Chapter 6

Asymmetric Epoxidation

第9次课 (陈加荣)

2016-04-13

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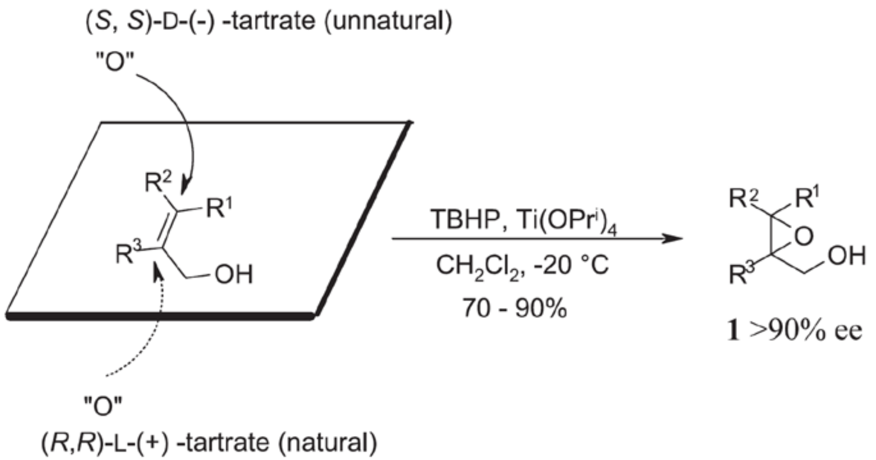
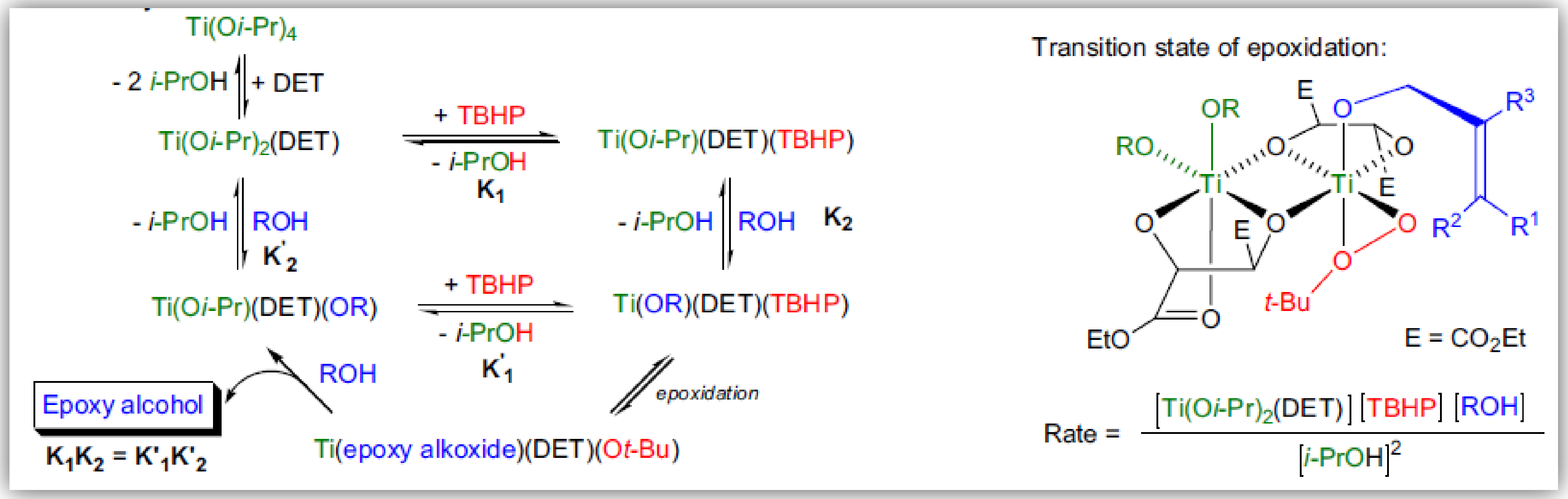
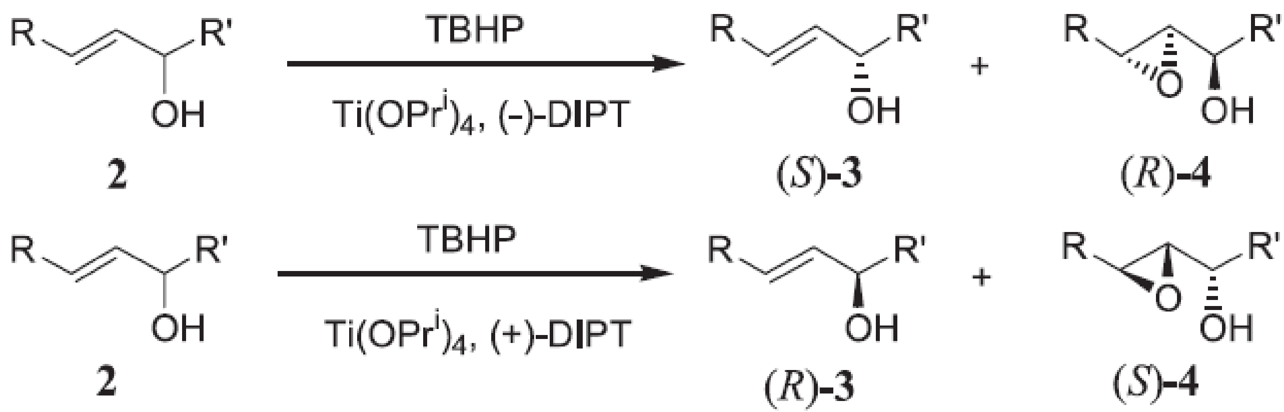
6.1 Asymmetric epoxidation of allylic alcohols—Sharpless epoxidation-1980



Sharpless epoxidation—the titanate-mediated epoxidation of allylic alcohols

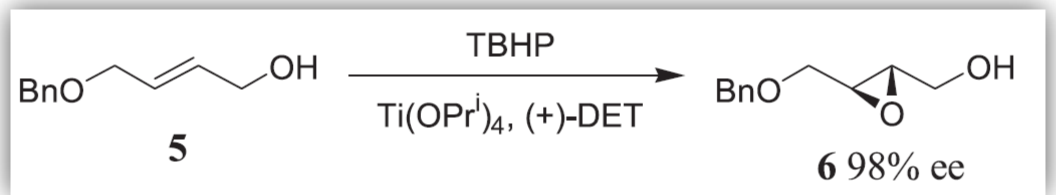


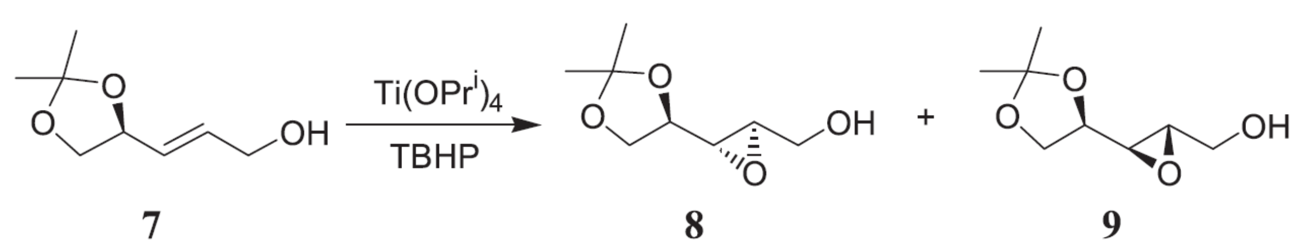
6.1 Asymmetric epoxidation of allylic alcohols—Sharpless epoxidation



Scheme 4–1. Kinetic resolution of secondary allylic alcohols.

6.1.1 The characteristics of Sharpless epoxidation

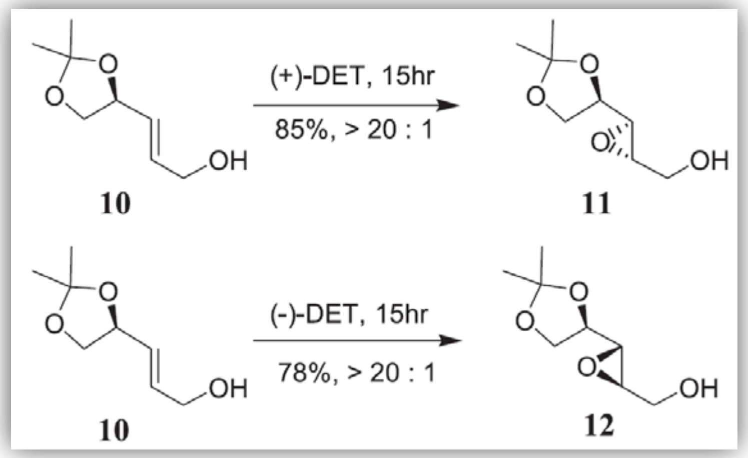


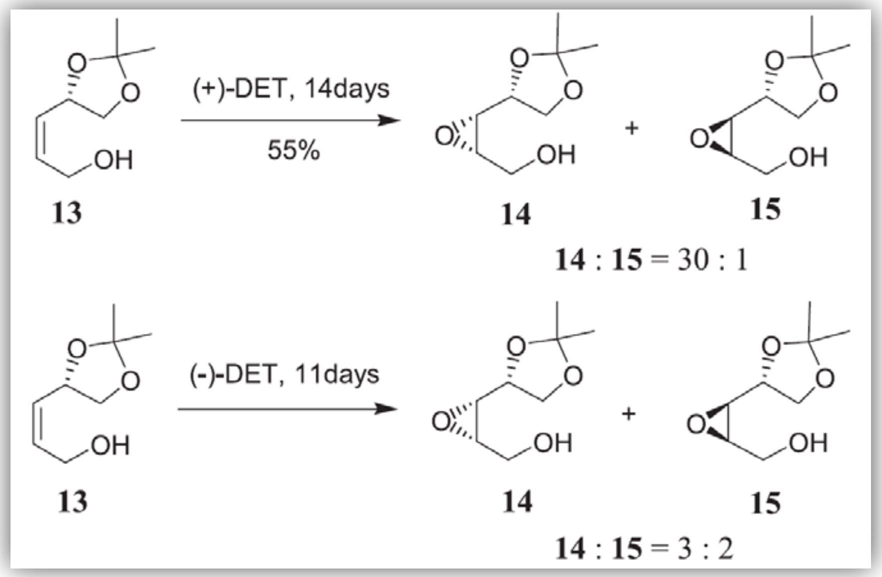


in the absence of tartrate: **8** : **9** = 2.3 : 1
in the presence of (+)-DET, mismatched, **8** : **9** = 1 : 22
in the presence of (-)-DET: matched, **8** : **9** = 90 : 1

Double asymmetric induction: the enantioselectivity depends on whether the configurations of the substrate and the chiral ligand are matched or mismatched.

(Z)-substituted allylic alcohols react much more slowly than the corresponding (E)-substituted substrates:





characteristics of Sharpless epoxidation

Simplicity: All the ingredients are inexpensive and commercially available.

Reliability: It succeeds with most allylic alcohols, although bulky substituents are deleterious.

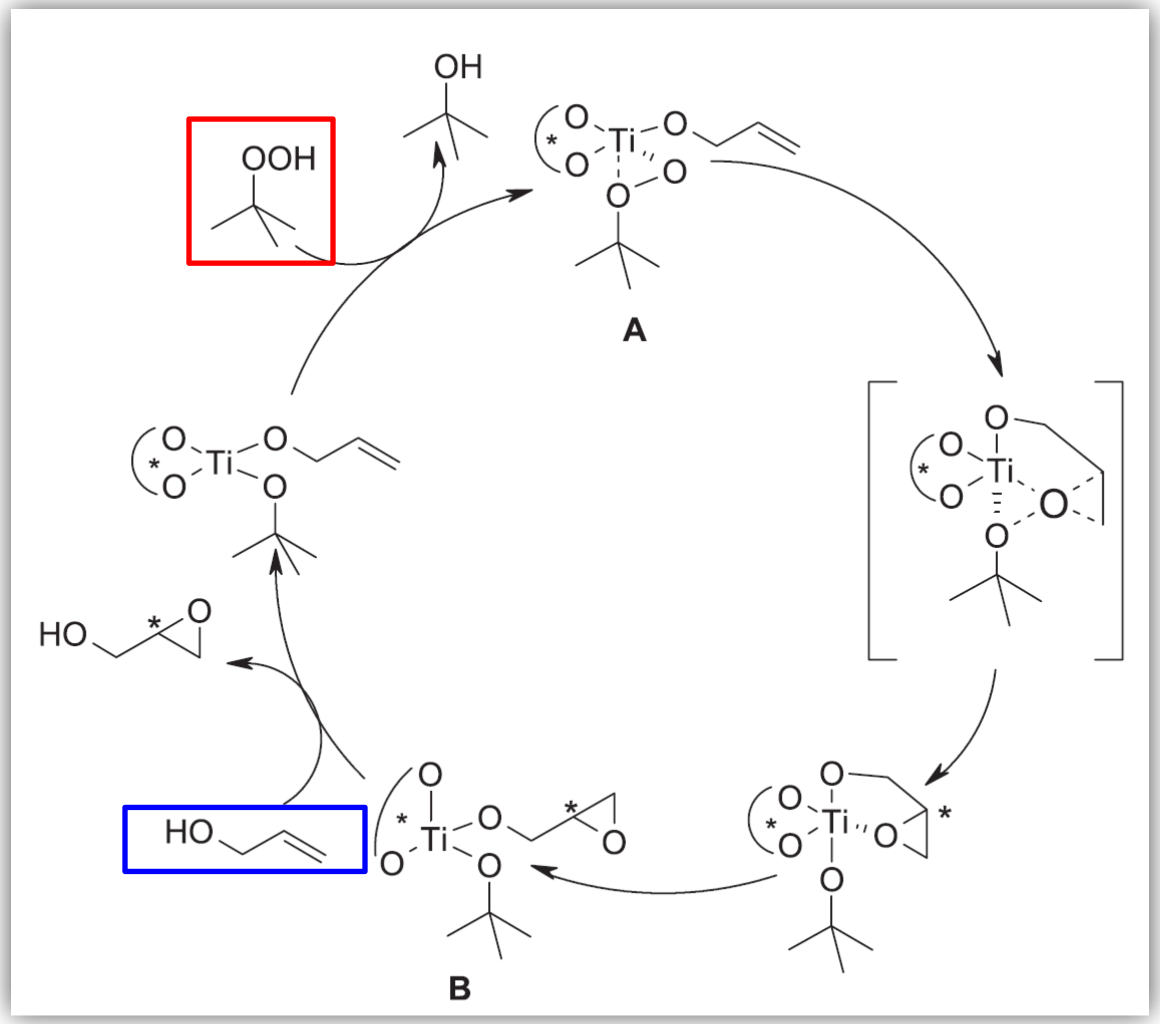
High optical purity: Optical purity of the product is generally >90% ee and usually >95% (99.5% ee is the highest measured accurately to date).

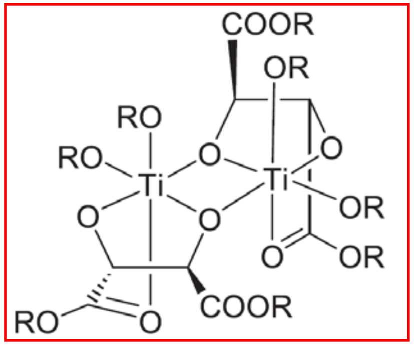
Predictable absolute stereochemistry: Thus far, when dealing with a prochiral allylic alcohol substrate, no exception to the rules has been observed.

Relative insensitivity to preexisting chiral centers: In allylic alcohols with preexisting chiral centers, the diastereofacial preference of the chiral titanium-tartrate catalyst is often strong enough to override diastereofacial preferences inherent in the chiral olefinic substrate.

Versatility of 2,3-epoxy alcohols as intermediates: New selective transformations widen the utility and significance of the reaction.

6.1.2 Proposed Mechanism

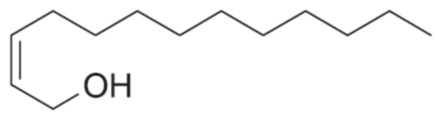
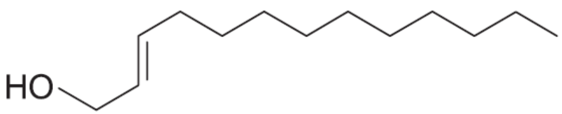
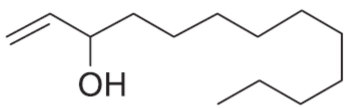




dinuclear Ti-tartrate complexes

6.1.3 Modifications and improvements of Sharpless epoxidation

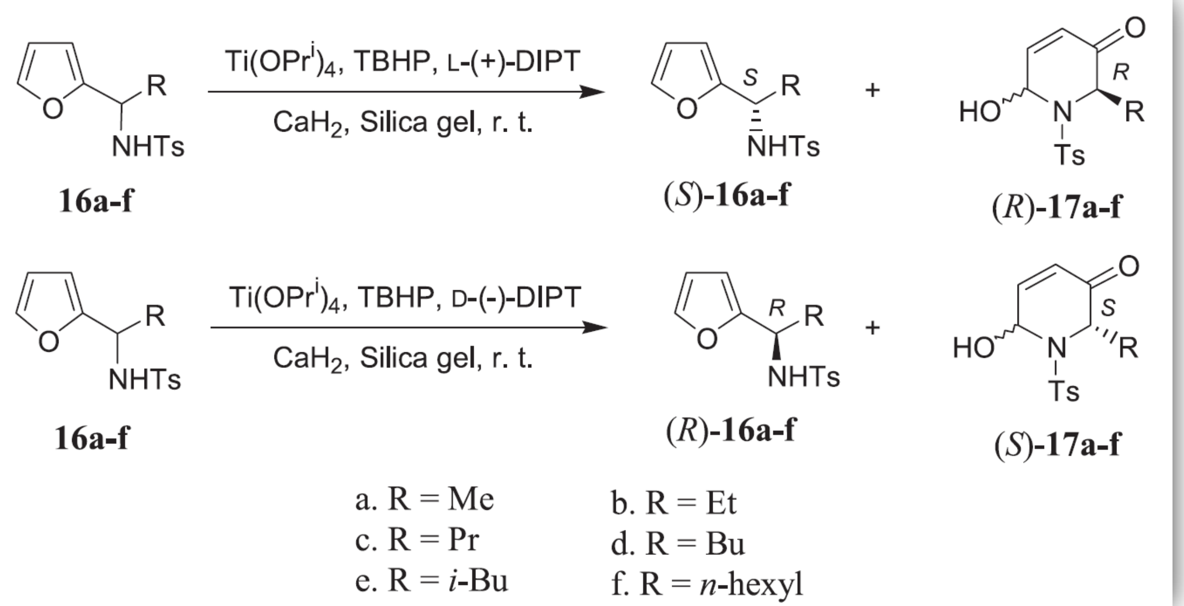
· *The CaH_2/SiO_2 System*: the reaction time in Sharpless epoxidation could be reduced dramatically by adding a catalytic amount of calcium hydride and silica gel to the reaction system.---Zhou, W.-S.

Substrate	Method	Time (h)	Yield (%)	$[\alpha]_D$	ee (%)	Config.
	A	96	76–80	−7.6	95	2*R*,3*S*
	B	8	76	−7.8		
	A	72	76–80	+26.5	96	2*S*,3*S*
	B	6	76.4	+25.9		
	A	360	81	+16.2	91	2*S*,3*S*
	B	25	84	+15.2		

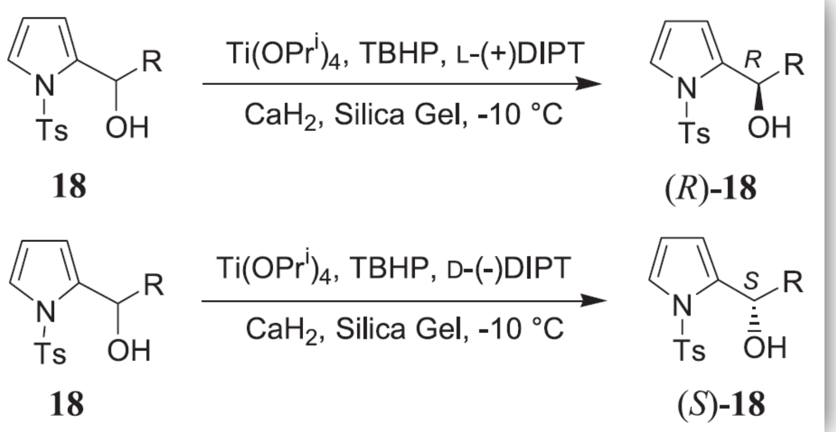
Conditions: Method A: Epoxidation using Sharpless reagent; method B: addition of 0.05–0.1 equivalent of calcium hydride and 0.1–0.15 equivalent of silica gel to the Sharpless reagent.

ee = Enantiomeric excess.

The CaH_2/SiO_2 System: Kinetic resolution

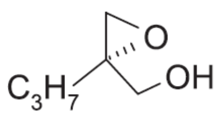


Tetrahedron Lett., **1991**, *32*, 1467.



Tetrahedron Asymmetry, **1991**, *2*, 767.

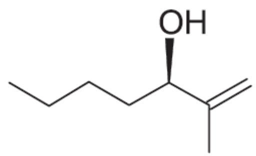
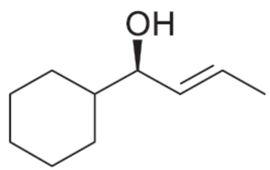
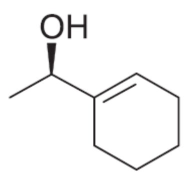
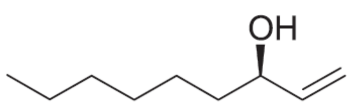
· *The 4 Å Molecular Sieves System:* the asymmetric reaction can be achieved with a catalytic amount of titanium *tetra*-isopropoxide and DET.---Sharpless

Product	Ti–Tartrate	Temp. (°C)	Time (h)	Yield (%)	ee (%)
	5/6.0	−20	2.5	85	94
	5/7.5	−20	3	89	>98
R = C_3H_7, Ph					
	10/14	−10	29	74	86
	10/14	−20	43		85
R = C_7H_{15}, $BnOCH_2$					
	4.7/5.9	−12	11	88	95
R = C_3H_7					
	5/7.5	−35	2	79	>98

ee = Enantiomeric excess.

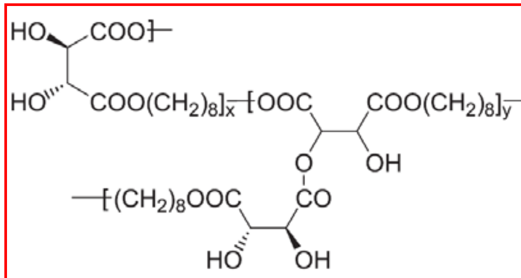
Lower catalyst loading

TABLE 4–3. Kinetic Resolution with (+)-DIPT

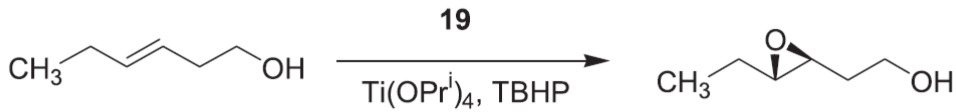
Product	Yield (%)	Conversion (%)	ee (%)
	93	53	94
	96	54	94
	93	63	>98
	92	51	86

ee = Enantiomeric excess.

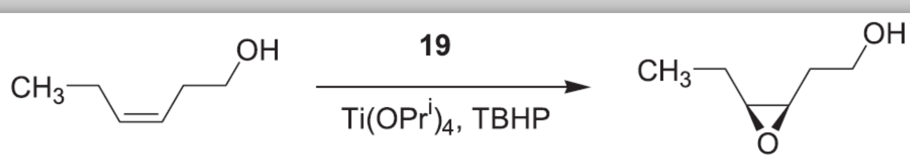
· *Asymmetric Epoxidation Using Polymer-Supported Ti(IV) Catalysts:* ease of separation from the reaction system, which allows their efficient recovery and potential reuse.----Canali



19



Entry	Ligands [(%), branching, crosslinking]	Molar ratio substrate: Ti: tartrate	Reaction time (days)	Yield (%)	ee (%)
1	DMT	100 : 100 : 120	10	58	29
2	3 (0%)	100 : 200 : 400	21	26	54
3	3 (8%)	100 : 200 : 400	5	45	54
4	3 (13%)	100 : 200 : 400	1	75	38

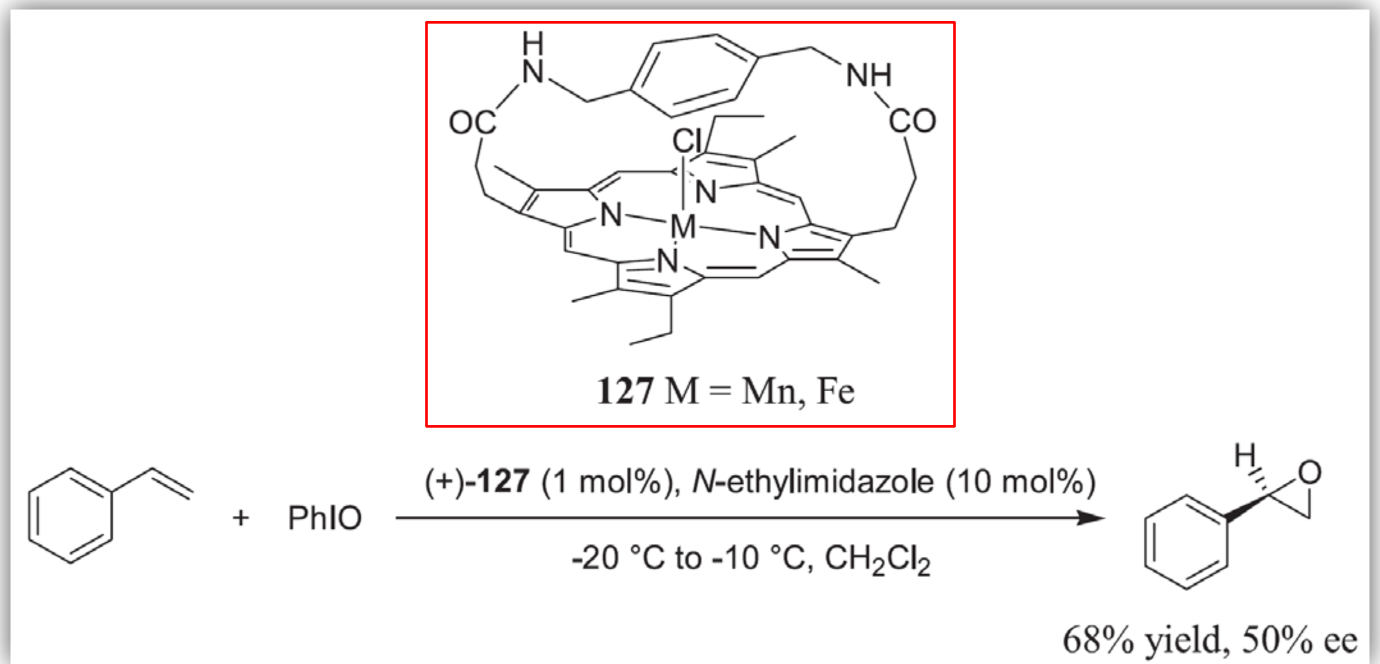


Entry	Ligands [(%), branching, crosslinking]	Molar ratio substrate: Ti: tartrate	Reaction time (days)	Yield (%)	ee (%)
1	DMT	100 : 100 : 120	6	15	28
2	3 (10%)	100 : 200 : 400	21	20	51
3	3 (13%)	100 : 200 : 400	1	52	41
4	3 (16%)	100 : 100 : 200	13	33	41

6.2 Epoxidation of unfunctionalized olefins

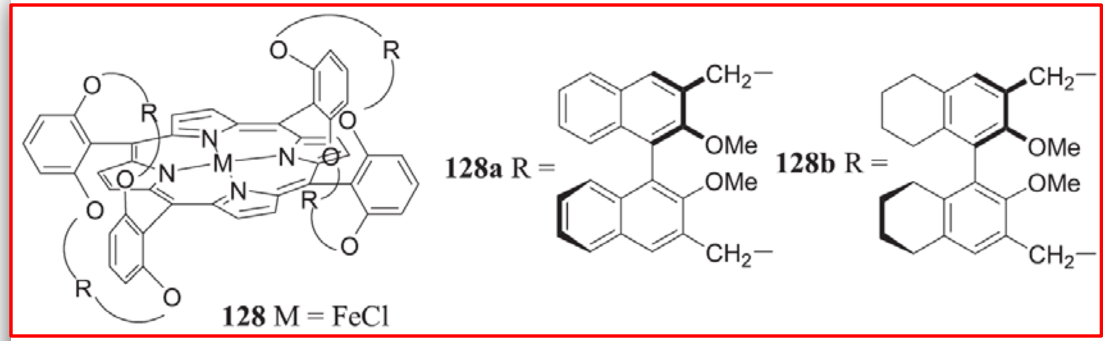
6.2.1 Catalytic Enantioselective Epoxidation of Simple Olefins by Porphyrin Complexes

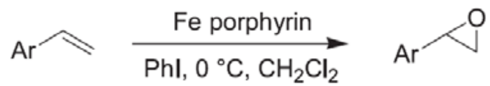
Konishi

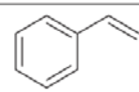
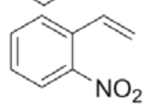
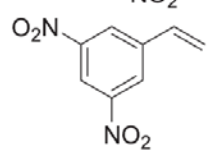
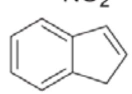


Porphyrin-metal complexes are natural mimetic substances that have attracted much attention during the past decade. The epoxidation of olefins by porphyrin complexes proceeds well, but with only modest enantioselectivity.

6.2.1 Catalytic Enantioselective Epoxidation of Simple Olefins by Porphyrin Complexes



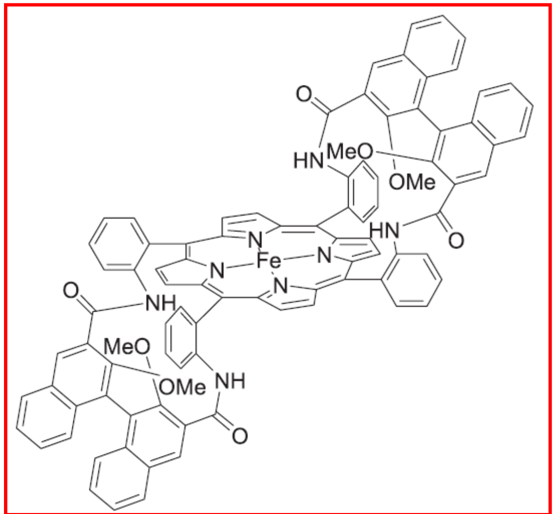


Entry	Substrate	ee (%)		Config.
		128a	**128b**	
1		20	56	*S*
2		80	89	*S*
3		74	82	*S*
4		10	70	1*S*,2*R*

Oxidant: PhIO

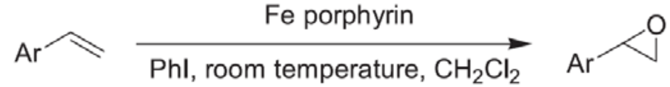
6.2.1 Catalytic Enantioselective Epoxidation of Simple Olefins by Porphyrin Complexes

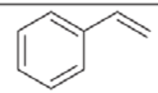
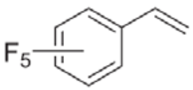
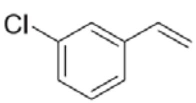
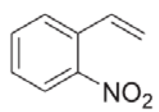
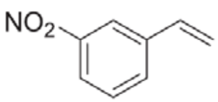
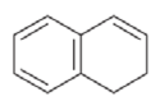
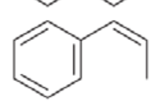
Collman



C2-symmetric catalyst
>75% ee
Oxidant: PhIO

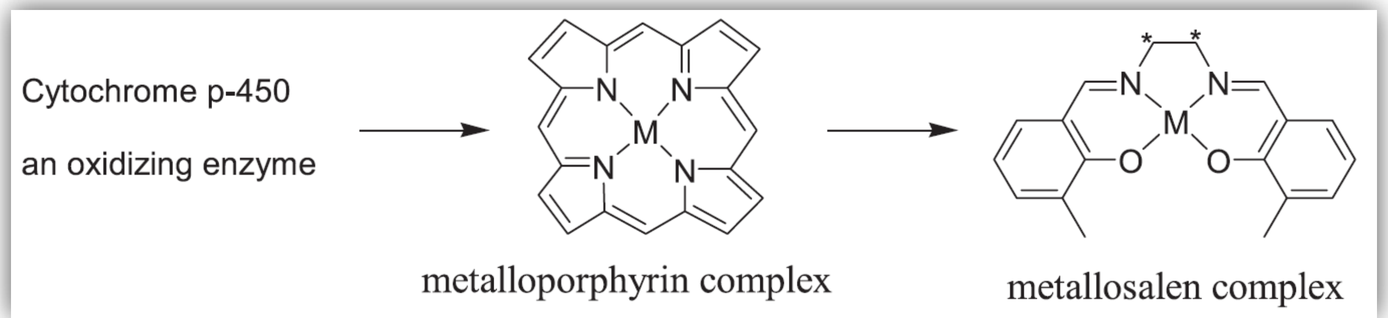
129



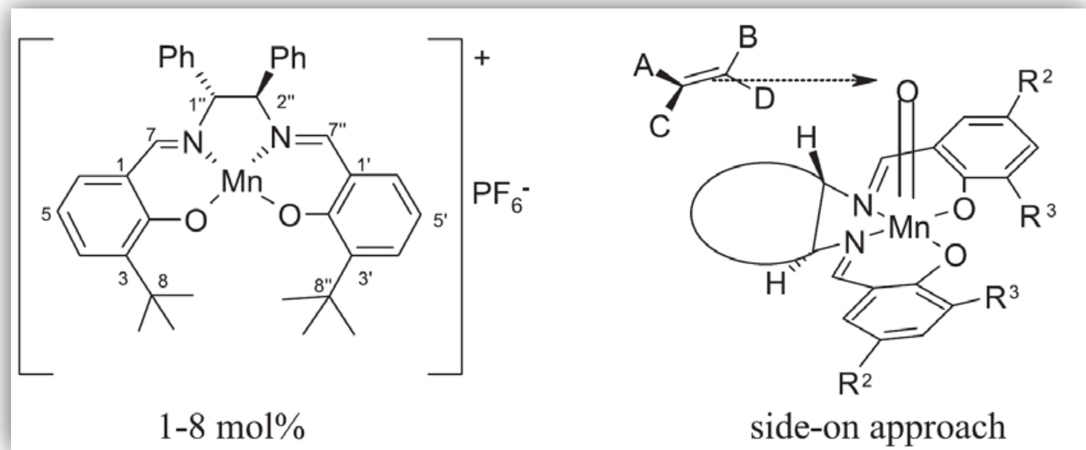
Entry	Substrate	Yield (%)	ee (%)	Config.
1		95	83	*S*
2		isolated yield 89	75	*S*
3		75	88	*S*
4		90	82	*S*
5		isolated yield 85	74	*S*
6		74	55	*S* *S*
7		78	72	*S*
8		isolated yield 75	68	*S*
9		80	55	1*S*,2*R*
10		78	49	1*S*,2*R*

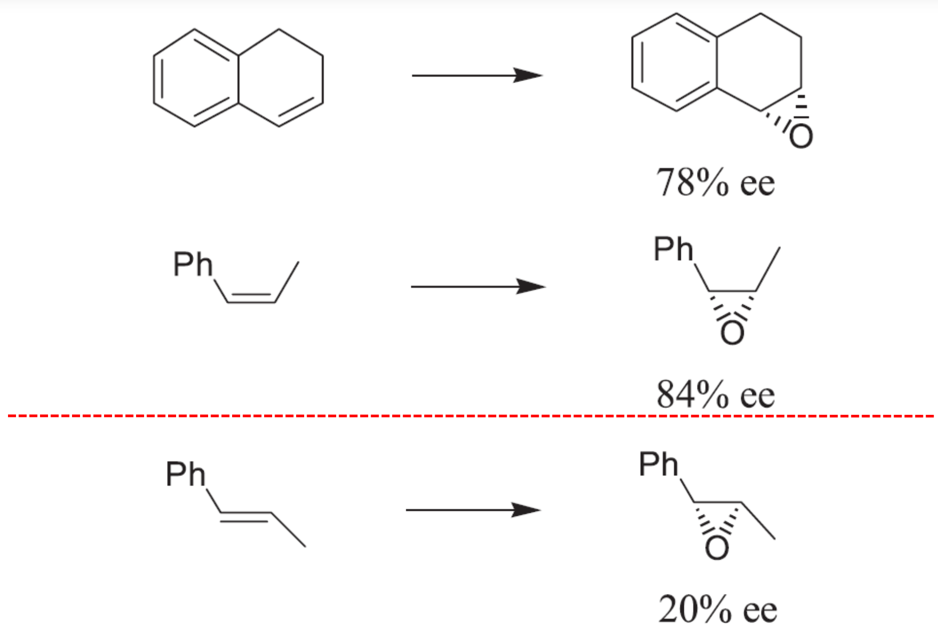
6.2.2 Catalytic Enantioselective Epoxidation of Simple Olefins by Salen Complexes

Jacobsen's & Katsuki's groups

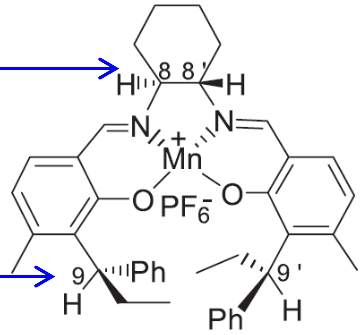


The course of the enantioselectivity is interpreted in terms of a side-on approach by the substrate to the active oxomanganese(V) intermediate:

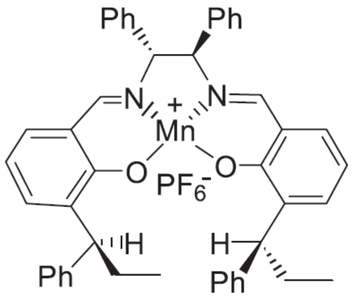




Katsuki

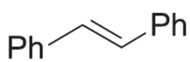
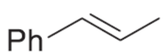
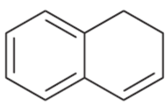
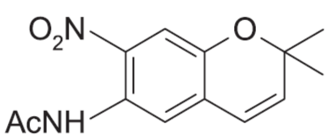
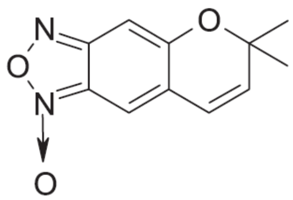


119



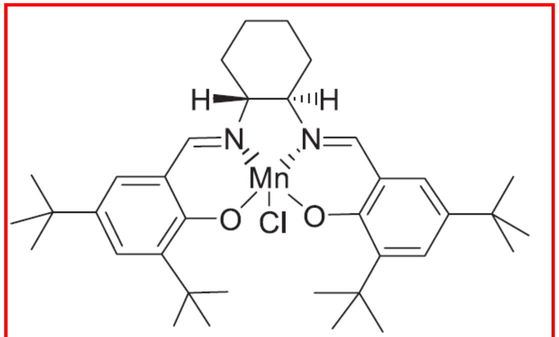
120

TABLE 4–18. Epoxidation of Unfunctionalized Olefins Catalyzed by 119
substrate:catalyst:iodosylbenzene = 1:0.025:1

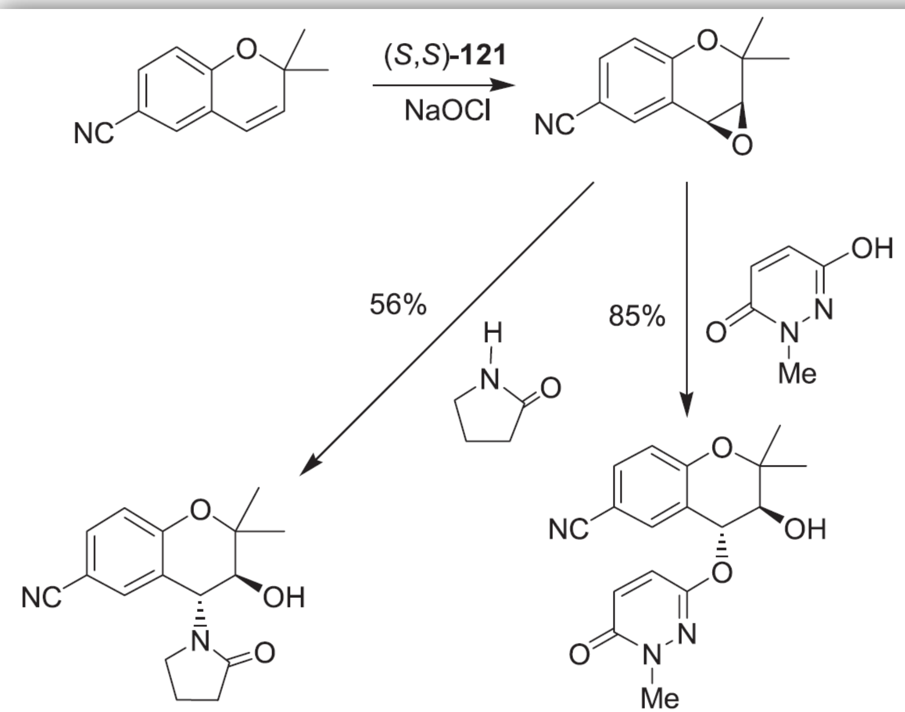
Substrate	ee (%)
	62
	9 (56 when **120** is used)
	91
	96
	94

ee = Enantiomeric excess.

· *Applications in organic synthesis-Example 1*



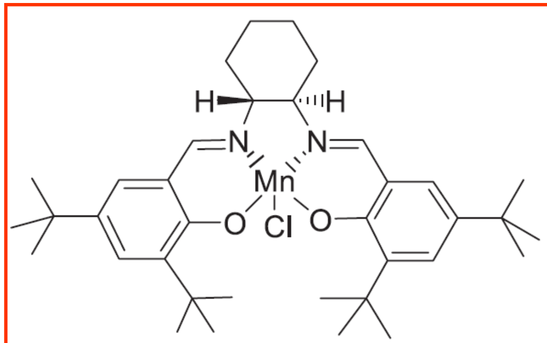
121 in both (*R*,*R*) and (*S*,*S*) form



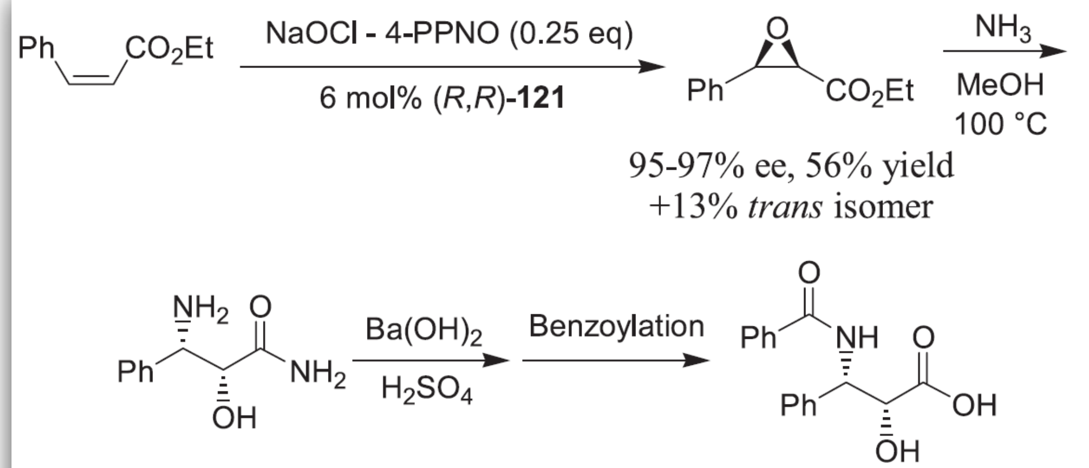
122 **123**

Both **122** and **123** are antihypertensive agents

▪ *Applications in organic synthesis-Example 2*

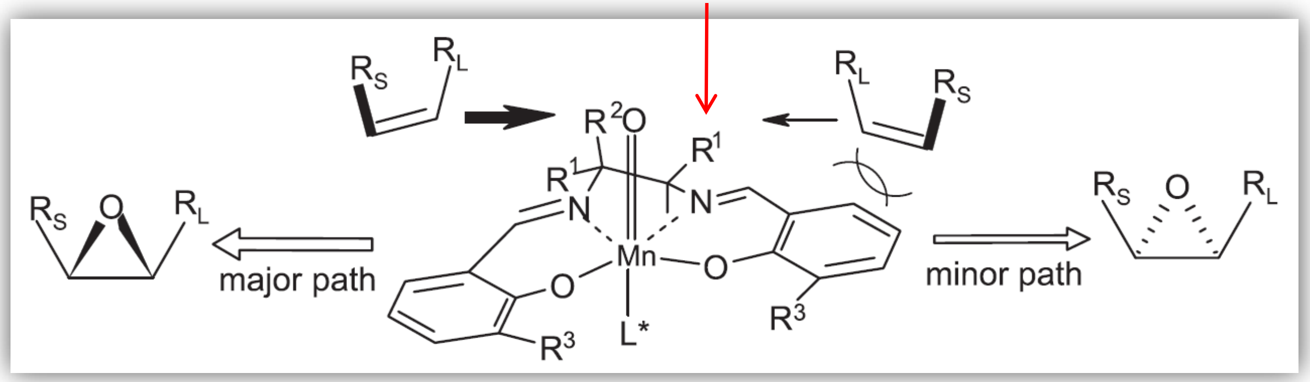


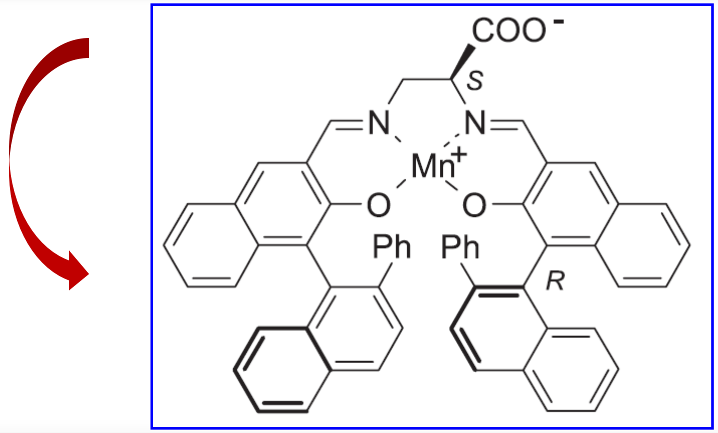
121 in both (*R*,*R*) and (*S*,*S*) form

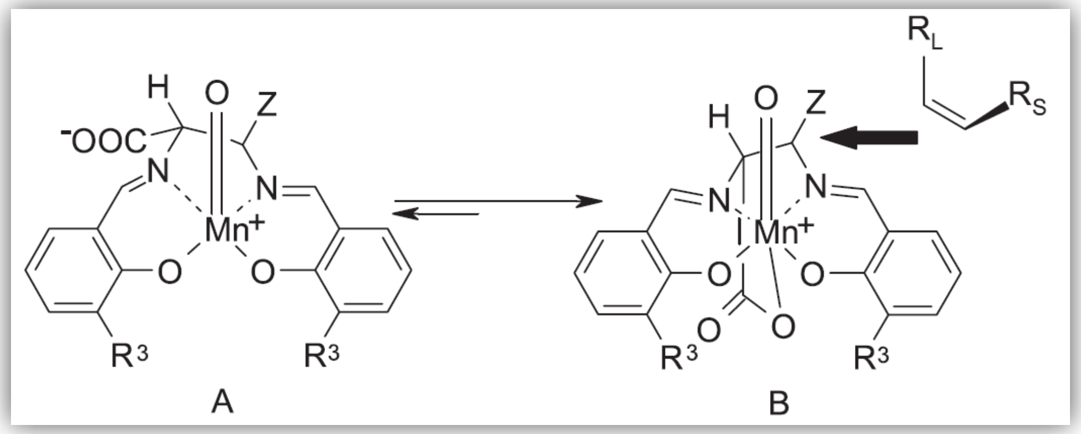


124, taxol side chain

Katsuki



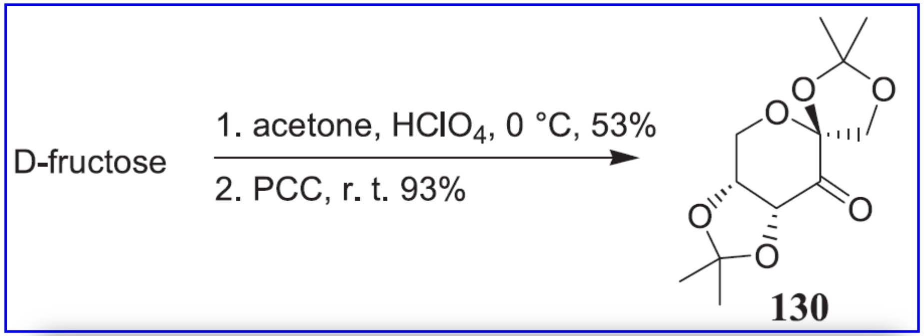


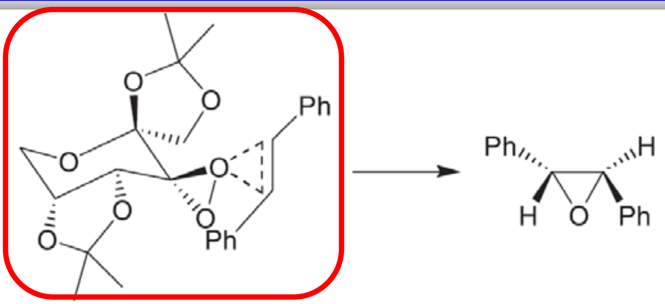


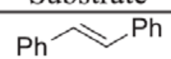
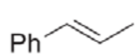
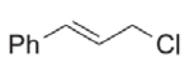
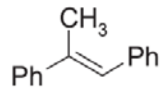
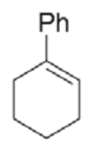
TL, **1998**, *39*, 4325.

Chiral Ketone from Carbohydrate

Shi



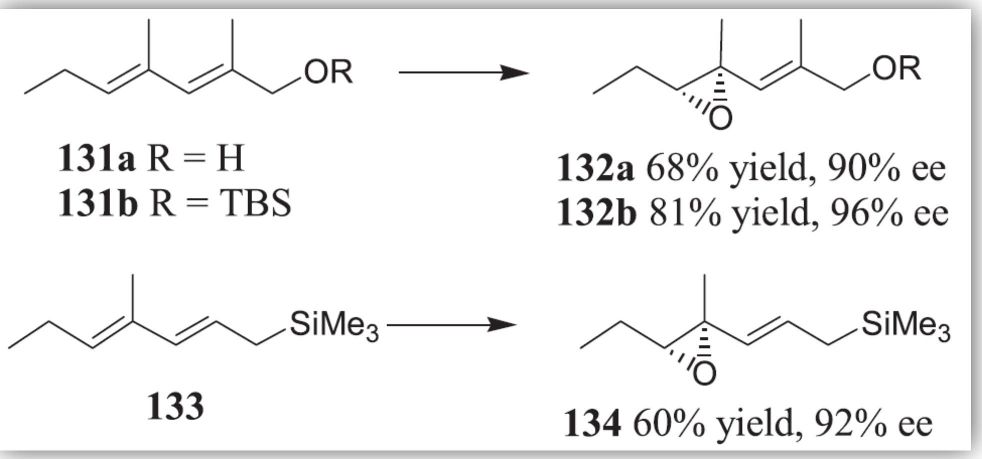


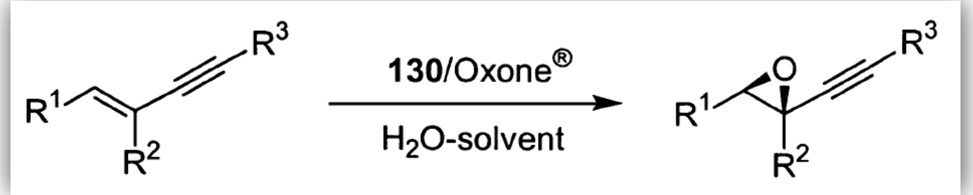
Substrate	Yield (%)	ee (%)	Config.
	73	>95	*R, R*
	81	88	*R, R*
	61	93	2*S*, 3*R*
	73	92	*R, R*
	69	91	*R, R*

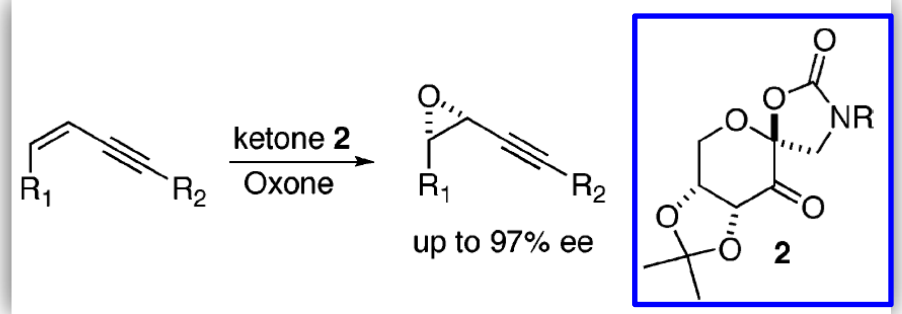
JACS, **1996**, *118*, 9806

Chiral Ketone from Carbohydrate----high chemoselectivity

Shi

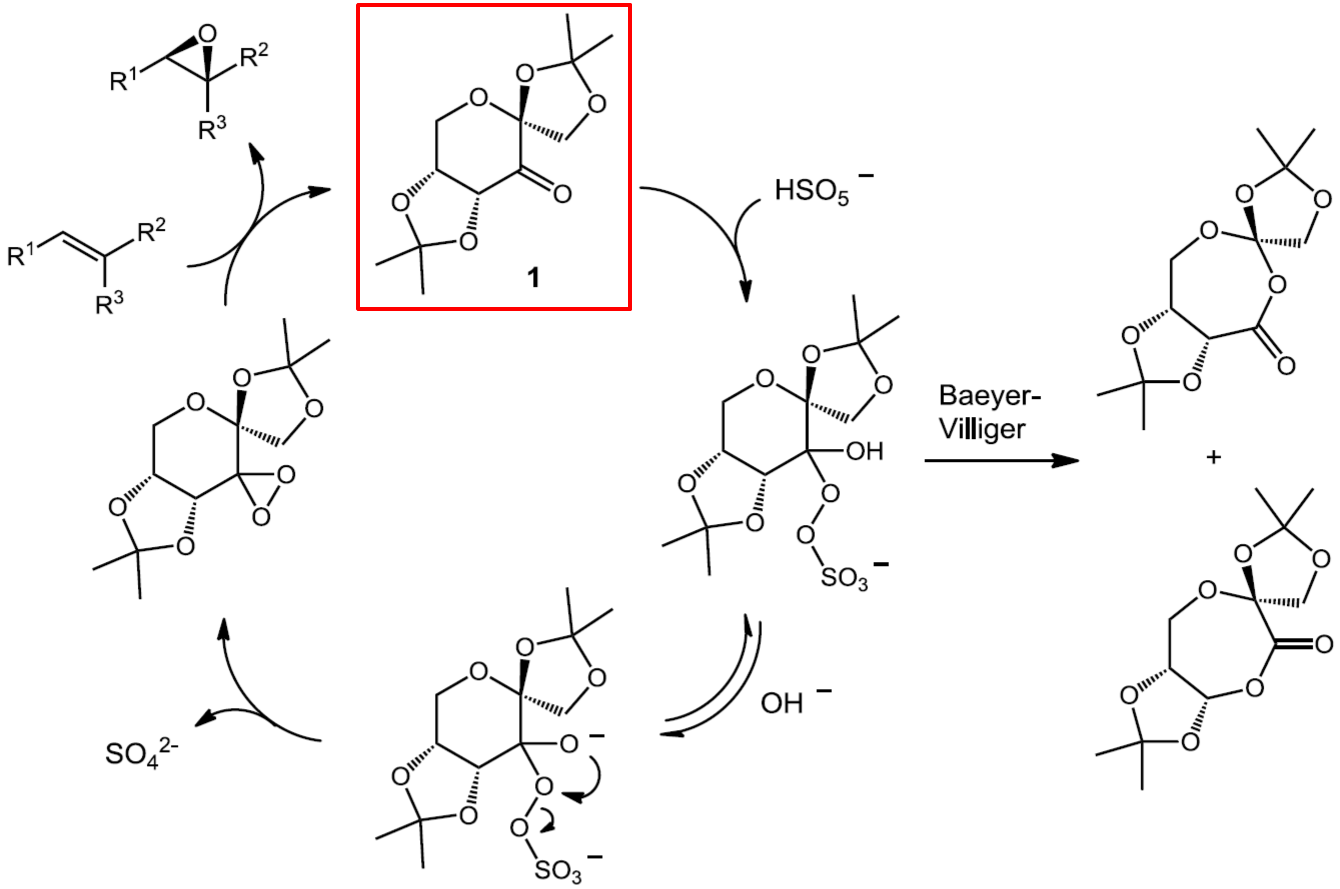






Chiral Ketone from Carbohydrate----high chemoselectivity

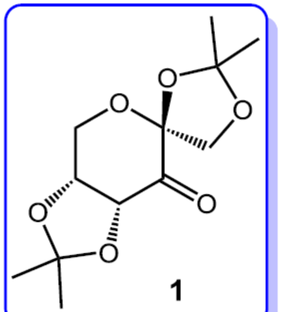
Shi



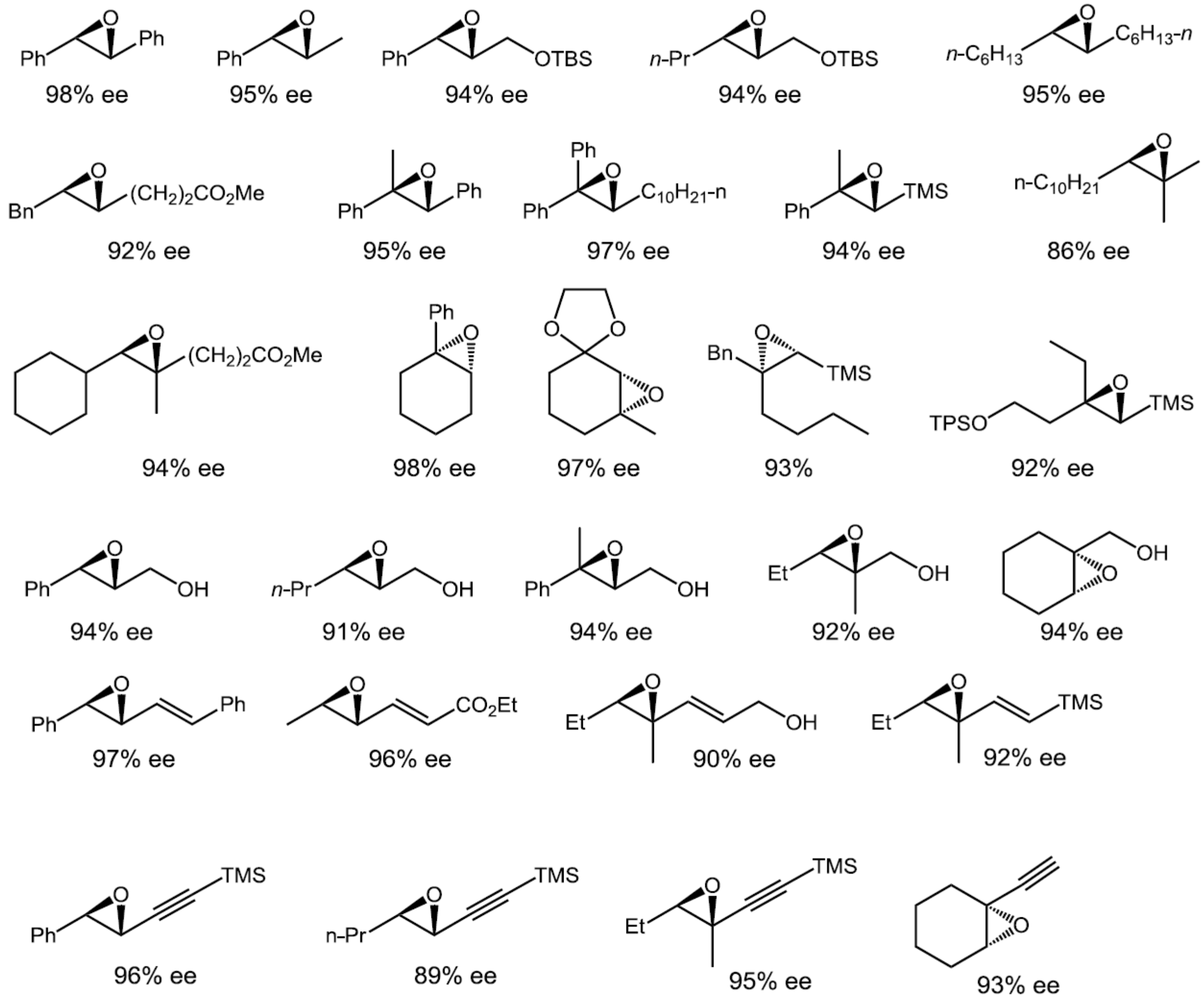
J. Am. Chem. Soc. **2005**, *127*, 6679.

Chiral Ketone from Carbohydrate----Substrate Scope

Shi

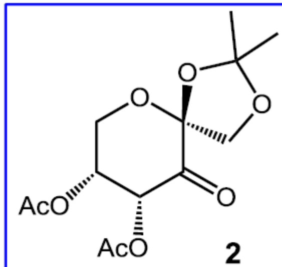


1



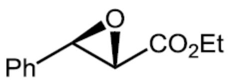
Chiral Ketone from Carbohydrate----Substrate Scope

Shi

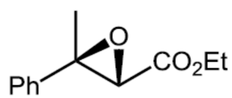


2

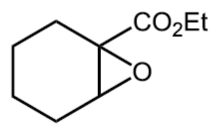
The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient α,β-unsaturated esters. A second-generation catalyst, incorporating electronwithdrawing acetate groups, slows the Baeyer-Villiger decomposition.



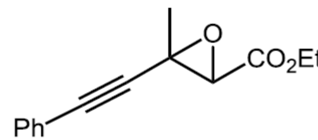
96% ee



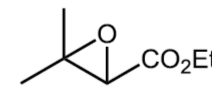
96% ee



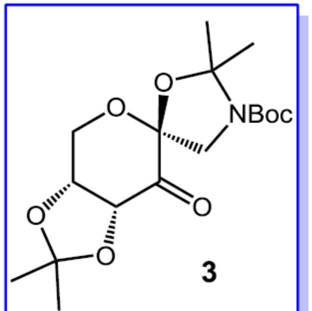
93% ee



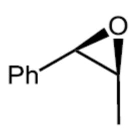
94% ee



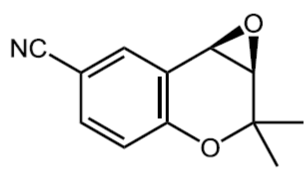
82% ee



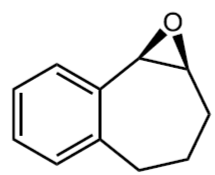
3



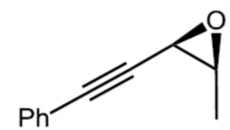
91% ee



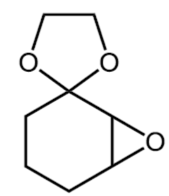
91% ee



91% ee

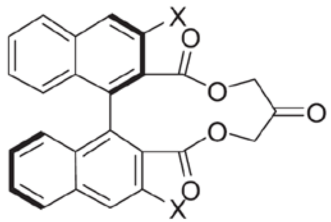


91% ee



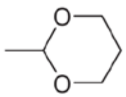
97% ee

Yang, D

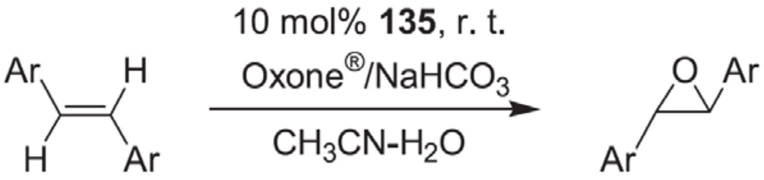


135

135a X = H
135b X = Cl
135c X = Br
135d X = I
135e X = Me
135f X = CH_2OCH_3
135g X =



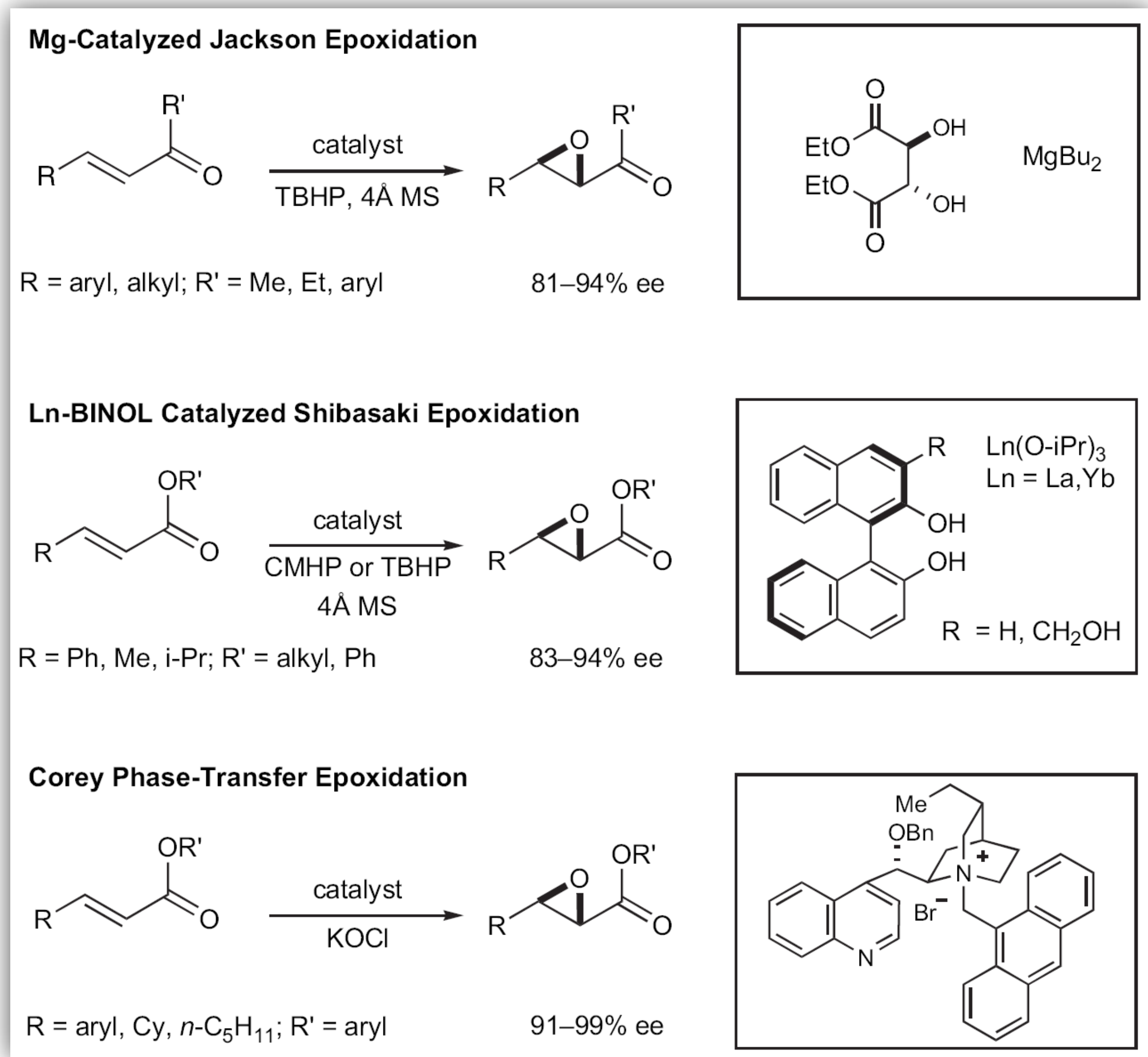
135h X = TMS



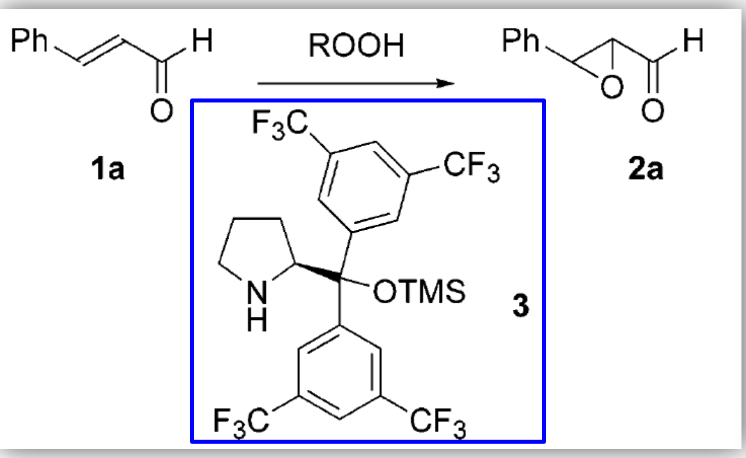
Cat.	Time (h)	Yield (%)	Config.	ee (%)
(*R*)-**135a**	1	91	*S*,*S*	47[a]
(*R*)-**135b**	2	95	*S*,*S*	76[a]
(*R*)-**135c**	3	92	*S*,*S*	75[a]
(*R*)-**135d**	22	90	*S*,*S*	32[a]
(*R*)-**135e**	1	93	*R*,*R*	56[a]
(*R*)-**135f**	1.8	92	*S*,*S*	66[a]
(*R*)-**135g**	0.7	95	*S*,*S*	71[a]
(*S*)-**135h**	20	-	*R*,*R*	44[a]
(*R*)-**135a**	6	82	*S*,*S*	87[b]
(*S*)-**135a**	6	80	*R*,*R*	87[b]

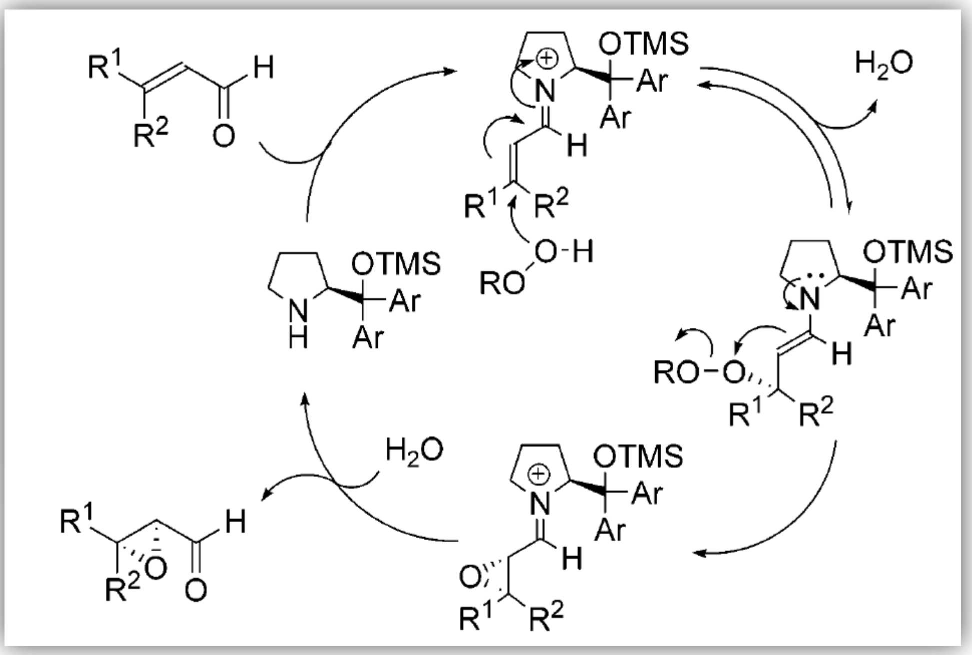
JACS,**1996**, *118*, 11311.

6.3 Asymmetric epoxidation of α, β-unsaturated carbonyl compounds

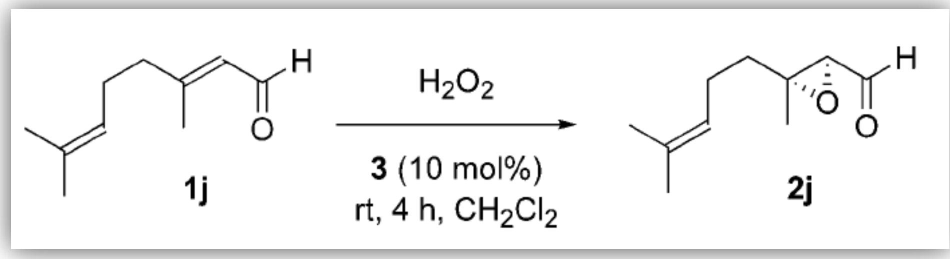


6.3 Asymmetric epoxidation of *α, β*-unsaturated carbonyl compounds



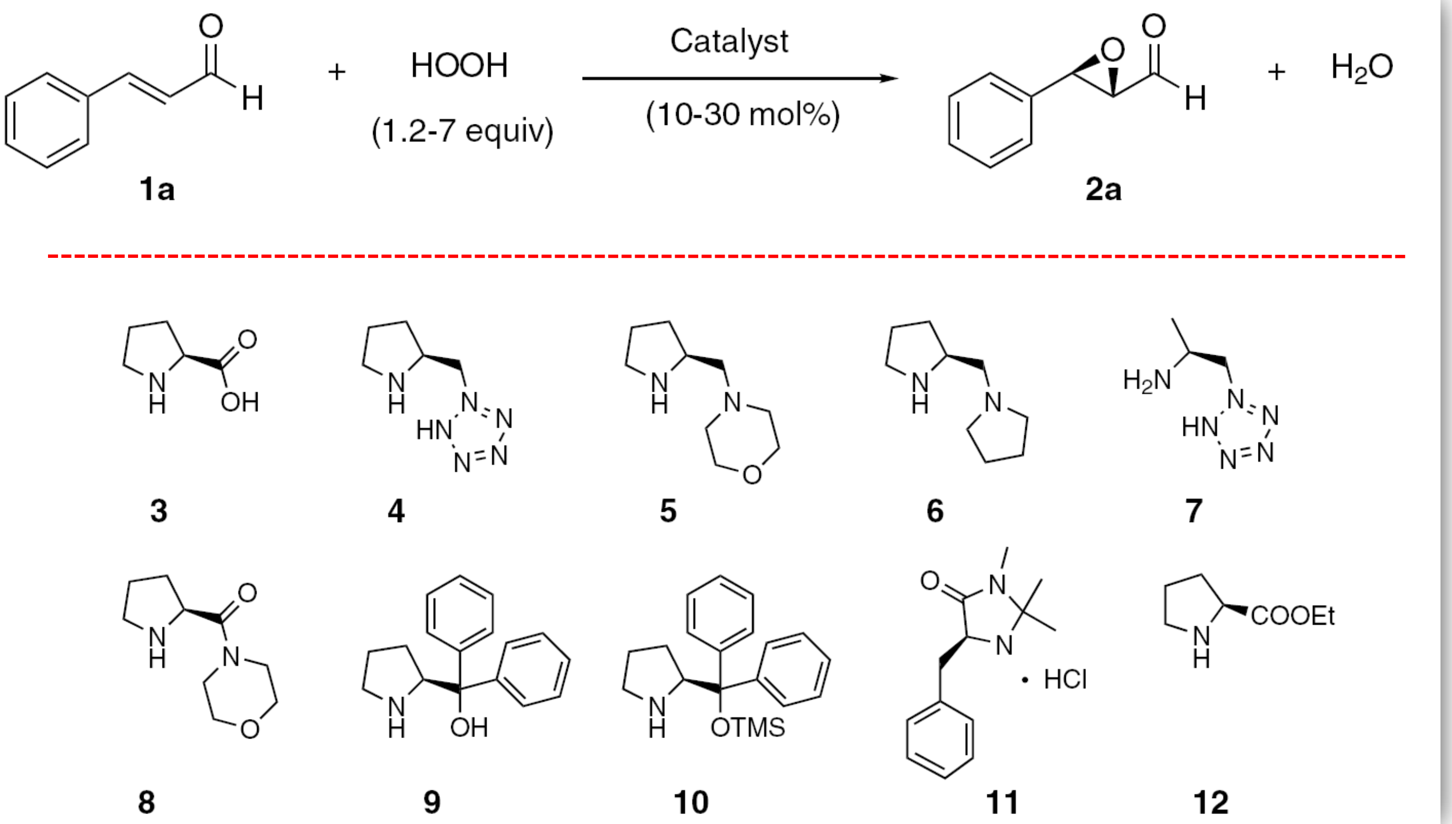


Jørgensen, K. A. et al. *JACS* **2005**, *127*, 6964-6965



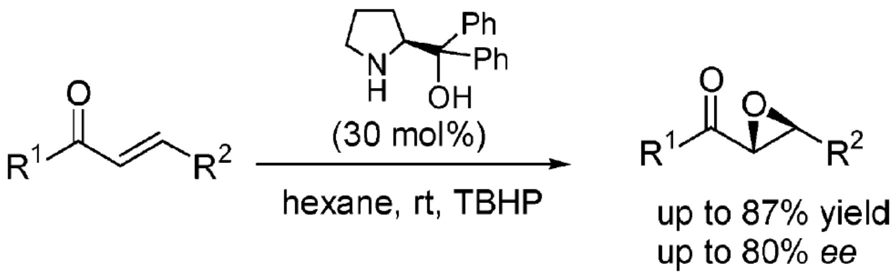
73% yield
85% ee

Córdova

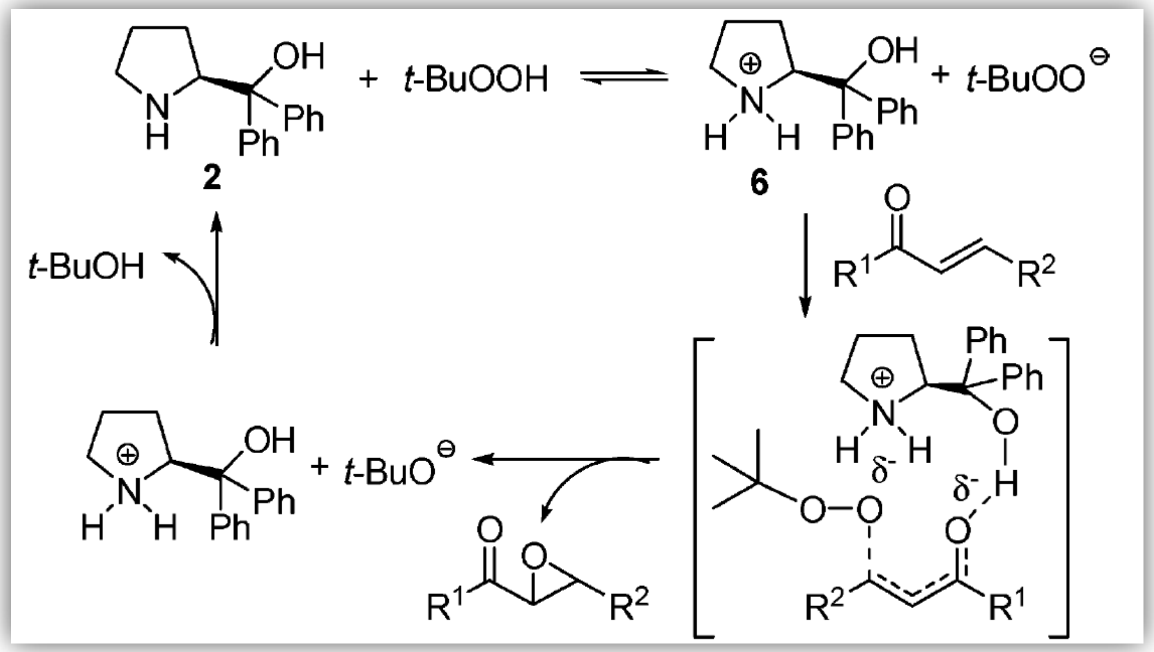


Tetrahedron Lett. **2006**, 47, 99-103.

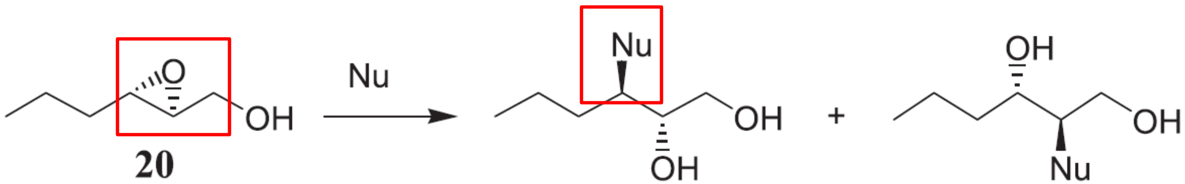
Lattanzi



OL, **2005**, *7*, 2579.



- *Ti(OPr^i)$_4$-Mediated Nucleophilic Opening of 2,3-Epoxy Alcohols.*



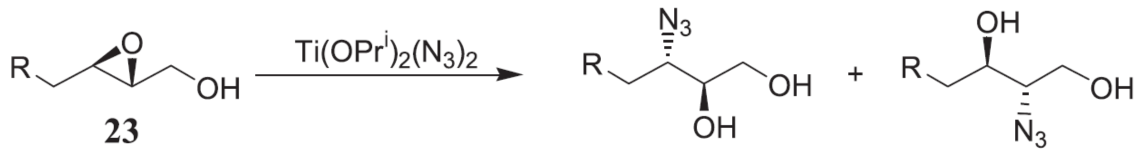
20 → **21** C-3 opening + **22** C-2 opening

Nucleophile	Ti(OPr^i)$_4$ (eq.)	Reaction Conditions	Regioselectivity (C-3/C-2)	Yield (%)
Et_2NH	0	Et_2NH (excess), reflux, 18 h	3.7/1	4
Et_2NH	1.5	Et_2NH (excess), r.t., 5 h	20/1	90
i-PrOH	0	*i*-PrOH (excess), reflux, 18 h		0
i-PrOH	1.5	*i*-PrOH (excess), reflux, 18 h	100/1	88
PhSH	0	PhSH (5.0 eq.), benzene, r.t., 22 h		0
PhSH	1.5	PhSH (1.6 eq.), benzene, r.t., 5 min	6.4/1	95
Me_3SiN_3	1.5	Me_3SiN_3 (3.0 eq.), benzene, reflux, 3 h	14/1	74

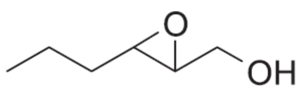
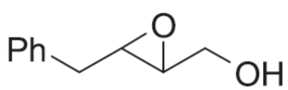
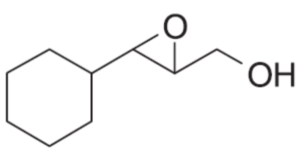
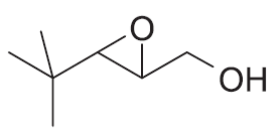
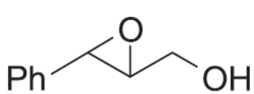
r.t. = Room temperature.

Improved efficiency and regioselectivity with Ti(O^{i}Pr)$_4$

· *Regioselective Azide Opening of 2,3-Epoxy Alcohols by [Ti(OPr^i)$_2$(N$_3$)$_2$] and Other Azidic Compounds.*

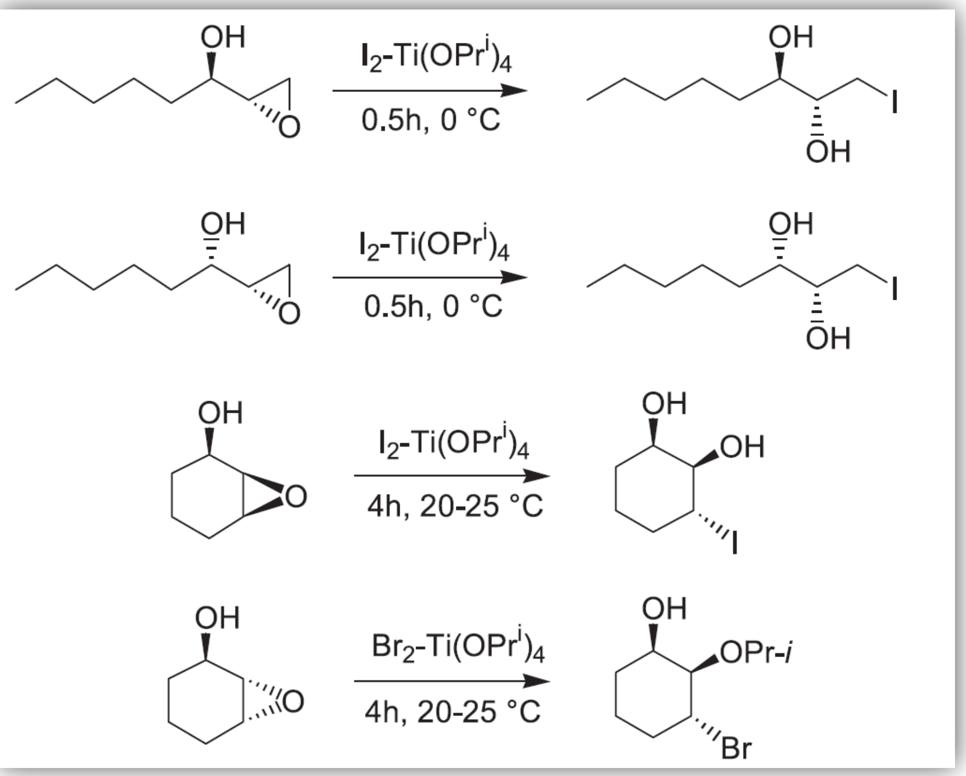


C-3 opening product C-2 opening product

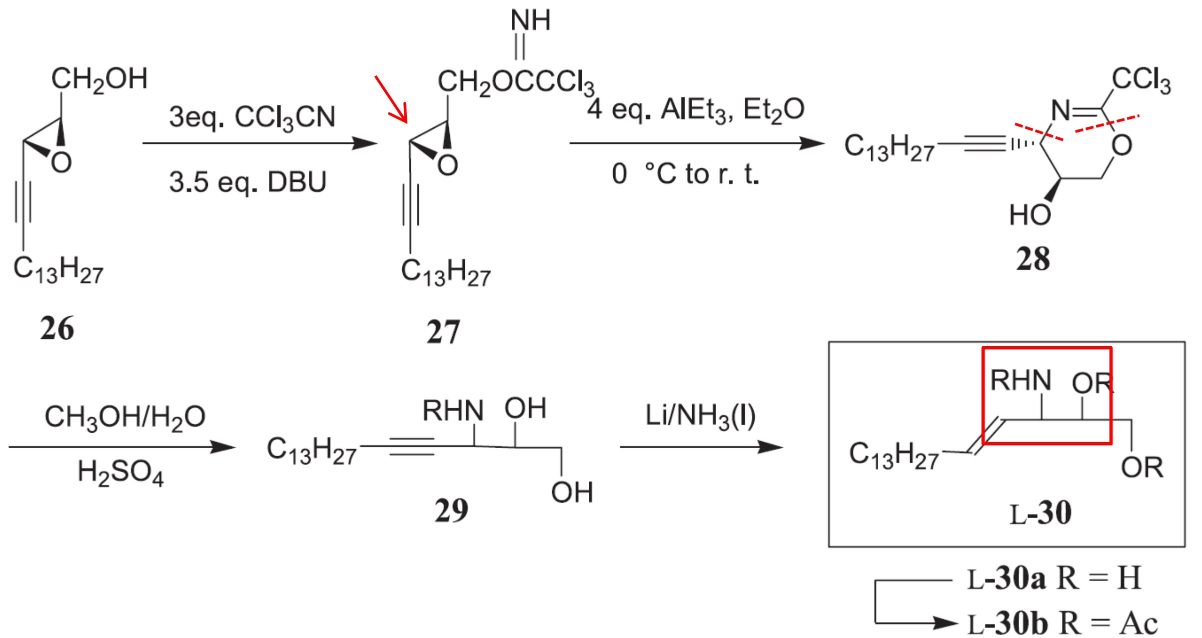
Entry	Substrate	Conditions	Regioselectivity C-3/C-2	Yield (%)
1		7 h[a]	5.8:1	95
2		0.08 h[b]	36:1	88
3		3.5 h[c]	1.4:1	71
4		0.16 h[b]	27:1	96
5		10 h[c]	1.7:1	93
6		0.25 h[b]	20:1	94
7		12 h[c]	1:100	47
8		0.75 h[b]	2:1	96
9		2.75 h[a]	100:1	100
10		0.08 h[d]	100:1	76

[a] NaN_3/NH_4Cl, 65°C, MeOH/H_2O = 8:1.
[b] Ti(OPr^i)$_2$(N$_3$)$_2$, benzene, 70°C.
[c] NaN_3/NH_4Cl, $CH_3OCH_2CH_2OH$:H_2O = 8:1; 124°C.
[d] Ti(OPr^i)$_2$(N$_3$)$_2$, ether, 25°C.

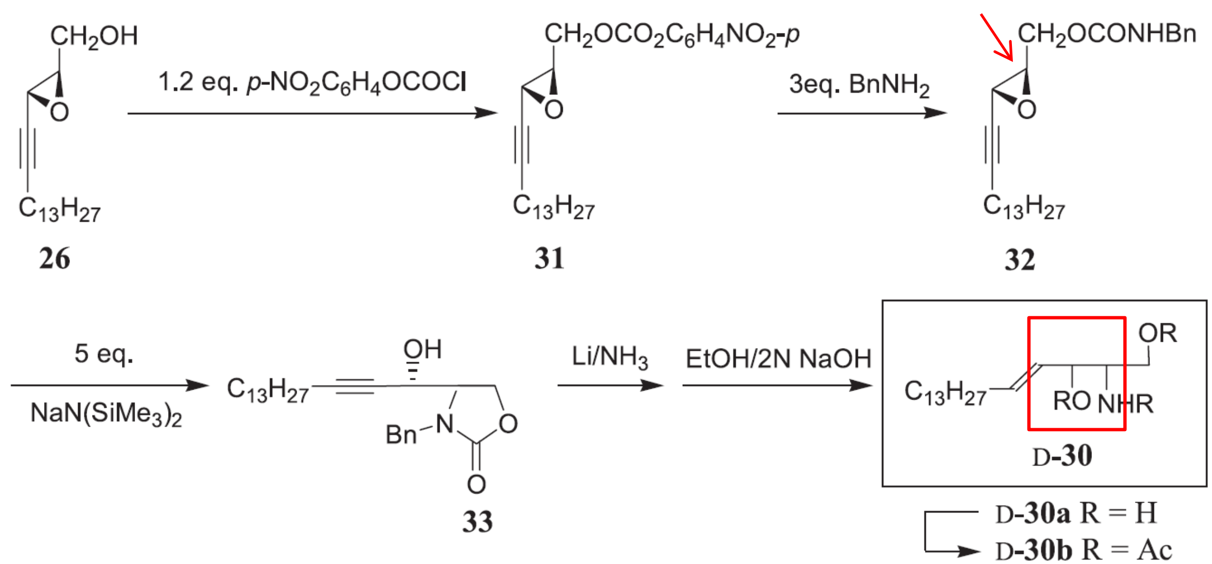
· *Ring-Opening Reactions of Epoxy Alcohols with* X_2-$Ti(OPr^i)_4$.



· *Opening by Intramolecular Nucleophiles-To improve regioselectivity*

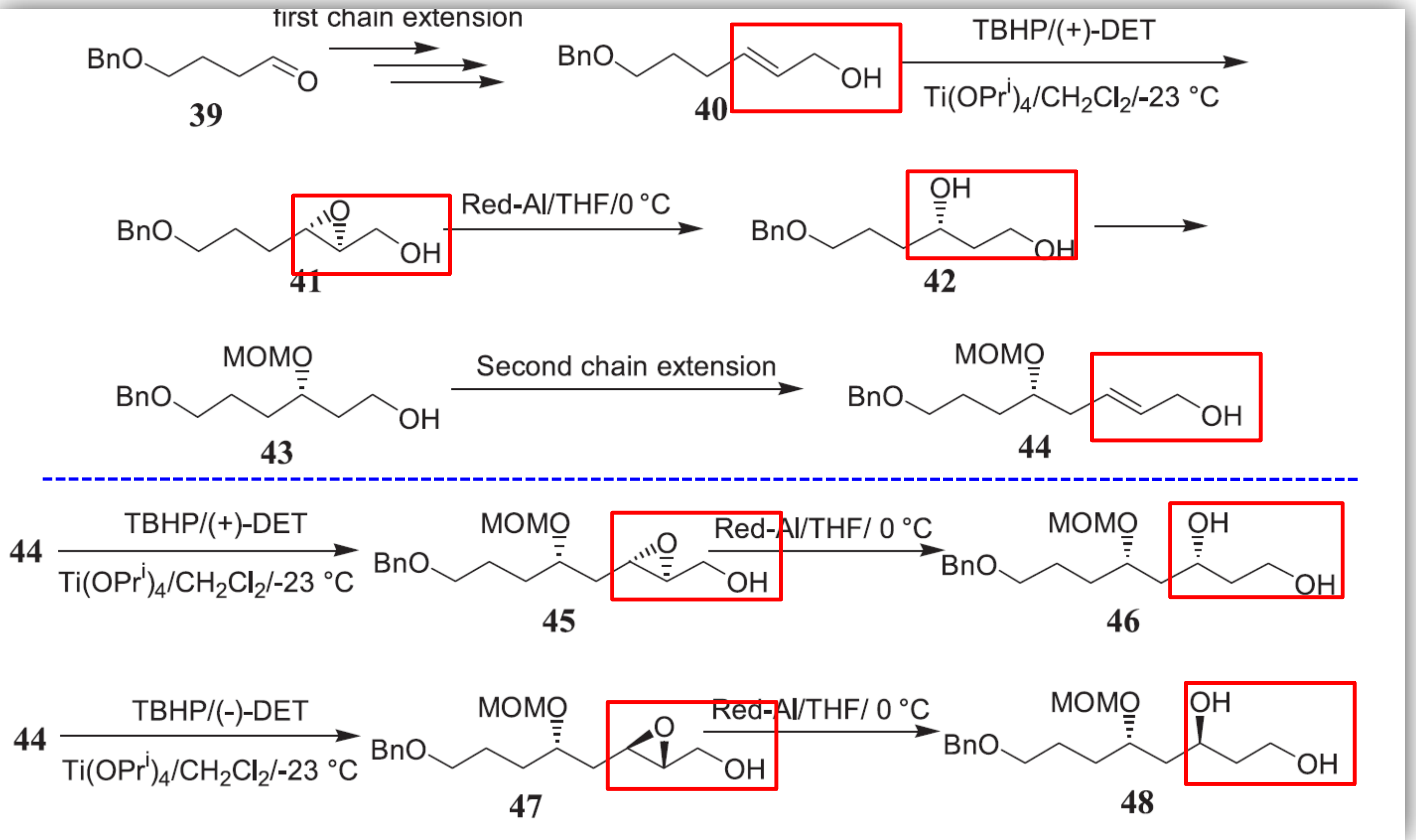


L-赤鞘氨醇

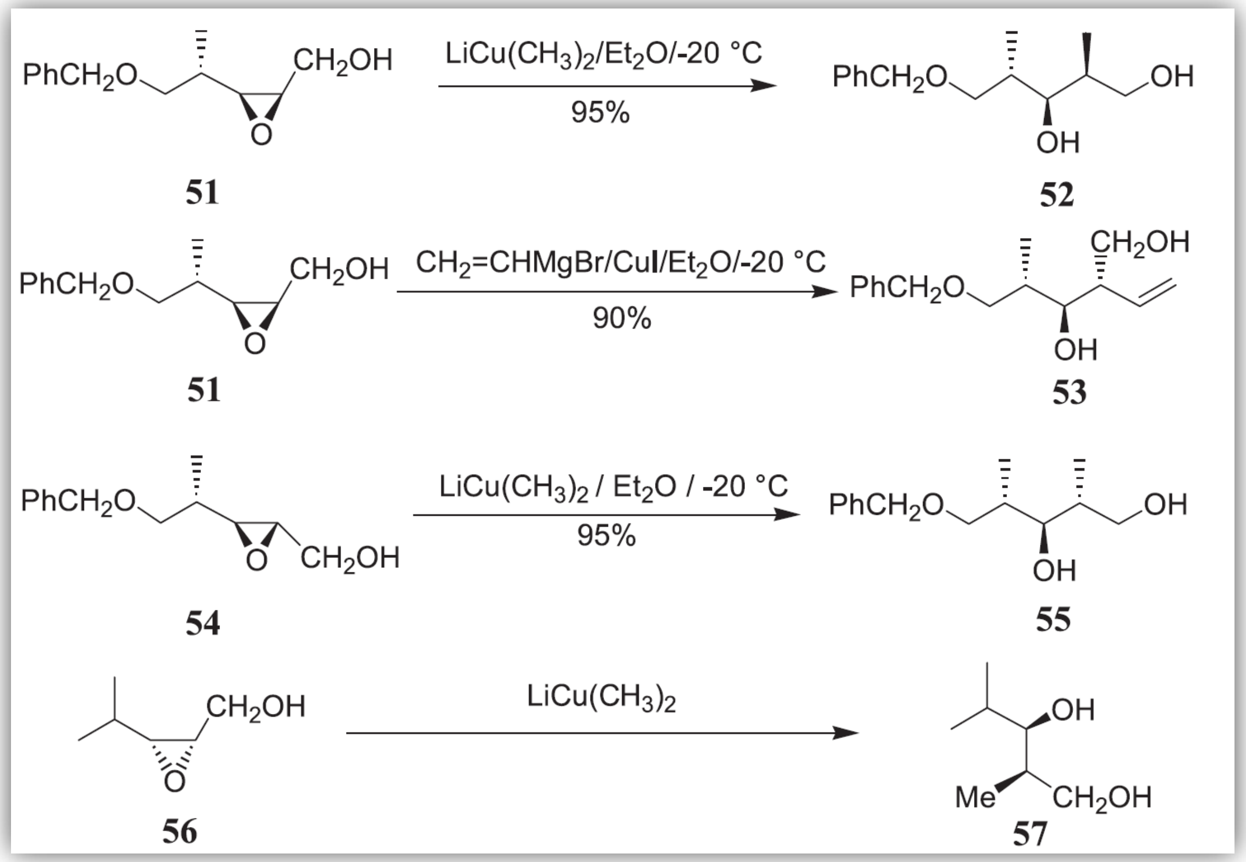


D-赤鞘氨醇

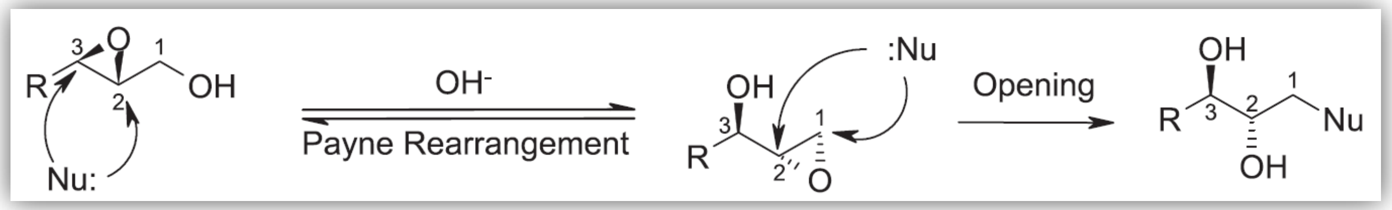
▪ *Opening by Metallic Hydride Reagents*

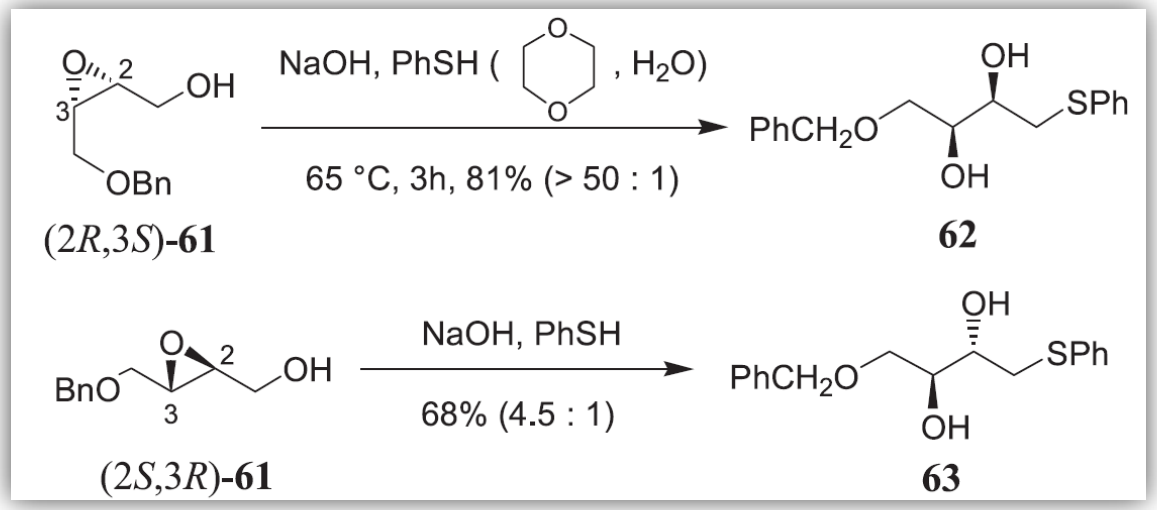


- *Opening by Organometallic Compounds*



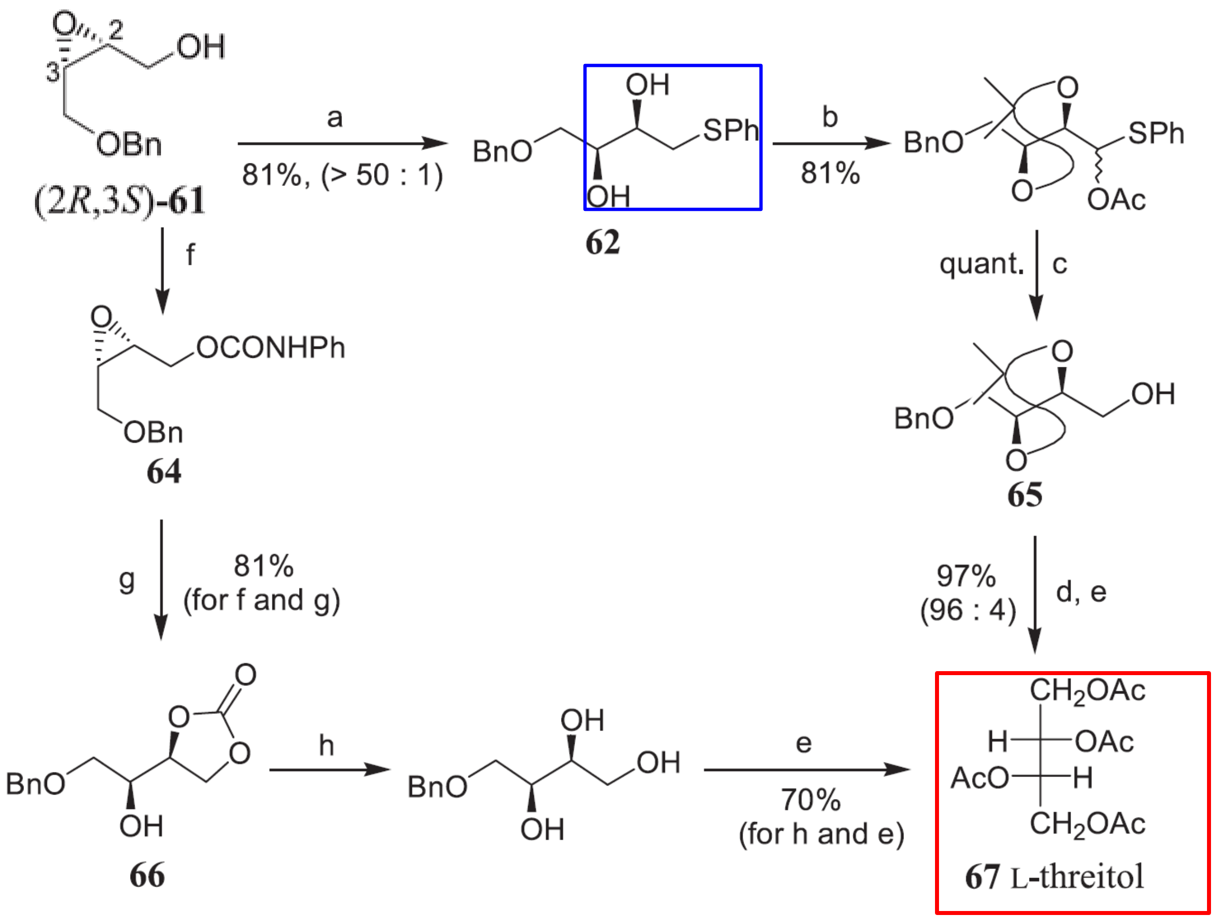
· *Payne Rearrangement and Ring-Opening Processes*





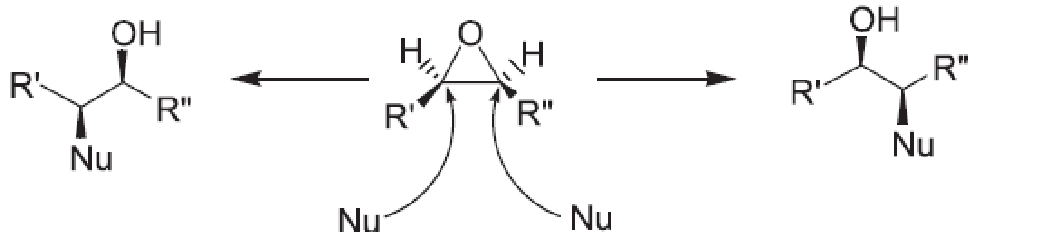
(2*R*,3*S*)-**61** → **62**

(2*S*,3*R*)-**61** → **63**

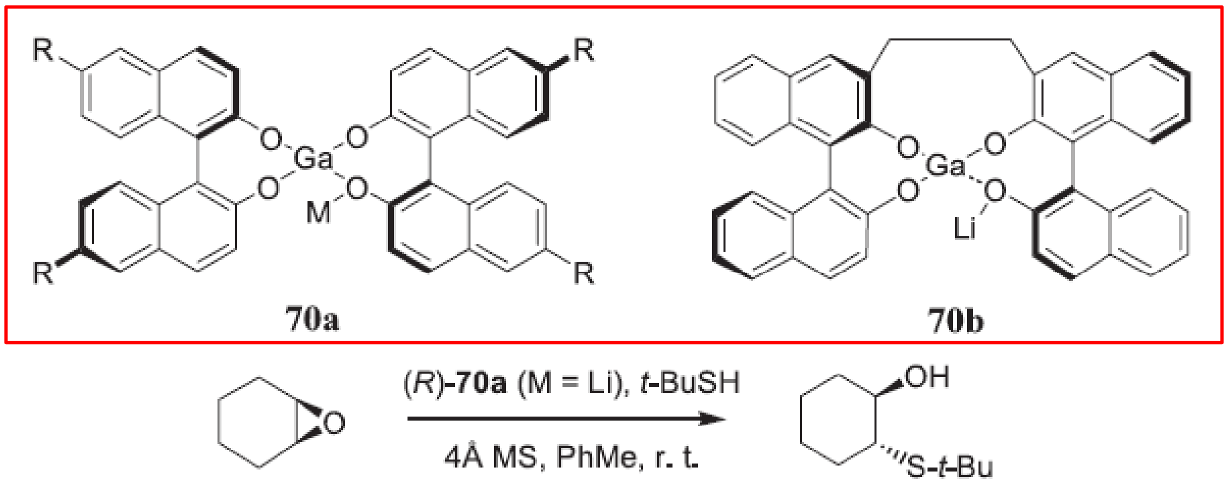


赤糖醇

Scheme 4–21. Asymmetric synthesis of tetritol isomers **67** and **69**. Reagents and conditions: a: NaOH, PhSH (dioxane, H_2O), 65°C, 3 h. b: (1) $Me_2C(OMe)_2$, H^+; (2) *m*-CPBA, CH_2Cl_2, −20°C, 1 h; (3) Ac_2O, NaOAc, reflux, 6 h. c: LAH, ether, 0°C, 1 h. d: MeOH, H^+, 70°C, 1 h. e: (1) H_2, Pd/C, acidic MeOH, 25°C, 6 h; (2) Ac_2O, C_5H_5N. f: PhNCO, $(Et)_3N$, CH_2Cl_2, 25°C, 24 h. g: 5% $HClO_4$, CH_3CN, 25°C, 24 h. h: NaOH, aq. MeOH, 25°C, 24 h.



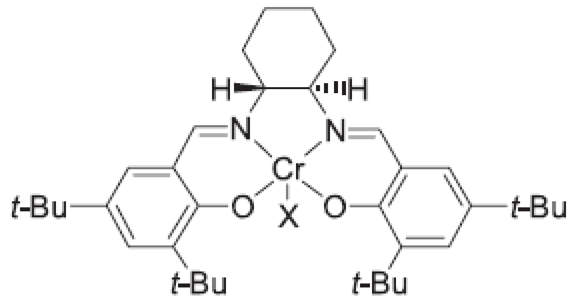
Scheme 4–22. Enantioselective ring opening of *meso*-epoxides (R′ = R″).



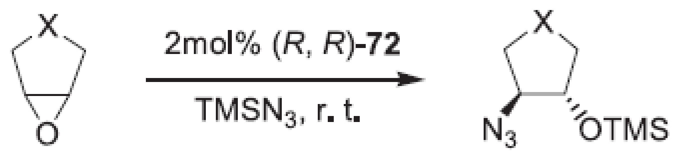
80% yield, 97% ee

Scheme 4–24. Gallium–lithium complex-catalyzed ring opening.

6.5 Asymmetric Desymmetrization of meso-Epoxides



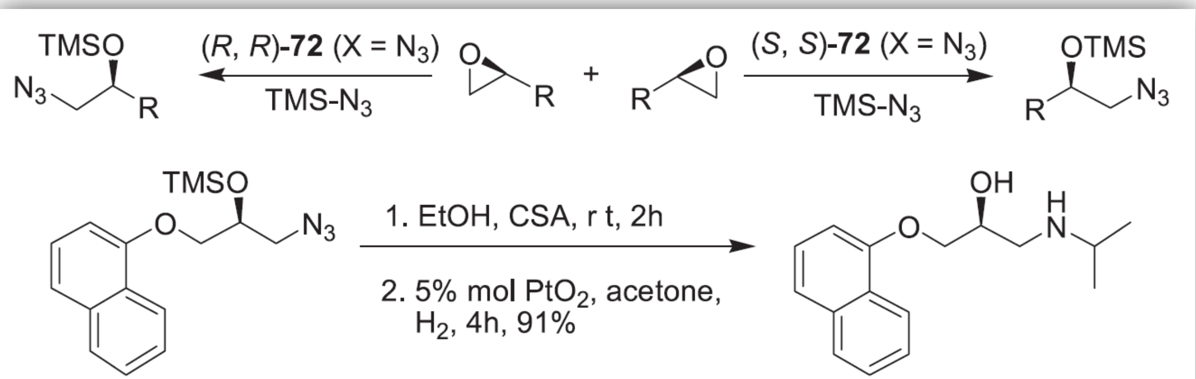
72 X = Cl, N_3



73

74 up to 97% ee

Scheme 4–26



(*S*)-propranolol
anti-hypertensive agent

Thanks for your attention!