

手性合成——不对称反应及其应用

Chapter 5

不对称Diels-Alder 反应

陈加荣

(第8次课)

2016年4月6日

Chapter 5.4 杂Diels-Alder 反应

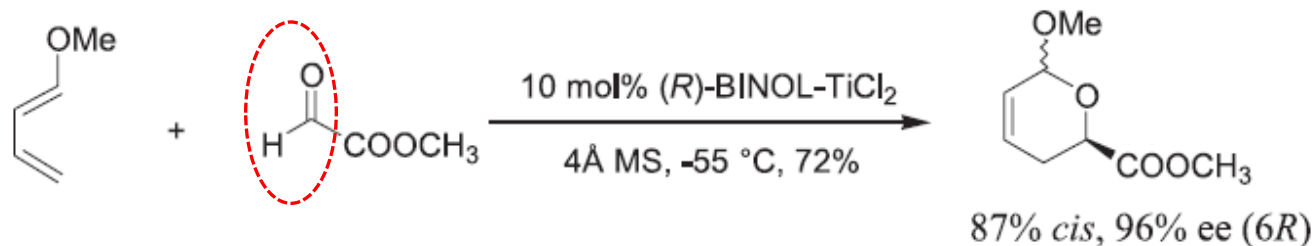
前面介绍的不对称Diels-Alder反应中成环的原子都是碳原子。此外，含有杂原子的底物在一定条件下也可作为双烯体或亲双烯体发生不对称环加成反应。这类反应称为杂Diels-Alder反应。

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。

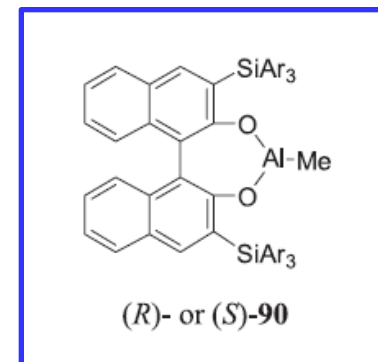
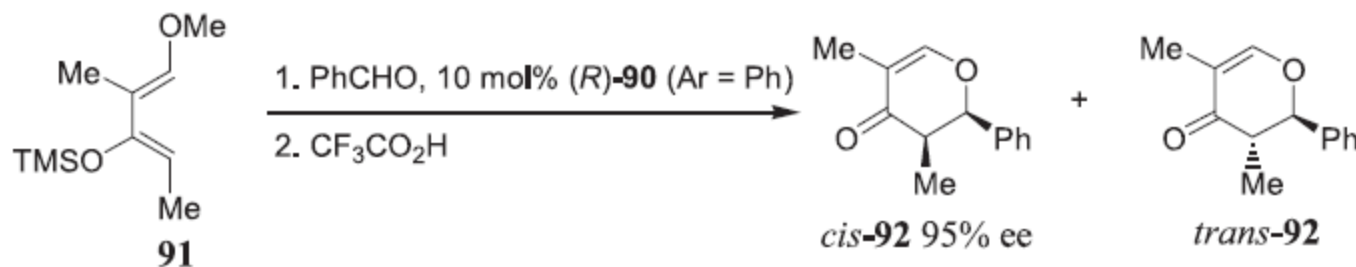
根据反应物中所含有的杂原子的不同，这类反应可分为氧杂Diels-Alder反应、氮杂Diels-Alder反应、硫杂Diels-Alder反应等。

Chapter 5.4.1 氧杂Diels-Alder 反应

含有氧原子的亲双烯体参与的Diels-Alder反应，称为氧杂Diels-Alder反应，氧杂Diels-Alder反应一般使用醛类作为反应物进行反应，使用的醛一般带有吸电子基团，或在反应中使用Lewis酸催化剂，以增加羰基的亲双烯体活性。



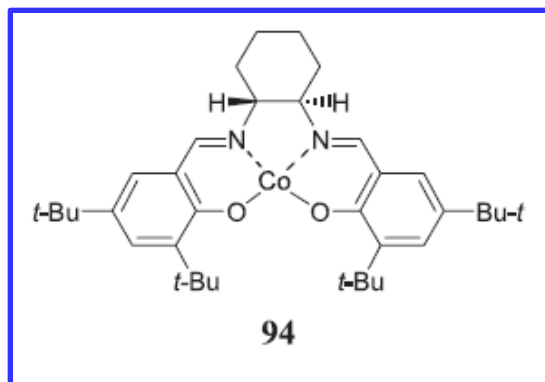
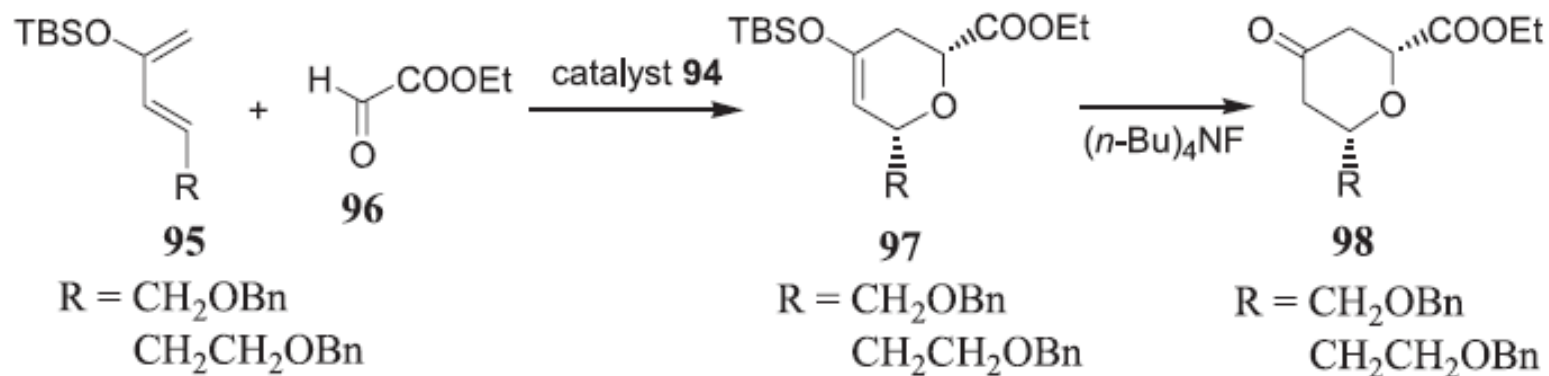
Mikami, K. *J. Am. Chem. Soc.* **1994**, *116*, 2812.



Danishefsky 双烯体

Yamamoto, H. et al. *J. Am. Chem. Soc.* **1988**, *110*, 310.

Chapter 5.4.1 氧杂Diels-Alder 反应



up to 75% yield
endo/exo > 99:1
up to 52% ee

Wu, Y. et al. *Tetrahedron Asymmetry* **1998**, 9, 2271.

Chapter 5.4.1 氧杂Diels-Alder 反应

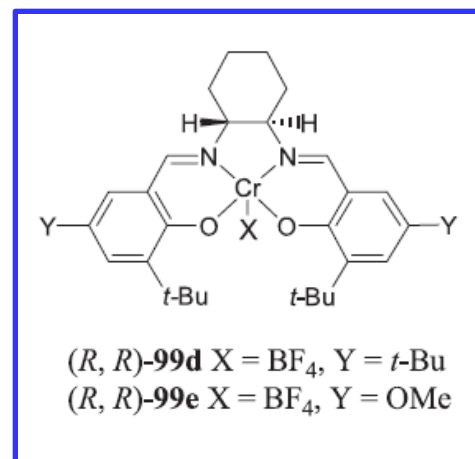
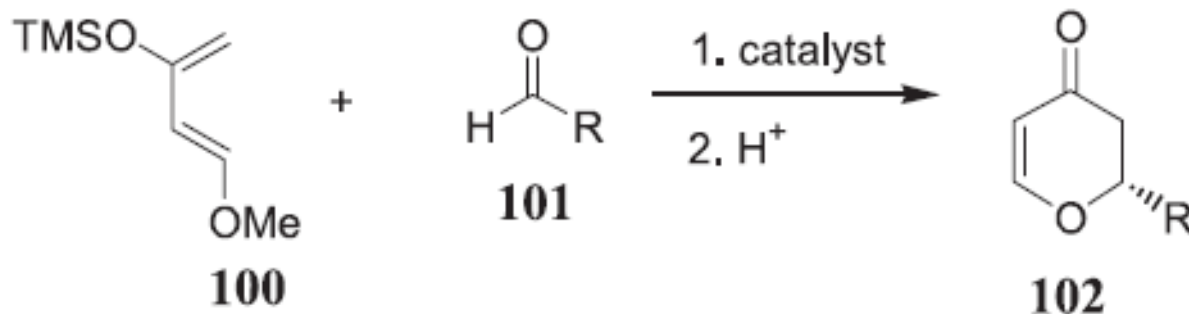
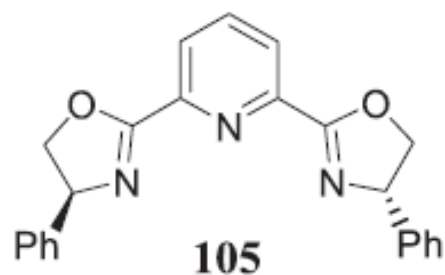
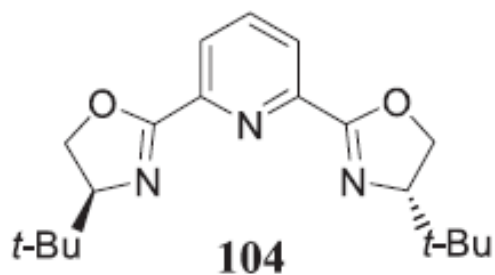
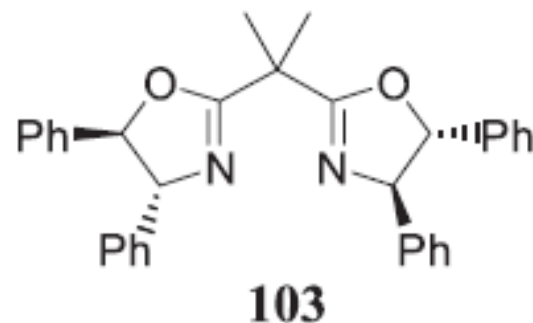
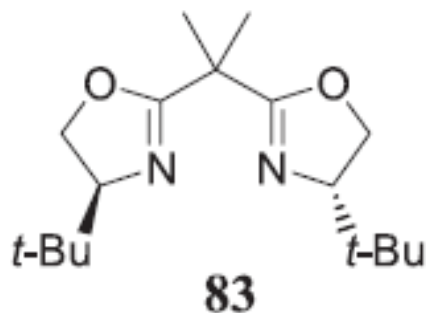
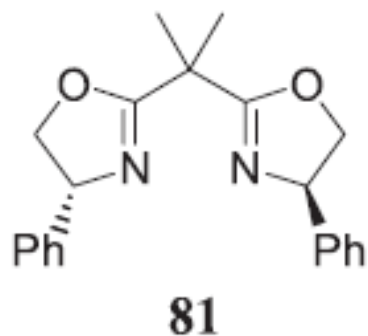


TABLE 5–5. Hetero Diels-Alder Reaction Catalyzed by **99**

Entry	R in Aldehyde	ee (%)	
		Catalyst 99d	Catalyst 99e
1	Ph	87	65
2	C ₆ H ₁₁	93	85
3	<i>n</i> -C ₅ H ₁₁	83	62
4	2-Furyl	76(99)	68
5	(<i>E</i>)-PhCH=CH	70	73(99)
6	<i>p</i> -BrC ₆ H ₄ CH ₂ OCH ₂	79	84(99)
7	<i>o</i> -ClC ₆ H ₄ COOCH ₂	83(99)	72

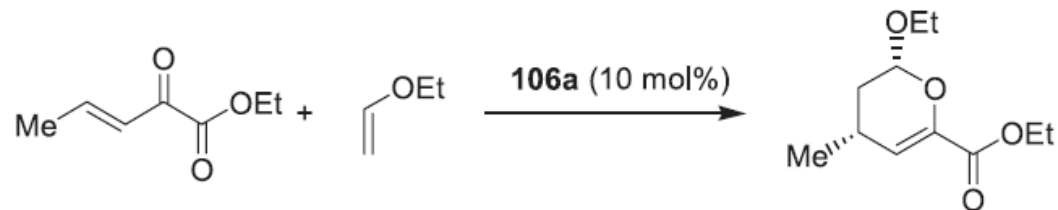
Jacobsen, E. N. et al. *J. Org. Chem.* **1998**, *63*, 403.

Chapter 5.4.1 氧杂Diels-Alder 反应

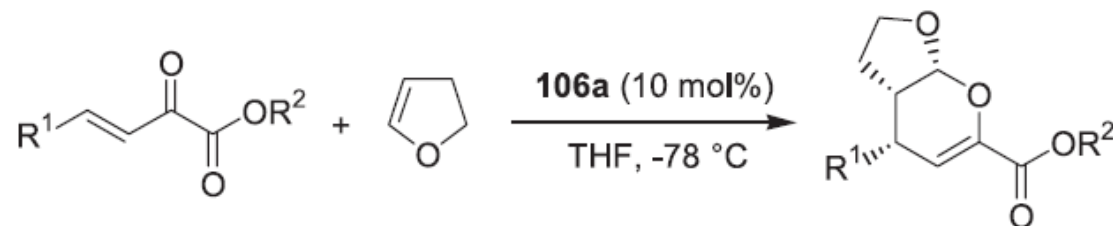


具有 C_2 对称性的双噁唑啉配体的铜配合物在不对称羟醛缩合反应及不对称Diels-Alder反应中都有较好的结果，同样，这类手性配体也可用于不对称杂Diels-Alder反应中。

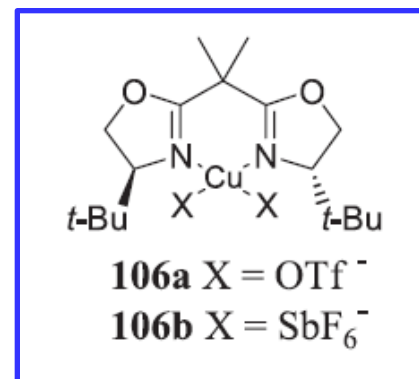
Chapter 5.4.1 氧杂Diels-Alder 反应(反电子需求)



Entry	Solvent	Temp. (°C)	Conver. (Yield, %)	ee (%)
1	CH ₂ Cl ₂	-45 °C	100	95.6
2	CH ₂ Cl ₂	-78 °C	100	97.5
3	THF	-45 °C	100	99.0
4	THF	-78 °C	100	99.7
5	CH ₃ NO ₂	-20 °C	100 (89 isolated yield)	75.8

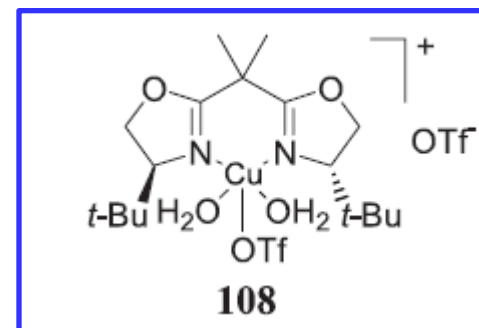
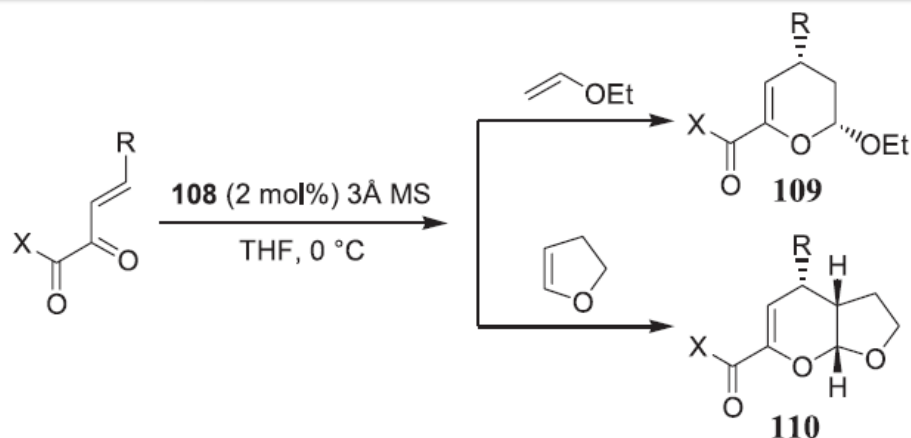


Entry	R ¹	R ²	Yield (%)	ee (%)
1	Me	Et	51	> 99.5
2	Ph	Me	96	99.5
3	OEt	Et	84	97.5



Jorgensen, K. A. et al. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2404.

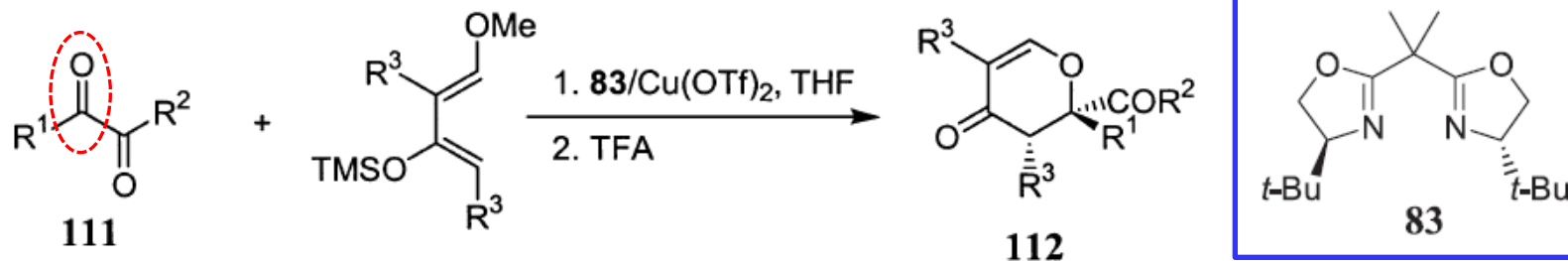
Chapter 5.4.1 氧杂Diels-Alder 反应(反电子需求)



Entry	X	R	Enol Ether	<i>endo/exo</i>	Yield (%)	ee (%)
1	OEt	Ph		> 20 : 1	93	97
2	OEt	<i>i</i> -Pr		22 : 1	95	96
3	OEt	Me		24 : 1	87	97
4	OEt	OMe		59 : 1	90	98
5	OEt	OEt		55 : 1	98	98
6	OEt	SBn		> 20 : 1	97	99
7	OEt	Ph		16 : 1	96	97
8	OEt	<i>i</i> -Pr		16 : 1	94	95
9	N(OMe)Me	Me		64 : 1	99	99

Evans, D. A. et al. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3372.

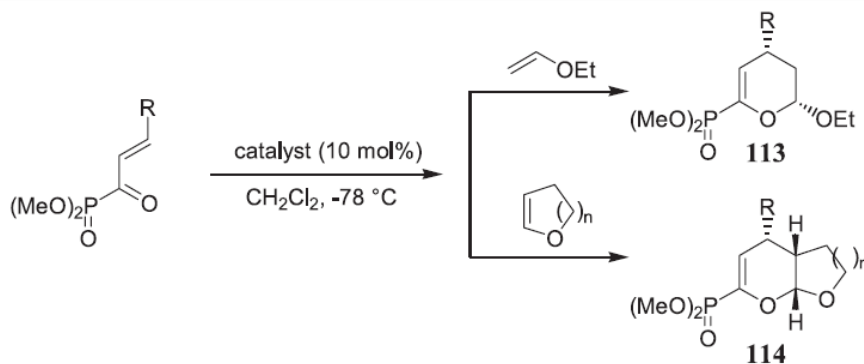
Chapter 5.4.1 氧杂Diels-Alder 反应



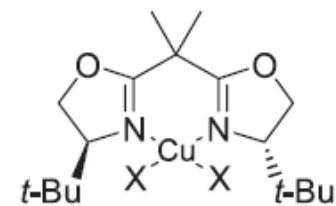
Entry	R ¹	R ²	Diene (R ³)	Catalyst (%)	Temp. (°C)	Time (h)	Yield (%)
1	Me	OMe	100 (H)	0.05	-78 to -40	20	90
2	Me	Me	100 (H)	0.05	-78	18	88
3	Me	Et	100 (H)	0.05	-78	20	76
4	Me	Ph	100 (H)	0.05	-78	20	25
5	Et	OMe	100 (H)	0.5	-78	30	70
6	Me	OMe	91 (Me)	2.5	-40	12	85
7	Ph	OEt	91 (Me)	2.5	-40	12	65
8	Me	Me	91 (Me)	2.5	-40	12	81

Jorgensen, K. A. et al. *J. Am. Chem. Soc.* **1998**, *120*, 8599.

Chapter 5.4.1 氧杂Diels-Alder 反应

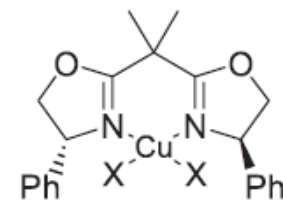


Entry	R	Enol Ether	Catalyst	<i>endo/exo</i>	Yield (%)	ee (%)
1	Me		106a	99 : 1	89	99
2	Me		106b	69 : 1	84	93
3	Me		107a	> 99 : 1	85	94
4	Me		107b	> 99 : 1	100	93
5	Me		106a	> 99 : 1	91	95
6	Me		106b	98 : 2	55	92
7	Ph		107b	167 : 1	98	98
8	Ph		107a	171 : 1	100	93
9	<i>i</i> -Pr		107b	146 : 1	99	96
10	<i>i</i> -Pr		106b	98 : 2	79	90
11	OEt		106b	> 99 : 1	98	97



106a X = OTf^-

106b X = SbF_6^-



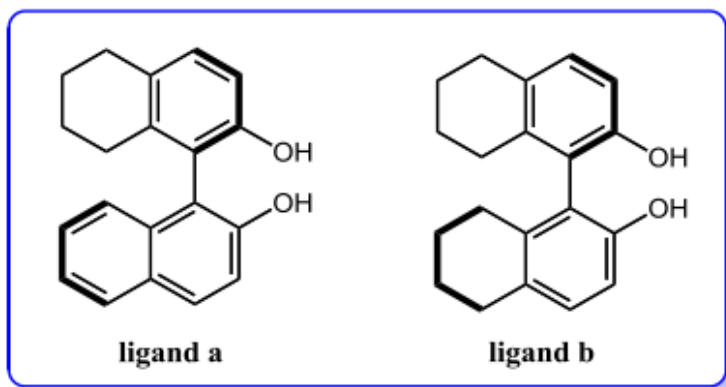
107a X = OTf^-

107b X = SbF_6^-

Evans, D. A. et al. *J. Am. Chem. Soc.* **1998**, *120*, 4895.

Chapter 5.4.1 氧杂Diels-Alder 反应

Ding:



*high-throughput screening of
a combinatorial library of
chiral titanium complexes*

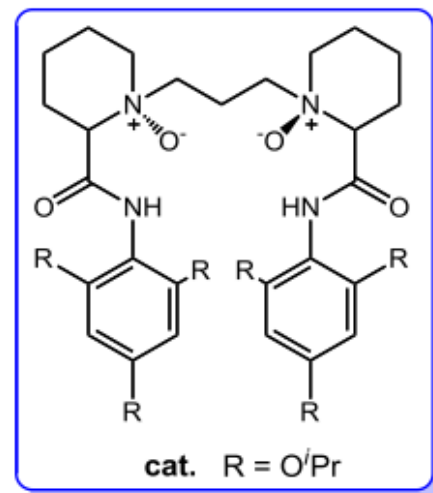
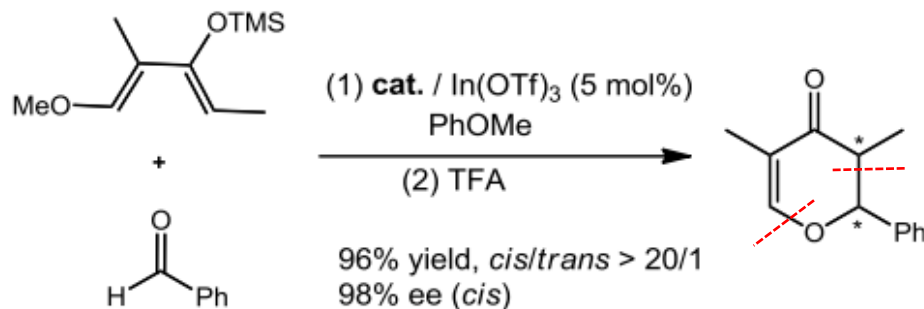


ligand a/Ti(OⁱPr)₄/**ligand a**
ligand a/Ti(OⁱPr)₄/**ligand b**

Oxo D-A ↓ **Danishefsky's diene +
a variety of aldehydes**

excellent yields and ee

Feng:

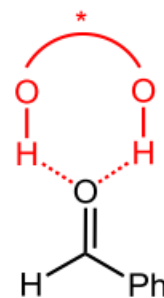
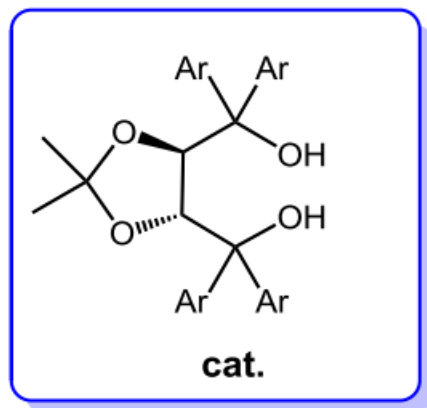
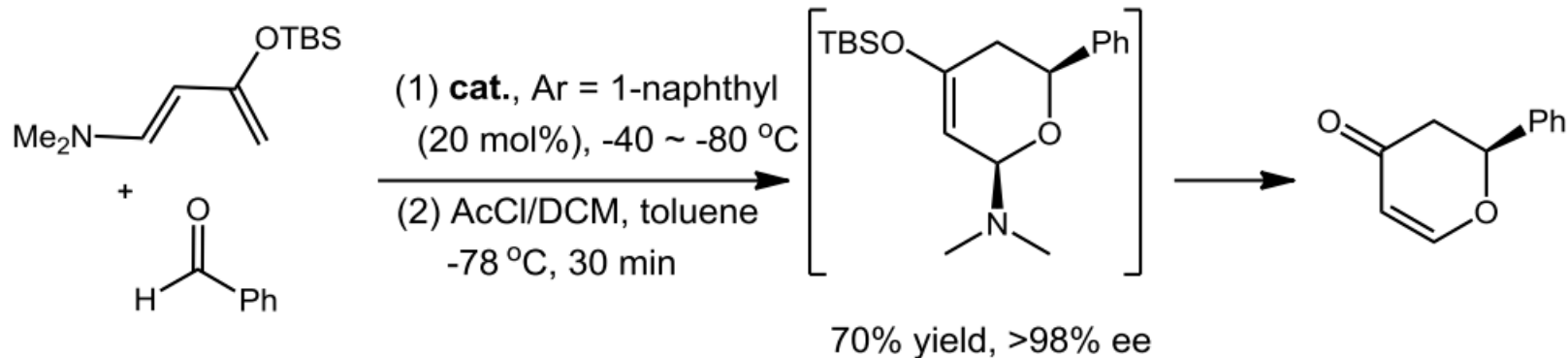


Ding, K.-L. et al. *J. Am. Chem. Soc.* **2002**, 124, 10.

Feng, X.-M. et al. *Angew. Chem. Int. Ed.* **2008**, 47, 1308.

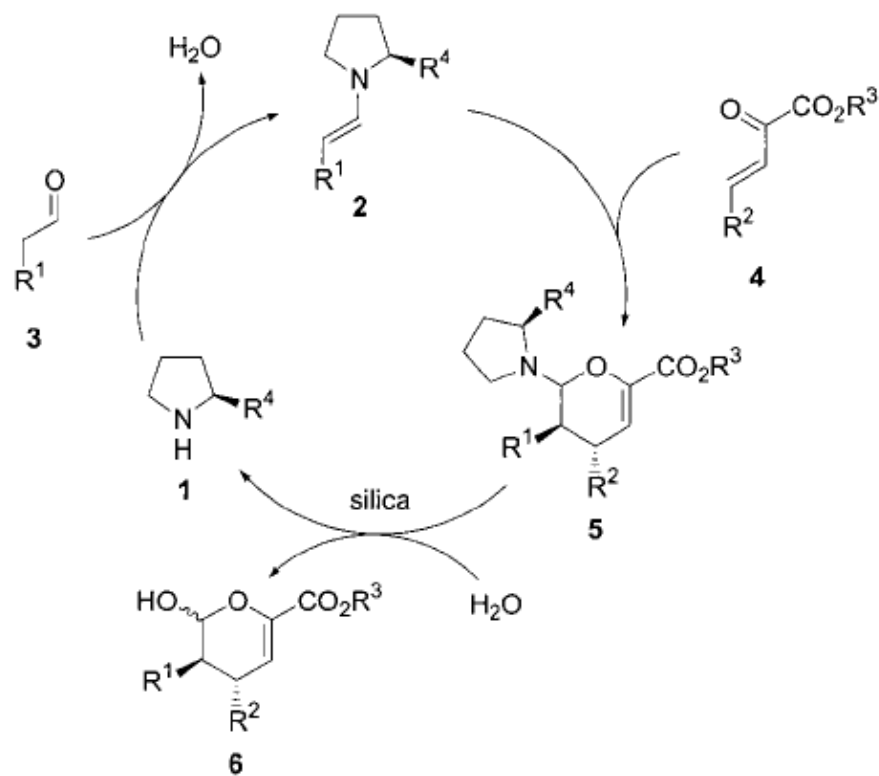
Chapter 5.4.1 氧杂Diels-Alder 反应

Oxo Diels-Alder Reactions-aldehyde as dienophile - **organocatalyst**



Rawal et al. *Nature* **2003**, 424, 146.

Chapter 5.4.1 氧杂Diels-Alder 反应(反电子需求)



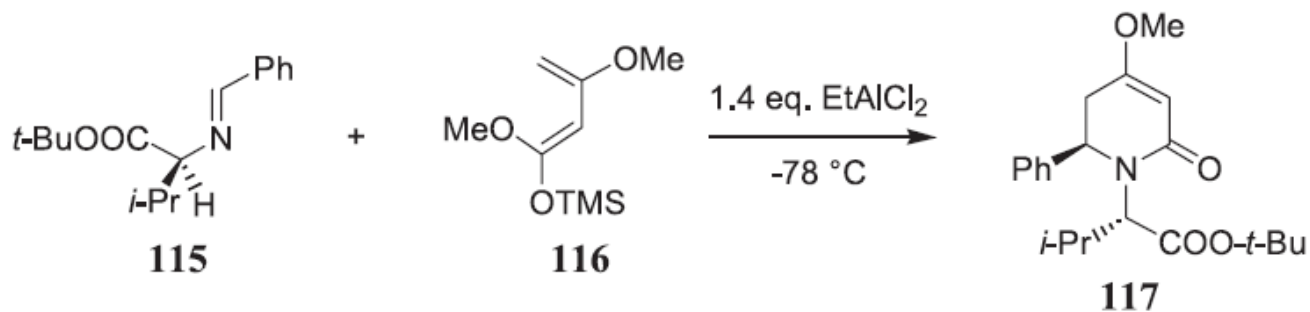
Jørgensen et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.

Chapter 5.4.1 氧杂Diels-Alder 反应(反电子需求)

Yu, X.-Y.; Chen, J.-R.; Wei, Q.; Cheng, H.-G.; Liu, Z.-C.; Xiao, W.-J.
Chem. Eur. J. **2016**, 10.1002/chem.201601227.

Chapter 5.4.2 氮杂Diels-Alder 反应

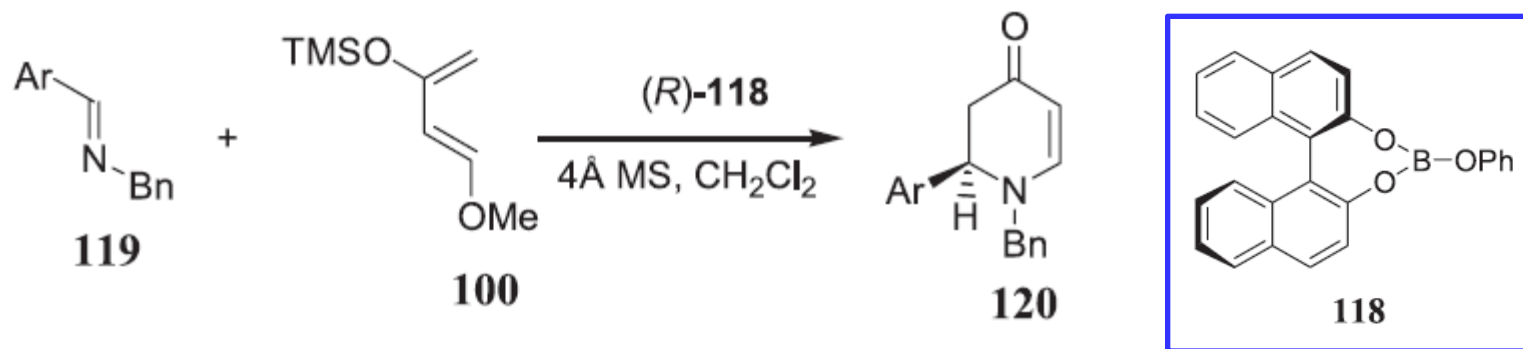
含有氮原子的亲双烯体参与的Diels-Alder反应，称为氮杂Diels-Alder反应。



Brassard 双烯体

de: up to 95%

Waldmann, H. et al. *Tetrahedron Asymmetry* **1991**, 2, 1231.

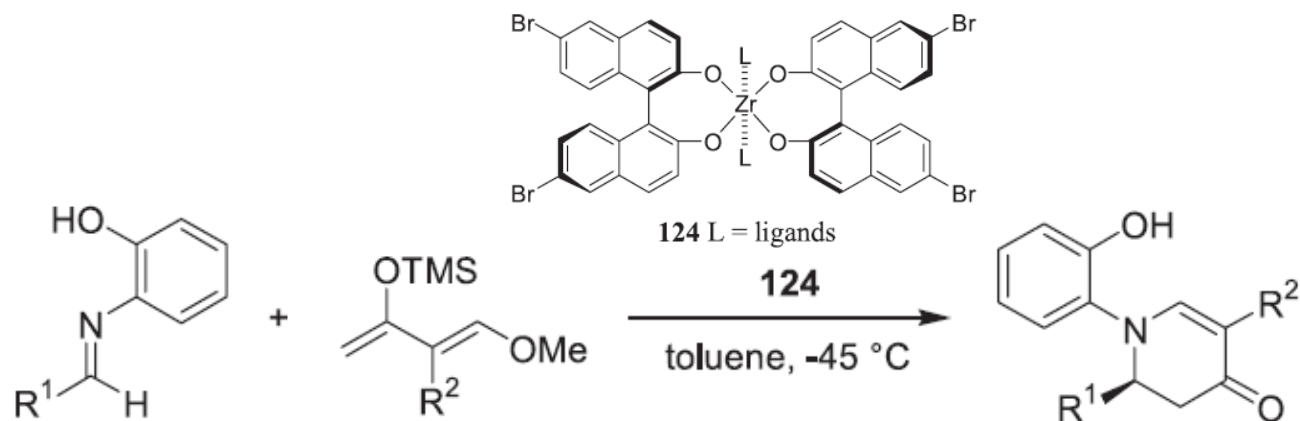


Danishefsky 双烯体

ee: up to 90%

Yamamoto, H. et al. *Tetrahedron* **1993**, 49, 1749.

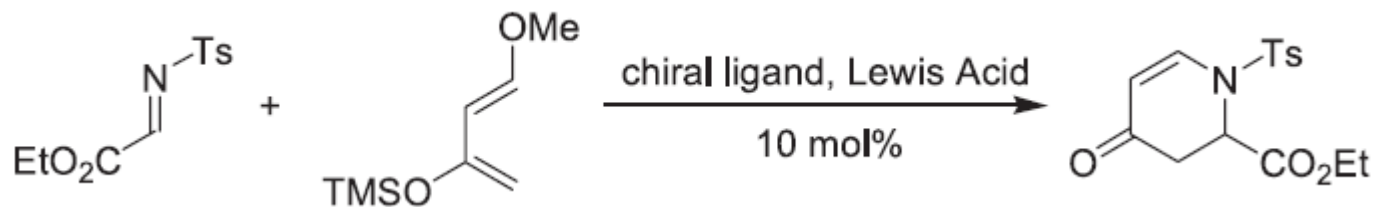
Chapter 5.4.2 氮杂Diels-Alder 反应



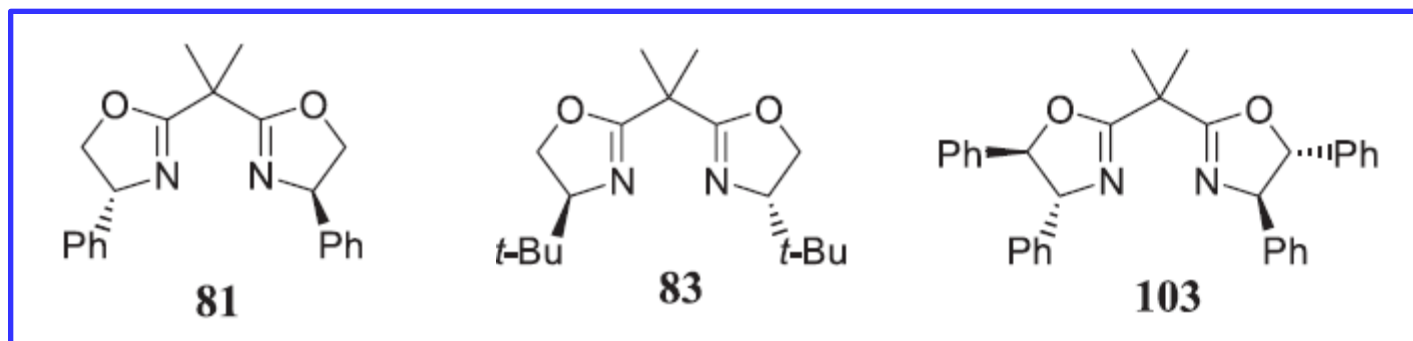
Entry	R^1	R^2	Catalyst (mol%)	Yield (%)	ee (%)
1	α -Nap	H	5	72	67
2	α -Nap	H	10	86	82
3	α -Nap	H	20	96	88
4	α -Nap	H	30	98	89
5	α -Nap	H	50	88	90
6	α -Nap	Me	10	79	89
7	α -Nap	Me	20	93	93
8	<i>o</i> -MePh	H	20	83	82

Kobayashi, S. et al. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 979.

Chapter 5.4.2 氮杂Diels-Alder 反应



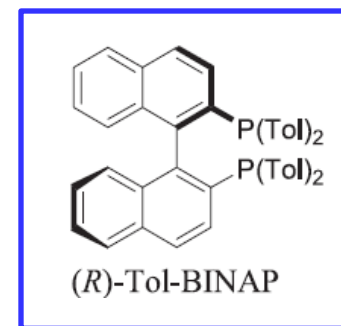
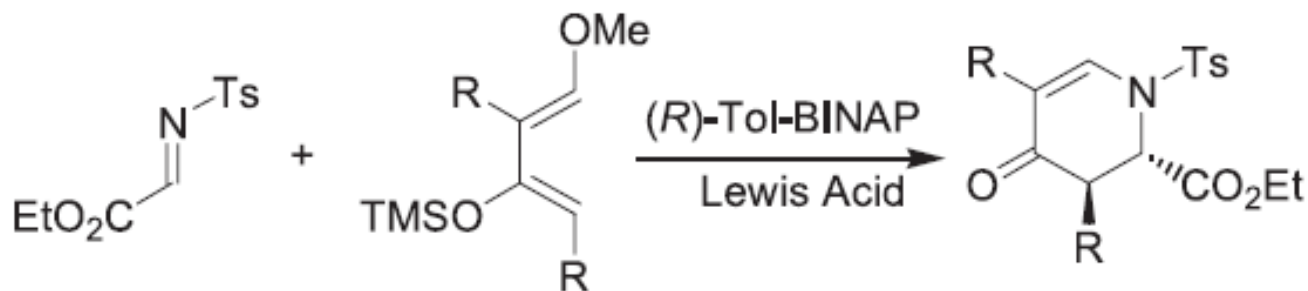
Entry	Ligand	Lewis acid	Yield (%)	ee (%)
1	81	Zn(OTf) ₂	74	17
2	83	2CuOTf·C ₆ H ₆	74	12
3	83	Cu(OTf) ₂	60	10
4	103	Zn(OTf) ₂	70	8



Chiral bis(oxazoline) ligands were not effective in the aza Diels-Alder reaction of α -imino ester with Danishefsky's diene

Jørgensen, K. A. et al. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3121

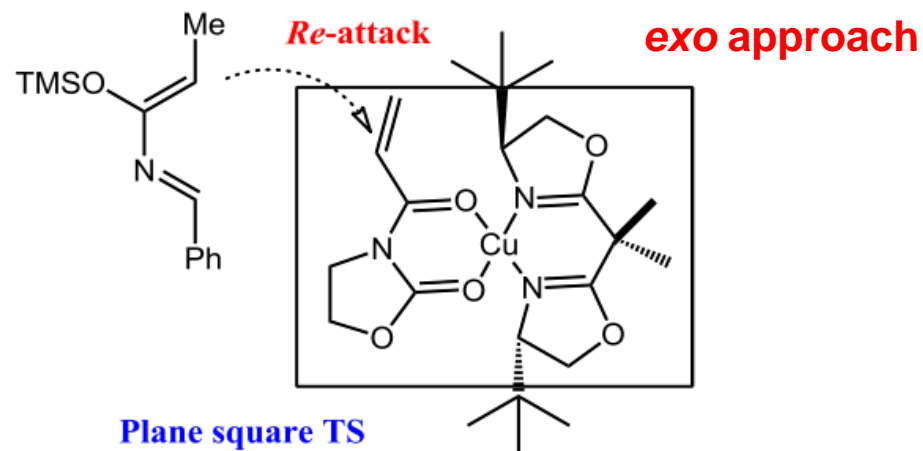
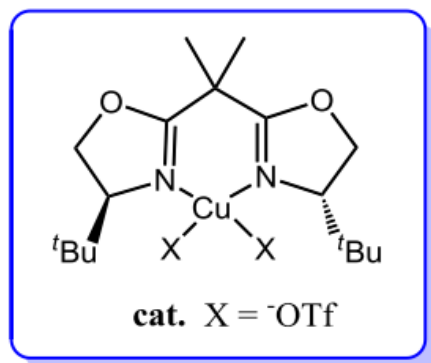
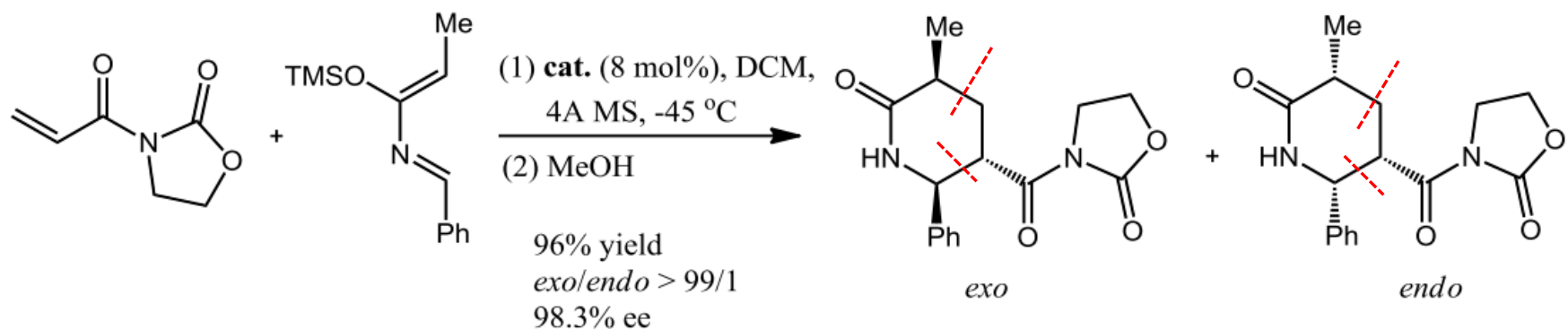
Chapter 5.4.2 氮杂Diels-Alder 反应



Entry	Lewis acid	Catalyst (mol%)	Diene (R)	Yield (%)	ee (%)
1	CuClO ₄ ·4MeCN	10	100 (H)	68	80
2	CuClO ₄ ·4MeCN	10	91 (Me)	67	94
3	CuClO ₄ ·4MeCN	5	91 (Me)	70	94
4	CuClO ₄ ·4MeCN	1	91 (Me)	70	96
5	CuClO ₄ ·4MeCN	10	91 (Me)	70	81

Jørgensen, K. A. et al. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 3121

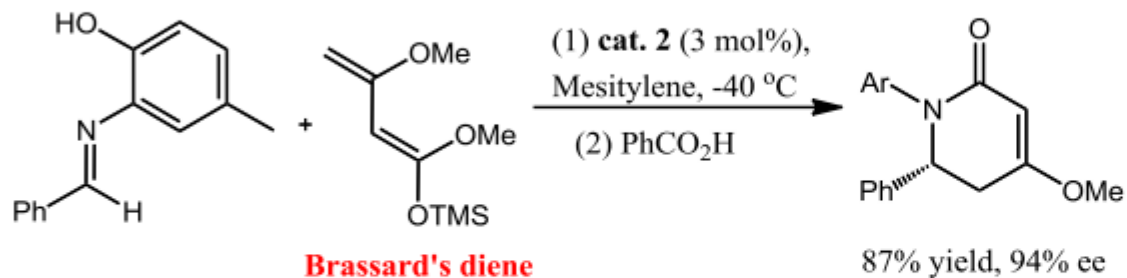
Chapter 5.4.2 氮杂Diels-Alder 反应



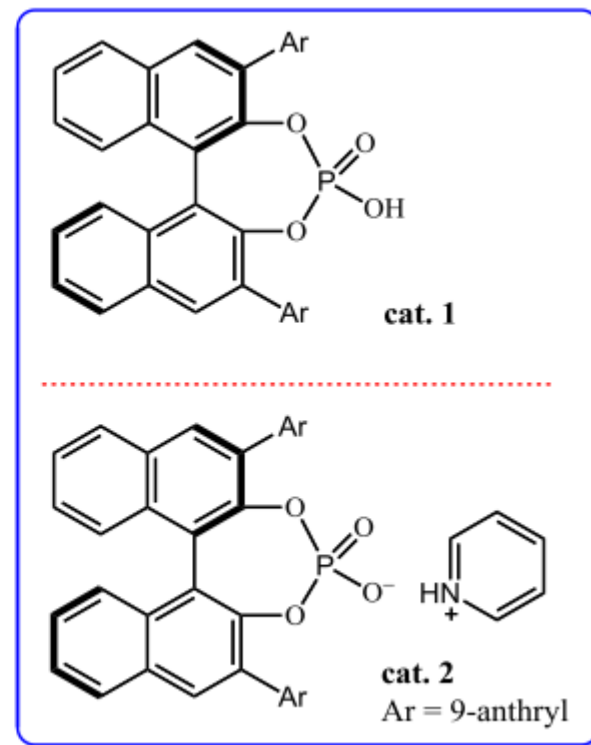
Ghosez, L. et al. *J. Am. Chem. Soc.* **1999**, 121, 2617.

Chapter 5.4.2 氮杂Diels-Alder 反应

Aza Diels-Alder Reactions.



NOTE: The Brassard's diene was not stable when acidic **cat. 1** was used. **Cat. 2** which can lower the acidity could be used in this rxn.



Akiyama *et. al.* *Angew. Chem. Int. Ed.* **2006**, 45, 4796.

Chapter 5.4.2 氮杂Diels-Alder 反应

反转电子要求的氮杂Diels-Alder 反应：

即缺电子的氮杂双烯与富电子的烯烃的环加成反应



Xiaoming Feng et al. *Angew. Chem. Int. Ed.* **2010**, 49, 3799.

Chapter 5.4.2 氮杂Diels-Alder 反应

反转电子要求的氮杂Diels-Alder 反应

Akiyama *et. al.* *J. Am. Chem. Soc.* **2006**, *128*, 13070.

Chapter 5.4.2 氮杂Diels-Alder 反应

反转电子要求的氮杂Diels-Alder 反应(Povarov反应)

Zhu, J. P. *et. al. J. Am. Chem. Soc.* **2009**, *131*, 4598.

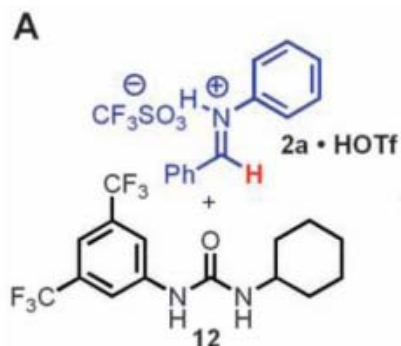
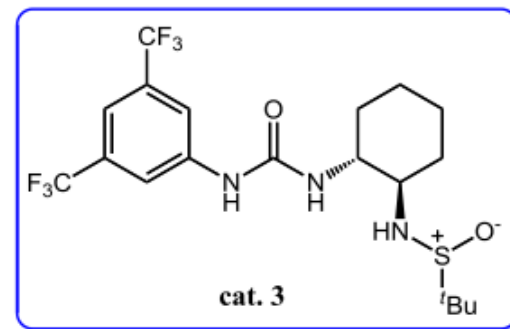
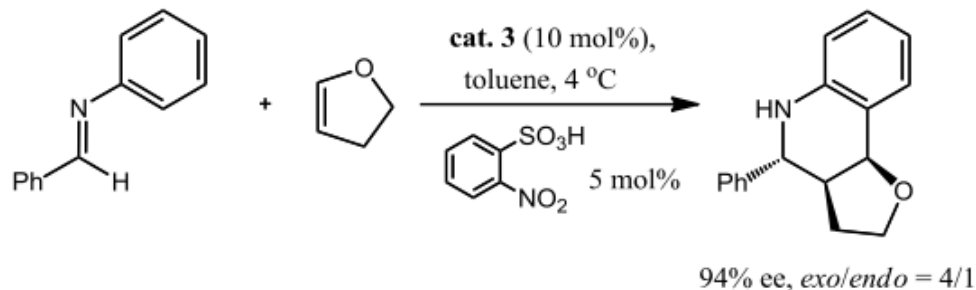
Chapter 5.4.2 氮杂Diels-Alder 反应

反转电子要求的氮杂Diels-Alder 反应

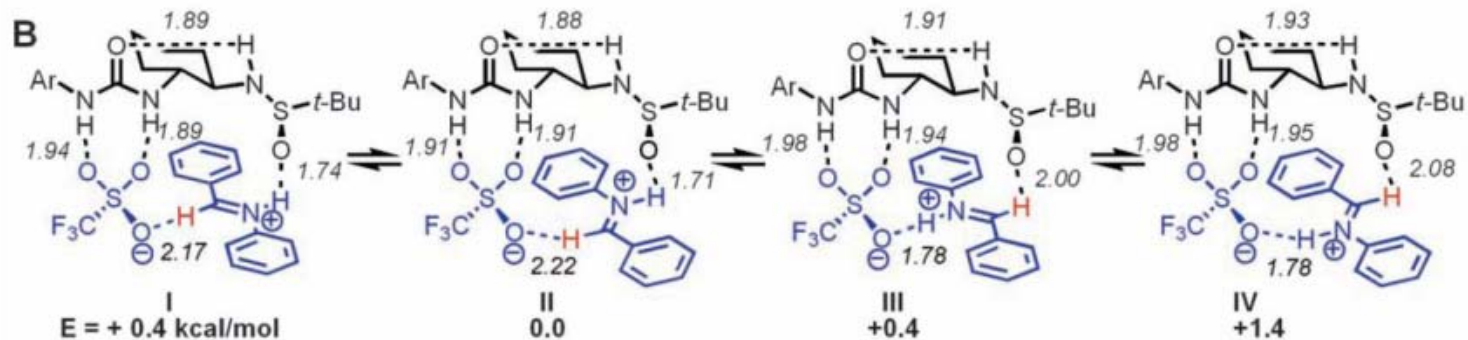
Ricci, A. *et. al. Chem. Commun.* **2010**, 46, 327.

Chapter 5.4.2 氮杂Diels-Alder 反应

反转电子要求的氮杂Diels-Alder 反应

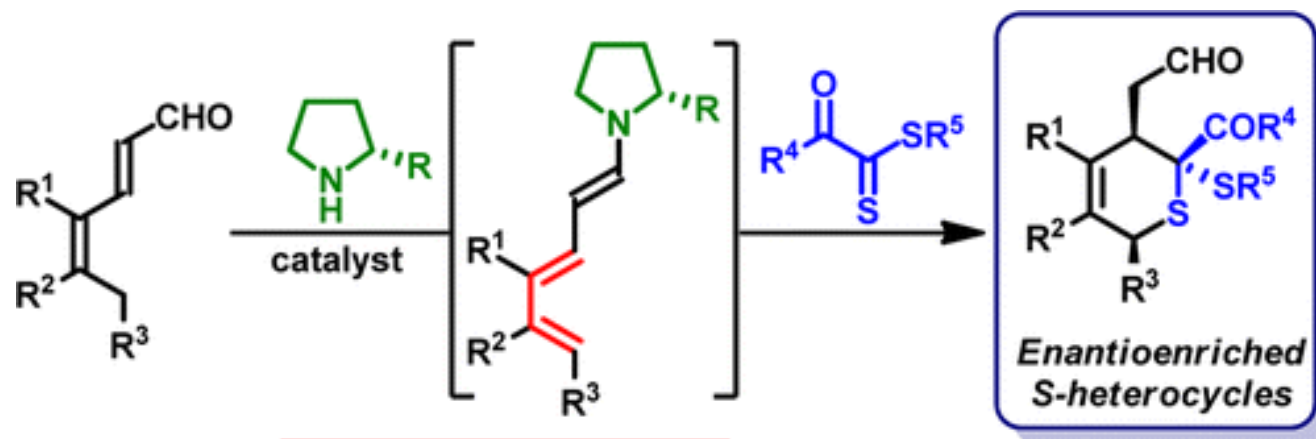


complex	Formyl ¹ H NMR shift (ppm)
2a · HOTf	7.99
2a · HOTf · 12	7.85
2a · HOTf · 1a	8.91



Jacobsen, E. N. *et al.* *Science*. **2010**, 327, 986.

Chapter 5.4.3 硫杂Diels-Alder 反应



In situ generated "dienes"

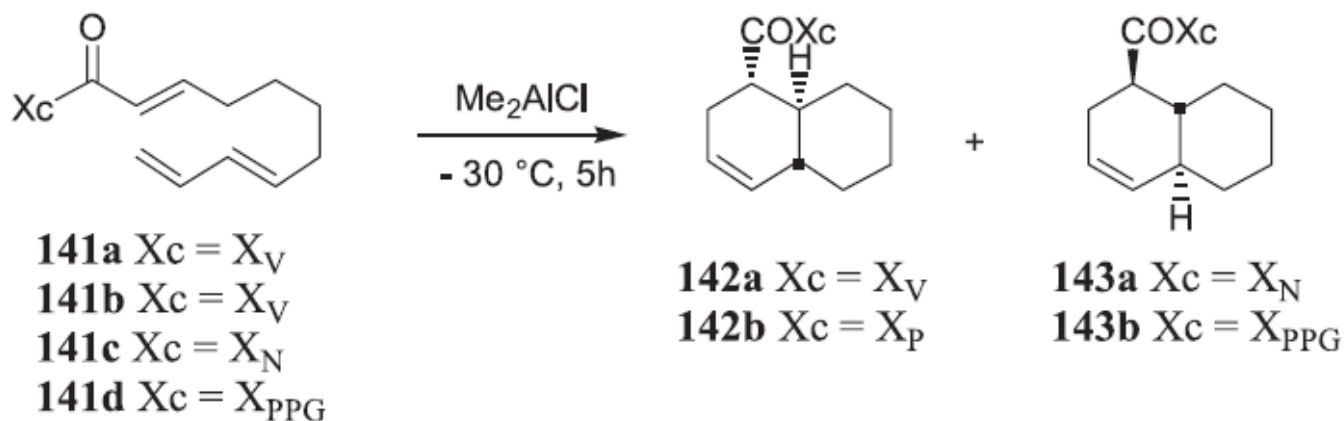
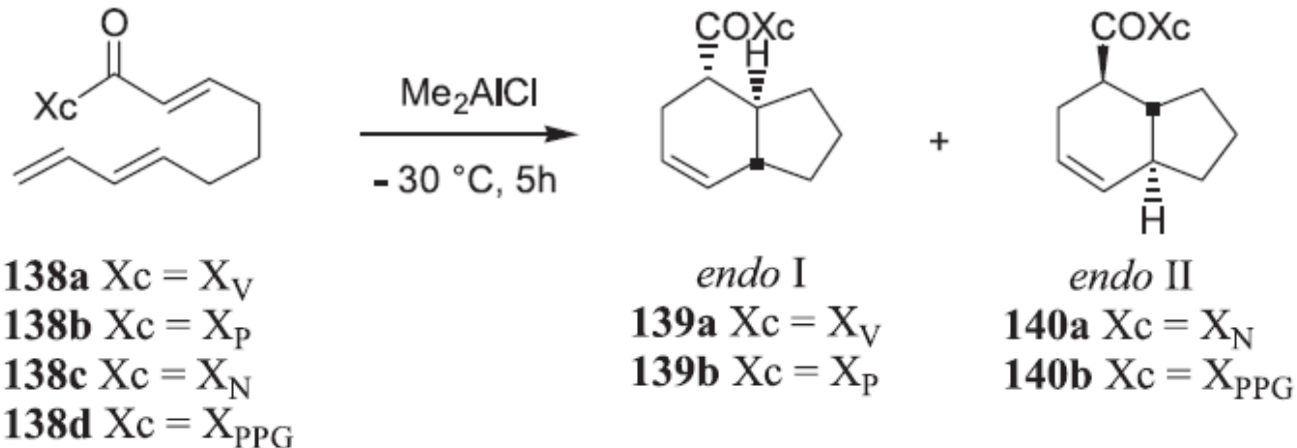
- ❑ Chiral catalyst linked to the diene
- ❑ No reactivity in the absence of catalyst

up to >95:5 dr, 97% ee

Jørgensen, K. A. et al. *J. Am. Chem. Soc.* **2013**, 135, 5200.

Chapter 5.5 分子内Diels-Alder 反应

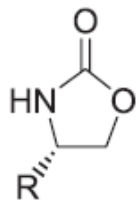
前面介绍的是分子间的Diels-Alder 反应，这类反应在制备有机合成的重要中间体中起到了很大的作用。此外，分子内的Diels-Alder 反应也是制备天然产物合成的中间体重要方法之一。



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

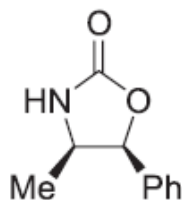
Chapter 5.5 分子内Diels-Alder 反应

手性辅剂Xc:

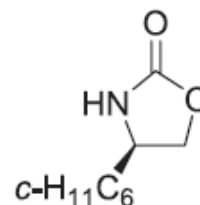


144a R = (CH₃)₂CH- (HX_V)

144b R = PhCH₂- (HX_P)



145 HX_N

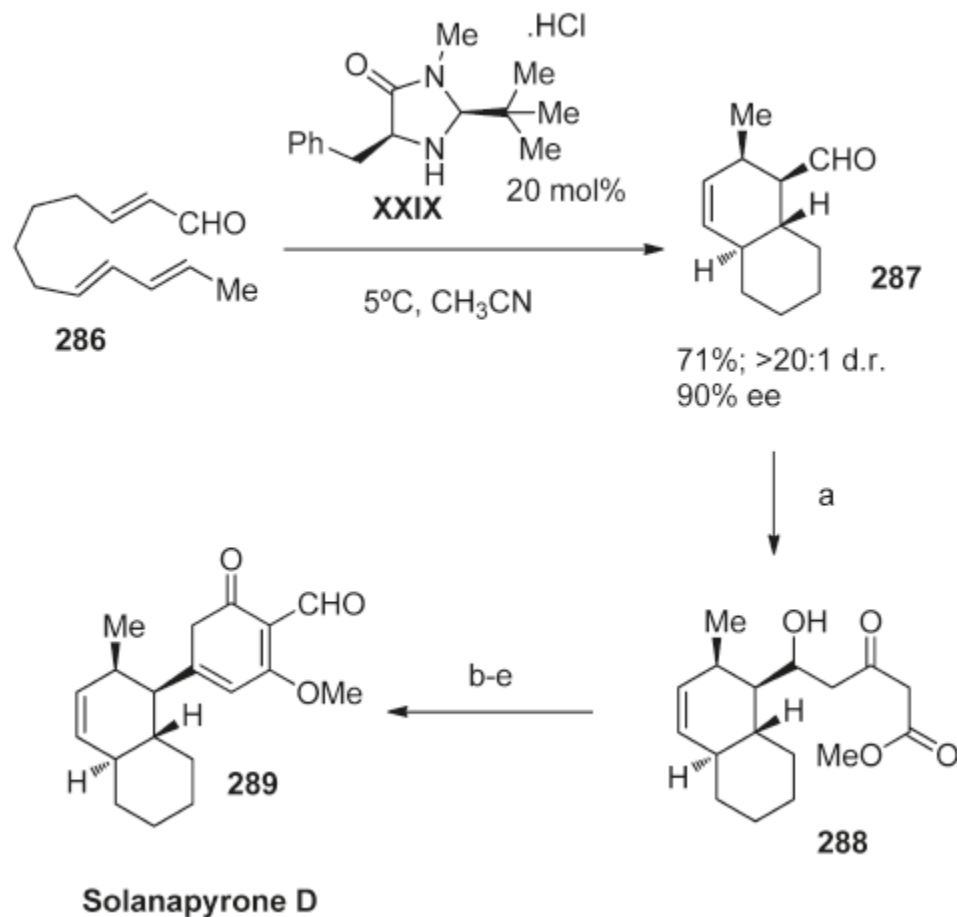


146 HX_{PPG}

Imide (Xc)	<i>endo</i> I: <i>endo</i> II	<i>endo</i> : <i>exo</i>	Purified Ratio	Yield (%)
138a (X _V)	83:17	>99:1	>99:1	60 (139a)
138b (X _P)	95:5	>99:1	>99:1	73 (139b)
138c (X _N)	15:85	>99:1	>99:1	70 (140a)
138d (X _{PPG})	3:97	>99:1	>99:1	65 (140a)
141a (X _V)	92:8	>30:1	>99:1	65 (142a)
141b (X _P)	97:3	>50:1	>99:1	88 (142b)
141c (X _N)	9:91	>50:1	>99:1	70 (143a)
141d (X _{PPG})	6:94	>30:1	>99:1	70 (143b)

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

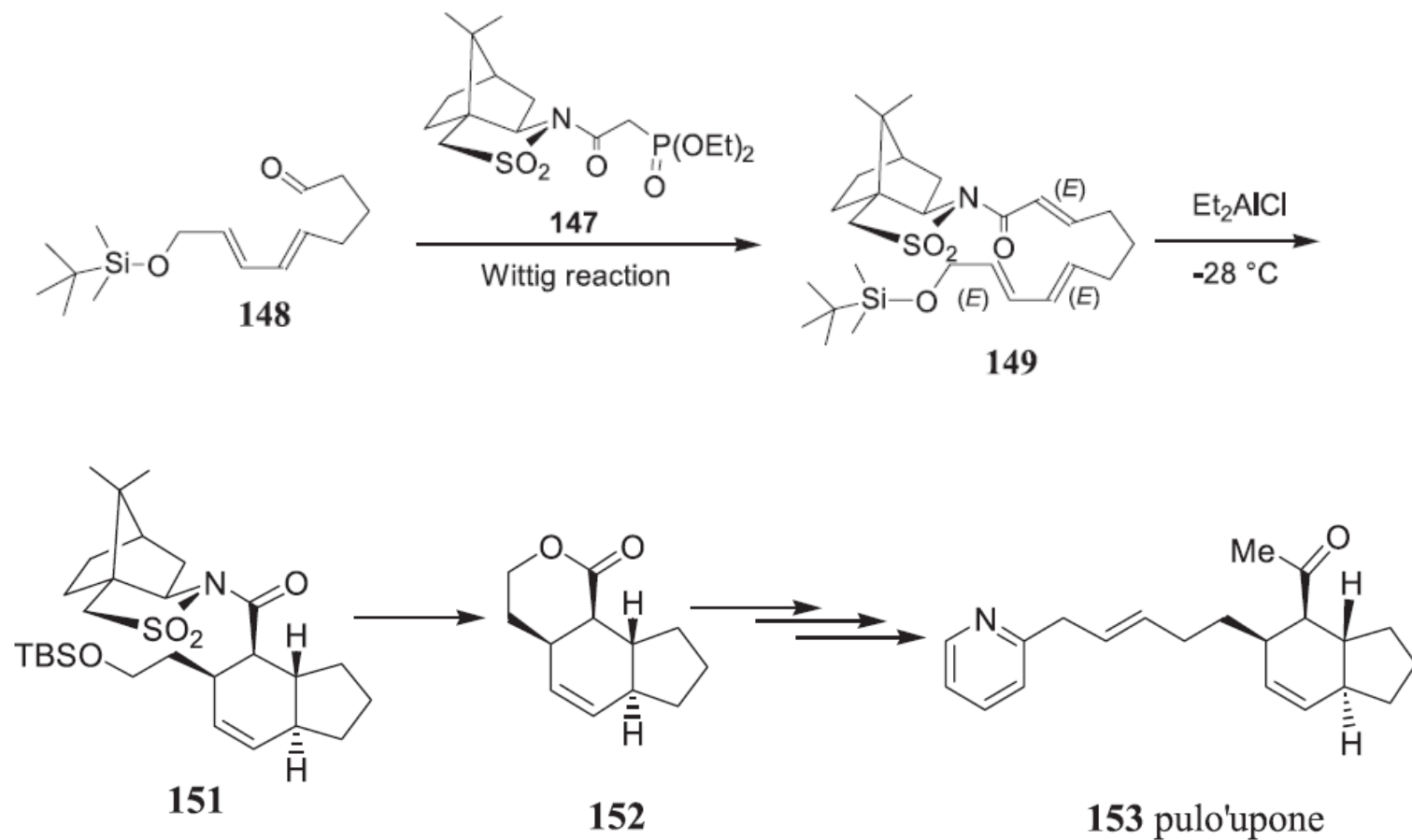
Chapter 5.5 分子内Diels-Alder 反应



- (a) Methyl acetoacetate bis (trimethylsilyl) enol ether, TiCl_4 , CH_2Cl_2 , -78°C .
(b) Dess-Martin periodinane, CH_2Cl_2 , 71%. (c) DBU, benzene, 60°C , 87%.
(d) Methyl *p*-toluenesulfonate, K_2CO_3 , DMF, r.t., 81%. (e) LDA, THF, -78°C to 0°C ; methyl formate, -78°C , 57%.

D. W. C. MacMillan. et al, *J. Am. Chem. Soc.* **2005**, *127*, 11616.

Chapter 5.5 分子内Diels-Alder 反应

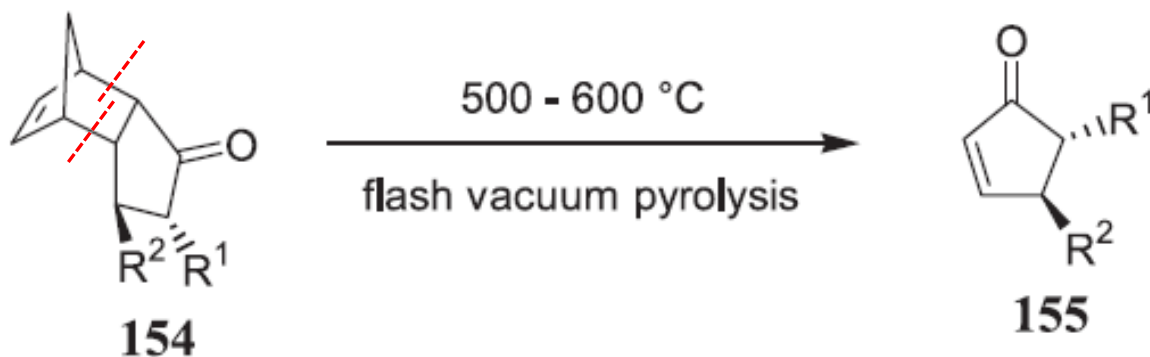


Oppolzer, W. et al. *Tetrahedron Lett.* **1988**, 29, 5885.

Oppolzer, W. et al. *Tetrahedron Lett.* **1985**, 26, 5437.

Chapter 5.6 逆Diels-Alder 反应

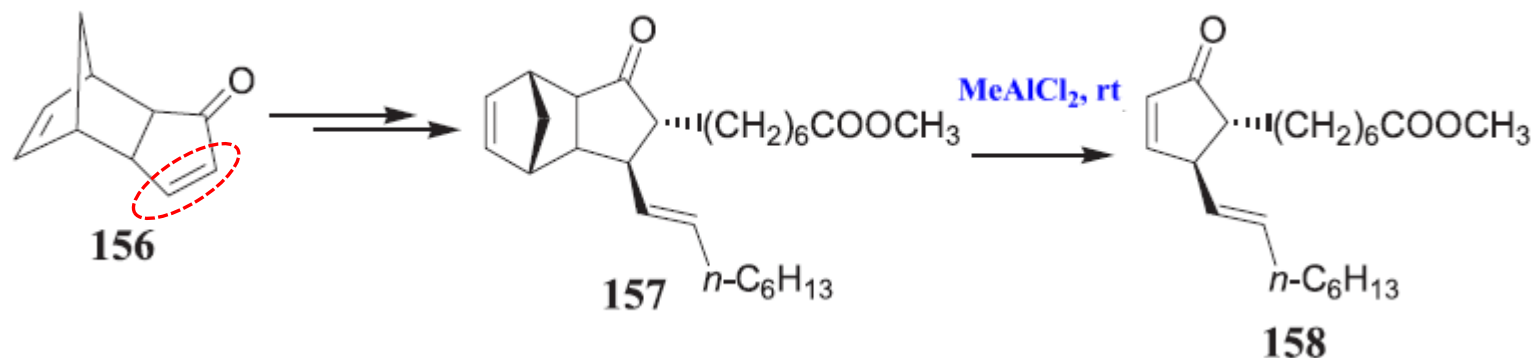
在某些条件下产生二烯和烯烃或含C=C双键化合物的逆反应过程。
Stork 在20世纪70年代引入的快速真空热裂解法已成为标准程序。
这个方法可以用来制备热力学上不稳定的化合物。



Stork, G. et al. *J. Am. Chem. Soc.* **1971**, 93, 3091.

Chapter 5.6 逆Diels-Alder 反应

应用实例：前列腺素A₁或A₂(158)的合成



NOTE: Lewis acid can help lower the reaction temperature in the Retro D-A

Noyori, R. et al. *J. Am. Chem. Soc.* **1985**, 107,3348.

Rouessac, F. et al. *Bull. Soc. Chim. Fr.* **1979**, II-273.