CHAPTER 1

ALKALOIDS AS CHIRALITY TRANSMITTERS IN ASYMMETRIC CATALYSIS

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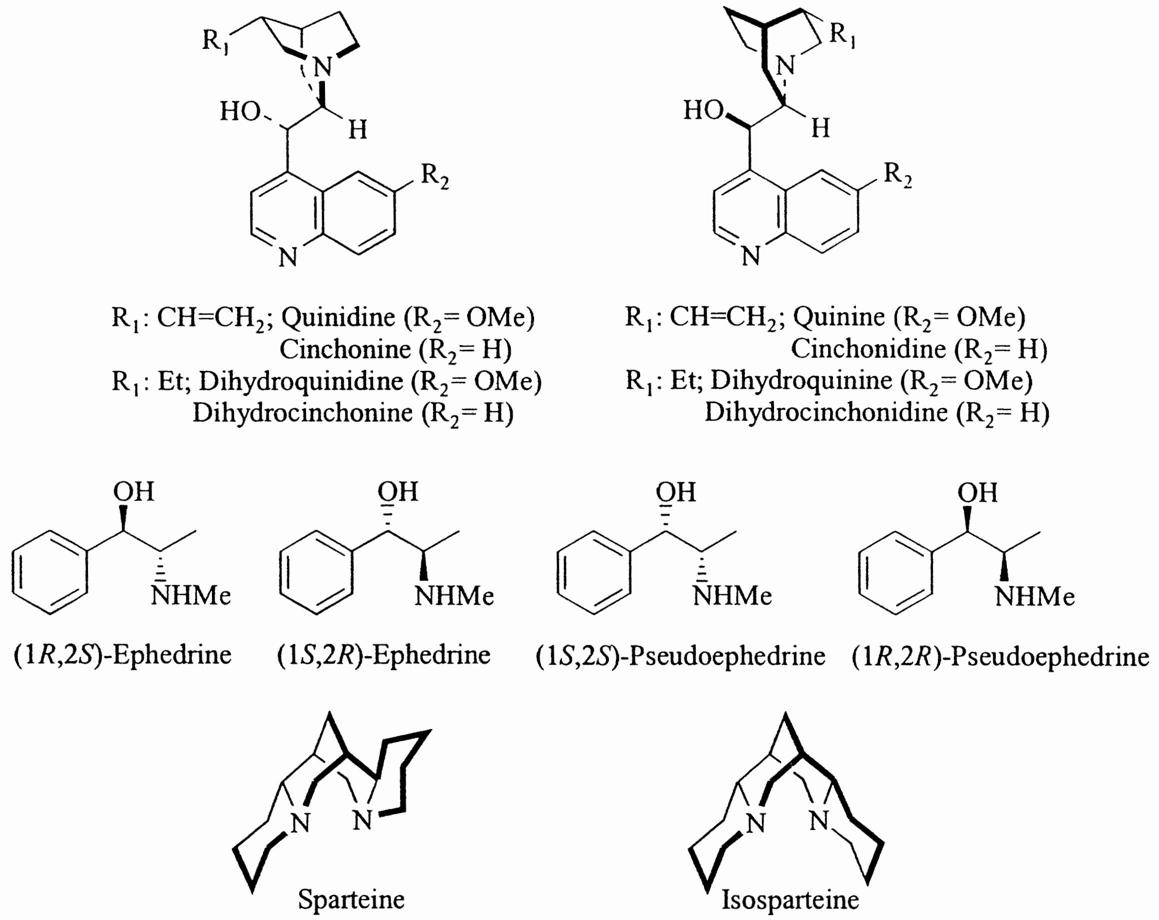
I. Introduction

During the last decade a number of powerful catalytic asymmetric reactions have emerged as a result of the growing need to develop more efficient and practical synthetic methods for biologically active compounds. A wide variety of chiral ligands and chiral catalysts have been designed and their catalytic efficiency has been investigated. Especially, since the pioneering work (*1*) of Wynberg, naturally occurring alkaloids have been extensively utilized in asymmetric catalysis as chiral ligands or as chiral catalysts themselves. The parent alkaliods (Figure 1) possess nitrogen surrounded by highly asymmetric environment. They are also inexpensive and readily available in both enantiomeric forms in most cases, and can easily be modified to a variety of different derivatives. A number of processes have gained wide acceptance, and some are even used on an industrial scale, e.g. heterogeneous hydrogenation of α-ketoesters catalyzed by cinchona alkaloid-modified Pt (Ciba-Geigy) (section II.A.*1*.), Sharpless asymmetric dihydroxylation of olefins (Chirex Ltd.) (section III.A.*1*.), asymmetric alkylation of indanones using cinchona alkaloid-derived chiral phase-transfer catalysts (Merck) (section IV.A.), and cinchona alkaloid-catalyzed 2,2-cycloaddition of ketene and chloral or trichloroacetone (Lonza) (section IV.I.), etc. This research area has been very fast growing, nevertheless there has been no review, since 1986 when the first review (*1*) by Wynberg was published. This review is an overview of recent activities in this area.



R_1: $CH=CH_2$; Quinidine (R_2= OMe)
Cinchonine (R_2= H)
R_1: Et; Dihydroquinidine (R_2= OMe)
Dihydrocinchonine (R_2= H)

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R_1: Et; Dihydroquinine (R_2= OMe)
Dihydrocinchonidine (R_2= H)

(1*R*,2*S*)-Ephedrine (1*S*,2*R*)-Ephedrine (1*S*,2*S*)-Pseudoephedrine (1*R*,2*R*)-Pseudoephedrine

Sparteine Isosparteine

FIGURE 1. Alkaloids frequently used as chirality transmitters in asymmetric catalysis

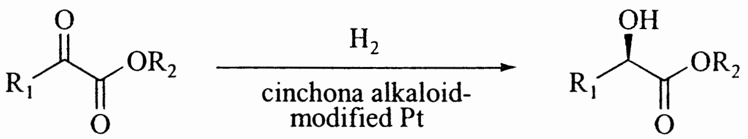
II. Enantioselective Carbon-Hydrogen Bond Formation

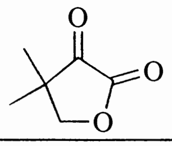
A. ASYMMETRIC CATALYTIC HYDROGENATION

1. Heterogeneous Asymmetric Carbonyl Hydrogenation

a. Asymmetric hydrogenation of α-ketoesters using cinchona alkaloid-modified Pt/Al_2O_3 (or Pt/C) catalysts. Asymmetric hydrogenation of α-ketoesters using cinchona alkaloid-modified Pt/Al_2O_3 (or Pt/C) catalysts (*2,3*), which was initially developed by Orito (*4-7*), is one of the most intensively studied areas in asymmetric catalysis, in which alkaloids are used as chirality transmitters. Over the last few years, Blaser (*8-15*) has made extensive studies of this reaction. Enantioselectivities up to 95% (*14*) were obtained by optimizing the catalyst, modifier, solvent, and reaction conditions (*4-15*) (Table I). Pretreatment of platinum on Al_2O_3 with hydrogen at high temperature (ca. 400 °C) is essential for high optical yields. Increasing the size of platinum particles by increasing the temperature with hydrogen led to more active and enantioselective catalysts (*8*). Hydrogenation of ethyl 2-oxo-2-phenylethanoate with unpretreated Pt/Al_2O_3 gave ethyl (-)-2-hydroxy-2-phenylethanoate in only 34% ee. After thermal treatment of the catalyst with hydrogen the ee increased to 84% ee.

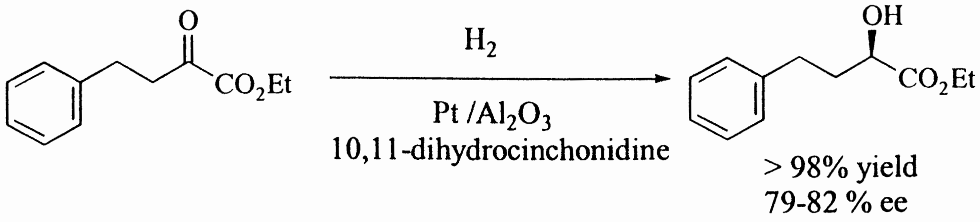
TABLE I
ASYMMETRIC HYDROGENATION OF α-KETOESTERS USING CINCHONA ALKALOID-MODIFIED Pt-CATALYSTS (from 2)



Substrate		Catalyst	Modifier	% ee
R_1	R_2			
Ph	Et	Pt / Al_2O_3	cinchonidine	89
Me	Et	Pt / Al_2O_3	dihydrocinchonidine	89 (95)[a]
n-Pr	Et	Pt / Al_2O_3	dihydrocinchonidine	57
Me	Me	Pt / Al_2O_3	dihydrocinchonidine	90
$PhCH_2CH_2$	Me	Pt / Al_2O_3	dihydrocinchonidine	85
$PhCH_2CH_2$	Et	Pt / Al_2O_3	dihydrocinchonidine	83 (91)[a]
$PhCH_2CH_2$	*n*-Bu	Pt / Al_2O_3	dihydrocinchonidine	82
		Pt / C	cinchonidine	82

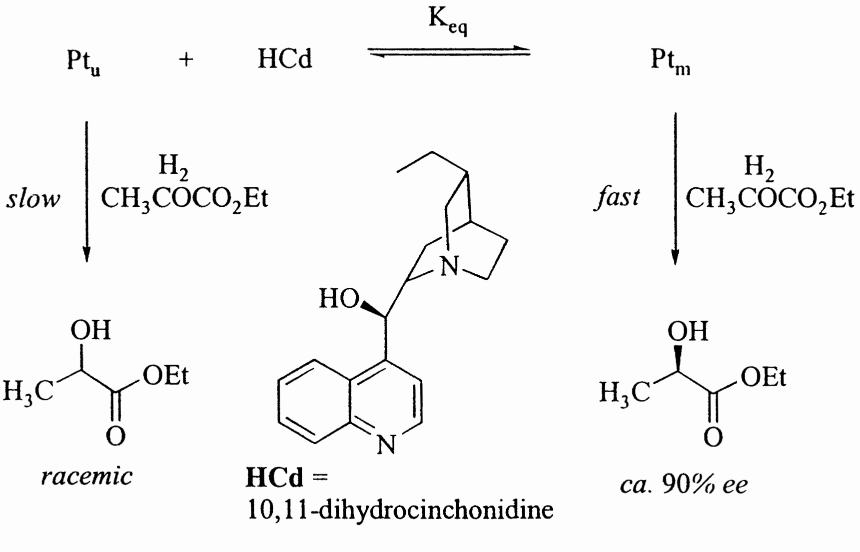
[a] solvent: toluene (acetic acid)

The practical utility was demonstrated in the synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutanoate, an ACE-inhibitor intermediate (*16*). The reaction with Pt/Al_2O_3 modified by dihydrocinchonidine can be carried out on 10-200 kg scale in greater than 98% chemical yield and in 79-82% optical yield (*2*) (Scheme 1).



SCHEME 1. Synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutanoate, an ACE-inhibitor intermediate

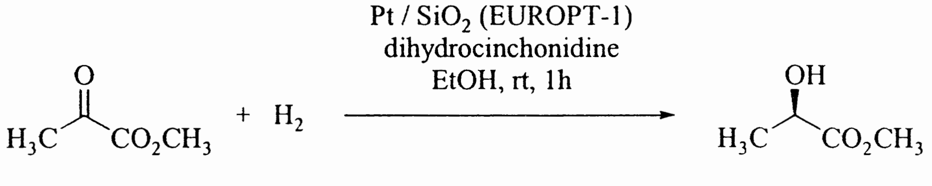
In the hydrogenation of α-ketoesters in the presence of cinchona alkaloid-modified Pt, alkaloid adsorption leads to a marked increase in reaction rate (*15*). Accordingly, this reaction can be classified as "ligand-accelerated catalysis (LAC)" (*17*). The initial rate for the enantioselective hydrogenation of α-ketoesters over chirally modified Pt catalysts is usually 5-20 times higher than that of the unmodified (racemic) reaction. The actual hydrogenation involves two kinds of reaction sites, chirally modified Pt(Pt_m) and unmodified Pt(Pt_u). Accordingly, the reaction is analyzed in term of a general two-cycle mechanism (Scheme 2). The first cycle is ligand-accelerated catalysis, which exhibits excellent enantioselectivity; the other cycle is a slow, chirally unmodified cycle to produce the racemic product. Both rate and product ee reach a maximum at extremely low concentration of alkaloid, corresponding to an alkaliod/Pt_{surf} ratio of 0.5 in toluene and 1 in ethanol (*15*). These data suggest that adsorption of the alkaloid on the metal surface is reasonably strong and/or only a small fraction of the surface is modifiable. A modified ensemble consists of one adsorbed alkaloid and 10-20 Pt atoms.



SCHEME 2. Two-cycle mechanism

However, unfortunately, the highly selective reaction is restricted to α-keto esters as substrates. Despite many efforts to broaden the application range of this reaction, the results have been disappointing. Only 20% ee or below, was obtained in the enantioselective hydrogenation of β-diketones, β-ketoesters, aryl alkyl ketones and α-methoxy ketones (*18,19*). Better enantioselectivities were achieved in the hydrogenation of α-diketones (33-38% ee) (*20*), 2,2,2-trifluoroacetophenone (56% ee) (*21*), cyclic ketoamide (47% ee) (*22*) and α-ketoamides (up to 60% ee) (*23*).

b. Asymmetric hydrogenation of α-ketoesters using cinchona alkaloid-modified Pt/silica (EUROPT-1) catalysts. The well characterized 6.3% Pt/silica (EUROPT-1) (*24-27*) catalyst was also developed to be an enantioselective catalyst (*28,29*) by modifying with alkaloids. The rate for the hydrogenation of α-ketoesters over chirally modified EUROPT-1 catalyst is 25 times higher than that of the unmodified reaction. Modification with alkaloid can be best carried out in ethanol solution in the presence of air using a pre-reduced Pt/silica. Before modification, Pt/silica should be pre-reduced with H_2 (1bar) at 100 °C for 1h. This exposure to air confers on the catalysts a high hydrogenation rate and enantioselectivity. In the hydrogenation of α-ketoesters, the highest optical yields exceeded 80% ee when dihydrocinchonidine was used as a chiral modifier. Cinchonidine gave lower enantioselectivity. The superiority of the dihydrocinchonidine modifier, compared to cinchonidine, was ascribed to a different adsorption behavior. Whereas cinchonidine might bond to the surface either with the quinoline ring system or the vinylic double bond, the adsorption of dihydrocinchonidine is only possible by the quinoline ring system (*28,29*).



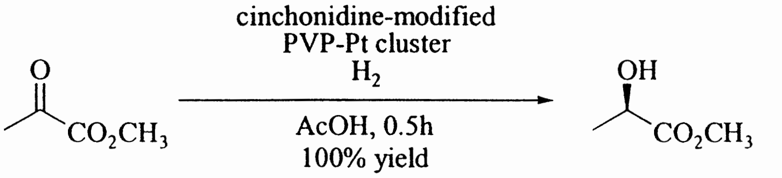
SCHEME 3. Enantioselective hydrogenation of methyl pyruvate using an alkaloid-modified EUROPT-1 catalyst

Other alkaloids such as codeine, 7,8-dihydrocodeine, brucine and strychnine, adsorbed on Pt/silica (EUROPT-1) also enhanced the rate of hydrogenation of methyl pyruvate and butane-2,3-dione, however, exhibited very low enantioselectivities (1-21% ee) (*30*).

c. Asymmetric hydrogenation of α-ketoesters using cinchona alkaloid-modified finely dispersed polyvinylpyrrolidine(PVP)-stabilized platinum clusters. Very recently, Liu and coworkers reported that finely dispersed polyvinylpyrrolidine(PVP)-stabilized platinum clusters modified with cinchonidine catalyzed the asymmetric hydrogenation of α-ketoesters, giving enantiomeric excesses in favor of (*R*)-(+)-methyl lactate up to 97.6% (*31*). The cinchonidine-modified PVP-Pt cluster immobilized onto alumina and a cross-linked polystyrene (PS) support also showed high enantioselectivities (91.3% ee for PVP-Pt/Al_2O_3 and 88.9% ee for PVP-Pt/PS, respectively) for the hydrogenation of methyl pyruvate

(*31*). The reaction runs best over a tiny cluster with a mean size of 1.4 nm (Scheme 4), which is quite different from Pt catalysts supported on aluminium oxide or carbon. As mentioned in section A.*1.a.*, the activity and enantioselectivity of cinchona alkaloid-modified Pt/Al_2O_3 (or Pt/C) increased by increasing particle size (*8*). When the particle size of cinchona alkaloid-modified Pt/Al_2O_3 (or Pt/C) is below 3.0 nm, both the activity and enantioselectivity decreased significantly.

It is also noteworthy that the protonated dihydrocinchonidine also functioned as the stabilizer of the Pt colloid (*32*). With excessive dihydrocinchonidine added into the reaction mixture to prevent agglomeration of the colloid, the hydrogenation of ethyl pyruvate was conducted at atmospheric pressure, and yielded products with an enantioselectivity of up to 78%. The activity of dihydrocinchonidine-stabilized platinum colloids decreases with increasing particle sizes as a result of decreasing dispersion.



97.6% ee with catalyst with particle diameter of 1.4 nm
93.6% ee with catalyst with particle diameter of 1.5 nm
95.9% ee with catalyst with particle diameter of 1.8 nm

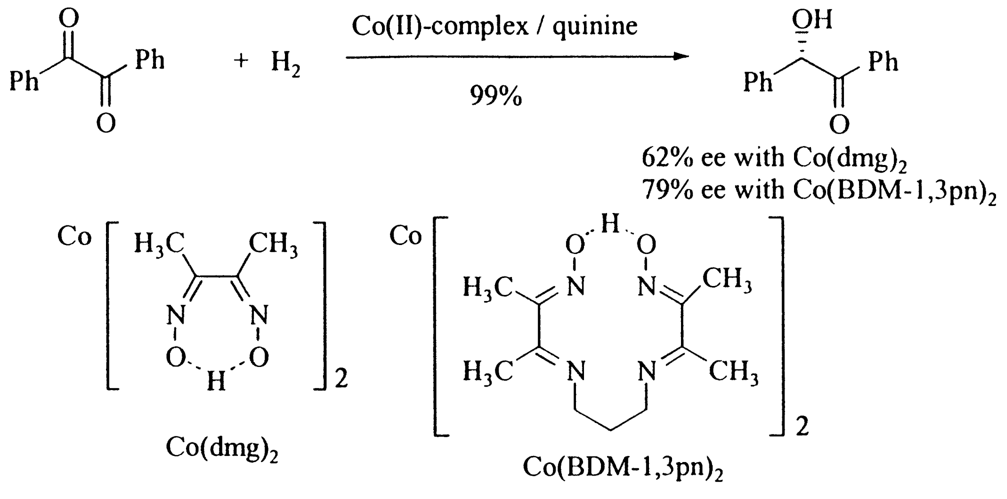
SCHEME 4. Enantioselective hydrogenation of methyl pyruvate using cinchonidine-modified PVP-Pt clusters

2. Co-Catalyzed Hydrogenation of 1,2-Diketones

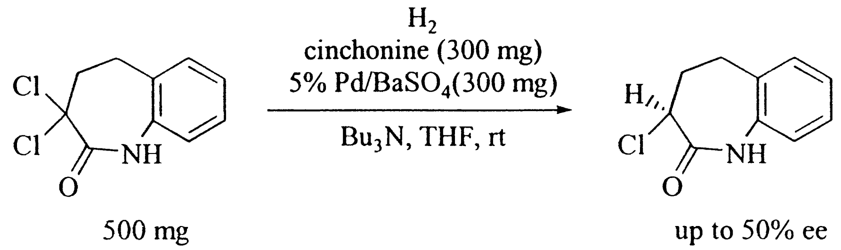
Cinchona alkaloids were also used as chirality transmitters in the Co-catalyzed hydrogenation of 1,2-diketones (Scheme 5) (*33-37*). The enantioselective hydrogenation of 1,2-diphenylethanedione with the catalytic system, $Co(dmg)_2$/quinine gave (*S*)-2-hydroxy-1,2-diphenylethanone in 99% yield and 62% ee (*33-36*). The enantioselectivity can be increased up to 78% by addition of one equivalent of benzylamine. With the catalyst, in which the mononegative 4,8-diaza-3,9-dimethyl-3,8-undecadiene-2,10-dionedioximato ($BDM\text{-}1,3pn^-$) was used as a ligand, 1,2-diphenylethanedione was hydrogenated to (*S*)-2-hydroxy-1,2-diphenylethanone in 99% yield and 79% ee (*37*).

3. Other Hydrogenations

The enantioselective hydrodehalogenation of the α,α'-dichlorobenzazepin-2-one with cinchona alkaloid-modified Pd- and Pt-catalysts was investigated by Blaser and coworkers (*38*). The best optical yields (up to 50% ee) were obtained with a 5% Pd/$BaSO_4$ catalyst modified with cinchonine in THF with NBu_3 as HCl acceptor. However, as shown in Scheme 6, very high modifier and catalyst concentrations were necessary to obtain good optical yields and reasonable reaction rates because the modifier decreases the catalyst activity.



SCHEME 5. Co-catalyzed hydrogenation of 1,2-diketones



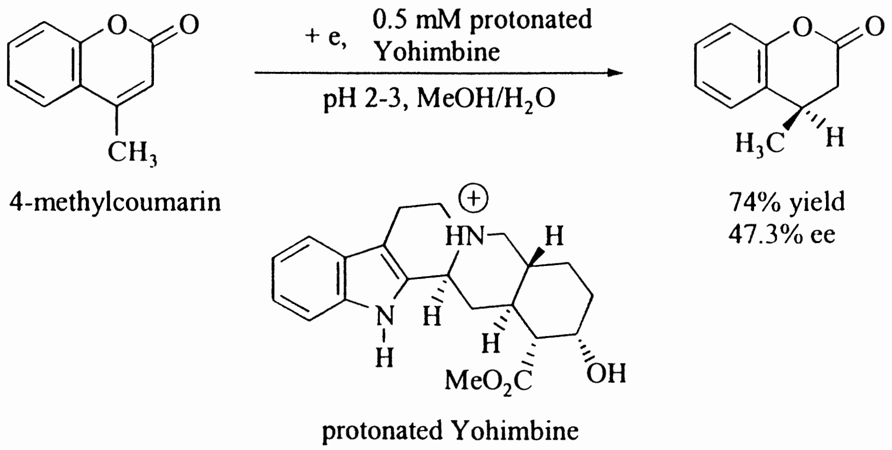
SCHEME 6. Enantioselective hydrodehalogenation of the α,α'-dichlorobenzazepin-2-one

Heterogeneous asymmetric hydrogenation of C=C bonds catalyzed by cinchona alkaloid-modified Pt has also been reported (*39*). However, the results are very disappointing because the most selective catalysts gave optical yields of <30%.

B. ALKALOID-INDUCED ENANTIOSELECTIVE ELECTROREDUCTION

Prochiral ketones, oximes and olefins can be electrochemically reduced to optically active alcohols, amines and alkanes in the presence of very small amounts of alkaloids, which are strongly adsorbed at the electrode (*40*). Pioneering work in the field of alkaloid-catalyzed enantioselective electroreduction has been done by Grimshaw and coworkers, who reduced 4-methylcoumarin in the presence of different alkaloids. With sparteine or yohimbine (+)-(*R*)-4-methyl-3,4-dihydrocoumarin was obtained with 17% or 12% ee, respectively (*41,42*). Recently, the optical yield of this reaction was increased up to 47.4% with yohimbine by systematic variation of the electrolysis conditions (Scheme 7) (*43*).

Electroreduction (*40*) using chiral quaternary ammonium salts as the supporting electrolytes has also been reported. Interestingly, for ketone reduction, the major enantiomer formed in the electroreduction was generally of opposite absolute configuration to that formed in the chemical reduction (*44*).

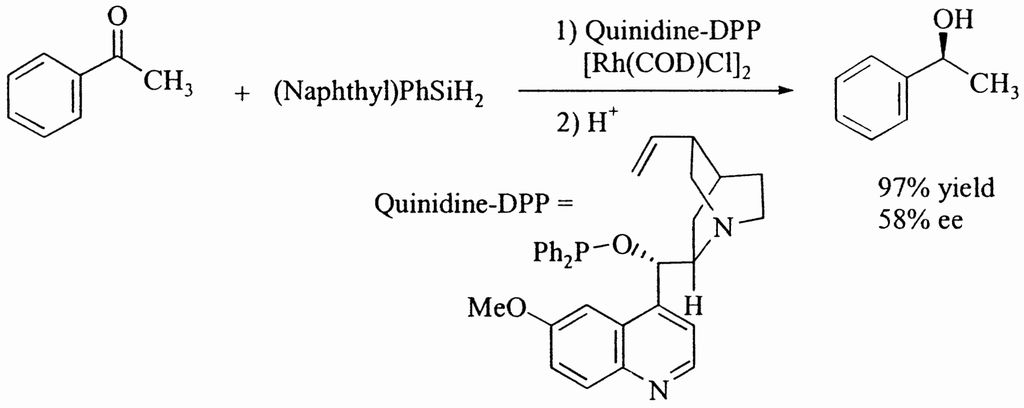


SCHEME 7. Catalytic enantioselective cathodic reduction of 4-methylcoumarin

C. OTHER KETONE AND IMINE REDUCTIONS

1. Enantioselective Hydrosilylation of Ketones

The use of phosphinite derivatives of cinchona alkaloids as chiral ligands in Rh(I)-catalyzed enantioselective hydrosilylation of aryl and alkyl ketones gave excellent chemical yield (88-98%), and, however, only low to moderate enantiomeric excess (5-58% ee) (*45*). For example, with quinidine-DPP (diphenyl phosphinite), (*S*)-1-phenylethanol was obtained in 97% yield and 58% ee by using α-naphthylphenylsilane as the reducing agent (Scheme 8). Chiral phase transfer catalysts **1** derived from alkaloids have also been used for the asymmetric hydrosilylation of 3-acetylpyridine (Scheme 9) (*46*).

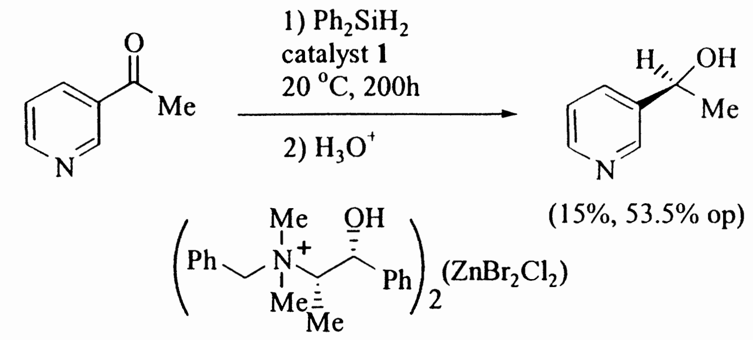


SCHEME 8. Rh-catalyzed asymmetric hydrosilylation of Ph(CO)CH$_3$ using quinidine-DPP as a chiral ligand

2. Additional Ketone and Imine Reductions

Additional ketone reductions catalyzed by cinchona (*47-49*) and ephedra alkaloids

(*47,48,50-55*) have been reported. Other imine reductions promoted by the cinchona and ephedra catalyst systems have been studied (*56*).



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SCHEME 9. Asymmetric hydrosilylation of 3-acetylpyridine catalyzed by **1**

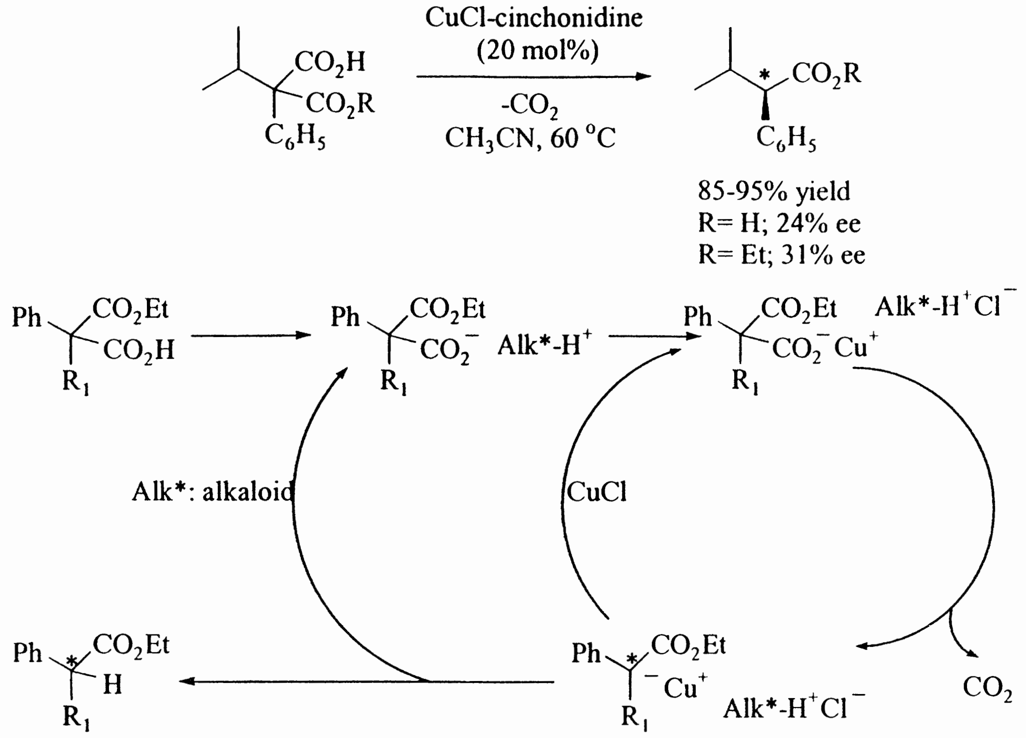
D. ENANTIOSELECTIVE PROTONATION

1. Catalytic Enantioselective Protonation of Prochiral Carbanions

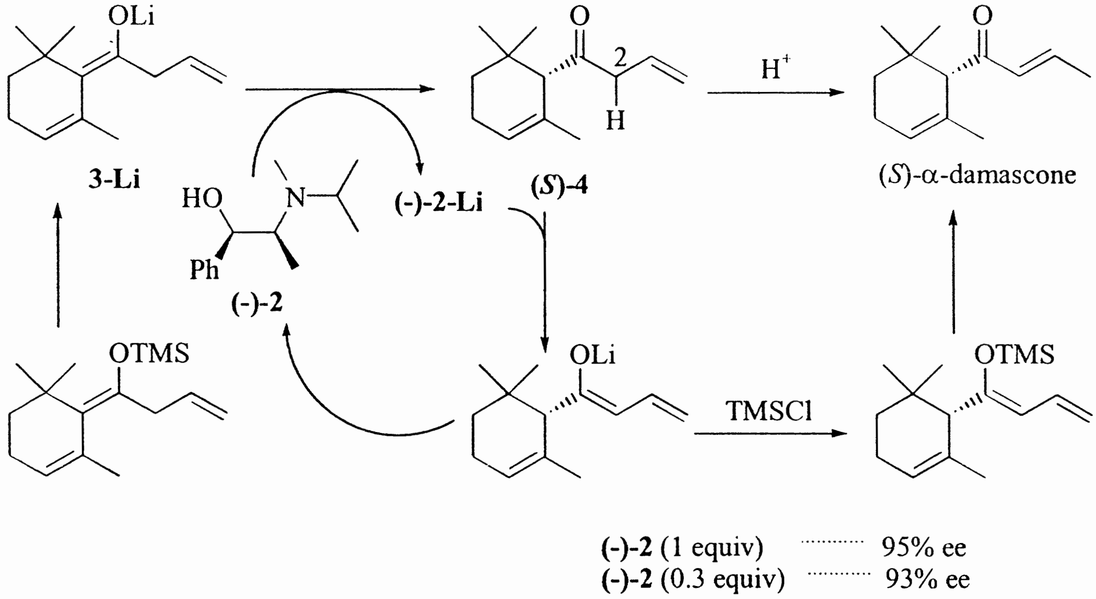
Only one reaction involving the asymmetric protonation of a prochiral carbanion catalyzed by alkaloids has been reported (*57-59*). Cu(I)-Catalyzed decarboxylation of racemic substituted malonic acids, followed by protonation of the intermediate carbanion by the HCl salt of alkaloid as a chiral proton donor gave the corresponding esters in up to 31% ee (Scheme 10) (*57*). Interestingly, inversion of the configuration in the product was observed when the alkaloids (quinine or cinchonidine) are acetylated (9-OAc). The substitution of copper (I) by silver (I) gave the same chemical yield for decarboxylation, but a lower optical yield. Other alkaloid-induced asymmetric decarboxylations of malonic acids have also been reported (*58,59*).

2. Catalytic Enantioselective Protonation of Prochiral Enols

Catalytic enantioselective protonation (*60-62*) of prochiral enol derivatives in the presence of catalytic amounts of cinchona and ephedra alkaloid derivatives as chiral proton donors is a very simple and attractive route for the preparation of optically active carbonyl compounds. During the last few years, this relatively new method has emerged as a powerful synthetic method for optically active carbonyl compounds, and has been successfully applied to the synthesis of some industrially important biologically active compounds, such as fragrances (*62*), antiinflammatory agents (*63-66*) and pheromones (*67,68*). For instance, Fehr (*69*) applied this method to the synthesis of α-damascone. (*S*)-α-Damascone, is an important perfume component. Protonation of enolate **3**-Li with 0.3 equivalents of *N*-isopropyl ephedrine (-)-**2** affords the α-damascone with 93% ee and 86% yield. This case is very particular, because the product ketone (*S*)-**4** is rapidly and exclusively deprotonated at C(2) (Scheme 11).

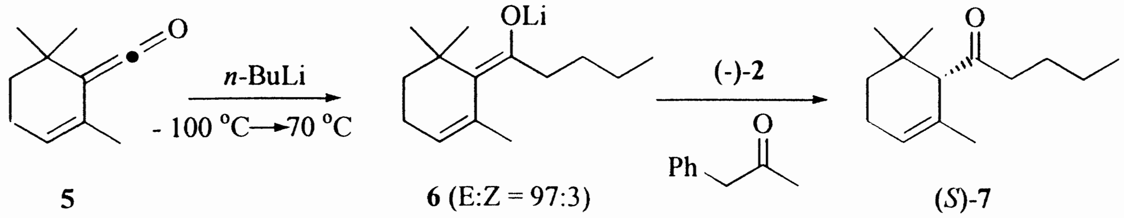


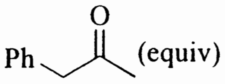
SCHEME 10. Asymmetric decarboxylation-protonation of racemic malonic acids



SCHEME 11. Autocatalytic enantioprotonation of 3-Li

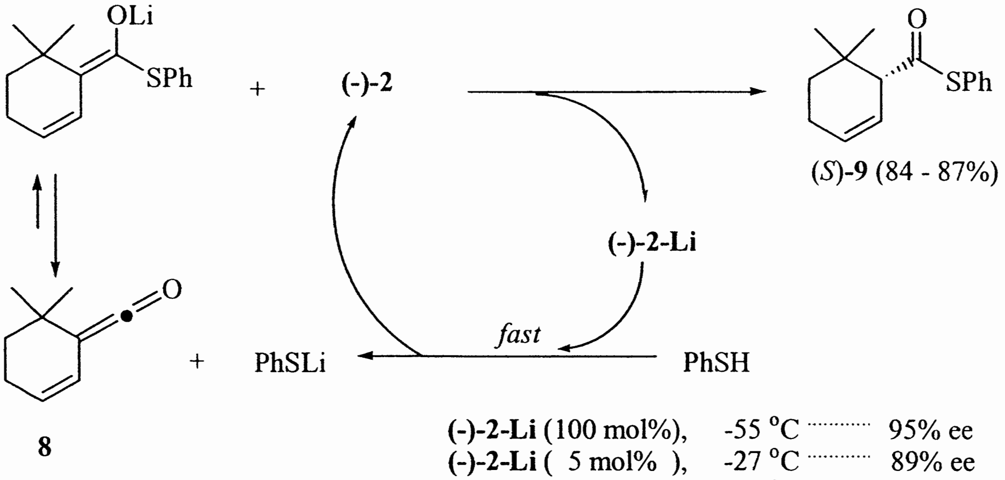
An analogous autocatalytic reaction, as shown in Scheme 11, is not possible with enolate **6**, which can be readily obtained from ketene **5** and *n*-BuLi, because the acidity of the C(2) protons of (*S*)-**7** is substantially weaker. To circumvent this problem, phenyl-2-propanone has been successfully used as an external, achiral proton donor (Scheme 12) (*69*). The protonation of **6** with catalytic amounts of (-)-**2**, followed by the addition of phenyl-2-propanone affords the butyl ketone (*S*)-**7** with an enantiomeric excess of up to 98%.



(-)-**2** (equiv)	 (equiv)	% ee
1.1	—	96
0.2	0.85	94
0.1	0.95	85
0.2	0.8, then TMSCl	98

SCHEME 12. Catalytic enantioselective protonation of **6**

Another impressive example is the synthesis of the industrially important (*S*)-α-cyclogeranium acid thioester **9** (*70*). Li-Salt of (-)-*N*-isopropyl ephedrine (-)-**2** catalyzes the addition of thiophenol to ketene **8** to give (*S*)-α-cyclogeranium acid thioester **9**. Thiophenol serves as both the nucleophile and the proton source. The rate of introduction of PhSH has to be kept low to prevent accumulation and to minimize the risk of enolate protonation of PhSH. As shown in Scheme 13, very high enantioselectivities (up to 89% ee) were achieved with as little as 2-5 mol% of (-)-**2**-Li. Of the other thiols tested, 4-chlorothiophenol, which is more acidic than PhSH, proved the most efficient (97% ee with 1 equiv (-)-**2**-Li; 90% ee with 0.05 equiv (-)-**2**-Li).



(-)-2-Li (100 mol%), -55 °C .... 95% ee
(-)-2-Li (5 mol%), -27 °C .... 89% ee
(-)-2-Li (2 mol%), -27 °C .... 77% ee

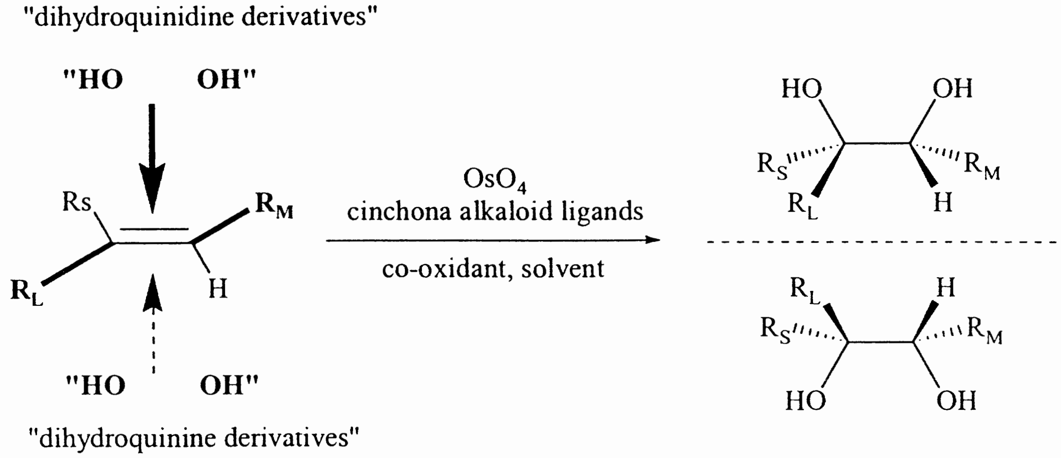
SCHEME 13. Catalytic enantioselective addition-protonation of thiophenol to a ketene

III. Asymmetric Oxidation

A. ASYMMETRIC DIHYDROXYLATION OF OLEFINS

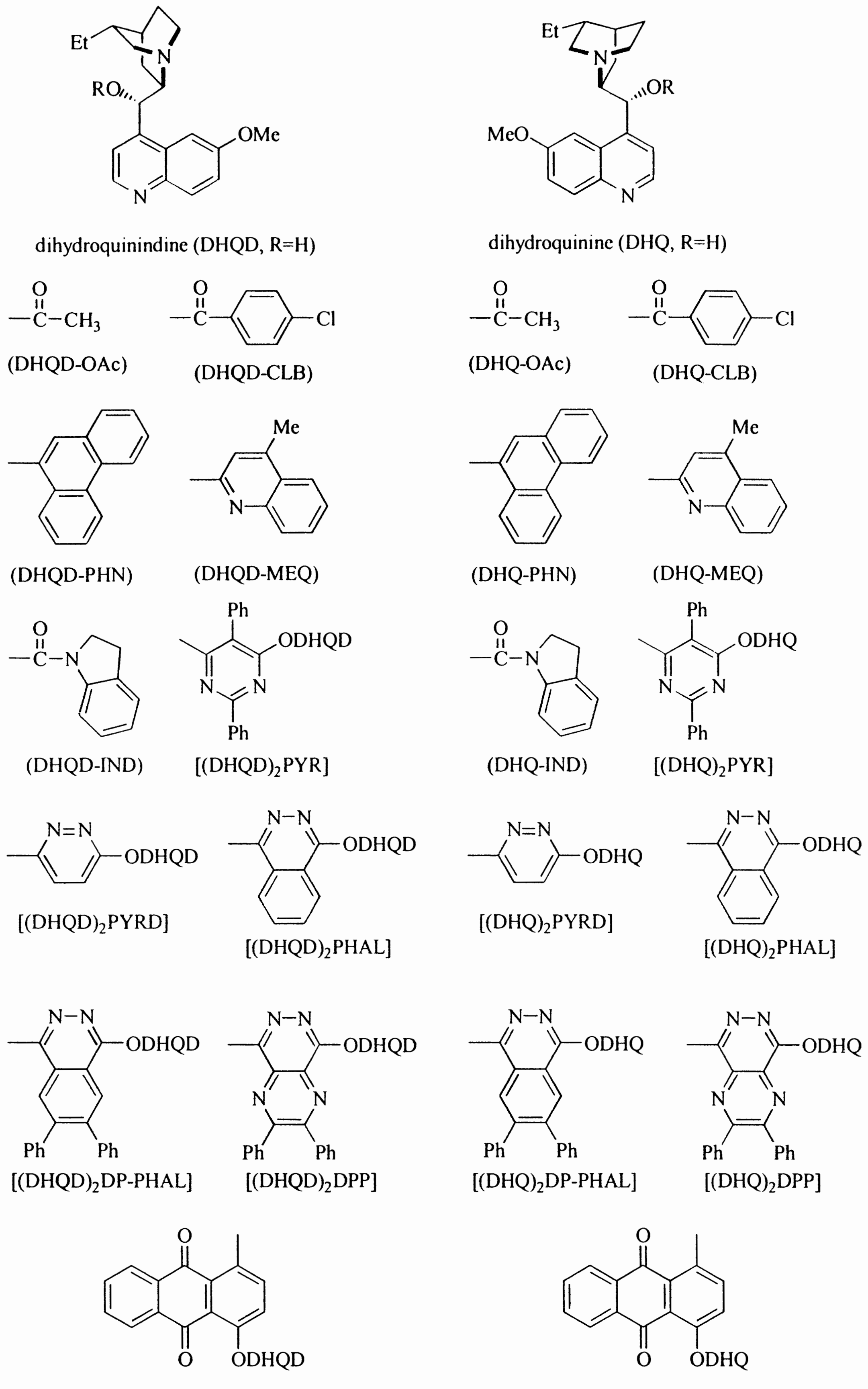
1. Sharpless Asymmetric Dihydroxylation of Olefins

The cinchona alkaloid-based catalytic asymmetric dihydroxylation of olefins (Scheme 14) is a very popular method that has been devised and continuously improved by Sharpless and coworkers (*71-75*). The method employs catalytic amounts of OsO_4 and dihydroquinidine or dihydroquinine derivatives (Figure 2) as chiral ligands together with *N*-methylmorpholine *N*-oxide (NMO) (*76,77*), potassium ferricyanide ($K_3Fe(CN)_6$) (*78*) or iodine (I_2) (*79,80*) as the co-oxidant. Dihydroquinidine- and dihydroquinine-derived auxiliaries have a pseudo-enantiomeric relationship that affords the antipodal diol products with similar enantioselectivities.



SCHEME 14. Asymmetric catalytic dihydroxylation of olefins (R_L, R_M, and R_S are respectively, the large, medium, and small substituents)

An asymmetric osmylation of olefins using stoichiometric amounts of dihydroquinidine acetate (DHQD-OAc) or dihydroquinine acetate (DHQ-OAc) was described in 1980 (*81*). Optical yields of up to 90 % were attained with *trans*-stilbene as the substrate. Although this reaction was a reliable synthetic method, the metal's cost and toxicity necessitated its use as a catalyst. In 1988, Sharpless discovered that the desired catalytic enantioselective reaction can be achieved selectively in aqueous acetone by using NMO as co-oxidant, catalytic amounts of OsO_4 and dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) or dihydroquinine *p*-chlorobenzoate (DHQ-CLB) as a chiral ligand (*82*). Under this catalytic condition, *trans*-stilbene was converted to the corresponding 1,2-diol in 80% yield with 88% ee. However, the ees of diol products obtained under this catalytic condition were initially lower than those produced by the stoichiometric reaction. Sharpless explained this discrepancy with two catalytic cycles mechanism (Scheme 15) (*82,83*).



dihydroquinindine (DHQD, R=H)

dihydroquinine (DHQ, R=H)

(DHQD-OAc) (DHQD-CLB) (DHQ-OAc) (DHQ-CLB)

(DHQD-PHN) (DHQD-MEQ) (DHQ-PHN) (DHQ-MEQ)

(DHQD-IND) [(DHQD)$_2$PYR] (DHQ-IND) [(DHQ)$_2$PYR]

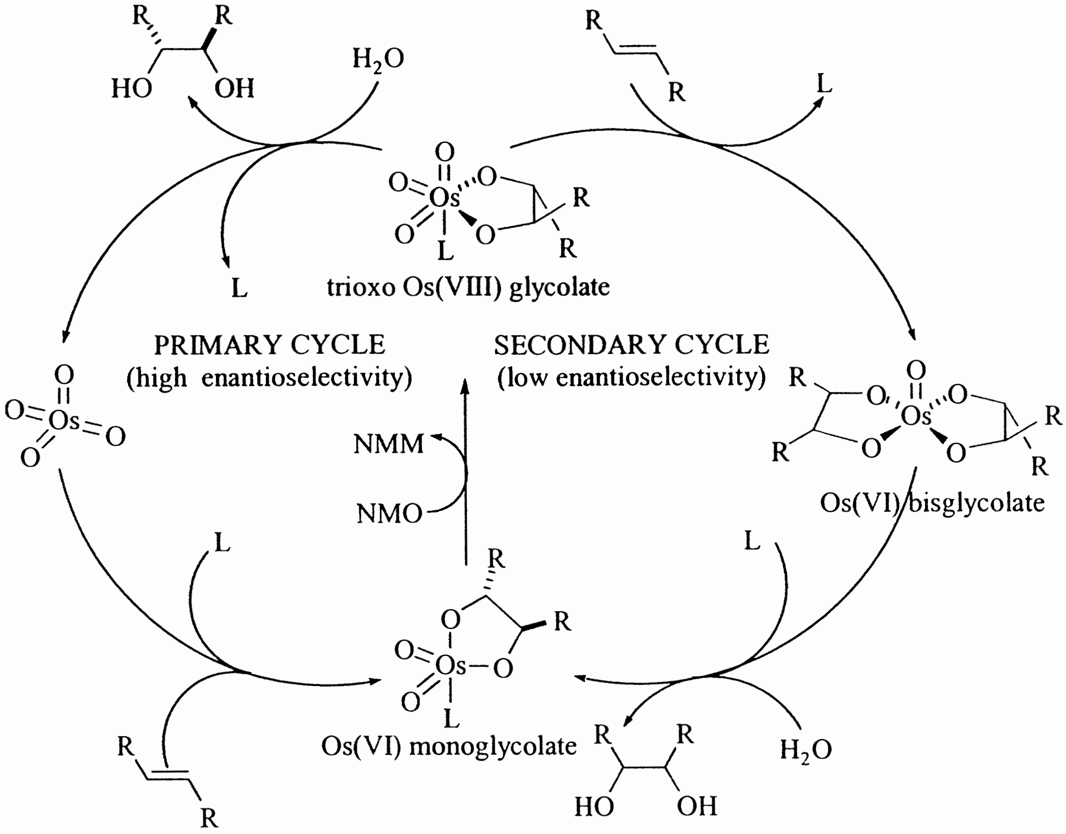
[(DHQD)$_2$PYRD] [(DHQD)$_2$PHAL] [(DHQ)$_2$PYRD] [(DHQ)$_2$PHAL]

[(DHQD)$_2$DP-PHAL] [(DHQD)$_2$DPP] [(DHQ)$_2$DP-PHAL] [(DHQ)$_2$DPP]

[(DHQD)$_2$AQN] [(DHQ)$_2$AQN]

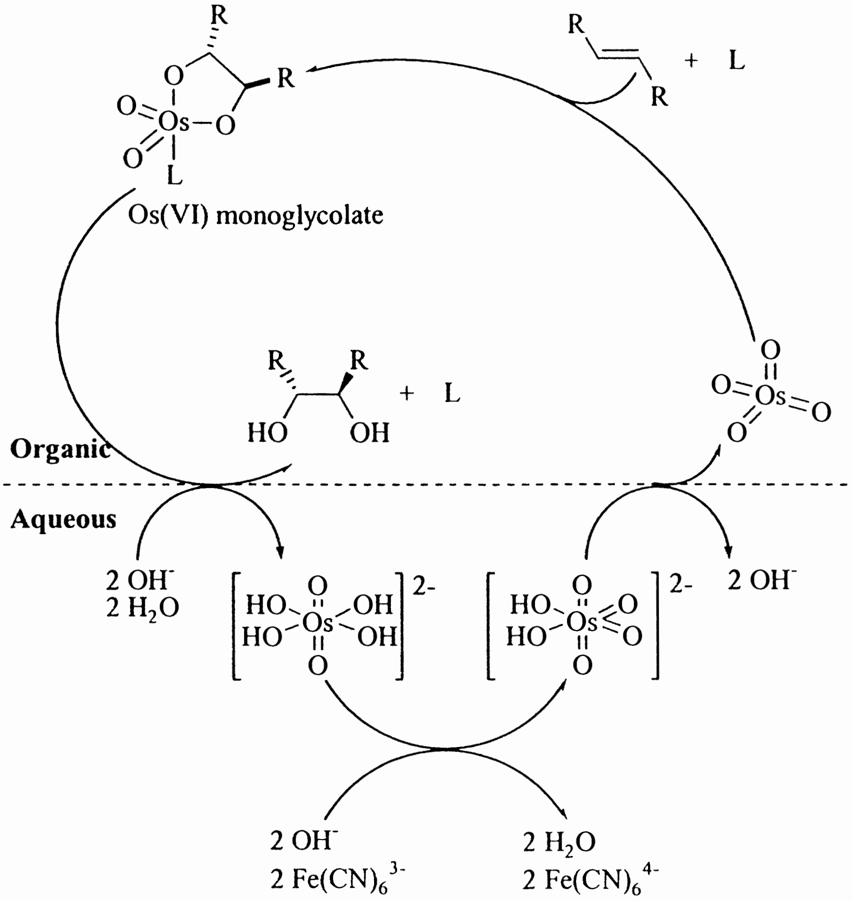
FIGURE 2. Structures of chiral ligands and their abbreviations

According to Sharpless, two competitive catalytic cycles operate, involving either direct hydrolysis of the reoxidized trioxo Os(VIII) glycolate ("first cycle") or its reaction with a second olefin to give an osmium(VI) bisglycolate ("second cycle") (*82,83*) (Scheme 15). Therefore, to minimize the low selectivity-generating second cycle the low concentration of substrates in the reaction mixture is essential, and thus, slow addition of the olefin is important to obtain high ees.



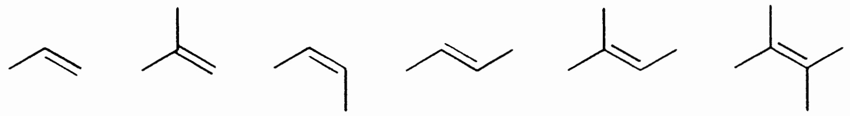
SCHEME 15. The two catalytic cycle in the AD reaction using NMO as cooxidant

Subsequently, Sharpless and coworkers found that use of potassium ferricyanide ($K_3Fe(CN)_6$) as co-oxidant in a 1:1 *t*-BuOH-H_2O two-layer system can suppress the second cycle and lead to high enantioselectivity (*84*). In this case, there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. Since the actual osmylation takes place in this layer, the resulting osmium(VI) monoglycolate undergoes hydrolysis, releasing chiral diol and ligand to the organic layer and $K_2OsO_2(OH)_4$ to the aqueous layer before its reoxidation to trioxo Os(VIII) glycolate can occur, and consequently entry of the Os(VIII) glycolate into the second cycle is prevented (Scheme 16). For the formation of the Os(VI) monoglycolate complex, two different mechanisms have been suggested: a [2+2]-addition of the olefin across an Os=O bond, followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate complex (*85-89*) or a concerted [3+2]-cycloaddition pathway (*90,91*).



SCHEME 16. Catalytic cycle of AD reaction with $K_3Fe(CN)_6$ as the co-oxidant

A systematic ligand optimization (Figure 2) study undertaken by Sharpless group has resulted in considerable improvement of the reaction's efficiency. The cinchona alkaloid ligands first recommended were the acetate (Ac) (*81*) and *p*-chlorobenzoate (CLB) of dihydroquinidine and dihydroquinine (*82,83*). Soon, the 9-*O*-(9′-phenanthryl) (PHN) ethers and 9-*O*-(4′-methyl-2′-quinolyl) (MEQ) ethers were found to be more efficient (*92*). Currently, the best systems are the bis-cinchona alkaloids having a heterocyclic spacer, especially phthalazine (PHAL) (*93,94*), diphenypyrimidine (PYR) (*95*) and anthraquinone (AQN) (*96*). PHAL ligands are recommended for 1,1- and 1,2-*trans*-disubstituted, as well as trisubstituted, olefins, but are especially well suited to accommodate olefins with flat aromatic substituents. PYR ligands are the ligands of choice for monosubstituted terminal olefins, especially aliphatic olefins. However, a limitation of the method is the low enantioselectivity usually obtained in the asymmetric dihydroxylation of *cis*-olefins. This drawback was surmounted by Wang and Sharpless, who used IND ligands (*97*). Tetra-substituted olefins generate osmate esters whose *in situ* hydrolysis is difficult. However, when the reaction is run with a higher amount of catalyst in the presence of $MeSO_2NH_2$, useful selectivities can sometimes be obtained with PHAL and PYR ligands (*98*).This broad applicability of Sharpless asymmetric dihydroxylation for nearly every class of olefins affords enormous utility in organic synthesis (Figure 3). Thus, both unfunctionalized substrates and functionalized olefins with nearly all kind of substituents attached to olefins can be dihydroxylated to give products in reasonable to very high selectivities. For examples, acrylic esters, unsaturated amides and ketones, dienes, enynes, vinyl silanes, acrolein acetals, and allylic halides, allylic phosphine oxides (*99,100*), allylic silanes (*101*) as well as allylic ethers and sulfur-containing olefins have been successfully dihydroxylated (*71,72*). Moreover, very recently, 1(*E*)-alkenylphosphonates were also successfully dihydroxylated to give a series of optically active threo-α,β-dihydroxyphosphonates (*102*).



Preferred ligand	PYR PHAL	PHAL	IND	PHAL	PHAL	PYR PHAL
ee range	30-97%	70-97%	20-80%	90-99%	90-99%	20-97%

FIGURE 3. Recommended ligand types for different olefin classes

Moreover, the AD reaction is a good example of ligand accelerated asymmetric catalysis (LAC), in which the alkaloid ligands enhance the rate by one to two orders of magnitude (*17,72,103*). For example, rate improvements up to 14,771-fold were observed for the AD reaction of 2-vinylnaphthalene with $(DHQD)_2PHAL$ as a ligand. Interestingly, the rate acceleration is significantly greater with the alkaloid derivatives than with a simple quinuclidine. For example, the $(DHQD)_2PHAL$ promoted reaction occurs between about 240 (2-vinylnaphthalene) and about 14 (1-decene) times faster than the reaction in the presence of quinuclidine. That is, the rate accelerations are not directly related to the ground-state binding energy between the ligand and OsO_4, which is higher for quinuclidine (K_{eq} for quinuclidine: 2630 $Lmol^{-1}$ in *t*-BuOH at 25 °C and K_{eq} for $(DHQD)_2PHAL$ ligand of 27.7 $Lmol^{-1}$ in *t*-BuOH at 25 °C). Instead, "enzyme-like" noncovalent binding in a binding pocket of the ligand seems to be the cause of the substantial rate accelerations and the ability to deliver high enantioselectivity.

Asymmetric dihydroxylations have already been successfully applied to the commercial synthesis of intermediates for pharmacologically active compounds, such as the taxol C-13 side chain (*104-106*), propranolol (*107*) and CL-316243 (*108*), which is a anti-diabetic and anti-obesity agent (Chirex Ltd. U.K.). Other industrially interesting biologically active compounds, such as diltiazem (*109,110*), carnitine and 4-amino-3-hydroxybutyric acid (*111*), azole antifungals (*112*), chloramphenicol (*113*), reticuline intermediates (*114*), camptothecin analogs (*115-117*), khellactone derivatives (*118*), and antimalarial active cyclopenteno-1,2,4-trioxanes (*119*), etc., have been successfully synthesized using catalytic asymmetric dihydroxylation (Figure 4). More detailed information for the synthetic application of asymmetric dihydroxylation is available in several reviews (*71-75*).

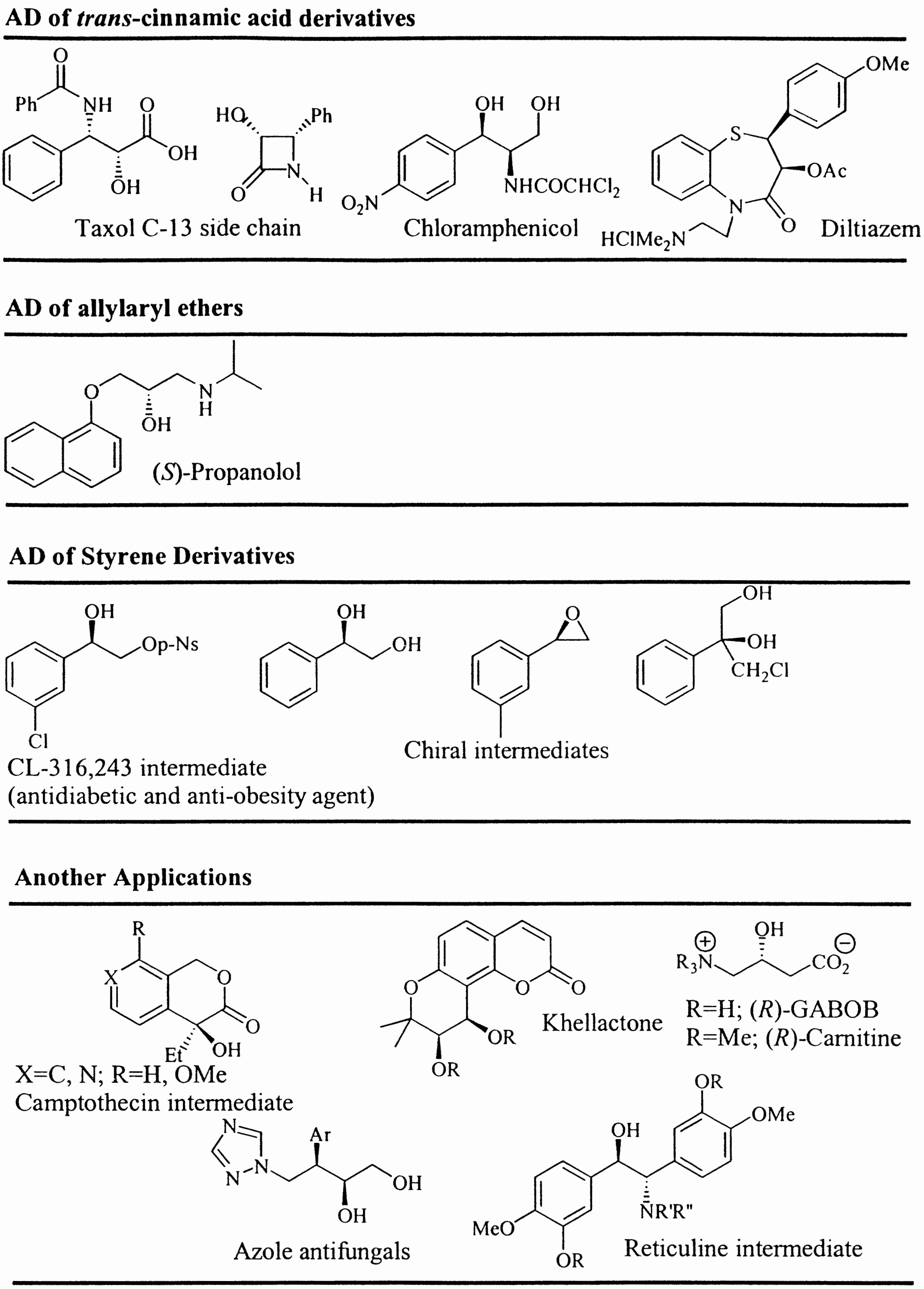


FIGURE 4. Synthetic applications of asymmetric dihydroxylations

2. Electrochemical Asymmetric Dihydroxylation of Olefins

Gao and coworkers (*71*) at Sepracor developed an efficient electrocatalytic AD reaction using Pt-electrodes and PHAL-ligand in a glass H-type cell. A 5% aqueous solution of phosphoric acid is used in the cathode compartment, and the reaction in the anode compartment is stirred vigorously. Under a controlled anode potential of 0.4 V (vs. Ag/AgCl) and with $(DHQD)_2PHAL$ as chiral ligand, α-methylstyrene was converted to (*R*)-2-phenyl-1,2-propanediol in 15 hours with an electrical consumption of 2.1 F/mol. The product was isolated in 100% yield with 92% ee. More recently, Torii and coworkers (*79,80*) performed highly efficient electrochemical Os-catalyzed AD of olefins with PHAL ligands in an undivided cell equipped with two Pt-electrodes under a constant current of 2 mA/cm^2 (applied voltage: 1.0-3.0 V). After passage of 2.33 F/mol of electricity, the desired diols were obtained in very high values both on %ee and conversion yield. In addition, under these electrochemical conditions, they could minimize the use of the amount of $K_2OsO_2(OH)_4$ (0.0005 equiv) and $K_3Fe(CN)_6$ (0.1 equiv) (Table II).

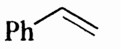
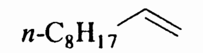
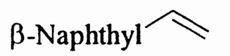
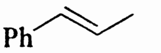
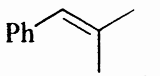
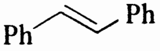
TABLE II
ELECTROCHEMICAL OS-CATALYZED AD OF STYRENE

Conditions	Sharpless conditions	Electrolysis Run		
		A	B	C
Styrene	1	1	1	1
K_2CO_3	3	3	3	3
$(DHQD)_2PHAL$	0.01	0.01	0.01	0.01
$K_3Fe(CN)_6$	3	0.3	0.1	0.1
$K_2OsO_2(OH)_4$	0.002	0.002	0.002	0.0005
Electricity (F/mol)	-	2.33	2.33	2.33
Time (h)		31.2	31.2	31.2
Temp. (°C)	0	0	0	0
% Yield	88	95	95	72
% ee	97.2	97.2	97.3	99.0

Moreover, instead of $K_3Fe(CN)_6$, I_2 was also found to be an efficient co-oxidant (*80*). Iodine-assisted asymmetric electro-dihydroxylation of olefins in either a *t*-BuOH/H_2O(1/1)-K_2CO_3/$(DHQD)_2PHAL$-(Pt) or *t*-BuOH/H_2O(1/1)-K_3PO_4/K_2HPO_4 /$(DHQD)_2PHAL$-(Pt) afforded the diols in high yields and with excellent enantiomeric excesses (Table III). Iodine was also used as an efficient co-oxidant for the chemical dihydroxylation, and excellent results were obtained with nonconjugated olefins, in contrast to the case of $K_3Fe(CN)_6$.

TABLE III

ELECTROCHEMICAL Os-CATALYZED AD OF OLEFINS USING I_2 AS OXIDANT

Olefin	% Yield	% ee	Config.
	96.0	97.1	*R*
	87.6	>99	*R*
	87.6	>99	*R*
	92.9	97.3	*R,R*
	86.0	86.0	*R*
 	88.2	88.2	*R,R*

Reaction conditions: $K_2OsO_2(OH)_4$ (0.0005 equiv), $(DHQD)_2PHAL$ (0.01 equiv), I_2 (0.5 equiv), K_3PO_4/K_2HPO_4 (1.2/1.8 equiv), electricity (2.33 F/mol), 31h, 0 °C.

3. Heterogeneous Asymmetric Dihydroxylation of Olefins

As mentioned in section III.A.*1*., the Sharpless asymmetric dihydroxylation (AD) reaction has become an important process in organic chemistry for the synthesis of optically pure vicinal diols. However, there are limitations to performing the catalytic AD reaction on a large scale due to the toxicity of osmium tetroxide and the high cost of preparing the cinchona alkaloid ligands. Recently, in order to explore the possibility of the repetitive use of both components, several solid-supported cinchona alkaloid derivatives have been employed (*120-133*). However, most of polymers require complicated synthetic manipulations and, moreover, their catalytic efficiency remained far from satisfactory. Some of recent studies in this area led to an improved level of enantioselectivity. Salvadori and coworkers (*132*) used polymer-bound dihydroquinine derivatives as ligands (Figure 5) in AD reactions, which were obtained by radical copolymerisation of the cinchona alkaloid monomers **10** using EGDMA as the cross-linking agent. Optical yields of products ranged from 65% to 99%. Janda and coworker (*129,131*) have developed a soluble, polymeric form **11** (Figure 6) of $(DHQD)_2PHAL$ from polyethylene glycol monomethylether (MeO-PEG) for use in catalytic asymmetric dihydroxylation. The ligand **11** was prepared in five steps, and dihydroxylation was studied using four different substrates. In several cases excellent ees were obtained. We have also recently reported (*133*) a successful heterogeneous asymmetric dihydroxylation AD using silica gel-supported cinchona alkaloids containing 1,4-bis(9-*O*-quininyl)phthalazine [$(QN)_2PHAL$] (SGS-$(QN)_2PHAL$, **12**) (Figure 7).

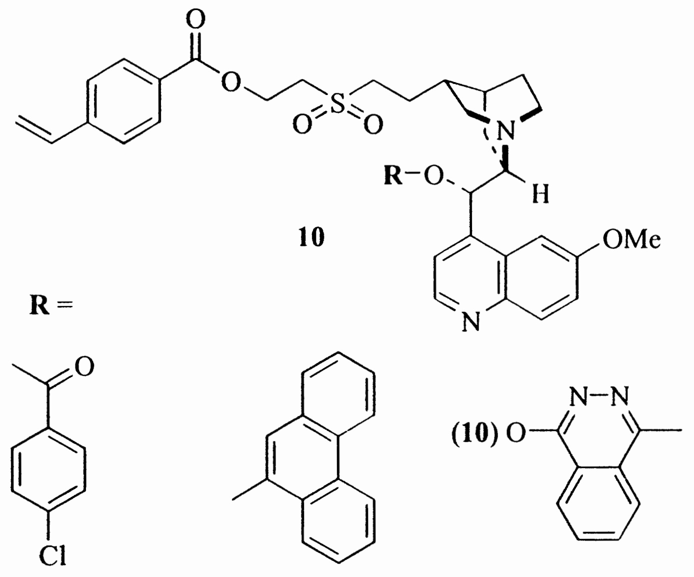
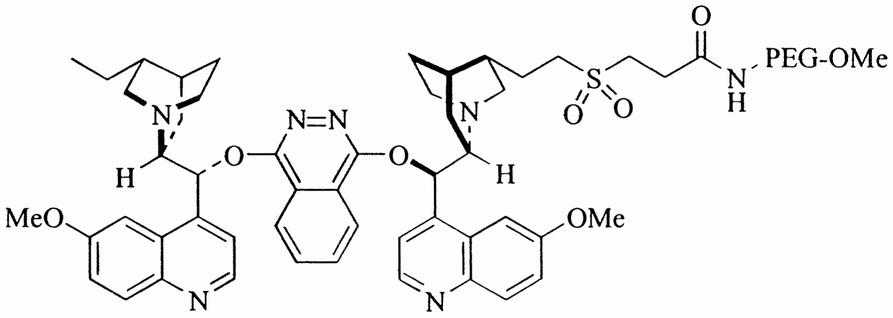
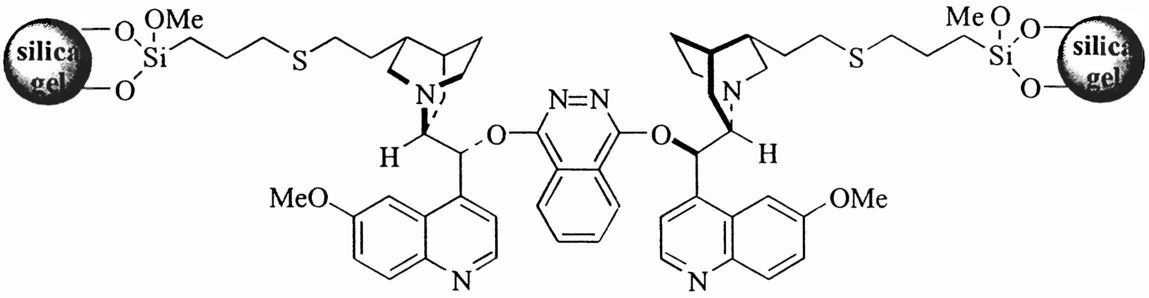


FIGURE 5. Salvadori's polymer-bound dihydroquinine derivatives



11

FIGURE 6. Janda's soluble polymer of $(DHQD)_2PHAL$



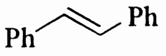
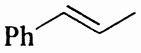
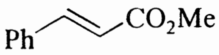
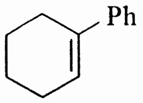
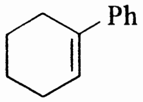
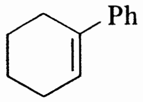
$SGS-(QN)_2PHAL$ (**12**)

FIGURE 7. Song's $SGS-(QN)_2PHAL$

Substrate studies (Table IV) included *trans*-stilbene, β-methyl-*trans*-styrene, methyl *trans*-cinnamate, and 1-phenyl cyclohexene. Yields of between 88% and 95%, and ees of greater than 92% in all cases, represent a marked improvement on other reported investigations. Moreover, $SGS-(QN)_2PHAL$, **12** revealed much greater binding ability for OsO_4 than its homogeneous analogue. Thus, the silica gel supported alkaloid-OsO_4 complex could be reused without any significant loss of enantioselectivity after simple filtration (entry 5). In the homogeneous solution, the complex formation of alkaloid and OsO_4 is in equilibrium. The binding constant K_{eq} for $(DHQD)_2$PHAL is 27.7 (*103*). Thus, the enantiomeric excess in the homogeneous reaction approaches the maximum value with increasing ligand concentration. For the best results the reaction usually requires excess of expensive alkaloid ligands to osmium. However, in our system, excellent ee has been achieved with only an equimolar amount of ligand to osmium (entry 6).

TABLE IV

HETEROGENEOUS AD USING SGS-$(QN)_2$PHAL

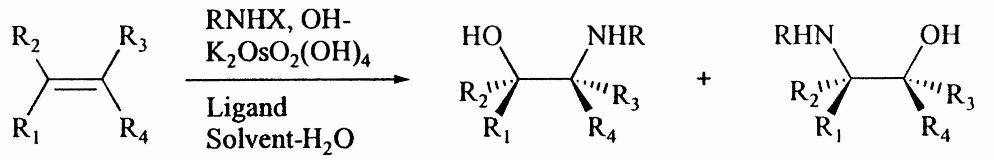
Entry	Olefin	Time	% Yield[b]	% ee[c]	Config[c]
1		25h	88	>99	*S,S*
2		15h	92	97	*S,S*
3		20h	93	95	*2R,3S*
4		15h	96	96	*S,S*
5[d]		21h	92	92	*S,S*
6[e]		16h	95	95	*S,S*

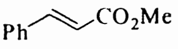
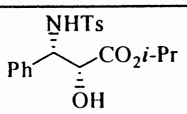
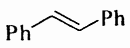
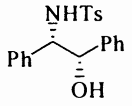
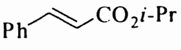
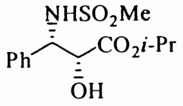
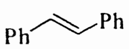
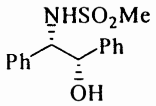
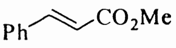
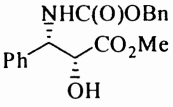
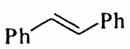
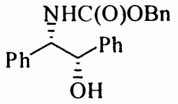
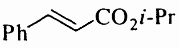
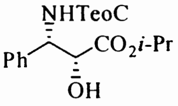
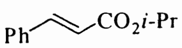
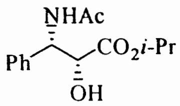
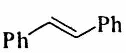
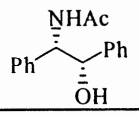
[a] The reaction conditions were not optimized: molar ratio of olefin/OsO_4/SGS- $(QN)_2$PHAL = 1/0.01/0.02; reaction temperature (10°C). [b] Isolated yields by column chromatography. [c] % ee and absolute configurations were determined by comparison of $[\alpha]_D$ with literature value. [d] Reaction was carried out with SGS-$(QN)_2$PHAL which had been used in entry 4 without further addition of OsO_4. [e] Molar ratio of olefin/OsO_4/SGS-$(QN)_2$PHAL = 1/0.01/0.01.

B. ASYMMETRIC AMINOHYDROXYLATION OF OLEFINS

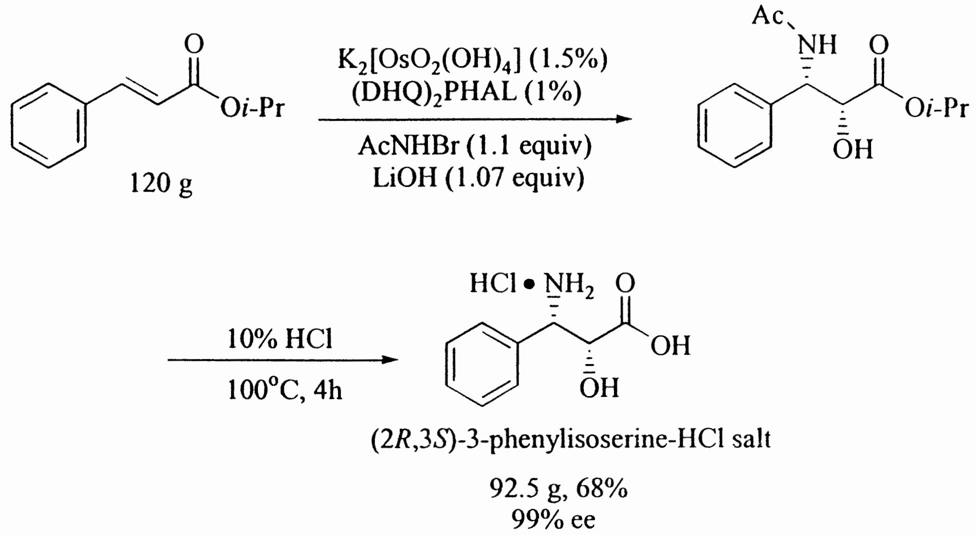
The osmium-catalyzed (*134,135*) or palladium-mediated (*136*) aminohydroxylation of olefins has been known for over 20 years. The resulting β-aminoalcohols are one of the most abundant structural elements in biologically active compounds, as well as the starting points in the design of many chiral ligands. However, attempts to develop this reaction into a catalytic, asymmetric process were not successful, until Sharpless and coworkers discovered efficient methods for this reaction in 1996 (*137-141*). This reaction first emerged as a process in which TsNClNa (Chloramine-T) (*137,138*) was used as the nitrogen source/oxidant. Subsequently, with the development of procedures which utilize carbamates- (*140*) and amide-derived oxidants (*141*) the substrate scope and selectivity was greatly improved (Table V). The products were obtained with moderate to high enantioselectivities, and with complimentary discrimination of the enantiotopic faces of the alkene by the two ligands, DHQ- and DHQD-derivatives. The same sense of the asymmetric induction as in the AD is observed, indicating that the transfer of chirality occurs by a similar pathway.

TABLE V
OS-CATALYZED ASYMMETRIC AMINOHYDROXYLATION OF OLEFINS



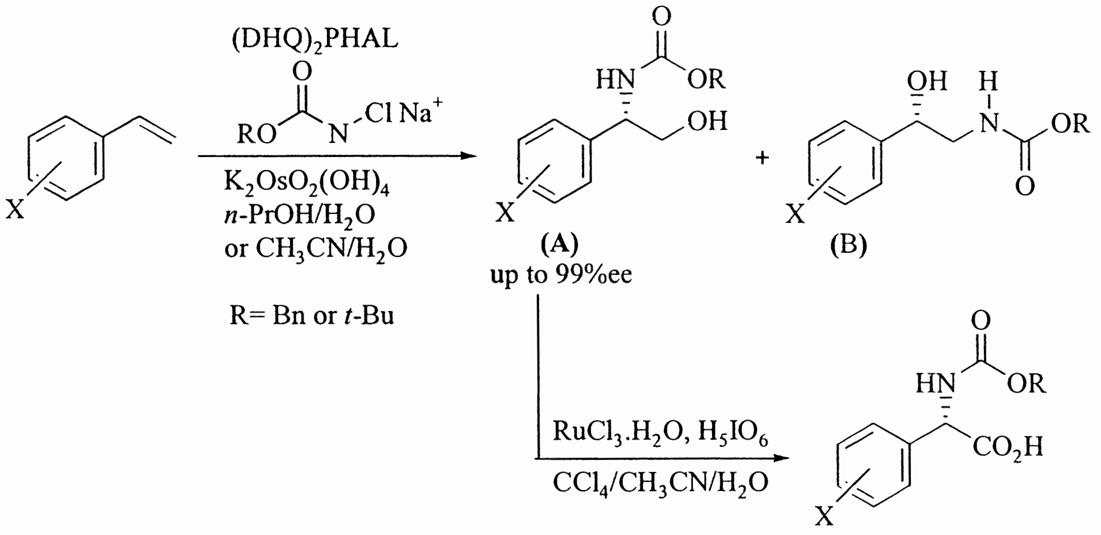
Substrate	Product	Nitrogen source and oxidant	Solvent	% ee (DHQ)$_2$PHAL	(DHQD)$_2$PHAL	Yield (%)	Ref.
		TsNClNa.3H$_2$O	CH$_3$CN-H$_2$O	81	-71	64	*137*
		TsNClNa.3H$_2$O	CH$_3$CN-H$_2$O	62	-50	52	*137*
		CH$_3$SO$_2$NClNa	*n*-PrOH-H$_2$O	94	-95	65	*139*
		CH$_3$SO$_2$NClNa	*n*-PrOH-H$_2$O	75	-82	71	*139*
		BnOC(O)NClNa	*n*-PrOH-H$_2$O	94	-97	65	*140*
		BnOC(O)NClNa	*n*-PrOH-H$_2$O	91	-88	92	*140*
		TeoCNNaCl	*n*-PrOH-H$_2$O	99	-99	70	*143*
		CH$_3$NHBr, LiOH	*t*-BuOH-H$_2$O	99	-99	81	*141*
		CH$_3$NHBr, LiOH	*t*-BuOH-H$_2$O	94	-93	50	*141*

The AA reaction was applied to the large-scale synthesis of (2*R*,3*S*)-3-phenylisoserine (*141*), a precursor for the side chain of the anticancer drugs taxol and taxotere. The AA of isopropyl *trans*-cinnamate was carried out in the presence of 1.5 mol% osmate salt and 1 mol% $(DHQ)_2PHAL$ using *N*-bromoacetamide as nitrogen source. The AA product was isolated by crystallization of the crude reaction mixture. Subsequent hydrolysis furnished the enantiomerically pure (2*R*,3*S*)-3-phenylisoserine as its HCl salt in 68% yield over two steps (Scheme 17). This amide-based AA protocol for the synthesis of the taxol C-13 side chain is superior to Sharpless's earlier AA- (*138*) or AD (*104-106*) approaches.



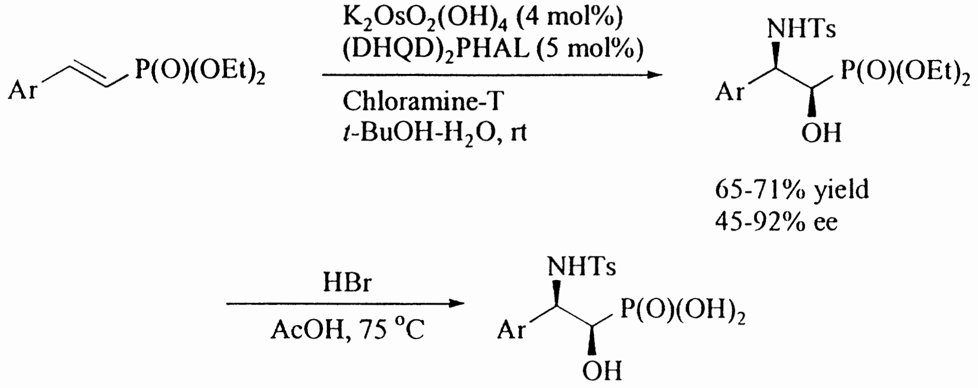
SCHEME 17. The synthesis of (2*R*,3*S*)-3-phenylisoserine as the taxol C13-side chain precursor

Another useful application of the AA reaction is the synthesis of optically pure α-arylglycinols. The catalytic asymmetric aminohydroxylation reaction of commercially available styrenes provides either (*R*)- or (*S*)-*N*-Cbz- or *N*-Boc-protected α-arylglycinols (Scheme 18) (*142-144*). The enantioselectivities are generally excellent and a subsequent oxidation step yields the corresponding α-arylglycines. The regioselectivity seems to be highly dependent on the nature of the styrenes as well as the choice of ligand, solvent and ligand-solvent combination. Phthalazine ligands such as $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ in *n*-PrOH favor the benzylic amine (A) over the benzylic alcohol regioisomer (B). In acetonitrile, the ratio of benzylic amines to benzylic alcohols (A/B) decreases significantly (*142*).



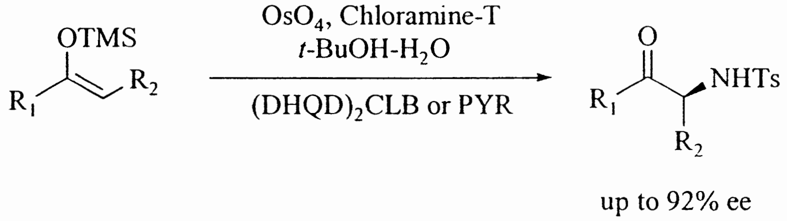
SCHEME 18. The synthesis of α-arylglycines via AA reaction

Recently, optically active β-amino-α-hydroxyphosphonic acids have been prepared by the asymmetric aminohydroxylation reaction of β-substituted vinylphosphonates followed by hydrolysis (Scheme 19) (*145*). The AA reaction of styrylphosphonate using $(DHQD)_2PHAL$ as chiral ligand afforded the corresponding β-amino-α-hydroxyphosphonate in 65% yield and 60% ee. After simple recrystallization and hydrolysis, β-amino-α-hydroxyphosphonic acid with high optical purity (>95% ee) was obtained.



SCHEME 19. Catalytic asymmetric aminohydroxylation of β-substituted vinylphosphonates

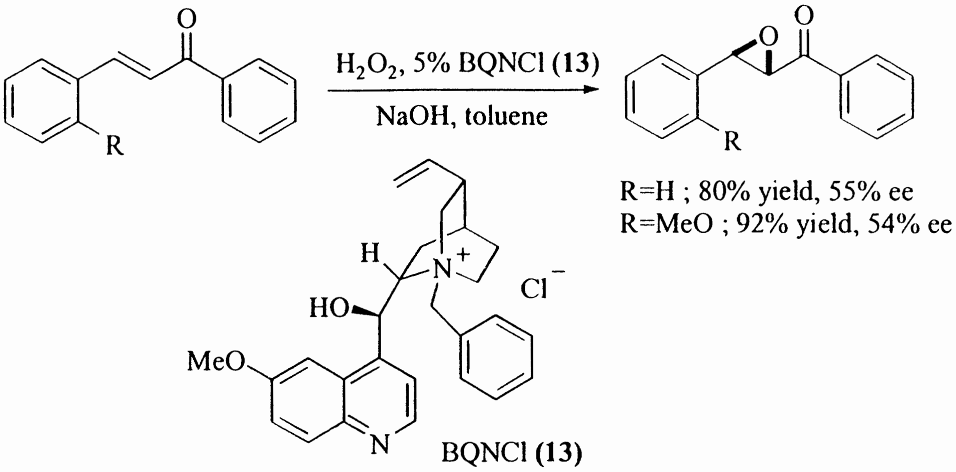
OsO_4-catalyzed aminohydroxylation of silyl enol ethers using cinchona alkaloids as chiral ligands and chloramine-T as the nitrogen source affords chiral α-amino ketones with an enantiomeric excess of up to 92% (Scheme 20) (*146*).



SCHEME 20. OsO_4-catalyzed asymmetric aminohydroxylation of silyl enol ethers

C. ASYMMETRIC EPOXIDATION OF ELECTRON-POOR OLEFINS

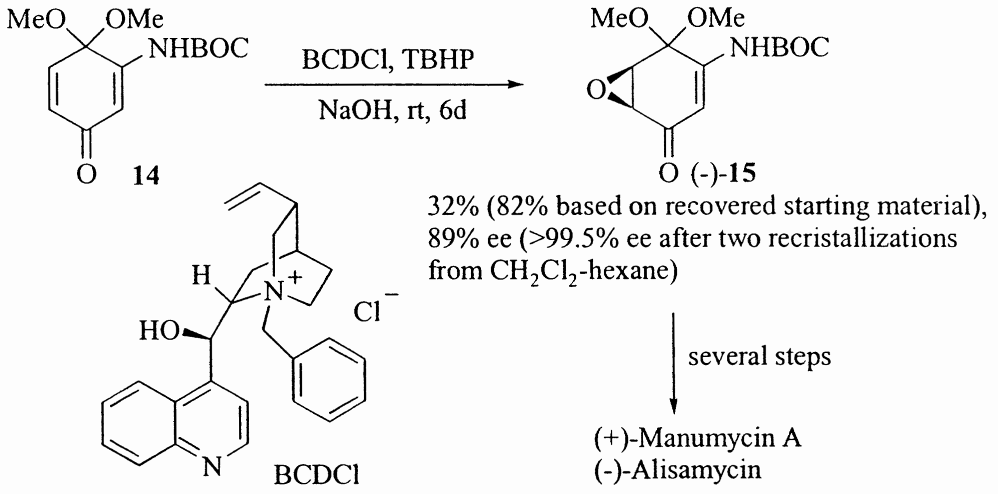
Cinchona alkaloid-derived quaternary ammonium salts as chiral phase transfer agents catalyze the asymmetric epoxidation of cyclic and acyclic electron-deficient alkenes, such as quinones and α,β-unsaturated carbonyl systems, with hydrogen peroxide, an alkyl hydroperoxide or sodium hypochlorite as the stoichiometric oxidant under basic conditions (*147-156*). Pioneering work of this reaction was done by Wynberg. However, the results were disappointing (ees generally <55%). Enantioselectivities as high as 55% ee were obtained in the epoxidation of *trans*-chalcone derivatives with basic hydrogen peroxide using *N*-benzylquininium chloride (BQNCl, **13**) (Scheme 21) (*147,149*). Epoxidation of *trans*-chalcone derivatives with sodium hypochlorite in the presence of **13** afforded a product with about 25% ee, comparable to that obtained by employing the H_2O_2/NaOH system. However, interestingly, the absolute configuration of the major enantiomer obtained with bleach was opposite to that obtained by using H_2O_2 as oxidant (*148*).



R=H ; 80% yield, 55% ee
R=MeO ; 92% yield, 54% ee

SCHEME 21. Asymmetric epoxidation of *trans*-chalcones using phase-transfer catalyst **13**

Wynberg's epoxidation procedure using chiral phase transfer catalysts was recently applied by Taylor and coworkers to the total synthesis of manumycin A (*157*) and alisamycin (*158*) (Scheme 22). The epoxidation of the enone **14** with *tert*-butyl hydroperoxide using *N*-benzylcinchonidinium chloride (BCDCl) as the catalyst gave the epoxide (-)-**15** in 32% yield (82% based on recovered **14**) and 89% ee. Two recrystallizations of the reaction product from dichloromethane-hexane gave enantiomerically pure (-)-**15** (>99.5% ee). However, surprisingly, the use of the pseudoenantiomeric *N*-benzylcinchonium chloride (BCNCl) which would produce (+)-**15**, also gave (-)-**15**, albeit in only 10% ee.



32% (82% based on recovered starting material), 89% ee (>99.5% ee after two recristallizations from CH_2Cl_2-hexane)

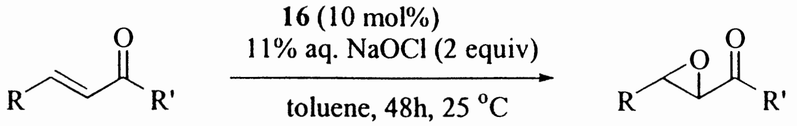
several steps

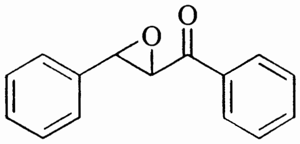
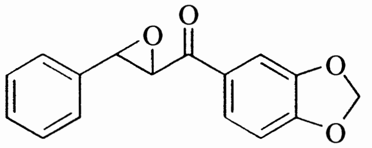
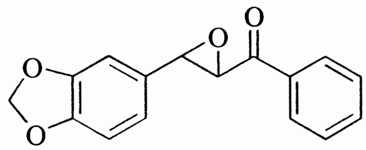
(+)-Manumycin A
(-)-Alisamycin

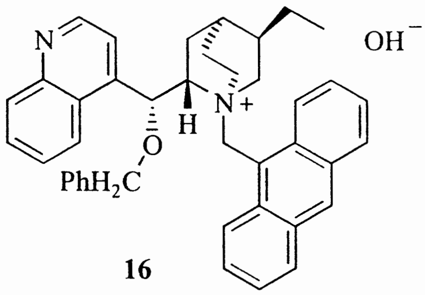
SCHEME 22. Synthesis of (+)-manumycin A and (-)-alisamycin

Very recently, much higher enantioselectivities (69-89% ee) have been achieved utilizing cinchona alkaloid-derived quaternary ammonium phase-transfer catalyst **16** bearing an *N*-anthracenylmethyl function, in conjunction with sodium hypochlorite as the oxidant (Table VI) (*159*).

TABLE VI
ENANTIOSELECTIVE EPOXIDATION OF *trans*-CHALCONE DERIVATIVES USING **16**



Product	% ee (sign of rotation)	% yield
	86 (+)	90
	89 (+)	95
	83 (-)	97

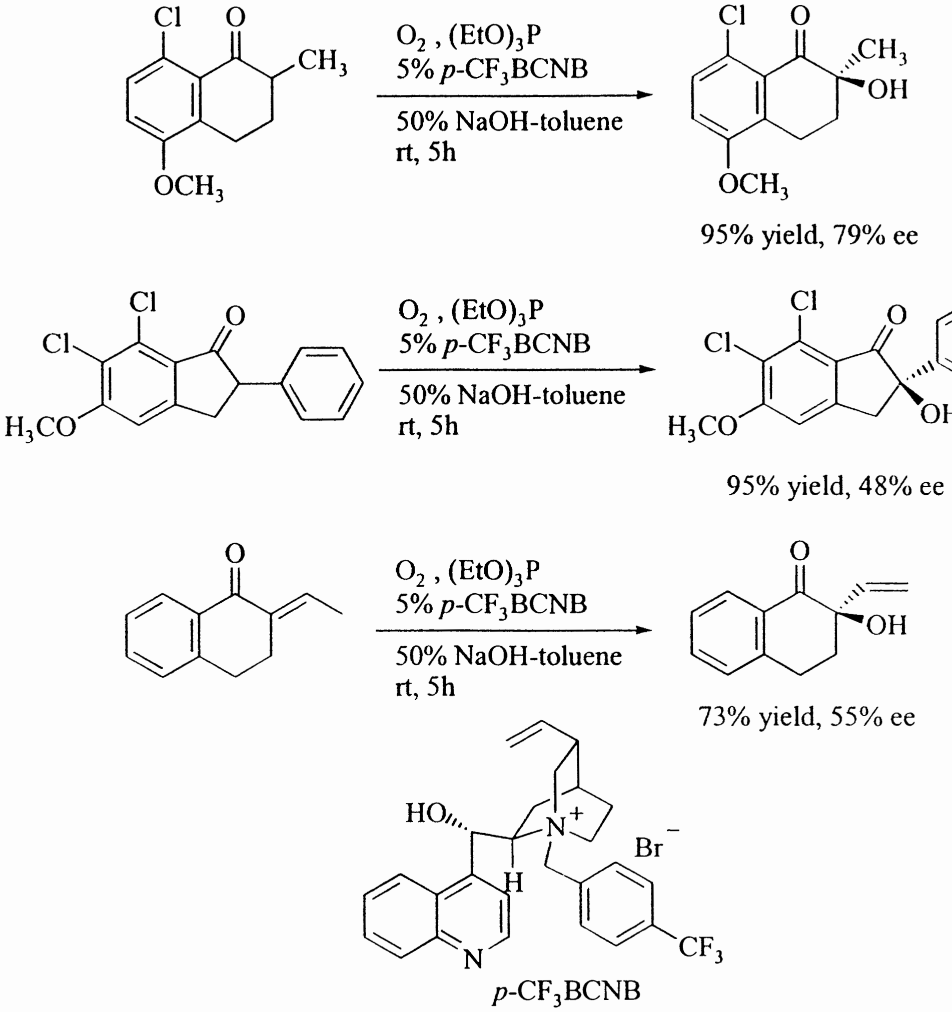


16

In another approach for the synthesis of non-racemic epoxides, direct epoxidation of benzaldehyde with dimethyl sulfide in the presence of chiral phase-transfer catalysts derived from ephedrine to give 2-phenyloxirane was also studied, however with little success (*160*).

D. ASYMMETRIC α-HYDROXYLATION OF KETONES

Ketones were converted by chiral PTC to optically active α-hydroxyketones with moderate asymmetric induction using molecular oxygen (Scheme 23) (*161*). Of the several different classes of quaternary ammonium salts examined, the best catalyst was *N*-(*p*-trifluoromethylbenzyl)cinchonium bromide (*p*-CF_3BCNBr). α,β-Unsaturated ketones are also effective as starting materials in this reaction. For instance, (*E*)-2-ethylidene-1-tetralone was oxidized to the α-hydroxy ketone under the same reaction conditions in 73% yield and 55% ee.



SCHEME 23. Asymmetric α-hydroxylation of ketones

A hydrogen-bonded ion-pair formation depicted in Figure 8 between the catalyst and the enolate accounts for the enantioselectivity.

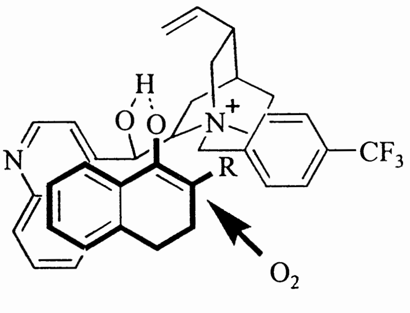
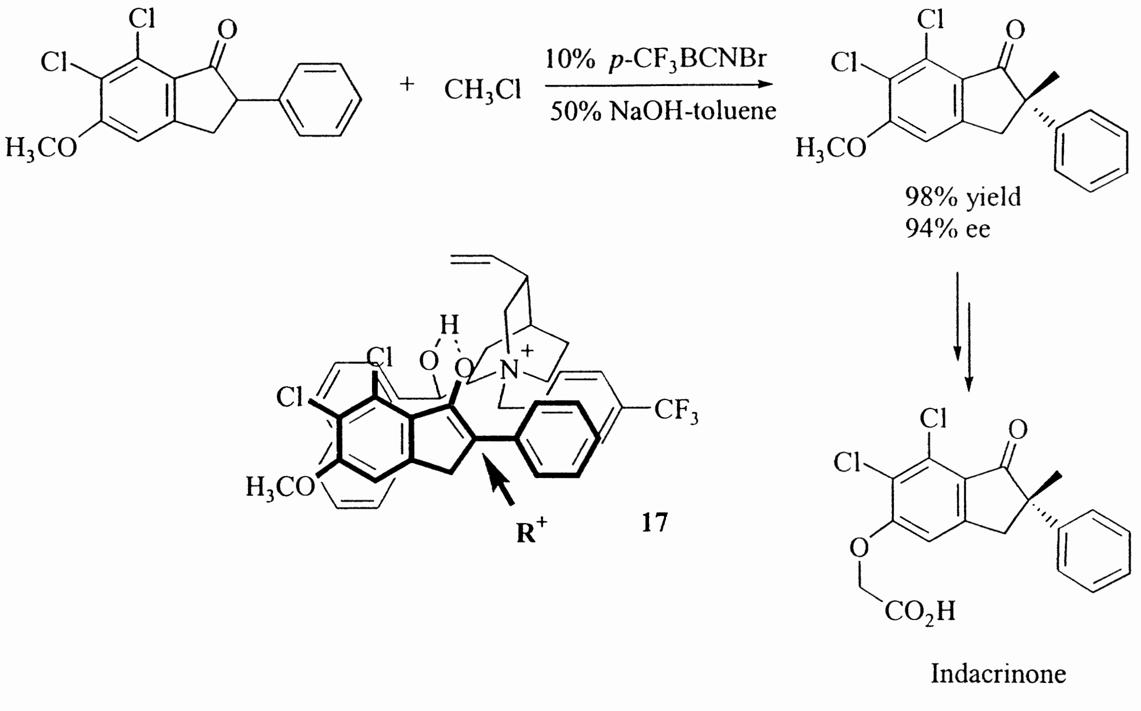


FIGURE 8. A hydrogen-bonded ion-pair formation

IV. Enantioselective Carbon-Carbon Bond Formation

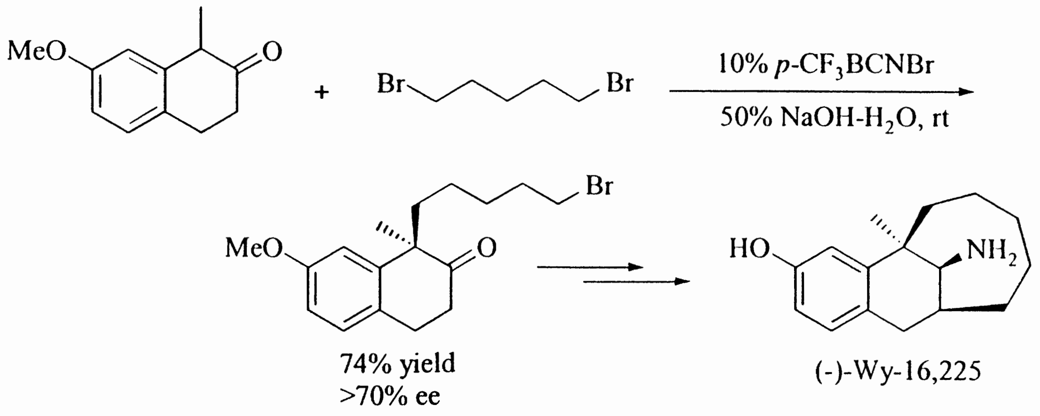
A. ASYMMETRIC ALKYLATION USING PHASE-TRANSFER CATALYSTS

Asymmetric alkylations can be performed in the presence of catalytic amounts of alkaloid-derived chiral phase transfer catalysts. The first remarkable success in this area was achieved by Dolling and coworkers, who performed the enantioselective methylation of indanone derivatives under PTC conditions (*162-164*). The numerous reaction variables were optimized and the kinetics and mechanism of the reaction were studied in detail. The phase transfer reaction of indanone derivative and methyl chloride in 50% NaOH-toluene using *N*-(*p*-trifluoromethylbenzyl)cinchonium bromide (*p*-CF_3BCNBr) gives the methylated product in 98% chemical yield and 94% ee (Scheme 24). Alkylation takes place through a hydrogen-bonded enolate/catalyst ion pair **17**, from the least hindered side. The product is a precursor of the antihypertensive drug, (*S*)-indacrinone.

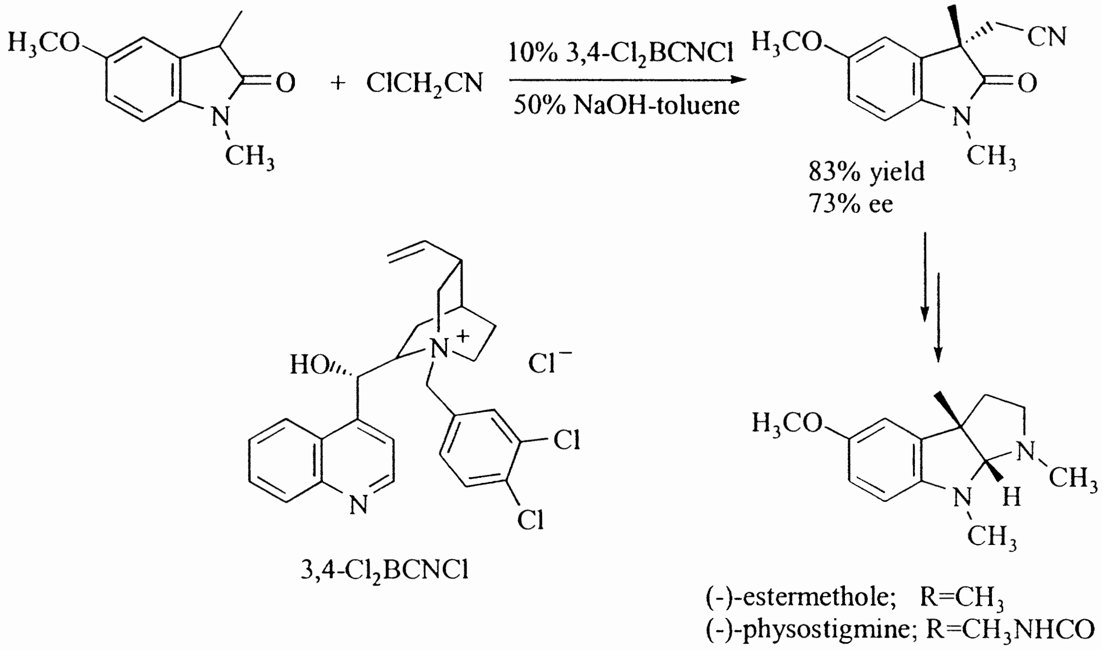


SCHEME 24. Asymmetric methylation of indanone derivative

Asymmetric induction in the phase-transfer alkylation of α-aryl substituted ketones, esters and lactones has also been evaluated (*165*). The potential of this method was demonstrated by the asymmetric synthesis of (-)-Wy-16,225, a bridged aminotetralin with potent analgesic properties (Scheme 25) (*165*). Similarly, asymmetric synthesis of (-)-estermethole and (-)-physostigmine, a clinically useful anticholinesterase agent, is accomplished by using phase-transfer alkylation of oxindoles (scheme 26) (*166*).



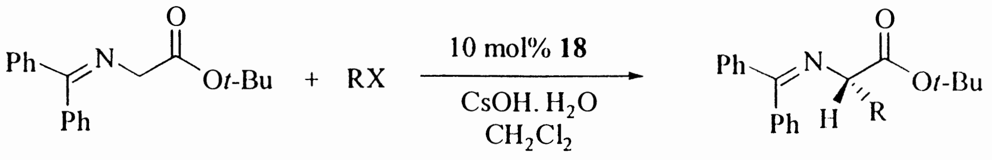
SCHEME 25. Asymmetric synthesis of (-)-Wy-16,225

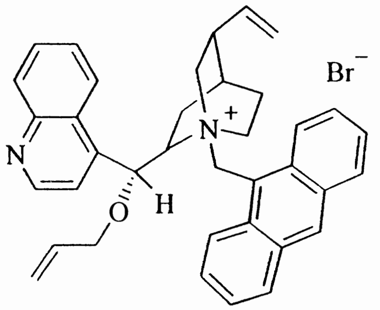


SCHEME 26. Asymmetric alkylation of oxindoles

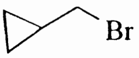
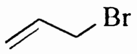
α-Amino acids can be prepared by alkylation of the *tert*-butyl glycinate-benzophenone Schiff base ester using chiral PTC derived from cinchona alkaloids (*167-172*). This reaction had been thoroughly studied by the pioneering work of O'Donnell and coworkers. However, the enantioselectivity of this reaction was not very high (66-75% ee) (*167-170*). The asymmetric synthesis of chiral α,α-dialkylamino acids by a related method gave less satisfactory results (up to 50% ee) (*169*). However, very recently, Corey and coworkers (*171,172*) reported highly efficient enantioselective enolate alkylation using a well-designed cinchonidine-derived chiral phase-transfer catalyst **18** (Table VII). In this reaction, they used solid cesium hydroxide monohydrate as the basic phase in order to minimize the possibility of water in the organic phase (CH_2Cl_2) and to allow the use of lower reaction temperatures (-60 °C to -78 °C) than are possible with 50% aqueous KOH or NaOH.

TABLE VII
ENANTIOSELECTIVE CATALYTIC PHASE-TRANSFER ALKYLATION



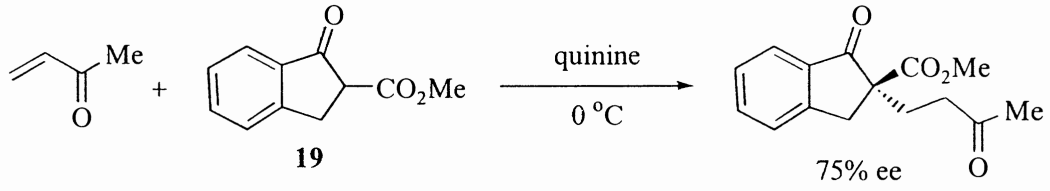


18

RX	% yield	% ee
CH_3I	71	97
EtI	82	98
$CH_3(CH_2)_4CH_2I$	79	99.5
	75	99
	89	97
$PhCH_2Br$	87	94
Ph_2CHBr	73	99.5

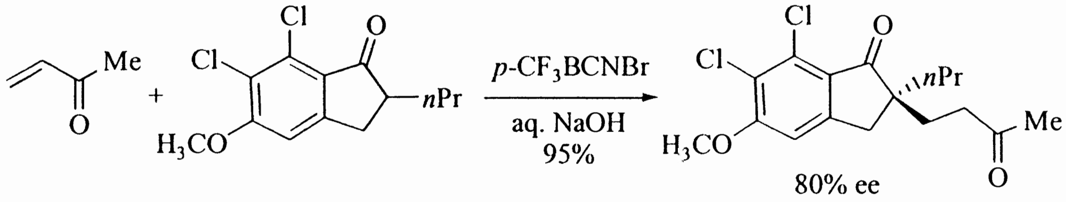
B. ASYMMETRIC MICHAEL ADDITION

When the Michael donors have a sufficiently low pKa, the asymmetric Michael addition can be catalyzed by chiral bases. The most interesting results are those of Wynberg and coworkers (*173-176*). They performed the reaction of **19** with methyl vinylketone in the presence of quinine or quinidine and obtained either enantiomer of the Michael adduct (Scheme 27). The reactions of other ketoesters or of nitromethane are less enantioselective.



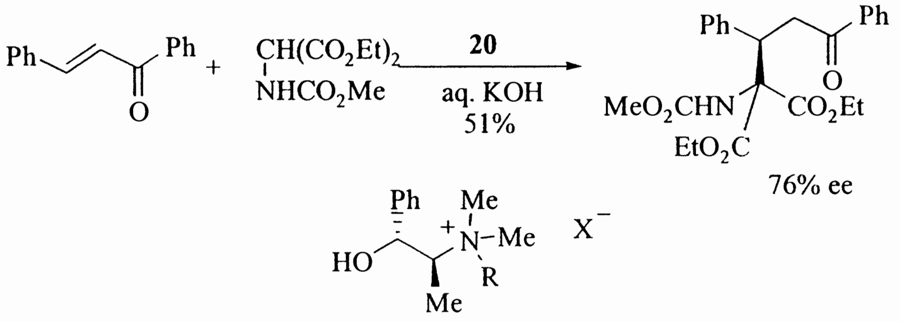
SCHEME 27. Asymmetric Michael addition catalyzed by cinchona alkaloid bases

Michael additions can also be performed under phase transfer conditions with an achiral base in the presence of a chiral quaternary ammonium salt as a phase transfer agent. Weinstock and coworkers (*177*) conducted the Michael addition of 2-propyl-1-indanone to methyl vinylketone in a two-phase 50% aqueous NaOH-toluene system containing *N*-(*p*-trifluoromethylbenzyl)cinchonium bromide (*p*-CF_3BCNBr) as the catalyst (Scheme 28). The presence of a free hydroxyl group on the cinchona derivatives is necessary to observe good asymmetric induction. As in the case of alkylation, the interpretation of these results relies on the formation of a hydrogen bond with the carbonyl of the α,β-unsaturated ketone, promoting its activation.



SCHEME 28

Ephedra alkaloid-derived quaternary ammonium salts **20** have also been employed in the Michael addition of protected glycinate to chalcone to yield optically active α-amino acid derivative (Scheme 29) (*178,179*). Michael adducts are obtained with good enantiomeric excess if the R substituent of **20** is 4-MeOC$_6$H$_4$ or 1-Np.



20 (R= 4-MeOC$_6$H$_4$, 1-Np)

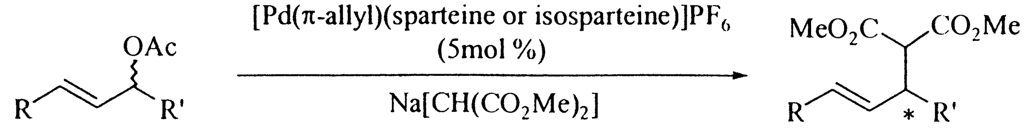
SCHEME 29. Asymmetric synthesis of α-amino acid derivatives by Michael addition

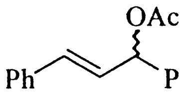
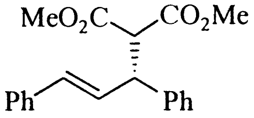
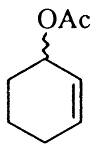
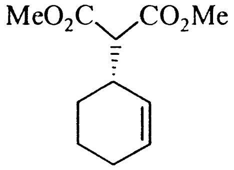
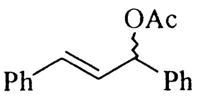
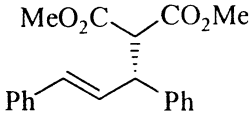
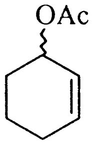
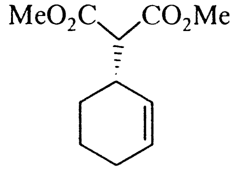
Conjugate addition of dialkylzincs to α-enones catalyzed by Ni(II)-complexes, based on norephedrine are also highly enantioselective (*180-183*).

C. Pd-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

Pd-catalyzed asymmetric alkylation reactions are useful synthetic methods for asymmetric C-C bond formation by allowing the Pd-catalyzed substitution of a nucleophile for a suitable leaving group in an allylic position (*184*). A number of chiral ligands have been developed for this kind of reaction. The readily available, naturally occurring alkaloid, (-)-sparteine has also been described as an effective chiral ligand for palladium-catalyzed asymmetric allylic alkylations (*185*). In some cases, high degrees of enantioselection were obtained (up to 85% ee). C$_2$-Symmetric (-)-α-isosparteine, which can be synthesized from (-)-sparteine in 2 steps (*186-188*), was also used by Kang and coworkers as a chiral ligand for asymmetric allylic alkylation (Table VIII) (*189*).

TABLE VIII
Pd-CATALYZED ASYMMETRIC ALLYLIC ALKYLATIONS (from 189)



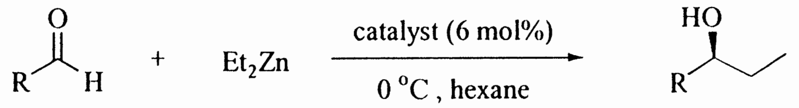
Ligand	Substrate	Product	% yield	% ee	Absolute config.
Sparteine			81	95	*R*
Sparteine			82[a]	50[a]	*S*
Isosparteine			86	88	*R*
Isosparteine			63	62	*S*

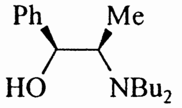
[a] Results reported in ref. 185

D. ENANTIOSELECTIVE ADDITION OF DIALKYLZINCS TO ALDEHYDES

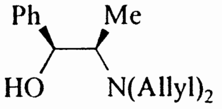
Catalytic enantioselective alkylation of aldehydes by chirally modified organometallics to give chiral secondary alcohols is one of the most important reactions in asymmetric synthesis (*190,191*). Whereas most of the attempts with organolithium or organomagnesium reagents have given disappointing results, very high enantioselectivities have been achieved by using dialkylzincs in combination with catalytic amounts of chiral β-aminoalcohols derived from norephedrines such as *N*,*N*-dibutylnorephedrine (DBNE) and *N*,*N*-diallylnorephedrine (DANE) (Table IX) (*190-193*). Dialkylzinc compounds do not react with aldehydes at room temperature, however, reactions do occur in the presence of catalytic amounts of aminoalcohols. A remarkable feature of these reactions is asymmetric amplification. Even when an aminoalcohol of low enantiopurity is used as a catalyst, the resulting secondary alcohol still often displays a high enantiomeric excess. This amplification mechanism has been studied in detail by Noyori (*191,194*).

TABLE IX
ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES CATALYZED BY NOREPHEDRINE-DERIVED AMINO ALCOHOLS





(1*S*,2*R*)-DBNE

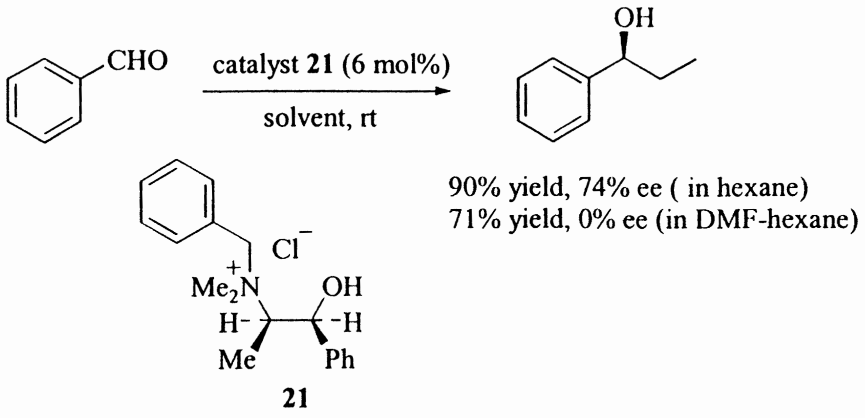


(1*S*,2*R*)-DANE

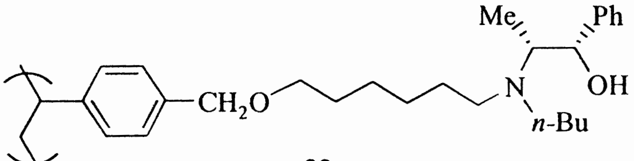
R	catalyst	yield (%)	% ee
Ph	(1*S*,2*R*)-DBNE	100	90
2-$MeOC_6H_4$	(1*S*,2*R*)-DBNE	100	94
4-$CF_3C_6H_4$	(1*S*,2*R*)-DBNE	92	91
4-FC_6H_5	(1*S*,2*R*)-DBNE	83	93
$PhCH_2CH_2$	(1*S*,2*R*)-DBNE	94	95
$(CH_3)_2CHCH_2$	(1*S*,2*R*)-DBNE	92	93
n-C_6H_{13}	(1*S*,2*R*)-DBNE	95	88
cyclo-C_6H_{11}	(1*S*,2*R*)-DBNE	94	78
n-C_8H_{17}	(1*S*,2*R*)-DBNE	95	87
n-C_8H_{17}	(1*S*,2*R*)-DANE	61	88

Diethylzinc has been added to benzaldehyde using an ephedra alkaloid-derived chiral quaternary ammonium salts, (1*S*,2*R*)-*N*-benzyl-*N*-methylephedrinium chloride (**21**) to give optically active secondary alcohols (Scheme 30) (*195*). This is an example in which the chiral catalyst affords a much higher enantioselectivity in the solid state than in solution. When benzaldehyde was treated with diethylzinc in hexane using **21** as a chiral solid state catalyst, (*S*)-1-phenylpropanol was obtained in 90% yield and 74% ee. In contrast, the reaction in DMF-hexane using the catalyst in solution **21** gave only racemic product in 71% yield. The degree of solvation of the ammonium cation of the catalyst is different between hexane and DMF. Very little solvation of the ammonium cation in hexane may be essential for the asymmetric induction. On the other hand, the oxygen or nitrogen atom of DMF strongly solvates the ammonium cation and may subsequently destroy the chiral complex of the ammonium catalyst and diethylzinc.

In another approach (*196-199*), polystyrene-bound *N*-butyl norephedrine **22** possessing a six-methylene spacer (Figure 9) has been used as a heterogeneous recyclable catalyst for the enantioselective addition of diethylzinc to aldehydes, producing secondary alcohols in high yields and with ees up to 82% (*198*).



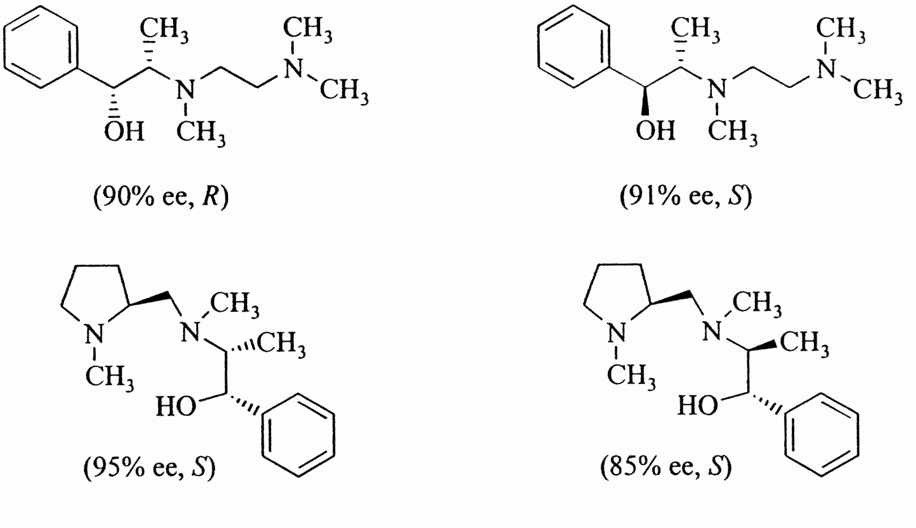
SCHEME 30. Addition of Et_2Zn to benzaldehyde catalyzed by the ephedrinium chloride **21**



22

FIGURE 9. Polystyrene-bound *N*-butyl norephedrine **22**

Tridentate lithium salts derived from ephedrine (Figure 10) can also catalyze the reaction of diethyl zinc with benzaldehyde to exhibit high enantioselectivity (up to 95% ee) (*200,201*).



(90% ee, *R*)

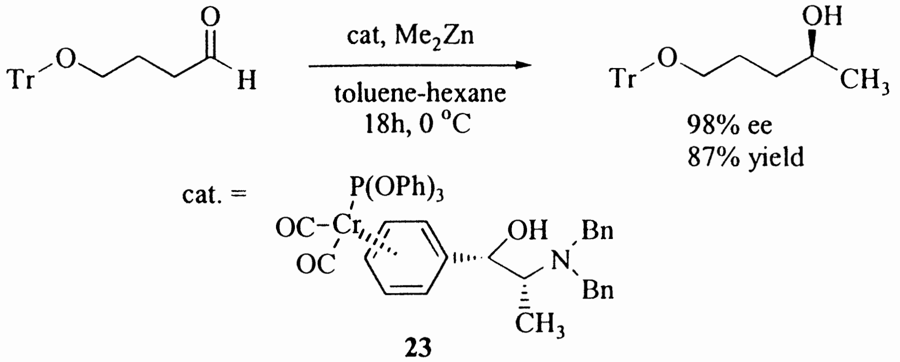
(91% ee, *S*)

(95% ee, *S*)

(85% ee, *S*)

FIGURE 10. Ephedrine-derived tridentate ligands

Other related sulfur derivatives of ephedra alkaloids (*202-205*) have also been used as catalysts in these reactions. Tricarbonyl chromium complexation of the aryl ring of ephedrine derivatives can lead to improved enantioselectivities (*206-208*). For example, the chromium complexed (1*S*,2*R*)-dibutylnorephedrine **23** can mediate the addition of dialkyl zincs to aldehydes giving *S*-carbinols in up to 99% ee (Scheme 31) (*208*).

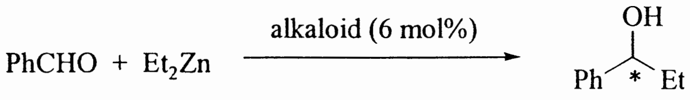


23

SCHEME 31. 1,2-Addition of Me_2Zn to aldehyde catalyzed chromium-complexed DBNE **23**

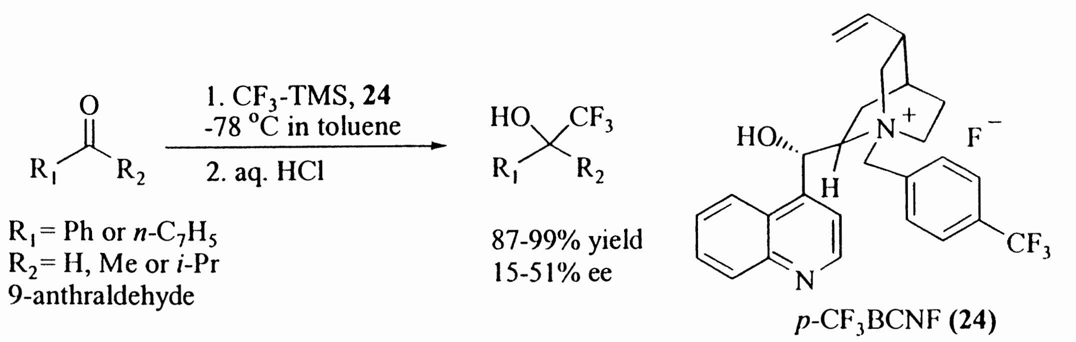
Cinchona alkaloids are also effective as chiral ligands for the 1,2-addition of diethylzinc to benzaldehyde (*209,210*). When diethylzinc is added to a solution of *o*-methoxybenzaldehyde in toluene in the presence of catalytic amounts of quinine, (+)-*o*-methoxyphenylethylcarbinol is formed in an ee of 92% (*209*). However, Buono and coworkers observed a very surprising effect of reaction temperature on reactivity and enantioselectivity in cinchona alkaloid-catalyzed 1,2-addition (Table X) (*210*). The best ee (73%) was obtained at elevated temperature (100 °C) and not, as could be expected, at a lower temperature. Through the appropriate choice of cinchona alkaloid, it is possible to obtain either enantiomers.

TABLE X
INFLUENCE OF REACTION TEMPERATURE ON ENANTIOSELECTIVITY IN CINCHONA ALKALOID-CATALYZED 1,2-ADDITION



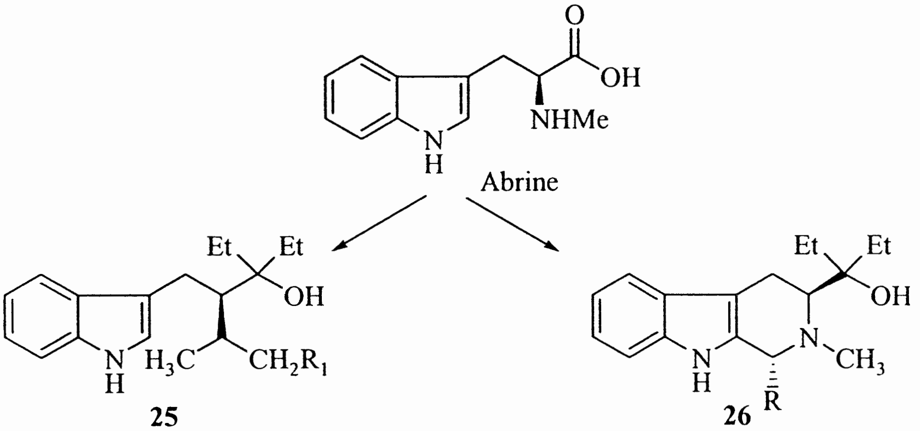
catalyst	reaction time (h)	reaction temp (°C)	% yield	% ee	config.
Quinine	38	-10	90	48	*R*
	16	rt	97	64	*R*
	0.25	100	95	73	*R*
Quinidine	38	-10	92	45	*S*
	16	rt	98	51	*S*
	0.25	100	96	69	*S*

Chiral quaternary ammonium fluorides, such as *N*-(*p*-trifluoromethylbenzyl) cinchonium fluoride (*p*-CF_3BCNF, **24**), also catalyze the asymmetric 1,2-addition of trifluoromethylzinc to aldehydes and ketones to give optically active 1-substituted-2,2,2-trifluoroethanols in nearly quantitative yields, but in only low to moderate ees (Scheme 32) (*211*).



SCHEME 32. Asymmetric trifluoromethylation of carbonyl compounds with CF_3-TMS catalyzed by **24**

Recently, a number of chiral β-amino alcohols such as **25**, **26** (Figure 11) derived from Abrine readily available from the seeds of *Abrus precatorius* have been prepared and used as chiral ligands for the enantioselective addition of diethylzinc with aldehydes (*212,213*). The compounds **25**, **26** gave excellent enantiomeric excess (94.2% and 97.6%, respectively) (*213*).



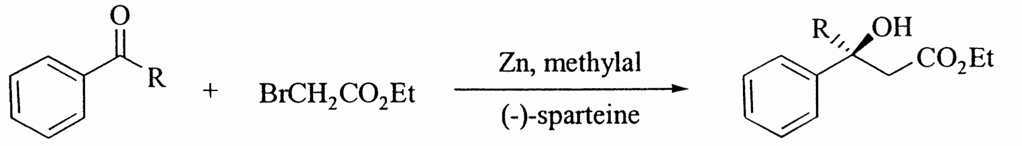
(94.2% ee, R_1= CH_2t-Bu)

(97.6% ee, R= CH_2t-Bu)

FIGURE 11. Chiral β-amino alcohols **25**,**26** derived from Abrine

E. ASYMMETRIC REFORMATSKY REACTION

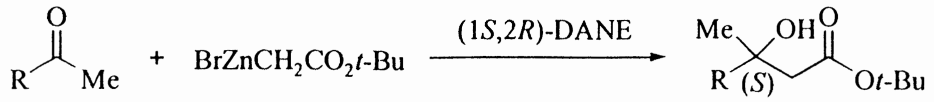
Sparteine was used as a zinc ligand as early as 1973 by Guette and coworkers in the Reformatsky reaction (*214*). A highly enantioselective reaction was observed with benzaldehyde. However, the Reformatsky reaction with ketones under the same conditions gave β-(*tert*-hydroxy)esters with only 7-39% ee (Scheme 33).



R=H; 38% yield, 95% ee
R=CH_3; 16% yield, 38%ee

SCHEME 33. Asymmetric Reformatsky reaction using sparteine as a ligand

Higher ees and better yields were obtained using *N,N*-diallylnorephedrine (DANE) as a chiral ligand in the enantioselective Reformatsky reaction of *tert*-butyl bromoacetate and ketones (73-75% ee) (Scheme 34) (*215*).

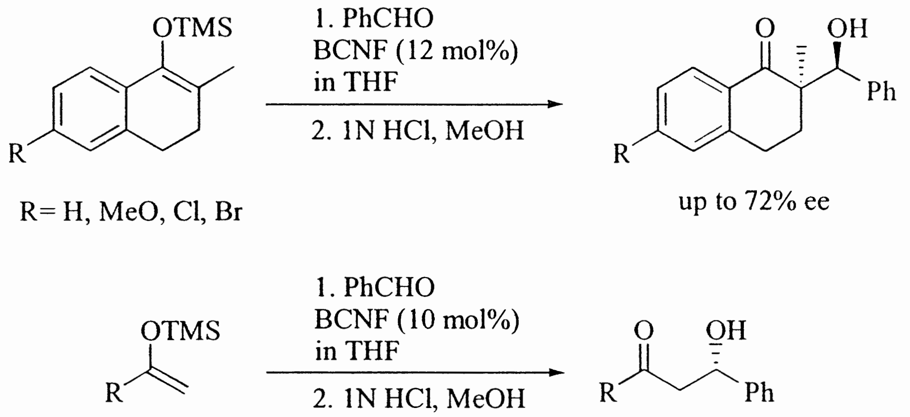


R= Ph; 65% yield, 74% ee
R= 2-Naphthyl; 38% yield, 75% ee
R= 4-FC_6H_4; 57% yield, 73% ee

SCHEME 34. Asymmetric Reformatsky reaction using DANE as a ligand

F. ASYMMETRIC ALDOL CONDENSATION

Asymmetric PTC aldol condensation of protected glycinate with aldehydes to give β-hydroxy-α-amino acid derivatives was reported (*216,217*). Unfortunately, the enantio- and diastereoselectivities in this reaction were very low (<12% ee). However, recently, moderate ees (up to 72% ee for the erythro isomer) were obtained in the catalytic enantioselective aldol reactions of benzaldehyde with silyl enol ethers by utilizing *N*-benzylcinchonium fluoride (BCNF) as a chiral catalyst (Scheme 35) (*218*).



R= H, MeO, Cl, Br

up to 72% ee

R= Ph, *t*-Bu

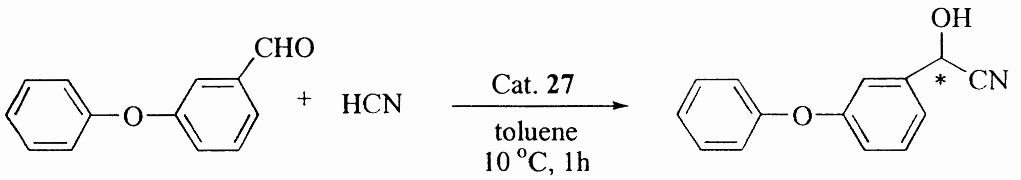
R= Ph; 65% yield, 39% ee
R= *t*-Bu; 62% yield, 62% ee

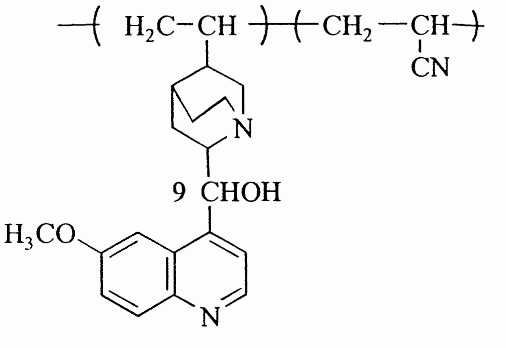
SCHEME 35. Enantioselective PTC aldol condensation

G. ASYMMETRIC CYANOHYDRIN SYNTHESIS

Optically pure cyanohydrins are versatile synthetic intermediates in the synthesis of a wide range of homochiral products such as α-hydroxy acids, β-hydroxy amines, and α-amino acid derivatives, etc., and have also been used as key intermediates in the synthesis of industrially important biologically active compounds (*219*). The usual synthetic route to cyanohydrins involves the addition of a cyanide source, such as HCN or TMSCN, to aldehydes or ketones in the presence of chiral catalysts (*219*). Cinchona alkaloids can also catalyze this type of reaction (*220-222*). In 1912, Bredig and Fiske discovered the enantioselective addition of hydrogen cyanide to aldehydes catalyzed by cinchona alkaloids, which is probably one of the earliest studied asymmetric catalysis (*220*). However, the asymmetric induction by alkaloids was very low. Recently, Danda and coworkers have used the polymers **27**, containing quinidine or quinine, to catalyze the asymmetric addition of HCN to 3-phenoxybenzaldehyde (*221*). Very interestingly, polymeric alkaloids exhibited higher enantioselectivities than those obtained with the corresponding monomeric alkaloids, quinidine and quinine (Table XI). For example, a polymer containing quinidine gave the (*S*)-isomer of cyanohydrin in 98% yield and 46% ee, whilst quinidine gave the (*S*)-isomer of the cyanohydrin in 97% yield and 22% ee. The reaction mixture is gel-like in the case of polymeric alkaloids, whereas it is homogeneous in the case of the corresponding monomers. This gelation would be preferable both to increase the enantioselectivity and to decrease the racemization of the products.

TABLE XI
ASYMMETRIC HYDROCYANATION OF 3-PHENOXYBENZALDEHYDE CATALYZED BY CINCHONA ALKALOIDS





27

catalyst	% yield	% ee
quinidine	97	22 (*S*)
quinine	93	5 (*R*)
27a	98	46 (*S*)
27b	97	20 (*R*)

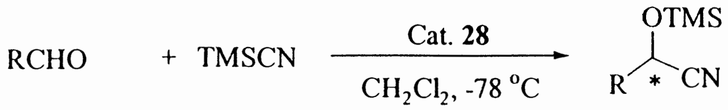
27a; poly(quinidine-co-acrylonitrile)
27b; poly(quinine-co-acrylonitrile)

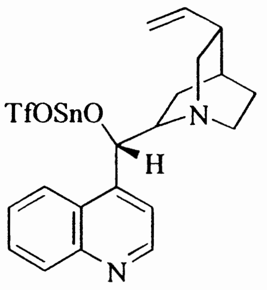
Mukaiyama *et al.* have reported the use of the chiral tin (II) species **28**, derived from cinchonine, as a Lewis acid catalyst for the asymmetric addition of trimethylsilyl cyanide to aliphatic aldehydes (Table XII) (*222*). The enantiomeric excesses (72-96% ee) obtained by this method are much higher than those reported for cyanohydrins prepared using only alkaloids as catalyst or using polymeric derivatives of alkaloids. However, benzaldehyde did not react with TMSCN under the same conditions.

Cinchona and ephedra alkaloid-derived quaternary ammonium salts were also utilized as chiral catalysts for the synthesis of *O*-acetyl cyanohydrins under phase-transfer conditions. However, only low optical rotations in the products were observed (*223*).

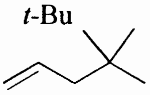
TABLE XII

ASYMMETRIC ADDITION REACTION OF TMSCN WITH ALDEHYDES USING Ti(II)-LEWIS ACID DERIVED FROM CINCHONIDINE



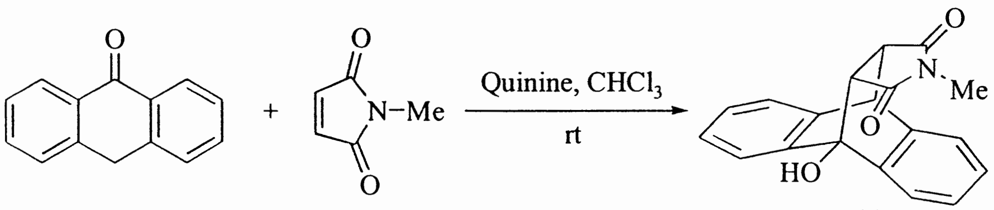


28

R	% yield	% ee
c-C_6H_{11}	89	72
n-C_8H_{17}	79	96
i-Pr	67	95
t-Bu	49	83
	27	93
Ph	0	—

H. ASYMMETRIC DIELS-ALDER REACTION

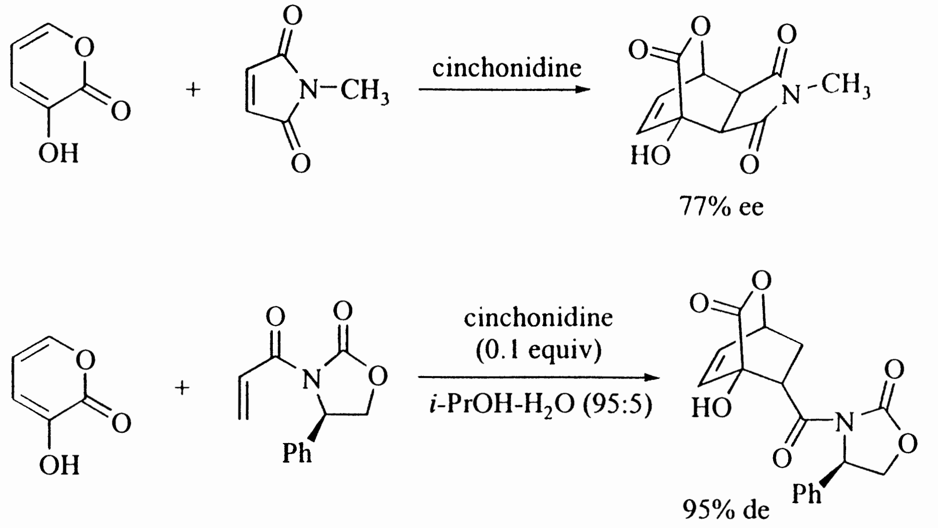
Diels-Alder reactions are usually catalyzed by Lewis acids, and several asymmetric acid-catalyzed reactions have been reported (*224*). However, Diels-Alder reactions catalyzed by bases are unusual and only a few asymmetric, base-catalyzed reactions are known. For example, the reaction of anthrone and *N*-methylmaleimide can be catalyzed by alkaloids (Scheme 36). However, only moderate ees were obtained (*225,226*).



98% yield
61% ee

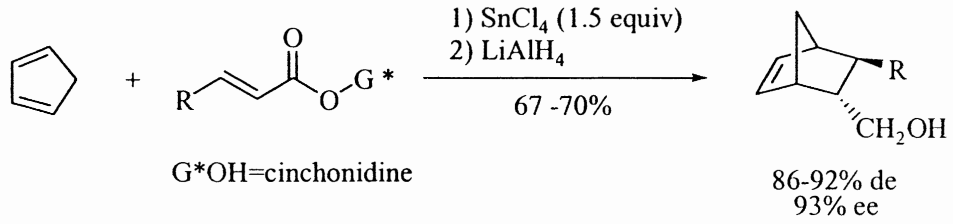
SCHEME 36. Quinine-catalyzed asymmetric Diels-Alder reaction

Recently, Nakatani and coworkers (*227-229*) reported that the reaction of 3-hydroxy-2-pyrone with an electron deficient dienophile can also be catalyzed by a base and afforded a Diels-Alder adduct in nearly quantitative yield (Scheme 37). In particular, when a cinchona alkaloid was used as an optically active base catalyst, up to 77% ee of the endo adducts was obtained in the reaction of 3-hydroxy-2-pyrone with *N*-methylmaleimide (*228*). In the presence of a cinchona alkaloid as a catalyst, the Diels-Alder reaction of 3-hydroxy-2-pyrone with chiral *N*-acryloyl oxazolidinone afforded a bicyclolactone adduct with high diastereoselectivities (up to 95% de), in almost quantitative yield (*229*).



SCHEME 37. Cinchonidine-catalyzed asymmetric Diels-Alder reaction

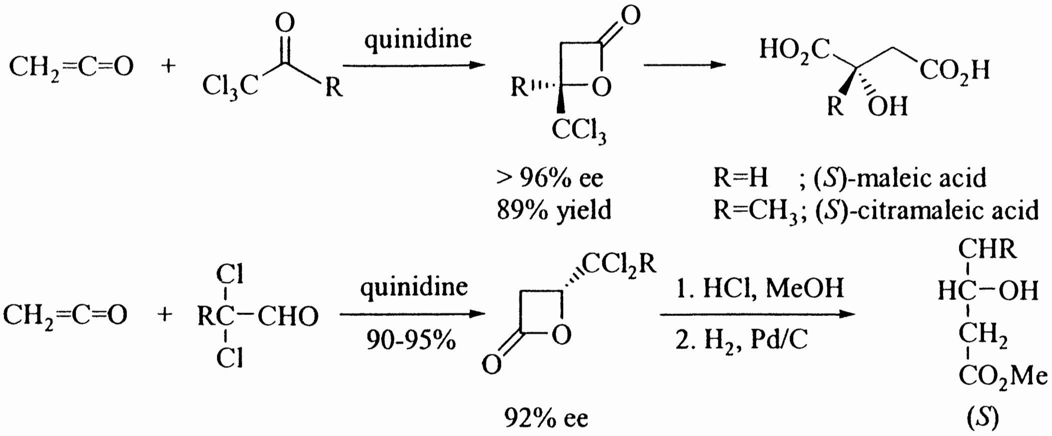
The use of cinchona alkaloids as chiral auxiliaries in the cycloadditions of cyclopentadiene with acrylic, crotonic or fumaric esters was also reported (*230*) (Scheme 38).



SCHEME 38. Asymmetric Diels-Alder reaction using cinchonidine as a chiral auxiliary

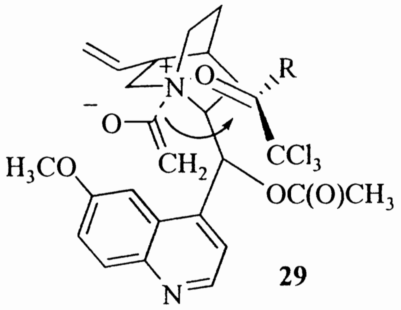
I. ASYMMETRIC 2,2-CYCLOADDITION OF KETENE AND ELECTRON-POOR ALDEHYDES OR KETONES

Acid chlorides (*231*) or ketenes (*232-237*) react with electron-poor aldehydes and ketones in the presence of optically active tertiary amines to give enantiomerically enriched β-lactones. The reaction of ketene with chloral or trichloroacetone has been studied in considerable detail by Wynberg. In the presence of catalytic amounts of cinchona alkaloid, the β-lactone is formed in virtually quantitative chemical and optical yield (up to 96% ee) (Scheme 39). This optical purity can be easily improved by a recrystallization of the β-lactones from methylcyclohexane. By the proper choice of the catalyst, either enantiomer of the β-lactone can be obtained. When quinidine is used as the catalyst the product has the (*R*) configuration, whereas the use of quinine gives access to the corresponding (*S*)-enantiomers. Thus, the reaction of 1,1,1-trichloroacetone with ketene in the presence of quinidine gives the β-lactone (*R*)-4-methyl-4-(trichloromethyl)oxetan-2-one from which (*S*)-citramalic acid, a useful chiral synthon of natural products (*238-240*), can be obtained by alkaline hydrolysis. Substitution of chloral for trichloroacetone in the cycloaddition reaction leads to the β-lactone, an intermediate in the production of (*S*)-malic acid. Similarly, the quinidine-catalyzed cycloaddition of ketene to 2,2-dichloroaldehydes gives β-lactones of high optical purities which are easily converted to the corresponding methyl (3*S*)-hydroxyalkanoates (*235*).



SCHEME 39. Enantioselective cycloaddition of ketene and electron-poor aldehydes or ketones

Wynberg proposed the transition state picture **29** for the ketene-chloral addition in the presence of quinidine (Figure 12) (*241*).

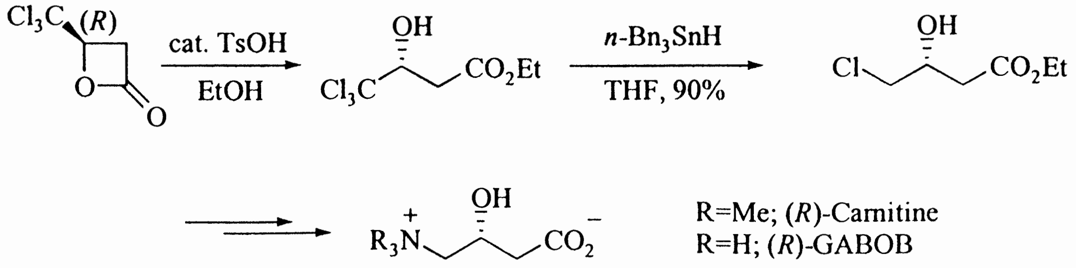


29

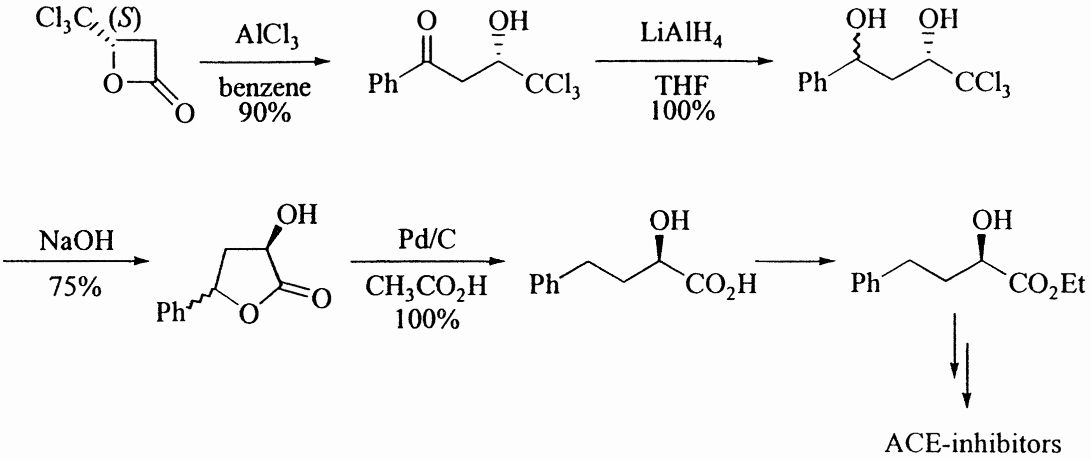
FIGURE 12. Ketene-chloral-quinidine acetate transition state

Song *et al.* reported that poly(cinchona alkaloid acrylate)s gave similar catalytic activity and enantioselectivity (up to 94% ee) compared to those of their monomeric alkaloids, quinidine and quinine (*242*).

(*R*)-4-(Trichloromethyl)oxetan-2-one can be easily converted to ethyl (*R*)-3-hydroxy-4-chlorobutyrate, a (*R*)-carnitine intermediate, by ethanolysis followed by selective bis-dechlorination of ethyl (*R*)-3-hydroxy-4,4,4-trichlorobutyrate (Scheme 40) (*243,244*). The optically pure β-lactone can serve an excellent chiral acylating agent under Friedel-Crafts-type conditions. The acylation of (*S*)-4-(trichloromethyl)oxetan-2-one with aromatic compounds provided an acylated product with a chiral trichloromethyl carbinol moiety, which can be used for the synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutanoate, an important precursor for the synthesis of angiotensin converting enzyme (ACE) inhibitors, e.g., enalapril (Scheme 41) (*245*).

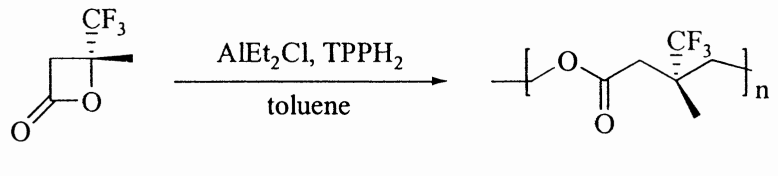


SCHEME 40. Synthesis of (*R*)-carnitine and (*R*)-GABOB from (*R*)-4-(trichloromethyl)oxetan-2-one



SCHEME 41. Synthesis of ethyl (*R*)-2-hydroxy-4-phenylbutanoate from (*S*)-4-(trichloromethyl)oxetan-2-one

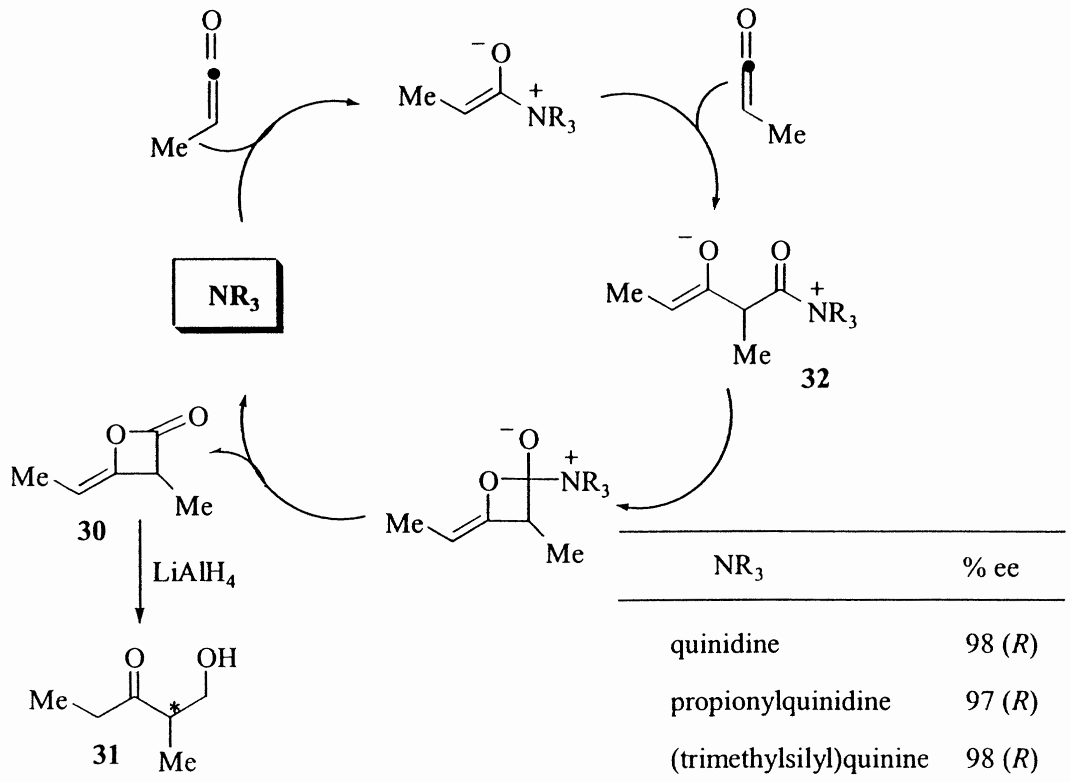
In the presence of catalysts such as $ZnEt_2/H_2O$ or $AlEt_3/H_2O$, optically active 2-substituted β-propiolactones readily polymerize to give optically active stereoregular polyesters exhibiting quite unique properties compared with the corresponding racemic polymers (Scheme 42) (*246-248*).



SCHEME 42. Synthesis of an optically active polyester from chiral β-propiolactone

J. ASYMMETRIC DIMERIZATION OF KETENES

Very recently, Calter has reported that cinchona alkaloids and their derivatives catalyze the dimerization of methylketene with high enantioselectivity (up to 98% ee), yielding β-lactone **30** via a formal Claisen condensation (Scheme 43) (*249*). This product could easily be transformed into a useful synthon for polypropionate synthesis. The dimerization of methylketene was carried out in the presence of 1 mol% of the alkaloid catalysts in THF at -78 °C. Due to the volatility and instability of the dimer **30**, the product was reduced with $LiAlH_4$ to produce the primary alcohol **31**. Possible conformations of ammonium enolate **32** derived from quinidine and methylketene was proposed.

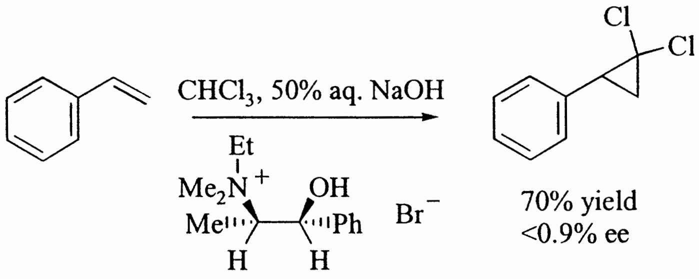


NR$_3$	% ee
quinidine	98 (*R*)
propionylquinidine	97 (*R*)
(trimethylsilyl)quinine	98 (*R*)
quinine	70 (*S*)
propionylquinine	54 (*S*)
(trimethylsilyl)quinine	93 (*S*)

SCHEME 43. Catalytic asymmetric dimerization of methylketene

K. ASYMMETRIC CYCLOPROPANATION

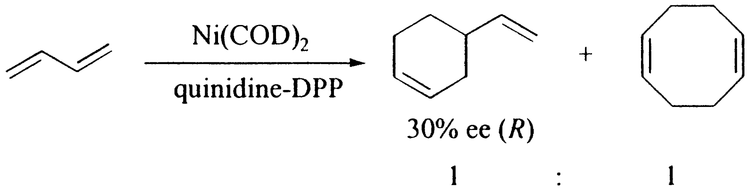
Although the asymmetric cyclopropanation of alkenes using an ephedrine-derived quaternary ammonium salt as a phase-transfer catalyst was reported early, the results were very disappointing (Scheme 44) (*250*). Another report of cyclopropanation has yielded, at best, low asymmetric inductions (*251*).



SCHEME 44. Catalytic asymmetric cyclopropanation of styrene

L. ASYMMETRIC DIMERIZATION OF BUTADIENE

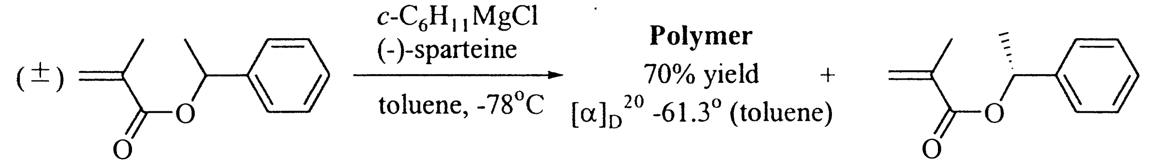
The dimerization of butadiene catalyzed by $Ni(COD)_2$ and quinidine-DPP as a chiral ligand gave rise to (*R*)-(+)-vinylcyclohexene with an ee of approximately 30%, accompanied with a selectivity for vinylcyclohexene versus cyclooctadiene of approximately 1 (Scheme 45) (*46,252*).



SCHEME 45. Catalytic asymmetric dimerization of butadiene

M. GRIGNARD-INDUCED ANIONIC POLYMERIZATION

Several sparteines, such as (-)-sparteine, (-)-α-isosparteine, (+)-6-benzylsparteine, etc., when combined with Grignard reagents catalyze the asymmetric polymerization of racemic α-methylbenzyl methacrylate (MBMA) in toluene at -78 °C (*253-257*). For instance, racemic 1-phenylethyl methacrylate is resolved efficiently by a cyclohexyl magnesium chloride-(-)-sparteine complex to give, at 70% conversion, optically active polymer and the unreacted monomer in greater than 90% ee (Scheme 46) (*253*). Similarly, reaction of racemic phenyl-2-pyridyl-*o*-tolylmethyl methacrylate in the presence of 4-fluorenyllithium and (+)- or (-)-2,3-dimethoxy-1,4-bis(dimethylamino)butane proceeds with a high degree of kinetic resolution (*258*).



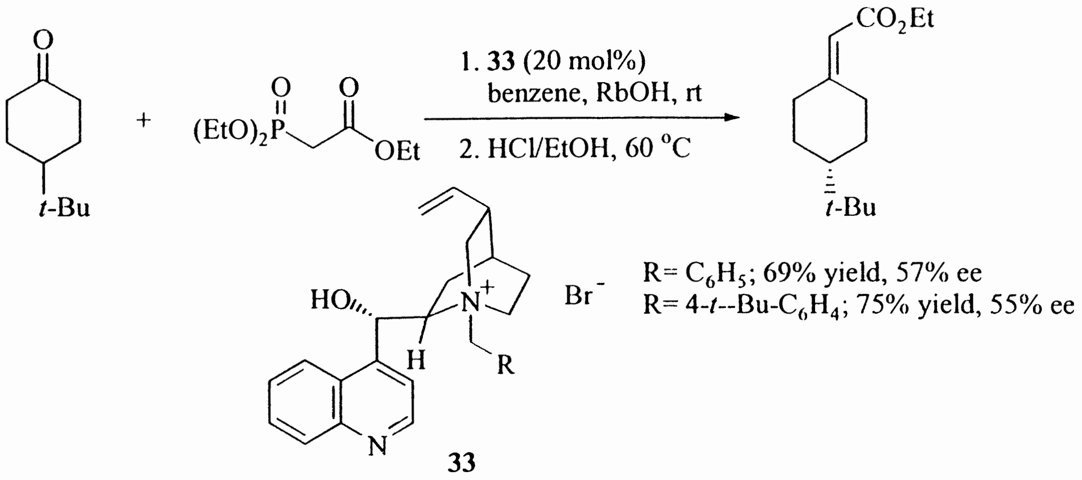
SCHEME 46. Catalytic asymmetric Grignard induced anionic polymerization

N. ASYMMETRIC HORNER-WADSWORTH-EMMONS REACTION

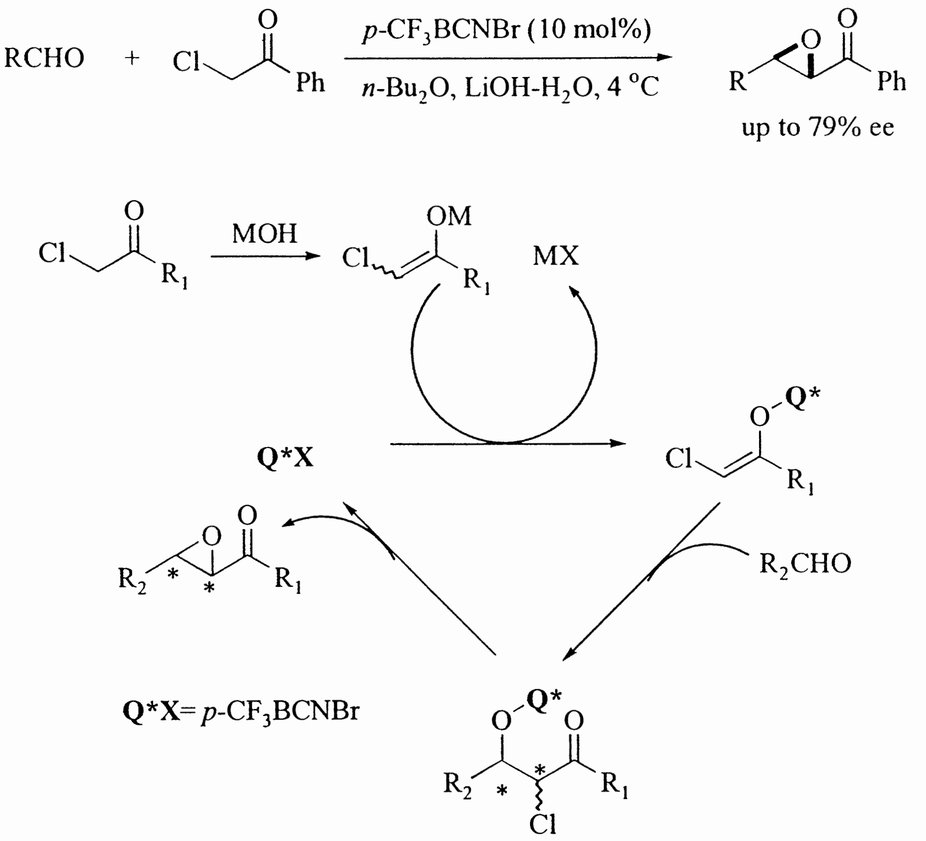
Very recently, Arai and coworkers (*259*) reported the first example of an asymmetric Horner-Wadsworth-Emmons reaction promoted by cinchonine-derived quaternary ammonium salts **33** as phase transfer catalysts (Scheme 47). Although catalytic activity and enantioselectivity are not high enough (up to 57% ee), these results will lead to further progress.

O. CATALYTIC ASYMMETRIC DARZENS CONDENSATION

A chiral quaternary ammonium salt derived from cinchonine catalyzes the asymmetric Darzens condensation under PTC conditions. The reaction of phenacyl chlorides with various aldehydes in dibutyl ether with LiOH monohydrate base in the presence of 10 mol% of *p*-CF_3BCNBr affords α,β-epoxyketones with moderate to good enantiomeric excess (up to 79% ee) (*260*). Scheme 48 shows the proposed catalytic cycle for the asymmetric Darzens condensation under PTC conditions.



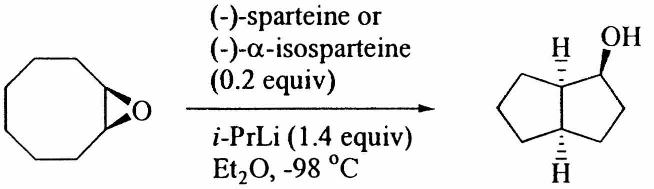
SCHEME 47. The catalytic asymmetric Horner-Wadsworth-Emmons reaction with PTCs



SCHEME 48. Catalytic asymmetric Darzens condensation under phase-transfer conditions and the proposed catalytic cycle

P. ENANTIOSELECTIVE α-DEPROTONATION-REARRANGEMENT OF ACHIRAL EPOXIDES

The enantioselective α-deprotonation-rearrangement of medium sized (8-, 9- and 10-membered) cycloalkene-derived achiral epoxides, using organolithiums in the presence of catalytic amounts of sparteine (*261*) or isosparteine (*262*) to give bicyclic alcohols in good yields and ees (up to 84% ee), has been recently reported (Scheme 49).



Using (-)-sparteine: 62% yield, 73% ee
Using (-)-α-isosparteine: 86% yield, 84% ee

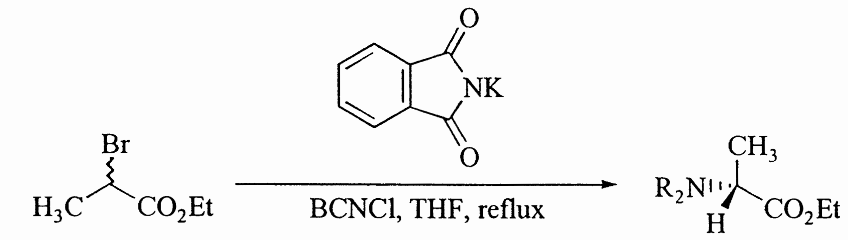
SCHEME 49. Asymmetric α-deprotonation-rearrangement of achiral epoxide

V. Enantioselective Carbon-Heteroatom Bond Formation

A. CARBON-NITROGEN BOND FORMATION

1. Synthesis of Optically Active α-Amino acids from α-Haloesters

Several groups have studied the synthesis of optically active α-amino acids from the inexpensive and readily available α-halo esters by displacement of the halides with phthalimide in the presence of cinchona alkaloid-derived quaternary ammonium salts as catalysts (Scheme 50) (*263-266*). Early studies, using chiral, nonracemic starting material, showed that this reaction occurred with partial inversion of configuration and likely involved a kinetic resolution (*265*).

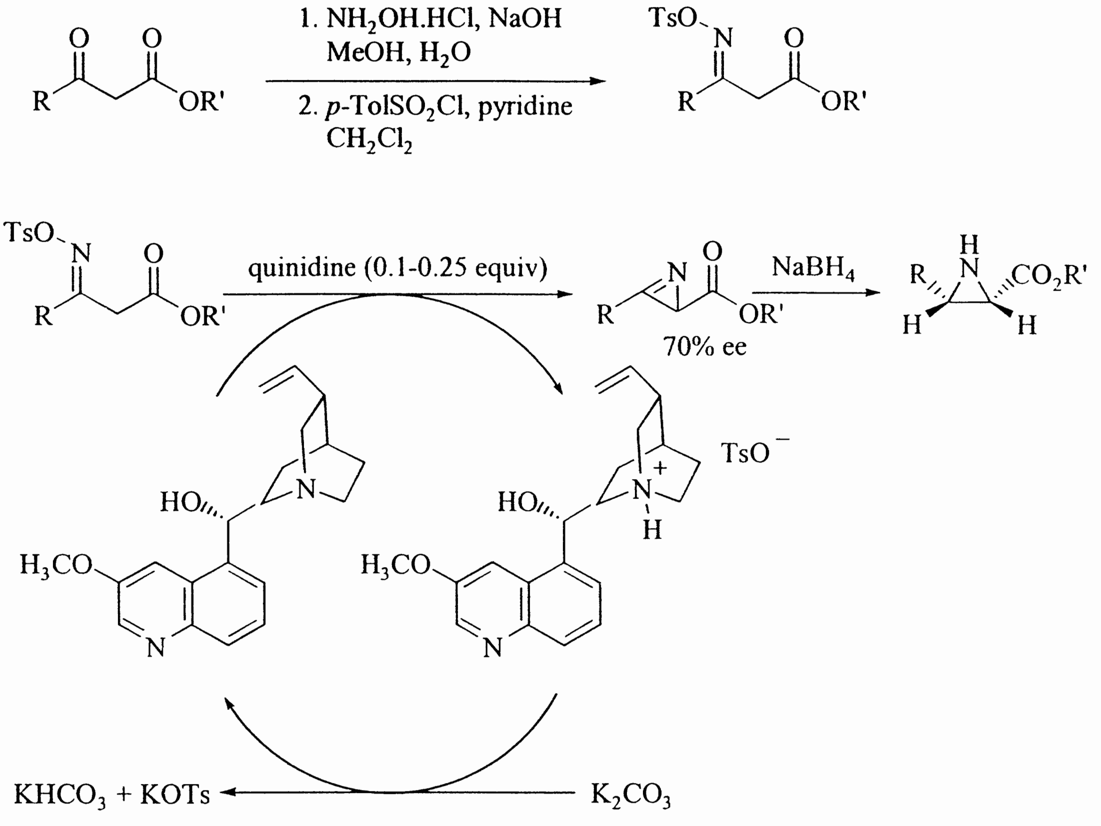


28% yield, 18.6% op

SCHEME 50. Asymmetric synthesis of optically active α-amino esters from a racemic α-halo ester

2. Catalytic Asymmetric Neber Reaction

Recently, Zwanenburg and coworkers (*267*) reported a novel catalytic asymmetric synthesis of aziridine carboxylic esters via the Neber reaction of ketoxime tosylates derived from 3-oxocarboxylic esters (Scheme 51). Quinidine catalyzes the Neber reaction of ketoxime tosylates in the presence of K_2CO_3 to give optically active aziridines (up to ~70% ee). However, with sparteine, brucine, and strychnine no optically active aziridine was formed. It was suggested that in the mechanisim for asymmetric induction the alkaloid bases form a tightly bound complex with the ketoxime tosylate. Since the presence of an alcohol function in the alkaloid base seems to be a prerequisite, it was suggested that hydrogen bonding of the base and the substrate through this hydroxyl group is a governing factor in the enantiodifferentiation during the abstraction of the methylene protons. This proposal is supported by the observation that in a hydroxylic solvent no asymmetric induction takes place and that additives such as LiCl, and especially H_2O, lower the optical yield considerably.

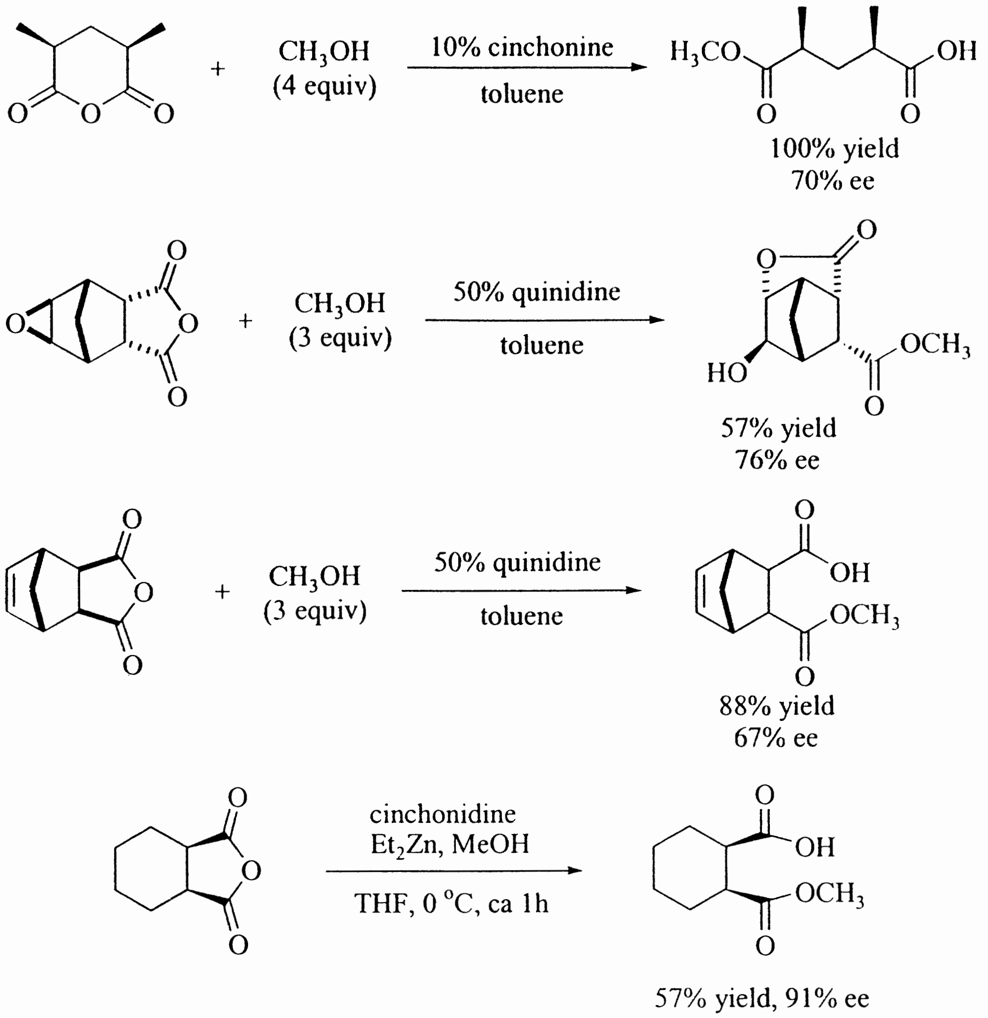


SCHEME 51. Catalytic asymmetric Neber reaction

B. CARBON-OXYGEN AND CARBON-SULFUR BOND FORMATION

1. Enantiotopic Differentiation Reaction of Meso-Cyclic Anhydrides (268-273)

In the presence of a cinchona alkaloid, certain cyclic carboxylic anhydrides with *meso* structures are converted to the chiral diacid monoesters in up to 76% ee (*268*). Quinine or cinchonidine and quinidine or cinchonine show opposite asymmetric induction. Asymmetric esterification of a prochiral cyclic anhydride can be also catalyzed by the complex formed from β-aminoalcohols, such as ephedrine or cinchona alkaloids, diethylzinc, and methanol. The use of (-)-ephedrine did not show a satisfactory selectivity. However, cinchona alkaloids effected a good to excellent diastereofacial discrimination (up to 91% ee) (Scheme 52) (*273*).



SCHEME 52. Asymmetric methanolysis of *meso*-cyclic anhydrides

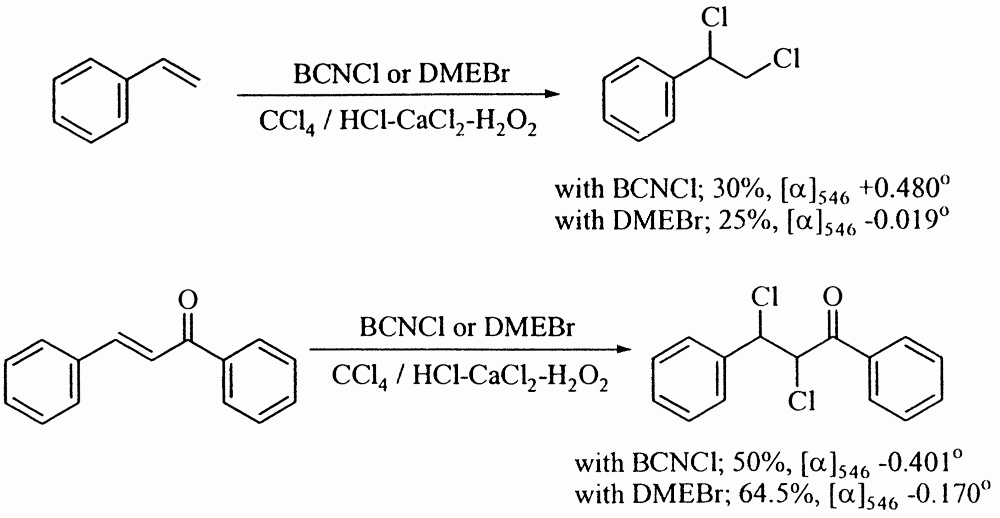
Polymer-supported quinine was also utilized for the asymmetric methanolysis of prochiral *cis*-2,4-dimethylglutaric anhydride. However, only low ees (up to 32% ee) were obtained (*270*).

2. *O- and S-Alkylations*

O-Alkylations with cinchona- and ephedra alkaloid-derived catalysts have been studied (*274*). The addition of thiophenol to cyclohexenone in the presence of cinchona alkaloid-derived quaternary ammonium salts gave the Michael adduct with 36% op in 85% yield (*275*). Other C-S bond formations with cinchona (*274,276-278*) and ephedra alkaloid (*274,275,279*) catalysts have been reported.

C. CARBON-HALOGEN BOND FORMATION

Very low asymmetric induction was observed in the addition of chlorine to alkenes under phase-transfer conditions using *N*-benzylcinchonium chloride (BCNCl) and *N*-dodecyl-*N*-methylephedrinium bromide (DMEBr) as catalysts (*280*) (Scheme 53). Alkaloid-catalyzed bromination of alkenes, which occurs with a maximum 5.5% optical yield was also reported (*281*).



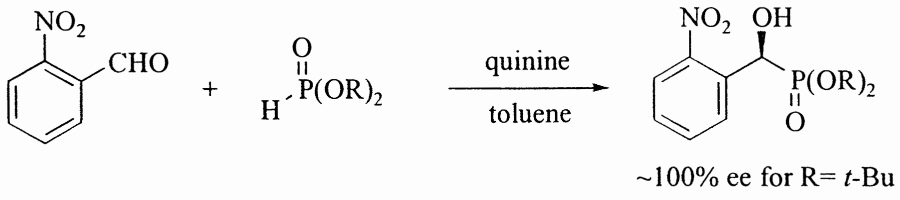
with BCNCl; 30%, $[\alpha]_{546}$ +0.480°
with DMEBr; 25%, $[\alpha]_{546}$ -0.019°

with BCNCl; 50%, $[\alpha]_{546}$ -0.401°
with DMEBr; 64.5%, $[\alpha]_{546}$ -0.170°

SCHEME 53. Catalytic asymmetric addition of chlorine to olefins

D. CARBON-PHOSPHOROUS BOND FORMATION

Cinchona alkaloids (e.g. quinine) catalyze the reaction between an aldehyde and a phosphite to produce an optically active α-hydroxyphosphonate ester (*1,282,283*). When the aldehyde has an *ortho* substituent such as nitro group, preferably one that aids in restricting the rotation of the aldehyde group, asymmetric induction takes place (*1*). The ees also increase (to nearly 100% for R= *t*-Bu) with an increasing bulk of the phosphonate ester, while the reaction rate decreases (Scheme 54) (*282*).



~100% ee for R= *t*-Bu

SCHEME 54. Cinchona alkaloid-catalyzed asymmetric addition of phosphite to an aldehyde

VI. Conclusion

This review has presented the current stage of asymmetric catalysis, in which alkaloids are utilized as chirality transmitters. As shown in many of the examples cited above, alkaloid-induced asymmetric catalysis has become a research field of great potential. A number of processes have gained wide acceptance, and some of them are even used on an industrial scale. However, in many cases a detailed knowledge of the mechanism is often unavailable. More careful and systematic studies to understand the details of the asymmetric induction step should be performed in the future. With such in-depth studies, it will be possible to design more efficient chiral ligands and catalysts that will lead to both high chemical yields and high levels of asymmetric induction.

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