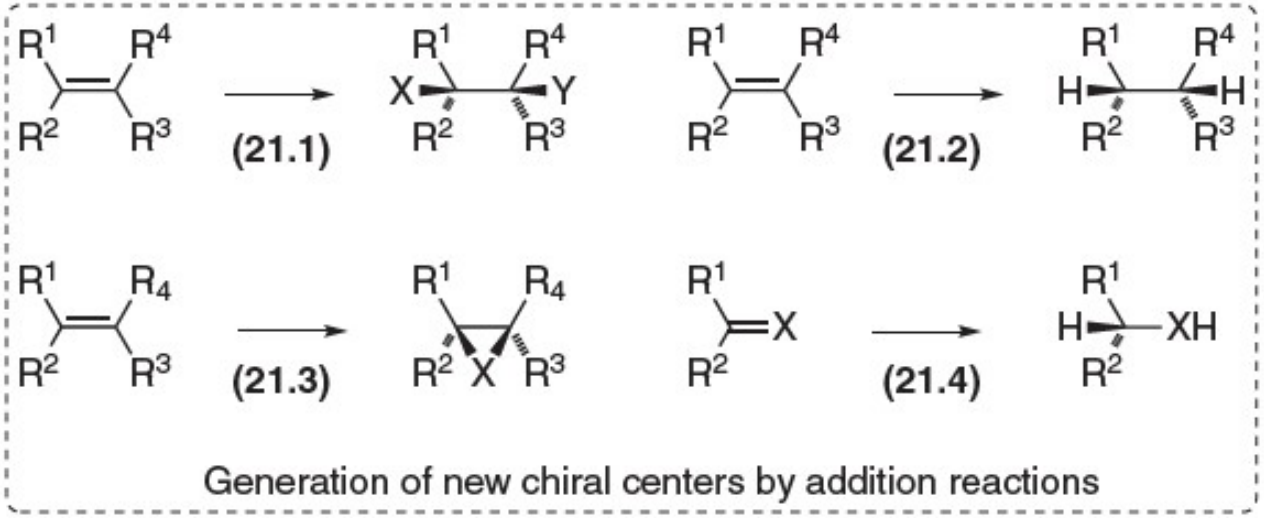
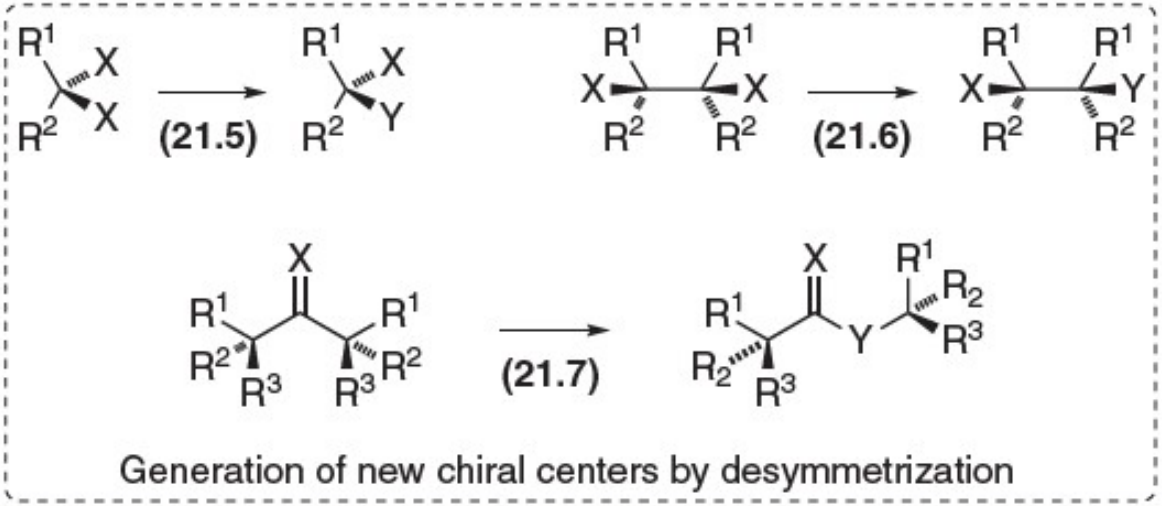
Chapter 21

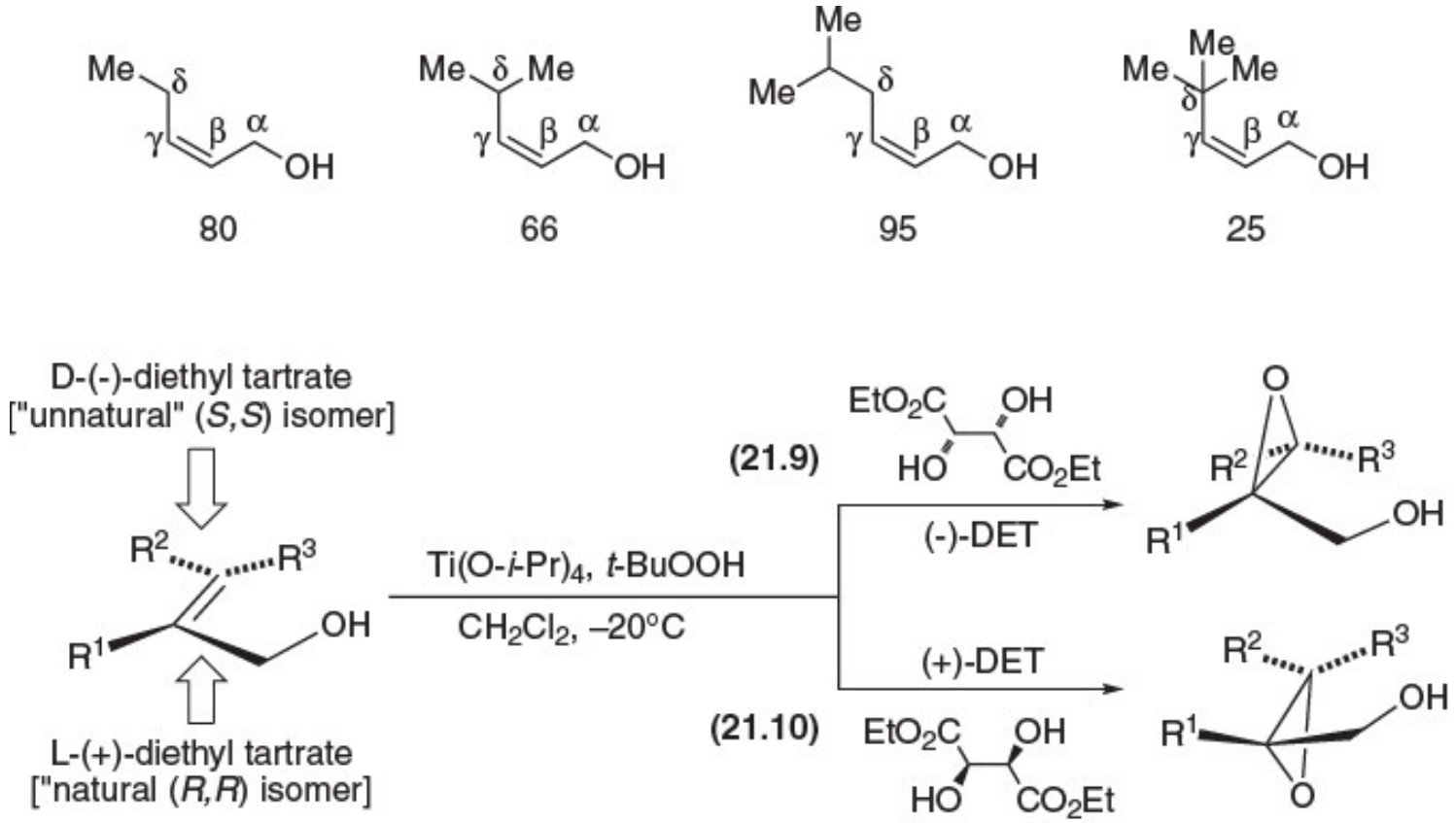
Figure 21.1





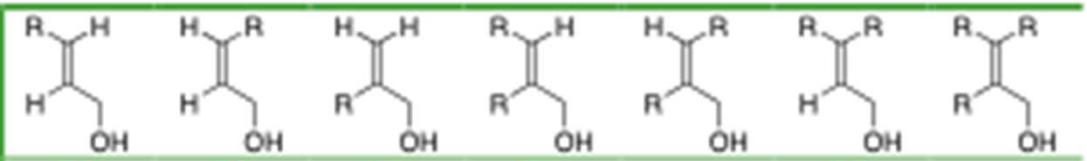
- Strategies for enantioselective redox

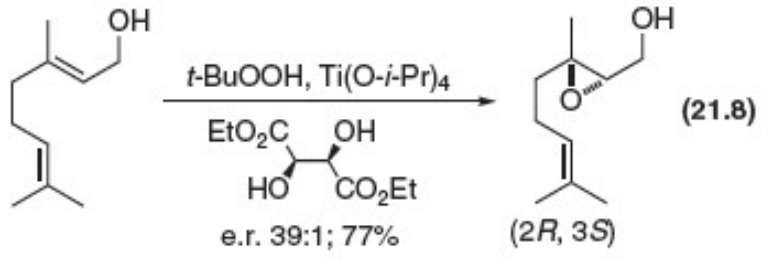
Figure 21.2



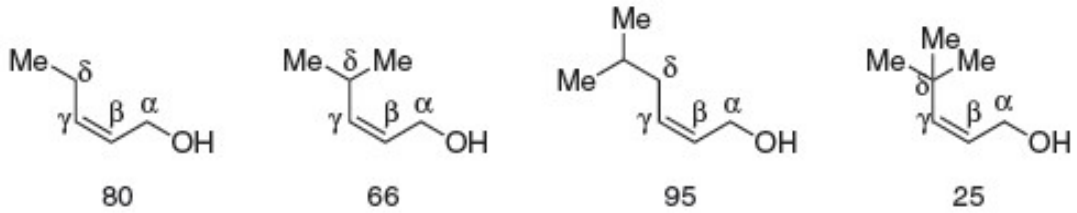
- Prediction of epoxide stereochemistry in the Sharpless asymmetric epoxidation

Factors affecting the Sharpless asymmetric epoxidation

Alcohol structure							
% Yield, (R=Me)	70	68	47	77	n.a.	25	n.a.
Range of % ee	92-98	25-95	85-95+	90-98+	78-91	86-95+	53-95

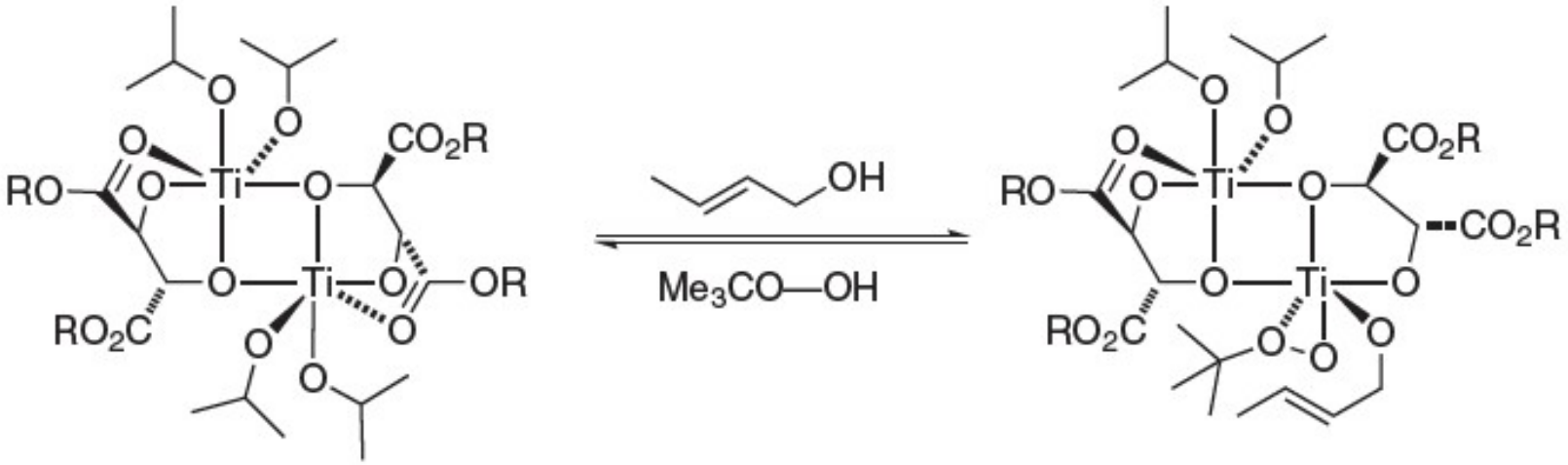


- Note that *cis* allylic alcohols give widely variable levels of enantioselectivity



- substitution in *cis* allylic alcohols reveals that substitution at the δ position lowers the enantioselectivity, while substitution at the ε position has little effect

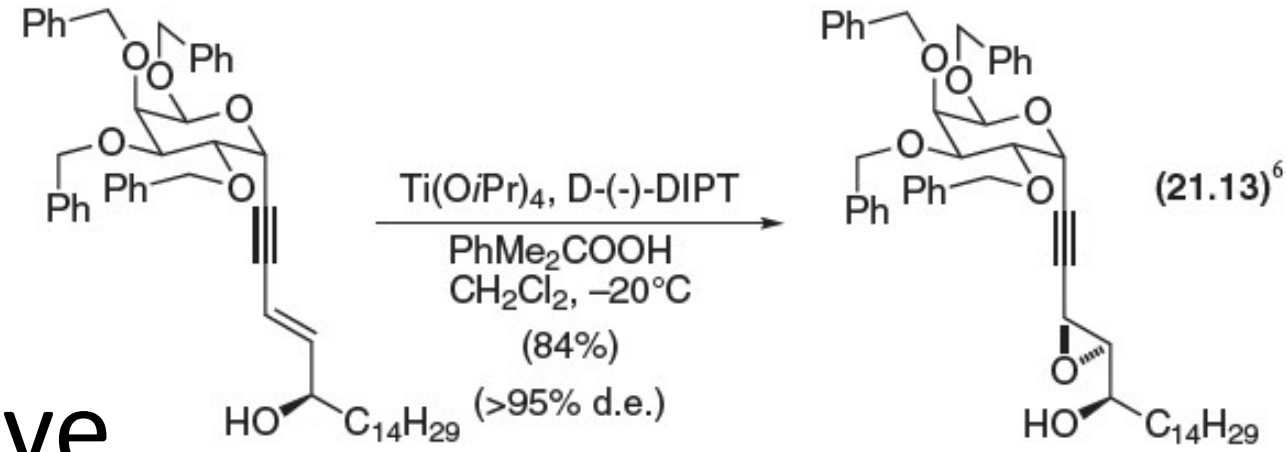
Figure 21.3

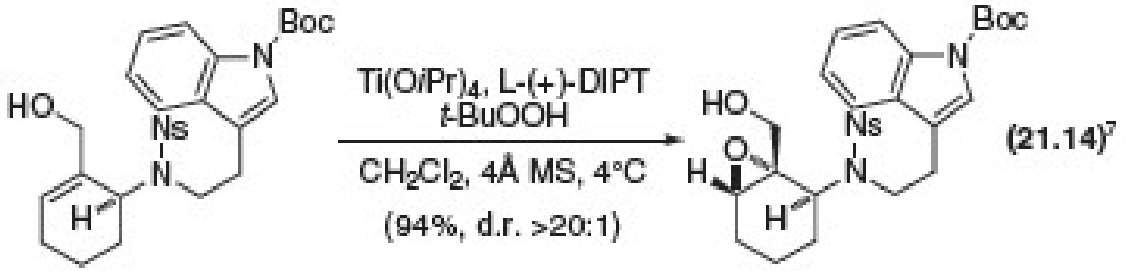


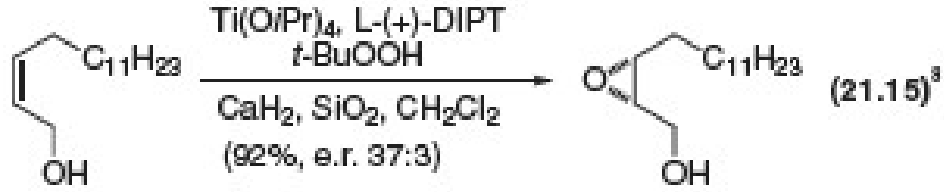
(21.11) (21.12)

- Proposed active species in the Sharpless asymmetric epoxidation

Representative Sharpless asymmetric epoxidation reactions







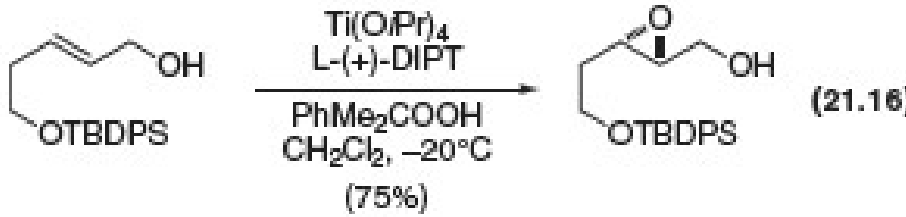
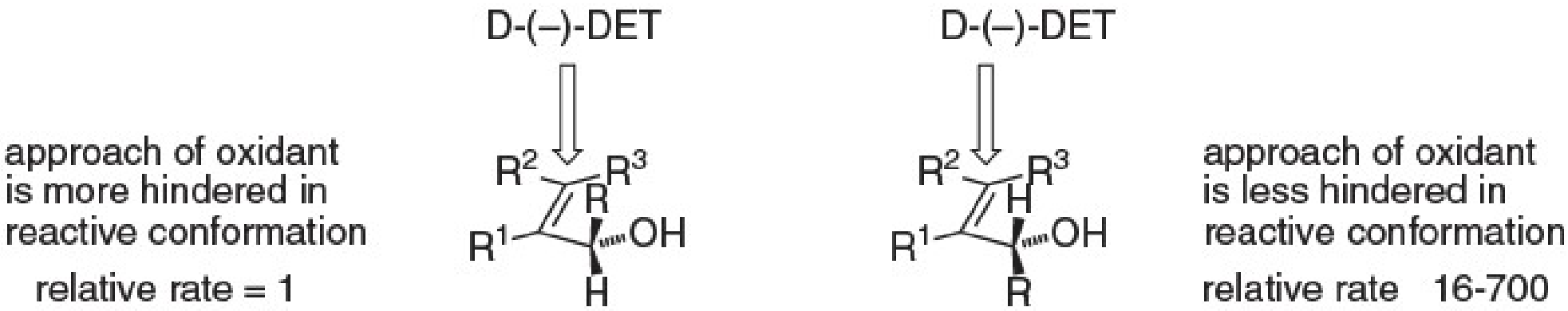
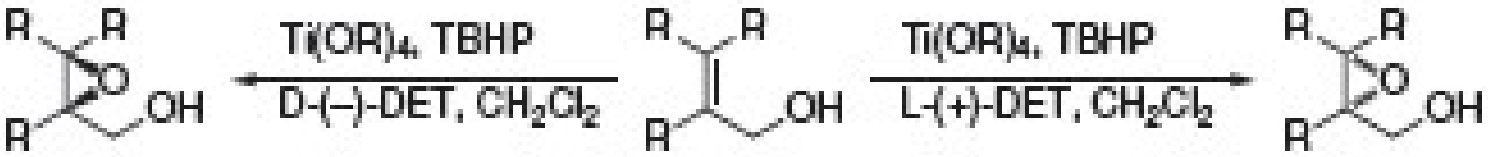


Figure 21.4



- Prediction of stereochemistry epoxidation of chiral allylic alcohols based on rate differential

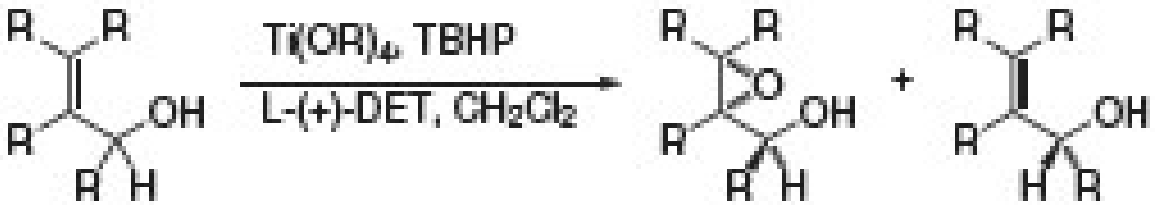
Reaction synopses: Sharpless asymmetric epoxidation



Reagents:

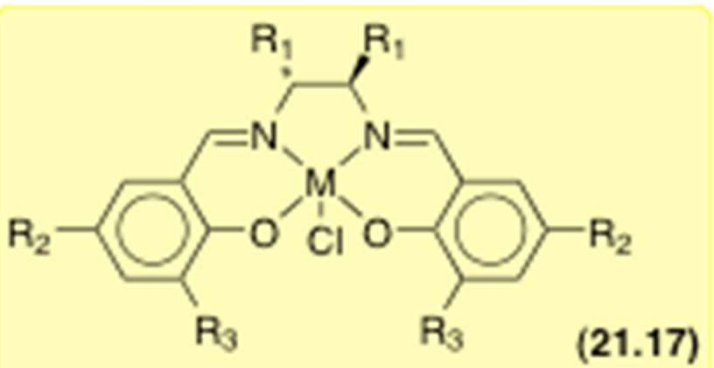
titanium alkoxide: $Ti(OCHMe_2)_4$, $Ti(OCMe_3)_4$
tartrate esters: diethyl tartrate (DET), diisopropyl tartrate (DIPT)
oxidant: *tert*-butyl hydroperoxide (Me_3COOH, TBHP);
cumyl hydroperoxide ($PhCMe_2OOH$); etc.
adjuvants: 4Å molecular sieves (4Å MS); CaH_2, SiO_2; etc.

Reaction synopses: Kinetic resolution of allylic alcohols



Reagents: as for asymmetric epoxidation

Representative Jacobson catalysts

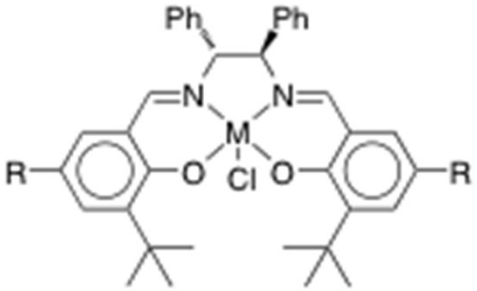


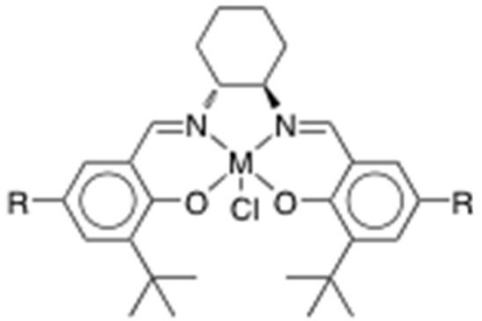
(21.17)

M = Mn or Cr
R_1 = Ph or $-(CH_2)_4-$
R_2 = R, Ar, OR
R_3 = *t*-Bu, $CHAr_2$

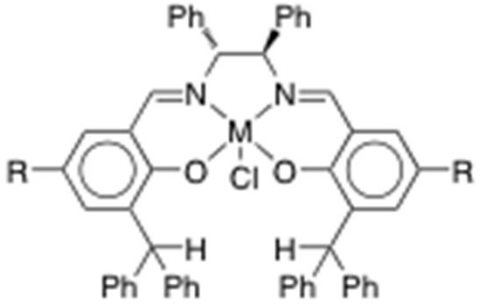
generic Jacobson catalyst

chiral directing influence is exercised by the chiral ethylenediamine unit





M = Mn or Cr
R_2 = R, Ar, OR



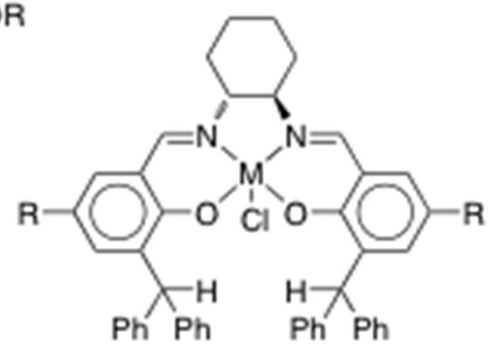
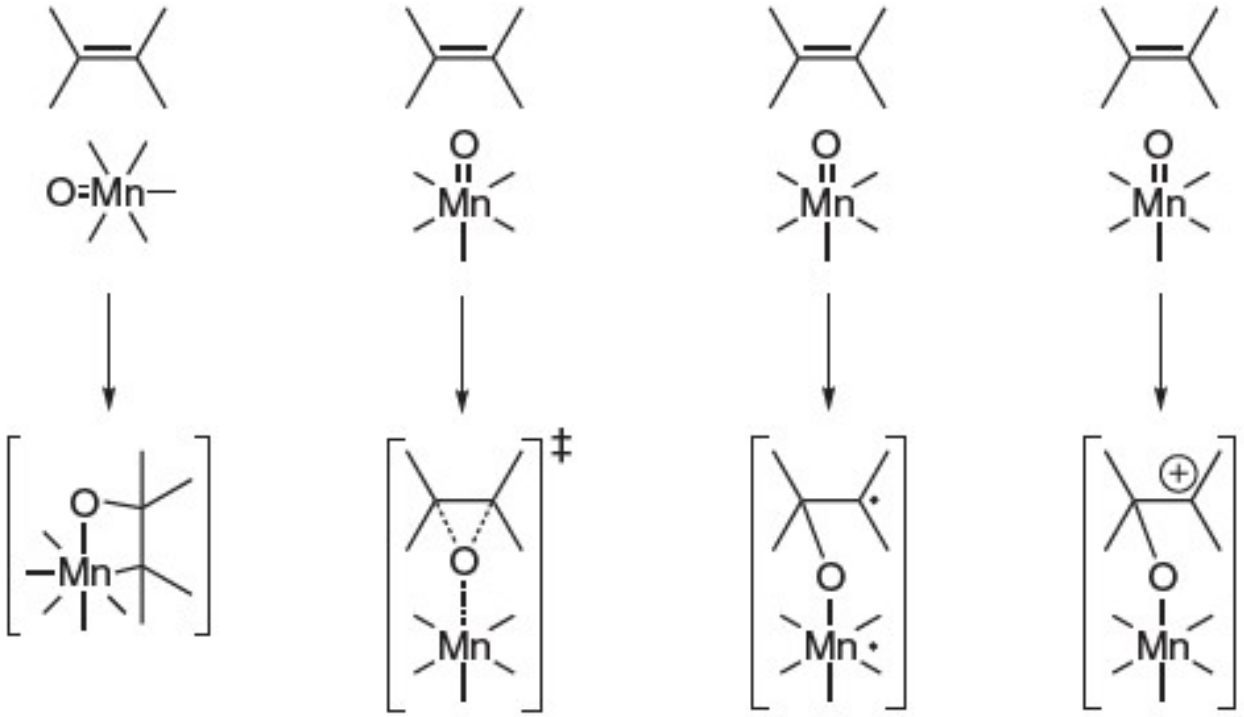
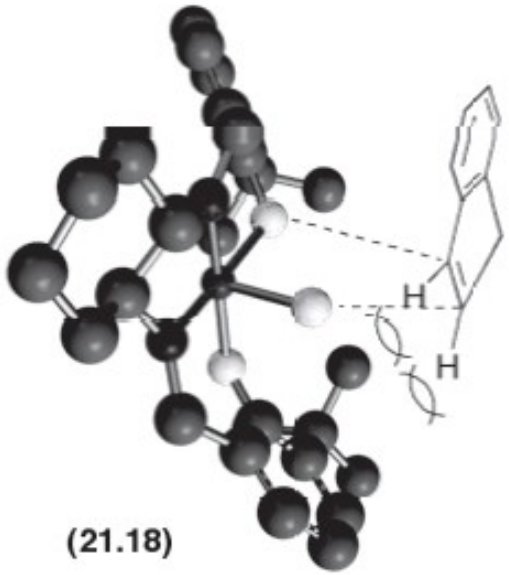


Figure 21.5

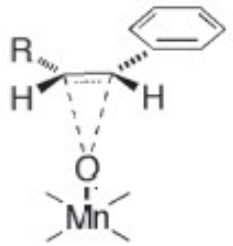


- Possible mechanisms for delivery of oxygen to the alkene.

Figure 21.6



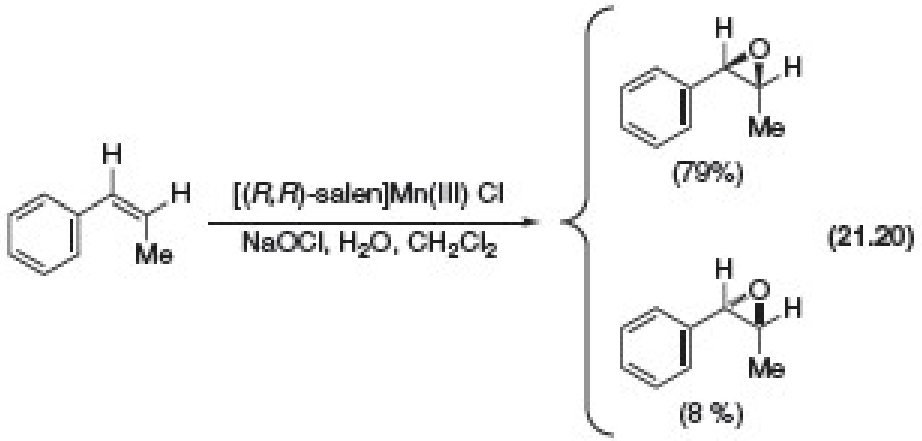
(21.18)



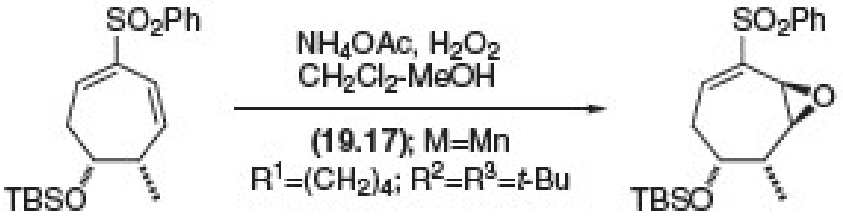
(21.19)

- Predicting the stereochemistry of olefin epoxidation using Mn (*S,S*)- salen complexes

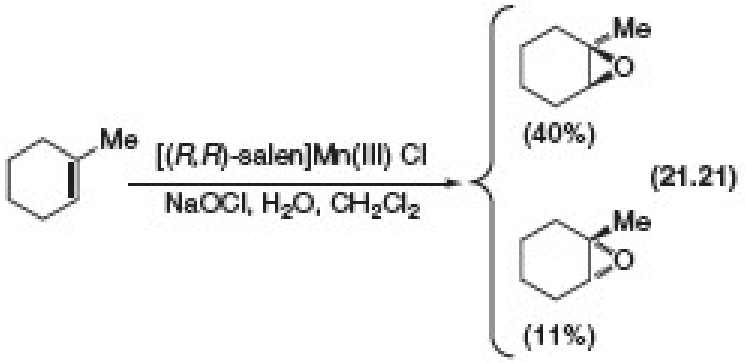
Representative epoxidations using Jacobson catalysts



(21.20)



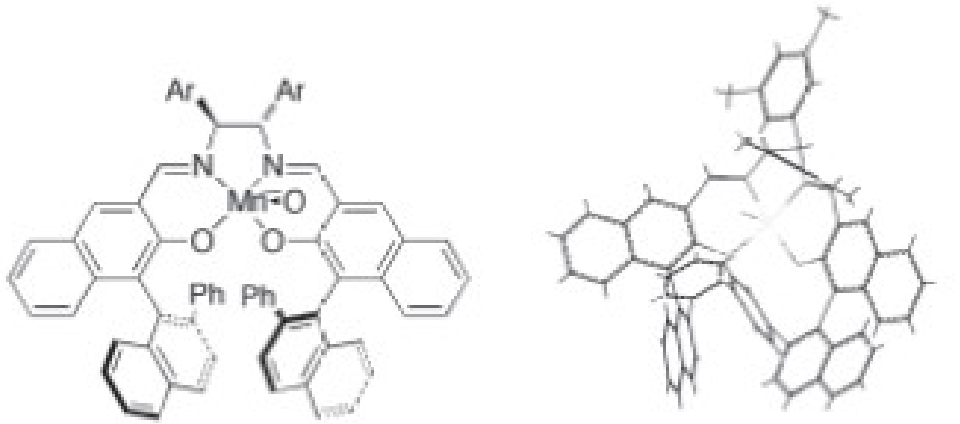
(21.22)



(21.21)

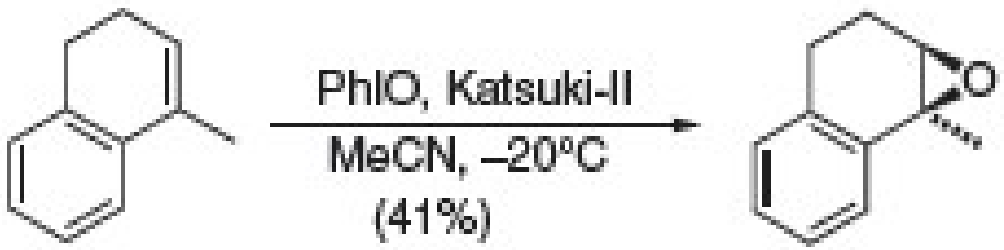
Katsuki catalysts

- chirality is incorporated into the groups labeled R_3 in the generic Jacobson catalyst
- the chiral directing influence is exercised by a binaphthyl unit rather than by the ethylenediamine moiety
- e.e. values are typically above 80%



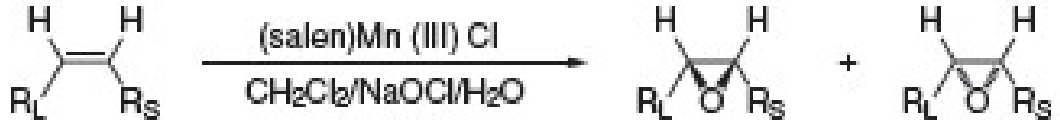
(21.23)

a second-generation Katsuki Catalyst



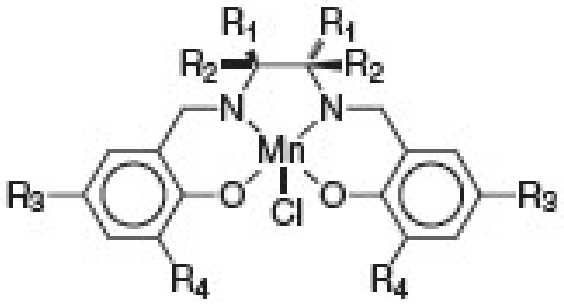
(21.24)

Reaction synopses: Jacobson-Katsuki epoxidation of unactivated alkenes



(*R*,*R*):	major	minor
(*S*,*S*):	minor	major

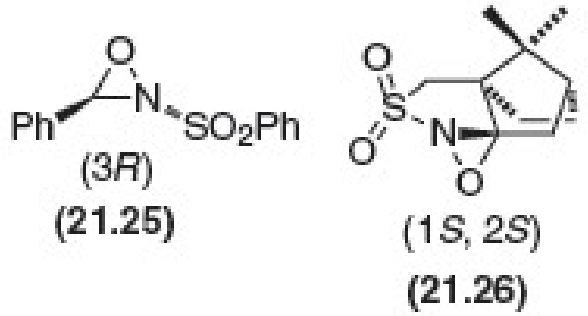
Enantioselectivity is higher for *cis*-disubstituted alkenes.
Enantioselectivity enhanced by donor ligands (e.g. NMMO, pyridine-*N*-oxide, etc.)
Reactivity often enhanced by ammonium ion additives

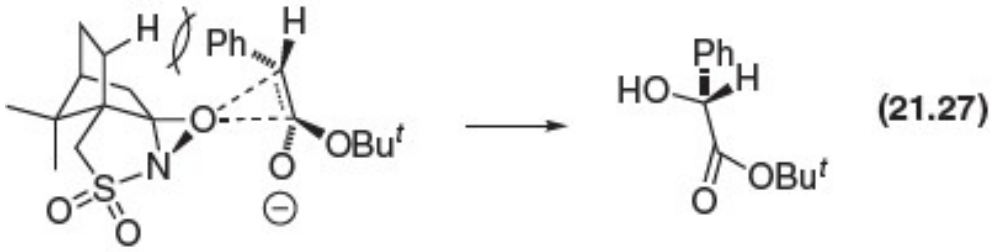


Jacobsen Catalyst	Katsuki Catalyst
R_1=Ar, $(CH_2)_4$ OR H	R_1=Ar, $(CH_2)_4$ OR H
R_2=H OR Ar, $(CH_2)_4$	R_2=H OR Ar, $(CH_2)_4$
R_3=R, OR	R_3=R, OR
R_4=*t*-Bu	R_4=CH(Ar)Ar'

Figure 21.7

- Preferred approach of the enolate anion to the chiral oxaziridine avoids steric congestion between the alkene substituent and the camphor framework.





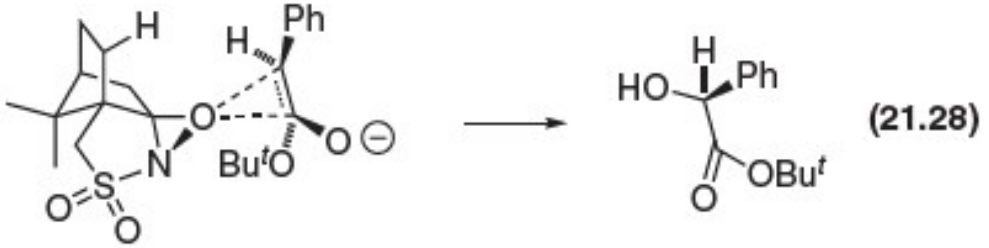
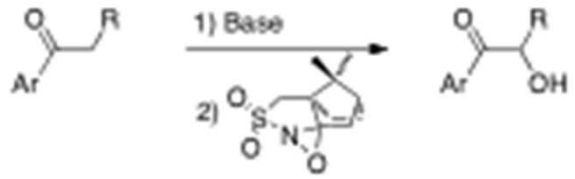
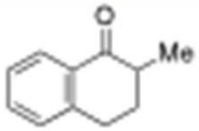
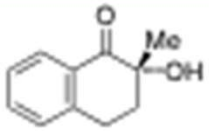
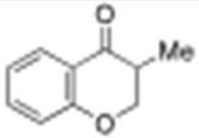
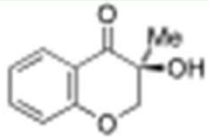
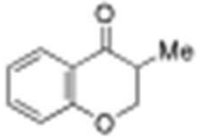
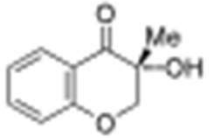
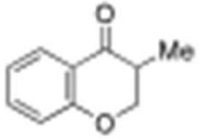
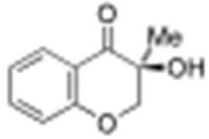
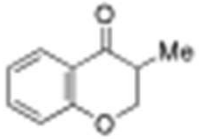
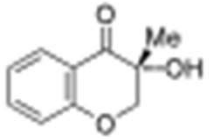
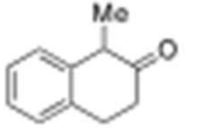
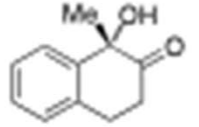
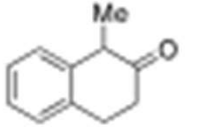
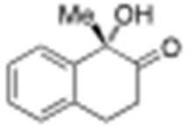
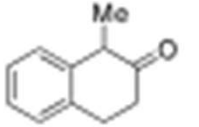
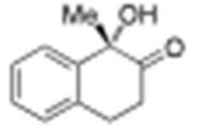
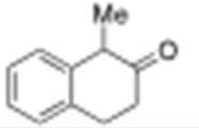
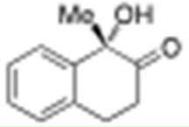
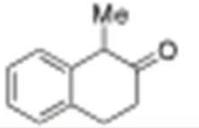
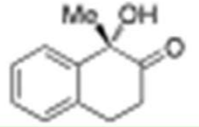


Table 21.2



Ketone	Base	Product	e.e.	Ketone	Base	Product	e.e.
	NaHMDS		95		LDA		30
	NaHMDS		71		LDA		64
	NaHMDS		96		NaHMDS		76
	NaHMDS HMPA		65		LDA		10
	NaHMDS		16		LDA		54

Stereochemical outcome of oxidation of enolates with the Davis camphorsulfonyloxaziridine

Representative oxidations with Davis oxaziridines

- oxidation of ester enolates with the Davis CSO does not always give high enantioselectivities
- an excellent reagent for effecting hydroxylation, even when no new chiral center is formed
- Enolates from deprotonation of saturated compounds or conjugate addition to α,β-unsaturated carbonyl compounds are both amenable to oxidation

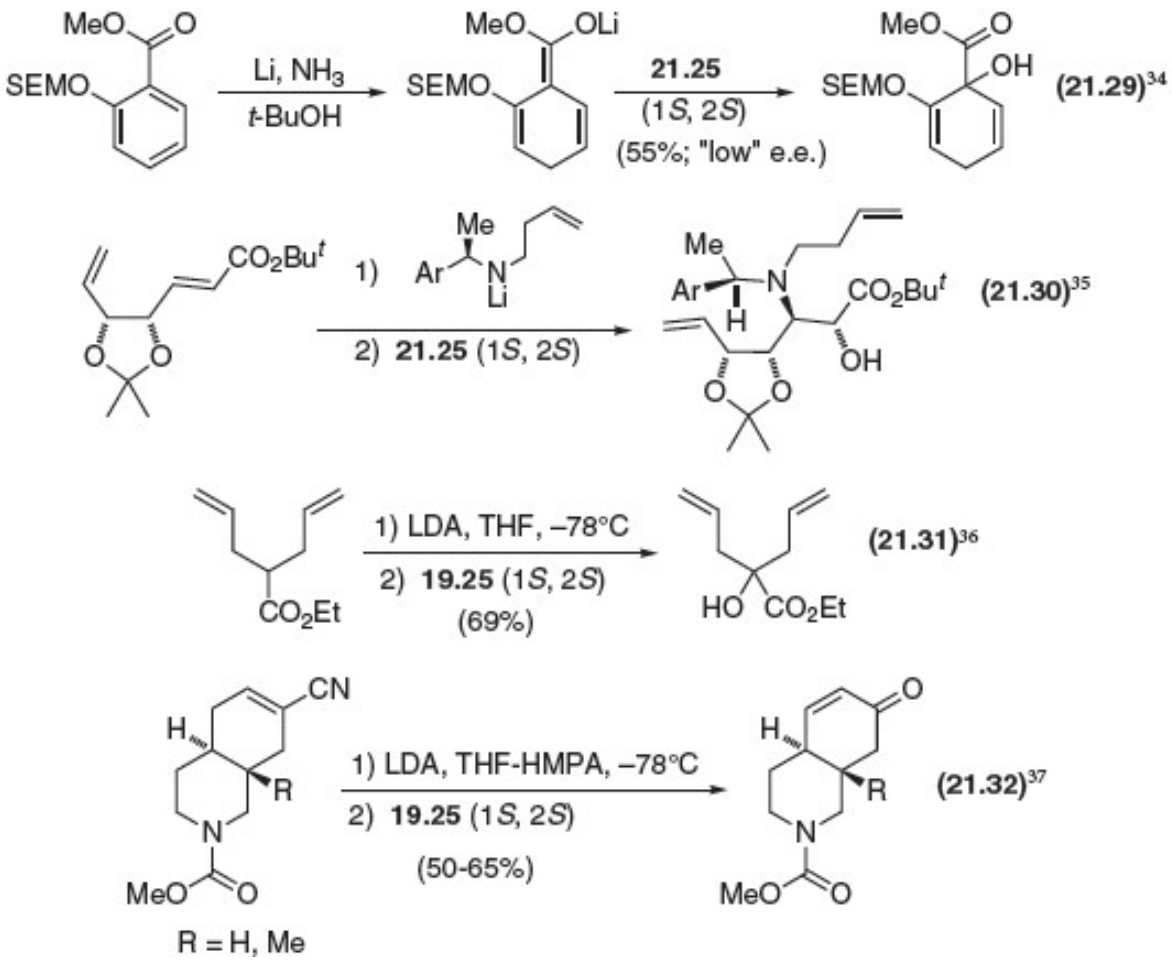
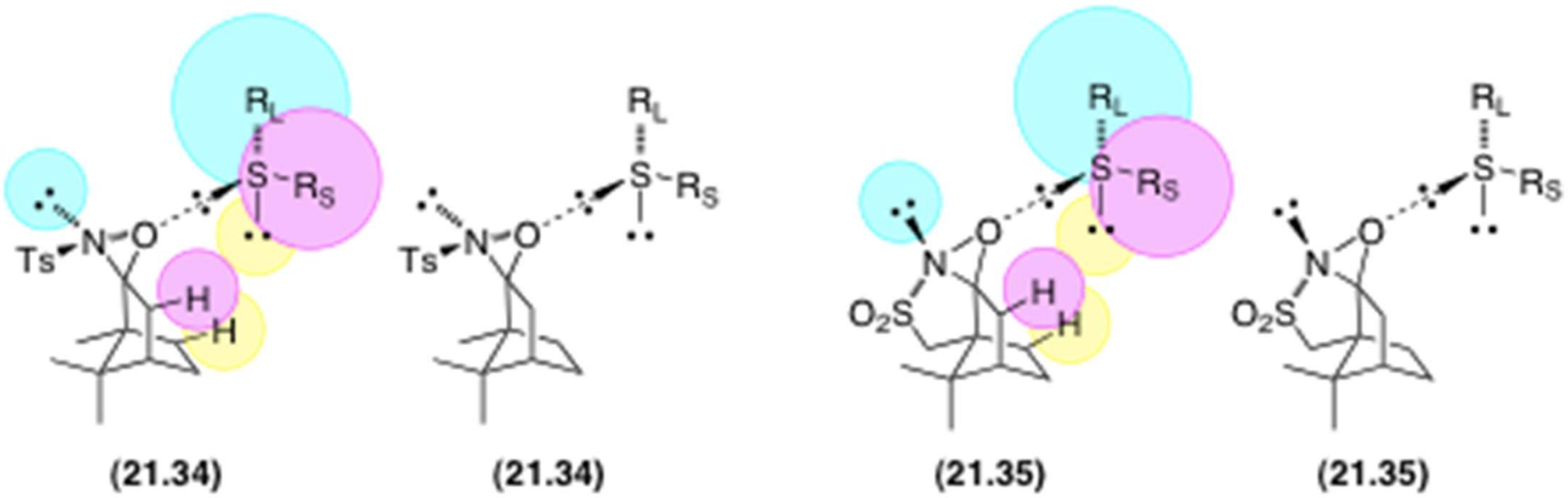
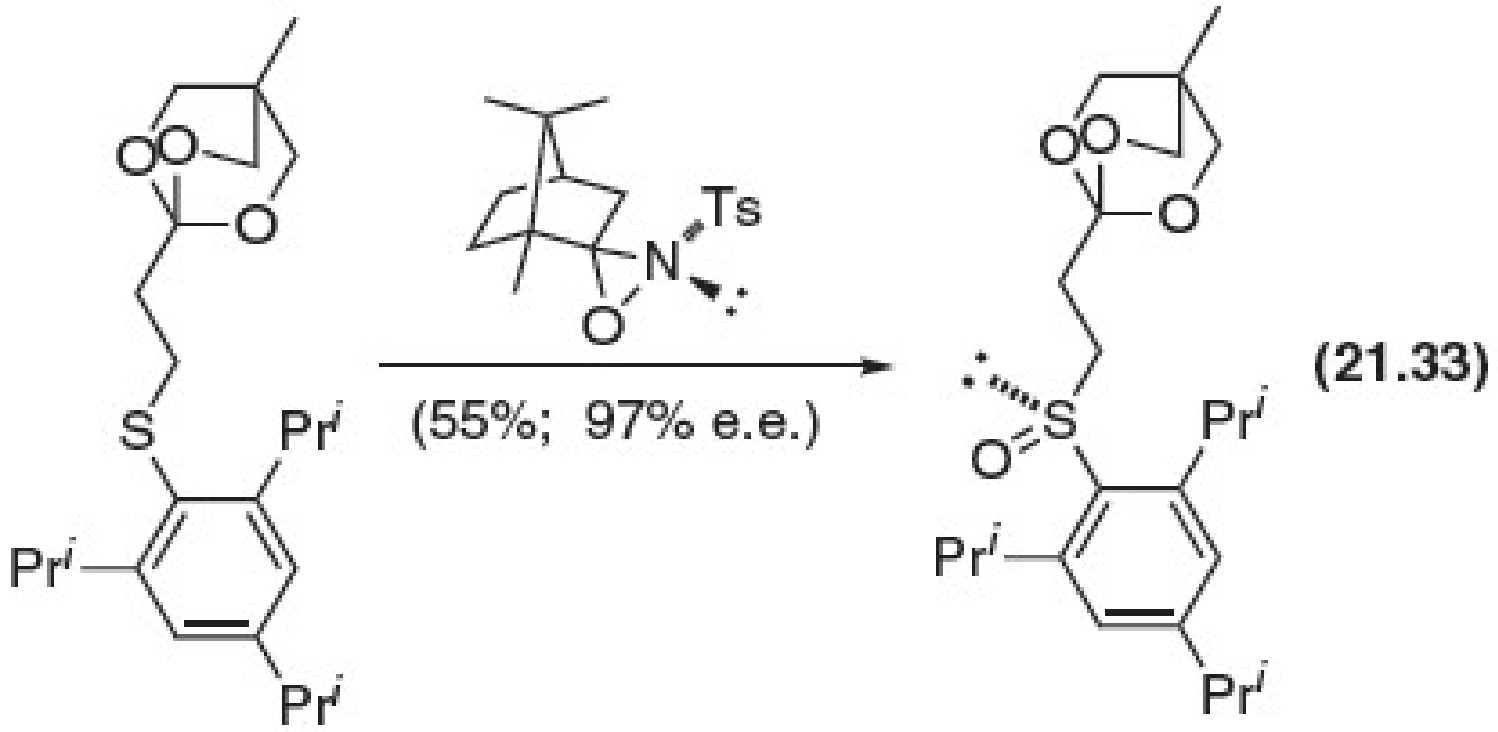


Figure 21.8



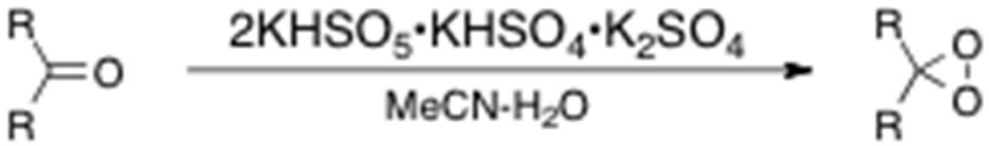
- A model for predicting the stereochemistry of the major epoxide by oxidation of sulfides with chiral oxaziridines

Representative sulfide oxidation with Daviz chiral oxaziridine

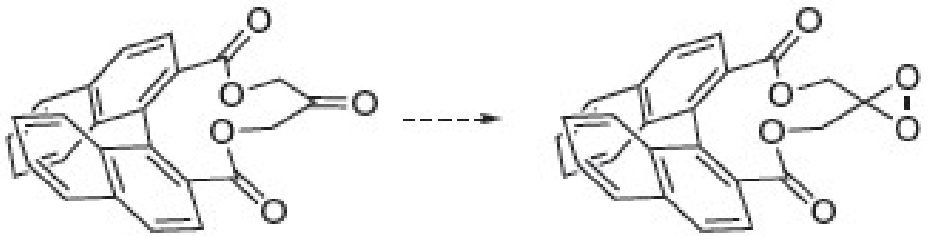


Chiral dioxiranes

- formed by oxidation of ketones with Oxone®



- C_2-symmetric dioxiranes are easily formed, but do not always give high e.e. levels in the product



- Shi epoxidation catalyst is based on chiral fructose derivatives

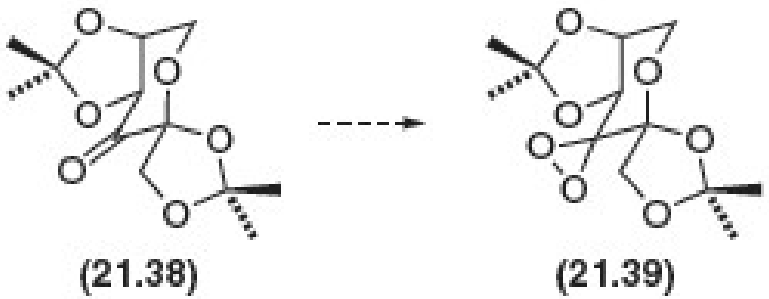
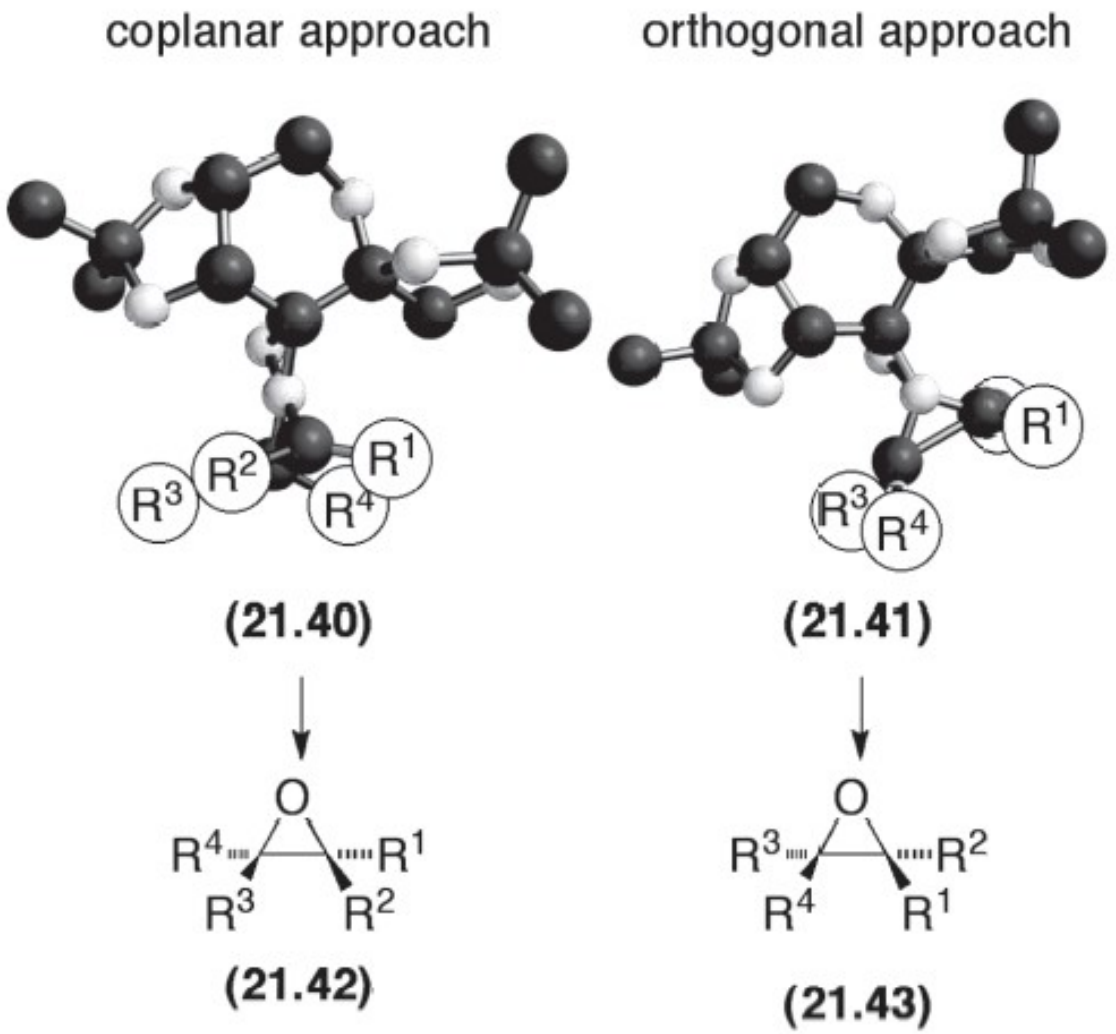


Figure 21.9

Competing activated complexes for the Shi epoxidation of alkenes.

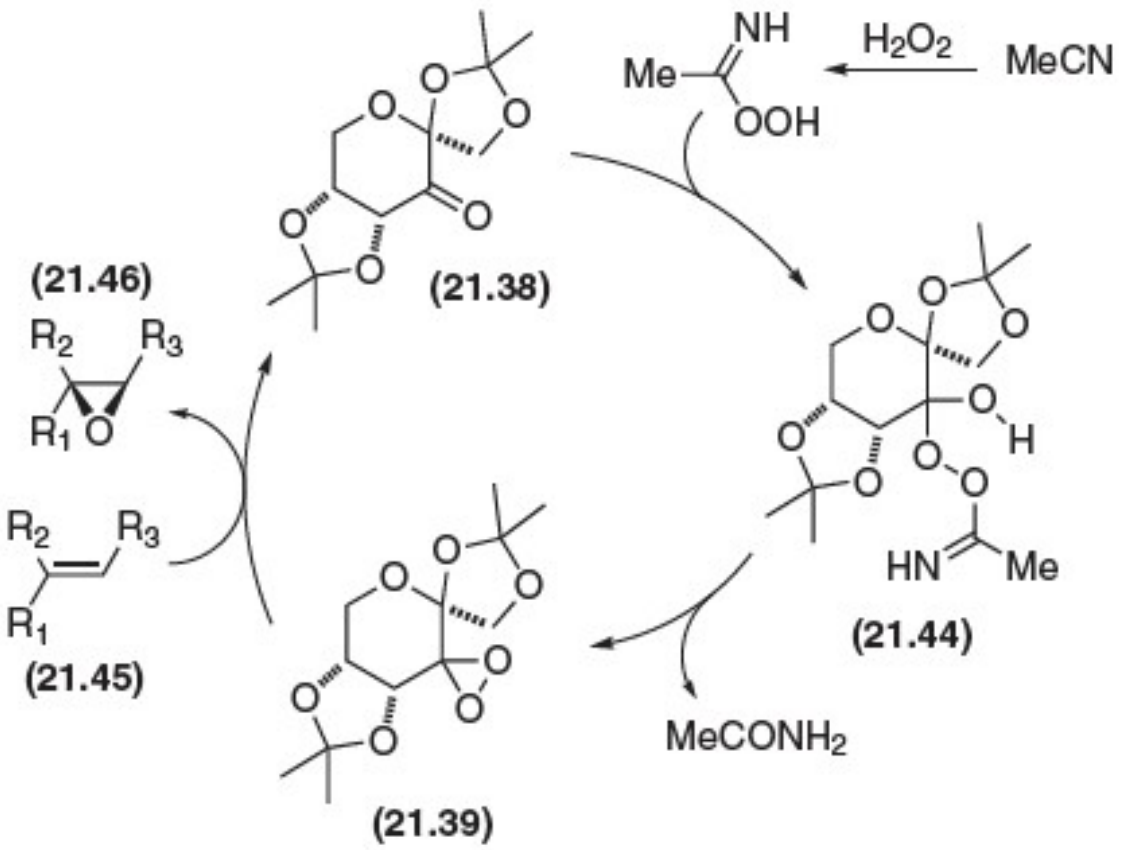


Tbale 21.3

- Effects of alkene structure on the enantioselectivity of the Shi oxidation of trisubstituted alkenes

R_1	R_2	R_3	% e.e. (e.r)
Ph	H	Ph	>95 (>39:1)
Ph	H	Me	88 (47:3)
Ph	—	$(CH_2)_4$ —	98 (99:1)
Ph	H	CH=CHPh	97 (197:3)
$PhCO_2$	—	$(CH_2)_4$ —	93 (193:7)
Ph	H	CH_2Cl	93 (193:7)
Ph	H	$(CH_2O)_2CH$	93 (193:7)
$C_{10}H_{21}$	Et	Et	89 (189:11)
Me_3C	—	$(CH_2)_4$ —	26 (63:37)
n-Bu	—	$(CH_2)_4$ —	79 (179:21)
Me	—	$(CH_2)_4$ —	81 (181:19)

Figure 21.10



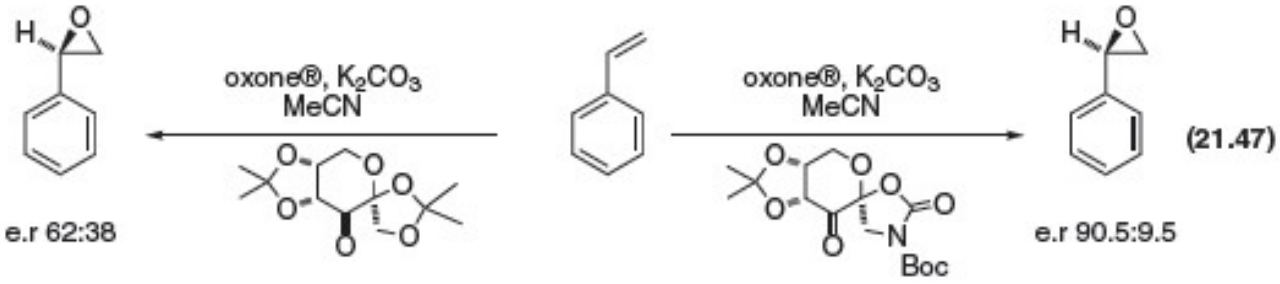
- Catalytic cycle for the Shi oxidation using hydrogen peroxide-acetonitrile as the stoichiometric oxidant.

Representative Shi epoxidations

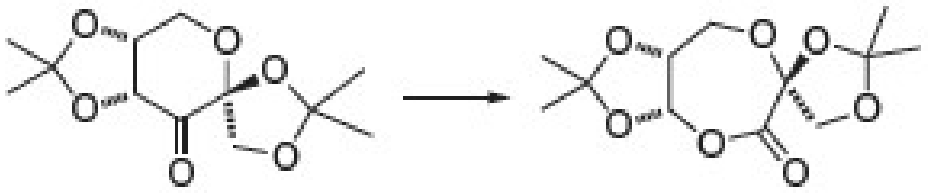
- epoxidation of terminal alkenes gives higher e.e. levels when a modified (urethane) catalyst is used

- Baeyer-Villiger oxidation of the ketone catalyst is a problem when the oxidation of electron-deficient alkenes is undertaken

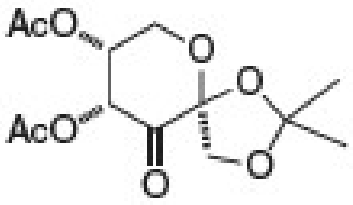
- Baeyer-Villiger oxidation of the catalyst can be reduced by using the modified catalysy where one dioxolane ring is replaced by a diacetate



(21.47)

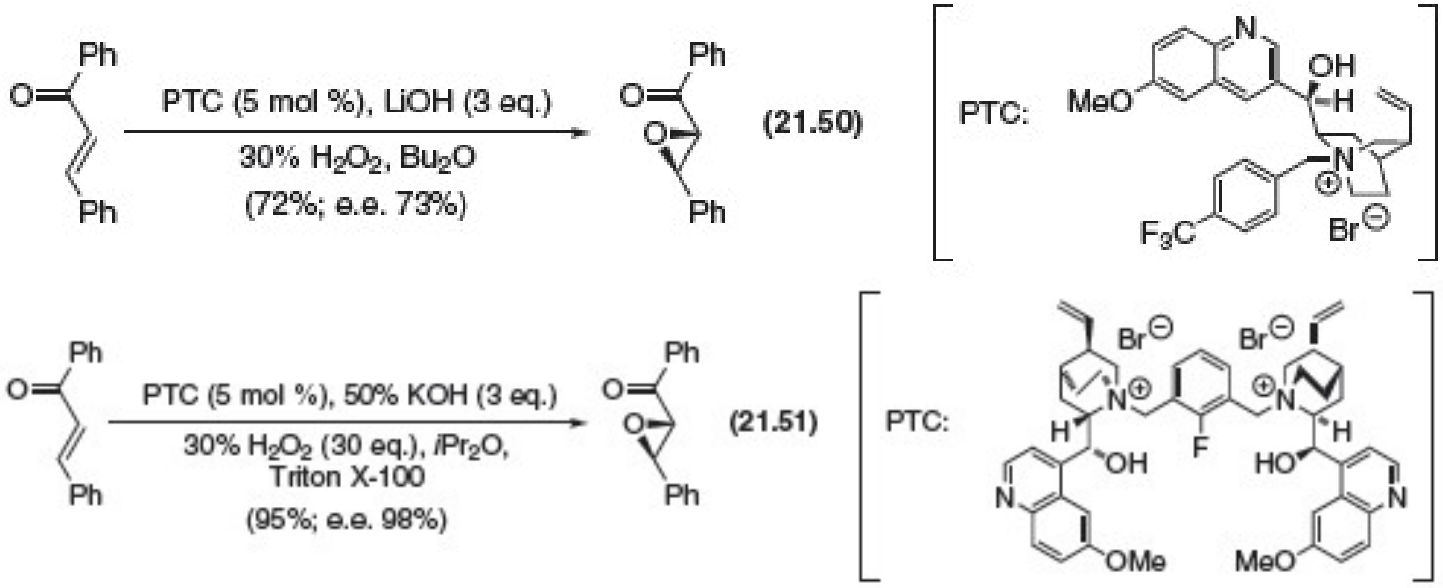


(21.48)



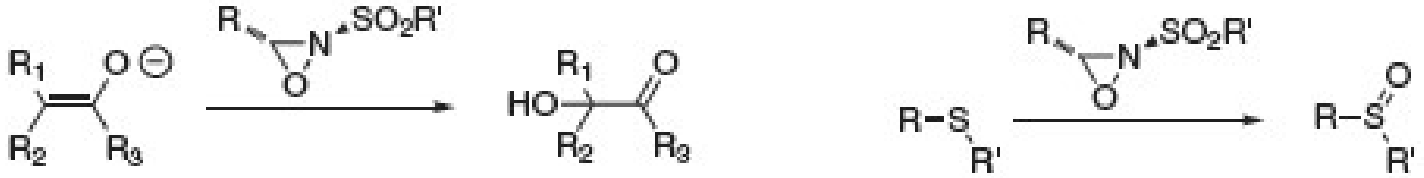
(21.49)

Epoxidation of enones with chiral phase transfer catalysts (PTC)



- PTC based on *Cinchona* alkaloids are efficient catalysts for asymmetric epoxidation of enones
- PTC based on dimeric *Cinchona* alkaloids are even more efficient catalysts for asymmetric epoxidation of enones

Reaction synopses: Oxidation with chiral oxaziridines



Reagents:

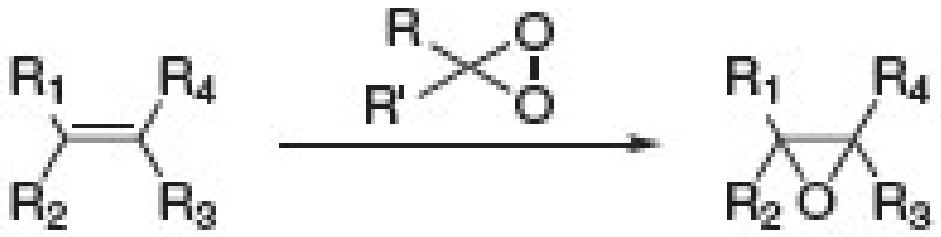
and enantiomers

or RR'C=NR", oxone®, $NaHCO_3$, MeCN-H_2O;
RR'C=NR", $(Ph_4P)(HSO_5)$, MeCN.

Solvent: Usually THF at low (–90 to –50°C) temperatures due to generation of enolate and oxidation being caried out in a single operation

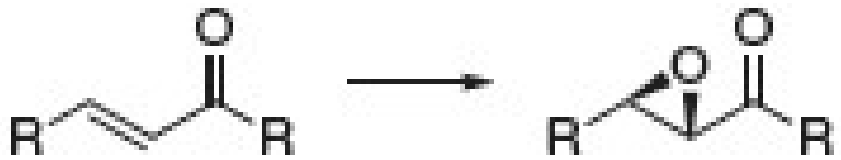
Enantioselectivity varies from high with ketone enolates, to marginal, with ester enolates. Reactivity is greater with oxaziridinium ions, but enantioselectivity may be modest.

Reaction synopses: Shi epoxidation



Reagents: $R_1R_2C{=}O$, oxone®, K_2CO_3, MeCN;
$R_1R_2C{=}O$, H_2O_2, K_2CO_3, MeCN; etc.

Reaction synopses: Enantioselective oxidation of conjugated carbonyl compounds



Reagents: H_2O_2, chiral phase transfer catalyst, R_2O, KOH; etc.

Table 21.4

Choosing an Asymmetric Epoxidation Method

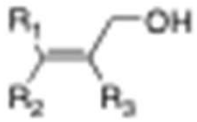
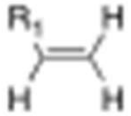
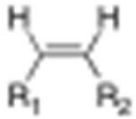
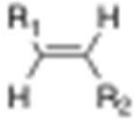
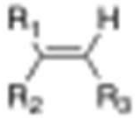
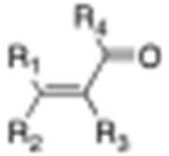
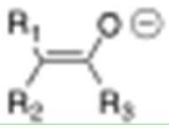
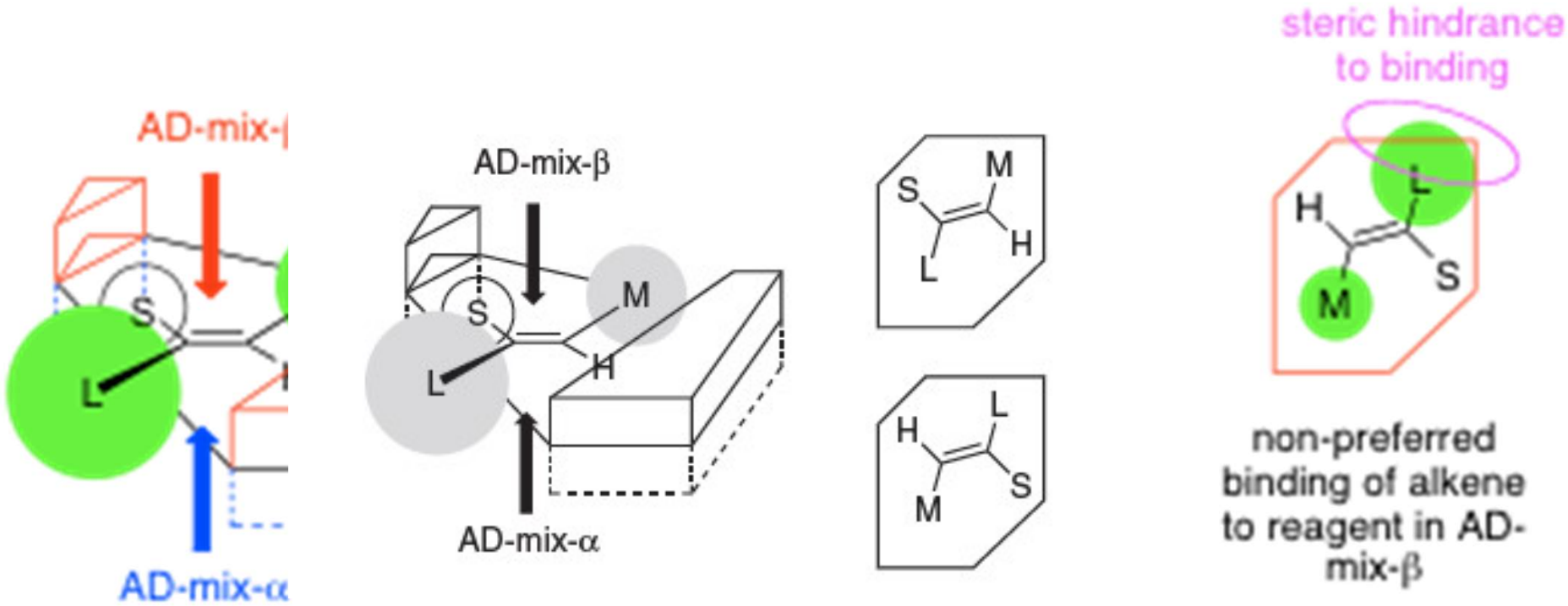
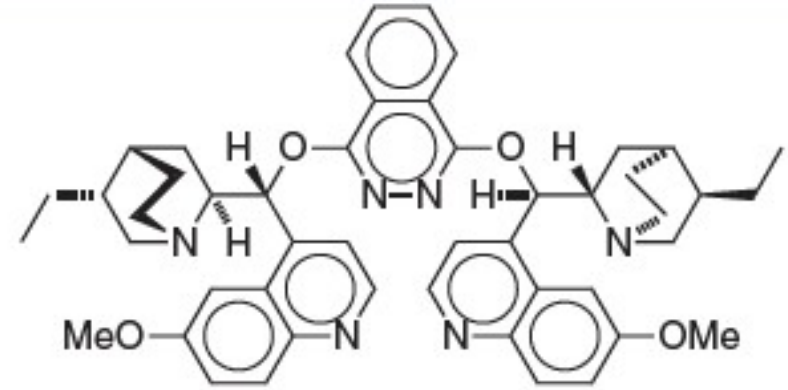
Alkene structure	Method
	Sharpless epoxidation
	Shi epoxidation
	Jacobsen-Katsuki epoxidation
	Shi epoxidation
	Shi epoxidation
	Epoxidation with dimeric *Cinchona* alkaloid phase transfer catalyst; Shi (modified catalyst) epoxidation
	Davis oxaziridine epoxidation

Figure 21.11

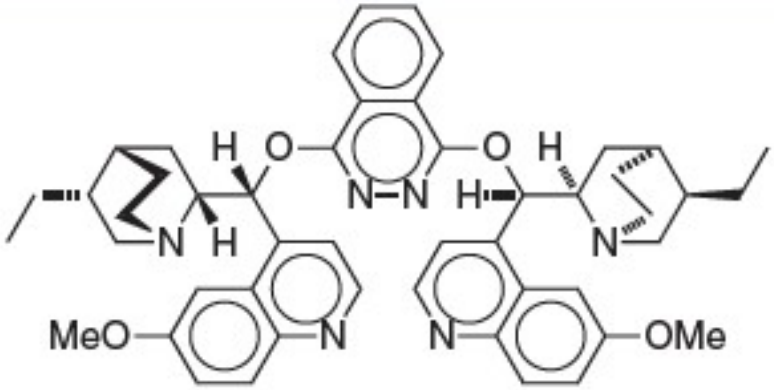


- Mnemonic for predicting absolute stereochemistry in hydroxylation of alkenes bearing large (L), medium-sized (M) and small (S) groups attached to the double bond.

AD-mix reagents



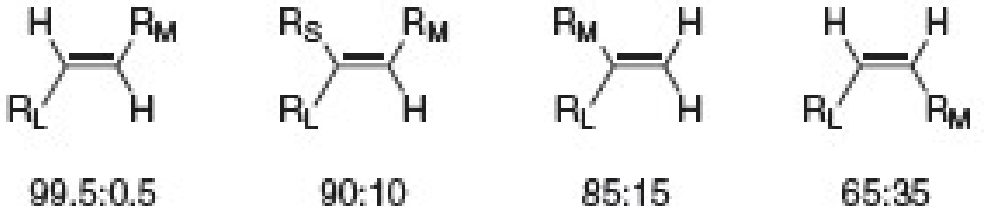
dihydroquinine-phthalazine dimer, $[DHQ]_2PHAL$
("AD-mix-α")

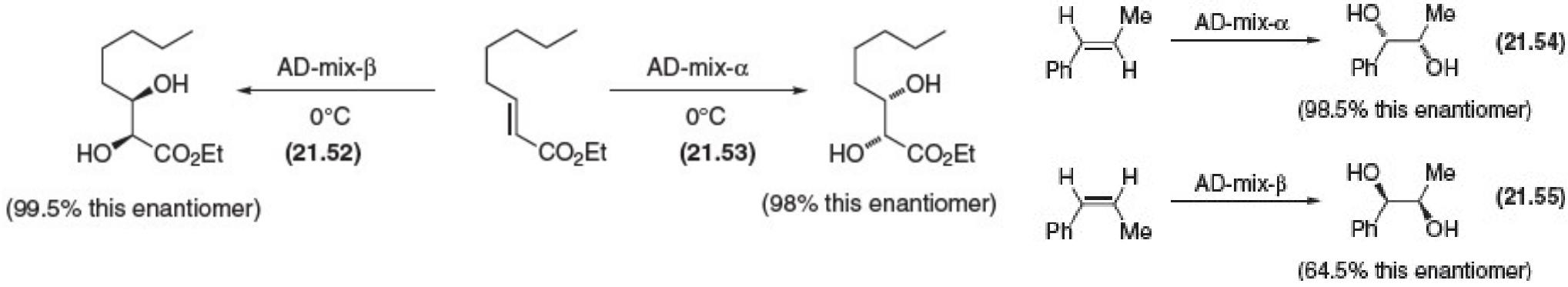


dehydroquinidine-phthalazine dimer, $[DHQD]_2PHAL$
("AD-mix-β")

- Commercially available reagents contain the ligand, $K_2OsO_2(OH)_4$ (the osmium oxidant), $K_3Fe(CN)_6$ (the secondary oxidant to regenerate the active osmium oxidation state), and K_2CO_3 (to hydrolyze the osmium intermediate).

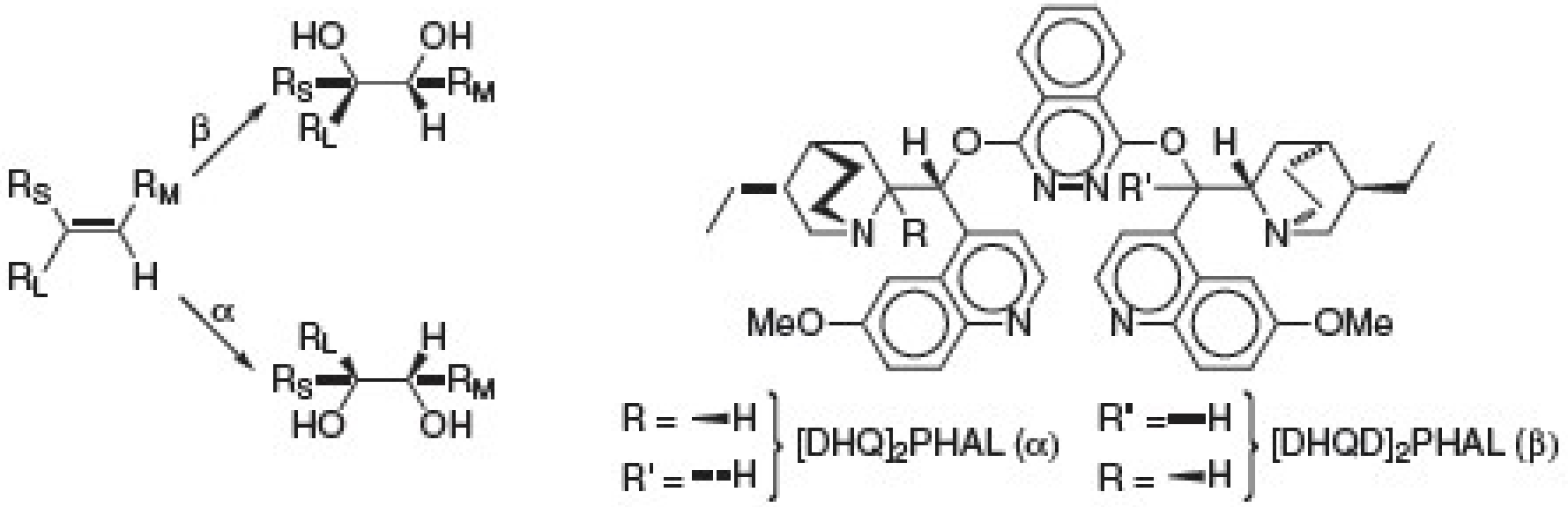
Effects of alkene stereochemistry on asymmetric dihydroxylation





- *Z* alkenes do not generally give high levels of asymmetric induction in the asymmetric dihydroxylation reaction

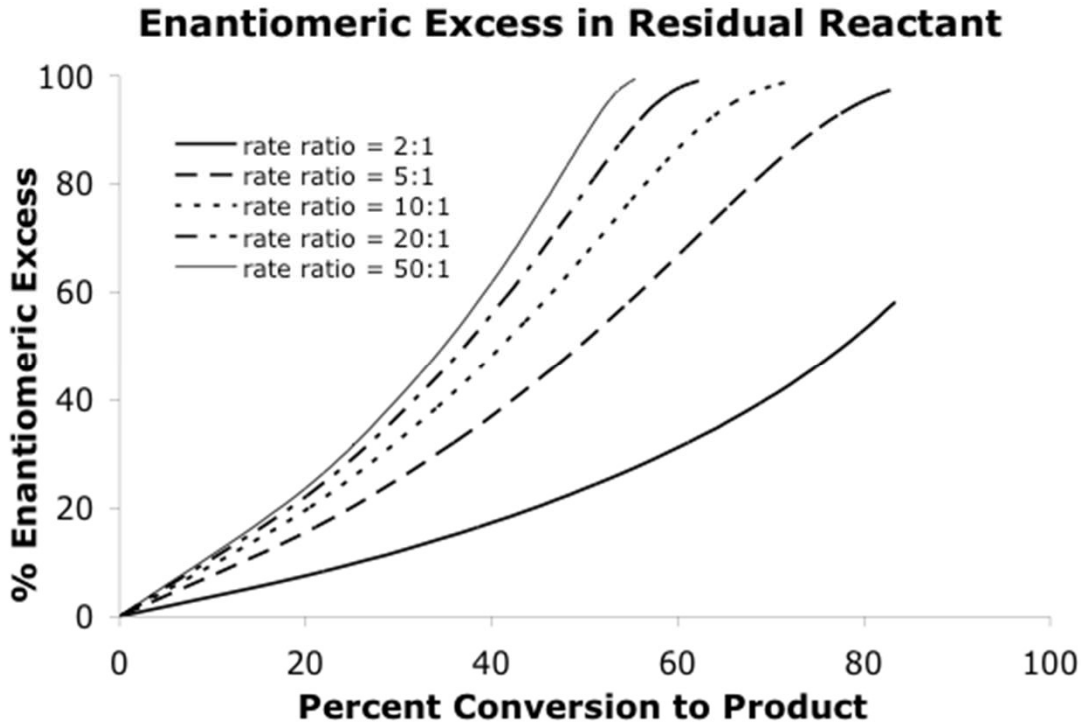
Reaction synopses: Asymmetric dihydroxylation



Reagents: $L^*/K_2OsO_4(OH)_2/K_3Fe(CN)_6$; L^*/K_2CO_3

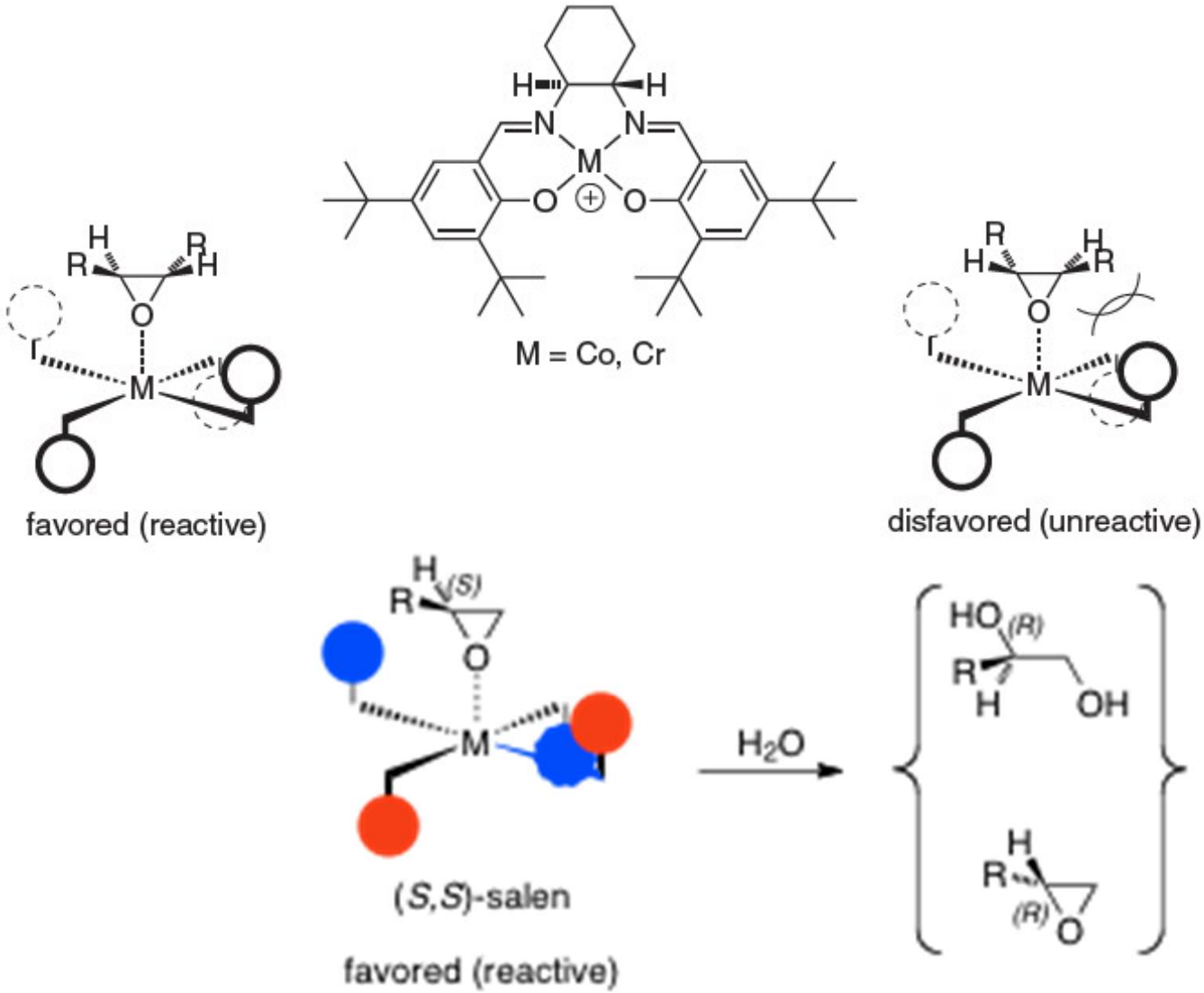
L^* = $(DHQ)_2PHAL$ (AD-mix-α) or $(DHQD)_2PHAL$ (AD-mix-β)

Figure 21.12



- Effect of rate ratio on the enantiomeric excess of the residual reactant in a kinetic resolution

Figure 21.13

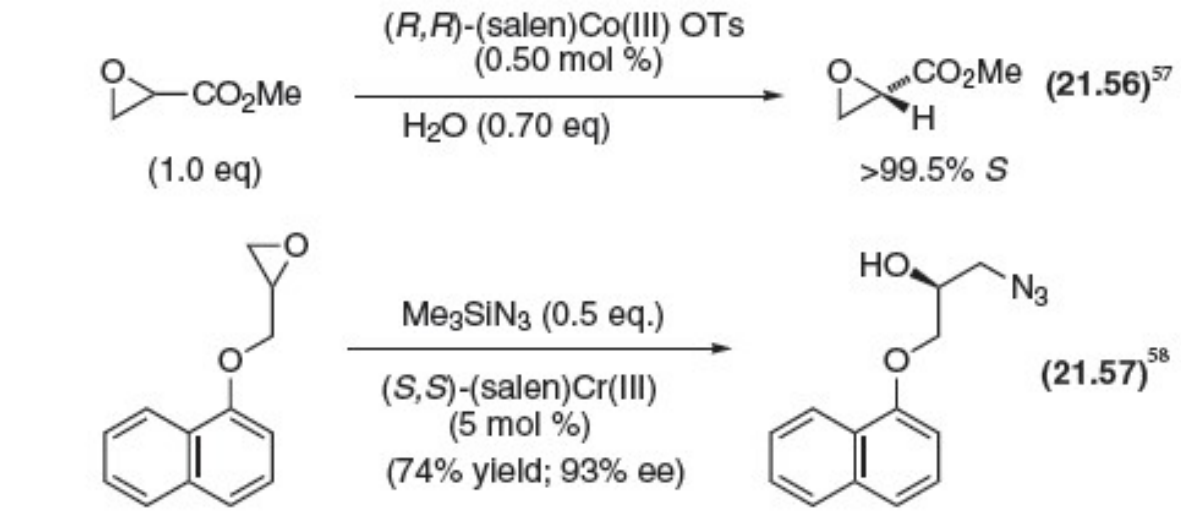


- (S,S)-(salen) catalysts and a mnemonic model for the binding of the epoxide to the catalyst.

Asymmetric epoxide hydrolysis catalyzed by salen complexes

- (*R*,*R*)- catalyst selectively promotes the hydrolysis of the *R* epoxide

- the strong stereochemical preference for ring opening is shown here, where the epoxide left is the (*R*,*R*) epoxide, and the completely hydrolyzed product is the (*S*,*S*)-tetraol



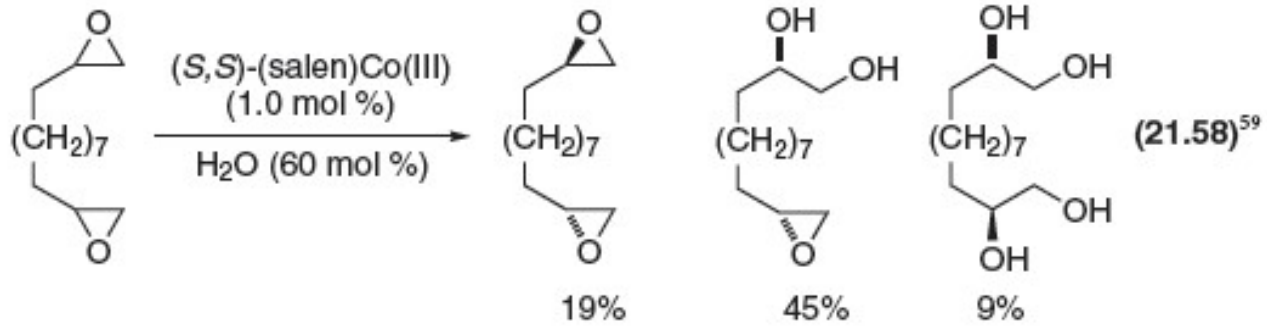
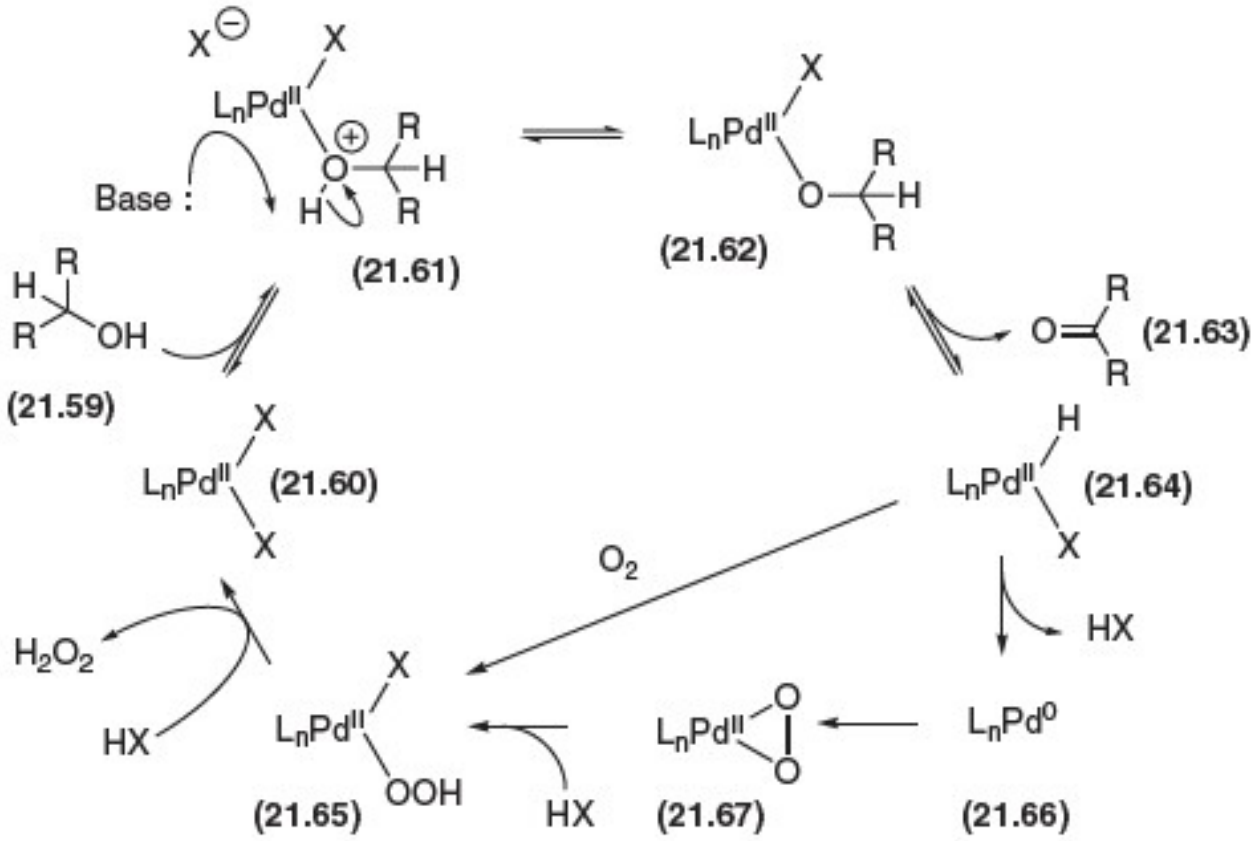


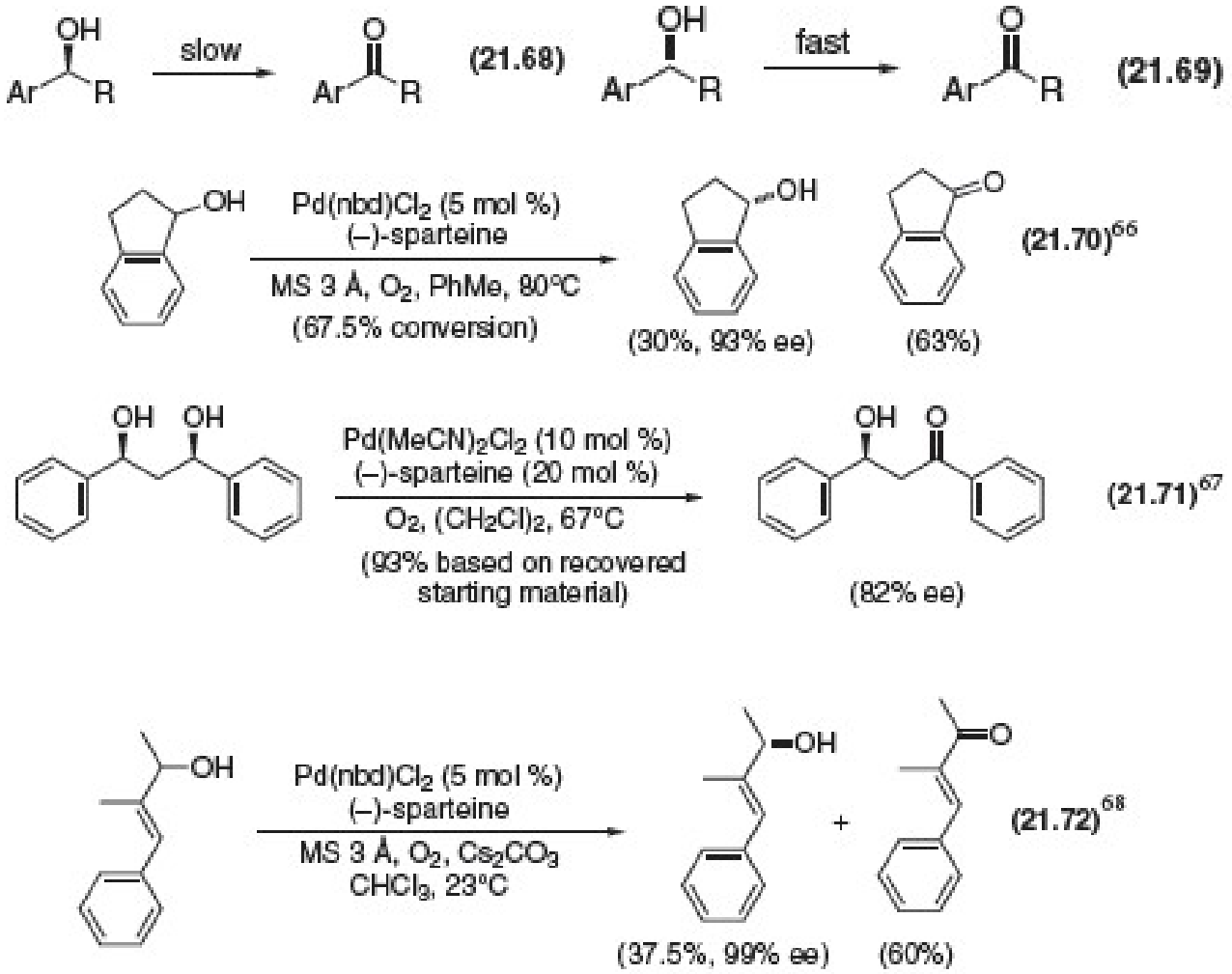
Figure 21.14



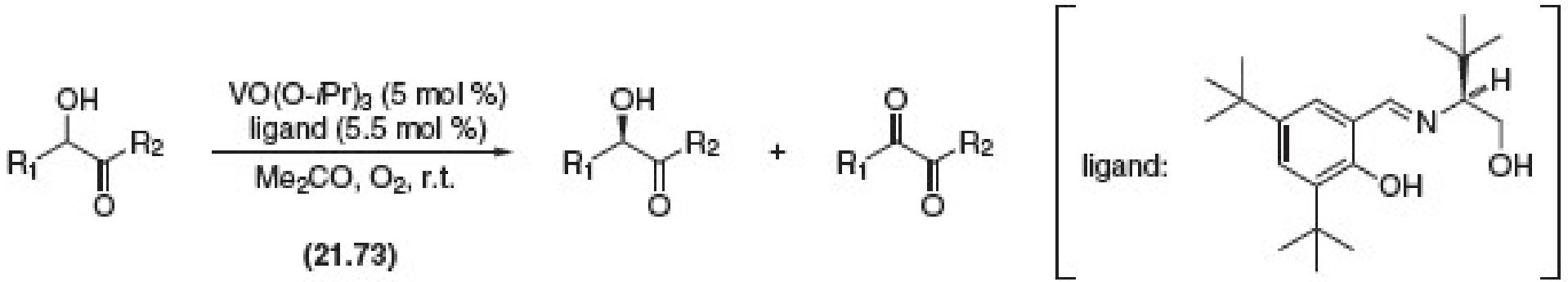
- Putative catalytic cycle for the oxidation of a secondary alcohol by molecular oxygen, catalyzed by a palladium (II) complex

Enantioselective Uemura oxidation of benzylic alcohols

- using (–)-sparteine as the chiral adjuvant in addition to pyridine, one can selectively oxidize *S* benzylic alcohols to the corersponding ketones
- This provides a method for the kinetic resolution of the alcohols because the remaining alcohol is enriched in the *R* enantiomer

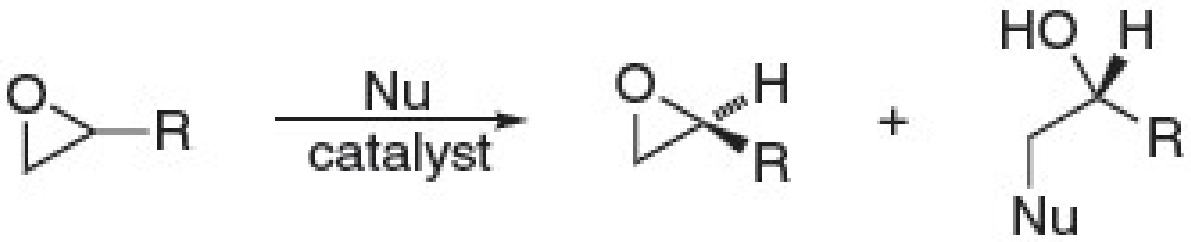


Vanadium-based enantioselective oxidation of α-ketols



- this reagent leads to relatively high e.e. at relatively low levels of conversion (52-62%)

Reaction synopses: Hydrolytic kinetic resolution of epoxides



Reagents:

catalyst: chiral (salen)Co(III) salen complex (0.5 mol %)

Nu: H—OH (70 mol %); Me_3SiN_3; etc.

no solvent used with liquid epoxides.

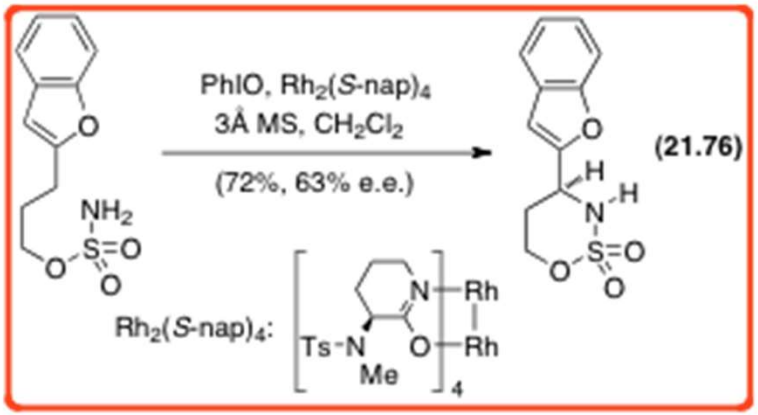
Reaction synopses: Enantioselective oxidation of secondary alcohols (Pd)

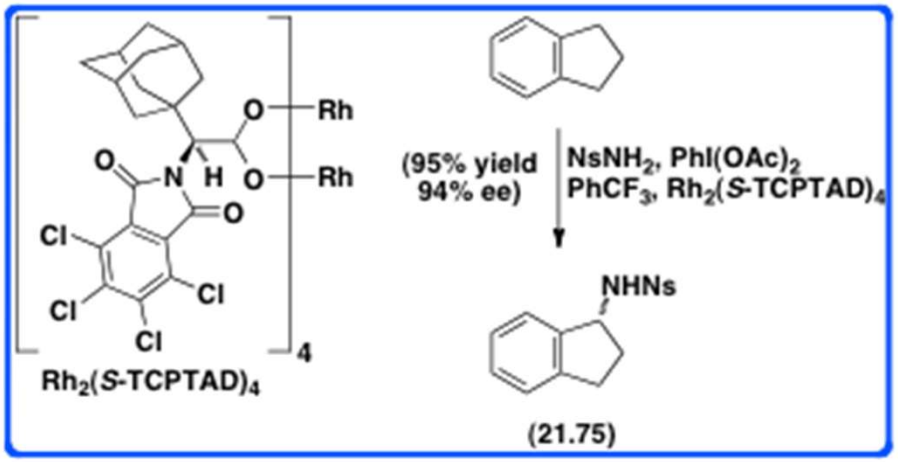
Reagents:
catalyst: $Pd(MeCN)_2Cl_2$; $Pd(nbd)Cl_2$; etc.
adjuvants: (–)-sparteine, other chiral diamines perform poorly; $CsCO_3$
solvent: PhMe, $(CH_2Cl_2)_2$, $CHCl_3$

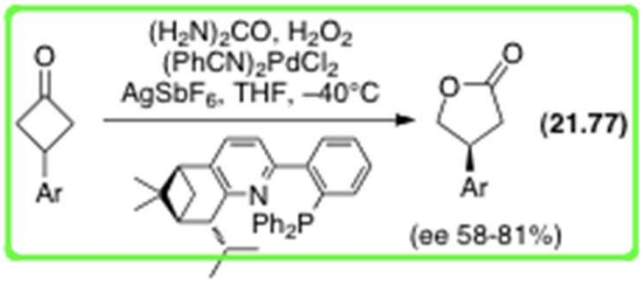
Reaction synopses: Enantioselective oxidation of secondary alcohols (V)

Reagents:
catalyst: $VO(O\text{-}i\text{-}Pr)_3$;
adjuvants: chiral salen ligand based on *tert*-leucine
solvent: MeCN, Me_2CO; etc.

Enantioselective insertion of nitrogen and oxygen

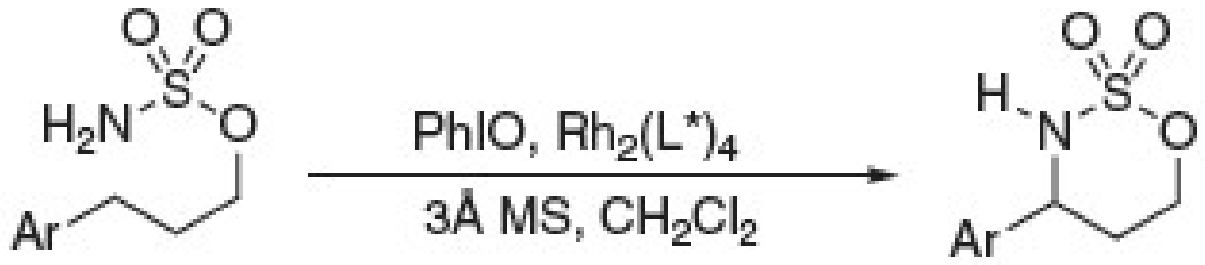






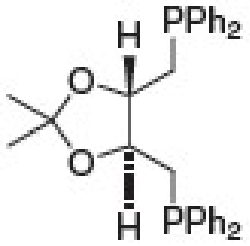
- intramolecular oxidation of sulfamate esters gives the cyclic sulfamates
- intermolecular insertion of *N*-sulfonylnitrenes gives chiralsulfonamides
- the enantioselectivity in the Baeyer-Villiger oxidation is highest with cyclobutanones, but still far short of that attainable with enzymes

Reaction synopses: Asymmetric nitrene insertion into C—H bonds

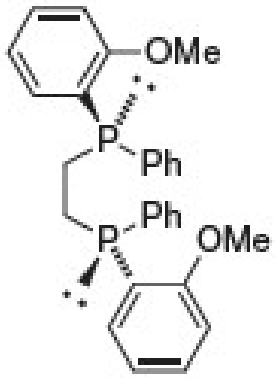


Configuration of product: L* = *S*-TCPTAD, *R*; L* = *S*-nap, *S*.

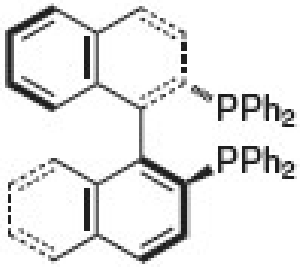
Standard types of chiral chelating ligands



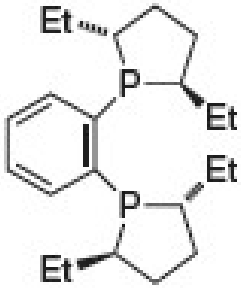
(21.78)
(*S*,*S*)-DIOP



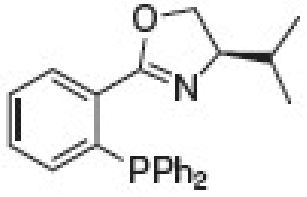
(21.79)
(*R*,*R*)-DIPAMP



(21.80)
(*S*)-BINAP



(21.81)
(*R*,*R*)-Et-DuPHOS

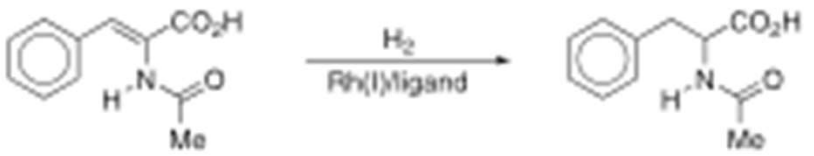


(21.82)
(*R*)-PHOX

- DIOP: chirality is from chiral carbons in the backbone
- DIPAMP: chirality is from chiral phosphorus atoms
- BINAP: chirality resides in the chiral binaphthyl unit
- DuPHOS: the chirality is due to the chiral carbons of the C_2-symmetric phospholane ring
- PHOX: the two coordinating atoms in this ligand are very different: one is hard (N) and one is soft (P); the chirality is due to the oxazoline ring

Table 21.5

Asymmetric hydrogenation of *Z*-2-(*N*-acetylamino)cinnamic acid with representative Rh(I) complexes



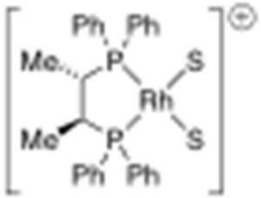
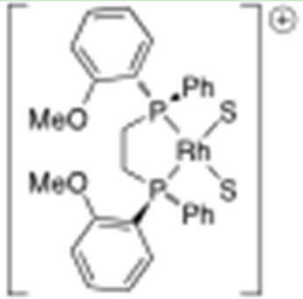
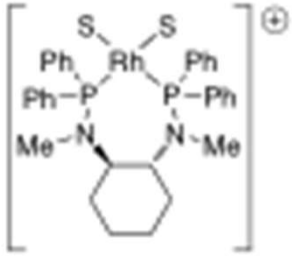
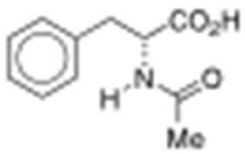
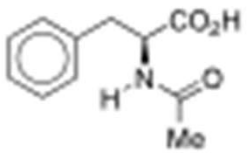
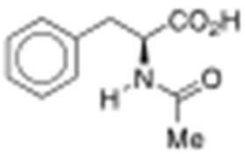
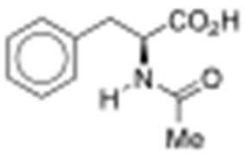
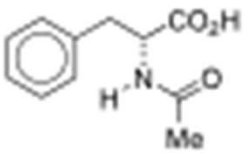
Catalyst	 (S,S)-CHIRAPHOS	 (R,R)-diPAMP	 (R,R)-DIOP	 (R,R)	 (S)-BINAP
Product					
e.r.	99.5:0.5	98:2	91:9	96:4	92:8

Figure 21.15

The (*S*)-BINAP and (*S,S*)-DIOP ligands have "axial" phenyl groups (in boxes) bound to phosphorus (shown schematically by the shaded ellipses; the darker one projects above the plane of the paper) in enantiomeric alignment when bound to rhodium (I), so we expect opposite chirality in the products of hydrogenation.

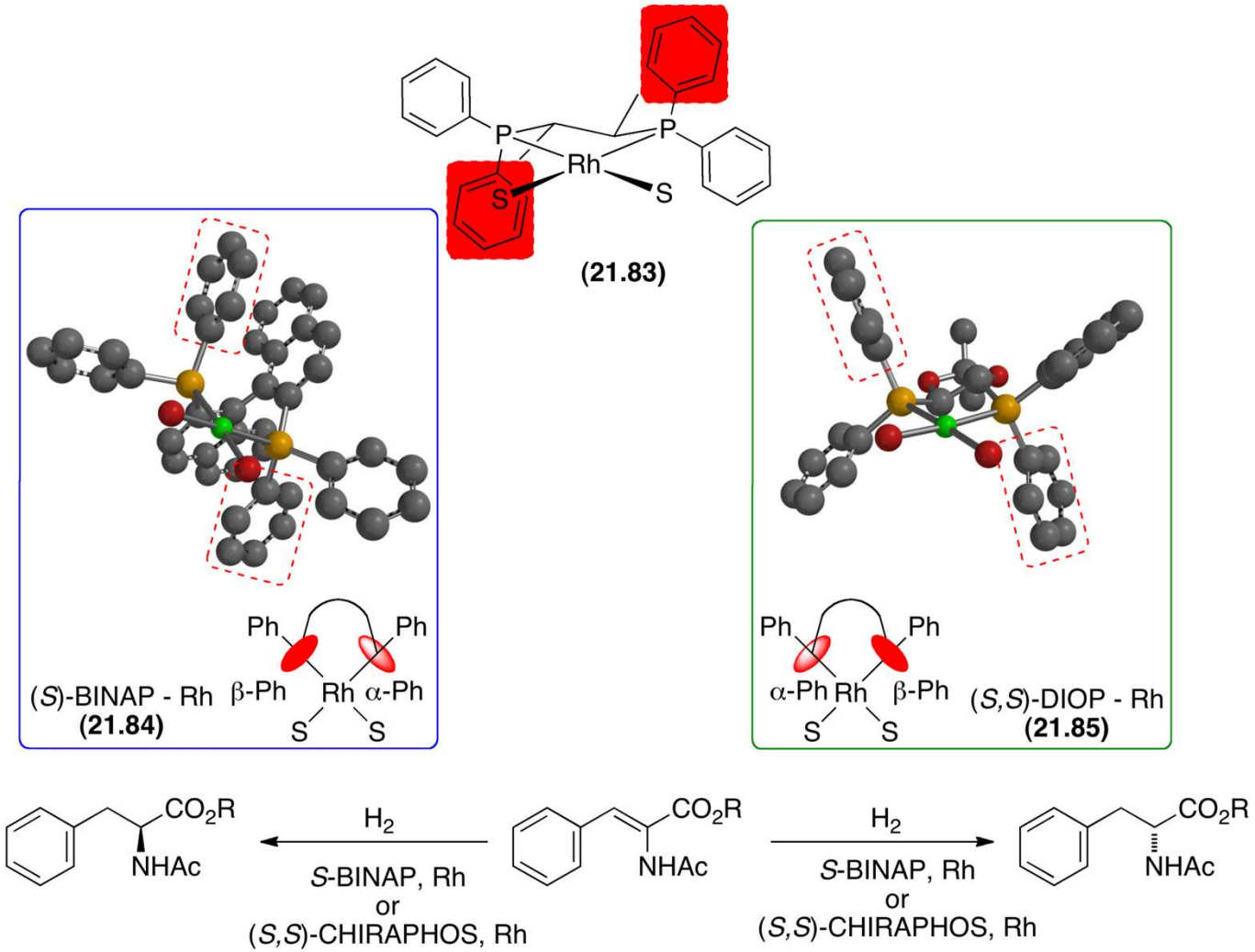
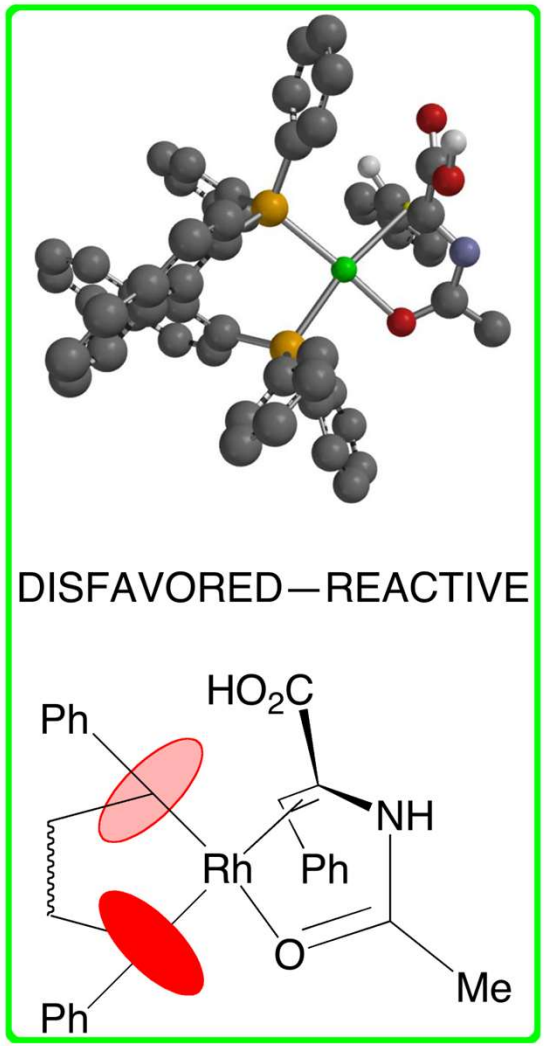


Figure 21.16

The two possible complexes between a rhodium (I) catalyst and an amidoacrylic acid. In the favored isomer, the complex does not react readily with hydrogen.



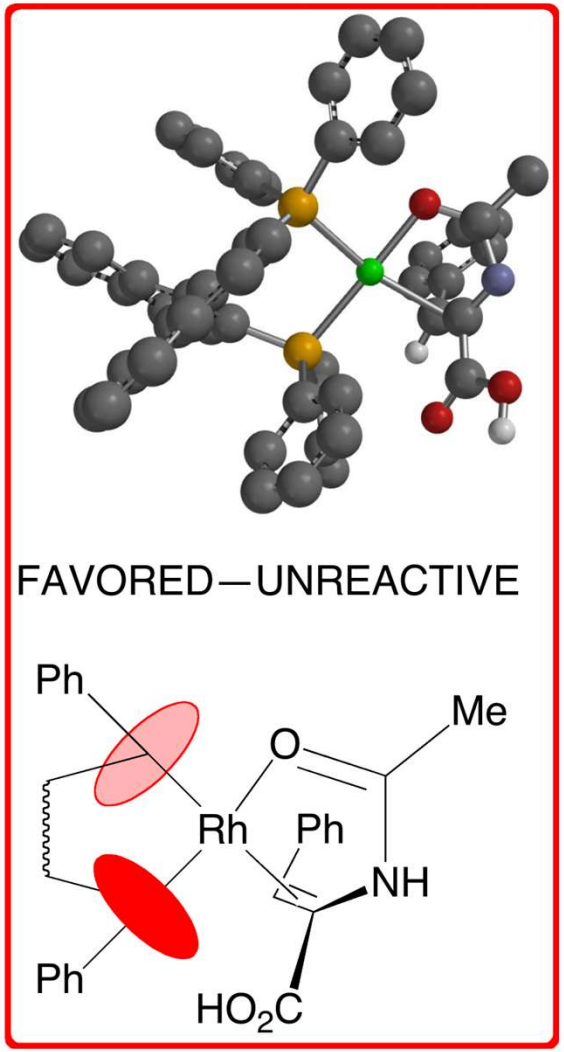
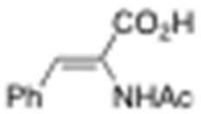
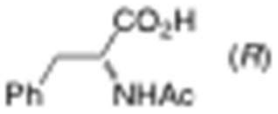
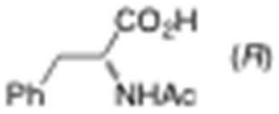
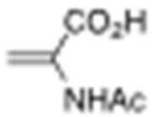
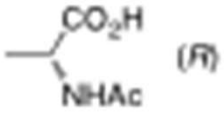
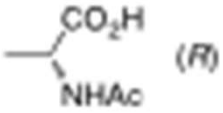
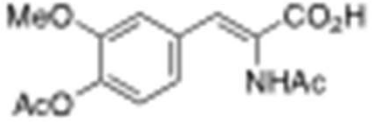
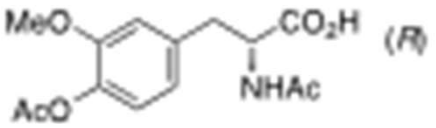
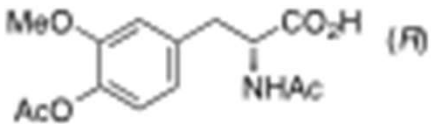


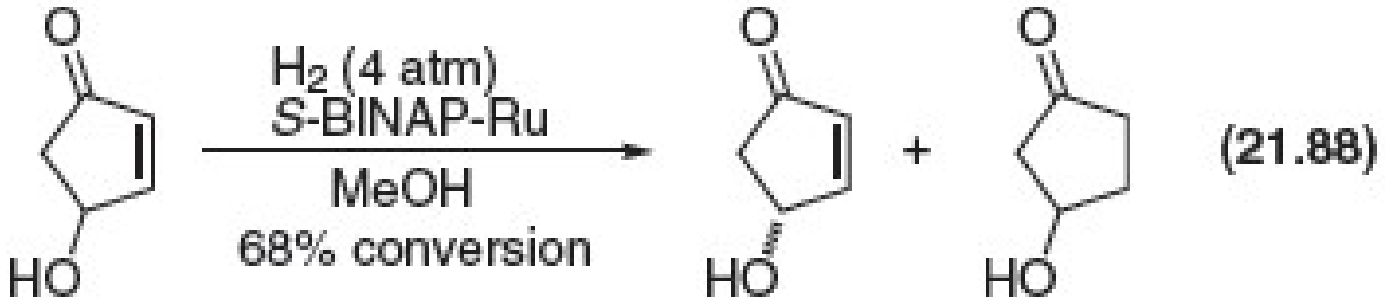
Table 21.6

Substrate	Rh–(*S*)-BINAP	Rh–(*R*,*R*)-DIOP
	 100% e.e.	 85% e.e.
	 98% e.e.	 73% e.e.
	 79% e.e.	 84% e.e.

Data taken from Takaya, H.; Ohta, T.;Noyori, R. In Ojima, I, Ed. *Catalytic Asymmetric Synthesis* (VCH: Weinheim, 1993), ch. 1.

Stereochemical outcome of hyrogenations with chiral rhodium (I)-BINAP and -DIOP catalysts

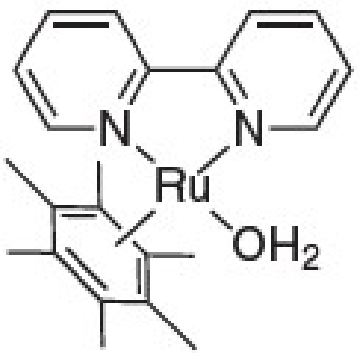
Kinetic resolution by hydrogenation



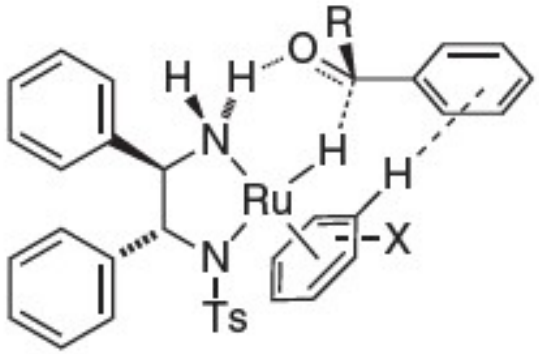
(21.88)

- The *S* enantiomer of the allylic alcohol hydrogenates much faster than the *R* enantiomer, leaving the remaining alcohol enriched in the *R* enantiomer
- this corresponds to an approximate rate ratio of 10:1

Figure 21.17



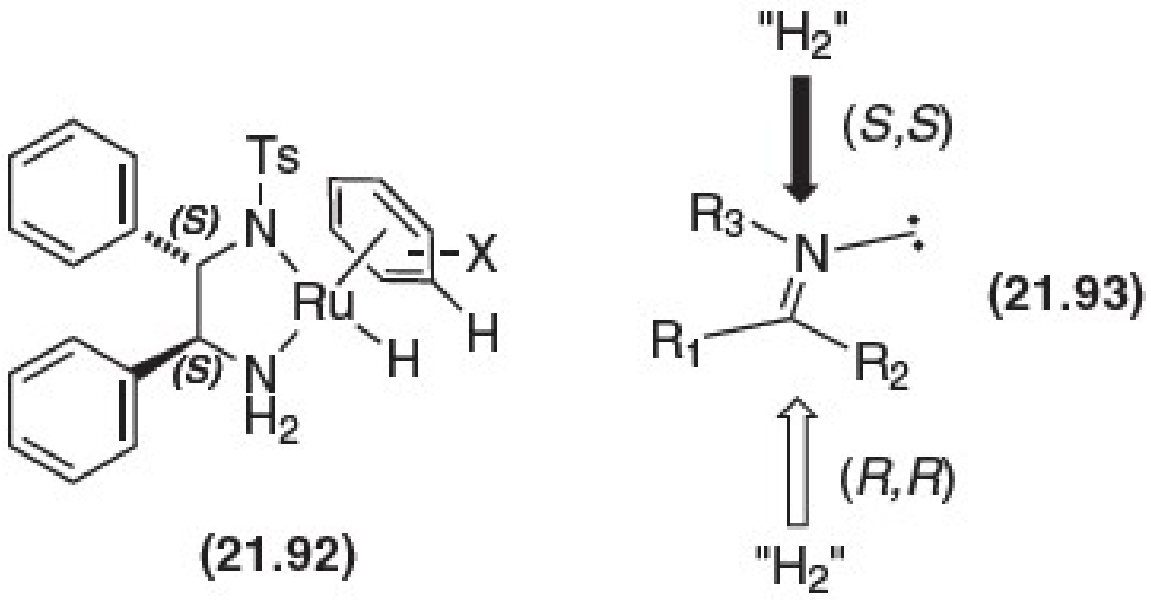
(21.89)



(21.91)

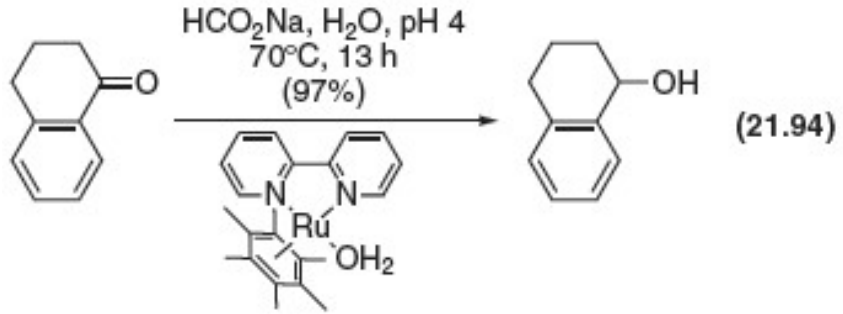
- η^6-Areneruthenium (II) catalysts for transfer hydrogenation of ketones and imines (left)
- model for predicting stereochemistry of the hydrogenation of ketones (right)

Figure 21.18

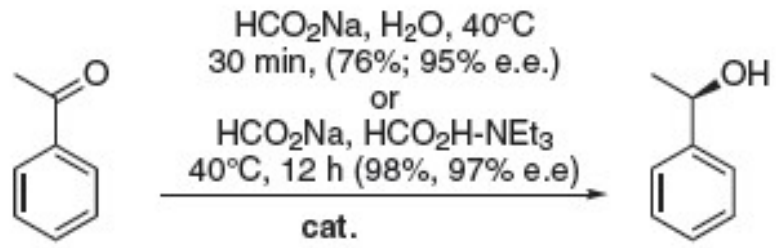


- Model for predicting outcome of asymmetric transfer hydrogenation of imines by TsDPEN complexes

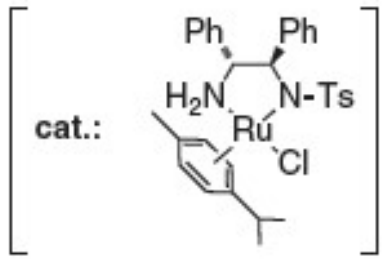
Transfer hydrogenation of aryl ketones using ruthenium TsDPEN complexes



(21.94)



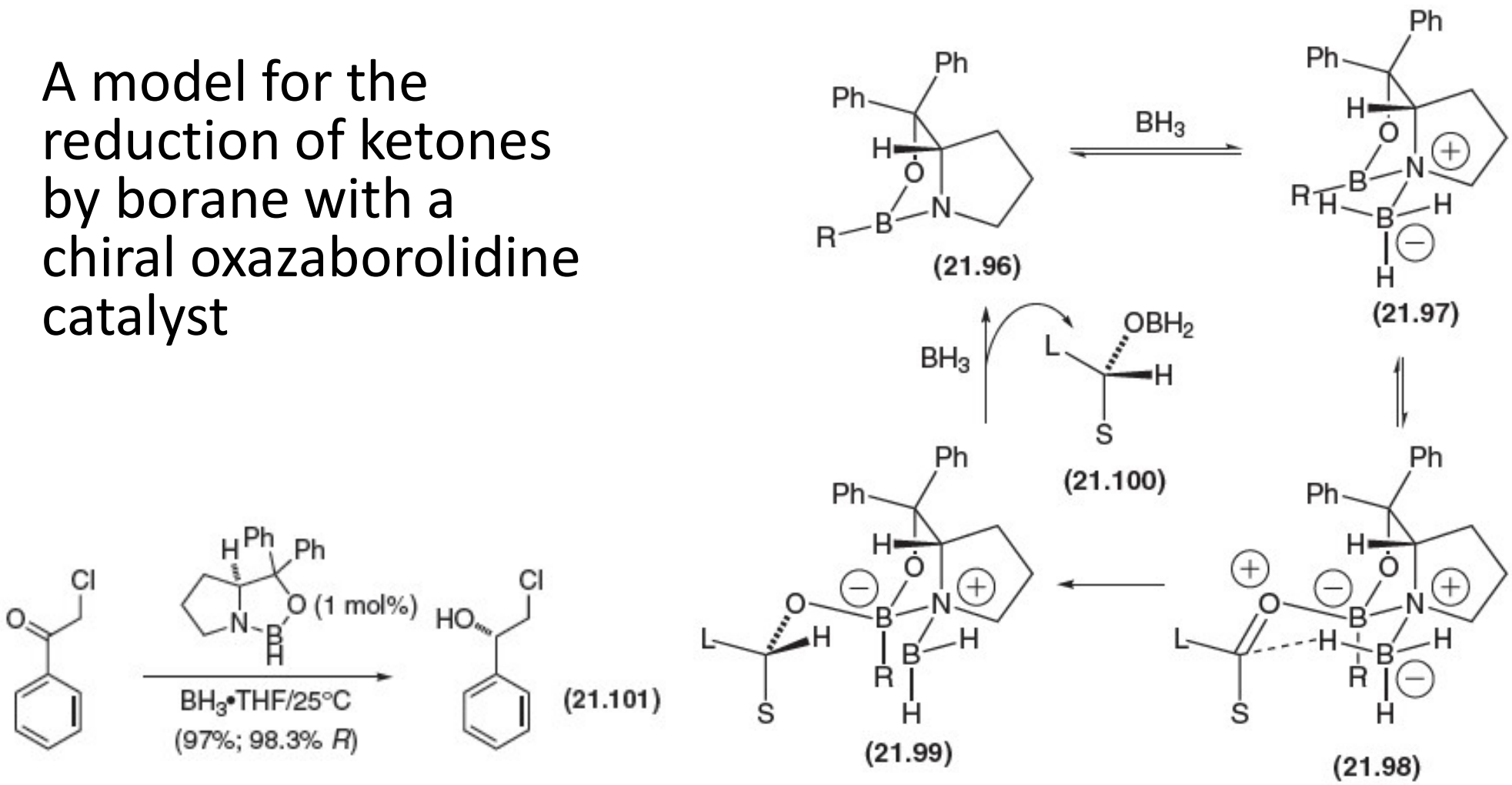
(21.95)



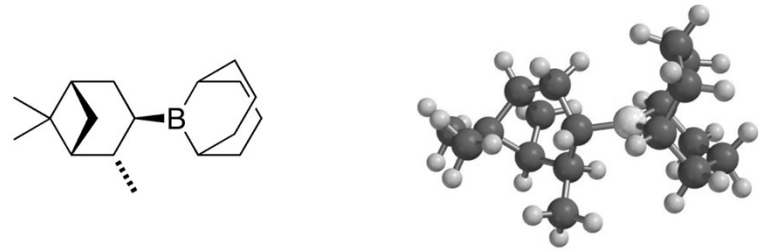
- sodium formate in water or the formic acid-triethylamine azeotrope can be used as the hydrogen source

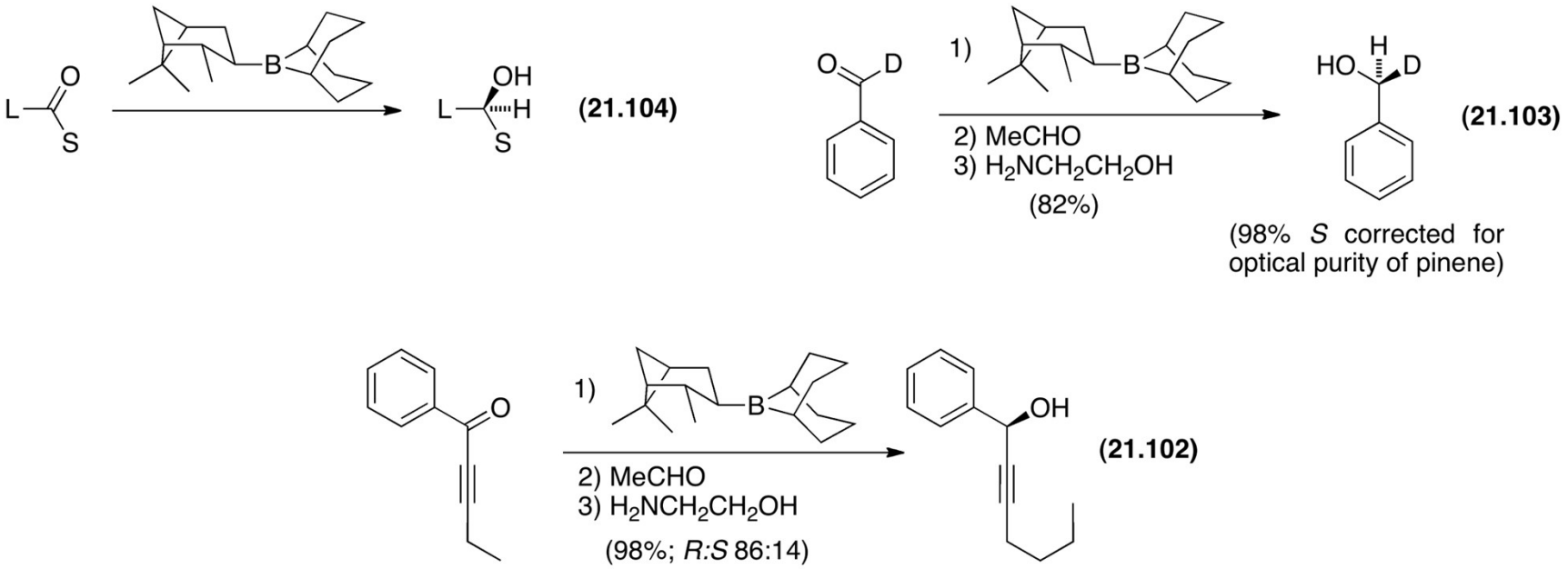
Figure 21.19

A model for the reduction of ketones by borane with a chiral oxazaborolidine catalyst



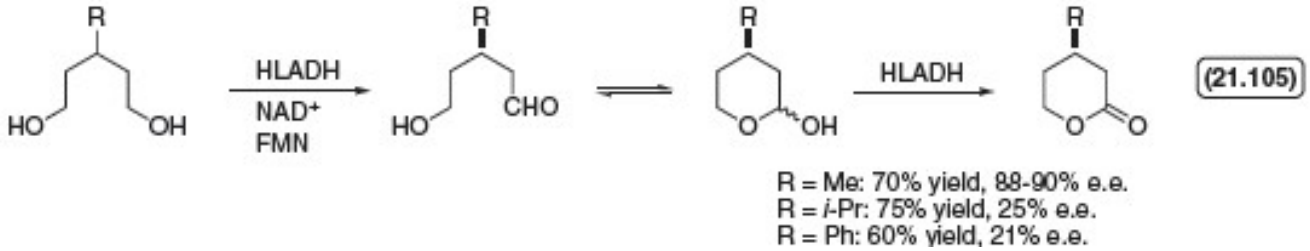
(R)-Alpine borane®

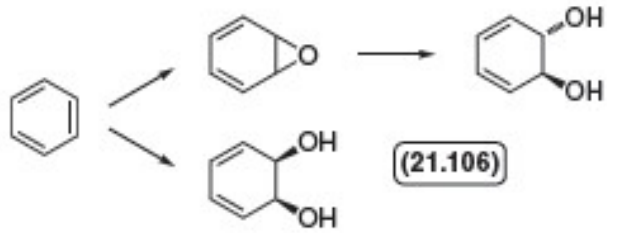


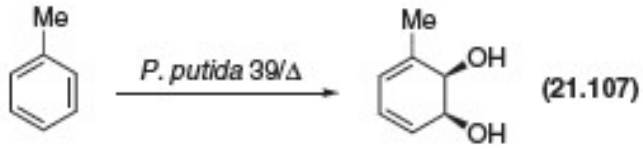


- reduction by hydrogen transfer from carbon is facile in boranes, especially 9-alkyl-9-borabicyclo[3.3.0]nonanes

Enzymes and microorganisms in synthesis



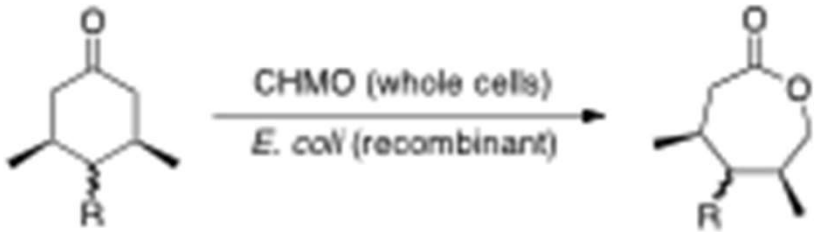




1) Oxidoreductases, which obviously catalyze redox reactions;
2) Transferases, which transfer groups from one molecule to another; these enzymes are generally too specific to be of general use synthetically;
3) Hydrolases, which hydrolyze a wide range of functional groups;
4) Lyases, which catalyze additions to π bonds and the eliminations that generate π bonds;
5) Isomerases, whose function is to isomerize the substrate (e.g. double bond migration or racemization); of all the enzyme-catalyzed reactions, these reactions are the most easily carried out without an enzyme;
6) Ligases, or Synthetases, which catalyze the formation of C—X and C—C bonds.

Table 21.7

Enantioselectivity in the Baeyer-Villiger oxidation of 4-substituted cyclohexanones by CHMO in recombinant *E. coli*



Substituent	Yield (%)	e.e (%)	Substituent	Yield (%)	e.e. (%)
cis-OH	77	99	*trans*-OH	80	96
cis-Cl	40	>99	*trans*-Cl	54	92
$=CH_2$	63	99	$(CH_2)_2$	65	>99
H	58	91			