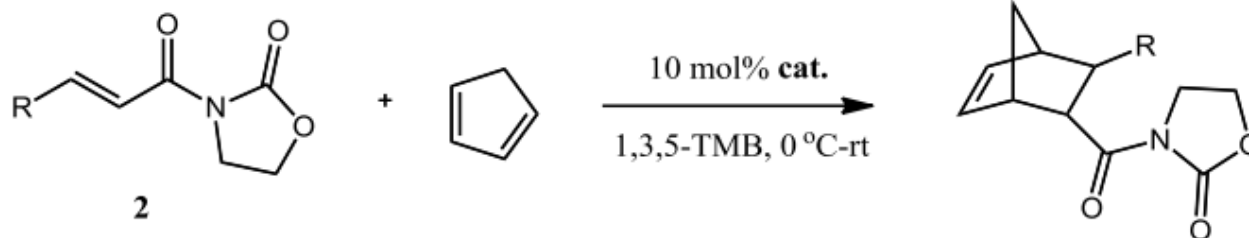
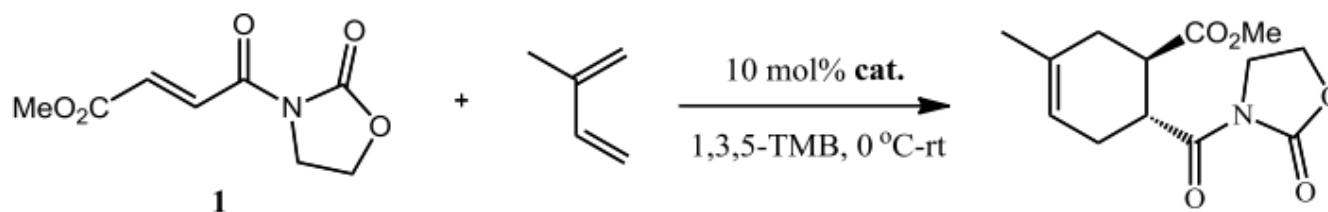
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应用Lewis酸金属络合物形式的手性催化剂能很好地将对映选择性引入Diels-Alder反应。

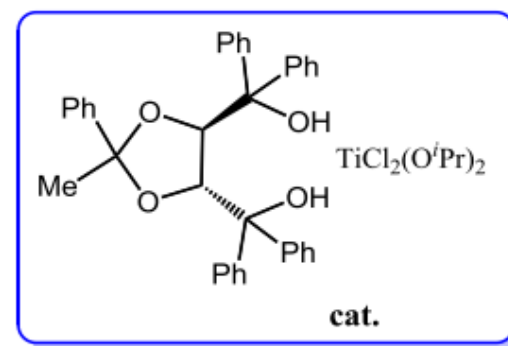
常用金属—— Ti, Cu, Sc, Zn, Al, Ni, Mg, Zr, La

## Chapter 5.3.1 Narasaka 催化剂

### Narasaka's Catalyst-Hydrogen bonding catalyst

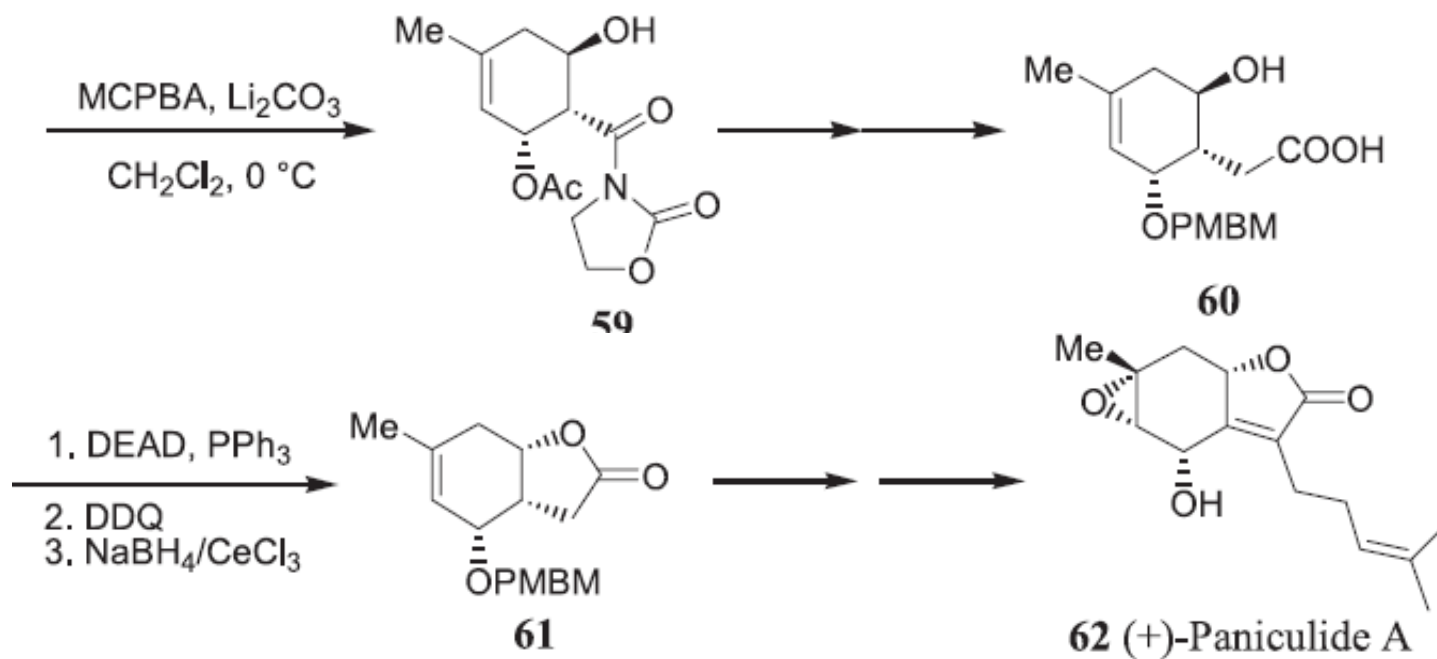
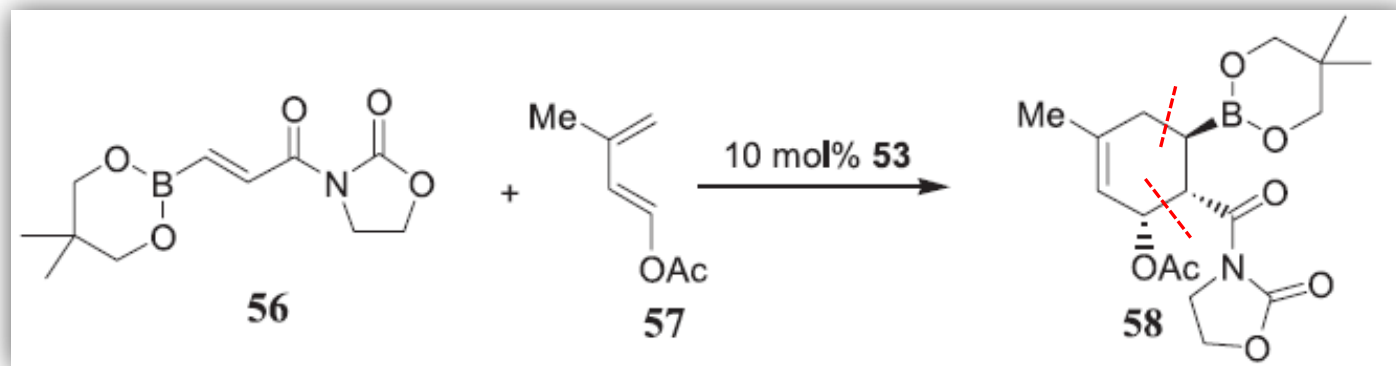


dienophile	yield (%) / ( <i>endo/exo</i> )	ee (%)
<b>2a</b> R = Me	90 (91/9)	91
<b>2b</b> R = Ph	97 (92/8)	82
<b>2c</b> R = Pr	75 (91/9)	75



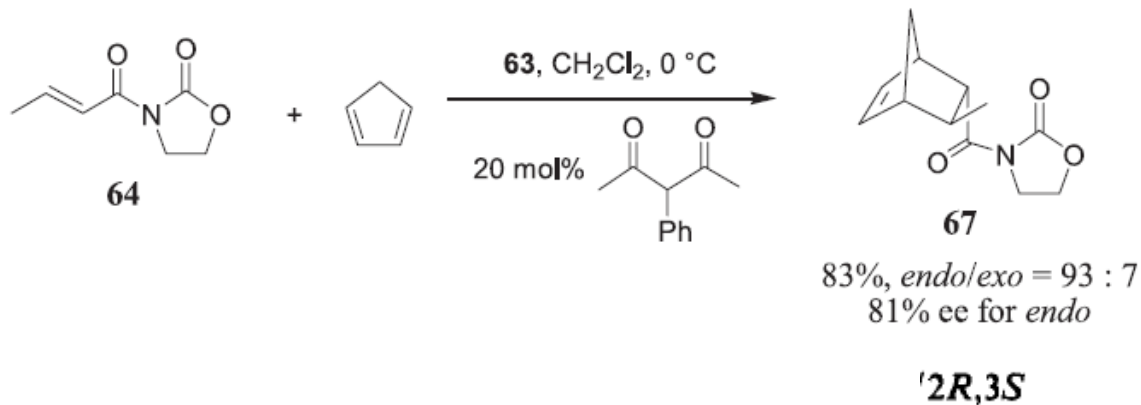
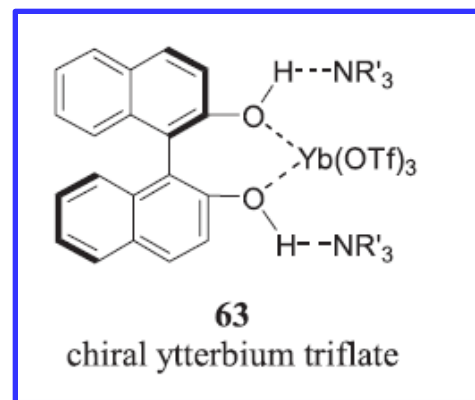
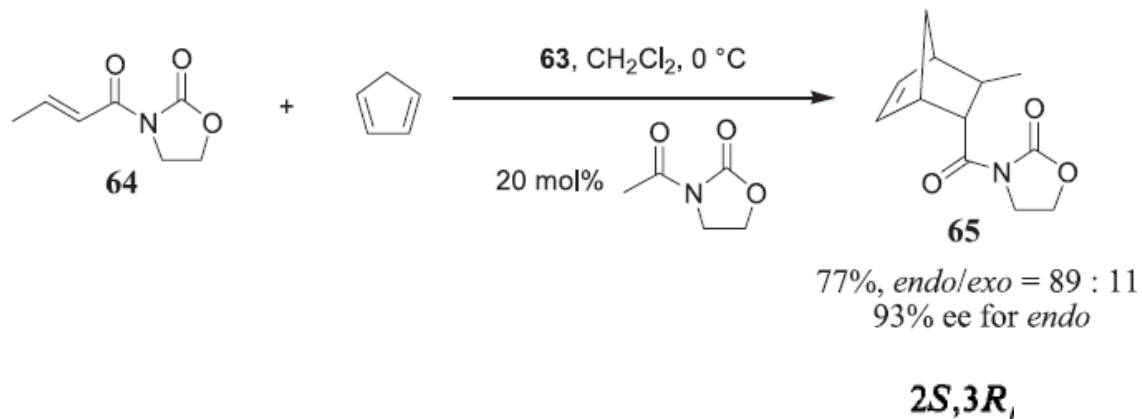
Narasaka, K. et al. *Chem. Lett.* **1987**, 2409.

Narasaka催化剂在倍半萜(+)-穿心莲组培内酯A [(+)-paniculide A] 合成中的应用：其中第一步对映选择性环加成是关键步骤。



Narasaka, K. et al. *Bull. Chem. Soc. Jpn.* **1994**, 67, 3327.  
21

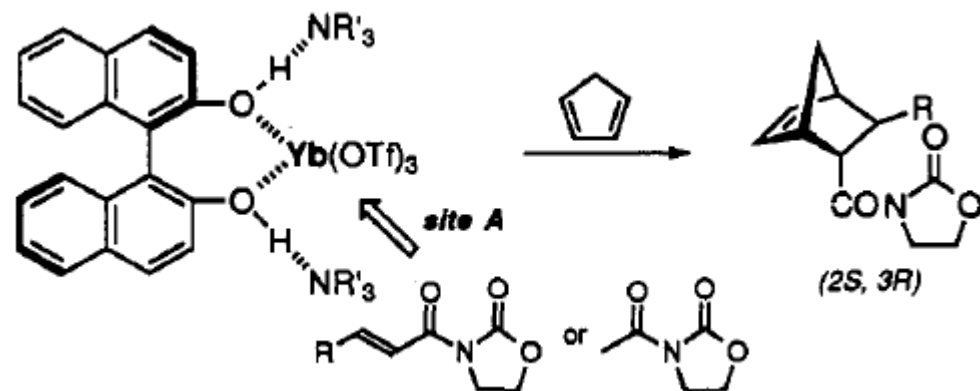
## Chapter 5.3.2 手性镧系金属催化剂



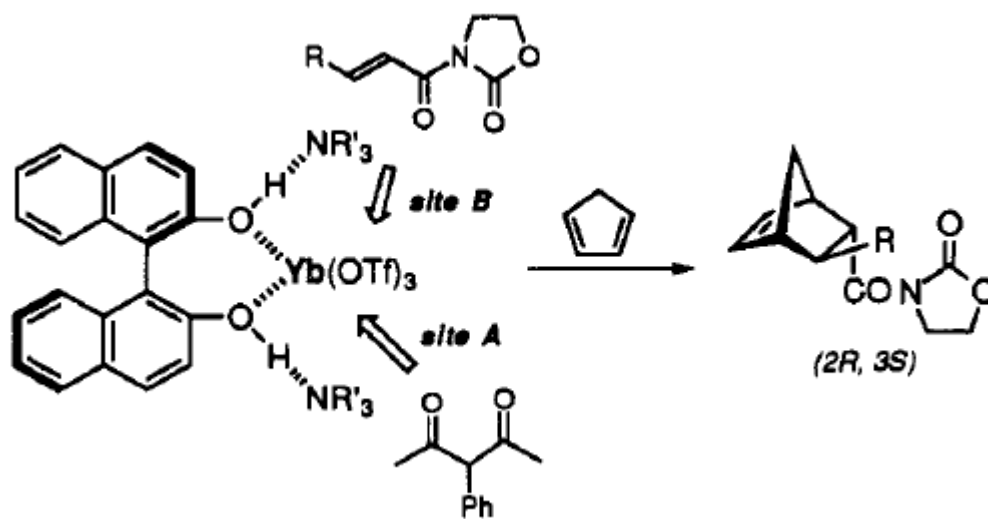
非手性配体，  
可用作稳定催  
化剂的添加剂，  
防止催化剂的  
老化。

Kobayashi, S. et al. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

## Chapter 5.3.2 手性镧系金属催化剂



*Si* attack

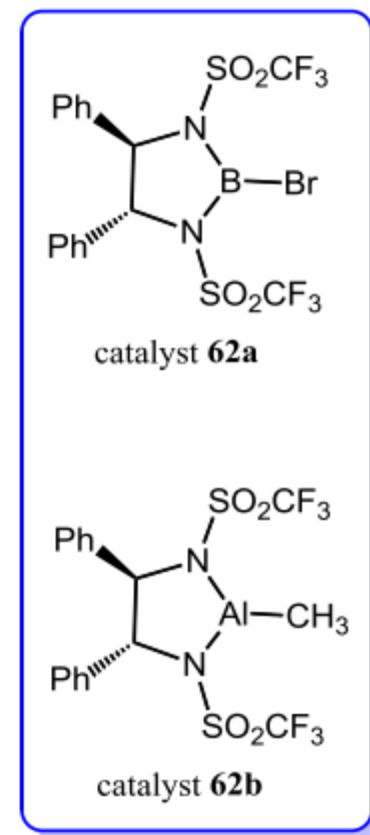
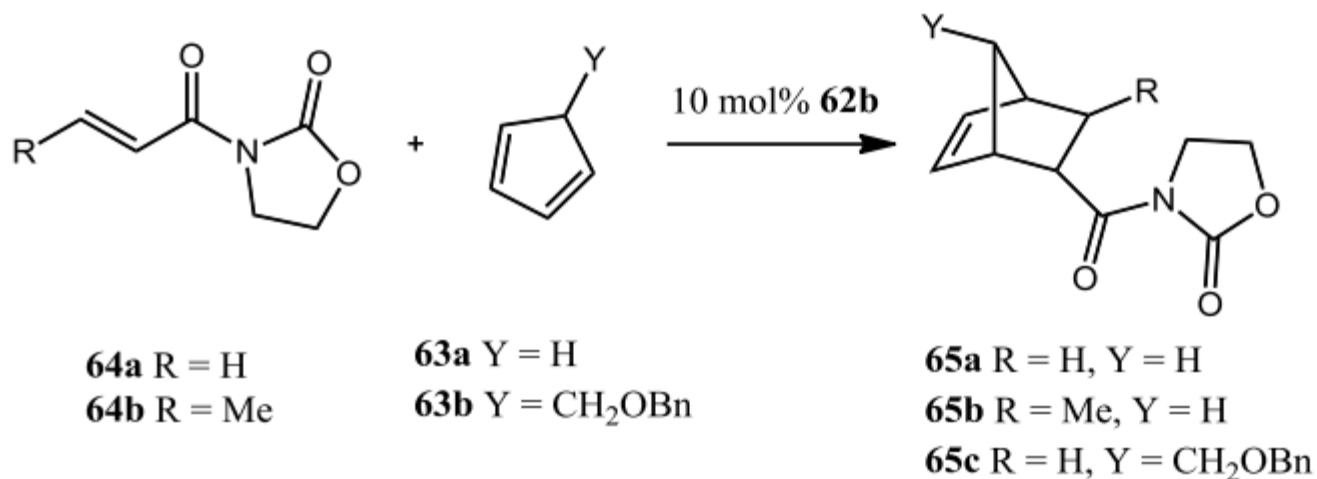


*Re* attack

Kobayashi, S. et al. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

## Chapter 5.3.3 双磺酰胺(Corey催化剂)

### Bissulfonamides (Corey's Catalyst)

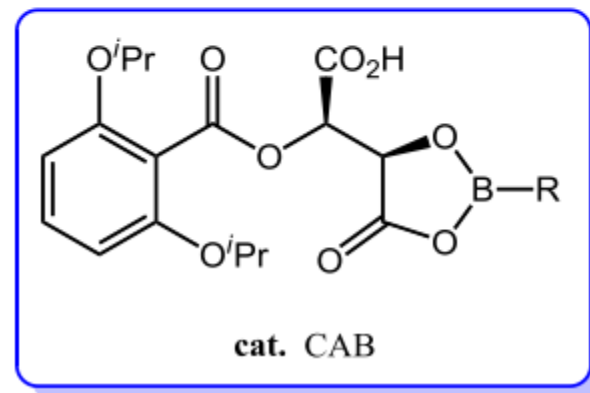
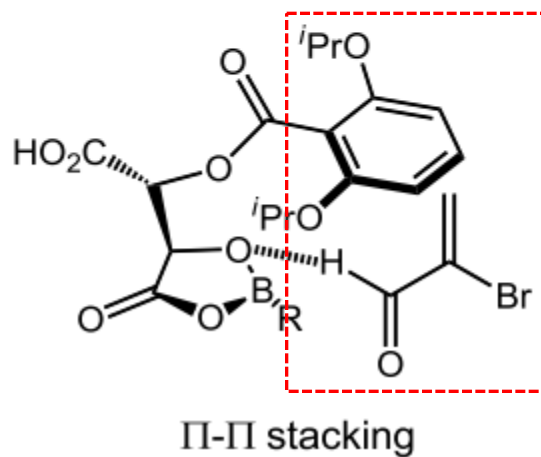
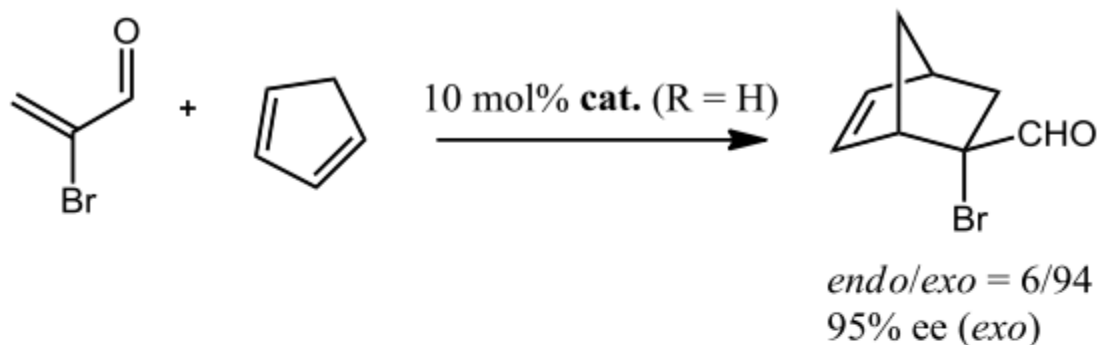


product	T/(°C)	yield (%) / ( <i>endo</i> / <i>exo</i> )	ee (%)
<b>65a</b>	-90	92 (> 50/1)	95
<b>65b</b>	-78	88 (96/4)	94
<b>65c</b>	-78	94	95

Corey, E. J. et al. *J. Am. Chem. Soc.* **1992**, *114*, 7938.

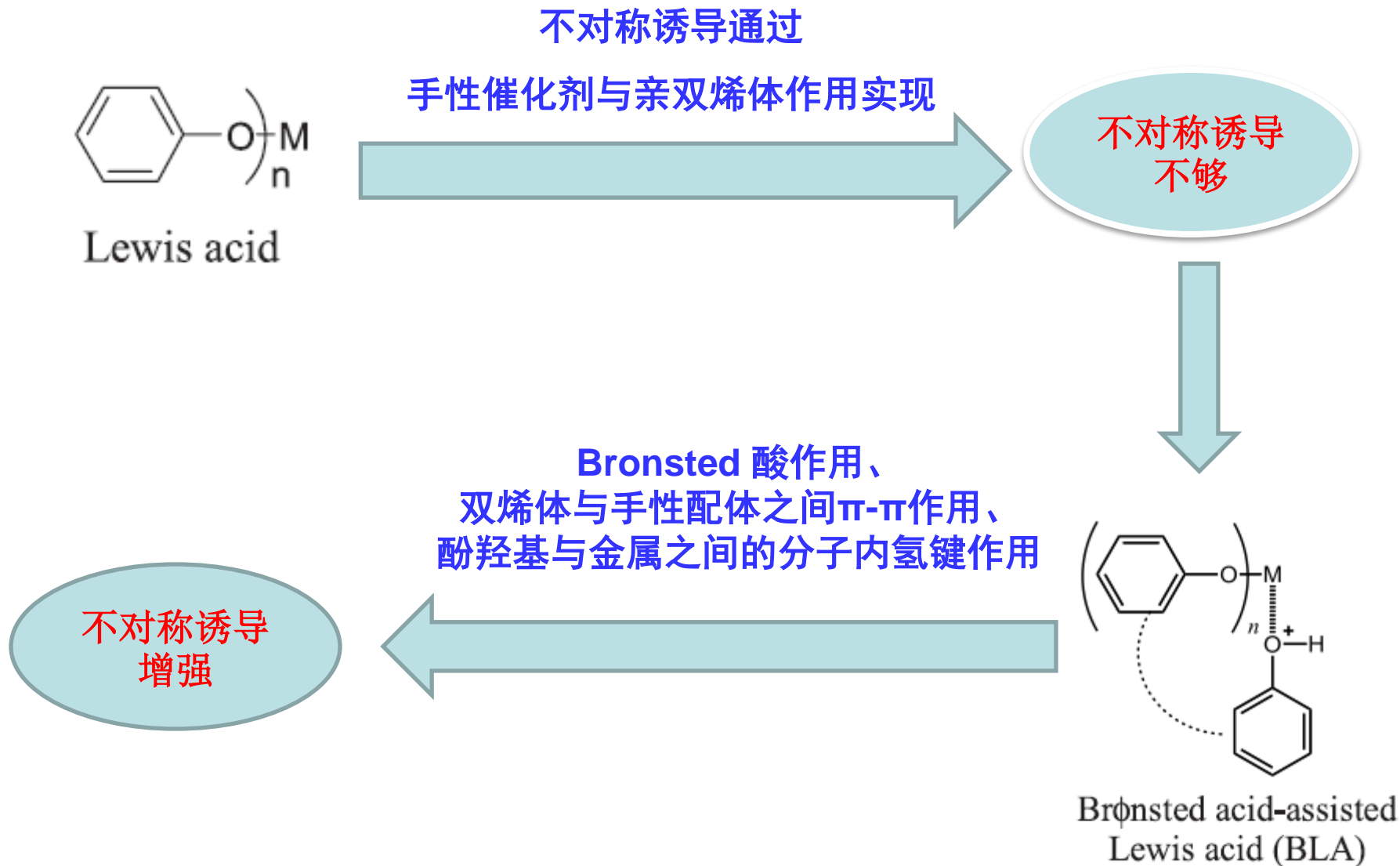
## Chapter 5.3.4 手性酰氧基硼烷(CAB)催化剂

这类催化剂是对映选择性Diels-Alder反应、杂Diels-Alder反应和其他反应的良好催化剂。

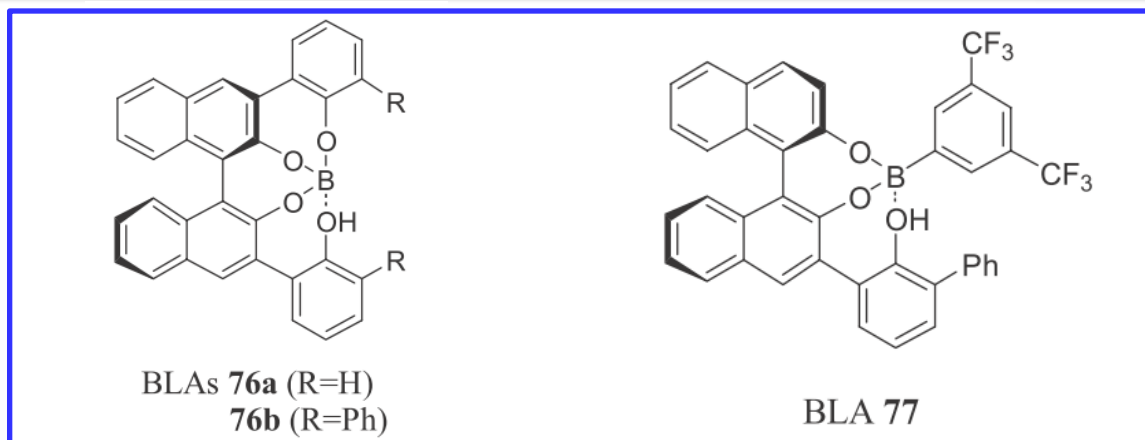


Yamamoto, H. et al. *J. Org. Chem.* **1993**, 58, 6917.

# Chapter 5.3.5 Bronsted 酸协助的手性Lewis酸(BLA)催化剂



## Chapter 5.3.5 Bronsted 酸协助的手性Lewis酸(BLA)催化剂



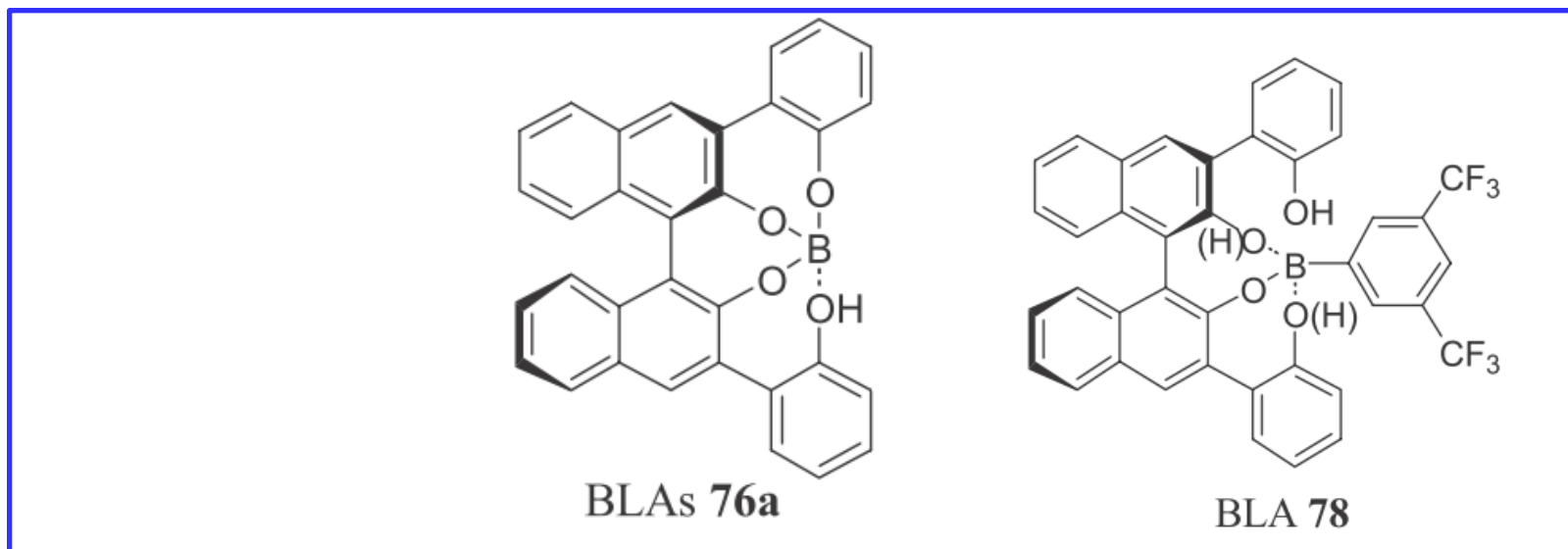
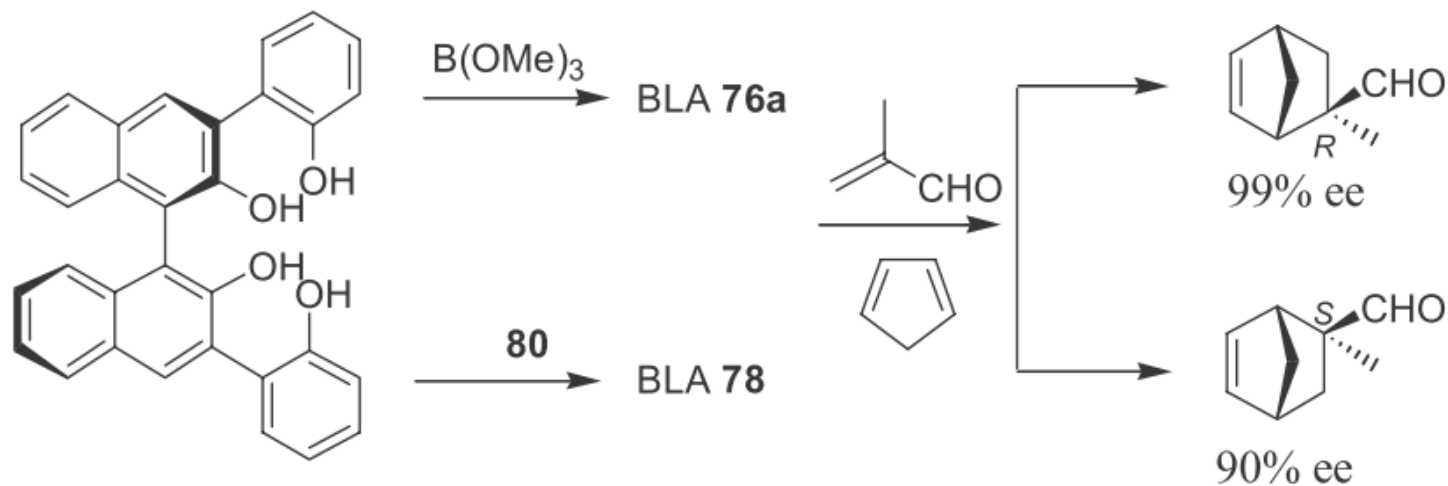
**TABLE 5–2. Enantioselective Diels-Alder Reaction of Various  $\alpha$ -Substituted  $\alpha,\beta$ -Enals with Cyclopentadiene Catalyzed by (*R*)-BLA 76a**

Entry	Dienophile	Yield (%) ( <i>exo:endo</i> )	ee (%) (config.)
1	$\alpha$ -Bromoacrolein	>99 (>99:1)	99 ( <i>S</i> )
2	$\text{CH}_2=\text{CMeCHO}$	>99 (>99:1)	99 ( <i>R</i> )
3	$\text{CH}_2=\text{CEtCHO}$	>99 (97:3)	92
4	( <i>E</i> )- $\text{MeCH}=\text{CHMeCHO}$	>99 (>99:1)	98
5	1-Formylcyclopentene	>99 (98:2)	93
6	$\text{CH}_2=\text{CHCHO}$	91 (9:91)	40 ( <i>R</i> )
7	$\text{CH}_2=\text{CHCHO}$	85 (14:86)	92 ( <i>R</i> ) <sup>a</sup>
8	( <i>E</i> )- $\text{MeCH}=\text{CHCHO}$	12 (11:89)	36 ( <i>R</i> )

ee = Enantiomeric excess. <sup>a</sup>(*R*)-**76b** was used instead of (*R*)-**76a**.

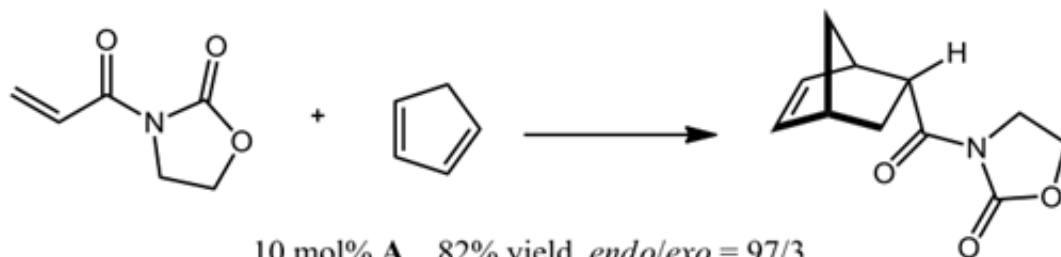
Yamamoto, H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 6920.

## Chapter 5.3.5 Bronsted 酸协助的手性Lewis酸(BLA)催化剂



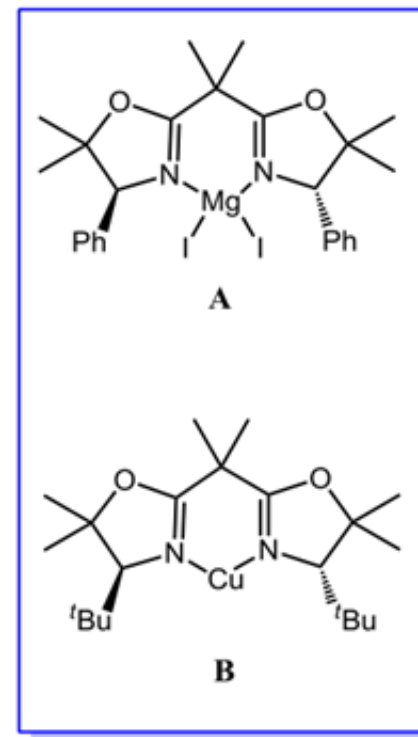
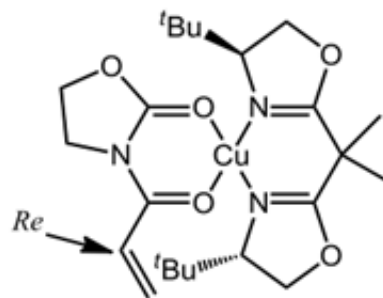
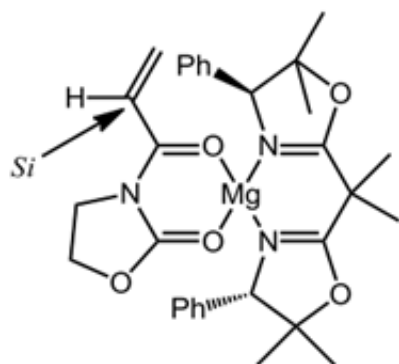
Yamamoto, H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 6920.

## Chapter 5.3.6 双噁唑啉催化剂



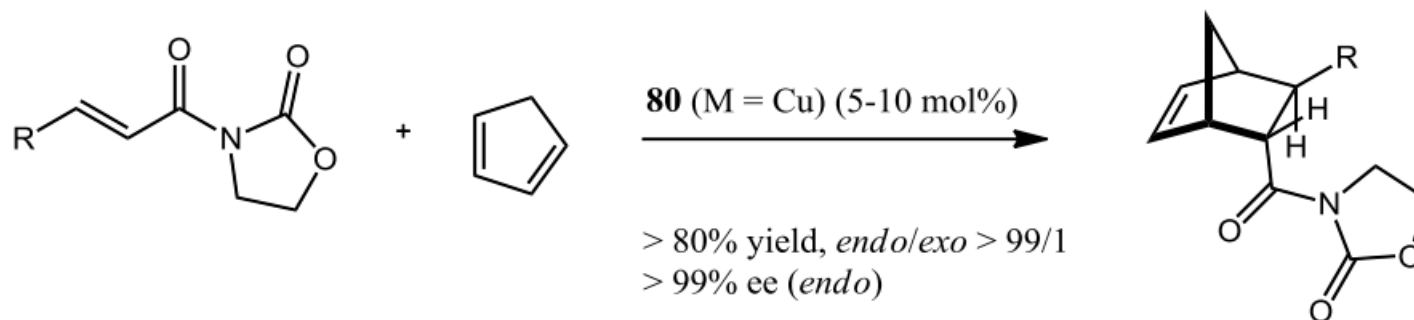
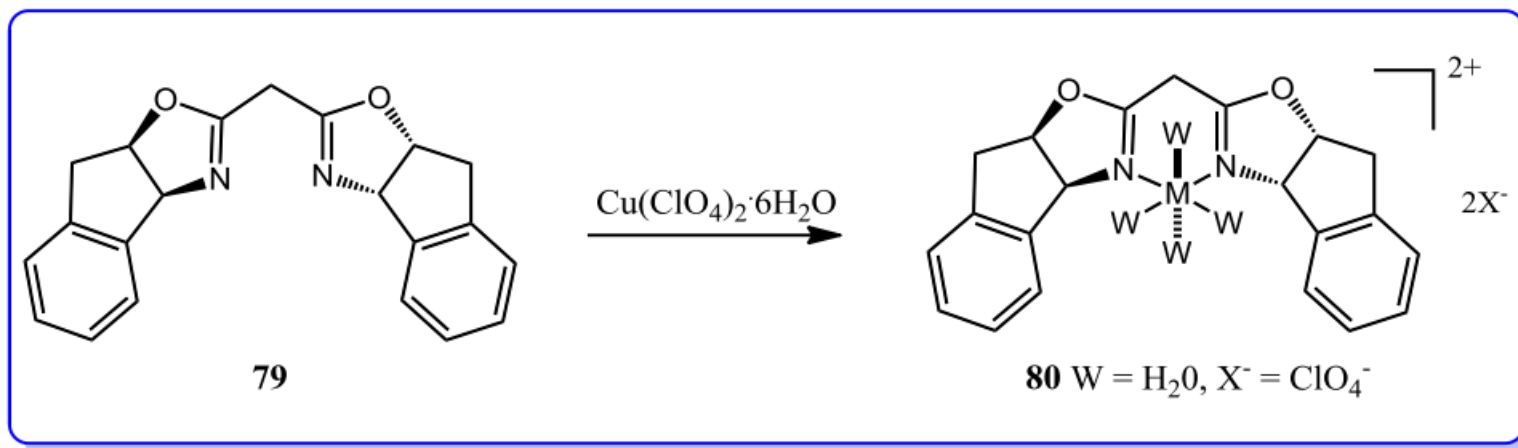
10 mol% A 82% yield, *endo/exo* = 97/3  
90.5% ee (*endo*)

10 mol% B *endo/exo* = 98/2  
>98% ee (*endo*) *ent*



Corey, E. J. et al. *J. Am. Chem. Soc.* **1991**, *113*, 728.  
Evans, D. A. et al. *J. Am. Chem. Soc.* **1993**, *115*, 6460.

## Chapter 5.3.6 双噁唑啉催化剂



**NOTES:** protic solvent should be avoided since it can kill the catalyst activity by coordinating with the metal

## Chapter 5.3.6 双噁唑啉催化剂

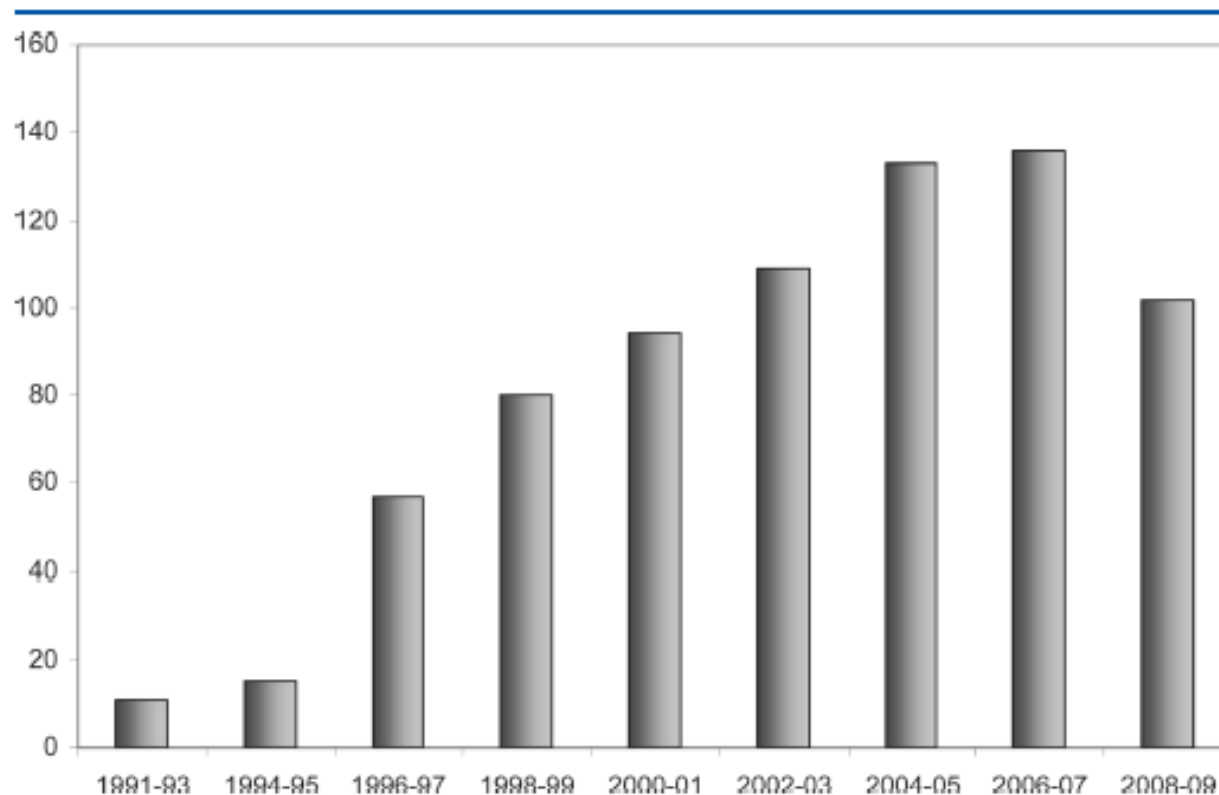


Figure 1. Number of papers dealing with  $C_2$ -symmetric chiral box ligands appearing in the literature since 1991.

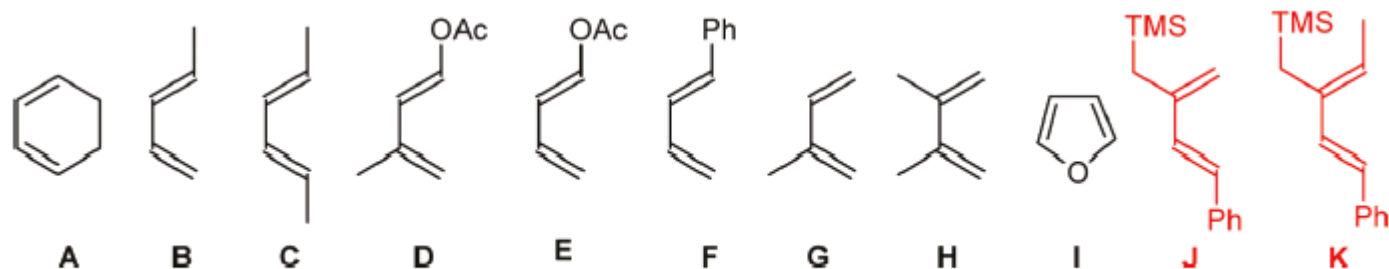
## Chapter 5.3.6 双噁唑啉催化剂

Table 66. Enantioselective Diels–Alder Reactions between Cyclopentadiene and 3-Acryloyl-2-oxazolidinone 216 (R = H) Catalyzed by [Box/MX<sub>n</sub>]

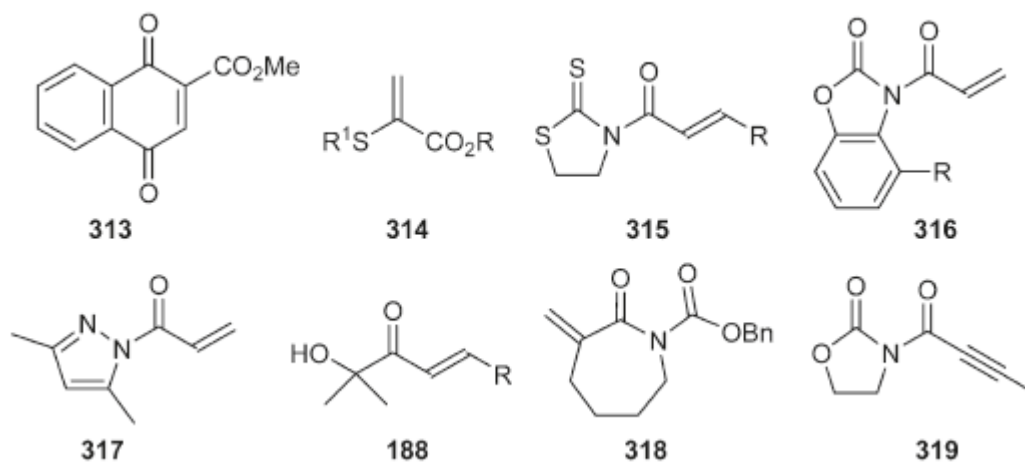
entry	R <sup>1</sup>	box	MX <sub>n</sub>	additives	solvent	yield (%)	endo/exo	endo ee (%) (conf.)
1	H,H	(S)-1	FeI <sub>3</sub> /I <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	85	96:4	82 (R)
2	H,H	(S)-1	Cu(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	92	95:5	30 (S)
3	H,H	(S)-2	Cu(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	86	98:2	>98 (S)
4	H,H	(S)-2	Cu(OTf) <sub>2</sub>		THF	>98	97:3	98 (S)
5	H,H	(S)-2	Cu(OTf) <sub>2</sub>		MeNO <sub>2</sub>	>98	92:8	84 (S)
6	H,H	(S)-2	Cu(OTf) <sub>2</sub>		MeCN	87	92:8	58 (S)
7	H,H	(S)-2	Cu(SbF <sub>6</sub> ) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	>95	96:4	>98 (S)
8	H,H	(S)-2	Cu(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup>		CH <sub>2</sub> Cl <sub>2</sub>	85	97:3	6 (S)
9	H,H	(S)-2	Co(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	85	90:10	50 (S)
10	H,H	(S)-2	Mn(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	80	85:15	50 (S)
11	H,H	(S)-2	Ni(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	75	90:10	40 (S)
12	H,H	(S)-2	Zn(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	85	95:5	38 (S)
13	H,H	(S)-2	LiOTf		CH <sub>2</sub> Cl <sub>2</sub>	89	85:15	14 (S)
14	H,H	(S)-2	Cd(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	80	90:10	10 (S)
15	H,H	(S)-2	Sm(OTf) <sub>3</sub>		CH <sub>2</sub> Cl <sub>2</sub>	78	80:20	racem.
16	H,H	(S)-2	Lu(OTf) <sub>3</sub>		CH <sub>2</sub> Cl <sub>2</sub>	75	75:25	racem.
17	(R)-Bn	(S)-2	Cu(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	100	99:1	>98 (S) <sup>b</sup>
18	(S)-Bn	(S)-2	Cu(OTf) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	20	>95:5	36 (S) <sup>b</sup>
19	H,H	(R)-1	Mg(ClO <sub>4</sub> ) <sub>2</sub>		CH <sub>2</sub> Cl <sub>2</sub>	>98	93:7	73 (S)
20	H,H	(R)-1	Mg(ClO <sub>4</sub> ) <sub>2</sub>	2H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	>98	95:5	73 (R)

## Chapter 5.3.6 双噁唑啉催化剂

### Various Dienes:



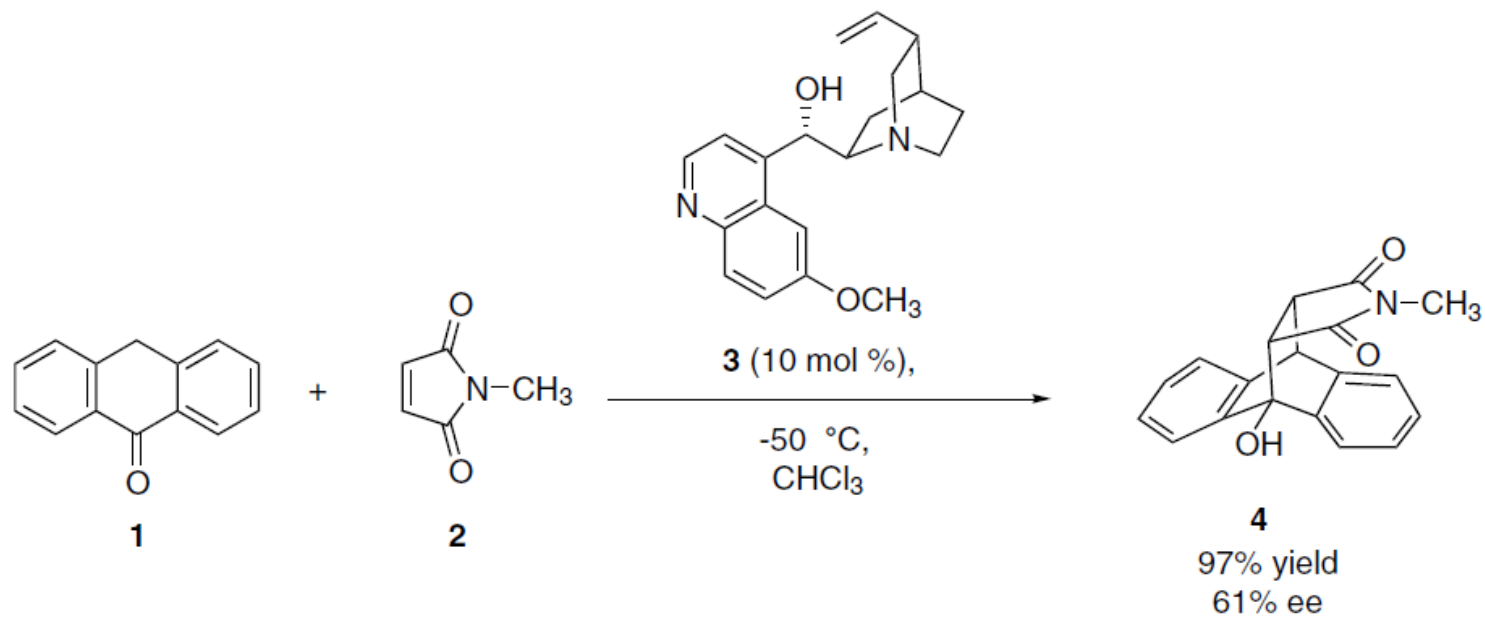
### Various Dienophiles:



K. A. Jørgensen. et al. *Chem. Rev.* **2011**, *111*, PR284–PR437.

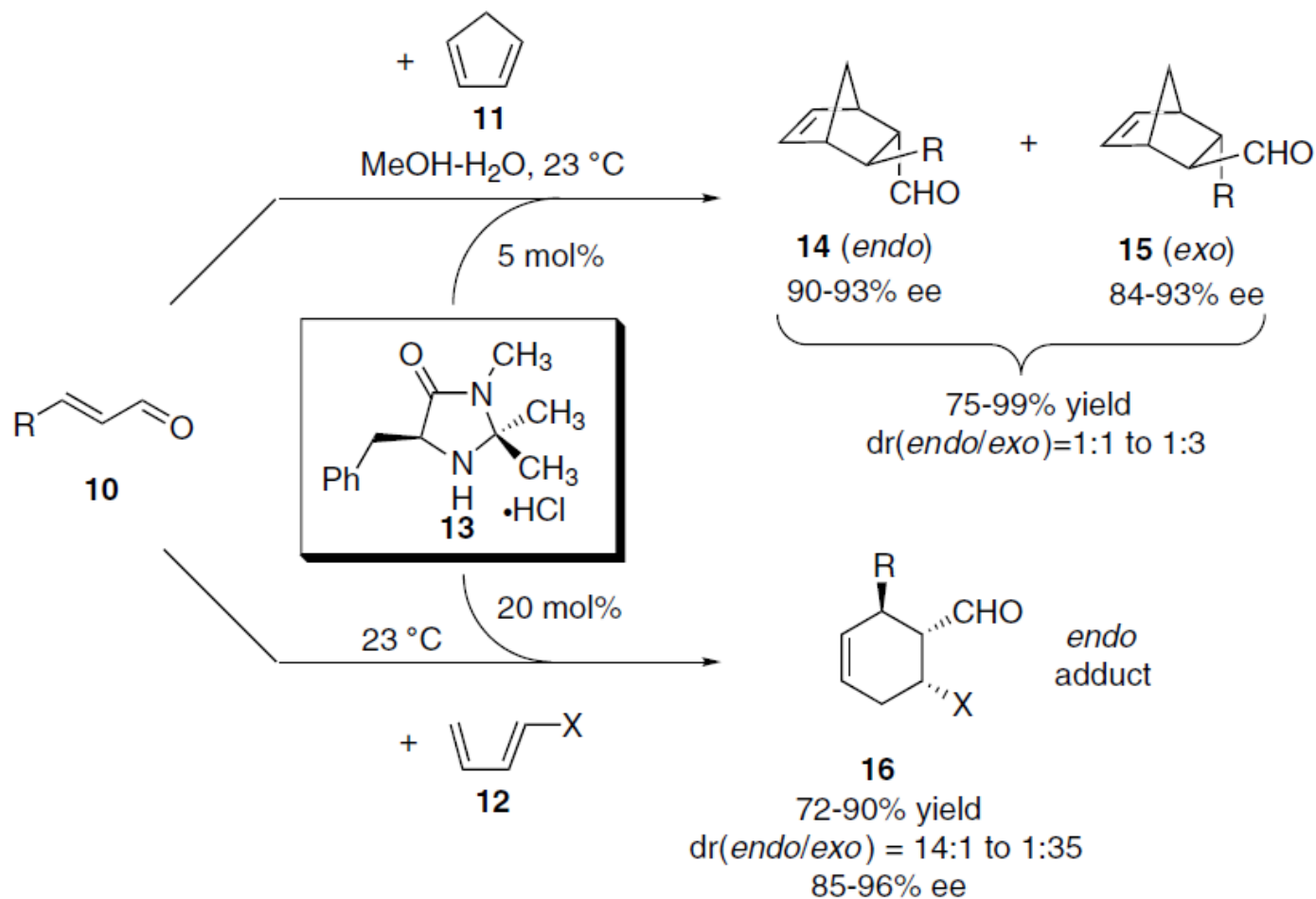
## Chapter 5.3.7 有机催化的Diels-Alder 反应

### 第一例有机催化的Diels-Alder反应



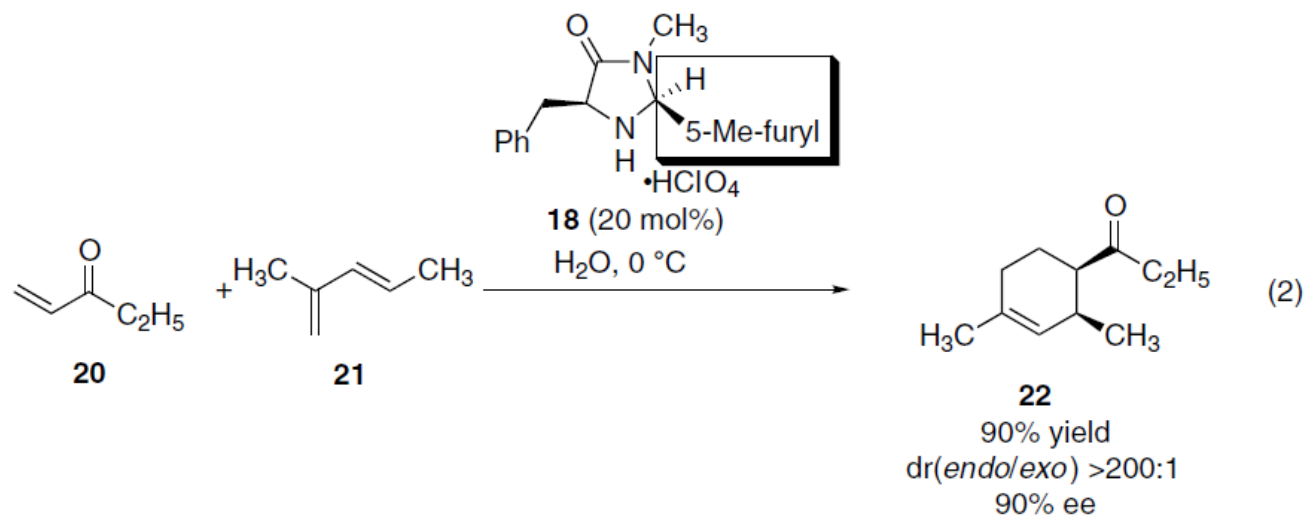
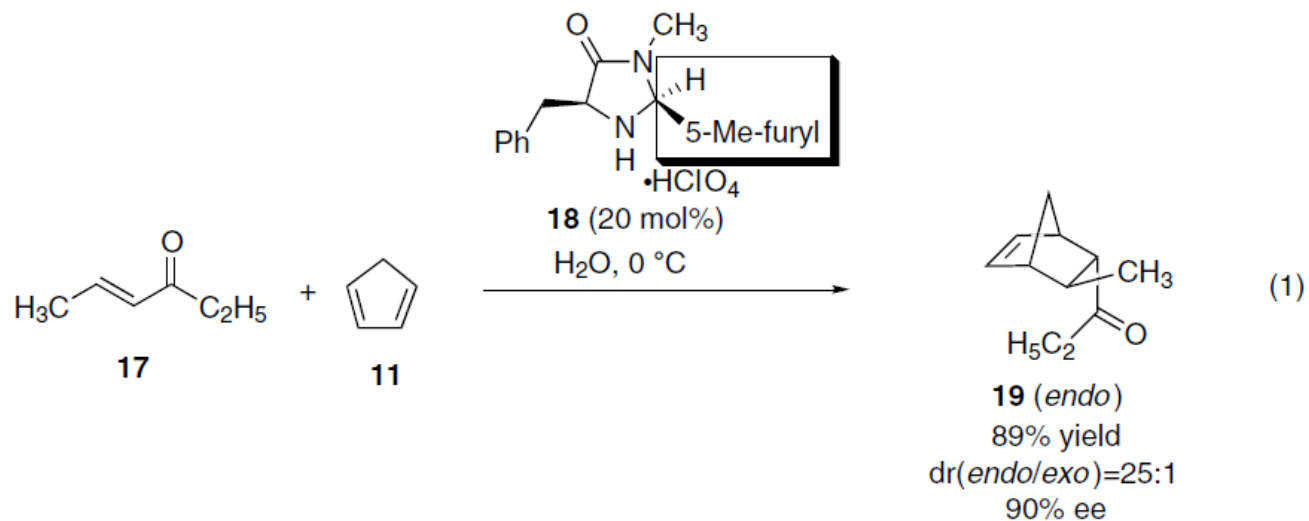
H. B. Kagan. et al. *Tetrahedron Lett.* **1989**, 30, 7403.

## Chapter 5.3.7 有机催化的Diels-Alder 反应



D. W. C. MacMillan. et al, *J. Am. Chem. Soc.* **2000**, 122, 4243.

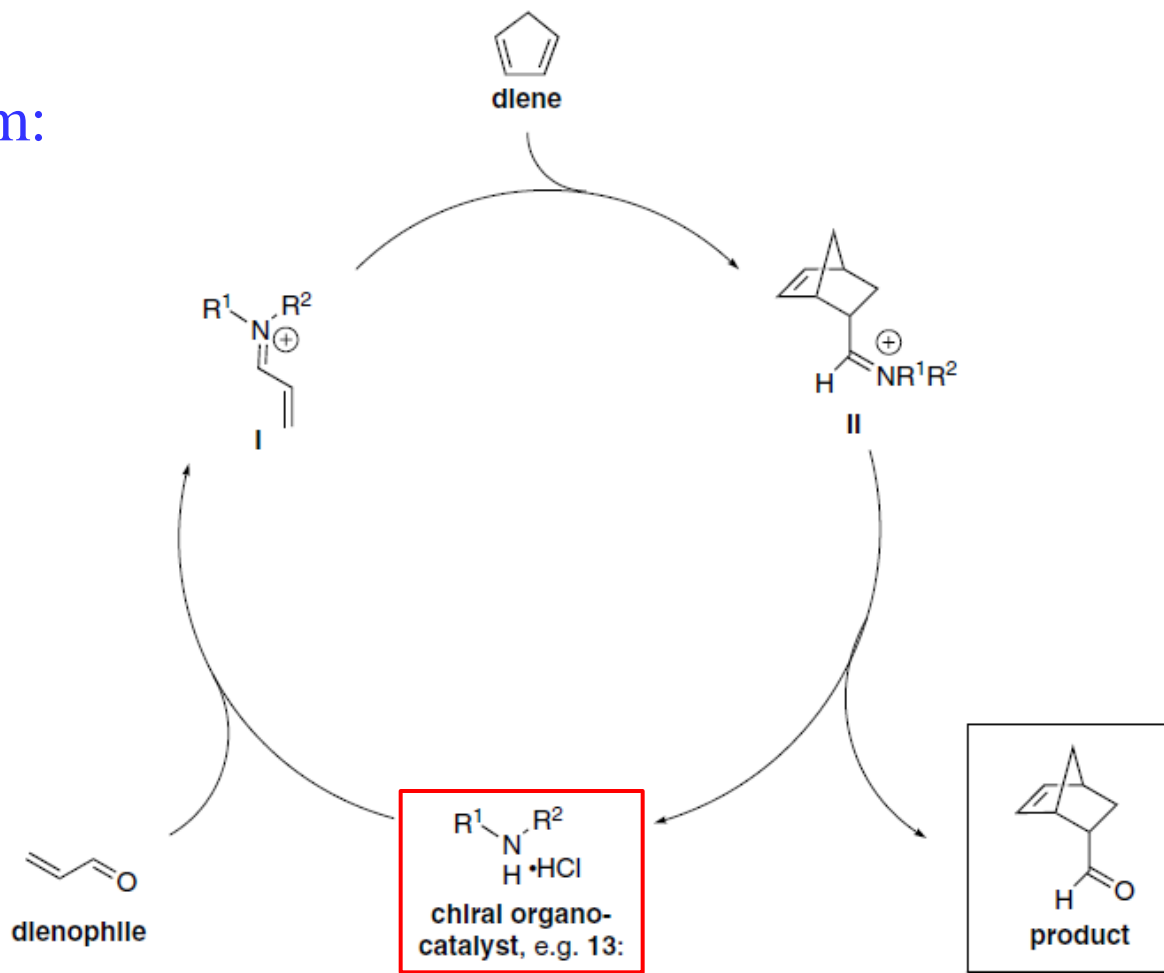
## Chapter 5.3.7 有机催化的Diels-Alder 反应



D. W. C. MacMillan. et al, *J. Am. Chem. Soc.* **2002**, 124, 2458.

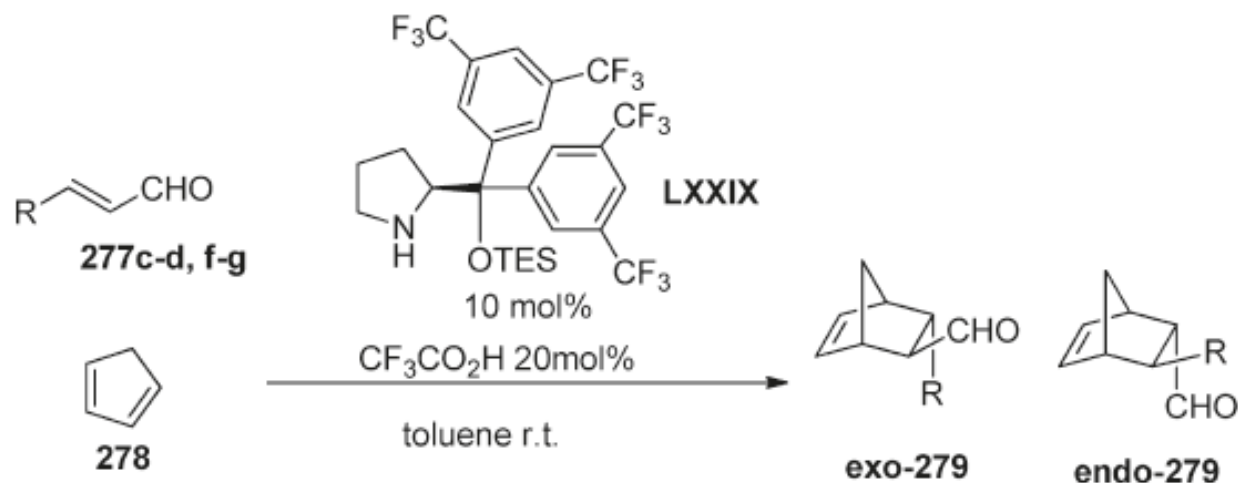
## Chapter 5.3.7 有机催化的Diels-Alder 反应

Mechanism:



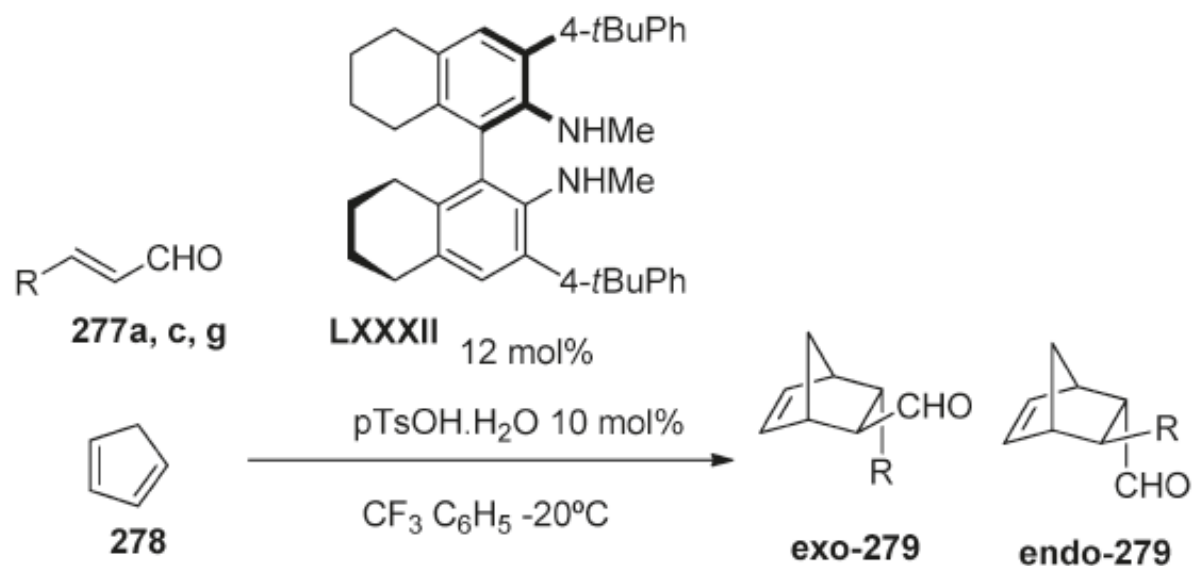
D. W. C. MacMillan. et al, *J. Am. Chem. Soc.* **2002**, 124, 2358.

## Chapter 5.3.7 有机催化的Diels-Alder 反应



**279c** R=Ph 99% 85:15 exo:endo; 97% ee exo; 88% ee endo  
**279d** R=2-furyl 89% 80:20 exo:endo; 94% ee exo; 78% ee endo  
**279f** R=n-Bu 75% 78:22 exo:endo; 94% ee exo; 91% ee endo  
**279g** R=CO<sub>2</sub>Et 92% 70:30 exo:endo; 84% ee exo; 64% ee endo

## Chapter 5.3.7 有机催化的Diels-Alder 反应

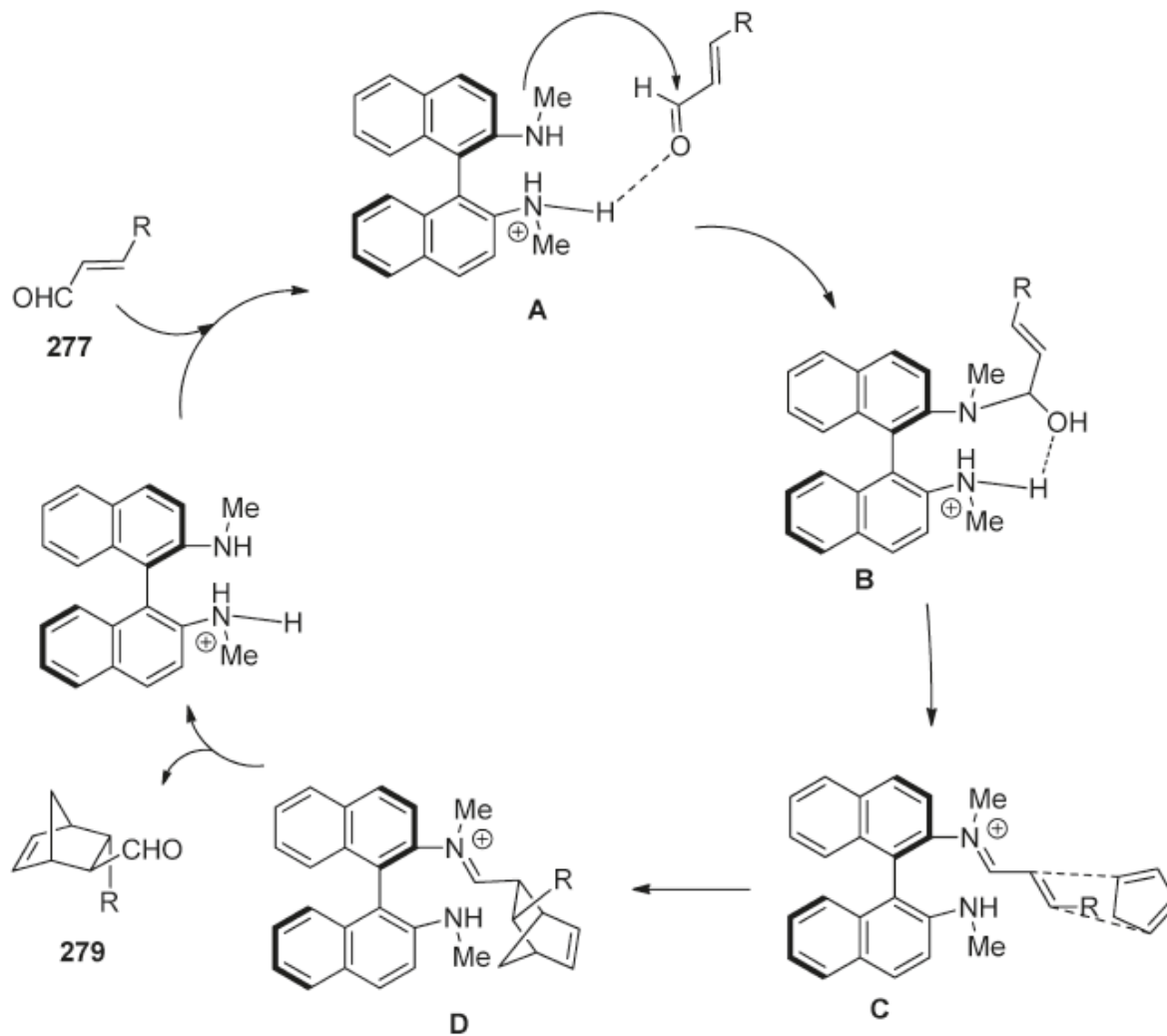


**279a** R=Me 72% >20:1 exo:endo; 88% ee exo

**279c** R=Ph 80% 13:1 exo:endo; 92% ee exo; 91% ee endo

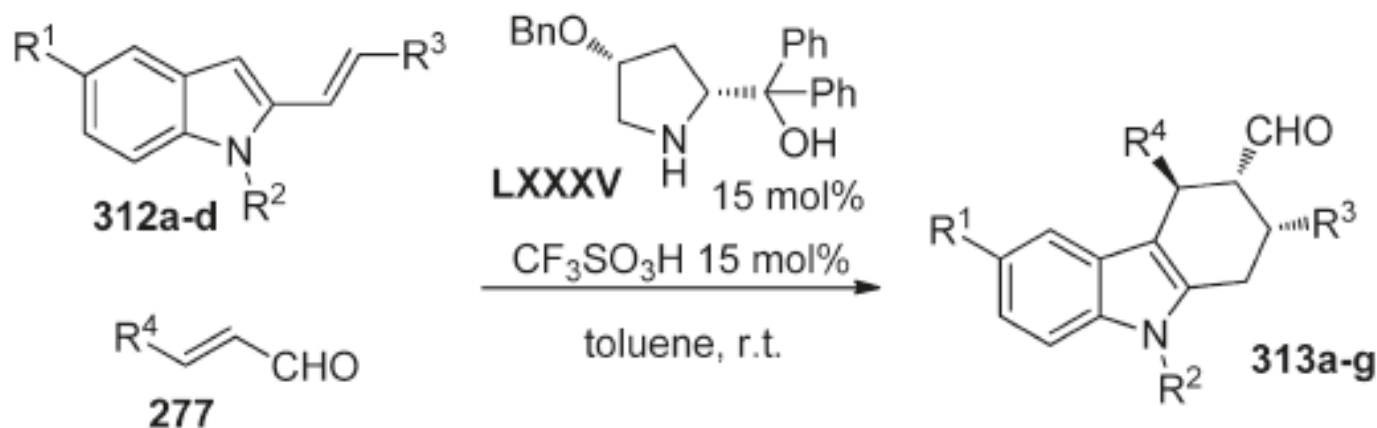
**279g** R=CO<sub>2</sub>Et 90% 5:1 exo:endo; 83% ee exo; 56% ee endo

## Chapter 5.3.7 有机催化的Diels-Alder 反应



Maruoka, K. *Org. Lett.* **2006**, *8*, 2687.

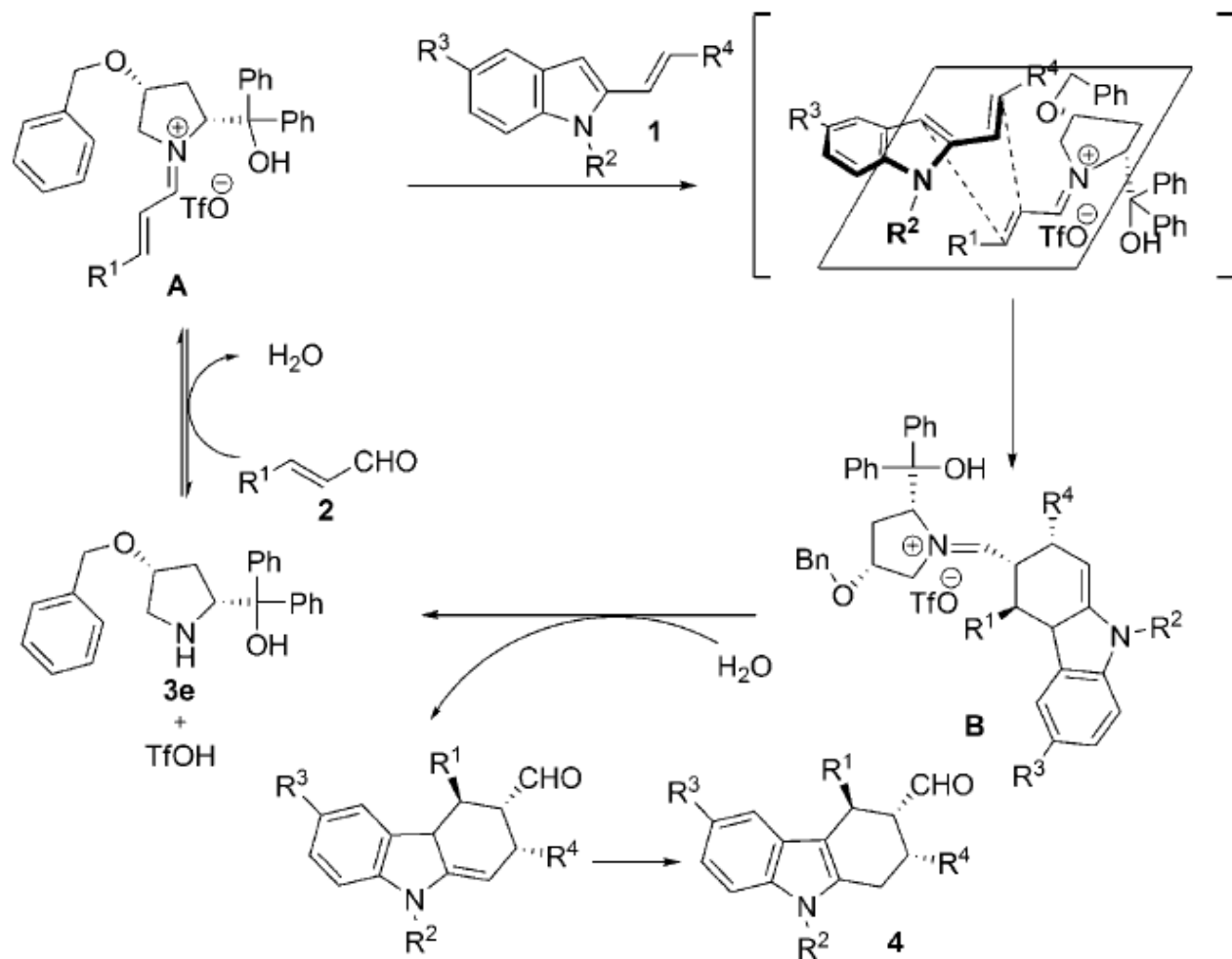
## Chapter 5.3.7 有机催化的Diels-Alder 反应



- 313a  $\text{R}^1=\text{H}$   $\text{R}^2=\text{Me}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{Ph}$  83%; 12:1 d.r.; 97% ee  
313b  $\text{R}^1=\text{H}$   $\text{R}^2=\text{Me}$   $\text{R}^3=p\text{BrC}_6\text{H}_4$   $\text{R}^4=\text{Ph}$  79%; 19:1 d.r.; 99% ee  
313c  $\text{R}^1=\text{H}$   $\text{R}^2=\text{Me}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{CO}_2\text{Et}$  72%; 12:1 d.r.; 98% ee  
313d  $\text{R}^1=\text{H}$   $\text{R}^2=\text{H}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{Ph}$  62%; 8:1 d.r.; 96% ee  
313e  $\text{R}^1=\text{H}$   $\text{R}^2=\text{allyl}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{Ph}$  66%; 6:1 d.r.; 68% ee  
313f  $\text{R}^1=\text{OMe}$   $\text{R}^2=\text{Me}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{Ph}$  76%; 12:1 d.r.; 98% ee  
313g  $\text{R}^1=\text{OMe}$   $\text{R}^2=\text{Me}$   $\text{R}^3=\text{Ph}$   $\text{R}^4=\text{Et}$  74%; 12:1 d.r.; 99% ee

Zhao, G. *Chem. Eur. J.* **2010**, *16*, 5853.

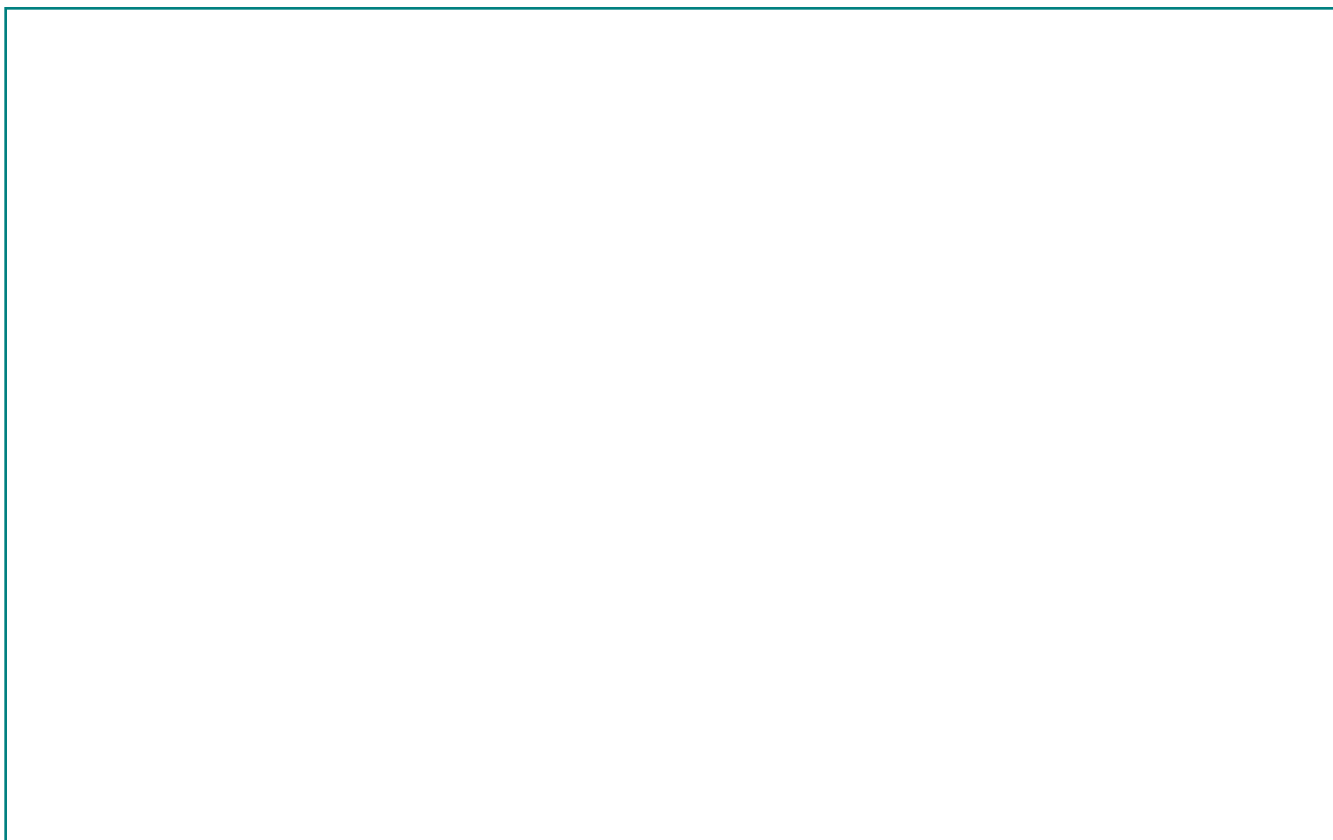
## Chapter 5.3.7 有机催化的Diels-Alder 反应



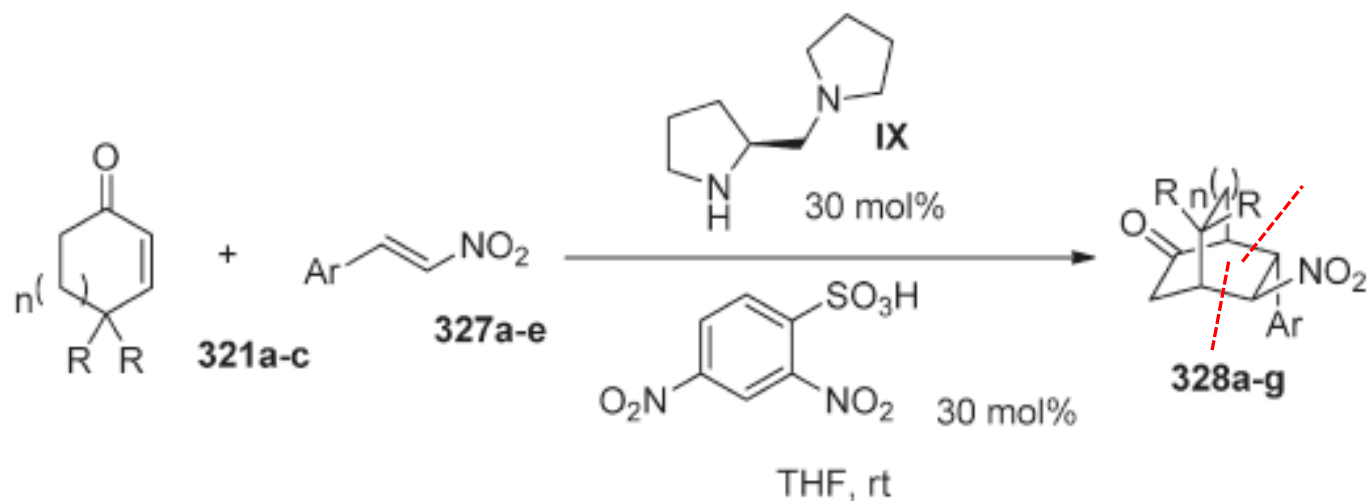
Zhao, G. *Chem. Eur. J.* **2010**, *16*, 5853.

## Chapter 5.3.7 有机催化的Diels-Alder 反应

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## Chapter 5.3.7 有机催化的Diels-Alder 反应-*Enamine Activation*



**328a**  $n=1$   $R=Me$   $Ar=Ph$  93%; >25:1 d.r.; 78% ee

**328b**  $n=1$   $R=Me$   $Ar=pOMeC_6H_4$ ; 57%; >25:1 d.r.; 75% ee

**328c**  $n=1$   $R=Me$   $Ar=pBrC_6H_4$ ; 92%; >25:1 d.r.; 77% ee

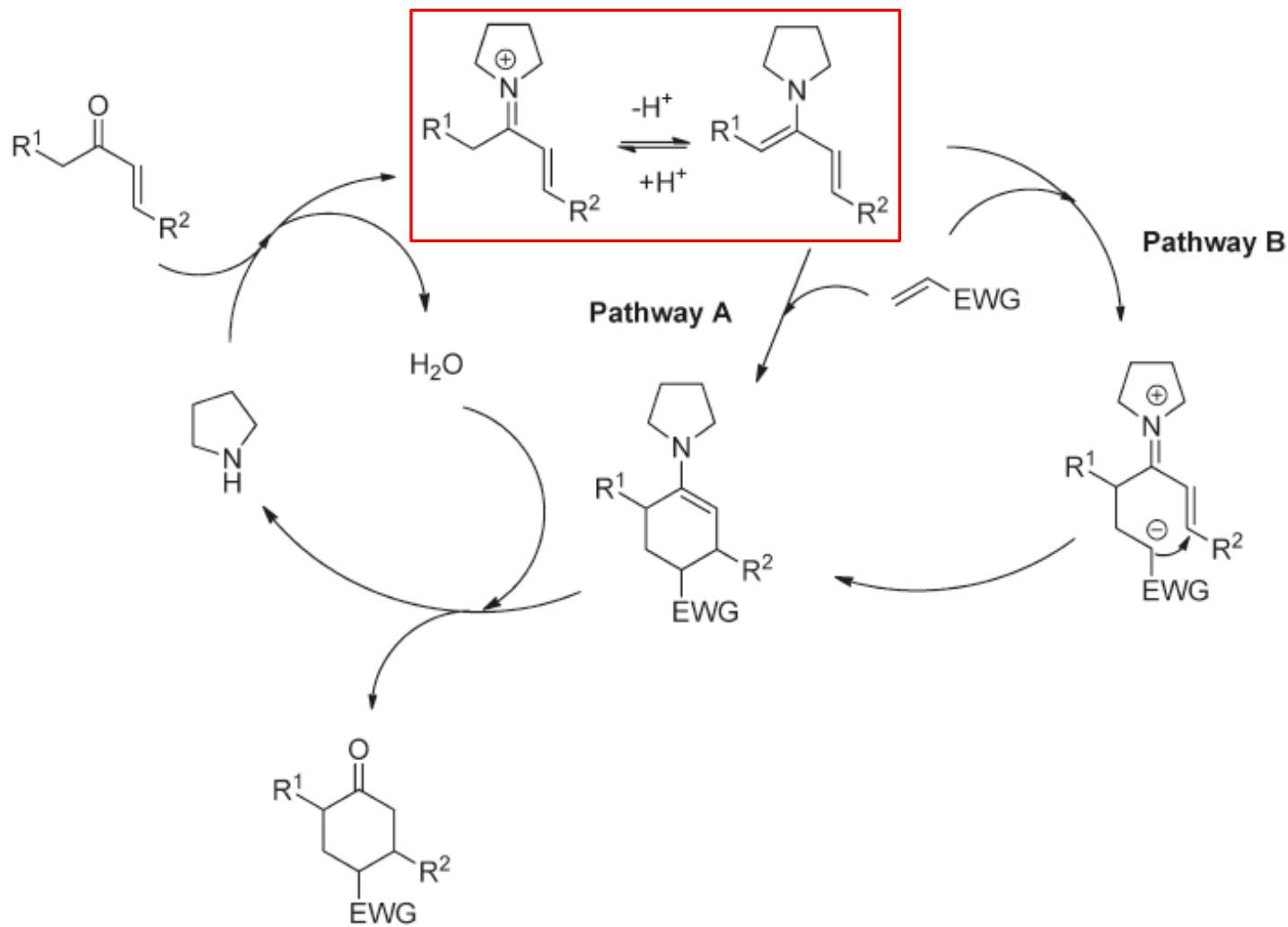
**328d**  $n=1$   $R=Me$   $Ar=mClC_6H_4$ ; 66%; >25:1 d.r.; 80% ee

**328e**  $n=1$   $R=H$   $Ar=Ph$  61%; >25:1 d.r.; 67% ee

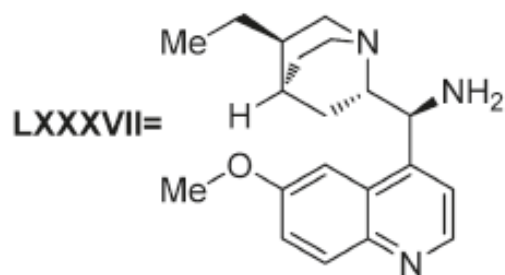
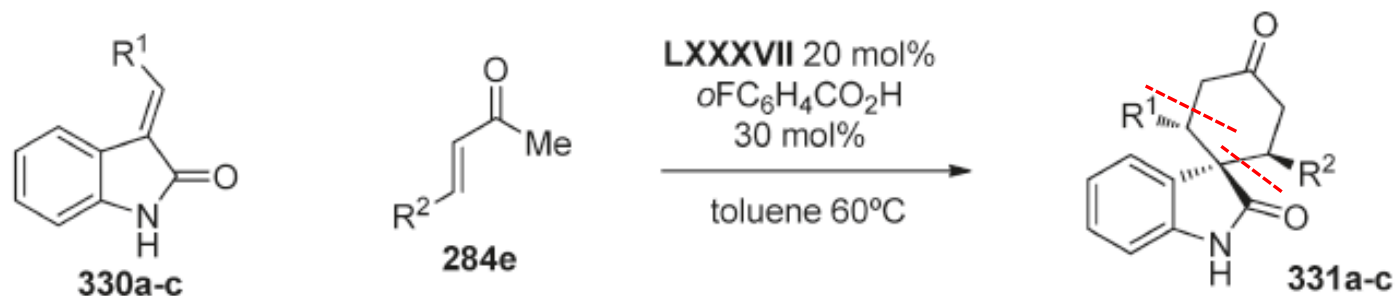
**328f**  $n=2$   $R=H$   $Ar=Ph$  80%; >25:1 d.r.; 71% ee

**328g**  $n=0$   $R=H$   $Ar=Ph$  66%; >25:1 d.r.; 32% ee

## Chapter 5.3.7 有机催化的Diels-Alder 反应-*Enamine Activation*



## Chapter 5.3.7 有机催化的Diels-Alder 反应-*Enamine Activation*



- 331a** R<sup>1</sup>=Ph R<sup>2</sup>=Ph 59%; >19:1 d.r.; 98% ee  
**331b** R<sup>1</sup>=*p*CNC<sub>6</sub>H<sub>4</sub> R<sup>2</sup>=Ph 76%; 6:1 d.r.; 92% ee  
**331c** R<sup>1</sup>=*p*ClC<sub>6</sub>H<sub>4</sub> R<sup>2</sup>=Ph 65%; 4:1 d.r.; 89% ee

Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.

## Chapter 5.4 杂Diels-Alder 反应

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前面介绍的不对称Diels-Alder反应中成环的原子都是碳原子。此外，含有杂原子的底物在一定条件下也可作为双烯体或亲双烯体发生不对称环加成反应。这类反应称为杂Diels-Alder反应。

由于生成的含氧、氮杂环产物（中间体）在天然产物及药物化学中具有重要意义，因此催化的不对称杂-Diels-Alder反应的研究备受关注。

根据反应物中所含有的杂原子的不同，这类反应可分为氧杂Diels-Alder反应、氮杂Diels-Alder反应、硫杂Diels-Alder反应等。